Oxygénation rénale et maladies rénales chroniques

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Service de Néphrologie CHUV
2 Février 2013
Champéry
Definition IRC:

**Table 2. Definition of Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by <em>either</em>:</td>
</tr>
<tr>
<td>• Pathological abnormalities; or</td>
</tr>
<tr>
<td>• Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests</td>
</tr>
<tr>
<td>2. GFR &lt;60 mL/min/1.73 m² for ≥3 months, with or without kidney damage</td>
</tr>
</tbody>
</table>

*Abbreviation: GFR, glomerular filtration rate*

http://www.kidney.org/professionals/kdoqi/guidelines_ckd
Prévalence IRC à Lausanne: étude CoLaus

Prevalence : ~10%

Ponte B, Pruijm M, Bochud M, NDT 2012, in revision
IRC: fortement lié à la mortalité

Meta-analysis
General population
1'230000 participants
Adjusted HR mortality risk increases as from eGFR<60 ml/min/173m2 and ACR>1mg/mmol

De Zeeuw, Ruggenenti, Lancet 2011
Pathogenèse IRC:

- Hypoxie

Stenvinkel, Massy, CJASN 2008,505-521
Hypoxie et rein: une longue histoire
Renal oxygenation in male Peruvian natives living permanently at high altitude

Renal oxygen uptake (AV difference of O2/ml/min) was 10-15ml/min/1.73m2 in both groups
Aukland Krog, Nature 1960

- Microelectrodes chiens et rats
- pO2 cortex 50mmHg
- pO2 medulla 10-20mmHg

Anatomical and Physiologic Features of the Renal Cortex and Medulla

Brezis M, Rosen S. 1995 NEJM; 332:647
Renal tissue pO2 level depends on:

**Delivery:** renal blood flow, renal microcirculation, Hct

**Consumption:** GFR and active tubular transport

<table>
<thead>
<tr>
<th></th>
<th>RB F</th>
<th>Na reabsorption</th>
<th>O2 consumption</th>
<th>Local PO2 (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex</td>
<td>90%</td>
<td>67%</td>
<td>27%</td>
<td>50</td>
</tr>
<tr>
<td>Medulla</td>
<td>10%</td>
<td>30%</td>
<td>67%</td>
<td>15</td>
</tr>
</tbody>
</table>

*Welch WJ. Clin Exp Pharmacol Physiol 2006; 33(10).*

*Epstein, Kidney Int: 51, 1997*
Hypoxie: PHD/HIF signalling

Dégradation par PHD-vHL-pathway

Stabilization et lien HIFβ

PHD=enzymes de classe 2-Oxoglutarate oxygenases (2OG), Propyl hydroxylase domains

FIH

O2-sens microRNA

VH Haase, fibrinogenesis and tissue repair 2012
HIF knock out leads to adverse outcome in AKI models

..récemment: IRC
HIF and fibrosis

In AKI, HIF knock out mice more adverse outcome, also more ischemia reperfusion injury

VH Haase, fibrinogenesis and tissue repair 2012
Animal studies: Renal hypoxia in streptozotocine-induced diabetes

dos Santos, Elisabete; Li, Lu-Ping; Ji, Lin; Prasad, Pottumarthi
Evidence of Tubular Hypoxia in the Early Phase in the Remnant Kidney Model

5/6 remnant kidney model
7d and 2w (extended RK)

Pimonidazole uptake increased (grey)

HIF expression increased

Renoprotective Properties of Angiotensin Receptor Blockers beyond Blood Pressure Lowering

Yuko Izuha,* Masaomi Nangaku,† Reiko Inagi,* Naoto Tominaga,* Toru Aizawa,* Kiyoshi Kurokawa,* Charles van Ypersele de Strihou,§ and Toshio Miyata*

*Institute of Medical Sciences and Division of Internal Medicine, Tokai University School of Medicine, Kanagawa, Japan; †Division of Nephrology and Endocrinology, University of Tokyo School of Medicine, Tokyo, Japan; and §Service de Nephrologie, Université Catholique de Louvain, Brussels, Belgium

Figure 3. Immunohistochemical analysis of pimonidazole, a hypoxic marker in the kidney. Pimonidazole accumulation was intense and ubiquitous in the cortex of SHR/NDmcr-cp rats that were given vehicle but markedly attenuated by olmesartan treatment. Magnification, ×100.
Angiotensin II Blockade Augments Renal Cortical Microvascular pO2 Indicating a Novel, Potentially Renoprotective Action

Jill T. Norman, Ray Stidwill, Mervyn Singer, Leon G. Fine

Anaesthetised Sprague-Dowley rats, cortical pO2 measured by porphyrin phosphorescence technique

enalapril
candesartan

Fig. 4. Effect of a single bolus of enalaprilat on cortical oxygenation after a decline in cortical microvascular pO2. After a fall of 5 mm Hg

Fig. 5. Effect of a single bolus of candesartan CV11974 on cortical microvascular pO2. Instrumented animals (n = 6) received 40 μg/kg

Norman et al, Nephron Phys 2003
Figure 2 HIF-1α expression in diabetic nephropathy. HIF-1α immunostaining in formalin-fixed, paraffin-embedded renal biopsy tissues from patients with diabetic nephropathy (DN). (A) Shown are non-affected control kidney tissue (nl. +, less than 25% of tubular epithelial cells are stained) and kidney tissue from a patient with severe DN (DN ++++, positive staining is detected in >50% of tubular epithelial cells). Arrows highlight cells with nuclear HIF-1α staining. (B) Summary of HIF-1α expression analysis in DN. DN cases are grouped according to tubulointerstitial injury score as previously described [53]. The number of biopsies with glomerular (gl) or tubular staining (t) is shown in brackets. -, absence of staining; +: 1-25% of cells per visual field with staining; ++: >25-50% and +++: >50% of cells with positive staining.
BOLD-MRI
Blood oxygenation-level dependent MRI

Pruijm et al, Int J Hypertension 2013, in press
Non-invasive monitoring of renal oxygenation using BOLD-MRI: a reproducibility study

Sonia C. Simon-Zoula,¹ Lucie Hofmann,² Andreas Giger,¹ Bruno Vogt,² Peter Vock,¹ Felix J. Frey² and Chris Boesch³ *

¹Institute of Diagnostic, Interventional and Pediatric Radiology, University and Inselspital, CH-3010 Berne, Switzerland
²Division of Nephrology/Hypertension, University and Inselspital, CH-3010 Berne, Switzerland
³Department of Clinical Research, University and Inselspital, CH-3010 Berne, Switzerland

Figure 1. First images (TE: 6 ms) of the series of 12 $T_2^*$-weighted images in coronal view (a) and axial view (b), showing positions of fixed size ROIs (a) and variable size ROIs (b) in medulla and cortex of both kidneys
**Iodinated contrast product**

**AUC:**
Highly significant effect in medulla, not in cortex

**MANOVA:**
Significant changes in the medulla over time
Tendency for changes in the cortex with time
Principe: signal $R_2^*$ \sim \% \text{ desoxyHb} \sim 1/pO_2$

Pruijm et al, Int J Hypertension 2013, in press
Salt intake and renal tissue oxygenation in normo- and hypertensive individuals measured by BOLD-MRI:

<table>
<thead>
<tr>
<th>Salt diet</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Salt</td>
<td>Low Salt</td>
</tr>
<tr>
<td><strong>Medulla</strong></td>
<td>31.3±0.6</td>
<td>28.1±0.8</td>
</tr>
<tr>
<td><strong>Cortex</strong></td>
<td>17.8±1.3</td>
<td>18.2±0.6</td>
</tr>
</tbody>
</table>

Pruijm, Hofmann et al. Hypertension 2010:1116-22
Effect of dark chocolate on renal tissue oxygenation as measured by BOLD-MRI in healthy volunteers

Pruijm, Hofmann, Stuber, Burnier, Vogt, Clin Nephrol, in revision
Blockade of the renin-angiotensin system and renal tissue oxygenation as measured with BOLD-MRI in patients with type 2 diabetes.
48 DM type 2 patients versus 67 controls

DM R2* higher than controls

Yet, within DM, it seems that R2* decreases (oxygenation increases) with advancing nephropathy

-Mean age increased from 51 to 65 y across stages of diabetic nephropathy according to Mogensen

-Hb decreased from 140 to 106 g/dl

Eur Journal of Radiology 2011
2010-Présent: Prognostic value of renal tissue oxygenation on renal disease progression in patients with hypertension and renal disease

- Cohort patients IRC-groupe contrôle-groupe enfants
- BOLD-IRM-US rénale-prise de sang-biobanque
- 1 infirmière de recherche- 1 méd ass de recherche- BNF
- En collaboration avec
  - Radiologie CHUV: prof Stuber et Dr E Fornari
  - Pédiatrie CHUV: prof Girardin et Dr Chehade
  - IUMSP CHUV: prof Murielle Bochud
  - Médecine interne Gdansk: prof Narkiewicz et Dr Piskunowicz

Stage I-IV Chronic Kidney Disease

baseline

1 year

BOLD-MRI*

BOLD-MRI*

BOLD-MRI*
Prognostic value of renal tissue oxygenation on renal disease progression in patients with hypertension and renal disease

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>CKD (n=75)</th>
<th>HTA (n=54)</th>
<th>Controls (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52±15</td>
<td>57±15</td>
<td>57±12</td>
<td>48±12</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>62</td>
<td>69</td>
<td>67</td>
<td>49</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>78±17</td>
<td>80±15</td>
<td>85±19</td>
<td>75±17</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27±5</td>
<td>27±4</td>
<td>29±6</td>
<td>26±5</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>133±19</td>
<td>133±18</td>
<td>144±17</td>
<td>120±12</td>
</tr>
<tr>
<td>Diastolic Blood pressure (mmHg)</td>
<td>77±12</td>
<td>76±13</td>
<td>83±11</td>
<td>72±10</td>
</tr>
<tr>
<td>eGFR (CKD-EPI, ml/min/1.73m²)</td>
<td>79±30</td>
<td>58±30</td>
<td>95±14</td>
<td>98±15</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>134±15</td>
<td>131±18</td>
<td>138±12</td>
<td>135±11</td>
</tr>
<tr>
<td>Urinary 24h sodium excretion (mmol)</td>
<td>165±95</td>
<td>172±100</td>
<td>174±109</td>
<td>148±77</td>
</tr>
<tr>
<td>Active smoking (yes/no)</td>
<td>10.2</td>
<td>5.9</td>
<td>14.7</td>
<td>13.2</td>
</tr>
</tbody>
</table>
No difference in R2*

28.7±2.1 vs 29.3±2.0 vs 29.2±2.4 sec\(^{-1}\)

\(p_{\text{anova}} = 0.37\)

17.4±1.2 vs 18.4±3.9 vs 17.3±1.9 sec\(^{-1}\)

\(p_{\text{anova}} = 0.09\)
Renal BOLD-MRI does not reflect renal function in chronic kidney disease

- 400 Patients
- 58 Patients not analyzable
- 342 Patients with measureable R2* values
  - 211 at 1.5 T — 129 M, 82 F
  - 131 at 3.0 T — 82 M, 49 F
- 280 Patients with R2* and eGFR
  - 172 at 1.5 T — 107 M, 65 F
  - 108 at 3.0 T — 68 M, 40 F
- 62 Patients w/o creatinine

- no standard hydration protocol
- no information on comorbidities
- creatinine measurement not standardized

Michaely, Schmieder, KI 2012
Inhibition of Prolyl Hydroxylases Increases Erythropoietin Production in ESRD

Wanja M. Bernhardt,* Michael S. Wiesener,*† Paul Scigalla,‡ James Chou,§ Roland E. Schmieder,* Volkmar Günzler,§ and Kai-Uwe Eckardt*

FG-2216

Healthy control

ESRD HD

ESRD anephric

JASN 21:2151-56, 2010
The Effect of Altitude on Dosing and Response to Erythropoietin in ESRD

M. Alan Brookhart,* Sebastian Schneeweiss,† Jerry Avorn,* Brian D. Bradbury,‡ Kenneth J. Rothman,*§ Michael Fischer,* Jyotsna Mehta,* and Wolfgang C. Winkelmayer**


N=341’731 patients US Renal Data System
Higher Hct and lower EPO at higher altitude
Discussion: BOLD-MRI and DM in humans in other studies

*Twenty DM patients, mean age 67y (49-77), eGFR 47 ml/min (14-71)
*Eight Healthy controls, mean age 35 y (30-45)

Zhen J Wang et al, University of California, Journal of MRI, 2011, 655-60
Pourquoi pas d’altération de R2* en IRC?

• Technique insuffisante

• Pas d’hypoxie chronique chez IRC
Explanation: T2* weighted coronal images of the kidneys (echo time = 6.0 ms) across worsening stages of CKD; A: non-CKD, B CKD IV

Pruijm, Piskunowicz, Hofmann, Vogt, Burnier, Int J Hyp, in press
Solution 1: Concentric objects method:
Piskunowicz, Hofmann, Pruijm, in preparation
Compartmental Analysis of Renal BOLD MRI Data

Introduction and Validation

Behzad Ebrahimi, PhD, Monika Glowiczki, MD, PhD, John R. Woollard, MSc, John A. Crane, BS, Stephen C. Textor, MD, and Lilach O. Lerman, MD, PhD

FIGURE 1. ROI selection in the 4 methods studied. The small (A) and large (B) manual ROI, the hybrid (C), and the compartmental (D) methods. In the hybrid method, ROIs were selected to exclude potential overlap within the compartments to minimize volume averaging.

FIGURE 2. A contrast-enhanced MDCT image (A), a corresponding MRI parametric $R_2^*$ map (B), and the resultant histogram showing the best fitted cortical and medullary curves (C). Region (1) shows the low $R_2^*$ components, such as urine, and (2) shows high $R_2^*$ components, such as highly vascular regions. The high $R_2^*$ value in the vicinity of a low...
FIGURE 4. Representative cortical and medullary curves obtained before and after furosemide administration. Cortical

FIGURE 5. Altman-Bland graphs comparing the bias and variation of $R_2^*$ in medulla (A) and cortex (B), derived from the compartmental (blank squares) and manual ROI (solid triangles) methods to the reference hybrid method. The biases in both methods were small, but the compartment method showed less variability (higher reproducibility).

<table>
<thead>
<tr>
<th>Renal Compartment</th>
<th>Compartmental Absolute</th>
<th>Response</th>
<th>Manual ROI Absolute</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulla</td>
<td>0.5 ± 1.4</td>
<td>0.1 ± 1.1</td>
<td>0.2 ± 2.5</td>
<td>0.0 ± 1.5</td>
</tr>
<tr>
<td>Cortex</td>
<td>0.0 ± 0.7</td>
<td>0.2 ± 0.7</td>
<td>0.7 ± 1.5</td>
<td>0.1 ± 2.0</td>
</tr>
</tbody>
</table>
Solution 2: Segmentation
Ou il n'y a pas d'hypoxie CHRONIQUE chez IRC?

A/ \( R^2* \) levels in operated rats (clipping of renal artery)

B/ \( R^2* \) levels in sham operated rats

Evolution of renal oxygen content measured by BOLD MRI downstream a chronic renal artery stenosis

Nicolas Rognant\(^1,2,3\), Fitsum Guebre-Egziabher\(^1,3,4\), Justine Bacchetta\(^3,5\), Marc Janier\(^3,6,7\), Bassem Hiba\(^7\), Jean Baptiste Langlois\(^7\), Rudy Gadet\(^7,9\), Maurice Laville\(^1,2,3\) and Laurent Juillard\(^1,2,3\)

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**Fig. 3.** (A) Evolution of \( R^2* \) in each zone of stenotic kidneys and (B) in each zone of sham-operated kidneys before surgery (baseline, BL) and on Days 4, 11, 18 and 25 thereafter. OM, outer medulla; OSOM, outer stripe of the outer medulla.
.5/6 remnant kidney model

measurements made after 6-8 weeks instead of 2 weeks in Manotham study
HIF stimulation: more than O2

O2

Inflammation

RAAS

VH Haase, JASN2013
Classical view: hypoxie chronique

Alternative view: hypoxie intermittente

Chronic Kidney Disease

glomerulosclerosis
reduced perfusion
capillary rarefaction and obliteration

stabilization of HIF-1α
renal epithelium

stabilization of HIF-2α
renal endothelium

interstitial cells

ECM modification through lysyl-oxidases
other HIF-1 regulated factors (e.g. PAI-1, TIMP-1, CTGF)
EMT

HIF's role in CKD progression is unclear:
cytoprotective factors
ROS scavenging
NO production
vascular remodeling

Kidney Fibrosis and Disease Progression

Restauration oxygenation
Conclusions:

• BOLD-IRM est un outil intéressant pour l’analyse non-invasive de l’oxygénation rénale, mais standardization et amélioration dans l’analyse des images est nécessaire.

• À l’heure actuelle, il y a une discrétion entre les données chez l’animal et chez l’homme.

• Vu l’arrivée de médicaments stabilisant HIF, plus d’études sont nécessaire afin de comprendre cette discrétion.
Un grand merci

**SKIPOGH team:**
Murielle Bochud
Michel Burnier
Sandrine Estoppey
Marc Maillard
Güler Guk
Sylvie Tremblay
Bélen Ponte
Daniel Ackermann
Idris Guessous
Georg Ehret
Fred Paccaud
PY Martin
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Ute Eisenberger
Philippe Vuistiner
Jan Staessen

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Bruno Vogt
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Matti Piskunowicz
Lucie Hofmann
Hassib Chehade
Valentina Forni
Elise Heuvelin
Julie Charollais
Matthias Stuber
Nicolas Chevrey
Sylvie Tremblay
Carole Zweiacker

**Colaus:**
Peter Vollenweider
Gérard Waebber
Pedro-Marquez Vidal
Yolande Barreau
Julien Vaucher
Signal Intensity

$\text{TE} = \text{echo time}$
Lausanne: Diabetics versus control groups:

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age</th>
<th>BMI</th>
<th>Urinary Sodium (mmol/24h)</th>
<th>Medullary R2*</th>
<th>Cortical R2*</th>
</tr>
</thead>
<tbody>
<tr>
<td>normotensive</td>
<td>10</td>
<td>27±7</td>
<td>23.4</td>
<td>187</td>
<td>30.5±1.7</td>
<td>18.6±1.3</td>
</tr>
<tr>
<td>hypertensive</td>
<td>8</td>
<td>29±6</td>
<td>25.6</td>
<td>158</td>
<td>29.1±1.7</td>
<td>17.6±0.8</td>
</tr>
<tr>
<td>chocolate</td>
<td>9</td>
<td>37±11</td>
<td>21.1</td>
<td>151</td>
<td>29.7±1.3</td>
<td>17.6±1.1</td>
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<tr>
<td>diabetics</td>
<td>11</td>
<td>64±8</td>
<td>35.3</td>
<td>200</td>
<td>28.5±1.3</td>
<td>17.8±1.5</td>
</tr>
</tbody>
</table>