



Selective Arterial Calcium Stimulation with Hepatic Venous Sampling in Patients with Recurrent Endogenous Hyperinsulinemic Hypoglycemia and Metastatic Insulinoma: Evaluation in Five Patients

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ABSTRACT

Selective arterial calcium stimulation (SACST) with hepatic venous sampling was performed in 5 patients (3 female, 2 male; age range, 53–73 y) with recurrent endogenous hyperinsulinemic hypoglycemia caused by metastatic insulinoma between January 2004 and December 2014. The biochemical results of SACST confirmed functional hepatic metastases alone ($n = 3$), peripancreatic lymph-node and hepatic metastases ($n = 1$), and occult insulinoma in the pancreatic bed ($n = 1$), thereby helping to guide management. SACST may be useful to determine the extent of functional metastatic insulinoma, particularly within the liver, and may provide clinicians with additional information to help guide the multidisciplinary management of patients with recurrent endogenous hyperinsulinemic hypoglycemia.

ABBREVIATIONS

CHA = common hepatic artery, GDA = gastroduodenal artery, LHA = left hepatic artery, RF = radiofrequency, RHA = right hepatic artery, SACST = selective arterial calcium stimulation, SMA = superior mesenteric artery

Selective arterial calcium stimulation (SACST) with hepatic venous sampling is an invasive interventional radiologic test used to localize functional, occult pancreatic insulinoma with a sensitivity of $> 90\%$ (1–3). However, the role of SACST in the evaluation of patients with recurrent endogenous hyperinsulinemic hypoglycemia following surgical management for insulinoma is unknown. Although noninvasive imaging may demonstrate hypervascular pancreatic, peripancreatic, and/or hepatic lesions, determining the

location and extent of functional insulinoma and/or additional occult tumors becomes an important consideration when determining further surgical and/or nonsurgical management (4). Here we review the utility of SACST with hepatic venous sampling for the identification of hyperfunctioning sites in patients with a history of surgically treated insulinoma and recurrent endogenous hyperinsulinemic hypoglycemia.

MATERIALS AND METHODS

After approval by the institutional review board, we conducted a Health Insurance Portability and Accountability Act-compliant retrospective review of 5 consecutive patients with recurrent endogenous hyperinsulinemic hypoglycemia caused by metastatic insulinoma who underwent SACST with hepatic venous sampling between January 2004 and December 2014.

SACST was performed as previously described (3,5). Via a transfemoral approach, a 5-F catheter was inserted into the right hepatic vein for blood sampling (or left hepatic vein if

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stimulating the left hepatic artery). Selective angiography was performed of the celiac artery, gastroduodenal artery (GDA), splenic artery, superior mesenteric artery (SMA), proper hepatic artery, left hepatic artery (LHA), right hepatic artery (RHA), and/or dorsal pancreatic artery. Following diagnostic angiography, calcium gluconate (0.025 mEq Ca^{2+} /kg) diluted to a 5-mL bolus was rapidly injected into the SMA (N = 5). A 5-F Chuang B catheter (Boston Scientific, Marlborough, Massachusetts) was used for SMA and celiac angiography. Selective stimulations were performed with various microcatheters to minimize vascular spasm and unintended alterations in arterial perfusion patterns. Five milliliters of blood was obtained from the hepatic vein before calcium injection (baseline, $t = 0$) and 20, 40, and 60 seconds afterward. Five milliliters of arterial blood was also obtained before injection of calcium gluconate from the SMA. This process was repeated with repositioning of the arterial catheter in the GDA ($n = 2$), splenic artery ($n = 3$), proper hepatic artery ($n = 1$), LHA ($n = 2$), and RHA ($n = 4$). Five minutes were allowed between arterial stimulations. Insulin concentrations were determined by the clinical laboratory (3). The relative fold increase in hepatic venous insulin concentration following calcium injection was calculated (3,6).

RESULTS

Patient 1

A 70-year-old woman with a history of an extended distal pancreatectomy and subsequent hepatic wedge resection for metastatic insulinoma presented with recurrent endogenous hyperinsulinemic hypoglycemia 20 years later. SACST was performed to determine the functionality of the peripancreatic lymph nodes and hepatic lesions seen on cross-sectional imaging. The biochemical results from SACST suggested functional peripancreatic lymph-node and hepatic metastases (Table). Given the extent of functional hepatic and extrahepatic disease, the patient was not eligible for cytoreductive surgery. At a follow-up of 8 years, the patient continued to undergo medical management with diazoxide.

Patient 2

A 53-year-old woman with a history of enucleation of a pancreatic-neck insulinoma and a subsequent distal pancreatectomy for recurrent hypoglycemia experienced a recurrence of hypoglycemic symptoms with evidence of multiple liver lesions on noninvasive imaging 4 years later. Diagnostic angiography showed multiple hypervascular liver lesions, and the biochemical results of SACST suggested functional hepatic metastases only (Table). The patient underwent multiple sessions of hepatic artery embolization and radiofrequency (RF) ablation for symptom control and eventually underwent orthotopic liver transplantation. Pathologic examination confirmed a low-grade metastatic neuroendocrine tumor that stained positive for insulin. At a follow-up of 13 years, the patient remained disease-free.

Patient 3

A 57-year-old woman with a history of a distal pancreatectomy for a nonfunctional islet-cell carcinoma of the pancreatic tail and multiple subsequent hepatic wedge resections and RF ablation treatments for liver metastases experienced hypoglycemic symptoms 16 months following the last procedure. Cross-sectional imaging showed evidence of new left hepatic lobe lesions (Fig a). Given that the patient had no previous hypoglycemia with known metastatic islet-cell carcinoma, it was hypothesized that her islet-cell tumor had developed the ability to produce insulin. The biochemical results of SACST suggested functional hepatic metastases in the left hepatic lobe but not the right hepatic lobe or remaining pancreas (Fig b-d, Table). The patient underwent combined left hepatectomy followed by wedge resection of a small segment VIII lesion and intraoperative RF ablation of two small right-lobe lesions seen on intraoperative ultrasonography (US). Pathologic examination confirmed eight islet-cell tumors in the left hepatic lobe, which now stained positive for insulin, and a necrotic nodule from the right hepatic lobe. Subsequently, recurrent hypoglycemia developed within a few months. Over the 7-year follow-up period, the patient has been managed with hepatic locoregional therapies and various cytotoxic and molecular-targeted agents for symptom control at an outside institution.

Patient 4

A 73-year-old man with a history of a spleen-preserving limited distal pancreatectomy for insulinoma of the pancreatic tail experienced recurrent symptoms 3 years after the operation and no evidence of disease on noninvasive imaging. The biochemical results of SACST suggested an occult lesion to the remaining pancreatic body or tail (Table). The patient underwent a distal pancreatectomy with peripancreatic lymphadenectomy. On pathologic examination, there were no pancreatic lesions identified; only chronic pancreatitis. However, 4 of 8 peripancreatic lymph nodes were positive for metastatic neuroendocrine carcinoma, staining positive for insulin. At 4-year follow-up, the patient had no recurrent hypoglycemia symptoms.

Patient 5

A 75-year-old man with a history of a pancreatoduodenectomy for an insulinoma of the head of the pancreas experienced recurrent fasting hypoglycemia 19 years after the initial operation with evidence of endogenous hyperinsulinemic hypoglycemia and no evidence of recurrent tumor on computed tomography (CT) and US. Biochemical results of SACST suggested bilobar hepatic metastases with no evidence of residual pancreatic insulinoma (Table). A subsequent liver magnetic resonance imaging study confirmed the presence of multiple bilobar hepatic metastases and potential extrahepatic spread. Given these findings, surgical intervention was deferred. The patient underwent management with dietary

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