# Computers in Critical Care and Pulmonary Medicine

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With 197 Figures and 29 Tables

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# Glucose-Insulin-Potassium Therapy Guided by a Glucose-Controlled Insulin Infusion System in Acute Myocardial Infarction

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A number of hormonal and metabolic alterations have been observed during acute myocardial infarction (AMI): There is a rapid increase of catecholamine and cortisol secretion; free fatty acid (FFA) serum levels are markedly elevated (Gupta et al. 1969; Januszewicz et al. 1971; Vetter et al. 1974); and insulin secretion may be inappropiately low. These alterations result in a disturbance of glucose utilization, so-called stress hyperglycemia. Moreover, under these conditions and due to the accumulation of free fatty acids in the ischemic myocardium, severe ventricular arrhythmias as well as a progression of myocardial cell damage are likely to occur (Kurien and Oliver 1970; Kurien et al. 1971; Oliver et al. 1968).

Glucose-insulin-potassium infusions (GIK) in AMI have been used in a number of clinical trials in order to overcome these deleterious effects (Mantle et al. 1981; Rogers et al. 1976, 1979; Sodi-Palleres et al. (1962)). Some of the postulated benefits of GIK treatment in AMI are: a decrease of FFA, a reduction of potassium efflux, a repletion of intracellular potassium stores, an enhancement of myocardial glucose utilization, a reduction of myocardial oxygen consumption, and an improvement in coronary perfusion. These changes should reduce severe life-threatening arrhythmias, limit infarct size, improve left ventricular function, and reduce hospital mortality (von Arnim and Bolte 1980; Brachfeld 1973; Kurien et al. 1971; Manke et al. 1981; Oliver 1973). With an "open loop" fixed GIK regime as in the studies mentioned above, severe hyperglycemia as well as hypoglycemia were not infrequently seen, because the degree of impairment of the insulin sensitivity could not be predicted. We therefore decided to use a glucose – controlled insulin infusion system (GCIIS); this involves applying "closed-loop" control during treatment with GIK according to the individual insulin sensitivity and thereby studying hormonal and metabolic patterns in AMI.

## Methods

Nine patients (eight male, one female; age 61.8 ± 8.8 years) with AMI admitted to our intensive care unit within 12 h after onset of chest pain received GIK for 24 h. The solution contained 430 g glucose, 166 U porcine regular insulin, and 133 mEq KCl per liter. The infusion rate was 0.9 ml/kg/h. Additional feedback – controlled insulin and/or glucose was given by the GCIIS (Biostator-Controller). The following constants were chosen: Mode 3:1, Var 100, BI 80, BD 60, and FI 500–1000. Insulin concentra-

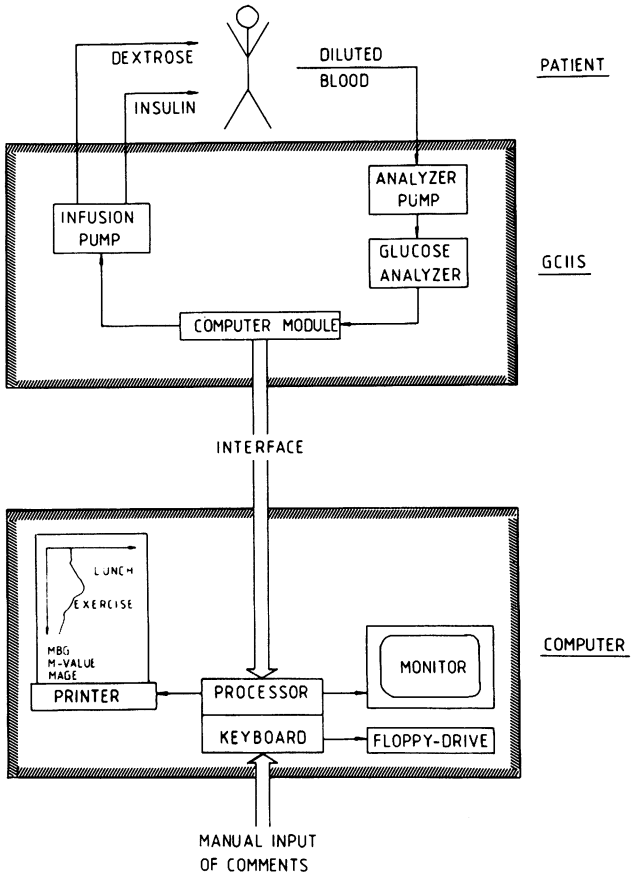


**Fig. 1.** Schematic diagram of device used for processing of GCIIS data

tion of the GIK solution was increased when blood glucose could not be kept below 250 mg/dl. Insulin, C-peptide, cortisol, GH, prolactin, and lactate were determined at 6-h intervals. FFAs were measured by gas-liquid chromatography (Tserng et al. 1981). Figure 1 shows a schematic diagram of the technical equipment. The patient is connected to the GCIIS. By means of an interface all data for blood glucose (BG), insulin infusion rate (IR), and dextrose infusion rate (DR) are transferred directly from the Biostator to a microcomputer for further processing (Muller-Esch et al. 1984). The microcomputer fulfils several functions:

1. *Monitoring:* BG, IR, and DR are plotted continuously
2. *Manual input:* comments concerning, for example, the actual therapy can be entered via the keyboard
3. *Calculations:* a BASIC computer program has been developed for the calculation of the glycemic indices mean blood glucose (MBG), M-value, and MAGE (Muller-Esch et al. 1984)
4. *Printer and floppy disks:* all values for BG, IR, and DR, as well as comments which appear in their time – related positions, and calculated parameters are plotted and documented on 5-in. floppy disks.

## Results

The insulin sensitivity – as measured by blood glucose concentrations and total insulin requirements during GIK – varied markedly. Figure 2a is an example from a patient with high insulin requirements. Initial BG is about 110 mg/dl, rising to more than 250 mg/dl after starting GIK infusion. Despite submaximal additional feedback-controlled insulin by the GCIIS, BG did not fall below 200 mg/dl. In contrast, in the patient shown in Fig. 2b, euglycemia during GIK could be obtained with only minor additional feedback-controlled insulin administration. And in another patient, additional feedback-controlled dextrose had to be given to prevent hypoglycemia during GIK, MBG being in the range of about 80 mg/dl (Fig. 2c).

According to these data we can divide our patients into two groups: in five patients (group A), a total of 309 ± 52 U insulin/24 h was sufficient to maintain fair glycemic control (Table 1, top). In four patients, however (group B), insulin concentration of GIK had to be partially multiplied because of marked hyperglycemia: insulin requirements were 1193 ± 258 U/24 h; despite this, we did not achieve nearly normal BG values or nearly normal glycemic indices (Table 1, bottom).

When compared to the "low insulin" group, the "high insulin" group presented with higher serum insulin levels *before* GIK treatment. *During* therapy, this group had higher values for C-peptide, cortisol, prolactin, and lactate. GH and glucagon did not differ significantly (Table 1).

**Table 1.** Insulin, C-peptide, glucagon, cortisol, GH, prolactin, and lactate serum levels during GCIIS-guided GIK therapy in patients with low insulin requirements (group A) and high insulin requirements (group B). The glycemic indices MBG, MAGE, and M-value are also shown. ($P < 0.05$ vs. group A)

*Group A (309 ± 52 U insulin/24 h, n = 5)*

| | 0 h | 6 h | 12 h | 18 h | 24 h |
|---|---|---|---|---|---|
| Insulin (mU/l) | 11.3 ± 7.5 | 191 ± 48 | 227 ± 181 | 289 ± 198 | 316 ± 219 |
| C-peptide (µg/l) | 2.6 ± 1.8 | 1.0 ± 0.7 | 0.6 ± 0.5 | 2.5 ± 4.1 | 2.1 ± 2.5 |
| Glucagon (ng/l) | 140 ± 25 | 158 ± 53 | 160 ± 84 | 176 ± 82 | 164 ± 74 |
| Cortisol (ng/ml) | 233 ± 131 | 172 ± 98 | 196 ± 95 | 212 ± 112 | 188 ± 92 |
| GH (ng/ml) | 2.1 ± 1.5 | 4.4 ± 2.9 | 4.2 ± 2.0 | 3.5 ± 2.5 | 2.1 ± 1.6 |
| Prolactin (µU/ml) | 398 ± 131 | 258 ± 64 | 242 ± 72 | 225 ± 79 | 248 ± 51 |
| Lactate (mmol/l) | 1.4 ± 0.5 | 2.0 ± 1.0 | 1.6 ± 0.8 | 1.3 ± 0.6 | 1.1 ± 0.3 |

MBG: 94 ± 28 MAGE: 51 ± 8 M-value: 17 ± 7

*Group B (1193 ± 258 U insulin/24 h, n = 4)*

| | 0 h | 6 h | 12 h | 18 h | 24 h |
|---|---|---|---|---|---|
| Insulin (mU/l) | ● 43 ± 22 | ● > 500 | ● > 500 | ● > 500 | ● > 500 |
| C-peptide (µg/l) | 8.0 ± 7.5 | ● 13.4 ± 12.9 | ● 15.0 ± 14.3 | 21.6 ± 22.9 | 12.3 ± 15.6 |
| Glucagon (ng/l) | 152 ± 77 | 87 ± 62 | 90 ± 73 | 124 ± 140 | 15.1 ± 169 |
| Cortisol (ng/ml) | 301 ± 224 | ● 418 ± 135 | ● 418 ± 174 | ● 412 ± 203 | ● 418 ± 186 |
| GH (ng/ml) | 3.1 ± 2.4 | 6.1 ± 2.4 | 3.0 ± 1.8 | 1.7 ± 1.4 | 1.5 ± 1.2 |
| Prolactin (µU/ml) | 590 ± 281 | ● 549 ± 182 | ● 489 ± 150 | ● 532 ± 135 | ● 681 ± 191 |
| Lactate (mmol/l) | ● 2.7 ± 1.3 | ● 3.5 ± 0.8 | 2.7 ± 0.9 | ● 2.7 ± 1.2 | ● 3.5 ± 1.4 |

● MBG: 234 ± 42 ● MAGE: 159 ± 57 ● M-value: 46 ± 15

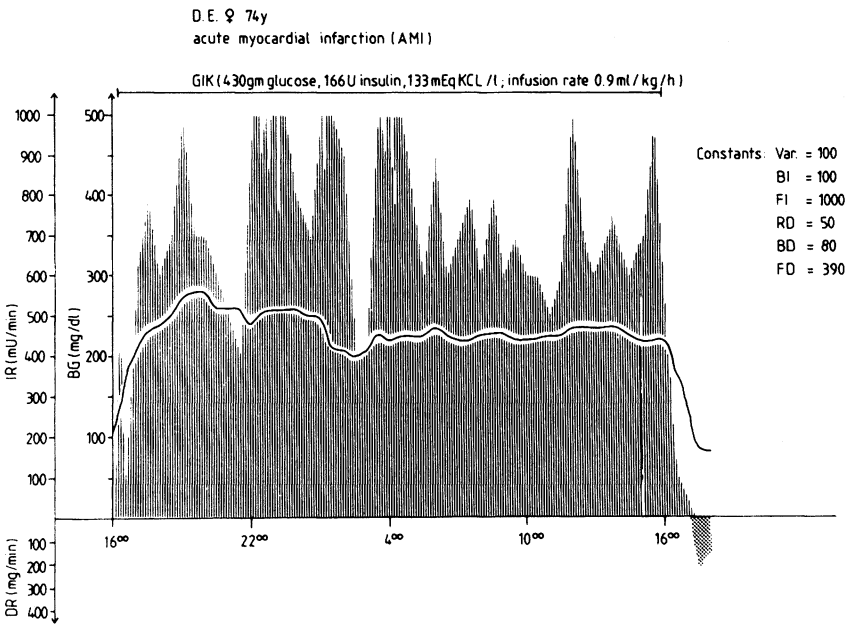


**Fig. 2a**

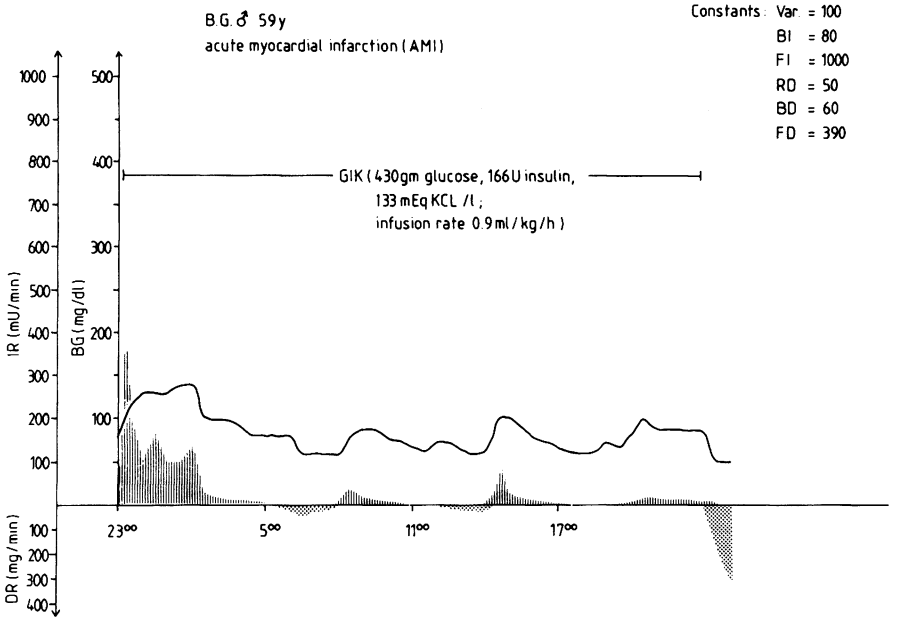


**Fig. 2b**

**Fig. 2a–c.** Blood glucose (BG), insulin infusion rate (IR), and dextrose infusion rate (DR) during GCIIS-guided GIK therapy in three patients with AMI

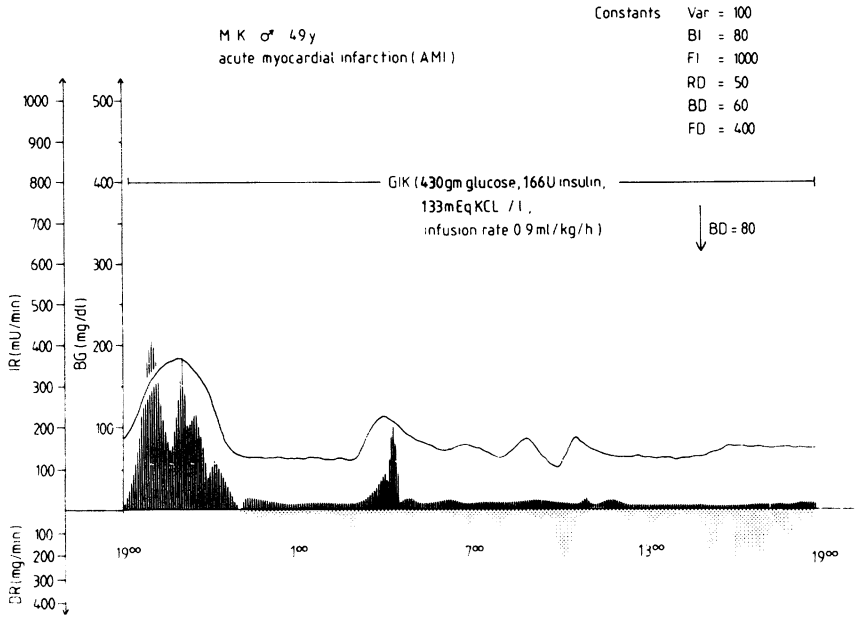


**Fig. 2c**

**Table 2.** Insulin, C-peptide, glucagon, cortisol, GH, prolactin, lactate, and blood glucose (BG) levels in seven conventionally treated patients with AMI as compared to four patients under GCIIS-guided GIK therapy (group B). ● $P < 0.05$ vs. controls)

| *Controls (n = 7)* | | | | | |
|---|---|---|---|---|---|
| | 0 h | 6 h | 12 h | 18 h | 24 h |
| Insulin (mU/l) | 35 ± 17 | 18 ± 11 | 26 ± 24 | 26 ± 24 | 39 ± 34 |
| C-peptide (μg/l) | 5.4 ± 2.9 | 4.9 ± 3.3 | 4.7 ± 3.2 | 6.4 ± 3.3 | 8.6 ± 6.2 |
| Glucagon (ng/l) | 323 ± 446 | 373 ± 537 | 348 ± 412 | 431 ± 497 | 443 ± 407 |
| Cortisol (ng/ml) | 239 ± 145 | 266 ± 192 | 218 ± 108 | 247 ± 171 | 229 ± 163 |
| GH (ng/ml) | 2.1 ± 3.1 | 2.9 ± 3.8 | 2.4 ± 2.7 | 3.3 ± 6.5 | 2.6 ± 2.6 |
| Prolactin (μU/ml) | 834 ± 895 | 445 ± 256 | 273 ± 106 | 228 ± 50 | 306 ± 74 |
| Lactate (mmol/l) | 2.1 ± 2.1 | 2.1 ± 1.8 | 1.7 ± 1.1 | 1.4 ± 0.5 | 1.4 ± 0.4 |
| BG (mg/dl) | 147 ± 38 | 157 ± 49 | 122 ± 23 | 144 ± 48 | 162 ± 72 |
| *Group B (1193 ± 258 U insulin/24 h, n = 4)* | | | | | |
| | 0 h | 6 h | 12 h | 18 h | 24 h |
| Insulin (mU/l) | 43 ± 22 | > 500 | > 500 | > 500 | > 500 |
| C-peptide (μg/l) | 8.0 ± 7.5 | 13.4 ± 12.9 | ● 15.0 ± 14.3 | 21.6 ± 22.9 | 12.3 ± 15.6 |
| Glucagon (ng/l) | 152 ± 77 | 87 ± 62 | 90 ± 73 | 124 ± 140 | 151 ± 169 |
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| Prolactin (μU/ml) | 590 ± 281 | 549 ± 182 | ● 489 ± 150 | ● 532 ± 135 | ● 681 ± 191 |
| Lactate (mmol/l) | 2.7 ± 1.3 | 3.5 ± 0.8 | 2.7 ± 0.9 | ● 2.7 ± 1.2 | ● 3.5 ± 1.4 |
| MBG: 234 ± 42 | | MAGE: 159 ± 57 | | | M-value: 46 ± 15 |

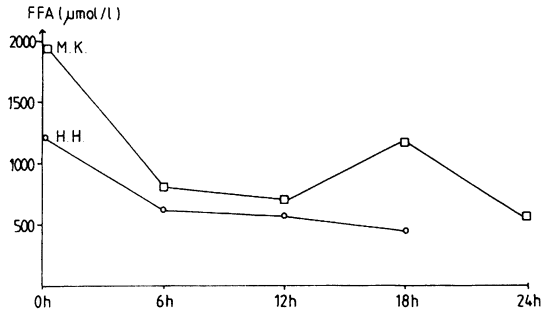


**Fig. 3.** Free fatty acids (FFA) during GCIIS-guided GIK therapy in two patients with AMI

Seven conventionally, treated patients with AMI served as controls (Table 2). In comparison with these patients without GIK, group B had higher serum levels for C-peptide, cortisol, prolactin, and lactate.

Serial FFA measurements in two patients show a decrease of FFA under GIK below the arrhythmia threshold (Oliver et al. 1968) of 1200 µmol/l (Fig. 3).

## Discussion

Because of the small number of patients we are not yet able to decide whether the observed hormonal-metabolic differences between the groups are directly correlated to the infarct size or wheter they reflect different systemic reactions, different hormonal-metabolic patterns, during AMI.

In conclusion, these preliminary data indicate that the impairment of insulin sensitivity and glucose utilization during AMI varies markedly. FFA can be reduced below the arrhythmia threshold. Further studies should compare metabolic, hemodynamic, and antiarrhythmogenic effects of GCIIS-guided GIK support in patients with AMI.

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