研究成果の刊行に関する一覧表

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Original Article

New Diagnostic Procedure for Primary Aldosteronism: Adrenal Venous Sampling under Adrenocorticotropic Hormone and Angiotensin II Receptor Blocker—Application to a Case of Bilateral Multiple Adrenal Microadenomas

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Formerly, the incidence of primary aldosteronism (PA) among patients with hypertension was believed to be less than 1%. However, recent studies have suggested a much higher incidence of 6.59%–14.4% among such patients. These findings suggest that many cases of PA caused by small aldosterone-producing adenoma (APA) or idiopathic hyperaldosteronism (IHA) have not been properly diagnosed. To make a more accurate diagnosis in such cases, we developed a new diagnostic procedure for localization of PA, namely, adrenal venous sampling under continuous infusion of adrenocorticotropic hormone (ACTH) and administration of angiotensin II receptor blocker (AVS with ACTH and ARB). Here, we confirm the efficacy of this procedure in the case of a 37-year-old male suspected of having PA. The anticipated diagnosis of PA was based on the presence of hypokalemia, low plasma renin activity (PRA), elevated plasma aldosterone concentration (PAC) and left adrenal mass. However, AVS with ACTH and ARB revealed the presence of bilateral multiple adrenal microadenomas. In the new AVS method, neither ACTH nor the renin-angiotensin system (RAS) exert any influence on the plasma aldosterone level, and a more accurate aldosterone secretary state and a more accurate assessment of the aldosterone secretion of both adrenal glands can be recognized than by conventional AVS. Use of this new method should enable identification of additional cases of APA among patients diagnosed with essential hypertension. (*Hypertens Res* 2002; 25: 145–152)

Key Words: **primary aldosteronism, adrenal venous sampling, adrenal microadenoma, adrenocorticotropic hormone (ACTH), angiotensin II receptor blocker (ARB)**

Introduction

Until recently, the prevalence rate of primary aldosteronism (PA) among patients with hypertension was 1% (*1–5*). However, in 1994, Gordon *et al.* (*6*) confirmed 17 cases of PA among 199 normokalemic hypertensives. Since then, many studies have reported much higher PA prevalence rates of 6.59%–14.4% among hypertensive patients (*7, 8*).

These findings suggest that microadenomas (APAs; less

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Table 1. Laboratory Findings

Serum creatinine	0.7 mg/dl
Blood urea nitrogen	12 mg/dl
Serum uric acid	6 mg/dl
Serum sodium	142 mEq/l
Serum potassium	3.3 mEq/l
Serum chloride	102 mEq/l
Plasma renin activity	<0.1 ng/ml/h
Plasma aldosterone concentration	176 pg/ml
Adrenocorticotropic hormone	29.5 pg/ml
Serum cortisol	6.7 μg/dl
Human ANP	9.7 pg/ml
Human BNP	<5 pg/ml
Plasma adrenaline	12 pg/ml
Plasma noradrenaline	148 pg/ml
Plasma dopamine	12 pg/ml
Urine potassium excretion	55.2 mEq/day
Urine aldosterone	21.7 μg/day
Urine cortisol	63.6 μg/day

than 3 mm in diameter) may occur frequently among patients diagnosed with essential hypertension but who show low plasma renin activity and a high plasma aldosterone concentration. This is particularly important in that APAs are difficult to diagnose by the usual imaging methods.

Localization of PA is generally performed by ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) and scintigraphy, but the spatial resolution of these tests is limited. In PA caused by microadenomas or idiopathic hyperaldosteronism (IHA), diagnosis by these tests is especially difficult, and thus adrenal venous sampling (AVS) is critical for final diagnosis.

However, there are some problems involved in AVS. Particularly in cases of APA, aldosterone secretion is highly sensitive to adrenocorticotropic hormone (ACTH) (*9*). ACTH secretion is highly influenced by stress or time course during AVS and may influence the findings of AVS. On the other hand, in IHA, aldosterone secretion is still regulated by the renin-angiotensin system (RAS) (*10*), which in turn is controlled by circulating body fluid status.

To avoid these influences, we developed a new method of AVS under continuous infusion of ACTH, to exclude the influence of endogenous ACTH and administration of angiotensin II receptor blocker (ARB) (*11*), and to block RAS. In this study, we applied this new method to a case of PA with apparent left adrenal mass detected by conventional diagnostic imaging. By this new method, we were able to make a diagnosis of bilateral multiple adrenal microadenomas.

Case Report

A 37-year-old male was diagnosed with hypertension in 1997, and received medical treatment in a local hospital. In August, 1998, hypokalemia (3.2 mEq/l) was identified, and the patient experienced flaccid paralysis in July, 1999. Primary aldosteronism was suspected based on the presence of hypokalemia (2.5 mEq/l), low PRA (<0.1 ng/ml/h), and elevated PAC (181 pg/ml). A left adrenal mass (5 mm in diameter) was identified using CT. The patient was admitted to our hospital for further examination and treatment in August, 1999.

The results of a physical examination performed on admission were unremarkable, except for obesity (height 178 cm, weight 93.8 kg, and body mass index 29.6) and blood pressure (BP) of 142/98 mmHg despite antihypertensive medication (5 mg amlodipine hydrochloride). The laboratory findings are summarized in Table 1. The serum potassium concentration was low (3.3 mEq/l) and 24-h urine collection analysis showed inappropriate kaliuresis (55.2 mEq/day) despite a potassium supplement (16 mEq/day). Endocrinological tests revealed low PRA (<0.1 ng/ml/h), high PAC (176 pg/ml) and high 24-h urine aldosterone excretion (21.7 μg/day). A CT scan disclosed a left adrenal mass, 5 mm in diameter, which showed a homogeneously low density and was not enhanced by contrast material (Fig. 1). The right adrenal gland appeared normal. Adrenal scintigraphy using ^{131}I adosterol with dexamethasone suppression (3 mg/day for 10 days) was performed, but the uptake of the tracer was low, and there was no obvious laterality in either adrenal gland.

Table 2 shows the concentrations of cortisol (C) and aldosterone (A) in samples obtained by conventional AVS. The A/C ratio in the right adrenal vein was 51.6–69.8, whereas the ratio in the left adrenal vein was 15.3–19.0, which was similar to the ratio in the inferior vena cava. These conventional AVS results suggested that the left adrenal mass identified by CT was a nonfunctioning tumor, and that an aldosterone-producing microadenoma existed in the right adrenal gland. To confirm our diagnosis, we performed adrenal venous sampling under continuous infusion of ACTH to circumvent the fluctuating plasma ACTH level on PAC, and administration of ARB for the suppression of any possible contribution of RAS to PAC (AVS with ACTH and ARB). The detailed protocol was as follows. 1) At 9:00 PM on the previous night and 6:00 AM. on the sampling day, ARB, Candesartan 8 mg, was administered. 2) Conventional adrenal venous sampling was started at 9:00 AM. The sampling of right adrenal vein was done last, and the catheter was wedged at the right adrenal vein. 3) Bolus i.v. injection of ACTH (Tetracosactide) 0.25 mg (25 IU) was performed. 4) Continuous infusion of ACTH (Tetracosactide; 2.5 μg/ml physiological saline) at the rate of 100 ml/h followed. 5) At 15 min after the start of the infusion, sampling was again started from the right adrenal vein. This time, the A/C ratio in the right adrenal vein was 49.4–56.5, similar to that by the conventional sampling performed previously. On the other hand, the ratio in the left adrenal vein was 33.0–35.7, which was significantly different from the ratio in the inferior vena

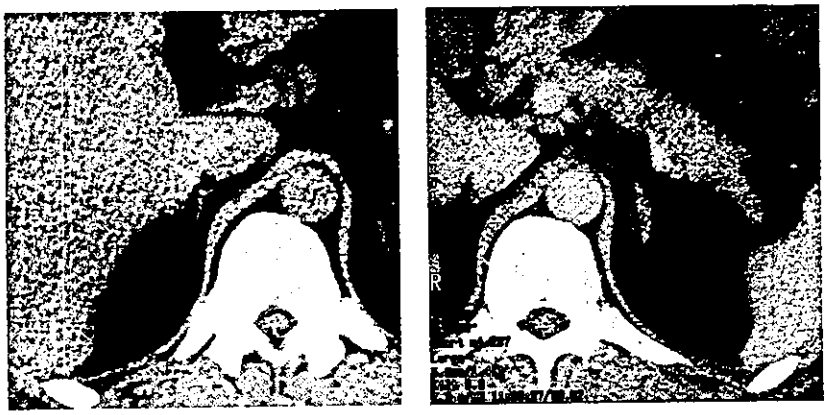

Fig. 1. *Abdominal CT enhanced by contrast material. The CT scan discloses a left adrenal mass, 5 mm in diameter, that shows a homogeneously low density and is not enhanced by contrast material. The right adrenal gland appears normal.*

Table 2. Conventional Adrenal Venous Sampling (Conventional AVS)

Sampling sites	Aldosterone (A) (pg/ml)	Cortisol (C) (μg/dl)	A/C ratio
Right adrenal vein	71,262	1,381	51.6
	54,599	782	69.8
Left adrenal vein	6,586	432	15.3
	10,235	539	19.0
Inferior vena cava (inferior)	305	20.7	14.7
Inferior vena cava (superior)	237	19.6	12.1
Right renal vein	270	17.1	15.8
Left renal vein	246	16.7	14.7

Table 3. Adrenal Venous Sampling under Continuous Injection of ACTH and Administration of ARB (AVS with ACTH and ARB)

Sampling sites	Aldosterone (A) (pg/ml)	Cortisol (C) (μg/dl)	A/C ratio
Right adrenal vein	66,295	1,342	49.4
	84,369	1,494	56.5
Left adrenal vein	22,454	629	35.7
	17,218	522	33.0
Inferior vena cava (inferior)	279	15.8	17.7
Inferior vena cava (superior)	237	19.6	12.1
Right renal vein	433	17.1	15.8
Left renal vein	404	16.7	14.7

cava (12.1–17.7), and the difference between the ratio in the left and right adrenal vein was reduced (Table 3). These results of AVS with ACTH and ARB suggested that the patient had bilateral adrenal lesions, which might be IHA or bilateral APAs.

In this case, the diagnosis was difficult to determine. After extensive discussion with the patient and members of the Department of Urology of our university, we decided to perform a left partial adrenalectomy including the mass. The reasons for this decision were as follows. While the pathophysiology of this case indicated hypersecretion of aldosterone from the bilateral adrenal glands, a visible mass was radiologically apparent in the left adrenal gland. Thus, we wanted to remove the mass to obtain the pathological features of the resected part and to see the postoperative changes in hormonal states, assuming that the mass resection would reduce the secretion of aldosterone to some extent.

Macroscopically, the resected part showed multiple nodules, about 1 mm in diameter, in addition to the mass which was found by CT (Fig. 2). Microscopic findings revealed the existence of multiple lesions which could be interpreted as nodules or adenomas, but at least one lesion was confirmed to be an adenoma (Fig. 3a, b). The zona glomerulosa showed prominent paradoxical hyperplasia (*12*). By immunohistochemical staining, the expression of steroidogenic enzymes, such as P450scc (cholesterol side-chain cleavage), 3β-HSD (hydroxysteroid dehydrogenase), P450c11 (11-hydroxylase), P450c17 (17-hydroxylase), and DHEA-ST (dehydroepiandrosterone sulfotransferase) (*13*, *14*) were examined. The lesions were positively stained for all of these enzymes except DHEA-ST. In paradoxical hyperplasia of the zona glomerulosa, the expression of 3β-HSD was negative, which excluded the possibility that this was a case of IHA.

The clinical course of this case is shown in Fig. 4. At first, serum potassium and BP were normalized by the treatment of potassium chloride and amlodipine administration. When spironolactone was administered, the levels of both serum potassium and BP were normalized. After the operation, the serum potassium level remained within the normal range without medication. The urinary amount of aldosterone decreased from 21.7 μg/day to 11.8 μg/day. With respect to the diurnal rhythm, before the operation the PAC showed ACTH-dependency. After the operation the PAC decreased,

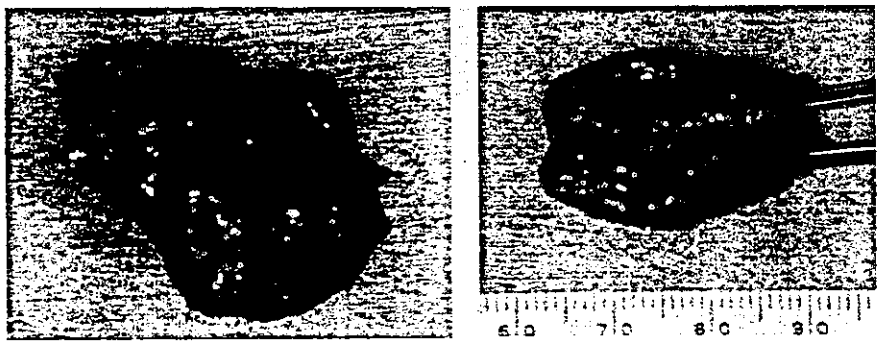

Fig. 2. *Macroscopic findings of the resected part of the left adrenal gland. The resected part shows multiple nodules, about 1 mm in diameter, in addition to the mass revealed by CT.*

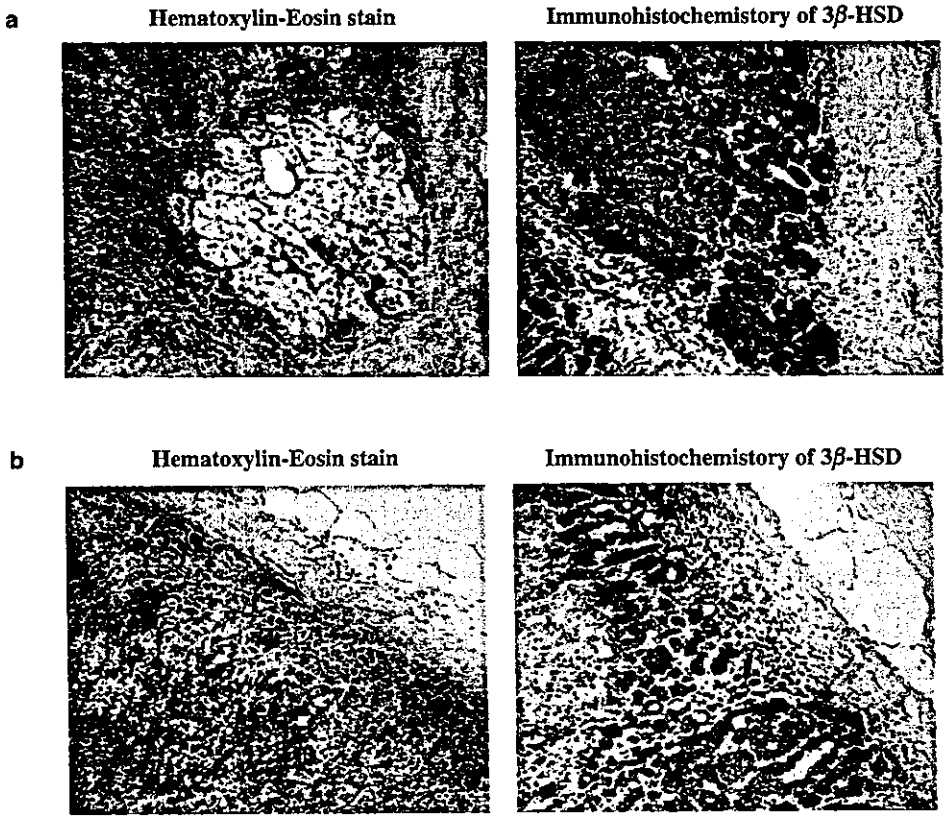

Fig. 3a. *Microscopic findings revealing the existence of multiple lesions that could be interpreted as nodules or adenomas. At least one lesion was confirmed to be an adenoma. The lesions were positively immunostained for steroidogenic enzymes such as 3β-HSD.* **b.** *Zona glomerulosa showing prominent paradoxical hyperplasia. The expression of 3β-HSD was negative at the zona glomerulosa, which excluded a diagnosis of IHA.*

but it still showed ACTH-dependency. Together, these clinical results indicated the presence of bilateral multiple APAs.

Methods

To investigate the significance of continuous infusion of ACTH, we studied the peripheral blood concentration of aldosterone and cortisol in two other PA patients after only bolus i.v. injection or continuous infusion followed by bolus i.v. injection of ACTH with the patients' informed consent. The detailed protocol was as follows. 1) At 9:00 AM after 30 min-bed rest, blood samples were taken as a control. 2) Bolus i.v. injection of ACTH (Tetracosactide) 0.25 mg (25 IU) was performed. 3) Blood samples were taken every 30 min

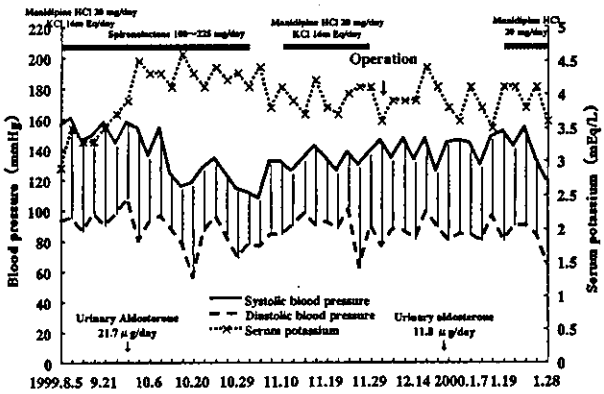

Fig. 4. *The clinical course of this case.*

up to 120 min. 4) The next morning at 9:00 AM, control blood samples were taken as on the previous day. 5) Bolus i.v. injection of ACTH (Tetracosactide) 0.25 mg, and continuous infusion of ACTH (Tetracosactide; 2.5 μg/ml physiological saline) at the rate of 100 ml/h followed. 6) Blood samples were taken every 30 min up to 120 min.

To investigate the effects of ARB administration, we also studied the change in BP and the peripheral plasma concentration of aldosterone during continuous infusion of angiotensin II (AII) with or without the pretreatment of ARB with the patients' informed consent. The detailed protocol was as follows. 1) At 8:30 AM after bed rest, the patient's BP monitoring (every 5 min) was started. 2) At 9:00 AM blood samples were taken as controls, and continuous infusion of AII at the dose of 0.25 ng/kg/min was started. 3) The dose of AII was doubled every 15 min. Immediately before the dose was increased, blood samples were taken. 4) If systolic BP rose above 30 mmHg compared with controls or above 180 mmHg, the administration of AII was stopped, and the final blood samples were taken. 5) At 9:00 PM and the next morning at 6:00 AM ARB, Candesartan 8 mg, was administered. 6) The following morning, sampling was again started following the same protocol as in 1)–4).

Results

Figure 5a shows the results of ACTH administration in the present patient, a 48-year-old male with PA (IHA) (PRA 0.27 ng/ml/h, PAC 175 pg/ml). The plasma aldosterone level was highest at 30 min after the bolus i.v. injection, then decreased gradually and was below the control level at 2 h post-injection. However, plasma aldosterone remained at a high level throughout the continuous infusion following bolus i.v. injection of ACTH. This phenomenon was considered to occur due to the short half-life of Tetracosactide, which is shorter than that of natural ACTH (*15*). The cortisol level showed no significant difference between the two methods. This difference between the change in aldosterone and the cortisol levels was considered to be partly due to the fact that the half-life of cortisol (60–90 min) is longer than that of aldosterone (about 20 min) (*16*). Figure 5b shows the results for another PA (APA) patient (Patient 2; 58 y.o., F, PRA 0.24 ng/ml/h, PAC 140 pg/ml) who was treated under the same protocol. Similar findings of plasma aldosterone

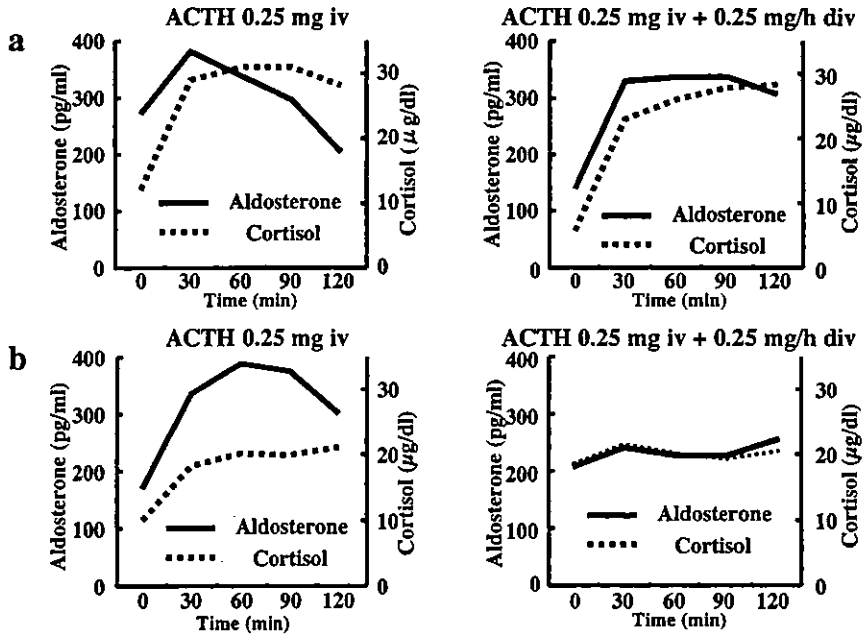

Fig. 5. *Peripheral blood concentrations of aldosterone and cortisol in Patients 1 (a) and 2 (b) after bolus i.v. injection or continuous infusion followed by bolus i.v. injection of ACTH, respectively.*

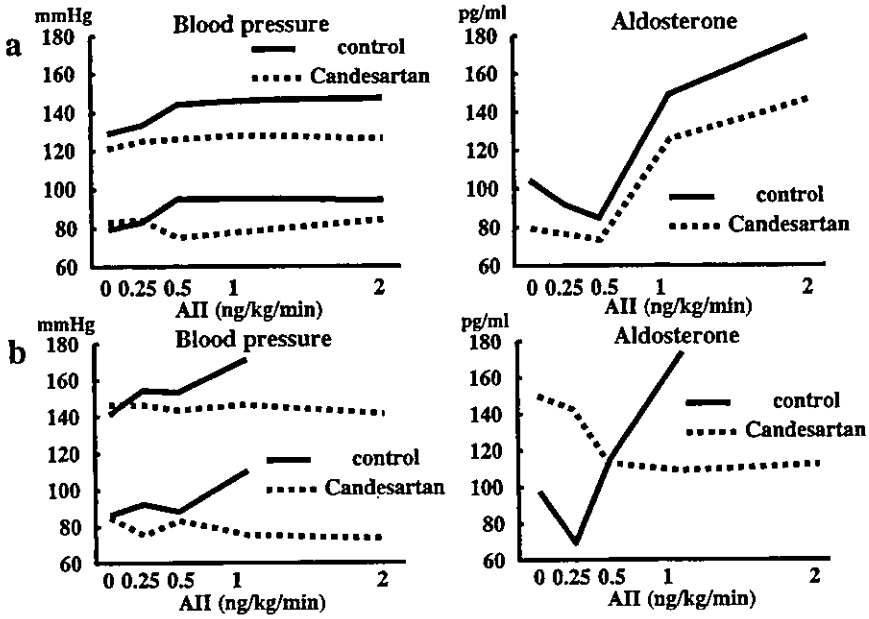

Fig. 6. *Blood pressure and peripheral plasma concentration of aldosterone in Patients 1 (a) and 2 (b) during continuous infusion of AII with or without ARB pretreatment (Candesartan: 8 mg at 9 PM on the previous day, and 8 mg at 6 AM on the examination day).*

and cortisol levels were observed. After the bolus i.v. injection, the plasma aldosterone level was highest at 1 h after the injection, and then it decreased gradually. The plasma aldosterone level remained high throughout the continuous infusion. And there were no significant differences in plasma cortisol level between the two methods. These findings suggest that continuous infusion after bolus i.v. administration is superior to bolus i.v. administration of ACTH.

Figure 6a shows the results of AII infusion for Patient 1. In controls who did not receive pretreatment of ARB, both systolic and diastolic BP rose to 15–20 mmHg under infusion of AII 2 ng/kg/min. In Patient 1, who was pretreated with ARB, there were no increases in BP throughout the AII infusion. The aldosterone level increased after the administration of AII >1 ng/kg/min in the control period without the pretreatment of ARB, and the maximal aldosterone level was 176 pg/ml by the treatment of AII 2 ng/kg/min. This aldosterone concentration was within the level usually observed in Patient 1, which suggests that the administered dose of AII was physiological and not pharmacological (*17*). Comparison between the control treatment and the treatment involving pre-administration of ARB revealed that the plasma aldosterone level was partially but not completely suppressed during AII infusion. Figure 6b shows the results for Patient 2. In controls, AII 1 ng/kg/min caused a BP increase to 170/110 mmHg. In the case of pretreatment with ARB, BP did not rise even under infusion of AII 2 ng/kg/min. The plasma aldosterone level never rose by AII infusion up to the dose of 4 ng/kg/min after the pretreatment of ARB. Taken together, these findings suggest that our new method of AVS with ACTH and ARB effectively avoids the influences of ACTH and the renin-angiotensin system. However, in Patient 1 (IHA), the increase in the plasma aldosterone level by AII was not completely suppressed by ARB. Thus further studies will be needed to decide the dose and timing of ARB administration.

Discussion

In this case, to circumvent several drawbacks in the use of conventional AVS to detect microadenomas, we developed a new diagnostic procedure for PA, consisting of AVS under continuous infusion of ACTH and administration of ARB (AVS with ACTH and ARB). By this new AVS method, a more accurate diagnosis could be made in the present case with bilateral multiple aldosterone-producing microadenomas. The new method clearly indicated that both adrenal glands were hypersecreting aldosterone.

Our decision to perform ACTH administration during AVS was based on previous findings that, in cases of APA, aldosterone secretion is highly dependent on ACTH, which in turn is highly influenced by stress or the time course of AVS. To solve this problem, we suppressed endogenous ACTH by exogenous ACTH administration. The method of ACTH injection during AVS was first described in 1969 (*9*), and has since been employed in numerous studies (*18–23*). Spark *et al.* (*15*) reported the effect of bolus ACTH administration (25 IU) on AVS, and Weinberger *et al.* (*23*) employed a continuous ACTH administration of 5 IU per hour, but no study has examined the validity of the dose or

timing of ACTH administration. There are a number of technical difficulties associated with AVS, and the procedure can sometimes take hours to carry out. In such protracted cases, if AVS is performed under bolus i.v. injection of ACTH, the concentration of aldosterone and cortisol might decrease during the administration. We therefore chose to use a continuous administration of ACTH followed by a bolus injection. In addition, we administered ARB to avoid any possible influence of the alteration of RAS on aldosterone secretion. In the present patient with IHA, aldosterone secretion was shown to be regulated by RAS, which was dependent on circulatory volume status.

From comparisons between bolus i.v. injection and continuous infusion followed by bolus i.v. injection of ACTH in two PA patients, we observed their time-course differences in PAC. The plasma aldosterone level remained high throughout the infusion period in both patients. Therefore, since AVS can sometimes take hours to carry out, it should be performed under continuous administration of ACTH followed by a bolus injection of ACTH.

AII has been reported to induce a dose-dependent increase in PAC in patients with IHA (*10, 24*). In most cases of APA, on the other hand, aldosterone is secreted independently from RAS, although some variants of APA show responsiveness to AII (*24–26*). These findings suggest that RAS must be blocked completely in order to obtain stable AVS findings. Our results suggest that the dose of ARB used here may be insufficient to adequately suppress the effects of RAS on aldosterone secretion. We are currently investigating a more appropriate protocol for ARB administration (*e.g.*, a dose of Candesartan up to 12 mg).

Our results suggest that the new method shown here, AVS with ACTH and ARB, should be applied to all patients suspected of having PA, based on its accuracy in determining the aldosterone secretion from both adrenal glands. This method would lead to identification of more patients with APA, which are cases of curable hypertension.

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Accelerated Reendothelialization With Suppressed Thrombogenic Property and Neointimal Hyperplasia of Rabbit Jugular Vein Grafts by Adenovirus-Mediated Gene Transfer of C-Type Natriuretic Peptide

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Background—Vein graft disease limits the late results of coronary revascularization. C-type natriuretic peptide (CNP) inhibits the growth of vascular smooth muscle cells. Given the effects of CNP on cGMP cascade, we hypothesized that transfected *CNP* genes modulate endothelial repair and thrombogenicity in the vein graft.

Methods and Results—Autologous rabbit jugular vein grafts were incubated ex vivo in a solution of adenovirus vectors containing *CNP* gene (*Ad.CNP*) or *Escherichia coli lac Z* gene (*Ad.LacZ*) and then interposed in the carotid artery. Reendothelialization, mural thrombi formation, and intima/media ratio were evaluated on the 14th and 28th postoperative days. More reendothelialization was seen in *Ad.CNP*-infected grafts than in *Ad.LacZ*-infected grafts both at 14 days (0.81 ± 0.05 versus 0.30 ± 0.14, $P<0.01$) and at 28 days (0.96 ± 0.01 versus 0.45 ± 0.08, $P<0.001$). The mural thrombus area was smaller in *Ad.CNP*-infected grafts than in *Ad.LacZ*-infected grafts. Neointimal thickening was significantly suppressed in the *Ad.CNP* group. The in vitro wound assay with human coronary artery endothelial cells revealed significant potentiation of the wound repair process by CNP and atrial natriuretic peptide administration.

Conclusions—Infected *Ad.CNP* accelerated reendothelialization and suppressed thrombosis and neointimal hyperplasia. The method may potentially prevent vein graft disease in patients undergoing coronary artery revascularization. **(*Circulation*. 2002;105:1623-1626.)**

Key Words: natriuretic peptides ■ viruses ■ grafting ■ genes

Accelerated atherosclerosis within grafted vein grafts allows only 38% to 45% of patency by the end of 10 postoperative years. During the first month after bypass surgery, vein graft attrition results from thrombotic occlusion, followed by late graft failure caused by neointimal hyperplasia.[1] Endothelium-dependent relaxation is demonstrated to be reduced in saphenous vein (SV) grafts compared with internal mammary artery (IMA) grafts.[2] Endothelial production of nitric oxide (NO) and prostacyclin is lower in veins than in arteries, and NO synthesis is further reduced in bypass grafting.[3] We reported reduced expression of guanylate cyclase A, the receptor for atrial natriuretic peptide (ANP) and brain natriuretic peptide, and less production of cGMP stimulated by ANP in SV compared with IMA.[4]

We previously demonstrated that natriuretic peptides inhibit vascular growth through the cGMP-dependent pathway.[5] Furthermore, C-type natriuretic peptide (CNP) is secreted from endothelial cells to act as an endothelium-derived relaxing peptide for vascular remodeling.[6,7] We also reported that endothelial CNP expression is progressively reduced in accordance with the severity of human coronary atherosclerosis.[8] Together with the recent findings that show that the cGMP pathway is involved in promotion of neovascularization[9] and inhibition of tissue factor or plasminogen activator inhibitor-1 expression,[10] in this study, we investigated the effect of adenoviral gene transfer of CNP on vein graft patency in rabbit jugular vein–carotid artery interposition graft procedures.

Methods

Construction of Recombinant Adenoviruses

We constructed a recombinant replication-defective adenoviral vector encoding the rat CNP cDNA, *Ad.CNP*, as previously reported.[11]

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