4D CONTRAST ENHANCED MRI OF THE DEVELOPING MOUSE KIDNEY

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Purpose

The kidney's major role in filtration depends on its high blood flow, concentrating and transport systems, and biochemical activation. These essential attributes contribute to a high vulnerability to drug-induced nephrotoxicity [1] and malformation of these functions can lead to renal injuries. MRI can be particularly sensitive in assessing diseases or toxic processes [2-3]. A method to follow the dynamic changes in structure and function is essential for screening toxicity. The normal developmental stage (juvenile to mature adult) will be an important baseline for identifying renal pathologies early. In this study, we acquired high spatiotemporal resolution datasets of the mouse kidney during development. The data were acquired with a cryogenic surface coil and a dynamic contrast enhanced (DCE) MRI sequence, allowing us to obtain a full 3D dataset (125 μm isotropic) every 7.7 sec over a 50-min scan. Structural and functional changes were measured in the three major regions of the kidney over a 17-week course.

Methods

Biological support: Mice (n=5) were imaged longitudinally at 6 points (3, 5, 7, 9, 13, 17 weeks). Animals were under isoflurane anesthesia and breathing freely. Contrast agent (gadofosveset trisodium) was injected as a bolus via tail vein catheter at a dose of 0.03 mmol/kg.

MRI: Imaging was performed with a cryogenic surface coil on a 7T Bruker system. A 3D UTE (center out) radial sequence was used to sample 13 uniform subvolumes of Fourier space (total views=40222, polar undersampling=2, TR=2.5ms, TE=20μs, FA=10°). Images were reconstructed by interleaving and sharing projections from the unique subvolumes using a sliding window approach, a technique known as radial keyhole imaging [4]. This yielded a 3D image (160^3 voxels) every 7.7 sec over 50 min (390 time points) of contrast enhancement and clearance.

Post-processing and analysis: Two image contrasts, including a maximum intensity projection (MIP) and a variance intensity projection (VIP), were used for segmenting three kidney regions—cortex (CO), outer medulla (OM), and inner medulla (IM). Volume of the kidney (KD) was determined by summing the three regions. The DCE dataset was used to produce a functional 3D time-to-peak (TTP) map (time of injection to peak enhancement). Volumes and TTP values in renal regions were measured throughout the development of the mice. Polynomial regression analysis (2^{nd}-order) was performed to determine relationship of structure and function with age [5].

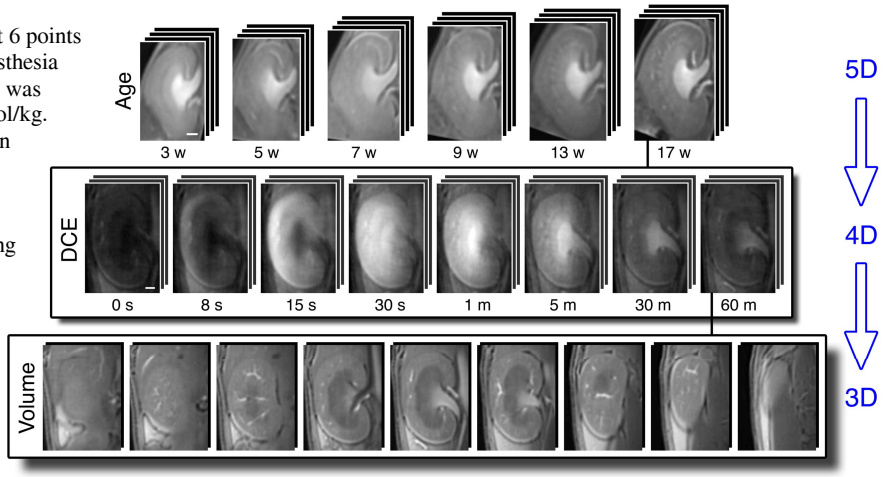

Fig 1. Datasets (5D) were acquired at 6 age points during normal development. Each age dataset is a DCE image (4D) with 390 time points. Each time point is a volume image (3D).

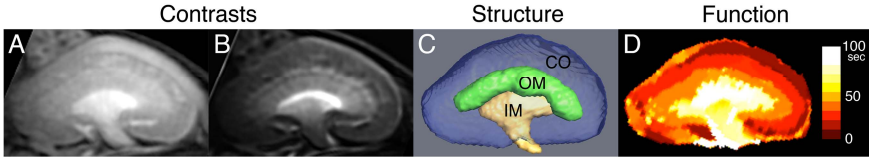

Fig 2. Two image contrasts: (A) MIP and (B) VIP. (C) Segmented renal regions (CO, OM, IM). (D) Functional TTP maps.

Results

Fig. 1 shows the images during development (5D), the DCE at one age (4D), and the volumes at one DCE time point (3D). Fig. 2 shows the two image contrasts (MIP and VIP), the segmented renal structures, and the functional TTP map. Fig. 3 plots the changes of renal region volumes and TTP values with age. Interval bands show one standard deviation from the mean at each age. The renal structure and function depended on the age (x) as follows (2^{nd}-order polynomial): 1) IM volume = $-0.015x^2+0.57x+2.5$, 2) OM volume = $-0.044x^2+1.5x+3.4$, 3) CO volume = $-0.49x^2+14.5x+42.8$, 4) KD volume = $-0.55x^2+16.6x+48.7$, 5) IM TTP = $-0.017x^2+2.5x+73.8$, 6) OM TTP = $-0.061x^2+3.8x+23.0$, and 7) CO TTP = $-0.02x^2+1.5x+8.0$.

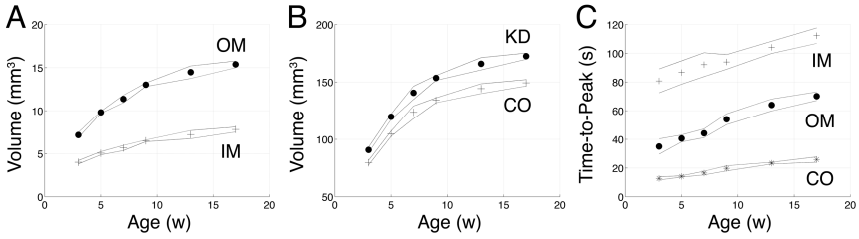

Fig 3. (A-B) Volumes of renal regions (IM, OM, CO, KD=total kidney). (C) TTPs of renal regions.

Discussion and Conclusion

In this study, we found that kidney volumes and TTPs increased monotonically with age, following a 2^{nd}-order polynomial function. The region volume was biggest in the CO and smallest in the IM throughout the development. The rate of growth was also fastest in the CO and slowest in the IM. The peak enhancement time was fastest in the CO and slowest in the IM at all ages. This is expected considering the function of the kidney starting with filtration in the CO and eventual excretion in the IM and renal papilla. The TTP values increased with age in all kidney regions, suggesting a slower enhancement and thus a decline in renal function with age. These structural and functional changes begin to plateau at 17 weeks of age, which can be expected as the mice approach adult maturity. The data acquired here provides a comprehensive assessment of the normal development in the mouse kidney at 6 age points, 390 dynamic time points, and 160×160×160 voxels (~200 GB total). The high spatiotemporal resolution 4D images will be especially important for comparing disease models with heterogeneous abnormalities, such as chronic kidney disease and polycystic kidney disease. These diseases require early detection and intervention before the kidney becomes fully developed and damages become irreversible [6].

References

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