ISSN 2472-1972

Selective Arterial Calcium Stimulation With Hepatic Venous Sampling in Immune-Mediated Hypoglycemia

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The purpose of the current study was to review the biochemical results of selective arterial calcium stimulation (SACST) with hepatic venous sampling in patients with immune-mediated hyperinsulinemic hypoglycemia. A retrospective review was undertaken of four patients with immune-mediated hyperinsulinemic hypoglycemia who underwent SACST with hepatic venous sampling from January 1996 to March 2014. Baseline systemic arterial and hepatic venous insulin concentrations (uIU/mL) were compared, and the absolute and relative-fold increase in hepatic venous insulin concentration after calcium stimulation was calculated. Baseline systemic arterial and hepatic venous insulin concentrations were elevated in all vessels sampled (range, 95 to 1704 uIU/mL), and there was no increase in the absolute or relative (1.0- to 1.3-fold) hepatic venous insulin concentration after calcium injection into any vessel. These data suggest that there are distinct biochemical responses to SACST in patients with immune-mediated hyperinsulinemic hypoglycemia compared with patients with endogenous, pancreatic-mediated hypoglycemia, such as insulinoma or nesidioblastosis.

Freeform/Key Words: hyperinsulinemic hypoglycemia, immune-mediated hypoglycemia, SACST, hepatic venous sampling

Selective arterial calcium stimulation (SACST) with hepatic venous sampling is an invasive interventional radiologic technique developed for preoperative localization of occult insulinoma with a sensitivity >90% in multiple studies [1–3]. The SACST technique is based on the observation that exogenous intra-arterial calcium differentially stimulates the release of insulin from pathologic pancreatic β-cells but not normal β-cells [4]. The original SACST criteria described by Doppman required at least a twofold rise in hepatic venous insulin concentration over baseline for positive insulinoma localization [2, 5].

More recently, it has been shown that the biochemical results of SACST can differentiate occult insulinoma from diffuse nesidioblastosis with high specificity in patients with endogenous or pancreatic-mediated hyperinsulinemic hypoglycemia and negative or inconclusive non-invasive localization studies [6]. In this study, patients with occult insulinoma had significantly higher elevations in maximum and relative hepatic venous insulin concentration after calcium injection compared with patients with diffuse nesidioblastosis [6]. As such, these data not only suggest that distinct pancreatic mechanisms of endogenous hyperinsulinemic hypoglycemia differentially respond to exogenous calcium but also that the twofold insulin gradient proposed

Abbreviations: GDA, gastroduodenal artery; mHVI, maximum hepatic venous insulin concentration; rHVI, relative fold increase in hepatic venous insulin concentration; SACST, selective arterial calcium stimulation; SMA, superior mesenteric artery; SPA, splenic artery.

Received 22 March 2017
Accepted 1 May 2017
First Published Online 4 May 2017

by Doppman may be too low for occult insulinoma diagnosis and localization. Accordingly, one of the main limitations of SACST is that, due to its invasive nature, the biochemical response of the pancreas to intra-arterial calcium in healthy normal control subjects has not been defined.

Immune-mediated hypoglycemia or insulin autoimmune syndrome is very rare and is associated with the presence of elevated levels of anti-insulin antibodies against endogenous insulin as well as high concentrations of β-cell polypeptides [7, 8]. Although the pathophysiologic mechanism for immune-mediated hypoglycemia is not completely understood, studies suggest that the antibodies sequester insulin and then release it unpredictably, thereby resulting in hypoglycemia [9]. Over a 19-year period at our institution, four patients underwent SACST as part of a work-up for hyperinsulinemic hypoglycemia, which was subsequently attributed to immune-mediated hypoglycemia. Given that these patients did not have underlying pancreatic pathology as a cause of their hypoglycemia, we sought to review the biochemical results of SACST with hepatic venous sampling in patients with immune-mediated hyperinsulinemic hypoglycemia.

1. Materials and Methods

After the study was approved by the Institutional Review Board, we conducted a HIPAA-compliant, retrospective review using the comprehensive electronic medical record to identify four patients with hyperinsulinemic hypoglycemia and negative noninvasive imaging who underwent SACST with hepatic venous sampling from January 1996 to March 2014 and who were subsequently diagnosed with immune-mediated hypoglycemia based on detection of anti-human insulin autoantibodies in the serum. Clinical, laboratory, and imaging data were collected.

A. SACST With Hepatic Venous Sampling

SACST was performed as an outpatient procedure by a single interventional radiologist using the same SACST protocol throughout the study period as previously described [3, 5]. With the patient 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 after selective catheterization of the celiac, gastroduodenal (GDA), splenic (SPA), and superior mesenteric (SMA) arteries as well as the dorsal pancreatic artery if necessary. After diagnostic arteriography, calcium gluconate (0.025 mEq Ca^{2+}/kg) diluted to a 5-mL bolus was rapidly injected into the GDA, SPA, and SMA. Five milliliters of blood were obtained from the right hepatic vein before the injection (baseline, t = 0) and 20, 40, and 60 seconds after calcium injection. Five minutes were allowed between arterial stimulations. Five milliliters of arterial blood were also obtained before injection of calcium gluconate from each systemic artery. Insulin concentrations were determined by the clinical laboratory as previously described [3, 6]. The maximum hepatic venous insulin concentration (mHVI; μIU/mL), defined as the highest absolute hepatic venous insulin concentration after calcium injection to the dominant artery, was calculated. The relative fold increase in hepatic venous insulin concentration (rHVI), defined as the fold increase in hepatic venous insulin concentration over baseline (t = 20, 40, or 60 divided by baseline, t = 0) after calcium injection to the dominant artery, was calculated. Baseline systemic arterial and hepatic venous insulin concentrations (uIU/mL) and the mHVI and rHVI values after calcium stimulation were compared.

2. Results

A. Clinical

Three female subjects and one male subject ranging in age from 45 to 80 years underwent SACST with hepatic venous sampling and were later diagnosed with immune-mediated

hypoglycemia based on detection of anti-human insulin antibodies in the serum (Table 1). All four patients were racially categorized as white. None of the patients had a history of diabetes, pancreatic surgery, or upper gastrointestinal tract surgery.

B. Biochemical Results of SACST With Hepatic Venous Sampling

Baseline systemic arterial and hepatic venous insulin concentrations were elevated in all vessels sampled (range, 95 to 1704 uIU/mL), and there was no increase in the absolute or relative hepatic venous insulin concentration (rHVI) after calcium injection into any vessel (1.0– to 1.3-fold) (Table 1). There were no hypervascular lesions identified in the pancreas during selective pancreatic angiography.

3. Discussion

The present data provide insight into the variation of biochemical responses to the SACST procedure in patients with immune-mediated hypoglycemia and build upon existing SACST data from patients with endogenous hyperinsulinemic hypoglycemic disorders, including insulinoma and nesidioblastosis [3, 6]. Specifically, the SACST data in these few patients suggest that elevated baseline systemic arterial and hepatic venous insulin concentrations in all vessels without an increase in hepatic venous insulin concentration after calcium injection may suggest immune-mediated hypoglycemia (Table 2).

In contrast, previous studies have demonstrated that the biochemical responses at SACST are very different in patients with insulinoma and nesidioblastosis [3, 6] (Table 2). Patients with insulinoma demonstrated elevated baseline hepatic venous insulin concentration with marked increase in both mHVI and rHVI after intra-arterial calcium stimulation, typically in one arterial distribution. Conversely, patients with nesidioblastosis demonstrated low or physiologic baseline hepatic venous insulin concentration with a minimal increase in the mHVI and a mild increase in the rHVI after intra-arterial calcium stimulation, typically in multiple arterial distributions. Moreover, the mean mHVI was 22.0 times higher and the mean rHVI 3.9 times higher in patients with insulinoma compared with patients with nesidioblastosis. Of note, the principal difference in the utilization of SACST between

Table 1. Demographic, Laboratory, and Baseline Systemic Arterial and Pre- and Postcalcium Injection Hepatic Venous Insulin Concentration from SACST in Four Patients with Immune-Mediated Hypoglycemia

	Age/Sex			
	80 y/Female	**61 y/Male**	**45 y/Female**	**73 y/Female**
Human insulin antibody, % bound[a] (normal <3%)	85	72	>90	73
Systemic free insulin, uIU/mL (normal 1.4–14.0)	76	22	37	NA[b]
SACST biochemical data[c]				
aSMA	1605	207	95	1070
aGDA	1421	201	97	1070
aSPA	1734	214	98	1070
vSMA	1591 → 1598 (1.0×)	197 → 227 (1.2×)	92 → 95 (1.0×)	1100 → 1060 (<1.0×)
vGDA	1636 → 1778 (1.1×)	197 → 240 (1.2×)	95 → 95 (1.0×)	1050 → 1030 (<1.0×)
vSPA	1557 → 1653 (1.1×)	200 → 261 (1.3×)	99 → 101 (1.0×)	1050 → 1030 (<1.0×)

[a]Proportion of radiolabeled insulin retained by the antibody during the binding assay.
[b]Not available.
[c]SACST biochemical data are presented as the baseline systemic arterial and pre/postcalcium hepatic venous insulin concentrations and relative fold increase in hepatic venous insulin concentration (in parentheses). a, baseline arterial sample from the indicated artery; v, hepatic venous sample after injection of the indicated artery with calcium.

Table 2. Summary Patterns of Biochemical Responses to SACST for Pancreatic (Insulinoma, Nesidioblastosis) and Immune-Mediated Hypoglycemia

	Insulinoma[a]	Nesidioblastosis[a]	Immune
Baseline HVI[b]	Elevated	Low/physiologic	↑↑↑ (A = V)
mHVI[d]	↑↑↑	↑	None
rHVI[e]	↑↑↑	↑↑	None

[a]As previously reported [3, 6].
[b]Baseline hepatic venous insulin (HVI) = 1) baseline systemic arterial insulin concentration from SMA, GDA, and SPA and 2) baseline HVI concentration prior to calcium injection into the SMA, GDA, and SPA.
[c]A = V means similar systemic arterial and hepatic venous insulin concentrations.
[d]Maximum HVI (mHVI) = highest absolute HVI concentration after calcium injection.
[e]Relative fold increase in HV insulin concentration (rHVI) is the fold increase in HV insulin concentration over baseline (t = 20, 40, or 60 divided by baseline, t = 0) after calcium injection.

nesidioblastosis and insulinoma is in the regional localization in insulinoma, in contrast to nesidioblastosis. Taken together, these data further support a distinct calcium-mediated mechanism for the release of endogenous insulin from pathologic pancreatic β-cells at SACST, such as in the case of insulinoma or nesidioblastosis [2, 3, 6].

Despite these findings, all patients undergoing a workup for endogenous hyperinsulinemic hypoglycemia should be screened for immune-mediated hypoglycemia and not subjected to SACST unless the diagnosis of endogenous hyperinsulinemic hypoglycemia remains in question. At the time that the four patients in this study were being evaluated for hyperinsulinemic hypoglycemia, immune-mediated hypoglycemia was almost unheard of in non-Asian patients and was thought to be exclusively a disorder of Asian patients [9]. The four patients in this study were racially categorized as white. Consequently, SACST was performed in these patients to assess for possible pancreatic pathology, such as occult insulinoma. However, it is now recognized that immune-mediated hypoglycemia can occur in patients from diverse racial groups [7, 9]. As such, patients being evaluated at our institution are now routinely screened for insulin autoantibodies and do not undergo SACST unless other diagnoses remain on the differential for hyperinsulinemic hypoglycemia.

There are limitations to this study. This was a retrospective review with a small number of patients. Additionally, given that these patients had an underlying explanation for their hypoglycemia, the biochemical results of SACST in true healthy normal control subjects remains unknown because it would be unethical to perform SACST in healthy normal control subjects.

In conclusion, these data provide further evidence for distinct biochemical responses to SACST in patients with endogenous, pancreatic-mediated hypoglycemia such as insulinoma or nesidioblastosis when compared with patients with non–pancreatic-mediated etiologies of hypoglycemia, such as immune-mediated hypoglycemia.

Acknowledgments

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Disclosure Summary: The authors have nothing to disclose.

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