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Insulinoma – how to localize the tumor?

Insulinom – kako lokalizovati tumor?

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Abstract

Background/Aim. Arterial stimulation with calcium and venous sampling (ASVS) enables us to reach the goal of avoiding that any patient with insulinoma undergoes a blind surgical exploration. Since ASVS is both a functional and morphological localization procedure, its sensitivity is not influenced by factors that are causing the insensitivity of usual anatomical and morphological procedures. Based on our own experience in preoperative localization of insulinoma, we indented to show why we believe that ASVS should be performed to all patients regardless of data collected from other preoperative localization methods. **Methods.** We have analyzed the accuracy of preoperative localization methods retrospectively. First anatomical and morphological procedures like transabdominal ultrasound (US), endoscopic ultrasound (EUS), computed tomography (CT) and magnetic resonance imaging (MRI) were done. Then we analyzed the data collected during a functional procedure which, at the same time, allows regionalization (ASVS). To estimate the accuracy, the results of every single method were correlated with the operative findings in all sixteen cases. **Results.** Prior to ASVS, fourteen patients underwent US, fifteen had CT, MRI was performed in eight patients and EUS in thirteen. Using only one of these methods enabled identification of tumors in five patients, using two methods in six patients while three and four in one patient each. For three patients, none of these methods was successful. ASVS revealed that all seen tumors were functional except three of the six visualized with two methods (US and EUS). In two of these three cases, US and EUS localized the tumors in pancreatic tail/body while ASVS accurately identified the tumors in pancreatic head. For these patients US and EUS showed false positive results. In the third of these patients EUS showed the tumor localized in pancreatic head, while US and ASVS accurately pointed to tail. This, too, was a false positive result of EUS. ASVS successfully provided regionalization data in three patients where other visualization methods failed. Operative and later histological findings confirmed the accuracy of ASVS in all sixteen patients including two patients that previously underwent distal pancreatectomy based on false positive EUS findings. **Conclusion**. Two patients, with accurate insulinoma regionalization in pancreatic head, obtained with ASVS, previously underwent unsuccessful distal pancreatectomy based on the false positive EUS findings. The same goes to three other patients with the false positive results obtained with other anatomical and morphological findings, as well as those three patients that had no preoperative visualization with other methods prior to ASVS. Therefore we suggest ASVS performing in each suspected insulinoma patient before the surgery, regardless of the data collected using other methods. This would enable us to test functional characteristics of visualized findings and to regionalize part of pancreas with uncontrolled insulin secretion when no suspicious changes were found.

Key words:
insulinoma; **diagnosis; calcium gluconate; injections, intra-arterial; sensitivity and specificity.**

Apstrakt

Uvod/Cilj. Arterijskom stimulacijom kalcijumom sa venskim semplovanjem (ASVS) se moze ostvariti cilj da nijedan bolesnik sa insulinomom ne ode na slepu eksploraciju pankreasa. Pošto je ASVS funkcionalno morfološka lokalizaciona procedura na njenu senzitivnost ne utiču faktori koji ograničavaju senzitivnost anatomsko-morfoloskih preoperativnih lokalizacionih pregleda. Cilj rada bio je da se na osnovu sopstvenog iskustva stečenog u preoperativnoj lokalizaciji insulinoma pokaže zašto smatramo da kod svih bolesnika bez obzira na rezultate drugih preoperativnih lokalizacionih pregleda treba uraditi ASVS. **Metode.** Tačnost anatomsko-morfoloskih pregleda [transabdominalnog ultrazvuka (UZ), kompjutereizovane tomografije (CT), nuklearne magnetne rezonance (NMR), endoskopskog ultrazvuk (EUZ) i funk-

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cionalno-regionalizacionog pregleda (ASVS)] za potrebe preoperativne lokalizacije insulinoma je retrospektivno analizirana. Tačnost nalaza svakog pojedinog pregleda je proverena upoređivanjem sa operativnim nalazom kod 16 uspešno operisanih bolesnika. **Rezultati.** Pre ASVS sa ciljem da se lokalizuju insulinomi kod 14 bolesnika je urađen UZ, kod 15 CT, MR kod osam bolesnika i kod 13 bolesnika EUZ. Samo jednim od navedenih pregleda, promena u pankreasu je identifikovana kod pet bolesnika, sa dva kod šest, a sa tri i četiri kod po jednog bolesnika. Kod tri bolesnice ni jedan od primenjenih pregleda nije identifikovao promene u pankreasu. ASVS je pokazala da su identifikovane promene funkcionalne kod svih bolesnika izuzimajući tri bolesnice od šest bolesnika kod kojih su sa po dva pregleda identifikovane promene u pankreasu. Kod dva od ove tri bolesnice UZ i EUZ su identifikovane promene u telu/repu dok je ASVS tačno regionalizovala tumore u glavi pankreasa– nalazi US i EUZ su bili lazno pozitivni. Kod tri. bolesnice EUZ je identifikovana promena u glavi dok su UZ i kasnije ASVS tačno lokalizovali insulinom u repu; EUZ nalaz je bio lazno pozitivan. ASVS je tačno regionalizovala insulinome kod tri bolesnice kod kojih drugim pregledima tumor nije lokalizovan. Operativnim i kasnijim histološkim nalazom je potvrđena tačnost ASVS kod svih 16 bolesnika uključujući i dvoje koji su ranije neuspešno operisani (distalna pankreatektomija) samo na osnovu, ispostavilo se, lažno pozitivnog nalaza EUZ. **Zaključak.** Dvoje bolesnika kod kojih je samo na osnovu lažno pozitivnog nalaza EUZ urađena neuspešna distalna pankreatektomija, moguća, da nije urađena ASVS, slična sudbina još tri bolesnice sa lažno pozitivnim nalazima anatomsko-morfoloških pregleda i neizvestan ishod operacije bez ASVS kod tri bolesnice kod kojih drugi preoperativni lokalizacioni pregledi nisu lokalizovali insulinome, opravdavaju stav da kod svih bolesnika sa insulinomom, bez obzira na rezultate anatomsko-morfoloških pregleda pre operacije, treba uraditi i ASVS sa ciljem da se provere funkcionalne karakteristike identifikovanih promena ili regionalizacije mesta nekontrolisanog lučenja insulina kada promene nisu identifikovane.

Ključne reči:
insulinom; dijagnoza; glukonati; injekcije, intraarterijske; senzitivnost i specifičnost.

Introduction

In adults that are not treated for diabetes mellitus, who, apart from hypoglycemic episodes, seem to be healthy persons, the usual cause for endogenic hyperinsulinemic hypoglycemias is insulinoma. Insulinomas are extremely rare with incidence of 4/1000000 [1], very small (90% < 2 cm) in 90% benign and in 90% solitary. Practically, all are tumors of the beta cells in pancreatic Langerhans islets. Insulinomas are causing hypoglycemias by uncontrolled secretion of insulin. This diagnosis comes to mind when Whipple's triad is present and when it can be provoked by prolonged fasting, of course in the presence of necessary biochemical criteria for an adequate diagnosis [2]. The only adequate treatment option is surgery. Preoperative tumor localization is a very important step between the diagnosis and surgery. An accurate tumor localization is essential for successful surgical outcome. The importance of the preoperative tumor localization is best represented by the commonly adopted position by relevant professionals that none of these patients should undergo a blind pancreatic exploration [3].

Insulinomas could be localized by anatomical and morphological procedures like ultrasound (US), endoscopic ultrasound (EUS), computed tomography (CT), magnetic resonance imaging (MRI) and angiography. Furthermore we could use arterial stimulation with calcium and venous sampling (ASVS) both as functional and morphological exam.

Sensitivity data differ significantly among various morphological procedures and between diagnostic centers. For US, the sensitivity is 16%–64% [3, 4], for CT 33%–64% [5], for MRI 40%–90%, for EUS 65%–92% [5, 6] and for angiography 29%–50% [7]. Indirectly, the small size and rare occurrence can contribute to the inconsistency of the results. Different diagnostic centers use different diagnostic tools. These tools differ in power of resolution as well. Therefore, technical reasons may in part influence such difference, because insulinomas of the same size might be identified in one center and missed in the other center with inferior diagnostic appliance. On the other hand, to achieve maximum results with owned technology, a certain level of skill, experience and devotion is much needed. Given the same technology, a diagnostic center with significantly more patients will have more chance to reach desired skill and experience. A good example of the importance of skill and experience is EUS with a sensitivity span from 65% to 92% [3, 4]. Another reason for different success rates between diagnostic centers might be the fact that each center develops and masters some of the localization procedures more than some others. This comes regardless of the overall similar relevance and renown of centers in insulinoma management. In one of such famous institutions for insulinoma management the US exams provide accurate localization in 65% [3] and in another with comparable experience only in 16% [4]. To sum up, results of anatomical and morphological diagnostic exams differ significantly, particularly if skill and experience requiring methods are used.

Nevertheless, despite sophisticated equipment and admirable skills and experience, some tumors remain unseen – false negative results, while some tumors that are found will not be functional, will not be insulinomas – false positive results.

Because it is both a morphological and functional method, ASVS substantially differs from the previously mentioned procedures. The sensitivity of the ASVS results is not influenced by the factors that are causing insensitivity or limitations of usual anatomical and morphological exams. Regardless of the center that reported the ASVS data, the sensitivity of results is quite uniform and reproducible. This diagnostic procedure can be performed with the same accuracy anywhere. When done after other visualization methods, ASVS enables an insight into the functionality of the change found and, if none was found, it provides sufficient regionalization of pancreatic area that contains insulinoma.

Methods

Data gathered during preoperative insulinoma localization in sixteen patients was analyzed retrospectively. Our group includes eleven women and five men. The age range was between 23 and 77 years. All patients underwent surgery from 2002 to 2013. Two patients in this group were unsuccessfully operated in other institutions. ASVS was done for each patient after performing the usual anatomical and morphological exams. The accuracy of each localization method was compared to operative and histological findings.

The first two ASVS exams (1996 and 2002) were done in accordance with the original protocol [8]. Later, from 2006 we have modified the procedure in a way that all venous sampling was undertaken from the right hepatic vein [9], arterial stimulation with calcium was applied both in proximal and distal part of the lineal artery [10] and the dose of calcium was fixed to 1.35 mEq – 3 mL of 10% calcium gluconate [11].

The procedure was: A catheter used for venous sampling was inserted through femoral vein and fixed to position in the right hepatic vein. The catheter used for angiography of celiac plexus was inserted through the femoral artery. Then, selective catheterization was performed for each of the following arteries: *a. gastroduodenalis*, *a. mesenterica superior*, proximal and distal part of *a. lienalis* and *a. hepatica*. After each selective catheterization angiography and stimulation with 3 mL of 10% of calcium gluconate were performed. Blood samples from the right hepatic vein were taken 30 seconds prior to immediately prior to and 30, 60, 90 and 120 seconds after the stimulation with calcium. A double or higher rise in insulin concentration compared to the starting value was considered diagnostically significant. Thus, when a diagnostic rise in insulin concentration after calcium stimulation was noted in *a. gastroduodenalis* and a. *mesenterica superior*, we considered that insulinoma was regionalized in pancreatic head or *procesus uncinatus*. When the above was found after the stimulation of both ends of *a. lienalis insulinoma* was regionalized in pancreatic tail. On the other hand, when it was seen after the stimulation of only proximal part of *a. lienalis*, the tumor was in the body of pancreas. A double or higher rise in insulin concentration after the stimulation of *a. hepatica* suggests metastatic disease in liver. If angiographic findings (angiography during procedure) are positive and correlate with functional and regionalization data, then ASVS adds localization value to the test. It becomes more than a functional and regionalization test.

Prior to ASVS in our group, thirteen patients underwent US, fifteen CT, eight MR and thirteen EUS.

Results

All sixteen patients had ASVS done in a previously described way. In every case, after the stimulation with calcium, a diagnostic rise of insulin was noted and that enabled an accurate localization or regionalization of the tumors. This was confirmed with the operative and histological findings. Prior to ASVS, 7 suspected tumors were seen with US, but for two, ASVS showed no functionality – false positive findings. CT and MRI identified 5 and 2 changes, respectively, and all of them were confirmed functional by ASVS. When EUS was used there were 10 noted as suspected tumors, but only 7 were confirmed functional by ASVS and other 3 were not functional – false positive results (Table 1).

Table 1

Imaging tehniques performed to the patients

Imaging tehnique	Performed (n)	Localized (n)	False positive (n)	Negative (n)
US	14	5	2	7
CT	15	5	/	10
MR	8	2	/	6
EUS	13	7	3	3
Angiography	16	3	3	10
ASVS	16	16	/	/

US – ultrasonography; CT – computed tomography; MR – magnetic resonance imaging; EUS – endoscopic ultrasound; ASVS – arterial stimulation with calcium and venous sampling; n – number of patients.

Basic demographic characteristics, preoperative diagnostic results and operative and histological findings for patients are given in Table 2.

For three patients (N^o 4, 10 and 14) without preoperative localization with anatomical and morphological exams ASVS provided accurate regionalization of insulinomas.

By using only one anatomical and morphological method suspected tumors were identified in five patients (N^o 2, 5, 6, 7, and 9). In those cases, ASVS confirmed functionality for each one. The findings obtained by two diagnostic methods identified suspected change in six cases (N^o 1, 3, 8, 12, 13 and 16). For three of them (N^o 1, 3 and 12), ASVS showed functionality, but in other three cases it did not. US and EUS indicated that the tumor was in pancreatic body, while ASVS accurately showed that insulinomas were present in pancreatic head. For both of them, US and EUS results were false positive. In the third patient of this group a suspected change was identified by EUS on pancreatic head while the US result suggested the body/tail segment. ASVS showed that the US finding was accurate and that EUS gave a false positive result. In our group, two patients had accurate localization achieved by three or four morphologic exams and their functionality was also confirmed with ASVS.

The patients N^o 14 and 15 had unsuccessful distal pancreactomy in other institutions 1.5 and 5 years earlier, respectively. The diagnoses were based on the false positive EUS results.

Angiography was performed in all patients. For three patients it was accurate and corresponded to the functional findings. In three cases, it was false positive – it did not correspond to the functionality findings. Eventually, for ten patients angiography was negative although the tumor was found later on false negative results.

All patients were monitored after the surgery for at least 1 year and had no hypoglycemic episodes.

Table 2

Basic demographic characteristics, preoperative diagnostic results, and operative findings

Patient	Age	Gender	US	CT	MR	EUS	Postive arterial territory	Gradient	Surgery	Size (cm)
1	46	Male	N	P tail	ND	P body/tail	Splenic	10	Distal pancreatectomy - tail	0.8
2	59	Female	N	N	N	P tail	Splenic	7	Distal pancreatectomy - tail	0.9
3	23	Male	N	P head	ND	P	GDA	20	Enucleation - head	1.0
4	62	Female	N	N	ND	N	Splenic	14	Distal pancreatectomy - tail	1.5
5	62	Male	P tail	N	ND	N	Splenic prox. Splenic dist.	14 21	Distal pancreatectomy and splenectomy - hilum of the spleen	2.0
6	74	Female	ND	ND	ND	P head	GDA SMA	8 6	Enucleation - head	1.2
7	23	Female	ND	N	N	P tail	Splenic prox. Splenic dist.	8,5 2,7	Distal pancreatectomy - tail	1.1
8	68	Female	P body/tail	N	ND	FP head	Splenic prox. Splenic dist.	6 8	Distal pancreatectomy - tail	1.1
9	77	Male	N	P tail	ND	ND	Splenic prox. Splenic dist.	4 6	Distal pancreatectomy - tail	1.0
10	40	Female	N	N	N	N	Splenic prox. Splenic dist.	8 10	Distal pancreatectomy - tail	1.0
11	43	Female	P tail	P tail	N	P tail	Splenic prox. Splenic dist.	10 12	Distal pancreatectomy - tail	1.4
12	35	Male	P head	N	P head	ND	SMA	3	Enucleation - head	1.5
13	56	Female	FP body	N	ND	FP body	GDA	6	Enucleation - head	1.2
14	41	Female	N	N	N	ND	SMA	8	Enucleatio - head	1.3
15	61	Male	P head	P head	P head	P head	SMA GDA	25 3,5	Enucleation - head	4.0
16	41	Female	FP body	N	N	FP body	GDA	20	Enucleation - head	1.0

P – positive; N – negative; ND – not done; FP – false positive; US – ultrasound; CT – computed tomography; MR – magnetic resonance; EUS – endoscopic ultrasound; GDA – gastroduodenal; SMA – superior mesenteric arteries.

Discussion

The diagnosis of endogenous hyperinsulinemic hypoglycemias, commonly caused by insulinomas, is based on the established criteria, so that its detection is not that difficult [2]. On the other hand preoperative localization of insulinomas inside pancreatic tissue is difficult. Exact localization is necessary since surgery is the only valuable option for a definitive treatment. Having accurate tumor localization enhances chances for the successful tumor resection, shortens the time of operation, and therefore reduces the number of unsuccessful operations and a need for reoperations to the minimum. Reoperations correlate with higher morbidity. Therefore it is necessary to do everything to avoid that a single patient undergoes a blind pancreatic exploration [3].

For preoperative localization, we can use several anatomical and morphological exams (US, EUS, CT, MRI, angiography) and ASVS that is both a functional and regionalization test.

Based on previously given limitations of anatomical and morphological exams, it is not possible to localize all insulinoma cases using only these procedures, causing some of insulinoma cases to remain unseen – false negative results. It is not rare that all morphological methods fail to localize the tumor (occult insulinomas). Sending such patients to surgery would be in fact an undesirable blind pancreatic exploration. Another problems are false positive results. Some changes that are seen are not functional, therefore are not insulinomas. A patient sent to surgery based on false positive results will not be successfully operated. Difficulties arising from false positive or false negative results can be overcome if after anatomical and morphological exams ASVS is performed. Unlike these methods, ASVS is a functional exam that can point to a specific region of pancreas as a possible tumor site – regionalization. If there is a concurrence of angiographic and functional part of the test in a suspected region (characteristic angiographic finding in the area with diagnostic rise in insulin levels) ASVS becomes a functionally-anatomical localization exam. Since ASVS is a functional test, limitations of other anatomical and morphological methods do not influence its results. Consequently, the reports about ASVS sensitivity are reproducible and uniform regardless of the institution where it was done. In all institutions that are performing ASVS almost all insulinomas will be regionalized or localized.

ASVS enables localization or regionalization of insulinomas that were unseen with other methods and if a suspected change was identified, it provides additional information about the functionality of the explored lesion – it determents if it is actually insulinoma. So, ASVS, on one hand prevents patients from undergoing a blind surgical exploration of pancreas, and, on the other hand, it prevents surgery based on false positive results.

By performing ASVS after other anatomical and morphological methods we used all its benefits. We had false negative findings in three patients, but after ASVS, the accurate regionalization was made and that prevented a blind pancreatic exploration and led to a successful surgical outcome.

False positive results may lead to unsuccessful surgery. An example of this is the outcome of our two patients that were diagnosed with insulinomas in pancreatic body based on false positive EUS results. Other anatomical and morphological exams were negative. Distal pancreactetomies were unsuccessful in both cases. One and a half and five years after that these patients were admitted to our institution and after performing ASVS, we have determined the presence of insulinomas in pancreatic head, which was followed by a successful surgical enucleation. If ASVS had been done prior to the surgery, both patients could have been accurately diagnosed (EUS findings would have been seen as false positive) and properly operated during their first hospitalization.

Being operated based on false positive findings could have been an outcome of three more patients if ASVS had not been done to them. Fortunately, ASVS was used to check the functionality of suspected pancreatic changes identified by anatomical and morphological exams and such scenario was avoided. Two of them had suspected tumors based on the US and EUS findings in pancreatic body, but ASVS accurately regionalized insulinomas in pancreatic head. Both patients had successful surgical enucleation of insulinomas from pancreatic head. Chances for these patients to be misguidedly operated based on false positive results were much higher since not just one, but two methods gave wrong localization of the tumor. As for the third patient, if ASVS had not been done she would have been in danger of undergoing a complex Whipple pancreatic operation. In this case the EUS result indicated that the tumor was in pancreatic head and US pointed to body and tail. EUS is considered to be the most sensitive tool for localization of insulinomas in pancreatic head, superior to US, so it is not such a dilemma which result would have been chosen as true. If surgery was in order, it could turn into Whipple section, since a tumor in pancreatic head can easily be missed by palpation even when the surgeon is experienced. Never the less ASVS showed the EUS result to be false positive and the US finding to be true. Distal pancreatctomy was performed and the unnecessary Whipple operation avoided.

Five patients had pancreatic changes identified only by one method. Unlike the unsuccessfully operated patients, these five patients had ASVS done before surgery, and, although it could go the other way, all tumors were functional. There were no false positive results and patients were successfully operated.

The common ground for all medical workers that are treating insulinoma patients is a desire to achieve an exact preoperative localization of the tumor. Since such a goal cannot be reached universally with the same equipment and methods, every institution in this line of work need to develop their own methodology. The only measure of success is a concurrence of operative and histological findings with preoperative localization procedures. All approaches are equally good if their results are the same, and ideal if all insulinomas are accurately localized [11–13].

Conclusion

Our approach to perform ASVS in each patient after other anatomical and morphological procedures, regardless of the results, is based on two facts. Firstly, by doing ASVS, we were able to localize insulinomas in patients with false negative results; secondly, in this way we could check functionality of identified changes and avoid to be misled by false positive results. We will continue with such practice since we consider it to be the only way to send patients to surgery without a fear of failure. ASVS will be performed until it is proven that it can be replaced with noninvasive localization methods such as scintigraphy of glucagon like peptid-1 (GLP-1) receptors.

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