Effects of cardiopulmonary bypass on glucose homeostasis after coronary artery bypass surgery

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Abstract

Objective: Hyperglycaemia is associated with increased mortality and morbidity after cardiac surgery. While surgical stress results in hyperglycaemia after all operations, it has been suggested that cardiopulmonary bypass is the dominating contributor after cardiac surgery. This study aimed to determine the contribution of cardiopulmonary bypass to hyperglycaemia after coronary artery bypass. Methods: Patients scheduled for primary coronary artery bypass grafting were randomised to surgery with or without cardiopulmonary bypass. All patients received continuous insulin infusions during the initial 24-h period. Glucose was infused (100 mg/kg per h) postoperatively in the intensive care unit but not during surgery. Blood glucose was measured 4 times daily until the third postoperative day. Serum insulin, insulin-like growth factor-1 and its binding protein were determined. Results: Average blood glucose during the day of surgery did not differ between groups, but 30% more insulin (P=0.003) was required when cardiopulmonary bypass was used. Blood glucose 2-3 h after meals was higher in patients using cardiopulmonary bypass during the first 3 postoperative days. Fasting blood glucose was still equally elevated 20-30% in both groups on the third postoperative day. Insulin-like growth factor-1 decreased more (P=0.01) and insulin-like growth factor binding protein-1 increased more (P<0.001) with cardiopulmonary bypass than without. The ratio of insulin-like growth factor-1 concentration to the concentration of its binding protein-1 was more negative (indicating greater catabolism) with cardiopulmonary bypass than without postoperatively. Conclusions: Glucose homeostasis is disturbed preoperatively for many non-diabetic patients undergoing coronary bypass surgery. Cardiopulmonary bypass exacerbates the catabolism and disturbed glucose homeostasis that is induced also to a lesser degree by surgery without cardiopulmonary bypass.

Keywords: Coronary artery bypass surgery; Off-pump; Cardiopulmonary bypass; Insulin-like growth factor I; Insulin-like growth factor binding proteins; Hyperglycaemia

1. Introduction

Recent studies have shown that even moderate hyperglycaemia contributes markedly to postoperative morbidity and mortality after cardiac surgery [1], to worsened outcome after percutaneous coronary intervention [2], after myocardial infarction [3], after stroke [4], and during intensive care [5]. The increased risk associated with hyperglycaemia applies to both patients with and without diabetes mellitus [1,2,5]. The few intervention studies suggest that the risk associated with hyperglycaemia is amenable to treatment with continuous insulin infusion [1,6]. Normoglycaemia, not insulin as such, seems to be the essential correlate [1]. Furthermore, the first 3 days after cardiac surgery seem to be the most important to prevent deep wound infections, particularly for avoiding mediastinitis [6].

Postoperative hyperglycaemia is seen not only in diabetics but will occur postoperatively in all patients due to an increase in insulin resistance induced by surgical trauma. Prophylactic measures that prevent or minimise this insulin resistance or 'surgical diabetes' may reduce postoperative mortality, morbidity and costs associated with even moderate postoperative hyperglycaemia.

The use of cardiopulmonary bypass (CPB) during coronary artery bypass grafting (CABG) has been suggested to be the major cause of perioperative hyperglycaemia after cardiac surgery, a plausible theory considering the coupling between the inflammatory response and determinants of glucose homeostasis [7]. The relative contributions of surgical stress and CPB with full heparinisation are not known.

The purpose of the present work was to determine the effect of CPB on glucose homeostasis during and 3 days after CABG performed with and without CPB. Whole blood glucose (B-glu) was the primary endpoint with the need for exogenous insulin and several endocrinological parameters as secondary endpoints.
2. Materials and methods

2.1. Patients

Patients suitable for OPCAB for elective first-time CABG were admitted to this randomised, prospective study after approval from the hospital’s Ethics Committee and patient informed consent. Fifty patients were randomised with the sealed envelope method to CABG with cardiopulmonary bypass (CPB group) or off-pump coronary artery bypass (OPCAB group). Exclusion criteria were known diabetes mellitus or other endocrinological disorders, a history of heart failure or severely reduced myocardial or kidney function. Data from randomised patients with fasting whole blood glucose (B-glu) ≥ 6.1 mmol/l were not used. All patients fasted overnight and received their normal anti-angina and beta-blocking medications on the morning of surgery.

2.2. Anaesthesia

Patients were premedicated with morphine (7.5-15 mg im). During induction they received 1000 ml Ringer acetate while anaesthesia was induced with 3-4 μg/kg fentanyl, 30-40 μg/kg midazolam, and variable amounts of propofol. Patients were paralysed with 0.5-0.7 mg/kg atracurium to facilitate intubation. According to local routines, mannitol (400 mg/kg) was given before CPB. Anaesthesia was maintained with isoflurane until CPB and thereafter with 0.1-0.3 mg fentanyl bolus and a continuous infusion of propofol until completion of surgery. Postoperatively patients received 1 g×4 paracetamol orally and intravenous ketobemidone (1 mg/ml).

2.3. Cardiopulmonary bypass

Standard non-pulsatile CPB with a centrifugal pump (Bio-Medicus, Medtronic) was used. The extracorporeal system was primed with Ringer acetate, and a Maxima Forte (Medtronic, Inc., Minneapolis, USA) membrane oxygenator was used. Cold blood cardioplegia was used in all patients. Core temperature was cooled or was allowed to drift to 34 °C. Heparin was given before CPB (3 mg/kg) to maintain ACT > 400 s. OPCAB patients were operated at normothermia via a standard median sternotomy and received 1 mg/kg heparin.

2.4. Glucose and insulin infusions

No glucose was given before or during surgery, but patients received a glucose infusion (100 mg/kg per h) postoperatively in the intensive care unit (ICU). An intravenous infusion of regular insulin in NaCl (1 unit/ml; Actrapid®, Novo Nordisk AB, Malmö, Sweden) via a motor syringe infuser was initiated in the operating room or ICU when B-glu exceeded 6 mmol/l with the goal of maintaining all values of B-glu < 6.9 mmol/l (local clinical policy at time of study). Patients returned to the ward mid-morning of the first post-operative day.

2.5. Blood sampling

On the day of surgery, B-glu was measured at four specific times (before anaesthesia, 12:00, 18:00, 24:00 o’clock) and whenever clinically indicated (10-20 tests which are not all quoted in Section 3). During the first 3 postoperative days, B-glu was determined 4 times daily (fasting and 2-3 h postprandial (10 am, 2 and 8 pm)).

2.6. Assay methods

B-glu was determined from whole blood by the glucose-hydrogenase method (HemoCue, Inc.; Ängelholm, Sweden). Serum glycylated haemoglobin (S-HbA1C) was determined by immunochemical methods (TINA-Quant, Roche Inc; Bromma, Sweden).

Immunoreactive insulin was measured by RIA using antibodies against porcine insulin, raised locally in guinea-pig, I-125-labelled porcine insulin as tracer, human insulin as standard (Novo Nordisk AB, Bagsvaerd, Denmark) and dextran-coated charcoal to separate bound from free insulin. This method is free of pro-insulin. The product of fasting B-glu and serum insulin, called Homeostasis Assessment Model (HOMA) is calculated as a measure of whole body insulin resistance [8].

Total insulin-like growth factor-1 in serum (IGF-1) was determined by radioimmunoassay (RIA) after acid ethanol extraction from its binding protein (IGFBP) and cryoprecipitation. To minimise interference with remaining binding proteins, des (1-3) IGF-1 was used as the radioligand in the IGF-1 RIA [9]. The intra- and inter-assay CV were 4 and 11%, respectively. Serum levels of IGF-1 do not vary with gender but decrease with age. Thus, IGF-1 values were also expressed as IGF standard deviation (IGFSO) scored calculated from the regression of the values of 247 healthy adult subjects [10,11]:

\[
\text{IGFSO} = (\log_{10}\text{IGF} - 1 + 0.00693 \times \text{Age} - 2.581)/0.12
\]

IGFBP-1 concentration in serum was determined by RIA as described by Pöva [12]. Sensitivity of the RIA was 3 μg/l and the intra- and inter-assays CV were 3 and 10%, respectively. The 95% confidence intervals for IGFBP-1 for normal men is 17.5-24.1 μg/l, and for pre- and post-menopausal women are 21.6-30.3 and 27.7-44.0 μg/l, respectively. [10]. The ratio of IGF-1/IGFBP-1 was calculated and reflects the concentration of free active IGF-1 [13].

2.7. Statistics

Data are presented as means ± SD. The paired or nonpaired Student’s t-test or in case of skew distributions the Wilcoxon’s matched pairs or Mann-Whitney’s U-tests were used to analyse two groups. Repeated measures analysis of variance was applied if there were observations at more than two points of time. The two-tailed Fischer’s exact test was employed to compare qualitative data. The null hypothesis was rejected if \( P < 0.05 \).
3. Results

Four patients, two in each group, were not included because of fB-glu ≥ 6.1 mmol/l, i.e. clinical diabetes mellitus that was not diagnosed before the operation. The postoperative period was uneventful for all patients except for one OPCAB patient who required extended ICU stay because of pulmonary complications and was withdrawn from the study, leaving 45 finally included patients.

Patient preoperative characteristics, number of anastomoses, duration of surgery, length of hospital stay or use of antibiotics did not differ in the two groups (Table 1). Preoperatively, HbA1C was > 5.2% in nine patients (20%) and fasting B-glu was ≥ 5.6 mmol/l (but < 6.1 mmol/l) in 11 (24%) of the patients. HbA1C or fB-glu was elevated in 15 (24%) of the patients. HbA1C or fB-glu was considerably higher than glucose homeostasis, though not classed as diabetes patients (33%), indicating a study population with impaired glycaemic control.

Average B-glu during the day of surgery did not differ significantly in the two groups, but 30% more infused regular insulin (P = 0.003) was required in the CPB group during the 24-h period beginning with surgery (Table 2). None of the patients received insulin on the ward. During postoperative days 2 and 3, fB-glu was increased relative to the preoperative levels, but did not differ in the two groups (Fig. 1). B-glu levels 2-3 h after meals during Day 1 through Day 3 were lower in the OPCAB group than in the CPB group (P = 0.01). On the morning of Day 3, fB-glu was still 20-30% greater (P < 0.001) than preoperative values (Table 2).

3.2. Serum-insulin and growth factors

Serum insulin was not determined at the end of surgery as exogenous insulin was being infused. Three days after the operation fasting serum insulin did not differ significantly from preoperative values or between the two groups (Table 2). HOMA, a measure of insulin resistance, increased from preoperative values or between the two groups (Table 2).

Total IGF-1 was significantly reduced (P < 0.001) at the end of surgery in both the CPB and the OPCAB groups without complete normalisation on the third postoperative day (Fig. 2a). Postoperative IGF-1 was lower in CPB than in OPCAB patients, but the difference was not significant on Day 3.

IGF-1 must be compensated for age before interpretation. The calculated age-compensated postoperative IGFSD score, for which negative values indicate the degree of

Table 1
Patient characteristics and measurements

<table>
<thead>
<tr>
<th></th>
<th>Cardiopulmonary bypass (n=23)</th>
<th>Off-pump coronary artery bypass (n=22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69 ± 11</td>
<td>64 ± 9</td>
<td>0.13</td>
</tr>
<tr>
<td>BMI</td>
<td>26 ± 3</td>
<td>27 ± 4</td>
<td>0.13</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>92 ± 21</td>
<td>88 ± 15</td>
<td>0.44</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>4.8 ± 0.4</td>
<td>5.0 ± 0.5</td>
<td>0.29</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>(27)</td>
<td>(17)</td>
<td>0.28</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>(45)</td>
<td>(43)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hyperlipidaemia (%)</td>
<td>(55)</td>
<td>(74)</td>
<td>0.22</td>
</tr>
<tr>
<td>Previous AMI (%)</td>
<td>(41)</td>
<td>(39)</td>
<td>1.00</td>
</tr>
<tr>
<td>Unstable angina (%)</td>
<td>(14)</td>
<td>(13)</td>
<td>1.00</td>
</tr>
<tr>
<td>Previous PCI (%)</td>
<td>(9)</td>
<td>(7)</td>
<td>0.22</td>
</tr>
<tr>
<td>Postoperative antibiotic treatment</td>
<td>(9)</td>
<td>(4)</td>
<td>0.61</td>
</tr>
<tr>
<td>Anastomoses (number)</td>
<td>2.5 ± 1.1</td>
<td>2.8 ± 0.9</td>
<td>0.32</td>
</tr>
<tr>
<td>Cardiopulmonary bypass (min)</td>
<td>72 ± 27</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Aortic cross-clamp (min)</td>
<td>42 ± 20</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Preop haemoglobin (g/l)</td>
<td>129 ± 16</td>
<td>130 ± 11</td>
<td>0.89</td>
</tr>
<tr>
<td>Post-op haemoglobin (g/l)</td>
<td>*100 ± 11</td>
<td>*105 ± 14</td>
<td>0.23</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>164 ± 26</td>
<td>157 ± 41</td>
<td>0.60</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>6.5 ± 2.8</td>
<td>6.6 ± 3.9</td>
<td>0.60</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average blood glucose (mmol/l)</td>
<td>6.5 ± 0.7</td>
<td>6.1 ± 0.9</td>
<td>0.09</td>
</tr>
<tr>
<td>Insulin required Day 1 (units)</td>
<td>85 ± 34</td>
<td>97 ± 22</td>
<td>0.003</td>
</tr>
<tr>
<td>Postoperative Day 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average blood glucose (mmol/l)</td>
<td>7.6 ± 1.2</td>
<td>6.7 ± 0.9</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Data as mean ± SD or %, BMI, body mass index; CPB, cardiopulmonary bypass; HbA1C, serum glycosylated haemoglobin (Reference level < 5.2%); AMI, acute myocardial infarction; PCI, percutaneous coronary intervention. *P < 0.001.
catabolism, was more negative in CPB than in the OPCAB group. This score had not normalised and did not differ between the groups 3 days after the operation (Fig. 2b).

There was a 3-4-fold increase in IGFBP-1 ($P < 0.001$) by the end of surgery in both groups that did not normalise by the third postoperative day (Fig. 3a). The level of IGFBP-1 was higher in CPB than in OPCAB patients both post-operatively and on Day 3.

IGF-1 that is free to act on its receptors is reflected by the ratio IGF-1/IGFBP-1 (Fig. 3b). This ratio was lower post-operatively in CPB patients (also indicating catabolism) than in OPCAB patients. CPB patients still had a lower IGF-1/IGFBP-1 than OPCAB patients on Day 3. On Day 3 neither group had yet completely returned to preoperative values.

4. Discussion

This study aimed to determine if cardiopulmonary bypass is a major contributor to the hyperglycaemia seen during and a few days after CABG. The primary findings are that CABG without CPB reduces the exogenous insulin required to maintain the same level of glucose homeostasis during the 24-h period beginning with surgery. Furthermore, a marginal improvement in glucose tolerance was also seen during the first three post-operative days, but that hyperglycaemia persists even in non-diabetic patients for at least 3 days after CABG. Changes in the insulin-like growth factor (IGF) system indicate that CPB contributes to the degree of catabolism after surgery. CPB contributes...
only marginally to the metabolic disturbances induced by surgery and will not alter the indication for OBCAB.

The problem of hyperglycaemia and insulin resistance after all operations increases with the extent of surgical trauma. While the role of CPB is not known, it has been suggested to be the major cause of hyperglycaemia seen after CABG [7]. This study was inspired by that hypothesis and by the recent evidence that even the moderate postoperative hyperglycaemia seen in non-diabetics is detrimental for outcome after CABG [1]. The primary goal of this study was to determine if glucose homeostasis as a clinical problem was improved if CPB was not used for CABG. Marginal but statistically significant improvements were found. Recent studies have shown that maintaining strict normoglycaemia results in surprisingly improved morbidity and mortality after cardiac surgery, particularly amongst critically ill patients, but the potential benefit of strict normoglycaemia for postoperative cardiac patients who are not critically ill is not known [1]. The average B-glu during intensive care was more easily controlled and required less insulin for the off-pump group in this study than for CABG with CPB. While fasting B-glu was not affected during the days following surgery, the 2-3 h postprandial B-glu values were often more elevated in the CPB group than the non-CPB patients. This is fully analogous to the distinction between impaired fasting blood glucose and impaired glucose tolerance which represent different deficiencies. Impaired glucose tolerance has been shown to correlate better with cardiovascular risk than fasting glucose values [14].

Average insulin concentrations preoperatively were rather high in the patients studied, which together with the high average Fb-glu and HbA1C indicate a population with metabolic syndrome. As all patients required insulin infusion during surgery, serum insulin measurements at the end of surgery were not a meaningful parameter. Interestingly, insulin concentrations were not elevated on the third day after surgery, in contrast to what might be expected and as was found previously for similar patients [15]. Whole body insulin resistance and beta-cell function together are often described according to the Homeostasis Assessment Model (HOMA), the product of fasting serum insulin and blood glucose [8]. HOMA increased 30% on the third postoperative day for patients operated with CPB, but the increase was entirely due to increased Fb-glu. The increase in HOMA suggests a persistent whole body insulin resistance on Day 3, but as HOMA could not be determined at the end of surgery, nothing can be said of its rate of decrease postoperatively. Other studies suggest that insulin resistance will remain elevated for a week or two after major surgery [16].

The insulin-like growth factor (IGF) system provides an emerging insight into hepatic insulin resistance both during the development of diabetes mellitus type 2 and during critical illness. The IGF’s stimulate glucose uptake and use in muscle and are stimulated by growth hormone and nutritional status [17]. The 30% decrease in total IGF-1 seen in both groups in the present study is not larger than that for general (hip) surgery [17]. About 99% of the total IGF is bound by IGF binding proteins produced by the liver and regulated by insulin at the transcriptional level. IGFBP-1 is one of six binding proteins. Only the free, unbound IGF can bind to receptors and can be represented by the ratio of IGF/IGFBP-1 [18,15]. That this ratio was inversely correlated with blood glucose on Day 3 for patients operated with CPB implies that the impaired glucose homeostasis in that group can partially be due to decreased IGF-1 bioavailability [17].

Catabolism is indicated by both the ratio IGF/IGFBP-1 and by the age-corrected deviation from normal IGF-1 values, the so-called IGF Standard Deviation (IGFSD, calculated as shown in Section 2) [18]. CPB seems to result in greater postoperative catabolism as IGF/IGFBP-1 decreased more for the CPB group both postoperatively and on the third postoperative day. Furthermore, IGFSD was depressed more after surgery with CPB than without, but this parameter was normalised by the third postoperative day in both groups.

IGFBP-1 increased equally in both groups with surgery and did not return to preoperative values by the third postoperative day. Normally, there is an inverse relationship between insulin and IGFBP-1, but Wallin showed that this relationship was disturbed immediately after sternal closure [15]. The IGFBP-1 increase results in a decrease in free IGF [18]. IGFBP-1 is associated with insulin resistance, and during critical illness increased IGFBP is associated with mortality and reflects hepatic insulin resistance [17]. It is also associated with mortality after myocardial infarction [unpublished data, KB].

The hypothesis that CPB has a central role in post-CABG hyperglycaemia was not unreasonable considering the association between inflammation, metabolic syndrome, and cardiovascular disease. Fasting, stress, cytokines, and insulin are known to influence the IGF/IGFBP system [19,20]. Off-pump CABG was expected to minimise many of the deleterious side effects of on-pump surgery, both inflammatory, neurological, renal and coagulation. Indeed, as was recently reviewed, the inflammatory response does seem to be reduced when CPB is avoided with differences seen in the systemic and cellular inflammatory response, complement activation, platelet-thromboglobulin, procalcitonin, and oxidative stress [21]. OBCAB is associated with shorter hospital stay, fewer intraoperative and pulmonary complications, fewer blood transfusions, and lower postoperative creatine kinase [22]. No difference in hospital stay or antibiotic use was found in this study, but it was not powered to answer that question. Three other factors which accompany the use of CPB can conceivably contribute to disturbed glucose metabolism: first, when CPB is used, heparin administration is at least tripled which results in increased non-esterified fatty acids. Secondly, even the modest temperature reduction used in CABG with CPB may affect both insulin secretion and glucose consumption. Both of these factors should not have effects that last much beyond the actual CPB period. Finally, the significance of activation due to the cardiotomy suction has not been resolved, but it could conceivably have effects with longer duration [23].

Perhaps more significant for glucose homeostasis is that stress hormones are not diminished with the elimination of CPB. Velissaris showed that plasma vasopressin and cortisol did not differ with CPB; in both cases they increased during the early postoperative phase and only partially recovered at 24 h [24]. Stress hormones are believed to produce hyperglycaemia acutely with surgery while anabolic steroids and IGF-1 account for more prolonged glucose dysregulation.

Study limitations include a reduced post-operative haematocrit with no dependable method for correcting the decreased IGF-1 value and increased IGFBP-1. Furthermore, the presence of two more females in the group using CPB (females 6 of 23) could affect the IGFBP-1 values which have some gender dependency. Finally, the results of this study may not be applicable to cardiac surgical patients without cardiovascular disease as about a third of the present study group had impaired glucose homeostasis preoperatively.

In summary, glucose homeostasis is disturbed preoperatively for even non-diabetic patients undergoing CABG. Cardiopulmonary bypass marginally exacerbates the catabolism and disturbed glucose homeostasis that is induced to a lesser degree by surgery without CPB. Decreased IGF-1 bioavailability may at least partially account for this disturbed glucose homeostasis. The marginal contribution of CPB to glucose dysregulation is unlikely to alter the indications for OBCAB.

References