

## Glucose Homeostasis and Insulin Secretion during Isoflurane Anesthesia in Humans

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The effect of isoflurane-air anesthesia on glucose tolerance in humans was investigated using two successive intravenous glucose tolerance tests (IVGTT). After a first IVGTT while awake, patients received a second IVGTT either while awake (group I), during anesthesia with isoflurane-air and pancuronium without surgical stimulation (group II), or during the same anesthetic technique but combined with surgery (group III). Isoflurane seemed to induce glucose intolerance (glucose disappearance rate  $K_{10-60 \text{ min}} = 1.628 \pm 0.462\% \text{ min}^{-1}$  [control] versus  $1.086 \pm 0.920\% \text{ min}^{-1}$  [anesthesia],  $P < 0.05$ ) partly due to a decreased glucose induced insulin response. Growth hormone and norepinephrine levels were also increased during anesthesia. Epinephrine levels were lowered by isoflurane anesthesia. Although glucose intolerance was marked during surgery ( $K_{10-60 \text{ min}} = 0.892 \pm 0.286\% \text{ min}^{-1}$ ), the glucose-induced insulin response remained similar to that observed in patients in group II, while growth hormone, cortisol, epinephrine, and norepinephrine concentrations increased significantly. These known stress factors thus seemed to enhance glucose intolerance through a diminished response to insulin action and/or an enhanced hepatic glucose output, rather than by further impairing pancreatic insulin secretion. (Key words: Anesthetics, volatile; isoflurane. Hormones: cortisol; growth hormone; insulin. Metabolism: glucose; glucose intolerance. Sympathetic nervous system: catecholamines; epinephrine; norepinephrine.)

ANESTHESIA AND SURGERY may alter many aspects of carbohydrate metabolism. Insulin secretion is depressed, in part, due to increased sympathetic activity and raised norepinephrine levels.<sup>1-4</sup> A rise in cortisol, growth hormone, and norepinephrine induces a stimulation of glucose production and catabolic processes that result in hyperglycemia. It has also been shown that the maximal glucose disposal rate in response to insulin is decreased during surgery.<sup>5</sup> Thus, hyperglycemia originates from both decreased glucose utilization and increased hepatic glucose output as a consequence to the increased catabolic processes.

The role of anesthetic drugs on glycoregulatory mechanisms remains, in part, unsettled. Epidural and low spinal anesthesia preserve glucose tolerance with a normal insulin release, presumably due to inhibition of

the epinephrine response to surgery.<sup>6,7</sup> Cortisol and growth hormone levels increased or remained unchanged during surgery.

Diminished insulin release has been demonstrated for halothane<sup>8</sup> and enflurane.<sup>9,10</sup> The reported effects of isoflurane in humans<sup>11-13</sup> remain controversial because, in these studies, no attempt was made to eliminate interfering surgical stimulation, concomitant medications, nitrous oxide, and lack of standardization.

In this study, the effects of isoflurane anesthesia on glucose assimilation and insulin secretion in response to glucose in humans were elucidated. The rate of insulin release and the effect of insulin on the glucose disappearance from plasma were analyzed following the intravenous administration of a glucose load. The magnitude of the early response of plasma insulin, presumably representing the discharge of an acutely releasable pool,<sup>14</sup> is reputed to be an important determinant of glucose tolerance measured as the plasma glucose disappearance rate.<sup>15</sup>

In addition, the neuroendocrine response to isoflurane anesthesia, including alteration of levels of cortisol, growth hormone, and catecholamines, was investigated.

### Materials and Methods

The study was approved by the University Ethical Committee. Twenty-six patients scheduled for general surgery gave informed consent following thorough explanation of the purpose and procedure of the study. All were healthy patients (ASA physical status I-II) with biochemical screening within normal range. Patients were excluded if they were pregnant or lactating; had history of allergy, alcoholism, or renal, hepatic, or endocrine disease; known drug dependence or chronic use of analgesics or tranquilizers, or had taken any drug known to interfere with or affect glucose metabolism or insulin release.

All patients fasted overnight, and all studies were started before 9 A.M. An indwelling catheter was inserted into a radial artery under local anesthesia for monitoring blood pressure and obtaining arterial blood samples for blood-gas analysis, glucose, and hormonal assays. An intravenous catheter was inserted into an antecubital vein for the administration of maintenance fluids (saline) and medications. All patients were premedicated with lorazepam ( $0.06 \text{ mg} \cdot \text{kg}^{-1}$ ) and glycopyrrolate ( $0.006 \text{ mg} \cdot \text{kg}^{-1}$ ) iv.

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All subjects were at bed rest during the entire study. Arterial blood samples for measurement of baseline plasma insulin and glucose were drawn 15, 20, and 30 min after insertion of the catheters. Samples for measurement of cortisol, growth hormone, and catecholamines were drawn 20 and 30 min after catheter placement. After these baseline measurements, each subject underwent a first intravenous glucose tolerance test (IVGTT).

Glucose ( $0.33 \text{ g} \cdot \text{kg}^{-1}$  body weight as 50% dextrose in water) was administered iv in 3 min. Zero-time was taken to be the moment when the glucose pulse had been injected. Arterial blood samples were then obtained at 1, 3, 5, 7, 10, 20, 30, 45, and 60 min after glucose administration for plasma glucose and insulin determinations, and at 30 and 60 min for catecholamines assays. After completion of this first IVGTT, the study procedure was as follows for the different groups.

#### GROUP I

The subjects were kept undisturbed for 30 min, and new baseline samples for glucose and hormone determinations were withdrawn 45 and 55 min after completion of the first test. A second IVGTT was done (*i.e.*, 2 h after the first test) under the same conditions and arterial blood samples were obtained at the same time intervals as after the first test. Additional blood samples for cortisol and growth hormone were taken at 30 and 60 min after the second glucose load.

#### GROUP II

The patients were transferred to the operating room where anesthesia was induced with thiopental  $4 \text{ mg} \cdot \text{kg}^{-1}$  iv, followed by succinylcholine  $1 \text{ mg} \cdot \text{kg}^{-1}$  for tracheal intubation. Anesthesia was maintained with isoflurane 1.5 MAC in air-oxygen (1:1, v:v) and pancuronium bromide  $3 \text{ mg}$  iv. Isoflurane was delivered from a calibrated vaporizer in a non-rebreathing circuit. Normocapnia was provided by controlled mechanical ventilation with arterial  $p_{\text{CO}_2}$  values ranging between 36 and 40 mmHg throughout the entire test procedure. Arterial blood samples were obtained 15 and 25 min after induction of anesthesia for measurement of plasma glucose and hormones. Injection of the second intravenous glucose load and collection of the post-injection blood samples for glucose and hormonal assays occurred at the same time intervals as in group I.

#### GROUP III

The anesthesia procedure was identical to that described for group II. Blood samples were obtained simi-

larly 15 min after induction of anesthesia. Surgical incision followed, and the second baseline blood sample was taken for measurement of plasma glucose and hormones. Five minutes later, the second IVGTT was performed as in group I.

The assignment of the patients to the respective groups occurred according to time availability of the surgical schedule.

#### ANALYTICAL METHODS

For measurement of plasma insulin, growth hormone and cortisol blood aliquots were collected on heparin and stored until the end of the study. After centrifugation at  $4^\circ \text{C}$ , plasma samples were frozen at  $-20^\circ \text{C}$  until time of assay. Plasma immunoreactive insulin levels were determined with a modification of the double antibody method.<sup>16</sup> A radioimmunoassay was used for the determination of plasma cortisol levels (Gamma coat<sup>125</sup>I cortisol R. I. A. Kit, Travenol-Genentech Diagnostics) and of human growth hormone (Pharmacia hGH R. I. A. 100, Pharmacia Diagnostics AB, Sweden). For measurement of plasma norepinephrine and epinephrine, arterial blood samples were collected in pre-chilled tubes containing heparin and, within 30 min, the plasma was separated at  $4^\circ \text{C}$ ,  $50 \mu\text{l}$  of sodium metabisulfite was added, and plasma samples were frozen at  $-20^\circ \text{C}$  for analysis. Catecholamines were assayed using a HPLC technique.<sup>17</sup> The limit of sensitivity of the assay was  $0.015 \text{ ng/ml}$  for norepinephrine (coefficient of variation 5%) and  $0.020 \text{ ng/ml}$  for epinephrine (coefficient of variation 15%). Plasma glucose was measured using the glucose oxidase method.

#### CALCULATED VALUES AND STATISTICS

Pre-stimulus levels of glucose and insulin were calculated as the mean of the measurements made before each IVGTT ( $n = 3$  for the first IVGTT,  $n = 2$  for the second IVGTT).

The glucose fractional disappearance rate  $K_G$  was calculated by the least squares analysis from the decline of plasma glucose levels, transformed to natural logarithms, between 10 and 60 min after each glucose load.<sup>18</sup> The acute insulin response to glucose was calculated as the mean of the changes of insulin levels from the pre-stimulus level at 1, 3, and 5 min after the glucose load ( $\bar{x} \Delta \text{IRI } 1-5 \text{ min}$ ). The total insulin output was estimated as the integrated area (linear trapezoidal method) under the insulin curve above baseline levels from 0 to 5 min (AUC IRI 0-5 min), from 0 to 10 min (AUC IRI 0-10 min), and from 0 to 60 min (AUC IRI 0-60 min). The cumulative insulin outputs per unit of glycemic stimulus, or index of insulinogenic reserve,<sup>19</sup> were calculated by dividing the area circumscribed by

TABLE 1. Patients Characteristics

	Group I	Group II	Group III
n	10	6	7
Sex ratio (F/M)	6/4	5/1	4/3
Age (y)	39.7 ± 9.7	43.7 ± 9.0	40.5 ± 14.8
Weight (kg)	65.15 ± 10.35	64.33 ± 14.43	62.71 ± 6.45
Height (cm)	166.75 ± 8.45	166.33 ± 11.68	165.14 ± 6.73
BMI kg · cm <sup>-2</sup> · 10 <sup>4</sup>	23.3 ± 2.8	23.0 ± 3.2	22.5 ± 4.8

Type of surgery: hysterectomy (2); laryngectomy (1); herniorraphy (2); venous stripping (2). BMI = body mass index (weight × height<sup>-2</sup> × 10<sup>4</sup>).

the insulin curve (*i.e.*, the increase of plasma insulin above baseline) by the corresponding area circumscribed by the glucose curve for the time intervals 0–5 min, 0–10 min, and 0–60 min.

Statistical analysis included one- and two-tailed Wilcoxon rank sum test for intragroup comparisons, and the Mann-Whitney U-test for intergroup comparison. The demographic variables and the baseline values were examined by one-way analysis of variance. Linear regression analysis was used for estimating glucose decay. Statistical significance was accepted if  $P < 0.05$ . All data are presented as mean values ± SD.

### Results

From the initial 24 patients, two were withdrawn from group II and one from group III for technical reasons. Two additional patients were included in

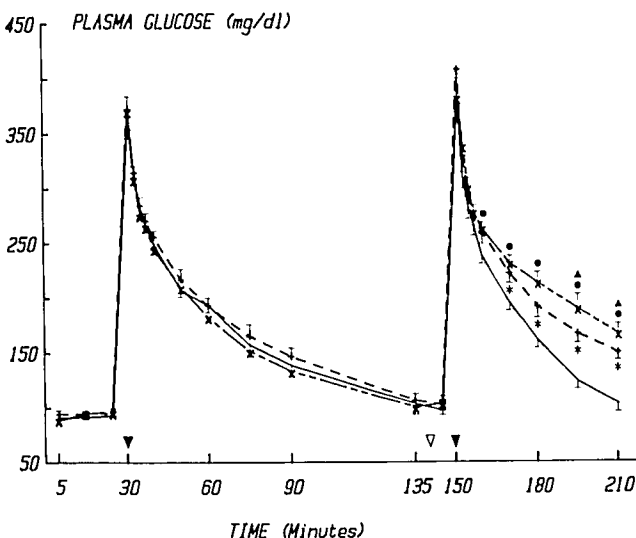


FIG. 1. Changes in plasma glucose concentrations during two successive IVGTT (mean values ± SEM). Group I: —; group II: +---+; group III: x · · · x. Filled arrows indicate end of the respective glucose injections, the open arrow the time of surgical incision in group III. \* $P < 0.05$  II versus I, • $P < 0.05$  III versus I, ▲ $P < 0.05$  III versus II.

TABLE 2. Changes in Glucose Disappearance Rates and Acute Insulin Response

	IVGTT 1	IVGTT 2
$K_G$ (% min <sup>-1</sup> )		
Group I (n = 10)	1.161 ± 0.188	1.628 ± 0.462*
Group II (n = 6)	1.108 ± 0.224	1.086 ± 0.092†
Group III (n = 7)	1.227 ± 0.222	0.892 ± 0.286‡
$\bar{x}\Delta IRI$ (1–5 min) (pg/100 $\mu$ l)		
Group I (n = 10)	254.6 ± 131.5	246.3 ± 101.7
Group II (n = 6)	217.7 ± 101.3	136.5 ± 33.8*†
Group III (n = 7)	287.3 ± 168.5	158.4 ± 108.3*†

\* Difference between first and second phase of test:  $P < 0.05$ .

† Difference versus corresponding test in group I:  $P < 0.05$ .

‡ Difference versus corresponding test in group II:  $P < 0.05$ .

group I. Therefore, the final analysis included ten patients in group I, six in group II, and seven in group III. The comparison of data on sex, age, weight, and height did not reveal any significant difference between groups (table 1). All body mass index values were within the normal range.

The mean plasma glucose concentrations are shown in figure 1. Baseline glucose values were comparable in all three groups. Following the first glucose load (IVGTT 1), the decay of plasma glucose was also similar for the three groups. During the second glucose load (IVGTT 2), glycemia was higher in group II patients than in those in control group I starting from the 20th minute. This same pattern of plasma glucose was observed in patients in group III; however, the persistent hyperglycemia occurred earlier and was more pronounced, so that the glucose levels at 45–60 min were significantly higher in those in group III than group II.

The glucose disappearance rates (table 2) during the first IVGTT were fairly low in all patients with no meaningful differences between the groups. In group I patients  $K_G$  increased markedly during the second test ( $P < 0.025$ ), whereas it did not change in those in group II and decreased in group III ( $P < 0.05$ ).

The mean baseline insulin levels (fig. 2) were significantly higher in group III patients than in those in group I ( $P < 0.02$ ). During the first IVGTT, the plasma insulin concentrations reached a peak during the first minute, but underwent large individual variations as reflected by the standard deviations. After the first IVGTT, the baseline levels of plasma insulin increased in patients in group I ( $P < 0.001$ ). In group III, no difference was evident between baseline insulin values before and after surgical incision. During the second IVGTT, insulin secretion apparently increased in group I patients, but was blunted in those in groups II and III as compared to the values obtained during the first IVGTT. Significant decreases of plasma insulin

concentrations appeared for patients in groups II and III at 3 min through 30 min.

The acute insulin response ( $\bar{x} \pm \Delta$  IRI [1-5 min]) was similar during the awake test in patients in all three groups, but decreased significantly during the second IVGTT in those in groups II and III (table 2) with no meaningful difference between them. When the parameters of early and total insulin output were compared (table 3), marked differences in response were observed during the second IVGTT. In group II and group III patients, the early and total insulin secretion were significantly decreased with regard to their control test and when compared to those in group I, a finding even more significant when the first 10 min of the IVGTT were considered.

Similar responses were also observed for the cumulative insulin outputs per unit of glycemic stimulus. Isoflurane anesthesia reduced the insulinogenic index by an average of 43.4%, while it was reduced by 54.7% by the combination of isoflurane and surgery.

Baseline mean plasma cortisol values (table 4) were similar in all three groups before the first and second IVGTT. Pairwise comparisons showed that, during the second IVGTT, cortisol increased significantly only during surgery in group III patients ( $P < 0.001$ ).

Growth hormone levels were increased during the

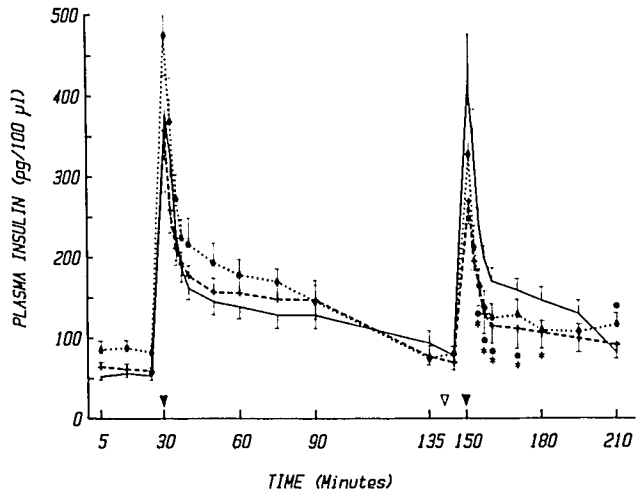


FIG. 2. Changes in plasma insulin levels during two successive IVGTT (mean values  $\pm$  SEM). Group I: —; group II: +---+; group III: ····. Same legend as in figure 1.

second baseline period in patients in groups II and III as compared to those in group I ( $P < 0.005$ ), and in patients in group III the post-incision value was greater than the value obtained before incision ( $P = 0.058$ ). During the second IVGTT, no change of plasma growth hormone level was apparent in patients in group

TABLE 3. Changes in Area Under Insulin Curve and Cumulative Insulin Outputs per Unit of Glycemic Stimulus ( $\Delta$ Insulin/ $\Delta$ glucose Ratio, Insulinogenic Index)

	0-5 Min	0-10 Min	0-60 Min
AUC IRI (pg·min/100 $\mu$ l)*			
Group I			
IVGTT 1	1195.9 $\pm$ 630.9	1860.6 $\pm$ 830.7	6055.3 $\pm$ 2521.6
IVGTT 2	1156.6 $\pm$ 505.9	1728.1 $\pm$ 690.6	4508.3 $\pm$ 2007.1
Group II			
IVGTT 1	998.4 $\pm$ 466.7	1659.5 $\pm$ 607.7	6294.1 $\pm$ 1969.5
IVGTT 2	630.4 $\pm$ 136.1 $\ddagger\ddagger\ddagger$	926.8 $\pm$ 332.0 $\S\ddagger\ddagger$	2994.9 $\pm$ 2104.3 $\nabla$ **
Group III			
IVGTT 1	1340.7 $\pm$ 790.8	2075.7 $\pm$ 1070.1	6696.0 $\pm$ 2739.0
IVGTT 2	736.7 $\pm$ 499.9	1049.8 $\pm$ 675.5 $\ddagger$ **	2983.0 $\pm$ 2041.3 $\nabla$ **
$\Delta$ INS/ $\Delta$ GLU $\ddagger$			
Group I			
IVGTT 1	1.138 $\pm$ 0.39	0.972 $\pm$ 0.395	0.942 $\pm$ 0.386
IVGTT 2	1.140 $\pm$ 0.497	0.959 $\pm$ 0.347	0.985 $\pm$ 0.348
Group II			
IVGTT 1	0.954 $\pm$ 0.429	0.865 $\pm$ 0.294	0.962 $\pm$ 0.277
IVGTT 2	0.589 $\pm$ 0.156 $\ddagger\ddagger\ddagger$	0.487 $\pm$ 0.197 $\nabla\ddagger\ddagger$	0.497 $\pm$ 0.399 $\nabla\ddagger\ddagger$
Group III			
IVGTT 1	1.372 $\pm$ 0.893	1.147 $\pm$ 0.655	1.129 $\pm$ 0.532
IVGTT 2	0.696 $\pm$ 0.462 $\ddagger$ **	0.544 $\pm$ 0.348 $\ddagger\ddagger\ddagger$	0.427 $\pm$ 0.315 $\nabla\ddagger\ddagger$

\* The area under the insulin curve represents the total insulin output estimated as the total incremental insulin area above baseline for each time period.

$\ddagger$  Indexes are calculated by dividing the area circumscribed by the insulin curve (*i.e.*, the increment above baseline level) by the corresponding area circumscribed by the glucose curve.

Levels of significance for difference between first and second phase of test (intragroup comparison):  $\ddagger P < 0.05$ ;  $\S P < 0.025$ ;  $\nabla P < 0.01$ .

Levels of significance for difference between corresponding test in group I (intergroup comparison): \*\* $P < 0.05$ ;  $\ddagger\ddagger P < 0.025$ ;  $\ddagger\ddagger\ddagger P < 0.01$ .

TABLE 4. Mean Plasma Cortisol and Growth Hormone Levels

Time	Cortisol ( $\mu\text{g/l}$ )			Growth Hormone (mU/l)		
	Group I	Group II	Group III	Group I	Group II	Group III
Baseline 1						
-15 min	139 $\pm$ 50	162 $\pm$ 44	187 $\pm$ 85	1.8 $\pm$ 4.2	2.3 $\pm$ 3.1	0.6 $\pm$ 0.4
-5 min	139 $\pm$ 51	147 $\pm$ 37	168 $\pm$ 76	1.8 $\pm$ 4.0	1.7 $\pm$ 1.7	0.6 $\pm$ 0.2
Baseline 2						
-15 min	116 $\pm$ 31	203 $\pm$ 108	199 $\pm$ 92	0.8 $\pm$ 1.0	4.0 $\pm$ 3.2†	6.1 $\pm$ 6.1†
-5 min*	—	—	224 $\pm$ 104	—	—	12.2 $\pm$ 7.3
IVGTT 2						
+30 min	107 $\pm$ 36	160 $\pm$ 78	248 $\pm$ 95†	0.6 $\pm$ 0.1	3.1 $\pm$ 4.9†	15.0 $\pm$ 10.9†‡
+60 min	127 $\pm$ 42	125 $\pm$ 57	261 $\pm$ 142†‡	0.7 $\pm$ 0.4	1.9 $\pm$ 2.8	16.0 $\pm$ 15.9†‡

\* Sample following surgical incision.

† Difference versus group I,  $P < 0.05$ .‡ Differences between groups II and III,  $P < 0.05$ .

I, but growth hormone secretion was increased in those in group II and, even more significantly, in group III ( $P < 0.005$ ).

No meaningful differences in plasma norepinephrine levels occurred during the first IVGTT (table 5). The levels of norepinephrine, however, were different during the second baseline period in group III patients ( $P < 0.01$ ). During the second IVGTT, no differences were seen between group I and II, but the norepinephrine levels were significantly increased in patients in group III as compared to those in group I ( $P < 0.01$ ) and group II ( $P < 0.05$ ).

The baseline epinephrine levels were comparable in all groups. No significant differences were seen during the first IVGTT between the different groups. During the second baseline, the epinephrine level decreased in group II and increased in group III. Following surgical incision in the latter group, plasma epinephrine concentration doubled ( $P < 0.001$ ). The epinephrine levels remained decreased in patients in group II ( $P < 0.05$  vs. group I) and increased in group III ( $P < 0.001$  vs. group I and  $P < 0.01$  vs. group II).

## Discussion

Results of the second IVGTT suggest a diminished glucose tolerance in patients anesthetized with isoflurane. The addition of surgery accentuated this response. No differences were noted in the early phase of the glucose decay, which was expected, considering that, during the first 15 min after an acute glucose load, the glycemic levels are dependent on distribution of the glucose dose, basal insulin levels, and renal spill-over.<sup>20</sup> In the non-anesthetized control group, the improvement following successive glucose administration was emphasized by the increase of the rate of glucose disappearance  $K_G$ . The improvement of carbohydrate tolerance following repeated glucose administration is known as the Staub-Traugott effect,<sup>21,22</sup> which has been shown to be associated with persistent elevation of serum immunoreactive insulin levels, a small decrease of growth hormone levels, and markedly lowered serum free fatty acids levels. In this study, the Staub-Traugott effect also occurred in the presence of raised baseline insulin levels prior to the second glucose load.

TABLE 5. Mean Plasma Norepinephrine and Epinephrine Levels

Time	Norepinephrine (pg/ml)			Epinephrine (pg/ml)		
	Group I n = 10	Group II n = 6	Group III n = 7	Group I n = 10	Group II n = 6	Group III n = 7
Baseline 1						
-15 min	172 $\pm$ 60	200 $\pm$ 74	174 $\pm$ 56	47 $\pm$ 43	51 $\pm$ 47	70 $\pm$ 31
-5 min	172 $\pm$ 62	163 $\pm$ 45	203 $\pm$ 95	38 $\pm$ 25	40 $\pm$ 12	87 $\pm$ 40
IVGTT 1						
+30 min	176 $\pm$ 68	200 $\pm$ 44	177 $\pm$ 71	40 $\pm$ 27	63 $\pm$ 59	97 $\pm$ 54
+60 min	178 $\pm$ 75	193 $\pm$ 60	177 $\pm$ 70	51 $\pm$ 40	58 $\pm$ 70	109 $\pm$ 68
Baseline 2						
-15 min	158 $\pm$ 65	208 $\pm$ 57	323 $\pm$ 181†	50 $\pm$ 49	27 $\pm$ 8†	78 $\pm$ 49
-5 min*	—	—	377 $\pm$ 215	—	—	160 $\pm$ 128
IVGTT 2						
+30 min	150 $\pm$ 76	203 $\pm$ 67	399 $\pm$ 165†‡	62 $\pm$ 46	20 $\pm$ 5†	236 $\pm$ 174†‡
+60 min	175 $\pm$ 64	207 $\pm$ 74	327 $\pm$ 109†‡	64 $\pm$ 72	21 $\pm$ 4†	206 $\pm$ 174†‡

\* Sample following surgical incision.

† Difference from group I,  $P < 0.05$ .‡ Differences between groups II and III,  $P < 0.05$ .

But, in the anesthetized patients, no such potentiation was seen. The impaired glucose-induced insulin response could be contributive to this absence of potentiation as the early phase insulin secretion was inhibited in both groups II and III. Similar observations were found for total insulin output and the cumulative insulin outputs per unit of glycemic stimulus.

Although different experimental protocols were used, similar findings have been reported with other halogenated anesthetics. Some hyperglycemia occurred during halothane<sup>23</sup> and enflurane<sup>24</sup> anesthesia during surgery, while a definite blunting of the insulin response to a glucose load appeared under halothane anesthesia in humans.<sup>25</sup> *In vitro* studies in the rat also suggested that enflurane inhibited glucose-stimulated insulin release<sup>26</sup> to an extent similar to that observed with halothane.

It is tempting to associate the decreased insulin output observed during isoflurane anesthesia with the impaired glucose utilization. Previous studies have demonstrated that acute insulin responses are nonlinearly related to the glucose dose, while a highly linear relationship existed between total insulin output and glucose load. But the intravenous glucose tolerance remained largely determined by the magnitude of the acutely releasable insulin pool.<sup>15</sup> Plasma insulin levels can also not be causally equated with secretion, as changes in hepatic insulin extraction may be important.<sup>27</sup> Therefore, insulin-glucose correlations based upon measurements of insulin concentrations in arterial blood can only approximate the real relationships between insulin and glucose at the pancreatic level.

The interpretation of the IVGTT in physiological terms is also debated on grounds of nonhomogeneity of glucose pools, insulin-dependence of hepatic glucose uptake and heterogeneity of the kinetics of glucose loss.<sup>28</sup> If the test remains valid for diagnostic purposes, it may, in particular, not be interpreted as a measure of tissue sensitivity to insulin or insulin resistance.

Furthermore, inhalation anesthesia might have induced splanchnic hemodynamic changes that could affect pancreatic blood flow and hepatic perfusion, thus impairing both insulin output and hepatic glucose uptake. However, it has been shown that autoregulation of hepatic blood flow appears to be sustained during isoflurane anesthesia,<sup>29</sup> while, in animals, pancreatic insulin output is fairly insensitive to extensive reductions of pancreatic blood flow.<sup>30</sup>

Concomitant hormonal changes could also contribute to the inhibition of insulin secretion. Catecholamines could be involved through the  $\alpha_2$ -adrenergic receptors of epinephrine, the most potent  $\alpha_2$ -adrenergic receptor stimulant.<sup>31</sup> Only during surgery were prominent increases in plasma levels of both catecholamines evident.

It thus seemed unlikely that the inhibitory effect of isoflurane anesthesia on plasma insulin levels was a result of increased sympathetic nervous system activity. A similar conclusion had been previously reported for halothane anesthesia.<sup>32</sup>

Glucose intolerance may also be induced by mechanisms other than impaired insulin secretion, such as a diminished peripheral glucose oxidation, a decreased biological response of tissues to insulin, or an increased hepatic glucose output. The results from this study argue for the last two possibilities. During isoflurane anesthesia, plasma growth hormone levels increased and surgery amplified this response. Growth hormone may directly inhibit glucose uptake in cells independent of insulin-induced glucose uptake,<sup>33</sup> and also increases hepatic glucose output in dogs.<sup>34</sup> It thus seems likely that this hormone would enhance glucose intolerance, particularly in the patients anesthetized with isoflurane during surgery where the largest increases in growth hormone concentrations were noted. Our results confirmed previous findings published by Oyama *et al.*<sup>13</sup>

Plasma cortisol levels were increased by isoflurane anesthesia alone, and adrenocortical stimulation was more pronounced during surgery. In the latter situation, cortisol could contribute to glucose intolerance through a glycogenolytic mechanism. Similar results in man have been reported.<sup>11,13,35</sup>

Thus, during isoflurane anesthesia without superimposed surgical stress, a direct effect of the anesthetic drug on insulin secretion seemed likely. Different hypothetical pathways can be proposed: interference with the microfilamentous-microtubular network of the B-cell<sup>36</sup> or with other systems contributing to insulin secretion,<sup>37</sup> inhibition of the ATP-ases involved in insulin secretion,<sup>38</sup> or a non-specific interaction with the cellular membrane, thereby inducing structural changes of membrane proteins (such as interference with the Calcium sensitive potassium channels).<sup>39</sup>

In summary, in this study, isoflurane anesthesia resulted in impaired insulin secretion in response to intravenous glucose, an effect not associated with increased circulating catecholamines. This inhibitory effect on insulin release contributed to a decreased glucose tolerance. In patients submitted to surgical stress, the adrenergic response and the increased levels of plasma cortisol and growth hormone further impaired glucose tolerance, probably through peripheral tissue effects, as glucose-induced insulin secretion was not decreased to a greater extent.

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