Lilach O. Lerman
Stephen C. Textor
Editors

Renal Vascular Disease

Springer

Renal Vascular Disease

Lilach O. Lerman • Stephen C. Textor
Editors

Renal Vascular Disease

Springer

Editors

Lilach O. Lerman, MD, PhD
Division of Nephrology
and Hypertension
Mayo Clinic
Rochester, MN
USA

Stephen C. Textor, MD
Division of Nephrology
and Hypertension
Mayo Clinic
Rochester, MN
USA

ISBN 978-1-4471-2809-0 ISBN 978-1-4471-2810-6 (eBook)
DOI 10.1007/978-1-4471-2810-6
Springer London Heidelberg New York Dordrecht

Library of Congress Control Number: 2014933678

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

We dedicate this book to the memory of our colleague and friend, Juan Carlos Romero, whose energy and enthusiasm were a constant source of inspiration to better understand the physiology of the kidney and blood pressure control. We hope that this text will reflect our gratitude for models and direction provided by masters in the field of hypertension, including Aram Chobanian, Hans Brunner, and Haralambos Gavras.

We are grateful to our spouses, Susan Bertram and Dr. Amir Lerman, for their patience and support throughout these projects.

Lilach O. Lerman, MD, PhD
Stephen C. Textor, MD

Preface

This is an exciting time for those working in the field of kidney vascular injury and repair. Despite, or perhaps partly because of, major advances in imaging diagnosis and therapy, large vessel occlusive disease of the renal arteries continues to pose major clinical challenges and can be a major source of confusion. In the United States and most western countries, atherosclerosis is the major cause of renovascular disease (RVD) and has been recognized as a major contributor to the development of renovascular hypertension for more than 80 years. Atherosclerotic RVD increases in prevalence with age and is a common incidental finding in the aging US and European populations. In recent years, clinical reports repeatedly implicate atherosclerotic RVD as a major contributor to resistant hypertension, refractory or sudden congestive heart failure, and parenchymal renal injury. Occasionally, RVD is associated with end-stage renal disease (ESRD). Widespread introduction of non-invasive methods for identification of RVD using ultrasound, CT, and MR imaging allows more facile identification of these syndromes than ever before.

Recent data suggest that the manifestations of RVD are far more complex than previously understood. The unique complexity of the kidney circulation and the regional metabolic requirements render it particularly susceptible to disturbances of both macro- and microvascular compartments. Hemodynamic processes affecting the main renal arteries are capable of initiating multiple responses, including stimulation of endocrine, paracrine, neurogenic, inflammatory, and fibrogenic pathways. Once fully activated, many of these processes become self-propagating and no longer depend on the original hemodynamic effects of the vascular disease. Hence, atherosclerotic RVD is characterized by a gradual transition from a primarily hemodynamic limit to kidney perfusion to an active inflammatory and fibrotic injury that fails to reverse after simply restoring vessel patency. See Fig. 1.

Importantly, both surgical and endovascular procedures aimed at restoring main renal artery patency alone regularly have proven ambiguous, if not actually disappointing. While individual case reports and selected series unequivocally establish “proof of principle” that renal revascularization sometimes can reverse accelerated hypertension and restore kidney function, these cases are exceptional. As with many procedures, their clinical value depends heavily upon careful patient selection. Wider application of revascularization and several prospective, randomized trials over the past two decades indicate only occasional benefit in groups of patients enrolled primarily on the basis of anatomically identified atherosclerotic RVD. How best to recognize the

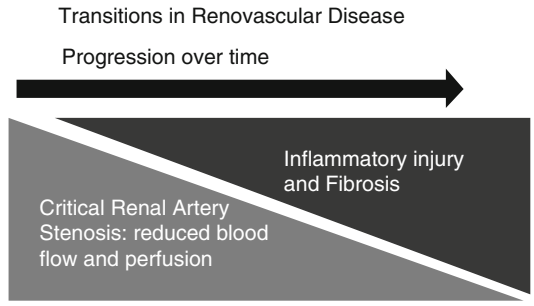


Fig. 1 Schematic illustration depicting the gradual transition from a purely hemodynamic limitation on blood flow (*far left*) induced by critical levels of renovascular occlusion to a state of parenchymal inflammation that stimulates tissue injury and eventual fibrosis within the kidney. Factors regulating the pace and degree of this transition are poorly understood. Restoration of large vessel patency can allow recovery of kidney function at some stages (likely at the *far left*), but at some point has little effect upon mechanisms that produce progressive kidney damage (*far right*). Although restoring kidney perfusion may be important, additional measures to abrogate inflammatory pathways may be necessary for recovery of function at more advanced stages

viability of kidneys beyond vascular occlusion and how to augment repair and restoration of function remain major challenges.

Nevertheless, substantial progress made over the past decade warrants revisiting the current status of the pathogenesis and treatment of atherosclerotic RVD. For example, our perception of the contribution of renal ischemia to the pathophysiology of the disease, recognition of microvascular remodeling evolving distal to the stenosis as determinants of reversibility of kidney injury, and novel treatment platforms all provide new and exciting opportunities in this field.

This book was undertaken with the goal of providing an accessible, current summary of renovascular disease. Few texts have addressed these disorders specifically. Perhaps the most recent publication in the USA was provided in 1996 by Drs. Novick, Scoble, and Hamilton. Much of that book was focused upon imaging and technical issues related to developments regarding renal revascularization pioneered by its authors. Since then, our understanding of RVD has evolved substantially, including current perspectives regarding the epidemiology of atherosclerotic RVD, its clinical manifestations, and the interaction with injury pathways related to the kidney. Our goal with this current text has been to provide comprehensive overviews of the clinical paradigms that are emerging, both as regards RVD and its role in chronic kidney disease (CKD), cardiovascular risk, and the cardiorenal syndromes. We have invited distinguished contributors to share their work which better defines our understanding of kidney oxygenation and metabolism. Sections addressing inflammatory vasculitides such as Takayasu's arteritis and fibromuscular dysplasias expand the perspective of large vessel disturbances and their effect on kidney function. Importantly, basic research directed at the mechanisms of kidney injury in both experimental models of RVD and clinical investigation is included here. These studies are providing truly novel paradigms that we believe will lead to "adjunctive" measures that may either

supplant or add to restoring blood flow in allowing recovering of renal microvascular injury and restoring kidney function.

It is our hope that assembling these materials will provide a useful resource for both clinicians and investigators willing to tackle the challenges of RVD. We believe that much of the confusion regarding clinical consequences and management of renal artery stenosis may be reduced by better understanding the varied stages and pathways that participate in cardiovascular and renal injury in this disorder.

Rochester, MN Lilach O. Lerman, MD, PhD
Rochester, MN Stephen C. Textor, MD

Contents

Contributors

Thomas C. Bower, MD Division of Vascular and Endovascular Surgery, Department of Surgery, Mayo Clinic College of Medicine, Rochester, MN, USA

Vincent J. Canzanello, MD Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

Alejandro R. Chade, MD Department of Physiology and Biophysics, Department of Medicine, Department of Radiology, University of Mississippi Medical Center, Jackson, MS, USA

Kiran B. Chandrashekar, MD Departments of Medicine and Nephrology, University of Mississippi Medical Center, Jackson, MS, USA

Leslie T. Cooper, MD Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

Alfonso Eirin, MD Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

William J. Elliott, MD, PhD Division of Pharmacology, Pacific Northwest University of Health Sciences, Yakima, WA, USA

Roger G. Evans, BSc (Hons), PhD Department of Physiology, Monash University, Melbourne, VIC, Australia

Eric R. Fenstad, MD, MSc Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

Shaun M. Gifford, MD, MS Department of Vascular and Endovascular Surgery, Mayo Clinic, Rochester, MN, USA

James F. Glockner, MD, PhD Department of Radiology, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN, USA

Monika L. Gloviczki, MD, PhD Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

Joseph P. Grande, MD, PhD Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Barbara A. Greco, MD Renal Division, Department of Medicine, Baystate Medical Center/Tufts New England Medical Center, Western New England Renal and Transplant Associates, Springfield, MA, USA

Stella P. Hartono, MD, PhD Student Mayo Graduate School, Mayo Clinic, Rochester, MN, USA

Sandra M.S. Herrmann, MD Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

Michael R. Jaff, DO Massachusetts General Hospital Institute for Heart, Vascular, and Stroke Care, Massachusetts General Hospital, Boston, MA, USA

Luis A. Juncos, MD, FAHA, FASN Departments of Medicine, Nephrology, and Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA

Luis I. Juncos, MD, MS, PhD Department of Medicine, J. Robert Cade Foundation, Cordoba, Argentina

Philip A. Kalra, MD Department of Renal Medicine, Salford Royal NHS Foundation Trust, Salford, UK

Garvan C. Kane, MD, PhD Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

Amir Lerman, MD Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

Lilach O. Lerman, MD, PhD Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

Arnaldo F. Lopez-Ruiz, MD Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA

Yoshiki Matsuo, MD, PhD Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

Sanjay Misra, MD, FSIR, FAHA Department of Vascular Interventional Radiology, Mayo Clinic, Rochester, MN, USA

Paul M. O'Connor, BS, PhD Department of Medicine, Georgia Regents University, Augusta, GA, USA

Gustavo S. Oderich, MD Department of Vascular and Endovascular Surgery, Mayo Clinic, Rochester, MN, USA

James Ritchie, MB, ChB Department of Renal Medicine, Salford Royal NHS Foundation Trust, Salford, UK

Ahmed F. Saad, MB, BCh Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

Stephen C. Textor, MD Division of Nephrology and Hypertension, Mayo Clinic College of Medicine, Rochester, MN, USA

Terri Jo Vrtiska, MD Department of Radiology, Mayo Clinic College of Medicine, Rochester, MN, USA

Ido Weinberg, MD, MSc Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA

Xin Zhang, MD Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

Part I

Epidemiology and Clinical Manifestations

Atherosclerotic Renovascular Disease: Epidemiology and Clinical Manifestations

1

James Ritchie and Philip A. Kalra

Abstract

Atherosclerotic renovascular disease (ARVD) is a frequently occurring condition, most commonly observed in patients with other macrovascular diseases. The presence of ARVD is associated with a significantly increased risk for cardiovascular morbidity and mortality. Although factors associated with systemic atheroma are implicated in the development of ARVD, the subsequent evolution of hypertension and renal impairment is more complex, with both whole organ and local factors playing important roles.

Keywords

Atherosclerotic renovascular disease • Epidemiology • Presentation • Prevalence • Prognosis • Progression • Renal artery stenosis • Risk factors

Abbreviations

AKI	Acute kidney injury
ARVD	Atherosclerotic renovascular disease
CAD	Coronary artery disease
CHF	Chronic heart failure
CKD	Chronic kidney disease
DUS	Doppler ultrasound
FPE	Flash pulmonary edema
PVD	Peripheral vascular disease
RAAS	Renin angiotensin aldosterone system
RAS	Renal artery stenosis
RCT	Randomized controlled trial
USRDS	United States Renal Data System

Introduction

The term atherosclerotic renovascular disease (ARVD) describes both partial and total atheromatous occlusions of the renal arteries. These luminal narrowings often occur in conjunction with macrovascular disease in other organ systems, and have complex relationships with end-organ damage to the kidneys. In this chapter we explore the epidemiology of ARVD and describe the clinical consequences of this somewhat heterogeneous condition.

J. Ritchie, MB, ChB • P.A. Kalra, MD (✉)
Department of Renal Medicine,
Salford Royal NHS Foundation Trust,
Stott Lane, Salford M6 8HD, UK
e-mail: jpritchie@mac.com; philip.kalra@srft.nhs.uk

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_1,

How Is ARVD Defined?

Anatomical Definition

ARVD refers to a spectrum of changes ranging from any atherosclerotic narrowing of the arteries supplying the kidneys, through focal stenosis of one or more renal arteries, renal ischemia and kidney atrophy, to the extreme of complete occlusion of the blood supply to one or both kidneys. Despite a wealth of published literature, consensus on what defines an anatomically "significant" atherosclerotic renal artery stenosis (RAS) does not exist. Typically, research publications employ angiographic measurements, with a RAS in excess of either 50, 60 or 75 % deemed to be "significant." Whilst this is by no means unreasonable, the limitations of this approach should be considered. Firstly, data in which expanded balloons were used to generate an aorto-renal pressure gradient in humans with a unilateral RAS demonstrated that only when a stenosis reached 70–80 % was there activation of the renin angiotensin aldosterone system (RAAS) [1]. Hence one could question the value of reports where RAS has been defined as <50 % – although an easy counterpoint to this argument would be the increased mortality seen with even low degrees of RAS [2], presumably largely due to extra-renal vascular disease including organ injury related to the systemic inflammatory state of atherosclerosis. Secondly, such absolute definitions fail to consider possible compound effects of bilateral disease; for example, is a unilateral 50 % stenosis of greater clinical significance than bilateral 40 % stenoses?

Syndromic Definition

Given that ARVD can be associated with perturbations in renal function, blood pressure, cardiac structure and function, and changes in mortality risk even where RAS is <50 %, it is clear that a single biplane angiographic measurement is a blunt tool for determining overall "significance" of disease. As such we would suggest that a stenosed renal artery, where there is associated evidence of either one or more of renal parenchymal damage, altered neuro-hormonal state or cardiac structural or functional change (with no alternative explanation), should be considered to be of clinical significance whatever the degree of RAS. We accept that this is somewhat esoteric, and much of the clinical data discussed in this chapter are based upon structural definitions. Hence (unless otherwise specified), we have taken >50 % focal RAS as being of clinically significance. The term "Ischemic Nephropathy" is now also widely utilized and refers to chronic kidney disease (CKD) that is caused by ARVD.

Potential Collateral Circulation of the Kidney

In the majority of cases, development of atheroma in the renal artery is a chronic process. As such there is normally reciprocal development of collateral vessels supplying the diseased kidney to maintain parenchymal viability. Typically these collateral vessels form from lumbar arteries with inferior mesenteric, testicular/ovarian and suprarenal arteries also recognized as potential sources [3]. These vessels are able to contribute over 50 % of basal renal blood flow. Animal models suggest that this collateral circulation begins to develop when main vessel stenosis exceeds 40–50 % [4].

Prevalence of ARVD

Unselected Populations

ARVD is often an asymptomatic disease, as it sometimes may be diagnosed only during investigation for other vascular pathology, or investigation of CKD. Despite the morbidity and mortality associated with the condition widespread screening is not justified for ARVD and as such limited data exist to describe the true population prevalence. Some of the best available information comes from a single study of "free-living" patients aged over 65 years living in the United States. Here, 834 patients underwent Doppler ultrasound (DUS) examination of their renal vessels, with an incidental RAS in excess of 60 %

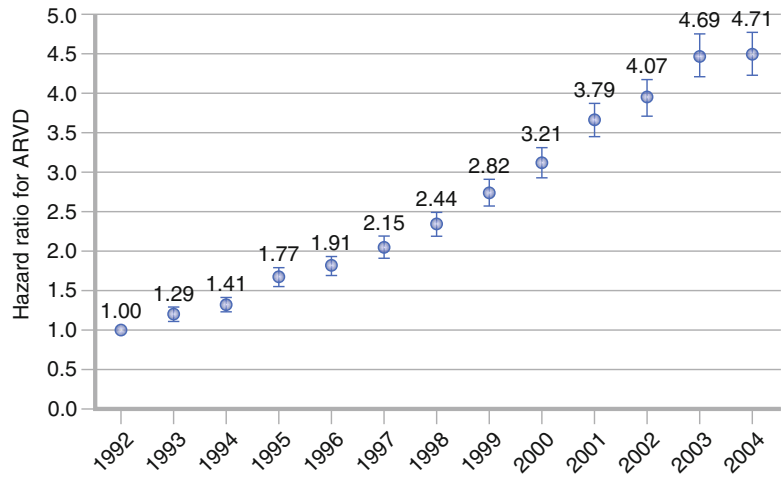


Fig. 1.1 Relative annual prevalence of ARVD in Medicare population between 1992 and 2004, with 1992 as comparator group (Adapted with permission from Kalra et al. [8])

identified in 6.8 % of patients (with 12 % of these being bilateral). Of note, patients with a positive investigation had significantly higher systolic blood pressures (142 vs. 134 mmHg, p = 0.007) [5]. This study is complimented by a review of over 1,900 computed tomography angiograms performed in potential renal transplant donors, where evidence of atherosclerotic RAS (severity not specified) was found in 5 % of patients; with a strong relationship to increasing age [6].

Registry Data

Further information can be gleaned from analysis of claims data obtained from the Medicare random 5 % denominator file and from coded diagnoses found in the reports of the US Renal Data System (USRDS). In an analysis of Medicare claims data from 1999 to 2001 (>1.1 million patients aged over 67 years), the prevalence of ARVD diagnosed in this elderly population was 0.54 % with an annual incidence for new diagnoses between 2000 and 2001 estimated at 3.7 cases per 1,000 patient years [7]. A subsequent study examining Medicare claims data from in excess of 16 million patients between 1992 and 2004 described a similar incidence (3.09 cases per 1,000 patient years) but noted a progressive increase in rates of diagnosis, with patients in the 2004 claims data 4.7 times more likely to receive a diagnosis of ARVD than those in the 1992 data [8] (Fig. 1.1). Although these analyses have not been repeated in more recent years within Medicare, data from the USRDS suggest a reversal in this trend with reports between 2004 and 2009 describing falls in the overall prevalence (1.0–0.7 %) and incidence (1.7–1.3 %) of ARVD as a cause of end-stage kidney disease in the US dialysis population [9]. The most likely explanation for this biphasic pattern is increased enthusiasm for investigation during the 1990s (with heightened physician awareness, improved access to diagnostic tools and ready availability of interventional treatment techniques), which has been tempered more recently in light of negative randomized controlled trials (RCT) into percutaneous intervention [10].

Ethnic Variation

There is apparent substantial worldwide variability in the primary cause of RAS, which in itself may represent variations in chronic disease burdens in different parts of the world. Atheromatous causes represent over 90 % of RAS cases in Western populations but sequelae from vasculitis are said to account for in excess of 60 % of cases diagnosed in India and South Asia. Despite these geographic differences, however, there does not appear to be a racial bias for development of ARVD. In 324 patients evaluated for potential renovascular hypertension, Caucasian ethnicity was not an independent risk factor for positive

investigation (OR 1.5, p=0.07) [11] and in the community based screening study by Hansen et al. ethnic distribution was identical between groups with positive and negative DUS investigations (23 % African-American, 77 % Caucasian) [5]. When comparison has been made between non-Caucasian populations investigated for ARVD, no significant difference in the proportion of positive investigations was noted between African-American and Hispanic patients [12]. No comparative studies have specifically addressed the Asian population; however, a single centre study of 202 Japanese patients with risk factors for ARVD found evidence of RAS >50 % in 20 % of patients investigated using magnetic resonance angiography [13]. In a Japanese population of 729 patients with known cardiac or cerebrovascular disease ARVD was present in 5.2 % of patients [14].

Prevalence in Selected Populations

Hypertensive Populations

Despite the frequent association of ARVD with hypertension, it is often questionable whether a given RAS lesion is causative; a rigorous definition of true "renovascular hypertension" necessitates cure or substantial improvement in hypertension after dilatation of RAS [15]. Although there has not been a specific study addressing the prevalence of RAS in the general hypertensive population, a figure of 2 % is widely quoted. Systematic review of angiographic studies of patients where renovascular hypertension was clinically suspected (e.g. elevated blood pressure at a young age; hypertension that was resistant to therapy) found a pooled prevalence of 14.1 % [16]. In another study in which patients presenting to a German Emergency Room with uncontrolled hypertension (>180 mmHg systolic and/or 100 mmHg diastolic) were screened for causes of secondary hypertension, significant RAS was identified in 8.1 % of patients [17]. The overall lack of data negatively affects the ability of physicians to predict the presence of ARVD in patients referred for investigation, with clinical suspicion for undiagnosed stenosis having a positive predictive value of only 40 % [18].

Chronic Kidney Disease and Dialysis

There are no data to inform us as to how rates of ARVD vary according to different stages of CKD. In the analyses of Medicare claims data, patients with CKD (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2) were between 2.55 [8] and 4.6 [7] times more likely to have ARVD than those with higher eGFR, but these data do not provide insight into cause/effect relationships. In an analysis of claims data from 160,000 incipient United States dialysis patients between 1996 and 2001, the overall prevalence of ARVD was 9.1 %, but less than half of these cases had ARVD coded as their primary cause of renal failure [19]. Again, as this analysis was based on claims data rather than on the results of comprehensive screening the true prevalence is likely to have been underreported. Indeed, rates of 22–41 % have been reported in smaller studies that screened sequential patients at initiation of dialysis [20, 21] (with bilateral disease present in 11–16 % of patients).

Prevalence in Patients with Other Macrovascular Disease

ARVD is very commonly associated with atheromatous disease in other vascular beds and these associations are emphasized in Medicare data analyses (Table 1.1) [7]. ARVD is frequently identified during investigation of patients with non-renal macrovascular diseases, although the clinical implications of this are not always certain. It is therefore of interest to specialists in many different disciplines including cardiology, vascular surgery, stroke medicine and hypertension. As a consequence there have been many studies undertaken in selected groups of patients with cardiovascular disease, and these populations are likely to be enriched with patients with ARVD.

Coronary Artery Disease

There are strong links between ARVD and coronary artery disease (CAD), with evidence of RAS (>50 %) found in 15 % of patients referred for diagnostic coronary angiography (with approximately one third of these patients having significant bilateral disease) [22, 23]. These figures have remained constant over the last two decades despite increased awareness of modifiable vascular risk factors over this time. Table 1.2 shows the

Table 1.1 Prevalence of ARVD in the US medicare population along with macrovascular risk factors

	Prevalence			
	No ARVD (n = 10,85,250)	ARVD (n = 5,875)	ARVD AHR (95 % CI)	*P*
AKI (%)	0.8	10.3	1.59 (1.43–1.77)	<0.0001
CKD	2.3	24.6	4.61 (4.27–4.98)	<0.0001
Hypertension	53.4	90.8	4.31 (3.93–4.73)	<0.0001
DM	17.9	32.5	0.89 (0.84–2.61)	0.0001
CAD	24.9	66.8	2.45 (2.3–2.61)	<0.0001
CCF	13.6	37.6	1.01 (0.94–1.07)	0.9
CVD/TIA	12	36.9	1.58 (1.49–1.67)	<0.0001
PVD	12.7	56	3.96 (3.74–4.2)	<0.0001
Mesenteric Ischemia	0.2	1.9	2.38 (1.93–2.93)	<0.0001
AAA	0.5	6.4	3.38 (3.0–2.81)	<0.0001

Adapted with permission from Kalra et al. [7]
AAA indicates abdominal aortic aneurysm, *CI* confidence interval, *DM* diabetes mellitus, *CCF* congestive cardiac failure, *TIA* transient ischemic attack *AHR* adjusted hazard ratio, *CKD* chronic kidney disease, *DM* diabetes mellitus, *CAD* coronary artery disease, *PVD* peripheral vascular disease, *CVD/TIA* cerebrovascular disease / transient ischemic attack, *AKI* acute kidney injury

more recent larger studies that have examined the comorbid presence of RAS in patients undergoing investigation for CAD [22, 24–30]. That the relationship between CAD and ARVD is most probably a marker of overall atheromatous burden has been highlighted by there being a significant relationship between the number of diseased coronary vessels and probability of concurrent RAS (odds ratio of RAS in the presence of triple vessel disease/previous coronary bypass graft 1.74, compared to lesser burden of CAD) [22, 25].

Heart Failure

As would be anticipated, the frequent association of ARVD with CAD and hypertension can result in structural heart disease which can be detected in the majority of patients; consequent syndromes of cardiac dysfunction are also highly prevalent. In series where renal vessels are imaged in patients with symptoms of chronic congestive cardiac failure (CHF), evidence of RAS >50 % can be found in approximately 30–50 % of patients [31, 32]. In a CHF population in Northern England patients with significant RAS were more likely to have renal dysfunction, be taking higher doses of diuretics but lower doses of angiotensin blocking agents, to have prolonged hospital admissions and a negative outcome [32]. Clinical presentations with sudden onset or "flash" heart failure can be life-threatening and may be the first indication of ARVD in about 10 % of patients. The true incidence of this condition may be under-estimated due to the fact that renovascular investigation is undertaken only in a minority of patients with abrupt onset left ventricular failure. Patients with bilateral significant RAS or a solitary functioning kidney are those at greatest risk of this condition. Many of these patients with ARVD and heart failure have preserved left ventricular function, highlighting the relevance of diastolic parameters and measures of ventricular eccentricity.

Cerebral Vascular Disease

RAS can often be identified in patients who have suffered a stroke, with the highest rates observed in patients who also have significant carotid stenosis. In a post-mortem series of 346 patients with clinical evidence of stroke, RAS >75 % could be identified in 10.4 % of all patients (12.1 % of patients with ischaemic stokes), with over four times as many patients with carotid stenosis (>50 %) having RAS than those without carotid stenosis [33]. When an earlier point of the natural history of vascular disease is considered, associations have been noted between the presence of ARVD and increased carotid-intimal thickness in patients with type II diabetes [34]. Although no data exist to describe progression to overt carotid vessel disease, carotid-intimal thickness is commonly used as a surrogate marker for cardiovascular risk.

Table 1.2 Major studies which have examined the co-morbid presence of both coronary artery disease and ARVD (qualification: >200 patients; study within the last two decades)

Author	Year of publication	Number of patients	Type of study	Prevalence of significant RAS	Factors associated with RAS
Ollivier et al. [24]	2009	650	Abdominal aortography following coronary angiography	14.5 % had RAS >50, 3.1 % bilateral disease	Male sex, multi-vessel CAD, hypertension, renal insufficiency
Cohen et al. [25]	2005	843	Abdominal aortography following coronary angiography	11.7 % had RAS ≥75 %	Older age, higher creatinine levels, PVD, number of cardiovascular drugs hypertension, female sex, and 3-vessel coronary artery disease or previous coronary artery bypass graft
Rigatelli et al. [26]	2005	205	Abdominal aortography following coronary angiography	19.5 % had RAS ≥50, 7.3 % bilateral	≥ 3-vessel CAD, age >65 years, and ≥3 cardiac risk factors
Wang et al. [27]	2003	203	Abdominal aortography following coronary angiography	14.8 % RAS ≥50, 2.6 % bilateral	Age, multivessel CAD
Rihal et al. [28]	2002	297	Hypertensive patients, abdominal aortography following coronary angiography	19.2 % RAS >50, 3.7 % bilateral, 7 % had RAS >70 %	Systolic blood pressure, CVA/TIA, cancer
Conlon et al. [29]	2001	3,987	Abdominal aortography following coronary angiography	4.8 % had unilateral RAS ≥75, 0.8 % bilateral ≥75 %	Female sex, increasing age, hypertension, CCF, increased creatinine
Uzu et al. [30]	1997	297	Autopsy series identifying patients who had suffered a MI	12 % had, 28.6 % of these had bilateral RAS	Hypertension, proteinuria and renal insufficiency
Harding et al. [22]	1992	1,235	Abdominal aortography following coronary angiography	>15 % had RAS >50, 11 % unilateral, 4 % bilateral disease	Age, severity of CAD, CCF, female sex, PVD

CAD coronary artery disease, *PVD* peripheral vascular disease, *CCF* congestive cardiac failure, *CVA/TIA* cerebrovascular accident/transient ischemic attack

Table 1.3 Major studies which have examined the co-morbid presence of both aorto-iliac/peripheral vascular disease and ARVD (qualification: >200 patients; study within the last two decades)

Author	Year of publication	Number of patients	Type of study	Prevalence of significant RAS	Factors associated with RAS
Amighi et al. [38]	2009	487	Peripheral angiography followed by renal angiography	15.6 % had RAS ≥60 %	
Androes et al. [39]	2007	200	Peripheral angiography followed by renal angiography	12 % had RAS ≥50 %	Hypertension, CAD, female, DM, aorto-iliac disease, age >60 years, multiple levels of PVD
Leertouwer et al. [40]	2001	386	PVD suspected	32.6 % had RAS ≥50, 22.8 % bilateral	Not analyzed
Iglesias et al. [37]	2000	201	Aorto-iliac	26.4 % had RAS >50 %	Not analyzed
Swartbol et al. [41]	1992	405	Peripheral angiography	49.1 %, 117 moderate, 14 severe RAS	Hypertension, age >70 years, smoking, pathological ECG
Olin et al. [35]	1990	395	PVD/AAA	33–39 % had RAS >50, 13 % bilateral	Hypertension, worse renal function
Salmon et al. [42]	1990	374	Peripheral angiography followed by renal angiography	13.9 % had RAS ≥50, 5.9 % bilateral	

CAD coronary artery disease, *PVD* peripheral vascular disease, *AAA* abdominal aortic aneurysm, *DM* diabetes mellitus

Abdominal and Peripheral Vascular Disease

Due to the close anatomic proximity, coexistent disease of the abdominal aorta is commonly seen with ARVD. In a series of consecutive patients investigated with aortography for either abdominal aortic aneurysm (n = 109) or aorto-occlusive disease (n = 21), 38 and 33 % of patients respectively had a RAS in excess of 50 % [35]. Comparable figures can be found in other angiographic series which report RAS >50 % in 24 % of patients with an abdominal aortic aneurysm [36] and in 26 % of patients investigated for aortoiliac disease [37]. Many studies have sought to determine the co-existence of RAS with peripheral vascular disease (PVD), and RAS >50 % can be found in 30–40 % of patients with symptomatic claudication; the larger studies are detailed in Table 1.3 [35, 38–42]. As is the case with ARVD and CAD, the presence of significant RAS in patients with PVD is associated with an increased risk for major cardiovascular events and death during follow up. Hence in a study of 483 patients with symptomatic PVD, those with severe RAS (15.6 % of all PVD patients had ≥60 % RAS) had a 2.5-fold increased risk for occurrence of any of myocardial infarction, stroke, amputation and death and a 2.9-fold increased risk for death, compared to patients without RAS [38] over a median follow up time of 15 months.

Risk Factors for Development of ARVD

Age

Although it is clear that prevalence of ARVD increases with age, a finding that has not altered in over 50 years [43], conflicting data exist regarding the role of "classical" vascular risk factors in the natural history of the condition. In our own local renovascular database, which comprises over 900 patients with ARVD referred from a 1.5 million population over 20 years, the median age of the population at ARVD diagnosis is 69.6 years and 8.6, 29 and 45.5 % are patients in their fifth, sixth

and seventh decades respectively; 87.1 % of patients are aged >60 years at study entry.

Smoking

Although high proportions of patients entered into interventional studies in ARVD have a smoking history (within ASTRAL 20 % were current smokers and 50 % ex-smokers [10]), there is no direct evidence that smoking per se increases risk for ARVD development. Data from our centre assessing 249 consecutive patients referred for diagnostic renal angiography did not show a significant difference in smoking history between patients with normal and abnormal renal vessels (55.4 % vs. 68.7 %) despite higher levels of non-renal (and renal) atheromatous disease in the ARVD patients [44]. In contrast, a smaller study of 48 hypertensive patients investigated for RAS found higher rates of smoking in patients with positive studies (19/21 vs. 16/27, p=0.04) [45]. It may have been important that the overwhelming majority of smokers with RAS in this study had a greater than 25 pack-year history. This finding has been replicated in a study of 45 incident dialysis patients investigated for possible ARVD. Here, ten patients had a positive study, with a significantly greater pack year history than those patients with normal renal vessels (37 vs. 17 pack years, p=0.016) [20]. These data support a cumulative risk for development of ARVD. Equally, given the adverse effects of smoking on renal plasma flow, it is probable that (even in the absence of a direct effect on the physical stenosis), smoking could further complicate the already compromised intra-renal hemodynamics [46], predisposing to greater renal dysfunction.

Diabetes

Analysis of Medicare claims data suggests a link between diabetes and ARVD, with higher rates of diabetes seen in patients with ARVD (32.5 % vs. 17.9 % in patients without ARVD) and diabetic patients 1.3 time more likely to be diagnosed with ARVD [7, 8]. These figures are comparable to the 30 % diabetes prevalence in patients recruited into ASTRAL. In the Medicare data, it is possible that higher rates of CKD in the ARVD patients were a relevant confounding factor. However, a systematic review of risk factors has shown a pooled prevalence of ARVD of 20 % in patients with diabetes and hypertension [16], making it likely that diabetes is a risk factor for development of ARVD.

Hyperlipidemia

Little data exist to specifically link hyperlipidemia with the development of ARVD, although as in the case with smoking, strong links with other atheromatous conditions make the relationship likely. Our own data showed a slightly higher prevalence of hyperlipidemia (serum total cholesterol >5.2 mmol/l) in patients found to have ARVD (61 % vs. 48 % in those without) [44]. Lipid profiles in ARVD patients follow the same pattern as in patients with coronary or carotid atheroma, with significantly reduced apolipoprotein A1 levels [47]. Other studies have shown increased levels of free-fatty acids (glycerol-glyceride) in patients with ARVD [48], though this may have more important implications for mortality than development of atheroma [49]. However, intervention with statins has been shown to prevent anatomical progression of RAS in a retrospective study, which provides some support to the pathogenic effect of hypercholesterolemia in renal atherogenesis [50].

Hypertension

Of all the classical risk factors for the development of atherosclerosis, hypertension is the hardest to link to ARVD due to potential cause and effect relationships with both RAS and CKD. However, it is clear that elevated blood pressure is a major determinant of CKD in ARVD as it is associated with more severe histological intrarenal damage in ARVD [51], with greater rates of eGFR loss, and with the development of renal atrophy [52]. As such hypertension is an important risk factor for ischemic nephropathy development despite the absence of direct causal evidence in RAS progression.

Novel Risk Factors

Several other circulating markers of cardiovascular risk have been evaluated regarding their relationship to ARVD e.g. Fibrinogen, highly sensitive C-reactive protein (hs-CRP), homocysteine, and lipoprotein(a) [53]. A positive relationship between both hs-CRP and homocysteine and ARVD has been shown in univariate analysis, but these associations have not been sustained in multivariate analysis, and so currently available data cannot inform us as to whether the elevated levels are a cause or result of ARVD [54].

Pathogenesis of Ischemic Nephropathy

Animal and human studies have shown that reduction in renal blood flow and activation of the RAAS typically occur only when RAS are high grade (>70–80 %), and yet reductions in eGFR are observed with RAS of all degrees (i.e. minimal through to high-grade). It follows that the etiology of renal impairment in ARVD is a multifactorial process, and not simply due to the "ischemic" effects of reduced blood flow within the kidney. Indirect confirmation of this hypothesis can be drawn from several studies which have failed to demonstrate an association between degree of RAS and level of renal function [55]. Importantly in ARVD, the amount of proteinuria (another marker of renal dysfunction and prognosis) does not relate to degree of RAS, although it is linked to level of renal function [56]. This suggests that damage to the "substance" or parenchyma of the kidney is the main arbiter of renal dysfunction.

Development of Renal Parenchymal Damage in ARVD

Whole Organ Factors

It is likely that a large proportion of the functional loss observed in ARVD relates to organ damage mediated by "whole organ factors" such as hypertensive damage and microembolization. In samples taken from kidneys nephrectomized due to severe RAS mediated hypertension, evidence of atheroembolic damage was observed in 39 % (though this may have in part been related to prior vascular instrumentation), with hypertensive damage seen in 52 % [51]. In this series of 62 patients, severe tubulointerstitial atrophy was a near universal finding (94 %), although advanced glomerulosclerosis was not a common finding.

Animal Models

This histological pattern of disease can be readily induced in animal model of RAS suggesting that local factors may play an important role. Indeed, animal models have recently shown the fascinating natural history of how renal damage beyond a RAS unfolds, but it should be remembered that these represent relatively short-term changes in uncomplicated, "pure" RAS – in humans, the pathogenesis is complicated by years of prior hypertension and atherosclerosis, and other contributing injurious factors including family history, smoking and medication.

Local Endothelial Factors

In porcine models tubulointerstitial fibrosis develops rapidly following induction of RAS [57]. This occurs in conjunction with a marked thinning of the small blood vessels within the renal tissues – microvascular rarefaction [58] – a recognized factor in progression of kidney disease [59]. These changes are thought to relate to local down-regulation of vascular endothelial growth factor production and increased oxidative stress (shown by reduced levels of superoxide dismutase) in stenosed kidneys [60]. As these microvascular alterations occur within a short space of time after RAS formation, this may represent an early point in the natural history of the disease.

Renin Aldosterone Angiotensin System (RAAS)

Chronic stimulation of the RAAS is a well recognized feature of ARVD, with experimental data stretching back almost 80 years [61]. In addition to haemodynamic effects, angiotensin II contributes to the development of renal damage by

enhancing expression of pro-fibrotic cytokines and growth factors, thus promoting tubulointerstitial fibrosis [62]. As such RAAS activation in ARVD likely has direct damaging effects as well as increasing vulnerability to acute changes in renal function precipitated by volume shifts. Increased levels of brain natriuretic peptide (released predominantly by cardiac myocytes, but also by glomerular epithelial and mesangial cells) may offer some protection from this by antagonizing the RAAS [63].

Effects of ARVD on the Contralateral Kidney

As the majority of ARVD patients have a unilateral stenosis, the question of why so many patients have an overall reduction in renal function (defined by the crude measure of eGFR in clinical practice) is frequently raised. The most pertinent observation is that non-stenosed contralateral organs often do not have a preserved GFR, and can have the same degree of functional impairment (measured by isotope GFR) as the diseased organ [64]. In a series of 60 patients with unilateral stenosis (including cases of <50 % stenosis and patients with fibromuscular disease), a significant difference in GFR between diseased and non-diseased sides was only observed where there was complete arterial occlusion on one side. When and how this reduction in function of the organ with the patent blood supply occurs is therefore a matter of clinical importance. Human histological studies have shown changes in non-stenotic organs which are very similar to those seen in RAS kidneys, and the effects of systemic hypertension on the contralateral organ function is thought to play a pre-eminent role [65]. Additionally, microvascular pressure mediated injury may be relevant in damage of the non-stenosed organ. This hypothesis is based on data from a series of 50 patients in whom magnetic resonance measurements of renal cortical volume were performed. Here there was a suggestion of compensatory hypertrophy in kidneys *contralateral* to a moderate/severe stenosis [66], which conceivably is a marker of glomerular hyperfiltration, and this is increasingly recognized as a long term risk factor for loss of renal function [67]. As with systemic hypertension, the pro-atherosclerotic milieu will also contribute to contralateral renal damage. In pig models, atheroma has been shown to exacerbate the effects of an induced physical stenosis and to associate with worse findings on histological examination [68, 69]. With evidence of intra-renal atherosclerotic disease in the majority of ARVD patients it is likely that the reduction in renal function is also related to the atheromic environment.

Identification of At-Risk Organs Earlier in the Natural History

As described previously, the parenchymal damage associated with ARVD is believed to be the main arbiter of renal dysfunction in ischemic nephropathy. It has been understood for some time that as the burden of parenchymal damage increases, renal volume is lost [66]. Complimentary to this is the concept of "*hibernating parenchyma*" – renal tissue which has reduced function as a direct result of the reduced blood flow associated with RAS, but which has not yet suffered irreversible histological damage [70]. Imaging studies suggest that it may be possible to identify kidneys with hibernating parenchyma before tissue is irretrievably damaged; one technique involves examining the ratio of parenchymal volume (measured by MRI) with isotope single kidney GFR values [71] (a high – volume:GFR signifying a kidney capable of improving its function with renal revascularization). In the future such techniques may help identify patients in the early and potentially modifiable stages of the natural history of their disease.

Progression of Disease in ARVD

The epidemiology of ARVD has changed over the last few decades. Many early reports detailing the natural history of atherosclerotic RAS were limited by either small patient numbers, consideration of specific disease presentations, and, importantly, they were generated in an era when vasculoprotective pharmacotherapy (particularly statins) was unavailable.

Progression of Stenosis

Historically the received wisdom was that ARVD was a progressive disease in terms of both degree of stenosis and loss of renal function. As discussed previously, it is now evident that the absolute degree of RAS has limited value in determination of GFR; equally it is now clear that rates of RAS progression are much lower than previously thought – once the patient is under treatment. One of the earliest serial arteriographic studies was reported in 1984 and showed the progression of RAS (defined as >75 % stenosis) to be 44 %, with progression to renal artery occlusion (RAO) seen in 16 % of 85 patients over 52 months mean follow up [72]. A study of 1,189 patients a decade later showed significant RAS progression in 11.1 % of patients during a mean interval of 2.6 years between angiographic studies [73]. Reports in the early 1990s observed significant progression of RAS in 35 % of patients at 3 years and 51 % of patients at 5 years [74]. This was associated with renal atrophy (>1 cm shrinkage on ultrasound) in 21 % of patients with significant RAS (>60 %) compared to 5.5 % in patients without RAS [52]. These figures are only of historical interest in the current era of statin therapy. Although available data are retrospective, in a study of 79 patients with ARVD, statin treated patients (n = 40) were much less likely to suffer progression of stenosis at 3-years (odds ratio 0.28, p = 0.01) than non-statin treated patients [50] (Fig. 1.2). Here evidence of RAS progression was observed in 6 % of the statin group vs. 30 % of the non-statin treated group. As such, and excluding acute luminal occlusions, rate of progression of RAS is now lower than before if appropriately treated.

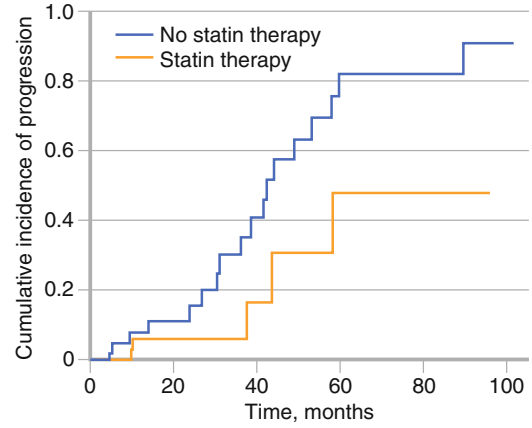


Fig. 1.2 Cumulative incidence of renal artery disease progression stratified according to treatment with or without statin therapy (Adapted with permission from Cheung et al. [50])

Progression of Renal Dysfunction

Just as there have been changes in the rate of RAS progression as the medical management of ARVD has improved, several cohort and trial data sets suggest that modern therapeutic regimes may be having a positive influence on rate of loss of renal function over time. The key pharmacotherapies include statins and angiotensin blockade which are now readily utilized. Large scale RCT data have shown an average rate of eGFR loss in the region of 1–2 ml/min/1.73 m^2/year [10] – figures comparable to most other causes of CKD [75]. However, it is recognized that subgroups of patients exist who lose function at a faster rate. Although it is not yet clear what patient phenotype are at highest risk from this, there is a view that this group may represent a distinct disease sub-type [76]. In parallel with a lower rate of loss of renal function has been a reduction in rates of progression to end stage kidney disease (ESKD). Between 1996 and 2000 in the United States the proportion of incident dialysis patients with a primary diagnosis of ARVD fell slightly from 5.5 to 4.7 % – despite an increased rate of investigation for and diagnosis of ARVD [19]. Our own single centre data that includes 809 ARVD patients diagnosed between 1990 and 2009 have shown a stepwise reduction in the proportion of patients progressing to renal replacement therapy depending upon year of diagnosis. Between 1995 and 2000, 3.5 % of patients diagnosed with ARVD progressed to ESKD, whilst comparable figures were 2.3 % in patients diagnosed between 2000 and 2005 and only 0.8 % of patients diagnosed after 2005 [43].

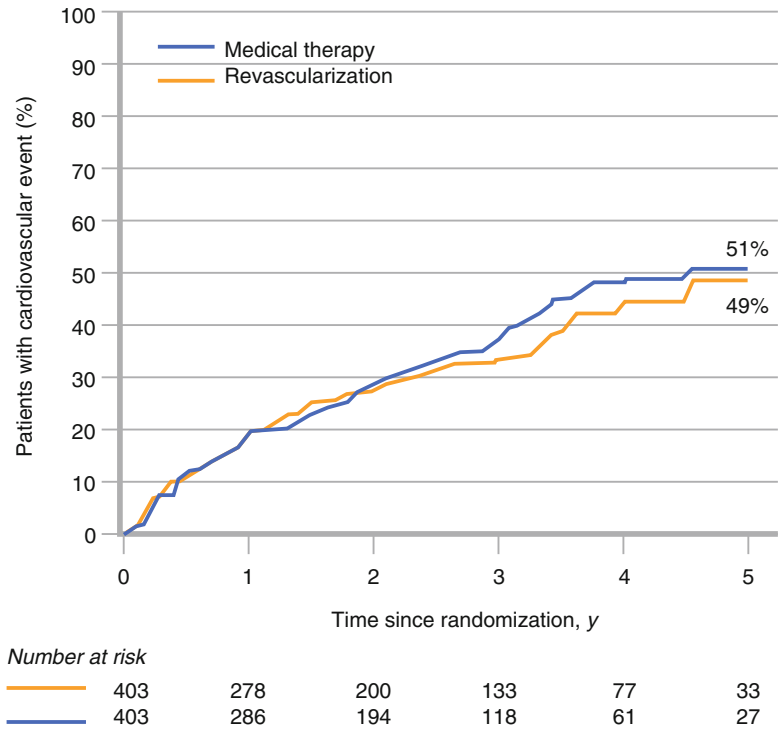


Fig. 1.3 ASTRAL Time to the first major cardiovascular event, which was defined as myocardial infarction, stroke, death from cardiovascular causes, hospitalization for angina, fluid overload or cardiac failure, coronary-artery revascularization, or another peripheral arterial procedure. Such events occurred in 141 patients in the revascularization group and in 145 patients in the medical-therapy group (hazard ratio, 0.94; 95 % CI, 0.75–1.19; P = 0.61) (Adapted with permission from ASTRAL Investigators et al. [10])

Development of Non-renal Vascular Disease

There are extremely strong associations between ARVD and other macrovascular diseases. Importantly this is an on-going relationship, with higher rates of newly diagnosed vascular pathology seen in ARVD populations compared to their non-ARVD counterparts as evidenced by Medicare data from a decade ago – annual stroke rate 18 vs. 5 %, congestive cardiac failure 20 vs. 6 %, peripheral vascular disease 26 vs. 5 % and ischaemic heart disease 30 % vs. 7 % [7]. The two most recently published RCT (both in the era of modern pharmacotherapy) have both observed an approximate 10 % annual incidence of major cardiovascular events (ASTRAL data shown in Fig. 1.3) [10, 77]. Given the links between CAD and ARVD, a relationship with other cardiac structural/functional parameters is to be expected. In a cross-sectional echocardiographic analysis, structural or functional abnormalities were observed in 95 % of ARVD patients (n = 79), with greater rates of left ventricular hypertrophy (78.5 % vs. 46 %), diastolic dysfunction (40.5 % vs. 12 %), and mass index (183 ± 74 vs. 116 ± 33 g/m^2) present when compared to age and eGFR matched controls [78]. When echocardiography was repeated in 51 ARVD patients at 12-months, a significant increase in left ventricular dilatation was observed with a concurrent increase in the degree of eccentricity in left ventricular hypertrophy [79]; there were no patients at this time point described as having a normal heart by echocardiographic criteria.

Clinical Presentations of ARVD

Many cases of ARVD are clinically silent, existing as part of a spectrum of diffuse vascular and/or chronic kidney disease. However, recognizable clinical presentations (or at least clinical scenarios in which ARVD should be considered) exist.

Heart Failure

The near universal prevalence of cardiac structural and functional disturbance found in ARVD has previously been discussed. This can translate into two clinical scenarios.

Chronic Heart Failure (CHF)

Chronic RAAS over activity (as found in ARVD) is a recognized factor in the development of abnormal left ventricular remodeling and dysfunction. With at least 30 % of elderly CHF patients having demonstrable evidence of RAS [31, 32], and over 13 % of patients in ASTRAL requiring admission for fluid overload/heart failure over a median follow-up period of 33 months [10], it is important to determine if ARVD is merely associated with CHF (perhaps playing a role in an ischemic etiology of heart failure), or if a causal relationship exists. Although there are some non-systematic data to suggest that renal artery revascularization can control symptoms of heart failure [80], the only published RCT that assessed the effects of intervention on cardiac structural parameters did not examine cardiac failure as an end-point [81]. Given the healthcare costs associated with CHF, this is an important field for further study.

Acute Cardiac Failure

Better defined is the syndrome of acute pulmonary edema associated with ARVD – a presentation often termed "flash pulmonary edema (FPE)." This is classically defined to be symptoms of acute left ventricular failure in the presence of preserved ventricular function. Whilst high grade, bilateral RAS (or high grade stenosis to a single functioning kidney) is recognized as a typical cause for this dramatic presentation (with 5–7 % of ARVD patients presenting in this manner [82]), other potential causes include cardiac ischemia or acute mitral valve dysfunction. In ARVD the postulated mechanism for development of FPE relates to excess aldosterone secretion. This leads both to volume expansion, but also to increased vascular permeability. Where this occurs in the presence of the increased vascular stiffness and left ventricular diastolic dysfunction associated with CKD and hypertension, abrupt physiological decompensation can result [83]. In the setting of a unilateral RAS the non-diseased kidney is able to suppress its own renin secretion so as to balance the aldosterone excess emanating from the stenosed side; however, this cannot occur as readily where disease is bilateral. Despite the frequency of cardiac abnormalities seen in ARVD, reductions in left ventricular systolic function are less frequent in comparison to the prevalence of diastolic abnormalities; hence is it likely our understanding of FPE will increase as more light is shed on the syndrome of "Heart failure with preserved ejection fraction" [84].

Renovascular Hypertension

ARVD is a recognized cause of secondary hypertension, accounting for 8 % of patients with uncontrolled blood pressure (>180 mmHg systolic and/or 100 mmHg diastolic), which compares with 14 % of such patients having primary or secondary hyperaldosteronism [17]. Although no specific data exist, it is likely that a higher prevalence of ARVD would be found if patients with treatment resistant (or refractory) hypertension were to be systematically screened for RAS. Given the extensive cardiovascular morbidity seen in ARVD, some patients actually have reduced blood pressure as a result of other health issues (e.g. CHF). This somewhat clouds the question of screening and suggests that alternative markers of vascular health (e.g. vascular stiffness or BNP assay) are as important as blood pressure when considering the clinical impact of ARVD.

Loss of Renal Function

Rapid Loss of Function

As detailed previously, the overall rate of progressive eGFR loss in ARVD is slow when considering large cohorts or study populations as a whole. However, a proportion of patients present with more rapid loss of renal function – within ASTRAL 97 patients (12 %) had seen an increase in serum creatinine in excess of 1.13 mg/dl or of 20 % from baseline in the 12-months prior to randomization [10]. Further analyses of the outcome and phenotypic characteristics of this sub-group are warranted as it is currently uncertain whether or not these patients had initially presented with acute kidney injury (AKI), or whether they continued to lose renal function at a faster rate than the remainder of the study population during extended follow-up. One hypothesis would be that these patients represent a sub-group in whom the "hydraulic"

Table 1.4 Number of patients exposed to renin angiotensin blockade (RAB) therapy including tolerability on retrospective and prospective follow-up

	Total who were prospectively on RAB n = 378	Retrospective intolerance or side effect to RAB n = 74	Prospective intolerance or side effect to RAB n = 21
Age (mean (SD), range) (years)	71.4 (9.3), 42–92	70.8 (9.9), 46–87	72.9 (8.7), 54–91
Unilateral RAS >60 %, n (%)	148 (39.2)	25 (33.8)	9 (42.9)
Bilateral RAS >60 %, n (%)	77 (20.4)	13 (17.6)	5 (23.8)

Adapted with permission from Chrysochou et al. [87]

effects of the RAS are more critical than parenchymal damage in determining renal dysfunction, and theoretically at least, a positive response to revascularization might be anticipated.

Acute Kidney Injury (AKI)

The incidence of AKI, either as a presenting feature or as a disease complication, is difficult to estimate in patients with ARVD. In our local data that involved 819 patients, we estimate that the rate of AKI as a presenting feature in ARVD is low – less than 2 % of the overall population. In the context of chronic ARVD, modest AKI typically develops where an acute insult reduces perfusion pressure in the renal circulation to the point where parenchymal viability is compromised. Anuric presentations are limited to scenarios in which there is acute vascular occlusion preceding collateral development [85]. This is typically in the context of high-grade bilateral disease, or stenosis of a single functioning kidney, and such patients would be at increased risk of flash pulmonary edema.

Intolerance of Renin-Angiotensin Blockade

There is evidence that angiotensin blockade (with angiotensin converting enzyme inhibitors or angiotensin receptor blockers) confers prognostic benefit in patients with ARVD [86]. However, as much as this is accepted, there is no doubt that these agents are under prescribed in ARVD due to concerns regarding their potential to cause rapid decline in renal function. This is despite the accumulating evidence that patients are able to tolerate careful introduction of these agents even in the context of bilateral disease [86, 87]. In a series of 621 patients with ARVD managed in this centre, a documented history of renal dysfunction related to angiotensin blockade was present in 71 (11 %). Of these patients, 40 were subsequently successfully re-challenged with angiotensin blockade (13 following revascularization) without acute decline in renal function (Table 1.4) [87]. If patients who underwent a percutaneous interventional procedure are excluded, this still suggests that the true incidence of intolerance of ARVD patients to these agents is under 7 %. The CORAL trial [88] encouraged angiotensin II receptor blockade for first line antihypertensive therapy within the study and should offer further evidence regarding the tolerability of these agents in a high-risk population.

Prognosis in ARVD

The presence of ARVD has significant prognostic implications.

Cardiovascular Morbidity

As we have described earlier, patients with ARVD suffer increased rates of macrovascular events and progressive disturbance in cardiac structure and function. Importantly, this increased risk exists even in patients with a <50 % stenosis, reflecting the systemic nature of this condition. In prospective follow-up of 300 patients with varying degrees of ARVD (using essential hypertension as a control group), patients with >50 % RAS had a hazard ratio for cardiovascular events of 2.8 and patients with a <50 % RAS a hazard ratio of 2.3 (p for both <0.05) [89]. In ASTRAL, new macrovascular events occurred at a rate of 10 % per year during 5 years of follow-up (Fig. 1.3) [10].

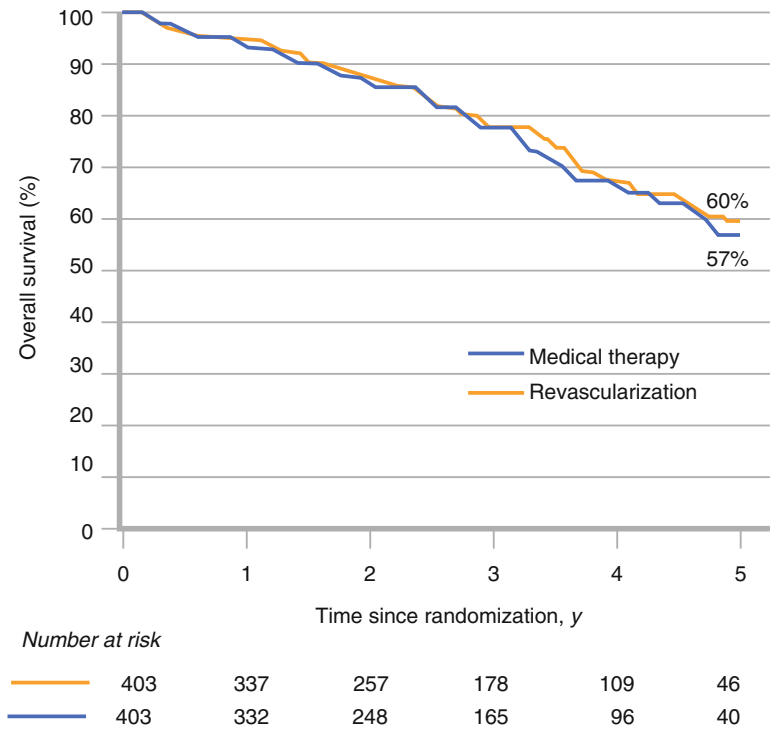


Fig. 1.4 ASTRAL: Kaplan–Meier Curves for Overall Survival. Of the 806 patients who were enrolled in the trial, 103 in the revascularization group and 106 in the medical-therapy group died during the 5-year study period (hazard ratio in the revascularization group, 0.90; 95 % CI, 0.69–1.18; P = 0.46) (Adapted with permission from ASTRAL Investigators et al. [10])

Mortality

As expected, given the high rates of vascular disease at baseline and cardiovascular events that subsequently occur during follow-up, mortality is high in ARVD. Medicare data from 2001 showed that the chance of death was over six times that of progression to ESKD [7]. Whilst is it likely that in the current era risk for death is lower (e.g. annual mortality rate in this Medicare data 16 % vs. 8 % in ASTRAL (Fig. 1.4), data analyzed in 2008), ARVD mortality is still considerably higher than in the general population (e.g. United Kingdom 2008 mortality rate for age group 65–69 years was approximately 2 %) and was comparable with the 11 % annual age-adjusted mortality in prevalent UK dialysis patients over the same time period. Limited historical data (again pre-statins) have suggested that the risk of death in ARVD is greater than in patients with most other causes of CKD, perhaps with the exception of diabetes. Also, there have not been any comparisons of outcome between different clinical presentations of ARVD. What is known is that adverse prognostic markers for mortality in ARVD include lower levels of baseline renal function (with marked increases in mortality where creatinine clearance, the forerunner of eGFR, at diagnosis is <25 ml/min) [90], proteinuria in excess of 1 g/24 h [56], and extra-renal arterial disease (discussed next). Despite identification of these risk factors, the direct mechanism by which ARVD increases risk for death is not defined. The syndromes of diffuse vascular disease and disturbed cardiac structure are doubtless relevant, with the effects of chronic RAAS activation almost certainly playing a significant role, although separating out the contributions of these factors would be near impossible because of their inter-dependency.

Mortality in Association with Other Macrovascular Disease

An increased burden of extra-renal macrovascular disease is associated with increased risk for death in ARVD irrespective of how the relationship is examined. In a single centre study of patients under follow-up for ARVD, mortality was increased in those who also had CAD or PVD, and highest in

patients who had both additional co-morbidities (% mortality over 50 months being 22 % for ARVD alone, 37 % for ARVD with PVD, 55 % with CAD and 64 % for ARVD with CAD and PVD) [91]. A reflection of this finding can be seen where patients with non-renal arterial disease are investigated for ARVD. In this setting, patients found to have significant RAS have a significantly increased risk for death: 2.9× risk for death for PVD with ARVD vs. PVD alone [38]; CAD with ARVD vs. CAD alone 89 % vs. 57 % 4-year mortality [29].

Mortality of ARVD Patients Receiving Dialysis

Reverse epidemiology is frequently observed in dialysis patients, with ARVD providing another example of where findings in the pre-dialysis setting do not directly transfer to the renal replacement therapy population. In an analysis of over 146,000 incident dialysis patients registered in the US-RDS between 1996 and 2001, those with a diagnosis of ARVD (9 % of all patients – though ARVD was only defined as the primary cause of ESKD in 5 %) had a significantly lower risk for death (HR 0.94, $p<0.0001$) than patients without ARVD despite them having higher risks for developing CAD, CHF, PVD or cerebrovascular disease [19]. This finding is in contrast with an earlier single centre report of 683 dialysis patients in which ARVD was associated with a markedly reduced median survival time (27 vs. 51-months for non-ARVD patients) [92]. It is most likely that the difference between these studies is representative of either unmeasured confounding or potential survivor bias.

Conclusion

ARVD remains a common but still underdiagnosed condition with significant prognostic implications. Better recognition of the associated clinical syndromes may increase diagnostic sensitivity and allow targeted therapy.

References

1. De Bruyne B, Manoharan G, Pijls NHJ, Verhamme K, Madaric J, Bartunek J, Vanderheyden M, Heyndrickx GR. Assessment of renal artery stenosis severity by pressure gradient measurements. J Am Coll Cardiol. 2006;48:1851–5.
2. Conlon PJ, Athirakul K, Kovalik E, Schwab SJ, Crowley J, Stack R, McCants CB, Mark DB, Bashore TM, Albers F. Survival in renal vascular disease. J Am Soc Nephrol. 1998;9:252–6.
3. Hietala SO, Kunz R. Collateral circulation in stenosis or occlusion of the renal artery. Cardiovasc Radiol. 1979;2:249–55.
4. Eliska O. Blood flow through the collateral circulation of the kidney. Angiologica. 1966;3:333–42.
5. Hansen KJ, Edwards MS, Craven TE, Cherr GS, Jackson SA, Appel RG, Burke GL, Dean RH. Prevalence of renovascular disease in the elderly: a population-based study. J Vasc Surg. 2002;36:443–51.
6. Lorenz EC, Vrtiska TJ, Lieske JC, Dillon JJ, Stegall MD, Li X, Bergstralh EJ, Rule AD. Prevalence of renal artery and kidney abnormalities by computed tomography among healthy adults. Clin J Am Soc Nephrol. 2010;5:431–8.
7. Kalra PA, Guo H, Kausz AT, Gilbertson DT, Liu J, Chen S-C, Ishani A, Collins AJ, Foley RN. Atherosclerotic renovascular disease in United States patients aged 67 years or older: risk factors, revascularization, and prognosis. Kidney Int. 2005;68:293–301.
8. Kalra PA, Guo H, Gilbertson DT, Liu J, Chen S-C, Ishani A, Collins AJ, Foley RN. Atherosclerotic renovascular disease in the United States. Kidney Int. 2009;77:37–43.
9. Collins AJ, Foley RN, Herzog C, Chavers BM, Gilbertson D, Ishani A, Kasiske BL, Liu J, Mau L-W, McBean M. Excerpts from the US Renal Data System 2009 Annual Data Report. Am J Kidney Dis. 2010;55:A6–7.
10. ASTRAL Investigators, Wheatley K, Ives N, et al. Revascularization versus medical therapy for renal-artery stenosis. N Engl J Med. 2009;361:1953–62.
11. Jazrawi A, Darda S, Burke P, Daccarett M, Stehlik J, David S, Zughaib M. Is race a risk factor for the development of renal artery stenosis? Cardiol Res Pract. 2009;2009:817987.
12. Alhaddad IA, Blum S, Heller EN, Beato MA, Bhalodkar NC, Keriaky GE, Brown EJ. Renal artery stenosis in minority patients undergoing diagnostic cardiac catheterization: prevalence and risk factors. J Cardiovasc Pharmacol Ther. 2001;6:147–53.
13. Tanemoto M, Saitoh H, Satoh F, Satoh H, Abe T, Ito S. Predictors of undiagnosed renal artery stenosis among Japanese patients with risk factors of atherosclerosis. Hypertens Res. 2005;28:237–42.
14. Kawarada O, Yokoi Y, Morioka N, Takemoto K. Renal artery stenosis in cardio-and cerebrovascular disease: renal duplex ultrasonography as an initial screening examination. Circ J. 2007;71:1942–7.
15. Stimpel M, Groth H, Greminger P, Lüscher TF, Vetter H, Vetter W. The spectrum of renovascular hypertension. Cardiology. 1985;72 Suppl 1:1–9.
16. de Mast Q, Beutler JJ. The prevalence of atherosclerotic renal artery stenosis in risk groups: a systematic literature review. J Hypertens. 2009;27:1333–40.
17. Börgel J, Springer S, Ghafoor J, et al. Unrecognized secondary causes of hypertension in patients with hypertensive urgency/emergency: prevalence and co-prevalence. Clin Res Cardiol. 2010;99:499–506.

18. Paven G, Waugh R, Nicholson J, Gillin A, Hennessy A. Screening tests for renal artery stenosis: a case-series from an Australian tertiary referral centre. Nephrology (Carlton). 2006;11:68–72.
19. Guo H, Kalra PA, Gilbertson DT, Liu J, Chen SC, Collins AJ, Foley RN. Atherosclerotic renovascular disease in older US patients starting dialysis, 1996 to 2001. Circulation. 2006;115:50–8.
20. Appel RG, Bleyer AJ, Reavis S, Hansen KJ. Renovascular disease in older patients beginning renal replacement therapy. Kidney Int. 1995;48: 171–6.
21. van Ampting JMAJ, Penne ELE, Beek FJAF, Koomans HAH, Boer WHW, Beutler JJJ. Prevalence of atherosclerotic renal artery stenosis in patients starting dialysis. Nephrol Dial Transplant. 2003;18: 1147–51.
22. Harding MB, Smith LR, Himmelstein SI, Harrison K, Phillips HR, Schwab SJ, Hermiller JB, Davidson CJ, Bashore TM. Renal artery stenosis: prevalence and associated risk factors in patients undergoing routine cardiac catheterization. J Am Soc Nephrol. 1992;2: 1608–16.
23. Khosla S, Kunjummen B, Manda R, et al. Prevalence of renal artery stenosis requiring revascularization in patients initially referred for coronary angiography. Catheter Cardiovasc Interv. 2003;58:400–3.
24. Ollivier R, Boulmier D, Veillard D, Leurent G, Mock S, Bedossa M, Le Breton H. Frequency and predictors of renal artery stenosis in patients with coronary artery disease. Cardiovasc Revasc Med. 2009;10:23–9.
25. Cohen MG, Pascua JA, Garcia-Ben M, et al. A simple prediction rule for significant renal artery stenosis in patients undergoing cardiac catheterization. Am Heart Assoc. 2005;150:1204–11.
26. Rigatelli G, Roncon L, Rinuncini M, Giordan M, Bedendo E, Panin S, Rigatelli G, Zonzin P. Angiographic characteristics of renal arterial disease over the spectrum of coronary artery disease. Am J Nephrol. 2005;25:116–20.
27. Wang Y, Ho DSW, Chen WH, Wang YQ, Lam WF, Shen ZJ, Lu CZ, Chui M. Prevalence and predictors of renal artery stenosis in Chinese patients with coronary artery disease. Intern Med J. 2003;33:280–5.
28. Rihal CS, Textor SC, Breen JF, McKusick MA, Grill DE, Hallett JW, Holmes DR. Incidental renal artery stenosis among a prospective cohort of hypertensive patients undergoing coronary angiography. Mayo Clin Proc. 2002;77:309–16.
29. Conlon PJ, Little MA, Pieper K, Mark DB. Severity of renal vascular disease predicts mortality in patients undergoing coronary angiography. Kidney Int. 2001;60:1490–7.
30. Uzu T, Inoue T, Fujii T, Nakamura S, Inenaga T, Yutani C, Kimura G. Prevalence and predictors of renal artery stenosis in patients with myocardial infarction. Am J Kidney Dis. 1997;29:733–8.
31. MacDowall P, Kalra PA, O'Donoghue DJ, Waldek S, Mamtora H, Brown K. Risk of morbidity from renovascular disease in elderly patients with congestive cardiac failure. Lancet. 1998;352:13–6.
32. de Silva R, Loh H, Rigby AS, Nikitin NP, Witte KKA, Goode K, Bhandari S, Nicholson A, Clark AL, Cleland JGF. Epidemiology, associated factors, and prognostic outcomes of renal artery stenosis in chronic heart failure assessed by magnetic resonance angiography. Am J Cardiol. 2007;100:273–9.
33. Kuroda S, Nishida N, Uzu T, Takeji M, Nishimura M, Fujii T, Nakamura S, Inenaga T, Yutani C, Kimura G. Prevalence of renal artery stenosis in autopsy patients with stroke. Stroke. 2000;31:61–5.
34. Horita Y, Tadokoro M, Taura K, Mishima Y, Miyazaki M, Kohno S, Kawano Y. Relationship between carotid artery intima-media thickness and atherosclerotic renal artery stenosis in type 2 diabetes with hypertension. Kidney Blood Press Res. 2002;25:255–9.
35. Olin JW, Melia M, Young JR, Graor RA, Risius B. Prevalence of atherosclerotic renal artery stenosis in patients with atherosclerosis elsewhere. Am J Med. 1990;88:46N–51.
36. Valentine RJ, Myers SI, Miller GL, Lopez MA, Clagett GP. Detection of unsuspected renal artery stenoses in patients with abdominal aortic aneurysms: refined indications for preoperative aortography. Ann Vasc Surg. 1993;7:220–4.
37. Iglesias JI, Hamburger RJ, Feldman L, Kaufman JS. The natural history of incidental renal artery stenosis in patients with aortoiliac vascular disease. Am J Med. 2000;109:642–7.
38. Amighi J, Schlager O, Haumer M, Dick P, Mlekusch W, Loewe C, Böhmig G, Koppensteiner R, Minar E, Schillinger M. Renal artery stenosis predicts adverse cardiovascular and renal outcome in patients with peripheral artery disease. Eur J Clin Invest. 2009;39:784–92.
39. Androes MP, Langan EM, Kalbaugh CA, Blackhurst DW, Taylor SM, Youkey JR. Is incidental renal arteriography justified in a population of patients with symptomatic peripheral arterial disease? Vasc Endovascular Surg. 2007;41:106–10.
40. Leertouwer TC, Pattynama PM, van den Berg-Huysmans A. Incidental renal artery stenosis in peripheral vascular disease: a case for treatment? Kidney Int. 2001;59:1480–3.
41. Swartbol P, Thorvinger BO, Pärsson H, Norgren L. Renal artery stenosis in patients with peripheral vascular disease and its correlation to hypertension. A retrospective study. Int Angiol. 1992;11:195–9.
42. Salmon P, Brown MA. Renal artery stenosis and peripheral vascular disease: implications for ACE inhibitor therapy. Lancet. 1990;336:321.
43. Chrysochou C, Kalra PA. Epidemiology and natural history of atherosclerotic renovascular disease. Prog Cardiovasc Dis. 2009;52:184–95.
44. Shurrab AE, Mamtora H, O'Donoghue D, Waldek S, Kalra PA. Increasing the diagnostic yield of renal angiography for the diagnosis of atheromatous renovascular disease. Br J Radiol. 2001;74:213–8.
45. Black HR, Cooper KA. Cigarette smoking and atherosclerotic renal artery stenosis. J Clin Hypertens. 1986;2:322–30.
46. Gambaro G, Verlato F, Budakovic A, Casara D, Saladini G, Del Prete D, Bertaglia G, Masiero M,

Checchetto S, Baggio B. Renal impairment in chronic cigarette smokers. J Am Soc Nephrol. 1998;9:562–7.
47. Scoble JE, de Takats D, Ostermann ME, Connolly JO, Scott NR, Beeso JA, Poyser KH, Peters TJ, Sherwood RA. Lipid profiles in patients with atherosclerotic renal artery stenosis. Nephron. 1999;83:117–21.
48. Hood B, Brolin I, Kjellbo H, Angervall G. Serum lipids in renal artery stenosis and other hypertensive states. I. Abdominal aorta, renal arteries and fasting serum lipid levels. Acta Med Scand. 1966;179: 575–82.
49. Pilz S, Scharnagl H, Tiran B, Seelhorst U, Wellnitz B, Boehm BO, Schaefer JR, März W. Free fatty acids are independently associated with all-cause and cardiovascular mortality in subjects with coronary artery disease. J Clin Endocrinol Metab. 2006;91: 2542–7.
50. Cheung CM, Patel A, Shaheen N, Cain S, Eddington H, Hegarty J, Middleton RJ, Cowie A, Mamtora H, Kalra PA. The effects of statins on the progression of atherosclerotic renovascular disease. Nephron Clin Pract. 2007;107:c35–42.
51. Keddis M, Garovic V, Bailey K. Ischaemic nephropathy secondary to atherosclerotic renal artery stenosis: clinical and histopathological correlates. Nephrol Dial Transplant. 2010;25:3615–22.
52. Caps MT, Zierler RE, Polissar NL, Bergelin RO, Beach KW, Cantwell-Gab K, Casadei A, Davidson RC, Strandness DE. Risk of atrophy in kidneys with atherosclerotic renal artery stenosis. Kidney Int. 1998;53:735–42.
53. Paraskevas KI, Hamilton G, Cross JM, Mikhailidis DP. Atherosclerotic renal artery stenosis: association with emerging vascular risk factors. Nephron Clin Pract. 2008;108:c56–66.
54. Dzielińska Z, Januszewicz A, Demkow M, et al. Cardiovascular risk factors in hypertensive patients with coronary artery disease and coexisting renal artery stenosis. J Hypertens. 2007;25:663–70.
55. Suresh M, Laboi P, Mamtora H, Kalra PA. Relationship of renal dysfunction to proximal arterial disease severity in atherosclerotic renovascular disease. Nephrol Dial Transplant. 2000;15:631–6.
56. Wright J, Shurrab A, Cheung C, Waldek S, O'Donoghue D, Foley R, Mamtora H, Kalra P. A prospective study of the determinants of renal functional outcome and mortality in atherosclerotic renovascular disease. Am J Kidney Dis. 2002;39:1153–61.
57. Chade AR, Kelsen S. Renal microvascular disease determines the responses to revascularization in experimental renovascular disease. Circ Cardiovasc Interv. 2010;3:376–83.
58. Iliescu R, Fernandez SR, Kelsen S, Maric C, Chade AR. Role of renal microcirculation in experimental renovascular disease. Nephrol Dial Transplant. 2010;25:1079–87.
59. Kang D-H, Kanellis J, Hugo C, Truong L, Anderson S, Kerjaschki D, Schreiner GF, Johnson RJ. Role of the microvascular endothelium in progressive renal disease. J Am Soc Nephrol. 2002;13:806–16.
60. Zhu X-Y, Chade AR, Rodriguez-Porcel M, Bentley MD, Ritman EL, Lerman A, Lerman LO. Cortical microvascular remodeling in the stenotic kidney: role of increased oxidative stress. Arterioscler Thromb Vasc Biol. 2004;24:1854–9.
61. Goldblatt H, Lynch J, Hanzal RF, Summerville WW. Studies on experimental hypertension: I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. J Exp Med. 1934;59:347–79.
62. Wolf G. Angiotensin II, as a mediator of tubulointerstitial injury. Nephrol Dial Transplant. 2000;15 Suppl 6:61–3.
63. Wolf K, Kurtz A, Pfeifer M, Höcherl K, Riegger GA, Krämer BK. Different regulation of left ventricular ANP, BNP and adrenomedullin mRNA in the two-kidney, one-clip model of renovascular hypertension. Pflugers Arch. 2001;442:212–7.
64. Farmer CK, Cook GJ, Blake GM, Reidy J, Scoble JE. Individual kidney function in atherosclerotic nephropathy is not related to the presence of renal artery stenosis. Nephrol Dial Transplant. 1999;14:2880–4.
65. Wright JR, Duggal A, Thomas R, Reeve R, Roberts IS, Kalra PA. Clinicopathological correlation in biopsy-proven atherosclerotic nephropathy: implications for renal functional outcome in atherosclerotic renovascular disease. Nephrol Dial Transplant. 2001;16:765–70.
66. Gandy SJ, Armoogum K, Nicholas RS, McLeay TB, Houston JG. A clinical MRI investigation of the relationship between kidney volume measurements and renal function in patients with renovascular disease. Br J Radiol. 2007;80:12–20.
67. Ruggenenti P, Porrini EL, Gaspari F, et al. Glomerular hyperfiltration and renal disease progression in type 2 diabetes. Diabetes Care. 2012;35:2061–8.
68. Urbieta-Caceres VH, Lavi R, Zhu X-Y, Crane JA, Textor SC, Lerman A, Lerman LO. Early atherosclerosis aggravates the effect of renal artery stenosis on the swine kidney. Am J Physiol Renal Physiol. 2010;299:F135–40.
69. Chade AR, Rodriguez-Porcel M, Grande JP, Zhu X, Sica V, Napoli C, Sawamura T, Textor SC, Lerman A, Lerman LO. Mechanisms of renal structural alterations in combined hypercholesterolemia and renal artery stenosis. Arterioscler Thromb Vasc Biol. 2003;23:1295–301.
70. Tuttle KR. Renal parenchymal injury as a determinant of clinical consequences in atherosclerotic renal artery stenosis. Am J Kidney Dis. 2002;39:1321–2.
71. Cheung CM, Chrysochou C, Shurrab AE, Buckley DL, Cowie A, Kalra PA. Effects of renal volume and single-kidney glomerular filtration rate on renal functional outcome in atherosclerotic renal artery stenosis. Nephrol Dial Transplant. 2010;25:1133–40.
72. Schreiber MJ, Pohl MA, Novick AC. The natural history of atherosclerotic and fibrous renal artery disease. Urol Clin North Am. 1984;11:383–92.
73. Crowley JJ, Santos RM, Peter RH, Puma JA, Schwab SJ, Phillips HR, Stack RS, Conlon PJ. Progression of renal artery stenosis in patients undergoing cardiac catheterization. Am Heart Assoc. 1998;136:913–8.

74. Caps M, Perissinotto C, Zierler R, Polissar N. Prospective study of atherosclerotic disease progression in the renal artery. Circulation. 1998;98: 2866–72.
75. Hoefield RA, Kalra PA, Baker P, Lane B, New JP, O'Donoghue DJ, Foley RN, Middleton RJ. Factors associated with kidney disease progression and mortality in a referred CKD population. Am J Kidney Dis. 2010;56:1072–81.
76. Valluri A, Severn A, Chakraverty S. Do patients undergoing renal revascularization outside of the ASTRAL trial show any benefit? Results of a single centre observational study. Nephrol Dial Transplant. 2011;27:734–8.
77. Bax L, Woittiez A-JJ, Kouwenberg HJ, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. Ann Intern Med. 2009;150(840–8):W150–1.
78. Wright JR, Shurrab AE, Cooper A, Kalra PR, Foley RN, Kalra PA. Left ventricular morphology and function in patients with atherosclerotic renovascular disease. J Am Soc Nephrol. 2005;16:2746–53.
79. Wright JR, Shurrab AE, Cooper A, Kalra PR, Foley RN, Kalra PA. Progression of cardiac dysfunction in patients with atherosclerotic renovascular disease. QJM. 2009;102:695–704.
80. Kane GC, Xu N, Mistrik E, Roubicek T, Stanson AW, Garovic VD. Renal artery revascularization improves heart failure control in patients with atherosclerotic renal artery stenosis. Nephrol Dial Transplant. 2010;25:813–20.
81. Marcantoni C, Zanoli L, Rastelli S, et al. Effect of renal artery stenting on left ventricular mass: a randomized clinical trial. Am J Kidney Dis. 2012;60: 39–46.
82. Green D, Kalra PA. The heart in atherosclerotic renovascular disease. Front Biosci. 2012;4:856–64.
83. Rimoldi SF, Yuzefpolskaya M, Allemann Y, Messerli F. Flash pulmonary edema. Prog Cardiovasc Dis. 2009;52:249–59.
84. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J. 2011;32:670–9.
85. Chrysochou C, Sinha S, Chalmers N, Kalra PR, Kalra PA. Anuric acute renal failure and pulmonary oedema: a case for urgent action. Int J Cardiol. 2009;132: e31–3.
86. Hackam DG, Duong-Hua ML, Mamdani M, Li P, Tobe SW, Spence JD, Garg AX. Angiotensin inhibition in renovascular disease: a population-based cohort study. Am Heart Assoc. 2008;156:549–55.
87. Chrysochou C, Foley RN, Young JF, Khavandi K, Cheung CM, Kalra PA. Dispelling the myth: the use of renin-angiotensin blockade in atheromatous renovascular disease. Nephrol Dial Transplant. 2011;27:1403–9.
88. Cooper C, Murphy T, Matsumoto A, Steffes M, Cohen D, Jaff M, Kuntz R, Jamerson K, Reid D, Rosenfield K. Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: rationale and design of the CORAL trial. Am Heart Assoc. 2006;152:59–66.
89. Dechering DG, Kruis H, Adiyaman A, Thien T, Postma CT. Clinical significance of low-grade renal artery stenosis. J Intern Med. 2010;267:305–15.
90. Cheung CM, Wright JR, Shurrab AE, Mamtora H, Foley RN, O'Donoghue DJ, Waldek S, Kalra PA. Epidemiology of renal dysfunction and patient outcome in atherosclerotic renal artery occlusion. J Am Soc Nephrol. 2002;13:149–57.
91. Shurrab AE, MacDowall P, Wright J, Mamtora H, Kalra PA. The importance of associated extra-renal vascular disease on the outcome of patients with atherosclerotic renovascular disease. Nephron Clin Pract. 2003;93:C51–7.
92. Mailloux LU, Napolitano B, Bellucci AG, Vernace M, Wilkes BM, Mossey RT. Renal vascular disease causing end-stage renal disease, incidence, clinical correlates, and outcomes: a 20-year clinical experience. Am J Kidney Dis. 1994;24:622–9.

Renal Vascular Fibromuscular Dysplasia

2

Barbara Ann Greco

Abstract

Fibromuscular dysplasia of the renal arteries is an idiopathic, non-inflammatory form of renal artery stenosis causing renovascular hypertension in children and younger adults. It is defined by pathognomonic angiographic and histologic findings. The pathogenesis of this disorder is unknown and evidence supports the likelihood of heterogeneous etiologies for this disorder. It is an important potentially curable form of renovascular hypertension. This chapter will discuss the epidemiology, clinical associations, and presentations of fibromuscular dysplasia and review treatment approaches and outcomes.

Keywords

Fibromuscular dysplasia • Renovascular hypertension • Nonatherosclerotic renal artery disease • Renal artery stenosis • Renal artery aneurysm • Non-inflammatory arteriopathy • Segmental arterial mediolysis

Introduction

Fibromuscular dysplasia (FMD) of the renal arteries is an idiopathic, non-inflammatory arteriopathy associated with proliferation of medial smooth muscle cells and fibrous tissue and is the second most common cause of renovascular hypertension after atherosclerotic renal artery stenosis (FRAS). It was first described in 1938 by Leadbetter and Burkland [1], and the name was first applied by McCormack et al. [2] that same year. In FMD, abnormalities of the structure of the arterial wall of medium and large vessels manifest as aberrancies in the vascular lumen with pathognomonic angiographic characteristics. This chapter will review the epidemiology, vascular distribution, angiographic and histological phenotypes, clinical presentations, and response to treatment of renal vascular FMD.

B.A. Greco, MD
Renal Division, Department of Medicine, Baystate Medical Center/Tufts New England Medical Center, Western New England Renal and Transplant Associates, 100 Wason Avenue, Suite 200, Springfield, MA 01107, USA
e-mail: barbara.greco@bhs.org

Epidemiology

FMD has been diagnosed in patients of all ages but is most commonly identified when patients between the ages of 15–50 present with

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_2, © Springer-Verlag London 2014

hypertension. There is currently an active and growing United States registry of adult patients with FMD encompassing cases from nine institutions. A recent interim report on this cohort shows the mean age at diagnosis was 51.9 years, with a broad range from 5 to 80 years [3]. The mean age of onset of hypertension was 43 years. Most of the patients currently in the registry data are white with less than 5 % Asian, Hispanic or black. The oldest age at diagnosis of FMD reported in the literature is 83 years, so this disorder can be missed for many years. In children, infantile cases have been reported with the range spanning all ages. There is a female predilection with up to 91 % of cases seen in women.

The prevalence of renovascular FMD has historically thought to be about 4 in 1,000 [4]. However, a review of 1,860 arteriograms of potential kidney donors identified FMD in 3.8 % [5]. In a smaller series of 716 potential kidney donors, 6.6 % were found to have angiographic evidence of FMD [6]. Therefore, the true prevalence is higher and this disorder is likely underdiagnosed.

Table 2.1 Associations with renal fibromuscular dysplasia

Alagille's syndrome
Alpha-1 antitrypsin deficiency
Alport's syndrome
Ask-Upmark kidney
Atherosclerotic renovascular disease
Celiac disease
Cigarette smoking
Coarctation of the aorta
Cocaine exposure-intrauterine
Collagen III glomerulopathy
Crohn's disease
Cystic medial necrosis
Ehlers-Danlos syndrome
Ergotamine preparations/methylsergide
Homocystinuria
Infantile myofibromatosis
Macrophagic myofasciitis
Marfan's syndrome
Medullary sponge kidney
Neurofibromatosis
Pheochromocytoma
Renal agenesis/dysgenesis
Tuberous sclerosis
William's syndrome

Etiology and Pathogenesis

Little is known about the pathogenesis of FMD. Though FMD is thought to be idiopathic, familial associations are reported in 7–11 % of cases. In one cohort of 104 patients with renal artery FMD, the familial cases were more likely to be multifocal and bilateral within the renal vasculature; familial cases were defined by having one first degree relative known to have the disorder [7]. In another report of 13 cases of FMD found in six families, carotid duplex ultrasound was used to look for associated carotid artery abnormalities in 47 family members vs. 47 controls with no known family history of FMD. Using a quantitative scoring method for carotid abnormalities, the authors identified significantly higher scores among family members of patients with FMD than controls and segregation analysis suggested an autosomal dominant transmission pattern [8]. Similarly, Mettinger and Ericson reported on 37 cases of stroke in patients with cerebrovascular FMD and noted a high prevalence of stroke among first degree relatives again suggesting an autosomal dominant pattern with reduced male penetrance [9]. Though proven familial FMD is rare, the presence of family history of stroke, cerebral aneurysms, and sudden death are reported in 54, 24 and 20 % of cases.

There have been a number of reports associating the presence of renovascular FMD with various genetic, congenital, and collagen vascular disorders. These are listed in Table 2.1.

Based on evidence of familial clustering and clinical associations, several candidate genes have been studied in association with FMD. Polymorphisms in the alpha-1-antitrypson gene were investigated in patients and families with FMD using duplex echo tracking evidence of carotid abnormalities; no association was found. Other genetic associations studied in FMD include the angiotensin I converting enzyme allele found in a higher frequency in patients with multi-focal FMD than age-matched controls, the elastin gene based on association between FMD and Williams' syndrome, and mutations of

JAGGED1 which encodes for a ligand for Notch receptors in FMD associated with Alagille's syndrome [10–14]. Familial syndromes of FMD and other congenital cardiac abnormalities have been reported [15]. Thus far, evidence for a unifying genetic association is inconclusive.

FMD has also been linked to a number of collagen vascular disorders including Alport's syndrome, Ehlers-Danlos syndrome and Marfan's [16–18]. This supports the hypothesis that the angiographic and histologic findings in FMD actually comprise the final common end points for a number of different pathogenetic processes leading to disordered collagen deposition and fibrosis in and around the arterial wall. The vascular form of Ehlers-Danlos syndrome, type IV, represents a genetic disease due to mutations in the gene for collagen III, COL 3A1. Abnormal secretion, fibrillogenesis, and deposition of collagen III lead to vascular fragility and laxity of joints and skin. Both familial and sporadic cases have been reported. Support for the concept that FMD represents a true collagen vascular disease comes from studies demonstrating abnormal vascular matrix collagen III expression and stability of procollagen III, the precursor of collagen type III, in arterial walls of cerebral aneurysms [19]. Genetic mutations in COL3A1 have also been associated with the development of abdominal aortic aneurysms without other features of Ehlers-Danlos syndrome. Olin et al. have reported ongoing study of the presence of COL 3A1 gene defects in patients with medial FMD and aneurysms or dissection [20]. We have a case of cerebral aneurysms associated with biopsy proven collagen III glomerulopathy in a 16 year old girl whose mother has angiographically proven FMD of the renal arteries.

Other clinical associations suggest that FMD may be due to abnormalities of fibroblast function. One example is the finding of angiographic lesions consistent with FMD in patients with infantile myofibromatosis, a rare disorder which is characterized by spindle cell tumors of the skin, soft tissues and viscera [21].

Finally, environmental, hormonal, and anatomic risk factors have been implicated in the pathogenesis of FMD. A history of cigarette smoking is present in 37 % of reported cases and is associated with more severe renal artery FMD manifestations than found in nonsmokers [22]. The female predominance among patients with FMD suggests a potential role for hormonal factors in the pathogenesis. Sixty-nine percent of the recently described registry cohort had been treated with hormonal therapy, either oral contraceptives or post-menopausal hormone replacement therapy [3]. Last, vascular trauma or stretching of the renal artery with resultant alterations in lumen and arterial wall structure has also been proposed as a potential pathophysiologic mechanism. This latter theory has little evidence basis but remains a hypothesis based on observations that FMD is more common in the right kidney where ptosis may lead to stretching of the vessel.

FMD in Children

FMD is the most common cause of renovascular hypertension reported in children. Between 11 and 60 % of pediatric cases of FMD are associated with genetic syndromes. In childhood cases of renovascular hypertension, bilateral abnormalities are seen in 53–78 % of cases with intrarenal vascular disease alone seen in 44 % of cases. However, most non-syndromic FMD in children is associated with a single branch artery stenosis. These children often have concomitant extrarenal disease and midaortic syndrome should be ruled out in all of them [23]. In childhood cases of renovascular hypertension due to renal vascular disease, other disorders should be considered depending on demographics and clinical presentation, including Takayasu arteritis, which will be discussed in Chap. 3. Blood pressure response to renal artery interventions in children with FMD is excellent. In three reported series, the cure rates were 67, 88 and 100 % [24–26]. The remainder of this chapter will focus on FMD in adults.

Vascular Distribution

In adults, FMD most often involves the renal and extracranial carotid arteries. The renal arteries are involved in 65–80 % of cases. Lesions of FMD are

Table 2.2 Fibromuscular dysplasia: vascular distribution

Vascular bed involved	% of total N = 374	Number imaged	% of patients imaged
Renal artery	78.6	369	79.7
Extracranial carotid artery	67.1	338	74.3
Intracranial carotid artery	9.3	206	35
Vertebral artery	21.9	224	36.6
Coronary artery	NR	NR	NR
Mesenteric artery	13.9	198	26.3
Lower extremity artery[a]	11.2	70	60
Upper extremity artery[a]	2.7	63	15.9
Aorta[b]	<1	145	<1

Adapted with permission from Olin et al. [3]
[a]Only a small number of patients in the registry underwent imaging of the extremities guided by clinical symptoms of claudication or ischemia
[b]Aortic aneurysms were found in 15 patients but no angiographic evidence of FMD of the aorta

most often identified in the middle and distal portions of the main renal arteries and can involve branch vessels in many cases. In 25–35% of cases, FMD is bilateral in the renal circulation. In addition, FMD can involve a number of extrarenal vascular beds including carotid and vertebrobasilar, coronary, mesenteric, celiac, splenic, brachial, and the limb peripheral vasculature. At least two vascular beds are involved in about a third of patients with FMD, and when multiple vascular beds are imaged in individuals with FMD, about 20 % have three beds involved and 10 % have four. Among patients with renovascular FMD, about 65 % have concomitant extracranial carotid or vertebrobasilar involvement [3, 27, 28]. There are reports of involvement of the arch of the aorta and descending thoracic aorta with FMD presenting as coarctation [29, 30]. The frequency of involvement of the various vascular beds is outlined in Table 2.2.

Histologic Classification and Angiographic Phenotypes

The structure of the arterial wall is shown in Fig. 2.1. The intima of the vascular wall consists of the endothelium, the internal elastic lamina,

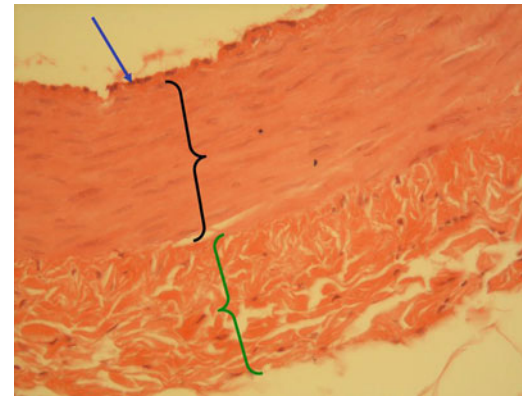


Fig. 2.1 The *blue arrow* is indicates the tunica intima. The *black bracket* represents the tunica media and the *green bracket* is the tunica adventitia. This is the wall of a normal muscular artery at 400× (Photo by Theresa Carrera; labeled by Janowski-Bell [71])

and a layer of connective tissue cells. The media consists of layers of smooth muscle cells, elastic fibers and collagen fibers. The external elastic lamina separates the media from the adventitia. The adventitia is comprised of predominantly collagen and adventitial cells. Fibrous structural proteins, adhesive glycoproteins and macromolecules such as proteoglycans and hyaluronic acid, are among the components responsible for normal extracellular matrix homeostasis of blood vessels and their surrounding adventitia and interstitium.

Based on the site of structural abnormality, the three types of renovascular FMD are classified as medial, intimal, and adventitial. Medial FMD is most common accounting for 85–100 % of cases in various series. There are three histologic subtypes of medial FMD: medial fibroplasia, perimedial fibroplasia and medial hyperplasia. Figure 2.2 demonstrates a cross section of an artery with medial FMD; compared to the histology of a normal renal artery there is disorganization and thickening of the wall structure. Medial fibroplasia, the most common histologic subtype, is characterized by alternating areas of thin and thick ridges of collagen with areas of homogeneous deposition of elastic tissue leading to areas of stenosis interspersed with areas of aneurismal sections characterized by fragmented internal elastic lamina. The loss of elastic structural integrity

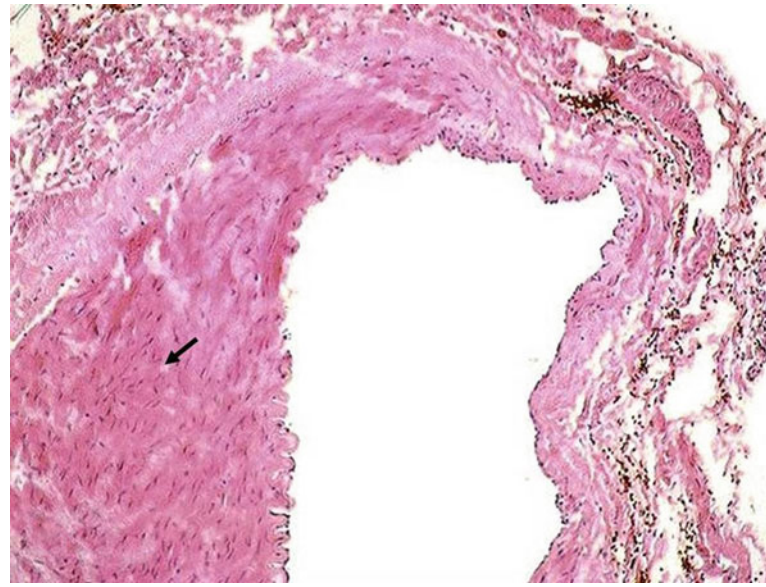


Fig. 2.2 Fibromuscular dysplasia: medial fibroplasia type with areas of thickening of the media with disorganization of smooth muscle cell layers (*arrow*) alternating with areas of media thinning and loss of internal elastic lamina (With permission from Paner [72])

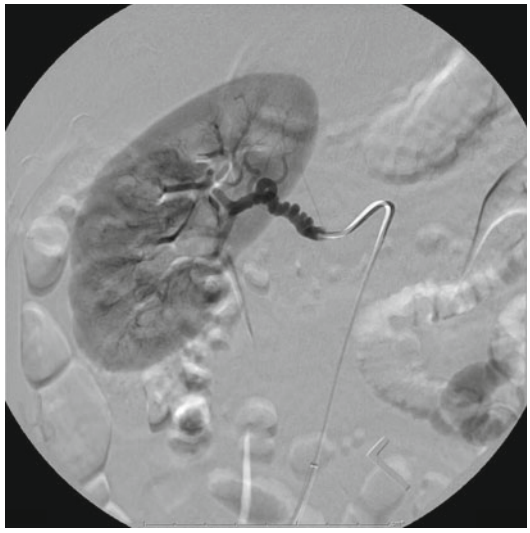


Fig. 2.3 Digital subtraction angiogram demonstrating the "string of beads" appearance of medial fibroplasia form of renal artery fibromuscular dysplasia

leads to ballooning or beading of the vessels such that the diameter of the beaded segment is larger than the diameter of the artery lumen. The classic angiographic appearance of medial fibromuscular dysplasia is a "string of beads" appearance with ballooning and beading of the lumen alternating with areas of constriction associated with bands or webbing of tissue within the lumen (Fig. 2.3). In perimedial fibroplasia, the diameter of the beads is smaller than that of the normal arterial segments. True smooth muscle hyperplasia occurs in the medial hyperplastic form of FMD and the angiographic equivalent is a concentric smooth narrowing of the lumen. A similar angiographic picture is seen with intimal fibroplasia, a much rarer form of FMD. The lumen narrowing in intimal fibroplasia is due to concentric deposition of collagen in the intima with fragmentation and duplication of the internal elastic lamina leading to elongated smooth luminal narrowing. Adventitial or periarterial FMD is the rarest histologic variant. Here, dense collagen replaces the normal fibrous tissue in the adventitia and may extend into the surrounding interstitium, but the remainder of the arterial wall layers remains intact. Angiographically, adventitial FMD manifests as severe luminal narrowing and may involve a long segment of the vessel [31] (Fig. 2.4a–c). Finally, renal artery aneurysms may also be seen in FMD and were identified in 5.6 % of the patients in the US registry. When present, 17 % of patients with aneurysm at any vascular site had more than one vascular site involved, up to four aneurysms [3].

The relationship between the histologic type of FMD and its angiographic correlate is shown in Table 2.3 [20, 32]. It is somewhat artificial to define separate types based on histology. In contemporary practice, there is rarely a pathologic

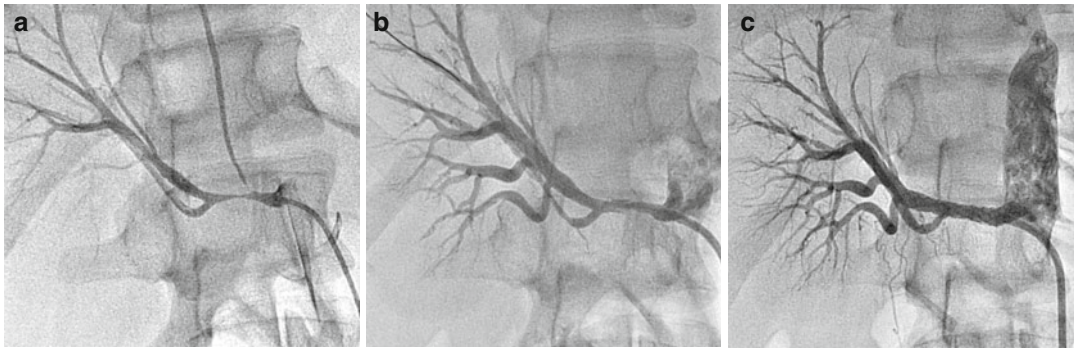


Fig. 2.4 (**a**) A renal arteriogram demonstrating n example of adventitial fibromuscular dysplasia causing near-occlusive stenosis of the mid-right renal artery. (**b**) Residual stenosis and dissection of the renal artery following angioplasty. (**c**) Angiography of the same vessel after stent deployment (With permission from Weiner et al. [70])

Table 2.3 Fibromuscular dysplasia: histologic classifications and angiographic phenotypes

Type	Frequency %	Histology	Angiographic appearance
Medial	85–100		
Medial fibroplasia	Most common	Collagen ridges/loss of elastic membrane	"String of beads" bead diameter larger than lumen
Perimedial fibroplasia	Rarer	Smooth muscle hyperplasia	"String of beads" bead diameter smaller than lumen
Medial hyperplasia	Rarest		Smooth stenosis without beads
Intimal	<10	Circumferential deposition of collagen in intima; fragmented or duplicated internal elastic lamina	Smooth stenosis, elongated and concentric
Adventitial	<1	Dense collagen replaces fibrous tissue in adventitia and surrounding tissue	Smooth stenosis or diffuse attenuation of vessel lumen

Adapted with permission from Vuong et al. [32]

specimen available to ascertain the exact type as most cases are not treated surgically. In addition, there is histologic overlap present in many cases. Alimi et al. examined histologic sections in 33 cases of FMD and found more than one wall layer involved in two thirds of the cases [33]. ARAS may co-exist with FMD, particularly in older patients.

Natural History

The natural history of FMD is not known. Meaney et al. in 1968 reported on a cohort of 48 patients with renal artery FMD followed with clinically driven serial arteriograms ranging from 6 months to 10 years following angioplasty [34]. Three of these patients had both atherosclerotic renovascular disease and FMD. Forty of the patients were women. At follow-up arteriography, nine of the 48 patients demonstrated either progression of the lesion identified initially or development of new lesions in a previously unaffected renal artery. Age was an important predictor of progression: none of those over the age of 40 at initial diagnosis had new disease on later evaluation. Schreiber et al. reported on 66 patients with medial fibroplasia involving the renal arteries who had subsequent arteriograms over a 20 year period. The pathology was confirmed at surgery or autopsy [35]. However, a large number of these had mixed ARAS and FMD lesions. Progression of the FMD was identified in up to 27 % of cases at follow-up angiography as far out as 3 years from the initial study. The mean age of these patients was 41 years. In this study, angiographic progression of

the luminal changes was not associated with significant changes in creatinine or renal size. However, in another small sequential angiography cohort, 37 % of patients had angiographic progression associated with reduction in renal length and cortical atrophy in 63 % of untreated post-stenotic kidneys [36]. Progression is generally not associated with loss of kidney function in any of these studies.

Our understanding of the natural history of FMD is limited by the lack of sensitivity of angiography to detect endoluminal changes. Indeed, even following successful angioplasty, the angiographic picture following the procedure may not appear much different than before intervention. In addition, many studies evaluating the natural history of disease failed to examine other vascular beds for the presence of new lesions or aneurysms. Therefore, given the current state of knowledge regarding natural history, patients with FMD should be followed periodically with imaging as guided by clinical parameters for detection of new lesions, particularly when symptoms or bruits arise.

Clinical Presentations

The most common clinical presentations of FMD are hypertension, headaches, dizziness and pulsatile tinnitus. In one study of 84 patients with pulsatile tinnitus, 42 % were found to have a vascular etiology, commonly FMD, arteriovenous fistulae, or intracranial aneurysms [37, 38]. Bruits over the carotids, epigastric, flank or abdominal regions or femoral arteries are common. About 5 % of patients will have no signs or symptoms with the arterial lesions found incidentally at the time of imaging for other indications. The relative frequency of clinical presentations as reported from the registry data is shown in Table 2.4. Stroke, transient ischemic attack, or amaurosis fugax related to cerebrovascular FMD occur in about 25 % of patients. The exact prevalence of intracranial aneurysms among those patients with cerebrovascular involvement with FMD is unclear with reports ranging from 7.3 % up to 50 % depending on the population screened [39]. Aneurysms are more common in the renal arteries than other beds.

Table 2.4 Clinical presentations of fibromuscular dysplasia

Carotid
Headaches
Asymptomatic bruit
Aneurysm or dissection
Transient ischemic attack
Cerebrovascular accident
Pulsatile tinnitus
Horner's syndrome
Vertebrobasilar
Neck pain
Dizziness
Imaging finding of aneurysm or dissection
Amaurosis fugax
Coronary
Myocardial infarction
Chest pain
Shortness of breath
Renal
Hypertension
Abdominal bruit
Renal infarction
Imaging finding of aneurysm or dissection
Retroperitoneal bleed
Azotemia
Mesenteric
Post-prandial abdominal pain
Weight loss
Bruit
Celiac artery aneurysm
Hepatic artery aneurysm/rupture
Hemobilia
Brachial
Arm fatigue with exertion
Iliac-popliteal
Claudication
Bruit
Aneurysm

While hypertension is the leading manifestation of renovascular FMD, some patients present with flank pain due to segmental or whole kidney renal infarction. Infarction may result either from dissection of a main or branch renal artery or from embolism to a segmental vessel by clot from a proximal aneurysm. Patients with renal infarction often have leucocytosis, elevated serum levels of lactate dehydrogenase, and microhematuria. Severe accelerated or malignant hypertension

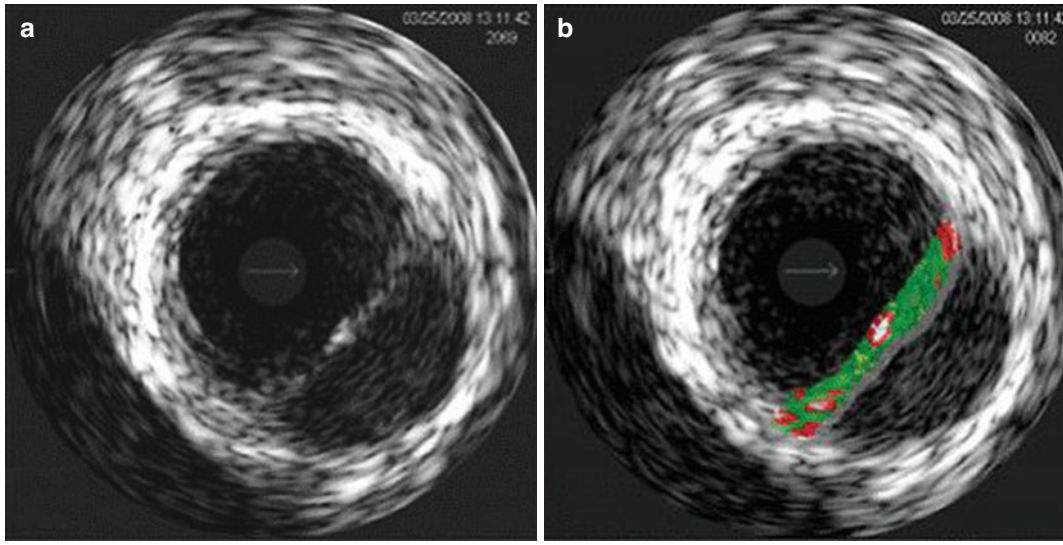


Fig. 2.5 Intravascular Ultrasound of Renal Artery Demonstrating a Fibrous Web. (**a**) Intravascular ultrasound image of intraluminal web/band in a renal artery with medial fibroplasia form of FMD. (**b**) Intravascular ultrasound image with virtual histology analysis of web/band demonstrating primarily fibrous tissue in the band. Color code: green-fibrous tissue; light green-fibrofatty tissue; red-lipid; white-calcium (With permission from Prasad et al. [40])

may be a consequence of the infarction. Acute kidney injury is usual when renal infarction occurs. Flank pain can also represent rupture of a renal artery aneurysm with retroperitoneal bleeding and anemia and even hypovolemic shock.

The diagnosis of FMD should be considered in patients with early onset of hypertension, particularly in women with onset hypertension before 40 years of age. The diagnosis of FMD should also be considered in patients with resistant hypertension, epigastric bruits, severe migraine headaches, pulsatile tinnitus, the presence of cervical bruits, history of transient ischemic attack, stroke or subarachnoid hemorrhage under the age of 60, the finding of vascular aneurysms in the aorta, cerebral or visceral arteries, renal infarction, or dissection of a renal, vertebrobasilar or carotid artery. Table 2.4 outlines the common clinical presentations of FMD.

Imaging Tests

The gold standard in terms of imaging for identification of renal artery FMD is conventional digital subtraction arteriography which provides visualization of the distal and branch vasculature of the kidney with greatest sensitivity and specificity of all screening modalities. Selective renal angiograms are necessary along with multiple views in order to adequately visualize the branch and intrarenal arteries. Angiography can detect the luminal abnormalities but is not accurate at estimating hemodynamic significance of an FMD lesion. This is true for all of the imaging screening modalities. Catheter angiography provides an opportunity to perform intravascular ultrasound (IVUS) which can provide important additional information on endovascular structural abnormalities and their effects on turbulence of blood flow. IVUS provides virtual histology with characteristic endoluminal findings including the presence of collagen-rich bands of tissue in ridges, spiral folds, and web-like membranes (Fig. 2.5a, b) [40]. At angiography, measurement of pressure gradients across the involved area can provide additional guidance to focus endovascular treatment to the areas of greatest hemodynamic significance and ensure all areas have been adequately treated. Systolic pressure gradients of 10–20 mmHg exist across even elongated areas of involvement and post-angioplasty measure-

ment can be used to assess efficacy of the balloon dilatation before completion of the study. Unlike with ARAS, post-treatment imaging in FMD may not look dramatically different from pre-treatment images particularly with the "string of beads" variant [41].

Computed tomography angiography (CTA) represents the second best imaging test for identification of FMD. In adults, CTA with multiplanar reconstructions has been shown to be nearly 100 % accurate and less invasive than conventional angiography. CTA requires proper post-imaging software to create three-dimensional reconstructions and requires between 100 and 150 cc of intravenous contrast. False positive "string of beads" findings have been reported due to pulsation and stair-step artifacts as well as overlapping structures (renal parenchyma or vein) [42]. Magnetic resonance angiography (MRA), though less sensitive for detecting abnormalities in the distal and small branch vessels than CTA, is often proposed as a preferred screening modality in children where avoidance of exposure to radiation is a priority. However, the gold standard for definitively ruling out FMD and other renal artery causes of renovascular hypertension in children is digital subtraction angiography which can detect small branch vessel abnormalities, atretic vessels, small aneurysms, and distal disease in small or accessory vessels which may be missed by MRA [25, 42].

Doppler ultrasonography is a good screening test for the presence of ARAS, which usually involves the ostium or proximal vessel. In non-atherosclerotic renovascular disease, particularly FMD, the lesions more often involve middle, distal, or even branch vessels and may be elongated with areas of both webbed stenosis and dilatations of the lumen leading to turbulence of blood flow without discrete focal stenosis. Whereas thresholds for duplex ultrasound parameters such as peak systolic velocity have been shown to be sensitive and specific predictors of the presence of >60 % luminal diameter narrowing in atherosclerotic disease, these parameters have not been stringently evaluated in the diagnosis of FMD. In addition, FMD can involve branch vessels not usually interrogated when these techniques are used. Similarly, polar accessory arteries are often missed by ultrasound. Furthermore, it is often difficult to visualize all segments of the main renal artery due to obesity, bowel gas, and other patient related and technical factors. In nonatherosclerotic renovascular disease such as FMD or Takayasu arteritis, the patients are younger with better preserved intrarenal vascular compliance and structure. Li et al. reported on differences in tardus-parvus wave forms from the interlobar arteries in patients with atherosclerotic and non-atherosclerotic renovascular disease. They found no significant differences in acceleration time but found significantly lower resistive indices in the nonatherosclerotic group consistent with the concept of preserved compliance in these younger patients. Their results suggest that analysis of the tardus-parvus waveform and identification of a drop off in resistive index beyond the stenotic segment may be more sensitive for detection of FMD than other indices [43]. The use of duplex ultrasound to follow patients after angioplasty has been proposed with initial post-treatment ultrasound obtained as baseline for later comparison at 6 and 12 months and yearly thereafter [44, 45]. Table 2.5 summarizes the considerations and caveats of the various imaging tests when screening for FMD.

Treatment of Renovascular Fibromuscular Dysplasia

Medical Therapy

Renovascular hypertension due to FMD can be treated medically in many cases. Unilateral renal artery involvement usually responds well to blockade of the renin-angiotensin-aldosterone system but additional agents are often needed when the hypertension is resistant. When the FMD is bilateral, there is a risk of acute kidney injury when angiotensin converting enzyme inhibitors or angiotensin receptor blockers are used. In most cases, this is reversible upon discontinuation of the antihypertensive agent. As

Table 2.5 Considerations in imaging renal artery fibromuscular dysplasia

Imaging modality	Advantages	Disadvantages
Angiography	"Gold standard"	Invasive
	Can do IVUS and measure	Radiation++[a]
	Systolic pressure gradient	Contrast++
Computed tomographic angiography	Excellent imaging sensitivity and specificity	Radiation+++
		Contrast+++
Magnetic resonance angiography	Gadolinium vs. iodinated contrast; no radiation	Limited visualization of distal and branch vessels
		Breathing and movement artifacts
Duplex ultrasonography	Inexpensive	Thresholds for hemodynamic significance unclear for FMD of various type
		Miss accessory and distal and branch vessel disease

+ to +++ refer to the amount of contrast or radiation exposure
[a]Refers to radiation exposure during angiography, which depends upon the duration of the fluoroscopic procedure

FMD is rarely associated with loss of renal function, medical therapy is a reasonable option, particularly for those patients who are older with longer duration of hypertension.

However, in younger patients with recent onset hypertension, there is a significant chance of cure of hypertension when endovascular treatment is undertaken. Therefore, the standard of care for these patients is consideration of percutaneous transluminal angioplasty (PTRA) or surgery depending on the anatomy of the renal artery lesions.

Renal Artery Angioplasty: No Stent

The endovascular treatment of choice for FMD is PTRA without stenting. The usual indication for intervention is renovascular hypertension with a goal of cure of hypertension in younger patients with shorter duration of hypertension. Other indications include renovascular hypertension resistant to medical therapy, intolerance of medical therapy, noncompliance with medical therapy, renal impairment or cortical loss from ischemia [46]. Percutaneous angioplasty should be performed by experienced interventionalists. With angioplasty, the vessel wall collagen webs are disrupted with the goal of reduced luminal narrowing and turbulence of blood flow. Experience is needed to determine the force and degree of dilatation required to adequately disrupt the fibrosis without rupturing the vessel. The technical aspects of endovascular treatment of FMD have been reviewed elsewhere [47]. In cases with multiple webs across a long segment of the vessel, multiple areas need to be treated. A common cause of poor response is inadequate treatment of the lesion. Angiographic visual inspection alone is not adequate to determine procedural success and is a poor surrogate for assessing the hemodynamic significance of lesions in FMD [48]. Finally, the rate of restenosis following endovascular treatment of renal artery FMD may be as high as 34 % (range 7–34) and may require repeat intervention. In a meta-analysis of treatment outcomes in FMD, the string of beads angiographic phenotype associated with medial hyperplasia had a worse response to intervention than non-medial disease [49–55]. This reflects the difficulty in determining hemodynamic significance of the angiographic abnormality in this disease where multiple areas of webbing and stenosis are present, the risk of insufficient treatment in this setting, as well as possible restenosis post-angioplasty.

Indications for Stents or Surgery in Renovascular Fibromuscular Dysplasia

Renal artery stenting in FMD is reserved for treating complications of angioplasty such as

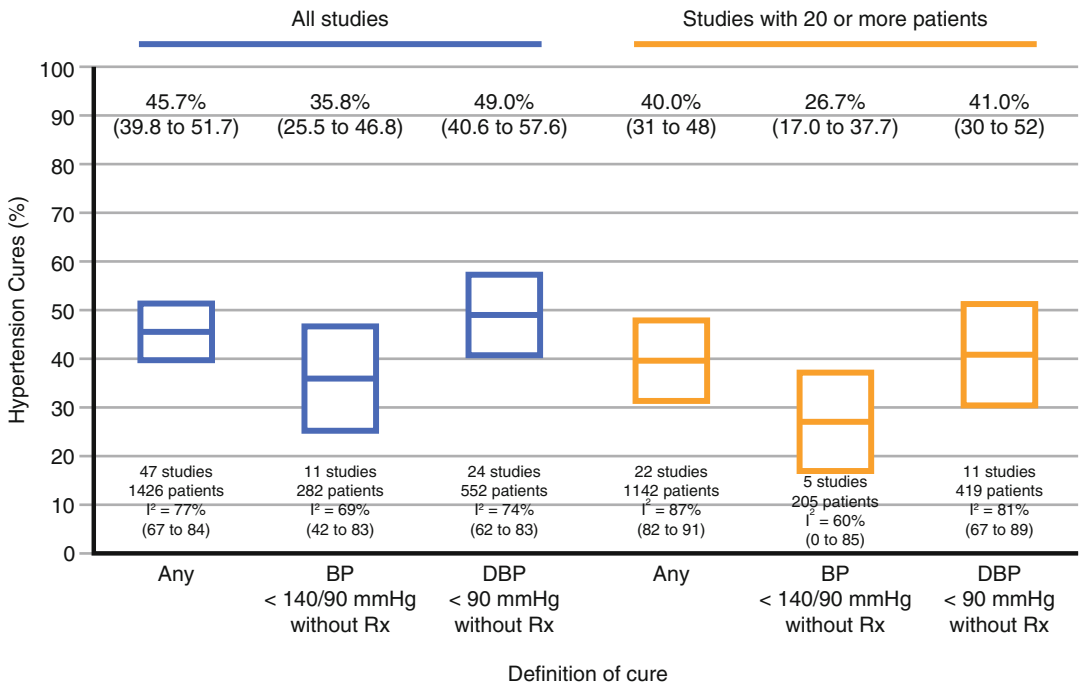


Fig. 2.6 Meta-analysis of hypertension cure rates following angioplasty (Adapted with permission from Trinquart et al. [57])

rupture or dissection of the renal artery [56]. Covered stents have also been used in cases with aneurysms to exclude the neck of the aneurysm from the renal circulation either prophylactically or in the setting of acute rupture.

Traditional indications for surgical approach to FMD include the presence of large renal artery aneurysms at locations not amenable to endovascular treatment with covered stents and resistant or complex stenoses which have failed endovascular approaches.

Treatment Outcomes

Favorable outcomes in terms of improvement or cure of hypertension are reported in 75–90 % of series. Technical success is common ranging from 68 to 100 % with the caveat that success is often defined by post-treatment angiographic visual inspection. A recent meta-analysis of 70 series reporting outcomes on 1,616 patients with FMD treated by PTRA and 1,014 treated surgically identified significant variability among reports in terms of definition of cure or improvement. Overall, the cumulative cure rate across studies was 45.7 % and improvement 86.4 % for patients treated by PTRA, with wide variability (Fig. 2.6). When the definition of cure used was blood pressure <140/90 on no medications, the cure rate for angioplasty is only 36 % and for surgical revascularization 55 % [57]. Significant factors predicting cure of hypertension include age at treatment, duration of hypertension and publication year, with later publications having lower cure rates (Fig. 2.7). In cases of unilateral FMD, a high negative predictive value of a captopril renogram has been reported [56]. The low cure rate reported has been attributed to the likelihood of nonhemodynamically significant lesions coexisting with essential hypertension, inadequate treatment of all significant areas, and restenosis. In one series of 35 older than average (mean age 61.9 years) patients with FMD treated with angioplasty and followed for a mean of 4.8 years, freedom from recurrent hypertension was seen in 93, 75 and 41 % at 1, 5 and 8 years respectively [58]. Analysis of outcomes in surgically

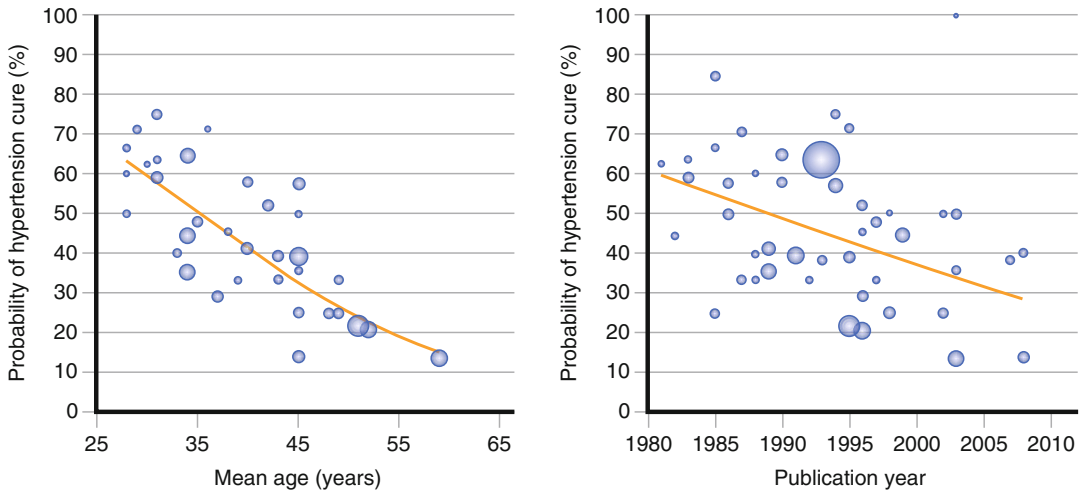


Fig. 2.7 Relationship between probability of hypertension cure and treatment age and vintage. meta-regression analyses assessing the relationship between the hypertension cure rate after angioplasty and mean age at treatment, publication year (Adapted with permission from Trinquart et al. [57])

treated patients showed similar variability in definition of hypertension cure and improvement, an overall cure rate of 57.5 % and combined cure and improvement of 88.3 % [20, 56, 59–67].

Complications of Renal Interventions

Complications of interventions to treat FMD occur in 12 % treated by endovascular approaches (range 0–48 %) with about half of these major complications. Analysis of complications among patients treated surgically was 17 % with a range of 5–28 %. These were predominantly major complications. Mortality related to treatment has been reported as 0.9 % following angioplasty and 1.2 % for surgery.

Summary: Management of Patients with Renovascular Fibromuscular Dysplasia

Patients with FMD in the renal arteries and hypertension should be treated medically with agents which block the renin-angiotensin system. Those younger in age, with short duration of hypertension, resistant hypertension, medical intolerance or noncompliance should be evaluated as candidates for PTRA. Patients older or with longer duration of hypertension should be counseled as to the risks of PTRA and the potential for improved hypertension control on fewer medications in order to make informed decisions regarding whether to embark on endovascular therapy. When PTRA has been performed, the reoccurrence of hypertension should prompt clinicians to consider repeat angiography with a view to assessment for inadequate treatment or recurrent stenosis requiring further endovascular or surgical therapy. When renal artery aneurysms are present, the risk/benefit ratio of conservative surveillance vs. either endovascular therapy with a covered stent or surgical repair should be undertaken. Women of childbearing age with renal artery aneurysms who plan future pregnancy should be treated before pregnancy. Patients with symptoms of pulsatile tinnitus, headaches, or other transient neurologic symptoms should undergo screening for the presence of intracranial or extracranial cerebrovascular involvement with FMD or aneurysms. Since the natural history of FMD is not fully elucidated, patients with FMD identified in any vascular territory should be followed long-term and screening imaging should be

performed based on clinical symptoms and course of blood pressure control. The ideal screening test will need to be patient specific; for some, repeat angiography will be required, for others, CTA may be able to identify new or recurrent stenoses; duplex ultrasound should be checked post-procedure in patients as a potential noninvasive functional test of recurrent stenosis [56].

Segmental Arterial Mediolysis

Segmental arterial mediolysis (SAM) is a rare vascular disorder presenting as hemorrhagic infarctions in the kidney, or sometimes catastrophic hemorrhages in the brain, abdominal cavity or retroperitoneum. In this disorder, mediolysis results from disruption of smooth muscle cell membrane by cytoplasmic vacuoles which usually involves segments of the arterial medial wall. These lesions can result in aneurismal dilatations initially and then luminal irregularities during the later healed phase. The segmental nature of the disorder can lead to a sting of beads appearance not unlike that of FMD due to intervening normal segments of artery. Dissections and thromboses of vessels may ensue. Most often, it is a time limited disease occurring at one point in time usually involving one vascular territory. The reparative vascular sequelae may remain long-term, including aneurysms and luminal abnormalities. Slavin et al. have proposed that subclinical presentations of SAM may account for later development of FMD, that in some cases this disorder may evolve into FMD or isolated aneurysms [68, 69]. The renal arteries are not uncommonly involved with SAM and gross hematuria due to renal infarction has also been reported. Angiographically, SAM can mimic polyarteritis nodosa.

References

1. Leadbetter WF, Burkland CE. Hypertension in unilateral renal disease. J Urol. 1938;38:611–26.
2. McCormack LJ, Hazard JB, Poutasse EF, editors. Obstructive lesions of the renal artery associated with remediable hypertension. Am J Pathol. 1958;34:582.
3. Olin JW, Froehlich J, Gu X, Bacharach JM, Eagle K, Gray BH, et al. The United States Registry for Fibromuscular Dysplasia: results in the first 447 patients. Circulation. 2012;125(25):3182–90.
4. Plouin PF, Perdu J, La Batide-Alanore A, Boutouyrie P, Gimenez-Roqueplo AP, Jeunemaitre X. Fibromuscular dysplasia. Orphanet J Rare Dis. 2007; 2:28.
5. Bondin D, Lanzman R, Schellhammer F, Oels M, Grotemeyer D, Baldus SE, et al. Fibromuscular dysplasia in living renal donors: still a challenge to computed tomographic angiography. Eur J Radiol. 2010; 75:67–71.
6. Cragg AH, Smith TP, Thompson BH, Maroney TP, Stanson AW, Shaw GT, et al. Incidental fibromuscular dysplasia in potential renal donors: long-term clinical follow-up. Radiology. 1989;172(1):145–7.
7. Pannier-Moreau I, Grimbert P, Fiquet-Kempf B, Vuagnat A, Jeunemaitre X, Corvol P, et al. Possible familial origin of multifocal renal artery fibromuscular dysplasia. J Hypertens. 1997;15(12 Pt 2):1797–801.
8. Perdu J, Boutouyrie P, Bourgain C, Stern N, Laloux B, Bozec E, et al. Inheritance of arterial lesions in renal fibromuscular dysplasia. J Hum Hypertens. 2007;21(5):393–400.
9. Mettinger KL, Ericson K. Fibromuscular dysplasia and the brain. I. Observations on angiographic, clinical and genetic characteristics. Stroke J Cereb Circ. 1982;13(1):46–52.
10. Perdu J, Gimenez-Roqueplo AP, Boutouyrie P, Beaujour S, Laloux B, Nau V, et al. Alpha1-antitrypsin gene polymorphisms are not associated with renal arterial fibromuscular dysplasia. J Hypertens. 2006;24(4):705–10.
11. Suzuki H, Daida H, Sakurai H, Yamaguchi H. Familial fibromuscular dysplasia of bilateral brachial arteries. Heart. 1999;82(2):251–2.
12. Bofinger A, Hawley C, Fisher P, Daunt N, Stowasser M, Gordon R. Alpha-1-antitrypsin phenotypes in patients with renal arterial fibromuscular dysplasia. J Hum Hypertens. 2000;14(2):91–4.
13. Bofinger A, Hawley C, Fisher P, Daunt N, Stowasser M, Gordon R. Polymorphisms of the renin-angiotensin system in patients with multifocal renal arterial fibromuscular dysplasia. J Hum Hypertens. 2001;15(3):185–90.
14. Marks SD, Gullett AM, Brennan E, Tullus K, Jaureguiberry G, Klootwijk E, et al. Renal FMD may not confer a familial hypertensive risk nor is it caused by ACTA2 mutations. Pediatr Nephrol. 2011;26(10): 1857–61.
15. Grange DK, Balfour IC, Chen SC, Wood EG. Familial syndrome of progressive arterial occlusive disease consistent with fibromuscular dysplasia, hypertension, congenital cardiac defects, bone fragility, brachysyndactyly, and learning disabilities. Am J Med Genet. 1998;75(5):469–80.
16. Schievink WI, Bjornsson J, Piepgras DG. Coexistence of fibromuscular dysplasia and cystic medial necrosis in a patient with Marfan's syndrome and bilateral carotid artery dissections. Stroke J Cereb Circ. 1994; 25(12):2492–6.

17. Schievink WI, Limburg M. Angiographic abnormalities mimicking fibromuscular dysplasia in a patient with Ehlers-Danlos syndrome, type IV. Neurosurgery. 1989;25(3):482–3.
18. Escamilla F, Espigares A, Hervas R, Fernandez MD, Vela R, Garcia T. Fibromuscular dysplasia with moyamoya phenomenon in a patient with Alport's syndrome. A type IV collagen disorder. Rev Neurol. 2000;30(8):736–40.
19. Kilic T, Sohrabifar M, Kurkaya O, Yildirim O, Elmaci I, Gunel M, et al. Expression of structural proteins and angiogenic factors in normal arterial and unruptured and ruptured aneurysm walls. Neurosurgery. 2005; 57(5):997–1007.
20. Olin JW, Pierce M. Contemporary management of fibromuscular dysplasia. Curr Opin Cardiol. 2008; 23(6):527–36.
21. Wright C, Corbally MT, Hayes R, McDermott MB. Multifocal infantile myofibromatosis and generalized fibromuscular dysplasia in a child: evidence for a common pathologic process? Pediatr Dev Pathol Off J Soc Pediatr Pathol Paediatr Pathol Soc. 2004;7(4): 385–90.
22. Bofinger A, Hawley C, Fisher P, Daunt N, Stowasser M, Gordon R. Increased severity of multifocal renal arterial fibromuscular dysplasia in smokers. J Hum Hypertens. 1999;13(8):517–20.
23. Bayazit AK, Yalcinkaya F, Cakar N, Duzova A, Bircan Z, et al. Reno-vascular hypertension in children: a nationwide survey. Pediatr Nephrol. 2007;9: 1327–33.
24. McTaggart SJ, Gulati S, Walker RG, Powell HR, Jones CL. Evaluation and long term outcome of pediatric renovascular hypertension. Pediatr Nephrol. 2000;14(10–11):1022–9.
25. Tullis K. Renal artery stenosis: is angiography still the gold standard in 2011? Pediatr Nephrol. 2011;26(6): 833–7.
26. Srinivasan A, Krishnamurthy G, Fontalvo-Herazo L, Nijs E, Keller M, Meyers K, et al. Angioplasty for renal artery stenosis in pediatric patients: an 11-year retrospective experience. J Vasc Interv Radiol. 2010;21(11):1672–80.
27. Liu CH, Wu D, Chin SC, Fu SC, Wu TC, Chang CH, et al. Cervicocranial fibromuscular dysplasia in Taiwanese ischemic stroke patients. Eur Neurol. 2012;67(3):129–35.
28. Pasquini M, Trystram D, Oppenheim C, Plouin PF, Touze E. Cervical and intracranial fibromuscular dysplasia. Presse Med. 2011;40(7–8):713–9.
29. Suarez WA, Kurczynski TW, Bove EL. An unusual type of combined aortic coarctation due to fibromuscular dysplasia. Cardiol Young. 1999;9(3):323–6.
30. Bornak A, Milner R. Diagnosing and treating atypical arterial pathologies of aortic arch vessels: dissection and fibromuscular dysplasia. Semin Vasc Surg. 2011;24(1):36–43.
31. MacNeill B, Rosenfeld K. Peripheral Intervention. In: Baim D, editor. Grossman's cardiac catheterization, angiography, and intervention. 7th ed. Philadelphia: Lippincott Williams and Wilkins; 2006.
32. Vuong PN, Desoutter P, Mickley V, Bultmann B, Rothenberger-Janzen K, Guyot H, et al. Fibromuscular dysplasia of the renal artery responsible for renovascular hypertension: a histological presentation based on a series of 102 patients. VASA Zeitschrift fur Gefasskrankheiten. 2004;33(1):13–8.
33. Alimi Y, Mercier C, Pellissier JF, Piquet P, Tournigand P. Fibromuscular disease of the renal artery: a new histopathologic classification. Ann Vasc Surg. 1992; 6(3):220–4.
34. Meaney TF. Progression of renal artery fibromuscular dysplasia in 42 patients as seen on angiography. Radiology. 1982;142(1):252–3.
35. Schreiber MJ, Pohl MA, Novick AC. The natural history of atherosclerotic and fibrous renal artery disease. Urol Clin N Am. 1984;11(3):383–92.
36. Goncharenko V, Gerlock Jr AJ, Shaff MI, Hollifield JW. Progression of renal artery fibromuscular dysplasia in 42 patients as seen on angiography. Radiology. 1981;139(1):45–51.
37. Sismanis A. Pulsatile tinnitus: contemporary assessment and management. Curr Opin Otolaryngol Head Neck Surg. 2011;19(5):348–57.
38. Waldvogel D, Mattle HP, Sturzenegger M, Schroth G. Pulsatile tinnitus: a review of 84 patients. J Neurol. 1998;245(3):137–42.
39. Begelman SM, Olin JW. Fibromuscular dysplasia. Curr Opin Rheumatol. 2000;12(1):41–7.
40. Prasad A, Zafar N, Mahmud E. Assessment of renal artery fibromuscular dysplasia: angiography, intravascular ultrasound (with virtual histology), and pressure wire measurements. Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv. 2009;74(2):260–4.
41. Olin JW, Sealove BA. Diagnosis, management, and future developments of fibromuscular dysplasia. J Vasc Surg. 2011;53(3):826–36.e1.
42. Sabharwal R, Vladica P, Coleman P. Multidetector spiral CT renal angiography in the diagnosis of renal artery fibromuscular dysplasia. Eur J Radiol. 2007; 61(3):520–7.
43. Li JC, Yuan Y, Qin W, Wang L, Dai Q, Qi ZH, et al. Evaluation of the tardus-parvus pattern in patients with atherosclerotic and nonatherosclerotic renal artery stenosis. J Ultrasound Med Off J Am Inst Ultrasound Med. 2007;26(4):419–26.
44. Gowda MS, Loeb AL, Crouse LJ, Kramer PH. Complementary roles of color-flow duplex imaging and intravascular ultrasound in the diagnosis of renal artery fibromuscular dysplasia: should renal arteriography serve as the "gold standard"? J Am Coll Cardiol. 2003;41(8):1305–11.
45. Helenon O, Correas JM, Chabriais J, Boyer JC, Melki P, Moreau JF. Renal vascular Doppler imaging: clinical benefits of power mode. Radiogr Rev Pub Radiol Soc N Am. 1998;18(6):1441–54; discussion 55–7.
46. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary. J Am Coll Cardiol. 2006;47:1239–312.

47. Meuse MA, Turba UC, Sabri SS, Park AW, Saad WE, Angle JF, et al. Treatment of renal artery fibromuscular dysplasia. Tech Vasc Interv Radiol. 2010;13(2):126–33.
48. Olin JW. Misconceptions about the diagnosis and treatment of fibromuscular dysplasia. Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv. 2009; 74(2):265–6.
49. Serter S, Oran I, Parildar M, Memis A. Fibromuscular dysplasia-related renal artery stenosis associated with aneurysm: successive endovascular therapy. Cardiovasc Interv Radiol. 2007;30(2):297–9.
50. Bloch MJ, Basile J. Diagnosis and management of renovascular disease and renovascular hypertension. J Clin Hypertens. 2007;9(5):381–9.
51. Fenves AZ, Ram CV. Renovascular hypertension: clinical concepts. Minerva Med. 2006;97(4):313–24.
52. Tanemoto M, Abe T, Chaki T, Satoh F, Ishibashi T, Ito S. Cutting balloon angioplasty of resistant renal artery stenosis caused by fibromuscular dysplasia. J Vasc Surg. 2005;41(5):898–901.
53. Gray BH. Intervention for renal artery stenosis: endovascular and surgical roles. J Hypertens Suppl Off J Int Soc Hypertens. 2005;23(3):S23–9.
54. Davies MG, Waldman DL. Fibromuscular dysplasia: catheter, cut or laissez faire? That remains the question. J Hum Hypertens. 2005;19(10):755–6.
55. Bloch MJ, Basile J. The diagnosis and management of renovascular disease: a primary care perspective. Part I. Making the diagnosis. J Clin Hypertens. 2003;5(3):210–8.
56. Elliott WJ, Martin WB, Murphy MB. Comparison of two noninvasive screening tests for renovascular hypertension. Arch Intern Med. 1993;153(6):755–64.
57. Trinquart L, Mounier-Vehier C, Sapoval M, Gagnon N, Plouin PF. Efficacy of revascularization for renal artery stenosis caused by fibromuscular dysplasia: a systematic review and meta-analysis. Hypertension. 2010;56(3):525–32.
58. Mousa AY, Campbell JE, Stone PA, Broce M, Bates MC, AbuRahma AF. Short- and long-term outcomes of percutaneous transluminal angioplasty/stenting of renal fibromuscular dysplasia over a ten-year period. J Vasc Surg. 2012;55(2):421–7.
59. Persu A, Touze E, Mousseaux E, Barral X, Joffre F, Plouin PF. Diagnosis and management of fibromuscular dysplasia: an expert consensus. Eur J Clin Invest. 2012;42(3):338–47.
60. Ham SW, Kumar SR, Wang BR, Rowe VL, Weaver FA. Late outcomes of endovascular and open revascularization for nonatherosclerotic renal artery disease. Arch Surg. 2010;145(9):832–9.
61. Tanemoto M, Abe T, Ito S. Treatment of fibromuscular dysplasia. Kidney Int. 2008;74(2):244; author reply.
62. Regnante RA, Obell JW, Gordon P. Renal artery stenosis: clinical and therapeutic implications. Med Health R I. 2008;91(10):315–9.
63. Marekovic Z, Mokos I, Krhen I, Goreta NR, Roncevic T. Long-term outcome after surgical kidney revascularization for fibromuscular dysplasia and atherosclerotic renal artery stenosis. J Urol. 2004;171(3): 1043–5.
64. Kumar A, Dubey D, Bansal P, Sanjeevan KV, Gulati S, Jain S, et al. Surgical and radiological management of renovascular hypertension in a developing country. J Urol. 2003;170(3):727–30.
65. Torres G, Terramani TT, Weaver FA. Ex vivo repair of a large renal artery aneurysm and associated arteriovenous fistula. Ann Vasc Surg. 2002;16(2):141–4.
66. Mitterbauer C, Oberbauer R. Rational decision making in the treatment of renal artery stenosis. Wien Klin Wochenschr. 2002;114(1–2):1–3.
67. Johnston 3rd WK, London ET, Perez RV. Renal autotransplantation for renovascular hypertension: extraperitoneal renal approach and use of the ovarian vein for vascular reconstruction. J Am Coll Surg. 2002;194(1):88–92.
68. Slavin RE, Saeki K, Bhagavan B, Maas AE. Segmental arterial mediolysis: a precursor to fibromuscular dysplasia? Mod Pathol Off J U S Can Acad Pathol. 1995; 8(3):287–94.
69. Slavin RE. Segmental arterial mediolysis: course, sequelae, prognosis and pathologic-radiologic correlation. Cardiovasc Pathol Off J Soc Cardiovasc Pathol. 2009;18(6):352–60.
70. Weiner RB, Kiernan TJ, Yan BP, Rosenfield K, Jaff M. Adventitial fibromuscular dysplasia of the renal artery: management challenges of nonatherosclerotic renal artery stenosis. Circulation. 2009;120(19): e157–8.
71. Janowski-Bell ME. Victoria College. Histology of blood vessels {Internet}. Used with permission. Available from: http://www2.victoriacollege.edu/dept/bio/Belltutorials/Histology%20Tutorial/Blood%20Vessels/Histology_of_Blood_Vessels.html.
72. Paner GP. Pathology for Urologists: Educational Program. Am Urol Assoc. 2012 {Internet}.2012 {updated 2012 August}. Available from: http://www.auanet.org/eforms/elearning/pathology/renovascular-disease/medial-fibrosis.cfm.

Congenital and Inflammatory Arteritides

3

Barbara A. Greco and Leslie T. Cooper

Abstract

Congenital vascular abnormalities and inflammatory arteritides are rare causes of renovascular hypertension with unique epidemiology and diagnostic and therapeutic considerations. Patients with these disorders require lifelong clinical management and can develop cardiovascular complications. This chapter provides an in-depth review of coarctation of the aorta and Takayasu arteritis as prototypical congenital and inflammatory disorders and provides an overview of other clinically relevant vascular disorders associated with renovascular hypertension.

Keywords

Renovascular hypertension • Takayasu arteritis • Coarctation of the aorta • Middle aortic syndrome • Radiation arteritis • Inflammatory arteritis • Congenital arteritis

Introduction

In addition to the fibromuscular dysplasias, renovascular hypertension can be caused by congenital abnormalities of vascular development and inflammatory disorders affecting the aorta and renal arteries. The most common cause of congenital renovascular hypertension is coarctation of the aorta. Takayasu arteritis is the most common inflammatory disorder affecting the aorta and renal arteries. This chapter will provide an overview of vascular morphogenesis and angiogenesis as a background for discussion of the major congenital and inflammatory arteritides. We emphasize prototypical disorders that cause renovascular hypertension, aortic coarctation, Takayasu arteritis, renal artery aneurysms, and radiation arteritis.

B.A. Greco, MD (✉)
Renal Division, Department of Medicine,
Baystate Medical Center/Tufts New England Medical Center, Western New England Renal and Transplant Associates, 100 Wason Avenue, Suite 200,
Springfield, MA 01107, USA
e-mail: barbara.greco@bhs.org

L.T. Cooper, MD
Department of Cardiovascular Diseases,
Mayo Clinic, 200 First Street SW, Gonda 5-368,
Rochester, MN 55905, USA
e-mail: cooper.leslie@mayo.edu

Normal Vascular Development

Arterial development during embryogenesis occurs by vasculogenesis followed by angiogenesis. Vasculogenesis involves the differentiation of

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_3,

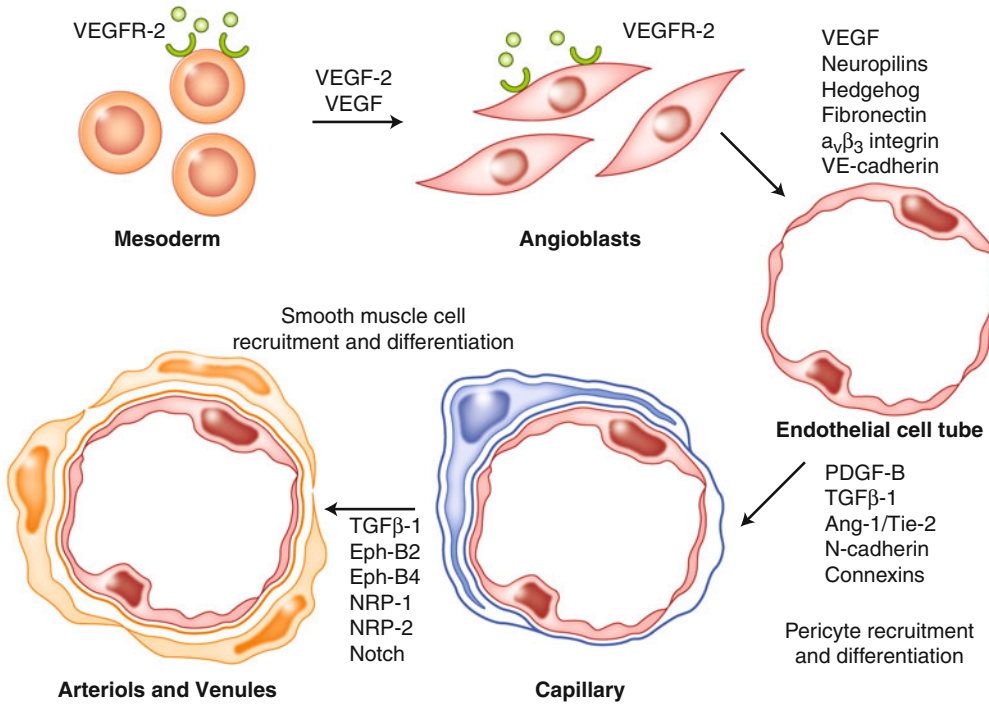


Fig. 3.1 Schematic of processes and factors involved in vascular morphogenesis. Vascular morphogenesis involves the recruitment and differentiation of cells from the mesoderm to form endothelial cell tube with subsequent recruitment of pericytes and smooth muscle cells involved in creating structural support and development of the vascular lumen. These processes are regulated by a number of sequential and overlapping regulatory processes mediated by fibroblast growth factor (*FGF*), vascular endothelial growth factor (*VEGF*), vascular endothelial (*VE*) and N–cadherin, platelet derived growth factor (*PDGF*), transforming growth factor-**β** (*TGF-β*), angiopoietin-1 (*Ang-1*), (*Tie-2*), ephrins (*Eph*), Notch, neurophilins (*NRP*) and others (Adapted with permission from Ribatti et al. [1])

endothelial cells from mesodermal cells to form a primary vascular plexus in the yolk sac. Endothelial cells derived from the paraxial mesoderm migrate to colonize cephalic vessels, vessels of the dorsal aorta, kidneys, limbs and body wall. Endothelial cells from the splanchnopleural mesoderm migrate to colonize the vessels of the visceral organs, and floor of the dorsal aorta. A subgroup of neural crest cells differentiates to form a mass of vascular smooth muscle cells responsible for the branch development of the carotids, subclavians, ductus arteriosus, and pulmonary arteries [1].

Angiogenesis involves a cascade of temporally and spatially overlapping events to meet the metabolic demands and oxygen needs of tissues and organisms. Normal vascular development involves coordination of a number of events from endothelial cell activation, proliferation and migration of a variety of cell types, to tube formation, branching, pruning, and distal anastomoses. Growth of vessels is led by specialized endothelial cells called tip cells which, via extensions known as filopodia, respond to ambient levels of vascular endothelial growth factor (VEGF) released by developing tissues under hypoxic conditions associated with increasing metabolic demand. The development of the vessel lumen and its diameter is determined by endothelial cell proliferation in response to local VEGF concentrations along with other regulatory factors [1] (Fig. 3.1). Normal expression of VEGF is critical to aortic development and VEGF allele knockout in mice leads to abnormal aortic development [2]. A process known as intussusceptive branching remodeling is responsible for the development of highly reproducible, organ-specific branching patterns. Regulatory factors and hemodynamic factors including blood flow and shear stress induced angiogenic signals mediate this process [3] (Fig. 3.2).

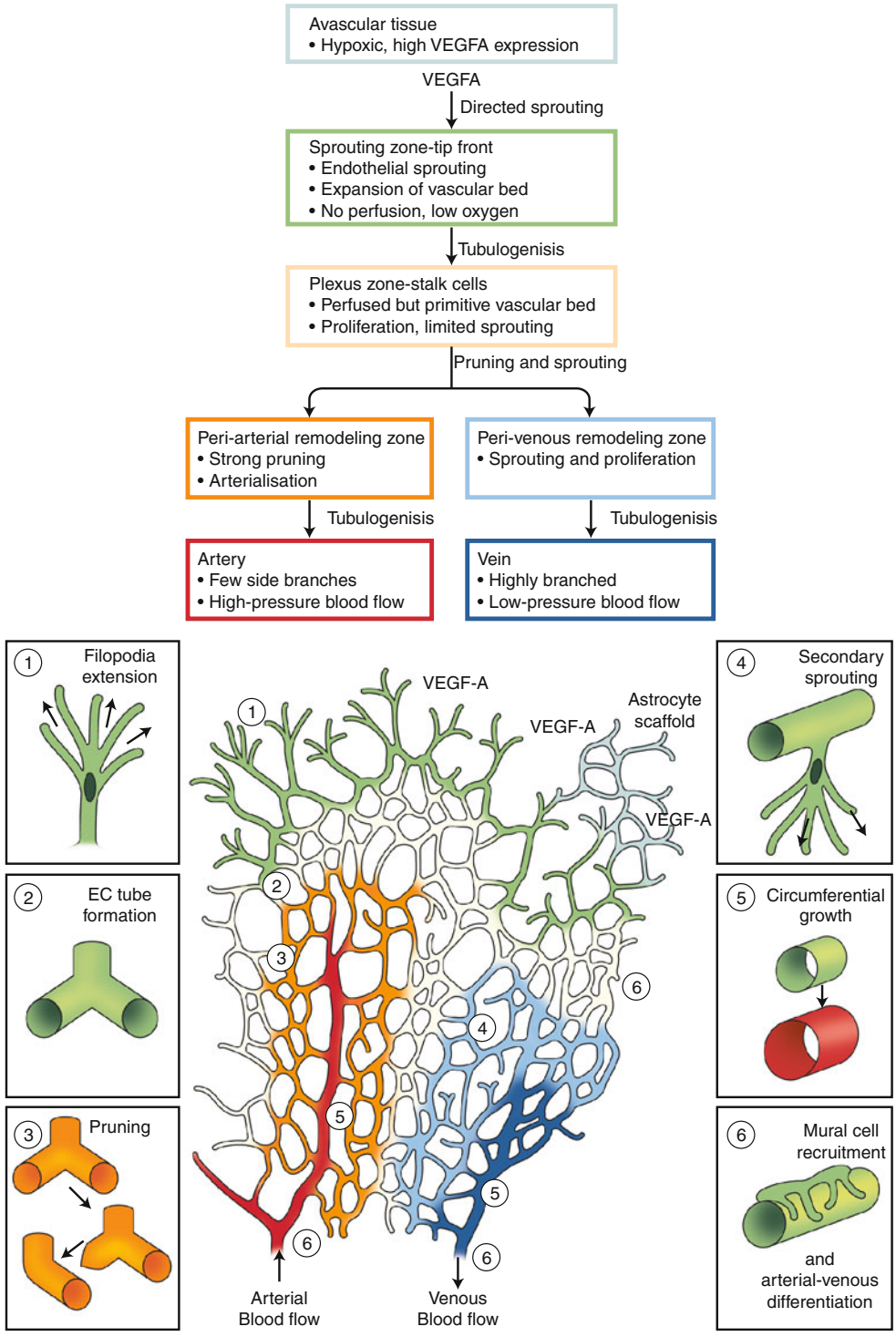


Fig. 3.2 Schematic diagram of sequence of vascular morphogenesis (Adapted with permission from Roca and Adams [120])

Embryologic development of the aorta originates from the truncus arteriosus, which ends in the aortic sac. Paired aortic arch arteries arise from the aortic sac and lead to paired dorsal aortas which fuse during the fourth week of gestation. These six paired aortic arches connecting the ventral and dorsal aortae give rise to the aortic arch and its major branch vessels [4] (Fig. 3.3a–c). VEGF signaling directs the migration of cells to populate these vessels. In addition to VEGF, a number of factors and regulatory pathways have been shown to be essential to normal vascular morphogenesis and remodeling. Among these, the Notch pathway includes a set of transmembrane ligands and receptors which participate as mediators of the differentiation of neural crest cells into vascular smooth muscle cells during the formation of the aortic arch. VEGF has been shown to induce the expression of both Notch ligand and receptors including Delta-like (D) and Jagged receptors, which, via cell-cell interactions, result in downstream effects regulating cell differentiation, arteriovenous specification, and homeostasis of vasculature in development and maturity (Fig. 3.4). Abnormal Notch signaling has been implicated as a cause of the very common congenital abnormality, patent ductus arteriosum, as well as the rare Alagille syndrome, a heritable multisystem disease characterized by bile duct insufficiency and cardiovascular abnormalities including coarctation of the aorta. In Alagille syndrome, defects in the Notch receptor Jagged 1 explain 95 % of cases [5].

The causes of most congenital and developmental vascular anomalies in humans are still unclear. A better understanding of the processes determining normal vascular development and homeostasis will likely improve our understanding of the pathogenesis of developmental abnormalities of the aorta and renal arteries. The long term goal of these efforts would be to impact the management of renovascular hypertension and its resultant cardiovascular morbidity and mortality.

Congenital Arteritides of the Aorta and Renal Arteries

Coarctation of the Aorta

Coarctation of the aorta is a congenital deformity of the aortic media and intima at the segment of aorta between the origin of the left subclavian artery and the ductus arteriosus. The coarctation is due to an obstructing membrane opposite the ductus or ligamentum arteriosum which results in narrowing of the lumen of the aorta at this site, medial retraction of the lesser curvature of the aorta, and often secondary dilatation of the arch (Fig. 3.5). Rarely, infants can present with pre-ductal coarctation and adults with post-ductal coarctation. Coarctation may be associated with aneurysms near the site of coarctation.

Localized aortic coarctation is often present independent of other congenital cardiac anomalies. However, a recent report of over 500 pediatric and adult patients with coarctation of the aorta screened with magnetic resonance imaging (MRI) and chart review identified concomitant cardiac abnormalities in 83 % of cases. The most common associated anomaly is the presence of a bicuspid aortic valve present in 59.6 % of this cohort with a range in the literature of 23–85 % of coarct cases [6]. Patent ductus arteriosus has been reported in 15–34 % of patients with coarctation. Eleven percent of infants with coarctation have a VSD. Other cardiac anomalies seen in patients with coarctation include subaortic stenosis, arch hypoplasia, quadricuspid aortic valves with regurgitation, transposition of the great vessels, aberrant subclavian artery and other arch vessel anomalies, left superior vena cava, mitral valve abnormalities, double outlet right ventricle, and atrial and ventricular septal defects, among others. This supports the concept that coarctation represents a diffuse developmental vascular disorder.

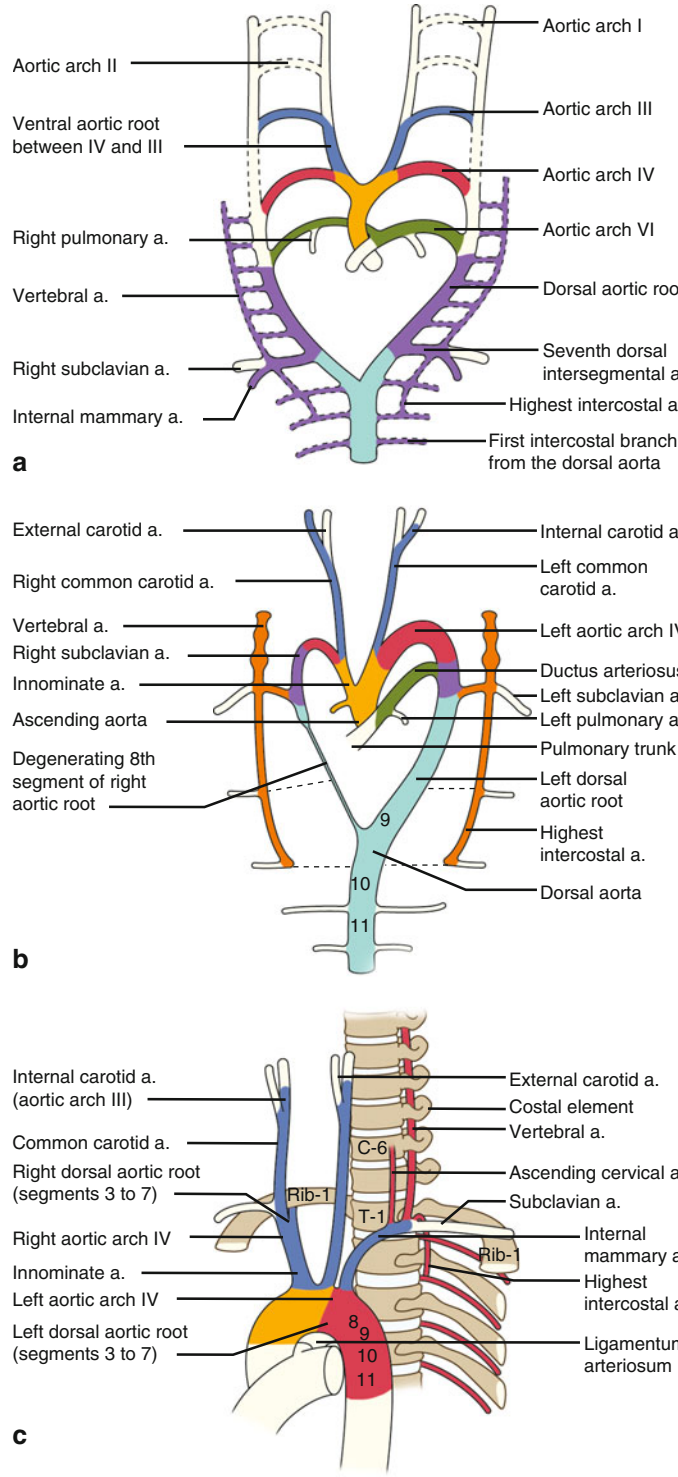


Fig. 3.3 (**a**–**c**) Formation of the aortic arch and major branches from arch vessels (Adapted with permission from Barry [121])

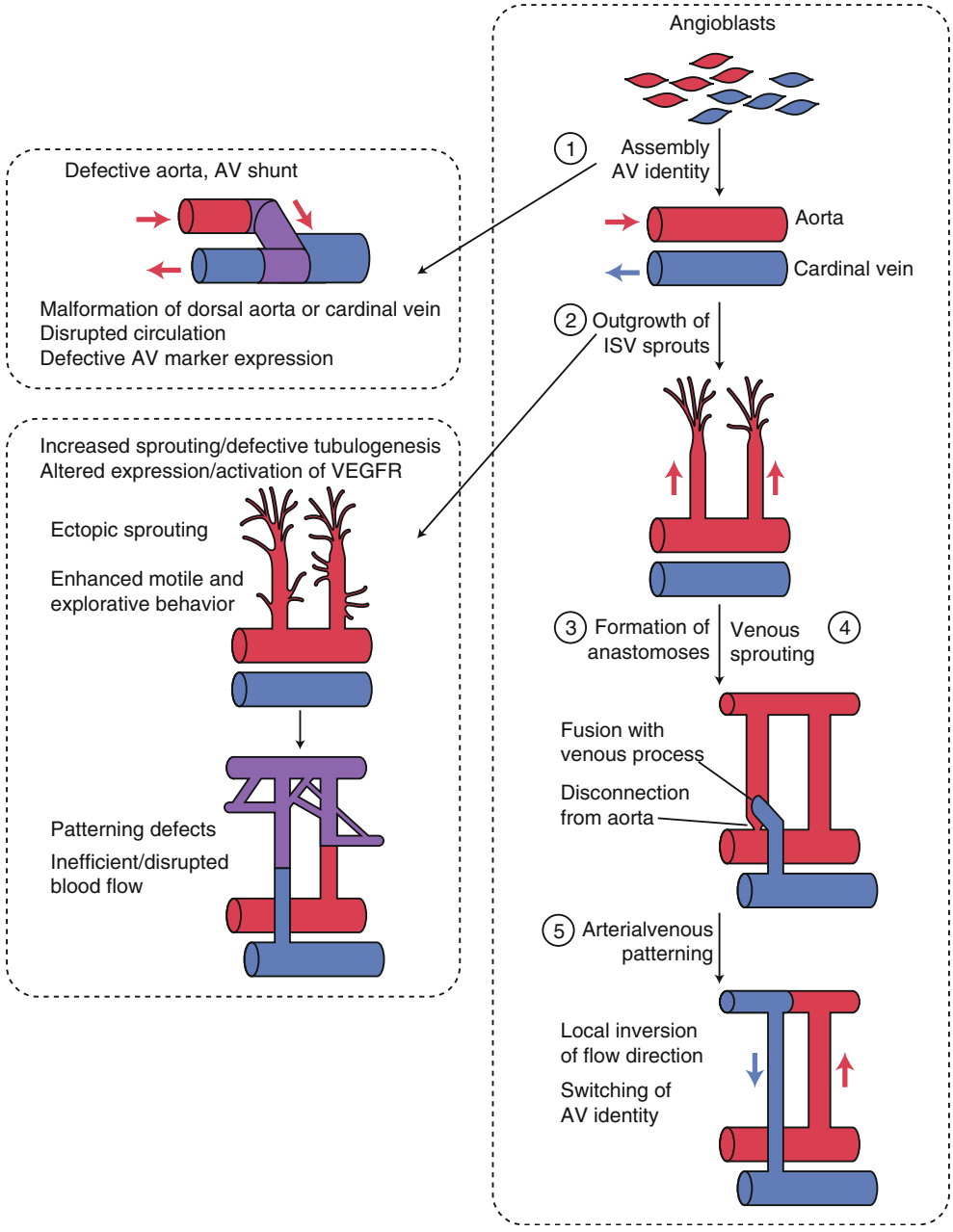


Fig. 3.4 Role of Notch in the normal and abnormal development of the dorsal aorta the Notch pathway is critical for normal formation of the dorsal aorta and circulatory connections. In zebrafish and mice, mutations in the Notch pathway result in abnormal branch patterning leading to abnormalities in circulation and blood flow (Adapted with permission from Roca and Adams [120])

Etiology

The cause of coarctation is an area of controversy. The fibrous tissue from the ligamentum arteriosum extends into the aorta. Based on this anatomic observation, one theory regarding coarctation is that stricture and closure of the ductus arteriosum results in tethering or kinking of the aorta at this site. Arguments against this concept include the location of the fibrous ridges

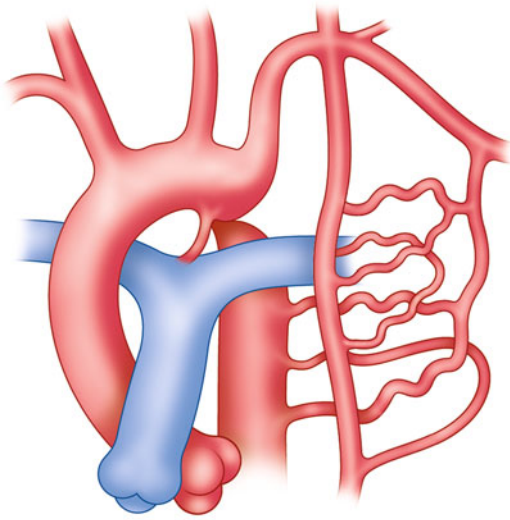


Fig. 3.5 Schematic representation of aortic coarctation drawing demonstrating the most common location of aortic coarctation at the level of The ligamentum arteriosum. Dilated collateral intercostal vessels are demonstrated on the right side of the figure (Adapted with permission from Brickner [51])

Table 3.1 Congenital and genetic disorders associated with aortic coarctation

Bicuspid aortic valve
Intracranial aneurysms
Alagille's syndrome
Turner syndrome
Williams syndrome
Dandy-Walker Malformation
Trisomy 13,18, 21
Shone complex
Noonan syndrome
Sturge-Weber syndrome
Scimitar syndrome
PHACE syndrome
Neurofibromatosis
CHARGE condition
Phenylketonuria
Andersen's syndrome
Mutations in KCNJ2 inward-rectifying potassium channel Kir2.1
In utero exposure to teratogens: arsenic, budesonide, anti-epileptic medications

in coarctation on the opposite wall of the aorta from the ligamentum arteriosum [7]. The second theory derives from our understanding of the importance of hemodynamics and blood flow on normal vascular morphogenesis as discussed previously. Abnormalities in blood flow during fetal development may impede the normal process of intussusceptive branching remodeling and lead to luminal abnormalities. In addition, gene deletions which might influence early fetal angiogenesis have been implicated in abnormal fetal aortic development based on animal studies. Syndromic and genetic disorders associated with coarctation of the aorta support the idea that coarctation likely represents the final outcome of a variety of mishaps which can occur in the complex process of normal aortic development [8].

Epidemiology

Partly because of advances in the management of patients with congenital heart disease, the American College of Cardiology and American Heart Association estimate that 1 in 150 adults over the next decade will have congenital heart disease. Coarctation of the aorta accounts for 5–10 % percent of all congenital cardiovascular abnormalities. The prevalence of coarctation is 1 in 2,500 births or 1 in 1,550 as reported from autopsy studies [9]. It is more common in whites than other races and has a 2:1 male to female predilection. Most cases of coarctation are thought to be sporadic. However, familial cases have been reported [10]. One study reported a fivefold increase in bicuspid aortic valves in first degree relatives of patients with coarctation and a 4 % incidence of congenital heart disease among offspring [11]. This supports the concept of genetic determinants of coarctation. The congenital and genetic syndromes which are associated with coarctation of the aorta are listed in Table 3.1.

Clinical Presentations

Coarctation of the aorta accounts for one third of hypertension in neonates and infants. In neonates, coarctation may go unnoticed during the first 7–10 days of life until closure of the patent ductus arteriosus which occurs in healthy infants between 48 and 96 h after birth [12]. A murmur

Table 3.2 Clinical presentation and physical findings in infants with coarctation

Hypertension with differential arm and leg blood pressure
Lower body cyanosis
Diminished femoral pulses
Differential pulse oximetry
Congestive heart failure
Tachypnea
Respiratory grunting
Diaphoresis with effort, feeding
Hypoxia
Cardiac examination abnormalities
Precordium visibly active
Left ventricular heave
Interscapular posterior thoracic murmur
Shock
Necrotizing enterocolitis

Table 3.3 Cardiovascular complications of coarctation in adults and older children

Renovascular hypertension
Aortic dilatation and rupture
Aortic dissection
Aortic insufficiency
Left ventricular hypertrophy
Congestive heart failure
Myocardial infarction
Claudication
Cerebral and intracranial aneurysms
Cerebral hemorrhage
Ischemic stroke
Infective endocarditis
Necrotizing enterocolitis/ischemic bowel

will be heard best over the posterior thorax. Hypertension may be mild. Cyanosis most notable in the lower extremities will be evident. When the patent ductus closes, the presentation may change dramatically. Because of inadequate time for collateral development, the infant will become more acutely hypertensive and display signs and symptoms of hypoxia and or hypoperfusion. Commonly, poor feeding with associated grunting, chest retractions, and diaphoresis with effort will be observed. Overt left sided congestive heart failure may develop due to the high after load presented by the coarctation. Peripheral cyanosis due to hypoperfusion below the coarct may be evident and more profound vascular insufficiency can result in renal failure or ischemic bowel evolving to necrotizing enterocolitis. Common physical examination findings and clinical presentations in neonates with coarctation are listed in Table 3.2.

Only 35 % of isolated coarctation cases present during the first year of life [13]. Coarctation may go undiagnosed in infancy particularly when there is a milder degree of aorta narrowing and better fetal collateral development. Hypertension is present in up to 90 % of cases identified in childhood. However, it can come to clinical attention because of cardiovascular sequelae such as aortic dissection or rupture, as listed in Table 3.3. Differential arm and leg blood pressures, defined as a greater than or equal to 20 mmHg difference, is present in only 39 % of cases of coarctation. More sensitive physical examination findings include a radial-femoral pulse delay and differential in pulse oximetry saturation between fingers and toes.

Because of extensive collateral development and increased flow in intercostal arteries, adults with coarctation may have palpable pulses in the intercostal spaces. This dilatation of the collaterals may present incidentally as a radiographic finding of notching of the ribs where the dilated vessels over time have affected rib cortical contour. Other plain film clues to coarctation include the "classic 3" sign of the configuration of the aortic region, an "E sign" esophagram, and in infants, cardiomegaly and pulmonary congestion. Murmurs of coarctation may be absent in up to 50 % of children and adults. When present, the murmur is heard best in the left sternal area and radiates to the posterior thorax at the mid-scapular region. The quality of the murmur is usually harsh, loud, and blowing and may extend into diastole because of continuous flow in the aorta. Patients may have carotid bruits due to high flows. A report from the Mayo Clinic found a fivefold increase in cerebral aneurysms among 100 adults with coarct compared to age matched healthy adults [14]. Therefore the authors recommended that these patients be screened for the presence of cerebral aneurysms with computed tomographic angiography (CTA) or MRA [15].

Diagnostic Testing

In neonates and infants, the diagnostic screening test of choice is echocardiography with doppler flow analysis and special attention to the aortic arch [16]. Measurement of the diameter at the isthmus in comparison to the diameter of the arch of the aorta and the descending aorta may provide improved diagnostic accuracy as a reflection of pre- and post-coarctation dilatation. Lu et al. found that the combination of arm differential blood pressures along with visualization of a posterior shelf and a low ratio of the diameters of the isthmus to descending aorta of <0.6 provided a sensitivity and positive predictive value of 91.7 % for the presence of coarctation and a negative predictive value of 99.3 % [17]. Fetal ultrasound may detect coarctation in up to 71 % of cases. Findings on prenatal echocardiography suggestive of coarctation include disproportion between the right and left ventricles and, in severe coarctation cases, disproportion of the sizes of the aorta and pulmonary artery [18]. Limitations of echocardiography include operator dependency, obstacles presented by chest wall deformities, and variable image quality based on equipment.

The gold standard for evaluation of coarctation of the aorta in children and adults is arteriography [19]. However, because of the invasive risks of angiography, computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) or the aorta are more often used and provide excellent diagnostic accuracy. CTA requires a large contrast load and radiation exposure. The use of MRA and clinical assessment has been shown to be more cost-effective than CTA in the diagnosis of coarctation [20]. Since movement and breathing can cause motion artifacts, MRA performed in children may require anesthesia. Emerging techniques using three-dimensional, time-resolved, and three-directionally velocity-sensitive MRI have been able to detect hemodynamic alterations and wall shear stresses at the site of coarctation or repair and up and down-stream from the stenosis. Using MRA acquired velocity data, this technology allows for accurate derivation of the pressure gradient across the coarctation segment [21, 22]. MRI imaging in patients with coarctation should include evaluation of the arch, lower aorta and the heart and mediastinal vessels to screen for other associated abnormalities. Figure 3.6 shows an MRA on a 32 year-old adult female with late diagnosis of coarctation associated with an adjacent aneurysm.

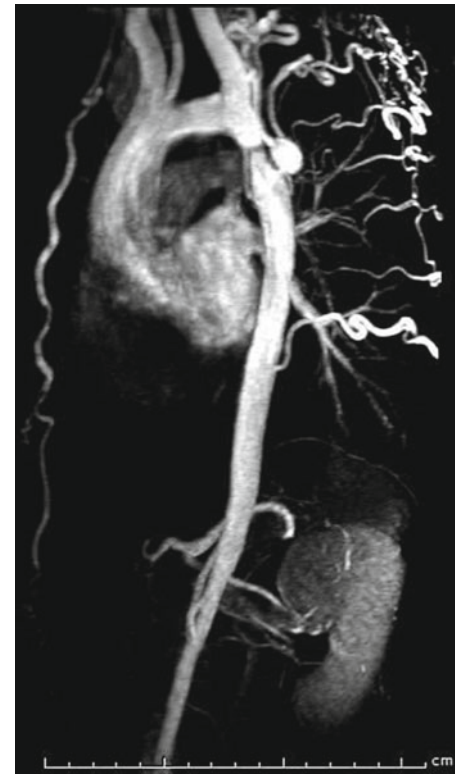


Fig. 3.6 Magnetic resonance image of aortic coarctation this magnetic resonance angiogram demonstrates aortic coarctation in a 32 years old woman with renovascular hypertension. There is a large aneurysm adjacent to the area of coarctation fed by collateral intercostal vessels which are markedly dilated

Treatment of Coarctation in Neonates and Infants

Untreated, patients with coarctation of the aorta generally do not survive beyond the age of 50 years. The most common causes of death include ischemic stroke, intracranial hemorrhage, myocardial infarction, congestive heart failure, aortic rupture or dissection, and other complications. Neonatal aortic coarctation is most often surgically treated urgently or within the first 3 months of life. Since catastrophic events can occur

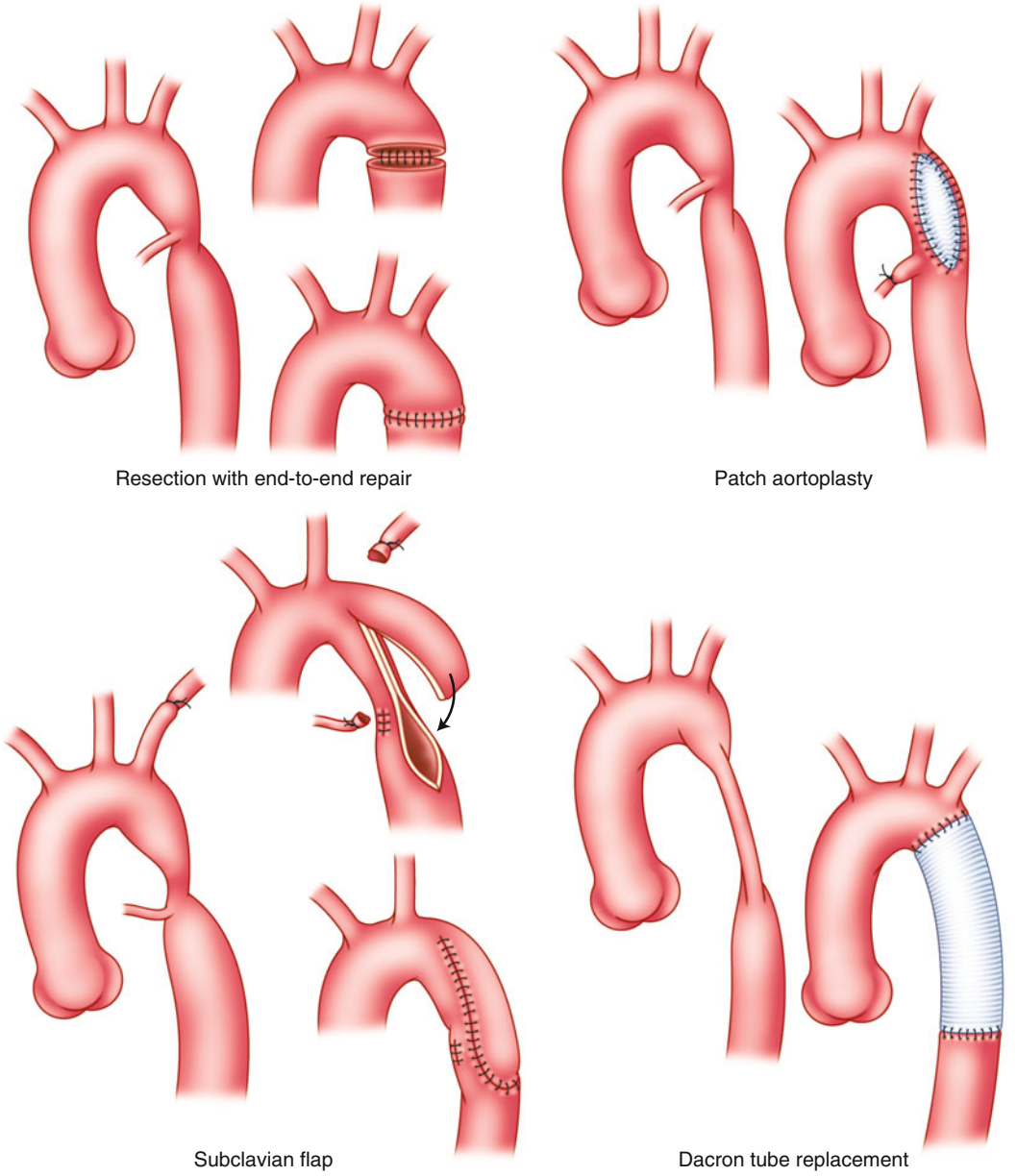


Fig. 3.7 Schematic diagram of surgical approaches to aortic coarctation (Adapted with permission from Morris [7] Chap. 276)

following closure of the patent ductus arteriosus, attempts to maintain ductus patency and relax the area of coarctation with administration of prostaglandin E1 can sometimes stabilize the clinical picture before surgery and allow time for preparations for surgery. This is less effective beyond 2–4 weeks of life. The preferred surgical approach, when feasible, is resection of the stenotic segment with end-to-end aortic anastomosis [23–25]. Aortic bypass graft insertion may be needed when the stenotic segment is too long for end-to end closure. The types of surgical repair of coarctation are shown schematically in Fig. 3.7. Complications of surgical coarctation repair include restenosis,

Table 3.4 Guidelines: indications for the treatment of coarctation in adults

Indication	Class	Level
American College of Cardiology/American Heart Association		
Peak-peak coarct gradient ≥20 mmHg	I	C
Peak-peak coarct gradient <20 mmHg in the presence of anatomic imaging evidence of significant coarct with radiologic evidence of collateral flow	I	C
European Society of Cardiology		
Non-invasive pressure difference >20 mmHg between upper and lower limbs, regardless of symptoms but with upper limb hypertension (>140/90 mmHg in adults), pathological blood pressure response during exercise, or significant LVH	I	C
Independent of the pressure gradient, hypertensive patients with ≥50 % aortic narrowing relative to the aortic diameter at the diaphragm level (on CMR, CT, or invasive angiography)	IIa	C
Independent of the pressure gradient and presence of hypertension, patients with ≥50 % aortic narrowing relative to the aortic diameter at the diaphragm level (on CMR, CT, or invasive angiography)	IIb	C

Adapted with permission from Warnes et al. [26] and Baumgartner et al. [27]

the development of aneurysms at the site of repair, and the rare occurrence of paralysis due to disruption of spinal perfusion [7].

Treatment in Older Children and Adults

Indications for treatment of coarctation in adults as defined by the American College of Cardiology/American Heart Association (ACC/AHA) in 2008 include an angiographically determined peak systolic pressure gradient across the coarct of at least 20 mmHg, or a gradient less than 20 mmHg associated with imaging evidence of coarctation and the presence of significant collateral flow [26]. Guidelines from the European Society of Hypertension published in 2010 defined indication for intervention as arm and leg blood pressure difference of at least 20 mmHg determined noninvasively associated with upper limb hypertension defined as blood pressure greater than 140/90, pathologic blood pressure response to exercise, or the presence of left ventricular hypertrophy [27]. These guidelines are summarized in Table 3.4.

The ACC/AHA guidelines recommend that the choice of treatment of coarctation with surgery versus percutaneous catheter interventions should be determined following multispecialty consultation with a team of cardiologists, interventionalists, and surgeons specializing in the treatment of adult congenital heart diseases. There are currently insufficient data guiding the optimal therapeutic approach in patients with coarctation [28]. Endovascular repair has become the preferred approach to treatment of older children and adults with coarctation and has a lower risk of paralysis and complications compared to surgery. Balloon angioplasty alone provides good short term results but with the disadvantage of restenosis rates as high as 50 % [29]. Predictors of poor outcome after balloon angioplasty include residual post-procedure systolic pressure gradient across the lesion, diameter of the aortic isthmus, and concomitant aortic hypoplasia. In addition, there is a significant risk of later development of aneurysms at the site of angioplasty. Therefore, aortic stenting is the preferred endovascular approach to both native and recurrent coarctation in older children and adults [30]. The mean age of patients who have undergone correction of coarctation using balloon-expandable or self-expanding bare metal stents varies from 19 to 33 years, with a range from 4 to 49 years in published series [31]. Limitations of primary stenting for the treatment of aortic coarctation in smaller children are based on the limits of expandable stents to address the continued growth of the aortic lumen. In addition, primary stenting requires a large sheath with potential for vascular damage. The stent alters distensibility and

compliance of the proximal aorta. Often, based on the degree of aortic stenosis at the site of coarctation, staged procedures are required which include both pre-dilation before stenting and subsequent repeated balloon dilatations. There are currently no stents approved by the FDA for the treatment of coarctation. Ideally, a stent used to treat coarct would be self-expanding within the range of growth of the aorta from childhood to adult size. There is an ongoing prospective single arm trial evaluating the effectiveness and safety of the Cheatham-Platinum stent used widely outside of the United States [32]. Antiplatelet therapy is recommended for 3–6 months following endovascular placement of an aortic stent, usually as dual therapy with both aspirin and clopidogrel, until endothelialization is complete [33].

Historically, complications of endovascular repair of coarctation were reported in as many as 35 % of cases and included ruptured balloons, stent migration, aortic intimal tears, dissections, femoral artery pseudoaneurysm formation, atheroembolism, and stroke, with death reported infrequently [34]. However, complication rates have decreased over the past decade. The Congenital Cardiovascular Study Consortium published comparative outcomes on over 350 patients from 36 institutions treated for coarctation between 2002 and 2010. The early complication rate in the subgroup of 217 patients with mean age 16.6 years treated by percutaneous angioplasty or stenting was only 9.8 and 2.3 %, respectively. Late complications, including dissection, aneurysm development, and restenosis occurred in 43.8 % of angioplasty cases but only 12.5 % of stented cases. Older age at time of repair is associated with higher complication rates [35].

Though surgical repair of coarctation is associated with higher complication rates, it is still indicated for elongated descending aortic stenosis and complex lesions including aneurysms. Among 72 patients treated surgically, the Consortium reported restenosis or late aneurysm development in 25 % [35]. Surgical mortality rates have also improved, reported at less than 1 %. Morbidity includes early postoperative paradoxical hypertension syndrome, phrenic nerve paralysis, laryngeal nerve paralysis, subclavian steal, and, rarely, spinal cord ischemia with paraplegia and mesenteric ischemia [36].

The ideal medical treatment prior to repair of coarctation is based entirely on expert opinion [26, 37]. Medical treatment of the hypertension associated with coarctation prior to definitive endovascular or surgical treatment should include beta-blockers which reduce the force experienced by the ascending aorta before the coarctation, and blockade of the renin-angiotensin-aldosterone system with close attention to renal function and peripheral perfusion. Pregnancy in female patients with coarctation of the aorta is associated with a high risk of pregnancy associated hypertension reported in up to 24 % of cases. In addition, women with a diagnosis of coarctation were more likely to have adverse cardiovascular outcomes after pregnancy, delivery by caesarean section, longer hospital stays and incur greater cost of hospitalization [38]. Yet, patients with residual arm-leg pressure gradients less than 20 mmHg usually fare well during pregnancy, can be delivered safely vaginally, and have outcomes similar to women without coarctation. For female patients during pregnancy in whom angiotensin-converting enzyme inhibitors are contraindicated, beta blockers such as labetolol can be used to manage hypertension associated with coarctation.

Treatment Outcomes

There is a high rate of cure of hypertension following surgical and endovascular repair of coarctation of the aorta. Success rates range between 69 and 80 % depending on patient age at follow-up. Patients treated surgically at a young age have the greatest chance of cure with those treated between the ages of 2 and 9 years having the same age-related incidence of developing late hypertension as the general population [39]. Early repair is associated with better blood pressure and vascular outcomes. The prevalence of late hypertension among patients treated for coarctation relates directly to the age of repair

and has been reported as 7 % among infants repaired in the first year of life, 16 % among those repaired at a mean of 8 years of age, and 48 % for adults treated at a mean of 35 years of age [40]. The development of hypertension in a patient treated for coarctation should prompt a search for restenosis. Yet, even in the absence of recurrent stenosis, coarctation of the aorta is associated with a high risk of hypertension at long-term follow-up with 30 % of those treated in infancy developing hypertension in adolescence and up to 55 % of patients having hypertension in mid-life. Risk factors include not only age at treatment of coarctation, use of prosthetic material in the repair, residual brachial-ankle blood pressure differences, and age at follow-up [41].

The pathophysiology of late hypertension among patients treated for coarctation is thought to relate to either inborn or acquired aortic noncompliance due to a number of factors, including contributions from reduced barorector sensitivity in the aortic arch, increased after load and aortic stiffness, abnormalities in aortic geometry, and early renal injury with sustained activation of the renin-angiotensin-aldosterone system [42]. The type of surgical repair influences the development of late hypertension, with the requirement for prosthetic grafts conferring higher risk [43]. Hypotheses regarding the mechanism explaining differences in outcome include residual aortic stiffness, impaired elastic properties of the aorta, collagen deposition in adjacent aortic segments, and higher gradients at the aorta-graft anastomoses [44, 45].

Pulse wave velocity measurements in patients following treatment for coarctation usually demonstrate abnormalities in upper but not lower limbs. Studies of endothelial function in patients treated for coarctation demonstrate impaired vascular reactivity and mechanical properties as measured by flow mediated dilation especially in upper extremity conduit arteries [46]. This usually occurs independent of the timing of repair, suggesting impaired vascular function is determined early by abnormal hemodynamics or more diffuse vascular abnormalities in the vasculature. Similar findings of arterial stiffness have been reported in normotensive adults who underwent childhood surgery for coarctation. In one cohort of adults (mean age 30 years), higher pulse wave velocity augmentation indices and abnormal flow mediated vasodilatation were present independent of the time interval from coarctation surgery [47]. Abnormal baroreceptor sensitivity has also been reported in infants with coarctation as compared to healthy controls [42, 48, 49] However, in one study pulse wave velocity was found to be normal in infants treated before 4 months of age yet elevated in patients treated later in infancy [50].

Treatment of coarctation improves survival but it remains below expected for age. The survival among children followed for 22 years and adults followed 6.8 years after repair of coarctation is over 87 %. Survival is best in patients treated before the age of 10 years. The relationship between age at treatment and survival suggests that those treated after the age of 40 have a 50 % 15 year survival and those treated between the ages of 20 and 40 have an expected 25 year survival of 75 % [51, 52]. These patients are at higher risk than the general population for a number of cardiovascular complications including restenosis at the level of the coarct segment, aortic aneurysm formation, aortic dissection, proximal aortic dilatation, cerebrovascular accidents premature atherosclerosis, endocarditis and aortic valve stenosis.

Post-coarctectomy Hypertension Syndrome

A syndrome of post-operative hypertension can occur within the first 2 days following repair of aortic coarctation. The pathophysiology is thought to involve activation of both the sympathetic nervous system and the renin-angiotensin-aldosterone system. Marked elevations in catecholamine release have been documented in some cases which return to normal within 3–4 days [53–55]. The mechanism of this surge in sympathetic activity is unclear. One hypothesis is that baroreceptor sensitivity has been reset by the presence of coarctation leading to

Table 3.5 Guidelines for the long term follow-up of patients with coarctation

Recommendation	Class	Level
Lifelong cardiology follow-up	I	C
Consultation with cardiologist with expertise in adult congenital heart disease	I	C
Yearly follow-up of surgical or endovascular repaired patients	I	B
Late postoperative thoracic aortic imaging to assess for aortic dilatation or aneurysm formation at intervals of 5 years or less	I	C
Close monitoring for resting or exercise-induced arterial hypertension	I	B
Hypertension should prompt evaluation for recoarctation	I	B
Hypertension should be treated aggressively	I	B
Routine exercise testing should be performed at intervals determined after consultation with an adult congenital heart disease expert	IIb	C

Used with permission from Warnes et al. [26]

a surge in feedback when blood pressure drops initially post-operatively. However, early drops in blood pressure have not been documented in most cases of post-coarctation hypertension syndrome. Another theory proposed by Pickering in 1977 is the activation of spinal sympathetic reflexes initiated by sudden high pressures in the descending aorta following repair of coarctation [56, 57]. It is thought that the later elevation in plasma renin activity seen during days 3–5 in these patients is mediated by this early surge in sympathetic activation. Transient post-coarctation hypertension has been reported to respond to a number of agents including angiotensin-converting enzyme inhibitors, nicardipine, nipride, clonidine, and esmolol [58].

Long Term Management of Patients with Coarctation

Patients treated for coarctation are at risk for late complications and should be monitored long term by a cardiovascular specialist. Complications include late restenosis and aneurysms at the site of repair or in the cerebrovascular circulation. Abnormal endothelial function also increases their risk of hypertension and premature atherosclerotic complications. Guidelines for the long-term clinical and imaging follow-up of patients treated early in life for coarctation are shown in Table 3.5.

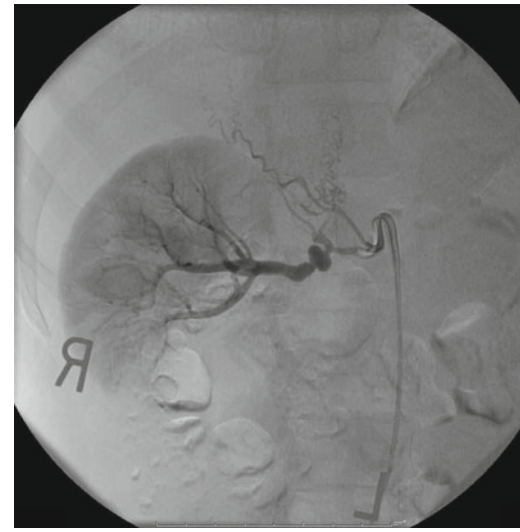


Fig. 3.8 Renal artery aneurysm digital subtraction renal arteriogram image showing a sacular renal artery aneurysm in a 45 years old Hispanic man presenting with accelerated hypertension

Non-atherosclerotic Renal Artery Aneurysms

Renal artery aneurysms have been reported in 0.1 % of the general population and are a rare cause of renovascular hypertension. Occurring 90 % of the time in the extraparenchymal regions of the renal vasculature, they are usually saccular aneurysms with a predilection for the branch points, most commonly the renal artery bifurcation (Fig. 3.8). Solitary aneurysms are most

common, and more often affect the right kidney than the left. There is an apparent female predilection. They may be bilateral in up to one-third of cases. Most often, renal artery aneurysms are found incidentally by arteriography or other vascular imaging modalities for other indications. The mean age of patients identified with renal artery aneurysms in a large cohort form the University of Michigan was 51 years [59]. The most common reported cause of renal artery aneurysms is fibromuscular dysplasia; other causes include atherosclerosis, idiopathic and congenital or associated with aortic coarctation, polyarteritis nodosa, other inflammatory disorders, neurofibromatosis, Ehlers-Danlos syndrome, Marfan's syndrome, post-traumatic or following dissection, and pregnancy [60].

Hypertension is present in about 75 % of patients with renal artery aneurysms. The mechanisms of hypertension in patients with aneurysms is speculated to include a number of pathophysiologic processes including concomitant renal artery stenosis reported in as many as 70 % of surgical cases, kinking or torsion of the renal artery, distal embolization due to thrombus, or arteriovenous fistula formation. Whether aneurysms develop as a consequence of arterial hypertension is unclear. In patients with fibromuscular dysplasia of the renal arteries, renovascular hypertension is often present. These patients can have associated renal artery aneurysms.

Rupture is the most dreaded complication of renal artery aneurysms though this occurs rarely. Patients with renal artery aneurysm rupture may present with Wunderlick syndrome: spontaneous renal hemorrhage confined to the subcapsular and perinephric space [61]. Clinically, these patients present with flank pain, hypovolemic shock, abdominal pain, a palpable flank mass and, often, hematuria. The size of the aneurysm has been implicated as a major risk factor for rupture with those greater than 2.5 cm proposed to have a higher risk of rupture; yet there are few data to support this. The indications for repair of renal artery aneurysms are still controversial with most recommending repair of symptomatic aneurysms (those associated with hypertension) over 2.0 cm. There are many case reports of rupture occurring during pregnancy with associated high maternal mortality rate [62]. This is thought to be due to the increase in blood volume and intra-abdominal pressure, Valsalva during delivery, and alterations in arterial wall characteristics due to hormonal changes. Therefore, consideration should be given to treating these aneurysms in women of childbearing age prior to pregnancy. Other potential complications of renal artery aneurysms include renal artery thrombosis, distal embolization and renal infarction, and arteriovenous fistula formation. Though uncomplicated aneurysms are generally asymptomatic, they may also cause flank pain or hematuria.

Both surgical and endovascular techniques have been employed in the treatment of renal artery aneurysms. Endovascular approaches include exclusion stent grafts, coil embolization, stent-coiling using bare metal stents across the neck of the aneurysm, and coil occlusion of the artery for distal aneurysms [63, 64]. Surgery involves aneurysmectomy and primary repair or bypass. In complex cases with intraparenchymal or multiple aneurysms, ex-vivo repair may be required. Reports of the effect of endovascular or surgical intervention on hypertension control are disappointing, with under 40 % demonstrating improvement [65].

Inflammatory Arteritides: Takayasu Arteritis

Inflammatory renovascular diseases are uncommon causes of renovascular hypertension that can lead to ischemia, focal infarctions and renal artery aneurysms (major disorders listed in Table 3.6). Clinicians should be aware of these disorders because without treatment they can lead to end stage renal disease and cardiovascular death. The remainder of this section focuses on the most common large and medium vessel vasculitis in children and young adults, Takayasu arteritis.

Table 3.6 Causes of inflammatory renal arteritis

Takayasu arteritis
Giant cell arteritis
Idiopathic aortitis in children
Connective tissue diseases
Systemic lupus erythematosis
Behçet's disease
Rheumatoid arthritis
Relapsing polychondritis
Classic medium vessel polyarteritis nodosa
Kawasaki disease
Radiation arteritis
Antibody mediated rejection intimal arteritis in renal transplant

Definition and Prevalence

Takayasu arteritis (TA) is an inflammatory, granulomatous arteritis involving the aorta and its first order branches. Alternative terms occasionally found in older literature include idiopathic arteritis and nonspecific aortoarteritis. TA was first described by Giovanna Battista Morgagni in 1761 [48] The disease is named for a Japanese ophthalmologist, Mikito Takayasu, who described retinal arteriovenous arcades associated with absent upper extremity pulses in 1908 [49]. Shimazu and Sano reintroduced the disease to Western literature and coined the term "pulseless disease" in 1951 [51].

The prevalence of TA varies with geography from as high as 1 in 3,000 in Japan to only 2.6 cases per million in the United States. It is more common in women than men with a female to male ratio of 8:1 in North America and 2:1 in India and South Africa. It is the most common large vessel vasculitis in adolescents and has been reported to be the most common cause of renovascular hypertension in parts of Asia.

Clinical Presentation

TA is differentiated from the more common disorders temporal (giant cell) arteritis (GCA) and atherosclerosis by clinical presentation and age of onset. TA can present in childhood but the average age of onset ranges from 25–41 years. In a large series of 272 cases described from South Africa, the mean age at diagnosis was 25 (range 14–66) [52]. In Europe, the median age of onset has been reported to be older at 41 years [53]. In contrast, the incidence of atherosclerosis and giant cell arteritis increases with age. Atherosclerosis is associated with traditional risk factors. Persons over age 50 years are primarily affected by both disorders.

Hypertension from proximal renal artery stenosis (RAS) or aortic coarctation is the most common presenting clinical feature in some case series, present in up to 93 % of patients. In the cohort of 272 South African patients with TA, 40 % had renal artery stenosis, 20 % had coarctation and 11 % had both [54]. Hypertension may be the sole manifestation in some cases. In the South African cohort, 142 of 272 patients had subclavian involvement, with a higher predilection for the left then right subclavian artery. In that series, stenoses also predominated in the renal arteries, and aneurysms were identified in a smaller subgroup [56]. However, in the Cleveland Clinic series, only 28 % had hypertension. In that series absent, diminished or asymmetric peripheral pulses were the most common presenting finding [57]. Thus, TA should be suspected in any child or young adult with abdominal, subclavian or carotid artery bruits in the setting of hypertension.

When malignant hypertension occurs, proteinuria and hematuria may be present. Nephrotic range proteinuria has been reported in patients with TA and found to be due to either secondary amyloidosis or focal segmental glomerulosclerosis associated with ischemic injury [60].

Arterial stenosis or embolism in the cervicocranial vasculature can present as stoke, acute visual loss, and arm or leg claudication. Occasionally aortic valve insufficiency secondary to ascending aortic dilatation may present as congestive heart failure. TA presents in about 50 % of patients with a prodrome characterized by low-grade fever, malaise, weight loss, night sweats, and fatigue. Nausea, headache and arthralgias may also be reported during this phase.

Table 3.7 The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis*

1. Development of symptoms or findings related to Takayasu arteritis at age <40 years
2. Development and worsening of fatigue and discomfort in muscles of one or more extremities while in use, especially the upper extremities
3. Decreased pulsation of one or both brachial arteries
4. Difference of >10 mmHg in systolic blood pressure between arms
5. Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta
6. Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental

Adapted with permission from Arend et al. [122]
*For purposes of classification, a patient shall be said to have Takayasu arteritis if at least three of these six criteria are present. The presence of any three or more criteria yields a sensitivity of 90.5 % and a specificity of 97.8 %

Diagnosis

The diagnostic criteria for TA proposed by Ishikawa et al. [66] were derived from observations in Japanese patients with TA. They include age less than 40 years at diagnosis or onset of signs and symptoms, involvement of the mid-subclavian artery as major criteria, and raised erythrocyte sedimentation rate (ESR), carotid artery tenderness, hypertension, aortic regurgitation, pulmonary artery lesions and involvement of the common carotid, brachiocephalic, descending thoracic or abdominal aorta as minor criteria. The presence of two major criteria, or one major and two or more minor criteria, or four minor criteria constitute the criteria for TA.

Subsequently, several modifications to the Ichikawa criteria for diagnosing TA have been made because of the differences in manifestations of disease in part based on disease phenotype [67]. The American College of Rheumatology suggest six criteria, including specific angiographic findings, to classify patients with TA and are shown in Table 3.7 [65]. The presence of three or more findings is reported to provide a sensitivity of 90.4 % and specificity of 97.8 % for the diagnosis of TA as compared to other vasculitides. However, the use of these criteria may have a lower specificity particularly in differentiating fibromuscular dysplasia (FMD) from TA.

The use of these criteria may be problematic in the setting of possible fibromuscular dysplasia (FMD) or the non-inflammatory entity of segmental arterial mediolysis (SAM). Particularly in children, FMD can present without the typical angiographic "string of beads" appearance of medial FMD and mimic TA. Because of the overlap of diagnostic criteria with other arteritides, a consensus conference focused on childhood vasculitis was held in 2005. In conjunction with the European League against Rheumatism (EULAR) and the Pediatric Rheumatology European Society (PRES), criteria for TA were proposed which included the presence of childhood hypertension. MRA, positron emission tomography (PET) scanning, CTA or intravascular ultrasound may identify evidence of thickening or edema of the vascular wall associated with the inflammation in TA [68]. The sensitivity and specificity of the new criteria reached 100 and 99 %, respectively, when angiographic criteria were included in a select cohort of 1,056 children [69].

The definition of disease activity is indicated by the development or worsening of at least two of the following: (1) systemic signs or symptoms including fever and arthralgias not attributable to another disorder, and (2) elevation of acute-phase reactants including C-reactive protein (CRP) and ESR in the absence of infection or malignancy, and (3) onset of signs or symptoms of vascular insufficiency (unequal or absent pulses, claudication, hypertension), and (4) vascular lesions in previously uninvolved territories detected on serial imaging [70–72]. Nonspecific biomarkers of inflammation including CRP and ESR are frequently elevated. Normocytic normochromic anemia, hypergammaglobulinemia, hypoalbuminemia and elevated transaminases are common. Fields et al. found that elevation of the sedimentation rate correlated with pathologic activity in operative vascular samples from patients undergoing surgery for TA with a sensitivity of 36 % and specificity of 83 % [58]. However, without pathologic tissue it is difficult to differentiate active and inactive phases of disease. Indeed, patients with TA not infrequently have extended periods of disease inactivity with periodic episodes of disease recurrence.

The distribution of vascular involvement and clinical syndromes appears to vary between Asian and North American cohorts. The ascending aorta and the aortic arch are commonly involved in Japanese cases while most North American series describe involvement of the descending thoracic and abdominal aorta and branches. In the NIH report, 38 % of patients had renal artery involvement [71]. Renal vascular lumen abnormalities including elongated stenoses, occlusions, and aneurysms result in renovascular hypertension (Fig. 3.8). Renal artery thrombosis can present as renal infarction or asymptomatic renal atrophy. Bilateral renal artery involvement is not unusual. In this setting, abdominal and renal artery bruits are commonly present.

Because of the systemic features of TA, the differential diagnoses for patients with TA includes other vasculitides and endovascular infections such as endocarditis and mycotic aneurysms, syphilis, tuberculosis, HIV, leprosy, neurofibromatosis, Marfan's and Ehlers-Danlos type IV syndromes, radiation arteritis, Behçets and Kawasaki disease, SAM and FMD.

Pathophysiology

The pathogenesis of TA is an area of active investigation. TA has been reported occasionally in patients with pre-existing auto-immune disorders including rheumatoid arthritis, systemic lupus erythematosis, amyloidosis, Crohn's disease and ulcerative colitis [71, 73]. In some cases of TA, the presence of antineutrophil cytoplasmic antibodies, positive rheumatoid factor, and elevated von-Willebrand factor-related antigen have been reported, supporting an adaptive immune response [74]. Elevated serum levels of Il-6, Il-12, Il-18 and metalloproteinase-9 have been associated with disease activity [7]. Chauhan et al. reported the presence of circulating anti-endothelial cell antibodies in patients with TA directed against heat shock proteins [75]. Sera from patients with TA has been shown to cause aortic endothelial cell apoptosis in vitro [76]. Recently, the Notch signaling pathway was found to be active in infiltrating T cells from patients with large vessel arteritis. Inhibition of this pathway in a humanized mouse model resulted in down regulated Th17 and Th1 responses [77]. Pending reports of a disease specific pathway amenable to immunologic modulation, these data collectively support a therapeutic strategy of initially broad immunosuppression.

An association between TA and mycobacterium tuberculosis (TB) in select populations has been postulated based on clinical data. First, in a series from South Africa, 91 % of pediatric cases of TA with average age at diagnosis of 8 years had positive Mantoux tests without active TB compared to a 5 % rate of positive skin test in the general pediatric population [78]. Twenty-two percent of these cases were either exposed to TB earlier in life or treated previously for TB. Among Japanese reports of cases of TA, 5–25 % had prior or active clinical tuberculosis as did 48 % of a cohort from Mexico [79]. Second, Morrison et al. demonstrated the presence of mycobacterium-like protein on the surface of spindle cells in pathologic sections of the aorta in patients with TA [80]. Finally, CD8 positive T-lymphocytes infiltrate the vessel wall in TA suggesting a host response similar to that associated with tuberculosis infection [81]. It has been postulated that a hypersensitivity to the purified protein derivative (PPD) in some of these patients may represent a type IV immunologic response to heat shock protein-65 which is one antigen associated with vascular inflammation in TA [82]. However, in a recent study from South Africa, the rate of latent TB infection in TA patients measured with QFT was similar to the rate in controls [83].

Histology

Pathologic specimens from patients with TA demonstrate granulomatous inflammation involving all layers of the vessel wall with Langerhans cells and central necrosis early in the disease. The inflammation results in later fibrosis leading to vascular stenoses, thrombosis, occlusions and aneurysm formation. The granulomatous reaction is patchy and segmental involving all three layers of the arterial wall. It is thought to

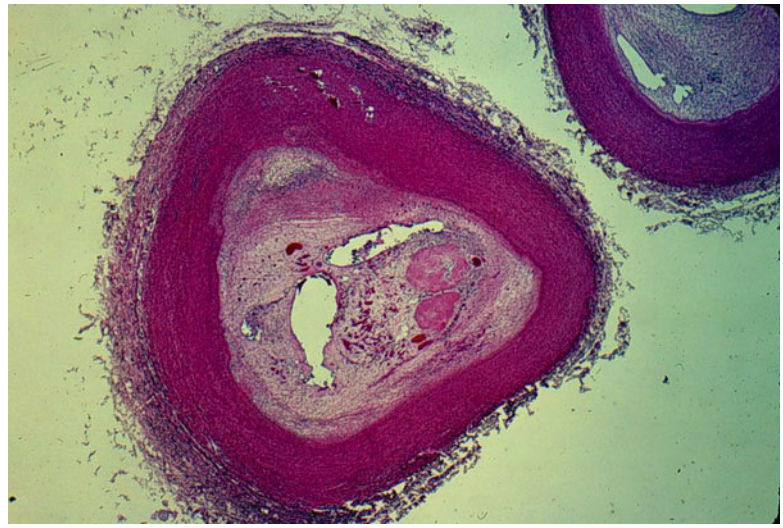


Fig. 3.9 Histologic section of a innominate artery with Takayasu Arteritis (Image provided courtesy of Dr. William D. Edwards, MD, Mayo Clinic)

be induced by T cells leading to monocyte adherence to the vessel wall and differentiation to macrophages with subsequent generation of a granulomatous reaction. Immunoglobulin G and M deposition and properdin have been identified in sections taken from vasculature of patients with TA. Glomerular pathology reported in association with TA is consistent with ischemia due to more proximal involvement of the renal arteries, with nonspecific glomerular involution and basement membrane wrinkling. Several case reports of TA with concomitant glomerular processes including IgA nephropathy, crescentic glomerulonephritis, membranoproliferative or mesangioproliferative glomerulonephritis, focal segmental glomerulosclerosis, and secondary amyloidosis have been published [84–87]. A histologic section from a patient with TA is shown in Fig. 3.9.

Genetic Susceptibility

A number of associations of TA with major histocompatability complex HLA antigens and reports of TA in monozygotic twins support a genetic susceptibility to TA. A recent Japanese study of 96 TA subjects revealed a significant association of a novel locus HLA-B67 ($P=0.00024$, odds ratio [OR] = 4.94) and B52 ($P<0.0001$; OR = 3.35), a conventional locus, with TA [88]. In older studies from Japan and Korea, TA has been associated with HLA 9 and 10, B5, BW40 and DR2. In a South African cohort, associations with DR4, DR7, DW3 and 12, DQW1 and BW52 have been reported. In the US, TA has been associated with HLA B22. In India associations with HLA B5 and B21 have been found [89, 90].

Imaging

MRA or CTA have largely replaced conventional angiography as the preferred imaging techniques for the diagnosis and monitoring of TA. A commonly used classification of types of TA based on angiographic findings was first published in 1996 [91] (Fig. 3.10). More recently, arteriographic lesions were identified in 145 patients with TA and 62 patients with GCA. Arterial involvement was contiguous in the aorta and usually symmetric in paired branch vessels for both TA and GCA. There was significantly more left carotid ($p=0.03$) and mesenteric ($p=0.02$) artery disease in TA and more left and right axillary ($p<0.01$) artery disease in GCA. However, classification schemes that attempted to distinguish TA from GCA based solely on angiography, misclassified most of the subjects. These data support the importance of a composite clinic, serologic, and imaging approach to TA diagnosis [84].

MRA has certain advantages over CTA as an imaging modality for TA because of adequate

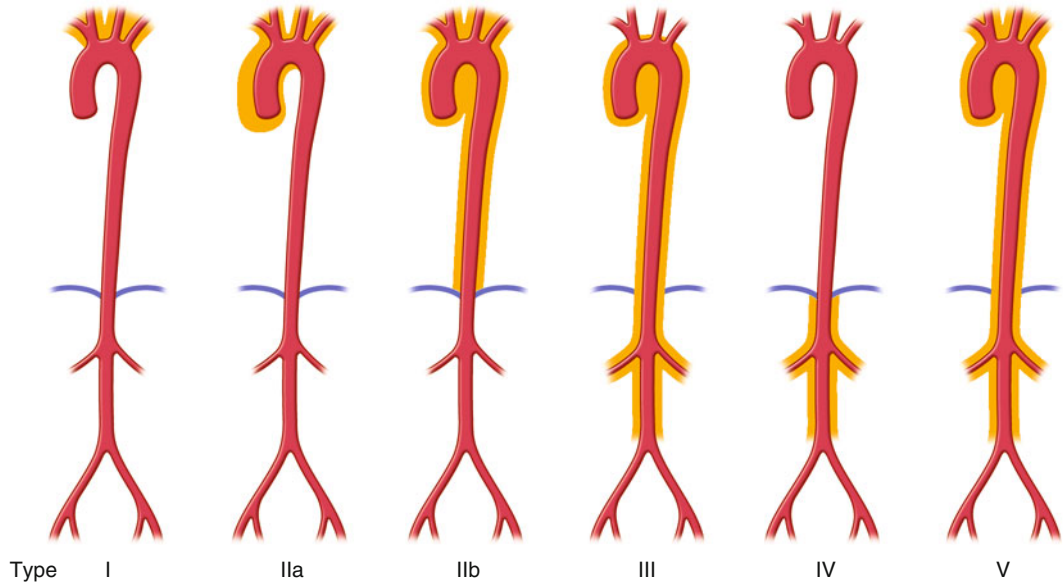


Fig. 3.10 Angiographic classification of Takayasu Arteritis (Adapted with permission from Hata et al. [91])

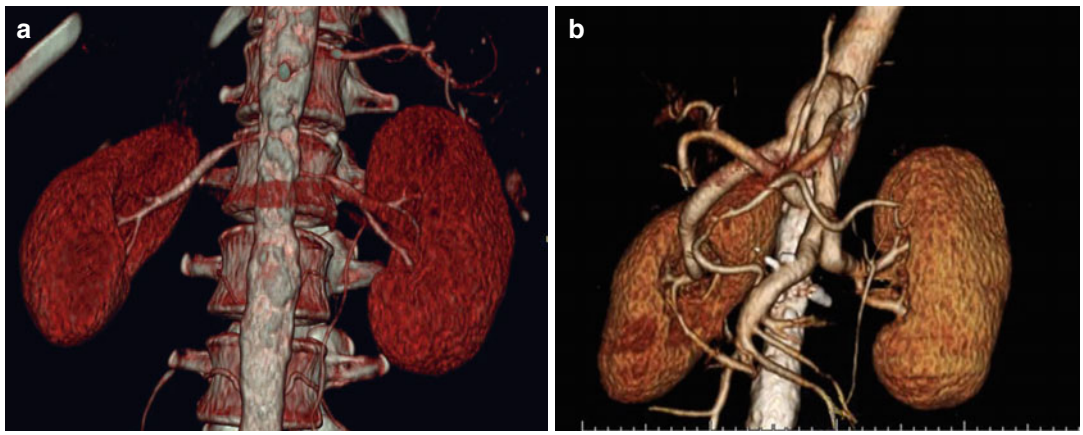


Fig. 3.11 (**a**, **b**) CT angiogram demonstrates aortorenal involvement in a 37 years old woman with Takayasu Arteritis (**a**) before and (**b**) after revascularization of both renal and superior mesenteric arteries with a supraceliac trifurcated Dacron bypass graft. Separate limbs are seen to the left renal artery, the right renal artery, and the superior mesenteric artery

spatial resolution for the majority of lesions that involve the proximal portion of aortic branch vessels and the descending aorta. MRA does not deliver ionizing radiation. Tissue characterization with T2-weighted short inversion recovery images may identify and track changes in the aortic and pulmonary artery wall thickness and correlate with active inflammation and edema of the vessel wall. In the late phase of the disease, MRA may demonstrate aortic arch dilatation and stenosis of the more distal aorta and proximal portions of the renal and other branch arteries (Fig. 3.11a, b). Computed tomography may provide more accurate quantification of wall thickness and quantification of vascular stenoses with a sensitivity and specificity for luminal changes of 93

and 98 % respectively. In some cases, arterial wall delayed enhancement may indicate active disease or fibrosis [92].

^{18}FDG-PET has been used to determine activity of vascular involvement with TA. In a study of 28 TA patients from Japan that used a visual grade for ^{18}FDG uptake in the vessel wall, uptake was observed in 18 of 24 patients with active disease and in only 5 of 14 patients with inactive disease. There was a significant association between clinical disease activity and disease activity judged by FDG-PET ($P=0.008$). Visual grade, standard uptake value intensity, and the number of vascular lesions with active ^{18}FDG uptake correlated with the ESR and CRP levels [93].

In a recent paper of 39 TA patients (median age, 30 years) ^{18}FDG-PET uptake was quantified by maximum standardized uptake value (max SUV). Disease activity gold standard was defined by the National Institutes of Health criteria. The maximal SUV was significantly higher in active disease (maximal SUV was 2.7 compared to 1.9 in those with inactive TA 1.9 and normal control subjects 1.8; $p<0.001$ each). At a maximum SUV cutoff of 2.1, the positive and negative predictive values of FDG-PET were respectively 96.2 and 84.6 %. In this study, the max SUV was actually superior to CRP ($p<0.05$) and ESR ($p<0.05$) [94].

Carotid artery duplex ultrasonography remains useful to quantify carotid stenosis by blood velocity. A velocity or wall thickness may indicate disease activity or response to therapy [70]. Echocardiography is helpful primarily in identifying aortic insufficiency which may be associated with aortic root dilatation. Patients with TA may have a dilated cardiomyopathy due to myocarditis or the long term impact of untreated hypertension [95].

Natural History

TA is a devastating disease which can result in death due to stroke, cerebral hemorrhage, aneurysm rupture, renal failure, myocardial infarction and congestive heart failure. The natural history probably varies with geography and ethnicity. The large South African reported a natural history characterized by an initial active disease period followed by a "burned-out" inactive phase with no further progression of arteritis [75]. The location of vascular involvement changed little over the 5 year follow up. However, data from other centers suggest some patients have recurrence of activity of disease superimposed on older vascular lesions. Significant morbidity with reduced functional status from the disease as well as the immunosuppressive therapy occurs in a substantial fraction of patients; a 3–4 % five year mortality rate has been reported in one young adult cohort [96–99].

Treatment

Most patients achieve symptomatic and biochemical remission with steroids at the core of immunosuppressive regimens. In a series from the National Institutes of Health, prednisolone or prednisone was used for 1–3 months with tapered or alternate day dosing schedules, starting at 1 mg/kg/day [100]. However, many patients require treatment for 1–2 years or longer and develop steroid related adverse effects. In the South African cohort, patients received oral prednisone 1 mg/kg for 1 month; the dose was gradually tapered according to symptoms to a maintenance dose which was continued for 2 years [101]. Of the 182 patients in the South African cohort who received steroids, inflammatory markers normalized, but none regained lost pulses or achieved angiographic reversal of arteritis.

Investigators at the Cleveland Clinic reported results of a treatment protocol which started with prednisone at similar dosages, tapering according to clinical response. Methotrexate was used if relapse occurred during the steroid taper at which time the dose of steroid was also increased to 10 mg above the last effective dose. Methotrexate was used at a dose of 15 mg/week up to 25 mg/week, day with folic acid 1 mg/day and double strength trimethoprim-sulfamethoxazole three times per week for prophylaxis against Pneumocystic jiroveci pneumonia. In cases of intolerance of methotrexate, alternative therapy

with azathioprine 2 mg/kg/day or mycophenolate mofetil at 1.5 g twice daily, or an anti-TNF agent was used. Oral cyclophosphamide was used in one patient at a dose of 2 mg/kg/day. In this cohort, 93 % of 30 patients followed longitudinally achieved remission. However, only 28 % achieved sustained remission using this protocol, with the remainder requiring additional and sometimes alternate, immunosuppressive therapies. Of the patients who achieved remission, 96 % relapsed, most while still on immunosuppressive therapy. Seventy percent of these patients required vascular interventions for localized ischemic disease [102]. Limited data from other centers suggest cyclophosphamide may also induce remission of disease in patients with potentially life threatening manifestations of TA [103].

Anti-tumor necrosis factor (TNF) therapies have been tried in patients with TA that remains active despite conventional immunosuppression. Strategies have included etenercept and infliximab in conjunction with steroids with promising results in a small number of patients [104]. In a recent series from the Mayo Clinic 20 patients with refractory TA (19 women, 17 white, 33 ± 10.2 years), seventeen patients (85 %) received infliximab, 2 patients (10 %) received adalimumab, and 1 patient (5 %) received etanercept. The median disease duration prior to the use of TNF inhibitors was 15.9 months before the use of TNF inhibitors. All 20 patients received prednisone. Other medication use included methotrexate (18 patients), azathioprine (5 patients), mycophenolate mofetil (3 patients), and cyclophosphamide (3 patients). The median duration of treatment with TNF inhibitors was 23.0 months (range 8.7–38.9 months). Treatment with TNF inhibitors resulted in disease remission in 18 (90 %) of 20 patients and sustained remission in 10 patients (50 %). Ten (83 %) of 12 patients were able to taper prednisone below 10 mg and 7 patients discontinued prednisone. However, 6 of the 18 patients achieving remission experienced relapse while receiving TNF inhibitors. Thus despite short-term benefit in many patients with refractory TA, one third of patients will relapse while receiving TNF inhibitors and a fifth will discontinue treatment because of adverse events [105].

Similar results were recently reported in a series of fifteen patients [median age 41 (range 17–61) years; 13 women] with active TA despite conventional immunosuppression. At initiation of infliximab therapy, 14 of 15 patients were treated with corticosteroids [prednisone; median dose 20 (range 5–35) mg/day], methotrexate (7) or azathioprine (4). Infliximab was used at median 5 (range 3–5) mg/kg at a median of every 6 (range 4–8) weeks. Only 13 (87 %) had a good or even partial response. By 1 year of follow up the steroid dose could be substantially lowered. Only one patient was still steroid-dependent after 12 months as compared to 8 before infliximab. As in the Mayo case series, adverse effects were common and sometimes severe, including two infusion-related reactions, one case of each of pulmonary tuberculosis, severe bacterial infection and Ebstein Barr Virus reactivation [106].

Because of the less than universal benefit and high adverse event rates from conventional immunosuppression and anti-TNF biologics, several novel immunomodulatory therapies have been explored. A prospective open-label study of 15 TA patients (mean age 36.2 years) with active disease despite therapy with corticosteroids and immunosuppressive agents received leflunomide 20 mg/day for at least 6 months and were followed up for a mean of 9.1 months. One of the 15 patients received leflunomide due to intolerance to current treatment. The frequency of patients with active TA decreased (93 % vs. 20 %, $p=0.002$), and the mean daily dose of prednisone (34.2 vs. 13.9 mg, $p<0.001$) and in the median values of ESR (29.0 vs. 27.0 mm/h, $p=0.012$) and CRP (10.3 vs. 5.3 mg/L, $p=0.012$). However, two patients (13.3 %) developed new angiographic lesions and 3 patients (20 %) experienced mild adverse events [107].

Minocycline has been tried as adjunctive to steroid therapy with some success in reducing activity of disease; the rationale is based on effects on minocycline to inhibit metalloproteinase activity in patients with TA [108]. Finally, one paper has described the use of an IL-6 receptor inhibitor tocilizumab in patients with refractory large-vessel vasculitis [109].

Surgery is sometimes required to manage symptomatic localized vascular insufficiency

once medical therapy has been optimized. Common indications for surgery in patients with TA include refractory renovascular hypertension, end organ or peripheral limb ischemia, cerebral ischemia, enlarging aneurysms, and severe aortic valve insufficiency [110]. In a Mayo Clinic series of TA patients, 17 % required revascularization for occlusive disease. Of these, 19 % had renovascular hypertension as the major indication for surgery. There were no deaths in this series. Twenty-six percent required graft revision over the mean follow-up period of 6.7 years. The risk of graft failure correlated with active disease, and no patients with quiescent disease required revision for graft failure. These data were confirmed in a retrospective multicenter study of 79 consecutive patients with TA (median age, 39 years; 79.7 % women) who underwent 166 vascular procedures (surgery (62.7 %) or endovascular repair, (37.3 %). After an average follow-up of 6.5 years, 70 complications were observed, including restenosis (n = 53), thrombosis (n = 7), bleeding (n = 6), and stroke (n = 4). The 10-year arterial complication-free survival rate was only 45 %. 37.5 % of surgical and 50 % of endovascular procedures had a post procedural complication. Patients who experienced complications had higher ESR ($P < 0.001$) and CRP ($P < 0.001$) and fibrinogen ($P < 0.005$) serum levels compared with those without complications. In multivariate analysis, inflammation at the time of revascularization was independently associated with the occurrence of arterial complications after the vascular procedure [111].

Approaches to treating renal artery involvement include aortorenal bypass, which is associated with a risk of occlusion if the disease is active at the time of surgery. Other procedures rely on finding other vessels with less involvement with arteritis to provide renal perfusion. These include renal autotransplantation to the iliac vessels, extra-anatomic repair using the splenic or hepatic arteries and nephrectomy in cases of renal atrophy and severe hypertension. Ideally, surgery should be deferred until disease activity is quiescent, though success in treating patient s with active, life or limb threatening disease has also been reported.

Middle Aortic Syndrome

Renovascular hypertension can be due to middle aortic syndrome characterized by segmental or elongated narrowing of the abdominal or distal descending aortic. The segmental aortic stenoses may occur at the level of the renal arteries or superior or inferior to them. Congenital coarctation involving the abdominal aorta and leading to middle aortic syndrome is rare, accounting for about 2 % of all coarctation, and has been attributed to impaired fusion of the two dorsal aortae.

When this type of coarctation occurs, proximal renal artery stenosis may occur in up to 80 % of cases and the mesenteric arteries may be involved in 25 % of cases [112]. Renal artery atresia, hypoplasia or dysplasia may accompany congenital midaortic syndrome or present as isolated causes of renovascular hypertension. There are numerous etiologies of this syndrome, the most common being TA. Other etiologies of middle aortic syndrome include congenital, Williams syndrome, neurofibromatosis, retroperitoneal fibrosis, mucopolysaccharidosis, fibromuscular dysplasia, giant cell arteritis, radiation exposure, or in utero infections such as rubella virus, syphilis, tuberculosis, rheumatic fever, and radiation therapy [113]. Overall, renal arteries are involved 63 % of the time and renal artery aneurysms may be present.

Hypertension is a common presenting finding with lower limb claudication, headache, easy fatigue, and stroke also reported presenting findings. Left untreated, most patients do not live beyond the age of 40 years. Historically, surgical revascularization had been the mainstay of therapy for midaortic syndrome. Procedures involving the renal arteries often require branch renal artery exposure and reconstruction and can provide excellent long term patency rates [114]. In one series representing the largest published surgical cohort, the median age at operation was 11 years. At an average of 10 years follow-up most patients remained normotensive with normal sexual function and good quality of life. Surgical bypass is required in most cases, sometimes with ex-vivo reconstruction of renal arteries and renal auto-transplantation [23].

Endovascular approaches to the treatment of middle aortic syndrome depending on the etiology have also been encouraging [115–117].

Radiation-Induced Renovascular Disease

Renovascular hypertension is an uncommon complication of abdominal radiation. The incidence among patients undergoing radiation to the retroperitoneum is not known. However, the onset of hypertension in one series ranged from 4 years to 20 years following exposure to at least 25 Gy of radiation. The median blood pressure was 171/102 in this cohort of predominantly male patients with median age of onset of delayed referral for hypertension at 39 years.

Radiation-induced renovascular disease should be considered when hypertension develops even decades following abdominal radiation. Patients may have received radiation for Hodgkin's disease, retroperitoneal lymphoma, seminoma, or nephroblastoma. Angiographically, the lesions looked similar to those of atherosclerotic RAS with the exception that the findings were limited to the treated region and not associated with diffuse aortic atherosclerosis. The proximal segments of the renal arteries are most often involved, but stenotic lesions involving the mid-vessel, vessel occlusion and hypoplastic renal arteries are also reported. Clues associated with radiation-induced RAS include associated segmental renal atrophy, particularly in those patients who had undergone radiation to the spleen or those with occluded arteries. Other findings consistent with radiation injury include retroperitoneal fibrosis, hepatic fibrosis, intestinal stenosis, and focal aortic calcifications in the zone of radiation [118].

Three primary types of lesions have been reported associated with radiation-induced RAS. These include myointimal proliferation consisting of intimal deposition of myofibroblasts, and collagen and fibrin with periarterial or adventitial fibrosis. The third histologic form of radiation-induced RAS is accelerated focal areas of atherosclerosis. In animal models of radiation, hypertension or hyperlipidemia are necessary concomitant risk factors for the development of radiation-induced RAS. Radiation predisposes the vessel wall to these insults partly by impairing focal nitric oxide and prostaglandin release which predisposes to segmental increases in shear stress and subsequent fibrosis [119].

Radiation-induced RAS responds to endovascular treatment and both angioplasty and stents have been employed successfully. Multiple insufflations may be necessary to achieve angiographic success using angioplasty. The risk of aneurysm at the site of treatment is apparently higher than with atherosclerotic disease. Successful surgical revascularization of radiation-induced RAS including aortorenal bypass, aortic implantation, and extra- anatomic approaches has been reported. Blood pressure response to treatment with endovascular and surgical revascularization is reportedly good with some cases of normalization of blood pressure.

References

1. Ribatti D, Nico B, Crivellato E. Morphological and molecular aspects of physiological vascular morphogenesis. Angiogenesis. 2009;12:101–11.
2. Holderfield MT, Hughes CC. Crosstalk between vascular endothelial growth factor, notch, and transforming growth factor-beta in vascular morphogenesis. Circ Res. 2008;102:637–52.
3. Iruela-Arispe ML, Davis GE. Cellular and molecular mechanisms of vascular lumen formation. Dev Cell. 2009;16:222–31.
4. Barry A. The aortic arch derivatives in human adult. Anat Rec. 1951;111:221–38.
5. Anderson LM, Gibbons GH. Notch: a mastermind of vascular morphogenesis. J Clin Invest. 2007;117:299–302.
6. Teo LL, Cannell T, Babu-Narayan SV, Hughes M, Mohiaddin RH. Prevalence of associated cardiovascular abnormalities in 500 patients with aortic coarctation referred for cardiovascular magnetic resonance imaging to a tertiary center. Pediatr Cardiol. 2011;32:1120–7.
7. Morris M. Coarctation of the aorta. In: McMillan J, Feigin R, DeAngelis C, Jones M, editors. Oski's pediatrics. Philadelphia: Lippincott Williams & Wilkins; 2006.
8. Kenny D, Hijazi ZM. Coarctation of the aorta: from fetal life to adulthood. Cardiol J. 2011;18:487–95.
9. Rosenthal E. Coarctation of the aorta from fetus to adult: curable condition or life long disease process? Heart. 2005;91:1495–502.

10. Wessels MW, Berger RM, Frohn-Mulder IM, Roos-Hesselink JW, Hoogeboom JJ, Mancini GS, Bartelings MM, Krijger R, Wladimiroff JW, Niermeijer MF, Grossfeld P, Willems PJ. Autosomal dominant inheritance of left ventricular outflow tract obstruction. Am J Med Genet A. 2005;134A:171–9.
11. Lewin MB, McBride KL, Pignatelli R, Fernbach S, Combes A, Menesses A, Lam W, Bezold LI, Kaplan N, Towbin JA, Belmont JW. Echocardiographic evaluation of asymptomatic parental and sibling cardiovascular anomalies associated with congenital left ventricular outflow tract lesions. Pediatrics. 2004;114:691–6.
12. Gittenberger-de Groot AC, Bartelings MM, Deruiter MC, Poelmann RE. Basics of cardiac development for the understanding of congenital heart malformations. Pediatr Res. 2005;57:169–76.
13. Kuehl KS, Loffredo CA, Ferencz C. Failure to diagnose congenital heart disease in infancy. Pediatrics. 1999;103:743–7.
14. Cohen M, Fuster V, Steele PM, Driscoll D, McGoon DC. Coarctation of the aorta. Long-term follow-up and prediction of outcome after surgical correction. Circulation. 1989;80:840–5.
15. Connolly HM, Huston 3rd J, Brown Jr RD, Warnes CA, Ammash NM, Tajik AJ. Intracranial aneurysms in patients with coarctation of the aorta: a prospective magnetic resonance angiographic study of 100 patients. Mayo Clin Proc. 2003;78:1491–9.
16. Holloway B, Rosewarne D, Jones R. Imaging of thoracic disease. Br J Radiol. 2011;84:S338–54.
17. Lu CW, Wang JK, Chang CI, Lin MT, Wu ET, Lue HC, Chen YS, Chiu IS, Wu MH. Noninvasive diagnosis of aortic coarctation in neonates with patent ductus arteriosus. J Pediatr. 2006;148:217–21.
18. Pascal CJ, Huggon I, Sharland GK, Simpson JM. An echocardiographic study of diagnostic accuracy, prediction of surgical approach, and outcome for fetuses diagnosed with discordant ventriculo-arterial connections. Cardiol Young. 2007;17:528–34.
19. MacNeil B, Rosenfeld K. Peripheral intervention. In: Bau D, editor. Grossman's cardiac catheterization, angiography and intervention. Philadelphia: Lippincott, WIlliams, and Wilkins; 2006.
20. Muzzarelli S, Meadows AK, Ordovas KG, Higgins CB, Meadows JJ. Usefulness of cardiovascular magnetic resonance imaging to predict the need for intervention in patients with coarctation of the aorta. Am J Cardiol. 2012;109:861–5.
21. Frydrychowicz A, Schlensak C, Stalder A, Russe M, Siepe M, Beyersdorf F, Langer M, Hennig J, Markl M. Ascending-descending aortic bypass surgery in aortic arch coarctation: four-dimensional magnetic resonance flow analysis. J Thorac Cardiovasc Surg. 2007;133:260–2.
22. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. Arthritis Rheum. 2007;56:1000–9.
23. Barral X, de Latour B, Vola M, Lavocat MP, Fichtner C, Favre JP. Surgery of the abdominal aorta and its branches in children: late follow-up. J Vasc Surg. 2006;43:1138–44.
24. Ebels T, Maruszewski B, Blackstone EH. What is the preferred therapy for patients with aortic coarctation–the standard gamble and decision analysis versus real results? Cardiol Young. 2008;18:18–21.
25. Vriend JW, van Montfrans GA, Romkes HH, Vliegen HW, Veen G, Tijssen JG, Mulder BJ. Relation between exercise-induced hypertension and sustained hypertension in adult patients after successful repair of aortic coarctation. J Hypertens. 2004;22:501–9.
26. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham Jr TP, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD. Acc/aha 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). Circulation. 2008;118:e714–833.
27. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E. Esc guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J. 2010;31:2915–57.
28. Padua LM, Garcia LC, Rubira CJ, de Oliveira Carvalho PE. Stent placement versus surgery for coarctation of the thoracic aorta. Cochrane Database Syst Rev. 2012;5:CD008204.
29. Cowley CG, Orsmond GS, Feola P, McQuillan L, Shaddy RE. Long-term, randomized comparison of balloon angioplasty and surgery for native coarctation of the aorta in childhood. Circulation. 2005;111:3453–6.
30. Wheatley 3rd GH, Koullias GJ, Rodriguez-Lopez JA, Ramaiah VG, Diethrich EB. Is endovascular repair the new gold standard for primary adult coarctation? Eur J Cardiothorac Surg. 2010;38:305–10.
31. Forbes TJ, Garekar S, Amin Z, Zahn EM, Nykanen D, Moore P, Qureshi SA, Cheatham JP, Ebeid MR, Hijazi ZM, Sandhu S, Hagler DJ, Sievert H, Fagan TE, Ringewald J, Du W, Tang L, Wax DF, Rhodes J, Johnston TA, Jones TK, Turner DR, Pedra CA, Hellenbrand WE. Procedural results and acute complications in stenting native and recurrent coarctation of the aorta in patients over 4 years of age: a multi-institutional study. Catheter Cardiovasc Interv. 2007;70:276–85.
32. Ringel RE, Gauvreau K, Moses H, Jenkins KJ. Coarctation of the aorta stent trial (coast): study design and rationale. Am Heart J. 2012;164:7–13.
33. Butera G, Manica JL, Chessa M, Piazza L, Negura D, Micheletti A, Arcidiacono C, Carminati M. Covered-stent implantation to treat aortic coarctation. Expert Rev Med Devices. 2012;9:123–30.

34. Chessa M, Carrozza M, Butera G, Piazza L, Negura DG, Bussadori C, Bossone E, Giamberti A, Carminati M. Results and mid-long-term follow-up of stent implantation for native and recurrent coarctation of the aorta. Eur Heart J. 2005;26:2728–32.
35. Forbes TJ, Kim DW, Du W, Turner DR, Holzer R, Amin Z, Hijazi Z, Ghasemi A, Rome JJ, Nykanen D, Zahn E, Cowley C, Hoyer M, Waight D, Gruenstein D, Javois A, Foerster S, Kreutzer J, Sullivan N, Khan A, Owada C, Hagler D, Lim S, Canter J, Zellers T. Comparison of surgical, stent, and balloon angioplasty treatment of native coarctation of the aorta: an observational study by the CCISC (congenital cardiovascular interventional study consortium). J Am Coll Cardiol. 2011;58:2664–74.
36. Egan M, Holzer RJ. Comparing balloon angioplasty, stenting and surgery in the treatment of aortic coarctation. Expert Rev Cardiovasc Ther. 2009;7:1401–12.
37. Hager A. Hypertension in aortic coarctation. Minerva Cardioangiol. 2009;57:733–42.
38. Krieger EV, Landzberg MJ, Economy KE, Webb GD, Opotowsky AR. Comparison of risk of hypertensive complications of pregnancy among women with versus without coarctation of the aorta. Am J Cardiol. 2011;107:1529–34.
39. Doshi A, Rao S. Coarctation of the aorta-management options and decision-making. Pediatr Ther. 2012;S5:006. doi:10.4172/2161-0665.S5-006.
40. Horlick EM, McLaughlin PR, Benson LN. The adult with repaired coarctation of the aorta. Curr Cardiol Rep. 2007;9:323–30.
41. Hager A, Kanz S, Kaemmerer H, Schreiber C, Hess J. Coarctation long-term assessment (coala): significance of arterial hypertension in a cohort of 404 patients up to 27 years after surgical repair of isolated coarctation of the aorta, even in the absence of restenosis and prosthetic material. J Thorac Cardiovasc Surg. 2007;134:738–45.
42. Polson JW, McCallion N, Waki H, Thorne G, Tooley MA, Paton JF, Wolf AR. Evidence for cardiovascular autonomic dysfunction in neonates with coarctation of the aorta. Circulation. 2006;113:2844–50.
43. Duara R, Theodore S, Sarma PS, Unnikrishnan M, Neelakandhan KS. Correction of coarctation of aorta in adult patients–impact of corrective procedure on long-term recoarctation and systolic hypertension. Thorac Cardiovasc Surg. 2008;56:83–6.
44. Kuhn A, Baumgartner D, Baumgartner C, Horer J, Schreiber C, Hess J, Vogt M. Impaired elastic properties of the ascending aorta persist within the first 3 years after neonatal coarctation repair. Pediatr Cardiol. 2009;30:46–51.
45. Kuhn A, Vogt M. Ascending aortic distensibility is impaired before and after surgical "repair" of coarctation. Ann Thorac Surg. 2006;81:2341; author reply 2341–2342.
46. de Divitiis M, Pilla C, Kattenhorn M, Zadinello M, Donald A, Leeson P, Wallace S, Redington A, Deanfield JE. Vascular dysfunction after repair of coarctation of the aorta: impact of early surgery. Circulation. 2001;104:I165–70.
47. Trojnarska O, Szczepaniak-Chichel L, Mizia-Stec K, Gabriel M, Bartczak A, Grajek S, Gasior Z, Kramer L, Tykarski A. Vascular remodeling in adults after coarctation repair: impact of descending aorta stenosis and age at surgery. Clin Res Cardiol. 2011;100:447–55.
48. Kenny D, Polson JW, Martin RP, Caputo M, Wilson DG, Cockcroft JR, Paton JF, Wolf AR. Relationship of aortic pulse wave velocity and baroreceptor reflex sensitivity to blood pressure control in patients with repaired coarctation of the aorta. Am Heart J. 2011; 162:398–404.
49. Kenny D, Polson JW, Martin RP, Paton JF, Wolf AR. Hypertension and coarctation of the aorta: an inevitable consequence of developmental pathophysiology. Hypertens Res. 2011;34:543–7.
50. Szczepaniak-Chichel L, Trojnarska O, Mizia-Stec K, Gabriel M, Grajek S, Gasior Z, Kramer L, Tykarski A. Augmentation of central arterial pressure in adult patients after coarctation repair. Blood Press Monit. 2011;16:22–8.
51. Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. N Engl J Med. 2000;342:256–63.
52. Pillutla P, Shetty KD, Foster E. Mortality associated with adult congenital heart disease: trends in the us population from 1979 to 2005. Am Heart J. 2009;158:874–9.
53. Choy M, Rocchini AP, Beekman RH, Rosenthal A, Dick M, Crowley D, Behrendt D, Snider AR. Paradoxical hypertension after repair of coarctation of the aorta in children: balloon angioplasty versus surgical repair. Circulation. 1987;75:1186–91.
54. Horigome H, Miyauchi T, Takahashi-Igari M, Maeda S, Matsui A. Increased plasma level of endothelin-1 following percutaneous balloon dilatation of aortic coarctation in children. Eur J Pediatr. 2003;162:543–4.
55. Serfontein SJ, Kron IL. Complications of coarctation repair. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2002;5:206–11.
56. Johnson D, Perrault H, Vobecky SJ, Trudeau F, Delvin E, Fournier A, Davignon A. Resetting of the cardiopulmonary baroreflex 10 years after surgical repair of coarctation of the aorta. Heart. 2001;85:318–25.
57. Pickering T. Parodoxical hypertension in post-op coarctation patients. Circulation. 1977;56:135–6.
58. Nakagawa TA, Sartori SC, Morris A, Schneider DS. Intravenous nicardipine for treatment of postcoarctectomy hypertension in children. Pediatr Cardiol. 2004;25:26–30.
59. Henke PK, Cardneau JD, Welling 3rd TH, Upchurch Jr GR, Wakefield TW, Jacobs LA, Proctor SB, Greenfield LJ, Stanley JC. Renal artery aneurysms: a 35-year clinical experience with 252 aneurysms in 168 patients. Ann Surg. 2001;234:454–62; discussion 462–463.
60. Eskandari MK, Resnick SA. Aneurysms of the renal artery. Semin Vasc Surg. 2005;18:202–8.
61. Katabathina VS, Katre R, Prasad SR, Surabhi VR, Shanbhogue AK, Sunnapwar A. Wunderlich syndrome: cross-sectional imaging review. J Comput Assist Tomogr. 2011;35:425–33.

62. Hwang PF, Rice DC, Patel SV, Mukherjee D. Successful management of renal artery aneurysm rupture after cesarean section. J Vasc Surg. 2011;54:519–21.
63. English WP, Pearce JD, Craven TE, Wilson DB, Edwards MS, Ayerdi J, Geary RL, Dean RH, Hansen KJ. Surgical management of renal artery aneurysms. J Vasc Surg. 2004;40:53–60.
64. Reiher L, Grabitz K, Sandmann W. Reconstruction for renal artery aneurysm and its effect on hypertension. Eur J Vasc Endovasc Surg. 2000;20:454–6.
65. Morita K, Seki T, Iwami D, Sasaki H, Fukuzawa N, Nonomura K. Long-term outcome of single institutional experience with conservative and surgical management for renal artery aneurysm. Transplant Proc. 2012;44:1795–9.
66. Ishikawa K. Diagnostic approach and proposed criteria for the clinical diagnosis of Takayasu's arteriopathy. J Am Coll Cardiol. 1988;12:964–72.
67. Sharma BK, Jain S, Suri S, Numano F. Diagnostic criteria for Takayasu arteritis. Int J Cardiol. 1996; 54(Suppl):S141–7.
68. Marks SD, Tullus K. Do classification criteria of Takayasu arteritis misdiagnose children with fibromuscular dysplasia? Pediatr Nephrol. 2010;25:989–90; author reply 991–992.
69. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, Buoncompagni A, Lazar C, Bilge I, Uziel Y, Rigante D, Cantarini L, Hilario MO, Silva CA, Alegria M, Norambuena X, Belot A, Berkun Y, Estrella AI, Olivieri AN, Alpigiani MG, Rumba I, Sztajnbok F, Tambic-Bukovac L, Breda L, Al-Mayouf S, Mihaylova D, Chasnyk V, Sengler C, Klein-Gitelman M, Djeddi D, Nuno L, Pruunsild C, Brunner J, Kondi A, Pagava K, Pederzoli S, Martini A, Ruperto N. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part ii: final classification criteria. Ann Rheum Dis. 2010;69:798–806.
70. Freitas DS, Camargo CZ, Mariz HA, Arraes AE, de Souza AW. Takayasu arteritis: assessment of response to medical therapy based on clinical activity criteria and imaging techniques. Rheumatol Int. 2012;32:703–9.
71. Hoffman GS. Takayasu arteritis: lessons from the American national institutes of health experience. Int J Cardiol. 1996;54(Suppl):S99–102.
72. Tann OR, Tulloh RM, Hamilton MC. Takayasu's disease: a review. Cardiol Young. 2008;18:250–9.
73. Li XM, Ye WL, Wen YB, Li H, Chen LM, Liu DY, Zeng XJ, Li XW. Glomerular disease associated with Takayasu arteritis: 6 cases analysis and review of the literature. Chin Med Sci J. 2009;24:69–75.
74. Cong XL, Dai SM, Feng X, Wang ZW, Lu QS, Yuan LX, Zhao XX, Zhao DB, Jing ZP. Takayasu's arteritis: clinical features and outcomes of 125 patients in China. Clin Rheumatol. 2010;29:973–81.
75. Chauhan SK, Tripathy NK, Nityanand S. Antigenic targets and pathogenicity of anti-aortic endothelial cell antibodies in Takayasu arteritis. Arthritis Rheum. 2006;54:2326–33.
76. O'Neil KM. Progress in pediatric vasculitis. Curr Opin Rheumatol. 2009;21:538–46.
77. Piggott K, Deng J, Warrington K, Younge B, Kubo JT, Desai M, Goronzy JJ, Weyand CM. Blocking the notch pathway inhibits vascular inflammation in large-vessel vasculitis. Circulation. 2011;123: 309–18.
78. Watts R, Al-Taiar A, Mooney J, Scott D, Macgregor A. The epidemiology of Takayasu arteritis in the Uk. Rheumatology (Oxford). 2009;48:1008–11.
79. Arnaud L, Haroche J, Limal N, Toledano D, Gambotti L, Costedoat Chalumeau N, Le Thi Huong Boutin D, Cacoub P, Cluzel P, Koskas F, Kieffer E, Piette JC, Amoura Z. Takayasu arteritis in France: a single-center retrospective study of 82 cases comparing white, North African, and black patients. Medicine (Baltimore). 2010;89:1–17.
80. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Takayasu arteritis and giant cell arteritis: a spectrum within the same disease? Medicine (Baltimore). 2009;88:221–6.
81. Fields CE, Bower TC, Cooper LT, Hoskin T, Noel AA, Panneton JM, Sullivan TM, Gloviczki P, Cherry Jr KJ. Takayasu's arteritis: operative results and influence of disease activity. J Vasc Surg. 2006;43: 64–71.
82. Hoffman GS, Ahmed AE. Surrogate markers of disease activity in patients with Takayasu arteritis. A preliminary report from the international network for the study of the systemic vasculitides (inssys). Int J Cardiol. 1998;66 Suppl 1:S191–4; discussion S195.
83. Karadag O, Aksu K, Sahin A, Zihni FY, Sener B, Inanc N, Kalyoncu U, Aydin SZ, Ascioglu S, Ocakci PT, Bilgen SA, Keser G, Inal V, Direskeneli H, Calguneri M, Ertenli I, Kiraz S. Assessment of latent tuberculosis infection in Takayasu arteritis with tuberculin skin test and quantiferon-tb gold test. Rheumatol Int. 2010;30:1483–7.
84. Grayson PC, Maksimowicz-McKinnon K, Clark TM, Tomasson G, Cuthbertson D, Carette S, Khalidi NA, Langford CA, Monach PA, Seo P, Warrington KJ, Ytterberg SR, Hoffman GS, Merkel PA. Distribution of arterial lesions in Takayasu's arteritis and giant cell arteritis. Ann Rheum Dis. 2012;71:1329–34.
85. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, Hoffman GS. Takayasu arteritis. Ann Intern Med. 1994;120:919–29.
86. Koide K. Takayasu arteritis in Japan. Heart Vessels. 1992;7(Suppl):48–54.
87. Soto ME, Espinola N, Flores-Suarez LF, Reyes PA. Takayasu arteritis: clinical features in 110 mexican mestizo patients and cardiovascular impact on survival and prognosis. Clin Exp Rheumatol. 2008;26: S9–15.
88. Takamura C, Ohhigashi H, Ebana Y, Isobe M. New human leukocyte antigen risk allele in Japanese patients with Takayasu arteritis. Circ J. 2012;76: 1697–702.
89. Heo JH, Kim M. Familial Takayasu's arteritis in female siblings. Rheumatol Int. 2011;31:815–8.

90. Lv N, Dang A, Wang Z, Zheng D, Liu G. Association of susceptibility to Takayasu arteritis in Chinese han patients with HLA-DPB1. Hum Immunol. 2011;72: 893–6.
91. Hata A, Noda M, Moriwaki R, Numano F. Angiographic findings of Takayasu arteritis: new classification. Int J Cardiol. 1996;54(Suppl):S155–63.
92. Kissin EY, Merkel PA. Diagnostic imaging in Takayasu arteritis. Curr Opin Rheumatol. 2004;16: 31–7.
93. Lee KH, Cho A, Choi YJ, Lee SW, Ha YJ, Jung SJ, Park MC, Lee JD, Lee SK, Park YB. The role of (18) f-fluorodeoxyglucose-positron emission tomography in the assessment of disease activity in patients with Takayasu arteritis. Arthritis Rheum. 2012;64:866–75.
94. Tezuka D, Haraguchi G, Ishihara T, Ohigashi H, Inagaki H, Suzuki J, Hirao K, Isobe M. Role of FDG PET-CT in takayasu arteritis: sensitive detection of recurrences. JACC Cardiovasc Imaging. 2012;5:422–9.
95. Pfizenmaier DH, Al Atawi FO, Castillo Y, Chandrasekaran K, Cooper LT. Predictors of left ventricular dysfunction in patients with Takayasu's or giant cell aortitis. Clin Exp Rheumatol. 2004;22:S41–5.
96. Bredemeier M, Rocha CM, Barbosa MV, Pitrez EH. One-year clinical and radiological evolution of a patient with refractory Takayasu's arteritis under treatment with tocilizumab. Clin Exp Rheumatol. 2012;30:S98–100.
97. Kusunose K, Yamada H, Tomita N, Nishio S, Niki T, Yamaguchi K, Koshiba K, Yagi S, Taketani Y, Iwase T, Soeki T, Wakatsuki T, Akaike M, Sata M. Serial imaging changes during treatment of Takayasu arteritis with pulmonary artery stenosis. Int J Cardiol. 2011;148:e47–50.
98. Ogino H, Matsuda H, Minatoya K, Sasaki H, Tanaka H, Matsumura Y, Ishibashi-Ueda H, Kobayashi J, Yagihara T, Kitamura S. Overview of late outcome of medical and surgical treatment for Takayasu arteritis. Circulation. 2008;118:2738–47.
99. Ohigashi H, Haraguchi G, Konishi M, Tezuka D, Kamiishi T, Ishihara T, Isobe M. Improved prognosis of Takayasu arteritis over the past decade–comprehensive analysis of 106 patients. Circ J. 2012;76:1004–11.
100. Wang H, Ma J, Wu Q, Luo X, Chen Z, Kou L. Circulating b lymphocytes producing autoantibodies to endothelial cells play a role in the pathogenesis of Takayasu arteritis. J Vasc Surg. 2011;53:174–80.
101. Arnaud L, Cambau E, Brocheriou I, Koskas F, Kieffer E, Piette JC, Amoura Z. Absence of mycobacterium tuberculosis in arterial lesions from patients with Takayasu's arteritis. J Rheumatol. 2009;36:1682–5.
102. Arnaud L, Haroche J, Mathian A, Gorochov G, Amoura Z. Pathogenesis of Takayasu's arteritis: a 2011 update. Autoimmun Rev. 2011;11:61–7.
103. Henes JC, Mueller M, Pfannenberg C, Kanz L, Koetter I. Cyclophosphamide for large vessel vasculitis: assessment of response by PET/CT. Clin Exp Rheumatol. 2011;29:S43–8.
104. Castillo-Martinez D, Amezcua-Guerra LM. Self-reactivity against stress-induced cell molecules: the missing link between Takayasu's arteritis and tuberculosis? Med Hypotheses. 2012;78:485–8.
105. Schmidt J, Kermani TA, Bacani AK, Crowson CS, Matteson EL, Warrington KJ. Tumor necrosis factor inhibitors in patients with Takayasu arteritis: experience from a referral center with long-term followup. Arthritis Care Res (Hoboken). 2012;64:1079–83.
106. Mekinian A, Neel A, Sibilia J, Cohen P, Connault J, Lambert M, Federici L, Berthier S, Fiessinger JN, Godeau B, Marie I, Guillevin L, Hamidou M, Fain O. Efficacy and tolerance of infliximab in refractory Takayasu arteritis: French multicentre study. Rheumatology (Oxford). 2012;51:882–6.
107. de Souza AW, da Silva MD, Machado LS, Oliveira AC, Pinheiro FA, Sato EI. Short-term effect of leflunomide in patients with Takayasu arteritis: an observational study. Scand J Rheumatol. 2012;41: 227–30.
108. Chirinos JA, Corrales VF, Lichtstein DM. Anca-associated large vessel compromise. Clin Rheumatol. 2006;25:111–2.
109. Salvarani C, Magnani L, Catanoso MG, Pipitone N, Versari A, Dardani L, Pulsatelli L, Meliconi R, Boiardi L. Rescue treatment with tocilizumab for Takayasu arteritis resistant to TNF-α blockers. Clin Exp Rheumatol. 2012;30:S90–3.
110. Ma J, Luo X, Wu Q, Chen Z, Kou L, Wang H. Circulation levels of acute phase proteins in patients with Takayasu arteritis. J Vasc Surg. 2010;51: 700–6.
111. Saadoun D, Lambert M, Mirault T, Resche-Rigon M, Koskas F, Cluzel P, Mignot C, Schoindre Y, Chiche L, Hatron PY, Emmerich J, Cacoub P. Retrospective analysis of surgery versus endovascular intervention in Takayasu arteritis: a multicenter experience. Circulation. 2012;125:813–9.
112. Saif I, Seriki D, Moore R, Woywodt A. Midaortic syndrome in neurofibromatosis type 1 resulting in bilateral renal artery stenosis. Am J Kidney Dis. 2010;56:1197–201.
113. Delis KT, Gloviczki P. Middle aortic syndrome: from presentation to contemporary open surgical and endovascular treatment. Perspect Vasc Surg Endovasc Ther. 2005;17:187–203.
114. Piercy KT, Hundley JC, Stafford JM, Craven TE, Nagaraj SK, Dean RH, Hansen KJ. Renovascular disease in children and adolescents. J Vasc Surg. 2005;41:973–82.
115. Gimenez-Roqueplo AP, Tomkiewicz E, La Batide-Alanore A, Moreau I, Paul JF, Raynaud A, Plouin PF. Stent treatment for pseudocoarctation and refractory hypertension in an elderly patient with Takayasu's arteritis. Nephrol Dial Transplant. 2000; 15:536–8.
116. Sharma S, Bahl VK, Saxena A, Kothari SS, Talwar KK, Rajani M. Stenosis in the aorta caused by non-specific aortitis: results of treatment by percutaneous stent placement. Clin Radiol. 1999;54:46–50.

117. Shim BJ, Youn HJ, Kim YC, Kim WT, Choi YS, Lee DH, Park C, Oh YS, Chung WS, Kim JH, Choi KB, Hong SJ, Jung SE, Hahn ST. Takayasu's arteritis treated by percutaneous transluminal angioplasty with stenting in the descending aorta. J Korean Med Sci. 2008;23:551–5.
118. Fakhouri F, La Batide AA, Rerolle JP, Guery B, Raynaud A, Plouin PF. Presentation and revascularization outcomes in patients with radiation-induced renal artery stenosis. Am J Kidney Dis. 2001;38:302–9.
119. Sugihara T, Hattori Y, Yamamoto Y, Qi F, Ichikawa R, Sato A, Liu MY, Abe K, Kanno M. Preferential impairment of nitric oxide-mediated endothelium-dependent relaxation in human cervical arteries after irradiation. Circulation. 1999;100:635–41.
120. Roca C, Adams RH. Regulation of vascular morphogenesis by Notch signaling. Genes Dev. 2007;21:2511.
121. Barry A. The aortic arch derivatives in the human adult. Anat Rec. 1951;111:221.
122. Arend WP, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum. 1990;33(8):1129–34.

Iatrogenic Renal Vascular Disease

4

Shaun M. Gifford and Gustavo S. Oderich

Abstract

The surge in endoluminal treatment of vascular disease has changed both management strategies and outcomes for patients. Renal artery intervention for both renal artery disease and associated vascular anomalies has not been isolated from the transformation in management. This change in treatment strategy has placed renal arteries at risk for iatrogenic injury during treatment. Awareness of the risks, identification of injuries when they occur, and an understanding of the varying modalities available for dealing with injuries is extremely important for the interventionist when caring for and preventing iatrogenic renal artery injuries.

Keywords

Renal • Iatrogenic • Endovascular • Injury • Artery • Angioplasty • Stent

Introduction

Management of diseases of the aorta and its branches has greatly evolved during the last decade. Recent technological developments have allowed less invasive approaches to treat arterial stenoses and aneurysms in different vascular beds using catheter-directed and hybrid interventions. Prior to the advent of endovascular technology, renal artery occlusive disease was treated primarily by open revascularization. Trans-aortic renal endarterectomy and renal artery bypass were the most frequently utilized techniques, and inadvertent iatrogenic injury was relatively uncommon and immediately treated once recognized at the time of the initial intervention. The risk of kidney loss was low, typically resulting from technical problems such as dissection of the native artery or graft kink. Deterioration of renal function under these conditions correlated with prolonged warm ischemia or technical complications encountered during the procedure. The most frequent complications, including graft thrombosis, atheroemboli leading to infarction, hematoma formation, and infection could be minimized by meticulous surgical technique and treated promptly once recognized.

In the more recent era, endovascular approaches to treat renal and aortic vascular lesions have been shown to reduce morbidity and

S.M. Gifford, MD, MS (✉) • G.S. Oderich, MD
Department of Vascular and Endovascular Surgery,
Mayo Clinic, 200 First Street, SW,
Rochester, MN 55904, USA
e-mail: gifford.shaun@mayo.edu;
oderich.gustavo@mayo.edu

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_4,

mortality as compared to open repair. Nonetheless, these interventions require catheter and guide-wire manipulations that pose new risks, not previously encountered with open surgery. Atheroemboli, infarction and acute thrombosis can occur with any endovascular or open intervention; arterial dissection and perforation can result from excessive dilatation, catheter or sheath manipulation and multiple guide-wire exchanges. These lesions are notoriously more common in patients with excessively calcified, eccentric renal artery lesions, or when aggressive angioplasty and stenting is performed with oversized balloons and stents. The interventionalist needs to be aware of the risks of endovascular treatment, utilize clinical judgment on selection of ideal anatomical lesions, and most importantly have finesse when performing these procedures, avoiding excessive catheter manipulations in order to minimize the frequency and sequelae of these complications.

In addition to the inherent risks of renal artery interventions, the kidney is subjected to potential risk of injury during endovascular procedures performed in many other vascular beds, because of its central location. Aortic interventions for aneurysmal and occlusive disease are typically performed in close proximity to the renal arteries. Other invasive procedures such as kidney biopsy, renal pelvic decompression, and interventions for nephrolithiasis may result in injury to the kidney parenchyma and renal artery, including arteriovenous fistula, pseudoaneurysm, or frank hemorrhage. This chapter summarizes the risk factors, management and long-term consequences of iatrogenic renal artery disease associated with renal artery and aortic endovascular interventions.

Renal Artery Interventions

Since the first description of renal artery angioplasty by Gruentzig and associates in 1978 [1], the procedure gained widespread acceptance with many short-term advantages over open revascularization, including less morbidity, blood loss and recovery time [2, 3]. It became evident from the initial experience that angioplasty of ostial lesions had a tendency for elastic recoil to occur, leading to vessel re-narrowing almost immediately after the intervention [4]. To prevent elastic recoil associated with angioplasty, Palmaz and associates developed balloon-expandable stents in 1987 [5, 6]. Subsequently, single-center reports and a prospective randomized study confirmed the superiority of renal artery stenting over angioplasty alone, with lower rates of restenosis and improved patency rates [2, 7, 8]. Currently, primary renal artery angioplasty has become the standard-of-care for treatment of atherosclerotic lesions, whereas angioplasty alone is used in select cases (small vessels, bifurcation lesions) and in patients with fibromuscular dysplasia.

Endovascular technology has improved with smaller profile balloons, catheters, guide-wires, drug-eluting and covered stents, and embolic protection devices. The original angioplasty balloons and hand-mounted stents were constructed on a larger platform (0.038-in.), with less flexible, more rigid material that was more prone to cause vessel trauma. Stent dislodgement due to poor balloon retention, a known complication of first-generation hand-mounted stents, are rare with current technology. Today most renal artery interventions are performed using a small profile (0.014 or 0.018-in.) system. Specially designed guiding catheters with rapid-exchange have facilitated these procedures, optimizing technology to the patient anatomy in order to minimize complications from excessive manipulation [9]. Despite these technological improvements, periprocedural complications during renal angioplasty and stenting can be problematic and a challenge to treat. The most frequent renal artery complications include dissection or perforation, rupture, embolization and contrast-induced nephropathy (CIN).

Dissection, Perforation, or Rupture

A spectrum of renal artery injuries can occur with any catheter-based manipulation. The incidence of renal artery dissection and rupture in large single-center reports and in the prospective studies are summarized in Table 4.1 [9–13]. Renal artery rupture is infrequent and is typically treated by gentle prolonged balloon inflation or placement of a covered stent. Guide-wire perforations should

Table 4.1 Renal artery angioplasty and stent interventions carry associated risk factors that are few in number, but carry significant comorbidity

Renal artery angioplasty and stenting technical complications					
Article	Arteries treated	Dissection (%)	Occlusion (main or branch vessel) (%)	Perforation (%)	Permanent hemodialysis (%)
Ivanovic et al. [11]	179	NR	2.8	NR	2.8
Nolan et al. [9]	96	NR	NR	1	1
Beek et al. [12]	61	5	1.6	1.6	1.6
Morris et al. [13]	308	1	2	1.6	0.33
Bonelli et al. [10]	396	5.6	0.9	1.6	0.25

Listed in this table are representative reviews demonstrating the accepted rates of renal artery complications
NR not reported

be immediately treated by coil embolization once recognized. If left untreated in the revascularized kidney, continued bleeding can lead to massive intraparenchymal or subcapsular hematomas which are aggravated by anticoagulation and antiplatelet therapy (Fig. 4.1a–d).

Renal artery dissection is one of the most frequent iatrogenic complications that occur during endovascular interventions. The cumulative incidence of renal artery dissection is <4 % [11]. Certain anatomical features associated with risk of dissection or vessel rupture include heavily calcified plaques, eccentric plaques and branch involvement by fibromuscular dysplasia, especially in patients who present with evidence of focal renal artery dissection. Focal dissections can be treated by repeat balloon dilatation or more frequently by placement of a second stent. Extensive dissections that involve small branches may be impossible to treat by endovascular means. In patients with complex dissections, open repair can be attempted using ex vivo surgical techniques, but prognosis is poor due to intolerance of the kidney to warm ischemia (Fig. 4.2a–d).

In contemporary reports, renal artery occlusion rates range from 1 to 3 %, almost invariably resulting from inadvertent renal artery dissection during angioplasty and stenting [13].

Embolization

Embolization or micro-embolization of atheroemboli is a recognized risk with catheter-based interventions. This can be problematic with renal artery interventions, particularly in the presence of a diseased aorta. Atheroembolism occurs with each one of the steps required to place stents in the renal arteries. It is most noticeable during the manipulation of the catheter that is required to select, engage and advance a guide-wire, catheter and stent into renal artery [14]. Inflation of a balloon or stent can also dislodge atheroemboli. Embolic protection devices have been designed to minimize risk of clinically significant emboli during coronary and carotid interventions. These devices have been successfully applied in the renal arteries [15, 16].

The anatomy of the renal artery can be unfavorable for use of embolic protection devices because of short length of the main renal artery or presence of early branch bifurcation [17]. Computed tomography angiography can be used to plan these interventions and improve selection of a specific embolic protection device. Some devices (Spider Rx, Angioguard, Accunet) have wider application in the renal arteries by better adapting to anatomical requirements, including vessel diameter (4–8 mm) and length before the renal artery bifurcation. Reports of renal artery interventions indicate that atherosclerotic debris is retrieved in 60–80 % of the patients using embolic protection [15, 18]. Most of these studies indicate stabilization or improvement of renal function in 90–99 % of the patients, with variable rates of embolic debris captured by the device. Nonetheless, routine use of embolic protection remains controversial, adds to the cost of these interventions, and may be potentially associated with iatrogenic complications including vessel spasm, dissection and perforation. The only prospective, randomized trial of renal artery stenting with or without embolic

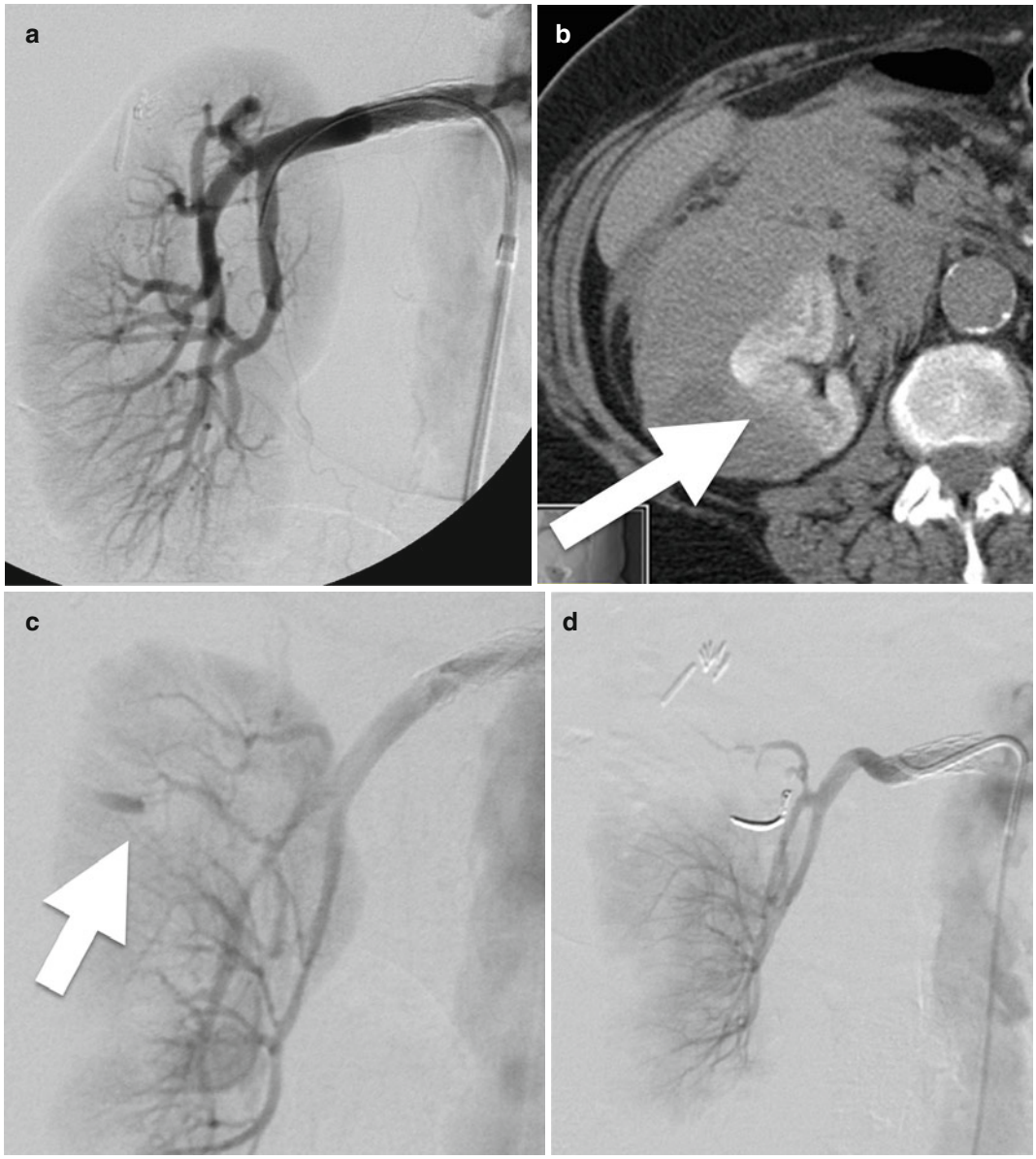


Fig. 4.1 (**a**) Successful renal artery stent is confirmed on post deployment renal angiogram. (**b**) Computed tomography evaluation obtained for severe back pain post angiogram demonstrates large retroperitoneal hematoma with active extravasation (*arrow*). (**c**) Repeat selective angiogram demonstrates active extravasation from a branch vessel (*arrow*), which was controlled successfully with coiling (**d**)

protection showed no difference in renal function outcomes [19]. Another argument against use of embolic protection is the observation that atheroemboli continue to occur days or weeks after renal artery angioplasty and stent placement, long after removal of embolic protection devices [20].

Renal Function Deterioration

Renal artery revascularization has been shown to stabilize or improve renal function in 40–55 % of the patients and deterioration of renal function occurs in 14–30 % of the patients after percutaneous renal

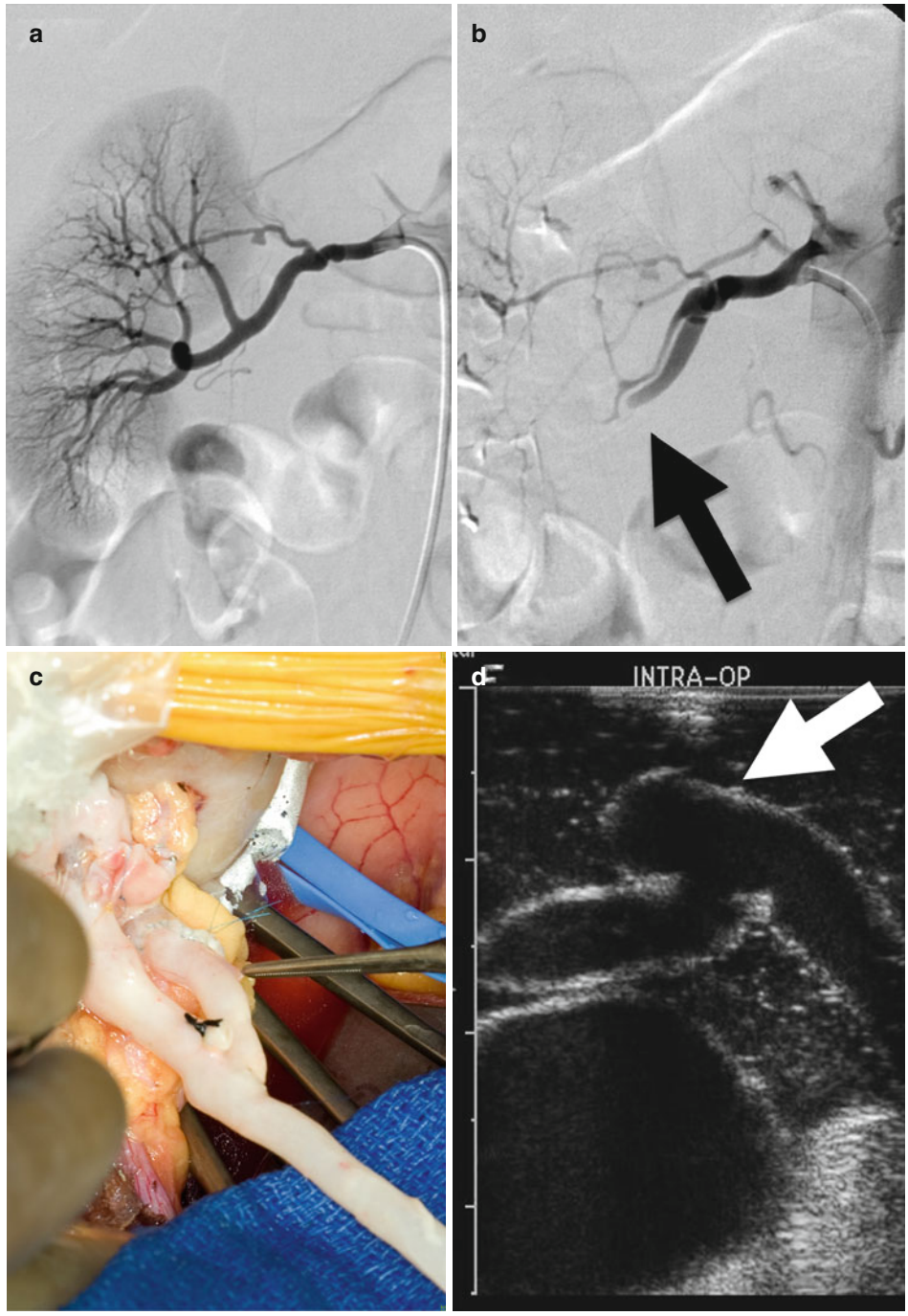


Fig. 4.2 (**a**) A renal artery stent was deployed in the proximal renal artery leading to more distal luminal irregularity. (**b**) Attempt at angioplasty led to dissection with loss of distal branch filling (*arrow*). (**c**) Ex vivo repair of the branch dissection was the only option available for renal salvage. (**d**) Intraoperative ultrasound (*arrow*) confirms adequate flow post repair

interventions [21]. The known causes for the decline are multi-factorial, including progression of chronic kidney disease, embolization, contrast-induced nephropathy and renal artery complications.

Reports on the impact of renal function secondary to endovascular intervention are quite variable throughout the literature making generalization difficult. Indications for intervention differ between studies and varying definitions of postoperative renal insufficiency and time periods to recovery prevent uniform reporting across specialty and procedure. A recent meta-analysis attempted to describe the impact of renal artery intervention on renal function; however, this study was unable to show improvement in renal function based largely on the above [22]. Timing of intervention before or after objective evidence demonstrates onset of renal dysfunction may have a direct impact on creatinine clearance, with studies supporting both early and late intervention [23, 24].

The impact of renal function deterioration secondary to renal artery intervention was demonstrated by Davies et al. In this large retrospective review, 20 % of patients had persistent increase in serum creatinine of >0.5 mg/dL. An eGFR under 30 mL/min/1.73 m^2, an unrepaired abdominal aortic aneurysm, diabetes, ipsilateral nephrosclerosis, and contralateral renal artery disease were associated with functional injury. This was found by multivariate analysis to be a negative predictor of survival with progression to renal failure, dialysis and death [25]. It is clear that more stringent guidelines for renal artery intervention need to be established and centered upon evidence based expected benefit before exposing patients to the real risk of intervention.

Non-vascular Renal Interventions

Invasive non-vascular related interventions carry inherent risks of injury to the kidney parenchyma and collecting system. Most common procedures include nephrostomy tube placement, nephrolithotomy, and kidney biopsies. Inadvertent injury to the renal artery branches can lead to intraparenchymal or subcapsular hematoma, pseudoaneurysm, arterio-venous fistula or persistent hematuria. Development of clot within the collecting system can lead to obstruction and deterioration of renal function [26, 27].

Endovascular Aortic Aneurysm Repair

Current estimates indicate that up to 15,000 abdominal aortic aneurysms may rupture annually [28]. Open repair offers durable results, but morbidity is significant and operative mortality averages 3–5 % in the largest reports [29, 30]. Endovascular aortic aneurysm repair (EVAR) has gained widespread acceptance and is currently the first option to treat infrarenal aortic aneurysms with suitable anatomy. Prospective randomized studies have confirmed that EVAR reduces operative time, blood loss, transfusion requirements, hospital stay, morbidity and mortality compared to open surgical repair [31, 32]. A critical requirement for successful aneurysm exclusion in EVAR is the presence of sufficient length of normal aorta (e.g., aortic neck) to provide adequate fixation to the endograft and to seal the aneurysm sac. Enlarging diameter throughout the course of neck length (tapering), short total length, angulation, and the presence of thrombus or calcium all limit the ability to obtain an adequate seal to exclude the aneurysm. To optimize fixation and seal, many of the stent grafts are placed in close proximity to the origins of the renal arteries, with potential hazard regarding development of renal artery obstruction. In some patients with short infrarenal necks or more extensive aneurysms, the renal arteries may be deliberately included in the repair with provision for placement of a protective renal artery stents through fenestrations or side cuffs, which are customized to the patient's anatomy.

Preservation of renal artery patency during EVAR is of critical importance for several reasons. Decline in renal function has been shown to be one of the most important predictors of mortality after open and endovascular aneurysm repair [33, 34]. Although there is modest decline in renal function after EVAR (1 ml/min/1.73 m^2 per year),

significant deterioration in renal function has been associated with inadvertent renal artery occlusion, renal artery complications (stenosis, plaque dislodgement or dissection) and use of fenestrated endografts [35, 36]. Haddad and associates reported that 23 of 72 patients (32 %) treated by fenestrated endografts for juxtarenal aneurysms had greater than 30 % decline in GFR, although the majority recovered by 6 months [36]. In another prospective non-randomized study of 287 patients treated by fenestrated endografts, renal function deterioration occurred in 20 % and was associated with presence of renal artery stenosis or kidney infarcts due to intra-procedural embolization or coverage of early branch bifurcations or accessory renal arteries by the stent graft [37].

Several factors account for the decline in renal function observed in some patients undergoing EVAR. Repeated doses of contrast agents during pre-operative diagnostic studies, implantation of stent grafts, and follow up surveillance are known to be nephrotoxic, particularly when administered to poorly hydrated patients or in those with chronic kidney disease. Endovascular instrumentation carries risk of atheroembolization, particularly in those patients with complex aneurysms and thrombus involving the renal arteries or who need adjunctive renal artery stenting. And finally, implantation of fenestrated endografts, which require placement of renal artery stents, can be technically challenging. These grafts are associated with higher rates of renal artery dissection and/or perforations compared to renal artery stent placement performed alone for occlusive disease [36–38]. Factors that contribute to renal artery complications during fenestrated repair are small renal artery diameter (<4 mm), tortuosity, occlusive disease, and need to use large profile platform and stiff guide-wire system to deliver side branch stents.

Inadvertent Renal Artery Coverage

Newer aortic stent graft designs allow repositioning the stent graft prior to complete deployment, ensuring protection of the renal artery and optimal seal during the deployment sequence. Other stent grafts have suprarenal fixation, which is an uncovered stent that extends above the renal arteries and is designed to improve fixation into the normal aorta and prevent migration of the stent. The presence of a suprarenal fixation stent may complicate placement of renal artery stents because of single or multiple stent struts crossing the renal artery ostia, assuming various configurations of encroachment that may impact blood flow or the cross-sectional luminal area [39–42]. Despite theoretical concerns regarding the potential negative impact of suprarenal fixation on renal function, experimental studies and clinical reports have compared infrarenal versus suprarenal fixation stents during EVAR with little to no difference between both stent designs [39–42]. Nevertheless, suprarenal fixation notably makes placement of renal stents more challenging in some patients because of difficulties in selective catheterization of the renal arteries, advancement of the sheath or guide catheter, and expansion of the stent which can be partially compressed by the suprarenal stent [43, 44].

Inadvertent coverage of the renal arteries is described in 0–6 % of patients undergoing EVAR [31, 32, 35, 41, 43, 44] (Fig. 4.3a, b).

In the prospective study that evaluated the Cook Zenith stent graft (Bloomington, IN), which has a suprarenal fixation stent, nine of 351 patients (2.5 %) had graft material impinging on renal ostia [41]. When noted and treated immediately by placement of a renal stent, this resulted in no sequela. However, as described previously, placement of renal stents in patients with suprarenal fixation can be difficult and may require use of stiff guide-wire system and large platform to provide enough support [43]. If renal artery impingement was not promptly recognized and treated, renal artery occlusion was a frequent complication [41] (Fig. 4.4a–c).

Technical difficulties may account for differences in outcomes of renal artery interventions during EVAR compared to renal interventions performed in the absence of EVAR. Hiramoto and associates reported the outcomes of 31 renal artery stents in 29 patients who had partial or complete renal artery coverage by the endograft [43]. In that report, there

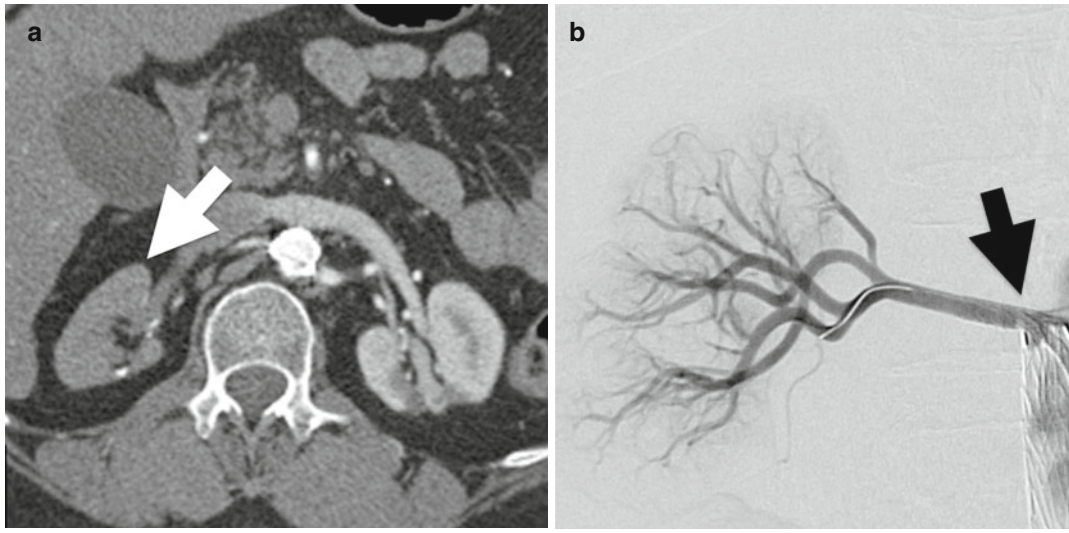


Fig. 4.3 (**a**) Post operative computed tomography after endovascular aortic repair shows compromised renal flow with poor contrast opacification (*arrow*). (**b**) Selected angiography after renal artery access demonstrates encroachment of the renal orifice (*arrow*) that required stenting

were two renal artery complications (6.5 %), including a stent occlusion and a renal artery dissection, potentially attributed to the use of stiffer guidewire system and larger platform [43]. Protrack and associates compared outcomes adjunctive renal artery stents in 51 patients who had EVAR with 362 patients who had renal artery stents without EVAR [44]. In the EVAR group, patients were more likely to have acute occlusions of the renal artery (4 % versus 0 %) and more likely to develop a rise in serum creatinine level (33 % versus 17 %). Excluding these early occlusions, late outcomes of restenosis and renal function deterioration were similar in both groups.

Placement of renal artery stents prior to EVAR can affect suitability for treatment of the aneurysm using endografts. Because renal artery stent is typically placed a few millimeters into the aorta, aortic stent grafts with suprarenal fixation or fenestrated stent grafts that extend above the renal arteries may no longer be adequately implanted in the patient's anatomy. These are important considerations when deciding the timing and sequence of repair in patients who have aortic aneurysms and renal artery disease warranting revascularization.

Renal Alignment During Fenestrated and Branched Endografts

Complex aortic aneurysms involving the renal and mesenteric arteries are technically more challenging to repair because of need to incorporate side branches into the repair. The minimal anatomic requirement for EVAR is the presence of an infra-renal aortic neck of at least 15 mm in length, without significant thrombus, calcification or angulation. Aneurysms encroaching the renal and mesenteric arteries are not suited for endovascular repair with standard endografts. Traditionally, these patients have been treated by open surgical repair, with an average operative mortality of 4 % in the largest reports [45]. Open repair carries higher morbidity and mortality because of more extensive exposure and dissection that is required when dealing with complex aneurysm and the visceral ischemia during aortic cross-clamp needed for more reconstruction of the visceral arteries [45]. It is logical to speculate that the advantages achieved with endovascular repair of infra-renal aneurysms pale in comparison to the potential for reduction in morbidity and mortality for treatment of more complex aneurysms that involve the visceral segment.

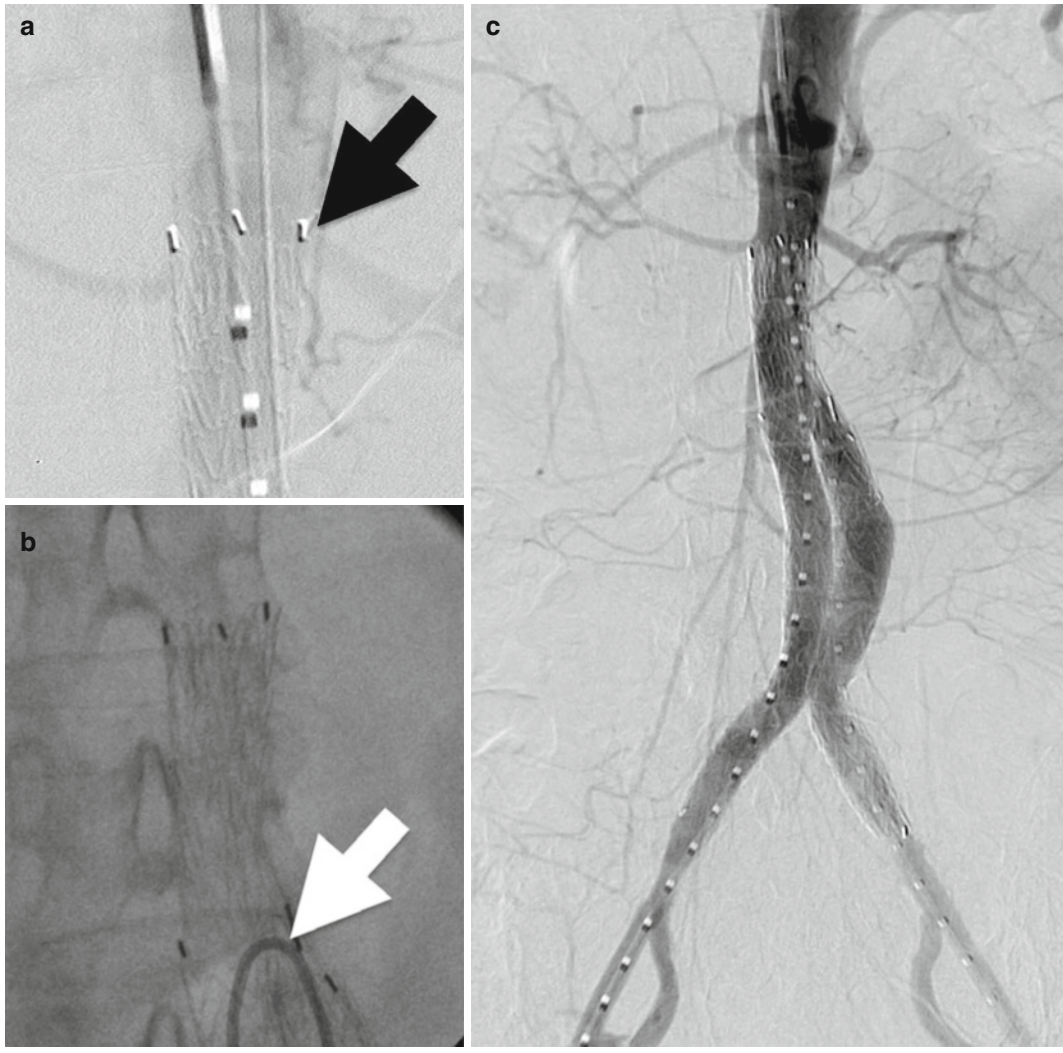


Fig. 4.4 (**a**) Bilateral renal artery filling is impaired on the post endovascular aortic graft deployment angiogram (*arrow*). (**b**) Access "up and over" the flow divider was obtained to assist with repositioning the aortic graft to a level below the renal arteries (*arrow*). (**c**) Post repositioning angiogram shows adequate renal artery filling

Recent technological advancements in stent graft design led to the development of fenestrations and branches, which allow incorporation of aortic side branches to treat patients with complex aneurysms using total endovascular technique. Fenestrated stent grafts (Fig. 4.5) utilize reinforced fenestrations or side holes, whereas branched stent grafts have pre-sewn cuffs.

Both designs require placement of bridging stents to align and provide seal by covering the connection gap between aortic stent graft and the target renal artery. A variety of complex anatomy has been successfully treated by these techniques. Renal and visceral ostia are accessed and bridging stents are placed to provide seal by covering the space between aortic stent graft and the target renal artery. Beyond the risk of deploying the aortic stent graft near renal artery ostia, these new grafts are deliberately constructed to incorporate the renal arteries into the repair, which is performed using catheter-based techniques, similar to what has already been described for treatment of renal occlusive lesions. Therefore, compared to simpler infrarenal aortic aneurysms, patients

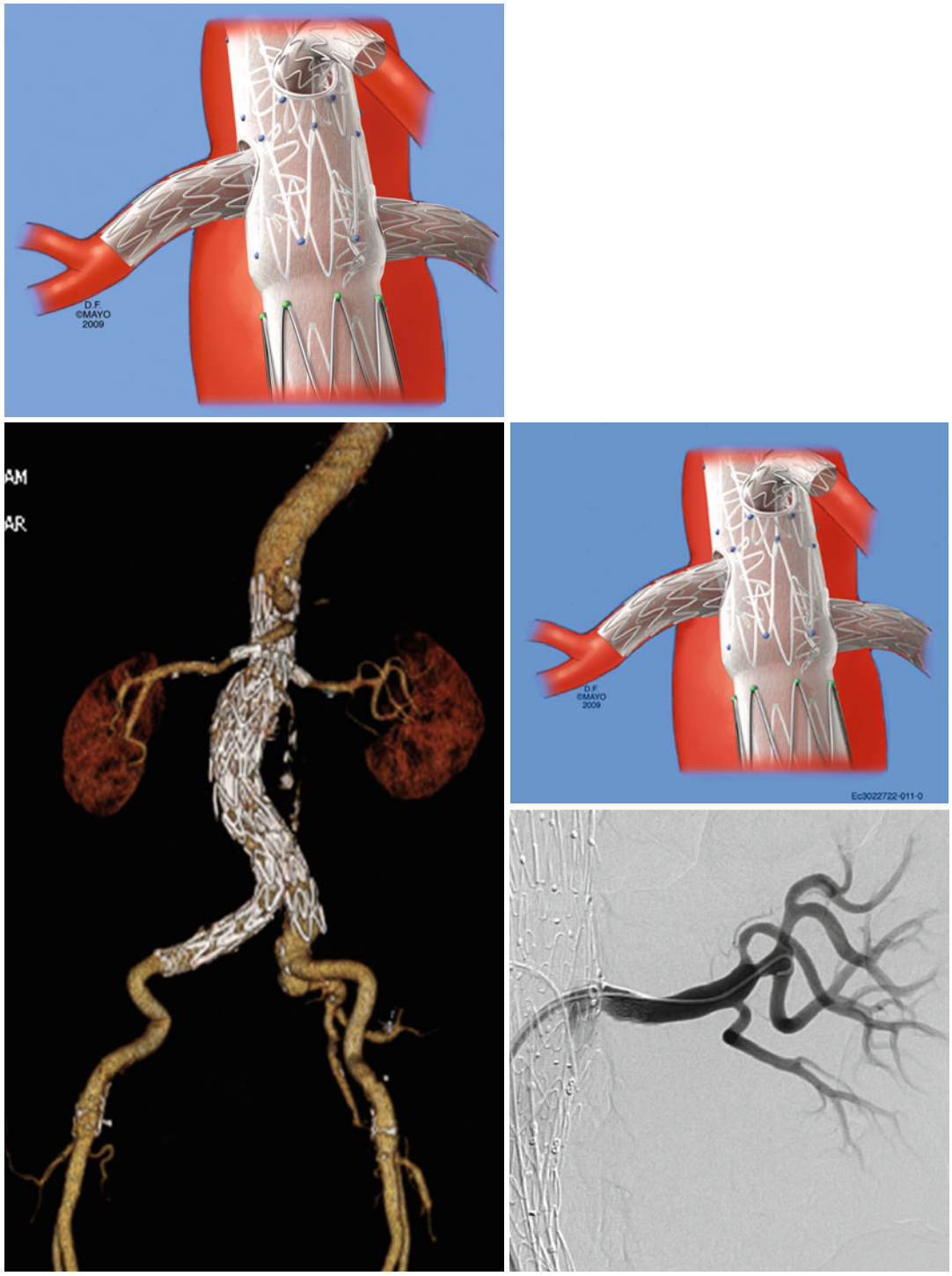


Fig. 4.5 Fenestrated aortic grafts utilize side holes that allow access to the renal arteries from within the graft. Stents are placed to bridge the gap between the aorta and renal artery leading to adequate filling after deployment (*Upper Right Image*: By permission of Mayo Foundation for Medical Education and Research. All rights reserved)

undergoing fenestrated repair are at increased risk of iatrogenic renal artery injury due to catheter manipulation, more complex anatomy, and use of larger doses of contrast media. All of these are associated with potentially higher rates of renal artery dissection or perforations compared to renal artery stent placement performed for occlusive disease [36–38].

Renal artery stenting is routinely performed during fenestrated repair to optimize seal and to avoid occlusion of the renal artery, which results from misalignment of the fenestration. Several single-center reports have demonstrated that patency of renal stents for this indication is superior to the results reported for patients with occlusive disease, averaging >95 % at 5 years [46–51]. Pooled results from the literature estimate a 6 % rate of renal artery occlusion in patients undergoing fenestrated endografts, but early reports had a number of patients with unstented fenestrations, a know factor associated with late renal artery occlusion [47]. A prospective multicenter study of 30 patients with 55 renal arteries treated by fenestrated endografts for juxtarenal aortic aneurysms has shown no operative deaths, acute occlusions or dialysis [52]. During follow up there were eight renal events, including renal artery stenosis in four patients, occlusion in two and segmental renal infarcts in two.

Long-term complications of renal artery stents include development of in-stent stenosis, similar to what occurs for renal stents placed for occlusive lesions, and kinks. Most frequently, covered stents are used during fenestrated repair, which differs from the standard treatment of renal occlusive lesions. Interestingly, covered stents have been shown to have superior patency rates compared to bare metal stents when used for renal alignment during fenestrated endovascular aortic repair. Mohabbat et al. reviewed the outcomes of 518 renal arteries treated by alignment stents during fenestrated endovascular repair. Freedom from stenosis at 3-years was significantly higher for covered stents (95 %) than for bare metal stents (89 %). Renal artery stent occlusion rate was 5 % for uncovered and 2 % for covered stents, and cumulative incidence of new permanent dialysis was 2 % for the entire cohort [37]. Similar to other reports, most renal artery occlusions resulted from technical issues encountered during the initial procedure (e.g., dissections, kinks), or to anatomical limitations because of concomitant occlusive disease small vessel diameter (<4 mm) [36, 37]. An interesting finding of the study was the difference in the location of restenosis observed with the two types of stents. Whereas restenosis associated with bare metal stents affected primarily the proximal stented segment, those with covered stents tended to occur distal to the stent edge. A possible explanation for restenosis in the proximal stent may be the over-dilatation or flare that is required during fenestrated repair, which may cause intimal and medial injury and a late hyperplastic response and restenosis. Conversely, graft coverage of this injured segment may impede in growth of tissue either by acting as a barrier or rendering the arterial wall ischemic.

Follow up of patients treated by fenestrated endografts is typically performed using computed tomography angiography and duplex ultrasound to evaluate for endoleaks, stent migration and branch vessel stent patency. Endoleaks at the attachment sites of the fenestration with the bridging stent has been reported in 1–3 % of the patients [36, 37, 46–52]. Migration is a rare occurrence given that these customized endografts have excellent fixation and are designed to be implanted in the normal aorta [36, 37, 46–52].

Conclusion

Iatrogenic renal artery injury and renal function deterioration in the setting of endovascular interventions are an important entity to understand. Variability exists in the population at risk for this unfortunate event and the procedures that carry increased risk. Clinicians must be aware so they can appropriately inform the individuals considering treatment, identify and manage events when they occur, and tailor treatment strategies in an effort to limit risk as much as possible.

References

1. Gruentzig A, Kuhlmann U, Vetter W. Treatment of renovascular hypertension with percutaneous transluminal dilatation of a renal artery stenosis. Lancet. 1978;1:801–2.
2. Baumgartner I, von Aesch K, Do DD, Triller J, Birrer M, Mahler F. Stent placement in ostial and nonostial atherosclerotic renal arterial stenosis: a prospective follow-up study. Radiology. 2000;216:498–505.
3. Corriere MA, Edwards MS. Revascularization for atherosclerotic renal artery stenosis: the treatment of choice? J Cardiovasc Surg (Torino). 2008;49(5): 591–608.
4. Canzanello VJ, Millan VG, Spiegel JE, Ponce PS, Kopelman RI, Madias NE. Percutaneous transluminal renal angioplasty in management of atherosclerotic renovascular hypertension: results in 100 patients. Hypertension. 1989;13(2):163–72.
5. Palmaz JC, Kopp DT, Hayash H. Normal and stenotic renal arteries: experimental balloon-expandable intraluminal stenting. Radiology. 1987;164:705–8.
6. Palmaz JC. The current status of vascular intervention in ischemic nephropathy. J Vasc Interv Radiol. 1998;9:539–43.
7. Van de Ven PJG, Kaatee R, Beutler JJ, Beck FJ, Woittiez AJ, Buskens E, et al. Arterial stenting and balloon angioplasty in ostial atherosclerotic renovascular disease: a randomized trial. Lancet. 1999; 353:282–6.
8. Leertouwer TC, GUssenhoven EJ, Bosch JL, van Jaarsveld BC, van Dijk LC, Deinum J, et al. Stent placement for renal arterial stenosis: where do we stand? A meta-analysis. Radiology. 2000;216:78–85.
9. Nolan BW, Schermerhorn ML, Rowell E, Powell RJ, Fillinger MF, Rzucidlo EM, Wyers MC, Zwolak RM, Walsh DB, Cronenwett JL. Outcomes of renal artery angioplasty and stenting using low-profile systems. J Vasc Surg. 2005;41:46–52.
10. Bonelli FS, McKusick MA, Textor SC, Kos PB, Stanson AW, Johnson CM, Sheedy 2nd PF, Welch TJ, Schirger A. Renal artery angioplasty: technical results and clinical outcome in 320 patients. Mayo Clin Proc. 1995;70(11):1041–52.
11. Ivanovic V, McKusick MA, Johnson CM, et al. Renal artery stent placement: complications at a single tertiary care center. J Vasc Interv Radiol. 2003;14: 217–25.
12. Beek FJ, Kaatee R, Beutler JJ, van der Ven PJ, Mali WP. Complications during renal artery stent placement for atherosclerotic ostial stenosis. Cardiovasc Intervent Radiol. 1997;20:184–90.
13. Morris CS, Bunnevie GJ, Najarian KE. Nonsurgical treatment of acute iatrogenic renal artery injuries occurring after renal artery angioplasty and stenting. AJR Am J Roentgenol. 2001;177(6):1353–7.
14. Hiramoto J, Hansen KJ, Pan XM, et al. Atheroemboli during renal artery angioplasty: an ex vivo study. J Vasc Surg. 2005;41:1026–30.
15. Holden A, Hill A, Jaff M, et al. Renal artery stent revascularization with embolic protection in patients with ischemic nephropathy. Kidney Int. 2006;70:948–55.
16. Edwards M, Corriere M, Craven T, et al. Atheroembolism during percutaneous renal artery revascularization. J Vasc Surg. 2007;46:55–61.
17. Thatipelli MR, Misra S, Sanikommu SR, Schainfeld RM, Sharma SK, Soukas PA. Embolic protection device use in renal artery stent placement. J Vasc Interv Radiol. 2009;20(5):580–6.
18. Henry M, Henry I, Polydorou A, Hugel M. Embolic protection for renal artery stenting. J Cardiovasc Surg (Torino). 2008;49(5):571–89.
19. Cooper CJ, Haller ST, Colyer W, Steffes M, Burket MW, Thomas WJ, Safian R, Reddy B, Brewster P, Ankenbrandt MA, Virmani R, Dippel E, Rocha-Singh K, Murphy TP, Kennedy DJ, Shapiro JI, D'Agostino RD, Pencina MJ, Khuder S. Embolic protection and platelet inhibition during renal artery stenting. Circulation. 2008;117(21):2752–60.
20. Scolari F, Tardanico R, Zani R, et al. Cholesterol crystal embolism: a recognizable cause of renal disease. Am J Kidney Dis. 2000;36:1089–109.
21. Safian RD, Textor SC. Renal-artery stenosis. N Engl J Med. 2001;344(6):431–42.
22. Ronden RA, Houben AJ, Kessels AG, Stehouwer CD, Leeuw PW, Kroon AA. Predictors of clinical outcome after stent placement in atherosclerotic renal artery stenosis: a systematic review and meta-analysis of prospective studies. Hypertension. 2010;28:2370–7.
23. Radermacher J, Chavan A, Bleck J, Vitzthum A, Stoess B, Gebel MJ, et al. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. N Engl J Med. 2001;344:410–7.
24. Zeller T, Frank U, Muller C, Burgelin K, Sinn L, Horn B, et al. Stent-supported angioplasty of severe atherosclerotic renal artery stenosis preserves renal function and improves blood pressure control: long-term results from a prospective registry of 456 lesions. J Endovasc Ther. 2004;11:95–106.
25. Davies MG, Saad WE, Peded EK, Mohiuddin IT, Naoum JJ, Lumsden AB. Implications of acute functional injury following percutaneous renal artery intervention. Ann Vasc Surg. 2008;22(6):783–9.
26. Maleux G, et al. Transcatheter embolization of biopsy-related vascular injuries in renal allografts. Long-term technical, clinical and biochemical results. Acta Radiol. 2003;44(1):13–7.
27. Vignali C, et al. Vascular injuries after percutaneous renal procedures: treatment by transcatheter embolization. Eur Radiol. 2004;14(4):723–9.
28. Lederle FA, Johnson GR, Wilson SE, et al. Rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair. JAMA. 2002;287:2968–72.
29. Lederle FA, Freischlag JA, Kyriakides TC, Padberg Jr FT, Matsumura JS, Kohler TR, Lin PH, Jean-Claude JM, Cikrit DF, Swanson KM, Peduzzi PN, Open Versus Endovascular Repair (OVER) Veterans Affairs Cooperative Study Group. Outcomes following

endovascular vs open repair of abdominal aortic aneurysm: a randomized trial. JAMA. 2009;302:1535–42.
30. Vemuri C, Ohman JW, Curci JA, Thompson RW, Geraghty PJ, Rubin BG, Sanche LA, Sicard GA, Jim J. Open abdominal aortic aneurysm repair: a decade of experience. Soc Clin Vasc Surg. 2013. Abstracts. http://symposium.scvs.org/abstracts/2013/P3.cgi.
31. EVAR Trial participants. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysms (EVAR trial 1): randomized controlled trial. Lancet. 2005;365:2179–86.
32. Blankensteijn JD, de Jong S, Prinssen M, et al. Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. N Engl J Med. 2005;352:2398–405.
33. Steyerberg EW, Kievit J, de Mol Van Otterloo JC, et al. Perioperative mortality of elective abdominal aortic aneurysm surgery: a clinical prediction rule based on literature and individual patient data. Arch Intern Med. 1995;155:1998–2004.
34. Biancari F, Hobo R, Juvonen T. Glasgow aneurysm score predicts survival after endovascular stenting of abdominal aortic aneurysms in patients from the EUROSTAR registry. Br J Surg. 2006;93:191–4.
35. Brown LC, Brown EA, Greenhalgh RM, Powell JT, Thompson SG, et al. Renal function and abdominal aortic aneurysm. The impact of different management strategies on long-term renal function in the UK endovascular aneurysm repair trials. Ann Surg. 2010;251:966–75.
36. Haddad F, Greenberg RK, Walker E, Nally J, O'Neil S, Kolin G, et al. Fenestrated endovascular grafting: the renal side of the story. J Vasc Surg. 2005;41:181–90.
37. Mohabbat W, Greenberg RK, Mastracci TM, Cury M, Morales JP, Hernandez AV. Revised duplex ultrasound criteria and outcomes for renal stents and stent grafts following endovascular repair of juxtarenal and thoracoabdominal aneurysms. J Vasc Surg. 2009;49:827–37.
38. Verhoeven ELG, Vourliotakis G, Bos W, Tielliu IF, Zeebregts CJ, Prins TR, et al. Fenestrated stent grafting for short-necked and juxtarenal abdominal aortic aneurysm: an 8-year single-center experience. Eur J Vasc Endovasc Surg. 2010;39:529–36.
39. Sun Z, O'Donnell ME, Winder J, Ellis PK, Blair PH. Effect of suprarenal fixation of aortic stent grafts on the renal artery ostia. J Endovasc Ther. 2007;14:650–60.
40. Walsh SR, Boyle JR, Lynch AG, et al. Suprarenal endografts fixation and medium-term renal function: a systematic review and meta-analysis. J Vasc Surg. 2008;47:1364–70.
41. Greenberg RK, Chuter TA, Lawrence-Brown M, Haulon S, Nolte L. Analysis of renal function after aneurysm repair with device using suprarenal fixation (Zenith AAA endovascular graft) in contrast to open repair. J Vasc Surg. 2004;39:1219–28.
42. O'Donnell ME, Sun Z, Winder RJ, Ellis PK, Lau LL, Blair PH. Suprarenal fixation of endovascular aortic stent grafts: assessment of medium-term to long-term renal function by analysis of juxtarenal stent morphology. J Vasc Surg. 2007;45:694–700.
43. Hiramoto JS, Chang CK, Reilly LM, Schneider DB, Rapp JH, Chuter TAM. Outcome of renal stenting for renal artery coverage during endovascular aortic aneurysm repair. J Vasc Surg. 2009;49:1100–6.
44. Protrack CD, Saad WA, Davies MG. Renal artery interventions during infrarenal endovascular aortic repair: a greater potential of subsequent failure? J Vasc Interv Radiol. 2010;21:459–64.
45. Tallarita T, Sobreira ML, Oderich GS. Results of open repair of pararenal aortic aneurysms: a tabular review of the literature. Ann Vasc Surg. 2010;25(1):143–9.
46. Nordon IM, Hinchliffe RJ, Holt PJ, Loftus IM, Thompson MM. Modern treatment of juxtarenal abdominal aortic aneurysms with fenestrated endografting and open repair – a systematic review. Eur J Vasc Endovasc Surg. 2009;38(1):35–41.
47. Verhoeven EL, Zeebregts CJ, Kapma MR, Tielliu IF, Prins TR, van den Dungen JJ. Fenestrated and branched endovascular techniques for thoracoabdominal aneurysm repair. J Cardiovasc Surg (Torino). 2005;46:131–40.
48. Amiot S, Haulon S, Becquemin JP, Magnan PE, Lermusiaux P, Goueffic Y, et al. Fenestrated endovascular grafting: the French multicenter experience. Eur J Vasc Endovasc Surg. 2010;39:537–44.
49. Troisi N, Donas KP, Austermann M, Tessarek J, Umscheid T, Torsello G. Secondary procedures after aortic aneurysm repair with fenestrated and branched endografts. J Endovasc Ther. 2011;18:146–53.
50. Greenberg RK, Eagleton M, Mastracci T. Branched endografts for thoracoabdominal aneurysms. J Thorac Cardiovasc Surg. 2010;140:S171–8.
51. Manning BJ, Agu O, Richards T, Ivancev K, Harris PL. Early outcome following endovascular repair of pararenal aortic aneurysms – triple versus double or single-fenestrated stent grafts. J Endovasc Ther. 2011;18:98–105.
52. Greenberg RK, Sternbergh C, Makaroun M, Ohki T, Chuter T. Intermediate results of a United States multicenter trial of fenestrated endografts repair for juxtarenal aortic aneurysms. J Vasc Surg. 2009;50:730–7.

Cardiorenal Syndromes: Renal Artery Disease and Congestive Heart Failure

5

Eric R. Fenstad and Garvan C. Kane

Abstract

Atherosclerotic renal artery stenosis commonly co-exists with systolic and/or diastolic heart failure and is an unfavorable prognostic indicator. The morbidity and mortality relates to a complex neurohormonal interplay whereby renal ischemia activates the renin angiotensin aldosterone axis resulting in sodium retention, arterial vasoconstriction, and accelerated end-organ damage. In a subset of patients, particularly with bilateral renal artery stenosis, acute episodes of severe hypertension may lead to "flash" pulmonary edema. Often sharing a common pathophysiology renal artery stenosis is especially common amongst heart failure patients with a 31 % incidence in those who undergo renal artery revascularization. The best course of treatment of renal artery stenosis in the setting of heart failure remains unclear. Although renal artery stenting has no effect on mortality, revascularization may lead to improved control of heart failure as evidenced by a reduction in hospital admissions and improvement in NYHA heart failure class.

Keywords

Renal artery stenosis • Systolic heart failure • Diastolic heart failure • Flash pulmonary edema • Cardiorenal syndrome

Introduction

Heart failure has emerged as the major cause of cardiovascular expenditure in the United States with a current prevalence of 5.7 million in the adult population, rising to a projected 10 million by the year 2030 [1, 2]. The high burden of disease represents a significant health and economic strain with major utilization of inpatient and outpatient services exceeding $25 billion annually [3–5]. Heart failure is now understood not to represent an isolated disorder of myocardial dysfunction but rather a complex systemic disease with dysregulation of hormonal, biochemical and pathophysiologic processes of the heart, kidney and vascular bed. With many shared regulatory mechanisms, and given that dysfunction of the heart so frequently leads to renal dysfunction and

E.R. Fenstad, MD, MSc • G.C. Kane, MD, PhD (✉)
Division of Cardiovascular Diseases, Mayo Clinic,
200 First Street, SW, Rochester, MN 55905, USA
e-mail: fenstad.eric@mayo.edu;
kane.garvan@mayo.edu

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_5, © Springer-Verlag London 2014

vice versa, management of the heart failure patient requires focus on the cardiorenal axis. Indeed the major advances in medical therapy for heart failure share targets that impact cellular regulation in broad tissue beds through focusing on systems such as the renin-angiotensin-aldosterone hormonal axis and the sympathetic nervous system.

Atherosclerosis and systemic hypertension, pathognomonic features of renal artery stenosis, are common causes of heart failure [6–8]. Renal artery stenosis is strongly associated with cardiovascular morbidity and mortality in patients with atherosclerotic disease [9, 10] and may impact the pathogenesis and control of heart failure. Renal artery stenosis has been associated with frequent abnormalities in left ventricular structure and function and acute episodes of left ventricular failure, often mediated through labile systemic hypertension and exacerbation of myocardial ischemia [11–14]. The presence of renal artery stenosis may also limit options for heart failure pharmacotherapy, such as the use of modulators of the renin–angiotensin-aldosterone system in patients with global renal ischemia (caused by either bilateral renal artery stenosis or stenosis to a solitary kidney), due to their potential to cause a simultaneous fall in glomerular filtration rate. Progressive renal artery stenosis may contribute to chronic kidney disease, a major determinant of outcome in patients with heart failure [14, 15].

In this chapter we will describe the central role of the cardiorenal axis in the syndrome of heart failure and focus our discussions on the archetypical cardiorenal syndrome, that of renal artery stenosis and heart failure.

Cardiorenal Syndromes

Renal disease and heart failure commonly coexist. The intricate interplay between the heart and kidneys is well documented with proper function of one organ dependent on homeostatic balance of the other. Risk factors for the development of heart failure include hypertension, obesity, hyperlipidemia, coronary artery disease, left ventricular dysfunction, tobacco use, diabetes mellitus, and chronic kidney disease [16, 17]. In a large registry of patients hospitalized for acute decompensated heart failure the most frequent co-morbidities were hypertension (72 %), coronary artery disease (58 %), diabetes mellitus (44 %), and renal dysfunction (29 %) [18]. Patients with renal disease and a marked reduction in glomerular filtration rate (creatinine ≥2 mg/dl) were more likely to be treated with intravenous vasoactive agents and had increased in-hospital mortality [18]. The development of acute kidney injury during hospital admission is a poor prognostic indicator in the setting of heart failure [14, 19] and advanced chronic kidney disease predicts future hospitalization [19, 20]. Furthermore, patients with chronic kidney disease are less likely to have reduced percutaneous coronary intervention success [21], and receive less optimal cardiac care due to impaired renal function [22, 23]. All of these perpetuate a vicious cycle of cardiac and renal impairment.

Recognized for decades but vaguely defined, cardiorenal syndromes were classified at a recent consensus conference [24]. The conference included experts in nephrology, cardiology, critical care, and cardiac surgery to define and classify cardiorenal syndromes, identify diagnostic biomarkers, and outline prevention and treatment strategies. Cardiorenal syndromes represent a group of "disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other [24]." Cardiorenal syndromes consist of five subtypes reflecting the sequence of events that leads to cardiac and renal dysfunction and bi-directional relationship between the two organ systems (Table 5.1). Despite concrete definitions, patients may transition between one subtype and another at different points in time.

Acute Cardiorenal Syndrome (Type 1)

Acute decompensated heart dysfunction in the form of acute heart failure or acute coronary syndrome, which causes acute kidney injury (Fig. 5.1). Acute heart failure may consist of hypertensive pulmonary edema with preserved ejection fraction, acute decompensated chronic

Table 5.1 Cardio-Renal syndromes

	Process	Typical scenario	Contributing features
Type 1	Acute heart failure leads to	Acute decompensated heart failure or coronary syndrome	Renal arterial hypoperfusion, contrast
Acute cardio-renal	2° kidney injury		Exposure, renal venous hypertension
Type 2	Chronic heart disease leads	Chronic heart failure (both systolic and diastolic)	As above, neurohumoral activation
Chronic cardio-renal	To 2° kidney injury		
Type 3	Acute renal failure	Acute severe decline in renal functions	Electrolyte abnormalities, sodium and fluid
Acute reno-cardiac	Leads to 2° cardiac injury		overload, hypertension
Type 4	Chronic kidney disease	Progressive renal dysfunction	As above, inflammatory and oxidative injury
Chronic reno-cardiac	Leads to 2° cardiac injury		Anemia, metabolic abnormalities

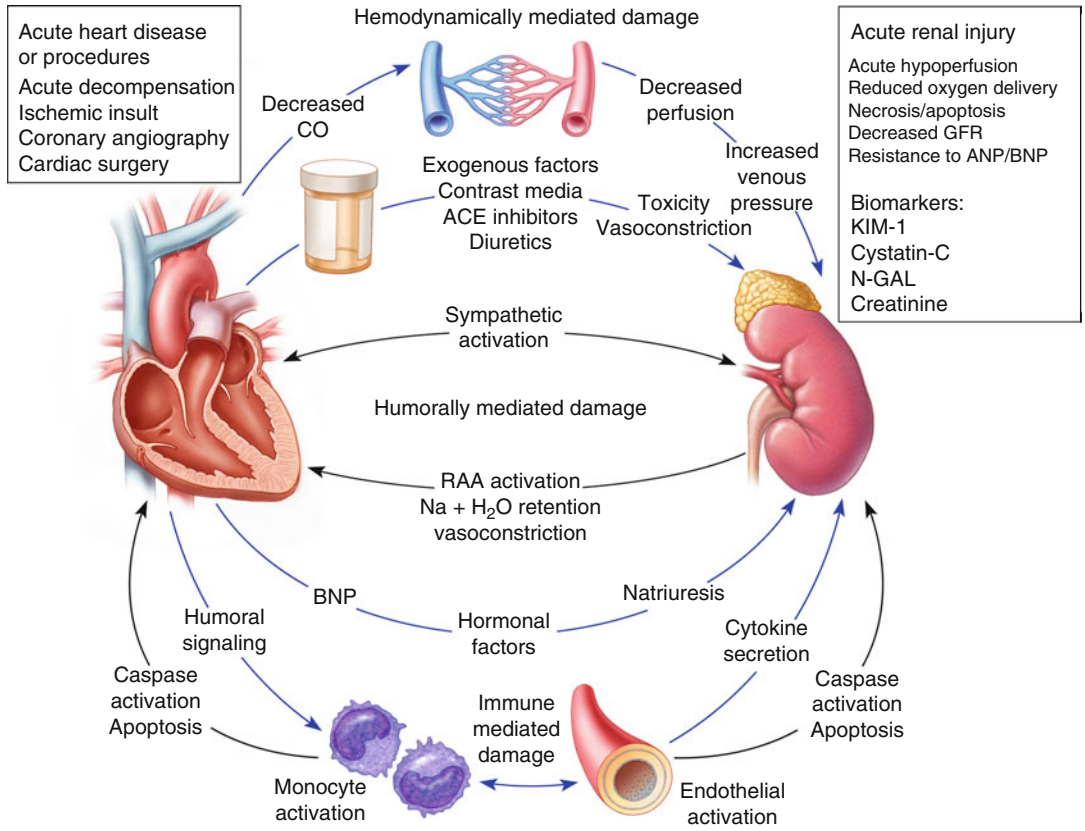


Fig. 5.1 Cardiorenal syndrome type 1. Pathophysiological interactions between heart and kidney in the setting of acute cardiac decompensation leading to acute kidney injury. *ACE* angiotensin-converting enzyme, *ANP* atrial natriuretic peptide, *BNP* B-type natriuretic peptide, *CO* cardiac output, *GFR* glomerular filtration rate, *KIM* kidney injury molecule, *N-GAL* neutrophil gelatinase-associated lipocalin, *RAA* renin angiotensin aldosterone (With permission from Ronco et al. [24])

heart failure, cardiogenic shock, or right ventricular failure. The precipitating factor for heart failure may include myocardial infarction, prolonged hypotensive episodes related to surgery or medication administration, and other prolonged ischemic episodes. Acute kidney injury accompanies acute ST elevation myocardial infarction approximately 10 % of the time [25]. The presence of acute kidney injury on admission to the hospital for heart failure is common, occurring in 29 % of this population [14] but up to 70 % in the setting of cardiogenic shock [26]. The development of acute kidney injury during admission for heart failure strongly predicts worse outcome with increased in-hospital mortality [14, 27, 28], hospital readmission [19], 1 year mortality [25], and prolonged hospitalization [19, 29].

Krumholz et al. [29] investigated hemodynamically stable patients admitted with heart failure who did not undergo percutaneous coronary intervention, or coronary artery bypass surgery. The investigators identified 1,681 patients over the age of 65 years and noted 28 % had a significant deterioration in renal function (defined in this study as a worsening in creatinine >0.3 mg/dl during hospitalization). The creatinine rise occurred within the first 7 days in 90 % of patients. Factors that were associated with the development of worsening renal function included: male gender, pulmonary congestion, systemic hypertension, tachycardia and advanced chronic kidney disease on admission. The presence of one of these risk factors equated to a 16 % risk of acute kidney injury with the risk rising to greater than 50 % if all were present. Acute renal injury was related to an increased length of hospital stay (by average of 2.3 days) and an increased financial cost approaching $2000. Moreover, inpatient (7 % vs. 3 %) and long-term mortality was worse (30 day 10 % vs. 6 %, and 6 month mortality 20 % vs. 17 %).

The development of acute kidney injury occurs frequently in patients with baseline chronic kidney disease but can also occur in those with "normal" baseline renal function. While the decline in glomerular filtration may be transient as demonstrated by Logeart et al. [19], it is often a marker for future events as illustrated in a study of 416 patients hospitalized for acute heart failure. After exclusion for cardiogenic shock, inotrope use, exposure to nephrotoxic agents, surgery, and severe chronic kidney disease (Cr >2.6 mg/dL), more than one-third of patients developed worsening renal function during admission. The mean increase in serum creatinine was 0.6 mg/dl and was related to similar risk factors as previously described with the addition of anemia and precipitating factors of either hypertensive crisis (15 % in worsening renal function vs. 8 % without worsening renal function) or acute coronary syndrome (17 % worsening renal function vs. 10 % without worsening renal function, $p=0.03$). Deterioration of renal function was transient in two-thirds of patients who recovered to their baseline glomerular filtration rate prior to discharge. Despite early recovery of renal function, the 6-month event rate for death or heart failure hospital admission was 38 % and was more frequent in those patients who had had transient renal dysfunction. This study highlights that even after excluding hemodynamically unstable patients and those patients who received potential renal insults (nephrotoxic agents or surgery), renal impairment is common, often transient, yet still poses a high risk for patients admitted for heart failure.

Several factors are thought to contribute to the development of type 1 cardiorenal syndrome including inadequate renal perfusion secondary to cardiac output impairment, increased central venous pressure secondary to volume overload and right heart failure leading to renal venous congestion, ascites and increased intra-abdominal pressure and diuretic resistance. The disrupted milieu that regulates vascular tone, renal blood flow, and central venous pressure results in excess production of vasoconstrictive mediators (e.g., epinephrine, endothelin, angiotensin) and resistance to and diminished release of endogenous vasodilatory agents (e.g., natriuretic peptide, nitric oxide).

Chronic Cardiorenal Syndrome (Type 2)

This syndrome reflects chronic heart failure or coronary disease that results in chronic kidney disease (Fig. 5.2). Chronic heart disease is a

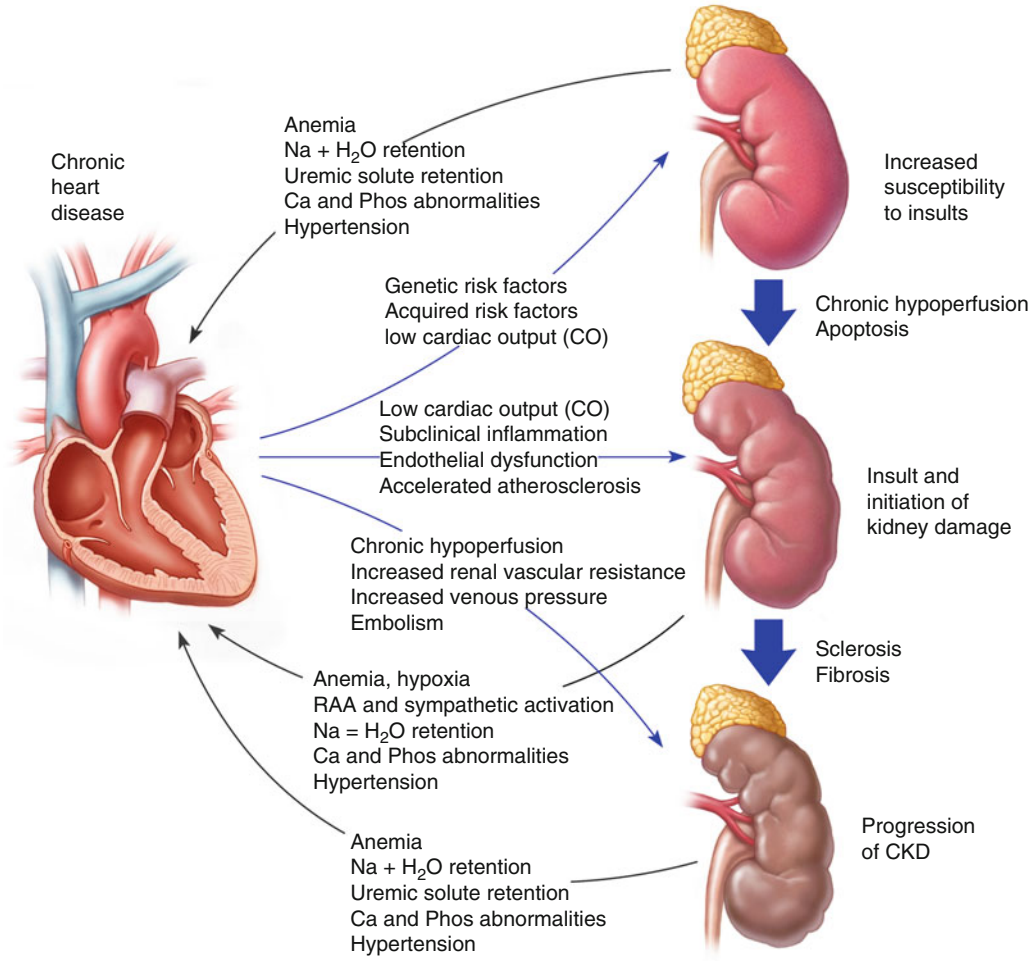
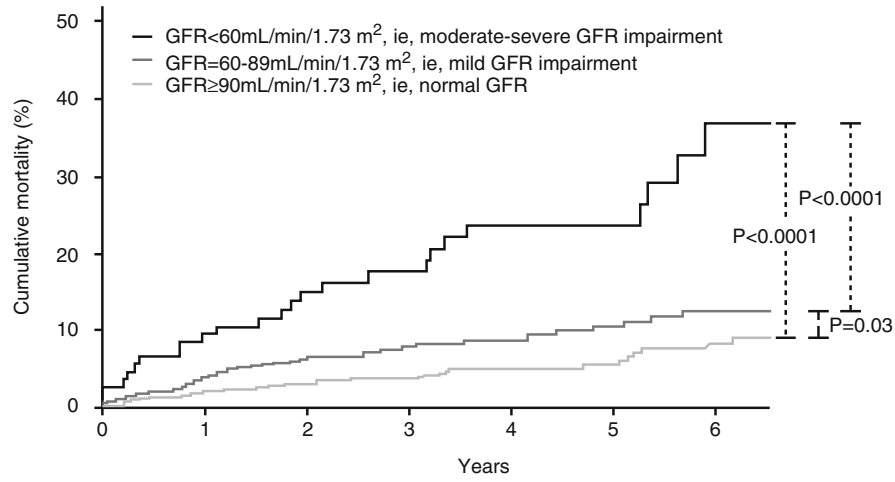


Fig. 5.2 Cardiorenal syndrome type 2. Pathophysiological interactions between heart and kidney in the setting of chronic abnormalities in cardiac function, e.g., chronic heart failure) leading to progressive chronic kidney disease (*CKD*). *LVH* left ventricular hypertrophy, *RAA* Renin Angiotensin Aldosterone (With permission from Ronco et al. [24])

broad term that includes chronic heart failure by any mechanism. This includes systolic heart failure, (both ischemic and non-ischemic) and heart failure with a preserved ejection fraction (diastolic heart failure). At risk characteristics of cardiorenal syndrome type 2 mirror those of type 1 and include older age, diabetes mellitus, acute coronary syndrome, simple and complex congenital heart disease, and systemic hypertension. These risk factors share a common thread as they predispose to development of generalized atherosclerosis, chronic low cardiac output, venous congestion, and in certain instances of congenital heart disease, chronic hypoxia. Atherosclerosis occurs on a micro and macrovascular level including the renal arterial bed resulting in chronic reduced renal perfusion, maladaptive neurohormonal activation resulting in further renal impairment.

Coexistent chronic kidney disease in patients with chronic heart failure is very common (ranging between 45 and 64 % [30, 31]). In a large cohort of patients with adults with congenital heart disease, Dimopoulos and colleagues [32] demonstrated chronic kidney disease to be highly prevalent at 50 % with the presence and severity of renal dysfunction being a highly predictive marker of higher mortality (Fig. 5.3). A reduction in renal



Patients at risk

GFR<60mL/min/1.73 m^2	102	90	76	63	51	51	16
GFR=60-89mL/min/1.73 m^2	451	425	370	297	253	176	122
GFR≥90mL/min/1.73 m^2	549	528	482	427	369	239	140

Fig. 5.3 Renal dysfunction associated with poor outcome in adult congenital heart disease. Unadjusted (Kaplan–Meier) cumulative mortality curves according to Glomerular filtration group (*GFR*) group. Patients with moderate or severe GFR reduction (<60 mL min^{-1} 1.73 m^{-2}) had a fivefold increased unadjusted mortality risk, which was apparent even from the first year of follow-up (With permission from Dimopoulos et al. [32])

clearance was related to age and the presence of cyanosis, left ventricular systolic dysfunction, diuretic use, and worse heart failure functional class. The 6-year mortality rate was five times higher in the group with chronic kidney disease.

Acute Renocardiac Syndrome (Type 3)

This syndrome involves acute kidney injury leading to abrupt heart injury, disease, or dysfunction (Fig. 5.4). The main mechanism of acute heart failure in these settings results from the interaction of acute volume overload, hypertension, endothelial dysfunction, electrolyte derangements, sympathetic and renin-angiotensin-aldosterone system activation and myocardial ischemia. Examples of primary cardiac dysfunction include uremic pericarditis, acidemia-induced vasoconstriction/ischemia, and hyperkalemia-induced arrhythmia or cardiac arrest secondary to acute kidney injury. Epidemiologically, cardiorenal syndrome type 3 is more fluid and defining this subtype presents a challenge because of different criteria for acute kidney injury, variable subclinical cardiac disease at baseline, and heterogeneity of the precipitating renal conditions.

Renal Artery Stenosis: Archetypical Cardiorenal Syndrome

The estimated incidence of atherosclerotic renal artery stenosis (RAS) (Fig. 5.5) is 3–4 per 1,000 patient-years but is higher in patients with systemic hypertension (2–5 %), patients over the age of 65 years of age (5–20 %), and in patients with coronary artery disease (33 %). Atherosclerotic RAS may affect 50 % or more of patients with heart failure [33–35]. Rihal and colleagues [9] demonstrated the commonality of incidental unilateral or bilateral renal artery stenosis in hypertensive patients undergoing clinically indicated coronary angiography. Of 297 patients with systemic hypertension undergoing coronary angiography, 28 % had renal artery stenoses <50 % while 7 % of patients had a flow-limiting narrowing >70 % (Fig. 5.6). Although serum creatinine did not correlate with the presence of atherosclerotic RAS, stroke/

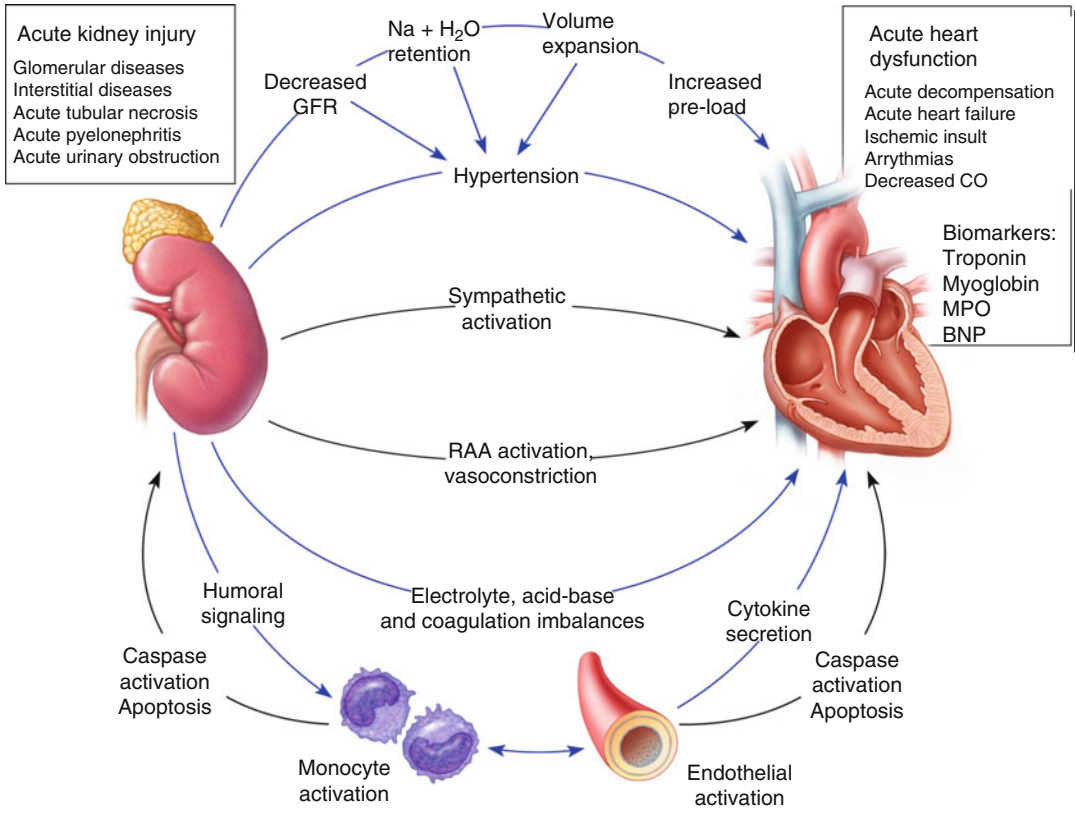


Fig. 5.4 Cardiorenal syndrome type 3. Pathophysiological interactions between heart and kidney in the setting of abrupt worsening of renal function, (e.g., acute kidney failure or glomerulonephritis) causing acute cardiac disorder (e.g., heart failure, arrhythmia, pulmonary edema). *MPO* myeloperoxidase; other abbreviations as in Fig. 5.1 (With permission from Ronco et al. [24])

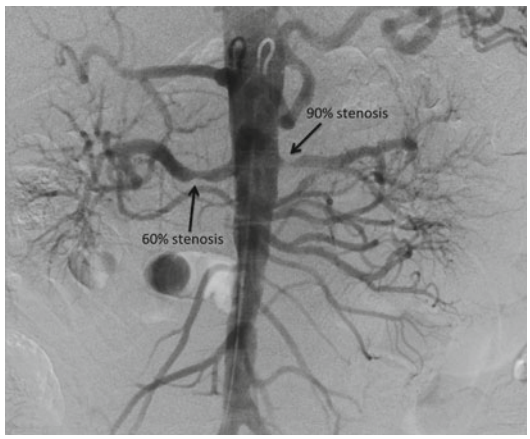


Fig. 5.5 Bilateral proximal atherosclerotic renal artery stenosis on renal angiography

transient ischemic attack and antihypertensive medication use was associated.

In a retrospective review of Medicare claims data, Kalra et al. [34] identified a prevalence of atherosclerotic RAS disease of 0.5 % in the general population but up to 5.5 % in those with chronic kidney disease. More recent data [35] indicate the incidence of atherosclerotic RAS diagnosis is rising (Fig. 5.7) as hazard ratios for diagnosis increased from 1.00 in 1992 to 4.71 in 2003.

Significance of RAS in Patients with Heart Failure

In patients with heart failure, the presence of atherosclerotic RAS is an unfavorable prognostic indicator for morbidity and mortality. The trend may be due to increased burden of disease and/or improved detection as imaging techniques evolved. In a European study of 366 patients with

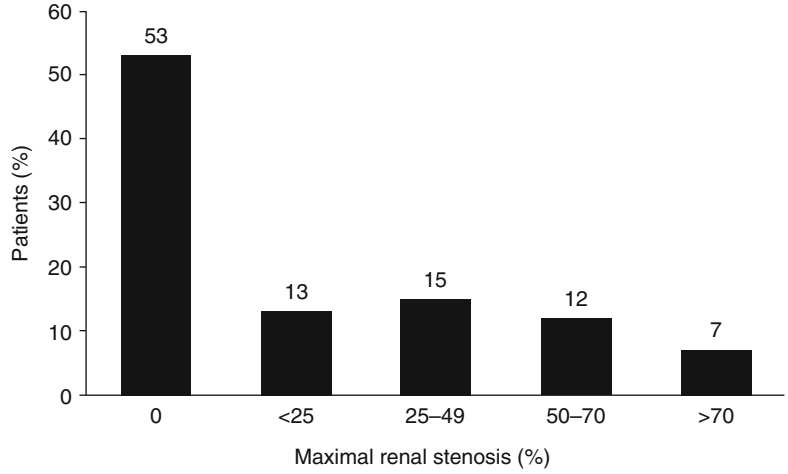


Fig. 5.6 Prevalence of incidental renal artery stenosis. Frequency distribution of the prevalence of incidental renal artery stenosis among 297 hypertensive patients undergoing coronary angiography; 3.7 % of patients had bilateral disease (With permission of Mayo Foundation for Medical Education and Research. All rights reserved. From Rihal et al. [9])

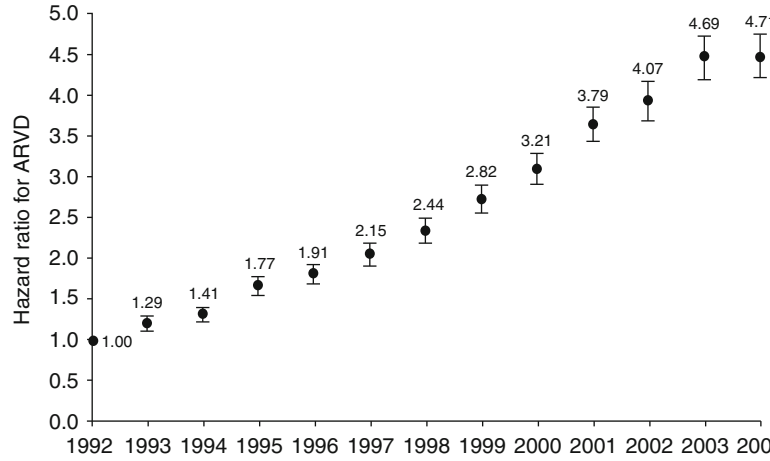


Fig. 5.7 Rising prevalence of renal artery stenosis. Unadjusted hazard ratios, with 95 % confidence intervals, for atherosclerotic renovascular disease (*ARVD*) by calendar year, with 1992 as the reference category (With permission from Kalra et al. [35])

left ventricular systolic dysfunction (left ventricular ejection fraction less than 50 %), 112 (31 %) had evidence of renal artery stenosis on magnetic resonance including 41 patients with bilateral disease (11 %) [36]. The presence of renal artery stenosis was associated with systemic hypertension, reduced glomerular filtration rate and older age. Over a median follow up of 33 months, heart failure patients with renal artery stenosis had more vascular admissions and an increased length of stay. Patients with renal artery stenosis had a higher all-cause mortality (48 % vs. 22 %, P=0.01) as well as greater cardiovascular mortality (33 % vs. 12 %, P=0.002) compared to heart failure patients without renal artery stenosis (Fig. 5.8). The true incidence and disease burden of atherosclerotic RAS may be underestimated because patients may be asymptomatic for years to decades. In fact, concomitant atherosclerotic RAS may often go undiagnosed. Unrecognized ante-mortem, at autopsy the prevalence of atherosclerotic RAS was 29 % in patients with chronic kidney disease who died [37].

Atherosclerotic RAS results in a complex neurohormonal interplay whereby renal ischemia triggers renin release, angiotensin production and aldosterone release; thereby resulting in a host of detrimental processes including arterial vasoconstriction, sodium retention, sympathetic nervous system activation, renal and myocardial fibrosis. Renal ischemia, renin-angiotensin-aldosterone system activation, and sodium retention ultimately cause an arterial pressure increase that accelerates end organ damage (left ventricular

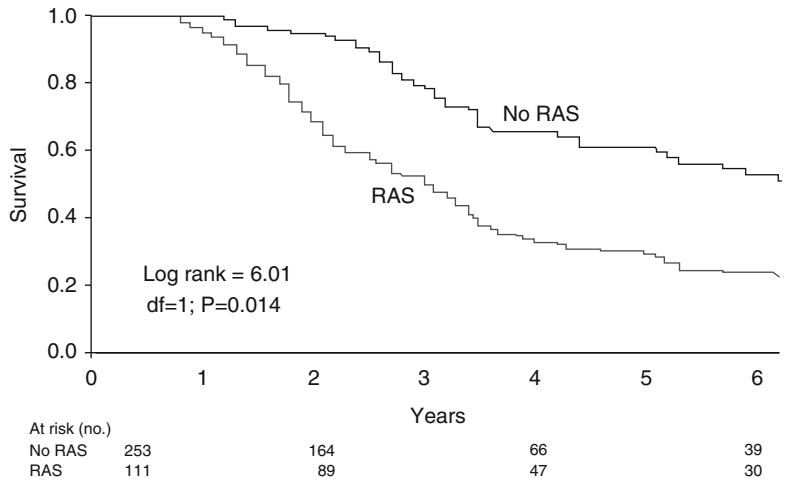


Fig. 5.8 Association of renal artery stenosis with outcome in chronic heart failure. Kaplan–Meier plot showing survival in patients with (n = 112) and without (n = 254) renal artery stenosis (*RAS*) (With permission from Bourantas et al. [36])

hypertrophy, accelerated atherosclerosis, and predisposition to stroke) [38]. Renal artery stenosis is a rare but well-recognized cause of resistant hypertension, hypertensive urgency/emergency, and flash pulmonary edema with new or recurrent heart failure exacerbations.

In 1988, Thomas Pickering first described flash pulmonary edema in the setting of hemodynamically significant, typically bilateral, renal artery stenosis. In a first series of 11 patients, seven had bilateral disease and on average had 2.3 episodes of flash pulmonary edema before a RAS diagnosis was confirmed [39]. Following surgical or percutaneous revascularization, 10 patients had no further episodes of flash pulmonary edema over a 6-month period. A subsequent series in 55 patients with RAS, pulmonary edema was documented in 23 % of patients and was associated with the presence of coronary artery disease, bilateral RA disease, or unilateral RA disease to a solitary kidney. Interestingly, in a separate case series of nine patients presenting with hypertensive emergency, flash pulmonary edema, and acute decompensated heart failure, levels of atrial natriuretic peptide approached 14 times the upper normal limits [40]. Following renal revascularization, atrial natriuretic peptide levels fell significantly (120 ± 63 pg/ml baseline, 48 ± 20 pg/ml post-revascularization) with improvement in heart failure symptoms.

A systematic review of 30,092 patients with atherosclerotic RAS demonstrated a prevalence of atherosclerotic RAS (>50 % stenosis) in 8.0 % of patients undergoing coronary angiography with an indication of coronary artery disease [41]. Bilateral disease was common, occurring in one-fifth of patients. Sporadic episodes of flash pulmonary edema in the presence of bilateral renal artery stenosis have since been named the "Pickering Syndrome." Of 87 cases in the literature, heart failure and left ventricular hypertrophy were diagnosed 40 and 50 % respectively.

An acute rise in left ventricular end diastolic pressure, the pressure at which the left ventricle fills, is one of the major driving forces that flood the alveolar space with fluid sometimes severe enough to be life-threatening. Three factors appear to cause flash pulmonary edema in the setting of bilateral renal artery stenosis: impaired diuresis, diastolic dysfunction with elevated blood pressure, and incompetence of the alveolar-capillary interface (Fig. 5.9). Chronic systemic hypertension with atherosclerotic RAS is associated with renin-angiotensin-aldosterone system activation, sympathetic activation, fluid and sodium retention, concentric left ventricular hypertrophy, accelerated atherosclerosis, and decreased arterial compliance. Under normal conditions, the aorta is distensible and accommodates each systolic wave of blood flow. However, as the aorta stiffens, the pulse wave reflects backward towards the heart thereby further increasing left ventricular systolic after load. The early adaptive myocardial hypertrophy gives way to

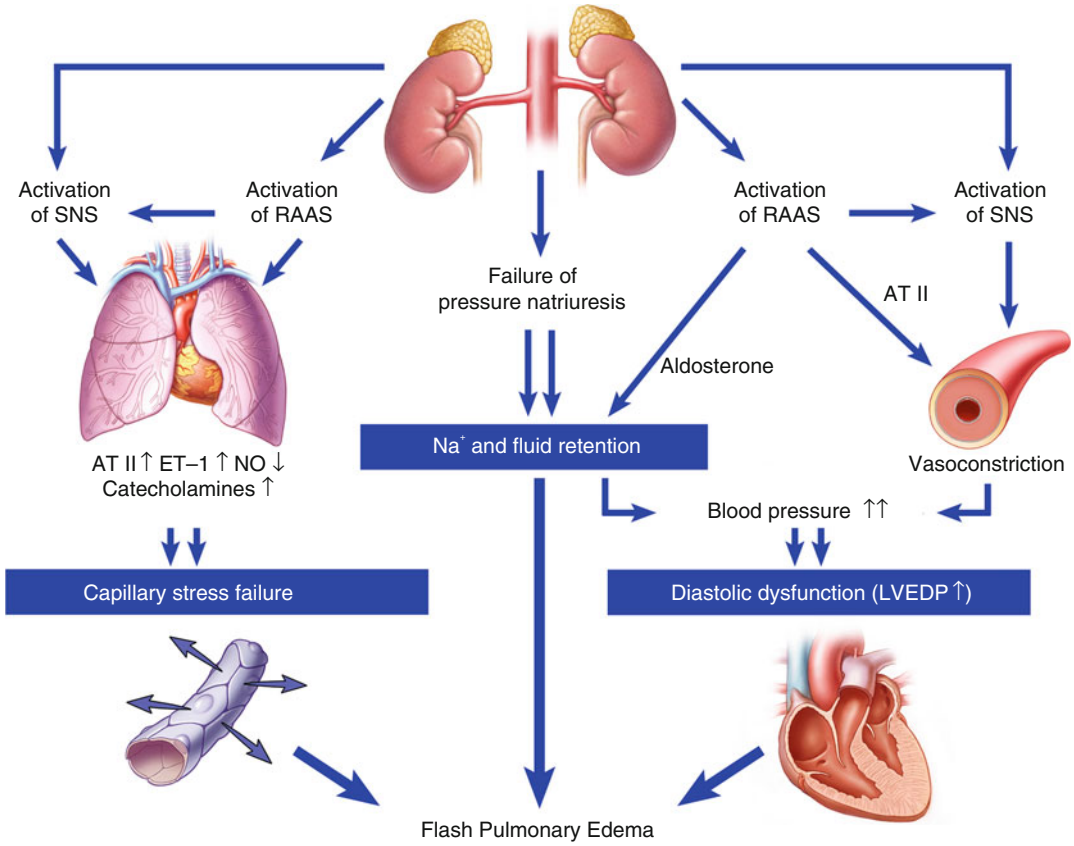


Fig. 5.9 The Pickering syndrome. Three main pathophysiological mechanisms contribute to the development of flash pulmonary edema: defective pressure natriuresis with sodium and fluid retention, increased left ventricular end-diastolic pressure associated with left ventricular hypertrophy and stiffening, and failure of the pulmonary capillary blood–gas barrier. *RAAS* renin–angiotensin–aldosterone system, *SNS* sympathetic nervous system, Na^+ sodium, *AII* angiotensin II, *ET-1* endothelin-1, *NO* nitric oxide (With permission from Messerli et al. [41])

progressive fibrotic change causing ventricular noncompliance that requires higher ventricular filling pressures leading to backpressure in the left atrium and resultant pulmonary venous hypertension. Fluid permeates through the alveolar-capillary interface once pulmonary capillary pressure acutely exceeds 20–25 mmHg with subsequent pulmonary edema [12].

Society guidelines for renal artery revascularization were proposed in 2005 [42] and updated in 2011[43] after the publication of the ASTRAL trial [44]. Indications for renal artery revascularization have remained unchanged and include the following conditions outlined in Table 5.2. Percutaneous renal artery revascularization remains a recommended intervention in RAS associated with acute cardiogenic pulmonary edema or acute decompensated heart failure and carries a Class I indication from the American Heart Association [42] yet the evidence remains observational [45, 46].

Review of the Mayo Clinic experience in patients with atherosclerotic RAS referred for percutaneous renal artery revascularization demonstrates the presence of systolic or diastolic heart failure in 31 % (50/163) of patients [11]. All patients had a creatinine ≥2.0 mg/dl and concomitant hypertension. The two groups were similar in patient characteristics with few exceptions. The group with heart failure had an increased use of antihypertensive medications but had similar frequency of coronary artery disease and diabetes as well as similar left ventricular ejection fraction. However, patients with heart failure had a

larger left atrial size and also higher left ventricular filling pressures as indicated by an E/e' >15 on transthoracic echocardiography, structural and functional markers typical for heart failure, suggesting in this cohort more likely diastolic heart failure. In patients undergoing renal artery stenting, the presence of heart failure was associated with worse outcome with 1- and 5-year mortality rates of 23 and 73 % respectively compared to 8 and 35 % in those without heart failure (Fig. 5.10) [11]. Even after adjusting for age, sex, and the degree of renal dysfunction, heart failure was significantly associated with death as well as progression to dialysis or renal transplant.

Table 5.2 Indications for renal artery revascularization: hemodynamically significant renal artery stenosis

1. With systemic hypertension that is:
(a) Accelerated
(b) Malignant
(c) In the setting of an unexplained unilateral small kidney
(d) Intolerant to medication
2. Which is atherosclerotic, bilateral and associated with progressive chronic kidney disease
3. Which is atherosclerotic, unilateral to a solitary functioning kidney and associated with progressive chronic kidney disease
4. Which is atherosclerotic and associated with recurrent unexplained heart failure or sudden unexplained pulmonary edema
5. Which is atherosclerotic and associated with unstable angina

In this study, the 50 patients with atherosclerotic RAS and heart failure undergoing percutaneous transluminal renal angioplasty and stenting were matched 1:1 with patients medically managed [11]. Despite similar patient characteristics with the exception of age (slightly younger in the revascularized group), renal artery stenting was associated with improved blood pressure control and use of less antihypertensive medications. While renal outcomes were similar, more patients in the revascularized group were able to start an ACE inhibitor for left ventricular systolic dysfunction (EF <40 %) due to improved renal function (20 % increase in glomerular filtration rate). Renal artery stenting was not associated with a reduction in mortality but was associated with better heart failure control and a fivefold reduction in hospital admissions (Fig. 5.11a–c) [11]. The effect on hospitalizations was seen early after the procedure and persisted for 3 years of follow up. After adjustment for age, sex, renal function, and heart failure functional class, the strongest predictor of hospital admission was whether or not the patient received renal artery stenting with a benefit seen in the stented group. The study highlights several important points regarding heart failure and atherosclerotic RAS. Heart failure is common in the setting of RAS and RA revascularization appears to lead to improved control of heart failure as evidenced by a reduction in hospital admissions and improvement in NYHA heart failure class.

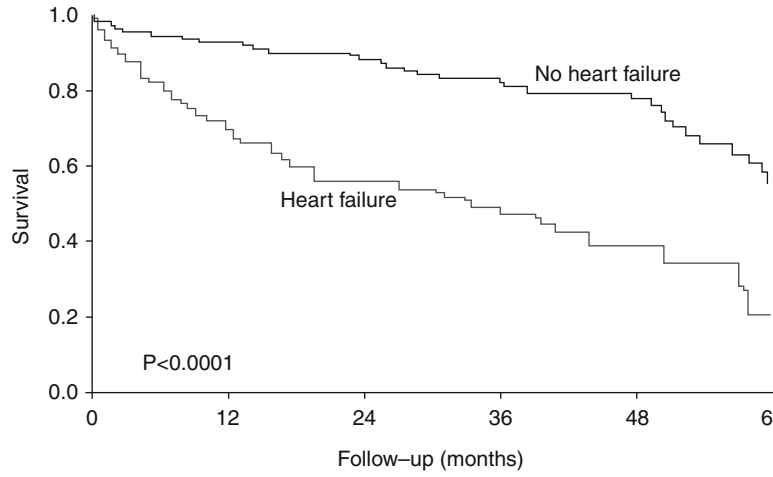


Fig. 5.10 Significance of heart failure in the setting of renal artery stenosis (*RAS*). In a cohort of patients with atherosclerotic RAS undergoing percutaneous renal artery revascularization, heart failure is associated with increased long-term mortality ($P < 0.0001$) (With permission from Kane et al. [11])

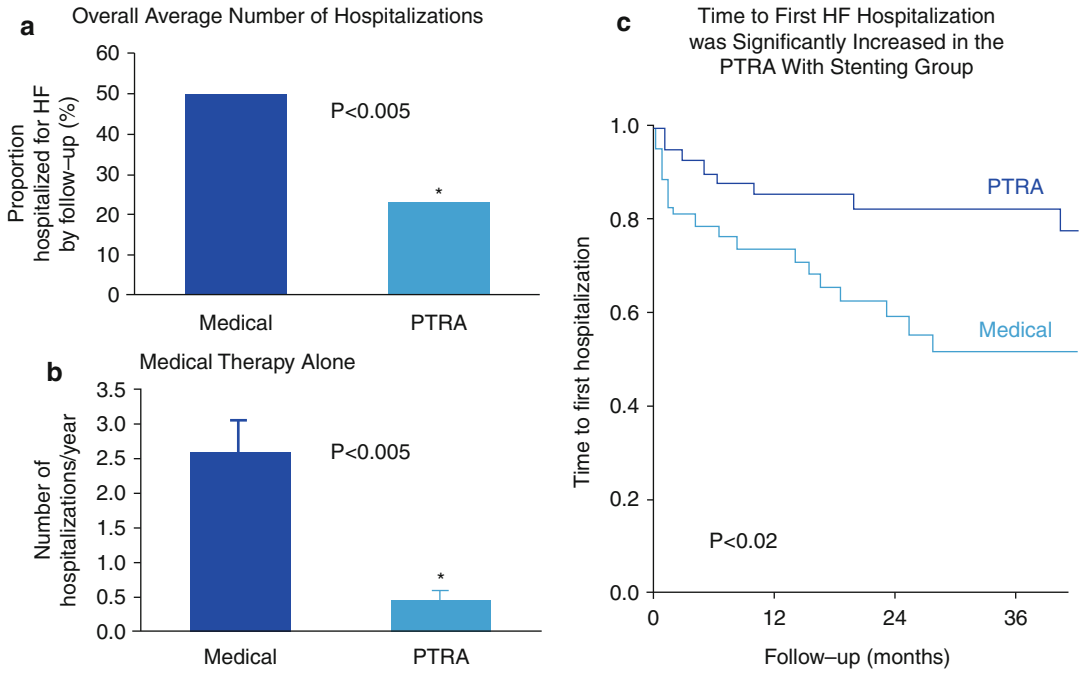


Fig. 5.11 (**a**–**c**) Renal artery revascularization and heart failure outcomes. Renal artery revascularization associated with a reduction in the proportion of patients hospitalized for heart failure (*HF*) (**a**) and the overall average number of hospitalizations (**b**) compared to medical therapy alone. The time to first HF hospitalization was significantly increased in the PTRA with stenting group (**c**). *P < 0.05 (With permission from Kane et al. [11])

These data are further supported by a recent systematic review where van den Berg et al. suggested a benefit towards percutaneous renal revascularization in patients with congestive heart failure or flash pulmonary edema [47]. The study included 19 case reports and six single center case series and retrospective studies, although did not include the Mayo Clinic data (Table 5.3) [47]. A total of 79 patients who had both renal artery stenosis and flash pulmonary edema were included in analysis. The majority of patients (85 %) had bilateral stenosis or stenosis to a solitary kidney. Following percutaneous RA revascularization, 72 % of patients (54/75) had no recurrence of flash pulmonary edema. In most episodes of recurrent flash pulmonary edema, RA restenosis was documented. Studies of revascularization of renal artery stenosis in heart failure patients are limited. Kane et al. [11] investigated the largest cohort to date while Gray et al. [72] identified 39 patients who received percutaneous renal artery stenting for recurrent flash pulmonary edema and heart failure symptoms. Revascularization led to a dramatic decrease in heart failure functional class and hospitalizations. According to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [73], the quality of the evidence is low and the strength of recommendation is weak in favor of renal artery revascularization for patients with flash pulmonary edema and atherosclerotic RAS and in patients with heart failure and atherosclerotic RAS [47]. Ideally, a randomized clinical trial would be designed for patients who present with heart failure and flash pulmonary edema in the setting of renal artery stenosis where patients would randomize to percutaneous renal artery revascularization versus medical management. The ASTRAL study failed to address this topic. The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial may partially help answer this question in a study of up to 1,080 patients with ≥60 % stenosis of the renal artery [74].

Table 5.3 Effect of angioplasty on the number of episodes of flash edema, serum creatinine and blood pressure

Authors and year of publication	Cases (no.)	Renal artery stenosis	No. of episodes of pulmonary edema before intervention	Intervention	Follow-up in months, mean (range)	No. of episodes of pulmonary edema after intervention	Change in serum creatinine (μmol/L) after intervention	Change in BP (mmHg) after intervention
Pelta et al. [48]	8	4 bilateral 4 unilateral	1 in 2 patients >1 in 6 patients	PTRA and stent; not clear how many unilateral/ bilateral	16.4 (3–27)	1 in 2 patients 0 in 6 patients	–	–
Noh et al. [49]	1	Unilateral	1	Stent	–	0	–	260/140 to 'normal'
Islam et al. [50]	1	Bilateral	2	PTRA and stent bilateral	–	0	−486	–
Kanamori et al. [51]	1	Bilateral	1	PTRA + stent right and stent left	–	0	−522	190/100 to 140/90
Chysochou et al. [52]	1	Solitary functioning kidney	1	PTRA + stent	8	–	−479 after hemodialysis and another −55 during follow-up	–
Wierema and Yaqoob [53]	4	3 lateral 1 unilateral	–	Stent in all, bilateral in 2/4	(1–94)	Relief	+27 (mean)	147/80 to 122/80 (mean)
Wykrzykowska et al. [54]	1	Unilateral	1	PTRA + stent	6	1	−159	SBP 200 to 160
Bali et al. [55]	1	Bilateral	Multiple	PTRA and stent bilateral	48	0	−115	146/98 to 'normal'
Kumar [56]	1	Bilateral	4	PTRA + stent right and stent left	3	0	−44	–
Vohra et al. [57]	1	Unilateral	1	PTRA and stent right	6	2	–	–
Pun et al. [58]	2	1 solitary functioning kidney 1 solitary kidney	2 1	PTRA + stent PTRA + stent	4 –	0 0	−250 after hemodialysis and another −10 during follow up −240	– –
Bittl et al. [59]	1	Bilateral	1	PTRA and stent bilateral	–	–	−88	'Improved'
Kiykim et al. [60]	1	Solitary functioning kidney	2	PTRA	8	–	362 to normal	195/115 to 'acceptable'
Aslam et al. [61]	1	Unilateral	Multiple	PTRA + stent	10	1	−53	240/110 to 'well controlled'
Basaria et al. [62]	1	Bilateral	Multiple	PTRA + stent bilateral	36	0	0	'Hypertensive' to 'normal'

(continued)

Table 5.3 (continued)

Authors and year of publication	Cases (no.)	Renal artery stenosis	No. of episodes of pulmonary edema before intervention	Intervention	Follow-up in months, mean (range)	No. of episodes of pulmonary edema after intervention	Change in serum creatinine (μmol/L) after intervention	Change in BP (mmHg) after intervention
Shamaieleh [63]	1	Bilateral	9	Stent bilateral	12	0	−88	–
Walker et al. [64]	1	Unilateral	4	PTRA	–	–	–	–
Missouris et al. [65]	8	8 bilateral	–	4 PTRA unilateral 4 bilateral	(2–38)	0	−7 to −70 (range) +14 in 1 patient	192/91 to 151/83 (mean)
Bloch et al. [66]	27	23 bilateral and 4 with solitary functioning kidney	≥1 in all patients	Stent, not clear how many unilateral/bilateral	18.4 (1–52)	Bilateral 17/22: 0, 5/22: ≥1 episodes of pulmonary edema Unilateral: 1/3: 0, 2/3: ≥1 episodes of pulmonary edema	17/22L −42 (mean); no statistically significant improvement in 5 patients with recurrence of flash edema after stenting	17/22: SBP 186 to 151, DBP 88 to 81 (mean); no statistically significant improvement in 5 patients with recurrence of flash edema after stenting
Nunez et al. [67]	1	Bilateral	Multiple	PTRA + stent bilateral	6	0	–	–
Planken et al. [68]	1	Solitary kidney	1	PTRA	6	0	−510	210/120 to 'normal'
Kwan et al. [69]	1	Bilateral	3	PTRA + stent bilateral 18	18	0	–	–
Messina et al. [70]	1	Solitary functioning kidney	Multiple	PTRA right and nephrectomy left	52	–	−97	230/110 to 120/80
Palmar et al. [71]	1	Solitary functioning kidney	3	PTRA	–	–	–	230/125 to 180/100
Pickering et al. [39]	11	7 bilateral 2 solitary kidney 2 unilateral	Multiple	PTRA unilateral in 8 patients (surgical revascularization in 3 patients)	6	0 (10/11)	−116 (mean) deterioration of renal function in 1 patient	−49/−27 (mean)

With permission from van den Berg et al. [47]

The majority of patients with atherosclerotic RAS have abnormal left ventricular structure and function compared to age and sex matched controls with chronic kidney disease. In a study of 79 patients with atherosclerotic RAS, only 4 (5.1 %) patients were free of systolic or diastolic dysfunction, regional wall motion abnormalities, or left ventricular hypertrophy [13]. In the cohort, 77 % of patients had congestive heart failure with echocardiographic evidence of diastolic dysfunction demonstrated in 75 % of patients. Diminished glomerular filtration rate, bilateral atherosclerotic RAS, high 24-h systolic blood pressure, and mean high 24-h mean arterial pressure predicted the presence of left ventricular hypertrophy. Those patients with diabetes and atherosclerotic RAS also were more likely to have dilated left ventricles, left ventricular hypertrophy, and a greater prevalence of diastolic dysfunction. Furthermore, patients with bilateral atherosclerotic RAS had a greater likelihood of clinically significant heart failure compared with unilateral disease (68 % of bilateral disease versus 37 % unilateral disease). Longitudinal follow-up in 51 of the patients (65 %) demonstrated progression to left ventricular hypertrophy in (eccentric > concentric) in a small proportion of patients (72 % at baseline, 81 % at 1-year). Left ventricular dimensions increased over time. The presence of left ventricular hypertrophy with worsening hypertrophy over time likely represents a maladaptive process from chronic exposure to high blood pressure and contributes to development of diastolic heart failure [75].

Data suggest that RA revascularization may regress left ventricular mass in men and women over time [76]. In 84 patients with either unilateral or bilateral renal artery stenosis of >60 %, balloon angioplasty and/or renal artery stenting resulted in a reduction of systolic blood pressure by 6 mmHg and a reduction in left ventricular mass (179 ± 49 g baseline versus 141 ± 31 g at 1-year follow up). Similarly, a smaller study of 20 patients with renovascular disease and pre/post-operative echocardiograms underwent renal artery revascularization [77]. Left ventricular systolic dysfunction (EF <50 %) was present in 2 of 20 patients at baseline while diastolic dysfunction was more commonly seen in 15 of 20 patients after exclusion of patients with significant mitral regurgitation. Post-revascularization follow up occurred over 6–12 months and demonstrated a marked reduction in left ventricular mass index but no change in diastolic function. Both studies demonstrated the presence of significant and pathologic left ventricular remodeling in patients with atherosclerotic RAS but also highlight reversibility to some degree. Whether the change translates to fewer patients progressing to overt systolic or diastolic heart failure and future heart failure hospital admissions is yet to be determined.

The pathophysiology of RAS varies depending on the presence of unilateral or bilateral disease. In unilateral disease, renal hypoperfusion causes increased renin release from the ischemic kidney. Renin then converts angiotensinogen to angiotensin I which is subsequently cleaved to angiotensin II by angiotensin-converting enzyme. Given angiotensin II-induced vasoconstriction and aldosterone release ensue along with a cascade of cardiovascular changes as a result of increased arterial pressure, increased sodium and fluid retention. The unaffected kidney attempts to compensate for the volume overload by stimulated pressure diuresis but is most often unsuccessful (Fig. 5.12). The mechanism of hypertension in bilateral renal artery stenosis or stenosis in the setting of a solitary kidney is classically volume-dependent. Sodium and fluid retention suppresses renin activity over time as the body lacks a compensatory mechanism (i.e., unaffected kidney) [78, 79]. However, with excessive diuresis, bilateral renal artery stenosis can convert to a renin-dependent hypertension with diuretic resistance which is commonly seen in patients treated for heart failure exacerbations. Underlying mechanisms of acute and chronic heart dysfunction implicate renin-angiotensin-aldosterone system activation, sympathetic activation, electrolyte derangements, endothelial dysfunction, hypertension, and pathologic cardiovascular maladaptation (e.g., medial vascular and cardiac myocyte hypertrophy and accelerated atherosclerosis).

In summary, renal artery stenosis commonly co-exists with systolic and/or diastolic heart

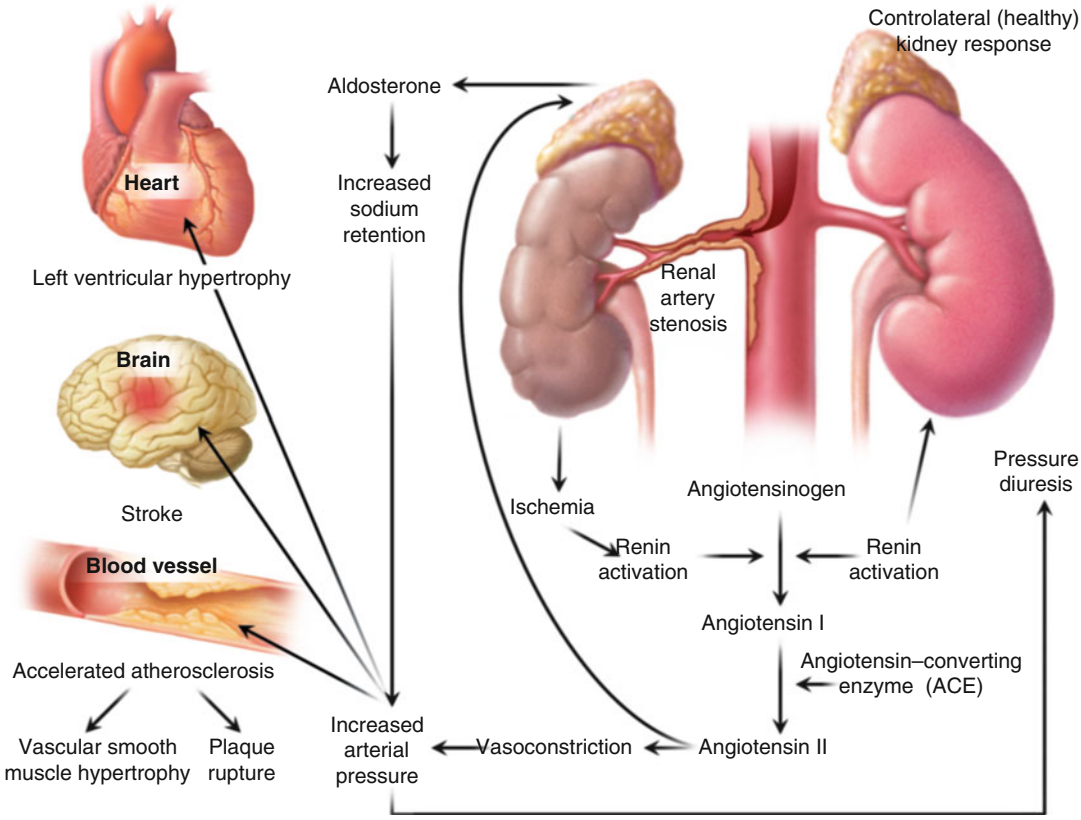


Fig. 5.12 Pathophysiologic implications of renal artery stenosis (With permission from Fenstad and Kane [80])

failure (a form of cardiorenal syndrome). The presence of both heart failure and renal artery stenosis portends a poor prognosis and is responsible for resistant hypertension, left ventricular hypertrophy, accelerated atherosclerosis, flash pulmonary edema, symptom exacerbations, and frequent heart failure hospitalizations. The pathophysiology relates to sympathetic activation, renin-angiotensin-aldosterone system activation, fluid and sodium retention, angiotensin-dependent vasoconstriction with often unsuccessful pressure diuresis from the unaffected kidney, and diuretic resistance. Although renal revascularization reduces admissions for heart failure, optimal long-term treatment remains controversial owing to the lack of robust randomized controlled studies involving renal revascularization versus medical therapy.

References

1. Roger VL, et al. Heart disease and stroke statistics–2012 update: a report from the American Heart Association. Circulation. 2012;125(1):e2–220.
2. Roger VL, et al. Trends in heart failure incidence and survival in a community-based population. JAMA. 2004;292(3):344–50.
3. Biermann J, et al. Economic burden of patients with various etiologies of chronic systolic heart failure analyzed by resource use and costs. Int J Cardiol. 2012;156(3):323–5.
4. Lee WC, et al. Economic burden of heart failure: a summary of recent literature. Heart Lung. 2004; 33(6):362–71.
5. Chen J, et al. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998–2008. JAMA. 2011; 306(15):1669–78.
6. Ho KK, et al. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol. 1993;22 (4 Suppl A):6A–13.

7. Kane GC, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. JAMA. 2011;306(8):856–63.
8. Levy D, et al. The progression from hypertension to congestive heart failure. JAMA. 1996;275(20):1557–62.
9. Rihal CS, Mayo Clinic, et al. Incidental renal artery stenosis among a prospective cohort of hypertensive patients undergoing coronary angiography. Mayo Clin Proc. 2002;77(4):309–16.
10. Conlon PJ, et al. Severity of renal vascular disease predicts mortality in patients undergoing coronary angiography. Kidney Int. 2001;60(4):1490–7.
11. Kane GC, et al. Renal artery revascularization improves heart failure control in patients with atherosclerotic renal artery stenosis. Nephrol Dial Transplant. 2010;25(3):813–20.
12. Rimoldi SF, et al. Flash pulmonary edema. Prog Cardiovas Dis. 2009;52(3):249–59.
13. Wright JR, et al. Left ventricular morphology and function in patients with atherosclerotic renovascular disease. J Am Soc Nephrol. 2005;16(9):2746–53.
14. Smith GL, et al. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol. 2006;47(10):1987–96.
15. McAlister FA, et al. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation. 2004;109(8):1004–9.
16. Bibbins-Domingo K, et al. Racial differences in incident heart failure among young adults. N Engl J Med. 2009;360(12):1179–90.
17. Dunlay SM, et al. Risk factors for heart failure: a population-based case–control study. Am J Med. 2009;122(11):1023–8.
18. Abraham WT, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Am Coll Cardiol. 2005; 46(1):57–64.
19. Logeart D, et al. Transient worsening of renal function during hospitalization for acute heart failure alters outcome. Int J Cardiol. 2008;127(2):228–32.
20. Dunlay SM, et al. Hospitalizations after heart failure diagnosis a community perspective. J Am Coll Cardiol. 2009;54(18):1695–702.
21. Rubenstein MH, et al. Are patients with renal failure good candidates for percutaneous coronary revascularization in the new device era? Circulation. 2000; 102(24):2966–72.
22. Wright RS, et al. Acute myocardial infarction and renal dysfunction: a high-risk combination. Ann Intern Med. 2002;137(7):563–70.
23. Berger AK, Duval S, Krumholz HM. Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. J Am Coll Cardiol. 2003; 42(2):201–8.
24. Ronco C, et al. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. Eur Heart J. 2010;31(6):703–11.
25. Goldberg A, et al. Inhospital and 1-year mortality of patients who develop worsening renal function following acute ST-elevation myocardial infarction. Am Heart J. 2005;150(2):330–7.
26. Jose P, et al. Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. J Am Soc Nephrol. 2006;17(10): 2886–91.
27. Hillege HL, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation. 2006;113(5):671–8.
28. Forman DE, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol. 2004;43(1):61–7.
29. Krumholz HM, et al. Correlates and impact on outcomes of worsening renal function in patients > or =65 years of age with heart failure. Am J Cardiol. 2000;85(9):1110–3.
30. Heywood JT, et al. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. J Card Fail. 2007;13(6):422–30.
31. Ahmed A, et al. Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity matched study. Am J Cardiol. 2007;99(3): 393–8.
32. Dimopoulos K, et al. Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease. Circulation. 2008;117(18): 2320–8.
33. de Silva R, et al. Epidemiology, associated factors, and prognostic outcomes of renal artery stenosis in chronic heart failure assessed by magnetic resonance angiography. Am J Cardiol. 2007;100(2):273–9.
34. Kalra PA, et al. Atherosclerotic renovascular disease in United States patients aged 67 years or older: risk factors, revascularization, and prognosis. Kidney Int. 2005;68(1):293–301.
35. Kalra PA, et al. Atherosclerotic renovascular disease in the United States. Kidney Int. 2010;77(1):37–43.
36. Bourantas CV, et al. Renal artery stenosis: an innocent bystander or an independent predictor of worse outcome in patients with chronic heart failure? A magnetic resonance imaging study. Eur J Heart Fail. 2012;14(7):764–72.
37. Kuroda S, et al. Prevalence of renal artery stenosis in autopsy patients with stroke. Stroke. 2000;31(1):61–5.
38. Garovic VD, Kane GC, Schwartz GL. Renovascular hypertension: balancing the controversies in diagnosis and treatment. Cleve Clin J Med. 2005;72(12):1135–44. 1146–7.
39. Pickering TG, et al. Recurrent pulmonary oedema in hypertension due to bilateral renal artery stenosis: treatment by angioplasty or surgical revascularisation. Lancet. 1988;2(8610):551–2.
40. Missouris CG, Belli AM, MacGregor GA. "Apparent" heart failure: a syndrome caused by renal artery stenoses. Heart. 2000;83(2):152–5.

41. Messerli FH, et al. Flash pulmonary oedema and bilateral renal artery stenosis: the Pickering syndrome. Eur Heart J. 2011;32(18):2231–5.
42. Hirsch AT, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006;113(11):e463–654.
43. Rooke TW, et al. 2011 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2011;58(19):2020–45.
44. Wheatley K, et al. Revascularization versus medical therapy for renal-artery stenosis. N Engl J Med. 2009;361(20):1953–62.
45. Blum U, et al. Treatment of ostial renal-artery stenoses with vascular endoprostheses after unsuccessful balloon angioplasty. N Engl J Med. 1997;336(7):459–65.
46. Henry M, et al. Stents in the treatment of renal artery stenosis: long-term follow-up. J Endovas Surg. 1999;6(1):42–51.
47. van den Berg DT, et al. The efficacy of renal angioplasty in patients with renal artery stenosis and flash oedema or congestive heart failure: a systematic review. Eur J Heart Fail. 2012;14(7):773–81.
48. Pelta A, et al. Flash pulmonary edema in patients with renal artery stenosis - the Pickering syndrome. Blood Press. 2010;20:15–9.
49. Noh HJ, et al. Flash pulmonary edema in a patient with unilateral renal artery stenosis and bilateral functioning kidneys. Korean Circ J. 2010;40:42–5.
50. Islam MA, et al. Percutaneous revascularization of occluded renal arteries in the setting of acute renal failure. Vasc Med. 2009;14:365–9.
51. Kanamori H, et al. Improvement of renal function after opening occluded atherosclerotic renal arteries. J Invasive Cardiol. 2009;21:E171–4.
52. Chrysochou C, et al. Anuric acute renal failure and pulmonary oedema: a case for urgent action. Int J Cardiol. 2009;132:e31–3.
53. Wierema TK, Yaqoob MM. Renal artery stenosis in chronic renal failure: caution is advised for percutaneous revascularization. Eur J Intern Med. 2008;19:276–9.
54. Wykrzkowska JJ, Williams M, Laham RJ. Stabilization of renal function, improvement in blood pressure control and pulmonary edema symptoms after opening a totally occluded renal artery. J Invasive Cardiol. 2008;20:E26–9.
55. Bali HK, Jha V. Nephrotic syndrome and recurrent pulmonary oedema in bilateral atherosclerotic renal artery stenosis: resolution following renal angioplasty and stenting. Natl Med J India. 2006;19:253–4.
56. Kumar SC. Bilateral renal artery stenosis presenting as flash pulmonary edema. J Assoc Physicians India. 2006;54:651–4.
57. Vohra HA, et al. Flash pulmonary edema manifesting for the first time after cardiac surgery: case report. Heart Surg Forum. 2005;8:E69–71.
58. Pun E, Dowling RJ, Mitchell PJ. Acute presentations of a renal artery stenosis in three patients with a solitary functioning kidney. Australas Radiol. 2004;48:523–7.
59. Bittl JA, Hirsch AT. Concomitant peripheral arterial disease and coronary artery disease: therapeutic opportunities. Circulation. 2004;109:3136–44.
60. Kiykim AA, et al. Two episodes of anuria and acute pulmonary edema in a losartan-treated patient with solitary kidney. Heart Vessels. 2004;19:52–4.
61. Aslam MS, Balasubramanian J, Greenspahn BR. Brachytherapy for renal artery in-stent restenosis. Catheter Cardiovasc Interv. 2003;58:151–4.
62. Basaria S, Fred HL. Images in cardiovascular medicine. Flash pulmonary edema heralding renal artery stenosis. Circulation. 2002;105:899.
63. Shamaieleh Q. Bilateral renal artery stenting in a patient with recurrent flash pulmonary edema. J Res Med Sci. 2002;9:56–8.
64. Walker F, Walker DA, Nielsen M. Flash pulmonary oedema. Lancet. 2001;358:556.
65. Missouris CG, Belli AM, MacGregor GA. 'Apparent' heart failure: a syndrome caused by renal artery stenoses. Heart. 2000;83:152–5.
66. Bloch MJ, et al. Prevention of recurrent pulmonary edema in patients with bilateral renovascular disease through renal artery stent placement. Am J Hypertens. 1999;12:1–7.
67. Nunez E, White CJ. Renal artery stent implantation in a patient with bilateral renal artery stenoses presenting with flash pulmonary edema. Int J Cardiovasc Intervent. 1998;1:49–53.
68. Planken II, Rietveld AP. Rapid onset pulmonary edema (flash edema) in renal artery stenosis. Neth J Med. 1998;52:116–9.
69. Kwan T, et al. Pulsus alternans in diastolic left ventricular dysfunction—a case report. Angiology. 1997;48:1079–85.
70. Messina LM, et al. Renal revascularization for recurrent pulmonary edema in patients with poorly controlled hypertension and renal insufficiency: a distinct subgroup of patients with arteriosclerotic renal artery occlusive disease. J Vasc Surg. 1992;15:73–80.

71. Palmar AH, Defeyter IR, Vandenbogaerde JF. Renal arterial stenosis as a cause of high output cardiac failure. Int J Cardiol. 1989;22:404–6.
72. Gray BH, et al. Clinical benefit of renal artery angioplasty with stenting for the control of recurrent and refractory congestive heart failure. Vasc Med. 2002; 7(4):275–9.
73. Guyatt GH, et al. Going from evidence to recommendations. BMJ. 2008;336(7652):1049–51.
74. Cooper CJ, et al. Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: rationale and design of the CORAL trial. Am Heart J. 2006;152(1):59–66.
75. Wright JR, et al. Progression of cardiac dysfunction in patients with atherosclerotic renovascular disease. QJM. 2009;102(10):695–704.
76. Rzeznik D, et al. Effect of renal artery revascularization on left ventricular hypertrophy, diastolic function, blood pressure, and the one-year outcome. J Vasc Surg. 2011;53(3):692–7.
77. Corriere MA, et al. Changes in left ventricular structure and function following renal artery revascularization. Ann Vasc Surg. 2010;24(1):80–4.
78. Brunner HR, et al. Hypertension of renal origin: evidence for two different mechanisms. Science. 1971;174(4016):1344–6.
79. Goldblatt H, et al. Studies on experimental hypertension: I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. J Exp Med. 1934;59(3):347–79.
80. Fenstad ER, Kane GC. Update on the management of atherosclerotic renal artery disease. Minerva Cardioangiol. 2009;57(1):95–101.

Part II

Pathophysiology

Models of Renovascular Disease

6

Xin Zhang and Alfonso Eirin

Abstract

Renal artery stenosis, often associated with multiple atherosclerotic risk factors, is a common cause of secondary hypertension, exacerbates cardiovascular disease, and leads to chronic renal failure. Therefore, it is critically important to elucidate the mechanisms responsible for disease progression and develop effective therapeutic strategies to treat these patients. Animal models have been extensively used as an experimental platform to mimic many features of human renovascular disease, and provide valuable information to probe its pathophysiology and downstream kidney injury. This chapter summarizes different methods used to develop and evaluate animal models of renovascular disease, often applying the Goldblatt two-kidney one-clip hypertension (2K1C) model in murine to large animal models, such as swine and canine. Finally, this chapter will examine different methods to monitor pathophysiological changes in renovascular hypertensive animal models and the use of therapeutic interventions, such as renal revascularization.

Keywords

Hypertension • Renovascular disease • Animal models • Renal artery stenosis • Renin-angiotensin system • 2K1C • Genetic engineering models • Atherosclerosis

A. Eirin, MD (✉) • X. Zhang, MD
Division of Nephrology and Hypertension,
Mayo Clinic, 200 First Street, SW, Rochester,
MN 55901, USA
e-mail: eirinmassat.alfonso@mayo.edu;
zhang.xin@mayo.edu

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_6,

Introduction

Renovascular disease is a progressive condition characterized by the narrowing or occlusion of one or both renal arteries, mainly due to atherosclerosis. Importantly, renal artery stenosis (RAS) can accelerate hypertension and renal failure, increasing cardiovascular morbidity and mortality [1]. Therefore, extensive experimental and clinical studies are important to elucidate the mechanisms underlying disease progression.

Animals have been used for many years as models of human disease, particularly for hypertension [2]. The use of animal models to mimic human renovascular disease allows the analysis of disease characteristics and its complications, facilitating development of novel therapeutic strategies. The purpose of this chapter is to summarize the main methods used to develop renovascular disease in different animal species, their features and their importance.

Two Kidney, One Clip Model

The first animal model to study hypertension was described by Goldblatt and coworkers in 1934 by partially constricting one or both renal arteries in dogs using a small adjustable silver clamp [3]. In 1938, Pickering and Prinzmetal evolved the clamps into clips to constrict the arteries in rabbit [4] and 1 year later this technique was adapted for use in rats by Wilson and Byron [5]. Since then, models of renal artery lesions have been successfully reproduced in a wide array of animals. Rats are by far the most popular species given the low cost and convenience of achieving large sample sizes in a short period of time because of their short gestation periods.

Generally, experimental models of renovascular hypertension can be established in three forms:

1. Two-kidney one-clip hypertension (2K1C) models, in which one renal artery is constricted, while the contralateral kidney increases sodium excretion as a functional response to hypertension;
2. One kidney one-clip hypertension (1K1C) models, in which one renal artery is constricted while the contralateral kidney is removed. Due to absence of compensatory increases in sodium and water excretion from the contralateral kidney, fluid is retained and the blood pressure is more dependent on sodium-fluid volume-expansion. The compensatory increase in sodium excretion from the contralateral kidney distinguishes the mechanism of hypertension in 2-kidney model from the 1-kidneys model;
3. Two-kidney two-clip hypertension (2K2C), which involves constriction of two renal arteries or the aorta above them. All of these experimental models have offered ample data on the mechanisms of development of renovascular hypertension and end-organ damage.

The unilateral RAS model (2K1C) remains fundamental for secondary form of experimental hypertension. The roles of renin-angiotensin system have been elucidated during renal artery obstruction as well as by pharmacologic blockade of the action or formation of angiotensin II. Increased release of renin and consequent formation of angiotensin II accounts for a large part of the hypertension in 2K1C. Circulating plasma renin activity (PRA) and aldosterone levels are increased most notably in the early phase of hypertension [6]. Blood pressure in experimental models of 2K1C rises gradually as a chronic response and approaches a plateau at 2 weeks after surgery. Concretely, development and persistence of hypertension in 2K1C can be separated into three theoretical temporal phases: Phase I, or the acute phase (which occurs 2–4 weeks after clipping the renal artery), and phase II, or the moderate phase (which occurs 5–9 weeks after clipping the renal artery), are both renin-dependent phases characterized by an elevation of PRA, thus indicating its prominent role in raising blood pressure. Phase III, or the chronic phase (usually observed 9 weeks or more after clipping the renal artery), is known as the volume-dependent phase during which PRA returns to normal, and hypertension is maintained by a rise in plasma volume, the action of local renin angiotensin aldosterone system (RAAS), or both [7] (Fig. 6.1). This dynamic pattern of renin-angiotensin system activation varies among species. Systemic PRA increases faster in rabbits than in rats or mice, but sustains longer in mice

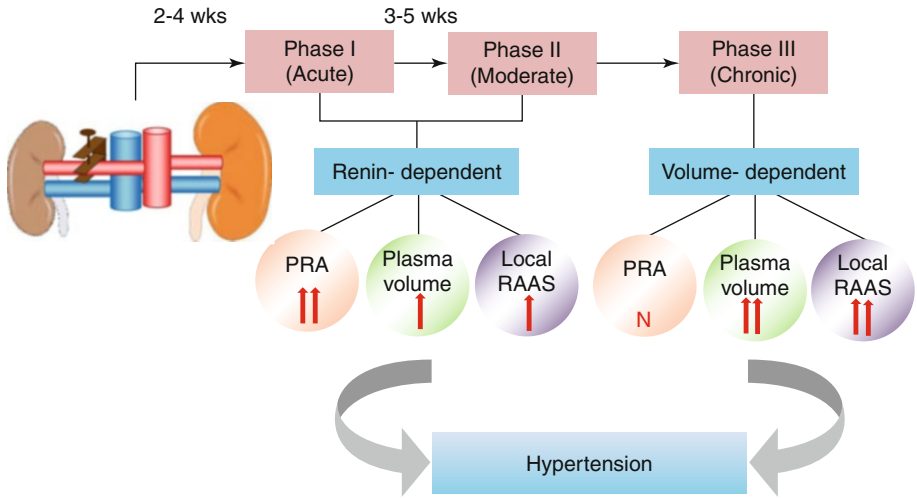


Fig. 6.1 Pathophysiological alteration during different courses of renovascular hypertension. Development of hypertension in 2K1C can be separated into three phases: Phase I, or the acute phase, occurs 2–4 weeks after clipping the renal artery, phase II, or the moderate phase, occurs 5–9 weeks after clipping the renal artery, and Phase III, or the chronic phase, usually observed 9 weeks or more after clipping the renal artery. Phase I and II are both renin-dependent and characterized by an elevation of plasma renin activity (*PRA*). Phase III is volume-dependent; PRA returns to normal during this phase, and hypertension is maintained by a rise in plasma volume resulted from local renin-angiotensin-aldosterone system (*RAAS*)

[8]. In dogs, the PRA elevates quicker, but rapid formation of collateral circulation makes this species more suitable for short duration of hypertension [9], in contrast to other species that may exhibit hypertension for many months [10–13].

Importantly, in these models, an immediate fall on renal blood flow (RBF) and markedly reduced glomerular filtration rate (GFR) characterize the affected ischemic kidney. As changing the clip diameter could produce different degrees of hypertension, the 2K1C model may also exhibit a variety of immediate renal hemodynamics changes given different grade of renal artery obstruction [14] that facilitates elucidating the pathophysiological alterations in RAS.

Genetic Mouse Models

Exploration of engineered genetic mouse models has added great value to the understanding of the roles of specific candidate system in the development of many forms of kidney disease. However, how precisely these components contribute to the pathogenesis of renovascular hypertension, particularly the downstream kidney pathology, remains to be defined, possibly due to the technical difficulty in performing surgery in small animals as well as the limited amount of sample harvested. Nevertheless, mouse models have provided critical information on the temporal evolution of kidney injury in RAS. Hitherto, few studies have implemented 2K1C in genetically modified models (gene addition or deletion). Genetic manipulation of vasoactive systems provided important information about the regulation of renovascular hypertension. Ang II type 1 receptor deficit has been shown to lower blood pressure in 2K1C mice compared to clipped wild type, while pharmacologic blockade of the AT2 receptor does not modify hypertension [15–17]. On the other hand, genetic disruption of the bradykinin B_2 receptor accelerates development of renovascular hypertension and superimposes arrhythmia [15–17], that bradykinin might protect against hypertension and its consequence. In addition, the patho-physiological role of oxidative stress have been assessed by manipulating the expression of different subunits of the reactive oxygen species forming enzyme, NAD(P)H oxidase. Gp91phox-knockout mice cause less severe hypertension, accompanied by increased

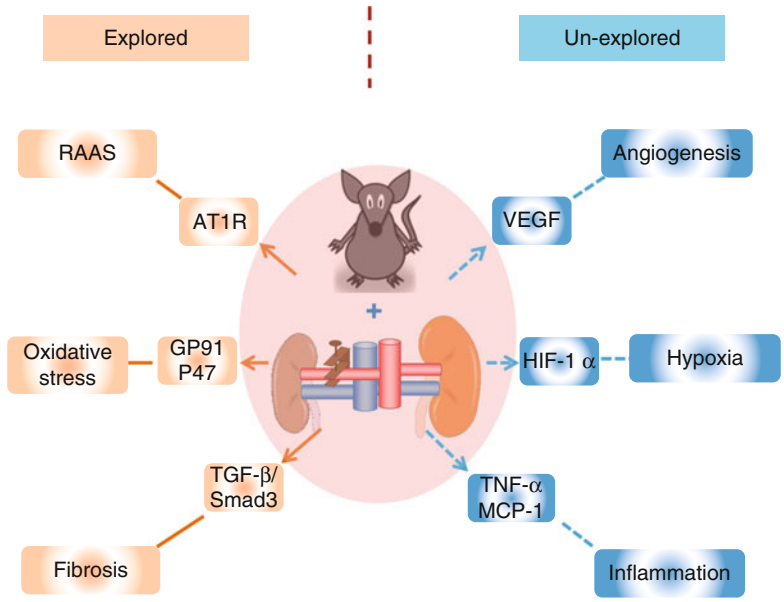


Fig. 6.2 Application of genetic engineering in two-kidney one-clip (2K1C) models. Target genes that have been explored in 2K1C are marked in *orange*. Proposed candidate genes for future investigation are marked in *blue*. As shown, genetic modification of the Angiotensin II receptor 1 (*AT1R*), NAD(P)H oxidase and Smad3 have exhibited their association with establishment of renin-angiotensin-aldosterone system (*RAAS*) associated hypertension, tissue damage and scarring. The roles of other relevant influencing genes, such as vascular endothelial growth factor (*VEGF*) and hypoxia-inducible factor (*HIF*)-1α, as well as tumor necrosis factor (*TNF*)-α and monocyte chemoattractant protein (*MCP*)-1 need to be clarified in future experiments. *TGF* tissue growth factor

endothelium-dependent relaxation to acetylcholine and vessel relaxation to nitric oxide [18]. P47 phox gene deletion additionally augments endothelial progenitor cells mobilization from the bone marrow to the kidney for tissue remodeling and repair [19]. Hence, the NAD(P)H oxidases not only aggravate hypertension, but also are linked to endothelial function and tissue repair in the post-stenotic kidney. Development of fibrosis in the clipped kidney has also been assessed using smad3 knockout, which dramatically alleviates renal fibrosis and atrophy (9 % reduction in weight) as compared to sclerotic wild-type kidneys (50 % reduction in weight) [20]. Interestingly, in a recent study using apolipoprotein E knockout mice model, establishment of 2K1C also promoted the formation of atheroma plaque in the muscular arteries (aorta and carotid artery) and upregulated monocyte chemotactic protein-1 expression in the atheroma area. As summarized in Fig. 6.2, these data have underscored the devastating effects and the potential pathways of renovascular hypertension. However, extensive studies are greatly warranted to explore the interaction of other injury factors with Ang II, including angiogenic and inflammatory factors, as well as tissue remodeling involving various target organs such as heart and brain.

Dog Models

Following the pioneering 2K1C dog model, several canine models of RAS have been described. For example, Andrei and colleagues have shown that unilateral constriction of the renal artery can be produced in the dog by progressive plication of the vessel wall with vascular sutures [21]. This process is repeated over a period of several hours until a predetermined reduction of RBF (measured with an electromagnetic flowmeter) is achieved. In contrast to other large animal models [22], optimal reduction in RBF results in a sustained increase in mean arterial pressure.

Similarly, unilateral RAS can be developed in dogs by placing an inflatable cuff around the renal artery, subsequently inflated in a series of steps over 90 min. Initially, the cuff is inflated to achieve a lower distal renal artery pressure of 60 mmHg, and further decreased to 40 mmHg over a period of 30 min. After 30 min, distal pressure is again lowered to 20 mmHg, and the cuff tubing firmly clamped. One day later, the cuff is further inflated to reduce RBF by an amount equivalent to 20 % of the value previously measured [23]. In this model, MAP is abruptly increased, remaining constantly elevated over a 25-day study period.

Swine Models

A model of unilateral RAS in swine has been achieved by placing an irritant coil in the main renal artery using fluoroscopy, which produces gradual proliferative neointimal and luminal narrowing [24]. Therefore, in this model, the development of hypertension within 5–10 days is a direct consequence of the progressive constriction of the renal artery, which produces chronic under perfusion of the renal parenchyma, developing multiple physiological characteristics of human renovascular hypertension. Importantly, the anatomy and physiology of the renal and cardiovascular system in the domestic pig are comparable to humans [25], allowing rapid translation into clinical studies. Comparable to other animal models, only a transient increase in PRA is observed, but systemic and renal oxidative stress remain elevated to sustain hypertension, influencing ischemic and hypertensive parenchymal renal injury [26]. Furthermore, hypertensive vascular changes, inflammation, fibrosis and other injurious pathways in the experimental ischemic kidney are similar to those reported in patients with severe renovascular disease [27]. Therefore, experiments using this model bear relevance and may shed light on the mechanisms underlying irreversible renal injury, helping the development of targeted interventions to preserve the stenotic kidney.

Swine Atherosclerotic RAS (ARAS) Model

Atherosclerosis is responsible for as many as 90 % of all cases of renovascular disease [28] and the presence of disseminated atherosclerosis produces additional detrimental effects that accelerate irreversible renal injury and scarring. Moreover, hypercholesterolemia and hypertension are major risk factors for coronary atherosclerosis [29] and their coexistence have important clinical implications for the pathogenesis of cardiovascular disease [30].

In 2002, superimposition of atherosclerosis on the swine RAS model was achieved by placing domestic pigs on a diet of 2 % cholesterol and 15 % lard initially at the time of RAS induction [31], and subsequently starting 6 weeks earlier. This diet increases total cholesterol, high-density lipoprotein, and low-density lipoprotein levels compared to animals fed regular pig chow [32].

Using this model, Chade and colleagues showed that coexistence of atherosclerosis and renal hypoperfusion was associated with greater renal functional impairment, compared with each condition alone [31]. Moreover, these findings were accompanied by elevated systemic and tissue oxidative stress levels, as well as proinflammatory and profibrotic changes in the stenotic kidney, suggesting a key role of atherosclerosis in accelerating and magnifying renal injury beyond the stenotic lesion. Similarly, the combination of hypercholesterolemia and hypertension accentuated myocardial [33] and contralateral kidney [34] microvascular dysfunction in this model, which were associated with alterations in systemic and myocardial tissue oxidative stress [33]. Therefore, concurrent atherosclerosis and RAS in this model facilitates identification of distinct detrimental effects on function and structure of the ARAS kidney as well as target organ injury.

Obesity and Metabolic Syndrome

Obesity is generally recognized as a chronic disease defined by excessive accumulation of fat stores in adipocytes and is frequently linked to

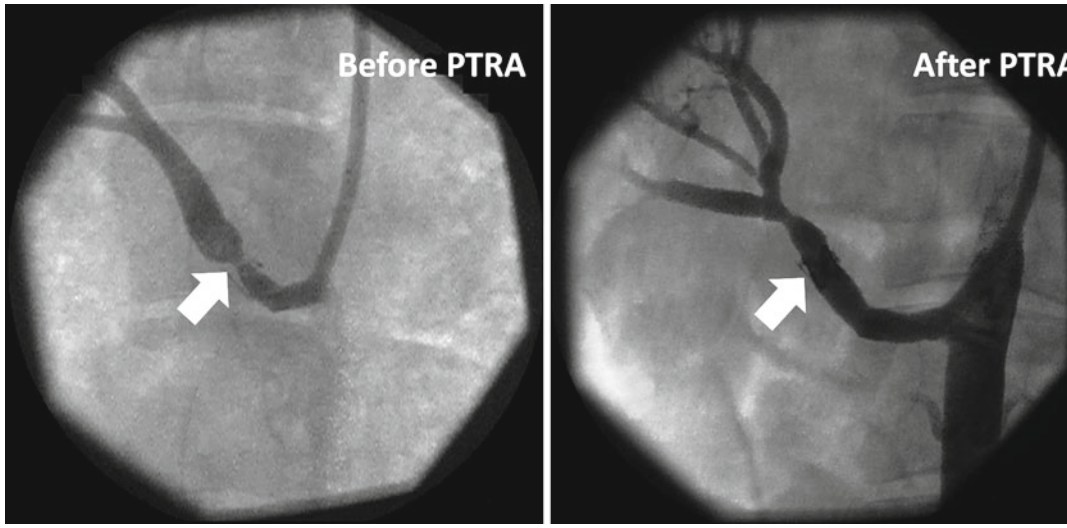


Fig. 6.3 Representative renal angiography from a pig with renal artery stenosis showing successful restoration of renal artery patency after revascularization (*arrow*). *PTRA* percutaneous transluminal renal angioplasty

inflammation in adipose tissue and insulin resistance in peripheral tissues. To date, obesity and the associated chronic inflammation and insulin resistance are among the most prevalent diseases in developed countries and impose enormous health detriments and economic burdens on the U.S. and global economies.

Importantly, obesity complicates kidney disease and may lead to poor outcomes of renovascular disease. Therefore, experimental models combining obesity and RAS may accentuate development of hypertension and/or target organ injury, providing closer simulation of the human disease. Availability of obesity-prone swine models may allow interrogating the complex interaction between obesity and RAS. For example, ossabaw pigs fed a 12–16 weeks high-fat/high-fructose diet leads to visceral adiposity (increased fat cell volume) and insulin resistance. Furthermore, we have recently shown that obesity and RAS synergistically increase renal inflammation, aggravate microvascular remodeling, and accelerates glomerulosclerosis [35]. These observations establish obesity as an important factor aggravating kidney damage in RAS, and suggest prevention of obesity and its consequence as an important strategy to combat kidney injury during chronic ischemia.

Revascularization

With the frequent use of renal revascularization in an attempt to restore renal function in RAS patients [36], an animal model amenable to angioplasty would be critical to assess this procedure. In recent years, the swine RAS model has been refined by implementing the use of percutaneous transluminal renal angioplasty and stenting (PTRA) to restore vessel patency (Fig. 6.3). In this model, restoration of blood flow is achieved by engaging a balloon catheter (on which a stent is mounted) in the proximal-middle section of the renal artery under fluoroscopic guidance, which is subsequently inflated, resulting in expansion of a tantalum stent to full balloon diameter. Then, the balloon is deflated and removed, leaving the stent embedded in the vascular wall. Although this model succeeds in decreasing blood pressure to normal levels after revascularization, renal structural and functional outcomes vary between the RAS and ARAS models. While PTRA leads to GFR recovery in non-atherosclerotic RAS pigs, it partially restores the renal microvascular network and fails to prevent renal scarring in the post-ischemic kidney [37]. Furthermore, when atherosclerosis is superimposed on RAS, microvascular rarefaction, tubulointerstitial injury, and renal dysfunction persist 4 weeks after

revascularization [32]. These observations correlate with data from large randomized clinical trials that showed no differences in renal function at follow-up between ARAS patients treated with PTRA combined with medical therapy and those treated with medical therapy alone, underscoring the clinical relevance of this experimental model.

Other Models of Renovascular Disease

Less common models of renovascular hypertension have been described in cats, rabbits, and monkeys. Perinephric compression of the renal parenchyma, first described by Page in 1939, may also lead to hypertension associated with increased activity of the renin-angiotensin aldosterone system, although extrinsic compression of the renal parenchyma represents a rare cause of secondary hypertension [38]. This model, known as "Page Kidney," is achieved by wrapping the kidney in cellophane or silk, leading to perinephritis and subsequent renal parenchymal compression. Furthermore, this model in dogs mimics many of the structural and functional characteristics observed in human heart failure (hypertrophy, fibrosis, and impaired relaxation), and has contributed to our understanding of target organ injury secondary to RAS [39]. Likewise, Nguyen et al. induced pressure overload in dogs by gradual constriction of one renal artery and studied changes in hemodynamics, cardiac dimensions, contractility indices, and circumferential wall stress over a period of 12 weeks. They found that end diastolic circumferential wall stress increased after renal artery constriction, but returned to baseline values as the heart hypertrophied, suggesting that hypertrophy normalizes end-diastolic, not peak-systolic wall stress [40].

Monitoring Pathophysiological Changes in Animal Models of RAS

Various methods have been utilized to detect decreased renal function in rodents. RBF can be measured by rotameter, electronic magnetic flow-meter, gamma scintillation probe, and more recently ultrasound and magnetic resonance imaging. Renal function can be evaluated by employing standard clearance techniques of creatinine clearance, fluorescein iso-thiocyanate conjugated inulin clearance or aminohippurate clearance, which in conjunction with urine collection through each ureter enables determination of split renal function [41].

In large animal models, physiological imaging techniques allow studying the single-kidney function and structure in vivo. These high resolution imaging tools provide a unique opportunity to assess and quantify renal tissue injury beyond the stenotic lesion, as well as target organ damage in these models. For example, multi-detector computer tomography (MDCT) is an ultra-fast scanner that can provide visualization of the stenotic kidney (Fig. 6.4), as well as quantifications of single kidney volume, regional perfusion, RBF, GFR, and tubular function. Furthermore, rescanning the animals 10 min after infusion of acetylcholine or sodium nitroprusside allows testing endothelium-dependent or independent vascular reactivity, an important determinant of renal outcomes after vascular intervention [42]. Indeed, MDCT allowed uncovering impaired urine concentration capacity in ARAS compared to RAS, probably due to greater tubular injury in these kidneys [31].

Similarly, blood oxygen level dependent MRI (BOLD-MRI) allows measurement of oxygenation in medullary and cortical regions of the kidney [43] (Fig. 6.5). The rationale for its use is supported by the fact that oxyhemoglobin is diamagnetic and has no effect on T2*, while deoxyhemoglobin is paramagnetic and decreases tissue T2*. Therefore, when the echo time of the gradient echo MRI acquisition increases, the MRI signal attenuation increases with increased concentration of deoxyhemoglobin. In addition, the change in oxygenation after systemic infusion of furosemide) can be used as a measure of oxygen-dependent tubular function. Furthermore, fractional kidney hypoxia determined by BOLD-MRI is directly related to chronically reduced blood flow and GFR in human subjects with essential and renovascular hypertension, revealing a unique potential of BOLD-MRI for assessing the severity of vascular occlusive kidney

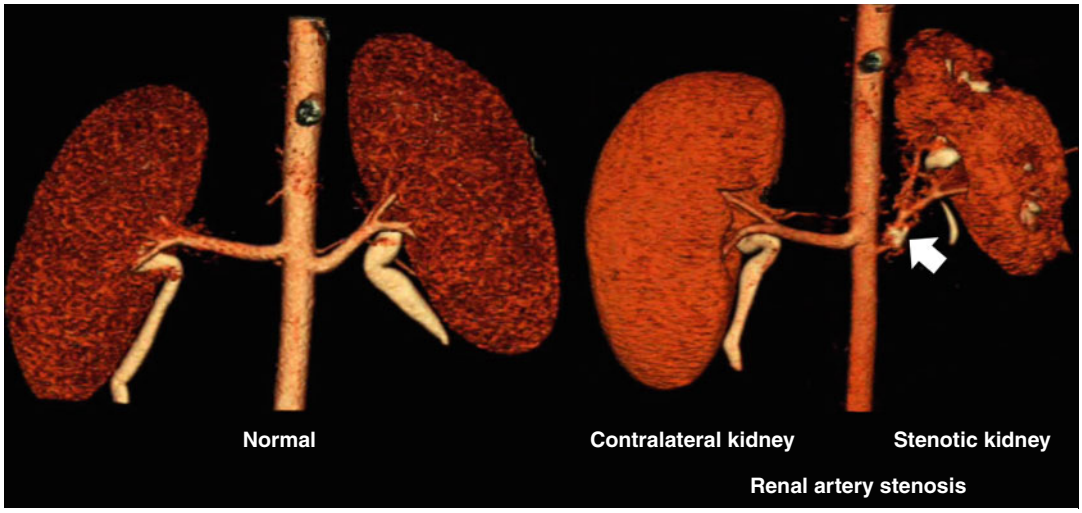


Fig. 6.4 Three-dimensional image obtained by multidetector computer tomography (*MDCT*) from a normal pig (*left*) and a pig with unilateral renal artery stenosis (*right*), demonstrating high-grade renal-artery stenosis (left kidney) after coil implantation (*arrow*). In addition, the poststenotic kidney shows increased collateral formation

disease, and potentially predicting renal functional response [44]. Indeed, BOLD-MRI has shown that despite unchanged arteriovenous oxygen gradient across stenotic kidneys, severe RAS does decrease intrarenal oxygenation and impairs tubular function [43, 45].

Micro-computed tomography (MCT) allows quantitative and qualitative analysis of the microvascular architecture of the kidney (Fig. 6.6). This technique involves of scanning at 0.5° angular increments at 6–18 μm resolution renal tissue sections previously perfused with an intravascular contrast agent [46]. Therefore, it allows assessment of the spatial density (number of vessels per tissue area), average diameter, and tortuosity (an index of angiogenesis) of microvessels (diameters <500 μm) in the renal cortex and medulla [32, 45]. Microvascular loss and increased tortuosity shown by MCT [46] lead to development of strategies tailored to restore the microcirculation [45].

Blood pressure measurements in small animals are often acquired indirectly by a tail-cuff method, but direct methods such as catheterization or telemetry transmitters are more accurate. The tail cuff method is commonly used for measuring blood pressure and pulse in rodents. In this method, tail pulse is detected by passing a tail-cuff sensor attached to an amplifier through the tail. Then, the tail is immobilized and heat transfer improved by passage of the tail through a narrow glass cylinder. Blood pressure measurements are obtained by manual inflation of the tail cuff to greater than 200 mmHg and release of the pressure. The amplified pulse is recorded and stored in a computer program that provides two tracings that start and stop at the same time. While the upper trace channel plots cuff systolic blood pressure, the lower trace channel monitors pulse pressure [47]. If used in conscious animals, it is important to firstly acclimatize them to the device, to prevent "white coat hypertension."

In addition, direct intra-arterial blood pressure can be monitored in rats and mice by placing a catheter in the left iliac artery, which is subsequently threaded to the level of the junction with the abdominal aorta. Then, the catheter is tunneled subcutaneously to exit the mouse at the nape. One day after surgery, the distal end of the catheter is connected to a transducer that records blood pressure. The amplitude and quality of the waveform trace obtained by this method permit the assessment of both systolic and diastolic pressures. Finally, blood pressure can also be monitored using a telemetry transmitter in small [48] and large [46] animal models of RAS

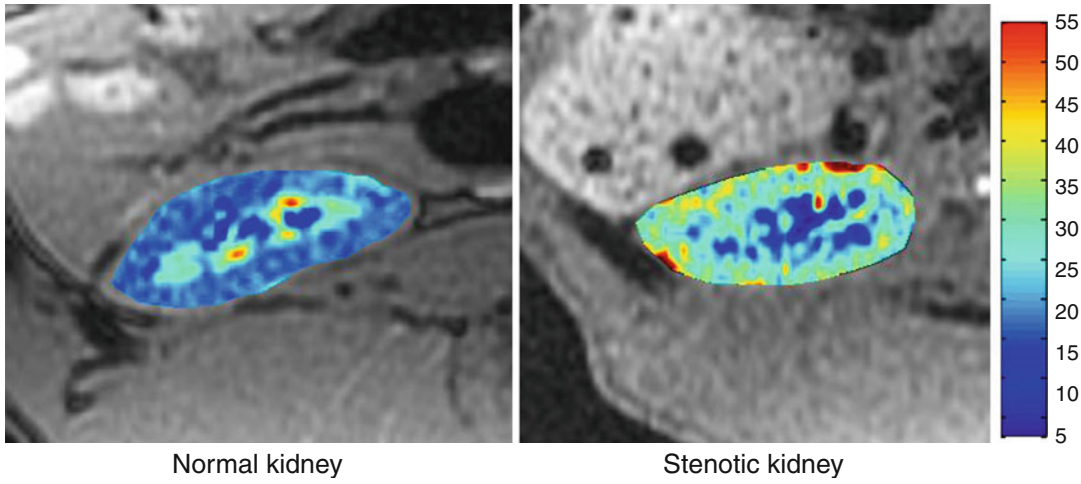


Fig. 6.5 Blood Oxygen Level-Dependent (BOLD) 3 T magnetic resonance imaging from a normal pig (*left*) and a pig with unilateral renal artery stenosis (*right*) showing hypoxic regions. The use of parametric maps (*scale*) allows quantification of R2* (level of deoxyhemoglobin). Low cortical R2* (*blue*) can be observed in the normal kidney, while the stenotic kidney shows areas of cortical and medullary deoxygenation (*red*). The medulla is physiologically more hypoxic (*green*, *yellow*) than the cortex in normal kidneys

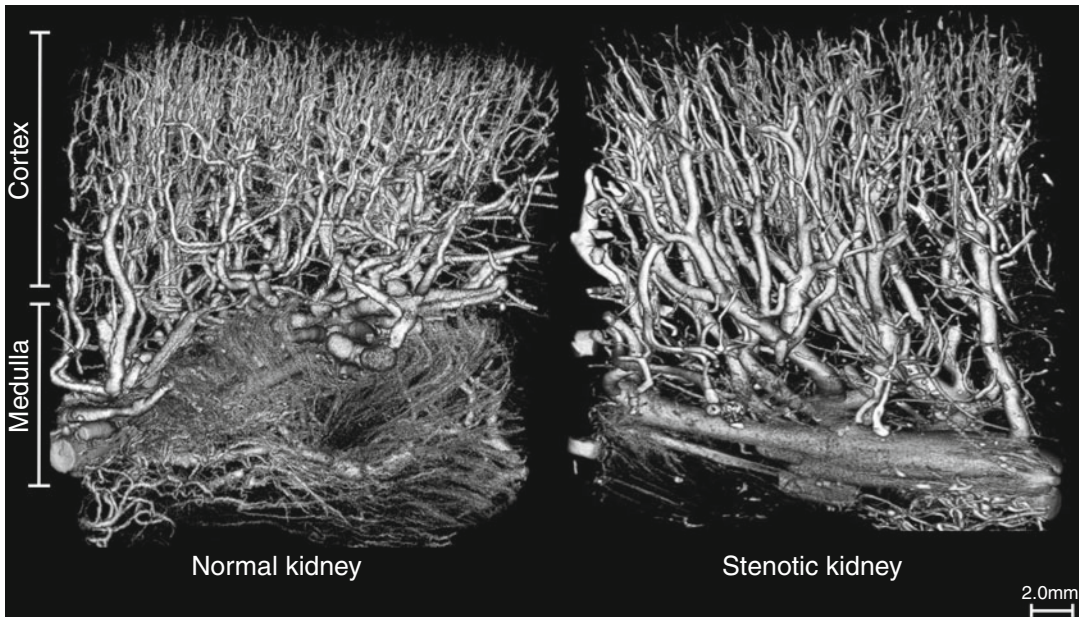


Fig. 6.6 Representative 3-dimensional tomographic images of the cortical microcirculation from a normal (*left*) and stenotic (*right*) swine kidney showing loss of cortical and medullary microvessels in the latter. The number of interlobar, arcuate, interlobular arteries, and small arterioles is reduced in the stenotic compared to the normal pig kidney

(Fig. 6.7). In pigs this device is implanted in the femoral artery at the time of RAS induction, allowing continuous daily measurement of mean arterial pressure for the duration of the study. Blood pressure can be recorded at short intervals (e.g., 5 min), and examined for diurnal variation, or averaged for more extended temporal patterns.

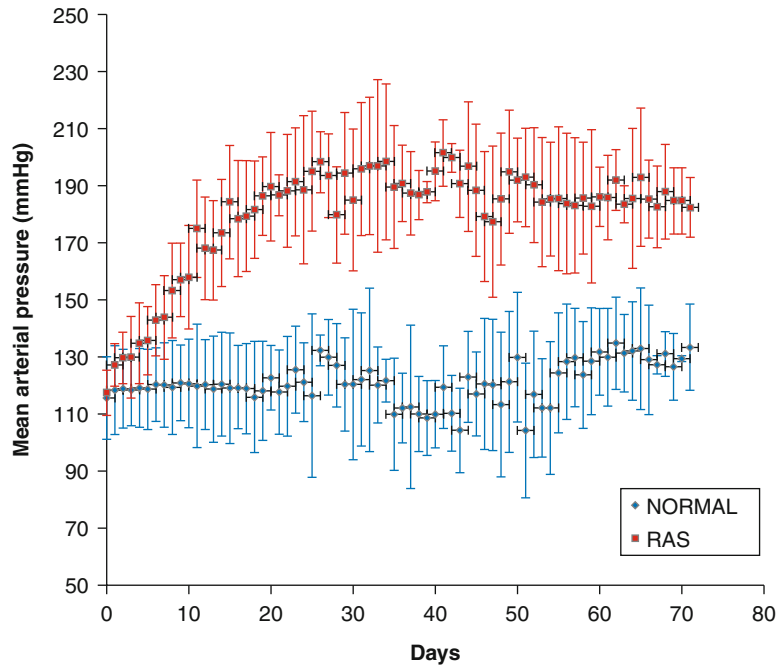


Fig. 6.7 Evolution of daily averages of mean arterial pressure measured by telemetry in normal pigs and pigs with unilateral renal artery stenosis (*RAS*) showing development of hypertension in RAS pigs within 1–2 weeks after coil implantation (at day 0)

Summary

Animal models of renovascular hypertension have provided powerful data that enriched our understanding of the mechanisms involved in the development and progression of the disease. Advantages of rodent models include the potential to explore the pathogenesis of RAS in genetically engineered animals, and practicality of using a large number of animals. However, limited tissue availability in small animal models may limit the extent of tissue studies oriented to evaluate the pathogenesis of the disease. In contrast, large animal models, like the dog or swine, mimic the chain of events and mechanisms of tissue injury observed in human RAS. Furthermore, these models have the potential to mimic myocardial injury secondary to RAS, representing unique research tools for the evaluation of the pathophysiology of renovascular disease and the development of adequate treatment strategies. Nevertheless, caution is mandated whenever translating results of studies performed in animals for implementation in humans, who, after all, constitute the optimal model of human disease.

References

1. Kalra PA, Guo H, Kausz AT, Gilbertson DT, Liu J, Chen SC, Ishani A, Collins AJ, Foley RN. Atherosclerotic renovascular disease in united states patients aged 67 years or older: risk factors, revascularization, and prognosis. Kidney Int. 2005;68:293–301.
2. Lerman LO, Chade AR, Sica V, Napoli C. Animal models of hypertension: an overview. J Lab Clin Med. 2005;146:160–73.
3. Goldblatt H, Lynch J, Hanzal RF, Summerville WW. Studies on experimental hypertension: I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. J Exp Med. 1934;59:347–79.
4. Pickering GW, Prinzmetal M. Experimental hypertension of renal origin in the rabbit. Clin Sci (Lond). 1938;3:357.
5. Wilson C, Byron FB. Renal changes in malignant hypertension: experimental evidence. Lancet. 1939;1:136–9.
6. Brunner HR, Kirshman JD, Sealey JE, Laragh JH. Hypertension of renal origin: evidence for two different mechanisms. Science. 1971;174:1344–6.
7. Martinez-Maldonado M. Pathophysiology of renovascular hypertension. Hypertension. 1991;17:707–19.
8. Amiri F, Garcia R. Renal angiotensin ii receptor regulation in two-kidney, one clip hypertensive rats: effect of ace inhibition. Hypertension. 1997;30:337–44.

9. Cerqua S, Samaan A. Cure of experimental renal hypertension. Clin Sci (Lond). 1939;40:113–8.
10. Goldblatt H, Kahn JR, Lewis HA. Studies on experimental hypertension: Xix. The production of persistent hypertension in sheep and goats. J Exp Med. 1943;77:297–307.
11. Goldblatt H. Studies on experimental hypertension: Iii. The production of persistent hypertension in monkeys (macaque) by renal ischemia. J Exp Med. 1937;65:671–5.
12. Goldblatt H. Experimental renal hypertension; mechanism of production and maintenance. Circulation. 1958;17:642–7.
13. Goldblatt H. Hypertension due to renal ischemia. Bull N Y Acad Med. 1964;40:745–58.
14. Anderson WP, Korner PI, Johnston CI. Acute angiotensin ii-mediated restoration of distal renal artery pressure in renal artery stenosis and its relationship to the development of sustained one-kidney hypertension in conscious dogs. Hypertension. 1979;1:292–8.
15. Danson EJ, Zhang YH, Sears CE, Edwards AR, Casadei B, Paterson DJ. Disruption of inhibitory g-proteins mediates a reduction in atrial beta-adrenergic signaling by enhancing enos expression. Cardiovasc Res. 2005;67:613–23.
16. Cervenka L, Horacek V, Vaneckova I, Hubacek JA, Oliverio MI, Coffman TM, Navar LG. Essential role of at1a receptor in the development of 2k1c hypertension. Hypertension. 2002;40:735–41.
17. Cohn HI, Harris DM, Pesant S, Pfeiffer M, Zhou RH, Koch WJ, Dorn 2nd GW, Eckhart AD. Inhibition of vascular smooth muscle g protein-coupled receptor kinase 2 enhances alpha1d-adrenergic receptor constriction. Am J Physiol Heart Circ Physiol. 2008; 295:H1695–704.
18. Jung O, Schreiber JG, Geiger H, Pedrazzini T, Busse R, Brandes RP. Gp91phox-containing nadph oxidase mediates endothelial dysfunction in renovascular hypertension. Circulation. 2004;109:1795–801.
19. Salguero G, Akin E, Templin C, Kotlarz D, Doerries C, Landmesser U, Grote K, Schieffer B. Renovascular hypertension by two-kidney one-clip enhances endothelial progenitor cell mobilization in a p47phox-dependent manner. J Hypertens. 2008;26:257–68.
20. Warner GM, Cheng J, Knudsen BE, Gray CE, Deibel A, Juskewitch JE, Lerman LO, Textor SC, Nath KA, Grande JP. Genetic deficiency of smad3 protects the kidneys from atrophy and interstitial fibrosis in 2k1c hypertension. Am J Physiol Renal Physiol. 2012;302:F1455–64.
21. Lupu AN, Maxwell MH, Kaufman JJ, White FN. Experimental unilateral renal artery constriction in the dog. Circ Res. 1972;30:567–74.
22. Krier JD, Crane JA, Eirin A, Zhu X-Y, Lerman A, Lerman LO. Hemodynamic determinants of perivascular collateral development in swine renal artery stenosis. Am J Hypertens. 2013;26:209–17.
23. Anderson WP, Ramsey DE, Takata M. Development of hypertension from unilateral renal artery stenosis in conscious dogs. Hypertension. 1990;16:441–51.
24. Lerman LO, Schwartz RS, Grande JP, Sheedy PF, Romero JC. Noninvasive evaluation of a novel swine model of renal artery stenosis. J Am Soc Nephrol. 1999;10:1455–65.
25. Curry 3rd BB. Animal models used in identifying gender-related differences. Int J Toxicol. 2001; 20:153–60.
26. Lerman LO, Nath KA, Rodriguez-Porcel M, Krier JD, Schwartz RS, Napoli C, Romero JC. Increased oxidative stress in experimental renovascular hypertension. Hypertension. 2001;37:541–6.
27. Keddis MT, Garovic VD, Bailey KR, Wood CM, Raissian Y, Grande JP. Ischaemic nephropathy secondary to atherosclerotic renal artery stenosis: clinical and histopathological correlates. Nephrol Dial Transplant. 2010;25:3615–22.
28. Safian RD, Textor SC. Renal-artery stenosis. N Engl J Med. 2001;344:431–42.
29. Zeiher AM, Krause T, Schachinger V, Minners J, Moser E. Impaired endothelium-dependent vasodilation of coronary resistance vessels is associated with exercise-induced myocardial ischemia. Circulation. 1995;91:2345–52.
30. Luscher TF, Tanner FC, Dohi Y. Age, hypertension and hypercholesterolaemia alter endothelium-dependent vascular regulation. Pharmacol Toxicol. 1992;70:S32–9.
31. Chade AR, Rodriguez-Porcel M, Grande JP, Krier JD, Lerman A, Romero JC, Napoli C, Lerman LO. Distinct renal injury in early atherosclerosis and renovascular disease. Circulation. 2002;106: 1165–71.
32. Eirin A, Zhu XY, Urbieta-Caceres VH, Grande JP, Lerman A, Textor SC, Lerman LO. Persistent kidney dysfunction in swine renal artery stenosis correlates with outer cortical microvascular remodeling. Am J Physiol Renal Physiol. 2011;300:F1394–401.
33. Rodriguez-Porcel M, Lerman A, Herrmann J, Schwartz RS, Sawamura T, Condorelli M, Napoli C, Lerman LO. Hypertension exacerbates the effect of hypercholesterolemia on the myocardial microvasculature. Cardiovasc Res. 2003;58:213–21.
34. Rodriguez-Porcel M, Krier JD, Lerman A, Sheedy 2nd PF, Romero JC, Napoli C, Lerman LO. Combination of hypercholesterolemia and hypertension augments renal function abnormalities. Hypertension. 2001;37:774–80.
35. Zhang X, Li ZL, Woollard JR, Eirin A, Ebrahimi B, Crane JA, Zhu XY, Pawar A, Krier JD, Jordan KL, Tang H, Textor SC, Lerman A, Lerman LO. Obesity-metabolic derangement preserves hemodynamics but promotes intra-renal adiposity and macrophage infiltration in swine renovascular disease. Am J Physiol Renal Physiol. 2013;305(3):F265–76.
36. Textor SC, Lerman L. Renovascular hypertension and ischemic nephropathy. Am J Hypertens. 2010;23: 1159–69.
37. Favreau F, Zhu XY, Krier JD, Lin J, Warner L, Textor SC, Lerman LO. Revascularization of swine renal artery stenosis improves renal function but

not the change in vascular structure. Kidney Int. 2010;78:110–8.
38. Babel N, Sakpal SV, Chamberlain RS. The page kidney phenomenon secondary to a traumatic fall. Eur J Emerg Med. 2010;17:24–6.
39. Munagala VK, Hart CY, Burnett Jr JC, Meyer DM, Redfield MM. Ventricular structure and function in aged dogs with renal hypertension: a model of experimental diastolic heart failure. Circulation. 2005;111:1128–35.
40. Nguyen TN, Chagas AC, Glantz SA. Left ventricular adaptation to gradual renovascular hypertension in dogs. Am J Physiol. 1993;265:H22–38.
41. DeForrest JM, Davis JO, Freeman RH, Watkins BE, Stephens GA. Separate renal function studies in conscious dogs with renovascular hypertension. Am J Physiol. 1978;235:F310–6.
42. Eirin A, Ebrahimi B, Zhang X, Zhu XY, Tang H, Crane JA, Lerman A, Textor SC, Lerman LO. Changes in glomerular filtration rate after renal revascularization correlate with microvascular hemodynamics and inflammation in swine renal artery stenosis. Circ Cardiovasc Interv. 2012;5:720–8.
43. Ebrahimi B, Gloviczki M, Woollard JR, Crane JA, Textor SC, Lerman LO. Compartmental analysis of renal bold mri data: introduction and validation. Invest Radiol. 2012;47:175–82.
44. Saad A, Crane J, Glockner JF, Herrmann SM, Friedman H, Ebrahimi B, Lerman LO, Textor SC. Human renovascular disease: estimating fractional tissue hypoxia to analyze blood oxygen level-dependent mr. Radiology. 2013;268(3):770–8.
45. Ebrahimi B, Li Z, Eirin A, Zhu XY, Textor SC, Lerman LO. Addition of endothelial progenitor cells to renal revascularization restores medullary tubular oxygen consumption in swine renal artery stenosis. Am J Physiol Renal Physiol. 2012;302:F1478–85.
46. Zhu XY, Chade AR, Rodriguez-Porcel M, Bentley MD, Ritman EL, Lerman A, Lerman LO. Cortical microvascular remodeling in the stenotic kidney: role of increased oxidative stress. Arterioscler Thromb Vasc Biol. 2004;24:1854–9.
47. Krege JH, Hodgin JB, Hagaman JR, Smithies O. A noninvasive computerized tail-cuff system for measuring blood pressure in mice. Hypertension. 1995;25:1111–5.
48. Lorenz JN, Lasko VM, Nieman ML, Damhoff T, Prasad V, Beierwaltes WH, Lingrel JB. Renovascular hypertension using a modified two-kidney, one-clip approach in mice is not dependent on the alpha1 or alpha2 na-k-atpase ouabain-binding site. Am J Physiol Renal Physiol. 2011;301:F615–21.

7 Macrovascular Disease: Pathobiology of Endothelial Function, Renal Artery Remodeling, and Plaque

Yoshiki Matsuo and Amir Lerman

Abstract

Atherosclerotic renal vascular disease (ARVD) is the most common cause of renal artery stenosis. Endothelial dysfunction is a systemic disorder and a critical element in the pathogenesis of atherosclerotic lesions. Endothelial dysfunction leads to ARVD, and in turn, ARVD exacerbates systemic endothelial function, establishing a vicious circle. Intravascular ultrasound demonstrates that renal artery plaques have a wide variety of atherosclerotic phenotypes including vulnerable plaque features. The plaque characteristics of the renal artery are associated with the mode of arterial remodeling. With a more detailed understanding of the pathophysiology of the renal atherosclerotic plaque, the treatment strategies for atherosclerotic renal artery disease will continue to develop.

Keywords

Endothelial dysfunction • Renal artery plaque • Remodeling • Intravascular ultrasound • Atherosclerosis • Renal artery stenosis

Endothelial Function

Endothelial Dysfunction

At one time endothelial cells were regarded as merely a passive barrier lining the lumen of the vascular beds. However, the endothelium is now recognized as the largest organ in the body that serves a number of important physiological functions. The endothelium participates in regulation of vascular smooth muscle tone, vascular permeability, leukocyte adhesion, lipid oxidation, inflammatory and immune responses, cell proliferation, angiogenesis, thrombosis, and platelet adhesion and aggregation. The endothelium regulates these processes by producing autocrine and paracrine factors such as nitric oxide (NO), prostaglandins, angiotensin II, endothelin, and other regulatory factors. These mediators provide a balance between vasodilation and vasoconstriction and thrombus and anticoagulation. NO produced by endothelial NO synthase (eNOS) or NOS III is the most potent vasodilator in the body and

Y. Matsuo, MD, PhD • A. Lerman, MD (✉)
Department of Cardiovascular Diseases,
Mayo Clinic, 200 First Street, SW,
Rochester, MN 55905, USA
e-mail: myoshikim@gmail.com;
lerman.amir@mayo.edu

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_7,

directly causes the underlying smooth muscle to relax. The endothelium synthesizes and releases NO in response to a variety of stimuli. Potent vasoconstrictors, such as angiotensin II and endothelin, antagonize the actions of NO to provide another mechanism of balance and control to endothelial modulation of vascular function [1]. The concept of endothelial vasodilator dysfunction arises from variations in blood flow observed in patients with atherosclerosis compared to healthy subjects. In healthy subjects, activation of eNOS causes vasodilation in both muscular conduit vessels and resistance arterioles. In contrast, in those with atherosclerosis, similar stimulation yields attenuated vasodilation in peripheral vessels and causes paradoxical vasoconstriction in coronary arteries, thus indicating a decrease in the bioavailability of NO [2]. Endothelial dysfunction occurs in the presence of risk factors of cardiovascular disease in the absence of atherosclerosis. Therefore, endothelial dysfunction represents a prodromal phase in the atherosclerosis process.

Development of endothelial dysfunction involves a decrease in the bioavailability of NO and an increase in production of vasoconstrictors such as such as angiotensin II, leading to an environment favorable for thrombosis and development of atherosclerosis. The endothelium produces chemokines, cytokines, and transcription factors such as nuclear factor-κB and activator protein-I that attract inflammatory cells including lymphocytes and macrophages. Decreased NO increases the tendency for lesion progression by enhancing vascular smooth muscle proliferation and migration, augmenting platelet activation, thrombosis, and pathological neovascularization, leading to formation of histologically identifiable atherosclerotic lesions. Once lesions have developed, atherosclerosis may result in a self-perpetuating process, which leads to progression of the atherosclerotic lesion and culminates in plaque rupture with arterial thrombosis.

Risk Factors for Endothelial Dysfunction

Atherosclerotic renal vascular disease (ARVD) and endothelial dysfunction share common risk factors. Given the profound involvement of endothelial dysfunction in the pathogenesis of atherosclerotic disease, most risk factors for cardiovascular disease were also found to be associated with endothelial dysfunction. These risk factors are associated with overproduction of reactive oxygen species or increased oxidative stress. These reactive oxygen species may reduce vascular NO bioavailability and promote cellular damage. Hence, increased oxidative stress is considered a major mechanism involved in the pathogenesis of endothelial dysfunction and may serve as a common pathogenic mechanism of the effect of risk factors on the endothelium [3].

ARVD as a Cause of Endothelial Dysfunction

Not only risk factors for atherosclerosis but also ARVD per se cause endothelial dysfunction. Previous studies showed that both experimental [4] and human renovascular hypertension [5] deteriorate endothelial dysfunction through production of oxidative stress [6]. ARVD leads to stimulation of the renin-angiotensin system and increased production of angiotensin II. Angiotensin II does not only cause vasoconstriction but also activate NAD(P)H oxidase, a major enzymatic source of reactive oxygen species that inactivate eNOS [7] as described previously. Therefore, ARVD leads to lower NO bioavailability and endothelial dysfunction. Endovascular revascularization for ARVD was demonstrated to lower oxidative stress and thereby improve NO bioavailability, leading to the improvement of endothelial function [8]. Accordingly, ARVD can exacerbate systemic endothelial function as well as renal dysfunction.

Special Considerations in View of ARVD

Indeed, the pathophysiology of endothelial function in ARVD is multifactorial and complex. ARVD is the most common disease of the renal arteries and associated with ischemic nephropathy, promoting chronic kidney disease progression. A previous study demonstrated that

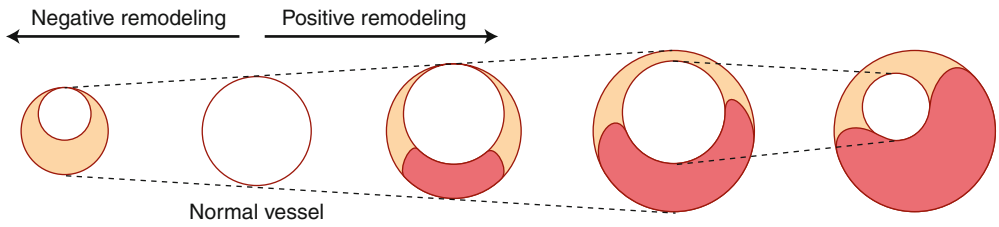


Fig. 7.1 Schematic illustration of arterial remodeling in the renal artery. In early atherosclerosis, artery size enlarges in response to the development of atherosclerotic plaques (positive remodeling). Therefore, lumen size is initially not affected by plaque growth until the lesion reaches 40 % area stenosis. Beyond this limit, a further increase in plaque decreases lumen area. A failure of the process of positive remodeling leading to shrinkage of arteries is referred to as negative remodeling

endothelial dysfunction assessed by an impaired endothelium-dependent vasodilatory response is associated with renal dysfunction in essential hypertensive patients [9]. Endothelial dysfunction, in turn, was associated with more rapid decline in glomerular filtration rate in patients with untreated hypertension and normal renal function at baseline even after adjustment for the known adverse effects of elevated systolic blood pressure [10]. This association could establish a vicious circle, which promotes the progression of both renal and vascular damage. This postulation is supported by the observation that robust microvascular endothelial function correlated with renal functional improvement after revascularization of a stenotic renal artery [11].

Renal Artery Remodeling

As the plaque develops, the entire vessel can enlarge or shrink in size. This is often referred to as vascular remodeling and plays a critical role in determining the luminal patency. In a postmortem study of coronary arteries, Glagov [12] originally described compensatory remodeling as an outward displacement of the arterial wall that compensates for the enlarging atheroma. This concept was confirmed by in vivo studies using intravascular ultrasound (IVUS) analysis. Once the plaque enlarges to accommodate more than 40 % of the vessel area, the vessel no longer enlarges and the lumen narrows as the plaque enlarges (Fig. 7.1). Likewise, all medium-sized arteries in peripheral arteries including renal, carotid, and iliac have been shown to remodel as well.

Plaque Morphology and Remodeling Pattern in ARVD

Histopathological studies demonstrated that positive remodeling is associated with infiltration of inflammatory cells, expression of pro-inflammatory cytokines, and increased protease activity [13], features which are recognized as major determinants of plaque vulnerability. On activation by interferon-gamma, macrophages within atheromatous plaques release proteolytic enzymes capable of degrading both the collagen and the muscular media, weakening the plaque fibrous cap and favoring plaque rupture. Interferon-gamma, produced by T-lymphocytes, may also contribute to the thinning of the fibrous cap by halting vascular smooth muscle cell collagen synthesis [14]. Plaques with positive remodeling are composed of lower collagen and smooth muscle cell content. In contrast, negative remodeling is associated with a stable fibrous plaque phenotype although it may aggravate narrowing of the lumen.

Recently, clinical interest has been focused on arterial remodeling in the peripheral arteries with the advent of IVUS imaging for endovascular revascularization. IVUS is the gold standard for characterization of atherosclerotic plaque on the arterial wall (Figs. 7.2 and 7.3). Conventional grayscale IVUS provides unique insight into the underlying substrate of atherosclerotic disease, and classical studies for the coronary artery have suggested the association of plaque echogenicity with histological composition despite the limitation to elucidate precise plaque components. Recently, advanced imaging techniques

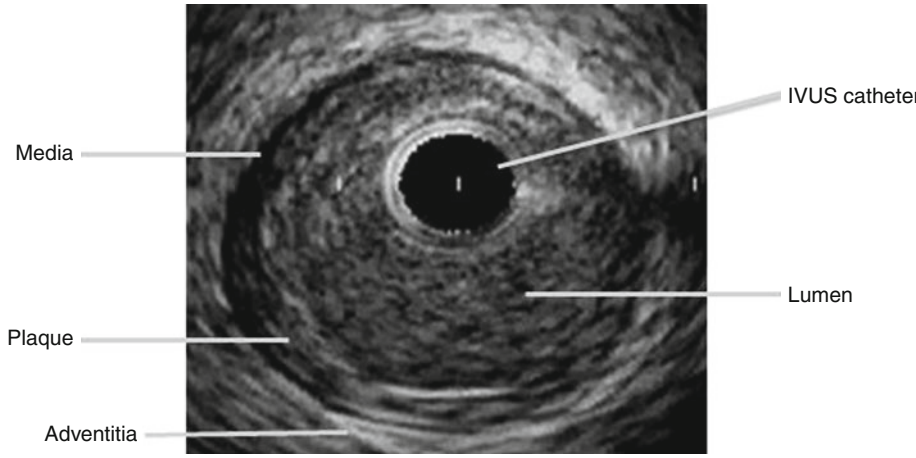


Fig. 7.2 A typical IVUS image of mild atherosclerotic plaque. A plaque with atherosclerotic change demonstrates three-layered appearance. The intima is identified if there is intimal hyperplasia (*plaque*). Media is made of homogeneous smooth muscle cells and does not reflect ultrasound (*dark*), and adventitia is collagen-rich reflecting ultrasound (*bright*). *IVUS* indicates intravascular ultrasound

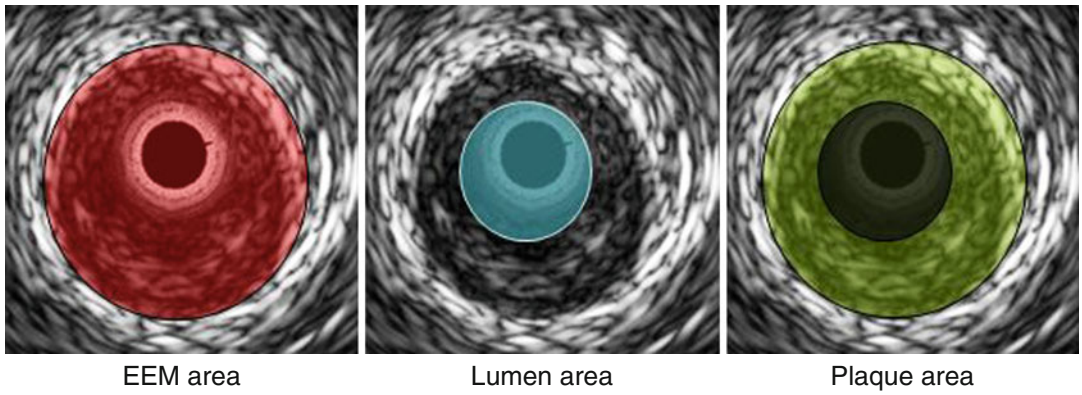


Fig. 7.3 Definition of IVUS parameters. Plaque area is determined by planimetry of the intimal leading edge and external elastic membrane (EEM) area. Plaque area is calculated as the difference between EEM area and lumen area; and plaque burden as plaque area divided by EEM area. *EEM* indicates external elastic membrane, and *IVUS* intravascular ultrasound

such as virtual histology IVUS (VH-IVUS) has been developed and widely used for plaque tissue characterization. This technique uses not only the envelope amplitude of the reflected radiofrequency-signals, as undertaken with gray-scale IVUS, but also the underlying frequency content to analyze the tissue components present in coronary plaques. This combined information is processed using autoregressive models and thereafter in a classification tree that determines four plaque tissue components: fibrous tissue (dark green), fibrofatty tissue (light green), necrotic core (red) and dense calcium (white) [15]. Plaques were classified by phenotype; fibroatheroma (further subclassified as thin-capped and thick-capped), fibrocalcific plaque and pathological intimal thickening (Fig. 7.4) [16].

Arterial remodeling in response to plaque accumulation has been observed in the renal arteries in vivo in humans. Arterial remodeling was defined by IVUS as the ratio of the external elastic membrane (EEM) area at the lesion site to the EEM area at a control reference site. Vessel area (EEM) was significantly associated with

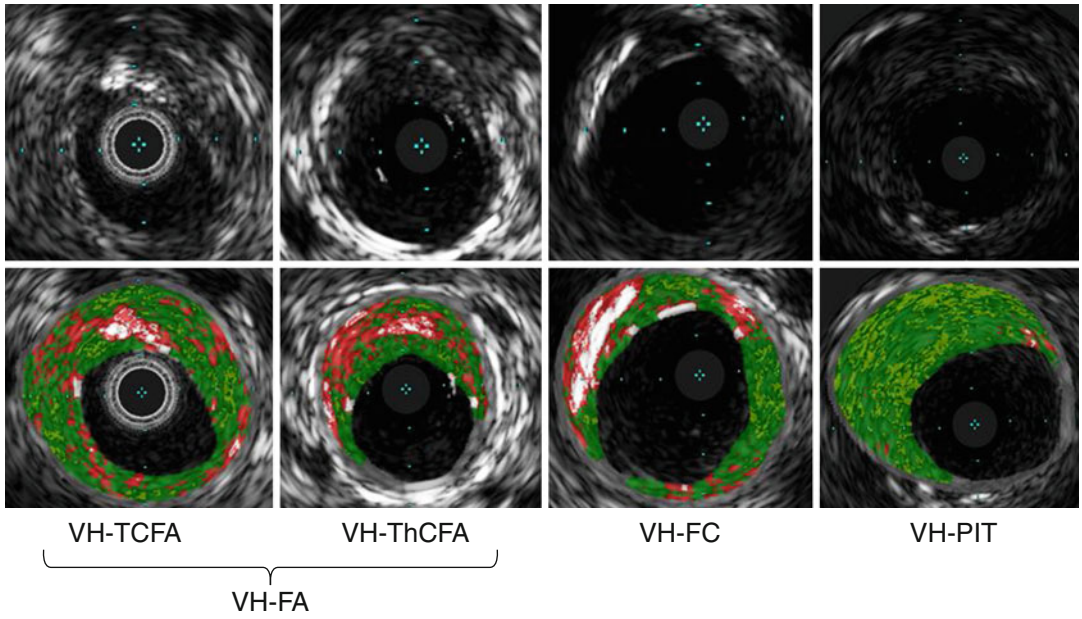


Fig. 7.4 VH-IVUS phenotype classification of renal artery plaques. Typical examples of VH-IVUS phenotype are shown. Renal plaques were classified as: (1) Fibroatheroma (*VH-FA*): plaque burden >40 %, confluent necrotic core >10 % plaque cross-sectional area, all for three consecutive frames; (2) Thin-capped fibroatheroma (*VH-TCFA*): fibroatheroma with the confluent necrotic core (>10 % of plaque cross-sectional area) in contact with vessel lumen for three consecutive frames; (3) Thick-capped fibroatheroma (*VH-ThCFA*): fibroatheroma (>10 % of confluent necrotic core for three consecutive frames) not fulfilling VH-TCFA criteria; (4) Fibrocalcific plaque (*VH-FC*): plaque with dense calcium >10 % plaque cross-sectional area in three consecutive frames, not meeting VH-FA definition; and (5) Pathological intimal thickening (*VH-PIT*): plaque not meeting VH-FA or VH-FC definitions and predominantly fibrous tissue. VH-IVUS display with four color code: *dark green* for fibrous tissue, *light green* for fibro-fatty tissue, *red* for necrotic core, and white for dense calcium. VH-IVUS indicates virtual histology intravascular ultrasound

plaque area. The degree of arterial remodeling of slices with plaque burden >40 % was attenuated compared with that seen with slices with plaque burden ≤40 %, suggesting that, in the renal artery, arterial remodeling delays luminal narrowing, similar to the previous observations in the coronary circulation [17].

Regarding arterial remodeling in the renal artery, VH-IVUS provides useful information on both anatomical variables and plaque tissue characteristics. Pre-intervention VH-IVUS imaging in ARVD patients demonstrated that plaques with positive remodeling had more phenotypes of atheromatous plaque than those with intermediate/negative remodeling (42 % vs. 4 %, p = 0.01) in a pattern similar to the coronary and carotid arteries (Fig. 7.5) [18]. In addition, percent necrotic area in the minimal lumen area was positively related to the degree of arterial remodeling [17]. These findings suggest that the arterial remodeling process in the renal artery is closely linked to the atherogenesis in renal plaques presented as plaque morphology, similar to the coronary artery.

Specific Lesion Morphology in the Renal Artery

Post-stenotic Dilatation in ARVD

Post-stenotic dilatation of greater than 20 % in diameter is often seen with modest to severe renal artery stenosis (Fig. 7.6) [19]. When the renal artery lumen narrows, blood flow accelerates to maintain the same volume across a narrower cross-sectional area. Accelerated jet flow tends to impact the artery wall distal to the stenosis,

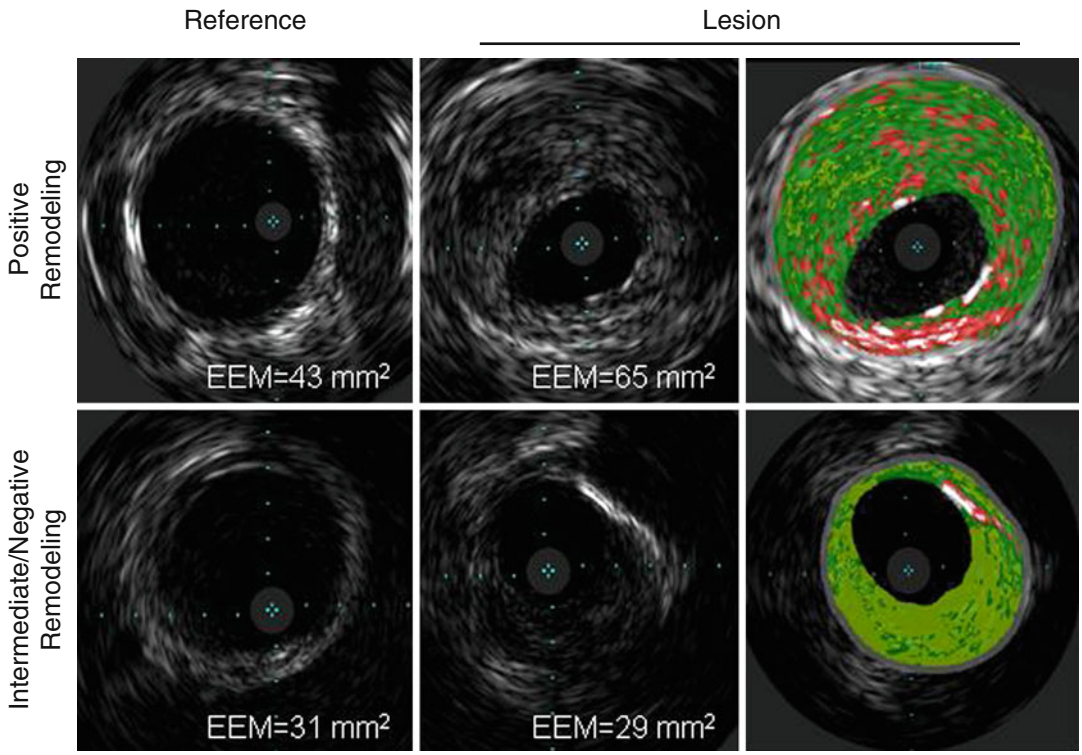


Fig. 7.5 IVUS images of arterial remodeling in the renal artery. Grayscale IVUS images (*top*, *middle*) show a lesion with positive remodeling and larger plaque burden (84 %). The vessel size (*EEM*) in the lesion is larger than that in the reference. Arterial narrowing occurs as a consequence of plaque growth beyond the point of compensation for plaque accumulation. The corresponding VH-IVUS (*top*, *right*) demonstrates thick-capped fibroatheroma. A lesion with intermediate/negative remodeling (*bottom*, *middle*) demonstrates the shrinkage of the vessel with the phenotype of pathological intimal thickening (*bottom*, *right*)

eventually producing post-stenotic dilatation [20]. Theoretically, it is related to the magnitude of the pressure gradient through the stenosis. However, it may not be present in the most severe and nearly occlusive stenoses that do not allow enough jet-flow through the lumen. Variations in vessel geometry, compliance, and vessel remodeling may determine the actual extent of post-stenotic dilatation. For this reason, post-stenotic dilatation should not be relied on as a primary indicator of hemodynamic significance.

Renal Artery Aneurysm

Renal artery aneurysm is a rare entity with an estimated incidence of 0.09 % [21]. The renal artery aneurysms may be congenital or degenerative, and may occur secondary to trauma, infection, vasculitis, neurofibromatosis, and Kawasaki's disease. Renal artery aneurysms are commonly located in extraparenchymal and in the mid and distal third of the renal artery, especially at the bifurcation of the main renal artery. The pathogenesis is the degeneration of elastic fibers and mediolysis leading to weakening of arterial wall and expansion of the artery from high intraluminal pressure [22]. Progressive renal dysfunction may occur secondary to embolization from thrombus in the aneurysm sac.

Renal Artery Plaque

Etiology of Renal Artery Stenosis

Renal artery stenosis is caused by a heterogeneous group of conditions, including atherosclerosis, fibromuscular dysplasia, vasculitis,

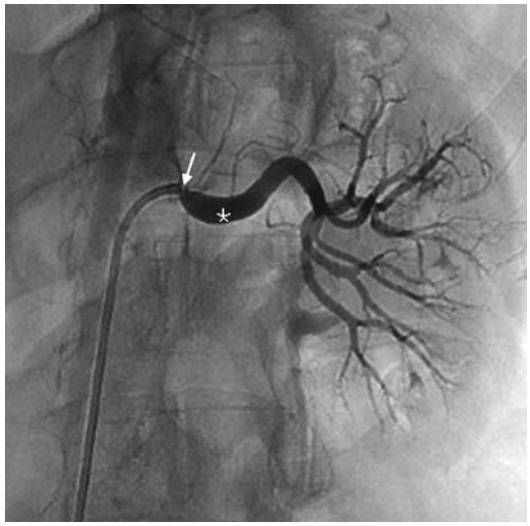


Fig. 7.6 An example of post-stenotic dilatation. A selective angiogram of left renal artery in a patient with atherosclerotic renal artery disease illustrates sever stenosis at ostium (*arrow*) and a post-stenotic dilation (*asterisk*)

neurofibromatosis, congenital bands, pheochromocytoma, extrinsic compression, emboli, aortic dissection, and radiation [23]. ARVD accounts for as much as 90 % of all cases of renovascular disease [24] and much attention has been focused on this disease entity.

Risk Factors Predicting for ARVD

Risk factors play an important role in initiating and accelerating the complex process of atherosclerosis in ARVD. Identification of risk factors that predispose to ARVD is crucial for the development of prevention strategies.

Most data were derived by extrapolation from large population studies primarily focusing on coronary heart disease [25–27], demonstrating that the risk factors for ARVD are generally similar to coronary artery diseases. However, given the higher prevalence of RAS in patients with peripheral artery disease (PAD) than in those with coronary artery disease, it may be reasonable to consider that cardiovascular risk factors have different impact on different arterial territories [28] and atherosclerosis may proceed through different pathophysiological pathways heterogeneously.

Traditional Risk Factors

There are limited and inconsistent data available. Factors associated with a higher risk of significant renal artery stenosis among 843 patients referred for cardiac catheterization include: older age, female sex, higher creatinine levels, hypertension, three-vessel coronary artery disease, PAD, diabetes, and the number of cardiovascular drugs [29]. Another study showed that old age and hypertension were closely associated with significant ARVD in 629 PAD patients [30]. These differences may result from dissimilar study population and screening methods.

Non-traditional Risk Factors

Recently, several emerging risk factors have been proposed as predictors of ARVD, namely creatinine, homocysteine, fibrinogen, C-reactive protein and lipoprotein (a). Previous study has demonstrated that creatinine and C-reactive protein seem to be the most promising predictors of ARVD, whereas the prognostic value of homocysteine, lipoprotein (a) and fibrinogen is not yet fully determined [31]. The establishment of a definite role for these emerging risk factors would result in earlier recognition and better management of ARVD.

Genetic Risk Factors

There has been compelling evidence indicates that atherosclerosis is, at least partially, genetically determined from several lines of research for PAD as well as coronary artery disease. Despite much of the research effort, there has been paucity data regarding genetic abnormalities contributing to the pathogenesis of ARVD. The current understanding of genetic risk factors for ARVD embodies extrapolation of information derived from new genetic mechanisms of PAD. Unlike monogenic vascular disease manifesting a Mendelian inheritance pattern, atherosclerotic PAD likely results from dozens or hundreds of genes interacting with each other and the environment to cause disease. From a genetic standpoint, therefore, atherosclerosis is a more complex disorder.

A few earlier studies addressed the possible role of candidate genes such as polymorphisms in genes of the renin-angiotensin system [32–35]

and eNOS [36] in renovascular disease. These approaches, referred as candidate gene studies, are based on preexisting knowledge about which genes and pathways are relevant to a disease. As candidate gene approaches are limited to priori hypotheses, a more comprehensive and unbiased scan of variations in all genes or in the entire genome is needed. To date, novel genetic approaches to genetics have emerged such as genome-wide association studies which do not rely on assumptions about relevant disease and require no previous information on gene function to select single nucleotide polymorphisms for genotyping. In coronary and peripheral artery disease, in multiple loci associated with cardiovascular disorders, the strongest and most consistent locus is with the intergenic portion of chromosome 9p21 [37, 38]. Variants at this locus have been reported to correlate with risk in myocardial infarction [39] and PAD [40, 41]. It is conceivable that there are similar associations of this locus with ARVD. Further studies are warranted to identify genetic factors underlying ARVD.

Plaque Distribution of ARVD

The ostium and proximal third of the main renal artery represent the most common atherosclerotic lesions [42], whereas segmental and diffuse lesions may be observed in advanced atherosclerotic disease cases [24]. The atherosclerotic plaque in the renal artery extends from the wall of the aorta into the ostium of the renal artery [43]. The caudal aspect of the renal ostium that diverts flow into the renal artery is the initiation site of atherosclerotic lesions in humans [44]. A study using porcine model showed increased low-density lipoprotein retention binding in the caudal region of the ostium enriched with collagen and proteoglycan, which could play a role in the increased susceptibility to atherosclerosis [45].

The extensive and widespread distributions of atherosclerotic disease into the intra-renal microvascular beds make the pathophysiology of ARVD more complex. In addition to atherosclerotic plaques in the main renal artery, atherosclerosis might also distribute in the poststenotic kidney and compromise the renal parenchyma and intrarenal vessels leading to the aggravation of renal hypoperfusion and tissue injury [46]. In patients with fibromuscular dysplasia, tissue injury including parenchymal fibrosis rarely develops [47], while a part of patients with ARVD showed the progressive deterioration of renal function even after successful revascularization [48]. Renal cortical perfusion correlated inversely with degree of stenosis in fibromuscular dysplasia [49], whereas, in patients with ARVD, the severity in renal cortical perfusion [49] and function [50] are not directly correlated with the angiographic degree of stenosis in the main renal artery. Thus, better understanding of extensive atherosclerotic distributions in ARVD would be of importance for assessment and treatment.

Morphology of ARVD

Renal Artery Calcium

Renal artery calcification occurs in early and advanced atherosclerosis. Once the lipid core is formed, calcium particles appear within smooth muscle cells and extracellularly within the lipid cores. With the progression to advanced lesions, calcium particles increase in size and form larger plates of calcium [51]. These calcified plaques can be detected and quantified by computed tomography in clinical practice. The extent of calcified plaque assessed by computed tomography is a valid and reproducible measure of the total atherosclerotic plaque burden, although a poor relation exists between the burden of calcium and the degree of luminal stenosis in a given arterial bed [52].

Previous studies have demonstrated that renal artery calcium is related with the presence of calcium located in the coronary, carotid, iliac arteries, the aorta, and the mitral and aortic annuli [53]. The presence of renal artery calcium is associated with higher odds for prevalent hypertension, independent of traditional risk factors for cardiovascular disease and the extent of calcified atherosclerosis in the non-renal vasculature [54]. Furthermore, renal artery calcium was associated with an increased risk of

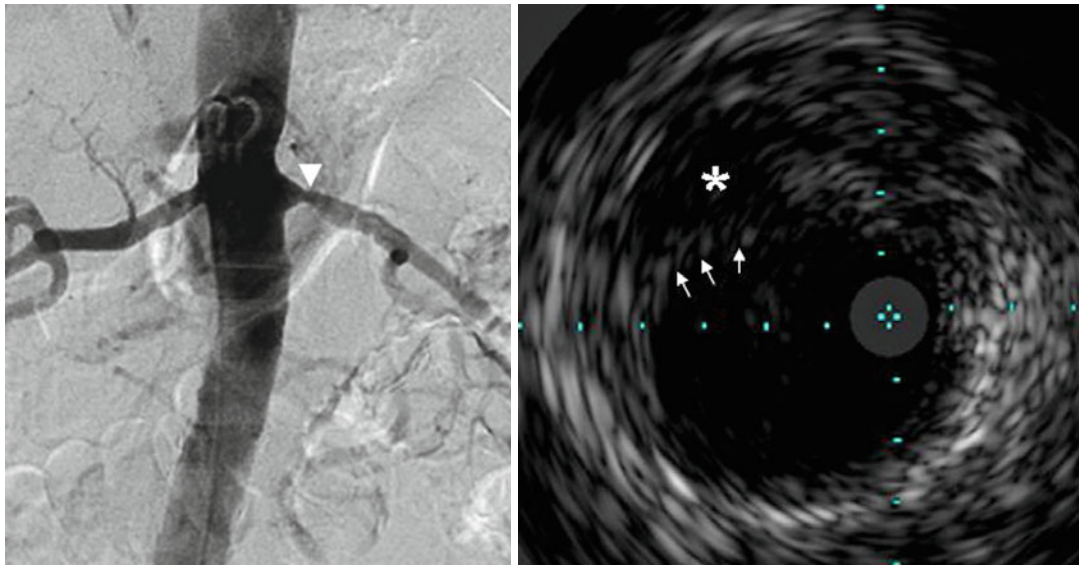


Fig. 7.7 Example images of a plaque rupture in the renal artery. Angiography shows severe stenosis in the left main renal artery (*arrowhead*). Corresponding IVUS shows a plaque rupture. An *asterisk* indicates a ruptured cavity communicating with the lumen and *arrows*, a disrupted residual fibrous cap fragment

all-cause mortality in healthy outpatient individuals, independent of demographic and traditional cardiovascular risk factors and vascular calcification in other locations [55].

Tissue Characterization of ARVD

Among different arterial beds (i.e., coronary, carotid, renal, and peripheral), little is known about the plaque characteristics in the renal arteries. A recent study using VH-IVUS for plaque characterization (Fig. 7.4) in patients with ARVD demonstrated that the most prominent plaque component was fibrous tissue, followed by fibrofatty, necrotic core, and dense calcium. Not surprisingly, this distribution of plaque components was not different from the coronary and carotid arteries. In terms of plaque phenotypes, however, renal artery plaques had less characteristics of fibroatheromas (22 % vs. 53 %) and more pathological intimal thickening (60 % vs. 18 %) compared to the coronary arteries in a comparative analysis study. In addition, the amount of necrotic core and dense calcium in renal artery plaque were less than those in the coronary artery [18]. These findings suggest that stable plaque phenotypes are more common in the renal arteries than the coronary arteries at the clinical manifestation, and plaque characteristics among different arterial beds are heterogeneous.

While renal stenting for ARVD yields improved technical success, atheroembolism can manifest as progressive renal failure occurring in approximately 20 % of patients [56] over weeks to months. As the stent crushes the plaque against the vessel wall, atheromatous fragments large enough to cause downstream occlusions and parenchymal damage have been shown to be released in ex vivo studies of renal artery stenting [57]. It has been hypothesized that imaging of renal artery plaque composition can identify plaques that are predisposed to causing distal embolization. A recent study showed that the change in estimated glomerular filtration rate after renal artery stenting was inversely correlated with mean percentage of necrotic core assessed by VH-IVUS [58]. This suggests that lesions containing large lipid-rich necrotic cores are predisposed to iatrogenic distal embolization. Thus, pre-intervention IVUS for ARVD might provide additional information by offering an accurate assessment of plaque composition as well as anatomical assessment.

Vulnerable Plaque in the Renal Artery

Atherosclerotic plaques that are prone to precipitate acute thrombotic occlusions are considered to be vulnerable plaques [59]. The classical definition of the vulnerable plaque encompasses histopathological features such as a large lipid core, the presence of inflammatory cells, and a thin fibrous cap. VH-IVUS has been the most widely applied imaging technology to visualize the aforementioned features of the vulnerable plaque in the coronary artery (Fig. 7.4). Based on substantial evidence for acute thrombosis in the coronary circulation, it is highly likely that it also occurs in the renal artery. The total occlusion of the renal artery due to acute thrombosis might be infrequent although there are little data available.

A previous VH-IVUS study [18] demonstrated that plaque ruptures (Fig. 7.7) and thin-capped fibroatheromas, the major precursor lesion for plaque rupture, were identified in 6 and 16 % of patients referred to endovascular intervention for ARVD with significant stenosis, respectively.

Plaque neovascularization in the intima and media is another hallmark of advanced atherosclerotic lesions [60]. The growth and extension of adventitial blood vessels called vasa vasorum into the intima occurs as a response to tissue hypoxia when the intima thickens beyond the diffusion limits of oxygen and nutrients [61]. These pathological microvessels are prone to rupture, and intraplaque hemorrhage accelerates plaque formation [62]. These changes are uniformly present in different arterial beds including the renal arteries in vulnerable patients [63], although the renal arteries showed a lower vasa vasorum density compared to coronary arteries [64].

The clinical significance of vulnerable plaques in the renal arteries is yet undetermined. Atherothrombosis may play a potential role in the pathophysiology of progressive renal disease or hypertension. IVUS examinations for ARVD are usually performed in combination with endovascular intervention for renal artery stenosis because of their invasive nature. On the other hand, most ARVD are clinically silent and identified during the investigation of other condition such as coronary or peripheral artery disease, whereas a minority are detected due to symptoms of hypoperfusion resulting from the narrowing of the renal artery. Therefore, the diagnosis of vulnerable plaques in the renal artery might rarely be made based on the presence of symptoms associated with atherothrombosis.

Taken together, renal artery plaques unexceptionally have a wide variety of atherosclerotic phenotypes including vulnerable plaque features according to patients' clinical status. Further studies are needed to elucidate the pathophysiology underlying atherosclerotic plaque development and the clinical sequela of plaque rupture in the renal circulation.

Disease Progression of ARVD

ARVD is a potentially progressive disease. The pertinent observations are variable according to indications for screening and the imaging modalities used for measurements.

In serial angiographic examinations [65], progression of renal artery atherosclerosis was observed in 44 % of 85 patients, and progression to complete occlusion was observed in 16 % during 52 months. Half of patients with less than 50 % stenosis demonstrated no change. The rate of progression to complete occlusion was 39 % in those with 75–99 % stenosis compared with 5 % in those with <50 % stenosis. Another large series of patients undergoing coronary angiogram demonstrated that significant disease progression was observed in 11 % over 2.6 years [66]. Although patients with severe renal artery stenosis are more likely to progress, significant stenosis may develop rapidly despite evidence of normal renal arteries at prior catheterization.

Renal artery duplex ultrasound has advantages of noninvasiveness, despite a limitation of reproducibility and operator-dependency. Renal arteries with significant stenosis (>60 %) measured by renal duplex ultrasonography have approximately a 20 % progression of disease per year and with 11 % progressing to renal occlusion within 2 years [67]. In another large prospective observational study, the cumulative incidence of progression to ≥60 % stenosis during 33 months period was 13 and 56 % for the renal arteries initially classified

as normal and <60 %, respectively, according to baseline degree of renal artery narrowing. Only 3 % (9 of the 295 renal arteries) progressed to total occlusion during the follow-up period. Seven of these were classified as those with ≥60 % stenosis at baseline [68]. In this study, systolic blood pressure ≥160 mmHg, diabetes, ipsilateral or contralateral stenosis ≥60 %, and occlusion of contralateral renal artery were identified as independent risk factors for plaque progression.

Most studies investigating natural history of ARVD were performed before modern treatment of risk factors for atherosclerotic cardiovascular disease. In an era when optimal medical therapy including aspirin, renin-angiotensin system antagonists, and intensive lipid-lowering therapy are widely used, a lower rate of ARVD progression would be expected.

For two decades IVUS-base imaging technology has been used for better plaque assessment in the coronary artery and provided valuable information on the characterization of plaque, the plaque progression and regression [69], and prognosis [70]. There are little data on the natural history of renal plaques based on plaque volume and composition. Further research may be warranted to answer the question.

Conclusion

Endothelial dysfunction is a systemic disorder and may play a role in the pathogenesis of ARVD. The pathophysiology of ARVD has been considered more profound than previously expected, and includes not only renal flow disturbance but also microvascular environment in the kidney. Recent IVUS studies demonstrate that atherosclerotic renal artery plaques have a wide variety of atherosclerotic phenotypes including vulnerable plaque features. Further studies are needed to determine the association of plaque morphology of the renal artery with risk factors, disease progression, renal function, therapeutic effects of medical and endovascular interventions, and future cardiovascular events. With a more detailed understanding of the pathophysiology of ARVD, the treatment strategies for ARVD will continue to develop.

References

1. Luft FC. Proinflammatory effects of angiotensin II and endothelin: targets for progression of cardiovascular and renal diseases. Curr Opin Nephrol Hypertens. 2002;11(1):59–66.
2. Ludmer PL, Selwyn AP, Shook TL, Wayne RR, Mudge GH, Alexander RW, Ganz P. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. N Engl J Med. 1986; 315(17):1046–51.
3. Lerman A, Zeiher AM. Endothelial function: cardiac events. Circulation. 2005;111(3):363–8.
4. Hegde LG, Srivastava P, Kumari R, Dikshit M. Alterations in the vasoreactivity of hypertensive rat aortic rings: role of nitric oxide and superoxide radicals. Clin Exp Hypertens. 1998;20(8):885–901.
5. Taddei S, Virdis A, Mattei P, Salvetti A. Vasodilation to acetylcholine in primary and secondary forms of human hypertension. Hypertension. 1993;21(6 Pt 2): 929–33.
6. Lerman LO, Nath KA, Rodriguez-Porcel M, Krier JD, Schwartz RS, Napoli C, Romero JC. Increased oxidative stress in experimental renovascular hypertension. Hypertension. 2001;37(2 Part 2):541–6.
7. Heiss C, Lauer T, Dejam A, Kleinbongard P, Hamada S, Rassaf T, Matern S, Feelisch M, Kelm M. Plasma nitroso compounds are decreased in patients with endothelial dysfunction. J Am Coll Cardiol. 2006; 47(3):573–9.
8. Higashi Y, Sasaki S, Nakagawa K, Matsuura H, Oshima T, Chayama K. Endothelial function and oxidative stress in renovascular hypertension. N Engl J Med. 2002;346(25):1954–62.
9. Perticone F, Maio R, Tripepi G, Zoccali C. Endothelial dysfunction and mild renal insufficiency in essential hypertension. Circulation. 2004;110(7):821–5.
10. Perticone F, Maio R, Perticone M, Sciacqua A, Shehaj E, Naccarato P, Sesti G. Endothelial dysfunction and subsequent decline in glomerular filtration rate in hypertensive patients. Circulation. 2010;122(4): 379–84.
11. Eirin A, Zhang X, Ebrahimi B, Zhu XY, Crane JA, Tang H, Lerman A, Textor SC, Lerman LO. Changes in glomerular filtration rate after renal revascularization correlate with microvascular hemodynamics and inflammation in swine renal artery stenosis. Circ Cardiovasc Interv. 2012;5(5):720–8.
12. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med. 1987;316(22):1371–5.
13. Pasterkamp G, Schoneveld AH, van der Wal AC, Haudenschild CC, Clarijs RJ, Becker AE, Hillen B, Borst C. Relation of arterial geometry to luminal narrowing and histologic markers for plaque vulnerability: the remodeling paradox. J Am Coll Cardiol. 1998;32(3):655–62.
14. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105(9):1135–43.

15. Nair A, Kuban BD, Tuzcu EM, Schoenhagen P, Nissen SE, Vince DG. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. Circulation. 2002;106(17):2200–6.
16. Calvert PA, Obaid DR, O'Sullivan M, Shapiro LM, McNab D, Densem CG, Schofield PM, Braganza D, Clarke SC, Ray KK, West NE, Bennett MR. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) Study. JACC Cardiovasc Imaging. 2011;4(8): 894–901.
17. Kataoka T, Mathew V, Rubinshtein R, Rihal CS, Lennon R, Lerman LO, Lerman A. Association of plaque composition and vessel remodeling in atherosclerotic renal artery stenosis: a comparison with coronary artery disease. JACC Cardiovasc Imaging. 2009;2(3):327–38.
18. Matsuo Y, Takumi T, Mathew V, Chung WY, Barsness GW, Rihal CS, Gulati R, McCue ET, Holmes DR, Eeckhout E, Lennon RJ, Lerman LO, Lerman A. Plaque characteristics and arterial remodeling in coronary and peripheral arterial systems. Atherosclerosis. 2012;223(2):365–71.
19. Prince MR, Schoenberg SO, Ward JS, Londy FJ, Wakefield TW, Stanley JC. Hemodynamically significant atherosclerotic renal artery stenosis: MR angiographic features. Radiology. 1997;205(1):128–36.
20. Ersoy H, Zhang H, Prince MR. Peripheral MR angiography. J Cardiovasc Magn Reson. 2006; 8(3):517–28.
21. Stanley JC, Rhodes EL, Gewertz BL, Chang CY, Walter JF, Fry WJ. Renal artery aneurysms. Significance of macroaneurysms exclusive of dissections and fibrodysplastic mural dilations. Arch Surg. 1975;110(11):1327–33.
22. Chimpiri AR, Natarajan B. Renal vascular lesions: diagnosis and endovascular management. Semin Intervent Radiol. 2009;26(3):253–61.
23. Tynes 2nd WV. Unusual renovascular disorders. Urol Clin North Am. 1984;11(3):529–42.
24. Safian RD, Textor SC. Renal-artery stenosis. N Engl J Med. 2001;344(6):431–42.
25. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham study. Am J Cardiol. 1976;38(1):46–51.
26. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. The ARIC investigators. Am J Epidemiol. 1989;129(4):687–702.
27. Lee ET, Welty TK, Fabsitz R, Cowan LD, Le NA, Oopik AJ, Cucchiara AJ, Savage PJ, Howard BV. The strong heart study. A study of cardiovascular disease in American Indians: design and methods. Am J Epidemiol. 1990;132(6):1141–55.
28. Faxon DP, Fuster V, Libby P, Beckman JA, Hiatt WR, Thompson RW, Topper JN, Annex BH, Rundback JH, Fabunmi RP, Robertson RM, Loscalzo J, American Heart Association. Atherosclerotic vascular disease conference: writing group III: pathophysiology. Circulation. 2004;109(21):2617–25.
29. Cohen MG, Pascua JA, Garcia-Ben M, Rojas-Matas CA, Gabay JM, Berrocal DH, Tan WA, Stouffer GA, Montoya M, Fernandez AD, Halac ME, Grinfeld LR. A simple prediction rule for significant renal artery stenosis in patients undergoing cardiac catheterization. Am Heart J. 2005;150(6):1204–11.
30. Ozkan U, Oguzkurt L, Tercan F, Nursal TZ. The prevalence and clinical predictors of incidental atherosclerotic renal artery stenosis. Eur J Radiol. 2009;69(3): 550–4.
31. Paraskevas KI, Hamilton G, Cross JM, Mikhailidis DP. Atherosclerotic renal artery stenosis: association with emerging vascular risk factors. Nephron Clin Pract. 2008;108(1):c56–66.
32. Missouris CG, Barley J, Jeffery S, Carter ND, Singer DR, MacGregor GA. Genetic risk for renal artery stenosis: association with deletion polymorphism in angiotensin 1-converting enzyme gene. Kidney Int. 1996;49(2):534–7.
33. Olivieri O, Trabetti E, Grazioli S, Stranieri C, Friso S, Girelli D, Russo C, Pignatti PF, Mansueto G, Corrocher R. Genetic polymorphisms of the renin-angiotensin system and atheromatous renal artery stenosis. Hypertension. 1999;34(5):1097–100.
34. Losito A, Parente B, Cao PG, Jeffery S, Afzal AR. ACE gene polymorphism and survival in atherosclerotic renovascular disease. Am J Kidney Dis. 2000;35(2):211–5.
35. Reis KA, Onal B, Gonen S, Arinsoy T, Erten Y, Ilgit E, Soylemezoglu O, Derici U, Guz G, Bali M, Sindel S. Angiotensinogen and plasminogen activator inhibitor-1 gene polymorphism in relation to renovascular disease. Cardiovasc Intervent Radiol. 2006;29(1): 59–63.
36. Page A, Reich H, Zhou J, Lai V, Cattran DC, Scholey JW, Miller JA. Endothelial nitric oxide synthase gene/gender interactions and the renal hemodynamic response to angiotensin II. J Am Soc Nephrol. 2005;16(10):3053–60.
37. Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, Dixon RJ, Meitinger T, Braund P, Wichmann HE, Barrett JH, König IR, Stevens SE, Szymczak S, Tregouet DA, Iles MM, Pahlke F, Pollard H, Lieb W, Cambien F, Fischer M, Ouwehand W, Blankenberg S, Balmforth AJ, Baessler A, Ball SG, Strom TM, Braenne I, Gieger C, Deloukas P, Tobin MD, Ziegler A, Thompson JR, Schunkert H, WTCCC and the Cardiogenics Consortium. Genomewide association analysis of coronary artery disease. N Engl J Med. 2007;357(5):443–53.
38. McPherson R, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, Hinds DA, Pennacchio LA, Tybjaerg-Hansen A, Folsom AR, Boerwinkle E, Hobbs HH, Cohen JC. A common allele on chromosome 9 associated with coronary heart disease. Science. 2007;316(5830):1488–91.
39. Helgadottir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, Jonasdottir A, Sigurdsson A, Baker A, Palsson A, Masson G, Gudbjartsson DF, Magnusson KP, Andersen K, Levey

AI, Backman VM, Matthiasdottir S, Jonsdottir T, Palsson S, Einarsdottir H, Gunnarsdottir S, Gylfason A, Vaccarino V, Hooper WC, Reilly MP, Granger CB, Austin H, Rader DJ, Shah SH, Quyyumi AA, Gulcher JR, Thorgeirsson G, Thorsteinsdottir U, Kong A, Stefansson K. A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science. 2007;316(5830):1491–3.

40. Helgadottir A, Thorleifsson G, Magnusson KP, Grétarsdottir S, Steinthorsdottir V, Manolescu A, Jones GT, Rinkel GJ, Blankensteijn JD, Ronkainen A, Jääskeläinen JE, Kyo Y, Lenk GM, Sakalihasan N, Kostulas K, Gottsäter A, Flex A, Stefansson H, Hansen T, Andersen G, Weinsheimer S, Borch-Johnsen K, Jorgensen T, Shah SH, Quyyumi AA, Granger CB, Reilly MP, Austin H, Levey AI, Vaccarino V, Palsdottir E, Walters GB, Jonsdottir T, Snorradottir S, Magnusdottir D, Gudmundsson G, Ferrell RE, Sveinbjornsdottir S, Hernesniemi J, Niemelä M, Limet R, Andersen K, Sigurdsson G, Benediktsson R, Verhoeven EL, Teijink JA, Grobbee DE, Rader DJ, Collier DA, Pedersen O, Pola R, Hillert J, Lindblad B, Valdimarsson EM, Magnadottir HB, Wijmenga C, Tromp G, Baas AF, Ruigrok YM, van Rij AM, Kuivaniemi H, Powell JT, Matthiasson SE, Gulcher JR, Thorgeirsson G, Kong A, Thorsteinsdottir U, Stefansson K. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. Nat Genet. 2008;40(2):217–24.
41. Björck HM, Länne T, Alehagen U, Persson K, Rundkvist L, Hamsten A, Dahlström U, Eriksson P. Association of genetic variation on chromosome 9p21.3 and arterial stiffness. J Intern Med. 2009;265(3):373–81.
42. Kaatee R, Beek FJ, Verschuyl EJ, vd Ven PJ, Beutler JJ, van Schaik JP, Mali WP. Atherosclerotic renal artery stenosis: ostial or truncal? Radiology. 1996;199(3):637–40.
43. Cicuto KP, McLean GK, Oleaga JA, Freiman DB, Grossman RA, Ring EJ. Renal artery stenosis: anatomic classification for percutaneous transluminal angioplasty. AJR Am J Roentgenol. 1981; 137(3):599–601.
44. Nguyen ND, Haque AK. Effect of hemodynamic factors on atherosclerosis in the abdominal aorta. Atherosclerosis. 1990;84(1):33–9.
45. Neufeld EB, Yu ZX, Springer D, Yu Q, Balaban RS. The renal artery ostium flow diverter: structure and potential role in atherosclerosis. Atherosclerosis. 2010;211(1):153–8.
46. Chade AR, Rodriguez-Porcel M, Grande JP, Zhu X, Sica V, Napoli C, Sawamura T, Textor SC, Lerman A, Lerman LO. Mechanisms of renal structural alterations in combined hypercholesterolemia and renal artery stenosis. Arterioscler Thromb Vasc Biol. 2003; 23(7):1295–301.
47. Textor SC, Lerman L. Renovascular hypertension and ischemic nephropathy. Am J Hypertens. 2010;23(11): 1159–69.
48. ASTRAL Investigators, Wheatley K, Ives N, Gray R, Kalra PA, Moss JG, et al. Revascularization versus medical therapy for renal-artery stenosis. N Engl J Med. 2009;361(20):1953–62.
49. Lerman LO, Taler SJ, Textor SC, Sheedy 2nd PF, Stanson AW, Romero JC. Computed tomography-derived intrarenal blood flow in renovascular and essential hypertension. Kidney Int. 1996;49(3): 846–54.
50. Suresh M, Laboi P, Mamtora H, Kalra PA. Relationship of renal dysfunction to proximal arterial disease severity in atherosclerotic renovascular disease. Nephrol Dial Transplant. 2000;15(5):631–6.
51. Stary HC. The development of calcium deposits in atherosclerotic lesions and their persistence after lipid regression. Am J Cardiol. 2001;88(2A):16E–9.
52. Sangiorgi G, Rumberger JA, Severson A, Edwards WD, Gregoire J, Fitzpatrick LA, Schwartz RS. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. J Am Coll Cardiol. 1998;31(1):126–33.
53. Allison MA, DiTomasso D, Criqui MH, Langer RD, Wright CM. Renal artery calcium: relationship to systemic calcified atherosclerosis. Vasc Med. 2006; 11(4):232–8.
54. Allison MA, Lillie EO, DiTomasso D, Wright CM, Criqui MH. Renal artery calcium is independently associated with hypertension. J Am Coll Cardiol. 2007;50(16):1578–83.
55. Rifkin DE, Ix JH, Wassel CL, Criqui MH, Allison MA. Renal artery calcification and mortality among clinically asymptomatic adults. J Am Coll Cardiol. 2012;60(12):1079–85.
56. Iannone LA, Underwood PL, Nath A, Tannenbaum MA, Ghali MG, Clevenger LD. Effect of primary balloon expandable renal artery stents on long-term patency, renal function, and blood pressure in hypertensive and renal insufficient patients with renal artery stenosis. Cathet Cardiovasc Diagn. 1996;37(3): 243–50.
57. Hiramoto J, Hansen KJ, Pan XM, Edwards MS, Sawhney R, Rapp JH. Atheroemboli during renal artery angioplasty: an ex vivo study. J Vasc Surg. 2005;41(6):1026–30.
58. Takumi T, Mathew V, Barsness GW, Kataoka T, Rubinshtein R, Rihal CS, Gulati R, McCue ET, Holmes DR, Eeckhout E, Lennon RJ, Lerman LO, Lerman A. The association between renal atherosclerotic plaque characteristics and renal function before and after renal artery intervention. Mayo Clin Proc. 2011;86(12):1165–72.
59. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, Fayad Z, Stone PH, Waxman S, Raggi P, Madjid M, Zarrabi A, Burke A, Yuan C, Fitzgerald PJ, Siscovick DS, de Korte CL, Aikawa M, Juhani Airaksinen KE, Assmann G, Becker CR, Chesebro JH, Farb A, Galis ZS, Jackson C, Jang IK, Koenig W,

Lodder RA, March K, Demirovic J, Navab M, Priori SG, Rekhter MD, Bahr R, Grundy SM, Mehran R, Colombo A, Boerwinkle E, Ballantyne C, Insull Jr W, Schwartz RS, Vogel R, Serruys PW, Hansson GK, Faxon DP, Kaul S, Drexler H, Greenland P, Muller JE, Virmani R, Ridker PM, Zipes DP, Shah PK, Willerson JT. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation. 2003;108(14): 1664–72.

60. Barger AC, Beeuwkes 3rd R, Lainey LL, Silverman KJ. Hypothesis: vasa vasorum and neovascularization of human coronary arteries. A possible role in the pathophysiology of atherosclerosis. N Engl J Med. 1984;310(3):175–7.
61. Geiringer E. Intimal vascularization and atherosclerosis. J Pathol Bacteriol. 1951;63(2):201–11.
62. Kolodgie FD, Gold HK, Burke AP, Fowler DR, Kruth HS, Weber DK, Farb A, Guerrero LJ, Hayase M, Kutys R, Narula J, Finn AV, Virmani R. Intraplaque hemorrhage and progression of coronary atheroma. N Engl J Med. 2003;349(24):2316–25.
63. Fleiner M, Kummer M, Mirlacher M, Sauter G, Cathomas G, Krapf R, Biedermann BC. Arterial neovascularization and inflammation in vulnerable patients: early and late signs of symptomatic atherosclerosis. Circulation. 2004;110(18):2843–50.
64. Hildebrandt HA, Gossl M, Mannheim D, Versari D, Herrmann J, Spendlove D, Bajanowski T, Malyar NM, Erbel R, Lerman LO, Lerman A. Differential distribution of vasa vasorum in different vascular beds in humans. Atherosclerosis. 2008;199(1):47–54.
65. Schreiber MJ, Pohl MA, Novick AC. The natural history of atherosclerotic and fibrous renal artery disease. Urol Clin North Am. 1984;11(3):383–92.
66. Crowley JJ, Santos RM, Peter RH, Puma JA, Schwab SJ, Phillips HR, Stack RS, Conlon PJ. Progression of renal artery stenosis in patients undergoing cardiac catheterization. Am Heart J. 1998;136(5):913–8.
67. Zierler RE, Bergelin RO, Isaacson JA, Strandness Jr DE. Natural history of atherosclerotic renal artery stenosis: a prospective study with duplex ultrasonography. J Vasc Surg. 1994;19(2):250–7.
68. Caps MT, Perissinotto C, Zierler RE, Polissar NL, Bergelin RO, Tullis MJ, Cantwell-Gab K, Davidson RC, Strandness Jr DE. Prospective study of atherosclerotic disease progression in the renal artery. Circulation. 1998;98(25):2866–72.
69. Gogas BD, Farooq V, Serruys PW, Garcìa-Garcìa HM. Assessment of coronary atherosclerosis by IVUS and IVUS-based imaging modalities: progression and regression studies, tissue composition and beyond. Int J Cardiovasc Imaging. 2011;27(2): 225–37.
70. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW, PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011;364(3):226–35.

Microvascular Disease

8

Alejandro R. Chade

Abstract

A healthy renal microcirculation is crucial to ensure adequate tissue perfusion, filtration and removal of toxins from the general circulation. Emerging evidence supports a role of renal microvascular (MV) disease in possibly determining the turning point between reversible and irreversible renal injury. Indeed, previous studies have shown that renal MV rarefaction correlates with the progressive deterioration of renal hemodynamics, filtration, and, tubular function. Furthermore, dysfunctional or damaged microvessels can compromise adequate renal perfusion and nutrition leading to tissue ischemia, which may in turn activate pro-inflammatory and pro-fibrotic factors that could promote renal parenchymal injury. This chapter will discuss the changes in renal MV function and structure and the role of MV disease on the initiation and progression of renal injury.

Either as a causative mechanism or a consequence of renal injury, increasing experimental and clinical evidence showed that pathological changes in the renal microvasculature accompany the development and progression of renal injury associated to hypertension, diabetes, obesity, and atherosclerosis. Previous studies have shown that systemic and renal MV disease is associated to cardiovascular risk factors even in the absence of major deterioration of renal function, implying that early changes in renal MV function could later serve as instigator of renal injury. Hence, this chapter will also focus on the development, progression, and mechanisms of renal MV disease in hypertension, diabetes, obesity, and atherosclerosis.

A.R. Chade, MD
Department of Physiology and Biophysics,
Department of Medicine,
Department of Radiology,
University of Mississippi Medical Center,
2500 North State Street, Jackson,
MS 39216-4505, USA
e-mail: achade@umc.edu

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_8,

Keywords

Microcirculation • Kidney • Renal function • Remodeling • Rarefaction • Cardiovascular • Risk factors

The Microcirculation: Definition and Role

The microcirculation is a network constituted by vessels between 0 and 200 μm in diameter that are embedded within organs and are responsible for the distribution of blood within tissues [1]. In general, each nutrient vessel entering an organ branches six to eight times before becoming arterioles (10–15 μm), which in turn splits two to five times into smaller vessels, reaching diameters of 9 μm or lower to supply blood to the smallest vascular network, the capillaries. The microcirculation is an organized and dynamic functional network that adapts to changes in the organ or tissue surroundings. Indeed, the tissue vascularity is determined by maximum blood flow needs and tightly regulated by factors that can promote physiological or pathological vascular constriction or dilatation, growth or regression. Healthy microvascular (MV) networks are pivotal for the normal organ function in the human body, by controlling the transportation of oxygen and nutrients and the removal of toxins. The blood flow is generally regulated by the specific needs of the tissues as long as the arterial pressure is sufficient to sustain tissue perfusion.

Renal Microcirculation

General Characteristics

Blood flow to the kidneys is normally one fifth of the cardiac output, which equals approximately 1,100 ml/min. The blood supply to the human kidneys is one of the highest and only 10 % of the delivered oxygen is sufficient to satisfy the renal metabolic demands [2]. The renal circulation has unique anatomical and functional characteristics (Fig. 8.1). The renal artery enters the kidney through the hilum and following the main renal artery and primary bifurcations, the renal vessels subsequently split in the kidney into interlobar, arcuate and interlobular arteries. Then, the smaller branching order afferent arterioles lead to the glomerular capillaries and the distal ends of the capillaries of each glomerulus join to form the efferent arterioles, followed by a second capillary network constituted by the peritubular capillaries surrounding renal tubules. The double capillary bed is a unique feature of the renal circulation that separates the filtering from the reabsorption process. Glomerular capillaries filter through a large amount of fluid and solutes (except the plasma proteins) whereas tubular capillaries are key participants in the filtration, secretion and reabsorption of minerals and removal of unwanted substances from the filtrate (and therefore from the blood) towards formation of urine. The capillary systems from cortex and medulla merge into the cortical venules that run in parallel to the arteriolar vessels and progressively form the interlobular, arcuate, interlobar, and renal vein, which leaves the kidney alongside the renal artery and ureter [4].

Role of the Renal Microcirculation in Renal Nutrition

The kidneys receive a larger than needed oxygen and nutritional supply since 1/5 of the total cardiac output goes through the organ maintaining renal tissue perfusion and viability. As in any other organ, a healthy renal microcirculation is crucial for a normal distribution of nutrients and removal of toxins, regardless of the abundant blood supply the kidneys receive. One of the characteristics of the renal microcirculation is the intimate association between renal excretory function and intra-renal hemodynamics, which are major players in determining the appropriately responsive excretory function over

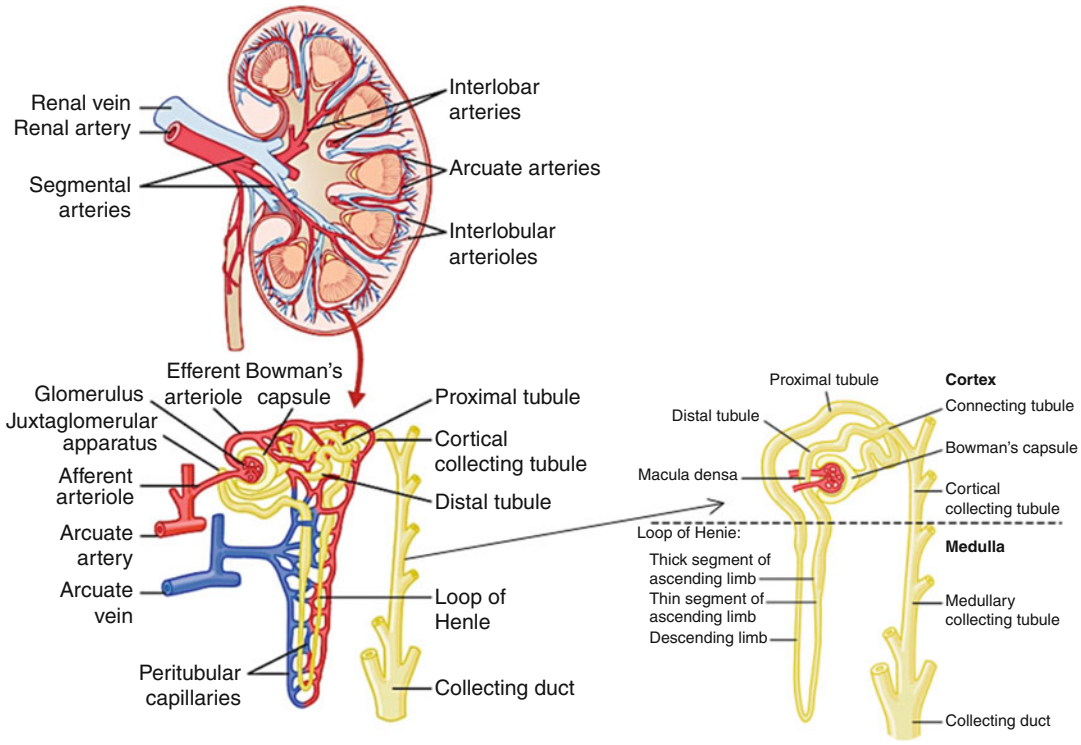


Fig. 8.1 Section of the human kidney showing the major vessels that supply the blood flow to the kidneys, a schematic representation of the microcirculation of the nephron (*red arrow*), and the basic tubular segments of the nephron (*black arrow*). The relative lengths of the different tubular segments are not drawn to scale (With permission from Hall [3])

the nutritional requirements of the renal parenchyma [2]. The importance of the microcirculation in maintaining the nutrition of the renal parenchyma is underscored by studies showing a correlation between progressive dysfunction and/or loss of renal microvessels with the progression of renal fibrosis [5–7]. Indeed, although the kidneys are capable of preserving their function over a broad range of autoregulation, a sustained deterioration of the renal microvasculature may lead to reduction in renal perfusion, a deficient nutrition, and ultimately development of fibrosis and a permanent damage of the renal tissue. It is possible that the deterioration of the renal microvasculature first compromises renal nutrition and then renal filtration and the excretory function. This notion is strongly suggested by experimental evidence in early atherosclerosis [8–12], diabetes [13], or obesity [14] in which renal MV disease and tissue damage occur without a significant deterioration of renal function, which appears at later stages of the disease or develops after addition of insults (e.g., renal ischemia, renal artery stenosis). Therefore, the nutritional role of the small vessels is crucial for not only maintenance of the renal structure, but also seems to play a role in instigating renal functional and structural injury when defective.

Role of the Renal Microcirculation in Renal Function

The total renal vascular resistance is determined by the sum of the resistances of interlobar, arcuate, and interlobular arteries, afferent and efferent arterioles, capillaries, and veins in the kidney. An increase in the resistance of any of these vascular segments may reduce renal blood flow (RBF), whereas a decrease will increase it if renal artery

and vein pressures remain constant. In turn, the changes in tone in afferent and efferent arterioles and in glomerular capillary pressure are the main determinants of glomerular filtration rate (GFR). Therefore, the resulting modifications in renal MV tone may result in changes in RBF and GFR separately or sometimes together and in a similar direction.

Following the efferent arterioles, the small vessels divide again and build the second capillary network going around the tubules. As mentioned earlier, glomerular capillaries play a central role in filtration and the peritubular capillaries are crucial for reabsorption and secretion of the glomerular filtrates towards formation of urine, which contribute to control of fluid homeostasis and regulation of blood pressure.

The majority of the evidence supporting the central role of the microvasculature in renal function comes from studies in which the density and/or function of the microvessels is reduced. It has been shown that functional and/or anatomical loss of renal microvessels (also known as MV rarefaction [15]) plays an important role in the reduction of RBF and GFR with normal aging [16], suggesting that regression of the small vessels is also a physiological event in the kidney. The loss of the contribution of renal microvessels to renal function is an important pathological event in renal disease and has been shown to impact renal hemodynamics [5, 6, 17] and function [18, 19]. Furthermore, the loss of peritubular capillaries has been indicated as the possible link between acute and chronic renal injury, suggesting capillary rarefaction as the turning point for the progression of renal damage towards chronic kidney disease [6]. This notion is supported by previous studies on hypertension, diabetes, acute and chronic renal ischemia, and aging, that underscored the importance of the renal MV network [4–6, 20–22].

Interestingly, as peritubular capillaries are among the first renal structures that are damaged when facing either acute or chronic insults, the capillary network surrounding the tubules as well as the vessels of smaller order (under 200 μm in diameter) seem to be capable of repair and proliferation (in both cortex and medulla) by targeted interventions [7, 23, 24]. Recent studies have shown that targeted administration of angiogenic cytokines or progenitor cells can recover the MV network, improve renal function and significantly reduce tissue injury [5, 7, 23, 25], implying plasticity of this MV network and underscoring the crucial role of the renal microcirculation in preserving renal function. The potential of targeted therapeutic interventions is beyond the scope of this section and will be discussed in chapters 19–21.

Microvascular Disease

Abnormalities in the microcirculation play an important role in the initiation and progression of several diseases [6, 26]. These abnormalities include vascular dysfunction, structural changes, and eventually, vascular loss, which may all compromise normal organ development and function and may deteriorate the responses of the tissue to injury. However, changes in MV tone will not always lead to MV remodeling and eventually MV rarefaction. Changes in vascular density are not always part of a pathological process and scenarios exist in which vessel constriction does not lead to vessel loss and is part of a normal physiological event. An example of this is the nonperfused capillaries that are recruited in skeletal muscle or the coronary flow reserve in case of a higher demand in a healthy patient.

Definition of Renal Microvascular Disease

A defective renal microcirculation, also known as MV disease, is a prominent pathological feature in chronic kidney disease (CKD), irrespective of the cause, and progresses as CKD evolves [27]. Experimental studies have shown that such changes are initially more evident at the cortical level, but suggest that they extend to the medulla as renal disease progresses [5, 7]. MV disease can compromise both the renal nutrition and renal function. Largely initiated by augmented vasoconstriction and endothelial dysfunction in

CKD [28], MV disease can alter renal blood flow and lead to a progressive decrease in peritubular capillary flow and consequently result in mild tubulo-interstitial ischemia [29], which could constitute both a cause and/or a consequence of damage in the kidney. Depending on the severity and duration of the stimulus causing long-term changes in tissue blood flow (e.g., increasing metabolic demands, reduced oxygen or glucose, increased reactive oxygen species, augmented MV shear stress [19, 20, 30]), sustained MV dysfunction can lead to alterations in the MV layers, resulting in permanent and often progressive modifications in MV shape, thickness, and diameter, a process also known as *vascular remodeling*. Eventually, combination of functional and structural MV changes can lead to the loss of the contribution (functional and/or anatomical) to organ function, a process that is known as *vascular rarefaction*. All these processes have been described in the vasculature of the kidney exposed to chronic renovascular disease. It is possible that they reflect different stages of the progression of renal damage, either as cause or possibly, as consequence.

Pathophysiology

Microvascular Endothelial Dysfunction

The integrity of the vascular endothelium is crucial for a normal exchange of solutes with the surrounding tissue and for control of vascular tone and permeability [31], vascular proliferation, and fluid homeostasis [32]. The endothelial cells are both targets and sources of vasoactive substances such as nitric oxide (NO), prostacyclin, angiotensin II or endothelin-1, to name a few. Endothelial dysfunction is the result of a combination of abnormal vasodilatory response of endothelial cells with an imbalance between substances that determines vascular tone, which are produced by or act on the endothelium [33]. Endothelial dysfunction has been implicated in the pathophysiology of hypertension [34], coronary artery disease [35], chronic heart failure [36], peripheral artery disease [37], diabetes [38], and chronic renal disease [39]. Furthermore, dysfunction of the vascular endothelium also favors the development of inflammation and thrombosis [40–43].

A central event in the development of endothelial dysfunction is the reduction in the bioavailability of NO, a potent vasodilator, anti-inflammatory and anti-aggregant gaseous molecule [44]. One of the most prominent mechanisms of the reduced vasodilatory responses in endothelial dysfunction is by increased inactivation of NO via reactive oxygen species (ROS). The reduction of NO is via ROS-mediated [45] quenching effects, which is pivotal in promoting vasoconstriction and ROS-mediated vascular inflammation, which may in turn further reduce NO bioavailability and perpetuates a potentially vicious circle of vasoconstriction and vascular damage. Additional mechanisms that may participate in promoting endothelial dysfunction are blunted production of NO by the endothelium (due to lack of co-factor tetra-hydro-biopterine) and reduced production of hyperpolarizing factors such as epoxyeicosatrienoic acids, hydrogen peroxide, or C-natriuretic peptide, among others [34].

A sustained vasoconstriction due to endothelial dysfunction could lead to reductions in tissue blood flow and consequently, diminished provision of nutrients and altered fluid homeostasis between intra- and extra-vascular spaces due to abnormal MV permeability. One of the consequences of an increase in MV permeability is the potential increase for extravasation of cytokines that may further expand tissue damage [9]. This complex but important sequence of events is considered to serve as a link between hypertension, CKD, and diabetes and the augmented risk of cardiovascular events. Furthermore, previous clinical [30–32] and experimental [6, 21, 46, 47] studies of both acute and chronic renal disease have demonstrated this cascade of events in the kidney.

A prolonged renal vasoconstriction could lead to reduced perfusion of the intra-renal MV network and subsequent defect on renal nutrition and, ultimately, renal hemodynamics and function. Thus, the loss of the contribution of small vessels (functional MV rarefaction [48]) could lead to a progressive renal functional and later structural damage in renal disease. The latter has

been demonstrated by interventions that can augment the systemic and renal bioavailability of NO [8, 10, 46, 49–53] through decreasing its degradation and/or stimulating sources of NO such as endothelial NO synthase (eNOS).

In summary, the severity of endothelial dysfunction plays a key role in determining the contribution of the vessels to renal hemodynamics and function. Furthermore, it is possible that by favoring additional deleterious mechanisms such as inflammation [54, 55], thrombosis [56], and the damaging of the extra-vascular space [57], endothelial dysfunction may promote the transition from functional to structural changes in the small vessels.

Microvascular Remodeling

Although in the medical literature MV remodeling often refers to pathological settings, this is a broad term that in general refers to progressive changes in vascular shape that may occur during development and disease [58]. Regardless of the underlying cause, a sustained reduction in tissue perfusion (as occur in renovascular disease) may activate several enzymes and growth factors, triggering morphological changes in the vascular lumen, vascular thickness, and on the outer layers of capillaries, resistance, and conduit vessels.

There are a number of growth factors that may directly or indirectly promote vascular remodeling [58, 59]. For instance, tissue transglutaminase is a cross-linking enzyme that promotes inward remodeling in small arteries exposed to chronic reductions of blood flow [60]. A prolonged vasoconstriction due to endothelial dysfunction can lead to entrenchment of reduced diameter that is sustained by this enzyme and its interaction with integrins on the organization of matrix components and vascular remodeling [51]. Another pro-fibrotic factor often involved in renal disease and with effects on small vessels is transforming-growth factor (TGF)-β, a powerful mediator of epithelial-to-mesenchymal transition and promoter of renal fibrosis [52, 61]. TGF-β exerts its multiple actions via specific receptors and mediators known as smads, and has direct effects on vascular proliferation and remodeling by promoting the reduction of vascular lumen, adventitial fibrosis and collagen matrix deposition around the vessel. Furthermore, TGF-β induces tissue proliferation and may also favor accumulation of extracellular matrix in the renal parenchyma by inhibiting matrix metalloproteinases (MMP) [62]. A deficiency in MMPs may lead to abnormal development of the vasculature as well as to deleterious changes in the pre-existent vasculature due to extracellular-matrix (ECM) accumulation. The MMP family is important for the development, expansion, and also preservation of the renal MV architecture. MMP-2 and -9 are the most active collagenases in the kidney and has been shown to have blunted activity in experimental models of renal disease [12], which correlate with significant MV disease and blunted renal function. Importantly, deficiencies in MMPs have also been reported in clinical studies [63, 64]. Another contributing factor to MV remodeling is connective tissue growth factor (CTGF), a peptide synthesized and secreted by fibroblasts after activation by TGF-β, which has direct effects on vascular remodeling [65] and serves as a downstream mediator of TGF-β -induced fibroblast collagen synthesis and collagen accumulation [66–68].

MV remodeling is a dynamic process that involves promoters and inhibitors of tissue proliferation. There are also factors that can counterbalance the effects of TGF- β and CTGF, such as hepatocyte growth factor (HGF), an anti-fibrotic and pro-angiogenic factor that has been shown to be capable of reducing renal fibrogenesis by attenuating CTGF-mediated induction of TGF-β [69]. This is a pleiotropic and ubiquitous growth factor that participates in tissue remodeling in the heart [70, 71], liver [72], and lungs [73], and is a powerful stimulus for vascular proliferation, repair, and angiogenesis [70, 74]. HGF seems to participate in MV protection, repair and proliferation in the kidney exposed to chronic low flow [46, 52].

It has been shown that MV remodeling correlates with renal scarring [75], which may subsequently induce additional changes in vascular morphology. Indeed, the build-up of scar tissue may oppose the normal expansion and development of the renal vasculature [76]. In turn, the ECM is a source of anti-angiogenic mediators

and promoters of vascular regression [77]. Thus, accumulation of ECM may impose an obstacle that constrains and limit vascular growth and expansion in the renal parenchyma, increase the interstitial pressure and consequently the pressure on the vessels [78], further stimulating MV remodeling.

Microvascular Rarefaction

The majority of the chronic degenerative diseases are characterized by large alterations in MV number that not only correlate, but also accelerate the development and progression of tissue fibrosis. Although vascular rarefaction implies the loss of vessels, two forms should be distinguished: a "functional rarefaction" that represents a pathological decrease in the number of perfused vessels without changing the number of anatomically present vessels, and "structural rarefaction," which refers to a physical reduction in the number of vessels in the tissue [15]. It is important to emphasize that these processes are not mutually exclusive. On the contrary, they can occur in a sequence since functional rarefaction could progress to structural rarefaction [79]. Both processes of MV rarefaction likely occur in chronic RVD.

Either by functional rarefaction (due to sustained vasoconstriction or endothelial dysfunction), structural rarefaction (remodeling and eventually regression and loss), or a combined sequence of both processes, the functional and/or anatomical reduction in MV availability can transiently or permanently deteriorate RBF, GFR, and tubular function. Supporting evidence has shown that MV rarefaction (usually first compromising the capillaries and arterioles) accompanies glomerulosclerosis and tubulo-interstitial fibrosis [4, 22, 25, 80, 81]. However, it is important to emphasize that MV rarefaction could also be considered as a downstream consequence in renal disease, suggesting a dual role as culprit and victim.

Several initiating mechanisms participate in the development of pathological MV rarefaction, and include a combined activation of signaling pathways, removal of survival factors, reductions in vessel perfusion [82, 83], and changes in vascular shape and in the dynamics of blood circulation. An example of this multifactorial process is provided by recent studies showing that reductions in the renal microvasculature after acute or chronic kidney injury results from endothelial phenotypic transition and apoptosis combined with an impaired regenerative capacity [21, 46].

The endothelial cells are capable of producing both pro- and anti-angiogenic cytokines. Indeed, an abnormal, insufficient, or absent angiogenic stimulus due to reduction in angiogenic cytokines such as vascular endothelial growth factor (VEGF) has been observed in both experimental and clinical settings [7, 27]. A deficient availability of VEGF seems to be a key event in the process of renal MV rarefaction. VEGF is a pivotal angiogenic cytokine that operates directly and in concert with other factors to stimulate cell division, migration, endothelial cell survival, and tube formation, which are key steps for generation, repair, and maintenance of the MV networks, including those in the kidney. VEGF promotes vascular proliferation and repair via powerful stimulation of the mobilization of endothelial cell progenitors [84, 85], which are pro-angiogenic and also a source of anti-fibrogenic factors [23, 24]. Experimental and clinical evidence suggest that chronic reductions of renal blood flow [5, 51], progressive glomerulopathies [86], or CKD [27] are sometimes associated with significant reductions in VEGF. A major stimulus for VEGF generation is hypoxia. However, VEGF rapidly increases in acute hypoxia [87], but eventually decreases when hypoxia is prolonged [88]. These particular characteristics of the VEGF biology have been recently demonstrated in vivo (swine model of renovascular disease [5, 89–91]) and in vitro (renal cells) [55], suggesting a bi-phasic regulation of VEGF during development of chronic hypoxia in the renal tissue. The reduction in the bioavailability of VEGF is not the sole cause of MV rarefaction. Indeed, reductions in upstream (e.g., HIF-1α, NO) and/or downstream mediators (e.g., angiopoietin-1) of VEGF-mediated angiogenic signaling in the kidney [5, 23, 91] have been shown to accompany the changes in VEGF underscoring the notion that mechanisms of MV disease and rarefaction are multifactorial.

As mentioned earlier, endothelial cells could act as victims of MV rarefaction but may also serve as initiators. Indeed, endothelial cells can release anti-angiogenic mediators that can promote MV regression. Angiostatin is a MMP-induced proteolytic cleavage product of plasminogen and a potent inhibitor of VEGF and downstream mediators [92, 93]. Angiostatin increases in renal ischemia and can inhibit angiogenesis by reducing VEGF-induced proliferation and repair of peritubular capillaries (consequently accelerating tubular and interstitial damage [94]), by promoting apoptosis of endothelial cells, and by disrupting capillary integrity leading to capillary dropout [95]. Another potent extracellular anti- angiogenic factor and inhibitor of cell proliferation that is highly expressed in the kidney is endostatin. Endostatin is elevated in patients with CKD and this increase correlates with renal impairment and damage and a decrease in progenitor cells, implying a role in the progressive MV rarefaction observed in CKD [96]. Endostatin inhibits VEGF-induced endothelial cell migration and binds to both renal endothelial and epithelial cells [97, 98]. It is highly expressed during the progression of tubulointerstitial injury and renal fibrosis [99]. Finally, in certain pathological conditions, anti-angiogenic splice variants of VEGF (VEGF-b isoforms) could be released and not only inhibit MV proliferation but may also promote MV regression [100].

A sustained and often progressive reduction in tissue perfusion in renovascular disease is also a powerful stimulus for the development of renal fibrosis. The accumulation of extracellular matrix in the kidney does not merely reflect the build-up of scarring tissue. On the contrary, the ECM constitutes an active source of potential anti-angiogenic mediators and inhibitors of cell proliferation that impact vascular proliferation and stabilization as well as remodeling and regression. Among these anti-angiogenic factors are the previously mentioned angiostatin, and also others that are highly expressed in kidneys such as MMP-10, angiopoietin-2, and thrombospondins [101]. These factors operate in concert blunting angiogenesis and also decreasing MV development and expansion by down-regulating, for example, other MMPs [10, 77]. An additional consequence of renal scarring on the existing vessels could be MV remodeling due to mechanical forces of the fibrotic tissue imposed on the vessels. Such changes on the pre-existing vasculature may also slow-down the normal circulation and impact the shear stress necessary to stimulate, for example, eNOS-derived NO that maintains vascular tone in remaining vessels, leading to MV functional and eventually structural closure [82, 83]. These suggest an interesting progressive deleterious mechanism in which the vessels and the extra-vascular tissues closely interact and could open potential avenues for novel therapeutic targets.

In summary, we can conclude that a decrease in the number and density of small vessels within the organs could be initiated by sustained vasoconstriction (functional rarefaction), that if continuous, may promote morphological changes that could ultimately lead into vascular regression and loss (structural rarefaction). In turn, an eventual loss of microvessels may further aggravate tissue damage and perpetuate a vicious circle of vasoconstriction-vascular remodeling-vascular loss-tissue injury (Fig. 8.2a–d).

Renal Microvascular Disease: Cause or Consequence of Renal Dysfunction?

Due to its multifactorial nature, it should be recognized that a specific cause of MV disease is quite difficult to identify. On the same line, MV disease could likely be the cause as well as the consequence of the progressive nature of many kidney diseases, including renovascular disease. Although renal artery stenosis is the main etiology of renovascular disease, this pathology is not only limited to overt obstructions of the main renal circulation. Indeed, previous studies have shown that renal MV dysfunction and damage could develop in the absence of significant reductions of blood flow or deterioration of renal function. For example, lipid abnormalities induce significant changes in the small vessels of the renal parenchyma, leading to abnormal MV

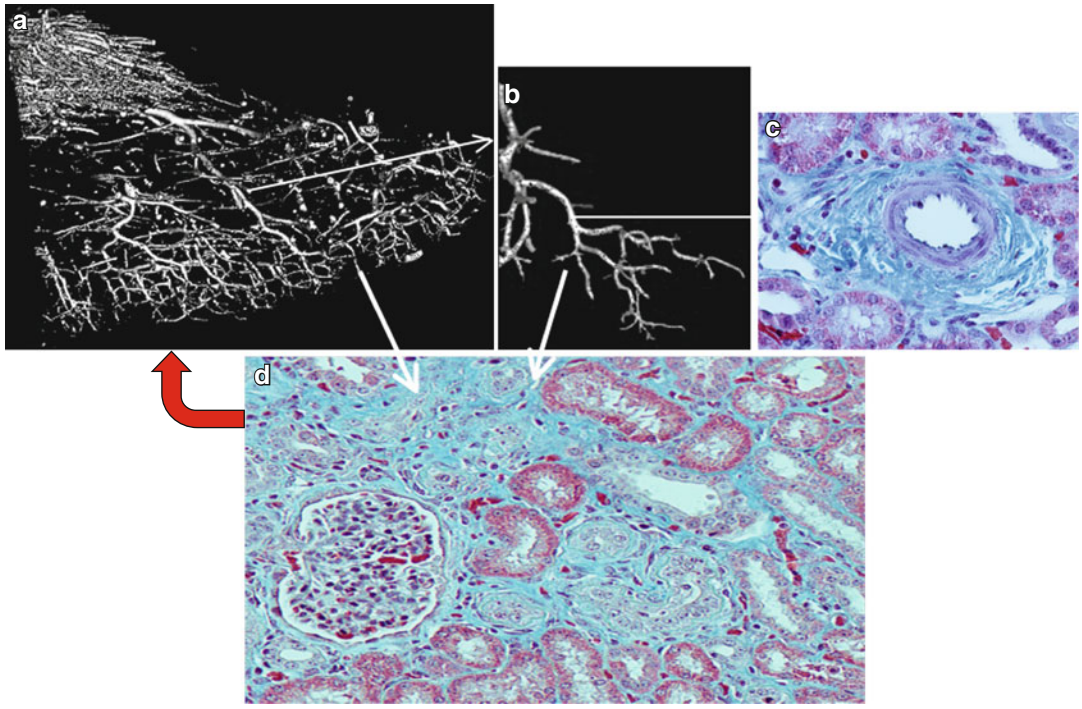


Fig. 8.2 Representative figure showing a 3D micro-CT reconstruction of the renal microvascular (MV) architecture (**a**), a tomographic "dissection" of a renal microvessels (**b**), and representative trichrome-stained renal cross sections showing MV remodeling (**c**, ×40) and fibrosis (**d**, ×20) of a kidney exposed to experimental renovascular disease due to renal artery stenosis. There is a progressive reduction in MV number (**a**) and remodeling (**b**, **c**) that correlates with (and likely promotes) the progression of renal fibrosis (**d**). In turn, it is possible that the build-up of scarred tissue in the renal parenchyma in turn induce changes in MV shape and morphology (*red arrow*), as could also be a source for promoters of MV regression

function and incipient damage without major impact on basal RBF or GFR [9, 10, 47, 102]. These changes are likely representative of what is observed in the early stages of atherosclerosis in humans and support the notion of MV disease as a possible initiator of renal damage. The notion of MV disease in the absence of major deterioration of renal function is extended by the MV dysfunction and damage that are observed in hypertension [47, 103], diabetes, or obesity [13, 104]. Hence, early changes in renal MV function could likely serve as instigators of renal dysfunction during progression of these cardiovascular risk factors.

On the other hand, blunted filtration or tubular function may lead to an abnormal recovery of elements or disposal of toxins by urine, which are critical steps for maintenance of fluid homeostasis. Therefore, it is also possible that a blunted renal function could promote MV dysfunction that may in turn further contribute to the progression of renal dysfunction and tissue injury. Thus, beyond the initiating role and order of which one comes first, the important message is the fact that MV disease is indeed a key contributor for the initiation and progression of renal damage in renal disease, and that targeting the small vessels may serve as a therapeutic intervention to prevent, halt, or reverse the progression of renal injury [7, 23, 24].

Cardiovascular Risk Factors and Renal Microvascular Disease

Abnormalities of the MV system are frequently observed at some stage during development and progression of hypertension, diabetes, obesity,

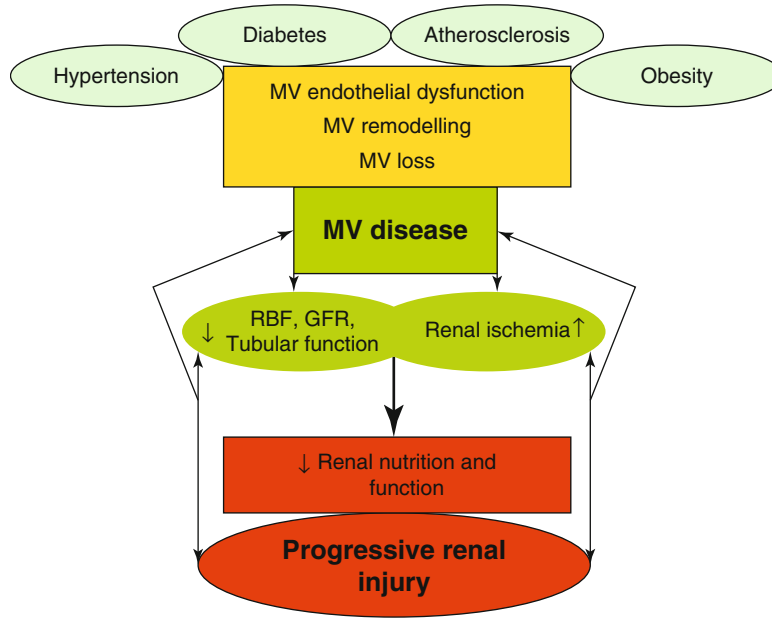


Fig. 8.3 Schematic illustration summarizing the changes in renal microvascular (MV) function, morphology, and number that could be observed during progression of hypertension, diabetes, atherosclerosis, and obesity. Renal MV disease leads to deterioration in renal nutrition and function, which is progressive and may result in evolving renal injury. In turn, progressive renal damage may further enhance MV disease and deterioration of the renal function, resulting in a potentially vicious circle

and dyslipidemia. For example, MV changes are not only hallmarks of the long-term complications of hypertension and diabetes, but are also present at their early stages and may be important in their pathogenesis and progression [15]. The kidney is not the exception, and changes in the renal microvasculature accompany the development and progression of renal injury associated with these prevalent CV risk factors. However, it is not entirely clear whether MV rarefaction is a primary initiating and causative mechanism of renal injury. I will cover in this section the current most prevalent CV risk factors capable of inducing renal MV disease, from dysfunction to permanent damage and eventually loss (Fig. 8.3).

Renal Microvascular Disease in Hypertension

Microvascular disease in hypertension covers the whole spectrum of MV damage. This is one of the most prevalent cardiovascular risk factors that may cause renal MV endothelial dysfunction and remodeling, ultimately resulting in tissue hypoxia [31]. The transmission of elevated blood pressure into the smaller MV networks promotes inward [15] eutrophic or hypertrophic arteriolar remodeling and capillary rarefaction, especially in highly perfused organs with relatively low vascular resistance, such as the kidney, heart, and brain [105]. In turn, dysfunction of the small vessels in the kidney could lead to rarefaction, which could be functional, associated with impaired recruitment of non-perfused capillaries or structural, associated with impaired angiogenesis and/or a slow disappearance of capillaries by apoptosis [48]. These changes in vascular structure can influence tissue blood flow resistance and markedly alter blood flow distribution and compromise renal function, which in turn contribute to hypertensive end-organ damage, by further increasing blood pressure, reducing tissue perfusion, and promoting target organ damage [17, 106].

An elevation of renal arterial pressure could increase vasa recta capillary pressure and renal interstitial fluid pressure [107], which could be transmitted within renal resistance vessels and glomeruli. Capillaries contain actin filaments which may indicate some form of contractility [108]. However, capillaries are relatively non-distensible and often the endothelial cell nuclei encroach on the lumen to reduce luminal cross-sectional area by 50 % or more, resulting in a slowing or diversion of the blood stream to other

vessels. Therefore, renal capillaries can contribute to vascular resistance control by virtue of their narrow caliber, by the reduction in their number (rarefaction), or possibly through their deformations [33, 48]. These forces may extend to the renal interstitial space, further compromise the small vessels, and ultimately contribute to the development of renal fibrosis, which is thought to be a consequence of the increased blood pressure and exaggerated formation of extracellular matrix in mesangial and vascular smooth muscle cells. The latter is considered as an adaptive response of the intra-renal circulation [33].

Hypertension-induced renal MV damage is mediated by numerous factors generated both systemically and locally in the kidneys. For example, potent vasoconstrictors such as angiotensin II and endothelin-1 have been widely studied on their role in generation and maintenance of hypertension and their contributions to MV disease. By inducing vasoconstriction (both directly and via generation of reactive oxygen species [109–111]) and by activating pro-inflammatory and pro-fibrotic mechanisms, angiotensin II and endothelin-1 can lead to significant increases in renal MV tone and initiate MV remodeling and damage [112] in the surrounding renal parenchyma. This notion is underscored by studies showing that blockade of these pathways [46, 113] in models of hypertension are associated with decreased MV rarefaction and damage and augmented MV proliferation. Although difficult to separate since these events may occur at the same time in the kidney exposed to hypertension, endothelial dysfunction and vasoconstriction are likely the initial steps of a deleterious sequence leading to renal MV remodeling and eventually rarefaction and subsequent tissue damage in hypertension.

Renal Microvascular Disease in Diabetes

Macrovascular and MV disease play a central role in the pathogenesis of diabetic complications. The progressive changes in MV number and function during evolution of diabetes play a central role in target-organ damage. Diabetes mellitus is an intriguing disease that can induce MV dysfunction, pathological MV proliferation (e.g., retinopathy [114]) or rarefaction (e.g., skeletal muscle [115], kidney [19]).

As diabetes progresses MV health decreases, eventually leading to chronic renal ischemia and progressive tubulointerstitial fibrosis [116]. The mechanisms behind MV disease in the diabetic kidney are multifactorial and triggered by a plethora of insults such as hyperglycemia-induced MV endothelial dysfunction [117], MV insulin resistance [118], augmented advanced-glycation end products (with a consequent reduced NO bioavailability and vasoconstriction) and increased secretion of cytokines and growth factors such as TGF-β and CTGF [119, 120]. Furthermore, diabetes-induced renal damage is also amplified by a significantly blunted ECM turnover, largely through reductions of MMP activity [121]. Hyperglycemia has been shown to play a deleterious role on the function of cell progenitors [122] and on the VEGF-eNOS pathway, leading to impairment of the angiogenic response [123]. In the kidney, it has been suggested that hyperglycemia is initially associated with high but ineffective VEGF signaling that translates into a progressive MV dysfunction and damage in early diabetes [124, 125]. Moreover, it has been recently reported that VEGF and NO, key promoters of renal MV proliferation and repair, progressively decreased in the diabetic kidney, which correlates with renal dysfunction, progressive damage and a reduction of renal MV density [13, 19] that is mainly evident in the glomerular and tubulo-interstitial capillary network. These deleterious changes are accompanied by blunted angiogenic activity but progressive MV rarefaction, MV remodeling, and early tubule-interstitial fibrosis as diabetes evolves and renal function is still preserved. Tubulo-interstitial damage is an important predictor of renal dysfunction in diabetic nephropathy that precedes the development of glomerulosclerosis. In addition, the severity of glomerular capillary rarefaction correlates with the degree of glomerulosclerosis, as the endothelial cell proliferation and MV repair capability is directly proportional to the degree of

glomerulosclerosis, indicating that MV disease in the diabetic kidney [126] is a pivotal process for the progression of renal injury.

These interesting findings first strongly suggest that MV disease in the diabetic kidney may affect both developing and pre-existent mature vessels [13]. Furthermore, the presence of renal MV disease and tissue damage before any changes in renal function support the notion that MV changes could be the initiating events in diabetic nephropathy that ultimately lead to a later deterioration of renal function in the diabetic kidney [13, 116, 127].

Renal Microvascular Disease in Dyslipidemia and Atherosclerosis

Atherosclerosis is a systemic and chronic inflammatory vascular disease that is associated with renal disease, both as cause and as consequence [128, 129], and compromises the function and structure of small and large vessels. The development of obstructive atherosclerotic plaques in the main renal artery or primary bifurcations, known as renal artery stenosis [130], is the main causes of chronic renovascular disease in older patients [131, 132]. A chronic obstruction of blood flow could progressively deteriorate renal function that may eventuate in CKD or ESRD [131, 133]. However, it has been shown that there is a lack of correlation between severity of renal dysfunction and renal stenosis suggestive of direct effects of atherosclerotic factors independent of the obstruction [134]. This indicates that the deleterious effects of atherosclerosis on the kidney are not defined only by the severity of the renal obstruction but possibly by atherogenic factors activated distal to the stenosis that affect the renal parenchyma. The build-up of atherosclerotic plaques obstructing renal blood flow reflects an advanced (and often more severe) stage of the disease, but has been demonstrated that earlier stages of the disease, with fatty streaks or no lipid accumulation, present significant MV disease and early structural changes [8, 10, 47]. Moreover, this notion is supported by the fact that resolution of the stenosis does not always recover renal function, as shown in human [131, 135] and experimental studies [81].

Previous studies suggest that atherosclerosis has direct effects on the kidney, largely because of intra-renal MV and glomerular disease that precedes the onset and may represent the silent phase of ischemic renal disease [47, 102, 136], being capable to initiate renal injury at an early stage. Experimental studies demonstrated that diet-induced lipid abnormalities resulted in renal endothelial dysfunction, intrarenal inflammation, fibrosis, and a significant vascular dysfunction, damage and remodeling [10, 47, 102, 137, 138] on the matured renal vasculature. Abundant oxidation of lipids (e.g., oxidized LDL) have been shown to impair eNOS activation, reduce intracellular level of NO and thereby inhibit VEGF-induced migration of endothelial cells, consequently impairing vascular proliferation and repair [139]. Furthermore, it has been recently shown that dyslipidemia superimposed on renal artery stenosis can also accelerate not only MV dysfunction and remodeling, but also MV loss in the renal cortex, underscoring ample deleterious effects of atherogenic factors on the renal parenchyma [81].

On the other hand, it has been shown that dyslipidemia can also stimulate MV proliferation in the kidney, but new vessel formation under these circumstances may be an adaptive response to local tissue fibrosis and inflammation. Although this is possibly a compensatory mechanism that sustains basal renal vascular function, the augmented vasculature is likely a result of an inflammation-induced angiogenesis [8, 9] resulting in the generation of partly dysfunctional vessels. Furthermore, the newly generated vessels may participate on the progression of renal functional and parenchymal injury due to increased MV permeability and abnormal endothelial function [9, 10]. Hence, early atherosclerosis is associated more with MV dysfunction, possibly functional rarefaction, and MV remodeling than actual loss of vessels. Nevertheless, it is possible that pro-fibrotic factors activated during atherogenesis in the kidney can contribute at a later

stage to MV loss or regression via ECM accumulation, as it was discussed earlier.

Renal Microvascular Disease in Obesity

Obesity is a growing public health problem in the United States that is reaching epidemic proportions. Recent studies have shown that over 30 % of the US adults are obese, and more than 60 % of adults and about 20 % of children and adolescents are overweight [140, 141]. Obesity has been shown to induce MV dysfunction, remodeling, and rarefaction partly due to abnormal vasodilatation [142, 143] and on impairing tissue perfusion directly and via obesity-associated hypertension and insulin resistance [144, 145], suggesting that MV disease could be an important causal factor in obesity-related disorders. Furthermore, obesity is a risk factor for the development of hypertension, diabetes, and lipid abnormalities, which are all prominent renal risk factors associated with significant MV disease. Therefore, it is possible that renal MV dysfunction and damage in obesity resulted from multiple direct and indirect (co-morbid-mediated) insults.

Evidence supporting obesity as a risk factor for renal MV disease is scant. Previous studies suggested that obesity can injure the kidneys both directly, by physical compression, and by sustained production of pro-inflammatory and growth-promoting factors leading to ECM proliferation, thickening of the glomerular and tubular basement membranes, and renal fibrosis [11, 78, 146]. Furthermore, a recent study in obese Zucker rats suggests that obesity promotes a progressive renal MV proliferation and remodeling (Fig. 8.4) possibly via up-regulation of inflammatory factors such as TNF-α and interleukin-6 [14]. The pathological inflammatory-induced angiogenesis observed in this study might reflect an initially compensatory mechanism that may serve to explain, for instance, the increase in GFR observed in obesity at early stages. Nevertheless, it is unlikely that obesity-induced MV changes are protective on the long run since the progression of inflammation may further promote renal injury as obesity advances and in turn aggravate MV dysfunction, remodeling and development and progression of renal fibrosis.

Summary and Conclusions

An intact and healthy renal microcirculation is vital to ensure tissue perfusion and adequate filtration and removal of toxins from the circulation. In turn, adequate perfusion of the renal tissue is critical to achieve successful renal repair in response to injury. Severity of MV damage and loss may determine the frontier between reversible and irreversible renal injury by promoting the progression of renal functional and structural damage. Chronic renovascular disease is a growing problem in the older population. Emerging evidence supports the notion that the extent and severity of renal damage in this disease seem to be largely mediated by renal MV disease. Indeed, MV dysfunction, remodeling, and loss as well as MV repair and MV proliferation can be activated (both in cortex and medulla) due and in response to different insults and with an impact on renal function [5, 7, 10, 23, 51, 91].

Furthermore, it is possible that as glomerulosclerosis and tubulo-interstitial fibrosis are the hallmark of the advanced stages of CKD and ESRD, MV disease may indeed represent the initial steps of renal injury and may be crucial for its progression. MV disease leads to inadequate perfusion and tissue ischemia. Ischemia is a powerful stimulus for activation of inflammatory and fibrotic cytokines leading to renal parenchymal injury, initiating a process that could eventuate in progressive and later irreversible renal injury. As discussed in this chapter, MV disease could also be a consequence of the progression of renal injury.

Several studies have shown that renal MV rarefaction correlates with the progressive deterioration of RBF, GFR, perfusion, and tubular function [5, 7, 23, 81]. Experimental evidence from our laboratory supports the notion that such changes in the kidney exposed to renovascular disease could partly be reversible by targeted protection of the renal microvasculature [5, 23]. Targeted

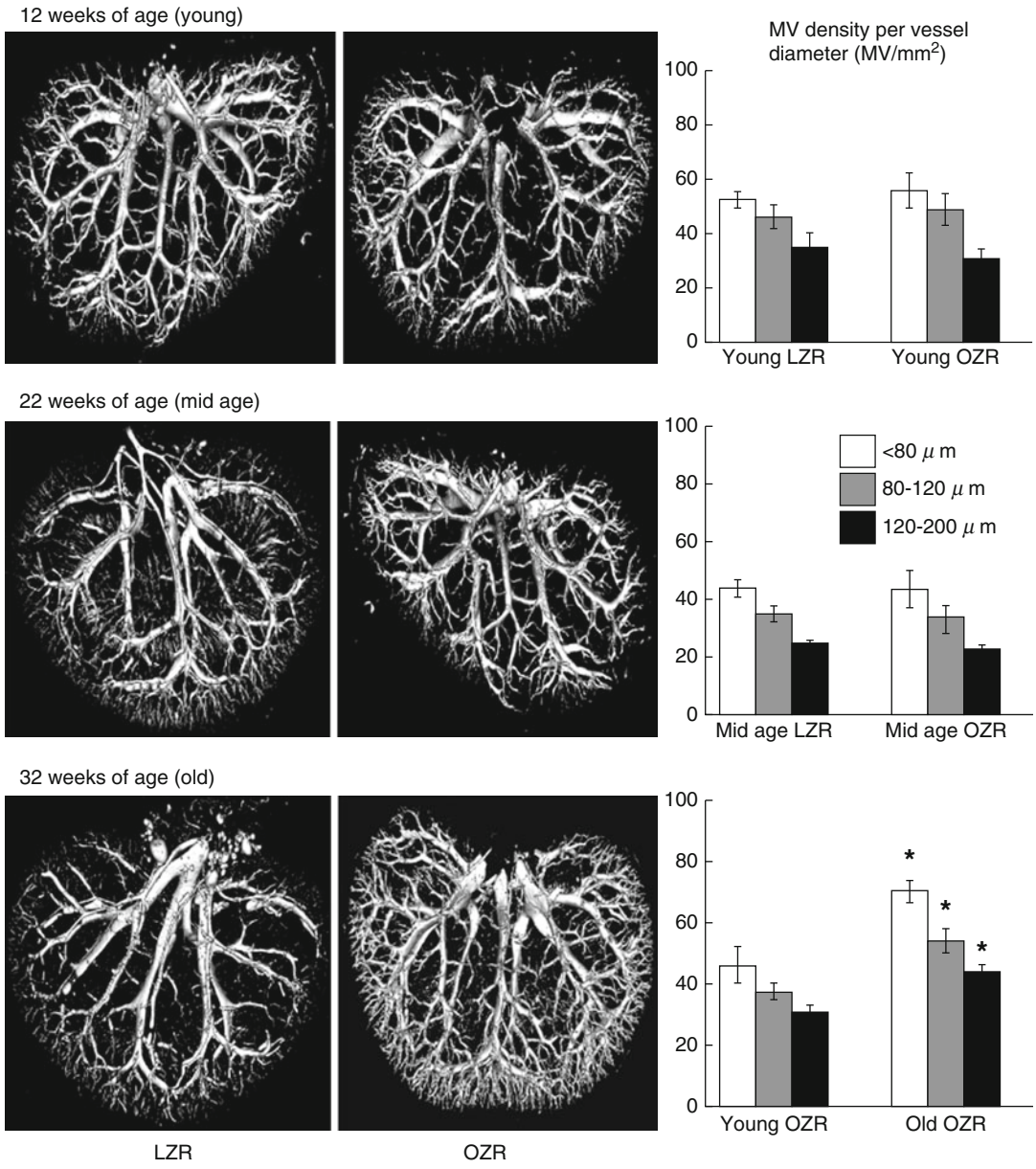


Fig. 8.4 Representative 3D tomographic images of the renal microcirculation and quantification of microvascular (MV) density per vessel diameter (0–80 μm, 80–120 μm, and 120–200 μm) from lean and obese Zucker rat kidneys after 12 (*top row*), 22 (*middle row*), and 32 (*bottom row*) weeks of age. Renal MV density progressively increased in obese Zucker rats after 32 weeks and longer exposure to obesity, compared to the lean animals. *$p<0.05$ vs. LZR (With permission from Iliescu and Chade [14])

interventions to enhance endogenous reno-protective mechanisms such as cell-based therapy or the use of angiogenic cytokines have shown promising results in experimental renovascular disease [1, 5, 7, 23, 24]. Furthermore, it is possible that reversal of MV disease by generation of new vessels and/or stimulation of MV repair contribute to restore filtration on partly damaged or hibernating [147, 148] nephrons that could still be recovered. These findings emphasize the importance of MV

disease in determining the progression of renal injury in chronic renovascular disease.

It is possible that an underestimation of the severity of renal MV disease plays a role in defining the success of established and some novel therapeutic interventions since dysfunctional or damaged vessels can progressively deteriorate renal perfusion, filtration, and tubular function, as we have shown. Therefore, future carefully designed prospective experimental and clinical studies should first concentrate on non-invasive assessment of the intra-renal MV architecture, distribution, and function. Furthermore, additional research is also needed to further establish the role of targeting renal MV disease as a feasible therapeutic strategies to preserve, protect, and hopefully recuperate the kidney under progressive deterioration.

Sources of funding: Supported by grant HL095638 from the National Institute of Health.
Disclosures: None. There are no conflicts of interest to disclose by the author.

References

1. Chade AR. Renovascular disease, microcirculation, and the progression of renal injury: role of angiogenesis. Am J Physiol Regul Integr Comp Physiol. 2011;300:R783–90.
2. Navar LG, Arendshorst WJ, Pallone TL, Inscho EW, Imig JD, Bell PD. The renal microcirculation. Comprehensive Physiology. 2011;550–683.
3. Hall JE. Guyton and Hall textbook of medical physiology. 12th ed. Philadelphia: Elsevier; 2011.
4. Kang DH, Anderson S, Kim YG, Mazzalli M, Suga S, Jefferson JA, Gordon KL, Oyama TT, Hughes J, Hugo C, Kerjaschki D, Schreiner GF, Johnson RJ. Impaired angiogenesis in the aging kidney: vascular endothelial growth factor and thrombospondin-1 in renal disease. Am J Kidney Dis. 2001;37:601–11.
5. Iliescu R, Fernandez SR, Kelsen S, Maric C, Chade AR. Role of renal microcirculation in experimental renovascular disease. Nephrol Dial Transplant. 2010;25:1079–87.
6. Basile DP. Rarefaction of peritubular capillaries following ischemic acute renal failure: a potential factor predisposing to progressive nephropathy. Curr Opin Nephrol Hypertens. 2004;13:1–7.
7. Chade AR, Kelsen S. Reversal of renal dysfunction by targeted administration of vegf into the stenotic kidney: a novel potential therapeutic approach. Am J Physiol Renal Physiol. 2012;302:F1342–50.
8. Chade AR, Krier JD, Rodriguez-Porcel M, Breen JF, McKusick MA, Lerman A, Lerman LO. Comparison of acute and chronic antioxidant interventions in experimental renovascular disease. Am J Physiol Renal Physiol. 2004;286:F1079–86.
9. Chade AR, Krier JD, Galili O, Lerman A, Lerman LO. Role of renal cortical neovascularization in experimental hypercholesterolemia. Hypertension. 2007;50:729–36.
10. Chade AR, Krier JD, Textor SC, Lerman A, Lerman LO. Endothelin-a receptor blockade improves renal microvascular architecture and function in experimental hypercholesterolemia. J Am Soc Nephrol. 2006;17:3394–403.
11. Chade AR, Lerman A, Lerman LO. Kidney in early atherosclerosis. Hypertension. 2005;45:1042–9.
12. Chade AR, Mushin OP, Zhu X, Rodriguez-Porcel M, Grande JP, Textor SC, Lerman A, Lerman LO. Pathways of renal fibrosis and modulation of matrix turnover in experimental hypercholesterolemia. Hypertension. 2005;46:772–9.
13. Maric-Bilkan C, Flynn ER, Chade AR. Microvascular disease precedes the decline in renal function in the streptozotocin-induced diabetic rat. Am J Physiol Renal Physiol. 2012;302:F308–15.
14. Iliescu R, Chade AR. Progressive renal vascular proliferation and injury in obese zucker rats. Microcirculation. 2010;17:250–8.
15. Levy BI, Schiffrin EL, Mourad JJ, Agostini D, Vicaut E, Safar ME, Struijker-Boudier HA. Impaired tissue perfusion: a pathology common to hypertension, obesity, and diabetes mellitus. Circulation. 2008;118:968–76.
16. Urbieta Caceres VH, Syed FA, Lin J, Zhu XY, Jordan KL, Bell CC, Bentley MD, Lerman A, Khosla S, Lerman LO. Age-dependent renal cortical microvascular loss in female mice. Am J Physiol Endocrinol Metab. 2012;302(8):E979–86.
17. Pessina AC. Target organs of individuals with diabetes caught between arterial stiffness and damage to the microcirculation. J Hypertens Suppl. 2007;25:S13–8.
18. Rabelink TJ, Wijewickrama DC, de Koning EJ. Peritubular endothelium: the achilles heel of the kidney? Kidney Int. 2007;72:926–30.
19. Lindenmeyer MT, Kretzler M, Boucherot A, Berra S, Yasuda Y, Henger A, Eichinger F, Gaiser S, Schmid H, Rastaldi MP, Schrier RW, Schlondorff D, Cohen CD. Interstitial vascular rarefaction and reduced vegf-a expression in human diabetic nephropathy. J Am Soc Nephrol. 2007;18:1765–76.
20. Mayer G. Capillary rarefaction, hypoxia, vegf and angiogenesis in chronic renal disease. Nephrol Dial Transplant. 2011;26:1132–7.
21. Basile DP, Friedrich JL, Spahic J, Knipe N, Mang H, Leonard EC, Changizi-Ashtiyani S, Bacallao RL, Molitoris BA, Sutton TA. Impaired endothelial proliferation and mesenchymal transition contribute to vascular rarefaction following acute kidney injury. Am J Physiol Renal Physiol. 2011;300:F721–33.
22. Bohle A, Mackensen-Haen S, von Gise H. Significance of tubulointerstitial changes in the renal cortex for the

excretory function and concentration ability of the kidney: a morphometric contribution. Am J Nephrol. 1987;7:421–33.
23. Chade AR, Zhu X, Lavi R, Krier JD, Pislaru S, Simari RD, Napoli C, Lerman A, Lerman LO. Endothelial progenitor cells restore renal function in chronic experimental renovascular disease. Circulation. 2009; 119:547–57.
24. Chade AR, Zhu XY, Krier JD, Jordan KL, Textor SC, Grande JP, Lerman A, Lerman LO. Endothelial progenitor cells homing and renal repair in experimental renovascular disease. Stem Cells. 2010;28:1039–47.
25. Kang DH, Hughes J, Mazzali M, Schreiner GF, Johnson RJ. Impaired angiogenesis in the remnant kidney model: ii. Vascular endothelial growth factor administration reduces renal fibrosis and stabilizes renal function. J Am Soc Nephrol. 2001;12:1448–57.
26. Bobik A. The structural basis of hypertension: vascular remodelling, rarefaction and angiogenesis/arteriogenesis. J Hypertens. 2005;23:1473–5.
27. Futrakul N, Butthep P, Laohareungpanya N, Chaisuriya P, Ratanabanangkoon K. A defective angiogenesis in chronic kidney disease. Ren Fail. 2008;30:215–7.
28. Zoccali C. Endothelial dysfunction in ckd: a new player in town? Nephrol Dial Transplant. 2008; 23:783–5.
29. Sila-asna M, Bunyaratvej A, Futrakul P, Futrakul N. Renal microvascular abnormality in chronic kidney disease. Ren Fail. 2006;28:609–10.
30. Paravicini TM, Touyz RM. Nadph oxidases, reactive oxygen species, and hypertension: clinical implications and therapeutic possibilities. Diabetes Care. 2008;31 Suppl 2:S170–80.
31. Fliser D. Perspectives in renal disease progression: the endothelium as a treatment target in chronic kidney disease. J Nephrol. 2011;23:369–76.
32. Endemann DH, Schiffrin EL. Endothelial dysfunction. J Am Soc Nephrol. 2004;15:1983–92.
33. Chade AR. Renal vascular structure and rarefaction. Compr Physiol. 2012;3(2):817–31.
34. Giles TD, Sander GE, Nossaman BD, Kadowitz PJ. Impaired vasodilation in the pathogenesis of hypertension: focus on nitric oxide, endothelial-derived hyperpolarizing factors, and prostaglandins. J Clin Hypertens (Greenwich). 2012;14:198–205.
35. Whayne Jr TF. Coronary atherosclerosis, low-density lipoproteins and markers of thrombosis, inflammation and endothelial dysfunction. Int J Angiol. 2007; 16:12–6.
36. Linke A, Recchia F, Zhang X, Hintze TH. Acute and chronic endothelial dysfunction: implications for the development of heart failure. Heart Fail Rev. 2003;8:87–97.
37. Gokce N, Keaney Jr JF, Hunter LM, Watkins MT, Nedeljkovic ZS, Menzoian JO, Vita JA. Predictive value of noninvasively determined endothelial dysfunction for long-term cardiovascular events in patients with peripheral vascular disease. J Am Coll Cardiol. 2003;41:1769–75.
38. Kistorp C, Chong AY, Gustafsson F, Galatius S, Raymond I, Faber J, Lip GY, Hildebrandt P. Biomarkers of endothelial dysfunction are elevated and related to prognosis in chronic heart failure patients with diabetes but not in those without diabetes. Eur J Heart Fail. 2008;10:380–7.
39. Stenvinkel P. Interactions between inflammation, oxidative stress, and endothelial dysfunction in end-stage renal disease. J Ren Nutr. 2003;13:144–8.
40. Aue G, Nelson Lozier J, Tian X, Cullinane AM, Soto S, Samsel L, McCoy P, Wiestner A. Inflammation, tnfalpha and endothelial dysfunction link lenalidomide to venous thrombosis in chronic lymphocytic leukemia. Am J Hematol. 2011;86:835–40.
41. Mazzoccoli G, Fontana A, Grilli M, Dagostino MP, Copetti M, Pellegrini F, Vendemiale G. Idiopathic deep venous thrombosis and arterial endothelial dysfunction in the elderly. Age (Dordr). 2012;34:751–60.
42. Mazzoccoli G, Grilli M, Ferrandino F, Copetti M, Fontana A, Pellegrini F, Dagostino MP, De Cata A, Vendemiale G. Arterial endothelial dysfunction and idiopathic deep venous thrombosis. J Biol Regul Homeost Agents. 2011;25:565–73.
43. Poredos P, Jezovnik MK. In patients with idiopathic venous thrombosis, interleukin-10 is decreased and related to endothelial dysfunction. Heart Vessels. 2011;26:596–602.
44. Wang D, Iversen J, Wilcox CS, Strandgaard S. Endothelial dysfunction and reduced nitric oxide in resistance arteries in autosomal-dominant polycystic kidney disease. Kidney Int. 2003;64:1381–8.
45. Vaziri ND, Ni Z, Oveisi F, Liang K, Pandian R. Enhanced nitric oxide inactivation and protein nitration by reactive oxygen species in renal insufficiency. Hypertension. 2002;39:135–41.
46. Kelsen S, Hall JE, Chade AR. Endothelin-a receptor blockade slows the progression of renal injury in experimental renovascular disease. Am J Physiol Renal Physiol. 2011;301:F218–25.
47. Chade AR, Rodriguez-Porcel M, Grande JP, Krier JD, Lerman A, Romero JC, Napoli C, Lerman LO. Distinct renal injury in early atherosclerosis and renovascular disease. Circulation. 2002;106:1165–71.
48. Antonios TF, Singer DR, Markandu ND, Mortimer PS, MacGregor GA. Structural skin capillary rarefaction in essential hypertension. Hypertension. 1999;33: 998–1001.
49. Cambonie G, Comte B, Yzydorczyk C, Ntimbane T, Germain N, Le NL, Pladys P, Gauthier C, Lahaie I, Abran D, Lavoie JC, Nuyt AM. Antenatal antioxidant prevents adult hypertension, vascular dysfunction, and microvascular rarefaction associated with in utero exposure to a low-protein diet. Am J Physiol Regul Integr Comp Physiol. 2007;292:R1236–45.
50. Chade AR, Rodriguez-Porcel M, Rippentrop SJ, Lerman A, Lerman LO. Angiotensin ii at1 receptor blockade improves renal perfusion in hypercholesterolemia. Am J Hypertens. 2003;16:111–5.
51. Chade AR, Zhu X, Mushin OP, Napoli C, Lerman A, Lerman LO. Simvastatin promotes angiogenesis and

prevents microvascular remodeling in chronic renal ischemia. FASEB J. 2006;20:1706–8.
52. Chade AR, Zhu XY, Grande JP, Krier JD, Lerman A, Lerman LO. Simvastatin abates development of renal fibrosis in experimental renovascular disease. J Hypertens. 2008;26:1651–60.
53. Chen JW, Hsu NW, Wu TC, Lin SJ, Chang MS. Long-term angiotensin-converting enzyme inhibition reduces plasma asymmetric dimethylarginine and improves endothelial nitric oxide bioavailability and coronary microvascular function in patients with syndrome x. Am J Cardiol. 2002;90:974–82.
54. Galle J, Quaschning T, Seibold S, Wanner C. Endothelial dysfunction and inflammation: what is the link? Kidney Int Suppl. 2003;63:S45–9.
55. Stenvinkel P. Endothelial dysfunction and inflammation-is there a link? Nephrol Dial Transplant. 2001; 16:1968–71.
56. Biegelsen ES, Loscalzo J. Endothelial function and atherosclerosis. Coron Artery Dis. 1999;10: 241–56.
57. Leopold JA, Loscalzo J. Clinical importance of understanding vascular biology. Cardiol Rev. 2000;8: 115–23.
58. Peirce SM, Skalak TC. Microvascular remodeling: a complex continuum spanning angiogenesis to arteriogenesis. Microcirculation. 2003;10:99–111.
59. VanBavel E, Bakker EN, Pistea A, Sorop O, Spaan JA. Mechanics of microvascular remodeling. Clin Hemorheol Microcirc. 2006;34:35–41.
60. Bakker EN, Buus CL, Spaan JA, Perree J, Ganga A, Rolf TM, Sorop O, Bramsen LH, Mulvany MJ, Vanbavel E. Small artery remodeling depends on tissue-type transglutaminase. Circ Res. 2005;96: 119–26.
61. Grande JP. Role of transforming growth factor-beta in tissue injury and repair. Proc Soc Exp Biol Med. 1997;214:27–40.
62. Baricos WH, Cortez SL, Deboisblanc M, Xin S. Transforming growth factor-beta is a potent inhibitor of extracellular matrix degradation by cultured human mesangial cells. J Am Soc Nephrol. 1999;10:790–5.
63. McLennan SV, Kelly DJ, Schache M, Waltham M, Dy V, Langham RG, Yue DK, Gilbert RE. Advanced glycation end products decrease mesangial cell mmp-7: a role in matrix accumulation in diabetic nephropathy? Kidney Int. 2007;72:481–8.
64. Rysz J, Banach M, Stolarek RA, Pasnik J, Cialkowska-Rysz A, Koktysz R, Piechota M, Baj Z. Serum matrix metalloproteinases mmp-2 and mmp-9 and metalloproteinase tissue inhibitors timp-1 and timp-2 in diabetic nephropathy. J Nephrol. 2007;20:444–52.
65. Wang R, Xu YJ, Liu XS, Zeng DX, Xiang M. Knockdown of connective tissue growth factor by plasmid-based short hairpin rna prevented pulmonary vascular remodeling in cigarette smoke-exposed rats. Arch Biochem Biophys. 2011;508:93–100.
66. Duncan MR, Frazier KS, Abramson S, Williams S, Klapper H, Huang X, Grotendorst GR. Connective tissue growth factor mediates transforming growth factor beta-induced collagen synthesis: down-regulation by camp. FASEB J. 1999;13:1774–86.
67. Qi W, Chen X, Poronnik P, Pollock CA. Transforming growth factor-beta/connective tissue growth factor axis in the kidney. Int J Biochem Cell Biol. 2008;40:9–13.
68. Qi W, Twigg S, Chen X, Polhill TS, Poronnik P, Gilbert RE, Pollock CA. Integrated actions of transforming growth factor-beta1 and connective tissue growth factor in renal fibrosis. Am J Physiol Renal Physiol. 2005;288:F800–9.
69. Inoue T, Okada H, Kobayashi T, Watanabe Y, Kanno Y, Kopp JB, Nishida T, Takigawa M, Ueno M, Nakamura T, Suzuki H. Hepatocyte growth factor counteracts transforming growth factor-beta1, through attenuation of connective tissue growth factor induction, and prevents renal fibrogenesis in 5/6 nephrectomized mice. FASEB J. 2003;17:268–70.
70. Caron A, Desrosiers RR, Langlois S, Beliveau R. Ischemia-reperfusion injury stimulates gelatinase expression and activity in kidney glomeruli. Can J Physiol Pharmacol. 2005;83:287–300.
71. Graff J, Harder S, Wahl O, Scheuermann EH, Gossmann J. Anti-inflammatory effects of clopidogrel intake in renal transplant patients: effects on platelet-leukocyte interactions, platelet cd40 ligand expression, and proinflammatory biomarkers. Clin Pharmacol Ther. 2005;78:468–76.
72. Kalousova M, Hodkova M, Dusilova-Sulkova S, Uhrova J, Tesar V, Zima T. Effect of hemodiafiltration on pregnancy-associated plasma protein a (papp-a) and related parameters. Ren Fail. 2006;28:715–21.
73. Desrosiers RR, Rivard ME, Grundy PE, Annabi B. Decrease in ldl receptor-related protein expression and function correlates with advanced stages of wilms tumors. Pediatr Blood Cancer. 2006;46:40–9.
74. McLennan SV, Wang XY, Moreno V, Yue DK, Twigg SM. Connective tissue growth factor mediates high glucose effects on matrix degradation through tissue inhibitor of matrix metalloproteinase type 1: implications for diabetic nephropathy. Endocrinology. 2004; 145:5646–55.
75. Kang DH, Kanellis J, Hugo C, Truong L, Anderson S, Kerjaschki D, Schreiner GF, Johnson RJ. Role of the microvascular endothelium in progressive renal disease. J Am Soc Nephrol. 2002;13:806–16.
76. Zhu XY, Rodriguez-Porcel M, Bentley MD, Chade AR, Sica V, Napoli C, Caplice N, Ritman EL, Lerman A, Lerman LO. Antioxidant intervention attenuates myocardial neovascularization in hypercholesterolemia. Circulation. 2004;109:2109–15.
77. Davis GE, Senger DR. Extracellular matrix mediates a molecular balance between vascular morphogenesis and regression. Curr Opin Hematol. 2008;15: 197–203.
78. Hall JE. The kidney, hypertension, and obesity. Hypertension. 2003;41:625–33.
79. Prewitt RL, Chen II, Dowell R. Development of microvascular rarefaction in the spontaneously hypertensive rat. Am J Physiol. 1982;243:H243–51.

80. Lee LK, Meyer TW, Pollock AS, Lovett DH. Endothelial cell injury initiates glomerular sclerosis in the rat remnant kidney. J Clin Invest. 1995;96:953–64.
81. Eirin A, Zhu XY, Urbieta-Caceres VH, Grande JP, Lerman A, Textor SC, Lerman LO. Persistent kidney dysfunction in swine renal artery stenosis correlates with outer cortical microvascular remodeling. Am J Physiol Renal Physiol. 2011;300:F1394–401.
82. Korn C, Augustin HG. Born to die: blood vessel regression research coming of age. Circulation. 2012;125:3063–5.
83. Wacker A, Gerhardt H. Endothelial development taking shape. Curr Opin Cell Biol. 2011;23:676–85.
84. Hattori K, Dias S, Heissig B, Hackett NR, Lyden D, Tateno M, Hicklin DJ, Zhu Z, Witte L, Crystal RG, Moore MA, Rafii S. Vascular endothelial growth factor and angiopoietin-1 stimulate postnatal hematopoiesis by recruitment of vasculogenic and hematopoietic stem cells. J Exp Med. 2001;193:1005–14.
85. Moore MA, Hattori K, Heissig B, Shieh JH, Dias S, Crystal RG, Rafii S. Mobilization of endothelial and hematopoietic stem and progenitor cells by adenovector-mediated elevation of serum levels of sdf-1, vegf, and angiopoietin-1. Ann N Y Acad Sci. 2001;938:36–45; discussion 45–7.
86. Rudnicki M, Perco P, Enrich J, Eder S, Heininger D, Bernthaler A, Wiesinger M, Sarkozi R, Noppert SJ, Schramek H, Mayer B, Oberbauer R, Mayer G. Hypoxia response and vegf-a expression in human proximal tubular epithelial cells in stable and progressive renal disease. Lab Invest. 2009;89:337–46.
87. Nakagawa T, Lan HY, Zhu HJ, Kang DH, Schreiner GF, Johnson RJ. Differential regulation of vegf by tgf-beta and hypoxia in rat proximal tubular cells. Am J Physiol Renal Physiol. 2004;287:F658–64.
88. Olszewska-Pazdrak B, Hein TW, Olszewska P, Carney DH. Chronic hypoxia attenuates vegf signaling and angiogenic responses by downregulation of kdr in human endothelial cells. Am J Physiol Cell Physiol. 2009;296:C1162–70.
89. Gomez SI, Warner L, Haas JA, Bolterman RJ, Textor SC, Lerman LO, Romero JC. Increased hypoxia and reduced renal tubular response to furosemide detected by bold magnetic resonance imaging in swine renovascular hypertension. Am J Physiol Renal Physiol. 2009;297:F981–6.
90. Warner L, Glockner JF, Woollard J, Textor SC, Romero JC, Lerman LO. Determinations of renal cortical and medullary oxygenation using blood oxygen level-dependent magnetic resonance imaging and selective diuretics. Invest Radiol. 2011;46:41–7.
91. Zhu XY, Chade AR, Rodriguez-Porcel M, Bentley MD, Ritman EL, Lerman A, Lerman LO. Cortical microvascular remodeling in the stenotic kidney: role of increased oxidative stress. Arterioscler Thromb Vasc Biol. 2004;24:1854–9.
92. Takahashi S, Shinya T, Sugiyama A. Angiostatin inhibition of vascular endothelial growth factor-stimulated nitric oxide production in endothelial cells. J Pharmacol Sci. 2010;112:432–7.
93. Zhu M, Bi X, Jia Q, Shangguan S. The possible mechanism for impaired angiogenesis after transient focal ischemia in type 2 diabetic gk rats: different expressions of angiostatin and vascular endothelial growth factor. Biomed Pharmacother. 2010;64:208–13.
94. Maeshima Y, Makino H. Angiogenesis and chronic kidney disease. Fibrogenesis Tissue Repair. 2010;3:13.
95. Basile DP, Fredrich K, Weihrauch D, Hattan N, Chilian WM. Angiostatin and matrix metalloprotease expression following ischemic acute renal failure. Am J Physiol Renal Physiol. 2004;286: F893–902.
96. Watorek E, Paprocka M, Dus D, Kopec W, Klinger M. Endostatin and vascular endothelial growth factor: potential regulators of endothelial progenitor cell number in chronic kidney disease. Pol Arch Med Wewn. 2011;121:296–301.
97. Ichinose K, Maeshima Y, Yamamoto Y, Kitayama H, Takazawa Y, Hirokoshi K, Sugiyama H, Yamasaki Y, Eguchi K, Makino H. Antiangiogenic endostatin peptide ameliorates renal alterations in the early stage of a type 1 diabetic nephropathy model. Diabetes. 2005;54:2891–903.
98. Karihaloo A, Karumanchi SA, Barasch J, Jha V, Nickel CH, Yang J, Grisaru S, Bush KT, Nigam S, Rosenblum ND, Sukhatme VP, Cantley LG. Endostatin regulates branching morphogenesis of renal epithelial cells and ureteric bud. Proc Natl Acad Sci U S A. 2001;98:12509–14.
99. Maciel TT, Coutinho EL, Soares D, Achar E, Schor N, Bellini MH. Endostatin, an antiangiogenic protein, is expressed in the unilateral ureteral obstruction mice model. J Nephrol. 2008;21:753–60.
100. Bates DO, Cui TG, Doughty JM, Winkler M, Sugiono M, Shields JD, Peat D, Gillatt D, Harper SJ. Vegf165b, an inhibitory splice variant of vascular endothelial growth factor, is down-regulated in renal cell carcinoma. Cancer Res. 2002;62:4123–31.
101. Hugo C, Daniel C. Thrombospondin in renal disease. Nephron Exp Nephrol. 2009;111:e61–6.
102. Chade AR, Rodriguez-Porcel M, Grande JP, Zhu X, Sica V, Napoli C, Sawamura T, Textor SC, Lerman A, Lerman LO. Mechanisms of renal structural alterations in combined hypercholesterolemia and renal artery stenosis. Arterioscler Thromb Vasc Biol. 2003;23:1295–301.
103. Fujii H, Takiuchi S, Kawano Y, Fukagawa M. Putative role of asymmetric dimethylarginine in microvascular disease of kidney and heart in hypertensive patients. Am J Hypertens. 2008;21:650–6.
104. Marcovecchio ML, Chiarelli F. Microvascular disease in children and adolescents with type 1 diabetes and obesity. Pediatr Nephrol. 2011;26:365–75.
105. Feihl F, Liaudet L, Waeber B. The macrocirculation and microcirculation of hypertension. Curr Hypertens Rep. 2009;11:182–9.
106. Greene AS, Tonellato PJ, Lui J, Lombard JH, Cowley Jr AW. Microvascular rarefaction and tissue vascular resistance in hypertension. Am J Physiol. 1989;256:H126–31.

107. Cowley Jr AW, Roman RJ, Krieger JE. Pathways linking renal excretion and arterial pressure with vascular structure and function. Clin Exp Pharmacol Physiol. 1991;18:21–7.
108. Brecker CG, Shustak SR. Contractile proteins in endothelial cells: comparison of cerebral capillaries with those in heart and skeletal muscle and with liver sinusoids. Circulation. 1972;45/46(Suppl II):87.
109. Reckelhoff JF, Romero JC. Role of oxidative stress in angiotensin-induced hypertension. Am J Physiol Regul Integr Comp Physiol. 2003;284:R893–912.
110. Romero JC, Reckelhoff JF. State-of-the-art lecture. Role of angiotensin and oxidative stress in essential hypertension. Hypertension. 1999;34:943–9.
111. Romero JC, Reckelhoff JF. Oxidative stress may explain how hypertension is maintained by normal levels of angiotensin ii. Braz J Med Biol Res. 2000;33:653–60.
112. Chatziantoniou C, Boffa JJ, Tharaux PL, Flamant M, Ronco P, Dussaule JC. Progression and regression in renal vascular and glomerular fibrosis. Int J Exp Pathol. 2004;85:1–11.
113. Battegay EJ, de Miguel LS, Petrimpol M, Humar R. Effects of anti-hypertensive drugs on vessel rarefaction. Curr Opin Pharmacol. 2007;7:151–7.
114. Josifova T, Schneider U, Henrich PB, Schrader W. Eye disorders in diabetes: potential drug targets. Infect Disord Drug Targets. 2008;8:70–5.
115. Marin P, Andersson B, Krotkiewski M, Bjorntorp P. Muscle fiber composition and capillary density in women and men with niddm. Diabetes Care. 1994;17:382–6.
116. Futrakul N, Futrakul P. Renal microvascular disease predicts renal function in diabetes. Ren Fail. 2012;34:126–9.
117. Gomes MB, Affonso FS, Cailleaux S, Almeida AL, Pinto LF, Tibirica E. Glucose levels observed in daily clinical practice induce endothelial dysfunction in the rabbit macro- and microcirculation. Fundam Clin Pharmacol. 2004;18:339–46.
118. Ko SH, Cao W, Liu Z. Hypertension management and microvascular insulin resistance in diabetes. Curr Hypertens Rep. 2011;12:243–51.
119. Raptis AE, Viberti G. Pathogenesis of diabetic nephropathy. Exp Clin Endocrinol Diabetes. 2001;109 Suppl 2:S424–37.
120. O'Donovan HC, Hickey F, Brazil DP, Kavanagh DH, Oliver N, Martin F, Godson C, Crean J. Connective tissue growth factor antagonizes transforming growth factor-beta1/smad signalling in renal mesangial cells. Biochem J. 2012;441:499–510.
121. Lupia E, Elliot SJ, Lenz O, Zheng F, Hattori M, Striker GE, Striker LJ. Igf-1 decreases collagen degradation in diabetic nod mesangial cells: implications for diabetic nephropathy. Diabetes. 1999;48:1638–44.
122. Zhang J, Zhang X, Li H, Cui X, Guan X, Tang K, Jin C, Cheng M. Hyperglycaemia exerts deleterious effects on late endothelial progenitor cell secretion actions. Diab Vasc Dis Res. 2013;10(1):49–56.
123. Biscetti F, Pitocco D, Straface G, Zaccardi F, de Cristofaro R, Rizzo P, Lancellotti S, Arena V, Stigliano E, Musella T, Ghirlanda G, Flex A. Glycaemic variability affects ischaemia-induced angiogenesis in diabetic mice. Clin Sci (Lond). 2011;121:555–64.
124. Nakagawa T. Uncoupling of the vegf-endothelial nitric oxide axis in diabetic nephropathy: an explanation for the paradoxical effects of vegf in renal disease. Am J Physiol Renal Physiol. 2007;292:F1665–72.
125. Siervo M, Tomatis V, Stephan BC, Feelisch M, Bluck LJ. Vegf is indirectly associated with no production and acutely increases in response to hyperglycaemia(1). Eur J Clin Invest. 2012;42:967–73.
126. Hohenstein B, Hausknecht B, Boehmer K, Riess R, Brekken RA, Hugo CP. Local vegf activity but not vegf expression is tightly regulated during diabetic nephropathy in man. Kidney Int. 2006;69:1654–61.
127. Futrakul N, Futrakul P. Vascular homeostasis and angiogenesis determine therapeutic effectiveness in type 2 diabetes. Int J Vasc Med. 2011;2011:971524.
128. O'Hare AM, Glidden DV, Fox CS, Hsu CY. High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the national health and nutrition examination survey 1999–2000. Circulation. 2004;109:320–3.
129. Bax L, van der Graaf Y, Rabelink AJ, Algra A, Beutler JJ, Mali WP. Influence of atherosclerosis on age-related changes in renal size and function. Eur J Clin Invest. 2003;33:34–40.
130. Safian RD, Textor SC. Renal-artery stenosis. N Engl J Med. 2001;344:431–42.
131. Dworkin LD, Murphy T. Is there any reason to stent atherosclerotic renal artery stenosis? Am J Kidney Dis. 2010;56:259–63.
132. Kalra PA, Guo H, Kausz AT, Gilbertson DT, Liu J, Chen SC, Ishani A, Collins AJ, Foley RN. Atherosclerotic renovascular disease in united states patients aged 67 years or older: risk factors, revascularization, and prognosis. Kidney Int. 2005;68:293–301.
133. Hansen KJ, Edwards MS, Craven TE, Cherr GS, Jackson SA, Appel RG, Burke GL, Dean RH. Prevalence of renovascular disease in the elderly: a population-based study. J Vasc Surg. 2002;36:443–51.
134. Lerman LO, Taler SJ, Textor SC, Sheedy 2nd PF, Stanson AW, Romero JC. Computed tomography-derived intrarenal blood flow in renovascular and essential hypertension. Kidney Int. 1996;49:846–54.
135. Textor SC, Wilcox CS. Renal artery stenosis: a common, treatable cause of renal failure? Annu Rev Med. 2001;52:421–42.
136. Textor SC. Ischemic nephropathy: where are we now? J Am Soc Nephrol. 2004;15:1974–82.
137. Chade AR, Best PJ, Rodriguez-Porcel M, Herrmann J, Zhu X, Sawamura T, Napoli C, Lerman A, Lerman LO. Endothelin-1 receptor blockade prevents renal injury in experimental hypercholesterolemia. Kidney Int. 2003;64:962–9.

138. Chade AR, Rodriguez-Porcel M, Herrmann J, Zhu X, Grande JP, Napoli C, Lerman A, Lerman LO. Antioxidant intervention blunts renal injury in experimental renovascular disease. J Am Soc Nephrol. 2004;15:958–66.
139. Chavakis E, Dernbach E, Hermann C, Mondorf UF, Zeiher AM, Dimmeler S. Oxidized ldl inhibits vascular endothelial growth factor-induced endothelial cell migration by an inhibitory effect on the akt/endothelial nitric oxide synthase pathway. Circulation. 2001;103:2102–7.
140. Baskin ML, Ard J, Franklin F, Allison DB. Prevalence of obesity in the united states. Obes Rev. 2005;6:5–7.
141. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among us children, adolescents, and adults, 1999–2002. JAMA. 2004;291:2847–50.
142. Caballero AE. Endothelial dysfunction in obesity and insulin resistance: a road to diabetes and heart disease. Obes Res. 2003;11:1278–89.
143. Pasarica M, Sereda OR, Redman LM, Albarado DC, Hymel DT, Roan LE, Rood JC, Burk DH, Smith SR. Reduced adipose tissue oxygenation in human obesity: evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response. Diabetes. 2009;58:718–25.
144. de Jongh RT, Serne EH, IJ RG, de Vries G, Stehouwer CD. Impaired microvascular function in obesity: implications for obesity-associated microangiopathy, hypertension, and insulin resistance. Circulation. 2004;109:2529–35.
145. Schindler TH, Cardenas J, Prior JO, Facta AD, Kreissl MC, Zhang XL, Sayre J, Dahlbom M, Licinio J, Schelbert HR. Relationship between increasing body weight, insulin resistance, inflammation, adipocytokine leptin, and coronary circulatory function. J Am Coll Cardiol. 2006;47:1188–95.
146. Hall JE, Kuo JJ, da Silva AA, de Paula RB, Liu J, Tallam L. Obesity-associated hypertension and kidney disease. Curr Opin Nephrol Hypertens. 2003;12:195–200.
147. Warncke J, David S, Kumpers P, Opherk JP, Haller H, Fliser D. A hibernating kidney – ischemic preconditioning in a renal transplant recipient with a proximal stenosis of the iliac artery. Clin Nephrol. 2008;70:168–71.
148. Cheung CM, Chrysochou C, Shurrab AE, Buckley DL, Cowie A, Kalra PA. Effects of renal volume and single-kidney glomerular filtration rate on renal functional outcome in atherosclerotic renal artery stenosis. Nephrol Dial Transplant. 2010;25:1133–40.

Blood Flow, Oxygenation, and Oxidative Stress in the Post-stenotic Kidney

9

Roger G. Evans and Paul M. O'Connor

Abstract

Renal ischemia, hypoxia and oxidative stress progress together over the course of renovascular disease, and thus appear to operate in a vicious pathological triangle. Renal ischemia is initially driven by the mechanical effect of the stenosis, and maintained in the medium term chiefly by activation of the systemic and intrarenal renin-angiotensin systems. In the longer term, ischemia is exacerbated by inflammation, fibrosis and microvascular rarefaction, at least partly driven by signaling cascades initiated by oxidative stress and tissue hypoxia. Oxidative stress in renovascular disease is initially driven by activation of the renin-angiotensin system, but other factors, such as the pro-oxidant effects of uremic toxins, likely also contribute in the longer term. Oxidative stress drives ischemia by the direct vasoconstrictor effects of reactive oxygen species such as superoxide, and through reduced bioavailability of the vasodilator nitric oxide. This microvascular dysfunction appears to be a major driver of microvascular remodeling and rarefaction. Ischemia drives tissue hypoxia by reducing oxygen delivery to tissue. Oxidative stress and the resultant reduction in nitric oxide bioavailability also promote hypoxia by reducing the efficiency of oxygen utilization in mitochondria. Reduced glomerular filtration leads to reduced renal oxygen consumption, so provides some protection against the development of tissue hypoxia, at least in mild or early stage renovascular disease. But, eventually, homeostasis of tissue oxygenation cannot be maintained, and tissue hypoxia ensues.

Keywords

Fibrosis • Inflammation • Microvascular rarefaction • Oxidative stress • Oxygen • Perfusion • Renal cortex • Renal medulla

R.G. Evans, BSc (Hons), PhD (✉)
Department of Physiology,
Monash University, Building 13F,
Melbourne, VIC 3800, Australia
e-mail: roger.evans@monash.edu

P.M. O'Connor, BSc, PhD
Department of Medicine, Georgia Regents University,
1459 Laney-Walker Blvd, CB2206, Augusta,
GA 30912, USA
e-mail: paoconnor@gru.edu

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_9,

Introduction

There is a general consensus that toxic interactions between renal ischemia, hypoxia, and inflammation and oxidative stress play a critical role in the pathogenesis of multiple forms of kidney disease (Fig. 9.1) [1]. However, our understanding of the nature of these interactions, and how they operate in the setting of specific renal pathologies, remains one of the great unknowns in the fields of nephrology and hypertension. In this chapter we will attempt to describe the current understanding of how these factors interact in the pathogenesis of renovascular disease (RVD). But before we can do this, we must first consider the basic anatomy, physiology and biochemistry which underlie the physiological regulation of regional kidney perfusion and oxygenation, and the sources and fates of reactive oxygen species in the kidney.

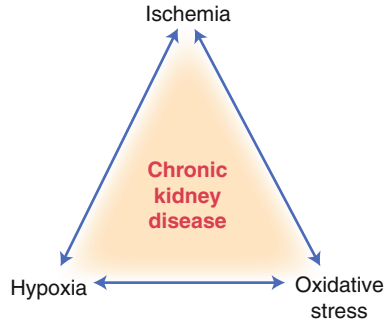


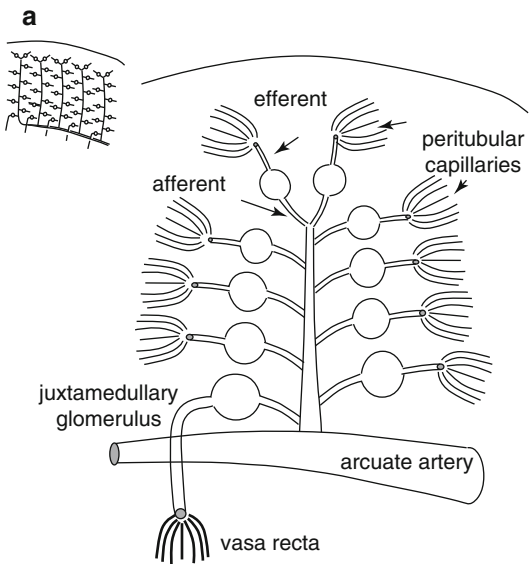
Fig. 9.1 The "toxic triangle" of ischemia, hypoxia and oxidative stress in the pathogenesis of chronic kidney disease. See text for details

Anatomy and Physiology

Renal Blood Flow, Local Perfusion, and Oxygenation

The architecture of the mammalian renal circulation is unique in at least three ways:

1. The renal circulation contains two sets of capillaries arranged in series (Fig. 9.2a, b). All blood flow through the kidney first passes through the glomerular capillaries, which are exposed to a relatively high hydrostatic pressure of 45–55 mmHg [2]. The high glomerular capillary pressure facilitates ultrafiltration of



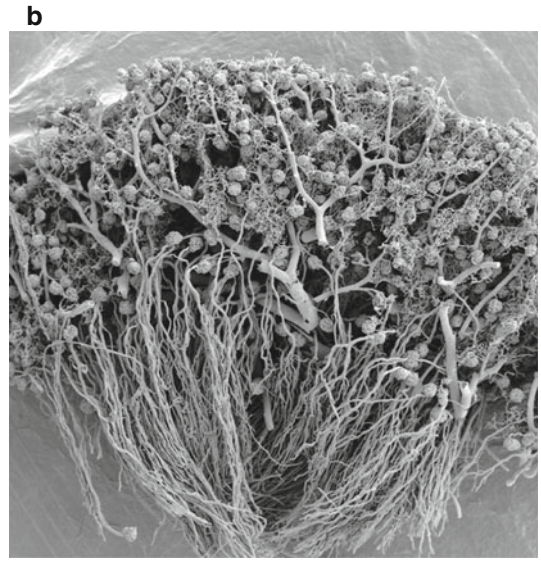


Fig. 9.2 The renal circulation. (**a**) shows a schematic representation of the arrangement of the cortical and medullary circulations. (**b**) shows a scanning electron micrograph of a portion of a methacrylate cast of the renal circulation, showing both the cortical and medullary regions. Note the presence of two sets of capillaries in series, and that the blood supply to the capillaries of the medulla (vasa recta) arises from the efferent arterioles of a sub-population of glomeruli in the juxtamedullary cortex (With permission from Evans et al. [3])

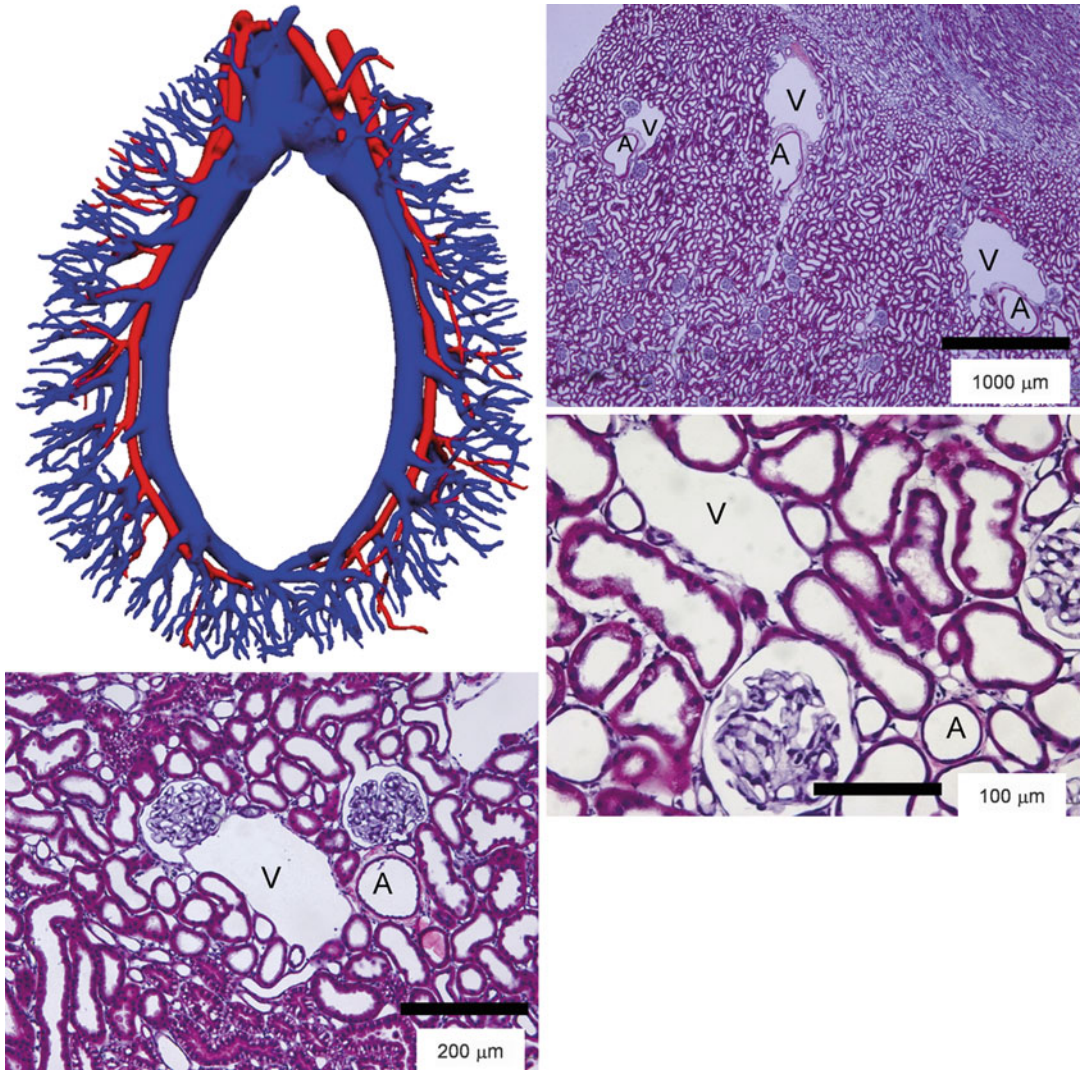


Fig. 9.3 Intimate counter-current arrangement of arteries and veins in the kidney. Larger arteries and veins, many of which are likely common to the cortical and medullary circulations, are intimately associated in a way which would promote arterial-to-venous oxygen shunting. Smaller arteries and veins, many of which will be specific to the cortical circulation, appear to be less intimately associated (With permission from Gardiner et al. [5])

the plasma into Bowman's space, the initial process in the production of urine. Blood flows from the glomerular capillaries to the efferent arterioles, and then to the second set of renal capillaries, the peritubular capillaries of the cortex and vasa recta of the medulla.

2. The kidney contains two vascular beds which are partly in series, but also partly in parallel (Fig. 9.2a, b) [3, 4]. The efferent arterioles of most glomeruli feed the cortical peritubular capillaries. But the efferent arterioles of approximately 10 % of glomeruli, located at the cortico-medullary border (the so-called juxtamedullary glomeruli), descend into the medulla to form the vasa recta capillaries. Thus, when we consider blood flow in the post-stenotic kidney, we must bear in mind that these two vascular territories can behave differently.
3. In the renal cortex, some arteries and veins are arranged in an intimate counter-current fashion not seen in other vascular beds (Fig. 9.3) [5]. This arrangement favors arterial-to-venous

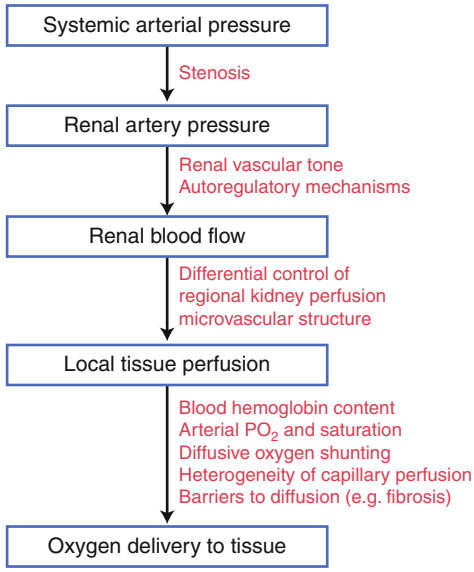


Fig. 9.4 Factors that control oxygen delivery to renal tissue. Modulating factors are shown in *red*

oxygen shunting, which acts to limit delivery of oxygen to renal tissue [5, 6]. Diffusive oxygen shunting also occurs in the renal medulla, between the descending and ascending vasa recta [7]. Diffusive oxygen shunting, in both the cortex and medulla, renders the kidney susceptible to hypoxia.

There are also four functional aspects of kidney that, if not unique, are critical to our understanding of the pathophysiology of RVD.

1. The kidney, or at least the cortical circulation, has remarkable autoregulatory capacity [8]. Autoregulation is the ability of an organ or tissue to maintain blood flow in the face of changes in perfusion pressure (Fig. 9.4). Most organs and tissues have some autoregulatory capacity, although this phenomenon is especially prominent in the kidney and brain. Autoregulation of blood flow is primarily mediated by a myogenic response, in that stretch of arterial vessels leads to their contraction [8]. The unique aspect of autoregulation of renal blood flow (RBF) is the presence of at least one additional negative feedback mechanism, tubuloglomerular feedback (TGF). TGF relies on the ability of changes in tubular flow/sodium chloride concentration in the distal nephron, to produce changes in afferent arteriolar tone through signaling mechanisms mediated via the macula densa [8]. For example, reduced tubular flow causes afferent arteriolar dilatation, which in turn increases single nephron blood flow and glomerular filtration rate (GFR), thus leading to increased tubular flow. Thus, TGF contributes to autoregulation of GFR as well as RBF. Autoregulation of GFR is also dependent on the renin-angiotensin system and its impact on efferent arteriolar tone. For example, if pressure falls within the afferent arteriole, renin is released from the juxtaglomerular apparatus, and the resultant generation of angiotensin II causes efferent arteriolar constriction, which supports glomerular capillary pressure (and so GFR) in the face of reduced arterial pressure [2]. As we will see later, this is a critical mechanism in the maintenance of GFR in the post-stenotic kidney. The capacity for autoregulation of medullary perfusion remains a matter of intense debate, despite many decades of intense study [4]. The balance of evidence indicates that the autoregulatory capacity of the medullary circulation is relatively poor compared with that of the renal cortex [9].
2. Most (~80 %) of the oxygen consumed within the kidney is used to drive Na+/K+-ATPase, which in turn drives all active reabsorptive processes within the kidney [10]. Thus, renal oxygen consumption, and so kidney oxygenation, varies with sodium reabsorption, both at the level of the whole kidney and at the level of individual nephron segments (Fig. 9.5). Sodium reabsorption, particularly in the distal nephron, is load dependent. Consequently, when GFR increases, and so the tubular sodium load increases, kidney oxygen consumption increases [10]. Moreover, shifts in sodium delivery to and from various segments of the nephron can alter oxygen consumption within these specific nephron segments. This phenomenon is nicely illustrated by the contrasting effects of diuretic agents acting on the proximal tubule, which act to increase cortical tissue PO_2, and loop

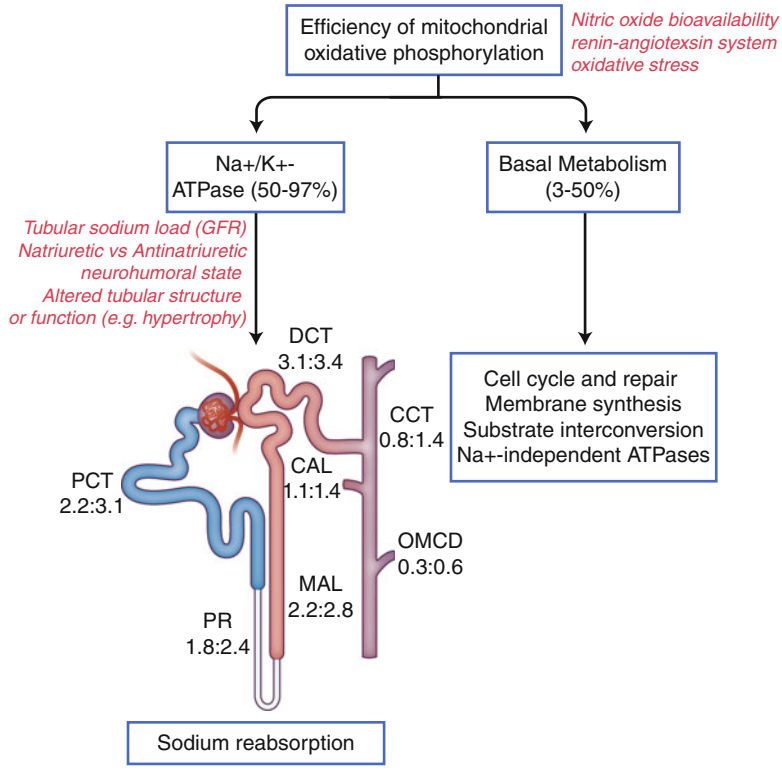


Fig. 9.5 Factors that influence oxygen consumption in the kidney. Modifying factors are shown in *red*. Na+/K+-ATPase, which drives sodium reabsorption from the renal tubule, is the major energy sink in the kidney. Estimates of the proportion of ATP used to drive Na+ transport in the kidney (50–97 %) versus that used for so-called "basal metabolism" differ widely in part because of the use of varying experimental conditions, but also because this proportion likely changes depending on the prevailing physiological conditions. Approximations of ATPase activity (nmol/mm/h) [124], are given for each nephron segment as Na+/K+-ATPase: total ATPase. *PCT* proximal convoluted tubule, *PR* pars recta, *MAL* medullary thick ascending limb, *CAL* cortical thick ascending limb, *DCT* distal convoluted tubule, *CCT* cortical collecting tubule, *OMCD* outer medullary collecting tubule

diuretics, which increase medullary tissue PO_2 [11]. Finally, factors that alter the efficiency of utilization of oxygen for sodium reabsorption, are able to alter tissue oxygen consumption and thereby tissue PO_2. One such factor is nitric oxide (NO), which competes with oxygen at the level of cytochrome oxidase, to inhibit mitochondrial oxygen utilization. NO also acts to increase tissue oxygen delivery through vasodilatation, and to directly inhibit sodium reabsorption (and so oxygen utilization). Thus, NO has at least three actions which promote kidney oxygenation. Consequently, when NO bioavailability is reduced under conditions of oxidative stress, kidney hypoxia can develop [12].

3. The renal circulation is relatively insensitive to changes in tissue oxygen concentration. In most tissues, including the brain and skeletal muscle, hypoxemia and/or tissue hypoxia results in vasodilatation, which acts to defend tissue oxygenation [10]. This mechanism is virtually absent in the kidney [13]. The absence of hyperemia in the kidney under hypoxic conditions is adaptive. It allows the functions of the kidney, in regulation of extracellular fluid volume (through glomerular filtration and tubular reabsorptive processes) and hematocrit (through the release of erythropoietin under hypoxic conditions), to operate unconfounded by effects of hypoxia on vascular tone. A price paid for this adaptation is the susceptibility of the kidney to hypoxia.

4. Cortical and medullary perfusion respond differently to vasoactive factors [3, 4]. Critically, medullary perfusion appears to be relatively insensitive to a wide range of vasoconstrictors, including angiotensin II, endothelins, and renal nerve activation. The precise mechanisms underlying this phenomenon remain unknown, but it is likely mediated at least in part by counter-regulatory vasodilatation mediated by prostanoids and NO. Structural differences between the juxtamedullary glomerular arterioles, which feed the vasa recta, compared with glomerular arterioles which feed the cortical peritubular capillaries, likely also play some role [3].

Reactive Oxygen Species

The term reactive oxygen species (ROS) refers to oxygen intermediates, including superoxide (O_2–), hydrogen peroxide (H_2O_2), the hydroxyl radical (OH), singlet oxygen ($O_2^{\cdot}$) and peroxinitrite (ONOO–), all of which vary in their half-life and chemical reactivity. Normal production of ROS is required by a number of physiological functions including host defense, cell signaling and apoptosis [14]. As ROS are highly reactive, cellular ROS levels must be maintained within strict limits to prevent damage to cellular components. This is achieved by balancing ROS production and ROS scavenging by anti-oxidant pathways. Antioxidant pathways include enzymatic ROS degradation by enzymes such as superoxide dismutase, catalase or glutathione peroxidase as well as endogenous antioxidants which can scavenge ROS once they are produced. Aberrant production of ROS, or loss of antioxidant pathways, can lead to cellular "oxidative stress," in which high ROS levels lead to pathological signaling and cellular damage. Oxidative stress is a common phenotype, and is thought to contribute to the progression of a number of renal disease states, including diabetic nephropathy [15], hypertension [16], ischemia-reperfusion injury [17], and RVD [18].

There are multiple sources of ROS within the kidney. Under normal physiological conditions the two greatest sources of ROS appear to be the mitochondria and enzymatic production by NADPH oxidase [19]. ROS are by-products of normal mitochondrial metabolism. That is, a small proportion of electrons escape the electron transport chain to form superoxide. This electron leak is thought to occur largely at complex 1 and complex 3 [20]. These ROS are thought to participate in cellular signaling. Mitochondrial damage is prevented by local antioxidant pathways including Mn-SOD, a mitochondrial specific form of superoxide dismutase [21]. Damage to the mitochondria, including that caused by ischemia or elevated ROS levels themselves can lead to mitochondrial dysfunction and increased mitochondrial ROS production [22]. Enhanced ROS production by the mitochondria in turn appears to be capable of stimulating other sources of ROS such as NADPH oxidase in a feed-forward mechanism [23, 24].

NADPH oxidase is an enzyme complex consisting of a number of subunits which produces O_2^- by transferring an electron from NADH/NADPH to molecular O_2 [25]. Multiple isoforms of NADPH oxidase are found within the kidney including NOX1, 2 and 4 which vary by gp91phox homologue (NOX) [26, 27]. Activation of NADPH oxidase involves the translocation of cytosolic subunits p47phox, p67phox and Rac1 and their binding to membrane associated p22phox and gp91phox to form the active enzyme complex [25]. The expression of NADPH oxidase isoforms varies by cell type, with NOX4 being highly expressed in renal epithelial cells and NOX2 the predominant isoform expressed in renal endothelial cells. A number of stimuli have been demonstrated to activate NADPH oxidase in the kidney. Importantly, angiotensin II is a potent activator of NADPH oxidase. Angiotensin II acutely stimulates NADPH oxidase via activation of AT_1 receptors and protein kinase C (PKC) signaling [28], a mechanism which appears to be important in the development of RVD [29]. Further, angiotensin II promotes expression of a number of subunits of NADPH oxidase within the kidney, which contribute to enhanced ROS levels following chronic elevations in circulating angiotensin II [30]. Recent evidence indicates

that within renal epithelial cells angiotensin II acts to stimulate ROS production via the activation of NOX4 rather than NOX2 or NOX1 [31]. These data are somewhat surprising given that NOX4 is thought to be constitutively active and does not require binding of cytosolic subunits. NOX4 is also highly expressed in a number of sub-cellular locations including the mitochondria and endoplasmic reticulum [32, 33], which may in part explain enhanced mitochondrial ROS production in response to angiotensin II. Another source of NADPH oxidase within the kidney is infiltrating immune cells. Monocytes express high levels of the NOX2 isoform of NADPH oxidase and are potent sources of O_2^-. Monocyte infiltration is a common phenotypic trait in a number of renal disease models in which oxidative stress is associated with disease progression, including angiotensin II mediated hypertension [34]. The relative contributions of vascular, endothelial and immune components to renal ROS production in physiological and disease states remain an area of intense investigation.

A number of feed forward systems participate in the development of oxidative stress in biological systems. As discussed previously, aberrant ROS production by sources such as mitochondria can signal increased O_2^- production by other cellular components such as NADPH oxidase [24]. In turn, increased ROS production by NADPH oxidase can lead to further mitochondrial dysfunction, promoting a vicious cycle of oxidative stress termed "ROS induced ROS production" [24]. NO is also a key modulator of cellular ROS levels. NO is produced by the enzyme NO synthase and acts as a powerful vasodilator and inhibitor of mitochondrial metabolism [35]. Importantly, NO reacts with superoxide to form ONOO-, limiting the bioavailability of O_2^- in vivo. NO can also directly inhibit production of O_2^- by NADPH oxidase by a cGMP dependent mechanism [36]. The net effect of high NO level is to limit O_2^- bioavailability. Conversely, oxidative stress limits the bioavailability of NO and promotes greater ROS production [37]. Just as NO appears to be able to inhibit the production of O_2^- by NADPH oxidase, oxidative stress can result in NOS uncoupling, resulting in this enzyme producing O_2^- rather than NO and further driving oxidative stress [38]. Loss of antioxidant pathways also appear to contribute to the vicious cycle of oxidative stress in a number of organ systems including the kidney [39].

Pathophysiology of Renal Perfusion, Oxygenation, and Oxidative Stress in Renovascular Disease

With the structural and functional peculiarities of the kidney, and the complex biology of ROS discussed previously in mind, we are now able to turn our thoughts to the dysregulation of renal perfusion and oxygenation in RVD, and the contribution of oxidative stress to this dysfunction. The major hemodynamic factor in renovascular disease is a fall in renal perfusion pressure, often but not always as a result of atherosclerotic renal artery stenosis [40]. Thus, we must consider how tissue perfusion, oxygenation and redox status respond acutely to reductions in renal perfusion pressure, and how they respond to and contribute to the chronic pathophysiological conditions imposed on the post-stenotic kidney. At least four factors complicate this task.

Firstly, we cannot consider ischemia, hypoxia and oxidative stress in isolation, since these factors interact in a "toxic triangle" (Fig. 9.1) which is a major driver in the development of kidney disease.

Secondly, the pathophysiological characteristics of RVD change with disease progression. Therefore, our discussion must consider temporal aspects of the pathophysiology of RVD, from the acute response to reduced renal perfusion pressure, to the hormonal and hemodynamic adjustments that occur subacutely in response to reduced renal perfusion pressure, to the chronic pathophysiological mechanisms that occur early and late in disease progression.

Thirdly, interpretation of the results of studies of the evolution of changes in renal hemodynamics/oxygenation/oxidative stress in renal artery stenosis must take into account its dependence on the nature of the experimental model. For example, in studies in which the renal artery is clipped

in rodents (e.g., two-kidney, one-clip (2K, 1K) hypertension), the clip is often implanted in relatively young animals, so that the stenosis gradually becomes more severe as the animal ages [41]. A similar scenario is likely to occur in more recently developed porcine models of renovascular disease, in which an irritant coil is placed within the renal artery [42]. In contrast, in some larger animal models an inflatable cuff can be used to produce an abrupt and stable stenosis. The latter provides the advantage that disease progression can be followed temporally from a single initiating stimulus, but it hardly recapitulates the human condition. Importantly, most of these models do not completely mimic the clinical condition, in which renal artery stenosis is often accompanied (indeed caused) by gradual development of atherosclerosis and other co-morbidities [40]. Increasingly, use of animal models of RVD that incorporate these co-morbidities, show that they make important contributions to the progression of renal disease and hypertension.

Fourthly, we must recognize that the cascades of pathophysiological processes resulting from unilateral renal artery stenosis differ markedly from those that result from bilateral renal artery stenosis [40].

Responses to Acutely Reduced Renal Artery Pressure

Renal Perfusion and Glomerular Filtration

Our understanding of the hemodynamic effects of acutely lowered renal perfusion pressure comes mainly from studies of the autoregulation of RBF and GFR. Apart from such acute studies, there is also a considerable literature describing the progressive changes in renal hemodynamics after mechanical initiation of renal artery stenosis in experimental animals.

It is generally accepted that there is a nonlinear relationship between the degree of stenosis and changes in renal hemodynamics, such that hemodynamically significant stenosis only occurs once the cross sectional area of the occlusion approaches 70–80 % [40, 43]. However, such a conceptual framework may be an oversimplification. Stenosis of ≥50 % is required to produce a trans-stenotic pressure gradient [44]. However, because of the autoregulatory capacity of the renal circulation, RBF is only reduced acutely by stenoses ≥60 %. Nevertheless, even relatively mild stenoses (~30 %) are associated with changes in the profile of the RBF waveform; specifically a reduction in the early systolic peak of RBF [44].

Renin release from the juxtaglomerular cells of the afferent arteriole provides a further complicating factor in our understanding of the renal hemodynamic response to acute renal artery stenosis [43–45]. Many studies, in which plasma renin activity had been measured in response to graded renal artery stenosis, provide evidence that renin release only occurs once the stenosis becomes so severe that it reduces RBF [43, 45]. But this conclusion is at odds with the results of studies of the effects of acute renal artery stenosis under conditions of blockade of the renin angiotensin system. Under such conditions, autoregulation of RBF is maintained, but autoregulation of GFR fails [46]. Thus, renin release from the juxtamedullary cells of the afferent arteriole likely occurs within the range of renal perfusion pressure associated with autoregulation of RBF, and in turn plays a critical role in autoregulation of GFR.

As alluded to earlier, perfusion of the cortical and medullary circulations are, at least in part, independently regulated. The response of the medullary circulation to reduced renal perfusion pressure remains a matter of controversy [9]. The balance of evidence indicates that the medullary circulation has less autoregulatory capacity than the cortical circulation, so one might expect that medullary perfusion can be reduced by stenoses too mild to alter total RBF or cortical perfusion. However, the response of the medullary circulation to reduced perfusion pressure is critically dependent on the prevailing experimental conditions, particularly extracellular fluid volume status. Thus, changes in medullary perfusion in response to reduced renal perfusion pressure are

often seen in volume expanded states [4]. Furthermore, it appears likely that inner medullary blood flow is more poorly autoregulated than outer medullary blood flow [9].

Renal Oxygenation

The responses of renal oxygenation to acute reductions in renal perfusion pressure have been studied using a range of techniques, including invasive studies using oxygen electrodes and optodes, and studies using non-invasive methods such as blood oxygen level-dependent magnetic resonance imaging (BOLD MRI). All of these methods have both strengths and limitations [47]. The BOLD-MRI technique is non-invasive, so can be applied to humans as well as experimental animals [48], and can be used in longitudinal studies to track the course of changes in kidney oxygenation during disease progression [49]. However, interpretation of studies using BOLD-MRI should be tempered by two caveats. Firstly, BOLD-MRI provides a measure of blood oxygenation, not tissue oxygenation. Because of the phenomenon of counter-current diffusive oxygen shunting in the renal cortex and medulla, intrarenal blood oxygenation and tissue oxygenation can change independently of each other [50]. Secondly, because the BOLD signal is generated by the properties of deoxyhemoglobin, it provides a better measure of oxygenation in the relatively hypoxic medulla than the better oxygenated cortex [51].

The effects of acute renal artery stenosis on kidney oxygenation will depend on the balance between changes in renal blood flow and local perfusion on the one hand, and glomerular filtration and tubular sodium reabsorption on the other. Thus, to truly understand the acute effects of renal artery stenosis on kidney tissue oxygenation we require knowledge of oxygen delivery and demand both at the whole kidney level and at the local tissue level. Unfortunately, due to the technical limitations of current methods, this is only partly possible [47].

In anesthetized animals with an intact renin-angiotensin system, acute renal artery stenosis is accompanied by reduced oxygenation of both the cortex and medulla (as determined by BOLD MRI) [52, 53]. Presumably, this reflects greater reductions in local oxygen delivery than consumption in response to reduced renal artery pressure. But when total renal oxygen delivery and consumption was measured in these studies, oxygen consumption was found to be reduced by at least as much as oxygen delivery, and fractional oxygen extraction was found to be remarkably stable in the face of renal ischemia [52, 53]. One possible explanation for this paradox is that acute reductions in renal perfusion pressure lead to changes in microcirculatory function that limit oxygen delivery to renal tissue. These changes could include increased heterogeneity of capillary perfusion which would reduce the efficiency of tissue oxygen extraction. Increased diffusive oxygen shunting, between arteries and veins in the renal cortex [54] and descending and ascending vasa recta in the medulla [7], could also contribute. Nevertheless, renal oxygen consumption remains a critical predictor of kidney oxygenation when renal artery pressure is reduced, as evidenced by the remarkable resistance of the kidney to hypoxia when renal perfusion pressure is reduced under conditions of blockade of the renin-angiotensin system, which blunts autoregulation of GFR but not RBF [46].

Reactive Oxygen Species

The roles of ROS in the responses of renal hemodynamics and oxygenation to acute renal artery stenosis have not, to our knowledge, been formally studied. Activation of the renin-angiotensin system occurs rapidly in response to reduced renal artery pressure, which likely activates superoxide production through upregulation of NADPH oxidase [55]. Indeed, superoxide appears to partly mediate vasoconstriction and antinatriuresis during acute renal arterial infusion of angiotensin II, in part through a direct vasoconstrictor effect of superoxide and in part through reduced NO bioavailability [56]. Nevertheless, the ability of angiotensin II to activate pathways leading to oxidative stress is likely to be more relevant to our consideration of the subacute and chronic consequences of renal artery stenosis.

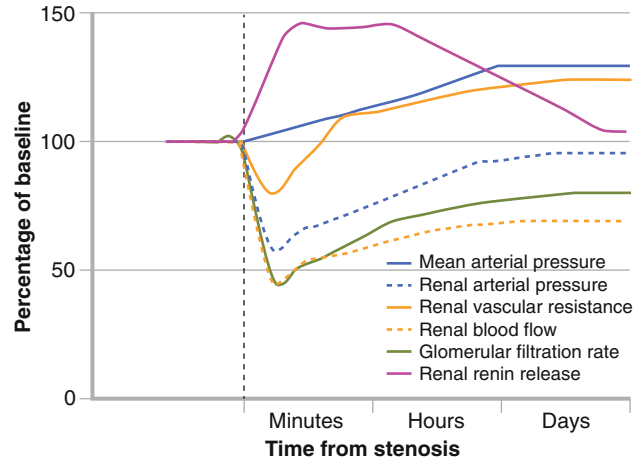


Fig. 9.6 Schematic view of the early time course of changes in systemic and renal hemodynamics, glomerular filtration rate and renal renin release after abrupt induction of a stable renal artery stenosis. Note that renal vascular resistance excludes the resistance imposed by the stenosis. See text for details

Subacute Responses to Reduced Renal Artery Pressure

These have been studied in large animals, particularly in chronically instrumented conscious dogs, in which inflation of a perivascular cuff induces a square-wave reduction in renal artery pressure (Fig. 9.6) [41, 57, 58]. The immediate response to inflation of a perivascular cuff, to reduce distal renal artery pressure to 20–60 mmHg, is vasodilatation presumably mediated by autoregulatory mechanisms, which lasts only a few minutes. Renal renin secretion is acutely increased within minutes of cuff inflation, and the consequent production of angiotensin II has two critical effects which act to increase arterial pressure distal to the cuff, which in turn allows glomerular capillary pressure to be maintained at a level adequate to drive glomerular filtration. Firstly, angiotensin II acts on the systemic circulation to increase systemic vascular resistance, and so systemic arterial pressure. The stenosis itself also makes a contribution to increased total peripheral resistance. Secondly, angiotensin II-induced vasoconstriction increases renal vascular resistance, particularly in the post glomerular circulation, which acts to reduce the effective resistance imposed by the stenosis and to increase glomerular capillary pressure. As distal renal arterial pressure rises towards its level before induction of the stenosis, plasma renin activity falls, presumably due to removal of the stimulus inducing renin release (the renal "barostat").

In the days to week following imposition of a moderate renal artery stenosis we are left with a situation in which renal vascular resistance is greater than normal, distal renal artery pressure is normal, or near normal, plasma renin activity is normal or only slightly elevated, renal blood flow and glomerular filtration rate are near normal, and fluid balance is restored at the cost of hypertension (Fig. 9.6) [41, 57, 58]. The mechanisms underlying increased renal vascular resistance, in the absence of activation of the endocrine renin-angiotensin system, have not been formally studied in large animal models. However, it is presumed that activation of the intrarenal renin-angiotensin system makes a major contribution [59, 60].

We are aware of no published studies of the evolution of changes in oxidative stress, regional kidney perfusion and kidney oxygenation over the first week of abrupt imposition of a renal artery stenosis. Such studies, and investigations of the role of the intrarenal renin/angiotensin system, are warranted.

Pathophysiology of the Chronically Post-stenotic Kidney

Experimental Models

Most of our understanding of the chronic pathophysiology of renovascular disease comes from experimental models characterized by gradual development of renal artery stenosis, such as is

achieved in mice, rats, and rabbits by placing a silver clip on one renal artery (2K1C hypertension), or in larger animals by placement of an irritant coil within the renal artery. These animal models also allow assessment of the impact of hypercholesterolemia and atherosclerosis on disease progression. This is important because hypercholesterolemia and atherosclerosis are often the direct cause of renal artery stenosis in humans. Hypercholesterolemia has both structural and functional effects on the renal circulation. These include vascular remodeling due to neovascularisation and endothelial dysfunction, mediated at least in part through oxidative stress [61]. Neovascularisation appears to be a compensatory response, which acts to maintain cortical perfusion in the face of altered vascular function [62]. On the other hand, hypercholesterolemia exacerbates the effects of renal artery stenosis on oxidative stress, inflammation, fibrosis, and tubular and vascular dysfunction (see details discussed next) [63]. The observations of a relatively poor correlation between stenosis severity and renal dysfunction in RVD [64] and that revascularization in RVD is not always effective in restoring renal dysfunction and fails to reverse vascular remodeling [40, 65], provide additional evidence that factors beyond the stenosis itself are critical in progression of renal dysfunction.

Renal Perfusion and Glomerular Filtration

The development of vascular remodeling, and in particular vascular rarefaction, is now seen as a hallmark of atherosclerotic RVD [40]. For example, using micro-CT, Zhu et al. demonstrated a marked reduction in microvascular density in a porcine model of renal artery stenosis [42]. These structural changes probably at least partly explain why cortical perfusion is reduced (although medullary perfusion is often well maintained) in chronic renovascular disease [66]. There are also functional effects of RVD on the renal vasculature. Responses of both cortical and medullary perfusion to acetylcholine are blunted in renovascular disease, at least in part due to oxidative stress [66]. Partial reversal of these structural and functional changes in the cortical circulation, and increased basal RBF and GFR, is seen after percutaneous transluminal renal artery stenting, to remove the stenosis, at least in a porcine model of RVD uncomplicated by hypercholesterolemia [67]. However, this treatment is much less effective when RVD is complicated by atherosclerosis [65]. Thus, renal artery stenosis, particularly when accompanied by hypercholesterolemia, appears to set in train a cascade of events, associated with oxidative stress, fibrosis, inflammation, apoptosis, vascular remodeling and endothelial dysfunction, which are at best only partially reversible. These observations in experimental animals likely provide at least a partial explanation for the lack of efficacy of stenting for treatment of renovascular disease, particularly that co-existing with atherosclerosis [40].

Multiple factors likely contribute to the altered structure and function of the renal circulation in renovascular disease (Fig. 9.7). Endothelium-dependent vasodilatation in the kidney is mediated by NO, vasodilator prostanoids (e.g., prostacyclin) and endothelium-derived hyperpolarizing factor [68]. The loss of endothelium-dependent vasodilation in the stenotic kidney appears to be mediated at least in part by reduced NO bioavailability, as evidenced by the blunted renal vasoconstriction observed in response to NO synthase blockade in the clipped kidney in 2K1C hypertension in rats [69], and in the stenotic kidney in patients with unilateral renal artery stenosis [70]. Renal vasoconstriction in response to NO blockade was greater in the non-stenotic kidney in unilateral RAS than in the kidneys of patients with essential hypertension, indicating increased dependence of endothelium-dependent vasodilatation in the non-stenotic kidney on NO bioavailability [70]. This notion is also supported by the results of studies in animal models of unilateral renal artery stenosis (as discussed in [70]). Taken collectively, available data indicate that the impact of unilateral renal artery stenosis on the role of NO in control of renal vascular tone depends upon the severity of the stenosis. As the stenosis becomes more severe the role of NO is progressively diminished in the clipped kidney [71], but if anything is exaggerated in the non-clipped kidney [69, 72]. An important consequence of the enhanced role of NO in the

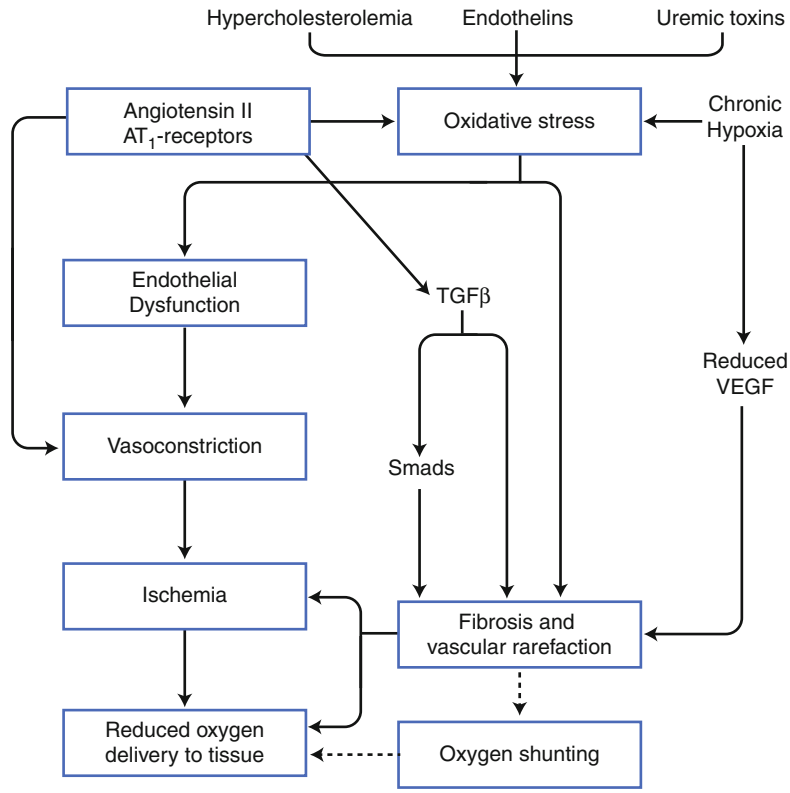


Fig. 9.7 Factors driving reduced oxygen delivery to tissue in chronic renovascular disease. *TGFβ* transforming growth factor β, *VEGF* vascular endothelial growth factor. Note that "oxygen shunting" refers to convective shunting, arising from heterogeneity of capillary perfusion, and diffusive shunting that occurs between arteries and veins in the cortex and descending and ascending vasa recta in the medulla. *Solid arrows* show established mechanisms. *Arrows* with *dotted lines* show mechanisms that are proposed but not established. See text for further details

non-clipped kidney is impaired autoregulation of RBF [73]. Renal artery stenosis increases prostaglandin E2 concentration in the kidney, and the vasoconstrictor response to cyclooxygenase inhibition, in a manner dependent on the severity of stenosis [71]. Thus, progressively more severe stenosis appears to lead to altered renal endothelial function in the stenotic kidney, from a dependence on NO to dependence on prostanoids [71].

There are complex interactions between angiotensin II and NO in RVD. In the normal kidney, AT_1-receptor activation by endogenous angiotensin II mediates cortical vasoconstriction, yet has little impact on the medullary circulation [74]. Activation of AT_2-receptors by endogenous angiotensin II has little impact on cortical or medullary perfusion in the normal rat kidney [74]. But in 2K1C hypertension in rats, the roles of AT_1- and AT_2-receptors in control of regional kidney perfusion and oxygenation are altered. Firstly, the contralateral kidney becomes less sensitive to the vasoconstrictor effects of angiotensin II mediated by AT_1-receptors [75, 76], but AT_2-receptors appear to exert a tonic vasoconstrictor effect on the medullary circulation [75]. In contrast, AT_2-receptor activation in the (early) clipped kidney appears to sustain renal cortical perfusion and oxygenation through release of NO, since administration of PD123319 results in cortical ischemia and hypoxia [77]. However, this effect seems to be lost in chronic 2K1C hypertension, at least in part due to the super-imposition of oxidative stress [78].

There is evidence that renal sympathetic drive is enhanced in RVD, which may in turn contribute to the development of hypertension [79]. The responsiveness of kidney to activation of the renal nerves, either through electrical stimulation [80] or reflex activation [81] appears to be relatively normal, with two important exceptions. Firstly, neurally-mediated renin release is blunted and secondly, neurally mediated vasoconstriction in the medullary circulation appears to be enhanced. These effects appear to be mediated predominantly by activation of the renin-angiotensin system, since they are recapitulated in hypertension induced by chronic infusion of angiotensin II [74].

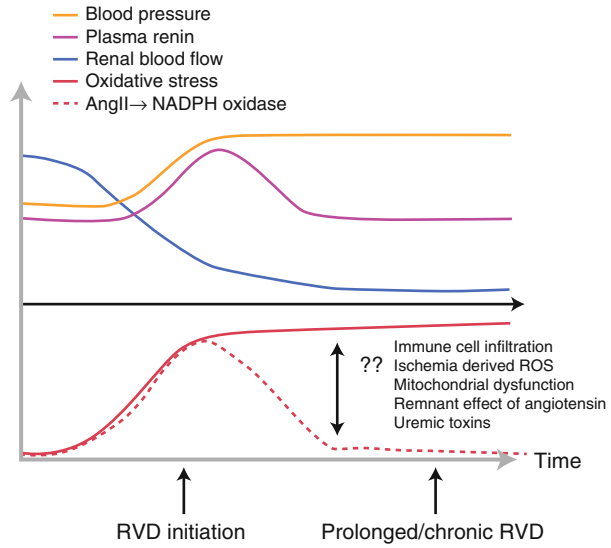


Fig. 9.8 Factors contributing to development of oxidative stress during the progression of renovascular disease (*RVD*). See text for details

Angiotensin II is also likely a major driver of fibrosis during the evolution of RVD, at least partly through stimulation of the fibrogenic cytokine transforming growth factor-β (TGF-β) (Fig. 9.7) [82]. Indeed, angiotensin II infusion in rats can lead to vascular rarefaction, in the absence of renal artery stenosis or hypercholesterolemia [82]. Recent evidence suggests that TGF-β signaling through Smad pathways is a major driver of fibrosis and atrophy in the clipped kidney in 2K1C hypertension in mice [83]. The relative roles of angiotensin II as opposed to other factors, in these effects, remains to be determined, although the observation that Smad3 deficiency in mice abrogates the cardiac fibrosis induced by chronic angiotensin II infusion is at least consistent with a role for angiotensin II [84]. Furthermore, AT_1-receptor activation can also induce Smad signaling independently of TGF-β, through mitogen-activated protein kinase (MAPK) activation, at least in vascular smooth muscle cells [85]. Inhibition of TGF-β/Smad signaling may at least partly explain the efficacy of statins in reducing fibrosis, renal dysfunction, endothelial dysfunction and vascular rarefaction in porcine models of RVD [86].

Oxidative Stress

Oxidative stress in renovascular disease has been evidenced by increased plasma isoprostanes and thiobarbituric acid reactive substances (TBARS), and reduced antioxidant enzymes such as glutathione peroxidase, superoxide dismutase and catalase in porcine RVD uncomplicated by hypercholesterolemia [87]. Furthermore, reduced endogenous superoxide dismutase activity and increased expression of subunits of NAD(P)H oxidase (p47phox and p67phox) has been observed in a porcine model of combined RVD and hypercholesterolemia [66]. Oxidative stress is at least partly driven by hypercholesterolemia in this model, since it is observed in animals with hypercholesterolemia but not RVD [61]. Activation of the renin/angiotensin system is also a major driver of oxidative stress in RVD. Indeed, chronic infusion of angiotensin II alone induces renal oxidative stress [88]. Plasma isoprostane levels are highly correlated with plasma renin activity in the early phases of RVD in pigs, but this association is lost as the disease progresses [87]. Thus, in chronic RVD, pathways of ROS formation unrelated to circulating plasma renin activity appear to be important in maintaining renal oxidative stress. This suggestion is supported by data from rats in which 12 months after induction of 2K-1C hypertension, treatment with the antioxidant Tempol was found to be significantly more effective than an AT_1 receptor blocker at reducing mean arterial pressure and improving renal blood flow and oxygenation in the clipped kidney [77]. The pathways responsible for maintaining elevated ROS levels within the kidney in chronic RVD remain unclear (Fig. 9.8).

Elevated arterial pressure can stimulate ROS production within the kidney [89]. However, elevated arterial pressure is unlikely to contribute to oxidative stress in RVD because post-stenotic renal arterial pressure is not elevated in RVD. Infiltration of immune cells is a common phenotype in hypertensive renal disease states and recruitment of infiltrating immune cells has been hypothesized to contribute to both up-regulation of the intra-renal renin-angiotensin system and renal oxidative stress [34, 90]. Activation of the intra-renal renin-angiotensin system, subtle renal injury or tissue hypoxia could potentially drive immune cell infiltration and contribute to maintenance of renal oxidative stress in chronic RVD [34]. To our knowledge the contribution of infiltrating immune cells to oxidative stress in chronic RVD disease has not been directly investigated.

The direct effects of ischemia/hypoxia on ROS production within the kidney are controversial. ROS production is an oxygen-dependent process and reductions in tissue oxygen availability limit ROS production by both NADPH oxidase and mitochondria, the chief sources of ROS in the kidney [91, 92]. However, the Km for O_2 of both NADPH oxidase and mitochondria is much less than normal tissue oxygen concentration, so the direct effects of ischemia to limit oxygen availability for ROS production may be offset by secondary effects of ischemia/hypoxia to promote ROS, at least during conditions of mild hypoxia. This idea is supported by observations of greater superoxide production in renal tubules at low oxygen concentration [93]. Cellular mechanisms that are capable of driving increased ROS production in ischemia/hypoxia have yet to be clearly identified. Within the kidney, one possibility is a switch to anaerobic metabolism and increased lactate production which may enhance NADPH oxidase activity [94, 95]. Loss of antioxidant pathways has also been proposed to maintain oxidative stress during chronic renal hypoxia [39]. Oxidative stress in advanced kidney disease is probably also driven by renal insufficiency and accumulation of uremic toxins (Figs. 9.7 and 9.8) [96]. However, the cellular mechanisms that drive oxidative stress in these states also remain unclear. Given the importance of ROS in the progression of RVD, further studies are warranted to delineate the cellular sources of ROS and the processes driving ROS production in chronic RVD.

Renal Oxygenation

Studies of the effects of RVD on intrarenal oxygenation have produced conflicting results, perhaps in part because of the use of different animal models, severity of stenosis, and time-scales of follow-up after induction of stenosis. Using BOLD-MR, Rognant and colleagues failed to detect hypoxia in the cortex or medulla in the 4 weeks after clipping the renal artery in 2K1C rats [49]. In contrast, using microelectrodes, Welch, Palm and colleagues have consistently observed cortical hypoxia in the clipped kidney in 2K1C rats [77, 78, 97]. In humans with RVD, BOLD MRI indicates relatively normal medullary oxygenation, and cortical hypoxia only in severe renal artery stenosis [98, 99]. Collectively, these observations suggest that compensatory mechanisms are able to protect kidney oxygenation in the face of renal artery stenosis. These compensatory mechanisms likely include the fact that reductions in GFR in the post-stenotic kidney lead to a reduced tubular sodium load, and thus reduced oxygen demand for sodium reabsorption. But these compensatory mechanisms can be overcome in the case of severe stenosis, particularly when associated with atherosclerosis (Fig. 9.9) [100].

Renal cortical hypoxia in RVD appears to be sustained by oxidative stress. Tempol increases cortical and medullary tissue PO_2 and cortical perfusion in the clipped kidney in chronic (early and late) 2K1C hypertension [78, 97]. Furthermore, chronic antioxidant therapy enhanced responses of cortical and medullary perfusion to acetylcholine in a porcine model of RVD associated with hypercholesterolemia, but did not improve basal cortical or medullary perfusion, or GFR [66]. The vascular rarefaction, relative ischemia, apoptotic activity, and fibrosis in the post-stenotic kidney in this porcine model was also greatly ameliorated by antioxidant treatment [42].

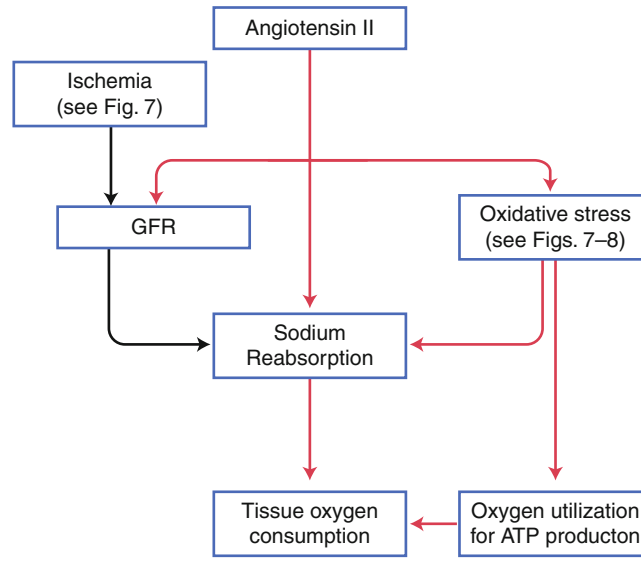


Fig. 9.9 Factors driving increased oxygen consumption in chronic renovascular disease. *Red arrows* show factors which increase oxygen consumption. *Black arrows* show factors which lead to reduced oxygen consumption. *GFR* glomerular filtration rate. See text for further details

The impact of oxidative stress on kidney oxygenation is likely mediated by the reduced oxygen delivery secondary to endothelial dysfunction and vascular rarefaction (Fig. 9.7), and reduced efficiency of renal oxygen utilization, due to reduced NO bioavailability (Fig. 9.9) [101, 102]. Renal venous PO_2 has been observed to be elevated in renovascular hypertension in humans [98]. This observation could be interpreted a number of ways. Firstly, it could merely reflect lesser oxygen demand in the post-stenotic kidney, driven by the reduced tubular sodium load. In support of this notion, there is strong evidence the increase in medullary oxygenation detected by BOLD MRI after treatment with the loop diuretic furosemide is blunted in severe RVD [103]. But one might expect such a phenomenon to be associated with *increased* kidney oxygenation, which has certainly not been observed. The other, intriguing possibility, is that RVD is associated by increased oxygen shunting in the post-stenotic kidney, which in turn limits the efficiency of oxygen extraction. As discussed earlier in this chapter, such oxygen shunting could be of a convective nature, perhaps mediated by increased heterogeneity of capillary perfusion, or diffusive, mediated by increased flux of oxygen from arteries to veins in the renal cortex and/or from descending to ascending vasa recta in the medulla (Fig. 9.7).

Role of Hypoxia in the Progression of RVD

While there is evidence of kidney hypoxia in RVD, the question of whether this hypoxia contributes to the progression of kidney disease remains unresolved. Largely, this is due to the fact that approaches have not been developed to allow hypoxia to be targeted specifically, so we must rely on indirect observation. In this context, a critical observation is that the effects of hypoxia on gene expression and signaling cascades appear to depend both on the duration and the severity of the hypoxic stimulus (Fig. 9.10). For example, acute hypoxia activates vascular endothelial derived growth factor (VEGF) expression in tubular epithelial cells [104], so would be expected to stimulate angiogenesis. But chronic (24 h) hypoxia inhibits VEGF-mediated signaling pathways in cultured human endothelial cells [105], and VEGF expression is relatively low in chronic kidney disease [106, 107], including in RVD [108], which could contribute to vascular rarefaction. Similarly, hypoxia inducible factors (HIFs) are upregulated by relatively mild hypoxia but can be downregulated when hypoxia is sustained and severe [12, 109]. HIFs appear to protect against tissue damage in acute kidney injury [12, 82, 110], but in chronic kidney disease may drive the expression of genes which promote disease progression [1, 106, 111].

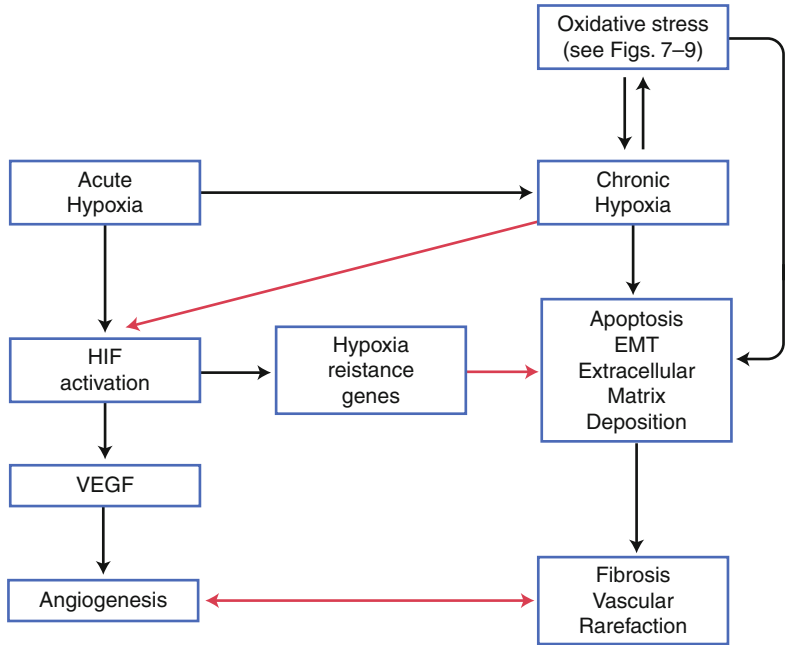


Fig. 9.10 Potential mechanisms by which hypoxia can initiate and maintain the pathogenesis of renovascular disease, especially development of fibrosis and microvascular rarefaction. Note that hypoxia-inducible factor (*HIF*) is activated in acute hypoxia, which can initiate angiogenesis through vascular endothelial growth factor (*VEGF*) and so inhibit vascular rarefaction, and inhibit apoptosis and extracellular matrix deposition through expression of hypoxia resistance genes. But in chronic hypoxia HIF is downregulation (*red arrows*), so hypoxia and oxidative stress act in concert to drive fibrosis and vascular rarefaction. *EMT* epithelial to mesenchymal transition. See text for further details

There is overwhelming evidence that hypoxia (1) can activate pro-inflammatory and profibrotic pathways, (2) contributes to the pathogenesis of acute kidney injury, and (3) evolves *pari passu* with most if not all forms of chronic kidney disease [106, 112–114]. Nevertheless, there is no "smoking gun"; direct evidence that tissue hypoxia is a critical pathogenic event rather than merely a consequence of chronic kidney disease. There is certainly good evidence that chronic hypoxia can lead to apoptosis and epithelial-to-mesenchyme transition, two processes that likely contribute to development of kidney disease and renal fibrosis [1, 82, 111, 112]. Other profibrotic effects of hypoxia include inhibition of the expression of collagenase and increased expression of metalloproteinase inhibitor 1 [115]. Hypoxia can also stimulate oxidative stress through stimulation of superoxide production via mitochondria, xanthine oxidase and NADPH oxidase [116], which likely also drives development of fibrosis [18, 61]. There is also evidence that hypoxia precedes development of renal fibrosis [114]. But we have not yet been able to tease out the relative contributions of hypoxia versus other factors in the development of any forms of kidney disease, including RVD. This is a major challenge that those of us working in the field of kidney oxygenation must focus on in our future endeavors.

Clinical Implications/Therapy

The preceding discussion has summarized the evidence that complex interactions between oxidative stress, ischemia and hypoxia may drive the progression of RVD. Does this provide any insights into the potential for better treatments for RVD? Revascularization has only limited

success [40, 117], probably in large part because it has limited efficacy in reversing the structural vascular abnormalities in RVD, and thus tissue hypoxia [67]. It has recently been argued that "functional" rarefaction, largely due to endothelial dysfunction, activates signaling cascades which in turn stimulate development of "structural" rarefaction which in turn represents a major driver of loss of renal function [108]. In support of this notion, treatments which ameliorate endothelial dysfunction and renal vasoconstriction such as antioxidants [18, 61], or treatments which blunt the upstream drivers of oxidative stress such as AT_1-receptor activation [82], or endothelin A-receptor activation [118] can blunt the development of vascular rarefaction and renal dysfunction. However, the efficacy of treatments targeting oxidative stress may be limited by the complexity of this system, as evidenced by recent findings of exacerbation of vascular rarefaction in RVD by chronic administration of the superoxide dismutase mimetic tempol, which the authors suggested may be due to increased bioavailability of hydrogen peroxide [119]. Development of RVD can also be blunted by treatments which more directly target microvascular rarefaction, such as intrarenal VEGF infusion [107, 108, 120] or endothelial progenitor cell therapy [108, 121, 122]. Thus, strategies targeting the functional and structural causes of renal ischemia will likely improve renal function as well as renal oxygenation.

Renal fibrosis will also promote tissue hypoxia by increasing the diffusion barriers between the sources of oxygen in the kidney (arteries, capillaries and veins) and the sites of oxygen consumption (tubular epithelial cells and other cell-types). Recent studies have identified multiple potential targets for inhibition of fibrosis, including TGF-β/Smad3 pathways [83]. Importantly, there is abundant experimental evidence that treatments that blunt fibrosis can also blunt vascular rarefaction, and vice versa [108]. In this context, targeting inflammation and the resultant oxidative stress with an agent such as bindarit, which inhibits production of monocyte chemoattractant protein-1, may be a useful therapeutic approach [123].

Renal oxygen consumption is also dysregulated in RVD, in that the efficiency of oxygen utilization for sodium reabsorption is decreased [97]. This phenomenon appears to be mediated by oxidative stress, generated both by activation of the renin-angiotensin system [97] and the accumulation of bioactive uremic toxins [96].

Thus, in conclusion, there appears to be considerable scope for development of treatments which are able to target both structural and functional damage to the kidney in RVD, and so improve renal perfusion and GFR, abrogate inflammation and oxidative stress, and improve kidney oxygenation.

Acknowledgements The authors' work has been supported by grants from the National Health and Medical Research Council of Australia (143603, 143785, 384101, 606601 & 1024575) and the American Heart Association (10SDG4150061).

References

1. Mimura I, Nangaku M. The suffocating kidney: tubulointerstitial hypoxia in end-stage renal disease. Nat Rev Nephrol. 2010;6:667–78.
2. Maddox DA, Deen WM, Brenner BM. Glomerular filtration. Compr Physiol. 2011;Suppl 25:545–638.
3. Evans RG, Eppel GA, Anderson WP, Denton KM. Mechanisms underlying the differential control of blood flow in the renal medulla and cortex. J Hypertens. 2004;22:1439–51.
4. Pallone TL, Edwards A, Mattson DL. Renal medullary circulation. Compr Physiol. 2012;2:97–140.
5. Gardiner BS, Thompson SL, Ngo JP, et al. Diffusive shunting between vessels in the pre-glomerular vasculature: anatomical observations and computational modeling. Am J Physiol Renal Physiol. 2012;303:F605–18.
6. O'Connor PM, Evans RG. Structural antioxidant defense mechanisms in the mammalian and nonmammalian kidney: different solutions to the same problem? Am J Physiol Regul Integr Comp Physiol. 2010;299:R723–7.
7. Zhang W, Edwards A. Oxygen transport across vasa recta in the renal medulla. Am J Physiol Heart Circ Physiol. 2002;283:H1042–55.
8. Just A. Mechanisms of renal blood flow autoregulation: dynamics and contributions. Am J Physiol Regul Integr Comp Physiol. 2007;292:R1–17.
9. Evans RG, Majid DS, Eppel GA. Mechanisms mediating pressure natriuresis: what we know and what we need to find out. Clin Exp Pharmacol Physiol. 2005;32:400–9.

10. Evans RG, Gardiner BS, Smith DW, O'Connor PM. Intrarenal oxygenation: unique challenges and the biophysical basis of homeostasis. Am J Physiol Renal Physiol. 2008;295:F1259–70.
11. Brezis M, Agmon Y, Epstein FH. Determinants of intrarenal oxygenation. I. Effects of diuretics. Am J Physiol. 1994;267:F1059–62.
12. Heyman SN, Evans RG, Rosen S, Rosenberger C. Cellular adaptive changes in AKI: mitigating renal hypoxic injury. Nephrol Dial Transplant. 2012;27: 1721–8.
13. Evans RG, Goddard D, Eppel GA, O'Connor PM. Factors that render the kidney susceptible to tissue hypoxia in hypoxemia. Am J Physiol Regul Integr Comp Physiol. 2011;300:R931–40.
14. Hanna IR, Taniyama Y, Szocs K, Rocic P, Griendling KK. NAD(P)H oxidase-derived reactive oxygen species as mediators of angiotensin II signaling. Antioxid Redox Signal. 2002;4:899–914.
15. Sedeek M, Gutsol A, Montezano AC, et al. Renoprotective effects of a novel Nox1/4 inhibitor in a mouse model of type 2 diabetes. Clin Sci (Lond). 2013;124(3):191–202.
16. Feng D, Yang C, Geurts AM, et al. Increased expression of NAD(P)H oxidase subunit p67(phox) in the renal medulla contributes to excess oxidative stress and salt-sensitive hypertension. Cell Metab. 2012;15: 201–8.
17. Basile DP, Leonard EC, Beal AG, Schleuter D, Friedrich J. Persistent oxidative stress following renal ischemia-reperfusion injury increases ANG II hemodynamic and fibrotic activity. Am J Physiol Renal Physiol. 2012;302:F1494–502.
18. Chade AR, Rodriguez-Porcel M, Herrmann J, et al. Antioxidant intervention blunts renal injury in experimental renovascular disease. J Am Soc Nephrol. 2004;15:958–66.
19. Taylor NE, Glocka P, Liang M, Cowley Jr AW. NADPH oxidase in the renal medulla causes oxidative stress and contributes to salt-sensitive hypertension in Dahl S rats. Hypertension. 2006;47:692–8.
20. Fato R, Bergamini C, Leoni S, Lenaz G. Mitochondrial production of reactive oxygen species: role of complex I and quinone analogues. Biofactors. 2008;32:31–9.
21. Zelko IN, Mariani TJ, Folz RJ. Superoxide dismutase multigene family: a comparison of the CuZn-SOD (SOD1), Mn-SOD (SOD2), and EC-SOD (SOD3) gene structures, evolution, and expression. Free Radic Biol Med. 2002;33:337–49.
22. Musatov A, Robinson NC. Susceptibility of mitochondrial electron-transport complexes to oxidative damage. Focus on cytochrome c oxidase. Free Radic Res. 2012;46(11):1313–26.
23. Dikalova AE, Bikineyeva AT, Budzyn K, et al. Therapeutic targeting of mitochondrial superoxide in hypertension. Circ Res. 2010;107:106–16.
24. O'Connor PM, Gutterman DD. Resurrecting hope for antioxidant treatment of cardiovascular disease: focus on mitochondria. Circ Res. 2010;107:9–11.
25. Drummond GR, Selemidis S, Griendling KK, Sobey CG. Combating oxidative stress in vascular disease: NADPH oxidases as therapeutic targets. Nat Rev Drug Discov. 2011;10:453–71.
26. Chabrashvili T, Tojo A, Onozato ML, et al. Expression and cellular localization of classic NADPH oxidase subunits in the spontaneously hypertensive rat kidney. Hypertension. 2002;39: 269–74.
27. Gill PS, Wilcox CS. NADPH oxidases in the kidney. Antioxid Redox Signal. 2006;8:1597–607.
28. Seshiah PN, Weber DS, Rocic P, Valppu L, Taniyama Y, Griendling KK. Angiotensin II stimulation of NAD(P)H oxidase activity: upstream mediators. Circ Res. 2002;91:406–13.
29. Heitzer T, Wenzel U, Hink U, et al. Increased NAD(P)H oxidase-mediated superoxide production in renovascular hypertension: evidence for an involvement of protein kinase C. Kidney Int. 1999; 55:252–60.
30. Sachse A, Wolf G. Angiotensin II-induced reactive oxygen species and the kidney. J Am Soc Nephrol. 2007;18:2439–46.
31. Massey KJ, Hong NJ, Garvin JL. Angiotensin II stimulates superoxide production in the thick ascending limb by activiating NOX4. Am J Physiol Cell Physiol. 2012;303(7):C781–9.
32. Lassegue B, Griendling KK. NADPH oxidases: functions and pathologies in the vasculature. Arterioscler Thromb Vasc Biol. 2010;30:653–61.
33. Graham KA, Kulawiec M, Owens KM, et al. NADPH oxidase 4 is an oncoprotein localized to mitochondria. Cancer Biol Ther. 2010;10:223–31.
34. Harrison DG, Guzik TJ, Lob HE, et al. Inflammation, immunity, and hypertension. Hypertension. 2011;57:132–40.
35. Palm F, Teerlink T, Hansell P. Nitric oxide and kidney oxygenation. Curr Opin Nephrol Hypertens. 2009;18:68–73.
36. Hong NJ, Garvin JL. Nitric oxide reduces flow-induced superoxide production via cGMP-dependent protein kinase in thick ascending limbs. Am J Physiol Renal Physiol. 2009;296:F1061–6.
37. Edwards A, Layton AT. Nitric oxide and superoxide transport in a cross section of the rat outer medulla. II. Reciprocal interactions and tubulovascular cross talk. Am J Physiol Renal Physiol. 2010;299:F634–47.
38. Vasquez-Vivar J, Hogg N, Martasek P, Karoui H, Pritchard Jr KA, Kalyanaraman B. Tetrahydrobiopterin-dependent inhibition of superoxide generation from neuronal nitric oxide synthase. J Biol Chem. 1999;274:26736–42.
39. Son D, Kojima I, Inagi R, Matsumoto M, Fujita T, Nangaku M. Chronic hypoxia aggravates renal injury via suppression of Cu/Zn-SOD: a proteomic analysis. Am J Physiol Renal Physiol. 2008;294: F62–72.
40. Textor SC, Lerman L. Renovascular hypertension and ischemic nephropathy. Am J Hypertens. 2010; 23:1159–69.

41. Anderson WP, Woods RL, Gao Y. Renovascular hypertension: information from experiments using conscious dogs. Clin Exp Pharmacol Physiol. 1991;18:29–32.
42. Zhu XY, Chade AR, Rodriguez-Porcel M, et al. Cortical microvascular remodeling in the stenotic kidney: role of increased oxidative stress. Arterioscler Thromb Vasc Biol. 2004;24:1854–9.
43. Rognant N, Rouviere O, Janier M, et al. Hemodynamic responses to acute and gradual renal artery stenosis in pigs. Am J Hypertens. 2010;23: 1216–9.
44. Schoenberg SO, Bock M, Kallinowski F, Just A. Correlation of hemodynamic impact and morphologic degree of renal artery stenosis in a canine model. J Am Soc Nephrol. 2000;11:2190–8.
45. Anderson WP, Johnston CI, Korner PI. Acute renal haemodynamic and renin-angiotensin system responses to graded renal artery stenosis in the dog. J Physiol. 1979;287:231–45.
46. Evans RG, Eppel GA, Michaels S, et al. Multiple mechanisms act to maintain kidney oxygenation during renal ischemia in anesthetized rabbits. Am J Physiol Renal Physiol. 2010;298:F1235–43.
47. Evans RG, Gardiner BS, Smith DW, O'Connor PM. Methods for studying the physiology of kidney oxygenation. Clin Exp Pharmacol Physiol. 2008;35: 1405–12.
48. Djamali A, Sadowski EA, Muehrer RJ, et al. BOLD-MRI assessment of intrarenal oxygenation and oxidative stress in patients with chronic kidney allograft dysfunction. Am J Physiol Renal Physiol. 2007;292:F513–22.
49. Rognant N, Guebre-Egziabher F, Bacchetta J, et al. Evolution of renal oxygen content measured by BOLD MRI downstream a chronic renal artery stenosis. Nephrol Dial Transplant. 2011;26:1205–10.
50. Evans RG, Leong CL, Anderson WP, O'Connor PM. Don't be so BOLD: potential limitations in the use of BOLD MRI for studies of renal oxygenation. Kidney Int. 2007;71:1327–8.
51. Warner L, Glockner JF, Woollard J, Textor SC, Romero JC, Lerman LO. Determinations of renal cortical and medullary oxygenation using blood oxygen level-dependent magnetic resonance imaging and selective diuretics. Invest Radiol. 2011;46:41–7.
52. Juillard L, Lerman LO, Kruger DG, et al. Blood oxygen level-dependent measurement of acute intrarenal ischemia. Kidney Int. 2004;65:944–50.
53. Warner L, Gomez SI, Bolterman R, et al. Regional decreases in renal oxygenation during graded acute renal arterial stenosis: a case for renal ischemia. Am J Physiol Regul Integr Comp Physiol. 2009;296: R67–71.
54. Gardiner BS, Smith DW, O'Connor PM, Evans RG. A mathematical model of diffusional shunting of oxygen from arteries to veins in the kidney. Am J Physiol Renal Physiol. 2011;300:F1339–52.
55. Evans RG, Fitzgerald SM. Nitric oxide and superoxide in the renal medulla: a delicate balancing act. Curr Opin Nephrol Hypertens. 2005;14:9–15.
56. Majid DS, Nishiyama A, Jackson KE, Castillo A. Superoxide scavenging attenuates renal responses to ANG II during nitric oxide synthase inhibition in anesthetized dogs. Am J Physiol Renal Physiol. 2005;288:F412–9.
57. Anderson WP, Korner PI, Johnston CI. Acute angiotensin II-mediated restoration of distal renal artery pressure in renal artery stenosis and its relationship to the development of sustained one-kidney hypertension in conscious dogs. Hypertension. 1979;1: 292–8.
58. Anderson WP, Denton KM, Woods RL, Alcorn D. Angiotensin II and the maintenance of GFR and renal blood flow during renal artery narrowing. Kidney Int Suppl. 1990;30:S109–13.
59. Kobori H, Nangaku M, Navar LG, Nishiyama A. The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. Pharmacol Rev. 2007;59:251–87.
60. Navar LG, Prieto MC, Satou R, Kobori H. Intrarenal angiotensin II and its contribution to the genesis of chronic hypertension. Curr Opin Pharmacol. 2011;11: 180–6.
61. Chade AR, Bentley MD, Zhu X, et al. Antioxidant intervention prevents renal neovascularization in hypercholesterolemic pigs. J Am Soc Nephrol. 2004;15:1816–25.
62. Chade AR, Krier JD, Galili O, Lerman A, Lerman LO. Role of renal cortical neovascularization in experimental hypercholesterolemia. Hypertension. 2007;50:729–36.
63. Urbieta-Caceres VH, Lavi R, Zhu XY, et al. Early atherosclerosis aggravates the effect of renal artery stenosis on the swine kidney. Am J Physiol Renal Physiol. 2010;299:F135–40.
64. Lerman LO, Taler SJ, Textor SC, Sheedy 2nd PF, Stanson AW, Romero JC. Computed tomography-derived intrarenal blood flow in renovascular and essential hypertension. Kidney Int. 1996;49:846–54.
65. Eirin A, Zhu XY, Urbieta-Caceres VH, et al. Persistent kidney dysfunction in swine renal artery stenosis correlates with outer cortical microvascular remodeling. Am J Physiol Renal Physiol. 2011;300:F1394–401.
66. Chade AR, Krier JD, Rodriguez-Porcel M, et al. Comparison of acute and chronic antioxidant interventions in experimental renovascular disease. Am J Physiol Renal Physiol. 2004;286:F1079–86.
67. Favreau F, Zhu XY, Krier JD, et al. Revascularization of swine renal artery stenosis improves renal function but not the changes in vascular structure. Kidney Int. 2010;78:1110–8.
68. Edgley AJ, Tare M, Evans RG, Skordilis C, Parkington HC. In vivo regulation of endothelium-dependent vasodilation in the rat renal circulation and the effect of streptozotocin-induced diabetes. Am J Physiol Regul Integr Comp Physiol. 2008;295:829–39.
69. Sigmon DH, Beierwaltes WH. Nitric oxide influences blood flow distribution in renovascular hypertension. Hypertension. 1994;23:I34–9.

70. Wierema TK, Houben AJ, Kroon AA, et al. Nitric oxide dependence of renal blood flow in patients with renal artery stenosis. J Am Soc Nephrol. 2001;12:1836–43.
71. Tokuyama H, Hayashi K, Matsuda H, et al. Stenosis-dependent role of nitric oxide and prostaglandins in chronic renal ischemia. Am J Physiol Renal Physiol. 2002;282:F859–65.
72. Sigmon DH, Beierwaltes WH. Degree of renal artery stenosis alters nitric oxide regulation of renal hemodynamics. J Am Soc Nephrol. 1994;5:1369–77.
73. Turkstra E, Braam B, Koomans HA. Impaired renal blood flow autoregulation in two-kidney, one-clip hypertensive rats is caused by enhanced activity of nitric oxide. J Am Soc Nephrol. 2000;11:847–55.
74. Evans RG, Head GA, Eppel GA, Burke SL, Rajapakse NW. Angiotensin II and neurohumoral control of the renal medullary circulation. Clin Exp Pharmacol Physiol. 2010;37:e58–69.
75. Duke LM, Widdop RE, Kett MM, Evans RG. AT(2) receptors mediate tonic renal medullary vasoconstriction in renovascular hypertension. Br J Pharmacol. 2005;144:486–92.
76. Bivol LM, Vagnes OB, Iversen BM. The renal vascular response to ANG II injection is reduced in the non-clipped kidney of two-kidney, one-clip hypertension. Am J Physiol Renal Physiol. 2005;289:F393–400.
77. Palm F, Onozato M, Welch WJ, Wilcox CS. Blood pressure, blood flow, and oxygenation in the clipped kidney of chronic 2-kidney, 1-clip rats: effects of tempol and Angiotensin blockade. Hypertension. 2010;55:298–304.
78. Palm F, Connors SG, Mendonca M, Welch WJ, Wilcox CS. Angiotensin II type 2 receptors and nitric oxide sustain oxygenation in the clipped kidney of early Goldblatt hypertensive rats. Hypertension. 2008;51:345–51.
79. Johansson M, Elam M, Rundqvist B, et al. Increased sympathetic nerve activity in renovascular hypertension. Circulation. 1999;99:2537–42.
80. Burke SL, Head GA, Lambert GW, Evans RG. Renal sympathetic neuroeffector function in renovascular and angiotensin II-dependent hypertension in rabbits. Hypertension. 2007;49:932–8.
81. Evans RG, Burke SL, Lambert GW, Head GA. Renal responses to acute reflex activation of renal sympathetic nerve activity and renal denervation in secondary hypertension. Am J Physiol Regul Integr Comp Physiol. 2007;293:R1247–56.
82. Nangaku M, Fujita T. Activation of the renin-angiotensin system and chronic hypoxia of the kidney. Hypertens Res. 2008;31:175–84.
83. Warner GM, Cheng J, Knudsen BE, et al. Genetic deficiency of Smad3 protects the kidneys from atrophy and interstitial fibrosis in 2K1C hypertension. Am J Physiol Renal Physiol. 2012;302:F1455–64.
84. Huang XR, Chung AC, Yang F, et al. Smad3 mediates cardiac inflammation and fibrosis in angiotensin II-induced hypertensive cardiac remodeling. Hypertension. 2010;55:1165–71.
85. Rodriguez-Vita J, Sanchez-Lopez E, Esteban V, Ruperez M, Egido J, Ruiz-Ortega M. Angiotensin II activates the Smad pathway in vascular smooth muscle cells by a transforming growth factor-beta-independent mechanism. Circulation. 2005;111:2509–17.
86. Chade AR, Zhu XY, Grande JP, Krier JD, Lerman A, Lerman LO. Simvastatin abates development of renal fibrosis in experimental renovascular disease. J Hypertens. 2008;26:1651–60.
87. Lerman LO, Nath KA, Rodriguez-Porcel M, et al. Increased oxidative stress in experimental renovascular hypertension. Hypertension. 2001;37:541–6.
88. Kopkan L, Castillo A, Navar LG, Majid DS. Enhanced superoxide generation modulates renal function in ANG II-induced hypertensive rats. Am J Physiol Renal Physiol. 2006;290:F80–6.
89. Polichnowski AJ, Jin C, Yang C, Cowley Jr AW. Role of renal perfusion pressure versus angiotensin II on renal oxidative stress in angiotensin II-induced hypertensive rats. Hypertension. 2010;55:1425–30.
90. De Miguel C, Guo C, Lund H, Feng D, Mattson DL. Infiltrating T lymphocytes in the kidney increase oxidative stress and participate in the development of hypertension and renal disease. Am J Physiol Renal Physiol. 2011;300:F734–42.
91. Chen Y, Gill PS, Welch WJ. Oxygen availability limits renal NADPH-dependent superoxide production. Am J Physiol Renal Physiol. 2005;289:F749–53.
92. Hoffman DL, Brookes PS. Oxygen sensitivity of mitochondrial reactive oxygen species generation depends on metabolic conditions. J Biol Chem. 2009;284:16236–45.
93. Li N, Yi FX, Spurrier JL, Bobrowitz CA, Zou AP. Production of superoxide through NADH oxidase in thick ascending limb of Henle's loop in rat kidney. Am J Physiol Renal Physiol. 2002;282:F1111–9.
94. Mohazzab HK, Kaminski PM, Wolin MS. Lactate and PO_2 modulate superoxide anion production in bovine cardiac myocytes: potential role of NADH oxidase. Circulation. 1997;96:614–20.
95. Zhou L, Stanley WC, Saidel GM, Yu X, Cabrera ME. Regulation of lactate production at the onset of ischaemia is independent of mitochondrial NADH/NAD+: insights from in silico studies. J Physiol. 2005;569:925–37.
96. Chiang CK, Tanaka T, Nangaku M. Dysregulated oxygen metabolism of the kidney by uremic toxins: review. J Ren Nutr. 2012;22:77–80.
97. Welch WJ, Mendonca M, Aslam S, Wilcox CS. Roles of oxidative stress and AT1 receptors in renal hemodynamics and oxygenation in the postclipped 2K,1C kidney. Hypertension. 2003;41:692–6.
98. Gloviczki ML, Glockner JF, Lerman LO, et al. Preserved oxygenation despite reduced blood flow in poststenotic kidneys in human atherosclerotic renal artery stenosis. Hypertension. 2010;55:961–6.
99. Gloviczki ML, Glockner JF, Crane JA, et al. Blood oxygen level-dependent magnetic resonance imaging identifies cortical hypoxia in severe renovascular disease. Hypertension. 2011;58:1066–72.

100. Gloviczki ML, Lerman LO, Textor SC. Blood oxygen level-dependent (BOLD) MRI in renovascular hypertension. Curr Hypertens Rep. 2011;13:370–7.
101. Palm F, Nordquist L. Renal tubulointerstitial hypoxia: cause and consequence of kidney dysfunction. Clin Exp Pharmacol Physiol. 2011;38:424–30.
102. Palm F, Nordquist L. Renal oxidative stress, oxygenation, and hypertension. Am J Physiol Regul Integr Comp Physiol. 2011;301:R1229–41.
103. Gomez SI, Warner L, Haas JA, et al. Increased hypoxia and reduced renal tubular response to furosemide detected by BOLD magnetic resonance imaging in swine renovascular hypertension. Am J Physiol Renal Physiol. 2009;297:F981–6.
104. Nakagawa T, Lan HY, Zhu HJ, Kang DH, Schreiner GF, Johnson RJ. Differential regulation of VEGF by TGF-beta and hypoxia in rat proximal tubular cells. Am J Physiol Renal Physiol. 2004;287:F658–64.
105. Olszewska-Pazdrak B, Hein TW, Olszewska P, Carney DH. Chronic hypoxia attenuates VEGF signaling and angiogenic responses by downregulation of KDR in human endothelial cells. Am J Physiol Cell Physiol. 2009;296:C1162–70.
106. Mayer G. Capillary rarefaction, hypoxia, VEGF and angiogenesis in chronic renal disease. Nephrol Dial Transplant. 2011;26:1132–7.
107. Chade AR, Kelsen S. Reversal of renal dysfunction by targeted administration of VEGF into the stenotic kidney: a novel potential therapeutic approach. Am J Physiol Renal Physiol. 2012;302:F1342–50.
108. Chade AR. Renovascular disease, microcirculation, and the progression of renal injury: role of angiogenesis. Am J Physiol Regul Integr Comp Physiol. 2011;300:R783–90.
109. Nangaku M, Rosenberger C, Heyman SN, Eckardt K-U. HIF regulation in kidney disease. Clin Exp Pharmacol Physiol. 2013;40(2):148–57.
110. Bernhardt WM, Campean V, Kany S, et al. Preconditional activation of hypoxia-inducible factors ameliorates ischemic acute renal failure. J Am Soc Nephrol. 2006;17:1970–8.
111. Haase VH. Oxygen regulates epithelial-to-mesenchymal transition: insights into molecular mechanisms and relevance to disease. Kidney Int. 2009;76:492–9.
112. Nangaku M, Inagi R, Miyata T, Fujita T. Angiotensin-induced hypoxia in the kidney: functional and structural changes of the renal circulation. Adv Exp Med Biol. 2007;618:85–99.
113. Heyman SN, Khamaisi M, Rosen S, Rosenberger C. Renal parenchymal hypoxia, hypoxia response and the progression of chronic kidney disease. Am J Nephrol. 2008;28:998–1006.
114. Fine LG, Norman JT. Chronic hypoxia as a mechanism of progression of chronic kidney diseases: from hypothesis to novel therapeutics. Kidney Int. 2008; 74:867–72.
115. Norman JT, Clark IM, Garcia PL. Hypoxia promotes fibrogenesis in human renal fibroblasts. Kidney Int. 2000;58:2351–66.
116. Abramov AY, Scorziello A, Duchen MR. Three distinct mechanisms generate oxygen free radicals in neurons and contribute to cell death during anoxia and reoxygenation. J Neurosci. 2007;27:1129–38.
117. Takumi T, Mathew V, Barsness GW, et al. The association between renal atherosclerotic plaque characteristics and renal function before and after renal artery intervention. Mayo Clin Proc. 2011;86: 1165–72.
118. Kelsen S, Hall JE, Chade AR. Endothelin-A receptor blockade slows the progression of renal injury in experimental renovascular disease. Am J Physiol Renal Physiol. 2011;301:F218–25.
119. Kelsen S, He X, Chade AR. Early superoxide scavenging accelerates renal microvascular rarefaction and damage in the stenotic Kidney. Am J Physiol Renal Physiol. 2012;303:F576–83.
120. Iliescu R, Fernandez SR, Kelsen S, Maric C, Chade AR. Role of renal microcirculation in experimental renovascular disease. Nephrol Dial Transplant. 2010;25:1079–87.
121. Chade AR, Zhu X, Lavi R, et al. Endothelial progenitor cells restore renal function in chronic experimental renovascular disease. Circulation. 2009;119: 547–57.
122. Ebrahimi B, Li Z, Eirin A, Zhu XY, Textor SC, Lerman LO. Addition of endothelial progenitor cells to renal revascularization restores medullary tubular oxygen consumption in swine renal artery stenosis. Am J Physiol Renal Physiol. 2012;302:F1478–85.
123. Zhu XY, Chade AR, Krier JD, et al. The chemokine monocyte chemoattractant protein-1 contributes to renal dysfunction in swine renovascular hypertension. J Hypertens. 2009;27:2063–73.
124. Gullans SR, Hebert SC. Metabolic basis of ion transport. In: Brenner BM, editor. Brenner and Rector's the kidney. 5th ed. Philadelphia: WB Saunders Company; 1996.

Tubulointerstitial Injury: Signaling Pathways, Inflammation, Fibrogenesis

10

Stella P. Hartono and Joseph P. Grande

Abstract

Renovascular hypertension (RVH) is an important cause of both renal and cardiovascular morbidity and mortality. Atherosclerosis is the most common etiology underlying the development of RVH. In the stenotic kidney, the development of interstitial fibrosis and tubular atrophy is associated with the influx of inflammatory cells. These morphologic alterations result from a complex interplay of several pathways involving the renin angiotensin system, oxidative stress, the TGF-β-Smad signaling pathway, and the mitogen-activated protein kinase (MAPK) pathway, leading to both local and systemic production of chemokines that promote ongoing inflammation and interstitial fibrosis. In this chapter, we will summarize recent human and experimental studies to determine how these signaling pathways interact and contribute to renal inflammation and fibrogenesis. Identification of these pathways will provide a mechanistic basis for the development of RVH and may provide the basis for novel therapeutic targets directed towards arresting the progression of renal disease in patients with renal artery stenosis.

Keywords

Renal artery stenosis • TGF-B • MAPK • Fibrosis • Inflammation • Macrophage • CCL2

Renal Artery Stenosis: Scope of the Problem

RVH results from a functional reduction in the diameter of one renal artery, leading to decreased flow distal to the stenosis. A substantial proportion of elderly hypertensive patients with new onset of end-stage renal disease of unclear etiology have been found to have significant renal artery stenosis [1]. Atherosclerotic

S.P. Hartono, MD, PhD Student
Mayo Graduate School, Mayo Clinic,
Rochester, MN 55905, USA
e-mail: hartono.stella@mayo.edu

J.P. Grande, MD, PhD (✉)
Department of Laboratory Medicine and Pathology,
Mayo Clinic, 200 First Street SW, Rochester,
MN 55905, USA
e-mail: grande.joseph@mayo.edu

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_10,

renal artery disease is by far the most common etiology underlying RVH [2]. In several large studies, atherosclerotic renal artery disease has been identified in approximately 7 % of individuals over 65 years of age and in up to one-half of patients with clinical manifestations of coronary artery disease or aortoiliac disease [3–5]. Surgical approaches to revascularize the kidney affected by renal artery stenosis have not consistently improved renal function; in up to one-quarter of patients, renal function deteriorates after interventions to restore blood flow [1, 5]. These disappointing results have prompted investigators to perform studies to define basic mechanisms of renal injury in patients with renal artery stenosis and RVH in order to discover novel therapeutic targets that will prevent renal disease progression.

Given that the most common etiology for renal artery stenosis is atherosclerosis, patients at risk for developing renal artery stenosis have similar risk factors for the development of generalized atherosclerosis – hyperlipidemia, cigarette smoking, diabetes, and essential hypertension. In addition to these well-established risk factors, recent studies have underscored a critical role for systemic inflammation in the progression of tissue lesions associated with atherosclerosis, RVH, and diabetic renal disease [6–8]. Systemic inflammation – as evidenced by increased plasma levels of IL-6 and other pro-inflammatory mediators – is found soon after surgery to correct renal artery stenosis and may be predictive of an increased risk of developing restenosis [9, 10]. Indeed, systemic inflammation in patients with advanced chronic kidney disease of any etiology may be responsible for the well-established risk of death from accelerated cardiovascular disease [11]. These observations have prompted a number of studies to better understand the link between local and systemic inflammation and the progression of RVD. These studies have uncovered a strong link between tissue inflammation and the development of fibrosis.

Histopathologic Findings in Humans with Severe Renal Artery Stenosis

The first step in understanding the link between tissue inflammation and the development of fibrosis has involved careful histopathologic examination of tissues as they are developing fibrosis. Along these lines, the clinical findings and histopathologic alterations in patients with severe renal artery stenosis which necessitated a nephrectomy of the atrophic kidney to treat intractable hypertension have recently been described [12]. Histopathologic features of kidneys rendered atrophic by renal artery stenosis include generalized tubular atrophy, a process characterized by flattening and simplification of tubular epithelium and thickening of tubular basement membranes (Fig. 10.1a, b). There is a generalized increase in interstitial fibrous tissue. In virtually all cases, focal mononuclear inflammatory infiltrates are identified in regions of fibrosis/atrophy. In 71 % of the nephrectomy specimens studied, there was relative glomerular sparing – although the ischemic wrinkling and folding of basement membranes was often seen, <10 % of glomeruli showed global glomerulosclerosis. In the remaining 29 % of nephrectomy specimens, the severe tubulointerstitial fibrosis was associated with extensive (>30 %) global sclerosis. The severity of interstitial fibrosis, tubular atrophy, and presence of extensive glomerulosclerosis were associated with small kidney size, as measured at the time of nephrectomy [12]. Atherosclerotic changes were identified within arteries in 98 % of nephrectomy specimens; medial hypertrophy indicative of hypertensive changes was observed in arteries in 52 % of nephrectomy specimens. Atheroembolic renal disease was found in 39 % of nephrectomy specimens. The severity of vascular lesions correlated with hypertension, dyslipidemia, presence of renal insufficiency, abdominal aneurysms, and history of myocardial infarction. Of the patients with nephrectomy specimens showing atheroembolic renal disease, 93 % had undergone a vascular

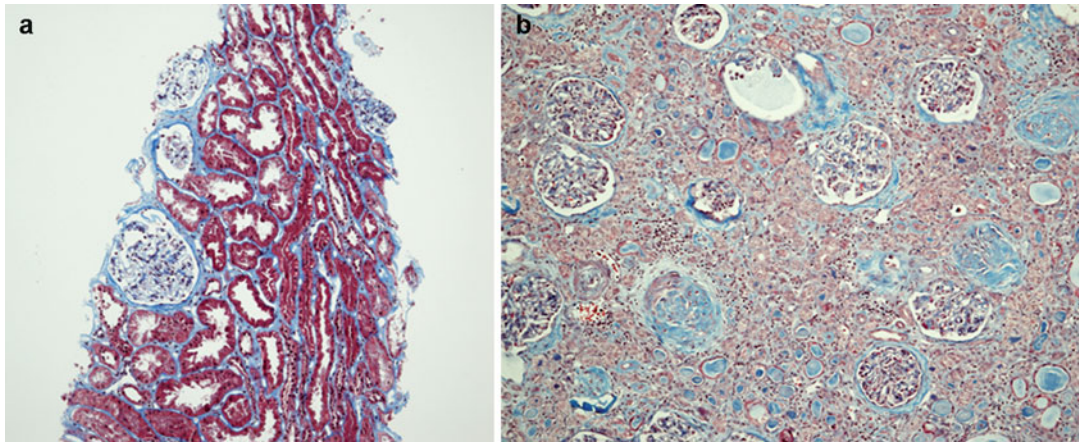


Fig. 10.1 (**a**) Trichrome stain of a renal biopsy obtained from a patient with no significant histopathologic abnormalities. Glomerular size, spacing, and architecture are normal. The tubules are back-to-back, with fine, delicate strands of blue-staining fibrous tissue in the interstitium. Note the absence of interstitial inflammation. (**b**) Trichrome stain of a renal section obtained from a patient with renal artery stenosis who underwent a nephrectomy for intractable hypertension. Note the decreased amount of space between glomeruli, indicative of severe renal atrophy. Several glomeruli are globally sclerotic. There is generalized flattening and simplification of the tubular epithelium. Note the focal interstitial inflammatory infiltrates, consisting predominantly of T cells and macrophages, within the interstitium. There is medial hypertrophy and intimal sclerosis of interstitial arteries, indicative of hypertension

procedure within the previous 3 years. Virtually all of the patients with hypertensive vascular lesions had concomitant atherosclerosis involving interlobular and arcuate-sized arteries [12].

Based on this descriptive and observational study, it is apparent that patients with end stage kidney disease due to renal artery stenosis have risk factors for generalized atherosclerosis and have severe intrarenal vascular disease. Furthermore, there is a strong histopathologic association between the presence of interstitial fibrosis and interstitial inflammation. In order to determine a mechanistic basis for these observations, investigators have employed animal models that mimic human RVD.

Animal Models of RVD

One of the most commonly employed models which recapitulates many of the features observed in human RVH involves the placement of a partial obstruction of one renal artery to induce unilateral renal artery stenosis (Fig. 10.2a, b) [13, 14]. In this "2-kidney, 1-clip" (2K1C) model, reduced renal perfusion in the stenotic kidney stimulates renin secretion, with subsequent increases in plasma angiotensin II levels, thereby provoking systemic hypertension. As a first step in defining pathways responsible for the development of renal fibrosis and inflammation, a time-dependent characterization of signaling pathways activated in the murine 2K1C model has been recently described [14]. In this model, the stenotic kidney undergoes atrophy, whereas the contralateral kidney enlarges at least in part through hyperplasia. As observed in human RVD, the stenotic kidney develops progressive interstitial fibrosis, tubular atrophy, and interstitial inflammation (Fig. 10.3a, b). The stenotic kidney shows marked and persistent increase in markers of cell proliferation and cell cycle activity, predominantly within tubular epithelial cells [14]. The development of atrophy in the stenotic kidney is associated with evidence of epithelial to mesenchymal transformation. An influx of inflammatory cells, predominantly T cells and macrophages, is

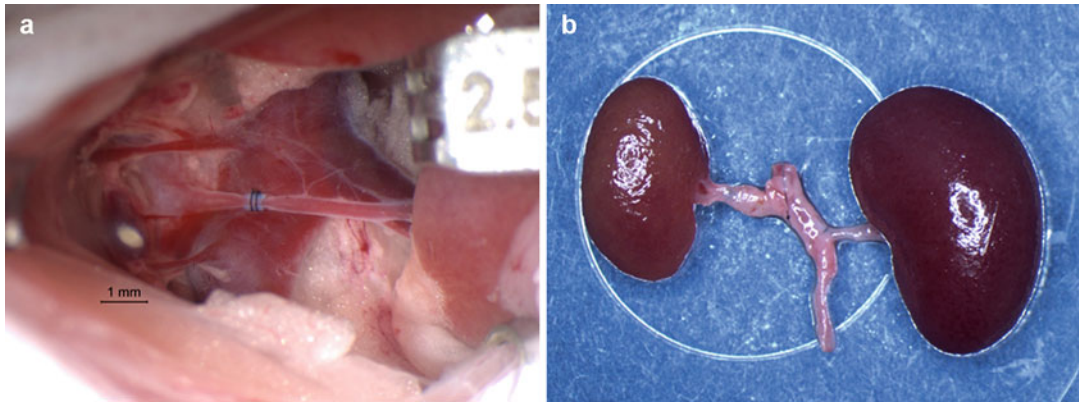


Fig. 10.2 (**a**) Photograph of kidney at time of stent placement. In this 2K1C model, a polytetrafluoroethylene cuff, internal diameter 200 μm, is placed on the right renal artery and fixed in place with two sutures. (**b**) Photograph of kidneys and aorta harvested 4 weeks after placement of the cuff. Note the asymmetry in the size of the left and right kidneys

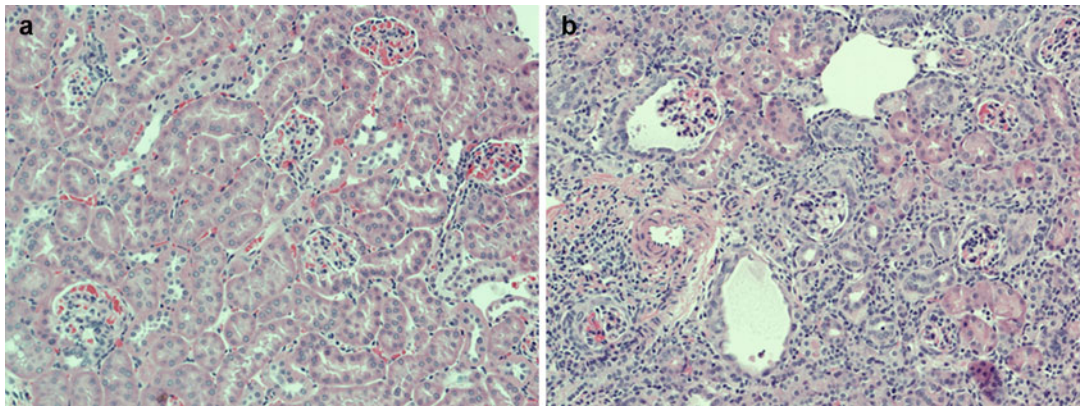


Fig. 10.3 (**a**) Histologic appearance of right kidney 6 weeks following sham procedure involving manipulation of right renal artery, but without placement of cuff. The architecture is essentially normal – there is no significant interstitial fibrosis, tubular atrophy, or interstitial inflammation. Glomeruli are normal. (**b**) Histologic section of right kidney obtained 6 weeks after placement of cuff. Note the severe tubular atrophy with focal interstitial fibrosis. The interstitial fibrosis is associated with infiltration of inflammatory cells, including T cells and macrophages

also observed early and throughout the atrophic process. The contralateral kidney, which does not develop any significant histopathologic alterations, shows transient increases in pathways associated with cell cycle activation and TGF-β1 expression [14]. No significant inflammation is noted within the contralateral kidney at any time point.

Although studies of renal artery stenosis in experimental animals have provided important mechanistic insights, these and many other studies are limited in that they do not address potential compounding effects of hyperlipidemia or metabolic syndrome, features which are strongly associated with the development of atherosclerotic renal artery stenosis and RVH in humans. In a porcine model of renal artery stenosis, early atherosclerosis induced by diet exacerbated damage in the stenotic kidney, compared with pigs fed a standard diet and subjected to a similar degree of renal artery stenosis [15]. The increased damage in the stenotic kidney was associated with oxidative stress [16]. Increased fibrosis and infiltrating lymphocytes and macrophages were observed in the stenotic kidney of atherosclerotic animals [16–18]. Although renal blood flow, overall glomerular filtration rate, and cortical

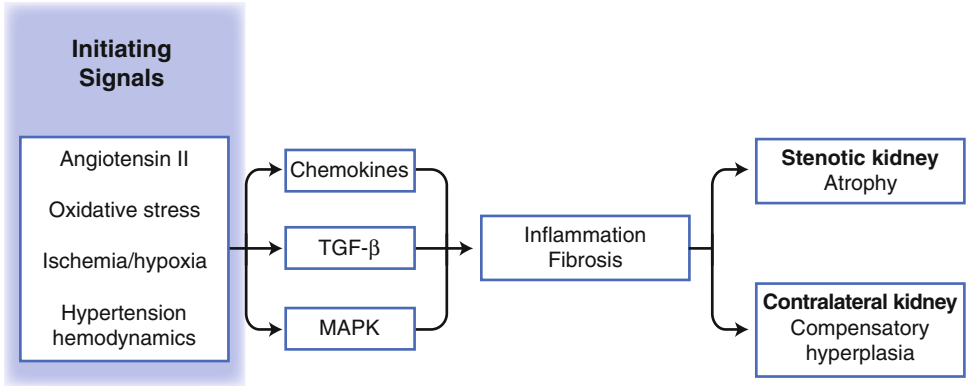


Fig. 10.4 In renal artery stenosis, several "initiating signals" combine to promote MAPK activation, chemokine synthesis, and TGF-**β** production. These critical signaling pathways are responsible for the characteristic interstitial fibrosis, interstitial inflammation, and tubular atrophy observed in the stenotic kidney. The contralateral kidney undergoes compensatory enlargement

perfusion were similarly decreased in atherosclerotic and non-atherosclerotic renal artery stenosis, medullary perfusion declined only in atherosclerotic animals subjected to renal artery stenosis [16]. It is possible that this decrease in medullary perfusion could be responsible for at least some of the damage seen in atherosclerotic renal artery stenosis, as the medulla is particularly vulnerable to hypoperfusion and ischemia. The importance of comorbid factors such as hyperlipidemia and metabolic syndrome is underscored by clinical observations indicating that parenchymal fibrosis of the stenotic kidney is rare in patients with fibromuscular dysplasia, but without hyperlipidemia [19].

Mechanisms of Renal Disease in Patients with RVH

Clinical and experimental studies have begun to provide mechanistic insights into the development of progressive renal fibrosis and inflammation in renal artery stenosis (Fig. 10.4). In hemodynamically significant renal artery stenosis, reduced renal perfusion stimulates renin secretion through the renal baroreceptor system, leading to increased plasma levels of angiotensin II. Activation of the renin-angiotensin system serves to preserve perfusion to the stenotic kidney, but at the cost of provoking systemic hypertension. Activation of angiotensin II within the stenotic kidney triggers a number of signaling pathways leading to the production of reactive oxygen species (ROS), activation of TGF-β, activation of the MAPK signaling pathways, and activation of the NF-κB signaling pathway, leading to chemokine generation [14]. The progressive renal dysfunction observed in the stenotic kidney does not appear to be simply a function of hypoperfusion and ischemia, as <10 % of normal renal blood flow is required to meet the metabolic needs of renal tissue [19]. Furthermore, the kidney is able to adapt to significant renal artery stenosis with preservation of renal oxygenation [20]. The importance of ROS in the progression of renal damage is underscored by studies in which experimental animals with unilateral renal artery stenosis were treated with Tempol, a superoxide antagonist. This intervention reduced blood pressure and prevented activation of a number of inflammatory and fibrogenic pathways including NF-κB, TGF-β, and matrix metalloproteinases [21].

The Renin-Angiotensin System and RVH

The kidney contains all elements of the renin-angiotensin system [22–24]. Renin is produced by the juxtaglomerular cells in response to low

perfusion pressure in the afferent renal artery, sympathetic nervous system activity, or in response to low sodium delivery to the macula densa of the distal convoluted tubule. Renin promotes the proteolytic conversion of angiotensinogen, made primarily in the liver, to angiotensin I. Angiotensin-converting enzyme, synthesized in the lung as well as the kidney and other tissues, converts angiotensin I to angiotensin II. Renal content of angiotensin II is higher than systemic levels, at least in part through local production. In the kidney, angiotensin II can be produced through an angiotensin-converting enzyme-independent pathway, which may reflect the proteolytic activity of other enzymes such as chymase [25]. Humans possess two receptors for angiotensin II: the type 1 (AT-1) and type 2 (AT-2) receptors. Stimulation of the AT-1 receptor promotes constriction of the efferent renal arteriole, leading to a decrease in renal plasma flow with subsequent increase in the glomerular filtration fraction. This action causes generalized increase in systolic blood pressure. The pro-inflammatory and pro-fibrogenic effects of angiotensin II are well documented. Angiotensin II promotes fibrosis through a number of mechanisms, including direct stimulation of TGF-β production, induction of TGF-β type 2 receptor expression, and direct stimulation of collagen production, with inhibition of collagenase production [26]. Angiotensin II increases TGF-β activity at least in part through upregulation of thrombospondin [27], a molecule which is a potent activator of latent TGF-β. Angiotensin II may promote fibrosis through TGF-β1-independent pathways including induction of endothelin-1 or connective tissue growth factor [28]. Angiotensin II is a potent stimulus for NF-κB activation, leading to the influx and activation of inflammatory cells. In patients with progressive chronic renal disease due to diabetes or other etiologies not related to RVH, there is compelling evidence that blockade of the renin-angiotensin system preserves renal function. Effects of angiotensin II blockade, through either angiotensin-converting enzyme inhibition or angiotensin receptor blockade, have been shown to reduce TGF-β expression, leading to subsequent reduction in fibrosis and inflammation. In experimental renal artery stenosis, there is evidence that angiotensin-converting enzyme inhibitors may exacerbate renal damage in the stenotic kidney, through reduction of renal perfusion pressure [5]. This reduction in renal perfusion pressure may actually exacerbate renal inflammation, as shown by recent evidence indicating that administration of a vasopeptidase inhibitor which inhibits angiotensin-converting enzyme and neutral endopeptidase induces a Th1 immune response in the stenotic kidney of rats subjected to 2K1C hypertension [29]. Furthermore, increased renal inflammation is noted in mice with knockout of the angiotensin type 1 receptors [30].

TGF-β and RVH

TGF-β plays a central role in a variety of pathways related to cell cycle regulation leading to hypertrophy, hyperplasia, apoptosis, MAPK activation, extracellular matrix synthesis and deposition, and inflammation [31, 32]. Angiotensin II is a potent stimulus for the production of TGF-β [5]. In recent years, signal transduction pathways responsible for the wide-ranging effects of TGF-β have been identified. Unlike most growth factors, which signal through transmembrane receptor tyrosine kinases, TGF-β signals through a set of transmembrane receptor serine/threonine kinases. The active receptor complex is formed by binding of ligand to the TGF-β type 2 receptor, recruitment and activation of the type 1 receptor, followed by intracellular phosphorylation of target proteins. Downstream mediators of TGF-β signaling include the Smad family of proteins. Smad2 and 3 are directly phosphorylated by the type 1 receptor kinase. Following phosphorylation, Smad2 and 3 associate with Smad4 and translocate to the nucleus, where the complex acts as a transcriptional regulator of target genes. TGF-β plays an important role in the chronic inflammation that accompanies extracellular matrix deposition during fibrosis. TGF-β is capable of promoting all steps necessary for transition of renal tubular epithelial cells to myofibroblasts,

a cellular source for extracellular matrix deposition in chronic renal disease. A critical role of TGF-β in regulation of proliferation and collagen IV production has been demonstrated in studies employing renal tubular epithelial cells derived from animals bearing a homozygous deletion of the TGF-β1 gene [33]. TGF-β1 knockout cells grow at a faster rate than wild-type cells matched for passage number and plating density. This increased growth rate is associated with lower expression of cell cycle inhibitors p21 and p27 in the knockout cells. Basal expression of α1(IV) and α2(IV) collagen mRNA and protein are significantly lower in the TGF-β1 knockout cells than in wild-type cells. However, the knockout cells respond to exogenous administration of TGF-β1 with increases in transcriptional activity and protein production [33]. In vivo studies employing TGF-β1 knockout animals are not practical, as these animals have an extremely high rate of embryonic lethality, with the few surviving mice developing a systemic inflammatory syndrome leading to death within 2–4 weeks of age. For this reason, investigators have employed mice with homozygous deletion of Smad proteins to study the role of TGF-β signaling in experimental models. Although Smad2 knockout mice are embryonic lethal, Smad3 knockout mice are viable. Smad3 knockout mice show accelerated healing of wounds, in association with decreased local inflammation. Recent studies have demonstrated that the stenotic kidney of 2K1C Smad3 knockout mice is remarkably resistant to the development of interstitial fibrosis, tubular atrophy, or interstitial inflammation, despite activation of the renin-angiotensin system and the development of systemic hypertension [34]. Smad3 knockout mice are also resistant to the deleterious effects of ischemia-reperfusion injury [35]. Similar protective effects have been observed in Smad3 knockout animals subjected to unilateral ureteric obstruction [36]. Smad3 is essential for the development of angiotensin-induced vascular fibrosis [37]. Angiotensin II, a potent stimulus for TGF-β1 production and activation [28], can induce Smad signaling through both TGF-β-dependent and TGF-β-independent pathways [38]. Smad3 deficiency does not protect against all forms of chronic tissue injury, a fact that may limit the efficacy of Smad3 as a therapeutic target to prevent tissue fibrosis and inflammation. For example, Smad3 knockout mice develop enhanced neointimal hyperplasia in response to vascular injury, albeit with less matrix deposition [39].

MAPK Pathways and RVD

The MAPK pathways are key intermediates in a number of critical signaling pathways that regulate hypertrophy, hyperplasia, atrophy/apoptosis, inflammation, and fibrosis. For example, The ERK, p38, and JNK pathways are all necessary for mitogenesis of cultured renal cells [40]. There is extensive crosstalk between MAPK and TGF-β signaling pathways in the development of interstitial fibrosis and inflammation. Angiotensin II rapidly activates the Smad signaling pathway in vascular smooth muscle cells through an ERK1/2-dependent but TGF-β1-independent pathway, although TGF-β is able to activate Smad3 at later time points [37]. ERK & p38 are essential signaling intermediates for TGF-β-stimulated collagen IV mRNA expression [41]. Inhibitors of ERK or p38 block TGF-β1-stimulated MCP1 production, thereby providing a mechanistic link between MAPK activation and inflammation [41]. In vitro studies have demonstrated that ERK is involved in epithelial to mesenchymal transformation [42–44].

In human diabetic nephropathy, p-ERK and p38 expression localize to regions of tubulointerstitial fibrosis and inflammation [45–48]. Both p38 and JNK are activated in experimental anti-glomerular basement membrane antibody-mediated glomerulonephritis [49]. In Dahl salt-sensitive rats, the development of hypertension is associated with persistent activation of ERK [50]. In a rat model of type 2 diabetes, hypertension accelerates the development of renal disease at least in part through induction of ERK and p38, as well as TGF-β [51]. Different MAPK pathways are activated in angiotensin II-dependent (p38 MAPK) versus angiotensin II-independent hypertension (ERK and JNK) [52]. Given that MAPK

pathways regulate proliferation, fibrosis, and inflammation, there has been interest in determining whether low molecular weight inhibitors of MAPK pathways may be used to prevent progression of chronic renal disease [53, 54]. The ERK inhibitor U0126 reduces acute renal injury in an experimental mesangial proliferative glomerulonephritis model [55]. The p38 inhibitor FR167653 prevents renal dysfunction and glomerulosclerosis in chronic Adriamycin nephropathy [56] and in experimental crescenteric glomerulonephritis [57]. The role of low molecular weight MAPK inhibitors in experimental or human RVH has not been adequately defined.

The Role of Inflammation in RVH

As in many other forms of experimental and human renal disease, the development of chronic renal damage in RVH is associated with pro-inflammatory chemokine generation and the influx of inflammatory cells, including T cells and macrophages. In patients with early atherosclerotic renal artery stenosis, increased numbers of CD4+ T cells, CD83+ dendritic cells, and CD86+ antigen-presenting cells were identified in peripheral blood and in the renal artery, compared to patients without atherosclerotic renal artery disease [58]. In a murine 2K1C model of RVH, increased expression of pro-inflammatory chemokines appears to precede the influx of circulating inflammatory cells, indicating that parenchymal cells of the kidney are capable of contributing to this pro-inflammatory signature. Angiotensin II is capable of directly and indirectly promoting renal inflammation; the MAPK pathways and TGF-β1 have been established as essential intermediates in this process. Influx of macrophages temporally coincides with onset of fibrogenesis, underscoring the close link between fibrogenic and pro-inflammatory signaling pathways [59].

There is accumulating evidence that inflammation may be a cause as well as a consequence of hypertension [6, 60]. In Dahl salt-sensitive rats, the development of hypertension is associated with the influx of T cells and macrophages. Treatment of these hypertensive animals with anti-inflammatory agents reduces blood pressure and renal damage [50]. Angiotensin II promotes vascular inflammation through an NAD(P)H oxidase-dependent pathway [61]. ROS, produced through angiotensin II-dependent or -independent pathways, activate a number of proinflammatory transcription factors such as NFκ-B, NRF2, and AP1 [62]. Oxidized lipoproteins activate proinflammatory pathways through interaction with toll-like receptors (TLRs), TLR4 in particular [63]. Treatment of pigs with RVH with the antioxidant Tempol reduces inflammation and subsequent renal damage [64–66]. In addition to stimulation of ROS generation, angiotensin II stimulates the production of a wide variety of chemokines and their receptors, including CCR5, CCL5 (RANTES), and TNF-α [67]. Treatment of angiotensin II-infused mice with the TNF-α antagonist etanercept prevents the development of hypertension and reduces angiotensin II-stimulated vascular superoxide production [68], further underscoring the link between chemokine/cytokine production, inflammation, and hypertension.

Macrophages have been shown to be a major cell type infiltrating the kidney during the development and progression of chronic kidney disease. Macrophages are capable of mediating a large number of pathways related to inflammation, fibrosis, wound healing, and repair. Depletion of macrophages with liposome clodronate reduces renal fibrosis in obstructive uropathy, experimental cyclosporine toxicity, acute allograft rejection, and in the early phase of acute kidney injury [69–71].

Of the many chemokines produced following tissue injury, recent studies have focused on a critical role of CCL2 (MCP-1) in promoting the influx and activation of macrophages, leading to ongoing inflammation and fibrosis. Experimental studies have shown that CCL2 is expressed in salt-sensitive hypertension and the 2K1C model of RVH [14, 50]. Angiotensin II stimulates CCL2 production through an NF-κB-dependent pathway [72]. In vitro studies have demonstrated that both the MAPK pathways and TGF-β are signaling intermediates leading to CCL2 production [41]. In vivo studies employing Bindarit,

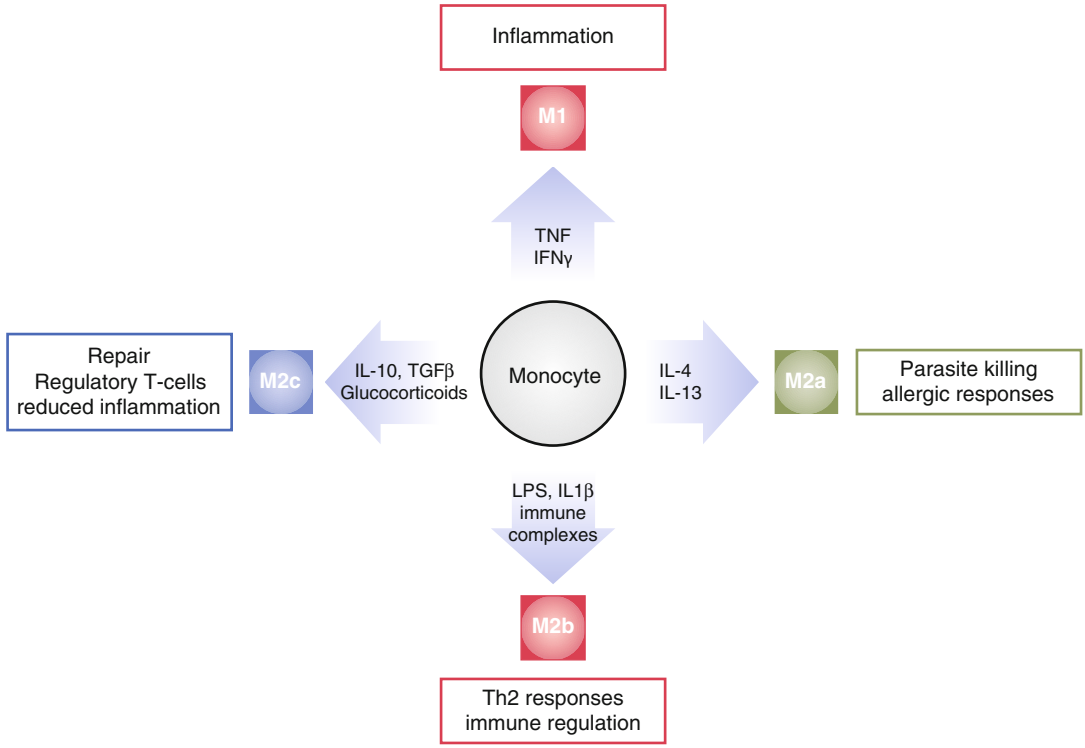


Fig. 10.5 Following renal injury, circulating monocytes infiltrate the kidney and are capable of differentiating along several pathways to produce macrophages with distinct functions

a selective inhibitor of CCL2 signaling, reduces inflammation and collagen deposition [73]. Bindarit is also effective in reducing neointimal hyperplasia after stent-induced injury [74].

Recent studies have demonstrated that infiltrating macrophages are capable of polarizing to carry out distinct functions (Fig. 10.5) [75]. The pro-inflammatory M1 macrophage produces a variety of mediators such as reactive oxygen and nitrogen species proteolytic enzymes, and pro-inflammatory chemokines may thereby promote tissue injury [71]. Macrophages that inhibit inflammation and promote wound healing and tissue repair have been called alternatively-activated macrophages, or M2 macrophages [76, 77]. Macrophages exposed to IL-4 or IL-13 polarize towards an M2a phenotype, which is associated with allergic reactions and killing of parasites. Macrophages exposed to immune complexes and IL-1β or LPS differentiate towards an M2b phenotype, which is associated with Th2 lymphocyte activation and immune regulation [76]. Macrophages exposed to IL-10 or TGF-β polarize towards an M2c phenotype, which is associated with matrix deposition and tissue remodeling. M2c macrophages have been shown to have a greater protective effect in some models than M2a macrophages in reducing tubular atrophy, interstitial expansion, and proteinuria. This may be in part due to induction of Cd4-positive Cd25-negative T cells into Fox3+-expressing T cells. Both M2a and M2c macrophages suppress CD8-positive T cell-mediated toxicity to tubular epithelial cells. In the murine 2K1C model of RVH, both M1 and M2 macrophages are identified in the stenotic kidney (Fig. 10.6a, b).

In an anti-glomerular basement membrane glomerulonephritis model, the onset of renal damage was associated with M1 polarization of macrophages. Treatment with the angiotensin II receptor antagonist olmesartan led to polarization of M1 to M2 macrophages and reduced renal injury [78]. In mice fed a high-fat diet, renal damage was associated with M1 polarization of macrophages;

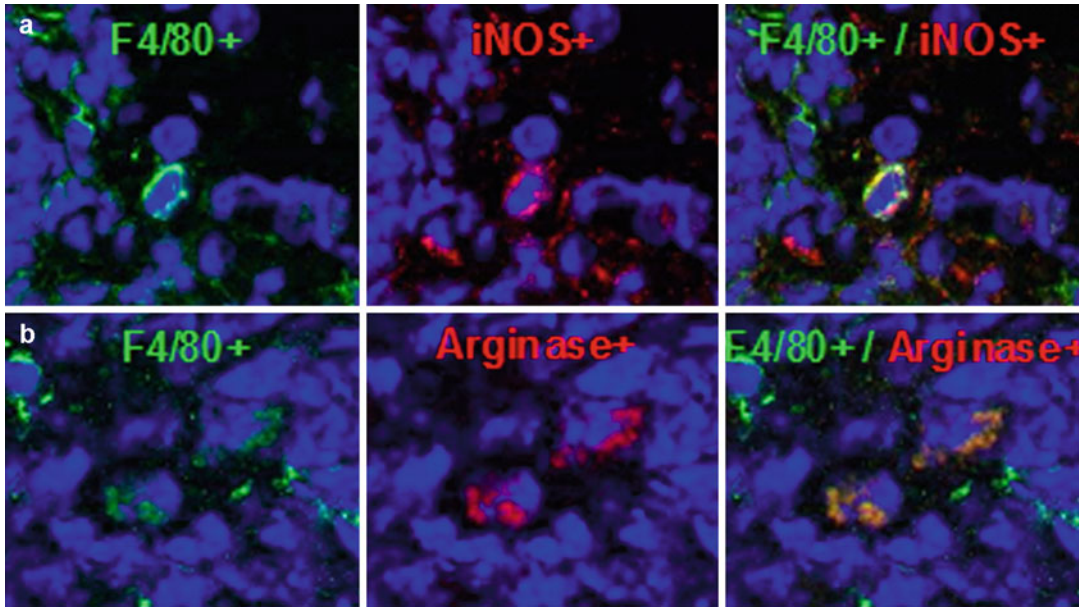


Fig. 10.6 (**a**) Fluorescent co-localization of the pan-macrophage marker F4/80 (*green*) and the M1 macrophage marker iNOS (*red*) in kidney 6 weeks after placement of a cuff to induce RVH. (**b**) Fluorescent co-localization of the pan-macrophage marker F4/80 (*green*) and the M2 macrophage marker arginase (*red*) in renal tissue obtained from mouse 6 weeks following cuff placement to induce RVH

treatment with an angiotensin I receptor blocker decreased macrophage infiltration and upregulated M2 macrophage markers [79].

The complexity of macrophage polarization in the development and progression of chronic renal injury is underscored by experimental studies in which the timing of macrophage depletion determines whether injury is reduced or exacerbated. For example, in unilateral ureteric obstruction, depletion of macrophages with cyclophosphamide soon after onset of injury has little effect on interstitial fibrosis, whereas depletion of macrophages during the repair phase promotes persistent scarring. Adoptive transfer of macrophages at this late phase reduces renal fibrosis [80].

Ex vivo administration of M1 or M2 macrophages in mice subjected to Adriamycin nephropathy maintain a stable phenotype for up to 4 weeks. In keeping with their polarized phenotype, mice infused with M1 macrophages showed exacerbated injury whereas mice infused with M2 macrophages showed decreased injury, chemokine generation, and inflammation [81]. Although M2 macrophages produce TGF-β, which has potent pro-fibrogenic properties, M2 macrophages transferred into mice with Adriamycin nephropathy showed decreased TGF-β production with time, with maintenance of an anti-inflammatory phenotype [82].

Based on these considerations, therapeutic interventions directed towards polarization of macrophages towards an M2 phenotype may provide a novel therapeutic target to promote resolution of inflammation and prevent progressive fibrosis in patients with RVH.

Summary and Conclusions

Management of patients with atherosclerotic RVD is not clear. Surgical attempts to promote revascularization improve kidney injury in only a subset of patients [83]. Recent human and experimental studies have defined a complex interplay between mitogenic, fibrogenic, and inflammatory pathways in the development and progression of chronic renal damage in patients with atherosclerotic RVH. Recent studies have shown

that interventions to target inflammation may preserve renal function in patients with atherosclerotic renal artery stenosis. Additional studies are needed to determine whether interventions directed towards polarization of macrophages towards an M2, "reparative" phenotype may preserve renal function.

References

1. Textor SC, Wilcox CS. Renal artery stenosis: a common, treatable cause of renal failure? Annu Rev Med. 2001;52:421–42.
2. Garovic VD, Textor SC. Renovascular hypertension and ischemic nephropathy. Circulation. 2005;112(9): 1362–74.
3. Iglesias JI, Hamburger RJ, Feldman L, Kaufman JS. The natural history of incidental renal artery stenosis in patients with aortoiliac vascular disease. Am J Med. 2000;109(8):642–7.
4. Valabhji J, Robinson S, Poulter C, Robinson AC, Kong C, Henzen C, Gedroyc WM, Feher MD, Elkeles RS. Prevalence of renal artery stenosis in subjects with type 2 diabetes and coexistent hypertension. Diabetes Care. 2000;23(4):539–43.
5. Textor SC. Managing renal arterial disease and hypertension. Curr Opin Cardiol. 2003;18(4):260–7.
6. Harrison DG, Guzik TJ, Lob HE, Madhur MS, Marvar PJ, Thabet SR, Vinh A, Weyand CM. Inflammation, immunity, and hypertension. Hypertension. 2011; 57(2):132–40.
7. Stouffer GA, Pathak A, Rojas M. Unilateral renal artery stenosis causes a chronic vascular inflammatory response in ApoE mice. Trans Am Clin Climatol Assoc. 2010;121(252–64):64–6.
8. Oliver E, McGillicuddy F, Phillips C, Toomey S, Roche HM. The role of inflammation and macrophage accumulation in the development of obesity-induced type 2 diabetes mellitus and the possible therapeutic effects of long-chain n-3 PUFA. Proc Nutr Soc. 2010;69(2):232–43.
9. Li J-J, Fang C-H, Jiang H, Huang C-X, Hui R-T, Chen M-Z. Time course of inflammatory response after renal artery stenting in patients with atherosclerotic renal stenosis. Clin Chim Acta. 2004;350(1–2):115–21.
10. Brountzos EN, Tavernaraki K, Gouliamos AD, Degiannis D, Chaidaroglou A, Panagiotou I, Arsenis G, Kelekis D, Vlahakos D. Systemic inflammatory response to renal artery percutaneous angioplasty with stent placement and the risk for restenosis: a pilot study. J Vasc Interv Radiol. 2009;20(2):186–91.
11. Schlager O, Amighi J, Haumer M, Sabeti S, Dick P, Mlekusch W, Loewe C, Koppensteiner R, Minar E, Schillinger M. Inflammation and adverse cardiovascular outcome in patients with renal artery stenosis and peripheral artery disease. Atherosclerosis. 2009;205(1):314–8.
12. Keddis MT, Garovic VD, Bailey KR, Wood CM, Raissian Y, Grande JP. Ischaemic nephropathy secondary to atherosclerotic renal artery stenosis: clinical and histopathological correlates. Nephrol Dial Transplant. 2010;25(11):3615–22.
13. Xie Q-y, Ming S, Yang T-l, Sun Z-L. Losartan reduces monocyte chemoattractant protein-1 expression in aortic tissues of 2K1C hypertensive rats. Int J Cardiol. 2006;110(1):60–6.
14. Cheng J, Zhou W, Warner GM, Knudsen BE, Garovic VD, Gray CE, Lerman LO, Platt JL, Romero JC, Textor SC, Nath KA, Grande JP. Temporal analysis of signaling pathways activated in a murine model of two-kidney, one-clip hypertension. Am J Physiol Renal Physiol. 2009;297(4):F1055–68.
15. Urbieta-Caceres VH, Lavi R, Zhu X-Y, Crane JA, Textor SC, Lerman A, Lerman LO. Early atherosclerosis aggravates the effect of renal artery stenosis on the swine kidney. Am J Physiol Renal Physiol. 2010;299(1):F135–40.
16. Chade AR, Rodriguez-Porcel M, Grande JP, Krier JD, Lerman A, Romero JC, Napoli C, Lerman LO. Distinct renal injury in early atherosclerosis and renovascular disease. Circulation. 2002;106(9):1165–71.
17. Heo HJ, Yun MR, Jung KH, Lee JY, Park JY, Lee SJ, Bae SS, Lee WS, Kim CD. Endogenous angiotensin II enhances atherogenesis in apoprotein E-deficient mice with renovascular hypertension through activation of vascular smooth muscle cells. Life Sci. 2007; 80(11):1057–63.
18. Chade AR, Rodriguez-Porcel M, Grande JP, Zhu X, Sica V, Napoli C, Sawamura T, Textor SC, Lerman A, Lerman LO. Mechanisms of renal structural alterations in combined hypercholesterolemia and renal artery stenosis. Arterioscler Thromb Vasc Biol. 2003;23(7):1295–301.
19. Lerman L, Textor SC. Pathophysiology of ischemic nephropathy. Urol Clin North Am. 2001;28(4):793–803, ix.
20. Gloviczki M, Lerman L, Textor S. Blood oxygen level-dependent (BOLD) MRI in renovascular hypertension. Curr Hypertens Rep. 2011;13(5):370–7.
21. Zhu XY, Chade AR, Rodriguez-Porcel M, Bentley MD, Ritman EL, Lerman A, Lerman LO. Cortical microvascular remodeling in the stenotic kidney: role of increased oxidative stress. Arterioscler Thromb Vasc Biol. 2004;24(10):1854–9.
22. Raizada V, Skipper B, Luo W, Griffith J. Intracardiac and intrarenal renin-angiotensin systems: mechanisms of cardiovascular and renal effects. J Investig Med. 2007;55(7):341–59.
23. Kobori H, Nangaku M, Navar LG, Nishiyama A. The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. Pharmacol Rev. 2007;59(3):251–87.
24. Lavoie JL, Sigmund CD. Minireview: overview of the renin-angiotensin system–an endocrine and paracrine system. Endocrinology. 2003;144(6):2179–83.
25. Morikawa T, Imanishi M, Suzuki H, Okada N, Okumura M, Konishi Y, Yoshioka K, Takai S,

Miyazaki M. Mast cell chymase in the ischemic kidney of severe unilateral renovascular hypertension. Am J Kidney Dis. 2005;45(3):e45–50.
26. Wolf G. Renal injury due to renin-angiotensin-aldosterone system activation of the transforming growth factor-beta pathway. Kidney Int. 2006;70(11):1914–9.
27. Zhou Y, Poczatek MH, Berecek KH, Murphy-Ullrich JE. Thrombospondin 1 mediates angiotensin II induction of TGF-beta activation by cardiac and renal cells under both high and low glucose conditions. Biochem Biophys Res Commun. 2006;339(2):633–41.
28. Leask A. TGFβ, cardiac fibroblasts, and the fibrotic response. Cardiovasc Res. 2007;74(2):207–12.
29. Steinmetz OM, Sadaghiani S, Panzer U, Krebs C, Meyer-Schwesinger C, Streichert T, Fehr S, Hamming I, van Goor H, Stahl RAK, Wenzel U. Antihypertensive therapy induces compartment-specific chemokine expression and a Th1 immune response in the clipped kidney of Goldblatt hypertensive rats. Am J Physiol Renal Physiol. 2007;292(2):F876–87.
30. Ouyang X, Le TH, Roncal C, Gersch C, Herrera-Acosta J, Rodriguez-Iturbe B, Coffman TM, Johnson RJ, Mu W. Th1 inflammatory response with altered expression of profibrotic and vasoactive mediators in AT1A and AT1B double-knockout mice. Am J Physiol Renal Physiol. 2005;289(4):F902–10.
31. Cheng J, Grande JP. Transforming growth factor-beta signal transduction and progressive renal disease. Exp Biol Med. 2002;227:943–56.
32. Cheng J, Grande J. Transforming growth factor-beta and kidney dysfunction. J Organ Dysfunct. 2009;5(3): 182–92.
33. Grande JP, Warner GM, Walker HJ, Yusufi AN, Cheng J, Gray CE, Kopp JB, Nath KA. TGF-beta1 is an autocrine mediator of renal tubular epithelial cell growth and collagen IV production. Exp Biol Med. 2002;227(3):171–81.
34. Warner GM, Cheng J, Knudsen BE, Gray CE, Deibel A, Juskewitch JE, Lerman LO, Textor SC, Nath KA, Grande JP. Genetic deficiency of Smad3 protects the kidneys from atrophy and interstitial fibrosis in 2K1C hypertension. Am J Physiol Renal Physiol. 2012;302(11):F1455–64.
35. Nath KA, Croatt AJ, Warner GM, Grande JP. Genetic deficiency of Smad3 protects against murine ischemic acute kidney injury. Am J Physiol Renal Physiol. 2011;301:F436–42.
36. Sato M, Muragaki Y, Saika S, Roberts AB, Ooshima A. Targeted disruption of TGF-beta1/Smad3 signaling protects against renal tubulointerstitial fibrosis induced by unilateral ureteral obstruction. J Clin Invest. 2003;112(10):1486–94.
37. Wang W, Huang XR, Canlas E, Oka K, Truong LD, Deng C, Bhowmick NA, Ju W, Bottinger EP, Lan HY. Essential role of Smad3 in angiotensin II-induced vascular fibrosis. Circ Res. 2006;98(8):1032–9.
38. Ruiz-Ortega M, Rodríguez-Vita J, Sanchez-Lopez E, Carvajal G, Egido J. TGF-β signaling in vascular fibrosis. Cardiovasc Res. 2007;74(2):196–206.
39. Kobayashi K, Yokote K, Fujimoto M, Yamashita K, Sakamoto A, Kitahara M, Kawamura H, Maezawa Y, Asaumi S, Tokuhisa T, Mori S, Saito Y. Targeted disruption of TGF-beta-Smad3 signaling leads to enhanced neointimal hyperplasia with diminished matrix deposition in response to vascular injury. Circ Res. 2005;96(8):904–12.
40. Cheng J, Thompson MA, Walker HJ, Gray CE, Diaz Encarnacion MM, Warner GM, Grande JP. Differential regulation of mesangial cell mitogenesis by cAMP phosphodiesterase isozymes 3 and 4. Am J Physiol Renal Physiol. 2004;287(5):F940–53.
41. Cheng J, Diaz Encarnacion MM, Warner GM, Gray CE, Nath KA, Grande JP. TGF-beta1 stimulates monocyte chemoattractant protein-1 expression in mesangial cells through a phosphodiesterase isoenzyme 4-dependent process. Am J Physiol Cell Physiol. 2005;289(4):C959–70.
42. Xie L, Law BK, Chytil AM, Brown KA, Aakre ME, Moses HL. Activation of the Erk pathway is required for TGF-beta1-induced EMT in vitro. Neoplasia. 2004;6(5):603–10.
43. Yang M, Huang H, Li J, Li D, Wang H. Tyrosine phosphorylation of the LDL receptor-related protein (LRP) and activation of the ERK pathway are required for connective tissue growth factor to potentiate myofibroblast differentiation. FASEB J. 2004;18(15): 1920–1.
44. Li JH, Wang W, Huang XR, Oldfield M, Schmidt AM, Cooper ME, Lan HY. Advanced glycation end products induce tubular epithelial-myofibroblast transition through the RAGE-ERK1/2 MAP kinase signaling pathway. Am J Pathol. 2004;164(4):1389–97.
45. Adhikary L, Chow F, Nikolic-Paterson DJ, Stambe C, Dowling J, Atkins RC, Tesch GH. Abnormal p38 mitogen-activated protein kinase signalling in human and experimental diabetic nephropathy. Diabetologia. 2004;47(7):1210–22.
46. Toyoda M, Suzuki D, Honma M, Uehara G, Sakai T, Umezono T, Sakai H. High expression of PKC-MAPK pathway mRNAs correlates with glomerular lesions in human diabetic nephropathy. Kidney Int. 2004;66(3):1107–14.
47. Sakai N, Wada T, Furuichi K, Iwata Y, Yoshimoto K, Kitagawa K, Kokubo S, Kobayashi M, Hara A, Yamahana J, Okumura T, Takasawa K, Takeda S, Yoshimura M, Kida H, Yokoyama H. Involvement of extracellular signal-regulated kinase and p38 in human diabetic nephropathy. Am J Kidney Dis. 2005;45(1):54–65.
48. Masaki T, Stambe C, Hill PA, Dowling J, Atkins RC, Nikolic-Paterson DJ. Activation of the extracellular-signal regulated protein kinase pathway in human glomerulopathies. J Am Soc Nephrol. 2004;15(7): 1835–43.
49. Stambe C, Atkins RC, Hill PA, Nikolic-Paterson DJ. Activation and cellular localization of the p38 and JNK MAPK pathways in rat crescentic glomerulonephritis. Kidney Int. 2003;64(6):2121–32.

50. Diaz Encarnacion MM, Warner GM, Gray CE, Cheng J, Keryakos HK, Nath KA, Grande JP. Signaling pathways modulated by fish oil in salt-sensitive hypertension. Am J Physiol Renal Physiol. 2008;294(6):F1323–35.
51. Imai G, Satoh T, Kumai T, Murao M, Tsuchida H, Shima Y, Ogimoto G, Fujino T, Kobayashi S, Kimura K. Hypertension accelerates diabetic nephropathy in Wistar fatty rats, a model of type 2 diabetes mellitus, via mitogen-activated protein kinase cascades and transforming growth factor-beta1. Hypertens Res. 2003;26(4):339–47.
52. Pellieux C, Sauthier T, Aubert JF, Brunner HR, Pedrazzini T. Angiotensin II-induced cardiac hypertrophy is associated with different mitogen-activated protein kinase activation in normotensive and hypertensive mice. J Hypertens. 2000;18(9):1307–17.
53. Jo SK, Cho WY, Sung SA, Kim HK, Won NH. MEK inhibitor, U0126, attenuates cisplatin-induced renal injury by decreasing inflammation and apoptosis. Kidney Int. 2005;67(2):458–66.
54. Bokemeyer D, Panek D, Kitahara M, Trzaskos JM, Muller CE, Hockemeyer J, Kunter U, Boor P, Floege J, Kramer HJ, Ostendorf T. The map kinase ERK regulates renal activity of cyclin dependent kinase 2 in experimental glomerulonephritis. Nephrol Dial Transplant. 2007;18(11):2232–9.
55. Bokemeyer D, Panek D, Kramer HJ, Lindemann M, Kitahara M, Boor P, Kerjaschki D, Trzaskos JM, Floege J, Ostendorf T. In vivo identification of the mitogen-activated protein kinase cascade as a central pathogenic pathway in experimental mesangioproliferative glomerulonephritis. J Am Soc Nephrol. 2002;13(6):1473–80.
56. Koshikawa M, Mukoyama M, Mori K, Suganami T, Sawai K, Yoshioka T, Nagae T, Yokoi H, Kawachi H, Shimizu F, Sugawara A, Nakao K. Role of p38 mitogen-activated protein kinase activation in podocyte injury and proteinuria in experimental nephrotic syndrome. J Am Soc Nephrol. 2005;16(9): 2690–701.
57. Wada T, Furuichi K, Sakai N, Hisada Y, Kobayashi K, Mukaida N, Tomosugi N, Matsushima K, Yokoyama H. Involvement of p38 mitogen-activated protein kinase followed by chemokine expression in crescentic glomerulonephritis. Am J Kidney Dis. 2001;38(6): 1169–77.
58. Kotliar C, Juncos L, Inserra F, de Cavanagh EM, Chuluyan E, Aquino JB, Hita A, Navari C, Sanchez R. Local and systemic cellular immunity in early renal artery atherosclerosis. Clin J Am Soc Nephrol. 2012;7(2):224–30.
59. Wang Y, Harris DC. Macrophages in renal disease. J Am Soc Nephrol. 2011;22(1):21–7.
60. Pauletto P, Rattazzi M. Inflammation and hypertension: the search for a link. Nephrol Dial Transplant. 2006;21(4):850–3.
61. Liu J, Yang F, Yang X-P, Jankowski M, Pagano PJ. NAD(P)H oxidase mediates angiotensin II-induced vascular macrophage infiltration and medial hypertrophy. Arterioscler Thromb Vasc Biol. 2003;23(5):776–82.
62. Luft FC. Workshop: mechanisms and cardiovascular damage in hypertension. Hypertension. 2001;37(2 Part 2):594–8.
63. Bjorkbacka H. Multiple roles of Toll-like receptor signaling in atherosclerosis. Curr Opin Lipidol. 2006; 17(5):527–33.
64. Chade AR, Rodriguez-Porcel M, Herrmann J, Krier JD, Zhu X, Lerman A, Lerman LO. Beneficial effects of antioxidant vitamins on the stenotic kidney. Hypertension. 2003;42:605–12.
65. Chade AR, Rodriguez-Porcel M, Herrmann J, Zhu X, Grande JP, Napoli C, Lerman A, Lerman LO. Antioxidant intervention blunts renal injury in experimental renovascular disease. J Am Soc Nephrol. 2004;15(4):958–66.
66. Chade AR, Krier JD, Rodriguez-Porcel M, Breen JF, McKusick MA, Lerman A, Lerman LO. Comparison of acute and chronic antioxidant interventions in experimental renovascular disease. Am J Physiol Renal Physiol. 2004;286(6):F1079–86.
67. Garcia GE. ANG II receptor antagonists as modulators of macrophages polarization. Am J Physiol Renal Physiol. 2010;298(4):F868–9.
68. Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, Goronzy J, Weyand C, Harrison DG. Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. J Exp Med. 2007;204(10):2449–60.
69. Carlos CP, Mendes GE, Miquelin AR, Luz MA, da Silva CG, van Rooijen N, Coimbra TM, Burdmann EA. Macrophage depletion attenuates chronic cyclosporine A nephrotoxicity. Transplantation. 2010;89(11):1362–70.
70. Prabhakar NR. Sensory plasticity of the carotid body: role of reactive oxygen species and physiological significance. Respir Physiol Neurobiol. 2011;178(3): 375–80.
71. Kitamoto K, Machida Y, Uchida J, Izumi Y, Shiota M, Nakao T, Iwao H, Yukimura T, Nakatani T, Miura K. Effects of liposome clodronate on renal leukocyte populations and renal fibrosis in murine obstructive nephropathy. J Pharmacol Sci. 2009;111(3):285–92.
72. Tsuchiya K, Yoshimoto T, Hirono Y, Tateno T, Sugiyama T, Hirata Y. Angiotensin II induces monocyte chemoattractant protein-1 expression via a nuclear factor-kappaB-dependent pathway in rat preadipocytes. Am J Physiol Endocrinol Metabol. 2006;291(4):E771–8.
73. Zhu XY, Chade AR, Krier JD, Daghini E, Lavi R, Guglielmotti A, Lerman A, Lerman LO. The chemokine monocyte chemoattractant protein-1 contributes to renal dysfunction in swine renovascular hypertension. J Hypertens. 2009;27(10):2063–73.
74. Ialenti A, Grassia G, Gordon P, Maddaluno M, Di Lauro MV, Baker AH, Guglielmotti A, Colombo A, Biondi G, Kennedy S, Maffia P. Inhibition of in-stent stenosis by oral administration of bindarit in porcine

coronary arteries. Arterioscler Thromb Vasc Biol. 2011;31(11):2448–54.
75. Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. J Clin Invest. 2012; 122(3):787–95.
76. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol. 2004;25(12):677–86.
77. Ricardo SD, van Goor H, Eddy AA. Macrophage diversity in renal injury and repair. J Clin Invest. 2008;118(11):3522–30.
78. Aki K, Shimizu A, Masuda Y, Kuwahara N, Arai T, Ishikawa A, Fujita E, Mii A, Natori Y, Fukunaga Y, Fukuda Y. ANG II receptor blockade enhances anti-inflammatory macrophages in anti-glomerular basement membrane glomerulonephritis. Am J Physiol Renal Physiol. 2010;298(4):F870–82.
79. Ma L-J, Corsa BA, Zhou J, Yang H, Li H, Tang Y-W, Babaev VR, Major AS, Linton MF, Fazio S, Hunley TE, Kon V, Fogo AB. Angiotensin type 1 receptor modulates macrophage polarization and renal injury in obesity. Am J Physiol Renal Physiol. 2011;300(5): F1203–13.
80. Nishida M, Okumura Y, Fujimoto S, Shiraishi I, Itoi T, Hamaoka K. Adoptive transfer of macrophages ameliorates renal fibrosis in mice. Biochem Biophys Res Commun. 2005;332(1):11–6.
81. Wang Y, Wang YP, Zheng G, Lee VW, Ouyang L, Chang DH, Mahajan D, Coombs J, Wang YM, Alexander SI, Harris DC. Ex vivo programmed macrophages ameliorate experimental chronic inflammatory renal disease. Kidney Int. 2007;72(3):290–9.
82. Cao Q, Wang Y, Zheng D, Sun Y, Wang Y, Lee VWS, Zheng G, Tan TK, Ince J, Alexander SI, Harris DCH. IL-10/TGF-β–modified macrophages induce regulatory T cells and protect against adriamycin nephrosis. J Am Soc Nephrol. 2010;21(6):933–42; 1 June 2010;10(10):2208–14.
83. Textor SC, Lerman L. Renovascular hypertension and ischemic nephropathy. Am J Hypertens. 2010;23(11): 1159–69.

11 Interaction Between Stenotic and Contralateral Kidneys: Unique Features of Each in Unilateral Disease

Luis A. Juncos, Kiran B. Chandrashekar, Arnaldo F. Lopez-Ruiz, and Luis I. Juncos

Abstract

Unilateral renal artery stenosis causes angiotensin II-dependent hypertension and leads to injury of the stenosed ipsilateral, as well as the non-stenosed contralateral kidney. While the hypertension is triggered by hypoperfusion-dependent renin release of the stenotic kidney, dysfunction of the contralateral kidney is what permits the blood pressure to remain elevated, and may even be the driving force behind the hypertension in the late stages. The differential function and crosstalk between the two kidneys are determined by the interaction among several neurohormonal pathways. Understanding the simultaneous processes taking place in both the ipsilateral and the contralateral kidneys should provide a better insight not only on the hypertensive process, but also on the mechanisms to progressive renal injury in this condition.

Keywords

Ipsilateral Kidney • Contralateral Kidney • Intrarenal Hemodynamics • Renorenal reflex • Glomerulosclerosis • Renal Crosstalk

L.A. Juncos, MD, FAHA, FASN
Departments of Medicine, Nephrology, and Physiology and Biophysics, University of Mississippi Medical Center, 2500 N State Street, Jackson, MS 39216, USA
e-mail: ljuncos@umc.edu

K.B. Chandrashekar, MD (✉)
Departments of Medicine and Nephrology, University of Mississippi Medical Center, Jackson, MS 39216, USA
e-mail: kchandrashekar@umc.edu

A.F. Lopez-Ruiz, MD
Department of Medicine, University of Mississippi Medical Center, Jackson, MS 39216, USA
e-mail: alopezruiz@umc.edu

L.I. Juncos, MD, MS PhD
Department of Medicine, J. Robert Cade Foundation, Pedro de Onate 253, Cordoba 5003, Argentina
e-mail: luis.juncos@jrobertcade.org.ar

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_11,

Introduction

Unilateral renal artery stenosis in patients with two functioning kidneys is a common cause of clinical hypertension, and leads to injury of the stenosed ipsilateral, as well as the non-stenosed contralateral kidney. The arterial stenosis causes the intrarenal arterial pressure of the stenosed kidney to fall, followed by an increase in renin (and angiotensin II) production, as well as sodium retention. These factors increase systemic blood pressure, which in theory should normalize the perfusion pressure and blood flow to the stenosed kidney. However, the contralateral non-stenosed kidney senses the increased blood pressure and responds by suppressing its renin secretion and increasing sodium excretion (via pressure natriuresis) in an attempt to lower blood pressure [1]. In fact, a fully functional non-stenosed contralateral kidney should potentially be able to normalize blood pressure. Yet, while the diuretic response of the contralateral kidney appears to blunt the increase in blood pressure, it is often insufficient to normalize it, thus implying that its function is not completely normal; indeed, pressure natriuresis is blunted in renovascular hypertension [1]. Moreover, any antihypertensive response from the contralateral kidney also sustains the hypoperfusion to the ipsilateral kidney and consequently maintains increased renin release from this kidney. Consequently, the two kidneys are effectively working against each other; the ipsilateral kidney increases renin and retains sodium in an attempt to protect its perfusion, while the contralateral kidney suppresses renin and excretes sodium, thereby preventing the blood pressure from reaching levels sufficient to restore perfusion to the stenotic kidney. Hence, while the contralateral kidney is not the causative factor, it clearly plays a permissive role in the development and maintenance of unilateral renovascular hypertension.

In the later stage of unilateral renovascular hypertension, when the renal injury has progressed, the ability of the contralateral kidney to excrete sodium declines substantially, resulting in volume expansion, which now plays a more prominent role in the maintenance of hypertension. For these reasons, understanding the functional and structural changes in the stenotic and the contralateral kidneys during the development and progression of unilateral renal arterial stenosis may help diagnostic and therapeutic decisions. In this chapter we will first provide an overview of the alterations present in the ipsilateral and contralateral kidneys during the course of unilateral renal artery stenosis, followed by a comparison of the functional, structural, and biochemical abnormalities between the two kidneys which may contribute to the maintenance of hypertension as well as progression of renal injury in the different phases of unilateral disease.

Contribution of Each Kidney to the Diverse Phases of Unilateral Renovascular Hypertension

Much of our knowledge regarding the pathophysiology of unilateral renal vascular hypertension is derived from the classic two-kidney one-clip (2K-1C) Goldblatt model of experimental hypertension. This model mimics human unilateral renovascular hypertension and allows us to study the individual role played by both the stenotic and contralateral kidneys. In this model, one renal artery has a compressive clip placed around it (or another device) that causes significant stenosis, while the contralateral kidney is left intact. The mechanisms that sustain hypertension, as well as the individual contributions of the ipsilateral and contralateral kidneys in this model, change over time. Three sequential phases of renovascular hypertension have been identified: an acute phase, a second or transition phase, and a chronic phase [2]. These phases vary significantly in onset and duration depending on the severity of the stenosis, species, conditions under which the animals were studied, and the state of salt and water balance. It is also uncertain whether these phases apply directly to human renal vascular disease. Nonetheless, they are helpful in understanding the pathophysiologic mechanisms that are operative (along with the contributions of each kidney) as the disease progresses (Table 11.1).

Table 11.1 The Contribution of each kidney to the sequential phases of the two kidney one clip Goldblatt hypertension model: changes in RBF, Juxtaglomerular renin production, intrarenal angiotensin II, and urinary sodium excretion (UxV_{Na}) are represented

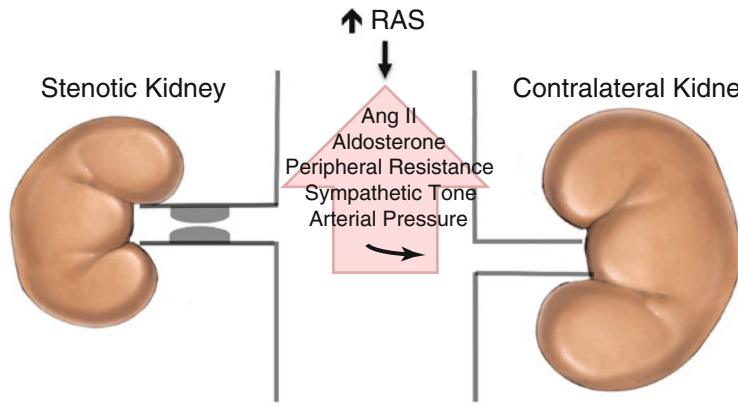
Phase	Kidney	RBF	Intrarenal renin	Intrarenal angiotensin II	UxV_{Na}	Role in increasing BP	BP falls after repairing stenosis/RAS blockade
Acute	Stenotic	↓	↑	↑	↓	↑↑	Yes
	Non-stenotic	↑/↓	↓	NC	NC	NS	
Transitional	Stenotic	↓	↑ or Normal[a]	↑	↓	↑↑	Yes
	Non-stenotic	↑/↓	↓	↑[a]	↑[b]	↑	
Chronic	Stenotic	↓	↑ or Normal[a]	↑	↓	↑	No
	Non-stenotic	NC or ↓	↓	↑[a]	↑[b]	↑↑	

Depending on the degree of stenosis the contralateral kidney may show incremental decreases in RBF
NC no change, *NS* not significant
[a]Inappropriately high for blood pressure levels
[b]Insufficient to normalize blood pressure

The acute phase begins immediately after the onset of a critical stenosis. It is characterized by a decrease in renal perfusion pressure and an ensuing decrease in sodium delivery to the macula densa in the stenosed kidney. This increases renin synthesis and release from the juxtaglomerular cells, resulting in a subsequent increase in plasma renin activity, angiotensin II, aldosterone, and eventually blood pressure [2]. The hypertension during this early-phase is dependent on the stimulation of the renin-angiotensin system in the stenosed kidney. Indeed, the hypertensive changes are absent in animals lacking functional angiotensin AT1 receptors, and can be prevented and/or reversed by blocking the renin angiotensin system via a variety of approaches, such as converting enzyme inhibitors and angiotensin receptor blockers [2]. The hypertension during this stage can also be abated by removing the stenosis [2]. The contralateral kidney is not playing as prominent a role in the development of hypertension during this acute phase; its role becomes progressively more important over time.

The second phase develops if the stenosis is not corrected during the acute phase. It consists of a transitional phase of variable duration. In this phase, the stenosed kidney continues to generate relatively high levels of renin-angiotensin, which in turn sustains an increase in peripheral resistance, and increases blood pressure. However, the contribution of the contralateral kidney is now more significant. While it responds to the increased pressure with a pressure natriuretic response, the magnitude of this response is not commensurate with the degree of blood pressure elevation. Consequently, despite relative volume expansion, secretion of renin from the hypoperfused ipsilateral kidney persists. Because the primary driving force behind the hypertension in this stage is still renin, removal of the stenosis, blockade of the renin-angiotensin system, or nephrectomy of the stenosed kidney will still lower the blood pressure.

In the third or chronic phase, the mechanisms maintaining the hypertension are multifactorial and include both a continued increase in peripheral resistance, as well as persistent volume expansion. Plasma renin activity in this phase varies significantly because of confounding conditions such as volume status and concurrent antihypertensive therapy. However, despite the relatively low levels of plasma renin activity and the inability of renin-angiotensin blockade to consistently normalize blood pressure, it is important to consider that (a) even normal levels of plasma renin activity (as commonly seen in humans) are still inappropriately elevated in the setting of hypertension, and (b) intrarenal levels of angiotensin II remain elevated in both the stenotic and contralateral kidneys. Therefore, the renin-angiotensin system is still playing a role, albeit not as dominant, in the hypertension and progressive renal injury in this phase. In effect, the elevated intrarenal angiotensin II levels, in conjunction with the prolonged exposure to the elevated blood pressure, are likely to be the main



↓ Renal Perfusion Pressure	↑ Renal Perfusion Pressure
JG Renin	**JG Renin**
– ↑ Renin in Renal Vein → Increases PRA	– ↓ Renin in Renal Vein
– ↑ AngII in Renal Veins	– ↓ AngII in Renal Veins
Intrarenal Renin Angiotensin System	**Intrarenal Renin Angiotensin System**
– ↑ Intrarenal Renin ↑ Intrarenal Angiotensinogen	– ↑ Intrarenal Renin ↑ Intrarenal Angiotensinogen
– ↑ Intrarenal ACE ↑ Intrarenal AngII	– ↑ Intrarenal ACE ↑ Intrarenal AngII
↑ Na reabsorption	**↓ Na reabsorption, but Blunted Pressure Natriuresis**

Fig. 11.1 Renin angiotensin aldosterone system in unilateral renal artery stenosis. As the renal blood flow falls in unilateral renal stenosis, renin and angiotensin content increases in the ipsilateral kidney. This is associated with increased sodium reabsorption in the stenosed kidney. The renin excess spills over to the systemic circulation increasing Aldosterone secretion. Efferent renal nerves from the stenosed kidney increases sympathetic tone. Hypertension results from the interplay of all these mechanisms. The contralateral kidney respond to sodium retention and hypertension by decreasing the synthesis of renin and angiotensin. But these changes are insufficient to lower blood pressure

culprits responsible for the substantial microvascular injury that develops in the contralateral kidney [2, 3]. This microvascular injury is associated with a further increase in renal vascular resistance and impairment of excretory function, thus leading to worsening of the volume expansion. Hence the renal microvascular injury is widely considered to be the primary cause of the sustained hypertension in this phase. Because the hypertension is now predominantly determined by the contralateral kidney, correcting the stenosis or removing the stenotic kidney no longer leads to reduction of the blood pressure. Indeed, removing the contralateral kidney (after correcting the stenosis) has been reported to correct the blood pressure.

Renin Angiotensin Aldosterone System (RAAS)

As mentioned before, activation of the renin angiotensin system instigates and plays a principal role in the maintenance of hypertension in all three phases of unilateral renal artery stenosis (Fig. 11.1 and Table 11.1). The increase in systemic angiotensin II levels is the result of increased renin production and secretion by the JG cells of the *stenotic kidney*. The ensuing increase in circulating angiotensin II levels and blood pressure inhibits renin production by the JG cells of *the contralateral kidney,* and this was thought to indicate that the activity of the renin-angiotensin system in this kidney was suppressed. However, both

kidneys remain very responsive to inhibition of the RAAS (even when plasma angiotensin II levels have normalized) suggesting that the effect of angiotensin II remains elevated in both kidneys [1, 4, 5]. It is now known that intrarenal levels of angiotensin II are dissociated from the circulating levels; in fact, intrarenal levels of angiotensin II are increased in both the stenotic as well as the contralateral kidney, and remain elevated in both kidneys even after systemic angiotensin II levels return towards normal [1, 4, 5]. The reasons for this dissociation are due to the contrasting mechanisms that regulate the systemic vs. intrarenal renin-angiotensin system. As mentioned before, the increase in systemic renin is primarily perfusion pressure-dependent and originates from the JG cells of the stenotic kidney. However, the increase in intrarenal angiotensin II is not dependent on increased renin from the JG cells, rather it is elicited by the elevated circulating angiotensin II levels [1, 4, 5].

Small incremental increases in circulating angiotensin II, as occurs during unilateral renal artery stenosis or infusion of angiotensin II, lead to increases in intrarenal angiotensin II to levels well above those observed in plasma [5]. This increase is not only the result of renal accumulation of angiotensin II, but also because of increased local production of angiotensin II. Indeed, the kidney possesses all of the elements necessary to produce angiotensin II, including renin (produced not only by the JG cells but also by tubular cells), angiotensinogen, and ACE, and the expression of these components are altered in both, the stenotic and contralateral kidney [4]. In the stenotic kidney, there is increased renin in the JG cells as well as in tubular cells of the connecting tubule and collecting duct, whereas the increased renin in the contralateral kidney is derived primarily by the tubular cells [6, 7]. There is also increased production of angiotensinogen in the proximal tubular cells, which is subsequently secreted into the tubules and spills over into the distal nephron segments in both kidneys, thus facilitating the increased formation of angiotensin I [7]. ACE, which is not only expressed on the endothelial cells, but also on the luminal membrane of the proximal and distal nephron segments, facilitates the continuous production of tubular/intrarenal angiotensin II, which is essential for the development of hypertension [8, 9]. Importantly, there is increased intrarenal ACE activity in the tubules of the non-stenotic kidney, and an additional ACE-independent pathway by chymase in the stenotic kidney, both of which may further augment angiotensin II formation. While the elevated angiotensin II levels down regulate the vascular AT1 receptors, tubular AT1 receptor levels are sustained in both kidneys, and it is the activation of these receptors that are largely responsible for the persistent increase in intrarenal angiotensin II uptake and production, as well as the renal dysfunction in both kidneys [10].

Renal Hemodynamic Changes During Unilateral Renal Artery Stenosis

The natural progression of renal hemodynamics in humans with renal artery stenosis is not known since the onset and progression of the stenosis is very gradual and not easily mimicked in experimental models. Stenosis of the renal artery does not significantly decrease the renal arterial perfusion pressure distal to the stenosis or the RBF until at least 70 % of the lumen is occluded. Once this point is reached, renal perfusion becomes critically dependent on arterial pressure and in fact may fluctuate significantly during the course of the day [11, 12]; it has been postulated that these periods of hypoperfusion may be an important contributor to renal injury in these kidneys [11]. Further encroachment upon the arterial lumen causes significant decreases in distal perfusion pressure, as well as blood flow to that kidney. However, these changes in the renal perfusion pressure, blood flow as well as function (of both the ipsilateral and contralateral kidneys) are not solely due to the degree of stenosis. They also depend on other factors such as changes in systemic arterial pressure, renal vascular resistance, vasoactive factors/hormones, etc., all of which may have variable effects depending on the timing and duration of their exposure. Despite

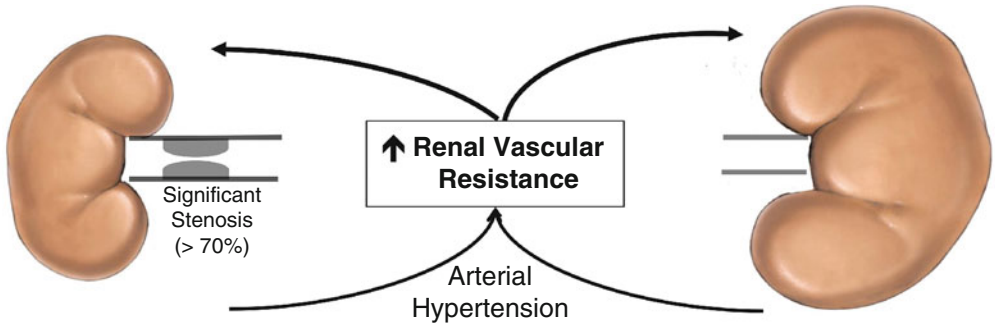
the shortcomings of animal models in which a stenosis is acutely created (compared to human renal artery stenosis which is almost always characterized by a gradual onset), the Goldblatt model of acute renal artery stenosis allows us to identify the early changes and consequently study the mechanisms by which renal dysfunction and injury progress.

Changes in the Acute/ Immediate Phase

Acute reductions in renal perfusion pressure trigger a series of progressive changes in both the ipsilateral and contralateral kidney (Table 11.1). The immediate response to the acute application of mild (70 %), moderate (87 %) and severe stenosis (95 %) was nicely described by Anderson et al. [11]. They found that acute application of unilateral renal artery stenosis tended to cause a biphasic response in arterial/aortic pressure, distal renal perfusion pressure as well as the RBF to both kidneys. The application of mild and moderate stenosis caused transient increases in arterial/aortic pressures that returned to normal within 90 min; only severe stenosis caused a sustained elevation in arterial/aortic pressure. The changes in distal perfusion pressure and RBF in the *stenotic kidney* tend to occur in tandem, except that the perfusion pressure alterations were more pronounced than the changes in blood flow. For instance, application of mild stenosis caused a mild (~20 mmHg), transient decrease in distal-RPP that was not accompanied by a decrease in ipsilateral RBF. On the other hand, application of moderate or severe stenosis caused much larger initial decreases in distal-RPP (by 75 and 80 %, respectively) accompanied by decreases in RBF. These responses also tended to be transient. In moderate stenosis, both the distal-RPP and RBF returned to normal within 60 min. In severe stenosis, distal-RPP returned toward normal, but it did so at a much slower rate and at the expense of an elevated arterial pressure and a large pressure gradient across the stenosis remained present. Despite this sluggish normalization of distal-RPP, RBF was near normal levels within 30 min. The stenotic kidney also exhibits a significant increase in resistance immediately following the stenosis. Anderson et al. imply that this increase in resistance, which also contributes substantially to the decrease in peripheral conductance, is a result of the hydraulic resistance of the stenotic narrowing of the renal artery and not directly due to an increase in the resistance in the distal renal vasculature [12]. *The contralateral kidney* does not exhibit any changes in its RBF following mild stenosis. With more severe stenosis, however, it exhibits a more variable response. In the Anderson study mentioned previously, there was a small decrease in contralateral RBF due to an increase in renal vascular resistance [11]. Administration of an ACE inhibitor prevented these effects implying that angiotensin II may be responsible for the vasoconstriction seen in these vessels during the early phase of renovascular hypertension. However, increased contralateral RBF (despite increased renal vascular resistance) has also been reported soon after creation of a stenosis, albeit at different time frames [13, 14].

Progression of the Changes in Renal Hemodynamics

Over time, if the stenosis persists, the blood flow to *the stenotic kidney* gradually increases, but usually remains significantly reduced compared to the pre-stenotic value. However, the reported changes are quite variable, likely due to degree and chronicity of stenosis, hydration status, kidney weights, and experimental conditions. Despite this, certain general tendencies can be recognized. Effective renal plasma flow, single nephron filtration rate, glomerular capillary pressure, Kf and proximal tubular flow are all decreased in the stenotic kidney [15, 16]. These hemodynamic changes are driven by an increase in pre-glomerular resistance (largely secondary to the stenosis). The decline in GFR can be progressive as shown by Himmelstein et al., who reported a progressive worsening of inulin clearance over the ensuing 4 weeks following establishment of stenosis [17]. Similar renal and glomerular hemodynamic patterns have been



Atrophy	Hypertrophy
↑ Preglomerular resistance	↑ Preglomerular resistance
↓ Renal Blood Flow	↑ Renal Blood Flow
↓ Effective Renal Plasma Flow	↑ Effective Renal Plasma Flow
↓ Single Nephron Filtration Rate	↑ Single Nephron Filtration Rate
↓ Glom. Capillary Pressure	↑ Glom. Capillary Pressure
↓ Kf	↓ Kf and Post Glom Resistance
↑ TGF	↓ TGF
↓ Proximal Tubular Flow	↓ Autoregulation

Fig. 11.2 Renal hemodynamic parameters during chronic renal artery stenosis. In a well-established chronic phase, significant (70 % stenosis or more) causes a fall in renal blood flow that is in part due to increased renal vascular resistance. This is followed by decreased effective renal blood flow, single nephron filtration rate, glomerular capillary pressure, filtration co-efficient (K_f) and proximal tubular flow, in the stenotic kidney. Renal blood flow may vary in this kidney depending on arterial blood pressure, hydration and other factors. The contralateral kidney, subjected to arterial hypertension, responds also by increasing pre-glomerular resistance, but renal blood flow may be unchanged or increased. Glomerular capillary pressure increases and may explain the increased single nephron filtration rate, despite decreased K_f and post glomerular resistance. Autoregulation is lost in the contralateral kidney probably related to impaired tubular-glomerular feedback

reported in humans; that is the stenotic kidney has a lower RBF (when corrected per gram of ipsilateral kidney weight), as well as decreased ERPF, and GFR [18] (Fig. 11.2).

On the other hand, blood flow to *the contralateral kidney* is usually unchanged or increased, but this has not been uniformly found [16, 18]. One factor that may contribute to the inconsistency is that there may be hypertrophy of the contralateral kidney following long-term renal artery stenosis; hence plasma flow may not be increased when corrected for kidney weight. The tendency towards increased flow is accompanied by increased effective renal plasma flow, single nephron filtration rate, glomerular capillary pressure, and pre-glomerular resistance, whereas Kf and post glomerular resistance are decreased in the contralateral kidney [19]. The increases in renal and glomerular hemodynamic parameters in the contralateral kidney occur despite increased renal vascular resistance in this kidney, which has been reported in both experimental and human renovascular hypertension [19]. However, the increased resistance is not appropriate for the blood pressure elevation; it is half that seen in the stenosed kidney, and more importantly it is insufficient to maintain normal glomerular pressures and

flows. Moreover, it fails to respond to decreases in blood pressure or amino acid infusion, demonstrating a loss of autoregulatory efficiency and of functional reserve, which may in part be due to decreased sensitivity of the tubuloglomerular feedback system [16, 20]. It is important to note that the loss of tubuloglomerular feedback sensitivity can help sustain total GFR (it allows for increased GFR of the contralateral kidney in the setting of decreased GFR in the stenosed kidney) and thus may be viewed as adaptive. However, it also allows for the increased glomerular capillary pressures and does not help prevent the drops in renal perfusion and filtration during times of hemodynamic stress, thus potentially worsening the progression of renal injury (Fig. 11.2).

Response of the Stenotic and Contralateral Kidneys to Correction of the Stenosis

This has been incompletely evaluated and the available data are not surprisingly quite variable, particularly in humans [21, 22]. Most studies have evaluated total renal function after revascularization, while few have assessed renal function in both the re-vascularized and the contralateral kidney. For instance, split renal function after renal angioplasty for arteriosclerotic or dysplastic unilateral renal artery stenosis, show that single-kidney GFR increases in the stenotic kidney and decreases in the contralateral kidney [21]. Both the usual hypoperfusion of the stenotic kidney and a proposed hyperperfusion of the non-stenotic contralateral kidney are reversed [23]. Overall, the available studies reporting split function suggest that stenting of the stenosis may cause stabilization or improvement of ipsilateral RBF and GFR, but a decrease in the function of the contralateral kidney. However, these results must be interpreted with caution as they were small studies in which patient selection may have biased the results; and therefore they may not apply to many or most patients with renal artery stenosis because of the presence of numerous confounding factors, (degree of microvascular disease, presence of diabetes, smoking, etc.), in these patients.

Factors Influencing the Function of the Ipsilateral vs Contralateral Kidney

As in other forms of hypertension, the high blood pressure and ensuing renal damage is the result of the interactions among diverse physiochemical factors, including alterations in renal hemodynamics, sympathetic nervous activity, various hormones, reactive oxygen species and other factors. The varied reactions of the stenosed and contralateral kidneys in response to these mechanisms determine renal dysfunction and injury, which lead to vascular, tubulointerstitial, inflammatory and fibrotic changes in both kidneys [3, 24] (summarized in Fig. 11.3).

Renal and Sympathetic Nervous System (SNS)

Over activity of the sympathetic nervous system can promote hypertension by facilitating the release of renin, as well as increasing renovascular resistance, and tubular reabsorption of sodium [25]. In unilateral renal artery stenosis there is a sustained increase in sympathetic activity, which may thus contribute to the long-term blood pressure elevation [26, 27]. This notion is supported by studies showing that plasma catecholamine levels, norepinephrine spillover rates, and muscle sympathetic nervous activity are commonly increased in human and experimental renovascular hypertension [27]. Direct measurements of renal sympathetic nervous activity (RSNA) to the kidneys are rather scarce, but the available data suggest that it is increased to the clipped kidney, but perhaps decreased to the contralateral kidney [28]. While the increased sympathetic tone originates primarily from the stenosed kidney, there are alterations in both the afferent and efferent limbs of both kidneys that may contribute to the perpetuation of hypertension [29]. In fact, the neural crosstalk between the two kidneys (renorenal reflexes) is consistently impaired and may contribute to the inadequate response of the contralateral

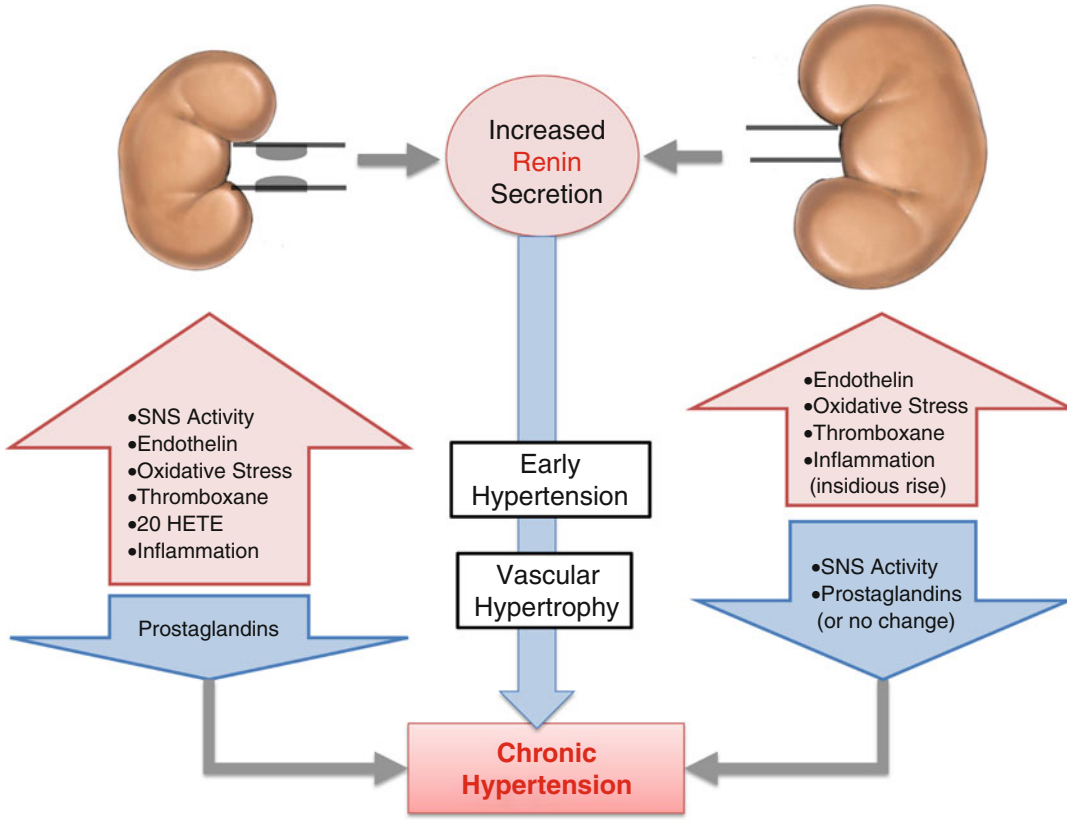


Fig. 11.3 Various factors influencing the function of the ipsilateral and contralateral kidney. Sympathetic Nervous System activity (*SNS*), endothelins and eicosanoids are some of the diverse physiochemical factors which vary in each kidney. The varied reactions of the stenosed and contralateral kidneys in response to these mechanisms and also to changes in renin contributes to the overall determination of renal dysfunction and injury, leading to vascular, tubulointerstitial, inflammatory and fibrotic changes in both kidneys

kidney to the hypertension [30] (Fig. 11.4a–c). Renorenal reflexes are neurohumoral-mediated responses occurring in one kidney in response to interventions on the same or opposite kidneys. In normal subjects, stimulation of renal mechanoreceptors or chemoreceptors activates ipsilateral afferent renal nerve activity, which decreases contralateral efferent renal nerve activity resulting in increased sodium excretion from this kidney. However, this reflex is impaired in renovascular hypertension; stimulation of the mechanoreceptors or chemoreceptors of either the clipped or unclipped kidney did not increase ipsilateral afferent renal nerve activity, nor did it decrease efferent renal nerve activity or increase salt excretion from the contralateral kidney [30]. Thus, there is strong evidence suggesting that the lack of inhibitory renorenal reflexes from the stenosed kidney may boost efferent renal sympathetic nervous activity, blunt contralateral natriuresis, and consequently contribute to arterial hypertension in this model.

The significance of the increase in sympathetic nervous activity and the impaired renorenal reflexes in renovascular hypertension is supported by studies demonstrating that blood pressure decreases following ganglionic blockade, peripheral sympathectomy, and destruction of selected regions in the anterior hypothalamus. Similar results are attained by administration of agents that reduce sympathetic outflow by

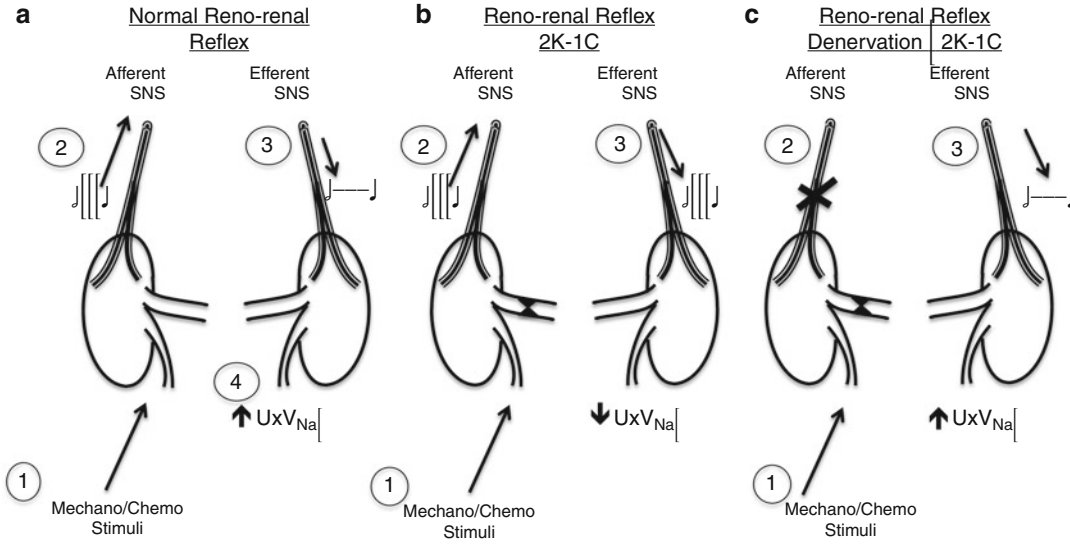


Fig. 11.4 Reno-renal reflex in unilateral renal artery disease. (**a**) Shows mechano or chemo- stimulation (1), increasing afferent renal nerve activity (2). This reduces renal efferent activity in the contralateral kidney (3), thus increasing sodium excretion in this contralateral kidney (4). (**b**) Shows the absence of reno-renal reflex; that is, efferent renal activity is not inhibited and consequently, renal sodium excretion decreases. (**c**) Shows that afferent renal denervation of the clipped kidney, leaves the efferent tone idle thus allowing for sodium excretion

stimulating the imidazoline and alfa-2 receptors in the rostral ventrolateral medulla (i.e., clonidine, moxonidine and rilmenidine) [31]. The participation of each kidney in modulating the sympathetic nervous system activity has been determined by renal denervation studies. The role of the stenotic kidney in driving the increase in sympathetic nervous system activity and blunting sodium excretion is inferred by studies showing that renal denervation or selective afferent renal nerve denervation of the stenotic kidney (via thoracolumbar dorsal rhizotomy), lowers blood pressure, reduces renin activity in the same (clipped) kidney, and increases urinary sodium excretion of both kidneys; an effect that is mimicked by clonidine [30]. In contrast, denervation of the contralateral non-stenotic kidney has a less consistent blood pressure lowering effect, but it decreases urinary sodium excretion and peripheral sympathetic nervous activity and normalizes renorenal responses in 2K-1C hypertensive rats; i.e., urinary sodium excretion increases in the ipsilateral kidney and falls in the contralateral one [32], suggesting that renal nerve activity of both kidneys and renorenal reflexes contribute to the hypertensive effect of renal artery stenosis.

In brief, current evidence clearly indicates that the SNS is activated and plays a role in the hypertensive effects of unilateral renal artery stenosis. Moreover, renorenal reflexes are impaired and may accentuate the typical increase in sympathetic nervous system activity of renovascular hypertension and foster hypertension by increasing sodium and water retention. Be that as it may, other factors may also be pertinent in the abnormal sympathetic responses present in renovascular hypertension. In this respect, McElroy et al. have shown altered adrenergic receptor affinity during 2K1C hypertension; it was heightened in the clipped (but not contralateral kidney) at 2-weeks, and elevated in both kidneys at 6 weeks [33]. However, the role of this alteration is unclear since receptor affinity was normalized by 12 weeks.

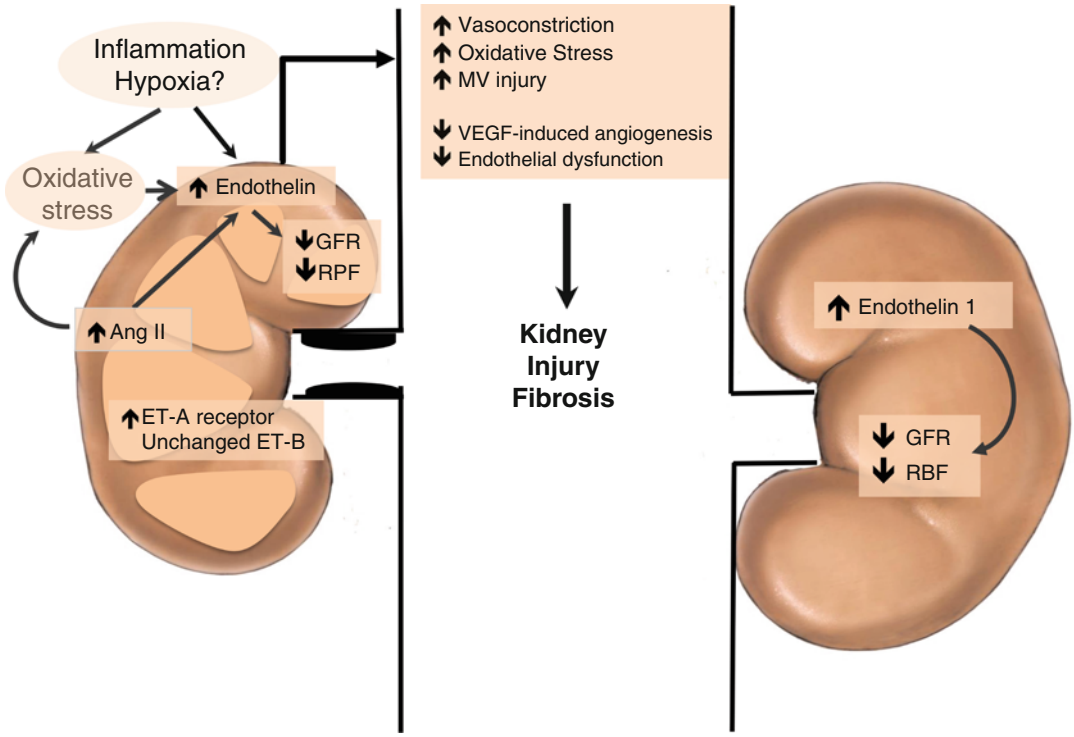


Fig. 11.5 Endothelin-1 and endothelin-a receptors in unilateral renal artery stenosis: the stenosed kidney increases cortical ET-1 expression in part induced by increased Ang II synthesis and in part due to persistent inflammation, oxidative stress and perhaps tissue hypoxia. In the medulla of the stenotic kidney increases ET-A expression while ET-B receptors are unchanged. The predominance of ET-A over ET-B receptors facilitates the pro-oxidative, vasoconstrictor and inflammatory effects of ET1. The contralateral kidney also exhibits increase in endothelin-1 and decrease in GFR and RBF

The Angiotensin-Endothelin-Oxidative Stress Axis

Increases in intrarenal angiotensin II stimulate the production of several factors, including endothelin-1 (ET-1) and oxidative stress, suggesting that they may also play an important role in the pathophysiology of renovascular hypertension [34]. Indeed, ET-1 mRNA, protein, and urinary excretion are all elevated in both kidneys throughout all phases of the two-kidney one clip model of hypertension. However, while the renal venous blood levels of ET-1 in the clipped kidney are elevated, the peripheral circulating levels are not increased [35]. The mechanisms for the increased ET-1 are multifactorial and appear to vary depending on the kidney and phase of renovascular hypertension (Fig. 11.5).

In the *stenotic kidney*, the increased ET-1 is initially triggered by the high levels of intrarenal angiotensin II. Indeed, ACE inhibitors and angiotensin receptor blockers reduce the expression and excretion of ET-1 from the stenosed kidney, but only in the early and transitional phase of unilateral renal artery stenosis (6–8 weeks). However, during the chronic phase (>12 weeks), other factors come into play, including, oxidative stress, inflammation, and perhaps regional hypoxia and all of them contribute to sustain the local ET-1 synthesis. This upregulation of ET-1 expression is mainly in the cortex, but is associated with a concurrent increase in medullary

ET-A receptor [35]. Activation of this receptor induces vasoconstriction, oxidative stress, endothelial dysfunction, microvascular rarefaction, and leads to renal injury [35]. It also attenuates the normal angiogenic response mediated by vascular endothelial growth factor (VEGF) [36]. In contrast to the ET-A receptor, expression of the ET-B receptor (a promoter of sodium excretion) is unchanged in either the cortex or medulla of the stenosed kidney. As a result, the renal hemodynamic effects of ET-A prevail, reducing GFR and RBF and increasing RVR in the stenosed kidney. In fact, early administration of an ET-A blocker in experimental renal artery stenosis prevented the reduction in GFR, RBF, as well as renal damage and microvascular density loss in the stenosed kidney, without reducing the blood pressure, PRA or intrarenal levels of angiotensin II [36]. In contrast, ET-A blockage in the late phase did not provide beneficial effects on the hemodynamic parameters or the renal damage. Moreover, long-term blockade of the ET-A receptor was reported by Hocher et al. to worsen fibrotic atrophy of the clipped kidney, without affecting blood pressure or PRA [37].

Endothelin-1 synthesis is also increased throughout all phases of renovascular hypertension in the *contralateral kidney*. The stimuli for its elevation here include the same factors as the stenotic kidney, and perhaps also increased shear stress changes; however, in this kidney, the ET-A receptors are not increased [35]. Blocking the ET-A receptor improved RBF and GFR of the unclipped kidney, but blunted the sodium loss of both kidneys in severely hypertensive 2K1C rats [38]. The contralateral kidneys of rats chronically treated with an ET-A blocker by Hocher et al. (mentioned previously) did not exhibit any exacerbation of their chronic renal fibrosis [37].

Oxidative Stress. Unilateral renal artery stenosis is often accompanied by a progressive increase in oxidative stress, as shown by an early (1 week) increase in plasma thiobarbituric acid-reactive species (TBARS) levels, as well as rising plasma PGF2a-isoprostanes levels that remain elevated and parallel the increase in mean arterial pressure, even after plasma renin activity has returned to baseline levels. This increase in the systemic levels is accompanied by a commensurate increase in not only the stenotic, but also the contralateral kidney; renal vein PGF-2α isoprostanes from the contralateral and the stenosed kidneys show similar elevations [39]. Moreover, the levels of antioxidant enzymes (glutathione peroxidase, catalase, CuZn-SOD, Mn-SOD) are also decreased in both kidneys throughout the duration of the stenosis [39]. Since oxidative stress in general, and isoprostanes have important renal effects including renal vasoconstriction, sodium retention and tubular epithelial damage, these results suggest that they may play a role in modulating function and injury in both kidneys [40] (Fig. 11.6). However, while there are substantial data showing that it contributes to renal dysfunction and damage of the stenotic kidney, its role in the contralateral kidney is not as thoroughly studied. This may be important to determine because the location of the increased oxidative stress (as determined by nitrotyrosine immunoreactivity) may be different in the two kidneys, in that, it is focused in and around the MD cells in the stenotic kidneys, but it is more concentrated in the afferent arterioles of the contralateral kidney [41].

Renal Eicosanoids in Unilateral Renal Artery Stenosis

Renal function is strongly modulated by the balance that exists between vasodilator (Prostaglandin-I_2; PGI_2 and Prostaglandin E_2; PGE_2) and vasoconstrictor prostanoids (thromboxane A_2; TxA_2). This balance can be altered by a variety of stimuli including angiotensin II. While angiotensin II can stimulates the synthesis of both, vasodilator and vasoconstrictor prostanoids, chronic exposure to angiotensin II and oxidative stress tilts the balance towards the vasoconstrictors prostaglandins, which may contribute to the maintenance of hypertension in the chronic phase of hypertension [42]. The stenotic kidneys have increased TxA_2 in renovascular hypertension; this increase may help maintain GFR and promotes hypertension by inciting the release of renin and therefore angiotensin II. The contralateral kidneys also excreted increased amounts of TxB_2 (a metabolite of TxA_2)

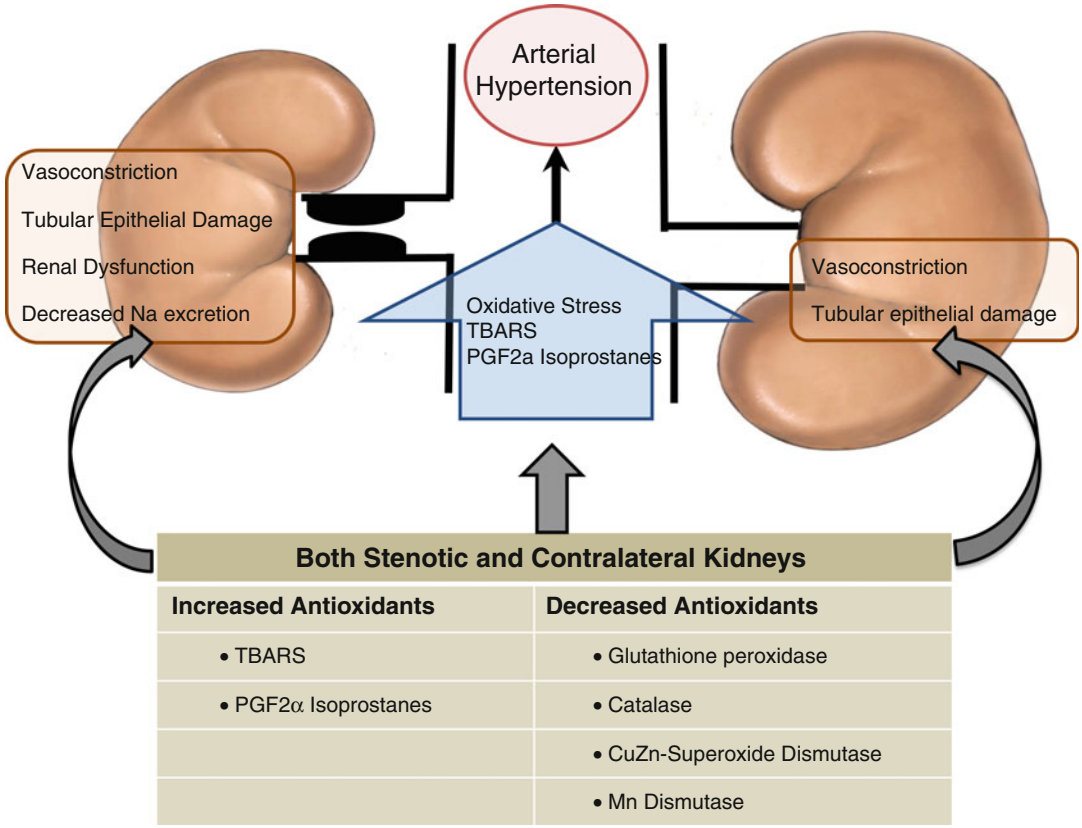


Fig. 11.6 Oxidative stress in unilateral renal artery stenosis: oxidative stress is increased in both the stenotic and the non stenotic kidneys during unilateral renal stenosis. This is reflected in the systemic circulation were oxidation causes vasoconstriction and increased blood pressure even after plasma renin activity decreases. Oxidative stress seems to contribute to renal dysfunction and tissue damage in the stenosed kidney but not in the contralateral kidney

and this elevation in TxB_2 is inversely proportional to the fall in GFR [17]. Elevation of thromboxane has also been reported in humans [43]. It is elevated in both kidneys, but especially in the contralateral kidney. These results suggest that enhanced thromboxane synthesis may contribute to the regulation or dysregulation of the kidneys in renovascular hypertension.

The vasodilator prostaglandins may also play an important role in modulating individual renal function in unilateral renal artery stenosis. They are important in protecting renal perfusion and function in states where perfusion is compromised, thus it is of no surprise that they play a role in the stenosed kidneys. However, in reality, both kidneys have high concentrations of PGE_2 in the early phases of 2K-1C hypertension, especially in the medullary regions [44], and have been suggested to play a critical role preserving renal function in these early stages of renovascular hypertension, at least in part via pre-glomerular vasodilation [45]. As the renovascular hypertension becomes more chronic, eicosanoid production declines, yet they may still play a role in protecting both kidneys (especially the clipped one) from a critical reduction in blood flow during this phase [45, 46]. *In the clipped kidney*, RBF decreases proportionally to the reduction in the renal artery lumen. While renal PGE_2 content increases modestly with moderate clipping, the administration of a COX 1 inhibitor does not change RBF. However, with severe stenosis, renal PGE_2 content falls markedly in both kidneys and yet, the administration of a COX inhibitor significantly lowers RBF of both kidneys. This indicates that, even at low concentrations

Table 11.2 Effect of cyclooxygenase (COX) inhibition on renal hemodynamics in the stenotic and contralateral kidneys during moderate and severe renal artery stenosis

	Stenotic kidney		Contralateral kidney	
	Before COX Inhibition	After COX Inhibition	Before COX Inhibition	After COX Inhibition
Moderate clipping (< 50% fall in RBF)				
Renal PGE2 content	200	110*	110	80
RPF	30	28	60	55
GFR	9	8	15	14
Severe clipping (> 70% fall in RBF)				
Renal PGE2 content	350	80*	110	80
RPF	20	6*	45	30*
GFR	9	3*	16	11*

Note: Data derived from several studies as indicated in text
* $p < 0.05$ vs. Before COX inhibition

PGE_2 exerts a protective effect on kidney hemodynamics [47] (Table 11.2).

The contralateral kidney shows changes in renal hemodynamics and renin release that are also partially explained by alterations in arachidonic acid metabolism. Although tissue PGE_2 and PGI_2 content in the contralateral kidney changes very little or may even decrease, administration of a prostaglandin inhibitor causes a significant fall both in RBF and in GFR, implying that renal hemodynamics in the non-clipped kidney are sustained by these vasodilator eicosanoids [17, 47] (Table 11.2). In fact, the protective effects of TxA_2 synthesis blockers may be partially due to shunting of endoperoxide substrate to PGI_2 [17]. However, despite the protective effects afforded by the renal eicosanoids, they do not suffice to normalize overall renal function.

It is important to point out that PGI_2 may have a dual effect in regulating blood pressure and renal function in renal artery stenosis. On one hand, it is a vasodilator and thus should blunt decreases in RBF and increases in blood pressure. However, it is also an important stimulus for renin release, thus it can exert a paradoxical effect on blood pressure in certain conditions. Indeed, Fujino et al. found that mice lacking the prostacyclin receptor have a decreased hypertensive response to renal artery stenosis [48]. However, the contribution of each individual kidney to this response is not understood.

Nitric Oxide (NO)

The regulation of NO in renovascular hypertension is multifaceted. Decreased sheer stress (due to the decreased blood flow in the stenosed kidney) inhibits NO production, whereas increased shear stress in the contralateral kidney and the increased angiotensin II levels increase NO production. During the earlier phases of mild renal artery stenosis, both the ipsilateral stenotic and contralateral kidneys exhibit elevated levels of the NO, as suggested by increased interstitial levels and urinary excretion of the NO products, nitrites and nitrates [49]. This increase in NO may attenuate the vasoconstrictor effects of angiotensin II and thus maintain perfusion of the kidneys [50]. Indeed, inhibiting synthesis of NO in both early as well as late phase of renovascular hypertension causes an exaggerated increase in renal vascular resistance and a decrease in RBF in both kidneys [50]. However, with progressively worse stenosis, the importance of NO in maintaining renal perfusion becomes very different between the kidneys (Fig. 11.7). In the severely stenosed kidney, the reduced flow/sheer stress may cause NO production to drop and its effect less pronounced. Indeed, urinary excretion of NO products decreases with severe stenosis, and inhibiting NO synthesis ceases to have an effect on ipsilateral RBF, suggesting that NO is less of a factor in preserving perfusion [51]. In fact, although angiotensin-AT2 receptor-dependent NO may help preserve oxygenation [52], maintenance of ipsilateral RBF during severe stenosis is more dependent on the vasodilator prostaglandins [47].

In marked contrast, NO becomes progressively more important in regulating the hemodynamics of the contralateral kidney as the severity of stenosis increases [49, 51]. This

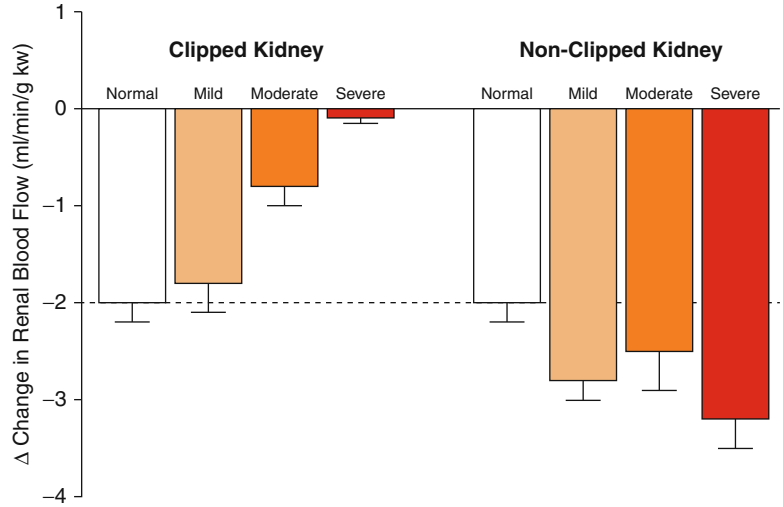
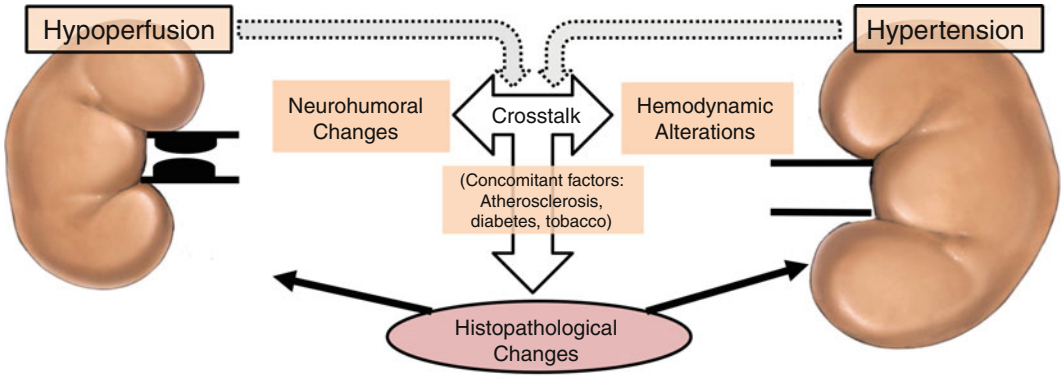


Fig. 11.7 Changes in the renal blood flow in response to N^G-nitro-L-arginine methyl ester (L-NAME) in normotensive and two-kidney one clip renovascular hypertensive animals with mild, moderate and severe stenosis

same pattern of NO dependency in the contralateral but not the stenosed kidney has also been reported in humans; in fact, the stenosed kidney does not seem to exhibit any tendency for NO mediated vasodilation [53]. The importance of NO in counteracting the vasoconstrictor effects of angiotensin II in this kidney has been demonstrated by Sigmon and Beierwaltes who found that blocking NO during even moderate stenosis decreased RBF in the contralateral kidney by >50 % [51]. In addition, the increased NO in this kidney may also offset other angiotensin II-induced changes in vascular and tubular function as well. Of particular importance is the attenuating effect of NO on tubuloglomerular feedback. The high intrarenal angiotensin II would be expected to enhance tubuloglomerular feedback, which in turn would accentuate the sodium retaining effects of angiotensin II. However, as mentioned previously, tubuloglomerular feedback responses in the contralateral kidney are not enhanced, rather they are blunted [15, 16]. The decreased responsiveness of the tubuloglomerular feedback system is associated with increased NO (nitrites/nitrates) and can be prevented by the inhibiting NO synthesis [54], suggesting that NO is largely responsible for the altered tubuloglomerular feedback responses and consequently the impaired autoregulatory efficiency present in this kidney (described previously in the renal hemodynamics section). Thus overall, NO is an important modulator of angiotensin II during unilateral renovascular hypertension, particularly in the contralateral kidney.

Additional Mediators of Inflammation, Fibrosis, and Renal Disease Progression

In addition to the factors mentioned in the previous sections, extensive exposure to increased levels of intrarenal angiotensin II, in association with high blood pressure and/or stenosis, can activate several inflammatory cytokines and proliferative factors [55, 56]. Activation of these signaling pathways culminates in renal inflammation, intrarenal microvascular disease, vascular rarefaction, and tubulointerstitial and glomerular fibrosis in the stenotic and the contralateral kidneys, driving the progressive injury in both kidneys [57]. Indeed, studies have demonstrated elevated levels of inflammatory mediators (e.g., monocyte chemoattractant protein-1, tumor necrosis factor-α; and interleukin-6), pro-fibrotic signaling chemokines (transforming growth factor-β1; TGF-β1), and proliferative factors [3, 55, 56]. These factors are markedly and persistently increased in the stenotic kidney, while changes in the contralateral kidney seem slower though unremitting. The interactions between these factors are what



Stenotic Kidney	Contralateral Kidney
Driving force: Hypoperfusion	Driving force: Systemic Hypertension
Decreased size and weight	Compensatory Hypertrophy
Tubular injury and atrophy	Nephrosclerosis and Tubular atrophy
Microvascular remodeling and rarefaction	Early mononuclear cell recruitment and matrix protein deposition mainly in interstitium
Glomeruli spared until advanced disease	Glomerular hypertension, hyperfiltration and glomerulosclerosis
Prominent Tubulointerstitial Changes	Prominent Tubulointerstitial Changes

Fig. 11.8 Other mediators and structural changes: hypoperfusion is the triggering event in the stenotic kidney, while the systemic hypertension incites the changes seen in its non-stenotic counterpart. These two main factors trigger a crosstalk between the neurohumoral and hemodynamic factors which along with several concomitant factors leads to histopathological damage in both kidneys

ultimately determine the progression of renal injury in each kidney (Fig. 11.8).

The TGF-β_1 signaling pathway is playing a critical role in cell cycle regulation, inflammatory response to tissue injury, and extracellular matrix accretion in both kidneys [58]. By activating the SMAD family of proteins, (particularly SMAD 3), TGF-β_1 induces fibrosis and renal atrophy in renal artery stenosis. Together with other cytokines, TGF-β_1 promotes the synthesis and activity of growth factors that modulate the renal tissue response to ischemia, including angiogenesis, collagen deposition and extracellular matrix turnover leading to interstitial injury and fibrosis [59]. The plasma level of TGF- β_1 are normal; but the levels of this cytokine vary in the two kidneys in that the stenotic kidney exhibits a persistent induction of TGF- β1 and SMAD3 expression when compared to the contralateral kidney, which contributes to accentuated interstitial inflammation, fibrosis and tubular atrophy seen in the stenotic kidney. In the 2K1C rat model, it takes 6 days after clipping for glomerular TGF-β_1 mRNA expression to rise in the stenosed kidney. These changes are not reflected in plasma levels even though tissue expression remains elevated by day 21 and 35 [60]. Studies in mice report that TGF- β1 content in the stenotic kidney does not rise until 2 weeks after clipping (instead of 6 days) but this increase is also sustained into the chronic phase of renal artery stenosis [61].

TGF-β_1 expression in the contralateral kidney is somewhat different than in the stenotic kidney. In rats it is unchanged for about 3 weeks after clipping, but then subsequently increases in this kidney, while TGF-β_1 expression is falling in the stenosed kidney [60]. Studies in mice differ somewhat in that while TGF- β1 increased in the contralateral kidney during the earlier phases of renal artery stenosis, this elevation was not sustained

into the chronic phase [61]. Nevertheless, this temporary upregulation of TGF- β_1 and SMAD3 was associated with compensatory hyperplasia in the same (contralateral) kidney [61].

The trigger for inducing TGF-β_1 appears to differ between the kidneys. It may be driven by the increased angiotensin II or result from the systemic hypertension. In the stenotic kidney, TGF-β_1 is initially increased in the setting of high angiotensin II levels and lower perfusion pressures, proposing that angiotensin II may be the predominant stimuli. However, it later declines despite the sustained increase in angiotensin II levels, perhaps due to down-regulation of AT1 receptors [60]. In contrast, the late increase in TGF-β_1 in the contralateral kidney is reversed by either angiotensin receptor blockade or triple antihypertensive therapy (hydralazine, reserpine, and hydrochlorothiazide) suggesting that the hypertension may in fact be responsible for the TGF-β_1 stimulation in this kidney. Regardless of the cause, TGF-β_1 signaling through SMAD3 likely contributes to the interstitial inflammation and fibrosis as well as tubular atrophy seen in the stenotic kidney.

Hypoperfusion may also contribute to the effect of TGF-β_1 on the stenotic kidney via activation of hypoxia inducible factor (HIF-1α). Growing evidence suggests a cross-talk between HIF-1α and TGF- β1/SMAD pathways which synergistically induce vascular endothelial growth factor (VEGF) leading to neovascularization [59]. While HIF-1α activation is normally cytoprotective by regulating vascular remodeling, erythropoiesis and other regenerative pathways [62], chronic HIF-1α activation has also been implicated in accentuating maladaptive responses like fibrosis, resulting in additional tissue destruction [62]. In the chronic phase of renal artery stenosis, the HIF-1α protein gets destabilized and attenuated due to a sustained increase in oxidative stress thus hampering tissue repair. In the long-term, lowered microvascular spatial density in the stenosed kidney could result from reduced HIF-1α and the subsequent decrease in VEGF [63]. Thus, the compensatory angiogenesis could be restricted by chronic hypoxia, thereby preventing the restoration of perfusion to the stenotic kidney.

Mitogen activated protein kinases (MAPK, also called Extracellular Signal-Regulated Kinase; ERK) are commonly expressed intracellular signaling molecules participating in cellular adaptive responses such as hypertrophy, hyperplasia, apoptosis and atrophy and thus they may participate in the renal growth responses during renal artery stenosis [64]. The ipsilateral and contralateral kidneys undergo different growth responses as the stenosis progresses. While the stenotic kidney endures fibrotic atrophy, the contralateral kidney experiences significant compensatory growth that results in part from hyperplasia similar to the one seen in subtotal nephrectomy [61]. Using a murine model of two-kidney one clip hypertension, Cheng et al. observed variable degrees of cell proliferation in both kidneys. ERK expression matched the severity in cell proliferation in each kidney. They noted that the contralateral kidney exhibited an increase in the phosphorylated ERK (p-ERK; the active form), but, this elevation was not sustained, the p-ERK levels get back to baseline after 11 weeks. The p-ERK levels in the stenotic kidney, however, were elevated throughout the experimental period [61]. The disparity in the p-ERK levels suggests that ERK may be involved in the changes occurring in the two kidneys. Moreover, several studies have also found interactive signaling mechanisms between TGF-β1 and ERK's, further restating the role of these kinases in the progression of renal injury [65].

Structural Changes in the Stenotic and Contralateral Kidney

The crosstalk between the multiple aforementioned hemodynamic and neurohumoral alterations, along with other concomitant factors (e.g., atherosclerosis, diabetes, tobacco exposure, etc.), lead to progressive, but disparate histopathological alterations in each kidney. The stenotic kidney undergoes a progressive reduction of its size and weight denoting renal parenchymal loss due to ischemia induced global atrophy. These changes start as early as 1 week after the 2K1C surgery [61]. The earliest and most consistent changes observed are tubulointerstitial changes.

The hypoperfusion and resultant activation of various pathways including angiotensin II, ROS, and ET-1, stimulate the production of pro-inflammatory and growth factors (e.g., MCP-1, IL-6, IL-8, IF-g), which together with the concomitant tubular injury lead to migration of B-lymphocytes, T-lymphocytes, and macrophages, as well as increased extracellular matrix turnover, collagen deposition, and apoptosis [55, 59, 66]. These processes lead to tubular atrophy (of both proximal and distal tubules) and also to excessive matrix accumulation and interstitial fibrosis. Moreover, prolonged hypoperfusion and/or vasoconstriction foster more permanent changes in the microcirculation. As with other forms of hypertension, microvascular remodeling (e.g., an increase in wall/lumen ratio) is quite prominent. In addition, the relative decrease in oxygen supply stimulates vessel growth via induction of hypoxia-inducible factor-1α and vascular endothelial growth factor. While this normally promotes compensatory new vessel formation, the increase in oxidative stress and other anti-angiogenic factors like thrombospondin, can suppress neovascularization, interfere with tissue repair by activating TGF-β and inhibiting matrix metalloproteinases [67]. This consequently leads to microvascular rarefaction; a hallmark of stenotic kidneys [59]. The severity of tubulointerstitial fibrosis and microvascular regression is linked to the renal dysfunction and thus, these changes could be potential therapeutic targets for the eventual reversibility of the injury.

In marked contrast to the vascular and tubulointerstitial compartments, the glomeruli are relatively spared until advanced stages of renal vascular hypertension. Initially, the glomeruli may appear smaller (due to hypoperfusion) but are essentially normal; indeed, ultra-structural analysis indicates that the renal glomerular integrity is preserved in 2K1C [68]. As the tubulointerstitial process advances, there is "crowding" of the glomeruli and marked increase in the number of atubular glomeruli (glomeruli not attached to a proximal tubule). In severe and chronic renovascular hypertension, there is initiation of glomerular cell apoptosis, basement membrane thickening, and expansion of the mesangial extracellular matrix, via similar signaling pathways as in the tubulointerstitial compartment, and ultimately progression to glomerulosclerosis [59, 69].

While the contralateral kidney undergoes compensatory hypertrophy/hyperplasia during early renovascular hypertension, it can eventually succumb to progressive renal injury, which contributes to the maintenance of the chronic phase of renovascular hypertension. The mechanism by which it is injured, however, is different from that in the stenotic kidney. The contralateral kidney is subject to many of the same neurohormonal and cytokine signaling pathways as the stenotic kidney, but with a fundamental difference: unlike the stenotic kidney, it is exposed to the systemic hypertension, and it is the hypertension that drives the pathologic process in this kidney. In fact, the changes seen in the contralateral kidney are similar to those seen in essential hypertension, and may be in part due to the presence of glomerular hypertension. Indeed, micropuncture studies have shown that glomerular hypertension and hyperfiltration are present in the nonclipped kidney of 2K1C rats (despite afferent arteriolar vasoconstriction) and reducing pre-glomerular resistance accelerates the progression of glomerulosclerosis. Having said this, while the alterations in glomerular hemodynamics have received the most attention, the tubulointerstitial injury may play an equally important role as in the stenotic kidney, in which tubuli and interstitium appear to be the initial sites of injury. Indeed, within a week after establishing 2K-1C hypertension, progressive expansion of the interstitial volume ensues together with infiltration of mononuclear cells and accumulation of fibronectin and various collagens in the renal interstitium, while vascular and glomerular lesions lag behind [70]. The initial vascular changes are that of medial hypertrophy of the walls of the arcuate, and interlobular arteries, as well as the afferent arterioles. This is followed by segmental hyalinosis with intrusion of blood constituents into the vessel wall, and ultimately severe concentric intimal fibrosis and variable luminal obliteration. The glomeruli follow a similar progression as the blood vessels. There is initially a mild to moderate increase in laminin, fibronectin and collagens,

followed by a progressive expansion of the mesangium and matrix accumulation that eventually leads to focal segmental and global sclerosis. Thus, renal injury of the non-stenotic kidney during renovascular hypertension is manifested by early mononuclear cell recruitment and deposition of matrix proteins primarily within the interstitium. The progressive interstitial inflammation and fibrosis, is associated with subsequent tubular atrophy, vascular remodeling and hyalinosis, and ultimately nephrosclerosis with possible focal segmental and global glomerulosclerosis. Hence, both kidneys in the 2K1C model suffer structural changes. This is largely a consequence of hypoperfusion in the stenotic kidney and hypertension in the contralateral. Both of these mechanisms (hypoperfusion and hypertension) trigger neurohumoral and signaling pathways that are responsible for the tubulointerstitial and glomerular changes.

In summary, while decreased perfusion to the stenosed kidney is the initiating event leading to hypertension in unilateral renal artery stenosis, it is the neurohormonal crosstalk between the kidneys that leads to the abnormal response of the contralateral kidney and allows for the development and maintenance of the hypertension. Identification of these mechanisms and the specific pathways that perpetuate the hypertensive response as well lead to the renal injury may enable the development of novel therapeutic targets that may improve the outcomes of these patients.

References

1. Navar LG, et al. Unraveling the mystery of Goldblatt hypertension. News Physiol Sci. 1998;13:170–6.
2. Martinez-Maldonado M. Pathophysiology of renovascular hypertension. Hypertension. 1991;17(5):707–19.
3. Chade AR, et al. Distinct renal injury in early atherosclerosis and renovascular disease. Circulation. 2002;106(9):1165–71.
4. Kobori H, et al. The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. Pharmacol Rev. 2007;59(3):251–87.
5. Navar LG, Kobori H, Prieto-Carrasquero M. Intrarenal angiotensin II and hypertension. Curr Hypertens Rep. 2003;5(2):135–43.
6. Prieto-Carrasquero MC, et al. Enhancement of collecting duct renin in angiotensin II-dependent hypertensive rats. Hypertension. 2004;44(2):223–9.
7. Navar LG, et al. Intratubular renin-angiotensin system in hypertension. Hypertension. 2011;57(3):355–62.
8. Largo R, et al. Angiotensin-converting enzyme is upregulated in the proximal tubules of rats with intense proteinuria. Hypertension. 1999;33(2):732–9.
9. Gonzalez-Villalobos RA, et al. Intrarenal angiotensin-converting enzyme induces hypertension in response to angiotensin I infusion. J Am Soc Nephrol. 2011;22(3):449–59.
10. Navar LG, et al. Renal responses to AT1 receptor blockade. Am J Hypertens. 2000;13(1 Pt 2):45S–54.
11. Anderson WP, Kline RL, Woods RL. Systemic and renal hemodynamic changes during acute unilateral renal arterial stenosis. Am J Physiol Heart Circ Physiol. 1985;249(5):H956–67.
12. Anderson WP, Ramsey DE, Takata M. Development of hypertension from unilateral renal artery stenosis in conscious dogs. Hypertension. 1990;16(4):441–51.
13. DeForrest JM, et al. Separate renal function studies in conscious dogs with renovascular hypertension. Am J Physiol. 1978;235(4):F310–6.
14. Zimmerman BG, Mommsen C, Kraft E. Sympathetic and renin-angiotensin system influence on blood pressure and renal blood flow of two-kidney, one clip Goldblatt hypertensive dog. Hypertension. 1980;2(1):53–62.
15. Ploth DW, et al. Autoregulation and tubuloglomerular feedback in normotensive and hypertensive rats. Kidney Int. 1977;12(4):253–67.
16. Ploth DW, et al. Impaired renal blood flow and cortical pressure autoregulation in contralateral kidneys of Goldblatt hypertensive rats. Hypertension. 1981;3(1):67–74.
17. Himmelstein SI, Klotman PE. The role of thromboxane in two-kidney, one-clip Goldblatt hypertension in rats. Am J Physiol. 1989;257(2 Pt 2):F190–6.
18. Kimura G, et al. Glomerular hypertension in renovascular hypertensive patients. Kidney Int. 1991;39(5):966–72.
19. Azar S, et al. Single-nephron pressures, flows, and resistances in hypertensive kidneys with nephrosclerosis. Kidney Int. 1977;12(1):28–40.
20. Navar LG. Renal autoregulation: perspectives from whole kidney and single nephron studies. Am J Physiol. 1978;234(5):F357–70.
21. Leertouwer TC, et al. Functional effects of renal artery stent placement on treated and contralateral kidneys. Kidney Int. 2002;62(2):574–9.
22. Koivuviita N, et al. The effect of revascularization of renal artery stenosis on renal perfusion in patients with atherosclerotic renovascular disease. Nephrol Dial Transplant. 2012;27(10):3843–8.
23. La Batide-Alanore A, et al. Split renal function outcome after renal angioplasty in patients with unilateral renal artery stenosis. J Am Soc Nephrol. 2001;12(6):1235–41.

24. Kotliar C, et al. Local and systemic cellular immunity in early renal artery atherosclerosis. Clin J Am Soc Nephrol. 2012;7(2):224–30.
25. Dibona G. The functions of the renal nerves. In: Reviews of physiology, biochemistry and pharmacology, vol. 94. Berlin/Heidelberg: Springer; 1982. p. 75–181.
26. Gao SA, et al. Reduced spontaneous baroreceptor sensitivity in patients with renovascular hypertension. J Hypertens. 2002;20(1):111–6.
27. Grisk O, Rettig R. Interactions between the sympathetic nervous system and the kidneys in arterial hypertension. Cardiovasc Res. 2004;61(2):238–46.
28. Johansson M, et al. Increased sympathetic nerve activity in renovascular hypertension. Circulation. 1999;99(19):2537–42.
29. Faber JE, Brody MJ. Afferent renal nerve-dependent hypertension following acute renal artery stenosis in the conscious rat. Circ Res. 1985;57(5):676–88.
30. Kopp UC, Buckley-Bleiler RL. Impaired renorenal reflexes in two-kidney, one clip hypertensive rats. Hypertension. 1989;14(4):445–52.
31. Head GA, Burke SL. Comparison of renal sympathetic baroreflex effects of rilmenidine and alpha-methylnoradrenaline in the ventrolateral medulla of the rabbit. J Hypertens. 2000;18(9):1263–76.
32. Katholi RE, et al. Importance of the renal nerves in established two-kidney, one clip Goldblatt hypertension. Hypertension. 1982;4(3 Pt 2):166–74.
33. McElroy ND, Zimmerman BG. Characterization of intrarenal arterial adrenergic receptors in renovascular hypertension. Hypertension. 1989;13(6 Pt 2):851–8.
34. Sasser JM, Pollock JS, Pollock DM. Renal endothelin in chronic angiotensin II hypertension. Am J Physiol Regul Integr Comp Physiol. 2002;283(1):R243–8.
35. Diekmann F, et al. Regulation of the renal endothelin system in the two-kidney, one clip renal hypertensive rat. J Cardiovasc Pharmacol. 2000;36(5 Suppl 1): S191–4.
36. Kelsen S, Hall JE, Chade AR. Endothelin-A receptor blockade slows the progression of renal injury in experimental renovascular disease. Am J Physiol Renal Physiol. 2011;301(1):F218–25.
37. Hocher B, et al. ETA receptor blockade induces fibrosis of the clipped kidney in two-kidney-one-clip renovascular hypertensive rats. J Hypertens. 2000;18(12): 1807–14.
38. Kassab S, et al. Effects of endothelin-A receptor antagonism on bilateral renal function in renovascular hypertensive rats. Fundam Clin Pharmacol. 2001;15(6):379–85.
39. Lerman LO, et al. Increased oxidative stress in experimental renovascular hypertension. Hypertension. 2001; 37(2):541–6.
40. Krier JD, et al. Vascular responses in vivo to 8-epiPGF2α in normal and hypercholesterolemic pigs. Am J Physiol Regul Integr Comp Physiol. 2002;283(2):R303–8.
41. Wilcox CS. Oxidative stress and nitric oxide deficiency in the kidney: a critical link to hypertension? Am J Physiol Regul Integr Comp Physiol. 2005; 289(4):R913–35.
42. Wilcox CS, Cardozo J, Welch WJ. AT1 and TxA2/PGH2 receptors maintain hypertension throughout 2K,1C Goldblatt hypertension in the rat. Am J Physiol Regul Integr Comp Physiol. 1996;271(4):R891–6.
43. Ruilope L, et al. Effect of furosemide on renal function in the stenotic and contralateral kidneys of patients with renovascular hypertension. Hypertension. 1983;5(6 Pt 3): V43–7.
44. Imanishi M, et al. Prostaglandin I(2)/E(2) ratios in unilateral renovascular hypertension of different severities. Hypertension. 2001;38(1):23–9.
45. Milot A, et al. Prostaglandins and renal function in hypertensive patients with unilateral renal artery stenosis and patients with essential hypertension. J Hypertens. 1996;14(6):765–71.
46. Kalaitzis C, et al. Role of eicosanoids of the contralateral kidney in maintenance of two-kidney, one-clip renovascular hypertension in rats. Scand J Urol Nephrol. 2007;41(5):362–6.
47. Tokuyama H, et al. Stenosis-dependent role of nitric oxide and prostaglandins in chronic renal ischemia. Am J Physiol Renal Physiol. 2002;282(5):F859–65.
48. Fujino T, et al. Decreased susceptibility to renovascular hypertension in mice lacking the prostaglandin I2 receptor IP. J Clin Invest. 2004;114(6):805–12.
49. Sigmon DH, Beierwaltes WH. Renal nitric oxide and angiotensin II interaction in renovascular hypertension. Hypertension. 1993;22(2):237–42.
50. Sigmon DH, Beierwaltes WH. Influence of nitric oxide in the chronic phase of two-kidney, one clip renovascular hypertension. Hypertension. 1998;31(2):649–56.
51. Sigmon DH, Beierwaltes WH. Degree of renal artery stenosis alters nitric oxide regulation of renal hemodynamics. J Am Soc Nephrol. 1994;5(6):1369–77.
52. Palm F, et al. Angiotensin II type 2 receptors and nitric oxide sustain oxygenation in the clipped kidney of early Goldblatt hypertensive rats. Hypertension. 2008;51(2):345–51.
53. Wierema TK, et al. Nitric oxide dependence of renal blood flow in patients with renal artery stenosis. J Am Soc Nephrol. 2001;12(9):1836–43.
54. Turkstra E, et al. Increased availability of nitric oxide leads to enhanced nitric oxide dependency of tubuloglomerular feedback in the contralateral kidney of rats with 2-kidney, 1-clip Goldblatt hypertension. Hypertension. 1999;34(4):679–84.
55. Zhu XY, et al. The chemokine monocyte chemoattractant protein-1 contributes to renal dysfunction in swine renovascular hypertension. J Hypertens. 2009;27(10):2063–73.
56. Sanchez-Elsner T, et al. Synergistic cooperation between hypoxia and transforming growth factor-beta pathways on human vascular endothelial growth factor gene expression. J Biol Chem. 2001;276(42):38527–35.
57. Textor SC, Lerman L. Renovascular hypertension and ischemic nephropathy. Am J Hypertens. 2010;23(11): 1159–69.
58. Warner GM, et al. Genetic deficiency of Smad3 protects the kidneys from atrophy and interstitial fibrosis in 2K1C hypertension. Am J Physiol Renal Physiol. 2012;302(11):F1455–64.

59. Lerman LO, Textor SC, Grande JP. Mechanisms of tissue injury in renal artery stenosis: ischemia and beyond. Prog Cardiovasc Dis. 2009;52(3):196–203.
60. Wolf G, et al. Regulation of glomerular TGF-beta expression in the contralateral kidney of two-kidney, one-clip hypertensive rats. J Am Soc Nephrol. 1998;9(5):763–72.
61. Cheng J, et al. Temporal analysis of signaling pathways activated in a murine model of two-kidney, one-clip hypertension. Am J Physiol Renal Physiol. 2009; 297(4):F1055–68.
62. Haase VH. Pathophysiological consequences of HIF activation: HIF as a modulator of fibrosis. Ann N Y Acad Sci. 2009;1177:57–65.
63. Chade AR, et al. Simvastatin promotes angiogenesis and prevents microvascular remodeling in chronic renal ischemia. FASEB J. 2006;20(10):1706–8.
64. Kyriakis JM, Avruch J. Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation. Physiol Rev. 2001;81(2):807–69.
65. Chin BY, et al. Stimulation of pro-alpha(1)(I) collagen by TGF-beta(1) in mesangial cells: role of the p38 MAPK pathway. Am J Physiol Renal Physiol. 2001; 280(3):F495–504.
66. Eirin A, et al. Inflammatory and injury signals released from the post-stenotic human kidney. Eur Heart J. 2012;6:6.
67. Chade AR, et al. Pathways of renal fibrosis and modulation of matrix turnover in experimental hypercholesterolemia. Hypertension. 2005;46(4):772–9.
68. Truong LD, et al. Experimental chronic renal ischemia: morphologic and immunologic studies. Kidney Int. 1992;41(6):1676–89.
69. Makino H, Sugiyama H, Kashihara N. Apoptosis and extracellular matrix-cell interactions in kidney disease. Kidney Int Suppl. 2000;77:S67–75.
70. Mai M, et al. Early interstitial changes in hypertension-induced renal injury. Hypertension. 1993;22(5): 754–65.

Part III

Diagnostic Evaluation: Imaging and Physiologic Studies

Renal Artery Duplex Ultrasonography

12

Ido Weinberg and Michael R. Jaff

Abstract

Renal artery duplex ultrasonography (RADUS) is a non-invasive, safe, inexpensive and accurate method for assessing the renal arteries. Common uses for RADUS include diagnosis of renal artery stenosis (RAS) in patients with clinical clues suggestive of the disease; surveillance of patients with known native or transplant artery RAS; following renal artery stent revascularization; and for corroboration after suspicious findings are found by other imaging modalities. The RADUS examination includes spectral Doppler velocities obtained from the abdominal aorta at the level of the renal arteries, throughout the entire renal artery, and in the renal parenchyma. It is noteworthy that as the kidneys are located in the retroperitoneum, imaging of native renal arteries with RADUS requires a high degree of technical skill and extensive training. Due to this and several other inherent limitations, use of other imaging modalities should be considered to corroborate RADUS findings prior to intervention.

Keywords

Renal artery stenosis • Renal artery duplex ultrasonography • Renal to aortic ratio • Renal resistive index • Renal artery stent revascularization

Introduction

Renal artery stenosis (RAS) is common and most often caused by aortic atherosclerosis which extends into the artery ostium. It is most prevalent in at-risk populations, such as patients with poorly controlled hypertension (HTN) [1] or among patients with coronary [2] and/or peripheral artery disease (PAD), where it has been found in up to 59 % of patients [3]. Potential clinical consequences of RAS include difficult to control hypertension, progressive renal

I. Weinberg, MD, MSc (✉)
Division of Cardiology, Department of Medicine, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA
e-mail: iweinberg@partners.org

M.R. Jaff, DO
Massachusetts General Hospital Institute for Heart, Vascular, and Stroke Care, Massachusetts General Hospital, 55 Fruit Street, Warren 905, Boston, MA 02114, USA
e-mail: mjaff@partners.org

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_12,

dysfunction and cardiac disturbance syndromes (recurrent congestive heart failure, refractory angina and "flash" pulmonary edema) [4, 5].

Multiple diagnostic tools are at a clinician's disposal when RAS is suspected. However, none surpasses an initial high index of suspicion based on a series of clinical "clues." A clinical algorithm has resulted in sensitivity and specificity of 65 % and 87 %, respectively when compared to nuclear renal scintigraphy before and after an angiotensin converting enzyme inhibitor was administered [6]. However, radionucleotide studies often are difficult to interpret in patients with chronic kidney disease, and the technique cannot be used to identify RAS reliably if the patient has bilateral disease or if only one kidney is present. Furthermore, accuracy has not been consistent among studies [7]. Plasma renin activity in it of itself, even with captopril stimulation, has poor accuracy due to overlap in patients with primary HTN [8].

Modern non-invasive methods include renal artery duplex ultrasonography (RADUS), computed tomography angiography (CTA) and magnetic resonance angiography (MRA), while invasive methods consist of contrast angiography (CA), intravascular ultrasound and translesional pressure measurements [9]. This chapter will concentrate on the role of RADUS.

Common uses for RADUS include screening for RAS, surveillance of patients with native artery RAS or after renal artery stent revascularization, and for corroboration after suspicious findings are found by other imaging modalities [10]. Recently published "appropriate use criteria" suggest that RADUS is reasonable to consider when evaluating patients with HTN that is resistant, malignant, difficult to control or present in patients younger than 35 years; unexplained increase in creatinine or renal failure in conjunction with aortic dissection and in patients with either HTN or elevated creatinine and unexplained size difference >1.5 cm between kidneys or an epigastric bruit [11]. Interestingly, these same criteria suggest that RADUS was inappropriate to use as a screening tool in asymptomatic patients with atherosclerosis in other vascular beds. Choosing RADUS over other modalities should include consideration of its various advantages and disadvantages as outlined in Table 12.1.

Table 12.1 Advantages and disadvantages of renal artery duplex ultrasound for detecting renal artery stenosis

Characteristic	Comments
Advantages	
Accurate when compared to other modalities	-see text-
Reproducible	
No radiation or contrast	
Suitable for patients with claustrophobia	
Inexpensive	
Disadvantages	
Requires high technical skill	Data cannot be obtained in as many as 20 % of patients [12]
Time consuming	Routinely, a complete bilateral exam may take as much as 1.5 h, especially in inexperienced hands
Divides RAS into broad categories	Currently RADUS criteria do not offer a finer differentiation than normal, 1–59 %, 60–99 % stenosis or renal artery occlusion
Inferior imaging of the distal renal artery	
Difficult to visualize accessory renal arteries	
Cannot image multiple vascular beds at once	A disadvantage particularly when trying to ascertain the etiology of RAS [13]
Focused on the kidneys and may miss extra-renal ancillary findings	
Limited in assessing renal artery pathology, other than atherosclerotic disease	Examples include dissection, segmental arterial mediolysis, vasculitis. Beading characteristic of medial fibroplasias type of the fibromuscular dysplasia can sometimes be seen
Difficult to use in obese patients	
Limited by overlying bowel gas	
Limited in patients who are tachypneic	Excessive movement of the renal arteries

RAS renal artery stenosis, *RADUS* renal artery duplex ultrasonography

Renal Artery Duplex Ultrasonography as an Epidemiological Tool

Although some small studies attempted to define the natural history of atherosclerotic RAS (ARAS) with a combination of CA and clinical surveillance, results have been heterogeneous [14]. Subsequently, similar attempts have been made with RADUS. Interpreting these studies should take into account the specific subjects studied as well as the exact manner by which events were defined. In an unselected sample of 750 Japanese patients with coronary, cerebrovascular or peripheral artery disease, ARAS was found in 40 by RADUS criteria and later confirmed by CA in 35 people [15]. Noting small numbers, subgroup analysis revealed ARAS to be most prevalent in patients with carotid and peripheral artery disease (20 %). Renal artery stenosis epidemiology has been studied further in the Cardiovascular Health Study, a longitudinal, population based cohort study of elderly outpatients [14, 16]. In 834 people in whom RAS ≥ 60 % was defined by peak systolic velocity (PSV) ≥ 180 cm/s, the prevalence was 6.8 % [16]. Prevalence of coronary artery disease was greater in patients with evidence of ARAS [17]. Follow up in 119 subjects 8 years later revealed that none of the patients previously diagnosed with ARAS progressed to renal artery occlusion and that new RAS was found in 9 of the 235 analyzed renal arteries [14]. Disease progression, defined as an increase in PSV greater than 2 standard deviations in the cohort (≥45 cm/s), occurred in 29 renal arteries. In another study that examined ARAS in 170 hypertensive patients, RAS progression was defined as an increase in PSV > 100 cm/s and occurred in 31 % over 5 years [18]. In another study 76 patients were prospectively followed over 3 years and anatomic progression was found in 20 % [19]. However, in this study RAS ≥ 60 % was defined by a combination of PSV ≥ 180 cm/s and RAR > 3.5. Thus, patients who had PSV ≥ 180 cm/s at the beginning of the study, but did not meet the RAR criterion, were not defined as having significant RAS. It is noteworthy that this study also reported 7 % of subjects progressed to occlusion.

Technique for Performance of Renal Artery Duplex Ultrasonography

As the kidneys are located in the retroperitoneum, imaging of native renal arteries with RADUS requires a high degree of technical skill and extensive training. In our vascular diagnostic laboratory, we have the following requirements for a technologist to perform RADUS independently:

- Hold the Registered Vascular Technologist (RVT) certification
- Observe 50 RADUS examinations by a trained and experienced colleague
- Attend an off-site 2-week hands-on training course specific to RADUS
- Perform 50 sequential RADUS exams under direct observation by a trained and experienced colleague
- Maintain documented ongoing proficiency in our regular quality assurance program

The RADUS examination includes spectral Doppler velocities obtained from the abdominal aorta at the level of the renal arteries, throughout the entire renal artery, and in the renal parenchyma [20]. The vascular testing division of the Intersocietal Accreditation Commission (ICAVL) has specified the minimum requirements for a complete RADUS examination (Table 12.2). Ideally, RADUS should be performed in the early morning hours after the patient has completed an overnight fast in order to minimize bowel gas overlying the renal arteries. Imaging is achieved from two approaches. First the aorta and renal arteries are interrogated from the supine, midline approach with the patient in the reverse Trendelenburg position. Subsequently, the patient is turned into the lateral decubitus position with the arm raised over the head in order to increase the imaging zone in the intercostal or subcostal space (Fig. 12.1a, b). In our vascular laboratory, we require that the entire renal artery from the ostium through the hilum of the kidney to be imaged and sampled in order to qualify as

Table 12.2 The vascular testing arm of the Intersocietal Accreditation Commission Guidelines for native renal artery duplex ultrasonography

Gray scale and/or color Doppler images must be documented as required by the protocol and must include at a minimum[a]:
Adjacent aorta at the level of the renal arteries
Renal arteries
Renal veins
Gray scale pole to pole renal length measurements
Spectral Doppler waveforms and velocity measurements must be documented as required by the protocol and must include at a minimum[a]:
Adjacent aorta at the level of the renal arteries
Proximal, mid and distal main renal artery
Parenchymal/hilar arteries (when appropriate)
Accessory renal artery (when present)
Renal veins, when appropriate (does not require velocity measurements)

Data from American College of Cardiology Foundation et al. [11]
[a]Measurements should be bilateral (when two kidneys are present)

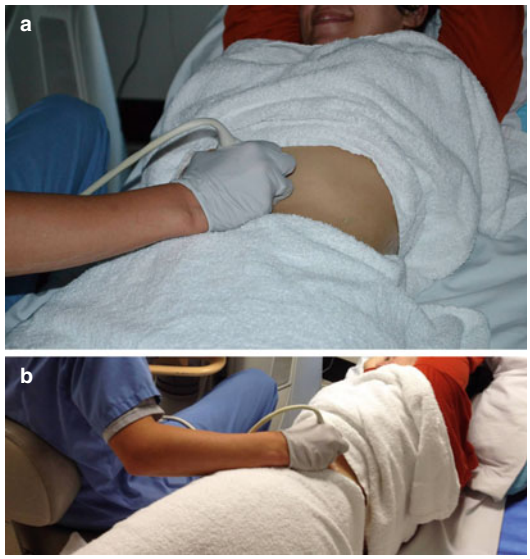


Fig. 12.1 (**a**, **b**) Renal artery duplex ultrasound patient and technologist positioning. (**a**) Midline approach. (**b**) Left flank approach. This is also replicated from the right

a complete examination. Interrogation of a transplanted renal artery and its related anastomosis to the inflow iliac artery is easier as it is typically more superficial.

A RADUS requires imaging equipment that includes low frequency (typically 2.25- to 4.0-MHz) curved linear- or phased array transducers. A vascular software package is also needed [20]. The examination begins with identification of the aorta in the sagittal plane throughout its length, assessing for an aneurysm or atherosclerosis while the patient is in the supine position. At the level of the renal arteries, the PSV is measured. The normal abdominal aortic PSV ranges from 40 to 100 cm/s. Next, the probe is rotated 90°, and each renal artery origin is located in the transverse plane (Fig. 12.2). The angle of insonation is maintained at 60° or less while imaging parallel to the direction of renal artery blood flow. Doppler spectral waveforms are obtained. The PSV is obtained in both renal arteries from the aortic origin to renal hilum. The presence of post-stenotic turbulence identified as the presence of as a chaotic Doppler spectral waveform with blunting of the peak of the waveform, should also be noted [21] (Fig. 12.3). This process is repeated from the flank approach (Fig. 12.4). A complete RADUS includes imaging of the kidney including maximal pole-to-pole renal length, demonstration of cortical, medullary and hilar blood flow and identification of associated findings such as cysts or masses (Figs. 12.5 and 12.6). Intrarenal sampling is performed at a 0° Doppler angle in the superior and inferior pole of the kidney, within the cortex and medulla.

Table 12.3 outlines common technical and interpretation errors in RADUS.

Native Renal Artery Duplex Ultrasonography

In a normal kidney, arterial flow is low resistance, demonstrating continuous flow during systole and diastole [22]. The two most common measures for assessing RAS are PSV and the ratio of the PSV as measured in the renal artery origin and the PSV in the aorta at the level of the renal artery, referred to as the renal aortic ratio (RAR). The RAR cannot be used when significant aortic disease is present (PSV > 100 cm/s) or

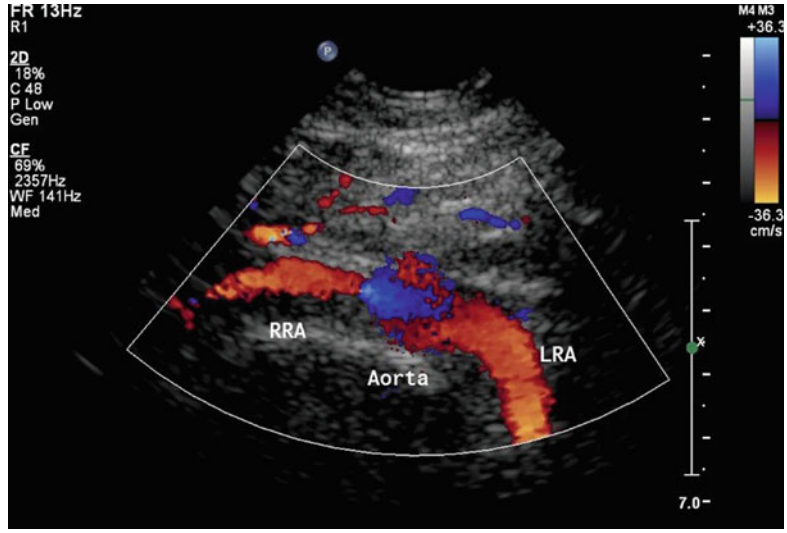


Fig. 12.2 Color flow renal artery duplex ultrasound from the midline approach demonstrating the aorta in transverse plane and the two renal arteries. *RRA* Right renal artery, *LRA* left renal artery

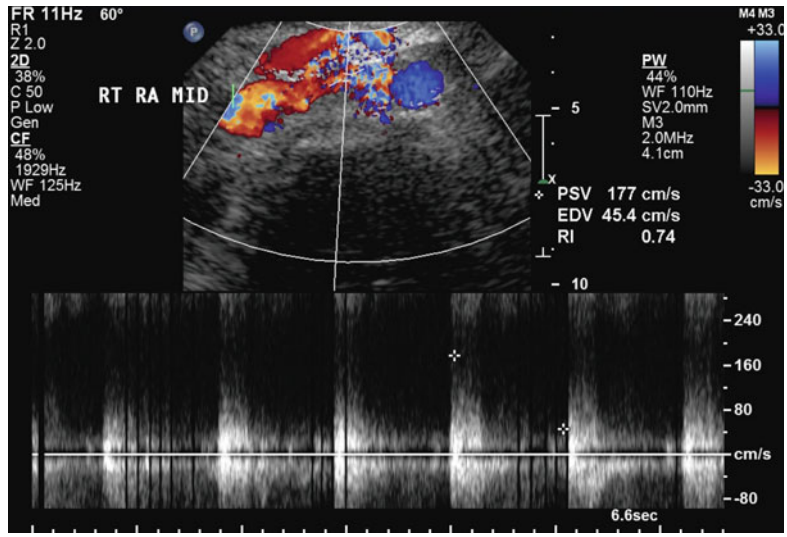


Fig. 12.3 Pulse wave Doppler and color flow renal artery duplex ultrasound demonstrating turbulent flow in the mid-distal renal artery. This suggests more proximal stenosis

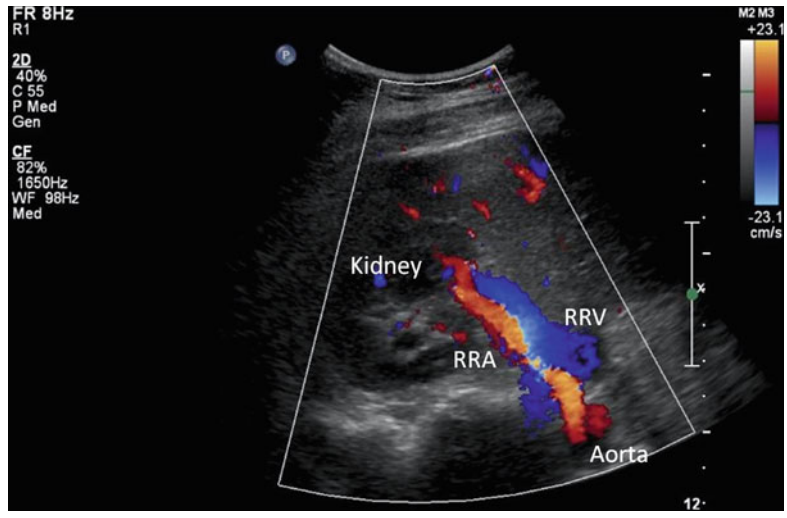


Fig. 12.4 Color flow renal artery duplex ultrasound from the right flank approach demonstrating the right renal artery (*RRA*) course from the renal hilum to the aorta. Notice the right renal vein (*RRV*)

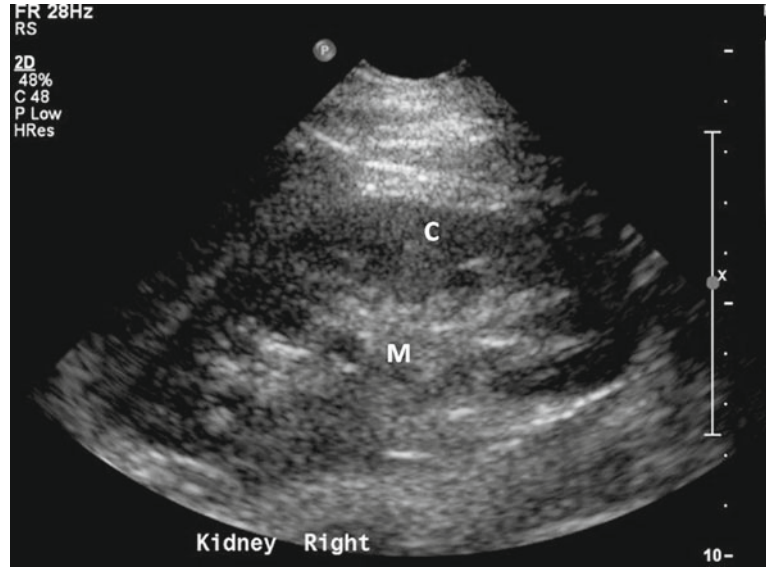


Fig. 12.5 A B-mode image of the right kidney from the flank approach demonstrating maximal pole-to-pole length and cortical thickness. Note the cortex (*C*) and medulla (*M*)

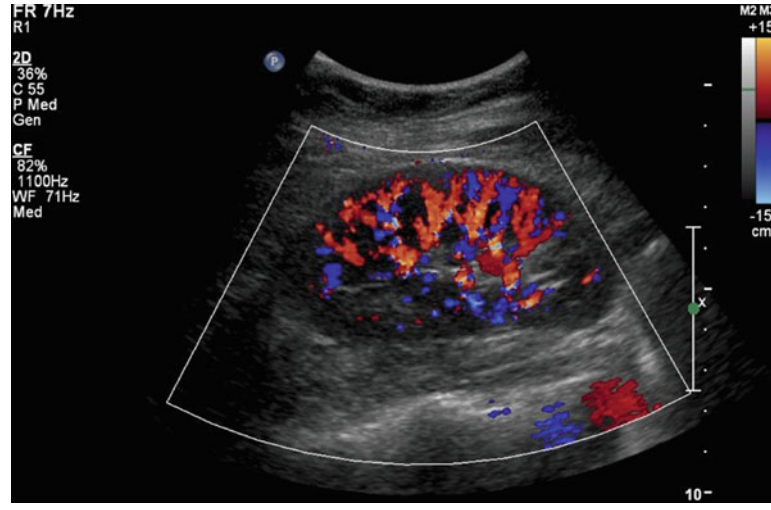


Fig. 12.6 Color flow image of cortical and medullary blood flow in the right kidney from the flank approach

Table 12.3 Common errors in renal artery duplex ultrasonography performance and interpretation

Mistake	Effect of the mistake	Ways to avoid the mistake
Measuring velocities with an incorrect Doppler angle	Erroneous velocity and therefore erroneous conclusions about the degree of stenosis	The Doppler angle should ideally be $\leq 60^{\circ}$ and parallel to the artery walls. A long enough segment of the artery should be available for interrogation
Interrogation of a different artery and mistakenly referring to this as the renal artery (lumbar, mesenteric)	Incorrect conclusions of the patency of the renal artery	It is best to identify each artery and to follow it to the kidney before starting to register flow velocities; look for the normal renal artery Doppler spectral image

Table 12.3 (continued)

Mistake	Effect of the mistake	Ways to avoid the mistake
Missing accessory renal arteries	The main renal artery may be patent, but a smaller accessory renal artery may be stenotic and result in renin-mediated hypertension	An excellent renal artery duplex ultrasound should include identification of the renal arteries but also of adjacent vessels. An attempt should be made to follow such arteries from the aorta to the kidney; in addition, imaging of the superior and inferior poles of the kidney may demonstrate differences in the RRI or spectral Doppler waveform, suggestive of an accessory renal artery
Missing the ostium of the renal artery by "spot checking" the artery	The measurement may not reflect the actual renal artery ostial velocity and significant renal artery stenosis may be missed	The probe should be "walked" from the aorta into the renal artery and then back into the aorta. The ostium is the location where atherosclerotic RAS occurs
Reporting an abnormal RAR	Misclassification of renal artery stenosis	A RAR can only be used if the flow velocity in the aorta at the level of the renal artery ranges 40–100 cm/s
Using criteria for native renal arteries on stented renal arteries	Misclassification of renal artery stenosis	The criteria for stented renal arteries are different than those for native arteries
Mistaking calcifications for a stent	Misclassification of renal artery stenosis and confusion regarding patient treatment and surveillance	Calcifications may be symmetrical and linear and may be mistaken for a stent. Patient history should be reviewed prior to performing the RADUS
Missing findings outside of the renal artery	Cysts and tumors may be overlooked. The appearance of the kidney and especially the cortex may suggest kidney viability	Kidney visualization should be part of an excellent renal artery duplex ultrasound. Abnormal findings should be documented
Reporting an incorrect renal resistive index	Reassurance of the status of the ipsilateral kidney	Perform Doppler angle independent assessment in the medullary branches of the kidney in the superior and inferior pole

PW pulse wave, *RAR* renal aortic ratio

in within an abdominal aortic aneurysm (PSV < 40 cm/s) [23].

Multiple studies have validated RADUS criteria for RAS, most often by comparison to CA as the "gold standard" (Table 12.4). Most have shown RADUS to have excellent sensitivity and specificity, most commonly reported to be above 80 %. An early retrospective analysis of 122 kidneys with single main renal arteries in 74 patients showed RADUS to have 93 % sensitivity, 98 % specificity, 98 % positive predictive value, 94 % negative predictive value, and an overall accuracy of 96 % as compared to CA [21]. The criteria that are most commonly used in clinical practice have been derived from a prospective, blinded study, in which 102 patients who were clinically suspected of having RAS underwent both RADUS and CA within 30 days of each other [44]. Using a PSV of ≥200 cm/s or a RAR of ≥3.5 resulted in sensitivity of 98 %; specificity 99 %; positive predictive value 99 %; and negative predictive value 97 %. Another retrospective comparison utilized the more accurate quantitative vessel analysis (QVA) method in 67 renal arteries, 34 of which demonstrated RAS ≥ 60 % [12]. Both PSV and RAR correlated with RAS; however, RAR was found to be more accurate by ROC curve analysis. More recently, several comparisons of RADUS derived criteria and estimated RAS as assessed by invasive translesional pressure gradients were performed. This method is considered to be more accurate in detecting hemodynamically significant RAS than visual estimation of degree of stenosis [53]. A first such study was performed in 75 renal arteries in 60 patients [25]. Renal artery DUS derived PSV demonstrated a sensitivity, specificity and accuracy of 89 %, higher than values derived for

Table 12.4 Summary of studies defining and validating duplex ultrasound criteria for native renal artery stenosis

Source	Year	Number of patients	Examined parameters				Criteria for RAS ≥ 60 %	Test performance		Comments
			PSV	RAR	AT	Ac		Sensitivity (%)	Specificity (%)	
AbuRahma et al. [24]	2012	313	X	X			PSV ≥ 285 cm/s; RAR ≥ 3.7	PSV – 67 RAR – 72	PSV – 90 RAR – 81	Analyzed for multiple cutoffs. RAR was just as good as PSV
Drieghe et al. [12]	2008	47	X	X			PSV > 200; RAR > 3.5	PSV – 100 RAR – 80	PSV – 31 RAR – 78	% Stenosis was assessed with pressure measurements
Kawarada et al. [25]	2006	60	X				PSV > 219 cm/s	89	89	Comparison to translesional pressure gradient >20 mmHg which corresponded with >50 % stenosis
Conkbayir et al. [26]	2003	50	X	X			Combination of PSV > 180–200 cm/s and RAR > 3.0	92	88	Both PSV values were found to be equally accurate when combined with RAR > 3.0
Nchimi et al. [27]	2003	91	X	X			PSV > 180 cm/s or RAR > 3.5	91	97	
de Haan et al. [28]	2002	78	X	X			Combination of PSV >180 cm/s and RAR >3.5	50	91.3	These authors could not show good test characteristics for RADUS compared with CA
Ripolles et al. [29]	2001	65			X	X	AT > 80 ms and Ac ≤ 1 m/s^2	89	99	Assessed for RAS > 75 %
Voiculescu et al. [30]	2001	36	X				PSV > 200 cm/s	96	89	Side-to-side RI difference was also studied
Claudon et al. [31]	2000	122	X	X			Combination of PSV cutoff of 140–200 cm/s and RAR cutoff of 3–3.5	80	80.8	An average of several centers was reported
Hua et al. [32]	2000	58	X	X	X	X	PSV ≥ 200 cm/s; RAR ≥ 3.5	PSV-91 RAR-72	PSV-75 RAR-92	Acceleration time >100 ms was less accurate
Motew et al. [33]	2000	41	X				PSV ≥ 200 cm/s	91	96	Hillar measurements did not add to the accuracy
Radermacher et al. [34]	2000	226	X		X		Combination of PSV > 180 cm/s or AT > 70 ms	96.7	98	Also utilized post-stenotic turbulence; Assessed for RAS >50 %

Souza de Oliveira et al. [35]	2000	50	X	X			PSV > 150 cm/s; RAR > 3.5	83.3	89.5	Results are for PSV, that trumped RAR
House et al. [36]	1999	63	X	X	X		PSV > 180 cm/s; RAR > 3; AT > 70 ms	85	76	A combination of PSV and RAR provided the best results as presented
Kaplan-Pavlovcic and Nadja [37]	1998	28	X	X			Combination of PSV > 180 cm/s and RAR > 3.5	83	81	
Mollo et al. [38]	1997	53	X		X		PSV > 150 cm/s; AT > 50 ms	75	100	PSV criteria detected RAS >50 %; AT was not sufficient for the diagnosis
Baxter et al. [39]	1996	73			X		AT > 120 ms	70	90	Detected RAS >70 %; RI did not differ between stenotic and non-stenotic kidneys
Burdick et al. [40]	1996	73			X	X	AT > 60 ms; Ac < 7.4 m/s^2	N/A	N/A	Compared with RAS >50 %
Miralles et al. [41]	1996	78	X	X			PSV > 198 cm/s; RAR > 3.3	PSV – 87.3 RAR – 76.4	PSV – 91.5 RAR – 92.4	RAR did not add to PSV
Miralles et al. [41]	1996	78	X	X			PSV > 198 cm/s; RAR > 3.3	PSV – 87.3	PSV – 91.5	RAR did not add to the diagnostic utility of RADUS
Missouris [42]	1996	21				X	Ac < 3.5 m/s^2	85	79	Values were improved by using contrast enhanced DUS
Helenon et al. [43].	1995	94	X				PSV ≥ 150 cm/s	89	99	PSV was combined with waveform analysis. The proximal renal artery could not be detected in 25 % of cases
Olin et al. [44]	1995	102	X	X			PSV ≥ 200 cm/s; RAR ≥ 3.5	98	99	EDV ≥ 150 cm/s was also claimed to be diagnostic for significant RAS, but disputed [45]
Kliewer et al. [46]	1993	57	X		X	X	PSV > 100 cm/s; AT > 70 ms; Ac ≤ 3 m/s^2			Only AT and Ac could differentiate between stenotic and non-stenotic renal arteries ($p<0.05$)

(continued)

Table 12.4 (continued)

Source	Year	Number of patients	Examined parameters				Criteria for RAS ≥ 60 %	Test performance		Comments
			PSV	RAR	AT	Ac		Sensitivity (%)	Specificity (%)	
Stavros et al. [47]	1992	56			X	X	AT > 70 ms; Ac < 3 m/s^2	N/A	N/A	
Antonica et al. [48]	1991	111	X		X	X	PSV > 130 cm/s or AT > 100 ms or Ac < 2.5 m/s^2	95	97	Limited discussion of the analysis that resulted in these parameters
Hoffmann et al. [49]	1991	41	X	X			PSV > 180 cm/s; RAR > 3.5	PSV – 95 RAR – 92	PSV – 90	Specificity was only 62 % for RAR
Hansen et al. [21]	1990	74		X			RAR ≥ 3.5	93	98	Prospective validation of criteria; RAR was combined with distal renal artery turbulence
Hawkins et al. [50]	1989	80		X			RAR ≥ 3.5	87		It is unclear what the degree of RAS was
Taylor et al. [51]	1988	29		X			RAR > 3.5	84	97	Prospective
Avasthi et al. [52]	1984	26	X				PSV > 100 cm/s	89	73	Presence of turbulent flow complemented the diagnosis

Table 12.5 Suggested renal artery duplex ultrasound criteria for renal artery stenosis

PSV[a]	RAR	Other findings	Interpretation
Native renal artery			
<200 cm/s	<3.5		Normal
<200 cm/s	<3.5	Post-stenotic turbulent flow, visible plaque	1–59 %
>200 cm/s	>3.5	Post-stenotic turbulence, visible plaque	60–99 %
No flow detected		Patent ipsilateral renal vein	Occluded
Stented renal artery[b]			
<240 cm/s			1–59 %
240–300 cm/s		Indirect findings must be used, including color evidence of in stent restenosis, color mosaic appearance within the stent, post-stenotic turbulence distal to the stent, and (if available), progression from a prior exam	Indeterminate
>300 cm/s			60–99 %
No flow detected			Occluded

PSV peak systolic velocity, *RAR* renal aortic ratio
[a]When there is discrepancy, absolute peak systolic velocity with post-stenotic turbulence is more important than RAR
[b]Different laboratories should standardize their criteria for stented renal arteries according to other imaging modalities locally

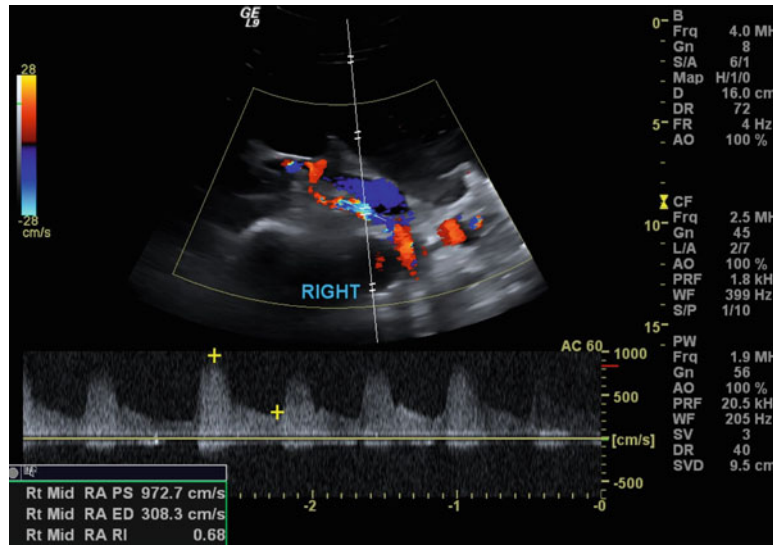


Fig. 12.7 Pulse wave Doppler measurements of flow velocity within the renal artery demonstrating marked increase in flow velocity denoting renal artery stenosis

the RAR. A second comparison was performed in 56 renal arteries in 47 patients [12]. Analysis by receiver operator characteristic (ROC) curves showed that PSV > 318 cm/s, end-diastolic velocity >73 cm/s and RAR > 3.74 best corresponded to CA proven RAS > 50 %, while commonly accepted criteria (Table 12.5) resulted in false positive results, especially when compared to pressures gradients. A RADUS demonstrating RAS can be seen in Fig. 12.7. Renal artery occlusion, on the other hand, is diagnosed by lack of arterial flow coupled by flow detected in the ipsilateral renal vein.

The renal resistive index (RRI) is another measure obtained during a complete RADUS examination. This is an ultrasound-derived technique designed to evaluate the status of parenchymal renal arterial perfusion. Peak systolic velocity and end-diastolic velocity (EDV) obtained in branches of the renal artery at the level of the medulla are used to calculate the RRI [20]. It is an angle independent measurement obtained in both the

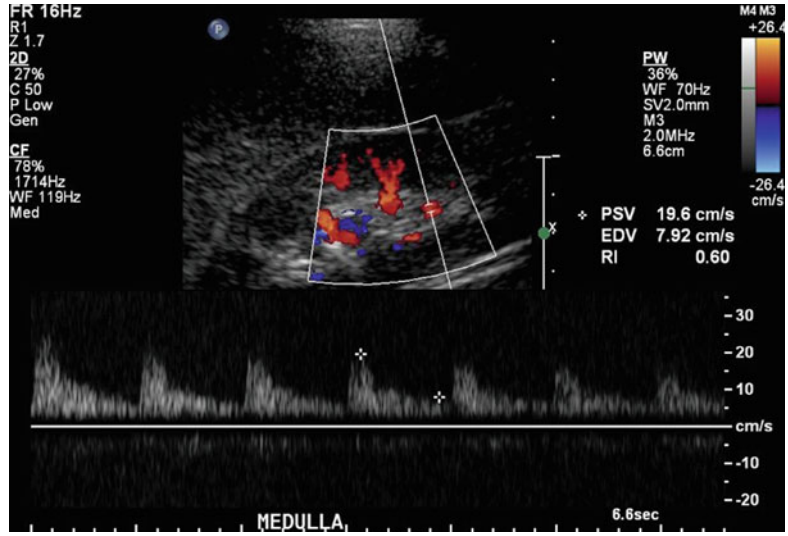


Fig. 12.8 Pulse wave Doppler measurements of flow velocity within the renal medulla and resistive index (*RI*) measurement

superior and inferior poles of the kidney. The resistive index is calculated by the following equation:

$$\left[1-\left(\frac{EDV}{PSV}\right)\right]\times 100$$

Thus, a lower RRI will theoretically suggest a "healthier" kidney (Fig. 12.8). Furthermore, according to one study, a RRI < 0.8 may suggest better clinical outcomes following renal revascularization [54], although this has been challenged by more recent publications [55]. Surprisingly, in two studies collectively examining 286 patients, the RRI was significantly lower in kidneys with RAS than in normal renal arteries [56, 57]. However, the RRI has questionable reliability. First, small measurement errors can result in significant changes in the calculated RRI. Also, conditions other than renal artery disease may affect the RRI. Examples include obstructive uropathy, hypotension, bradycardia and a peri-nephric fluid collection [22]. The RRI may have more utility in surveillance of transplanted kidneys [58].

Another approach is to calculate the difference in RRI between the two kidneys (ΔRRI). In a comparison of 40 CA proven normal renal arteries with 29 renal arteries with varying degrees of RAS, a ΔRRI > 0.05 was found to correlate with RAS > 50 % [57]. Another study comparing ΔRRI between 59 patients with RAS > 70 % and 155 patients with normal renal arteries also reported the ΔRRI to be significantly higher in patients with RAS [56]. All patients were hypertensive. A ΔRRI of 0.08 produced sensitivity of 92.5 % and specificity 97.5 % in a ROC curve analysis.

Other alternatives to PSV and RAR have been suggested. One such alternative is the acceleration time (AT), obtained from spectral analysis of Doppler waveforms from renal hilar vessels by means of a flank approach. The AT is a measure of waveform dampening. Theoretically, a longer AT points to a dampened waveform resulting from a more proximal stenosis. There are data to suggest that significant changes in renal artery waveform contour only occur with very severe stenosis [46]. Most studies have found AT to be useful in the detection of RAS (Table 12.4). Conversely, in a retrospective analysis of 76 kidneys in 41 patients, 51 of which had CA proven RAS > 60 %, hilar flow analysis has been reported to have lower sensitivity and accuracy as compared to conventional RADUS criteria [33].

Contrast enhanced DUS is another method that has been attempted with the purpose of simplifying the RADUS exam. Several seconds after injection of a contrast agent, it ultrasonographically enhances the arterial circulation for several minutes. Theoretically this should result in easier localization of the renal arteries and quicker acquisition of measurements. In a prospective comparison of conventional RADUS, contrast

enhanced RADUS and CA in 21 hypertensive patients, examination time was shorter and sensitivity and specificity were improved for Acceleration <3.75 m/s^2 when contrast was used [42]. In this context, acceleration referred to the slope of the line between the start of systole to the early systolic peak.

Other duplex derived methods for the diagnosis of RAS including the pulsatility index [59] and waveform analysis from the main renal artery [47, 60] have not proven to be useful clinically. Indirect imaging of the distal main renal artery or parenchymal branches, demonstrating a parvus et tardus waveform, is used by some as a criterion for a proximal stenosis. However, the accuracy of this method as a single data point is inferior to direct imaging of the main renal artery [39].

Recently several novel ultrasound-derived criteria have been reported. Power Doppler generates a color map that reflects the cumulative density of red blood cells within an examined volume of arterial blood. In a small study of nine patients power Doppler was found to be more sensitive and specific for RAS than conventional Doppler [61]. B-flow imaging (BFI) is a non-Doppler ultrasound technology that utilizes high frequency digital encoded sound waves to generate a real-time picture of blood flow in a display that resembles an angiogram [62]. In a comparison of BFI and RADUS in 51 patients with angiographically proven RAS > 50 %, the two techniques performed similarly. Sensitivity and specificity for BFI and PSV were 88 and 94 % and 100 and 71 %, respectively. Seven renal arteries were excluded because of excessive abdominal gas. Velocimetric waveform analysis is another technique that allows calculation of maximal acceleration (ACC_{max}) within early systole and the maximal acceleration index ($AI_{max} = ACC_{max}/PSV$). Saeed et al. retrospectively examined the utility of these measures in 169 patients who underwent both angiography and duplex ultrasonography and found sensitivity and specificity for ACC_{max} to be 85 and 75 %, respectively and for AI_{max} 83 and 79 %, respectively [63]. No direct comparison was made with PSV or RAR. Until larger prospective validation studies have been completed, we routinely use renal artery PSV and RAR as our main criteria for detecting RAS.

It should be noted that despite widespread clinical use of RADUS criteria that rely on these studies, they all suffer from the well-recognized limitation of verification bias. These studies have performed the comparison study (i.e., CA) based on the result of RADUS. When the reference standard procedure depends on the investigated test, a reliable estimate of diagnostic accuracy is precluded. Theoretically, to obtain valid accuracy estimates of RADUS criteria, all subjects should undergo both RADUS and CA regardless of preliminary RADUS results [64].

Another important note is the considerable variability between studies for similar measures (Table 12.4). This could theoretically be explained by variations in operator experience between studies; however, there are no data to support this hypothesis. Notwithstanding, in a meta-analysis the PSV was the most accurate parameter with sensitivity and specificity of 85 and 92 %, respectively [7].

Finally, RADUS has also demonstrated accuracy in the diagnosis and surveillance of renal artery fibromuscular dysplasia (FMD), albeit in a small series. It may identify the typical beaded appearance of the medial fibroplasia variant and suggest mid or distal artery involvement by PSV measurements [65, 66].

Ultrasound Surveillance Criteria Following Renal Artery Stent Revascularization

When discussing stented (as opposed to native) renal artery DUS, two issues should be mentioned. The first is the timing of surveillance after the procedure. While there are no prospective comparative studies, patients are usually followed within a month from the procedure, after 6 months and after 12 months and annually thereafter. It is noteworthy that the aforementioned appropriateness criteria denoted surveillance during the first year post-procedure as having uncertain value and found surveillance to be appropriate only after this interval [11]. The second issue is the choice of DUS criteria for in-stent restenosis

(ISR). Theoretically, the DUS criteria for ISR may differ from those of native RAS because of altered arterial compliance and thus altered blood flow patterns [64]. Similar to native renal arteries, DUS criteria for renal ISR have been derived from comparisons of RADUS with CA and similarly different reports resulted in somewhat different values for both PSV and RAR in the diagnosis of ISR. Thus, in some publications both PSV and RAR are reported to be higher in ISR than in native RAS, while in others these values were actually lower. A retrospective analysis examined the value of PSV and RAR as compared to CA for detecting ISR > 50 % in 33 renal stents and found a PSV > 226 cm/s and a RAR > 2.7 to offer optimal ROC curves (sensitivity and specificity of 100 and 90 % and sensitivity and specificity of 100 and 94 % for PSV and RAR, respectively) [67]. In the RENAISSANCE trial, a prospective, single-arm, renal artery stenting study, an 86.6 % concordance was found between RADUS and CA in 30 lesions [68]. The RADUS criteria for ISR used to correlate with CA ISR ≥ 50 % were a RAR ≥ 3.5 or an absolute PSV ≥ 225 cm/s in association with post-stent turbulence. In another study, a retrospective analysis of 47stented renal arteries in 30 patients by using ROC curves, a PSV of 250 cm/s was associated with a sensitivity of 59 %, specificity of 95 %, an accuracy of 83 %, and a positive predictive value of 87 % [64]. Another retrospective comparison of PSV and RAR between 31 patients with angiographically proven ISR and 30 patients with angiographically proven native RAS suggested that a PSV of 395 cm/s and an RAR of 5.1 most valuable for detecting ISR ≥ 70 % (sensitivity of 83 %, specificity of 88 %, and accuracy of 87 % and sensitivity of 94 %, specificity of 86 % and accuracy of 88 %, for PSV and RAR, respectively) [69]. As there are no uniform criteria for renal ISR, before re-intervention is attempted clinicians should consider the clinical indications first (i.e., worsening blood pressure control or declining renal function) in conjunction with the abnormal DUS result and not act on just the abnormal DUS result alone [69].

Some controversy exists regarding RADUS criteria for covered renal stents (as opposed to bare-metal stents). To date, one retrospective analysis of prospectively collected data of addressed this matter by reporting DUS criteria for covered and uncovered renal artery stents placed in conjunction to endovascular repair of abdominal aortic aneurysms [70]. Six of 231 covered stents developed ISR and the authors reported that a PSV > 280 cm/s and a RAR > 4.5 resulted in optimal detection of these events, by comparing RADUS, CTA and CA findings.

Transplant Renal Artery Duplex Ultrasonography

Transplant RADUS is performed in order to identify pathology in the transplant kidney, artery, vein and collecting system. It is usually first performed soon after surgery and later routinely or based on patient clinical and biochemical characteristics. The discussion hereafter will focus on the transplant renal artery. As the renal transplant graft is usually placed extraperitoneally and superficially, most commonly in the right lower abdominal quadrant, use of a high frequency probe should be considered to achieve optimal visualization of structures [71]. The transplanted kidney arterial inflow anastomosis type depends on donor and recipient anatomy and may be end to end (EE) to the internal iliac artery or end to side (ES) with either the internal or, more commonly, the external iliac artery [72]. The IAC-vascular division guidelines for transplant RADUS are similar to those for native arteries (Table 12.2), with variations that include the need to examine the peri-transplant region with gray scale images, the arterial anastomosis with spectral Doppler waveforms and velocity measurements as well as the venous anastomosis with spectral Doppler waveforms [11]. It should be noted that as external iliac artery stenosis can result in impaired blood flow to the transplanted kidney, this artery should also be interrogated as part of a complete examination [73]. Furthermore, transplant renal arteries have two characteristics that may cause elevated PSV without stenosis. First, an ES anastomosis may result in local tortuosity and second, a transplant kidney tends to undergo hypertrophy and may be supplied by a higher than normal blood volume.

Also, there is significant normal variability of PSV in transplant renal arteries [74]. Published PSV that have been shown to identify transplant RAS range between 150 and 300 cm/s [75–77]. These have relied on relatively small series. Other measures have therefore been added to supplement the PSV such as the AT and the renal artery: external iliac artery ratio (RIR), though considerable variability has been noted with these criteria as well [74]. A retrospective analysis of 38 transplant renal arteries with severe RAS, 19 representing each kind of anastomosis, was undertaken and revealed the AT to be similar between EE and ES types, while PSV was much higher in the EE type of anastomosis [72]. This analysis did not, however, have a control group and therefore could not assess for a cutoff for the diagnosis of RAS. A recent comparison of RADUS, MRA and CA was performed in 10 transplant renal arteries found to have CA proven RAS > 50 % and 12 arteries in patients in whom stenosis was not suspected clinically [73]. The best accuracy for RAS detection was achieved with PSV > 250 cm/s, AT > 0.1 s and RIR > 2. As a single measure, AT offered the best results, while RI did not differ between the groups. A PSV > 200 cm/s resulted in better sensitivity (90 % vs. 70 %). To further overcome the aforementioned physiologic changes in transplant renal artery blood flow a study of RADUS characteristics in 14 transplant renal arteries with CA proven stenosis ≥80 % used a ratio of the renal artery PSV to the PSV in the interlobar renal arteries >13 as a discriminator [78]. Finally, the intraparenchymal AT was significantly longer when RAS was present in a comparison between 15 transplant renal arteries without stenosis and 4 arteries with RAS > 50 % [79].

Other Findings on RADUS

As stated, a complete RADUS should include bilateral visualization of the entire length of the renal artery and also of the kidney parenchyma. In a prospective surveillance of 101 kidneys for an average of 14.4 months, 26 % of 49 kidneys with RAS > 60 % demonstrated >1 cm length reduction, while atrophy was absent in all other patients [80]. In another prospective surveillance of 204 kidneys over a mean of 33 months renal atrophy, defined as 1 cm length reduction, occurred in 20.8 % of patients with RAS ≥ 60 %, more than in patients with normal or less severe stenosis (5.5 % and 11.7 %, respectively, $P = 0.009$) [81]. Cortical thickness should also be evaluated. A study comparing cortical thickness between contralateral kidneys in 26 patients with unilateral RAS found significant differences in both cortical thickness and kidney length as assessed by CTA [82]. Furthermore, the technician and interpreting physician must be vigilant for the presence of unusual findings such as FMD, benign cysts or tumor. Fibromuscular dysplasia is suspected when peak systolic velocity is elevated in the mid or distal renal artery. In addition, a typical beaded appearance will suggest the medial fibroplasia variant of FMD. If present, the location, size and number of benign cysts should be documented [83]. Lack of flow within a cyst should be documented as opposed to tumor masses that may present with neovascularization or with echogenic material within the mass [84]. Any suspicion for tumor should prompt recommendation of a more sophisticated examination.

Conclusion

RADUS is an inexpensive, convenient and accurate method for assessing native, stented and transplant renal arteries for stenosis. While it has inherent limitations, it is the most commonly used tool for screening and surveillance of patients with RAS. Use of other imaging modalities and correlation with local outcomes should be utilized to corroborate RADUS findings prior to intervention.

References

1. Davis RP, Pearce JD, Craven TE, Moore PS, Edwards MS, Godshall CJ, Hansen KJ. Atherosclerotic renovascular disease among hypertensive adults. J Vasc Surg. 2009;50:564–70, 571.e1–3; discussion 571.
2. Rihal CS, Textor SC, Breen JF, McKusick MA, Grill DE, Hallett JW, Holmes Jr DR. Incidental renal artery stenosis among a prospective cohort of hypertensive patients undergoing coronary angiography. Mayo Clin Proc. 2002;77:309–16.

3. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WR, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor Jr LM, White CJ, White J, White RA, Antman EM, Smith Jr SC, Adams CD, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B, American Association for Vascular Surgery, Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, ACC/AHA Task Force on Practice Guidelines Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease, American Association of Cardiovascular and Pulmonary Rehabilitation, National Heart, Lung, and Blood Institute, Society for Vascular Nursing, TransAtlantic Inter-Society Consensus, Vascular Disease Foundation. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006;113:e463–654.
4. Textor SC. Current approaches to renovascular hypertension. Med Clin North Am. 2009;93: 717–32.
5. Manske CL, Sprafka JM, Strony JT, Wang Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. Am J Med. 1990;89:615–20.
6. Zoccali C, Mallamaci F, Finocchiaro P. Atherosclerotic renal artery stenosis: epidemiology, cardiovascular outcomes, and clinical prediction rules. J Am Soc Nephrol. 2002;13 Suppl 3:S179–83.
7. Williams GJ, Macaskill P, Chan SF, Karplus TE, Yung W, Hodson EM, Craig JC. Comparative accuracy of renal duplex sonographic parameters in the diagnosis of renal artery stenosis: paired and unpaired analysis. AJR Am J Roentgenol. 2007;188: 798–811.
8. Jose A, Kaplan NM. Plasma renin activity in the diagnosis of primary aldosteronism: failure to distinguish primary aldosteronism from essential hypertension. Arch Intern Med. 1969;123:141–6.
9. Safian RD, Textor SC. Renal-artery stenosis. N Engl J Med. 2001;344:431–42.
10. Dworkin LD, Cooper CJ. Clinical practice. Renal-artery stenosis. N Engl J Med. 2009;361:1972–8.
11. American College of Cardiology Foundation (ACCF), American College of Radiology (ACR), American Institute of Ultrasound in Medicine (AIUM), American Society of Echocardiography (ASE), American Society of Nephrology (ASN), Intersocietal Commission for the Accreditation of Vascular Laboratories (ICAVL), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Cardiovascular Computed Tomography (SCCT), Society for Interventional Radiology (SIR), Society for Vascular Medicine (SVM), Society for Vascular Surgery (SVS), Mohler 3rd ER, Gornik HL, Gerhard-Herman M, Misra S, Olin JW, Zierler RE, Wolk MJ, Mohler 3rd ER. ACCF/ACR/AIUM/ASE/ASN/ICAVL/SCAI/SCCT/SIR/SVM/SVS 2012 appropriate use criteria for peripheral vascular ultrasound and physiological testing part I: arterial ultrasound and physiological testing: a report of the American College of Cardiology Foundation appropriate use criteria task force, American College of Radiology, American Institute of Ultrasound in Medicine, American Society of Echocardiography, American Society of Nephrology, Intersocietal Commission for the Accreditation of Vascular Laboratories, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Interventional Radiology, Society for Vascular Medicine, and Society for Vascular Surgery. J Am Coll Cardiol. 2012;60:242–76.
12. Drieghe B, Madaric J, Sarno G, Manoharan G, Bartunek J, Heyndrickx GR, Pijls NH, De Bruyne B. Assessment of renal artery stenosis: side-by-side comparison of angiography and duplex ultrasound with pressure gradient measurements. Eur Heart J. 2008;29:517–24.
13. Weinberg I, Jaff MR. Nonatherosclerotic arterial disorders of the lower extremities. Circulation. 2012;126:213–22.
14. Pearce JD, Craven BL, Craven TE, Piercy KT, Stafford JM, Edwards MS, Hansen KJ. Progression of atherosclerotic renovascular disease: a prospective population-based study. J Vasc Surg. 2006;44: 955–62; discussion 962–3.
15. Kawarada O, Yokoi Y, Morioka N, Takemoto K. Renal artery stenosis in cardio-and cerebrovascular disease: renal duplex ultrasonography as an initial screening examination. Circ J. 2007;71:1942–7.
16. Hansen KJ, Edwards MS, Craven TE, Cherr GS, Jackson SA, Appel RG, Burke GL, Dean RH. Prevalence of renovascular disease in the elderly: a population-based study. J Vasc Surg. 2002;36: 443–51.
17. Edwards MS, Hansen KJ, Craven TE, Bleyer AJ, Burke GL, Levy PJ, Dean RH. Associations between renovascular disease and prevalent cardiovascular disease in the elderly: a population-based study. Vasc Endovascular Surg. 2004;38:25–35.
18. Caps MT, Perissinotto C, Zierler RE, Polissar NL, Bergelin RO, Tullis MJ, Cantwell-Gab K, Davidson RC, Strandness Jr DE. Prospective study of

atherosclerotic disease progression in the renal artery. Circulation. 1998;98:2866–72.
19. Zierler RE, Bergelin RO, Davidson RC, Cantwell-Gab K, Polissar NL, Strandness Jr DE. A prospective study of disease progression in patients with atherosclerotic renal artery stenosis. Am J Hypertens. 1996;9:1055–61.
20. Roman MJ, Naqvi TZ, Gardin JM, Gerhard-Herman M, Jaff M, Mohler E, American Society of Echocardiography, Society of Vascular Medicine and Biology. Clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification: a report from the American Society of Echocardiography and the Society of Vascular Medicine and Biology. J Am Soc Echocardiogr. 2006;19:943–54.
21. Hansen KJ, Tribble RW, Reavis SW, Canzanello VJ, Craven TE, Plonk Jr GW, Dean RH. Renal duplex sonography: evaluation of clinical utility. J Vasc Surg. 1990;12:227–36.
22. Platt JF. Duplex Doppler evaluation of native kidney dysfunction: obstructive and nonobstructive disease. AJR Am J Roentgenol. 1992;158:1035–42.
23. Soares GM, Murphy TP, Singha MS, Parada A, Jaff M. Renal artery duplex ultrasonography as a screening and surveillance tool to detect renal artery stenosis: a comparison with current reference standard imaging. J Ultrasound Med. 2006;25:293–8.
24. Aburahma AF, Srivastava M, Mousa AY, Dearing DD, Hass SM, Campbell JR, Dean LS, Stone PA, Keiffer T. Critical analysis of renal duplex ultrasound parameters in detecting significant renal artery stenosis. J Vasc Surg. 2012;56(4):1052–9, 1060.e1; discussion 1059–60.
25. Kawarada O, Yokoi Y, Takemoto K, Morioka N, Nakata S, Shiotani S. The performance of renal duplex ultrasonography for the detection of hemodynamically significant renal artery stenosis. Catheter Cardiovasc Interv. 2006;68:311–8.
26. Conkbayir I, Yucesoy C, Edguer T, Yanik B, Yasar Ayaz U, Hekimoglu B. Doppler sonography in renal artery stenosis. An evaluation of intrarenal and extrarenal imaging parameters. Clin Imaging. 2003;27:256–60.
27. Nchimi A, Biquet JF, Brisbois D, Reginster P, Bouali K, Saive C, Magotteaux P. Duplex ultrasound as first-line screening test for patients suspected of renal artery stenosis: prospective evaluation in high-risk group. Eur Radiol. 2003;13:1413–9.
28. de Haan MW, Kroon AA, Flobbe K, Kessels AG, Tordoir JH, van Engelshoven JM, de Leeuw PW. Renovascular disease in patients with hypertension: detection with duplex ultrasound. J Hum Hypertens. 2002;16:501–7.
29. Ripolles T, Aliaga R, Morote V, Lonjedo E, Delgado F, Martinez MJ, Vilar J. Utility of intrarenal Doppler ultrasound in the diagnosis of renal artery stenosis. Eur J Radiol. 2001;40:54–63.
30. Voiculescu A, Hofer M, Hetzel GR, Malms J, Modder U, Grabensee B, Hollenbeck M. Noninvasive investigation for renal artery stenosis: contrast-enhanced magnetic resonance angiography and color Doppler sonography as compared to digital subtraction angiography. Clin Exp Hypertens. 2001;23:521–31.
31. Claudon M, Plouin PF, Baxter GM, Rohban T, Devos DM. Renal arteries in patients at risk of renal arterial stenosis: multicenter evaluation of the echo-enhancer SH U 508A at color and spectral Doppler US. Levovist Renal Artery Stenosis Study Group. Radiology. 2000;214:739–46.
32. Hua HT, Hood DB, Jensen CC, Hanks SE, Weaver FA. The use of colorflow duplex scanning to detect significant renal artery stenosis. Ann Vasc Surg. 2000;14:118–24.
33. Motew SJ, Cherr GS, Craven TE, Travis JA, Wong JM, Reavis SW, Hansen KJ. Renal duplex sonography: main renal artery versus hilar analysis. J Vasc Surg. 2000;32(462–9):469–71.
34. Radermacher J, Chavan A, Schaffer J, Stoess B, Vitzthum A, Kliem V, Rademaker J, Bleck J, Gebel MJ, Galanski M, Brunkhorst R. Detection of significant renal artery stenosis with color Doppler sonography: combining extrarenal and intrarenal approaches to minimize technical failure. Clin Nephrol. 2000;53:333–43.
35. Souza de Oliveira IR, Widman A, Molnar LJ, Fukushima JT, Praxedes JN, Cerri GG. Colour Doppler ultrasound: a new index improves the diagnosis of renal artery stenosis. Ultrasound Med Biol. 2000;26:41–7.
36. House MK, Dowling RJ, King P, Gibson RN. Using Doppler sonography to reveal renal artery stenosis: an evaluation of optimal imaging parameters. AJR Am J Roentgenol. 1999;173:761–5.
37. Kaplan-Pavlovcic S, Nadja C. Captopril renography and duplex Doppler sonography in the diagnosis of renovascular hypertension. Nephrol Dial Transplant. 1998;13:313–7.
38. Mollo M, Pelet V, Mouawad J, Mathieu JP, Branchereau A. Evaluation of colour duplex ultrasound scanning in diagnosis of renal artery stenosis, compared to angiography: a prospective study on 53 patients. Eur J Vasc Endovasc Surg. 1997;14:305–9.
39. Baxter GM, Aitchison F, Sheppard D, Moss JG, McLeod MJ, Harden PN, Love JG, Robertson M, Taylor G. Colour Doppler ultrasound in renal artery stenosis: intrarenal waveform analysis. Br J Radiol. 1996;69:810–5.
40. Burdick L, Airoldi F, Marana I, Giussani M, Alberti C, Cianci M, Lovaria A, Saccheri S, Gazzano G, Morganti A. Superiority of acceleration and acceleration time over pulsatility and resistance indices as screening tests for renal artery stenosis. J Hypertens. 1996;14:1229–35.
41. Miralles M, Cairols M, Cotillas J, Gimenez A, Santiso A. Value of Doppler parameters in the diagnosis of renal artery stenosis. J Vasc Surg. 1996;23:428–35.
42. Missouris CG, Allen CM, Balen FG, Buckenham T, Lees WR, MacGregor GA. Non-invasive screening

for renal artery stenosis with ultrasound contrast enhancement. J Hypertens. 1996;14:519–24.
43. Helenon O, el Rody F, Correas JM, Melki P, Chauveau D, Chretien Y, Moreau JF. Color Doppler US of renovascular disease in native kidneys. Radiographics. 1995;15:833–54; discussion 854–65.
44. Olin JW, Piedmonte MR, Young JR, DeAnna S, Grubb M, Childs MB. The utility of duplex ultrasound scanning of the renal arteries for diagnosing significant renal artery stenosis. Ann Intern Med. 1995;122:833–8.
45. Appel RG, Bleyer AJ, Hansen KJ. Duplex scanning of renal arteries for stenosis. Ann Intern Med. 1996;124:370–1.
46. Kliewer MA, Tupler RH, Carroll BA, Paine SS, Kriegshauser JS, Hertzberg BS, Svetkey LP. Renal artery stenosis: analysis of Doppler waveform parameters and tardus-parvus pattern. Radiology. 1993;189:779–87.
47. Stavros AT, Parker SH, Yakes WF, Chantelois AE, Burke BJ, Meyers PR, Schenck JJ. Segmental stenosis of the renal artery: pattern recognition of tardus and parvus abnormalities with duplex sonography. Radiology. 1992;184:487–92.
48. Antonica G, Sabba C, Berardi E, Buonamico P, Paolo C, Vulpis V, Ettorre G, Pirrelli A, Albano O. Accuracy of echo-Doppler flowmetry for renal artery stenosis. J Hypertens Suppl. 1991;9:S240–1.
49. Hoffmann U, Edwards JM, Carter S, Goldman ML, Harley JD, Zaccardi MJ, Strandness Jr DE. Role of duplex scanning for the detection of atherosclerotic renal artery disease. Kidney Int. 1991;39:1232–9.
50. Hawkins PG, McKnoulty LM, Gordon RD, Klemm SA, Tunny TJ. Non-invasive renal artery duplex ultrasound and computerized nuclear renography to screen for and follow progress in renal artery stenosis. J Hypertens Suppl. 1989;7:S184–5.
51. Taylor DC, Kettler MD, Moneta GL, Kohler TR, Kazmers A, Beach KW, Strandness Jr DE. Duplex ultrasound scanning in the diagnosis of renal artery stenosis: a prospective evaluation. J Vasc Surg. 1988;7:363–9.
52. Avasthi PS, Voyles WF, Greene ER. Noninvasive diagnosis of renal artery stenosis by echo-Doppler velocimetry. Kidney Int. 1984;25:824–9.
53. White CJ. Optimizing outcomes for renal artery intervention. Circ Cardiovasc Interv. 2010;3:184–92.
54. Radermacher J, Chavan A, Bleck J, Vitzthum A, Stoess B, Gebel MJ, Galanski M, Koch KM, Haller H. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. N Engl J Med. 2001;344:410–7.
55. Zeller T, Frank U, Muller C, Burgelin K, Sinn L, Bestehorn HP, Cook-Bruns N, Neumann FJ. Predictors of improved renal function after percutaneous stent-supported angioplasty of severe atherosclerotic ostial renal artery stenosis. Circulation. 2003;108:2244–9.
56. Riehl J, Schmitt H, Bongartz D, Bergmann D, Sieberth HG. Renal artery stenosis: evaluation with colour duplex ultrasonography. Nephrol Dial Transplant. 1997;12:1608–14.
57. Schwerk WB, Restrepo IK, Stellwaag M, Klose KJ, Schade-Brittinger C. Renal artery stenosis: grading with image-directed Doppler US evaluation of renal resistive index. Radiology. 1994;190:785–90.
58. Radermacher J, Mengel M, Ellis S, Stuht S, Hiss M, Schwarz A, Eisenberger U, Burg M, Luft FC, Gwinner W, Haller H. The renal arterial resistance index and renal allograft survival. N Engl J Med. 2003;349:115–24.
59. Bardelli M, Jensen G, Volkmann R, Aurell M. Non-invasive ultrasound assessment of renal artery stenosis by means of the Gosling pulsatility index. J Hypertens. 1992;10:985–9.
60. Barozzi L, Pavlica P, Sabattini A, Losinno F, Dondi M, De Fabritiis A, Amato A, Zuccala A. Duplex and Doppler color echocardiography for the study of renovascular hypertension. Comparison with arteriography. Radiol Med. 1991;81:642–9.
61. Manganaro A, Ando' G, Salvo A, Consolo A, Coppolino F, Giannino D. A comparison of Power Doppler with conventional sonographic imaging for the evaluation of renal artery stenosis. Cardiovasc Ultrasound. 2004;2:1.
62. Tola M, Yurdakul M, Ozbulbul NI. B-flow imaging for the measurement of residual lumen diameter of renal artery stenosis. J Clin Ultrasound. 2012;40:85–90.
63. Saeed A, Bergstrom G, Zachrisson K, Guron G, Nowakowska-Fortuna E, Fredriksen E, Lonn L, Jensen G, Herlitz H. Accuracy of colour duplex sonography for the diagnosis of renal artery stenosis. J Hypertens. 2009;27:1690–6.
64. Fleming SH, Davis RP, Craven TE, Deonanan JK, Godshall CJ, Hansen KJ. Accuracy of duplex sonography scans after renal artery stenting. J Vasc Surg. 2010;52:953–7; discussion 958.
65. Olin JW, Sealove BA. Diagnosis, management, and future developments of fibromuscular dysplasia. J Vasc Surg. 2011;53:826–36.e1.
66. Das CJ, Neyaz Z, Thapa P, Sharma S, Vashist S. Fibromuscular dysplasia of the renal arteries: a radiological review. Int Urol Nephrol. 2007;39:233–8.
67. Bakker J, Beutler JJ, Elgersma OE, de Lange EE, de Kort GA, Beek FJ. Duplex ultrasonography in assessing restenosis of renal artery stents. Cardiovasc Intervent Radiol. 1999;22:475–80.
68. Rocha-Singh K, Jaff MR, Lynne Kelley E, RENAISSANCE Trial Investigators. Renal artery stenting with noninvasive duplex ultrasound follow-up: 3-year results from the RENAISSANCE renal stent trial. Catheter Cardiovasc Interv. 2008;72:853–62.
69. Chi YW, White CJ, Thornton S, Milani RV. Ultrasound velocity criteria for renal in-stent restenosis. J Vasc Surg. 2009;50:119–23.
70. Mohabbat W, Greenberg RK, Mastracci TM, Cury M, Morales JP, Hernandez AV. Revised duplex criteria and outcomes for renal stents and stent grafts following endovascular repair of juxtarenal and

thoracoabdominal aneurysms. J Vasc Surg. 2009;49: 827–37; discussion 837.
71. Browne RF, Tuite DJ. Imaging of the renal transplant: comparison of MRI with duplex sonography. Abdom Imaging. 2006;31:461–82.
72. Gao J, Li JC, Xiao MS, Ng A, Trost D, Goldstein M, Kapur S, Wang J, Serur D, Dai Q, Jiang YX, Min RJ. Color duplex sonography in severe transplant renal artery stenosis: a comparison of end-to-end and end-to-side arterial anastomoses. Clin Imaging. 2009;33: 116–22.
73. de Morais RH, Muglia VF, Mamere AE, Garcia Pisi T, Saber LT, Muglia VA, Elias Jr J, Piccinato CE, Trad CS. Duplex Doppler sonography of transplant renal artery stenosis. J Clin Ultrasound. 2003;31:135–41.
74. Loubeyre P, Abidi H, Cahen R, Tran Minh VA. Transplanted renal artery: detection of stenosis with color Doppler US. Radiology. 1997;203:661–5.
75. Erley CM, Duda SH, Wakat JP, Sokler M, Reuland P, Muller-Schauenburg W, Schareck W, Lauchart W, Risler T. Noninvasive procedures for diagnosis of renovascular hypertension in renal transplant recipients–a prospective analysis. Transplantation. 1992;54: 863–7.
76. Baxter GM, Ireland H, Moss JG, Harden PN, Junor BJ, Rodger RS, Briggs JD. Colour Doppler ultrasound in renal transplant artery stenosis: which Doppler index? Clin Radiol. 1995;50:618–22.
77. Montanes Medina P, Medina Lopez RA, Torrubia Romero FJ, Dominguez Anguiano M, Cruz Navarro N, Rus Herrera F, Munoz Terol J, Rocha Castilla JL. Renal artery stenosis in the transplant patient. Arch Esp Urol. 1999;52:771–6.
78. Li JC, Ji ZG, Cai S, Jiang YX, Dai Q, Zhang JX. Evaluation of severe transplant renal artery stenosis with Doppler sonography. J Clin Ultrasound. 2005;33:261–9.
79. Gottlieb RH, Lieberman JL, Pabico RC, Waldman DL. Diagnosis of renal artery stenosis in transplanted kidneys: value of Doppler waveform analysis of the intrarenal arteries. AJR Am J Roentgenol. 1995;165: 1441–6.
80. Guzman RP, Zierler RE, Isaacson JA, Bergelin RO, Strandness Jr DE. Renal atrophy and arterial stenosis. A prospective study with duplex ultrasound. Hypertension. 1994;23:346–50.
81. Caps MT, Zierler RE, Polissar NL, Bergelin RO, Beach KW, Cantwell-Gab K, Casadei A, Davidson RC, Strandness Jr DE. Risk of atrophy in kidneys with atherosclerotic renal artery stenosis. Kidney Int. 1998;53:735–42.
82. Mounier-Vehier C, Lions C, Devos P, Jaboureck O, Willoteaux S, Carre A, Beregi JP. Cortical thickness: an early morphological marker of atherosclerotic renal disease. Kidney Int. 2002;61:591–8.
83. de Bruyn R, Gordon I. Imaging in cystic renal disease. Arch Dis Child. 2000;83:401–7.
84. Kier R, Taylor KJ, Feyock AL, Ramos IM. Renal masses: characterization with Doppler US. Radiology. 1990;176:703–7.

CT Angiography of the Renal Arteries

13

Terri Jo Vrtiska

Abstract

Imaging of the renal arteries using noninvasive tools such as high resolution CT angiography (CTA) has largely replaced catheter angiography in the assessment of a variety of clinical indications including depicting renal donor anatomic variation, assessing renal luminal abnormalities and demonstrating complex postoperative reconstructions. This chapter reviews the indications, techniques and applications for renal arterial CTA as well as presents future directions for state-of-the-art CT scanners and processing techniques.

Keywords

Renal • Arterial • Computed tomography • CTA

Indications for Renal Arterial CT Angiography

During the past decade, CT Angiography (CTA) has become a standard noninvasive imaging modality for presentation of renal vascular anatomy and pathology. CTA has evolved from relatively slow acquisitions by single spiral scanners to rapid acquisitions by 64, 128 and 256-multichannel CT systems. In most practices, advanced imaging techniques, such as CTA, have largely replaced catheter angiography in the majority of diagnostic renal arterial studies [1]. The continued evolution of these imaging techniques provides an extremely accurate, time-efficient, and cost-effective diagnostic evaluation for medical management of renal arterial disease as well as creating a precise roadmap prior to surgical intervention. High-resolution CTA images are obtained for a variety of indications. For example, a hypertensive individual may undergo renal CTA to exclude renal artery stenosis, fibromuscular dysplasia or dissection. Tailored renal CTA examination for specific pathology might include determining if vasculitis involves the renal arteries or the extent of renal aneurysmal changes. Preoperative renal CTA planning can be useful for nephron-sparing surgery prior to resection of renal masses or as post-procedural follow-up of renal stenting or surgical revascularization. In addition, CT protocols can be augmented with

T.J. Vrtiska, MD
Department of Radiology,
Mayo Clinic College of Medicine,
200 First Street SW, Rochester, MN 55905, USA
e-mail: vrtiska.terri@mayo.edu

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_13,

supplemental acquisitions for evaluation of the renal parenchyma, opacification of the urinary collecting systems or depicting extrarenal pathology without the administration of additional iodinated contrast material. Appropriate tailoring of these imaging sequences can be made with only a minimal increase in acquisition time and optimization of the study for the smallest possible radiation dose to an individual patient.

Optimization of Renal Arterial CTA Acquisitions

Continued evolution of CT equipment has allowed arterial vasculature to be imaged in exquisite detail by combining high resolution (sub-millimeter) increments with rapid (sub-second) acquisition timing. Optimal acquisition parameters are required to accurately depict the main renal arteries and segmental artery branches including attention to IV contrast injection, bolus timing and acquisition technique. Adequate intravenous access is essential for optimal opacification and depiction of the renal arteries. Typically, a 20 gauge or larger IV catheter is placed in the antecubital or forearm veins of either upper extremity allowing IV contrast rates of 4–5 cc/s using a power injector. A typical renal CTA bolus is 100- to 125-mL of nonionic iodinated contrast material with a concentration of 300–370 mg/mL. A dual-headed injector allows the iodinated contrast material bolus to be followed by an IV flush of 30 cc of normal saline clearing contrast material from the upper extremity veins which maximizes contrast utilization. The amount of contrast material can be modified based on patient weight and renal function. The CTA can be acquired automatically at a fixed interval of 15–25 s or more commonly is obtained using automated bolus-tracking techniques with a region of interest placed in the abdominal aorta triggering the scan acquisition when it reaches a preset level of density, typically 100–140 Hounsfield units (HU).

Adequate anatomic coverage is critical for acquisition of optimal renal CTAs, most commonly extending from the celiac artery to the distal common iliac arteries including accessory renal arteries arising from the lower abdominal aorta (Fig. 13.1) or the common iliac arteries. In patients with suspected anatomic variation such as horseshoe kidney (Fig. 13.2), pelvic kidney (Fig. 13.3), crossed-fused renal ectopia or renal transplantation, extended coverage into the entire pelvis is preferred. Acquisition and reconstruction parameters vary but ideal slice thickness of 1–1.5 mm should be obtained with a 50 % overlap in order to create optimal 3D postprocessing. Additional 2–2.5 mm axial and coronal reconstructions can be created from the original dataset for diagnostic image review and interpretation.

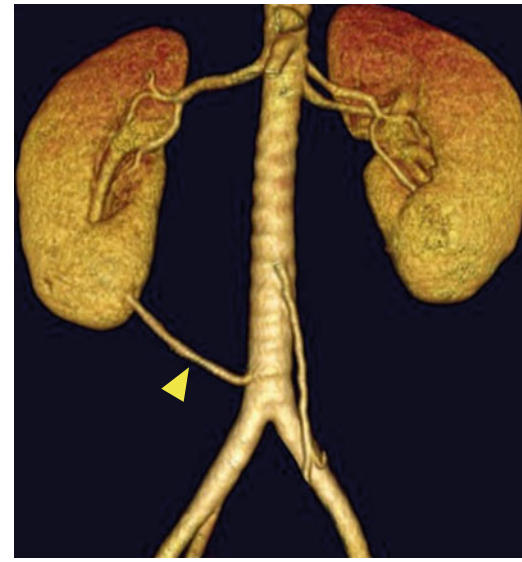


Fig. 13.1 Volume rendered computed tomography angiogram (CTA) of the renal arteries with an accessory renal artery (*arrowhead*) arising from the lower abdominal aorta near the aortic bifurcation

Supplementary imaging sequences can be acquired during the CT acquisition as appropriate for the clinical indication. For example, calculi are optimally visualized on precontrast CT images and precontrast HU measurements are useful in determination of enhancement characteristics of renal masses. Delayed venous phase imaging at 70–80 s can be considered for evaluation of renal vein anatomy, renal parenchymal abnormalities and renal perfusion characteristics. Excretory phase imaging can be added to the CTA exam for a one-stop combined evaluation of renal vasculature, renal parenchyma and urothelium.

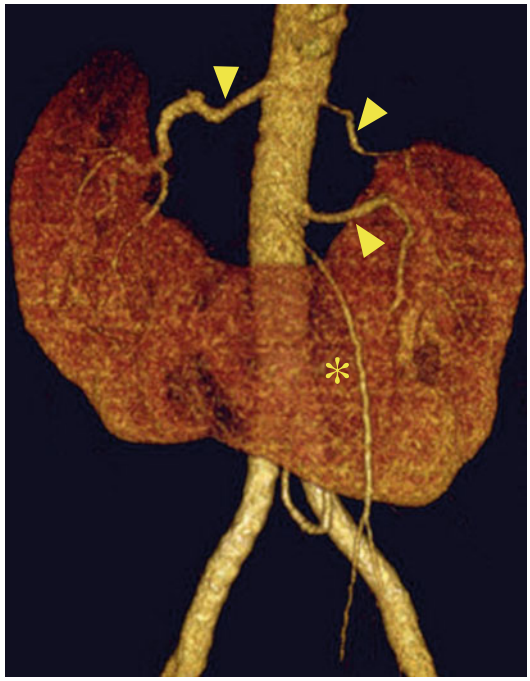


Fig. 13.2 Volume rendered CTA of a horseshoe kidney supplied by three renal arteries (*arrowheads*). The inferior mesenteric artery is noted with an *

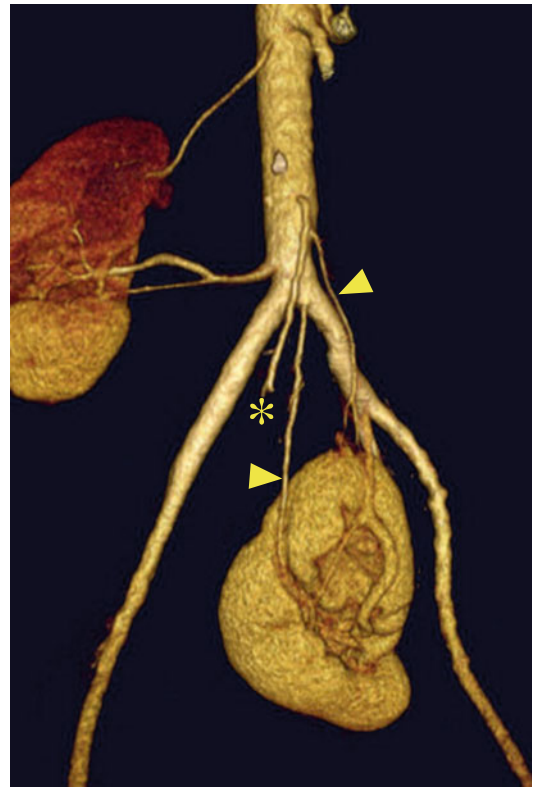


Fig. 13.3 Volume rendered CTA including a normally positioned right kidney supplied by two renal arteries and a pelvic kidney also supplied by two renal arteries (*arrowheads*). The inferior mesenteric artery is denoted by an *

Careful attention to radiation dose should be reviewed with the CT technologist performing the examination including limiting longitudinal craniocaudal coverage to the appropriate acquisition length. For example, overscanning into the chest or lower pelvis increases unnecessary radiation dose to radiosensitive structures such as the breasts or gonadal tissue. Acquiring precontrast acquisition using lower dose techniques and thicker sections (3–5 mm) also decreases the overall radiation dose. Application of mA modulation, auto-kV utilization as well as noise reduction computer algorithms are additional techniques that allow optimal visualization of the renal arteries at the lowest radiation dose.

Comparison to Other Modalities

The ability to acquire exams with increased spatial resolution and faster exam times provides the key benefits of CTA when compared to MR angiography (MRA). Depicting the extent of atheromatous calcification, which cannot be demonstrated on MRA, is another advantage. However, MRA can be obtained without radiation exposure or iodinated contrast material thus providing an optimum imaging alternative in pregnant patients as well as patients with severe iodinated contrast allergy or decreased renal function. CTA does require radiation exposure for image acquisition; however, the accuracy is less operator-dependent and especially useful in patients with a large body habitus when compared to ultrasound. The gold standard for arterial diagnostic evaluations has traditionally been invasive catheter-directed angiograms; however, cross-sectional techniques (CTA and MRA) have largely replaced the necessity for an invasive diagnostic examination (Table 13.1).

Table 13.1 Comparisons of renal arterial computed tomography angiography, magnetic resonance angiography, ultrasound and catheter angiography

	CTA	MRA	US	Cath angio
Radiation	Yes	No	No	Yes
Resolution	Isotropic	Near-isotropic	NA	4 1p/mm
Iodinated contrast	Yes	No	No	Yes
Operator dependence	No	No	Yes	Yes
Resistive indices	No	No	Yes	No
Pressure gradients	No	No	No	Yes
Total exam time (est)	5–10 s	15–20 s	20–30 min	20–30 min
Invasiveness	No	No	No	Yes
3D post-processing	Yes	Yes, automated	No	No
Contraindications (relative and absolute)	Severe contrast allergy	Pacemaker, claustrophobia, some aneurysm clips and implanted devices	None	Severe contrast allergy

Display of Variant Anatomy and Pathology with Multiplanar 2D and 3D Reconstructions

Using current computer technology, the acquired CT exam volume of data can be easily reviewed on a workstation in the traditional axial plane as well as oblique, coronal and sagittal planes maintaining isotropic display in the x, y and z axes using modern 64 channel and greater CT scanners. 3D rendering techniques such as volume-rendered (VR), curved multi-planar reconstruction (MPR) and maximum-intensity-projection (MIP) can be used by the radiologist to clarify anatomic relationships and the extent of pathologic changes. The post processed 2D and 3D images can be provided to clinicians in order to succinctly demonstrate important diagnostic information and provide educational information to patients.

Renal Donor Evaluation

Renal transplantation is currently an optimal treatment choice for end-stage renal disease. In the past, combinations of imaging exams were often used in the preoperative assessment of living renal donors including invasive catheter angiogram combined with intravenous urography. The large flank incision used for harvesting of the donated kidney provided direct visualization of the renal arterial and venous vasculature. Currently, renal donor harvesting is typically performed laparoscopically necessitating a careful preoperative roadmap of the renal vasculature. Fortunately, advances in CTA provide an accurate and complete evaluation of the donated kidney by combining visualization of the renal arteries, renal veins and urographic images into one diagnostic CT exam. Multiphase imaging techniques have been commonly used in the evaluation of renal donors including precontrast, angiographic, venographic and excretory phase imaging. However, newer techniques such as combined angiographic and excretory phase imaging [2] provide accurate imaging details of the renal vasculature while significantly decreasing radiation dose. When correlated with catheter angiography or intraoperative findings, CTA has demonstrated high sensitivity and accuracy of 95–99 % in determination of the arterial number and branching pattern as well as venous variants [3–5]. Important renal donor CT information includes:

1. Renal arterial branching pattern with a prehilar branching pattern described as less than 15–20 mm (Fig. 13.4)
2. Number of renal arteries and veins with accessory renal arteries occurring in 25–28 % of patients [3, 4, 6]
3. Anomalous renal artery and/or venous anatomy including circumaortic or retroaortic left renal veins
4. Renal parenchymal and extrarenal abnormalities including renal cell carcinoma or chronic atrophic pyelonephritis.

The arterial and venous phase images are commonly sent to post-processing workstations

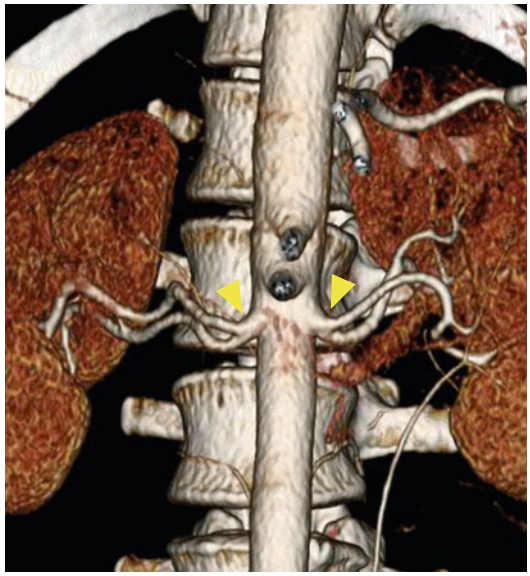


Fig. 13.4 Volume rendered CTA for a preoperative renal donor examination demonstrates early bifurcation (<10 mm) of the renal arteries bilaterally (*arrowheads*)

to reconstruct tailored 3D imaging sets, which maximally demonstrate renal anatomy and anatomic variants. Efficient processing times and dedicated protocols allow the individualized images to be made rapidly available to the referring physicians to provide preoperative planning details. In addition, the intuitive display of the 3D CTA images during the patient-physician discussions help provide instructive details to the patient regarding surgical approaches.

Renal Arterial Atherosclerotic Ostial Stenosis

Some patients undergoing CTAs of the renal arteries may be hypertensive and this noninvasive evaluation is performed to exclude an underlying treatable cause. While an anatomic cause only occurs in a few percent of patients with hypertension, atherosclerotic renal artery stenosis is the culprit in 90 % of these patients [7] with progressive disease to occlusive changes in 3–16 % [7]. Typical changes of renal arterial atheromatous stenosis involve the renal ostia and proximal 10–20 mm of the renal artery and may include mural thrombus, calcification, ulceration and post-stenotic dilatation (Fig. 13.5a–c). While there remains debate regarding the unqualified imaging method of choice for hemodynamically significant renal artery stenosis either due to atheromatous disease or fibromuscular dysplasia, CTA has demonstrated high sensitivity and specificity (92–94 %, 93–99 %) [8, 9] with a more recent study of 50 consecutive patients documenting sensitivity of 100 %, specificity of 98 % and accuracy of 98 % [10] when compared with digital subtraction angiography. CTA is also a useful guide for preprocedural planning in determination of the length of the stenotic segment, sizing criteria for balloon dilatation or stent placement and branching patterns. Current treatment of renal artery stenosis with renal artery stenting has been shown to be superior to percutaneous transluminal angioplasty alone [11] with longer patency rates. Complications of renal artery stent placement include development of in-stent restenosis from intimal hyperplasia in 17–21 % of patients [12, 13]. Follow-up of renal arterial stent placement can be performed with excellent diagnostic accuracy for detection of significant in-stent stenosis (>50 %) using new 64-detector CTA techniques including sensitivity of 100 %, specificity of 99 %, negative predictive value of 100 % and positive predictive value of 90 % [13] when compared to catheter angiography. In addition, current CTA acquisition parameters allow exams to be performed at approximately 50 % of the radiation exposure used in early CTA exams [12].

In addition to the evaluation of the renal arterial luminal changes, CTA provides a detailed evaluation of the renal parenchyma including associated focal scarring or global parenchymal loss. Careful review of the diagnostic CT images may also demonstrate an alternate secondary cause for hypertension such as an adrenal mass (aldosteronoma, pheochromocytoma (Fig. 13.6a, b), aortic coarctation or renal mass.

Fibromuscular Dysplasia

Advances in CT technology with high resolution techniques have improved visualization of more subtle renal arterial intimal abnormalities

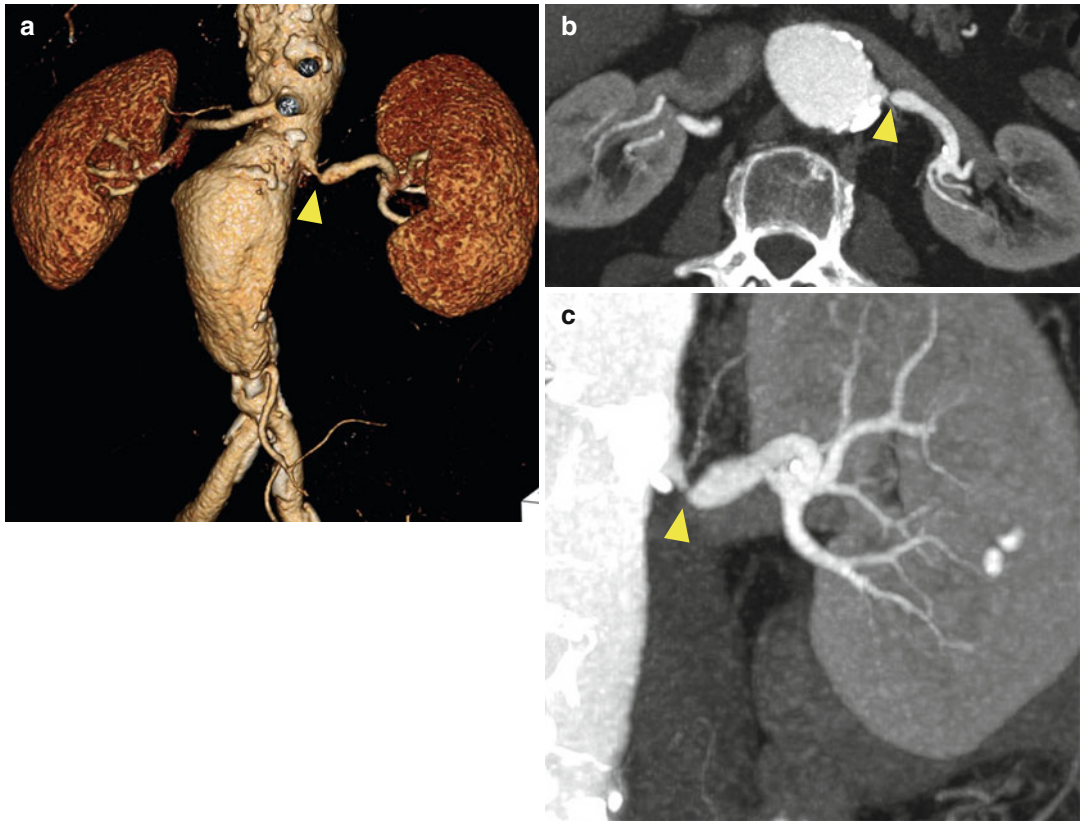


Fig. 13.5 (**a**) Volume rendered CTA demonstrated a high grade short segment stenosis just beyond the origin of the left renal artery (*arrowhead*). (**b**) Axial imaging demonstrates the high grade stenosis (*arrowhead*) with mild poststenotic dilatation. (**c**) Coronal imaging also demonstrates the focal stenosis (*arrowhead*) with mild poststenotic dilatation

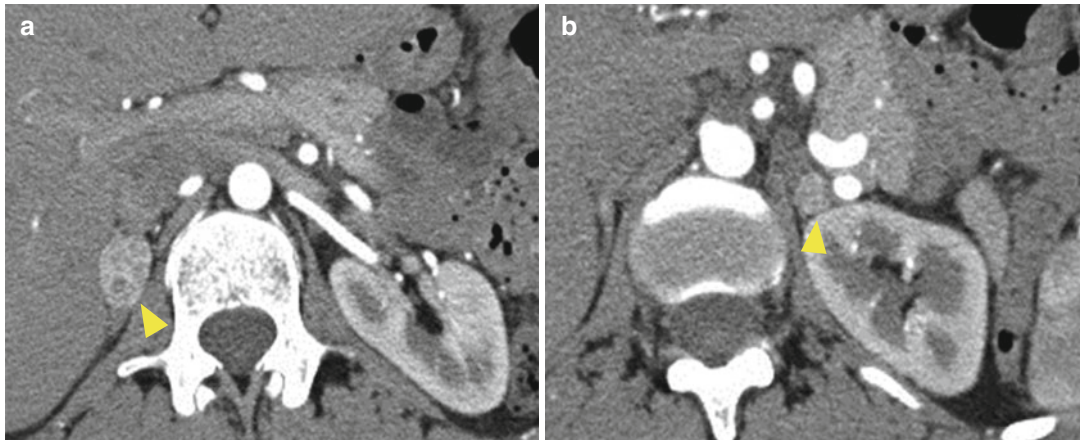


Fig. 13.6 (**a**, **b**) Axial CT images in a 45 year old female with hypertension and a history of Neurofibromatosis type 1. A hypervascular nodule in the right and left adrenal glands (*arrowheads*) were surgically removed and pathologically confirmed as bilateral pheochromocytomas

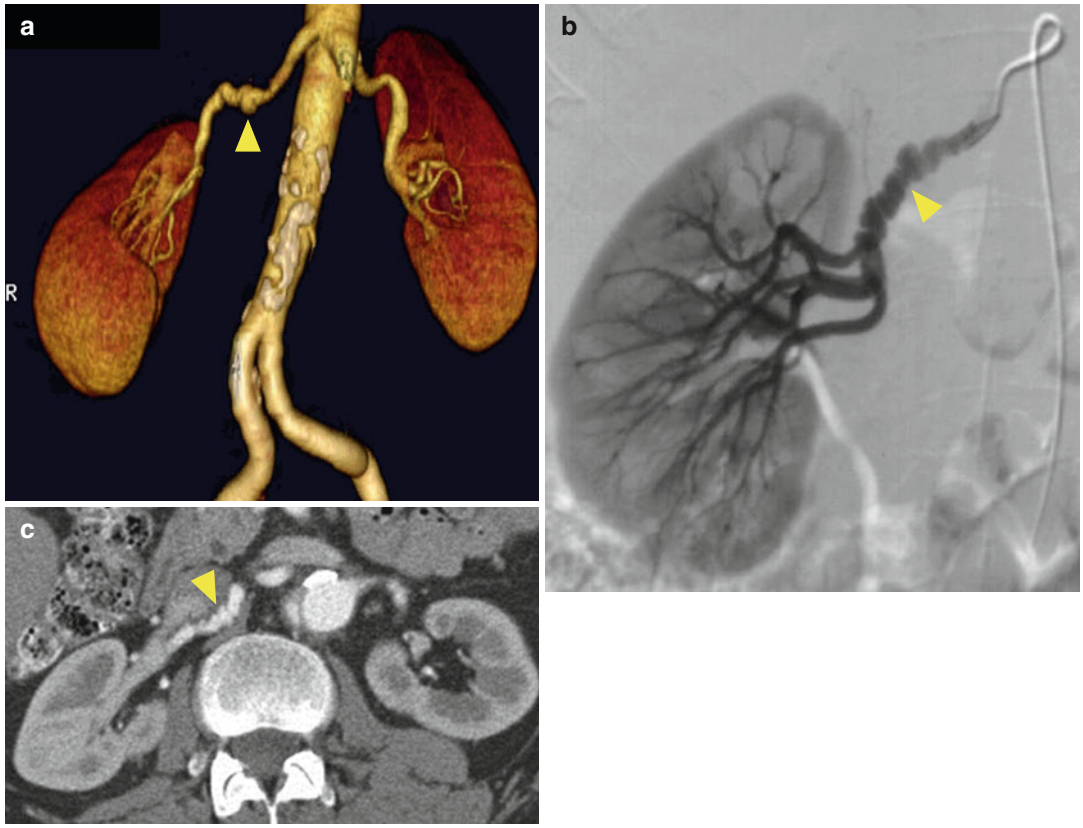


Fig. 13.7 (**a**) Volume rendered CTA demonstrating a classic "string of pearls" consistent with fibromuscular dysplasia (FMD) (*arrowhead*) in the right renal artery. (**b**) Catheter angiogram confirmation of FMD in the same patient (*arrowhead*). (**c**) Axial CT source images demonstrating typical changes of FMD in the mid main right renal artery (*arrowhead*)

such as fibromuscular dysplasia (FMD). Initial publications [14] using early CT technology reliably detected renal artery FMD, but did not advocate for replacement of catheter-directed angiograms. Subsequent publication demonstrated 100 % detection rate of renal arterial FMD by CTA [15] when compared to catheter angiography. Current state-of-the-art CT scanners provide improved spatial resolution compared to earlier exams with accuracy in detection of FMD equivalent or slightly superior to MR angiography [16, 17]; however, both of these technologies are continually evolving.

While renal artery stenosis is most commonly due to atheromatous disease, the majority of the remaining 10–20 % of stenotic renal arteries is due to renal artery FMD [18, 19]. The prevalence of FMD in the general population is rare but has been estimated at nearly 4 % [20] with a 3:1 predominance of females to males, most commonly in the 30–50 year old age group. FMD is divided into subtypes based on the involved layer of the arterial wall (intima, media or adventitia) [21]. Medial FMD is the most common resulting in the classic "string of pearls" appearance both on catheter angiography and CTA. Intimal FMD and adventitial fibroplasia are less common and cannot be separated into distinct subtypes by CTA but can be suspected with tubular segments of stenosis. Involvement of more than one arterial wall layer also occurs pathologically.

The findings of FMD on CTA include most commonly the beaded or string of pearls characteristics (Fig. 13.7a–c) which can be associated with more focal aneurysmal disease. Additional findings on CTA include an arterial

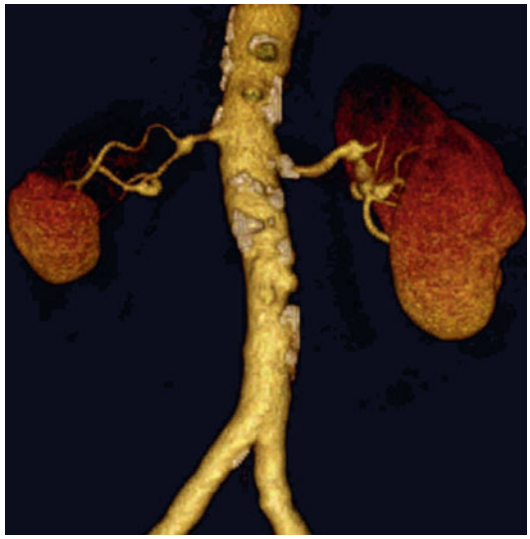


Fig. 13.8 Volume rendered CTA demonstrates severe long tubular stenoses in the right renal artery consistent with a variant of FMD typically arising from pathologic changes in the intima or adventitia

segment of long smooth narrowing, unifocal band-like stenosis or tubular stenosis (Fig. 13.8). Unlike proximal atheromatous changes of the renal artery, FMD is most common in the mid to distal main renal arteries but can extend into the first division branches. Bilateral disease occurs in 60 % of cases [21]. Complications of FMD can also be depicted on CTA including dissection, occlusion or thrombosis.

An additional rare, noninflammatory disease which most commonly involves the visceral arteries including the renal arteries is segmental arterial mediolysis (SAM) which affects the small to medium arterial distribution and has equal distribution between men and women. Some authors consider SAM to be a variant of or precursor to FMD [22–25]. The average age of presentation is in the fifth decade of life. The etiology of this disorder is unknown and lack of familiarity with the imaging findings can result in misdiagnosis of vasculitis or even neoplasm. CTA has been shown to be a useful imaging tool in the diagnosis and follow-up of patients with SAM [24]. Patients most commonly present with abdominal, flank or chest pain and may be hypertensive or have hematuria. Findings of SAM include dissections, aneurysms, intramural hematomas, occlusions (Fig. 13.9a, b) [25, 26] and more commonly involves the mesenteric arteries (70 %) with the renal arteries involvement in 50 % [26]. Approximately 50 % of patients progress and 50 % resolve or decrease [26].

Renal Arterial Dissection and Thrombosis

Spontaneous renal arterial dissection is a rare cause of acute flank pain in the ER setting and is often accompanied with hypertension. The dissection is thought to result from an intramural hemorrhage or entrance of blood into the arterial wall through an intimal tear [27]. Underlying risk factors for spontaneous renal arterial dissection include atheromatous disease, renal arterial aneurysm, FMD, connective tissue disease (such as Ehlers-Danlos syndrome) or extension from an aortic dissection [27]. Current CTA technology allows direct visualization of the dissected intimal flap (Fig. 13.10a, b). Additional imaging findings of a renal arterial dissection include irregular dilatation and narrowing of the opacified arterial lumen, thrombosis of a renal arterial segment and/or regions of decreased perfusion to the renal parenchyma supplied by the dissected or thrombosed renal artery. Management options include conservative observational therapy with or without anticoagulation as well as surgical or endovascular intervention.

CTA also provides accurate determination of luminal patency and presence of renal arterial perfusion abnormalities or infarction from thromboembolic disease (Fig. 13.11a, b). CTA findings include a central low attenuation thrombus/embolus within the renal artery. The thromboembolism often originates from the heart or from irregular and ulcerated thoracoabdominal atheromatous disease. Emboli to the renal arteries can also be associated with atrial fibrillation, postmyocardial infarct emboli, bacterial endocarditis or atrial myxomas. Associated renal parenchymal perfusion changes most commonly consist of wedge-shaped parenchymal defects or global decreased perfusion changes to the involved kidney.

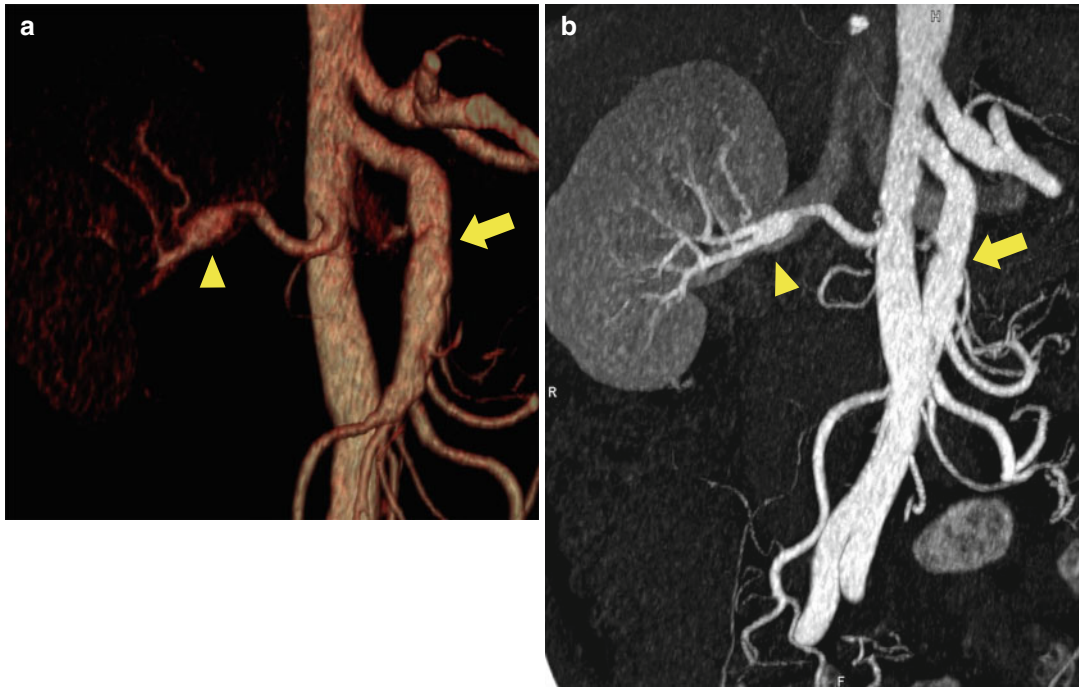


Fig. 13.9 (**a**, **b**) Volume rendered CTA (**a**) and a Maximum Intensity Projection (MIP) image (**b**) with focal aneurysmal changes in the right renal artery (*arrowhead*) and diffuse dilatation of the superior mesenteric artery (*arrow*) consistent with CTA findings of segmental arterial mediolysis (SAM)

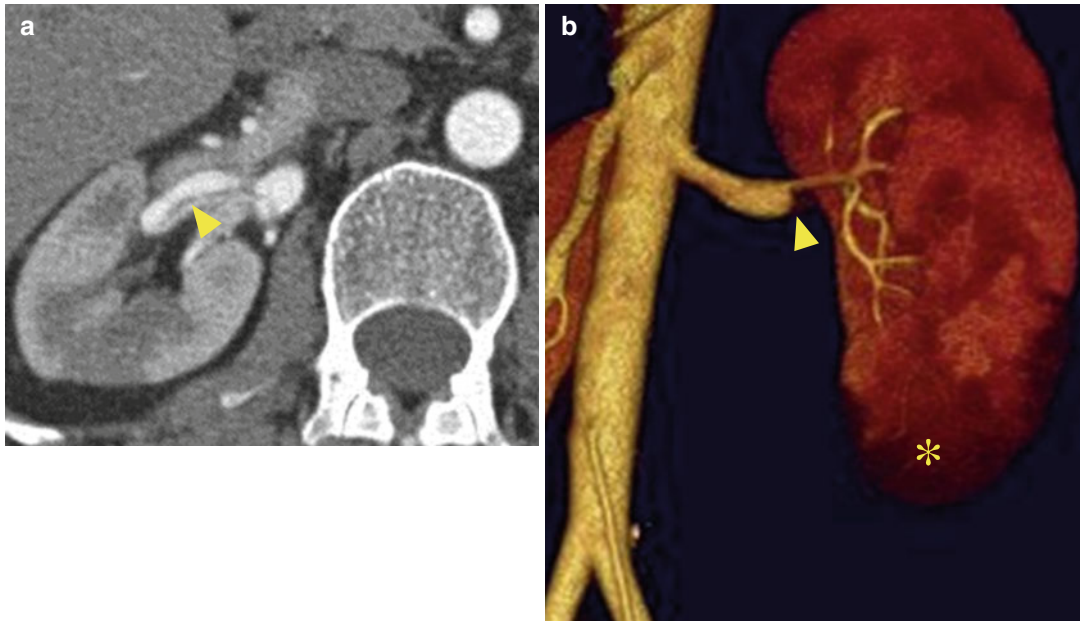


Fig. 13.10 (**a**) Axial CT image with intimal dissection extending into the anterior division of the right renal artery (*arrowhead*). (**b**) Volume rendered CTA demonstrates the abrupt occlusion from prior dissection and intramural hematoma involving the distal left renal artery. Note the decreased perfusion to the lower pole of the left kidney (*)

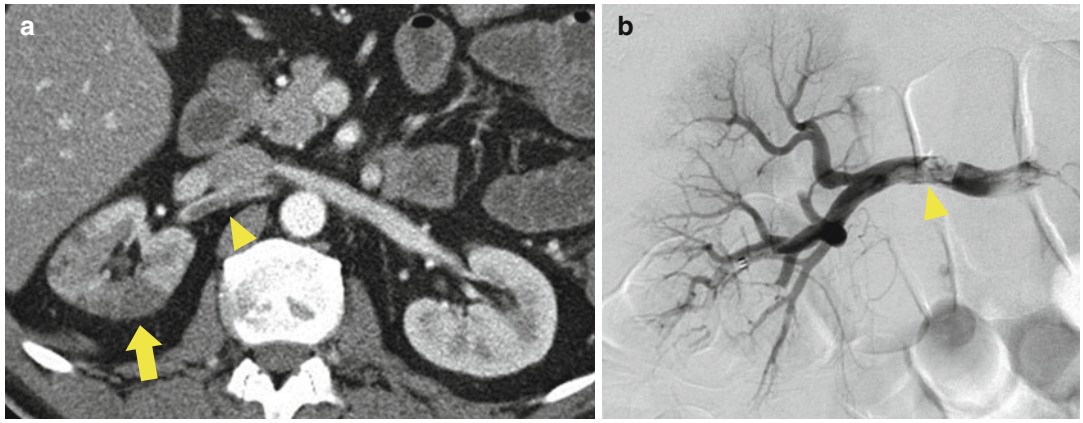


Fig. 13.11 (**a**, **b**) Axial images from a CTA (**a**) and catheter-directed renal angiogram (**b**) with focal embolus in the main right renal artery (*arrowhead*). Associate decreased parenchymal perfusion is evident in the lateral and posterior right kidney (*arrow*)

Vasculitis

Noninvasive vascular imaging such as CTA has replaced catheter angiography in the evaluation and follow-up of vasculitis given the great advantage of evaluation of both the arterial wall as well as luminal changes. Systemic vasculitides frequently involve the renal arteries. The large vessel vasculitides most commonly resulting in renal arterial abnormalities include giant cell (temporal) arteritis and Takayasu arteritis. CTA demonstrates not only the circumferential and concentric wall thickening of active inflammatory changes but also the stenosis of the renal arterial ostia either unilaterally or bilaterally (Fig. 13.12a, b). Less commonly, aneurysms and occlusions are detected. A medium vessel vasculitis involving the kidneys that has been demonstrated by CTA using the latest technological advancements is polyarteritis nodosa (PAN) [28]. Areas of decreased parenchymal perfusion and infarction are associated with renal involvement in PAN and can be confused with pyelonephritis. Multiple small intrarenal arterial aneurysms measuring 1–5 mm are occasionally demonstrated by CTA typically occurring in the intrarenal arterial distribution of the distal interlobar arteries [28]. Associated changes of the renal arteries include ectasia, occlusion and rare aneurysmal rupture [29].

Renal Arterial Aneurysm

Aneurysms uncommonly involve the renal arteries occurring in 0.1 % of the population [30]. Renal arterial aneurysms (RAAs) are more commonly seen in women and are typically solitary and unilateral (Fig. 13.13a–c). Saccular RAAs are more frequent (79 %) than the fusiform type and are most commonly located at the distal bifurcation of the main renal artery [30–32]. The fusiform type of aneurysm is commonly associated with changes of renal artery medial FMD. RAAs are commonly asymptomatic and discovered incidentally [31] but complications such as hypertension, renal infarction, rupture, renal arterial thrombosis and arteriovenous fistula do occur. Fortunately, the risk of spontaneous rupture of a RAA is very low. Specific risk factors for RAA rupture include premenopausal women, pregnancy and increasing size of the aneurysm. The largest clinical experience with RAA was described by Henke et al [31] in a retrospective evaluation of 252 RAAs over 35 years in 168 patients and used to develop recommendations for management of RAAs that were recently confirmed by Morita et al [33]. Options for RAAs intervention include aneurysmectomy, renal arterial bypass, embolization, endovascular stenting and nephrectomy.

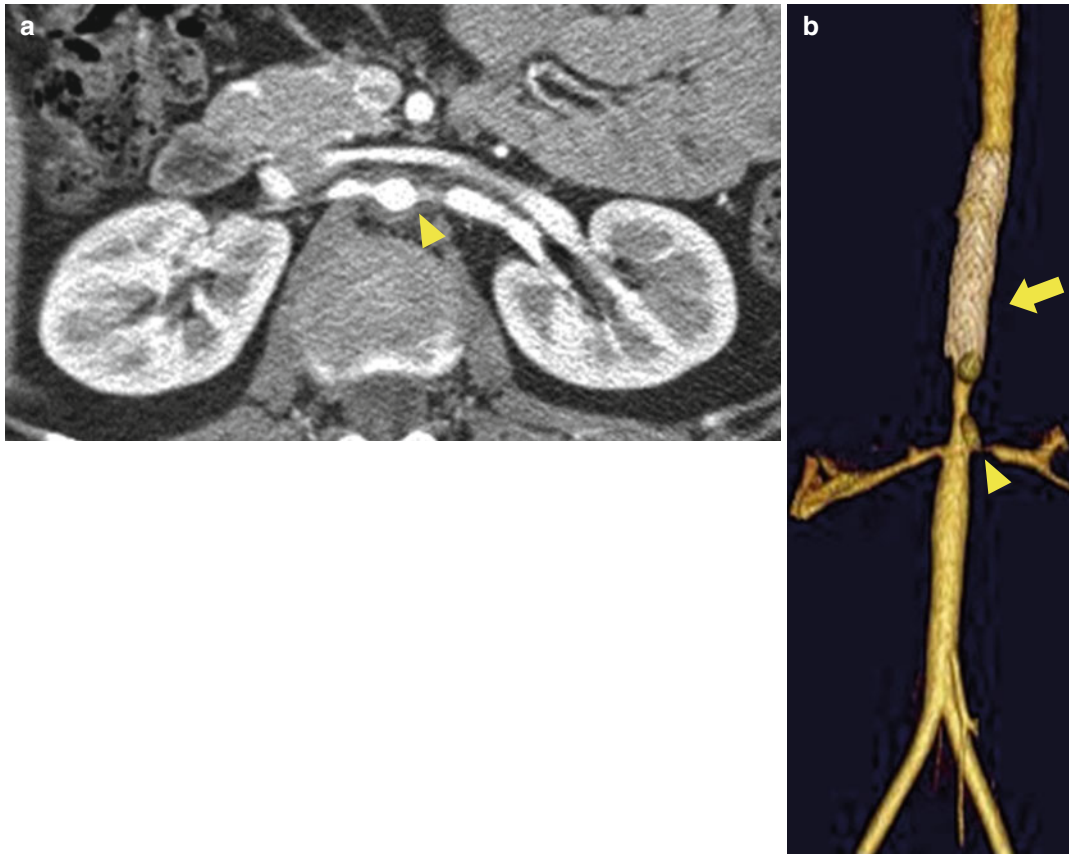


Fig. 13.12 (**a**) Axial images from a CTA demonstrates a rind of circumferential wall thickening surrounding the abdominal aorta at the level of the renal arteries consistent with vasculitis resulting in high grade stenosis at the origin of the left renal artery. (**b**) Volume rendered CTA image demonstrates the high grade stenosis at the origin of the left renal artery below a stented segment of the descending thoracic aorta (*arrow*)

Diseases most commonly associated with RAAs are hypertension and FMD [30], but RAAs also occur with segmental arterial mediolysis [26], arteritis, Marfan's syndrome, Ehlers Danlos Type IV and neurofibromatosis. An additional rare disease associated with multiple tiny renal peripheral intrarenal aneurysms is polyarteritis nodosa (Fig. 13.14a, b).

CTA is helpful to determine the size, contour and calcification of a single or multiple RAAs. In addition, CTA accurately depicts the anatomic relationship of the aneurysm to the main renal artery as well as to segmental intrarenal branches. Careful follow-up measurements and comparisons using sequential renal CTA exams exclude aneurysm enlargement or rupture and help determine the appropriate timing for endovascular or open surgical intervention.

Renal Trauma

High-grade injuries involving the renal artery occur in 11 % of traumatic injuries to the kidney [34] and are classified by the American Association of Surgeons in Trauma grading system [34, 35] as a Grade 4 injury when involving the renal artery or vein with a contained hemorrhage, whereas avulsion of the renal hilum that devascularizes the kidney is a Grade 5 injury. Renal arterial injuries include renal arterial dissection, occlusion and thrombosis (Fig. 13.15),

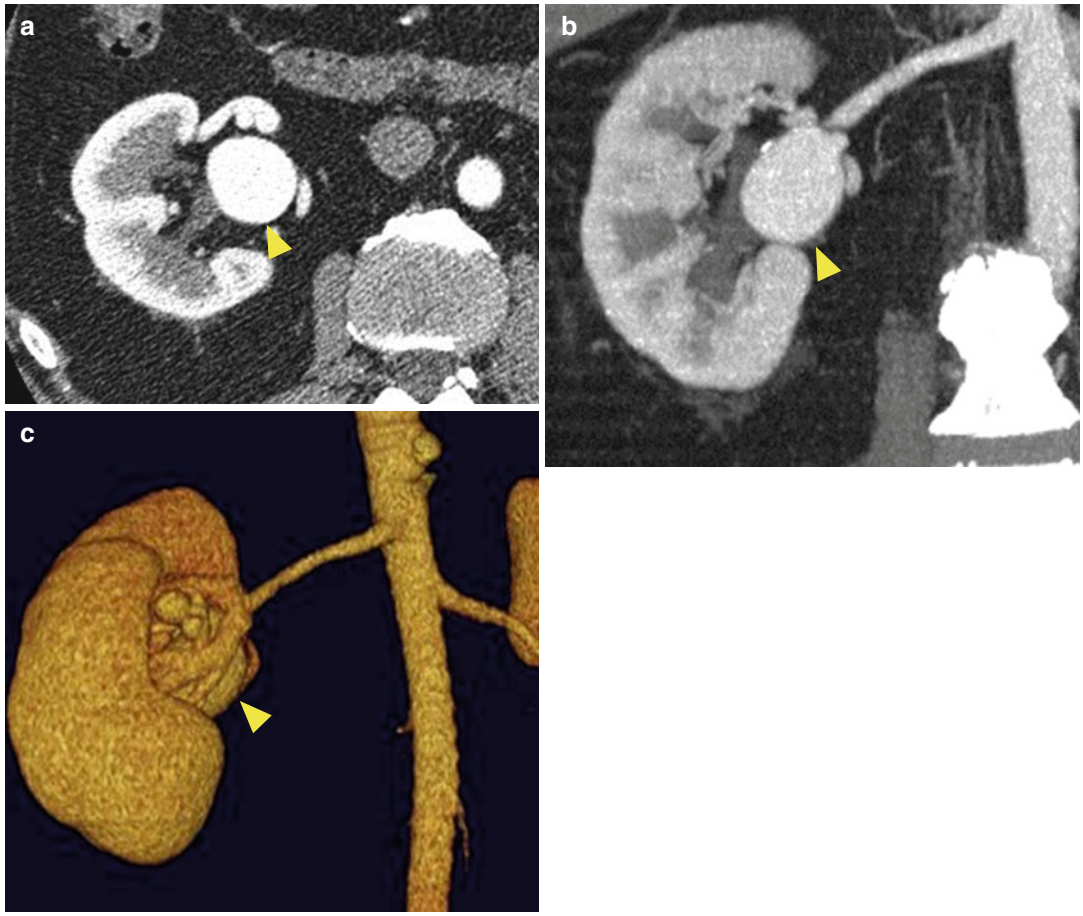


Fig. 13.13 (**a**–**c**) Axial images (**a**), coronal MIP image (**b**), and volume rendered 3D image (**c**) from a renal CTA demonstrates a well-circumscribed renal artery aneurysm (*arrowhead*) in the right renal hilum measuring 25 mm in diameter with minimal mural thrombus or calcification

which may be associated with perfusion changes to the involved renal parenchyma segment. Extraluminal contrast extravasation or renal arterial pseudoaneurysm are CTA findings which also denote a renal pedicle injury [36].

Nephron-Sparing Surgery/Follow-up

CTA is useful for preoperative evaluation prior to resection of renal masses such as renal cell carcinoma. Renal interventions are being performed using less invasive surgical techniques for laparoscopic removal of renal tumors. Appropriate indications for nephron-sparing surgery (NSS) have expanded beyond that of a solitary kidney, an abnormal contralateral kidney, multiple bilateral renal tumors or decreased renal function. Detection of 50 % of renal cell carcinomas are made incidentally [37] given the extensive availability and utilization of advanced cross-section imaging. By combining the earlier tumor detection and advances in NSS techniques, the indications for resection of renal masses using NSS have expanded to include the incidental, small (<4 cm) cortical renal mass (Fig. 13.16a, b) or the peripheral, exophytic mass without metastases. CTA is an important preoperative planning tool for small tumors that can be resected using these techniques by accurately depicting renal arterial and venous anatomy [38]. In addition, accurate display of the renal arterial supply of large renal tumors is determined in 98 % of cases [39] and the depiction of renal vein invasion provides a

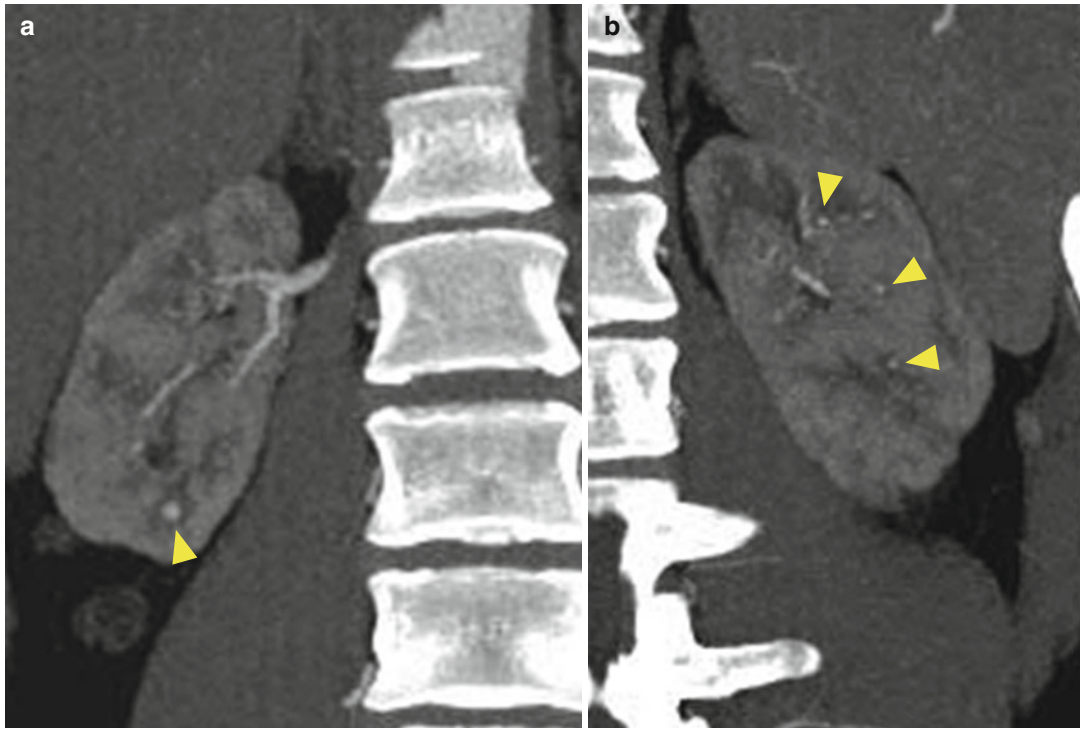


Fig. 13.14 (**a**, **b**) Coronal MIP images demonstrate multiple small peripheral intra-arterial aneurysms (*arrowheads*) consistent with polyarteritis nodosa (PAN)

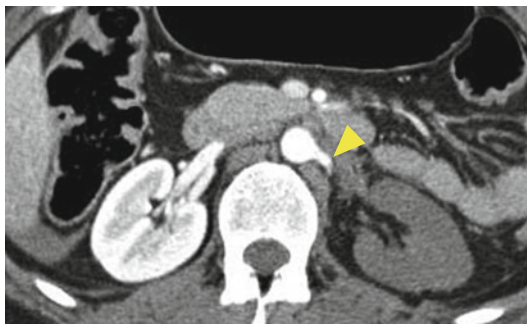


Fig. 13.15 Axial CTA images following motor vehicle accident in a 25 year old male demonstrate abrupt occlusion of the left renal artery (*arrowhead*) with lack of perfusion to the left kidney consistent with traumatic left renal artery injury

helpful preoperative planning tool with a high positive and negative predictive value by renal CTA (92 and 97 % respectively) [40]. The extent of IVC thrombus by CT is also a useful imaging planning contribution by depicting presence of tumor thrombus above the diaphragm potentially altering the surgical approach to tumor resection.

Future Opportunities in CTA of the Kidneys

Optimization of renal artery CTA in the future includes technique enhancement along with continued radiation dose reduction using both hardware and software advancements. The newest advances in CT technology include dual energy CT (DECT) acquisitions, low kV CTA and iterative reconstruction techniques, which are providing new avenues for the evaluation of renal arterial anatomy and pathology using the lowest radiation doses. With DECT, the acquisition of images at two different kilovoltages (typically 80 and 140 kVp) provides new opportunities for specific material characterization and separation of anatomic structures [41, 42]. For example, renal arterial wall atheromatous calcification could be separated from the opacified lumen with improved depiction of renal arterial stenosis such has been currently applied to calcified lower extremity arterial vasculature [43] and the carotid arteries [44]. DECT also provides for rapid

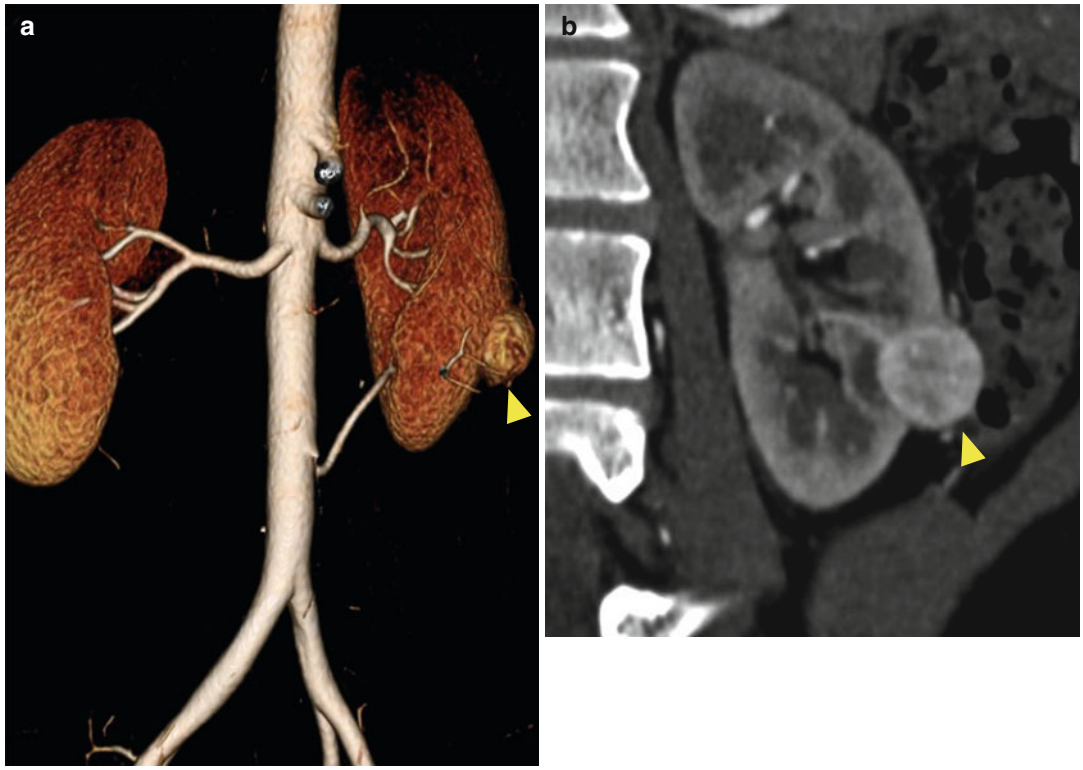


Fig. 13.16 (**a**, **b**) Volume rendered 3D CTA (**a**) and coronal reconstruction (**b**) demonstrate a 2.5 cm intensely hypervascular exophytic mass arising from the lateral lower pole of the left kidney (*arrow*) which was shown to represent a small renal cell carcinoma at surgical resection

characterization and separation of bones which enhances rendering of 3D CTA exams. In addition, virtual noncontrast CT imaging can be created from the contrast enhanced CT data for precontrast measurements of indeterminate renal masses or detection of urinary calculi [42]. Low kV CTA exams allow improved visualization of high attenuation structures such as small intrarenal arterial branches [45, 46] by taking advantage of the specific attenuation characteristics including the molecular properties (k-edge) of iodine at lower kVs. Application of low kV imaging in the appropriate (typically smaller) patients can result in reduced radiation dose as well as potential reduction in the volume of iodinated contrast material needed for a renal arterial CTA [45, 46]. Finally, while decreases in tube voltage and radiation doses are a beneficial direction in the optimal care of patients with renal arterial disease, these improvements can be negated by an increase in image noise and a decrease in image quality. Fortunately, additional advances in CT technology including reconstruction of imaging data through advanced computer algorithms termed iterative reconstruction [47] can offset the challenges of image noise and potential image quality reduction while lowering radiation dose by 50 % or greater.

Conclusion

CTA provides a highly accurate evaluation of the renal arteries. Continued advances in CT scanner acquisitions and image post-processing technologies will continue to further the accurate depiction and diagnosis of renal arterial anatomy and pathology at the lowest possible radiation dose tailored to the specific clinical need of the patient.

References

1. Glockner JF, Vrtiska TJ. Renal MR and CT angiography: current concepts. Abdom Imaging. 2007;32:407–20.
2. Zamboni GA, Romero JY, Raptopoulos VD. Combined vascular-excretory phase MDCT angiography in the preoperative evaluation of renal donors. AJR Am J Roentgenol. 2010;194:145–50.
3. Holden A, Smith A, Dukes P, Pilmore H, Yasutomi M. Assessment of 100 live potential renal donors for laparoscopic nephrectomy with multi-detector row helical CT. Radiology. 2005;237:973–80.
4. Gluecker TM, Mayr M, Schwarz J, Bilecen D, Voegele T, Steiger J, et al. Comparison of CT angiography with MR angiography in the preoperative assessment of living kidney donors. Transplantation. 2008;86:1249–56.
5. Pozniak MA, Balison DJ, Lee Jr FT, Tambeaux RH, Uehling DT, Moon TD. CT angiography of potential renal transplant donors. Radiographics. 1998;18:565–87.
6. Pollak R, Prusak BF, Mozes MF. Anatomic abnormalities of cadaver kidneys procured for purposes of transplantation. Am Surg. 1986;52:233–5.
7. Safian RD, Textor SC. Renal-artery stenosis. N Engl J Med. 2001;344:431–42.
8. Willmann JK, Wildermuth S, Pfammatter T, Roos JE, Seifert B, Hilfiker PR, et al. Aortoiliac and renal arteries: prospective intraindividual comparison of contrast-enhanced three-dimensional MR angiography and multi-detector row CT angiography. Radiology. 2003;226:798–811.
9. Rountas C, Vlychou M, Vassiou K, Liakopoulos V, Kapsalaki E, Koukoulis G, et al. Imaging modalities for renal artery stenosis in suspected renovascular hypertension: prospective intraindividual comparison of color Doppler US, CT angiography, GD-enhanced MR angiography, and digital substraction angiography. Ren Fail. 2007;29:295–302.
10. Fraioli F, Catalano C, Bertoletti L, Danti M, Fanelli F, Napoli A, et al. Multidetector-row CT angiography of renal artery stenosis in 50 consecutive patients: prospective interobserver comparison with DSA. Radiol Med. 2006;111:459–68.
11. Leertouwer TC, Gussenhoven EJ, Bosch JL, van Jaarsveld BC, van Dijk LC, Deinum J, et al. Stent placement for renal arterial stenosis: where do we stand? A meta-analysis. Radiology. 2000;216:78–85.
12. Manousaki E, Perisinakis K, Karantanas A, Tsetis D. MDCT angiography assessment of renal artery in-stent restenosis: can we reduce the radiation exposure burden? A feasibility study. Eur J Radiol. 2011;79:224–31.
13. Steinwender C, Schutzenberger W, Fellner F, Honig S, Schmitt B, Focke C, et al. 64-Detector CT angiography in renal artery stent evaluation: prospective comparison with selective catheter angiography. Radiology. 2009;252:299–305.
14. Beregi JP, Louvegny S, Gautier C, Mounier-Vehier C, Moretti A, Desmoucelle F, et al. Fibromuscular dysplasia of the renal arteries: comparison of helical CT angiography and arteriography. AJR Am J Roentgenol. 1999;172:27–34.
15. Sabharwal R, Vladica P, Coleman P. Multidetector spiral CT renal angiography in the diagnosis of renal artery fibromuscular dysplasia. Eur J Radiol. 2007;61:520–7.
16. Willoteaux S, Faivre-Pierret M, Moranne O, Lions C, Bruzzi J, Finot M, et al. Fibromuscular dysplasia of the main renal arteries: comparison of contrast-enhanced MR angiography with digital subtraction angiography. Radiology. 2006;241:922–9.
17. Vasbinder GB, Nelemans PJ, Kessels AG, Kroon AA, Maki JH, Leiner T, et al. Accuracy of computed tomographic angiography and magnetic resonance angiography for diagnosing renal artery stenosis. Ann Intern Med. 2004;141:674–82; discussion 682.
18. Youngberg SP, Sheps SG, Strong CG. Fibromuscular disease of the renal arteries. Med Clin North Am. 1977;61:623–41.
19. Liu PS, Platt JF. CT angiography of the renal circulation. Radiol Clin North Am. 2010;48:347–65, viii–ix.
20. Cragg AH, Smith TP, Thompson BH, Maroney TP, Stanson AW, Shaw GT, et al. Incidental fibromuscular dysplasia in potential renal donors: long-term clinical follow-up. Radiology. 1989;172:145–7.
21. Persu A, Touze E, Mousseaux E, Barral X, Joffre F, Plouin PF. Diagnosis and management of fibromuscular dysplasia: an expert consensus. Eur J Clin Invest. 2012;42:338–47.
22. Lie JT. Segmental mediolytic arteritis. Not an arteritis but a variant of arterial fibromuscular dysplasia. Arch Pathol Lab Med. 1992;116:238–41.
23. Slavin RE, Saeki K, Bhagavan B, Maas AE. Segmental arterial mediolysis: a precursor to fibromuscular dysplasia? Mod Pathol. 1995;8:287–94.
24. Michael M, Widmer U, Wildermuth S, Barghorn A, Duewell S, Pfammatter T. Segmental arterial mediolysis: CTA findings at presentation and follow-up. AJR Am J Roentgenol. 2006;187:1463–9.
25. Filippone EJ, Foy A, Galanis T, Pokuah M, Newman E, Lallas CD, et al. Segmental arterial mediolysis: report of 2 cases and review of the literature. Am J Kidney Dis. 2011;58:981–7.
26. Kalva SP, Somarouthu B, Jaff MR, Wicky S. Segmental arterial mediolysis: clinical and imaging features at presentation and during follow-up. J Vasc Interv Radiol. 2011;22:1380–7.
27. Stawicki SP, Rosenfeld JC, Weger N, Fields EL, Balshi JD. Spontaneous renal artery dissection: three cases and clinical algorithms. J Hum Hypertens. 2006;20:710–8.
28. Ozaki K, Miyayama S, Ushiogi Y, Matsui O. Renal involvement of polyarteritis nodosa: CT and MR findings. Abdom Imaging. 2009;34:265–70.
29. Stanson AW, Friese JL, Johnson CM, McKusick MA, Breen JF, Sabater EA, et al. Polyarteritis nodosa: spectrum of angiographic findings. Radiographics. 2001;21:151–9.

30. Stanley JC, Rhodes EL, Gewertz BL, Chang CY, Walter JF, Fry WJ. Renal artery aneurysms. Significance of macroaneurysms exclusive of dissections and fibrodysplastic mural dilations. Arch Surg. 1975;110:1327–33.
31. Henke PK, Cardneau JD, Welling 3rd TH, Upchurch Jr GR, Wakefield TW, Jacobs LA, et al. Renal artery aneurysms: a 35-year clinical experience with 252 aneurysms in 168 patients. Ann Surg. 2001;234: 454–62; discussion 62–3.
32. Eskandari MK, Resnick SA. Aneurysms of the renal artery. Semin Vasc Surg. 2005;18(4):202–8.
33. Morita K, Seki T, Iwami D, Sasaki H, Fukuzawa N, Nonomura K. Long-term outcome of single institutional experience with conservative and surgical management for renal artery aneurysm. Transplant Proc. 2012;44:1795–9.
34. Tinkoff G, Esposito TJ, Reed J, Kilgo P, Fildes J, Pasquale M, et al. American Association for the Surgery of Trauma Organ Injury Scale I: spleen, liver, and kidney, validation based on the National Trauma Data Bank. J Am Coll Surg. 2008;207:646–55.
35. Moore EE, Shackford SR, Pachter HL, McAninch JW, Browner BD, Champion HR, et al. Organ injury scaling: spleen, liver, and kidney. J Trauma. 1989;29: 1664–6.
36. Kawashima A, Sandler CM, Ernst RD, Tamm EP, Goldman SM, Fishman EK. CT evaluation of renovascular disease. Radiographics. 2000;20:1321–40.
37. Sheth S, Scatarige JC, Horton KM, Corl FM, Fishman EK. Current concepts in the diagnosis and management of renal cell carcinoma: role of multidetector ct and three-dimensional CT. Radiographics. 2001;21 Spec No:S237–54.
38. Kumar S, Neyaz Z, Gupta A. The utility of 64 channel multidetector CT angiography for evaluating the renal vascular anatomy and possible variations: a pictorial essay. Korean J Radiol. 2010;11:346–54.
39. Ferda J, Hora M, Hes O, Ferdova E, Kreuzberg B. Assessment of the kidney tumor vascular supply by two-phase MDCT-angiography. Eur J Radiol. 2007; 62:295–301.
40. Welch TJ, LeRoy AJ. Helical and electron beam CT scanning in the evaluation of renal vein involvement in patients with renal cell carcinoma. J Comput Assist Tomogr. 1997;21:467–71.
41. Graser A, Johnson TR, Chandarana H, Macari M. Dual energy CT: preliminary observations and potential clinical applications in the abdomen. Eur Radiol. 2009;19:13–23.
42. Vrtiska TJ, Takahashi N, Fletcher JG, Hartman RP, Yu L, Kawashima A. Genitourinary applications of dual-energy CT. AJR Am J Roentgenol. 2010;194: 1434–42.
43. Brockmann C, Jochum S, Sadick M, Huck K, Ziegler P, Fink C, et al. Dual-energy CT angiography in peripheral arterial occlusive disease. Cardiovasc Intervent Radiol. 2009;32:630–7.
44. Thomas C, Korn A, Ketelsen D, Danz S, Tsifikas I, Claussen CD, et al. Automatic lumen segmentation in calcified plaques: dual-energy CT versus standard reconstructions in comparison with digital subtraction angiography. AJR Am J Roentgenol. 2010;194: 1590–5.
45. Pinho DF, Kulkarni NM, Krishnaraj A, Kalva SP, Sahani DV. Initial experience with single-source dual-energy CT abdominal angiography and comparison with single-energy CT angiography: image quality, enhancement, diagnosis and radiation dose. Eur Radiol. 2012;23:351–9.
46. Cho ES, Yu JS, Ahn JH, Kim JH, Chung JJ, Lee HK, et al. CT angiography of the renal arteries: comparison of lower-tube-voltage CTA with moderate-concentration iodinated contrast material and conventional CTA. AJR Am J Roentgenol. 2012;199: 96–102.
47. Winklehner A, Karlo C, Puippe G, Schmidt B, Flohr T, Goetti R, et al. Raw data-based iterative reconstruction in body CTA: evaluation of radiation dose saving potential. Eur Radiol. 2011;21:2521–6.

Renal MR Angiography

14

James F. Glockner

Abstract

Renal MR angiography is frequently performed for noninvasive assessment of the renal arteries, usually in the setting of hypertension or renal insufficiency unresponsive to medical therapy. A variety of techniques are currently available, and examinations can be performed with or without intravenous gadolinium contrast agents. The most common contrast-enhanced and non-contrast techniques will be reviewed, along with their advantages and disadvantages, followed by a discussion of the various clinical indications for renal MRA, including an examination of the true accuracy of renal MRA for detecting clinically significant renal artery stenosis. Finally, recent and future developments in the field are assessed.

Keywords

MR angiography • MRI • Non-contrast MRA • Contrast-enhanced MRA • Phase contrast MRA • Renal artery stenosis • Atherosclerosis • Hypertension

Introduction

Evaluation of the renal arteries and veins is a common imaging request, most frequently in the setting of hypertension unresponsive to conventional medical therapy. While duplex sonography is often the first examination performed, this technique has a number of well-recognized limitations, including relatively poor anatomic visualization of the vessels, difficulty identifying the renal arteries in large patients, and performance variability depending on the experience and ability of the technologist. Renal MR angiography (MRA) and CT angiography (CTA) are therefore often performed either as an initial diagnostic examination or as a secondary noninvasive test when sonography is limited or indeterminate.

The mainstay of renal MR angiography has long been gadolinium-enhanced 3D MRA: this is a fast, accurate, and fairly simple technique which is widely employed for assessing virtually all vascular territories. Recent concerns regarding the development of nephrogenic systemic fibrosis (NSF) following gadolinium administration in

J.F. Glockner, MD, PhD
Department of Radiology, Mayo Clinic
College of Medicine, Mayo Clinic,
200 First Street, SW, Rochester, MN 55905, USA
e-mail: glockner.james@mayo.edu

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_14,

patients with renal failure have led to a significant reduction in the volume of renal MRA performed in most radiology practices: in some respects this is unfortunate, since gadolinium-enhanced MRA is a safe procedure in nearly all patients with mild-moderately reduced renal function; however, it has had the beneficial effect of stimulating the development of several effective non-contrast MRA techniques.

In this chapter, the technical aspects of the most common contrast-enhanced and non-contrast renal MRA techniques will be discussed, followed by a brief consideration of less widely employed methods as well as accessory functional techniques. The clinical indications for renal MR angiography and venography are discussed, along with the somewhat controversial issue of the accuracy of these techniques in detecting significant renal artery stenosis (RAS). Finally, recent developments and future directions are summarized.

Contrast-Enhanced Renal MRA

Contrast-enhanced renal MRA involves a fast 3D spoiled gradient echo pulse sequence performed in conjunction with intravenous bolus injection of a gadolinium-based contrast agent. Acquisition is coordinated with arrival of the contrast bolus in the abdominal aorta and renal arteries [1–5]. While the concept of timing the acquisition to capture the peak of the contrast bolus is somewhat analogous to conventional angiography and CT angiography, gadolinium contrast agents behave in a fundamentally different manner – they are not directly imaged, but instead exert an indirect effect on adjacent water protons in blood, reducing their T1 relaxation time and thereby increasing the signal intensity of arterial blood. The typical contrast-enhanced (CE) MRA sequence also has the effect (through relatively high flip angles and short repetition times (TRs)) of suppressing or saturating background tissue not exposed to gadolinium. Additional background suppression can be achieved by adding fat suppression pulses to the standard MRA pulse sequence (at a small cost in additional imaging time) or by subtracting the contrast-enhanced sequence from a pre-contrast mask acquisition (this method can generate misregistration artifacts in patients who are not consistent breath holders).

3D CE renal MRA is an attractive technique for a number of reasons: acquisition times are short enough to be encompassed within a reasonable breath hold, thereby greatly reducing or eliminating respiratory motion artifact. The short acquisition time is also helpful in preventing or minimizing venous contamination from the relatively rapid renal circulation. The reliance on gadolinium for image contrast reduces or eliminates many of the well-known artifacts associated with time-of-flight and phase contrast techniques. Three dimensional data acquisition coupled with excellent background suppression means that 3D reconstruction is relatively straightforward using any of the currently available methods such as maximum intensity projection (MIP) or volume rendering. The relative invisibility of calcium, while to some extent a limitation, can also be advantageous in allowing clear visualization of the renal artery lumen in patients with extensive arterial calcification. General advantages of MRI include the lack of ionizing radiation or iodinated contrast. MRA is generally considered a safe alternative to CTA or conventional angiography in patients with renal insufficiency, although there has been some recent controversy regarding the nephrotoxic effects of gadolinium contrast agents, particularly in high doses.

Limitations of 3D CE renal MRA involve fundamental constraints imposed by the requirement for acquisition during suspended respiration and during the first pass of the contrast bolus. Since spatial resolution is typically related to the number of phase encoding steps acquired in two dimensions, higher spatial resolution images require longer acquisition times. Additionally, as spatial resolution improves, voxel size decreases, and SNR diminishes – eventually the reduced SNR can compromise image quality. In general,

spatial resolution in renal 3D CE MRA has been considered adequate to detect significant (>50 %) stenosis of main renal arteries; it is limited in detection of stenoses in small accessory vessels, and may have reduced sensitivity for detection of subtle fibromuscular dysplasia. The typical voxel size for renal MRA in clinical practice today ranges between 1.5 and 3 mm^3: this resolution, while adequate for evaluation of main renal arteries, is significantly lower than the resolution achieved by conventional angiography as well as state-of-the-art multi-detector row CTA. Although flow-related artifacts are minimized with 3D CE MRA, they can occur, and 3D CE MRA probably tends to overestimate the severity of stenoses when compared to conventional angiography. These artifacts can be accentuated on MIP images, for example the appearance of short segment occlusion in the setting of critical stenosis, emphasizing the importance of viewing source images and thin section multi-planar reconstructions when interpreting these examinations. Usually this slight overestimation is not problematic; however, in cases where a stenotic lesion falls close to the boundary between moderate and severe, relatively subtle differences can determine whether or not a patient will proceed to conventional angiography and intervention. The lack of visible calcium may be advantageous as noted previously; however, it is also a limitation, since this information is useful to physicians contemplating renal artery stent placement or percutaneous transluminal angioplasty. General limitations of MRI include a small percentage of patients unable to undergo examinations because of claustrophobia or gadolinium contrast agent allergy. Patients with pacemakers, automatic internal cardiac defibrillator (AICD) devices, and certain aneurysm clips and implanted electronic devices are excluded from MRI.

Non-contrast Renal MRA

Non-contrast renal MRA is both an old and new technique and its recent growth is undoubtedly a result of concerns regarding the association of gadolinium contrast agents with nephrogenic systemic fibrosis (NSF) in patients with severely reduced renal function [6–8]. NSF is a sclerotic disease involving the skin and internal organs bearing some resemblance to scleroderma and causing significant morbidity and mortality. Most recent investigations have focused on modified steady state free precession (SSFP) pulse sequences [9–14]. SSFP sequences are attractive for their high vascular signal to noise ratio, short acquisition times, and inherent flow compensation. Most current commercially available versions of this technique involve the application of a spatially or slab-selective inversion pulse over the kidneys and renal arteries followed by a delay represented by the inversion time (TI). During the delay, the spins in this region recover magnetization via T1 relaxation, and at the correct TI (typically 1,100–1,400 ms) this signal reaches a null point. Meanwhile, arterial blood flowing into the slab during this time is not saturated, and has high signal intensity and high contrast relative to the suppressed background tissue. The relatively long inversion times required for this technique also necessitate some form of respiratory gating, and acquisition times, although much longer than the breath-held contrast-enhanced MRA technique, are still reasonable, usually in the range of 4–6 min. The 3D SSFP technique has demonstrated sensitivity and specificity for detection of significant renal artery stenosis fairly similar to contrast-enhanced MRA in several small single center trials, and may provide improved visualization of intra-renal arterial branches.

Limitations of this technique include artifacts related to irregular respiration, as well as problems with adequate visualization of the renal arteries in patients with slow arterial flow, since the extent of the visualized vascular tree depends on the distance that inflowing blood can travel within the specified inversion time. Spatial resolution can in theory be very high, since there are no limitations on acquisition time related to the length of the contrast bolus or the patient's breath hold capacity; however, in practice spatial resolution has generally been slightly lower than that

achieved in 3D CE MRA since longer acquisition times tend to lead to irregularities in respiration and degraded image quality.

Additional Techniques

Phase Contrast MRA

Phase contrast (PC) acquisitions encode velocity and flow information by applying short gradient pulses along the direction or directions of flow followed by a similar gradient pulse in the opposite direction. Stationary spins accumulate no net phase shift; however, spins moving in the direction of the gradient accumulate a net phase shift that is proportional to their velocity. Two sets of images are traditionally generated in phase contrast acquisitions: magnitude images reflecting anatomy, and phase images which provide velocity data on a pixel by pixel basis.

Magnitude images from 3D PC MRA have been used to assess the severity of a renal artery stenosis demonstrated on CE MRA: signal dropout is related to intravoxel dephasing caused by disordered flow in the region of a severe stenosis [15–17]. Two-dimensional cine phase contrast (cine PC) acquisitions are gated to an ECG (electrocardiogram) or peripheral pulse tracing and allow velocity and flow measurements throughout the cardiac cycle. Velocity measurements can be used in much the same manner as duplex sonography: loss of the characteristic early systolic peak, for example, is a good indication of hemodynamically significant stenosis [18, 19]. A recent multicenter study reported that the combined approach of 3D CE MRA with cine PC velocity profile analysis yielded the lowest interobserver variability and excellent agreement with conventional angiography [20]. More sophisticated analysis can be performed by combining the functional flow data from cine PC measurements with anatomic information from 3D CE MRA to construct a computational fluid dynamic model of the renal artery. Yim et al. have shown that this approach can be used to accurately predict the pressure gradient across a stenotic renal artery [21]. 3D cine PC can also be performed, allowing direct measurement of three-dimensional velocity profiles, rather than calculation from mathematical models. These are much longer acquisitions, however, and little work in this area has been done in the renal arteries.

2D and 3D SSFP

Unmodified 3D SSFP pulse sequences are more widely available than the inversion recovery, respiratory gated versions described previously. 3D SSFP acquisitions do not require gadolinium contrast agents and can be performed during breath holding, and generally are adequate for detection of significant stenosis in the proximal main renal arteries. The absence of background suppression, fat suppression, and venous suppression, however, means that 3D reconstructions are difficult, and separation of arteries from veins, particularly near the renal hilum, can be challenging.

2D SSFP images are rarely used in renal MRA, for the reason that the minimal achievable slice thickness is in the range of 2–4 mm, which is marginal for accurate detection of significant stenosis in a relatively small artery. On the other hand, overlapping 2D SSFP images can be obtained rapidly without breath-holding in patients unable to suspend respiration or unable to tolerate a longer respiratory-triggered acquisition, and therefore this technique is occasionally useful for excluding severe proximal disease in the renal arteries [22].

2D and 3D Time-of-Flight MRA

Time-of-flight (TOF) is one of the oldest MRA techniques, and does not require gadolinium contrast. This method relies on sequential acquisition of gradient echo images which results in saturation of spins in the imaging slice – blood flowing into the slice within the repetition time (TR) is unsaturated and therefore has much higher signal intensity. The limitations of TOF MRA in the abdomen are related to the long acquisition times and consequent motion artifact on images

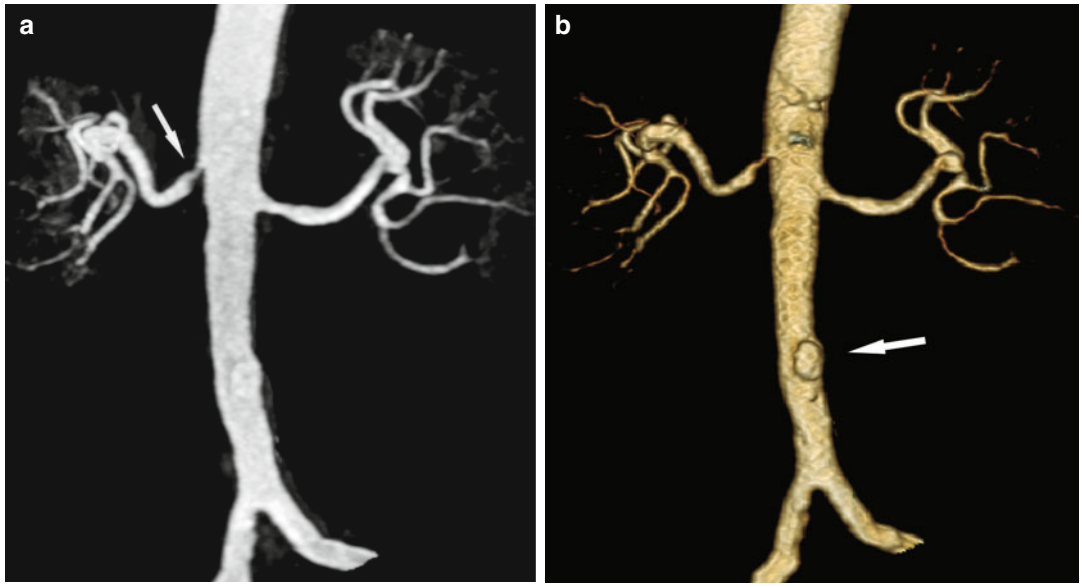


Fig. 14.1 (**a**, **b**) Maximum intensity projection (**a**) and volume-rendered images (**b**) from 3D CE MRA performed on an 84 year old patient with hypertension unresponsive to medication demonstrate marked focal narrowing of the proximal right renal artery (*arrow* in **a**) and mild narrowing of the proximal left renal artery. Notice also a penetrating ulcer in the distal abdominal aorta, better seen on the volume-rendered image (*arrow* in **b**)

acquired without respiratory triggering, which is not widely available for this technique. An additional limitation is that vessels oriented along the acquisition plane may have reduced signal intensity due to in-plane saturation effects, which can be a significant problem for visualizing the renal arteries in an axial acquisition plane.

Clinical Utility

Atherosclerotic Renal Artery Stenosis

The clinical indication for the vast majority of renal MRA examinations is assessment of the renal arteries in the setting of drug resistant hypertension and/or renal insufficiency (Figs. 14.1a, b, 14.2a, b, and 14.3). Atherosclerotic RAS is the most common cause of secondary hypertension, and it is estimated that RAS accounts for 5 % of all patients with hypertension and approximately 15 % of patients who develop end stage renal disease.

Renal MRA has been evaluated extensively for assessing renal artery stenosis, and most studies have found it to be highly accurate in most cases [2–5, 18–20]. A meta-analysis of 39 studies, for example, concluded that the sensitivity and specificity of gadolinium-enhanced MRA were 97 and 85 % respectively [23]. A second meta-analysis looked at multiple modalities and found that both CTA and MRA were highly accurate, with an area under the ROC curve of 0.99 [24]. On the other hand, several studies have had less successful results [25–28], the most notable of which is probably the multi-center RADISH trial published in 2004 [25], which demonstrated only moderate intraobserver agreement and combined sensitivity and specificity of 62 and 84 % for detection of significant renal artery stenosis.

The truth probably lies somewhere between the extremely high accuracy achieved in small single center studies and the disappointing results of the RADISH trial. Poor performance of renal MRA is frequently the result of technical inadequacies, often in combination with problematic patients. Spatial resolution is an important consideration, particularly when evaluating stenosis of small arteries with average diameter of 4–5 mm. Near isotropic spatial resolution on the order of 1 mm^3

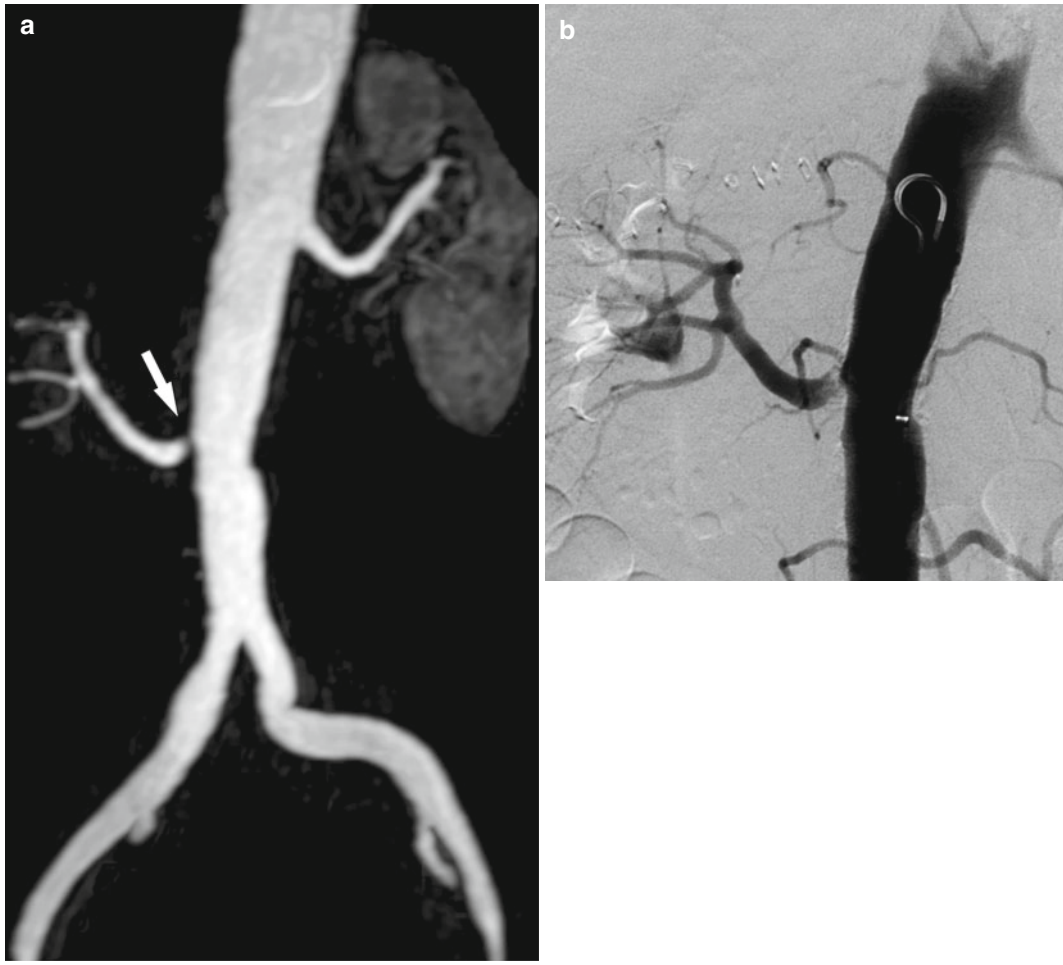


Fig. 14.2 (**a**, **b**) Maximum intensity projection image (**a**) from 3D MRA in a 76 year old female with medication-resistant hypertension demonstrates severe stenosis of the proximal right renal artery (*arrow*). Conventional angiogram in a similar projection (**b**) also reveals severe right renal artery stenosis

can probably be achieved in many cases, but this requires parallel imaging along with its reduction in SNR and associated artifacts, as well as careful prescription of the imaging volume in order to minimize the acquisition time. Unfortunately, there is often a direct relationship between acquisition time and spatial resolution, and this can in turn lead to significant motion artifact in patients who cannot suspend respiration for the duration of the acquisition. Similar considerations apply in non-contrast renal MRA, where irregular respirations, which tend to worsen as the scan time increases, may also lead to significant motion artifact in the resulting images. A successful examination with optimal image quality, then, often depends on adjustment of several imaging parameters according to the patient's size, anatomy, and breath holding ability.

Fibromuscular Dysplasia (FMD)

Fibromuscular dysplasia is a nonatherosclerotic noninflammatory vascular disorder which occurs most often in women aged 20–60 years and commonly involves the renal and extracranial carotid arteries, although any vascular territory can be affected. The renal arteries are affected in 75 % of FMD patients, with bilateral involvement in >35 %.

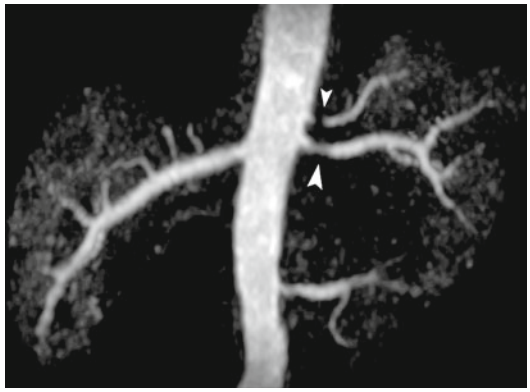


Fig. 14.3 A 55 year old female with chronic renal failure and severe hypertension. Maximum intensity projection image from 3D SSFP non-contrast renal MRA demonstrates a single right renal artery without significant stenosis and three left renal arteries. The superior and middle left renal arteries show severe proximal stenosis (*arrowheads*), with mild proximal narrowing of the inferior left renal artery

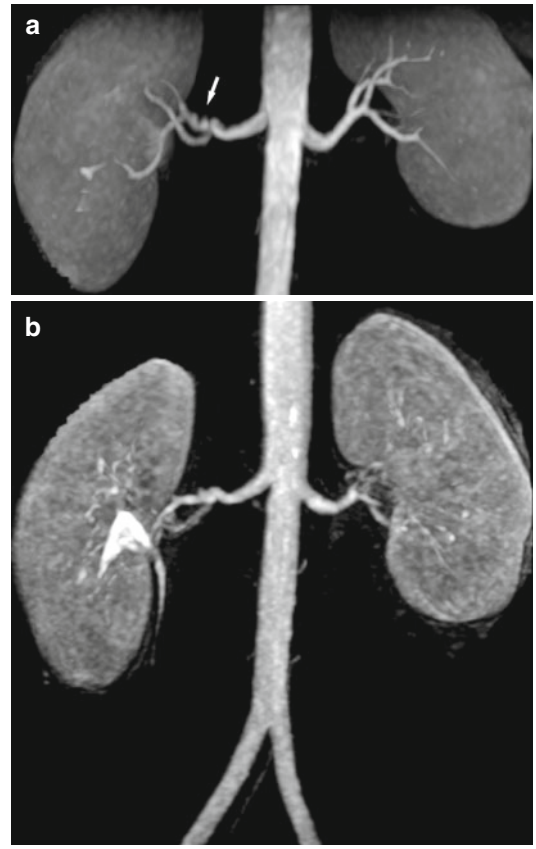


Fig. 14.4 (**a**, **b**) A 38 year old female with drug resistant hypertension. MIP images from non-contrast (**a**) and contrast-enhanced (**b**) 3D renal MRA demonstrate beading of the mid-distal right main renal artery consistent with fibromuscular dysplasia (*arrow*). More subtle changes of the distal left renal artery are better seen on the contrast-enhanced MRA

The accuracy of renal MRA for detection of hemodynamically significant FMD has not been adequately assessed in the literature. It seems reasonable to expect that MRA might be less successful in detecting FMD in comparison to atherosclerotic RAS since FMD lesions are more commonly shorter and more frequently involve the mid-distal main renal artery as well as segmental intra-renal branches, all of which are smaller and generally less well seen with MRA. Indeed, one of the explanations cited for the poor performance of MRA in the RADISH trial was the high prevalence of FMD in that study population. Nevertheless, MRA can detect many patients with significant FMD (Fig. 14.4a, b), and the recently developed non-contrast MRA techniques may eventually reveal a higher sensitivity, since they frequently demonstrate superior visualization of distal renal artery segments in comparison to CE MRA.

Renal Cell Carcinoma

Staging of renal cell carcinoma is a relatively common indication for abdominal MRI. While highly vascular tumors are sometimes embolized prior to surgical resection, and demonstration of this along with mapping the arterial supply of the lesion can be obtained with renal MRA, a more common clinical question involves MR venography: tumor thrombus involving the renal vein or inferior vena cava (IVC) is discovered in 4–10 % of patients, and approximately 50 % of these have extension of tumor thrombus into the intrahepatic IVC or right atrium.

Contrast-enhanced MRI is highly accurate for detection of renal vein and IVC thrombus, and the distinction between bland and tumor thrombus is usually straightforward. Non-contrast MR venography (MRV) is also very effective at

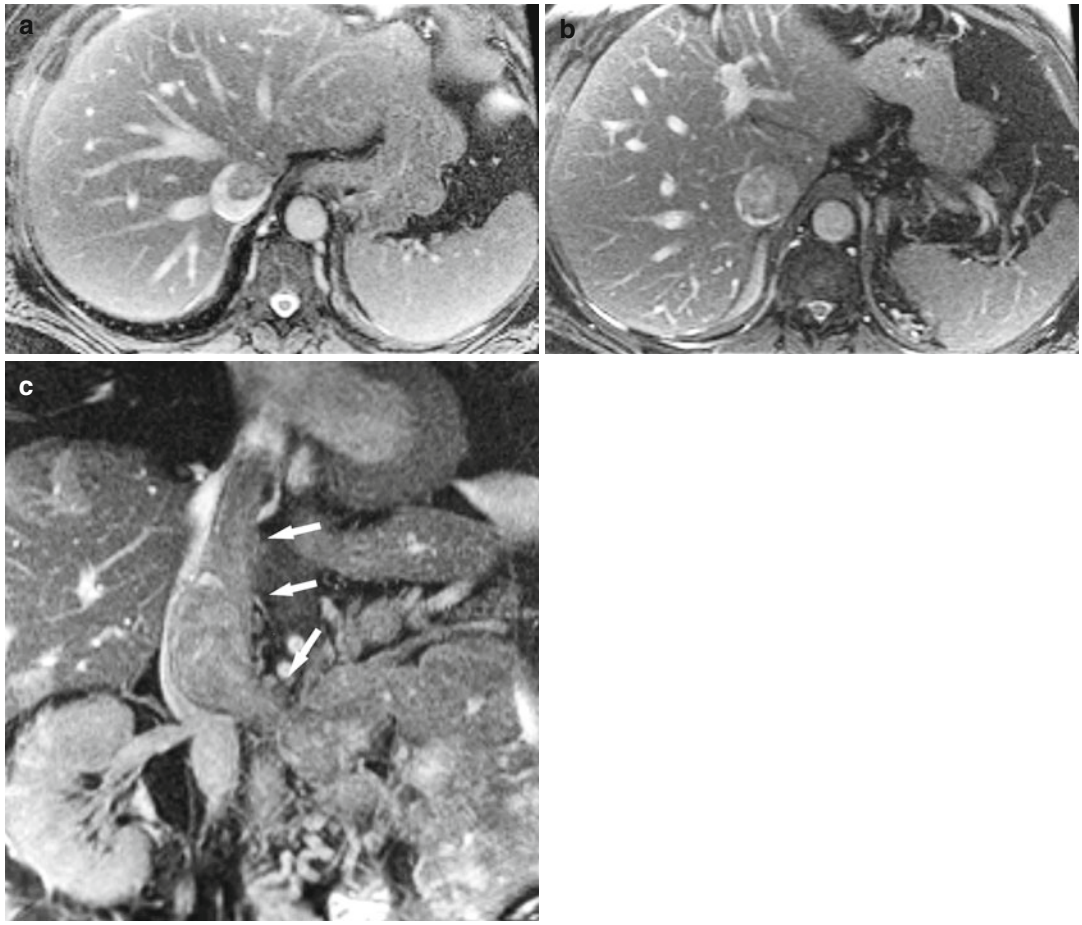


Fig. 14.5 (**a**–**c**) A 58 year old male with renal mass. Axial (**a**, **b**) and coronal (**c**) fat-suppressed 2D SSFP images demonstrate heterogeneous tumor thrombus expanding the left renal vein and extending superiorly in the IVC to the right atrium (*arrows* in **c**). Notice also the large ill-defined left renal mass

detecting renal vein and IVC thrombus, in particular 2D or 3D SSFP acquisitions, in patients with significant renal insufficiency or contrast allergies (Fig. 14.5a–c) [29].

Renal Transplantation

End stage renal disease is increasing in prevalence, with large numbers of patients on waiting lists for kidney transplants. Living donor transplantation is increasing, as are less invasive laparoscopic techniques for harvesting donor kidneys. While most transplantation centers employ a comprehensive CT angiography, venography, and urography protocol to screen potential renal donors, several authors have demonstrated that MRI performs just as well, without subjecting donors to radiation exposure [30–34].

MRI is also an effective tool for assessing the post-operative renal transplant recipient (Fig. 14.6a, b). Renal MRA/MRV can assess arterial and venous anastomoses and also identify renal or perirenal fluid collections and collecting system abnormalities [35, 36]. Non-contrast MRA techniques are particularly attractive in this population, where renal insufficiency is a frequent accompaniment of post-transplantation complications [37].

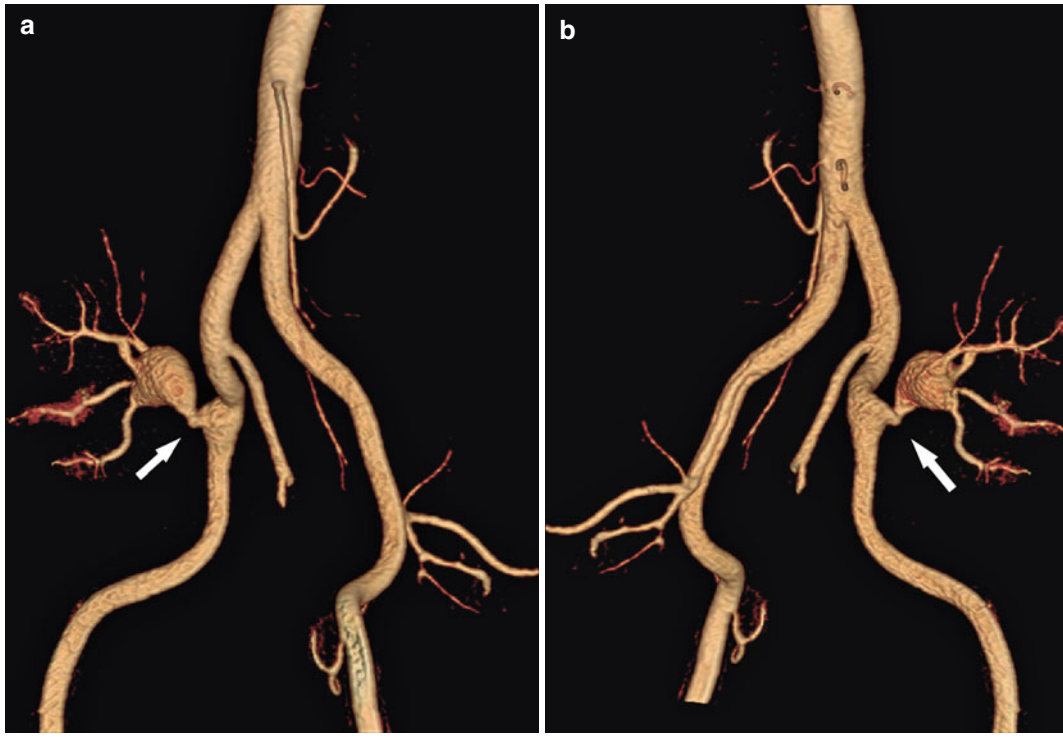


Fig. 14.6 (**a**, **b**) Anterior (**a**) and posterior (**b**) volume-rendered images from contrast-enhanced 3D MRA in a patient with a renal transplant and hypertension demonstrate stenosis and torsion of the transplant main renal artery near its origin (*arrows*) with aneurysmal dilatation distal to this

Renal Artery Aneurysms

Renal artery aneurysms are often incidentally detected in patients whose kidneys or renal arteries are imaged for other indications. The clinical relevance of renal artery aneurysms is uncertain; however, the risk of rupture increases with increasing diameter, and MRA provides a safe, non-invasive technique for their detection and characterization (Fig. 14.7a, b) [38].

Recent and Future Developments

Recent advances in contrast-enhanced MRA involve reduced acquisition times through the application of parallel imaging techniques, time-resolved MRA, new gadolinium contrast agents, and higher field strength magnets. Parallel imaging is a technique in which the number of phase encoding steps is reduced by a factor of 2 or greater by using spatial information available from the signal in each of the individual phased array coil elements to reconstruct the missing information [39, 40]. Since phase encoding is performed in two directions in 3D MRA (frequency encoding is performed in one direction), parallel imaging can be employed in two dimensions, with corresponding gains in acquisition time. Parallel imaging can be used to shorten the acquisition time for a given spatial resolution, which is very helpful for patients with limited breath hold capacity, or to increase spatial resolution without increasing the acquisition time – and in fact spatial resolution on the order of 1 mm^3 can be achieved for renal MRA with reasonable acquisition times. Parallel imaging requires multi-element phased array surface coils, which are widely available, with the maximal acceleration roughly proportional to the number of coil elements. Limitations of parallel

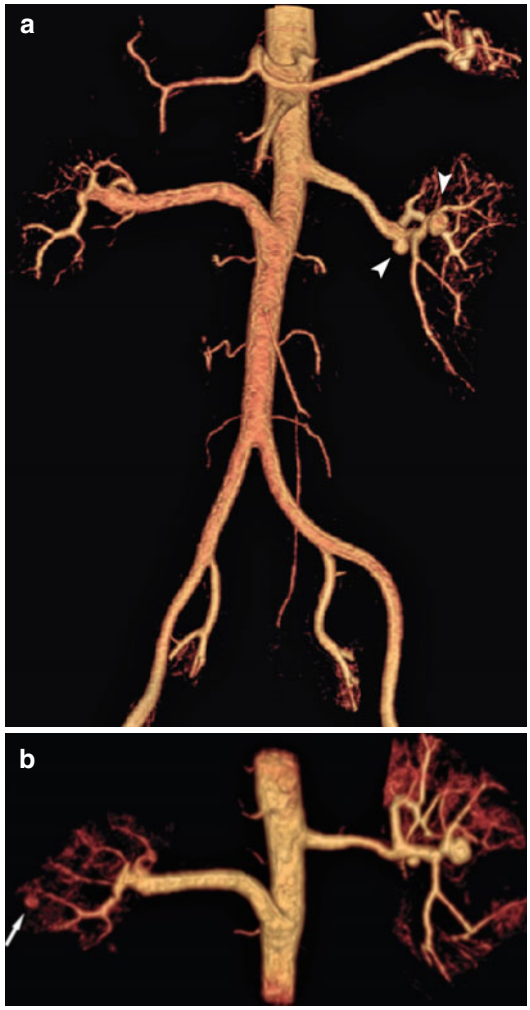


Fig. 14.7 (**a**, **b**) A 61 year old male with history of renal artery aneurysms requiring right sided renal artery bypass graft. Volume rendered images from contrast-enhanced MRA (**a**) and non-contrast MRA (**b**) demonstrate two small aneurysms in segmental left renal artery branches (*arrowheads*). Notice the small peripheral aneurysm in the right kidney faintly seen on the non-contrast MRA (*arrow*) as well as small aneurysms of the splenic artery on the contrast-enhanced MRA

imaging include image artifacts, which generally increase as the acceleration increases, and loss of SNR as acceleration increases. Parallel imaging, along with additional k-space undersampling strategies, view sharing techniques, and sparse data reconstruction methods can be combined to allow time-resolved contrast-enhanced MRA with excellent spatial resolution and temporal resolution on the order of a few seconds. The utility of these techniques for renal MRA is not entirely clear; however, they may also be helpful in patients with limited breath hold capacity and may reduce motion artifact seen during longer breath holds and allow improved visualization of subtle vascular abnormalities such as fibromuscular dysplasia [41]. An additional potential benefit lies in the possibility of using reduced doses of gadolinium contrast, particularly when coupled with a high field strength (3 T) magnet [42].

Higher magnetic field strength systems, the vast majority of which are 3 T magnets, are becoming widely available. 3 T offers some advantages for contrast-enhanced renal MRA. Since signal strength scales linearly with field strength, in theory SNR should be doubled at 3 T in comparison to 1.5 T. This is not quite true in practice, but SNR gains are nevertheless significant. An additional effect of higher magnetic field strength is a lengthening of tissue T1 relaxation times while the relaxivity of gadolinium-based contrast agents remains relatively unchanged – this is beneficial in 3D CE MRA in that background tissue becomes more saturated at 3 T for similar imaging parameters, meaning that background suppression is improved, and also that lower contrast doses may be employed.

Summary

Renal MRA is an effective technique for assessing the renal vasculature, and when images of high quality are obtained, is highly accurate for detecting significant renal artery stenosis. The recent implementation of new non-contrast MRA techniques provides additional flexibility for assessment of patients in whom gadolinium-based contrast agents are contraindicated.

References

1. Prince MR, Yucel EK, Kaufman JA, et al. Dynamic gadolinium-enhanced three-dimensional abdominal MR arteriography. J Magn Reson Imaging. 1993;3: 877–81.
2. Schoenberg SO, Rieger J, Weber CH, et al. High spatial resolution MR angiography of renal arteries with integrated parallel acquisitions: comparison with digital subtraction angiography and US. Radiology. 2005; 235:687–98.
3. Kramer U, Kambiz N, Laub G, et al. High-resolution magnetic resonance angiography of the renal arteries using parallel imaging acquisition techniques at 3.0 T. Invest Radiol. 2006;41:125–32.
4. Stacul F, Gava S, Belgrano M, et al. Renal artery stenosis: comparative evaluation of gadolinium-enhanced MRA and DSA. Radiol Med. 2008;113:529–46.
5. Slanina M, Zizka J, Kizo L, et al. Contrast-enhanced MR angiography utilizing parallel acquisition techniques in renal artery stenosis detection. Eur J Radiol. 2010;75:e46–50.
6. Cowper SE, Robin HS, Steinberg SM, et al. Scleromyxoedema-like cutaneous diseases in renal dialysis patients. Lancet. 2000;356:1000–1.
7. Grobner T. Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol Dial Transplant. 2006;21:1104–8.
8. Weinreb JC, Kuo PH. Nephrogenic systemic fibrosis. Magn Reson Imaging Clin N Am. 2009;17: 159–67.
9. Miyazaki M, Akahane M. Non-contrast enhanced MR angiography: established techniques. J Magn Reson Imaging. 2012;35:1–19.
10. Maki JH, Wilson GJ, Eubank WB, et al. Steady-state free precession MRA of the renal arteries: breath-hold and navigator-gated techniques vs. CE-MRA. J Magn Reson Imaging. 2007;26:966–73.
11. Wyttenbach R, Braghetti A, Wyss M, et al. Renal artery assessment with nonenhanced steady-state free precession versus contrast-enhanced MR angiography. Radiology. 2007;25:186–95.
12. Glockner JF, Takahashi N, Kawashima A, et al. Non-contrast renal artery MRA using an inflow inversion recovery steady state free precession technique (Inhance): comparison with 3D contrast-enhanced MRA. J Magn Reson Imaging. 2010;31: 1411–8.
13. Mohrs OK, Petersen SE, Schulze T, et al. High-resolution 3D unenhanced ECG-gated respiratory-navigated MR angiography of the renal arteries: comparison with contrast-enhanced MR angiography. AJR Am J Roentgenol. 2010;195:1423–8.
14. Khoo MMY, Deeab D, Gedroye WMW, et al. Renal artery stenosis: comparative assessment by unenhanced renal artery MRA versus contrast-enhanced MRA. Eur Radiol. 2011;21:1470–6.
15. Duda SH, Schick F, Teufl F, et al. Phase-contrast MR angiography for detection of atherosclerotic renal artery stenosis. Acta Radiol. 1997;38:287–91.
16. Miller S, Schick F, Duda SH, et al. Gd-enhanced 3D phase-contrast MR angiography and dynamic perfusion imaging in the diagnosis of renal artery stenosis. Magn Reson Imaging. 1998;16:1005–12.
17. Hood MN, Ho VB, Corse WR. Three-dimensional phase-contrast magnetic resonance angiography: a useful clinical adjunct to gadolinium-enhanced three-dimensional renal magnetic resonance angiography? Mil Med. 2002;167:343–9.
18. Michaely HJ, Schoenberg SO, Ittrich C, et al. Renal disease: value of functional magnetic resonance imaging with flow and perfusion measurements. Invest Radiol. 2004;39:698–705.
19. Zhang HL, Schoenberg SO, Resnick LM, et al. Diagnosis of renal artery stenosis: combining gadolinium-enhanced three-dimensional magnetic resonance angiography with functional magnetic resonance pulse sequences. Am J Hypertens. 2003;16:1079–82.
20. Schoenberg SO, Knopp MV, Londy F, et al. Morphologic and functional magnetic resonance imaging of renal artery stenosis: a multireader tricenter study. J Am Soc Nephrol. 2002;13:158–69.
21. Yim PJ, Cebral JR, Weaver A, et al. Estimation of the differential pressure at renal artery stenoses. Magn Reson Med. 2004;51:969–77.
22. Iozelli A, D'Orta G, Aliprandi A, et al. The value of true-FISP sequence added to conventional gadolinium-enhanced MRA of the abdominal aorta and its major branches. Eur J Radiol. 2009;72: 489–93.
23. Tan KT, Van Beek EJR, Brown PWG, et al. Magnetic resonance angiography for the diagnosis of renal artery stenosis: a meta-analysis. Clin Radiol. 2002;57:617–24.
24. Boudewijn G, Vasbinder C, Nelemans PJ, et al. Diagnostic tests for renal artery stenosis in patients suspected of having renovascular hypertension: a meta-analysis. Ann Intern Med. 2001;135:401–11.
25. Boudewijn G, Vasbinder C, Nelemans PJ, et al. Accuracy of computed tomographic angiography and magnetic resonance angiography for diagnosing renal artery stenosis. Ann Intern Med. 2004;141:674–82.
26. Soulez G, Pasowicz M, Benea G, et al. Renal artery stenosis evaluation: diagnostic performance of gadobenate dimeglumine-enhanced MR angiography – comparison with DSA. Radiology. 2008;247:273–85.
27. Schneider G, Pasowicz M, Vymazal J, et al. Gadobenate dimeglumine and gadofosveset trisodium for MR angiography of the renal arteries: multicenter intraindividual crossover comparison. AJR Am J Roentgenol. 2010;195:476–85.

28. Rountas C, Vlychou M, Vassiou K, et al. Imaging modalities for renal artery stenosis in suspected renovascular hypertension: prospective intraindividual comparison of color Doppler US, CT angiography, gd-enhanced MR angiography, and digital subtraction angiography. Ren Fail. 2007;29:295–302.
29. Lee CU, Glockner JF. Vascular staging of renal and adrenal malignancies with a noncontrast enhanced steady state free precession technique. J Magn Reson Imaging. 2011;33:1406–13.
30. Hussain SM, Kock MCJM, Ijzermans JNM, et al. MR imaging: a one stop shop modality for peroperative evaluation of potential living kidney donors. Radiographics. 2003;23:505–20.
31. Tan SP, Bux SI, Kumar G, et al. Evaluation of live renal donors with three-dimensional contrast-enhanced magnetic resonance angiography in comparison to catheter angiography. Transplant Proc. 2004;36:1914–6.
32. Rajab A, Khabiri H, Pelletier RP, et al. Magnetic resonance angiography for preoperative evaluation of potential kidney donors. J Surg Res. 2004;120: 195–200.
33. Al-Saeed O, Ismail M, Sheikh M, et al. Contrast-enhanced three-dimensional fast spoiled gradient magnetic resonance angiography of the renal arteries for potential living renal transplant donors: a comparative study with digital subtraction angiography. Australas Radiol. 2005;49:214–7.
34. Bhatti AA, Chugtai A, Haslam P, et al. Prospective study comparing three-dimensional computed tomography and magnetic resonance imaging for evaluating renal vascular anatomy in potential living donors. BJU Int. 2005;96:1105–8.
35. Jain R, Sawhney S. Contrast-enhanced MR angiography (CE-MRA) in the evaluation of vascular complications of renal transplantation. Clin Radiol. 2005;60: 1171–81.
36. Gufler H, Weimer W, Neu K, Wagner S, Rau WS. Contrast enhanced MR angiography with parallel imaging in the early period after renal transplantation. J Magn Reson Imaging. 2009;29:909–16.
37. Liu X, Berg N, Sheehan J, et al. Renal transplant: non-enhanced renal MR angiography with magnetization-prepared steady-state free precession. Radiology. 2009;251:535–42.
38. Browne RFJ, Riordan EO, Roberts JA, et al. Renal artery aneurysms: diagnosis and surveillance with 3D contrast-enhanced magnetic resonance angiography. Eur Radiol. 2004;14:1807–12.
39. Van den Brink JS, Watanabe Y, Kuhl CK, et al. Implications of SENSE MR in routine clinical practice. Eur J Radiol. 2003:46:3–27.
40. Glockner JF, Hu HH, Standley DW, et al. Parallel imaging: a user's guide. Radiographics. 2005;25:1279–97.
41. Nchimi A, Brisbois D, Materne R, et al. Free-breathing accelerated gadolinium-enhanced MR angiography in the diagnosis of renovascular disease. AJR Am J Roentgenol. 2009;192:1531–7.
42. Morelli JN, Fei A, Runge VM, et al. Time-resolved MR angiography of renal artery stenosis in a swine model at 3 T using gadobutrol with digital subtraction angiography correlation. J Magn Reson Imaging. 2012;36:704–13.

Radionuclide Studies

15

William J. Elliott

Abstract

Nuclear medicine scans were rather widely used in the 1980s–1990s to screen patients for renal artery disease. The most popular scans were performed after oral captopril (25–50 mg), using either ^{99m}Tc-diethylenetriamine-penta-acetic acid or ^{99m}Tc-mercaptoacetyltriglycine, which have similar, but slightly different, features. Characteristic changes on the excretory renograms were relatively straightforward to detect, especially when compared to a study that was done without captopril pre-treatment. Centers that developed experience with the test typically reported better performance characteristics than centers with smaller numbers of patients. Over the entire literature (excluding case reports and serial publications from the same investigators), captopril scintigrams had a mean weighted sensitivity of 77 % (range 9–100 %) and specificity of 78 % (range 44–100 %) over 71 reports involving 5,068 patients evaluated by angiography for renal artery stenosis. Many investigators have reported that a positive captopril-stimulated renal scintigram predicts a beneficial effect of revascularization on blood pressure (i.e., renovascular hypertension), but several large series disagree. Since the failure of randomized clinical trials to demonstrate a benefit of revascularization over intensive medical management, the role of renal nuclear medicine scans has declined. Such techniques may still be useful, especially in patients with normal renal function, when other modalities are not easily available, and blood pressure remains uncontrolled or renal function deteriorates.

Keywords

Captopril renography • Captopril scintigraphy • Excretory renograms • Renal artery stenosis • Renovascular hypertension • Sensitivity • Specificity

W.J. Elliott, MD, PhD
Division of Pharmacology, Pacific Northwest
University of Health Sciences,
Yakima, WA 98901, USA
e-mail: wj.elliott@yahoo.com

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_15,

Historical Overview

Radionuclide studies of renal function began in the late 1950s, with the synthesis and testing of ^{131}I-labelled 3,5-diiodo-4-pyridon-*N*-acetic acid, diethanolamine salt (diodrast), which underwent renal excretion, as well as some competing hepatic extraction. It was rather quickly replaced by ^{131}I-labeled orthoiodohippurate (hippuran), which is cleared ~80 % by tubular secretion, and 20 % by glomerular filtration. Although most often used at that time for estimating split renal function (using two scintillation counters of sodium iodide crystals, placed on the skin overlying each kidney), several early reports suggested that the time-dependent shapes of the excretory renograms were reproducibly and characteristically altered in the setting of renal artery stenosis. Because of the cumbersome nature of percutaneous radionuclide signal detection, relatively high doses of radiation, and other technical issues, rapid-sequence intravenous pyelography became the accepted standard method of screening for renal artery disease in the United States, until the mid- to late-1970s.

Gamma cameras revolutionized the practice of nuclear medicine in the early to mid-1970s, by making it possible to obtain high-quality images from deep tissues, using a variety of tracers. The renal radiopharmaceutical, ^{99m}Tc-labeled diethylenetriamine-penta-acetic acid (DTPA), is secreted nearly totally by glomerular filtration, emits 140 keV gamma rays, and has an emission half-life of ~6 h (independent of the relatively rapid renal excretion of the parent acid). These advantageous properties made it the most popular agent for nuclear medicine scans for at least two decades.

In the mid-1980s, ^{99mTc}-mercaptoacetyltriglycine (MAG3) was developed, which had about a 60 % first-pass renal extraction fraction (nearly all due to tubular secretion), compared to only 20 % for DTPA. Consequently, MAG3 has generally become the preferred radiopharmaceutical for patients with impaired renal excretory function. Some investigators have reported that it is more sensitive for bilateral renal artery stenosis than DTPA, but in general, the performance characteristics of the two agents are similar (for details, see discussion to come).

By serendipity in 1983, captopril was discovered to impressively alter the normal excretory renogram. The physiology of this effect is still debated, but the simplest explanation may be captopril's effect to acutely reduce circulating angiotensin II levels, which causes dilation of the efferent arteriole (which is more sensitive to angiotensin II than the afferent arteriole), followed by an acute reduction in glomerular filtration. This phenomenon can be observed not only with nuclear medicine scans that measure renal function, but also with ultrasound or quantitative angiographic detection. Over the next decade, many groups reported their experience with the "captopril-DTPA renal scan" as a screening test for renal artery stenosis. As with many new tests, the initial results were generally quite positive, but, over time, it was recognized that the test had many potential confounders (see next discussion for details). The time-dependent change in pooled sensitivity and specificity of the captopril DTPA test, drawn from reports with the largest numbers of included subjects (discussed next), is shown in Fig. 15.1. The variability of the test's performance characteristics, and the emergence of putatively better screening tests were highlighted in a very selective meta-analysis of screening tests for renal artery stenosis in 2001 [1]. This was followed by a "not recommended" designation by the American College of Cardiology/American Heart Association's Task Force on Peripheral Arterial Disease in 2006 [2].

There are many challenges to a proper understanding of the many causes of variability in radionuclide screening tests for renovascular hypertension. One is the distinction between diagnostic criteria for renovascular hypertension vs. renal artery stenosis. The former can classically be made only retrospectively, *after* demonstrating a lowered blood pressure, despite the same or fewer medications, 6–12 weeks after a procedure to open the stenotic artery. The latter, however, is an anatomical diagnosis, and can be made by one of a number of criteria, including (classically) a ≥75 % luminal narrowing, or a ≥50 % luminal narrowing with a post-stenotic

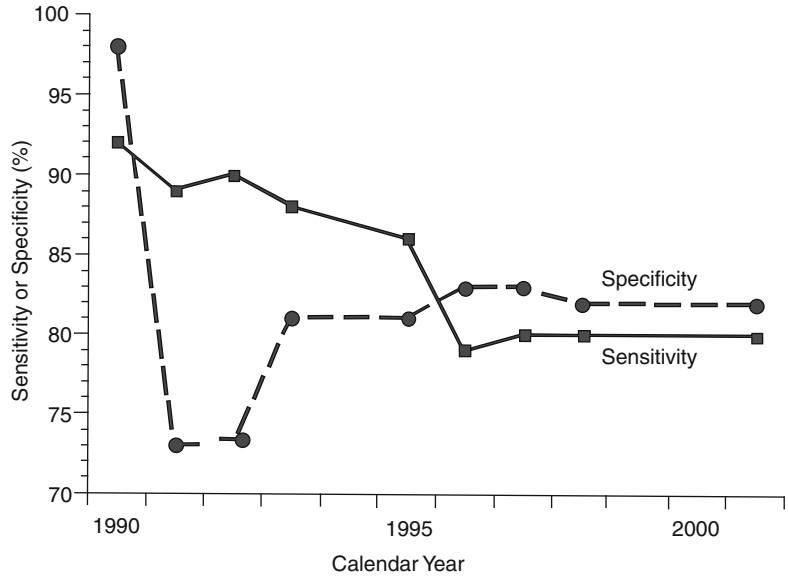


Fig. 15.1 Cumulative sensitivity and specificity of captopril-stimulated excretory renograms for renal artery stenosis in reports with large numbers of patients (i.e., ≥100 angiograms) reported from 1989 to 2001

dilatation, as demonstrated on a renal arteriogram. Today, however, many authors use a less-stringent criterion of ≥50 % stenosis, as observed on many different types of vascular imaging studies (digital subtraction intravenous angiogram, computed tomographic angiography, magnetic resonance angiography, etc.). Secondly, much of the reporting of a correlation between the results of nuclear medicine screening tests and angiography is done by radiologists, who often analyze their data using a "per-artery" approach, rather than a "per-patient" approach. This avoids problems with post-nephrectomy subjects, or those with multiple renal arteries to a single kidney, but complicates summary statistics that are based on individual patient data (which are often most useful to physicians who order these tests).

Technique

Although many "simplified" approaches to nuclear medicine screening for renal artery disease have been proposed, procedure guidelines have been written (and updated in 1998 [3]) by the Society for Nuclear Medicine. These were the first steps to standardize the protocol by which patients usually receive an oral water load (typically 7 mL/kg of body weight), followed 30–60 min later by 25–50 mg of oral captopril (often crushed to hasten absorption), and subsequently, 60 min later, an intravenous injection of radionuclide. Many variations on this common sequence have been suggested, including oral furosemide, stopping chronic angiotensin converting-enzyme (ACE) inhibitors for five serum half-lives before the test (which probably increases sensitivity just a little), pre-procedure intravenous saline (or at least a line for it, in case of hypotension), blood pressure and heart rate monitoring during and after the procedure, etc. Many centers perform the initial scan after captopril administration, and repeat it without captopril if the initial scan is abnormal. Other centers perform the initial scan without captopril, and, a few hours later, repeat the scan an hour after oral captopril, using a higher dose of radionuclide; this can be advantageous for patients who come from a distance.

Data Processing and Interpretation

Many different systems have been developed to analyze and report the results of radionuclide screening tests for renal artery disease. Most authorities recommend examining the early

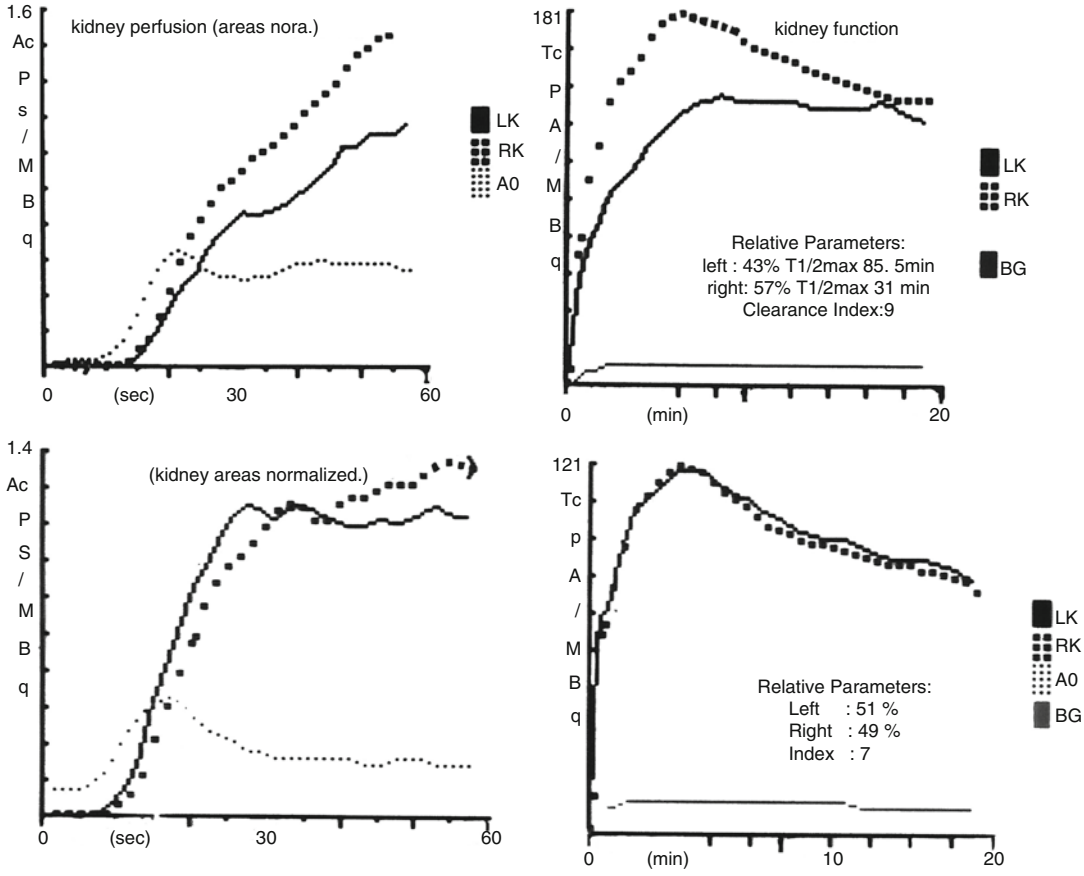


Fig. 15.2 Results of ^{99m}Tc-MAG3 excretory renograms from a 68-year old woman with resistant hypertension (initial blood pressure 192/108 mmHg despite maximum FDA-approved doses of chlorthalidone, amlodipine, atenolol, doxazosin, and lisinopril) and a serum creatinine of 1.5 mg/dL (estimated glomerular filtration rate of 37 mL/min/1.73 m^2). After discontinuing lisinopril for 5 days, the initial scan (after 25 mg oral captopril) showed decreased initial uptake (0–60 s after injection) by the left kidney (*upper left panel*), and a prolonged expiratory phase, with a 43/57 split in uptake (*left*/*right*) at 2–3 min (*upper right panel*). Three days later, the scan was repeated without captopril, which showed initial uptake that was similar bilaterally (*lower left panel*), similar excretory curves, and a 51/49 split in uptake (*left*/*right*) at 2–3 min (*lower right panel*). A week later, selective renal angiography showed a 75–80 % stenosis in the left main renal artery, with post-stenotic dilatation, which was successfully treated with balloon angioplasty and a stent. Six weeks later, her office blood pressure was 128/78 mmHg, while taking only chlorthalidone, atenolol, and lisinopril, and it remained well controlled over 6 years of follow-up, with no deterioration in renal function. *LK* left kidney, *RK* right kidney, *AO* aorta, *BG* background (Acknowledgement: The author thanks Derrick Owsley for assistance with the refinement and production of Fig. 15.2)

distribution of tracer (typically 60–90 s post-injection) for asymmetry (Fig. 15.2), comparing the uptake in background-subtracted regions of interest corresponding to each kidney during a specified interval (typically 1–3 min) after injection (Fig. 15.2), time to maximum activity for each kidney (Fig. 15.2), and a ratio of the remaining activity 20 min after injection to the maximum (particularly for MAG3, which is "normal" if <0.3) [3, 4]. Although each of these parameters may indicate an abnormality, the most specific diagnostic criterion for renovascular hypertension is the change in the renogram, with vs. without ACE-inhibitor. These changes have been most reproducibly detected across different readers [5, 6].

A family of representative curves has been promulgated as an aid to the interpretation of excretory renograms (Fig. 15.3) [3]. In general, a normal renogram after an ACE-inhibitor (Curve A in Fig. 15.3) predicts a low probability (<10 %) of renovascular hypertension. "Worsened renograms" (e.g., Curves B and C in Fig. 15.3), reduction in relative uptake by one kidney, prolongation of the renal and parenchymal transit time (or time to peak), or increase in the 20-min/peak ratio, all increase the post-test probability of renal artery disease. On the other hand, curves that show a delayed excretion without a washout phase (Curve D in Fig. 15.3), or background patterns (Curves E or F in Fig. 15.3) are best considered "intermediate probability [3]" or "non-diagnostic [7]," as either may be simply a consequence of diminished renal excretory function. A difference of 10 % in the post- vs. pre-captopril scans for tracer uptake by the kidneys, 1–3 min after injection has been proposed (but not universally accepted [7–9]) as one criterion for a "high probability" DTPA scan [3, 10], with 5–9 % considered an "intermediate response." Recent publications have demonstrated improvements in the correlation between captopril-stimulated renograms and renal angiograms after either adopting standardized criteria for the interpretation of the nuclear medicine studies [11], or use of neural networks [12].

Captopril or Other Pharmacological Options

Because of concerns about variability in the rate of absorption of oral captopril, intravenous enalaprilat (40 μg/kg) was proposed as an alternative method of obtaining ACE-inhibitor-stimulated nuclear medicine studies. In several comparative studies in animals and humans, few differences were noted. The 1998 procedure guideline recommends either agent as acceptable [3].

Like ACE-inhibitors, angiotensin receptor blockers (ARBs) can also cause an acute reduction in glomerular filtration in patients with renovascular hypertension. The effects of oral captopril on excretory renograms have been compared with those of either oral valsartan or losartan in 25 or 32 patients with renal artery stenosis, and interpreted using standard protocols. Consistent with known differences in the t_{max} of these drugs (2–4 vs. 1 h) after oral administration, valsartan was inferior to captopril [13], but losartan was not significantly different [14], in producing detectable changes in excretory renograms. Twelve of 13 patients with renal artery stenosis treated with a chronic ARB showed the expected changes in MAG3 excretory renograms after oral administration of captopril; three showed similar changes, even without captopril [15]. No false-positive results were seen in 13 patients with essential hypertension who were also treated with a chronic ARB. These limited data suggest that captopril scintigraphy may perform adequately in ARB-treated patients.

Several groups have studied aspirin (20 mg/kg, orally) [16], compared to captopril [17–19], as a possible stimulus for changes in renal scintigraphy in 12–75 patients with renal artery stenosis. When given acutely, this dose of aspirin inhibits renal prostaglandin synthesis, and reduces both renal blood flow and stimulation of the renin-angiotensin system in patients with renovascular hypertension. This method avoids some of the risk of acute hypotension seen with captopril, but appears to have performance characteristics similar to captopril scintigraphy [17–19].

Potential Confounders of the Interpretation of Radionuclide Studies

The results of excretory renograms can be affected by many different factors, as noted previously. Perhaps the most important is the presence of an elevated serum creatinine. Patients with this condition, by definition, have abnormal radionuclide studies (typically with type D or E curves in Fig. 15.3), and a high risk of ischemic nephropathy (if renal artery disease is present). Such patients risk acute kidney injury after

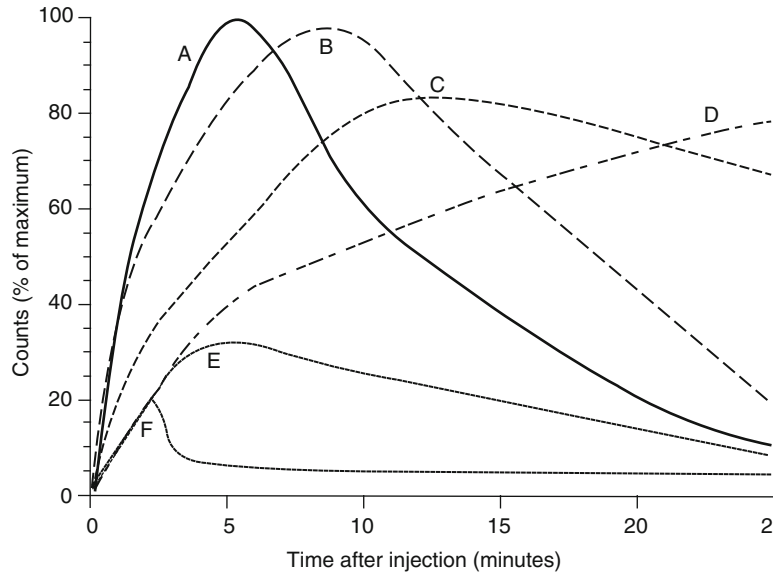


Fig. 15.3 "Typical" curves for time-dependent excretory renograms after intravenous injection of radiopharmaceutical (typically DTPA or MAG3). Curve *A* is "normal;" Curves *B–D* show various degrees of "worsening," and Curves *E* and *F* are better considered "non-diagnostic," as they are often seen in patients with impaired renal excretory function (Adapted with permission from [3])

radiocontrast injection, nephrogenic fibrosing dermopathy after gadolinium administration, so screening them for renal artery disease usually involves an initial Doppler ultrasound, rather than a radionuclide scan. Because a change in the lateralization of tracer uptake may be the most sensitive of the diagnostic criteria for radionuclide scans for renal artery disease, patients with baseline asymmetric renal function (worst-case scenario: solitary kidney) also have an increased risk of false-positive scans. Similarly, bilateral renal arterial disease is more difficult to detect with DTPA than with MAG3, but in either situation, completely symmetric uptake is uncommon. Acute hypotension after administration of captopril has been associated with poor renal perfusion and falsely-positive scan results. Two groups have reported that calcium antagonists can cause false-positive captopril scans [20, 21], which can complicate the ability to control blood pressure during the evaluation of the typical person with resistant hypertension who is suspected of renal artery disease. Rarer causes of false-positive tests include volume depletion, unilateral renal obstruction or venous thrombosis, compression of the renal hilum (e.g., from abscess or hematoma), or any condition that causes relative ischemia unilaterally. False-negative results are slightly more likely if captopril is given acutely, during chronic ACE-inhibitor therapy, with volume expansion and bilateral disease.

Results of Screening for Renal Artery Stenosis in Large Studies

Meta-Analyses and Systematic Reviews

In 2000, a review of 12 then-recent studies involving 2,291 patients, comparing the results of ACE-inhibitor scintigraphy and other testing for renal artery stenosis, concluded that the sensitivity and specificity were 93 and 92 %, although the sensitivity was artificially elevated because only 1,140 of the patients had renal angiography [4, 22]. The next year, a systematic review identified 172 reports about captopril scintigraphy, reviewed the full text of 25 studies, and selected only 14 for meta-analysis [1]. This highly-selective process was designed to include only reports that: (1) used intra-arterial angiography as the "gold standard" for renal artery stenosis; (2) tested subjects because of clinical suspicion of renovascular hypertension; (3) specified criteria and cutoff values for a "positive" test; and (4) provided absolute numbers of tests falling into each of the four diagnostic categories (true- or

false-positive, true- or false-negative). Five screening tests were compared after construction of receiver-operator curves, which showed that captopril scintigraphy had better diagnostic performance than measurement of the plasma renin activity before and after oral captopril ("the captopril test"), but was slightly worse than ultrasonography, and significant worse than magnetic resonance imaging, or computed tomographic angiography. For captopril scans, there was no significant difference between the performance of DTPA (six studies) or MAG3 (eight studies). Studies that included >50 subjects had significantly better performance than smaller studies, perhaps due to expertise that grows with experience. Although the authors cited lack of standardized criteria to define a positive test, differences across reports in case-mix, prevalence of renal artery disease (7.6–69.7 %), anatomical tests vs. functional tests, and analysis on a per-artery vs. per-patient basis, much of the heterogeneity of study results remained unexplained.

A much more inclusive systematic review of the literature was carried out in 2004 [23], and updated in 2009 [24]. All published data comparing 56 [23] (updated to 71 [24]) reports of ACE-inhibitor renography with renal angiography were included. Efforts were made to avoid data duplication, by selecting only the most recent of serial publications from a given group of investigators. The most impressive outcome of the meta-analysis was the striking statistically significant heterogeneity of the reported results ($P < 10^{-8}$ by Riley-Day test). In the 2004 data, across 4,295 subjects who had both captopril renograms and angiography, the overall sensitivity of the scan was 79 %, with a specificity of 82 % [23]. Five years later, the database included 5068 subjects, and the overall sensitivity was 77 % (range: 9–100 %), with a specificity of 78 % (range: 44–100 %) [24].

Individual Large Studies

The largest experience with renal scintigraphy and angiography was reported by Dutch investigators, who collected data from 505 subjects with suspected renovascular hypertension referred to their center from 1978 to 1992 [8]. Renal artery stenosis (≥50 %) was present in 52 % (bilateral in 19 %). Unlike many other investigators, they found only a little difference in the diagnostic performance characteristics of the renal scan, either without (n = 225) or after (n = 280) captopril. They chose a single-kidney fractional uptake of 37 % after captopril to define a positive test, which afforded a 90 % specificity, and 68 % sensitivity. They concluded that, although captopril scintigraphy was the most effective diagnostic procedure to reduce the number of normal arteriograms in patients suspected of renovascular hypertension, its usefulness as a diagnostic test is questionable, and has not been improved by the introduction of captopril or MAG3.

These results differed from those of a 16-center study in Europe, which performed DTPA scans after captopril and angiograms in 380 patients suspected of renovascular hypertension [25]. The diagnosis was made if angiography showed ≥70 % stenosis; captopril renograms were interpreted using multiple criteria, similar to those later published by the Society of Nuclear Medicine [3]. Overall, the sensitivity of the test was 83 %, with 93 % specificity, but the subgroup of patients with abnormal renal function always had lower specificity. Renal impairment, nephropathy, and prior treatment with ACE-inhibitors and diuretics were significantly more common in patients with false-positive scans; false-negative scans occurred more often in patients with lesser degrees of, and unilateral, renal artery stenosis.

A report of the experience at the Utrecht University Hospital described 158 patients who underwent both captopril scintigraphy (with MAG3) and angiography (using ≥50 % stenosis as the diagnostic criterion) [26]. In this group with a 63 % prevalence of renal artery stenosis (26 % bilateral), the sensitivity and specificity of the captopril scan were 83 and 75 %, respectively, as interpreted using the 1998 procedure guidelines [3]. Only 1 of 30 subjects with bilaterally identical renograms (21 of which were normal) had a stenosis by angiography, suggesting

that intrinsic renal disease is a more common cause of identical excretory renograms than renal artery disease.

A much less optimistic conclusion was reached in a consecutive series of 140 hypertensive patients evaluated with 25 mg of captopril before a DTPA scan, followed by renal arteriography at Duke University [9]. Only 22 % of patients had ≥50 % stenosis of a renal artery at angiography. The overall sensitivity and specificity for the captopril scan were 74 and 44 %, respectively. The investigators indicated that their population differed from others with respect to patient selection (i.e., lower prevalence of stenoses), race/ethnicity, use of calcium antagonists during testing, captopril dose, and interpretation of renograms. They could not discern which of these (if any) accounted for the difference between their experience and those of other centers.

The largest of several reports correlating the results of a captopril scan using DTPA and renal arteriography in Bologna, Italy concerns 132 patients [27]. In this population, the prevalence of ≥50 % stenosis was 52 %, although 11 % more patients had an arterial stenosis <50 %. Captopril renograms were analyzed for split renal function (90–150 s after injection), appearance of tracer into the pelvicalyceal system, and upslope of the excretory renogram. Overall, the sensitivity of the captopril renogram was 92 %, with a specificity of 97 %; none of the patients with a stenosis <50 % had a positive captopril scintigram.

A more comprehensive analysis of the results of screening of 131 patients for renal artery stenosis, using conventional and captopril renography, as well as Doppler ultrasound, was published by investigators from Aarhus, Denmark [28]. Their population had a 21 % prevalence of renal artery stenosis ≥50 %, with 14 % having stenosis ≥70 % by angiography. Excretory renograms were interpreted using the European Multicenter Study methodology [25]. As might be expected, overall sensitivity was slightly better for the higher-grade stenosis definition (89 % vs. 75 %), but specificity was slightly lower (76 % vs. 78 %). They also noted that the specificity of change in the excretory renogram after captopril (compared to a non-captopril scan) was 96 %.

The largest of the several reports regarding the Yale Vascular Center experience with captopril scintigraphy included 113 patients who subsequently underwent renal arteriography [29]. A stenosis of ≥75 % (or 50–75 % if accompanied by a post-stenotic dilatation) was seen on angiography in 51 % of the patients. Captopril scintigraphy was interpreted using a locally-derived set of criteria that served as precursors of the subsequent Society of Nuclear Medicine guidelines [3]. Overall, the captopril scan was 91 % sensitive and 87 % specific for renal artery stenosis, regardless of serum creatinine >1.5 mg/dL (46 patients) or diuretic use, although concomitant ACE-inhibitor use during testing reduced the sensitivity to 75 % (12 of 16 patients).

Screening 104 patients with suspected renovascular hypertension at the Royal Free Hospital in London, using captopril DTPA renography, followed by different types of renal angiography, resulted in 27 being diagnosed with renal artery stenosis [30]. Captopril scans were interpreted based on a local algorithm that had been developed in a pilot study. Overall, the sensitivity was 93 % and the specificity was 70 % for the scan. Sensitivity was reduced (to 75 %) in the 26 patients with renal impairment, but was not affected by bilateral stenoses. Four of six patients who showed improvements in excretory renograms after captopril had a recent presentation of "accelerated hypertension."

Of the several reports regarding captopril scintigraphy using MAG3 in Bologna, the largest included 102 hypertensive patients who underwent renal angiography within 4 weeks of renal scintigraphy [31]. Renal artery stenosis (>50 %) was found in 53 % (bilateral in 21 %), although 27 arteries had <50 % stenosis. Overall the sensitivity of the MAG3 captopril scan was 91 %, with a specificity of 84 %. The most characteristic predictors for renal artery disease were prolonged parenchymal transit time and a longer time to peak in the post-captopril study.

For ethical reasons, only 100 of the 150 patients who had positive screening by either

captopril scintigraphy or the "captopril test" in Chicago were subjected to renal angiography [10]. The prevalence of renal artery stenosis (≥75 %, or 50–74 % with post-stenotic dilatation) was 59 % (13 % bilateral) in those who underwent angiography. Captopril renograms were interpreted using a version of an algorithm that was similar to that eventually adopted by the Society of Nuclear Medicine [3]. The sensitivity of the captopril scan was 92 %, with a specificity of 80 %, for renal artery stenosis, among those who had angiography; these parameters were not significantly affected by renal impairment, bilateral disease, or previous diuretic or beta-blocker therapy. All performance characteristics of the captopril scan were significantly higher than those of the "captopril test."

Two other groups have reported the results of similarly large series of patients, using a different approach to the correlation of scintigrams and angiography, as the latter was performed first, typically for reasons unrelated to the suspicion of renovascular hypertension. In Montréal, over a 3-year period, 898 patients underwent abdominal angiography, of whom 195 were either hypertensive or were suspected of having ischemic nephropathy [32]. These patients then underwent renal scintigraphy using three different radiopharmaceuticals, including ^{99m}Tc-DTPA, but without oral captopril. Overall, 47 % of the patients had renal artery stenosis (>70 %). For the DTPA scan alone, the overall sensitivity and specificity were both 68 %; for all three scans, they were significantly higher, at 77 and 84 %, respectively. Unfortunately, their subsequent series of 41 patients who were evaluated with three different screening tests, and renal angiography showed a the captopril MAG3 scan (interpreted using standard guidelines [3]) to have a sensitivity of only 41 % and specificity of 82 %, despite a prevalence of renal artery stenosis of 76 % (≥50 % stenosis) [33].

In an attempt to interpret the results of renal angiography performed after cardiac catheterization, 131 patients in British Columbia who had "incidental" renal artery stenosis (≥50 %) discovered during this procedure were evaluated by MAG3 nuclear renography; captopril was used in 98 [34]. In only 7 of 77, or 9 % of, patients who had both baseline and post-captopril scans were the renograms positive, suggesting functionally significant renal artery stenosis. Although captopril renogram positivity was the only characteristic (of eight clinical parameters) associated with unilateral renal artery stenosis >70 %, renal angioplasty, in a cohort that overlapped with the patients in this study, was unable to demonstrate preservation of renal function [35]. These investigators therefore question whether stenoses found incidentally in the renal bed during coronary catheterization are really important.

Results for Prediction of Blood Pressure Response After Angioplasty

In 1992, [22] a systematic review of the available English-language literature concluded that the DTPA scintigram had a sensitivity of 93 % and specificity of 95 % for renovascular hypertension (defined as improvement in blood pressure after intervention, which has since been standardized [36]). This result was based on three early reports involving only 205 patients; a supplemental analysis of six studies reporting outcomes with captopril-induced changes to excretory renograms (four with iodohippurate, two with DTPA) was not nearly as optimistic. An update in 2000 summarized 12 studies, and claimed that 92 % (255 of 289) of patients with a positive ACE-inhibitor renogram experienced a blood pressure response after revascularization [4]. This selective review did not include data from some studies that had previously reported lower predictive values [10, 37]. Since 2000, however, the literature has been mixed about the ability of a captopril renogram to predict either blood pressure or renal function outcomes after an intervention for renal artery stenosis.

Intention-to-treat analyses of the randomized Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) clinical trial were confounded by a large proportion of crossovers during the year-long follow-up (2 of 56 assigned to

angioplasty, 22 of 50 assigned to drug therapy alone) [38]. Prior to randomization, abnormal scintigrams were seen in 65 % of subjects in both groups, and significantly more remained abnormal in the drug-treated group (than the angioplastied group) at both 3 and 12 months of follow-up. Improvement of scintigrams after successful renal angioplasty has been noted by other investigators [39]. Subsequent *post-hoc* analyses of DRASTIC revealed that only patients with bilateral stenoses benefited from angioplasty [40]. An abnormal captopril renogram was not associated with improved BP or renal function after intervention, although the precise numbers of patients involved in these analyses were not provided.

Perhaps because captopril renography was not as useful as other screening techniques in identifying patients with renal artery stenosis in Uppsala, Sweden [41], the best predictor of blood pressure lowering after revascularization, which occurred in 63 % of their 152 patients was normal baseline renal function. They found no significant predictive value of renal resistance index (by Doppler ultrasound), abnormalities on the captopril renogram, or other screening modalities [42]. Ten of the 15 patients with "high-probability captopril renograms had improved blood pressures 12 months after revascularization, compared to 14 of 22 with low or intermediate-probability scans.

The largest reported experience from Montréal involved 74 patients who underwent a number of screening tests before technically successful angioplasty ± stent (in 52) [43]. Although calculated creatinine clearances did not change, blood pressures were, on average, significantly lower 3 months after angioplasty, with 31 patients "improved" and six "cured." Twenty-one of the 36 patients with a blood pressure response had positive captopril scans; 20 of 35 patients without a response had negative scans, leading to a sensitivity of 58 % and specificity of 57 %. Results of renal Doppler measurements and renal size were much better predictors of a blood pressure response than a captopril scan.

A retrospective review of diagnostic and therapeutic procedures in Helsinki found only 20 patients (a 3.8 % prevalence in their referral population) with renovascular hypertension after angiography and therapy; all had positive captopril renograms, but the specificity of the scan was only 72 % among patients who underwent angiography [44]. In an updated analysis, 24 of 35 patients had improved blood pressures after intervention, which was more common in patients with >10 % differential uptake on captopril renography (15 of 18, compared to 4 of 11 with <10 % differential uptake, $P = 0.015$) [45]. However, in multivariate analyses, younger age and unilateral disease predicted better outcomes; the captopril scan was useful only in predicting renal artery occlusion, if the ipsilateral isotopic clearance was <10 % (7 of 8 for 88 % sensitivity, and 17 of 21, for 81 % specificity).

In a report from Taiwan involving 60 patients with hypertension and diabetic nephropathy, 10 were found to have positive captopril renograms, and all had a blood pressure response after revascularization [46]. The remaining 50 had normal or intermediate probability renal scans that were unchanged after captopril, and had their blood pressures controlled over 6 months with antihypertensive drug therapy (including captopril).

In a consecutive series of 50 patients with ≥60 % renal artery stenosis seen between 2000 and 2003 in Duesseldorf, Germany, only 18 experienced a blood pressure fall after revascularization [47]. As with other German centers, the renal resistance index (by Doppler ultrasound) was the strongest predictor of outcome, followed by renal vein renin measurements. Renography at this center was performed without captopril, so no data are available from these patients about the potential usefulness of this modality in predicting outcomes.

The existing data are summarized in Table 15.1 [48–57]. Unfortunately, many reports (especially those with pessimistic conclusions) have not provided discrete patient-level data that could be incorporated into this table, so these overall predictive values are likely to be overestimates [37,

Table 15.1 Summary of numbers of patients with "positive captopril-stimulated scintigram," followed by a "positive blood pressure response" after revascularization in large series

Author	Patients with "positive blood pressure response to revascularization"	Patients with "positive" captopril renogram	Percent (%)
Oei et al. [48]	15	16	94
Erbsloh-Möller et al. [49]	15	16	94
Geyskes et al. [50]	53	59	90
Mann et al. [51]	20	27	74
Postma et al. [37]	12	22	54
Dondi et al. [52]	32	33	97
Roccatello et al. [53]	30	33	90
Elliott et al. [10]	51	54	94
Jensen et al. [54]	16	16	100
Meier et al. [55]	26	29	90
Fommei et al. [25]	41	43	95
Harward et al. [56]	39	39	100
Mittal et al. [57]	19	19	100
Eklöf et al. [42]	10	15	67
Soulez et al. [43]	21	36	58
Helin et al. [44]	15	18	83
Lin et al. [46]	10	10	100

38, 40]. In addition, because many of these reports predate guidelines for execution and interpretation of nuclear medicine scans [3], as well as reporting of outcomes after revascularization [36], there is greater heterogeneity across these reports than appears in this table. Other sources of bias may also be present: for example, some centers have been less likely to recommend revascularization if the pre-procedural captopril renogram had been normal [10].

Comparisons with Other Screening Modalities

Unfortunately, none of the available screening tests for renal artery stenosis is perfect, and each has its strengths and limitations. Even computed tomographic or magnetic resonance angiography studies that were deemed superior to older techniques in 2001 [1] were found, on reevaluation in 2004 [58], to be imperfect. In many centers, Doppler ultrasound is preferred, as it is non-invasive, inexpensive, and has been useful in predicting a blood pressure response after revascularization (using a renal resistance index of <80 mmHg). It is notoriously operator-dependent, and less useful in obese patients with overlying bowel gas, patients with branched renal arteries, and for many patients with fibromuscular disease. In the most inclusive recent summary [24], it had highly significant inhomogeneity ($P<10^{-15}$ by Riley-Day test) across reports. Nonetheless, its mean weighted sensitivity was 83 % (range 17–100 %), with a specificity of 84 % (range 55–100 %), over 67 reports involving 4,640 patients.

Computed tomographic angiography provides excellent image quality, but requires intravenous contrast injection, which increases the risk of acute kidney injury. It is more expensive and time-consuming to process and interpret than either Doppler ultrasound or captopril scintigraphy. Over 18 reports involving 1,336 patients [24], there was significant ($P<0.0001$) inhomogeneity, partly due to four studies that report nearly perfect performance characteristics [1, 24]. Overall in these reports, computed tomographic angiography had a mean weighted sensitivity of 84 % (range: 63–100 %), with specificity of 91 % (range: 56–100 %).

Magnetic resonance angiography provides excellent image quality with no radio-opaque contrast injection, but gadolinium contrast is

contraindicated for patients with Stage 3 or higher chronic kidney disease, which includes many with suspected renal artery stenosis. Although it is expensive, often does not detect distal stenoses or restenosis within a stent, and can be problematic for patients with claustrophobia, 71 reports involving 3,069 patients indicated that its mean weighted sensitivity is 90 % (range: 54–100 %), with a specificity of 86 % (range: 21–100 %) [24]. It is likely that individual patient factors, local availability and expertise in execution and interpretation, as well as cost, will likely drive the selection of a specific modality to screen for renal artery stenosis in a particular moderate-risk hypertensive patient.

The Future?

It is currently difficult to acquire pre-authorization approval for many tests for renal artery disease, including nuclear medicine scans. Part of this is due to the results of at least four recent randomized trials showing no benefit over medical management on either blood pressure control or renal function. There is also a reluctance to spend money on tests that are themselves imperfect, and frequently lead to greater utilization of healthcare resources (including very expensive angiography and angioplasty). This situation has led to a decline in the number of nuclear scans performed worldwide, as well as in the numbers of publications about recent experience with these tests.

It may be possible that newer radiopharmaceuticals can improve on the diagnostic performance of DTPA and even MAG3 in screening for renal artery stenosis. A report of 41 patients studied with the glomerularly-filtered ^{51}Cr-EDTA and tubularly-secreted ^{99m}Tc-dimercaptosuccinic acid showed reduced uptake after captopril only with the former in 21 patients who eventually were diagnosed with renal artery stenosis [59]. Perhaps because of the small number of patients, however, per-patient performance characteristics and prediction of blood pressure response to revascularization procedures were not provided.

Another distinct area in which there still appears to be ongoing use of nuclear medicine scans for renovascular hypertension is in pediatric patients. Because many children have remediable causes of their hypertension, screening tests are more often performed than in adults. Although renovascular hypertension is rare in children, as reflected in a recent survey in Turkey [60], recent reports of captopril renal scans to screen for it in children have given mixed results [61]. The largest experience was reported from Egypt, in which 81 children who had captopril renography were studied [62]. Positive scans were seen in 24 of the 51 with renal artery disease, and 8 were falsely-positive, resulting in only 48 % sensitivity and 73 % specificity. In Chile, 20 children (including two newborns) were screened using captopril renography; six of seven with renovascular hypertension, and only one of 13 without it, were positive [63]. Three non-diagnostic scans were seen in children with severely decreased renal excretory function.

Another relatively neglected, but potentially fruitful, area is cost-effectiveness of screening, diagnosis and treatment of renovascular hypertension. A 1996 cost-analysis concluded that captopril-stimulated nuclear medicine screening was the most valuable initial strategy in patients with normal kidney function if the pre-test probability of renovascular disease was >30 % [64]. Some agree [4, 7, 45], but others recommend Doppler ultrasound [42, 43, 65]. None of these analyses have accounted for the wide geographic variation in cost of testing, which has increased dramatically across all healthcare facilities during the last 15 years [66].

Conclusion

Nuclear medicine scans were moderately popular as screening tests for renal artery disease in the late 1980s and 1990s. However, even in experienced hands, captopril-stimulated excretory renograms have imperfect performance characteristics that, especially in patients with a moderate absolute risk of renal artery disease, result in too many expensive and risky renal angiograms. According to recent guidelines, less expensive and less

invasive tests (e.g., Doppler ultrasound) or tests that can more easily distinguish both anatomical and functional abnormalities (e.g., magnetic resonance imaging with blood oxygen-level dependent contrast) are more likely to be recommended. Many centers have suggested that captopril-associated changes on excretory renograms predict a beneficial effect of revascularization on blood pressure, but the largest experience (in Holland), as well as that of many other centers, strongly disagree. Because few nuclear medicine scans to screen for renal artery disease are currently being performed, it is likely that this controversy will not be resolved, even by the usual techniques of "Evidence-Based Medicine."

References

1. Vasbinder GBC, Nelemans PJ, Kessels AG, Kroon AA, de Leeuw PW, van Engelshoven JM. Diagnostic tests for renal artery stenosis in patients suspected of having renovascular hypertension: a meta-analysis. Ann Intern Med. 2001;135: 401–11.
2. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006;113:e463–654.
3. Taylor Jr AT, Fletcher JW, Nally Jr JV, et al. Procedure guideline for diagnosis of renovascular hypertension: Society of Nuclear Medicine. J Nucl Med. 1998;39: 1297–302.
4. Taylor A. Functional testing: ACEI renography. Semin Nephrol. 2000;5:437–44.
5. Krijnen P, Oei HY, Claessens RA, Roos JC, van Jaarsveld BC, Habbema JD. Interobserver agreement on captopril renography for assessing renal vascular disease. J Nucl Med. 2002;43:330–7.
6. Tondeur M, Sand A, Ham H. Interobserver reproducibility in the interpretation of captopril renograms from patients suspected of having renovascular hypertension. Clin Nucl Med. 2004;29:479–84.
7. Blaufox MD, Fine EJ, Heller S, et al. Prospective study of simultaneous orthoiodohippurate and diethylenetriaminepentaacetic acid captopril renography. The Einstein/Cornell Collaborative Hypertension Group. J Nucl Med. 1998;39:522–8.
8. van Jaarsveld BC, Krijnen P, Derkx FH, Oei HY, Postma CT, Schalekamp MA. The place of renal scintigraphy in the diagnosis of renal artery stenosis. Fifteen years of clinical experience. Arch Intern Med. 1997;157:1226–34.
9. Svetkey LP, Wilkinson Jr R, Dunnick NR, et al. Captopril renography in the diagnosis of renovascular disease. Am J Hypertens. 1991;4:711S–5.
10. Elliott WJ, Martin WB, Murphy MB. Comparison of two nonivasive screening tests for renovascular hypertension. Arch Intern Med. 1993;153: 755–64.
11. Thorsson O, Bjuväng A, Granerus G. Advantages of standardized criteria for the interpretation of angiotensin-converting enzyme inhibition renography. Nucl Med Comm. 2009;30:449–54.
12. Nielsen M, Granerus G, Ohlsson M, Holst H, Thorsson O, Edenbrandt L. Interpretation of captopril renography using artificial neural networks. Clin Physiol Funct Imaging. 2005;25:293–6.
13. Karanikas G, Becherer A, Wiesner K, Dudczak R, Kletter K. ACE inhibition is superior to angiotensin receptor blockade for renography in renal artery stenosis. Eur J Nucl Med Mol Imaging. 2002;29: 312–8.
14. Günay EC, Oztürk MH, Ergün EL, et al. Losartan renography for the detection of renal artery stenosis: comparison with captopril renography and evaluation of dose and timing. Eur J Nucl Med Mol Imaging. 2005;32:1064–74.
15. Picciotto G, Sargiotto A, Petrarulo M, Rabbia C, De Filippi PG, Roccatello D. Reliability of captopril renography in patients under chronic therapy with angiotensin II (AT1) receptor antagonists. J Nucl Med. 2003;44:1574–81.
16. Imanishi M, Yano M, Okurmura M, et al. Aspirin renography in the diagnosis of unilateral renovascular hypertension. Hypertens Res. 1998;21:209–13.
17. Maini A, Gambhir S, Singhai M, Kher V. Aspirin renography in the diagnosis of renovascular hypertension: a comparative study with captopril renography. Nucl Med Comm. 2000;21:325–31.
18. van de Ven PJ, de Klerk JM, Mertens LJ, Koomans HA, Beutler JJ. Aspirin renography and captopril renography in the diagnosis of renal artery stenosis. J Nucl Med. 2000;41:1337–42.
19. Ergün EL, Caglar M, Erdem Y, Usalan C, Ugur O, Duranay M. Tc-99m DTPA acetylsalicylic acid (aspirin) renography in the detection of renovascular hypertension. Clin Nucl Med. 2000;25: 682–90.

20. Claveau-Tremblay R, Turpin S, De Braekeleer M, Brassard A, Leblond R. False-positive captopril renography in patients taking calcium antagonists. J Nucl Med. 1998;39:1621–6.
21. Ludwig V, Martin WH, Delbeke D. Calcium channel blockers: a potential case of false-positive captopril renography. Clin Nucl Med. 2003;28:108–12.
22. Mann SJ, Pickering TG. Detection of renovascular hypertension: state of the art. Ann Intern Med. 1992;117:845–53.
23. Elliott WJ. Chapter 8: Secondary hypertension: renovascular hypertension. In: Black HR, Elliott WJ, editors. Hypertension: a companion to Braunwald's heart disease. 1st ed. Philadelphia: Elsevier; 2007. p. 93–105.
24. Elliott WJ. Chapter 8: Renovascular hypertension. In: Black HR, Elliott WJ, editors. Hypertension: a companion to Braunwald's heart disease. 2nd ed. Philadelphia: Elsevier; 2013. p. 69–79.
25. Fommei E, Ghione S, Hilson AJW, et al. Captopril radionuclide test in renovascular hypertension: a European multicentre study. Eur J Nucl Med. 1993;20:617–23.
26. Balink H, Mertens IJ, Stevens H, van Rijk PP, Beutler JJ, De Klerk JM. Captopril renography and the relevance of abnormal but bilateral identical curves in the diagnosis of renal artery stenosis. Nucl Med Comm. 2001;22:971–4.
27. Dondi M, Levorato M, Corbelli C, et al. Detection of renal artery stenosis by means of captopril renography with ^{99m}Tc-DTPA. Contrib Nephrol. 1990;79:181–5.
28. Pedersen EB, Egeblad M, Jørgensen J, Nielsen SS, Spencer ES, Rehling M. Diagnosing renal artery stenosis: a comparison between conventional renography, captopril renography and ultrasound Doppler in a large consecutive series of patients with arterial hypertension. Blood Press. 1996;5:342–8.
29. Setaro JF, Chen CC, Hoffer PB, Black HR. Captopril renography in the diagnosis of renal artery stenosis and the prediction of improvement with revascularization: The Yale Vascular Center experience. Am J Hypertens. 1991;4:698S–705.
30. McLean AG, Hilson AJW, Scoble JE, et al. Screening for renovascular disease with captopril-enhanced renography. Nephrol Dial Transplant. 1992;7:211–5.
31. Dondi M. Captopril renal scintigraphy with ^{99m}Tc-mercaptopacetyltriglycine (^{99m}Tc-MAG_3) for detecting renal artery stenosis. Am J Hypertens. 1991;6:737S–40.
32. Turpin S, Lambert R, Milot A, Taillefer R, Leveille J, Lefebvre B. A physiologic approach to renal scintigraphy: application to evaluation of hypertension. Clin Nucl Med. 1995;20:206–10.
33. Qanadli SD, Soulez G, Therasse E, et al. Detection of renal artery stenosis: prospective comparison of captopril-enhanced Doppler sonography, captopril-enhanced scintigraphy, and MR angiography. AJR Am J Roentgenol. 2001;177:1123–9.
34. Schachter ME, Zalunardo N, Rose C, et al. Incidental atherosclerotic renal artery stenosis in patients undergoing elective coronary angiography: are these lesions significant? Am J Nephrol. 2009;29:434–9.
35. Zalunardo N, Rose C, Starovoytov A, et al. Incidental atherosclerotic renal artery stenosis diagnosed at cardiac catheterization: no difference in kidney function with or without stenting. Am J Nephrol. 2008;28:921–8.
36. Rundback JH, Sacks D, Kent KC, American Heart Association Councils on Cardiovascular Radiology, High Blood Pressure Research, Kidney in Cardiovascular Disease, Cardio-Thoracic and Vascular Surgery, and Clinical Cardiology, and the Society of Interventional Radiology FDA Device Form Committee. American Heart Association, et al. Guidelines for the reporting of renal artery revascularization in clinical trials. Circulation. 2002;106:1572–85.
37. Postma CT, van Oijen AHAM, Barentsz JO, et al. The value of tests predicting renovascular hypertension in patients with renal artery stenosis treated by angioplasty. Arch Intern Med. 1991;151:1531–5.
38. van Jaarsveld BC, Krijnen P, Pieterman H, et al. The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. Dutch Renal Artery Stenosis Intervention Cooperative Study Group. N Engl J Med. 2000;342:1007–14.
39. Anfelter P, Granerus G, Stenström H, Eriksson P, Nyström FH. The effect of percutaneous dilatation of renal artery stenosis on captopril renography in hypertension. Blood Press. 2005;14:359–65.
40. Krijnen P, van Jaarsveld BC, Deinum J, Steyerberg EW, Habbema JD. Which patients with hypertension and atherosclerotic renal artery stenosis benefit from immediate intervention? J Hum Hypertens. 2004;18:91–6.
41. Eklöf H, Ahlström H, Magnusson A, et al. A prospective comparison of duplex ultrasonography, captopril renography, MRA, and CTA in assessing renal artery stenosis. Acta Radiol. 2006;47:764–74.
42. Eklöf H, Bergqvist D, Hägg A, Nyman R. Outcome after endovascular revascularization of atherosclerotic renal artery stenosis. Acta Radiol. 2009;50:256–64.
43. Soulez G, Therasse E, Qanadli SD, et al. Prediction of clinical response after renal angioplasty: respective value of renal Doppler sonography and scintigraphy. AJR Am J Roentgenol. 2003;181:1029–35.
44. Helin KH, Tikkanen I, van Knorring JE, et al. Screening for renovascular hypertension in a population with relatively low prevalence. J Hypertens. 1998;16:1523–9.
45. Helin KH, Lepäntalo M, Edgren J, Liewendahl K, Tikkanen T, Tikkanen I. Predicting the outcome of invasive treatment of renal artery disease. J Intern Med. 2000;247:105–10.
46. Lin CC, Shiau YC, Li TC, Kao A, Lee CC. Usefulness of captopril renography to predict the benefits of renal artery revascularization or captopril treatment in hypertensive patients with diabetic nephropathy. J Diabetes Complications. 2002;16:344–6.

47. Voiculescu A, Schmitz M, Plum J, et al. Duplex ultrasound and renin ratio predict treatment failure after revascularization for renal artery stenosis. Am J Hypertens. 2006;19:756–63.
48. Oei HY, Geyskes GG, Dorhout Mees EJ, Puylaert CB. The significance of captopril renography in renovascular hypertension. Contrib Nephrol. 1987;56:95–103.
49. Erbslöh-Möller B, Dumas A, Roth D, Sfakianakis GN, Bourgoignie JJ. Furosemide I-131 hippuran renography after angiotensin-converting enzyme inhibition for the diagnosis of renovascular hypertension. Am J Med. 1991;90:23–9.
50. Geyskes GG, de Bruyn AJG. Captopril scintigraphy and the effect of percutaneous transluminal angioplasty on blood pressure in 94 patients with renal artery stenosis. Am J Hypertens. 1991;4:685S–9.
51. Mann SJ, Pickering TG, Sos TA, et al. Captopril renography in the diagnosis of renal artery stenosis: accuracy and limitations. Am J Med. 1991;90: 30–40.
52. Dondi M, Fanti S, De Fabritiis A, et al. Prognostic value of captopril renal scintigraphy in renovascular hypertension. J Nucl Med. 1992;33:2040–4.
53. Roccatello D, Picciotto G, Rabbia C, Pozzato M, De Filippi PG, Piccoli G. Prospective study on captopril renography in hypertensive patients. Am J Nephrol. 1992;12:406–11.
54. Jensen G, Moonen M, Aurell M, Granerus G, Volkmann R. Reliability of ACE-inhibitor-enhanced Tc-99m DTPA gamma camera renography in the detection of renovascular hypertension. Nucl Med Comm. 1993;14:169–75.
55. Meier GH, Sumpio B, Setaro JF, Black HR, Gusberg RJ. Captopril renal scintigraphy: a new standard for predicting outcome after renal revascularization. J Vasc Surg. 1993;17:280–7.
56. Harward TR, Poindexter B, Humber TS, Carlton LM, Flynn TC, Seeger JM. Selection of patients for renal artery repair using captopril testing. Am J Surg. 1995;170:183–7.
57. Mittal BR, Kumar P, Arora P, et al. Role of captopril renography in the diagnosis of renovascular hypertension. Am J Kidney Dis. 1996;28:209–13.
58. Vasbinder GB, Nelemans PJ, Kessels AG, Renal Artery Diagnostic Imaging Study in Hypertension (RADISH) Study Group, et al. Accuracy of computed tomographic angiography and magnetic resonance angiography for diagnosing renal artery stenosis. Ann Intern Med. 2004;141:674–82.
59. Chaves AAR, Buchpiguel CA, Praxedes JN, Bortolotto LA, Sapienza MT. Glomerular filtration rate measured by ^{51}Cr-EDTA clearance: evaluation of captopril-induced changed in hypertensive patients with and without renal artery stenosis. Clinics. 2010;65:607–12.
60. Bayazit AK, Yalcinkaya F, Cakar N, et al. Renovascular hypertension in children: a nationwide survey. Pediatr Nephrol. 2007;22:1327–33.
61. Reusz GS, Kis E, Cseprekát O, Szabó AJ, Kis E. Captopril-enhanced renal scintigraphy in the diagnosis of pediatric hypertension. Pediatr Nephrol. 2010;25:185–9.
62. Abdulsamea S, Anderson P, Biassoni L, et al. Pre- and postcaptopril renal scintigraphy as a screening tool for renovascular hypertension in children. Pediatr Nephrol. 2010;25:317–22.
63. Lagomarsino E, Orellana P, Muñoz J, Velásquez C, Cavagnaro F, Valdés F. Captopril scintigraphy in the study of arterial hypertension in pediatrics. Pediatr Nephrol. 2004;19:66–70.
64. Blaufox MD, Middleton ML, Bongiovanni J, Davis BR. Cost efficacy of the diagnosis and therapy of renovascular hypertension. J Nucl Med. 1996;37: 171–7.
65. Bolduc JP, Oliva VL, Therasse E, et al. Diagnosis and treatment of renovascular hypertension: a cost-benefit analysis. AJR. 2005;184:931–7.
66. Van Helvoort-Postulart D, Dirksen CD, Nelemans PJ, et al. Renal artery stenosis: cost-effectiveness of diagnosis and treatment. Radiology. 2007;244:505–13.

Measurement of the Renin-Angiotensin System

16

Sandra M.S. Herrmann

Abstract

Renovascular disease irrespective of the cause activates multiple pressor systems, most specifically the renin-angiotensin-aldosterone system (RAAS). This complex hormone system exerts several renal and vascular effects, and seminal studies have outlined the sentinel importance of this system in the context of renovascular disease. Experiments using Goldblatt's classic 2 kidneys-1-clip model generate the prototype of angiotensin-dependent hypertension (Laragh, Am J Hypertens 4:541S–545S, 1991; Pickering, Semin Nucl Med 19:79–88, 1989). In humans, numerous methods to assess the levels of these hormones in the plasma have been proposed to characterize the hemodynamic significance of renovascular disease and to provide guidance on who will benefit of revascularization. However, in recent years, many of these diagnostic methods have been abandoned due to complex work-up, relatively low sensitivity and specificity, and the advent of more reliable non-invasive imaging techniques (Covic and Gusbeth-Tatomir, Prog Cardiovasc Dis 52:204–208, 2009). Although one could argue that the pressure in identifying the pressors roles has decreased, since preservation of function has become the most predominant argument, still, characterization of the RAAS system is important since it may provide useful additional information, including those for important therapeutic decisions.

Several screening laboratory tests have been proposed over the years to identify patients with renovascular hypertension. Some of these studies remain based on the identification of the activation of the RAAS system and some may depend on the comparison of the kidneys side-by-side assuming that one kidney is not affected. However, even under the best conditions, these studies are rarely more than 80 % sensitive or specific. As a result, their value as predictors depends greatly on the pretest probability

S.M.S. Herrmann, MD
Division of Nephrology and Hypertension,
Mayo Clinic, 200 First Street, SW,
Rochester, MN 55902, USA
e-mail: herrmann.sandra@mayo.edu

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_16, © Springer-Verlag London 2014

of renovascular disease. Moreover, functional tests are heavily dependent upon test conditions, including volume status, sodium intake and antihypertensive medications, which can affect levels of this complex hormone system.

Keywords

Hypertension • Renal artery stenosis • Renovascular disease • Physiologic studies • Renin-angiotensin system

Introduction

Physiologic studies have long been proposed as fundamental to understanding the basis for blood pressure control. Planning therapy and potential intervention for renovascular disease has been heavily dependent on developing diagnostic tools to support such measures.

Evaluation of Renin-Angiotensin System

Renovascular disease activates multiple pressor systems, most specifically the renin-angiotensin-aldosterone system (RAAS). This complex hormone system exerts several renal and vascular effects, and seminal studies have outlined the sentinel importance of this system in the context of renovascular disease. Experiments using Goldblatt's classic 2 kidneys-1-clip model generate the prototype of angiotensin-dependent hypertension [1, 2]. In humans, numerous methods to assess the levels of these hormones in the plasma have been proposed to characterize the hemodynamic significance of renovascular disease and to provide guidance on who will benefit of revascularization. However, in recent years, many of these diagnostic methods have been abandoned due to complex work-up, relatively low sensitivity and specificity, and the advent of more reliable non-invasive imaging techniques [3]. Still, characterization of the RAAS system is important since it may provide useful additional information, including those for important therapeutic decisions.

Several screening laboratory tests have been proposed over the years to identify patients with renovascular hypertension. Some of these studies remain based on the identification of the activation of the RAAS system and some may depend on the comparison of the kidneys side-by-side assuming that one kidney is not affected. However, even under the best conditions, these studies are rarely more than 80 % sensitive or specific. As a result, their value as predictors depends greatly on the pretest probability of renovascular disease. Moreover, functional tests are heavily dependent upon test conditions, including volume status, sodium intake and antihypertensive medications, which can affect levels of this complex hormone system.

Role of Functional Studies in Renovascular Hypertension

Peripheral Plasma Renin Activity

Experimental studies have emphasized that transient activation of the RAAS system is necessary for development of renovascular hypertension. Renin leads to increased circulating angiotensin II, aldosterone and ultimately total blood volume. Other animal studies demonstrated that blockage of the RAAS system using angiotensin-converting enzyme (ACE) inhibitor was able to prevent 2-kidney 1-clip renovascular hypertension [4]. These observations advocated the use of plasma renin activity (PRA) as a diagnostic tool to identify renovascular hypertension and to predict blood pressure response to renal revascularization. However, the elevation of renin is temporary and significant activation of plasma renin occurs only after decrease in the poststenotic pressure of at least 10–20 % and this corresponds to degrees of luminal stenosis of 70–80 % (Fig. 16.1) [5, 6].

The transient nature of this process makes the measurement of the peripheral venous PRA disappointing in clinical use and makes the utilization of PRA as a screening test for the diagnosis of renovascular hypertension less often now than it was in the past. Peripheral venous PRA

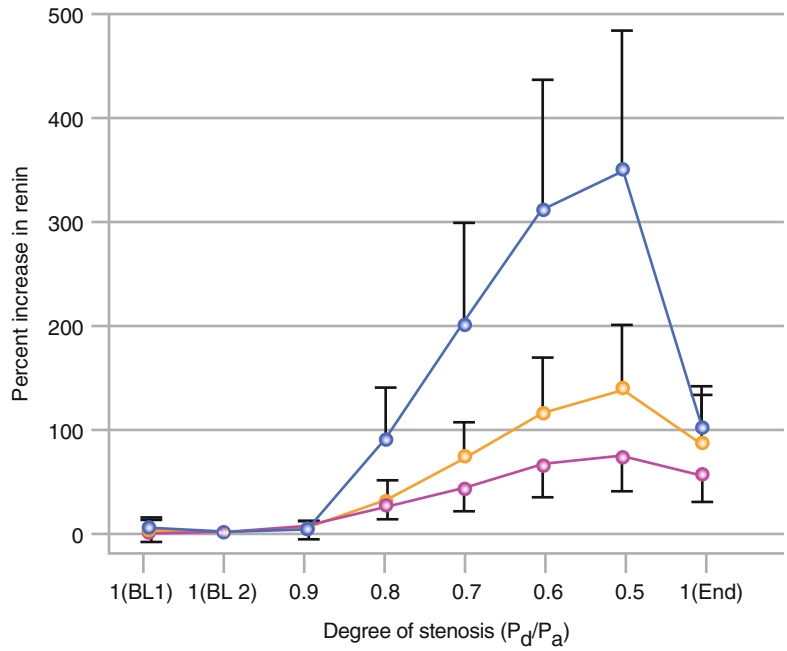


Fig. 16.1 Effects of balloon induced, unilateral, controlled, graded stenosis (expressed as P_d/P_a ratio) on plasma renins concentration in the aorta (*red circles*), in the vein of the stenotic kidney (*orange circles*), and in the vein of the non-stenotic kidney (*blue circles*). *BL1* baseline before stenting, *BL2* baseline after stenting, P_a mean aortic pressure, P_d mean pressure distal to the renal artery stenosis (Adapted with permission from De Bruyne et al. [5])

is not sensitive enough under routine conditions to reliably diagnose renovascular hypertension and false-negative results have been reported in patients with confirmed renovascular hypertension [7]. Furthermore, PRA is elevated in only half of the patients and is variably affected by ethnicity, age, medications, volume status and other variables [8]. For all these reasons, and the fact that approximately 20 % of the patients with essential hypertension also have elevated PRA, therefore measurement of PRA has a limited value in screening for renal artery stenosis [9]. However, Egan and colleagues have shown another utility for the use of PRA, i.e., as a guide to optimize therapy for patients with uncontrolled hypertension. Renin test-guided treatment has been showed to achieve better blood pressure control when compared with the clinician approach without the use of PRA measurements. This study was undertaken even when PRA was measured in the setting of prior medication use or under unusual conditions of blood sampling or processing [10]. Mechanistically, this study supports the concept of blood pressure elevation by chronic angiotensin II-mediated vasoconstriction, created by the persistent rather than transitory plasma renin elevation.

Captopril-Enhanced Renography

The use of radionucleotide renography using captopril allows evaluation of the renovascular disease by side-by-side comparison of blood flow and filtration between the two kidneys. Diethylenetriaminepentaacetic acid (DTPA) and mercapto-acetyltriglycine (MAG 3) are the most commonly used radionucleotides. Since MAG 3 is secreted effectively by the proximal tubule, it is more reliable than DTPA in patients with renal insufficiency [11]. The criteria for renovascular disease for this technique include (1) a decrease in the percentage of uptake of the isotope by the affected kidney to <40 % of the total, (2) delayed time to peak uptake of the isotope to >10–11 min, well above the normal value of 6 min and (3) delayed excretion of the isotope with retention at 25 min or >20 % [8]. The use of nonstimulated scans are only of limited value since false-negative results may occur in 20–25 % of the studies [12]. The addition of captopril and comparison with (non-captopril) baseline values accentuates the hemodynamic differences between the kidney with stenosis and the one without. However, characteristic changes seen on captopril renography are frequently absent in patients with unilateral poorly functioning small

kidney and bilateral renovascular disease. Among patients with bilateral disease, asymmetry was identified in the more severely affected kidney, but the presence or absence of stenosis in the contralateral kidney could not be reliably identified [13]. Most importantly, the sensitivity and specificity of renograms is decreased for patients who have serum creatinine levels >2 mg/dL. As summarized in a recent meta-analysis, the sensitivity of renography ranges from 58 to 95 % and its specificity ranges from 17 to 100 %, even when studies were performed in selected patients who had an intervention based on positive results on angiography [14]. Currently, due to several limitations of these studies, renography is mainly used to verify the relative function of each kidney prior to proceeding with therapeutic nephrectomy

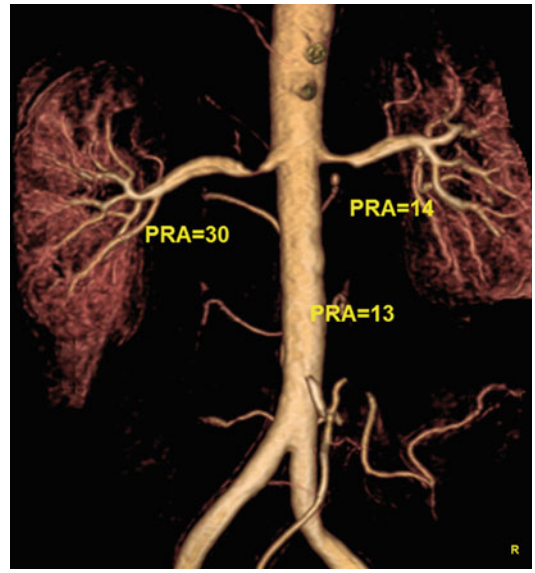


Fig. 16.2 Gadolinium-enhanced MR angiogram depicting severe right renal artery stenosis with ipsilateral elevation of PRA (ng/mL/h) as compared to the left contralateral kidney and IVC

Renal Vein Measurements

Measurement of renin in renal vein (RVR) samples is a tool used to specifically identify the role of the pressor kidney. Renin activity is increased in the stenotic kidney and suppressed in the contralateral non-stenotic kidney. In the past, renal vein renin (RVR) measurements were widely used to plan surgical renal revascularization for hypertension [15]. The usefulness of using RVR measurements was important since they demonstrated better positive predictive values for the blood pressure response to therapy, and because the high risk of surgical revascularization, this used to be an important tool to plan surgical revascularization. Using the renal vein renin ratio levels, of the affected or more severely affected kidney to that to the contralateral kidney >1.5 has a predictive positive value for blood pressure improvement up to 92 % in some studies (Fig. 16.2) [16]. In a second analysis, Vaughn and colleagues demonstrate that the "net contribution" of PRA from the stenotic kidney (defined as 100 * [(renal vein PRA – infrarenal vena cava (IVC) PRA)/IVC PRA]) >24 % indicates excessive production of renin, levels >48 % in the stenotic kidney and contribution < 23 % for the other renal artery meet Vaughan criteria for curability in patients with unilateral disease [17, 18]. In the case both renal arteries values are above 23 %, the presence of bilateral disease is suggested. However, this method is only applicable when inferior vena cava renin is at least 1 ng/ml/h.

An important caveat to applying this methodology is to manage the conditions for RVR testing. The degree of lateralization is sensitive to volume status, concurrent medications and arterial pressure levels. As an example, Strong and colleagues indicated that lateralization can be demonstrated in non-lateralizing kidneys by administration of diuretics or low sodium diet [19]. In current practice, the assessment of renal vein renin occurs in the setting of volume expansion with normal saline, usually undertaken prior the procedure in order to protect the kidney of contrast-induced nephropathy [20]. Although widely used in the past to identify candidates for surgical revascularization, use of renal vein renin measurements fell out of favor during the era of expanding endovascular angioplasty and stenting. Because of all these variabilities, some studies demonstrated poor sensitivity and poor positive predictive value [21, 22]. On the other hand, nearly 50 % of patients without lateralization may demonstrate improvement of blood pressure after revascularization. In addition to volume expansion, this lack of lateralization has been

attributed to multiple reasons including inaccurate renal vein catheterization, non-simultaneous sampling and problems related to bilateral or segmental lesions [23]. Nonetheless, ambiguous results from recent endovascular trials suggest that careful patient selection may benefit from revisiting this diagnostic approach. In those cases in which it is important to identify the pressor kidney, especially in the cases of complete occlusion causing kidney atrophy and resistant hypertension, renal vein renin determination could be an important tool. It may be helpful with the decision to pursue additional therapeutic procedures, such as nephrectomy in order to improve blood pressure control or optimize heart failure control [24–26].

References

1. Laragh JH. On the mechanisms and clinical relevance of one-kidney, one-clip hypertension. Am J Hypertens. 1991;4:541S–5.
2. Pickering TG. Renovascular hypertension: etiology and pathophysiology. Semin Nucl Med. 1989;19:79–88.
3. Covic A, Gusbeth-Tatomir P. The role of the renin-angiotensin-aldosterone system in renal artery stenosis, renovascular hypertension, and ischemic nephropathy: diagnostic implications. Prog Cardiovasc Dis. 2009;52:204–8.
4. Garovic V, Textor SC. Renovascular hypertension: current concepts. Semin Nephrol. 2005;25:261–71.
5. De Bruyne B, Manoharan G, Pijls NH, et al. Assessment of renal artery stenosis severity by pressure gradient measurements. J Am Coll Cardiol. 2006;48:1851–5.
6. Drieghe B, Madaric J, Sarno G, et al. Assessment of renal artery stenosis: side-by-side comparison of angiography and duplex ultrasound with pressure gradient measurements. Eur Heart J. 2008;29:517–24.
7. Canzanello VJ, Textor SC. Noninvasive diagnosis of renovascular disease. Mayo Clin Proc. 1994;69:1172–81.
8. Herrmann SM, Textor SC. Diagnostic criteria for renovascular disease: where are we now? Nephrol Dial Transplant. 2012;27:2657–63.
9. Wilcox CS. Use of angiotensin-converting-enzyme inhibitors for diagnosing renovascular hypertension. Kidney Int. 1993;44:1379–90.
10. Egan BM, Basile JN, Rehman SU, et al. Plasma renin test-guided drug treatment algorithm for correcting patients with treated but uncontrolled hypertension: a randomized controlled trial. Am J Hypertens. 2009;22:792–801.
11. Derkx FH, Schalekamp MA. Renal artery stenosis and hypertension. Lancet. 1994;344:237–9.
12. Pedersen EB. Angiotensin-converting enzyme inhibitor renography. Pathophysiological, diagnostic and therapeutic aspects in renal artery stenosis. Nephrol Dial Transplant. 1994;9:482–92.
13. Mann SJ, Pickering TG, Sos TA, et al. Captopril renography in the diagnosis of renal artery stenosis: accuracy and limitations. Am J Med. 1991;90:30–40.
14. Vasbinder GB, Nelemans PJ, Kessels AG, Kroon AA, de Leeuw PW, van Engelshoven JM. Diagnostic tests for renal artery stenosis in patients suspected of having renovascular hypertension: a meta-analysis. Ann Intern Med. 2001;135:401–11.
15. Pickering TG, Sos TA, Vaughan Jr ED, et al. Predictive value and changes of renin secretion in hypertensive patients with unilateral renovascular disease undergoing successful renal angioplasty. Am J Med. 1984;76:398–404.
16. Maxwell MH, Rudnick MR, Waks AU. New approaches to the diagnosis of renovascular hypertension. Adv Nephrol Necker Hosp. 1985;14:285–304.
17. Pickering TG, Sos TA, Vaughan Jr ED, Laragh JH. Differing patterns of renal vein renin secretion in patients with renovascular hypertension, and their role in predicting the response to angioplasty. Nephron. 1986;44 Suppl 1:8–11.
18. Vaughan Jr ED, Buhler FR, Laragh JH, Sealey JE, Baer L, Bard RH. Renovascular hypertension: renin measurements to indicate hypersecretion and contralateral suppression, estimate renal plasma flow, and score for surgical curability. Am J Med. 1973;55:402–14.
19. Strong CG, Hunt JC, Sheps SG, Tucker RM, Bernatz PE. Renal venous renin activity. Enhancement of sensitivity of lateralization by sodium depletion. Am J Cardiol. 1971;27:602–11.
20. Bartorelli AL, Marenzi G. Contrast-induced nephropathy. J Interv Cardiol. 2008;21:74–85.
21. Gill-Leertouwer TC, Gussenhoven EJ, Bosch JL, et al. Predictors for clinical success at one year following renal artery stent placement. J Endovasc Ther. 2002;9:495–502.
22. Roubidoux MA, Dunnick NR, Klotman PE, et al. Renal vein renins: inability to predict response to revascularization in patients with hypertension. Radiology. 1991;178:819–22.
23. Marks LS, Maxwell MH. Renal vein renin: value and limitations in the prediction of operative results. Urol Clin North Am. 1975;2:311–25.
24. Rossi GP, Cesari M, Chiesura-Corona M, Miotto D, Semplicini A, Pessina AC. Renal vein renin measurements accurately identify renovascular hypertension caused by total occlusion of the renal artery. J Hypertens. 2002;20:975–84.
25. Kane GC, Textor SC, Schirger A, Garovic VD. Revisiting the role of nephrectomy for advanced renovascular disease. Am J Med. 2003;114:729–35.
26. Kane GC, Xu N, Mistrik E, Roubicek T, Stanson AW, Garovic VD. Renal artery revascularization improves heart failure control in patients with atherosclerotic renal artery stenosis. Nephrol Dial Transplant. 2010;25:813–20.

17 Blood Oxygen Level Dependent (BOLD) MR Analysis of Tissue Oxygenation in Atherosclerotic Renal Artery Stenosis

Ahmed F. Saad and Stephen C. Textor

Abstract

While atherosclerotic Renal Artery Stenosis (ARAS) is a common cause of secondary hypertension and poses a threat to kidney viability, the degree to which reduced blood flow to cortical or medullary segments leads to a reduction in tissue oxygenation and/or increased overall oxygen consumption is not well understood. These studies have been limited due to the lack of an adequate method to assess tissue oxygenation in humans. BOLD (blood oxygen-level-dependent) magnetic resonance imaging detects local levels of tissue deoxyhemoglobin without requiring contrast. The normal kidney circulation consistently develops tissue oxygen gradients, leaving some areas within the deep sections of medulla relatively hypoxic, reflected by corresponding differences in cortical and medullary R2* values. Moderate reductions in renal blood flow that occur with ARAS do not invariably lead to renal hypoxia, likely due to both a surplus of oxygenated blood and a parallel decrease in GFR and tubular reabsorption of sodium that leads to decrease in Oxygen consumption. However, at some point, vascular occlusion threatens the viability of the kidney and can lead to loss of kidney function. In this chapter we will review the implementation of BOLD MRI in the diagnosis and management of renovascular disease.

Keywords

Renal artery stenosis • Oxygen • BOLD MRI • Hypertension • Renal hypoxia and renovascular imaging

A.F. Saad, MB, BCh (✉)
Division of Nephrology and Hypertension,
Mayo Clinic, Rochester, MN 55905, USA
e-mail: saad.ahmed@mayo.edu

S.C. Textor, MD
Division of Nephrology and Hypertension,
Mayo Clinic College of Medicine,
E19, Rochester, MN 55905, USA
e-mail: stextor@mayo.edu, textor.stephen@mayo.edu

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_17,

Introduction

Atherosclerotic renal artery stenosis (ARAS) remains one of the most common causes of secondary hypertension and when severe can also threaten the viability of the post-stenotic kidney. Occlusive vascular disease reduces blood flow and glomerular filtration (GFR), activates pressor systems, and ultimately leads to renal atrophy and chronic kidney disease [1, 2].

Defining the relationships between arterial blood flow and tissue oxygenation within the kidney poses a major challenge, in part due to the complexity of renal circulation and distribution of blood flow. The kidney normally is highly perfused, exhibits the highest rate of blood flow per tissue weight, and has the smallest arterio-venous differences in oxygen saturation of any organ, consistent with its filtration function and limited overall net oxygen consumption [3, 4]. By these criteria, the kidney is abundantly oxygenated as compared to other organs. A striking feature, however, is the non-uniformity of tissue oxygenation within the kidney. Under normal conditions, a gradient of oxygenation develops within the renal parenchyma from a highly perfused cortex falling to much lower levels in the deep medulla resulting from significant differences in both blood supply and oxygen consumption between the renal cortex and medulla [5, 6]. Portions of the medulla thus are functionally hypoxic under normal conditions and considered particularly susceptible to ischemic and/or other forms of acute kidney injury [6–8].

Remarkably, a decrease in RBF does not invariably lead to renal hypoxia, likely due to both a surplus of oxygenated blood and a parallel decrease in GFR and tubular reabsorption of sodium that leads to decrease in Oxygen consumption. Studies of intra-renal mechanisms of blood flow distribution emphasize that cortex and medulla can be regulated independently under some conditions [9]. However, at some point, vascular occlusion threatens the viability of the kidney and can lead to loss of kidney function, which may/may not be reversible after restoration of blood flow with revascularization [10]. Eventually, vascular occlusion leads to tissue fibrosis and can lead to end stage kidney disease (ischemic nephropathy) [11–13]. Determining when occlusive vascular lesion actually threatens kidney oxygenation and viability remains an elusive goal. Blood Oxygen Level-Dependent (BOLD) MRI is a noninvasive method developed in recent years that holds the promise of allowing improved understanding of regional tissue oxygenation within the kidney. In this chapter we will provide a review of some of the principles involved in BOLD MRI and summarize our current understanding of the implementation of BOLD MRI in renovascular hypertension.

Renal Blood Flow and Tissue Oxygenation

Renal blood flow is higher than any other organ with respect to organ weight, consistent with its primary function for blood filtration. The largest portion of renal blood flow is directed towards the cortex and filtration within cortical glomeruli. A fraction of post-glomerular blood flow is directed to the medulla and provides the basis for active tubular solute transport, preserving osmotic gradients and allowing urinary concentration [6]. The anatomical arrangement within the medulla aligns the tubules and the vasa recta in parallel fashion with a hairpin turn within deep medullary segments. This feature maximizes urine concentration by countercurrent exchange and allows diffusion of oxygen from the arterial side to venous side. In addition, the thick ascending limb is responsible for active reabsorption of chloride and sodium, an energy-dependent process that requires a large amount of oxygen. As a result, these circumstances combine to generate a hypoxic milieu that is progressively more evident in deep medullary segments. Because of nearly constant levels of oxygen depletion in this region, the kidney is particularly susceptible to ischemic injury especially in the outer medulla [5, 6].

ARAS represents a large vessel disorder that eventually obstructs the vascular lumen. Renal blood flow and perfusion pressure change only minimally until the vessel lumen cross- sectional area falls by 70–80 %. When a “critical” degree of stenosis is attained, renal hypoperfusion leads to a cascade of events from activation of the

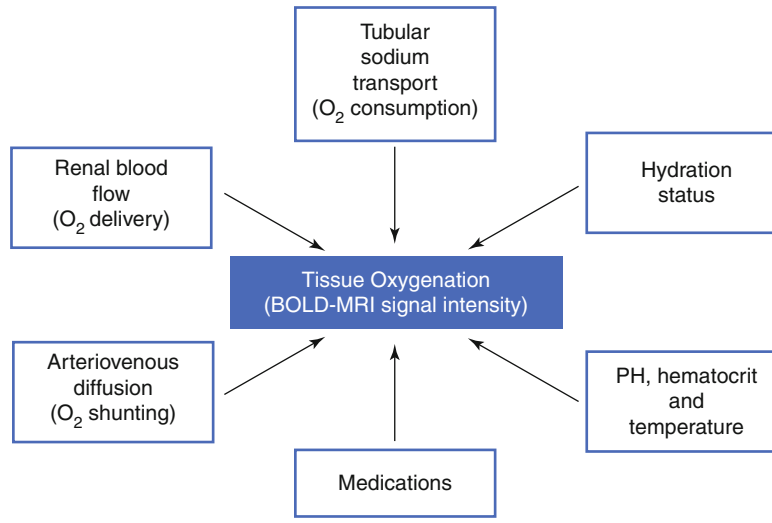


Fig. 17.1 Factors affecting kidney tissue oxygenation, and therefore BOLD-MRI signal intensity

renin-angiotensin system to the rarefaction of small renal vessels, kidney fibrosis, loss of function, and atrophy [14]. Studies of oxygen delivery and consumption in anesthetized rabbits indicate that acutely reduced filtration and oxygen consumption can leave tissue oxygen levels stable even if cortical blood flow is reduced by up to 40 % [15, 16]. A smaller portion of blood flow is delivered to deeper medullary regions of the kidney via post-glomerular vasa recta; in these regions, active metabolic processes dependent upon aerobic energy pathways lead to oxygen consumption and local areas of hypoxia, even within normal kidneys, report estimates of medullary pO_2 ranging between 10 and 20 mmHg [6] but rise to 41 mmHg after administration of furosemide intravenously. Hence, low medullary pO_2 reflects combined effects of reduced blood flow and increased oxygen consumption related to solute transport in the Loop of Henle [17, 18]. Local gradients of cortical and medullary oxygenation are closely regulated, sometimes independently from each other. Remarkably, these regions can tolerate reduced blood flow with compensatory changes by numerous vasoactive systems within the circulation. In a rat model, for example, angiotensin II infusion produces a 40 % decrease of cortical perfusion, but medullary perfusion can remain unchanged, apparently protected by prostaglandin E2 synthesis [19]. Quantitative changes in the degree of arteriovenous shunting as a result of changes in renal blood flow appear to maintain the oxygen tension and adjust local areas of blood supply, but also may render some focal regions more susceptible to hypoxia [15] (Fig. 17.1).

Measurements of Renal Oxygenation and Evaluation of Hypoxia

Direct measurement of renal tissue pO_2 has been achieved experimentally using invasive microelectrodes [5, 20] or an advanced laser-based probe [21]. Severely hypoxic tissue can be mapped histopathologically using reduction of Pimonidazole by nicotinamide adenine dinucleotide phosphate (NADPH) in biopsy or post-mortem samples [22]. Pimonidazole mapping is limited by being sensitive only to pO_2 less than 10 mmHg. Recently, Hypoxia inducible factor-α (HIF-α) has been proposed for an endogenous marker of hypoxia [23]. These and other invasive and/or post-mortem methods [24] are not readily applicable to humans.

Evaluation of Kidney Tissue Deoxyhemoglobin Using BOLD MRI

Development of Blood Oxygen Level Dependent (BOLD) MR depends upon the fact that magnetic properties of blood reflect the state of hemoglobin oxygenation. Deoxyhemoglobin is paramagnetic

whereas oxyhemoglobin is diamagnetic [25]. The presence of deoxyhemoglobin affects the T_2* relaxation time of neighboring water molecules and in turn influences the MRI signal of T_2*-weighted (gradient echo) images. The rate of spin dephasing R_2* (= $1/T_2$*) thereby is closely related to the tissue content of deoxyhemoglobin. Since the oxygen tension (pO_2) of capillary blood generally is thought to be in equilibrium with the surrounding tissue, changes estimated by BOLD MRI are interpreted as changes in tissue pO_2 [26–29]. BOLD MRI measurements of renal cortex and medulla [27] correlate with data obtained using invasive microelectrodes [5]. For example, in experiments using either microelectrodes or BOLD MRI, furosemide improves medullary oxygenation while acetazolamide, which produces diuresis, acts on the proximal tubule in the renal cortex and therefore induces little change in the medullary oxygenation [5, 27, 28].

A set of parametric images of R2* is generated from the BOLD sequence data by fitting signal intensity data from each echo on a voxel-by-voxel basis to an exponential function describing the expected signal decay as a function of echo time (TE) and solving for the unknown value of R2*. Parametric maps of R2* co-registered over the image illustrate the R2* translation of renal structures. Typically, cortex can be identified by lower R2* values, with a gradient developing to higher R2* levels in the deeper medullary sections [30, 31].

Parametric imaging can make the selection of ROIs more focused, especially when the deeper parts of the medulla are targeted, and allows the exclusion of artifacts induced by adjacent tissue anomalies from areas outside the kidneys [32, 33].

Data from swine experiments using oxygen sensing electrodes within various cortical and medullary locations within the kidney demonstrate tissue oxygen saturation consistent with deoxyhemoglobin levels identified using BOLD MRI [17, 34]. Average levels of tissue oxygen tension in the mammalian kidney range from 50 to 55 mmHg in cortex to as low as 15–20 mmHg in the deep sections of the medulla [5]. These levels coincide with a range of hemoglobin oxygen saturation, which falls steeply from 85 to 15 %, thereby making this a range favorable for detection using BOLD imaging. Further experimental studies in rats [35, 36] and other models [34, 37] using oxygen probes confirm that tissue oxygen levels fall by 45–50 % in moving from cortex to deep medullary regions.

Comparison of 1.5 and 3 T BOLD MR to Study Kidney Oxygenation

Because deoxyhemoglobin functions effectively as an imaging "contrast agent," BOLD MR studies comparing 1.5 and 3.0 T magnetic fields indicate that BOLD MRI measurements at high field strength amplifies differences between cortical and inner medullary regions of the kidney. Maneuvers that reduce oxygen consumption related to tubular solute transport (e.g., Furosemide administration) allow functional evaluation of transport-related activity as a determinant of tissue oxygenation. Reduced response to alterations in oxygen consumption can be detected at 3 T more effectively than at 1.5 T and may provide real-time tools to examine developing parenchymal injury associated with impaired oxygenation [33].

Application of Renal BOLD MRI

BOLD MRI allows non-invasive evaluation of renal oxygenation not only in animals but also in humans. Initial studies in humans suggested that this method could identify alterations in subjects after administration of nephrotoxic contrast [38], allograft injury [39], water loading, and occlusive renal arterial disease [30, 31]. Some authors had postulated that hemodynamic injury from nephrotoxin exposure produces local hypoxia as a "final common pathway" related to kidney injury [40]. Administration of cyclosporine, for example, does in fact lead to a rise in medullary R2* levels, suggesting medullary rise in deoxyhemoglobin [41]. Surprisingly, conditions that severely limit tubular metabolic activity, such as acute interstitial inflammation associated with transplant rejection, acute tubular necrosis, or even nonfunctioning renal atrophy beyond an occluded vessel, are associated with normal or low deoxyhemoglobin in both cortical and medullary regions [31, 42]. These findings were interpreted to indicate that severe reductions in GFR and active solute transport are associated with reduced oxygen consumption, therefore leaving measured R2* levels (and thus deoxyhemoglobin)

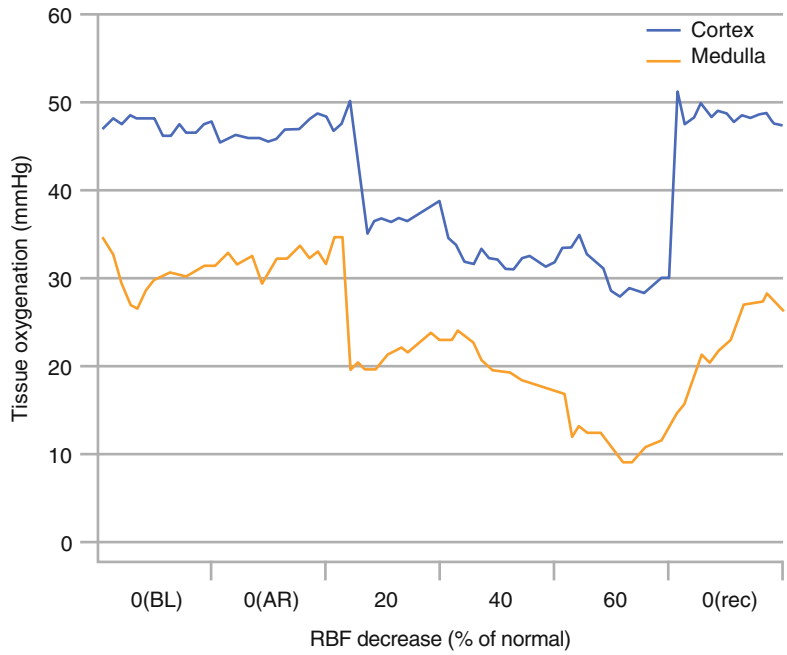


Fig. 17.2 Tissue levels of oxygen tension (measured by oxygen-sensitive probes in anesthetized swine) in cortex and medulla. This figure illustrates both differences and baseline and changes in renal tissue Po_2 at different levels of main renal artery blood flow. Renal cortex and medulla tissue oxygenation measured during a control period [0(BL)] and after stepwise decreases in RBF induced by a constricting clamp from baseline [(0 (AR)], by 20 % (20), 40 % (40), 60 % (60), and recovery [0 (Rec)] (Adapted with permission from Warner et al. [37])

low. BOLD MRI has been used to show that Angiotensin II receptor blocker could partially ameliorate intrarenal hypoxia in chronic kidney disease patients [43]. In a recent study in diabetic subjects, they exhibited hypoxia of the renal medulla, but not much of the renal cortex. In subjects who had progressed to more advanced stages of diabetic nephropathy, renal medullary hypoxia was alleviated whereas progressive cortical hypoxia developed [44].

Hypertension

BOLD MRI has been applied to some forms of essential hypertension. Experimental studies in rats indicate that medullary blood flow (and presumably medullary oxygenation status) is reduced in hypertensive models, and more importantly, that reduced medullary blood flow itself may be sufficient to produce hypertension [45, 46]. This is supported by demonstrable reduction of nitric oxide (NO) in hypertensive rat attributed to endothelial dysfunction. All these studies were performed using invasive microelectrodes or Doppler flow probes in rat kidneys. In a rat model BOLD MRI showed that medullary R2* exhibited minimal changes to nitric oxide synthase (NOS) inhibition, substantially reduced compared to normotensive controls [47]. Studies in hypertensive African Americans demonstrate higher R2* levels associated with increased medullary volume and sodium reabsorption as compared with whites. These data support a role for increased oxygen consumption and were associated with markers of increased oxidative stress in African Americans that may accelerate hypertension and target organ injury [48].

Renovascular Disease

Has application of BOLD MRI affected our understanding of atherosclerotic renovascular disease? Renal artery stenosis (RAS) is a common cause of secondary hypertension and obviously has consequences for intrarenal oxygenation when severe. Initial studies by Juillard et al. [49] identified a progressive rise in R2* in both cortex and medulla after stepwise acute reductions in renal blood flow produced by increasing levels of stenosis in a swine model. Warner et al. showed that graded reduction in blood flow acutely decrease tissue oxygenation measured by oxygen electrodes that also appear as changes in R2* signal under similar conditions [37] (Fig. 17.2). These changes are more pronounced in the medulla than the cortex,

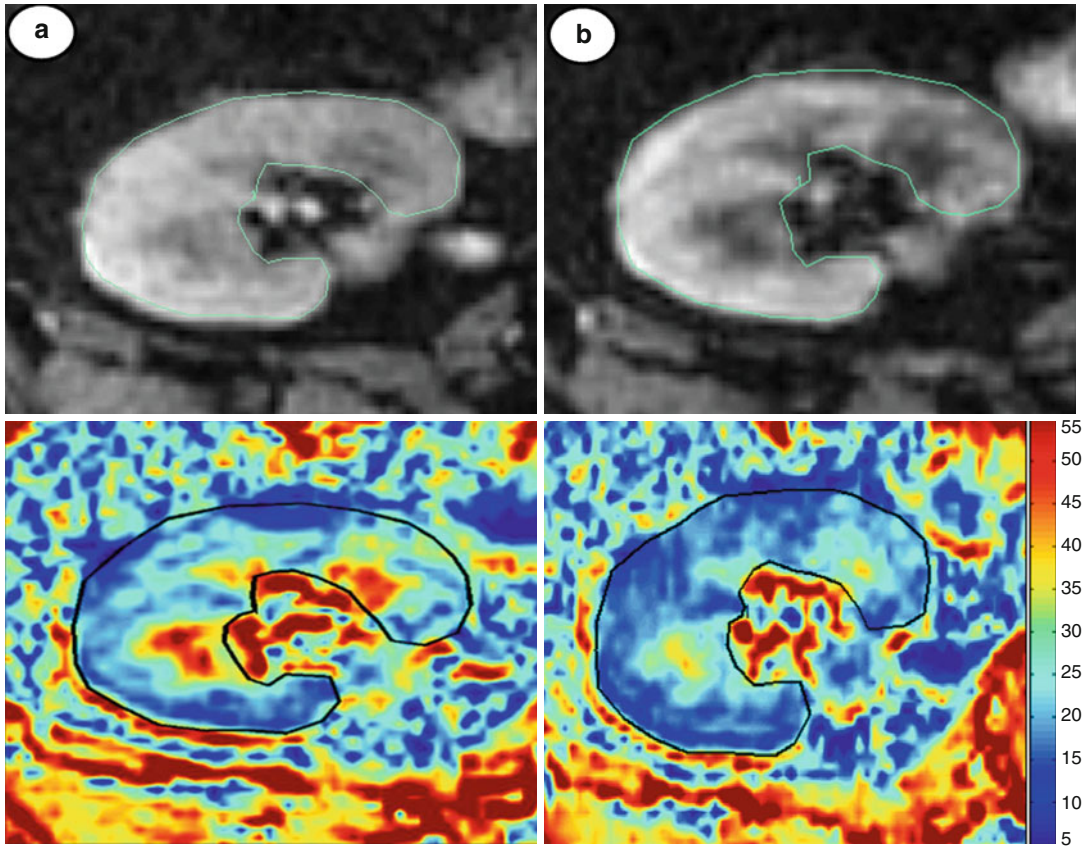


Fig. 17.3 (**a**, **b**) Examples of axial T2 images (*upper row*) and parametric R2* maps (*lower row*) outlining the kidneys in a patient with hypertension before (**a**) and after (**b**) administration of intravenous furosemide. Furosemide led to lower R2* levels, especially in the medulla within 15 min, suggesting that deoxyhemoglobin levels in this region reflected furosemide-suppressible oxygen consumption

despite proportional reductions in O_2 delivery and consumption during graded ARAS. Alford et al. confirmed these data using an acute renal artery obstruction model and observed significant increase in renal R_2* values. The contralateral kidney showed no such change. They also demonstrated the R_2* values return to baseline upon releasing the obstruction [50].

Initial studies using 1.5 T MR were conducted in patients with a variety of renovascular lesions, some of which included total arterial occlusion. Axial slices of kidneys from 25 patients with ARAS were examined and values for R2* in cortex and medulla determined using observers selected regions of interest. These data identified heterogeneities within regions of the kidney associated with large vessel ARAS, some of which obviously followed regional distribution of segmental arterial stenosis [30]. These data confirm in human subjects the general ability to distinguish cortical and medullary oxygenation and identify the role of solute reabsorption by noting the change in medullary R2* after furosemide administration (Fig. 17.3a, b). Surprisingly, values of R2* in medullary regions of kidneys with total occlusion did not differ appreciably from cortex. These results suggested that lack of filtration and solute absorption is associated with minimal oxygen consumption, in agreement with similar data presented in renal transplant patients during episodes of acute allograft rejection with interstitial injury and reduced GFR [51].

Our group undertook further studies to examine tissue oxygenation using higher magnet strength (3 T) in humans with atherosclerotic renal artery stenosis. We studied patients with unilateral ARAS (Doppler ultrasound measurements >260 cm/s) under controlled conditions as part of an inpatient protocol; all patients were treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers during fixed sodium intake of 150 mEq per day. Kidney function was reasonably preserved (creatinine <1.7 mg/dL) and diuretics were limited to thiazides. Data from those individuals were compared with age-matched patients with essential hypertension undergoing the same protocol. Cortical and medullary blood flows and volumes were determined by multidetector computed tomography [31]. Results of these studies confirmed the value of higher magnet strength to distinguish differences in cortical and medullary oxygenation. The hemodynamic significance of these lesions was supported by reductions in blood flow and kidney volumes as compared both to contralateral kidneys and those from essential hypertension. Renal vein renin levels were markedly elevated compared to essential hypertension. As expected, tissue medullary (deepest section of the medulla or the most hypoxic zone) deoxyhemoglobin, as reflected by R2* values, was higher compared with the cortical R2* for both groups. Surprisingly, average levels of cortical and medullary R2* in these ARAS patients did not differ from those of the patients with essential hypertension or from those of the contralateral, normally perfused kidney. Despite reductions in blood flow in the stenotic kidneys sufficient to elevate levels of plasma renin activity, levels of R2* were similar to those in the other patients, indicating preservation of the cortical and medullary oxygenation in these patients under these conditions. Importantly, both GFR and the response of medullary R2* in the stenotic kidney to furosemide administration were reduced compared with the contralateral kidneys. These data suggest that oxygen consumption related to solute transport in the stenotic kidney is less than the contralateral kidney under these conditions. In fact the contralateral kidney may increase its metabolic activity as it assumes some of the filtration and reabsorption functions of the stenotic kidney. We interpret these data to demonstrate a remarkable intrarenal adaptation in the stenotic kidney that effectively preserves oxygenation gradients between cortex and medulla despite reduced blood flow and GFR. One explanation is that the fall in GFR reduces solute filtration, thereby reducing the "workload" and metabolic energy requirements in the medulla. These observations are supported by with similar findings in a chronic rat model of mild renovascular hypertension; they showed that after 4 weeks, no renal hypoxia could be detected in the kidney downstream to a renal artery stenosis. The fact that oxygenation is preserved despite substantial falls in blood flow partly may explain the observations in clinical trials that kidney function may remain stable during antihypertensive drug therapy, sometimes for many years [10].

The ability of the kidney to adapt reduced blood flow obviously has limits, however. We extended our human protocol studies using MDCT and BOLD MRI to patients with more advanced reductions in blood flow, defined as loss of tissue mass and (Doppler ultrasound measurements >384 cm/s) with cortical atrophy (Table 17.1). Levels of serum creatinine could be as high as 2.5 mg/dL. As compared to less severe ARAS, both kidney volume and tissue perfusion in the cortical regions were further reduced (Fig. 17.4). Not surprisingly, levels of cortical R2* were elevated in this group, suggesting that overt tissue hypoxia was developing. Deep medullary regions continued to have high R2* absolute levels that did not differ from those in otherwise normal kidneys. The fraction of axial slices medullary tissue with elevated R2* levels was considerably larger, however. These results demonstrate that severe vascular occlusion eventually overwhelms the capacity of the kidney to adapt to reduced blood flow, manifest as overt cortical hypoxia as measured by blood oxygen level–dependent MRI.

Are the published results in ARAS contradictory? We believe not, but they do emphasize the complexity in this disorder. Based on initial studies, early protocols have focused on selecting

Table 17.1 Example of recent reports of BOLD MR R_2* values described for cortical and medullary regions obtained at (3 T) magnet strength in human subjects

Study	Year	Cortex	Medulla	Comments
Li et al. [52]	2004	21.8	37.4	Healthy volunteers
Tumkur et al. [53]	2006	14.5	30.3	Baseline normal
Prujim et al. [54]	2010	18.2	28.1	Normal, Low NA
Prujim et al. [54]	2010	17.8	31.3	Normal, High NA
Gloviczki et al. [32]	2011	17.8	36.8	Essential Hypertension, 150 mEq NA
Gloviczki et al. [32]	2011	15.7	37.8	Moderate ARAS
Gloviczki et al. [32]	2011	21.6	39.1	Severe ARAS
Pei et al. [55]	2012	18.79	25.07	CKD

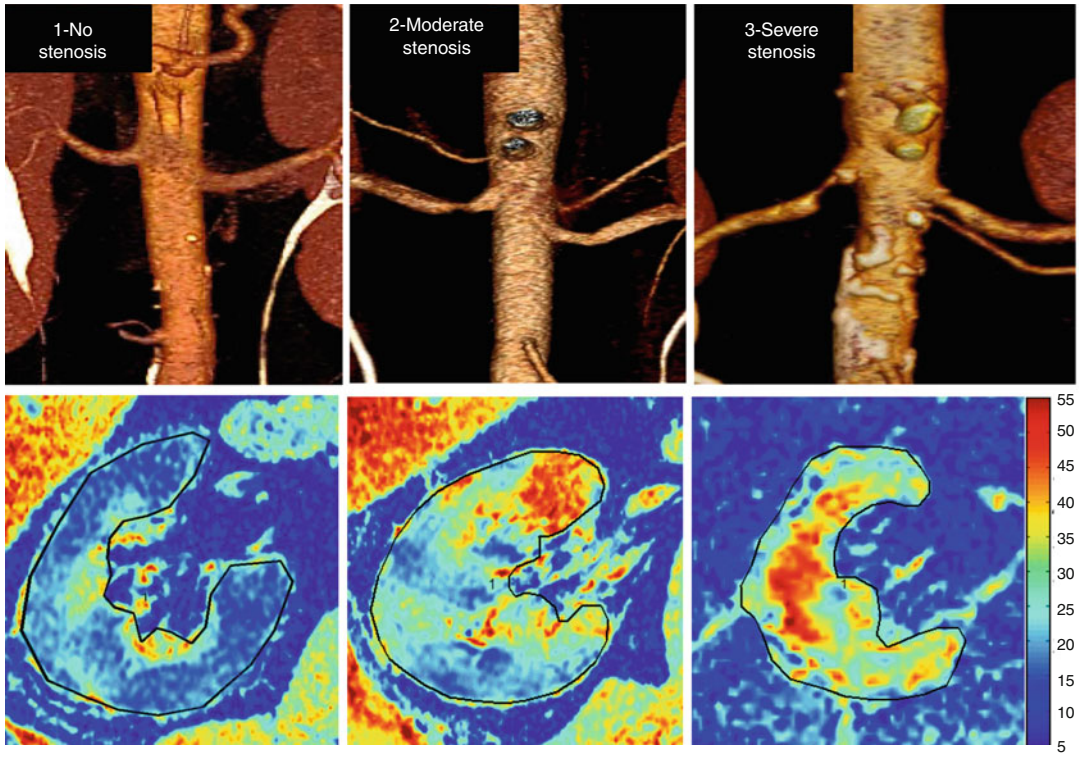


Fig. 17.4 CT angiographic images (*upper row*) of the right kidneys illustrating three patients with (1) no renal artery stenosis (2) moderate renal artery stenosis and (3) severe renal artery stenosis. Below each in the bottom row are corresponding axial images with R2* parametric maps illustrating higher fraction with elevated deoxyhemoglobin (*orange-red*) evident with progressively more severe disease. Note that areas in each slice are heterogeneous, with more uniform cortical values but widely varying R2* levels at different depths and locations within each slice

focal regions of interest to identify a single value for R2* in cortex and a single value in medulla [31, 56]. This approach is problematic, particularly in subjects with heterogeneous vascular disease, as it is challenging to differentiate between cortex and medulla, moreover, the precision and reproducibility of R2* values will be affected by the size and location of ROI. Larger ROIs that include the entire medullary compartments may provide more representative and less variable mean values, but often include multiple medullary and cortico-medullary overlap zones with different hemodynamics [33]. Small, selective ROIs are less vulnerable to volume averaging, but may be

skewed by fluctuations caused by spatial and temporal heterogeneity in oxygen distribution within the kidney, particularly in the medulla [57]. Recently, we suggested a new method of BOLD MR analysis that somehow avoids these problems mentioned previously, called the "fractional tissue hypoxia" method, defined as the percentage of R2* values above 30 s^{-1} on axial slices rather than selected cortical and medullary sites, values from this method correlated inversely with renal blood flow, tissue perfusion and glomerular filtration rate in patients with renovascular disease [58]. Studies using somewhat different methods for analyzing R2* (an average level over entire coronal image slices) indicate a slightly higher level of R2* in subjects with preserved kidney volumes that responded favorably to renal revascularization [59]. We believe these data define a level of "adaptation" that preserves tissue oxygenation both in cortex and medulla over a range of renal blood flow, analogous in some respects to the role of autoregulation in preserving stable renal blood flow and GFR over a range of renal perfusion pressures. When the level of renal blood flow falls below some threshold, oxygenation can no longer be preserved and hypoxia develops. These observations are consistent with the acute experimental data that demonstrated a rise in R2* levels only when the fall in blood flow approached 80 %.

Limitations and Future Directions

Application of BOLD MR is by no means standardized or routine. Some authors argue that effects related to spacial distribution of blood or magnetic field non-homogeneities may limit application of these tools. In a recent publication Michaely et al. [60] could not identify evident correlation between R2* (defined by ROI selection) values and renal function in patients with different stages of CKD as defined by eGFR in a large cohort with a wide variety of kidney disease. For these studies, BOLD imaging was added to MR studies undertaken for a broad range of indications without regard to sodium intake, medications (including those that alter oxygen delivery and/or consumption, such as ACEI/ARBs or diuretics) and the specific etiology of the underlying kidney disease. The authors conclude that gross measures of cortical and medullary oxygenation do not depend directly on the level of eGFR, These results directly contradict the hypoxia/common final pathway hypothesis [40] that predicts reduced renal oxygenation in CKD, at least in the early stages. However, limitations in the study protocol must be addressed. Hydration status and sodium balance were not uniform among the subjects, the use of medications that might alter oxygen delivery and/or oxygen consumption, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antioxidants, and diuretics, was not assessed. Subjects with later stages of CKD are more likely to be taking these agents. Moreover, recent data suggest an added level of complexity in the relationship between renal tissue hypoxia and CKD. Renal tissue oxygenation may depend not only on the severity of CKD but also on the etiology of the underlying kidney disease [61]. Our studies up to now have been conducted under conditions with controlled sodium intake, standardized drug therapy, and excluded other obvious conditions that might affect tissue oxygenation (e.g., advanced renal failure, diabetes). Importantly, methods for analyzing BOLD images are not standardized. As can be seen in the previous figures, maps of R2* indicate considerable local heterogeneities within image slices. The premise that observer selected regions of interest that lead to characterization of single values of R2* that apply to the entire cortex or entire medulla represents the most valid approach merits critical study. Further studies need to address stability in renal oxygenation over time and particularly the changes in ARAS associated both with medical therapy and with renal revascularization. It is likely that developing methods that more realistically address observer selected ROIs and that acknowledge the heterogeneities of oxygenation, particularly within the medulla, will be essential to advancing this field [58]. A further objective is to define more precisely exactly how variation in tissue oxygenation is related to activation—or possibly reversal—of parenchymal tissue injury in this disorder. Our

overall goal is to improve the use of BOLD MRI to allow more precise identification of kidneys at risk from vascular injury that may benefit from renal revascularization and/or adjunctive measures to repair the kidney before irreversible kidney damage develops.

Conclusion

BOLD MRI is a noninvasive technique that requires no contrast or radiation that has great potential as a functional tool to evaluate patients with ARAS. Initial studies indicate a complex relationship between changes in blood flow that allows adaptation to reduced perfusion and GFR that nonetheless preserve a normal cortical-to-medulla gradient of deoxyhemoglobin. More severe vascular compromise ultimately overwhelms these adaptive changes, leading to overt cortical hypoxia and expansion of medullary hypoxic zones. It is likely those additional processes that modify regional oxygenation in the kidney, such as diabetes, circulatory failure, and others also may affect these processes. At this point, standardized protocols and evaluation of ARAS with BOLD remain investigational. We believe that careful application and analysis of BOLD MR will provide critical insights into early disruption of renal physiology and function prior to the onset of irreversible renal injury. Clinical applications may identify patients that are free from the risks of "hypoxic" injury, or conversely, identify those most likely to gain from measures to reverse disorders of impaired tissue oxygenation.

References

1. Textor SC. Ischemic nephropathy: where are we now? J Am Soc Nephrol. 2004;15(8):1974–82.
2. Garovic VD, Textor SC. Renovascular hypertension and ischemic nephropathy. Circulation. 2005;112(9):1362–74.
3. O'Connor PM. Renal oxygen delivery: matching delivery to metabolic demand. Clin Exp Pharmacol Physiol. 2006;33(10):961–7.
4. Evans RG, Gardiner BS, Smith DW, O'Connor PM. Intrarenal oxygenation: unique challenges and the biophysical basis of homeostasis. Am J Physiol Renal Physiol. 2008;295(5):F1259–70.
5. Brezis M, Heyman SN, Epstein FH. Determinants of intrarenal oxygenation. II. Hemodynamic effects. Am J Physiol. 1994;267(6 Pt 2):F1063–8.
6. Brezis M, Rosen S. Hypoxia of the renal medulla – its implications for disease. N Engl J Med. 1995;332(10):647–55.
7. Klenzak J, Himmelfarb J. Sepsis and the kidney. Crit Care Clin. 2005;21(2):211–22.
8. Heyman SN, Rosenberger C, Rosen S. Regional alterations in renal haemodynamics and oxygenation: a role in contrast medium-induced nephropathy. Nephrol Dial Transplant. 2005;20 Suppl 1:i6–11.
9. Evans RG, Eppel GA, Anderson WP, Denton KM. Mechanisms underlying the differential control of blood flow in the renal medulla and cortex. J Hypertens. 2004;22(8):1439–51.
10. Wheatley K, Ives N, Gray R, Kalra PA, Moss JG, Baigent C, et al. Revascularization versus medical therapy for renal-artery stenosis. N Engl J Med. 2009;361(20):1953–62.
11. Alcazar JM, Rodicio JL. Ischemic nephropathy: clinical characteristics and treatment. Am J Kidney Dis. 2000;36(5):883–93.
12. Coen G, Manni M, Giannoni MF, Bianchini G, Calabria S, Mantella D, et al. Ischemic nephropathy in an elderly nephrologic and hypertensive population. Am J Nephrol. 1998;18(3):221–7.
13. Jacobson HR. Ischemic renal disease: an overlooked clinical entity? Kidney Int. 1988;34(5):729–43.
14. Textor SC, Lerman L. Renovascular hypertension and ischemic nephropathy. Am J Hypertens. 2010;23(11):1159–69.
15. Evans RG, Eppel GA, Michaels S, Burke SL, Nematbakhsh M, Head GA, et al. Multiple mechanisms act to maintain kidney oxygenation during renal ischemia in anesthetized rabbits. Am J Physiol Renal Physiol. 2010;298(5):F1235–43.
16. O'Connor PM, Kett MM, Anderson WP, Evans RG. Renal medullary tissue oxygenation is dependent on both cortical and medullary blood flow. Am J Physiol Renal Physiol. 2006;290(3):F688–94.
17. Warner L, Glockner JF, Woollard J, Textor SC, Romero JC, Lerman LO. Determinations of renal cortical and medullary oxygenation using blood oxygen level-dependent magnetic resonance imaging and selective diuretics. Invest Radiol. 2011;46(1):41–7.
18. Gomez SI, Warner L, Haas JA, Bolterman RJ, Textor SC, Lerman LO, et al. Increased hypoxia and reduced renal tubular response to furosemide detected by BOLD magnetic resonance imaging in swine renovascular hypertension. Am J Physiol Renal Physiol. 2009;297(4):F981–6.
19. Sadowski J, Badzynska B. Specific features and roles of renal circulation: angiotensin II revisited. J Physiol Pharmacol. 2006;57 Suppl 11:169–78.
20. Liss AG, Liss P. Use of a modified oxygen microelectrode and laser-Doppler flowmetry to monitor changes in oxygen tension and microcirculation in a flap. Plast Reconstr Surg. 2000;105(6):2072–8.
21. Braun RD, Lanzen JL, Snyder SA, Dewhirst MW. Comparison of tumor and normal tissue oxygen tension measurements using OxyLite or microelectrodes

in rodents. Am J Physiol Heart Circ Physiol. 2001;280(6):H2533–44.
22. Zhong Z, Arteel GE, Connor HD, Yin M, Frankenberg MV, Stachlewitz RF, et al. Cyclosporin A increases hypoxia and free radical production in rat kidneys: prevention by dietary glycine. Am J Physiol. 1998; 275(4 Pt 2):F595–604.
23. Rosenberger C, Heyman SN, Rosen S, Shina A, Goldfarb M, Griethe W, et al. Up-regulation of HIF in experimental acute renal failure: evidence for a protective transcriptional response to hypoxia. Kidney Int. 2005;67(2):531–42.
24. Evans RG, Gardiner BS, Smith DW, O'Connor PM. Methods for studying the physiology of kidney oxygenation. Clin Exp Pharmacol Physiol. 2008;35(12):1405–12.
25. Pauling L, Coryell CD. The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin. Proc Natl Acad Sci U S A. 1936;22(4):210–6.
26. Dunn JF, Swartz HM. Blood oxygenation. Heterogeneity of hypoxic tissues monitored using bold MR imaging. Adv Exp Med Biol. 1997;428:645–50.
27. Prasad PV, Edelman RR, Epstein FH. Noninvasive evaluation of intrarenal oxygenation with BOLD MRI. Circulation. 1996;94(12):3271–5.
28. Prasad PV, Epstein FH. Changes in renal medullary pO2 during water diuresis as evaluated by blood oxygenation level-dependent magnetic resonance imaging: effects of aging and cyclooxygenase inhibition. Kidney Int. 1999;55(1):294–8.
29. Prasad PV. Evaluation of intra-renal oxygenation by BOLD MRI. Nephron Clin Pract. 2006;103(2):c58–65.
30. Textor SC, Glockner JF, Lerman LO, Misra S, McKusick MA, Riederer SJ, et al. The use of magnetic resonance to evaluate tissue oxygenation in renal artery stenosis. J Am Soc Nephrol. 2008;19(4):780–8.
31. Gloviczki ML, Glockner JF, Lerman LO, McKusick MA, Misra S, Grande JP, et al. Preserved oxygenation despite reduced blood flow in poststenotic kidneys in human atherosclerotic renal artery stenosis. Hypertension. 2010;55(4):961–6.
32. Gloviczki ML, Lerman LO, Textor SC. Blood oxygen level-dependent (BOLD) MRI in renovascular hypertension. Curr Hypertens Rep. 2011;13(5):370–7.
33. Gloviczki ML, Glockner J, Gomez SI, Romero JC, Lerman LO, McKusick M, et al. Comparison of 1.5 and 3 T BOLD MR to study oxygenation of kidney cortex and medulla in human renovascular disease. Invest Radiol. 2009;44(9):566–71.
34. Pedersen M, Dissing TH, Morkenborg J, Stodkilde-Jorgensen H, Hansen LH, Pedersen LB, et al. Validation of quantitative BOLD MRI measurements in kidney: application to unilateral ureteral obstruction. Kidney Int. 2005;67(6):2305–12.
35. Li LP, Ji L, Santos EA, Dunkle E, Pierchala L, Prasad P. Effect of nitric oxide synthase inhibition on intrarenal oxygenation as evaluated by blood oxygenation level-dependent magnetic resonance imaging. Invest Radiol. 2009;44(2):67–73.
36. Palm F, Connors SG, Mendonca M, Welch WJ, Wilcox CS. Angiotensin II type 2 receptors and nitric oxide sustain oxygenation in the clipped kidney of early Goldblatt hypertensive rats. Hypertension. 2008;51(2):345–51.
37. Warner L, Gomez SI, Bolterman R, Haas JA, Bentley MD, Lerman LO, et al. Regional decreases in renal oxygenation during graded acute renal arterial stenosis: a case for renal ischemia. Am J Physiol Regul Integr Comp Physiol. 2009;296(1):R67–71.
38. Hofmann L, Simon-Zoula S, Nowak A, Giger A, Vock P, Boesch C, et al. BOLD-MRI for the assessment of renal oxygenation in humans: acute effect of nephrotoxic xenobiotics. Kidney Int. 2006;70(1): 144–50.
39. Djamali A, Sadowski EA, Muehrer RJ, Reese S, Smavatkul C, Vidyasagar A, et al. BOLD-MRI assessment of intrarenal oxygenation and oxidative stress in patients with chronic kidney allograft dysfunction. Am J Physiol Renal Physiol. 2007;292(2): F513–22.
40. Nangaku M. Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. J Am Soc Nephrol. 2006;17(1):17–25.
41. Kristensen DH, Pedersen M, Gron MC, Flyvbjerg A, Madsen M, Frokiaer J, et al. Intrarenal blood oxygenation and renal function measured by magnetic resonance imaging during long-term cyclosporine treatment. Transplant Proc. 2005;37(8): 3302–4.
42. Park SY, Kim CK, Park BK, Huh W, Kim SJ, Kim B. Evaluation of transplanted kidneys using blood oxygenation level-dependent MRI at 3 T: a preliminary study. AJR Am J Roentgenol. 2012;198(5): 1108–14.
43. Manotham K, Ongvilawan B, Urusopone P, Chetsurakarn S, Tanamai J, Limkuansuwan P, et al. Angiotensin II receptor blocker partially ameliorated intrarenal hypoxia in chronic kidney disease patients: a pre-/post-study. Intern Med J. 2012;42(4):e33–7.
44. Yin WJ, Liu F, Li XM, Yang L, Zhao S, Huang ZX, et al. Noninvasive evaluation of renal oxygenation in diabetic nephropathy by BOLD-MRI. Eur J Radiol. 2012;81(7):1426–31.
45. Cowley AW, Mattson DL, Lu SH, Roman RJ. The renal medulla and hypertension. Hypertension. 1995;25(4):663–73.
46. Cowley AW, Roman RJ, Fenoy FJ, Mattson DL. Effect of renal medullary circulation on arterial-pressure. J Hypertens. 1992;10:S187–93.
47. Li L, Storey P, Kim D, Li W, Prasad P. Kidneys in hypertensive rats show reduced response to nitric oxide synthase inhibition as evaluated by BOLD MRI. J Magn Reson Imaging. 2003;17(6):671–5.
48. Textor SC, Gloviczki ML, Flessner MF, Calhoun DA, Glockner J, Grande JP, et al. Association of filtered sodium load with medullary volumes and medullary hypoxia in hypertensive African Americans as compared with whites. Am J Kidney Dis. 2012;59(2): 229–37.

49. Juillard L, Lerman LO, Kruger DG, Haas JA, Rucker BC, Polzin JA, et al. Blood oxygen level-dependent measurement of acute intra-renal ischemia. Kidney Int. 2004;65(3):944–50.
50. Alford SK, Sadowski EA, Unal O, Polzin JA, Consigny DW, Korosec FR, et al. Detection of acute renal ischemia in swine using blood oxygen level-dependent magnetic resonance imaging. J Magn Reson Imaging. 2005;22(3):347–53.
51. Djamali A, Sadowski EA, Samaniego-Picota M, Fain SB, Muehrer RJ, Alford SK, et al. Noninvasive assessment of early kidney allograft dysfunction by blood oxygen level-dependent magnetic resonance imaging. Transplantation. 2006;82(5):621–8.
52. Li LP, Vu AT, Li BS, Dunkle E, Prasad PV. Evaluation of intrarenal oxygenation by BOLD MRI at 3.0 T. J Magn Reson Imaging. 2004;20(5):901–4.
53. Tumkur SM, Vu AT, Li LP, Pierchala L, Prasad PV. Evaluation of intra-renal oxygenation during water diuresis: a time-resolved study using BOLD MRI. Kidney Int. 2006;70(1):139–43.
54. Pruijm M, Hofmann L, Maillard M, Tremblay S, Glatz N, Wuerzner G, et al. Effect of sodium loading/depletion on renal oxygenation in young normotensive and hypertensive men. Hypertension. 2010;55(5):1116–22.
55. Pei XL, Xie JX, Liu JY, Wang S, Tian XK. A preliminary study of blood-oxygen-level-dependent MRI in patients with chronic kidney disease. Magn Reson Imaging. 2012;20(3):330–5.
56. Simon-Zoula SC, Hofmann L, Giger A, Vogt B, Vock P, Frey FJ, et al. Non-invasive monitoring of renal oxygenation using BOLD-MRI: a reproducibility study. NMR Biomed. 2006;19(1):84–9.
57. Lubbers DW, Baumgartl H. Heterogeneities and profiles of oxygen pressure in brain and kidney as examples of the pO2 distribution in the living tissue. Kidney Int. 1997;51(2):372–80.
58. Saad A, Crane J, Glockner JF, Herrmann SMS, Friedman H, Ebrahimi B, et al. Human renovascular disease: estimating fractional tissue hypoxia to analyze blood oxygen level–dependent MR. Radiology. 2013;268(3):770–8.
59. Chrysochou C, Mendichovszky IA, Buckley DL, Cheung CM, Jackson A, Kalra PA. BOLD imaging: a potential predictive biomarker of renal functional outcome following revascularization in atheromatous renovascular disease. Nephrol Dial Transplant. 2012;27(3):1013–9.
60. Michaely HJ, Metzger L, Haneder S, Hansmann J, Schoenberg SO, Attenberger UI. Renal BOLD-MRI does not reflect renal function in chronic kidney disease. Kidney Int. 2012;81(7):684–9.
61. Neugarten J. Renal BOLD-MRI and assessment for renal hypoxia. Kidney Int. 2012;81(7):613–4.

Tissue Histopathologic Injury in Renovascular Occlusive Disease

18

Monika L. Gloviczki and Stephen C. Textor

Abstract

Many histopathologic findings within post-stenotic kidneys are nonspecific and represent conditions associated with aging, atherosclerosis and pre-existing hypertension. Two major abnormalities reported in patients with renovascular disease (RVD) are arteriolar nephrosclerosis and atheroembolic renal lesions. Other chronic renal "ischemia" markers include tubular atrophy, interstitial fibrosis and arteriolar sclerosis, but are less specific.

Recent data demonstrate that intra-renal oxygenation in renovascular disease (RVD) is affected in a patchy way and produces local alterations that can ultimately lead to irreversible tissue damage. Moreover, kidney injury has the tendency for progressive deterioration even after the primary causal factor is eliminated.

Transvenous or transjugular renal biopsy, requiring retrograde access through the venous system, was recently proposed as an alternative for patients with contraindications for percutaneous biopsy. This technique was used in a prospective study to examine histopathologic changes in biopsies from kidneys with moderate unilateral renal artery stenosis, compared with renal tissue specimens from normal kidney donors, and nephrectomy samples for total vascular occlusion. Tissue from affected kidneys has provided evidence for complex injury pathways in atherosclerotic RVD that include activation of Transforming Growth Factor-β (TGF- β) and accumulation of tissue macrophages in addition to progressive interstitial fibrosis. These data support a transition from a hemodynamic

M.L. Gloviczki, MD, PhD (✉)
Division of Nephrology and Hypertension,
Mayo Clinic, 200 First Street SW,
Rochester, MN 55905, USA
e-mail: gloviczki.monika@gmail.com

S.C. Textor, MD
Division of Nephrology and Hypertension,
Mayo Clinic College of Medicine,
E19, Rochester, MN 55905, USA
e-mail: stextor@mayo.edu, textor.stephen@mayo.edu

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_18,

disorder to one with inflammatory and fibrotic injury that does not reverse entirely with restoration of blood flow alone.

Direct examination of kidney tissue obtained by biopsy might contribute to both understand the disease process and to identify those individuals likely to benefit (or not) from measures to restore blood flow or other treatment modalities.

Keywords

Renovascular disease • Kidney biopsy • Ischemic nephropathy • Arteriolar nephrosclerosis • Atheroembolic renal lesions • Tubular atrophy • Interstitial fibrosis • Arteriolar sclerosis

Introduction

The process of hemodynamic and signaling events leading to tissue fibrosis associated with renovascular disease (RVD) remains poorly understood. Some would argue that direct examination of kidney tissue obtained by biopsy provides the potential to both understand the disease process and to identify those individuals likely to benefit (or not) from measures to restore blood flow or other treatment modalities. Many patients tolerate decreased renal blood flow without detectable damage of kidney parenchyma for years despite even further reduction in systemic and renal perfusion pressures during antihypertensive drug therapy. The incidence of disease progression towards complete renal artery occlusion has been reported from 9 to 16 % within the first 2 years of the follow-up, although more than 50 % of patients have some degree of progressive stenosis [1–5]. While controversial, the evolution of atherosclerotic RVD to the irreversible injury associated with end-stage renal disease (ESRD) is probably underestimated. The percentage of patients with renal artery stenosis was estimated as 40.8 % in cohorts of newly diagnosed patients with ESRD and renal failure was present in 27.5 % of patients with accidentally discovered renal artery stenosis [6]. Among predictive factors for significant RVD several authors list age >60 and elevated serum creatinine and/or creatinine clearance <50 mL/min, coronary artery disease and peripheral vascular anomalies [7, 8]. With the rise of the mean age of US population we can expect substantial increase in the incidence of atherosclerotic renal stenosis and its consequences – including ESRD. This observation stresses the importance of better understanding of the factors leading to the renal function impairment in renovascular disease. Identification of specific pathways responsible for progressive renal injury and interventions to block these pathways offer the potential to preserve the post-stenotic kidney [9].

Blood pressure control alone does not seem to be a reliable marker for progressive renovascular disease, especially in the present time when the development of antihypertensive therapy offers a considerable number of possibilities.

Importantly, revascularization procedures frequently fail to restore kidney function and to stop the progression towards ESRD. The potential benefit of surgical revascularization in carefully selected patients was demonstrated by Novick et al. in 1987 [10], showing that renal function was improved in 58 % of patients and only 11 % experienced post-operative deterioration. A well-developed collateral arterial supply with retrograde filling of the renal vessels and a renal biopsy with well- preserved glomeruli predicted recovery [1, 11, 12]. For patients with serum creatinine >4 mg/dL Novick and Scoble [1] recommended performing intra-operative renal biopsy to evaluate the severity of renal injury. This chapter will explore the potential role for examination of kidney tissue in the management of renovascular disease.

Histopathology of the Kidney in Renovascular Disease

Many histopathologic findings within post-stenotic kidneys are nonspecific and represent conditions associated with aging, atherosclerosis and pre-existing hypertension. Two major abnormalities reported in patients with renovascular disease are arteriolar nephrosclerosis and atheroembolic renal lesions consistent with widespread hypertensive and vascular disease. Dean and colleagues [13] proposed "recent deterioration" as the most useful clinical marker to identify patients likely to benefit from surgical revascularization, particularly in the case of elderly patients with other comorbidities. Close examination of glomeruli has been emphasized as a marker for viability after restoration of renal blood flow. Other chronic renal "ischemia" markers include tubular atrophy, interstitial fibrosis and arteriolar sclerosis, but are less specific [1, 11, 12].

Recent data demonstrate that intra-renal oxygenation in RVD is affected in a patchy way and produces local alterations that can ultimately lead to irreversible tissue damage [9, 14]. The severity of chronic renal damage score, glomerulosclerosis and interstitial volume are correlated with renal functional outcome in the atherosclerotic renovascular disease [15]. An important characteristic of many forms of kidney injury is the tendency for progressive deterioration even after the primary causal factor is eliminated [16].

Morphological changes were studied in a model of renal ischemia with blood flow reduced from 120 to 20 mL/min for 3 weeks [17]. When renal flow was below 80 mL/min the authors observed loss of glomerular volume, tubular dilatation, tubular cast formation, tubular atrophy, interstitial fibrosis, arteriolar thickening and glomerular hyalinization. Electron microscopic studies showed loss of glomerular microvasculature, unfolding of glomerular vascular tuft, appearance of blind ending vessels and disruption of glomerular architecture, as well as narrowing of medullary blood vessels and neovascularization.

Experimental animal studies indicate complex processes that injure the kidney beyond renovascular lesions. A hypercholesterolemic rat model [18] demonstrates that RVD increases the availability of oxidative injury species, including ox-LDL, pro-fibrotic and cytotoxic substrates for renal mesangial, epithelial, and endothelial cells.

One-clip renovascular hypertensive rats fed with high-fat-sucrose diet were used to examine renoprotective effect of sesamin, an agent that increases availability of nitric oxide [19]. The Western blotting tests detected the expression of endothelial nitric oxide synthase (eNOS) and structural abnormalities were revealed by pathology cortical slides with PAS and Masson's staining. Sesamin reversed structural and functional parameters and decreased oxidative stress by the upregulation of eNOS expression in the stenotic and contralateral kidney.

A mouse with unilateral renal artery stenosis was used as a model to study signaling pathways of RVD [20]. In this work contralateral kidney showed minimal histopathologic abnormalities. The post stenotic kidney demonstrated activation of transforming growth factor beta (TGF-β), interstitial fibrosis, tubular atrophy and interstitial inflammation. An unexpected proliferative response involved tubular epithelial cells in the post-stenotic atrophic kidney. The role of TGF-β/Smad3 signaling mechanisms were examined further in mice with targeted disruption of exon 2 of the Smad3 gene [21]. Genetic deficiency of Smad3 protected the kidney from atrophy and interstitial fibrosis.

Gradually progressive RVD in swine models has provided substantial data regarding the pathogenesis of this disorder. The atherosclerotic milieu (defined by cholesterol feeding) and RAS combine to interfere with renal tissue remodeling and increased fibrosis in the post-stenotic kidney [22]. A daily supplement of antioxidant vitamin C improved renal functional response and decreased structural injury [23]. Another experiment in this model showed that intra-renal administration of vascular endothelial growth factor (VEGF) preserved microvascular structures and was associated with reduced fibrosis [24].

Human pathology has been studied primarily in nephrectomy samples. Correlations between clinical and histopathological findings in ischemic nephropathy secondary to atherosclerotic

renal artery stenosis were object of a study [25] of a cohort of 62 patients who underwent nephrectomy for renovascular disease, usually to remove a "pressor" kidney. The authors showed significant tubulointerstitial atrophy with relative glomerular sparing as a predominant injury (71 % of patients). Glomerulosclerosis was present in 23 % of cases. Not surprisingly, severe histopathological anomalies were more frequent in the smaller kidneys. Typical vascular changes (atheroembolic, atherosclerotic and hypertensive) were present in 39, 98, and 52 % of patients, respectively. Histologic diagnosis of vascular involvement correlated with the presence of hypertension, dyslipidemia, renal insufficiency and cardiovascular morbidity such as myocardial infarction and abdominal aortic aneurysm. Statin therapy was associated with a lesser renal fibrosis as demonstrated by staining for transforming growth factor beta.

Technical Considerations of Renal Biopsy in Atherosclerotic RAS

Percutaneous native kidney biopsy has been developed extensively since the 1960s [26]. Percutaneous ultrasound guided biopsy is most often performed in the outpatient setting and does carry a small, but definite, risk of hemorrhage [27, 28]. Introduction of direct ultrasound localization of the biopsy needle and automated needle have been associated with reduced complications' rate [29, 30]. It is most often performed to delineate the etiology and/or stage of active glomerular disorders, usually with normal sized kidneys. In the Parrish [31] cohort of 14,492 subjects only one death occurred after 1980, and global mortality associated with renal biopsies was 0.12 %.

Transvenous or transjugular renal biopsy requires retrograde access through the venous system, most often the jugular vein. It was proposed first in the 1990s as an alternative for patients with contraindications for percutaneous biopsy [32]. Swine research model served to assess this method [33] and showed a successful acquisition of the right renal cortical samples with the 19-gauge, side-cut biopsy needle with a blunt-tip stylet utilizing fluoroscopic guidance. Safety studies with angiography and venography done immediately before and after biopsy indicated a low rate of hemorrhage. Results from transvenous renal biopsies were compared to percutaneous biopsies a French cohort of consecutive 800 patients [34]. Effectiveness and safety of both methods appeared to be similar with tissue core adequate for histopathologic diagnosis in 98.2 % of cases. Four major complications occurred with transjugular renal biopsy and three with percutaneous biopsy.

The principal indications for transvenous biopsy have been combined kidney and liver biopsy and/or clotting disorders [35–37]. Transjugular renal biopsy was also evaluated in patients with acute renal failure who required venous catheter placement for hemodialysis [37, 38].

Recognized complications have been reported in up to 13 % patients undergoing transvenous biopsy, usually in patients with hepatic failure [39]. Only 6–7 % of complications are major requiring an intervention (transfusion, surgery or interventional radiology procedure). Recent experience with transvenous kidney biopsy showed the frequency of major complications from 1 % [34] to 2.6 % cases [36] and 11.8 % [40]. Bleeding is the most prevalent complication and a coagulation profile is usually obtained before the procedure including the hemoglobin level, prothrombin time, international normalized ratio (INR), partial thromboplastin time and platelet count [26, 36]. In one of the studies 13 % of patients required blood transfusion [41]. However, transvenous methods are applied most often to high risk patients.

Incidence of complications is particularly elevated in patients with clotting disorders. Rychlik et al. [35] compared patients with and without coagulopathy and reported respectively 34 % versus 7 % complication rate.

Microscopic hematuria is common. However, only 10 % of patients experience macroscopic hematuria, often associated with arteriovenous fistulae [26, 31]. Spontaneous resolution of hematuria occurs usually in 48–72 h, even though it can persist for 2–3 weeks in small percentage

of patients [26, 31, 42]. Transfusions and surgery for hemostasis are rarely required [26, 31, 42].

Cases of massive hematuria are believed to be related to intrarenal arterio-venous fistulae (AVF) [31]. Frequency of AVF is estimated between 15 and 18 % as showed on the post-biopsies angiographic evaluation [26]. Most of the cases are asymptomatic and spontaneously resolve within 2 years [26].

Perinephritic hematomas are commonly observed and were found in 57–85 % of patients on the post-biopsy CT [43, 44]. In the majority of cases there are no symptoms associated, but a decrease in hemoglobin could be observed [42]. Some patients (1–2 %) report flank pain and swelling [26]. Minor hematomas were found in 52 % of patients after transvenous biopsy performed in Mayo Clinic [36] and were considered as minor complications.

Among another complications, aneurysms were noted in less than 1 % of patients [26].

Prospective Study in Patients with Moderate Unilateral ARAS

To examine histopathologic changes in atherosclerotic RVD, we undertook a prospective examination of tissue obtained in nondiabetic patients with moderate unilateral ARAS. These individuals were undergoing inpatient protocol including evaluation of blood flow and tissue oxygenation determined by Blood Oxygen Level Dependent Magnetic Resonance (BOLD MR), which could be compared with data from subjects with essential hypertension [45, 46].

Participants in this study were submitted to a 3-day inpatient protocol in the clinical research unit. Comprehensive renal artery stenosis and kidneys evaluation was undertaken in standardized dietary conditions. On the third protocol day, transvenous renal biopsy was obtained in patients with right renal artery stenosis after completion of multi-detector computed tomography (MDCT) studies to measure renal blood flow (RBF) and tissue perfusion. Renal tissue oxygenation was measured by BOLD 3-T MR performed on the second day.

Tissue from 12 transvenous biopsies of these study patients were compared with renal tissue specimens from age and gender matched normal kidney donors (n = 15) at kidney implantation, and nephrectomy samples for total vascular occlusion due to ARAS (n = 65) [47].

Histopathological slices were prepared using Hematoxylin and eosin (H&E), periodic acid Schiff (PAS), and Masson's Trichrome (MT) stains (Fig. 18.1). Banff '97 grading system assigned scores for interstitial, glomerular and vascular lesions. The extent of interstitial fibrosis, inflammation and vascular changes were evaluated as continuous variables from 0 to 100 %. TGF-β tissue immunostaining was graded on the following scale: 0 = 0 %, 1 < 25 %, 2 = 25–50 %, 3 > 50 %.

Cellular infiltrates of biopsies were examined using immunohistochemical staining for macrophage cell marker CD68, lymphocyte T-cell markers CD3 and CD134, as well as lymphocyte B cell marker CD20. Stained cells were counted using an automatic setting with a colorimetric threshold.

These data demonstrated significant correlations between hemodynamic changes in the post-stenotic kidney (decreased renal blood flow) and the percentage of interstitial inflammation, interstitial fibrosis and tubular atrophy identified on transjugular biopsy specimens. The degree of tubular atrophy reached more than 60 % in nephrectomy specimens (Fig. 18.2).

Renal tissue TGF-β immunoreactivity score was higher in moderate ARAS compared to normal kidneys and those with total occlusion (mean score 2.4 ± 0.7 vs $1.5 + 1.1$ in nephrectomy group and vs 0 ± 0 in donors, $p < .01$) (Fig. 18.3).

For moderate ARAS specimens, the percentage of total renal blood flow delivered to the post-stenotic kidney (RBF fraction and absolute RBF on the affected side) was inversely related to the trichrome estimates of fibrosis ($R = -0.58$, $p < .01$) and interstitial inflammation ($R = -.62$, $p = .01$).

Tissue CD68+ macrophages rose with disease severity (from 2.2 ± 2.7 in normal to 22.4 ± 18 cells/high power field in nephrectomy samples, $p < .001$) (Fig. 18.3). CD3+ cells were also higher in moderate ARAS and nephrectomy samples.

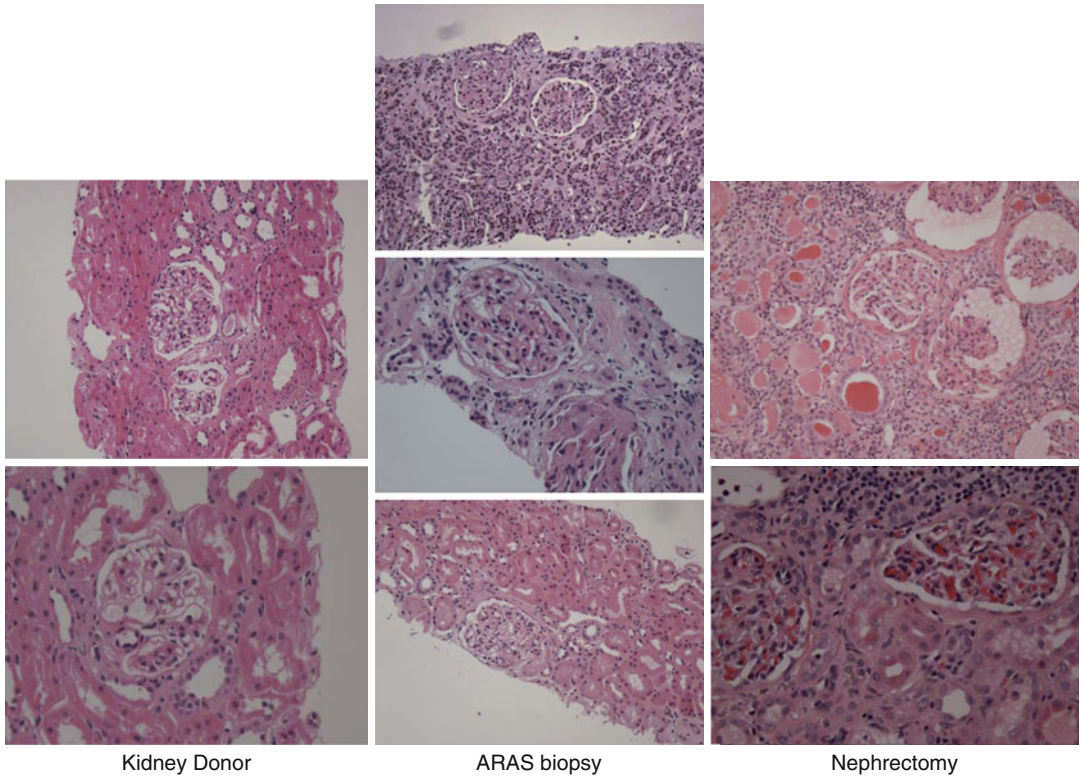


Fig. 18.1 Examples of H&E sections from Kidney donors, Moderate ARAS and Nephrectomy

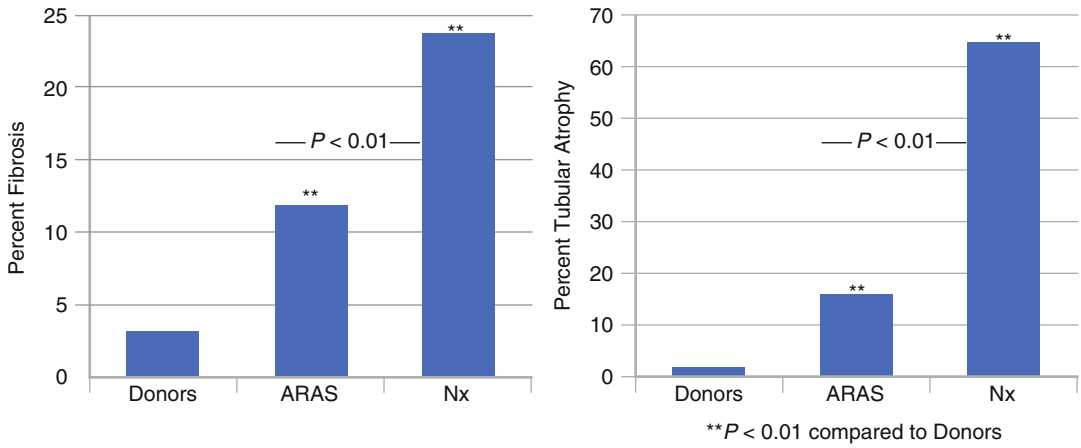


Fig. 18.2 Atherosclerotic renal artery stenosis is associated with tubular atrophy and interstitial fibrosis, but less than total occlusion. *Donors* Kidney donors group, *ARAS* Moderate ARAS group, *Nx* Nephrectomy group

TGF-β stimulation within the human kidney parenchyma in patients with severe vascular occlusive disease was a function of reduced RBF and was associated with macrophage infiltration. Taken together, these observations suggest that occlusive RVD associated with atherosclerosis activates pro-inflammatory pathways with diffuse tissue staining for TGF-β at an early stage. This is

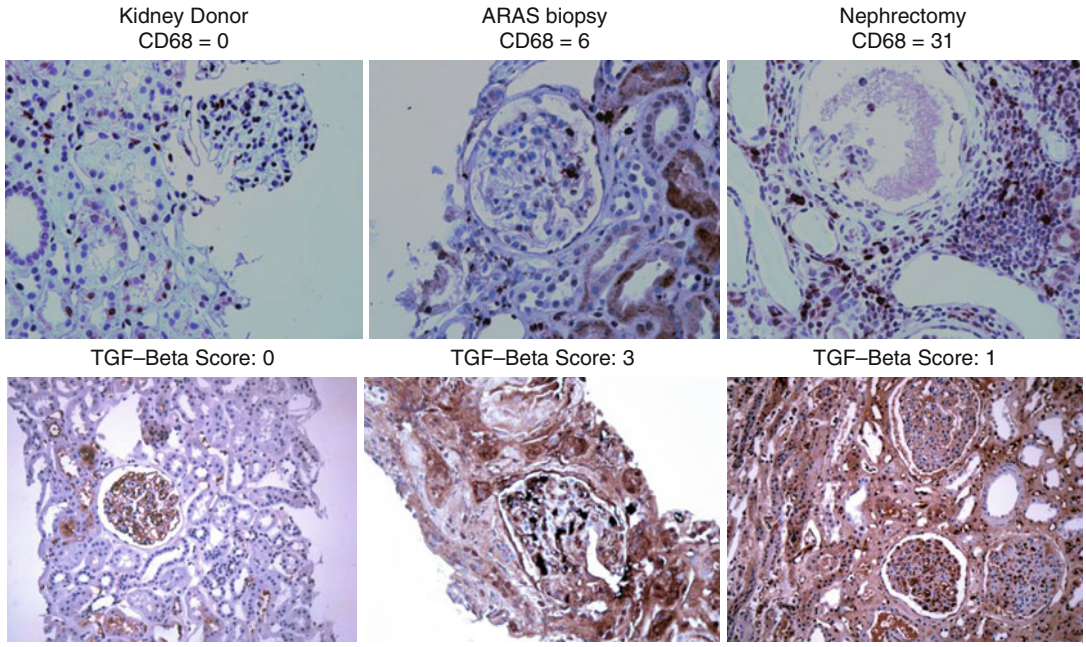


Fig. 18.3 Tissue staining for TGF-β demonstrated widespread expression in ARAS that was not evident in normal kidneys and was much less evident in samples from nephrectomy tissue with total occlusion in. TGF-β was identified within parenchymal and glomerular regions independent of the degree of tubular atrophy or evident fibrosis. Macrophages (CD 68 positive cells) number rose significantly in moderate ARAS and in Nephrectomy group

associated with accumulation of both T-cells and macrophages, even in some patients with relatively preserved tissue oxygenation. Measurement of renal venous cytokine markers confirm complex signaling from post-stenotic kidneys with net release of interleukin-6 and tumor necrosis factor (TNF-alpha), as well as neutrophil gelatinase-associated lipocalin (NGAL) [48].

Conclusion

Tissue samples from post-stenotic kidneys demonstrate complex pathology that likely reflects both pre-existing comorbidities and changes related to RVD. Transvenous biopsies offer an alternative to percutaneous sampling that may be especially relevant to kidneys with reduced blood flow and may provide safer, directed access to affected tissue as compared with percutaneous biopsy. Although there is no consensus about the role of kidney biopsy in the clinical management of renovascular disease, it may be a valuable diagnostic tool in some clinical cases. Tissue from affected kidneys has provided evidence for complex injury pathways in atherosclerotic RVD that include activation of TGF-β and accumulation of tissue macrophages in addition to progressive interstitial fibrosis. These data support a transition from a hemodynamic disorder to one with inflammatory and fibrotic injury that does not reverse entirely with restoration of blood flow alone.

References

1. Novick AC, Scoble JGH, editors. Renal vascular disease. London: WB Saunder Company Ltd; 1996.
2. Stewart BH, Dustan HP, Kiser WS, Meaney TF, Straffon RA, McCormack LJ. Correlation of angiography and natural history in evaluation of patients with renovascular hypertension. J Urol. 1970;104:231–8.
3. Schreiber MJ, Pohl MA, Novick AC. The natural history of atherosclerotic and fibrous renal artery disease. Urol Clin North Am. 1984;11:383–92.
4. Tollefson DF, Ernst CB. Natural history of atherosclerotic renal artery stenosis associated with aortic disease. J Vasc Surg. 1991;14:327–31.

5. Zierler RE, Bergelin RO, Isaacson JA, Strandness Jr DE. Natural history of atherosclerotic renal artery stenosis: a prospective study with duplex ultrasonography. J Vasc Surg. 1994;19:250–7; discussion 7–8.
6. de Mast Q, Beutler JJ. The prevalence of atherosclerotic renal artery stenosis in risk groups: a systematic literature review. J Hypertens. 2009;27:1333–40.
7. Harding MB, Smith LR, Himmelstein SI, et al. Renal artery stenosis: prevalence and associated risk factors in patients undergoing routine cardiac catheterization. J Am Soc Nephrol. 1992;2:1608–16.
8. Corradi B, Malberti F, Farina M, et al. Chronic renal failure due to atheromatous renovascular disease in the elderly. Contrib Nephrol. 1993;105:167–71.
9. Lerman LO, Textor SC, Grande JP. Mechanisms of tissue injury in renal artery stenosis: ischemia and beyond. Prog Cardiovasc Dis. 2009;52:196–203.
10. Novick AC, Ziegelbaum M, Vidt DG, Gifford Jr RW, Pohl MA, Goormastic M. Trends in surgical revascularization for renal artery disease. Ten years' experience. JAMA. 1987;257:498–501.
11. Zinman L, Libertino JA. Revascularization of the chronic totally occluded renal artery with restoration of renal function. J Urol. 1977;118:517–21.
12. Schefft P, Novick AC, Stewart BH, Straffon RA. Renal revascularization in patients with total occlusion of the renal artery. J Urol. 1980;124:184–6.
13. Dean RH, Tribble RW, Hansen KJ, O'Neil E, Craven TE, Redding 2nd JF. Evolution of renal insufficiency in ischemic nephropathy. Ann Surg. 1991;213:446–55; discussion 55–6.
14. Gloviczki ML, Lerman LO, Textor SC. Blood oxygen level-dependent (BOLD) MRI in renovascular hypertension. Curr Hypertens Rep. 2011;13:370–7.
15. Wright JR, Duggal A, Thomas R, Reeve R, Roberts IS, Kalra PA. Clinicopathological correlation in biopsy-proven atherosclerotic nephropathy: implications for renal functional outcome in atherosclerotic renovascular disease. Nephrol Dial Transplant. 2001;16:765–70.
16. Lopez-Novoa JM, Rodriguez-Pena AB, Ortiz A, Martinez-Salgado C, Lopez Hernandez FJ. Etiopathology of chronic tubular, glomerular and renovascular nephropathies: clinical implications. J Transl Med. 2011;9:13.
17. Moran K, Mulhall J, Kelly D, et al. Morphological changes and alterations in regional intrarenal blood flow induced by graded renal ischemia. J Urol. 1992;148:463–6.
18. Eddy AA. Interstitial fibrosis in hypercholesterolemic rats: role of oxidation, matrix synthesis, and proteolytic cascades. Kidney Int. 1998;53:1182–9.
19. Wu XQ, Kong X, Zhou Y, Huang K, Yang JR, Li XL. Sesamin exerts renoprotective effects by enhancing NO bioactivity in renovascular hypertensive rats fed with high-fat-sucrose diet. Eur J Pharmacol. 2012; 683:231–7.
20. Cheng J, Zhou W, Warner GM, et al. Temporal analysis of signaling pathways activated in a murine model of two-kidney, one-clip hypertension. Am J Physiol Renal Physiol. 2009;297:F1055–68.
21. Warner GM, Cheng J, Knudsen BE, et al. Genetic deficiency of Smad3 protects the kidneys from atrophy and interstitial fibrosis in 2K1C hypertension. Am J Physiol Renal Physiol. 2012;302:F1455–64.
22. Chade AR, Rodriguez-Porcel M, Grande JP, et al. Mechanisms of renal structural alterations in combined hypercholesterolemia and renal artery stenosis. Arterioscler Thromb Vasc Biol. 2003;23:1295–301.
23. Chade AR, Rodriguez-Porcel M, Herrmann J, et al. Antioxidant intervention blunts renal injury in experimental renovascular disease. J Am Soc Nephrol. 2004; 15:958–66.
24. Favreau F, Zhu XY, Krier JD, et al. Revascularization of swine renal artery stenosis improves renal function but not the changes in vascular structure. Kidney Int. 2010;78:1110–8.
25. Keddis MT, Garovic VD, Bailey KR, Wood CM, Raissian Y, Grande JP. Ischaemic nephropathy secondary to atherosclerotic renal artery stenosis: clinical and histopathological correlates. Nephrol Dial Transplant. 2010;25:3615–22.
26. Silkensen JR, Kasiske BL, editors. Laboratory assessment of renal disease: clearance, urinalysis, and renal biopsy. 7th ed. Philadelphia: Saunders; 2004.
27. Voss DM, Lynn KL. Percutaneous renal biopsy: an audit of a 2 year experience with the Biopty gun. N Z Med J. 1995;108:8–10.
28. Fraser IR, Fairley KF. Renal biopsy as an outpatient procedure. Am J Kidney Dis. 1995;25:876–8.
29. Burstein DM, Schwartz MM, Korbet SM. Percutaneous renal biopsy with the use of real-time ultrasound. Am J Nephrol. 1991;11:195–200.
30. Burstein DM, Korbet SM, Schwartz MM. The use of the automatic core biopsy system in percutaneous renal biopsies: a comparative study. Am J Kidney Dis. 1993;22:545–52.
31. Parrish AE. Complications of percutaneous renal biopsy: a review of 37 years' experience. Clin Nephrol. 1992;38:135–41.
32. Mal F, Meyrier A, Callard P, et al. Transjugular renal biopsy. Lancet. 1990;335:1512–3.
33. Lakin PC, Pavcnik D, Bloch RD, et al. Percutaneous transjugular kidney biopsy in swine with use of a side-cutting needle with a blunt-tipped stylet. J Vasc Interv Radiol. 1999;10:1229–32.
34. Cluzel P, Martinez F, Bellin MF, et al. Transjugular versus percutaneous renal biopsy for the diagnosis of parenchymal disease: comparison of sampling effectiveness and complications. Radiology. 2000;215: 689–93.
35. Rychlik I, Petrtyl J, Tesar V, Stejskalova A, Zabka J, Bruha R. Transjugular renal biopsy. Our experience with 67 cases. Kidney Blood Press Res. 2001;24:207–12.
36. Misra S, Gyamlani G, Swaminathan S, et al. Safety and diagnostic yield of transjugular renal biopsy. J Vasc Interv Radiol. 2008;19:546–51.
37. Levi IM, Ben-Dov IZ, Klimov A, Pizov G, Bloom AI. Transjugular kidney biopsy: enabling safe tissue diagnosis in high risk patients. Isr Med Assoc J. 2011;13: 425–7.

38. Ahmed MS, Patel A, Borge MA, Picken MM, Leehey DJ. Simultaneous transjugular renal biopsy and hemodialysis catheter placement in patients with ARF. Am J Kidney Dis. 2004;44:429–36.
39. Lefaucheur C, Nochy D, Bariety J. Renal biopsy: procedures, contraindications, complications. Nephrol Ther. 2009;5:331–9.
40. See TC, Thompson BC, Howie AJ, et al. Transjugular renal biopsy: our experience and technical considerations. Cardiovasc Intervent Radiol. 2008;31:906–18.
41. Sarabu N, Maddukuri G, Munikrishnappa D, et al. Safety and efficacy of transjugular renal biopsy performed by interventional nephrologists. Semin Dial. 2011;24:343–8.
42. Wickre CG, Major JL, Wolfson M. Perinephric abscess: an unusual late infectious complication of renal biopsy. Ann Clin Lab Sci. 1982;12:453–4.
43. Ginsburg JC, Fransman SL, Singer MA, Cohanim M, Morrin PA. Use of computerized tomography to evaluate bleeding after renal biopsy. Nephron. 1980;26:240–3.
44. Alter AJ, Zimmerman S, Kirachaiwanich C. Computerized tomographic assessment of retroperitoneal hemorrhage after percutaneous renal biopsy. Arch Intern Med. 1980;140:1323–6.
45. Gloviczki ML, Glockner JF, Lerman LO, et al. Preserved oxygenation despite reduced blood flow in poststenotic kidneys in human atherosclerotic renal artery stenosis. Hypertension. 2010;55:961–6.
46. Gloviczki ML, Glockner JF, Crane JA, et al. Blood oxygen level-dependent magnetic resonance imaging identifies cortical hypoxia in severe renovascular disease. Hypertension. 2011;58:1066–72.
47. Gloviczki ML, Keddis MT, Garovic VD, et al. TGF expression and macrophage accumulation in atherosclerotic renal artery stenosis. Clin J Am Soc Nephrol. 2013;8(4):546–53.
48. Eirin A, Gloviczki ML, Tang H, et al. Inflammatory and injury signals released from the post-stenotic human kidney. Eur Heart J. 2013;34:540–8a.

Part IV

Treatment of Renovascular Hypertension and Ischemic Nephropathy: Management Strategies

Medical Management of Renovascular Disease

19

Vincent J. Canzanello

Abstract

All patients with renovascular disease will require antihypertensive drug therapy during some stage of their disease. At least in the case of atherosclerotic renovascular disease, most patients will remain hypertensive to some degree despite a technically successful intervention such as balloon angioplasty and stenting or surgical revascularization. Additionally, given the equivocal results of recent intervention trials, medical management alone is becoming increasingly popular. These trials have also demonstrated the increasing effectiveness of currently available antihypertensive drug regimens. Most regimens are based upon the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Progressive worsening in renal function or clinically significant hyperkalemia during medical management with these drugs has not been common during these recent prospective trials though most participants had only mild degrees of renal impairment at enrollment. The use of calcium channel blockers, diuretics, and vasodilators also form an important part of medical management of hypertension whereas attention to other risk factors for progressive atherosclerotic disease such as dyslipidemia, hyperglycemia, and tobacco use should not be overlooked. Finally, laparoscopic nephrectomy remains an option in the patient with poorly controlled hypertension and a severely ischemic kidney that is not amenable to revascularization.

Keywords

Renovascular hypertension • Renovascular disease • Renal atherosclerosis • Drug therapy • Medical management • Angiotensin converting enzyme inhibitors • Angiotensin receptor blockers

Introduction

All patients with renovascular hypertension will require treatment with antihypertensive drugs during some stage of their disease. The duration, intensity and complexity of treatment can vary

V.J. Canzanello, MD
Division of Nephrology and Hypertension,
Mayo Clinic, 200 First Street, SW,
Rochester, MN 55905, USA
e-mail: canzanello.vincent@mayo.edu

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_19,

widely. In the newly diagnosed young woman with fibromuscular dysplasia (FMD), the abrupt onset of hypertension coupled with a high clinical index of suspicion for renovascular disease often results in a relatively brief (weeks to months) course of drug therapy followed by curative revascularization [1, 2]. In the case of hypertension associated with atherosclerotic renovascular disease (ARVD), essential hypertension was usually present beforehand and most patients were treated with one or more antihypertensive drugs for several years before worsening blood pressure control or unexplained deterioration in renal function led to the discovery of underlying renovascular disease. Unlike the case with FMD, most patients with ARVD will continue to require antihypertensive drug therapy despite successful renal revascularization, and not infrequently at similar doses and number of drugs used prior to intervention [3]. Additionally, several retrospective and prospective studies to be reviewed in this chapter demonstrate that many patients with ARVD with or without renal insufficiency can be successfully managed medically for years. For these reasons, the clinician should be familiar with the benefits and risks of the drugs, treatment regimens, and monitoring approaches employed in this challenging patient population.

Choosing the Best Candidate for Medical Therapy

Perhaps the most difficult aspect in the management of a hypertensive patient with renovascular disease is the decision to treat medically or to proceed with revascularization, either surgically or with balloon angioplasty (with or without stent placement) [4–6]. The decision is less difficult in the case of a young woman with FMD who may face a lifetime of multiple antihypertensive drugs compared to revascularization where the chance of cure or improvement of hypertension is likely. Clearly, the latter option is preferable in this situation. At the other end of the spectrum is an elderly hypertensive patient with extensive ARVD, multiple comorbidities, and advanced renal insufficiency (for example, with a serum creatinine of 3 mg/dl or higher). This person has a significant risk associated with revascularization and is much less likely to derive clinical benefit in terms of blood pressure control and improvement in renal function [7]. Few would argue that this patient, managed without revascularization, has a very high risk of subsequent cardiovascular morbidity and mortality [8], but on the other hand, there are few data to support the fact that this risk is substantially reduced by revascularization even if blood pressure control is improved [9, 10]. While the underlying renal disease may progress, most patients will die of complications from atherosclerotic involvement of other vascular beds such as the coronary, cerebrovascular, and peripheral vascular circulations. Indeed, in a review of medically managed elderly patients with extensive ARVD treated at our institution, adequate blood pressure control was generally achieved with patients rarely progressing to end stage renal disease due to ischemic nephropathy per se and having survival rates similar to patients undergoing revascularization [11].

Unfortunately for the clinician, most patients fall somewhere between the previously described two extremes. The majority of these patients will be older (i.e., above 60 years of age), have atherosclerosis as the cause of their renovascular disease, and will have varying degrees of renal insufficiency. It is this group that is the predominant focus of this chapter. Several patient characteristics associated with a suboptimal clinical outcome following renal revascularization are shown in Table 19.1.

The concept of progression of ARVD continues to evolve as discussed elsewhere in this book. In addition, more attention towards other cardiovascular risk factors such as more aggressive control of dyslipidemia and diabetes mellitus and cessation of cigarette smoking are other confounding factors that may have important roles in delaying the progression of renovascular lesions [18]. This is also the group that recent prospective randomized studies have suggested little benefit of revascularization compared to medical therapy given equivalent degrees of blood pressure control [19–23]. In view of the results of these clinical trials, the results of which the largest and probably best done, i.e., CORAL [24] are not yet available, some

Table 19.1 Clinical characteristics associated with unfavorable blood pressure or renal function outcomes following renal revascularization

Advanced age [3, 12]
Advanced renal insufficiency (serum creatinine ≥3.0 mg/dl) [4, 9, 13]
Atherosclerotic as opposed to fibromuscular dysplastic etiology [14, 15]
Renal resistance-index by Doppler sonography ≥80 [16]
Decreased renal size (<9 cm by radiograph or ultrasound) [17]

Table 19.2 Clinical scenarios where surgical or endovascular intervention should be considered

Hypertension that cannot be controlled despite maximum medical therapy
Progressive decline in renal function in the setting of bilateral renal artery stenoses or stenosis to a solitary functioning kidney
Otherwise unexplained recurrent pulmonary edema or angina in the setting of bilateral renal artery stenoses or stenosis to a solitary functioning kidney (revascularization may also allow the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers for heart failure with less risk of worsening renal function)

Data from Canzanello [26]

authors have expressed concern that a certain subset of patients with ARVD are being deprived of the potential benefit of renovascular intervention [25]. Such a subset of patients where surgical or endovascular intervention should be considered is listed in Table 19.2 [26].

Evolution of Medical Therapy for the Treatment of Renovascular Hypertension

The Era Before Angiotensin Converting Enzyme Inhibitors

One of the first reports of the medical treatment of renovascular hypertension was published in 1963 by Dustan et al. [27]. In this study of 32 patients, control or substantial improvement of hypertension was achieved in 41 % using a combination of hydralazine, guanethidine, and a thiazide diuretic. Through the 1970s, control or improvement rates average about 40–50 % using the previously mentioned drugs and other combinations including propranolol and methyldopa [28].

The Angiotensin Converting Enzyme Inhibitor Era

In the early 1980s, the introduction of the angiotensin converting enzyme inhibitors (ACEIs) into clinical practice led to significant improvement in the management of hypertension associated with renovascular disease. One of the first and largest studies of the use of ACEIs in the treatment of renovascular hypertension was that reported by Hollenberg [29]. This study included 269 patients with predominantly atherosclerotic renovascular disease including 56 % with bilateral renal artery stenoses or a stenosis to a solitary functioning kidney. The mean age of these patients was 50 years and 41 % of patients has a baseline serum creatinine of 1.5 mg/dl or higher. Most patients' blood pressures had not been controlled on three or more traditional antihypertensive drugs such as diuretics, sympatholytics and vasodilators. These patients were subsequently hospitalized and had their baseline drugs replaced with captopril, starting at 25 mg/day and titrating upwards to a 3 dose/day regimen culminating in an average daily dose of almost 400 mg. Diuretics followed by beta blockers were used as second and third-line agents. At the end of 3 months of follow-up, the overall blood pressure control rate (based upon a definition of target diastolic blood pressure less than 95 mmHg at the time) was 74 %. An additional 8 % of patients had a partial response. Captopril was discontinued in 13 % of patients predominantly for rash, dysgeusia, and/or proteinuria, as might be expected given the high doses employed. Surprisingly, relatively small changes in renal function occurred with mean serum creatinine levels increasing by 0.6 and 0.3 mg/dl in those patients with baseline azotemia and normal renal function, respectively.

The next largest study of medical therapy using ACEIs was that of Franklin and Smith [30]. This prospective randomized double-blind study

compared the efficacy of enalapril 5–40 mg/day plus hydrochlorothiazide versus a combination of timolol 10 mg, hydralazine 50 mg twice daily, and hydrochlorothiazide in 75 patients with renovascular hypertension. Atherosclerosis was the etiology of renovascular disease in 81 % of patients. Forty-four percent of patients had bilateral stenoses. Mean baseline blood pressure and serum creatinine measurements were 172/102 mmHg and 1.4 mg/dl, respectively. Over the course of this 8-week study, systolic blood pressures decreased 32 and 20 mmHg in the enalapril and control groups, respectively, whereas diastolic blood pressures decreased 20 and 18 mmHg, respectively. Defining a diastolic blood pressure of ≤90 mmHg as a "good" response, this goal was achieved in 94 % of the enalapril group and in 82 % of the control group. With respect to renal function, 20 % of patients in the enalapril group and 3 % in the control group had an increase in serum creatinine of 0.3 mg/dl or more. Of note, there were no episodes of acute oliguric renal failure even among the 18 patients with bilateral renal artery stenoses treated with enalapril plus hydrochlorothiazide, although the largest increases in serum creatinine occurred in those patients with baseline renal insufficiency and having the most severe degrees of bilateral renal artery stenoses.

More recently, five additional studies have explored the role of medical therapy in the management of hypertension associated with renovascular disease [19–23]. All of these studies were randomized trials of medical therapy versus percutaneous transluminal balloon angioplasty (PTA) with or without stenting and focused upon patients with ARVD and normal or moderately impaired renal function. The pertinent blood pressure outcomes are summarized in Table 19.3.

In the first study by Plouin et al. [19], which was limited to patients with unilateral renal artery stenosis, all subjects were first stabilized to a diastolic blood pressure of less than 110 mmHg with a combination of slow-release nifedipine with add-on therapy being clonidine and prazosin. Atenolol, furosemide, and/or enalapril was added to the baseline regimen in the 26 patients randomized to medical therapy to achieve a goal diastolic blood pressure less than 95 mmHg. While 7/26 (27 %) of this group eventually required PTA to control the blood pressure, the final achieved blood pressure in those remaining in the medical treatment group at the end of the 6 month study was no different from the PTA group (141/84 vs 140/81 mmHg, respectively) albeit at the price of receiving a greater number of drugs. No patient in the medical treatment group developed clinically important renal insufficiency.

In the second study by Webster et al. [20], equivalent numbers of patients with unilateral and bilateral disease (27 vs 28) were included. All patients were required to have a baseline diastolic blood pressure of 95 mmHg or greater on at least 2 antihypertensive drugs. Prior to randomization to medical therapy or PTA, all participants were subjected to a 4 week run-in period on a regimen including atenolol, a thiazide diuretic, and/or a calcium channel blocker. Of note, ACEIs were not permitted during this study. Following randomization, additional drug choices included furosemide, methyldopa, and prazosin. The blood pressure responses 6–12 months were characterized according to bilateral or unilateral stenosis group. In the medically treated patients, those in the unilateral group had an unimpressive change in blood pressure from 171/90 at the end of the run-in period to 168/91 mmHg. Importantly, however, this was not different from the PTA group. In the bilateral stenoses group, the medically treated patients fared similar to the medically treated unilateral group whereas the PTA group had a significant decrease in systolic blood pressure from 185/95 to 152/83 mmHg. There were no significant differences in serum creatinine throughout the study in any of the groups. The authors concluded that, in patients with bilateral renal artery stenoses, PTA can result in modest improvement in systolic blood pressure compared with medical therapy. Actually, one might conclude from the data that neither therapy led to satisfactory blood pressure control. From the clinician's viewpoint, however, this study had several limitations such as the proscription of ACEI use (which almost certainly would have improved blood pressure outcome in the medically treated group) and the fact that stenting of

Table 19.3 Prospective medical treatment trials of renovascular hypertension

Author (year) [Ref.]	N(age, years)	Duration of Study (months)	Drug regimen	Baseline BP (mmHg)	Final BP (mmHg)	Comments
Hollenberg (1983) [29]	236(50)	3	Captopril ± diuretic ± beta blocker	DBP > 110	NA	74 % achieved DBP <95
Franklin and Smith (1985) [30]	75(60)	2	Enalapril + diuretic	172/102	140/82	94 % achieved DBP ≤ 90
Plouin et al. (1998) [19]	49(59)	6	Nifedipine ± clonidine ± prazosin ± enalapril ± atenolol	149/89[a]	141/84[a]	7/26 crossed over to angioplasty for refractory hypertension
Webster et al. (1998) [20]	55(61)	12	Atenolol + diuretic + calcium channel blocker ± methyldopa ± prazosin	Unilateral: 171/90 Bilateral: 179/93	168/91 171/91	SBP improved in bilateral group treated with angioplasty
Van Jaarsveld et al. (2000) [21]	106(60)	12	Amlodipine + atenolol or enalapril + diuretic	180/103	163/96	23/50 crossed over to angioplasty for refractory hypertension
STAR (2009) [22]	76 (67)	24	All classes, 65 % on ACEI or ARB	163/82	155/79	20 % controlled to < 140/90, 1 cross-over to intervention
ASTRAL (2009) [23]	403 (70)	60	All classes, 38 % on ACEI or ARB	152/76	141/70	24 (6 %) cross-overs to intervention

SBP systolic blood pressure, *DBP* diastolic blood pressure, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker
[a]Average 24-h blood pressure by ambulatory monitoring

the renal arteries was not employed which might have improved PTA outcomes.

The third of these studies of medical therapy versus PTA was that of van Jaarsveld et al. [21]. Fifty patients were randomized to medical therapy and 56 to PTA. Approximately 20 % in each group had bilateral renal artery stenoses. The medical regimen consisted of stepped dosing of either amlodipine plus atenolol or enalapril plus hydrochlorothiazide with addition of other unspecified drugs as needed to achieve a goal diastolic blood pressure of less than 95 mmHg. By 3 months, 22/50 (44 %) of the medically treated patients had failed to reach the goal blood pressure or developed progressive renal insufficiency (≥0.2 mg/dl increase in serum creatinine) and underwent PTA with good blood pressure and renal outcome. It was not stated whether or not patients with bilateral disease were more likely to fail medical therapy. In those patients remaining in the medical group, blood pressure at 12 months of follow-up was similar to the angioplasty group, 159/91 vs 160/93 mmHg while taking 2.4 vs 1.9 drugs, respectively. Additionally, renal function was similar in both groups.

In the fourth [22] and fifth [23] of these studies, the renal arteries of patients in the intervention group were usually stented following balloon angioplasty. The **ST**ent placement in patients with **A**therosclerotic **R**enal artery stenosis and impaired renal function trial (STAR) [22] randomized 76 and 64 patients with at least one 50 % or greater renal artery stenosis (mean age 67 years and mean serum creatinine 1.6 mg/dL) to medical therapy or intervention, respectively. There was an approximately 50–50 split between patients with unilateral vs bilateral stenotic disease in each treatment group. Two-thirds of the medically treated group received ACEIs or angiotensin receptor blockers (ARBs). At the end of 2 years of follow-up, there were no significant differences in blood pressure control, number of antihypertensive drugs, progression of renal insufficiency or cardiovascular morbidity or mortality. Only one patient assigned to medical therapy underwent stenting for refractory hypertension. Limitations to this study were inclusion of a substantial number of patients with unilateral disease and stenosis just over 50 %, a degree that may be of borderline hemodynamic significance. The **A**ngioplasty and **S**tenting for **R**enal **A**rtery **L**esions trial (ASTRAL) randomized 403 and 403 patients (mean age 70 years, mean serum creatinine 1.7 mg/dL) to medical therapy or intervention, respectively [23]. Most patients had at least one or more stenoses greater than 70 %. All classes of antihypertensive drugs were allowed and 38 % of patients were on an ACEI or ARB. At the end of 5 years, as with STAR, there were no significant differences in blood pressure control, number of antihypertensive drugs, renal function, or cardiovascular outcomes. Twenty-four patients (6 %) in the medical therapy group eventually crossed over to the intervention group, presumably for refractory hypertension. A significant limitation to this trial was the fact that participation was limited to only those patients for whom the physician was "uncertain" as to the benefit of each treatment (medical vs intervention). As with STAR, a substantial number of participants had unilateral stenoses in the 50–70 % range and normal baseline renal function.

In summary, these studies demonstrate that a majority of patients with ARVD can be safely and effectively managed with medical therapy, at least compared with balloon angioplasty with or without stenting. It is reassuring that in most of these studies, ACEIs or ARBs were part of the drug regimen and were apparently well tolerated. Presently there are no data available regarding the use of the direct renin inhibitor aliskiren in the treatment of hypertension associated with ARVD.

As referred to previously, a report from our institution also suggests that blood pressure can be well controlled and renal function maintained with medical therapy alone in older patients with extensive ARVD [11]. In this retrospective study, 68 patients (mean age 72 years, 31 % with bilateral stenoses or stenosis to a solitary functioning kidney) did not undergo initial revascularization for a variety of reasons. Their clinical data were assessed an average of 39 months following the initial renal arteriogram. During this interval, average blood pressure was 157/83 mmHg at baseline and 155/79 mmHg at latest follow-up.

One-third of patients achieved a blood pressure less than 140/90 mmHg and almost two-thirds of the entire group achieved a blood pressure less than 160/95 mmHg. The average number of drugs required per patient increased from 1.6 to 1.9. Of note, almost one-third of patients were treated with ACEIs. During follow-up, the mean serum creatinine for the group rose from 1.4 to 2.0 mg/dl whereas 15 % of patients demonstrated a greater than 50 % increase over their baseline value. Two patients underwent revascularization during the follow-up interval, one for refractory hypertension and one for progressive renal insufficiency. Only one patient reached end-stage renal disease due to ischemic nephropathy. The overall survival of the entire cohort was similar to the reported 4 year survival of a cohort of similar patients managed with balloon angioplasty and stenting of the renal arteries [9].

Concerns About Medical Therapy

Acute Renal Failure

The occurrence of acute or subacute renal failure following the initiation of ACEI inhibitor therapy in patients with renovascular hypertension was first described in the early 1980s [31, 32]. This phenomenon was confined almost exclusively to those patients with either bilateral renal artery stenoses or stenosis of the artery to a solitary functioning kidney and was initially estimated to occur in 23–38 % of these patients [33, 34]. On the other hand, many studies have demonstrated that clinically significant changes in renal function are uncommon in patients with unilateral renal artery stenosis and who are receiving this class of drugs [14]. To confuse the issue further, acute renal failure after the initiation of ACEI therapy has been reported in patients documented to have no significant renal artery stenoses [35–37], an observation that has limited the diagnostic usefulness of this phenomenon to identify renovascular disease. Of interest are the findings of Testani et al. that patients with heart failure who developed early worsening renal function upon initiation of ACEI therapy had a significant survival benefit compared to similar degrees of renal dysfunction in a placebo treated group [38].

In one of the largest and well done studies to date, van de Ven and coworkers were able to provoke a 20 % increase in serum creatinine in all of 52 patients with severe bilateral renal artery stenoses treated with an ACEI (with or without a loop diuretic) for 4–14 days [39]. Similar increases in serum creatinine also occurred in 37 and 13 % of patients with unilateral stenoses and normal renal arteries, respectively. Acute renal failure did not occur in any patients and all changes in renal function were reversible upon stopping either the loop diuretic or the ACEI. Additionally, in the two clinical trials on ACEI in ARVD discussed previously [29, 30] acute renal dysfunction was rarely encountered despite including a large fraction of patients with extensive occlusive disease.

Progressive Renal Ischemia

This is one of the most important concerns for the clinician caring for a patient with renovascular disease. Atherosclerotic renovascular disease is inherently a progressive disorder. Prospective studies [40, 41], however, have demonstrated a lower progression rate in medically treated patients than suggested by earlier retrospective analyses [42]. On the other hand, these lesions can progress and lead to advanced renal insufficiency and end stage renal disease despite successful revascularization [7, 14]. It is reassuring that in the randomized trials of medical therapy versus balloon angioplasty discussed previously [19–23], renal outcomes were no different between the two modalities. Since optimal management of hypertension will, in most cases, require ACEI therapy, concern has been expressed that this class of drug might hasten progressive renal ischemia by reducing blood flow distal to a renal artery stenosis. There have been isolated clinical reports of renal artery thrombosis in patients with unilateral atherosclerotic renal artery stenoses treated with ACEI [43]; however, in most instances it is difficult to blame the medical therapy as opposed to progression of the

underlying stenotic lesion [34]. Indirect evidence suggesting that progressive ischemic nephropathy is rare during ACEI therapy is provided by large-scale clinical trials in heart failure patients [14]. These trials contained a large fraction of patients with ischemic cardiomyopathy and since up to 20 % of patients with coronary artery disease also have previously unrecognized renovascular disease [44, 45], progressive renal insufficiency is this subpopulation might be postulated, but was not observed. Transient increases in the serum creatinine level usually responded to a reduction in the diuretic dose and continuation of the ACEI. Additionally, ACEIs [46–48] and, more recently, ARBs [49, 50] continue to demonstrate important benefits in terms of reducing cardiovascular morbidity and mortality and limiting progression of both diabetic and nondiabetic renal disease, comorbidities present in the majority of patients with atherosclerotic renovascular disease. It is likely, therefore, that most medically managed patients with renovascular disease will be on these drugs or at least have other clinically important indications for their use.

It is important, however, to avoid precipitous falls in systemic blood pressure which might predispose both to acute renal failure or renal artery occlusion. Methods to avoid this situation include the temporary discontinuation of diuretic therapy during the initiation of ACEI treatment (to reduce the risk of volume depletion) and the slow addition and titration of other antihypertensive drugs. Recommendations for monitoring renal function during medical therapy will be discussed later in this chapter and have been reviewed by Palmer [51].

Hyperkalemia

Increases in the serum potassium level ≥0.5 mEq/L have been reported in 0.4–5 % of patients receiving ACEIs [52]. Risk factors for hyperkalemia include baseline renal dysfunction, diabetes mellitus, congestive heart failure, and the concomitant use of potassium supplements or other drugs known to impair the renal excretion of potassium such as potassium-sparing diuretics. Clinically significant hyperkalemia was a rare occurrence in the multiple clinical trials discussed previously and should be preventable given appropriate attention to those patients at high risk. The serum potassium should be monitored at regular intervals, usually within 1 week of starting an ACEI and then every 3–6 months depending on the level of risk. If the serum potassium is above 5.5 mEq/L, a non-potassium sparing diuretic should be added to the regimen. Replacement of a thiazide diuretic with a loop diuretic is usually successful and should allow continued treatment with an ACEI. Another approach may be substitution of an angiotensin receptor blocker in place of the ACEI. In a crossover study by Bakris and coworkers in a group of patients with glomerular filtration ≤60 mL/min/1.73 m^2 and normal baseline serum potassium levels, treatment with lisinopril produced a significantly greater increase in the potassium concentration than did the angiotensin receptor blocker valsartan, 0.28 vs 0.12 mEq/L, respectively [53].

A Personal Approach to the Medical Management of Hypertension Associated with Renovascular Disease

There are no set guidelines for the medical management of these patients. It is important to avoid the use of nonsteroidal antiinflammatory drugs, which can exacerbate both hypertension and renal dysfunction. Of equal importance is attention towards those factors contributing to progression of atherosclerosis such as dyslipidemia, cigarette smoking, and diabetes mellitus. In general, it has usually been an inability to control the blood pressure despite 2 or 3 drugs that led to the initial evaluation culminating in the diagnosis of renovascular disease. In the author's experience, most of these patients are already receiving a calcium channel blocker and variable numbers are taking beta blockers or other sympatholytic agents. Many are also receiving a thiazide diuretic, which, in turn, has limited effectiveness in those patients with renal insufficiency (e.g., serum creatinine above 1.5 mg/dl or glomerular

filtration rate <30 ml/min). A sizeable fraction of patients had previously received an ACEI or ARB, which may have been discontinued either due to the precipitation of acute renal insufficiency or, more likely, because of the clinician's reluctance to continue them (for the reasons discussed previously) once the diagnosis of renovascular disease was made. Given the success of ACEIs or ARBs in the previously cited clinical trials, this drug class should usually be a part of the medical regimen. A prudent approach is to withhold diuretic therapy for several days and then begin low dose ACEI or ARB therapy (e.g., lisinopril, 2.5 mg/day or losartan 25 mg/day). Serum electrolytes, blood urea nitrogen, and creatinine levels should be checked within 1 week. If renal function remains stable or the increase in serum creatinine is less than 20 % of baseline, the dose can be increased, and depending on blood pressure response, diuretic therapy can be reintroduced. It is not clear from the current literature at what level of baseline renal dysfunction that ACEIs or ARBs should be avoided; however, these drugs have been safely used in many diabetic and nondiabetic patients having with serum creatinine levels up to 4 mg/dl [47, 54]. If a significant increase in the serum creatinine occurs, the ACEI or ARB should be discontinued. In addition, Onuigbo has recently suggested that acute or subacute declines in renal function following the initiation of ACEI or ARB therapy (for renal artery stenosis, proteinuria or chronic kidney disease in general) may be more common than generally suspected and that these drugs be avoided or stopped in patients with otherwise unexplained deterioration in renal function [55, 56].

In those patients whose blood pressure does not respond to a regimen including a diuretic, ACEI or ARB, a calcium channel blocker, and a beta blocker, several additional options exist. The author's preference is for the addition of a vasodilator, typically minoxidil in males, starting at 2.5 mg/day and hydralazine in females (to avoid hirsuitism), starting at 25 mg twice daily. Since most patients are already on a beta blocker, reflex tachycardia is generally not an issue. Clonidine can be used in those patients in whom beta blocker therapy is contraindicated. Fluid retention/edema associated with vasodilator therapy can be minimized by careful attention to weight and adjusting the loop diuretic dose accordingly. Furosemide, due to its relatively short duration of action, should be taken on a twice daily schedule with the second dose taken in the late afternoon, not the evening, to avoid producing nocturia. The author's usual starting dose is 20 mg twice daily. In those patients who complain of urinary urgency while taking furosemide, replacement with torsemide, a loop diuretic with a more gradual onset of action and prolonged effect may be helpful and allow once daily dosing. The usual starting dose is 5 mg once daily. Finally, another drug class I have found effective and well-tolerated is a long-acting oral nitroglycerin preparation such as isosorbide mononitrate.

With respect to monitoring the patient during the titration phase of these drugs, it is prudent to encourage the use of out-of-office blood pressure measurements with an accurate device and to monitor renal function approximately every 2 weeks. Once stabilized, there is no clear-cut consensus on the best method of follow-up. Some authorities recommend monitoring blood pressure and serum creatinine levels every 3 months and noninvasive renal imaging (e.g., using renal artery duplex scanning) to assess renal size and progression of stenotic lesions every 6–12 months [57]. Others recommend periodic nuclear imaging studies that provide estimates of blood flow and glomerular filtration rates for each kidney [2]. This test may be particularly helpful in those patients with normal baseline renal function where the serum creatinine level alone may be an insensitive indicator of progressive renovascular disease. These are all probably reasonable recommendations with two caveats. First, in a patient with FMD, since the disease itself is not typically progressive and the lesions are often difficult to assess noninvasively, simply following the blood pressure and yearly renal function tests may be adequate. Secondly, in the patient with advanced atherosclerotic RVD and who was originally considered a poor candidate for revascularization, one might question the need for routine follow-up imaging studies since these are unlikely to prompt subsequent intervention.

Management Options in the Patient Who Is Failing Medical Therapy

Failure to achieve satisfactory blood pressure control has become less common given the large number of potent antihypertensive drugs currently available. If the patient has a renal artery lesion considered to be technically amenable to revascularization, balloon angioplasty or surgery should be considered at this point. Unfortunately, refractory hypertension is not infrequently related to a severely ischemic atrophic kidney that is not amenable to revascularization. In the patient with FMD, the kidney is usually not atrophic, but is not amenable to revascularization due to the location or complexity of the stenotic lesions. The mechanism of hypertension in this setting is almost certainly due to continued renin secretion from the affected kidney and would be expected to respond to high doses of ACEIs. It is possible, however that the degree of converting enzyme inhibition is incomplete or that angiotensin II is being produced by alternative pathways [58]. Given this rationale, I have occasionally used the combination of an ACEI and an ARB in this setting with good results. The therapeutic benefit of such a combination has also been recently demonstrated in patients with heart failure [59] and proteinuric renal disease [60]. The potential risks of dual renin-angiotensin blockade in chronic kidney disease have recently been reviewed [61] and this approach requires careful monitoring of blood pressure, serum potassium, and renal function. The aldosterone antagonist spironolactone has made a significant resurgence as an effective drug for resistant hypertension of diverse etiologies (particularly in patients with obesity and/or obstructive sleep apnea) [62–64]. In addition, it has antiproteinuric effects shown clinically and renoprotective effects demonstrated experimentally [62]. I have generally found a greater antihypertensive benefit adding spironolactone 25–50 mg/day to an ACEI or ARB as opposed to adding an ACEI to an ARB or vice versa. Once again, however, blood pressure, serum potassium, and renal function must be followed closely-usually weekly until stable.

If the combination of an ACEI and ARB or aldosterone antagonist cannot be used or is ineffective, a remaining option is nephrectomy. In a review of the Mayo Clinic experience, 74 patients with refractory hypertension underwent nephrectomy of an atrophic nonfunctioning kidney [65]. After a mean follow-up of 4.1 years, the blood pressure was significantly improved in 78 % of patients and there was no significant decline in renal function at least during the first year following nephrectomy. Thomaz et al. recently demonstrated long term improvement in blood pressure control and preservation in renal function following nephrectomy in a group of 51 patients with an atrophic kidney due to severe renal artery stenosis although the majority of patients had fibromuscular dysplasia [66]. Elhage et al. have also reported success with this approach [67]. The widening availability and safety of laparoscopic nephrectomy will no doubt increase the attractiveness of this therapeutic option.

Finally, since the renal sympathetic nerves play a role both essential and renovascular hypertension [68, 69] and renal sympathetic denervation by radiofrequency ablation has been effective for the treatment of resistant hypertension, this procedure might potentially be useful in the management of renovascular hypertension although there are no clinical data yet available to support this approach [70].

References

1. Aurell M, Jensen G. Treatment of renovascular hypertension. Nephron. 1997;75:373–83.
2. Safian RD, Textor SC. Renal artery stenosis. N Engl J Med. 2001;344:431–42.
3. Xue F, Bettmann MA, Langdon DR, Wivell WA. Outcome and cost comparison of percutaneous transluminal angioplasty, renal arterial stent placement, and renal arterial bypass grafting. Radiology. 1999; 212:378–84.
4. Canzanello VJ, Garovic VD. Renal vascular disease: a vexing challenge for the clinician. Prog Cardiovasc Dis. 2009;52:181–3.
5. Baumgartner I, Lerman LO. Renovascular hypertension: screening and modern management. Eur Heart J. 2011;32:1590–8.
6. Lao D, Parasher PS, Cho KC, Yeghiazarians Y. Atherosclerotic renal artery stenosis-diagnosis and treatment. Mayo Clin Proc. 2011;86:649–57.
7. Hallet JW, Textor SC, Kos PB, et al. Advanced renovascular hypertension and renal insufficiency: trends

in medical comorbidity and surgical approach from 1970 to 1993. J Vasc Surg. 1995;21:750–9.
8. Conlon PJ, Athirakul K, Kovalik E, et al. Survival in renal vascular disease. J Am Soc Nephrol. 1998; 9:252–6.
9. Dorros G, Jaff M, Mathiak L, et al. Four-year follow-up of Palmaz-Schatz stent revascularization as treatment for atherosclerotic renal artery stenosis. Circulation. 1998;98:642–7.
10. Butterly DW, Schwab SJ. Renal artery stenosis: the case for conservative management. Mayo Clin Proc. 2000;75:435–6.
11. Chabova V, Schirger A, Stanson AW, McKusick MA, Textor SC. Outcomes of atherosclerotic renal artery stenosis managed without revascularization. Mayo Clin Proc. 2000;75:437–44.
12. Helin K, Lepantalo M, Edgren J, Liewendahl K, Tikkanen T, Tikkanen I. Predicting the outcome on invasive treatment of renal artery disease. J Intern Med. 2000;247:105–10.
13. Paulsen K, Klow NE, Rogstad B, et al. Preservation of renal function by percutaneous transluminal angioplasty in ischaemic renal disease. Nephrol Dial Transplant. 1999;14:1454–61.
14. Textor SC. Renovascular hypertension and ischemic nephropathy. In: Brenner BM, editor. Brenner and Rector's the kidney. 8th ed. Philadelphia: Saunders; 2008. p. 1528–66.
15. Giroux M-F, Soulez G, Therasse E, et al. Percutaneous revascularization of the renal arteries: predictors of outcome. J Vasc Interv Radiol. 2000;11:713–20.
16. Radermacher J, Chavan A, Bleck J, et al. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. N Engl J Med. 2001; 344:410–7.
17. Jacobson HR. Ischemic nephropathy: an overlooked clinical entity? Kidney Int. 1988;34:729–43.
18. Silva VS, Martin LC, Franco RJ, et al. Pleiotropic effects of statins may improve outcomes in atherosclerotic renovascular disease. Am J Hypertens. 2008;21:1163–8.
19. Plouin P-F, Chatellier G, Darne B, Raynaud A. Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis: a randomized trial. Hypertension. 1998;31:823–9.
20. Webster J, Marshall F, Abdalla M. Randomised comparison of percutaneous angioplasty vs continued medical therapy for hypertension patients with atheromatous renal artery stenosis. J Hum Hypertens. 1998; 12:329–35.
21. van Jaarsveld BC, Krijnen P, Pieterman H, et al. The effect of balloon angioplasty on hypertension in atherosclerotic renal artery stenosis. N Engl J Med. 2000; 342:1007–14.
22. Bax L, Arend-Jan JW, Kouwenberg HJ, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function. Ann Intern Med. 2009;150:840–8.
23. The ASTRAL Investigators. Revascularization versus medical therapy for renal-artery stenosis. N Engl J Med. 2009;361:1953–62.
24. Cooper CJ, Murphy TP, Matsumoto A, et al. Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: rationale and design of the CORAL trial. Am Heart J. 2006;152:59–66.
25. Textor SC. Issues in renovascular disease and ischemic nephropathy: beyond ASTRAL. Curr Opin Nephrol Hypertens. 2011;20:139–45.
26. Canzanello VJ. Renovascular disease. In: Daugirdas JT, editor. Handbook of chronic kidney disease. Philadelphia: Wolters Kluwers/Lippincott William and Wilkins; 2011. p. 240–50.
27. Dustan HP, Page IH, Poutasse EF, et al. An evaluation of treatment of hypertension associated with occlusive renal arterial disease. Circulation. 1963;27: 1018–33.
28. Hollenberg NK. Medical therapy for renovascular hypertension: a review. Am J Hypertens. 1988;1: 338S–43.
29. Hollenberg NK. Medical therapy of renovascular hypertension: efficacy and safety of captopril in 269 patients. Cardiovasc Rev Rep. 1983;4:852–75.
30. Franklin SS, Smith RD. Comparison of effects of enalapril plus hydrochlorothiazide versus standard triple therapy on renal function in renovascular hypertension. Am J Med. 1985;79(Suppl 3C):14–23.
31. Hricik DE, Browning PJ, Kopelman R, Goorno WE, Madias NE, Dzau VJ. Captopril-induced functional renal insufficiency in patients with bilateral renal-artery stenoses or renal-artery stenosis in a solitary kidney. N Engl J Med. 1983;308:373–6.
32. Curtis JJ, Luke RG, Whelchel JD, Diethelm AG, Jones P, Dustan HP. Inhibition of angiotensin-converting enzyme in renal-transplant recipients with hypertension. N Engl J Med. 1983;308:377–81.
33. Jackson B, Matthews PG, McGrath BP, Johnston CI. Angiotensin converting enzyme inhibition in renovascular hypertension: frequency of reversible renal failure. Lancet. 1984;1:225–6.
34. Hricik DE, Dunn MJ. Angiotensin-converting enzyme inhibitor-induced renal failure: causes, consequences, and diagnostic uses. J Am Soc Nephrol. 1990;1: 845–58.
35. Thind GS. Renal insufficiency during angiotensin-converting enzyme inhibitor therapy in hypertensive patients with no renal artery stenosis. J Clin Hypertens. 1985;4:337–43.
36. Toto RD, Mitchell HC, Lee H-C, Milam C, Pettinger WA. Reversible renal insufficiency due to angiotensin converting enzyme inhibitors in hypertensive nephrosclerosis. Ann Intern Med. 1991;115:513–9.
37. Bridoux F, Hazzan M, Pallot JL, et al. Acute renal failure after the use of angiotensin-converting-enzyme inhibitors in patients without renal artery stenosis. Nephrol Dial Transplant. 1992;7:100–4.
38. Testani JM, Kimmel SE, Dries DL, Coca SG. Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. Circ Heart Fail. 2011;4:685–91.

39. van de Ven PJG, Beutler JJ, Laatee R, Beek FJA, Mali WPTM, Koomans HA. Angiotensin converting enzyme inhibitor-induced renal dysfunction in atherosclerotic renovascular disease. Kidney Int. 1998;53:986–93.
40. Guzman RP, Zierler RE, Isaacson JA, Bergelin RO, Strandness Jr DE. Renal atrophy and arterial stenosis: a prospective study with duplex ultrasound. Hypertension. 1994;23:346–50.
41. Zierler RE, Bergelin RO, Davidson RC, Cantwell-Gab K, Polissar NL, Strandness Jr DE. A prospective study of disease progression in patients with atherosclerotic renal artery stenosis. Am J Hypertens. 1996;9:1055–61.
42. Schreiber MJ, Pohl MA, Novick AC. The natural history of atherosclerotic and fibrous renal artery disease. Urol Clin North Am. 1984;11:383–92.
43. Hoefnagels WHL, Thien T. Renal artery occlusion in patients with renovascular hypertension treated with captopril. BMJ. 1986;292:24–5.
44. Vetrovec GW, Landwehr DM, Edwards VL. Incidence of renal artery stenosis in hypertensive patients undergoing coronary angiography. J Interv Cardiol. 1989;2:69–76.
45. Harding MB, Smith LR, Himmelstein SI, et al. Renal artery stenosis: prevalence and associated risk factors in patients undergoing routine cardiac catheterization. J Am Soc Nephrol. 1992;2:1608–16.
46. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med. 1993;329:1456–62.
47. Maschio G, Alberti D, Janin G, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. N Engl J Med. 1996;334:939–45.
48. The Heart Outcomes Prevention Evaluation Study. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2000;342:145–53.
49. Lewis EJ, Hunsicker LG, Clarke W, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345:851–60.
50. Brenner BM, Cooper ME, de Zeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345:861–9.
51. Palmer BF. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what to do if the serum creatinine and/or serum potassium concentration rises. Nephrol Dial Transplant. 2003;18:1973–5.
52. Drug Facts and Comparison 2002. Pocket version. 6th ed. St. Louis: Facts and Comparisons; 2001.
53. Bakris GL, Siomos M, Richardson D, et al. ACE inhibition or angiotensin receptor blockade: impact on potassium in renal failure. Kidney Int. 2000;58:2084–92.
54. Giatras I, Lau J, Levey AS, for the Angiotensin-Converting Enzyme Inhibition and Progressive Renal Disease Study Group. Effects of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. Ann Intern Med. 1997;127:337–45.
55. Onuigbo MA. Analytical review of the evidence for renoprotection by renin-angiotensin-aldosterone system blockade in chronic kidney disease-a call for caution. Nephron Clin Pract. 2009;113:c63–70.
56. Onuigbo MAC. Can ACE, inhibitors and angiotensin receptor blockers be detrimental in CKD patients? Nephron Clin Pract. 2011;118:c407–19.
57. Plouin P-F, Rossignol P, Bobrie G. Atherosclerotic renal artery stenosis: to treat conservatively, to dilate, to stent, or to operate? J Am Soc Nephrol. 2001;12: 2190–6.
58. McLaughlin K, Jardine AG. Angiotensin converting enzyme inhibitors and angiotensin receptor (AT1) antagonists: either or both for primary renal disease. Nephrol Dial Transplant. 1999;14:25–8.
59. Hamroff G, Katz SD, Mancini M, et al. Addition of angiotensin II receptor blockade to maximal angiotensin-converting enzyme inhibition improves exercise capacity in patients with severe congestive heart failure. Circulation. 1999;99:990–2.
60. Russo D, Pisani A, Balletta MM, et al. Additive antiproteinuric effect of converting enzyme inhibitor and losartan in normotensive patients with IgA nephropathy. Am J Kidney Dis. 1999;33:851–6.
61. Ku E, Park J, Vidhun J, Campese V. The hazards of dual renin-angiotensin blockade in chronic kidney disease. Arch Intern Med. 2009;169:1015–8.
62. Sowers JR, Whaley-Connell A, Eptein M. Narrative review: the emerging clinical implications of the role of aldosterone in the metabolic syndrome and resistant hypertension. Ann Intern Med. 2009;150: 776–83.
63. de Souza F, Muxfelt E, Fiszman R, Salles G. Efficacy of spironolactone therapy in patients with true resistant hypertension. Hypertension. 2010;55:147–52.
64. Heshka J, Ruzicka M, Hiermath S, McCormick BB. Spironolactone for difficult to control hypertension in chronic kidney disease; an analysis of safety and efficacy. J Am Soc Hypertens. 2010;4:295–301.
65. Kane GC, Textor SC, Schirger A, Garovic VD. The role of nephrectomy in refractory hypertension and atherosclerotic renal artery occlusion. Am J Med. 2003;114: 729–35.
66. Thomaz MJ, Lucon AM, Praxedes JN, Bortolotto LA, Srougi M. The role of nephrectomy of the atrophic kidney in bearers of renovascular hypertension. Int Braz J Urol. 2010;36:159–70.
67. Elhage O, Sahai A, Challacombe B, Murphy D, Scoble J. Role of laparoscopic nephrectomy for refractory hypertension in poorly functioning kidneys. Ann R Coll Surg Engl. 2011;93:25–6.
68. Johannson M, Elam M, Rundqvist B, Eisenhofer G, et al. Increased sympathetic nerve activity in renovascular hypertension. Circulation. 1999;18:2537–42.
69. Johansson M, Friberg P. Curr Hypertens Rep. 2000;2:319–26.
70. Thomas G, Shishehbor MH, Bravo EL, Nally JV. Renal denervation to treat resistant hypertension: guarded optimism. Cleve Clin J Med. 2012;79: 501–10.

Endovascular Treatment of Renal Artery Stenosis

20

Sanjay Misra

Abstract

Renal artery stenosis can result in uncontrolled hypertension, kidney failure, or pulmonary edema. In this chapter, treatment of renal artery stenosis using stents is discussed. In addition, outcomes and expected results are described.

Keywords

Renal artery stenosis • Stent • Treatment

Introduction

For patients with symptomatic atherosclerotic renal artery stenosis, the preferred method of revascularization is renal artery stent placement. Renal artery stenosis can cause uncontrolled hypertension, decrease in kidney function, or cardiac heart failure [1, 2]. There are good data demonstrating that stent placement is superior to angioplasty, especially for ostial stenosis [3]. Earlier vascular stents were designed on a 0.035-in. platform which required manual crimping and placement of the stent onto the balloon [4, 5]. Today, stent technology has evolved to a reduced profile and is on 0.014-in. balloon catheter platform [6]. One major advantage of the lower profile systems is that they produce less atheroembolism during stent deployment. The ability to restore renal blood flow using endovascular stenting undoubtedly has allowed effective recovery and stabilization of kidney function in patients that would not have been selected for surgical revascularization in the past.

Randomized Control Trials of Renal Artery Angioplasty and Stent Placement

There have been several randomized trials which have compared endovascular treatment of renal artery stenosis (angioplasty or stent placement) to medical therapy [7–10]. Each of these studies failed to identify differences in kidney functional outcomes between the endovascular group and medical therapy group. However, several methodological flaws exist in these studies. For example, the recently reported trial results from the ASTRAL study which investigated the role of renal artery stent placement plus medical therapy

S. Misra, MD, FSIR, FAHA
Department of Vascular Interventional Radiology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
e-mail: misra.sanjay@mayo.edu

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_20,

versus medical therapy for preserving kidney function concluded that there was no benefit to renal artery stent placement [11]. These included the following:

1. Randomization of the patients was based on multiple different imaging modalities that have different sensitivities and specificities and there was no core lab to reconcile these differences [12].
2. Revascularization was only performed in 317 patients and attempted in 335. Pre-study statistical planning called for 403 patients.
3. 25 % percent of the patients had glomerular filtration rates >50 ml/min^2 and hence had little potential for benefit in kidney function.
4. The degree of stenosis less than 70 % was observed in 40 % of the patients which likely was not severe enough to benefit from treatment.
5. The study was underpowered. For 80 % power, they needed to enroll 346 patients in each arm and the stent arm did not have enough patients.

Endovascular Stent Placement

A typical stent procedure is performed by inserting a guide catheter of different shapes through either a femoral artery or radial/brachial artery approach [13]. Using the guide catheter, a selective angiogram is performed. Once the decision has been made to treat the stenosis, the patient is systemically heparinized to achieve an activated coagulation time greater than 250-ms. Through the guide catheter, a 0.014-in. wire is inserted and advanced across the stenosis. An angiogram is performed to demonstrate that the wire is in good position. Next a balloon is inflated to match the nominal diameter of the non-diseased renal artery. The proximal end of the stent is often flared so that the stent can approximate the ostium of the renal artery (Fig. 20.1a, b).

Use of Embolic Protection Devices

Another major advantage of low profile stent technology is that it allows adjunctive use of embolic protection devices (EPD) along with stent placement. The embolic protection devices were originally designed for use in coronary or carotid artery applications. There are many different embolic protection devices which are available which have different specifications based on features of vascular landing zones, diameter of the device, and size of the filter pores [14]. These devices are advanced across the stenosis through the guide catheter distal to the stenosis. The device is allowed to oppose the renal artery. Next, the renal artery stent is advanced and deployed. After that, the balloon of the stent is removed and the EPD device is captured. An example of treating a patient with renal artery stenosis using and EPD is shown in Fig. 20.1c, d.

Figure 20.2a is angiogram of renal artery stenosis on the left. Figure 20.2b shows the placement of embolic protection device across the stenosis.

There are several single institution studies and one randomized controlled study for the use of embolic protection devices. The single site studies have demonstrated that the use of EPD with renal artery stent placement is associated with stabilization or improvement in kidney function in more than 80 % of the patients [15–23].

The single randomized study was associated with mixed results with EPD and stent placement [24]. This was a study where the primary endpoint was estimated glomerular filtration (eGFR) 1-month after renal artery stent placement in a group of 100 patients with an average eGFR of 54 ml/min. This study investigated the interaction between adjunctive pharmacologic therapy using a IIB/IIIA inhibitor and EPD and stent placement using a 2 by 2 randomization scheme. This study used a first generation EPD (Angioguard) and found improved eGFR only in the group that received IIB/IIA and EPD suggesting an interaction between platelet aggregation and kidney function improvement.

A recent small study from our institution demonstrated improvement in kidney function in patients with baseline eGFR treated with EPD and stent placement compared to those that did not receive the use of an EPD [25]. Currently, we use EPDs during stenting for the treatment of renal artery stenosis in patients with advanced

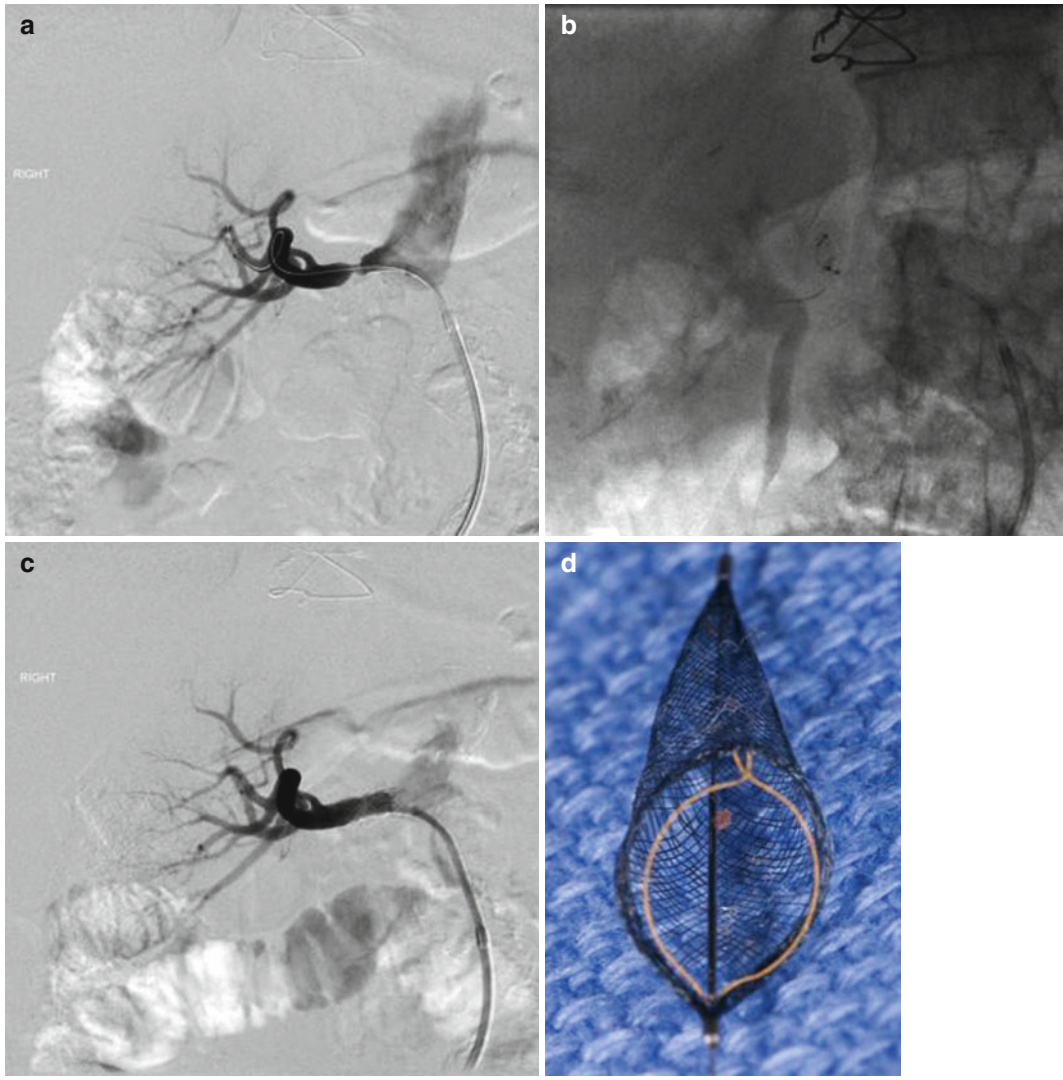


Fig. 20.1 (**a**–**d**) Placement of renal artery stent with embolic protection device. (**a**) shows an atherosclerotic renal artery stenosis. (**b**) shows the placement of the SpideRx embolic protection device. (**c**) shows the placement of a stent with good angiographic result. (**d**) shows debris captured during the procedure

chronic kidney disease, typically baseline eGFR less than 30 ml/min with anatomy favorable to EPD deployment.

Drug Eluting Stent Placement

Drug eluting stents designed for coronary arteries sometimes have been used to treat renal artery stenosis with the goal of reducing restenosis. They have been used to treat complicated stenosis involving early bifurcation stenosis or those involving accessory renal artery stenosis or small diameter main renal arteries [26, 27]. In addition, they have been used to treat in-stent stenosis after non-eluting renal artery stent therapy [28]. The largest available stents have diameters of 4.5-mm which can be inflated to 4.7-mm thus limiting the use in larger more typical renal artery stenosis.

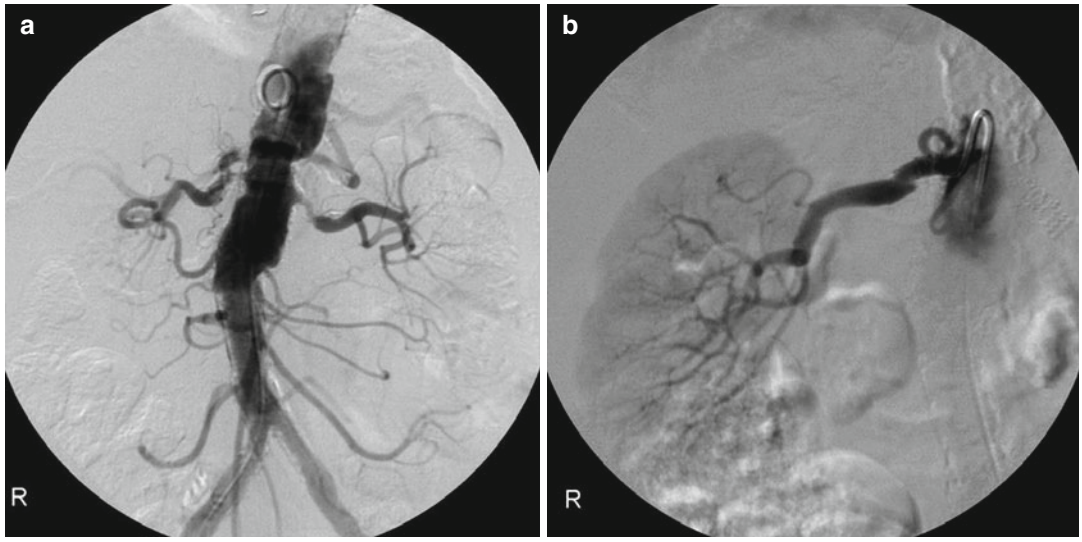


Fig. 20.2 (**a**, **b**) Placement of renal artery stent with dissection. (**a**) shows bilateral atherosclerotic renal artery stenosis. (**b**) shows dissection of the renal artery after placement of a stent

Follow-Up of Patients After Stent Placement

Patients need to be followed carefully after renal artery stent placement to ensure that the renal artery stent remains patent and does not lead to restenosis. A typical follow-up evaluation will consist of blood pressure measurement, review of medications, assessment of kidney function and renovascular duplex ultrasound to determine patency. In addition, blood work and urine analysis for proteinuria will be determined. Patients are often placed on dual anti-platelet therapy consisting of Plavix and baby aspirin for 3–6 months after the procedure. Finally, cardiovascular risk factors need to be intensively treated monitored including diabetes, weight reduction, smoking cessation, and anti-hyperlipidemic medications. Typically, patients are encouraged to return at 1, 3, 6, 12, 18, 24 months after initial stent placement and yearly thereafter [29].

Outcomes for Hypertension

Large single center studies and meta analyses have demonstrated that renal artery stent placement helps reduce blood pressure and decrease the number of anti-hypertensive medications [2, 27, 30, 31]. In our practice, the typical reduction in systolic blood pressure is 20-mmHg with a decrease in diastolic blood pressure requiring fewer antihypertensive medications [30]. Predictors of a improved blood pressures have been proposed to include a segmental renal artery duplex resistive index (RI) <0.8 [30]. However, only one observational study has demonstrated that a RI of <0.8 is a predictor of a successful outcome. Others have been less consistent and unable to reproduce these results [32].

Outcomes for Preserving or Improving Kidney Function

It is estimated that 12–18 % of the patients progressing to renal replacement therapy have renal artery stenosis [33]. Identifying useful predictors s of a successful outcome after stent placement for preserving renal function has been the goal of many studies [32, 34–39]. Patients with more severely decreased kidney function at baseline have worse outcomes than those with better baseline kidney function. Several factors have been reported to be associated with less favorable outcomes including baseline kidney function, proteinuria, diabetes mellitus, and increased

RI, with decreased kidney size [32, 34–39]. Interestingly, repeated observational studies have reported being able to improve kidney function and thus remove the need for dialysis [40]. Moreover, others indicate that a strong predictor of an improvement in kidney function is a 1/eGFR response [41]. Recently, results of one study suggested that using iothalamate scans to determine GFR for patients with RAS provided more accurate guidance as compared to eGFR based on serum creatinine with the calculation for eGFR obtained from the Modification in Diet and Renal Disease formula [42].

Complications After Renal Artery Stent Placement

There are multiple potential complications associated with renal artery stent placement. These include femoral artery closure complications, dissection of the renal artery, embolization into the kidney, rupture of the renal artery and contrast medium induced nephropathy [43]. The prevalence of these complications is estimated to be 0.5–10 %. With the advent of lower profile systems for placing renal artery stents, atheroembolic events have been reduced.

Treatment of Restenosis

Restenosis of the renal artery lesion after stent placement occurs in 20–30 % of patients by 9–12 months [44]. This is often diagnosed with serial duplex scans where the velocity of the blood increases over time. In our laboratory, velocity of blood flow after stent placement >300 cm/s is highly indicative of restenosis [45]. These patients can present with clinical symptoms of renal artery stenosis with uncontrolled hypertension or kidney dysfunction. Treatment options for in-stent restenosis include angioplasty, re-stenting with a bare metal stent, covered stent, drug eluting stent, or cutting balloon. There are few studies that systematically compare the different treatment options. In some cases with recurrent, severe symptoms associated with renovascular occlusion, surgical reconstruction or bypass has been effective (see Chap. 21).

Conclusion

In conclusion, stent placement for symptomatic renal artery stenosis due to atherosclerotic disease is the preferred treatment modality. Clinical outcomes after treatment can be difficult to predict and careful patient selection is warranted. Patients need to be carefully followed after stent placement.

References

1. Safian RD, Textor SC. Renal-artery stenosis. N Engl J Med. 2001;344:431–42.
2. Dorros G, Jaff M, Mathiak L, Dorros II, Lowe A, Murphy K, He T. Four-year follow-up of palmaz-schatz stent revascularization as treatment for atherosclerotic renal artery stenosis. Circulation. 1998;98:642–7.
3. van de Ven P, Kaatee R, Beutler J, Beek F, Woittiez A, Buskens E, Koomans H, Mali W. Arterial stenting and balloon angioplasty in ostial atherosclerotic renovascular disease: a randomised trial. Lancet. 1999;353:282–6.
4. Palmaz JC, Garcia OJ, Schatz RA, Rees CR, Roeren T, Richter GM, Noeldge G, Gardiner Jr GA, Becker GJ, Walker C, et al. Placement of balloon-expandable intraluminal stents in iliac arteries: first 171 procedures. Radiology. 1990;174:969–75.
5. Dorros G, Jaff M, Jain A, Dufek C, Mathiak L. Follow-up of primary palmaz-schatz stent placement for atherosclerotic renal artery stenosis. Am J Cardiol. 1995;75:1051–5.
6. Sapoval M, Zahringer M, Pattynama P, Rabbia C, Vignali C, Maleux G, Boyer L, Szczerbo-Trojanowska M, Jaschke W, Hafsahl G, Downes M, Beregi J, Veeger N, Talen A. Low-profile stent system for treatment of atherosclerotic renal artery stenosis: the great trial. J Vasc Interv Radiol. 2005;16(8):1195–2002.
7. Kumbhani DJ, Bavry AA, Harvey JE, de Souza R, Scarpioni R, Bhatt DL, Kapadia SR. Clinical outcomes after percutaneous revascularization versus medical management in patients with significant renal artery stenosis: a meta-analysis of randomized controlled trials. Am Heart J. 2011;161:622.
8. Bax L, Woittiez AJ, Kouwenberg HJ, Mali WP, Buskens E, Beek FJ, Braam B, Huysmans FT, Schultze Kool LJ, Rutten MJ, Doorenbos CJ, Aarts JC, Rabelink TJ, Plouin PF, Raynaud A, van Montfrans GA, Reekers JA, van den Meiracker AH, Pattynama PM, van de Ven PJ, Vroegindeweij D, Kroon AA, de Haan MW, Postma CT, Beutler JJ. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. Ann Intern Med. 2009;150(840–848):W150–841.

9. Webster J, Marshall F, Abdalla M, Dominiczak A, Edwards R, Isles CG, Loose H, Main J, Padfield P, Russell IT, Walker B, Watson M, Wilkinson R. Randomised comparison of percutaneous angioplasty vs continued medical therapy for hypertensive patients with atheromatous renal artery stenosis. Scottish and Newcastle Renal Artery Stenosis Collaborative Group. J Hum Hypertens. 1998;12: 329–35.
10. Plouin PF, Chatellier G, Darne B, Raynaud A. Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis: a randomized trial. Essai Multicentrique Medicaments vs Angioplastie (EMMA) Study Group. Hypertension. 1998;31: 823–9.
11. Wheatley K, Ives N, Gray R, Kalra PA, Moss JG, Baigent C, Carr S, Chalmers N, Eadington D, Hamilton G, Lipkin G, Nicholson A, Scoble J. Revascularization versus medical therapy for renal-artery stenosis. N Engl J Med. 2009;361:1953–62.
12. Textor SC. Pitfalls in imaging for renal artery stenosis. Ann Intern Med. 2004;141:730–1.
13. Rodriguez Granillo G, van Dijk L, McFadden E, Serruys P. Percutaneous radial intervention for complex bilateral renal artery stenosis using paclitaxel eluting stents. Catheter Cardiovasc Interv. 2005;64: 23–7.
14. Thatipelli MR, Sabater EA, Bjarnason H, McKusick MA, Misra S. Ct angiography of renal artery anatomy for evaluating embolic protection devices. J Vasc Interv Radiol. 2007;18:842–6.
15. Thatipelli MR, Misra S, Sanikommu SR, Schainfeld RM, Sharma SK, Soukas PA. Embolic protection device use in renal artery stent placement. J Vasc Interv Radiol. 2009;20:580–6.
16. Misra S, Gomes MT, Mathew V, Barsness GW, Textor SC, Bjarnason H, McKusick MA. Embolic protection devices in patients with renal artery stenosis with chronic renal insufficiency: a clinical study. J Vasc Interv Radiol. 2008;19:1639–45.
17. Hagspiel KD, Stone JR, Leung DA. Renal angioplasty and stent placement with distal protection: preliminary experience with the filterwire ex. J Vasc Interv Radiol. 2005;16:125–31.
18. Henry M, Henry I, Klonaris C, Polydoru A, Rath P, Lakshmi G, Raacopal S, Hugel M. Renal angioplasty and stenting under protection: the way for the future? Catheter Cardiovasc Interv. 2003;60:299–312.
19. Holden A, Hill A. Renal angioplasty and stenting with distal protection of the main renal artery in ischemic nephropathy: early experience. J Vasc Surg. 2003;38: 962–8.
20. Holden A, Hill A, Jaff MR, Pilmore H. Renal artery stent revascularization with embolic protection in patients with ischemic nephropathy. Kidney Int. 2006;70:948–55.
21. Edwards MS, Craven BL, Stafford J, Craven TE, Sauve KJ, Ayerdi J, Geary RL, Hansen KJ. Distal embolic protection during renal artery angioplasty and stenting. J Vasc Surg. 2006;44:128–35.
22. Singer GM, Setaro JF, Curtis JP, Remetz MS. Distal embolic protection during renal artery stenting: impact on hypertensive patients with renal dysfunction. J Clin Hypertens (Greenwich). 2008;10:830–6.
23. Misselt AJ, McKusick MA, Stockland A, Misra S. Use of kissing embolic protection devices in the treatment of early bifurcation renal artery stenosis: a case report. J Vasc Interv Radiol. 2009;20:1240–3.
24. Cooper CJ, Murphy TP, Matsumoto A, Steffes M, Cohen DJ, Jaff M, Kuntz R, Jamerson K, Reid D, Rosenfield K, Rundback J, Agostino RD, Henrich W, Dworkin L. Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: rationale and design of the coral trial. Am Heart J. 2006;152:59–66.
25. Khosla A, Misra S, Greene EL, Pflueger A, Textor SC, Bjarnason H, McKusick MA. Clinical outcomes in patients with renal artery stenosis treated with stent placement with embolic protection compared with those treated with stent alone. Vasc Endovascular Surg. 2012;46:447–54.
26. Misra S, Sturludottir M, Mathew V, Bjarnason H, McKusick M, Iyer VK. Treatment of complex stenoses involving renal artery bifurcations with use of drug-eluting stents. J Vasc Interv Radiol. 2008;19:272–8.
27. Misra S, Thatipelli MR, Howe PW, Hunt C, Mathew V, Barsness GW, Pflueger A, Textor SC, Bjarnason H, McKusick MA. Preliminary study of the use of drug-eluting stents in atherosclerotic renal artery stenoses 4 mm in diameter or smaller. J Vasc Interv Radiol. 2008;19:833–9.
28. Zeller T, Sixt S, Rastan A, Schwarzwälder U, Müller C, Frank U, Bürgelin K, Schwarz T, Hauswald K, Brantner R, Noory E, Neumann F-J. Treatment of reoccurring instent restenosis following reintervention after stent-supported renal artery angioplasty. Catheter Cardiovasc Interv. 2007;70:296–300.
29. American College of Cardiology Foundation, American College of Radiology, American Institute of Ultrasound in Medicine, American Society of Echocardiography, American Society of Nephrology, Intersocietal Commission for the Accreditation of Vascular Laboratories, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Interventional Radiology, Society for Vascular Medicine, Society for Vascular Surgery, Mohler 3rd ER, Gornik HL, Gerhard-Herman M, Misra S, Olin JW, Zierler RE, Wolk MJ, Mohler 3rd ER. ACCF/ACR/AIUM/ASE/ASN/ICAVL/SCAI/SCCT/SIR/SVM/SVS 2012 appropriate use criteria for peripheral vascular ultrasound and physiological testing part I: arterial ultrasound and physiological testing: a report of the American College of Cardiology Foundation appropriate use criteria task force, American College of Radiology, American Institute of Ultrasound in Medicine, American Society of Echocardiography, American Society of Nephrology, Intersocietal Commission for the Accreditation of

Vascular Laboratories, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Interventional Radiology, Society for Vascular Medicine, and Society for Vascular Surgery. J Am Coll Cardiol. 2012;60:242–76.
30. Radermacher J, Chavan A, Bleck J, Vitzthum A, Stoess B, Gebel MJ, Galanski M, Koch KM, Haller H. Use of doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. N Engl J Med. 2001;344:410–7.
31. Lederman RJ, Mendelsohn FO, Santos R, Phillips HR, Stack RS, Crowley JJ. Primary renal artery stenting: characteristics and outcomes after 363 procedures. Am Heart J. 2001;142:314–23.
32. Zeller T, Frank U, Muller C, Burgelin K, Sinn L, Bestehorn HP, Cook-Bruns N, Neumann FJ. Predictors of improved renal function after percutaneous stent-supported angioplasty of severe atherosclerotic ostial renal artery stenosis. Circulation. 2003;108:2244–9.
33. van Ampting JM, Penne EL, Beek FJ, Koomans HA, Boer WH, Beutler JJ. Prevalence of atherosclerotic renal artery stenosis in patients starting dialysis. Nephrol Dial Transplant. 2003;18:1147–51.
34. Watson PS, Hadjipetrou P, Cox SV, Piemonte TC, Eisenhauer AC. Effect of renal artery stenting on renal function and size in patients with atherosclerotic renovascular disease. Circulation. 2000;102:1671–7.
35. Sivamurthy N, Surowiec SM, Culakova E, Rhodes JM, Lee D, Sternbach Y, Waldman DL, Green RM, Davies MG. Divergent outcomes after percutaneous therapy for symptomatic renal artery stenosis. J Vasc Surg. 2004;39:565–74.
36. Beutler JJ, Van Ampting JM, Van De Ven PJ, Koomans HA, Beek FJ, Woittiez AJ, Mali WP. Long-term effects of arterial stenting on kidney function for patients with ostial atherosclerotic renal artery stenosis and renal insufficiency. J Am Soc Nephrol. 2001;12:1475–81.
37. Korsakas S, Mohaupt MG, Dinkel HP, Mahler F, Do DD, Voegele J, Baumgartner I. Delay of dialysis in end-stage renal failure: prospective study on percutaneous renal artery interventions. Kidney Int. 2004;65:251–8.
38. Marone LK, Clouse WD, Dorer DJ, Brewster DC, Lamuraglia GM, Watkins MT, Kwolek CJ, Cambria RP. Preservation of renal function with surgical revascularization in patients with atherosclerotic renovascular disease. J Vasc Surg. 2004;39:322–9.
39. Silva JA, Potluri S, White CJ, Collins TJ, Jenkins JS, Subramanian R, Ramee SR. Diabetes mellitus does not preclude stabilization or improvement of renal function after stent revascularization in patients with kidney insufficiency and renal artery stenosis. Catheter Cardiovasc Interv. 2007;69:902–7.
40. Thatipelli M, Misra S, Johnson CM, Andrews JC, Stanson AW, Bjarnason H, McKusick MA. Renal artery stent placement for restoration of renal function in hemodialysis recipients with renal artery stenosis. J Vasc Interv Radiol. 2008;19:1563–8.
41. Harden P, MacLeod M, Rodger R, Baxter G, Connell J, Dominiczak A, Junor B, Briggs J, Moss J. Effect of renal-artery stenting on progression of renovascular renal failure. Lancet. 1997;349:1133–6.
42. Madder RD, Hickman L, Crimmins GM, Puri M, Marinescu V, McCullough PA, Safian RD. Validity of estimated glomerular filtration rates for assessment of baseline and serial renal function in patients with atherosclerotic renal artery stenosis: implications for clinical trials of renal revascularization. Circ Cardiovasc Interv. 2011;4:219–25.
43. Ivanovic V, McKusick MA, Johnson III CM, Sabater EA, Andrews JC, Breen JF, Bjarnason H, Misra S, Stanson AW. Renal artery stent placement: complications at a single tertiary care center. J Vasc Interv Radiol. 2003;14:217–25.
44. Rocha-Singh KJ, Novack V, Pencina M, D'Agostino R, Ansel G, Rosenfield K, Jaff MR. Objective performance goals of safety and blood pressure efficacy for clinical trials of renal artery bare metal stents in hypertensive patients with atherosclerotic renal artery stenosis. Catheter Cardiovasc Interv. 2011;78:779–89.
45. Taylor DC, Kettler MD, Moneta GL, Kohler TR, Kazmers A, Beach KW, Strandness Jr DE. Duplex ultrasound scanning in the diagnosis of renal artery stenosis: a prospective evaluation. J Vasc Surg. 1988;7:363–9.

Surgical Revascularization

21

Thomas C. Bower and Gustavo S. Oderich

Abstract

Surgical treatment of renovascular disease changed with the advent of stenting and the introduction of more potent anti-hypertensive medications. Currently, surgical renal revascularization is relegated to patients with recurrent in-stent stenosis, complex fibromuscular disease and renal aneurysms, children and adolescents with renovascular disease, and renal artery bypass or endarterectomy done in conjunction with aortic aneurysm repair or aortofemoral bypass for occlusive disease. Renal artery reconstructions are done with a variety of techniques, and are best done before there is irreversible renal parenchymal damage. Open surgical renal reconstruction has become more complex since the advent of stenting. Careful surgical planning, renal protection, and technical execution of the operation are keys to success.

Keywords

Renal artery revascularization • Renal artery bypass • Renal artery endarterectomy • Renal artery aneurysm • Renal artery fibromuscular disease • Ex-vivo renal artery repair or reconstruction

Introduction

Surgical treatment for most renal vascular diseases changed with the introduction of potent anti-hypertensive medications and renal artery angioplasty and stenting. This change is highlighted at our own institution, where the Division of Vascular and Endovascular Surgery at Mayo Clinic performed between 80 and 120 primary renal artery reconstructions per year in patients with atherosclerotic disease prior to 2002. In recent years, the number of open surgical reconstructions in our group averaged about 30–40 per

T.C. Bower, MD (✉)
Division of Vascular and Endovascular Surgery, Department of Surgery, Mayo Clinic College of Medicine, Rochester, MN 55904, USA
e-mail: bower.thomas@mayo.edu

G.S. Oderich, MD
Department of Vascular and Endovascular Surgery, Mayo Clinic, 200 First Street, SW, Rochester, MN 55904, USA

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_21,

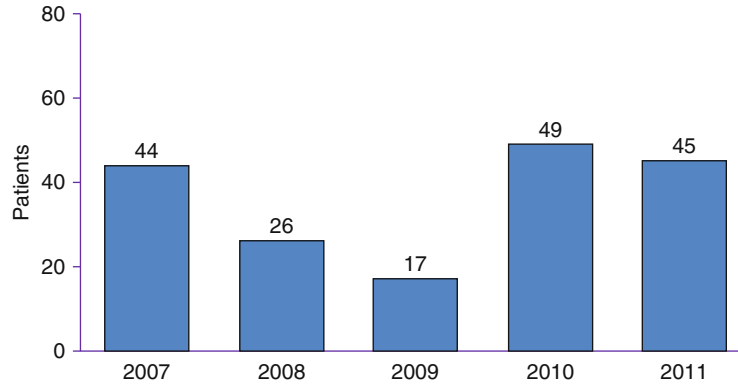


Fig. 21.1 Numbers of primary renal artery reconstructions done at Mayo Clinic each year from 2007 to 2011 (Adapted with permission of Mayo Foundation for Medical Education and Research. All rights reserved. From Bower et al. [1])

year, increased last year, and most of them are complex (Fig. 21.1).

Currently, surgical renal revascularization is relegated to patients with recurrent in-stent restenosis for atherosclerotic disease; complex fibromuscular disease; renal artery aneurysms; children and adolescents with renovascular disease; and renal artery reconstructions done in conjunction with repair of abdominal aortic aneurysms or aortofemoral reconstructions for occlusive disease [1].

Indications

The primary indication for surgical or endovascular intervention for renovascular disease should be failure of medical therapy. Such therapy includes angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statins, and tobacco cessation [2–4]. Treatment choice is influenced by patient comorbidities and anatomic factors, both of which affect operative risk and technical outcome. Our surgical group works closely with the nephrologists, to determine the need for intervention. Moreover, these decisions are influenced by best medical evidence, personal and institutional experiences.

Surgeons and nephrologists continue to struggle with the timing of, and predicted response from, renal reconstruction for occlusive lesions. While the primary goal of therapy is to improve hypertension and protect renal function, these goals remain elusive for the individual patient because of the variable pathophysiologic responses of the kidney to decreased blood flow. The kidney responds to ischemia unlike other major organs. Not every patient with a high grade renal artery stenosis develops significant hypertension, progressive renal dysfunction, or both. Why some patients with high grade stenoses have only modest hypertension, and others develop severe hypertension or renal function decline remains an enigma. Reductions in renal blood flow activate the renin angiotensin system, one of the primary targets of medical therapy. Adrenergic responses also occur, and these pathways now are treated with denervation procedures. However, it may be the release of fibrogenic cytokines that leads to scarring and irreversible damage to the renal parenchyma when the critical threshold of renal blood flow and tissue oxygenation is exceeded. Since some of these pathways are activated in the absence of decreased renal oxygen tension, our ability to predict responses to renal intervention is difficult [1].

Currently, renal artery intervention is offered to patients with accelerated, resistant, or poorly-controlled hypertension; renal function decline; and cardiac destabilization syndromes such as flash pulmonary edema, congestive heart failure or unstable angina [4]. Individuals with significant renal artery stenosis and accelerated hypertension who are intolerant to medications also are candidates for intervention. To date, there is no

single test or battery of tests that consistently predicts a positive response for each patient. We use a combination of clinical and laboratory criteria, renal resistive indices based on ultrasound imaging and changes in renal parenchymal thickness or size as gauges for intervention. A novel technique has been introduced by Textor and Glockner, called Blood Oxygen Level Dependent magnetic resonance imaging [5]. In concept, the magnetic properties of oxygenated and deoxygenated hemoglobin, and the response to a furosemide challenge, are used to assess oxygen tensions within various areas of the kidney. As renal blood flow volume and glomerular filtration rates begin to decrease, cortical and medullary oxygenation initially is preserved, although there is a reduction in the furosemide-suppressible oxygen consumption (FSOC) of the kidney. Progressive loss in the FSOC response suggests histologic injury. While preliminary data are being accrued with this technique, the authors hope the test may be a tool to differentiate normal or at-risk tissue from that which already is irreversibly damaged.

Treatment

Our last detailed outcome analysis of open surgical renal reconstructions at Mayo Clinic was from 1998 to 2002 [6]. Of the 311 patients operated, 198 (63.7 %) were for atherosclerosis, 81 (26 %) were performed as part of other reconstructions, 21 (6.8 %) were done for fibromuscular disease, and the remaining 11 (3.5 %) were done because of renal artery trauma or pseudoaneurysm.

Surgical Approach and Technique

The renal artery can be surgically reconstructed by a bypass or endarterectomy. Endarterectomy works well for atherosclerotic lesions confined to the first 2 cm of the artery, though it is technically more demanding than bypass for most patients. Aorto-renal bypass is used if the disease extends beyond the first 2 cm of the renal artery. These reconstructions are done through a midline incision if the aorta requires replacement for occlusive or aneurysmal disease. A transperitoneal infracolic exposure works well. There are several key steps needed for a technically successful outcome (Fig. 21.2a–d). First, the inferior mesenteric vein is ligated and divided along with its adjacent lymphatics, which allows the surgeon to incise an avascular tissue plane at the base of the left transverse mesocolon. This opens up the space around the pararenal aorta with upward and lateral retraction of the viscera. Next, the left renal vein is mobilized by ligating and dividing the gonadal, adrenal, and lumbar vein branches. The latter branch should be carefully ligated because in some patients, the renal artery lies in close proximity. Renal vein mobilization allows the surgeon to retract the vein cephalad or caudad to isolate the pararenal aorta. For endarterectomy, the renal arteries are circumferentially mobilized for 3 or 4 cm beyond the origins, so that the artery can be everted into the aorta. On the right side, one or more lumbar veins may require ligation and division to provide adequate mobilization of the renal artery. Large lumbar veins should be suture ligated at their confluence with the inferior vena cava to avoid troublesome bleeding. We find it best to place the proximal aortic cross-clamp between the superior mesenteric (SMA) and celiac arteries for endarterectomy. This allows ample room for the surgeon to see the origins of the renal arteries from within the aorta. Exposure of the supra-mesenteric aorta requires ligation and division of adrenal or phrenic artery branches; and division of the musculotendinous fibers of the crura of the diaphragm, which often are adherent to the lateral sides of the aorta. These maneuvers provide a secure place for the aortic cross clamp (Fig. 21.2d). Sequence of clamping depends on whether concomitant aortic reconstruction is done. In general, clamps are placed on the distal aorta or iliac arteries first, then the SMA and renal arteries, and finally the supramesenteric aorta. The aorta is opened vertically above the renal artery origins, which may require extension

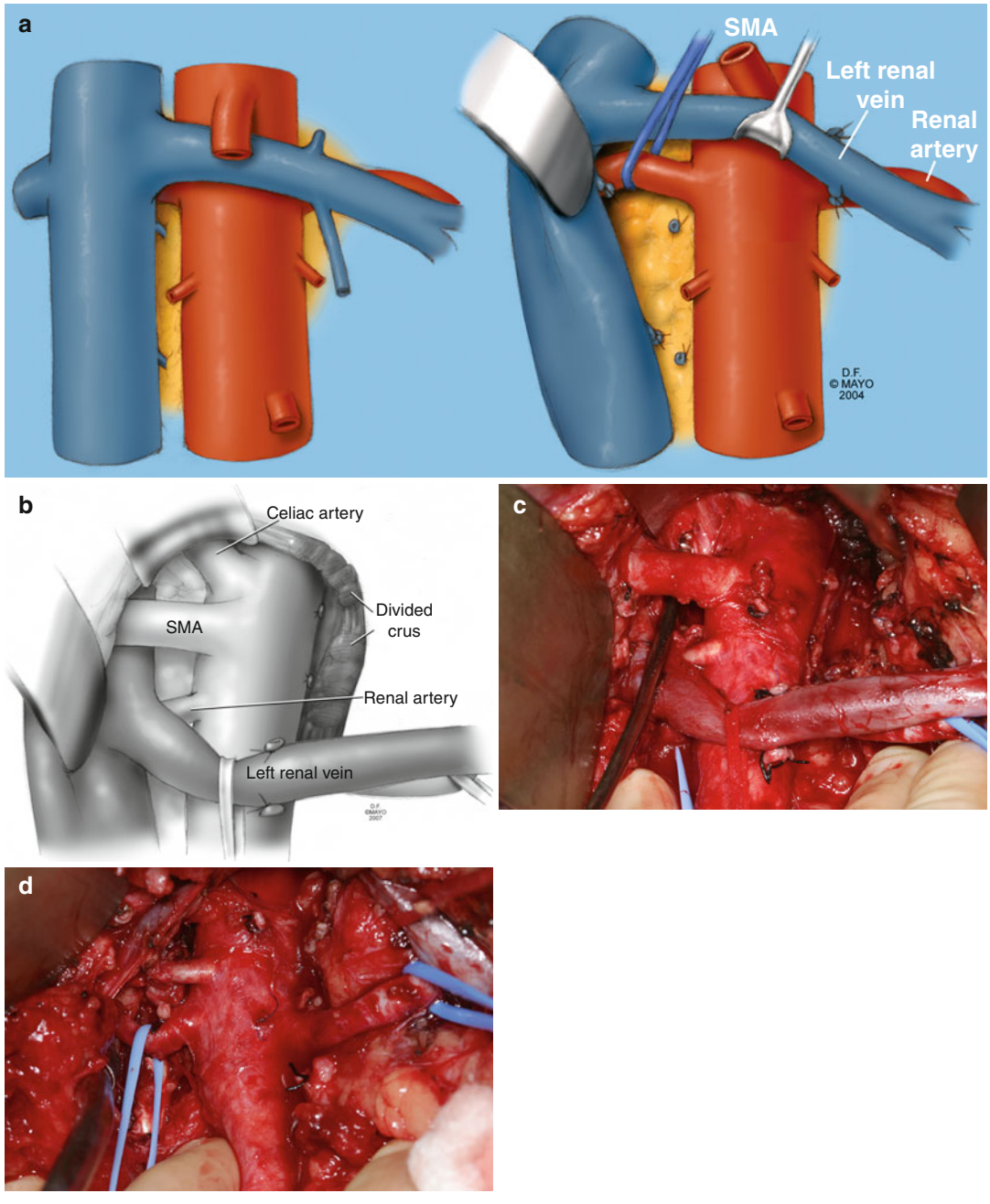


Fig. 21.2 (**a**–**d**) The left renal vein crosses anteriorly over the aorta and covers access to the renal arteries as shown in (**a**). The left renal vein branches are ligated and divided to afford access to the renal arteries. The crura of the diaphragm must be divided on either side of the aorta to provide a secure place for the aortic clamp, as shown in (**b**–**d**) (**a**, **b**: With permission of Mayo Foundation for Medical Education and Research. All rights reserved)

of the aortotomy to the left side of the SMA. An endarterectomy plane is created between the plaque and the aortic side wall. A button is cut around the origin of the renal artery, so that the renal artery can everted to provide adequate removal of the plaque and control of the endpoint

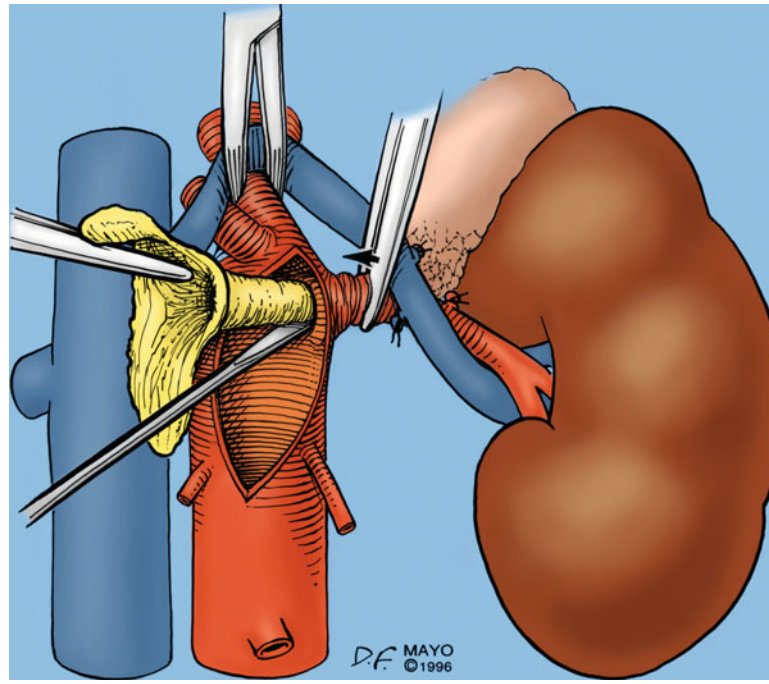


Fig. 21.3 Schematic drawing of a transaortic renal artery renal artery endarterectomy. *Arrow* shows direction of movement of the plaque during the endarterectomy. (With permission of Mayo Foundation for Medical Education and Research. All rights reserved)

(Fig. 21.3). Once the endarterectomy is completed on both sides, the aortotomy is closed primarily with running Prolene suture. Back-bleeding and fore-bleeding from the aorta, visceral and renal arteries is done prior to transfer of the aortic clamp to an infrarenal position. Generally, renal ischemia time is well under 30 min with this technique. Aortic reconstruction then proceeds as needed. Mobilization of the left renal vein and renal arteries is done in similar fashion if a bypass is done. However, the aorta does not have to be exposed proximal to the renal artery origins in most circumstances. The aortic reconstruction is done with a prosthetic graft, often with pre-sewn 6–7 mm graft limbs to serve as the renal bypasses. The distal renal artery is clamped, the proximal renal artery is ligated and divided, and the renal artery is spatulated. The artery may be infused with cold renal perfusion solution if the surgeon anticipates a long, warm ischemia time. The distal anastomosis is completed in an end-to-end fashion. Back-bleeding and fore-bleeding is allowed prior to completion of the anastomosis and restoration of blood flow to the renal artery, so that no thrombus or debris is washed into the kidney. Some deep or obese patients, or those with fragile renal arteries, are best served by performing the distal renal artery anastomosis first, so that no tension is placed on the artery. A heel and toe suture facilitates the anastomosis (Fig. 21.4a, b). The bypass grafts originate from either the anterolateral or lateral wall of the native aorta or graft. Once renal reconstructions are completed by any technique, intraoperative duplex imaging is performed to assess technical outcome. We have found this adjunct to be critical in preventing early failure of the renal reconstruction.

Patients who do not require aortic reconstruction can have renal artery bypass from the aorta, hepatic, or iliac arteries via a right or left medial visceral rotation with the kidney left in place. The exposure can be done through a midline or subcostal incision, depending on body size and the width of the costal margin. In most circumstances, the proximal anastomosis is done first, followed by the distal one, except for patients who require an ex vivo reconstruction. This technique

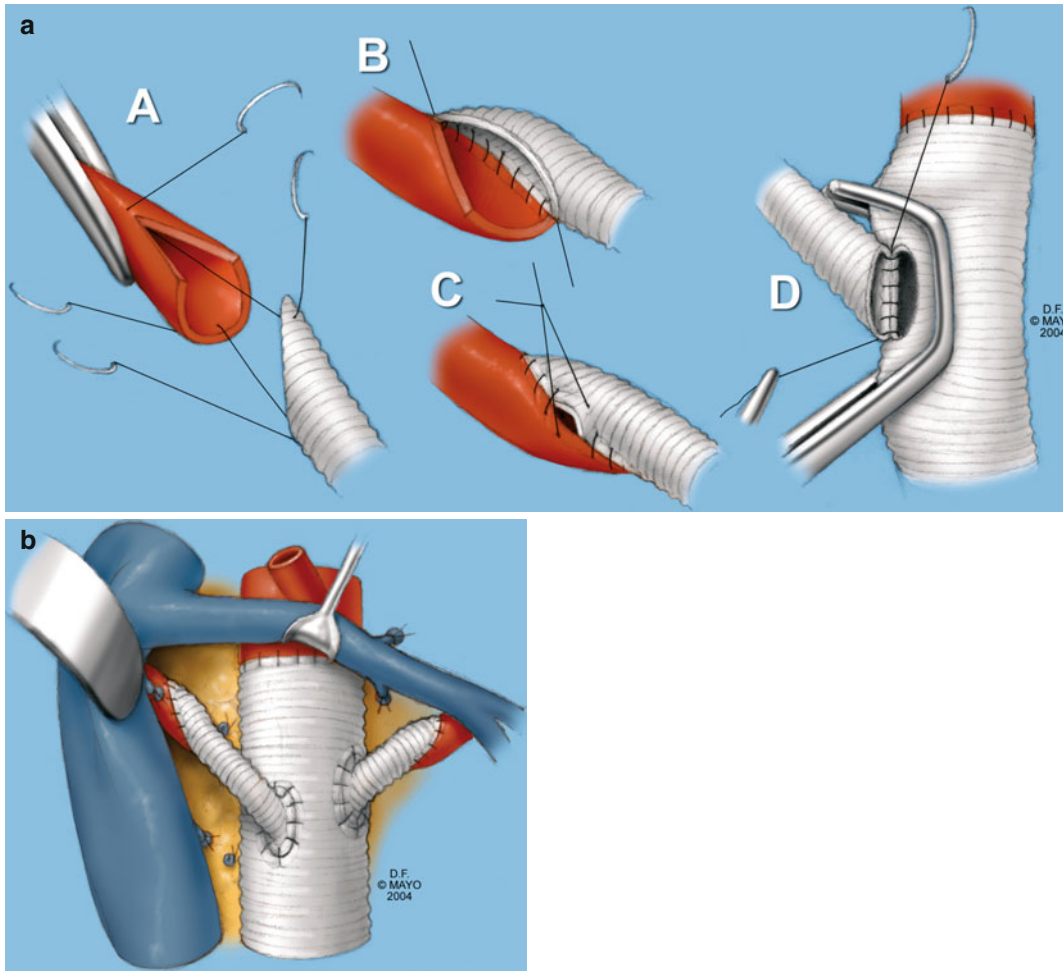


Fig. 21.4 (**a**, **b**) Schematic drawing showing the technical steps of an aortorenal bypass, including the heel and toe suture. The bypasses originate on the anterolateral or lateral sides of the aortic graft (**a**, **b**: With permission of Mayo Foundation for Medical Education and Research. All rights reserved)

is outlined later in the chapter. If the aorta or iliac arteries are calcified or moderately stenotic, inflow from the hepatic or splenic arteries works well provided the celiac artery is not stenotic. High risk patients for aortic clamping also benefit from these alternative inflow sources.

Atherosclerotic Disease

The number of cases performed, and the demographics of patients operated for atherosclerotic renal artery disease, has changed at our institution over the past several decades (Table 21.1).

Table 21.1 Changes in demographics for patients undergoing open renal artery reconstruction

	Time period		
	1970–1980	1980–1993	1998–2002
Operations (N)	652	991	198
Age (years)	63.5	68.0	67
Gender (M:F)	3:1	3:1	1.4:1
CR <2 mg/dL (%)	85	69	81
CR >2 mg/dL (%)	15	31	19

Between 1970 and 1980, approximately 65 renal revascularizations were done per year. This number increased to a maximum of 76 operations

Table 21.2 Selected series of surgical renal artery revascularization 2000–2005

	#	%		Renal function response, %		Hypertension response, %		Perioperative outcome, %	
Author	Pts.	Bil. repair	Preop RI	Improved	Unchanged	Cured	Improved or stable	Death	Morbidity
Hansen	232	64	100	58	35	11	76	7.3	30
Paty[a]	414	NR	4	26	68	NR		5.5	11.4
Cherr	500	59	49	43	47	73	12	4.6	16
Marone	96	27	100	42	41	NR		4.1	NR
Mozes	198	65	57	28	67	2	59	2.5	19

[a]Pts. operated for either hypertension or renal salvage. Improvement was noted in 26, 68 % remained stable, and 6 % worsened. Specific renal function decline occurred in 3 %

per year in the 13 year period between 1980 and 1993, but decreased in the last analysis to approximately 40 cases per year. While men needed operation more often than women through the 1990s, there was little gender difference in the period from 1998 to 2002. In the 1990s, individuals with stage 4 chronic kidney disease accounted for almost one-third of the group [7]. Thirty-day mortality was 3 %, even with advanced kidney disease, and nearly 75 % of patients needed aortic reconstruction. Freedom from dialysis was approximately 75 % at 5 years. Age over 75 years, congestive heart failure, and a preoperative serum creatinine greater than 2 mg/dL predicted a significantly higher risk of perioperative mortality. Even for patients with a preoperative serum creatinine more than 3 mg/dL, only 9 % needed early postoperative dialysis, and two thirds remained dialysis free at 5 years. By 2002, the number of men and women were nearly equal, most were operated when the serum creatinine was less than 2 mg/dL, and only one-fifth had stages 2, 3 or 4 chronic kidney disease.

Of the 198 patients surgically treated between 1998 and 2002, 67 % of the patients had bilateral reconstructions and concomitant aortic reconstruction. Thirty-day mortality was 2.5 %, and the risk of renal failure or early renal artery occlusion was ≤1.5 %, which we believe is related to our routine use of intraoperative completion duplex ultrasound imaging. Importantly, dialysis free survival was 76 % at 5 years [6].

A summary of selected series of surgical renal artery revascularization between 2000 and 2005 is shown in Table 21.2 [6, 8–11]. Operative mortality ranged from 2.5 to 7.5 %, and morbidity of any type occurred in 11–30 % of patients. Advanced age and congestive heart failure contributed to the 4.6 % overall mortality rate in the series by Cherr et al. [8]. All but one of the 23 patients who died within 30 days of operation in this report had bilateral renal reconstruction, or renal reconstruction combined with aortic or mesenteric artery revascularization. Specifically, the mortality rate for unilateral or isolated renal artery repair was 0.8 %, whereas that which followed combined aortic and bilateral renal artery reconstruction was 6.9 %, a significant difference.

Only a small percentage of patients had hypertension cured among the series reported [6–11], but the majority had improvement in blood pressure and renal function, the latter determined by estimated glomerular filtration rates in recent reports The Wake Forest group documented cure of hypertension in only 12 % of patients, improvement in 73 %, and no change in 15 % [8]. The mean GFR increased significantly after operation, with 43 % of patients showing improvement in renal function based on a 20 % or greater change in glomerular filtration rate. Preoperative chronic kidney disease, diabetes mellitus, and severe aortic occlusive disease were independently associated with death or dialysis during follow-up. Blood pressure cure and improvement in renal function significantly improved dialysis-free survival. Interestingly, only patients with improvement in renal function had an increase in survival free from dialysis. Those with unchanged or worsened renal function had lower dialysis-free survival.

The authors suggest that severe hypertension is the key preoperative characteristic associated with clinical benefit, and improvement in renal function after operation stands as the most important response to predict dialysis-free survival. Factors that favored recovery of renal function include severe preoperative hypertension, bilateral or global atherosclerotic renovascular disease from renal artery stenoses exceeding 95 %, or patients with renal artery occlusion and acute, rapidly deteriorating renal function.

There are few randomized trials comparing surgical treatment to either best medical therapy or angioplasty. A study by Uzzo et al. [12] in 2002, randomized 52 patients either with bilateral renal artery stenoses, or stenosis involving a solitary kidney, to medical or surgical treatment. The primary outcome measure was event free survival, which was shown to be similar at 74 months by statistical analysis. Importantly, patients with chronic kidney disease did better with operation than with medical treatment, but the specifics of medical treatment were undefined. In 2009, Balzer compared operation to renal artery angioplasty in 49 patients with at least 70 % renal artery stenosis [13]. There was no significant difference in primary patency, hypertension, or renal function response between the two groups, though both groups demonstrated some improvement in blood pressure and renal function.

Failed Endovascular Revascularization

In our current practice, the primary indication for open surgical renal artery reconstruction for atherosclerosis, in the absence of aortic disease, is a patient who fails renal artery stenting. These patients often have multiple prior endovascular interventions, with stents that encroach into the bifurcation of the renal artery. Open repair is more challenging because of inflammation and the need for more distal reconstruction. Although analysis is ongoing, these patients seem to be older and have more comorbidities than the aforementioned surgical groups [1].

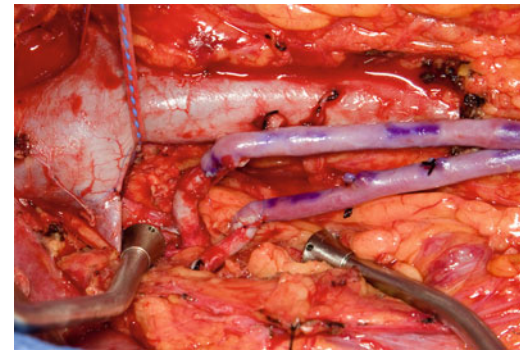


Fig. 21.5 Patient with recurrent instent restenosis extending to the renal artery bifurcation. The reconstruction was done using a bifurcated saphenous vein bypass graft taken from the common iliac artery to each of the two primary renal artery branches (With permission of Mayo Foundation for Medical Education and Research. All rights reserved. From Bower et al. [1])

Operations are more common in women, who have smaller arteries than men; and reconstructions are often to the primary branches or the distal main renal artery which makes operations more complex (Fig. 21.5). Concomitant aortic reconstruction is avoided and inflow is chosen from the hepatic, splenic or iliac arteries. Renal protection is paramount for patients who require complex renal reconstruction and have either chronic kidney disease or a solitary kidney. In these circumstances, we more aggressively use cold renal perfusion solutions and topical cooling than what was required in the past. For some patients, a modified ex vivo technique, used by the Wake Forest group is helpful [14]. This technique leaves the kidney in situ and avoids renal vein division, as used in ex vivo reconstructions. Modified ex vivo repair can be done when the reconstruction is taken to the distal main renal artery or the primary branches, especially in asthenic patients. The periureteral collaterals are occluded with a large vessel loop. A clamp is placed across the renal vein, and the renal artery is ligated and divided. Only a small venotomy is made in the renal vein, and the kidney is perfused with at least 300 mL of a cold renal perfusion solution until the effluent is clear. Topical slush is applied. At times, unique techniques are needed for revascularization as shown in Fig. 21.6a, b.

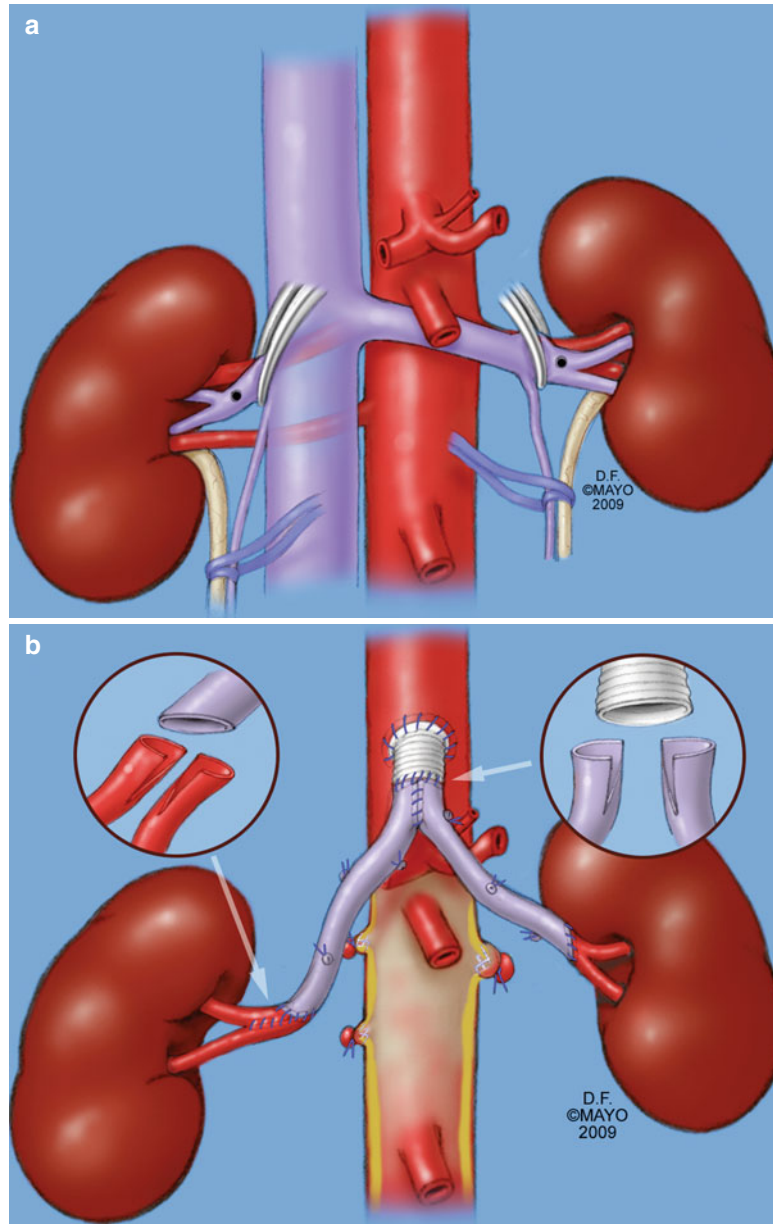


Fig. 21.6 (**a**, **b**) Patient with bilateral, recurrent instent restenosis involving both right and a single left renal artery. Her aorta was calcified from the origin of the superior mesenteric artery through the iliac arteries, the latter having moderate instent stenoses. The challenge was to obtain adequate inflow, but minimize warm renal ischemia. The reconstruction was done using a modified ex vivo technique A pantaloons graft was fashioned from the supraceliac aorta using an 8 mm Hemashield graft and a bifurcated saphenous vein graft (**b**). The renal artery branches were sewn together first using a modified ex vivo technique to minimize warm renal ischemia time (**a**, **b**: With permission of Mayo Foundation for Medical Education and Research. All rights reserved)

Fibromuscular Dysplasia

Patients with complex fibromuscular disease pose similar challenges. In analysis of patients treated for FMD between 1998 and 2004 at Mayo Clinic, 25 of the 26 patients had hypertension, 8 had aneurysm, 6 had failed prior angioplasty, and 1 had renal artery stenosis secondary to chronic dissection [15]. Patient age averaged 47 ± 14 years. The most common arterial reconstruction was aortorenal bypass, used for 28 of the 32 affected arteries. The other reconstructions included hepatorenal bypass or aneurysmorrhaphy, with or without patch angioplasty, in 2 each. Seventeen needed reconstruction to the primary branches. Saphenous vein was the most common conduit. Two grafts failed and another graft became stenotic over time, all in men who had

prosthetic conduits. Response to hypertension is more predictable in this patient group compared to those with atherosclerotic disease, with nearly 90 % of the patients having cured or improved hypertension

In 2007, the Wake Forest Group reported the outcomes of branched renal artery reconstructions with cold perfusion protection [14]. Seventy-eight renal arteries were repaired using ex vivo techniques for 49 kidneys, and in situ techniques in the remaining 29. The most common pathology was renal artery aneurysm in 50, followed by fibromuscular disease in 37, atherosclerosis in 5 and arteritis in 2. Reconstructions were done primarily with saphenous vein in 69, with the remainder comprised of hypogastric artery, polytetrafluroethylene grafts, composite grafts or aneurysmorrhaphy. A mean of 2.8 ± 1.6 branches were repaired with a mean cold ischemia time of 125 min. There were five early failures which resulted in nephrectomy in three and successful operative revision in one. Primary patency was 85 % at 12 months. There was 1 in-hospital death (mortality rate of 1.3 %) in a patient with advanced cirrhosis who had a large symptomatic renal artery aneurysm but developed postoperative hemorrhage which led to multisystem organ failure. Two late deaths occurred, one at 8.4 years and the other at 14.2 years after operation, yielding a 10-year product-estimate survival of 90 %. Hypertension was present in over 93 % of patients prior to operation, and was cured in 15 % and improved in 65 %.

While endovascular techniques have been applied to select patients with renal artery aneurysms, individuals with complex fusiform aneurysms involving the primary or secondary branches still require open reconstruction. Ex vivo or modified ex vivo surgical techniques are often needed (Fig. 21.7a–c). With ex vivo repair, a T-incision is made in Gerota's fascia, and the kidney is circumferentially mobilized. The ureter and adjacent soft tissues are isolated with a large vessel loop as described for the modified ex vivo technique. The renal artery and vein are divided, and the kidney is elevated to the abdominal wall. The renal vein stump includes a small cuff of vena cava on the right side, whereas an oblique venotomy is made for the left renal vein. In some cases, the main renal artery and primary branches can be dissected free prior to division of the artery. If the aneurysm is hilar in location or intimately adherent to the adjacent vein branches, it is safer to divide the main renal artery and vein, cold perfuse the kidney, and then complete the dissection (Fig. 21.8a, b). The kidney is infused with a cold hypertonic solution comprised of saline, albumin and heparin. Intravenous mannitol is given before and after the cross-clamp. The kidney is flushed until the effluent from the renal vein is clear, and the kidney is placed in an ice slush bath which allows ample time for meticulous reconstruction of the branches. Autogenous saphenous vein or hypogastric artery is used for the reconstruction. The distal anastomoses are done with either running or interrupted suture depending on the size of the artery. The kidney is placed back in its bed, the renal vein anastomosis is performed first, and the suture is tied approximately 2 mm away from the vein to allow for expansion of it with restoration of blood flow (growth factor). The graft is passed anterior to the vena cava and sewn to the aorta.

Children and Adolescents

Children and adolescents with renovascular hypertension either have intimal fibromuscular disease; developmental or congenital disorders such as neurofibromatosis, mid-aortic coarctation, or diffuse aortic hypoplasia (Fig. 21.9a–c) [16]. Included in this group are patients with Takayasu's arteritis. The University of Michigan group has one of the largest experiences in treatment of pediatric patients with abdominal aortic coarctation [16–19]. Their most recent report discusses treatment of 53 patients with abdominal aortic coarctation, treated either by thoracoabdominal bypass, patch aortoplasty, or interposition aortic grafting [17]. Dr. Stanley and colleagues found developmental disease as the etiology of the coarctation in 48, inflammatory aortitis in only 4, and iatrogenic trauma in one. In contrast to other reports, 37 of the 53 patients had suprarenal coarctation, 12 had intra-renal stenosis, and the remaining 4 had an infrarenal coarctation.

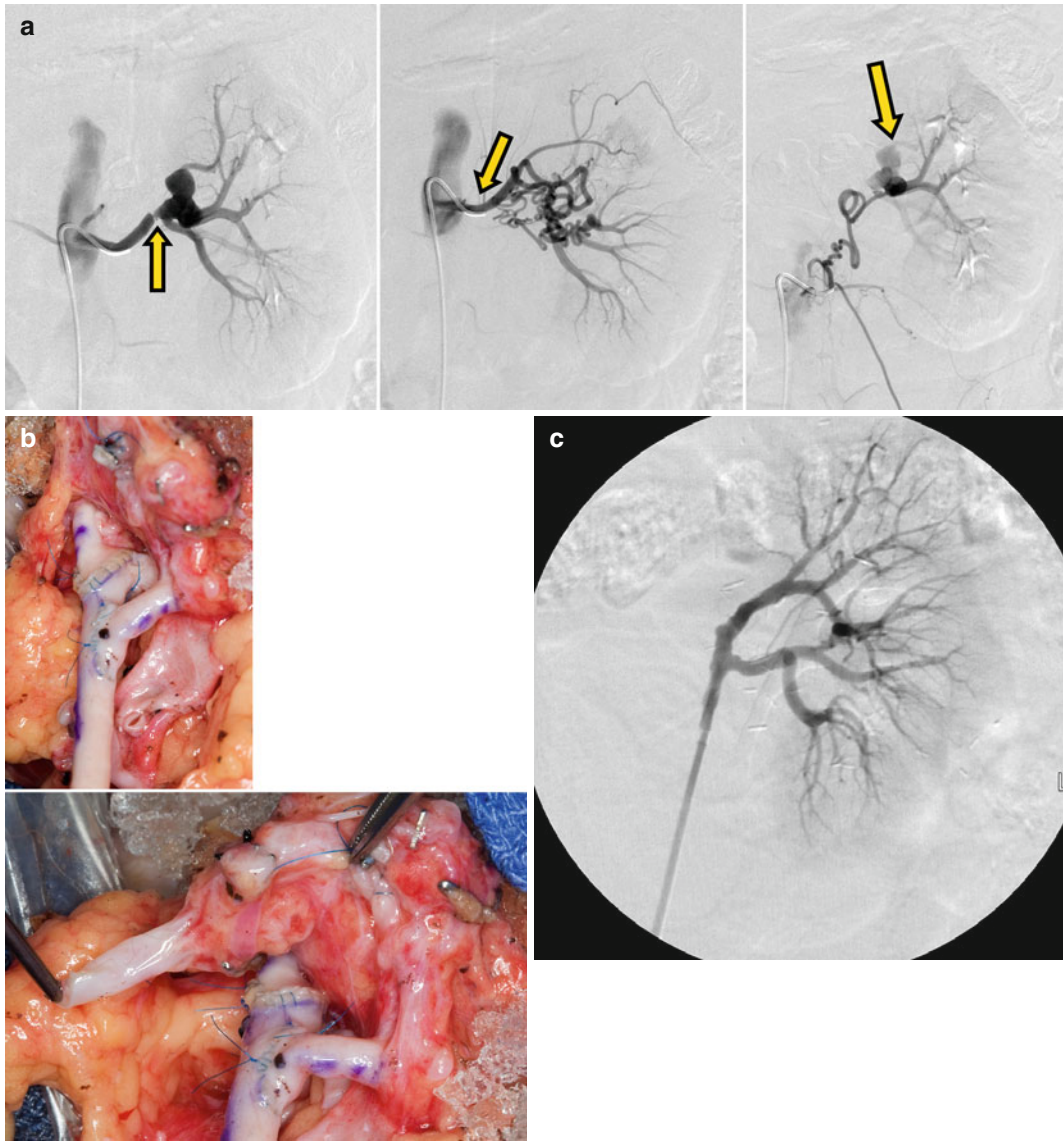


Fig. 21.7 (**a**–**c**) Patient with hypertensive spells, renal artery stenoses (*arrow*) and an aneurysm. The main renal artery had a high grade stenosis with a 2.5 cm aneurysm beyond it (**a**). There was collateral refilling of the main renal artery from an upper pole branch (*arrow*) and the gonadal artery (*arrow*). An ex vivo reconstruction was performed using saphenous vein as the arterial conduit (**b**). Postoperative arteriogram showing a widely patent reconstruction (**c**). (All: With permission of Mayo Foundation for Medical Education and Research. All rights reserved. From Bower et al. [1])

Co-existing occlusive disease was found in the visceral arteries in 33 patients and in the renal arteries in 46. Aortic and renal-related hypertension occurred in all but three patients, and only a small number had lower extremity ischemia or intestinal angina. Their preferred reconstruction was an aortoplasty unless the aortic segment was too long, fibrotic, or small. Renal artery stenoses were corrected concomitantly as clinically needed, but few underwent reconstruction of the superior mesenteric or celiac arteries. In general, renal artery reimplantation is preferred to bypass, and hypogastric artery is preferred over saphenous vein because of late aneurysmal degeneration of

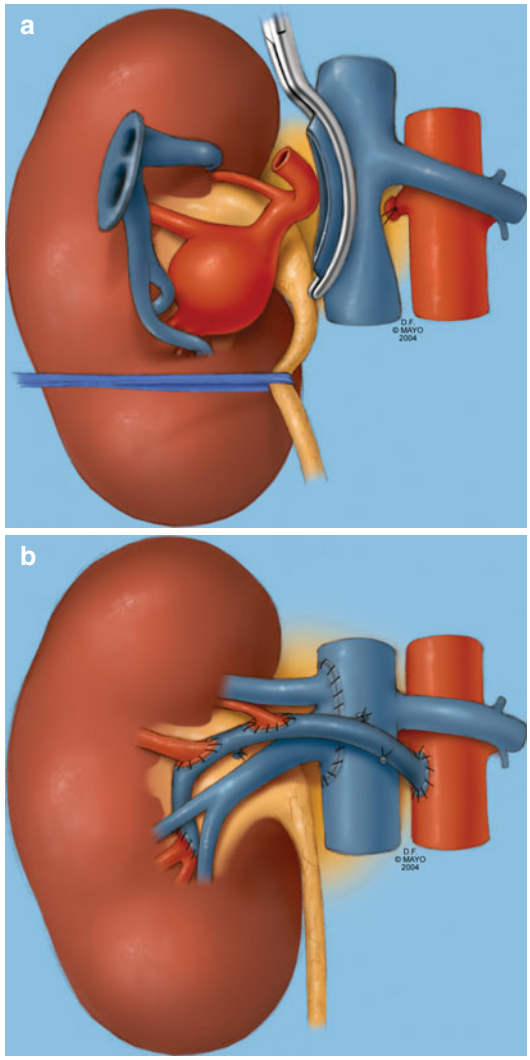


Fig. 21.8 (**a**, **b**) Schematic drawing of an ex vivo reconstruction in a patient whose hilar aneurysm was intimately adherent to the adjacent renal veins. A complex ex vivo reconstruction was done using saphenous vein as the conduit. Note the cuff of vena cava taken with the right renal vein, so that the venous anastomosis does not become stenotic (**a**). The primary and secondary renal artery branches were individually attached to the vein graft (**b**) (Both: With permission of Mayo Foundation for Medical Education and Research. All rights reserved)

vein grafts. The reconstructions for aortic coarctation were exceedingly durable, and only eight secondary renal or visceral reoperations and three aortic procedures were required during late follow-up. There was no perioperative mortality associated either with primary or secondary procedures, a reflection of the technical excellence of the surgeons in this group. Angioplasty and stenting has been used to treat aortic coarctation causing secondary renovascular hypertension, but recurrent stenosis rates are higher than with open reconstructions [20]. Intuitively, this technology may be applicable to short segment coarctations which do not involve the renal or visceral artery origins. Management of patients with aortic coarctation and renal artery disease secondary to Takayasu's disease warrant comment. The key to ensure long-term durability in these patients is to perform the aortic or branch vessel reconstructions to healthy, non-inflamed arteries (Fig. 21.10a, b). Sometimes, a small piece of the artery can be sent to pathology to exclude the presence of inflammatory or giant cells in the wall before the arterial anastomosis is performed. In a study by Fields et al. [21] for whom 97 % of arterial reconstructions were done for occlusive lesions, the best outcomes were seen in patients with chronic disease no longer requiring steroids, whereas the worst outcomes occurred in those with acute presentations unresponsive to steroids. As a general principle, patients with active disease should first be medically managed whenever possible, with high dose steroids and other immunosuppressant agents as necessary to control the acute inflammatory phase.

Complex Aortic Repair

Renal revascularization is necessary for patients with complex aortic aneurysms or dissections. In years past, patients with thoracoabdominal aortic aneurysms had the renal arteries reimplanted onto the aortic graft as a patch, often reimplanting the right renal, superior mesenteric and celiac arteries together, with a separate bypass to the left renal. Current techniques avoid patches because of the risk of late patch graft aneurysms.

Debranching of the visceral and renal arteries, with separate graft limbs originating from the

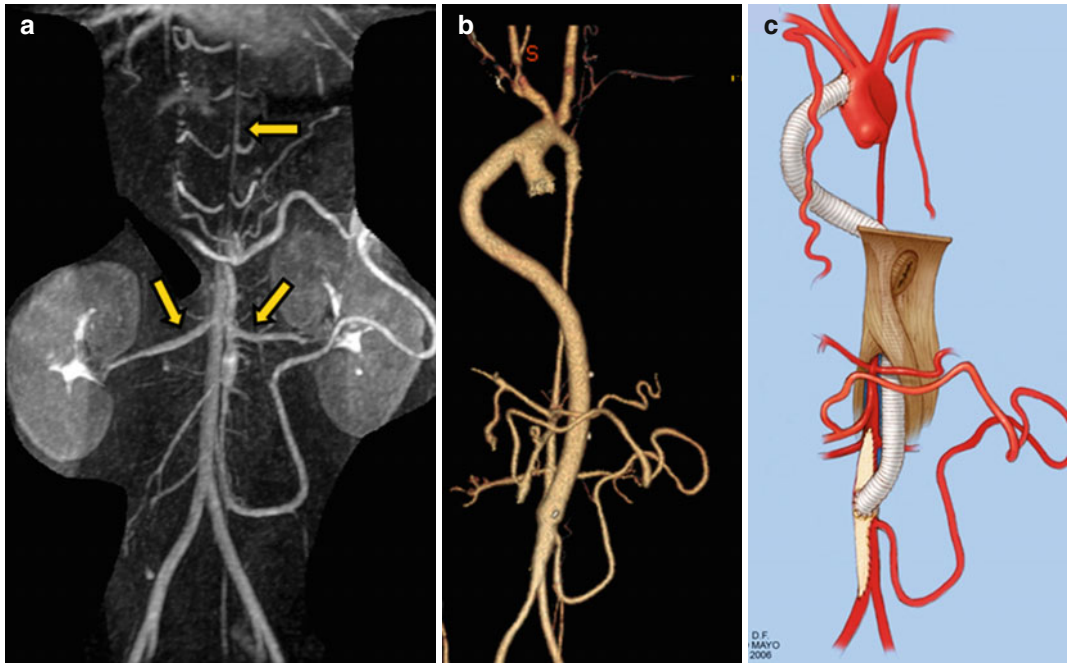


Fig. 21.9 (**a**–**c**) Young man with diffuse thoracic and upper abdominal coarctation (**a**). Portions of the thoracic aorta measured no more than 3 mm in diameter. He had poorly controlled hypertension, left ventricular hypertrophy, and short distance exertional dyspnea. An ascending aorta to infrarenal aortic bypass was done after a patch was placed on the aorta, extending from above the renal arteries onto the right common iliac. A postoperative CTA is shown in (**b**), schematically represented in (**c**). The (*top arrow*) shows the hypoplastic thoracic aorta (diffuse coarctation), (*Bottom arrows*) show renal arteries (**c**: With permission of Mayo Foundation for Medical Education and Research. All rights reserved)

aortic graft, now is preferred in our practice for thoracoabdominal and complex abdominal aortic aneurysms (Figs. 21.11a, b and 21.12a–d). While this technique adds more time to the operation, it is our belief that patients have less physiologic stress, shorter visceral and renal ischemia times, and a lower risk of late aneurysms, factors which affect early and late outcomes. The most difficult artery to reconstruct during open thoracoabdominal aneurysm repair, especially if it is diseased, is the right renal because it is the furthest away from the surgeon in the operative field. If atherosclerotic disease causes moderate to high grade stenosis and is isolated to the origin of the artery, an endarterectomy is done and the artery reimplanted onto the aortic graft, or bypassed. Some groups advocate placement of covered or bare metal stents into the right renal artery to correct a stenosis, which obviates the need for endarterectomy [22]. The stent is placed into the artery under direct vision. This technique is useful when the surgeon is concerned that endarterectomy will not achieve an adequate distal endpoint.

Several adjuncts are utilized to reduce warm ischemia time to the viscera, kidneys, spinal cord, and extremities during thoracoabdominal aortic aneurysm repair. The choice of technique depends on whether there is dissection, atheromatous disease or dilatation of the distal aortic arch; the extent of the thoracoabdominal or abdominal aneurysm; and whether patient anatomy will allow for a sequential clamping of the aortic aneurysm as the reconstruction proceeds from proximal to distal. Left atriofemoral bypass with mild systemic cooling is a popular technique, and achieves these perfusion goals if the aorta can be sequentially clamped. If the aorta is

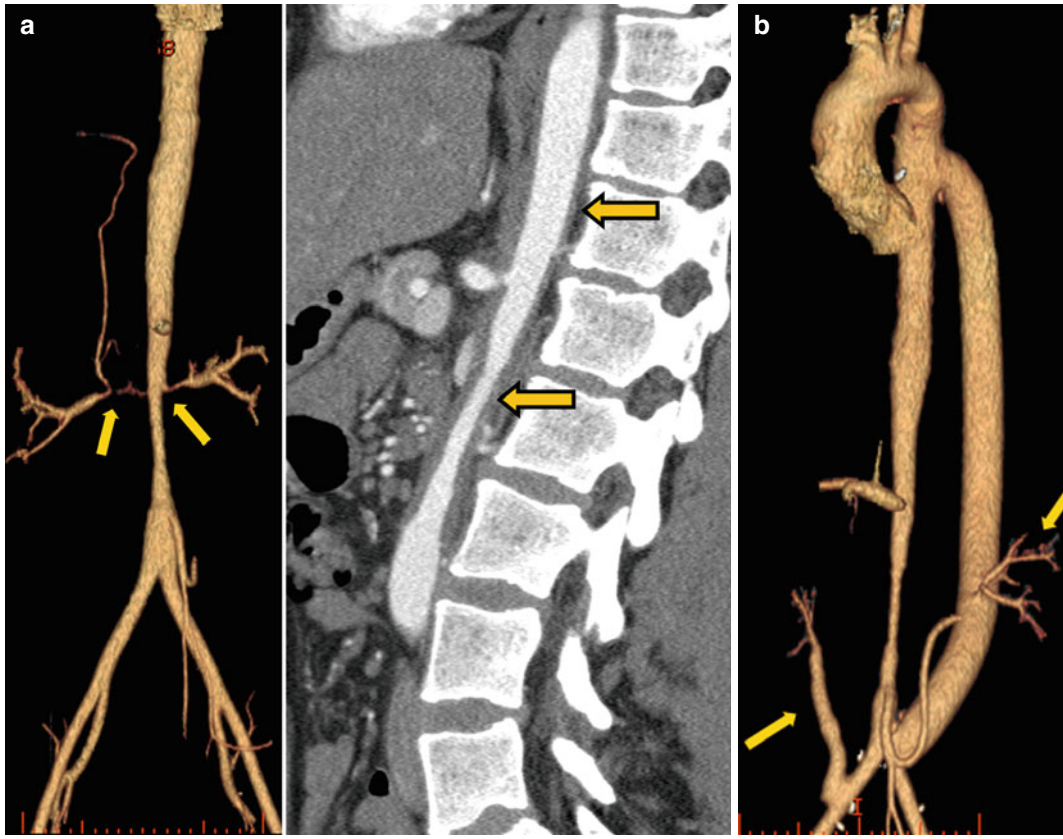


Fig. 21.10 (**a**, **b**) Teenager with 5 drug hypertension, Takayasu's arteritis, abdominal aortic coarctation with thickening of the lower descending thoracic aorta (*middle pannel*). She had bilateral renal artery stenoses (*left pannel*) (**a**). Reconstruction was performed with a descending thoracic to aortic bifurcation bypass, a right iliorenal (*arrow*) saphenous vein bypass, and reimplantation of the left renal artery (**b**) (Both: With permission of Mayo Foundation for Medical Education and Research. All rights reserved. From Bower et al. [1])

too diseased for distal clamping, then separate perfusion cannulas are brought from the bypass circuitry and placed into the visceral and renal arteries. Cerebrospinal fluid drainage is an adjunct used with this technique to improve spinal cord perfusion pressure. Cardiopulmonary bypass and hypothermia, with a brief period of circulatory arrest to perform the proximal aortic anastomosis, provides excellent organ protection without the need for a CSF drain. We prefer this technique for patients in whom the distal aortic arch is dilated or diseased, and for thoracoabdominal aneurysms that involve most of the thoracic and abdominal aorta, whether or not there is associated chronic aortic dissection. The downside of this technique is coagulopathy that occurs after the patient is rewarmed following the bypass run.

Complex abdominal aortic aneurysms that involve the renal artery origins can safely be reconstructed with a variety of techniques, depending on the quality of the aortic wall around the renal and visceral artery origins [23, 24]. One option is to bypass the visceral and left renal arteries with branched grafts from the lower thoracic aorta before aortic clamping. In other cases, one renal artery (usually the right one) and the visceral arteries are included in a beveled proximal aortic graft anastomosis, with the remaining renal artery reimplanted as a button, or reconstructed with a

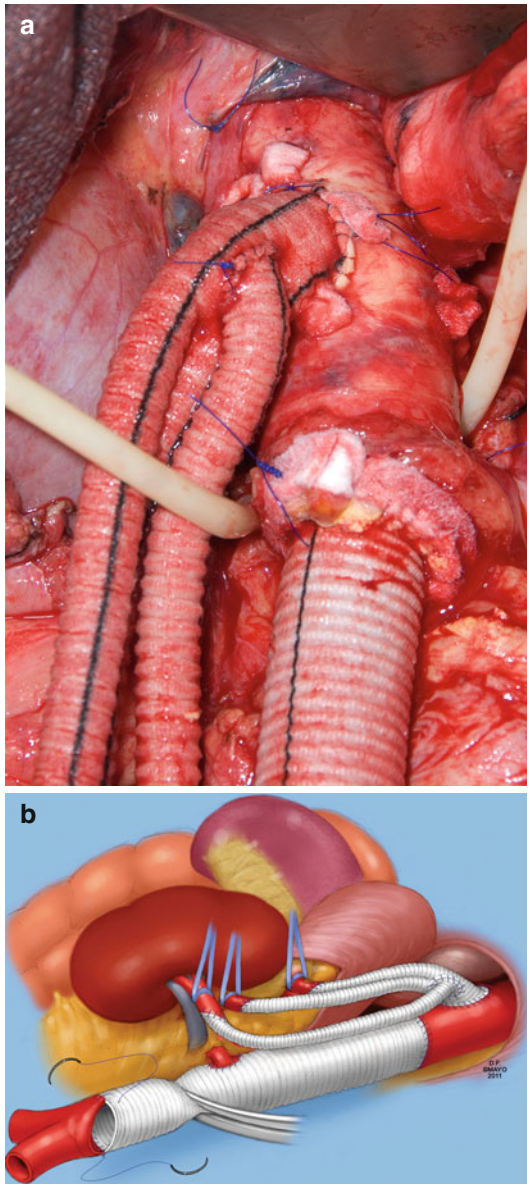


Fig. 21.11 (**a**, **b**) Patient with an extent III thoracoabdominal aortic aneurysm, which involved the lower descending thoracic and the entire abdominal aorta. The celiac, superior mesenteric and left renal arteries were reconstructed with a trifurcated graft originating from normal aorta above the aneurysm (**a**, **b**). The right renal artery was reimplanted onto the graft as shown in (**b**) (**b**: With permission of Mayo Foundation for Medical Education and Research. All rights reserved)

bypass. Rarely, a patient with a pararenal aortic aneurysm, who has normal quality aorta at the SMA origin, can be reconstructed with a fish mouth technique, which avoids reimplantation or bypass of the renals. This anastomosis requires the suture line be sewn close to the renal artery origins, and is facilitated by starting the anastomosis from the base of the SMA, and utilizing a parachute suture technique. Infusion of cold renal perfusion solutions to protect the kidney is used when the aortic repair is confined to the abdomen, and when warm renal ischemia time is expected to exceed 30 min. The cold perfusate is placed into the renal artery at 15 min intervals.

Hybrid aortic repair involves both open surgical reconstruction of the renal and/or visceral arteries, and placement of a stent graft in the aorta to repair an aneurysm (Fig. 21.13). This technique was developed by Dr. William Quinones-Baldrich at UCLA to reduce morbidity and mortality for patients with complex aortic aneurysms who cannot tolerate a large thoracoabdominal incision because of cardiopulmonary dysfunction [25]. The operations can be done at one operation; or staged, in which transabdominal visceral and renal reconstructions are done at one procedure, and the stent graft is placed at a second operation. Staged reconstructions have the advantage of decreasing the total time for the repair, though it requires two anesthetics. Moreover, a staged reconstruction for a thoracoabdominal aneurysm may allow development of a spinal cord collateral artery network, which could lower the risk of ischemic spinal cord injury when placement of the aortic stent graft will cover "critical" spinal arteries [26]. A disadvantage of a staged procedure is potential rupture of the aneurysm between the two operations. Success of this operation, in our opinion, is based on patient selection. Clearly, operations to separately reconstruct the visceral and renal arteries in deep or obese patients are technically demanding, which adds to the length and stress of the operation.

In summary, renal artery reconstructions are done utilizing a variety of techniques for a wide range of pathologies. Intervention for occlusive lesions is best done before a patient sustains irreversible renal parenchymal damage, though the optimal timing of renal revascularization remains a challenge. Open surgical renal reconstructions

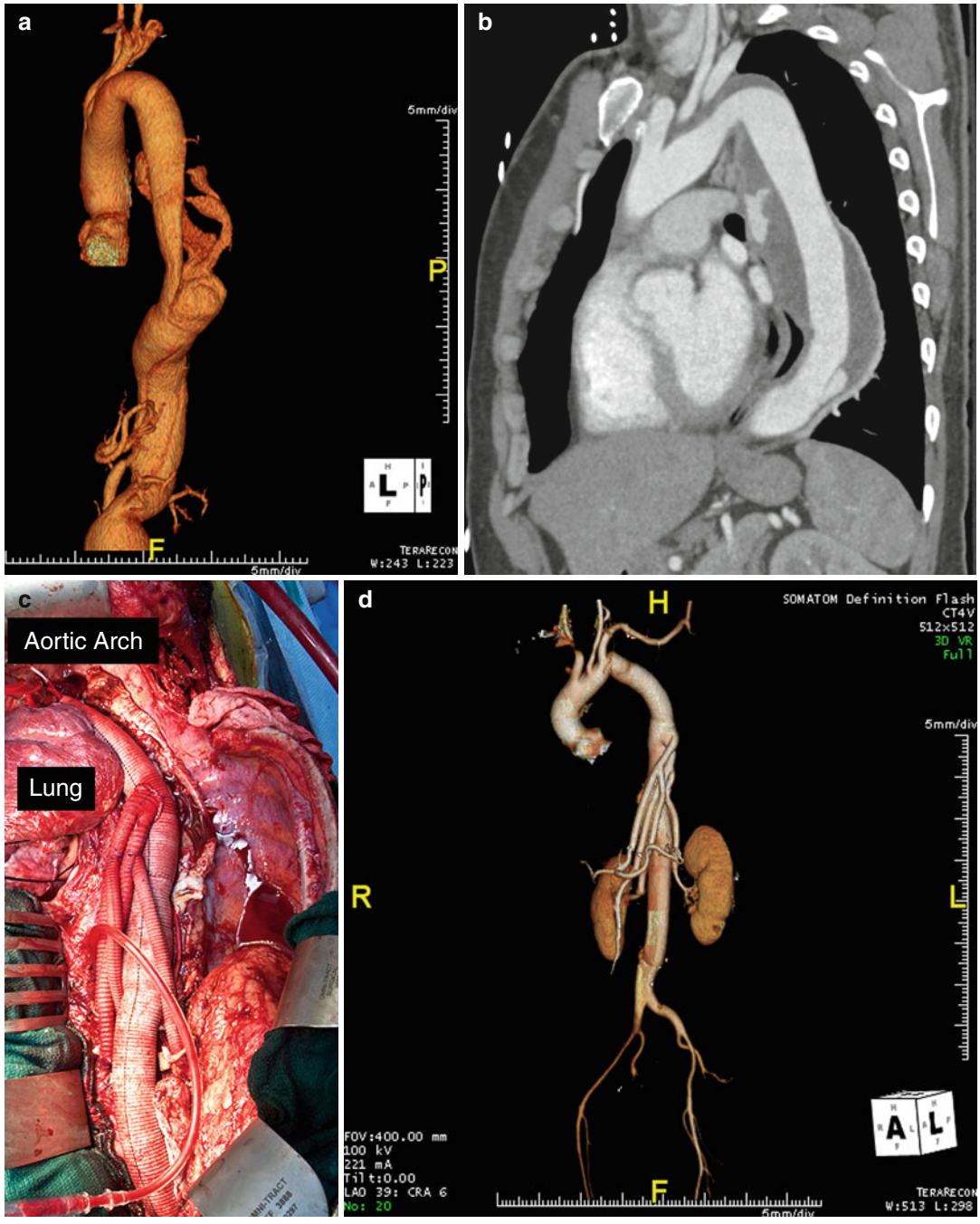


Fig. 21.12 (**a**–**d**) Young man with a progressive symptomatic Stanford type B aortic dissection and aneurysmal degeneration of the thoracic and abdominal aorta. The true lumen was so compressed that it resulted in significant renovascular hypertension (**a**, **b**). The patient was reconstructed using cardiopulmonary bypass, hypothermia, and a brief period of circulatory arrest to perform the upper aortic anastomosis. The visceral and renal arteries all were reconstructed with separate grafts, as shown in (**c**). Postoperative CT angiogram showing widely patent aortic and branch vessel reconstructions (**d**)

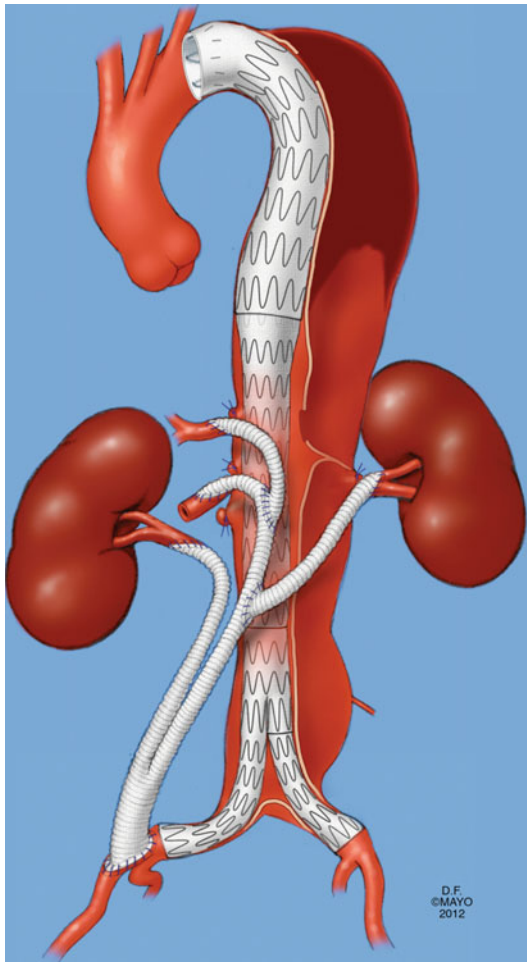


Fig. 21.13 Schematic representation of a hybrid reconstruction done for a combination of aortic dissection and thoracoabdominal aortic aneurysm. The visceral and renal arteries were reconstructed with a retrograde bypass graft originating from the right common iliac artery bifurcation. At a second stage, endoluminal stent grafts were placed to exclude the aneurysm and dissection. The branches to the visceral and renal arteries assume a variety of configurations, based on patient anatomy and depth (With permission of Mayo Foundation for Medical Education and Research. All rights reserved)

have become more complex since the advent of stenting. Careful surgical planning and technical execution of the operation are keys to success for patients with recurrent in-stent renal artery stenosis, complex fibromuscular disease or renal aneurysm, long segment thoracic or abdominal aortic coarctation, or complex thoracoabdominal and abdominal aortic aneurysm or dissection.

References

1. Bower TC, Duncan AA, Kalra M, Oderich GS, Toomey BJ, Gloviczki P. Current indications and results of surgical reconstructions for renal artery disease at Mayo Clinic. In: Gloviczki P, Shields RC, Bjarnason H, Becquemin JP, Gloviczki P, editors. Mayo Clinic international symposium. Torino: Edizioni Minerva Medica; 2011. p. 190–5.
2. Edwards MS, Corriere MA. Contemporary management of atherosclerotic renovascular disease. J Vasc Surg. 2009;50:1197–210.
3. White CJ, Olin JW. Diagnosis and management of atherosclerotic renal artery stenosis: improving patient selection and outcomes. Cardiovasc Med. 2009;6:176–90.
4. Shetty R, Amin MS, Jovin IS. Atherosclerotic renal artery stenosis: current therapy and future developments. Am Heart J. 2009;158:154–62.
5. Textor SC, Glockner JF, Lerman L, Misra S, McKusick MA, Riederer SJ, Grande JP, Gomez S, Romero JC. The use of magnetic resonance to evaluate tissue oxygenation in renal artery stenosis. J Am Soc Nephrol. 2008;19:780–8.
6. Mozes G, Bower TC, Kalra M, et al. Surgical outcome of renal artery revascularization for atherosclerotic disease. Presented at the Society for Vascular Surgery meeting, Chicago, Illinois, June 2005.
7. Hallett Jr JW, Textor SC, Kos PB, Nicpon G, Bower TC, Cherry Jr KJ, Gloviczki P, Pairolero PC. Advanced renovascular hypertension and renal insufficiency: trends in medical comorbidity and surgical approach from 1970 to 1993. J Vasc Surg. 1995;21(5):759–60.
8. Cherr GS, Hansen KJ, Craven TE, Edwards MS, Ligush Jr J, Levy PJ, Freedman BI, Dean RH. Surgical management of atherosclerotic renovascular disease. J Vasc Surg. 2002;35:236–45.
9. Hansen KJ, Cherr GS, Craven TE, Motew SJ, Travis JA, Wond JM, Levy PJ, Freedman BI, Ligush Jr J, Dean RH. Management of ischemic nephropathy: dialysis-free survival after surgical repair. J Vasc Surg. 2000;32:472–82.
10. Paty PS, Darling SP III C, Lee D, Chang BB, Roddy SP, Kreienberg PG, Lloyd WE, Shah DM. Is prosthetic renal artery reconstruction a durable procedure? An analysis of 489 bypass grafts. J Vasc Surg. 2001;34:127–32.
11. Marone LK, Clouse WD, Dorer DJ, Brewster DC, LaMuraglia GM, Watkins MT, Kwolek CJ, Cambria RP. Preservation of renal function with surgical revascularization in patients with atherosclerotic renovascular disease. J Vasc Surg. 2004;39:322–9.
12. Uzzo RG, Novick AC, Goormastic M, Mascha E, Pohl M. Medical versus surgical management of atherosclerotic renal artery stenosis. Transplant Proc. 2002;34:723–5.
13. Balzer K, Pfeiffer T, Rossbach S, Voiculescu A, Modder U, Godehardt E, et al. Operative vs interventional treatment for ostial renal artery occlusive disease (RAOOD): results of a prospective randomized trial. J Vasc Surg. 2009;49:667–74; discussion 674–5.

14. Crutchley TA, Pearce JD, Craven TE, Edwards MS, Dean RH, Hansen KJ. Branch renal artery repair with cold perfusion protection. J Vasc Surg. 2007;46: 405–12.
15. Carmo M, Bower TC, Mozes G, Nachreiner RD, Textor SC, Hoskin TL, Kalra M, Noel AA, Panneton JM, Sullivan TM, Gloviczki P. Surgical management of renal fibromuscular dysplasia: challenges in the endovascular era. Ann Vasc Surg. 2005;19:208–17.
16. Stanley JC, Criado E, Upchurch GR, Brophy PD, Cho KJ, Rectenwald JE. Pediatric renovascular hypertension: 132 primary and 30 secondary operations in 97 children. J Vasc Surg. 2006;44:1219–29.
17. Stanley JC, Criado E, Eliason JL, Upchurch Jr GR, Berguer R, Rectenwald JE. Abdominal aortic coarctation: surgical treatment of 53 patients with a thoracoabdominal bypass, patch aortoplasty, or interposition aortoaortic graft. J Vasc Surg. 2008;48:1073–82.
18. Graham LM, Zelenock GB, Erlandson EE, Coran AG, Oindenaur SM, Stanley JC. Abdominal aortic coarctation and segmental hypoplasia. Surgery. 1979;86: 519–29.
19. Upchurch Jr GR, Henke PK, Eagleton MJ, Grigoryants V, Sullivan VV, Wakefield TW, et al. Pediatric splanchnic arterial occlusive disease: clinical relevance operative treatment. J Vasc Surg. 2002;35:860–7.
20. Carr JA. The results of catheter-based therapy, compared with surgical repair of adult aortic coarctation. J Am Coll Cardiol. 2006;47:1101–7.
21. Fields CE, Bower TC, Cooper LT, Hoskin T, Noel AA, Panneton JM, Sullivan TM, Gloviczki P, Cherry Jr KJ. Takayasu's arteritis: operative results and influence of disease activity. J Vasc Surg. 2006;43(1): 64–71.
22. Patel R, Conrad MF, Paruchuri V, Kwolek CJ, Cambria RP. Balloon expandable stents facilitate right renal artery reconstruction during complex open aortic aneurysm repair. J Vasc Surg. 2010;51:310–6.
23. West CA, Noel AA, Bower TC, Cherry Jr KJ, Gloviczki P, Sullivan TM, Kalra M, Hoskin TL, Harrington JR. Factors affecting outcomes of open surgical repair of pararenal aortic aneurysms? A 10-year experience. J Vasc Surg. 2006;43(5):921–7; discussion 927–8.
24. Knott AW, Kalra M, Duncan AA, Reed NR, Bower TC, Hoskin TL, Oderich GS, Gloviczki P. Open repair of juxtarenal aortic aneurysms (JAA) remains a safe option in the era of fenestrated endografts. J Vasc Surg. 2008;47(4):695–701.
25. Quinones-Baldrich W, Jimenez JC, DeRubertis B, Moore W. Combined endovascular and surgical approach (CESA) to thoracoabdominal aortic pathology: a 10-year experience. J Vasc Surg. 2009;49(5): 1125–34.
26. Bischoff MS, Di Luozzo G, Griepp EB, Griepp RB. Spinal cord preservation in thoracoabdominal aneurysm repair. Perspect Vasc Surg Endovasc Ther. 2011;23(3):214–22.

Part V

Beyond Restoring Renal Blood Flow: The Future of Renovascular Disease and Renal Repair

Future Mechanisms of Reversing Kidney Injury

22

Lilach O. Lerman

Abstract

The search for effective strategies to protect the stenotic kidney or to facilitate recovery of kidney function has been the holy grail of the field of renal vascular disease and renovascular hypertension. Over the past few years, a number of novel interventions have been applied in an attempt to blunt and reverse functional and structural kidney remodeling distal to renal artery stenosis. Many of these interventions were designed to target specific deleterious cascades that are activated in the post stenotic kidney, such as mitochondrial injury, inadequate intrinsic regeneration mechanisms, downregulation of angiogenic pathways, and processes that promote inflammation or fibrosis. Emerging strategies show promise to revitalize the renal parenchyma regardless of restoration of proximal renal arterial patency. Such developments could improve our success in treating this important cause of kidney injury and cardiovascular morbidity and mortality.

Keywords

Renal artery stenosis • Inflammation • Fibrosis • Regenerative medicine • Revascularization

Endogenous Mechanisms for Restoration of Blood Delivery to the Stenotic Kidney

The irrefutable link between obstruction in the renal artery and a reduction in renal blood flow to generation of renovascular hypertension has been shown for the first time in 1934 by Goldblatt and colleagues in a dog model [1]. Since then, obstruction of the renal artery has been shown to induce reproducible increases in blood pressure in many experimental models. A decrease renal arterial luminal diameter has been subsequently shown in humans to account to between 5 and 10 % of cases of hypertension, which has been designated "renovascular hypertension."

Given this causal relationship, the observation that restoration of renal arterial luminal patency does not consistently lead to a decrease in blood pressure or improvement in renal function has

L.O. Lerman, MD, PhD
Division of Nephrology and Hypertension,
Mayo Clinic, 200 First Street, SW,
Rochester, MN 55905, USA
e-mail: lerman.lilach@mayo.edu

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6_22,

been baffling. As described in other chapters in this book, a large number of clinical trials has shown that revascularization of a stenotic renal artery does not consistently lead to improved control of blood pressure or an increase in glomerular filtration rate. A number of factors may account for this inability of revascularization to preserve renal function, as outlined in other sections of this book. The search for alternative strategies to protect the stenotic kidney or to facilitate recovery of kidney function by revascularization has been the holy grail of the field of renal vascular disease and renovascular hypertension.

It is important to remember that the kidney has potent endogenous mechanisms to facilitate and instigate its repair. One of the mechanisms activated during chronic and gradual obstruction of the renal artery is development of collateral circulation. The mechanisms and protective effects conferred by collateral vessels have been profoundly investigated in the coronary circulation, in which development of collateral vessels bypassing an obstructed coronary artery is linked to lower morbidity and mortality secondary to obstructive coronary artery disease. In the cardiac circulation, collateral vessels may emerge by recruitment of existing native collaterals or by *de novo* formation of new vessels [2]. The mechanisms involving recruitment of native collaterals in the ischemic territory seem to include dilatation of existing vessels during a decrease in renal perfusion pressure, a decrease in shear stress, and an increase availability of vasodilators. The angiogenic mechanisms that lead to formation of new vessels involve upregulation of pro-angiogenic growth factors in the ischemic territory, possibly mediated by increased influx of inflammatory cells, such as macrophages, that drill pathways for budding vessels.

Changes in shear stress are likely dominant mechanisms that underlie development of collateral vessels in the renal circulation. The collateral vessels in the kidney develop in three phases that again include the recruitment of native vessels that perfuse the kidney, which subsequently mature within about 1 day. This process is followed by new vessel formation, which instigates within a few days to form a network of collaterals around the obstructed segment. In addition to direct peri-stenotic collaterals, new vessels also seem to emerge from other vascular sources, including the aorta and other major arteries in the vicinity of the kidney, which enter either the renal hilum or penetrate the renal capsule [3].

Of course, elevation of blood pressure is a major mechanism by which the kidney can immediately respond to a decrease in renal perfusion pressure, and increase its perfusion pressure and blood supply. In response to injury to the renal parenchyma, the kidney decreases its filtration and metabolic function in order to decrease workload and minimize hypoxia. Several renal structures can enter a form of hibernation, which decreases tubular cell death and increases the regenerative capacity of the tubules [4]. The kidney also recruits resident stem cells that exist in several niches in the kidney, including the Bowman Capsule and the renal medulla. Circulating bone-marrow derived progenitor cells are mobilized in response to kidney ischemia and home to the stenotic kidney, stimulated by homing and injury signals such as stem cell derived factor-1, stem cell factor, as well as inflammatory mediators [5, 6]. These cells are retained in the kidney and seem to participate in its repair process [6]. Nevertheless, the majority of renal reparative cells is derived from resident stem cells rather than from circulating bone marrow derived stem cells.

Maneuvers to Decrease Revascularization Injury

Ischemic/Reperfusion and Mitochondrial Injury

Ischemia/reperfusion injury (IRI) has been studied predominantly in the context of acute kidney injury or kidney transplantation, and is suggested to involve an increase in oxidative stress due to the influx of oxygen and generation of reactive oxygen species at the reperfusion stage. Generation of reactive oxygen species under these circumstances appears to be mediated by mitochondrial injury and opening of the mitochondrial

permeability transition pore (mPTP). Depletion of adenine nucleotide levels also leads to opening of the renal mPTP, a high conduction channel that forms in the inner mitochondrial membrane during insults and may lead to apoptosis, inflammation, and fibrosis. Excessive reactive oxygen species production in turn exacerbates mPTP opening, leading to mitochondrial depolarization and release of cytochrome C from the inner mitochondrial membrane into the cytosol, one of the earliest stages in the cascade of apoptosis.

A recent study has shown in a rat model of IRI that administration of a drug that prevents mPTP opening protected mitochondrial structure and respiration during early reperfusion, accelerated recovery of ATP, reduced apoptosis and necrosis of tubular cells, and abrogated tubular dysfunction [7]. Furthermore, infusion of this drug during endovascular revascularization of the stenotic renal artery in pigs confers renal protection and results in improved renal function and structure 4 weeks later, compared to a group that was treated with saline vehicle [8]. These results implicate mPTP formation in the mechanism of injury during PTRA. This may also have an inflammatory component, because several studies have shown release of inflammatory mediators such as interleukin-6 or monocyte chemo attractant protein-1 during or shortly after revascularization of an occluded renal artery. Clearly, this area warrants additional research.

Pharmacological Approaches

Numerous studies have shown the substantial efficacy of HMG-CoA reductase inhibitors ("statins") for lowering plasma cholesterol levels. Furthermore, a considerable body of evidence has also established the pleotropic effects of statins, which involve improvement in vascular structure and function independent of their lipid lowering properties. In patients with renovascular disease, a recent population-based cohort study in over 4,000 patients older than 65 years of age has demonstrated that statin treatment is associated with improved prognosis in elderly patients with renovascular disease (adjusted hazard ratio of 0.51, 95 % confidence intervals 0.46–0.57) [9]. Furthermore, statins decrease the rate of progression of renal insufficiency and overall mortality, irrespective of the progression of the severity of the obstructive lesion in the renal artery [10], suggesting that statins exert their beneficial effects by targeting intrarenal injury.

Interestingly, statins have also shown impressive potency for treatment of acute conditions in cardiovascular medicine. In patients with acute coronary syndrome, statins appear to reduce hospital mortality when treatment is initiated of the first day of hospitalization [11]. Statin treatment also reduces cardiovascular events in patients with chronic kidney disease, who also have either stable coronary artery disease or acute coronary syndrome [12]. It is important to note that studies have shown that pre-treatment with high doses of statins in patients undergoing percutaneous coronary intervention led to a 44 % reduction in periprocedural myocardial infarction (odds ratio 0.56, 95 % confidence interval 0.44–0.71), as well as major adverse cardiac events within 30 days after the procedure [13]. These observations warrant similar studies to be performed in patients with renovascular disease undergoing percutaneous revascularization of the stenotic renal artery.

Additional intriguing possibilities to improve kidney function or the success of revascularization include the use of acetylcysteine, which has been proposed to offer some protection in contrast nephropathy. However, such studies remain to be performed.

Pre-conditioning

A recent study assessed the potential application of remote ischemic pre-conditioning to attenuate contrast medium induced acute kidney injury in patients with impaired renal function undergoing elective coronary angiography [14]. Pre-conditioning was applied by intermittent arm ischemia achieved by inflation and deflation of a blood pressure cuff. This study showed a substantial decrease in acute kidney injury in the patients undergoing remote ischemic pre-conditioning (odds ratio 0.21, 95 % confidence

interval 0.07–0.57). It would be interesting to apply a similar maneuver before revascularization to explore whether it could offer benefit to patients with renovascular disease

Enhancement of Intra-renal Microcirculation

Cell-Based Repair

Studies over the past decade have established the contribution of renal vascular disease to kidney damage in patients with an obstructive lesion in the main renal artery. However, microvascular disease, the hallmark of atherosclerotic disease, does not spare the kidney. In patients and animal models of renovascular disease, both obliteration and remodeling of intrarenal microvessels have been consistently observed in the post-stenotic kidney. This microvascular loss appears to correlate with poor recovery of the kidney following revascularization of the stenotic renal artery, confirming the contribution of the microcirculation to kidney injury. Loss of renal function and inability to recover it after revascularization seems to particularly correlate with the density of microvessels in the outer cortex [15], but the mechanistic underpinning of the specific significance of these microvessels remains to be shown. Yet, a corollary of these observations is that restoration of the renal microcirculation may potentially contribute to increase viability of the kidney and at least partial restoration of its function.

An important approach developed over the past few years involves cell-based therapy. Administration of endothelial progenitor cells, isolated and expanded from peripheral blood, into the stenotic kidney, improved renal function as well as the success of revascularization in a pig model of renal artery stenosis [16–18]. Such cells seem to be responding to specific injury and homing signals that are released from the stenotic kidney and facilitate homing, adherence, engraftment, and retention of circulating cells in injured organs [5]. Subsequently, mesenchymal stem cells isolated from adipose tissue, have also shown marked potency in improving kidney recovery after revascularization [19]. Endothelial progenitor cells appear to have more potent pro-angiogenic properties, which facilitate directly development of capillaries and small blood vessels, although they seem to confer greater salutary effects in the cortex than in the medulla [18]. Mesenchymal stem cells, on the other hand, are immunomodulatory and immune- privileged and have better efficacy in attenuating inflammation, an important component of the cascade leading to deterioration of kidney function and structure in renovascular disease [20]. In addition, they contribute to generation of blood vessels, although this might be achieved indirectly by blunting inflammation and fibrosis. These techniques lend themselves to potential use in humans. Several questions remain to be resolved, such as the feasibility of using allogeneic versus autologous cells, the optimal dose, route, and timing of cell delivery, etc. Clinical trials are needed to determine the feasibility of implementing this technique in human renovascular disease.

Angiogenic Growth Factors

The integrity, function, and density of renal microvessels can be enhanced by direct delivery of angiogenic growth factors. A recent study has shown that intrarenal delivery of vascular endothelial growth factor [21] or hepatocyte growth factor [22] can reverse kidney dysfunction and decrease its injury in an experimental renovascular disease swine model. These effects might be achieved by increased density of intra-renal microvessels, and speculatively collateral vessels as well. Overall, these renal protective effects of these angiogenic growth factors warrant additional studies and might also prove promising for translation to clinical medicine.

Anti-fibrotic Interventions

Tubulointerstitial fibrosis is a common denominator in many forms of kidney disease and characterizes the development of chronic ischemia. Studies suggest that in atherosclerotic renovascular

disease, kidney damage is mediated in part by increased deposition of extracellular matrix, as well as attenuated removal of scar tissue from the kidney interstitium, overall resulting in irreversible fibrosis to kidney tissue. One attractive approach to arrest deterioration of kidney disease would be to interfere with the fibrogenic process.

Most of the approaches that have been attempted so far have been experimental. Among the most common drugs that could be used for this purpose are blockers of the renin-angiotensin-aldosterone system, such as angiotensin converting enzyme inhibitor or angiotensin receptor blockers. These have been discussed in length in other sections of this book. In addition, endothelin-1 is an important mitogen, which is expressed in large amounts in the kidney, particularly in the renal medulla, and both its receptors, ET-A and ET-B, are also widely expressed in the kidney. The ET-A receptor usually mediates vasoconstriction and fibrogenesis, whereas ET-B contributes to release on nitric oxide and sodium secretion. A 6-week treatment with an ETA receptor blocker, initiated immediately after induction of renal artery stenosis, preserves kidney function and microvascular density and reduces apoptosis, inflammation, and glomerular sclerosis [23]. Therefore, ETA receptor blockade shows promise to slow the progression of renal injury and experimental renovascular disease. Blockade of the ETB receptor would likely be less favorable as it could block sodium excretion. Further studies are needed to examine the ability of endothelin-1 blockade to reverse existing kidney injury and the feasibility of using this approach in humans.

Other factors involved in renal fibrosis that are downstream to these mechanisms could include cell cycle inhibitors, inhibitors of the mitogen activated protein kinase (MAPK), or the transforming growth factor (TGF)-β pathway. In mice with two kidney, one clip (2K1C) hypertension, genetic depletion of the TGF-β effector smad-3, which in turn eliminates TGF-β signaling, significantly attenuated atrophy, interstitial fibrosis, and inflammation in the post stenotic kidney [24]. Therefore, abrogation of TGF-β smad-3 signaling confers protection against development of fibrosis and atrophy in the stenotic kidney. Taken together, these observations suggest that interference with fibrogenesis in the stenotic kidney may improve its fate.

Decrease in Tissue Inflammation/ Immune Responses

As described in another section of this book, development of both acute and chronic ischemia in the kidney is characterized by substantial inflammatory cell infiltration into the injured kidney. These subsequently release cytokines that induce damage in the kidney tissue. Activated fibroblasts in turn deposit extracellular matrix, contributed to the cascade of kidney tissue remodeling. Interference with this pathway could therefore, arrest one of the early steps in the vicious cycle that induces kidney injury in the post-stenotic kidney. Monocyte chemoattractant protein (MCP)-1 is an important chemokine, which mediates attraction of monocytes into sites of inflammation. Systemic blockade of MCP-1 improved renal blood flow, glomerular filtration rate, and endothelial function in the stenotic swine kidney and decreased tubular interstitial (albeit not vascular) oxidative stress, inflammation, and fibrosis [25]. Studies are needed to target specifically the population of inflammatory (M1) macrophages phenotype.

Statins, mentioned earlier, also decrease inflammation in many models of vascular injury. In pigs, statin upregulated inhibitors of TBF-β signaling and attenuated epithelial to mesenchymal transition, thereby decreasing renal fibrosis [26]. Studies in pigs with renovascular disease have shown the potential of antioxidants to decrease kidney injury [27, 28]. Chronic administration of antioxidants appears to be superior to acute administration, as it improves not only hemodynamic effects such as vasoconstriction, but also chronic remodeling of the kidney tissue [29]. In a rat model, the superoxide anion scavenger tempol has been shown to be more effective than an angiotensin II receptor blocker in increasing oxygen consumption efficiency in the stenotic kidney [30]. However, negative results

from clinical trials using antioxidants as the primary or secondary prevention do not encourage routine use of this approach in humans. The potential efficacy of immuno-suppressants such as, Sirolimus or Rituximab, are yet to be tested in renovascular disease, but could be attractive options to decrease activation of the innate immune system, which is evident in severely stenotic kidneys.

Novel Injury Modulators

Several novel modulators of tissue injury should also be considered and evaluated in the context of renovascular disease. For example, given the evident apoptosis observed in the stenotic kidney, prior to substantial fibrosis, survival factors such as humanin or stat3 could potentially be boosted pharmacologically in order to improve the survival of renal cells. Along the same lines, blockade of apoptosis, a pre-programmed cell death, might be able to salvage some of the apoptotic, tubular, endothelial, organelle, or glomerular cells. In addition, agents that can induce hibernation, or suspend animation, could be useful in slowing the process of remodeling towards irreversible kidney damage and allow renal cells to survive in under conditions of lower perfusion, pressure, and oxygen tension. Similarly, diuretics that inhibit sodium reabsorption and oxygen consumption can decrease the workload on tubules and improve kidney tissue oxygenation.

Summary: Future Directions

In summary, abundant new developments in our understanding of the mechanisms that lead to kidney dysfunction and structural alterations may afford opportunities of interrupting the vicious cycle that propagates kidney damage before it becomes irreversible. A number of such maneuvers that have been proposed or tested in the cardiovascular system might potentially be adopted to protect the kidney as well. Novel imaging methods now allow high-resolution illustration of kidney structure and function to an extent never shown before, and may allow identification and discrimination of new therapeutic targets. Multi-disciplinary collaboration of scientists involved in both basic and clinical research should be encouraged to acquire knowledge, increase our understanding of mechanisms, and develop methods for early detection, monitoring, and management of the post stenotic kidney. Such developments could improve our success in treating this important cause of kidney injury and cardiovascular morbidity and mortality.

References

1. Goldblatt H, Lynch J, Hanzal RF, Summerville WW. Studies of experimental hypertension: I. Production of persistent elevation of systolic blood pressure by means of renal ischemia. J Exp Med. 1934;59:347.
2. Zhu XY, Daghini E, Chade AR, Versari D, Krier JD, Textor KB, Lerman A, Lerman LO. Myocardial microvascular function during acute coronary artery stenosis: effect of hypertension and hypercholesterolaemia. Cardiovasc Res. 2009;83:371–80.
3. Krier JD, Crane JA, Eirin A, Zhu XY, Lerman A, Lerman LO. Hemodynamic determinants of perivascular collateral development in swine renal artery stenosis. Am J Hypertens. 2013;26:209–17.
4. Eirin A, Ebrahimi B, Zhang X, Zhu XY, Tang H, Crane JA, Lerman A, Textor SC, Lerman LO. Changes in glomerular filtration rate after renal revascularization correlate with microvascular hemodynamics and inflammation in swine renal artery stenosis. Circ Cardiovasc Interv. 2012;5(5):720–8.
5. Chade AR, Zhu XY, Krier JD, Jordan KL, Textor SC, Grande JP, Lerman A, Lerman LO. Endothelial progenitor cells homing and renal repair in experimental renovascular disease. Stem Cells. 2010;28:1039–47.
6. Eirin A, Gloviczki ML, Tang H, Gossl M, Jordan KL, Woollard JR, Lerman A, Grande JP, Textor SC, Lerman LO. Inflammatory and injury signals released from the post-stenotic human kidney. Eur Heart J. 2013;34:540–8.
7. Szeto HH, Liu S, Soong Y, Wu D, Darrah SF, Cheng FY, Zhao Z, Ganger M, Tow CY, Seshan SV. Mitochondria-targeted peptide accelerates ATP recovery and reduces ischemic kidney injury. J Am Soc Nephrol. 2011;22:1041–52.
8. Eirin A, Li Z, Zhang X, Krier JD, Woollard JR, Zhu XY, Tang H, Herrmann SM, Lerman A, Textor SC, Lerman LO. A mitochondrial permeability transition pore inhibitor improves renal outcomes after revascularization in experimental atherosclerotic renal artery stenosis. Hypertension. 2012;60:1242–9.
9. Hackam DG, Wu F, Li P, Austin PC, Tobe SW, Mamdani MM, Garg AX. Statins and renovascular

disease in the elderly: a population-based cohort study. Eur Heart J. 2011;32:598–610.
10. Silva VS, Martin LC, Franco RJ, Carvalho FC, Bregagnollo EA, Castro JH, Gavras I. Pleiotropic effects of statins may improve outcomes in atherosclerotic renovascular disease. Am J Hypertens. 2008; 21:1163–8.
11. Angeli F, Reboldi G, Garofoli M, Ramundo E, Verdecchia P. Very early initiation of statin therapy and mortality in patients with acute coronary syndrome. Acute Card Care. 2012;14:34–9.
12. Shibui T, Nakagomi A, Kusama Y, Atarashi H, Mizuno K. Impact of statin therapy on renal function and long-term prognosis in acute coronary syndrome patients with chronic kidney disease. Int Heart J. 2010;51:312–8.
13. Patti G, Cannon CP, Murphy SA, Mega S, Pasceri V, Briguori C, Colombo A, Yun KH, Jeong MH, Kim JS, Choi D, Bozbas H, Kinoshita M, Fukuda K, Jia XW, Hara H, Cay S, Di Sciascio G. Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: a collaborative patient-level meta-analysis of 13 randomized studies. Circulation. 2011;123:1622–32.
14. Er F, Nia AM, Dopp H, Hellmich M, Dahlem KM, Caglayan E, Kubacki T, Benzing T, Erdmann E, Burst V, Gassanov N. Ischemic preconditioning for prevention of contrast medium-induced nephropathy: randomized pilot RenPro Trial (Renal Protection Trial). Circulation. 2012;126:296–303.
15. Eirin A, Zhu XY, Urbieta-Caceres VH, Grande JP, Lerman A, Textor SC, Lerman LO. Persistent kidney dysfunction in swine renal artery stenosis correlates with outer cortical microvascular remodeling. Am J Physiol Renal Physiol. 2011;300:F1394–401.
16. Chade AR, Zhu X, Lavi R, Krier JD, Pislaru S, Simari RD, Napoli C, Lerman A, Lerman LO. Endothelial progenitor cells restore renal function in chronic experimental renovascular disease. Circulation. 2009;119:547–57.
17. Eirin A, Zhu XY, Li Z, Ebrahimi B, Zhang X, Tang H, Korsmo MJ, Chade AR, Grande JP, Ward CJ, Simari RD, Lerman A, Textor SC, Lerman LO. Endothelial outgrowth cells shift macrophage phenotype and improve kidney viability in Swine renal artery stenosis. Arterioscler Thromb Vasc Biol. 2013;33: 1006–13.
18. Ebrahimi B, Li Z, Eirin A, Zhu XY, Textor SC, Lerman LO. Addition of endothelial progenitor cells to renal revascularization restores medullary tubular oxygen consumption in swine renal artery stenosis. Am J Physiol Renal Physiol. 2012;302:F1478–85.
19. Eirin A, Zhu XY, Krier JD, Tang H, Jordan KL, Grande JP, Lerman A, Textor SC, Lerman LO. Adipose tissue-derived mesenchymal stem cells improve revascularization outcomes to restore renal function in swine atherosclerotic renal artery stenosis. Stem Cells. 2012;30:1030–41.
20. Zhu XY, Krier JD, Lerman A, Lerman LO. Mesenchymal stem cells and endothelial progenitor cells decrease renal injury in experimental swine renal artery stenosis through different mechanisms. Stem Cells. 2013;31(1):117–25.
21. Chade AR, Kelsen S. Reversal of renal dysfunction by targeted administration of VEGF into the stenotic kidney: a novel potential therapeutic approach. Am J Physiol Renal Physiol. 2012;302:F1342–50.
22. Stewart N, Chade AR. Renoprotective effects of hepatocyte growth factor in the stenotic kidney. Am J Physiol Renal Physiol. 2013;304:F625–33.
23. Kelsen S, Hall JE, Chade AR. Endothelin-A receptor blockade slows the progression of renal injury in experimental renovascular disease. Am J Physiol Renal Physiol. 2011;301:F218–25.
24. Warner GM, Cheng J, Knudsen BE, Gray CE, Deibel A, Juskewitch JE, Lerman LO, Textor SC, Nath KA, Grande JP. Genetic deficiency of Smad3 protects the kidneys from atrophy and interstitial fibrosis in 2K1C hypertension. Am J Physiol Renal Physiol. 2012; 302:F1455–64.
25. Zhu XY, Chade AR, Krier JD, Daghini E, Lavi R, Guglielmotti A, Lerman A, Lerman LO. The chemokine monocyte chemoattractant protein-1 contributes to renal dysfunction in swine renovascular hypertension. J Hypertens. 2009;27:2063–73.
26. Chade AR, Zhu XY, Grande JP, Krier JD, Lerman A, Lerman LO. Simvastatin abates development of renal fibrosis in experimental renovascular disease. J Hypertens. 2008;26:1651–60.
27. Chade AR, Rodriguez-Porcel M, Herrmann J, Zhu X, Grande JP, Napoli C, Lerman A, Lerman LO. Antioxidant intervention blunts renal injury in experimental renovascular disease. J Am Soc Nephrol. 2004;15:958–66.
28. Chade AR, Rodriguez-Porcel M, Herrmann J, Krier JD, Zhu X, Lerman A, Lerman LO. Beneficial effects of antioxidant vitamins on the stenotic kidney. Hypertension. 2003;42:605–12.
29. Chade AR, Krier JD, Rodriguez-Porcel M, Breen JF, McKusick MA, Lerman A, Lerman LO. Comparison of acute and chronic antioxidant interventions in experimental renovascular disease. Am J Physiol Renal Physiol. 2004;286:F1079–86.
30. Palm F, Onozato M, Welch WJ, Wilcox CS. Blood pressure, blood flow, and oxygenation in the clipped kidney of chronic 2-kidney, 1-clip rats: effects of tempol and Angiotensin blockade. Hypertension. 2010;55:298–304.

Index

L.O. Lerman, S.C. Textor (eds.), *Renal Vascular Disease*,
DOI 10.1007/978-1-4471-2810-6, © Springer-Verlag London 2014