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**The effect of revascularization of renal artery stenosis on renal perfusion in patients with atherosclerotic renovascular disease**

Niina Koivuviita1, Kaisa Liukko2, Nobu Kudomi3, Vesa Oikonen5, Risto Tertti1, Ilkka Manner4, Tero Vahlberg5, Pirjo Nuutila1 and Kaj Metsärinne1

1Department of Medicine, Turku University Hospital, PL 52, Kiinamyllynkatu 4-8, Turku 20521, Finland, 2Turku PET Centre, University of Turku, Turku, Finland, 3Department of Medical Physics, Faculty of Medicine, Kagawa University, Japan, 4Department of Radiology, Turku University Hospital, Turku, Finland and 5Department of Biostatistics, University of Turku, Turku, Finland

*Correspondence and offprint requests to: Niina Koivuviita; E-mail: niina.koivuviita@tyks.fi*

**Abstract**

**Background.** Only a small fraction of patients with atherosclerotic renovascular disease (ARVD) treated with revascularization have improved renal function after the procedure. It has been suggested that this may be due to effects of renal microvascular disease. Our aim was to measure the effect of renal artery stenosis (RAS) revascularization on renal perfusion in patients with renovascular disease.

**Methods.** Seventeen renovascular disease patients were treated by dilatation of unilateral (N = 8) or bilateral (N = 9) RAS (N = 23 kidneys), mainly because of uncontrolled or refractory hypertension. The patients were studied before and after (103 ± 29 days) the procedure. Renal perfusion was measured using quantitative positron emission tomography (PET) perfusion imaging.

**Results.** Although renal perfusion correlated inversely with the degree of RAS in patients with renovascular disease, it did not change after revascularization.

**Conclusions.** Our data support the notion of former clinical trials that angiographic severity of RAS does not determine the response to revascularization. Quantitative PET perfusion imaging is a promising tool to noninvasively measure renal perfusion for the assessment of physiological impact of RAS.

**Keywords:** atherosclerotic renovascular disease; imaging; renal artery stenosis; revascularization

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**Introduction**

Atherosclerotic renovascular disease (ARVD) has become an increasingly recognized clinical condition, especially in older [1] and in otherwise atherosclerosis-prone populations, such as patients with hypertension, chronic kidney disease (CKD), coronary heart disease, congestive heart failure and peripheral vascular disease [2–5]. This increase in prevalence has led to a dramatically growing use of percutaneous transluminal renal angioplasty (PTRA) during the past 20 years [6]. However, the results in investigations of renal functional or cardiovascular outcomes after the revascularization procedures have been very variable [7–9]. Recently, it has been suggested that the poor outcomes after the PTRA could be attributable to the damage in the stenotic kidney parenchyma, especially the reduction of microvascular density [10, 11], changes mainly evident at the cortical level, which control almost 80% of the total renal blood flow (RBF).
Most studies in humans evaluating the response of PTRA to renal function are limited to changes in serum creatinine and glomerular filtration rate (GFR) [11, 12], both of which only indirectly reflect renal perfusion and filtration and cannot determine the distribution of renal function between both kidneys [13]. In the present study, we measured noninvasively a single-kidney perfusion and the effect of renal artery stenosis (RAS) revascularization by positron emission tomography (PET) using 15O-labelled water in patients with ARVD.

Subjects and Methods

Subjects

Seventeen patients with ARVD, seven patients with CKD but without renovascular disease and ten healthy volunteers were included in the study. The patients were recruited from the nephrology outpatient clinic of Turku University Hospital. ARVD was defined as a stenosis of >60% of the renal artery as determined by digital subtraction angiography.

All patients and controls gave a written informed consent. The study was approved by the Ethical Committee of the Turku University Central Hospital and it was conducted in accordance with the Declaration of Helsinki as revised in 1996.

Study design

Each patient was studied twice, once before the dilatation of RAS and the second time 103 ± 29 days after revascularization. The imaging studies were performed after a 10-h overnight fast. Alcohol, smoking and caffeine were prohibited for 3 days before assessment. Subjects with symptoms of acute infections within a week prior to or during the study were excluded from the analysis. A venous catheter was inserted into an antecubital vein for injecting [15O] H2O. All patients were instructed to interrupt their antihypertensive medication on the study day and angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) medication 3 days before the study day.

Image acquisition, processing and correction

Renal perfusion was measured with GE Advance PET tomography (General Electric, Milwaukee, Wisconsin) as previously described [14]. PET data were corrected for dead time, decay and measured photon attenuation. Images were processed with the standard reconstruction algorithm (standard = the ordered-subsets expectation-maximization method using a Hann filter with a cut-off frequency of 4.6 mm).

Calculation of RBF

Regions of interest (ROI) for the whole cortical region of the kidneys were drawn on a summed reconstructed image on an average of six coronal planes. For the calculation of renal perfusion from the PET study, the input function was estimated using an average time activity curve (TAC) from descending aorta cavity ROIs [15] drawn on average three planes.

Delay between the renal and aorta TAC was corrected, but due to the large size of the aorta, recovery correction was not considered necessary. Renal perfusion images were generated from the reconstructed dynamic image and the obtained input function by a basis function method assuming a single-tissue compartment model [14]. The renal perfusion was represented by the clearance rate (k2) multiplied with the physiological partition coefficient, i.e. $p_{phys} = 0.94 \text{ mL/g}$ [14]. The mean renal perfusion values were obtained from the renal perfusion images using ROIs drawn on summed images.

Statistical analysis

Results are expressed as mean values ± SD. Normality of variables was assessed by the Shapiro–Wilk test. The difference between before and after the dilatation measurements was tested using the Student’s paired t-test or Wilcoxon signed rank test, when appropriate. The comparison between the groups was performed by two-sample t-test or Mann–Whitney U-test, when appropriate. Correlations were calculated using Pearson’s correlation coefficients. All statistical analyses were performed with SAS statistical program package, version 9.2 (SAS Institute Inc. Gary, NC). Statistical significance was inferred at $P < 0.05$.

Results

Baseline and follow-up demographic and clinical data

The characteristics of the study subjects are shown in Table 1. Coronary heart disease is defined by symptomatic angina, positive exercise stress test, angiographic evidence of coronary artery disease or history of previous myocardial infarction. Cerebrovascular disease is defined by history, clinical signs and/or radiologic confirmation of a transient ischaemic attack or cerebrovascular accident. Peripheral vascular disease is defined by symptoms of intermittent claudication, previous surgery for lower limb arterial insufficiency and/or angiographic evidence of significant stenosis in one or more blood vessels that supply lower limbs.

Renal artery revascularization

The indication for revascularization in all patients was refractory or treatment-resistant hypertension.

Unilateral RAS patients ($n=8$): five patients had stenosis in the right renal artery and three patients at the left side. Two of the patients had two renal arteries to the stenosed kidney; the dilated atherosclerotic stenoses were in the larger arteries. All but one patient received a stent during the angioplasty procedure and the technical outcome was good in every patient (no residual stenosis after dilatation).

Bilateral RAS patients ($n=9$): three patients had significant RAS of the dilated side and total occlusion of the contralateral side unsuitable for dilatation. In five patients, both left and right renal arteries were dilated. In one
Patient revascularization was done only to the left side, while the stenosis in the right was marginal (ca. 50%). Two of the patients had two renal arteries, but the stenosis was in the dominant artery. All patients received at least one stent during the procedure. Unlike in unilateral RAS patients, some degree (≤25%) of residual stenosis was seen in most of the bilateral RAS patients after dilatation. In one patient, the renal artery was dissected during the stent placement and a surgical bypass operation was done. All patients were on antihypertensive medication. Fourteen patients used either ACEIs or ARBs, and beta blockers, 13 used calcium channel blockers and 16 used diuretics. Two patients used a combination of two medications, four patients used a combination of three, four patients a combination of four, five patients a combination of five and two patients a combination of six medications. After dilatation, the number of antihypertensive medications remained stable in 47% of the patients (8 out of 17 patients), increased in 12% of the patients (2 out of 17) and decreased in 41% of the patients (7 out of 17). Although blood pressure did not decrease after revascularization in ARVD patients, there was a statistically nonsignificant (P = 0.07) tendency for a decrease in the number of antihypertensive medications (Table 2).

The estimated GFR (eGFR) remained stable after dilatation (Table 2). The eGFR was significantly lower in the

Table 1. Baseline data

<table>
<thead>
<tr>
<th></th>
<th>ARVD (N = 17)</th>
<th>Unilateral RAS</th>
<th>Bilateral RAS</th>
<th>CKD (N = 7)</th>
<th>Healthy (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>17</td>
<td>8</td>
<td>9</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Age (year)</td>
<td>69 ± 11</td>
<td>66 ± 8</td>
<td>71 ± 13</td>
<td>72 ± 5</td>
<td>60 ± 8</td>
</tr>
<tr>
<td>Male/female</td>
<td>7/10</td>
<td>4/4</td>
<td>3/6</td>
<td>6/1</td>
<td>7/3</td>
</tr>
<tr>
<td>Plasma creatinine (µmol/L) mean (range)</td>
<td>114 (64–241)</td>
<td>107 (65–218)</td>
<td>115 (64–241)</td>
<td>293 (136–578)</td>
<td>84 (64–98)</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>56 ± 23</td>
<td>62 ± 24</td>
<td>54 ± 21</td>
<td>22 ± 12</td>
<td>75 ± 6</td>
</tr>
<tr>
<td>Diabetes (all type 2)</td>
<td>9/17</td>
<td>2/8</td>
<td>7/9</td>
<td>4/7</td>
<td>0</td>
</tr>
<tr>
<td>CHD (%)</td>
<td>6/35%</td>
<td>1/13%</td>
<td>5/56%</td>
<td>3/43%</td>
<td>0</td>
</tr>
<tr>
<td>PVD (%)</td>
<td>4/24%</td>
<td>1/13%</td>
<td>3/33%</td>
<td>3/43%</td>
<td>0</td>
</tr>
<tr>
<td>CVD (%)</td>
<td>5/29%</td>
<td>1/13%</td>
<td>4/44%</td>
<td>1/14%</td>
<td>0</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>4/24%</td>
<td>1/13%</td>
<td>3/33%</td>
<td>2/26%</td>
<td>0</td>
</tr>
<tr>
<td>24-h Urinary protein (g/d)</td>
<td>0.5 ± 1.1</td>
<td>0.6 ± 1.3</td>
<td>0.4 ± 1.0</td>
<td>0.4 ± 0</td>
<td>0</td>
</tr>
<tr>
<td>HB g/L</td>
<td>138 ± 11</td>
<td>140 ± 11</td>
<td>135 ± 11</td>
<td>116 ± 10</td>
<td>143 ± 10</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.0 ± 1.3</td>
<td>5.3 ± 1.7</td>
<td>4.7 ± 1.0</td>
<td>4.3 ± 0.8</td>
<td>5.3 ± 0.8</td>
</tr>
<tr>
<td>Low-density lipoprotein Cholesterol (mmol/L)</td>
<td>2.5 ± 0.7</td>
<td>2.7 ± 0.4</td>
<td>2.3 ± 0.8</td>
<td>2.3 ± 0.6</td>
<td>3.2 ± 0.8</td>
</tr>
<tr>
<td>Ca × Pi (mmol/L)</td>
<td>2.6 ± 0.5</td>
<td>2.7 ± 0.5</td>
<td>2.4 ± 0.6</td>
<td>2.9 ± 0.8</td>
<td>2.1 ± 0.6</td>
</tr>
<tr>
<td>Parathyroid hormone (ng/L)</td>
<td>102 ± 20</td>
<td>84 ± 9</td>
<td>116 ± 12</td>
<td>144 ± 55</td>
<td>47 ± 16</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.
CHD, coronary heart disease; PVD, peripheral vascular disease; CVD, cerebrovascular disease; HB, blood haemoglobin.

Table 2. Baseline and follow-up data of the eGFR, blood pressure and number of antihypertensive medications

<table>
<thead>
<tr>
<th></th>
<th>ARVD (N = 17) Baseline</th>
<th>Follow-up</th>
<th>CKD (N = 7) Baseline</th>
<th>Healthy (N = 10) Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (mL/min)</td>
<td>56 ± 23</td>
<td>59 ± 25</td>
<td>22 ± 12</td>
<td>75 ± 6</td>
</tr>
<tr>
<td>sBP (mmHg)</td>
<td>193 ± 26</td>
<td>185 ± 25</td>
<td>189 ± 32</td>
<td>130 ± 11</td>
</tr>
<tr>
<td>dBP (mmHg)</td>
<td>89 ± 13</td>
<td>91 ± 15</td>
<td>81 ± 11</td>
<td>79 ± 6</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>124 ± 15</td>
<td>122 ± 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of antihypertensive medications</td>
<td>4.1 ± 1.2</td>
<td>3.5 ± 1.3</td>
<td>3.1 ± 1.3</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.
ARVD, atherosclerotic renovascular disease; eGFR, estimated glomerular filtration rate; sBP, systolic blood pressure; dBP, diastolic blood pressure; MAP, mean arterial pressure.

Fig. 1. Correlation of RAS with renal perfusion in stenosed kidneys (N = 23). RAS, renal artery stenosis.
nine diabetic patients than in the nondiabetic patients, both at the baseline and the follow-up (45 ± 18 versus 68 ± 22 mL/min, baseline, and 50 ± 22 versus 70 ± 25 mL/min, follow-up, $P < 0.05$).

**Renal perfusion**

The mean cortical renal perfusion value (including both kidneys) in ARVD patients was $1.49 ± 0.5$ mL/min/g tissue at baseline and $1.40 ± 0.5$ mL/min/g tissue after RAS revascularization, $P = \text{NS}$. For comparison, the mean cortical perfusion value in healthy volunteers was $1.82 ± 0.3$ mL/min/g tissue, and for the CKD patients it was $1.26 ± 0.5$ mL/min/g tissue, $P < 0.05$. The perfusion did not correlate with the eGFR in ARVD patients. However, in the whole group, including healthy volunteers, CKD and ARVD patients, the mean cortical renal perfusion value was correlated with the eGFR, Pearson’s correlation coefficient $0.45$, $P < 0.01$.

The cortical renal perfusion in stenosed kidneys was highly correlated with the degree of RAS before revascularization, $P < 0.01$ (Figure 1). The mean cortical perfusion value in the 23 stenosed kidneys was $1.43 ± 0.4$ mL/min/g tissue before dilatation and was $1.29 ± 0.5$ mL/min/g tissue after the RAS revascularization, $P = \text{NS}$ (Figure 2). In unilateral RAS patients, the mean cortical perfusion value in stenosed kidneys was $1.5 ± 0.6$ mL/min/g tissue, and in the contralateral kidneys $1.8 ± 0.7$ mL/min/g tissue, $P = \text{NS}$. After revascularization, there was no statistically significant change in the perfusion values (Figure 3).

The cortical renal perfusion was lower in the nine diabetic patients than in the nondiabetic ARVD patients, both at the baseline and after the dilatation ($1.28 ± 0.3$ versus $1.70 ± 0.5$ mL/min/g tissue, baseline, $P = 0.07$, and $1.29 ± 0.3$ versus $1.56 ± 0.6$ mL/min/g tissue, follow-up, $P = 0.28$). However, the change in flow was not statistically significant.

In five patients, the mean arterial pressure was decreased although the number of antihypertensive medications remained the same, from $124 ± 16$ mmHg (baseline) to $111 ± 18$ mmHg (follow-up). Three of these patients had bilateral RAS and two unilateral. However, the mean cortical renal perfusion value (both kidneys) was unchanged after the revascularization procedure ($1.50 ± 0.7$ mL/min/g tissue at the baseline and $1.53 ± 0.2$ at the follow-up, $P = \text{NS}$) also in this patient population.

The eGFR was over 20% improved in three patients with the revascularization. There was a trend towards better perfusion, from $1.21 ± 0.3$ at the baseline to $1.43 ± 0.1$ mL/min/g tissue after the procedure. However, the change was not statistically significant, likely due to the small number of patients.

By combining those eight patients, whose either mean arterial pressure or eGFR improved after revascularization, they had somewhat better perfusion after the revascularization procedure when compared with the remaining nine patients ($1.47 ± 0.2$ versus $1.51 ± 0.3$ mL/min/g tissue at the baseline and $1.47 ± 0.2$ versus $1.34 ± 0.6$ mL/min/g tissue after the procedure). However, the difference between these two groups after the procedure was not statistically significant.

**Discussion**

In the present study, we analysed the effect of RAS revascularization in treatment-resistant hypertensive ARVD patients on renal PET perfusion. Our results show a negative correlation between the degree of RAS and the cortical renal perfusion at baseline. However, dilatation of RAS did not improve the renal perfusion.

The development of less invasive interventional techniques in the treatment of RAS has allowed more complex patients to be treated with PTRA. Although the technical outcome of this procedure with stents is generally excellent [16], no net effect on renal function as determined by serum creatinine or calculated GFR has been demonstrated [17, 18]. The reason for this discrepancy between the technical success rate and outcomes remains unclear [19].

The degree of the renal artery obstruction that causes significant haemodynamic changes in renal perfusion has been one topic of debate. Based on the flow studies with
latex casts to induce the luminal occlusion or on the studies of the magnitude of renin release related to the poststenotic gradient, it has been indicated that definitive haemodynamic effects develop only after luminal occlusion of 75–85% [20]. In the experimental RAS in pigs, however, it has been shown that renal perfusion gradually decreases in correlation with RAS already from 20% of renal artery occlusion [21]. In our study, we detected a gradual decrease in the cortical renal perfusion after 60% of RAS (Figure 2).

As in the heart, where perfusion is an integrated measure of blood flow through both the large epicardial coronary arteries and the microcirculation [22], similarly in kidneys the cortical perfusion is a combination of flow through renal arteries and microvasculature. In an experimental model, the stage of renal microvascular function appeared to be a key to determine the response to revascularization [10]. Recently, in an experimental model mimicking early chronic human renovascular disease, it has been shown that in the stenotic kidneys microvascular rarefaction develops as the renovascular disease evolves, and the decrease in the number of vessels in the stenotic kidneys is associated with a decline in renal perfusion. Furthermore, restoration of the renal microvascular architecture and normalization of RBF and GFR have been demonstrated after intrarenal administration of vascular endothelial growth factor [23].

The measurement of RBF in humans is difficult to obtain noninvasively. All noninvasive methods used to measure single-kidney RBF have limitations. Computed tomography and magnetic resonance imaging are difficult to use in patients with chronic renal failure (CRF) because of nephrotoxicity of contrast agents. Renograms provide nonquantitative measurements because of the lack of tissue attenuation correction and are not interpretable in patients with CRF and in the presence of RAS [24]. Currently, the most powerful technique to quantify perfusion noninvasively in the human heart is PET [22]. We and others have previously shown that PET with H_2^15O as a tracer is also one of the few techniques capable of quantification of RBF and cortical blood flow in vivo [14, 15, 25, 26]. Middlekauff et al. used PET to show that cortical RBF decreases and renal vascular resistance increases in response to static handgrip exercise and that exogenous adenosine produces reflex renal vasoconstriction [27, 28]. Alpert et al. [25] also reported the ability of PET and H_2^15O to measure basal renal perfusion in humans with different levels of kidney function. Similarly, in our study, there was a statistically significant difference in the flow between the healthy volunteers and the CKD patients. H_2^15O is a nearly freely diffusible tracer, and without pharmacological activity, so its kinetics is solely related to flow and is not altered by changes in metabolism. Moreover, H_2^15O is nephrotoxic and safe to use in patients with CRF. This is especially important considering that almost all renovascular patients also have chronic renal insufficiency.

At the moment, there is no technique that allows the direct visualization of the renal microcirculation in vivo. In the heart, the assessment of the microcirculation relies on the measurement of parameters that reflect the functional state of the myocardium, e.g. absolute myocardial blood flow and coronary flow reserve (CFR). CFR is the magnitude of the increase in coronary flow between basal coronary perfusion and maximal coronary vasodilatation. Maximal hyperaemia can be induced with intracoronary or intravenous infusion of adenosine or an intravenous infusion of dipyridamole. Since flow resistance is primarily determined by the microvasculature, CFR is a measurement of the ability of the microvasculature to respond to a stimulus and therefore presumably of the function of the small vessels. Since it has been shown that the CFR is a prognosticator of CV events, the renal flow reserve (RFR) might provide more information about the state of the renal microvasculature than the resting perfusion that did not change after revascularization.

Studies with intravascular Doppler have shown that the RFR is less marked than the coronary circulation [29, 30]. While the CFR, i.e. the hyperaemic-to-basal blood flow ratio, is 4 or 5, a RFR of >2.5 is difficult to achieve, possibly because of the lower basal renal vascular resistance compared with coronary vascular resistance. The xenon (133Xe) washout technique has been also used for the assessment of an RFR with acetylcholine [31] and adenosine [32]. However, these methods are all invasive. Since PET allows noninvasive quantification of renal perfusion, PET would be a promising tool for future studies on RFR.

However, there are also some problems to be solved when using PET for quantifying renal perfusion. Although the contrast in the PET parametrical images may indicate a relatively sharp cortical boundary, the accuracy of its location should be interpreted cautiously. Thus, it is likely that placement of cortical ROIs included an unknown admixture of medullary flow, due to spatial resolution and partial-volume effects because of the complicated structure of the kidney. However, as we have previously shown, when renal perfusion is calculated from the clearance rate (k_c) instead of the uptake rate (k_u) of H_2^15O, it minimizes the effect of partial volume (the effect of tissue mixture of the kidney) [14]. The spatial resolution is also improving as currently all PET systems are manufactured as PET-computed tomography scanners.

Renal perfusion is notoriously heterogeneous [25]. In our healthy subjects, the distribution of renal cortical perfusion was homogenous, and there was no difference in perfusion between the two kidneys. In contrast, the perfusion maps of patients with CKD and ARVD showed a heterogeneous pattern of cortical flow. The ROIs were drawn over the whole cortical region, and the mean perfusion value was used for further analyses. As a consequence, it is possible that after revascularization the heterogeneity could have decreased and also that the less perfused areas had done their ‘share’ of the work. Examining this will be important in the future. In addition, the possible role of cholesterol embolism during the revascularization procedure causing heterogeneity of flow is one of the factors that need to be taken into account.

Clinically, there are similarities between ARVD and stable coronary artery disease. There seems to be no benefit from revascularization of RAS, as detected in large clinical trials [9, 11]. However, there are experimental data on the beneficial effects of simvastatin on renal function and renal morphology [33]. The future calls for
effective methods to evaluate the effects of different treatment strategies, both interventional and medical, on patients with ARVD. In this respect, PET offers a promising, quantitative, low-risk and non-invasive assessment of renal perfusion in ARVD patients.

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Conflict of interest statement. None declared.

References


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