Two non-invasive GFR-estimation methods in rat models of polycystic kidney disease: 3.0 Tesla dynamic contrast-enhanced MRI and optical imaging

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Purpose

Understanding the cystogenesis of polycystic kidney disease and measurement of disease progression is essential for correct diagnosis and establishment of appropriate treatment options in order to avoid end stage renal disease. The intention of our study was to assess kidney morphology and to measure GFR according to disease severity in small animal models of polycystic kidney disease. Translational research on renal insufficient PCK and PKD/Mhm rats, both models of polycystic kidney disease and healthy SD rats was conducted. The performance of two non-invasive GFR estimation methods was analysed: 3.0 Tesla MRI on a clinical scanner and Optical Imaging. Data obtained was compared with hemodynamic parameters of kidney function and histopathological findings of the kidneys in healthy SD rats and PCK and PKD/Mhm rats suffering from polycystic kidney disease.
Methods and Materials

Twenty-three male rats, divided into 3 groups, were studied: 1. Healthy SD rats, 2. PKD/Mhm rats and 3. PCK rats. Animal models 2 and 3 resemble human autosomal dominant polycystic kidney disease. Initially all animals underwent blood sampling for determination of surrogate markers of kidney function. Optical Imaging of glomerular filtration rate was performed transcutaneously in a CRI Maestro small animal imaging system (CRI Corporation, Woburn, MA, USA) with the fluorescent kidney marker fluorescein-isothiocyanate-labelled sinistrin (FITC-S). Morphologic and dynamic renal imaging was carried out on a clinical 3.0T Scanner (Siemens MAGNETOM Trio, Siemens Healthcare Sector, Erlangen, Germany) equipped with a 32 receiver channel using a dedicated 8-element whole-body small animal coil for rats. Renal perfusion analysis was performed with the PMI-software with data fitting to a 2-compartment filtration model. MR-GFR and Optical Imaging GFR values were analysed in all study groups. Kidney weight was recorded and histopathological examination of the kidneys was performed in all animals. Renal medulla and cortex were analyzed microscopically (software Leica QWIN). Cyst-fibrosis ratio was assessed in the PCK and the PKD/Mhm rats according to a 5 point scale.
Results

SD rats demonstrated physiological laboratory parameters of kidney plasma surrogate markers (urea $41.6 \pm 3.1$ mg/dl; creatinine $0.28 \pm 0.07$ mg/dl). Kidney function surrogate parameters were comparably elevated in PCK rats (urea $87.1 \pm 7.7$ mg/dl and creatinine $0.6 \pm 0.1$ mg/dl) and in PKD/Mhm rats (urea $97.7 \pm 6.7$ mg/dl; creatinine $0.6 \pm 0.07$ mg/dl). The T2-w 2D BLADE-TSE sequence with fat saturation proved most sensitive for delineation and demarcation of small cystic changes in the kidneys on MRI. The time resolved 2D SR-Turbo FLASH sequence was well suited for semiquantitative calculation of perfusion and filtration parameters. In all animals histopathological examination of the kidneys was performed. The cyst score did not exceed grade 4 in the PKD/Mhm rats. The PCK rats had cyst scores between grade 4 and 5.

MRT assessed GFR-values and Optical Imaging GFR results showed a tremendous intra-method bias (SD rats Optical Imaging GFR $1.08 \pm 0.13$ ml/min /100g bw vs. MRT-GFR $0.084 \pm 0.019$ ml/min /100g bw; PKD/Mhm rats Optical Imaging GFR $0.67 \pm 0.12$ ml/min /100g bw vs. MRT-GFR $0.033 \pm 0.012$ ml/min /100g bw; PCK rats Optical Imaging GFR $0.66 \pm 0.14$ ml/min /100g bw vs. MRT-GFR $0.01 \pm 0.003$ ml/min /100g bw). Both methods confirmed higher GFR values in the SD rats compared to PKD/Mhm rats. Optical Imaging did show comparable GFR values in PCK and PKD/Mhm rats, as could be expected from the renal surrogate parameters urea and creatinine. In contrast, MRT-GFR demonstrated significantly lower GFR values in the PCK rats compared to the PKD/Mhm rats.
Fig. 0: Most homogenous renal parenchymal delineation was demonstrated in the coronal HASTE (A), BLADE (B) and VIBE post contrast (C) sequence, especially for the SD rats. The T2-w 2D HASTE sequence suffered from blurring artifacts in all animals (A). Renal cortex and medulla of the PKD/Mhm rats was characterized by small cystic lesions in the coronal HASTE (A), BLADE (B) and VIBE post contrast (C) sequence. In one animal, right sided hydronephrosis was diagnosed, best visible on the VIBE sequence post contrast (C). The PCK rats presented with enlarged kidneys and increased renal volume in the coronal HASTE (A), BLADE (B) and VIBE post contrast (C) sequence. Major hepatic and renal cyst formations were best visible in the BLADE sequence (B).
There was limited renal contrast uptake in the VIBE sequence due to advanced kidney function disorder (C).

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**Fig. 0:** Kidney function surrogate markers plasma creatinine (mg/dl) and plasma urea plotted against optical GFR (ml/min/100g bw) (A, C) and MRT GFR (ml/min/100g bw) (B,D). Optical GFR shows comparable GFR and plasma surrogate marker concentrations for PCK and PKD/Mhn rats. In contrast the MR-GFR technique shows lower GFR values for PCK rats compared to PKD-Mhn rats, although plasma surrogate marker
concentrations are comparable in the two animal models. Both methods show highest GFR values and lowest surrogate marker concentrations for the healthy SD rats.

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**Fig. 0:** Homogenous histological appearance of the kidneys in a SD rat. Histologically intact renal cortex and medulla (A), also in the enlarged view of the cortex (B). Very few middle sized cysts in a PKD/Mhm rat with grade 2-3 cyst score in the renal cortex (B). Enlarged polycystic kidneys in a PCK rat with macroscopic irregular surface of the kidneys (A) and cortical polycystic disruption visible on the enlarged longitudinal section (B).
Conclusion

MRT is very valuable for morphologic kidney assessment in animal models of polycystic kidney disease. Nevertheless, the applied PMI analysis for MRT based GFR determination presently seems to be unsuitable for GFR estimation in small animals with polycystic kidney disease. A promising alternative is the transcutaneous GFR assessment with Optical Imaging performed in this study which is also independent of blood and urine sampling. The achieved results with Optical Imaging are in line with the expected results based on plasma surrogate parameters.


