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Comparative Review of Imaging Methods used for diagnosing Renal Artery Stenosis (RAS)

Short Title: Imaging Methods used for diagnosing RAS

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Abstract

This comparative review examines the efficacy of different imaging methods to detect and quantify renal artery stenosis. Detection of renal artery stenosis is important because it can lead to renovascular hypertension which is the most common form of secondary hypertension. Furthermore, it is important that a RAS is detected as early as possible as it is a potentially correctable cause of hypertension, if detected at an early stage.[1] Thereby, enabling it to potentially be treated using a minimally invasive drug treatment regime rather than the more invasive percutaneous transluminal renal angioplasty without or with stent placement or surgery. There are currently a number of different types of imaging modalities used to image the renal artery and determine if a stenosis is present, each of these modalities has its own positive and negative aspects, which will be discussed in turn.

Introduction

The renal system has a number of important functions, such as removing waste products from the blood, controlling blood pressure, controlling the manufacture of red blood cells and helping to maintain healthy bones. There are a number of different causes of renal artery stenosis (RAS): atherosclerosis or fibromuscular dysplasia (FMD), traumatic thrombosis, non-traumatic thrombosis, thromboembolism, renal or aortic dissection to name just a few. However, the most common cause of RAS is atherosclerosis which accounts for 90 % of cases with FMD being the second most common accounting for about 8-9%, this article will focus only on the former cause of RAS.[1,2]

If a stenosis is present in the renal artery due to atherosclerosis, it is commonly associated with clinical syndromes such as renovascular hypertension, ischemic nephropathy and pulmonary oedema.[2, 3,4] Additionally, it is associated with increased risk of cardiovascular mortality. Atherosclerotic RAS is a common, progressive problem that increases in prevalence with age[3] and it is recognised as an important cause of secondary hypertension accounting for up to 10 % of cases in unselected populations, and up to 32 % of selected populations.[1, 4, 5] Approximately 60 million people suffer from hypertension in the USA alone which highlights the magnitude of the problem.[4, 6] Furthermore, with atherosclerotic disease, renal ischemia may also lead to secondary renal failure as well as complicating congestive heart failure. Atherosclerotic RAS usually develops near the ostia within 10 mm of the aortic wall.[7] Current evidence also suggests that the presence of atherosclerotic plaque in the renal artery is indicative of the presence of plaque at other sites in the body such as the carotid or coronary arteries, which further adds to the cardiovascular risk.[8,9,10] It has been found at autopsy that the prevelance of patients who were identified as having a Myocardial Infarction and significant RAS was 12 %, furthermore, 11 % of patients who died of stroke were also found to have significant RAS. [11, 12] All of this negatively affects the long-term prognosis and quality of life for individuals with RAS, in addition to representing a significant cost to the healthcare system. In the literature published to date, threshold values varying between 50, 60 and 70 % reduction of internal diameter have been considered to be hemodynamically significant depending on the imaging modality used to determine the stenosis.[2,5,13,14,15,16] Since secondary hypertension is potentially curable the early detection of RAS is important as it offers the possibility of various antihypertensive drug treatments, which are considerably less invasive and poses less risk to the patient than revascularisation through percutaneous transluminal renal angioplasty or surgery.[3,4,5,6,7] If left untreated however, this progressive disease has many associated morbidities including progressive renal insufficiency, myocardial infarction, congestive heart failure, stroke and death.[8,9,10]

Consequently, there is much interest in the initiation and progression of atherosclerotic disease in the renal artery, the relationship between stenosis, hypertension and end-stage renal failure, and whether more accurate stenosis assessment techniques would improve patient outcome.[8] Despite the availability of non-invasive diagnostic tests, such as ultrasound, magnetic resonance imaging and computed tomographic angiography, IA-DSA still remains the gold standard for anatomic diagnosis of renal artery stenosis.[15,16,17] However, IA-DSA is an invasive procedure and therefore carries a small risk of serious complications such as arterial dissection, adverse contrast reactions, a loss of kidney function and other major morbidities.[10,16]

The choice of imaging procedure will depend on the availability of the diagnostic tool, the experience and local accuracy of the chosen modality, and patient characteristics (e.g., body size, renal function, contrast allergy, and presence of prior stents or metallic objects that may serve as contraindications to MRA techniques). Each of the different imaging techniques will be discussed in turn and Table 1 provides a comparison of all of the imaging techniques used to detect renal artery stenosis in terms of the type of procedure, its safety and associated cost per examination.

Different imaging techniques used to diagnose renal artery stenosis

Intra-Arterial Digital Subtraction Angiography

Intra-arterial digital subtraction angiography (IA-DSA) still remains the gold standard for anatomical diagnosis of RAS; an example image is shown in Figure 1.[13-18] This imaging technique offers excellent spatial and temporal resolution for visualisation of the main and branch renal artery stenosis, additionally, a functional assessment of the hemodynamic significance can be directly measured by crossing a stenosis with a catheter or wire suitable for pressure measurements.[14,-18] Furthermore, with the recent improvements in contrast resolution due to flat panel technology, this has resulted in a reduction in the amount of iodinated contrast agent being used per procedure thereby slightly reducing the cost associated with the procedure.[10] A further consequence of the contrast resolution of the technique improving is that contrast agents other than iodinated ones can now be used in the procedure such as carbon dioxide or gadolinium which reduces the risk associated with nephrotoxiticy being induced in the procedure.[15] Another advantage of this imaging technique is that if a hemodynamically significant stenosis is identified during the imaging procedure, treatment can be carried out in the same session. There is some difficulty in determining the sensititivity and specificity of IA-DSA in terms of the diagnosis of clinically relevant RAS as it is primarily used as the gold standard in the different comparative studies. However, it has been reported in a number of studies that the interobserver agreement for the detection of clinically relevant stenosis with this technique is not perfect, due in part to the 2-dimensional nature of the technique as well as the variations in estimating the minimum and reference diameters, with reported κ values ranging from 0.65 to 0.78.[22-24] The manner in which the stenosis is graded, that is most stenosis are located at the origin and usually the non diseased reference vessel segment used is distally located which is often larger due to poststenotic enlargement leading to an underestimation of the stenosis. The small risks and complications such as bleeding, anaphylaxis and contrast induced nephropathy, mentioned in the previous section also have to be considered as.[16] Furthermore, in a study investigating the costs associated with the IA-DSA, Computed Tomography angiography and magnetic resonance angiography when diagnosing a renal artery stenosis it was found that IA-DSA was the most costly.[10]

Magnetic resonance angiography

Contrast-enhanced Magnetic resonance angiography (MRA) is performed with Gadolinium to obtain visualization of the renal arteries and abdominal vasculature, Figure 2(a) presents an example MRA image of a normal renal artery and kidney. Comparison with IA-DSA in a number of investigations have found a range of sensitivities ranging from 62% to 100% and specificities of 70% to 100% for detection of RAS, the exact details of each study in terms of whether the study was prospective or retrospective, the number of patients included and the level of stenosis which was regarded as clinically significant are provided in Table 2[17-19] Table 2. Advancements in MRI such as single breath hold 3D contrast-enhanced MRA and sensitivity encoding (SENSE) sequences have provided improvements in spatial resolution and image quality, reduced artefacts and increased diagnostic confidence.[19, 24, 25,] Adverse reactions to Gadolinium have been reported and its possible association with nephrogenic systemic fibrous.[20] Therefore, there is growing interest in non-contrast MRA which has showed a sensitivity of 78% and a high specificity of 91%. [22, 23] Also MRI has the advantage of providing a functional assessment of blood flow and organ function. Combining anatomical imaging with functional pulse sequences has the potential to increase sensitivity and specificity of MRA in a more comprehensive evaluation of the renal arteries and kidneys.[15] Functional MR sequences such as 3-D phase-contrast MRA, 2-D cine phase-contrast MRI, diffusion-weighted MR imaging and quantitiative perfusion imaging have all lead to improved diadnosis of hemodynamically significant renal artery stenosis with reduced interobserver variatibilty being found with 2-D cine phase-contrast MRI.[15] However, it still has limitations and these include; underestimation of mild stenosis and overestimation of severe stenosis, although it is possible to determine a hemodynamically significant stenosis, inability to image patients with metal implants, claustrophobia as well as the associated high cost per examination.[10, 15]

Computed Tomography angiography

Computed tomography angiography (CTA) produces excellent 3D images of the aorta and renal arteries, an example of which is shown in Figure 2(b). CTA has a range of sensitivity and specificity values for detecting significant RAS ranging from 62% to 100% and ranging from 56% to 99%, respectively, compared with IA-DSA, the exact details of each study in terms of whether the study was prospective or retrospective, the number of patients included and the level of stenosis which was regarded as clinically significant are provided in Table 3.[8,10,14,27,29-35] One of the major advantages of Computed Tomography Angiography is it's excellent spatial resolution which lead to the acquisition of accurate anatomical images of the renal arteries during contrast enhancement.

Compared with IA-DSA it has superior contrast resolution providing excellent soft tissue visualisation and since 3-D datasets are acquired it is possible to view the anatomy from any angle similar to that of MRA. Investigations comparing both CTA and MRA have found that the accuracy of both techniques at diagnosing renal artery stenosis is comparable.[14,29,33] Although the non-ionsing nature of MRA provides MRA with an added advantage as the major disadvantage of CT is that it involves the use of ionising radiation. Just as it the case with MRA, CT it requires the administration of iodinated contrast and is therefore, not an ideal first line method for patients with renal insufficiency because of the risk of inducing contrast nephropathy.[21] Other disadvantages include its inability to provide physiological information which is important when it comes to deciding the management of the patient, long processing times (30 - 90 minutes) and its inability to image persons who weigh more than 125 kg.[15]

Ultrasound

Ultrasound is considered to be an ideal first-line imaging technique for renal artery stenosis due to the fact that it is a non-ionising, noninvasive, low cost and does not require the administration of a contrast agent for hemodynamic information to derived from the examination.[36,37] The ultrasound mode Duplex ultrasound (US) combines the direct visualisation of the renal arteries via B-mode imaging with Doppler measurement of the velocity of blood flow in the main renal artery and within the kidney. While Triplex ultrasound combines the direct visualisation of blood flow in the renal arteries through a colour map superimposed on the moving blood within the vessel and regional Doppler measurements of the velocity of blood flow in the renal artery can be obtained. In Figure 3 an example of a Triplex ultrasound image of right-sided ostial renal artery stenosis is shown. This combination allows anatomical evaluation and hemodynamic assessment. Ultrasound can be used to assess renal artery stenosis directly by imaging the renal artery or indirectly by imaging the intraraenal parenchymal arteries known also as the interlobar or segmental arteries. The different Doppler parameters which have been used to diagnose RAS through the direct approach are peak systolic velocity (PSV) and renal-aortic PSV ratio (RAR) while the assessment through the indirect approach have used parameters such as systolic acceleration ratio and acceleration time.[37,38,40-43] The direct parameters are considered the more important and the indirect parameters are viewed as only contributing minor additional information.[44] Typically, the maximum velocity through the narrowest point of the stenosis is used to classify the severity based on the fact that, for a constant flow rate, a tighter constriction leads to higher velocities through the stenosis. The most generally accepted criteria for the identification of a hemodynamically significant RAS (generally 50% or 60% stenosis) is a PSV in the renal artery greater than 180-200 cm s^{-1} at the site of the lesion or a RAR of 3.5.[16, 36, 37] In a recent meta-analysis, Williams et al., (2007)[31] found the PSV to be the most accurate test parameter with sensitivity and specificity of 85% and 92% respectively.

Overall US, compared with IA-DSA, has a sensitivity of 67% to 98% and a specificity of 54% to 99% for detecting RAS, the exact details of each study in terms of whether the study was prospective or retrospective, the number of patients included and the level of stenosis which was regarded as clinically significant are provided in Table 4.[8,16,26,29,31,32,33,37,38,39,45-48] It is an excellent test to monitor renal artery patency after endovascular treatment or surgical revascularization of RAS.[39, 40] Limitations of ultrasound examination include its dependence on operator skill, the diminished ability to visualise accessory renal arteries, determining high velocities at depth without aliasing occurring and the difficulty to image obese patients, breathless patients and those with overlying bowel gas.[41,42]

It has several advantages over MRA and CTA: it is widely available, non-invasive, non-toxic and inexpensive, furthermore, with the experienced operator it is reliable.[15,3] all of which are positioning US methods as first-line methods for the evaluation of renovascular diseases (RVDs).[43,45] The most recent published guidelines have emphasised the leading position of US, followed by CT (except in cases of renal failure) and MRA for the first-line evaluation of RAS.[43,45] This shows a shift in the previous recommended tests of MRA and DSA. Duplex ultrasound is the most utilized method for non-invasive imaging of the renal arteries as it is the most widely available equipment and not as expensive as MRI, CT and DSA techniques.[38] Furthermore, there has been an increased use of ultrasound contrast agents in the detection of renal artery stenosis. This has been largely due to the fact that these echo-enhancing agents have been found to improve the strength of the Doppler signal from deep vessels or of signals from slow moving flow. This has led to an increase in the number of examinations which were deemed to be diagnostic in multicentre studies.[42, 49] The enhanced backscatter signals of ultrasound contrast agents from the renal arteries has been found to improve diagnostic efficacy by improving the operator's ability to visualise the anatomy of the renal arteries and thus decrease the number of inadequate Doppler studies.[42,49-52] It has been found that Doppler ultrasound examinations with the use of contrast agent have been used to select patients for renal artery PTA procedures and for follow-up of these patients.[53]

Conclusions

Recent and ongoing technological developments in medical imaging, in particular ultrasound and MR, are allowing more challenging anatomical areas such as the renal arteries, to be imaged more easily. Arguably, there is even the potential to replace the current gold standard of IA-DSA. Furthermore, both MR and ultrasound offer the potential to investigate RAS in a non-invasive and non-ionising manner. An issue which needs to be resolved however, before the different imaging techniques can be adequately compared is the criteria for a haemodynamically significant stenosis, whether it is to be >50, >60 or >70 %, since it is difficult for current imaging modalities to distinguish between a 50 and 60 % stenosis.[42] However, no ideal technique currently exists for the detection of RAS as each outlined in this review has associated limitations, therefore the choice of the best test depends on availability and on the experience of the imaging team within the department.

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Tables

Table 1: Comparison of Imaging Modalities

Modality	*US*	*MRI*	*CT*	*IA-DSA*
Procedure	Non-invasive	Non-invasive	Non-invasive	Invasive
Safety (radiation)	Non-ionising	Non-ionising	Ionising	Ionising
Spatial resolution [a]	0. 3- 3 mm	~ 1 mm	~ 1 mm	~ 1 mm
Portability	Excellent	Poor	Poor	Intermediate
Cost of diagnostic work-up [b]	€250	€ 950	€ 450	€ 1,800

[a] Szabo[36]
[b] Approximate costings for Private Hospital, Dublin, Ireland May 2009

Table 2 Diagnostic performance of MRA studies for the detection of RAS in patients suspected of RVH, NG = not given

First Author and Year	No. of patients	No. of arteries	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Stenosis (%)	Contrast	Study type
Thronton et al., (1999)[24]	62	NG	88	98	NG	NG	50	yes	Prospective
Shetty et al., (2000)[25]	51	NG	96	92	NG	NG	NG	yes	Prospective
De Cobelli et al., (2000)[26]	45	90	100	93	86	100	50	yes	Prospective
Vasbinder et al., (2001)[8]	288	NG	88-100	75-100	NG	NG	50-70	yes	Meta analysis
Willmann et al., (2003)[27]	46	NG	93	100	96	100	50	yes	Prospective
Vasbinder et al., (2004)[14]	356	NG	62	84	49	90	50	yes	Prospective
Patel et al., (2005) [28]	NG	NG	90-100	76-94	NG	NG	50/60	yes	Meta analysis
Eklöf et al., (2006) [29]	58	NG	98	70	NG	NG	60	yes	Retrospective
Hirsch et al., (2006)[32]	34	68	84	74	57	92	50	yes	Retrospectively
Rountas et al., (2007)[33]	129	132	90	94	75	98	50	yes	Prospective
Stacul et al., (2008)[17]	26	57	83	76	63	91	50	yes	Prospective
Utsunomiya et al., (2008)[23]	26	56	78	91	64	96	NG	no	Retrospectively

Table 3 Diagnostic performance of CTA studies for the detection of RAS in patients suspected of RVH, NG = not given

First Author and Year	No. of patients	No. of arteries	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Stenosis (%)	Contrast	Study type
Kaatee et al., (1997)[34]	71	166	96	96	96	96	50	non ionic	Prospective
Wittenburg et al., (1999)[35]	82	197	96	99	NG	NG	NG	iodinated	Prospective
Vasbinder et al., (2001)[8]	317	NG	94-100	65-97	NG	NG	50-70	NG	Meta analysis
Willmann et al., (2003)[26]	46		92	99	87	100	50	iodinated	Prospective
Vasbinder et al., (2004)[14]	356	NG	64	92	68	91	50	NG	Prospective
Hirsch et al.,(2006) [32]	NG	NG	59-96	82-99	NG	NG	50/60	NG	Meta analysis
Eklof et al., (2006) [29]	58	NG	100	56	NG	NG	60	non ionic	Retrospective
Fraioli et al., (2006)[30]	50	99	100	97	98	98	50	iodinated	Prospective
Rountas et al., (2007)[33]	129	132	94	93	71	99	50	non ionic	Prospective

Table 4 Diagnostic performance of Duplex Ultrasound studies for the detection of RAS in patients suspected of RVH, NG = not given

First Author and Year	No. of patients	No. of arteries	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Stenosis (%)	Doppler criteria	*Study type*
Olin et al., (1995) [47]	102	187	98	98	99	97	60	>200 cm/s	*Prospective*
De Cobelli et al., (2000)[26]	45	91	79	93	85	90	50	>200 cm/s	*Prospective*
Souza et al., (2000) [48]	50	96	67	98	NG	NG	50	>180 cm/s	*Prospective*
Vasbinder et al., (2001) [8]	1592	NG	79	96	NG	NG	50-70	NG	*Meta analysis*
Nchimi et al., (2003)[45]	91	178	91	97	88	94	60	>180 cm/s	*Prospective*
Hirsch et al., (2006) [32]	NG	NG	84-98	62-99	NG	NG	50/60	>180 cm/s	*Meta analysis*
Eklöf et al., (2006) [29]	58	NG	80	54	NG	NG	60	>180 cm/s	*Retrospective*
Li et al., (2006)[46]	91	187	81	NG	NG	NG	50	>150 cm/s	*Prospective*
Soares et al., (2006)[37]	67	67	97	79	NG	NG	60	>200 cm/s	*Retrospective*
Staub et al., (2007)[38]	49	93	92	80	87	88	50	>200 cm/s	*Retrospective*
Rountas et al., (2007)[33]	129	132	75	90	60	95	50	>200 cm/s	*Prospective*
Williams et al., (2007)[31]	NG	2785	85	92	NG	NG	50/60	100-200 cm/s	Meta analysis

Figures

Figure 1: Focal high-grade atherosclerotic stenosis involving the ostium of the right renal artery (arrow) imaged using IA-DSA. Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA

Figure 2 (a) Contrast enhanced MRA with three right and two left renal arteries and severe stenosis of the inferior left renal artery (b) CTA showing bilateral RAS (thin arrows). Reproduced from [Stenotic arterial lesions in a young woman, T Jaconelli, C Jones, N Warnock, A Fawzi, Postgrad Med J doi: 10.1136/pgmj.2010.102988, 2010] with permission from BMJ Publishing Group Ltd.[53]

Figure 3 Atheroschlerotic plaque (proximal renal artery) Ultrasound Spectral Doppler waveforms in the right segmental renal arteries. Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA