Imaging studies in renovascular hypertension

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Imaging studies in renovascular hypertension

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Chapter

1

Introduction

Introduction

The clinical presentation of renovascular disease varies significantly between patients, ranging from incidental findings of renal artery stenosis on angiography to severe hypertension and progressive loss of renal function. Renovascular disease is in approximately two thirds of the adult population caused by atherosclerosis, whereas the second most common cause is fibromuscular dysplasia (1).

Renal artery stenosis leading to renovascular hypertension is the most frequent cause of secondary hypertension with an estimated prevalence of 3-5% in the general population of hypertensive patients (2). Progression of atherosclerotic renovascular disease can lead to loss of renal volume and subsequent deterioration of renal function in a considerable percentage of patients and, when present bilaterally, result in end-stage renal failure (3). Early identification of renal artery stenosis in (hypertensive) patients poses an important clinical challenge, since surgical or percutaneous treatment of these lesions may improve blood pressure control and/or stabilize renal function, even though this has been disputed in a recent publication (1,2,4,5).

To date, conventional x-ray angiography still is considered as the most accurate method to assess the presence and severity of renal artery stenosis. However, its invasive nature and high costs, in addition to the requirement to use nephrotoxic contrast medium and radiation, make this procedure less appropriate as a screening modality in the general hypertensive population with its relatively low prevalence of renal artery stenosis.

The ideal screening procedure to select patients for renal angiography should be simple, easy applicable, non- (or minimally) invasive and highly accurate both for the detection of renovascular disease and for assessment of its clinical significance. In search of such a test, several non-invasive imaging methods (e.g. intravenous pyelography and intravenous digital subtraction angiography) were proposed but were later discarded because of insufficient results (1,2,6). Likewise, reported results concerning captopril renography have shown contradictory results, especially in patients with bilateral disease (7-9).

Duplex ultrasound has the potential to combine direct visualization of the renal arteries with acquisition of flow velocity profiles, thus providing both anatomical and functional information and has been advocated as the optimal screening test. However, the results of studies concerning the validity of duplex ultrasound are sometimes conflicting and there is no general agreement about its value as a screening test for renovascular disease (10,11). In chapter 2 the accuracy of duplex ultrasound for the diagnosis of renal artery stenosis in a group of hypertensive patients is evaluated.

Early studies on magnetic resonance (MR) angiography of the renal arteries performed without the use of paramagnetic contrast medium, such as time-of-flight (TOF MRA) and phase-contrast MR angiography (PC-MRA), yielded variable results with respect to detection of renal artery disease (12,13). Artefacts caused by the pulsatility of blood flow, that hinder image interpretation could, at least partially, be responsible for this variation in test accuracy. In chapter 3 a prospective study is described in which cardiac synchronization is introduced in a three-dimensional phase-contrast MR angiographic technique (3D PC-MRA) as a possible solution to overcome these pulsatility artefacts.

In recent publications dedicated computed tomography (CT) and magnetic resonance (MR) protocols were introduced for volumetric data acquisition with high contrast-enhancement of the renal vessels yielding high sensitivities and specificities for detection of main renal

artery stenosis (14-19). However, most publications on CT and MR angiography of the renal arteries address primarily atherosclerotic renovascular pathology. The presence of fibromuscular dysplasia is mentioned in only a few publications and, with the exception of Bergri et al (20), no separate assessment of the test performance in this subgroup is indicated. Yet, the good long-term results for renal revascularisation of stenoses secondary to fibromuscular dysplasia make early and accurate identification of these patients imperative (21). Results of a prospective multicenter study (RADISH-study) concerning the validity of MR angiography (MRA) and CT angiography (CTA) to diagnose renal artery stenosis in hypertensive patients show an overall poor performance of both tests, contrary to the results of all other published studies (22). A striking difference with the other studies was the relatively high proportion of patients with fibromuscular dysplasia in this series, which may have contributed to the poor tests performances. In chapter 4, the phase-contrast MRA (PC-MRA), gadolinium enhanced MRA (CE-MRA) and CTA data of all patients from the RADISH-study with angiographically proven renal artery fibromuscular dysplasia are analysed. The feasibility of the MR angiography (MRA) and CT angiography (CTA) techniques was evaluated in the assessment of fibromuscular dysplasia and to identify possible sources of error in depiction of this renal artery disorder.

However, similar to other imaging methods employed in the diagnosis of renal artery stenosis, these techniques solely rely on the morphologic assessment of the renal arteries. In order to assess the hemodynamic, and possibly the therapeutic, consequences of a particular arterial lesion, additional functional tests are still required.

Phase-contrast MR imaging (PC MR), which goes beyond morphologic imaging by allowing quantitative evaluation of flow dynamics, has been suggested as a non-invasive modality for renal artery blood flow analysis. In combination with cardiac triggering, flow rates can be determined at specified phases of the cardiac cycle, which enables evaluation of the flow rates as a function of time. To date, published studies show varying success in renal blood flow measurement, in which respiratory motion appears to be a considerable source of error (23,24). Synchronisation with respect to respiratory motion, along with cardiac triggering, seems to be necessary to obtain accurate, reproducible flow data (25,26). Results concerning the feasibility and reproducibility of two respiration controlled PC MR techniques to measure the blood flow in the individual renal arteries in healthy volunteers are presented in chapter 5.

In chapter 6, the accuracy of 2D PC MR flow quantification is further analysed in patients suspected of having renovascular hypertension by comparing the results of these measurements with those obtained by the intra-arterial ^{133}Xe washout technique. In the same chapter, the 2D PC MR flow data were related to functional renal information as obtained by selective arterial and venous renin sampling in order to assess the presence of renal artery stenosis.

The objectives of this thesis are:

1. To assess the accuracy of duplex ultrasound for the diagnosis of renovascular disease in a cohort of hypertensive patients.
2. To evaluate the usefulness of three-dimensional phase-contrast magnetic resonance angiography (3D PC-MRA) performed with cardiac synchronisation in the assessment of renal arteries.

3. To investigate the accuracy of 3D PC-MRA, contrast-enhanced MRA (CE-MRA) and spiral CT angiography (CTA) in the diagnosis of renal artery fibromuscular dysplasia and to identify possible sources of error in this group of patients that may have contributed to the overall poor tests performances and to give suggestions for further improvement.
4. To study the accuracy and usefulness of 2 dimensional phase contrast magnetic resonance (2D PC MR) renal artery flow measurements.

Outline of this thesis:

- Chapter 2 describes the diagnostic accuracy of duplex ultrasound in detecting renal artery stenosis in seventy-eight hypertensive patients.
- Chapter 3 evaluates the accuracy of 3D PC-MRA of the renal arteries performed with cardiac synchronisation in a study with 38 patients, using intra-arterial angiography as standard of reference.
- Chapter 4 describes the analysis of MRA and CTA data of all patients from the RADISH study with angiographically proven renal artery fibromuscular dysplasia.
- In Chapter 5 the validity and reproducibility of cardiac gated, respiratory controlled 2D PC MR renal artery flow quantification is assessed in 12 healthy volunteers.
- Chapter 6 addresses the accuracy of 2D PC MR renal artery flow measurements in hypertensive patients by comparing the results of these measurements with those obtained by $^{133}\text{Xenon}$ washout; and relates 2D PC MR flow measurements to functional renal information as obtained by selective arterial and venous renin sampling.
- Chapter 7 consists of the summary of this thesis, the conclusions and recommendations.

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Chapter 2

Renovascular disease in patients with hypertension: detection with duplex ultrasound.

de Haan MW, Kroon AA, Flobbe K, Kessels AGH, Tordoir JH, van Engelshoven JMA, de Leeuw PW.

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Abstract

The aim of this study was to evaluate the accuracy of duplex ultrasound for the diagnosis of renovascular disease in a cohort of hypertensive patients. In seventy-eight patients suspected of renovascular hypertension on clinical grounds duplex ultrasound examination of the renal arteries was performed. Renal angiography was used as the standard of reference. Duplex ultrasound was inconclusive in 11 kidneys (7%). None of the supernumerary renal arteries was detected with duplex ultrasound. The overall prevalence of significant renovascular disease ($\geq 50\%$ stenosis) was 20%. Based on the combination of parameters at thresholds commonly applied in current literature: i.e. $PSV_{max} > 180$ cm/sec and $RAR > 3.5$, the overall sensitivity of duplex ultrasound for detection of hemodynamically significant renovascular disease was 50.0% with a specificity of 91.3% (PPV: 87.9%; NPV: 59.1). Lowering the thresholds for both parameters improved the test results at the cost of a significant increase of false positive examinations. In a population of hypertensive patients clinically suspected of renovascular hypertension, only limited results for duplex ultrasound could be acquired in the detection of renovascular disease. This result, in combination with the wide range of sensitivities and specificities published in international literature and the relatively large number of incomplete examinations does not support the general application of duplex ultrasound as a screening procedure for detection and assessment of renovascular disease.

Introduction

Identification of renovascular disease in hypertensive patients remains important as correction of renal artery stenosis may improve blood pressure control or stabilize renal function (1,2,3). Conventional x-ray angiography still is the most accurate method to assess the presence and severity of renal artery stenosis. However, its invasive nature and high costs make this procedure unsuitable as a screening modality in a population of patients with a low prevalence of renal artery stenosis. Several less invasive tests (including captopril renography) have been proposed to select patients for angiography (4-7). Magnetic Resonance Angiography (MRA) has shown promising results as a non-invasive imaging modality for assessing the renal arteries, but to date fails to depict the hilar and parenchymal renal arteries. Also, CT angiography shows excellent depiction of the first segments of the renal arteries, at the expense of a relatively large amount of (nephrotoxic) contrast material and radiation.

Duplex ultrasound has the potential to combine direct visualization of the renal arteries with acquisition of flow velocity profiles, thus providing both anatomical and functional information and has been advocated as the optimal screening test. However, the results of studies concerning the validity of duplex ultrasound are sometimes conflicting and there is no general agreement about its value as a screening test for renovascular disease (8,9).

The aim of this study was to evaluate the accuracy of duplex ultrasound for the diagnosis of renal artery stenosis in a cohort of unselected hypertensive patients with clinical suspicion of renovascular disease using conventional renal angiography as standard of reference. In addition, we tried to determine the most useful combination of thresholds for the applied ultrasound parameters.

Materials and methods

Patients

Over a period of 3 years, 78 consecutive patients with malignant, accelerated and/or treatment-resistant hypertension (blood pressure > 160/100 mm Hg despite treatment with 2 or more antihypertensive drugs), loss of renal function after angiotensin-converting enzyme (ACE) inhibition, unilateral loss of kidney volume or unexplained deterioration of renal function (change in serum creatinin >20 μ mol/l within 12 months) were examined by both colour duplex ultrasound and conventional x-ray angiography of the renal arteries.

The results of 7 patients were excluded from analysis because duplex ultrasound was performed only after endoluminal renal intervention. Thus, data of 71 patients was available for evaluation and comparison. Thirty-three (46%) of these patients were men and thirty-eight women; mean age was 55 years (range 20 - 78 years).

Duplex ultrasound

The ultrasound studies were performed using a colour duplex scanner with a 2.5 and/or 5.0 MHz probe (Aloka Company Europe, Hoofddorp, The Netherlands) with the patient in supine position. Patients were either fasting or had received a clear-liquid diet since midnight on the day before the examination. The patients were examined in anterior, lateral and anterolateral position. The renal length was recorded for each kidney. Doppler samples were taken along the course of the renal arteries as well as in the abdominal aorta

at the level of the renal arteries. Peak velocity readings were obtained by means of angle correction with Doppler-to-vessel angle of less than 60° and a 2 mm Doppler gate width. Following published criteria, a peak systolic velocity in the renal artery (PSV_{max}) of more than 180 cm/sec and its ratio to the peak systolic velocity in the abdominal aorta (RAR) of 3.5 or more were used to discriminate a renal artery stenosis of $\geq 50\%$ (10-12). A renal artery stenosis of $< 50\%$ was defined as $PSV_{max} > 180$ cm/sec in combination with a $RAR < 3.5$. The grey-scale images were not used to confirm or refute a diagnosis of renal artery stenosis. Renal artery occlusion was diagnosed when there was no flow signal in the renal artery and a low amplitude velocity signal from the renal parenchyma. The ultrasound studies were interpreted without knowledge of the results of angiography. Two vascular technicians experienced in the use of Doppler techniques performed all examinations. The technicians often sought the help of their colleague for patients who were difficult to examine. No difference was noted in the accuracy of the results or in the quality of the studies between the two technicians who participated in our study. The examination time lasted between 45 and 60 minutes for both sides.

Conventional Angiography

Angiography of the abdominal aorta and renal arteries was performed in the anteroposterior view with injection of 35 ml contrast material through a 5-F pigtail catheter (William Cook Europe, Bjaeverskov, Denmark) positioned at the level of the renal arteries. If the renal arteries were not adequately depicted, additional angiographic series were obtained in oblique projections and/or selective renal angiography was performed with an end-hole catheter (William Cook Europe).

For the purpose of this study two independent observers, who were unaware of the duplex ultrasound results and/or clinical history interpreted the angiographic examinations again. The status of the renal artery was graded into four categories: normal; less than 50% stenosis; greater than 50% stenosis; or occluded. Renal arteries with evidence of fibromuscular dysplasia (FMD) were graded as significantly stenosed ($\geq 50\%$). The two observers reviewed discordant cases together to come to a consensus decision.

Statistical Analysis

Sensitivity and specificity and positive and negative predictive values regarding the detection of significant renal artery stenosis were calculated at the level of the separate kidneys as well as at the level of patients with the results of conventional angiography as the standard of reference. Determination of the best threshold of the duplex ultrasound parameters included receiver-operator curve analysis (ROC) and calculation of sensitivity, specificity and positive and negative predictive values at various thresholds.

Results

A total of 141 kidneys were examined in 71 patients. One kidney could not be examined because it had previously been removed surgically.

The duplex ultrasound study was unsuccessful in 11 kidneys (7%) due to the presence of bowel gas and/or obesity. Of the remaining 130 kidneys, 106 (81.5%) showed a single renal artery. Twenty-four kidneys (18.4%) had supernumerary renal arteries on angiography, one

of which showed a significant stenosis. None of these accessory renal arteries were detected with duplex ultrasound.

On the basis of angiographic findings, 104 kidneys without stenotic lesions or with mild renal artery stenosis ($< 50\%$) were identified. In 24 kidneys (18.4%) significant renal artery stenosis ($\geq 50\%$) was noted, including 9 arteries with fibromuscular dysplasia (7%). Total occlusion of the renal artery was seen in 2 kidneys (1.5%), resulting in an overall prevalence of significant renovascular disease of 20%.

The range of renal size in the group of kidneys without or mild renal artery stenosis ($< 50\%$) was 8.4 – 12.9 cm (mean length 10.7 cm), whereas the range in the group of kidneys with significant renal artery stenosis was 8.0 – 12.2 cm (mean length 10.6 cm).

The mean values and standard deviations of a peak systolic velocity (PSV_{max}) and peak renal to aortic velocity ratio (RAR) in relation to the angiography results are presented in Table 1.

Table 1: Duplex ultrasound parameters recorded from the renal arteries.

Results Angiography						
Results Duplex	Normal	Stenosis < 50%	Stenosis >50%	FMD	Occlusion	
PSV_{max} (SD)	199.0 (59.33)	139.8 (46.98)	256.5 (103.71)	167.9 (52.56)	150.0 (74.95)	
RAR (SD)	1.75 (0.9)	2.13 (0.88)	4.66 (2.71)	2.41 (1.06)	2.8 (1.97)	
Total number	83	21	15	9	2	130

Note: Data are presented as mean and standard deviations (sd's). FMD= fibromuscular dysplasia; PSV_{max} = peak systolic velocity; RAR= ratio of peak renal artery velocity to aortic velocity.

Table 2: Comparison between angiography and Duplex ultrasound in relation to the percentage of renal artery stenosis in hypertensive patients suspected of having renovascular disease.

Results Angiography						
Results Duplex	Normal	Stenosis < 50%	Stenosis >50%	FMD	Occlusion	Total number
Normal	72	17	4	5	1	99
Stenosis < 50%	4	2	0	3	0	9
Stenosis $\geq 50\%$	7	2	11	1	0	21
Occlusion	0	0	0	0	1	1
Total number	83	21	15	9	2	130

Note: Renal artery stenosis < 50%: $PSV_{max} > 180$ cm/sec and $RAR < 3.5$; Renal artery stenosis $\geq 50\%$: $PSV_{max} > 180$ cm/sec and $RAR > 3.5$. FMD= fibromuscular dysplasia

Based on the combination of these parameters at thresholds commonly applied in current literature: i.e. $PSV_{max} > 180$ cm/sec and $RAR > 3.5$, the results of the duplex ultrasound examination at the level of the separate kidneys compared to the angiographic findings are displayed in Table 2 (11-13). Excluding inconclusive examinations and using a $\geq 50\%$ stenosis or the presence of fibromuscular dysplasia on angiography as the diagnostic criterion for hemodynamically significant renovascular disease, these results show an overall sensitivity of 50% and a specificity of 91%. The overall positive (PPV) and negative (NPV) predictive values were 59% and 88% respectively. At the level of the individual patient the validity parameters show only marginal improvement with a sensitivity of 55% and a specificity of 84% (PPV 57%; NPV 82%).

Figure 1. Receiver operating characteristic (ROC) curves showing sensitivity for detection of renal artery stenosis ($\geq 50\%$) vs. 1-specificity for different PSV_{max} and RAR cut-off values.

Receiver operating characteristic (ROC) analysis of the applied ultrasound parameters show comparable curves for both PSV_{max} and RAR (Figure 1).

To improve the validity parameters of our duplex ultrasound examination, the results were also analysed for both the PSV_{max} and RAR at other thresholds. At a constant threshold of the RAR the ROC-curve and its area under the curve (AUC) for the PSV_{max} were determined. By calculating this AUC at different values of the RAR threshold the optimal RAR threshold was obtained. In the corresponding ROC-curve the optimal threshold of the PSV_{max} could be derived.

This resulted in lower thresholds for both duplex ultrasound parameters. Lowering the peak systolic velocity threshold to 110 cm/sec yielded a sensitivity of 85% and a specificity of 51%. Similarly, lowering the threshold for the renal aortic ratio to 1.7 yielded a sensitivity of 81% and a specificity of 56%. Combining these parameter thresholds resulted in a sensitivity of 81% and a specificity of 64% (Table 3).

Table 3. Detection of renal artery stenosis: results for duplex ultrasound parameters at different thresholds and combinations.

Parameter threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PSV > 180 cm/sec	61.5	86.5	53.3	90.0
RAR > 3.5	50.0	90.4	56.5	87.9
Combination PSV > 180 cm/sec and RAR > 3.5	50.0	91.3	59.1	88.0
PSV > 110 cm/sec	84.6	51.0	30.1	93.0
RAR > 1.7	80.8	55.8	31.3	92.1
Combination PSV > 110 cm/sec and RAR > 1.7	80.8	63.5	35.6	93.0

Note: PSV= peak systolic velocity; RAR= renal aortic ratio; PPV= positive predictive value; NPV= negative predictive value.

Grading fibromuscular dysplasia (FMD) as significant renovascular disease ($\geq 50\%$), duplex ultrasound reached a sensitivity of 11% with a specificity of 81% in this subgroup of patients.

Discussion

The results of this study, carried out in a population of patients with clinically suspected renovascular disease, show only moderate results of colour duplex ultrasound in the detection of renal artery stenosis.

The clinical presentation of renovascular disease varies significantly between patients, ranging from incidental findings of renal artery stenosis on angiography to severe hypertension and progressive loss of renal function. Identification of renal artery stenosis still seems useful since surgical or percutaneous treatment of these lesions may improve blood pressure control and/or stabilize renal function, even though this has been disputed in a recent publication (14).

Numerous diagnostic tests have been proposed to identify patients with renovascular disease. However, none of them has received widespread clinical acceptance. The ideal screening procedure should be simple, non- (or minimally) invasive and highly accurate both for the detection of renovascular disease and for assessment of its clinical significance. Duplex ultrasound has been proposed as a promising modality in this respect, but reported data over the last 10 years have shown contradictory results in terms of its diagnostic accuracy. Some investigators report remarkable success, while others have reported dismal results in large unselected patient groups (15,16).

A recent study declared duplex ultrasound to be most valuable not only in the screening for renal artery disease but also to estimate its functional significance by means of determination of the resistive index (17). The duplex ultrasound performance in this study, however (i.e. sensitivity 97%; specificity 98%), was derived from a previous report by the same authors in a selected group of patients with a high prevalence of renovascular disease

Table 4. Synthesis of studies concerning the detection of renovascular disease by duplex ultrasound vs. angiography, using three different duplex ultrasound strategies.

4a Duplex data acquisition using the traditional criteria (PSVmax, RAR) in the renal artery only (RA)

Authors	Year	Kidneys (n=)	Patients (n=)	Data Acquisition	Sensitivity (%)	Specificity (%)	Prevalence (%)	Super-numerary arteries (%)	Missing observations (%)	Odd's Ratio
Breitenseher ⁹	1992	34	17	RA	17	89	20	21	32	1.7
Miralles ¹⁵	1993	92	46	RA	90	91	37	11	0	91
Olin ²⁰	1995	187	102	RA	98	98	66	9	8	2401
Strotzer ¹¹	1995	110	55	RA	88	85	9	15	10	42
Miralles ²¹	1996	156	78	RA	87	91	37	12	8	68
Vigna ²²	1998	196	98	RA	69/89	98/97	25	16	6	109/262
Kaplan ¹²	1998	56	28	RA	83	81	42	-	20	20.8
House ²³	1999	125	63	RA	85	76	22	11	13	17.9
Claudon ¹³	2000	382	191	RA	79	98	38	13	24	184
This study	2001	141	71	RA	50	91	20	18	7	10.1

4b Duplex data acquisition by spectral waveform analysis in the intrarenal vasculature (IR).

Bardelli ²⁴	1992	98	49	IR	79	94	41	-	0	59
Schwerk ²⁵	1994	142	72	IR	82	92	24	1	0	52
Strunk ²⁶	1995	99	50	IR	69	90	17	42	4	20
Pedersen ²⁷	1996	262	131	IR	75	76	35	-	0	9.5
Postma ²⁸	1996	114	57	IR	47	97	37	-	9	28.7
Baxter ⁸	1996	143	73	IR	89	97	27	14	16	262
Lucas ²⁹	1996	104	53	IR	68	91	21	13	3	21.5
Oliva ¹⁰	1998	135	71	IR	81	98	35	-	0	209
Johansson ³⁰	2000	242	121	IR	84	94	19	-	0	82.3

4c Duplex data acquisition by direct visualization of the renal artery in combination with spectral waveform analysis in the main and segmental arteries (SARA).

Handa ³⁴	1988	40	20	SARA	100	93	25	-	0	∞
Zoller ³⁵	1992	172	86	SARA	84	99	13	-	8	520
Postma ³⁶	1992	122	61	SARA	63	86	52	11	25	10.5
Dondi ³⁷	1992	125	63	SARA	85	76	32	-	5	17.9
Kliewer ³¹	1993	93	36	SARA	57	69	30	15	0	3.0
Spies ³⁸	1995	268	135	SARA	94	92	22	8	27	180
De Cobelli ³⁹	2000	90	45	SARA	79	93	31	14	1	50

Note: Odds Ratio: sensitivity x specificity / {1 - sensitivity} x {1 - specificity}.

(58%) (18). Therefore, implicit adoption of these test performance parameters to a non-selected population with a relatively low prevalence for renovascular disease (2.3%) seems somewhat premature and raises doubts about whether the resistive index has the same prognostic significance for the remaining patients with stenosis not detected by duplex ultrasound.

In the present study, duplex ultrasound parameters at thresholds commonly applied in international literature were used: peak systolic velocity >180 cm/sec (PSV_{max}) and peak renal to aortic velocity ratio > 3.5 (RAR), resulting in an overall sensitivity of 50% and a specificity of 91% (PPV: 59%; NPV: 88%). This relatively low positive predictive value is acceptable for a screening test since it reflects the fact that a degree of overcalling is desirable to minimize false-negative rates. However, the negative predictive value, which is a more important predictor of the usefulness of a parameter in this respect, may prove to be too low for general screening purposes.

Post-hoc improvement of our duplex ultrasound results could be obtained by lowering both parameter thresholds. Based on ROC-curve analysis, including calculation of the respective area's under the curve, the preferred combination of the PSV_{max} and RAR could be derived for the detection of renal artery stenosis. At thresholds for the PSV_{max} and RAR of 110 cm/sec and 1.7 respectively, this combination showed reasonable results in terms of sensitivity, specificity and predictive values (Table 3).

This reduction in duplex parameter thresholds contrasts with the otherwise wide range of established criteria published in international literature (13). The contrast can be explained by a systematic underestimation of the peak systolic velocity resulting in relatively low threshold values for both PSV_{max} and RAR in our study group, which in itself reflects the notorious operator dependency of the ultrasound examination in general. By using the combined parameters of peak systolic velocity and renal aortic ratio at these lower thresholds, we could have been 93% confident that a negative results means that a renal artery is free from significant stenosis with a consequential decrease in positive predictive value (Table 3). In our study, this would have resulted in a reduction of false negative examinations by eight patients at a cost of angiographic examinations in 38 patients with a false positive outcome. Yet, the clinical implementation of screening tests such as duplex ultrasound is not determined by its validity results only. Other factors, such as population structure, pre-test likelihood and cost-effectiveness also influence the actual usefulness, which may lead to disparity in appreciation of test results in different clinical circumstances. All incomplete examinations (11 kidneys) were excluded from our results, whereas these data should be added as a positive result since they would require angiography in a screening setting. Based on the angiographic results in this sub-group of patients and on the traditional threshold parameters, sensitivity and specificity for duplex ultrasound would have been 57% and 86% respectively.

Supernumerary renal arteries were noted on angiography in 18% of the kidneys ($n=24$), but none of these were detected with duplex ultrasound. Visualization of a single normal renal artery does not exclude the possibility of a stenotic supernumerary renal artery. Although the influence of stenoses in small supernumerary renal arteries is not completely understood, the examination should be marked as inadequate and further limiting the outcome of our data and, therefore, the usefulness of duplex ultrasound.

Duplex ultrasound performed particularly poor in patients with fibromuscular dysplasia ($n=5$), resulting in a sensitivity of 11% and specificity of 81%, with duplex parameters which

fall within the normal range of non-diseased vessels (Table 1). This observation might be caused by fundamental differences in underlying pathology compared to atherosclerotic renovascular disease. Also, the prerequisite to evaluate the entire length of the renal artery including the more peripheral segment, which, even in experienced hands is cumbersome, may be another explanation for this lack of discriminating power. However, the number of patients with FMD in our group is far too small to allow for a well-founded discussion in this matter.

Compared to other studies in which only patients screened for renovascular hypertension were included, our results fall well within the wide range of reported data in terms of specificity, sensitivity and number of inadequate examinations. In our study as well as in others (Table 4a), the duplex ultrasound data of supernumerary renal arteries were excluded from evaluation, thereby accepting a number of inadequate examinations since these vessels may be as large as the main renal arteries and therefore of hemodynamic significance (9,11-13, 19-23).

In order to overcome these limitations, others have suggested the technique of duplex ultrasound examination of the intrarenal vasculature (8, 10, 24-30). Analysis of the Doppler spectral waveform, with several criteria, i.e. mean resistive index, tardus-parvus phenomena and acceleration time, has been proposed as an alternative to detect upstream stenosis. With the lateral approach to the kidney, duplex examination of the intrarenal arteries is easier to perform resulting in a higher number of complete examinations than with direct scanning of the renal arteries. Furthermore, recording of changes in Doppler velocity waveform pattern downstream in the segmental arteries makes it possible, at least in theory, to detect stenotic lesions in main, supernumerary and segmental arteries, although this hypothesis has been argued by others (31). Despite these theoretical advantages the range in sensitivities and specificities remains relatively wide: 57%-100% and 69%-99% respectively (Table 4b). These discrepancies can be partly attributed to the variability in criteria and degree of stenosis. However, the intrarenal parameters are probably influenced by several complex factors (i.e. pulse, diastolic blood pressure), which may also account for the differences in the tabulated results (32,33).

Figure 2. Sensitivity vs. 1-specificity in 25 studies concerning detection of renovascular disease with duplex ultrasound vs. angiography, using three different duplex ultrasound strategies.

Note: Duplex data acquisition using the traditional criteria (PSV_{max}, RAR) in the renal artery only (+); or by direct visualization of the renal artery in combination with spectral waveform analysis in the main and segmental arteries (+); or by spectral waveform analysis in the intrarenal vasculature (O). Present study using traditional parameter thresholds: PSV_{max} >180 cm/sec and RAR > 3.5 (#). Present study using lowered parameter thresholds: PSV_{max} >110 cm/sec and RAR > 1.7 (♦)

Direct visualization of the main renal arteries with duplex ultrasound combined with Doppler spectral waveform analysis in the main and segmental renal arteries (31, 43-39) does not seem to result in significantly better results with sensitivities ranging from 47–89% and specificities from 76–98% (Table 4c).

The range and variety of sensitivities and specificities in the quoted studies cannot be explained by the application of different cut-off points. This is demonstrated in figure 2, as it is not possible to fit one summary receiver- operating curve (SROC) over the marks representing the different studies and ultrasound strategies (40).

For quantitative analysis of the literature data the diagnostic Odds Ratio (= sensitivity x specificity / {1 – sensitivity} x {1 – specificity}) was calculated for each study (Table 4a-c). The Spearman rank correlation coefficients between diagnostic Odds Ratio's of the separate studies and a number of study variables, i.e. number of patients, prevalence of renovascular disease, year of publication, are less than 0.3, indicating a lack of influence of these variables on the diagnostic performance of duplex ultrasound. A sound explanation for the wide range of Odds Ratio's (Table 4) cannot be deduced from the indicated variables in the respective study protocols. Yet, apart from differences in composition of the study population, the different levels of experience with duplex ultrasound in the institutions concerned is likely to account for a substantial part of this variety in results.

In conclusion, in a population of hypertensive patients suspected of renovascular hypertension on clinical grounds, duplex ultrasound proved to have limited value for detection of renovascular disease when commonly applied parameter thresholds: PSV_{max} 180 cm/sec and $RAR > 3.5$ were used. In addition, the relatively large number of incomplete examination in combination with the wide range of results published in international literature does not support the general application of duplex ultrasound as a screening procedure for detection and assessment of renovascular disease.

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Chapter 3

Renovascular disease in patients with hypertension: detection with systolic and diastolic gating in three-dimensional, phase-contrast MR angiography.

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Abstract

Objective: To evaluate the usefulness of three-dimensional, phase-contrast magnetic resonance (MR) angiography performed with cardiac synchronisation in the assessment of renal arteries.

Materials and methods: Thirty-eight patients, 24 men (mean age 60.0 years), 14 women (mean age 55.0 years) underwent three-dimensional, phase-contrast MR angiography performed without gating, with systolic gating, and with diastolic gating. Conventional angiography was used as standard of reference.

Results: The sensitivity for the detection of all stenoses ($>0\%$) was 93% with systolic gating, 92% with diastolic gating, and 77% without gating. However, there was no statistically significant difference between the three techniques in the diagnosis of hemodynamic

significant stenoses ($>50\%$). The mean arterial length depicted was significantly better with diastolic gating than with either of the other techniques ($p < .0001$). Vascular disease was significantly overestimated with systolic gating relative to estimation without ($p = .030$) or with diastolic ($p = .008$) gating.

Conclusion: Three-dimensional, phase-contrast MR angiography has good image quality and enables assessment of renovascular disease. Cardiac gating shows limited improvement of these results.

Introduction

Renal artery stenosis is the most frequent cause of secondary hypertension, with an estimated prevalence of 3%-5% in the general population of people with hypertension (1-3). Detection of renovascular pathology in patients with hypertension and/or renal failure has become especially important, because correction of arterial stenoses by means of percutaneous transluminal angioplasty or surgery may cure hypertension (4-7).

To date, radiographic angiography is considered the most accurate method of assessing the presence and severity of renal artery stenosis. Because this examination is invasive, it is not suitable for screening a population of patients with a low prevalence of renal artery stenosis.

Several non-invasive imaging methods (e.g. intravenous pyelography, intravenous digital subtraction angiography) have been proposed for such a population but were later discarded because of the insufficient results (1,2,8). Duplex ultrasound (US) has been reported to have contradictory results (9-12). To our knowledge, the most widely used non-invasive test at the present time is renal scintigraphy performed after the administration of captopril; however, the results are problematic especially in patients with bilateral disease (13-17).

In the last few years, several magnetic resonance (MR) angiographic techniques have been proposed for examination of patients suspected to have renovascular disease (2,18-23). However, sensitivity and specificity have been variable in these studies with respect to the detection of renal artery disease. Two-dimensional, time-of-flight (TOF) MR angiography has been reported to have a sensitivity of 53% - 100% (specificity, 97% - 78%); two-dimensional, phase-contrast MR angiography has been noted to have a sensitivity of 80% (specificity, 91%) (22,24-27). Publications concerning three-dimensional TOF MR angiography indicate a sensitivity and specificity of 100% and 76%, respectively, whereas those concerning three-dimensional, phase-contrast MR angiography indicate a sensitivity and specificity of 84% and 97%, respectively (23,28). The benefit of gadolinium enhancement in three-dimensional, MR angiography has been mentioned in recent publications (sensitivity, 94%; specificity, 98%); however, these publications have had images of the distal arterial segments of inconsistent quality (29-32).

The variability of these results could be related to artefacts that hinder image interpretation; these artefacts may be due to the pulsatility of blood flow or to differences in MR angiographic techniques, patient selection and/or interpretation criteria. We performed a prospective study to test the validity of three-dimensional, phase-contrast MR angiography and to evaluate the usefulness of cardiac synchronisation by comparing the image quality and validity of three different three-dimensional, phase contrast MR angiographic techniques: one sequence without cardiac synchronisation, one sequence with systolic gating, and one sequence with diastolic gating. Radiographic angiography was used as the standard of reference.

Materials and methods

Patient Selection

In the pilot phase of this study, the MR angiography sequence used to depict the renal arteries was optimised. Imaging parameters were evaluated in ten healthy volunteers

without hypertension and in two patients with proved renovascular disease (9 men and 3 women, mean age 39.0 years).

In the second phase of this study, all patients with hypertension who were referred by the Department of Internal Medicine for radiographic angiographic evaluation of the renal vessels (38 consecutive patients; 24 men [mean age, 60 years; range, 37 - 78 years]; 14 women [mean age, mean age 55 years; range, 24 - 74 years]) were prospectively enrolled over a period of six months (February - July 1994).

These patients had therapy-resistant hypertension (blood pressure > 160/100 mm Hg during extensive treatment), and most of them had undergone routine evaluation for renovascular hypertension. Evaluation included performance of laboratory tests, ultrasound of the kidneys, and renal scintigraphy.

Criteria for participation in the study included willingness to give informed consent, lack of standard contraindications to MR imaging (e.g. pacemaker, claustrophobia, or ocular metallic fragments) and our ability to perform the MR examination within 48 hours before to the radiographic angiographic procedure. The study was approved by the human investigation committee of our institute

MR Angiography

MR Angiography of the renal arteries was performed with a 1.5 Tesla whole-body MR imager (ACS, Philips Medical Systems, Best, The Netherlands). The body coil was used for signal transmission and reception. No intravenous contrast material was administered. The patient breathed normally during data acquisition. No abdominal compression was used. To localize the renal arteries, a T1-weighted gradient echo multistack scout view was obtained at the level of the kidneys. The field of view (FOV) was 500 mm, the matrix was 256 x 256, the section thickness was 15.0 mm, the repetition time was 22.0 msec and the echo time 7.0 msec (22.0/7.0), and the flip angle was 20°. Images were obtained in the coronal and transverse planes.

Subsequently, three separate three-dimensional, phase contrast MR angiographic sequences were performed in each patient: a sequence without gating, a sequence with systolic gating, and a sequence with diastolic gating. T1-weighted, gradient-echo images were obtained in the transversal plane with the following parameters: 27.0/8.5 20° flip angle, two signals

Table 1: Summary of Imaging Parameters of the Three Three-dimensional, Phase-contrast MR Angiographic Pulse Sequences.

Parameter	No gating	Systolic gating	Diastolic gating
Number of reconstructed sections	50	30	30
Flow-encoded velocity (cm/s)	45	45	35
Gate delay (msec)		109-125	250-300
Gate width (msec)		220	350
Examination time (min)	8	12-19	8-11

Note: Imaging was performed with T1-weighted gradient echo with 27.0/8.5; a 20° flip angle, a 103x128 matrix, and two signals acquired. A presaturation slab below the lower pole of the kidneys was obtained.

acquired, 75% partial echo sampling, 200 x 140 mm FOV, 103 x 128 matrix, 12 mm³ acquired voxel size (5 mm³ reconstructed voxel size), and 45 cm/sec flow-encoded velocity (Table 1).

Fourier interpolation was used to reconstruct sections thinner than those acquired. In the sequence performed without gating, 32 sections were acquired and reconstructed to 50 2.0 mm-thick sections. In the sequences performed with systolic or diastolic gating, 18 sections were acquired and reconstructed to 30 2.0 mm-thick sections. The outer 10% on both sides was discarded.

To reduce the venous signal from the inferior vena cava, a transverse presaturation slab (60.0 mm thick) inferior to the lower pole of the kidneys was acquired. The maximum intensity projection (MIP) algorithm was used to create angiographic projections. To standardize our procedure as much as possible, MIPs were obtained in only the transverse, coronal and sagittal planes.

Figure 1. Diagrams of cardiac gating, based on a two-dimensional velocity map of the blood flow in the aorta just above the level of the kidneys. (a) Three-dimensional, phase-contrast MR angiography performed with systolic gating. The acquisition gate is set up at the upper 30-40% of the systolic peak. (b) Three-dimensional, phase-contrast MR angiography performed with diastolic gating. The acquisition starts the halfway point on the downward slope of the systolic peak.

Note: 1=Gate delay; 2=Gate width; ECG= electrocardiogram.

Before the three-dimensional sequences with cardiac gating were performed, a two-dimensional (cardiac-triggered) velocity map of the blood flow in the aorta just above the level of the kidneys was obtained to determine the gate delay and gate width in relation to the R-wave peak on the electrocardiogram in each patient (Fig. 1). T1-weighted, gradient-echo, transverse flow-velocity images were obtained with 20.0/8.5, a 25° flip angle, a 200 mm FOV, a 128 x 128 matrix, a single section, an 8 mm section thickness, a 120 cm/sec flow-encoded velocity, 25 acquisition phases per R-R interval, and retrospective cardiac synchronisation.

The imaging parameters in the sequences with cardiac gating were the same as those in the sequences performed without gating, except for the number of sections, flow-encoded velocity (with diastolic gating) and the implementation of gate delay and width (Table 1).

Cardiac gating in the three-dimensional imaging studies was performed in a steady state mode, in which the radio-frequency pulses and gradients continue throughout the entire heart cycle; however, data acquisition was limited to the selected gate. By adjusting the

gate delay and gate width relative to the patient's cardiac R-wave on the electrocardiogram, data acquisition could be performed in any desired portion of the velocity curve as was shown on the flow velocity map.

In the sequence performed with systolic gating, data were acquired in the upper 30 - 40% of the systolic peak on the velocity map (Fig 1a); this resulted in a gate delay of 109 - 125 msec and a gate width of 220 msec. Examination time for this pulse sequence ranged from 12 to 19 minutes, and flow-encoded velocity was 45 cm/sec.

In the three-dimensional MR angiographic sequence performed with diastolic gating, the acquisition gate started at the halfway point on the downward slope of the systolic peak flow on the velocity map. In most cases, this resulted in a gate delay of 250 - 300 msec and a gate width of 350 msec. The flow-encoded velocity was 35 cm/sec, and the examination time for this pulse sequence was 8-11 minutes (Fig 1b).

In both sequences performed with cardiac gating, the gate delay and gate width had to be adjusted to the heart rate of the patient.

Conventional Angiography

Conventional angiography of the abdominal aorta and renal arteries was performed in the anteroposterior view with 45 ml of iohexol (Omnipaque 140, Nycomed AS, Oslo, Norway) injected through a 5-French pigtail catheter (William Cook Europe AS, Bjaeverskov, Denmark) positioned at the level of the renal arteries. If the renal arteries were not clearly depicted, additional intra-arterial digital subtraction angiography was performed in oblique projections, or selective renal angiography was performed with an end-hole catheter (William Cook Europe AS, Bjaeverskov, Denmark).

Image Analysis

Separate hard copies were made of each of the three-dimensional, phase-contrast MR angiographic image sets (sets obtained without gating, with systolic gating, or with diastolic gating), including the MIPs in three planes (sagittal, coronal and transverse) and original cross-sectional images; patient data and imaging parameters were not displayed. Two radiologists independently evaluated each set: one vascular radiologist (D.K.) and one MR radiologist (J.M.A.v.E). Neither had prior knowledge of the clinical patient data.

Each image set was assessed concerning image quality, venous vessel overlap, number of renal arteries per kidney, vessel segment depiction, and grading of renovascular disease. The overall image quality of each image set was scored on a three-point scale (good, moderate, poor). The presence of venous vessel overlap, which hindered image interpretation, was scored on a two-point scale (yes, no). The worst result noted by either one of the observers in both these observations was accepted as the definitive score.

The number of renal arteries was assessed, and each artery was divided into three separate segments: proximal, middle and distal. Depiction of each segment in the three image sets was assessed and noted on a three-point scale (good, moderate or poor). The two radiologists reached consensus in a second round whenever there was disagreement between the individual interpretations of vessel segment depiction. Furthermore, the length of the renal artery depicted with each sequence was measured for the quantitative assessment of the image quality.

Four grades were used to categorize the severity of renovascular disease: Grades were based on the most severe reduction of arterial diameter compared with the diameter of

the most normal-appearing segment proximal or distal to the stenosis. Grade 1 was mild disease (stenosis of <50%), defined as mere luminal narrowing; grade 2, moderate disease (stenosis of 50-74%), defined as reduction in diameter with focal flow void (< 5mm); grade 3, severe disease (stenosis of 75-99%), defined as a longer region of signal intensity loss ($\geq 5\text{mm}$) with distal recurrence of flow signal intensity; and grade 4, occlusion (9).

The radiographic angiograms were blindly assessed with respect to the number of renal arteries and the presence of renovascular disease by a radiologist who had no prior knowledge of the clinical data of the patients or the results of the MR angiograms. Renal artery stenoses on radiographic angiograms were graded as they were on MR angiograms.

Statistical Analysis

Pearson correlation coefficients were used to compare the results of both observers concerning the depiction of renal arteries in each three-dimensional, phase-contrast MR angiographic image set. The Fisher exact test was used to compare the depiction of the different vessel segments between the three three-dimensional, phase-contrast MR angiographic image sets. The interobserver variability with respect to the presence and absence of renal artery stenosis was calculated for each imaging technique and expressed in κ values. κ is a measurement of agreement in excess of what is expected by chance and was calculated according to the formula $\kappa = (Po - Pe) / (1 - Pe)$, where Po is the observed and Pe the expected proportion of agreement (33). A paired Student t-test was used to differentiate between the depicted arterial lengths in the three pulse sequences.

To evaluate the differences in grading of renovascular disease, the McNemar test (exact distribution) was used. Only the arteries, which were seen by both observers in all three three-dimensional, phase-contrast MR pulse sequences were included in this test.

Sensitivity and specificity of each three-dimensional MR angiographic technique were calculated. The standard of reference was negative when the radiographic angiogram showed no vascular disease. For clinically significant stenoses, the standard of reference was negative when the radiographic angiogram showed minor vascular disease with a reduction in lumen diameter of 50% or less.

Results

In 95% of the 38 patients ($n=36$) all three three-dimensional, phase-contrast MR angiographic pulse sequences were performed. In two patients, only two pulse sequences were performed; this was due to logistic problems. During the 6-month interval of our study only three patients were excluded: Two patients had claustrophobia, and one patient had metal fragments in the back (probably from a grenade explosion during World War II). One of these three patients had significant renal artery stenosis at radiographic angiography.

Radiographic angiography revealed a total of 89 renal arteries in these 38 patients (seven patients had 3 or more arteries depicted). Sixty-five arteries (73%) were considered normal. In a total number of 17 patients (45%) 12 arteries had mild stenosis (< 50%); nine, moderate stenosis (50 - 74%) and one, severe stenosis (75 - 99%). Two arteries were occluded. In 10 patients (26%), at least one hemodynamically significant stenosis could be demonstrated. No fibromuscular dysplasia-induced stenosis, lesion in an accessory renal artery, or branch vessel disease was demonstrated.

Table 2: Overall Quality of Renal Artery Depiction on Images Obtained with Three Three-dimensional, Phase-contrast MR Angiographic Pulse Sequences in 38 Patients.

Image Quality	No Gating (n=37)	Systolic Gating (n=38)	Diastolic Gating (n=37)
Good	22 (59)	27 (71)	27 (73)
Moderate	11 (30)	9 (24)	6 (16)
Poor	4 (11)	2 (5)	4 (11)

Note: Quality of depiction was determined by the two observers. The worst result of the two was used. Data are numbers of patients. Numbers in parentheses are percentages.

Table 2 provides information concerning the overall image quality in the three image sets. Superposition of the renal arteries by adjacent vascular structures, particularly the renal veins and inferior vena cava was seen in the majority of the images obtained without gating; however, this affected image interpretation in only four patients. The images obtained with systolic gating showed vessel overlap in six patients, impairing optimal image assessment in three. The images obtained with diastolic gating showed overlap in nine patients, affecting interpretation in two.

The interobserver agreement for the detection of renal arteries was very good in all three three-dimensional MR angiographic image sets (1.00, 0.96 and 0.94 in the images obtained without gating, with systolic gating, and with diastolic gating, respectively). All accessory renal arteries ($n = 13$), whenever present, were included in the MR imaging volume interest on images obtained with all three techniques. Of 87 renal arteries 82 (94%) were seen by both observers on the images obtained without gating; 83 (95%) were seen by both observers on images obtained with systolic gating, and 84 (96%) were seen by one observer and 83 (95%) by the other on image obtained with diastolic gating. Table 3 lists the number of overlooked renal arteries in the three series.

Table 3: Number of Renal Arteries Overlooked by Two Observers.

Observer	No Gating (n=87)	Systolic Gating (n=89)	Diastolic Gating (n=87)
1	5 (6)	4 (4)	3 (3)
2	5 (6)	4 (4)	4 (4)

Note: Numbers in parentheses are percentages.

Images with a poor overall image quality were excluded from further evaluation. The depicted vessel segments, the length of the artery depicted and the presence of renovascular disease could be assessed on images obtained in 33 patients without gating, on images obtained in 36 patients with systolic gating, and on images obtained in 33 patients with diastolic gating.

The results concerning separate vessel segment depiction are summarized in table 4. Depiction of all proximal arterial segments was considered to be good in 32 patients on

images obtained with cardiac gating (systolic and diastolic), but in only 13 patients on images obtained without gating ($p < .0001$, Fisher's exact test). Likewise, the visualisation of the distal renal artery segment was noted as good on images obtained with diastolic gating in 11 patients, but on none of the images obtained with systolic gating or without gating ($p < .0001$, Fisher's exact test).

Table 4: Depiction of Separate Vessel Segments of the Renal Arteries at Three Three-dimensional, Phase-contrast MR Angiographic Pulse Sequences according to Consensus of the Two Observers.

Depiction	No Gating (n=33)			Systolic Gating (n=36)			Diastolic Gating (n=33)		
	Proximal Segment	Middle Segment	Distal Segment	Proximal Segment	Middle Segment	Distal Segment	Proximal Segment	Middle Segment	Distal Segment
Good	13	30	0	32*	31	0	32*	32	11*
Moderate	20	3	10	4	4	12	1	1	18
Poor	0	0	23	0	1	24	0	0	4

Note: Data are numbers of patients

* Statistically significant according to Fisher exact test results ($p < .0001$).

With exclusion of the images with poor overall image quality and the number of overlooked renal arteries (Table 2, 3), the mean lengths of the renal artery depicted on the three separate three-dimensional, phase-contrast MR angiographic image sets were assessed by the MR radiologist. On the images obtained without gating, the mean length of the arteries depicted ($n=74$) was 3.4 cm (range, 0.3-7.0 cm), whereas the length of the arteries depicted on the images obtained with systolic gating ($n=81$) was 3.5 cm (range, 0.2 - 6.8 cm). On the images obtained with diastolic gating, the mean length of the arteries depicted ($n=76$) was 4.6 cm (range, 1.7 - 8.2 cm). These differences between the images obtained with diastolic gating and the images obtained with the other two sequences were statistically significant ($p < .0001$, paired t-test).

Results for the grading of renovascular disease by both observers are summarized in Table 5.

Table 5: Grading of Renovascular Disease with Three-dimensional Phase-contrast MR Angiography versus Radiographic Angiography in 66 Arteries.

MR Angiographic grading relative to conventional angiographic grading	No Gating		Systolic Gating		Diastolic gating	
	MR Radiologist	Vascular Radiologist	MR Radiologist	Vascular Radiologist	MR Radiologist	Vascular Radiologist
Underestimation	3	5	1	2	1	3
Concurrence	58	56	54	57	62	61
Overestimation	5	5	11	7	3	2

Note: Only the arteries seen by both the MR radiologist and the vascular radiologist are included

Only the arteries that were seen by both observers in all three sequences were included. With findings of radiographic angiography as the standard of reference, the difference between overestimation by the MR radiologist with three-dimensional, phase-contrast MR angiography performed with systolic gating and the overestimation with MR angiography performed without gating ($p = 0.030$, McNemar test) or with diastolic gating ($p = .008$, McNemar test) was statistically significant. Although the trend to overestimate renovascular disease with systolic gating is also seen in the results of the vascular radiologist, the differences between pulse sequences were not statistically significant.

The interobserver agreement (κ value) concerning the detection of renovascular disease (normal versus abnormal) by using the no gating, systolic gating, and diastolic gating was .62, .82, and .86 respectively. The image interpretations of the MR radiologist were used to calculate the validity of each three-dimensional, phase-contrast MR angiographic image set concerning the presence of renovascular disease.

Table 6: Findings of Renal Artery Stenosis (>0%).

Results	No Gating (n=33)	Systolic Gating (n=36)	Diastolic Gating (n=33)
Findings			
True-positive	10	14	11
False-negative	3	1	1
False-positive	0	1	0
True-negative	20	20	21
Statistics			
Sensitivity (%)	77	93	92
Specificity (%)	100	95	100

Note: Data are numbers of patients

Table 6 summarizes the results of the three-dimensional MR angiographic pulse sequences concerning the detection of renovascular stenosis (> 0%). Findings of radiographic angiography were used as the standard of reference. In three patients, a stenotic lesion (stenosis of < 50%) seen on radiographic angiography was not seen (false-negative finding) on images obtained without gating; in one patient, a stenotic lesion (stenosis of <50%) was not visible on images obtained with systolic or diastolic gating.

Retrospectively, these lesions remained non-visible. The overall sensitivity of the three-dimensional, phase-contrast MR angiographic images obtained without gating for the diagnosis of renal artery disease (stenosis > 0%) was 77%, with a specificity of 100%. The images obtained with systolic gating had an overall sensitivity of 93% (specificity, 95%). With the images obtained with diastolic gating, overall sensitivity was 92% (specificity, 100%).

The sensitivity of all three three-dimensional, phase-contrast MR angiographic images in the diagnosis of a haemodynamically significant stenosis (> 50%) was 100%, with a

specificity of 96% (26 of 27 patients; no gating) to 82 % (23 of 28 patients; systolic gating) to 96% (26 of 27 patients; diastolic gating).

Discussion

The results of this prospective study confirm the value of MR angiography of the renal arteries as a non-invasive screening modality in patients with clinically suspected renovascular hypertension (2,8, 34-38). We obtained diagnostic three-dimensional, phase-contrast MR angiograms of the renal arteries with highly accurate interpretation results in 95% of the patients. There was good interobserver correlation, and it was possible to reach a sensitivity and specificity of 93% and 95%, respectively, for diagnosing renal artery stenosis ($>0\%$) on images obtained with systolic gating and of 100% and 96% for diagnosing hemodynamically significant stenosis ($>50\%$) on images obtained without gating or diastolic gating, respectively. Cardiac gating improved the image quality in some patients at the cost of a longer scan time but did not improve the test validity in the diagnosis of haemodynamically significant stenoses.

We have used a three-dimensional, phase-contrast MR angiographic technique, which combines the good spatial resolution and signal-to-noise ratio (S/N) of the three-dimensional acquisition and optimal background suppression of the phase contrast pulse sequence. This technique allows inspection of the vessels from any projection and overcomes the major drawback of two- and three-dimensional, TOF MR angiography: reduced sensitivity to in-plane flow because of saturation. This reduced sensitivity to in-plane flow may be particularly important because the renal arteries tend to run in the transverse plane. The three-dimensional, phase-contrast MR angiographic technique, on the other hand, is much more time-consuming and more sensitive to motion (respiration) than are two- and three-dimensional, TOF and two-dimensional, phase-contrast MR angiography. Furthermore, phase-contrast MR angiography has an increased sensitivity to signal loss from intravoxel spin-phase dispersion, which is due to disturbed or turbulent flow. This may lead to overestimation of renovascular disease and can pose problems, particularly in the assessment of the vessel origins. In addition, the pulsatility of blood flow may cause artefacts (ghosting) in MR angiography (in both phase-contrast and TOF) that can lead to false-positive image interpretations concerning the presence of renovascular stenosis. Cardiac gating may suppress these artefacts, as well as blurring, because of the movement of the vessel during the cardiac cycle (39-45). To investigate the usefulness of cardiac gating in three-dimensional, phase-contrast MR angiography of the renal arteries, we designed a prospective study to compare three-dimensional, phase-contrast MR angiography performed with systolic gating, with diastolic gating, and without gating with radiographic angiography.

The overall image quality of the three image sets did not show a statistically significant difference, although cardiac gating improved the overall image quality in some patients (Table 2, Fig 2). In the small number of patients with images of poor overall quality, severe arterial disease in both the aorta and the renal arteries was proved at radiographic angiography. These poor results are probably related to signal intensity loss caused by turbulent and/or high-velocity flow.

Figure 2. (a-f) Maximum intensity projections in transverse and coronal planes of three separate three-dimensional, phase-contrast MR angiographic pulse sequences (T1-weighted gradient echo, 27.0/8.5, 20° flip angle) in a 48-year-old male patient. (a,d) Three-dimensional, phase-contrast MR angiograms obtained without cardiac gating show good signal intensity in the distal aorta and superposition of adjacent vessels (due to a higher number of sections). (b,e) Three-dimensional, phase-contrast MR angiograms obtained with systolic gating show excellent signal intensity in the distal aorta, no superposition, and moderate contrast in the distal segment of the renal arteries. (c,f) Three-dimensional, phase-contrast MR angiograms with diastolic gating show poor signal intensity in the distal aorta, no superposition, and good contrast in the distal segment of renal arteries. (g,h) Original cross-sectional images; they are essential for optimal assessment of the renal arteries. (i) Radiographic angiogram shows no renovascular disease. Because of the non-isotropic voxel size, the MIP image quality in the transverse plane is superior to the image quality in the coronal plane.

Superposition from overlapping vessels posed no statistically significant problem in this study. On images obtained with diastolic gating, as opposed to images obtained with the other two sequences, areas of signal intensity representative of the adjacent venous structures were present to some extent, because of the lower velocity-encoding values used; however, this affected image interpretation in only a limited number of patients.

Figure 3. Maximum intensity projections in transverse (a-c) and coronal (e-g) plane of three separate three-dimensional, phase-contrast MR angiographic pulse sequences (T1-weighted gradient echo, 27.0/8.5, 20° flip angle) in a 65-year-old male patient. (a,e) Three-dimensional, phase-contrast MR angiograms obtained without gating show a normal right renal artery and minimal reduction of the vessel diameter (stenosis of < 50%; grade 1) on the left side. (b,f) Three-dimensional, phase-contrast MR angiograms obtained with systolic gating show a grade 1 lesion near the orifice of the right renal artery and a grade 2 lesion (stenosis of 50 -74%) on the left side. (c,g) Three-dimensional, phase-contrast MR angiograms obtained with diastolic gating show a grade 1 lesion on both sides. (d,h) Radiographic angiograms show hemodynamically insignificant (stenosis of < 50%) renovascular disease on both sides, which confirms the results obtained with diastolic gating.

Because the original cross-sectional images were particularly helpful and essential for optimal assessment of the renal arteries, interpretation was always based on both the MIPs and these transverse images (Fig. 2). Additional MIP images in planes other than the coronal, sagittal and transverse planes and/or image post processing might have been helpful but were not used in this study. A minority of the accessory renal arteries, although inside the imaging volume of interest, were not seen on the images obtained without gating or on the images obtained with cardiac gating (Table 3). This is probably due to the small diameter of these vessels. Nondepiction of these vessels poses a diagnostic dilemma, although the potential influence of stenoses in small accessory renal arteries on blood pressure is not completely understood.

Cardiac gating improved depiction of the proximal renal artery segment (Table 4), which is especially important because a large majority of the atherosclerotic lesions typically involve the proximal part of the vessel (46). The assessment of the distal renal artery segment with images obtained diastolic gating was significantly ($p < .0001$) better (as was the mean length depicted significantly [$p < .0001$] longer) than it was with images obtained with either of the other techniques (Table 4). This was presumably due to the lower flow-encoded velocity in combination with the slower and less pulsatile flow during the gating period. The resolution was inadequate to evaluate the intrarenal vessels.

Discrepancies between MR angiography and radiographic angiography in grading the severity of stenosis, as have been mentioned by others (2,9,10,12), are caused by the presence of turbulent flow in the stenosis and the poststenotic vessel segment, which results in signal intensity loss on MR angiograms. Recent publications have shown that this signal intensity loss increases with increasing (systolic) flow velocity (19,20), which results

Figure 4. Maximum intensity projections in transverse (a-c) and coronal (e-g) plane of three separate three-dimensional, phase-contrast MR angiographic pulse sequences (T1-weighted gradient echo, 27.0/8.5, 20° flip angle, transverse plane) in a 49-year-old male patient. (a,e) Three-dimensional, phase-contrast MR angiograms obtained without gating show superposition of adjacent vessels and no vascular disease of the right renal artery. The left renal artery has two stenotic lesions (stenosis of 50-74%). (b,f) Three-dimensional, phase-contrast MR angiograms obtained with systolic gating show no superposition of adjacent vessels and no disease on the right side. Poor image contrast of the left renal artery, caused by a severe stenosis (stenosis of 75-99%) near the orifice. (c,g) Three-dimensional, phase-contrast MR angiograms obtained with diastolic gating show no superposition, a normal right renal artery, and two stenotic lesions on the left side (50-74%). (d,h) Radiographic angiograms confirm findings in c and g of two stenotic lesions on the left side (arrow).

in a considerable overestimation of arterial stenoses. Data acquisition during diastole with slower flow velocities may reduce this signal loss and is considered more capable to accurately quantify the degree of vascular disease. However, in our study, neither flow compensation nor cardiac gating or the use of a very short echo time (8 msec) was sufficient to entirely compensate for this signal intensity loss, partly because of the relatively large voxel size. Therefore, overestimation of stenotic lesions remained a problem in this study (Table 5).

The need to predict the optimum velocity-encoding value in advance and the limited range around this optimum are additional problems of phase-contrast MR angiography of the renal arteries (44), because the flow rate in a stenotic artery is unpredictable and may be very different from the flow rate in the contralateral artery.

On the basis of the results of the MR radiologist only, there was a statistically significant difference between overestimation of renovascular disease on the images obtained with systolic gating and the overestimation with MR angiography performed without gating or with diastolic gating. Although the relatively small number of diseased arteries in this study does not allow any firm conclusion, three-dimensional, phase-contrast MR angiography performed with diastolic gating does seem better for assessment of the severity of renovascular disease (Fig 3,4). Assessment of the functional influence of stenoses with selective MR phase-contrast flow quantification in the renal arteries, which will be more feasible in the near future, will probably reduce the importance of visual grading of renal artery disease.

The sensitivity of the detection of stenosis ($>0\%$) was high with images obtained with systolic (93%) or diastolic (92%) gating; however, for the images obtained without gating, the overall sensitivity was only 77% (Table 6). These numbers yield negative predictive values of 95% for images obtained with either systolic or diastolic gating and 78% for images obtained without gating. The differences are probably related to the poorer image quality, especially in the proximal vessel segment. All patients with images of poor overall quality were excluded from this evaluation because we thought that these images would not justify any interpretation of renovascular disease. In a clinical setting, radiographic angiography will be indicated in this group of patients. Postulating that every examination with poor overall image quality indicates (by definition) severe vascular disease at radiographic angiography and including these images in a retrospective statistical analysis would have improved the results of three-dimensional, phase-contrast MR angiography in general. On the other hand, we would have reduced the differences in sensitivity and specificity between the sequences performed without gating and those performed with gating.

The overall sensitivity for detection of significant stenoses ($> 50\%$ stenosis) in our study was 100% in all three phase-contrast MR angiographic sequences, with a specificity of 96% (no gating) to 82% (diastolic gating). These sensitivity and specificity calculations were based on the independent interpretations of the MR radiologist only. If we had used the combined interpretations of both radiologists, or of the vascular radiologist alone, the results, in terms of sensitivity and specificity, would have slightly decreased, in spite of the good interobserver agreement.

The results of this study indicate that three-dimensional, phase-contrast MR angiography is a highly sensitive technique for the detection of renovascular disease and, therefore, is suitable as a non-invasive screening modality. In a clinical setting we would have refrained correctly from more than 50% of the radiographic angiographic examinations of the patients in this study group on basis of their MR angiographic results alone.

Cardiac gating improved the results concerning (overall) image quality, sensitivity for diagnosing mild stenotic lesions ($< 50\%$) and grading of vascular disease, at the cost of a substantially prolonged examination time. Because these improvements seem to be of relatively limited clinical importance, we decided to refrain from cardiac synchronisation on a routine basis in our three-dimensional, phase-contrast MR angiographic screening procedure in patients suspected to have renovascular hypertension. Cardiac gating, particularly diastolic gating, may be helpful in some patients only.

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Chapter

4

Fibromuscular dysplasia of the renal arteries: comparison of spiral CT angiography, MR angiography and conventional angiography

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Abstract

Objective: To test the feasibility of MR angiography (MRA) and CT angiography (CTA) techniques in the assessment of renal artery fibromuscular dysplasia with the objective to identify possible sources of error in depiction of this renal artery disorder.

Materials and methods: Image data of the phase-contrast MRA (PC-MRA), gadolinium enhanced MRA (CE-MRA) and CTA examinations of 29 consecutive patients with angiographically proven renal artery fibromuscular dysplasia were analyzed by two observers. Detection rate, location and extent of fibrodysplastic lesions (n=40) were recorded, supplemented with a lesion-to-lesion analysis by comparing the PC-MRA, CE-MRA and CTA images with intra-arterial digital subtraction angiography (ia-DSA).

Results: A total number of 26 PC-MRA's, 27 CE-MRA's, and 29 CTA's were available for evaluation. In terms of detection rate CTA (81.6%) performed significantly better than CE-MRA (42.9%), and PC-MRA (26.5%). The detection rate of renal artery abnormalities decreased with the increase of its distance from the aortic ostium in all three imaging techniques. Likewise, the extent of the fibromuscular dysplastic lesions influenced the detection rate considerably in all three imaging modalities: mild manifestations were seen in only 10%, 29% and 60% of cases with respectively PC-MRA, CE-MRA and CTA, whereas severe lesions were detected in respectively 60, 91 and 100%.

Conclusion: The present study shows that neither PC-MRA, neither CE-MRA, nor CTA can reliably diagnose renal artery fibromuscular dysplasia.

Introduction

Systemic hypertension is an important risk factor for both myocardial infarction and cerebral stroke. Identification of an underlying treatable cause of hypertension poses a major challenge in the management of a hypertensive patient. Renovascular disease, albeit rare, is the most common cause of secondary hypertension with an estimated prevalence of 3-5% in the overall population with hypertension. Renal artery stenosis can be treated by means of percutaneous endovascular interventions such as balloon angioplasty and/or stent implantation, or surgical techniques in order to facilitate blood pressure control and preservation of the renal function. Seventy percent of the renal artery stenoses are atheromatous in origin (1), whereas the next most common cause is fibromuscular dysplasia. This noninflammatory dysplastic process is characterized by abnormalities in the fibromuscular lining of the renal artery. The classic angiographic presentation of the most common form of fibromuscular dysplasia, medial fibroplasia, is characterized by multiple aneurysms separated by focal narrowing: string-of-beads-sign, involving the mid and distal renal artery. These abnormalities are predominantly present in persons aged 25-50 years and are more common in females. The excellent long-term results of percutaneous or surgical intervention of fibrodysplastic lesions make early identification of these patients an important clinical challenge (2).

Conventional angiography still is considered the standard of reference in the diagnosis of renovascular pathology. More recently, dedicated CT and MR protocols were introduced for volumetric data acquisition with high contrast-enhancement of the renal vessels yielding high sensitivities and specificities for the detection of main renal artery stenosis (3-6).

However, in most studies that reported sensitivities up to 100% for MRA and CTA to detect renal artery stenosis, either the prevalence of fibromuscular dysplasia was quite low or patients with fibromuscular dysplasia were excluded from the analysis. Some authors have indicated that the results of CTA and MRA to diagnose fibromuscular dysplasia in the renal arteries is less favourable (7,8), but, with the exception of Bergri et al (9), no separate assessment of the test performance in this subgroup of patients is reported.

Recently published results of a prospective multicenter study (RADISH-study) concerning the validity of CE-MRA and CTA to diagnose renal artery stenosis in hypertensive patients show an overall poor performance of both tests with sensitivities ranging from 57% - 67% for MRA and from 61% - 69% for CTA. Specificity ranged from 77% - 90% for MRA and from 89% - 97% for CTA (10). A striking difference with other studies was the relatively high proportion in this series of patients with fibromuscular dysplasia: 38% of all patients with renal artery stenosis.

The purpose of the present study was to scrutinize the MRA and CTA data of all patients from the RADISH-study with renal fibromuscular dysplasia as detected on ia-DSA in order to identify possible sources of error in the depiction of this renal artery disorder that may have contributed to the overall poor test performances and to give suggestions for further improvement.

Materials and methods

Patients

This study is part of the afore mentioned Dutch multicenter study (RADISH-study; "Renal Artery Diagnostic Imaging Study in Hypertension") in which the results of PC-MRA, CE-MRA and CTA of the renal arteries in patients suspected of renovascular hypertension were compared with the results of ia-DSA as the standard of reference, in order to establish the validity of MRA and CTA to diagnose renal artery stenosis. Details about the RADISH-study are comprehensively described elsewhere (10, Appendix). In brief, over a 3-year period 402 hypertensive patients between 18 and 75 years of age and with a diastolic blood pressure of ≥ 95 mm Hg were included in the study. These subjects were prospectively recruited from the outpatients' clinics of the Internal Medicine departments of three large teaching hospitals and three university hospitals in the Netherlands. In order to raise the pre-test probability of the presence of renal artery stenosis, patients had to exhibit at least one of the commonly accepted clinical clues for the presence of renal artery stenosis (10). All included patients were scheduled to have their MRA, CTA and ia-DSA examination within a three-month window.

Twenty-nine of the 402 patients (7%) proved to have fibromuscular dysplasia on ia-DSA as assessed in consensus by three vascular radiologists. These 29 patients were included in the present study. In the 29 patients studied, 57 main renal arteries and 11 supernumerary renal arteries (9 patients) were identified on ia-DSA; one renal artery was occluded. Intra-arterial DSA showed unilateral fibromuscular dysplasia in 17 patients (58%); bilateral fibromuscular dysplasia in 11 patients (38%), and 1 patient had fibromuscular dysplasia in one renal artery and a hemodynamically significant atherosclerotic stenosis of $\geq 50\%$ in the contralateral artery. Thus a total number of 40 fibromuscular dysplastic lesions in 29 patients were available for analysis.

The institutional review board of each participating hospital had approved the study protocol, including this subgroup analysis, and patients were required to sign an informed consent form prior to inclusion in the study.

Imaging techniques

Each participating hospital was equipped with state-of-the art MR scanners (1.0 or 1.5 Tesla), helical CT scanners (single or multiple detector-row systems), and DSA systems. Due to the variety of manufacturers and models of imaging equipment, each hospital was allowed to use the scan protocol which was considered optimal for its setting. Also, the hospitals were allowed to change the scan protocols during the study when new insights emerged or in case upgrades on the machinery were installed. Information about manufacturers, scan protocols, and used contrast agents is shown in table 1. Intra-arterial DSA was performed by means of catheterization of the suprarenal aorta through the right or left femoral artery by using a 4-Fr or 5-Fr pigtail or other non-selective catheter. Images were obtained in anteroposterior view. When visualization of the renal vasculature was considered inadequate, additional oblique projections and/or selective renal angiograms were obtained. Intra-arterial DSA was the standard of reference.

Table 1: Protocols for PC-MRA, CE-MRA, CTA, and Ia-DSA

No. of subjects included	Den Bosch 2	Maastricht 19	Nijmegen 4	Tilburg 2	Utrecht 1	Veldhoven 1
MRA						
Manufacturer MR scanner and field strength ‡						
3D PC-MRA						
FOV - mm	GE 1.5T	Philips 1.5T	Siemens 1.5T	Philips 1.0T	Philips 1.5T	Philips 1.0T
Matrix	300*300	260*130	320*200	260*130	260*130	260*130
acquisition slice thickness - mm / no. of slices	256*128	256*163	112*256	256*128	256*163	265*128
TR - msec / TE - msec / FA - degrees	2.5/28	1.5/64	2.5/32	1.5/64	1.5/64	1.5/64
Acquisition voxel size - mm3	25/6/35	15/5/0/20	11.5/9/0/20	17.4/6.4/15	15.1/5/0/20	17.0/6.1/20
Velocity encoding - cm/s	6.0	4.9	8.9	6.2	4.9	6.2
Scan duration - seconds	45	45	45	45	45	45
	410	306	410	356	305	350
3D CE-MRA						
FOV - mm	480*288	512*302 (400*400)	420*263	420*315	400*320	450*338
Matrix	512*192	512*261 (400*296)	512*192	512*163	512*196	384*293
acquisition slice thickness - mm / no. of slices	3.0/ 28	2.2/29 (1.9/35)	2.8/32	3.0/25	3.0/20	2.4/38
TR - msec / TE - msec / FA - degrees	5.6/1.2/40	5.6/1.6/40 (5.0/1.5/40)	4.6/1.8/30	9.0/2.8/40	8.6/2.1/45	6.3/1.7/40
Profile ordering technique	centric	centric	linear	linear	centric	centric
Acquisition voxel size - mm3	7.0	4.3 (2.6)	5.0	6.3	4.8	4.3
Scan duration - seconds	20	26 (27)	20	26	28	22
Name contrast agent §	Magnevist	Magnevist	Magnevist	Omniscan	Magnevist	Prohance
MI of contrast agent / injection rate - ml/second	30/ 2.5	30/3.0 (30/2.5)	14/2.5	20/2.5	30/2.0	30/2
CTA						
Manufacturer CT scanner ‡						
Collimation -mm / pitch	GE	Picker	Siemens	Philips	Philips	Philips
Name contrast agent §	3 / 1.5	2.5 / 0.7	3 / 1.0	3 / 1.0	3 / 1.0	3 / 1.0
MI of contrast agent / injection rate (ml/second)	Omnipaque 300	Omnipaque 350	Omnipaque 350	Omnipaque 300	Ultravist	Iomeron 300
Scan duration - seconds	120/ 3.0	140/4.0	120/ 3.0	120/4.5	130/3.0	140/4.0
	25	25	30	30	30	25
DSA						
Manufacturer DSA equipment ‡						
Image intensifier (cm)	GE	Philips	Siemens	Philips	Philips	Philips
Matrix	35	38	40	38	38	38
Name contrast agent §	1024	1024	1024	512	512	1024
Approximate amount of contrast agent - ml	Omnipaque 300	Omnipaque 300	Omnipaque 240	Omnipaque 300	Ultravist	Iomeron 300
Injection rate (aorta) - ml/second	90	60	160	40	90	60
	15	15	20	20	15	10 to 15

‡ GE Medical Systems, Milwaukee, Wisconsin, USA; Elscint Ltd., Haifa, Israel; Philips Medical Systems, Best, the Netherlands; Siemens Medical Solutions, Erlangen, Germany

§ Omnipaque and Omnican are products of Nycomed Amersham, Oslo, Norway; Magnevist and Ultravist are products of Schering AG, Berlin, Germany; Iomeron and Prohance are products of Bracco Byk Gulden, Konstanz, Germany

Image evaluation

As part of the RADISH-study, two, respectively three and three experienced observers retrospectively evaluated the PC-MRA, CE-MRA and CTA image data. Assessment was performed independently and the observers were blinded for all other diagnostic data and clinical results. Digital image data of all MRA and CTA exams were read on a workstation (Easy Vision, release 4.2.1, Philips Medical Systems, Best, The Netherlands), which was equipped with all common post-processing facilities including maximum intensity projection, shaded surface display and multi planar reformatting. The observers were allowed to use any of these post-processing techniques additional to the source images. Additionally, analysis of all PC-MRA, CE-MRA and CTA data of the patients with angiographically proven fibromuscular dysplasia was performed in consensus by two observers, using the same workstation and post-processing techniques. Both observers were informed about the purpose of the study and of the presence of fibromuscular dysplasia in one of the renal arteries but not of its location. The number of normal arteries and of arteries with evidence of dysplasia and/or significant stenotic disease was recorded. These interpretations were compared with the corresponding data of the RADISH-study. The location of the fibromuscular dysplastic lesions on ia-DSA was expressed in centimeters from the aortic ostium. The extent of fibromuscular dysplasia was indicated on a three-point scale (severe, moderate, mild). Subsequently, a lesion-to-lesion analysis was performed in order to assess possible specific pitfalls in the depiction of fibromuscular dysplasia of the renal arteries. For this assessment two observers compared in consensus the PC-MRA, CE-MRA and CTA data with the corresponding ia-DSA images of all arteries with angiographically proved fibromuscular dysplasia. A standard form was used to collect all relevant data.

Statistical analysis

Since we selected only patients with fibromuscular dysplasia, no realistic account of the total number of the false-positive results of PC-MRA, CE-MRA and/or CTA could be derived. Therefore, apart from detection rate, no information on the test validity of any of the three tests could be obtained.

The influence of severity and location on the detection of fibromuscular dysplasia was assessed using the Chi-square test or, if appropriate, the Fisher exact test, after dichotomisation of the results.

Results

The clinical characteristics of the 29 patients with angiographically proven fibromuscular dysplasia are shown in Table 2.

Except for the distribution of gender, no statistically significant differences were found for the characteristics of the 29 subjects included in this analysis as compared to the total group of 402 patients included in the RADISH-study (10).

In 26 patients (90%; 52 kidneys), all three imaging studies, i.e. PC-MRA, CE-MRA and CTA were performed. As a consequence of their claustrophobia two patients were not submitted to the MR examination; in one patient the MR examination was limited to only a CE-MRA for the same reason. Thus, a total number of 26 PC-MRA's, 27 CE-MRA's, and 29 CTA's were available for evaluation. Due to problems with digital data transfer with

Table 2. Demographic and clinical characteristics of the 29 patients with angiographically proven fibromuscular dysplasia.

Male : female		4 : 25
Age – yr	median; mean $\pm$ SD (range)	53; 50,9 $\pm$ 9.2 (30-66)
Systolic blood pressure at baseline* - mmHg	mean $\pm$ SD (range)	183 $\pm$ 17.7 (140-228)
Diastolic blood pressure at baseline* - mmHg	mean $\pm$ SD (range)	111 $\pm$ 11.4 (90-138)
Years with known hypertension	mean $\pm$ SD (range)	6,3 $\pm$ 8.4 (0-38)
Smoking habit	smokers - no. (%)	12 (41)

Note: * All patients were included on the basis of a diastolic blood pressure of ≥ 95 mmHg. Blood pressures presented here were either measured at the time of inclusion or in the time period between inclusion and hospital admission for ia-DSA.

one of the participating hospitals however, the imaging studies of two patients could not be analysed. Both patients had mild unilateral fibromuscular dysplasia on ia-DSA.

All PC-MRA, CE-MRA, and CTA images were considered to be of enough of diagnostic quality by the eight independent observers of the RADISH-study. However, during subsequent analysis in the present study two PC-MRA and five CE-MRA studies were considered of non-diagnostic quality, including 2, respectively 7 kidneys with fibromuscular dysplasia. The performance of the three imaging tests in terms of their potential to detect fibromuscular lesions as executed within the framework of the RADISH-study and the present study are tabulated in table 3.

Table 3: Number of detected and missed fibromuscular lesions with all three imaging techniques by independent, blinded observers from the RADISH-study (Obs. 1-8) compared to the results of two observers in consensus with prior knowledge of the presence of fibromuscular dysplasia in the present study (Consensus).

	PC-MRA			CE-MRA				CTA			
	Obs. 1	Obs. 2	Consensus	Obs. 3	Obs. 4	Obs. 5	Consensus	Obs. 6	Obs. 7	Obs. 8	Consensus
Detected	7	5	9 (26%)	10	8	10	15 (43%)	17	10	16	31 (82%)
Not detected	29	31	23	27	29	27	13	23	30	24	7
Non-diagnostic			2				7				
Total	36	36	34*	37	37	37	35*	40	40	40	38*

Note: * Due to problems with digital data transfer with one of the participating hospitals, the imaging studies of two patients were not available for this analysis. Both patients had mild unilateral fibromuscular dysplasia on ia-DSA.

Figure 1: Distribution of distances of the fibro-muscular dysplastic in the renal arteries in centimeters from the aortic ostium.

The location of the fibromuscular dysplastic lesions on ia-DSA expressed in centimeters from the aortic ostium is shown in figure 1.

In table 4 the relation between the extent and location of fibromuscular dysplasia and the number of detected lesions as obtained with all three imaging techniques are indicated.

Table 4: Extent and location of fibromuscular dysplasia in relation to the number of detected and missed fibromuscular dysplastic lesions obtained with all three imaging techniques by two observers in consensus with prior knowledge of the presence of fibromuscular dysplasia.

		Extent FMD on ia-DSA			Distance of FMD from the aortic ostium on ia-DSA		
		Mild	Moderate	Severe	≤ 2.5 cm	2.5-3 cm	> 3 cm
PC-MRA	Detected	1	2	6	1	7	1
	Not detected	9	10 (2)	4	3 (1)	8	12 (1)
	p value	0.009			0.05		
CE-MRA	Detected	4	1	10	2	8	5
	Not detected	3 (3)	9 (4)	1	3	5 (2)	5 (5)
	p value	0.0001			0.5		
CTA	Detected	6	13	12	4	16	11
	Not detected	4	3	0	2	0	5
	p value	0.07			0.11		

Note: The presented p values are calculated after dichotomisation of the test results by combining the mild and moderate results, respectively the ≤ 2.5 cm and 2.5-3 cm results. Numbers in parentheses are not detected lesions as a result of non-diagnostic examinations.

Severe fibromuscular dysplastic lesions on ia-DSA were seen on PC-MRA in only 6 cases (60%), whereas 10 (91%) respectively 12 (100%) were noted with CE-MRA and CTA. The lesion-to-lesion analysis demonstrated that the characteristic string-of-beads sign, considered pathognomonic for (medial) fibromuscular dysplasia, could be seen on the CE-MRA and CTA images in 80%, respectively 95% of cases, although in some vessels only discrete irregularities were noted. Relatively large, hilar aneurysms were seen in two cases. On the PC-MRA the presence of fibromuscular dysplasia in the renal arteries was suggested by an abrupt drop in signal intensity with or without a distal recurrence of flow signal in 50% of cases (Figure 2).

Figure 2: Bilateral renal artery FMD on DSA (a); suggested by an abrupt drop in signal intensity in the renal arteries with (right renal artery) and without (left renal artery) distal recurrence of flow signal on PC-MRA (b); and presented as (discrete) vessel wall irregularities in both renal arteries on CE-CTA (c) and CTA (d).

Discussion

The major finding of this study is that neither MR angiography nor CT angiography can reliably identify renal artery fibromuscular dysplasia in patients suspected of renovascular hypertension. Even in this artificially composed population with a very high prevalence of fibromuscular dysplasia the observers frequently failed to identify this renal artery abnormality despite prior knowledge of the presence of this disease in one of the renal arteries. The results of CTA were better than CE-MRA, which in turn performed better

than PC-MRA, but with none of the three techniques a detection rate of $\geq 82\%$ for the presence of fibromuscular dysplasia could be reached.

These results, though disappointing, confirm the assumption that MRA and CTA techniques are, to date, inadequate for non-invasive evaluation of renal artery fibromuscular dysplasia (7,8). As a result of the inclusion criteria the pre-test likelihood for renal artery stenosis in the initial group of patients from the RADISH-study was high compared to the general population. Further increase of the pre-test likelihood by identifying factors which are thought to be associated with fibromuscular dysplasia might be difficult, since, apart from gender, no discriminating clinical features were found in this sub-group of patients relative to the initial group of patients from the RADISH-study. There was a significant female predominance in our group of patients ($\text{♂} : \text{♀} = 4 : 25$), whereas the age of these patients was relatively high as compared to international literature: mean 51 ± 9 years (range 30-66), median 53 years. This is not in accordance with the internationally accepted, young adult profile of patients with fibromuscular dysplasia (Table 2).

The limited spatial resolution in relation to the relatively small calibre of the segmental arteries is likely to be one of the limiting factors (7,8). Also, motion artefacts can influence the image quality of the more distal part of the renal arteries, typically the segment of presentation of fibromuscular dysplasia. A recent MR study demonstrated the presence of significant renal motion in caudo-cranial direction during sustained breath-hold at end inspiration, ranging from -5.2 to 23.1 mm and -16.6 to 32.5 mm, respectively (for a scan duration of 26 seconds). The observed average displacement of the kidney during breath-hold CE-MRA was greater than the typically employed voxel size, jeopardizing the reliability of CE-MRA interpretation of the distal renal artery segments (11). This phenomenon may result in incorrect diagnoses, and is likely to affect image quality on CTA as well. These limitations seem to apply also to our data since PC-MRA, being the technique with the longest acquisition time, produced the worst results as opposed to CE-MRA and, more distinctly to CTA. Furthermore, the probable presence of a peripherally located renal artery disease like fibromuscular dysplasia in combination with a relatively poor depiction of the peripheral renal artery segment on MRA resulted in a number of non diagnostic examinations in this study.

The detection rate of renal artery abnormalities fell with the increase in their distance from the aortic ostium in all three imaging techniques: of all abnormalities located more than 3.0 cm from the aortic ostium only 8% were detected with PC-MRA, whereas with CE-MRA and CTA 33%, respectively 68% of the lesions were noted, as opposed to 40%, respectively 55% and 91% for the more proximally located lesions (Table 4).

Likewise, the extent of the fibromuscular dysplastic lesions influenced the detection rate considerably in all three imaging modalities. Mild manifestations of renal artery fibromuscular dysplasia were seen in only 10%, 29% and 60% of cases with respectively PC-MRA, CE-MRA and CTA, whereas severe lesions were detected in 60, 91 respectively 100% of cases resulting in a statistically significant difference between the combined grades 1 and 2 compared to grade 3 with both MR techniques (Table 4).

A lesion-to-lesion analysis was performed in order to get a better understanding of the potential pitfalls and/or limitations of PC-MRA, CE-MRA and CTA in the detection of fibromuscular dysplasia in the renal arteries. Four frequently encountered sources of error could be identified; 1) Superpositioning from overlapping vessels, caused by a suboptimal

Figure 3: Distal manifestation of fibromuscular dysplasia in the right renal artery on DSA (a); suggested by discreet outpouchings on the PC-MRA source images (b); and on the multi planar reformatted images on CE-MRA (c) and CTA (d)

timing of data acquisition relative to the arrival of the contrast bolus; 2) A downward and/or tortuous course of the renal artery making interpretation of the source images alone virtually impossible and necessitating advanced (free-curved) multi-planar reformatting; 3) The distal manifestation of fibromuscular dysplasia, together with the multiple (perihilar) branching; and 4) Relatively long fibromuscular dysplastic lesions with only discreet aneurysmal outpouchings (figure 3).

In conclusion, the present study shows that neither PC-MRA, neither CE-MRA nor CTA can reliably diagnose renal artery fibromuscular dysplasia. Future technologic developments, particularly focusing on a more rapid data acquisition and improvement of spatial resolution seem necessary before these techniques can be fully implemented in daily practice. Pending these improvements, ia-DSA remains the gold standard for the detection of renal artery fibromuscular dysplasia.

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Chapter 5

Renal artery blood flow: quantification with breath-hold or respiratory triggered phase-contrast MR imaging.

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Abstract

The aim of this study was to evaluate the validity and reproducibility of breath-hold and respiratory triggered phase-contrast (PC) MR imaging techniques in the measurement of renal artery blood flow. In twelve healthy subjects cardiac-gated PC flow measurements were obtained in the renal arteries using a breath-hold and a respiratory triggered technique. The flow measurements were repeated in each separate renal artery. Comparison between the sum of flow measurements in the renal arteries and the difference in aortic flow measurements above and below the renal arteries served as an internal control. The flow measurements showed a good reproducibility both with the breath-hold ($r = 0.92$, $p < 0.0001$) and with the respiratory triggered ($r = 0.91$, $p < 0.0001$) technique. The validity of both methods was good and did not differ statistical significantly. Reproducible quantitative measurements of renal artery blood flow are possible with respiratory controlled, cardiac-gated, PC MR imaging.

Introduction

Renal artery stenosis is the most frequent cause of secondary hypertension, with an estimated prevalence of 3-5% in the general population of people with hypertension (1,2). Identifying hypertensive patients with renovascular disease could allow for potential curative therapy. Correction of arterial stenoses by means of percutaneous transluminal angioplasty (PTRA) or surgical techniques shows normalisation or improvement of the hypertension in the majority of these patients (3-5). However, in 10 - 30 % there is no response to these therapeutic regimens (5,6) and it seems unpredictable who will respond and who will not. Moreover, many aortograms obtained for other reasons demonstrate renal artery stenosis in normo-tensive patients.

Up to now the decision to correct renal artery stenosis in hypertensive patients is predominantly based upon morphologic information (stenosis > 50 %) provided by current imaging techniques, including intra-arterial digital subtraction angiography (ia-DSA), computed tomographic angiography, and magnetic resonance (MR) angiography (7,8). Doppler sonography is used for non-invasive detection of renal artery stenosis with varying results concerning diagnostic accuracy because quantification of renal artery blood flow is influenced by a variety of errors inherent in the indirect calculation of Doppler parameters (9,10,11). Various functional tests, for example para-aminohippuric acid (PAH) clearance, venous renin sampling and radionuclide renography are either indirect measures of disease or yield only total renal flow, rather than unilateral flow to each kidney (12,13,14).

Knowledge of blood flow in the individual renal artery in patients with hypertension would provide a better understanding about the pathophysiology of renovascular hypertension and this information might be important in the therapeutic management of these patients. Furthermore, measurements of renal artery blood flow could serve as a non-invasive test for follow-up after PTRA or surgical reconstruction and for evaluation of various vasoactive agents.

Recent publications indicate that high-resolution 3D gadolinium-enhanced MR angiography is the preferred MR angiography technique for morphologic assessment of the renal arteries. Other MR angiographic techniques (i.e. phase-contrast and time-of-flight) show limitations in depicting small-calibre vessels and distal renal artery segments (15). However, phase-contrast MR imaging (PC MR), which goes beyond morphologic imaging by allowing quantitative evaluation of flow dynamics, may be used to determine the hemodynamic significance of renovascular disease. Flow quantification with PC MR uses the velocity-dependent phase shifts of flowing spins (16). In combination with cardiac triggering, flow rates can be determined at specified phases of the cardiac cycle. This enables the flow rates to be studied as a function of time. The accuracy of PC flow measurement has been validated *in vitro* and *in vivo* (17,18).

In the past few years, several phase-contrast MR techniques have been proposed for quantification of blood flow in the renal arteries (19, 20). However, the reported results show varying success in renal blood flow measurement compared to results obtained by means of para-aminohippurate (PAH) clearance. Respiratory motion, which causes the renal arteries to move during data acquisition, appears to be a considerable source of error in these measurements (20,21, 22). Synchronisation with respect to respiratory motion, along with cardiac triggering, seems to be necessary to obtain accurate, reproducible flow data (22, 23).

The aim of this study was to determine the feasibility and reproducibility of two respiration controlled PC MR techniques: a breath-hold sequence, and a respiratory triggered sequence, to measure blood flow in the individual renal arteries.

Materials and Methods

Subjects

Twelve subjects (8 male, 4 female, mean age 35 years, range 23 - 48 year) were recruited. All volunteers were normotensive and without known underlying renal disease. Criteria for participation in the study included willingness to give informed consent, and lack of standard contra-indications to MR imaging (e.g. pacemaker, claustrophobia, or ocular metallic fragments). The ethical review board of our institute approved the study.

MR imaging technique

All images were acquired on a 1.5 Tesla whole-body MR system (ACS II, Philips Medical Systems, Best, The Netherlands), using the quadrature body coil for signal transmission and reception. No abdominal compression was used.

To localize the renal arteries, a T1-weighted gradient echo multistack scout view was obtained at the level of the kidneys (TR/TE: 22.0/7.0, 20° flip angle, 15.0 mm slice-thickness, FOV: 500 mm, 256 x 256 matrix). Images were obtained in the coronal and transverse planes.

Subsequently, a non-gated three-dimensional phase-contrast MR angiographic (3D PC-MRA) sequence was performed for morphological assessment of the renal arteries (8).

T1-weighted, gradient-echo images were obtained in the transverse plane with the following parameters: TR/TE: 27.0/8.5, 20° flip angle, two signals averaged, 75% partial echo sampling, 200 x 140 mm FOV, 128 x 103 acquisition matrix, using a 256 reconstruction matrix and 45 cm/sec flow-encoded velocity. Fourier interpolation was used to reconstruct sections thinner than those acquired. In the sequence performed without gating, 32 sections of 4 mm were acquired, reconstructed to 64 slices of 2.0 mm. The outer 10% on both sides was discarded resulting in 50 slices of 2 mm.

To reduce the venous signal from the inferior vena cava, a transverse presaturation slab (60.0 mm thick) was placed inferior to the lower pole of the kidneys. The maximum intensity projection (MIP) algorithm was used to create angiographic projections in the transverse, coronal and sagittal plane. Both the MIPs and the original transverse images were used to select an image plane perpendicular to the studied artery for flow quantification.

A flow compensated turbo gradient-echo phase-contrast MR (PC MR) technique was used for flow data acquisition with the following parameters: FOV 180 x 90, TR/TE 12.0/7.0, 25° flip angle, 7.0 mm slice-thickness, two signals averaged allowing fold-over suppression in the phase-encoding direction (anterior-posterior), 128 x 96 acquisition matrix, using a 128 reconstruction matrix, in-plane voxel size 1.4 x 1.9 mm, cardiac triggering, 8 phases per cardiac cycle, linear profile order, 10 profiles per heart phase, flow-encoded velocity 120 cm/sec. Electrocardiography was used for cardiac synchronisation.

Flow quantification was performed both with a breath-hold (acquisition time 30 seconds), and a respiratory triggered technique (acquisition time 2 minutes). Images were obtained perpendicular to the right and left renal artery 8 -15 mm from their aortic origin.

In order to acquire information about the reproducibility of the flow measurements, flow quantification in each separate renal artery was repeated within 5 minutes in each subject without changing the scan-parameters and/or off-centres.

As an internal validation of the measurements, flow data were obtained in each renal artery separately and in the abdominal aorta superior and inferior to the origins of the renal arteries. To avoid inclusion of the superior mesenteric artery, the position of the slices was carefully planned on the MIP's of the non-gated 3D PC-MRA sequence. Postulating that no other (major) vessel originates from the involved aortal segment contains that, with accurate flow measurements, the sum of flow volumes in the renal arteries and inferior aorta is the same as in flow volume measured in the aorta superior to the renal artery origins.

Consequently, 12 separate flow measurements were performed in each individual.

Evaluation and Statistics

To ensure optimal vessel demarcation and measurement reproducibility, all phase-contrast flow data were analysed in a contour detection program, on an off-line workstation (Sun Microsystems, Mountain View, California, U.S.A.). The employed automated region of interest (ROI) definition algorithm defined the region on the phase-contrast MR images bounded by an operator-defined ellipse drawn generously around the vessel on the modulus images. Instantaneous flow (millilitres per second) was calculated from the individual velocity images by integrating velocity (centimeters per second) across the area (square centimeters) of the vessel. Mean flow in each vessel was calculated as the average of instantaneous flows across the cardiac cycle.

The interobserver agreement was determined by calculating the Pearson correlation coefficients for both the breath-hold and the respiratory triggered flow measurements.

Validity assessment of both techniques was based on differences between the in- and outgoing flows.

Results

Non-gated three-dimensional phase-contrast MR angiography (3D PC-MRA) revealed a total of 26 renal arteries in the 12 subjects. Two subjects showed an accessory renal artery. None of the visualized arteries showed renovascular disease on the non-gated 3D PC-MRA images. The waveforms in the renal arteries showed a continuous forward flow characteristic of an arterial system with low peripheral resistance. The aortic waveforms showed a more pulsatile flow pattern with a phase of retrograde flow during diastole.

The flow measurements in the renal arteries showed a good reproducibility with Pearson correlation coefficients of 0.92 and 0.91 ($p < 0.0001$) for the breath-hold and respiratory triggered technique respectively (Fig 1a and 1b).

The residual flow, i.e. the difference between flow measured in the superior aorta (inflow) and the sum of measurements of both renal arteries and inferior aorta (outflow), should be equal to zero. The standard deviations of this residual flow with the mean set to zero are for the breath-hold and respiratory triggered 11.4 and 9.3 respectively. These values do not differ significantly (F-test: $p = 0.23$).

Figure 1 a, b: Scatter plot of the first and second flow measurement with orthogonal regression line.

Note: Δ right renal artery $\bullet$ left renal artery

In one subject a relatively large residual flow was noted: 680.6 ml/min using the breath-hold technique, respectively 434.0 ml/min with the respiratory triggered technique, probably caused by poor positioning of the flow-acquisition slices. If these deviating results would have been omitted, the difference in standard deviations for the breath-hold and the respiratory triggered technique, namely 4.2. and 8.6 respectively, becomes statistically significant ($p=0.01$), thus favouring the breath-hold technique.

Likewise, the independent MRA measurements of the total renal blood flow (RBF) calculated from the sum of renal artery flows concurred well with the RBF calculated from the aortic difference (Fig 2a and 2b).

Figure 2 a, b: Scatter plot of the total renal blood flow calculated from the sum of renal flows and from the aortic difference.

Discussion

Respiration controlled MR phase imaging promises to be a reliable technique for non-invasive measurement of blood flow in the renal arteries. The obtained absolute flow measurements in the renal arteries and abdominal aorta correspond well with results of other published studies (20-24).

Comparison between the in - and outgoing flows, i.e. flow in the superior abdominal aorta vs. flows in the renal arteries and inferior abdominal aorta, served as an internal control from which information was derived about the accuracy of the MR technique. The degree of reproducibility, which to our knowledge has not been addressed in recent literature, was evaluated by repeating the separate flow measurements in the renal arteries without changing scan-parameters and/or off-centres. Thus 12 separate flow measurements, i.e. 6 with the breath-hold and 6 with the respiratory triggered technique, were performed in each individual. In this study these independent measurements yielded overall concurring and reproducible results with both the breath-hold and the respiratory triggered technique.

The optimal method for flow data acquisition and evaluation in the renal arteries is not yet certain. Several published reports show reliable flow measurements using MR techniques without respiratory synchronisation (19,21,24,25), whereas others identify respiratory motion as a significant potential source of error in quantitative flow assessment in the renal arteries (20,22,23). This contrast could be related to differences in the location of the parasagittal imaging plane with respect to the aorta, since respiration is likely to have a more significant influence on motion of the renal vessels in the periphery than in their central segment.

Misalignment between slice direction and vessel axis and partial volume effects due to the limited in-plane resolution are other potential sources of error. Great care was taken to localize the renal arteries on MR angiography, using both MIP's in three different planes and the original transverse images, and (double-) angulating the slice perpendicular to the flow axis.

With a typical R-R interval of 850 msec. (70 bpm), respiratory synchronisation, along with cardiac triggering, permitted a temporal resolution of only about 107 msec, allowing reproducible assessment of the mean renal artery blood flow. However, the relative low temporal resolution of this technique does not allow qualitative analysis of flow profiles, which might be necessary in patients with more complex flow patterns. In a recent publication Schoenberg et al (26) described a cardiac-gated cine phase-contrast MR technique, without respiratory synchronisation, with a temporal resolution from 32 to 16 msec. This technique enabled him to analyse the pulsatile properties of the renal artery waveform and to identify different segments of the flow profile. However, reduction of the mean renal blood flow proved to be the only statistically significant parameter in accurate differentiation between hemodynamically relevant high-grade ($\geq 50\%$) stenosis and low-grade ($< 50\%$) stenosis. Maximum velocity and time to systolic maximum were more sensitive to changes at lower degrees ($< 50\%$) of stenosis.

Published reports indicate that differences from right to left in excess of 15% (calculated by dividing the difference from right to left by the average of the two) are abnormal (18). Measurements in this study showed asymmetry in all subjects to some extent: mean difference 8.6% and 13.0% for the breath-hold and respiratory triggered technique

respectively. In two subjects a mean right-to-left difference greater than 15% was noted with the breath-hold technique, as opposed to three subjects with the respiratory triggered technique.

In summary, quantitative assessment of renal artery blood flow may prove to be important in the clinical evaluation of patients with renal artery pathology. Furthermore, measurement of renal blood flow could serve as a non-invasive test for follow-up after PTRR or surgical reconstruction and for evaluation of various vasoactive agents.

This preliminary study shows that reproducible quantitative measurements of renal artery blood flow are possible with respiratory controlled, cardiac-gated, phase-contrast MR imaging. Our data show a slight preference for the breath-hold technique compared to the respiratory triggered technique. However, the study is limited by the small sample size ($n=12$) and the composition of the subject-group (i.e. healthy, relatively young volunteers), which makes extrapolation of the results to the daily practice difficult. Further and larger studies in (hypertensive) patients comparing different MRA techniques mutually and with other methods, and studies that address the reproducibility of the various techniques would be worthwhile.

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Chapter 6

PC-MR flow quantification in renal arteries; comparison with $^{133}\text{Xenon}$ washout measurements.

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Abstract

To assess the accuracy of 2D phase-contrast MR (2D PC MR) renal artery flow measurements, data obtained with this technique were compared to those acquired with the ^{133}Xe washout procedure. In addition, the 2D PC MR flow data were related to functional renal information as derived from selective arterial and venous renin sampling. In 53 patients suspected of having renovascular hypertension MR angiography of the renal arteries was performed, followed by a three-step angiographic procedure: 1) selective venous and arterial renin sampling; 2) assessment of the renal blood flow by means of the ^{133}Xe washout technique and 3) conventional renal angiography. After initial assessment, 71 kidneys were left for analysis. The overall prevalence of renovascular disease $\geq 50\%$ stenosis was 18%. Mean renal blood flow as assessed with the 2D PC MR technique showed a significant correlation with the ^{133}Xe washout flow measurements, with a Pearson correlation coefficient of 0.69 (two-tailed; $p < 0.01$). Phase-contrast MR blood flow measurements correlated poorly with the presence and/or severity of renovascular disease on conventional angiography ($r=0.1$, $p=0.36$). Likewise, no statistically significant correlation with either venous renin levels or the renin ratio could be identified. In conclusion, measurement of renal artery blood flow using a 2D phase-contrast MR technique is technically feasible. However, the mean renal artery blood flow correlates poorly with either the presence of renovascular disease on angiography or with renin levels. Further improvement of this technique is necessary before it can be applied on a larger scale.

Introduction

Magnetic resonance angiography (MRA) is a promising non-invasive imaging modality for the screening of renovascular disease (1-3). Recent publications indicate that high-resolution 3D gadolinium-enhanced MR angiography is the preferred MR angiographic technique for assessment of the renal arteries (4-7). However, similar to other imaging methods employed in the diagnosis of renal artery stenosis, most MRA techniques solely rely on the morphologic assessment of the vasculature. To assess the hemodynamic consequences of a particular arterial lesion, additional functional tests are still required.

Published reports concerning several non-invasive techniques (eg, duplex ultrasound and/or nuclear clearance techniques) show a great variety in diagnostic accuracy as well as various specific limitations of these tests in the assessment of renal artery blood flow (8-10). Therefore, the demand for a reliable, non-invasive screening method remains valid (11).

Magnetic resonance phase-contrast (PC MR) protocols have been proposed to provide the desired functional information through direct, non-invasive 2D PC MR renal artery flow quantification. The accuracy of this technique was verified, both in vivo and in vitro, by comparison with other non-invasive (eg, duplex ultrasound and/or nuclear clearance techniques) and invasive techniques (implantation of ultrasound probes) or by internal validation by comparing aortic flow measurements above the renal arteries with the total flow through the renal arteries and aorta distal of these arteries (12-14).

In the current study the $^{133}\text{Xenon}$ washout technique was used as an independent test for comparative evaluation of the acquired 2D PC MR renal artery flow data in hypertensive patients. The $^{133}\text{Xenon}$ washout technique requires selective arterial catheterisation to allow local disposition of the tracer and therefore has the potential to provide information about blood flow of both kidneys separately.

The primary objective of this investigation was to assess the accuracy of the 2D PC MR flow measurements in patients suspected of having renovascular hypertension by comparing the results of these measurements with those obtained by $^{133}\text{Xenon}$ washout.

In addition, the 2D PC MR flow data were related to functional renal information as obtained by selective arterial and venous renin sampling to assess the presence of renal artery stenosis. In this respect, conventional renal angiography was used as the standard of reference for the diagnosis of renal artery disease.

Materials and methods

Patients

Over an 11-months period, all patients who were referred by the Department of Internal Medicine for angiographic evaluation of the renal arteries were prospectively enrolled in the present study. Selection criteria included malignant, accelerated and/or treatment-resistant hypertension, hypertensive retinopathy grade III or IV, loss of renal function after ACE inhibition, unilateral loss of kidney volume or unexplained deterioration of renal function (change in serum creatinine $> 20 \mu\text{mol/l}$ within 12 months).

Three weeks before angiography all antihypertensive medication was discontinued. In addition, patients were asked to use a salt-restricted diet containing 55 mmol of sodium per day during the last week prior to admission. The rationale for the latter is that data on renal blood flow or renin secretion should always be interpreted in relation to sodium

intake and that standardisation, therefore, is mandatory. Adherence to this diet was checked by measuring 24-hour sodium output at the time of admission to the hospital. The institutional review board had approved the study protocol, and patients were required to sign an informed consent form before they were included in the study.

Diagnostic protocol

The protocol of this study was fitted with a strict sequence of diagnostic modalities in order to avoid mutual influences; therefore the MRA examination was always performed one day before the conventional angiography was planned.

During the angiographic procedure, three separate, successive steps were taken: 1) selective renal venous and arterial renin sampling; 2) assessment of renal blood flow by means of the ^{133}Xe washout technique and finally 3) conventional, intra-arterial renal angiography. Only after completion of the first two steps, contrast material was administered.

MR imaging technique

All images were acquired on a 1.5 Tesla whole-body MR system (Gyrosan NT, release 6; Philips Medical Systems, Best, the Netherlands), using the quadrature body coil for signal transmission and reception. No abdominal compression was used.

After localizing the renal arteries, a non-gated 3D phase-contrast MR angiographic (3D PC-MRA) sequence was performed to visualize the renal arteries (12). T1-weighted gradient-echo images were obtained in the transverse plane with the following parameters: TR/TE 27.0/8.5, flip angle 20°, two signals averaged, 75% echo sampling, 200 x 140 mm FOV, 103 x 128 mm, acquisition matrix, using a 256 reconstruction matrix, and flow-encoded velocity range (Venc) of 45 cm/s. Fourier interpolation was used to reconstruct sections thinner than those acquired.

To reduce the venous signal from the inferior caval vein, a transverse presaturation slab (60.0 mm thick) was placed inferior to the lower pole of the kidneys. The maximum intensity projection (MIP) algorithm was used to create angiographic projections in the transverse, coronal and sagittal planes. Both the MIP's and the original transverse images were used to select an acquisition plane to the artery studied for flow quantification.

A 2D PC MR technique was used for flow data acquisition during normal breathing with the following parameters: TR/TE: 14/6; flip angle 20°, FOV: 300 x 210 mm, slice thickness: 6 mm; acquisition matrix: 256 x 108, and Venc: 120 cm/s. The scan was retrospectively triggered using a peripheral pulse unit (PPU), yielding 25 heart phases at a frequency of 65 heartbeats/min. within a scan time of ≈ 2 minutes. The flow data were obtained in a plane perpendicular to the right and left renal artery, 8 to 15 mm from the origin.

To ensure optimal vessel demarcation and measurement reproducibility, all quantitative 2D PC MR flow measurements were analysed using a contour detection program on an off-line workstation (Sun Microsystems, Mountain View, California, U.S.A.). The automated region of interest definition algorithm selected the region on the 2D PC MR images within an operator-defined ellipsis drawn generously around the vessel on the modulus images. Instantaneous flow (ml/sec) was calculated from the individual velocity images by integrating velocity (cm/sec) across the area (cm²) of the vessel. Mean flow in each vessel was calculated as the average of instantaneous flows across the cardiac cycle.

Angiographic procedure

The procedure was carried out in the angiosuite of the department of radiology, which is equipped with both an X-ray system and NaI (TI) gamma spectroscopy system. After selective catheterisation of the renal vessels and before any intra-arterial contrast material was given, blood samples for determination of active plasma renin concentration (APRC) were drawn simultaneously from aorta and both renal veins.

Subsequently, mean renal blood flow (MRBF) for each kidney was assessed by means of the ^{133}Xe washout technique (15). Only after completion of these measurements, diagnostic intra-arterial renal angiography was performed with a commercially available digital subtraction system (Integris 5000; Philips Medical Systems; Best, The Netherlands). Angiographic images of the abdominal aorta and renal arteries were obtained in anteroposterior and left and right oblique views with injection of 30 ml iohexol (Omnipaque 300; Nycomed, Oslo, Norway) through a 4-F Universal Flush catheter (Cordis Europe, Roden, The Netherlands) positioned at the level of the renal arteries. Selective renal angiography was performed in the majority of cases with injection of 12 ml iohexol through a 5-F end-hole Cobra-2 or Simmons-2 catheter (Cordis Europe, Roden, the Netherlands).

Three experienced interventional radiologists, who were blinded to the MR angiographic results independently read and interpreted the conventional angiograms. For cases in which the three observers had conflicting interpretations of the angiograms (> 10% difference in degree of stenosis), a fourth interventional radiologist was asked to establish a definite diagnosis, based on his review of all three separate interpretations as well as on the angiographic images.

Intra-arterial ^{133}Xe washout technique

The principles of the inert gas washout technique are based on the work of Kety (16). For any substance carried to an organ by the blood, it is evident that the amount which enters the organ within a specified time interval must equal the amount of that substance, which, during the same time interval, leaves the organ, plus the amount which is accumulated and metabolised in that organ. In the case of an inert unmetabolized substance such as xenon, no conversion takes place. Thus, derived from several equations, monitoring the disappearance of ^{133}Xe from the organ will allow calculation of flow per unit volume of tissue (15).

The Xenon washout curves were analyzed as described earlier (15-18). In brief, after subtraction of background radiation, the disappearance of ^{133}Xe from the kidney, measured by an extra-corporal gamma-probe, is analyzed mathematically using a two-phase exponential decay. Occasionally, a monophasic decline in activity is observed and the curve analyzed accordingly. The mean renal blood flow (MRBF) is calculated as the weighted average of the fast and the slow component (18). All analyses were performed using Prism 3.0 software.

To convert the relative blood flow per kidney as determined from ^{133}Xe washout technique to absolute blood flow per kidney it is necessary to know the total tissue volume of the separate kidneys. For this purpose computer tomography (CT) was introduced as an independent imaging modality, since the MR scout images were thought to be insufficient for adequate assessment of the kidney volume. Spiral CT was performed with a commercially available double-helix scanner (Elscint Ltd, Haifa, Israel). After

localizing the level of the kidneys, a volume acquisition was performed with the following protocol: 120 kV at 350 mA, 30 seconds continuous exposure, 2.5-mm collimation, and 1.3 mm/sec table speed. The axial source images were postprocessed on an off-line workstation (Sun Microsystems, Mountain View, California, U.S.A.). The volumes of the kidneys were calculated by multiplying the renal surface area on every individual slice (mm²) by the slice thickness (mm) and adding up all slice volumes.

When performed this way, the ¹³³Xenon washout study provides an accurate estimate of renal blood flow and in our hands has a variability of 8% for repeated measurements (19).

Statistical Analysis

Conventional angiography was regarded as the standard of reference for detection of renal artery stenosis. A significant stenosis was defined as luminal narrowing exceeding 50% of the vessel diameter. Renal arteries with evidence of fibromuscular dysplasia were graded as significantly stenosed ($\geq 50\%$).

Statistical differences were assessed using the two-sample Student's *t*-test. Associations between the renal artery blood flow quantification techniques, or active plasma renin ratio ($\text{APRC}_{\text{vein}} - \text{APRC}_{\text{aorta}} / \text{APRC}_{\text{aorta}}$) and conventional renal angiography were calculated using the Pearson correlation coefficient and orthogonal regression analysis.

Results

Fifty-three patients with 106 kidneys were prospectively enrolled in this study: The mean age was 55 years (range, 30 to 79), and 60% were men. Mean systolic blood pressure measured at three separate, consecutive occasions was 188 mmHg; mean diastolic blood pressure was 109 mmHg. Serum creatinine averaged 109 $\mu\text{mol/l}$. Conventional renal angiography showed supernumerary arteries in 16 kidneys (15%), with one kidney that showed three separate renal arteries. Total occlusion of the renal artery was found in three kidneys.

Kidneys with supernumerary renal arteries were excluded from analysis because a mismatch between the ipsilateral individual renal arteries in these cases could occur during the blinded first two steps of the angiographic procedure: sampling and ¹³³Xenon washout studies. Also, the kidneys with a total occlusion of the renal artery were discarded.

In 14 of the remaining 87 kidneys (16%), the 2D PC MR quantitative flow images showed insufficient quality for automatic contour detection due to improper slice positioning and/or to flow voids during systole caused by proximal stenoses. In another two (unilateral) cases it was not possible to obtain ¹³³Xenon washout information, probably due to poor positioning of the intra-arterial catheter, thus leaving 71 corresponding 2D PC MR and ¹³³Xenon washout flow measurements for further analysis.

In this group of 71 kidneys, conventional angiography showed four arteries with mild renovascular disease (20% - 50% stenosis) and significant renal artery stenosis ($\geq 50\%$) in 13 arteries (overall prevalence 18%). Significant bilateral disease was seen in three patients.

2D PC MR versus ¹³³Xenon washout flow measurements

Assessment of MRBF with the 2D PC MR technique correlated significantly with the ¹³³Xenon washout flow measurements (Figure 1), with a Pearson correlation coefficient of 0.69 (two-tailed; $p < 0.01$).

Figure 1: Scatter plot of the corresponding renal artery flow measurements obtained by 2D PC MR technique and ^{133}Xe washout technique.

Note: $y = 2.2x - 420$; $r = 0.69$; $p < 0.01$

Excluding two outlying results with relatively high renal artery blood flow measurements obtained with both techniques would have resulted in a correlation coefficient of 0.51. The MRBF to the right kidney was 322 ml/sec. and to the left kidney 347 ml/sec. (overall mean flow per kidney 334 ml/sec) using the 2D PC MR technique for flow quantification. Using ^{133}Xe washout for flow quantification these respective flow data were 323 ml/sec., 318 ml/sec. and 321 ml/sec.

Flow measurements in relation to the presence of renal artery stenosis

The 2D PC MR renal artery blood flow measurements correlated poorly with the presence and/or severity of renovascular disease (% of stenosis) on conventional renal angiography ($r=0.1$, $p=0.36$) (Figure 2). Furthermore, in patients with unilateral renovascular disease on angiography no significant difference in 2D PC MR blood flow measurements between both kidneys could be detected.

Adjusting the 2D PC MR flow measurements to the renal volume by calculating the renal flow index: Flow (ml/min) / kidney volume (cm^3) and relating these to the presence and/or severity of renovascular pathology on conventional angiography failed to show a statistically significant relation. Similar observations in relation to the presence of renovascular disease were noted using the ^{133}Xe washout technique for renal artery flow quantification, further acknowledging the good correlation between the two independent techniques.

Active plasma renin concentration (APRC) in the aorta averaged 24 mU/l. In both the right and left renal veins, mean renin concentrations were 27 mU/l. No statistically significant correlation between the renal artery flow measurements using 2D PC MR or ^{133}Xe washout and the active plasma renin ratio ($\text{APRC}_{\text{vein}} - \text{APRC}_{\text{aorta}} / \text{APRC}_{\text{aorta}}$) could be identified ($r=0.4$, $p=0.1$; and $r=0.3$, $p=0.26$, respectively).

Figure 2: Scatter plot of the renal artery flow measurements obtained by 2D PC MR ($\blacktriangle$) technique and ^{133}Xe washout technique (O) versus degree of stenosis.

Discussion

The present data show that the use of 2D phase-contrast MR (2D PC MR) blood flow measurements enables hemodynamic evaluation of the renal arteries in a cohort of hypertensive patients with clinical suspicion of renovascular disease. The absolute flow measurements in the renal arteries are comparable with results of other published series (14,20). As demonstrated in Figure 1, the 2D PC MR renal artery flow measurements correlated significantly with the corresponding renal artery flow data as obtained independently by the ^{133}Xe washout technique, with a Pearson correlation coefficient of 0.69 (two-tailed; $p < 0.01$). This is a promising level of correlation, especially considering that these flow measurements are not completely identical; that is 2D PC MR relates directly to the renal artery flow, whereas ^{133}Xe washout represents the flow through the renal microcirculation.

The calculated correlation is influenced to some extent by the two outliers shown in Figure 1, with relatively high renal artery blood flow measurements obtained with both techniques. Analysis without these two values would have resulted in a correlation coefficient of 0.51. The dispersion in the scatter plot in Figure 1 rises with the increase in measured MRBF, indicating a stronger correlation between the two methods at flow levels that are particularly relevant for the distinction between hemodynamically significant and non-significant renovascular disease.

Despite this correlation, we failed to identify a statistically convincing relationship between the presence and/or severity of renovascular pathology on conventional, intra-arterial renal angiography, and either 2D PC MR or ^{133}Xe washout data technique for flow quantification. Moreover, in patients with unilateral renovascular disease we could not find a significant difference in blood flow between the two kidneys with either technique.

Likewise, no statistically significant correlation could be identified between active plasma renin ratio as a measure of functional hemodynamic abnormalities and the renal flow data with the use of either 2D PC MR or the ¹³³Xenon washout technique.

Given the correlation between the two independent flow quantification techniques, the lack of discriminating power of 2D PC MR flow quantification for assessing the presence of renovascular disease cannot, a priori, be attributed to inaccuracies of the applied MR technique.

Our observations contrast with those from several publications in international literature on this topic (13,21). This seems, at least partially, related to methodological differences. For instance, as opposed to Binkert et al. (21) we did not inject paramagnetic contrast prior to the phase-contrast flow acquisition, which might have allowed for a better delineation of the renal arteries and thereby a more accurate detection of the transverse vessel area (22). Moreover, we did not include a qualitative analysis of the flow velocity curve, since a reduction of MRBF is considered to be the most important parameter for differentiating between significant and non-significant renal artery stenosis (13). Finally, the differences in prevalence of renovascular disease between the respective studies make dissimilarities in inclusion criteria and patient selection probable, which will affect the result of these examinations and make mutual comparisons cumbersome.

Apart from the procedural differences, more fundamental explanations of physiological nature must be considered. Data in literature indicate that the degree of stenosis does not correlate well with flow measurements (23). Therefore, relating a single deviating renal artery flow measurement to the presence and/or severity of renal artery stenosis may prove to be unjustified. Serial, selective renal artery flow measurements under controlled circumstances may be necessary in order to detect changes of mean renal artery flow volume over time. Furthermore, a chronic and slowly progressive disorder like renovascular disease triggers various compensatory mechanisms in one or both kidneys to maintain a normal renal artery blood flow, possibly even up to a very late stage of the disease. Thus, adaptation of endothelial function may take place at a much earlier stage of renovascular disease than what is now considered as significant stenosis (19). Moreover, the negligible difference in flow measurements between normal and abnormal kidneys can also be explained by either adaptation of the abnormal kidney or by underlying disease, for example, nephrosclerosis, in the "normal" kidney.

Even with serial renal artery flow measurements the adaptation of a kidney to a stenotic lesion might not be fully appreciated. Serial quantitative studies of renoparenchymal perfusion with pharmacological challenges such as captopril may be necessary to obtain the essential functional information that allows to define the therapeutic options for a particular patient.

A major shortcoming of this study relates to the lack of a sufficient number of patients with significant renovascular disease on conventional angiography. This limits statistical assessment of the measurements in relation to the degree of stenosis and makes additional research imperative. A second limitation is relatively high number of excluded original examinations, particularly reflecting the delicacy of the 2D PC MR flow quantification technique in patients. Furthermore, we did not repeat the 2D PC MR flow renal artery flow measurements in order to assess the reproducibility of these flow measurements. However, in a previously published study we have shown that quantitative measurement of renal artery blood flow with 2D PC MR is highly reproducible (12). Still, the spread of MR

results in the present study calls for further improvements before wide spread clinical application of this technique can be advocated.

In conclusion, the good correlation between two independent flow quantification techniques, that is 2D PC MR and $^{133}\text{Xenon}$ washout, indicates that mean renal artery blood flow assessment using a 2D PC MR technique is feasible. However, the poor correlation of both techniques with either the presence of renovascular disease on conventional angiography or the active plasma renin ratio demonstrates a lack of discriminating power of our study protocol for the functional evaluation of the renal arteries.

Perspective

Despite the good correlation of 2D PC MR flow with another independent, method ($^{133}\text{Xenon}$ washout) to measure renal blood flow, many more studies are necessary to establish the place of MR flow quantification for the detection of the presence and degree of renal artery stenosis. Also, more work is needed to evaluate whether MR flow data obtained either under basal conditions or after, for instance, captopril challenge, are able to detect whether a stenosis leads to abnormal physiology and ultimately true renovascular hypertension.

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Chapter

7

General discussion

General discussion

Hypertension is probably one of the more important health problems in the developed countries. The prevalence of hypertension depends on both the (racial) composition of the population and the criteria used to define the condition. In a population of Dutch adults, approximately 14% of both males and females have a diastolic blood pressure greater than 95 mm Hg (1). Even in its mild forms, hypertension is a progressive disease with severe atherosclerotic complications and end organ damage, eg, cardiomegaly, congestive heart failure, retinopathy, a cerebrovascular accident, and/or renal insufficiency, if left untreated. Although the understanding of the pathophysiology of an elevated arterial pressure has increased, in majority of cases its etiology is still unknown.

Renal artery stenosis (RAS) is the most frequent cause of secondary hypertension, with an estimated prevalence of 3%-5% in the general population of people with hypertension (2-4). The clinical presentation of RAS varies significantly between patients, ranging from incidental findings of renal artery stenosis on angiography in normotensive persons to severe hypertension and progressive loss of renal function. Therefore, the diagnosis of renovascular hypertension (RVH), which suggests a causal relationship between RAS and hypertension, cannot be made in most patients.

Possibly as a consequence of these contingencies, it is still unknown if percutaneous renal artery angioplasty or stent placement is superior to medical therapy or surgical revascularisation in reducing cardiovascular morbidity and mortality or in preserving renal size and function (5). Nevertheless, identification of RAS, preferably in combination with assessment of its hemodynamic effect on the renal perfusion, in patients with hypertension and/or renal failure remains important, because correction of arterial stenoses may improve blood pressure control and/or stabilize renal function in a certain number of these patients (6-10).

Various imaging techniques can be applied for the detection of RAS. These can be divided in functional tests: (captopril) renography and duplex ultrasound; and morphological methods including MR angiography (MRA), CT angiography (CTA) and intra-arterial digital subtraction angiography (ia-DSA). The latter test is still regarded the most accurate method to assess the presence and severity of renal artery stenosis. However, its invasive nature and high costs make this procedure unsuitable as a screening modality in a population of patients with a low prevalence of renal artery stenosis.

Captopril renography measures the physiological effects of angiotensin II on renal autoregulation of glomerular filtration rate (GFR). Supposedly a fall in GFR after administration of captopril indicates hemodynamically significant RAS. This non-invasive test has been reported to be highly sensitive (91%-94%) and highly specific (84%-95%) in detecting RAS. However, recent studies have demonstrated less impressive results with considerable variation in inter- and intra-observer interpretations especially in patients with small kidneys and/or bilateral disease (11-16).

Likewise, duplex ultrasound has been advocated as the optimal non-invasive screening test, because it has the potential to combine direct visualization of the renal arteries with acquisition of flow velocity profiles, thus providing both anatomical and functional information. Yet, the relatively large number of incomplete examinations in combination with the wide range of results published in international literature does not seem to support the general application of duplex ultrasound as a screening procedure for

detection and assessment of renovascular disease. The results of our study on duplex ultrasound of the renal arteries (chapter 2) show an overall sensitivity of only 50% (specificity: 91%; PPV: 88%; NPV: 59%) for detecting hemodynamically significant renovascular disease when commonly applied parameters were used at internationally accepted thresholds: i.e. PSV > 180 cm/sec and RAR > 3.5. Obtaining these parameters requires evaluation of the entire length of the renal artery, which, even in experienced hands is cumbersome. Therefore, waveform analysis of the intrarenal vasculature with several criteria, i.e. mean resistive index, tardus-parvus phenomena and acceleration time, has been proposed as an alternative to detect upstream stenosis (17). This was further accentuated in a recent study where duplex ultrasound was suggested to be the most valuable non-invasive test, not only in screening for renal artery disease but also to estimate its functional significance by means of determination of the resistive index (18). However, the intrarenal parameters are influenced by several complex factors including pulse rate and diastolic blood pressure, which seems reflected by the wide range of reported sensitivities and specificities for detection of significant renovascular disease: 57%-100% and 69%-99% respectively, despite the theoretical advantages of this approach.

In the last decade, several magnetic resonance (MR) angiographic techniques have been proposed for examination of patients suspected to have renovascular disease. The two more basic techniques used in MRA: time-of-flight (TOF) and phase-contrast (PC), display the anatomic details of vasculature without using intravenous contrast material. TOF-MRA is based on contrast formation by the inflow of unsaturated spins (blood) into surrounding saturated spins (perivascular tissue). This technique has a reduced sensitivity to in-plane flow because of rapid saturation of inflowing spins, that may hamper depiction of the renal arteries. Furthermore, TOF-MRA has the tendency to overestimate (the presence of) renovascular disease, which is also reflected by the wide range of reported results.

In the phase-contrast technique (PC-MRA) the phase shift of the signals from the protons is recorded. Because moving spins have different phase shifts, the protons in the flowing blood may be discriminated from the stationary ones (perivascular tissue). Phase-contrast MRA has the tendency to overestimate (the presence of) renovascular disease as a result of artefacts caused by the pulsatility of blood flow and by its increased sensitivity to signal loss from intravoxel spin-phase dispersion, due to disturbed or turbulent flow. Since cardiac gating may suppress these artefacts, we designed a prospective study in a limited number of patients to evaluate the usefulness of three-dimensional (3D) PC-MRA performed with cardiac synchronisation in the assessment of renal arteries (chapter 3). In accordance with data reported in the international literature, the results of this study indicate that 3D PC-MRA is a highly sensitive and specific technique for the detection of renovascular disease.

Yet, these promising results could not be reproduced in the subsequent prospective, multicenter study (RADISH-study) in which the overall sensitivity of PC-MRA for detection of significant renovascular disease ranged from 51% to 56% with specificities ranging from 86% to 91% (19, Appendix). Interestingly, in the same study comparable results for gadolinium enhanced MRA (CE-MRA) and CTA were noted, even though recent publications indicate that these techniques may be preferred for non-invasive assessment of the renal arteries (20-22). Methodological differences between our study and the RADISH-study, including dissimilarities in patient selection, study design and image evaluation, may, at least partially, account for this contrast in outcome. Furthermore,

similar to most other studies that reported high sensitivities, the 3D PC-MRA study (chapter 3) did not contain patients with fibromuscular dysplasia as opposed to the RADISH-study which included a relatively high proportion of patients with fibromuscular dysplasia (38% of all patients with significant renovascular disease).

The presence of fibromuscular dysplasia in the renal arteries seems especially relevant and is possibly a qualifying parameter in the presentation of test results because, as shown in chapter 4, neither PC-MRA, neither CE-MRA nor CTA can reliably diagnose this disorder. This is particularly relevant because we also found that there are no clinical features that can identify patients with fibromuscular dysplasia, except perhaps that the condition occurs more commonly in females than in males. A meta-analysis by Martin et al (23) showed a mean cure rate of renovascular hypertension (i.e. restoration of blood pressure to less than 140/90 mm Hg without antihypertensive medication) of 44 % for renal revascularisation of stenoses related to fibromuscular dysplasia, as opposed to almost no cure when the renal artery stenosis was caused by atherosclerosis. Therefore, the cure rate of for (medial) fibromuscular dysplasia is sufficiently high to recommend revascularisation and underlines that early identification of these patients is important (10). Technologic developments, particularly focusing on more rapid data acquisition and improvement of spatial resolution, seem essential before either MRA or CTA can be fully implemented in daily practice. Eventually, CTA may prove to be the preferred non-invasive imaging modality of the renal arteries because of its significantly shorter acquisition time compared to MRA, thanks to the recently introduced multi-detector, helical CT technique. Pending these improvements, ia-DSA remains the gold standard for the detection of renovascular pathology.

Nevertheless, the challenge of diagnosing renovascular disease does not only rest in purely morphological identification of renal artery pathology, but also, and this is probably more important, in the determination of its effect on renal blood flow and kidney perfusion. In two studies, we have shown that non-invasive flow quantification in the renal arteries by means of 2D phase-contrast MR (2D PC MR) is technically feasible. In a relatively small group of healthy volunteers reproducible measurements could be obtained (chapter 5), whereas in hypertensive patients the 2D PC MR blood flow measurements corresponded reasonably well with renal artery flow data as obtained independently by the ^{133}Xe washout technique (chapter 6).

However, a statistically convincing relationship between these 2D PC MR flow measurements and both the presence and/or severity of renovascular pathology on ia-DSA and the degree of renin stimulation could not be identified. Similar to data published by Wierema et al, no significant difference in blood flow between the two kidneys could be demonstrated in patients with unilateral renovascular disease (24).

This could mean that adaptation of renal endothelial function may take place at a much earlier stage of renovascular disease than what is now considered as significant stenosis. Consequently a normal renal artery blood flow could be maintained, possibly even up to a very late stage of the disease. Therefore, serial, selective renal artery flow measurements under controlled circumstances seem necessary to detect changes of mean renal artery flow volume over time. Additional quantitative studies of renoparenchymal perfusion with pharmacological challenges such as captopril may be necessary to obtain the essential functional information that allows to define the therapeutic options for a particular patient. Given the present status of MR flow quantification in the renal arteries and the expected

improvements of the technique in the near future, we believe that MR flow quantification will become indispensable for the non-invasive functional assessment of renovascular pathology.

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Chapter

8

Summary
Samenvatting
Dankwoord
Curriculum vitae
Appendix

Summary

Hypertension is probably one of the more important health problems in the developed countries. Depending on the racial composition of the study and the criteria used to define this condition, the prevalence of hypertension may reach 15% in the adult population. Even in its mild forms, hypertension is a progressive disease with severe atherosclerotic complications and end organ damage if left untreated. In the majority of cases, the etiology of hypertension is unknown.

Renal artery stenosis (RAS) is the most frequent cause of secondary hypertension, with an estimated prevalence of 3%-5% in the general population of hypertensive patients. Identification of RAS in patients with hypertension and/or renal failure, preferably in combination with assessment of its hemodynamic effect on renal perfusion, poses an important clinical challenge, since surgical or percutaneous treatment of these lesions may improve blood pressure control and/or stabilise renal function in a certain number of these patients.

To date, conventional x-ray angiography still is considered as the most accurate method to assess the presence and severity of renal artery stenosis. However, its invasive nature and high costs, in addition to the requirement to use nephrotoxic contrast medium and radiation, make this procedure less appropriate as a screening modality. The ideal screening procedure to select patients for renal angiography should be simple, non- (or minimally) invasive and highly accurate both for the detection of renovascular disease and for assessment of its clinical significance. This thesis focuses on the diagnostic performance of several non-invasive radiological techniques for detection and evaluation of renovascular disease.

Chapter 2 discusses a study that evaluated the accuracy of duplex ultrasound for the diagnosis of renal artery stenosis in a cohort of seventy-eight hypertensive patients with clinical suspicion of renovascular disease. Based on the combination of the peak systolic velocity (PSV_{max}) and peak renal to aortic velocity ratio (RAR) at thresholds commonly applied in current literature: i.e. $PSV_{max} > 180$ cm/sec and $RAR > 3.5$, the results of the duplex ultrasound examination showed an overall sensitivity of 50%, a specificity of 91% and positive (PPV) and negative (NPV) predictive values of 59% and 88% respectively. These results, although disappointing, fall well within the wide range of internationally reported data in terms of specificity, sensitivity as well as in number of inadequate examinations and do not seem to support general application of duplex ultrasound as a screening procedure for detection and assessment of renovascular disease.

In the last decade several magnetic resonance (MR) angiographic techniques have been proposed for examination of the renal vasculature. Phase-contrast magnetic resonance angiography (PC MRA) has shown variable results with respect to detection of renal artery disease. Artefacts caused by the pulsatility of blood flow, that hinder image interpretation could, at least partially, be responsible for this variation in test accuracy. In chapter 3, the value of cardiac synchronisation on image quality and validity of three-dimensional PC-MRA (3D PC MRA) of the renal arteries is explored in a cohort of 38 consecutive patients. The main results of this study indicate that 3D PC MRA is a highly sensitive technique for the detection of renovascular disease, whereas implementation of cardiac gating on a routine basis is not supported by its limited improvement of these results.

Following, in chapter 4 the performance of MR and CT angiography in the detection of the second most common form of renal artery stenosis: fibromuscular dysplasia was analyzed. This noninflammatory dysplastic process is characterized by abnormalities in the fibromuscular lining of the renal artery, seen as multiple aneurysms separated by focal narrowing: string-of-beads-sign on angiography. In 40 kidneys (29 patients) with angiographically proven fibromuscular dysplasia in the renal arteries, neither PC-MRA, neither contrast enhanced MRA (CE-MRA), nor CTA showed reliable results in diagnosing this renal artery disorder. Even in this artificially composed population with a very high prevalence of fibromuscular dysplasia the observers frequently failed to identify fibromuscular dysplasia despite prior knowledge of the presence of this disease in one of the renal arteries. The results of CTA were better than CE-MRA, which in turn performed better than PC-MRA, but with none of the three techniques a detection rate of $\geq 82\%$ for the presence of fibromuscular dysplasia could be reached. Further analysis showed that both extend of fibromuscular dysplasia as well as the distance of these lesions from the aortic ostium influenced the results in all three techniques. The limited spatial resolution in relation to the relatively small caliber of the segmental arteries, together with motion artifacts influencing the image quality of the more distal part of the renal arteries were identified as possible causes for the poor performance of the three non-invasive imaging modalities.

The challenge of diagnosing renovascular disease does not only rest in purely morphological identification of renal artery pathology, but also, and this is probably more important, in the determination of its effect on renal blood flow and kidney perfusion. In chapter 5, a technique that goes beyond purely morphologic imaging of arteries is evaluated for non-invasive quantitative assessment of renal artery flow dynamics: 2D phase-contrast MR flow quantification. The aim of the presented study was to determine the feasibility and reproducibility of two respiration controlled PC MR techniques: a breath-hold sequence, and a respiratory-triggered sequence, to measure blood flow in the individual renal arteries. In twelve healthy subjects reproducible quantitative measurements of renal artery blood flow with both respiratory controlled, cardiac-gated, phase-contrast MR techniques was possible. However, the limited sample size of this study together with the composition of the subject-group (i.e. healthy, relatively young volunteers) made extrapolation of the results to the daily practice premature and called for larger, comparative studies in patients.

Therefore, the study described in the chapter 6 was a logical continuation of this line of investigation. In this study the ^{133}Xe washout technique was used as an independent test for comparative evaluation of the accuracy of the 2D PC MR renal artery flow measurements obtained in patients suspected of having renovascular hypertension. In addition, the 2D PC MR flow data were related to functional renal information as acquired by selective arterial and venous renin sampling in order to assess the presence of renal artery stenosis. The results showed a good correlation of 2D PC MR flow quantification with the ^{133}Xe washout technique to measure renal artery blood flow. However, a poor correlation of both techniques with both the presence of renovascular disease on conventional angiography, and the degree of renin stimulation, was also noted. This lack of discriminating power of 2D PC MR flow quantification for functional assessment of the renal arteries calls for further improvement before it can be applied on a larger scale.

In conclusion, the detection of renovascular disease with either MR or CT angiography is far from perfect. In view of the recently introduced multi-detector helical technique, CTA may eventually prove to be the preferred non-invasive imaging modality of the renal arteries because of its significantly shorter acquisition time compared to MRA. The quantitative studies on the other hand, indicate that 2D PC MR flow quantification may well become a key instrument in the non-invasive functional assessment of renovascular pathology

Samenvatting

Hypertensie of hoge bloeddruk is een relatief veel voorkomend gezondheidsprobleem in de Westerse wereld. Afhankelijk van de raciale samenstelling van de bestudeerde patiënten groep en de gehanteerde definities voor deze aandoening kan de prevalentie van hypertensie in een groep van volwassen personen oplopen tot 15%. Hypertensie is een progressieve ziekte en heeft, als de ziekte niet wordt behandeld, zelfs in milde vorm ernstige complicaties tot gevolg: hartaanval, beroerte (een herseninfarct of -bloeding) of hartfalen. In de meerderheid van de gevallen blijft oorzaak van hypertensie onbekend waardoor de mogelijkheid van gerichte preventie en/of behandeling wordt beperkt.

Nierarterie stenosen (vernauwingen van de nierslagader) zijn, hoewel schaars, de meest voorkomende vorm van secundaire hypertensie met een geschatte prevalentie van 3-5% in een algemene populatie van hypertensieve personen. Het aantonen van nierarterie stenosen bij patiënten met hypertensie en/of progressief nierfunctie verlies is een belangrijke klinische uitdaging, omdat percutane dan wel chirurgische correctie van de stenosen in een bepaald aantal van hen kan leiden tot een betere bloeddruk controle en/of behoud van nierfunctie. Tot op heden wordt conventionele röntgen angiografie nog steeds beschouwd als de meest betrouwbare methode om de aanwezigheid en de ernst van nierarterie stenosen te bepalen. De hoge kosten, het invasieve karakter en de noodzakelijke toepassing van straling en nefrotoxisch contrast, maken deze procedure evenwel minder geschikt als screeningstest.

Om patiënten te kunnen selecteren voor een dergelijk angiografisch onderzoek zou men in het ideale geval de beschikking hebben over een eenvoudige en niet- (of minimaal) invasieve test met een hoge betrouwbaarheid voor het aantonen van nierarterie stenosen. In dit proefschrift wordt het vermogen van enkele niet-invasieve, radiologische technieken om nierarterie afwijkingen op te sporen en functioneel te evalueren nader onderzocht.

In hoofdstuk 2 wordt een studie gepresenteerd waarin de nauwkeurigheid van duplex echografie voor het opsporen van nierarterie stenosen wordt geëvalueerd in een cohort van 78 hypertensieve patiënten met klinische verdenking op nierarterie afwijkingen. Met name is een combinatie van een tweetal erkende Doppler parameters onderzocht: piek systolische snelheid (PSV_{max}) en de ratio tussen de piek snelheden in nierarterie en aorta (RAR), hierbij gebruikmakend van internationaal geaccepteerde drempelwaarden voor hemodynamisch significante stenosen ($PSV_{max} > 180$ cm/sec; $RAR < 3,5$).

In de onderzochte groep patiënten is een sensitiviteit bereikt van slechts 50% voor het aantonen van ernstige nierarterie stenosen met een specificiteit van 91% en een positief (PPV), en negatief (NPV) voorspellende waarde van 59%, respectievelijk 88%. Hoewel teleurstellend vallen deze resultaten, wat betreft sensitiviteit en specificiteit en aantal onvolledige onderzoeken binnen het (brede) bereik van de internationaal gepubliceerde resultaten. Uitgaande van deze gegevens kan worden geconstateerd dat algemene toepassing van duplex echografie als screeningstest voor detectie en evaluatie van nierarterie afwijkingen onvoldoende onderbouwd is.

Gedurende de afgelopen jaren zijn als alternatief voor duplex echografie verschillende magnetische resonantie (MR) technieken ontwikkeld om de nierarteriën af te beelden. Met één van deze MR technieken: phase-contrast magnetische resonantie angiografie (PC-MRA) zijn met betrekking tot het vaststellen van nierarterie stenosen zeer wisselende resultaten geboekt. Hinderlijke artefacten veroorzaakt door de pulsatiliteit van de bloedstroom

zouden, ten minste deels verantwoordelijk kunnen zijn voor deze variatie in testresultaten. Als mogelijke oplossing van dit probleem is de waarde van cardiale synchronisatie op de beeldkwaliteit van drie dimensionale PC-MRA (3D PC-MRA) nader bekeken in een groep van 38 patiënten. De resultaten van deze studie, zoals beschreven in hoofdstuk 3, laten zien dat 3D PC-MRA een zeer gevoelige test is voor het aantonen van nierarterie stenosen, waarbij de toegevoegde waarde van cardiale synchronisatie echter zodanig beperkt blijkt dat routinematige toepassing er van niet zinvol is.

Zeventig procent van de nierarterie stenosen zijn van atherosclerotische origine, terwijl de volgende meest voorkomende oorzaak fibromusculaire dysplasie is. Deze noninflammatoire dysplastische aandoening wordt gekarakteriseerd door afwijkingen in de fibromusculaire wandlaag van de nierarteriën en manifesteert zich angiografisch als multiple focale verwijdingen afgewisseld met korte vernauwingen: het "kralensnoer" teken.

In hoofdstuk 4 wordt de nauwkeurigheid bestudeerd van zowel MR als CT angiografie om dergelijke fibromusculaire dysplastische afwijkingen in de nierarteriën aan te tonen. In 40 nieren (29 patiënten) met angiografisch aangetoonde fibromusculaire dysplasie waren zowel PC-MRA, contrast versterkte MRA (CE-MRA), als CTA niet in staat om de afwijkingen betrouwbaar af te beelden. Zelfs in deze kunstmatig samengestelde groep van patiënten met een zeer hoge prevalentie van fibromusculaire dysplasie blijken de waarnemers veelvuldig niet in staat de aandoening te identificeren, ondanks voorkennis over de aanwezigheid er van.

De resultaten van CTA zijn beter dan CE-MRA en PC-MRA, maar met geen van de drie technieken kan een detectiegraad van meer dan 82% worden bereikt. Additionele analyse wijst uit dat de zowel ernst van fibromusculaire dysplasie als de afstand van de afwijkingen ten opzichte van de nierarterie oorsprong van invloed zijn op de testresultaten van alle drie de technieken. Als mogelijke verklaring voor de slechte resultaten van de drie technieken wordt de beperkte spatiële resolutie in relatie tot het kleine kaliber van de bloedvaten geïdentificeerd. Voorts blijken bewegingsartefacten, met name optredend in het meer perifere deel van de nierarteriën een belangrijke verstoring te geven van beeldkwaliteit en beeldinterpretatie.

De uitdaging om afwijkingen aan de nierarteriën te diagnostiseren is niet beperkt tot de puur morfologische weergave van deze bloedvaten, maar omvat ook het vaststellen van de functionele invloed van deze afwijkingen op de bloedstroom naar, en doorstroming van, de nieren. In hoofdstuk 5 wordt een techniek geëvalueerd die in staat is om zowel de nierarteriën af te beelden als de bloedstroom naar de nieren kwantitatief te bepalen: 2D phase-contrast MR flow quantification. Het belangrijkste doel van deze studie was de toepasbaarheid en reproduceerbaarheid vast te stellen van twee verschillende, ademhaling gecontroleerde 2D PC MR technieken (breath-hold; respiration triggered) voor bepalen van de bloedstroom in de afzonderlijke nierarteriën. In twaalf gezonde vrijwilligers blijken met beide ademhaling gecontroleerde, cardiac-gated 2D PC MR technieken reproduceerbare kwantitatieve analyses van de nierarterie doorstroming mogelijk. Echter, de geringe omvang van deze studie alsmede de samenstelling van de bestudeerde populatie (gezonde, relatief jonge vrijwilligers) beperkte de mogelijkheid om de behaalde resultaten naar de dagelijkse praktijk te extrapoleren en vroeg om aanvullende, vergelijkend studies in patiënten.

De in hoofdstuk 6 beschreven studie vormt derhalve een logische voortzetting van bovenbeschreven onderzoekslijn. In deze studie wordt wederom de bloedstroom door de

individuele nierarteriën berekend, echter ditmaal in hypertensieve patiënten met klinische verdenking op nierarterie afwijkingen en met de $^{133}\text{Xenon}$ washout techniek als onafhankelijke vergelijkende test. Om ook de invloed van de nierarterie afwijkingen te kunnen evalueren worden de 2D PC MR bloedstroom berekeningen vergeleken met functionele informatie van de nieren, zoals deze wordt verkregen door selectieve arteriële en veneuze renine sampling. De aldus verkregen bloedstroom bepalingen laten een goede correlatie zien tussen de 2D PC MR methode en de $^{133}\text{Xenon}$ washout techniek.

Helaas wordt ook een slechte correlatie gesignaleerd van beide technieken met zowel de aanwezigheid van nierarterie afwijkingen op de conventionele angiografie als met de renine ratio. Het discriminerend vermogen van het toegepaste studie protocol om nierarteriën en/of nierarterie afwijkingen functioneel te evalueren blijkt derhalve van slechts beperkte waarde en maakt verder onderzoek noodzakelijk.

Geconcludeerd kan worden dat het vermogen van MR en CT angiografie om nierarterie afwijkingen op te sporen verre van volmaakt is. Dankzy de recent geïntroduceerde multi-detector techniek, is het mogelijk dat het CT angiografisch onderzoek op termijn de modaliteit van eerste keuze wordt voor het in beeld brengen van nierarteriën. Anderzijds geven de kwantitatieve analyses in dit proefschrift aan dat 2D PC MR flow quantification een belangrijk instrument kan worden bij de non-invasieve functionele evaluatie van nierarterie pathologie

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Curriculum vitae

De auteur van dit proefschrift werd geboren op 9 maart 1959 in 's Gravenhage geboren. In 1978 behaalde hij zijn VWO diploma aan het Haags Montessori Lyceum in 's Gravenhage. In datzelfde jaar begon hij met de studie geneeskunde aan de Rijksuniversiteit te Leiden, alwaar in 1986 het artsexamen werd afgelegd. Na zijn afstuderen werkte hij gedurende ruim 2 jaar als arts-assistent niet in opleiding (AGNIO) op de afdeling heelkunde van het Rode Kruis Ziekenhuis (hoofd dr. J.J. Hamming) 's Gravenhage, gevolgd door een veel kortere periode wederom als AGNIO ditmaal op de afdeling heelkunde van het Westeinde Ziekenhuis (hoofd dr. R.K.J. Koumans) in dezelfde stad. In 1989 werd met de opleiding tot radioloog gestart in het academisch ziekenhuis Maastricht (opleiders: prof. dr. B.K. Janevski en prof. dr. J.M.A. van Engelshoven). Na zijn registratie tot radioloog op 1 april 1995 werd hij aangesteld als stafid aan de afdeling radiologie van het academisch ziekenhuis Maastricht.

In 1990 is hij gehuwd met Catharien Romijn. Samen hebben ze drie zonen: Gijs (1992), Derk (1994) en Bas (1995).

Appendix

The RADISH-study

As a sequel to the initial pilot study on three-dimensional phase-contrast MR Angiography (3D PC-MRA) of the renal arteries (chapter 3) a prospective multicenter study was designed to evaluate the validity of MRA and computed tomographic angiography (CTA) in a large group of patients: the RADISH-study. This study was designed as a comparative study of PC-MRA, gadolinium enhanced MRA (CE-MRA), CTA and the gold standard ia-DSA to detect the presence of renal artery stenosis.

Over a three-years period, subjects were prospectively recruited from the outpatients' clinics of the Internal Medicine departments of three large teaching hospitals and three university hospitals in the Netherlands. All hypertensive patients between 18 and 75 years of age with diastolic blood pressure of >95 mm Hg were eligible for participation. In order to raise the pre-test probability of the presence of renal-artery stenosis, patients had to exhibit at least one of the commonly accepted clinical clues for the presence of renal-artery stenosis. All included patients were scheduled to have their PC-MRA, CE-MRA, CTA, and ia-DSA within three months after inclusion. Eight observers either judged the PC-MRA, CE-MRA and CTA exams and were unaware of all other results. Four vascular radiologists judged the ia-DSA exams. Luminal narrowing of $\geq 50\%$ as well as all cases of fibromuscular dysplasia were defined as clinically relevant stenoses.

Due to the variety of manufacturers and models of imaging equipment, each hospital was allowed to use the scan protocols which were considered optimal for its setting. Information about manufacturers, scan protocols, and used contrast agents is shown in table 1, chapter 4. The severity of the stenoses as seen on CE-MRA and CTA was categorized on a five point scale (0% to 19% [scale 1]; 20% to 49% [scale 2]; 50% to 74% or fibromuscular dysplasia [scale 3]; 75% to 99% [scale 4]; and total occlusion 100% stenosis; [scale 5]). Four grades were used to categorize the severity of renovascular disease on PC-MRA: grade 1 was mild disease (stenosis of $<50\%$), defined as mere luminal narrowing; grade 2, moderate disease (stenosis of 50-74%), defined as reduction in diameter with focal flow void (< 5 mm); grade 3, severe disease (stenosis of 75-99%), defined as a longer region of signal intensity loss (> 5 mm) with distal recurrence of flow signal intensity; and grade 4, occlusion.

The interobserver agreement for the evaluation of PC-MRA, CE-MRA and MRA images was calculated using linear kappa statistics. In case an observer found a PC-MRA, CE-MRA or MRA exam to be non-evaluative, this exam was considered as a positive test result in the analyses.

Out of 402 included patients, 356 patients who underwent CE-MRA, CTA and ia-DSA could be evaluated, including 333 patients who underwent all four tests (PC-MRA, CE-MRA, CTA and ia-DSA). The prevalence of hemodynamically significant renal artery stenosis (RAS) in the group of 356 patients was 20%: 45 patients with atherosclerotic lesions and 27 patients with fibromuscular dysplasia. The prevalence of RAS in the 333 patients who underwent all four tests was also 20%: 41 patients with atherosclerotic lesions and 27 patients with fibromuscular dysplasia.

For the detection of renal artery stenosis, moderate interobserver agreement was found with a kappa value of 0.57 for PC-MRA; the kappa values ranged from 0.40 to 0.51 for

CE-MRA and from 0.59 to 0.64 for CTA. Overall, sensitivity ranged from 51% to 56% for PC-MRA, from 57% to 67% for CE-MRA and from 61% to 69% for CTA. Specificity ranged from 86% to 91% for PC-MRA, from 77% to 90% for CE-MRA and from 89% to 97% for CTA. These findings are contrary to the results of all other published studies on the validity of PC-MRA, CE-MRA and CTA, which all give much higher estimates for both sensitivity and specificity (up to 100%). Phase-contrast MRA showed comparable results to CE-MRA and CTA for the detection of clinically relevant renovascular disease, which again seems in contrast to the internationally accepted, but not well-founded idea that CE-MRA is the preferred MR angiographic technique for assessment of the renal arteries. Potential causes of error for the observed discrepancy include differences in prevalence of both RAS and/or fibromuscular dysplasia, differences in inclusion of supernumerary renal arteries and different definitions of hemodynamically significant renal-artery stenosis. Whichever the cause, these contrasts in outcome warrant further research to establish the place of PC-MRA, CE-MRA and CTA for the assessment of renovascular disease before widespread clinical application of this technique can be advocated.

It can be expected that both MRA and CTA will improve with the advent of new technologic developments, such as more rapid acquisition by multi detector-row CTA or faster MR hardware and software. These developments may necessitate new prospective diagnostic studies, but until that time ia-DSA remains the preferred test for the detection of renal artery stenosis.

M.W. de Haan for the Renal Artery Diagnostic Imaging Study in Hypertension (RADISH) study group.
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