GROWTH HORMONE AND BLOOD-GLUCOSE CONCENTRATIONS DURING CARDIOPULMONARY BYPASS

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SUMMARY

Plasma growth hormone (plasma GH) and blood-glucose concentrations were measured in 23 patients undergoing open heart surgery with moderate hypothermia. A significant increase in blood-glucose concentration occurred with sternotomy and increased during bypass, partly as a result of the exogenous glucose load from the perfusate. Following bypass, the blood-glucose remained above the pre-anaesthetic concentration, and this elevation persisted into the period following surgery. Plasma GH also increased with surgery and remained elevated during perfusion. The highest concentrations occurred following bypass when normal temperature had been regained.

Significant increases in plasma growth hormone (GH) concentrations have been shown to occur during general surgery (Glick et al., 1963; Oyama and Takazawa, 1971). Salter, Fluck and Stimmler (1972) found very high concentrations of growth hormone in five patients undergoing open heart surgery, but the precise timing of the samples in relation to events during anaesthesia and bypass were not given in detail.

The present study was undertaken to correlate more fully plasma GH and blood-glucose concentrations with the major anaesthetic and surgical events during open heart surgery.

PATIENTS AND METHODS

Twenty-three consecutive patients undergoing open heart surgery were studied. Informed consent was obtained from all the patients. There were 11 males aged 36–70 years (mean 52.5) and 12 females aged 30–65 years (mean 45.3); 14 had mitral valve replacements, six had aortic valve replacements, two had aortic and mitral valves replaced and one had the mitral valve repaired. There were two deaths in the series.

Anaesthesia.

Following premedication with papaveretum 0.2 mg/kg (maximum dose 15 mg), and with hyoscine 0.004 mg/kg (maximum dose 0.4 mg), anaesthesia was induced with thiopentone followed by pancuronium, which was the muscle relaxant used in every patient. When arterial blood-gas measurements had been made, the inspired oxygen concentration and minute volume were adjusted to maintain PaO₂ at 100–150 mm Hg and PaCO₂ at about 40 mm Hg. Either fentanyl or phenoperidine was used to provide supplementary i.v. analgesia.

Cardiopulmonary bypass.

All patients were perfused using the Q100 Bentley Temptrol disposable oxygenator. The priming volume was approximately 2600 ml and this comprised 1 litre of 24-hr-old acid disodium citrate dextrose (ACD) blood neutralized with sodium bicarbonate 8.4% and sodium chloride 10% and diluted with Hartmann's solution. Previous studies in our laboratory revealed, in a similar group of patients, that this results in a blood haematocrit in the patient in the early stages of perfusion of about 30%. A flow rate of 2.4 litre/min/m² was used with total body cooling to 30°C.

During perfusion, additions of, alternately, ACD blood 500 ml and 5% dextrose in water 500 ml were added to the oxygenator to maintain the “level” constant within the oxygenator. The volume of these additions varied between 500 ml and 2000 ml, depending on the duration of perfusion and the amount of blood lost during the open heart procedure.

In all patients, bypass was discontinued during rewarming. Heparinization was achieved with heparin 3 mg/kg i.v. before commencing bypass, and reversed with protamine 6 mg/kg as soon as bypass was discontinued.
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Times of sampling.
As the duration of open heart surgery varied from patient to patient, samples of blood were taken according to events rather than at fixed time intervals:
(1) Immediately before induction of anaesthesia.
(2) Between induction of anaesthesia and commencement of surgery. (During this time catheters for the measurement of arterial and venous pressure were inserted and all monitoring apparatus was set up.)
(3) After sternotomy.
(4) 10 min after heparinization, but before bypass.
(5) At the lowest body temperature.
(6) 30 min after reaching the lowest temperature.
(7) As normal temperature was regained and bypass discontinued.
(8) 30 min after regaining normal temperature.
(9) In the intensive care unit after cardio-respiratory function had become stable.

Laboratory methods.
Blood was taken from the radial artery cannula. Blood-glucose was estimated by the glucose oxidase method within 24 hr of collection. Blood for estimation of GH was centrifuged immediately and the plasma was deep frozen. Plasma GH was assayed by a double antibody radio-immunoassay (Buckler, 1970) and reported in micro-units of the International Reference preparation of human GH. All serial samples on the same subjects were estimated initially in the same assay, although frequently samples required repeat assay at greater dilutions.

Statistical methods.
All the tests of statistical significance which are quoted in the text were performed using the Student t test on the mean differences between paired samples.

Body temperature.
At the time of samples 1 and 10, the temperature was recorded from the axilla; at other times it was recorded from a mid-oesophageal thermocouple.

RESULTS

Blood-glucose concentration.
The mean values for blood-glucose, with SEM and range, are shown in table I. Figure 1 shows these values, together with those of the plasma GH.
The mean pre-anaesthesia value (77 mg%) was within the normal range for fasting blood-glucose concentration and this increased to 99 mg% (P<0.005) with sternotomy, and to 158 mg% (P<0.001) after heparinization. There were further large increases in association with the glucose load from the perfusate during bypass. At the lowest temperature, the mean blood-glucose concentration was 259 mg% after an average of 150 ml of dextrose 5% had been given. Thirty minutes later the mean value was 323 mg%, 545 ml of dextrose 5% having been given. During rewarming, the blood-glucose increased to a mean of 358 mg%. At the time of sample 8 an average total of 925 ml of dextrose 5% had been administered. Although the blood-glucose concentration was lower (131 mg%) in the intensive care unit, this was still significantly greater than normal (P<0.001).

<table>
<thead>
<tr>
<th>Sample</th>
<th>Temperature (°C)</th>
<th>Blood-glucose concentration (mg/100 ml)</th>
<th>Growth hormone concentration (μunit/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
<td>n</td>
</tr>
<tr>
<td>(1) Pre-induction</td>
<td>36.5</td>
<td>36.0–37.5</td>
<td>20</td>
</tr>
<tr>
<td>(2) Before surgery</td>
<td>36.3</td>
<td>37.2–35.4</td>
<td>23</td>
</tr>
<tr>
<td>(3) After sternotomy</td>
<td>35.8</td>
<td>37.8–35.0</td>
<td>22</td>
</tr>
<tr>
<td>(4) After heparinization</td>
<td>35.5</td>
<td>36.8–34.0</td>
<td>22</td>
</tr>
<tr>
<td>(5) Lowest temperature</td>
<td>28.5</td>
<td>31.0–27.6</td>
<td>23</td>
</tr>
<tr>
<td>(6) Lowest temperature</td>
<td>30.2</td>
<td>36.0–29.6</td>
<td>23</td>
</tr>
<tr>
<td>+30 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(7) Rewarming</td>
<td>35.6</td>
<td>38.0–30.0</td>
<td>23</td>
</tr>
<tr>
<td>(8) Normal temperature</td>
<td>36.5</td>
<td>37.6–35.6</td>
<td>23</td>
</tr>
<tr>
<td>+30 min</td>
<td>36.5</td>
<td>39.4–35.0</td>
<td>23</td>
</tr>
<tr>
<td>(10) Stable cardio-</td>
<td>37.2</td>
<td>39.0–34.8</td>
<td>18</td>
</tr>
</tbody>
</table>
pulmonary function
GROWTH HORMONE AND GLUCOSE CHANGES DURING BYPASS

FIG. 1. Plasma GH and blood glucose concentrations. Mean values and SEM. H=heparinization. Shaded area represents time on bypass.

Growth hormone.

Measurements of plasma GH are shown in table I and depicted graphically in figures 1 and 2. The mean pre-anaesthetic value of plasma GH (7 µunit/ml) was within the accepted range for resting patients. One patient had a very high concentration (100 µunit/ml). This may have been the result of late premedication and, consequently, this patient's results have been excluded from the statistical analyses. Plasma GH did not increase significantly with anaesthesia, but the commencement of surgery was associated with an increase (30 µunit/ml; P<0.025). There was no significant further increase following heparinization (31.09 µunit; P>0.01). The measurements, during hypothermia, were not significantly different from the pre-bypass values. However, the mean values after normal temperature had been regained (46 µunit; P<0.001) and half an hour later (59 µunit; P<0.0025) were both greater than that after sternotomy. As in the case of blood-glucose, the GH concentration, although decreased (31 µunit/ml) when cardiorespiratory stability had been regained, was still significantly greater than the pre-anaesthetic value (P<0.025).

Wide variations were noted in the plasma GH concentrations. A histogram (fig. 3) was constructed of the number of patients who had plasma concentrations greater than 25 µunit/ml (mean pre-anaesthetic concentration plus three standard deviations). In two patients, none of the 10 samples had concentrations greater than this value, whereas eight patients had one sample greater than 25 µunit/ml. There appeared to be two groups of patients. One group of 11 patients had less than five samples with values above 25 µunit/ml. A second group of 12 patients had five or more samples with values above 25 µunit/ml. Statistical data for these two groups are shown in tables II and III and are expressed graphically in figure 2.

Temperature.

Table I shows the mean body temperature and the range of values at each of the sampling stages.

Table II. Plasma GH (µunit/ml) in 12 patients who had five or more values greater than 25 µunit/ml. (n=number of samples.)

<table>
<thead>
<tr>
<th>Sample</th>
<th>n</th>
<th>Mean</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Pre-induction</td>
<td>11</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>(2) Before surgery</td>
<td>12</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>(3) After thoracotomy</td>
<td>12</td>
<td>46</td>
<td>8</td>
</tr>
<tr>
<td>(4) After heparinization</td>
<td>11</td>
<td>46</td>
<td>8</td>
</tr>
<tr>
<td>(5) Lowest temperature</td>
<td>12</td>
<td>54</td>
<td>7</td>
</tr>
<tr>
<td>(6) Lowest temperature +30 min</td>
<td>12</td>
<td>63</td>
<td>14</td>
</tr>
<tr>
<td>(7) Rewarming</td>
<td>12</td>
<td>57</td>
<td>13</td>
</tr>
<tr>
<td>(8) Normal temperature</td>
<td>12</td>
<td>73</td>
<td>14</td>
</tr>
<tr>
<td>(9) Normal temperature +30 min</td>
<td>12</td>
<td>92</td>
<td>18</td>
</tr>
<tr>
<td>(10) Stable cardiorespiratory</td>
<td></td>
<td>53</td>
<td>15</td>
</tr>
</tbody>
</table>

Fig. 2. Plasma GH concentrations. Mean values and SEM for two groups of patients. H=heparinization. Shaded area represents time on bypass.

Fig. 3. Distribution of plasma GH values.
**TABLE III. Plasma GH (μunit/ml) in 11 patients who had more than five values less than 25 μunit/ml. (n=number of samples.)**

<table>
<thead>
<tr>
<th>Sample</th>
<th>n</th>
<th>Mean</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Pre-induction</td>
<td>9</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>(2) Before surgery</td>
<td>11</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>(3) After thoracotomy</td>
<td>10</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>(4) After heparinization</td>
<td>11</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>(5) Lowest temperature</td>
<td>11</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>(6) Lowest temperature +30 min</td>
<td>11</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>(7) Rewarming</td>
<td>11</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>(8) Normal temperature</td>
<td>11</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>(9) Normal temperature +30 min</td>
<td>11</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>(10) Stable cardiorespiratory function</td>
<td>10</td>
<td>20</td>
<td>5</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Many factors influence the plasma GH concentrations and many of these could be implicated in open heart surgery. Stresses of many kinds, such as anxiety (Glick et al., 1963), overnight starvation (Roth et al., 1963) and trauma (Oyama and Takazawa, 1971; Glick et al., 1963) cause release of GH.

Acute changes in the blood-glucose concentration influence GH release; usually an increase in blood-glucose reduces plasma GH, while a rapid reduction in glucose will cause an increase in plasma GH concentrations (Roth et al., 1963). However, it has been suggested that it is the utilization of glucose rather than the absolute concentration which regulates GH secretion (Glick et al., 1963). Body temperature is also related to plasma GH concentration, which increases with an increase in temperature and is reduced in association with hypothermia (Buckler, 1973). Heparinization, by activating lipase, stimulates lipolysis and increases plasma free fatty acids (FFA) (Tsushima, Sakuma and Irie, 1970) which inhibit GH secretion.

Decreased glucose utilization has been reported to occur during surgery (Wright, Henderson and Johnston, 1974). In patients undergoing cardiopulmonary bypass, the increased secretion of cortisol (Reier, George and Kilmaro, 1973) and catecholamines (Alexander et al., 1969; Replogle et al., 1962) will contribute further towards the depression of glucose utilization. Furthermore, in spite of hyperglycaemia, the secretion of insulin is suppressed until rewarming takes place (Hewitt et al., 1972; Stremmel, Schlossen and Koehnlein, 1972).

Decreased glucose utilization has been shown to increase GH secretion (Glick et al., 1963), and this may be responsible for the continued high GH concentrations during bypass, in spite of hyperglycaemia, hypothermia and heparinization, all of which might be expected to reduce plasma GH secretion.

In our patients, the blood-glucose concentration was beginning to decrease 30 min after normal temperature had been regained (fig. 1). This could be the result of the removal of the exogenous glucose load from the perfusate and an increase in insulin secretion after rewarming. At this time plasma GH concentrations were highest. The following factors may account for this:

1. Increase in body temperature from approximately 30°C to 37°C in a mean time of 38 min.
2. Reversal of heparinization leading to a reduction in plasma FFA (Moffitt et al., 1971).
3. The surgical stimulus in the presence of "light" anaesthesia, especially following rewarming, may stimulate the hypothalamic release of growth hormone releasing hormone.

Blood-glucose and plasma GH concentrations remained significantly in excess of the pre-anesthetic values when the patients were in the intensive care unit and had stable cardiorespiratory function. However, it has been shown that depression of glucose utilization, albeit to a lesser degree than that which occurs during surgery, persists for several days after operation (Wright, Henderson and Johnston, 1974). The return of consciousness following such major surgery may also be associated with various stresses leading to an increased secretion of GH and other hormones.

Cardiac arrhythmia commonly occurs after bypass, and although there are many factors involved in its aetiology, it has been suggested (Salter, Fluck and Stimmler, 1972) that it may be secondary to the high GH concentrations, leading to increased FFA concentrations which have been shown to cause arrhythmias in dogs (Kurien and Oliver, 1970). Only two of our patients developed a serious arrhythmia, and both died as a result of irreversible ventricular fibrillation immediately following bypass. The first patient, a 30-year-old woman, had severe rheumatic heart disease and a grossly enlarged heart. She had been on long-term diuretic therapy and during bypass, in spite of the administration of potassium chloride, her serum potassium concentration remained low. The highest concentration of plasma GH in this patient was 26 μunit/
ml before heparinization, and the value was 16 µunit/ml when she developed the arrhythmia.

The second patient was a 55-year-old man. His plasma GH had increased from 4 µunit/ml before anaesthesia to 60 µunit/ml following heparinization, and remained high until death. However, in this patient, as in the previous patient, many factors could be implicated in the causation of the arrhythmia. He had undergone resection of an aortic aneurysm combined with aortic valve replacement, necessitating a bypass time of 238 min, following which he had severe bleeding.

The two groups of patients who exhibited different GH responses were analysed with respect to age, sex, weight, perfusion time and blood-glucose concentrations. No correlation with any of these factors was found and the significance of the difference in response is not yet understood.

During cardiopulmonary bypass lipid metabolism is dominant (Moffitt et al., 1971). These high concentrations of plasma GH are not only a reflection of the stress of open heart surgery, but also serve to provide FFA as a substrate for energy production until glucose utilization and carbohydrate metabolism return to normal. However, should the ability of the liver to metabolize plasma FFA be exceeded, ketosis will result. It has been suggested by Tepperman (1968) that this can lead to poor myocardial function which is especially detrimental in patients recovering from bypass. It may be that there is an “optimum concentration” of plasma GH for good myocardial function. Use of the anaesthetic technique based on large i.v. doses of morphine (Dalton, 1972) which modifies the plasma GH response (Reier, George and Kilmaro, 1973) may be beneficial to these patients.

ACKNOWLEDGEMENTS

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CONCENTRATIONS D'HORMONE DE LA CROISSANCE ET DE LA GLUCOSE DU SANG PENDANT DES DERIVATIONS CARDIO-PULMONAIRES

RESUME

On a mesure les concentrations de plasma de l'hormone de la croissance (plasma GH) et de glucose du sang sur 23 malades ayant subi une intervention chirurgicale à coeur ouvert et n'ayant qu'une hypothermie modérée. Une importante augmentation de la concentration de la glucose du sang s'est produite à la suite de la sternotomie et elle a augmenté pendant la dérivation, surtout en raison de la charge exogène de glucose venant de la perfusion. Après la dérivation, la glucose du sang est restée à une concentration supérieure à celle constatée avant l'anesthésie et cette élévation s'est maintenue pendant la période qui a suivi l'intervention. Le plasma GH a aussi augmenté pendant l'intervention chirurgicale et il est resté élevé pendant la perfusion. Les plus fortes concentrations se sont produites après la dérivation alors que la température était redevenue normale.
WACHSTUMSHORMONE UND BLUTGLUKOSEKONZENTRATIONEN WÄHREND HERZ-LUNGEN-UMLEITUNG

ZUSAMMENFASSUNG

CONCENTRACIONES EN HORMONA DEL CRECIMIENTO Y GLUCOSA DE LA SANGRE DURANTE DESVIACIÓN CARDIOPULMONAR

SUMARIO
Se midieron en 23 pacientes en los que se practicó cirugía a corazón abierto con hipotermia moderada las concentraciones en hormona del crecimiento del plasma (plasma GH) y de glucosa de la sangre. Tuvo lugar un aumento significativo de la concentración de glucosa en la sangre con esternotomía y aumentó durante la desviación, parcialmente como resultado de la carga exogena de glucosa del perfusado. Después de la desviación, la glucosa de la sangre permaneció por encima de la concentración preanestésica, y esta elevación persistió en el siguiente período de cirugía. El plasma GH también aumentó con la cirugía y permaneció elevado durante la perfusión. Las concentraciones más altas tuvieron lugar después de la desviación cuando se logró una temperatura normal.