Prediction and assessment of responses to renal artery revascularization with dynamic contrast-enhanced magnetic resonance imaging: a pilot study

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Lim SW, Chrysochou C, Buckley DL, Kalra PA, Sourbron SP. Prediction and assessment of responses to renal artery revascularization with dynamic contrast-enhanced magnetic resonance imaging: a pilot study. Am J Physiol Renal Physiol 305: F672–F678, 2013. First published June 26, 2013; doi:10.1152/ajprenal.00007.2013.—The aim of this study was to assess the potential of dynamic contrast-enhanced (DCE) MRI to predict and evaluate functional outcomes after renal artery revascularization for renal artery stenosis (RAS). The single-kidney glomerular filtration rate (SK-GFR) was measured in 15 patients with atherosclerotic RAS with DCE-MRI and radioisotopes at baseline and 4 mo after revascularization. DCE-MRI also produced measurements of blood flow, blood volume, extraction fraction, tubular transit time, and functional volume. Stented kidneys (n = 22) were divided into three response groups on the basis of the changes in radioisotope SK-GFR: improved (n = 5), stable (n = 13), and deteriorated (n = 4). A good agreement was found between SK-GFR values from DCE-MRI and radioisotopes (correlation coefficient: 0.91). Before intervention, kidneys that improved had lower extraction fraction, higher blood volume, longer tubular transit time, and lower SK-GFR. After intervention, improved kidneys had increased functional volume, and deteriorated kidneys had reduced functional volume and extraction fraction. Revascularization improved blood flow and blood volume in all groups. This pilot study led to the hypothesis that well-vascularized kidneys with reduced extraction fractions are most likely to benefit from revascularization. More generally, DCE-MRI has the potential to replace radioisotope measurement of SK-GFR and may improve patient management by providing additional information on tissue perfusion.

dynamic contrast-enhanced magnetic resonance imaging; glomerular filtration rate; perfusion; renal artery stenosis; revascularization

ATHEROSCLEROTIC RENOVASCULAR DISEASE (ARVD) is a progressive condition that affects the normal function of kidneys due to inadequate blood supply and downstream damage caused by cytokine release and hypertension (36). ARVD accounts for 90% of renal artery stenosis (RAS) in the Western population, and the aging community possesses a higher risk of developing the condition (7, 9). Patients may be asymptomatic depending on the degree of renal dysfunction, as a partially or normally functioning contralateral kidney may compensate for the affected kidney (18). ARVD is associated with hypertension, which may eventually lead to chronic and end-stage renal disease (6). The priority of ARVD management is to prevent further renal impairment. This can be done by conventional blood pressure control with medical therapy or by renal revascularization with angioplasty and stenting (7).

The results of a recent Angioplasty and Stenting for Renal Artery Lesions trial (35) do not support the broad application of renal revascularization in atherosclerotic RAS, and selection of patients for this procedure remains controversial (32). This is due to the associated risks and complications of the procedure and the fact that only a minority of patients derive net renal benefit (2, 32). This highlights a need for identifying the patients that are likely to benefit (6), but current prognostic indexes are insufficient to characterize RAS severity and identify intrarenal parenchymal injury (36). The degree of stenosis in particular is a poor measure of outcome, as it bears no relation to the severity of intrarenal injury and the resulting renal impairment (18, 30). There is a need for indexes that characterize the extent of irreversible renal parenchymal damage, which may be a major factor in these heterogeneous outcomes (7).

A promising technique in this respect is dynamic contrast-enhanced (DCE) MRI, which enables measurements of the single-kidney glomerular filtration rate (SK-GFR) as well as tissue perfusion and vascularity (3, 4, 11, 12, 17, 20, 21, 23). DCE-MRI has long been proposed as an alternative to radioisotope techniques for SK-GFR measurements (13, 26), which are cumbersome, time consuming, and underused in clinical practice. DCE-MRI leads to SK-GFR measurements that agree well with the gold standard (4, 34) and offers a more complete assessment of renal pathophysiology through the additional information on perfusion (16, 28). This may be particularly relevant in the context of revascularization for RAS. SK-GFR is a measure of the functional status, but perfusion parameters characterize the state of the microvasculature and may therefore reflect the extent of irreversible parenchymal damage more directly. A recent preclinical study (5) has suggested that the blood volume fraction is a potential outcome predictor, as preserving the integrity of the microvasculature is an important factor in increasing the probability of successful reperfusion.

The aims of this study were to assess the potential of DCE-MRI in the prediction and assessment of responses to revascularization in patients with atherosclerotic RAS and to generate working hypotheses to guide the setup of larger prospective studies. Radioisotope measurements of SK-GFR were used as independent gold standards to determine the response.

METHODS

Subject selection. This study was approved by the local Research Ethics Committee. Patients referred to the Renal Department of Salford Royal Hospital between 2007 and January 2010 for ARVD and who were deemed to be suitable for renal revascularization on clinical grounds were approached to participate in this study. Written informed consent was obtained from 45 patients before their partici-
pation in this research study. Of these patients, 30 patients had ARVD with significant RAS and were treated by percutaneous transluminal renal angioplasty with stenting. The inclusion criteria were >60% RAS based on magnetic resonance angiography and one or more of the following: poorly controlled hypertension, advanced renal dysfunction, deteriorating renal function, or flash pulmonary edema. The 15 excluded patients had signs possibly suggestive of ARVD, such as vascular bruits or discrepant kidney sizes, but no evident RAS detectable on magnetic resonance angiography. Due to the increasing awareness of the risk of developing nephrogenic systemic fibrosis caused by gadolinium exposure, extraprecautionary steps were introduced to exclude gadolinium use in 12 patients with an estimated GFR of <30 ml/min. In addition, one patient was excluded from MRI due to a leaking heart valve, a relative contraindication to MRI. Two other patients were removed from the analysis: one patient died before the second scan and one patient was removed because DCE-MRI data acquisition was interrupted. This left 15 ARVD patients who received both DCE-MRI and radioisotope SK-GFR assessment at baseline and 4 mo after the procedure. Twenty-two of the thirty kidneys were stented, as seven patients had bilateral revascularization and eight patients had unilateral revascularization.

Radioisotope SK-GFR. Radioisotope measurement of SK-GFR was performed with standard nuclear medicine techniques (24, 26, 27). The global GFR was first measured with 51Cr-EDTA clearance, and patients then underwent 99mTc-dimercaptosuccinic acid (DMSA) scintigraphy to assess the differential static radioisotope uptake of each kidney. The individual kidney function was calculated by dividing the global GFR according to the percentage of the uptake of 99mTc-DMSA on scintigraphy.

The daily variation in radioisotope SK-GFR has been shown to be 8.8% (26). A clinically relevant change in individual renal function was therefore defined as a >15% and >1 ml/min increase or decrease of radioisotope SK-GFR at 4 mo postrevascularization compared with baseline. The absolute cutoff of 1 ml/min was imposed to account for small, low-GFR kidneys, which may experience a large increase in percent change that does not correspond to a large change in absolute value (in ml/min). After revascularization, kidneys were initially classified as having improved, remained stable, or deteriorated based on the following thresholds:

- Improved (radioisotope SK-GFR increased by at least 1 ml/min and by >15%)
- Deteriorated (radioisotope SK-GFR decreased by at least 1 ml/min and by >15%)
- Stable (changes between the above two definitions)

**DCE-MRI measurement.** MR examinations were performed using a 3.0-T MR whole body scanner (Philips Achieva, Philips Medical Systems) and a phased-array body coil for signal reception. DCE-MRI was acquired with a three-dimensional spoiled gradient echo sequence with the following parameters: repetition time = 5.0 ms, echo time = 0.9 ms, field of view = 400 x 400 x 100 mm, flip angle = 17°, parallel acquisition using a SENSE factor = 2, approximate acquisition matrix = 128 x 84 x 10, and reconstructed matrix after zero-filling = 128 x 128 x 20. This resulted in a temporal resolution of 2.1 s/volume. After the acquisition of scout images (sagittal, coronal, and axial planes), a three-dimensional renal imaging volume was acquired using a T1-weighted spoiled gradient echo acquisition in the oblique coronal plane. The volume encompassed both kidneys and the descending aorta, which were obtained in a single breathhold. For DCE images, a quarter dose of 0.025 mmol/kg Gd-tetraazacyclododecanetetraacetic acid (Dotarem, Guerbet, France) was injected at a rate of 3 ml/s. To allow for the acquisition of nonenhanced baseline images, the sequence and injection of contrast agent were initiated simultaneously. Patients were advised to breathe normally throughout the DCE acquisition.

**DCE-MRI postprocessing.** Postprocessing was performed offline on exported DICOM images with PMI 0.4 software (Platform for Research in Medical Imaging) written in IDL 6.3 (1, 28). Analysis was performed by one of the authors (S. W. Lim), who was blinded to the radioisotope values, patient information, the time point of the acquisition (pre- or postprocedure), or the treatment status of the kidney (stented or not).

A narrow rectangular region of interest (ROI) was first drawn within the aorta on the coronal slice of a dynamic series to extract an arterial input function. To minimize infow effects and bolus dispersion, the arterial ROI was chosen just below the point where the renal arteries branch off. Pixel-by-pixel deconvolution analysis was performed to generate maps of blood flow and volume of distribution (11). A whole kidney parenchymal ROI was segmented semiautomatically by setting a threshold on the volume of distribution map and manually excluding the extrarenal pixels. Concentration-time curves for the kidney and aorta were approximated by subtracting the precontrast signal from the dynamic signal. The concentration-time curves of the selected ROIs were fitted with a two-region filtration model, which models the capillary bed as a well-mixed compartment and the tubular space as a plug-flow region (28, 29).

This procedure produced four independent parameters for each kidney: blood flow (in ml/min x 100 ml⁻¹), blood volume (in ml/min x 100 ml⁻¹), extraction fraction (in %), and tubular mean transit time (in min). A DCE-MRI measurement of SK-GFR was derived as the product of the parenchymal ROI volume, extraction fraction, blood flow, and (1 – hematocrit) (28).

**DCE-MRI parameters.** Blood flow measures the amount of blood (in ml) delivered to the kidney per minute and per 100 ml kidney tissue. In most organs, it is interpreted as a direct index of tissue perfusion, but in the kidney, most of the blood flow supports filtration. Blood volume measures the amount of blood (in ml) in 100 ml kidney tissue and is therefore a direct index of the tissue’s vascularity. Extraction fraction measures how much of the blood plasma delivered to the tissue is filtered out by the glomeruli (in %). It can therefore be seen as a measure of the “efficiency” of the glomeruli in filtering the blood and, together with blood flow and kidney size, determines the GFR. The effect of a reduction in blood flow (e.g., by the effect of a stenosis) on the kidney’s GFR can be compensated by an increase in extraction fraction. Conversely, improving blood flow by intervention does not necessarily lead to an improvement in GFR, as other mechanisms may downregulate the extraction fraction. Tubular mean transit time measures how long it takes for a contrast agent molecule to pass through the tubular system, i.e., the average time between being filtered out by the glomeruli and leaving the kidney through the collecting system. This parameter has rarely been evaluated but may present an index of the kidneys’ concentrating capacity and/or may indicate the presence of downstream tubular or ureteral defects.

A fifth independent parameter is the volume of the parenchymal ROI created as defined above in DCE-MRI postprocessing. Effectively, this procedure selects all renal voxels with a mean contrast enhancement significantly larger than the noise in the data. Renal voxels that do not take up the contrast agent by perfusion and/or filtration will not be counted as part of the parenchymal ROI. Hence, its volume may be different from the “anatomic” or “morphological” volume as outlined on standard T1- or T2-weighted MRI sequences. To avoid any confusion with such conventional methods of measuring renal volume, we refer to the volume of the parenchymal ROI defined in this study as “functional volume” (in ml).

**Statistical analysis.** To avoid possible confusion, the gold-standard SK-GFR value derived from the radioisotope measurement is consistently referred to as “radioisotope SK-GFR” and the DCE-MRI parameter as “SK-GFR.” All statistical analyses were performed in Excel (Excel 2007, Microsoft). Sixty estimates of SK-GFR were validated against radioisotope SK-GFR by linear regression analysis and a paired Student’s t-test. To evaluate the predictive power of MR parameters, unpaired Student’s t-tests were used to compare the differences in pretherapy values between the three response groups (improved vs. stable, stable vs. deteriorated, and deteriorated vs.
RESULTS

Validation. The difference between SK-GFR and radioisotope SK-GFR was not significant (Fig. 1). Linear regression analysis gave a slope of 0.96 with an intercept of 0.15 ml/min and a correlation coefficient ($R$) of 0.91. Bland-Altman analysis showed a mean difference of $-0.7$ ml/min with a 95% confidence interval of $(-12$ and $+11$ ml/min).

Response prediction. Table 1 shows preprocedure DCE-MRI parameters in stented kidneys in each response group, and Figure 2 shows the differences between the groups graphically. Kidneys that improved after the intervention had a significantly lower functional volume, longer tubular transit time, and lower SK-GFR compared with those that remained stable. None of the other differences were significant, but the changes under therapy of SK-GFR showed the same trends as the deteriorated group in blood flow, blood volume, and extraction fraction, but opposite trends in tubular transit time, SK-GFR, and functional volume.

Contralateral kidneys. Table 3 shows pre- and postprocedure values in the eight unstented kidneys; seven kidneys remained stable and one kidney deteriorated. None of the DCE-MRI parameters showed a significant change in those that remained stable. The changes under therapy of SK-GFR values of the single deteriorated kidney did not follow the changes seen in radioisotope SK-GFR. The pretherapy extraction fraction of the unstented kidneys ($10 \pm 2.8\%$) was significantly higher than their stented contralateral kidneys ($7.4 \pm 3.4\%$).

DISCUSSION

Validation. Agreement and correlation between SK-GFR values derived from MRI and isotopes were stronger than in a previous study (17) despite the use of a significantly simpler analysis model: we used a four-parameter, two-compartment model applied to a single whole parenchyma concentration-time curve (28) compared with a six-parameter, three-compartment model that requires prior segmentation of the cortex and medulla (17). The number of kidneys evaluated was larger than in those previous studies, and a wide range of SK-GFR values from very low to normal were included in the population. Hence, the agreement between the SK-GFR values provides strong evidence that DCE-MRI with this approach has the potential to replace radioisotope methods.

There is room to improve the correlation further as the analysis in this study was performed without a correction for breathing motion. Since these data were acquired under free breathing, it is likely that the scatter in the results can be reduced by adding motion correction to the analysis. Regular breathing motion appears as oscillations or structured noise on the kidney time curves. This noise has a zero mean, so it does not cause a net shift in the curves, and one would therefore not

**Table 1. Response predictions**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Deteriorated Kidneys</th>
<th>Stable Kidneys</th>
<th>Improved Kidneys</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of kidneys/group ($n = 22$ total stented kidneys)</td>
<td>4</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Preprocedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood flow, ml·min$^{-1}$·100 ml$^{-1}$</td>
<td>$219 \pm 62$</td>
<td>$208 \pm 101$</td>
<td>$209 \pm 122$</td>
</tr>
<tr>
<td>Blood volume, ml/100 ml</td>
<td>$35 \pm 4.2$</td>
<td>$39 \pm 9.8$</td>
<td>$44 \pm 8.8$</td>
</tr>
<tr>
<td>Extraction fraction, %</td>
<td>$9.5 \pm 4.3$</td>
<td>$9.5 \pm 3.5^*$</td>
<td>$6.1 \pm 2.7$</td>
</tr>
<tr>
<td>Tubular MTT, min</td>
<td>$2.3 \pm 0.8$</td>
<td>$2.8 \pm 0.6$</td>
<td>$3.9 \pm 1.5$</td>
</tr>
<tr>
<td>Functional volume, ml</td>
<td>$174 \pm 51$</td>
<td>$178 \pm 70$</td>
<td>$143 \pm 57$</td>
</tr>
<tr>
<td>SK-GFR, ml/min</td>
<td>$22 \pm 15$</td>
<td>$19 \pm 14$</td>
<td>$11 \pm 8.3$</td>
</tr>
<tr>
<td>Radioisotope SK-GFR, ml/min</td>
<td>$24 \pm 17$</td>
<td>$22 \pm 13$</td>
<td>$12 \pm 8.9$</td>
</tr>
</tbody>
</table>

Values are means ± SD for the preprocedure parameters in stented kidneys for each response group. MTT, mean transit time; SK-GFR, single-kidney glomerular filtration rate. *Statistically significant difference compared with the improved group.
expect it to affect the mean SK-GFR values in a significant way. Indeed, the mean difference with the gold standard (0.7 ml/min) was so small that there is little room for improvement. However, noise in the data will cause noise in the results, so the breathing-induced noise is most likely a main contributor to the scatter of the points around the mean of 0.7 ml/min. Removing or minimizing it may thus allow for a further reduction in the 95% confidence interval of (11002 11001 12 and 11001 11 ml/min). This can be done at the acquisition level by sequence optimization and/or at the postprocessing level by including registration methods.

A possible limitation for a wider use of DCE-MRI is the risk of nephrogenic systemic fibrosis (NSF) (14). Current insights, however, suggest that the risk is close to 0% when stable macrocyclic agents are used (33). Studies have shown that these are safe in patients with stage 4 chronic kidney disease (8) and that patients with early-stage chronic kidney disease have a negligible risk for developing NSF (19). Hence, despite the recognized risk of NSF, there remains a rationale for contrast-enhanced MRI in clinical practice. Moreover, in contrast to renal scintigraphy, DCE-MRI does not involve ionizing radiation and, therefore, may enable a more regular followup.

Response prediction. The strongest trend in the pretherapy values was that kidneys with lower extraction fractions are more likely to benefit from the intervention. This is a new observation, as extraction fraction is the ratio of filtration rate to blood flow and therefore can only be determined by methods that are able to measure both.

The observed trend in pretherapy SK-GFR contradicts the hypothesis that severely reduced SK-GFR indicates irreversible damage and, therefore, a poor response. The data showed that the lower SK-GFR in good responders is not due to a reduced blood flow, as might be suggested by a simplistic “hydraulic” theory. Instead, the reduced extraction fraction in this group suggests the presence of neurohormonal effects or protective mechanisms attempting to prevent further downstream damage, rather than a true underlying parenchymal injury. A study conducted by Ramos et al. (25) also showed a similar predictive value of baseline GFR. They observed significant GFR improvement in patients with severe RAS and renal function impairment, demonstrating that the optimal beneficial effects on renal function may be anticipated in patients with low baseline renal function.

The trends in blood volume agree with a recent preclinical study (5) that has shown that preservation of the renal microvascular architecture in a stenotic kidney improves the renal response to angioplasty. If the microvasculature is damaged, it is unlikely that parenchymal damage can be reversed by revascularization. A small blood volume indicates that the number of functioning blood vessels is reduced. The blood volume may therefore be a better measure of the hemodynamic significance of a stenosis than the degree of stenosis, as the

<table>
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<th>Deteriorated Kidneys</th>
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<th>Improved Kidneys</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of kidneys/group (n = 22 total stented kidneys)</td>
<td>4</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Blood flow, ml-min⁻¹, 100 ml⁻¹</td>
<td>226 ± 42</td>
<td>224 ± 109</td>
<td>285 ± 115</td>
</tr>
<tr>
<td>Blood volume, ml/100 ml</td>
<td>55 ± 6.8*</td>
<td>41 ± 6.3</td>
<td>56 ± 17</td>
</tr>
<tr>
<td>Extraction fraction, %</td>
<td>7.1 ± 4.4*</td>
<td>9.0 ± 1.6</td>
<td>5.5 ± 2.4</td>
</tr>
<tr>
<td>Tubular MTT, min</td>
<td>2.7 ± 0.8*</td>
<td>2.8 ± 0.5</td>
<td>2.8 ± 0.5</td>
</tr>
<tr>
<td>Functional volume, ml</td>
<td>160 ± 52*</td>
<td>179 ± 82</td>
<td>194 ± 48*</td>
</tr>
<tr>
<td>SK-GFR, ml/min</td>
<td>18 ± 16</td>
<td>20 ± 14</td>
<td>15 ± 6.2</td>
</tr>
<tr>
<td>Radioisotope SK-GFR, ml/min</td>
<td>18 ± 13</td>
<td>21 ± 13</td>
<td>17 ± 12</td>
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Values are means ± SD for the postprocedure parameters in stented kidneys for each response group. *Statistically significant difference compared with preprocedure values.

Fig. 2. Trends in the pretherapy values of all independent parameters (A–E) and both SK-GFR measurements (F and G). A–G show means ± SE for the following three response groups: deteriorated (○), stable (●), and improved (○). MTT, mean transit time.
latter often bears no relation to the severity of intrarenal injury and the resulting renal impairment (6, 7, 30). This hypothesis is in agreement with clinical comparisons in MR angiography, which have suggested that perfusion parameters reflect hemodynamic significance of RAS more directly (1).

Tubular transit time is a parameter that has not been considered in this context, but the results suggest that it may have predictive power. On average, contrast agent passage through the tubular system is 1.7 times slower in the kidneys that improved (3.9 min) compared with those that deteriorated (2.3 min). The data suggest a downstream, nonvascular effect of RAS as it slowed down the transit of the contrast agent through the tubular system. A possible hypothesis is that tubular transit time is positively correlated with the kidney’s concentrating capacity.

Response assessment. The majority of kidneys (59%) remained stable after revascularization and showed no changes in any of the parameters (Table 2 and Fig. 3). Those that deteriorated did so by very little (∼4 ml/min on average) and were indistinguishable from the stable group on the basis of their pretherapy values. In this group, the procedure did have the effect of significantly increasing blood volume, but this did not lead to an improvement in any of the functional parameters, and small but significant reductions in functional volume and extraction fraction were detected. On the other hand, due to the absence of a control group, it is not clear how they would have progressed had they not been stented. Hypothetically, the increase in blood volume might indicate that the intervention had a protective effect on the microvasculature.

The kidneys that improved did so with an equally small amount (∼4 ml/min on average), and even after therapy, the SK-GFR of this group remained lower than in the other groups. The extraction fraction remained the same, and compared with the other groups, was equally low as before stenting. These observations support the idea that revascularization has reactivated hibernating parenchyma that previously did not contribute to overall function. Under normal conditions, only ∼10% of the blood flow to the kidney is needed to meet the basal metabolic demands (32). Therefore, kidneys are less susceptible to RAS changes in the absence of other preexisting factors.

### Table 3. Contralateral kidneys

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Deteriorated Kidneys</th>
<th>Stable Kidneys</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preprocedure</td>
<td>Postprocedure</td>
</tr>
<tr>
<td>No. of kidneys/group (n = 8 total unstented kidneys)</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Blood flow, ml·min⁻¹·100 ml⁻¹</td>
<td>204</td>
<td>395</td>
</tr>
<tr>
<td>Blood volume, ml/100 ml</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>Extraction fraction, %</td>
<td>5.9</td>
<td>5.4</td>
</tr>
<tr>
<td>Tubular MTT, min</td>
<td>4.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Functional volume, ml</td>
<td>256</td>
<td>258</td>
</tr>
<tr>
<td>SK-GFR, ml/min</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Radioisotope SK-GFR, ml/min</td>
<td>21</td>
<td>21</td>
</tr>
</tbody>
</table>

Values are means ± SD for pre- and postprocedure parameters in the unstented kidneys for the three response groups. None of the differences between pre- and postprocedure values were significant.
renal disease (31). However, a significant and sustained reduction of perfusion in the presence of RAS can lead to the loss of functional parenchyma. Results from previous studies (6, 7) have led to the hypothesis that kidneys with functional improvement represent a subgroup whose renal dysfunction is a result of hemodynamic effect on the hibernating ischemic tissue. Hibernating parenchyma is defined as tissue that is not contributing to the overall SK-GFR due to a reduced delivery of blood but has not yet suffered the sustained reduction in perfusion that would cause irreversible parenchymal changes. Restoring flow in those tissues improves SK-GFR, without requiring an increased extraction fraction (6, 7).

At present, there are no robust techniques for evaluating hibernating parenchyma in clinical practice. A promising experimental approach involves the assessment of the volume-to-GFR ratio of an individual RAS kidney (6). Assessment of deoxygenated blood within the kidneys by blood oxygen level-dependent MR imaging with R2*, and considering this in relation to GFR, may also have the potential to demonstrate kidneys whose blood flow might improve after revascularization (10).

**Contralateral kidneys.** The majority of unstented kidneys remained stable (7 of 8 kidneys, or 87%). In this group, none of the functional parameters showed any change after the intervention, suggesting that the function of most kidneys without a significant stenosis is not affected by stenting of the contralateral kidney. The key distinguishing factor between the unstented kidneys and their stented contralaterals is the increased extraction fraction, which offers separate evidence that this is a key prognostic indicator.

In the unstented kidney that deteriorated, MR values were in contradiction to the radioisotope SK-GFR. Inspection of the DCE-MRI images for this case revealed that they were strongly affected by breathing motion, and the posttreatment case was one of the outliers in the Bland-Altman plot (Fig. 1). This case shows the importance of correcting for breathing motion in the DCE-MRI data, if this method is to fully replace current gold standards (22).

**Study limitations.** This pilot study aimed to generate hypotheses for future work rather than provide definitive evidence. The number of kidneys studied was low, specifically in the groups that deteriorated or improved. The significance levels were correspondingly weak, and some effects that appear systematic on a visual inspection did not reach statistical significance. Apart from the sample size, a major factor is that the effect of therapy on function was very small. This is evidenced by the fact that the changes of radioisotope SK-GFR under therapy, which are used as a basis for classification and are therefore biased, did not reach significance. Future studies should include more kidneys that show a greater improvement in function.

No control group was available of matched patients with RAS who received no revascularization. Such data would be useful in providing information regarding the natural disease progression, specifically in defining in more absolute terms what constitutes a deterioration or improvement. Moreover, the response was only assessed at one fixed time point after intervention (4 mo). Little is known about temporal changes in the response, but it is possible that some patients would have been classified differently if responses had been assessed at a different time. A bias in the results also exists because patients with more severely reduced renal function were not included in this study due to the risk of NSF.

A validation of the vascular parameters of blood flow and volume was not performed in this study as in vivo gold standards are not readily available in clinical practice. A comparison with typical literature values is also problematic as the population is highly heterogeneous and these parameters are most likely abnormal. However, it seems safe to conclude that the blood volume values are unrealistically high. A possible reason is the contribution of the interstitial space (15). The indicator exchange between the blood pool and interstitium is so rapid that these spaces behave as one well-mixed space and thus cannot be separated in a reliable manner. Experimentally, this was demonstrated by the observation that a two-compartment model, where one compartment represents the tubuli, describes the data very well (28). In effect, this implies that the parameter currently interpreted as blood volume actually represents blood and interstitial volume together. That explains why its magnitude is larger than that expected for blood alone and may also explain why the predictive value of this parameter was less apparent than expected. Any increase in microvascular volume may be partly masked by a corresponding reduction in the interstitial space, and vice versa. A possible resolution is the use of a three-compartment model (15), but in view of the rapid exchange rates, this may require a corresponding improvement in data quality to reveal this additional fine structure. Alternatively, one may consider the use of intravascular or slowly extravasating agents, but that may not allow a measurement of GFR in the same acquisition (37).

A second potential source of overestimation in the vascular parameters is the use of a simple baseline subtraction to estimate concentrations. This assumes a linear dependence of signal on concentration, but it is well known that this relation is nonlinear in MRI, particularly at higher concentrations. In this study, we injected a relatively small dose of contrast agent (quarter of a standard dose), so that the effect is much smaller than in typical DCE-MRI studies. The good agreement with the isotope GFR values provides some retrospective evidence for this. The effects on the vascular parameters may be larger as they are more sensitive to errors in the peak arterial concentration (28). Indeed, the blood flow values are in the normal range for healthy kidneys, which is unexpected in the presence of a stenosis. The error is to a large extent systematic and therefore may preserve differences between patients and time points. Nevertheless, it is likely that the uncertainty in the vascular parameters can be reduced by a more accurate nonlinear signal analysis, but this requires additional quantitative imaging for calibration purposes (B1, T1).

**Conclusions.** In providing additional information on the state of the microvasculature, DCE-MRI may improve the prediction and assessment of outcome of revascularization in patients with RAS. Provided that the risk of NSF can be minimized, DCE-MRI has the potential to be a one-stop diagnostic and prognostic tool and replace radioisotope measurements of SK-GFR in this context.

The specific working hypotheses suggested by this study are as follows. First, kidneys with increased blood volume fraction and reduced extraction fraction are most likely to benefit from revascularization. We thus postulate that these two parameters are markers of hibernating parenchyma. Finally, successful therapy leads to improvements in SK-GFR through an increase in perfusion rather than extraction efficiency and by reactivation of hibernating parenchyma.
ACKNOWLEDGMENTS
The results presented in this report have not been previously published in whole or part, except in abstract format.

GRANTS
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DISCLOSURES
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AUTHOR CONTRIBUTIONS

REFERENCES