Renovascular hypertension with low-to-normal plasma renin: clinical and angiographic features

Gian Paolo ROSSI*, Edoardo PAVAN*, Matteo CHIESURA-CORONA†, Michael BADER‡, Giovanni PAGANINI*, Maurizio CESARI*, Renzo DE TONI*, Gian Pietro FELTRIN†, Detlev GANTEN‡ and Achille C. PESSINA*

*Departments of Clinical and Experimental Medicine, University of Padua and Azienda Ospedaliera, University Hospital, via Giustiniani, 2 35126 Padova, Italy, †Institute of Radiology, University of Padua and Azienda Ospedaliera, University Hospital, via Giustiniani, 2 35126 Padova, Italy, and ‡Max Delbruck Center for Molecular Medicine Berlin-Buch, Robert Rössle Strasse 10, D-13125 Berlin, Germany

(Received 23 January/24 June 1997; accepted 4 July 1997)

1. Low-to-normal renin renovascular hypertension (RVH) and the accuracy of renal vein renin ratios were investigated in 129 consecutive patients referred for suspected RVH. Forty-nine had essential hypertension, 29 unilateral renoparenchymal hypertension and 56 renal artery obstruction. Of the latter, 86% were diagnosed retrospectively as RVH, based on fall in blood pressure with correction of renal ischaemia. We measured baseline, captopril-stimulated and renal vein plasma renin activity (PRA) levels, as well as several other parameters.

2. PRA was low-to-normal in 37% of the RVH patients [low-to-normal renin (LNR-) RVH group] and elevated in the remaining 63% [high-renin (HR-) RVH group]. In the LNR-RVH group, low-to-normal renin levels, by immunoreactive active renin and plasma renin concentration measurements, and a blunted response of PRA to captopril, were seen. As compared with HR-RVH, LNR-RVH patients had a longer duration of hypertension ($P < 0.05$), higher serum $K^+$ ($P = 0.04$) and lower diastolic blood pressure ($P = 0.02$). However, they did not differ for the other variables, including the fall in blood pressure after correction of renal ischaemia. Although the number of bilateral stenoses was similar in the two groups, no patient in the LNR-RVH group had total renal artery occlusion compared with 53% in the HR-RVH group ($P = 0.00015$). The accuracy of renal vein renin indices were high enough to justify their use only in the patients with total occlusion of a renal artery.

3. Thus LNR-RVH is common in patients with longstanding hypertension without a totally occluded renal artery. Since the sensitivity of renin measurements is low, cure of hypertension would be precluded for more than one third of RVH patients, if these tests were a prerequisite for identifying RVH.

INTRODUCTION

Renovascular hypertension (RVH) is currently increasingly recognized due to aging of the population and improved diagnostic tools [1–3]. It is widely accepted that renal artery obstruction, by decreasing renal perfusion pressure, turns on transcription of the renin gene and the synthesis of renin [1, 4], with ensuing increased angiotensin (Ang) II generation. The latter can maintain glomerular filtration rate (GFR) at the cost of increased vascular resistance and systemic blood pressure (BP). Thus, RVH has been regarded as the prototype of renin-dependent hypertension [5], and the measurement of baseline and stimulated plasma renin activity (PRA) in peripheral and renal vein blood has therefore been widely used for its identification [6–9]. Renal vein renin indices have been proposed for assessing the contribution of enhanced renin secretion to the pathogenesis of RVH and predicting the outcome of renal revascularization [7–10]. However, even after stimulation of renin secretion with different agents, these tests were found to have a high false negative rate, which was attributed to several factors, including inhibition of renin enzymic activity, technical failure in either the measurement of PRA or the sampling procedure and drug interference [8, 9, 11, 12]. Consequently, cure of hypertension after correction of renal ischaemia has become the sole indisputable criterion for diagnosing RVH, but, being retrospective, it is of limited value from the clinical and therapeutic standpoint. The possibility that not all cases of RVH are mediated through the renin–angiotensin system (RAS) has also been suggested, based on anecdotal clinical reports [13]. Indeed, activation of the RAS has not been a consistent finding in all forms and at all stages of RVH [12, 14, 15], but no systematic investigation of 'low-renin' RVH in humans has been carried out thus far.

Key words: angiography, immunoradiometric assay, plasma renin concentration, renal vein renin studies, renin, renovascular hypertension.

Abbreviations: Ang, angiotensin; BP, blood pressure; EH, essential hypertension; GFR, glomerular filtration rate; HR, high renin; IRMA, immunoreactive active renin; LNR, low-to-normal renin; PRA, plasma renin activity; PRC, plasma renin concentration; PTRA, percutaneous transluminal renal angioplasty; RAS, renin–angiotensin system; RPH, renoparenchymal hypertension; RVH, renovascular hypertension; RVRI, renal vein renin indices.

Correspondence: Dr G. P. Rossi.
Accordingly, the purposes of this study were to investigate: (1) the prevalence of low-to-normal renin (LNR) RVH in a series of consecutive patients referred for suspected RVH; (2) the clinical and humoral features useful for diagnosing this condition; and (3) the diagnostic accuracy of the renal vein renin studies in this setting.

A preliminary account of this study was presented at the 15th Meeting of the International Society of Hypertension, Melbourne, 20–24 March 1994.

PATIENTS AND METHODS

Between January 1988 and October 1996, 129 patients (62 females and 67 males, aged 45±14, range 14–75 years) were referred to our institution for suspected RVH. This was based on onset of hypertension before age 35 years or after age 60 years [16], and/or the finding of severe refractory hypertension, and/or an abdominal bruit, and/or a small kidney observed by ultrasound imaging or renal scintigraphy. They underwent a diagnostic work-up comprising measurements of baseline and captopril-stimulated PRA, renal vein renin studies and digital subtraction angiography. Measurement of plasma renin concentration (PRC), immunoreactive active renin (IRMA) and split GFR were also performed in subsets of patients.

The hormonal profiling was carried out after withdrawal of any antihypertensive drug and of non-steroidal anti-inflammatory drugs for at least 2 weeks, while on a 100–200 mmol/day Na+ intake. Compliance with this sodium intake regimen was previously verified in a parallel series, which showed an average daily sodium excretion of 99±48 mmol (SD). The captopril test was performed as follows: between 8.00 hours and 9.00 hours, after the subjects had been fasting overnight and lying quietly in the supine position for at least 1 h. Blood for PRA was collected into pre-chilled tubes containing 200 μl of Na2EDTA, with the utmost care to avoid sampling any blood segments containing 200 μl of Na2EDTA, with the utmost care to avoid any stress to the patient. Blood samples were taken again 45 min after administration of 50 mg of captopril by mouth [17–20]. The patients were kept fasting and lying throughout the test [17, 19, 20] for the following reasons: (1) to exclude the risk of symptomatic orthostatic hypotension, which was previously occasionally seen in a pilot study; and (2) for the sake of standardization. Samples were centrifuged immediately at 3000 g at 4°C for 15 min and the supernatant was collected and frozen at −20°C until assayed. PRA was measured by a commercially available kit (Ares Serono, Milan, Italy; supine normal values with a daily sodium intake of 100–200 mmol; 0.33–1.73 pmol h⁻¹ ml⁻¹) as generation of Ang I after incubation for 2 h at 37°C, pH 6.0.

PRC was measured with the same kit and general methodology, but with an excess of exogenous human angiotensinogen added to each sample before incubation. For this purpose plasma of transgenic rats TGR (hAOGEN 1623) was used, harbouring the entire human angiotensinogen gene, containing 1.1 kb of the 5' flanking sequence, five exons, four introns and 2.4 kb of the 3' flanking sequences. These animals over-produce human angiotensinogen, but their renin is unable to cleave it because of its well-known species-specificity [21]. In addition, in order to avoid the potentially confounding effect of Ang I generated by the rat RAS, the rat plasma was previously incubated for 12 h at 37°C, i.e. until a plateau for the generation of Ang I was attained.

Plasma IRMA was measured using a commercially available kit (IRMA; Diagnostics Pasteur, Marnes-La Coquette, France; supine normal values 7–50 pg/ml with a 100–200 mmol Na⁺ diet daily) [22].

Total and split GFR was assessed by ⁹⁹ᵐTc pertechonate diethylene-triaminepenta acetic acid clearance according to the method of Gates [23].

Renal vein renin studies were performed between 8.00 hours and 12.00 hours, after the subjects had been fasting overnight and kept lying quietly in the supine position for at least 1 h. Blood for PRA was collected as mentioned above by selective catheterization of the renal veins with the Seldinger technique via the femoral vein. In all cases the time elapsed between blood sampling from one side and the other was within 5 min. Results were evaluated by using: (i) the ratio of affected and unaffected side (PRA value in renal vein blood from the ischaemic kidney/PRA value in renal vein of blood from the contralateral kidney, V_{isch}/V_{ctl}); (ii) the ratio of unaffected side and infrarenal inferior vena cava blood (V_{cel}/PRA value in renal vein blood from the inferior vena cava, V_{cel}/A); and (iii) the renal venous-arterial PRA difference relative to arterial levels from the affected [V_{isch}/A] and unaffected [(V_{cel}/A)] kidney (Vaughan’s criteria) [7].

Digital subtraction angiography was performed via the femoral artery approach using a commercially available apparatus (Philips, DVI-II, Eindhoven, The Netherlands). The severity and aetiology of renal artery obstruction was diagnosed by well-established criteria [24], which in our hands were found to be accurate, when compared to both the surgical and pathological diagnosis. In brief, atherosclerotic renal artery stenosis was diagnosed when the proximal one-third or the orifice of the main renal artery was affected by a localized, eccentric or circumferential plaque; renal artery dysplasia was diagnosed when the middle and distal thirds of the main renal artery were involved and/or the process extended into the secondary branches, and/or when the classical beaded appearance was evident [25–30]. The degree of stenosis was considered to be haemodynamically significant when greater than 70%, since renal blood flow and perfusion pressure have been shown to fall sharply beyond that cut-off value [27]. The presence of nephroangiosclerosis...
was evaluated angiographically based on well-established criteria [28] as well as on the experience derived from previous microangiographic studies on explanted kidneys [29, 30]. The damage was graded into five classes for each side as follows: grade 0, no damage; grade 1, moderate tortuosity, pruning and/or crowding of interlobar arteries; grade 2, severe tortuosity, pruning and/or crowding of interlobar arteries, thinning of the renal cortex but maintained corticomedullary separation; grade 3, the same as grade 2 but without corticomedullary separation and with some radiolucency of the outer cortex; and grade 4, no parenchymal opacification. An overall score of renal parenchymal damage was then calculated by adding up the grades for each side.

Sensitivity, specificity and accuracy were calculated by commonly used equations [31].

Since renal blood flow and perfusion pressure have been shown to fall when the degree of stenosis attains 70% [27], correction of renal ischaemia was undertaken, regardless of the renin data, in the presence of a haemodynamically significant stenosis [32]. The effect of correction of renal ischaemia on BP was assessed by comparing the untreated BP closest to the procedure or that during hormonal profiling; in treated patients comparison was made while they were taking the same antihypertensive agents as before.

Aetiology of hypertension

RVH was diagnosed in the presence of both haemodynamically significant renal artery stenosis, as defined above, or renal artery occlusion, and a decrease of BP after correction of renal ischaemia, i.e. if the patients were either cured or improved (i.e., they exhibited at least a 10% decrease in mean BP and/or a decrease in the number and/or dosage of drugs needed to attain a normal BP), according to the cooperative study on RVH [6]. Assessment of the result of correction of renal ischaemia on BP was carried out after at least 6 months (range 6 months–6 years) and was based on at least three BP measurements, according to the World Health Organization recommendations. Reno-parenchymal hypertension (RPH) was diagnosed in the presence of a unilateral or bilateral disease primarily involving the renal parenchyma as shown by history, the results of urinalysis, urine culture, renal ultrasound examination and the nephrographic phase of renal angiography.

Essential hypertension (EH) was diagnosed based on exclusion of known causes of secondary hypertension at a thorough clinical evaluation, which included, besides renal digital subtraction angiography, measurements of supine and standing plasma aldosterone levels and, in selected cases, urine catecholamines excretion rate and adrenal computed tomography scan.

Statistical analysis

Results are expressed as means±SD, or median and range for variables not normally distributed. Comparison of RVH, EH and RPH groups was carried out by one-way analysis of variance followed by post hoc Duncan’s test for multiple comparison, Kruskall–Wallis and Mann–Whitney’s non-parametric test, whenever appropriate [33]. Comparison of BP values before and after correction of RVH was carried out with paired Student’s t-test. Pearson’s correlation coefficient for analysis of the PRA, PRC and IRMA measurements was also used. A P value lower than 0.05 was considered statistically significant. All analyses were carried out with the SPSS-PC+ statistical package (version 3.0, SPSS Inc, Chicago, IL, U.S.A.).

RESULTS

Clinical characteristics of the patients

The clinical characteristics of the patients, as diagnosed according to the criteria specified above and to the flow chart depicted in Fig. 1, are shown in Table 1. In 48 patients who had renal artery obstructions, renal ischaemia was either corrected [by percutaneous transluminal renal angioplasty (PTRA) in 31, and aorto-renal by-pass in five] or eliminated by nephrectomy (in eight) (Table 2). A combination of PTRA+nephrectomy, by-pass+nephrectomy and PTRA+by-pass surgery was used in four patients with bilateral obstructions.

As a result of these procedures, mean BP decreased from 133±18 mmHg to 104±13, mean ± SD, P<0.0001) in this group. In addition, all patients were either cured (n = 16, 33.3%), or improved (n = 32, 66.7%), at follow-up. Thus, RVH was retrospectively diagnosed in these patients. In another patient with long-standing hypertension, correction of atherosclerotic renal artery stenosis with a technically successful PTRA did not improve BP control; therefore this patient was included in the group with EH. Eight additional patients, who had tight renal artery stenoses with post-stenotic dilatation and evidence of severe ischaemia at a 99mTc pertechnetate diethylene-triamine penta acetic acid scan, refused any revascularization procedure. The PRA levels were low-to-normal in four patients and elevated in the remaining four. Although likely to have RVH on clinical grounds, they were excluded from the study for lack of retrospective confirmatory diagnosis. Of interest is the fact that, at follow-up, four of these patients developed end-stage renal disease and one of them was dead after 24 months. In the 48 patients with proven RVH, the aetiology of renal artery obstruction was fibrodysplasia in 21 patients (15 female and 6 male, age 40±15), atherosclerosis in 25 patients (9 female and 16 male, age 59±9, P = 0.013 compared with fibrodysplasia) and vasculitis in two patients. Forty-nine patients had no renal artery obstruction and were
diagnosed as essential hypertensives. Twenty-four patients without renal artery abnormalities were diagnosed as renorenal parenchymal hypertensives (Table 1). One additional patient with very high PRA values was diagnosed with a renin-secreting tumour and has been described in detail elsewhere [34].

Comparison of RVH, EH and RPH patients (Table 1)

The RVH patients were significantly \((P<0.05)\) older than those in the other two groups; their diastolic, systolic and mean BPs were similar. In addition, their total serum cholesterol and serum creatinine levels were higher \((P<0.05)\) and GFR in the ischaemic kidney was lower than that of EH patients. The three groups were also similar with respect to all the other parameters, with the exception of both supine and captopril-stimulated PRA, which were significantly \((P<0.05)\) higher in the RVH as compared with the EH group (Table 1).

Comparison of LNR-RVH and high renin (HR)-RVH patients (Table 2)

From the results of PRA measurements it was evident that 4 (8%) and 14 (29%) of the 48 patients

<table>
<thead>
<tr>
<th>Table 1. Clinical features of the RVH, EH and RPH patients. Abbreviations: BMI = Body mass index; SBP, DBP, MBP = systolic, diastolic and mean blood pressure; TChol = total serum cholesterol; HDL-Chol = HDL cholesterol; BUN = blood urea nitrogen; SCr = serum creatinine; PRA = plasma renin activity; K+ = serum potassium levels; NS = not significant.</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVH (n = 48)</td>
</tr>
<tr>
<td>Females/males</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
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<tr>
<td>Pulse pressure (mmHg)</td>
</tr>
<tr>
<td>Known duration of hypertension (months)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>TChol (mmol/l)</td>
</tr>
<tr>
<td>HDL-Chol (mmol/l)</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
</tr>
<tr>
<td>BUN (mmol/l)</td>
</tr>
<tr>
<td>Scr (mmol/l)</td>
</tr>
<tr>
<td>PRA (pmol h(^{-1}) ml(^{-1}))</td>
</tr>
<tr>
<td>Captopril-stimulated PRA (pmol h(^{-1}) ml(^{-1}))</td>
</tr>
<tr>
<td>K+ (mmol/l)</td>
</tr>
<tr>
<td>Total GFR (ml/min/m(^2) BSA)</td>
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<tr>
<td>Ischaemic kidney GFR (ml/min/m(^2))</td>
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<tr>
<td>Contralateral kidney GFR (ml/min/m(^2))</td>
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</tbody>
</table>
with confirmed RVH had low and normal plasma renin levels respectively (Table 2). In these LNR-RVH patients baseline supine PRA was below the upper normal range and similar to that of EH and RPH patients (Tables 1 and 2). Furthermore, their PRA exhibited a blunted response both standing up (results not shown) and after captopril, as compared with the remaining RVH patients (HR-RVH), whose levels were markedly elevated.

From the clinical standpoint, the LNR-RVH patients had a longer duration of hypertension, higher serum K+ levels, and tended to be slightly older than the HR-RVH patients. However, they did not differ for the remaining demographic and biochemical variables and for BP levels (Table 2). More importantly, the LNR- and HR-RVH patients did not differ for the significant and long-lasting decrease of BP which was seen after correction of renal ischaemia (Fig. 2).

From the angiographical standpoint, there were nine (50%) cases of fibrodysplasia among the LNR-RVH patients and 12 (40%) among the HR-RVH patients (not significant). Atherosclerosis was observed in the remaining nine (50%) LNR-RVH and 16 (53%) HR-RVH group (not significant) patients; two additional patients in this group had a vasculitis. None of the LNR-RVH patients had total occlusion of a renal artery, as compared with 16 (53%) HR-RVH atherosclerotic patients (P = 0.00015). As a result, a significantly lower degree of renal artery obstruction was found in the former as compared with the latter (Table 2). In addition, a significantly higher ratio of the longitudinal diameter of the two kidneys was found in LNR-RVH as compared with HR-RVH patients (not significant).

### Table 2. Clinical features of the RVH patients classified by PRA levels

<table>
<thead>
<tr>
<th>Variables</th>
<th>LNR-RVH (n = 18)</th>
<th>HR-RVH (n = 30)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females/Males</td>
<td>7/11</td>
<td>18/12</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52 ± 16</td>
<td>49 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>24.7 ± 4.1</td>
<td>24.6 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>179 ± 35</td>
<td>180 ± 32</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>104 ± 14</td>
<td>112 ± 10</td>
<td>P = 0.0231</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>129 ± 19</td>
<td>137 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>Known duration of hypertension (months)</td>
<td>108 (24-240)</td>
<td>7.5 (1-192)</td>
<td>P = 0.029</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71 ± 9</td>
<td>74 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>TChol (mmol/l)</td>
<td>5.77 ± 1.02</td>
<td>5.84 ± 1.21</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-Chol (mmol/l)</td>
<td>1.13 ± 0.28</td>
<td>1.30 ± 0.45</td>
<td>NS</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>1.55 ± 1.18</td>
<td>1.44 ± 0.84</td>
<td>NS</td>
</tr>
<tr>
<td>BUN (mmol/l)</td>
<td>7.02 ± 2.12</td>
<td>6.98 ± 3.31</td>
<td>NS</td>
</tr>
<tr>
<td>SCr (µmol/l)</td>
<td>10.5 ± 25</td>
<td>11.4 ± 48</td>
<td>NS</td>
</tr>
<tr>
<td>Supine PRA (pmol h⁻¹ ml⁻¹)</td>
<td>0.60 (0.08-0.99)</td>
<td>3.74 (1.82-17.51)</td>
<td>P = 0.0001</td>
</tr>
<tr>
<td>Captopril-stimulated PRA (pmol h⁻¹ ml⁻¹)</td>
<td>0.96 (0.12-4.84)</td>
<td>11.46 (3.34-64.26)</td>
<td>P = 0.0001</td>
</tr>
<tr>
<td>K+ (mmol/l)</td>
<td>4.26 ± 0.44</td>
<td>3.95 ± 0.54</td>
<td>P = 0.042</td>
</tr>
<tr>
<td>Total GFR (ml/min/m² BSA)</td>
<td>63 ± 35</td>
<td>74 ± 35</td>
<td>NS</td>
</tr>
<tr>
<td>Ischaemic kidney GFR (ml min⁻¹ m⁻²)</td>
<td>28 ± 25</td>
<td>20 ± 19</td>
<td>NS</td>
</tr>
<tr>
<td>Contralateral kidney GFR (ml min⁻¹ m⁻²)</td>
<td>55 ± 20</td>
<td>54 ± 25</td>
<td>NS</td>
</tr>
<tr>
<td>Degree of stenosis of renal artery (%)</td>
<td>87 ± 13</td>
<td>95 ± 9</td>
<td>P = 0.020</td>
</tr>
<tr>
<td>Aetiology of renal artery disease (FDP-ATS)</td>
<td>9.9</td>
<td>12.16*</td>
<td>NS</td>
</tr>
<tr>
<td>No. of unilateral/bilateral stenoses</td>
<td>12.6</td>
<td>20.10</td>
<td>NS</td>
</tr>
<tr>
<td>No. of occluded/non-occluded arteries</td>
<td>0.18</td>
<td>16.14</td>
<td>P = 0.00015</td>
</tr>
<tr>
<td>Score of nephroangiosclerosis</td>
<td>2.15 ± 1.24</td>
<td>2.16 ± 1.25</td>
<td>NS</td>
</tr>
<tr>
<td>Longitudinal diameter of ischaemic/contral. kidney</td>
<td>0.92 ± 0.16</td>
<td>0.74 ± 0.20</td>
<td>P = 0.009</td>
</tr>
</tbody>
</table>

**Fig. 2.** Effect of correction of renal ischaemia in the 48 patients classified as renovascular hypertensive. The patients were divided into two groups according to their baseline PRA levels. One group with elevated PRA levels was defined as HR-RVH, n = 30, (hatched bars). The other with low-to-normal PRA levels as LNR-RVH, n = 18, (open bars). A significant decrease of BP with correction of renal ischaemia with no difference between groups was observed.
compared with HR-RVH (Table 2). Taken together, these findings indicate a lower degree of ischaemia in LNR-RVH patients. At variance, the score of nephroangiosclerosis did not differ between groups.

Comparison of PRA, PRC and IRMA measurements in LNR-RVH patients

In LNR-RVH the renin levels were confirmed to be low-to-normal also in all the three samples collected from both renal veins and the inferior vena cava by the IRMA (n = 8 patients) and PRC (n = 6) methods. Although the number of LNR-RVH patients investigated was small, the comparison of the results of the IRMA and PRA measurements showed agreement between the two methods (r = 0.38, P = 0.06). Only few samples fell above (three patients) and below (two patients) the 95% confidence band, but the vast majority were scattered around the identity regression line. Similar results were obtained by comparing the PRC and PRA methods, with only few samples (the three of one patient and one out of the three of two additional patients) falling outside of the 95% confidence band. It is of interest, that an elevated PRC value was found in a sample of renal vein blood draining from the ischaemic kidney of a patient who had low-to-normal values in the inferior vena cava and the contralateral vein.

Renal vein renin studies (Table 3)

Sensitivity, specificity and accuracy of the renal vein renin indices are shown in Table 3. The RVRI were calculated on: (i) the whole population of patients with suspected RVH (panel A); (ii) after exclusion of the LNR-RVH patients (panel B); (iii) after exclusion of all patients without high peripheral PRA (panel C); and (iv) only in the HR-RVH patients with total occlusion of the renal artery and the high PRA EH and RPH patients (panel D).

In the whole population, the Vaughan's indices [7] provided a higher sensitivity but a lower specificity, as compared with the ratio between the two sides or the contralateral side and the inferior vena cava. A clear-cut improvement in both sensitivity and accuracy was attained by restricting the analysis to the high PRA patients, and particularly to RVH patients with a totally occluded renal artery.

DISCUSSION

In this study, consecutive patients clinically selected because of suspected RVH, i.e. with an increased pre-test probability of RVH, were investigated. To diagnose RVH the strict criterion of the fall of BP after correction of renal ischaemia was followed, although BP may not decrease after revascularization in all RVH patients due to atheroem-
bolic disease and/or glomerulosclerosis. A substantial proportion (44%) of these patients had in fact renal artery obstruction and in 86% of them the diagnosis of RVH was confirmed by the fall in BP after correction of renal ischaemia. The very high cure-improvement rate attained in this study is of course an outcome of the strict criterion used for diagnosing RVH retrospectively, which makes our results not directly comparable with those of other studies on RVH (see for review [35, 36]). Although we measured peripheral baseline, captopril-stimulated, and renal vein PRA in all patients, with the utmost care to avoid untoward effect of all factors potentially capable of altering renin synthesis and secretion rate [37], we found no evidence of elevation of supine baseline PRA in over one third of RVH patients. In addition, these latter patients exhibited a blunted PRA response to acute stimulation with captopril [17, 18]. The captopril test was carried out in the supine position [17, 20] and therefore the PRA response might have been lower than that observed in other studies where sitting patients were tested [18]. Nevertheless, our LNR-RVH neither attained the cut-off value of PRA increase after captopril, which was considered to be diagnostic of RVH in our laboratory [17, 19], nor did they show overt elevation of PRA with standing up, two findings which are fully consistent with the observation that the response to captopril is dependent on baseline renin profile [38]. Since no evident elevation of PRA in the renal vein blood was found, we can conclude that these patients had no evidence of enhanced renin synthesis.

Low-renin RVH has been reported previously [39] and attributed to renin-independent mechanisms, which may be triggered by renal ischaemia [13] and/or underestimation of renin levels due to methodological problems in the PRA assay, technical failure, drug interference, an upward shift in the Ang II/BP relationship due to long-standing hypertension, and renal failure [1, 8, 9, 12, 39]. The participation of renin-independent mechanisms has been supported by some studies of RVH [13, 40, 41]. In rats with 2 kidney, 1 clip (2 K-1 C) hypertension, MacDonald et al. [41] showed that excision of the clipped kidney normalized BP consistently, at variance with the competitive Ang II antagonist I-Sar-8-Ala Ang II [41]. Furthermore, although immunization against Ang II abolished the pressor effect of exogenous renin and angiotensin, it did not decrease BP in all 1 K-1 C rabbits, thereby suggesting that Ang II is not the sole pathogenic mechanism in RVH [14]. The hypothesis of a blunted synthesis and secretion of vasodepressor renal-derived factors, such as medullolipin I [42], needs to be mentioned in this context. It is worthwhile noting that low-to-normal renin levels have also been observed in most studies on renal vein renin levels in RVH [1, 8, 9, 40, 43]. They were attributed to technical failure in the assay and thereby excluded from the calculation of RVRI [1, 8, 9, 43]. Artifactual underestimation of renin levels by the PRA measurement was previously found in congestive heart failure and liver cirrhosis, where concomitant activation of the RAS and impaired angiotensinogen synthesis may lead to a non-zero-order kinetics of Ang I generation [44, 45]. The possibility of inhibition of renin in vitro by circulating neutral lipids of unknown origin has also been reported [46]. To rule out these possibilities, we measured plasma renin by the PRC and IRMA assays, i.e. two methods which are unaffected by plasma angiotensinogen concentration. With a novel PRC assay, taking advantage of the availability of human angiotensinogen produced by transgenic rats overexpressing the human angiotensinogen gene [21], we found that the low-to-normal renin levels of a substantial proportion of the RVH patients were not due to a limiting amount of angiotensinogen. This conclusion was further confirmed by the results of IRMA measurements [22, 47], which make unlikely also an underestimation of renin by the PRA method due to circulating inhibitors of renin. Thus, a technical failure is unlikely in this study and therefore an RVH with low-to-normal plasma renin levels commonly occurs, although its mechanisms remain to be elucidated.

Nephroangiosclerosis, glomerulosclerosis, atheroembolic disease, chronic renal failure, and the ensuing plasma volume expansion, may decrease renin secretion and eventually cause irreversible hypertension in RVH patients [48]. In the experience of Vaughan et al. [43], the overall accuracy of the captopril test sharply fell (from 96% to 70%) when patients with renal insufficiency were taken into account. None of our RVH patients had renal failure (Table 2); furthermore, no evidence of a more severe nephroangiosclerosis in the LNR-RVH than in the HR-RVH group was found with angiography (Table 2), making these explanations unlikely. During chronic Ang II infusion and the chronic phase of experimental 2 K-1 C hypertension, as well as in man, an upward shift of the Ang II/BP relationship has been described [1, 4, 48]. It was attributed to several mechanisms, including an increased arterial and arteriolar wall-to-lumen ratio, a rise in cardiac output, a central and postganglionic facilitation of sympathetic discharge, a resetting of the baroreceptors, and finally, an enhancement of the aldosterone-stimulating effect of Ang II [4]. All these mechanisms may account for a reinforcement of the pressor effect of Ang II with time, and thereby for persistence of hypertension despite normal renin levels. We have investigated neither the aforementioned mechanisms nor the effect of RAS blockade on BP, and therefore cannot solve the question of whether Ang II participates in causing low-to-normal renin RVH. However, our results support the hypothesis that there is a continuum of renin secretion, which may be inversely related to duration of hypertension and aging [48, 49].

Experimentally, plasma renin returns to normal in chronic 2 K-1 C hypertension [1, 4]. The chrono-
logical changes in renin and BP after clipping the renal artery have been depicted by a three-phase scheme, the first two being characterized by elevation of renin and BP and full reversibility upon unclipping. In the third phase hypertension persists within four days [50]. A clinical counterpart of this tri-phasic pattern of RVH may exist in humans, although the exact duration of each phase is unknown. This is because it is rather difficult to assess accurately the duration of hypertension in humans and almost impossible to establish the exact timing for a renal artery obstruction to become haemodynamically relevant. The fact that in our LNR-RVH patients the duration of hypertension was longer, and the age tended to be older, than in HR-RVH patients, suggests that they might have been diagnosed at a later stage of their RVH. Nevertheless, the clear-cut decrease of BP with correction of their renal ischaemia indicates that the 'second' phase of RVH, which is still prone to reversibility of hypertension upon correction of ischaemia, lasts much longer in humans than in experimental 2 K-1 C hypertension. This is the most important of our findings from the practical standpoint and underscores the causative role of renal ischaemia and the potential curability even of longstanding human RVH. Furthermore, it implies that renin measurements may be inaccurate to discriminate between RVH patients in phase II and III or to identify patients having EH with concomitant renovascular disease [1, 51]. The results of sensitivity, specificity and accuracy of the renal vein indices are in keeping with this view (Table 3) and fully consistent with an earlier report [15]. With the preliminary exclusion of patients with low-to-normal renin levels, higher specificity and accuracy were attained, but the sensitivity of such indices remained unsatisfactory, thereby showing their limited diagnostic and prognostic value. This conclusion fully agrees with those of several other reports [8, 11, 15, 40, 52]. In a two-centre study, Rappelli et al. [40] found that one fifth of RVH patients were cured or improved, by either PTRA or surgery, despite negative RVRI. In addition, almost half of their 96 hypertensive patients with renal artery stenosis, 92% of whom were either cured or improved by correction of renal ischaemia, had low-to-normal PRA levels [40]. Negative RVRI in considerable percentages of RVH patients have also been reported by others [8, 11], despite the fact that up to one third of the patients were excluded from the analysis because of either low (<0.65 pmol h⁻¹ ml⁻¹) PRA levels in the inferior vena cava or a sum of Vaughan's indices [7] of both kidneys <0.48 [8]. Even with these exclusion criteria, BP decreased in 84% of the RVH patients with normal RVRI in a retrospective study of 123 patients [9]. A higher (89%) negative predictive value of RVRI was found by others in 143 angiographically studied patients, but only a small minority (14%) of them had RVH [12]. Thus, the available data and the present results indicate that RVRI have limited diagnostic and prognostic value in RVH, probably with the exception of patients with a totally occluded renal artery. In the latter, collateral blood supply, along with the profound fall in perfusion pressure, sets the stage for the most marked stimulation of renin synthesis and secretion, as shown by the fact that all such patients in this study had very high PRA levels and a very high renal vein (V_{isch} - A)/A. Consequently, the sensitivity and accuracy of the RVRI were high enough to justify their use for identifying RVH in these patients (Table 3, panel d).

In conclusion, more than one third of the patients with proven RVH have low-to-normal plasma renin levels and are likely to be in the 'second phase of the RVH stage', where hypertension is potentially correctable upon correction of ischaemia, at the time of referral. Accordingly, they would be excluded from a definitive cure of hypertension if the screening procedures were based upon baseline, captopril-stimulated PRA and/or renal vein studies, as has been repeatedly proposed [2, 3, 36, 43, 53, 54], but not unanimously accepted [15, 35, 55]. This consideration is of major concern because a subset of RVH patients are elderly and therefore form a group of hypertensives at particular risk of complications [56, 57].

ACKNOWLEDGMENTS

This work was supported by The Italian National Research Council (CNR) — Targeted Project 'Prevention and Control of Disease Factors (FATMA)'. Sub-project '8', Contract N. 91.00.218 PF41 115.06.654 and by a grant to G.P.R. from Regione Veneto, Azienda Ospedaliera di Padova, Ricerca Sanitaria Finalizzata Nr. 539/01/94, Venezia, Italy. We are grateful to Drs. Barbara Mazzucco, Renato Moro, Alfredo Sacchetto, and Lucia Zanin of our Department for their help in selecting the patients and reviewing their charts.

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