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【 ORIGINAL ARTICLE 】

Should the Selective Arterial Secretagogue Injection Test for Insulinoma Localization Be Evaluated at 60 or 120 Seconds?

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Abstract:

Objective The selective arterial secretagogue injection (SASI) test is considered indispensable for the accurate localization of insulinoma. However, the optimum timing of the post-injection evaluation is controversial, as some studies recommend 60 seconds [SASI (60 seconds)] while others support 120 seconds [SASI (120 seconds)]. The aim of this study was to determine the optimum timing for the SASI test evaluation for insulinoma localization.

Methods Thirteen patients with surgically proven insulinoma were studied retrospectively. For the SASI test, immunoreactive insulin (IRI) was determined at baseline and at 30, 60, 90, and 120 seconds after calcium gluconate injection. A two-fold or greater increase in IRI over the baseline value was considered positive. The localization abilities of SASI (60 seconds) and SASI (120 seconds) were then compared.

Results In 13 patients, a secretagogue was injected into 40 arteries supplying the pancreas. In the SASI (60 seconds) and SASI (120 seconds), the respective findings were as follows: positive predictive value, 72.2% and 68.2%; false positive rate, 25.0% and 35.0%; and rate of positivity in the head and body/tail, 38.5% and 46.2%. When the artery with the largest change was taken as the dominant artery, the localization detection sensitivity was 76.9% for SASI (60 seconds) and 92.3% for SASI (120 seconds). The sensitivity of morphological imaging techniques for localization ranged from 61.5-91.7%.

Conclusion Compared with SASI (60 seconds) or morphological imaging, the insulinoma localization ability of SASI (120 seconds) was superior. Given these findings, we believe that the IRI level should be measured at 120 seconds in the SASI test.

Key words: insulinoma, selective arterial secretagogue injection test, arterial stimulation and venous sampling, localization, optimum timing

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Introduction

Insulinoma is the most common functional pancreatic neuroendocrine neoplasm (PNEN) (1-4). Many insulinomas are small in size, with 82% less than 2.0 cm and 47% less than 1.0 cm in diameter (1). The localization ability with morphological imaging for such small lesions is insufficient; the rates range from 34.3-65% for transabdominal ultrasonography, 44.4-80% for enhanced computed tomography

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(CT), 47.4-70% for magnetic resonance imaging (MRI), and 29-60.0% for digital subtraction angiography (DSA) (1, 5, 6). Even the localization ability of endoscopic ultrasonography (EUS), ranging from 73.9-94% across various reports, is inadequate (1, 5, 6).

The selective arterial secretagogue injection (SASI) test utilizes the hormone-secretion of a functional PNEN for localization. Regardless of the tumor size, the SASI test can localize insulinomas with an excellent sensitivity of 84-100% (7-16). For the SASI test, a secretagogue is injected into the arteries supplying the pancreas (ASPs) and the hepatic arteries (HAs), and blood is sampled from a catheter placed in the hepatic vein. Based on the differential increase in the serum immunoreactive insulin (IRI) level following injection, the insulinoma location is determined (1, 3, 5-16). An artery with a two-fold or greater increase in the IRI level over the baseline value is considered positive. However, the timing of this evaluation has varied across reports. Some studies define the IRI increase at 0-60 seconds as positive, while others support an evaluation at 0-120 seconds (7-18). The optimum evaluation timing for insulinoma localization remains controversial, and there are no reports with a concrete determination yet.

In the present study, we compared the 60- and the 120-second SASI evaluations after secretagogue injection in order to ascertain the most appropriate timing for determining positive results for insulinoma localization.

Materials and Methods

Patients

From October 2000 to June 2014, we evaluated 33 patients with suspected insulinoma. Fifteen of these patients were diagnosed with insulinoma and underwent an SASI test for localization. None of the patients had concurrent multiple endocrine neoplasia type 1. In the present study, detailed information from the SASI test was available for 13 patients. The mean age of the patients was 52.5±17.7 years (range, 20-75 years), and 11 (84.6%) were women. None of the patients had concurrent multiple endocrine neoplasia type 1. In all cases, Whipple's triad was observed, and positive results were obtained in the fasting test. The mean tumor size was 13.8±5.2 mm (range, 9-27 mm). Based on the World Health Organization Classification (2010), 9 (69.2%) were graded as G1, 2 (15.4%) as G2, and 2 were undetermined. Hepatic metastasis was not found in any of the patients on morphological imaging. None of the patients had gastroduodenal or splenic artery anomalies. The hypoglycemic symptoms disappeared in all patients after surgery, with no recurrence.

SASI technique

The SASI test was performed as described by Doppman et al. (18) as summarized below. After abdominal arteriography, a catheter was selectively placed into the ASP and HA. Calcium gluconate (0.025 mEq/kg) was injected into each artery. Blood was sampled from a catheter placed in the right hepatic vein, and the IRI levels were determined at baseline and 30, 60, 90, and 120 seconds after the calcium injection. The IRI levels were measured via chemiluminescent immunoassay (ARCHITECT® Insulin; Abbott Japan, Chiba, Japan) at the central laboratory of Kyushu University Hospital. In all cases, the secretagogue was injected into the gastroduodenal artery (GDA), superior mesenteric artery (SMA), and splenic artery (SpA). In some cases, the dorsal pancreatic artery (DPA), proper hepatic artery (PHA), left hepatic artery (LHA), middle hepatic artery (MHA), and right hepatic artery (RHA) were used for additional injection. After stimulation through the hepatic arteries, blood was sampled from the corresponding hepatic veins. When the ratio of the maximum post-stimulation IRI level to the baseline level was ≥2, the result was considered positive. If multiple arteries were positive in any one case, the artery with the greatest ratio was taken as the dominant artery (10, 18). A positive result in the GDA or the SMA localized the tumor to the pancreatic head (Ph), a positive result in the SpA to the pancreatic body (Pb)/pancreatic tail (Pt), and a positive result in the DPA to the Pb. When the HAs were positive, hepatic metastasis was diagnosed (10, 18).

Morphological imaging

Morphological imaging tests were conducted preoperatively in accordance with the standard protocol at the time of the study. All patients underwent CT, MRI, and DSA; EUS was carried out in 12 patients, excluding 1. We referred to the clinical reports from the radiologist and the endoscopist for insulinoma localization. The localization abilities of these modalities were then compared with those of the SASI test.

Results

The SASI test was carried out in 13 patients with insulinoma, and the secretagogue was injected into a total of 59 arteries (40 ASP and 19 HA). Table 1 shows the maximum increase rate of the IRI level in each artery for each patient; the upper row shows the SASI test values up to 60 seconds, and the lower row shows the SASI test values up to 120 seconds. Figure shows the IRI level changes in cases 1, 7, and 11 (Figure).

SASI tests for arteries supplying the pancreas

Among the ASPs (n=40), 18 arteries (45.0%) were positive for SASI (60 seconds), and 22 (55.0%) were positive for SASI (120 seconds) (Table 1, 2). For SASI (60 seconds), cases 7 and 11 (15.4%) did not show any positive arteries, but both presented with positive arteries when the evaluation timing was extended to 120 seconds (Table 1, Figure b and c). Among the ASPs, the false-positive rate was 25.0% for SASI (60 seconds) and 35.0% for SASI (120 sec-

Table 1. Increase in IRI Level (x-fold) and Tumor Localization by SASI Tests. For Each Case, the Upper Rows: SASI (60 seconds), the Lower Rows: SASI (120 seconds).

Case No.	ASP				HA				Tumor localization	
	GDA	SMA	SpA	DPA	PHA	LHA	RHA	MHA	SASI	Surgery
1	**3.0**	**2.7**	**3.0**	-	0.6	-	-	-	-	Ph
	3.0	**2.7**	**3.0**	-	0.6	-	-	-	-	
2	1.1	**26.4**	0.9	-	1.1	-	-	-	Ph	Ph
	1.3	**26.4**	1.0	-	1.4	-	-	-	Ph	
3	**3.4**	1.1	**11.8**	-	-	1.4	1.6	1.3	Pb/Pt	Pb
	5.5	1.1	**11.8**	-	-	**2.1**	1.6	**3.6**	Pb/Pt	
4	1.3	0.7	0.6	**2.4**	-	1.1	1.1	-	Pb	Pb
	1.3	0.9	0.7	**2.4**	-	1.1	1.1	-	Pb	
5	1.1	**10.9**	1.7	-	1.2	-	-	-	Ph	Ph
	1.6	**10.9**	1.7	-	1.4	-	-	-	Ph	
6	**2.0**	**2.8**	**21.9**	-	-	1.0	0.9	-	Pb/Pt	Pt
	2.0	**2.8**	**21.9**	-	-	1.0	1.1	-	Pb/Pt	
7	0.8	1.2	1.3	-	0.9	-	-	-	-	Pb
	0.8	1.2	**3.6**	-	0.9	-	-	-	Pb/Pt	
8	1.3	1.6	**35.6**	-	-	1.2	1.9	1.0	Pb/Pt	Pb
	2.6	1.6	**35.6**	-	-	1.7	**2.0**	1.0	Pb/Pt	
9	**15.4**	0.8	1.1	-	1.4	-	-	-	Ph	Ph
	15.4	0.8	**3.5**	-	1.4	-	-	-	Ph	
10	1.4	1.1	**20.9**	-	-	1.4	0.9	-	Pb/Pt	Pb
	1.4	1.1	**20.9**	-	-	**2.2**	1.0	-	Pb/Pt	
11	1.4	1.2	0.8	-	-	0.6	0.6	-	-	Ph
	2.4	1.5	0.9	-	-	0.7	0.6	-	Ph	
12	**7.4**	**11.2**	0.8	-	-	-	-	-	Ph	Ph
	11.3	**11.2**	1.2	-	-	-	-	-	Ph	
13	**4.5**	1.1	**19.3**	-	-	-	-	-	Pb/Pt	Pt
	4.5	1.1	**19.3**	-	-	-	-	-	Pb/Pt	

Bold numerals indicate values with more than 2-fold increase. Bold numerals with underlines indicate the maximum response in each case. IRI: immunoreactive insulin, SASI test: selective arterial secretagogue injection test, ASP: arteries supplying the pancreas, HA: hepatic arteries, GDA: gastroduodenal artery, SMA: superior mesenteric artery, SpA: splenic artery, DPA: dorsal pancreatic artery, PHA: proper hepatic artery, LHA: left hepatic artery, MHA: middle hepatic artery, RHA: right hepatic artery

onds), giving positive predictive values of 72.2% and 68.2%, respectively (Table 2). The rate of positivity in both Ph and Pb/Pt were 38.5% for SASI (60 seconds), and 46.2% for SASI (120 seconds) (Table 1). When the dominant artery (the artery showing the greatest increase) was assessed for tumor localization, 10 for SASI (60 seconds) and 12 for SASI (120 seconds) matched the surgical findings, resulting in localization sensitivities of 76.9% and 92.3%, respectively (Table 1, 3).

SASI tests for hepatic arteries

For the HAs (n=19), SASI (60 seconds) did not show any positive arteries, and the false-positive rate was 0.0%, while SASI (120 seconds) found 4 positive arteries, with a false-positive rate of 21.1% and positive predictive value of 0.0%. In the present study, there were no patients with hepatic metastasis, and therefore, the sensitivity could not be evaluated (Table 2).

Comparison between SASI tests and morphological imaging for tumor localization

The localization ability of the SASI tests were compared with those of morphological imaging (Table 3). CT was capable of identifying tumors in 9 of 13 cases (69.2%). MRI was capable of locating tumors in 8 of 13 cases (61.5%). EUS was capable of localizing tumors in 11 of 12 cases (91.7%), showing the best performance among morphological imaging techniques. The localization ability of DSA was 69.2% (9/13). When these results were compared with those of the SASI tests for insulinoma localization, SASI (120 seconds) emerged as the best with a sensitivity of 92.3% (Table 3).

Discussion

Surgical resection is the only radical treatment for insulinoma (19). As blind resection without determining the location of the insulinoma is not recommended, accurate preoperative localization is indispensable (20). The SASI test for

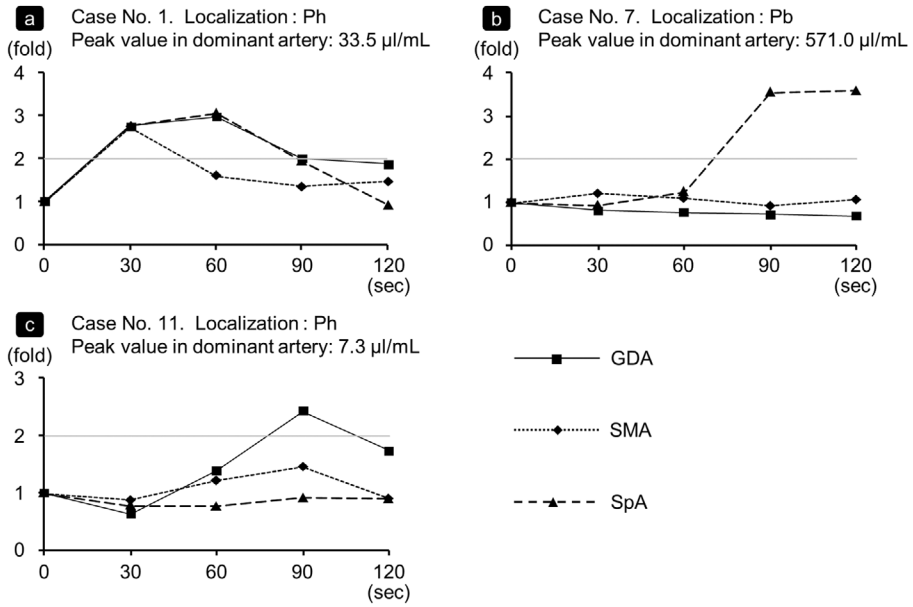

Figure. **Graph for SASI test results (a: Case 1, b: Case 7, c: Case 11). The vertical axis represents the increase in the immunoreactive insulin level, and the horizontal axis represents the time after secretagogue injection. "Localization" shows the location of the tumor confirmed at surgery. The tumor could not be accurately located by the SASI test at all in Patient 1. SASI (60 seconds) could not determine the tumor location in Patients 7 and 11, while SASI (120 seconds) was able to accurately locate the tumor in these patients.**

Table 2. **Summary of the Results of the SASI Tests.**

	SASI (60 sec)	SASI (120 sec)
Arteries supplying the pancreas (n=40)		
Positive artery - n (%)	18 (45.0)	22 (55.0)
False-positive artery - n (%)	5(12.5)	7 (17.5)
False-positive rate	25.0%	35.0%
Positive predictive value	72.2%	68.2%
Hepatic arteries (n=19)		
Positive artery - n (%)	0 (0.0)	4 (21.1)
False-positive artery - n (%)	0 (0.0)	4 (21.1)
False-positive rate	0.0%	100.0%
Positive predictive value	N/A	0.0%

SASI test: selective arterial secretagogue injection test, N/A: not available

insulinoma was first reported by Doppman et al. in 1991 and has since become widely used (18). The procedure and outcome interpretation have now been modified by different institutions. Various reports have been published regarding the SASI test, and there are two major methods: SASI (60 seconds) and SASI (120 seconds), with differences in terms of the timing of the result evaluation (Table 4) (7-16). Previous studies have reported that SASI (120 seconds) has a superior insulinoma localization ability compared with SASI (60 seconds) [SASI (60 seconds): 85.1% (n=94), SASI (120 seconds): 98.9% (n=88)] (Table 4). However, a straightforward comparison is not possible due to background differences such as patient population, dosage of calcium gluconate, and the method of insulin assay.

In our study, at 92.3%, the insulinoma localization sensitivity of SASI (120 seconds) was superior to that of SASI (60 seconds). The reason for this superiority was that evaluation at 60 seconds could not identify any arteries with an IRI increase of ≥2-fold in cases 7 and 11 (15.4%), making it impossible to localize the tumor. In these two cases, the positive arteries became identifiable by conducting the evaluation at 120 seconds, allowing for accurate localization (Table 1, Figure b and c). Lo et al. also reported that, in 2 of 18 insulinoma cases (11.1%), no positive arteries were found at 60 seconds after calcium injection (9). The incidence of such cases in our study was similar. If the IRI levels had been determined at 120 seconds in the study cited above, localization might have been possible. Therefore, we consider that the IRI level changes should be observed up to 120 seconds after secretagogue injection in order to avoid

Table 3. The Localization Diagnosis Rate of the SASI Tests and Morphological Imaging Modalities.

	SASI test (n=13)		CT (n=13)	MRI (n=13)	EUS (n=12)	DSA (n=13)
	60 sec	120 sec				
Localization diagnosis	76.9%	92.3%	69.2%	61.5%	91.7%	69.2%

SASI test: selective arterial secretagogue injection test, CT: computed tomography, MRI: magnetic resonance imaging, EUS: endoscopic ultrasonography, DSA: digital subtraction angiography

Table 4. Evaluation Timing and Sensitivities of SASI Test for Localization of Insulinoma in Previous Studies.

SASI tests evaluated in 0 - 60 sec				SASI tests evaluated in 0 - 120 sec			
Reference	year	n	Sensitivity	Reference	year	n	Sensitivity
7	2000	9	89%	12	1999	6	100%
8	2000	11	91%	13	2001	11	100%
9	2000	18	77.8%	14	2004	27	96%
10	2009	45	84%	15	2009	28	100%
11	2016	11	90.9%	16	2016	16	100%
Total		94	85.1%	Total		88	98.9%

SASI test: selective arterial secretagogue injection test

missing any delayed positive results from tumor-feeding arteries.

However, our study also revealed a disadvantage with conducting an evaluation at 120 seconds after secretagogue injection: namely, an increase in the rate of false-positive results (Table 2). The possible reason for this drawback is that positive results in non-tumor-feeding arteries might overlap with areas of vascular supply, presence of collateral circulation, stimulation of insulinoma by recirculation of calcium gluconate, or leakage of calcium gluconate during injection (10, 11, 17, 18, 21). In addition, a maximum 6.4-fold IRI elevation in the SASI test has been reported in a patient clinically confirmed to have no insulinoma (17, 21). Therefore, caution in interpretation is required. The falsely positive arteries in SASI (120 seconds) may have been related to recirculation in particular, since the increase increased over time. In the present study, SASI (120 seconds) could not accurately localize the tumor in only case 1 (7.7%) (Table 1, Figure a). In this case, the SASI test was positive in the GDA and the SpA with the same increase rate. Possible reasons for this may be stimulation of insulinoma by overlapping feeding regions and leakage of calcium gluconate at the time of injection.

Regarding SASI (120 seconds) in the present study, 2 regions (Ph and Pb/Pt) tested positive in 6 cases (46.2%). Therefore, we had to determine which artery was the dominant one. Guettier et al. reported that multiple arteries were positive in about half of 45 insulinoma cases in the SASI test, and the artery with the largest increase ratio was defined as the dominant artery for an evaluation (10). Some studies have suggested that a ≥3-fold IRI level elevation over the baseline should be a criterion for a positive result, while others state that a ≥2-fold IRI level elevation with an IRI peak level ≥100 μU/mL should be a criterion (11, 12). However, in case 11 of this study, the peak IRI level of the tumor-feeding artery reflected only a slight reaction (IRI peak level 7.3 μU/mL, maximum 2.4-fold increase) (Table 1, Figure c). Accordingly, we consider that the artery with the greatest increase ratio should be deemed the tumor-feeding artery for accurate localization.

It was difficult to evaluate the localization ability of the SASI test for hepatic metastasis, as insulinoma with hepatic metastasis was found only in 3-9% of cases (2, 4-6). In the present study, no hepatic metastasis was found, and therefore, the sensitivity of the SASI test for localization of hepatic metastasis could not be evaluated. For the SASI (120 seconds), the HA became falsely positive in 21.1% of HAs, and therefore, caution in interpretation is required (Table 1, 2). Guettier et al. found that localization was possible in only one of three cases with hepatic metastasis of insulinoma (10). In gastrinoma, the sensitivity of the SASI test for the localization of hepatic metastasis was also reported to be low (22). Based on the above observations, the usefulness of the SASI test for localizing hepatic metastasis of insulinoma appears to be limited.

Compared with morphological imaging, SASI (120 seconds) shows superior localization ability, as mentioned in many reports (5, 8, 10, 13). In the present study, EUS showed high localization ability (91.7%) comparable to the SASI test. This might be because the insulinomas in the present study were relatively large (9-27 mm). Furthermore, EUS is often performed after other morphological imaging

modalities, and the EUS data are examined in detail with reference to the results of other modalities. Thus, its localization ability may have been augmented. Nuclear medicine imaging, which is also used as a functional imaging modality, is less invasive than the SASI test. The most frequently used modality at present is somatostatin receptor scintigraphy. However, as the expression rate of somatostatin receptor type 2a is low in insulinoma, the sensitivity rate is low (≤50%) (5, 23, 24). Glucose-like peptide 1 (GLP-1) receptor is known to be expressed in more than 90% of insulinomas, and GLP-1 receptor imaging is considered useful (19, 25, 26). According to a report (25), GLP-1 receptor scintigraphy using ^{111}In-DOTA-exendin-4 showed excellent sensitivity (100%). However, very few facilities are equipped to perform this modality, and the number of cases was small. Therefore, further investigation is required in this area.

In conclusion, in the present study, SASI (120 seconds) produced the best results for insulinoma localization when compared with SASI (60 seconds) and morphological imaging techniques. Therefore, the evaluation of SASI test at 0-120 seconds is recommended for insulinoma localization. When multiple arteries are positive, it is appropriate to assume the artery with the greatest IRI level increase to be the dominant artery.

The authors state that they have no Conflict of Interest (COI).

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