Renovascular Hypertension and Plasma Renin Activity

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Two cases of suspected renovascular hypertension are presented. The discussion includes (a) the utility and proper interpretation of plasma renin activity (PRA) values in blood samples obtained from the renal veins, (b) the limited value of obtaining peripheral blood PRA measurements in such cases, and (c) the variables and problems in the analytical techniques for PRA.

Presentation of the Cases

Case 1

This 25-year-old white man was admitted to Barnes Hospital for evaluation of long-standing progressive hypertension. He had a 15-year history of hypertension, which apparently had been evaluated at age 10, at which time no specific etiology was found. Blood pressure had been fairly well controlled on several drugs, but during the past year it had become increasingly difficult to control, ranging from 150/110 mmHg to 190/130 mmHg. At the time of admission, he was receiving the following antihypertensive medications: methyldopa, 1.0 g daily; propranolol, 480 mg daily; and hydrochlorothiazide, 100 mg daily. His family history indicated hypertension and heart disease in parents, grandparents, and siblings. At admission, the blood pressure was 170/110 mmHg and retinal examination revealed arteriosclerotic changes. No abdominal bruit was noted and the rest of the physical examination was unremarkable. Laboratory data at admission included normal values for sodium, potassium, chloride, creatinine, serum urea nitrogen, aspartate aminotransferase (EC 2.6.1.1), lactate dehydrogenase (EC 1.1.1.27), creatine kinase (EC 2.7.3.2), bilirubin, glucose, total protein, leukocyte count, hemoglobin, and urinalysis. The chest roentgenogram was normal and the electrocardiogram revealed left ventricular hypertrophy with minor, nonspecific changes. Intravenous pyelography was normal, but isotopic renal scan showed focal retention of radioisotope in the upper pole of the left kidney, with the left and right kidneys contributing 44 and 56% of total renal function, respectively. The amounts of vanillylmandelic acid and catecholamines in a 24-h urine sample were normal. Renal arteriography demonstrated that there was 99% stenosis at the origin of a segmental artery supplying the upper pole of the left kidney. The remaining renal arteries appeared normal. Values for PRA on samples obtained during selective venous catheterization after restriction of dietary sodium for two days are shown in Figure 1 and were: inferior vena cava, 9.6 ng/mL per hour (2.7 ng/L per second), left renal vein, 24.3 ng/mL per hour (6.8 ng/L per second) and right renal vein, 10.0 ng/mL per hour (2.8 ng/L per second). The upper pole of the left kidney was removed without surgical complications. Histologically, this segment showed generalized parenchymal atrophy and juxtaglomerular cell hyperplasia. Postoperatively, blood pressure declined towards normal, ranging from 120-140/80-100 mmHg while the patient was receiving methyldopa, 1 g daily. Four months after surgery he was normotensive (130/88 mmHg) while receiving the same dose of methyldopa.

Case 2

This 36-year-old white woman was admitted to Barnes Hospital for evaluation of possible renovascular hypertension. She had discontinued the use of birth control pills six months before her admission, because of mild hypertension. Neither the patient nor any family member had a history of hypertension, renal disease, or heart disease. Two months before her admission to Barnes Hospital she was evaluated at another hospital for worsening hypertension. At that time an intravenous pyelogram, isotopic renogram, and renal arteriography indicated probable renovascular hypertension. The patient remained asymptomatic and was given no medication.

At the time of admission to Barnes Hospital the patient's physical examination showed no abnormalities except for a blood pressure of 180/130 mmHg. No abdominal bruit was audible. Laboratory tests done at this time revealed the following abnormal values: potassium, 3.0 mmol/L; total protein, 63 g/L; total calcium, 2.1 mmol/L; and hemoglobin, 113 g/L. Values for vanillylmandelic acid and catecholamines in a 24-h urine sample were within normal limits. Blood pressure (range 150/100 to 100/75 mmHg) was partly controlled by a 1 g/day...
dosage of methyldopa. Isotopic renal scan revealed delayed uptake and excretion bilaterally, with the right kidney contributing only 28% of total function. Repeat arteriography showed two right renal arteries rather than the usual one, with the inferior artery apparently the major one. An attempt to cannulate the superior artery was unsuccessful, but it appeared normal. The inferior artery was 90% occluded 2 cm distal to the aortic junction. A possible aneurysm was noted near the hilum of the right kidney. The left renal artery appeared normal. Samples for PRA measurements were obtained at the time of selective venous catheterization after the patient received 10 mmol of sodium per day in the diet for two days and 20 mg of furosemide approximately 12 h before blood sampling. These values (Figure 1) were: right renal vein 44.2 ng/mL per hour (11.3 ng/L per second); left renal vein, 7.3 ng/mL per hour (2.0 ng/L per second); and inferna vena cava, 6.9 ng/mL per hour (1.9 ng/L per second).

A surgical bypass of the stenotic area of the right inferior renal artery was performed with a graft from the saphenous vein, and an aneurysm near the hilum was resected. A postoperative renal scan showed improved but still impaired right renal function, with the right kidney now contributing 35% of total function. A postoperative renal arteriogram showed patency of the vein graft, but there was a possible arterial constriction near the area of the resected aneurysm. The blood pressure did not decline after surgery; it generally ranged from 165/100 to 155/100 mmHg, with occasional readings up to 190/110 mmHg. Control of blood pressure to preoperative values was attained by therapy with methyldopa, 1 g daily, and hydrochlorothiazide, 50 mg daily. Followup examination six months after surgery revealed mild hypertension (140/100 mmHg) while the patient was receiving 1.5 g of methyldopa daily and 50 mg of hydrochlorothiazide daily.

Discussion

The discussion of these cases is divided into two parts. In the first we consider the methodological aspects of the PRA measurements and in the second the clinical use of PRA measurements, especially as they relate to the diagnosis of renovascular hypertension. The biochemistry and physiology of the renin–angiotensin system have been well considered elsewhere (1–3) and will not be reiterated in detail here.

Measurement of Renin Activity

Analytical method. Renin concentration cannot be directly measured routinely; instead, all assays for clinical use measure its ability to catalyze the conversion of angiotensinogen to angiotensin I (Figure 2). Such measurement of PRA is complicated by the lack of a single well-defined substrate, necessitating the use of endogenous substrate, and also by the presence of activators and inhibitors, which requires that sample dilution be minimized. The enzymatic activity is ultimately quantitated by measuring the product (angiotensin I) by radioimmunoassay. Many variations in the assay have been described (4), but the major variables in the PRA assay appear inter-related and include (a) the pH during incubation, (b) the extent of sample dilution during incubation, (c) the choice of inhibitor of converting enzymes and angiotensinases, and (d) duration of incubation.

The pH at which plasma should be incubated can influence the values for PRA. Because the pH optimum for the renin reaction is in the range 5.5–6.0 (1, 5, 6), this pH is used in many assays, the pH being adjusted either with buffer (6, 7) or acid (1, 5). Alternatively, some workers advocate incubation at pH 7.4, again either with or without exogenous buffer in the reaction mixture (8, 9).

The data supporting use of a pH of 7.4 are those of Oparil et al. (8), who reported inconsistent differences in PRA measured at pH 5.5 and 7.4 and also showed measurable apparent PRA at pH 5.5, but not 7.4, in the plasma of nephrectomized patients. They concluded that non-renin proteases are activated at the lower pH and that measurement at the higher pH is more suitable. However, others have found measurable PRA in nephrectomized patients at both pH’s (5) and consistently higher values in patients’ samples at the optimal pH of 5.5–6.0 (6, 10). The arguments in favor of using a pH of 5.5–6.0 have been succinctly stated by Heise (11), and we used this pH in the assays performed on the patients presented here.

The method of control of pH during the incubation has also varied. The important problem in this regard is the unpredictable results found for PRA when plasma is diluted (5, 12). For this reason, many workers have tried to control the pH by adding small amounts of concentrated acid to plasma. Such approaches have three major problems: (a) upward drift in pH during incubation, due to CO2 diffusion, (b) technical complexity of adjusting the pH individually for each sample, and (c) possible inaccuracies in measuring the pH of plasma with routine laboratory pH equipment rather than with instruments specifically designed for blood-pH measurements. The use of buffers such as citrate or phosphate to control pH at 5.5–6.0 has been advocated, but we have found that the final pH after measured proportions of these buffers were added to plasma was more inconsistent than when maleate buffer was used (unpublished results). The conditions used in our
Fig. 3. Angiotensin I generated during the course of incubation in a case of suspected renovascular hypertension

Samples were from the right renal vein (RRV), the inferior vena cava below the renal veins (I, IVC Below), the left renal vein (O, LRV), and the inferior vena cava above the renal veins (D, IVC Above). PRA was routinely assayed as follows: 1 mL of 0.3 mol/L maleate buffer (pH 5.20 at 37 °C) is added to 2 mL of plasma. This adjusts the pH (37 °C) to 5.8 ± 0.1. Phenylmethylsulfonyl fluoride (final concentration, 0.04 mmol/L) is added to each tube and duplicate samples are incubated at 37 °C. One of the tubes is removed from the 37 °C bath and placed in an ice slurry after 15 min and the second at 60 min. Samples are kept in the cold or frozen until aliquoted for radioimmunoassay. The radioimmunoassay is performed with duplicate samples using solid-phase antibody tubes (Clinical Assays, Cambridge, MA 02139). Each tube contains 100 μL of sample to obtain optimum sensitivity. Standards for the radioimmunoassay are calibrated with the international standard available from the National Institute for Biological Standards and Control (Research Standard A for Asp^1-Ile^4-angiotensin I; Holly Hill, Hampstead, London NW 3 6 RB U.K.)

assay consist of mixing 2.0 mL of plasma with 1.0 mL of maleate buffer (0.3 mol/L, pH 5.20). This results in a final pH of 5.7–5.9, which remains unchanged for at least 3 h at 37 °C.

Degradation of angiotensin I by converting enzyme and angiotensinases (Figure 2) must be inhibited during incubation. Several agents and combinations of agents have been used for this purpose (4–6, 8, 12, 13). Ethylenediaminetetraacetic acid (EDTA) effectively inhibits both converting enzyme and angiotensinases and can conveniently be used when the blood sample is collected. Other agents such as diisopropylfluorophosphate, dimercaprol, β-hydroxyquinolone, and, more recently, phenylmethylsulfonyl fluoride have been used in various concentrations and combinations. The effectiveness of these inhibitors may also depend on the pH used during the incubation. For example, the use of dimercaprol plus β-hydroxyquinolone has been reported to be less effective at pH 5.5–6.0 than at pH 7.4 (5, 8). The use of phenylmethylsulfonyl fluoride at pH 5.5–6.0 in conjunction with the ethylenediaminetetraacetic acid in the plasma provides adequate protection and was used in the assays performed on our patients. This agent is recommended over diisopropylfluorophosphate because it is equally effective but far less toxic owing to its lower volatility (13).

The linearity of the reaction can be of major concern, because only endogenous substrate is utilized (5, 13, 14). There has been considerable debate as to whether or not zero-order kinetics can be obtained. With our assay, as with others, nonlinearity of angiotensin I production with time is rarely encountered unless the PRA is markedly increased or incubations are continued for longer than 1 h. However, the linearity is routinely monitored by assaying angiotensin I at the end of two time intervals: 15 min and 1 h.

The possibility of nonlinearity must always be considered in samples from renal veins because high PRA values may be encountered, and an accurate ratio of the PRA values for samples from the renal veins on each side is essential. Figure 3 shows an example of this problem in a patient with suspected renovascular hypertension. As can be seen, the angiotensin I generated from the sample from the right renal vein is nonlinearly related to time after 60 min, whereas the other samples are linearly related for 3 h. If a 3-h incubation had been used, as is commonly done, and all the reactions had been assumed to be linear, the resulting PRA values would be 147 ng/mL per hour (40.8 ng/L per second) for the right renal vein and 65.1, 66.1, and 70.7 ng/mL per hour (18.1, 18.4, and 19.6 ng/L per second) for the other three samples. The resulting ratio of PRA in samples from right and left renal veins would be 2.2. The true value for renin activity of the sample from the right renal vein, as measured by the rate up to 60 min, is 331 ng/mL per hour (91.9 ng/L per second), which results in a ratio of 4.6. Thus many renin methods in which linearity is assumed would seriously underestimate the ratio. Because of these potential problems, we re-assay samples with PRA values exceeding 100 ng/mL per hour (27.8 ng/L per second) or those with indications of nonlinearity from the results for the two points (i.e., they don’t extrapolate to zero), using at least four time points as shown in Figure 3.

Despite the differences between assays for PRA used by many laboratories and by the various manufacturers of kits and reagents, valid clinical results may still be obtained with any given assay. In a large collaborative study by Bangham et al. (14), PRA values from 17 laboratories using a wide variety of techniques yielded similar ranking sequences (highest to lowest) for PRA on seven test samples. Similarly, Fyhquist et al. (10) showed correlations ranging from 0.81–0.99 between various methods on the same samples. These results suggest that if appropriate reference ranges are used, linearity of the reaction is checked, and excessive dilution of the samples before incubation is avoided, assessment of PRA values by various techniques should result in similar clinical conclusions.

Sample collection and storage. Several factors related to collection and storage can influence PRA values. Like many others, we use ethylenediaminetetraacetic acid-treated plasma for convenience, because we then need not add the ethylenediaminetetraacetic acid to the reaction mixture. After blood collection we place the tubes in ice, keeping the sample at 4 °C during transport and centrifugation, and then store the plasma at −70 °C. Recently, Sealey et al. (15) suggested that sample handling at room temperature would be better, because of an apparent activation of a prorenin at 4 °C that results in 17% higher values, but this finding has not been confirmed by others (16).

The temperature at which samples are stored may also be a factor, again owing to possible protease activation of prorenin, but the data are conflicting. Prorenin is thought to be fully activated if plasma is stored at −5 °C for four days (15). An earlier suggestion by these authors that prorenin might be activated on long-term storage at −20 °C (17) was retracted and the data were attributed to an unstable freezer, which allowed samples to thaw (15). Others have found storage at −20 °C to have no effect on PRA values (18), but a recent report (16) stated that storage of samples at −20 °C led to 22% higher PRA values than when samples were kept at 4 °C. The time of storage was not specified and these authors suggested storing samples at 4 °C. However, at this temperature, others (19, 20) have noted an increase in renin values after storage.
for a few days. Thus, it is apparent that there is disagreement concerning sample handling and storage; for that reason we still handle our specimens at 4 °C and store them for a short time (no longer than one week) at -70 °C.

Several other factors (Table 1), generally related to blood-volume changes and drugs, that may influence PRA values (1, 3, 21) will not be considered further here. As in the cases presented here, measurement of renal-vein PRA probably does not require strict control of these variables because relative, rather than absolute, values are being considered, although stimulation (by means of sodium restriction or diuretic administration, or both) of the renin–angiotensin system is preferred before sampling (see below).

Clinical Use of Plasma Renin Activity Measurements

The appropriate use of PRA measurements in evaluating hypertension is a subject of substantial controversy. The two major features of the controversy are (a) whether there is any value in using PRA results to subclassify patients with essential hypertension, and (b) which hypertensive patients should receive a complete workup for the presence of secondary (curable) hypertension.

Hypertension affects about 20% of the adult population in the United States and is a major factor associated with risk of congestive heart failure, stroke, renal failure, and coronary artery disease (22). More than 90% of the hypertensive patients have essential hypertension for which a cause cannot be clearly identified. Several studies (1, 21, 23) conclude that these patients can be classified as low renin (30%), normal renin (60%), or high renin (10%) (21). The controversy deals with the meaning of such classifications. Some workers have felt that the prognosis and preferred mode of treatment are different for low-renin hypertension, while many others do not (1, 21, 23). Classification of essential hypertension on the basis of PRA values currently should be considered a research tool and is not recommended for clinical practice.

The second controversy concerns which patients should have extensive laboratory workup to identify potentially curable secondary hypertension, of which the major types are renovascular hypertension (as in our cases), primary hyperaldosteronism, pheochromocytoma, Cushing’s syndrome, and coarctation of the aorta. The arguments for (22) and against (24) extensive evaluation of all hypertensive patients have been presented elsewhere. The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (25) recommends that the extensive laboratory evaluation for hypertension should be reserved for selected patients who are judged from history, physical examination, and routine laboratory procedures such as hematocrit, urinalysis, creatinine, potassium, and electrocardiogram to be likely to have one of the secondary causes of hypertension.

An extensive evaluation of the hypertension in the cases presented here was justified based on these criteria. The first patient required a complete evaluation on the basis of his age alone (25 years old) and the fact that he was becoming increasingly resistant to medical therapy. The second patient required a thorough evaluation, again on the basis of her relatively young age (36 years old) and history of rather sudden onset of hypertension (about six months).

Of the major secondary causes of hypertension, measurement of PRA has an important role in the evaluation of two: primary aldosteronism and renovascular hypertension (1). The remainder of the discussion will focus on the use of PRA in the diagnosis of renovascular hypertension, which is by far the major cause of secondary hypertension and was the primary consideration in the patients presented here.

PRA measurements in the peripheral blood have not proved to be a reliable indicator of renovascular hypertension. A review by Marks and Maxwell (26) showed that of 196 patients with surgically correctable renovascular hypertension, only 56% had an increase in PRA in the peripheral blood. Measuring PRA after stimulation with furosemide (27, 28), after suppression by saline infusion (28, 29), or with comparison to sodium excretion (30) has been considered to improve the diagnostic reliability of PRA measurements in peripheral blood. However, even with stimulation or suppression, measurements of PRA in the peripheral blood have insufficient accuracy to preclude performing more definitive tests such as measurements of renal-vein PRA (28, 29, 31).

Recently the use of a challenge test with infused sarcosine-alanine-angiotensin II (Saralasin), a competitive antagonist of angiotensin II, has been proposed as a simple, helpful test for use in evaluating renovascular hypertension (32, 33). In this test, a decrease in blood pressure after infusion of Saralasin is thought to indicate the presence of renin-dependent hypertension, of which renovascular hypertension is one form. Even though patients have already been presented in whom a negative Saralasin test was associated with curable renovascular hypertension (34), this test has a high probability of being a valuable adjunct to the diagnostic tests currently available, because it only requires blood pressure readings and is therefore quite simple.

<table>
<thead>
<tr>
<th>Table 1. Factors Affecting PRA Valuesa</th>
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<tbody>
<tr>
<td>I. Decreased PRA</td>
</tr>
<tr>
<td>A. Expanded fluid volume</td>
</tr>
<tr>
<td>1. Salt loads</td>
</tr>
<tr>
<td>2. Mineralocorticoid excess</td>
</tr>
<tr>
<td>3. Renal insufficiency</td>
</tr>
<tr>
<td>B. Depression of sympathetic nervous system activity</td>
</tr>
<tr>
<td>1. Autonomic dysfunction</td>
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<tr>
<td>2. Treatment with adrenergic neuronal blockers: reserpine, methyldopa, guanethidine sulfate, clonidine hydrochloride</td>
</tr>
<tr>
<td>3. Treatment with β-adrenergic blockers: propranolol hydrochloride</td>
</tr>
<tr>
<td>C. Potassium loads</td>
</tr>
<tr>
<td>II. Increased PRA</td>
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<tr>
<td>A. Decreased fluid volume</td>
</tr>
<tr>
<td>1. Salt deprivation or wastage</td>
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<tr>
<td>2. Decreased effective plasma volume</td>
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<tr>
<td>a) Diuretic therapy</td>
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<tr>
<td>b) Chronic edematous states (cirrhosis, nephrosis)</td>
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<tr>
<td>c) Upright posture</td>
</tr>
<tr>
<td>B. Decreased renal perfusion</td>
</tr>
<tr>
<td>1. Therapy with peripheral vasodilators: hydralazine hydrochloride, prazosin hydrochloride, diazoxide, sodium nitroprusside</td>
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<tr>
<td>2. Renal ischemia</td>
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<tr>
<td>C. Increased sympathetic nervous activity: exercise, stress, hyperthyroidism</td>
</tr>
<tr>
<td>D. Hypokalemia</td>
</tr>
<tr>
<td>E. Increased renin substrate</td>
</tr>
<tr>
<td>1. Pregnancy</td>
</tr>
<tr>
<td>2. Therapy with estrogen</td>
</tr>
<tr>
<td>III. Variable</td>
</tr>
<tr>
<td>A. Spontaneous fluctuations and circadian rhythm</td>
</tr>
<tr>
<td>B. Menstrual cycle</td>
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*a Modified from Kaplan (21)
Renal-Vein Plasma Renin Activity

The usefulness of bilateral renal-vein PRA measurements as a predictive test for detecting surgically correctable renovascular hypertension is enhanced by the fact that the demonstration of renal artery stenosis in a hypertensive patient is not sufficient evidence on which to make the diagnosis of renovascular hypertension. In a series of 295 unselected autopsies, renal artery stenosis was present in 49% of 256 who had been normotensive and in only 77% of 39 who had been hypertensive (35). Moreover, the association of hypertension and renal disease is also insufficient evidence, because an early review found only 19% of such patients to be cured of hypertension by unilateral nephrectomy (36). It is now thought that a renal arterial lesion must be shown to be functionally significant, i.e., it must reduce blood flow to the kidney by an amount sufficient to render at least a portion of the kidney ischemic. Surgically correctable renovascular hypertension therefore can be diagnosed only by verifying that there is a substantial difference in the functional capacity of the involved kidney as compared to the contralateral (and presumed normal) one (37). Thus, the diagnosis of renovascular hypertension entails demonstration of renal lesion through tests such as rapid-sequence intravenous pyelography, arteriographic methods, and renal-scanning techniques, and demonstration of a functional abnormality by renal split-function studies (31) or differential renal-vein PRA measurements. Because renal split-function studies require regional anesthesia, are lengthy to perform, and have major and minor complications in 11% of patients, differential PRA measurement in the renal veins is the most commonly used measure of functional abnormalities.

A recent review of the literature indicates that of 386 patients who had lateralization of renal-vein PRA (based upon the criterion for abnormal ratios established in each series), 267 (93%) were cured or improved by corrective surgery (26). However, falsely negative ratios presented a serious problem because 64 of 128 patients whose renal-vein PRA determinations did not lateralize were improved or cured by surgery.

Several factors may be responsible for this disturbingly high percentage of “false-negative” results, including sampling errors and the presence of intermittent sporadic patterns of renin release. A sporadic pattern of renin release may result in spurious ratios if there is a time delay between bilateral sampling of blood from the renal veins. This has led to the recommendation that both renal veins be simultaneously sampled by placing two catheters, one in each renal vein (26). This has recently been challenged (37) because in uncomplicated cases the delays in obtaining samples are minimal. A single-catheter technique is usually used at Barnes Hospital.

When renal-vein PRA is measured, samples are obtained by venous catheterization from the inferior vena cava, and from the left and right renal veins. Mixing of blood of nonrenal origin during sampling from the renal vein may therefore present a problem. This is especially possible on the left side, because the gonadal vein usually drains into the left renal vein, and if the catheter is not well beyond the entrance of the gonadal vein then the sample may contain blood both from the renal and gonadal veins. Some have advocated simultaneous measurement of p-aminohippurate to detect such a problem (31). The rationale for this is that about 90% of infused p-aminohippurate is cleared in a single passage through the kidney. Therefore, if it is infused during the procedure, its concentration in the renal vein should be 10% of that in the vena cava.

Falsely low values may also be obtained in segmental renovascular disease or when the patient has not been maximally stimulated to produce renin. In our first patient, segmental renovascular hypertension was present but the renal-vein PRA ratio (2.2) was still abnormal. Others have shown that in similar patients falsely low ratios can be obtained unless the blood is sampled from veins draining the affected segment (38). Recent data have also indicated a greater predictability of surgical success if the renin samples are obtained after sodium depletion and (or) diuretic administration (26, 29, 39), as in these two cases. Sampling blood from the renal veins after infusion of angiotensin II inhibitors has recently given encouraging results as well (40, 41).

Another variable is the manner of calculating the data. The most frequently used method of interpretation is to calculate the ratio of PRA from the two renal-vein blood samples. In various series, ratios of >1.4–2.5 (affected side/nonaffected side) have been used as the criteria for lateralization and surgical curability. Unfortunately, the cut-off value separating normal and abnormal renal-vein blood PRA ratios appears to have been rather arbitrarily defined by many investigators (26). The appropriate cut-off would appear to be about 1.8, based upon two large series in which the upper limits of “normality” were 1.63 and 1.96 in patients with essential hypertension (26, 42).

Another means of calculating the results is the renal systemic index. This is calculated by subtracting the PRA value of blood from the inferior vena cava from the value for the renal vein and dividing by the value for the inferior vena cava. A systemic index value of >0.45 in the affected kidney in conjunction with a value approaching 0 in the contralateral kidney is considered indicative of surgical curability (30, 43, 44), and initial results of the use of this mode of calculation have been encouraging (43, 44). In the present two patients, both the renal-vein PRA ratios (2.2 and 6.0) and the renal systemic indices (case 1: 0.60 involved kidney, 0.04 contralateral kidney; case 2: 0.84 and 0.05) would be highly predictive of a surgical cure. However, only one patient (case 1) was obviously improved by surgery. In the second case there is a possibility of a residual stenosis as indicated by a postoperative arteriogram, and this patient would appear to be a good candidate for further investigation. Nevertheless an abnormal renal vein PRA does not always predict surgical success.

Conclusions

PRA measurements on samples obtained during selective renal vein catheterization are useful in predicting surgical curability in the presence of renal artery stenosis and hypertension. Calculations of renal-vein PRA ratios continue to be the standard technique for evaluating these data, but false-negative tests present a significant problem. Sampling errors may be responsible for several of these false negative tests and may be assessed in part by simultaneous determinations of p-aminohippurate clearance on the samples. Appropriate stimulation of the renin–angiotensin system before venous catheterization by sodium restriction or diuretic therapy, or both—and possibly also the infusion of converting enzyme inhibitor—appears to eliminate many of these falsely negative ratios. Measurement of peripheral venous PRA has not proven to be a reliable indicator of surgically curable renovascular hypertension. The use of blood-pressure response after infusion of specific inhibitors of the renin–angiotensin system to indicate renin-dependent hypertension is promising but not as yet established.

The measurement of PRA is adequate for diagnostic purposes if care is taken to use buffers to obtain the desired pH (5.5–6.0 or 7.4), appropriate angiotensinase inhibitors are used, the linearity of the reaction is checked, and the samples are not excessively diluted before incubation.
References