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Selective Intra-Arterial Calcium Stimulation Test for the localisation of insulinomas: an Australian hospital experience

Short Title: Insulinoma localisation

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Abstract

Background

Insulinomas are rare tumours of the pancreas and the commonest cause of hypoglycaemia in non-diabetic adults. They can be cured by surgery but require precise localisation. The aim of this study was to assess the utility of the selective intra-arterial calcium stimulation test (SIACST) in patients with an insulinoma to correctly localise the tumour.

Methods

Medical records of patients with a diagnosis of insulinoma or who underwent a SIACST were retrospectively reviewed. Localisation of lesions by SIACST was compared to endoscopic US (EUS) and radionuclide imaging studies and verified against findings at surgery.

Results

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Twenty four patients (mean age 58 years, 16 females, 20 with insulinoma) underwent SIACST. The SIACST correctly localised the insulinoma in 17 of 20 patients (85%). Localisation rate for CT was 55% and 75% for EUS and GLP-1 receptor scan.

Conclusions

SIACST test provided incremental diagnostic information in patients with insulinoma who had equivocal non-invasive imaging pre-operatively. This technique remains an essential diagnostic tool when a lesion is not localised by other methods.

Key words

Endocrine Surgery, Insulinoma, Selective Intra-Arterial Calcium Stimulation Test (SIACST), Endoscopic ultrasound (EUS), Localisation

Background

Insulinomas are rare tumours of the pancreas that secrete insulin autonomously and are the commonest cause of hypoglycaemia in non-diabetic adults.[1] Fasting neuroglycopaenic symptoms, Whipple's triad (neuroglycopaenic symptoms at the time of hypoglycaemia which resolve when hypoglycaemia is corrected), and a positive 72-hour fast are essential to the diagnosis.[2] The majority (>90%) of

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insulinomas are benign, solitary and small.[3] Rarely, the presentation of nesidioblastosis and islet hypertrophy mimics that of an insulinoma.[4,5] After a diagnosis of hyperinsulinaemic hypoglycaemia is made the next step in the diagnostic process is the localisation of the tumour. This is because pancreatic resection or tumour enucleation is the preferred treatment and is curative.[6] Pre-operative localisation can be challenging as insulinomas may not be visualised by non-invasive imaging modalities. Rates of localisation have been reported to be anywhere between 15 and 64%[7-10] for computed tomography (CT) and trans-abdominal ultrasound (US) and between 55-90% for magnetic resonance imaging (MRI) .[7-9] In the circumstances where non-invasive imaging is unhelpful, more sophisticated techniques such as selective intra-arterial calcium stimulation testing with hepatic venous sampling (SIACST), endoscopic ultrasound (EUS) or molecular-based imaging targeting somatostatin receptor subtype-2 ([^{68}Ga-DOTA-octreotate PET/CT or Dotatate scan) or glucagon-like peptide-1 receptors (^{68}Ga-DOTA-exendin-4 PET/CT or GLP-1R scan) are recommended.[11]

Of the above tests the SIACST, introduced into practice by Doppman, is considered the 'gold-standard'.[12] SIACST relies on the fact that calcium is a potent secretory stimulus to abnormal (but not normal) beta-cells.[13] Therefore, an intra-arterial injection of calcium into a pancreatic region of interest only results in an increase in hepatic venous insulin concentration in the presence of an abnormality. [13] A rise in hepatic vein insulin concentration following calcium injection into a single pancreatic

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artery implies the presence of an insulinoma, while an increase in more than one artery could suggest a tumour in the water-shed area supplied by two or more vessels or non-insulinoma pancreatogenous hypoglycaemia syndrome (NIPHS) secondary to nesidioblastosis or islet-hypertrophy, post-bariatric surgery hypoglycaemia or sulphonylurea use.[14] Whilst vascular anomalies are by no means a contraindication to SIACST, they can affect the stimulation aspect resulting in false negative venous sampling if the radiologist is not aware. There are only few reports of diagnostic accuracy of SIACST, or comparison of the performance of SIACST to the more contemporary techniques of EUS and molecular-based imaging.

The primary aim of this retrospective study was to assess the diagnostic accuracy of SIACST to localise the tumour in patients who had an insulinoma confirmed at surgery. Our secondary aim was to compare the usefulness of newer modalities such as EUS or functional imaging such as, , Dotatate PET/CT or GLP1R PET/CT with SIACST in a subgroup of patients.

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Method

We undertook a retrospective chart review of patients (identified from a departmental database) who had a SIACST or histological diagnosis of insulinoma at St. Vincent's Health, Melbourne, Australia, between 1/1/2000 and 31/12/2018. The indication for performing SIACST was a negative or inconclusive non-invasive imaging result or clinician preference. Several patients were referred to our institution solely for SIACST with the initial workup of hypoglycaemia and non-invasive studies performed at an external hospital. The project was approved as a quality and risk assessment study by the ethics committee and individual patient consent was not required.

Our protocol for the SIACST is modelled on that described by Doppman.[12] Briefly, a catheter is placed via the right femoral artery and the arteries supplying the pancreas are sequentially cannulated. The cannula placement sites are at the origin of the proximal splenic, gastroduodenal, superior mesenteric and inferior pancreatico-duodenal artery, the distal splenic artery (mid-point) and the common hepatic artery (past the origin of the gastroduodenal artery – to stimulate the liver only). At each site, angiography is performed to define territories of supply, vascular anomalies and possibly a tumour blush. Calcium gluconate (0.0025 mEq/kg) is then injected sequentially at each site. A second catheter in the right hepatic vein is used to collect samples for insulin at 120 seconds prior to and at 30, 60, 90 and 120 seconds post calcium gluconate injection.

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A positive SIACST was defined as a greater than two-fold increase in insulin concentration sampled from the right hepatic vein (Doppman's Criteria).[12,14] a positive insulin response following calcium injection in the gastroduodenal, superior mesenteric or inferior pancreaticoduodenal artery indicates an insulinoma in the head or uncinate process of the pancreas. A positive result in the proximal but not the distal splenic artery suggests a lesion in the body. A response in both the proximal and distal splenic runs suggests a lesion in the tail of the pancreas and a response following injection of the common hepatic artery indicates liver metastases. As the data was collected over 18 years, more than one interventional radiologist performed the SIACST. The individual experience of this procedure is therefore limited.

Results

The charts of 26 patients were available for review. Two underwent surgery without a SIACST and had insulinoma on histology. Twenty four patients had a SIACST and 23 underwent surgery with insulinoma confirmed in 20 (three had nesidioblastosis). One patient had a positive response in all vascular territories (suggestive of diffuse nesidioblastosis) and was medically managed (figure S1). Patient demographics and clinical features are summarised in Table 1 and S1.

A positive SIACST was found in 22/24 patients (92%) (figure S1). Of the 22 patients with a positive SIACST, 21 underwent surgery, and the SIACST correctly localised

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the pancreatic territory of the insulinoma at surgery in 17 (85%). In one patient (patient 17), a discordant rise in insulin following stimulation of the splenic arteries was obtained with the SIACST, however at surgery a discrete lesion in the uncinate process of the pancreas was found and confirmed as an insulinoma. Of the remaining three patients, two (patient 21&22) had a positive result following stimulation of the proximal and distal splenic arteries and underwent gradient-guided excision of the body and tail of the pancreas (with transection at the portal vein) as no tumour was localised at surgery. The third patient (patient 23) had a rise in insulin levels in multiple territories and underwent a sub-total pancreatectomy. Nesidioblastosis was confirmed in all three patients.

Two patients with a negative SIACST still proceeded to surgery given the high clinical suspicion of an insulinoma and this diagnosis was subsequently confirmed at surgery. On review of these two cases, all catheters during the SIACST were correctly positioned. In one patient (patient 16), at the time of surgery the insulinoma was found to be completely exophytic. Perhaps there was anomalous arterial supply which may explain the failure of the SIACST to localise the tumour. In the remaining case (patient 14), despite an insulinoma being found at surgery (12mm insulinoma in the head and 13mm insulinoma in the body of pancreas respectively), the post stimulation rise in insulin in the hepatic vein failed to reach the two-fold rise in insulin levels as per Doppman's criteria.[12]

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In regard to other more contemporary imaging techniques, eight of the 20 patients with insulinoma underwent EUS, two had a ^{111}Indium-octreotide scan, one had a Dotatate PET/CT scan, three had a GLP-1 receptor scan and one had both a Dotatate PET/CT and GLP-1R receptor scan (Table 1, Table S2-4). Of the eight patients who had EUS, the study was positive in six (75%). In seven of these patients the SIACST correctly localised the insulinoma. In the remaining patient in this group, the SIACST resulted in a positive insulin response but there was anatomical discordance with the surgically proven localization of the tumour as discussed above. In this case, EUS correctly identified an insulinoma in the uncinate process of the pancreas.

Dotatate PET/CT and Indium-octreotide scan failed to detect the insulinoma in all patients who underwent these studies. In contrast, GLP-1R PET/CT revealed a focal lesion compatible with an insulinoma in three of the four patients who had this scan, with surgical confirmation at the anatomical site identified by the scan in all three. As previously reported, in the other patient, the GLP-1R PET/CT scan result was more in keeping with a diagnosis of nesidioblastosis but at the time of surgery a discrete 8mm insulinoma at the junction of body and the tail of the pancreas was resected with resolution of symptoms.[15] Retrospective review of this patient's Dotatate PET/CT scan following surgery in a centre specializing in neuroendocrine tumours, suggested that the diagnosis of an insulinoma had been missed during the initial reporting of the scan. In all patients who underwent molecular-based functional imaging the SIACST correctly localised the insulinoma.

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Discussion

Insulinomas are rare beta-cell tumours of the pancreas. Although often solitary and benign, multiple tumours can be seen in 2-3% of sporadic cases and more often (10%) in the multiple endocrine neoplasia type 1 (MEN1) syndrome.[16] About 5-10% of insulinomas are malignant and <2% can be extra-pancreatic.[17] Medical management is suboptimal and surgery is curative. Laparoscopic tumour enucleation is the preferred method, but requires accurate localisation and a suitably located tumour.

Recently, hyperinsulinaemic hypoglycaemia from causes other than insulinoma is being increasingly recognised amongst adults. These include NIPHS due to nesidioblastosis and islet hypertrophy and the post-prandial hypoglycaemia syndrome seen in post-bariatric surgery patients.[18] Whilst post-prandial hypoglycaemia is more common in NIPHS a small proportion of insulinomas (6%) may also present with solely post-prandial symptoms.[19] Therefore due to considerable overlap in the clinical presentation of insulinoma and NIPHS accurate pre-operative localisation is needed for optimal surgical planning.

Amongst the non-invasive imaging modalities used in insulinoma localisation, trans-abdominal US has a sensitivity of 65%, triple-phase CT and MRI between 60-80%.[13] These are often first-line investigations due to their availability. Molecular imaging studies have reported higher sensitivities of 90% for Dotatate PET/CT and 97% for

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GLP-1R PET/CT but are not freely available.[20,21] More invasive techniques such as EUS and intra-operative US have reported sensitivities of >90%, with intra-operative US plus complete mobilization and manual palpation of the pancreas by an experienced surgeon between 92-98%.[5,13]

The SIACST is a well-established interventional radiologic technique used for pre-operative localisation of insulinoma.[12] Amongst the pre-operative localisation studies, it has the highest sensitivity of between 95-100%.[9] In approximately 60% of cases a tumour blush (Figure S2) will be seen in the angiographic phase. In cases where a tumour is not visualised at angiography the data obtained during the post-stimulation sampling phase can be used to guide the surgeon to the region of the pancreas for gradient-guided localisation and resection.[22] For example when no lesion is identified by structural imaging or angiography, SIACST may direct the initial surgical exploration to the head, body or tail and facilitate successful intra-operative palpation and ultrasound. Rarely, when a patient with severe symptoms unresponsive to medical management has a positive SIACST but no confirmatory imaging (such as in focal nesidioblastosis), a judicious proximal or distal pancreatic resection may be considered.

Advantages of the SIACST include confirming that the visualised lesion(s) detected on pre-op imaging are indeed functional. SIACST also aids preoperative planning by excluding other functioning tumours or areas of regional hyper-function. Whilst a

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post-stimulation increase in insulin in a single or adjacent vascular territory will suggest a localised insulinoma, step-ups in multiple arterial distributions would be characteristic of diffuse beta-cell hyper-function suggestive of nesidioblastosis, NIPHS, post-bariatric surgery, and sulphonylurea-induced hypoglycaemia. Thus it provides additional information if an isolated tumour is not found at operation by intra-operative US or palpation.

Successful surgery for insulinoma also requires preservation of residual pancreatic function. Accurate localisation minimises the need for more extensive surgery such as blind distal or sub-total pancreatectomy, which can lead to pancreatic insufficiency long-term. Moreover, as insulinomas can occur throughout the pancreas (most missed insulinomas at surgery are in the thicker head and uncinate portions of the pancreas) blind-distal pancreatectomy can often result in a failed procedure requiring re-operation with increased morbidity. When SIACST is not available intra-operative selective venous sampling for insulin utilising a rapid insulin assay has been described but has not been validated at our institution.[23]

Whilst some authors recommend SIACST following a failed first operation for a tumour, we routinely perform a SIACST when pre-operative imaging has failed to identify a tumour, is equivocal or discordant.[13] In our series, the SIACST had a high yield for accurately localising an insulinoma without any adverse events. In the two cases in which the test was negative, one was deemed to be negative because there

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was no rise in insulin in the hepatic vein following stimulation of target vessels and one test failed because of possible anatomically discordant aberrant blood supply to an exophytic tumour. These two tests could all be classified as "false negatives".

Most patients in our study progressed to SIACST having failed to convincingly localise an insulinoma on anatomical imaging. Therefore direct comparisons with other studies examining the usefulness of various imaging modalities for insulinoma detection are difficult to make. However, the sensitivity of SIACST to accurately localise insulinoma in the pre-operative setting has been reported at 84% and 88% in two other series.[14,24] A lower sensitivity of 63% was found in one series with a high number of false negative and SIACST discordant results.[7] Possibly this finding was due to less stringent attention to the placement of catheters during the procedure and the criteria used for the interpretation of a positive insulin gradient. In contrast, higher sensitivity of 92.8% was reported in one study that included a careful review of all arteriography, biochemical, anatomic and perfusion data and not reliance on the biochemical results of Doppman's criteria alone.[25]

In patients where traditional imaging modalities have failed to localise an insulinoma, our small series confirms that SIACST remains an important component of the diagnostic workup. In addition to providing the anatomical location, the SIACST also provides evidence of a functional lesion. While recent studies of GLP-1R based functional imaging demonstrate high accuracy for insulinoma localisation, our

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experience demonstrates potential limitations and not all benign insulinomas express the GLP-1 receptor.[21,26] Therefore, we suggest that when pre-operative non-invasive anatomic and molecular imaging studies are concordant surgery can be considered without additional localisation studies (Figure S3). However, when they are negative, equivocal or discordant or multiple lesions are encountered, we recommend that an EUS and/or SIACST test should be performed to localise the tumour prior to surgery. Although EUS has been reported to have excellent sensitivity and is particularly useful to detect tumours in the head and uncinate process of the pancreas, some insulinomas are located in regions which are more difficult to visualise by EUS.[27] Therefore, we regard EUS and SIACST as complementary studies

Our study has several limitations. It is retrospective, the numbers are small. Data on non-invasive imaging modalities was not uniformly available for all patients and was not standardised as many were referred for the SIACST alone. The modalities used for localisation have also evolved with time (for example multiphase-CT/MRI vs. dual-phase CT/MRI) impacting detection rates. In our series, both EUS and SIACST seemed to underperform compared to previous literature. A possible explanation is that EUS and SIACST are both operator dependent procedures. As the early part of this series dates to the years 2000-2010, only a small proportion of our patients underwent EUS and functional imaging. Therefore, conclusions comparing the utility of these less invasive tests with the more invasive and operator-dependent SIACST are difficult to make. Given the rarity of insulinomas, a prospective study evaluating

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specific diagnostic algorithms would require a large multi-centre collaboration.

In summary, whilst SIACT still remains the gold standard for accurate preoperative localisation of insulinomas the advancements in molecular-based imaging studies now provide additional opportunities for non-invasive localisation of tumours. With the increasing availability of these techniques it will be of interest to see if the SIACST becomes redundant in the future. In the meantime, we suggest that multi-phasic CT/MRI, molecular-based imaging, EUS and SIACT are complementary and provide incremental diagnostic information. Whilst SIACST may have limited utility when other non-invasive studies localise the tumour, it may still have a role in establishing the functionality of the tumour(s), especially when multiple lesions are visualised and a focused or minimally invasive surgical approach is preferred. Maintaining expertise with SIACST is essential as there will continue to be a small number of insulinomas that remain undetected by both structural and functional imaging techniques.

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List of Supporting Information

Table S1: Operative procedure
Table S2-4: Comparison of investigations for regionalising areas of hyper-function (S2), Comparison of investigations used for localisation insulinoma (S3) and Sensitivity of investigations for localising insulinoma (S4)
Figure S1: Patient flow chart
Figure S2: Tumour blush visualised in the angiographic phase of the SIACST
Figure S3: Diagnostic algorithm for localisation insulinoma

Table 1: Patient demographics and clinical features

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No	Age (years)	Sex	Histology	Insulinoma		SIACST		EUS	Non-Invasive Imaging Studies			
				Size	Location	Positive	Localised		CT	Dotatate scan	GLP-1 scan	Other
1	59	F	Insulinoma	11	Tail	Yes	Yes	+	-	ND	+	##
2	30	M	Insulinoma	15	Body	Yes	Yes	ND	+	ND	+	
3	82	F	Insulinoma	15	Head	Yes	Yes	ND	+	ND	ND	
4	83	F	Insulinoma	15	Head	Yes	Yes	ND	+	ND	ND	
5	33	F	Insulinoma	15	Tail	Yes	Yes	+	-	ND	ND	
6	76	F	Insulinoma	10	Tail	Yes	Yes	ND	-	ND	ND	
7	50	F	Insulinoma	20	Head	Yes	Yes	+	+	ND	ND	
8	45	M	Insulinoma	15	Tail	Yes	Yes	-	-	ND	ND	#, ##
9	48	F	Insulinoma	12	Head	Yes	Yes	ND	+	ND	ND	
10	71	F	Insulinoma	45	Tail	Yes	Yes	ND	+	ND	ND	
11	78	F	Insulinoma	15	Tail	Yes	Yes	ND	+	ND	ND	
12	60	F	Insulinoma	15	Body	Yes	Yes	ND	+	ND	ND	
13	76	M	Insulinoma	20	Head	Yes	Yes	ND	+	ND	ND	
14	71	M	Insulinoma	13	Body	No	N/A	ND	+	ND	ND	
15	41	M	Insulinoma	10	Tail	Yes	Yes	ND	-	ND	ND	#
16	81	F	Insulinoma	15	Exophytic at Neck	No	N/A	ND	+	ND	ND	##
17	45	F	Insulinoma	12	Head	Yes	No	+	-	ND	ND	
18	82	F	Insulinoma	10	Junction of body / head	Yes	Yes	+	-	-	+ [1]	
19	34	F	Insulinoma	8	Tail	Yes	Yes	+	-	ND	+	
20	47	F	Insulinoma	14	Head	Yes	Yes	-	-	-	ND	###
21	29	F	Nesidioblastosis			Yes	N/A	-	-	-	ND	##
22	24	M	Nesidioblastosis			Yes	N/A	-	-	-	-	
23	88	M	Nesidioblastosis			Yes	N/A	-	-	-	ND	
24	57	M	Medical Management			Yes	N/A	ND	-	ND	ND	

+=positive
-=negative
+[1]=diffuse uptake suggestive of nesidioblastosis
#= negative [111]Indium octreotide scan
##=negative MRI
###= positive MRI
ND = not done
NA=not available
N/A=not applicable

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