Diagnostic aspects of renovascular hypertension

Citation for published version (APA):

Schreij, G. (1995). *Diagnostic aspects of renovascular hypertension*. [Doctoral Thesis, Maastricht University]. Datawyse / Universitaire Pers Maastricht. <https://doi.org/10.26481/dis.19951220gs>

Document status and date:

Published: 01/01/1995

DOI:

[10.26481/dis.19951220gs](https://doi.org/10.26481/dis.19951220gs)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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**DIAGNOSTIC ASPECTS OF
RENOVASCULAR HYPERTENSION**

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CIP-GEGEVENS KONINKLIJKE BIBLIOTHEEK, DEN HAAG

Schreij, Gerrit

Diagnostic aspects of renovascular hypertension / Gerrit Schreij. - Maastricht : Universitaire Pers Maastricht. - III.

Proefschrift Rijksuniversiteit Limburg Maastricht. - Met lit. opg. - Met samenvatting in het Nederlands.

ISBN 90-5278-207-5

Trefw.: renovasculaire hypertensie ; diagnostiek / renografie.

Production: Datawyse | Universitaire Pers Maastricht

DIAGNOSTIC ASPECTS OF RENOVASCULAR HYPERTENSION

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Rijksuniversiteit Limburg te Maastricht,
op gezag van de Rector Magnificus, Prof. Mr. M.J. Cohen,
volgens het besluit van het College van Dekanen,
in het openbaar te verdedigen
op woensdag 20 december 1995 om 16.00 uur

door

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CONTENTS

I.	Introduction and rationale	9
II.	Renovascular hypertension: a survey of the literature	13
	1. General aspects of renovascular hypertension	15
	.1 Prevalence of renovascular hypertension	
	.2 Pathological conditions causing renal artery stenosis	
	.3 Natural history of renal artery stenosis	
	.4 Renal artery stenosis and hypertension	
	.5 Clinical clues suggesting renovascular hypertension	
	2. Screening and diagnostic tests in renovascular hypertension	21
	.1 Screening tests	
	a. Ultra sound and Doppler ultra sound	
	b. Renography with and without ACE-inhibition	
	.2 Functional screening tests: Renin and renin ratio's	
	a. Peripheral venous renin	
	b. Renal vein renin and renin ratio's	
	c. Captopril test	
	.3 Conformational tests	
	a. DSA	
	b. Renal angiography and MRI angiography	
	3. Therapy in renovascular hypertension	28
	.1 Introduction, drug and interventional therapy	
	.2 Results of intervention	
	a. Surgery	
	b. Percutaneous transluminal angioplasty and intravascular stents	
	c. Comparing intervention treatment options	
III.	Comparison of office and serial automatic blood pressure readings in renovascular and essential hypertension	43
IV.	Prospective evaluation of the value of clinical clues for the diagnosis of renal artery stenosis in hypertensive patients	49
V.	Relation between the degree of stenosis in renovascular disease and renographic characteristics	59
VI.	Interpretation of renography by nuclear medicine physicians	69
VII.	Comparison of baseline and post-captopril renal blood flow measurements as determined with first-pass radionuclide angiography in hypertensive patients suspected of having renal artery stenosis	79
VIII.	The "captopril test", with blood pressure and peripheral renin as response variables in hypertensive patients with a high likelihood of having renal artery stenosis	87
IX.	Renal and venous endothelin in hypertensive patients with or without renal artery stenosis	99

X.	Renal extraction of atrial natriuretic peptide in hypertensive patients with or without renal artery stenosis	107
XI.	Interpretation of renal angiography by radiologists	119
XII.	General discussion	129
XIII.	Summary	133
XIV.	Samenvatting	137
	Dankwoord	139
	Curriculum vitae	141

CHAPTER I

INTRODUCTION AND RATIONALE

INTRODUCTION AND RATIONALE

Hypertension is a major public health problem in the western world. It is a common, usually asymptomatic yet readily detectable disorder which, when left untreated, leads to serious cardiovascular complications.

Although the prevalence of essential hypertension both in the general population and in specialized referral clinics always exceeds all other forms of secondary hypertension, it is common practice and often recommendable to look for a specific underlying condition that is causing the hypertension.

The most frequent form of secondary hypertension is renal hypertension, being either parenchymal or renovascular in origin. Renovascular hypertension (RVHT) is an incompletely understood form of secondary hypertension; although decreased perfusion of renal tissue due to stenosis of a main or branch renal artery initially activates the renin-angiotensin-aldosterone system, the pathophysiological mechanisms that maintain an increased arterial pressure remain elusive.

As RVHT is a potentially curable form of hypertension, early diagnosis is mandatory.

Before starting to perform a screening test for RVHT in a patient with high blood pressure, the clinician has to estimate the probability of finding a renal artery stenosis in that particular patient. The clinician will do this on the basis of presenting clinical signs and symptoms, some of which are more indicative for RVHT than others. The first step in the work-up of patients with hypertension suspected of having RVHT is to perform one or more screening tests. For the detection of renal artery stenosis, there are three commonly used screening tests available ie: duplex echo Doppler, renography and the captopril test.

With the duplex Doppler technique one measures blood flow velocities in the renal arteries. However, even in the hands of experienced investigators, as many as 15% of patients cannot be evaluated by this method. Moreover, this technique is highly dependent on the skills of the operator.

Renal scintigraphy with and without ACE-inhibition is by far the most frequently used test in the outpatient setting. After intravenous injection of a radio-labelled tracer the kidneys can be visualised separately. Since interruption of the renin-angiotensin system in unilateral renal artery stenosis leads to impairment of renal function on the affected side, the administration of an ACE-inhibitor may enhance the asymmetry between the affected and the non-affected side. Despite the widespread use of renal scintigraphy as a screening test in RVHT, little is known about the diagnostic performance of nuclear medicine physicians with respect to their interpretation of baseline, captopril and paired renograms.

One should also bear in mind that, although most clinicians consider narrowing of the arterial lumen hemodynamically significant when it exceeds 50%, it is not exactly known at which degree of renal artery stenosis kidney function is altered in such a way that changes in renographic parameters occur. The captopril test is based on the exaggerated rise in the peripheral plasma renin level that occurs in patients with renal artery stenosis after a single dose of captopril. However, depending on the criteria for a positive test, the sensitivity and specificity of this test range considerably in most studies.

Although a large amount of research has been devoted to the role of the renin-angiotensin-aldosterone system in renal artery stenosis, so far the significance of this system for the pathogenesis of renovascular hypertension remains controversial. It may be that other vasoactive hormones like endothelins or atrial natriuretic peptides play a more important role in the maintenance of renovascular hypertension and it is conceivable that measurement of the renal release or extraction of these hormones can be used in the work-up of patients with RVHT.

Finally, angiography of the renal arteries is considered to be the "gold standard" by which the diagnosis of a stenosis is made, but little is known about the accuracy of the interpretation of renal angiograms by radiologists. This is surprising as clinical decisions about surgical correction or angioplasty of a stenotic lesion in the renal artery often are based on the radiologist's interpretation of the angiogram.

Whereas the prevalence of RVHT in the hypertensive population selected to undergo a screening or diagnostic test can vary considerably, depending on the selection criteria used, little emphasis has been put on the variability of the reader's interpretation of such tests.

In this thesis we will focus primarily on the use of selection criteria (clinical clues and symptoms) and on the interpretation of screening and conformational tests in hypertensive patients suspected of having renal artery stenosis.

To this following questions are addressed in this thesis:

- 1) Are blood pressure patterns in RVHT different from those in patients with essential hypertension?
- 2) What is the value of clinical clues for the diagnosis of RVHT?
- 3) When patients are selected on the basis of clinical clues, what will be the diagnostic yield of the "captopril test"?
- 4) What is the smallest degree of renal artery stenosis that is associated with changes in renographic parameters?
- 5) Is the noninvasive measurement of renal blood flow as determined from first-pass radionuclide angiography a useful tool for screening purposes in patients suspected of having renovascular hypertension?
- 6) Is the renal extraction of endothelin and atrial natriuretic peptide in patients with RVHT different from those in patients with essential hypertension?
- 7) What is the variability of the reader's interpretation of renograms and renal angiograms?

CHAPTER II

RENOVASCULAR HYPERTENSION; A SURVEY OF THE LITERATURE

Schreij G, Leeuw de PW

submitted

RENOVASCULAR HYPERTENSION; A SURVEY OF THE LITERATURE

GENERAL ASPECTS OF RENOVASCULAR HYPERTENSION

1.1 Prevalence of renovascular hypertension

Although the prevalence of hypertension has been well documented in epidemiological studies, the prevalence of renovascular hypertension (RVHT) in the hypertensive population as a whole is not exactly known. Since there is no perfect screening test for the detection of RVHT, reported prevalences are dependent on the accuracy of the screening test used¹⁻³. Hospital-based studies usually report high prevalences of more than 10%⁴⁻¹⁰, although during a three years period the incidence of RVHT in adult hypertensive patients in the Mayo Clinics was only 1.82%¹¹ (see table 1).

Berglund et al.¹² found in a random population sample of Swedish men aged 47-54 years a prevalence of RVHT of 0.60% in subjects with blood pressures above 175/115 mmHg. An equally low prevalence of 0.13% was found in the Hypertension Detection and Follow-up Program¹³, a stepped care program of patients aged 30-69 years. A retrospective analysis of 1000 hypertensive patients aged 20-70 year by Danielson and Dammström¹⁴ reported a prevalence of 1% for RVHT. Finally, in a ten-year period the prevalence of RVHT in a family practice serving a population of approximately 300.000 middle-class white inhabitants was 0.15%¹⁵.

In more recent reports, however, estimates of the prevalence of RVHT within hypertensive populations amount to about 1 to 2%^{16,17}.

The majority of the population-based prevalence studies have been conducted in Sweden or Denmark whereas the American studies usually are hospital-based. Most of the recent hospital-based surveys on the prevalence of RVHT find percentages of around 5%¹⁸⁻²⁰, or lower².

Much higher prevalence rates have been reported in certain selected groups of hypertensive subjects, such as those with grade III and IV hypertensive retinopathy^{21,22}. Severe hypertensive retinopathy in patients with RVHT is mainly seen in association with atherosclerotic renal artery lesions^{21,23,24}. In patients with hypertension and a "typical" abdominal murmur the prevalence of renal artery stenosis is about 50%^{9,21,25}.

Whether diabetes mellitus leads to a higher prevalence of renal artery stenosis is not exactly known; while some authors report an increased number of cases^{26,27} others do not²⁸. In contrast to white patients, black patients seem to have a far lower prevalence of RVHT^{2,21,29-31}. During a 10-year observation period Keith³¹ found that a clinically significant renal artery stenosis was an uncommon finding in adult black hypertensives. He concluded that, since RVHT is rare in adult blacks, intensive investigation for this entity is justified only in patients with definite suggestive findings.

A higher frequency of smoking is consistently found among patients with RVHT (both atherosclerosis and fibromuscular dysplasia) compared with age matched patients with essential hypertension^{32,33}.

In the pediatric hypertensive population the prevalence of renal hypertension is much higher than in adults³⁴⁻³⁷, ranging from 45% to 94%. After renal insufficiency RVHT is the second most common type of secondary hypertension and accounts for about 20% of hypertensive patients^{36,38}. The prevalence of renal artery stenosis is even more outspoken in younger age groups^{36,39}. Pediatric renovascular hypertension is usually caused by fibromuscular dysplasia, and principally affects the main renal artery but developmental anomalies of the renal artery can also account for a substantial percentage of cases, even up to 40%^{40,41}. Deterioration of renal function, however, is uncommon in pediatric patients with non-malignant renovascular hypertension^{37,42}.

Table 1. Studies reporting prevalence of renovascular hypertension (% of RVHT)

REFERENCE	AGE	n	% RVHT	TYPE OF STUDY
Dustin ⁶ 1963	adults	617	28	hospital-based
DeBakey ⁴ 1964	..	1125	20	..
Kennedy ²⁰ 1965	..	750	6.1	..
Hood ⁵ 1967	..	685	14	..
Gifford ¹⁹ 1969	..	4939	4.5	..
Tucker ¹¹ 1975	..	6414	1.8	..
Bech ¹⁸ 1975	..	482	5	..
Berglund ¹² 1976	47-54 year	798	0.6	population-based
Rudnick ¹⁵ 1977	adults	665	0.15	family practice
Danielson ¹⁴ 1981	20-70 year	1000	1	population-based referred cases
Lewin ¹³ 1985	30-69 year	5485	0.06	stepped care program
v Bockel ¹⁷ 1990	adults	-	2	hospital-based
Korobkin ³⁶ 1976	under 20 year	101	24	pediatric clinic
Korobkin ³⁶ 1976	under 5 year	10	60	..

n= number of patient with hypertension that fulfilled the criteria for analysis.

1.2 Pathological conditions causing renal artery stenosis

a. Atherosclerosis

Atherosclerotic lesions account for approximately two-thirds of all renal artery stenoses, with men being affected twice as often as women^{2,4,5,7,9,17,27,43-48}. This sex difference is less apparent or even reversed in advanced age^{49,50}.

In both males and females the prevalence of atherosclerotic renal artery stenosis is clearly age-dependent. While males are more frequently affected in the younger age groups, woman are in the older age groups. However, this pattern may simply reflect selection bias due to excess mortality among middle-aged men.

Atherosclerosis may be limited to the renal artery only, but is often a manifestation of generalized disease. Lesions commonly occur in the proximal one-third of the artery, they are usually eccentric, and may be complicated by poststenotic dilatation^{45,49,51}. The predilection side of the stenosis is essentially similar in the left and right renal artery⁴⁹. In case of unilateral disease, some investigators find a greater prevalence of atherosclerotic stenosis on the left side^{7,49,52-54} but others on the right⁴⁵.

In many cases, plaques in the wall of the aorta may encroach on the ostium of the renal artery^{23,45,55,56}. There is a strong tendency for atherosclerotic lesions to occur bilaterally^{7,49,52,53,55,57}. A severe stenosis of one renal artery is often accompanied by atherosclerotic disease of the other side^{44,49,50}. Involvement of a major renal artery branch is uncommon, and is seen in only about 5% of the cases⁴.

Although in approximately 15% to 20% of patients with atherosclerotic renal artery stenosis, lesions are not associated with significant atherosclerotic disease elsewhere²⁷, the occurrence of symptoms of extrarenal atherosclerosis can be substantial^{7,45,50,58}.

Atherosclerotic lesions may be complicated by atheromatous emboli, medial dissection, subintimal hemorrhage and calcifications^{46,59-61}. In postmortem studies, renal localisations of cholesterol embolism are found in over 90% of the cases^{62,63}.

In longstanding hypertension in patients over 50 years old, a decline in renal function should always suggest atherosclerotic renal artery occlusion, with ischemia and multiple spontaneous cholesterol emboli⁶³⁻⁶⁷. This complication of atherosclerotic renal artery disease can lead to a gross reduction in size with a smooth or fine granular surface of the kidney^{23,44,66}. Since bilateral atherosclerosis is common, patients with an atrophic kidney may have unsuspected stenosis in the contralateral, normal-sized kidney.

Multiple cholesterol emboli from atherosclerotic lesions can be the cause not only of chronic progressive renal failure but also of acute renal failure, the latter usually after triggering events like aortic surgery or arterial catheterisation procedures⁶⁸⁻⁷⁰.

Severe intrarenal stenosis is especially seen at necropsy in longstanding diabetes mellitus^{49,71}. It is noteworthy that renal artery stenosis seems to protect the ischemic kidney from developing diabetic nephropathy^{72,73}.

b. Fibromuscular dysplasia (FMD)

Fibromuscular dysplasia or hyperplasia (FMD), first described by Leadbetter in 1938⁷⁴, is a non-atherosclerotic, non-inflammatory vascular disease of unknown origin that involves medium-sized and small arteries. FMD accounts for about a quarter to a third of all cases of renal artery stenosis^{2,46,75}. In unilateral FMD the right renal artery is more often involved than the left one^{76,77}. Nephroptosis also is frequently associated with FMD of the right renal artery. Nevertheless, bilateral involvement of the renal arteries is not uncommon.

FMD is a disease that is mainly seen in children^{37,40,42,78,79} and young adult women^{2,27,43,46,47,76,77,81-83}. For instance, in a large series of patients a 93% female predominance in a group of 113 operated patients was reported⁸⁴.

In nephroptosis, posture-dependent changes in renal artery diameter may cause intermittent stenosis. Such an intermittent stretching of the arterial smooth cells results in an increase in production of collagen matrix⁷⁷ and might have an additional effect on the evolution of FMD^{85,86}.

Progression of fibromuscular dysplasia has been confirmed by serial angiography but seems less than in atherosclerotic renal artery stenosis^{48,87}. Total occlusion of the artery is an uncommon finding, especially in medial fibroplasia, and, when present is often caused by renal artery dissection. Dissection of the renal artery in such a case can be recognized arteriographically when a segment of the artery exhibits some sleeve-like narrowing, and this segment remains prolonged opacified with contrast medium⁷⁶.

There is no unifying classification for FMD, but in the final report of the Working Group on Renovascular Hypertension of 1987²⁷, there is a proposal to use the classification of Harrison and MacCormack⁸⁸ that was later revised by Stanley³⁰. Since that time this classification has been more or less accepted and replaces the former classifications of the Cleveland and Mayo Clinics⁸⁷. This histological subtyping of FMD is based on the predominant site of dysplasia in the arterial wall.

Intimal fibroplasia

Histologically, there is circumferential accumulation of irregularly arranged fibrous tissue in the intima with no inflammatory component. Medial and adventitial structures keep their integrity. It is the most common form of fibromuscular dysplasia in children. In adults it accounts for less than 5% of the cases.

Medial fibromuscular dysplasia

Medial fibromuscular dysplasia is the dominant form and is subdivided into three forms: medial fibro(dys)plasia (frequency 60-85%), medial hyperplasia (frequency 1-15%) and perimedial dysplasia (frequency 10-25%)

- Medial fibro(dys)plasia is characterized by extensive medial changes with a dense fibroproliferative process manifested by an increase in collagen and ground substance with loss of smooth muscle. Accumulations of dysplastic fibrous tissue, alternating with medial thinning and disruption and replacement of smooth muscle account for stenosis, mural dilatations and microaneurysms. In the renal artery, the distal two-thirds are typically involved and the lesion often extends into the branch arteries. This type of fibromuscular dysplasia has also been noted in the internal carotid, iliac, axillary and epicardiac coronary artery⁷⁷.
- Medial hyperplasia is caused by excessive focal concentric proliferation of smooth muscle without fibrotic changes. It involves the middle or distal part of the renal artery and does not affect branching or segmental vessels.
- Perimedial dysplasia is an unusual accumulation of elastic tissue between the media and adventitia with a noticeable increase in medial ground substance surrounding intact smooth muscle cells, with little change of normal intimal structures.

Periarterial (periadventitial) fibroplasia

This type of fibromuscular dysplasia is the rarest. In this disease, fibroplasia with collagen encompasses the adventitia and extends into the surrounding periarterial tissue^{77,87}.

c. Miscellaneous disorders causing renal artery stenosis

A variety of conditions causing renal artery stenosis through intrinsic or extrinsic compression have been reported such as extranodal pheochromocytoma^{89,90} and neurofibromatosis^{41,91-93} of the renal artery. Rarely, Takayasu's arteritis^{27,61,94}, polyarteritis nodosa of the renal artery^{95,96} or Ehlers-Danlos type IV⁷⁷ are seen.

1.3 Natural history of renal artery stenosis

The understanding of the natural history and progression of renovascular disease is important because antihypertensive drug therapy, while capable of controlling blood pressure, has little or no influence on the disease process of the renal arteries or of other vessels. Surgical and percutaneous transluminal angioplastic management must also be evaluated in the light of a comparison between results of intervention and data on the natural history of the untreated condition. Knowledge of the natural history is also important with respect to the decision to recommend reconstructive surgery for preserving renal function. Last but not least, a relevant matter is the problem of recurrence of disease in bypass vessels after surgical management, in particular in patients with FMD.

Several follow-up studies have been conducted on the natural history of renal artery stenosis in patients who were managed non-operatively and who underwent one or more repeat renal angiograms^{45,48,75,76,88,97}. These studies demonstrate that both atherosclerosis and all forms of FMD can progress with time, independently of blood pressure control. The percentage of patients that showed progression of renal artery disease in these studies varied between 36%-44% for atherosclerotic disease^{45,48,75,98}, and between 10%-100% for FMD^{48,75,76,88,97}.

In the context of atherosclerotic disease it has to be realized that both in men and in women the prevalence of atherosclerotic renal artery stenosis is age-dependent, men being more frequently and more severely affected in the younger age groups.

Unilateral atherosclerotic renal artery stenosis has a high likelihood of progression to occlusion and is also associated with a 40% probability that a contralateral stenosis will develop within four years after diagnosis^{45,48}. Thus, atherosclerotic renovascular disease often manifests itself when a significant stenosis has developed in one kidney, after the other kidney has previously and silently lost function owing to renal artery occlusion.

The study of Schreiber et al.⁴⁸ is a very interesting one, not only because it demonstrated progression of the vascular obstruction but also because the rate of progression could be calculated from their data. Patients with atherosclerosis on their initial angiogram show an average monthly

rate of progression (absolute change in percent of stenosis over time in months) of about 1.5%. This rate of progression appeared to be constant and independent of the initial percentage of stenosis. A decline in overall renal function and a decrease in kidney size were more common in those patients in whom progressive stenosis developed. The risk of progression to complete occlusion was particularly great in renal arteries with more than 75% stenosis on the initial angiogram, and the greater the degree of stenosis, the sooner total occlusion occurred.

In FMD, medial fibroplasia is the most common form and in approximately one third of these cases progression of the abnormality can be demonstrated angiographically. However, progression to total occlusion or renal failure is seldom or never seen^{48,75,97}. Thus, despite the progressive nature of this form of FMD the risk of losing renal function over time due to progressive arterial occlusion is small. As a corollary, in this case surgical revascularisation or percutaneous transluminal angioplasty for the restoration or preservation of renal function is difficult to justify⁷⁵. However, it may not be easy to identify this form of FMD or to distinguish it on an angiographic image from perimedial fibroplasia. This is important to note because, patients with perimedial fibroplasia, medial hyperplasia and intimal fibroplasia are at a substantial risk for developing high grade renal artery stenosis that might threaten long term renal function^{75,88,97}. Development of FMD in bypass vessels has so far not been encountered⁸⁸.

1.4 Renal artery stenosis and hypertension

In normotensive patients who underwent aortography for a variety reasons the presence of (often severe) renal artery stenosis, both of the fibromuscular dysplastic type and of the atherosclerotic type is not uncommon and similar data come from necropsy studies^{55,59,102-104}. However, less than 3-5% of the patients reported in these studies were under the age of 50 years. It is also known that repair of a renal artery stenosis does not always lead to normalization of blood pressure. Thus, the presence of a renal artery stenosis in a hypertensive patient does not necessarily point to a relationship between the stenosis and the elevated pressure.

In patients with hypertension the hemodynamic significance of a renal artery stenosis can be demonstrated only by one objective finding: that is improved control or cure of the hypertension after correction of the stenosis. Nevertheless, when correction of the stenosis does not result in improved hypertension control or cure, hypertension may still be caused by the stenosis, in particular when blood pressure has remained elevated for a prolonged period of time¹⁰². On the other hand, renovascular hypertension may exist on top of essential hypertension.

*A stenosis with a significant reduction in flow*¹⁰³ may act as the *primum movens*, but bring about homeostatic mechanisms and changes that in due course maintain the hypertension by a whole spectrum of pathophysiological derangements.

1.5 Clinical clues suggesting renovascular hypertension

The selection of patients to be evaluated for possible RVHT poses a dilemma for the physician. Since RVHT occurs in 0.15% to over 10%, dependent on the population of hypertensive subjects, some selection of those in whom a further work-up is necessary, has to be made. The decision to evaluate a patient for possible RVHT should thus be made on an individual basis depending on clinical signs and symptoms. For instance, an elderly patient with normal renal function for many years who is easily managed with antihypertensive drugs will not need further investigations. On the other hand, a young patient with an acceleration of hypertension does need evaluation.

Clinical clues that may help to identify patients at risk for RVHT are well recognized in the literature, and have been defined by the Cooperative Study Group on Renovascular Hypertension²⁷ as well as by others^{2,7,23,47,104-111}. In the final report of the Working Group on Renovascular

Hypertension²⁷ it was recommended that the following clinical clues (table 2) should alert the clinician to the possibility of renovascular hypertension.

Table 2. Clinical Clues Suggesting Renovascular Hypertension²⁷

-
- Systolic-diastolic epigastric, subcostal, or flank bruit.
 - Accelerated or malignant hypertension.
 - Unilateral small kidney discovered by any clinical study.
 - Severe hypertension in child or young adult, or after the age of 50.
 - Sudden development or worsening of hypertension at any age.
 - Hypertension and unexplained impairment of renal function.
 - Sudden worsening of renal function in a hypertensive patient.
 - Hypertension refractory to appropriate three-drug regimen.
 - Impairment of renal function in response to ACE-inhibition.
 - Extensive occlusive disease in coronary, cerebral, and peripheral circulation.
-

On the basis of these characteristics and clinical clues one can select patients who are likely to have renal artery stenosis. However, in none of these studies, except in the one by Anderson et al.² the investigations provided data on the prevalence of the selected clinical characteristics in patients with RVHT, as compared with other hypertensive patients. A summary of the risk of having RVHT in relation to different clinical findings in an unselected hypertensive population with a prevalence of RVHT of 3% is given by Anderson et al.² (table 3).

All of these conditions apply, irrespective of whether patients are on antihypertensive medications or not.

Table 3. Risk of RVHT in relation to different clinical findings²

-
- Unlikely to have RVHT with:
serum potassium <3.4 mmol/l and DBP <90 mmHg
 - A two to threefold increased prevalence of RVHT with:
DBP >110 mmHg
age of onset of hypertension 51-60.
age of onset >60 with elevated DBP.
 - A four to sixfold increased prevalence of RVHT with:
age of onset of hypertension >60.
serum potassium 2.9-3.3 mmol/l.
serum potassium <3.4 mmol/l with DBP >90 mmHg
 - A seven to ninefold increased prevalence of RVHT with:
age of onset >60 with DBP >110 mmHg
serum potassium 2.3-2.8 mmol/l.
-

Concluding remarks

The prevalence of RVHT is less than 1% in the general population of hypertensive subjects, approximately 5% in hospital-based populations, and even higher in patients referred to specialized hypertensive clinics. High prevalence rates of RVHT are present in certain groups of hypertensive subjects, such as those with grade III and IV hypertensive retinopathy, those with a "typical" abdominal murmur and those patients with a history of smoking.

In the pediatric hypertensive population RVHT is the second most common type of secondary hypertension. In two-third of cases the cause of RVHT is atherosclerotic disease; less common causes are FMD, arteritis, extrinsic compression by tumours and neurofibromatosis.

Both atherosclerosis and all forms of FMD can progress, independently of blood pressure control

and lead to a decline in renal function. The prevalence of atherosclerosis increases with age and atherosclerotic renovascular disease often manifests itself in the older patient when a significant stenosis has developed in one kidney after the other kidney has previously and silently lost function owing to renal artery occlusion.

It is not always justifiable to label hypertension in the presence of renal artery stenosis as renovascular hypertension. Moreover, essential and renovascular hypertension may coexist. Alternatively, it is even possible that the raised blood pressure is the cause of the stenosis and not the other way around, i.e., hypertension increases the risk of atherosclerotic disease, which may also involve the renal arteries.

With the help of certain clinical clues and symptoms it is possible to select hypertensive patients with a high likelihood of having RVHT for further work-up.

SCREENING AND DIAGNOSTIC TESTS IN RENOVASCULAR HYPERTENSION

2.1 Screening tests

Although RVHT has a relatively low prevalence in an unselected population of hypertensives, the fact that this condition can be cured or improved and that loss of renal function can be prevented, calls for the availability of a simple, noninvasive screening test that can preferably be carried out in an outpatient setting. Certain clinical characteristics can hint to the presence of RVHT but many patients with the condition are clinically indistinguishable from patients with essential hypertension.

Atherosclerotic renovascular disease is more common in the general population than has hitherto been thought¹¹². This information stems both from angiographic studies in patients with asymptomatic renal disease^{113,114} and from patients presenting with a decline in renal function during ACE-inhibitor therapy¹¹⁵. In non selected autopsy series, the prevalence of atherosclerotic renal artery stenosis is 18% in patients over 65 years and 42% in patients over 75 years⁴⁹.

Thus, one can expect that in an aging population there will be an increasing need for screening and detection of renal artery disease. In the following the most frequently used screening tests will be discussed, leaving aside intravenous urography (IVU or IVP) which nowadays is considered to be obsolete in this respect¹¹⁶.

a. *ultra sound and echo Doppler ultra sound*

Apart from defining differences in pole-to-pole length and parenchymal thinning, both of which are not sensitive for detecting RVHT^{117,118}, ultrasound techniques can be used to exclude other abnormalities that can cause secondary hypertension such as hydro-nephrosis¹¹⁹ or tumours adjacent to the renal arteries⁸⁹.

The use of ultrasound Doppler instruments to evaluate renal blood flow patterns only permits a distinction to be made between normal and abnormal. Normal Doppler flow signals reflect a rather well defined flow pattern with only a small variation (narrow spectrum) of blood velocities across the vessel lumen¹²⁰. At a narrowed segment, blood flow velocities increase. In the poststenotic segment, the flow becomes non-laminar, multidirectional, and disturbed. Various investigators have evaluated the sensitivity and specificity of several Doppler criteria for the diagnosis of renal artery stenosis.

The most important abnormal hemodynamic parameters for the detection of a stenosis are^{120,121}:

- peak blood velocity greater than 100 cm/sec. in a focal area along the length of a renal artery
- a ratio of peak aortic velocity to peak renal artery velocity of more than 3.5
- absence of blood flow velocity during diastole
- absence of any detectable blood velocity, denoting occlusion
- broad-band Doppler frequency spectra due to focal blood velocity disturbances

In table 4 the sensitivity and specificity of different Doppler ultrasound criteria for the diagnosis of renal artery stenosis are given¹²⁰⁻¹²⁵.

A differentiation between renal artery stenosis and increased flow resistance, for instance due to parenchymatous nephropathy, is difficult^{120,125,126}. Combining different Doppler criteria, one may augment the predictive value of the technique, but which combination of Doppler criteria is the best is still unknown. Nevertheless, (colour) duplex ultrasound, a more refined procedure, appears to yield a high diagnostic accuracy of more than 90%^{121,125,127-130}. For instance, comparing peak systolic velocity of aorta and renal artery colour Doppler systolic waveform signals gives a high accuracy in screening for renal artery stenosis¹²⁹. But others find the colour duplex ultrasound unsatisfactory for screening for renal artery stenosis, because the renal vasculature unlike carotid arteries lies deeper, is smaller, and is often obscured by bowel gas or fat and prone to anatomic variability including multiplicity^{120,129,131}.

Table 4. Sensitivity and specificity of Doppler ultrasound criteria for the diagnosis of RAS¹²⁰⁻¹²⁵

Hemodynamic alterations	Doppler criteria	normal range	stenosis d.r. > 50%	sensitivity	specificity
Acceleration of flow in narrow segment	abnormal peak	50-100 cm/s	> 100cm/s	42%	92%
Jet effect normalized to the aorta velocity	ratio of renal to aortic syst.peak velocities	< 3.5	> 3.5	91%	95%
Turbulence in the stenotic segment	broadening of Doppler spectra*	> 11%	< 11%	83%	100%
Increased impedance	ratio of end-diast.to peak syst.velocities	0.36-0.05	< 0.05	na	na
Complete obstruction	no flow in a clearly imaged renal artery	present	absent	31%	88%

*=percentage of area of spectral window to enfold the waveform; d.r.=diameter reduction; na=not available

In the follow-up after successful percutaneous transluminal angioplasty or bypass surgery, it is a good screening instrument for the detection of restenosis^{129,132,133}.

A quantitative estimate of progression of the stenosis¹³⁴ and of loss of renal parenchyma¹³⁵ can be made with Doppler ultrasound. In patients with more than 60% stenosis Doppler ultrasound analysis revealed that 19% of them would lose 1 cm or more in kidney length at 1 year¹³.

b. Renography with or without ACE-inhibition

Renography for the diagnosis of renal artery stenosis was introduced in the sixties¹³⁶ and has been widely used ever since. In a meta-analysis of several arteriographically controlled studies, in which I¹³¹ hippuran renography without ACE inhibition was done in 934 patients with renal artery stenosis and 951 patients without stenosis, a composite sensitivity of 74% and a specificity of 77% was found¹³⁷.

There are several reasons for the rather low sensitivity and specificity of standard renography. False positive test results can be caused by a wide variety of relatively common conditions causing asymmetrical renal size and function, such as parenchymal renal disease and collecting system obstruction¹³⁸. False negative findings may be due to adaptive mechanisms in the post-stenotic kidney¹³⁹.

There are several pathophysiological studies that prove that ACE inhibition in experimental renovascular hypertension could enhance the sensitivity of renography¹⁴⁰⁻¹⁴³.

Despite variability in selection of patients and diagnostic criteria in the various angiographically controlled studies, the screening value of captopril-induced changes in renography is much better than that of the standard renogram with a sensitivity and specificity both for unilateral and bilateral renal artery stenosis of around 85% and 75% respectively when hippuran is used as a marker¹⁴⁴⁻¹⁴⁹, and around 85% and 90% respectively for 99m Tc DTPA renography¹⁵⁰⁻¹⁶⁰ (table 5). Results of studies where 99m Tc MAG-3 has been used as tracer substance probably fall in the same range, but such data are still preliminary^{161,162}.

Comparing the different forms of renography after ACE-inhibition, most investigators consider the sensitivity and specificity of the hippuran renogram better than those of a DTPA renogram^{145,146,148,149,156} although some claim it to be the other way around¹⁴⁷.

Table 5. Results and operating characteristics of captopril renography in different studies

Author	Type*	Number of patients prevalence of RVHT or RAS	Definition of RAS**	Criteria ***	Sensitivity	Specificity	
Hippuran renography							
Geyskes ¹⁴⁴	1987	RVHT	34/44%	-	F + P	86%	89%
Sfakianakis ¹⁴⁵	1988	RVHT	31/53%	> 60%	F + E + P	67%	100%
Svetkey ¹⁴⁷	1989	RVHT	56/18%	> 50%	F	80%	42%
Mann ¹⁴⁸	1991	RAS	55/64%	> 70%	F + E	83%	85%
Erbslöh ¹⁴⁹	1991	RVHT	50/56%	> 50%	E + P	96%	95%
DTPA renography							
Fommei ¹³²	1987	RAS	39/31%	-	F	83%	85%
Geyskes ¹⁴⁴	1987	RVHT	34/44%	-	F	86%	89%
Sfakianakis ¹⁵⁵	1987	RVHT	36/50%	> 60%	F + P	100%	100%
Mahler ¹⁵¹	1988	RAS	44/34%	-	F	85%	72%
Dondi ¹⁵²	1989	RAS	105/35%	> 50%	P	92%	97%
Chen ¹⁵³	1990	RAS	50/46%	> 75%	F + E	91%	93%
Mann ¹⁴⁸	1991	RAS	55/64%	> 70%	F + E	94%	95%
Setaro ¹⁵⁴	1991	RAS	113/51%	> 75%	F + E	91%	87%
Postma ¹⁵⁷	1991	RVHT	22/45%	> 50%	F	60%	100%
Svetkey ¹⁵⁸	1991	RVHT	140/22%	> 50%	F	74%	44%
Dondi ¹⁵⁹	1992	RVHT	51/82%	> 50%	F + E	87%	93%
Dey ¹⁶⁰	1993	RAS	88/51%	> 75%	E	67%	79%

* type refers to the diagnosis: either to renal artery stenosis (RAS) or to renovascular hypertension (RVHT);

** definition of RAS = percentage of stenosis considered to be significant, - = not specified.

*** criteria = criteria used to define a positive scan were based either on quantitative indexes, such as uptake (F=function) or time to peak activity/residual activity (E=excretion), or on a qualitative or semi-quantitative analysis of renogram patterns (P=pattern)

The best scintigraphic criterion in both hippuran and DTPA scintigraphy is a difference in uptake of tracer before and after ACE-inhibition^{132,144-146,148,149,151,153,163,164}, in only one study with hippuran it was a difference in time-to-peak¹⁴⁴. A lengthening of the time- to-peak interval is, however, not a very sensitive criterion neither in ACE inhibition hippuran nor in DTPA renography.

Both in hippuran- and in DTPA- and in MAG-3 renography it is a combination of criteria, namely the differences in uptake, in time-to-peak interval (when more than 5 min.), and in retention that makes them highly sensitive and specific for detecting RVHT or RAS^{144,148,153}. In this respect, the study done by Chen et al.¹⁵³ is very interesting, because it shows the accuracy and predictive values

of the different criteria chosen.

For the diagnosis of segmental renal artery stenosis 99m Tc DMSA (dimercapto succinic acid) renography seems to be the most sensitive method¹⁶⁵.

To some extent renography after ACE-inhibition can predict the effect of interventional therapy on blood pressure^{132,147,149,154,159,166,167}. However, for the individual case it is difficult to predict the effect of intervention on blood pressure. Sequential renograms can be used as an indication of improvement of renal function after intervention^{156,166,167}.

Although a lot of research has been done in this area, there are still some main issues concerning the diagnostic value of renography that need to be established. These questions are of two kinds, namely technical and clinical^{153,168,169}, and can be formulated as follows:

1. Which isotope (DTPA or MAG-3) should be used to maximize diagnostic accuracy?
2. Should the test be interpreted quantitatively, or semiquantitatively?
3. Are both baseline and post-captopril renal scintigrams necessary?
4. Is post-captopril renal scintigraphy helpful to detect or exclude an abnormal renal artery anatomy in patients who on the basis of certain clinical criteria are likely to have such an abnormality.
5. Can post-captopril renal scintigraphy predict the outcome of renal vascularization?
6. Is renography an accurate method for detecting significant RAS or its clinical consequence: renovascular hypertension.

2.2 Functional screening tests: Renin and renin ratio's

a. *Peripheral venous renin*

Among the many intra-and extrarenal factors that influence the renin concentration in peripheral blood are renal perfusion pressure, sympathetic activity, volume status and sodium and potassium balance.

It is known that patients with essential hypertension can have low, normal or high plasma renin concentrations¹⁷⁰. In about 10% of patients with essential hypertension raised renin levels are found whereas on the other hand even under strictly standardised conditions only 50% of patients with renovascular hypertension have raised renin levels¹⁷¹. In malignant or accelerated hypertension, whatever the cause, peripheral renin levels are usually elevated. In large series of patients with hypertension the plasma renin concentration shows no relationship with etiology or severity of hypertension^{171,172}.

In most centres it is common practice to take renin samples under basal conditions and, to relate the results to urinary sodium excretion.

From the above mentioned data it is obvious that a given peripheral renin level is unlikely to distinguish patients with EH from those with RVHT and that it is of little value in the diagnosis of renovascular hypertension or to predict the outcome of a therapeutic intervention^{173,174}.

b. *Renal vein renin (baseline and after ACE-inhibition) and renin ratios*

In order to link an angiographically proven renal artery stenosis to functional sequelae, many investigators have measured renal vein renin levels in both uni- and bilateral stenosis. The determination of the renal vein renin ratio in RVHT has been used as a screening method, as a diagnostic tool and as a parameter to predict the response of blood pressure after intervention therapy.

In a review of 58 studies that for the most part used a baseline ratio (affected to contralateral kidney) of 1.5 or more as a diagnostic criterion, a sensitivity of 80% and a specificity of 62% was reported¹⁷⁵. Stimulation of renin secretion by ACE-inhibition improve sensitivity without compromising specificity¹⁷⁶⁻¹⁷⁸.

A stenotic-to-contralateral renal vein renin ratio greater than 1.5, an increment in renal venous

renin (V) over the arterial (A) renin level (ischemic kidney V-A/A) greater than 0.48 in the ischemic kidney¹⁷⁹ with suppression of the contralateral renin ratio (contralateral kidney V-A/A) to below 0.13¹⁸⁰ are all considered to be important criteria in determining the importance of a stenosis but they have rarely been related to the results of intervention therapy.

Since the stenotic-to-contralateral renin ratio (baseline and after ACE-inhibition) is used to predict the response of blood pressure to therapeutic intervention, the predictive values should ideally be calculated in relation to the final interventional outcome: cured or improved versus no benefit. However, it should be stressed that a substantial amount of patients with no clear lateralization of renin secretion may still benefit from PTRAs or surgery, and it would be unwise to withhold such a procedure if no renin lateralization or suppression can be found. This point of view is supported by series with large numbers of patients who underwent a successful PTRAs, irrespective of the outcome of renin measurements^{181,182}.

c. "The captopril challenge test"

The effect of ACE inhibition, in order to distinguish patients with essential hypertension from those with RVHT and to discriminate in the latter group between those who would and those who would not benefit from an interventional procedure, can be studied with respect to,

1. blood pressure
2. on peripheral plasma renin levels and
3. a combination of 1 and 2.

Some authors find the magnitude of the hypotensive response to be significantly greater in RVHT than in essential hypertension¹⁸³ but most authors describe a considerable overlap there being no significant difference between groups^{1,171,184-189}. Of interest is that in some studies the blood pressure response is related to the initial peripheral renin level¹⁹⁰⁻¹⁹². The acute hemodynamic response to captopril sometimes predicts the post-interventional blood pressure in patients with RVHT¹⁷⁸ but other studies failed to find such a relationship^{193,194}.

The increase in stimulated plasma renin activity can be studied according to Müller and coworkers¹⁸⁴, the first ones who claimed a 100% sensitivity and a 95% specificity in distinguishing patients with renovascular hypertension from those with essential hypertension. Others have also found excellent sensitivity and acceptable specificity using Müllers criteria^{171,183,195} (table 6). Salvetti et al.¹⁸⁸, on the other hand, find the sensitivity for all these criteria to be below 25% and these poor results have been confirmed by Idrissi et al.¹⁸⁶ and by Postma et al.¹⁸⁷. When an absolute value of stimulated plasma renin activity is taken as cut-off point^{1,147,164,171,183,185,195} or when a certain percentage increase is taken^{183,190} the predictive value of the captopril test may be enhanced. Combining peripheral renin levels with the blood pressure response does not seem to improve the predictive value of the test^{1,171}. A reason for this finding is not clear, but may be due to the fact that the height of blood pressure shows no relation to peripheral or renal vein renin levels.

Table 6. Captopril test: sensitivity and specificity

Author		Number of patients prevalence of RAS	Sensitivity	Specificity
Derkx ¹⁷¹	1985	179/50%	93%	84%
Salvetti ¹⁸⁸	1987	62/40%	20%	95%
Müller ¹⁸⁴	1986	198/20%	100%	95%
Kutkuhn ¹⁹⁰	1988	67/43%	89%	100%
Idrissi ¹⁸⁶	1988	102/26%	16%	93%
Svetky ¹⁴⁷	1989	57/19%	73%	72%
Gosse ¹⁹⁶	1989	103/12%	73%	84%
Degenhart ¹⁹⁵	1989	113/21%	79%	97%
Postma ¹⁸⁷	1990	149/30%	34%	91%
Frederickson ¹⁸³	1990	100/29%	100%	80%
Elliot ¹⁷⁸	1993	150/39%	76%	81%

From the above mentioned data one may conclude that the captopril test cannot in its hemodynamic response distinguish patients with RVHT from those with essential hypertension. Also, renin responses show a wide variability that is not easy to explain but which certainly restricts the usefulness of the test. One should bear in mind, however, that in the various studies patients were highly selected and the incidence of renal artery stenosis was very high, and ranging between 12%¹⁹⁶ and 50%^{1,171}. Also important to note is that patients may have differed in sodium status as the diet was restricted in Derkx's¹⁷¹, Atkinson's¹⁹³ and both of Salvetti's¹⁸⁸ studies but not in that of Müller¹⁸⁴, Kutkuhn¹⁹⁰ and Idrissi¹⁸⁶. Studies also differ with respect to the position of the patient which was supine in all studies except in those by Imai's¹⁸⁵, Müller¹⁸⁴ and Frederickson¹⁸³.

Rather than taking the hodgepodge of all these data, it would be better to standardize this inexpensive and non-invasive test and to do prospective studies and relate the results of this standardized captopril test to the final results of interventional therapy.

2.3 Conformational tests

a. *Digital subtraction*

Digital subtraction angiography (DSA), provides computerized electronically enhanced images of contrast containing vessels by subtracting out the background, leaving an image of contrast outlining the lumen of the vessel only.

DSA can be done with contrast injected intravenously (IVDSA) or during intra-arterial angiography (IADSA). In the case of IVDSA contrast is injected into a peripheral vein or through a central venous catheter placed in the right atrium. However, apart from some advantages, the method has major disadvantages¹⁹⁷ (table 7).

Table 7. Advantages and disadvantages of IVDSA ¹⁹⁷

Disadvantages
- Artifacts introduced through patients movements.
- Inadequate visualization of the renal arteries because of overlying bowel, superimposition of vessels.
- Inadequate concentration of contrast which can lead to relatively poor spatial resolution of distal branches.
- Large contrast dose.
Advantages
- No intra-arterial procedure.
- Can be done in an outpatient setting.
- Late images as IVU/IVP.

When the results of IVDSA and of standard arteriography are compared most authors find an overall accuracy in detecting renal artery stenosis of about 70% to 80% which, if inadequate visualisation of the renal arteries is excluded increases to above 90%^{19,20}. However, several investigators have the impression that IVDSA often misjudges the diagnosis^{198,202} or underestimates the degree of disease²⁰².

In a study by Svetkey et al.²⁰³, in which the accuracy of IVDSA in defining renal anatomy before kidney donation was compared with that of standard renal arteriography, IVDSA did not detect 38% of multiple renal arteries, 19% of renal artery stenoses and 85% of other abnormalities that might preclude kidney donation. Furthermore, in 7% of the cases the data suggested abnormal IVDSA despite normal anatomy on conventional arteriography.

b. Renal angiography and MRI angiography

Aortography, if necessary together with selective arteriography of the renal arteries and often in combination with intra-arterial DSA of the renal arteries is considered to be the "gold standard". This procedure also offers the opportunity to perform a percutaneous transluminal angioplasty. It is now generally accepted that this procedure should be performed in all patients with positive screening tests as well as in patients with accelerated or malignant hypertension. Patients should be eligible for this procedure only if they are suitable candidates for reconstructive surgery, percutaneous transluminal angioplasty, or placement of an intravascular stent.

Selective renal arteriography is not a screening test, but it is the final procedure to confirm the suspected diagnosis. It is a very reliable method to ascertain the diagnosis of renovascular disease. In the Cooperative Study⁵² only one false negative arteriogram of a segmental stenosis was discovered at surgery, and 4 false positives (1.7%).

It is fair to state that, a stenosis is most likely to cause RVHT, but as indicated before it is not exactly known at what percentage of luminal reduction hypertension ensues. Most investigators would now consider a diameter reduction of 50% on angiography to be significant. A luminal reduction of 50% corresponds to a cross sectional luminal area reduction of approximately 80%^{52,103}. Some studies, however, report renovascular hypertension in patients with a stenosis of less than 50%^{38,52}. We must conclude that the determination of the degree of arterial luminal reduction in renal artery stenosis, that is hemodynamically significant or potentially threatening kidney function is still an unresolved problem.

Abnormal vascular patterns, such as multiple or aberrant renal arteries are more often found in hypertensive than in normotensive patients²⁰⁴. From this point of view it is important to note that oblique and selective arteriograms are required to demonstrate the anatomy and morphology of the renal arteries in patients suspected of having a renal artery stenosis. One can recognize a number of potentially deceptive patterns of renal artery stenosis, many of which undoubtedly are not detected when only a simple anterior-posterior flush aortogram is done²⁰⁵ (table 8).

Table 8. Common deceptive patterns of renal artery stenosis

-
- Stenosis of main renal artery originating from anterior or posterior aortic wall
 - Stenosis of a renal artery coursing in the anterior posterior plane
 - Superposition of two renal arteries to the kidney with stenosis in one
 - Masking of renal artery stenosis by other intra-abdominal arteries
 - Total occlusion of a segmental or accessory renal artery
 - Ventral right accessory lower pole renal artery
-

This clearly demonstrates the need for multiple and selective angiographic views of the renal arteries, preferably in combination with IADSA.

The interpretation of the angiographic pattern can be difficult in the presence of multiple and aberrant vessels and in the case of extensive collateral circulation. A stenosis in a renal artery branch may pose a diagnostic problem, because such a lesion can be easily overlooked, yet can be

the cause of RVHT in a number of cases^{4,206}. For instance, Debakey et al.⁴ reported a 5% incidence of renal artery branch stenosis. A very proximal renal artery stenosis occasionally may be difficult to differentiate from aortic lesions which, obviously, may have consequences for therapeutic decisions²⁰⁶.

The major disadvantage of the intra-arterial procedure is, that it carries some risk. In the Cooperative Study²⁰⁹ there was a fatality rate of 0.11% and a nonfatal major complication rate of 1.2%, the latter being mainly arterial dissection.

Intra-arterial DSA is of comparable quality but in depicting distal abnormalities of the vascular system it may be less superior²¹⁰.

Most of the atherosclerotic lesions of the renal artery originate in the artery itself, yet large atherosclerotic plaques can overhang the renal ostium, thereby producing a functional renal artery stenosis; atherosclerotic lesions in the renal artery can be contiguous with these plaques²⁰⁸. Luminal narrowing that is confined purely to the renal artery begins at least 2-3 mm beyond a widely patent ostium and remains completely within the boundaries of the renal artery proper. On the basis of these angiographic patterns, lesions can be classified as renal, aortic or of mixed type²⁰⁸. Most of the atherosclerotic lesions involve the proximal third part of the renal artery near the aortic ostium. Lesions elsewhere in the trunk are relatively uncommon although irregularities at multiple sites are common.

The lesions of FMD, in contrast to those of atherosclerosis, characteristically involve the middle and distal portions of the main renal artery, but often extend into the renal arterial branches. In only a few cases there is involvement of the proximal portion and this is seen in particular when the entire length of the main artery is involved^{30,76,87,97}. Intimal fibroplasia, perimedial dysplasia and medial hyperplasia give rise to a single smooth lesion as seen on angiography and are difficult to differentiate radiologically. Intimal fibroplasia in children and young adults appears in the main renal artery as a long, irregular tubular stenosis. Medial and perimedial fibroplasia give an appearance of a "string of beads", due to areas of thickening of the media, interspersed by areas of aneurysmal dilatation^{30,76,87}.

Recent advances in magnetic resonance imaging (MRI) angiography represent a significant progress towards achieving non-invasive diagnosis of vascular disease since it enables the detection of flow within vessels. Good visualization of the renal vasculature usually is possible with this approach but reliable quantification of a stenosis not always^{211,212}. Both two- and three-dimensional approaches have been investigated. The three-dimensional approach gives a better delineation of vessels, but is more susceptible to motion artifacts because of longer acquisition times²¹³. The technique has a high sensitivity but tends to overestimate stenosis and occasionally incorrectly diagnoses an occlusion^{211,212,214}. Technical improvements such as the cardiac-gated 3D technique may overcome this problem²¹⁵. Most importantly, in contrast to Doppler ultrasound and IVDSA almost all patients can be scanned successfully. Nevertheless, many more studies are needed to better determine the diagnostic value and the place of this method.

THERAPY IN RENOVASCULAR HYPERTENSION

3.1 Introduction

The two major indications for treatment in renal artery stenosis are:

1. to cure hypertension or to improve control of blood pressure
2. to preserve renal function.

The decision whether or how to treat (pharmacologically, angioplasty or surgery) should be dictated by the specific type of disease, its natural history, its location, extensiveness of renal artery involvement and degree of stenosis on the one hand, and individual patient characteristics such as

age, general condition and, in particular, advanced generalised atherosclerotic disease on the other. Clinical success after intervention (angioplasty or surgery) in RVHT as far as blood pressure is concerned, may be defined in terms of cure or improvement. Cure is usually defined as a fall in diastolic blood pressure below 90 mmHg without administration of antihypertensive medication. The definition of improvement varies considerably among the different studies²¹⁶. No two studies use the exact same definition of improvement. Many of the definitions are complex and based on a certain percentage fall in diastolic blood pressure and a reduction in medication. However, in most studies diastolic blood pressure is required to fall by at least 10% or 15% and has to be between 90 and 110 mmHg.

Concerning the preservation of renal function, we should remember that the natural history of renal artery stenosis, is one of gradual progression of stenosis and in the end worsening of renal function⁴⁸. The risk of progression of stenosis is particularly obvious in atherosclerotic stenosis of more than 60% luminal reduction where decline in renal function or renal failure in case of bilateral disease is a predictable outcome. In patients with more than 60% stenosis progression to total occlusion occurs in 5% at 1 year and in 11% at 2 years; progression to occlusion may be totally asymptomatic¹³⁴. During a 56-month follow-up period of untreated patients narrowing of the diameter of the renal artery was found to progress with about 5% per year²¹⁷. The rate of progression is, however, not linear but often occurs quite rapidly most likely and may be complicated by atherosclerotic plaque rupture or subintimal bleeding²¹⁸.

Deterioration of renal function with evidence of renal ischemia (decrease in the size of the kidney) is an indication for revascularisation¹³³, but the criteria for pursuing arteriographic evaluation are poorly defined and there are no reliable ways to predict success of interventional therapy^{219,220}.

Unfavourable prognostic factors are: small kidney size (less than about 9 cm in length), poor visualization of the kidney in the nephrographic phase, no excretion of contrast material, and no filling of the renal artery distal to the occlusion^{216,219}. Atherosclerotic renal artery disease is an other unfavourable factor^{216,219}. The response to balloon dilatation is greatest in cases in which the serum creatinine is less than 265 $\mu\text{mol/L}$ ^{82,216,220} (table 9).

Table 9. Unfavourable factors for success after intervention

On angiography

- Small kidney size; less than about 9 cm in length
- Poor visualization of the kidney in the nephrographic phase
- No excretion of contrast material
- No filling of the renal artery distal to the occlusion

Other factors

- Serum creatinine more than 265 $\mu\text{mol/l}$
- Atherosclerotic stenosis

Clinical success concerning renal function is usually defined as a decrease in serum creatinine to normal levels or to 20% below the level before interventional therapy.

Until a decade or two ago and before angioplasty, better surgical revascularization techniques and more potent antihypertensive drugs were introduced, the only treatment options were nephrectomy or (less effective) drug therapy. In this era the central issue was whether operative treatment or drug therapy offered the most benefit. In a widely cited report, published in 1974, on patients with atherosclerotic RVHT, mortality over 7 to 14 years was 73% in patients receiving drug treatment and 30% in those who underwent surgery⁴⁷.

Apart from a high postoperative mortality rate (up to 10%) in these older studies^{47,221,222}, the majority of deaths in the follow-up period in both medical and surgical treatment groups were due to treatment failures, and its consequences on the vascular system.

The impact of these early studies comparing surgery, usually nephrectomy, with medical therapy now seems limited. Presently, in many patients with renal artery stenosis blood pressure can

effectively be controlled by antihypertensive drugs alone and concerns about treatment has shifted from blood pressure control to the preservation of the function of the affected kidney.

As for renal function, recent studies^{223,224} demonstrate an ongoing and progressive decline in renal function in patients with renal artery stenosis in whom hypertension is well controlled by drugs alone. Thus, a so-called "wait and see" approach may be justified only in fragile elderly patients with easily controlled blood pressure and stable renal function. However, the weak points of such an approach are²²⁵:

- the lack of drugs that effectively block the progression of renal artery disease
- the lack of reliable methods to monitor progression of stenosis
- unexpected occurrence of atherosclerotic plaque rupture, often accompanied by atheromatous emboli or subintimal bleeding leading to rapid progression of the degree of stenosis and decline of renal function.

Surgical reconstruction and percutaneous transluminal angioplasty (PTA), if necessary with the placement of an intravascular stent, are the two main options for active treatment of renovascular disease at the present time.

3.2 Results of intervention

a. surgery

When the success rates of surgery and angioplasty are compared, both appear to be equal in atherosclerotic disease but surgery gives a better result than angioplasty in fibromuscular disease with a success rate ranging from 80-95% in curing or improving hypertension²²⁶⁻²³⁰.

Although angioplasty is advised as first line therapy for hypertension and to preserve renal function, surgical revascularization is recommended for a number of indications such as extensive renal artery involvement, repair of total renal artery occlusion, branch renal artery stenosis and renal artery aneurysms^{4,229,231,232} (table 10).

There is some debate about whether an ostial atherosclerotic stenosis is a contraindication for angioplasty, because of the high risk of restenosis after successful intervention²³³. Sometimes a balloon-expandable stainless steel stent may reduce the risk of restenosis²⁴³.

In atherosclerotic disease surgical management is more often done for the preservation of renal function and less commonly for treatment of hypertension.

Table 10. Surgery is recommended as first line therapy in:

-
- Atherosclerotic ostial renal artery disease
 - Branch renal artery disease
 - Renal artery aneurysm
 - Repair of total renal artery occlusion
 - Extensive renal artery involvement both in FMD and atherosclerosis, especially if present over a length of more than 3 cm
 - Unsuccessful percutaneous transluminal angioplasty
-

To allow for a stepwise approach to bilateral renal artery stenosis or multiple vascular lesions and to avoid operating in a diseased or scarred aorta it is possible to make use of splenic and hepatic arteries for renal revascularisation²³⁵. Complex renal artery lesions can also be reconstructed by extra-corporeal surgery and autotransplantation (workbench procedure)²³⁶.

b. *percutaneous transluminal angioplasty (PTA) and intra-vascular stents*

Since the introduction of percutaneous transluminal angioplasty²³⁷ this procedure has been widely accepted as therapy in renovascular disease. Technically successful PTA is possible in about 90% of patients, with a complication rate of around 9%²¹⁶.

Technical failures or unsuccessful dilatation of the stenosis is usually due to inability to cross the stenosis with a guidewire, to a rigid calcified plaque, or to an ostial lesion^{232,238,239}. However, advances in guidewire and catheter technology have helped to make PTA much safer and more successful not only for stenoses in the main renal artery but also stenoses in branch arteries²⁴⁰.

The maximum benefit of PTA on blood pressure commonly occurs already before the patient is discharged from hospital. Long-term follow-up data also show favourable results²³⁹. However, the overall conclusion of many studies^{216,241} concerning PTA is that the procedure confers clear benefit in fibromuscular disease, but not so much in atherosclerotic lesions.

Considerable improvement in renal function after PTA has been reported by some but in a overview of published series (table 11) Ramsay²¹⁶ found the mean improvement in serum creatinine levels after angioplasty to be only 12 $\mu\text{mol/l}$ and not to be significantly different from the levels before intervention.

Table 11. Overview of angioplasty in 691 patients²¹⁶

-	Technical success rate 84%
-	Overall cure rate 24%
	Atherosclerotic disease 19%
	Fibromuscular disease 50%
-	Overall improved management of hypertension 24%
-	Mean improvement in serum creatinine levels after angioplasty 12 $\mu\text{mol/l}$ and not significantly different from the value before intervention
-	Complication rate 9.1%

PTA has become the treatment of choice for renal artery stenosis. Nevertheless, about 15% of renal artery stenoses cannot be properly dilated and benefit can be limited, especially with ostial lesions²³⁹. In the latter case the technical success is in the range of 20-25%^{242,243} and the frequency of restenosis after a technical successful PTA is 35%²³³.

Since intravascular stents can be incorporated into the arterial wall and remain patent for a long time, balloon expandable stents, are placed in the ostium of the renal artery^{231,244}. The indications for placing a stent in the renal artery are: renal artery ostial lesions, restenosis after successful PTA, artery recoil and artery dissection, for instance after PTA. The first reports in ostial lesions look promising^{234,244-246}, but experience is still limited.

c. *Comparing intervention treatment options*

In comparing treatment modalities for patients with fibromuscular dysplasia Lüscher et al.²⁴⁷ found, that although the three study groups were not strictly comparable the different therapeutic approaches (drug therapy, surgery and PTA) were equally effective in controlling blood pressure. In general, angioplasty gives satisfactory results in fibromuscular dysplasia with an overall cure rate of 50%, but in atherosclerotic renovascular disease this is less than 20%²¹⁶. Since angioplasty is simpler and safer than surgery it is generally accepted as the treatment of choice for atherosclerotic renal artery disease. Although many non-randomized studies report equal efficacy of angioplasty and surgery in atherosclerotic disease²⁴⁸, there is only one recently published prospective randomized study of PTA versus surgery²²⁶. In this study the two approaches were found to be equally effective in controlling blood pressure and the authors recommend angioplasty as first choice with intensive follow-up and aggressive re-intervention in case of restenosis.

Technically, PTA was successful in 83% and operation in 97% of the patients. The primary patency rate after 24 months was 75% in the PTA group and 96% in the operative group in

technically successful cases. Hypertension was cured or improved after additional treatment in 90% of the patients after PTA and in 86% after operation.

In conclusion, both atherosclerotic and fibromuscular renal artery disease are progressive in nature leading to worsening of renal function, particularly in atherosclerotic stenosis of more than 60%. Antihypertensive drug treatment can control blood pressure in the majority of patients with renal artery stenosis but it will not halt the progression of disease. PTA is the treatment of choice both in fibromuscular dysplasia and in atherosclerotic disease but major concerns remain with respect to the treatment of stenoses at the origin of the renal arteries.

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CHAPTER III

COMPARISON OF OFFICE AND SERIAL AUTOMATIC BLOOD PRESSURE READINGS IN RENOVASCULAR AND ESSENTIAL HYPERTENSION

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Journal of Human Hypertension 1992;6:189-191

COMPARISON OF OFFICE AND SERIAL AUTOMATIC BLOOD PRESSURE READINGS IN RENOVASCULAR AND ESSENTIAL HYPERTENSION

SUMMARY

Office blood pressures were compared with those obtained using a thirty minute recording with an automatic device (Dianamap) in thirty patients with essential hypertension and nineteen subjects with hypertension and renal artery stenosis. When matched for age and sex, no differences were found between both group of patients with respect to their office or automatically recorded blood pressures. The difference between office and automatically assessed systolic blood pressure was similar in both groups. The difference in diastolic pressure was slightly larger in the group with renal artery stenosis. The number of patients showing a pressure drop greater than 10 mmHg was comparable in the two groups.

We conclude that blood pressure levels obtained in the office overestimate "true" blood pressure not only in essential but also in renovascular hypertension.

INTRODUCTION

Most studies concerning cardiovascular complications in the course of hypertension are based on office blood pressure readings¹. However, there is increasing evidence that certain abnormalities like left ventricular hypertrophy correlate better with ambulatory than with office blood pressures². Frequently, the latter are higher than average ambulatory pressures, a phenomenon usually referred to as white coat hypertension³. It is often difficult therefore, to assess the severity of hypertension without prolonged measurements.

Whilst 24-hour monitoring of blood pressure may provide a useful index of the total pressure load over a certain period of time, it is not essential to apply such technology for evaluating whether patients display a cuff response, i.e. have higher pressures in than outside the office. Even short term registrations with an automatic device may be sufficient in this respect⁴.

It is often implicitly assumed that a cuff response occurs mainly in patients with essential hypertension, but there is no compelling data to show that the phenomenon is less prevalent in subjects with renovascular hypertension, in whom a more sustained and higher blood pressure might be anticipated⁵. In the present study, therefore, we compared office blood pressure and those obtained during a 30 min. registration with an automatic device in patients with essential or renovascular hypertension.

PATIENTS AND METHODS

Forty-nine consecutive patients who underwent selective renal angiography were included in this study. On angiography 19 of these patients (39%) had significant renal artery stenosis (RAS), which was bilateral in 5 of them. The cause of the vascular lesion was presumed to be atherosclerotic in all subjects. Patients without stenoses were classified as having essential hypertension (EH). Before patients were informed about the angiographic studies the mean of three

systolic and three diastolic readings were measured in supine position at five-minute intervals in the office was recorded in all of them. These pressures were taken after 10 minutes of rest with a mercury sphygmomanometer (cuff size 13 x 32 cm); phase V of the Korotkoff sounds was used for diastolic pressure. Subsequently, supine blood pressure was also assessed at the same arm by means of an automatic device (Dinamap 1846, Critikon, Tampa Fla., USA) for 30 min. at 5 min. intervals on a separate day. The first and average systolic pressure were recorded as well as the first and average diastolic pressure.

Treatment was similar during both sessions in all patients. For each patient we calculated the difference between average office and automatic blood pressure and in both groups of patients the number of individuals with a pressure drop of more than 10 mmHg was counted.

In view of the non-normal distribution of the data results are expressed as median and ranges. For statistical comparison between groups the Mann-Whitney U test was applied. Differences were considered significant when the p value did not exceed 5%.

RESULTS

Median age was higher in patients with RAS as compared to those with EH: 46 (range 22-73) vs 40 (range 16-62) years; $p < 0.05$. RAS occurred more frequently in females (67 vs 35%; $p < 0.05$) and was associated with a lower creatinine clearance: 83 (range 26-140) vs 105 (range 73-141) ml/min; $p < 0.05$. Creatinine clearance correlated inversely with percentage of stenosis ($r = -0.43$; $p < 0.05$).

The mean systolic and diastolic blood pressure in the office as well as the first and average systolic and diastolic blood pressure obtained with the Dinamap were comparable in both groups. However, in order to verify that blood pressure levels are not higher or more sustained in RAS we also compared the nineteen RAS patients with 19 of the essential hypertensive controls, matched for age and sex. As shown in table 1, these two groups did not differ with respect to the duration of hypertension and the number of antihypertensive drugs taken. Moreover, no significant differences were apparent for systolic or diastolic office pressures and for first or average automatic blood pressures. Both groups showed a similar decline in pressure when automatic readings were compared to those obtained in the office and the percentage of patients who dropped their pressure during the half-hour registration by more than 10 mmHg was also similar in both groups. In absolute terms this difference between average office and average automatic blood pressure was greater in patients with renal artery stenosis, although this was statistically significant only for diastolic pressure.

Intra-individual variability of blood pressure recordings was comparable in the two groups. Variations in systolic values during automatic registrations ranged from 7 to 70 mmHg in essential hypertensives and from 113 to 46 mmHg in the others. For diastolic pressure ranges were 5 to 35 mmHg respectively.

None of the differences was statistically significant. Intra-individual variations in office pressure were much smaller but again not different between the groups.

DISCUSSION

Data on blood pressure variability in patients with renovascular hypertension are scarce, but available information suggests a blunted circadian rhythm of blood pressure in patients with renal artery stenosis^{6,7}. However, it is not entirely clear from these studies whether reduced variability relates to the etiology of hypertension or rather to its severity.

Table 1. Duration of hypertension, number of drugs used and blood pressure readings in subjects with RAS and EH (matched for age and sex)

	RAS n=19		EH n=19	
Duration (months)	68	(1-240)	72	(3-240)
Number of drugs*	1	(0-4)	1	(1-3)
OBP systolic	185	(140-290)	184	(140-220)
ABP systolic (first)	163	(146-171)	170	(148-229)
ABP systolic (avg)	153	(120-190)	154	(120-185)
OBP diastolic	111	(80-130)	114	(84-140)
ABP diastolic (first)	95	(78-124)	106	(78-120)
ABP diastolic (avg)	88	(62-120)	96	(77-122)
OBP-ABP (systolic)	28	(5-95)	25	(0-69)
OBP-ABP (diastolic)	30	(10-55)	18	(0-46)
Percentage of patients with a pressure drop > 10 mmHg				
-systolic		77%		70%
-diastolic		85%		70%**

* number of drugs used at first visit; ** $p < 0.05$; OBP=office blood pressure (mean of three readings); ABP=30 minute automatic blood pressure (avg=average of these readings); All blood pressure values represent mmHg; Data are expressed as median with range

The present study did not address the circadian variability of blood pressure but, instead, focused on the fall in blood pressure during a 30 minute registration period with an automatic device, the accuracy of which has been demonstrated⁸. In a way, therefore, we tested for the presence or absence of a cuff response in office. If hypertension is more fixed and sustained in renovascular hypertension than in essential hypertension, one would expect less of a cuff response in the former. However, the results of our study show that neither office nor short-term automatic blood pressure readings discriminate between hypertensives with and without renal artery stenosis. In both groups a similar difference was seen when the two types of recordings were compared and even after matching for age and sex, office and automatic blood pressure levels were comparable in RAS and EH. Moreover, the absolute fall in pressure and the percentage of patients with a pressure drop greater than 10 mmHg tended, if anything, to be enhanced in renovascular patients.

Although these data suggest that hypertension is not more severe in RAS than in EH, the lack of a substantial difference between the two groups with respect to their fall in pressure during automatic recording could simply be due to the fact that they had the same blood pressure to begin with. Nevertheless, our findings do not support the contention that a cuff response is rare in secondary hypertension. Although one should realize that the data are preliminary and taken from a selected patient group, it seems justified to conclude that renovascular patients are as likely as other hypertensives to show a pressor response (or for that matter, white coat hypertension) when confronted with the physician. This is important information, since so far studies on the occurrence of a cuff response have been limited to patients with essential hypertension.

This study reaffirms that casual office readings are unreliable and may lead to overtreatment⁹. The data also have relevance for everyday practice because a search for secondary hypertension often is initiated when office pressures remain elevated despite treatment.

Ambulatory blood pressure readings probably correlate better with complications of hypertension than do office pressures^{2,10}, but larger trials are needed to substantiate this more firmly^{9,11}.

Although the thirty-minute automatic blood pressure readings undeniably give valuable information as to the short term variability of blood pressure, they can not replace 24-hour ambulatory registrations.

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CHAPTER IV

PROSPECTIVE EVALUATION OF THE VALUE OF CLINICAL CLUES FOR THE DIAGNOSIS OF RENAL ARTERY STENOSIS IN HYPERTENSIVE PATIENTS

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submitted

PROSPECTIVE EVALUATION OF THE VALUE OF CLINICAL CLUES FOR THE DIAGNOSIS OF RENAL ARTERY STENOSIS IN HYPERTENSIVE PATIENTS

SUMMARY

In 49 consecutive hypertensive patients in whom a diagnosis of renovascular hypertension is suspected on clinical clues, as is suggested by the Working Group on Renovascular Hypertension, an angiographically controlled study is done into the value of these clinical clues in relation to the final diagnosis either renal artery stenosis (RAS) or essential hypertension (EH) if no renal artery disease was present.

Selecting patients in whom a diagnosis of renovascular hypertension is suspected only on clinical clues resulted in a high prevalence (41%) of angiographically proven RAS and renography will be of minimal value in this population. A positive renography did have the best diagnostic accuracy in those patients who had signs of atherosclerotic disease with a post-test probability test of 78%.

A history of smoking with a diastolic blood pressure above 110 mmHg is a very sensitive clue for renovascular hypertension and the more clinical clues a hypertensive patient has the more likely a diagnosis of RAS should be considered.

All patients (4 out of 20) with more than 3 clinical clues had RAS and patients with the clinical clue "small kidney on ultra-sound" and an additional clinical clue had a 54% probability of RAS, while patients with a "small kidney on ultra-sound" and no additional clinical clue had a 100% probability of not having RAS.

All patients with a diastolic blood pressure >110 mmHg and a history of smoking had RAS on renal angiography.

INTRODUCTION

A major challenge in the work-up of patients with hypertension remains the identification, by means of accurate screening tests, of those with renal artery stenosis (RAS). Patients suspected of having this condition usually are selected for renal angiography on the basis of clinical clues, abnormal results of laboratory investigations or the results of screening tests such as post captopril renography, the "captopril challenge test" and Doppler ultra-sound studies^{1,2,3,4,5,6}. The clinician will combine the outcome of the various investigations and decide whether or not to proceed with a renal angiogram.

Based on a retrospective analysis, the Working Group on Renovascular Hypertension¹ has formulated a number of clinical clues that are suggesting the presence of renovascular hypertension. Although these clinical clues are known for many years now, there are only two studies^{7,8} that included patients on the basis of these clinical clues and then evaluated the accuracy of screening tests.

The aim of the present study was to evaluate prospectively, and angiographically controlled, the value of these clinical clues and their relation to the results of baseline and post-captopril renography in patients in whom a diagnosis of renovascular hypertension is suspected.

PATIENTS AND METHODS

During the period 1992-1993 fifty-three hypertensive patients, who were referred to the Hypertension Clinic for evaluation of their hypertension were selected for renal angiography on the basis of clinical clues only. These clues were adapted from those of the Working Group of Renovascular Hypertension with slight modifications (table 1).

Inclusion was possible for one or more of these clinical criteria; table 2 lists reasons for exclusion.

Table 1. Clinical clues (inclusion criteria)

1	Hypertension with a history of smoking; diastolic pressure above 110 mmHg.
2	Typical systolic-diastolic epigastric, subcostal or flank vascular bruit.
3	Accelerated or malignant hypertension without a history of smoking.
4	Sudden development or worsening of hypertension at any age.
5	Severe hypertension, diastolic pressure above 110 mmHg in young adulthood, or after age of 50 years.
6	Hypertension refractory to appropriate three drug regimen.
7	Sudden worsening of renal function in a hypertensive patient or unexplained impairment of renal function.
8	Unilateral small kidney discovered by any clinical study.
9	Impairment in renal function in response to angiotensin converting enzyme inhibition (reversible raise of creatinine concentration of more than 20 μ mol/l).
10	Extensive occlusive disease in coronary, cerebral, and peripheral circulation.
11	Grade III or IV hypertensive retinopathy.

Table 2. Exclusion criteria

-	Patients under 18 and above 75 years of age.
-	Patients with cardiac decompensation NYHA classification 2, 3 and 4.
-	Female patients who are pregnant.
-	Patients who can not be without ACE-inhibition during a period of 3 weeks or diuretics for 3 days.

Patients with malignant or accelerated hypertension were immediately admitted to hospital and included in this study on admission.

In the others antihypertensive medication, if any, was gradually withdrawn first over a period of 3 weeks. On the day prior to angiography a 60 min. automatic blood pressure registration was obtained by means of a Dinamap 1846 (Criticon Tampa USA). To this end the patient was placed in supine position on a couch and blood pressure was measured every 10 min.; the mean of the last three readings was used for data analysis.

On the same day all patients underwent a Tc-MAG-3 (Technetium 99m-mercaptoacetyl-triglycine) renography at baseline and 2 hours after an oral dose of 25 mg. of captopril (baseline and post-captopril renography).

All renograms were evaluated by the same two nuclear medicine physicians, who were unaware of the angiographic results. Their judgement of the renograms was based on visual interpretation and three well established criteria for the diagnosis of renal artery stenosis (RAS) on post-captopril renography⁹.

In all patients who entered into the study selective renal angiography was performed via the transfemoral route. The renal angiogram was considered positive for renal artery stenosis if a luminal reduction of more than 50% was present¹⁰.

Statistical methods

Statistical methods for comparing groups included the two way t-test for numerical data and the χ^2 test of independence or Fisher's exact test, where appropriate, for nominal data. A $p < 0.05$ was considered statistically significant. The sensitivity, specificity, positive and negative predictive values were calculated according to accepted methods.

The post probabilities of a positive or a negative test were calculated according to Bayes' theorem¹¹.

RESULTS

Of the fifty-three patients who were included in the study four were withdrawn in the period between inclusion and time of angiography, for personal reasons ($n=2$), because of heart failure after myocardial infarction shortly after inclusion ($n=1$) and because angiography could not be performed for technical reasons ($n=1$). Thus, forty-nine patients were left for analysis of whom 20 (41%) appeared to have renal artery stenosis (13 unilateral and 7 bilateral) with an arterial luminal diameter reduction of more than 50% on angiography. The remaining twenty-nine patients had no renal artery disease whatsoever on angiography and they were considered to have essential hypertension (EH) as other forms of secondary hypertension had already been excluded.

The localisation and kind of renovascular disease (atherosclerosis (ATH) or fibromuscular dysplasia (FMD), and gender distribution is given in table 3.

Table 3. Localisation, kind of renal artery disease and gender distribution

	Unilateral	Bilateral	Male/female
Atherosclerosis (60%)	7	5	5/7
Fibromuscular dysplasia (40%)	6	2	3/5
	13	7	

PATIENT CHARACTERISTICS

Clinical characteristics of patients with RAS or EH are given in table 4.

The mean age of patients with RAS tended to be higher than in patients with EH but if patients with FMD are left out of the analysis the difference in age between patients with RAS or EH is statistically significant (66 ± 6 vs 52.0 ± 15 years $p < 0.01$). Mean age was similar in patients with bilateral atherosclerotic RAS and in those with unilateral atherosclerotic disease. Patients with FMD did not differ in age from patients with EH (57 ± 4 vs 52.0 ± 15 years $p = 0.07$).

There was no significant difference with respect to the duration of hypertension, number of anti-hypertensive drugs or number of clinical clues between both groups. Whereas diastolic blood pressure was comparable in the two groups systolic blood pressure was significantly higher in patients with RAS, (178 ± 30 vs 162 ± 16 mmHg $p < 0.05$). There was a statistically significant difference between both groups in the levels of cholesterol (6.8 ± 1.8 vs 5.9 ± 1.0 mmol/L $p < 0.001$). When patients with FMD are left out of the analysis, the differences between the levels of cholesterol (7.5 ± 1.5 vs 5.9 ± 1.0 mmol/L, $p < 0.05$) is even more apparent.

None of the FMD-RAS subjects had vascular complications (CVA, myocardial infarction or claudication).

Table 4. Results of history, number of antihypertensive drugs and laboratory investigations (mean values and ranges) in 20 patients with RAS and 29 patients 29 with EH and significance of difference.

	#20 RAS	#29 EH	Sign
Male/female	8/12	18/11	ns
Mean age (years)	62.5	52.0	p=0.06
Duration of hypertension (years)	6.8	6.8	ns
Number of antihypertensive drugs	2 (1-3)	1 (1-3)	ns
Number of inclusion criteria	2 (1-5)	2 (1-3)	p=0.06
Systolic BP mmHg	178 (149-231)	162 (136-209)	p<0.05
Diastolic BP mmHg	102 (87-119)	103 (75-129)	ns
Left ventricular hypertrophy	5	6	ns
Creatinine level $\mu\text{mol/l}$	111 (62-220)	93 (61-145)	p<0.01
Renal impairment	8	6	ns
Proteinuria	7	7	ns
Serum potassium <3.6 mmol/L	1	1	ns
Cholesterol level mmol/l	6.8 (4.2-10.2)	5.9 (4.2-7.5)	p<0.001
Hypercholesterolemia	8	11	ns
Diabetes mellitus	0	1	ns

Creatinine normal values 53 - 97 $\mu\text{mol/l}$; Proteinuria = more than 300 mg/l

Value of clinical clues

The value of the various clinical clues for the diagnosis of RAS as well as their predictive values are given in table 5. When one considers the diagnostic accuracy of the clinical clues, it is clear that some of these clinical clues, namely history of smoking combined with a diastolic blood pressure >110 mmHg, evidence of extensive atherosclerotic occlusive disease and hypertensive retinopathy grade III and IV have a good positive predictive value of 100% but the negative predictive value of all clinical clues still ranges from 48%-71%.

Table 5. Number of clinical clues in relation to diagnosis in 20 patients with RAS and 29 patients with EH and their positive (PV+) and negative (PV-) predictive value.

Clinical clue	n	RAS present	no RAS present	PV+ %	PV- %
History of smoking;DBP>110 mmHg*	8	8 (100%)	0	100	71
DBP >110 mmHg in young or age>50	22	6 (27%)	16 (73%)	27	48
"Typical vascular bruit"	2	2 (100%)	0	100	62
Accelerated or malignant HT	6	3 (50%)	3 (50%)	50	60
Sudden development/worsening HT	7	3 (43%)	4 (57%)	43	60
Unresponsive to 3 anti-HT drugs	4	3 (75%)	1 (25%)	75	62
Unexplained renal impairment	12	7 (58%)	5 (42%)	58	65
Small kidney on ultra sound	19	7 (27%)	12 (63%)	37	57
Renal function worsening under ACE-Inhibition	2	1 (50%)	1 (50%)	50	60
Extensive occlusive disease	2	2 (100%)	0	100	62
Evidence of ATH disease**	13	10 (82%)	3 (18%)	77	72
Hypertensive retinopathy grade III or IV	2	2 (100%)	0	100	62

* indicates a statistically significant difference between the 2 groups; * p<0.001 ** p<0.01; DBP=diastolic blood pressure

If the clinical clues are clustered in 3 groups i.e. a cluster of hypertensive clues (clues number 3,4,5,6), a cluster of renal impairment clues (clues number 7,8,9) and a cluster of atherosclerosis clues (evidence for atherosclerotic disease in at least one organ) then in relation to the angiographic diagnosis the sensitivity is 70%, 55% and 50% respectively (table 6).

Table 6. Comparison of renography and of clinical clues in relation to the angiographic diagnosis.

Cluster of clues	Hypertensive clues		Renal impairment clues		Atherosclerotic clues	
	renogr	clues	renogr	clues	renogr	clues
Sensitivity	36%	70%	64%	55%	70%	50%
Specificity	68%	24%	62%	41%	67%	90%
+ Pred.value	42%	39%	46%	39%	88%	77%
- Pred.value	63%	54%	72%	57%	40%	72%

renogr. = renogram; clues = clinical clues; pred. = predictive

Analysis of results of renography and their relation to clinical clues

In this study population of hypertensive patients suspected of having renovascular abnormalities the prior probability (prevalence) of RAS is 41% (20 out of 49 patients). Of the 20 patients with RAS, 10 baseline and 10 post-captopril renographies were considered positive and of the 29 patients with EH, 19 baseline and 19 post-captopril renographies were considered negative for renal artery stenosis. Both for baseline and post-captopril renography this resulted in a sensitivity of 50%, a specificity of 66% and a positive and negative predictive value of 50% and 66%.

Given a prior probability of 41% will yield a post-probability of a positive and of a negative baseline or post-captopril renography of 50% and 34% (prevalence of RAS in those with a positive test and in those with a negative test).

Analysis of angiographic data in relation to the different clusters of clinical clues shows baseline or post-captopril renography to have the best accuracy in the atherosclerosis cluster with a post-test probability of 78% for a positive test of 18% for a negative test (table 7).

Table 7. Post-test probability of a positive (PPP) and a negative (PPN) renography result in all 49 patients (prior probability of 41%) and in different clusters of clinical clues

	PPP	PPN
In all patients	60%	31%
Cluster of hypertensive clues	46%	39%
Cluster of renal impairment clues	71%	23%
Cluster of atherosclerotic clues	78%	18%

Major confounders for false positive baseline and post-captopril renographies were a unilateral small kidney without renal artery disease (n=5) and multiple renal arteries (n=5).

Renography versus clinical clues in relation to the angiographic diagnosis

If we compare the results of renography and of clinical clues (as a diagnostic screening procedure) in measuring the diagnostic power in relation to the final angiographic diagnosis (table 6) in different clusters of clues it is clear that clinical clues have a far better diagnostic power than renography.

DISCUSSION

This study shows the different clinical variables and clues in patients with RAS and essential hypertension. A selection of patients only on the basis of clinical clues will yield high prevalence rates of RAS, above 30%^{7,8} and in our patient group 41% which is about 6-8 times higher than the 5% estimated prevalence of RAS in hospital-based surveys^{12,13}.

The prevalence of atherosclerotic vascular complications, renal impairment and hypercholesterolemia in our series in relation to a diagnosis of RAS or EH is fully in agreement with previous reports^{1,2,14}.

Careful interpretation of clinical clues provides valuable information to identify patients in whom further evaluation for RAS is needed. The Cooperative Study on Renovascular Hypertension¹ provided the first large scale study to define the clinical clues suggestive of RVHT. Andersson² analyzed these clinical clues and signs in 3520 patients referred by their physicians for a 1-day blood pressure study to evaluate the presence of secondary forms of hypertension. He found the height of diastolic blood pressure to be a strong indicator for renovascular hypertension but did not relate this clinical clue to a history of smoking.

Elliot⁷ in a comparative study of "captopril challenge test" and captopril renography required that patients in whom a diagnosis of RAS is suspected had at least two clinical clues before angiography of the renal arteries was done.

Others^{8,15} feel that only 1 clinical clue is sufficient to continue with a captopril renography and regardless of this result to do a renal angiography. Our study shows that 25% of patients with proven RAS have only 1 clinical clue and that the most powerful clinical clue is: a history of smoking with a diastolic RR > 110 mmHg. In the Cooperative Study on Renovascular Hypertension¹ this clinical clue was not mentioned but the role of smoking has been emphasized both for patients with FMD and ATH-RAS as a higher frequency of smoking is found among patients with RAS in comparison to age-matched patients with EH^{16,17}.

In our study severe or accelerated hypertension without a history of smoking is not a very reliable predictor of RAS.

Furthermore, we found all patients with more than 3 clinical clues to have RAS.

From the results of our study it is clear that selecting patients in whom diagnosis of renovascular is suspected on clinical clues will yield a high prevalence of RAS and that patients having a history of smoking with a diastolic RR > 110 mmHg, or having more than 3 clinical clues will have a almost 100% probability for RAS and those with a "small kidney" on ultra-sound and more than one clinical clue have a high (>50%) probability for RAS. On the other hand, patients with a "small kidney" on ultra-sound and no additional clinical clue have a very low probability of having RAS. In our study population of patients in whom a diagnosis of renovascular hypertension was suspected and who were selected on clinical clues a high prevalence of RAS was found of 41%.

Given a pre-test prevalence of 41%, the post-test probability of a positive renography increases the prevalence in these patients with a positive test (renography) to 60% while in patients with a negative test result the prevalence decreases to 31%. But as is shown in table 7 the renography best predictive results are in those patients who have signs of atherosclerotic disease where the post-test probability of a positive test is 78% and of a negative test 18%.

Finally, the results of our study show that selecting hypertensive patients in whom a diagnosis of renovascular hypertension is suspected on clinical clues will yield a high prevalence of renal artery stenosis and renography will not add much to this. We found a history of smoking with a diastolic blood pressure above 110 mmHg to be a very sensitive clue for renovascular hypertension and the more clinical clues a hypertensive patient has the more likely a diagnosis of RAS becomes.

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CHAPTER V

RELATION BETWEEN THE DEGREE OF STENOSIS IN RENOVASCULAR DISEASE AND RENOGRAPHIC CHARACTERISTICS

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Journal of Nuclear Medicine

RELATION BETWEEN THE DEGREE OF STENOSIS IN RENOVASCULAR DISEASE AND RENOGRAPHIC CHARACTERISTICS

SUMMARY

Rationale

It is not known at what degree of renal artery stenosis changes in the renogram start to occur. Therefore, the present study was designed to determine from which degree of renal artery stenosis onwards changes in renographic parameters may be found.

Methods

We related the angiographic severity of luminal narrowing in renal artery stenosis to I^{131} -hippuran renographic characteristics in 72 patients who had been selected for renal angiography because a diagnosis of renovascular hypertension was suspected.

Results

Comparing non-stenotic kidneys with stenotic kidneys, significant differences in T_{max} , $T_{1/2}$ and counts under the curve to T_{max} were apparent already at 30% of arterial luminal narrowing. In patients with unilateral renal artery stenosis, the difference in counts under the curve to T_{max} between pairs of kidneys also was significantly different at 30% of stenosis. Patients with bilateral stenosis on the other hand could not be differentiated well from patients with essential hypertension because the value of T_{max} on either side or the difference of T_{max} between the two kidneys and the values of the other parameters were similar except for the difference in counts to T_{max} . On the basis of these findings it seems that in renographic terms bilateral RAS does not "mimic" unilateral stenosis, but rather resembles a normal situation.

Conclusion

It was found that in renal artery disease significant renographic changes can occur already at 30% of arterial luminal narrowing.

INTRODUCTION

Renovascular hypertension is a retrospective diagnosis that can only be made with certainty when correction of the stenosis leads to normalisation or improvement of blood pressure. In the work-up of patients in whom renovascular hypertension is suspected renography is often performed for screening purposes. Accordingly, changes in certain renographic parameters are used to predict the presence of renal artery stenosis (RAS). However, in a meta-analysis Havey¹ found the sensitivity and specificity of screening I^{131} -hippuran renography (without ACE-inhibition) to be only around 75%. It may be that this disappointing result stems from our inability to establish reliably whether a certain degree of stenosis is hemodynamically important.

In the literature there is no consensus about what percentage of renal arterial narrowing should be considered hemodynamically significant. While some authors argue that only stenoses of 75% or more are significant^{2,3,4}, others favour a percentage of more than 50%^{5,6}. There are even reports indicating that correction of a stenosis with a luminal narrowing of less than 50% may cure renovascular hypertension⁷.

From I^{123} -hippuran renography studies in animals it is known that a slight degree of stenosis (25% reduction in renal blood flow) can already bring about changes in renographic parameters⁸. Moreover, in hypertensive man a diminution of 10-30% of renal perfusion pressure is able to activate the renin-angiotensin system⁹. However, to our knowledge, there are no studies in humans that have attempted to determine the smallest degree of renal artery stenosis that may be associated with changes in renographic parameters.

Therefore, we analyzed the data of 72 patients in whom an angiogram was available and related the renographic characteristics in these subjects to the angiographic findings.

PATIENTS, MATERIALS AND METHODS

Seventy-five patients who had been referred to the Hypertension Clinic for evaluation of their hypertension were included in this study. All of them had a diastolic blood pressure above 100 mmHg on at least three occasions and they had been selected for renal angiography because a diagnosis of renovascular hypertension was suspected on clinical grounds, such as those formulated by the Working Group on Renovascular Hypertension¹⁰ or on the basis of I^{131} -hippuran renography. All patients underwent angiography via the femoral approach and they were given 40 ml of contrast material for the aortic films and, if necessary, an additional 10 ml for the selective ones. Abdominal aortic and renal angiograms were taken in the anterior-posterior projection. Oblique projections were performed when deemed necessary to better visualize stenoses or parts of the vasculature that are obscured by superposition of organs⁷.

Prior to the angiographic evaluation patients had undergone renography with 9.3 MBq I^{131} -hippuran according to accepted standard procedures. Images were obtained by means of a gamma-camera with the patient in recumbent position. The appropriate region of interest was chosen over both kidney's with a little amount of tracer. Immediately after I^{131} -hippuran had been administered intravenously counts were recorded every 20 seconds during 20 min and computed¹¹.

Before renography all patients were given 300 ml of fluids to guarantee an urine output of at least 1 ml per min. during the investigations.

For the present study the renal angiograms were assessed together with the I^{131} -hippuran renograms.

The renographic data of patients with a fractional uptake of tracer by a kidney of less than 10% (less than the blood background activity) were excluded from analysis. This was the case in 3 patients who otherwise had a normal renal blood supply on their angiogram.

Evaluation of angiograms

Two radiologists evaluated the angiograms together and formulated their final judgement about the percentage of renal artery narrowing being present. On the films the pre- and post-stenotic renal arterial lumen diameter was measured in millimetres by marking the luminal contours as these were seen with a magnifying glass. The percentage of stenosis was calculated at the point of greatest narrowing by calculating the ratio of normal minus stenotic lumen and normal lumen diameter.

Evaluation of I^{131} -hippuran renography

For the analysis of the renogram the following renographic parameters were used (fig.1):

- a. *the angles of the perfusion phase (PP angle) and of the secretion phase (SP angle).*

As a quantitative parameter for the steepness of the initial upstroke (perfusion phase) and the steepness of the second part of this curve (inclination of the initial curve towards the early part of the secretion phase, which is just before the maximum count rate), the tangents of the respective angles were calculated.

- b. *the fractional uptake of tracer by each individual kidney* was calculated from the total renal counts, during the first 1-3 min. of recording.

- c. *time to maximum count rate (Tmax)* was defined as the time interval from injection to the time of maximum count rate for each of the two kidneys.
- d. *the half time (T_{1/2})* was defined as the time interval from maximum activity above the kidney to the point of half maximal count rate.
- e. *counts to Tmax and total counts* were measured as the area under the curve to Tmax (CTmax) or during the 20 min. of recording (CT20).
- f. *differences in Tmax, T_{1/2}, CTmax and CT20* between the two kidneys were calculated as follows:
 - for normal kidneys: the value of the right kidney minus the value of the left one
 - for unilateral RAS: for Tmax and T_{1/2}, the value of the affected side minus the value of the contralateral side and for CTmax and CT20 the reverse
 - for bilateral RAS: in conformity with unilateral RAS, with the greater stenotic side being considered as the affected one
- g. *ratio CTmax and CT 20* was defined as CTmax or CT20 right kidney/left kidney:
 - for unilateral RAS: affected side/contralateral side
 - for bilateral RAS: in conformity with unilateral RAS, with the greater stenotic side being considered as the affected one.

Figure 1. Different parameters of renography

Analysis of renographic parameters in relation to the degree of stenosis on the renal angiogram

Since the aim of our study was to evaluate, taking the angiogram as starting point, at what percentage of RAS alterations in the renogram would occur, we did not include the visual interpretation of scintigraphic curves and sequential renographic images by nuclear medicine physicians in our analysis. Rather, the renographic parameters were analyzed in relation to the degree of stenosis, as found on the renal angiogram. This was done for three different cut-off points of arterial luminal narrowing (ALN), namely at a luminal narrowing greater than either 20%, 30% or 50%. Each cut-off point represents a degree of luminal narrowing below which a stenosis is considered to be absent.

For instance, an artery with an ALN of 38% is considered to be stenotic in the analyses with cut-off points of 20% and 30% but to be non-stenotic in the analysis with a cut-off point of 50%. We refrained from analysing the data at cut-off points greater than 50% because this would leave too few patients for a meaningful evaluation. Depending on these various cut-off points for each

analysis kidneys with their corresponding renographic parameters were categorized into three groups: no stenosis, unilateral stenosis and bilateral stenosis.

Statistics

The difference in age between patients with or without renal artery disease was compared with the two way t-test. The various renographic parameters at the different cut-off points of ALN were compared with a Mann-Whitney U test or a Kruskal-Wallis test.

To determine at which degree of ALN significant renographic changes would occur, discriminant analysis was performed. For this type of analysis the degree of ALN was taken as the independent variable and the different renographic parameters were considered as dependent variables; significance was determined with Wilks' lambda test.

Results are expressed as medians and ranges. A $p < 0.05$ was considered to denote statistical significance.

RESULTS

Patient characteristics

Of the 75 patients included in the study three were subsequently excluded because the fractional uptake of tracer in one of their kidneys was less than 10%. Forty-five patients with no renal artery disease were considered to have essential hypertension (EH) as other causes of hypertension had already been excluded. Their kidneys were classified as normal. Twenty-seven patients had RAS and their final angiographic diagnosis included unilateral RAS ranging from 14%-99% in 18 patients and bilateral RAS with a luminal narrowing ranging from 17%-90% in 9 patients.

Of the 36 stenosed arteries, 31 were diagnosed as being atherosclerotic of origin while the remainder demonstrated fibromuscular dysplasia. The cause of bilateral disease was atherosclerosis except for one case.

The clinical characteristics of patients with EH and RAS are given in table 1.

Age in the entire group ranged from 22 to 73 years; the median age in patients with renal artery disease was not different from that in patients with EH. Systolic and diastolic blood pressures were similar in both groups. RAS was associated with a lower creatinine clearance, ($p < 0.05$) which correlated inversely with the percentage of ALN ($r = -0.43$, $p < 0.05$).

The number of patients with no stenosis, unilateral or bilateral stenosis at the different cut-off points of ALN are given in table 2.

Table 1. Patient characteristics, median and ranges.

	Essential hypertension n=45	Renal artery stenosis n=27
Male/female	26/19	14/13
Age (year)	42 (28-69)	47 (22-73)
Body surface area (m ²)	1.8	1.8
Systolic BP	184 (140-220)	185 (140-290)
Diastolic BP	114 (84-140)	111 (80-130)
Creatinine clearance (ml/min)	105 (73-141)	83 (26-140)*

BP = blood pressure; * = significantly different from essential hypertension $p < 0.05$

Table 2. Number of patients with no stenosis, unilateral stenosis or bilateral stenosis when different cut-off points of ALN are used for the diagnosis of stenosis.

Cut-off point for ALN	No stenosis	Unilateral stenosis	Bilateral stenosis	Total number
20%	49	16	7	72
30%	52	16	4	72
50%	58	11	3	72

Analysis of the renograms

PP angles and SP angles

For patients with EH (normal kidneys), the values for the PP angles and SP angles ranged from 70° to 89° and from 35° to 84° respectively. The median value for the PP angle was 82°, both for the left and the right kidney with an average difference between left and right kidney for this variable of less than one degree. Median values of the SP angle were 69° on the left side and 68° on the right with a median difference of less than two degrees between the two kidneys.

For patients with RAS, the values for the PP angles and SP angles ranged from 50° to 89° and from 28° to 87° respectively. At the different cut off points of ALN (20%, 30%, 50%) the median values for the PP angles of stenotic kidneys were 82°, 83° and 82°; for SP angles these values were 63°, 64° and 67°.

There were no significant differences between normal and stenotic kidneys with respect to their PP or SP angles. Moreover, values of PP and SP angles were not related to the degree of stenosis.

Fractional uptake of tracer by each individual kidney

The fractional uptake of tracer by normal kidneys (patients with EH), expressed as a percentage of total renal uptake, ranged from 33% to 67%; when leaving those patients with an abnormal creatinine clearance i.e. below 100 ml/min, normalized for 1.73 m² body surface area out of the analysis, the fractional uptake ranged from 43-58% (both, median 50%) with on average no significant difference between the value of the left kidney and that of the right one.

In patients with RAS the fractional uptake ranged from 13% to 87% (median in unilateral RAS 48%, in bilateral RAS 50%). Based on the analysis per group of kidneys, a significant difference in uptake was found at a cut-off point for ALN of 50% between the various groups of kidneys: 50% (range 33-87%) for non-stenotic kidneys, 44% (range 14-65%) for stenotic kidneys and 53% (range 13-80%) for kidneys contralateral to a stenotic one. Compared to normal kidneys (either normal or contralateral) fractional uptake was significantly reduced in stenotic kidneys ($p < 0.01$), although it should be stressed that there were several kidneys with a normal fractional uptake.

Time intervals: Tmax and T½

a) Tmax

In patients with EH no statistical difference was found in Tmax values between the left and the right kidney (medians 192 and 216 sec.; range: left side 90 to 528 sec., right side 72 to 480 sec.).

In patients with RAS, median Tmax of the affected kidneys was 228 sec. (median in uni-lateral RAS 228, range 72-1038 sec.; median in bi-lateral RAS 198 sec., range 72-378 sec.) and on the contralateral side 210 sec. (range 102-1038 sec.).

Median values and ranges of Tmax and T½ for different cut-off points for ALN are presented in table 3.

Significant differences in Tmax were found at the various cut-off points for ALN: comparing non-stenotic with stenotic kidneys at 20%, $p < 0.05$, at 30%, $p < 0.05$, at 50%, $p < 0.05$ and comparing contralateral with stenotic kidneys only at 30%, $p < 0.05$.

In patients with EH the median value of the difference in Tmax between the two kidneys was

12 sec (range -240 to 348 sec.) which was not significantly different from both groups of patients with RAS. This was true at all cut-off points for ALN.

b) $T\frac{1}{2}$

In all normal kidneys, no statistical difference was found in $T\frac{1}{2}$ values between the left and the right side (medians 272 and 276 sec, range, left side 20 to 498 sec., right side 20 to 482 sec). At a cut-off point of 50% stenosis there was a significant difference between groups of kidneys (for non-stenotic vs stenotic vs contralateral kidneys 282 vs 603 vs 300 sec. respectively; $p < 0.05$). When comparing non-stenotic kidneys with all stenotic kidneys, a significant difference for $T\frac{1}{2}$ was found at cut-off points for ALN of 30% ($p < 0.05$) and 50% ($p < 0.01$) (see table 3). The median difference in $T\frac{1}{2}$ between two kidneys in patients with EH is 48 sec. (range 6 to 708 sec.) and in patients with RAS 120 sec. (range 160 to 346 sec.). Right minus left differences in $T\frac{1}{2}$ were similar in the various groups of patients at the different cut-off points for ALN.

When the ALN as seen on the angiogram is taken as a starting point, the renographic data come out as follows:

- 1) In patients with unilateral stenosis the absolute Tmax on the stenotic side is a better indicator of RAS when it is compared to the Tmax of normal kidneys than when it is compared to that of the contralateral kidney of the same patient.
- 2) In patients with bilateral stenosis the value of Tmax on either side or the difference of Tmax between the two kidneys is in no way different from that in patients with EH.

Table 3. Median values and ranges of Tmax and $T\frac{1}{2}$ in sec. at different cut-off points for ALN for diagnosis of stenosis

Cut-off point for ALN	Non-stenotic kidneys		Stenotic kidneys		Contralateral kidneys	
	Tmax	$T\frac{1}{2}$	Tmax	$T\frac{1}{2}$	Tmax	$T\frac{1}{2}$
20%	204 72-1074	279 6-1038	222* 72-1038	474 72-1128	195 72-822	366 60-960
30%	204 72-1074	271 6-1038	237* 72-1038	474* 72-1128	180** 72-822	402 60-960
50%	210 72-1074	282 6-1038	222* 72-1038	603* 72-1128	159 72-342	300 60-960

* $p < 0.05$ as compared to non-stenotic kidneys; ** $p < 0.05$ as compared to stenotic kidneys

Counts to Tmax and total counts; CTmax and CT20

a) CTmax

The median CTmax in normal kidneys was 235.10^6 counts (range 61.10^6 to 952.10^6) and 153.10^6 in stenotic ones (range 41.10^6 to 1877.10^6) (median in uni-lateral RAS 164.10^6 and in bi-lateral RAS 135.10^6).

At a cut-off point for ALN of 50%, a significant difference was found between groups of kidneys (non-stenotic vs stenotic vs contralateral, 236.10^6 vs 130.10^6 vs 211.10^6 , $p < 0.05$). When comparing CTmax of non-stenotic kidneys with all stenotic ones, a significant difference was already found at a cut-off point for ALN of 30% (234.10^6 vs 143.10^6 , $p < 0.05$) and this difference was more apparent at a cut-off point for ALN of 50% ($p < 0.01$).

In patients with EH the median of the difference in CTmax between both kidneys is -27.10^6 (range -245.10^6 to 120.10^6). In patients with RAS this was 6.10^6 with a range of -332.10^6 to 351.10^6 (median 4.10^6 in uni-lateral RAS and 14.10^6 in bi-lateral RAS). At a cut-off point for

ALN of 30% the difference in CTmax between pairs of kidneys was significantly different between groups of patients, in patients with EH, unilateral RAS and bilateral RAS respectively (-25.10^6 vs 6.10^6 vs 57.10^6 , $p < 0.05$) This difference became more significant at 50% ALN.

b) CT20

The median of the total counts in normal kidneys was 259.10^6 (range 59.10^6 to 1930.10^6) and in stenotic kidneys 235.10^6 (range 26.10^6 to 2799.10^6) with a median of 324.10^6 in uni-lateral RAS and of 201.10^6 in bi-lateral RAS.

There were no significant differences between normal and stenotic kidneys with respect to their CT20 or between groups of patients at the different cut-off points for ALN.

c) ratio's CTmax and CT 20

For patients with EH (normal kidneys), the median value of the ratio's for CTmax and CT20 were 0.96 (range 0.72-1.46) and 0.90 (range 0.77-1.49) respectively. In patients with RAS the median value of the ratio's for CTmax and CT20 were 1.07 (range 0.18-3.74) and 1.11 (range 0.16-4.00) respectively.

There were no significant differences between patients with EH or patients with RAS with respect to ratio's of CTmax and CT 20 at the different cut-off points for ALN.

DISCUSSION

In the visual interpretation of renographic studies the angle and steepness of the first part of the renographic curve are often considered to be important parameters for the diagnosis of RAS, in particular after ACE-inhibition¹². However, these two angles have hardly been studied as a quantitative parameter in relation to RAS. Our data demonstrate these parameters to be insensitive for the diagnosis of uni- or bilateral RAS.

Fractional uptake of I^{131} -hippuran can vary considerably in patients with EH¹³ but it is a sensitive criterion for the diagnosis of RAS^{14,15} as is also confirmed in our study although at a ALN of 50%.

Our analysis of renographic data in relation to the degree of arterial luminal reduction indicates, that if changes in renographic parameters occur, they tend to do so already at an ALN of 30%. In particular, with this degree of stenosis significant differences in time intervals (Tmax and $T_{1/2}$) and total counts under the curve to Tmax (CTmax) between non-stenotic and stenotic kidneys were seen. Fractional uptake of tracer was significantly different between groups of kidneys (non-stenotic vs stenotic vs contralateral) at luminal narrowing of 50%. Thus, the results of the present study suggest that renographic changes occur relatively early in renal artery stenosis. However, a prospective study will be necessary to evaluate whether such changes in the renogram can be used for screening patients for RAS.

The Tmax and $T_{1/2}$ are sensitive renographic parameters and together with the CTmax and the difference in CTmax between the two kidneys, these parameters probably give maximum differentiation between patients with EH and those with RAS. A prolonged Tmax seems to be a highly specific predictor of the blood pressure response after interventional therapy¹⁶.

In our analysis, patients with bilateral stenosis could not be differentiated well from patients with EH except for the difference in counts to Tmax. On the basis of the present findings we feel that renographically bilateral RAS does not "mimic" unilateral stenosis, but, contrary to the literature^{17,18} rather resembles a normal situation.

In conclusion, our study to determine at which degree of renal artery stenosis changes in renographic parameters occur, indicates that renographic changes occur already at 30% of arterial narrowing and this finding may plea for early intervention.

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CHAPTER VI

INTERPRETATION OF CAPTOPRIL RENOGRAPHY BY NUCLEAR MEDICINE PHYSICIANS

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Journal of Nuclear Medicine

INTERPRETATION OF CAPTOPRIL RENOGRAPHY BY NUCLEAR MEDICINE PHYSICIANS

SUMMARY

Rationale

Different investigators may show considerable variation in their interpretation of renograms. The present study, therefore, was designed to assess the intra- and inter-observer variability and diagnostic accuracy of nuclear medicine physicians in their evaluation of baseline and captopril renograms.

Methods

The diagnostic performance of three experienced nuclear medicine physicians with respect to their interpretation of baseline, captopril and paired renograms was assessed. To this end, the readers evaluated the renograms of 28 hypertensive patients in whom a diagnosis of renovascular hypertension was suspected on the basis of clinical clues. All patients also underwent angiography. The readers were unaware of the angiographic diagnosis.

Results

Thirteen of the 28 patients proved to have renal artery stenosis (8 unilateral and 5 bilateral) on renal angiography. The concordance in the renographic diagnoses between the three readers was reasonably good, with an intra-observer agreement and κ (observed agreement corrected for chance) ranging from 64%-89% and from 0.52-0.75 respectively and an inter-observer agreement and κ ranging from 68%-86% and from 0.61-0.82.

However, the sensitivity of their interpretation of paired baseline plus captopril renograms in relation to the angiographic diagnosis is poor and below 50%.

The post-test probability of RAS in case of a negative renographic study was found to be rather similar to the pre-test probability (prevalence) of 46%. The post-test probability of RAS when the paired renogram was positive increased to around 60% when the readers were blinded as to which renogram was the one after captopril but decreased below 25% when they were aware of which of the two renograms was obtained after captopril.

Conclusions

The intra- and inter-observer agreement between experienced nuclear medicine physicians who evaluate renograms was found to be reasonably good. The sensitivity and post-test probability of their renographic diagnosis in relation to the angiographic diagnosis, however, was rather poor. Blinding readers as to which renogram is the pre- and post captopril image seems to enhance their diagnostic accuracy in case of positive scans.

INTRODUCTION

Physicians often have to rely on the results of diagnostic tests that indicate the presence or absence of a disease or of an abnormal function. The interpretation of such tests, however, may show considerable bias and, hence, different investigators may not agree on their final diagnosis.

A common strategy to establish the reliability of a diagnostic test is to measure intra- and inter-observer variability by asking one or more observers to evaluate the same test at two separate

occasions. With this approach, the observed agreement for two cardiologists who examine the same electrocardiogram of different patients may be 57% with a kappa (κ)-value (observed agreement corrected for chance) of 0.3¹, whilst a 97% agreement with a κ -value of 0.67 for two radiologists examining the same set of mammograms may be found².

To determine the level of intra- and inter-observer agreement with respect to the renographic diagnosis of renal artery stenosis (RAS) in patients in whom there is a high clinical suspicion for this abnormality, we evaluated the visual interpretations of baseline and captopril renograms by three experienced nuclear medicine physicians.

In addition, we studied the accuracy of their renographic diagnosis in relation to the results of renal angiography, the gold standard³.

PATIENTS AND METHODS

Twenty-eight consecutive hypertensive patients in whom renovascular hypertension was suspected on clinical grounds⁴ underwent 99m Tc-MAG-3 (Technetium 99m-mercaptoacetyltriglycine) renography at baseline and 2 hours after an oral dose of 25 mg. of captopril.

Before renography all patients were given 300 ml of fluids to guarantee an urine output of at least 1 cc per min. during the investigations. Subsequently, renal angiography was performed in all patients irrespective of the renographic diagnosis.

The baseline and captopril renograms of all 28 patients were evaluated during two rounds by three independent nuclear medicine physicians (readers). They were unaware of the final angiographic diagnosis.

During the first round the readers evaluated the images twice, 6 weeks apart and without knowing which one of the two renograms had been obtained after captopril.

The data from this evaluation round were used to assess intra- and inter-observer agreement.

During the second round they were asked to evaluate the same set of renograms paired-wise while the pre- and post-captopril images were indicated as such.

The data from this second evaluation round were used to assess the accuracy of the renographic diagnoses in relation to those based on the results of renal angiography.

This was done because in routine clinical practice, the nuclear medicine physicians will know which renogram is obtained at baseline and which after captopril. Nevertheless, we used the data from both evaluation rounds to assess whether blinding the readers had any impact on their diagnostic accuracy.

For the evaluation of the renograms, the nuclear medicine physicians had the sequential renographic images, the renographic curves and the value of such variables as fractional uptake, time intervals, total counts and integrated counts at different time intervals at their disposal. Their conclusions were based on visual interpretation as well as on 3 well-established criteria for diagnosing RAS as they have been formulated for a post-captopril DTPA renogram⁵; in the present study these latter criteria were adopted for Tc-MAG-3 renography, i.e.:

- percentage uptake of Tc-MAG-3 by one kidney less than 40% of the total uptake
- delayed time to peak uptake of TC-MAG-3 in the affected kidney, by more than 5 minutes
- delayed excretion of Tc-MAG-3, with retention at 15 minutes, as a fraction of peak activity by more than 20% as compared to the contralateral kidney.

Each time the readers reported their diagnosis on a three-point scale on which they had to state the probability of RAS being present: low (<50%), intermediate (50%-75%) or high ($\geq 75\%$). No objective criteria were formulated for these three categories. If, in their opinion, this probability was greater than 50% (intermediate and high probability), they also had to indicate on which side they thought the stenosis to be present.

During the first round the readers also had to state which one of the two renograms was the one obtained after captopril.

When a patient had no angiographic abnormalities, the correct renographic diagnosis had to be: less than 50% (low) probability of RAS being present. When unilateral or bilateral stenosis was found on angiography, the correct renographic diagnosis was the one that indicated an intermediate or a high probability for the presence of RAS. Furthermore, in unilateral stenosis the correct side had to be indicated. For bilateral stenoses on the angiogram the correct renographic diagnosis was either bilateral or unilateral stenosis.

Statistical analysis.

Calculations were made for observed agreement (OA) and κ (observed agreement corrected for chance agreement) as parameters for both intra- and inter-observer variability⁶. Inter-observer variability was calculated on the basis of the presumed probability level for the presence of RAS as indicated by the readers on the three point scale (low, intermediate and high).

To determine the intra-observer variability the results of the two evaluations of renograms during the first round were compared; intra-observer variability was again calculated in terms of OA and κ .

Sensitivity, specificity, positive and negative predictive values and likelihood ratio's were calculated according to accepted methodology⁶.

Likelihood ratio's were calculated only for probability levels of $\geq 50\%$ (intermediate and high) as indicated by the reader. The positive and negative likelihood ratio's of each individual physician were added and divided by 3 and these average values were used to calculate the post-test probability of a positive and a negative renogram according to Bayes's theorem⁷. In this way a comparison is made between the pre-test and the post-test probability of angiographically proven RAS in patients with a negative or a positive renogram.

RESULTS

Thirteen patients proved to have RAS (8 unilateral and 5 bilateral) as defined by more than 50% luminal reduction on angiography³ while 15 patients had normal renal arteries and were diagnosed as having essential hypertension (EH).

Intra- and inter-observer variability for the renographic diagnosis

The data from the first evaluation; where readers did not know which was the baseline and which the post-captopril renogram were used to assess intra- and inter-observer variability.

The result are summarized in tables 1 and 2.

a. *intra-observer agreement (table 1)*

Among the 3 physicians the intra-observer agreement for baseline and captopril renograms varied from 64-89%, with a κ ranging from 0.52-0.75. The data for captopril renograms did not differ significantly from those for the baseline renograms. When renograms of patients with bilateral stenosis were removed from the analysis the intra-observer agreement and κ for baseline and captopril renograms ranged from 35%-70% and from 0.25-0.70 respectively. With respect to the choice which of the two renograms was the one after captopril, the correctness of choice varied from 71-96% with a intra-observer agreement ranging from 46-93%.

Table 1. Intra-observer agreement (OA) and κ for renographic diagnosis by 3 nuclear medicine physicians (A,B, and C) * = intra-observer agreement with respect to the choice which one of the two renograms was the one obtained after captopril. The readers were unaware as to which one of the renograms had been obtained after captopril.

Intra-observer agreement	A	B	C
OA for 28 baseline renograms	71%	89%	82%
OA for 28 captopril renograms	64%	79%	79%
OA for all 56 renograms	68%	84%	79%
κ for all 56 renograms	0.52	0.75	0.65
OA on type of renogram*	46%	68%	93%

b. inter-observer agreement (table 2)

Between the 3 different readers the observed agreement and κ ranged from 68%-86% and from 0.61-0.82 respectively for the evaluation of baseline renograms at an intermediate diagnostic probability level. These figures improved to 96-100% and 0.95-1.0 respectively when the reader was convinced of a high probability for RAS to be present. A similar pattern is seen for the captopril renograms where the observed agreement and κ ranged from 64%-78% and from 0.57-0.74 respectively at the intermediate probability level and from 93-96% and 0.91-0.95 respectively when the investigator was convinced of a high probability of RAS being present.

Results of measurements of inter-observer agreement tended to be slightly but not significantly better when renograms of patients with bilateral stenosis were removed from the analysis.

Table 2. Observed agreement (OA) and κ of the renographic diagnosis of MAG-3 baseline and captopril renograms by 3 readers at different levels of probability of RAS being present (interm = intermediate level, high = high level).

The readers were unaware as to which one of the renograms had been obtained after captopril.

Baseline renogram	OA interm	OA high	κ interm	κ high
A vs B	82%	96%	0.78	0.95
A vs C	68%	100%	0.61	1.0
B vs C	86%	96%	0.82	0.95
Captopril renogram	OA interm	OA high	κ interm	κ high
A vs B	78%	96%	0.74	0.95
A vs C	64%	96%	0.57	0.95
B vs C	75%	93%	0.69	0.91

Renographic versus angiographic diagnosis

The results of the evaluation of the paired renograms (baseline plus captopril) in relation to the angiographic diagnoses are presented in table 3.

In this study, the prevalence of renal artery stenosis proved to be 46%. When renographic diagnoses of the individual physicians are compared with the gold standard (angiography) the results were as follows:

First evaluation round (readers blinded as to which of the two renograms was obtained after captopril).

For renographic diagnosis with an intermediate probability the sensitivity was less than 50% (range 8-46%) with a specificity above 65% (range 67-93%). When only diagnosis with a high probability

level were taken into account sensitivity decreased to values below 20% with a specificity approaching 100%.

On average, positive and negative predictive values of the paired renograms were 63% and 58% respectively at the intermediate probability level; both predictive values improved to values above 75% at a high diagnostic probability level.

Table 3. Different statistical parameters of the renographic diagnosis of baseline, captopril and paired renography at intermediate level of probability of RAS being present in relation to renal angiography.

Renography	Physician A	Physician B	Physician C
Baseline*			
Sensitivity	46%	23%	8%
Specificity	80%	93%	93%
PV ⁺	67%	75%	50%
PV ⁻	63%	58%	54%
Captopril*			
Sensitivity	38%	38%	15%
Specificity	67%	87%	93%
PV ⁺	50%	71%	67%
PV ⁻	56%	62%	56%
Paired images**			
Sensitivity	9%	23%	23%
Specificity	47%	40%	33%
PV ⁺	20%	25%	23%
PV ⁻	39%	62%	67%

* = readers unaware as to which is the baseline or captopril renogram; ** = readers aware as to which is the baseline or captopril renogram; PV⁺ and PV⁻ = positive and negative predictive value.

Second evaluation round (readers knew which of the two renograms was taken after captopril).

The average sensitivity (both at an intermediate and at a high level of probability) was below 25% (range 5-25%) with an average specificity below 50% (range 25-57%).

During both evaluations rounds the three physicians agreed in their renographic diagnoses in 46%-75% of the cases. When these cases where there was complete concordance between the readers were considered separately, the average sensitivity in relation to the renal angiographic diagnosis was below 30% (8-36%) with an average specificity below 60% (48-67%).

In this patient sample the pre-test probability of angiographically proven RAS is 46%. Given an average calculated positive likelihood ratio of 2.2 during the first (blinded) round and 0.3 during the second round, the post-test probability of a positive renography comes out at levels of around 60% and below 25% respectively.

The post-test probability of a negative test (average likelihood ratio of 1.1 and 2.3) resulted in a post-test probability during both rounds of around 45%, which is close to the pre-test probability.

DISCUSSION

In the work-up of hypertensive patients in whom a diagnosis of renovascular hypertension is suspected, captopril renography alone or a paired study (combination with a baseline investigation) is considered to be an essential diagnostic test. However, no well-established criteria have been formulated for a positive test result^{5,8,9,10}. Different renographic studies use different criteria to

define a positive test or do not define such criteria at all¹¹. Moreover, criteria validated for DTPA renography^{5,8,9} do not necessarily hold for MAG-3 renography. Apart from renographic patterns (the so called visual interpretation), the most widely used scintigraphic parameters in renography are uptake, time to peak, peak activity and residual activity^{5,8,9,10}. Thus, considerable variability may exist in the interpretation of test results and accuracy may not always be guaranteed.

In the present study, we determined the level of agreement between three experienced nuclear medicine physicians with respect to their renographic diagnoses, both in terms of intra- and inter-observer variability and as an index of accuracy in relation to the final angiographic diagnoses.

The intra-observer agreement and κ for the renographic diagnoses ranged from 64%-89% and from 0.52-0.75 respectively for both baseline and captopril renography.

As far as the inter-observer variability is concerned, both for baseline and captopril renograms, we found the observed agreement and κ , to range from 68%-100% and from 0.61-1.0 at different levels of probability.

This is relatively good in comparison with other examples in the literature of clinicians interpreting diagnostic tests^{12,13}. In the blinded evaluation the agreement on the type of renogram (baseline or captopril) varied from 71%-96% with an intra-observer agreement, ranging from 46-93%.

There were no major differences between the three nuclear medicine physicians with respect to their diagnostic accuracy and all three performed better when they thought RAS to be present with a high probability level. However, overall the sensitivity of the physicians interpretation of the paired renograms as verified by renal angiography was rather low and less than 25%.

Moreover, the sensitivity did not improve even when the three physicians agreed about the diagnosis.

Given a 46% pre-test probability (prevalence) of angiographically proven RAS in our patient population the post-test probability of a negative renographic study is close to the pre-test probability of 46%.

Therefore, the value of a negative renogram in the work-up of these patients is nil. In case of positive renographic study the figures differ depending on whether readers are blinded or not as to which renogram is the one obtained after captopril. Whereas the post-test probability of RAS being present fell below 25% in the open session, it was increased to 60% in the blinded evaluation. Apparently, therefore, nuclear medicine physicians tend to perform better when they do not know which is the baseline and which the captopril renogram.

Thus, it may be that a priori knowledge of the captopril-induced changes may introduce diagnostic bias. Although one of the conclusions from this study may be that the diagnostic accuracy of nuclear medicine physicians with respect to the renographic studies need improvement, one could equally well argue that the criteria to define a positive or negative MAG renography need to be scrutinized.

Finally, we have to bear in mind that a diagnosis of renal artery stenosis in a hypertensive patient does not necessarily mean that the patient has renovascular hypertension. In clinical practice however, captopril renography is being used to screen patients for angiography. Therefore, the study was designed simply to assess how nuclear medicine physicians differ with respect to the renographic diagnosis.

In conclusion, the results of our angiographically controlled study of the diagnostic performance of three nuclear medicine physicians in their interpretation of renograms indicate that the intra- and inter observer agreement is reasonably good but that their interpretation of the renogram shows poor sensitivity and post-test probability in comparison to the angiographic diagnosis. Blinding the reader as to which renogram is the pre- and post captopril image results in a better diagnostic accuracy for positive scans. Taking all data together, we suggest not to perform renographic studies in the work-up of hypertensive patients in whom a diagnosis of renovascular hypertension is already strongly suspected on the basis of clinical clues.

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CHAPTER VII

COMPARISON OF BASELINE AND POST-CAPTOPRIL RENAL BLOOD FLOW MEASUREMENTS AS DETERMINED WITH FIRST-PASS RADIONUCLIDE ANGIOGRAPHY IN HYPERTENSIVE PATIENTS SUSPECTED OF HAVING RENAL ARTERY STENOSIS.

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provisionally accepted Journal of Nuclear Medicine

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SUMMARY

In 48 hypertensive patients in whom a diagnosis of renovascular hypertension was suspected on clinical grounds, an angiographically controlled prospective study was performed to determine whether renal blood flow measurements using first-pass radionuclide angiography with 99m-Tc-MAG-3 could be helpful in the diagnostic work-up of these patients.

Data from 29 patients with normal renal arteries and 19 patients with uni- or bilateral renal artery stenosis were analyzed.

In patients with normal kidneys the mean value of renal blood flow (RBF) measurements ranged from 10.5% to 10.9% of cardiac output (CO). Only small stenotic and small kidneys with normal renal arteries showed a significant reduced baseline RBF as compared with normal kidneys (both $p < 0.05$); this difference disappeared after ACE-inhibition only for small kidneys with normal renal arteries.

In patients with stenosed kidneys RBF tended to be reduced both at baseline and after captopril, but the differences with normal kidneys were not statistically significant.

After ACE-inhibition RBF increased in the majority of kidneys, but post-captopril RBF data did not differ significantly from those at baseline.

We conclude that RBF measurements using first-pass radionuclide angiography with 99m-Tc-MAG-3 either before or after ACE-inhibition cannot reliably discriminate between patients with essential hypertension and patients with renal artery stenosis.

INTRODUCTION

In 1987, Peters et al.¹ described a technique for noninvasive measurement of organ blood flow, which was based on the fractional distribution of cardiac output (CO). When applied to the renal circulation, this method yielded values of renal blood flow that were similar to accepted normal values. Using 99m-Tc-DTPA as tracer the investigators estimated renal blood flow (RBF) in normal subjects to be $10.4 \pm 1.2\%$ of CO for the left kidney and $9.0 \pm 1.1\%$ of CO for the right one. There was a consistent difference of about 1.5 % of the CO at the expense of the right kidney, a phenomenon which was attributed to interference with uptake of tracer by the spleen¹.

Both in patients with essential hypertension (EH) and in those with renal artery stenosis (RAS) renal blood flow may be reduced, although in the latter category of patients no correlation between the reduction in flow and the angiographic grading of the stenosis is apparent². However, in RAS the RBF usually is reduced only on the affected side and a further decrease may occur after ACE-inhibition³. Therefore, the measurement of individual kidney flows may reveal whether a renal artery stenosis is present or not. Since Peters and coworkers performed their studies with DTPA, which is a marker for glomerular filtration, it may be speculated that the use of MAG-3, an agent that is excreted both by glomerular filtration and tubular excretion⁴, will improve the diagnostic yield of the measurements. Thus, the present study was designed to evaluate prospectively whether in hypertensive patients in whom a diagnosis of renovascular hypertension is suspected, measure-

ments of RBF from first-pass radionuclide angiography, at baseline and 2 hours after ACE-inhibition, are able to detect renal artery stenosis.

PATIENTS AND METHODS

Forty-eight consecutive patients in whom a diagnosis of renovascular hypertension was suspected on clinical grounds⁵ and in whom antihypertensive medication had been discontinued for at least two weeks were included in this study. In all of them 99m-Tc-MAG-3 measurements of RBF by first-pass radionuclide angiography¹ were performed on two separate days. In random order on one of these days baseline data were obtained while on the other RBF was determined two hours after the patients had been given an oral dose of 25 mg. of captopril. Patients remained supine during the entire investigations. Before RBF measurements, all patients were given 300 ml of fluid to guarantee an urine output of at least 1 ml per min.

A bolus volume of about 1 ml. saline solution containing 148 MBq 99m-Tc-MAG-3 was given followed by rapid flushing with saline according to standard procedures⁷. Regions of interest (ROI) over the relevant organs (left and right kidney, right lung, left ventricle and abdominal aorta) were drawn and their time-activity curves were integrated and calculated according to the Peters method¹. During the second measurement of RBF the same ROI corrected for depth over the kidneys were used. The RBF was calculated as percentage of CO as computed over the right lung (RBF/CO-L), the left ventricle (RBF/CO-LV) and the abdominal aorta (RBF/CO-A)^{1,6}.

In all patients an ultrasound examination of the kidneys and renal angiography was performed. Renal angiograms were analyzed according to accepted methods⁸. In patients with RAS the degree of luminal narrowing was determined by calculating the ratio of the luminal diameter at the point of greatest stenosis and at the normal part of the artery as seen on angiography. A luminal reduction of more than 50% was considered to denote a significant renal artery stenosis.

In patients with EH sometimes small kidneys are found that have a normal blood supply. To account for this phenomenon the pole-to-pole length of each kidney was measured during ultrasonography. A kidney was classified as small when the contralateral kidney exceeded its size by 10% and no abnormalities were seen on angiography.

Renal function was assessed by plasma creatinine levels.

Statistical Analysis

The analysis of RBF measurements was performed per group of kidneys, i.e. normal and small kidneys in patients with EH and stenotic and contralateral kidneys in patients with RAS.

For group comparisons the two way t-test and the Mann Whitney-U test were applied while changes in RBF after captopril were analyzed by the paired t-test. Frequencies in different groups were compared with Fischer's exact test.

A comparison of the number of kidneys in each group with an increase or decrease in RBF after captopril of more than 2% of CO was performed. This percentage is similar to the mean increase in RBF induced by ACE inhibition as has been found by Peters² in stenotic kidneys. In this way one may get an impression about the number of kidneys with a substantial change in RBF.

Data are expressed as means $\pm$ sd and 95% confidence intervals (CI) of the mean.

A p-value <0.05 was considered to denote statistical significance. The power of the study to detect a 5% difference in RBF between normal and stenotic kidneys was 85%.

RESULTS

On angiography 29 patients proved to have normal renal arteries and they were diagnosed as having EH. On ultrasound examination, 8 of them had a unilateral small kidney with a pole-to-pole length ranging from 7.0 to 10.2 cm; kidneys contralateral to such small kidneys ranged from 10.0-12.2 cm in length. Thirteen patients had unilateral and six had bilateral RAS and their kidney length ranged from 6.0 to 12.5 cm.; four of these stenotic kidneys differed in length by more than 10% from their counterpart.

In patients with RAS mean serum creatinine and mean age were significantly higher than in patients with EH: 111 ± 32 vs 93 ± 26 $\mu\text{mol/L}$, ($p < 0.01$) and 64 ± 6 vs 51 ± 15 years ($p < 0.0001$) respectively. All patients with RAS were older than 50 years.

For the analysis of RBF, the data of 50 normal kidneys, 8 small kidneys with no renal artery disease, 25 kidneys with RAS and 13 kidneys contralateral to a stenosis were available.

Although measurements based on the aorta ROI gave the highest values for RBF, no significant differences were found between the three methods to calculate RBF in the various groups of kidneys, either for the determinations at baseline or for those after captopril.

The majority of kidneys showed an increase in RBF after captopril: 64% of the normal kidneys, 63% of the small kidneys, 52% of the stenotic kidneys and 54% of the contralateral kidneys. When comparing stenotic to contralateral kidneys there was no difference in the number of kidneys with an increase in RBF of 2% or more of CO. The number of kidneys with a decrease in RBF after captopril of more than 2% of CO did not differ between the various groups either.

Patients with essential hypertension.

normal kidney group

Average RBF in the 50 normal kidneys ranged from 10.5% to 10.9% of CO at baseline and from 11.2% to 12.6% of CO after captopril for the various methods to calculate RBF (table 1). Differences between RBF determinations at baseline and after captopril were small and not statistically significant for any of the methods used to calculate RBF.

Table 1. Mean values $\pm$ sd and 95% confidence intervals for RBF measurements in 29 patients with EH (50 normal and 8 small kidneys) and 19 patients with RAS (25 stenotic and 13 contralateral-to-stenotic kidneys). Data are expressed as percentages of CO as computed over aorta (RBF/CO-A), right lung (RBF/CO-L) or left ventricle (RBF/CO-LV) at baseline (BL) and after captopril (CP)

	50 normal kidneys in patients with EH	8 small kidneys in patients with EH	25 stenotic kidneys in patients with RAS	13 contralateral kidneys in patients with RAS
BL RBF/CO-A	$10.9\% \pm 5.2$ (10.5-13.4)	$6.6\% \pm 1.7^*$ (5.2-8.0)	$9.3\% \pm 5.4$ (7.1-11.6)	$10.8\% \pm 4.2$ (8.3-13.4)
CP RBF/CO-A	$12.6\% \pm 5.0$ (11.2-14.0)	$7.9\% \pm 3.5$ (5.0-10.8)	$8.9\% \pm 4.4$ (7.1-10.7)	$10.6\% \pm 3.6$ (8.5-12.8)
BL RBF/CO-L	$10.7\% \pm 4.1$ (9.5-11.9)	$6.6\% \pm 2.0^{**}$ (4.9-8.2)	$8.2\% \pm 4.4$ (6.4-10.1)	$9.3\% \pm 3.5$ (7.2-11.4)
CP RBF/CO-L	$11.4\% \pm 3.9$ (10.3-12.5)	$6.8\% \pm 2.9$ (4.8-8.8)	$8.2\% \pm 4.3$ (6.4-10.0)	$9.2\% \pm 3.8$ (6.9-11.5)
BL RBF/CO-LV	$10.5\% \pm 4.2$ (9.3-11.7)	$6.6\% \pm 1.3^{***}$ (5.6-7.7)	$8.8\% \pm 4.9$ (6.8-10.8)	$10.5\% \pm 3.7$ (8.2-12.7)
CP RBF/CO-LV	$11.2\% \pm 4.0$ (10.1-12.4)	$7.1\% \pm 2.5$ (5.1-9.2)	$7.8\% \pm 4.0$ (6.0-9.3)	$9.4\% \pm 3.7$ (7.2-12.6)

Difference between small kidneys and all normal kidneys in patients with EH; $*p < 0.01$, $**p < 0.05$, $***p < 0.001$

The difference in RBF between pairs of normal kidneys ranged from 0.1%-8.4% of CO for the various RBF measurements at baseline and from 0.4%-9.7% for measurements after captopril. Although RBF data tended to be lower in right kidneys, differences between left and right kidneys were not significant (table 2).

Table 2 Mean values $\pm$ sd for RBF measurements in 25 normal left and right kidneys and 8 small kidneys of 29 patients with essential hypertension. Data are expressed as percentages of CO as computed over aorta (RBF/CO-A), right lung (RBF/CO-L) or left ventricle (RBF/CO-LV) at baseline (BL) and after captopril (CP)

Patients with EH	25 normal left kidney's	25 normal right kidney's
BL RBF/CO-A	13.8% $\pm$ 5.3	0.0% $\pm$ 4.5
CP RBF/CO-A	14.0% $\pm$ 5.6	11.2% $\pm$ 4.0
BL RBF/CO-L	12.1% $\pm$ 4.0	9.2% $\pm$ 3.7
CP RBF/CO-L	12.6% $\pm$ 4.5	10.3% $\pm$ 2.9
BL RBF/CO-LV	12.0% $\pm$ 4.2	9.0% $\pm$ 3.6
CP RBF/CO-LV	12.4% $\pm$ 4.4	10.1% $\pm$ 3.1

small kidney group

On average, RBF for all 8 small kidneys was similar at 6.6% of CO at baseline and ranged from 6.6% to 7.9% of CO after captopril for the various methods to calculate RBF (table 1). Again, changes in RBF after captopril were not statistically significant, the average difference between RBF determinations at baseline and after captopril ranging from 0.2% to 1.3% of CO in the small kidneys and from 0.2 to 0.9% of CO in the contralateral ones.

The difference in RBF measurements between the normal kidney and the small one for the 8 individual patients ranged from -1.6% to +15% (mean value 6.4%) at baseline and from -1.0% to +15.2% (mean value 7.8%) after captopril.

In the whole group of patients with EH, there was a statistically significant difference ($p < 0.05$) for the RBF measurements in small kidneys ($n=8$) and in normal kidneys ($n=50$) at baseline but this difference disappeared after captopril.

Patients with renal artery stenosis.

The mean baseline and mean post-captopril RBF of all affected kidneys ($n=25$) and of the contralateral ones ($n=13$) in patients with RAS are given in table 1. Although there was a trend in kidneys with a stenosis to have a reduced RBF, there were no significant differences between stenotic kidneys and contralateral ones for RBF measurements at baseline, or after captopril and no significant changes were induced by captopril in either group of kidneys.

Both mean baseline and mean post-captopril RBF of the affected kidneys or of the contralateral ones in patients with RAS were not significantly different from those of normal kidneys of patients with EH.

small kidney group

Average RBF for all 4 small kidneys ranged from 4.4% to 5.3% of CO at baseline for the various methods to calculate RBF with no significant change in RBF after captopril.

The mean RBF of these 4 small kidneys with RAS was significantly lower than that of normal sized kidneys with RAS ($n=21$) and than that of normal kidneys in patients with EH (both $p < 0.05$).

DISCUSSION

In their studies Peters and coworkers failed to find significant differences in RBF between normal, stenotic and contralateral-to-stenotic kidneys². However, they used DTPA, a glomerularly filtered agent, as the marker substance. Since MAG-3 renal clearance has a linear relationship with effective renal plasma flow⁴, this agent could be an attractive alternative tracer to detect differences in renal flow. Theoretically, measurements of split RBF before and after ACE-inhibition in patients suspected of having renovascular hypertension, could be helpful in the diagnostic work-up of such patients. For this reason, we conducted a prospective angiographically controlled study of RBF measurements from first-pass radionuclide angiography¹, at baseline and 2 hours after ACE-inhibition.

Our data show that measurements based on the aorta ROI give the highest values for RBF although these do not differ significantly from those derived from the other methods to calculate RBF. Thus, our results are in agreement with those of Bell and Peters⁶ who also found that organ blood flow measurements based on the aorta ROI yielded higher values than when the left ventricle or lung was used as ROI.

In patients with EH, we found the average values of RBF determinations to be in the range of 10.5% to 10.9% of CO, which is close to the values found by Peters et al.^{1,2} in such patients. Like in normal subjects¹, RBF tended to be lower in right kidneys than in left ones, but the difference was not statistically significant. Although the explanation for this finding is not readily apparent, it is thought to be due to greater interference with uptake of tracer by the spleen¹.

We further found that ACE-inhibition stimulated RBF in the majority of kidneys, both in EH and RAS patients, although differences between RBF measurements at baseline and after captopril never became statistically significant.

Our RBF data obtained with 99m-Tc-MAG-3 are comparable to those obtained by Peters with 99m-Tc-DTPA, except for the fact that the latter investigators found a statistically significant RBF increase after ACE-inhibition in both normal and stenotic kidneys^{1,2}. Since DTPA is primarily a marker for glomerular filtration, while MAG-3 uptake more reflects renal blood flow, the discrepant results between Peters' group and ours with respect to the effect of ACE-inhibition may be due to a greater role of angiotensin II in maintaining glomerular filtration than in regulating renal perfusion.

Our results also suggest that RBF measurements before and after ACE-inhibition in patients in whom a diagnosis of renovascular hypertension is suspected on clinical grounds, cannot discriminate reliably between patients with EH and those with RAS, at least when MAG-3 is used as the tracer. Moreover, in patients with EH and small kidneys significantly reduced values of RBF may be found which are even lower than those in patients with RAS.

In conclusion, therefore, our data demonstrate that measurements of RBF from first-pass radionuclide angiography using 99m-Tc-MAG-3 are of little help as a diagnostic test in patients in whom a diagnosis of renovascular hypertension is suspected on clinical grounds.

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CHAPTER VIII

THE "CAPTOPRIL TEST", WITH BLOOD PRESSURE AND PERIPHERAL RENIN AS RESPONSE VARIABLES IN HYPERTENSIVE PATIENTS WITH A HIGH LIKELIHOOD OF HAVING RENAL ARTERY STENOSIS

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Journal of Human Hypertension 1995;9:741-6

THE "CAPTOPRIL TEST", WITH BLOOD PRESSURE AND PERIPHERAL RENIN AS RESPONSE VARIABLES IN HYPERTENSIVE PATIENTS WITH A HIGH LIKELIHOOD OF HAVING RENAL ARTERY STENOSIS

SUMMARY

In forty-six hypertensive patients in whom a high level of clinical suspicion for renovascular hypertension was present on the basis of clinical clues, a captopril test was performed with either 25 mg. of captopril or placebo on two separate days, to determine prospectively the value of the captopril test. Blood pressure and peripheral renin were used as response variables. All patients had discontinued their antihypertensive medication and were not salt depleted. In all patients a selective renal angiography was performed irrespective of the results of the captopril test. Twenty patients proved to have uni- or bilateral renal artery stenosis (RAS) giving a prevalence of 43%.

After the placebo and after captopril there were no significant changes (absolute or proportional) in BP values between patients with essential hypertension (EH) or RAS, either for all measurements or if only the fall in blood pressure was taken into account.

The receiver operator characteristic curves of both baseline and post-captopril peripheral renin levels indicate that the captopril test does not discriminate appropriately between patients with EH and RAS.

Therefore, we would not advise the use of the captopril test as a screening test for RAS in hypertensive patients in whom a high level of clinical suspicion for RAS is already present.

INTRODUCTION

The use of angiotensin converting enzyme (ACE) inhibitors in hypertensive patients may enable the clinician to distinguish patients with essential hypertension (EH) from those with renal artery stenosis (RAS). The so-called captopril (challenge)-test is a convenient screening procedure with little risk for the patient. The effect of ACE inhibition can be studied using either the magnitude and duration of the fall in blood pressure, or changes in renin levels as outcome variables (1-16).

Some authors found the magnitude of the hypotensive response to be significantly greater in patients with RAS than in those with essential hypertension^{1,2} but in most studies there is a considerable overlap with no significant differences in duration and magnitude of the ACE-inhibitor induced fall in pressure (3-10). Likewise, the increments in renin levels show a wide splay, thereby limiting the usefulness of the test. Combining the renin data with BP responses does not seem to improve the performance of the captopril-test either^{3,16}.

To evaluate whether a captopril-test has any value when the pre-test probability for the presence of RAS is already high, we set up a prospective study to determine the performance of the captopril-test in hypertensive patients in whom a diagnosis of renovascular hypertension was strongly suspected on the basis of certain clinical clues¹⁷. Since the administration of an ACE-inhibitor also leads to a fall in plasma aldosterone¹⁸, we measured aldosterone levels as well to determine whether changes in this hormone would differ between EH and RAS patients.

PATIENTS AND METHODS

Fifty-three patients, who were referred to the Out Patient Department for analysis of their hypertension, were selected for renal angiography when any one of the clinical clues mentioned in table 1 was present. These selection criteria were adapted from the Working Group on Renovascular Hypertension¹⁷. Four patients were not included in the present study, the reasons being refusal on personal grounds (n=2), heart failure and myocardial infarction shortly after selection (n=1) and technical problems that precluded angiographic examination (n=1). Thus forty-nine patients were enrolled in the study proper. All of them underwent a captopril-test with, in randomized order, either a placebo or 25 mg of captopril on two separate days at least 1 week apart.

Table 1. Clinical clues (selection criteria)*

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1. Hypertension with a history of smoking;diastolic pressure above 110 mmHg.
2. Typical systolic-diastolic epigastric, subcostal or flank vascular bruit.
3. Accelerated or malignant hypertension without a history of smoking.
4. Sudden development or worsening of hypertension at any age.
5. Severe hypertension, diastolic pressure above 110 mmHg in young adulthood, or after age 50 years.
6. Hypertension refractory to appropriate three drug regimen.
7. Sudden worsening of renal function in a hypertensive patient or unexplained impairment of renal function.
8. Unilateral small kidney discovered by any clinical study.
9. Impairment of renal function in response to angiotensin converting enzyme inhibition.
10. Extensive occlusive disease in coronary, cerebral, or peripheral circulation.
11. Grade III or IV hypertensive retinopathy.
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* Clinical clues (selection criteria) modified after the Working Group on Renovascular Hypertension.

Twenty-four hour urine collections for determination of sodium excretion were obtained during the 2 days prior to the two tests. Since sodium depletion is known to enhance the hypotensive and renin stimulating effect of ACE-inhibition⁴, patients with a urinary sodium excretion of less than 50 mmol per day were excluded from analysis.

At least 3 weeks before the study, antihypertensive drugs, if any, were discontinued. All tests were performed at 8.30 hr in the morning after a overnight fast.

An intravenous catheter was inserted into an antecubital vein and throughout the procedure patients remained in supine position. After 30 min. of rest, 25 mg of captopril or a placebo tablet was given orally. Just before drug administration and again after 2 hours¹⁹ blood was drawn from the catheter for the measurement of peripheral renin and aldosterone.

Blood pressure (BP) was measured with an automatic device (Dinamap) at regular intervals: every 3 min. during the 30 min. before drug administration and every 10 min. for 120 min. thereafter. The averages of the last 3 BP recordings of the first 30 min. were taken as baseline values. The averages of every 3 BP recordings during each period of 30 min. following drug administration as well as the lowest recording of each 30 min. period were used for analysis of captopril-induced changes. Moreover, the lowest BP reading at any time during the entire registration period was recorded.

Irrespective of the results of the tests selective renal angiography was performed in all patients via the transfemoral route. The renal angiogram was considered positive for renal artery stenosis when a luminal reduction of more than 50% was present²⁰.

For the evaluation of the peripheral renin data the criteria applied by Müller et al.⁴ could not be used by us because of differences in the renin assay and because renin levels were taken 120 min. after captopril rather than after 60 min. We therefore constructed receiver operator characteristic

curves (ROC) taking different renin levels as a cut-off point.

Active plasma renin concentrations (APRC) were measured by the IRMA method²¹ (Pasteur Diagnostics, Marnes la Coquette, France). Aldosterone was measured by a RIA method (Diagnostic Products Corporation, Apeldoorn, The Netherlands).

Analysis and statistics

Data are expressed as medians and ranges. Differences in percentages between groups were compared with the χ^2 test.

Differences in age, serum creatinine, blood pressure and hormone values were evaluated with the Mann Whitney U-test.

Differences in hormone levels after captopril were compared with Wilcoxon test.

Sensitivity, specificity, predictive values and post-test probabilities are calculated according to accepted methods²². False positive rate is defined as 1 minus specificity. Correlation coefficients were calculated according to Spearman. A p-value <0.05 was considered statistically significant.

RESULTS

Of the 49 patients three (all with EH) were excluded because they excreted less than 50 mmol of sodium on the two days before the captopril-test. Data from 46 patients were thus available for analysis. Twenty of these proved to have RAS (13 unilateral and 7 bilateral disease) of more than 50% arterial luminal narrowing (8 with fibromuscular dysplasia and 12 with atherosclerotic disease), while 26 patients had no renal artery abnormalities and were considered to have EH. Of the 13 patients with unilateral RAS, 8 patients had a stenosis of more than 70% and 5 patients had a stenosis between 50% and 70%. Of the patients with bilateral disease 6 had a stenosis of more than 70% in at least one renal artery and one patient had bilateral disease with a stenosis between 50% and 70% on both sides.

The clinical characteristics of both patient groups are given in table 2. Compared to patients with EH, patients with RAS were significantly older. Moreover, they had a higher baseline systolic pressure and higher serum creatinine.

Both on the placebo day and on the captopril day baseline renin levels were not significantly different between both patient groups but aldosterone levels were. Baseline renin levels were elevated in 11 (41%) out of 26 patients with EH and in 11 (55%) out of 20 RAS patients (4 out of 7 with bilateral RAS and 5 out of 13 with unilateral RAS). When these patients with high renin EH are excluded from the analysis then both on the placebo day and on the captopril day baseline renin levels were significantly higher in the RAS group ($p < 0.0001$).

In the eleven patients with EH and high renin levels at baseline, renin value was significantly higher than in patients with RAS (51.6 vs 34.4 mU/l, $p < 0.01$). On renal angiography 4 of these patients proved to have multiple renal arteries (baseline renin value 54.7 mU/l) while 4 other patients with multiple renal arteries had low baseline renin levels (median value 7.4 mU/l).

Table 2. Clinical characteristics of the 26 patients with EH and the 20 patients with RAS (medians and ranges).

	EH (n=26)		RAS (n=20)		Sign.*
Male/female	15/11	8/12			
Age (years)	52	(24-74)	66	(50-75)	p<0.05
History of smoking	9		11		ns
Creatinine ($\mu\text{mol/L}$)	87	(61-145)	93	(62-220)	p<0.05
Baseline systolic BP mmHg					
placebo day	154	(122-201)	178	(144-228)	p<0.05
captopril day	157	(136-209)	172	(149-231)	p<0.05
Baseline diastolic BP mmHg					
placebo day	101	(88-126)	109	(92-122)	ns
captopril day	100	(75-129)	106	(87-119)	ns
Baseline renin (mU/l)					
placebo day	25.7	(2.2-76)	30.2	(5.9-173)	ns
captopril day	24.6	(1.1-99)	34.4	(7.0-126)	ns
Baseline aldosterone (nmol/l)					
placebo day	0.35	(0.06-1.26)	0.39	(0.22-2.69)	p<0.01
captopril day	0.35	(0.06-0.87)	0.42	(0.11-2.96)	p<0.001

* statistical significance (Mann-Whitney U-test)

Blood pressure response

Both on the placebo day and on the captopril day baseline diastolic and mean arterial pressures were comparable in both patient groups while systolic blood pressure was significantly higher during both test procedures in the RAS group (both $p<0.05$). After the placebo there were no significant changes in BP in either the EH or the RAS group.

Neither after the placebo nor after captopril were significant differences (absolute or proportional) in blood pressure responses between patients with EH and those with RAS observed at any time.

After captopril the lowest systolic and diastolic blood pressure, both in the EH and in the RAS group was reached at 90 min.

The greatest median change for systolic BP was 16 mmHg (2-60) in RAS patients and 11 mmHg (2-54) in EH; for diastolic BP these values were 9 mmHg (0-22) and 10 mmHg (0-18) respectively.

In only one patient with RAS, severe hypotension occurred about 20 min after captopril. On renal angiography she proved to have total occlusion of the left renal artery with a 60% stenosis in the right one. In contrast, two other patients with a total occlusion on one side and a high-graded stenosis on the other did not become hypotensive.

Depending on their fall in mean arterial blood pressure (MAP) patients were classified in two different groups: a fall in MAP less than 20% ($n=32$) or greater than 20% ($n=14$)⁸. The clinical characteristics of these groups of patients are given in table 3. The number of patients in each of these groups was comparable. Only two patients, (one in each group) had a fall in MAP of more than 30%.

When blood pressure responses were analyzed using 70% stenosis rather than 50% as cut-off point, results were comparable.

Table 3. Clinical characteristics, hormone values of patients with EH and with RAS with a fall in MAP of more and less than 20% after captopril medians and ranges

Fall in MAP	< 20%	≥ 20%
EH patients		
n	19	7
Age (years)	45 (29-70)	63 (24-74)
Creatinine (μmol/l)	90 (74-145)	88 (61-124)
Baseline renin (mU/l)	24.9 (1.1-99)*	24.3 (5.1-73)**
Post captopril renin	39.8 (1.1-273)	46.2 (5.1-77.3)
Baseline aldosterone (nmol/l)	0.32 (0.06-0.87)	0.4 (0.16-0.65)
Post captopril aldosterone	0.26 (0.06-1.3)	0.21 (0.07-0.44)
RAS patients		
n	13	7
Age (years)	67 (50-75)	65 (62-75)
Creatinine (μmol/l)	89 (62-212)	96 (72-220)
Baseline renin (mU/l)	34.6 (7-120.3)*#	34.3 (12.6-126)**
Renin post-captopril	85.1 (9.4-776)#	48.2 (12.3-151)
Baseline aldosterone (nmol/l)	0.41 (0.17-2.96)	0.43 (0.11-0.86)
Post captopril aldosterone	0.23 (0.13-1.02)	0.25 (0.13-0.7)

difference statistically significant: **= $p < 0.05$, *= $p < 0.01$ for differences between groups and #= $p < 0.0001$ for change within group; normal value serum creatinine 53-102 μmol/L; normal value renin level recumbent 11.2-28.8 mU/L

Peripheral renin and aldosterone response

On the placebo day no significant changes in hormone levels occurred. After captopril, patients with EH displayed a significant rise in renin from 24.6 to 41.6 mU/l ($p < 0.0001$) while in patients with RAS renin rose from 34.4 to 58.7 mU/l ($p < 0.0001$). Post-captopril levels of renin were significantly higher in the RAS group ($p < 0.0001$) (figure 1).

Figure 1. Renin (APRC) median values (mU/l) in 26 patients with EH and in 20 patients with RAS
P = on placebo day C = on captopril day 0 = baseline value 120 = value after 120 min

Both EH patients with a fall in MAP of less than 20% and those with a fall in MAP greater than 20% had significantly lower baseline renin levels than RAS patients with a comparable blood pressure response (table 3). Patients with RAS with a hypotensive MAP response of less than 20% had a significant change in renin level after captopril from 34.6 to 85.1 mU/l ($p < 0.0001$) while those with a hypotensive MAP response of more than 20% and all EH patients display a much smaller change in renin. The relationship between sensitivity and false positive rate for the baseline and post-captopril renin levels is shown in the receiver-operator characteristic curves (ROC) (figure 2). These ROC curves indicate that both baseline and post-captopril renin levels fail to discriminate appropriately between patients with EH and RAS. For instance, a sensitivity of about 80% (whether baseline or post-captopril) is associated with a false positive rate of about 65%.

Six out of 26 patients with EH and three out of 20 patients with RAS had a rise in renin level of more than 100%.

A significant difference in baseline aldosterone levels was observed between both groups (0.35 vs 0.42 nmol/l $p < 0.001$) but only patients with RAS had a significant fall in aldosterone after captopril (from 0.42 to 0.25 nmol/l $p < 0.05$). Both EH and RAS patients, when classified according to their fall in MAP, had a decrease in aldosterone level, but this was never significant in an absolute or in a proportional sense.

In both groups of hypertensive patients, no correlations were found between baseline renin and baseline aldosterone or their changes.

Again, similar data were obtained when 70% rather than 50% was considered to denote a significant stenosis.

As stated above, three patients with EH were excluded from analysis because their urine sodium excretion was less than 50 mmol/24h. None of them, however, had a blood pressure fall of more than 10%. Their renin levels were as follows; baseline: 6.8, 42.5, 56.7 mU/l; post-captopril: 19.7, 127.5, 69.7 mU/l respectively.

Figure 2. Receiver operator characteristic curve of baseline and post-captopril renin levels

Of the 20 patients with RAS, seven had a favourable response²³ to intervention (all angioplasty) and eight (six angioplasty, two surgery) no response. In five patients no intervention was performed for

various reasons.

The acute hemodynamic response and the renin response to captopril in the 7 patients who had a favourable response after intervention were not statistically different from those observed in the patients with no response and there was no influence of the degree of stenosis on the results of intervention. Moreover, no significant difference in serum creatinine was apparent between those with a favourable response (91, range 62-136 $\mu\text{mol/L}$) and those with no response after intervention (88, range 71-109 $\mu\text{mol/L}$).

DISCUSSION

In the present study we evaluated prospectively the value of the captopril-test in a hypertensive population in whom a diagnosis of renovascular hypertension is already strongly suspected on the basis of clinical clues.

Like others⁴ we excluded patients with a sodium excretion of less than 50 mmol per day to avoid enhanced hypotensive or renin responses.

In our group of hypertensive subjects selected according to the suggestions of the Working Group on Renovascular Hypertension¹⁷ twenty patients proved to have uni- or bilateral stenosis with an arterial luminal reduction of more than 50% on angiography (prevalence 43%). There are only a few studies in which patients were selected on such clinical clues and in these studies also a high prevalence of RAS was reported^{24,25}.

Baseline diastolic pressure turned out not to be different between patients with EH and those with RAS, but their systolic BP was. This difference in systolic blood pressure could at least in part be due to a difference in age. Alternatively, it could reflect widespread atherosclerotic disease in patients with RAS.

In our study, neither the magnitude nor the duration of the fall in BP can reliably distinguish patients with RAS from those with EH. This is in accordance with the results of most other studies, although different response criteria have been employed by others. Several authors have found a considerable overlap and no significant differences in the percentage or absolute fall in blood pressure³⁻¹¹.

Postma⁸ divided his patients on the basis of a decline in MAP of more or less than 20% and found patients with a decline of less than 20% to have lower baseline and stimulated renin levels. We found, on the contrary, that baseline renin levels were not different in those two groups. This may be due to differences in patient selection, such as the number of patients with high renin EH. However we also found that in patients with RAS only those with a fall in BP of less than 20% had a significant increase in renin after captopril; this exaggerated response may have precluded a greater fall in pressure.

In patients with RAS the acute hemodynamic response to captopril may²⁶ or may not^{27,28} predict the BP response after angioplasty or surgery. In the seven RAS patients who had a favourable response to intervention, we did not find the BP changes after captopril to be of any predictive value.

Captopril, when given orally, takes 1 to 2 hours to achieve a peak concentration and a maximum (therapeutic) effect. Al Furaih and co-workers¹⁹ with frequent sampling found the maximum renin increase after 25 mg of captopril to occur at a mean time of 113 min. Although most studies report renin sampling after one hour, in our study hormone sampling was done after two hours for this reason.

In our patient group with a high prevalence (43%) of RAS, baseline renin levels and the increase in plasma renin after captopril had only a poor predictive significance as is shown in the receiver operator characteristic curves. A good sensitivity of these tests is always at the cost of a high false positive rate. It should also be clear from our results that any criterion such as those proposed by Müller et al.⁴ or by Postma et al.⁹ will show unfavourable predictive values for RAS. For instance, Postma et al.⁹ found their criterion, a rise in renin level of more than 100%, to have a sensitivity

of 54% and a specificity of 74%. In his series, with a prevalence of RAS of 29.5%, the post-test probability of a positive test, or the probability that a patient with a positive test has RAS is 44% and the probability that a patient with a negative test has no RAS is 79%. In our series of 46 patients, 6 out of 26 patients with EH and 3 out of 20 patients with RAS had a rise in renin of more than 100%. Both the results from Postma's study and in our own data make it clear that Postma's fourth criterion cannot serve as a good screening parameter. Furthermore, our results contradict the computer-calculated relationship between the prevalence of RAS and the predictive value of the captopril-test as put forward by Derkx et al.¹⁶ In their model with a prevalence of 43% of RAS the captopril-test should have a sensitivity of 85% and a specificity of 80%. This discrepancy between our observed results and those expected on the basis of their computer-calculated model is probably caused by the fact that the computer model is based on data from patients with severe or therapy-resistant hypertension.

Our results of the captopril-test are more in line with those of Salvetti et al.¹⁰ and Idrissi et al.⁷ who also reported a disadvantageous outcome. However our data indicate that patients with EH independently from the magnitude of the fall in MAP have a significant lower baseline renin level than patients with RAS. Only RAS patients with a fall in MAP of less than 20% had a significant increase in renin levels after captopril. Thus, this group of RAS patients seems to have an exaggerated renin response and this response may have precluded a greater fall in pressure.

Baseline aldosterone levels were lower in EH patients and a significant reduction of aldosterone levels was seen only in RAS patients. This is contrary to the results of Salvetti¹⁰ who found a significant reduction in both patient groups. Other factors, however, such as sodium status may account for the fact that aldosterone levels did not show a significant decrease in patients with EH.

In conclusion, the results of our study in hypertensive patients suspected of having renovascular hypertension on the basis of clinical criteria indicate that the captopril-test is a poor screening test for renal artery stenosis both in terms of BP response and in terms of renin response. We would, therefore not advise the use of the captopril-test as a screening test for RAS in hypertensive patients in whom a high level of clinical suspicion for RAS is already present.

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CHAPTER IX

RENAL ARTERIAL AND VENOUS ENDOTHELIN IN HYPERTENSIVE PATIENTS WITH OR WITHOUT RENAL ARTERY STENOSIS

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Blood Pressure 1994;3:370-374

RENAL ARTERIAL AND VENOUS ENDOTHELIN IN HYPERTENSIVE PATIENTS WITH OR WITHOUT RENAL ARTERY STENOSIS

SUMMARY

Immunoreactive endothelin (ir-ET) levels were measured in the renal veins and aorta of 43 untreated hypertensive patients immediately before renal angiography. None of the patients used antihypertensive medication. Twenty-seven patients had renal artery stenosis, 17 of which were unilateral and 10 bilateral. Seven of the 17 patients with unilateral RAS had an elevated renin ratio. Of the 16 patients with essential hypertension 6 had a unilateral small kidney with normal blood supply. Although there was a trend towards higher levels of ir-ET in patients with renal artery stenosis, no significant differences in ir-ET levels (venous or arterial) was found between different groups of patients or groups of kidneys.

Median ir-ET extraction ranged from 4-31% in the different groups of kidneys but no significant differences were shown between groups of kidneys.

In conclusion, our data demonstrate that endothelin levels and renal endothelin extraction are comparable in essential hypertension and in hypertension associated with renal artery stenosis. Whereas renal uptake of endothelin is the rule, some kidneys, however, release this peptide irrespective of presence or absence of RAS. It is of interest that all kidneys with a normal blood supply received ir-ET.

INTRODUCTION

Immunoreactive endothelins are very potent vasoconstrictor peptides that cause a profound constriction in various vascular beds^{1,2}, including that of the human kidney^{3,4}, and that are thought to play an important role in the regulation of vasomotor tone⁵. So far, three iso-peptides of endothelin (ET-1, ET-2 and ET-3) have been described. ET-2 seems to be produced in the kidney and ET-3 in nervous tissue⁶. ET-1, on the other hand, originates from the endothelium¹ and may not only, in an autocrine or paracrine fashion, act on vascular smooth muscle cells, but may also spill into the blood. Therefore, even though it is rapidly catabolized in the circulation⁷, ET-1 could serve as a circulating hormone^{8,9}. In this way the peptide may be involved in the pathogenesis and maintenance of different forms of hypertension.

Plasma ir-ET levels are elevated in pulmonary hypertension¹⁰ and in renal failure^{11,12} but are reported to be normal or elevated in essential hypertension^{8,12,13,14}. Normally, ir-ET is extracted by the kidneys⁴, but it is unknown whether this mechanism persists in renovascular hypertension. Indeed, recent data which have been reported in abstract form only and comprising small numbers of patients, suggest that ir-ET in renal venous blood of stenotic kidneys may be either normal¹⁵ or elevated¹⁶. It is possible, therefore, that the release of ir-ET is enhanced in kidneys with an impaired blood supply. To investigate this further, we determined ir-ET levels in the aorta and both renal veins from patients suspected of having renal artery stenosis, immediately prior to renal angiography.

PATIENTS AND METHODS

Forty-three patients who had been referred to the Hypertension Clinic for evaluation of their hypertension were included in this study. All of them had a diastolic blood pressure above 100 mmHg on at least three occasions and they were selected for renal angiography because a diagnosis of renovascular hypertension was suspected on clinical grounds or on the basis of MAG-3 renography.

Antihypertensive medication, if any, was gradually withdrawn before the study so that none of the patients used antihypertensive drugs for at least two weeks before the angiographic procedure.

Selective renal catheterization was performed via the transfemoral route and blood samples for the determination of renin and ir-ET were drawn simultaneously from the aorta (A) and from the renal veins (V) before any contrast material had been administered.

The renal angiogram was considered positive for renal artery stenosis (RAS) when the arterial lumen was reduced by 50% or more¹⁷. Patients with no renal artery stenosis were considered to have essential hypertension (EH) as other causes of hypertension had already been excluded.

In the patients with EH a pole-to-pole length measurement of their kidneys was performed on the angiographic films; a kidney was classified as small when the contralateral kidney exceeded its size by 10% or more.

On the basis of the angiographic findings and the vein- to -artery renin ratio patients were classified into 4 groups:

- group I : patients without RAS and normal pole- to -pole kidney length
- group II : patients without RAS but with an unilateral small kidney
- group III : patients with unilateral RAS
- group IV : patients with bilateral RAS

In all patients renal function was assessed by determining plasma creatinine.

Active plasma renin was measured by the IRMA method (Pasteur Diagnostics, Marnes la Coquette, France).

ir-ET measurements

Immunoreactive endothelin (ir-ET) was measured by a sensitive and specific competitive protein-binding radioimmunoassay (Nichols Institute Diagnostics, Wychem, The Netherlands) following extraction of plasma over Sep-Pak C₁₈ columns.

The performance characteristics of this assay in our laboratory are as follows: sensitivity: 0.76 pmol/l; intra-assay variability 4.6%; inter-assay variability 6.4%; cross-reactivity: ET-1 100%, ET-2 52%, ET-3 96%, Big ET 7%.

The results of the assay were not corrected for recovery which averaged 90-97% (spiking of plasma samples).

The fractional extraction of ir-ET was calculated from the formula $A-V/A \times 100\%$.

As our measurements did not reveal any significant differences in hematocrit, between arterial and venous blood, hormonal data were not corrected for hematocrit.

Statistics

The Mann-Whitney U test was applied for comparing numerical data from groups of patients and groups of kidneys.

Correlations between ir-ET levels on the one hand and age, diastolic and systolic blood pressure, creatinine, arterial and venous renin levels on the other were obtained by Spearman's correlation coefficient. Differences in frequencies between different groups were calculated with a χ^2 -test. Data are expressed as medians and ranges.

Analysis of variance was used for the ir-ET levels in relation to the different groups of patients.

A $p < 0.05$ was considered statistically significant.

RESULTS

On renal angiography 16 patients (8 males) proved to have normal renal arteries and they were diagnosed as having EH. Measurement of pole-to-pole length showed 6 of them to have a unilateral small kidney with an otherwise normal blood supply. Twenty-seven patients (14 males) had RAS, 17 of which were unilateral and 10 bilateral. Seven of the 17 patients with unilateral RAS had an elevated renin ratio (≥ 1.5).

The clinical characteristics of the four patient groups are given in table 1.

Considering the number of kidneys, there were 20 normal kidneys, 6 small kidneys without renal artery disease, 6 normal kidneys contralateral to small kidneys, 37 kidneys with RAS (17 from the unilateral RAS group and 20 from the bilateral RAS group) and 17 kidneys contralateral to a stenosis.

Patients with EH (group I and II) were significantly younger than patients with RAS (group III and IV): 51 (range 32-73) vs 64 (range 50-76) years ($p < 0.001$) and they had better renal function: creatinine medians 89 (range 61-145) vs 96 $\mu\text{mol/l}$ (range 61-306), $p < 0.05$. No significant differences were found between diastolic and systolic blood pressure between patients with EH and RAS.

No significant differences were found in arterial renin levels between the different groups of patients.

In patients with unilateral renal artery stenosis, there was no significant difference in age or renal function, for those with an elevated and those with a normal renin ratio.

ir-ET levels

The results of the arterial ir-ET measurements per group of patients are presented in table 1.

Arterial ir-ET levels ranged from 1.00-3.44 pmol/l with medians ranging from 1.56-2.24 pmol/l in the different groups. Although there was a significant trend towards higher levels in patients with RAS in the overall analysis of variance, no significant differences in arterial ir-ET levels between individual groups of patients were found. In patients with unilateral RAS no significant difference was apparent between those with an elevated and those with a normal renin ratio for arterial ir-ET levels (medians 2.28 pmol/l vs 1.84 pmol/l) and ir-ET levels in the veins of the affected kidney (medians 1.56 pmol/l vs 1.76 pmol/l).

No correlations between venous or arterial ir-ET levels on the one hand and age, diastolic and systolic blood pressure, creatinine and venous and arterial renin levels on the other were found.

ir-ET extraction

A kidney having a venous ir-ET level which is lower than the corresponding arterial level extracts ir-ET. Sixteen out of the 20 normal kidneys (80%), all of 6 (100%) small kidneys, 5 out of 6 (83%) normal kidneys contralateral to small kidneys, 25 out of the 37 (68%) stenotic kidneys and 14 out of the 17 (82%) contra-lateral kidneys appeared to extract ir-ET. There was no significant difference in the number of kidneys extracting ir-ET between the various groups of kidneys.

The results of the venous ir-ET measurements and the fractional extraction per group of kidneys are presented in table 2. The fractional extraction of ir-ET ranged from -49% to +62% in the different groups of kidneys. No significant differences in ir-ET extraction fraction was found between groups of kidneys. No correlations between ir-ET extraction fraction and age, diastolic and systolic blood pressure, creatinine level or renin levels (venous or arterial) were found.

Table 1. Median and ranges of clinical characteristics and of arterial renin and ir-ET levels per group of patients.

	Group I EH n=10 normal kidney	Group II EH n=6 small kidney	Group III RAS n=17 unilateral	Group IV RAS n=10 bilateral
Male	6	2	9	5
Female	4	4	8	5
Age (year)	52 (32-73)	52 (37-69)	63 (50-76)	65 (38-76)
Creatinine*	79 (61-112)	90 (74-145)	96 (61-306)	113 (67-220)
DBP# mmHg	107 (100-132)	110 (102-136)	109 (104-120)	110 (102-124)
SBP# mmHg	165 (138-208)	164 (144-208)	181 (150-208)	180 (142-230)
Renin mU/l				
median	39.5	45.2	35.2	36.1
ranges	5.9-119	5.1-229	5.9-292	11.4-144
ir-ET pmol/l				
median	1.56	1.64	2.24	2.12
ranges	1.0-3.0	1.28-2.28	1.20-3.44	1.41-3.00

uni-RAS: unilateral renal artery stenosis; bi-RAS: bilateral renal artery stenosis; *creatinine normal values 53-110 $\mu\text{mol/l}$; #DBP, SBP: diastolic and systolic blood pressure

DISCUSSION

The results of the present study indicate that ir-ET levels as measured immediately before renal angiography in the renal veins and aorta of hypertensive patients are comparable in patients with EH and those with uni- or bilateral RAS. In this respect, it is important to note that at the time of the study all patients were untreated and that blood samples were drawn before any contrast material had been given.

Since the introduction of a radioimmunoassay for the determination of endothelin some groups have reported high levels of ir-ET in patients with essential hypertension^{12,14} whereas others have reported normal values^{8,13,18}. The reason for this difference is not well understood, although it may be related to differences in renal function. Shichiri et al.¹² found ir-ET levels to be higher in patients with essential hypertension and normal renal function and in hypertensive patients with renal failure (non-dialysed and hemodialysed) as compared to matched normotensive controls.

Although we did not determine ir-ET levels in a control group of normotensive patients we failed to find differences in ir-ET levels in patients with essential hypertension as compared to those with renovascular hypertension and no correlation with serum creatinine was found.

Miyauchi et al.¹⁸ dividing their study population of normotensive and hypertensive subjects into two age groups (young adults, 20 to 34 years versus middle aged 35 to 59 years) found elevated ir-ET levels to be related to age rather than to hypertension. In contrast, we found no relation between age and ir-ET levels but in our series only 3 patients (with EH) were below 35 years.

To our knowledge there are only two studies^{15,16} that have reported (in abstract form) on measurements of ir-ET in renal venous plasma. Yoshimi et al.¹⁵ found ir-ET levels in the stenotic kidney of patients with renovascular hypertension to be within normal ranges. On the other hand, Giussani et al.¹⁶ found an increase in plasma ir-ET in subjects with RAS and high levels of angiotensin II. Although we did not measure angiotensin II levels in our patients we did not find a relationship of venous and arterial ir-ET levels with renin levels in any of our patient groups or groups of kidneys. Also, we did not find differences in arterial or venous ir-ET levels from the

affected kidneys in patients with unilateral RAS and either an elevated or a normal renin ratio. Renal uptake of ir-ET has been reported by different investigators^{4,15,16} and is confirmed in our study where 77% of the kidneys had a lower venous ir-ET level than the corresponding arterial level. Renal uptake of ir-ET is seen both in healthy normotensive subjects⁴ and in renovascular hypertension^{15,16}, and this was confirmed in our study both for the affected and the contralateral kidneys of patients with RAS and for kidneys of patients with essential hypertension with either normal or small kidneys. However, there was no significant difference in ir-ET extraction between different groups of kidneys. Although data ranged widely, it should be emphasized that irrespective of the presence of a stenotic artery some kidneys (23%) do release ir-ET. The significance of this finding is uncertain at the present time, but certainly warrants further investigation.

In conclusion, our data demonstrate that ir-ET levels and renal ir-ET extraction are comparable in essential hypertension and in hypertension associated with renal artery stenosis. Whereas renal uptake of ir-ET is the rule, some kidneys, however, release this peptide irrespective of presence or absence of RAS. It is of interest that all kidneys with a normal blood supply received ir-ET.

Table 2. Median and ranges of venous endothelin levels (nmol/l) and endothelin extraction fraction per group of kidneys

Group of kidneys	Endothelin venous	Fractional endothelin extraction
Normal n=20		
median	1.50	+10.5%
range	0.76-2.72	-35% - +39%
Right side		
median	1.38	+14%
Left side		
median	1.74	+7%
Small n=6		
median	1.18	+31%
range	0.76-1.92	-15% - +48%
Contralateral to small n=6		
median	1.20	+36%
range	0.76-1.08	-15% - +62%
Uni-RAS n=17		
median	1.76	+4%
range	1.08-3.24	-33% - +60%
Contralat n=17		
median	1.92	+5%
range	0.96-2.84	-19% - +56%
Bi-RAS n=20		
median	1.96	+8%
range	0.76-4.00	-49% - +57%
All RAS n=37		
median	1.92	+8%
range	0.76-4.00	-49% - +60%

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CHAPTER X

RENAL EXTRACTION OF ATRIAL NATRIURETIC PEPTIDE IN HYPERTENSIVE PATIENTS WITH OR WITHOUT RENAL ARTERY STENOSIS

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Accepted by Hypertension

RENAL EXTRACTION OF ATRIAL NATRIURETIC PEPTIDE IN HYPERTENSIVE PATIENTS WITH OR WITHOUT RENAL ARTERY STENOSIS

SUMMARY

Atrial Natriuretic Peptide (ANP) levels were measured in the renal veins and aorta of 49 untreated hypertensive patients immediately before renal angiography. Twenty-one patients had renal artery stenosis (RAS), 13 of which were unilateral and 6 bilateral. Five of the 13 patients with unilateral RAS had an elevated renin ratio (≥ 1.5). Patients with RAS were older ($p < 0.01$) and had higher systolic blood pressures ($p < 0.05$) than patients with essential hypertension (EH).

Arterial levels of ANP were significantly higher in patients with unilateral or bilateral RAS than in patients with EH ($p < 0.05$). Patients with EH and left ventricular hypertrophy (LVH) had a significantly higher arterial ANP level than those with no LVH (40 vs 26 fmol/ml, $p < 0.05$) but in patients with RAS, arterial ANP levels were similar between those with or without LVH.

Renal venous ANP levels were significantly higher in stenotic kidneys than in normal kidneys. Moreover, in unilateral RAS, stenotic kidneys of patients with an elevated renin ratio (≥ 1.5) had a significantly higher renal venous ANP level than stenotic kidneys of patients with a normal renin ratio (30 vs 17 fmol/ml, $p < 0.05$). However, the median fractional extraction of ANP was similar around 0.50 (range from 0-0.83) in normal kidneys of patients with EH, and in stenotic and contralateral kidneys of patients with RAS.

A significant inverse correlation between arterial ANP and renal venous APRC was found for normal kidneys $r = -0.62$, $p < 0.01$, of patients with EH without LVH. However for stenotic kidneys no such relationship was apparent.

A significant correlation between arterial ANP and the arterio-venous difference of ANP ($r = +0.92$ $p < 0.001$) was found. This relationship was similar for normal and for stenotic kidneys.

The data suggest that saturation of ANP extraction through the kidneys does not occur and is probably independent of renal blood flow.

INTRODUCTION

Atrial Natriuretic Peptide (ANP) is a cardiac hormone with multiple actions¹. For instance, ANP interacts at several levels with the renin-angiotensin-aldosterone system: it inhibits renal renin secretion, suppresses aldosterone release and attenuates the vasoconstrictor effects of angiotensin II^{2,3}. Therefore, it has been suggested that ANP may act as an endogenous antagonist to the renin-angiotensin-aldosterone system^{2,4}.

In normal human volunteers plasma levels of ANP are inversely related to plasma renin⁵ and similar data have been found in patients with essential hypertension^{6,7}. However, in some studies, dealing predominantly with patients with low-renin essential hypertension, no such association could be detected⁸. In patients with renovascular hypertension a relationship between renin and ANP levels is also absent^{9,10,11}.

Both in healthy individuals^{12,13,14} and in patients with essential or renovascular hypertension, the renal fractional extraction of ANP has been found to be approximately 0.50^{9,11,15}. However, Sudir and co-workers found a renal extraction around 0.60-0.70 in normal subjects¹⁶. On the other hand, Pederson and co-workers¹⁰ reported much lower ANP extraction ratios in renovascular

hypertension, there being no difference between the affected and the unaffected kidney (median values 0.25 and 0.29). Since in the latter study patients were extensively treated with antihypertensive drugs, including diuretics, at the time of sampling, it cannot be excluded that antihypertensive medication reduces renal extraction of ANP. In the study of Bruun and co-workers¹⁵ patients were on unrestricted sodium intake and antihypertensive medication was continued when necessary. In two other studies patients with renal artery stenosis had been selected on the basis of a renal vein renin ratio greater than 1.5^{9,11} or excluded if they had evidence of secondary organ damage such as left ventricular hypertrophy¹¹.

Since the renin-angiotensin-aldosterone system plays a major role in renovascular hypertension, we were interested in the relationship between the renal fractional extraction of ANP and renin release in untreated patients who were studied under standardized conditions. Therefore, we measured arterial and renal venous levels of ANP, renin and angiotensin II in patients suspected of having renal artery stenosis, immediately prior to renal angiography.

PATIENTS AND METHODS

Forty-nine patients who had been referred to the Hypertension Clinic for evaluation of their hypertension were included in this study. All of them had a diastolic blood pressure above 100 mmHg on at least three occasions and they were selected for renal angiography because a diagnosis of renovascular hypertension was suspected on clinical grounds or on the basis of MAG-3 renography.

Antihypertensive medication, if any, was gradually withdrawn before the study so that none of the patients used antihypertensive drugs for at least two weeks before the angiographic procedure. Sodium intake was standardized at 55 mmol per day.

Selective renal catheterization was performed via the transfemoral route and blood samples for the determination of renin, angiotensin II, aldosterone and ANP were drawn

simultaneously from the aorta and the renal veins, before any contrast material had been administered.

The renal angiogram was considered positive for renal artery stenosis (RAS) when the arterial lumen was reduced by 50% or more¹⁷. Patients with no renal artery stenosis were considered to have essential hypertension (EH) as other causes of hypertension had already been excluded.

In all patients global renal function was assessed by plasma creatinine.

Biochemical measurements

Active plasma renin concentration (APRC) was measured by the IRMA method (Pasteur Diagnostics, Marnes la Coquette, France)¹⁸. Angiotensin II was determined by radio-immunoassay following Ph Phenyl column extraction (Amersham Int. Amersham, UK)¹⁹.

Aldosterone was assayed by means of a solid-phase protein-binding RIA (antibody coated tubes) (Diagnostic Products Corporation, Los Angeles, U.S.A.)²⁰.

Atrial natriuretic peptide was measured by a competitive protein-binding radioimmunoassay (RIA) (Nichols Institute Diagnostics, Wychem, The Netherlands) following extraction of plasma over Sep-Pak C₁₈ columns²¹.

The performance characteristics of the ANP assay in our laboratory are as follows: sensitivity: 4.5 fmol/ml; intra-assay variability 7.0%; inter-assay variability 12.9%.

The fractional extraction of ANP was calculated from the formula $A-V/A$, where A is the arterial concentration and V the renal venous one.

As our measurements did not reveal any significant differences in hematocrit between arterial and venous blood, hormonal data were not corrected for hematocrit.

Statistics

Data are expressed as medians and ranges.

The Mann-Whitney U test was applied for comparing numerical data from groups of patients and groups of kidneys.

Correlations between variables were obtained by Spearman's correlation coefficient.

A $p < 0.05$ was considered statistically significant.

RESULTS

On renal angiography 27 patients (17 males) proved to have normal renal arteries and they were diagnosed as having essential hypertension (EH). Twenty-one patients (9 males) had renal artery stenosis (RAS), 13 of which were unilateral and 8 bilateral.

The clinical characteristics of both patient groups are given in table 1.

Five of the 13 patients with unilateral RAS had an elevated renin ratio (≥ 1.5). Considering the number of kidneys, there were 54 normal kidneys, 29 kidneys with RAS (13 from the unilateral RAS patients and 16 from the bilateral RAS patients) and 13 kidneys contralateral-to a stenosis.

Patients with EH were significantly younger than patients with RAS. No significant differences between patients with EH and RAS were found in renal function and diastolic blood pressure. Systolic blood pressure was significantly higher in patients with RAS ($p < 0.05$). There was no significant difference between both groups with respect to the duration of hypertension, number of antihypertensive drugs used or the number of patients with left ventricular hypertrophy (LVH).

In patients with unilateral renal artery stenosis, there were no significant differences in age, blood pressure or renal function, for those with an elevated and those with a normal renin ratio.

Table 1. Median and ranges of clinical characteristics and of arterial hormone levels per group of patients

	Essential hypertension n=27	Renal artery stenosis n=21
Male	17	9
Female	10	12
Age (year)	52 (25-73)	64 (38-76)#
SBP (mmHg)	160 (138-208)	187 (150-208)#
DBP (mmHg)	108 (100-132)	109 (104-130)
LVH (n)	6	5
Creatinine ($\mu\text{mol/l}$)	87 (61-140)	93 (62-220)
APRC (mU/l)	32 (1-90)	41 (4.4-182)
Angiotensin II (pmol/l)	5.2 (0-33)	6.1 (0-246)
Aldosterone (nmol/l)	0.41 (0.08-1.64)	0.48 (0.06-2.16)
ANP (fmol/ml)	28 (7.6-93)	40 (18-201)#

SBP = systolic blood pressure; DBP = diastolic blood pressure; LHV = left ventricular hypertrophy; APRC = active plasma renin concentration; ANP = atrial natriuretic peptide # = $p < 0.05$ (as compared to patients with essential hypertension).

Arterial hormone levels

No significant differences were found in arterial APRC, angiotensin II and aldosterone levels between patients with EH and those with RAS (both for patients with unilateral and bilateral disease).

Arterial ANP levels were significantly higher in patients with RAS (median 40; range 18-201 fmol/ml), than in patients with EH (median 28; range 7.6-93 fmol/ml) ($p < 0.05$). This was true both for patients with unilateral (43 fmol/ml) and for those with bilateral RAS (39 fmol/ml).

In patients with unilateral RAS a significant difference in arterial ANP levels was apparent between

those with an elevated and those with a normal renin ratio (70 vs 37 fmol/ml, $p < 0.05$). Arterial aldosterone and angiotensin II levels in these two groups were similar.

When patients with RAS were matched for arterial APRC with patients with EH, patients with RAS still had significantly higher arterial ANP levels ($p < 0.01$).

Patients with EH and electrocardiographic evidence of LVH ($n=6$) had a significantly higher arterial ANP level than those without LVH: 40 (range 34-93) vs 26 (range 7.6-49) fmol/ml; $p < 0.05$. However, in patients with RAS arterial ANP levels were similar between those with ($n=5$) or without LVH: 49 (range 26-201) vs 39 (range 18-107) fmol/ml. In both groups of hypertensive patients arterial AII and aldosterone levels were similar in those with or without LVH.

Renal venous hormone levels and ANP extraction

Renal venous levels of APRC were significantly higher in unilateral and bilateral stenotic kidneys than in normal ones (both $p < 0.05$), but renal venous levels of aldosterone and angiotensin II were similar in the different groups of kidneys.

The renal venous ANP levels and the fractional extraction of ANP per group of kidneys are given in table 2. Differences in renal venous ANP levels mirrored those in arterial blood and were significantly higher in the venous effluent of kidneys with a stenotic artery than in that of normal kidneys, with similar levels for unilateral and bilateral RAS kidneys. Contralateral to-stenotic kidneys also tended to have a higher venous ANP level than normal kidneys. Likewise, in unilateral RAS stenotic kidneys of patients with an elevated renin ratio (≥ 1.5) had a significantly higher renal venous ANP level than stenotic kidneys of patients with a normal renin ratio (median 30; range 8.3-40 vs 17; range 13-23 fmol/ml, $p < 0.05$).

Renal venous levels of ANP in patients with EH were significantly higher for those with LVH than for those without LVH (median 19; range 12-34 vs 13 range 7.3-41 fmol/ml, $p < 0.01$).

Table 2. Median and ranges of renal venous ANP (fmol/ml) and fractional extraction of ANP per group of kidneys

Group of kidneys	Renal venous ANP level	ANP extraction
EH n=54		
all	14 (7.3-41)	+0.53 (0.04-0.75)
left side	14 (8.1-41)	+0.53 (0.04-0.75)
right side	14 (7.3-35)	+0.51 (0.12-0.75)
Uni-RAS n=13		
all	21#(8.3-40)	+0.53 (0.38-0.79)
in stenotic kidneys with a renin ratio ≥ 1.5 n=5	30 (8.3-40)	+0.53 (0.43-0.79)
renin ratio < 1.5 n=8	17 (13-23)	+0.53 (0.38-0.62)
contralateral n=13	19 (10-36)	+0.56 (0-0.83)
Bi-RAS n=16		
all	21#(14-114)	+0.49 (0.06-0.65)
left side	22 (14-114)	+0.45 (0.32-0.60)
right side	20 (16-80)	+0.50 (0.06-0.65)
Both uni-and bilateral RAS n=29	21#(8.3-114)	+0.50 (0.06-0.79)

Difference with normal kidneys, # = $p < 0.05$

The median arterio-venous differences of ANP levels were: 15 (range 0.4-66), 17 (range 1.3-120) and 24 (0-87) fmol/ml for normal, stenotic and contralateral kidneys respectively. Gradients were not different between these groups of kidneys.

The median fractional extraction of ANP amounted 0.53 (range 0.04-0.75), 0.50 (range 0.06-0.79) and 0.56 (range 0-0.83) respectively in these three groups of kidneys. All kidneys, but one, extracted ANP from the circulation irrespective of the presence of a stenotic artery. In patients with unilateral RAS fractional extraction of ANP is similar for those with an elevated renin ratio (≥ 1.5) and those with low renin ratio (< 1.5), both 0.53.

As shown in fig.1 a significant correlation between arterial ANP and the arterio-venous difference of ANP was found ($r = +0.92$; $p < 0.001$ $y = -15 + 0.58 x$). This relationship was similar for normal ($r = +0.90$, $p < 0.001$ $y = -7 + 0.60x$) and for stenotic kidneys ($r = +0.94$, $p < 0.001$ $y = -18 + 0.57x$).

Figure 1. Relation of arterial ANP and difference of arterial and renal venous ANP
 • normal kidneys, X kidneys with RAS, Z contralateral kidneys

A significant inverse correlation between arterial ANP and renal venous APRC was found in normal kidneys ($r = -0.62$, $p < 0.01$, $y = 72 - 0.84x$) in patients with EH without LVH. However, for stenotic kidneys no such relationship was apparent (fig.2).

No correlation between blood pressure, creatinine or AII on the one hand and arterial or venous levels of ANP on the other were found. Also, no correlation was found between age, blood pressure, creatinine and arterial or venous hormone levels on the one hand and the arterio-venous difference of ANP or fractional extraction of ANP on the other.

Figure 2. Relation of arterial ANP and renal venous renin in normal kidneys of patients with EH, without LVH

Results of intervention in relation to ANP levels

Of the 21 patients with RAS, seven had a favourable response²² to intervention (all angioplasty) and nine (seven angioplasty, two surgery) no response. In five patients no intervention was performed for various reasons.

Arterial or venous ANP levels and extraction of ANP were similar in the patients who had a favourable response after intervention and those with no response.

DISCUSSION

The results of the present study demonstrate that irrespective of their condition, the fractional extraction of ANP is similar in all kidneys, being approximately 0.50 albeit with a wide range (0-0.83). These data are in line with those of others who also found fractional extraction of ANP through the kidneys to be around 0.50^{9,12,15,16}. The constant relationship between arterial ANP levels and the arterio-venous difference of ANP (in both normal and stenotic kidneys) suggests that saturation of ANP extraction by the kidney does not occur and that the extraction efficiency - probably is independent of renal blood flow. It appears, therefore, that differences in ANP levels between patients with EH and those with RAS are unlikely to be due to decreased clearance of ANP by the kidneys.

Our data further indicate that circulating ANP levels are significantly higher in patients with RAS (both unilateral and bilateral) than in patients with EH. It is improbable, however, that the elevated ANP levels in RAS are caused by enhanced activity of the renin-angiotensin system. First of all, when matched for arterial renin patients with RAS still had significantly higher arterial ANP levels than patients with EH. Moreover, we failed to find a relationship between ANP and angiotensin II levels. Thus the renin-angiotensin-aldosterone system is probably not dominantly involved in the elevation of ANP levels.

However, in patients with unilateral RAS and an elevated renin ratio (indicating hemodynamic significance of the stenosis), arterial ANP levels were significantly higher than in patients with a normal renin ratio. So, it may be that another humoral factor is responsible for the elevation of the ANP levels but it would be speculative to suggest that this factor is secreted by the ischemic kidney.

Although raised circulating levels of ANP have been reported also in essential hypertension⁸, in particular in patients with signs of left ventricular hypertrophy⁷, this is not an uniform finding^{22,23}. In our study, patients with EH and LVH had significantly higher arterial ANP levels than those without LVH, but in patients with RAS, levels were similar between those with or without LVH. It is known that in animals with LVH the ventricle secretes substantial amounts of ANP²⁴ and that patients with hypertrophic cardiomyopathy but without apparent congestive symptoms express ANP immuno-histochemically in their left and right ventricle²⁵. However, the mechanism underlying the association between enhanced ANP-release and LVH in patients with EH remains uncertain. Conceivably, an elevation of ANP levels in hypertension may reflect impaired ventricular compliance, but apparently this association is lost in patients with RAS.

From experimental renal artery occlusion in animals it is known that during the period of ischemia not only the renin-angiotensin-aldosterone system is activated but that there is also a sustained increase in plasma ANP levels²⁶. Angiotensin II has been shown to promote the release of ANP in animals²⁷ and in humans²⁸. Although this effect of angiotensin II has been ascribed to its hemodynamic action leading to increased atrial wall stretch²⁸, other mechanisms may be involved as well^{1,28}. Since ANP possesses an antihypertrophic action on vascular smooth muscle cells²⁹ and since AII stimulates the growth of vascular smooth muscle cells³⁰, ANP may be elevated in RAS as a counterregulatory mechanism, independently from the presence of LVH. However, the absence of a relationship between arterial or renal venous ANP levels on the one hand and renal arterial and venous levels of angiotensin II on the other in our study does not support this hypothesis.

We also found an inverse relationship between arterial ANP and renal venous renin in patients with EH. In patients with RAS this relationship was disturbed. These data, therefore, suggested that ANP may suppress renin release only under conditions of normal flow. In ischemic kidneys, on the other hand, another stimulus for renin release apparently is able to overcome the suppressing effect of ANP.

In conclusion, our data demonstrate that arterial and renal venous levels of ANP are elevated in untreated patients with uni- or bi-lateral RAS, and that patients with EH and LVH have significantly higher plasma ANP levels than those without LVH. Renal ANP extraction is comparable in essential hypertension and in hypertension associated with renal artery stenosis. Furthermore, a constant relationship between arterial ANP levels and the arterio-venous difference of ANP was observed for all kidneys suggesting no saturation of ANP extraction by the kidneys and an extraction efficiency that is independent of renal blood flow. Moreover, in patients with renovascular hypertension, arterial and venous ANP levels and extraction of ANP do not show a relationship with the response after intervention.

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CHAPTER XI

INTERPRETATION OF RENAL ANGIOGRAPHY BY RADIOLOGISTS

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submitted

INTERPRETATION OF RENAL ANGIOGRAPHY BY RADIOLOGISTS

ABSTRACT

Purpose

Different investigators may show considerable variation in their interpretation of renal angiograms. The present study, therefore, was designed to assess the intra- and inter- observer variability and diagnostic accuracy of radiologists in their evaluation of renal angiograms.

Materials and Methods

The angiograms of fifty patients (100 renal arteries), who had been referred for evaluation of their high blood pressure, were assessed by three independent radiologists to measure intra- and inter-observer variability of their diagnostic performance.

Results

The difference between two estimates of the degree of stenosis ranged from 0 to 65% for the individual readers and from 0 to 75% between two readers.

Bland-Altman plots showed that, although the average difference between two estimates of individual readers or of pairs of readers is small and less than 10%, the standard deviation is considerable, ranging from 17-23%.

A post-hoc analysis using two different cut-off points of stenosis (50% or 75%) showed that intra- and inter-observer agreement ranged from 77-85% with a κ ranging from 0.71-0.78 when stenoses of more than 50% were considered abnormal, whereas, when a stenosis of more than 75% was considered to be abnormal, the intra-observer agreement ranged from 86-94% with a κ ranging from 0.86-0.91. In this case the inter-observer agreement ranged from 83-91% with a κ ranging from 0.74-0.81.

Conclusions

The results of our study on the diagnostic performance of three experienced radiologists in their interpretation of renal artery angiograms indicate that the intra- and inter observer agreement with respect to their estimates of the degree of stenosis and the site of greatest stenosis are rather poor.

INTRODUCTION

Physicians often have to rely on the results of diagnostic tests that indicate the presence or absence of a disease or of an abnormal function. The interpretation of such tests, however, may show considerable variation and, hence, different investigators may not agree on their final diagnosis.

A common strategy to establish the reliability of a diagnostic test is to measure intra- and inter-observer variability by asking one or more observers to evaluate the same test results at two separate occasions. With this approach, accuracy and reproducibility of the angiographic estimation of coronary artery stenosis was found to vary considerably in some studies, ranging from 58-93%^{1,2,3}. On the other hand, when digital subtraction and filmscreen angiography of the lower limb were compared, only a small yet significant difference emerged with respect to the grading of stenoses in the superficial femoral artery while no difference in the grading of stenoses in popliteal, lower leg, or dorsalis pedis arteries was found⁴.

Little is known about the accuracy of the interpretation of renal angiograms by radiologists. This is surprising as clinical decisions about surgical correction or angioplasty of a stenotic lesion in the renal artery often are based on the radiologist's interpretation of the angiogram. Therefore, to determine the intra- and inter-observer agreement with respect to the estimation of the degree of renal artery stenosis (RAS), we evaluated the interpretations of renal angiograms by three experienced radiologists.

PATIENTS AND METHODS

The renal angiograms of sixty-two hypertensive patients were randomly selected for this study. The angiograms of twelve patients were withdrawn because one or both kidneys had multiple renal arteries or because images were of poor quality. All patients had been referred to the Hypertension Clinic for evaluation of their high blood pressure. They had a diastolic blood pressure above 100 mm Hg on at least three occasions and they were selected for renal angiography because a diagnosis of renovascular hypertension was suspected on clinical grounds or on the basis of 99m Tc-MAG-3 renography. Renal angiography was performed via the femoral approach (Seldinger technique) and the patients were given 40 ml of contrast material for the aortic films and, if necessary, an additional 10 ml for the selective ones. Abdominal aortic and renal angiograms were taken in the anterior-posterior projection. Oblique projections were performed when deemed necessary to better visualize stenoses or parts of the vasculature that were obscured by superposition of organs.

Evaluation of renal angiograms

The angiograms of fifty patients (100 renal arteries) were assessed twice, 4 weeks apart, by three independent experienced radiologists (A, B and C). For the evaluation of these angiograms the radiologists had the plain and sequential images at their disposal. The readers had to select the site of greatest stenosis or occlusion. On the films the pre- and post-stenotic renal arterial lumen diameter was measured in millimetres with a measuring rod. For each renal artery the percentage of stenosis, if any, was determined at the site of the greatest degree of narrowing by calculating the ratio between normal minus stenotic lumen and normal lumen diameter.

In addition, the readers had to state in which part of the renal artery the maximum percentage of stenosis was present (origo, first, second or third part of the artery) and what they thought the presumed pathological condition of the renal artery disease was, i.e. either atherosclerosis (ATH) or fibromuscular disease (FMD).

Statistical analysis

The intra-observer agreement was determined from the results of the two reading sessions. The inter-observer agreement, however, was calculated from the results of the first session only, so as to have an optimal measurement of reliability without bias⁵.

Calculations were made for observed agreement (OA) and κ (observed agreement corrected for chance agreement) as parameters for intra- and inter-observer variability⁶. As a further measure for the agreement within or between readers Pearson correlation coefficients were calculated with respect to the correlation between the two estimates of individual readers or for any pair of estimates of two different readers. In addition, plots were constructed according to Bland and Altman⁷ to assess the agreement within or between observers. In these figures, the average degree of stenosis of two estimates is plotted against the difference of these two estimates.

Both for intra- and for inter-observer agreement a post-hoc analysis was performed in two rounds using two different cut-off points of stenosis (either 50% or 75%), meaning that in the first round all diagnoses of more than 50% stenosis (50% cut-off point) were considered abnormal, whereas in the second round only diagnoses of more than 75% stenosis (75% cut-off point) were considered

abnormal. In this way one may get an impression about the readers' agreement in case one considers a stenosis of more than 50%, or more than 75% to be clinically significant. These two cut-off points were chosen because some clinicians advocate to intervene therapeutically when the degree of stenosis exceeds 50%⁸ while others favour intervention only with stenotic lesions of 75% or more⁹.

RESULTS

Intra-observer variability

Out of the 100 renal arteries, readers A, B and C thought some degree of stenosis to be present in 64, 75 and 65 cases respectively. The number of cases in which readers thought a stenosis to be present at one session but not at the other was negligible (table 1).

Table 1. Intra-observer agreement with respect to the diagnosis of stenosis

	Number of cases stenosis present or not		
	-	+/-	+
A	36	1	63
B	25	1	74
C	35	0	65
average	32	1	67

The number of cases in which the reader noted a stenosis to be present (+) or not (-) during both reading sessions or present in one and absent in the other session (+/-).

In case of stenosis, the mean difference between the estimates of from first and the second session were: $-2 \pm 20\%$, $-4 \pm 17\%$, $-2 \pm 22\%$ for the individual readers A, B and C respectively. These differences are plotted according to Bland and Altman in figures 1 to 3. Pearson correlation coefficients for the relationship between the first and the second estimate were 0.75, 0.71 and 0.73 respectively.

Figure 1. Bland-Altman plot of the reader A

Figure 2. Bland-Altman plot of the reader B

Figure 3. Bland-Altman plot of the reader C

The difference between the two estimates of the individual readers ranged from 0 to 65%. On average, in 33 out of the 100 cases (33%) the difference was 25% or less, in 7 cases (7%) between 25% and 50% and in 3 cases (3%) it was more than 50%.

In the post-hoc analysis where only stenoses of 50% or more were considered to be abnormal or clinically significant, the intra-observer agreement concerning the diagnosis ranged from 77 to 84% with a κ ranging from 0.71 to 0.76. In the analysis using 75% stenosis as the cut-off point the intra-observer agreement ranged from 86-96% with a κ ranging from 0.86-0.91 (table 2).

Table 2. Intra-observer agreement (OA) and κ when all stenoses of more than 50% were considered to be abnormal or when all stenoses of more than 75% were considered to be abnormal

	50% stenosis as cut-off point		75% stenosis as cut-off point	
	OA	κ	OA	κ
A	78%	0.71	94%	0.91
B	84%	0.74	96%	0.91
C	77%	0.76	86%	0.86

Leaving the origin of the renal artery as a site of stenosis out of the analysis, there is very good agreement between the two readings concerning the site of greatest stenosis (OA, on average, more than 95%), but if all sites of stenosis are considered, the intra-observer agreement ranges from 86-92%. In about one-third of the cases the individual readers indicated the greatest stenosis to be in the origin of the renal artery. For this location, the intra-observer agreement between the two sessions ranged from 70 to 92%.

With the exception of only one case the three readers always came to the same diagnosis during the two sessions as far as the presumed pathological condition of the renal artery disease was concerned (99% observed agreement; 79 ATH, 20 FMD, 1 no agreement).

Inter-observer variability

Out of the 100 renal arteries that each pair of readers A and B, B and C, and A and C evaluated, these pairs noted some degree of stenosis in 76, 77 and 59 of the cases respectively (on average in 71 out of 100 cases, 71%). In a number of cases one reader thought a stenosis to be present while the other did not (table 3). In these cases the difference between the two estimates was always less than 25%.

In case of stenosis, the mean difference between the estimates of the first and second reader were: $-8 \pm 22\%$, $-8 \pm 23\%$, $+2 \pm 22\%$ for the different pairs of readers A vs B, A vs C and B vs C respectively. These differences are plotted according to Bland and Altman in figures 4 to 6. Pearson correlation coefficients for the relationship between the estimates for the various pairs were respectively 0.74, 0.62 and 0.78.

Table 3. Inter-observer agreement with respect to the diagnosis of stenosis.

	number of cases stenosis present or not		
	-	+/-	+
A vs B	24	10	66
B vs C	23	9	68
A vs C	41	9	50
on average	29	9	62

The number of cases in which the readers noted a stenosis to be present (+) or not (-) during both reading sessions or present in one and absent in the other session (+/-).

The difference between the estimates of any two readers ranged from 0-75%. On average, in 42 out of the 100 cases (42%) this difference was 25% or less, in 10 cases (10%) between 25% and 50% and in 5 cases (5%) it was more than 50%.

In the post-hoc analysis where stenoses of 50% or more were considered to be abnormal or clinically significant, the inter-observer agreement concerning the diagnosis ranged from 82 to 85% with a κ ranging from 0.72 to 0.78. In the analysis using 75% stenosis as the cut-off point the inter-observer agreement ranged from 83-91% with a κ ranging from 0.74-0.81 (table 4).

Table 4. Inter-observer agreement (OA) and κ when all stenoses of more than 50% were considered to be abnormal or when all stenoses of more than 75% were considered to be abnormal.

	50% stenosis as cut-off point		75% stenosis as cut-off point	
	OA	κ	OA	κ
A vs B	82%	0.73	91%	0.81
B vs C	84%	0.72	90%	0.79
A vs C	85%	0.78	83%	0.74

Leaving the origin of the renal artery as a site of stenosis out of the analysis, there is very good agreement between pairs of readers concerning the site of greatest stenosis (OA, on average, more than 95%), but if all sites of stenosis are considered, the inter-observer agreement ranges from 74-77%. In about 45% of the cases, the pairs stated the greatest stenosis to be in the origin of the renal artery. For this location, the inter-observer agreement between the readers was, on average, only 46%.

With the exception of 4 cases the readers always came to the same diagnosis with respect to the presumed pathological condition of the renal artery (96% observed agreement; 81% ATH, 15% FMD and 4% no agreement).

Figure 4. Bland-Altman plot of the readers A and B

Figure 5. Bland-Altman plot of the readers A and C

Figure 6. Bland-Altman plot of the readers B and C

DISCUSSION

In the work-up of hypertensive patients in whom a diagnosis of renal artery stenosis is suspected, renal angiography is accepted as a highly reliable method for the detection of renovascular disease, and considered to be the gold standard^{10,11}. To evaluate the diagnostic accuracy of radiologists with respect to their angiographic diagnosis of renal artery stenosis and to assess their opinion on the degree and site of maximal stenosis, we determined the intra- and inter-observer agreement between three independent experienced radiologists. The evaluation was based on their interpretation of 50 renal angiograms (100 renal arteries).

The results of our study show appreciable differences in performance for the individual readers and, in particular, also between readers. For instance, in 10% of the cases the difference between two observers with respect to their grading of stenosis ranged from 25 to 50% and in 5% of the cases this difference even exceeded 50%. Intra-observer differences of more than 50% were also observed.

The plots according to Bland and Altman show that, although the average differences between the two estimates for an individual reader or of the pairs of readers is small and less than 10%, the standard deviations are considerable, ranging from 17-23%. These data, therefore, indicate that there is an enormous amount of disagreement in the interpretation of renal angiograms, both within and between readers.

Pearson correlation coefficients for intra-observer and inter-observer relationships ranged from 0.71-0.78 and from 0.62-0.78 respectively. So, also these correlations suggest a rather poor reproducibility of the estimates of the degree of stenoses.

When a stenosis of more than 50% is considered to be abnormal or clinically significant, the intra- and inter-observer agreement appear to be roughly similar ranging from 77-85% with a κ ranging from 0.71-0.78. On the other hand, when only stenoses of more than 75% are considered to be significant, the intra-observer agreement appears to be better than the inter-observer agreement. The degree of intra- and inter-observer agreement when a stenosis of more than 50% or more than 75% is used as cut-off point may be considered substantial¹² but is not at all as good as one would require from an investigation that is considered to be the gold standard.

Leaving the origin of the renal artery as a site of stenosis out of the analysis, there is very good agreement concerning the site of greatest stenosis (OA above 95%), but the intra-observer agreement falls to 86-92%, and the inter-observer agreement to 74-77% when all sites of stenosis are taken into account. The readers could not agree about the origin of the artery as the site of maximal stenosis in more than 50% of the cases, the intra-observer agreement in this case being 88%. Since stenoses at the origin of the renal artery may require another therapeutic strategy than angioplasty alone¹³, this finding may have important clinical consequences. Indeed, some clinicians advocate initial bypass surgery or placement of a stent for ostial atherosclerotic lesions to avoid the high failure rates of angioplasty¹³, but, as our data show, in these instances one cannot always rely on the angiographic diagnosis.

The intra-observer agreement concerning the presumed pathological condition was 99%, while the inter-observer agreement was 96%; in those cases, where there was no agreement, lesions were focal which makes the roentgenologic distinction between FMD (intimal or medial hyperplasia) and atherosclerotic lesions notoriously difficult¹⁴.

In conclusion, the results of our study on the diagnostic performance of three experienced radiologists in their interpretation of renal angiographic films indicate that the intra- and inter-observer agreement can vary considerably as far as the degree of stenosis and the presumed site of greatest stenosis is concerned. These results emphasize the need for a proper reference frame for the evaluation of renal angiograms.

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GENERAL DISCUSSION

In this chapter the main findings of the studies presented in this thesis will be discussed and put in perspective. Overall, our data can be categorized as follows:

- Presenting clinical signs and symptoms.
- Diagnostic tests and conformation of the diagnosis.
- Pathophysiological mechanisms of renovascular hypertension.

Presenting clinical signs and symptoms

Since renovascular hypertension is the most frequent form of secondary hypertension, clinicians will have to estimate the probability of finding this entity on the basis of certain presenting clinical signs and symptoms. The severity of blood pressure may be one of these signs. It is commonly held that patients with renovascular hypertension exhibit a much more sustained and higher blood pressure, perhaps even without a cuff response, than patients with essential hypertension. Indeed, in our studies differences in mainly systolic blood pressure were found between patients with essential hypertension and those with renal artery stenosis (RAS). However, such differences may simply be due to selection as patients with renal artery stenosis were older and frequently had symptoms of atherosclerotic disease (Ch.IV). Moreover, the blood pressure differences were based on office readings only. Blood pressure patterns during 24-hour or shorter monitoring periods may provide more reliable information about the severity of hypertension and may be helpful to identify patients who display a cuff response. Nevertheless, during thirty-minute recordings with an automatic device we found office and automatically recorded blood pressures to be comparable in subjects with RAS and in patients with essential hypertension. Thus, neither office nor short-term automatic blood pressure readings discriminate between hypertensives with and without renal artery stenosis (Ch.III). Also a pressure drop greater than 10 mmHg during the automatic recordings (a measure of cuff response?) was equally frequent in both groups (Ch.III).

The significance of certain clinical clues in selecting patients for further work-up of renal artery stenosis is very important. Selecting patients on the basis of clinical clues, as suggested by the Working Group on Renovascular Hypertension, will yield a high prevalence of renal artery stenosis (RAS). This was confirmed in our angiographically controlled studies where the prevalence of RAS was more than 40%, which is about 6-8 times higher than the 5% estimated prevalence of RAS in hospital-based surveys (Ch.IV and VII). We found some clinical clues to be more indicative for the presence of renal artery stenosis than others. A history of smoking with a diastolic blood pressure above 110 mmHg, or having a "small kidney on ultra-sound" with an additional clinical clue and symptoms of atherosclerosis in at least two other organs are very sensitive markers of RAS. The same is true for patients with more than three clinical clues (Ch.IV).

Diagnostic tests and confirmation of the diagnosis

For the detection of renal artery stenosis, renal scintigraphy with or without ACE-inhibition is by far the most frequently used test in the outpatient setting. However, as shown in Ch.IV this test performs poorly in predicting the presence of renal artery stenosis. A positive renography did have the best diagnostic accuracy in terms of post-test probability in those patients who had signs of atherosclerotic disease (Ch. IV). Considering the pre- and post-test probability of RAS in such patients we feel that there is no need for renographic studies in these patients. In such cases one should proceed directly to angiography. On the other hand, in our opinion, patients presenting with a "small kidney on ultra-sound" and no additional clinical clue carry a low probability of having RAS and therefore, should be considered to have essential hypertension (Ch.IV).

Most clinicians consider narrowing of the arterial lumen to be hemodynamically significant when it exceeds 50%. However, our study (Ch.V) shows that renographic parameters may change at a

relatively small degree of arterial luminal narrowing. To determine the smallest degree of renal artery stenosis that may be associated with changes in the renogram, we related the severity of the angiographically determined luminal narrowing in renal artery stenosis to renographic characteristics. It was found that in renal artery disease renographic changes can occur already at 30% of arterial narrowing and that, in renographic terms, bilateral renal artery stenosis does not "mimic" unilateral stenosis, but rather resembles a normal situation (Ch.V). Thus, a clinically significant arterial luminal reduction may start at a modest degree of stenosis which suggest that the significance of a stenosis in terms of blood pressure control is probably dependent upon individual adaptive mechanisms. In support of this view is the fact that patients can have a severe renal artery stenosis without hypertension; perhaps such patients are better equipped to mobilize adaptive mechanisms than others in whom lesser degrees of renal artery stenosis are associated with high blood pressure. These considerations may provide one explanation for the poor results obtained with renography as a screening test.

Another explanation may be that the interpretation of renographic images is subject to error. Despite the widespread use of renography, little is known about the diagnostic performance of nuclear medicine physicians with respect to their interpretation of renograms. By measuring the intra- and inter observer variability of nuclear medicine physicians in their evaluation of baseline and captopril renograms we hoped to get more insight in their diagnostic accuracy. Their interpretation was based on visual examination of the renographic curves as well as on well-established criteria for diagnosing renal artery stenosis. The sensitivity and post-test probability of their renographic diagnosis in relation to the angiographic diagnosis was found to be rather poor. Interestingly, blinding the physicians as to which renogram is the pre- and post captopril image seemed to enhance their diagnostic accuracy in case of positive scans (Ch.VI).

Taken together, the data clearly show that renography has only limited value in the screening for RAS. To a large extent this may be due to the effect of "inappropriate" changes (small degree of stenosis, small kidney with normal vasculature) or the absence of changes in renographic parameters in bilateral RAS and to a lesser extent on variability in the interpretation by nuclear medicine readers (Ch.IV and VI).

The captopril test which assesses the renin dependency of hypertension is another screening test to identify patients, who in case of positive findings will need subsequent investigation for renal artery stenosis. In a study, where patients were selected on the basis of the aforementioned clinical clues, the diagnostic yield of the captopril test was also found to be limited (Ch.VIII). The results of our study, therefore, confirm the growing consensus in the literature, that the captopril test, although initially introduced as a very sensitive and specific test, has only marginal potential in screening for RAS.

Thus, in our opinion these two tests (captopril test and renography) are no reliable screening tests for the detection of RAS.

Although we did not perform research on duplex Doppler studies this technique is known to be highly dependent on the skills of the operator and even in the hands of experienced investigators, as many as 15% of patients cannot be evaluated appropriately.

One should bear in mind that almost all studies reporting on the screening value of a particular test are biased, because they have not been performed prospectively, do not or insufficiently mention the criteria to select patients, or exclude patients from renal angiography in case of a negative screening test result. Consequently, we can never be informed about the real false negative rates of these tests. In our studies we did not exclude patients with a negative screening test for renal angiography. So, our data allow to estimate the false negative rates of these tests (Ch.VI and VIII).

Since the screening value of baseline and captopril renography and the captopril test were found to be so poor in our studies, we were looking for other ways to screen patients for renal artery stenosis. From a theoretical point of view the measurement of individual kidney blood flow could

have diagnostic potential. In this respect it is fortunate that Peters and co-workers recently introduced a noninvasive method to measure renal blood flow from first-pass radionuclide angiography. Although they themselves already questioned their method, we examined the use of this technique for screening purposes. Unfortunately, this technique was not found to be a useful tool for that intention (Ch.VII).

Finally, the results of our study on the diagnostic accuracy of nuclear medicine physicians prompted us to investigate the diagnostic accuracy of radiologists in their interpretation of renal angiograms, the gold standard. The data from that study (Ch.XI) indicate that the intra- and inter-observer agreement concerning estimates of the degree of stenosis and the site of greatest stenosis can vary considerably.

In conclusion, selecting patients suspected of having RAS on the basis of clinical clues is very helpful in determining those patients that need further work-up, but the use of the captopril test and renography in these patients is of limited screening value. Furthermore, the interpretation of renal angiograms by radiologists does not seem to have the diagnostic accuracy one should expect from the gold standard.

Pathophysiological mechanisms of renovascular hypertension

So far, the significance of the renin-angiotensin-aldosterone system in the pathogenesis and, in particular, the maintenance of renovascular hypertension remains controversial. Other vasoactive hormones like endothelins or natriuretic peptides may play a more important role in the maintenance of renovascular hypertension. For this reason we were interested in plasma levels and the renal extraction of endothelins and atrial natriuretic peptide (ANP). We found that endothelin levels and renal endothelin extraction are comparable in essential hypertension and in hypertension associated with renal artery stenosis. Renal uptake of endothelin was present in the majority of kidneys with patients with EH and RAS. Although some kidneys appeared to release endothelin, this phenomenon cannot be used for screening purposes (Ch.IX). Despite the fact that the circulating endothelin peptides represent some of the most potent endogenous vasoconstrictor agents, there is as yet no clear evidence to indicate that they are involved in the pathogenesis of hypertension. However, the current rapid development of selective endothelin receptor antagonists will hopefully help to settle this issue more conclusively within the near future.

ANP levels, on the other hand, were found to be significantly higher in patients with RAS than in patients with essential hypertension. Nevertheless, the renal extraction of ANP is comparable in essential hypertension and in hypertension associated with renal artery stenosis. Furthermore, our investigations revealed significantly higher arterial ANP levels in patients with unilateral RAS and an elevated renin ratio (≥ 1.5) than in those with a normal renin ratio. In addition, a significant reciprocal correlation between ANP and renin levels in the renal veins was found in patients with essential hypertension but not in patients with RAS (Ch.X). One can only speculate about the meaning of these findings and the role of ANP in the maintenance of renovascular hypertension. In heart failure ANP exerts an important compensatory, modulating role on the activity of the renin-angiotensin system, but what this interaction is in hypertension remains to be unravelled.

The large overlap in ANP levels in patients with or without renal artery stenosis is the main reason why the determination of ANP levels in hypertensive subjects cannot be used for screening purposes.

Future perspectives for research in the field of renovascular hypertension

In our opinion further research in the field of renovascular hypertension should concentrate on the following goals:

- 1) To develop better tests to visualize renal artery stenosis; preferably, these are tests that can be conducted in an outpatient setting and that are non-invasive.

In this respect new promising developments are:

- Magnetic Resonance Angiography (MRA) together with 2-D and 3-D time to flight and phase contrast techniques. The main advantages of this method are its non-invasive character and the avoidance of ionising radiation. It has the potential to measure renal artery blood velocity and total renal blood flow.

- Spiral CT angiography. This is a promising method of identifying renal artery stenosis, but an intravenous injection of contrast medium is necessary and the volume required is often greater than that used for arteriography. Nevertheless, spiral CT angiography has the advantage of being non-invasive. Furthermore, this method gives not only information about the vessel lumen but also the vessel wall and the location of plaques in the renal artery.

- 2) To develop tests which predict the results of intervention, when a stenosis is found to be present.

New radiopharmaceutical tracers and better criteria to define the hemodynamic significance of a stenosis are required. It is astonishing, that no two authors reporting on the results of renographic studies use the same technique to perform renograms or use the same criteria for evaluation. It is remarkable that we are still using arbitrary criteria, to define a positive test for renography despite many technical variations.

Thus for renography test conditions, methodology, diagnostic criteria and patient selection certainly warrant further investigation.

Finally the mechanisms that initiate and maintain hypertension in patients with renal artery stenosis but, in particular, also the mechanisms that counteract a rise in blood pressure need to be scrutinized further. Only when we understand the pathophysiological basis of renovascular hypertension will it be possible to develop new methods and techniques to diagnose and adequately treat patients with this condition.

SUMMARY

After a brief introduction to the studies described in this thesis, in

Chapter II an overview of the epidemiology, clinical features and natural history, screening and diagnostic procedures, and therapeutic intervention in renovascular hypertension is given.

Chapter III to XI deal with the various studies that have been performed and the main questions that were addressed in these studies are formulated.

Chapter III

Is the fall in blood pressure during a 30 minute registration period with an automatic device different in patients with EH from the one in patients with renovascular hypertension?

It is known that casual (office) blood pressure readings are unreliable due to the so-called cuff response. To be better informed about a patient's blood pressure, automatically assessed recordings are often necessary. It is usually assumed that a cuff response occurs mainly in patients with essential hypertension (EH), but there is no compelling data to show that this phenomenon is less prevalent in subjects with renovascular hypertension, in whom a more sustained and higher blood pressure might be anticipated.

In a comparative study of automatically assessed blood pressure recordings in patients with EH (n=19) and renovascular hypertension (n=19), the difference between office and automatically assessed blood pressure during 30 min. appeared to be similar in both groups. The number of patients showing a pressure drop greater than 10 mmHg also was comparable in both groups. Blood pressure levels obtained in the office were found to overestimate "true" blood pressure not only in essential but also in renovascular hypertension.

Chapter IV

Can we identify hypertensive patients with renal artery stenosis by means of presenting clinical signs and symptoms or with combinations of these, and what is the value of renography as a screening test in such a selected population?

Selecting patients on the basis of clinical clues (as have been formulated by the Working Group on Renovascular Hypertension in their final report in 1987) resulted in a high prevalence (41%) of angiographically proven RAS. A history of smoking with a diastolic blood pressure above 110 mmHg was found to be a very sensitive clue for renovascular hypertension and the more clinical clues a hypertensive patient has the more likely a diagnosis of RAS is. All patients with more than 3 clinical clues had RAS and patients a "small kidney on ultra-sound" and an additional clinical clue had a 54% probability of RAS, while patients with a "small kidney on ultra-sound" and no additional clinical clue had a 100% probability of not having RAS.

Renography (both baseline and post-captopril) was of minimal value in this selected population. A positive renogram did have the best diagnostic accuracy in those patients who had signs of atherosclerotic disease with a post-test probability of a positive renogram of 78%.

Chapter V

What is the smallest degree of renal artery stenosis that may be associated with changes in renographic characteristics?

In the literature there is no consensus about what percentage of renal arterial narrowing should be considered hemodynamically significant in patients with renovascular disease.

From this point of view it would be of interest to relate the angiographic findings of different patients to their renographic characteristics in order to establish the smallest degree of renal artery stenosis that may be associated with changes in renographic characteristics.

We related the angiographic severity of luminal narrowing in renal artery stenosis to I¹³¹-hippuran

renographic characteristics in 72 patients who had been selected for renal angiography because a diagnosis of renovascular hypertension was suspected. Comparing non-stenotic kidneys with stenotic kidneys, significant differences in T_{max}, T_{1/2} and counts under the curve to T_{max} were apparent already at 30% of arterial luminal narrowing. In patients with unilateral renal artery stenosis, the difference in counts under the curve to T_{max} between pairs of kidneys also was significantly different at 30% of stenosis.

The study also showed that patients with bilateral stenosis could not be differentiated well from patients with essential hypertension because the value of T_{max} on either side or the difference of T_{max} between the two kidneys and the values of the other parameters were similar except for the difference in counts to T_{max}. On the basis of these findings it seems that in renographic terms bilateral RAS does not "mimic" unilateral stenosis, but rather resembles a normal situation.

Thus, in renal artery disease significant renographic changes can occur already at 30% of arterial luminal narrowing.

Chapter VI

What is the diagnostic performance of nuclear medicine physicians with respect to their interpretation of baseline, captopril and paired renograms and how do these results relate to renal angiography?

Numerous reports have documented a sensitivity and specificity ranging from 50%-95% for baseline and post-captopril renography as a screening test for renal artery stenosis.

Nuclear medicine physicians interpreting renograms base their conclusions on visual interpretation and on some established criteria for making a diagnosis of renal artery stenosis.

The diagnostic performance of experienced nuclear medicine physicians with respect to their interpretation of baseline, captopril and paired renograms, however, has not been prospectively assessed in relation to the results of renal angiography, the so-called "gold standard".

The results of our study showed that the concordance in the renographic diagnoses of 56 renograms between three experienced nuclear medicine physicians was reasonably good, with an intra-observer agreement and κ ranging from 64%-89% and from 0.52-0.75 respectively and an inter-observer agreement and κ ranging from 68%-86% and from 0.61-0.82 respectively. However, the sensitivity of their interpretation of paired baseline plus captopril renograms in relation to the angiographic diagnosis was poor and below 50%.

The post-test probability of RAS in case of a negative renographic study was found to be rather similar to the pre-test probability (prevalence) of 46%. The post-test probability of RAS when the paired renogram was positive increased to around 60% when the readers were blinded as to which renogram was the one after captopril but decreased below 25% when they were aware of which of the two renograms was obtained after captopril.

Chapter VII

Are measurements of renal blood flow from first-pass radionuclide angiography are performed in hypertensive patients in whom a diagnosis of renovascular hypertension is suspected helpful to detect renal artery stenosis?

In 1987, Peters and co-workers described a technique for noninvasive measurement of organ blood flow, which was based on the fractional distribution of cardiac output. When applied to the renal circulation, measurements of individual kidney blood flow may indicate whether a renal artery stenosis is present or not.

We performed measurements of renal blood flow from first-pass radionuclide angiography in 29 patients with EH and in 19 patients with RAS. In patients with normal kidneys the mean value of renal blood flow (RBF) measurements ranged from 10.5% to 10.9% of cardiac output. Only small stenotic and small kidneys with normal renal arteries showed a significant reduced baseline RBF as compared with normal kidneys; this difference disappeared after ACE-inhibition only for small kidneys with normal renal arteries.

In patients with stenosed kidneys RBF tended to be reduced both at baseline and after captopril, but the differences with normal kidneys were not statistically significant. After ACE-inhibition RBF increased in the majority of kidneys, but post-captopril RBF data did not differ significantly from those at baseline.

We conclude that RBF measurements using first-pass radionuclide angiography with ^{99m}Tc -MAG-3 either before or after ACE-inhibition cannot reliably discriminate between patients with essential hypertension and patients with renal artery stenosis.

Chapter VIII

When hypertensive patients are selected on the basis of presenting clinical clues suggestive for renovascular hypertension, what will be the performance of the captopril test?

Since there is no pathognomonic sign or clinical clue identifying renal artery stenosis in hypertensive patients, a single noninvasive diagnostic test, easily performed in a outpatient facility and with a high predictive value would be the ideal screening test.

Angiotensin converting enzyme inhibitors given to hypertensive patients may enable the clinician to distinguish patients with EH from those with hypertension and renal artery stenosis. The so-called captopril test is a practical but controversial screening test studying the effect of ACE inhibition on blood pressure (magnitude and duration of fall in blood pressure) and changes in renin levels. From the results of the captopril test on these two parameters it may be possible to identify patients with renovascular hypertension.

After placebo and after captopril no significant changes (absolute or proportional) in blood pressure values were found between patients with EH ($n=26$) or RAS ($n=20$), either for all measurements or if only the fall in blood pressure was taken into account.

Receiver operator characteristic curves of both baseline and post-captopril peripheral renin levels were constructed, which indicate that the captopril test does not discriminate appropriately between patients with EH and RAS. Therefore, we would not advise the use of the captopril test as a screening test for RAS in hypertensive patients in whom a high level of clinical suspicion for RAS is already present.

Chapter IX

Are endothelin levels elevated in renovascular hypertension and is there a difference in renal extraction between kidneys of patients with essential hypertension compared to kidneys with a renal artery stenosis?

Circulating endothelin has been suggested to play a role in local vascular regulation.

As such it could be involved in the pathogenesis and maintenance of renovascular hypertension.

In our study endothelin levels and renal endothelin extraction were found to be comparable in EH and in hypertension associated with renal artery stenosis. Whereas renal uptake of endothelin was the rule, some kidneys, however, released this peptide irrespective of presence or absence of RAS. It is of interest that all kidneys with a normal blood supply released endothelin.

Chapter X

Are elevated levels of atrial natriuretic peptide in renovascular hypertension due solely to increased secretion or is an alternation in the renal extraction of this peptide responsible for this phenomena?

We studied the relationship between the renal fractional extraction of atrial natriuretic peptide (ANP) and renin in untreated patients under standardized conditions.

Arterial levels of ANP were found to be significantly higher in patients with unilateral or bilateral RAS than in patients with EH. Patients with EH and left ventricular hypertrophy (LVH) had a significantly higher arterial ANP level than those with no LVH but in patients with RAS, arterial ANP levels were similar between those with or without LVH.

Renal venous ANP levels were significantly higher in stenotic kidneys than in normal kidneys but

fractional extraction of ANP was similar around 0.50 (range from 0-0.83) in normal kidneys of patients with EH, and in stenotic and contralateral kidneys of patients with RAS. A significant correlation between arterial ANP and the arterio-venous difference of ANP was found. This relationship was similar for normal and for stenotic kidneys. The data of our study suggest that saturation of ANP extraction through the kidneys does not occur and probably is independent of renal blood flow.

Chapter XI

What is the diagnostic performance in terms of intra- and inter-observer agreement of experienced radiologists with respect to their interpretation of renal angiography?

Little is known about the accuracy of the interpretation of renal angiograms by radiologists. This is surprising as clinical decisions about surgical correction or angioplasty of a stenotic lesion in the renal artery often are based on the radiologist's interpretation of the angiogram. Can renal angiography really be considered the "gold standard"?

In this study on the diagnostic performance of three radiologists the difference between two estimates of the degree of stenosis ranged from 0 to 65% for the individual readers and from 0 to 75% between two readers.

Bland-Altman plots showed that, although the average difference between two estimates of individual readers or of pairs of readers is small and less than 10%, the standard deviation is considerable, ranging from 17-23%.

A post-hoc analysis using two different cut-off points of stenosis (50% or 75%) showed that intra- and inter-observer agreement ranged from 77-85% with a κ ranging from 0.71-0.78 when stenoses of more than 50% were considered abnormal, whereas, when a stenosis of more than 75% was considered to be abnormal, the intra-observer agreement ranged from 86-94% with a κ ranging from 0.86-0.91. In this case the inter-observer agreement ranged from 83-91% with a κ ranging from 0.74-0.81.

The results of our study on the diagnostic performance of these three experienced radiologists in their interpretation of renal artery angiograms indicate that the intra- and inter observer agreement with respect to their estimates of the degree of stenosis and the site of greatest stenosis are rather poor.

SAMENVATTING

Na een korte inleiding wordt in **hoofdstuk II** een overzicht gegeven van epidemiologie, natuurlijk beloop, klinische aspecten, screenings-testen en therapie van renovasculaire hypertensie.

Hoofdstuk III betreft een onderzoek waarin gekeken wordt naar bloeddruk patronen gedurende 30 min. automatische bloeddrukmetingen bij patiënten met essentiële hypertensie (EH) en patiënten met een stenose van de nierarterie (RAS). De resultaten tonen aan dat er geen significante verschillen in bloeddruk patronen zijn en dat het aantal patiënten met een bloeddruk daling van meer dan 10 mmHg tijdens automatische bloeddruk meting (een maat voor de zogenaamde cuff response?) vergelijkbaar is. Overigens blijken bij incidentele metingen van de bloeddruk hogere bloeddruk waarden te worden gevonden in beide groepen patiënten.

In **hoofdstuk IV** wordt een onderzoek beschreven waarbij is gekeken naar de waarde van klinische karakteristieken (zoals aangegeven door de Working Group on Renovascular Hypertension in 1987) bij de selectie van patiënten met hypertensie. In de groep van patiënten geselecteerd op basis van deze karakteristieken vinden wij een hoge prevalentie van RAS, nl. 46%. De meest gevoelige combinatie van karakteristieken blijkt te zijn: roken tezamen met een diastolische bloeddruk van meer dan 110 mmHg.

Verder blijken alle patiënten met meer dan drie karakteristieken RAS te hebben. In de groep van patiënten met "één kleine nier bij echografie" blijken diegenen die er nog een andere karakteristiek bij hadden een 54% waarschijnlijkheid op RAS te hebben, terwijl diegenen zonder een extra karakteristiek geen RAS te hebben.

Renografisch onderzoek heeft als screenings test dan ook vrijwel geen waarde bij deze patiënten.

Aangezien niet goed bekend is bij welke mate van vernauwing van een nier-arterie significant hemodynamische veranderingen optreden, onderzochten we in **hoofdstuk V** bij 72 patiënten wanneer renografische veranderingen optreden.

Het blijkt dat significante renografische veranderingen al bij 30% vernauwing van een arterie kunnen optreden.

In **hoofdstuk VI** worden de resultaten van het onderzoek naar de diagnostische vaardigheden van drie nucleair geneeskundigen gegeven bij de beoordeling van 28 basale en 28 captopril renogrammen. Wat betreft de renografische diagnose blijken zij het redelijk goed met elkaar eens te zijn. Echter, als men hun renografische beoordeling vergelijkt met de resultaten van röntgenologisch onderzoek (angiografie), hetgeen als de gouden standaard kan worden beschouwd, dan blijken de beoordelingen van de nucleair geneeskundigen een sensitiviteit van minder dan 50% te hebben.

In 1987 werd een nieuwe methode beschreven voor het meten van de bloed-doorstroming door de nier met behulp van nucleaire angiografie. In **hoofdstuk VII** geven we de resultaten van metingen met deze techniek bij 48 patiënten met hoge bloeddruk. Metingen van de bloeddoorstroming van de nieren werden verricht om te zien of veranderingen in de doorstroming na toediening van captopril gebruikt kunnen worden voor de diagnostiek van vernauwing in de nier slagader.

Na toediening van captopril worden met deze techniek echter geen significante verschillen in de bloed doorstroming van de nieren tussen patiënten met EH en die met RAS waargenomen.

De captopril test is een test die gebruikt wordt om patiënten met hoge bloeddruk te screenen op de eventuele aanwezigheid van RAS. De vraagstelling in **hoofdstuk VIII** is of bij patiënten die geselecteerd zijn op grond van klinische karakteristieken zoals beschreven in hoofdstuk IV, de captopril test nog een aanvullende waarde heeft.

Het blijkt dat de captopril test (veranderingen in bloeddruk en in renine spiegels) bij deze patiënten van weinig waarde is.

Endotheline is een hormoon dat een (plaatselijke) werking heeft op de bloedvaten. Het is mogelijk dat endotheline een rol speelt bij hypertensie ten gevolge van RAS. Om beter inzicht in de werking van endotheline bij RAS (**hoofdstuk IX**) te verkrijgen onderzochten we de extractie van dit

hormoon in patiënten met RAS en met EH. De extractie van endotheline door de nieren bleek niet significant verschillend te zijn bij deze patiënten, echter alle kleine nieren van mensen met EH gaven endotheline af aan de circulatie.

Atrial natriuretisch hormoon (ANP) is afkomstig uit de voorkamers van het hart en speelt een rol bij o.a. de vocht/volume regulatie. Het onderzoek naar de rol van ANP (**hoofdstuk X**) in RAS toont aan dat ANP spiegels verhoogd zijn bij patiënten met RAS in vergelijking met patiënten met EH. Bij de laatste groep hebben diegenen met linker hartkamer hypertrofie (LVH) hogere ANP spiegels dan diegene zonder LVH.

De extractie van ANP door de nieren is gelijk in alle onderzochte groepen patiënten (ongeveer 50%). We konden verder aantonen dat verzadiging van extractie niet optreedt en dat de extractie waarschijnlijk niet afhankelijk is van de bloed doorstroming door de nier.

In **hoofdstuk XI** worden de resultaten van het onderzoek naar de diagnostische vaardigheden van drie röntgenologen bij de beoordeling van 50 angiogrammen van de nieren beschreven. De intra- en inter-observator overeenstemming met betrekking tot de beoordeling van de angio's t.a.v de graad van vernauwing van een nier slagader varieert respectievelijk van 0-65% en van 0-75%.

In een post-hoc analyse, waarbij een graad van vernauwing groter dan 50% of groter dan 75% als klinisch significant wordt beschouwd bleek de intra- en inter-observator overeenkomst te variëren respectievelijk van 77-85% met een κ variërend van 0.71-0.78 en van 83-94% met een κ van 0.74-0.91. Deze gegevens wijzen erop dat de beoordeling van angio's door röntgenologen te wensen overlaat.

DANKWOORD

Peter de Leeuw dank ik voor alle hulp bij de opzet, de uitvoering en uitwerking van de in dit proefschrift beschreven onderzoeken. Legio malen heb ik van de onuitputtelijke opslag capaciteit van jouw astrocyten gebruik mogen maken. Deze opslag capaciteit ligt uitgesproken rechts van de mediaan, evenals het aantal herschreven versies van ieder hoofdstuk.

Guus Flendrig dank ik hartelijk voor zijn speciale introductie in het academisch woud dat begon met de woorden "ik ben het baasje hier" en alles wat je daarna voor me hebt gedaan. Je was altijd vol interesse naar de resultaten van de onderzoeken. Helaas, en het doet me nog altijd veel verdriet dat je te vroeg bent overleden. De laatste woorden die je tegen mij zei gingen over dit proefschrift; "Kom op Gerrit nog een tabelletje". Ze staan in mijn geheugen gegrift.

De mensen van de hypertensie/nefrologie werkgroep, in het bijzonder Paul van Es voor alle organisatie en planning van de onderzoeken en de prettige samenwerking. Maar niet te vergeten Carlo Gaillard, Arie Lavrijssen, Maarten Christiaans, Ton Luik, Karel Leunissen en Paul Schiffrers voor al hun belangstelling, nuttige suggesties en patienten.

Ger Ritsema en Ard Vreugdenhil bedank ik voor hun inzet in het prille begin toen het maar niet wilde vlotten. Maar gij ziet, het is er toch van gekomen.

Verder dank ik de mensen van de afdeling Nucleaire Geneeskunde voor de prettige samenwerking. In het bijzonder Guido Heidendal, Marinus van Kroonenburgh, Harry van der Pol (Maasland Z.H. Sittard) en Servé Halders.

Tevens dank ik Jos van Engelshoven, Kiam Oei, Dirk Koster en Michiel de Haan van de afdeling radiodiagnostiek van het azM voor hun hulp en prettige samenwerking bij het tot stand komen van dit proefschrift.

De verpleging van de Intensive Care (D3 en F3) en B5 dank ik voor hun begrip en stilzwijgen als ik moe van het "onderzoeken" weer eens kwam uitrusten op de afdeling.

Tiny Wouters dank ik hartelijk voor de hulp bij de voorbereiding van dit manuscript.

CURRICULUM VITAE

De schrijver van dit proefschrift werd geboren op 04-02-1948 te 's-Gravenhage.

In 1968 werd op het Montessori lyceum te Rotterdam het HBS-B eindexamen behaald.

Van 1968 tot 1975 studeerde hij medicijnen aan Rijks Universiteit te Utrecht met een jaar onderbreking i.v.m. verblijf in de V.S. Het eerste deel van het doctoraal examen werd cum laude in 1973 afgelegd. Op 25-07-1975 behaalde hij zijn arts-examen.

Van 1975 tot 1977 bereidde hij zich voor op zijn werkzaamheden in de tropen (stages chirurgie, verloskunde en kindergeneeskunde), afgesloten met de nationale tropen cursus in Amsterdam.

Van 1977 tot 1981 was hij werkzaam als tropen arts in Afrika, eerst als algemeen arts in Kisumu (Kenya) later als public health officer in Niamey (Niger).

Van 1981 tot 1986 volgde hij zijn opleiding tot algemeen internist bij Prof WH Birkenhäger in het Zuider ziekenhuis te Rotterdam. Registratie als internist vond op 01-09-1986 plaats.

Daarna was hij werkzaam als chef de clinique in het van Wheel Bethesda ziekenhuis te Dirksland.

Sinds 1990 is hij werkzaam in het Academisch ziekenhuis te Maastricht (AZM) bij de werkgroep algemene interne geneeskunde.

Hij is geregistreerd als intensivist en werkt als IC coördinator op de algemene intensive care (afdeling D3 en F3). Daarnaast doet hij de polikliniek voor infectie-, tropische- ziekten en AIDS.

Binnen het AZM is hij lid van de geneesmiddelen commissie, de infectie commissie en de commissie bloed-overdraagbare ziekten. Tevens is hij lid van de FTO (farmaco-therapeutisch overleg) voor de regio zuid/Zuid Limburg.

Binnen de Faculteit der Geneeskunde van de Universiteit Limburg is hij lid van de vaardigheidstoets beoordelings commissie.

Hij is getrouwd met Inez Whipple Risselada en zij hebben vier zonen.