On Renal Artery Stenosis

by

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Abstract

Renal artery stenosis (RAS) is a potentially curable cause of hypertension and azotemia. Besides intra-arterial renal angiography there are several non-invasive techniques utilized to diagnose patients with suspicion of renal artery stenosis. Removing the stenosis by revascularization to restore unobstructed blood flow to the kidney is known to improve and even cure hypertension/azotemia, but is associated with a significant complication rate.

To visualize renal arteries with x-ray techniques a contrast medium must be used. In a randomized, prospective study the complications of two types of contrast media (CO₂ and ioxaglate) were compared. CO₂ was not associated with acute nephropathy, but induced nausea and had lower attenuation differences compared to ioxaglate. Acute nephropathy was related to the ioxaglate dose and the risk was evident even at very low doses if the patients were azotemic with creatinine clearance <40 ml/min.

Evaluating patients for clinically relevant renal artery stenosis can be done utilizing several non-invasive techniques. MRA was retrospectively evaluated and shown to be accurate in detecting hemodynamically significant RAS. In a prospective study of 58 patients, evaluated with four methods for renal artery stenosis, it was shown that MRA and CTA were significantly better than ultrasonography and captopril renography in detecting hemodynamically significant RAS. The standard of reference was trans-stenotic pressure gradient measurement, defining a stenosis as significant at a gradient of ≥15 mmHg. The discrepancies were mainly found in the presence of borderline stenosis.

The outcome of percutaneous revascularization procedures showed a technical success rate of 95%, clinical benefit in 63% of treated patients, 30-day mortality 1.5% and major complication rate of 13%. The major complication rate for patients with baseline serum creatinine >300µmol/l was 32%. Our results compare favorably with published studies and guidelines.

Conclusion: CO₂ can be used to lower the dose of iodinated contrast medium, which can be nephrotoxic. MRA should be favoured for detecting renal artery stenosis. Endovascular revascularization is an efficient technique for treating renal artery stenosis.

Key words: Renal artery obstruction. Comparative studies. Contrast media, adverse events. Revascularization.

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DEDICATION

To my beloved Anna, Josefin, Björn and Ella.

“Life is not a journey to the grave with the intention of arriving safely in a pretty and well preserved body, but rather to skid in broad side, thoroughly used up, totally worn out, and loudly proclaiming -- WOW -- What a Ride!”

Unknown.
LIST OF PAPERS

The thesis is based on the following papers:

   J Vasc Interv Radiol 2005 16(1): 57-65

II. Renal artery stenosis evaluated with magnetic resonance angiography using intraarterial pressure gradient as the standard of reference. A multireader study.
   H Eklöf, H Ahlstöm, A Boström-Ardin, D Bergqvist, S Karacagil, B Andrén and R Nyman.
   Accepted for publication in Acta Radiologica.

III. A prospective comparison of duplex ultrasonography, Captopril renography, MRA and CTA in assessing renal artery stenosis.
   H Eklöf, H Ahlstöm, D Bergqvist, A Hägg, LG Andersson, B Andrén and R Nyman.
   In manuscript

IV. Outcome of endovascular treatment in renal artery stenosis,
   Hampus Eklöf, David Bergqvist, Anders Hägg, Rickard Nyman.
   In manuscript
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<tr>
<td>ACE</td>
<td>Angiotensin Converting Enzyme</td>
</tr>
<tr>
<td>ARAS</td>
<td>Atherosclerotic Renal Artery Stenosis</td>
</tr>
<tr>
<td>CO₂</td>
<td>Carbon dioxide gas</td>
</tr>
<tr>
<td>CTA</td>
<td>Computed Tomography Angiography</td>
</tr>
<tr>
<td>DSA (catheter directed)</td>
<td>Digital Subtraction Angiography</td>
</tr>
<tr>
<td>FMD</td>
<td>Fibromuscular dysplasia</td>
</tr>
<tr>
<td>Gd</td>
<td>Gadolinium</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>MRA</td>
<td>Magnetic Resonance Angiography</td>
</tr>
<tr>
<td>PGM (trans-stenotic)</td>
<td>Pressure Gradient Measurement</td>
</tr>
<tr>
<td>PSV</td>
<td>Peak Systolic Velocity</td>
</tr>
<tr>
<td>PTRA</td>
<td>Percutaneous Transluminal Renal Angioplasty</td>
</tr>
<tr>
<td>PTRS</td>
<td>Percutaneous Transluminal Renal Stent placement</td>
</tr>
<tr>
<td>RAR</td>
<td>Renal aortic ratio</td>
</tr>
<tr>
<td>RAS</td>
<td>Renal Artery Stenosis</td>
</tr>
<tr>
<td>RI</td>
<td>Resistance Index</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver Operating Characteristic (curve)</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasonography</td>
</tr>
<tr>
<td>2D</td>
<td>Two dimensional</td>
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<tr>
<td>3D</td>
<td>Three dimensional</td>
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INTRODUCTION

Renal artery stenosis (RAS) is a potentially curable cause of hypertension, impaired renal function and “flash pulmonary edema”. Diagnosing renovascular disease is important for several reasons:

1- It may be difficult to manage pharmacologically.
2- High-renin hypertension is associated with an increased rate of cerebrovascular and cardiovascular complications.
3- The lesions are progressive and may result in renal artery occlusion despite adequate medical management.
4- Renovascular disease is a common cause of endstage renal disease, especially in elderly patients.
5- In many cases the hypertension is correctable and renal function is preserved if properly diagnosed and treated.

Greatly improved antihypertensive drugs have changed the indication for revascularization. Most patients with hemodynamic significant RAS and hypertension are today well controlled by 1-3 antihypertensive drugs compared to previously when malignant hypertension was a common indication for revascularization.

Contrast enhanced MRA of the large arteries of the body including renal arteries was presented 1993 [1] and introduced at our radiological department in 1995. Initially it was useful only if the studied vasculature could be kept free from motion, which caused severe artifacts. When the acquisition times became shorter and the resolution improved, MRA became useful also for abdominal and renal vessels. Accurate visualization of RAS and determination of its hemodynamic and clinical effect are required to select the best treatment. Correction of RAS has improved the quality of life for many but is associated with a small but significant morbidity and mortality.

Patients with severely reduced renal function have previously not been evaluated for RAS as the nephrotoxic effects of iodinated contrast media used at endovascular procedures would be more deleterious than the possible gain in renal function by revascularization. The nephrotoxic effect is dose dependant and usually not a problem, except in dehydrated or azotemic patients. CO₂ is promoted as a non-nephrotoxic contrast medium with few side effects, but with no randomized studies confirming this claim [2].

In the late 1990’s our routine changed when contrast enhanced MRA became a reliable noninvasive diagnostic test for renal arteries and a new angiographic suite, prepared for CO₂-angiographies, was installed. CO₂-angiographies visualizes arterial stenosis less clearly than when examined with iodine containing contrast medium, but when combined with simultaneous pressure gradient measurement of aorta and each renal artery the resulting evaluation was considered to be adequate. Revascularization would usually require a small dose of iodinated contrast medium for correct stent placement. Azotemic patients have since 1997 been evaluated and treated for RAS more liberally than previously.

New diagnostic techniques are developed to improve the detection of patients with RAS. The advantage is that they are non-invasive but there are conflicting results regarding their accuracies. Two problems are the use of different reference standards and varying definitions for success in validation studies. Thus, there is a need for defining which technique to select when evaluating patients with suspicion of RAS.

This thesis is based on four studies evaluating diagnosis and treatment of RAS: randomized study of CO₂ and Ioxaglate regarding their nephrotoxicity, retrospective study of MRA in detecting RAS, prospective study of four non-invasive diagnostic methods for detecting RAS and retrospective study of the clinical outcome after endovascular RAS-treatment.
2. HISTORICAL BACKGROUND

Bright reported (1836) the first potential association between hypertension and renal disease [3]. Tigerstedt and Bergman of Sweden discovered renin (1898), a substance extracted from rabbit kidneys which caused hypertension when injected into healthy rabbits [4]. Goldblatt showed the relation between occlusion of renal arteries and hypertension (1934) and that renovascular hypertension could be treated by nephrectomy [5]. The first patient successfully treated for renovascular hypertension by nephrectomy (1938) was a 5-year old child with severe hypertension and an ischemic kidney [6]. Treatment changed with introduction of renal artery revascularization by surgery (1954) and by balloon angioplasty (1978) [7, 8].

Basic hemodynamic studies by Mann (1938) showed that the lumen-area of the carotid artery may be reduced by 50% without any change in blood flow, and by as much as 90% before a 50% reduction in blood flow occurs [9]. “Critical stenosis” was defined (1963) as the degree of stenosis when flow and pressure is beginning to be affected, further relatively small increase in the degree of stenosis cause significant reductions in flow and pressure. The presence of “critical stenosis” has been confirmed by experimental, mathematical and clinical studies [10-12].

Smith (1956) reviewed 575 cases of nephrectomy for renovascular hypertension and found that only 26% of patients were cured of hypertension [13]. In a Swedish study of 58 patients randomized to surgical reconstruction or PTRA, the major complication rates were 17% for PTRA and 31% for surgery, impairment of renal function after treatment and clinical outcome were similar. The authors recommend PTRA as initial therapy for unilateral atherosclerotic RAS [14]. Steinbach reported (1997) an outcome after reconstructive surgery for atherosclerotic RAS: cure of hypertension in 35%, improvement in 37%; renal function improved in 35% and the 30-day mortality was 2.2% [15]. Darling et al (1999) reported their experience from 687 surgical reconstructions of RAS: mortality of 5.5% totally, 10.5% for patients undergoing bilateral reconstructions and 30% for emergency surgery of aortic aneurysm and bilateral renal artery reconstructions [16]. A meta-analysis of endovascular revascularization of RAS (2000) including 1322 patients showed a cure rate for hypertension of 20%, improved hypertension in 49% and improved renal function in 30% [17]. Endovascular revascularisation of RAS is expected to have a 30-day mortality rate of ≤1% and major complication rate ≤10% [18].

3. NORMAL KIDNEY FUNCTION

Normally the two kidneys are supplied by one artery each but anomalies are common with accessory arteries reported in 20-30% of the patients in angiography- or autopsy studies [19]. The two kidneys together contain about 2 400 000 nephrons, and each nephron is capable of forming urine by itself. The nephron is basically composed of a glomerulus where fluid is filtered from blood to Bowmans capsule and a long tube in which the fluid is converted into urine on its way to the pelvis of the kidney [20]. The function is to clean blood from waste products (mainly creatinine from protein metabolism), regulate the salt and water balance within a narrow range which is essential for all body functions, release erythropoietin which stimulates production of oxy-
gen carrying red blood cells and control renal auto-
regulation as well as the central blood pressure by
release of renin. These functions require a high basal
blood flow estimated to 20% (range 13-30%) of car-
diac output or 400ml/min/100g tissue (equaled only
by maximum coronary flow rate) [20]. Variations in
renal blood flow are related to for example intake
of protein [21, 22]. The capacity of the two healthy
kidneys to fulfill their function is more than twice
of what the body requires but normally deteriorates
over time. This is part of normal aging and is seen
as a decrease in kidney blood flow to about 45% of
normal by the age of 80 in otherwise healthy people.
Hence donation of a kidney can be performed with-
out causing azotemia in the young donor.

4. RENAL BLOOD FLOW
Blood flow (Q) through a vessel is determined by
two factors: 1- the pressure difference between the
two ends (∆P) and 2- the vascular resistance (R).
Blood flow can be described by Eq 1.

\[ Q = \frac{\Delta P}{R} \]

Equation 1.

Vascular resistance is the impediment to blood
flow in a vessel. It will increase when the blood flow
changes from laminar to turbulent flow, by obstruc-
tions reducing the vessel lumen and by constricting
distal arterioles. Increased velocity of the passing
blood will compensate for a mild-moderate stenosis.
Beyond a certain degree of stenosis the increased
velocity can no longer compensate for the reduction
of radius of the artery (flow changes from laminar-
to turbulent flow). At that point the transport of blood
is physically limited by the stenosis [23].

4.1 Autoregulation
Renal blood flow is autoregulated, normally for
blood pressure ranging from 70-160 mmHg, by a
myogenic response of the afferent arteriole and by
the tubuloglomerular feedback of the “juxtaglomer-
ular apparatus” affecting both the afferent and effer-
ent arteriole. The myogenic response acts directly on
changes in the perfusion pressure of the glomerulus.
The “juxta glomerular apparatus” is located in the
junction of the distal tubule, the afferent and the
efferent arterioles of the same nephron. This location
is optimal for a tubuloglomerular feedback system.
Alterations in the flow rate or ion composition of
the distal tubule are detected and a signal is sent to
the arterioles. They respond by vasodilatation of the
incoming (afferent) arteriole and constriction of the
outgoing (efferent) arteriole or the opposite, so as to
regulate the glomerular filtration rate. The concen-
tration of chloride ions in the distal tubule is one
important signal for this feedback system. The com-
plex process of tubuloglomerular feedback involves
release of renin with activation of angiotensin II,
complemented by a variety of hormones and vasoac-
tive substances such as norepinephrine, dopamine,
endothelin, prostaglandins, thromboxane A2, his-
tamine, platelet derived growth factor, leukotrienes
and others [24].

Hypertension induced by the kidney through the
renin-angiotensin system serves to increase the renal
perfusion pressure when autoregulation fails.
5. PATHOPHYSIOLOGY OF RENAL ARTERY STENOSIS

RAS is the result of an abnormal process in the arterial wall but it is seldom of hemodynamically significance until the lumen diameter is reduced by ≥50%, see Fig 1.

5.1 Etiology of renal artery stenosis

The two main causes of RAS are atherosclerosis and FMD.

Most common is atherosclerosis (90%), often seen in patients over the age of 50. It usually affects the proximal part of the main renal artery or the aortorenal orifice, Fig 2.

FMD (<10%) is a common expression for several diseases affecting the intima, media or adventitia of the vessel wall. It is primarily seen in females 15-50 years old, affecting the distal main renal artery or the segmental branches with a typically beaded, aneurysmal appearance on angiography [25], Fig 3.

Rare causes are thromboembolic disease, arterial dissection, inflammatory processes in the artery wall (Takayasu disease, polyarteritis nodosa, post radiation), external compression from tumors adjacent to the renal artery (neurofibromatosis, lymphoma), retroperitoneal fibrosis, primary arterial tumor (sarcoma or myxoma) and iatrogenic (restenosis after vascular surgery or angioplasty, vessel injury during nonvascular surgery).

6. PREVALENCE

RAS is the most common cause of secondary hypertension with a reported prevalence ranging from 1% to 5% in a general hypertensive population [26]. The prevalence increases with age, smoking and occlusive atherosclerotic disease in other parts of the body. A prevalence of 20% was reported in a group of patients with refractory hypertension referred for coronary angiography [27] and 41% in a study of patients ≥45 years of age starting dialysis for end-stage renal disease [28].

7. NATURAL HISTORY

FMD is a progressive disease associated with dissection and thrombosis.

Atherosclerosis is a generalized and progressive disease. Among patients with ARAS, progression was reported in 51% of renal arteries five years after diagnosis, including 18% of initially normal vessels [29]. Serial duplex US follow-up showed a progression after three years in 35% of patients with ARAS and in 18% of the initially normal renal arteries [30]. Progression to occlusion is rare. The risk of renal artery disease progression is highest among individuals with elevated systolic blood pressure, diabetes mellitus and preexisting high-grade stenosis in either renal artery [30].
Figure 2.
MRA image of atherosclerotic stenosis of left renal artery.

Figure 3.
8. HEMODYNAMIC EFFECTS OF ARTERIAL STENOSIS

A stenosis does not produce any changes in pressure or flow before the cross-sectional lumen area has been reduced by more than 75% corresponding to ≥50% concentric diameter reduction [9-12, 31-34]. The degree of stenosis required before flow is affected (critical stenosis) depends on variables as flow velocity, blood viscosity, vascular resistance of the specific organ and length-shape-multiplicity of stenosis. The relationship between pressure drop and the radius of the stenosis is exponential once the critical stenosis is reached (the loss of energy is inversely related to the fourth power of the radius of the stenosis). Flow and blood pressure distal to the critical stenosis is reduced in parallel [11]. For a stenosis of the renal artery to cause hypertension or azotemia it has to reduce the glomerular perfusion pressure.

8.1 Poiseuille’s formula

The hemodynamic influence by a stenosis can be estimated by the Poiseuille’s formula, which applies to steady, laminar flow of a homogenous fluid in a straight tube with rigid walls (Eq 2).

\[ Q = \pi \Delta P r^4 / (8L\eta) \]

Equation 2.

Q=flow, \( \pi = 3.14 \), \( \Delta P = \) pressure gradient, \( r = \) radius of lumen, \( L = \) length of stenosis, \( \eta = \) fluid viscosity.

The rate of blood flow is directly proportional to the forth power of the radius of the vessel, which illustrates that the diameter of a blood vessel is the most important factor in determining the blood flow through the vessel. The resistance across a stenosis can be much higher than predicted by Poiseuille’s formula, as the clinical situation does not fulfill the criteria for Poiseuille’s formula due to: 1-turbulence and flow separation, 2-pulsatile blood flow, 3-blood not being a homogenous fluid with uniform viscosity but a suspension of blood cells in plasma.

8.2 Goldblatt models

Two-kidney-one-clip model

An obstruction is produced in one renal artery by a mechanical clip while the contralateral kidney is functioning and left unobstructed (Fig 4). The clip causes renal ischemia and the following changes occur in the acute face:

1- Increased renin secretion from the stenotic kidney.
2- Hypertension by vasoconstriction due to angiotensin II.
3- Suppression of renin secretion from the contralateral kidney.
4- Reduced renal blood flow due to intrarenal vasoconstriction.
5- Stimulation of aldosterone production.
6- Increased reabsorption of sodium (Na⁺) and water, resulting in accumulation of body water.
7- Nephrectomy of ischemic kidney will cure hypertension.

One-kidney-one-clip or two-kidney-two-clip model

In the one-kidney-one-clip model, one kidney is removed and a clip obstructs the remaining renal artery (Fig 5). In the two-kidney-two-clip model, clips obstruct both renal arteries. In these two situations the pathophysiology differs from the previous model, as there is no functioning contralateral kidney that can excrete the overload of water and sodium. The early phase is very short and the chronic phase is reached much faster. Clinical signs are based on water overload and symptoms include recurrent pulmonary edema and unstable angina, which respond well to revascularization.
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Figure 4.
Illustration based on Goldblatt’s studies [5].
A- The “2 kidney-1 clip” model.
B- Nephrectomy of ischemic kidney cured hypertension.

Figure 5.
Goldblatt’s models illustrating ischemia of all nephrons and no remaining kidney with unobstructed blood flow.
A- The “2 kidney-2 clip” model.
B- The “1 kidney-1 clip” model.
8.3 Intra-arterial trans-stenotic pressure gradient measurement (PGM)

Any degree of RAS where blood-flow is impaired to the kidney (from critical stenosis to occlusion) is a hemodynamically significant stenosis. Stenosis of 50-75% may or may not be of significance. A stenosis must be proven to affect the blood flow before revascularization is considered. Intra-arterial trans-stenotic PGM is helpful when in doubt, also recommended in guidelines [18]. It is routinely used at many centers to evaluate arterial stenosis before and after revascularization.

In the RAS guidelines there is no consensus on the definition of “hemodynamically significant stenosis” when it comes to the degree of anatomical narrowing or the pressure gradient over the lesion. Their recommendations refer to earlier reports that have used trans-stenotic pressure gradients of ≥20 mmHg peak systolic or ≥10 mmHg mean.

Inducing high blood flow by exercise is used when evaluating ischemic heart disease and ischemia of the legs, as symptoms often are related to physical activity. During inactivity the patient will not experience ischemic pain from legs or chest. In case of ischemic renal disease it is not validated if maximizing renal blood flow will improve the diagnostic performance or improve the clinical outcome of revascularization. Renal blood flow varies normally adapting to the body’s functional needs depending on factors like meat digestion, body temperature, stress, medications etc. We also know from flow mechanics that the hemodynamic effect of a stenosis is directly related to the flow through it. Thus it might be helpful to use vasodilatory drugs during physiological RAS-examinations to detect hemodynamically significant RAS.

The PGM need careful calibration and can be significantly influenced if the endhole of the catheter lies against the wall of the vessel. The size of the catheter can also influence the measurements by exaggerating the gradient across the lesion. The effect of catheter size will mainly be seen in severe stenosis (>80%) and in small arteries like accessory renal arteries [35], in a predictable way as shown by Leiboff [36]. Another drawback with PGM is that it will not differentiate between mild stenosis and no stenosis. Guidewires can also be used for recording blood pressures [37]. As the wire is much thinner than the catheter it will not exaggerate the gradient as much as a catheter when passed across the stenosis.

9. SYMPTOMS OF RAS

RAS may cause hypertension, recurrent pulmonary edema and impaired renal function (including end-stage renal disease requiring dialysis or renal transplantation). Research based on Tigerstedt-Bergman and Goldblatt’s evidence has led to our present understanding of the renin-angiotensin-aldosterone system [4, 5].

9.1 Renovascular hypertension

It is important to distinguish between morphological RAS and renovascular hypertension. Severe RAS has been reported in normotensive patients at autopsy studies [38] and angiographic studies [39].

In its early phase hypertension is dependent on the renin-angiotensin-aldosterone system. As the kidneys accumulate sodium and water, the extra-cellular fluid volume will expand and in a later “chronic phase” hypertension is volume dependent and renin release is suppressed [25]. Treatment of renovascular hypertension with angiotensin II inhibitors or angiotensin receptor blockers is possible in the early phase but less effectively in the chronic phase. Revascularization or nephrectomy will result in natriuresis (excretion of Na+ and water) and lowered blood pressure in both phases.
9.2 Renovascular azotemia (ischemic nephropathy)

Azotemia is the result of reduced number of functioning nephrons. It may be caused or worsened by RAS. Other causes include glomerulonephritis, pyelonephritis, microembolisation of cholesterol or thrombi, obstruction of urine excretion, traumatic loss of kidney tissue, congenital absence of kidney tissue, malignancies, polycystic kidney disease and urinary tract obstructions.

Occlusive vascular disease can affect either the main renal artery as in RAS or the small, distal renal arterioles as in nephrosclerosis. Nephrosclerosis on the other hand is a progressive occlusion of end arterioles with resulting permanent loss of nephrons (Fig 6). Hypertension accelerates the process of nephrosclerosis. Severe nephrosclerosis will reduce renal blood flow by increasing the peripheral resistance. This may be seen as a flattened arterial pulse curve. Flow studies by duplex US will show increased RI values, Fig 7. RAS may induce azotemia by reduced blood flow in the ischemic kidney and accelerated nephrosclerosis due to hypertension in the contralateral kidney.

Nephrosclerosis is recognized on angiography as thin or missing small arteries in the cortical vasculature of the kidney. Older people often have a combination of ARAS and other renal disease. This combination may explain the poor clinical improvement in spite of technically successful revascularization in some patients.

Figure 6.
Illustration of nephrosclerosis seen as a generalized disease with multiple stenotic lesions of peripheral arterioles of the kidneys.
Estimating the renal function may be done for individual renal GFR by combining plasma-clearance with scintigraphic renography. An alternative is to estimate the total value of GFR by plasma clearance. GFR can also be estimated by the Cockcroft-Gault Equation (Eq 3) using serum creatinine, bodyweight and age [40].

Using only serum creatinine as a measure of renal function is a very crude but simple, cheap and often used technique. Serum creatinine is affected by the individual’s muscle mass, muscular injury, meat intake and renal function. When GFR is reduced to ≤40% of normal, serum creatinine will always be increased to a pathological level.

9.3 Flash pulmonary edema and unstable angina
Severe RAS affecting all nephrons (Illustrated by Goldblatt’s one-kidney-one-clip and two-kidney-two-clip models) with accumulation of fluid and sodium may induce unstable angina pectoris and acute pulmonary edema with or without renal failure. It has an acute onset, may be difficult to treat and may be recurrent.

Males = \((1.2 \times (140\text{-age}) \times \text{weight})/s\text{-creatinine}\).

Females = \(((140\text{-age}) \times \text{weight})/s\text{-creatinine}\).

Equation 3.
Estimated creatinine clearance based on the Cockcroft-Gault equation.

Age in years, weight in kg, serum creatinine in µmol/l.
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9.4 Examples of RAS

The degree of RAS and the number of functioning nephrons will determine the patient's symptoms and signs, Table 1.

Table 1.

<table>
<thead>
<tr>
<th>RAS</th>
<th>Obstructed renal blood flow</th>
<th>Reduced perfusion pressure</th>
<th>Comments</th>
<th>Symptoms &amp; signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Normal renal artery</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Nonsignificant RAS</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Compensation by autoregulation</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Significant RAS HT±azot±flash pulmonary edema</td>
</tr>
</tbody>
</table>

1- Normal renal artery and unobstructed renal blood flow.

2- RAS but unobstructed renal blood flow. Nonsignificant RAS.

3- RAS with reduced blood flow but compensated by autoregulation and thus normal renal perfusion. Neither reduced GFR nor hypertension will be induced. Experiments have shown the canine perfusion pressure to be adequate as long as the acutely reduced systolic BP is above 70 mmHg [41]. The effect of chronic hypoperfusion on the autoregulatory function has not been studied.

4- RAS reducing the perfusion pressure to some nephrons, which will activate the Renin-angiotensin system and cause hypertension. Due to the renal functional overcapacity, no dysfunction will be noted until more than half of all nephrons are affected.
If >60% of nephrons are under-perfused, azotemia will be the result. This is the case in bilateral severe RAS or in patients with one functioning kidney and severe RAS. In case of accumulation of total body water, flash pulmonary edema may be added to the symptoms.

Microembolization to the kidneys from atherosclerotic plaques may damage some nephrons and induce azotemia. Stenosis of the smaller arteries in the cortex or medulla of the kidneys seen in nephrosclerosis, secondary to hypertension may induce hypertension and azotemia.

10. HOW TO TREAT SYMPTOMS SECONDARY TO RAS?
Pharmacological treatment of hypertension and lifestyle alterations are the basis for treating any kind of hypertension. Correction of RAS can be done by endovascular or surgical techniques. Correction of ARAS by lowering of blood lipids is a new, interesting and theoretically attractive alternative. It is presently being evaluated in the ongoing STAR study which aims to compare the effects of renal artery stent placement together with medication vs. medication alone on renal function in ARAS patients [42]. Revascularisation is considered when a 3-drug antihypertensive combination fail to reduce the blood pressure to the target level, if renal function deteriorates, if the length of one kidney is reduced >1 cm and in cases of recurrent pulmonary edema.

Renal revascularization is any procedure restoring unobstructed blood flow to the kidney. Surgery was the only option until 1978 but endovascular revascularization has emerged as the preferred method for correcting symptomatic RAS. See Fig 8 illustrating two catheters with balloon-mounted stent. PTRA and surgery have been shown to be equally efficient in treating ARAS when combined with intensive follow-up and aggressive reintervention [14]. Reconstructive surgery or nephrectomy are used when percutaneus treatment fails or if revascularization is combined with aortic repair.

This attitude not to revascularize earlier can be questioned. Renovascular hypertension is induced by the nephrons to increase the perfusion pressure in the glomerulus of some nephrons. By lowering the systemic blood pressure of this person we have in reality accepted chronic hypoperfusion with likely
loss of these nephrons [43]. They may be too few to cause a change in serum creatinine but could be important for renal function later in life.

If a hemodynamically significant RAS is found in a patient without any clinical symptoms of RAS, this patient should be carefully followed with regard to blood pressure, renal function and pulmonary edema. Risk factors should be modified (smoking, blood lipids, hypertension, physical inactivity, etc). There is no scientific evidence to support prophylactic revascularisation.

11. PREDICTORS FOR CLINICAL SUCCESS AFTER REVASCULARISATION

Many diseases may cause hypertension, renal impairment and pulmonary edema. With increasing age, the number of disease-processes affecting the human body is increased. Even if the RAS does affect the flow to the kidney, it is still not granted that symptoms will be relieved by revascularization as RAS may not be the only disease-process causing symptoms.

Today there are still no predictors for when revascularization of RAS will improve hypertension or renal function. Clinical improvement of azotemia after technically successful surgery or PTRA is seen in <30% of patients. There is a study indicating that the RI from the renal blood flow curve evaluated with duplex US is a negative predictor. It is stated that a “RI of at least 80 reliably identifies patients with renal-artery stenosis in whom angioplasty or surgery will not improve renal function, blood pressure, or kidney survival” [44]. This still has to be confirmed by others.

Chronic hypoperfusion injury will result in loss of glomerular filtration rate that can be reversible or permanent [45]. Histological changes vary from minimal perceptive changes to glomerular collapse, tubular atrophy and interstitial fibrosis. The degree of renal parenchymal injury is not dependent on reduced perfusion pressure alone.

Animal studies show that “slow onset gradual reduction of renal perfusion pressure produces functional and morphologic consequences different from those observed with acute ischemic injury. Mechanisms by which chronic renal perfusion deficits produce tissue injury have been reviewed and may include disruption of vascular regulation, energy storage molecules, cellular ion gradients, free radical generation, and disruption of cytoskeletal configuration and repair mechanisms.” [45].

12. ECONOMY

The price for evaluation of renal arteries is officially, year 2005 at “Akademiska sjukhuset” (Swedish currency in SEK, $ 1=7.50 SEK): 1 500 for duplex US, 6 500 for MRA, 5 000 for DTA, 5 100 for Captopril renogram and 7 500 for DSA.

The price for percutaneous revascularization of RAS 15-23 000 (without or with stent placement), add cost for hospitalization 3-5 days and follow-up with duplex US at 1, 6 and 12 months post PTRA which then accumulates to approximately 20-28 000. This cost shall be compared to the cost of medication and dialysis, which are alternatives for patients with RAS. A 3-drug treatment costs approximately 8 000/year and dialysis 3 times/week costs 470-780 000/year.
13. DIAGNOSTIC TESTS FOR RENAL ARTERY STENOSIS

Poiseuille’s formula can be related to the different methods for evaluating a stenosis. In Fig 9 the various parts of the modified formula are related to the different diagnostic methods.

Perfusion studies cannot be directly related to this formula.

Validation studies often include one or two index tests being evaluated against a standard of reference. Comparing accuracies of different techniques from separate studies is very difficult as patient selection, definitions for significant stenosis or clinical outcome seldom are the same.

13.1 Morphological evaluation of RAS

There are many difficulties in evaluating the morphological degree of RAS. Asymmetrical stenosis, multiple stenoses in the same segment, short stenosis as in FMD, suboptimal projection, tortuous artery, RAS followed by a poststenotic dilatation, settings of window and level at the workstation; all add to the difficulties of grading the stenosis. Observer variations is also a major problem [46, 47], especially in RAS of 40-70% diameter reduction.

13.2 Digital subtraction angiography (DSA)

DSA is the standard of reference in validation studies of new techniques for evaluating blood vessels. It is based on x-ray technique requiring a contrast medium for visualizing arteries, most often an iodine containing contrast medium or CO₂ gas.

13.3 Magnetic resonance angiography (MRA)

Images of the vasculature can be obtained by different MRA techniques. “Time of flight” and “Phase-contrast” are MRA-techniques based on flow-related enhancement requiring long examination times and are distorted by movement of the vessel. By intravenous injecting of MR-contrast, usually Gd, the signal-to-noise ratio is increased, improving the image quality by shortening scan times. Examination time can be dramatically reduced, flow artifacts eliminated and distortion of movement due to heart beats and respiration can be controlled thus enabling visualization of abdominal vessels like renal arteries. For renal MRA it has been shown in a meta-analysis that contrast enhanced MRA is superior to flow dependent techniques [48]. 3D-reconstructions allow viewing the arteries from any direction, which

**Figure 9.**
Modified formula.

\[ v \pi r^2 = \frac{\Delta P}{R} \]

- Doppler ultrasonography
- PGM
- RI from Doppler ultrasonography
- Morphology
- DSA, MRA, CTA

\[ v=velocity \ of \ blood \ passing \ the \ stenosis, \ \pi=pi \ (3.14), \ r=radius \ of \ the \ stenosis, \ \Delta P=pressure \ gradient \ across \ the \ stenosis, \ PGM=Pressure \ Gradient \ Measurement, \ RI=Resistance \ Index, \ DSA=Digital \ Subtraction \ Angiography, \ MRA=Magnetic \ Resonance \ Angiography, \ CTA=Computed \ Tomography \ Angiography. \]
is not possible with DSA (in the newest DSA equipments with rotational angiography capacity, similar 3D-reconstructions can be created).

As the dose of Gd required for MRA is very low and thus not nephrotoxic this method is well suited for patients with reduced renal function. Recent advances in the technique have eliminated most artifacts from calcifications and improved resolution with accuracy equalling CTA [49]. These three factors together rendered MRA the top ranking of all non-invasive studies for diagnosing RAS.

Drawbacks of MRA are severe artifacts from renal stents of stainless steel (alternative stents of other material are available but have not replaced the old type), patients with claustrophobia usually refuse MR-examinations and some metallic implants are not recommended to be exposed to the magnetic fields, thus making patients carrying them not eligible for MR studies. The availability of MR-scanners with trained staff and the relatively high price for MR-examination are other problems.

13.4 Computed tomography angiography (CTA)
This is an examination with very high resolution and a good accuracy for visualizing any blood vessel in the body. 3D-reconstructions are possible. It has been shown to have an accuracy similar to MRA but as it exposes the patient to radiation and large volumes of potentially nephrotoxic contrast media it is restricted to patients not suitable for MRA.

14. HEMODYNAMIC AND FUNCTIONAL TESTS FOR EVALUATION OF RAS
Renal artery flow dynamics can be evaluated by percutaneous duplex US [50], intravascular US [51] and MRA [33]. Renal function is evaluated by perfusion studies such as Captopril renogram [52] and MRA [53]. Split renal function also described as the relative function of the two kidneys, can be evaluated by scintigraphic renography but also by CTA [54].

14.1 Duplex US (percutaneous)
The renal blood flow can be evaluated both by direct studies of flow velocities in the renal arteries and by indirect evaluation of the flow curve in the peripheral arteries in the kidney. It is the least expensive and a non-invasive study with good accuracy if conclusive but hampered by many non-conclusive studies. By combining direct and indirect criteria results have improved [50, 55]. One study implies that duplex US can predict the clinical outcome after revascularization of RAS, based on RI >80 which predicts failure [44].

The problems include: the standard of quality is highly operator dependent, technical failures of 0-25%, the variety of criteria for significant RAS, the examination can not be reevaluated and the sensitivity/specificity varies between 77%/46% [56] and 97%/98% [50].

14.2 Captopril renography
A radioactive substance is injected i.v. and the uptake in the kidneys is recorded by a gamma camera. Time-activity curves are obtained from the kidneys both before and after oral intake of Captopril. The split renal function is calculated as the fraction of one kidney of the total renal function. The time-activity curves are evaluated according to complex criteria [52]. In patients with severely reduced renal function, Captopril renography is believed to be less accurate [52, 57, 58].

The finding is an estimation of renal function and it is believed to also diagnose renovascular hypertension. It is not a study for RAS. Most studies have used DSA as the standard of reference with RAS >50-60% diameter reduction as criteria for significant RAS. It is known that RAS with 40-75% diameter reduction may or may not affect renal blood flow. Hence the conflicting sensitivities/specificities reported can be due to an imperfect standard of reference. The role of this technique in evaluating patients for RAS
is questioned [59]. The cost for an examination is equivalent to CTA and somewhat less than MRA in our hospital [60].

14.3 Pressure gradient measurement (PGM)
Trans-stenotic PGM evaluates the pressure on both sides of a stenosis (see sec 8.3, page 18). It indicates if a stenosis limits the blood flow or not, but which level to use for classifying a stenosis as significant is not defined in guidelines but are known to vary [18]. Clinical effects of limitations in blood flow depend on which organ is affected.

14.4 Intravascular US
Intravascular US is a technique to evaluate the vessel wall and hemodynamics of blood flow during catheter directed angiography, known since 1991 but used by few [51, 61-63]. We have until now chosen not to invest in this technique as it adds cost and procedure time without any clear benefits.

14.5 MRA perfusion studies
The parenchymal uptake of the contrast medium in the kidneys is recorded over time (Fig 10). This technique is similar to Captopril renogram but is not used in clinical practice. Signal intensity is measured from the two kidneys for 20 minutes.

14.6 CTA split renal function evaluation
The uptake of contrast medium in the two kidneys can be measured and the relative uptake can be calculated. This has been shown to correlate well to the findings of scintigraphic renography [54, 64] but is not yet used in clinical practice.

15. COMPLICATIONS OF PTRA AND PTRS
The drawbacks of DSA are the procedure related complications: puncture of an artery, manipulation of catheters inside the arteries, nephrotoxicity of contrast medium and exposure of the patient to radiation. The most common complications are related to the site of arterial puncture such as pseudoaneurysm, bleedings and hematomas, which are usually of minor importance for the well being of the patient. Serious complications are rare but include arterial dissections, thrombo-embolic and cholesterol embolization, arterial rupture during angioplasty and renal impairment. Exposure to radiation is a problem when the patients are children or young adults but of minor importance for the elderly as radiation-induced malignancies requires long time to evolve.
Figure 10.
Time-intensity curves obtained from MRA perfusion study.
The two curves represent signal intensity of one kidney each.
GENERAL AIM

To improve the care of patients with clinical manifestations of renal artery stenosis.

SPECIFIC AIMS

To prospectively evaluate the nephrotoxicity of CO₂ and Ioxaglate in a randomized study.

To retrospectively evaluate MRA for detection of RAS.

To prospectively evaluate MRA, CTA, Captopril renography and duplex US for detection of RAS.

To retrospectively evaluate the clinical outcome of PTRA and PTRS.
MATERIAL AND METHODS

PATIENTS

Patients in all four studies have been evaluated for RAS with renal angiography and trans-stenotic PGM at the Dept of Radiology, Akademiska sjukhuset, Uppsala, Sweden. Indications for these investigations were difficulty to treat hypertension and/or progressive renal dysfunction. Some patients were included in more than one study. Patients with transplanted kidneys or treated with renovascular surgery were excluded.

Study I prospectively evaluates the renal toxicity of iodinated contrast medium (Ioxaglate) and CO2. One hundred and twenty-three patients were included from March 1999 to February 2001. Patients with serum creatinine <200 µmol/l were randomized to receive either CO2 or Ioxaglate.

Serum creatinine was controlled the day preceding angiography and at 1-2-14 days after angiography. Additional controls were taken in case of renal impairment. An increase of serum creatinine >25% was considered significant. Analysis was based on the frequency of increased serum creatinine in the two randomized groups. A second analysis of all patients evaluated the correlation between amount of contrast medium and serum creatinine.

Study II evaluates 3D-Gd-MRA in detecting ARAS with hemodynamic influence. Thirty patients were included from October 1997 to September 2000. Three independent readers studied MRA on hard copy films and determined the image quality, the number of arteries to each kidney and graded the degree of RAS for each main renal artery. The x-ray reports were read by one investigator, collecting data on results of PGM, which were used as gold standard. Interobserver variation, sensitivity and specificity for each reader to correctly grade RAS as hemodynamic significant or not and ROC curves to find the optimal cut off for when a RAS should be considered hemodynamically significant on MRA were determined. The discrepancies were analysed.

Study III compares the diagnostic accuracies for duplex US, Captopril Renography, multislice CTA and 3D-Gd- MRA in diagnosing hemodynamically significant RAS (atherosclerotic and FMD) defined by a peak systolic pressure gradient ≥15 mmHg. Fifty-eight hypertensive patients with suspicion of RAS were prospectively included for examination with all techniques, from June 2001 to June 2004. The discrepancies for each technique were analysed.

Study IV evaluates the clinical outcome for 152 patients treated in 203 procedures for ARAS by percutaneous revascularization from January 1997 to October 2003. Clinical outcome includes 30-days complications as well as the effect on hypertension control and renal functional change. Beneficial outcome included improved renal function with 25% reduced serum creatinine or improved control of hypertension, as defined in the guidelines by Society of Interventional Radiology and the American Heart Association [65]. Data were collected from up to 7 charts/patient at our hospital and their respective local hospitals and from primary health care physicians.
EQUIPMENT
Renal angiographies were performed with a Siemens Multistar Plus T.O.P. (Siemens, Forchheim, Germany) 40 cm image intensifier or a Philips DVI (Philips Medical systems, Best, the Netherlands) 35 cm image intensifier.

US was performed with a Acuson Sequoia (Siemens, Forchheim, Germany).

The Captopril renogram was performed with a Picker SX-300 Digital Dyna Camera (Cleveland, Ohio, USA) equipped with a LEGP parallel hole collimator after an intravenous bolus injection of 80 MBq 99mTc-MAG3.

CTA was performed with a Siemens Somatom 4 Plus and a Siemens Sensation (Siemens, Forchheim, Germany).

MRA was performed with a Philips ACS-NT 1.5T using a phased-array receiver coil (Philips Medical systems, Best, the Netherlands).

TECHNICAL PROCEDURES
DSA
Femoral approach according to Seldinger [66] was used in all procedures. A 6-F introducer (40 cm long Balkin up and over, COOK, Denmark) was placed with its tip near the renal arteries with a catheter coaxially placed through the introducer, into the aorta. The aortogram was made using a 4-F pigtail catheter (Omniflush, Angiodynamics USA) and then each renal artery was examined selectively with a 4-F end-hole catheter (SHK 1.0, 65 cm long, Cordis, Johnson&Johnson, USA). The technique was modified when necessary by the use of guiding catheters and 0.018- 0.014 inch catheter-guidewire systems. CO2 was used as contrast medium to reduce the iodine dose in patients at risk of renal impairment.

PGM was performed before deciding to intervene and also to evaluate the result of revascularization. Angioplasty and stent placement were performed with an “over the wire system” (0.035 inch) using a stiff guide wire. All patients were well hydrated before the procedure and hospitalized after the procedure for 2-4 days.

PGM
The trans-stenotic PGM was performed by simultaneously recording blood pressure in the 6-F introducer (the tip in the abdominal aorta near the renal artery) and the 4-F catheter (coaxially placed into the renal artery) using an electronic recorder (Siemens SC 8000). The zero level was set prior to examining each patient. The absolute values of systolic, diastolic and mean blood pressure, for the aorta and each renal artery, were recorded. The gradient was calculated as the difference between the aortic and renal artery peak systolic blood pressure.

The gradient was considered hemodynamically significant if the peak systolic gradient was ≥15 mmHg.

Duplex US
The 4V1, 6C2 or 5C1 transducers were used for the majority of 2D, color-Doppler and power-Doppler examinations. Direct criteria were used for classifying the degree of stenosis as described previously [67]. PSV were measured in the aorta at the level of the renal arteries and in the renal arteries (proximal, middle, distal and at stenosis-suspected areas). The angle-correction was <60°. Renal-aortic PSV ratio (RAR) was calculated.

For a RAS to be classified as hemodynamically significant (>60% diameter reduction), required RAR >3.5 and PSV >180 cm/s, see Table 2.

Captopril Renography
The hour prior to examination the patient was hydrated orally (5-7 ml water/kg b.w.). Diuresis was estimated by voiding before and after the study. Patients not on medication with ACE-inhibitor or
“angiotensin receptor blockers” underwent a baseline renography 3-4 hours before Captopril Renography. One hour prior to Captopril Renography the patient received 25 mg Capoten orally, blood pressure being monitored every 15 minutes. The patients were examined in a supine position, with their back against the gamma camera. One hundred and eighty frames (128x128 pixels) of 1 second per frame the first minute and thereafter 10 seconds per frame were recorded starting simultaneously with an intravenous bolus of 80 MBq 99mTc-MAG3.

ROIs were drawn manually around the kidneys and the heart area, and automatically for the extra-renal areas. The time-activity curve generated from the heart ROI was used as the plasma input curve. Time-activity curves were obtained from the kidney ROIs (gross renograms) and extrarenal backgrounds. The extrarenal background curves were subtracted from the gross renograms after normalisation to the respective kidney area, resulting in the net renograms. Calculation of uptake index (UI) of each kidney was made by linear regression analysis of the relation between the corrected net renogram (net renogram divided by plasma curve) and the corrected plasma integral curve (plasma integral curve divided by plasma curve). UI is the slope of the regression line. The split renal function (%) was calculated as the fraction of one kidney of the total renal function.

CTA
CTA was performed with a 4 or 16-channel scanner and nonionic contrast medium (Iopromide 300 mg I/mL, Schering, Berlin, Germany) was given i.v. (96±13 ml at 3-4 ml/s). The bolus triggered image acquisition started 4 seconds after an increase in attenuation of 100 Hounsfield units (HU), in the upper abdominal aorta. The protocol used had a tube potential of 120 kV, tube current 215 mA (typical value, Care Dose was used), rotational time 0.5 s, detector collimation 16 x 0.75 mm and table movement 12 mm/rotation. Images were reconstructed with an increment of 0.7 mm, image thickness 1 mm, and with a standard abdomen filter. The images were transferred to a workstation (Leonardo, Siemens, Forchheim, Germany) and reconstructed into maximal intensity projections (MIP), shaded surface display (SSD) and volume rendering technique (VRT).

Table 2.
Criteria for classification of renal artery stenosis, by duplex US.

<table>
<thead>
<tr>
<th>Renal artery diameter reduction</th>
<th>Renal artery PSV (cm/s)</th>
<th>RAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;180</td>
<td>&lt;3.5</td>
</tr>
<tr>
<td>&lt;60%</td>
<td>≥180</td>
<td>&lt;3.5</td>
</tr>
<tr>
<td>≥60%</td>
<td>≥180</td>
<td>≥3.5</td>
</tr>
<tr>
<td>Occlusion</td>
<td>No signal</td>
<td>-</td>
</tr>
</tbody>
</table>

PSV=peak systolic velocity. RAR=renal-to-aortic PSV ratio.
After an initial survey to define the volume of interest, a fluoroscopic scan (BolusTrak) was used for bolus timing. 40 ml of either Magnevist (0.5 mmol/L Schering, Berlin, Germany) or Omniscan (0.5 mmol/L Amersham Health, Oslo, Norway) was injected through a cannula inserted in a forearm vein, connected to a power injector (Spectris, Medrad, Indianola, PA, U.S.A.), with an injection rate of 2-3 ml/s followed by a saline flush of 20 ml at a rate of 2-3 ml/s. Imaging was made with a three-dimensional (3D) radio frequency spoiled GRE sequence during breath hold. MR parameters (FOV/matrix/acquisition slice thickness/slices/TR/TE/flipangle/scan duration) were initially defined as 290x275mm/256x195/3.5mm/36/4.6ms/1.4ms/30°/17s without SENSE, resulting in an acquisition voxel size of 1.13x1.13x3.5 mm³. Later it was upgraded to 450x427.5/400x304/3mm/50/4ms/1.36ms/30°/20s and SENSE factor 2 resulting in an acquisition voxel size of 1.12x1.12x3 mm³. Central k-space filling was used, which means that the central part of k-space was acquired in the beginning of the scan.

For evaluation purpose, maximum intensity projections (MIPs) were created on the operator's console using standard software. Eighteen MIPs covering 180 degrees around the longitudinal axis were made. In addition edited MIPs and multiplanar reconstructions were made in the axial plane on a work-station (Easyvision, Philips, Best, The Netherlands). Together with original slices these reconstructions, on hard copy films, were used for evaluation.
RESULTS

STUDY I
Of 123 included patients 82 could be randomized (serum creatinine was <200 µmol/l). The amount of injected CO₂ did not relate to an increase in serum creatinine level. The amount of injected Ioxaglate was significantly correlated with an increase in serum creatinine (p=0.01).

There were no significant differences in mean serum creatinine before or after angiography in the two randomized groups. In six of seven patients with >25% increase in serum creatinine, the baseline creatinine clearance was <40 ml/min (estimated by Cockcroft-Gault eq.). These six patients received an average 18 g iodine during angiography (range 6-50 g).

STUDY II
The average sensitivity/specificity to detect RAS with lumen diameter reduction of ≥50% on MRA was 96%/75%. Nine accessory renal arteries were found on DSA in 6 of 30 patients giving a prevalence of 20%. On MRA each reader identified four of the nine accessory renal arteries, a detection rate of 44%. Analysis of discrepancies showed that only 6 of 26 wrongly graded RAS on MRA were method related due to calcification-artifacts, simple errors accounted for three discrepancies and the remaining 17 (65%) discrepancies on MRA were borderline cases (40-80% stenosis). There was substantial agreement in observations between the three readers in classifying RAS on MRA as hemodynamically significant or not when using a 60% cut-off (Cohen’s kappa 0.69, 0.62 and 0.74).

3D-Gd-MRA is an adequate non-invasive method for evaluating RAS, limited mainly by poor detection rate for accessory renal arteries. When screening for RAS, a 50% cut-off is adequate for referral to DSA.
STUDY III

Twenty-two accessory renal arteries, in 15 patients, were found on DSA giving a prevalence of 26%. The prevalence of RAS was 77%. Analysis of the sensitivity/specificity based on both patients and kidneys, is presented for each method in Table 3. Borderline RAS in this study accounted for the majority of discrepancies for all techniques. Calcifications resulted in artifacts on CTA but MRA visualised the lumen of calcified arteries adequately. Stents placed in the renal artery caused artifacts on MRA-images, completely obscuring that part of the vessel. CTA on the other hand could visualize the lumen inside the stent. Duplex US was non-conclusive in 18% of all patients.

MRA and CTA were significantly better than duplex US and Captopril renography in detecting hemodynamically significant RAS.

Table 3.
Accuracy in detecting hemodynamically significant renal artery stenosis

<table>
<thead>
<tr>
<th>Technique (patient basis)</th>
<th>PGM</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;15 mm Hg</td>
<td>≥15 mm Hg</td>
<td></td>
</tr>
<tr>
<td>US (57)</td>
<td>-</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>CR (56)</td>
<td>-</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>6</td>
<td>26</td>
</tr>
<tr>
<td>CTA (44)</td>
<td>-</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>4</td>
<td>35</td>
</tr>
<tr>
<td>MRA (53)</td>
<td>-</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>3</td>
<td>42</td>
</tr>
<tr>
<td>DSA (57)</td>
<td>-</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>1</td>
<td>36</td>
</tr>
</tbody>
</table>

B. Analysis performed on kidney basis. n = kidneys

<table>
<thead>
<tr>
<th>Technique (kidney basis)</th>
<th>PGM</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;15 mm Hg</td>
<td>≥15 mm Hg</td>
<td></td>
</tr>
<tr>
<td>US (102)</td>
<td>-</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>12</td>
<td>44</td>
</tr>
<tr>
<td>CR (100)</td>
<td>-</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>15</td>
<td>31</td>
</tr>
<tr>
<td>CTA (81)</td>
<td>-</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>13</td>
<td>44</td>
</tr>
<tr>
<td>MRA (92)</td>
<td>-</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>3</td>
<td>54</td>
</tr>
<tr>
<td>DSA (103)</td>
<td>-</td>
<td>38</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>3</td>
<td>50</td>
</tr>
</tbody>
</table>

Duplex ultrasonography (US), Captopril renography (CR), Computed Tomography Angiography (CTA), Gd-3D magnetic resonance angiography (MRA) and catheter directed Digital Subtraction Angiography (DSA).
ON RENAL ARTERY STENOSIS

STUDY IV

The technical success rate was 95% for 203 endovascular procedures for atherosclerotic RAS. The clinical outcome showed benefit regarding hypertension in 59% and for azotemia in 15%. The 30-day mortality rate was 1.5% and major adverse events 12.8%. Diabetes was the only variable correlating to negative clinical outcome of revascularization. The rate of complications was related to impaired renal function, being 32% for the 25 patients with baseline serum creatinine >300 µmol/l.

Serious complications occurred in 9 procedures of 28 (32%) for the 25 patients with baseline serum creatinine >300 µmol/l. They included four deaths within 30 days (age-baseline serum creatinine: 82y-454, 66y-345, 79y-463, 74y-452), one suspected cholesterol embolization resulting in dialysis at 6 months (age-baseline serum creatinine: 71y-550). The remaining 4 patients had no sequelae of the complications, 3 actually improved in serum creatinine >25% at six months and one had a temporary increase in serum creatinine >25% but at six months it had returned to baseline level (contrast medium induced nephropathy). Improved renal function (reduction in serum creatinine >25%) was at one year seen in 5 patients of 25 (20%) and at five years 3 of these 5 were still free from dialysis while one was dead and one was dialysis dependent.
ON RENAL ARTERY STENOSIS

GENERAL DISCUSSION

NEPHROPATHY AND CONTRAST MEDIA
In study I it was shown that the risk of renal impairment was increased with increasing doses of iodinated contrast medium. In patients with poor renal function (creatinine clearance <40 ml/min) this risk was substantial. Even small doses of iodine contrast medium were shown to result in a significantly increased serum creatinine in those patients. Serum creatinine is a crude measure of renal function. In order to better identify patients at risk it seems reasonable to estimate their creatinine clearance by the Cockcroft-Gault equation (Eq 3, page 20). The estimation with this equation includes serum creatinine, age, sex and weight of the patient and is a more reliable measure than serum creatinine alone.

The main message from study I was that every measure should be taken to reduce the dose of iodinated contrast medium in order to minimize the risk of contrast medium induced renal impairment during renal angiography. CO2 was shown not to be nephrotoxic and can thus be used as contrast medium to reduce the dose of iodine. Diluting it with saline can also reduce the iodine dose. It is possible to dilute standard iso-osmolar dimeric, nonionic contrast medium (140 mg iodine/ml) with saline to 70 mg iodine/ml and still obtain reasonable angiograms. Another study has shown that dimeric, nonionic contrast medium (iodixanol) might be less nephrotoxic than low-osmolar, nonionic, monomeric contrast medium (iohexol) in high-risk patients [68]. It has been shown that the contrast dose as well as the procedure time can be reduced by having an anatomical map from MRA before performing PTRA or PTRS [69].

Gd has been suggested as an alternative contrast medium to reduce the nephrotoxic risk of iodine containing contrast media. Gd in small doses will produce good images of the vasculature when used with MRA, while higher doses are required when used with DSA to obtain images with adequate attenuation and quality. The high Gd doses required at DSA are nephrotoxic and Gd is not recommended to replace iodinated contrast media in patients with azotemia undergoing PTRA or PTRS [70, 71].

PGM AS STANDARD OF REFERENCE
The effect of a stenosis is a hemodynamic influence on the circulation to the kidney. Therefore, it seems logical to evaluate the degree of stenosis with PGM rather than using a morphological method. This idea is also recommended by general guidelines [65]. The main problem with PGM is to choose the correct cut-off value, which is reflected by the variability in recommended values in the literature. However, none of these values have been validated to clinical outcome after revascularisation [65].

Most would agree that RAS ≥80% is hemodynamically significant and that RAS<40% is not. Those RAS with diameter reduction of 40-80% might be of hemodynamical significance but it cannot be adequately determined based on morphology only. This was also the result shown in study III when DSA was evaluated with PGM as standard of reference for 103 renal arteries. When the RAS was >70% the gradient was found to be >15 mmHg for all. When the RAS was <40% the gradient was <15 mmHg except for one short, ostial RAS not seen on DSA and for one asymmetric RAS. Hence most discrepancies (5 of 8) were from 40-70% RAS. Therefore, it seems reasonable to use 15 mmHg as the cut-off value.

Interobserver variation was shown to be a significant problem when evaluating RAS based on DSA [72]. It has also been shown that it is impossible to distinguish between 50-60% or 60-70% RAS on DSA [46]. It may be due to the renal arteries being tortuous and asymmetric RAS. The arterial margins
may be blurry making it difficult to select appropriate reference points. In FMD the degree of stenosis is very difficult to evaluate by morphological methods. Also evaluating the technical result after angioplasty can be difficult based on angiographic morphology. These factors are not a problem when using PGM.

PGM will not differentiate a normal vessel from a RAS when the diameter reduction is less than 40%, as shown in hemodynamic studies and predicted by the concept of critical stenosis [9, 11, 12, 33]. The catheter passing a stenosis reduces lumen area, and can exaggerates the transstenotic gradient in a predictable manner [36], but first when the catheters outer diameter is close to the inner diameter of the stenosis [35]. Successful clinical outcome is correlated to a reduction of the transstenotic gradient for iliac artery revascularisation [73-75]. Such a report on revascularisation of RAS does not exist.

**IMAGING FOR DETECTION OF RAS**

The perfect non-invasive test for detection of RAS does not yet exist. The functional tests relying on some feature of the renin-angiotensin system (Captopril renography, Captopril test, renal vein renin sampling) have been associated with unacceptably high rates of false negative results. The morphological tests are today preferred [49].

MRA and CTA have evolved over the past years as the two techniques with best accuracy for detecting atherosclerotic RAS [49]. This was demonstrated in study III. MRA has additional advantages over CTA as it has lesser artifacts from calcifications, an improvement we noticed between studies II and III. It can also be used in azotemic patients due to the low amount of Gd contrast medium used with low risk of inducing renal impairment. MRA and CTA also have the advantage over duplex US that the angiograms can be reviewed and be used as an anatomical map for planning the revascularization procedure.

Duplex US is the most utilized method for non-invasive imaging of the renal arteries combining direct visualization of the arteries through B-mode with duplex measurement of the blood flow velocity, with a possibility of both anatomic evaluation and hemodynamic assessment. However, it is highly operator-dependent and has a high rate of non-conclusive studies, shown in study III and by others [76]. The visualization of renal arteries can be difficult in adipose patients and in the presence of bowel gas. When the examination was conclusive, the accuracy was similar to MRA and CTA.

The direct US criteria used in study III for RAS >60% (Table 4) might partly explain the high rate of false negative examinations. The sensitivity would improve (from 72 to 88%) if the criteria for significant RAS was based only on PSV in the renal artery of >180 cm/s as recommended by Hollenbeck [77]. Using indirect criteria based on intrarenal Doppler curves, when direct visualization of the renal arteries are non-conclusive, might further improve the results [50].

Captopril renography evaluates aspects of renal function, but was shown to have a poor accuracy in detecting hemodynamic significant RAS in study III and by others [59, 78]. Azotemia is claimed to reduce the accuracy, which could not be confirmed in study III. The results were poor irrespective if the patients were azotemic or not.

Other studies presenting better results for Captopril renography than ours have used DSA or MRA as standard of reference with 50-60-70% RAS as cut-off [57, 79, 80]. However, the use of different reference standards cannot explain this difference in results as PGM and DSA showed a good correlation in study III. Different criteria for selecting patients can only partly explain the differences in results. Other methodological problems of study III include the possible dependence of Captopril renography on renin release for a positive finding, as this release may vary over
Table 4.
Reported outcomes of atherosclerotic renal artery stenosis treated with PTRA or PTRS compared to Study III and recommended threshold values in guidelines.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients No</th>
<th>Tech success</th>
<th>Benefit HT</th>
<th>Benefit azot</th>
<th>Mortality 30-d</th>
<th>Major compl</th>
<th>Restenosis rate (%)</th>
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<td>Tuttle</td>
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<td>van de Ven</td>
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<td>81</td>
<td>57% PTRA</td>
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<td>17%</td>
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<td>PTRA vs PTRS</td>
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<td>Baumgartner</td>
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<td>Bloch</td>
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<td>Sivamurthy</td>
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<td>Nolan</td>
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<td>Eklöf in manuscript</td>
<td>2005</td>
<td>152</td>
<td>95%</td>
<td>60%</td>
<td>15%***</td>
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</table>

Definitions of beneficial outcome regarding azotemia: serum creatinine decrease of 15%=*, 20%=**, 25%=***; increase of estimated creatinine clearance: ≥10ml/min=#, not defined=##.
time; low dose of Captopril given (25 mg instead of 50 mg) and without discontinuing antihypertensive medication.

Based on the results in study III the following routine is suggested for evaluation of RAS: Patients should be evaluated for RAS only if they are candidates for revascularization. The indications for revascularization of RAS should be progressive loss of renal function, recurrent pulmonary edema, difficulty to control hypertension with ≥3 drugs or side effects of antihypertensive medication not tolerable by the patient. Patients with severe symptoms or high likelihood according to the "Clinical prediction rule" [81] may be referred directly for DSA. Mapping of the vasculature before DSA, by MRA or CTA, is an advantage as it may reduce the DSA-related procedure time and contrast dose. At present, MRA seems to be preferred as the first test. CTA can be used in case of stent in any of the renal arteries or if contraindications for MRA exist due to claustrophobia, metal implants etc. If evaluation is non-conclusive or in case of suspicion of >40% lumen reduction, it is recommended that the patient is referred for DSA with PGM. Duplex US or CTA can be useful in immediate and longterm follow-up studies as MRA cannot evaluate stented arteries. Scintigraphic evaluation with Captopril renography cannot be recommended for evaluating RAS.

**TREATMENT OF RAS**

Revascularization of RAS is preferably done by endovascular angioplasty, without or with stent placement. Presently >90% of all renal revascularization procedures at our hospital are endovascular procedures. In the remaining procedures open surgery is used.

Technical success of endovascular revascularization has improved over time to ≥95%, but not the clinical outcome (Table 4). Stent placement has allowed endovascular treatment of patients with more advanced atherosclerotic disease including ostial renal lesions. The rate of restenosis of ostial RAS has been shown to decrease from 48% without stent to 14% with stent and ostial lesions are preferable treated with stents [82]. Study III also indicate lower rate of restenosis after PTRS (14%) compared to PTRA (28%).

At one year, the clinical outcome after endovascular revascularization of RAS was beneficial for >60% of the treated patients in study IV. Even in patients with serum creatinine >300 at baseline an improvement in serum creatinine was found in 20% of patients. Similar results are reported for patients >75 years of age with improved renal function in 26% [83].

The high rate of serious complications in the severely azotemic patients may have been induced by the angiography procedure. However, as the
patients were all relatively old with poor renal function, it cannot be ruled out that the progressive renal impairment and high mortality rate could be part of the natural disease progress in some of the cases. As we have not analyzed the rate at which the renal function deteriorated before and after revascularization, it cannot be determined if there was a change in the rate of declining renal function. Five of the azotemic patients with serum creatinine>300 had a substantial improvement of the renal function and were probably saved from dialysis. Further studies are needed in order to better identify which patient will benefit or not.

Predictors for this purpose have been studied but none is yet accepted in clinical practice. The degree of damage to peripheral arterioles of the kidney results in reduced kidney size, reduced function (seen on split renal function on Captopril renography, urography, CTA, and MRA) and as nephrosclerosis on renal angiography. These measures are all very crude. RI from duplex US is based on the resistance of the renal arterioles secondary to nephrosclerosis. RI is suggested as a predictor [44] but must be evaluated by others before it can be accepted. Recently, elevated brain natriuretic peptide has been suggested to predict blood pressure response after stent revascularization in patients with renal artery stenosis [90], also this needs to be confirmed. Studies on endothelial function and disturbed oxidative stress [91] may also provide us with useful information regarding whom to revascularize. Recovery of renal function after reconstruction of RAS has been shown to be a strong predictor for dialysis-free survival [92].
CONCLUSION

1. CO₂ is not nephrotoxic and can be used as contrast medium to reduce the dose of iodine containing contrast media during catheter directed renal procedures.

2. Borderline stenosis (40-70% RAS) accounted for a majority of interpretation discrepancies between different imaging techniques and PGM.

3. MRA and CTA were significantly better than duplex US and Captopril renography in detecting hemodynamically significant RAS. MRA is preferred before CTA.

4. Revascularization of RAS by endovascular angioplasty, without or with stent placement had an excellent technical success rate of 95%, and the clinical outcome was at one year beneficial for >60% of the treated patients.

5. Complications due to endovascular revascularization seem highly related to the degree of azotemia.
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SUMMARY IN SWEDISH

Njurartärstenos är en förträngning av ett eller flera blodkärl, som leder blod till njurarna. När förträngningen överstiger ca 60% av kärldiametern begränsas blodflödet till njurarna. Vid otillräcklig blodtillförsel utsöndrar njurarna ett ämne (renin), som aktiverar renin-angiotensin systemet, vilket höjer blodtrycket i kroppen för att återställa flödet till njurarna. Njurartärstenos kan orsaka högt blodtryck (hyperton) och försämrad njurfunktion. Av alla patienter med hyperton är njurartärstenos orsaken i ca 1%. Vid svårbehandlad hyperton kan dock prevalensen öka till 20%. Hyperton kan oftast behandlas framgångsrikt med mediciner. Njurartärstenos kan resultera i försämrad njurfunktion, som kan kräva behandlingar för rening av blodet med med dialys och eventuellt njurtransplantation.

För att återställa flödet till njuren kan stenosen korrigeras med operation eller ballongvidgning. Flera studier har visat att detta kan bota eller lindra hypertonin samt förbättra njurfunktionen. Eftersom behandling med ballongvidgning, den idag vanligaste tekniken, kan vara förenad med risk för komplikationer har man tagit fram följande strikta kriterier för vilka patienter som kan vara lämpliga att behandla:

- Blodtrycket går ej att få ner till adekvata nivåer trots användandet av minst 3 olika mediciner.
- Medicinerna ger biverkningar som ej är tolerabla.
- Njurfunktionen försämras.


Rekommenderad referensmetod är renal angiografi baserad på röntgenstrålar, tunn kateter som oftast via ljumsken placeras i stora kroppspulsådern och kontrastmedel som sprutas in i njurens blodkärl. På senare tid rekommenderas även tryckmätning av blodtryck på båda sidorna av stenosen. Detta görs i samband med renal angiografi. Även ballongvidgning av njurartärstenos kan utföras i samband med renal angiografi. Komplikationerna är relaterade till införandet av slangar i blodkärlen och injektion av kontrastmedlet.

Resultaten av ballongvidgning varierar i olika rapporter och det finns nu internationella riktlinjer för hur ingreppen bör utföras och frekvensen komplikationer som är rimligt. Resultaten vid Akademiska sjukhuset för ballongvidgning av njurartärstenos har inte utvärderats tidigare, men antalet ingrepp har ökat från <20 ballongvidgningar 1995 till >60 1999.
Studie 1 avsåg att utvärdera två olika kontrastmedels (CO₂ och jodkontrastmedel) påverkan på njurfunktionen. Kontrastmedel valdes genom lottning för varje patient. Resultatet visade att dosen jodkontrastmedel, men inte CO₂, var korrelerat till njurfunktionsförsämring. Patienter med nedsatt njurfunktion före undersökningen hade stor risk att drabba av ytterligare försämring av njurfunktionen när jodkontrastmedel användes, även vid mycket små mängder.

Slutsatsen blev att användandet av jodkontrastmedel bör begränsas.

Studie 2 avsåg att utvärdera hur känslig magnetkameraundersökning (MRA) var att påvisa njurartärstenos. Trettio patienter med arteriosklerotisk njurartärstenos undersöktes med MRA och referens metoden renal angiografi med tryckmätning av blodtryck på båda sidorna av stenosen. Resultatet visade att MRA var en känslig teknik att upptäcka stenoser. Problem med artefakter noterades när kärlväggen innehöll stora förkalkningar eller metallnät (stent).

Slutsats blev att MRA är bra för påvisande av njurartärstenos.

Studie 3 var en prospektiv studie där fyra metoder jämfördes för att klargöra vilken metod som var känsligast för att påvisa njurartärstenos. Femtiotre patienterna med misstänkt njurartärstenos undersökes med duplex ultrasonografi, Captopril renografi, MRA, DTA (datortomografi angiografi) och referens metoden renal angiografi med tryckmätning. MRA och DTA var signifikant känsligare än övriga metoder att påvisa njurartärstenos. Duplex ultrasonografi missade många stenoser och undersökaren var ofta osäker på diagnosen. Dock finns flera möjligheter att förbättra denna teknik. Captopril renografi lyckades oftast ej påvisa njurartärstenoserna.

Slutsatsen blev att MRA och CTA är känsligast för påvisande av njurartärstenos. Captopril renografi kan ej rekommenderas för utredning av patienter med misstänkt njurartärstenos.

Studie 4 var en retrospektiv genomgång av journaler från 152 patienter, som genomgått 203 procedure med ballongvidgning av njurartärstenos på Akademiska sjukhuset. Procedurerna var tekniskt lyckade i 95% när det gällde att återställa flödet till njurarna. Drygt 60% av patienterna förbättrades i sin hypertoni och/eller njurfunktion. Inom 30 dagar avled 1.5% och allvarliga komplikationer drabbade 13% av patienterna. Våra resultat bedöms som goda jämfört med publicerade studier och internationella riktlinjer. Vi kunde inte identifiera några faktorer som före behandlingen kunde förutsäga resultaten av behandlingen. Diabetes var korrelerat till sämre resultat efter behandlingen. Kraftigt nedsatt njurfunktion var korrelerat till allvarliga komplikationer.

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ON RENAL ARTERY STENOSIS


