

C-Reactive Protein Levels Following Acute Myocardial Infarction

Effect of insulin infusion and tight glycemic control

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Acute myocardial infarction (AMI) triggers an inflammatory reaction, which plays an important role in myocardial injury (1). Inflammatory markers such as C-reactive protein (CRP) reflect the extent of myocardial necrosis and correlate with cardiac outcomes following AMI (2–4).

Hyperglycemia has proinflammatory effects, inducing the release of inflammatory cytokines (5) and is associated with increased mortality from AMI (6,7). Conversely, insulin-based therapy in patients following AMI may confer survival benefits, but the mechanism is unclear (8–11). Insulin suppresses the inflammatory response (12), but it is uncertain if the anti-inflammatory effect of insulin therapy depends on glycemic status.

The Hyperglycemia: Intensive Insulin Infusion In Infarction (HI-5) study is a multicentered randomized trial of insulin infusion for hyperglycemic patients with AMI. In this substudy, we examined the relationship between blood glucose levels (BGLs) and the inflammatory response (CRP levels) following AMI and evaluated the effect of insulin-based infusion therapy.

RESEARCH DESIGN AND METHODS

— In the HI-5 study, patients presenting with AMI within 24 h who either had known diabetes or admission BGL ≥ 7.8 mmol/l were recruited. AMI was defined by a plasma troponin T

level of 0.1 $\mu\text{g/l}$. Following written consent, patients were randomized to either intensive or conventional therapy. Intensive therapy consisted of insulin-dextrose infusion for at least 24 h. Patients were given 5% dextrose at 80 ml/h, while the insulin infusion was titrated to keep BGL between 4 and 10 mmol/l. Patients in the conventional group continued their usual diabetic treatments except metformin, which was ceased during the peri-infarct period in both groups. The BGLs of each patient were recorded at eight predetermined time points during the first 24 h of treatment to calculate his/her mean glucose. Patients with ST-segment elevation AMI received reperfusion therapy, and all patients were given aspirin, β -blockers, and statins unless contraindicated. In this substudy, blood for CRP was sampled at baseline and repeated the next morning. CRP was measured by rate nephelometry, and the lower limit of detection was 1.0 mg/l.

Continuous variables were expressed as median and interquartile range, and a Mann-Whitney test was used to compare CRP levels and mean glucose between intensive and conventional groups. Correlation between various study parameters and CRP levels was assessed by Spearman's rank correlation analysis. $P < 0.05$ was considered statistically significant.

RESULTS — Among the 110 patients enrolled in this substudy, 57 were ran-

domized to intensive therapy, while 53 received conventional therapy. Age (mean [range]) (63 years [51–71] vs. 65 years [53–75]), sex (75 vs. 83% were men), cardiac risk factors, and diabetic status (42 vs. 47%) of patients in the two groups were not different. Patients in the intensive and conventional groups were comparable in terms of infarct type (75 vs. 72% with ST-segment elevation AMI), reperfusion therapy (72 vs. 68%), peak creatinine phosphokinase (1,282 units/l [341–2,474] vs. 1,250 units/l [552–2,830]), and admission BGL (9.7 mmol/l [8.5–12.9] vs. 9.9 mmol/l [8.6–13.4]). Patients in the intensive group received a median insulin dose of 1.67 units/h (1.10–2.42) during the first 24 h. Three subjects died during admission, two of whom were from the conventional group. The mean glucose in the first 24 h was lower in the intensive than in the conventional group (7.5 mmol/l [6.4–8.5] vs. 8.5 mmol/l [6.8–9.9], $P = 0.014$). CRP levels were not different between the two groups at baseline, but median CRP level on the second postinfarct day was significantly higher in the conventional group (24.3 mg/l [10.0–58.2]) than intensive group (10.8 mg/l [6.2–25.1]) ($P = 0.004$) (Fig. 1).

There was a positive correlation between serum CRP levels on day 2 and mean glucose of the entire substudy cohort in the first 24 h (Spearman's $\rho = 0.201$, $P = 0.039$). However, this was not significant among patients in either treatment group alone. Serum CRP on day 2 was independent of patients' age, sex, diabetes status, prior statin use, previous AMI, peak creatinine phosphokinase, AMI type, or reperfusion therapy. There was no association between serum CRP on day 2 and the insulin dose in the intensive group.

CONCLUSIONS — We demonstrated that maintaining normoglycemia with insulin-dextrose infusion in the first 24 h following AMI attenuated the rise of serum CRP. It is possible that insulin inhibits the release of CRP through an anti-

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Abbreviations: AMI, acute myocardial infarction; BGL, blood glucose level; CRP, C-reactive protein; HI-5, Hyperglycemia: Intensive Insulin Infusion In Infarction.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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See accompanying editorial, p. 3017.

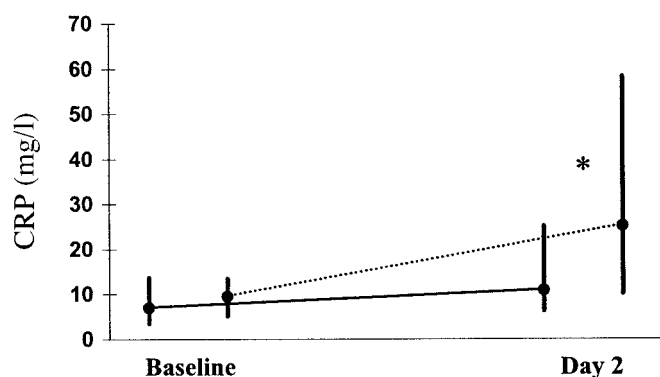


Figure 1—Median serum CRP levels (with interquartile range) for intensive (solid line) and conventional (dotted line) groups at baseline and on day 2. P = 0.004 (median serum CRP level between the two groups on day 2).

inflammatory effect, but the positive correlation between mean glucose level during first 24 h and serum CRP on day 2 suggests that the lowering of glucose level from insulin infusion contributes to the suppression of infarct-related inflammatory response.

Myocardial necrosis following AMI induces free radical generation and triggers the inflammatory cascade. Reperfusion therapy may also lead to further intensification of the inflammatory reaction, with the recruitment of neutrophils into the reperfused myocardium (1). Although this inflammatory response is important in the healing process, it can also extend myocardial injury, and anti-inflammatory strategies have been successful in reducing infarct size in animal models (13,14).

Hyperglycemia is associated with increased mortality following AMI (6,7). Acute hyperglycemia is proinflammatory, inducing the release of cytokines by an oxidative mechanism, resulting in neutrophil-mediated injury of the reperfused myocardium (1,5). On the other hand, insulin exerts anti-inflammatory effects independent of glycemia, and this can have important implications following myocardial ischemia. Insulin not only suppresses the expression of nuclear factor κ B in endothelial cells, but also inhibits plasminogen activator inhibitor-1, thus facilitating clot dissolution following AMI (15–17). In an intensive care unit study, maintaining normoglycemia with insulin infusion inhibited CRP levels and improved survival (18). In another study of AMI patients, insulin infusion attenuated the rise of CRP and enhanced fibrinolysis (19). In our current study, the

CRP attenuation was not dependent on insulin dose. One explanation is that sicker patients (probably with higher CRP levels) are more insulin resistant and hence require a greater amount of insulin to achieve normoglycemia.

It is likely that both insulin therapy and maintaining tight glycemic control are important in suppressing infarct-related inflammatory response. It remains to be determined if this degree of CRP attenuation translates into improved clinical outcomes. Results of the clinical component of HI-5 study will be available in early 2005.

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