



## Review

# Acute hyperglycaemia: a 'new' risk factor during myocardial infarction

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High admission blood glucose levels after acute myocardial infarction are common and are associated with an increased risk of death in subjects with and without diabetes. In this review, the possible toxic action of acute hyperglycaemia is discussed in order to explain the worse prognosis in subjects with myocardial infarction and concomitant hyperglycaemia. The possible usefulness of intensive insulin treatment is also discussed.

## Introduction

In recent years, much attention has been given to the evidence that the concomitant occurrence of hyperglycaemia in patients admitted to intensive care units with an acute myocardial infarction (MI) enhances the risk of mortality and morbidity, whether the patient has diabetes or not.<sup>1</sup>

In some cases, the elevation of glucose could simply be a marker of pre-existing, but not yet detected, type 2 diabetes or impaired glucose tolerance (IGT).<sup>2</sup> This may mean that besides being causal, elevated glucose also could be a marker of existing insulin resistance and/or beta-cell failure that may contribute to the poor prognosis through other mechanisms. However, a positive association between hyperglycaemia at the time of the event and subsequent mortality from MI has frequently been reported.<sup>3–13</sup> Consequently, understanding the possible mechanisms through which hyperglycaemia worsens the prognosis of a MI, as well the effectiveness of its control during acute MI, seems to be of great relevance.

## The effect of acute hyperglycaemia on MI

In MI, an increased plasma glucose level has been demonstrated to be capable of inducing such electrophysiological

alterations as to favour the occurrence of arrhythmias, whose outcome could be fatal.<sup>14</sup> This is consistent with the evidence that an acute increase of glycaemia in normal subjects produces a significant QT elongation,<sup>15</sup> a phenomenon confirmed in an *in vitro* model of working heart from rat.<sup>16</sup>

Acute hyperglycaemia is independently associated with impaired left ventricular function,<sup>17</sup> and with a larger infarct size due to an increased incidence of the no-reflow phenomenon.<sup>18</sup> Moreover, studies in animals have shown that acute hyperglycaemia abolishes ischaemic pre-conditioning.<sup>19</sup> Finally, a worse myocardial performance has been demonstrated in patients with acute MI and concomitant hyperglycaemia.<sup>20</sup>

The association of MI with increased thrombophilia is an old finding.<sup>21,22</sup> It has been reported that increased platelet activation after an MI is correlated with hyperglycaemia in non-diabetic patients.<sup>23</sup>

The possible role of hyperglycaemia in the activation of blood coagulation has previously been reviewed.<sup>24</sup> It emerges that acute glycaemic variations are matched with a series of alterations in coagulation that are likely to cause a thrombosis. Acute hyperglycaemia induces a shortening of the fibrinogen half-life,<sup>25</sup> and increases in fibrinopeptide A,<sup>26</sup> fragments of pro-thrombin,<sup>27</sup> in factor VII,<sup>28</sup> and in platelet aggregation,<sup>29</sup> which are all phenomena suggesting increased activation of thrombosis.

A growing body of evidence suggests that MI is associated with local and systemic inflammation.<sup>30</sup> Indeed,

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inflammatory cells infiltrate nearly all plaques; culprit lesions of infarcted hearts appear to be particularly enriched in activated T-cells.<sup>31</sup> Although circulating immune markers are also chronically elevated in patients with chronic stable angina, a transient burst of T-cell activation can only be detected in patients with unstable angina and MI,<sup>32</sup> suggesting that immune factors might precipitate plaque complications such as thrombus formation and vasoconstriction at the site of the culprit lesion. A recent paper demonstrated an association between inflammatory immune markers and functional cardiac outcome in patients with a first uncomplicated MI.<sup>33</sup> Stress hyperglycaemia was found to be associated with amplified inflammatory immune reactions and worse functional cardiac outcome.<sup>33</sup> Interestingly enough, acute hyperglycaemia in healthy subjects and in patients with impaired glucose tolerance or overt diabetes produces a rise in inflammatory markers.<sup>34–36</sup> Following this line of thought, it might be speculated that the detrimental effect of stress hyperglycaemia in acute MI might also stem from its ability to increase inflammation.

Endothelial dysfunction plays a key role in cardiovascular disease:<sup>37</sup> endothelial dysfunction is a common feature after an MI.<sup>38</sup> In patients with MI treated with thrombolysis, severe endothelial dysfunction in the infarct-related arteries is observed early.<sup>39</sup> Many studies have shown that an acute increase of glycaemia worsens endothelial function,<sup>40,41</sup> therefore suggesting that hyperglycaemia-induced endothelial dysfunction can also contribute to the damaging effect of hyperglycaemia during an MI.

### **Oxidative stress as a pathogenic factor underlying the effect of acute hyperglycaemia**

Oxidative stress is a well-recognized pathogenic process for atherosclerosis and cardiovascular disease.<sup>42</sup> The processes through which acute hyperglycaemia works is probably through the production of free radicals.<sup>43</sup> Both indirect and direct evidence supports this concept.

Indirect evidence is obtained through the use of antioxidants. The fact that antioxidants can hinder some of the effects acutely induced by hyperglycaemia, endothelial dysfunction,<sup>44–46</sup> activation of coagulation,<sup>27</sup> and inflammation,<sup>35,36</sup> suggests that the action of acute hyperglycaemia is mediated by the production of free radicals.

Direct evidence is linked to the estimate of the effects of acute hyperglycaemia on oxidative stress markers. It has been reported that during glucose oral challenge, a reduction in the antioxidant defences,<sup>47</sup> and an increase in markers of oxidative stress is observed.<sup>43</sup> More interestingly, new data come from studies on a new compound namely nitrotyrosine. 3-Nitrotyrosine is thought to be a relatively specific marker of oxidative damage mediated by peroxynitrite,<sup>48</sup> and it has recently been

demonstrated to be an independent predictor of cardiovascular disease.<sup>49</sup>

Nitrotyrosine formation is detected during acute hyperglycaemia in the artery wall of monkeys,<sup>50</sup> and in working hearts from rats during hyperglycaemia,<sup>51</sup> but also in the plasma of healthy and diabetic subjects.<sup>52,53</sup>

Compelling evidence is also accumulating which suggests a role for oxidative stress as a putative mechanism finally leading to plaque denudation and activation through increased endothelial cell apoptosis.<sup>38</sup> Thus, oxidative stress, irrespective of atherosclerotic disease stages, seems to represent a key phenomenon in acute vascular disease progression.<sup>38</sup> Hyperglycaemia generating oxidative stress by itself, can therefore contribute to worsen such a condition.

### **Therapeutic prospects**

The DIGAMI Study published in 1995 re-ignited interest in the use of insulin following acute MI.<sup>54</sup> It first reported on the feasibility of the use of an insulin–glucose infusion following MI in patients with a plasma glucose level of  $\geq 11$  mmol/L;<sup>54</sup> a later paper reported the 1 year mortality and morbidity results.<sup>55</sup> The final paper published in May 1999 reported the long-term mortality data.<sup>56</sup> 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 an MI.<sup>54–56</sup> However, not all were convinced by the results, particularly the mechanisms of action and whether the benefits accrued were solely from the insulin–glucose infusion used acutely.<sup>57,58</sup> The question concerning the use of insulin–glucose infusion during MI is still open; a recent trial did not show beneficial effect on total mortality in patients treated by primary angioplasty for acute MI.<sup>59</sup>

However, it is necessary to distinguish between a favourable metabolic effect of glucose–insulin infusion and the control of acute hyperglycaemia. 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 (FFAs), which are known to be associated with a deterioration of clinical outcome and may have toxic effects of their own on the myocardium.<sup>60,61</sup> Incidentally, it is reasonable that the toxic effect of FFAs is also mediated through free radical generation.<sup>62</sup> However, it is remarkable that glucose exerts several direct and powerful damaging effects, as described above, which are all able to worsen the prognosis of MI. Therefore, the true open question is whether hyperglycaemia, when present during a MI, has to be treated with intensive insulin therapy even in non-diabetic patients. While waiting for specific trials, it should be helpful to consider that intensive insulin therapy has already shown a beneficial effect in critically ill patients,<sup>63</sup> where normoglycaemia, rather than the infused insulin dose, is related to the beneficial effects of intensive insulin therapy.<sup>64</sup>

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