



## Diagnosis of Small Adrenal Pheochromocytomas by Adrenal Venous Sampling with Glucagon Stimulation Test

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### ABSTRACT

**Background:** Pheochromocytoma develops in 0.1-0.5% of the hypertensive population between the ages of 30-50 years and is classically characterized by either sustained or paroxysmal hypertension, flushing, sweating, palpitations, and severe anxiety.

**Objectives:** To demonstrate the safety and usefulness of bilateral adrenal venous sampling (BAVS) in patients with pheochromocytoma, but with negative imaging results

**Patients and Methods:** We used BAVS with glucagon stimulation (1 mg, IV bolus) and measured stimulated fractionated catecholamines (norepinephrine [NE] and epinephrine [EPI]).

**Results:** We performed BAVS with glucagon stimulation on 41 patients who presented with signs and symptoms highly suggestive of the presence of pheochromocytoma, and also had equivocal imaging results. Twenty patients were diagnosed with unilateral pheochromocytoma. The minimum predictive cut-off value for the EPI ratio of affected vs. unaffected sides in diagnosing a unilateral pheochromocytoma was 6.8 (sensitivity; 88.9%, specificity, 87.5%,  $P = 0.001$ ). The minimum predictive cut-off value for the norepinephrine (NE) ratio of affected vs. unaffected sides was 3.8 (sensitivity; 90%, specificity; 81.2%,  $P = 0.001$ ). The 2-min post glucagon-stimulated levels of affected versus unaffected adrenals were: EPI;  $29,162 \pm 8,756$  vs.  $1,136 \pm 546$  pg/ml (ratio = 25.7) and NE;  $7,156 \pm 1,399$  vs.  $760 \pm 228$  pg/ml (ratio = 9.4). The EPI:NE ratio on the affected side was significantly higher (4.1 vs. 1.5,  $P < 0.001$ ). During the follow-up period, patients who did not require post-operative medication were those who had a shorter duration of hypertension ( $4.8 \pm 3$  vs.  $10 \pm 10.8$  years).

**Conclusions:** BAVS with glucagon stimulation is a safe and useful approach for early diagnosis of pheochromocytoma.

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### ► Implication for health policy/practice/research/medical education:

BAVS with glucagon stimulation will lead to early diagnosis of microscopic pheochromocytoma, thus preventing chronic complications like atherosclerosis, and untoward events like myocardial infarction and stroke.

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## 1. Background

Pheochromocytoma occurs in 0.1%-0.5% of the hypertensive population between the ages of 30-50 years. This

condition is classically characterized by either sustained or paroxysmal hypertension, flushing, sweating, palpitations, and severe anxiety. Delays in diagnosis can lead to fatal cardiovascular events (1-4). Definitive diagnosis of pheochromocytoma is established by positive biochemical tests that are based on measurements of either plasma or urine metanephrines and catecholamines (1, 5, 6). In addition, if the tumor is large enough, it can be detected by computerized tomography (CT), magnetic resonance imaging (MRI), or meta-iodobenzylguanidine scanning (MIBG) (1, 6). Recently, positron emission tomography (PET) scanning has also proved to be effective in detection of primary and metastatic pheochromocytomas (7). However, limitations of these diagnostic modalities are apparent in the case of so-called biochemically silent tumors (7-10). Some pheochromocytomas only secrete catecholamines periodically, with the result that tumors may go undetected if the biochemical diagnosis is based on measurements of catecholamines alone (11, 12). Although metanephrines are continuously released from tumors, procedures for their measurement in plasma or urine are still unavailable in many countries, or are considered to be too expensive (13). Furthermore, some tumors secrete only dopamine, with no clinical symptoms or signs of catecholamine excess (14). Finally, because of an increase in the use of CT and MRI scans, there is an increasing incidence of adrenal incidentalomas, most of which are non-functional (15-17). Bilateral adrenal venous sampling (BAVS) with stimulation has been used for the diagnosis and localization of both cortisol- and aldosterone-producing adrenal adenomas (15, 18, 19). However, although its usefulness in diagnosis of pheochromocytoma has been shown in the past (18, 20-31), no studies have yet demonstrated the outcome and usefulness of such sampling combined with glucagon stimulation.

## 2. Objectives

In the present study, we report 41 cases with clinical signs and symptoms suggestive of adrenal pheochromocytoma and who underwent BAVS with glucagon stimulation. The majority of patients presented with normal biochemical results and equivocal imaging studies. Through sampling with glucagon stimulation and analysis of catecholamine gradients, we successfully identified 25 patients with unilateral tumors, 16 with suspected bilateral lesions, and 5 without tumors. The objective of this report was to demonstrate that BAVS with glucagon stimulation is a safe and useful test for localizing small adrenal pheochromocytomas, thereby enabling early diagnosis before the development of cardiovascular, and other organ, complications due to catecholamine excess.

## 3. Patients and Methods

### 3.1. Subjects

Forty-one patients, 20 males and 21 females, aged 15 to

67 years (mean  $39.7 \pm 13.4$  years), highly suspected to have pheochromocytoma, consented to undergo BAVS with glucagon stimulation. Mean age at the onset of hypertension was  $34 \pm 13$  years. Mean duration of hypertension was  $6.2 \pm 7.2$  years. The highest mean systolic blood pressure was  $187.4 \pm 35.2$  mm Hg and the highest mean diastolic blood pressure was  $108 \pm 15.5$  mm Hg. The majority of patients had paroxysmal hypertension, headache, palpitations, and dizziness, while others had flushing, weakness, and severe anxiety.

### 3.2. Methods

All 41 cases underwent complete history and physical examinations. Serum potassium was requested, and if lower than 3.7 mmol/L (normal value [NV]: 3.8-5.3), plasma renin activity (mean:  $15.93 \pm 27.84$ ; NV: 1.31-3.95 ng/mL/h,  $n = 9$ ) was measured (17). CT of the adrenals with contrast (3 mm cut) was performed which showed no definite mass in any of the patients, except one, where left apoplexy was noted. Some patients presented for consult with elevated plasma or urine catecholamine or metanephrine levels. Others consented to undergo BAVS, even though they had normal biochemical results, they had clear signs and symptoms related to catecholamine excess.

### 3.3. Venous Sampling and Glucagon Stimulation Test

Patients continued their anti-hypertensive medications in the peri-sampling period. The Procedure was scheduled in the morning. If necessary, a nitroprusside or nicardipine drip, was used to maintain blood pressure to at least 140 mm Hg systolic and 90 mm Hg diastolic before, during, and after the sampling. The procedure was scheduled for the morning after an overnight fast. All patients were premedicated with diphenhydramine and nalbuphine for preemptive analgesia. A monitored anesthesia care (MAC) technique was applied during the procedure, with incremental sedation as necessary using IV midazolam and nalbuphine to maintain a sedated, calm, and cooperative patient, who was still arousable. The venous sampling procedure was performed using the Seldinger technique (percutaneous guidewire placement technique). The femoral vein was accessed and catheterization of the left renal vein was achieved through the inferior vena cava, followed by cannulation of the left adrenal vein. Catheter position was confirmed by low-pressure contrast medium venogram (Figure 1a). Three to 4 mL of the left adrenal vein blood was aspirated and discarded, followed by low-pressure aspiration of 10 mL of blood for baseline samples. A Simmon's II catheter was pulled down to the level of the external iliac veins where 10 mL of blood for a baseline peripheral sample was taken. The Simmon's II catheter was replaced with a 5-F Mallinckdroft Cobra II catheter with a side hole, and cannulation of the right adrenal vein was carried out. The position of the catheter was confirmed by venogram (Figure 1b). Glucagon (1 mg, IV bolus) (28, 31, 32), was

administered through the antecubital vein, followed by collection of stimulated blood samples after 2 min by repeat selective sampling maneuvers, as described above, starting at the right adrenal vein and then to the left. The first samples were sent to Specialty Laboratories Inc., Santa Monica, California, USA and then to National University Hospital (NUH) in Singapore for determination of fractionated plasma catecholamines, NE, EPI, and dopamine by high-performance liquid chromatography (HPLC). Eventually NUH sent the samples to the Mayo Clinic, Rochester, USA. Initially, baseline samples were assayed, but eventually only stimulated samples were studied. In the stimulated samples, serum cortisol levels were also analyzed to determine catheter position and to provide a denominator to control for the relative dilution of catecholamines in samples from each side (4). Only NE and EPI gradients were analyzed in the study. Initially, patients with significant gradients (>2 from baseline) on one side were diagnosed to have unilateral pheochromocytoma and were subjected to unilateral adrenalectomy. For patients with suspected bilateral adrenal lesions, the side with the higher stimulated catecholamine response was labeled as dominant and the side with the lesser response was labeled non-dominant. Thereafter, as the number of patients increased, a statistical analysis of the gradient was formulated accordingly. The minimum predictive cut-off value for the EPI ratio of the affected vs. unaffected side in diagnosing unilateral pheochromocytoma was 6.8 with a sensitivity of 88.9% and specificity of 87.5% ( $P = 0.001$ ). A ratio of 20.4 would yield a specificity of 100% with a sensitivity of 83.3%. The minimum predictive cut-off value for the NE ratio of affected vs. unaffected sides in diagnosing unilateral pheochromocytoma was 3.8 with a sensitivity of 90% and specificity of 81.2% ( $P = 0.001$ ). The majority of patients tolerated the procedure with no untoward events. Patients were given an option to have the dominant adrenal removed.

#### 4. Results

Bilateral adrenal venous sampling with glucagon stimulation Of the 41 patients, 20 were diagnosed to have unilateral pheochromocytoma, 16 patients with suspected bilateral lesions, and 5 with normal results (EPI < 100 pg/ml, NE < 750 pg/ml). There was no significant difference in the clinical profiles of patients diagnosed with unilateral tumors and those with suspected bilateral lesions (Table 1). The endocrine profiles of patients diagnosed with unilateral pheochromocytoma are shown in Table 2. Marked elevations in EPI and NE levels in the affected adrenals compared to the unaffected side were noted. The mean of the 2 min post-glucagon stimulation levels of affected vs. unaffected adrenals were: EPI; 29,162 ± 8,756 vs. 1,136 ± 546 pg/ml (ratio; 25.7) and NE; 7,156 ± 1,399 vs. 760 ± 228 pg/ml (ratio = 9.4). The EPI:NE ratio on the affected side was significantly higher than on the unaffected side (4.1 vs. 1.5,  $P < 0.001$ ). The catecholamine hypersecretion observed in the adrenals was not seen in the periphery,

**Table 1.** Comparative Clinical Profiles of Patients with Unilateral vs. Suspected Bilateral Pheochromocytoma Diagnosed by Bilateral Adrenal Venous sampling with Glucagon Stimulation<sup>a</sup>

	Unilateral Tumor (n = 20)	Suspected Bilateral (n = 16)
Age, y		
Mean ± SD	39.7 ± 14	40 ± 14
Range	15–67	18–65
Sex, No.		
Male	6	10
Female	14	6
Age at onset of hypertension, y		
Mean ± SD	33 ± 13	36 ± 14
Range	15–57	12–63
Duration of hypertension, y		
Mean ± SD	7.4 ± 1.9	5.2 ± 1.6
Range	1.2–37	1.2–28
Highest systolic BP, mmHg		
Mean ± SD	194 ± 37	175 ± 26
Range	130–300	130–220
Highest diastolic BP, mmHg		
Mean ± SD	108 ± 12	108 ± 12
Range	90–130	90–130

<sup>a</sup>  $P = N.S$

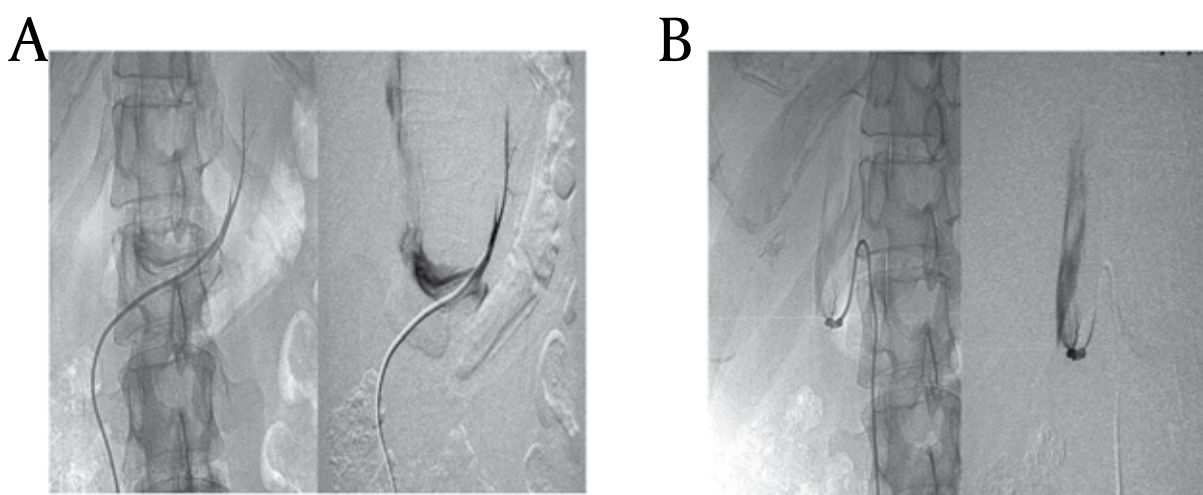
**Table 2.** Stimulated Fractionated Catecholamine Levels in Patients with Unilateral Pheochromocytoma Diagnosed by Bilateral Adrenal Venous Sampling with Glucagon Stimulation

	Unilateral Tumor		Ratio
	Affected Side	Contralateral Side	
EPI <sup>a</sup> , pg/mL, Mean ± SE	29,162 ± 8,756	1,136 ± 546	25.7
NE <sup>a</sup> , pg/mL, Mean ± SE	7,156 ± 1,399	760 ± 228	9.4
Ratio of EPI <sup>a</sup> :NE <sup>a</sup>	4.1	1.5	

<sup>a</sup> Abbreviations: EPI, Epinephrine; NE, Norepinephrine

with the following results being found: EPI; 307 ± 112, NE; 505 ± 85, EPI:NE ratio = 0.61 pg/ml.

Table 3 describes the endocrine profile of patients with suspected bilateral adrenal lesions. The adrenal side with the greater stimulated catecholamine response was labeled as the dominant side, while the side with the lesser response was labeled as the non-dominant side. Our data showed that both sides were actively functioning: EPI; 27,765 ± 8081 vs. 10,980 ± 2,960 pg/ml (ratio = 2.5) and NE; 11,445 ± 4,626 vs. 4,897 ± 1,980 pg/ml (ratio = 2.3). However, the EPI:NE ratio was similar on both sides (2.42 vs. 2.24). Likewise, the catecholamine hypersecretion that was observed in the adrenals was not seen in the periphery: EPI; 158 ± 20, NE; 414 ± 68 (EPI:NE ratio = 0.38 pg/ml).



**Figure 1.** Cannulation and Venogram of the Left (a) and Right (b) Adrenal Vein During Bilateral Adrenal Venous Sampling with Glucagon Stimulation. A) Left Adrenal Vein: Cannulation of the left adrenal vein with low pressure contrast confirmation of catheter position. B) Right Adrenal Vein: Cannulation of the right adrenal vein with low pressure contrast confirmation of catheter position.

**Table 3.** Stimulated Fractionated Catecholamine Levels in Patients with Suspected Bilateral Pheochromocytoma Diagnosed by Bilateral Adrenal Venous Sampling with Glucagon Stimulation.

Marker	Suspected Bilateral Tumors		Ratio
	Dominant <sup>a</sup> Side	Non-Dominant <sup>b</sup> Side	
Epinephrine, pg/mL, Mean ± SE	27,764 ± 8081	10,980 ± 2,960	2.5
Norepinephrine, pg/mL, Mean ± SE	11,445 ± 4,626	4,897 ± 1,980	2.3
Ratio of EPI <sup>c</sup> :NE <sup>c</sup>	2.42	2.24	

<sup>a</sup> Dominant; the adrenal side with the higher glucagon-stimulated response

<sup>b</sup> Non-dominant; the adrenal side with the lower glucagon-stimulated response

<sup>c</sup> Abbreviations: EPI, Epinephrine; NE, Norepinephrine

**Table 4.** Follow-up of 20 Pheochromocytoma Patients who Underwent Unilateral Adrenalectomy.

	Group 1 <sup>a</sup> , (n=11)	Group 2 <sup>b</sup> , (n=9)
Follow-up, Mo, Mean ± SD	46.4 ± 9.5	45.0 ± 9.7
Preoperative BP, Mean ± SD, mm Hg		
Systolic	190.0 ± 48.0	202.9 ± 17.6
Diastolic	105.5 ± 12.0	113.3 ± 10.0
Follow-up BP, Mean ± SD, mm Hg		
Systolic	120 ± 12.6 <sup>c</sup>	132.22 ± 13.9 <sup>d</sup>
Diastolic	77.3 ± 10.0 <sup>e</sup>	82.22 ± 9.7 <sup>f</sup>
Duration of HPN y, Mean ± SD	4.8 ± 3.0	10.2 ± 10.8

<sup>a</sup> Group 1; did not require anti-HPN drugs postoperatively

<sup>b</sup> group 2; required anti-HPN drugs postoperatively

<sup>c</sup>  $P < 0.001$ , group 1 preoperative vs. postoperative follow-up systolic BP

<sup>d</sup>  $P < 0.0008$ , group 1 preoperative vs. postoperative follow-up diastolic BP

<sup>e</sup>  $P < 0.0006$ , group 2 preoperative vs. postoperative follow-up systolic BP

<sup>f</sup>  $P < 0.0005$  group 2 preoperative vs. postoperative follow-up diastolic BP

#### 4.1. Histopathology

Of the 20 patients diagnosed with unilateral tumors, 18 underwent adrenalectomy. Two with suspected bilateral lesions opted to have the dominant side removed. Histopathology using hematoxylin-eosin staining revealed polygonal cells in a lobular arrangement, interrupted by delicate fibrovascular septae. The cells had large vesicular nuclei with prominent nucleoli. The cytoplasm was granular and faintly basophilic. Tumor size, measured in 6 patients early in the study, ranged from 2.9 x 3.0 mm to 9.2 x 2.3 mm. Histopathology showed 2 nodules on the excised adrenals from 4 patients with unilateral disease. Eleven cases that were studied for chromogranin A showed positive results, further confirming the diagnosis of pheochromocytoma (4). In 1 case, there was adrenal vein thrombosis. A CT scan of this patient showed adrenal apoplexy on the same side as that where pheochromocytoma was identified by adrenal vein sampling.

#### 4.2. Postoperative Follow-Up

During the postoperative follow-up period (6–12 years), 11 patients did not require anti-hypertensive medication (group 1). Of those that did require anti-hypertensive drugs (group 2), 5 patients needed only monotherapy, while 4 required 2 drugs in order to maintain BP in the range of 110–150 mmHg systolic and 70–90 mm Hg diastolic. The postoperative systolic and diastolic blood pressure levels in both groups were found to be significantly lower than preoperative levels, as follows: group 1 (preoperative vs. postoperative, mmHg): systolic; 191 ± 48 vs. 120 ± 12.6 ( $P < 0.001$ ), diastolic; 105 ± 12 vs. 77 ± 10 ( $P < 0.0008$ ), group 2: systolic; 205 ± 17 vs. 127 ± 11 ( $P < 0.0006$ ), diastolic; 114 ± 11 vs. 80 ± 10 ( $P < 0.0005$ ). Although not statistically different, patients who required medications postoperatively tended to have a longer duration of hypertension (group 1 vs. group 2; 6.8 ± 3 vs. 12 ± 10.8 years).

Interestingly, upon follow-up, the condition of 1 subject appeared to have evolved into a syndrome. Her blood pressure was maintained in the range of 90–120 mmHg systolic and 60–80 mmHg diastolic with losartan (50 mg daily). However, 18 months later, the patient was diagnosed to have a prolactin-secreting macroadenoma of the pituitary and underwent transsphenoidal pituitary surgery. She was maintained on cabergoline, postoperatively. After 6 months, the patient started to complain of periodic episodes of hot flushes, weakness, and muscle pains, compatible with carcinoid syndrome (30).

## 5. Discussion

This study establishes the safety and usefulness of BAVS with glucagon stimulation in the localization of small adrenal pheochromocytomas, particularly in patients with equivocal imaging or biochemical tests. Furthermore, we were able to demonstrate that early diagnosis may prevent the development of atherosclerosis, as shown in the group of patients with < 5 years history of hypertension, who did not require post-operative anti-hypertensive drugs.

### 5.1. Diagnosis by Hormonal Assessment

The need to definitively diagnose potentially lethal diseases with unpredictable courses has led to the advancement of plasma catecholamine measurements. To date, determination of plasma metanephrines is the test that provides the highest sensitivity and specificity for diagnosis of pheochromocytoma (1, 5, 6). However, definitive diagnoses using catecholamine measurement tests alone can only be made when tumors are actively secreting catecholamines at the time of sample collection. In at least 50% of pheochromocytomas, catecholamines are secreted episodically, while 20–30% of pheochromocytomas are biochemically silent, either because of their small size or the absence of catecholamine-synthesizing enzymes (9, 11). To overcome some of these problems, the measurement of plasma metanephrines was introduced for the diagnosis of pheochromocytoma (9, 11, 13, 14). However, although metanephrines are continuously secreted from tumors (5), and tests measuring their plasma levels yield the highest sensitivity and specificity in the biochemical diagnosis of adrenal pheochromocytomas (1, 5–7), these tests have a very limited availability and many centers still depend on measurements of plasma or urine catecholamine levels. However, the lack of sensitivity of catecholamine measurements can be partially overcome by the implementation of glucagon stimulation or clonidine suppression tests (33, 34). In a report by Grossman and colleagues (34), measurements of NE levels using a glucagon stimulation test (1 mg glucagon, IV bolus) yielded a higher specificity when compared to a clonidine suppression test (0.3 mg/70 kg body wt, clonidine tablet) (100 vs. 67%, respectively), but had a lower sensitivity (81 vs. 97%, respectively). However, the use of normetanephrine as a parameter in the clonidine test

increases its specificity to 100% as shown by Eisenhofer and his group (33).

### 5.2. Venous Sampling

To date, various advancements in imaging modalities have not proved to be superior in localizing and lateralizing small adrenal pheochromocytomas. Our series, which utilized glucagon to stimulate the pheochromocytoma (35), has shown favorable sampling results with no significant adverse events. This is due to the adequate control of patient blood pressure during the peri-sampling period, placing the patient at ease by giving light anesthesia, and most importantly, the performance of an experienced team. The seemingly unfavorable and equivocal outcomes of venous sampling procedures for diagnosis of pheochromocytoma that have been reported in the past (21–23) were likely due to the lack of stimulation applied during the procedure. In 1 of our subjects, baseline results were equivocal (data not shown), but stimulated fractionated catecholamine results clearly lateralized the tumor. Although the usefulness of analyses of catecholamine gradients between the two adrenals for localization of pheochromocytoma has been demonstrated in the past (20, 21, 25, 27, 29, 30), our group is the first to report such gradient ratio differences after glucagon stimulation. The dilemma of the diagnosis of “silent” pheochromocytomas has also been raised in a previous report by Timmers et al (9). Likewise, by stimulation with glucagon during sampling we can definitively rule out the presence of pseudopheochromocytoma, described by the group of Sharabi et al (36). The increasing incidence of adrenal incidentalomas has added to existing problems regarding the evaluation of adrenal masses. The prevalence of unsuspected adrenal masses is about 0.6% in abdominal CT scan series and is between 1.4–8.7% in unselected autopsy series (37). This signifies that a significant number of patients with pheochromocytoma died undiagnosed (38). In our series, except for the patient with apoplexy and a few patients with equivocal adrenal hyperplasia in the CT scan, the majority of our cases did not show any definitive tumor, suggesting that venous sampling can localize suspected adrenal pheochromocytomas (7). Another important clinical advantage of utilizing stimulation in venous sampling is that antihypertensive drug use can be maintained prior to the procedure. This prevents untoward cardiovascular and neurological consequences, especially in patients suspected to have pheochromocytoma. BAVS with glucagon stimulation, albeit invasive, yielded a high sensitivity and specificity in our study.

### 5.3. Clinical follow-Up

The optimal therapy for pheochromocytoma is prompt surgical removal of the tumor, since unresected tumors may lead to a lethal hypertensive crisis (39). The late recognition of pheochromocytoma oftentimes leads to progressive atherosclerosis and cardiac and neurologic

complications that may be fatal (3). It is evident from our present findings that we were able to diagnose pheochromocytoma at an early stage before any complications or untoward events occurred in our patients, whose duration of hypertension was <5 years. The normalization of blood pressure postoperatively with no requirement for medication supports the conclusion that these patients were effectively cured. However, continued follow-up is important for monitoring the occurrence of new pheochromocytomas (40).

In summary, we have reported the usefulness of BAVS with glucagon stimulation in the early diagnosis and localization of small pheochromocytomas, particularly in cases with equivocal imaging results.

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