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Magnetic Resonance Imaging in Atherosclerotic Renal Artery Stenosis: The Update and Future Directions from Interventional Perspective

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Keywords

Atherosclerosis · Renal artery stenosis · Endovascular treatment · Magnetic resonance imaging

Abstract

Background: Atherosclerotic renal artery stenosis (ARAS) is a condition where the renal arteries become narrowed due to atherosclerosis, leading to reduced blood flow to the kidneys and various renal complications. The effectiveness of interventional treatments, such as renal artery angioplasty and stenting, remains debated, making patient selection for these procedures challenging. ***Summary:*** This review focuses on the diagnosis and management of ARAS, with a particular emphasis on the potential role of functional magnetic resonance imaging (MRI) in evaluating renal function and mechanisms. By summarizing current diagnostic approaches and outcomes of interventional treatments, the review highlights the importance of informed clinical decision-making in ARAS management. Functional MRI emerges as a promising noninvasive tool to assess renal function, aiding in patient stratification and treatment planning. ***Key Messages:*** The efficacy of interventional treatments for ARAS requires further investigation and careful patient selection. Functional MRI holds promise as a noninvasive means to assess renal function and mechanisms, potentially guiding more effective clinical decisions in ARAS management. Advancing research in diagnostic methods, particularly functional MRI, can enhance our understanding and improve the treatment outcomes for ARAS patients.

Introduction

Atherosclerotic renal artery stenosis (ARAS) is defined as the renal atherosclerotic plaques resulting in narrowing of the main renal arteries or its branches [1]. ARAS is the prominent cause of renal artery stenosis (RAS). The prevalence is approximately 7% among the elderly aged 65 years and older and up to 20% among those with diabetes and secondary hypertension [2]. Severe RAS manifests as decreased blood flow, followed by activation of the renin-angiotensin system, decreased glomerular filtration rate, tubulointerstitial fibrosis, leading to serious complications such as secondary hypertension, ischemic nephropathy, left ventricular dysfunction, pulmonary edema, and cerebro-cardiovascular events [3].

Anatomically, relieving the narrowing in the renal arteries, restoring the blood flow to the kidney, and inhibiting the activated renin-angiotensin system, would

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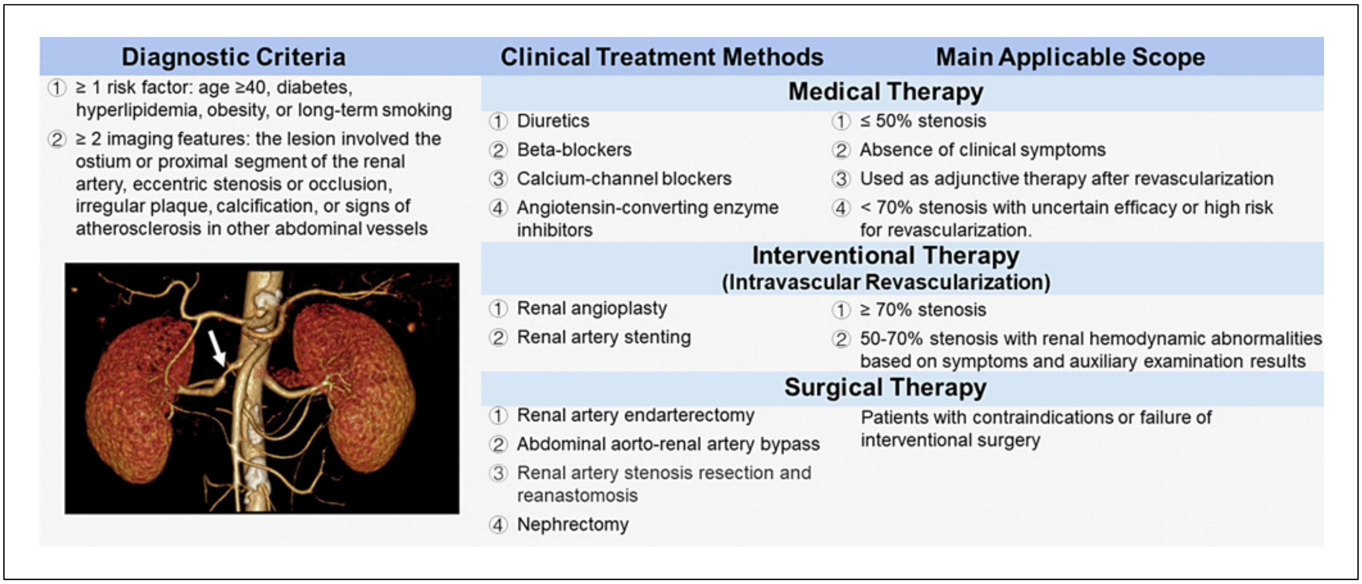


Diagnostic Criteria	Clinical Treatment Methods	Main Applicable Scope
① ≥ 1 risk factor: age ≥40, diabetes, hyperlipidemia, obesity, or long-term smoking ② ≥ 2 imaging features: the lesion involved the ostium or proximal segment of the renal artery, eccentric stenosis or occlusion, irregular plaque, calcification, or signs of atherosclerosis in other abdominal vessels	**Medical Therapy**	
	① Diuretics ② Beta-blockers ③ Calcium-channel blockers ④ Angiotensin-converting enzyme inhibitors	① ≤ 50% stenosis ② Absence of clinical symptoms ③ Used as adjunctive therapy after revascularization ④ < 70% stenosis with uncertain efficacy or high risk for revascularization.
	Interventional Therapy (Intravascular Revascularization)	
	① Renal angioplasty ② Renal artery stenting	① ≥ 70% stenosis ② 50-70% stenosis with renal hemodynamic abnormalities based on symptoms and auxiliary examination results
	Surgical Therapy	
	① Renal artery endarterectomy ② Abdominal aorto-renal artery bypass ③ Renal artery stenosis resection and reanastomosis ④ Nephrectomy	Patients with contraindications or failure of interventional surgery

Fig. 1. Overview of atherosclerotic renal artery stenosis.

control hypertension, enhance renal function, and lower the risk of cardiovascular events [4, 5]. However, controversies remain among clinicians regarding the improvement of renal function and the antihypertensive effect after renal artery stenting for RAS [6, 7]. Three large randomized controlled trials (Cardiovascular Outcomes in Renal Artery Stenosis [CORAL], revascularization versus medical therapy for renal-artery stenosis [ASTRAL], Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and Impaired Renal Function [STAR]) revealed that renal artery angioplasty did not show efficacy in terms of vascular control compared with medical therapy [8–10]. The above findings have been questioned due to the uneven distribution (few cases with severe stenosis) of patients that excluded patients who could potentially benefit from interventional therapy [11]. Recently, multiple small studies have demonstrated that patients with ARAS who have severe complications, such as resistant hypertension and rapid decline of kidney function, are more likely to benefit from interventional treatment [12–15]. Therefore, it is a clinical challenge to select patients with potential benefits to assist in the development of clinically optimized treatment options for patients with ARAS (Fig. 1).

Imaging techniques, such as magnetic resonance angiography (MRA), computed tomography angiography (CTA), or Doppler ultrasound, are crucial in the diagnosis of RAS [16]. Magnetic resonance imaging (MRI) stands out as being noninvasive, radiation-free, and multiparameter, with the potential for future functional applications [17]. Traditionally, contrast-enhanced MRI can improve image contrast, but its application has been constrained in patients with RAS due to the risk of renal fibrosis caused by contrast agents [18]. Therefore, this article will provide an overview of current diagnosis of ARAS and renal functional evaluation by MRI and highlight future directions.

Diagnostic Utility of MRA in RAS

Preoperative assessment of the degree of RAS is essential for determining the treatment options [17]. CTA is currently the screening tool for preoperative angiography of the kidney with high sensitivity [19]; however, CTA carries a risk of radiation exposure, requires exogenous contrast agents that are potentially nephrotoxic, and cannot be performed in patients allergic to iodine contrast agents [20]. In contrast, MRA has the benefits of no ionizing radiation, high repeatability, and a low incidence of adverse reactions with gadolinium contrast agents [20]. MRA for preoperative examination of the kidney has been increasingly studied as MRI technique has continued to advance [21]. This section will review the MRA in the assessment of renal arteries. Renal artery MRI is divided into contrast-enhanced MRA and non-contrast-enhanced MRA (NCE-MRA). However, contrast-enhanced scan is not recommended for patients with renal insufficiency as it can lead to nephrogenic fibrosis, limiting its application [18]. In the largest study to date, which included 400 renal arteries from 201 patients for analysis, the agreement between NCE-MRA and contrast-enhanced MRA for the detection of RAS was excellent ($p < 0.001$) [22]. The study suggests that NCE-MRA is an alternative option for assessing RAS.

NCE-MRA has been increasingly investigated for the assessment of renal vessels. Currently, steady-state-free precession MRI is widely used for imaging renal arteries, with a superior signal-to-noise ratio and spatial resolution. According to its principle, the contrast of the tissue depends on the T2/T1 ratio [23]. Soft tissue demonstrates hypointense due to the proximity of T2 and T1 values, while fluid appears hyperintense due to the long T2 and higher T2/T1 ratio, thus there is a good contrast between blood and soft tissues [23]. Previous study has demonstrated that this technique has a high diagnostic value for RAS, with sensitivity and specificity values ranging from 72 to 98% [24]. However, balanced steady-state-free precession is problematic in 3T MRI due to band artifacts caused by magnetic field inhomogeneities [25]. With technological innovations, a study in 2021 revealed that magnetization-prepared gradient echo echo-planar imaging sequence of NCE-MRA is a promising technique that can reduce the scanning time and improve the image quality compared to the previous scanning method [26]. Nevertheless, since this study was conducted on healthy subjects and lacked applications pertaining to RAS, its future potential of the technique needs to be further explored.

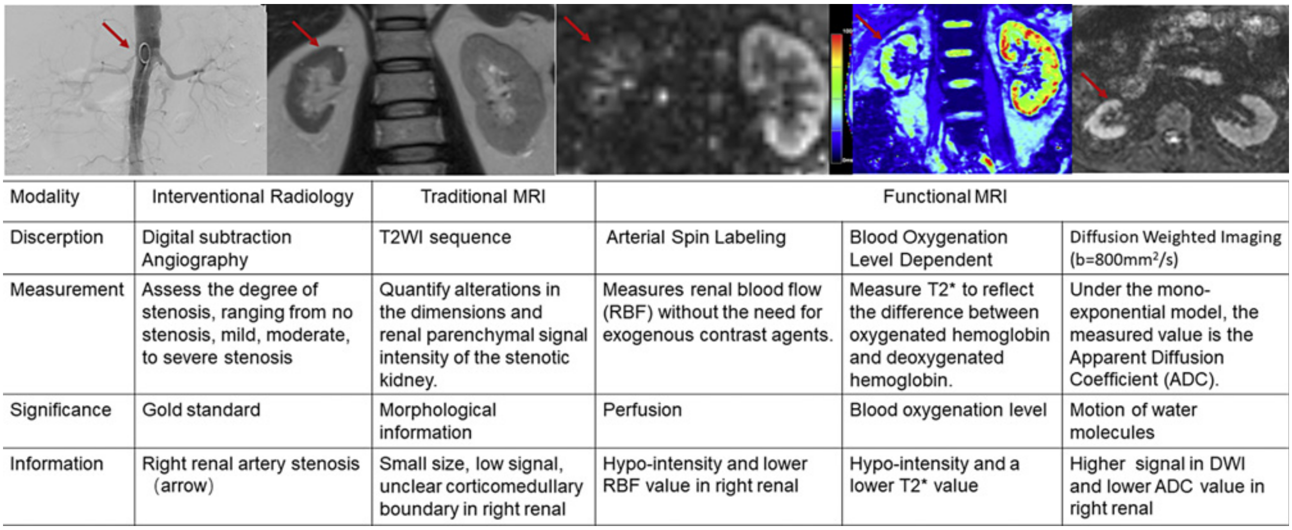
Functional MRI: Noninvasive Assessment of Renal Function

The common indicators that clinicians currently use to assess renal function presently are serological and urine indicators, which are accessible, inexpensive, and cost-effective. However, these indicators have low sensitivity and may not accurately reflect the deep-level pathophysiological changes of renal injury [27]. ARAS is associated with ischemic renal injury, which is morphologically characterized by decreased renal volume and lobulated kidney. But morphological changes are hysteretic. Hence, the timely and early prediction of clinical renal function outcomes and the quest for biomarkers of renal function improvement are the challenges of clinical research. Quantitative functional MRI not only provides anatomical images of tissues, but it also quantitatively extracts parameters of biological properties of reactive tissues [28, 29]. Functional multiparameter MRI can be employed for the kidney to reflect changes in the water content, oxygenation level, and blood perfusion of kidney tissue throughout the disease process as follows (Fig. 2).

Arterial Spin Labeling for Renal Function Assessment

Arterial spin labeling (ASL) technique uses hydrogen protons in arterial blood as an endogenous contrast agent, and the T1 signal of region of interest tissue before and after labeling is subtracted to produce perfusion contrast, thereby obtaining the red blood flow (RBF) value to evaluate renal perfusion [30]. The advantage is that it allows noninvasive quantitative evaluation of tissue perfusion without the use of exogenous contrast agents. ASL is divided into pulsed arterial spin labeling, continuous arterial spin labeling, and pseudo-continuous arterial spin labeling according to different labeling methods [31]. In 2020, a consensus on renal ASL was published by 23 MRI technologists, which showed that pseudo-continuous arterial spin labeling combined with background inversion suppression sequence has good repeatability and high image signal-to-noise ratio, making it applicable for clinical studies [32].

The kidney is the most highly perfused organ in the human body, with the blood flow of the renal cortex dominating (approximately 94%). Blood supply to the kidneys comes from a single system, is distributed between segments, and has no collateral circulation, providing a theoretical basis for the application of ASL [32]. ASL allows for the noninvasive measurement of the local blood perfusion of the kidney, and its repeatability and reliability have been recognized by most scholars [16, 33–36]. At present, ASL has been preliminarily applied in the diagnosis of acute and chronic kidney injury [16], obstructive hydronephrosis [33], kidney tumor [34], kidney allograft [35], and RAS [36]. Some researchers have found that the RBF values of the renal cortex and medulla in patients with acute kidney injury were markedly lower than those in the control group [37]. According to research by Cai et al. [38], cortical RBF values were lower in patients with chronic kidney disease than in healthy volunteers ($p < 0.01$), and these RBF values were positively correlated with estimated glomerular filtration rate. Fenchel et al. [39] demonstrated that renal RBF values were noticeably lower in patients with severe RAS (145 ± 59 mL/100 g/min) and were significantly different from those without or with mild (240 ± 33 mL/100 g/min), moderate (216 ± 61 mL/100 g/min) RAS. Additionally, there was a significant negative correlation between the level of perfusion and the degree of stenosis, and a significant positive correlation with the



Modality	Interventional Radiology	Traditional MRI	Functional MRI		
Discerption	Digital subtraction Angiography	T2WI sequence	Arterial Spin Labeling	Blood Oxygenation Level Dependent	Diffusion Weighted Imaging ($b=800mm^2/s$)
Measurement	Assess the degree of stenosis, ranging from no stenosis, mild, moderate, to severe stenosis	Quantify alterations in the dimensions and renal parenchymal signal intensity of the stenotic kidney.	Measures renal blood flow (RBF) without the need for exogenous contrast agents.	Measure T2* to reflect the difference between oxygenated hemoglobin and deoxygenated hemoglobin.	Under the mono-exponential model, the measured value is the Apparent Diffusion Coefficient (ADC).
Significance	Gold standard	Morphological information	Perfusion	Blood oxygenation level	Motion of water molecules
Information	Right renal artery stenosis (arrow)	Small size, low signal, unclear corticomedullary boundary in right renal	Hypo-intensity and lower RBF value in right renal	Hypo-intensity and a lower T2* value	Higher signal in DWI and lower ADC value in right renal

Fig. 2. Insight into digital subtraction angiography, traditional and functional MRI.

perfusion values measured by single-photon emission computed tomography.

Currently, there are few studies applying ASL to assess ARAS. Moreover, abdominal motion artifacts (respiration, gastrointestinal peristalsis, pulsation of great vessels, etc.) and gases in the digestive tract increase the inhomogeneity to the magnetic field [40], which results in a decrease in the signal-to-noise ratio of the images. As stable RBF values are of great significance for us to quantitatively assess renal function and the severity of various pathological damages, ASL also faces new challenges.

Blood Oxygenation Level Dependent Imaging for Renal Function Evaluation

Blood oxygenation level dependent (BOLD)-MRI, is a rapid imaging technique that does not require the use of contrast agents, enables noninvasive monitoring of tissue oxygenation and can be used repeatedly in a short amount of time [41]. BOLD-MRI utilizes the changes in the local magnetic field in local tissues triggered by paramagnetic deoxyhemoglobin in blood for imaging, and the concentration of deoxyhemoglobin in the tissue is quantitatively evaluated with apparent spin-spin relaxation rate ($R2^*$, $R2^* = 1/T2^*$) [41]. The R2* value is directly proportional to the concentration of deoxyhemoglobin in the tissue and inversely proportional to the oxyhemoglobin concentration [42]. Since the concentrations of oxyhemoglobin and deoxyhemoglobin are influenced by the partial pressure of oxygen, the partial pressure of oxygen in tissues can be indirectly assessed by measuring the change in R2* values [43]. One study [44] found that the R2* values of the renal cortex and medulla had a good correlation with the tissue oxygen partial pressure; an increase in R2* values suggested a decrease in oxygen partial pressure and a decrease in tissue oxygen content; a decrease in R2* values suggested an increase in oxygen partial pressure and an increase in oxygen content.

BOLD-MRI can determine renal corticomedullary injury in RAS by measuring R2* values. An experimental animal study [45] observed a dramatic increase in renal corticomedullary R2* values following the clipping of the renal artery, however R2* levels dropped after 4 weeks of clipping. This is due to the total atrophy and loss of function of the kidney after prolonged clipping of the renal artery, which prevents accurate measurement of R2* values. Thus, it was concluded that BOLD-MRI cannot be used for the diagnosis of patients with completed renal atrophy. According to Gloviczki et al. [46], when RBF and eGRF decreased in patients with RAS, the change in the renal corticomedullary R2* values was not obvious in patients with mild and moderate RAS, and the R2* values remained the same when measured again after 3 months; however, the renal corticomedullary R2* values were significantly higher in patients with severe RAS (of more than 60%). This suggests that the oxygen content of the kidney can remain stable when RAS is not severe, whereas severe stenosis causes severe hypoxia in the cortex and medulla, which leads to decreased renal function [47]. Recently, Lal et al. [47] applied BOLD-MRI to compare the R2* values of post-stenotic kidneys with contralateral kidneys, kidneys from patients with essential hypertension, and kidneys from healthy subjects. Four groups of kidneys were included in this study for comparison, including 92 kidneys with RAS, 37 contralateral kidneys from patients with unilateral RAS, 62 kidneys from patients with essential hypertension, and 40 kidneys from healthy controls. Changes in R2* before and after administration of furosemide were calculated and compared between different groups. The results showed no difference in baseline cortical R2* values between the groups. The response of stenotic kidneys to furosemide was reduced compared to that of the essential hypertension group and healthy controls ($p < 0.001$). In the renal volume decrease subgroup (classified by whether it was greater than 7 cm), higher mean cortical R2* values were observed in the kidney on the renal artery stenotic side. The study concluded that R2* values on BOLD-MRI differed markedly between kidneys with and without RAS and suggested that BOLD-MRI has predictive value for revascularization [48]. Li et al. [48] conducted a prospective study of transplanted kidneys with the aim of measuring perfusion and oxygenation changes in the transplanted kidney by ASL and BOLD-MRI, respectively. The study performed ASL and BOLD-MRI in 7 patients with transplanted RAS and seven age- and sex-matched normal kidney transplant recipients. In the transplanted RAS group, cortical perfusion was dramatically lower in terms of ASL compared to normal controls (129.9 ± 46.6 mL/100 g vs. 202.4 ± 47.7 mL/100 g, $p = 0.01$) [49]. Interestingly, there was no statistically significant difference in BOLD-MRI. However, the sample size of this study was small, and the conclusions of the study need further confirmation.

In summary, BOLD-MRI presents a noninvasive method for assessing kidney oxygenation status in patients with ARAS and renal insufficiency. Currently, only a limited number of studies have employed BOLD-MRI to evaluate the oxygenation status in renal nonneoplastic diseases. However, the stability of measurements of BOLD-MRI is influenced by the state of drinking, sodium intake, and increased inhomogeneity of the magnetic field due to abdominal motion artifacts (respiration, gastrointestinal peristalsis, pulsation of great vessels, etc.) and gases in the digestive tract [50]. Specifically, sodium intake may affect the measurements, but there's currently no consensus on the required sodium intake before scanning due to practical challenges in controlling subjects' sodium intake [51]. Thus, the application of BOLD-MRI in RAS also has limitations.

Mathematical Model for Multi-B-Values Diffusion-Weighted Magnetic Resonance Imaging in Renal Function Analysis

DW-MRI is a noninvasive imaging method that facilitates the detection of irregular Brownian motion of water molecules within living tissues [52]. The apparent diffusion coefficient (ADC) value in the direction of the diffusion gradients is often used to measure the diffusion capacity of water molecules in living organisms under physiological state, with the higher the ADC value, the freer the diffusion of water molecules and the greater the range of motion [53]. The kidney, with its high water content, active molecular diffusion, and abundant blood supply, makes an ideal organ for the application of diffusion-weighted magnetic resonance imaging (DWI) [54]. Glomerular filtration, reabsorption, and secretion function are closely related to water molecule transport. As a result, the kidney is one of the ideal organs for DWI application.

The theoretical basis of the traditional ADC model is to assume that the motion of water molecules in the human body is normally distributed, while in fact most tissues are not normally distributed and exhibit complicated behavior due to intercellular structure, degree of intra- and extracellular restriction, permeability of the cell membrane, and differences in the physicochemical properties of free and bound water, with the actual signal attenuation deviating from a linear distribution at b >1,000 s/mm^2 [52]. A complementary model to ADC is the intravoxel incoherent motion (IVIM) model, another mathematical representation for DWI [55]. IVIM is a complement to conventional DWI by separating microcirculatory perfusion from water molecule diffusion through the DWI technique of using multiple b-values and biexponential fitting of signal attenuation curves, to obtain the true diffusion coefficient (D), the pseudo-diffusion coefficient (D*), and the perfusion fraction (f) [55]. Where D is a parameter value measuring the true diffusion of water molecules, and D* is a parameter value related to microcirculatory perfusion within a voxel; f is the ratio of microcirculatory perfusion within a voxel, tubular fluid flow to the overall diffusion effect [55]. The main pathological manifestations of atherosclerotic nephropathy are glomerulosclerosis and tubulointerstitial fibrosis [56, 57]. These histological changes can lead to renal water molecule diffusion and blood perfusion changes, and IVIM is able to detect these abnormal changes sensitively. In terms of functional imaging of RAS, IVIM has been less studied, with most of the early studies being animal studies [57, 58], and there is a lack of evidence-based research on its use in ARAS. However, IVIM has been studied in diabetic nephropathy and acute kidney injury. According to Feng et al. [59], diabetes mellitus patients with normal urine albumin-to-creatinine ratio had greatly reduced renal corticomedullary D values and highly increased cortical f values and D* values. This finding suggests that the kidney had restricted diffusion of water molecules and was in a hyperperfused state before abnormal albuminuria was clinically detected. As the disease progresses to the microalbuminuria stage, both renal cortex D value and medullary f value decrease, while the cortical f value increases further, indicating that the renal cortex has a certain reserve capacity for injury and the medulla is more vulnerable to ischemia and hypoxia. Deng et al. [60] showed similar findings to Feng et al. [59], suggesting that f and D values are imaging indicators for the evaluation of early diabetic kidney disease. The decrease in D value may be due to a reduction in extracellular space brought about by changes such as thickening of the glomerular basement membrane, swelling of tubular epithelial cells and proliferation of mesangial cells, etc., while early pathological changes such as increased RBF, tubular, and intraglomerular fluid flow can cause an increase in f value; the difference in this study is that there is no statistical difference in D* values. The reasons for this are that the changes in renal capillary density are not apparent in the early stages of the disease and the repeatability of the D* measurements needs to be improved. The above results indicate that IVIM can reflect renal function and microstructure information noninvasively and quantitatively.

But there is no consensus on the current findings, which may be related to factors such as different instruments and equipment used and scanning parameters, the relatively low signal-to-noise ratio of the images and the relatively small sample size of the study. Multicenter studies with optimized parameters and larger sample sizes are needed in the future to confirm its value in renal disease.

Look beyond MRI

Radiomics and Deep Learning

Radiomics is a recent post-processing method for computer image processing and big data mining. Driven by advances in pattern recognition and image processing techniques, radiomics provides access to more objective and quantitative features that are difficult to identify with the naked eye compared to traditional imaging phenotypic features [61, 62]. The foundation of radiomics and deep learning based on renal functional MRI is that chronic kidney disease is a group of heterogeneous diseases that lead to changes in renal function. These changes yield different signals in various regions of the kidney, and the signals change in response to changes in renal function [63]. Applying artificial intelligence (AI) techniques to functional imaging will help enhance disease diagnosis and identify diagnostic efficacy, which will improve the assessment of prognosis [64]. In 2021, Liang et al. [65] conducted a controlled study of healthy New Zealand rabbits and New Zealand rabbits with clipped renal arteries by extracting texture analysis parameters of MRI functional imaging to assess early renal ischemia-reperfusion injury. This study confirmed that T2WI_S (3,–3) Inverse_Difference_Moment correlated most strongly with brush border destruction, renal tubular epithelial edema, necrosis, and casts (r = 0.56, −0.58, 0.62, and 0.69, respectively; all $p < 0.001$). BOLDS (4, −4) correlation showed the strongest correlation with interstitial inflammatory cell infiltration ($r = 0.63$, $p < 0.001$). SWI_S (4,4) Difference_Entropy was most highly correlated with microvascular density ($r = 0.61$, $p < 0.001$). The above study mostly used texture analysis, lacked a multicenter validation group, and had fewer parameters for texture analysis; more AI-related studies are needed to transform the progress of multi-parameter data into clinical applications.

Application of Multiple Modalities

On the one hand, digital subtraction angiography is not only the gold standard diagnostic modality but can also be used as revascularize tool for treatment. Previous studies have demonstrated that features extracted from postprocedural digital subtraction angiography could be potential biomarkers for assessing treatment outcomes of intracranial aneurysms [65]. On the other hand, Doppler ultrasonography is one of the common screening tool for RAS with quantitative parameters [66]. Up to now, there has been limited research investigating the use of multiple modalities or multi-parameters to evaluate patient outcomes. In future, the combination of those modalities could lead to more efficient treatment and better clinical outcomes, ultimately enabling personalized treatment.

Conclusion

Interventional treatment of ARAS is controversial. In future, we aim to selectively screen patients with potential benefits in subsequent studies to aid in the development of clinically optimized treatment options for patients with ARAS to protect renal function. Functional MRI has made significant strides in mechanism-based investigations of kidney tissue. In the meantime, with the development of big data in medicine, functional MRI combined with AI has a good prospect of application in atherosclerotic nephropathy, and its application in the efficacy of interventional treatment of ARAS needs to be further confirmed by large multicenter research.

Conflict of Interest Statement

The authors report no relevant conflicts of interest.

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Author Contributions

Jia Fu collected the details and wrote the manuscript. Yinghua Zou designed the analysis. Zhiyong Lin, Bihui Zhang, Li Song, Naishan Qin, Jianxing Qiu, and Min Yang contributed to the conception of the study.

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