Disease of the Renal Vessels

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With each kidney typically serviced by a single artery and vein, one may expect that any interruption in the vascular supply must be treated to preserve organ function. However, the kidneys can continue to operate even in the presence of high-grade arterial stenosis, with many studies demonstrating a much more complex disease dynamic than the conceptually simple 'vessel obstruction renal failure' model.

Renal Artery Disease

Despite a wealth of publications investigating renal artery stenosis (RAS), there is surprisingly little consensus on what constitutes *significant* disease. Although experimental data have shown that renal perfusion is not reduced until a stenosis reaches approximately 70 %, clinical experience tells us that patients with lower burdens of disease frequently may have both elevated blood pressure and reduced eGFR. These changes are due to renal parenchymal damage downstream of the stenosis; RAS is also associated with altered neurohormonal status and cardiac structural abnormalities. For this reason, RAS can be considered to be clinically significant where it exists in tandem with *any* of these factors.

In the Western world 90 % of RAS is due to atheromatous disease, with fibromuscular disease accounting for the majority of the remainder. Elsewhere, vasculitic stenosis is more prevalent.

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Non-atheromatous Renal Artery Stenosis

Vasculitis

In Indian and South Asian populations, almost 60 % cases of RAS are vasculitic, whereas in Caucasian populations this is extremely rare. Takayasu's arteritis is the most common form of vasculitis in Asia and affects females more than males with ratios of up to 9:1 reported. Presentation is typically before the fifth decade of life. The disease follows two clinically distinct phases. The first phase is inflammatory with mononuclear leukocytes and scattered multinucleated giant cells observed within the vessels on histological examination. The second is described as *pulseless disease* in which progressive fibrosis results in stenoses. The diagnosis is often delayed as symptoms are often non-specific but should be considered in young Asian women with constitutional symptoms such as fevers, arthralgia, hypertension and an acute phase response (raised ESR/CRP). In the chronic phase features of end-organ ischaemia predominate such as claudication and difficult to control hypertension. If suspected it is important to check blood pressures in all limbs and examine across the vascular tree for bruits, and whole body MRA is helpful in assessing the extent of involvement (Fig. 34.1). The territory of blood vessel affected further describes the disease. Within the Indian population, Takayasu's disease of the descending thoracic and abdominal aorta is the most common pattern. This explains the high incidence of associated RAS.

In the acute or inflammatory phase of the disease, Takayasu's disease is treated using corticosteroids ±cyclophosphamide, methotrexate or increasingly with biologicals such as anti-TNF-α monoclonal antibodies. However, due to limitations in local health care in developing countries, the majority of patients present with secondary hypertension in the chronic pulseless phase of disease. In this context, revascularisation is an appropriate intervention, with combined clinical and angiographic success rates of over 90 % following balloon angioplasty reported [1].

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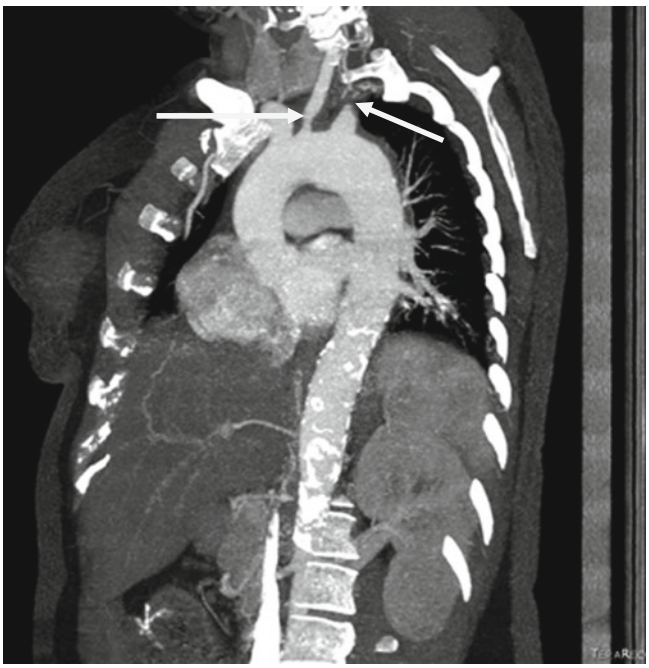

Fig. 34.1 Takayasu's arteritis in a young Asian woman with difficult hypertension and undetectable pulses in left arm. The images show occlusion of the left subclavian artery (1, *right arrow*) near its origin and stenosis of the left common carotid (surrounded by inflammatory tissue) (2, *left arrow*)

Fibromuscular Disease

Fibromuscular disease (FMD) accounts for approximately 10 % of diagnosed cases of RAS in Western populations.

Although FMD can involve any arterial bed, up to 75 % of cases affect the renal vessels (with one-third bilateral). The best estimates of FMD prevalence are obtained from patients undergoing assessment for potential renal donation. Here, as many as 4–7 % of patients have angiographic evidence of FMD. As this can be considered a relatively 'healthy' population, the true population prevalence may be higher.

Aetiology

FMD is neither inflammatory nor atherosclerotic, with the cause(s) poorly elucidated. Although the vast majority of affected patients are female (at a ratio of 9:1), the reason is unclear, with no evidence of a link between increased oestrogen exposure (including from use of oral contraceptives) and development of disease.

Genetic factors almost certainly play a part in the development of FMD, most likely a dominant trait with variable penetrance. However, limited patient numbers make it hard to reach firm conclusions about genetic linkage. Reports of a familial link in 11 % of FMD patients are not consistently duplicated, and other data have rebutted a potential link with alpha-1-antitrypsin deficiency. Work into other potential genetic factors is ongoing as is investigation of a 'two-hit' hypothesis, with some data describing higher rates of disease and more severe disease in smokers (although again conflicting reports exist) [2].

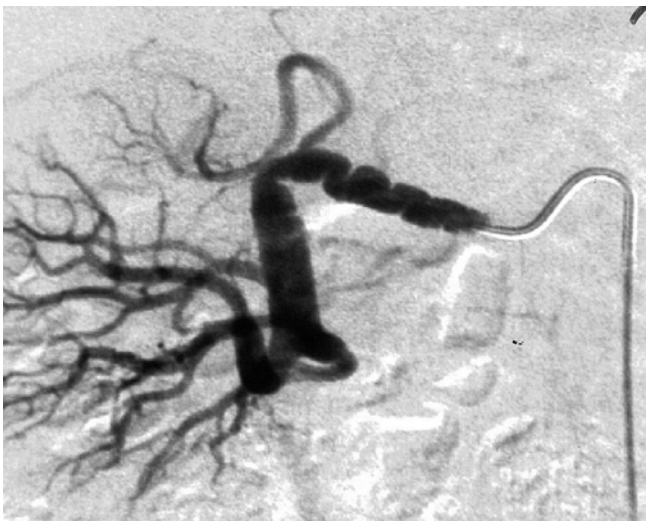

Fig. 34.2 Direct angiography in fibromuscular disease. Medial fibroplasia causing multiple stenoses giving rise to the classical 'string of beads' appearance

Pathology

FMD can be described both histologically (based on the layer of arterial wall involved) and anatomically (based upon angiographic appearance). An abnormality of the intimal and adventitial layers is very rare, with disease of the medial layer the commonest cause of renal FMD. Medial disease can be further subclassified (in order of increasing frequency) into medial hyperplasia, perimedial fibroplasia and medial fibroplasia. Medial fibroplasia accounts of almost 80 % of cases of renal FMD and gives rise to the 'string of beads' appearance on angiography. Potentially these beads can become macro-aneurysmal with a risk of rupture.

Diagnosis

FMD is typically suspected in women aged <35 years presenting with unexplained hypertension. Before proceeding immediately to renal imaging, it is important to consider other points in the history that may suggest a need for more detailed vascular investigations – e.g. mesenteric ischaemia, intermittent claudication or previous neurological symptoms. A thorough examination for vascular bruits is appropriate for the same reason. Laboratory measurements may be misleading as although FMD leads to reductions in renal mass, serum creatinine values are usually within the 'normal' range.

Direct angiography is the gold standard investigation for identifying FMD (Fig. 34.2), although the invasive nature of this test means that indirect methods such as computed tomography angiography (CTA) and magnetic resonance

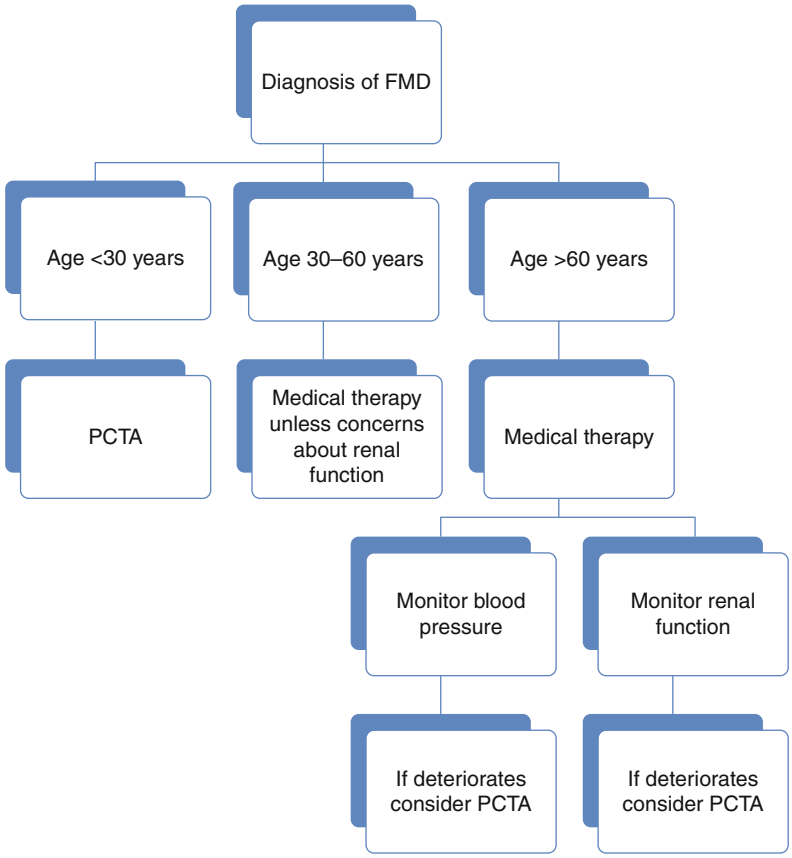

Fig. 34.3 Potential management algorithm for fibromuscular disease. Percutaneous transluminal angioplasty (*PCTA*)

angiography (MRA) are generally accepted to be first-line investigations. The major limitation of indirect angiography is poor specificity in identifying branch vessel disease.

Differential Diagnosis

The angiographic appearance of FMD easily distinguishes it from atheromatous disease, and the non-inflammatory nature of the condition facilitates the use of simple blood markers of inflammation (e.g. CRP/ESR) in distinguishing it from a vasculitic aetiology. A more challenging differential diagnosis is segmental arterial mediolysis. This is a poorly understood condition that may actually be a subtype of FMD. Here, spontaneous arterial occlusion, aneurysm formation and dissection can all occur – typically associated with severe pain from infarction of visceral organs. The acute onset pain and presentation in a more elderly population (50–80 years old) help distinguish segmental arterial mediolysis from FMD.

Treatment

Historically, percutaneous transluminal angioplasty without stenting (PCTA) has been considered as first-line therapy for hypertension secondary to FMD. However, no form of revascularisation (surgical or percutaneous) has ever been compared to medical therapy in a randomised controlled trial (RCT). With the primary aim of therapy being to control blood pressure, patient age (perhaps a surrogate marker of disease duration) appears to be an important factor. In patients aged <30 years, PCTA for FMD has a cure rate (defined as blood pressure <140/90 mmHg off antihypertensive medications) in excess of 60 %. This progressively falls to under 15 % in patients aged >60 years [3]. It is unclear whether the reduced cure rate represents an evolution of the natural history of the disease process or an increased incidence of coexistent primary hypertension with older age. Current opinion favours managing older patients with medical therapy and reserving PCTA for cases in which blood pressures cannot be controlled or renal function begins to deteriorate [2]. For young patients with both newly diagnosed hypertension and FMD, PCTA may be more appropriate as first-line therapy. Registry data will describe long-term outcomes and better inform treatment decisions in the future. Figure 34.3 suggests a basic treatment algorithm.

Atheromatous Renal Artery Disease

The umbrella term renal artery stenosis is useful to describe physical loss of luminal diameter, but fails to distinguish between atheromatous and non-atheromatous causes. A more specific term is atheromatous renovascular disease (ARVD).

Most clinical studies of ARVD have considered the respective roles of revascularisation and medical therapy. The open surgical techniques pioneered in the 1950 and 1960s have been almost entirely replaced by percutaneous approaches. Percutaneous interventions were introduced in the 1980s and have evolved with improvements in technology from angioplasty alone to angioplasty and stenting, or primary stenting, which offer higher rates of long-term vessel patency. Despite these continued improvements, *no RCT has ever demonstrated superiority of an interventional approach over standard medical therapy for clinical outcomes such as progressive renal dysfunction, cardiovascular or renal events or mortality*. However, many questions remain, as the ARVD population *cannot* be considered a single homogenous group.

Prevalence

Many cases of ARVD are clinically silent, making it difficult to accurately estimate disease prevalence. Interpretation of available data is complicated both by temporal changes in availability of diagnostic tools and also by changes in attitudes towards use of these resources following publication of 'negative' RCTs such as the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial [4]. With these caveats considered, the most definite statement that can be made is that ARVD is not rare in the general population aged >65 years (annual incidence 0.5 %; prevalence 7 %) and is recognised as a primary cause of ESKD in a proportion of these patients (annual incidence of ESKD due to ARVD 1.3–1.7 %; prevalence 0.7–1 %) [5]. Ethnicity is not a significant factor in the development of ARVD.

Populations enriched with other vascular disease have higher rates of ARVD. Given the anatomical proximity of the abdominal aorta and the iliac vessels to the renal arteries, it is unsurprising that 20 and 40 % of patients with atheromatous disease in these respective areas have ARVD. However, the association extends to more distant vascular beds, with high rates of ARVD found in patients with carotid (10 %) and coronary (40 %) disease.

Although ARVD is a recognised cause of hypertension (and patients with ARVD are invariably hypertensive), it is often uncertain whether elevations in blood pressure are a cause or consequence of ARVD. Histological study supports the possibility that both pathological processes often coexist – renal biopsies from ARVD patients show a 50:50 split between presence of lone intrarenal atherosclerotic disease and intrarenal atherosclerotic disease with additional intrarenal hypertensive disease [6].

Screening the hypertensive population does not seem to increase identification of ARVD. Unselected screening data of hypertensive patients (>180 mmHg systolic and/or 100 mmHg diastolic) presenting to the emergency room describes an 8 % prevalence of ARVD. However higher rates of all cause RAS (including, e.g. FMD) are described when young hypertensive patients or patients with abdominal bruits are screened, with a pooled prevalence rate of 14 %. This suggests a need for more targeted investigations.

Aetiology

Despite the significant associations with other vascular pathologies, the effects of classical risk factors for development of atherosclerosis are less clear in ARVD than, e.g. coronary artery disease. Although the associations of CKD with smoking and diabetes may skew the data, single centre comparison of patients investigated for ARVD did not describe a difference in smoking rates or prevalence of diabetes mellitus between patients with normal or abnormal renal angiograms. This is despite higher rates of other vascular disease in the patients found to have ARVD [7]. The surprising lack of effect of smoking is confirmed in other data, but systematic reviews appear to suggest that increased rates of ARVD are observed in diabetic patients [8].

Given that patients with a single kidney can have an eGFR in the normal range, it is not immediately clear why unilateral RAS should lead to loss of renal function. It is most likely that renal parenchymal damage, secondary to 'flow-independent' effects of the stenosis (e.g. hypertension/micro-emboli), is the main arbiter of functional loss. In support of this, there is no correlation between degree of stenosis and level of proteinuria in ARVD, but an inverse relationship between eGFR and proteinuria. Indeed level of proteinuria is emerging as a possible marker of likelihood of improvement in eGFR following revascularisation. Even minor elevations (>0.6 g/24 h) correspond to large reductions in the chance of renal functional benefit from intervention [9].

Investigation for ARVD

As for any patient with CKD, measurement of baseline blood pressure, renal function and proteinuria should be performed. However, the key decision in the investigation for ARVD is which imaging modality is most appropriate.

Does a Patient with Asymmetrical Kidneys on Ultrasound Require Further Investigation?

Recent RCT data into the effect of revascularisation on prognosis in ARVD have at times been misinterpreted as a reason not to investigate the renal vessels where there is asymmetry of the kidneys on ultrasound. It is important to recognise that RAS is not the sole cause of differing kidney sizes, with primary renal dysplasia and reflux nephropathies typically

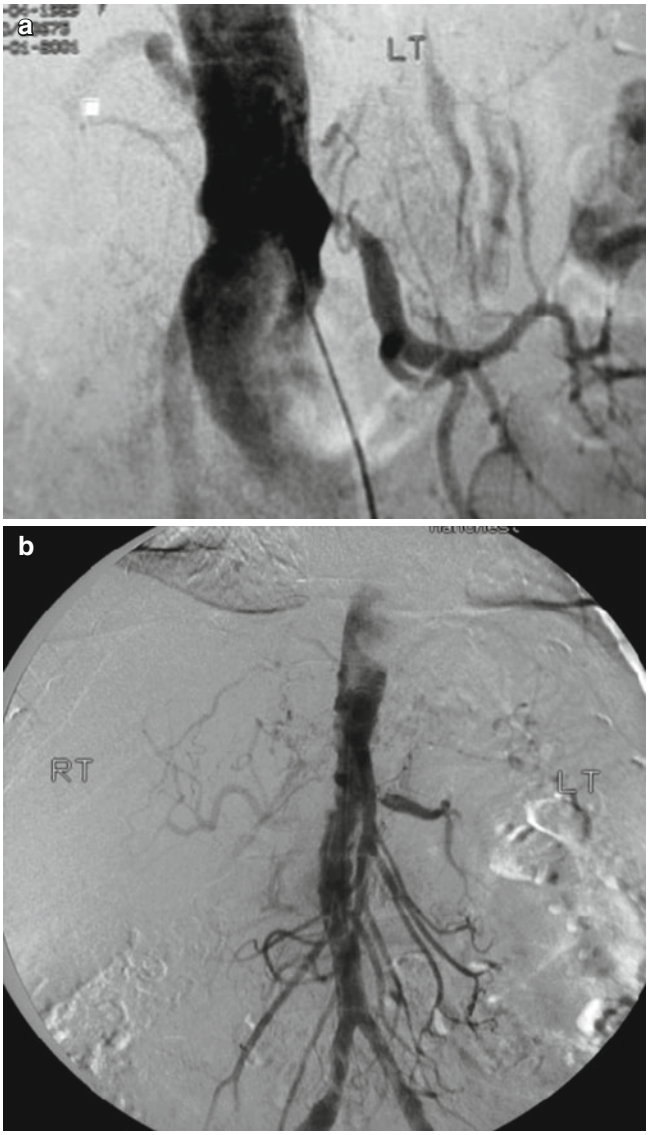

Fig. 34.4 Direct angiography in atherosclerotic renal vascular disease. (**a**) Seventy per cent left renal artery stenosis. (**b**) Right renal artery occlusion and 98 % left renal artery stenosis

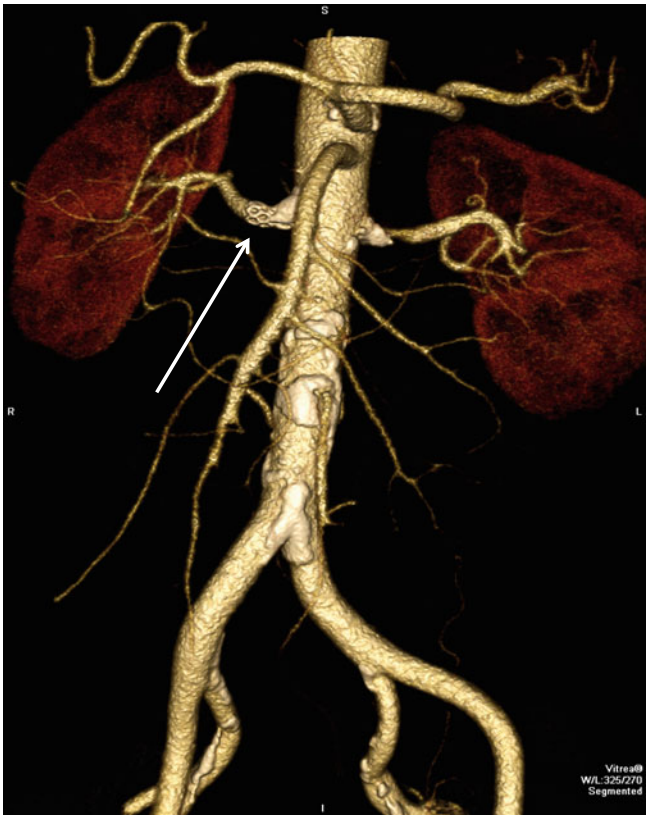

Fig. 34.5 Computed tomography angiography in atherosclerotic renal vascular disease. Reconstructed CT angiogram demonstrating patent left renal artery and patent right-sided renal artery stent (*arrow*)

resulting in asymmetric organs. As such, further investigation into the cause of renal asymmetry (and for associated complications) should be considered. Thus the decision centres around which is the best diagnostic tool?

Renal Artery Imaging

Direct angiography (Fig. 34.4) has been championed as the gold standard for diagnosis of ARVD, but it is an invasive procedure, only provides 2-D views and no functional data. As such, a variety of indirect methods have been adopted to minimise patient risk. Captopril renography has fallen into disuse; as although sensitive and specific for identification of unilateral stenoses, it is less reliable in the context of impaired renal function. Whilst local resources will play a key role in choice of investigation, duplex ultrasound (DUS), computed tomography angiography (CTA – Fig. 34.5) and magnetic resonance angiography (MRA) are all viable options to diagnose ARVD. In patients with mild to moderate (e.g. eGFR >30 ml/min) *and stable C*KD, all three investigations are comparable in terms of sensitivity and specificity and have negative predictive values in excess of 98 % [10]. Table 34.1 further compares the three techniques.

Where patients present with acute kidney injury or advanced renal dysfunction, there are often concerns that the iodinated contrast given for CTA may precipitate contrast-induced nephropathy. Although the likelihood of this is low (with online risk calculators available), the risk can act as a barrier to use of CTA. In the same settings, there is a potential risk of nephrogenic systemic fibrosis associated with the gadolinium-based contrast agents used during MRA. Therefore, in these specific settings, DUS is the most desirable test.

Cardiac Imaging

In over 95 % of patients with ARVD, an abnormality of either left ventricular function or structure can be demonstrated on transthoracic echocardiography, with risk of deterioration in all these parameters over time [11]. Baseline

Table 34.1 Diagnostic imaging techniques for atherosclerotic renovascular disease

Technique	Advantages	Disadvantages
Duplex ultrasound	Entirely non-invasive	Time consuming
	No contrast or radiation	Operator dependent
	Able to monitor disease progression	Technical failure rate >10 % (bowel gas, obesity, etc.)
Computed tomography angiography	Widely available tool	Contrast and radiation exposure Risk of contrast nephropathy
	Reproducible results	Calcified vessels can limit interpretability of images
	Most sensitive technique	Can overestimate stenosis
Magnetic resonance angiography	No risk of contrast nephropathy	Can overestimate stenosis
	No radiation	Risk of nephrogenic systemic fibrosis
	Reproducible images	

cardiac imaging is therefore an appropriate request. Currently this is of more prognostic than therapeutic benefit, although there is some limited evidence describing improvements in cardiac structure following renal artery revascularisation. Whilst published reports lack end point data, and RCT evidence is lacking, this is an area of great interest. High-quality randomised data comparing cardiac structural outcomes between medical and interventional therapy is anticipated later in 2012 [12].

Revascularisation

As of 2012, there have been five RCTs published comparing medical therapy with or without percutaneous revascularisation in ARVD. These studies (and others currently in progress) are summarised in Tables 34.2 and 34.3. A range of clinical outcome measures, rate of change in renal function and blood pressure and hard end points such as death, cardiovascular events and progression to renal replacement therapy have been assessed. No trial has shown a conclusive benefit of revascularisation over medical therapy for any outcome measure.

The first three trials published between 1998 and 2000 used angioplasty alone. Subsequently, it was established that better long-term angiographic outcomes occurred when angioplasty was coupled with bare metal stenting (PTRAS). This technique was therefore adopted for more recent trials [4, 14]. This difference in interventional technique limits direct comparison between RCTs. Small patient numbers, short follow-up periods and low rates of statin/rennin angiotensin blockade use in early trials further limit their applicability to current practice. The most recently published trial, ASTRAL, is by far the largest study (806 patients recruited worldwide compared with 140 in the next largest RCT) and has the longest follow-up period (mean >3 years). As such, much of current practice is based on data from this study. Its principal inclusion criterion was that, in a patient with anatomically significant RAS, it should be unclear whether the patient might benefit from revascularisation. Trial data was therefore skewed towards low-risk patients, who were the majority randomised in the trial. Higher-risk presentations of ARVD (who would potentially have the greatest benefit from revascularisation) were underrepresented in ASTRAL.

Stable CKD or Incidentally Diagnosed ARVD

Available evidence does not support revascularisation for patients with stable CKD. Real-world experience has duplicated trial findings, emphasising the need to focus on appropriate medical therapy for these patients. Acceptance of this finding is important to minimise risk of complications from intervention (discussed below). Whilst incidentally diagnosed ARVD could be considered to be the same as ARVD with stable CKD, specific outcome data exist for patients found to have RAS during another angiographic procedure. In line with trial data, when incidental cases of ARVD were compared between those that were revascularised versus those who were not, no difference was seen in terms of blood pressure or renal function at 12 months.

The overall lack of benefit from revascularisation when examining renal dysfunction as a primary outcome measure is almost certainly due to the slow rate of loss of renal function seen in ARVD. The annual eGFR loss associated with ageing is around 0.7 ml/min/1.73 m^2/year, with the average rate of loss in ARVD only slightly higher than this. As such, any longitudinal difference in renal function between medical and interventional groups would be subtle and require an RCT to be powered to very high patient numbers to identify a statistical difference. This raises the possibility that an interventional study would be more likely to identify differences in cardiovascular event (CVE) rates. Whilst ASTRAL showed almost identical CVE rates in each treatment group (with an annual event rate of 10 %/year), this was not the primary study end point, and other ongoing studies, most notably the Cardiovascular Outcomes in Renal Atherosclerotic Lesions trial (CORAL), have been designed to specifically answer this question.

Table 34.2 Published randomised controlled trials in atherosclerotic renovascular disease

Trial and intervention	Patient number and baseline details	Medications	Primary end points	Secondary end points	Limitations	Results
SNRASCG	55 patients	A2B – 0 %	Change in BP and sCr	Number of drugs to control BP	No angiotensin blockade	No differences between groups within follow-up period
1998	57%male	Statin – not documented			6-month follow-up period	
PCTA	Age 60				Small patient number	
	sCr 159 μmol/L					
	BP 190/100	Antiplatelet – all per protocol				
EMMA	49 patients	A2B – unclear	Change in ABP	Complication rate	Small patient numbers	No difference in ABP.
1998	73 % male	Statin – not documented		Daily dose of blood pressure medications	6-month follow-up period	Reduced daily dose in PCTA group
PCTA	Age 59	Antiplatelet – all per protocol				
	sCr 103 μmol/L					
	BP 150/90					
	Minimum stenosis 60 %					
DRASTIC	106 patients	A2B – 22 %	Change in blood pressure at 3 and 12 months	Number of drugs to control BP	50 % cross over from medical to interventional arm	No difference in manual BP at 3 or 12 months
2000	61 % male	Statin – 39 %		Daily dose of blood pressure medications	Short follow-up period	Reduction in BP at 12 months when measured by automated device for revasc group
PCTA [13]	Age 60	Antiplatelet – all in PCTA group. Unclear in medical group		Creatinine clearance		Reduction in number of drugs for revasc group
	sCr 1.25 mg/dl					
	BP 179/104					
	Minimum stenosis 50 %					
STAR	140 patients	A2B – 56 %	20 % reduction in creatinine clearance	Complication rate	28 % of patients randomised to PTRAS not revascularised	No difference in creatinine clearance or BP
2009	63 % male	Statin – all per protocol		Blood pressure change	High procedural complication rate – 3 patient deaths; 1 patient dialysis dependent	No cardiac event or mortality difference
PTRAS [14]	Age 66	Antiplatelet – all per protocol		Cardiovascular events		High complication rate in interventional group
	sCr 149 μmol/L			Mortality		
	BP 161/82					
	Minimum stenosis >50 %					
ASTRAL	806 patients	A2B – 42 %	Rate of change in renal function	Blood pressure change	No reference lab	No difference between arms for any end point
2009	63%male	Statin – 95 %		Time to cardiovascular or renal event	Patients felt likely to benefit from revascularisation potentially excluded	
PTRAS [4]	Age 70	Antiplatelet – 77 %		Mortality		
	sCr 179 μmol/L					
	BP 150/76					
	Av. stenosis 75 %					

Study abbreviations: *SNRASCG* The Scottish and Newcastle Renal Artery Stenosis Collaborative Group, *EMMA* The Essai Multicentrique Medicaments vs. Angioplastie Study Group, *DRASTIC* The Dutch Led Renal Artery Stenosis Intervention Cooperative Study Group, *STAR* The Stent Placement for Renal Artery Stenosis Trial, *ASTRAL* The Angioplasty and Stenting for Renal Artery Lesions Trial. Year listed is year of publication
Abbreviations: *PCTA* percutaneous renal angioplasty, *PTRAS* percutaneous renal angioplasty and stenting, *A2B* angiotensin blockade, *ABP* ambulatory blood pressure, *sCr* serum creatinine, *BP* blood pressure, *Revasc* revascularised

Table 34.3 Ongoing randomised controlled trials in atherosclerotic renovascular disease

Study	Recruitment information	Primary end point	Other information
CORAL	Target of 1,080 patients Minimum 60 % stenosis with 20 mmHg pressure gradient or 80 % stenosis with no pressure gradient Blood pressure >155 mmHg despite 2+ antihypertensive medications	Composite event-free survival from cardiovascular and renal events (cardiovascular or renal death, stroke, myocardial infarction, admission with congestive heart failure, progressive loss of renal function)	947 patients recruited Standardised medical therapy Embolic protection devices used in a proportion of patients Due to report 2013
NITER	Target of 100 patients Minimum 70 % stenosis	Composite of death, renal replacement therapy and >20 % reduction in eGFR	
RADAR	Target of 300 patients	Change in eGFR over 12 months	Measurements of BNP made as part of protocol Also assesses change in heart failure status Study terminated due to slow recruitment progress
RASCAD [12]	Single centre study. Target 168 patients All patients undergoing coronary angiography screened for ARVD	Positive screens randomised to medical therapy to PTRAS Primary end point progression of left ventricular hypertrophy	Early results presented – no difference in progression of LVH between the 2 arms

Study abbreviations: *CORAL* Cardiovascular Outcomes in Renal Atherosclerotic Lesions trial, *NITER* Nephropathy Ischemic Therapy trial, *RADAR* A randomised, multi-centre, prospective study comparing best medical treatment versus best medical treatment plus renal artery stenting in patients with haemodynamically relevant atherosclerotic renal artery stenosis, *RASCAD* Stenting of Renal Artery Stenosis in Coronary Artery Disease
Abbreviations: *ARVD* atherosclerotic renovascular disease, *eGFR* estimated glomerular filtration rate, *BNP* brain natriuretic peptide, *LVH* left ventricular hypertrophy

Will New Investigations and Improved Revascularisation Techniques Alter Outcomes?

The negative findings of RCTs were not predicted due to a range of case reports and series describing benefit from intervention. It is likely that selection bias accounts for the bulk of this discrepancy. Hence, more focused selection of patients likely to benefit from revascularisation (discussed below) may be an important approach. In addition to an increased recognition of the need for accurate clinical phenotyping, there is the potential that serum biomarkers could aid selection of patients most likely to benefit. Of a range of markers under investigation, the most promising thus far is brain natriuretic peptide (BNP). Studies assessing BNP level in relation to blood pressure response from revascularisation have shown that patients with a BNP level >50 pg/ml (average baseline eGFR 66 ml/min/1.37 m^2) have a higher likelihood of a blood pressure reduction following PTRAS. This finding is more marked in patients with a >70 % stenosis or refractory hypertension [15]. The Sirolimus-Eluting vs. Bare Metal Low Profile Stent for Renal Artery Treatment trial failed to demonstrate significant benefit of drug-eluting stents at 2 years. More promising is the use of embolic protection devices (EPD). Crossing a renal artery lesion with an undeployed stent risks causing disruption of the stenosis and release of downstream emboli. These emboli may contribute to the rapid eGFR losses noted when patients with CKD stage 1 or 2 undergo revascularisation. Dual antiplatelet therapy at the time of PRTA can reduce the proportion of patients with distal embolisation from 50 to 36 % [16], but use of downstream EPD to capture larger particles is an attractive proposition. In a small pilot RCT where these devices have been deployed in conjunction with glycoprotein IIa/IIIb inhibition, significant improvements in eGFR have been seen at 1 month (compared with eGFR reductions in other treatment groups) [17].

A final consideration is long-term outcome data from existing studies. Given the slow rate of loss of renal function in ARVD, it is possible that even a 3-year follow-up period is too short a time frame to describe a functional benefit from revascularisation. Additionally, the possibility of lower long-term rates of cardiovascular events in revascularised patients due to improved cardiac remodelling must be considered. Future analysis of data from ASTRAL may add weight to, or refute, these propositions.

Acute and Chronic Heart Failure

Approximately 5 % of patients with ARVD present with flash pulmonary oedema (FPO). Although this patient group has yet to be investigated in an RCT or case control series, this presentation is accepted as an indication for PTRAS [18]. Despite the lack of high-grade evidence, this approach is appropriate based on what data are available – an unmatched series of 39 patients with FPO showed a significant reduction in hospitalisation rates following revascularisation from 2.4/year to 0.3/year [19].

As discussed above, significant cardiac structural changes are observed in ARVD, and over 30 % of elderly patients with chronic heart failure (CHF) have coexistent ARVD [20].

With examples of cardiac structural benefit described following revascularisation, there is interest in the potential role of PTRAS in the treatment of chronic heart failure. High-quality data with end point information is lacking, but case series describe improved NYHA status and reduced hospitalisation rates following intervention [19]. Further data may arise from cardiac imaging sub-studies of ASTRAL (there was a trend to reductions in heart failure admissions noted in the revascularisation group of the main study) and the Stenting of Renal Artery Stenosis in Coronary Artery Disease (RAS-CAD) study [12].

Renin-angiotensin blockade is recognised as an important therapy in treatment of both CHF and ARVD with morbidity and mortality benefits. Though angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are well tolerated in ARVD, there remains a small group of patients for whom these treatments are associated with a significant decline in renal function. Revascularisation can allow safe use of renin-angiotensin blockade in previously intolerant patients [21]. As such, intervention can be considered a tool to facilitate optimal medical therapy.

Renal Anatomical Parameters

Although increased mortality is observed in patients with higher degrees of stenosis, a direct causal link cannot be made, due to increased coexistent coronary disease in these patients. Sub-analyses of patients with >70 % RAS in RCT data have not shown any difference in outcome following PTRAS than in patients with a lower percentage stenosis. As such, the degree of lumen loss is not considered a reliable guide to intervention.

In contrast to vascular anatomical details, renal volume at the time of angiography has the potential to become a key tool in identifying patients suitable for revascularisation. A subset of patients who receive dramatic functional benefit from revascularisation are thought to have renal tissue which, whilst not functioning, has yet to undergo irreversible damage – so-called hibernating parenchyma. Studies which have related the isotopic GFR of the kidney with RAS to its parenchymal volume (measured by MRI) suggest that selecting organs with the highest volume-GFR ratio can potentially select patients most likely to improve renal function following PTRAS [22]. Though not yet a routine clinical tool (and complicated by use of gadolinium as a contrast agent), this may prove to be important in future.

Rapid Loss of Renal Function and Refractory Hypertension

Refractory hypertension (defined as a blood pressure >160/90 mmHg despite three or more different antihypertensive agents) is considered by some as a potential indication to revascularise a patient with RAS. In part, this position is supported by an early RCT published by the Dutch Renal Artery Stenosis Intervention Cooperative Study Group (DRASTIC) [13]. Although the study was not powered to examine this end point, patients saw reductions in their blood pressure from an average of 190/111 mmHg at 3 months to 169/102 mmHg at 12 months suggesting further studies with this group are warranted. Within ASTRAL, a limited prespecified analysis of patients with rapidly declining renal function (greater than a 20 % or 100 μmol/L increase in serum creatinine in the 12 months before enrolment into the study) was performed. For the 96 patients fitting these criteria, there was a non-significant reduction in serum creatinine at 12 months in the revascularisation group compared to the medical group. Firm conclusions were limited by the wide confidence intervals observed, but again a patient-level meta-analysis of trials could add clarity.

Further work into patients with rapid loss of renal function is limited by the lack of a consensus definition. However, even in the more robustly defined field of acute kidney injury (AKI), data on the role of revascularisation is also limited. There are reports of escape from acute dialysis following revascularisation (typically in the context of bilateral disease or a single functioning kidney). However, these cases almost certainly consider acute arterial occlusion resulting in parenchymal ischaemia rather than the more common scenario of decompensation of a collateral circulation that has developed from, e.g. lumbar or capsular vessels. In the latter example intervention to the disturbed main vessel haemodynamics may have little to do with the AKI, and as such, intervention is futile.

Complications of Revascularisation

Although there is a possibility that minor complications (e.g. discomfort) may be over-reported in RCT data, it is clear that PTRAS has potentially serious side effects and should not be undertaken lightly. Meta-analysis of 687 patients represented in data published between 1991 and 1998 found that 9 % of renal angioplasty procedures resulted in a serious complication (e.g. significant blood loss, renal infarction, loss of renal function), with an overall 1 % mortality rate. Although the serious adverse event rate within ASTRAL was lower (6.8 %), there were 2 deaths, but there were 3 deaths related to only 46 PTRAS procedures in STAR.

Medical Therapy

Given the overall 'negative' findings in trials of revascularisation versus medical therapy in ARVD, an understanding of appropriate use of pharmacotherapy is vital. Despite this, a lack of concordance between trials makes it difficult to define optimal medical therapy. We would suggest that renin-angiotensin blockade in conjunction with statin therapy should be considered first-line treatment for all patients with

ARVD, with antiplatelet agents strongly considered on a case-by-case basis. These interventions have benefits in excess of blood pressure and proteinuria reduction and should be complimented by general measures to manage risk in CKD such as smoking cessation advice, good diabetic control and taking exercise.

Renin-Angiotensin Blockade

The importance of tight blood pressure control is well recognised in all cause CKD, with a widespread appreciation that blockade of the renin angiotensin aldosterone system (RAAS) provides renal benefits in excess of those delivered solely by the associated blood pressure reduction. In ARVD these agents reduce both blood pressure and risk of mortality to a greater extent than other antihypertensive agents.

Historically RAS has been considered a contraindication to RAAS blockade due to concerns over associated deterioration in renal function. However, only a minority of patients (even those with significant bilateral disease) are unable to tolerate supervised introduction of RAAS blockade [21], with any changes in eGFR reversible on withdrawal of the agent.

Second-Line Treatment of Hypertension

For ARVD patients with blood pressure not controlled by RAAS inhibition, data on second- and third-line agents is scarce. CORAL has defined thiazide diuretics as a second-line agent (replaced by loop diuretics where there is advanced renal dysfunction), with beta-blockers and calcium channel blockers third-line agents. Although no outcome data support use of diuretics in ARVD, the understanding that resistant hypertension in CKD is often due to underuse of diuretics, and especially that salt-water retention is increased by RAAS overstimulation, makes these agents a logical choice.

Support for use of beta-blockade comes from recognition of increased local sympathetic and adrenergic activity in ARVD. This local increase is associated with elevated serum noradrenaline concentrations which have been linked to both reduced eGFR and the increased cardiovascular mortality. There are some data which suggest that beta-blockade following revascularisation leads to improved renal functional outcomes and lower rates of re-stenosis. Renal artery denervation, which has been shown (in a non-ARVD population) to reduce peripheral blood pressure, may be helpful, but as yet there are no data in the ARVD population to support its use.

Statins

The evidence supporting statin therapy in ARVD has a clear narrative. Though early case reports describing regression of stenosis with statin therapy have not been duplicated, it is certain that rate of progression of stenosis is slowed. In addition, statin-treated patients (even with a normal lipid profile) have been shown to have lower rates of death and progression to dialysis [23].

Revascularised patients also benefit from treatment with statins, with a reduction in risk of death of over 80 %. Although the mechanism of benefit is not clear it is most likely achieved through a composite effect of reduced renal fibrosis, reduced left ventricular hypertrophy and the wider cardiovascular advantages of these agents.

Antiplatelet Therapy

The historical perspective of antiplatelet therapy in all forms of atheromatous disease makes an objective assessment of the role of these agents in ARVD challenging. With the coexistent burden of vascular disease in ARVD, the use of antiplatelets is easy to justify. Although the DOPPS study did not identify a benefit of aspirin therapy in dialysis-dependent patients, sub-analysis of patients with mild to moderate CKD in primary prevention studies have shown significant reduction in the rate of vascular events, albeit with a significant increase in bleeding risk [24]. Less information is available regarding alternative agents such as clopidogrel (which may have reduced pharmacological activity in CKD).

The time point for which there is definitive evidence for antiplatelet agents in ARVD is at time of intervention. The amount of micro-emboli released during stenting is significantly reduced by clopidogrel loading in combination with aspirin therapy (although the long-term functional benefits are not yet established).

A summary of the basic considerations and management for the more common clinical presentations of renovascular disease is provided in Table 34.4.

Renal Artery Embolic Disease

Cholesterol Emboli

Cholesterol embolisation occurs when cholesterol crystals are released following the rupture of an atheromatous plaque. These crystals can occlude any small vessel, precipitating a multisystem disorder. Although the true incidence and prevalence are unknown, cholesterol embolisation is typically described as a disease of the over 60s (with a male preponderance) and may account for between 5 and 10% of cases of acute kidney injury within this demographic.

Risk factors

Given the link between cholesterol embolisation and pre-existing atheromatous disease, it is unsurprising that risk factors are common between these conditions (age over 60 years, hypertension, diabetes, smoking history, Caucasian). More clinically relevant are the precipitants for embolisation, which *have* changed over time. Whilst 20–30 years ago, spontaneous plaque rupture was

Table 34.4 Example clinical scenarios

Scenario	Actions	
Patient aged <30 years presenting with hypertension	Examine for bruits Indirect angiography to investigate for FMD	Good candidate for angioplasty if angiogram shows FMD
Patient with eGFR 20 ml/min and asymmetric kidneys on ultrasound	Do not expose to gadolinium. Image renal vessels with either DUS or CTA	Consider admission for hydration for CTA
Elderly patient with chronic CKD stage 3 and renal artery stenosis	Address lifestyle factors – e.g. smoking, diabetic control	Prescribe angiotensin blockade as first-line blood pressure control. Commence statin and consider antiplatelet agent
Patient presenting with recurrent acute onset pulmonary oedema	Assess left ventricular function. If systolic function preserved, perform indirect renal angiography	If significant bilateral renal artery stenosis, consider referral for revascularisation
Patient with suspected renal artery stenosis and previously preserved renal function presenting acutely dialysis dependent	Doppler imaging of renal vessels	Refer for renal artery angioplasty and stenting
Greater than 25 % reduction in eGFR following initiation of angiotensin blockade to treat chronic heart failure	Consider volume state and concurrent nephrotoxic drugs Indirect renal angiography	If significant stenosis and no other culprit medications, consider revascularisation
Patient with uncontrolled symptoms of CHF and renal artery stenosis	Review echocardiograms regarding LVMI	If uncontrolled symptoms, increased LVMI and significant stenosis, consider revascularisation

FMD fibromuscular disease, *DUS* duplex ultrasound, *CTA* computed tomography angiography, *CHF* chronic heart failure, *LVMI* left ventricular mass index, *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease

almost the sole cause, the greatly increased use of interventional endovascular techniques has resulted in over 75 % of contemporary cases being iatrogenic. Coronary angiography appears to carry the highest risk, with approximately 20 cases per 1,000 procedures. Additionally, anticoagulation can precipitate cholesterol emboli, although this is a rare complication [25].

Presentation

As with vasculitis, disease presentation depends entirely on the vessels involved. Severe acute kidney injury is relatively rare, with only the minority of patients having a significant abrupt rise in serum creatinine within a few days of an interventional procedure. Mostly there is slow, progressive loss of renal function spread over a period in excess of 4 weeks. This is suggestive of two distinct pathologies – the first where a large crystal burden causes acute vascular occlusion within the kidney and a second where there is either slow sustained emboli release and/or a regional inflammatory response to emboli dispersed to the kidney.

In patients with renal involvement, the two other most commonly affected organ systems are the skin (presenting with livedo reticularis, blue toes, purpura, ulceration and gangrene) and the gastrointestinal tract (presenting with non-specific abdominal pain, bleeding, ischaemic bowel, pancreatitis). Neurological manifestations are less common and harder to define; but where retinal embolisation occurs, this should dramatically raise the index of suspicion for the diagnosis.

Diagnosis

It is highly likely that many minor or clinically asymptomatic cases of cholesterol embolisation go undetected, especially following endovascular revascularisation therapy.

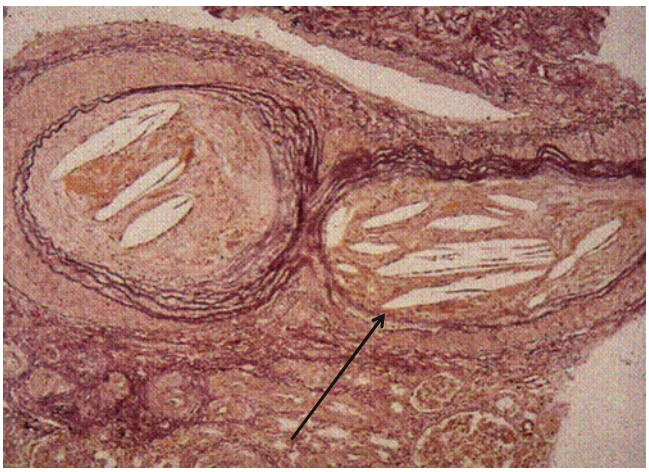

Fig. 34.6 Renal biopsy demonstrating small vessel cholesterol atheroemboli (*arrow*)

However, the presence of acute/subacute renal dysfunction in the context of a clear precipitant and other signs of peripheral embolisation is sufficient to confirm the diagnosis of cholesterol embolisation. Where this triad does not exist (and if retinal emboli cannot be demonstrated on fundoscopy), tissue is required to make a definitive diagnosis and exclude conditions such as small vessel vasculitis. Renal biopsy is the gold standard test (providing a positive diagnosis in over 75 % of cases – Fig. 34.6), but samples from other areas, e.g. skin, can be valuable if this is contraindicated.

Prior to biopsy, there are few serum markers of diagnostic use, but new onset proteinuria (assuming no coexisting renal disease cause) may be suggestive. A relationship between cholesterol embolisation and hypocomplementaemia is not

consistently reported, and the presence of this should perhaps direct more attention to the possibility of other diagnoses such as subacute bacterial endocarditis. Of more clinical use is the presence of systemic eosinophilia, which, although transient, is commonly seen at high levels where there is cholesterol embolisation. This finding, although sensitive, is not specific and should also prompt consideration of acute interstitial nephritis if there has been a newly introduced medication.

Treatment

There is no definitive treatment for cholesterol embolisation, and between 40 and 60 % of patients suspected to have the diagnosis require acute dialysis with a significant proportion remaining dialysis dependent. Withdrawal of any clear precipitant is a vital first step. Thereafter, the mainstay of treatment is statin therapy. Although there is a lack of randomised data or a mechanistic explanation, there is good, prospective, evidence that these agents reduce risk for ESKD [26]. There is no large-scale evidence of benefit for corticosteroids and use is often limited to patients with severe multisystem disease.

Renal Artery Thromboembolism

Renal artery thromboembolism, if not immediately treated, leads to irreversible renal parenchymal damage and loss of renal function. Unfortunately, due to the non-specific nature of the symptomatology and the rarity of the condition, this is often a delayed diagnosis.

Pathology

The primary source of emboli causing renal infarction is cardiac (typically left atrial clots secondary to atrial fibrillation), although cases linked to sickle cell disease and septic emboli are reported.

Presentation and Diagnosis

Most patients are aged over 60 years and present with severe acute onset flank/abdominal pain, which can be associated with a fever and nausea and vomiting. There is no gender or racial preponderance.

Whilst the presence of new onset dipstick haematuria/proteinuria is supportive of renal thromboembolism, the key to making the diagnosis is a high index of clinical suspicion and expedient angiographic imaging (either direct angiography or CTA, as USS has very low sensitivity). When reviewing imaging it should be understood that up to 10 % of cases present with bilateral thrombi.

Treatment

The rarity of the condition makes treatment recommendations difficult. Prompt initiation of anticoagulation with i.v. heparin (followed by warfarin when stable) is the accepted first step, followed by percutaneous thrombolysis or thrombectomy as soon as possible. Renal functional prognosis is highly dependent on speed of diagnosis and treatment [27].

Renal Vein Disease

Diseases of the renal veins are rare and mainly limited to three disease presentations.

Renal Vein Thrombosis

Aetiology

In adults, renal vein thrombosis (RVT) most commonly occurs in the context of nephrotic level protein loss, typically in association with membranous nephropathy. However, associations with other glomerular diseases (e.g. lupus), malignancy (e.g. renal cell carcinoma) and hypercoagulable states (e.g. protein C & S deficiency, postpartum) are also described. Whilst the risk of all types of thromboembolic events is elevated in nephrotic states, RVT is one of, if not the most common. Why this should be the case is uncertain, but reduced renal vein pressures and increased local thrombin production secondary to glomerular injury are two proposed factors.

Diagnosis

Where RVT is acute, occlusive and bilateral, AKI will develop. However, most patients slowly develop a progressive thrombus, allowing the development of a collateral venous system. These two distinct pathologies account for the disparity in reported incidence of venous thromboembolic events in patients with membranous nephropathy when considering overt clinical presentations (less than 10 %) versus those identified by screening (50–80 %) [28].

The key symptom of an acute thrombus is loin or flank pain, typically associated with a fever, nausea and vomiting or occasionally presenting as pulmonary emboli. Leucocytosis and dipstick haematuria are common, making pyelonephritis a key differential diagnosis. Chronic thrombi are usually non-occlusive, asymptomatic and characterised by increased proteinuria and subtle alterations in renal function.

Treatment

There is no defined *gold standard* treatment strategy for renal vein thrombosis. The decision will depend mainly on local expertise and experience, but also in part on which kidney is affected (with the left kidney less likely to rupture in the setting of acute venous occlusion due to a pre-existing collateral drainage system). Thrombolysis can be considered where there are bilateral renal vein thrombi or

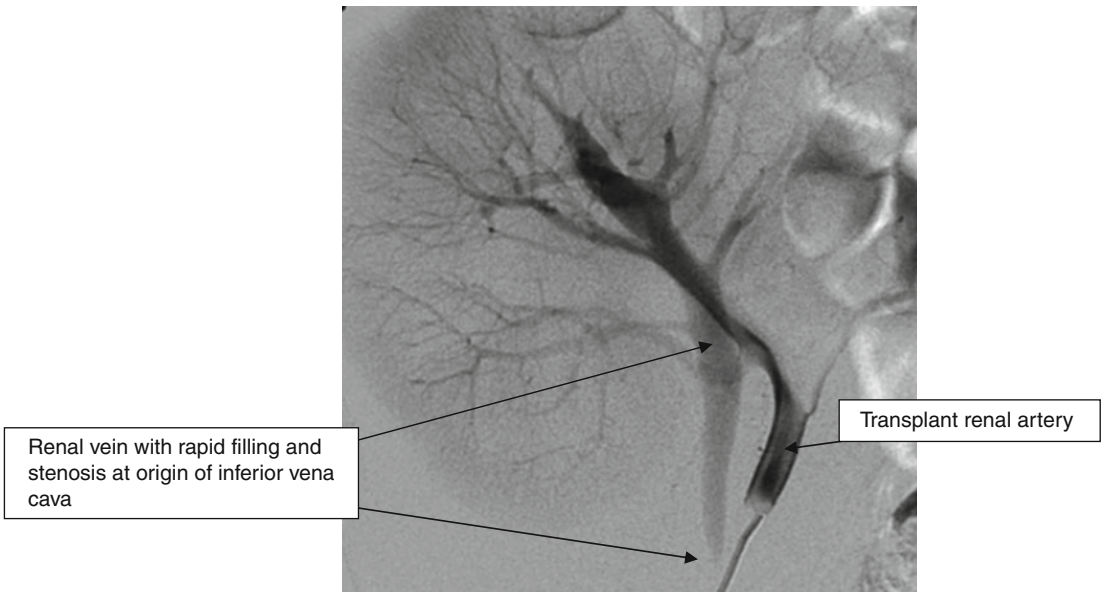

Fig. 34.7 Renal vein stenosis in a renal transplant with an arteriovenous fistula. Angiogram shows very rapid (almost simultaneous) venous return and a venous stenosis at the point of the inferior vena cava

pulmonary embolus, with medical anticoagulation (using warfarin or low molecular weight heparin) then used as chronic therapy. These agents can be utilised as first-line therapy in less severe cases. Interventional approaches including percutaneous thrombectomy, surgical venous bypass and nephrectomy are available. However, these approaches tend to be reserved for cases of extensive clot or where there is risk of capsular rupture.

Renal Vein Stenosis

Very rarely the renal vein can suffer a non-occlusive stenosis resulting in proteinuria and or reduced function. The diagnosis is easily missed and may only be picked up incidentally in the venous phase of contrast studies (see Fig. 34.7).

Left Renal Vein Entrapment Syndrome

Left renal vein entrapment (also referred to as the 'nutcracker syndrome') results from entrapment of the renal vein between the abdominal aorta and the superior mesenteric artery. The presentation can be at any age and is classically with left flank pain (which can extend to the left testicle) with non-visible or visible haematuria or orthostatic proteinuria. Diagnosis can be made either by ultrasound or computed tomography imaging.

Treatment of the 'nutcracker syndrome' is dependent on the severity of symptoms. In the most extreme cases, renal vein stenting, surgical venous bypass and autotransplantation have all been used [29].

Lymphatic Disease

Cystic dilatation of renal lymphatic channels, renal lymphangiomatosis (also called cystic lymphangioma or renal lymphangiectasia), is an exceptionally rare condition in which the renal lymphatics fail to adequately drain, resulting in structural malformations. The kidneys can enlarge to such a size that they may mimic polycystic disease or cause an obstructive uropathy. As there is minimal effect on renal function, management is normally conservative. The exception is during pregnancy in which the condition may be exacerbated to the point of requiring percutaneous drainage [30].

Internet Resources

The Fibromuscular Dysplasia Registry: http://www.fmdsa.org

Contrast nephropathy risk calculator: http://www.qxmd.com/calculate-online/nephrology/contrast-nephropathy-post-pci

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