Published in final edited form as:

Surgery. 2015 July ; 158(1): 162–172. doi:10.1016/j.surg.2015.03.004.

Impact of variant pancreatic arterial anatomy and overlap in regional perfusion on the interpretation of selective arterial calcium stimulation (SACST) with hepatic venous sampling for preoperative localization of occult insulinoma

Scott M. Thompson, B.A., Adrian Vella, M.D., F. John Service, M.D., Ph.D., Clive S. Grant, M.D., Geoffrey B. Thompson, M.D., and James C. Andrews, M.D

College of Medicine, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA

Abstract

Background—To determine the impact of variant pancreatic arterial anatomy and overlap in regional perfusion on the interpretation of selective arterial calcium stimulation (SACST) with hepatic venous sampling for preoperative localization of occult insulinoma.

Methods—An IRB-approved retrospective review was undertaken of 42 patients with surgically confirmed, occult insulinoma who underwent SACST from 1/1996 to 3/2014. Location of the insulinoma was initially predicted based on the biochemical results of SACST alone according to Doppman's criteria. Pancreatic arteriograms were reviewed blinded to the biochemical results and the regional perfusion of each artery assessed. The anatomic and perfusion data were combined with the biochemical results to make a second prediction and compared to the surgical findings.

Results—The biochemical results were positive in one, two and three arterial distributions in 73.8%, 21.4% and 4.8% of patients, respectively. The celiac trunk and SMA anatomy were aberrant in 38.1% and 35.7% of patients, respectively. Clinically significant variations included dorsal pancreatic artery (DPA) replaced to SMA (21.4%) and celiac stenosis (4.8%). Significant variation and overlap in regional pancreatic perfusion was observed, particularly for the SMA. Sensitivity for insulinoma localization was 54.8% (diagnostic arteriography), 73.8% (biochemical data), 88.1% (biochemical, anatomic, perfusion data) and 92.8% (arteriographic, biochemical, anatomic, perfusion data).

Conclusion—Careful review of the pancreatic arterial anatomy and regional perfusion is critical for correct interpretation of the biochemical results of SACST and improves the sensitivity of localization for occult insulinoma, particularly in the presence of pancreatic arterial variants or overlap in regional perfusion.

© 2015 Published by Mosby, Inc.

Corresponding Author: Scott M. Thompson, Medical Scientist Training Program, College of Medicine, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA, Fax: (507) 255-7872, Phone: (507) 250-3902, thompson.scott@mayo.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

Selective intraarterial calcium stimulation with hepatic venous sampling (SACST) is an interventional radiologic technique used preoperatively to regionalize insulinomas in patients with biochemical evidence of endogenous hyperinsulinism and negative or inconclusive cross-sectional imaging i.e. occult insulinoma.^{1, 2} The technique is based upon the observation that supra-physiologic concentrations of calcium differentially stimulate beta-cells within insulinomas to secrete insulin in contrast to normal pancreatic beta-cells.³⁻⁵ The original SACST criteria described by Doppman required at least a two-fold rise in hepatic venous insulin concentration over baseline for a positive localization. According to Doppman, a positive response after injection of the superior mesenteric artery (SMA) localized the insulinoma to the inferior pancreatic head and uncinate process. A positive result after gastroduodenal artery (GDA) injection localized the insulinoma to the superior pancreatic head or neck and a positive response to the splenic artery (SPA) injection to the pancreatic body and tail.¹ The localization information helps to guide the endocrine surgeon as to the type and extent of surgical resection.⁶

Previous studies have identified significant variation in pancreatic arterial anatomy.⁷⁻¹¹ Moreover, a recent study evaluating the vascular supply to regions of the pancreas using computed tomography (CT) during arteriography revealed significant variation and overlap in pancreatic regional perfusion by the major pancreatic arteries.¹² Doppman's original criteria for interpreting the biochemical results of SACST do not take into account the impact of variant pancreatic arterial anatomy and regional perfusion for localization of occult insulinoma. Therefore, the aim of the present study was to evaluate the impact of variant pancreatic arterial anatomy and regional perfusion on the interpretation of SACST for preoperative localization of occult insulinoma.

Materials and Methods

After approval by the Institutional Review Board, we conducted a HIPAA-compliant, retrospective review using the comprehensive electronic medical record system of all patients with surgically confirmed occult insulinoma who underwent preoperative SACST in the period from January 1, 1996 to March 5, 2014. This time period was selected based on the introduction of SACST into clinical practice at our institution. Patients who did not give approval for the use of their medical record for research purposes and patients with metastatic insulinoma were excluded. Demographic, clinical, imaging, surgical and pathology data were collected.

Patient selection for SACST

The approach to management of insulinoma at our institution has been described previously.⁶ In all patients an initial effort to localize insulinoma utilizes noninvasive modalities including transabdominal ultrasound (TUS) and/or triple-phase computed tomography (CT) of the pancreas. During the study period in this paper, 46 out of 229 (20.0%) patients evaluated at our institution for insulinoma confined to the pancreas underwent SACST. SACST was performed due to negative non-invasive imaging, negative EUS, patient and/or outside endocrinology referral specifically for SACST or inconclusive

preoperative localization including 1) atypical or equivocal lesion morphology or enhancement on non-invasive imaging modalities, 2) MEN-1 patients with multiple (>1) pancreatic lesions on imaging and need to determine which lesion(s) may be functional, 3) patients with postprandial symptoms and need to confirm that lesion(s) observed by cross-sectional imaging were indeed functional and 4) patients with prior failed pancreatic exploration elsewhere and need to confirm that lesion(s) observed by cross-sectional imaging were functional.

Selective Arterial Calcium Stimulation with Hepatic Venous Sampling (SACST)

SACST was performed as an outpatient procedure as previously described.¹³ Under conscious sedation, 5Fr catheters were inserted into both the right femoral artery and vein using the Seldinger technique. Under fluoroscopic guidance, the venous catheter was positioned in the right hepatic vein for blood sampling. Standard pancreatic arteriography was performed following selective catheterization of the celiac, gastroduodenal (GDA), splenic (SPA) and superior mesenteric (SMA) arteries as well as the dorsal pancreatic artery (DPA) if necessary. Following diagnostic arteriography, calcium gluconate (0.025 mEq Ca^{2+}/kg) diluted to a five-milliliter bolus was rapidly injected into the GDA, SPA and SMA as well as the DPA in select cases. Five milliliters of blood were obtained from the right hepatic vein prior to the injection (baseline, $t=0$) and 20, 40 and 60 seconds post calcium injection. Five minutes were allowed between arterial stimulations. Five milliliters of arterial blood were also obtained prior to injection of calcium gluconate from each systemic artery. Insulin concentrations were determined by electrochemiluminescent immunoassay (Roche Diagnostic Corp., Indianapolis, IN) by the clinical laboratory.

SACST Review and Interpretation

Blinded review of SACST occurred in a step-wise manner. First, localization of the insulinoma was initially predicted by an independent observer (SMT) blinded to any patient information based on the biochemical results from SACST alone using Doppman's criteria—doubling of the hepatic insulin concentration after SMA stimulation localized the insulinoma to the uncinate process and inferior head, after GDA stimulation to the superior head and neck and after SPA stimulation to the body and tail.^{1, 13, 14} Next, the arteriograms were reviewed by an experienced interventional radiologist (JCA) blinded to the biochemical results to determine 1) the pancreatic arterial anatomy including the celiac trunk and its major branches—GDA, SPA, DPA, common hepatic artery (CHA), proper hepatic artery (PHA), left gastric artery (LGA) and right (RHA) and left hepatic artery (LHA)—and the SMA; 2) the region(s) of the pancreas perfused by each vessel using surgical pancreatic anatomy criteria and 3) evidence of a tumor stain.^{15, 16} The anatomic, perfusion and biochemical data were then combined to independently predict insulinoma localization. Finally, both predictions were compared to the surgical and pathology findings. Localization by arteriography alone was defined as evidence of a tumor stain on the arteriogram independent of the biochemical results. Localization by anatomic and regional perfusion was defined as an interpretation of the biochemical results in the context of the anatomical perfusion of the pancreas by each vessel.

Data Management and Statistical Methods

Study data were collected and managed using REDCap electronic data capture tools.¹⁷ Data were subsequently analyzed using JMP 8.0 (Raleigh, NC). Descriptive statistics were generated.

Results

Patient Data

Fifty patients with biochemical confirmation of insulinoma requiring blood glucose of < 50 mg/dl, concomitant insulin level of > 3-6 μ IU/ml depending on type of assay to verify measurable insulin was present during symptomatic hypoglycemia, elevated c-peptide level of 1.2 ng/ml, negative sulfonylurea screen, negative or inconclusive non-invasive preoperative localization studies and surgically confirmed occult insulinoma were identified who underwent SACST during the time period from January 1, 1996 to March 5, 2014.⁶ Four patients were excluded because they did not give consent for the use of their medical record for research purposes and four patients were excluded due to final diagnosis of metastatic insulinoma. The final review included forty-two patients. Demographic, clinical, surgical and pathologic data are summarized in Table 1 and Table 2. There were no post-operative deaths and no recurrence of hypoglycemic symptoms.

Selective Arterial Calcium Stimulation (SACST)

Forty-two patients underwent forty-four SACST procedures. The test was repeated in two patients due to initial uninterpretable data (see **Repeat SACST section**). There were no immediate, short-term or long-term complications due to the SACST procedure. In particular, there were no hypoglycemic episodes following calcium injection during SACST.

Biochemical Data: Hepatic Venous Insulin Concentration—The median maximal rise in insulin concentration over baseline from the dominant artery was 15.9-fold (range: 2.1 to 141.7-fold). The percent biochemically positive arterial distributions by vessel are summarized in Table 3.

Pancreatic Arterial Anatomy—The celiac trunk and superior mesenteric arterial anatomy were aberrant in sixteen patients (38.1%) and fifteen patients (35.7%), respectively (Table 4). Clinically significant variations included dorsal pancreatic artery (DPA) replaced to SMA (N=9; 21.4%; Figure 1A and 1B) and celiac stenosis (N=2; 4.8%) (Figure 2A).

Portal Venous Anatomy—Forty-one patients (97.6%) had patent superior mesenteric vein (SMV), splenic vein (SPV) and portal vein (PV). One patient had a partially occluded splenic vein (SPV) near the splenic hilum with numerous varices draining into left renal vein causing a porto-systemic shunt (see **Repeat SACST section**) (Figure 3).

Pancreatic Regional Perfusion by Vessel—Significant variation and overlap in regional pancreatic perfusion by the major pancreatic arteries was observed, particularly for the SMA (Table 5). For example, the SMA perfused the uncinate process alone in 31.0% of patients but the entire pancreas in 19.0% of patients.

SACST Localization—Diagnostic arteriography alone had a sensitivity of 54.8% for insulinoma localization. Incorporating pancreatic arterial anatomic and regional perfusion data with biochemical data improved sensitivity of localization over biochemical data alone from 73.8% to 88.1%. Diagnostic arteriography in combination with biochemical, pancreatic arterial anatomy and regional perfusion data improved sensitivity of localization to 92.9%. There were two patients in whom the biochemical data from SACST were positive but non-localizing and one patient in whom the biochemical results were negative and failed to demonstrate a two-fold increase in hepatic venous insulin concentration in any arterial distribution.

Repeat SACST—Two of forty-four SACST procedures produced initial uninterpretable biochemical data. In the first patient, hepatic venous insulin levels were unchanged following calcium stimulation in all arteries. Diagnostic arteriography identified a partial splenic vein occlusion in the splenic hilum with drainage into the left renal vein (Figure 3A). Systemic arterial insulin levels were higher than the hepatic venous insulin levels suggesting porto-systemic shunting through the splenic hilar collaterals. Repeat splenic artery stimulation with sampling from the left renal vein identified a 11 to 18-fold increase in insulin levels, localizing the adenoma to the pancreatic tail, later confirmed at surgical exploration (Figure 3B and 3C). In the second patient, the baseline systemic arterial insulin value prior to the SMA injection and the hepatic venous insulin concentration for the SMA stimulation at time 0 (SMA was the first artery stimulated) were elevated relative to other samples. As we were unable to explain these data, the study was repeated. The second study was performed with stimulation of the GDA, SPA and followed by stimulation in the SMA. This repeat study was positive only with the SMA stimulation, localizing the adenoma to the uncinate process – a finding confirmed at surgery.

Comparison of SACST with inconclusive preoperative localization studies—19 of 42 patients (45.2%) had inconclusive non-invasive preoperative localization studies and 23 of 42 (54.8%) had negative non-invasive localization studies. SACST confirmed the preoperative localization study and correctly localized the insulinoma in 16 of 19 patients (78.9%) with initial inconclusive non-invasive localization. In 3 of 19 patients, SACST correctly localized the insulinoma whereas the initial non-invasive localization studies gave a false positive localization. In a final patient with MEN-1, SACST was positive but non-localizing for the multiple lesions seen on cross-sectional imaging.

Discussion

Adult hypoglycemic disorders resulting from endogenous hyperinsulinism may be complex to evaluate and manage.⁶ Insulinoma is the most common cause of adult endogenous hyperinsulinemic hypoglycemia but is relatively uncommon with an incidence of approximately four cases per million per year.¹⁸ These tumors are most often small, solitary, benign, and intrapancreatic with an even distribution throughout the gland.^{18, 19} Although most often sporadic (90%), the tumors may be part of the multiple endocrine neoplasia type 1 (MEN-1) syndrome resulting in multiple islet cell tumors (< 10%).^{18, 20, 21} Pancreatic resection or enucleation is the treatment of choice for insulinoma with cure rates of 98% at experienced centers.¹⁹

Preoperative anatomic localization helps the surgeon plan the type and extent of surgery and may influence a decision to undertake a laparoscopic versus an open surgical approach. Almost as important is the fact that prior localization facilitates patient counseling during the process of obtaining informed consent. Although intraoperative ultrasound combined with intraoperative palpation were highly successful in the present cohort of patients with occult insulinoma, it is known that blind pancreatic exploration may fail 2% of the time.^{22, 23} As such, the practice at our institution is to preoperatively localize insulinomas in order to obviate the need for blind pancreatic exploration. Preoperative localization or regionalization is achieved with a combination of noninvasive and invasive imaging. Despite advances in noninvasive cross-sectional imaging techniques such as ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI), insulinomas less than 2.0 cm in size remain difficult to localize.²⁰ In a large series, approximately one-quarter to one-third of insulinomas were not localized with non-invasive imaging and required invasive techniques for pre-operative localization.⁶

During the study period in this paper, 70-80% of patients had successful preoperative localization with non-invasive imaging while only 20% of patients underwent SACST (46 out of 229 patients evaluated at our institution with insulinoma confined to the pancreas).⁶ Therefore, SACST is performed in a relatively small proportion of insulinoma patients. The average insulinoma size was 1.6 cm with 50% of the insulinomas less than 1.3 cm, thereby supporting previous studies that demonstrate that small insulinomas are difficult to detect non-invasively. An alternative, invasive modality to SACST for the localization of occult insulinoma is endoscopic ultrasound (EUS). EUS combined with FNA can provide anatomic, pathologic and potentially biochemical data with an insulin assay.²⁴ However, such data is dependent on identification of a lesion that can be biopsied by EUS. In general, if a solitary lesion observed at EUS has a typical morphologic appearance for an islet cell tumor, we do not advocate for biopsy since the information provided rarely changes management, exposes patients to the risk of biopsy and may delay pancreatic exploration for possible enucleation to ensure inflammation is minimized. Although precise preoperative localization is not always possible, the functional data from SACST can regionalize the insulinoma to the left or right of the SMV and help guide directed surgical exploration with intraoperative ultrasound.

Previous studies on SACST have reported sensitivities ranging from 40% to 100% in localizing occult insulinoma.^{25, 26} However, these studies have not considered the impact of variant pancreatic arterial anatomy and regional perfusion on the interpretation of SACST. In the present study, the regions of the pancreas perfused by the SMA and GDA differed to varying degrees from that which was assumed by Doppman's criteria in 69% and 74%, of patients respectively. Clinically significant variations included replacement of dorsal pancreatic artery to SMA in nine patients (21.4%; Figure 1A and 1B) and celiac stenosis in two patients (4.8%). These findings have several implications. First, in the presence of DPA replaced to SMA, the SMA may perfuse the entire pancreas (Figure 1). In the present series, the SMA perfused the entire pancreas in 19.0% of patients and the pancreatic uncinate process and head alone in less than 43% of patients (Table 5). Based on Doppman criteria, positivity in the SMA would localize an insulinoma in the uncinate process and inferior head, thereby supporting surgical exploration to the right of the SMA and an enucleation or

pancreatoduodenectomy for definitive treatment. However, blind interpretation may result in a false positive localization, thereby supporting an incorrect surgical procedure.

Second, in the presence of celiac stenosis, calcium injection into the GDA does not provide localizing information (Figure 2A). In such cases, the SMA may supply the entire pancreas via retrograde flow through the GDA and common hepatic artery further complicating localization (Figure 2A). Third, anomalous venous drainage was rare, occurring in only one patient (2.4%) in the present series. However, the presence of splenic varices resulted in a porto-systemic shunt from the splenic vein to the left renal vein and a false negative initial localization following splenic artery injection (Figure 3). Repeat SACST with injection of the splenic artery and subsequent venous sampling from the left renal vein localized the insulinoma to the distal pancreatic body and tail. As such, high baseline arterial but not venous insulin concentrations should raise concern for a porto-systemic shunt.

Given the variation in pancreatic perfusion by SMA, application of Cone-beam CT during the SMA arteriogram may help to better define the three-dimensional perfusion of the pancreas by the SMA.^{12, 27} Our predictions of regional pancreatic perfusion are based on planar arteriograms which is a limitation. Previous studies have used CT obtained with arterial contrast injection to define regional pancreatic perfusion.^{16, 27} With the newly available Cone-beam CT technology available in many angiography suites, this may be added to the SACST procedure. Moving forward, we plan to obtain Cone-beam CT studies during the SMA injection for the baseline angiographic phase of the calcium stimulation, as this is the artery with the most clinically relevant anatomic variation.

Of the forty-two patients with insulinoma confined to the pancreas, the biochemical results were positive (≥ 2.0 fold) in one arterial distribution in thirty-one patients (73.8%), two distributions in nine patients (21.4%) and three distributions in two patients (4.8%) (Table 3). However, given the significant variation and overlap in regional perfusion distributions, the order of calcium gluconate injection may be relevant, particularly for SMA/GDA (N=3) or SMA/SP (N=3) when DPA replaced to SMA, because insulinomas contained within two or more overlapping perfusion distributions may theoretically be depleted of insulin on repeat stimulation resulting in falsely lower hepatic venous insulin concentrations. Additionally, although the majority of patients demonstrated positivity in only one arterial distribution, approximately 26% of patients had multiple arterial distributions that were positive: SMA/GDA (N=3), GDA/SPA (N=4), and SMA/SPA (N=2), SMA/GDA/SPA (N=1) and SMA/GDA/DP (N=1). As such, interpretation and localization following positivity in two or more arterial distributions depends on the overlap of regional perfusion of the pancreas. For example, when positivity in both the SMA and SPA, if the SMA perfuses the entire pancreas and the SPA perfuses the body and tail, by deduction the lesion is likely in the pancreatic body or tail or at least to the left of the SMA. Alternatively, when positivity in the SMA but not the SPA, if the SMA perfuses the entire pancreas, by deduction the lesion is likely to the right of the SMA in the pancreatic uncinate process or head (Figure 2). Lastly, positivity in two non-overlapping arterial distributions raises the concern for multiple insulinomas or nesidioblastosis, particularly in patients with a history of gastric bypass surgery or MEN-1 syndrome.²⁸

In the present study, arteriography alone demonstrated a sensitivity of 54.8%, similar to previous studies.^{1, 13, 29-31} Application of Doppman's criteria for interpretation of biochemical data alone demonstrated a sensitivity of 73.8%. However, incorporation of arteriography in combination with biochemical and pancreatic arterial and regional perfusion data improved sensitivity of localization to 92.9%. These data are similar to the largest published series with SACST from the NIH reporting a range of sensitivities from 84%-94% over an 18-year period.^{1, 2, 13, 14, 32} Taken together, these findings suggest that clinically significant variation in pancreatic arterial anatomy and overlap in regional perfusion impacts the interpretation of SACST and may result in localization errors.

Overall there were two patients in whom the biochemical data from SACST were positive but non-localizing and one patient in whom the biochemical results were negative and failed to demonstrate a two-fold increase in hepatic venous insulin concentration in any arterial distribution. In one patient, there was celiac stenosis and the DPA was replaced to the SMA resulting in perfusion of the entire pancreas by the SMA. The biochemical results from SACST demonstrated a 19.6-fold increase following injection of the SMA. Given the overlap in pancreatic regional perfusion, the results of SACST were positive but non-localizing. A subsequent EUS demonstrated a 3.5cm hypoechoic mass in the pancreatic uncinate process. The patient underwent surgical exploration with both intraoperative ultrasound and palpation which confirmed a 3.4 cm tumor in the pancreatic uncinate process with successful enucleation. In the second patient with a history of MEN-1 syndrome and gastric bypass surgery, the results of SACST were positive in the SMA (3.4×), GDA (5.6×) and SPA (8.5×) but non-localizing. The GDA and SMA supplied the pancreatic uncinate process, head, neck and proximal body while the SPA supplied the entire pancreatic body and tail. Given the concern for possible nesidioblastosis, the patient underwent a distal pancreatectomy, which demonstrated 0.2cm and 0.8cm islet cell tumors staining positive for insulin at the junction between the body and tail but no evidence for nesidioblastosis. This latter case illustrates both the impact of overlapping pancreatic perfusion from multiple arterial distributions on the interpretation of SACST as well as the importance of considering both nesidioblastosis and insulinoma in patients undergoing SACST. The third patient in whom the biochemical results failed to demonstrate a two-fold increase in hepatic venous insulin concentration in any arterial distribution had standard pancreatic arterial and venous anatomy. The patient did not have elevated baseline arterial or venous hepatic insulin levels. The negative results could not be explained by technical or laboratory error. The arteriogram did suggest a small hypervascular lesion in the pancreatic body. The patient underwent surgical exploration with intraoperative ultrasound which identified a 0.7cm tumor in the pancreatic body which was enucleated and stained positive for insulin.

In recent years, noninsulinoma pancreatogenous hypoglycemic syndrome (NIPHS) developing after Roux-en-Y gastric-bypass surgery for medically complicated obesity has been associated with diffuse islet cell hyperplasia or nesidioblastosis.²⁸ NIPHS patients may be offered partial pancreatectomy to reduce their beta islet cell mass and hypoglycemic symptoms.³³ Interestingly, there were four patients with surgically confirmed insulinoma in the present cohort who developed postprandial hyperinsulinemic hypoglycemia after Roux-en-Y gastric-bypass surgery. As such, both nesidioblastosis and insulinoma need to be considered in the differential in patients with a history of Roux-en-Y gastric-bypass surgery

undergoing SACST, as illustrated by the case of the patient with a history of gastric bypass surgery and a positive but non-localizing SACST described above. Service et al. previously reported a positive response in one (N=1), two (N=3) and three (N=2) arterial distributions from SACST in six patients with surgically confirmed nesidioblastosis and a history of Roux-en-Y gastric-bypass surgery, thereby suggesting that positivity in multiple arterial distributions may be suggestive of nesidioblastosis. However, in the present study, SACST demonstrated a positive response in one (N=3) and three (N=1; MEN-1) arterial distributions in patients with a history of gastric bypass surgery and one (N=29), two (N=11) and three (N=2) arterial distributions in patients without a history of gastric bypass surgery. As such, positivity in multiple arterial distributions may not reliably differentiate between nesidioblastosis and insulinoma in patients with a history of Roux-en-Y gastric-bypass surgery, particularly if there are non-overlapping arterial distributions. In cases of multiple positive arterial distributions, the regional perfusion of each vessel needs to be carefully reviewed to identify mutually exclusive or overlapping arterial distributions while whole gland positivity is non-localizing.

In summary, clinically and angiographically significant variation in pancreatic arterial anatomy is common. The major pancreatic arteries may perfuse overlapping distributions resulting in a two-fold or greater rise in hepatic venous insulin concentration following different arterial calcium stimulations yet only one insulinoma. As such, an insulin step-up in two or more arterial distributions should not be interpreted as exclusively nesidioblastosis or diffuse beta-islet cell hyperplasia but may include insulinoma. Although diagnostic arteriography alone has a sensitivity of just over 50% for localizing insulinoma, combined with SACST it is highly sensitive (>90%) for localizing small, occult insulinoma. Table 6 summarizes potential recommendations for problems encountered with the technique and interpretation of SACST.

Careful review of the pancreatic arterial anatomy and regional perfusion is critical for correct interpretation of the biochemical results of SACST and improves the sensitivity of localization for occult insulinoma. Importantly, the results of SACST should be interpreted by a multidisciplinary team with expertise in interventional radiology, endocrinology and endocrine surgery. Finally, both nesidioblastosis and insulinoma should be considered in the differential diagnosis of patients with a history of Roux-en-Y gastric-bypass surgery and evidence of endogenous hyperinsulinism who undergo SACST.

Acknowledgments

Funding Information: This publication was supported by CCaTS Grant Number TL1 TR000137 from the National Center for Advancing Translational Science (NCATS). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. Specifically, this grant supported Mr. Thompson's M.D.-Ph.D. training program.

References

1. Doppman JL, Miller DL, Chang R, Shawker TH, Gorden P, Norton JA. Insulinomas: localization with selective intraarterial injection of calcium. *Radiology*. 1991; 178:237–41. [PubMed: 1984311]

2. Guettier JM, Kam A, Chang R, Skarulis MC, Cochran C, Alexander HR, et al. Localization of insulinomas to regions of the pancreas by intraarterial calcium stimulation: the NIH experience. *J Clin Endocrinol Metab.* 2009; 94:1074–80. [PubMed: 19190102]
3. Kaplan EL, Rubenstein AH, Evans R, Lee CH, Klementsich P. Calcium infusion: a new provocative test for insulinomas. *Ann Surg.* 1979; 190:501–7. [PubMed: 226013]
4. Kato M, Doi R, Imamura M, Okada N, Shimada Y, Hosotani R, et al. Response of human insulinoma cells to extracellular calcium is different from normal B cells. *Dig Dis Sci.* 1998; 43:2429–38. [PubMed: 9824130]
5. Wollheim CB, Sharp GW. Regulation of insulin release by calcium. *Physiol Rev.* 1981; 61:914–73. [PubMed: 6117094]
6. Placzkowski KA, Vella A, Thompson GB, Grant CS, Reading CC, Charboneau JW, et al. Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987–2007. *J Clin Endocrinol Metab.* 2009; 94:1069–73. [PubMed: 19141587]
7. Bertelli E, Di Gregorio F, Bertelli L, Mosca S. The arterial blood supply of the pancreas: a review. I. The superior pancreaticoduodenal and the anterior superior pancreaticoduodenal arteries. An anatomical and radiological study. *Surg Radiol Anat.* 1995; 17:97–106. 1–3. [PubMed: 7482159]
8. Bertelli E, Di Gregorio F, Bertelli L, Civeli L, Mosca S. The arterial blood supply of the pancreas: a review. III. The inferior pancreaticoduodenal artery. An anatomical review and a radiological study. *Surg Radiol Anat.* 1996; 18:67–74. [PubMed: 8782310]
9. Bertelli E, Di Gregorio F, Bertelli L, Civeli L, Mosca S. The arterial blood supply of the pancreas: a review. II. The posterior superior pancreaticoduodenal artery. An anatomical and radiological study. *Surg Radiol Anat.* 1996; 18:1–9. [PubMed: 8685804]
10. Bertelli E, Di Gregorio F, Bertelli L, Orazioli D, Bastianini A. The arterial blood supply of the pancreas: a review. IV. The anterior inferior and posterior pancreaticoduodenal aa., and minor sources of blood supply for the head of the pancreas. An anatomical review and radiologic study. *Surg Radiol Anat.* 1997; 19:203–12. [PubMed: 9381324]
11. Bertelli E, Di Gregorio F, Mosca S, Bastianini A. The arterial blood supply of the pancreas: a review. V. The dorsal pancreatic artery. An anatomic review and a radiologic study. *Surg Radiol Anat.* 1998; 20:445–52. [PubMed: 9932331]
12. Sakuhara Y, Kodama Y, Abo D, Hasegawa Y, Shimizu T, Omatsu T, et al. Evaluation of the vascular supply to regions of the pancreas on CT during arteriography. *Abdom Imaging.* 2008; 33:563–70. [PubMed: 18180986]
13. Doppman JL, Chang R, Fraker DL, Norton JA, Alexander HR, Miller DL, et al. Localization of insulinomas to regions of the pancreas by intra-arterial stimulation with calcium. *Ann Intern Med.* 1995; 123:269–73. [PubMed: 7611592]
14. Doppman JL, Miller DL, Chang R, Gorden P, Eastman RC, Norton JA. Intraarterial calcium stimulation test for detection of insulinomas. *World J Surg.* 1993; 17:439–43. [PubMed: 8362527]
15. Thompson, GB.; G, C.; Farley, DR. Surgical Treatment and Management of Insulinomas. In: Pollock, RE.; C, S.; Ross, MI.; Perrier, NE., editors. *Advanced Therapy in Surgical Oncology.* Vol. 1. Hamilton: BC Decker Inc; 2008. p. 423–30.
16. Delaney, CP.; Netter, FH. *Netter's surgical anatomy and approaches.* Philadelphia: Saunders; 2014. p. xviii, 653
17. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009; 42:377–81. [PubMed: 18929686]
18. Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma—incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clin Proc.* 1991; 66:711–9. [PubMed: 1677058]
19. Grant CS. Insulinoma. *Best Pract Res Clin Gastroenterol.* 2005; 19:783–98. [PubMed: 16253900]
20. Abboud B, Boujaoude J. Occult sporadic insulinoma: localization and surgical strategy. *World J Gastroenterol.* 2008; 14:657–65. [PubMed: 18205253]
21. Service FJ. Insulinoma and other islet-cell tumors. *Cancer Treat Res.* 1997; 89:335–46. [PubMed: 9204199]

22. Sweet MP, Izumisato Y, Way LW, Clark OH, Masharani U, Duh QY. Laparoscopic enucleation of insulinomas. *Arch Surg*. 2007; 142:1202–4. discussion 5. [PubMed: 18086988]
23. Thompson GB, Service FJ, van Heerden JA, Carney JA, Charboneau JW, O'Brien PC, et al. Reoperative insulinomas, 1927 to 1992: an institutional experience. *Surgery*. 1993; 114:1196–204. discussion 205–6. [PubMed: 8256226]
24. Sotoudehmanesh R, Hedayat A, Shirazian N, Shahraeeni S, Ainechi S, Zeinali F, et al. Endoscopic ultrasonography (EUS) in the localization of insulinoma. *Endocrine*. 2007; 31:238–41. [PubMed: 17906369]
25. Brandle M, Pfammatter T, Spinas GA, Lehmann R, Schmid C. Assessment of selective arterial calcium stimulation and hepatic venous sampling to localize insulin-secreting tumours. *Clin Endocrinol (Oxf)*. 2001; 55:357–62. [PubMed: 11589679]
26. Wong M, Isa SH, Zahiah M, Azmi KN. Intraoperative ultrasound with palpation is still superior to intra-arterial calcium stimulation test in localising insulinoma. *World J Surg*. 2007; 31:586–92. [PubMed: 17322973]
27. Tanaka T, Sakaguchi H, Anai H, Yamamoto K, Morimoto K, Nishiofuku H, et al. Catheter position for adequate intra-arterial chemotherapy for advanced pancreatic cancer: evaluation with CT during arterial injection of contrast material. *J Vasc Interv Radiol*. 2004; 15:1089–97. [PubMed: 15466795]
28. Service GJ, Thompson GB, Service FJ, Andrews JC, Collazo-Clavell ML, Lloyd RV. Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. *N Engl J Med*. 2005; 353:249–54. [PubMed: 16034010]
29. Geoghegan JG, Jackson JE, Lewis MP, Owen ER, Bloom SR, Lynn JA, et al. Localization and surgical management of insulinoma. *Br J Surg*. 1994; 81:1025–8. [PubMed: 7922054]
30. Gunther RW, Klose KJ, Ruckert K, Beyer J, Kuhn FP, Klotter HJ. Localization of small islet-cell tumors. Preoperative and intraoperative ultrasound, computed tomography, arteriography, digital subtraction angiography, and pancreatic venous sampling. *Gastrointest Radiol*. 1985; 10:145–52. [PubMed: 2987076]
31. Aoki T, Sakon M, Ohzato H, Kishimoto S, Oshima S, Yamada T, et al. Evaluation of preoperative and intraoperative arterial stimulation and venous sampling for diagnosis and surgical resection of insulinoma. *Surgery*. 1999; 126:968–73. [PubMed: 10568199]
32. Brown CK, Bartlett DL, Doppman JL, Gorden P, Libutti SK, Fraker DL, et al. Intraarterial calcium stimulation and intraoperative ultrasonography in the localization and resection of insulinomas. *Surgery*. 1997; 122:1189–93. discussion 93–4. [PubMed: 9426437]
33. Vanderveen KA, Grant CS, Thompson GB, Farley DR, Richards ML, Vella A, et al. Outcomes and quality of life after partial pancreatectomy for noninsulinoma pancreatogenous hypoglycemia from diffuse islet cell disease. *Surgery*. 2010; 148:1237–45. discussion 45–6. [PubMed: 21134557]

Figure 1. SACST in a patient with DPA arising from SMA. (A) Selective SMA arteriogram demonstrates DPA replaced to the SMA (white arrowhead) with perfusion of the entire pancreas and filling of the transverse pancreatic artery off the DPA (white arrow). Note that with forced injection there is reflux through the GDA (white asterisk). (B) Selective DPA arteriogram demonstrates filling of the transverse pancreatic artery (white arrow) and a hypervascular mass in the pancreatic body (white arrowhead). Note venous catheter in the right hepatic vein (white asterisk). (C) Graph of biochemical data from SACST demonstrates a 53-fold rise in hepatic venous insulin concentrations over baseline sixty seconds after calcium injection into the SMA. No rise after injection of GDA or SPA was observed. Surgical exploration confirmed a 1.5 cm tumor staining positive for insulin at the junction of the pancreatic body and tail.

Figure 2. SACST in a patient with celiac stenosis. **(A)** Selective SMA arteriogram demonstrates filling of the entire SMA and celiac artery distributions due to celiac stenosis. **(B)** Selective SPA arteriogram demonstrates perfusion of the pancreatic body and tail to the left of the SMA (white arrowheads). Selective diagnostic angiography of the SMA, GDA or SPA did not identify any hypervascular lesions within the pancreas. **(C)** Graph of biochemical data from SACST demonstrates a 20-fold rise in hepatic venous insulin concentration over baseline sixty seconds after calcium injection into the SMA but no rise after injection of the SPA. The GDA was not injected with calcium due to celiac stenosis and retrograde flow via the SMA. Surgery confirmed a 3.4 cm tumor staining positive for insulin in the pancreatic uncinate process.

Figure 3.

SACST in the presence of a porto-systemic shunt from splenic vein to left renal vein. **(A)** Portal venous phase following selective SPA diagnostic arteriogram demonstrates multiple splenic hilar varices draining into the left renal vein (white arrowheads). Biochemical data from SACST demonstrated no rise in hepatic venous insulin concentration following calcium stimulation of the SMA, GDA or SPA. **(B)** Selective SPA arteriogram during repeat SACST with venous sampling from the left renal vein (white arrowhead). Selective diagnostic angiography of the SMA, GDA or SPA did not identify any hypervascular lesions within the pancreas. **(C)** Graph of biochemical data from SACST demonstrates an 11 to 18-fold rise in venous insulin concentrations over baseline beginning 20 seconds after calcium injection into the SPA with venous sampling from the left renal vein (SPA/LRV) but no rise in venous insulin concentrations after calcium injection into the SPA or DPA with venous sampling from the right hepatic vein (SPA/RHV, DPA/RHV). Surgery confirmed a 1.3 cm tumor staining positive for insulin in the distal pancreatic tail at the splenic hilum surrounded by numerous splenic varices.

Table 1
Demographic and clinical data of 42 patients who underwent SACST for pre-operative localization of occult insulinoma

Age (yr) (median, range)	48.6 (18.7-76.7)
Gender	N (%)
Female	27 (64.3)
Male	15 (35.7)
Insulinoma Etiology	
Sporadic	38 (90.5)
MEN-1	4 (9.5)
Prior Gastric Bypass	4 (9.5)
Symptom Occurrence	
Fasting	28 (66.7)
Postprandial *	9 (21.4)
Both †	5 (11.9)

* History of gastric bypass surgery (N=3)

† History of gastric bypass surgery (N=1)

Table 2
Surgical and pathology data of 42 patients who underwent SACST for pre-operative localization of occult insulinoma

Surgical Management	N (%)
Enucleation	23 (54.8)
Distal Pancreatectomy	18 (42.9)
Pancreaticoduodenectomy	1 (2.3)
Intraoperative Ultrasound	34 (81.0)
Correct Localization	34 (100.0)
Intraoperative Palpation	38 (90.5)
Correct Localization	34 (89.5)
Pathology	
Total Number of Insulinomas	50
Size, largest diameter (mean±SD)	1.6 ± 0.9 cm
Insulinoma Distribution	N (%)
Sporadic	38
1 tumor	36 (94.6)
2 tumors	1 (2.7)
3 tumors	1 (2.7)
MEN-1	4
1 tumor	1 (25.0)
2 tumor	2 (50.0)
4 tumors	1 (25.0)

Table 3

Percent biochemically positive (≥ 2.0 fold increase) arterial distribution(s) by vessel from SACST.

+ Vessel(s)	N (%)
1 Distribution	31 (73.8)
SMA	8 (19.1)
GDA	3 (7.1)
SPA	20 (47.6)
2 Distributions	9 (21.4)
SMA / GDA	3 (7.1)
SMA / SPA	2 (4.8)
GDA / SPA	4 (9.5)
3 Distributions	2 (4.8)
SMA/GDA/SPA	1 (2.4)
SMA/GDA/DPA	1 (2.4)

SMA = superior mesenteric artery; **GDA** = gastroduodenal artery; **SPA** = splenic artery; **DPA** = dorsal pancreatic artery

Table 4
Variant pancreatic arterial anatomy by pancreatic angiography

Arterial Variation	N (%)
DPA replaced to SMA	9 (21.4)
DPA arising from distal celiac trunk	2 (4.8)
DPA arising from CHA	1 (2.4)
Celiac artery stenosis	2 (4.8)
CHA replaced to SMA	2 (4.8)
LHA replaced to LGA	7 (16.7)
LHA replaced to CHA	1 (2.4)
RHA replaced to celiac trunk	4 (9.5)
RHA replaced to SMA	3 (7.1)

DPA=Dorsal pancreatic artery; **SMA** = superior mesenteric artery; **GDA** = gastroduodenal artery; **SPA** = splenic artery; **CHA**=common hepatic artery; **LHA** = left hepatic artery; **RHA**= right hepatic artery; **LGA**= left gastric artery

Table 5

Variation in regional pancreatic perfusion by selective arteriography of the SMA, GDA, SPA and DPA.

Pancreatic Region	SMA (N=42)	GDA (N=42)	SPA (N=42)	DPA (N=11)
Whole Pancreas	8 (19.0)*	1 (2.4)	-	1 (9.1)
UN	13 (31.0)	-	-	-
HD	-	3 (7.1)	-	-
NK	-	-	-	1 (9.1)
BD	-	-	1 (2.4)	-
T	-	-	2 (4.8)	-
UN + iHD	3 (7.1)	-	-	-
UN + HD	2 (4.8)	7 (16.6)	-	-
UN + HD + NK	2 (4.8)	14 (33.3)	-	-
UN + HD + BD	-	-	-	1 (9.1)
UN + NK	6 (14.2)	-	-	2 (18.1)
UN + NK + pBD	3 (7.1)	-	-	1 (9.1)
UN + NK + BD	-	-	-	1 (9.1)
UN + HD + NK + pBD	1 (2.4)	1 (2.4)	-	-
UN + iHD + NK	1 (2.4)	-	-	-
UN + iHD + NK + BD + T	1 (2.4)	-	-	1 (9.1)
UN + BD + T	-	-	-	1 (9.1)
UN + pBD	1 (2.4)	-	-	-
UN + HD + NK + pBD	1 (2.4)	-	-	-
HD + NK	-	11 (26.2)	-	-
HD + NK + pBD	-	2 (4.8)	-	-
sHD + NK + pBD	-	1 (2.4)	-	-
HD + NK + BD + T	-	1 (2.4)	-	-
NK + BD + T	-	-	3 (7.1)	1 (9.1)
NK + pBD	-	-	-	1 (9.1)
BD + T	-	-	34 (80.9)	-
dBD + T	-	-	2 (4.8)	-
No pancreatic perfusion	-	1 (2.4)	-	-

SMA = superior mesenteric artery; **GDA**= gastroduodenal artery; **SPA**= splenic artery; **DPA**= dorsal pancreatic artery; **UN** = Uncinate process; **HD** = pancreatic head; **NK** = pancreatic neck; **BD** = pancreatic body; **T** = pancreatic tail; **iHD** = inferior pancreatic head; **sHD** = superior pancreatic head; **pBD** = proximal pancreatic body; **dBD** = distal pancreatic body.

* Severe celiac stenosis with retrograde flow through SMA to entire pancreas and liver (N=1)

Table 6
SACST interpretation issues and recommendations

SACST Issue	Recommendation
<ul style="list-style-type: none"> • Variant: DPA replaced to SMA • Problem: SMA may perfuse the entire pancreas 	<ul style="list-style-type: none"> • Do not blindly interpret positive SMA as a lesion in the inferior pancreatic head or uncinata • Attempt to perform selective arteriograms and calcium injection of both the SMA and DPA to better define regional perfusion of each vessel • Consider cone-beam CT during selective injections of the SMA and DPA to better define the three- dimensional perfusion of the pancreas by each vessel • The combined anatomic, perfusion and biochemical data may help regionalize the lesion to the left or right of the SMV based on deduction of vessel perfusion
<ul style="list-style-type: none"> • Variant: Celiac artery stenosis • Problem: Calcium injection into the GDA does not provide localizing information due to retrograde flow 	<ul style="list-style-type: none"> • Do not inject GDA with calcium • Attempt to selectively catheterize more distal pancreatic vessels such as the dorsal pancreatic artery • Consider endoscopic ultrasound if not already performed.
<ul style="list-style-type: none"> • Variant: Splenic varices • Problem: Porto-systemic shunt from the splenic vein to adjacent veins (i.e. left renal vein) may result in a false negative localization following injection of the splenic artery followed by hepatic venous sampling 	<ul style="list-style-type: none"> • Carefully review the pancreatic venous drainage prior to calcium injection to assess for patent portal venous system and evidence of varices. • Perform venous sampling from both the hepatic vein and systemic vein (i.e. left renal vein). • A high baseline arterial but not venous insulin concentration should raise concern for a porto-systemic shunt or exogenous insulin administration
<ul style="list-style-type: none"> • Problem: Insulin step-up in two or more arterial distributions due to overlapping regional pancreatic perfusion by the major pancreatic vessels 	<ul style="list-style-type: none"> • Do not interpret results as exclusively nesidioblastosis but may also include insulinoma, especially in patients with a history of gastric-bypass surgery • Consider both nesidioblastosis and insulinoma in the differential diagnosis of patients with a history of Roux-en-Y gastric-bypass surgery and evidence of endogenous hyperinsulinism who undergo SACST.
<ul style="list-style-type: none"> • Problem: Positive but non-localizing SACST 	<ul style="list-style-type: none"> • Consider EUS if not already performed • Consider repeat SACST
<ul style="list-style-type: none"> • Problem: Uninterpretable biochemical data 	<ul style="list-style-type: none"> • Check with lab to verify the correct labeling of samples • Request repeat analysis by the laboratory, if possible • Review arteriogram for evidence of possible porto- systemic shunt • Repeat SACST or consider EUS if not already performed

DPA=dorsal pancreatic artery; SMA = superior mesenteric artery; GDA = gastroduodenal artery; SMV = superior mesenteric vein; EUS = endoscopic ultrasound