Arterial stimulation with simultaneous venous sampling for localizing insulinomas

Zhiyuan Wu 1, Tingwei Su 2, Daming Wu 3, Xiaoyi Ding 1, Zhongmin Wang 1, Wei Huang 1, Ziyin Wang 1, Qin Liu 1, Hua Zhang 3

ABSTRACT

Purpose: The present study aimed to assess the accuracies of arterial stimulation with simultaneous venous sampling (ASVS) in preoperative localization of insulinomas.

Materials and Methods: A cohort consisting of 6 males and 14 females (median age, 48.5y; range, 28–62y) with pathologically proven insulinomas were included in this study. Selective angiographies were performed with the superior mesenteric artery (SMA), gastroduodenal artery (GDA), proximal splenic artery, and midsplenic artery in all individuals. Then ASVS procedures were followed after angiographies for these arteries. Clinical characteristics of the patient and the tumor number, location, and size were recorded. The accuracy of preoperative localization of insulinomas was tested.

Results: A total of 22 tumors were identified by histopathological diagnosis. The mean size of the tumor was 1.40±0.60cm. Five tumors were in the head/neck region and 17 in the body/tail region. ASVS accurately localized 17/20 (85%) cases with only biochemical data and 19/20 (95%) cases with biochemical data and angiography images. Variant pancreatic arterial anatomy was revealed in 2 false cases with inferior pancreatic artery replaced by the superior mesenteric artery.

Conclusion: ASVS was highly accurate in localizing insulinomas and should be performed in most of the patients with suspected insulinomas before the operation.

Keywords: insulinomas; arterial stimulation with simultaneous venous sampling; localization diagnosis

INTRODUCTION

Insulinomas are the most frequent among all the functional endocrine pancreatic tumors (1). Fasting hypoglycemia is the most common clinical symptom. Surgical resection of the tumor is usually curative (2). An accurate preoperative localization of insulinomas is critical. Clinically, these tumors are small and can be difficult to localize; thus preoperative localization is key to successful surgical management. Several diagnostic modalities have been reported for the localization of insulinomas (3, 4). Computed tomography (CT) is the preferred imaging technique. In addition, retrospective studies have suggested an improved performance for the detection of insulinomas with 83–94% sensitivity (5-7), while the prospective detection rate was extremely low, and 63% in one of the studies (5).

Selective intraarterial calcium injection of the major pancreatic arteries [arterial calcium stimulation (CaStim)] with hepatic venous sampling for insulin, also known as arterial stimulation with simultaneous venous sampling (ASVS), is a method to localize discrete insulin-secreting islet cell tumors in the regions of the pancreas (8). ASVS was developed and has been used at NIH since 1989 (9). A number of articles have reported that ASVS had the highest accuracy for localizing insulinomas as compared to CT, magnetic resonance imaging (MRI), arteriography, and ultrasonography (9-11). Thus, ASVS is a useful method for localizing insulinomas when conventional imaging techniques fail (12) and should be considered routinely before surgery to ensure accurate localization of insulinomas (10). The present study assessed the accuracies of ASVS in preoperative localization of insulinomas at Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

MATERIALS AND METHODS

Patients

This single-center retrospective study was approved by the institutional review board of our hospital. Although the requirement for informed consent was waived, written informed consents for the ASVS procedure were obtained from all patients or their family. In our hospital, all patients with suspected insulinomas were recommended for ASVS procedures. From January 2016 to May 2017, a total of 23 patients underwent ASVS procedures at the...
Department of Interventional Radiology in our hospital. Dynamic enhanced CT and/or magnetic resonance imaging (MRI) examinations were also performed on these patients. Among them, 20 patients underwent surgical resection and were diagnosed pathologically.

**ASVS procedures**

ASVS procedures were performed by two senior interventional radiologists (35 and 29y of experience, respectively). All patients were fasting for 6h before ASVS procedures. A transfemoral venous catheter (5F SIM1 Imager™ II Angiographic Catheter with two side-holes, Boston Scientific Co., Natick, MA, USA) was inserted and positioned with the distal end in the right hepatic vein in proximity to the junction with inferior vena cava. The hepatic venous samples were collected via this catheter. Digital subtraction angiography (DSA; Innova, GE Healthcare, Milwaukee, WI, USA) was performed with selective injections of nonionic contrast medium (Iohexol 350 mg/mL, GE Healthcare Co., Ltd, Shanghai, China) diluted to a volume of 5mL with normal saline (Shanghai Sine Pharmaceutical Co., Ltd, Shanghai, China) subsequently, the insulin levels were measured. One peripheral antecubital infusion of 5% dextrose was continued during the length of the procedure.

**Interpretation of the ASVS response**

Firstly, the angiography images were analyzed. With respect to the biochemical data, the positive response was defined as a 2-fold step-up in baseline hepatic insulin post-calcium injection. In the absence of an anatomical variant in angiography images, a positive response was noted when GDA or SMA was injected to predict the head/neck lesions. In addition, the positive response was observed when a proximal splenic artery or midsplenic artery was injected to predict the body/tail lesions. If more than one injection sites elicited a positive response, the dominant site was used to predict the tumor localization.

**Statistical analyses**

Fasting glucose levels were recorded before and after the operations. The tumor number, location, and size were also recorded postoperatively. The fasting glucose levels before and after operations were compared with Wilcoxon test (paired samples). The surgical and pathology results were considered as gold standard and were compared to the ASVS results. Then, the tumor localization accuracies of ASVS procedures were calculated. Statistical significance level was set at 0.05. Data were analyzed using MedCalc 12.1 (MedCalc Software, Mariakerke, Belgium).

**RESULTS**

Demographic, biochemical, and pathological data

Of the 20 patients, the ratio of male to female was 6:14, the median age was 48.5 (range, 28–62). The mean fasting glucose level before the operation was 2.97±0.88mmol/L that increased to 8.15±3.34mmol/L after the operation; the difference was statistically significant (p<0.0001). The increase in the levels of fasting glucose postoperatively proved a successful operation. During the study period, all patients underwent surgical resection to obtain tumor samples. A total of 22 tumors were identified by histopathological diagnosis in these 20 cases, of which 17 cases presented only one lesion, 1 case had 3 lesions, and 1 case had 2 lesions.

| Case | Age  | Sex | Fasting glucose level (mmol/L) | Location | Surgical and pathology results |
|------|------|-----|--------------------------------|----------|--------------------------------|
|      | Preoperative | Postoperative | | | Number | Size (cm) |
| No.1 | 52   | M   | 2.23                           | tail     | 1                             | 3   |
| No.2 | 63   | F   | 4.4                            | body     | 1                             | 1.5 |
| No.3 | 90   | M   | 2.8                            | tail     | 1                             | 1.7 |
| No.4 | 48   | M   | 3.84                           | tail     | 1                             | 1   |
| No.5 | 39   | F   | 3.5                            | neck     | 1                             | 1.2 |
| No.6 | 44   | F   | 2.5                            | head     | 1                             | 1   |
| No.7 | 31   | M   | 2.62                           | -        | 0                             | -   |
| No.8 | 28   | F   | 4.7                            | body     | 1                             | 0.7 |
| No.9 | 50   | F   | 2.1                            | tail     | 1                             | 1.5 |
| No.10| 40   | F   | 2.2                            | head     | 1                             | 1.3 |
| No.11| 40   | M   | 4.4                            | tail     | 1                             | 2.6 |
| No.12| 54   | F   | 2.64                           | tail     | 1                             | 2   |
| No.13| 45   | F   | 2.44                           | body     | 1                             | 1.5 |
| No.14| 50   | M   | 3.9                            | head     | 1                             | 2   |
| No.15| 49   | F   | 3.7                            | body     | 1                             | 1.5 |
| No.16| 62   | F   | 2.35                           | body     | 1                             | 1.1 |
| No.17| 50   | F   | 2.2                            | body     | 3                             | 1.2, 1.4, 1.2 |
| No.18| 45   | F   | 2.4                            | tail     | 2                             | 1.7 |
| No.19| 60   | F   | 2.58                           | body     | 1                             | 1.5 |
| No.20| 43   | F   | 2.14                           | head     | 1                             | 1   |

*Case No. 7, no tumor was detected even after almost total pancreatectomy*
The remaining case did not present any lesions although most parts of the pancreas were resected. The mean tumor size was 1.40±0.60cm. Five tumors were in the head/neck region and 17 in the body/tail region. The data of these 20 patients were summarized in Table 1.

Results of angiography

Angiographies were performed with the SMA, GDA, proximal splenic artery, and midsplenic artery in all individuals. The vascular tumor blushes were observed in 12/20 (60%) cases (Fig. 1); 5 were in the head/neck region and 7 in the body/tail region. Variant pancreatic arterial anatomy was revealed in 2 cases with inferior pancreatic artery (IPA) replaced by SMA (Fig. 2). The incidence of anatomical variation was 10% (2/20).

Figure 1. Angiography and ASVS results of one case. (a) The vascular tumor blush was seen in the body/tail region (arrow). (b) Insulin level increased 2.29-fold after calcium injection at the dominant artery (midsplenic artery) as predicted by the body/tail lesion.

Figure 2. ASVS in the presence of variant pancreatic arterial anatomy. (a) Angiographic imaging revealed an oval vascular tumor blush in the body/tail region of the pancreas (arrow). The blood supply was from IPA that was replaced by SMA. (b) Insulin level increased 7.04-fold after calcium injection at the dominant artery (SMA) as predicted by the head/neck lesion.

Results of ASVS

ASVS correctly localized the tumors in 17/20 (85%) cases based on the biochemical data. The median increase in the stimulated hepatic insulin concentration was 9.5-fold above baseline at the dominant artery. In a majority of the cases, the time required to reach the peak level was 30 or 60s after calcium injection. No hypoglycemic, hypercalcemic, allergic, bleeding, thrombotic, or other complications were noted in any of the cases. In 2 cases with variant pancreatic arterial anatomy, only biochemical data could not localize the tumors accurately. The positive response from SMA predicted the head/neck lesions. However, the IPA was replaced by SMA, such that these 2 cases could predict the body/tail lesions (Fig. 2). Furthermore, the surgically proven insulinoma regionalized to the body/tail region, but not the head/neck. Combining the biochemical data and angiography images, tumors in 19/20 (95%) were localized accurately.

DISCUSSION

Accurate preoperative localization of insulinomas is conducive to eliminate the need for blind distal pancreatectomy and avoid reoperation (13). Several invasive or noninvasive modalities have been developed for preoperative localization. The specificity of ASVS for insulinomas is based on the assumptions that the tumor will have a dominant arterial supply and calcium elicits a unique response on tumor cells; also, normal β-cell function is suppressed relative to the tumor cells (14, 15).
Several studies (9-11, 16-18) reported that ASVS was vastly superior to abdominal US, CT, or MRI as a localization tool for insulinomas, and was suggested to be considered routinely before operation (10). In the present cohort, ASVS presented a high accuracy (85%) in the localization of insulinomas with 3 false results; however, this result was primarily based on the biochemical data.

The reasons for false results of ASVS include anatomical variants, multifocal or diffused disease, and technical flaws (9, 19). Two of the false cases in this study were attributed to arterial variation. A combination of ASVS and angiography images provides both anatomical and functional data that are not available by other localization techniques (20). In these 2 false cases, vascular tumors in the body/tail region of pancreas were revealed in the angiographic images. Thus, angiography data were critical for accurate interpretation of the test results.

REFERENCES

1. Oberg K, Eriksson B. Endocrine tumours of the pancreas. Best Pract Res Clin Gastroenterol 2005; 19: 753-781.
2. Grama D, Eriksson B, Martensson H, et al. Clinical characteristics, treatment and survival in patients with pancreatic tumors causing hormonal syndromes. World J Surg 1992; 16: 632-639.
3. Lin XZ, Wu ZY, Tao R, et al. Dual energy spectral CT imaging of insulinoma-Value in preoperative diagnosis compared with conventional multi-detector CT. Eur J Radiol 2012; 81: 2487-2494.
4. Zhu L, Xue H, Sun H, et al. Insulinoma Detection With MDCT: Is There a Role for Whole-Pancreas Perfusion? AJR Am J Roentgenol 2017; 208: 306-314.
5. Fidler JL, Fletcher JC, Reading CC, et al. Preoperative detection of pancreatic insulinomas on multiphasic helical CT. AJR Am J Roentgenol 2003; 181: 775-780.
6. Gouya H, Vignaux O, Augui J, et al. CT, endoscopic sonography, and a combined protocol for preoperative evaluation of pancreatic insulinomas. AJR Am J Roentgenol 2003; 181: 987-992.
7. Liu Y, Song Q, Jin HT, et al. The value of multidetector-row CT in the preoperative detection of pancreatic insulinomas. Radiol Med 2009; 114: 1232-1238.
8. Morera J, Guillaume A, Courtheoux P, et al. Preoperative localization of an insulinoma: selective arterial calcium stimulation test performance. J Endocrinol Invest 2006; 39: 455-463.
9. Guettier JM, Kam A, Chang R, et al. Localization of insulinomas to regions of the pancreas by intraarterial calcium stimulation: the NIH experience. J Clin Endocrinol Metab 2009; 94: 1074-1080.
10. Morganstein DL, Lewis DH, Jackson J, et al. The role of arterial stimulation and simultaneous venous sampling in addition to cross-sectional imaging for localisation of biochemically proven insulinoma. Eur Radiol 2009; 19: 2467-2473.
11. Wiesli P, Brandle M, Schmid C, et al. Selective arterial calcium stimulation and hepatic venous sampling in the evaluation of hyperinsulinemic hypoglycemia: potential and limitations. J Vasc Interv Radiol 2004; 15: 1251-1256.
12. Smith A, Thornton PS, Gallianni CA, et al. A 14-year old girl with reversible hypoglycemic episodes: the role of ASVS. Pediatr Dev Pathol 2015; 18: 80-83.
13. Goh BK, Ooi LL, Cheow PC, et al. Accurate preoperative localization of insulinomas avoids the need for blind resection and reoperation: analysis of a single institution experience with 17 surgically treated tumors over 19 years. J Gastrointest Surg 2009; 13: 1071-1077.
14. Gaeke RF, Kaplan EL, Rubenstein A, et al. Insulin and proinsulin release during calcium infusion in a patient with islet-cell tumor. Metabolism 1975; 24: 1029-1034.
15. Brunt LM, Veldhuis JD, Dilley WG, et al. Stimulation of insulin secretion by a rapid intravenous calcium infusion in patients with beta-cell neoplasms of the pancreas. J Clin Endocrinol Metab 1986; 62: 210-216.
16. Won JG, Tseng HS, Yang AH, et al. Intra-arterial calcium stimulation test for detection of insulinomas: detection rate, responses of pancreatic peptides, and its relationship to differentiation of tumor cells. Metabolism 2003; 52: 1320-1329.
17. Pereira PL, Roche AJ, Maier GW, et al. Insulinoma and islet cell hyperplasia: value of the calcium intraarterial stimulation test when findings of other preoperative studies are negative. Radiology 1998; 206: 703-709.
18. Lo CY, Chan FL, Tam SG, et al. Value of intra-arterial calcium stimulated venous sampling for regionalization of pancreatic insulinomas. Surgery 2000; 128: 903-909.
19. Thompson SM, Vellis A, Service FJ, et al. Impact of variant pancreatic arterial anatomy and overlap in regional perfusion on the interpretation of selective arterial calcium stimulation with hepatic venous sampling for preoperative localization of occult insulinoma. Surgery 2015; 158: 162-172.
20. Jackson JE. Angiography and arterial stimulation venous sampling in the localization of pancreatic neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2005; 19: 229-239.