

The role of bilateral inferior petrosal sinus sampling in the diagnostic evaluation of Cushing syndrome

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ABSTRACT

Bilateral inferior petrosal sinus sampling is the gold standard diagnostic assay in identifying the pituitary source of adrenocorticotrophic hormone secretion in Cushing syndrome. The noninvasive assays used in the workup of Cushing syndrome are often misleading or ambiguous, yielding sensitivities of up to only 80%. Inferior petrosal sinus sampling, however, is highly accurate and safe when performed in experienced centers. We review here the historical and technical details of the procedure, with emphasis on the relevant anatomy and a discussion of possible rare complications.

Key words: • ACTH-secreting pituitary adenoma
• inferior petrosal sinus sampling • Cushing syndrome

Cushing syndrome is an uncommon condition with an estimated incidence of 1 per 500 000 persons (1) that results in increased mortality and impaired health (2). The vast majority of cases are due to adrenocorticotrophic hormone (ACTH)-secreting pituitary adenomas, which may be successfully treated with surgical resection. Noninvasive biochemical and imaging assays, including the high-dose dexamethasone suppression test and pituitary MRI, are limited because of their relatively low sensitivity. Bilateral inferior petrosal sinus sampling (BIPSS) is highly sensitive and specific for accurately diagnosing pituitary Cushing syndrome and may be helpful in lateralizing the location of the adenoma. BIPSS is therefore considered the gold standard for identifying the pituitary gland as the source of ACTH secretion in Cushing syndrome (3).

Clinical considerations

Cushing syndrome is an endocrine disorder that results from hypercortisolism that involves the hypothalamus-pituitary-adrenal axis (Fig. 1). Classic symptoms are nonspecific and include rapid central weight gain, moon facies, thinning of the skin with purple striae, hirsutism and baldness, hyperglycemia, hypertension, menstrual irregularities or impotence, and proximal muscle weakness (4). The diagnosis of Cushing syndrome may be complicated, particularly in cases of ambiguous clinical findings in patients with isolated symptoms or with atypical presentations, such as episodic hypercortisolism (5–7). Initial laboratory tests include urinary free cortisol, late-night salivary cortisol, and the low-dose dexamethasone suppression test. These tests are used to diagnose hypercortisolemia (8). Once Cushing syndrome has been demonstrated, further evaluations are targeted at identifying the cause.

Cushing syndrome is most frequently due to exogenous administration of glucocorticoid drugs. Endogenous Cushing syndrome may be caused by cortisol- or ACTH-secreting tumors (Table) (9, 10), and the majority of cases are due to Cushing syndrome, which refers specifically to an ACTH-secreting pituitary adenoma (11). First-line testing includes measuring plasma ACTH levels (12). Low ACTH levels indicate ACTH-independent Cushing syndrome, which is further evaluated with abdominal cross-sectional imaging to identify an adrenal cause of hypercortisolemia.

High plasma ACTH indicates ACTH-dependent Cushing syndrome, which may be pituitary or ectopic in origin. Pituitary sources include hormone-secreting adenomas. Ectopic sources include carcinoid and neuroendocrine tumors, gastrinomas, medullary thyroid carcinomas, pheochromocytomas, bronchoalveolar carcinomas, and pancreatic carcinomas (13).

To distinguish pituitary from ectopic ACTH secretion, evaluation begins with noninvasive tests—the high-dose dexamethasone suppression test,

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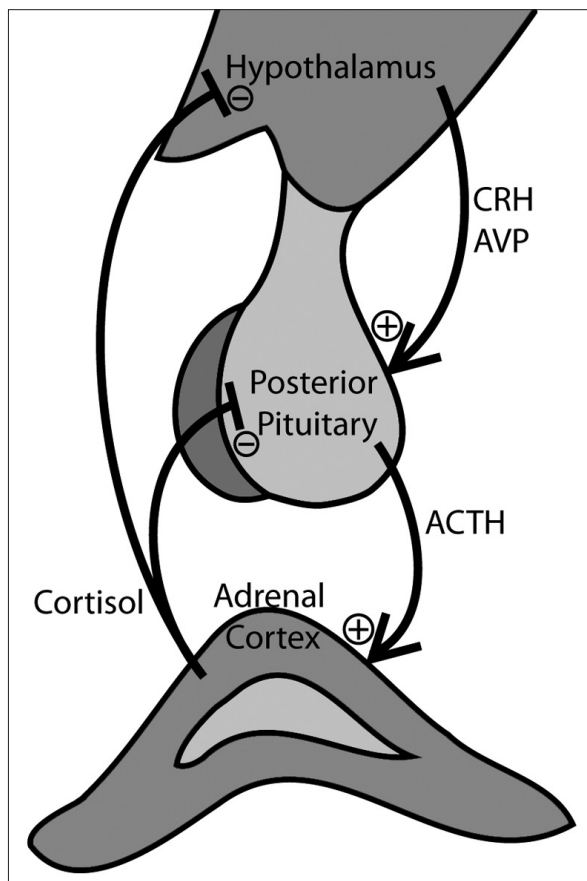


Figure 1. Hypothalamic-pituitary-adrenal axis. Hypothalamic secretion of corticotropin-releasing hormone (CRH) and vasopressin (AVP) is stimulated by hypoglycemia, hypoxia, fever, pain, hypotension, and normal circadian rhythms. CRH and AVP in turn stimulate the secretion of adrenocorticotrophic hormone (ACTH) by the anterior pituitary. ACTH stimulates the adrenal cortical secretion of glucocorticoids, including cortisol. Cortisol in turn inhibits CRH and ACTH release via negative feedback. In ACTH-independent Cushing syndrome, ACTH levels are low, and excess cortisol usually originates from a pituitary source. In ACTH-dependent Cushing syndrome, ACTH levels are high, and there is either a pituitary source of ACTH (Cushing syndrome) or an ectopic source of ACTH.

Table. Endogenous causes of Cushing syndrome (9, 10)

ACTH-dependent	
Pituitary source (Cushing syndrome)	67%
Ectopic source	10%
ACTH-independent	
Adrenal adenoma	13%
Adrenal carcinoma	7%
Other	2%

nuses are just lateral to the pituitary fossa and contain the carotid artery and cranial nerves (23). They are interconnected by four intercavernous pathways. The anterior and posterior intercavernous sinuses are present in all people and run in front of and behind the pituitary (24). The inferior intercavernous sinus, coursing along the sellar floor between the anterior and posterior pituitary lobes, is absent in a small number of people; however, it is usually present in three forms (plexus-like, venous lake, and mixed). Finally, the basilar plexus is present in all people, is located along the dorsum sellae, and is the largest interconnection in most cases (24).

Hypophyseal veins exit the anterior pituitary lobe and drain into a plexiform venous network overlying the pituitary surface, which in turn drains laterally into the intercavernous and cavernous sinuses. In spite of the broad communication between the cavernous sinuses, venous drainage from the pituitary is unilateral under normal physiologic conditions (23). This fact theoretically enables BIPSS to lateralize ACTH-secreting pituitary adenomas and necessitates bilateral sampling, as unilateral sampling could provide false-positive results (23). The inferior petrosal sinus (IPS) drains the cavernous sinus posteriorly, passes through the anterior jugular foramen, and drains into the internal jugular vein. As the IPS courses through the dura, it receives tributaries from the dura, pons, medulla, internal auditory meatus, and anterior condylar vein, which communicates with the plexus surrounding the twelfth cranial nerve in the hypoglossal canal (25).

There is interperson variability in the position of the junction of the IPS into

the corticotropin-releasing hormone (CRH) stimulation test, and eventually, cross-sectional imaging (12). The primary noninvasive diagnostic assay, the high-dose dexamethasone suppression test, is based on the fact that the secretion of ACTH by a pituitary adenoma is inhibited by high doses of dexamethasone, whereas ectopic sources of ACTH are not. However, this test offers only 60% to 80% sensitivity and specificity (8, 14). The CRH stimulation test relies upon the fact that most pituitary tumors respond to CRH administration by increasing ACTH secretion and, thus, cortisol levels. Unfortunately, many ectopic ACTH-secreting tumors also respond in this way, limiting interpretation of the results (15).

Pituitary gadolinium-enhanced MRI with fine cuts through the sella turcica is indicated in patients with ACTH-dependent Cushing syndrome (8) and is far superior to CT imaging (16). However, interpretation of noninvasive cross-sectional imaging is complicated by the high prevalence (10% to 20%) of nonfunctioning pituitary incidentalomas (17–19). Conventional spin echo imaging yields a sensitivity of only 50%

to 60%, although spoiled gradient-recalled acquisition sequences can increase this sensitivity to approximately 80% (20). Dynamic contrast-enhanced MRI may also improve imaging accuracy, given that adenomas tend to be slowly enhancing (21). False-negative MR results are due to microadenomas that are too small to detect by imaging, which is unfortunate given that most ACTH-secreting adenomas are subcentimeter (i.e., microadenomas) (19). Given that MRI can be equivocal in half of the patients tested, only relatively large lesions (>6 mm) detected on MRI with supporting biochemical confirmation and expected clinical symptoms reliably confirm the diagnosis of Cushing syndrome (12).

If these noninvasive tests fail to distinguish Cushing syndrome from ectopic ACTH secretion or if they provide equivocal or ambiguous results, BIPSS with CRH stimulation is indicated for further evaluation (22).

Anatomic considerations

Knowledge of the pituitary venous drainage is essential for the BIPSS technique (Fig. 2). The cavernous si-

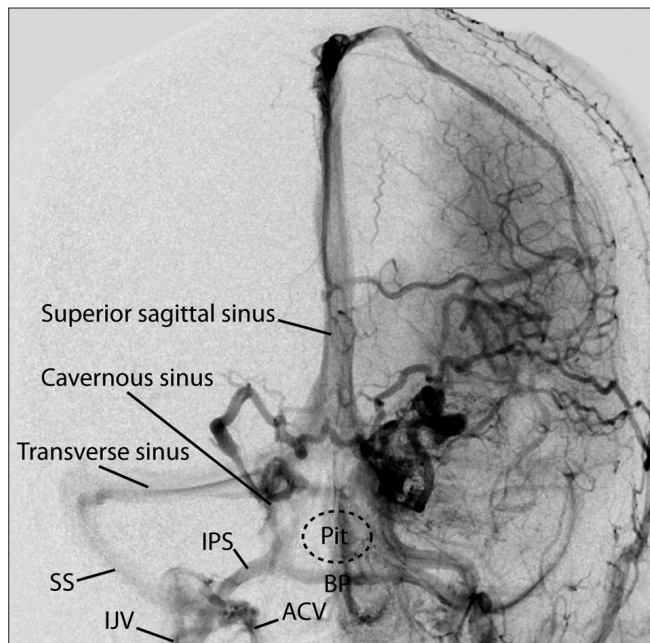


Figure 2. Inferior petrosal sinus anatomy. A venous-phase coronal image from a carotid angiogram demonstrates the venous anatomy at the skull base. This patient was being evaluated for a carotid-cavernous fistula. There is consequent diffuse abnormal dilatation of the venous system, allowing clear visualization of the sinus and venous anatomy. Pit, expected location of the pituitary; IPS, inferior petrosal sinus; SS, sigmoid sinus; ACV, anterior condylar vein; BP, basilar venous plexus; IJV, internal jugular vein.

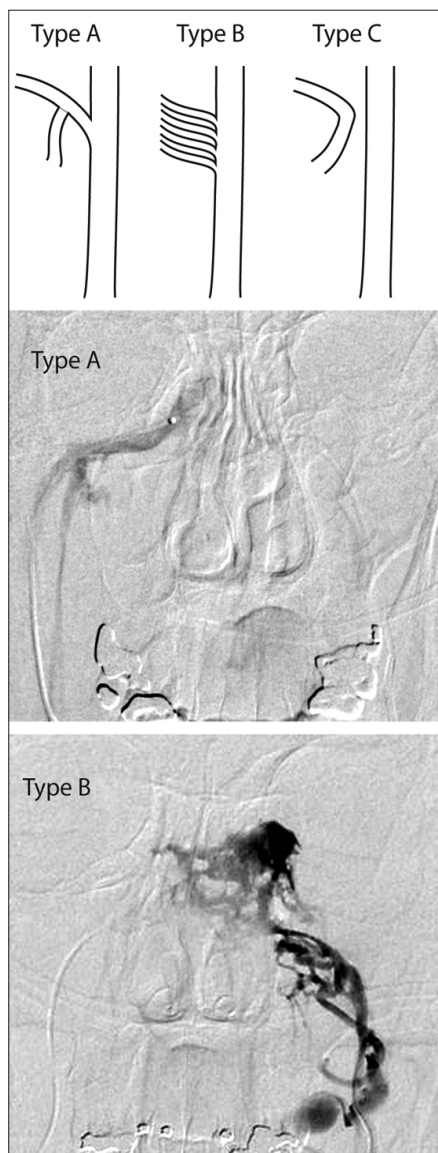


Figure 3. Patterns of inferior petrosal sinus drainage into the internal jugular vein. The diagram demonstrates three relevant anatomical patterns. Most commonly (Type A), the IPS drains directly into the internal jugular vein. The junction of the anterior condylar vein (ACV) is either absent, diminutive, or well defined (Types I and II by prior classifications). Less commonly (Type B), there is a plexus of small veins comprising the IPS drainage. Least commonly (Type C), the IPS drains into the vertebral venous plexus via the ACV.

the internal jugular vein. The IPS typically joins the internal jugular vein at the level of the inferior margin of the jugular foramen, roughly 6 mm below its entry into the foramen, although in some patients, the junction may be extracranial or within the foramen. Rarely, the junction is intracranial or the IPS drains into the sigmoid sinus rather than into the internal jugular vein. Within the jugular foramen, the diameter of the IPS is 2 to 4 mm (25).

In addition to variability in the position of the junction, there is also variation in its anatomic form (26). Four types of variant anatomy have been described (27). Most commonly (Type I; 45%), the IPS drains directly into the internal jugular bulb, with absent or nearly absent communication with the anterior condylar vein (ACV). In Type II anatomy (24%), the IPS anastomoses with the ACV before draining into the internal jugular vein. The ACV drains into the vertebral venous plexus. In Type III anatomy (24%), the IPS drains

into the internal jugular vein as a plexus of veins rather than as a single vein. This plexus also drains partly into the vertebral venous plexus. In the uncommon Type IV anatomy, the IPS drains solely or predominantly into the vertebral venous plexus via the ACV. The connection between the IPS and jugular vein in this case is hypoplastic or does not exist. This configuration is reported to be present in up to 7% of patients (27), though another study reported that it existed in less than 1% (25).

Bonelli and colleagues (28) suggested redefining this classification system, such that Type I and II anatomy differ based on the distance between the IPS-ACV anastomosis and the IPS-internal jugular vein junction. In our experience, the key anatomical consideration is to define the junction of the IPS and ACV if there is one and to advance the catheter past it so that IPS samples are not diluted by drainage from the ACV. We therefore suggest three relevant types of anatomy, essentially combining types I and II into a single Type A (Fig. 3).

Anatomic variations can obscure the interpretation of BIPSS results. For example, when the IPS is hypoplastic (Type IV or C), BIPSS yields false-negative results (29). Furthermore, the IPSs are also asymmetric in as many as 40% of patients (13, 30), leading to errors in lateralization. For this reason, venous angiography is routinely done during BIPSS prior to sampling to avoid such interpretative errors.

Historical considerations

Dr. Harvey Cushing was an American neurosurgeon who first described Cushing syndrome in the 1930s (31). Trans-sphenoidal surgery for pituitary tumors had been developed by Dr. Hermann Schloffer in the early 1900s, but it was abandoned by the 1920s because of its high mortality. From 1910 to 1925, Dr. Cushing worked to refine the trans-sphenoidal approach, but he instead transitioned to the transcranial approach, which had lower complication rates. Building on the teaching of his predecessors Drs. Normal Dott and Gerard Guiot, Dr. Jules Hardy began using intraoperative fluoroscopy and introduced the operative microscope, which significantly decreased morbidity and increased the success of the procedure (32, 33). The use of transsphenoidal

noidal surgery for Cushing syndrome spread during the 1970s, and now it is the treatment of choice, resulting in posttreatment survival rates similar to the general population (34).

Improvements in the surgical techniques motivated advances in the diagnostic tools. BIPSS as a diagnostic modality for Cushing syndrome was established in the 1970s. A case report in 1977 was the first to describe catheterization of and sampling of ACTH from the IPS to diagnose Cushing syndrome in a patient with perplexing clinical and laboratory features (35). This was followed by a case series in 1981 demonstrating the safety and efficacy of BIPSS in distinguishing Cushing syndrome from ectopic ACTH production, highlighting the importance of selecting the IPS, because measurements from the jugular veins were nondiagnostic (36).

The most important development in the BIPSS technique since that time has been the introduction of CRH administration during the procedure. CRH stimulates ACTH secretion in normal patients and in those with pituitary adenomas (37). Landolt et al. (38) were the first to administer CRH during BIPSS, and they demonstrated that CRH enhances the distinction between normal tissue and adenoma, therefore improving the sensitivity of BIPSS considerably.

Technical details and considerations

The standard protocol at our institution is to sample ACTH peripherally and from both IPSs before and after CRH administration. The procedure is performed under conscious sedation to enable monitoring of symptoms indicating complications. For example, because of the high sensitivity of the jugular fossa periosteum, catheterization that is too high will result in patient otalgia (23), which can only be assessed if the patient is conscious.

After the patient is prepped, 21 gauge micropuncture needles are used to access both common femoral veins in order to place a 6 F sheath into the right femoral vein and a 5 F sheath into the left femoral vein. The larger sheath is used on the right for peripheral sampling while the 5 F Davis catheter is in place. We then administer 3 000–5 000 units of heparin. In addition to refraining from cannulating the IPS too centrally, heparin ad-



Figure 4. Bilateral inferior petrosal sinus sampling technique. A coronal image shows placement of 5 F catheters within the internal jugular veins and 2.8 F microcatheters that have been advanced into the IPS bilaterally. Hand injection demonstrates Type A anatomy on the right, with a well-defined junction of the IPS and anterior condylar vein. Note that the optimal microcatheter position entails advancing the microcatheter beyond the anterior condylar vein and that there is mild reflux of contrast into the contralateral IPS.

ministration is important to avoid IPS and cavernous sinus thrombosis (22).

Through each femoral vein sheath, we advance a 5 F Davis catheter into the contralateral internal jugular vein, using a hydrophilic guidewire for wire manipulations. We then advance 2.8 F microcatheters over a 0.018" guidewire, directing them medially at the C1-2 level to cannulate the orifice of the IPS (13), without entering clival veins (23). Hand injection of contrast is used to outline the anatomy of the inferior petrosal, cavernous, and intercavernous sinuses. Optimal position is obtained when hand injection demonstrates ipsilateral IPS filling with contralateral reflux (23). Assessing the anatomy is essential because there are anatomic variants that can affect the interpretation of the results, as described above (29, 30). If the anterior condylar vein is found to anastomose with the IPS, then the microcatheter must be advanced beyond this junction within the IPS to avoid diluting the samples. Both catheters should be placed symmetrically, and intermittent fluoroscopy is used to confirm their correct position during the procedure (Fig. 4).

When the catheter positions are confirmed, two baseline samples are obtained from both IPSs as well as

from the right femoral sheath. We then administer CRH (Acthrel, 1 µg/kg; Ben Venue Laboratories, Ohio, USA) peripherally. Repeated sampling is obtained from both IPSs and from the right femoral vein sheath 3, 5, 10 and 15 min after the injection. These tubes are then placed in an ice bath and immediately transported to the laboratory for analysis after the sampling is complete.

After the samples are obtained, both femoral sheaths are removed and manual compression is used to obtain hemostasis before transferring patients to the recovery room. The entire procedure requires 1 to 2 hours. The patient is observed under strict bed rest for 4 hours before discharge the same day.

To interpret the results, the ratio of IPS to peripheral (IPS/P) ACTH level is calculated. Baseline IPS/P $\geq$ 2 or CRH-stimulated IPS/P $\geq$ 3 confirms Cushing syndrome (22). False-negative rates for BIPSS range from 1% to 10%. Such cases can be further evaluated by normalizing the ratio to prolactin levels, which must be measured at the time of BIPSS in a similar manner to what has been described elsewhere (22).

Because the drainage of the pituitary gland occurs predominantly via the ipsilateral IPS, the results theoretically may be used to deduce the lateraliza-

tion of the adenoma, although such results are controversial. An intersinus ratio of at least 1.4 has been considered as evidence of ipsilateral localization of an adenoma. Studies have demonstrated an accuracy of 50% to 100% (78% overall) using surgical findings as the gold standard, and accuracy is not improved with CRH administration (39). Therefore, irrespective of lateralization suggested by the BIPSS findings, surgeons routinely perform a full exploration of the entire pituitary gland rather than a hemihypophysectomy based solely on BIPSS results.

Complications

BIPSS is a safe procedure when performed by experienced interventional radiologists. The most common complication is groin hematoma from femoral access, occurring in at most 3%–4% of patients (25). Serious complications are very rare. In a series of 508 procedures at the NIH, there was one serious neurologic complication (pontine hemorrhage) and one patient with a severe vasovagal reaction (25). Three other patients in this series had transient complaints such as vertigo or paresthesias without abnormalities on brain CT or MRI. The authors described an additional case report at another institution of a patient with nausea and symptoms of a medial medullary syndrome who was found to have a non-hemorrhagic right medullary infarction. In a more recent study of 86 BIPSS procedures, two patients had transient CN VI palsies (40). Another group reported a venous subarachnoid hemorrhage causing acute obstructive hydrocephalus in one patient out of the 94 procedures performed at their institution (41). In another series of 44 BIPSS, there was one case of pontomedullary dysfunction, with MRI demonstrating a brainstem infarction (42). Given how rare such complications are, it is difficult to deduce what factors may increase risk, although catheter choice and variant venous anatomy may contribute.

Thromboembolic events have also occasionally been reported. Patients with Cushing syndrome are already at risk given their hypercoagulable state. In one series published at Vanderbilt University, 2 of 34 patients with Cushing syndrome developed deep venous thrombosis after BIPSS, with one of these patients expiring from a pul-

monary embolism (43). However, this center did not routinely heparinize patients periprocedurally. At another site, out of 94 procedures, there was one lower extremity deep venous thrombosis (41). Another group reported deep venous thrombosis in two patients undergoing BIPSS and discussed the importance of prophylactic anticoagulation in this patient group (44).

Accuracy and utility

When performed in experienced centers, BIPSS is highly accurate in diagnosing Cushing syndrome. In a meta-analysis review of 21 studies, the overall sensitivity and specificity of BIPSS were found to be 96% and 100%, respectively (39). CRH administration increases sensitivity such that it approaches 100% (45). At our institution, in a review of 185 BIPSS procedures for 179 patients from 1986 to 2002, there was 90% sensitivity and 67% specificity, with a 5% false-negative rate (46), in line with data reported by other centers. Given the low negative predictive value in that study (20%), the authors suggested that trans-sphenoidal exploration is indicated in patients with negative studies and no identifiable ectopic ACTH sources.

When compared with other diagnostic modalities, BIPSS is consistently more accurate. For instance, using stringent diagnostic criteria, Wiggam et al. (47) reported sensitivities of 48% for high-dose dexamethasone testing, 70% for CRH testing, and 82% for BIPSS. Compared with cross-sectional imaging, BIPSS is also superior. Kaskarelis et al. (48) reported an accuracy of 50% for MRI and 88% for BIPSS in 54 patients. Colao et al. (49), in a study of 84 patients, reported sensitivities of 40% for CT, 50% for MRI, and 90% for BIPSS, although noninvasive imaging was superior in lateralizing adenomas (75%–80% for CT and MRI versus 65% for BIPSS).

Even though BIPSS is more accurate than any other diagnostic modalities in routine use, because it is more invasive and costly, its application varies among institutions. There is general consensus that BIPSS is indicated only once ACTH-dependent hypercortisolemia has been firmly established (13, 22). In other words, BIPSS is not meant to diagnose Cushing syndrome, but to diagnose a pituitary source of ACTH hypersecretion.

There is also general agreement that BIPSS is always indicated when noninvasive testing yields conflicting or equivocal results (9, 12, 22). In some institutions, BIPSS is routinely performed in all patients evaluated for Cushing syndrome, even those with definitive noninvasive workups (50), given the high prevalence of pituitary incidentalomas and the excellent accuracy and safety of BIPSS in experienced hands (50). One retrospective study of 193 patients with ACTH-dependent Cushing syndrome compared clinical outcomes between a group with clear-cut noninvasive testing and no BIPSS versus a group with equivocal noninvasive testing who did undergo BIPSS. All patients received trans-sphenoidal surgery. The authors reported no difference in remission rate or recurrence between the two groups after surgery and concluded that selective application of BIPSS in the evaluation of Cushing syndrome does not lead to misdiagnosis (51). However, prospective studies comparing broad as opposed to selective application have not been done, and currently there are no formal societal guidelines (22).

Alternative procedures

Because of the technically demanding nature of BIPSS, some have studied a less demanding alternative, internal jugular venous sampling. Doppman et al. (52) collected jugular and inferior petrosal samples from 20 patients with Cushing syndrome and reported a sensitivity of 80% for jugular venous sampling compared with a 95% sensitivity for BIPSS. Another group reported a sensitivity of 94% for BIPSS and 83% for jugular venous sampling at specificities of 100%, a difference that was not statistically significant (53). The authors concluded that jugular venous sampling may be used in centers lacking technical expertise, although negative findings should be reevaluated with BIPSS.

Because BIPSS has not consistently provided accurate lateralization of adenomas, cavernous sinus sampling has been studied as an alternative procedure, with the idea that the cavernous sinus, which is in closer proximity to the pituitary, would provide more accurate ACTH gradients (54). Results have been mixed, and conclusions regarding its safety and accuracy are awaiting a larger case series (55).

Because CRH is not always available in all institutions, some have used desmopressin (a synthetic analog of vasopressin) instead to stimulate the pituitary during BIPSS. Several small series have suggested that this alternative may be safe and effective, although larger confirmatory studies have not yet been done (22).

At present, BIPSS with CRH stimulation remains the gold standard in the evaluation of Cushing syndrome.

As a conclusion, Cushing syndrome is an uncommon endocrine disorder caused by excess pituitary secretion of ACTH that leads to hypercortisolemia. Frequently, exclusion of extrapituitary sources of ACTH is difficult, given the limited sensitivity of noninvasive tests. BIPSS offers a sensitivity and specificity approaching 100%. Careful delineation of the patient's venous anatomy and attention to technical considerations, including proper catheter placement and periprocedural heparinization, are essential to provide a safe procedure with interpretable results. While some have begun to study alternative techniques, such as cavernous sinus sampling or pituitary stimulation with desmopressin, BIPSS with CRH administration is the current gold standard for diagnosing Cushing syndrome.

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Conflict of interest disclosure

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