

Clinical Utility of Selective Intra-arterial Calcium-stimulated Hepatic Venous Sampling in Regionalisation of Insulinomas—The Singapore Experience

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Abstract

Introduction: To evaluate the efficacy and safety of selective intra-arterial calcium-stimulated hepatic venous sampling (ASVS) as a preoperative regionalisation modality for insulinomas. **Design and Methods:** Four patients with biochemically-proven endogenous hyperinsulinism and negative spiral computed tomographic (CT) pancreas were subjected to ASVS between October 1999 to May 2001. Results obtained from ASVS were compared with localisation studies using either magnetic resonance imaging (MRI) or endoscopic ultrasonography (EUS); and these were confirmed surgically whenever possible. **Results:** ASVS led to a definitive regionalisation in all 4 patients evaluated; the predicted location of the insulinoma matched the findings intraoperatively in all 3 patients who were operated upon. These were all proven to be insulinoma histologically. However, 1 patient showed a positive ASVS result in samples obtained from the left hepatic vein only. In the patient who was unable to undergo surgical resection due to other co-morbid factors, his ASVS findings were corroborated by localisation obtained from the MRI study. Conversely, EUS was found to give an incorrect localisation of insulinoma in 1 patient. Adverse effects were encountered in 3 patients (2 with mild hypotension and 1 with transient atrial fibrillation); however, premature termination of the procedure was not necessary in any of the patients. **Conclusion:** ASVS is accurate and reliable for regionalisation of insulinoma, especially in patients who do not have an obvious, unequivocal tumour using high quality current-generation MRI scans.

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Introduction

Insulinomas are small tumours with dimensions that seldom exceed 2.0 cm in diameter.¹ Preoperative non-invasive localisation using trans-abdominal ultrasound and conventional computed tomography (CT) detect only between 25% and 60% of insulinomas.² Among the more invasive techniques, pancreatic arteriography visualised 35% of small (<2 cm) insulinomas, while portal venous sampling localised insulinomas in 77% of cases.³

Due to the slight but significant morbidity of portal venous sampling, Doppman et al⁴ developed a technique based on stimulating the release of insulin using selective intra-arterial injections of calcium gluconate as a secretagogue^{5,6} and then measuring insulin levels in the hepatic veins (ASVS). Other more sophisticated techniques

that have been used to improve insulinoma localisation in the recent years include magnetic resonance imaging (MRI)⁷ and endoscopic ultrasonography (EUS).^{8,9}

We assess the utility of ASVS in tumour localisation in 4 consecutive subjects (between October 1999 to May 2001) with a clinical and biochemical picture consistent with insulinoma but negative spiral CT finding.

Subjects and Methods

Methods

Four patients with spontaneous hypoglycaemia and inappropriate hyperinsulinism in the face of negative sulfonylurea screen and normal finding on contrast-enhanced dual-phase spiral CT were subjected to ASVS. All patients gave written informed consent for the procedure.

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The patients also underwent either EUS using an Olympus EUM-20 echo-endoscope with 7.5/12 MHz transducer or MRI using a 1.5T scanner of the pancreas, or a combination of both. Those who subsequently underwent surgical exploration were subjected to intra-operative ultrasonography (IOUS) of the pancreas using Accuson XP10, USA 7MHz transducer. Table I shows the baseline characteristics of the patients. Results of the localisation findings using the various imaging modalities compared with ASVS are summarised in Table II.

Clinical Data

Case 1

A previously healthy 73-year-old retired nurse complained of tremulousness, palpitations, perspiration and dizziness occurring weekly for 2 years, precipitated by strenuous housework and relieved by food and sugars.

Hypoglycaemia from endogenous hyperinsulinism was

confirmed by clinical and laboratory findings after an overnight fast followed by a treadmill exercise stress test. Spiral CT of the pancreas was however normal.

EUS showed a well-defined hypoechoic lesion measuring 13 x 17 mm in the region of the head of the pancreas. MRI demonstrated a 17-mm mass with low signal on fat-suppressed T1-weighted and high signal on T2-weighted images in the uncinate process of the pancreas which enhanced with gadolinium in the late portovenous phase. ASVS was then performed which showed an insulin peak corresponding to an insulin hypersecreting lesion in the region of the uncinate process of the pancreas.

During laparotomy, a lesion measuring 15 mm was confirmed on the posterior aspect of the uncinate process of the pancreas using IOUS. The tumour was identified and enucleated with histopathological confirmation of an insulinoma. She was well and free of hypoglycaemic symptoms postoperatively.

TABLE I: PATIENT CHARACTERISTICS

	Case 1	Case 2	Case 3	Case 4
Race/Age (y)/Sex	Chinese/73/Female	Chinese/29/Male	Chinese/66/Male	Chinese/30/Female
Presentation	Dizziness, tremors, palpitations, cold sweats	Exercise-induced dystonia, confusion, weight gain	Syncope, confusion, tremors, palpitations, cold sweats, weight gain	Unsteady gait, dystonia, paraesthesia, weight gain
Duration	2 years	8 months	10 years	4 months
Plasma glucose (mmol/L)	2.2	1.9	1.2	1.9
Plasma insulin* (mU/L)	139.6	9.4	13.4	8.5
Plasma C-peptide* (µg/L)	13.7	1.9	5.0	2.5
Use of diazoxide (at any time)	Yes	No	Yes	Yes

* Factor for conversion to SI units: Insulin (pmol/L): x7.18; C-peptide (nmol/L): x0.33

TABLE II: LOCALISATION FINDINGS

	Case 1	Case 2	Case 3	Case 4
Race/Age (y)/Sex	Chinese/73/Female	Chinese/29/Male	Chinese/66/Male	Chinese/30/Female
Spiral CT	Negative	Negative	Negative	Negative
Endoscopic ultrasound	13 x 17 mm lesion in head of pancreas	7.5 x 8.7 mm lesion in the mid-body of pancreas	Not done	Not done
MRI	17-mm mass in the uncinate process	Not done	18-mm lesion in the uncinate process	12 x 9 mm lesion in the body of the pancreas
ASVS	Insulin peak regionalised to the uncinate process	Insulin peak regionalised to the body and/or tail of the pancreas	Insulin peak regionalised to the uncinate process	Insulin peak regionalised to the body of the pancreas
Intraoperative ultrasound	15-mm lesion on the posterior aspect of the uncinate process	15-mm lesion at the tip of the pancreatic tail	Patient not operated	Lesion noted in the body of the pancreas
Histopathology	Insulinoma in the uncinate process	Insulinoma at the tip of the pancreatic tail	Not available	Insulinoma in the body of the pancreas

ASVS: arterial stimulation venous sampling; CT: computed tomography; MRI: magnetic resonance imaging

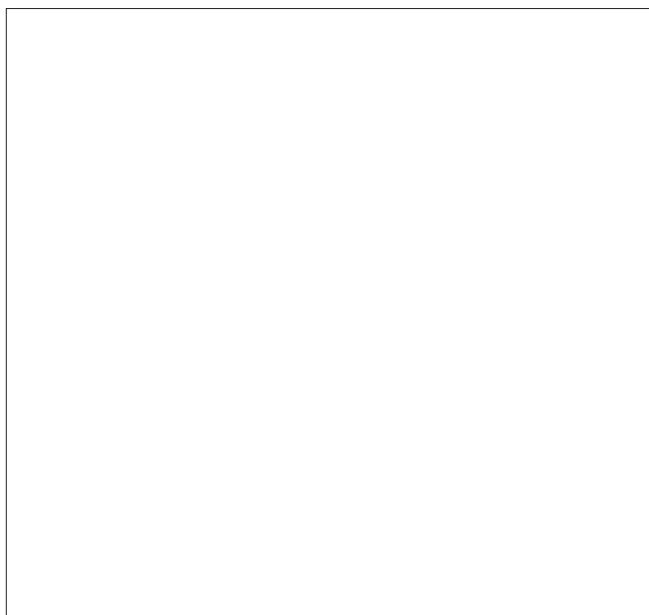


Fig. 1. MRI of Case 3 showing an 18-mm lesion in the uncinate process (arrow) on post contrast T1-weighted image.

Case 2

A 29-year-old army officer presented with frequent episodes of fatigue, impaired mental concentration and paroxysmal dystonia of his feet when running. These episodes were associated with hunger and perspiration and were relieved by food and sugary drinks, leading to a weight gain of 6 kg over 8 months.

Laboratory tests showed unprovoked hypoglycaemia with inappropriate hyperinsulinaemia, suggesting the presence of an insulinoma. Spiral CT was negative for pancreatic lesions. Findings from EUS suggested a lesion measuring 7.5 x 8.7 mm in the mid-body of the pancreas behind the splenic vein. ASVS was then performed which showed an insulin peak corresponding to an insulin-producing lesion encompassing the body and/or tail of the pancreas.

During laparotomy, a 15-mm tumour was grossly visible at the tip of the pancreatic tail adjacent to the splenic hilum. Although IOUS did not reveal any other lesions within the pancreas, a subtotal pancreatectomy was performed for fear of missing out another lesion in the mid-body of the pancreas as identified by EUS. Histopathology revealed only a solitary insulinoma at the tip of the pancreatic tail. He was cured postoperatively but required long-term surveillance for future development of islet cell insufficiency.

Case 3

A 66-year-old businessman experienced episodic tremors, diaphoresis, palpitations, irritability, confusion, diplopia

and syncopal attacks for almost a decade. The symptoms were aborted by sugar intake that resulted in a pronounced weight gain of more than 20 kg.

He was admitted to our hospital for treatment of tuberculosis of the cervical spine. When fasted for other reasons, he was discovered to have spontaneous, intractable hypoglycaemia with inappropriate endogenous hyperinsulinism. Spiral CT did not show any obvious pancreatic lesion.

MRI showed an 18-mm lesion in the uncinate process with low signal intensity on T1-weighted and high signal on T2-weighted images characteristic of an insulinoma (Fig. 1). ASVS was then performed which showed an insulin peak corresponding to an insulin-producing lesion in the region of the uncinate process.

As this patient was a high-risk surgical candidate because of tetraplegia complicating his spinal tuberculosis, he was treated with diazoxide and frequent meal intake to maintain normoglycaemia.

Case 4

A 30-year-old housewife presented with recurrent episodes of unsteady gait associated with paresthesia and mild dystonic posturing of her legs for 4 months. This occurred mostly in the morning and the typical episode would improve after breakfast. This led to excessive food intake and a weight gain of 3 kg over 4 months.

Laboratory tests showed unprovoked hypoglycaemia with inappropriate hyperinsulinaemia, suggesting the presence of an insulinoma. Spiral CT of the pancreas appeared normal. MRI with gadolinium contrast revealed a 12 x 9 mm lesion at the pancreatic body with enhancing characteristics consistent with an islet cell tumour. ASVS was subsequently performed which showed an insulin peak corresponding to an insulin-producing lesion in the body of the pancreas.

During laparotomy, a solitary lesion was found in the body of the pancreas with IOUS. The tumour was enucleated and confirmed histologically to be an insulinoma. She remained free of hypoglycaemia postoperatively.

ASVS Methodology

Patients who were on diazoxide treatment had the drug discontinued for at least 48 hours prior to the procedure. Pancreatic arteriography was performed by selectively injecting non-ionic contrast media (Omnipaque) into the superior mesenteric, gastroduodenal and splenic arteries.

After each selective arteriogram, calcium gluconate (10% v/v), diluted with saline to a volume of 5 mL, was injected into the selectively catheterised artery at a dose of 0.025 to 0.05mEq Ca^{2+} /kg body weight.

If a vascular lesion consistent with an insulinoma was seen on angiography, the vessel supplying this region was studied last to reduce the risk of hypoglycaemia occurring during the procedure.

Blood samples (5 mL) were obtained from both the right and left hepatic veins at 0, 30, 60 and 120 seconds after intra-arterial calcium infusion. Plasma was separated in a refrigerated centrifuge and stored at -20°C until insulin levels were measured.

Plasma insulin concentrations were measured by microparticle enzyme immunoassay (Abbott AXSYM, IL); whereas plasma C-peptide concentrations were measured by radioimmunoassay (DPC®, CA).

ASVS Interpretation

Plasma insulin concentrations at various time points post selective intra-arterial calcium injections were plotted for each patient according to sampling from the right and left hepatic veins, respectively. A positive response is defined as a greater than 2-fold increase in insulin levels from the baseline within 30 to 120 seconds post calcium stimulation, which is indicative of an insulinoma in that portion of the pancreas supplied by the artery studied. In this regard, the gastroduodenal and superior mesenteric arteries supply the pancreatic head and uncinate process (via the pancreaticoduodenal arcade); the splenic artery supplies the body and tail of the pancreas.

Results

All the patients showed positive insulin gradients, thus establishing an intrapancreatic source of insulin hypersecretion despite the absence of tumour blush on pancreatic angiography. In the 3 cases operated upon, each

of the tumour was found in the correct anatomical region of the pancreas as predicted by the territory of its vascular supply (Figs. 2 & 3). Notably, insulin levels start to peak between 60 and 120 seconds following intra-arterial calcium injection into an artery supplying the region of the pancreas with an insulinoma.

When comparing the results obtained from the right and left hepatic vein sampling respectively, a comparable insulin gradient was noted from either hepatic veins in 3 patients, whereas 1 patient (Case 2) showed a steep insulin gradient in samples obtained from the left hepatic vein only (Fig. 3). In this subject, the study would have negative result if ASVS were performed with the right hepatic venous sampling alone.

All our cases tolerated ASVS without any significant morbidity. Asymptomatic mild hypoglycaemia was present in 2 patients (Cases 1 and 4), but this resolved quickly at the end of the procedure. Transient sensation of warmth was the most common adverse effect, occurring in all 4 patients. Three subjects experienced nausea (Cases 2, 3 and 4) and 2 had hypotension (Cases 3 and 4) which occurred during intra-arterial calcium administration that was mild and short-lived. Only the first case suffered atrial fibrillation, but this was transient and resolved spontaneously towards the end of ASVS.

Discussion

Although IOUS and manual palpation remain the gold standard for insulinoma localisation, preoperative localisation studies are commonly performed because even experienced centres failed to detect between 5% and 10% of insulinomas intraoperatively.² The utility of ASVS in insulinoma localisation represented a significant

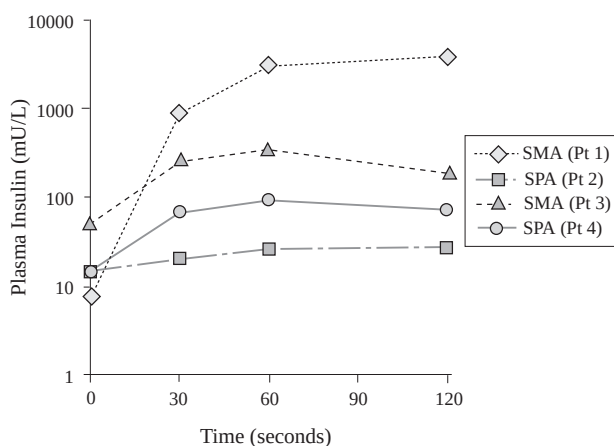


Fig. 2. Insulin levels in the right hepatic vein of the 4 patients following selective intra-arterial calcium injection into the superior mesenteric artery (SMA), gastroduodenal artery (GDA) and the splenic artery (SPA). For illustrative purposes, the artery that evoked a positive response is selected for each patient. Note that only the second patient who had a flat response in this diagram demonstrated an insulin gradient in the SPA when sampled from the left hepatic vein.

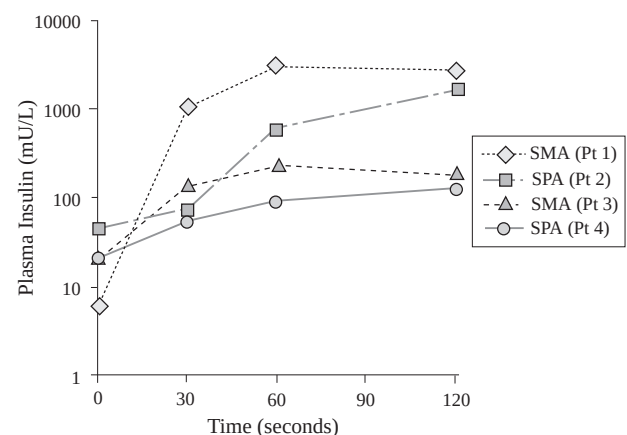


Fig. 3. Insulin levels in the left hepatic vein of the 4 patients following selective intra-arterial calcium injection into the superior mesenteric artery (SMA), gastroduodenal artery (GDA) and the splenic artery (SPA). For illustrative purposes, the artery that evoked a positive response is selected for each patient.

breakthrough in this regard with pioneering work by Doppman and co-workers, and this was soon corroborated by others.^{3,4,10-15} In the rare patient with no obvious, unequivocal insulinoma identified by non-invasive imaging modalities, ASVS may provide the only localising information and allow an informed resection, or alert the endocrinologist to the rare occurrence of a diffuse disease such as islet cell hyperplasia or adult nesidioblastosis.

Our preliminary experience supports the utility and safety of ASVS to accurately regionalise the lesion. Theoretically, the preceding angiography that accompanies ASVS can localise a highly vascular tumour by producing a “tumour blush” effect. However, this was absent in all our cases, underscoring the size-dependent nature of the “tumour blush” effect. Conversely, ASVS involves functional study for tumour regionalisation that is fully independent of the tumour size. The principle of this functional study is based on the observation that calcium stimulates acute insulin release from an insulinoma but not from normal islet β -cells.^{3,5,6}

It has been widely accepted that sampling the right hepatic vein alone is sufficient for ASVS, as many investigators had previously suggested that insulin gradients from the left hepatic vein were redundant and could be omitted. Unexpectedly, 1 of our patients (Case 2) demonstrated a flat insulin response in the right hepatic vein samples but showed a pronounced insulin gradient in the left hepatic vein samples. The differential insulin rise between the right and left hepatic veins observed in this patient remained unclear and the utility of bilateral hepatic venous sampling may deserve further evaluation.

We found a false positive insulin peak at 30 seconds from the splenic artery (SPA) stimulation in Case 1. The reason for this is unclear since the angiogram revealed no obvious collateral vessels between the SPA and the superior mesenteric artery (SMA). However, this transient smaller gradient which vanished by 120 seconds was relatively insignificant when compared with the overwhelming and sustained rise in insulin levels when calcium was injected into the superior mesenteric artery. Furthermore, the profound difference in peak insulin step-up (390 vs. 15) would suggest that the 15-fold rise from SPA stimulation was relatively insignificant. In Doppman’s series, false positive non-localising studies accounted for 3 out of 28 patients, in which SPA stimulation was falsely positive. In all 3 cases, the tumour was located in the proximal body of the pancreas.³ Such falsely-localising insulin gradients due to collaterals have also been described by Defreyne et al.¹⁶ In such instances of dual insulin peaks, a Japanese group has suggested that only the one with a maximum insulin level that exceeds 150 μ U/mL will be considered positive.¹⁷

Pertaining to anatomical imaging techniques, EUS is

limited by operator-dependency as illustrated by our patient (Case 2) in which EUS resulted in a false localisation. Both spiral CT scan and MRI are good imaging modalities for pancreatic tumours, although the reported sensitivities vary depending on the centres.^{3,5,18} Our experience showed the new generation MRI to be superior to CT in detecting small islet cell tumours. For instance, the use of short T1 inversion recovery (STIR) sequences sharpens the contrast between the insulinoma and the normal pancreas further by making the lesion appear hyperintense. While CT scan remains a cost-effective imaging tool for insulinomas, the new generation MRI scanning should be performed in subjects with negative or inconclusive CT findings.

Despite being an invasive procedure, ASVS can be performed safely in the hands of an experienced interventional radiologist. Patients should be carefully monitored during calcium administration, as minor side effects are not uncommon as demonstrated by our cases. Relative contraindications to ASVS include patients with certain conditions such as hypercalcaemic syndromes, cardiac disease (especially those on cardiac glycosides) and renal failure. Our preliminary experience shows that ASVS is helpful for pre-operative localisation of insulinomas that failed detection by non-invasive imaging modalities.

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