Experience with the Biostator for diagnosis and assisted surgery of 21 insulinomas

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Abstract
Surgical removal is the treatment of choice for insulinomas. Definitive biochemical diagnosis of organic hyperinsulinism has to be established before surgery. These tumors are sometimes undetected by preoperative imaging investigations and, in addition, surgical management may also be complicated by the absence of palpable tumors or the presence of multiple tumors. We report the value of the euglycemic clamp technique for diagnosis and surgical treatment in 21 patients with confirmed insulinomas. Data were compared with 12 controls, and nine patients were retested after surgery. During the euglycemic hyperinsulinic clamp, the mean C-peptide value was 3.6 ± 2.2 ng/ml and it remained high (3.8 ± 2.5 ng/ml), despite exogenous hyperinsulinemia (1762.7 ± 233.2 μU/ml for the highest plateau). In contrast, the C-peptide concentration declined in 12 control patients (0.3 ± 0.1 ng/ml, P < 0.001) and after successful surgery in nine retested patients (0.3 ± 0.2 ng/ml, P < 0.01). During continuous glucose monitoring, successful removal of the insulin-secreting tumor was accompanied by an increase in plasma glucose concentrations and a loss of requirement for endogenous glucose within 36 min (range 28–43 min). The continuing requirement for glucose after the ablation of the tumor revealed the existence of additional and initially undetected tumors in four patients, among whom two had the multiple endocrine neoplasia type I (MEN I) syndrome.

We conclude that the euglycemic hyperinsulinic clamp is a reliable and convenient diagnostic test for insulinoma, as it is both safe (no hypoglycemia) and relatively brief (3×90 min). Glucose monitoring and glucose clamping provide a reliable indicator of complete removal of insulin-hypersecreting tissue, especially in patients with occult or multiple tumors.

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Introduction
Insulinomas are the most frequent endocrine tumors of the pancreas, causing recurrent episodes of fasting hypoglycemia and giving rise to substantial morbidity (1). The demonstration of low plasma glucose (less than 2.5 mmol/l or 45 mg/dl) in the presence of a high serum insulin (≥6 μU/ml) is regarded as being diagnostic of hypoglycemia secondary to an insulinoma (2). As the secretion of insulin may be intermittent (3), further diagnostic tests are often required. Insulin-stimulative secretion tests are now obsolete, as they give false positive results (4), and the insulin-induced C-peptide suppression test may be unpleasant, and hazardous because of the risk of hypoglycemia (5); furthermore, its interpretation requires knowledge of the influence of body mass index (BMI) and age (6). Prolonged fasting remains the gold standard (7), although its long duration (up to 72 h) is uncomfortable and may present a hazard in the elderly and in patients in poor health.

As normal insulin secretion is subject to feedback inhibition by exogenous insulin (8–10), patients with insulinoma are characterized by a lack of appropriate negative feedback response of C-peptide to insulin infusion during maintenance of euglycemia using the euglycemic clamp technique. However, previous reports on this technique, including our previous preliminary data (11–14) have involved only short series of patients.

We now report our experience with this technique in 21 consecutive patients and in 12 healthy controls. The euglycemic hyperinsulinic clamp was used to test the degree of suppression of endogenous C-peptide secretion during three plateaus of increasing insulin concentration. Furthermore, 10 patients underwent the C-peptide suppression test and a prolonged supervised fast. Recovery of feedback regulation of insulin secretion was also retested by the euglycemic clamp in nine patients after removal of their insulinoma.

Once a biochemical diagnosis of an insulinoma has been made, it has to be borne in mind that 40% of insulinomas are less than 1 cm in diameter, and may therefore escape detection during preoperative investigations (echography, computed tomography (CT) scan, arteriography) (15). As there may also be uncertainty
about the number and localization of the tumors, we report our experience using euglycemic control (an adaptation of the euglycemic clamp technique, without infusion of insulin), for the intraoperative management of patients with insulinoma(s).

Patients and methods

Patients

The euglycemic hyperinsulinic clamp was performed as a diagnostic test in 10 women and 11 men aged from 21 to 68 years. The diagnosis of an insulin-secreting islet-cell tumor was suspected on the development of symptomatic hypoglycemia with low plasma glucose concentrations in presence of inappropriate plasma insulin concentrations, either spontaneously or during a supervised 72-h fast in 10 patients (Table 1).

Only 12 of the 21 patients (57%) had true positive images on ultrasonography (three of 17), CT scan (seven of 18) and arteriography (seven of 18). In addition, there were three false-positive CT scans and two false-positive angiograms. Histological proof of the tumoral nature of the endocrine tissue was obtained in all patients. Unique, benign insulinomas were confirmed for 15 patients.

Multiple tumors were found in four patients. Benign insulinomas were found in three of these patients, among them two had multiple endocrine neoplasia type I (MEN I) syndrome; a pseudocyst in the head of the pancreas, which gave a false-positive preoperative image, was associated with an insulinoma in one case. Three patients presented islet-cell carcinomas, with liver metastases in two and regional invasion in one patient.

Twelve volunteers with normal BMI ranging from 20 to 25 kg/m² and aged 20–48 years were used as healthy controls.

Methods

Diagnostic test: the euglycemic hyperinsulinemic clamp

Euglycemic clamping was performed using an artificial pancreas (Biostator GCIIS; Laboratoire Miles, Epernon, France) working on a 9:1 mode. The patients were awake and supine throughout the clamp procedures. An indwelling catheter was inserted into an antecubital vein for infusion of glucose and insulin. A second catheter was inserted in a hand vein for blood sampling. The hand on the side of the sampling catheter was maintained at 60°C by an electric blanket, permitting arterialization of the venous blood. Three basal samples for assay of plasma glucose, insulin (Pharmacia, Stockholm, Sweden; lower limit of detection 5 µU/ml) and C-peptide (Mallinkrodt, Dietzenbach, Germany; lower limit of detection of C-peptide, 0.3 ng/ml) were obtained before the start of the clamp study; thereafter, samples were obtained at 10-min intervals for insulin and C-peptide assays, during the last 40 min

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Plasma glucose, plasma insulin, and C-peptide were recorded simultaneously either during spontaneous symptomatic hypoglycemia or during prolonged fasting. In addition to the primary hyperparathyroidism and insulinoma, patient 10 developed a lung carcinoid syndrome, and patient 12 developed a prolactin-secreting pituitary tumor.
of each insulin plateau. Exogenous insulin (Actrapid Human, Novo, Copenhagen, Denmark) was infused at a constant rate with an infusion pump (Harvard Apparatus; Ealing, Les Ulis, France) and a 1-min prime was followed by three successive 90-min infusions of 2, 4, and 8 mU/kg/min. Glucose (20%) was administered by the artificial pancreas to maintain glycemia at a basal value (80 mg/dl).

Endogenous insulin secretion was monitored by determining C-peptide secretion during the euglycemic hyperinsulinemic clamp. Euglycemic clamp studies were repeated in nine patients (Nos 5, 6, 7, 8, 9, 16, 18, 20, and 21) after their operation, using the same procedure.

**Peroperative euglycemic control** The night before operation, oral food was withheld and blood glucose concentrations were maintained in the normal range by means of intravenous administration of glucose solutions. In the operating room, the patients were connected to the artificial pancreas. The Biostator was programed to maintain blood glucose at the preselected value of 95 mg/dl by means of a glucose infusion, as in the euglycemic clamp technique, but without insulin infusion. The requirement for dextrose was taken to reflect insulinoma activity (16, 17).

**Statistical analysis**

All data are presented as mean ± S.E.M.

Intergroup differences were compared with the Mann–Whitney rank sum test at each time point of the clamp procedure. C-peptide baseline values and during the clamp, before and after surgery, were compared by the Wilcoxon signed-rank test for matched pairs.

Statistical significance was assumed applying the Bonferroni correction for α < 0.05.

**Results**

**Euglycemic hyperinsulinemic clamp technique as an aid to diagnosis of insulinoma**

During the insulin clamp, mean plasma insulin concentrations increased to similar plateau values in the three groups (1762.7 ± 233.2 μU/ml in patients; 1410.5 ± 128.7 μU/ml in controls; 1646.7 ± 263.5 μU/ml in the retested patients). Euglycemia was maintained throughout the study (mean intraindividual variability of 9.2 ± 1.0%) (Fig. 1).

In patients, C-peptide concentrations were initially 3.6 ± 2.2 ng/ml and remained high throughout the test [3.8 ± 2.5 ng/ml (range 1.5–12.5 ng/ml) during the last plateau]. In contrast, C-peptide concentrations were almost completely suppressed in the control group (from 2.2 ± 0.5 to 0.3 ± 0.1 mg/ml; P < 0.001). The cutoff point that clearly distinguished patients with insulinoma from controls was 0.3 ng/ml, the lower limit of detection of the assay, during the last plateau. Similarly, in the nine patients retested after their operation, C-peptide was suppressed from 1.9 ± 0.6 ng/ml to 0.3 ± 0.2 ng/ml (P < 0.01) (Fig. 2).

The duration of the test was 270 min. No hypoglycemic attack occurred during the procedure, thus the clamp test was found more comfortable by the 10 patients who experienced both fasting and clamp studies.

**Euglycemic control as an aid during surgery**

In 17 patients, the tumor was identified (by preoperative or peroperative studies), and peroperative glucose requirements disappeared, after resection (enucleation or distal pancreatectomy) of the suspected tumor. Blood glucose concentrations increased, while glucose infusion from the Biostator decreased rapidly to zero. The mean time between the increase in glycemia or the complete cessation of the infusion of glucose by the artificial pancreas (or both) and the removal of the secreting tumor(s) was 36 min (range 28–43 min). This group of patients included the two patients (Nos 2 and 4) with carcinoma and liver metastases, from whom only the pancreatic tumors were removed.

In four patients (including two with MEN I), tumors that had been localized before and during the operation were resected, without loss of the requirement for exogenous glucose. In patient 8, preoperative imaging revealed a tumor located in the head of the pancreas. Despite enucleation of this tumor, large amounts of glucose were still required to maintain euglycemia, and a second tumor was found after re-examination of the pancreatic head. Histology showed that the two tumors included endocrine tissue.

In patient 10 (MEN I), the CT scan localized a unique adenoma that was removed by enucleation. A persistent requirement for glucose indicated the presence of an occult tumor, and careful re-exploration of the gland revealed a second insulinoma, localized at the isthmus, which was duly resected.

In patient 12 (MEN I), preoperative imaging revealed only a tumor located at the head of the pancreas; despite removal of this tumor, dextrose infusion was still required, and a second tumor was palpated and resected. In view of a continuing glucose requirement, distal pancreatectomy was performed. Pathological examination of the excised tissue indicated the presence of three other insulinomas. The rate of glucose infusion decreased from 507 to 54 mg/min, but not to zero. A further tumor was found on re-examination of the head of the pancreas, and was excised. The blood glucose concentration returned to normal and the requirement for exogenous glucose disappeared. In all, eight tumors were removed from this patient.

In patient 21, preoperative imaging gave a false-positive result, and a pseudocyst was removed from the
head of the pancreas. The persistence of a requirement for glucose enabled discovery of a unique endocrine tumor in the posterior wall, at the junction of the tail and the body, which had not been detected before surgery.

No hypoglycemic attack occurred during surgery, because blood glucose was monitored continuously. No patient experienced sufficient hyperglycemia to require short-term postoperative insulin, because the glucose infusion was titrated to the blood glucose concentration during anesthesia.

All patients with benign insulinomas were cured after the first surgical procedure. The 15 patients with benign unique insulinomas were cured at a mean duration of follow-up of 52 months (range 28–145 months). Among the remaining six patients, two (Nos 10 and 12) with benign multiple adenomas were still free from hypoglycemic episodes at 8 and 6 years respectively, one patient (No. 6) died after operation, from a lung embolism, and, of the three patients with malignant insulinomas, patient 4 died after operation from digestive hemorrhage, patient 2 survived 4 years after

Figure 1 Mean of the means (± s.e.m.) of C-peptide (○) and insulin (●) at each time point of the euglycemic hyperinsulnemic clamp (A) before surgery, (B) in controls, and (C) after surgery. Single-sided error bars are shown.
tumoral reduction and chemotherapy, and patient 10 has remained euglycemic 9 years after tumoral reduction and six cycles of chemotherapy associated with radiotherapy.

Discussion

We present here our experience of the clamp technique using an artificial pancreas as an aid for both diagnosis and surgical treatment of insulinoma. In our series of patients, increasing the plasma insulin concentration by means of an intravenous infusion of insulin failed to suppress C-peptide concentrations in all patients with insulinoma. In contrast, suppression of C-peptide was observed in all the normal volunteers. The difference between the two groups was statistically significant from the time of the first plateau, and C-peptide concentrations had diverged markedly, with a clear cutoff point, by the third plateau. Basal C-peptide values were not statistically different between the two groups, showing that the failure of hyperinsulinemia to suppress C-peptide secretion in patients was due to their autonomous insulin secretion, rather than to increased concentrations of C-peptide. The BMI of our control group was normal. It may be argued that the difference between patients and controls might be less clearcut if hyperinsulinic obese controls were used. Although this possibility cannot be excluded, it should be pointed out that a previous report has shown that the degree of C-peptide suppression differed little between non-obese controls (with normal basal values) and obese controls (with increased basal values) (18). Furthermore, after the removal of insulinoma from nine patients, each completely recovered normal suppression of C-peptide secretion by hyperinsulinemia.

There are no reports on the sensitivity and specificity of the C-peptide suppression test in comparison with the prolonged supervised fast for the diagnosis of insulinoma. In our study, 10 patients underwent the two tests. Our data confirm that a decision to end the fast is not easy to make, as four of the patients who were eventually shown to have insulinoma were fasted for the full 72-h period without exhibiting symptoms or signs of hypoglycemia.

Conversely, one patient (No 16) reproduced symptoms of hypoglycemia, but had plasma glucose concentrations above the hypoglycemic range. The C-peptide suppression test may be especially useful in such cases, as it has (in our hands) 100% sensitivity and probably 100% specificity. Although the supervised prolonged fast remains the gold standard and β-cell polypeptide assays may also be helpful (19) for the diagnosis of insulinoma, the euglycemic clamp technique has several advantages. It does not provoke hypoglycemia, which is inevitable during fasting, and it can be carried out in any patient, regardless of their physical fitness or clinical condition. The test also has the advantage of not being affected by BMI or age. Moreover, the duration of clamp technique is relatively short (270 min) in comparison with the 72 h that may be required for the fasting test – although it is rare for patients with insulinoma to require fasting for that duration. The drawback of glucose clamping is that it is relatively complex. Also, as the endocrine pancreas may secrete endogenous insulin in response to an even moderate increase in glucose, a bolus intravenous dose of glucose should not be given, because it may result in a falsely positive plasma C-peptide concentration (20).

Patients with insulinomas can expect a normal life span if their treatment is complete (21). However, incomplete excision may arise from uncertainty about
the localization of the tumor (preoperative imaging was found to give false-negative results in about 50% of patients in the present series) and the number of tumors (10% of insulinomas are multiple). In this respect, it should be borne in mind that patients with MEN I have a high incidence (50%) of multiple tumors (22).

Peroperative euglycemic control with the artificial pancreas offers a unique aid for the management of patients with insulinoma. First, because anesthetic management during operation of insulinomas may be complicated by the wide swings in blood glucose concentrations, hypoglycemia may occur during removal of the tumor, whereas continuous administration of glucose may increase postablational hyperglycemia and may mask useful information about the completeness of tumor resection. Continuous monitoring of glucose concentrations with the artificial pancreas enables a rapid response to events that may alter blood glucose concentration during surgery. Second, the increase in blood glucose and the loss of requirement for glucose infusion during surgery for an islet-cell insulin-secreting tumor are good indicators of the complete removal of the insulin-secreting site(s) (23–25). In the present study, a hyperglycemic rebound, a decrease in the infusion of dextrose by the artificial pancreas, or both, within 36 min after the resection indicated complete resection of all insulin-secreting tissue. In contrast, a continued requirement for glucose after removal of a suspected islet-cell lesion is indicative of the existence of additional hyperfunctioning islet-cell tissue. Using this technique, all our patients with benign insulinomas and one with carcinoma were cured by a single surgical treatment. There was no evidence of hyperplasia or desidioblastosis, confirming that insulinoma was not missed. Apart from the pathological findings, successful surgical treatment in our patients was confirmed by the absence of hypoglycemic episodes and normal plasma glucose value over the follow-up period (52 months). The clamp technique thus avoids reintervention, particularly in patients with multiple or occult insulinomas, although very long-term relapse in patients with MEN cannot be excluded. Furthermore, in our experience, peroperative glucose monitoring aids the surgeon, not only to check that all secreting tissue is removed, but also to avoid blind resection of healthy pancreatic tissue. Overall, peroperative glucose monitoring increases the rate of primary cures, while reducing postoperative morbidity and mortality.

In conclusion, the clamp technique can be of help for the diagnosis of insulinoma and it represents, in our opinion, a model of excellent endocrine surgery.

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