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Measurement of kidney perfusion by magnetic resonance imaging: comparison of MRI with arterial spin labeling to *para*-aminohippuric acid plasma clearance in male subjects with metabolic syndrome

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Abstract

Background. Magnetic resonance imaging with arterial spin labeling (MRI–ASL) is a non-invasive approach to measure organ perfusion. We aimed to examine whether MRI–ASL kidney perfusion measurements are related to measurements of renal plasma flow (RPF) by *para*-aminohippuric acid (PAH) plasma clearance and whether changes of kidney perfusion in response to treatment with telmisartan can be detected by MRI–ASL.

Methods. Twenty-four patients with metabolic syndrome and an estimated creatinine clearance according to Cockroft and Gault of ≥60 ml/min were included in the study. Kidney perfusion was assessed by MRI–ASL measurements of a single coronal kidney slice (with flow-sensitive alternating inversion recovery and true fast imaging with steady-state processing sequence) and by measurements of RPF using PAH plasma clearance before and after 2 weeks of treatment with the angiotensin receptor blocker telmisartan. All MRI–ASL examinations were performed on a 1.5 T scanner.

Results. Two weeks of therapy with telmisartan led to a significant increase of RPF (from 313 ± 47 to 348 ± 69 ml/min/m, $P = 0.007$) and MRI–ASL kidney perfusion measurements (from 253 ± 20 to 268 ± 25 ml/min/100 g, $P = 0.020$). RPF measurements were related with MRI–ASL kidney perfusion measurements ($r = 0.575$, $P < 0.001$). Changes of RPF measurements and changes of MRI–ASL kidney perfusion measurements in response to treatment with telmisartan revealed a close relationship when expressed in absolute terms ($r = 0.548$, $P = 0.015$) and in percentage changes ($r = 0.514$, $P = 0.025$).

Conclusions. Perfusion measurement of a single coronal kidney slice by MRI–ASL is able to approximate kidney perfusion and to approximate changes in kidney perfusion due to pharmacological intervention.

Keywords: kidney perfusion; magnetic resonance imaging; *para*-aminohippuric acid plasma clearance; renal plasma flow

Introduction

Impairment of kidney perfusion is a marker of organ damage in a variety of morbidities including hypertension, obesity, metabolic syndrome, diabetes and atherosclerosis. Measurement of kidney perfusion, however, is still difficult in clinical trials. Doppler sonography is a useful non-invasive adjunct to detect stenosis of renal artery or haemodynamic signs of alterations in the peripheral vessels resistances (pulsatility or resistance indices) but does not allow exact quantification of tissue perfusion rates [1–3]. Radionuclide scintigraphy [4,5] is invasive due to the use of an exogenous radioactive tracer, limiting its use in clinical trials and under special conditions (i.e. pregnancy). For research purposes, traditional clearance technique is considered to be the gold standard. However, it is also invasive, requires substantial human resources and is associated with negative aspects such as long examination duration and the rare possibility of side effects (anaphylaxis among others). For this reason, a non-invasive, reproducible and quick method to quantify kidney perfusion is desirable.

Due to its high physiologic perfusion (both kidneys receive 20% of the cardiac output but their total weight is only ~300 g), the kidney is an ideal candidate for perfusion imaging by magnetic resonance imaging with arterial spin labeling (MRI–ASL). MRI–ASL uses the water spins of blood as an endogenous tracer. Therefore, this method does not need a contrast agent and is non-invasive. In recent years, several MRI–ASL techniques, including flow-sensitive alternating inversion recovery (FAIR) technique, have been developed mainly to measure brain perfusion [6,7]. With respect to the kidneys, MRI–ASL approaches, including FAIR True-FISP technique, have recently been demonstrated to lead to clinically valuable kidney perfusion measurements with an examination time of no longer than 5 min [8,9].

In view that MRI–ASL might be a potential tool to assess kidney perfusion in clinical trials, we were interested whether measurements of kidney perfusion by MRI–ASL might be related to renal plasma flow (RPF) measurements by *para*-aminohippuric acid (PAH) constant infusion input clearance technique. Moreover, we were interested whether MRI–ASL is capable of measuring changes in kidney perfusion due to pharmacological intervention. Changes in renal haemodynamics and kidney perfusion can be achieved by inhibition of the renin–angiotensin system. Renin–angiotensin system blockade results in dilation of the afferent and in particular efferent glomerular arteriole, thereby decreasing renal vascular resistance and increasing renal perfusion. Data from a recent trial demonstrated that inhibition of the renin–angiotensin system with telmisartan increased kidney perfusion in hypertensive subjects with type 2 diabetes [10]. Therefore, it is rational to suggest that treatment with telmisartan might also lead to an increase in kidney perfusion in hypertensive subjects with the metabolic syndrome.

The aim of this study was to compare kidney perfusion measurements obtained with both methods, MRI–ASL and PAH plasma clearance, in a clinical trial setting. The objectives of this study were to analyze whether MRI–ASL perfusion measurements are related to RPF measurements assessed by PAH plasma clearance and whether changes of kidney perfusion in response to treatment with telmisartan assessed by MRI–ASL are related to changes of RPF assessed by PAH plasma clearance.

Materials and methods

Study population and study design

Study participants were recruited via advertisements in local newspapers. At a screening visit, a thorough physical examination was performed, blood samples were taken for laboratory analyses and subjects were checked for inclusion and exclusion criteria. Inclusion criteria were: male gender; age between 18 and 65 years; and subjects with at least three of the following five criteria of the metabolic syndrome: abdominal obesity defined by waist circumference ≥102 cm, blood pressure ≥130/85 mmHg, hypertriglyceridaemia ≥150 mg/dl, low HDL cholesterol <40 mg/dl and hyperglycaemia indicated by a fasting glucose ≥110 mg/dl. Exclusion criteria were: mean seated blood pressure <130/85 or ≥180/110 mmHg, atrial fibrillation or atrioventricular blockade grade II or higher, history of myocardial infarction, unstable angina pectoris, congestive heart failure New York Heart Association class III/IV, renal impairment (estimated creatinine clearance of <60 ml/min according to the formula of Cockroft and Gault), hepatic disease and any form of secondary arterial hypertension. The patients were permitted to stay on their usual antihypertensive medication as prescribed by the discretion of their family physician. However, patients on angiotensin-converting enzyme inhibitor or angiotensin receptor blocker were switched to alternative antihypertensive medication (amlodipin and/or hydrochlorothiazide and/or either metoprolol or atenolol) at least 4 weeks prior to examination of the renal haemodynamics. Before enrolment in the study, informed written consent was obtained from each participant. The study protocol was approved by the Clinical Investigations Ethics Committee of the University of Erlangen-Nürnberg and conducted according to the Good Clinical Practice guidelines.

Assessment of kidney perfusion by magnetic resonance imaging with arterial spin labeling

MRI–ASL was performed on a 1.5 T scanner (Magnetom Symphony, Siemens, Erlangen, Germany) using a flow-sensitive alternating inversion recovery (FAIR) True-FISP sequence. The FAIR and true fast imaging with steady-state processing (True-FISP) approach combines a FAIR perfusion preparation and a True-FISP data acquisition strategy. The perfusion measurement is based on two data acquisitions, one with a global inversion prepulse followed by one with a slice selective prepulse (FAIR). The prepulses lead to a labeling of blood water spins. In contrast to the global inversion prepulse, the slice selective inversion prepulse only labels the blood water spins inside the kidney but not the inflowing blood water spins. Subtraction of both images therefore reflects the local perfusion. A third image without the FAIR preparation pulse was measured to normalize the signal intensities on each patient. The technical and theoretical background of the sequence has been previously described in detail [8]. MRIs as performed in the current study are illustrated in Figure 1. All patients were examined in supine position with a body phased array coil (Siemens) in combination with the spine coil (Siemens). The FAIR True-FISP parameters were: repetition time 4.9 ms, echo time 2.5 ms, effective inversion time 1200 ms, flip angle 70°, field of view 360 mm and inplane resolution 2.3 mm × 1.2 mm. All images were measured during expiration in breath hold. Breath-hold time was 18 s. Slices were positioned in an oblique coronal orientation to match the longitudinal axis of both kidneys. Slice thickness was 8 mm.

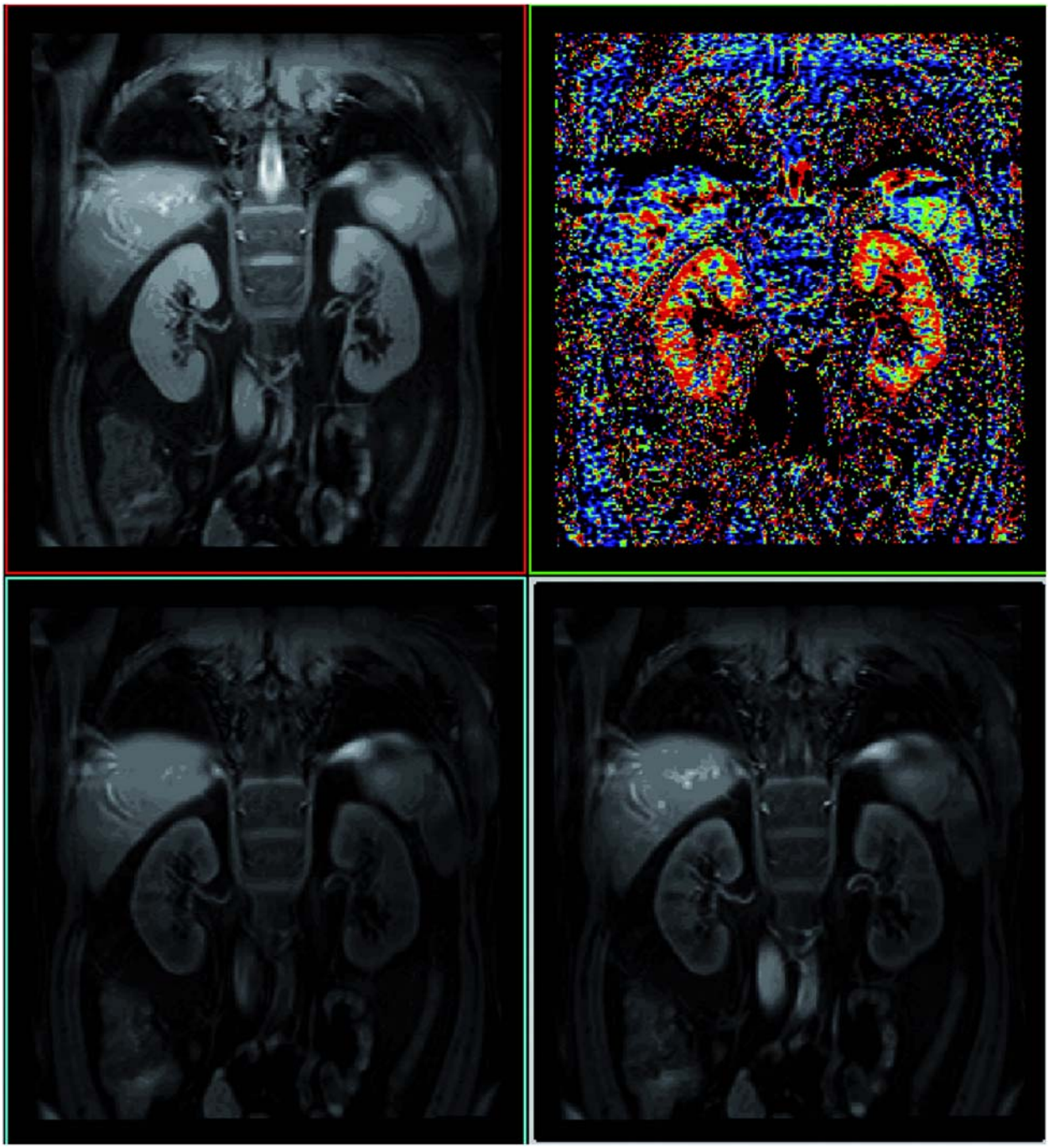

Fig. 1. Magnetic resonance imaging with arterial spin labeling (MRI–ASL): in the upper left corner image without FAIR preparation, upper right corner calculated perfusion map with color encoding, lower left corner image with non-selective prepulse (no perfusion) and lower right corner image with slice selective prepulse (perfusion image).

Care was given to similarly position the slices in all subjects, and crucial attention was made to match the same slice position in both study time points within one subject. The perfusion of each kidney was assessed pixel by pixel, and the average perfusion of the whole area of the kidney within the slice was calculated. Pixel with non-physiological high perfusion (>600 ml/min/100 g, e.g. blood vessels) and pixels without perfusion (<3 ml/min/100 g, e.g. pyelon) were excluded from the evaluation. The average of the perfusion values of both kidneys was used for analyses. In all subjects, MRI–ASL data were analyzed and post-processed by the same radiologist (J.R., with 10 years of experience in MRI and 2 years of experience in MRI perfusion techniques), who was blinded to the date of the examinations and the clinical and clearance data of the study participants. MRI–ASL data were analyzed on external Windows-based computer using a dedicated software (Prof. Hornegger, Informatik 5, University of Erlangen-Nürnberg, Erlangen, Germany).

The assessment of renal perfusion by MRI–ASL and renal hemodynamic parameters by constant infusion input clearance technique took place in parallel in the MR scanner room. Subjects rested in a supine position for 20 min prior to start of the examinations and remained supine during the MRI–ASL and clearance examination of the kidneys. Examination was performed in the morning between 8 and 11 am. In face of the study duration of 2.5–3 h, subjects were not on a fasting state as they were

Table 1. Clinical characteristics of study participants at the screening visit (after 12 h of fasting)

Characteristic	Value
Age (years)	42.3 ± 9.7
Waist circumference (cm)	110 ± 10
Weight (kg)	103 ± 14
Height (cm)	180 ± 5.8
Body mass index (kg/m²)	31.9 ± 4.3
Body surface area (m²)	2.22 ± 0.2
Systolic blood pressure (mmHg)	144 ± 10
Diastolic blood pressure (mmHg)	90.0 ± 9.8
Mean arterial pressure (mmHg)	108 ± 8.3
Heart rate (b.p.m.)	70.4 ± 9.2
Glucose (mg/dl)	99.8 ± 10.3
HbA1c (%)	5.64 ± 0.4
Triglycerides (mg/dl)	147 ± 70
Cholesterol (mg/dl)	220 ± 36
HDL cholesterol (mg/dl)	44.9 ± 7.0
LDL cholesterol (mg/dl)	153 ± 30
C-reactive protein (mg/l)	0.30 (0.1–0.7)
Urea (mg/dl)	33.0 ± 8.6
Creatinine (mg/dl)	0.93 ± 0.1

HbA1c, glycosylated hemoglobin; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol.

allowed to have a light breakfast (without coffee or soft drinks) in the morning before examination. In three subjects, MRI–ASL images were invalid due to poor image quality.

The intraobserver coefficient of variation for measurement of kidney perfusion by MRI–ASL with FAIR True-FISP was analyzed in a separate cohort comprised of 10 healthy volunteers. In this cohort, the intraobserver coefficient of variation, assessed by four measurements in each volunteer (two consecutive measurements at two different days), was 7.21%.

Clearance examination and assessment of systemic hemodynamics

To determine RPF and glomerular filtration rate, constant infusion input clearance technique without urine sampling, as suggested by Cole *et al.* [11], was applied. Renal vascular resistance and filtration fraction were calculated as previously described [12]. The principle of the constant infusion input clearance technique is that, under steady-state conditions, the excreted amount of PAH (Clinalfa, Basel, Switzerland) and inulin (Inutest®, Fresenius, Linz, Austria) is equal to the infused dose of the compounds. In brief, subjects maintained a supine position throughout the examination, which took place in parallel to the MRI–ASL examination. A catheter was inserted into the left antecubital vein for infusion of PAH and inulin. A second catheter was inserted into the right antecubital vein to obtain blood samples. After intravenous bolus infusion, which was adjusted for body weight, of inulin and PAH over 15 min, a subsequent intravenous constant infusion, which was also adjusted for body weight, of inulin and PAH over 105 min was applied to reach a steady state between input and renal excretion of the tracer substances, as previously described in detail [13]. Blood samples to determine inulin and PAH concentration were drawn at −5 and 0 and 115 and 120 min. Systemic hemodynamic parameters (i.e. blood pressure and heart rate) were monitored by means of an oscillometric device (Dinamap 1846 SX, Criticon, Norderstedt, Germany).

Laboratory measurements

Blood samples for measurement of PAH and inulin levels were stored until all study participants had completed the study (up to 12 months). Then blood samples for determination of PAH and inulin concentrations were analyzed altogether on one single day in our laboratory. PAH was measured using previously described methods [14]. Inulin was indirectly measured by converting inulin to fructose and subsequently measuring fructose by an enzymatic method (716260; Boehringer Mannheim, Mannheim, Germany) as outlined in detail elsewhere [15]. Each blood sample was measured in duplicate with a coefficient of variation of <5%. In two subjects, PAH data before treatment with telmisartan were discarded as invalid by the laboratory quality criteria.

Statistical analyses

All statistical analyses were carried out using SPSS software (release 15.0, SPSS Inc., Chicago, IL, USA). The sample size was estimated from results of earlier studies based on standard deviations of PAH measurements [10,16,17] and previously observed changes of RPF due to blockade of the renin–angiotensin system in our laboratory [10,16,17]. The sample size of $n = 24$ was chosen to detect an estimated increase of RPF of 10% from a hypothesized RPF of 570 ml/min at baseline in response to treatment with telmisartan 80 mg over a period of 2 weeks with a power of 0.80 assuming a standard deviation of 95 ml/min. MRI–ASL data and PAH plasma clearance data were analyzed blinded, separately and independently from each other prior to the merge of all data.

Table 2. Systemic haemodynamic, clinical and renal hemodynamic parameters before and after 2 weeks of treatment with telmisartan 80 mg once daily

Characteristic	Before telmisartan	After 2 weeks of treatment with telmisartan	*P*-value
Systolic blood pressure (mmHg)	144 ± 9.4	132 ± 21	0.012
Diastolic blood pressure (mmHg)	85.2 ± 7.0	80.9 ± 16	0.124
Mean arterial pressure (mmHg)	105 ± 6.0	97.9 ± 7.2	<0.001
Heart rate (b.p.m.)	78.0 ± 13	78.3 ± 14	0.907
Glucose (mg/dl)	109 ± 17	108 ± 16	0.755
HbA1c (%)	5.64 ± 0.3	5.62 ± 0.3	0.526
Triglyceride (mg/dl)	176 ± 90	178 ± 82	0.901
Cholesterol (mg/dl)	206 ± 35	207 ± 35	0.810
HDL cholesterol (mg/dl)	43.1 ± 6.8	42.6 ± 7.2	0.465
LDL cholesterol (mg/dl)	139 ± 27	142 ± 30	0.380
C-reactive protein (mg/l)	0.19 (0.1–0.4)	0.23 (0.1–0.7)	0.104
Urea (mg/dl)	31.3 ± 6.6	32.6 ± 7.2	0.141
Creatinine (mg/dl)	0.93 ± 0.2	0.91 ± 0.1	0.327
Renal plasma flow (ml/min)	562 ± 82	624 ± 119	0.007
Renal plasma flow (ml/min/m)	313 ± 47	348 ± 69	0.007
Filtration fraction (%)	19.6 ± 1.9	17.9 ± 2.8	0.001
Renal vascular resistance (mmHg/ml/min)	193 ± 31	165 ± 37	0.001
Glomerular filtration rate (ml/min)	110 ± 13	109 ± 12	0.878
Kidney perfusion by MRI–ASL (ml/min/100 g)	253 ± 20	268 ± 25	0.020

HbA1c, glycosylated hemoglobin; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; MRI–ASL, magnetic resonance imaging with arterial spin labeling.

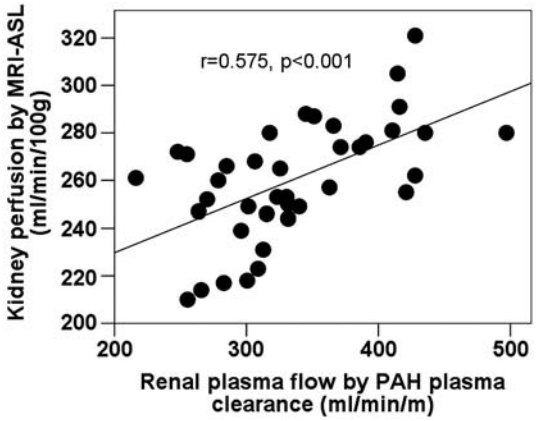

Fig. 2. Correlation between kidney perfusion assessed by MRI–ASL (ml/min/100 g) and renal plasma flow assessed by PAH plasma clearance (ml/min/m) (both values before and after treatment with telmisartan are shown; $r = 0.575$, $P < 0.001$).

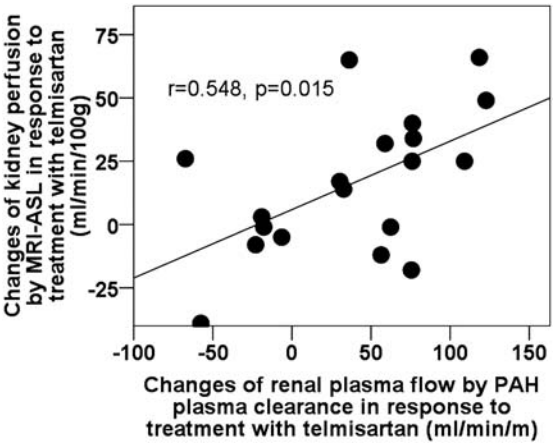

Fig. 3. Correlation between the absolute changes of kidney perfusion assessed by MRI–ASL (ml/min/100 g) and the absolute changes of renal plasma flow assessed by PAH plasma clearance (ml/min/m) during 2 weeks of treatment with telmisartan 80 mg once daily ($r = 0.548$, $P = 0.015$).

Results are given as mean ± standard deviation for parametric data and as median (interquartile range) for non-parametric data. Changes due to treatment with telmisartan over 2 weeks were evaluated using paired tests: paired Student's *t* test and Wilcoxon test were used for parametric and non-parametric data, respectively. Correlation analyses were performed using Pearson's correlation coefficient. Two-tailed values of $P < 0.05$ were considered statistically significant.

Results

Main clinical characteristics of the 24 study participants at the screening visit after a fasting period of at least 12 h are given in Table 1. Systemic hemodynamic, clinical and renal haemodynamic parameters before and after 2 weeks of treatment with telmisartan 80 mg once daily are given in Table 2. Systolic blood pressure and mean arterial pressure decreased during the 2 weeks of treatment with telmisartan, whereas the reduction in diastolic blood pressure did not reach the level of statistical significance. Heart rate, glucose and lipid parameters, C-reactive protein as well as urea and creatinine values were similar after 2 weeks of treatment with telmisartan compared to pre-treatment levels.

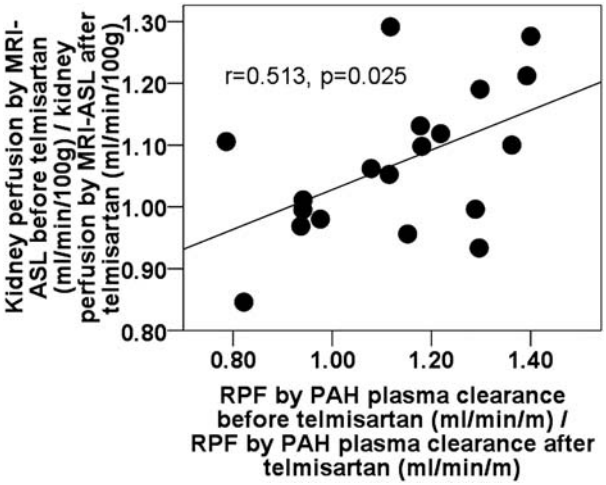

Fig. 4. Relationship of the ratio of measurements before and after treatment with telmisartan of kidney perfusion measurements by MRI–ASL (ml/min/100 g) and renal plasma flow measurements by PAH plasma clearance (ml/min/m) ($r = 0.513$, $P = 0.025$).

Measurements of PAH plasma and inulin plasma clearances revealed that, in response to treatment with telmisartan over 2 weeks, RPF (ml/min, ml/min/m) increased, whereas filtration fraction and renal vascular resistance decreased (Table 2). Glomerular filtration rate did not change (Table 2). MRI–ASL data revealed an increase in kidney perfusion during treatment with telmisartan (Table 2). RPF assessed by PAH plasma clearance and kidney perfusion assessed by MRI–ASL revealed a significant relationship [$r = 0.601$, $P < 0.001$ (RPF, ml/min) and $r = 0.575$, $P < 0.001$ (RPF, ml/min/m)] (Figure 2). Moreover, the absolute change of RPF assessed by PAH plasma clearance and the absolute change of kidney perfusion assessed by MRI–ASL in response to treatment with telmisartan were significantly related [$r = 0.557$, $P = 0.013$ (RPF, ml/min) and $r = 0.548$, $P = 0.015$ (RPF, ml/min/m)] (Figure 3). Similarly, the percentage change of RPF assessed by PAH plasma clearance and the percentage change of kidney perfusion assessed by MRI–ASL in response to treatment with telmisartan were significantly related [$r = 0.514$, $P = 0.025$ (RPF; ml/min, ml/min/m)]. To assess whether the relationship between both methods is independent from kidney mass, we further investigated the relationship of both methods by analyzing the relationship of the ratio of the measurements before and after treatment with telmisartan between the two methods. These analyses revealed a significant relationship between both methods [$r = 0.513$, $P = 0.025$ (RPF; ml/min, ml/min/m)] (Figure 4).

Discussion

To the best of our knowledge, this is the first study directly comparing measurements of kidney perfusion by MRI with a PAH clearance method. In the present study, kidney

perfusion measurements assessed by MRI–ASL were related to RPF measurements assessed by PAH plasma clearance. Moreover, changes in kidney perfusion in response to a 2-week treatment period with telmisartan could be detected by MRI–ASL and were related to the observed changes of RPF assessed by PAH plasma clearance when expressed in absolute terms and also in percent changes. Moreover, MRI–ASL with FAIR True-FISP revealed high reproducibility. Our study therefore indicates that the assessment of perfusion of a single coronal kidney slice using MRI–ASL with FAIR True-FISP sequence is capable of approximating kidney perfusion as well as approximating changes of kidney perfusion in response to pharmacological intervention.

Of note, our current MRI–ASL methodology measures kidney perfusion of a single coronal kidney slice. Therefore, it is possible that this approach might not exactly reflect the perfusion of the whole kidney. This might be the reason why the correlation coefficient revealed only a moderate relationship between MRI–ASL with FAIR True-FISP measurements and RPF by PAH plasma clearance. Moreover, it is unclear whether the ratio of cortical and medullary perfusion of the coronal kidney slice that was analyzed by MRI–ASL with FAIR True-FISP reflects the exact cortex-to-medulla ratio of the whole kidney. Previous studies [8,9] using MRI–ASL with FAIR True-FISP demonstrated that perfusion in the renal cortex is three to four times greater than in the renal medulla. In the present study, we calculated the average perfusion of all renal pixels in one central coronal slice. A differentiation of the cortical and medullary perfusion was not possible in our study set up due to our scanner software that is currently available. Furthermore, MRI–ASL kidney perfusion measurements are given per 100 g kidney mass. Thus, deviations from average kidney mass may lead to over- or underestimation of kidney perfusion measurements when measurements are based on MRI–ASL with FAIR True-FISP only. Measurement of kidney mass with MRI in addition to MRI–ASL with FAIR True-FISP measurements will allow correcting MRI–ASL FAIR True-FISP measurements for kidney mass. Such an approach is more time and resources consuming but might improve the sensitivity. Especially in subjects with kidney disease that are expected to have larger or smaller kidneys, correction of MRI–ASL with FAIR True-FISP measurements for kidney mass might certainly be necessary. Of note, in the current study, the relationship of kidney perfusion measurements by MRI–ASL with FAIR True-FISP and RPF by PAH plasma clearance were independent from kidney mass, as demonstrated in the correlation analysis assessing the relationship between the ratio of kidney perfusion by MRI–ASL before and after treatment with telmisartan and RPF by PAH plasma clearance before and after treatment with telmisartan.

An initial study with the FAIR True-FISP sequence revealed that MRI–ASL is capable of performing kidney perfusion images of high diagnostic quality in 12 healthy volunteers and one patient with a renal transplant in his pelvis [8]. Similarly, the FAIR–UFLARE sequence, as another MRI–ASL technique, was found to lead to valuable kidney perfusion images with high diagnostic quality in a cohort of 10 healthy volunteers [18]. Moreover, MRI–ASL with the FAIR True-FISP sequence appeared to be suitable for quantitative kidney perfusion measurement in patients with renal artery stenosis as MRI–ASL data was related with renal artery stenosis grade and with single photon emission computed tomography perfusion values in a cohort of 12 patients with renal artery stenosis and six patients with arterial hypertension but without renal artery stenosis [9]. In a recent study, a qualitative agreement between MRI–ASL and scintigraphy with respect to kidney perfusion measurements [19] was found. The MRI–ASL kidney perfusion values obtained in our current study are well in line with previous reports using the same technique (FAIR True-FISP) [8,9] as well as with data from a study using FAIR–UFLARE technique [18].

The major advantages of MRI–ASL methodology in comparison to other methods to measure kidney perfusion, i.e. in particular PAH clearance techniques and renal scintigraphy with 99mTc-MAG3, are its non-invasive nature, quick performance within a few minutes and low consumption of human resources. PAH clearance, even if performed as PAH plasma clearance (in the current study), takes over 2 h, is expensive, invasive and bears potential side effects such as anaphylaxis among others. Renal scintigraphy with 99mTc-MAG3 can be performed within an hour and was found to be closely related to *o*-iodohippuric acid clearance [20], but its use is limited due to the radioactivity (even if it is low) of the labeled tracer. Therefore, it is certainly not reasonable and not well accepted to screen or follow up patients at increased risk for cardio- and renovascular disease (i.e. subjects with hypertension and metabolic disorders) with 99mTc-MAG3 renal scintigraphy for evaluation of renal organ damage. Moreover, both PAH plasma clearance and renal scintigraphy with 99mTc-MAG3 have potential side effects as anaphylaxis among others. Clearly, in some conditions (e.g. subjects with some types of metal implantates or with claustrophobia), MRI cannot be applied. Of note, kidney perfusion measurements with MRI–ASL are currently a research tool, and further research as well as improvements in methodology and software will be necessary before it can be implemented in clinical practice.

Inulin and PAH clearances, determined by the conventional method of continuous intravenous infusion with blood and urine sample collections, have been considered the gold standards for measuring glomerular filtration rate and RPF, respectively. The need for timed urine collections and complete rechecking of the bladder are obvious limitations of this classical inulin and PAH clearance technique. Thus, alternative approaches that solely use determinations of inulin and PAH in plasma or serum were developed and validated [11], called inulin plasma and PAH plasma clearances. In numerous previous studies, we and others have found these methods to be valid, reliable and more applicable than methods relying on urine collections [10–12,17,21]. However, these methods also have limitations. First, inulin has a relatively high molecular weight (~5200 Da), and it may take >12 h for complete equilibrium of inulin with the total extracellular space [22]. Incomplete distribution might cause plasma or serum levels to become higher than those expected at steady state, and

the glomerular filtration rate may differ in some patients if measured by the inulin plasma clearance with the constant infusion technique (at most 10% difference according to unpublished data obtained in 12 healthy subjects). Second, because PAH is not completely excreted in normal subjects, the PAH plasma clearance overestimates the PAH renal clearance by ~10–20% [11,23]. However, the bias is constant because the extraction of PAH by the kidney is constant (~90%) and similar in subjects if the RPF is >300 ml/min [11,24]. A third limitation of our study is that the study participants were allowed to have a small breakfast since serum fructose interferes with the measurement of inulin. In our study, inulin was measured indirectly by converting inulin to fructose and subsequently measuring fructose by an enzymatic method. Fructose is used as a sweetener in soft drinks, snacks and jam. Sucrose is also metabolized to fructose in the intestine. However, measurements of inulin concentrations prior to the start of inulin infusion did not show, in any case, measurable concentrations.

The assessment of physiological variables in overweight and obese subjects is confounded by the issue of whether size-corrected values are more meaningful than absolute values. It was demonstrated that, when related to body surface area, inappropriately low values of RPF were calculated for overweight and obese patients [25]. In the current study, we show RPF in absolute values and also corrected RPF for height per meter. Indexing RPF data to height was found to be more accurate in overweight and obese patients than correcting for body surface area [25]. An alternative approach might be indexing RPF for lean body weight. We did not use lean body weight for correcting RPF because, according to the mathematical equations, the only determinant of lean body weight is height [lean body weight for males (females) = 50 kg (45.5) + 2.3 kg/height in inches]. Hence, the results with lean body weight as a correcting factor would be the same as those with height, but additional calculations would be required.

We have recently demonstrated that treatment with telmisartan increases RPF in hypertensive subjects with diabetes mellitus [10]. An improvement of kidney perfusion by inhibition of the renin–angiotensin system was also reported from animal studies [26,27] and other studies in humans with diabetes mellitus [17,28]. In the study by Fliser *et al.*, chronic angiotensin II type 1 receptor blockade with olmesartan decreased plasma 8-isoprostane 15(s)-8-*iso*-prostaglandin F_{2a} concentrations, indicating a reduction of oxidative stress, whereas nitric oxide metabolism (plasma nitrate and nitrite) and asymmetric dimethylarginine blood levels did not change [28]. Renal vascular resistance and blood pressure decreased in parallel to the increase in RPF in subjects with diabetes mellitus [28]. Thus, angiotensin II type 1 receptor blockade might improve RPF not only by direct haemodynamic effects at the post-glomerular site but also via reduction in inflammation and oxidative stress in subjects with diabetes mellitus. The current study demonstrates that treatment with telmisartan also improves RPF in hypertensive subjects with the metabolic syndrome. The increase in RPF in response to treatment with telmisartan in the current study is comparable to previous findings from our laboratory in hypertensive subjects with diabetes mellitus [10]. In contrast, in humans [29,30] and dogs [31] with renal artery stenosis, inhibition of the renin–angiotensin system was shown to decrease kidney perfusion.

In conclusion, our study demonstrates that MRI–ASL perfusion measurements of a single coronal kidney slice are capable of approximating kidney perfusion and approximating changes in kidney perfusion. Future work should focus on improving the explanatory power of MRI–ASL as a tool for analyzing kidney perfusion. Especially, strategies to differentiate between cortical and medullary perfusion and corrections for total kidney mass should be implemented.

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Effects of renal volume and single-kidney glomerular filtration rate on renal functional outcome in atherosclerotic renal artery stenosis

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Abstract

Background. Renal functional outcome is unpredictable after revascularization of high-grade atherosclerotic renal artery stenosis (RAS). 'Hibernating' parenchyma describes acute parenchymal injury where renal dysfunction is potentially reversible with treatment of the stenosis. We analysed renal parenchymal volume (PV) and single-kidney glomerular filtration rate (SK-GFR) characteristics to identify kidneys with hibernating parenchyma and hence determine renal functional outcome after revascularization.

Methods. Fifty patients with ≥50% RAS underwent baseline analyses: (i) PV using magnetic resonance imaging; (ii) radioisotopic SK-GFR. Twenty-one patients (27 kidneys) underwent renal revascularization and 29 medical therapy alone.

Results. Patients with revascularized kidneys manifesting high PV:SK-GFR showed improvement in global estimated GFR compared to conservatively managed counterparts at 6 months and 1 year (6 months: 6.2 ± 2.9 *versus* -3.7 ± 6.8, $P = 0.038$; 1 year: 3.5 ± 3.0 *versus* -5.1 ± 5.1 ml/min/1.73 m^2, $P = 0.021$). Twelve revascularized patients (16 kidneys) underwent repeat SK-GFR 4 months post-revascularization. Six of 16 revascularized kidneys had high baseline PV:SK-GFR and showed improved SK-GFR compared to kidneys with low or normal PV:SK-GFR (6.3 ± 2.0 *versus* -0.9 ± 4.2 ml/min, $P = 0.002$).

Conclusions. Our data suggest that, after revascularization, GFR improvement is likely if there is a disproportionately higher baseline PV:SK-GFR in the RAS kidney. Analysing these parameters can potentially identify these 'hibernat-