EFFECT OF PHENTOLAMINE ON THE METABOLIC RESPONSE TO GYNAECOLOGICAL SURGERY

E. S. WALSH, J. L. PATERSON, K. MASHTER AND G. M. HALL

SUMMARY
The effect of the infusion of phentolamine 0.5 mg min⁻¹ on the metabolic response to gynaecological surgery was investigated. In comparison with a control group of patients, phentolamine was associated with a significant increase in plasma insulin concentration after 30 and 60 min of surgery. The glycaemic response to surgery was decreased by α-adrenergic blockade, but this was only significant after 120 min of surgery. The hypotension produced by the administration of phentolamine was well tolerated.

The use of drugs with α-adrenergic blocking properties, such as the neuroleptic compounds droperidol and chlorpromazine, is common in anaesthetic practice. In addition, agents such as phentolamine are often used for the short-term control of hypertension during anaesthesia. The cardiovascular effects of α-adrenergic blocking drugs are well known, but little attention has been given to the metabolic consequences of the administration of such agents during surgery. The purpose of the present study, therefore, was to examine the effects of a phentolamine infusion on the metabolic and endocrine response to gynaecological surgery.

METHODS
Twenty healthy women, admitted for Fallopian tubal surgery, were investigated. They were allocated randomly to receive either an infusion of phentolamine 0.5 mg min⁻¹ or an equivalent volume of 0.9% sodium chloride solution. The nature of the study and the potential hazards were explained to all patients before consent was obtained. The study was approved by the ethics committee of Hammersmith Hospital.

All patients were premedicated with papaveretum 15 mg and hyoscine 0.3 mg i.m. 90 min before surgery. On arrival in the anaesthetic room the duration of starvation before operation was determined and a central venous catheter was inserted percutaneously from an antecubital fossa vein to permit blood sampling and the administration of i.v. fluids. After the patient had rested for 10 min a control blood sample was collected and heart rate, arterial pressure and aural temperature measured. An infusion of either phentolamine 0.5 mg min⁻¹ or an equivalent volume of 0.9% sodium chloride solution was started in the contralateral arm and maintained for the duration of the experiment. Fifteen minutes after the start of the infusion another blood sample was collected and the physiological measurements repeated.

Anaesthesia was then induced with thiopentone, the trachea was intubated following the administration of pancuronium and the lungs ventilated with 70% nitrous oxide in oxygen supplemented with 0.5% halothane. Ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 4.0–4.5% (Vickers, Datex). Sodium chloride solution 0.9% was infused during surgery at a rate of 6 ml kg⁻¹ h⁻¹. Measured blood loss did not exceed 150 ml.

Blood samples were collected at 30-min intervals during surgery and were analysed for glucose, glyceral, lactate and alanine by methods described previously (Hall et al., 1980). Plasma insulin values were determined by radioimmunoassay (Cooper et al., 1980). The concentrations of each metabolite and insulin were estimated in duplicate and the coefficients of variation were: glucose 2.7%, lactate 2.9%, glyceral 4.0%, alanine 4.9% and insulin 5.0%. At the same time as the blood sample was collected the heart rate, arterial pressure and aural temperature were recorded (Holdcroft, Hall and Cooper, 1979).

On the 4th day after operation the skinfold thick-
REFERENCES
nesses of the patient were measured and the percentage of fat to body weight calculated (Durnin and Rahaman, 1974).

The results are expressed as mean values (±SEM). A two-way analysis of variance was used in both groups to determine the presence of a significant change in mean values with time. A hierarchical two-way analysis of variance was used to assess the significance of any difference in mean values between the two groups.

**RESULTS**

Details of the patients studied are shown in table I. There was no significant difference between the two groups of patients.

The changes in metabolites, haematocrit and aural temperature are shown in table II. There was a significant increase in blood glucose from 3.70 to 4.52 mmol litre⁻¹ (P < 0.05) after 60 min of surgery in the control group of patients and the hyperglycaemia persisted for the duration of surgery. In the phentolamine patients, blood glucose increased significantly (P < 0.05) only after 30 min of surgery and the glycaemic response was significantly less than the control group after 120 min (P < 0.05). Blood lactate increased significantly (P < 0.05) after 90 and 120 min of surgery in both groups of patients. There was no significant change in either blood alanine or plasma glycerol concentrations during the study, although the plasma glycerol value in the phentolamine patients was increased significantly (P < 0.05) compared with the control group after

**TABLE I.** Details (mean ± SEM) of the two groups of patients

<table>
<thead>
<tr>
<th></th>
<th>Saline (n = 10)</th>
<th>Phentolamine (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>32.2 ± 2.0</td>
<td>30.0 ± 1.5</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>60.6 ± 2.9</td>
<td>60.4 ± 2.8</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>31.4 ± 2.0</td>
<td>32.4 ± 1.7</td>
</tr>
<tr>
<td>Duration of starvation (h)</td>
<td>16.5 ± 0.9</td>
<td>14.4 ± 0.8</td>
</tr>
</tbody>
</table>

**TABLE II.** Mean (± SEM) concentrations of substrates, haematocrit and temperature at the following times: S1 = control, S2 = 15 min after saline or phentolamine, S3, S4, S5 and S6 = 30, 60, 90 and 120 min after commencement of surgery respectively. Significance of difference of means from S1 shown by *P < 0.05, **P < 0.01 and ***P < 0.001. Difference between groups for each variable shown in final column. n.s. = not significant

<table>
<thead>
<tr>
<th></th>
<th>S1</th>
<th>S2</th>
<th>S3</th>
<th>S4</th>
<th>S5</th>
<th>S6</th>
<th>Phentol. v. saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol litre⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3.70 ± 0.18</td>
<td>3.83 ± 0.20</td>
<td>4.23 ± 0.23</td>
<td>4.52 ± 0.29*</td>
<td>4.66 ± 0.29*</td>
<td>5.20 ± 0.26**</td>
<td>*P &lt; 0.05</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>3.70 ± 0.18</td>
<td>3.92 ± 0.18</td>
<td>4.38 ± 0.20*</td>
<td>4.13 ± 0.26</td>
<td>4.24 ± 0.21</td>
<td>4.32 ± 0.28*</td>
<td></td>
</tr>
<tr>
<td>Lactate (mmol litre⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.97 ± 0.24</td>
<td>1.01 ± 0.19</td>
<td>1.06 ± 0.15</td>
<td>1.23 ± 0.16</td>
<td>1.28 ± 0.16*</td>
<td>1.49 ± 0.15*</td>
<td></td>
</tr>
<tr>
<td>Phentolamine</td>
<td>0.93 ± 0.15</td>
<td>0.78 ± 0.10</td>
<td>0.95 ± 0.07</td>
<td>1.09 ± 0.09</td>
<td>1.17 ± 0.09*</td>
<td>1.17 ± 0.11*</td>
<td>n.s.</td>
</tr>
<tr>
<td>Alanine (μmol litre⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>188 ± 27</td>
<td>196 ± 28</td>
<td>144 ± 12</td>
<td>141 ± 22</td>
<td>153 ± 22</td>
<td>148 ± 21</td>
<td>n.s.</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>147 ± 20</td>
<td>134 ± 13</td>
<td>134 ± 21</td>
<td>130 ± 19</td>
<td>137 ± 12</td>
<td>172 ± 22</td>
<td></td>
</tr>
<tr>
<td>Glycerol (μmol litre⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>144 ± 13</td>
<td>123 ± 21</td>
<td>214 ± 39</td>
<td>187 ± 22</td>
<td>184 ± 19</td>
<td>170 ± 22</td>
<td>*P &lt; 0.05</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>170 ± 23</td>
<td>199 ± 24</td>
<td>200 ± 25</td>
<td>184 ± 20</td>
<td>203 ± 10</td>
<td>209 ± 13</td>
<td>S2</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>36.0 ± 0.1</td>
<td>35.8 ± 0.1</td>
<td>35.6 ± 0.1**</td>
<td>35.5 ± 0.1***</td>
<td>35.5 ± 0.1***</td>
<td>35.4 ± 0.2***</td>
<td>n.s.</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>35.9 ± 0.1</td>
<td>35.8 ± 0.1</td>
<td>35.4 ± 0.1**</td>
<td>35.3 ± 0.2***</td>
<td>35.2 ± 0.2***</td>
<td>35.1 ± 0.2***</td>
<td></td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>39.8 ± 0.5</td>
<td>39.4 ± 0.4</td>
<td>38.8 ± 0.3*</td>
<td>38.0 ± 0.5**</td>
<td>37.0 ± 0.3***</td>
<td>36.3 ± 0.3***</td>
<td>*P &lt; 0.05</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>41.5 ± 0.4</td>
<td>40.5 ± 0.4</td>
<td>39.2 ± 0.4**</td>
<td>38.8 ± 0.5***</td>
<td>37.8 ± 0.4***</td>
<td>37.5 ± 0.4***</td>
<td>S1</td>
</tr>
</tbody>
</table>
15 min of phentolamine. The haematocrit decreased significantly to 36.3% ($P < 0.001$) in the control group and to 37.5% ($P < 0.001$) in the phentolamine patients after 120 min of surgery. The aural temperature decreased to 35.1°C ($P < 0.001$) at the end of the study in the phentolamine patients, but this was not significantly different from the 35.4°C ($P < 0.001$) in the control patients.

Changes in plasma insulin are shown in figure 1. The infusion of phentolamine for 15 min before surgery was associated with a significant increase ($P < 0.01$) in insulin from 4.0 to 7.9 μU.litre$^{-1}$. This increase persisted during surgery, whereas the control group showed the characteristic decrease in circulating insulin ($P < 0.05$) after 30 and 60 min of surgery. There was a significant difference ($P < 0.05$) in insulin concentrations between the two groups of patients after 30 and 60 min of surgery.

There was no significant change in either heart rate or mean arterial pressure during surgery in the control group of patients (fig. 2). However, the infusion of phentolamine before surgery was associated with a significant increase ($P < 0.01$) in heart rate from 75 to 98 beat min$^{-1}$ and a significant decrease ($P < 0.01$) in mean arterial pressure from 82 to 73 mm Hg. These cardiovascular changes persisted throughout surgery in the α-blocked patients so that the mean arterial pressure was 59 mm Hg and the heart rate 93 beat min$^{-1}$ after 120 min of surgery.

**DISCUSSION**

The failure of insulin secretion to respond to the hyperglycaemia of surgery is well documented and is assumed to be a result of the α-adrenergic inhibitory effects of the circulating catecholamines on the β-cells of the pancreas (Traynor and Hall, 1981). There is, however, little direct evidence to support this view and Allison, Tomlin and Chamberlain (1969) failed to observe any improvement in insulin response to i.v. glucose during a phentolamine infusion in two patients undergoing surgery. The results of the present study confirm the importance of adrenergic activity in modulating insulin secretion in the basal state before surgery (Robertson and Porte, 1973) and demonstrate that phentolamine significantly increases plasma insulin during surgery (fig. 1). Alpha-blockade produced only a two-fold increase in insulin compared with the control group, which agrees with the suggestion of Porte and Robertson (1973) that adrenergic control is exerted over a small storage pool of insulin.

It is tempting to infer that the increase in insulin in the phentolamine patients was responsible for the reduction in the glycaemic response to surgery by augmenting the utilization of glucose peripherally and by decreasing hepatic glucose production. It is important to note, however, that in the period before surgery there was no change in blood glucose in
spite of an increase in plasma insulin from 4.0 to 7.9 nmol litre\(^{-1}\). An increase in hepatic glyco-
genesis is an important component of the hyper-
glycaemic response to surgery (Stjernström, Jor-
feldt and Wiklund, 1981) and is thought to be 
mediated by stimulation of alpha-adrenergic receptor (An-
tonis et al., 1967; Syvalahti et al., 1977). It is 
probable that inhibition of catecholamine-induced, 
hepatic glycoegenolysis in the phentolamine patients 
was a major factor in reducing the hyperglycaemic 
response to surgery.

Alpha-adrenergceptors are involved in the control 
of secretion of other glyceregulatory hormones.
Growth hormone release from the pituitary is inhi-
bited by phentolamine (Imura et al., 1971), but this 
is unlikely to have influenced the glucose response 
in the present study since we have observed previ-
ously that growth hormone secretion during surgery 
does not alter the glucose response (Cooper et al., 
1979). The adrenergic control of glucagon secretion 
is complex, but in general is increased by \(\beta\)
-adrenergic stimulation (Unger and Orci, 1976). The 
administration of phentolamine in other stressful 
states such as exercise showed no effect on the 
plasma glucagon response (Galbo, Christensen and 
Holst, 1977). In a separate study, we have shown 
only a small, insignificant increase in plasma 
glucagon from 5.6 to 11.0 nmol litre\(^{-1}\) during pelvic 
surgery (unpublished observations), which suggests 
that glucagon secretion is unlikely to be a major 
factor in the regulation of blood glucose.

Lipolysis in adipose tissue is particularly sensitive 
to \(\beta\)-adrenergic stimulation, but is also subjected to 
inhibition by \(\alpha\)-adrenergceptors (Fain, 1973). On this 
basis, phentolamine infusion during surgery would 
be expected to exacerbate lipolysis as shown by 
changes in plasma glycerol. The failure of \(\alpha\)- 
blockade to increase plasma glycerol significantly in 
the present study may be attributed to the concur-
rent stimulation of the secretion of insulin, a potent 
antilipolytic hormone.

In conclusion, alpha-adrenergic blockade during 
surgery reverses the usual insulin suppression and 
attenuates the hyperglycaemia. The associated 
hypotension was well tolerated by the young, healthy 
patients used in this study. We suggest that the 
use of drugs during anaesthesia with \(\alpha\)-blocking 
properties may confer metabolic advantages, in par-
ticular by increasing secretion of the key anabolic 
hormone insulin.

---

**REFERENCES**

Some effects of anaesthesia and surgery on carbohydrate and 
fat metabolism Br J Anaesth., 41, 588

Antonis, A., Clarke, M. L., Hodge, R. L., Molony, M., and 
Pulkington, T. R. E. (1967). Receptor mechanisms in the 
hyperglycaemic response to adrenaline in man Lancet, 1, 
1135

Cooper, G. M., Holdcroft, A., Hall, G. M., and Alaghband-
Zadeh, J. (1979) Epidural analgesia and the metabolic re-

Imura, H., Kato, Y., Ikeda, M., Monmoto, M., and Yanvata, 
M. (1971). Effect of adrenergic-blocking or-stimulating agents 
on plasma growth hormone, immunoreactive insulin and blood 
free fatty acid levels in man J. Clin. Invest., 50, 1069

Porter, D., and Robertson, R. P. (1973) Control of insulin 
secretion by catecholamines, stress and the sympathetic nerv-
sous system. Fed. Proc., 32, 1792

of basal insulin secretion in man Diabetes, 22, 1

Stjernstrom, H., Jorfeldt, L., and Wiklund, L. (1981). Interrela-
tionship between splanchnic and leg exchange of glucose and 
other blood-borne energy metabolites during abdominal surg-

Cardioselective (metoprolol) and non-selective (propranolol) 
\(\beta\)-blockade and glucose homeostasis Ann. Clin Res., 9, 
292.

Traynor, C. and Hall, G. M. (1981). Endocrine and metabolic 
changes during surgery: anaesthetic implications. Br. J. 
Anaesth., 53, 153.

Unger, R. H. and Orci, L. (1976) Physiology and pathophysiology 

---

**ACKNOWLEDGEMENTS**

We are grateful to Mr Raoul Margara and Mr Mike Darling for 
permission to study the patients. Tracey Harrison provided 
skilled secretarial assistance.
Nous avons étudié l'effet d'une perfusion de phentolamine 0,5 mg min\(^{-1}\) sur la réponse métabolique à la chirurgie gynécologique. Si l'on compare les résultats à ceux d'un groupe de patientes témoins, l'administration de la phentolamine s'accompagne d'une augmentation significative de la concentration plasmatique d'insuline après 30 et 60 min de chirurgie. La réponse hyperglycémique à la chirurgie est diminuée par le blocage alpha-adrénergique, mais ceci ne devient significatif qu'après 120 min de chirurgie. L'hypotension induite par l'administration de phentolamine a été bien tolérée.

ZUSAMMENFASSUNG
Wir untersuchten die Wirkung von Phentolamin-Infusionen (0,5 mg min\(^{-1}\)) auf die metabolischen Auswirkungen von gynäkologischen Operationen. Im Vergleich zu einer Kontrollgruppe fanden wir bei Patienten, die Phentolamin erhalten hatten, einen signifikanten Anstieg der Plasma-Insulin-Konzentration von 30 und 60 min nach der Operation. Der durch die Operation bedingte Abfall des Blutzuckers wurde durch alpha-adrenerge Blockade vermindert. Dies war aber erst 120 min nach der Operation signifikant. Den durch Phentolamin hervorgerufenen Blutdruckabfall vertrugen die Patienten gut.

SUMARIO
Se investigó el efecto de la infusión de 0,5 mg min\(^{-1}\) de fentolamina en la respuesta metabólica a la intervención ginecológica. La fentolamina vino asociada con un incremento significativo de la concentración de insulina en el plasma después de transcursados de 30 a 60 min de la intervención quirúrgica, en comparación con un grupo de pacientes de control. La respuesta glicémica a la intervención quirúrgica disminuyó mediante un bloqueo \(\alpha\)-adrenérgico, pero esto tuvo carácter significativo después de haber transcursado 120 min después de la operación. La hipotensión producida por la administración de fentolamina se toleró bien.