Reduced cortical oxygenation predicts a progressive decline of renal function in patients with chronic kidney disease

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Renal tissue hypoxia is a final pathway in the development and progression of chronic kidney disease (CKD), but whether renal oxygenation predicts renal function decline in humans has not been proven. Therefore, we performed a prospective study and measured renal tissue oxygenation by blood oxygenation level-dependent magnetic resonance imaging (BOLD-MRI) in 112 patients with CKD, 47 with hypertension without CKD, and 24 healthy control individuals. Images were analyzed with the twelve-layer concentric objects method that divided the renal parenchyma in 12 layers of equal thickness and reports the mean R2* value of each layer (a high R2* corresponds to low oxygenation), along with the change in R2* between layers called the R2* slope. Serum creatinine values were collected to calculate the yearly change in estimated glomerular function rate (MDRD eGFR). Follow up was three years. The change in eGFR in CKD, hypertensive and control individuals was -2.0, 0.5 and -0.2 ml/min/1.73m^2/year, respectively. In multivariable regression analysis adjusted for age, sex, diabetes, RAS-blockers, eGFR, and proteinuria the yearly eGFR change correlated negatively with baseline 24 hour proteinuria and the mean R2* value of the cortical layers, and positively with the R2* slope, but not with the other covariates. Patients with CKD and high outer R2* or a flat R2* slope were three times more likely to develop an adverse renal outcome (renal replacement therapy or over a 30% increase in serum creatinine). Thus, low cortical oxygenation is an independent predictor of renal function decline. This finding should stimulate studies exploring the therapeutic impact of improving renal oxygenation on renal disease progression.

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Chronic kidney disease (CKD) is a major public health problem.[1] Diabetes, arterial hypertension (AH), and proteinuria are well-known risk factors for disease progression, but predicting the evolution of CKD remains a difficult task. For incompletely understood reasons, the glomerular filtration rate (GFR) of some CKD patients will hardly decrease over the years, whereas in others, it will rapidly progress toward end-stage renal disease. The early identification of CKD patients at risk of progressive renal function decline (progressors) would allow a more focused distribution of health care resources and improved planning of renal replacement methods. However, a multitude of circulating or urinary biomarkers has been proposed to predict outcome, so far with inconsistent results.[2]

Renal tissue hypoxia is considered as the common final pathway in the development and progression of CKD, irrespective of its cause.[3] Animal studies have provided evidence of this hypothesis, yet data in humans were limited for a long time due to the lack of a method to assess renal tissue oxygenation noninvasively in humans. This situation has changed thanks to the development of blood oxygenation level–dependent magnetic resonance imaging (BOLD-MRI).[4] In brief, BOLD-MRI uses the paramagnetic properties of deoxyhemoglobin to assess tissue oxygenation: the higher the local deoxyhemoglobin levels are, the higher the so-called apparent relaxation rate R2* (s^{-1}) is and the lower local tissue oxygen content is, assuming that blood p_{O_2} is in equilibrium with tissue p_{O_2}. BOLD-MRI is performed without contrast and therefore is an ideal method for patients with CKD. Standardization of the examinations and refinements in the methods to analyze the images has resulted in a reproducible technique with low interobserver variability.[5]

Recent BOLD-MRI studies have demonstrated that the R2* values of renal parenchyma are higher in CKD patients,

suggesting lower renal tissue oxygenation.[6–8] Differences in R2* between CKD patients and healthy controls have been mainly reported in the cortex, whereas medullary oxygenation seems relatively well preserved at a lower GFR.

Acute decreases in medullary R2* levels have been described after the administration of furosemide and are greater in young persons with preserved renal function compared with older persons or patients with CKD.[9,10] The effect of furosemide has been explained by the fact that it blocks the Na^+-K^+-$2Cl^-$ transporter in the thick ascending loop of Henle, will acutely decrease oxygen-consuming active sodium transport, and increase local pO_2.[11] BOLD-MRI combined with i.v. furosemide is therefore considered by many as a functional test: the greater the change is in R2*, the more functional tubuli that are still present.[12]

To the best of our knowledge, the reported BOLD-MRI studies were all cross-sectional or short-term interventional studies, and it remains therefore unknown whether renal tissue hypoxia (high baseline R2* values) or furosemide-induced changes in R2* predict renal function decline in humans. The aim of this study was therefore to assess whether renal tissue oxygenation as measured with BOLD-MRI is associated with renal function decline in a cohort of CKD patients, hypertensive patients without CKD, and normotensive controls.

RESULTS

A baseline visit was performed in 226 participants (120 CKD patients, 62 hypertensive patients, and 44 healthy controls). Fifteen participants were excluded due to the inability to undergo BOLD-MRI (unexpected claustrophobia or other contraindication for MRI). Seven patients were excluded because of insufficient image quality. A total of 10 hypertensive patients and 11 controls did not want to return for a follow-up visit and were therefore also excluded. Baseline characteristics of the remaining 183 participants are shown in Table 1. In the CKD group, 28 patients had diabetic nephropathy, 33 had hypertensive nephropathy, and 21 had glomerulonephritis. Details of the measured radiological and arterial parameters are shown in Table 2. An example of BOLD-MRI of a healthy volunteer and a CKD patient is shown in Figure 1 (see Methods section for details). More detailed information on other causes of CKD, baseline estimated GFR (eGFR), and BOLD-MRI results according to the underlying cause of CKD are provided in Supplementary Table S1.

The follow-up period (mean ± SD) for all participants was 3.0 ± 1.1 years (3.2 ± 1.2 for CKD, 2.7 ± 1.0 for AH, and 2.7 ± 0.7 for controls). On average, 5.3 ± 2.7 creatinine values were available per individual (6.6 ± 2.6 for CKD, 3.7± 1.7 for AH, and 2.9 ± 0.7 for controls).

The yearly eGFR change was, respectively, −2.0 ± 6.0, 0.5 ± 4.9, and −0.2 ± 5.3 ml/min per 1.73 m^2 per year in CKD, hypertensive patients, and controls (P_{ANOVA}= 0.027); the evolution of the eGFR over time per group is shown graphically in Supplementary Figure S1.

Table 1 | Baseline characteristics of CKD patients, hypertensive patients, and normotensive controls

Characteristics	CKD	AH	Control	P_{ANOVA}
N	112	47	24	
Age (yr)	56 ± 14	56 ± 11	47 ± 11	0.008
Sex (% female)	31.9	35	48	0.21
Diabetes (%)	25.0	16.7	0	0.004
Hypertension (%)	79.8	100	0	<0.001
Creatinine (μmol/l)	151 ± 89	75 ± 13	72 ± 15	<0.001
eGFR (ml/min per 1.73 m^2)	55 ± 29	90 ± 15	97 ± 14	<0.001
Body mass index (kg/m^2)	28 ± 5	28 ± 5	26 ± 5	0.3
Systolic BP (mm Hg)	135 ± 19	142 ± 16	121 ± 14	<0.001
Diastolic BP (mm Hg)	77 ± 12	82 ± 10	74 ± 11	0.0048
Urinary 24-hr volume (l)	2.2 ± 0.8	1.9 ± 0.7	2.1 ± 1.2	0.18
Urinary 24-hr sodium (mmol)	167 ± 88	164 ± 84	153 ± 79	0.57
Hemoglobin (g/dl)	130 ± 18	137 ± 13	135 ± 11	0.05
Hematocrit (%)	38 ± 5	40 ± 3	40 ± 3	0.04
Glycemia (mmol/l)	6.6 ± 2.3	6.2 ± 1.3	5.4 ± 1.1	0.04
Concomitant medications				
RAS blockers (%)	62.6	38.6	0	<0.001
Calcium antagonists (%)	29.8	33.9	0	<0.001
Beta-blockers (%)	28.1	37.5	0	<0.001
Diuretics (%)	22.6	19.6	0	<0.001
Statins (%)	49	32	6.3	<0.001

AH, arterial hypertension; ANOVA, analysis of variance; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAS, renin-angiotensin system.

Results of uni- and multivariable regression analysis including all participants, with yearly eGFR change as a dependent (outcome) variable and age, sex, group, diabetes, renin-angiotensin system blockers, baseline eGFR, and proteinuria as independent variables, are shown in Table 3. In fully adjusted models, the yearly change in eGFR correlated negatively with baseline 24-hour proteinuria (regression coefficient β ± SE per gram of proteinuria: −1.49 ± 0.60, P = 0.012) and mean R2* value of the outer (cortical) layers (β/second^{-1}: −0.44 ± 0.16, P = 0.009), but not with the other

Table 2 | Radiologic and arterial parameters according to group

Parameters	CKD	AH	Control	P_{ANOVA}
N	112	47	24	
Magnetic resonance imaging				
Outer R2* (s^{-1})[a]	21.2 ± 3.1	20.6 ± 1.7	20.4 ± 2.5	0.04
Inner R2* (s^{-1})[b]	24.2 ± 2.6	24.4 ± 1.8	24.6 ± 2.1	0.68
R2* slope (hertz per % depth)	7.2 ± 2.8	8.7 ± 3.0	9.4 ± 3.0	<0.001
Delta inner R2* (s^{-1})[c]	2.2 ± 1.2	3.0 ± 1.4	3.2 ± 1.1	<0.001
Ultrasound				
Renal length (mm)	108.3 ± 12.6	114.9 ± 12.2	113.8 ± 8.7	0.002
Renal resistive index	0.71 ± 0.09	0.67 ± 0.07	0.64 ± 0.04	<0.001
Pulse wave analysis				
PWV car-fem (m/s)	9.5 ± 2.7	10.2 ± 2.9	7.9 ± 1.3	<0.001

AH, arterial hypertension; ANOVA, analysis of variance; car-fem; carotid-femoral; CKD, chronic kidney disease; PWV, pulse wave velocity.
[a]Outer R2*: mean R2* of the 3 most superficial, cortical layers of renal parenchyma.
[b]Inner R2*: mean R2* of the 8th to 10th layer (corresponding to medulla) of renal parenchyma.
[c]Delta inner R2* represents the change in R2* of the inner layers 15 minutes after i.v. furosemide.