

# Bilateral inferior petrosal sinus sampling in the diagnosis of Cushing disease

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**Abstract:** Bilateral inferior petrosal sinus sampling (BIPSS) is a minimally invasive procedure performed in the workup of adrenocorticotrophic hormone (ACTH)-dependent Cushing syndrome (CS). Because noninvasive tests in the evaluation of CS patients lack sensitivity, BIPSS is the gold standard in diagnosing Cushing disease (CD), which is a pituitary source of excess ACTH. Here, the pathophysiology of CD and procedural details of BIPSS are reviewed.

**Keywords:** pituitary adenoma, Cushing disease, inferior petrosal sinus, venous sampling

## Introduction

Cushing syndrome (CS) carries an increased morbidity and mortality<sup>1</sup> with an estimated incidence of one per 500,000 persons.<sup>2</sup> Most cases of endogenous CS are caused by Cushing disease (CD), characterized by an adrenocorticotrophic hormone (ACTH)-secreting pituitary adenoma that may be surgically resected for a cure. Noninvasive imaging and laboratory tests have low sensitivity, confounding diagnosis. Bilateral inferior petrosal sinus sampling (BIPSS) is sensitive and specific, and is therefore the gold standard assay for diagnosing CD.<sup>3</sup>

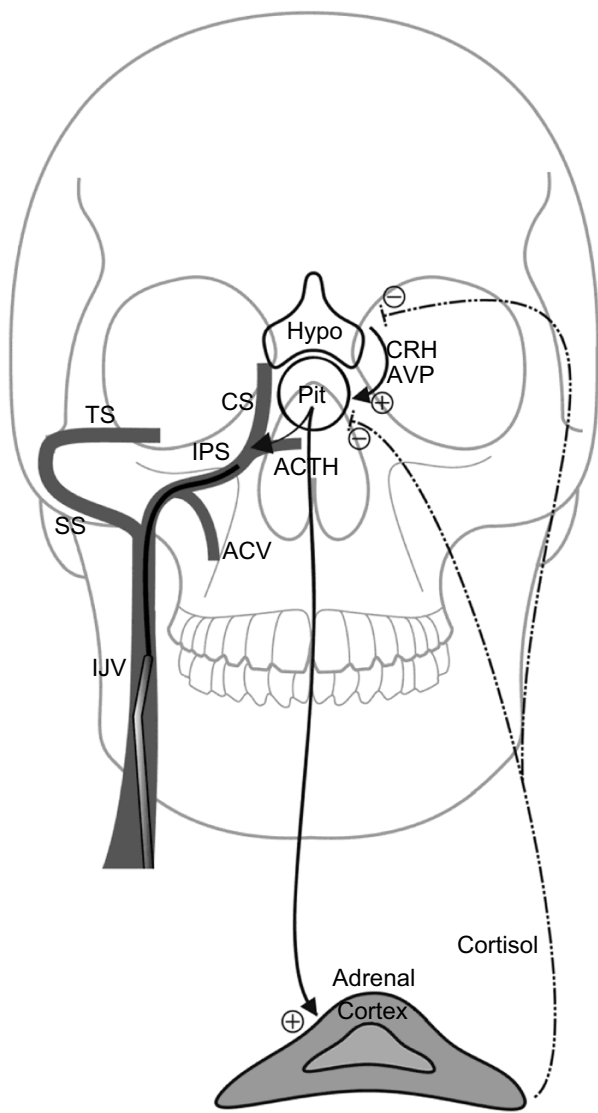
## Pathophysiology of Cushing disease

CS is an endocrine disorder involving the hypothalamus-pituitary-adrenal axis (HPAA), leading to excess cortisol (Figure 1). Symptoms include central obesity, moon facies, and proximal muscle weakness, dermatologic changes, including thin skin, purple striae, baldness, and hirsutism, and metabolic derangements, including hypertension, hyperglycemia, menstrual irregularities, and impotence.<sup>4</sup>

In the normally functioning HPAA, the hypothalamus secretes corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to secrete ACTH. ACTH in turn stimulates adrenal cortical secretion of cortisol. Hypothalamic secretion of arginine vasopressin (AVP) also stimulates anterior pituitary secretion of ACTH. By a negative feedback loop, cortisol inhibits pituitary secretion of ACTH and hypothalamic secretion of CRH. In the case of an ACTH-secreting pituitary adenoma, ACTH is secreted without hormonal stimulation. Therefore, despite negative feedback loops triggered by excess cortisol, ACTH is autonomously secreted, further increasing cortisol levels, leading to Cushingoid signs and symptoms.

Recent progress has uncovered potential pathways underlying increased ACTH secretion and corticotroph tumorigenesis. Synthesis of proopiomelanocortin (Pomc), the precursor of ACTH, is upregulated by an epidermal growth factor receptor

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**Figure 1** Anatomy and physiology of HPA.

**Notes:** Hypothalamic (Hypo) secretion of CRH and AVP induce pituitary (Pit) secretion of ACTH. ACTH stimulates adrenal cortical secretion of cortisol, which in turn negatively modulates CRH and ACTH secretion. Pituitary secretion of ACTH is measured in the IPS. The ACV usually drains into the IPS before venous blood returns to the IJV. The IPS is accessed with a microcatheter (black tube), which is advanced via a five-French guiding catheter (gray tube) in the IJV. (+) indicates stimulatory pathway; (–) indicates inhibitory pathway.

**Abbreviations:** HPAA, hypothalamus-pituitary-adrenal axis; CRH, corticotropin-releasing hormone; AVP, arginine vasopressin; ACTH, adrenocorticotrophic hormone; IPS, inferior petrosal sinus; ACV, anterior condylar vein; IJV, internal jugular vein; TS, transverse sinus; SS, sigmoid sinus; CS, cavernous sinus.

(EGFR) pathway.<sup>5</sup> Recently, *USP8* mutations, present in a third of corticotroph adenomas in the setting of CD, have been shown to increase EGFR levels, in turn stimulating Pomc and consequently ACTH levels.<sup>6</sup> Such important investigation not only elucidates the pathogenesis of CD, but also suggests possible therapeutic and diagnostic strategies.

The pituitary gland is drained by hypophyseal veins that empty into a plexiform venous network overlying the pituitary surface, in turn draining laterally into the intercavernous

and cavernous sinuses. Despite broad intercavernous communication, pituitary venous drainage is often unilateral, necessitating bilateral venous sampling to avoid false negatives.<sup>7</sup> The cavernous sinus empties into the superior petrosal sinus posteriorly and superiorly, and the inferior petrosal sinus (IPS) posteriorly and inferiorly. The IPS in turn empties into the internal jugular vein after passing through the anterior jugular foramen. The IPS usually joins the internal jugular vein at the inferior jugular foramen margin, about 6 mm below its foraminal entry, though there is interperson variability. The diameter of the IPS is 2–4 mm within the jugular foramen.<sup>8</sup>

The IPS is the vein most proximal to the pituitary gland that can safely accommodate a microcatheter for venous sampling and measurement of pituitary ACTH secretion. Here, dilution due to contribution from other veins, such as the anterior condylar vein (ACV), is minimized.

The purpose of sampling the IPS is to identify a pituitary source of excess ACTH to diagnose CD. While CS is most often caused by exogenous glucocorticoid administration, endogenous CS may be due to ACTH- or cortisol-secreting tumors (Table 1).<sup>9,10</sup> Most endogenous CS cases are caused by an ACTH-secreting pituitary adenoma (CD).

Noninvasive workup

Patients with suspected CS are first evaluated to diagnose hypercortisolemia, with laboratory tests, including urinary free cortisol, late-night salivary cortisol, and the low-dose dexamethasone suppression test (Figure 2).<sup>11</sup>

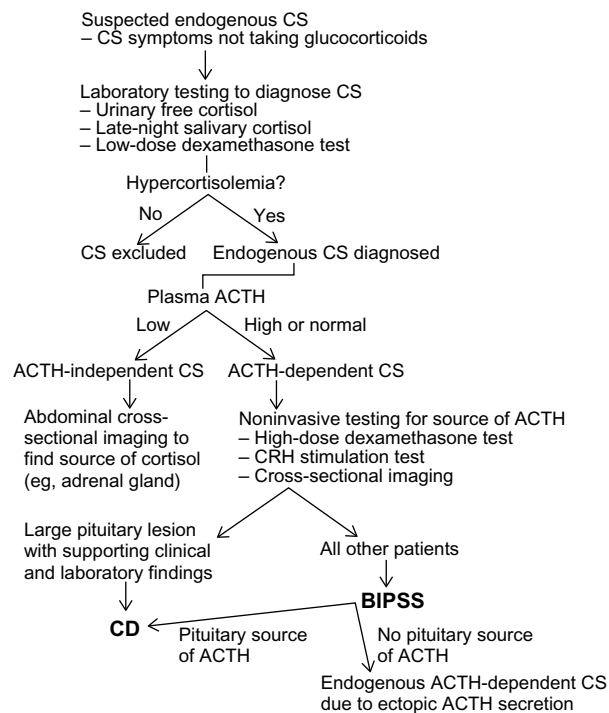
Once hypercortisolemia has been established, the next step is to identify the cause. First, plasma ACTH levels are measured.<sup>12</sup> Low ACTH levels suggest ACTH-independent CS; abdominal cross-sectional imaging may reveal an adrenal cause of excess cortisol secretion. High or normal plasma ACTH suggests ACTH-dependent CS, and may be due to pituitary etiologies (hormone-secreting adenomas), or due to ectopic sources (gastrinomas, carcinoid and neuroendocrine tumors, pheochromocytoma, medullary thyroid

**Table 1** Endogenous causes of CS

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

**Notes:** Data from Boscaro and Arnaldi;<sup>9</sup> and Nieman.<sup>10</sup>

**Abbreviations:** CS, Cushing syndrome; ACTH, adrenocorticotrophic hormone; CD, Cushing disease.



**Figure 2** Workup of patients with suspected CD.

**Abbreviations:** CD, Cushing disease; CS, Cushing syndrome; ACTH, adrenocorticotropic hormone; BIPSS, bilateral inferior petrosal sinus sampling.

carcinoma, pancreatic carcinoma, and bronchioloalveolar carcinoma).<sup>13,14</sup>

Pituitary and ectopic ACTH secretion can be distinguished by noninvasive laboratory assays – the CRH stimulation test, the high-dose dexamethasone suppression test, and cross-sectional imaging.<sup>12</sup> The high-dose dexamethasone suppression test is the primary noninvasive diagnostic test; high-dose dexamethasone inhibits pituitary adenoma secretion of ACTH but does not usually inhibit ectopic ACTH sources of ACTH. However, sensitivity and specificity are only 60%–80%.<sup>11,15</sup> The CRH stimulation test involves administering CRH, which induces most pituitary tumors to increase ACTH secretion, in turn upregulating cortisol levels that are measured peripherally. However, many ectopic ACTH-secreting tumors also respond to CRH; hence, this test cannot necessarily distinguish pituitary and ectopic sources.<sup>16</sup>

Pituitary gadolinium-enhanced MRI, which is superior to CT, is performed for patients with ACTH-dependent CS, and can have sensitivity of roughly 80%.<sup>11,17,18</sup> However, because of the high prevalence (10%–20%) of nonfunctioning pituitary incidentalomas,<sup>19–21</sup> the finding of a pituitary lesion does not definitively diagnose CD. Furthermore, microadenomas may be too small to detect by imaging, leading to false negatives.<sup>21</sup> Only large lesions (>6 mm) on MRI with supporting clinical symptomatology and laboratory

confirmation can be considered diagnostic of CD.<sup>12</sup> In all other cases, BIPSS with CRH stimulation is indicated for further evaluation.<sup>22</sup>

## BIPSS procedure

Most often, BIPSS is performed by sampling ACTH peripherally and from both IPSs before and after CRH (Acthrel; Ben Venue Laboratories, Ohio, USA) administration. In the US, CRH is typically given at a dose of 1 µg/kg, by slow intravenous push over 30 seconds; in other countries, a typical dose is 100 µg. Conscious sedation is preferred to allow for the monitoring of symptoms suggesting complications. A 6-French sheath is advanced into the right femoral vein, and a five-French sheath into the left femoral vein. The larger sheath allows for sampling from the common femoral vein, while a 5-French catheter is in place distally. Subsequently, 3,000–5,000 units of heparin are given to prevent cavernous sinus and other venous thrombosis.

Next, 5-French Davis catheters are advanced through each femoral vein sheath into the contralateral internal jugular vein, followed by 2.8-French microcatheters, directed medially at the C1–2 level to access the orifice of the IPS<sup>14</sup> without entering clival veins.<sup>7</sup> Both catheters are positioned symmetrically.

Once catheter positions are confirmed, two baseline ACTH specimens are collected from the right femoral sheath (peripheral specimen) and both IPSs. CRH is then administered peripherally. Repeat ACTH sampling from the periphery and both IPSs is obtained 3 minutes, 5 minutes, 10 minutes, and 15 minutes after the injection of CRH. Samples are collected in tubes that are placed on ice before transport to the laboratory. Upon completion of sampling, both femoral sheaths are removed, and manual compression is used to obtain hemostasis before transferring patients to the recovery room for a rest of approximately 4 hours. In our experience, groin hematoma occurs rarely, and thus protamine is not routinely administered.<sup>23,24</sup>

In experienced centers, BIPSS sensitivity and specificity approach 100%,<sup>25</sup> particularly when CRH administration is incorporated.<sup>26</sup>

## BIPSS results interpretation

Interpreting BIPSS results involves calculating the ratio of IPS to peripheral (IPS/P) ACTH levels assessed (Table 2). The diagnosis of CD is confirmed by a baseline IPS/P  $\geq 2$  or CRH-stimulated IPS/P  $\geq 3$ .<sup>22</sup>

Some researchers have tried to extrapolate lesion lateralization from the results, by calculating an intersinus ACTH

**Table 2** Example of BIPSS results

Time	Baseline	3 minutes	5 minutes	10 minutes	15 minutes
Peripheral	30	45	72	160	189
Left	92	531	1,255	1,732	1,349
Right	165	753	3,640	4,250	1,903
Left IPS/P	3.1	11.8	17.4	10.8	7.1
Right IPS/P	5.5	16.7	50.6	26.6	10.1

**Notes:** ACTH levels (pg/mL) assessed from the left and right IPS, and a peripheral vein (right common femoral) at baseline and various time points after CRH administration are presented. This patient had a pathology-proven right pituitary ACTH-secreting adenoma causing CD. The IPS/P ratio is calculated as the ACTH value from the IPS divided by the value from the peripheral vein; CD is confirmed by baseline IPS/P  $\geq 2$  or CRH-stimulated IPS/P  $\geq 3$ .

**Abbreviations:** BIPSS, bilateral inferior petrosal sinus sampling; IPS/P, inferior petrosal sinus/peripheral; ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; CD, Cushing disease.

ratio, taking ratios  $\geq 1.4$  as an evidence of ipsilateral adenoma localization. However, reported accuracy, with surgical findings as the gold standard, ranges from 50% to 100%.<sup>25</sup> Thus, full surgical exploration of the entire pituitary gland is commonly performed in lieu of hemihypophysectomy, regardless of lateralization suggested by BIPSS.

## BIPSS procedure pearls

### Assuring adequate catheter positioning

As the goal of BIPSS is to sample venous outflow from the pituitary gland in the vein most proximal to the gland but without a risk of complication, the microcatheter should be advanced beyond the junction with ACV to prevent sample dilution. Catheterization that is too central should be avoided; because the jugular fossa periosteum is highly sensitive, high catheterizations will cause otalgia, which can be assessed symptomatically as long as the patient is sedated but not intubated.<sup>7</sup> Hand injections are used to delineate venous anatomy and demonstrate adequate positioning, obtained when ipsilateral IPS filling is seen with contralateral reflux (Figure 3).<sup>7</sup> Once the catheters are in place and sampling begins, intermittent fluoroscopy should be performed to assure the catheters remain positioned throughout.

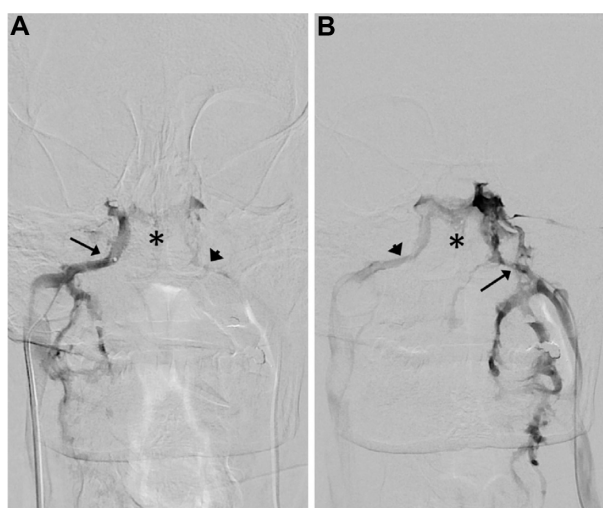
### Variant anatomies of IPS-internal jugular venous junction

An assessment of venous anatomy may reveal variants that influence result interpretation.<sup>27,28</sup> In many (45%) people, the IPS empties in the internal jugular vein without significant contribution from the ACV. In other patients (25%), there is an anastomosis of the IPS with the ACV before joining the internal jugular vein, while in others (25%), the IPS joins the internal jugular vein as a plexus of veins, rather than a single vein (Figure 4). Specimens may be diluted by ACV contribution, and noting such an anastomosis with the IPS should prompt catheterization more centrally to avoid dilution. Least commonly (1%–5%), the IPS empties primarily through the

ACV into the vertebral venous plexus.<sup>8,29</sup> In this scenario, the IPS may not be amenable to catheterization, precluding sampling. Delineating the venous anatomy is therefore essential to performing successful BIPSS.

## Avoiding complications

In the hands of an experienced interventional radiologist, BIPSS is a safe procedure with few complications. Groin hematoma from femoral access is the most common complication, seen in fewer than 5% of patients,<sup>8</sup> similar to other procedures requiring common femoral venous access.<sup>30</sup> Very rarely, serious complications have been reported, including brainstem hemorrhages or nonhemorrhagic brainstem infarctions.<sup>8,31</sup> These constitute only one or two cases of hundreds of sampling procedures, obscuring the cause of such adverse events, which could be related to catheter choice, for example.

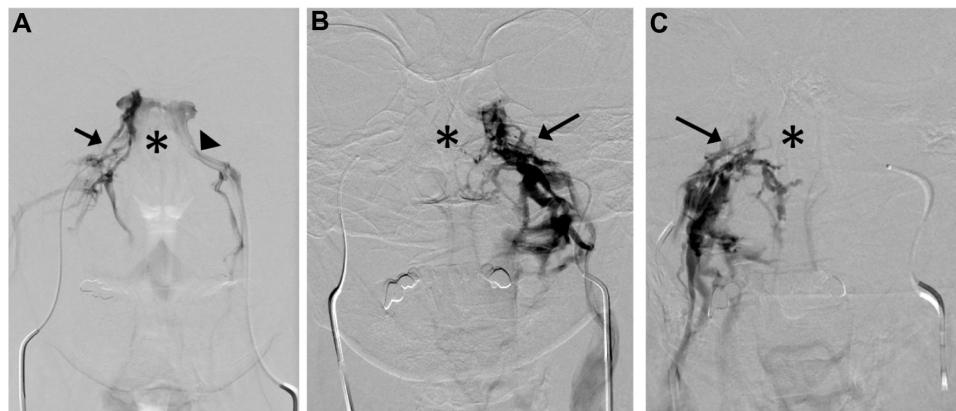


**Figure 3** Digital subtraction angiography views of the IPSs.

**Notes:** (A) Black arrow indicates the position of the right microcatheter within the IPS. Contrast injection demonstrates opacification of the cavernous sinus and the contralateral IPS (arrow head); (B) Black arrow indicates the position of the left microcatheter within the IPS. Contrast injection demonstrates opacification of the cavernous sinus and the contralateral IPS (arrowhead). Black star indicates the expected position of the pituitary gland.

**Abbreviation:** IPS, inferior petrosal sinus.





**Figure 4** Variant IPS anatomy in digital subtraction angiography.

**Notes:** (A) The left IPS (arrowhead) is a single vein as demonstrated by reflux from contralateral IPS contrast injection. The arrow indicates at least three right-sided IPS veins. Contrast injection from the presumed (B) left and (C) the right IPSs reveal a plexus of veins (arrows). (A–C) \*indicates the expected location of the pituitary gland.

**Abbreviation:** IPS, inferior petrosal sinus.

Occasionally, thromboembolic events occur, as may be expected in the hypercoagulable state of CS. These primarily include cavernous sinus thrombosis, and deep venous thrombosis potentially leading to pulmonary embolism.<sup>32–34</sup> Routine heparinization is an essential step to avoiding thromboembolic complications, and venous thrombosis will almost never be encountered if such measures are taken.

## Newer techniques improving diagnostic accuracy and reducing complications

Because of reported false negative rate ranging from 1% to 10%, efforts have been made to increase the certainty of diagnosis of ectopic sources of ACTH, when a pituitary source is not identified during BIPSS. Specifically, prolactin levels in the collected venous specimen is considered to accurately demonstrate that the sample is truly from the pituitary venous effluent.<sup>35</sup> While some studies suggest that prolactin may be used to demonstrate correct catheter positioning and to normalize measured ACTH levels,<sup>36</sup> because of the high cost of the assay, samples are stored until ACTH results are received, and only used if results indicate an ectopic source. Such samples can then be assessed for prolactin to confirm the adequacy of sampling and prevent false negative outcomes.<sup>37–39</sup>

The primary technological advance enabling correct catheter positioning and reducing complications is the incorporation of microcatheters, which became more commonly used in the 1990s.<sup>40</sup> Such devices allow for more central catheterization of the IPS, and likely have lower rates of venous thrombosis.

## Hormonal stimulation with desmopressin

Because CRH is not always available, some researchers have used desmopressin (DDAVP, a synthetic analog

of vasopressin) in its place to stimulate the pituitary during BIPSS, given at a dose of 10 µg intravenously. Several small series suggest that this alternative may be safe and effective.<sup>22</sup> In a series of 18 patients who underwent BIPSS with DDAVP, the procedure produced similar laboratory findings compared with sampling with CRH stimulation, and the sensitivity was 95%.<sup>24</sup> Because of its low cost compared with CRH, DDAVP administration may become routine in the future; however, larger series verifying its safety and efficacy are pending.

## Conclusion

CD is a rare endocrine disease characterized by hypercortisolemia caused by excess ACTH secreted by the pituitary. Distinguishing pituitary sources from the ectopic sources of ACTH is challenging because of the limited accuracy of noninvasive assays. BIPSS is the gold standard diagnostic test with sensitivity and specificity of nearly 100%. Understanding venous anatomical variation, intraprocedural heparinization, and attending to optimal catheter positioning and sample handling are all essential aspects to maximizing procedural safety and technical success.

Though BIPSS is more accurate than other diagnostic tests, it is not used as frequently as one might argue it should be due to its invasiveness and cost. However, it is generally agreed that BIPSS is indicated for ACTH-dependent hypercortisolemia<sup>14,22</sup> and when noninvasive assays yield equivocal results.<sup>9,12,22</sup> Because of the high prevalence of pituitary incidentalomas, some institutions routinely perform BIPSS for all patients evaluated for CD.<sup>41</sup> It is imperative for interventional radiologists to reach out to referring providers caring for patients with possible CD to optimize care for these patients.

## Disclosure

The authors report no conflicts of interest in this work.

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