Radiology

Toward Rapid Noninvasive Measurement of Kidney Perfusion

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Perfusion is vital to the health of the kidney. Decreased renal perfusion due to hypovolemia, surgery, sepsis, or cardiac failure can lead to ischemic acute kidney injury (1). Chronic kidney disease (CKD) is the final common pathway of many renal disorders, including chronically reduced perfusion caused by renal artery stenosis (2). Patients with CKD have decreased kidney perfusion compared with healthy individuals (3). Ischemia is closely related to renal perfusion and implicated as a factor in the progression of CKD (4). Perfusion is also crucial for the health of transplanted kidneys and may help differentiate between acute rejection, in which perfusion is decreased, and acute tubular necrosis, in which perfusion is preserved but renal excretion is impaired (5).

Because of the importance of renal perfusion, numerous methods of perfusion estimation have been developed. Invasive whole-kidney methods include the placement of catheters in the renal artery or vein to measure flow by means of thermodilution or intravascular Doppler US. Para-aminohippurate injected intravenously is completely filtered by the kidneys, and its concentration in urine is a measure of renal perfusion. However, urine para-aminohippurate measurement is of limited usefulness in patients with oliguria or anuria. Nuclear medicine renal scans allow semiquantitative assessment of perfusion during tracer wash-in. Dynamic CT perfusion measurement is also possible but involves considerable radiation dose because of the necessary repeated scanning of the same tissue (6). Multiple methods of perfusion estimation have been developed with MRI, including phase-contrast imaging of the renal artery to quantify total renal blood flow, analysis of enhancement kinetics with intravenous administration of gadolinium-containing contrast agents, arterial spin labeling, and intravoxel incoherent motion (7). These methods are promising but complex, involving long scanning times and expensive equipment.

Because of its portability and low cost, US offers the potential for real-time bedside renal perfusion assessment. Contrast material–enhanced US signal has been shown to correlate with renal perfusion measured with other methods, although quantification of perfusion is not straightforward (8).

In this issue of *Radiology*, Welsh et al (9) have approached the problem of renal perfusion measurement with a quantitative noncontrast US method known as fractional moving blood volume (FMBV). This method relies on the power Doppler US signal to estimate the fraction of each image voxel that is occupied by moving blood. In a voxel completely contained within a blood vessel, 100% of the volume is occupied by moving blood and the power Doppler signal has its maximum value. A voxel containing no moving blood gives no power Doppler signal. Voxels containing some fraction of moving blood will give Doppler signal proportional to the volume of moving blood. With this method, a pixel-by-pixel estimate of moving blood volume fraction is generated, presumably representing the perfusion in the corresponding tissue voxel.

There are a number of factors that complicate the measurement of FMBV. The strength of the power Doppler signal depends on the attenuation of the ultrasound beam, which depends on depth from the transducer and the structure of tissues through which the sound beam has passed. The FMBV method corrects for variation of the power Doppler signal with depth and image location by identifying large blood vessels within the image. Each large blood vessel provides a reference power Doppler intensity for 100% moving blood, which can be used to calibrate the signal from voxels in the immediate neighborhood. If no large blood vessels can be identified in a region of the image, this local calibration of power Doppler signal is not possible and estimates of FMBV in this region will be less accurate, based only on tissue depth. Blood in the center of large vessels tends to form rouleaux (stacks or clumps of red blood cells), which are more echogenic than individual red blood cells. This effect must also be compensated for by a heuristic correction based on the power spectrum of the Doppler signal (10).

To evaluate a method of perfusion measurement, a reference standard is needed. Microsphere injection is thought to be an accurate method of perfusion measurement.

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See also the article by Welsh et al in this issue.

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Microspheres are tiny plastic beads just large enough to lodge in capillary beds. A known quantity of microspheres is injected into the arterial system, typically into the left atrium or ventricle. The spheres lodge in capillary beds, where they remain indefinitely. The number of microspheres lodged in a volume of tissue corresponds to the perfusion of that tissue at the time the spheres were injected. An arterial blood draw just after injection of microspheres is used to relate the number of spheres to the blood volume. The test animal is eventually sacrificed. The tissue of interest is excised and analyzed to determine the number of spheres present in a given volume of tissue. Spheres of various color can be injected at various time points and independently measured to give perfusion estimates at multiple time points within the same animal. Although microsphere analysis is considered a reference standard for perfusion, several factors can influence its accuracy—including imperfect mixing of blood in the heart and aorta and variation in the timing or technique of arterial sampling. In the kidney, medullary blood flow is downstream from the capillary glomeruli in the renal cortex, so microspheres lodge mostly in the renal cortex, resulting in artificially low estimates of medullary perfusion.

Welsh et al studied nine pigs with both US FMBV measurement and microsphere injection. Surgery was performed on one kidney to create a renal artery stenosis. The perfusion of the surgically altered kidney was measured at four time points with varying degrees of induced stenosis corresponding to approximately 100%, 75%, 50%, and 25% renal blood flow. At each level of stenosis, perfusion was measured with FMBV derived from three-dimensional power Doppler imaging with two US machines from different vendors. To eliminate experimental variation as much as possible, the US probes were mounted in a fixed external framework. Microspheres of different colors were injected before and after each FMBV measurement. A total of eight injections of different color microspheres was performed, two for each of the four levels of renal artery stenosis. A US flow probe was also placed around the stenosed renal artery as an additional measure of renal blood flow, with measurements obtained before and after each FMBV measurement.

FMBV measurements from the two US systems showed excellent agreement. Measurement of FMBV correlated strongly with perfusion measured with microspheres, with r^2 values of 0.79 and 0.74 for the two vendors' systems. These results suggest that FMBV may be a useful method for the measurement of kidney perfusion. However, some caution is appropriate when interpreting these results. Two microsphere measurements of perfusion were performed at each level of arterial stenosis in each pig, before and after measurement of FMBV. Welsh et al reported a strong correlation between these two measurements, with $r^2 = 0.72$. This suggests good reproducibility of the microsphere measurements. However, this correlation is based on a linear regression with a slope of 0.81 and *y*-intercept of 0.483 mL/min/100 g. Because each pair of measurements should give the same value, the correct linear regression model would have a slope of 1.0 and a zero *y*-intercept. Analysis of the microsphere data with this model will yield a coefficient of determination worse than the reported r^2 of 0.72. In contrast, the two measurements of flow with the Doppler probe around the renal artery before and after FMBV resulted in an r^2 value of 0.91. Given the variability of the repeated microsphere results, one can reasonably question whether microspheres are a reproducible and appropriate reference standard for evaluating perfusion measurement methods. In addition, the crucial aspect of calibration of power Doppler for the FMBV method relies heavily on depth from the transducer. This may work well in pigs, where the kidneys are accessible through a relatively short sound path through the abdomen with a ventral or lateral approach. However, the kidneys in humans are typically deeper in the body, with more variable intervening soft tissue. Therefore, calibration of the power Doppler signal levels in human kidneys may be more difficult than in pig kidneys.

Notwithstanding these concerns, the work of Welsh et al supports the plausibility of the FMBV method as a means of measuring renal perfusion and may motivate additional investigation. Future work may confirm the results of this study and further develop the FMBV technique to translate this noninvasive and rapid method of renal perfusion measurement to clinical application.

Disclosures of Conflicts of Interest: disclosed no relevant relationships.

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