SECTION 10

The Patient with Hypertension

CHAPTER 207

The structure and function of renal blood vessels

Karlhans Endlich and Rodger Loutzenhiser

Branching pattern and wall structure

The renal vasculature displays a high level of organization, reflecting the close relationship between structure and function in the kidney (Lemley and Kriz, 1994; Dworkin and Brenner, 1996). The branching pattern and the ultrastructure of renal vessels are specialized with respect to:

- the glomerular capillary network and its supply, where a high capillary pressure drives glomerular filtration
- the peritubular capillaries, where massive reabsorption takes place
- the renal medulla, where urine concentration is controlled by the countercurrent system.

Last but not least the renal vessels supply the metabolic needs of the kidney tissue. However, the high tissue perfusion of the kidney by far exceeds its metabolic demands. The vascular organization varies to a certain degree between species. The description presented in this chapter refers to the general pattern of the renal vasculature and includes peculiarities of the human kidney.

Each kidney is supplied by one renal artery. The renal artery branches at the hilus giving rise to the interlobar arteries which enter the renal parenchyma at the corticomedullary border. Each interlobar artery undergoes further divisions into the arcuate arteries. These vessels are called arcuate arteries because they run along the corticomedullary border resulting in an arch-like pattern.

Cortex

The next level of branching after the arcuate arteries yields the cortical radial arteries ('interlobular arteries' in the old but still frequently used nomenclature). The cortical radial arteries ascend radially from the arcuate arteries within the cortex. During their course through the cortex, the cortical radial arteries undergo several divisions and give rise to the afferent arterioles. Occasionally, an aglomerular branch of the cortical radial artery reaches the renal capsule at the kidney surface. The afferent arterioles of mid-cortical and superficial glomeruli originate exclusively from the cortical radial arteries, while the afferent arterioles of the juxtamedullary glomeruli frequently branch off at the level of the arcuate arteries.

The feeding vessel of the glomerulus, the afferent arteriole, branches into several primary capillaries from which the interconnected capillary network of the glomerular tuft is established. A detailed description of the glomerular capillary network can be found in Chapter 43. The glomerular capillary network is drained by the efferent arteriole which has already formed within the glomerulus. While the efferent arterioles of mid-cortical and superficial glomeruli divide into the capillaries of the peritubular network of the cortex, the wider efferent arterioles of juxtamedullary glomeruli become the vasa recta supplying the renal medulla.

The peritubular capillaries form a dense meshwork around the tubules of the cortex. In the cortical labyrinth, where the convoluted parts of the proximal and distal tubules are located, peritubular capillaries form a round-meshed network. In the medullary rays, containing the straight parts of the tubules, a long-meshed network of peritubular capillaries is observed. Both capillary meshworks are fed by mid-cortical and superficial efferent arterioles in such a way that different efferent arterioles participate in the supply of one nephron.

The blood of the cortical capillaries is collected by venules which drain into cortical veins. The cortical veins accompany the cortical radial arteries in the cortical labyrinth and empty into the arcuate veins. A part of the cortical capillary network is directly connected to the arcuate veins. In contrast to the arcuate arteries, which are end arteries, the arcuate veins form true anastomosing arches. In humans, a second type of cortical veins has been described. These veins collect the blood of the outer cortex, and traverse the cortex from the surface to the corticomedullary border, where they empty into the arcuate veins.

Medulla

The renal medulla is supplied by the efferent arterioles of the juxtamedullary glomeruli. As the juxtamedullary efferent arterioles enter the outer stripe, they branch into the descending vasa recta. Branches of the juxtamedullary efferent arterioles/descending vasa recta that feed true capillaries are sparse in the outer stripe. In contrast, a large part of descending vasa recta terminates in the inner stripe, where they form a dense round-meshed capillary plexus. The remainder of descending vasa recta reaches the inner medulla. Here the descending vasa recta successively terminate in a less dense long-meshed capillary plexus, which supplies the inner medulla.

The blood of the capillaries in the renal medulla is collected by venous vessels: the ascending vasa recta. The ascending vasa recta which drain the capillary plexus of the inner medulla successively join—as they emerge—the descending vasa recta

forming the vascular bundles. The vascular bundles traverse the outer medulla as compact anatomical structures. Ascending and descending vasa recta are arranged in a checkerboard pattern in vascular bundles. This countercurrent arrangement facilitates diffusional exchange between ascending and descending vasa recta, thereby minimizing dissipation of solutes from the inner medulla.

The capillary plexus of the inner stripe is drained by a second type of ascending vasa recta. These ascending vasa recta do not join the vascular bundles. Instead, they ascend in the interbundle spaces and traverse the outer stripe constituting the main 'capillaries' in this region. This type of ascending vasa recta possesses a large contact area with the tubules in the outer stripe. The close arrangement of ascending vasa recta and tubules is supported by a very scarce interstitium, which contrasts with the well-developed interstitium of the inner medulla. Both types of ascending vasa recta finally empty into the arcuate veins and into the distal part of the cortical veins.

Structure

The intrarenal arterial vessels up to the proximal part of the afferent arteriole are similar to the arteries and arterioles of the same size in other regions of the body. In the distal part of the afferent arteriole, the smooth muscle cells are replaced by the renin-secreting juxtaglomerular cells. Since the number of renin-positive cells in the afferent arteriole can vary considerably under experimental conditions, smooth muscle cells of the afferent arteriole are likely to transdifferentiate into renin-secreting cells and vice versa. Endothelial cells are coupled by gap junctions in the cortical radial artery and in the proximal afferent arteriole. By contrast, the coupling of the smooth muscle cells in these vessels appears to be sparse. However, myoendothelial contacts containing gap junctions are frequently observed in cortical radial arteries and afferent and efferent arterioles.

The glomerular capillaries are lined with fenestrated endothelium, the fenestrae of which do not possess diaphragms. The continuous basement membrane is covered by pericyte-like cells called visceral glomerular epithelial cells or podocytes. For a detailed description of the structure of the glomerular capillaries, the reader is referred to Chapter 43. The efferent arterioles of superficial and mid-cortical glomeruli usually possess one layer of smooth muscle cells, which becomes looser in the distal portions.

The peritubular capillaries are made up by a fenestrated endothelium. The fenestrae, which are closed by diaphragms, comprise about 50% of the capillary surface area. The proteinaceous nature of the diaphragms is responsible for the high permeability of the peritubular capillaries for water and small hydrophilic solutes. The cortical veins, which drain the peritubular capillaries, retain the fenestrated capillary wall structure implicating some reabsorptive function. It is only at the arcuate veins that smooth muscle cells emerge, providing the arcuate veins with a regular venous vessel wall.

The efferent arterioles of the juxtamedullary glomeruli clearly differ from their cortical counterparts in that they possess two to four layers of smooth muscle cells. The smooth muscle cell layers are progressively lost as the efferent arterioles of the juxtamedullary glomeruli branch into the descending vasa recta. The descending vasa recta are still lined by a continuous endothelium, but smooth muscle cells are replaced by contractile pericytes. The capillary plexus of the inner stripe and the inner medulla are made up of an endothelium with fenestrae closed by diaphragms—like the peritubular capillaries in the cortex. The ascending vasa recta keep the fenestrated capillary structure of the capillary plexus.

Vessel innervation

The intrarenal arteries, the afferent and efferent arterioles, and the descending vasa recta are innervated by postganglionic sympathetic nerves. These nerves regulate vascular tone via the release of transmitters with norepinephrine (noradrenaline) being the main transmitter. Neuropeptide Y has been identified as a frequent co-transmitter. Vasoactive intestinal peptide and substance P have also been described as co-transmitters (DiBona and Kopp, 1997).

Function of the renal vasculature

The kidneys receive > 20% of cardiac output corresponding to a renal blood flow (RBF) of about 1.0–1.2 L/min resulting in a tissue blood perfusion of about 4 mL/min/g. One human kidney contains about 1 million glomeruli, from which a mean single glomerulus blood flow (GBF) of 500 nL/min can be calculated. Considering this high blood perfusion of the renal tissue and the low oxygen extraction of 7%, it becomes immediately clear that meeting metabolic demands is not the central task of the renal vasculature. Instead, the main regulatory functions of the renal vasculature are to enable and to regulate glomerular filtration, peritubular reabsorption, and medullary urine concentration. To accomplish these functions, specific hydrostatic pressures have to be maintained in the different capillary networks of the kidney. In more recent years it has become apparent that, in addition to regulating renal function, the vasculature also plays a critical role in protecting the kidney against hypertensive injury. Both of these functions involve a regulation of the pressure profile within the renal microvasculature.

In the glomerular capillaries, the hydrostatic pressure ranges from 40 to 60 mmHg under physiological conditions as measured in various animal species. For filtration to occur, glomerular capillary pressure has to exceed the sum of the capillary oncotic pressure (~20 mmHg) and the hydrostatic pressure in Bowman's space (~12 mmHg), which is needed to push the filtrate and finally the urine through the tubular system into the renal pelvis. The unusual high hydrostatic pressure in the glomerular capillaries largely exceeds the sum of the two counteracting pressures (~32 mmHg), preventing filtration equilibrium being reached too early along the glomerular capillaries. In addition, the extremely high blood flow in the glomerular capillaries further ascertains that filtration proceeds practically along the whole length of the glomerular capillaries, without reaching filtration equilibrium too early, thereby maximizing glomerular filtration rate (GFR).

The situation is completely opposite in the peritubular capillaries. Here, the capillaries should take up what is reabsorbed by the tubules (mainly water and sodium chloride). Accordingly, hydrostatic pressures in peritubular capillaries range between 10 and 15 mmHg—well below the oncotic pressure, which has considerably increased to about 35 mmHg at the beginning of the peritubular network due to glomerular filtration. Though difficult to measure, the hydrostatic pressure in the interstitium is thought

to be close to 0 mmHg. As a result of extensive branching, flow velocity in peritubular capillaries is low, allowing the kidney to exploit the net inward filtration force until filtration equilibrium is reached.

Glomerular filtration

The regulation of glomerular filtration is a central task of the renal vasculature (Maddox and Brenner, 1996). To understand the importance of the renal vessels for the regulation of GFR, one has to consider the determinants of GFR. Single nephron GFR (SNGFR) depends on the ultrafiltration coefficient (K_f) and on the mean effective filtration pressure ($<p_{eff}>$):

$$SNGFR = K_f \times <p_{eff}>$$

The ultrafiltration coefficient K_f is the product of the filtration surface area (S) and the hydraulic permeability (k): $K_f = S \times k$. The hydraulic permeability (k) of glomeruli (20–30 nL/min/mm Hg per mm^2) is one to three orders in magnitude higher than the hydraulic permeability of continuous capillaries. By micropuncture of glomerular capillaries, it was demonstrated that the ultrafiltration coefficient K_f can change in response to physiologically relevant stimuli. However, it remains still unsettled whether changes in the ultrafiltration coefficient K_f are brought about by variation of the filtration surface area or by variation of hydraulic permeability or both. Mesangial contraction has been claimed to be able to reduce filtration area. On the other hand, changes in the molecular structure of the podocyte slit diaphragm may be able to alter hydraulic permeability. Continuing progress in elucidating the molecular equipment of podocyte foot processes will shed light on the regulation of the ultrafiltration coefficient K_f (cf. Chapter 43).

The regulation of the mean effective filtration pressure $<p_{eff}>$ is well understood. The effective filtration pressure is obtained by subtracting the capillary oncotic pressure and the hydrostatic pressure in Bowman's space from the capillary hydrostatic pressure. Because the capillary oncotic pressure increases along the capillaries due to filtration, which leaves the plasma proteins behind, effective filtration pressure decreases progressively. To obtain the mean effective filtration pressure $<p_{eff}>$, the effective filtration pressure p_{eff} therefore has to be integrated over the length coordinate of the capillaries. Both capillary hydrostatic pressure and blood flow affect the driving force for filtration directly, or indirectly by changing the rapidity with which filtration equilibrium is approached. Thus, elevating glomerular capillary pressure or glomerular capillary blood flow both increase SNGFR, with the former usually having the stronger impact on SNGFR. Both of these parameters are controlled by the renal vasculature.

The principal capacity to regulate glomerular haemodynamics resides in the pre- and post-glomerular arterial and arteriolar vessels. The glomerular capillaries form a branched and interconnected network, with many parallel flow channels and offer little haemodynamic resistance. While there are distinct differences in the function and properties of the differing segments of the pre-glomerular vasculature, the cortical radial artery and the afferent arteriole together are the primary determinants of pre-glomerular vascular resistance (R_{pre}). The post-glomerular vascular resistance (R_{post}) depends on the efferent arteriole. The resistance of peritubular capillaries and the venous vessels are negligible. GBF depends on the sum of the pre- and post-glomerular vascular resistances. By contrast, the ratio between the post-glomerular and total vascular resistances determines glomerular pressure (p_{glom}).

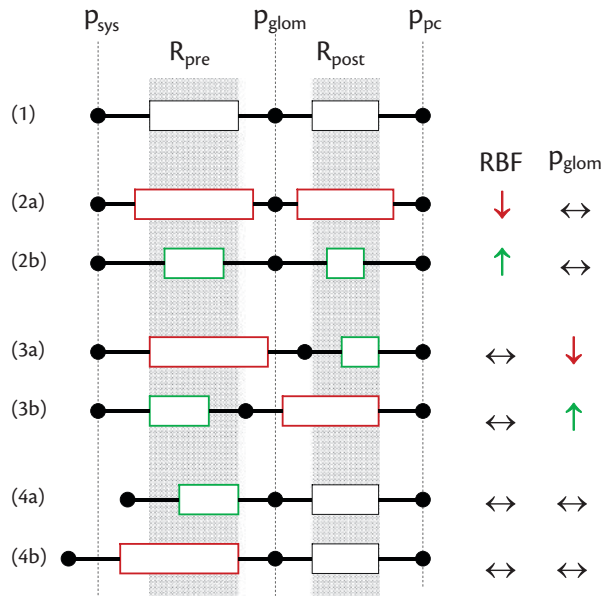

Fig. 207.1 Regulation of renal haemodynamics by pre- and post-glomerular vascular resistances.
The regulation of renal blood flow (RBF) and glomerular capillary pressure (p_{glom}) by pre-glomerular vascular resistance (R_{pre}) and by post-glomerular vascular resistance (R_{post}) is illustrated. (1) Baseline condition. (2) Proportionally equal changes in pre- and post-glomerular resistances affect RBF, while p_{glom} remains unchanged; (2a) vasoconstriction; (2b) vasodilation. (3) Shifting a part of resistance between pre- and post-glomerular vessels without changing total vascular resistance selectively affects p_{glom}, while RBF remains constant; (3a) pre-glomerular vasoconstriction and post-glomerular vasodilation; (3b) pre-glomerular vasodilation and post-glomerular vasoconstriction. (4) If systemic blood pressure (p_{sys}) varies, RBF and p_{glom} will be maintained by appropriate changes in pre-glomerular resistance; (4a) fall in blood pressure and pre-glomerular vasodilation; (4b) rise in blood pressure and pre-glomerular vasoconstriction. Peritubular capillary pressure (p_{pc}) is assumed to be constant in all examples. ↑ = increase; ↓ = decrease; ↔ = no change.

$$GBF \text{ depends on}: R_{pre} + R_{post}$$

$$p_{glom} \text{depends on}: R_{post} / \left(R_{pre} + R_{post}\right)$$

Pre- and post-glomerular vascular resistances can be adjusted independently, resulting in differing effects on GBF and p_{glom}. This is illustrated in Fig. 207.1. Small diameter changes evoke significant alterations in resistance, as calculated from Poiseuille's law. For example, a homogenous vasodilation of renal vessels by 10% will increase GBF by 46%.

Peritubular reabsorption

Several factors facilitate the massive reabsorption that occurs in the peritubular capillaries: low hydrostatic pressure, high oncotic pressure, and low flow velocity due to extensive branching. The fenestrated endothelium in the peritubular capillaries further facilitates the reabsorption of water and solutes. Fenestrae in the endothelium

are closed by diaphragms preventing leakage of plasma proteins into the interstitium, but also limiting the hydraulic permeability which is reported to be 0.6 nL/min/mmHg per mm^2 in peritubular capillaries. The extent to which hormones and other mechanisms regulate the permeability of peritubular capillaries remains largely unknown. The Starling forces favouring reabsorption in the peritubular capillaries facilitate glomerular–tubular balance, a phenomenon whereby an increase in GFR results in enhanced proximal tubular reabsorption. When GFR increases the plasma protein concentration in the capillaries is elevated, and the increased oncotic pressure enhances peritubular capillary reabsorption from the interstitium.

Medulla

The renal medulla receives only 10–15% of total RBF. Notwithstanding, medullary blood flow plays a crucial role in the urinary concentrating mechanism due to the countercurrent arrangement of descending and ascending vasa recta in the vascular bundles. This anatomical arrangement of vasa recta prevents the loss of solutes from the medulla, helping to maintain osmotic gradients. At the same time, oxygen and nutrients are unable to enter the inner medulla in relevant amounts, because they rapidly diffuse from descending into ascending vasa recta. Thus the special architecture of the medullary microcirculation accounts for the special metabolic situation and the high ischaemic vulnerability of the renal medulla.

Diameter changes of juxtamedullary efferent arterioles and of descending vasa recta control medullary blood flow independently from cortical blood flow. Many vasoactive hormones act on the vascular smooth muscle cells of juxtamedullary efferent arterioles and/or on the contractile pericytes of descending vasa recta. The endocrine hormones arginine vasopressin and angiotensin II in particular are potent constrictors of juxtamedullary efferent arterioles and descending vasa recta (Navar et al., 1996; Pallone and Silldorff, 2001). In addition, medullary blood flow is regulated by many paracrine hormones (Navar et al., 1996; Pallone and Silldorff, 2001; Pallone et al., 2003), including adenosine, bradykinin, endothelin, and nitric oxide. Renal medullary interstitial cells are a rich source of many paracrine vasoactive hormones.

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CHAPTER 208

Regulation of vasomotor tone in the afferent and efferent arterioles

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The cellular basis of vascular smooth muscle tone

An elevation in intracellular free calcium ion (Ca^{2+}) concentration ($[Ca^{2+}]_i$) plays a key role in the contractile responses of all muscle types. In striated and cardiac muscle, Ca^{2+} binds to troponin C causing a shift in the alignment of thin filament proteins, eliminating the hindrance and allowing the constitutively active myosin ATPase to facilitate cross-bridge cycling and contraction. By contrast, smooth muscle is regulated by proteins associated with the thick myosin filaments. Smooth muscle myosin ATPase is not basally active, but rather requires the phosphorylation of the associated 20 kDa regulatory myosin light chains (LC_{20}). As shown in Fig. 208.1, elevations in $[Ca^{2+}]_i$, by Ca^{2+} influx and Ca^{2+} released from the sarcoplasmic reticulum (SR), activate the Ca^{2+}-dependent enzyme myosin light chain kinase (MLCK). Activated MLCK phosphorylates LC_{20}, activating myosin ATPase and initiating vasoconstriction. Dephosphorylation is facilitated by myosin light chain phosphatase (MLCP). Reductions in $[Ca^{2+}]_i$ reduce MLCK activity, favouring LC_{20} dephosphorylation and vasodilation.

Vasoconstriction may also be associated with Ca^{2+} sensitization, which is characterized by an increase in contractile tone even at low $[Ca^{2+}]_i$. This is commonly achieved by activation of the small GTPase RhoA and its downstream target Rho-associated kinase (ROK). ROK phosphorylates the myosin targeting subunit of MLCP, inhibiting phosphatase activity, thereby shifting the dynamics in favour of LC_{20} phosphorylation. MLCP is also regulated by CPI-17, which inhibits MLCP when phosphorylated by protein kinase C (PKC). In smooth muscles expressing this system, PKC activation shift the balance towards phosphorylation, increasing tone at low levels of $[Ca^{2+}]_i$. While MLCK requires $[Ca^{2+}]_i$, LC_{20} is also a substrate for two Ca^{2+}-independent kinases: integrin-linked kinase (ILK) and zipper-interacting protein kinase (ZIPK) (Walsh 2011). At present we know little of the physiologic mechanisms involved in the regulation of ILK and ZIPK by agonists. Their actions on LC_{20}, however, differ qualitatively from those of MLCK. MLCK phosphorylates LC_{20} exclusively at serine-19 (Ser^{19}). By contrast, ILK and ZIPK phosphorylate LC_{20} at Ser^{19} and at threonine-18 (Thr^{18}). While the degree of LC_{20} phosphorylation at Ser^{19} may account for the level of steady-state force attained, the additional phosphorylation at Thr^{18} slows the rates of LC_{20} dephosphorylation and relaxation (Sutherland and Walsh, 2012). Of interest, LC_{20} diphosphorylation (phosphorylation at both Ser^{19} and Thr^{18}) has been implicated in vascular regions exhibiting vasospasm and may play a role in pathophysiologic vasoconstriction (Walsh, 2011).

Investigations into the roles of these diverse signalling pathways are hampered by the lack of specific inhibitors for key kinases, such as ILK and ZIPK. Inhibitors for ROK are available and several laboratories have shown ROK inhibition to attenuate afferent and efferent arteriolar responses to virtually every vasoconstrictor agonist tested (Cavarape et al., 2003a, 2003b; Nakamura et al., 2003; Roos et al., 2006; Inscho et al., 2009). Such findings suggest a broad role of ROK in receptor signalling or an important permissive role of basal activity (Puetz et al., 2009). In support of the latter, ROK inhibition blocks afferent arteriolar responses evoked by direct membrane depolarization, although this is not a uniform finding (Nakamura et al., 2003; Roos et al., 2006). Myogenic responses are also blocked by current ROK inhibitors (Roos et al., 2006; Shi et al., 2006). The specificity of kinase inhibitors is always a concern and the available ROK inhibitors are no exception (Puetz et al., 2009). Moreover, in addition to its role in smooth muscle signalling, ROK is involved in many other cell processes, including non-muscle cell motility and the regulation of the cytoskeleton (Burridge and Wennerberg, 2004). Accordingly, blockade of ROK may influence force transfer in a manner independent of its actions on LC_{20} phosphorylation.

Investigations of LC_{20} phosphorylation in afferent and efferent arterioles had been limited by the extremely small size of these vessels and minute amount of material for biochemical analysis. Recent advances in this area, however, have led to highly sensitive techniques allowing quantification of LC_{20} phosphorylation in single native renal arterioles. Recent studies using this approach reveal that angiotensin II evokes Ser^{19}-phosphorylation of LC_{20} in afferent arterioles; whereas endothelin-1 causes LC_{20} phosphorylation at both Ser^{19} and Thr^{18} (diphosphorylation) (Takeya et al., 2008, 2015). LC_{20} diphosphorylation suggests endothelin-1 elicits afferent arteriolar vasoconstriction, in part, by a Ca^{2+}-independent pathway. This finding may explain why the afferent arteriolar vasoconstriction elicited by endothelin-1 is less sensitive to L-type Ca^{2+} channel blockers and could provide insights into the role of endothelin-1 in pathologic renal vasoconstriction.

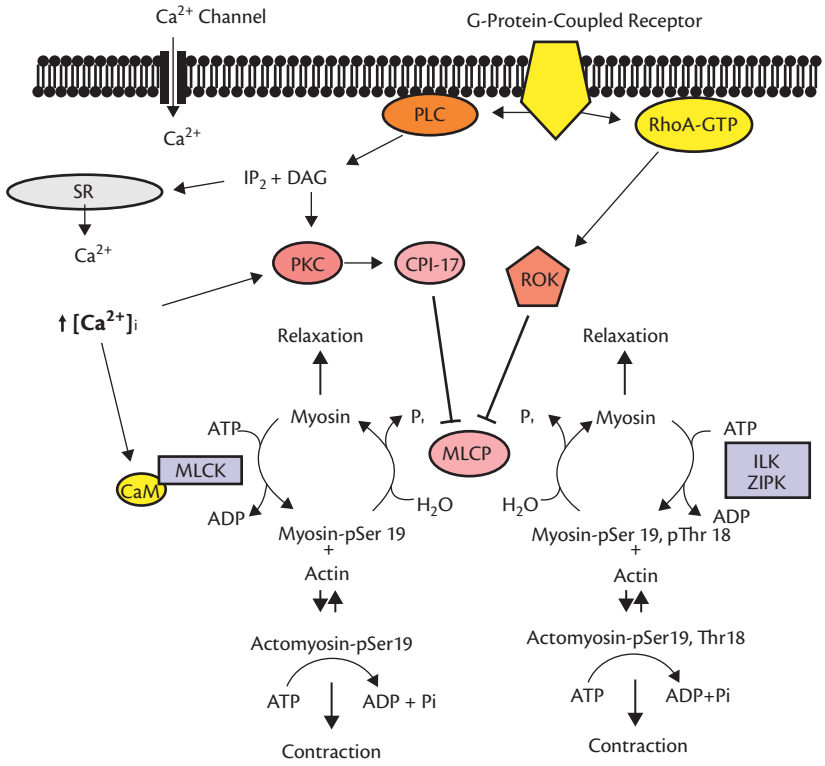

Fig. 208.1 Signal transduction pathways leading to smooth muscle contraction. G-protein coupled receptor activation or membrane depolarization elevate intracellular $[Ca^{2+}]_i$ by activating Ca^{2+} entry processes and/or initiating Ca^{2+} release from the sarcoplasmic reticulum (SR). Elevated $[Ca^{2+}]_i$ increases myosin regulatory light chain (ML_{20}) phosphorylation at serine-19 by calmodulin-dependent myosin light chain kinase (MLCK). Ca^{2+}-sensitization occurs by inhibition of myosin light chain phosphatise (MLCP) via Rho-associated kinase (ROK) and/or protein kinase C (PKC)/CPI-17 pathways. Ca^{2+}-independent LC_{20} diphosphorylation (at both serine-19 and threonine-18) can occur in some settings via integrin-linked kinase (ILK) and zipper-interacting protein kinase (ZIPK). The pathways regulating ILK and ZIPK activities are not resolved.

Differing smooth muscle mechanisms in afferent and efferent arterioles

Given the physiologic need to regulate GFR and the fact that afferent and efferent arterioles exert opposing effects on glomerular capillary pressure (P_{GC}), it is perhaps not surprising that the properties of the smooth muscles comprising these vessels are remarkably different. For example, afferent myocytes express the myosin heavy chain B isoform, which exhibits a faster cycling rate than the A isoform, which is expressed in efferent myocytes (Shiraishi et al., 2003). Even the morphology differs. Myocytes of the afferent arteriole have the typical spindle shape seen in most smooth muscles, whereas those of the efferent arteriole are bifurcated at each end (Loutzenhiser and Loutzenhiser, 2000). Most importantly, however, are the differences in Ca^{2+} entry mechanisms and in the influence of membrane potential. Like other resistance vessels, the afferent arteriole is exquisitely sensitive to membrane depolarization and hyperpolarization, whereas the efferent arteriole is not. The underlying reason for these differences is that only the afferent arteriole relies on voltage-activated Ca^{2+} channels.

Voltage-activated Ca^{2+} channels

Voltage-activated Ca^{2+} channels play a critical role in most resistance vessels and are activated by membrane depolarization. Dihydropyridine Ca^{2+} channel blockers such as nifedipine are highly selective for L-type Ca^{2+} channels and fully block the afferent arteriolar responses to most stimuli. Efferent arteriolar responses are insensitive to these agents, but contractile responses of the descending vasa recta are also prevented by L-type Ca^{2+} channel blockers (Zhang et al., 2010). Indirect methods evaluating Ca^{2+}influx in intact isolated arterioles using fluorescent probes also demonstrate that nifedipine selectively blocks Ca^{2+} entry in the afferent versus efferent arteriole (Loutzenhiser and Loutzenhiser, 2000). Recent 'patch-clamp' studies (Fig. 208.2) demonstrate in a direct manner a relatively large nifedipine-sensitive L-type Ca^{2+} current in native myocytes of afferent arterioles, but no detectable voltage-activated Ca^{2+} current in (cortical) efferent arteriolar myocytes (Smirnov et al., 2013). These findings are consistent with observations based on molecular approaches which demonstrated the expression of L-type Ca^{2+} channel protein in afferent, but not in cortical efferent arterioles (Hansen et al., 2001). Protein for L-type Ca^{2+} channels is found, however, in juxtamedullary efferent arterioles (Hansen et al., 2001), supporting an early report that juxtamedullary efferent arterioles may differ functionally from those of the cortex (Helou and Marchetti, 1997). Nevertheless, L-type Ca^{2+} channel blockers do not appear to reverse angiotensin II-induced vasoconstriction in juxtamedullary efferent arterioles (Carmines and Navar, 1989).

Messenger RNA for T-type Ca^{2+} channels was also found to be present in afferent arterioles, outer medullary vasa recta, and juxtamedullary efferent arterioles, but not in cortical efferent arterioles

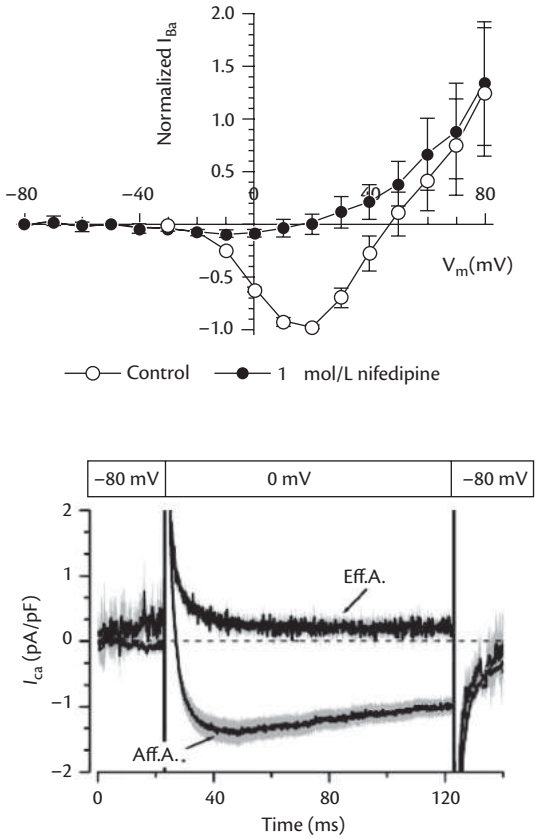

Fig. 208.2 Voltage-activated Ca^{2+} currents in afferent and efferent arteriolar myocytes. (Upper panel) Current/voltage plot illustrating nifedipine-sensitive L-type divalent cation current seen in afferent arteriolar myocytes (10 mM Ba^{2+}). Note complete blockade of current by nifedipine. (Lower panel) Inward Ca^{2+} current in afferent myocytes evoked by depolarizing voltage (0 mV from holding potential of −80 mV in 1.5 mM Ca^{2+}). Note lack of Ca^{2+} current in efferent arteriolar myocytes exposed to same protocol.
Figure modified with permission from Smirnov et al. (2013).

(Hansen et al., 2001). T-type Ca^{2+} channels are activated at more negative membrane potentials and, unlike L-type, rapidly inactivate, thus the nomenclature '*t*ransient' and '*l*ong-lasting'. A number of studies found that, unlike the dihydropyridines, Ca^{2+} channel blocking agents that act on both L- and T-type Ca^{2+} channels, such as mibefradil and efonidipine, elicit efferent as well as afferent arteriolar vasodilation (Hayashi et al., 2007). While this finding prompts speculation that T-type Ca^{2+} channels contribute to signalling in both vessels, a number of observations are inconsistent with this premise. Depolarization activates T-type Ca^{2+} channels, but does not elicit vasoconstriction in efferent arterioles and nifedipine does not block T-type Ca^{2+} channels, but fully dilates afferent arteriolar responses sensitive to mibefradil and efonidipine (Hayashi et al., 2003). It is suggested that the efferent arteriolar actions of T-type Ca^{2+} channel blockers may involve intracellular actions on SR Ca^{2+} release and/or indirect actions involving endogenous vasodilators and the suppression of renin release (Hayashi et al., 2003). If T-type Ca^{2+}channels are expressed in renal arterioles, the expression does not appear to result in functional sarcolemmal channels as T-type Ca^{2+} currents could not be detected in afferent or efferent arteriolar myocytes (Smirnov et al., 2013). It is important to note that presently there are no available data on Ca^{2+} currents in juxtamedullary efferent arteriolar myocytes. Patch clamp studies have, however, been performed on the smooth muscle like pericytes controlling the diameters of descending vasa recta capillaries, and L-type, but not T-type, Ca^{2+} currents were found (Zhang et al., 2010).

Ca^{2+} mechanisms in the efferent arteriole

Consistent with the lack of voltage-gated Ca^{2+} currents in the cortical efferent arteriole, membrane depolarization does not produce a contractile response in this vessel and does not cause an increase in $[Ca^{2+}]_i$ or a stimulation of Ca^{2+} influx, as assessed by Ca^{2+}-sensing fluorescent probes (Loutzenhiser et al., 1989; Carmines et al., 1993; Loutzenhiser and Loutzenhiser, 2000). Moreover, the contractile response of the *in situ* efferent arteriole to angiotensin II is not associated with membrane depolarization (Loutzenhiser et al., 1997). Nevertheless, angiotensin II does stimulate Ca^{2+} entry in the isolated efferent arteriole (Loutzenhiser and Loutzenhiser, 2000). However, while removal of extracellular Ca^{2+} greatly attenuates the sustained efferent arteriolar vasoconstriction evoked by angiotensin II, it does not completely abolish the response, suggesting both Ca^{2+}-dependent and Ca^{2+}-independent mechanisms are involved (Takenaka et al., 1997).

The Ca^{2+} entry mechanism in the efferent arteriole is not well characterized. Candidates include a TRP channel and store-operated Ca^{2+} entry. Store-operated Ca^{2+} entry (SOCE) mediates voltage-independent Ca^{2+} signalling in a number of cell types and is triggered by the depletion of intracellular Ca^{2+} stored in the endoplasmic reticulum (ER) or SR, generally via activation of phospholipase C (PLC) and the formation of inositol 1,4,5-trisphosphate (IP_3). Depletion of the ER or SR is sensed by STIM-1, which is thought to elicit SOCE by activating TRPC and/or Orai 1 Ca^{2+} channels (Hewavitharana et al., 2007). TRP channel proteins are expressed in afferent and efferent arterioles (Takenaka et al., 2002), but to date, there is no information on STIM-1 and Orai 1 expression.

SOCE is activated experimentally by depleting SR/ER Ca^{2+} stores using SR/ER Ca^{2+} ATPase (SERCA) inhibitors. This manipulation activates Ca^{2+} entry in native efferent myocytes, but not in afferent arteriolar myocytes (Loutzenhiser and Loutzenhiser, 2000). However, SERCA inhibitors do not initiate efferent arteriolar vasoconstriction nor do they fully block the subsequent response to angiotensin II (Takenaka et al., 1997; Imig et al., 2001). Efferent vasoconstriction can be evoked by manipulations that directly activate G-proteins and this response and the vasoconstriction elicited by angiotensin II are both blocked by PLC inhibition (Takenaka et al., 2002). Angiotensin II responses of the afferent and efferent arteriole are both mediated by the AT_1 receptor, however, selective inhibition of the G_i proteins abolishes only the efferent response to angiotensin II, suggesting important differences in receptor coupling. Efferent responses to angiotensin II are also partially inhibited by blocking PKCα, whereas this manipulation does not affect responses of the afferent arteriole or cortical radial artery (Roos et al., 2006). Finally, SKF-96365, a non-selective Ca^{2+} channel blocker, inhibits SOCE in single efferent myocytes, angiotensin II-mediated Ca^{2+} signalling in intact efferent arterioles, contractile responses of the *in situ* efferent arteriole, and Ca^{2+} currents in expressed TRP channels over similar concentrations (Loutzenhiser and Loutzenhiser, 2000; Takenaka et al.,

2002). While the identity of the voltage-independent Ca^{2+} channel in the efferent arteriole awaits final identification, the above findings indicate important roles not only for Ca^{2+} entry, but also for PLC activation, IP_3-mediated release of intracellular Ca^{2+} and Ca^{2+} independent signalling.

Regulation of membrane potential

PLC and IP_3-mediated release of SR Ca^{2+} also play critical roles in the activation of the afferent arteriole; however, this vessel is largely regulated by membrane potential and L-type Ca^{2+} channel activity. Stimuli that evoke afferent arteriolar vasoconstriction do so, at least in part, by membrane depolarization. For example, angiotensin II elicits depolarization and contractile responses of afferent arterioles correlate closely with magnitude of depolarization (Loutzenhiser et al., 1997). While details of the mechanisms mediating agonist-induced afferent arteriolar depolarization are not fully resolved, considerable indirect evidence implicates a role of Cl^- channels. Indanyloxyacetic acid, a Ca^{2+}-activated Cl^- channel blocker, reverses the vasoconstrictor and membrane depolarization responses to endothelin-1 and adenosine (Takenaka et al., 1992; Hansen et al., 2007) and the vasoconstrictor responses to angiotensin II and norepinephrine (noradrenaline) (Carmines, 1995; Takenaka et al., 1996). Similarly, reducing extracellular $[Cl^-]$, which causes a positive shift in the reversal potential of Cl^- channels, potentiates vasoconstrictor responses to angiotensin II and norepinephrine (Takenaka et al., 1996). The molecular identity of the Ca^{2+}-activated Cl^- channels involved in smooth muscle signalling is currently unknown. Activation exhibits an absolute requirement for elevations in $[Ca^{2+}]_i$, which may be initiated by the release of SR Ca^{2+} stores and possibly sustained by Ca^{2+} entry (Leblanc et al., 2005). Accordingly, inhibition of PLC or of IP_3-mediated Ca^{2+} release may prevent afferent arteriolar vasoconstriction by inhibiting Cl^- channel activation. However, there are obvious shortcomings of a model proposing that these channels are activated by Ca^{2+} release and that their activity is then sustained by the rise in $[Ca^{2+}]_i$ evoked by depolarization. This simplistic scheme would result in a positive feedback and the precisely graded vasoconstrictor responses that are observed could not be attained. This suggests a more complex regulation and emerging evidence implicates a possible role of protein kinases (Leblanc et al., 2005). It is interesting in this regard that Cl^- channels are also involved in activation of vasa recta pericytes and patch clamp studies of these cells reveal a Cl^- current that is activated by Ca^{2+} and regulated by a kinase, possibly similar to MLCK (Lin et al., 2010).

While membrane depolarization increases the open probability of L-type Ca^{2+} channels leading to vasoconstriction, membrane hyperpolarization has the opposite effect and results in afferent arteriolar vasodilation. In smooth muscle, outward or hyperpolarizing currents are generally due to an increased K^+ conductance. Four classes of K^+ channels are of importance in the renal vasculature: the inward rectifier (K_{IR}), the ATP-sensitive (K_{ATP}), the voltage-activated (K_V), and the large conductance Ca^{2+}-activated (BK_{Ca}). These K^+ channels play important roles in regulating afferent arteriolar reactivity and are likely to be involved in alteration in afferent arteriolar reactivity associated with pathologic states (Sorensen et al., 2012).

K_{IR} appears to play a dominant role in establishing the negative membrane potential of the afferent arteriole under resting conditions. Blockade of K_{IR} causes afferent arteriolar membrane depolarization and vasoconstriction, even when *in situ* vessels are perfused at very low arterial pressures (Chilton and Loutzenhiser, 2001). By contrast, blockade of K_{ATP}, K_V, or BK_{Ca} does not elicit renal vasoconstriction under basal conditions (Sorensen et al., 2012). K_{IR} is not generally expressed in large conduit arteries, but is commonly found to be a dominant current in resistance vessels (Ko et al., 2008). This is true in the kidney, as K_{IR} is not expressed in the arcuate artery (Prior et al., 1989) or proximal cortical radial artery, but its expression increases with decreasing size in the latter (Chilton et al., 2011). K_{IR} is also expressed in the myocytes of the afferent arteriole and efferent arteriole (Chilton et al., 2008), and in the pericytes regulating the descending vasa recta (Cao et al., 2006). Perhaps, in part, because of its limited distribution, we know little of how K_{IR} is regulated. In some vessels K_{IR} is inhibited by PKC (Ko et al., 2008). This does not appear to be the case with the afferent arteriole, as activation of PKC by phorbol ester does not elicit vasoconstriction (Kirton and Loutzenhiser, 1998).

The rectification properties of K_{IR} are modified by K^+ binding at the outer vestibule of the channel. Accordingly, while increasing extracellular K^+ ($[K^+]_o$) shifts the reversal potential to more positive values, this manipulation also increases the outward component of the current. Modest increases in $[K^+]_o$ (5–10 mM) thereby elicit hyperpolarization and vasodilation in vessels expressing K_{IR} (Ko et al., 2008). This mechanism is of physiologic importance in the cerebral and muscular vasculature, as increased activity causes elevations in $[K^+]_o$; however, its role in the kidney is not understood. It has been suggested that K^+, released by the endothelium, serves as a hyperpolarizing factor (EDHF) in endothelium-dependent vasodilation (Ko et al., 2008), but blockade of K_{IR} does not affect the EDHF response of the afferent arteriole (Wang and Loutzenhiser, 2002). Nevertheless modest increases in $[K^+]_o$ dilate the afferent arteriole and distal cortical radial artery. This manipulation also causes hyperpolarization of the efferent arteriole, but does not cause vasodilation since voltage-activated Ca^{2+} influx does not play a role in this vessel (Chilton et al., 2008).

K_{IR} channels also play an essential role in the transmission of electrical signals along small vessels, as transmission is prevented by blockade of these channels (Jantzi et al., 2006). Electrical coupling is achieved by gap junctions. Coupling along the continuous layer of endothelial cells provides the primary pathway for longitudinal conduction while signals are transmitted to the underlying myocytes via myoendothelial gap junctions and spread by gap junctions coupling adjacent myocytes (Bagher and Segal, 2011). Gap junctions are formed by the docking of hemichannels or connexons on adjacent cells. Each connexon is a hexamer of connexin subunits (Cxs). The pattern of Cx isoform expression within the renal microvasculature is similar to that seen in other vascular beds. Cx40 is the dominant endothelial isoform, but Cx37 and Cx43 are also expressed on these cells. Cx37, Cx40, Cx43, and Cx45 are all expressed on the myocytes and, of these, evidence suggests Cx45 to be predominant (Sorensen and Holstein-Rathlou, 2012). The distribution of K_{IR} and Cx expression, extending from the distal cortical radial artery to the vasa recta suggests the possibility of complex electrical communication. However, length constants in the range of 300–400 microns have been measured in the pre-glomerular vasculature (Steinhausen et al., 1997; Wagner et al., 1997). This is considerably smaller than those seen in other vascular beds (Bagher and Segal, 2011). We are only beginning to discern the physiologic

role of electrical coupling in the renal vasculature and how coupling is normally regulated and how it is altered by disease (Sorensen and Holstein-Rathlou, 2012). Electrical coupling provides for uniform constrictor responses to focal release of transmitters at nerve varicosities and likely plays a role in synchronizing segmental vascular responses. Newer techniques developed to quantify renal vascular coupling in physiologic settings may shed light on these issues (Holstein-Rathlou et al., 2011).

While K_{IR} is the dominant K^+ channel regulating membrane potential in the resting pre-glomerular resistance vessel, K_V and BK_{Ca} play important roles in modifying the responses to depolarizing stimuli. K_V and BK_{Ca} channels are both activated by membrane depolarization and voltage-activation of BK_{Ca} is potentiated by elevations in $[Ca^{2+}]_o$ (Ledoux et al., 2006). These channels become active when the vessels are exposed to depolarizing stimuli and serve as a 'break', opposing the depolarization and vasoconstriction. In addition to activating an inward current (e.g. Cl^- channel), agonists may inhibit K_V and BK_{Ca} through PKC, thereby facilitating depolarization (Ko et al., 2008). BK_{Ca} is also inhibited by 20-HETE (20-hydroxyeicosatetraenoic acid) (Roman 2002). BK_{Ca} is generally activated by vasodilators acting via protein kinase A (PKA) and protein kinase G (PKG) (Ko et al., 2008). K_V is similarly linked to vasodilation via the PKA pathway in some vascular tissues (Cole et al., 1996). The roles of K_V and BK_{Ca} in PKA- and PKG-dependent renal vasodilation are not clear. Blockade of BK_{Ca} does not prevent PKG-dependent renal vasodilation (Sorensen et al., 2012), however, the actions of PKG on smooth muscle are pleotropic in character, involving alterations in G-protein/receptor coupling, Ca^{2+} sequestration and LC_{20} phosphorylation pathways (Morgado et al., 2012) and blocking only one mechanism may not fully prevent vasodilation. The actions of PKA are similarly complex. Many questions remain in regard to the roles of K_V and BK_{Ca} in the renal microvasculature, including which channel subtypes are expressed and the cellular mechanisms involved in their regulation.

K_{ATP} is inhibited at physiologic levels of ATP and is not activated under basal conditions (Sorensen et al., 2012). The open probability of K_{ATP} increases when ATP levels are reduced, or more precisely when the ADP/ATP ratio is elevated (Cole and Clément-Chomienne, 2003). K_{ATP} is activated with metabolic stress and, for example, mediates hypoxia-induced vasodilation in several vascular beds, including the microvasculature of the kidney (Loutzenhiser and Parker, 1994). K_{ATP} is also activated, at normal levels of ATP, by PKA and plays a key role in the actions of some cAMP-dependent renal vasodilators (Cole and Clément-Chomienne, 2003; Sorensen et al., 2012). As pointed out above, however, not all cAMP-dependent vasodilators activate K_{ATP}. A striking example of this involves adenosine, which elicits renal vasodilation by activating high- and low affinity adenosine A_2 receptors (A_{2a} and A_{2b}) (Hansen and Schnermann 2003). Both receptors are coupled to cAMP in the afferent arteriole, but only the A_{2a} response involves K_{ATP} (Tang et al., 1999). A possible explanation relates to a 'compartmentalization' of cAMP. Thus, elevations in cAMP within differing receptor-effector micro-domains may evoke qualitatively different responses (Morgado et al., 2012). Like K_V and BK_{Ca}, K_{ATP} is also inhibited by PKC (Cole and Clément-Chomienne, 2003). Since K_{ATP} is not active in the basal state and is not activated by depolarization or $[Ca^{2+}]_i$, its inhibition does not facilitate depolarization, but rather affects the vessels ability to respond to specific vasodilators. Through this mechanism, for example, afferent arteriolar vasoconstriction elicited by agonists, such as angiotensin II, may be preferentially preserved in the face of vasodilators acting via K_{ATP} (Sorensen et al., 2012).

Differential regulation of pre- and post-glomerular resistance

A number of vasodilators preferentially act on the afferent arteriole. The most important, from a clinical viewpoint, is prostaglandin E_2 (PGE_2). PGE_2 is synthesized at multiple sites within the kidney and is the major renal prostaglandin produced (Hao and Breyer, 2008). A complex relationship exists between renal PGE_2 and angiotensin II. PGE_2, released from the macula densa in response to reduced distal delivery, acts on juxtaglomerular cells to evoke renin release and angiotensin II directly stimulates renal PGE_2 formation. There are four known PGE_2 receptors (EP1–EP4). The afferent arteriolar vasodilatory effects of PGE_2 are mediated by EP4 (Tang et al., 2000). This receptor is coupled to Gs and, when activated, increases cAMP. While the ionic mechanisms are not known, PGE_2 does elicit hyperpolarization of the *in situ* afferent arteriole (unpublished observation) and selectively blocks angiotensin II vasoconstriction of the afferent arteriole, without affecting the efferent arteriole (Edwards, 1985; Tang et al., 2000).

This interaction likely explains a previously confusing issue. Based on *in vivo* data, it had been argued that angiotensin II preferentially acts on the efferent arteriole, whereas, *in vitro* studies directly evaluating microvascular responses *in vitro* found angiotensin II potently constricts both afferent and efferent arterioles (Navar et al., 1996; Loutzenhiser et al., 2006). A likely explanation is that in settings associated with elevated PGE_2, angiotensin II does, indeed, preferentially constrict the efferent arteriole. This mechanism is critical in clinical settings associated with compromised renal perfusion. For example, blockade of angiotensin II may cause renal insufficiency in patients with bilateral renal arterial stenosis (Mimran and Ribstein, 1989). Similarly, PGE_2 attenuates abnormal pre-glomerular vasoconstriction in settings associated with hypotension or volume contraction. By interfering with this mechanism, non-steroidal anti-inflammatory drugs (NSAIDs) can trigger vasomotor acute renal insufficiency in susceptible patients. For this reason NSAID use is contraindicated in clinical settings as such as advanced congestive heart failure or hepatorenal syndrome (Akinbamowo et al., 2008).

Atrial natriuretic peptides and natriuretic peptide C (ANP, CNP) have unique effects on the renal vasculature. Of the three natriuretic peptide receptors (NPR), only NPR-A and NPR-B have known biologic activities. NPR-B is selective for CNP and dilates both the afferent and efferent arterioles (Endlich and Steinhausen, 1997). By contrast NPR-A is activated by ANP and while it dilates the afferent arteriole, it constricts the efferent arteriole, thereby elevating P_{GC} and GFR (Marin-Grez et al., 1986; Endlich and Steinhausen, 1997). Both receptors are membrane-bound guanylyl cyclases and the signalling is mediated by cGMP and PKG. As is seen with other cGMP-dependent vasodilators, ANP is more effective in dilating the afferent arteriole when tone is established by an agonist, rather than, for example, myogenic tone (Hayashi et al., 1990). This suggests that membrane hyperpolarization is not the prominent mechanism and explains the lack of ANP on renal autoregulation (Paul et al., 1987). The cellular mechanism underlying the efferent arteriolar vasoconstrictor response to ANP is unresolved, but likely involves compartmentalization of signalling, as cGMP is normally

associated with vasodilation. Of interest, ANP also constricts small splenic vessels by activating NPR-A receptors and cGMP is implicated in this action (Andrew and Kaufman, 2003).

Nitric oxide (NO) also acts via cGMP, but activates a cytosolic form of guanylyl cyclase and dilates both afferent and efferent arterioles. While cGMP-independent actions of NO are reported, these occur only at very high concentrations in the afferent arteriole and do not appear to be involved in its physiologic actions (Trottier et al., 1998). NO is formed in the kidney by endothelial NO synthase (eNOS) and by the macula densa, which expresses high levels of neural NO synthase (nNOS). Endothelium-dependent vasodilators, such as acetylcholine and bradykinin, act in part by NO. Shear stress, increased by elevated blood flow velocity or viscosity, also causes the endothelium to release NO and elicits renal vasodilation (Chen et al., 1989; Endlich et al., 1999). Shear stress may also play a significant role in the selective modulation of efferent arteriolar tone. As described by Elger et al. (1998) the most proximal segment of the efferent arteriole narrows and exhibits a conspicuous bulging of the endothelial cells into the vessel lumen. These endothelial cells express both eNOS and nNOS. The authors suggest that this site may be a shear sensor regulating efferent tone in response to increases in filtration fraction. Thus increases in haematocrit and blood viscosity may trigger NO-dependent efferent vasodilation, reducing P_{GC} and returning filtration fraction to normal limits. This interesting hypothesis has not been fully evaluated, but represents another possible mechanism of independently regulating efferent tone. Moreover, it is suggested that a loss of this mechanism for controlling efferent arteriolar tone may contribute to the renal injury associated with inhibition of renal NOS activity and possibly diabetic nephropathy (Griffin et al., 2012).

When eNOS and prostaglandin synthesis are inhibited, endothelium-dependent vasodilators continue to elicit responses. In this situation, the vasodilations are mediated by 'endothelium-derived hyperpolarizing factors' or EDHFs. Evidence suggests that multiple EDHFs mediate the afferent arteriolar responses to different dilators (Imig et al., 2001; Wang et al., 2003). A common component of the responses attributed to EDHFs, however, involves small and intermediate conductance Ca^{2+}-activated potassium channels (SK_{Ca} and IK_{Ca}) that are found predominantly in endothelial cells (Wang et al., 2003) and is inhibited by connexin-mimetic peptides (De Vriese et al., 2002). Accordingly this 'EDHF' appears not to be due to a released 'factor', but rather is mediated by electrical coupling between the smooth muscle and endothelium.

It is important to note that while NO, acting via cGMP, dilates both afferent and efferent arterioles, EDHF, acting by membrane hyperpolarization, dilates only the afferent arteriole (Wang and Loutzenhiser, 2002). Endothelial NO production is reduced by ageing, hypertension, diabetes, and by endogenous inhibitors associated with chronic kidney disease (Baylis, 2012). In such settings, the shift from NO to EDHF may result in higher efferent arteriolar tone thereby contributing to a disruption of P_{GC} regulation and glomerular hypertension.

The renal myogenic response

Over a century ago, Bayliss first described the constrictor responses exhibited by blood vessels exposed to elevated pressure (Bayliss, 1902). He coined the term 'myogenic' to indicate that the response did not depend on innervation, implicating a mechanism originating within the muscle wall. Bayliss intuitively suggested its purpose was to maintain a constant blood flow in the face of increased blood pressure, a concept that has survived to this day. Over the years, the term 'myogenic' has come to be applied to all smooth muscle responses elicited by elevated pressure or stretch. Much of what we know of the 'myogenic mechanism' is from studies of vessels much larger than the renal arterioles. In large vessels, myogenic responses may manifest as an ability to resist pressure-induced diameter increases, rather than vasoconstriction and increased resistance. While this type of response does not contribute to autoregulation of blood flow, it is likely important in preventing the formation of aneurysms, as pressure-induced increases in diameter cause a progressive increase in wall tension if unopposed. Just as there are differing myogenic responses, there are likely underlying differences in myogenic mechanisms.

In the renal vasculature, the intermediate and distal segments of the cortical radial artery and the afferent arteriole constrict upon exposure to elevated pressure and contribute to pressure-induced increases in renal vascular resistance. This response is prevented by L-type Ca^{2+} channel blockers and is associated with membrane depolarization (Harder et al., 1987). It is therefore not surprising that efferent arteriole does not exhibit a myogenic response. Unlike the response to agonists, myogenic vasoconstriction does not appear to involve Cl^- channels, but rather may be mediated by stretch-activated cation channels, as the response is blocked by Gd^{3+} and not altered by changes in the Cl^- gradient (Takenaka et al., 1998a, 1998b). It has also been suggested that degenerin/epithelial Na^+ channel (ENaC) proteins may serve as mechanosensors in renal resistance vessels (Drummond et al., 2008). While ENaC currents have yet to be demonstrated in vascular myocytes and the role of ENaC in the renal myogenic response is an area of current controversy, gene deletion of beta-ENaC was recently shown to impair renal autoregulation (Ge et al., 2012).

The role of K^+ channel modulation in the renal myogenic response is not resolved. Early studies implicated a critical role of 20-HETE and BK_{Ca} channel inhibition, but evidence suggests that BK_{Ca} is activated during the myogenic vasoconstriction, as its inhibition by other means potentiates the response (Sorensen et al., 2012). A complication impeding the final resolution of the 'myogenic mechanism' is that myogenic reactivity can be modulated by a variety of factors. Thus, 20-HETE is likely a modulator of the response. PKC has also been implicated in myogenic signalling and PKC inhibition blocks the afferent arteriolar myogenic vasoconstriction (Kirton and Loutzenhiser, 1998). K_V channels are an important target of PKC and pre-treatment with a K_V blocker abolishes the effects of subsequent PKC inhibition, suggesting that the basal activity of PKC plays a permissive role, but may not be involved in myogenic signalling (Kirton and Loutzenhiser, 1998). Thus, PKC may also be a modulator. Indeed, PKC activation by phorbol ester or by agonists such as angiotensin II and endothelin-1 markedly potentiates myogenic reactivity of the afferent arteriole (Kirton and Loutzenhiser, 1998). As discussed above (Fig. 208.1), PKC activation plays an important role in Ca^{2+} sensitization via phosphorylation of CPI-17 and inhibition of MLCP activity (Walsh, 2011). Of interest, phospholipase C, which is upstream of PKC, appears to be involved in mediating the myogenic response in the most proximal segments of the cortical radial

artery (Takenaka et al., 1998a), although again the nature of its involvement remains to be determined. The predominance of K_{IR} channels in the cortical radial arteries and afferent arteriole may also play a permissive role in the myogenic responses of these vessels, as K_{IR} amplifies electrical signalling (Smith et al., 2008) and the blockade of these channels inhibits myogenic vasoconstriction in the afferent arteriole (Chilton et al., 2011). Finally, ROK is widely implicated in myogenic signalling (Hill et al., 2009) and ROK inhibition completely abolishes the myogenic response of the afferent arteriole (Shi et al., 2006).

When evaluating the mechanisms underlying the renal myogenic vasoconstriction, a key consideration is the kinetics of the response. Biochemical pathways such as ROK-mediated Ca^{2+}-sensitization or IP_3-mediated release of SR Ca^{2+} stores are slower than mechanical mechanisms such as stretch-activation of a cation channel or stretch-induced Ca^{2+} release. The renal myogenic response is remarkably fast. Bayliss noted the speed of the renal vascular response in his original report, and also pointed out that, unlike the other vascular beds, the kidney's response to pressure is initiated almost immediately (Bayliss, 1902). More modern techniques reveal that the myogenic response of the *in vivo* intact kidney is initiated within 400 ms and proceeds with a half-time of 3–5 seconds (Young and Marsh, 1981; Just and Arendshorst, 2003). *In vitro* studies examining the afferent arteriolar response are consistent with these findings, reporting an initial delay of 200–300 ms and a time constant of 4 seconds (Loutzenhiser et al., 2002). It is important to note that the *in vitro* afferent arteriolar myogenic response is much faster than those of other myogenic arteries, such as isolated mesenteric and cerebral resistance arteries (Hill et al., 2009). These vessels typically exhibit delays of several seconds and have time constants in the range of 1–2 minutes. While the reasons behind these differences are not fully understood, it is likely that the smaller myocyte size, the greater surface area to volume ratio, and the high Ca^{2+} current density (Smirnov et al., 2013) all contribute to the kinetics of the afferent arteriole. As illustrated in Fig. 208.3 the myocytes comprising the afferent arteriole are exceedingly small compared, in this case, to the myocytes of the larger and much slower mesenteric resistance artery.

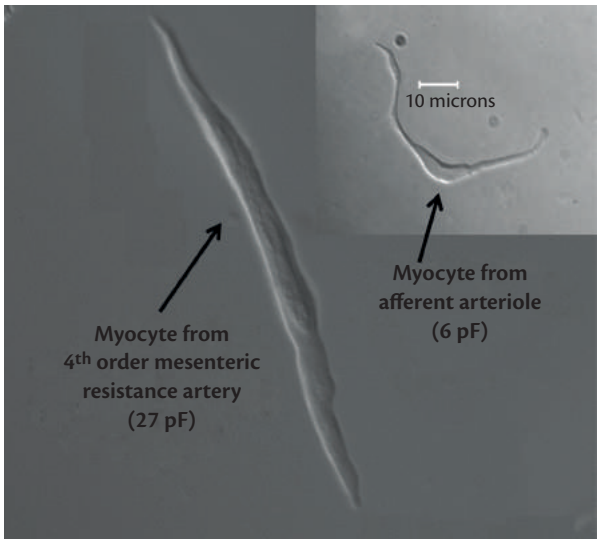

Fig. 208.3 Myocytes isolated from afferent arteriole and 4th order mesenteric resistance artery. Images presented at same scale (insert 10 microns). Note the extremely small size of afferent arteriolar myocyte compared to that of the mesenteric resistance artery. As described in text, smaller myocyte size may contribute to more rapid kinetics of the afferent arteriole.
Image of mesenteric artery myocyte was provided by Dr Francis Plane, University of Alberta.

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CHAPTER 209

Tubuloglomerular feedback, renal autoregulation, and renal protection

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Tubuloglomerular feedback

The kidneys filter and process the entire plasma volume approximately 60 times each day. Early investigators recognized that blood volume preservation required that the capacity to reabsorb this massive amount of filtrate must not be overwhelmed. Specifically, the delivery of filtrate to the distal segment, which normally reabsorbs only a fraction of the filtered load, must be precisely regulated. The unique anatomical relationship between the early distal nephron and its glomerular vascular pole, described more than 60 years ago by Goormaghtigh (1937), provided a potential site for such regulation. The early distal tubule of each nephron makes direct contact with the vascular pole of its originating glomerulus. This site, which includes the juxtaglomerular apparatus, is important for the regulation of renin secretion, stimulating secretion in response to reduced distal sodium delivery. It is also the site responsible for tubuloglomerular feedback (TGF) by which distal delivery of filtrate influences vascular tone.

Changes in distal delivery are sensed at the macula densa, the portion of the early distal tubule that contacts the glomerular vessels. Tubular fluid reaches the macula densa via the thick ascending limb (TAL). This segment actively transports Na^+, but is impermeable to water. Accordingly, as NaCl is reabsorbed, the filtrate is diluted. Since active transport is flow dependent, high flow rates are associated with elevated salt concentration and low flow rates with a more dilute tubular fluid. The NaCl concentrations thus reflect distal delivery and are sensed by the Na^+-K^+-$2Cl^-$ cotransporter (NKCC2) of the macula densa cells (Bell et al., 2003a). Increased distal delivery of filtrate results in elevated substrate for NKCC2, increasing the activity of the transporter and altering membrane potential and/or $[Ca^{2+}]_i$, causing the macula densa cells to release ATP (Bell et al., 2003b). Artificially increasing TAL flow rate or directly applying NaCl to the macula densa elicits afferent arteriolar vasoconstriction, reducing glomerular capillary pressure (P_{GC}) and glomerular filtration rate (GFR). The return of GFR thus completes the TGF 'feedback' loop initiated by the increase in GFR and distal delivery. ATP itself is capable of eliciting afferent arteriolar vasoconstriction, and ATP has been suggested to contribute directly to TGF through activation of P2 purinergic receptors (Nishiyama and Navar, 2002). Prevailing evidence suggests, however, that the TGF response is mediated primarily by adenosine which is formed by the ecto-5′-nucleotidase-dependent dephosphorylation of ATP and constricts the afferent arteriole by acting on the adenosine A_1 receptor (Schnermann and Briggs, 2008). It is of interest that adenosine is a relatively weak constrictor of the afferent arteriole when acting alone and it is only in the presence of angiotensin II, acting on AT_1 receptors, that adenosine exerts a strong afferent arteriolar vasoconstrictor response (Schnermann and Briggs, 2008). Thus, angiotensin II is a required co-factor of the TGF response. Fig. 209.1 summarizes the prevailing view of the mechanisms underlying the TGF response.

Much of this pathway has been discerned from studies using gene deletion. Thus, deletion of either the adenosine A_1 receptor, ecto-5′-nucleotidase, or the angiotensin II AT_{1a} receptor will fully prevent the expression of a TGF response (Schnermann and Briggs, 2008). Curiously, mice lacking TGF do not appear to exhibit disturbances in volume homeostasis. However, the requirement for angiotensin II suggests that TGF might be more important in volume-depleted states. In any event, a more complete understanding of the physiologic role of TGF in volume regulation awaits additional investigations. The vast clinical experience with patients receiving chronic treatment with loop diuretics also indicates that compensatory mechanisms prevent excess volume loss even when TGF mechanisms are impaired. By blocking the NKCC transporter, loop diuretics not only increase distal delivery, but also block the TGF response.

The unique anatomical relationship between the early distal tubule and the vascular pole of the glomerulus and the ability of the macula densa to sense and respond to alterations in distal delivery clearly point to an important regulatory role. While the classic view of the feedback response is that of a pre-glomerular vasoconstriction that limits excess distal delivery, it is important to note that normal renal function critically requires that an adequate level of distal delivery be maintained. The primary sites at which sodium reabsorption is regulated in response to changes in blood volume are located in the late distal tubule and the cortical collecting duct. For Na^+ to be regulated, filtrate must reach these sites. Indeed, while tubular mechanisms may compensate for increases in distal delivery, severely reduced distal delivery is generally associated with volume retention. This is seen, for example, in patients with congestive heart failure and cirrhosis. In this regard, it is important

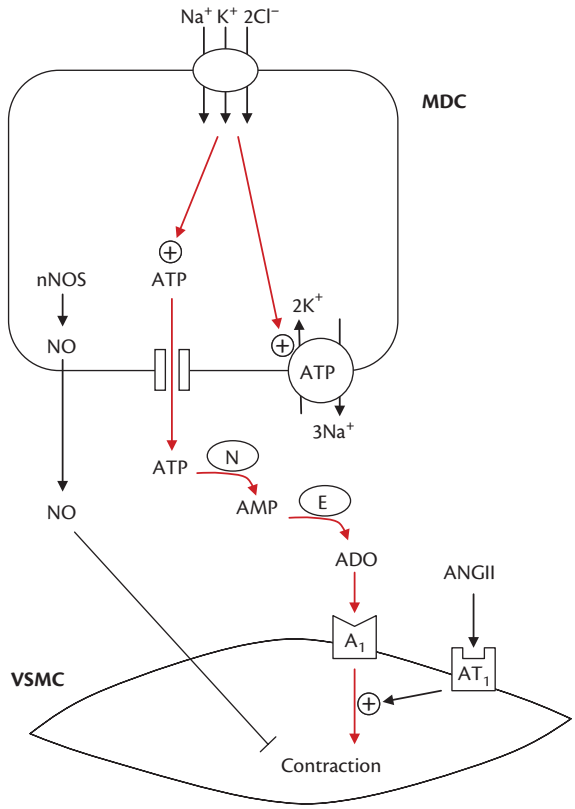

Fig. 209.1 Signalling pathway of tubuloglomerular feedback (TGF). Signal transduction starts at the luminal side of macula densa cells (MDC) with NaCl transport by the Na^+-K^+-$2Cl^-$-cotransporter. High rates of distal delivery trigger the release of ATP, which is converted to adenosine (ADO) via the actions of nucleoside triphosphate diphosphohydrolase-1 (N) and ecto-5′-nucleotidase (E). Increasing concentrations of Ado in the basolateral compartment of MDC and diffusion to vascular smooth muscle cells (VSMC) of the afferent arteriole trigger vasoconstriction. A_1 = adenosine A_1 receptor; AT_1 = angiotensin II (ANGII) AT_1 receptor; nNOS = neuronal nitric oxide synthase.

to note that severe reductions in distal delivery do cause the macula densa to release prostaglandin E_2 (PGE_2) (Peti-Peterdi et al., 2003), an important renal vasodilator. Less is understood concerning the regulation of macula densa nitric oxide (NO) production, however, reduced TAL Na^+ transport and blockade of NKCC increase tubular NO levels (Levine et al., 2004). A TGF-mediated vasodilator response, involving PGE_2 would be an effective means of attenuating inappropriate pre-glomerular vasoconstriction if distal delivery were impaired. Future investigations addressing this issue are needed.

Autoregulation of renal blood flow and glomerular filtration rate

The kidney has an intrinsic ability to regulate both blood flow and GFR in the face of changes in perfusion pressure. This autoregulation is accomplished by the myogenic response and TGF. Experimentally, autoregulation is demonstrated by subjecting the kidney to sudden increases in blood pressure, as, for example, in the early studies of Bayliss (1902), or by clamping the aorta above the kidney and following the response to reduced pressure. It is important to note at the onset that, although the responses evoked by these two procedures are both termed 'renal autoregulation', different vascular mechanisms may be involved. Reductions in pressure reduce the levels of myogenic- and TGF-dependent pre-glomerular tone, and to the extent that each contributes to basal vascular tone, both contribute to autoregulation. As pressure is further reduced, the autoregulatory range of GFR may exceed that of blood flow. Reduced pressure and reductions in GFR that impair distal delivery stimulate the release of renin and PGE_2. As described in Chapter 208, in the presence of PGE_2, angiotensin II predominantly constricts the efferent arteriole, preserving P_{GC} and GFR.

Increases in blood pressure activate the myogenic mechanism and the constrictor TGF response. Each acts selectively on pre-glomerular vessels simultaneously regulating blood flow and GFR. The relative contribution of the two mechanisms has been the subject of a long-standing debate. The myogenic mechanism is capable of eliciting stronger responses over a wider range of pressure changes and is likely more important at higher pressures. Consistent with this view, the myogenic component appears to be dominant in dynamic autoregulatory studies employing transfer function and frequency domain analyses (Holstein-Rathlou and Marsh, 1994). It is important to note that, while there is relatively little myogenic tone at basal blood pressures of 80–90 mmHg, the TGF mechanism is known to 'reset' in such a way as to maintain maximal sensitivity around the new set point (Thomson et al., 1998). Accordingly, alterations in TGF-dependent tone may be more important in the response evoked experimentally by acutely reducing pressure. This type of autoregulatory response is impaired in mice lacking the adenosine A_1 receptor and in rats treated with furosemide to block TGF (Hashimoto et al., 2006). When responses are evoked by acute increases in pressure, furosemide blocks a fraction of the response (Just and Arendshorst, 2003). Accordingly, while both the myogenic mechanism and TGF contribute to autoregulation, their relative contributions may vary with different experimental conditions.

Fluctuations in blood pressure occur over a broad range of time scales. Autoregulation can occur only over those frequencies at which compensatory changes in vascular resistance are fast enough to prevent corresponding changes in blood flow. Fig. 209.2 illustrates a blood pressure power spectrum seen in a conscious rat. Aside from the peak due to the heart rate (6 Hz in the rat), the larger-amplitude fluctuations are due to lower frequency events, such as diurnal variations in activity. Shown in the top of this figure are the natural frequencies of the myogenic mechanism and TGF as revealed by frequency domain analysis (Holstein-Rathlou and Marsh, 1994). As previously described, the myogenic vasoconstriction occurs with little delay and proceeds with a time constant of approximately 4 seconds. Accordingly, the upper frequency at which adjustments in myogenic tone can compensate for changes in pressure is in the range of 0.2–0.3 Hz. By contrast, activation of TGF requires that the pulse wave of increased GFR travels the length of Henle's loop before being sensed at the macula densa. This signal then triggers ATP release, adenosine formation, and diffusion to the afferent arteriole. Obviously, the TGF response is much slower and is capable of compensating for blood pressure changes at much lower frequencies (0.05 Hz or slower). The two systems obviously interact since both affect the afferent arteriole and the marked differences in the response times complicate this interaction. The kinetics of the myogenic response clearly sets the upper

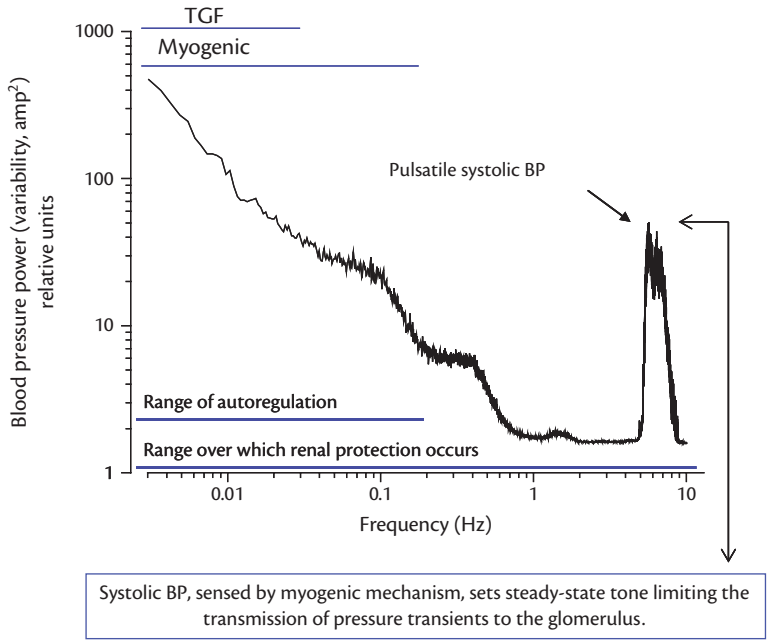

Fig. 209.2 Blood pressure power spectrum of conscious rat. Blood pressure variability, plotted as 'power' (amplitude squared), at different frequencies. Note that below the heart rate (6 Hz in rat), slower frequency events exhibit higher power. Operating frequencies of myogenic mechanism (< 0.3 Hz) and TGF (< 0.05 Hz) limit frequency range over which vasculature can compensate for pressure changes to achieve autoregulation. Renal protection, however, must be attained over full range of frequencies. This is achieved by ability of afferent arteriole to set steady-state myogenic tone in response to changes in the rapidly oscillating systolic blood pressure.
Figure modified with permission from Loutzenhiser et al. (2006).

limit of autoregulation (Fig. 209.2). Accordingly, compensatory changes in renal vascular resistance can prevent changes in GFR and blood flow from occurring in response to pressure fluctuations of 3–4 seconds and longer (< 0.3 Hz). As shown in Fig. 209.2, this is the frequency range at which the largest amplitude fluctuations in blood pressure occur.

Renal autoregulation provides a constant filtered load and stabilizes the pressure profile within the microcirculation. Accordingly, a widely held view is that renal autoregulation is essential for normal renal function and volume homeostasis. Nevertheless, a growing number of animal models demonstrate severe impairments in renal autoregulation and none display abnormalities in volume regulation (Loutzenhiser et al., 2006). Autoregulation is experimentally defined as the acute vascular response that defends renal blood flow and GFR from sudden changes in blood pressure. It is generally assumed that loss of this acute response would affect the renal haemodynamic impact of sustained hypertension. Evidence suggests, however, that renal blood flow and GFR are stabilized in the face of chronic changes in blood pressure even when acute autoregulatory responses are impaired (Loutzenhiser et al., 2006). It has been suggested that a third renal autoregulatory mechanism with slower kinetics may be involved, although its nature, at present, is unresolved (Just et al., 2001, 2003; Siu et al., 2009).

Importance of autoregulatory mechanisms in renal protection

The glomerular capillaries are exposed to mechanical forces arising from the pulsatile nature and normally high value of P_{GC} (Drumond and Deen, 1991). Increases in P_{GC} beyond normal levels are strongly linked to the development of glomerular injury and clearly contribute to the progression of glomerulosclerosis and chronic kidney disease (CKD) (Bidani and Griffin, 2002; Endlich and Endlich, 2012). Indeed hypertension is a leading cause of end-stage renal disease (ESRD) and contributes to the primary role of diabetes in ESRD. However, in spite of the clear link between renal injury and hypertension the vast majority of hypertensive patients are spared, as the individual risk is < 0.5% (Bidani et al., 2013). Nevertheless hypertension plays a major role in the progression of most forms of CKD including diabetic nephropathy. These observations are explained by the existence of renal protective mechanisms that normally prevent the transmission of systemic hypertension to the glomerular capillaries. These are the same mechanisms that contribute to the acute autoregulatory response.

While a loss of the acute autoregulatory response does not impact on volume regulation or a chronic stabilization of renal haemodynamics, this impairment is invariably associated with an increased susceptibility for hypertensive renal injury in animal models and similar results are reported for humans (Loutzenhiser et al., 2006). Thus for the clinician, the primary importance of renal autoregulation may be its value as an indicator of renal protection. Loss of renal autoregulatory capacity may thus suggest the need for aggressive treatment of hypertension.

The use of radiotelemetry has allowed an accurate assessment of the quantitative relationships between blood pressure and glomerular injury in animal models. Such studies illustrate that kidneys with intact autoregulation are protected against hypertensive injury when blood pressures remain within the autoregulatory range. It is only when blood pressures exceed the limit of autoregulation that glomerular injury is seen. However, when autoregulation is impaired, as, for example, in the rat remnant kidney model of CKD, the vulnerability to such injury is markedly augmented and

occurs at much lower pressures. In both situations, the glomerular injury correlates quantitatively with the increases in blood pressure (Bidani et al., 2013). An identical relationship between injury and blood pressure is seen in CKD animals receiving antihypertensive therapies. In general, reductions in glomerular injury correlate with the blood pressure-lowering effects without affecting the slope relationship between the two parameters. The clear exceptions are the L-type Ca^{2+} channel blocking agents, which attenuate the hypertension but increase the slope, such that more injury occurs at any level of blood pressure increase (Griffin et al., 1995; Griffin and Bidani, 2008). This effect is due to the general ability of Ca^{2+} channel blockers to dilate the afferent arteriole and to the specific effects of these agents on the mechanisms mediating acute autoregulation.

Of the autoregulatory mechanisms, the faster myogenic response is likely most important in providing renal protection (Bidani, et al. 2009). The component of the blood pressure that is most closely linked to end-organ damage and renal injury is the rapidly oscillating systolic pressure. Accordingly, to achieve protection, the vasculature must be capable of adapting to elevations in this signal. As illustrated in Fig. 209.2, however, the systolic pressure pulsations occur beyond the frequency range of autoregulation. Thus, the oscillating pulse is associated with corresponding oscillations in renal blood flow, an observation that led to the previously held view that such rapid events are handled passively by the renal vasculature. Recent studies suggest that this may not be the case and that the afferent arteriole has the potential to respond exclusively to the systolic pressure signal (Loutzenhiser et al., 2002). This attribute is due to the unique kinetic features of the myogenic response, specifically the rapid onset of the contraction and the longer delay in the relaxation or offset of the response (Loutzenhiser et al., 2002; Williamson et al., 2008). As illustrated in Fig. 209.2, the afferent arteriole senses changes in the systolic pressure and adjusts steady-state tone in response to this signal. Steady-state tone changes with a time constant of 3–4 seconds, providing autoregulatory adjustments, but the level of tone is set by the systolic signal, providing protection over the entire frequency range of the blood pressure power spectrum (Loutzenhiser et al., 2006).

Summary

The unique structural and functional properties of the renal vasculature are essential in facilitating the massive filtration and reabsorptive processes required for normal renal function. The afferent and efferent arterioles have evolved distinct activation mechanisms that allow an independent regulation of the inflow and outflow resistances of the glomerular capillaries and physiologic control of P_{GC} and GFR. Specifically, pre-glomerular vessels are regulated by membrane potential alterations affecting the activity of L-type voltage-activated Ca^{2+} channels; whereas voltage-independent mechanisms regulate the efferent arteriole. These properties underlie the physiologic control of P_{GC}, for example, by PGE_2, during conditions of reduced renal perfusion and the stabilization of P_{GC} when the kidney is exposed to pressure fluctuations. The latter is accomplished by both TGF- and the myogenic-mediated pre-glomerular vasoconstriction. The renal myogenic mechanism, which has the potential to adjust steady-state tone in response to the oscillating systolic pressure signal, additionally plays an essential role in protecting the kidney from the damaging effects of hypertension.

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CHAPTER 210

The kidney and control of blood pressure

Olga Gonzalez-Albarrán and Luis M. Ruilope

Introduction

The existence of a relation between cardiac hypertrophy and the kidney was first noted by Bright in 1836 even before it was possible to measure blood pressure. Mahomed demonstrated a link with blood pressure 40 years later and also reflected on the vicious cycle of hypertension and kidney disease shown in Fig. 210.1 (Cameron and Hicks 1996; Turner 2014). He also noted hypertension occurring in the absence of overt renal disease.

At the simplest level, mean arterial pressure (MAP) is the result of multiplying cardiac output (CO) by peripheral resistance (PR).

$$MAP = CO \times PR$$

An elevation in arterial blood pressure can then be the consequence of a derangement in volume regulation or may arise as a consequence of an imbalance between factors enhancing or opposing vasoconstriction.

The kidney participates in the regulation of both volume and vasoconstriction (Box 210.1). Some defect in renal function must be present in any type of arterial hypertension, whether primary or secondary. We also know that elevation in systemic blood pressure irrespective of its cause may further damage an abnormal kidney (Fig. 210.1). However, hypertension seems likely to be the primary cause of renal damage less frequently than we used to think (see Chapter 211).

Salt and water excretion

Pressure natriuresis

An elevation in renal perfusion pressure results in an increased excretion of sodium and water, a phenomenon known as pressure-natriuresis diuresis. Guyton et al. (1972) proposed that pressure natriuresis promotes the excretion of sodium and water until blood volume is diminished sufficiently to return arterial blood pressure back to normal values. If this was unmoderated, eventually this would over-ride all other blood pressure control mechanisms.

Pressure natriuresis is intrinsic to the kidney, because it can be demonstrated using an isolated perfused kidney preparation (Aperia et al., 1971). It is also independent of changes in glomerular filtration rate (GFR) and in renal blood flow (RBF), as depicted in Fig. 210.2. Variations in salt intake are followed by an exponential increase in natriuresis, but under normal circumstances they are accompanied only by very small changes in arterial pressure. Many factors, summarized in Box 210.2, are implicated in the endocrine and paracrine regulation of this phenomenon.

Autoregulation of GFR and RBF is due to pre-glomerular vasoconstriction that impedes the transmission of an elevated systemic arterial pressure to the glomeruli and peritubular capillaries of the kidney (see Chapter 44).

Salt sensitivity

Pressure natriuresis is impaired in all forms of hypertension, including human essential hypertension (Hall et al., 1990), as despite increased pressures, sodium excretion is the same as in normotension. However, in response to changes in salt intake, patients segregate into those in whom arterial pressure is relatively insensitive to changes in the sodium content of the diet and those exhibiting relevant changes in arterial pressure with changes in salt intake (salt sensitive). Fig. 210.3 depicts the pressure-natriuresis relationship in these two groups. Salt-insensitive hypertensives exhibit a shift of pressure-natriuresis curve to higher pressures in parallel with the normal curve. In contrast, in salt-sensitive hypertensives in whom plasma renin activity is frequently low, the curve is also shifted to higher levels of arterial pressure, but the slope is flat. When salt content in the diet is low, blood pressure is normal, but it increases progressively, when the salt content in the diet is increased. Hall (1991) postulated that the presence of a flat slope indicates that additional abnormalities of renal function must be present besides a simple increase in glomerular resistance.

Salt sensitivity has been shown to be particularly prevalent in black, in obese, and in elderly hypertensive patients. These are frequently associated with diminished renal function and by a significantly enhanced cardiovascular risk. Both renal and cardiovascular risk have been shown to run in parallel, and, in fact, mild alterations in renal function constitute the best predictors of an increased cardiovascular risk (Ruilope et al., 2001). Salt sensitivity

Box 210.1 Renal regulation of volume and vasoconstriction

- Regulation of volume:
  - Excretion of water and electrolytes (in particular sodium)
- Regulation of vasoconstriction:
  - Secretion of renin and other vasoconstrictive substances
  - Secretion of vasodepressor substances.

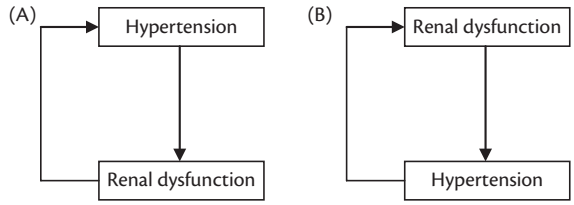

Fig. 210.1 Relationship between the kidneys and arterial pressure. Renal dysfunction can be the origin of arterial hypertension (B) or can be the consequence of the elevation in arterial pressure (A).

is frequently associated with microalbuminuria, absence of the nocturnal decrease in arterial pressure, and absence of modulation of renal blood flow in response to sodium loading.

The renin–angiotensin system

The renin–angiotensin system (RAS) serves as one of the most powerful regulators of arterial pressure and sodium balance. As can be seen in Fig. 210.4, in response to various stimuli that compromise blood volume, extracellular fluid volume, arterial pressure, stress, and trauma, three major mechanisms are activated: the macula densa, baroreceptor reflex, and the sympathetic nervous system. All three mechanisms stimulate renin release by the cells of the juxtaglomerular apparatus.

Renin

Renin hydrolyses angiotensinogen that is synthesized in the liver to form angiotensin I. This decapeptide is rapidly converted to angiotensin II by the angiotensin-converting enzyme (ACE) present primarily in the lungs and endothelial cells. Further angiotensin metabolites such as angiotensin (2-8), angiotensin (1-7), and angiotensin (3-8) also have biological actions, which may be mediated via alternative receptors.

Renin hypersecretion by the kidney is overtly responsible for hypertension in humans in two clinical situations. First, when renin is hypersecreted secondary to the existence of a renin-secreting tumour known as haemangiopericytoma (Mimran, 1994). Second, when renin is secreted as a result of stenosing lesions in the renal vessels, causing renal ischaemia as in renovascular hypertension or in dialysis-resistant hypertension in patients with advanced renal disease (Wilkinson et al., 1970); see Chapters 212, 213.

Angiotensin II

Angiotensin II, an octapeptide, is the most active component of this system and is responsible for its most relevant actions. Angiotensin II plays a central role in regulating extracellular fluid volume as well as systemic vascular resistance.

Angiotensin II binds in humans to at least two receptors, AT_1 and AT_2 receptors. Most known effects are mediated through the AT_1 receptor, including vasoconstriction, aldosterone and vasopressin release, salt and water retention through the kidney, and sympathetic activation, as well as important autocrine and paracrine effects on cell proliferation and migration and on extracellular matrix formation. AT_2 receptor stimulation seems to broadly counteract the effect of the binding of angiotensin II to the AT_1 receptor. Its effects are vasodilatory and antiproliferative. The expression of the AT_2 receptor is high in embryonic tissue and low in adult lifetime. The AT_2 receptor is re-expressed, however, in various pathological situations, suggesting that the AT_2 receptor plays a role in pathophysiology (De Gasparo and Bullock, 2000).

Angiotensin II has many actions besides its renal effects. Experimentally, chronic infusion of angiotensin II offers some insight into the complexity of mechanisms involved in the genesis of hypertension even when this single cause can be defined (Fig. 210.5). Under physiological conditions the main task of angiotensin is to increase sodium reabsorption by the kidney in order to maintain volume homeostasis, depicted in Fig. 210.6.

Long-term effects of exposure to elevated angiotensin

When the correlation between plasma angiotensin II concentration and arterial pressure values is examined in patients with renin-secreting tumours, blood pressure values are much higher

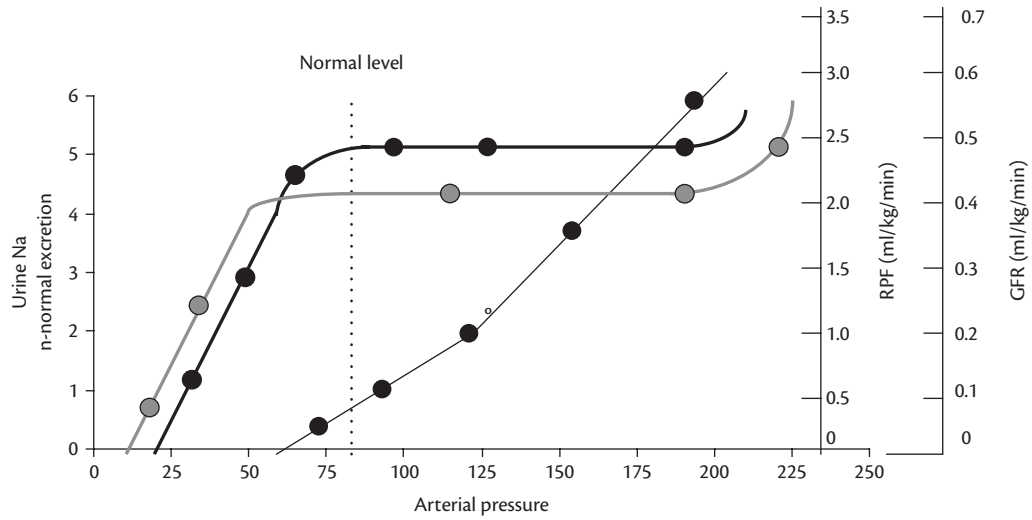

Fig. 210.2 Schematic representation of the pressure natriuresis and autoregulation of renal haemodynamics for the long-term control of arterial pressure. This figure represents the relationship between arterial pressure, natriuresis, glomerular filtration rate (GFR), and renal blood flow (RBF). The latter parameters remain constant within the limits of autoregulation, which operates in the range of perfusion pressure values between about 80 and 200 mmHg.

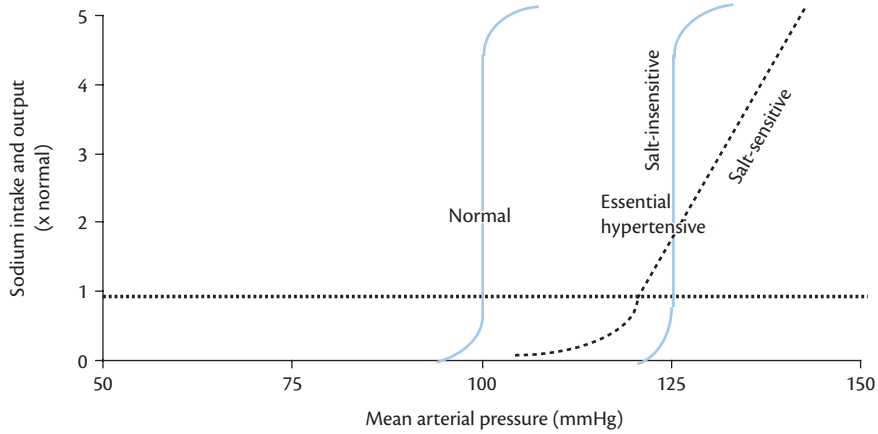

Fig. 210.3 Pressure natriuresis relationship between arterial pressure and sodium content.

Box 210.2 Factors participating in the regulation and control of pressure-natriuresis

- Renal nerves
- Prostaglandins
- Angiotensin II
- Atrial natriuretic peptide
- Nitric oxide
- Kallikrein-kinin system
- Vasopressin.

than those obtained by infusing angiotensin II to achieve similar plasma concentrations (Brown et al., 1979). An analogous phenomenon has been demonstrated in rabbits and rats. Infusion of doses of angiotensin II that were insufficient to cause an acute increase in arterial pressure, when infused chronically over a period of days were capable of causing a gradual increase in arterial blood pressure (Dickinson and Lawrence, 1963).

This slow-pressor effect of angiotensin II has been attributed to several mechanisms. First, blood pressure becomes salt sensitive because circulating angiotensin II is no longer suppressed in response to elevated blood pressure or because the balance between angiotensin II and nitric oxide in tissues is disturbed. Second, it increases oxidative stress (Chapter 112). Reactive oxidant species diminish the synthesis of nitric oxide, scavenge nitric oxide thus

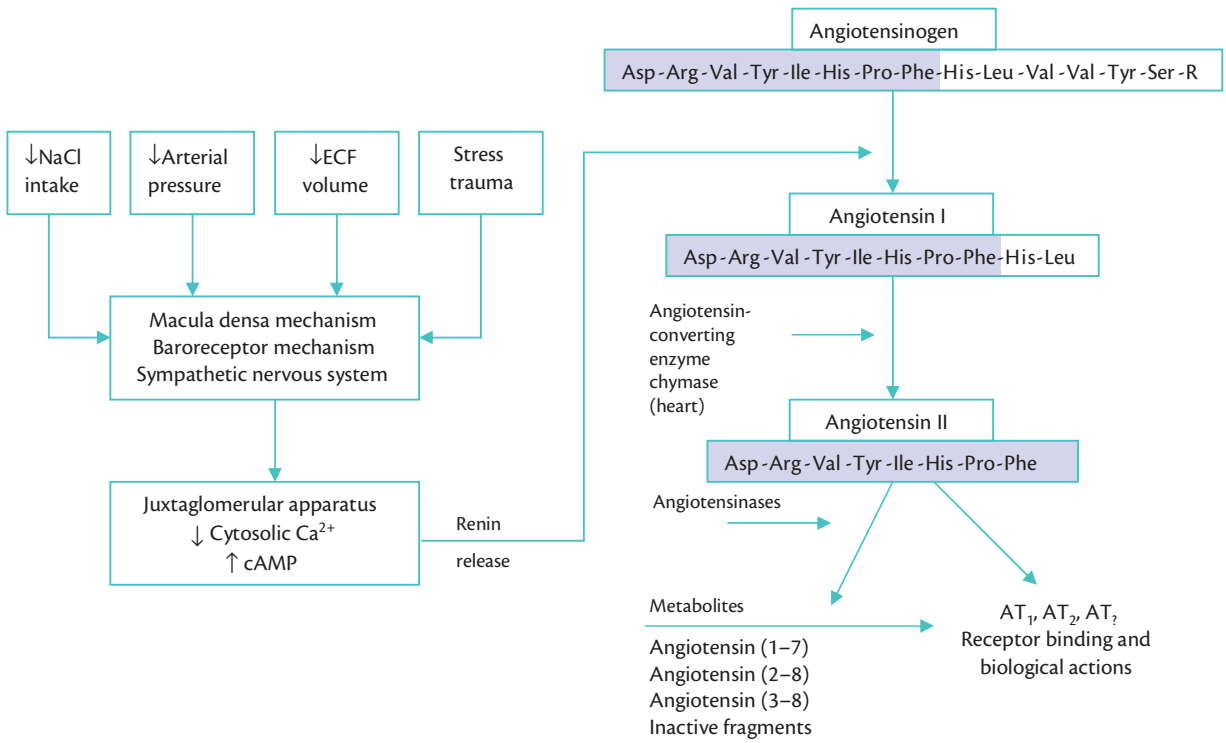

Fig. 210.4 Scheme of the renin–angiotensin system.

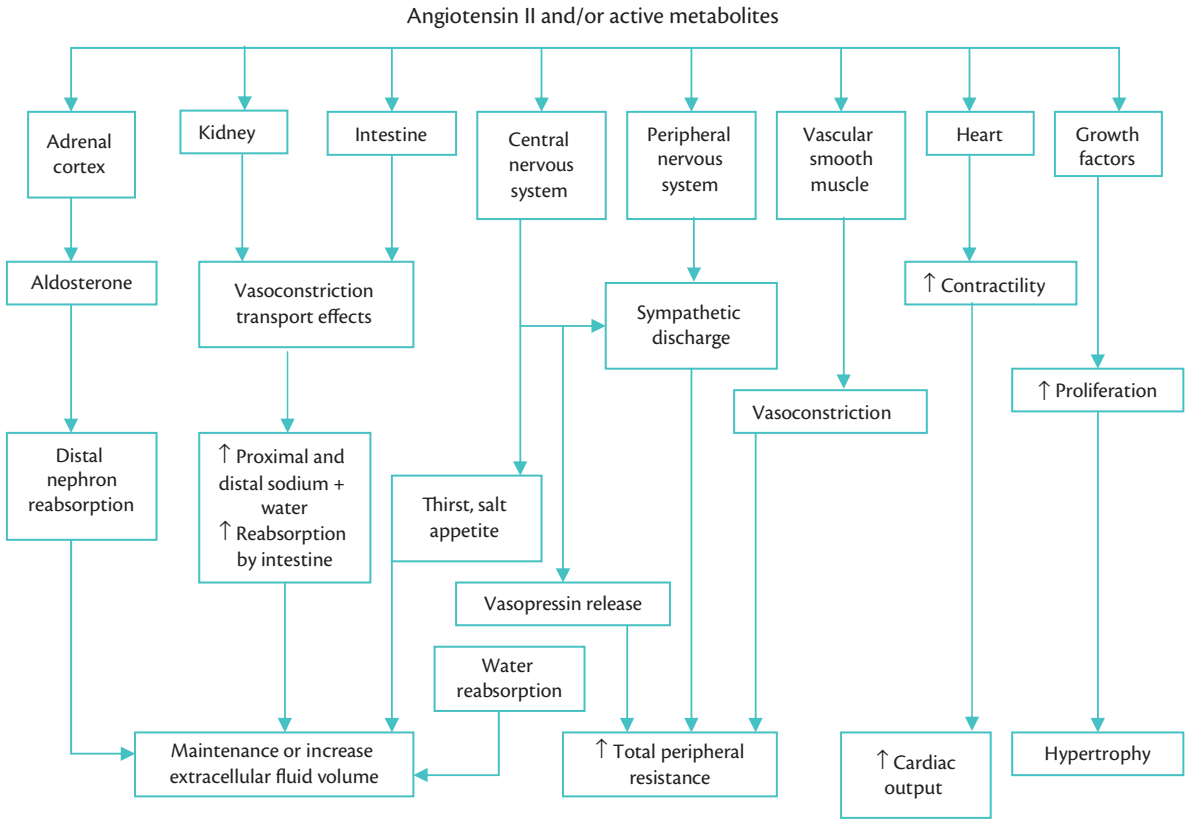

Fig. 210.5 Actions of angiotensin II and other active metabolites of the renin–angiotensin system.

reducing its bioavailability, and cause lipid oxidation resulting in the formation of vasoconstrictor prostanoids. Third, it causes vascular hypertrophy because of its known trophic effects (Dickinson, 1981; Lever, 1986; Elijovich et al., 1998).

Vascular remodelling

It was initially thought that high peripheral arterial resistance was maintained through structurally fixed luminal narrowing of resistance vessels. However, it emerged that the decrease in wall:lumen

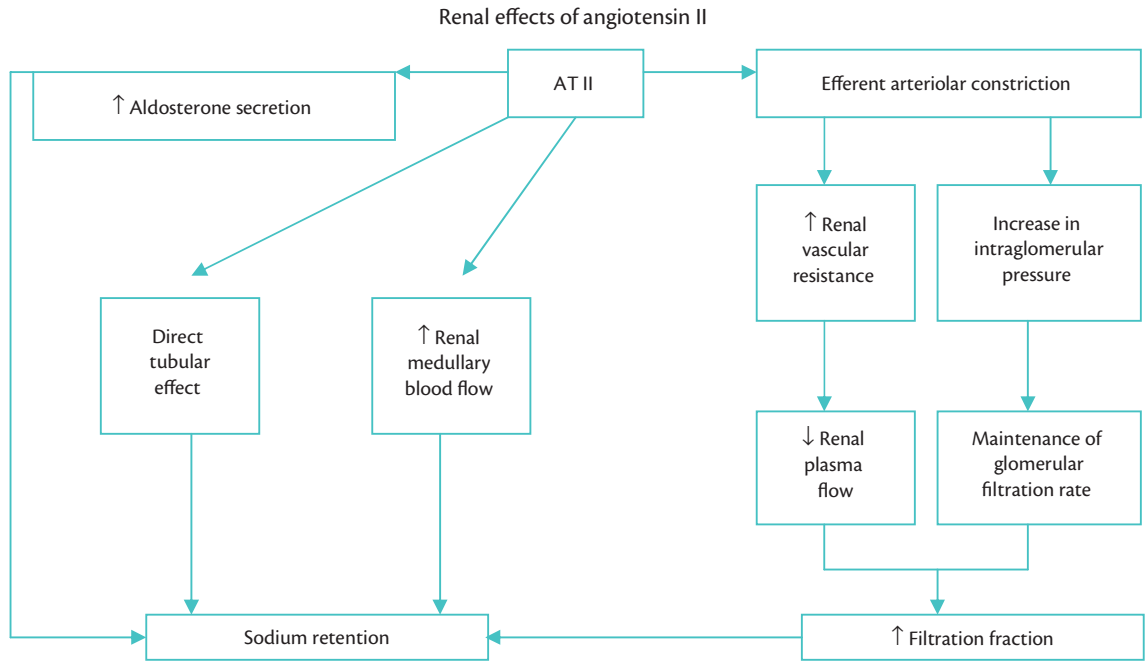

Fig. 210.6 Mechanisms by which angiotensin II facilitates sodium retention.

ratio of resistance vessels is not the consequence of hypertrophy or hyperplasia, but of rearrangement of the media around a reduced lumen (remodelling) (Mulvany, 1994). Hypertrophy or remodelling of resistance vessels, facilitated by the slow-pressor mechanism of angiotensin II or by other mechanism(s), increases resistance to flow even at maximal vasodilatation. It contributes to the maintenance of arterial hypertension since in elegant experiments Scandinavian investigators showed that after remodelling of resistance vessels, the pressor dose–response curve was much steeper (Folkow, 1982; Mulvany, 1994).

Local activation of the RAS

All components of the RAS have been demonstrated in a number of tissues so angiotensin receptors are also activated by angiotensin II formed locally (Deinum and Schalekamp, 2000). The kidney secretes renin in to the circulation to be delivered to extrarenal tissues including heart, brain, and vessels to form both angiotensins I and II in these tissues. Activation in local tissue compartments does not necessarily parallel the concentration of these peptides in plasma (Komine et al., 2002).

An example of this situation is diabetes mellitus where levels of circulating components of the system are low, but the intrarenal synthesis of angiotensin II is increased (Price et al., 1999). In this situation, angiotensin II acts as a paracrine and autocrine hormone. Tissue RASs are of potential clinical relevance in light of the growing evidence that the beneficial effects of ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in heart failure, post-myocardial infarction, arterial hypertension, and renal disease do not depend solely on their actions on the circulating renin–angiotensin.

Prophylactic effects of RAS inhibition

Data from two large clinical trials showed prevention of hypertension in patients with normal or high-normal blood pressure by drugs which block the RAS. In the TROPHY study (Julius et al., 2006), 772 individuals with systolic blood pressure between 130 and 139 mmHg or diastolic blood pressure between 85 and 89 mmHg were randomized to the angiotensin-receptor antagonist candesartan 16 mg daily or placebo. At the end of the 4-year trial period, significantly fewer patients in the candesartan arm developed hypertension. A relative risk reduction of 15.6% in favour of the treatment arm was calculated. During the first 2 years, the relative risk reduction in favour of active treatment arm was even greater (66.3%). After 2 years the treatment was interrupted and blood pressure tended to return to the levels of the control group.

In PHARAO (Lüders et al., 2008), 1008 individuals with systolic blood pressure within the same limits of the TROPHY trial were randomized to the ACEI ramipril 5 mg daily or placebo. The relative risk reduction for the incidence of hypertension was 34.4% in the ramipril arm.

The RAS blocker effects suggest that ramipril and candesartan, in addition to conferring a blood pressure lowering effect per se, slow the development of hypertension by interfering with the vascular or neurohumoral causes of increased vascular tone.

Renal nerves

The sympathetic nervous system has been implicated in the pathogenesis of essential hypertension and in the spontaneously hypertensive rat (Folkow, 1982). There is a good correlation between arterial pressure and renal nerve activity measured in crossbreeds of spontaneously hypertensive rats (Judy et al., 1976). Acute renal denervation shifts the relationship between sodium excretion and arterial pressure towards lower pressure values (Roman and Cowley, 1985). Activation of sympathetic tone markedly blunts pressure natriuresis in conscious dogs (Ehmke et al., 1990). These findings indicate that the renal nerves exert a tonic influence on the pressure-natriuresis relationship. In humans with mild arterial hypertension, when compared to normal individuals, sympathetic overactivity resulting from mental stress is accompanied by a greater increase in arterial pressure and in GFR as well as a blunted natriuretic response (Schneider et al., 2001). Renal capacity to excrete sodium returned to normal after the administration of an ACEI. This indicates that angiotensin II is involved in blunting of the pressure natriuresis, which is observed in individuals with mild hypertension during activation of the sympathetic nervous system.

In human hypertension, white-coat and masked hypertension are characterized by adrenergic overdrive (Grassi et al., 2007), and altered night-time blood pressure profiles may be associated with dysregulated sympathetic activation (Grassi et al., 2008, 2009).

Renal afferent nerves can also increase the activity of the sympathetic nervous system in situations of renal ischaemia, such as renovascular hypertension or chronic renal failure of different origins (Johansson and Friberg, 2000; Orth et al., 2001). Interestingly, in the presence of chronic renal failure the participation of the sympathetic nervous system can also be counteracted by the administration of an ACEI (Ligtenberg et al., 1999).

Finally, a correlation is found between sodium balance and activity of the sympathetic nervous system. Folkow and Ely (1987) demonstrated in normotensive and spontaneously hypertensive rats that a high sodium intake increases the amount of neurotransmitter released per nerve impulse at noradrenergic nerve endings. Salt restriction had the opposite effect. This effect was particularly pronounced in hypertensive rats. De Champlain et al. (1969) have shown an increased turnover of noradrenaline in deoxycorticosterone-salt hypertension, an example of volume-mediated hypertension. Chemical sympathectomy has shown to prevent the development of hypertension in the same model (Okuno et al., 1983). Salt loading has also been shown to alter the activity of central alpha-2-adrenergic receptors, resulting in a hypertensive hyperadrenergic state (Gavras and Gavras, 2001).

Renal denervation

Renal denervation has been used in large number of experimental models, revealing the potential usefulness of renal denervation as a therapeutic strategy. Bilateral renal denervation prevented or attenuated the development of hypertension in a large number of diverse animal models of experimental hypertension including genetic, salt sensitive, obesity-related, renovascular, and other hypertension models (DiBona et al., 1997, 2002). Experimental models of obesity-related hypertension, which are commonly associated with sodium retention and increased sympathetic nervous system activation, have shown that renal denervation abolished the increase in blood pressure and the sodium retention. Those data demonstrated long-term durability of benefit and no adverse effects on renal function following surgical denervation (Kassab et al., 1995).

Sodium retention is at least in part attributable to renal sympathetic efferent nerve activity, which can be abolished by renal nerve

ligation. The ligation of renal nerves protects against expression of postprandial natriuretic resistance and the development of congestion or rises in ventricular filling pressures.

The use of radiofrequency energy to selectively target and disrupt renal nerves in man was described in 2011 (see Chapter 217). Promising early data were contradicted by the results of a very carefully designed randomized controlled trial, but it is possible that we have not heard the last word.

Renal depressor mechanisms

Early experiments suggested that the positive sodium and water balance could not entirely explain the hypertension that follows bilateral nephrectomy. A renomedullary antihypertensive function was demonstrated in different animal models of arterial hypertension (Swales, 1993). Interstitial cells in the renal medulla contain two classes of antihypertensive lipid. One compound known as medullipin I is an inactive prohormone and requires conversion by the liver to the active compound medullipin II that is responsible for the arterial pressure lowering activity of the renal medulla (Muirhead et al., 1994). Its role in arterial blood pressure control seems to depend on its capacity to vasodilate, to inhibit sympathetic tone, and to promote natriuresis (Bergstrom et al., 1998). A deficit in renomedullary depressor substances does not seem to be causally involved in the genesis of all forms of hypertension. At least in one experimental model of hypertension, the spontaneously hypertensive rat, the droplet content of interstitial cells is increased and an appropriate increase is seen in response to a low salt intake (Kett et al., 2001).

Other systems or substances produced by the renal tissue and vessels that participate in the renal regulation of arterial pressure through haemodynamic or tubular effects are prostaglandins, the peptides of the kallikrein-kinin system, nitric oxide, and endothelin (Cowley and Roman, 1996).

Transplanting hypertension implicates kidneys

One line of evidence for the importance of the kidney in hypertension comes from observations on transplantation of the kidney of a hypertensive animal or hypertensive human donor.

Cross-transplantation experiments between hypertensive strains of rats and normotensive controls have shown that the blood pressure values of the recipient reach levels similar to those of the donor. Dahl et al. (1972) used two strains of rats that were completely different with respect to the arterial pressure response to salt feeding. One of the strains developed high arterial pressure when fed a high-salt diet, while the other did not. The recipient animals developed hypertension (Figs 210.7 and 210.8). The transplantation experiments can be interpreted as the transplantation of a primary renal abnormality. Similar results were seen when the kidneys from spontaneously hypertensive rats, stroke-prone spontaneously hypertensive rats, and Milan hypertensive rats were transplanted into the respective normotensive counterparts (Elijovich et al., 1998).

Observations in human renal transplantation are supportive. A graft from a hypertensive donor, presumably genetically programmed for hypertension, can transmit not only chronic hypertension, but also susceptibility to a greater rise in arterial pressure and more severe kidney impairment compared to recipients of grafts from normotensive donors (Guidi et al., 1998). On the other hand, kidneys from normotensive donors without a family history of arterial hypertension, when grafted into hypertensive recipients who had developed end-stage renal disease due to nephrosclerosis, led to permanent normotension (Curtis et al., 1983).

What is the renal abnormality in essential hypertension?

Most single-gene disorders that cause hypertension involve genes that are expressed in or act via the kidney. Genome-wide association studies have been less conclusive, results suggesting small effects from many genes, but accounting for only a small part of the total blood pressure variability (Munroe et al., 2013).

Salt sensitivity

There is a well-documented connection between hypertension and salt intake in man and animals. The link between diet and arterial pressure could reside in the presence of a renal abnormality consisting in a restricted ability to excrete sodium (Woolfson and de Wardener, 1996). In agreement with this hypothesis, the offspring of hypertensive parents experience a significant increase in arterial pressure in response to volume expansion with saline (Grim et al., 1979). This is accompanied by accelerated natriuresis (Wiggins et al., 1978), similar to that described in established hypertension.

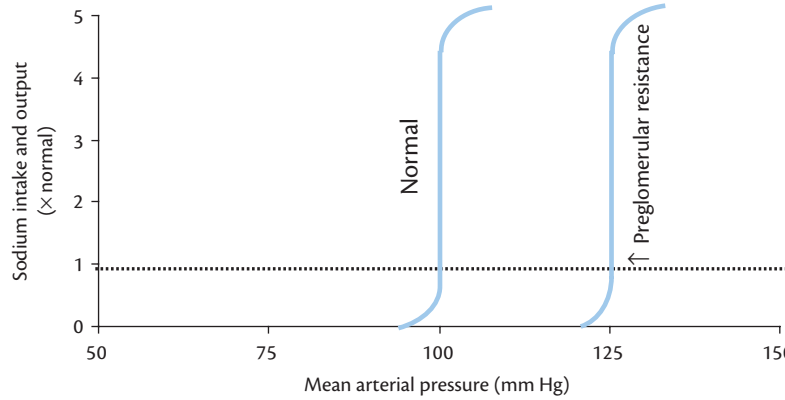

Fig. 210.7 Effect on arterial pressure of the transplantation of a kidney from a normotensive rat to a hypertensive rat and vice versa.

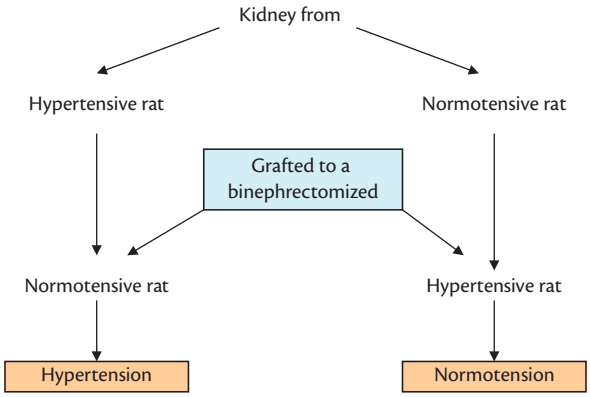

Fig. 210.8 Evolution of renal vasoconstriction during the development and maintenance of essential hypertension.

Nephron number

A congenital reduction in the number of nephrons or in the filtration area per glomerulus (Brenner et al., 1988), or the presence of nephron population heterogeneity with a subpopulation of ischaemic nephrons hypersecreting renin chronically (Sealey et al., 1988), are other theories proposed to explain a primary renal origin of arterial hypertension. A low number of nephrons increases the risk of both hypertension and progressive renal disease (discussed further in Chapter 138).

Subtle acquired renal injury

The transplantability of hypertension could also be explained by the presence of subtle renal injury in donor kidneys (Johnson et al., 2002). As expressed by Johnson et al. and also by Ruilope et al. (1994), a key mediator for the hypothesis was the linkage of microcirculatory dysfunction, particularly glomerular afferent arteriolar narrowing, to salt sensitivity.

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CHAPTER 211

The effect of hypertension on renal vasculature and structure

Ulrich Wenzel, Thorsten Wiech, and Udo Helmchen

Lessons from experimental models

The experimental models of chronic renal hypertension in dogs devised by Goldblatt provided the opportunity to study the structural effects of hypertension (Goldblatt et al., 1934, 1938). The experimental model of unilateral renal artery stenosis, referred to later as two-kidney, one-clip hypertension, has one important advantage, that is, the clipped kidney is protected from the effects of hypertension. This provides a control organ with which vascular lesions occurring within the contralateral non-clipped kidney of the same animal can be compared. These experiments documented the unique ability of the altered intrarenal vascular bed to initiate and sustain a vicious circle, that is, hypertension causes vascular lesions, which, in turn, further increase blood pressure. The morphological similarities between these experimentally produced vascular lesions and those seen in benign and malignant nephrosclerosis in human kidneys are striking. The following description of acute and chronic hypertensive lesions is derived from the rat models of two-kidney, one-clip hypertension and desoxycorticosterone acetate (DOCA) salt hypertension as well as from genetic models such as spontaneously hypertensive rats and Dahl rats.

Vascular lesions

Three different types of pre-glomerular vascular change may develop in the non-clipped kidneys of animals with two-kidney, one-clip hypertension:

1. Medial thickening
2. Segmental hyalinosis
3. Widening of the intimal space: the intima becomes organized by collagen synthesizing cells resulting in onion-like appearance of narrowed vessels.

Medial thickening

The first type of vascular change is characterized by medial thickening of the intrarenal arterial and arteriolar walls, leading to an increased wall-to-lumen ratio. It is not clear if these changes in the kidney are also associated with an increased number of vascular cells and increased synthesis of vascular wall material, or whether they can be produced just by a remodelling of the vascular wall, that is, redistribution of existing cells and material (Mulvany and Aalkjaer, 1990). Data suggest that smooth muscle cell hypertrophy rather than hyperplasia is responsible for the medial thickening. Elevated DNA content of arteries in hypertension may be secondary to a marked increase in cells showing nuclear polyploidy and infiltration of blood-borne cells (Owens et al., 1981; Chobanian et al., 1984). Remodelling is usually an adaptive process that occurs in response to long-term changes in haemodynamic conditions, but it may subsequently contribute to the pathophysiology of hypertension and renal disease (Gibbons and Dzau, 1994). The structural adaptation to the hypertensive state and the functional implications have been studied intensively by Folkow and colleagues (Folkow, 1990). Observations on altered resistance vessels in hypertension led them to suggest that vascular hypertrophy and arterial pressure are linked in a positive feedback relationship, in which minor but persistent overactivity of a pressor mechanism is amplified by hypertrophy. These changes have also been shown to be valid for the renal vascular bed (Lundgren 1974; Berecek et al., 1980). Changes in the extracellular matrix in the aortic vascular wall caused by experimental hypertension have been described (Brecher et al., 1978). It is likely that these changes also occur in the renal vasculature (Boffa et al., 1999).

Segmental hyalinosis

The second type of renal vascular alteration consists of segmental hyalinosis of the vessel wall, affecting mainly the interlobular arteries and afferent arterioles. This can be explained by the inability of local areas of these vessel segments to withstand the increased stress, resulting in a critical vascular dilatation. Broad gaps between the underlying endothelial cells may occur temporarily, followed by an intrusion of blood constituents into the vessel walls and by focal necrosis of medial smooth muscle cells (Figs 211.1 and 211.2). Indeed, segmental hyalinosis is more often associated with dilatation than with narrowing of the vessel lumen. These changes can also be produced if pressure is increased by other procedures, such as injection of angiotensin II, catecholamines, or vasopressin (Giese, 1964a, 1964b). Since the hyaline vascular changes are considered to be potentially reversible, this type of arterial and arteriolar lesion might be assumed to be negligible. In practice, however, such lesions may reduce the autoregulatory potency of pre-glomerular vessels, favouring a transient exposure of the glomerular capillaries

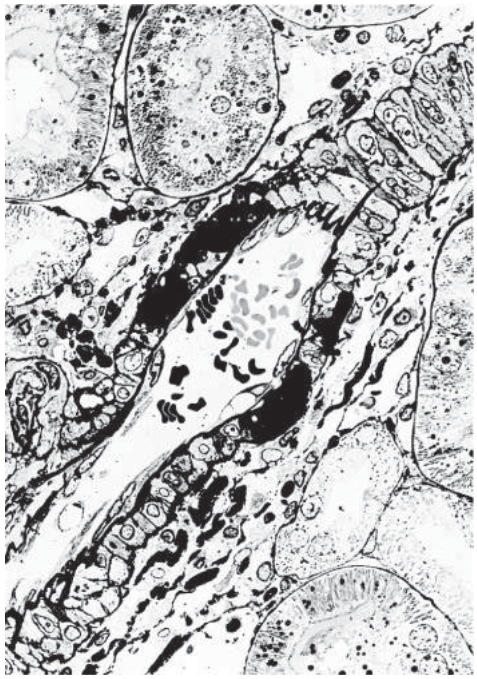

Fig. 211.1 Non-clipped kidney: focal medial necrosis (plasma insudation, hyalinosis) of an interlobular artery 24 hours after unilateral renal artery constriction (immersion fixation, semithin section, silver impregnation; magnification ×420).

to abnormally increased filling pressures with the consequent development of hypertension-induced structural glomerular lesions. In the early stages, these consist of focal and segmental destruction of the glomerular tufts, affecting endothelial, mesangial, and visceral epithelial cells. Capillary aneurysms may complicate these early glomerular lesions, finally resulting in focal and segmental glomerulosclerosis (Fig. 211.3). The loss of glomeruli will be followed by patchy tubular atrophy and interstitial fibrosis (Fig. 211.4). Thus, despite its potential reversibility, in the long term pre-glomerular focal hyalinosis may contribute to a gradual loss of nephrons, and hence to the hypertensive state itself, by progressively reducing the renal excretory capacity.

Widening of the intimal space

The third and most severe type of hypertensive renal vascular lesion is closely related to 'malignant nephrosclerosis' (Fahr, 1925), a condition which really marks the final stage of a sequence of structural changes that develop mainly within the interlobular arteries. Initially, there is usually a widening of the intimal space which is entered by plasmic and corpuscular blood constituents that separate the endothelial cells from the internal elastic membrane (Fig. 211.5). Later, the intima becomes organized by collagen synthesizing cells, resulting in the typical onion-like appearance of these substantially narrowed vessels (Fig. 211.6). Frequently, an increased number of epithelioid juxtaglomerular cells are observed. The importance of blood pressure fluctuation for vascular and glomerular injury was demonstrated by Bidani and colleagues: continuous radiotelemetric monitoring of conscious rats showed an exceedingly close correlation of glomerulosclerosis in individual animals with the number of blood pressure fluctuations (Bidani et al., 1993, Griffin et al., 2004).

The essential part played by intrarenal vascular lesions in the maintenance of hypertension, even after its primary cause has been removed, can be demonstrated by the following experiment in two-kidney, one-clip hypertensive rats (Fig. 211.7): removal of

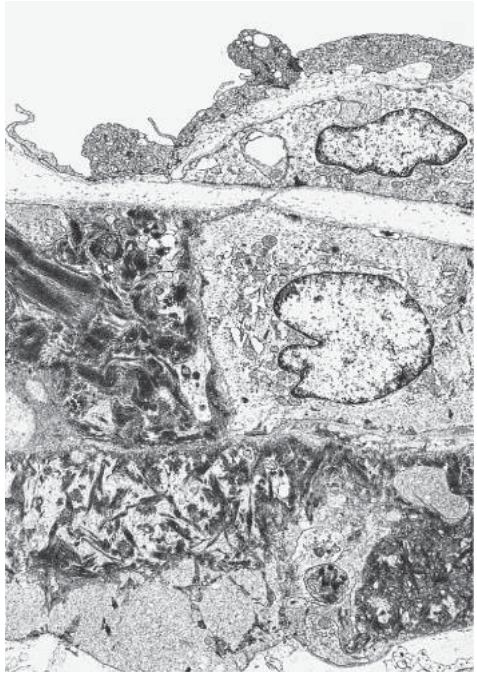

Fig. 211.2 Non-clipped kidney: electron microscopy findings in a hyaline segment of an interlobular artery 4 days after unilateral renal artery constriction. Plasmic constituents including fibrin precipitate within the partially necrotic media (immersion fixation, transmission electron microscopy; magnification ×9000).

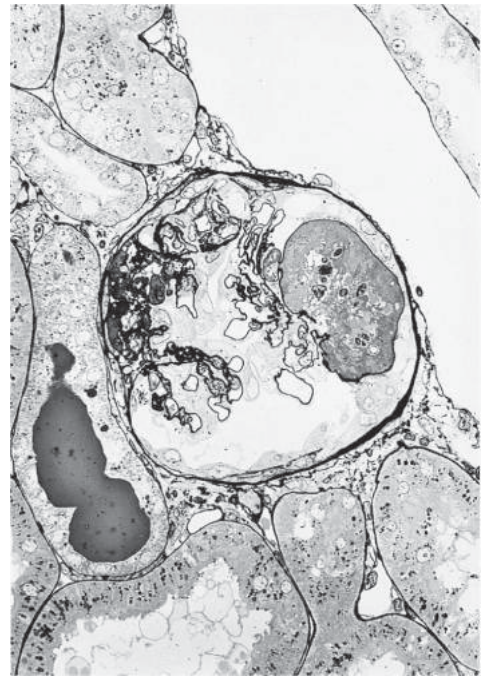

Fig. 211.3 Non-clipped kidney: capillary aneurysm and segmental sclerosis within a glomerulus 8 days after unilateral renal artery constriction (pressure-adjusted perfusion fixation, semithin section, silver impregnation; magnification ×360).

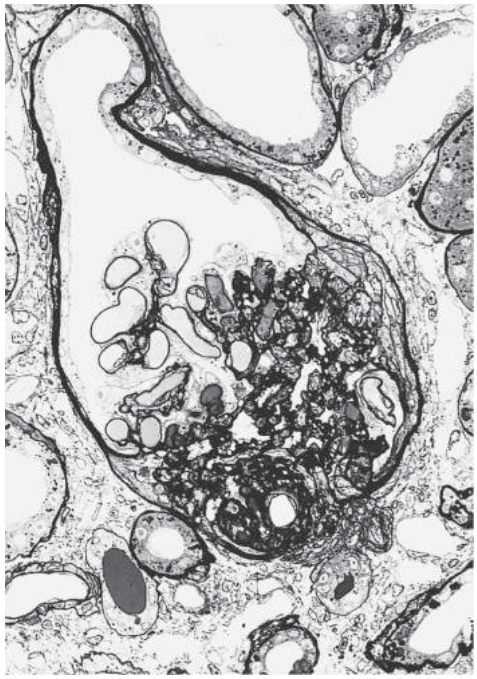

Fig. 211.4 Non-clipped kidney: glomerulosclerosis, tubular atrophy, and interstitial fibrosis 2 months after unilateral renal artery constriction (pressure-adjusted perfusion fixation, semithin section, silver impregnation; magnification ×360).

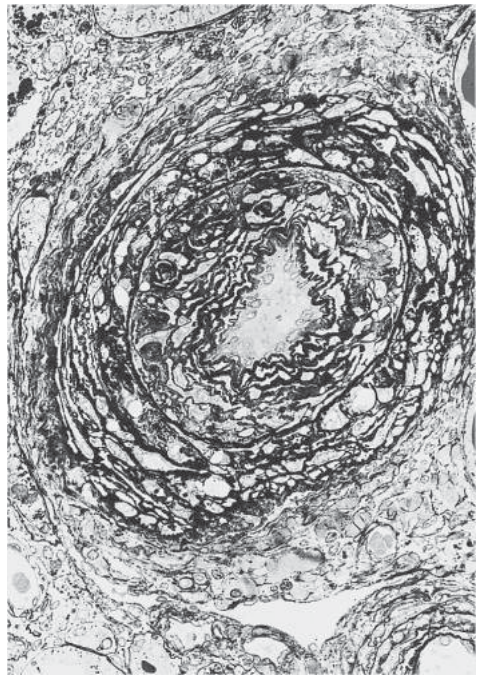

Fig. 211.6 Non-clipped kidney: late stage of malignant nephrosclerosis with concentric highly narrowing intimal fibrosis in an interlobular artery 4 months after unilateral renal artery constriction (pressure-adjusted perfusion fixation, semithin section, silver impregnation; magnification ×420).

the renal artery clip after maintenance of the hypertensive state for 1 year causes the blood pressure to decrease. However, this is temporary and hypertensive levels are regained within 1 week. This 'post-Goldblatt hypertension' may be a result of general atherosclerosis which may have developed during the preceding hypertensive period. Removal of the previously non-clipped kidney allows normotension to be maintained, indicating the pathogenic role of renal vascular disease including adaptive and destructive structural changes, such as severely obliterating lesions of interlobular arteries and afferent arterioles accompanied by focal glomerular sclerosis, tubular atrophy, and interstitial fibrosis. In contrast, at the end of the experiment the previously clipped kidneys of the same animals showed only minor focal vascular, glomerular, and tubular interstitial lesions that were obviously not sufficient to re-induce hypertension.

Rettig et al. (1990) have also demonstrated that the non-clipped kidney can not only sustain but also induce hypertension:

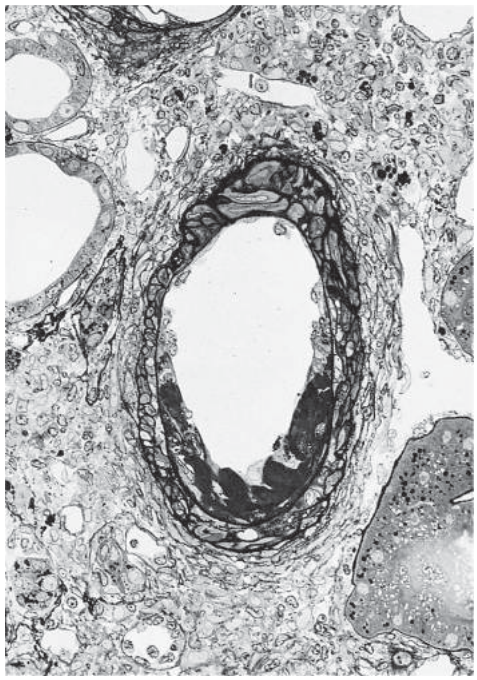

Fig. 211.5 Non-clipped kidney: early stages of malignant nephrosclerosis with widening of the intimal space containing plasmic material in an interlobular artery 2 months after unilateral renal artery constriction (pressure-adjusted perfusion fixation, semithin section, silver impregnation; magnification ×360).

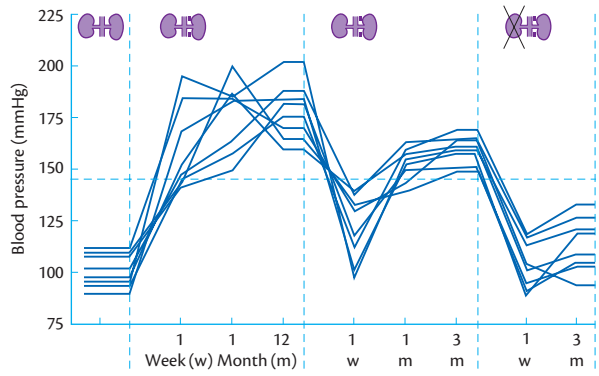

Fig. 211.7 Two-kidney, one-clip hypertension of 12 months' duration: post-Goldblatt hypertension after removal of the renal artery clip; sustained normotension after removing the previously non-clipped kidney. Reproduced with permission from Helmchen et al. (1984).

transplantation of non-clipped kidneys from two-kidney, one-clip hypertensive rats induced sustained hypertension in the normotensive recipients.

The lesions described above may also play a role in patients with 'pseudo renal artery stenosis syndrome'. In response to angiotensin-converting enzyme inhibitor therapy, these patients have clinical signs suggestive of renal artery stenosis despite patent renal arteries. It is believed that long-standing hypertension has caused sufficient intrarenal arteriolar hypertrophy and sclerosis to interfere with renal blood flow and to induce the functional pattern of renal artery stenosis (Pettinger et al., 1989; Toto et al., 1991).

Increased glomerular perfusion and the elevation of glomerular capillary pressure is one possible mechanism underlying the subsequent structural damage within the glomerulus (Brenner 1985; Klahr et al., 1988; and see Chapter 136). A close link between glomerular hypertrophy and sclerosis has been demonstrated (Fogo and Ichikawa, 1989, 1991); however, this concept is not supported by all studies (Wenzel et al. 2002). Analysis of individual glomeruli showed a biphasic pattern of these two parameters. Early development of glomerular sclerosis takes place together with hypertrophy of the glomerulus, and further advancement of sclerosis occurs with shrinkage in glomerular size (Fogo and Ichikawa, 1989, 1991). This finding was first described in the renal ablation model (Yoshida et al., 1989), but has also been demonstrated in the non-clipped kidney of rats with renovascular hypertension (Wenzel et al., 1992). Harvey et al. (1992) examined renal biopsies and found that glomeruli from hypertensive patients were larger than those from normotensive patients. The enlargement of glomeruli was probably a consequence of the loss of functioning glomeruli due to global sclerosis, which is, in turn, due to ischaemia. A reduced number of glomeruli with an increased volume were also found in patients with essential hypertension (Keller et al., 2003). This concept is discussed in Chapter 138.

The glomeruli have been a focal point of interest, particularly in view of the hyperfiltration hypothesis involving the degradation and sclerosis of remaining nephrons. However, the notion that tubulointerstitial fibrosis may be the cause rather than the result of decreased glomerular function has received strong support (Luft and Haller, 1995; and see Chapters 136, 137, 140). It has been reported that an early expansion of the interstitial volume precedes hypertensive vascular changes and glomerular injury in the non-clipped kidney of renovascular hypertensive rats (Mai et al., 1993). Increased matrix deposition was primarily found within the interstitium. Moreover, tubulointerstitial proliferation and dense focal interstitial monocyte/macrophage influx was found in the non-clipped kidney. These changes could be caused by mechanical damage of the renal microvasculature including obstruction of the postglomerular interstitial capillary network.

Hypertension and inflammation

Recent studies have shown that both innate and adaptive immunity contribute to hypertension. Macrophages and T cells accumulate in the perivascular fat, the heart, and the kidney of hypertensive patients, and in animals with experimental hypertension. RAG-1$^{-/-}$ mice, which lack both T and B cells, have blunted hypertensive responses to prolonged angiotensin II infusion or DOCA salt challenge. Adoptive transfer of T cells, but not B cells, led to a complete restoration of the hypertensive response to these stimuli, strongly implicating T cells in the genesis of hypertension (Guzik et al., 2007; Harrison et al., 2010, 2012). The kidney is also a target of inflammatory cells in hypertension. Hypertension stimulates lymphocytic infiltration in the kidney, and immunosuppressive therapy prevents this and reduces renal damage while lowering blood pressure in some cases but not in others (reviewed in Harrison et al., 2010). Much of the knowledge about the immune system has come from studies in mice, but the relevance to human immunology, diseases, and therapy has been challenged recently (Shay et al., 2013). That the earlier discussed mouse-derived inflammation data are of clinical relevance is shown Fig. 211.8. Immunohistochemistry analysis of a kidney biopsy from a patient with malignant nephrosclerosis shows dense infiltration of CD3-, CD4- and CD8-positive T cells as well as CD20 positive B cells next to the typical vascular lesion. Even nodular accumulation of CD20-positive B cells can be found.

Nephrosclerosis in mice

Mice with targeted disruption of genes implicated in the development and progression of hypertension are valuable tools for the study of mechanisms leading to organ injury. The kidney is a clear target organ for hypertensive end-organ damage characterized by proteinuria, inflammation, and fibrosis. Arterial hypertension leads to profound renal damage in rats but not in all mice strains. C57BL/6 mice in particular appear to be very resistant to hypertensive end-organ damage (Hartner et al., 2003). In addition, C57BL/6 mice are also very resistant against renal injury due to hypertension by angiotensin II infusion (Wesseling et al., 2005). Therefore it is difficult to study hypertensive renal disease in genetically modified mice because the C57BL/6 strain serves as a background for many transgenic and knockout mouse models. Therefore, a new model of arterial hypertension in C57BL/6 mice was created by combining DOCA salt and chronic angiotensin II infusion. This model shows glomerular and tubulointerstitial hypertensive renal injury with proteinuria in the nephrotic range within 3 weeks after induction of hypertension and is helpful to examine hypertensive end-organ damage in knockout mice (Kirchhoff et al., 2008, Krebs et al., 2012) (Fig. 211.9).

Nephrosclerosis in human kidney

Renal tissue damage that develops in hypertensive patients is non-specific. This is valid not only for the glomerulosclerosis, tubular atrophy, and interstitial fibrosis that are seen in the advanced stage, but also for the pre-glomerular lesions that are characteristic of, but not diagnostic for, hypertensive disease. These lesions do not allow differentiation between the different causes of high blood pressure, or even that hypertension is the cause.

Light and electron microscopy studies of vascular lesions in kidneys from patients with essential hypertension are indistinguishable from those in the contralateral or unprotected kidney of individuals with renovascular hypertension (Fisher et al., 1966). The traditional use of the term 'nephrosclerosis', comprising the benign or malignant variety, encompasses a wide range of morphological findings, including primary injuries of the vessel walls and early and late tissue reactions.

'Hypertensive' lesions may not be hypertensive

Light microscopy shows that the component of benign nephrosclerosis found most regularly is segmental hyalinization of interlobular arteries and afferent arterioles (Fig. 211.10). It preferentially affects

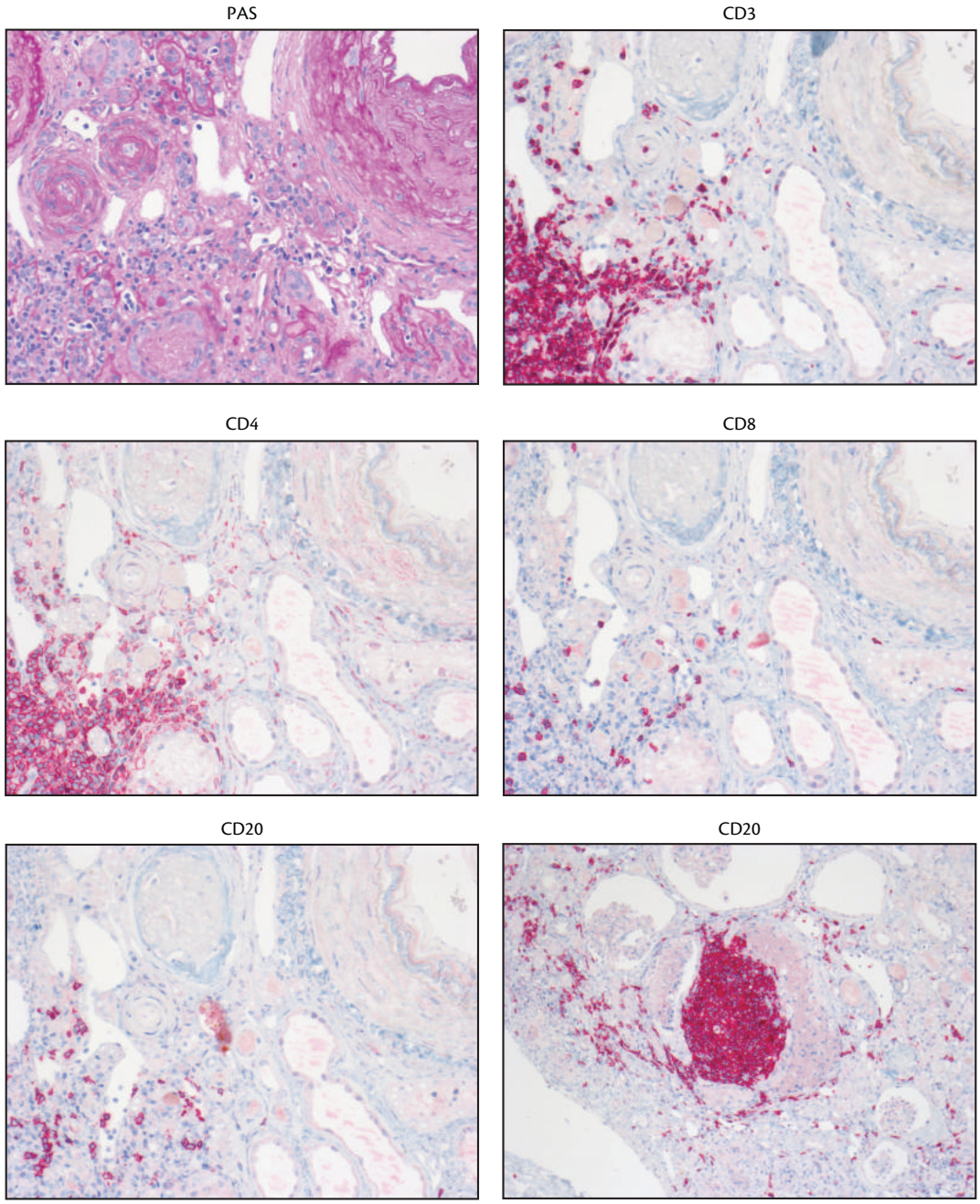

Fig. 211.8 PAS staining and immunohistochemistry for CD3-, CD4-, and CD8-positive T cells are shown in a kidney biopsy from a patient with malignant hypertension. Moreover, CD20 positive B cells are found in a scattered pattern as well as in nodules.

the media which then shows a diminished number of smooth muscle cell nuclei; the lumen of the hyalinized segments is not necessarily narrowed. Immunofluorescence and electron microscopy techniques have made possible the demonstration of several plasma constituents, such as immunoglobulins (IgM) and complement components (Clq, C3) within the hyalinized areas (Valenzuela et al., 1980) (Fig. 211.11). Thus arterial and arteriolar hyalinosis in humans, as in animal models, can be regarded as the structural result of an insudation of plasma constituents into the vessel walls during a period of increased permeability (Fisher et al., 1966). The vascular hyalinization of benign nephrosclerosis is one of the most frequent findings on light microscopy of kidney biopsies. Many kidney biopsies taken from patients with minor mono- or oligosymptomatic renal disease show benign nephrosclerosis as the only pathological change (Katafuchi and Takebayashi, 1987; Harvey et al., 1992). This may have clinical implications, since nephrosclerosis is frequently the only morphological diagnosis in patients with chronic renal disease at the start of dialysis (Malangone et al., 1989). The evidence for a relationship between mild to moderate hypertension and either nephrosclerosis or end-stage renal disease (ESRD) remains circumstantial and controversial. The Framingham population studies, which identified risk factors for cardiovascular

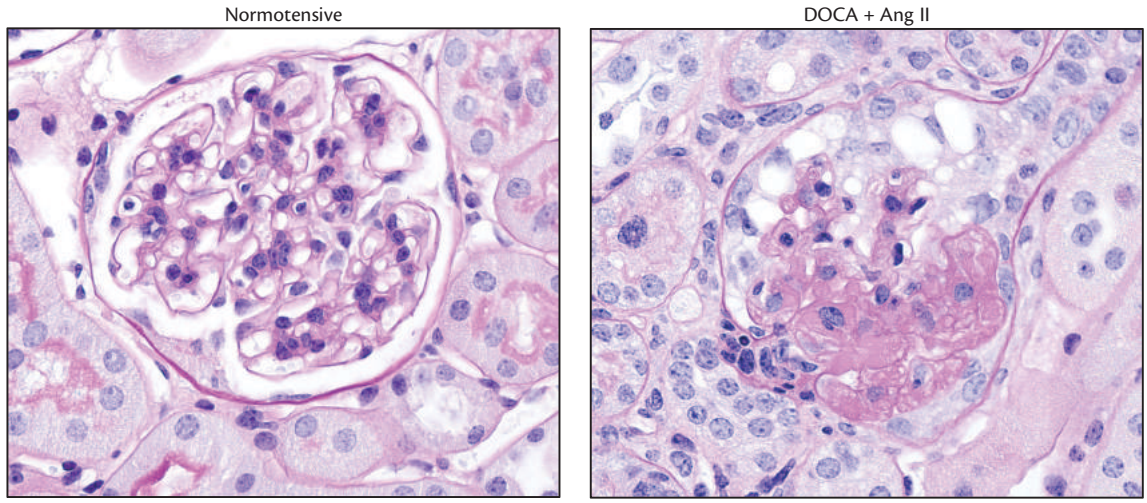

Fig. 211.9 Glomerular morphology revealed by PAS staining (×200 magnification). DOCA + Ang II induces focal and segmental injury in the glomeruli of the hypertensive mice with capillary obsolescence with plasma insudation and matrix expansion.
Reproduced with permission from Krebs, C., Fraune, C., Schmidt-Haupt, R., *et al.* (2012). CCR5 deficiency does not reduce hypertensive endorgan damage in mice. *Am J Hypertension*, 25, 479–86.

morbidity and mortality, did not evaluate the impact of hypertension on renal failure because of the low incidence of renal failure in that population (Kannel, 1983). Patients with essential hypertension do not routinely undergo diagnostic renal biopsy. However, from 80 kidney biopsies in hypertensive patients with moderate renal insufficiency, 65% showed only benign or malignant nephrosclerosis as diagnosis, suggesting that both can be a definite cause of chronic renal insufficiency (Caetano et al., 2001).

The frequency of hypertension as a reported cause of ESRD has reportedly increased. This is seemingly paradoxical since effective pharmacological control of blood pressure in the past two decades has led to a decrease in the prevalence of malignant hypertension as well as cardiovascular morbidity related to hypertension. It should be noted, however, that the very protective effect of antihypertensive therapy against cardiovascular disease, by improving life expectancy, may prolong the time available for hypertensive renal disease to progress, thus increasing in the long run the number of patients suffering from terminal renal disease (Caetano et al., 1999). As a consequence, previously most hypertensive patients likely died from cardiovascular events before advanced nephrosclerosis

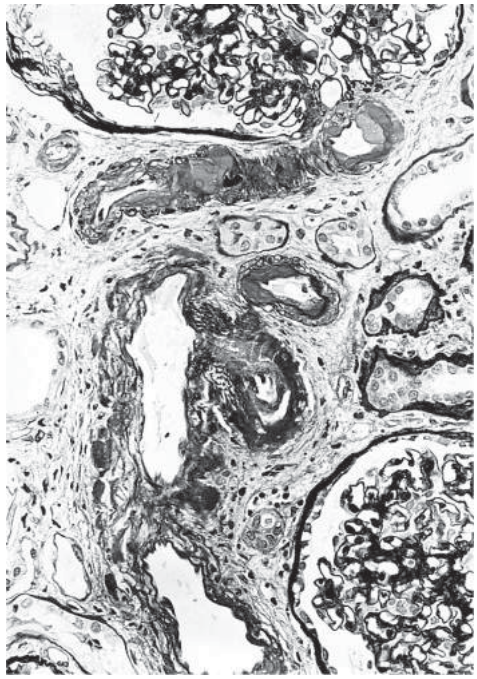

Fig. 211.10 Benign nephrosclerosis: segmental hyalinization of interlobular arteries and afferent arterioles; focal tubular atrophy and interstitial fibrosis. Renal biopsy of a hypertensive man, aged 36 years, with IgA nephropathy (periodic acid–Schiff reagent; magnification ×360).

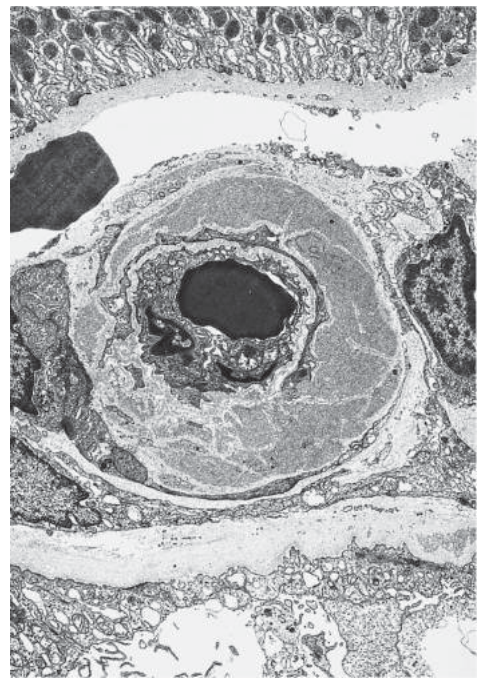

Fig. 211.11 Benign nephrosclerosis: plasmic material within the partially destroyed media of a peripheral interlobular artery. Renal biopsy of the same patient as in Fig. 211.10 (transmission electron microscopy; magnification ×4800).

became manifest. Hypertensive nephrosclerosis started to stand out as a presumed cause of ESRD only in the early 1980s, coinciding with a steady increase in the mean age of new dialysis patients. Meanwhile the rate of ESRD exceeds mortality among African Americans with 'hypertensive nephrosclerosis' (Alves et al., 2010). Increased serum creatinine at baseline, proteinuria, and age are independent predictors for the development of a renal event in patients having the presumed diagnosis of nephrosclerosis (Segura et al., 2001).

Nephrologists identify hypertension as the aetiology of nephrosclerosis in 25% of patients initiating renal replacement therapy in the United States (Weisstuch and Dworkin, 1992). The percentage is lower in Europe and Australia. In a study performed in Leicester, England, which followed 176 patients with essential hypertension with suboptimal blood pressure control for 14 years, no patient reached ESRD (Tomson et al., 1991). Kincaid-Smith (1999) wrote: 'Benign hypertension does not cause clinically significant renal damage. The kidney in benign hypertension remains normal in both size and function.' However, Kincaid-Smith's data pertain to a period that started in the 1960s. Perhaps at these times patients suffering from arterial hypertension died from cardiovascular events before reaching ESRD due to hypertensive nephrosclerosis.

Nephrosclerosis in Africans

The risk of hypertensive ESRD is believed to be greater in the black population (Rostand et al., 1982). However, nephrologists are twice as likely to label an African American patient as having hypertensive nephrosclerosis as a white patient, when presented with identical clinical history (Freedman et al., 1995). The strong association of this diagnosis with polymorphisms of the *APOL1* gene (see Chapter 341), which is also implicated in genetic focal segmental glomerulosclerosis, suggests that the association with hypertension may be secondary; unless the gene predisposes to hypertensive injury. In contrast, a close agreement between clinical and histological diagnosis of hypertensive nephrosclerosis could be demonstrated in African Americans as shown by Fogo and co-workers. In nearly 85% of these patients, renal histological examination was consistent with the clinical diagnosis by revealing the presence of exclusively vascular lesions (Fogo et al., 1997). It has been demonstrated that strict blood pressure control can stabilize renal function in black patients thought to have hypertensive nephrosclerosis (Toto et al., 1995).

Other causes of nephrosclerosis

The estimates of the likelihood of essential hypertension causing ESRD vary among countries and between renal units depending upon the enthusiasm with which a primary diagnosis is pursued (Brown and Whitworth, 1992). It also seems that renovascular disease, ischaemic nephropathy, and cholesterol microembolization may either cause or accelerate renal insufficiency in a larger portion of the atherosclerotic population with hypertension and renal insufficiency than previously recognized (Jacobson, 1988; Alcazar and Rodicio, 2000). Hypertension-induced benign nephrosclerosis may also accompany and aggravate other renal disorders. Clinical and pathological studies have indicated that the progression of IgA glomerulonephritis and the development of chronic renal failure may be enhanced by hypertension-induced intrarenal vascular lesions (Feiner et al., 1982). Segmental hyalinosis of interlobular arteries and efferent arterioles is frequently observed at a time when the glomerular and tubular interstitial structures are still completely preserved, and this probably reflects the earliest hypertension induced intrarenal lesion. Arterial fibroplasia is a better correlate of high blood pressure than is parenchymal fibrosis, suggesting that blood pressure relates less to the renoprival state of nephron loss than it does to renal ischaemia in patients with nephrosclerosis (Tracy, 1992). Theoretically, it may undergo remission, although it may also be followed by focal and segmental glomerular damage. In the early stages of the glomerular injury, the capillary loops adjacent to the vascular pole characteristically show a widening of the mesangium, swelling of endothelial cells, and sometimes an occlusion of the lumina filled with condensed material derived from the plasma. Thereafter, formation of an irregular basement membrane and segmental extracapillary cell proliferations may lead to capsular adhesions, finally resulting in focal and segmental glomerulosclerosis (Fig. 211.12).

Malignant hypertension

While there is debate about the role of hypertension in 'benign' nephrosclerosis, it is acknowledged to be central to malignant hypertension (Chapter 216). Renal dysfunction remains an important cause of morbidity and mortality (van den Born et al., 2005). Most kidney biopsies of patients with malignant hypertension show an obliterative vasculopathy with fibrinoid necrosis and sometimes thrombosis of interlobular arteries, as described in Chapter 216.

Ischaemic lesions

A second type of glomerular lesion is characterized by the ischaemic collapse of the glomerular tuft. This is more frequently seen in kidneys with pronounced narrowing of the pre-glomerular vessels, as is commonly observed in malignant nephrosclerosis (Fig. 211.13). Ischaemic wrinkling collapse of the glomerular tuft is seen much more commonly in hypertensive nephrosclerosis than is focal glomerulosclerosis, which is the characteristic lesion

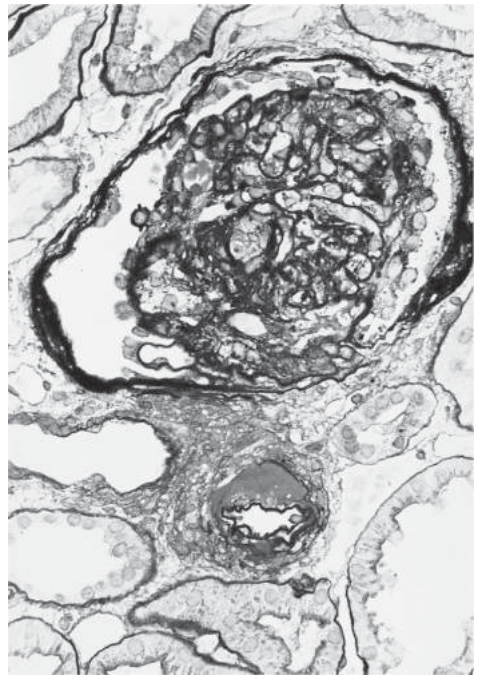

Fig. 211.12 Focal glomerulosclerosis in benign nephrosclerosis. Renal biopsy of a hypertensive man aged 41 years (periodic acid–Schiff reagent; magnification ×360).

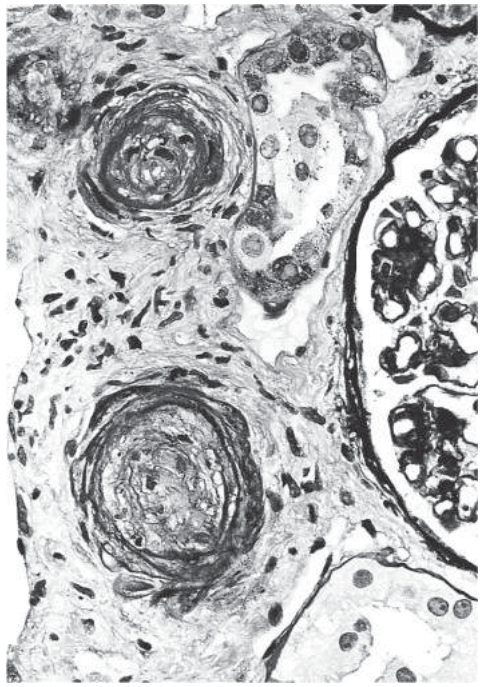

Fig. 211.13 Malignant nephrosclerosis: interlobular arteries with obliterating proliferative 'endarteritis Fahr'. Ischaemic collapse of capillary loops of an adjacent glomerulus. Renal biopsy of a man aged 32 years with accelerated hypertension (periodic acid–Schiff reagent; magnification ×360).

of the adapted hyperperfused nephron. The occurrence of irreversible hypertension-related glomerular injury marks the transition to 'decompensated benign nephrosclerosis', which carries an increased risk of steadily advancing tubular atrophy and interstitial fibrosis (Bohle and Ratschek, 1982). Progression to chronic renal insufficiency may be inevitable. Kannel (1977, p. 908) stated that there is nothing benign in any kind of hypertension. From the morphological point of view, one may add that there is nothing benign in nephrosclerosis. The principal difference between the two forms of nephrosclerosis is that the structural changes of the so-called benign variety are mainly confined to the media, particularly during the early stages, whereas even the early lesions of malignant nephrosclerosis predominantly affect the intimal space. It is this subendothelial compartment of the vascular wall that becomes widened, initially containing plasma and corpuscular blood constituents, but during the later stages also containing numerous myointimal cells as well as collagen fibres. Although medial fibrinoid necrosis may also occur, the intimal process is the first phenomenon and remains dominating, potentially leading to an extreme narrowing of the vascular lumen. The term 'malignant nephrosclerosis' actually covers quite different morphological findings (see Chapter 216); at different stages a subendothelial oedema, an intimal cell proliferation ('endarteritis'), or the onion-like appearance of intimal scarring may predominate. The initial intimal oedema is assumed to be reversible following effective lowering of blood pressure (Helmchen and Kneissler, 1976). This may be important, and suggests that even this type of nephrosclerosis may not necessarily be 'malignant'. As in experimental animals, malignant nephrosclerosis in the human kidney also develops predominantly in the interlobular arteries and afferent arterioles. Secondary to a progressive narrowing of these vessels, hyperplasia of the juxtaglomerular epithelioid cells, ischaemic collapse of the glomerular tufts, tubular atrophy, and interstitial fibrosis may follow (Heptinstall, 1953) (Fig. 211.13). These morphological findings reflect the two basic mechanisms of the vicious circle of hypertension: the activation of the renin–angiotensin system and the impairment of the excretory renal capacity. Functionally, the situation resulting when hundreds of intrarenal arteries are significantly narrowed is comparable to severe stenosis of the main renal artery. In the presence of renal artery stenosis or malignant nephrosclerosis, pharmacological blockade of the renin–angiotensin system may be regarded as an effective antihypertensive therapy. However, this may cause a further undesired reduction in the residual glomerular filtration rate and may also accelerate tubular atrophy owing to reduction of the angiotensin II-dependent tone of the efferent arterioles (Collste et al., 1979; Helmchen et al., 1982; Hricik et al., 1983; Groene and Helmchen, 1986).

Conclusion

It remains to be determined whether high blood pressure alone is sufficient to cause malignant nephrosclerosis in humans. Although the evidence seems to be conclusive in patients with renal hypertension, experimental results show that even under well-defined conditions additional factors might be required to initiate the crucial intimal thickening. If high blood pressure alone is the cause of malignant hypertension, the widespread use of antihypertensive medication and the increasing frequency of diagnosis of mild to moderate hypertension should have the effect that malignant hypertension becomes less common. However, there is only limited evidence for this, and the incidence of malignant hypertension in the United Kingdom has failed to decline (Lip et al., 1994).

In advanced malignant nephrosclerosis, autopsy and biopsy material do not indicate whether hypertension is the cause or the result of the vascular disorder, and there is evidence that malignant nephrosclerosis can develop in previously normotensive patients suffering from haemolytic uraemic syndrome or from postpartum acute kidney injury (Bohle et al., 1973, 1976; Thoenes and John, 1980). MacMahon (1966) suggested that most cases of malignant nephrosclerosis were hypertensive in origin. It is probable that inflammation, humoral factors, and pressure play a role in the process of malignant nephrosclerosis. In any case, strict antihypertensive therapy should be encouraged and recovery of renal function is possible (see Chapter 216).

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CHAPTER 212

Ischaemic nephropathy

Helen Alderson, Constantina Chrysochou, James Ritchie, and Philip A. Kalra

Introduction

Ischaemic nephropathy is caused by haemodynamically significant obstruction in both renal arteries, or in one artery where a solitary kidney is present. In 1934, Goldblatt demonstrated that unilateral renal artery stenosis could lead to bilateral renal damage through the development of chronic hypertension (Goldblatt, 1934). Although renal impairment resulting from renovascular hypertension is important and may coexist with ischaemic nephropathy, this chapter focuses more specifically on ischaemic renal damage occurring downstream of renal artery stenosis.

Epidemiology

Establishing the true incidence of ischaemic nephropathy is challenging, not least because a precise definition for this condition does not exist. Many studies are undertaken in select patient groups and do not always report on an aetiological relationship between renal artery disease and renal dysfunction. There may be confounding by the high rates of coexistent diabetes and hypertension. In the Western world, the major cause of ischaemic nephropathy is atherosclerotic renovascular disease (ARVD). Although fibromuscular dysplasia may lead to significant narrowing of the renal artery it is unusual for this to result in ischaemic renal damage, suggesting that other factors within the milieu of atherosclerosis are important.

Risk factors for ARVD are the same as for other atheromatous conditions, with prevalence increasing with age in autopsy studies (Schwartz and White, 1964). There are few studies to determine the prevalence of ARVD and ischaemic nephropathy in the general population. Hansen et al. demonstrated a 6.8% prevalence of renal artery stenosis ≥ 60% in healthy US adults > 65 years of age (Hansen et al., 2002). A further study looked at a US Medicare population of patients aged > 67 years in the period 1998–1999 and showed an ARVD incidence of 0.54% or 3.7/1000 patient-years (Kalra et al., 2005).

In selected or 'atheromatously enriched' patient groups, prevalence is higher with studies showing 20% prevalence in those with coexistent diabetes and hypertension (95% confidence interval 15.4–25.5%) (de Mast and Beutler, 2009). In those with coronary artery disease, prevalence of renal artery stenosis is high, between 11% and 19.5% in angiography studies (Cohen et al., 2005; Rigatelli et al., 2005; Ollivier et al., 2009).

It is difficult to estimate the proportion of cases of end-stage kidney disease (ESKD) caused by ischaemic nephropathy, not least because hypertension and diabetes are often coexistent. Registry data suggest renovascular disease is responsible for approximately 2% of cases of ESKD in the United States (Fatica et al., 2001). However, ARVD is defined as the primary disease in 10.8% of incident UK dialysis patients > 65 years of age (Farrington et al., 2009). In a study of 269 older patients with hypertension or chronic kidney disease (CKD) without an established aetiology, the presence of renal artery stenosis was determined with colour duplex ultrasound. Prevalence was shown to increase with age, affecting 11% of 50–56-year-olds, 18% of 60–69-year-olds, and 23% of those > 70 years of age (Coen et al., 2003).

Causes of ischaemic nephropathy

The causes of ischaemic nephropathy are the causes of renal artery stenosis as outlined in Chapter 213 with the addition of aortic diseases such as middle aortic syndrome (MAS) (Box 212.1).

Middle aortic syndrome

MAS is a rare condition, referring to an isolated narrowing of the abdominal aorta and visceral arteries. This descriptive term was first coined by Sen in 1963, although clinical descriptions date back to the nineteenth century (Sen, 1963). In > 90% of cases there is coexistent renal artery stenosis, leading to renovascular hypertension and in some cases renal ischaemia.

MAS is a clinicoanatomical description of a smooth tubular narrowing of the abdominal aorta without evidence of inflammation. It does not refer to the aetiology of the condition which may be embryological in origin (Panayiotopoulos et al., 1996). It has been associated with Williams syndrome and neurofibromatosis, suggesting a genetic component. Although cases may resemble fibromuscular dysplasia it is a separate entity and is distinct from Takayasu disease and other inflammatory arteritides (Sumboonnanonda et al., 1992)

Box 212.1 Causes of ischaemic nephropathy

- Fibromuscular disease (Chapter 213)
- Atherosclerotic renal disease (Chapter 213)
- Takayasu arteritis (Chapter 213)
- Middle aortic syndrome (this chapter)
- Aortic dissection and other causes of occlusion of the aorta.

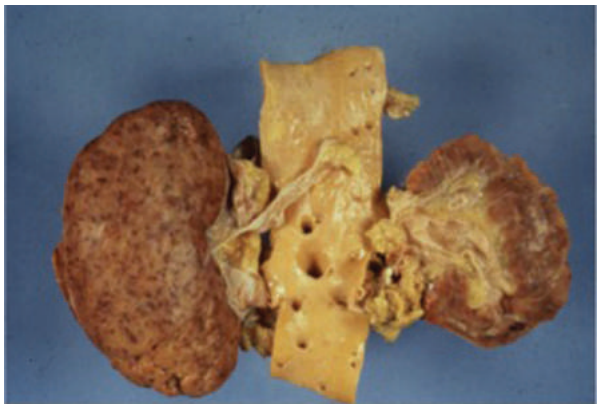

Fig. 212.1 Autopsy specimen demonstrating atrophy of left kidney due to significant renal artery stenosis. Note the abnormal appearance of the normal-sized right kidney—due to hypertensive parenchymal injury.

MAS predominantly affects children and young adults, with median age at presentation of 2.7 years in one retrospective review (Tummolo et al., 2009), with the youngest case reported in the literature to date being a 9-day-old neonate (Sethna et al., 2008). It presents with hypertension of the upper limbs, often with weak peripheral pulses and abdominal bruits. Claudication may be present, although the development of extensive collaterals means that this is often an asymptomatic condition. Abdominal angina may occur as a result of narrowing of the superior mesenteric artery and presentations with heart failure have also been described.

MAS is diagnosed on angiography. Ninety per cent of cases can be successfully managed, but without treatment death invariably occurs by the fourth decade (Panayiotopoulos et al., 1996). Medical therapy for hypertension is the initial treatment of choice for most patients, although failure of medical therapy, worsening renal function, claudication, and intestinal ischaemia may necessitate radiological or surgical intervention (Sethna et al., 2008).

Transluminal balloon angioplasty can be associated with high re-stenosis rates and can be complicated by aneurysm formation and vessel rupture (Lewis et al., 1988). Increasing success is being observed with stenting procedures, although re-stenosis remains a problem (Brzezinska-Rajszys et al., 1999).

Surgery is reserved for cases that are not amenable to percutaneous intervention or where re-stenosis has occurred. Procedures may include aortic bypass and re-implantation of renal arteries, aortic graft insertion or reconstruction, and in some cases autologous renal transplantation. Timing of surgery requires careful consideration and expert planning; where possible it is delayed until adolescence to reduce the need for repeat procedures as the child grows (Tummolo et al., 2009).

Clinical features

Ischaemic nephropathy most commonly presents as CKD. Although renovascular disease is usually associated with low or normal levels of proteinuria, this can sometimes be prominent in some patients with chronic ischaemic nephropathy without other apparent cause. Proteinuria and CKD are discussed here. The other manifestations of ischaemic nephropathy are those of renal artery stenosis as described in Chapter 213:

- Acute kidney injury and rapid decline in renal function
- Hypertension
- Renin angiotensin blocker (RAB)-induced acute kidney injury
- Flash pulmonary oedema

Chronic kidney disease

CKD is the commonest presentation of ARVD. It may be asymptomatic or discovered after investigating features attributable to renal artery stenosis or occlusion. In the majority of these patients, hypertension is a feature, but the role of hypertension in contributing to renal damage is unclear (see Chapter 211).

Disease in smaller vessels, and irreversible effects of ischaemia, presumably explain why there is not universal benefit from revascularization in patients with ARVD and CKD.

Proteinuria

Proteinuria is usually absent or mild but in some patients may be nephrotic range. Several case studies have reported significant proteinuria in the context of renal artery stenosis (Montoliu et al., 1979; Eiser et al., 1982; Sato et al., 1989). In each of these case studies, proteinuria was associated with high renin levels and normal renal biopsy. It resolved fully on removal of the stenotic kidney. In a subsequent case study, administration of an angiotensin-converting enzyme inhibitor also led to resolution of the proteinuria with relapse on drug withdrawal (Docci et al., 1992). These findings suggest that high renin levels could be the driving force for the observed proteinuria in some patients.

There is an association between chronic ischaemia in ARVD and focal segmental glomerulosclerosis (FSGS). Thadhani et al. reported a retrospective case series of 59 native renal biopsies with FSGS. Eight of these cases had ARVD, seven of whom presented with significant proteinuria. On follow-up, all of the patients had increasing serum creatinine (Thadhani et al., 1996). Changes of benign nephrosclerosis (significance discussed in Chapter 211) are common.

The presence of proteinuria in ARVD highlights the importance of renal parenchymal damage as a determinant of the severity of ischaemic nephropathy (Makanjuola et al., 1999). It must be remembered that patients with ARVD often have coexistent hypertension and diabetes, both of which may be important contributing factors to the presence of proteinuria.

Pathology of ischaemic nephropathy

In a human autopsy study, Marcussen demonstrated a reduction in tubule numbers and marked tubular atrophy in kidneys where renal artery stenosis was present in comparison to autopsy cases without renal artery disease. Glomeruli were preserved, but they did not connect to normal tubules and interstitial fibrosis was present (Marcussen, 1991).

Histological examination of 62 small post-nephrectomy kidneys taken from humans affected by severe renal artery stenosis was reported by Keddis et al. The most common histological finding was severe tubulointerstitial atrophy with relative glomerular sparing. Some kidneys demonstrated global glomerulosclerosis but this was a less common finding (Keddis et al., 2010). These features are shown in Fig. 212.2. In atherosclerotic renal disease, particularly but not necessarily after an acute deterioration, evidence of cholesterol embolization may be seen (Fig. 212.3).

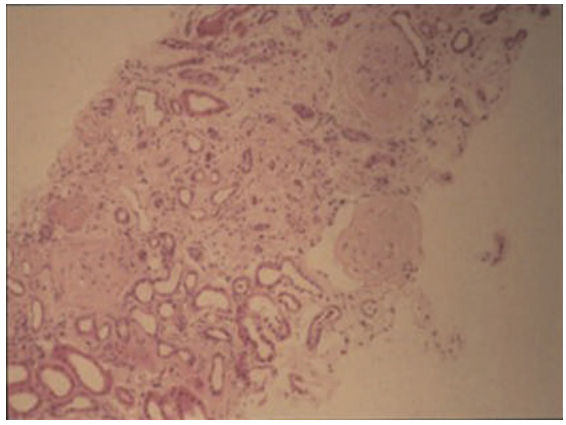

Fig. 212.2 Histopathological appearances in ARVD demonstrating widespread tubular loss and interstitial fibrosis with glomerulosclerosis (haematoxylin and eosin (H&E) ×10).
Courtesy of Dr R. Reeve, Consultant Histopathologist, Salford Royal Hospital, Salford, UK.

A single-centre analysis of 25 renal biopsies from patients with histology typical of atherosclerotic nephropathy demonstrated that the severity of histopathological damage and reduction in interstitial volume in this cohort were associated with worse renal function, proteinuria, and systolic hypertension and predictive of future worse renal functional outcome (Wright et al., 2001).

Renal artery occlusion leads to a marked reduction in renal function, but the relationship between lesser degrees of renal artery narrowing and renal function is less predictable (Textor, 1994; Suresh et al., 2000; Cheung et al., 2002).

Management

Management of the different causes of ischaemic nephropathy is discussed in Chapter 215.

Outcomes

Outcomes appear to have improved considerably, possibly due both to better therapies for atherosclerotic disease and greater ability to image renal arteries to identify less aggressive disease.

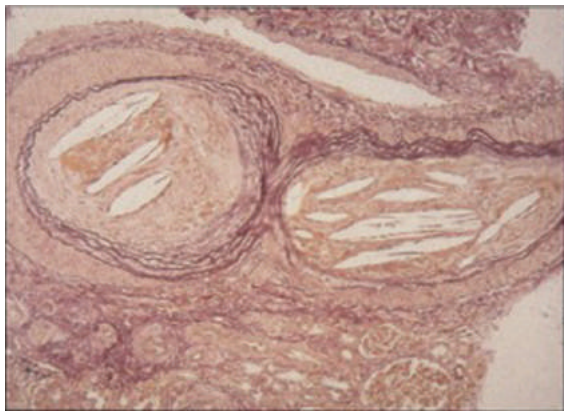

Fig. 212.3 Histopathological appearances of cholesterol emboli within the renal interlobular artery (H&E).

Renal outcomes

Earlier studies focused on renal artery imaging. In the 1980s, Shreiber et al. studied 80 patients who had serial renal angiograms over a mean follow-up period of 52 months. There was progression of renal artery stenosis in 44% of the study group with renal artery occlusion observed in 16% (Schreiber et al., 1984). Later studies show much lower rates of progression. A study in the 1990s showed progression of renal artery stenosis in 11.1% of the 1189 cases studied over a mean follow-up of 2.6 years (Crowley et al., 1998).

However, there is no clear correlation between rate of progression of the stenotic lesion and renal function or other clinical outcomes (see Chapter 215) (Fig 212.4). Cheung et al. studied 142 patients with unilateral renal artery occlusion and either a normal contralateral renal artery or one with a stenotic lesion. There was no relationship between baseline renal function and contralateral renal anatomy. Furthermore, vascular anatomy had no impact on the rate of change in renal function over the 31-month follow-up period. There was an average rate of loss of renal function of 4.1mL/min/year (Cheung et al., 2002). A similar rate of loss of function was observed in an analysis of 51 patients with bilateral renal artery stenosis who received medical management. Over a mean follow-up period of 51 months, the average rate of loss of renal function was 4mL/min/year (Baboolal et al., 1998). Intrarenal ischaemia and parenchymal disease, the latter thought to be due to hypertensive and atherosclerotic injury, appear to be more important than the degree of stenosis in determining outcomes in ARVD.

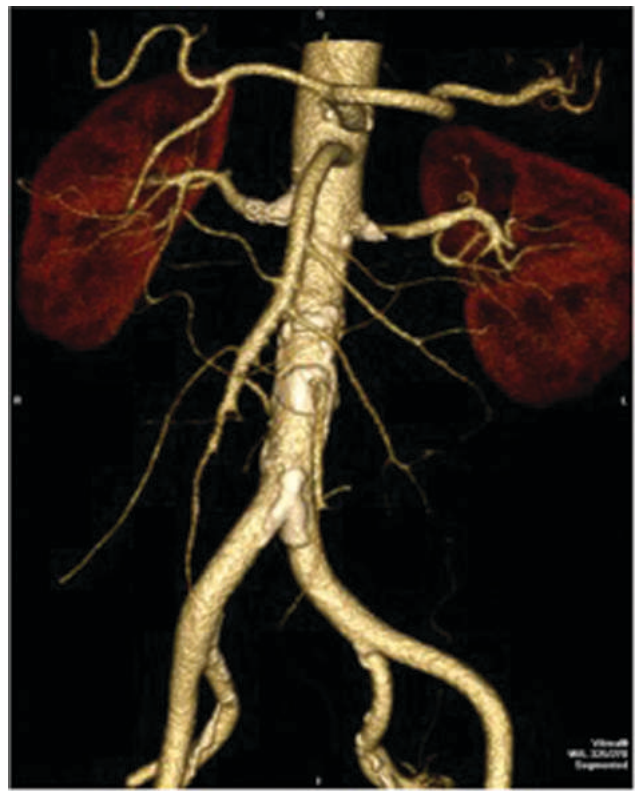

Fig. 212.4 CT renal angiogram. There is a stent within the first part of the right renal artery.
Image courtesy of Professor Jon Moss, Consultant Interventional Radiologist, Gartnavel Hospital, Glasgow, UK.

Better predictors of functional outcome in ARVD appear to be glomerular filtration rate (GFR) at baseline and renal atrophy. Caps et al. performed serial duplex ultrasound scans on 204 patients over a 2-year follow-up period. Renal atrophy was defined as > 1 cm shrinkage in bipolar length. Twenty per cent of those with renal artery stenosis showed atrophy, compared with only 5.5% in normal kidneys. Hypertension, degree of stenosis, and reduced renal blood flow were all predictive of atrophy. Renal atrophy was associated with increased creatinine at follow-up (Caps et al., 1998).

Can collateral circulation explain differences?

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. In a series of 39 patients, 17 had a collateral circulation identified on angiography (Hietala and Kunz, 1979). These vessels are able to contribute > 50% of basal renal blood flow and may be another explanation as to why severity of renal artery stenosis does not necessarily correlate with renal function, and also why renal infarction is unusual in ARVD. Animal models suggest that this collateral circulation begins to develop when main vessel stenosis exceeds 40–50% (Eliška, 1966).

In ARVD, renal arteries are not the major determinant of outcome

Patients presenting with ARVD invariably have significant vascular co-morbidity and survival is poor with more patients dying from cardiovascular disease than progressing to ESRF. In an investigation of the elderly US Medicare population, the annual mortality amongst patients with ARVD was 16.3%. The average mortality in patients without ARVD was 6.4% (Kalra et al., 2005). Mailloux et al. found that patients with ARVD had a worse prognosis after initiation of dialysis than patients with other primary renal diseases. Median survival was 27 months for ARVD patients (Mailloux et al., 1994). Other studies suggest that the high mortality rate of patients with ARVD receiving dialysis is simply a reflection of the general burden of atherosclerosis and co-morbidities in this population rather than the renal artery stenosis per se (Guo et al., 2006).

Numerous investigators have looked at factors that determine survival in patients with ARVD. Baseline estimated GFR (Wright et al., 2002), proteinuria (Chrysochou et al., 2009), and the presence of extrarenal macrovascular disease (Conlon et al. 1998; Shurrab et al., 2003) have all been shown to be significant factors. Targeting modifiable risk factors may favourably affect prognosis. The progression of renal artery stenosis lesions has already been discussed above.

Interestingly the presence of renal artery stenosis has been shown to be an adverse prognostic factor amongst patients presenting with other vascular disease. Conlon et al. studied the effect of renal artery stenosis on the prognosis of 3987 patients undergoing elective diagnostic coronary angiography. Renal artery stenosis of > 75% was associated with a 4-year survival of 57%, which compared adversely with a survival of 89% in those patients without significant renal artery stenosis. The degree of renal artery stenosis was also shown to be important in this cohort of patients with coronary disease (Conlon et al. 2001).

Management of vascular risk is central to the treatment of patients with atherosclerotic ischaemic nephropathy (see Chapter 215).

Pathophysiology and pathogenesis

Given that ischaemic nephropathy is not solely related to the degree of renal artery narrowing, it is important to consider the pathogenesis of this condition in more detail.

Renal artery narrowing and blood flow

In the nineteenth century, Poiseuille described how flow along a vessel is proportional to vessel length and blood viscosity but inversely proportional to the radius to the power of 4. So, relatively small changes in vessel diameter can lead to significant increases in resistance to flow.

May et al. demonstrated that a reduction in canine femoral artery blood flow was seen when vessel diameter was reduced by 50%. There did not appear to be any flow reduction before this threshold but after this level flow reduced dramatically (May et al., 1963). These findings were echoed by Schoenberg et al. who showed a fall in renal blood flow at > 50% reductions in vessel diameter (Schoenberg et al., 2002). Imanishi et al. showed a reduction in renal artery blood flow at > 75% stenosis in the dog, and hypertension when renal artery stenosis was > 70% (Imanishi et al., 1992). These data suggest that there may be a threshold stenosis before renal blood flow is reduced and after which renal damage and ischaemic nephropathy may develop. However, in atherosclerotic renovascular disease, atheromatous plaque formation may not be uniform or continuous. Furthermore, vessel diameter and blood flow are not the sole determinants of renal function in this situation; possibly atheroemboli and other facts play a part (see below). The rarity of ischaemic nephropathy in fibromuscular disease is an indication of this.

Pressure-dependent flow

In the presence of renal artery stenosis, renal blood flow may be sensitive to changes in blood pressure as well as vessel calibre. Textor et al. investigated the relationship between renal blood flow, blood pressure, and renal function in 16 patients. Nitroprusside was used to induce a reduction in blood pressure. In the eight subjects with unilateral renal artery disease, a reduction in blood pressure did not cause reduced renal blood flow. Conversely, in the eight subjects with bilateral severe stenosis (all arteries > 70% stenosis) a reduction in blood pressure did lead to a marked but reversible reduction in renal blood flow (Textor et al., 1985). This pressure dependency of flow was obliterated by re-vascularization. Nahman and Maniam demonstrated a dramatic reduction in renal artery pressure gradient with angioplasty, but this did not correlate with an improvement in functional outcome (Nahman and Maniam, 1994). So in severe renal artery stenosis, aggressive antihypertensive therapy may precipitate a decline in renal function.

Ischaemic renal damage

When blood flow is insufficient to meet renal metabolic demands, tubular ischaemia ensues (Textor and Wilcox, 2001). In rats subject to 28 days of renal artery stenosis, significant tubulointerstitial damage occurred with chronic inflammatory infiltrates seen in the interstitium; B lymphocytes, T-helper lymphocytes, and macrophages were all present (Truong et al., 1992). Gobe et al. also

showed interstitial apoptosis and necrosis in the presence of renal artery narrowing in rats (Gobe et al., 1990).

Although individual episodes of renal injury as a result of tissue hypoperfusion may be recoverable, repeated episodes may provoke mechanisms that lead to tissue fibrosis and diminishing renal function (Nath et al., 2000).

Renal microcirculation

Tissue hypoperfusion and hypoxia result in loss of renal microvasculature (Chade and Kelsen, 2010; Chade, 2011). Microvasculature refers to vessels 0–200 μm in diameter, so encompasses all vessels from capillaries to interlobular arteries and veins. Microvascular damage leads to tubulointerstitial ischaemia and fibrosis (Sila-asna et al., 2006) and may affect the success of revascularization procedures.

In the context of ischaemia, neovascularization within the microvasculature occurs to sustain tissue perfusion (Chade et al., 2007). The microvasculature maintains plasticity and is able to regulate angiogenesis in response to changes in local metabolic requirements (Levy, 2006). Vascular endothelial growth factor may play an important part in this reparative process (Chade and Kelsen, 2010).

Other mechanisms of damage and fibrosis

Atherosclerosis is increasingly recognized as a state of chronic inflammation and endothelial dysfunction. In a swine model of renal artery stenosis, hypercholesterolaemia resulted in detrimental effects on renal function (Chade et al., 2002). Histological examination of the swine kidneys showed fibrotic changes, particularly evident in the tubular and glomerular compartments (Chade et al., 2003). Mediators are postulated to include oxygen free radicals and vasoconstrictors such as angiotensin II, thromboxane A2, endothelin-1, and noradrenaline (norepinephrine), but the determinants of progressive renal fibrosis in these circumstances need further elucidation.

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CHAPTER 213

Renal artery stenosis: clinical features and diagnosis

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Constantina Chrysochou, and Philip A. Kalra

Epidemiology

Renal artery stenosis (RAS) and occlusion (RAO) describe reduction of and complete loss of patency. A range of pathophysiological processes, each with varying prognostic and treatment implications, can cause this. Renal artery stenosis in children is described in Chapter 218 (Box 218.2).

Fibromuscular disease

Prevalence

Fibromuscular disease (FMD) is a condition that is neither inflammatory nor atherosclerotic, and which accounts for approximately 10% of cases of renovascular hypertension (Safian and Textor, 2001). Though generally perceived to be rare, with previous estimates of a 0.4% prevalence in the hypertensive population (Plouin et al., 2007), it is likely that FMD is instead underdiagnosed. The wide spectrum of presentations, ranging from asymptomatic disease to extreme cases that clinically mimic vasculitis (Olin, 1991), may contribute to this. Four studies have retrospectively reviewed the prevalence of FMD in 3181 patients where renal angiography was performed as part of a screening process for kidney donation. Although radiological criteria varied between studies, the overall prevalence of FMD was 4.4% with a range of 3.8–6.6% (Cragg et al., 1989; Neymark et al., 2000; Andreoni et al., 2002). There is a marked female preponderance with women affected at a ratio of 9:1 compared to men (Olin and Sealove, 2011). Familial clustering may also occur, with one series reporting a familial link in 11% of FMD patients (Pannier-Moreau et al., 1997).

Territories affected

Any arterial bed can be affected by FMD. The renal vessels are the most commonly involved territory with 75% of patients having evidence of disease here (35% of whom have bilateral disease). The carotid and vertebral arteries are the next most commonly affected sites. A small proportion of patients can present with diffuse disease affecting a range of smaller vessels; in extreme cases this presentation can mimic a necrotizing vasculitis (Slovut and Olin, 2004; Olin, 2007). Table 213.1 summarizes the most recent data on the distribution of vascular beds affects in FMD (Olin et al., 2012).

Causal factors in the development of FMD are poorly understood. Many plausible associations are inconsistently or tentatively described.

Gender

Due to the female preponderance of FMD, oestrogen exposure has been hypothesized as a causal factor; however, no positive link has been described when surrogate measures of endogenous oestrogen exposure has been defined by number of pregnancies (Lüscher et al., 1987), or when exogenous oestrogen is defined by use of oral contraceptives (Sang et al., 1989). An alternative hypothesis, that renal arteries in females are more prone to repeated stretching micro-trauma due to their greater mobility than in men, has also been shown to be false (Sang et al., 1989).

Smoking

The greatest body of evidence for a causal linkage in FMD exists for smoking. In a case–control study of 71 patients with a mixture of normal and abnormal renal vessels (due both to atheroma and FMD), 71% of patients with FMD had a smoking history compared to 41% of patients with normal renal arteries (Nicholson et al., 1983). A similar finding has been described in another case–control study where a history of smoking was associated with an odds ratio of 4.1 for the presence of FMD (95% confidence interval 1.5–10.9, $P = 0.003$) (Sang et al., 1989). New data from the Fibromuscular Disease Registry suggest this causal association may be weaker than previously thought. Of the first 447 patients enrolled, only 37% had a history of tobacco exposure, although in those with a smoking history the mean number of pack-years was 22 ± 23 (Olin et al., 2012). This may support a two-hit hypothesis in which smoking may relate to increased risk for development of FMD and/or increased risk for more severe disease (Bofinger et al., 1999).

Genetic linkage

As FMD can remain clinically undetected, association studies are limited in their ability to describe a pattern of inheritance. There is a belief that an autosomal dominant trait with variable penetrance may exist (Rushton, 1980). However, in data from the Fibromuscular Disease Registry, only 7% of the first 447 recruited patients were known to have a first- or second-degree relative with an established diagnosis of FMD (Olin et al., 2012). This is a lower figure than reported in a previous screening study, where evidence of FMD was seen in 11% of first-degree relatives (Perdu et al., 2007). Larger studies are required before firm conclusions can be made.

Table 213.1 Prevalence of fibromuscular disease and associated in complications in the main vascular territories

Vascular bed	Prevalence of fibromuscular disease	Prevalence of dissection when investigated	Prevalence of aneurysm when investigated
Renal	80%	22%	33%
Carotid artery	74%	75%	21%
Vertebral artery	37%	17%	3%
Mesenteric	26%	5%	7%

Data adapted from the first 447 patients recruited to the United States Registry for Fibromuscular Dysplasia (Olin et al., 2012).

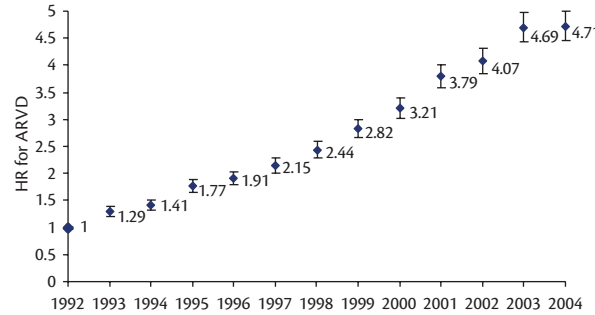

Fig. 213.1 Unadjusted hazard ratios, with 95% confidence intervals for atherosclerotic renovascular disease in United States Medicare claims data by calendar year with 1992 as reference category.

Reprinted by permission from Macmillan Publishers Ltd: *Kidney International*, Philip A Kalra, Haifeng Guo, David T Gilbertson, Jiannong Liu, Shu-Cheng Chen et al., Atherosclerotic renovascular disease in the United States, 77/1, copyright 2010.

Small series had suggested that alpha-1-antitrypsin deficiency may be associated with the development of FMD (Schievink et al., 1998). A recent large-scale case–control study has demonstrated this to be false. Here, 161 patients with FMD were compared to 1085 control patients who were subgrouped into hypertensive, normotensive, and female hypertensive cohorts (Perdu et al., 2006). No significant difference in any of three recognized alpha-1-antitrypsin polymorphisms existed between groups.

Atherosclerotic renovascular disease

The term atherosclerotic renovascular disease (ARVD) implies both anatomical significance and a syndromic meaning. The anatomical meaning defines a focal RAS caused by atheromatous narrowing. The syndromic meaning reflects the fact that ARVD is associated with changes in blood pressure, renal function, and cardiovascular disease elsewhere in the body and hence cardiovascular prognosis even where the absolute measured loss of lumen diameter is small. As such, use of the term ARVD can be taken to imply the presence of an atheromatous RAS, but the term RAS does not always imply atherosclerotic disease.

Prevalence

Unselected populations and registry data

Estimates of prevalence vary widely. Of 1957 US patients investigated by computed tomography angiography during assessment for kidney donation, 3.5% had sufficient atheromatous stenosis to preclude donation (Lorenz et al., 2010). Prevalence was strongly related to patient age: 0.4% of those < 39 years, 2.2% of those aged 40–49, 9.5% aged 50–59, and 24.6% aged > 60 years. An ultrasound screening programme of 834 'free-living' patients aged > 65 identified a RAS > 60% in 6.8% of patients, with 12% of these stenoses being bilateral (Hansen et al., 2002). In an analysis of the United States Medicare 5% denominator file (which includes only patients aged > 67 years) between 1999 and 2001, 0.54% of patients had an established diagnosis of ARVD, with an annual incidence of 3.7 cases per 1000 patient years (Kalra et al., 2005). The lower figures in this study represent the fact that these are claims data and many cases of atherosclerotic RAS are clinically silent. Further analyses of claims data from 16 million patients between 1992 and 2004 described a progressive increase in rate of diagnosis, with patients in the 2004 claims data almost five times as likely to receive a diagnosis of ARVD (Kalra et al., 2009) (Fig. 213.1). Although no analysis of this scale has been repeated, data from subsequent reports of the United States Renal Data System suggest a change in this trend with prevalence of end-stage renal disease secondary to diagnosed ARVD falling from 1.0% to 0.7% and incidence from 1.7% to 1.3% (Collins et al., 2010). The changing rates of diagnosis are not believed to reflect a true change in disease burden, rather greater access to diagnostic tools in the early 2000s, with reduced enthusiasm for investigation in more recent times following negative trials into percutaneous revascularization.

Enriched populations

ARVD is associated with other atheromatous vascular disease. The prevalence of ARVD in patients with coronary, carotid, and peripheral arterial disease is well described. The prevalence of ARVD increases with age, as does the prevalence of atheroma in other vascular beds (Chrysochou and Kalra, 2009). Despite this and the links between ARVD and other macrovascular disease states, the evidence for classically recognized vascular risk factors leading directly to the development of RAS is often lacking.

Coronary artery disease and congestive heart failure

A wide range of studies have assessed associations between ARVD and suspected and diagnosed coronary artery disease. In a meta-analysis of studies including patients undergoing diagnostic coronary angiography for suspected coronary artery disease the pooled prevalence of ARVD was found to be 10.5% (de Mast and Beutler, 2009). Higher figures are described when selection criteria are applied. In hypertensive patients undergoing coronary angiography up to 28% of patients have been found to have > 50% RAS (Aqel et al., 2003), with a pooled prevalence in meta-analysis of 17.8% (de Mast and Beutler, 2009). The probability of incidental ARVD being identified during coronary angiography increases with age (Aqel et al., 2003) and with higher levels of atheromatous disease. Where concomitant cerebral and peripheral arterial disease exist in patients undergoing diagnostic coronary angiography, the relative risk for identification of ARVD is increased by a factor of three- to fourfold (Rihal et al., 2002; Aqel et al., 2003). Higher burdens of coronary atheroma are also associated with an increased likelihood for the presence of ARVD with a 1.6-fold increase in risk for RAS associated with each diseased coronary artery (Rihal et al., 2002). This finding has been validated in a systematic review of > 7000 patients, where overall 5.5% of patients with a single diseased coronary artery, 9.7% with two diseased coronary arteries,

and 15.1% of patients with three abnormal coronary vessels had undiagnosed ARVD (de Mast and Beutler, 2009).

Two studies have screened patients with congestive heart failure (defined by ejection fraction) for ARVD. In these studies, RAS > 50% was found in between 30% and 50% of patients (MacDowall et al., 1998; de Silva et al., 2007). In the second study the presence of peripheral oedema was independently associated with the presence of RAS. These studies may underestimate the prevalence of ARVD in heart failure as almost all patients with ARVD can be shown to have some form of cardiac abnormality (Wright et al., 2005), though some of these features may associate with the syndrome of heart failure with a normal ejection fraction (Leong et al., 2010). Patients with ARVD can present with acute decompensated heart failure or 'flash pulmonary oedema'. This is discussed in greater detail below.

Aorto-iliac and peripheral vascular disease

The presence of aorto-iliac disease is strongly associated with coexistent ARVD. Significant renal artery disease has been described in 24–38% of patients with abdominal aortic aneurysm (Olin et al., 1990; Valentine et al., 1993), 24% of patients with suspected aorto-iliac disease (Iglesias et al., 2000), and 33% of patients with aorto-occlusive disease (Olin et al., 1990). RAS has been reported in up to 30% of patients with peripheral vascular disease (Leertouwer et al., 2001), though figures of 12–16% are more consistently reported (Androes et al., 2007; Amighi et al., 2009). As with coronary artery disease, patients with other atheromatous disease in addition to peripheral vascular disease have a greater probability of ARVD being identified, with the strongest association seen with aorto-iliac disease (Androes et al., 2007).

Cerebrovascular disease

In a comparison of 15 diabetic patients with and without RAS > 50%, increased carotid intimal thickness, a predictor for increased stroke risk (Hurst et al., 2007), was observed in patients with atherosclerotic renal artery disease (Horita et al., 2002). In an autopsy series of 346 patients who died of a stroke, RAS was found in 12% of those who had suffered an ischaemic stroke and carotid stenosis in 33%. Of the patients with carotid disease, 24% had RAS compared to 6% of those with normal calibre carotid vessels (Kuroda et al., 2000). Where patients with known ARVD are screened for carotid disease moderate disease can be found in 26% of patients and severe disease in 18% (Missouris et al., 1998).

Advanced kidney disease

As reductions in glomerular filtration rate (GFR) have been linked to greater systemic volumes of atheroma (Nozue et al., 2012), though not necessarily faster progression of plaque size (Rigatto et al., 2009), it is credible that a higher prevalence of ARVD will be observed in patients with lower levels of renal function. No data exist to describe incidence and prevalence of ARVD between stages of chronic kidney disease (CKD). In analyses of United States registry data, patients coded with CKD were 2.5–4.6 times more likely to be coded as having ARVD than the non-CKD population (Kalra et al., 2005, 2009). In screening studies of incident dialysis patients, significant ARVD can be found in 22–41% of patients (Appel et al., 1995; van Ampting et al., 2003), with 5.2% of incident dialysis patients in the United States between 1996 and 2001 having ARVD coded as their primary cause of end-stage kidney disease (Guo et al., 2006).

Hypertension

Although almost all patients with ARVD are hypertensive, only a minority of unselected patients with hypertension will have significant ARVD. In addition to impaired cardiac function potentially confounding data (Wright et al., 2005), the crossover between essential hypertension, renovascular hypertension, and the elevated blood pressure associated with CKD further challenges interpretation of results. No study has described the prevalence of ARVD in an unselected hypertensive population. The clearest data come from studies in which the probability of a secondary cause of hypertension is maximal. Where patients with either resistant hypertension or onset of hypertension at a young age are considered the prevalence of RAS is 14% (de Mast and Beutler, 2009). This figure rises to 20% in hypertensive diabetic patients.

Ethnic variation

As noted above, atherosclerotic RAS is typically perceived as a disease of the developed world. Despite this, ethnicity does not appear to strongly modify risk for development of ARVD. In a retrospective analysis of 323 patients (193 Caucasian, 130 non-Caucasian) who underwent screening for RAS during coronary or peripheral angiography due to the presence of resistant hypertension, Caucasian ethnicity was not statistically significantly associated with a positive study (odds ratio in multivariate analysis 1.5 (0.8–2.1), P = 0.07) (Jazrawi et al., 2009). A population screening study of asymptomatic elderly subjects found a prevalence of ARVD in 6.9% of white and 6.7% of African American participants (Hansen et al., 2002). A further study screening for undiagnosed ARVD in African American and Hispanic patients described similar proportions of positive renal studies in each group, 9% and 7% respectively (Alhaddad et al., 2001). No comparative data exist between Asian and non-Asian populations, however here it is possible that prevalence of ARVD is less, although the possibility of ascertainment bias must be considered. In 750 Japanese patients with confirmed or suspected disease in another vascular bed, ultrasound evidence of RAS was found in 5.2% of patients, with angiographic confirmation in 4.8% (Kawarada et al., 2007). A higher figure was described in a Japanese study of 202 patients with at least one of hypertension, diabetes mellitus, or hyperlipidaemia. Although patients in this study were younger, 20.8% were found to have RAS > 50% on magnetic resonance angiography.

Diabetes mellitus

In randomized trials of intervention in ARVD, there is a 30% prevalence of diabetes (ASTRAL Investigators et al., 2009), and a 32.5% prevalence in United States registry data. Although the presence of reduced renal function should be considered as an important confounder, diabetic patients are at increased risk for being diagnosed with ARVD (hazard ratio 1.3 (1.2–1.4), P < 0.001) (Kalra et al., 2005, 2009). A systematic review of papers describing the prevalence of RAS > 50% in hypertensive patients with diabetes found a pooled prevalence of 20% (de Mast and Beutler, 2009).

Smoking

Cigarette smoking has deleterious effects on renal plasma flow (Gambaro et al., 1998; and see Chapter 103) and is inextricably linked to the development of atherosclerotic disease (Howard et al., 1998). Given the high proportion of patients diagnosed with ARVD who have a positive smoking history and the often incidental nature of the diagnosis (ASTRAL Investigators et al., 2009), this

association is almost certainly valid, even if direct proof of causation is limited. In a study of 48 patients investigated for ARVD due to hypertension, 90% of patients found to have significant stenosis had a smoking history compared to 59% of those without significant renal artery disease (Black and Cooper, 1986). In this study, patients found to have ARVD almost universally had greater than a 25-pack-year history. Similar findings have been presented in a cohort of 45 incident dialysis patients screened for undiagnosed RAS using duplex ultrasound. The 10 patients with > 60% stenosis had a significantly longer smoking career (37 vs 17 pack-years, P = 0.0016) (Appel et al., 1995), suggesting cumulative exposure is relevant.

Hyperlipidaemia

A clear link exists between hyperlipidaemia and the development of extrarenal atheroma (Kim et al., 2012). As treatment with statin therapy retards progression of ARVD (Cheung et al., 2007) it is reasonable to assume that hyperlipidaemia is also involved in the development of renal atheroma. This hypothesis is supported by similar perturbations seen in the lipid profiles of patients with ARVD as in those with carotid and coronary atheroma (Scoble et al., 1999). A single-centre study of 249 patients with CKD in whom a clinical suspicion of ARVD existed noted a greater proportion of the 83 patients found to have significant RAS had a serum total cholesterol in excess of 5.2 mmol/L (61% vs 48%) (Shurrab et al., 2001). In addition to modulating risk for the development of ARVD, persisting hyperlipidaemia likely impacts risk for death (see Chapter 102).

Hypertension

As both cause and effect relationships exist between hypertension and CKD and overlap exists between essential hypertension and renovascular hypertension, demonstration that elevated blood pressure directly leads to RAS is impossible. Links between persistently elevated blood pressure and renal atrophy (Caps et al., 1998) and histological evidence of intrarenal damage (Keddis et al., 2010) are discussed further in Chapter 211.

Novel risk factors

Circulating markers of cardiovascular risk associated with development of atherosclerosis in the general population such as homocysteine (Boushey et al., 1995) and highly sensitive C-reactive protein (hs-CRP) (Singh et al., 2008) have been studied in ARVD. In a series of 333 patients undergoing coronary angiography who were screened for ARVD, positive associations between homocysteine, hs-CRP and fibrinogen levels, and the presence of ARVD were observed in univariate, but not multivariate analysis (Dzielińska et al., 2007). These markers and asymmetric dimethylarginine may prove to have greater utility in stratifying patients in relation to risk of progression of atherosclerosis (Zoccali et al., 2002).

Takayasu disease

This is the leading cause of renovascular hypertension in Indian and South-Asian populations, where it accounts for up to 60% of cases (S. Sharma et al., 1996).

Other conditions

Case reports of RAS in antineutrophil cytoplasmic antibody-associated conditions also exist (Jamoussi et al., 2010) and in a series of 77 patients with antiphospholipid syndrome, 26% of patients were found to have significant renal ostial stenosis on indirect angiographic imaging of the renal arteries (Sangle et al., 2003).

Clinical features

Fibromuscular dysplasia

Fibromuscular dysplasia can affect any part of the vascular tree. Recent years have seen an explosion in the availability of information following the founding of the United States Registry for Fibromuscular Dysplasia in 2008. The renal arteries are the most commonly involved vessels (58% of cases), followed by cervico-cranial arteries (32%) (Mettinger, 1982). The coexistence of fibromuscular dysplasia within specific vascular beds is not known (Plouin et al., 2007), but registry data show most patients are affected in more than one territory (Kim et al., 2013). Females are most affected by fibromuscular dysplasia at a ratio of 9:1 compared to males (Olin and Sealove, 2011). When the renal vessels are involved, presentation is typically described as being with hypertension diagnosed before 35 years of age. However, patients are often diagnosed at a later age due in part to a lack of clinical suspicion (Olin et al., 2012). In this setting, epigastric bruits are present in 18% of cases and flank bruits in 6% (Poloskey, 2012). The presence of bruits in either of these locations is highly specific but not sensitive for the presence of renal fibromuscular dysplasia (specificity 93%, sensitivity 24%) (Poloskey, 2012). Although FMD can reduce renal mass, function is typically preserved with < 3% of patients presenting with renal insufficiency (Kim et al., 2013). Flank pain is more common in men than women (Kim et al., 2013).

Clinical evidence of disease outside of the renal vessels should also be considered. Patients with extrarenal disease may have symptoms of mesenteric ischaemia (Guill et al., 2004) or claudication (Olin and Sealove, 2011). More likely than these is the presence of non-specific neurological symptoms. In extreme cases, cervico-cranial FMD can present as a stoke or transient ischaemic attack (Olin and Sealove, 2011), however symptoms of neck pain (27%), headache (57%) (Mettinger, 1982; Kim et al., 2013), and pulsatile tinnitus (33%) (Waldvogel et al., 1998; Kim et al., 2013) are more common. On physical examination, 31% of all patients with fibromuscular dysplasia have a cervical bruit, with a sensitivity and specificity of 45% and 94% for the presence of carotid and/or vertebral disease (Poloskey, 2012). Horner's syndrome can be observed in 5–12% of patients. Table 213.2 describes the frequency of presenting symptoms in FMD and Box 213.1 highlights diagnostic clues.

Classification of fibromuscular disease

Currently FMD can be classified histologically, or anatomically, with relationships existing between the observed anatomical pattern and histological abnormalities. The histological grading system proposed in the 1970s (Harrison and McCormack, 1971; Stanley et al., 1975) describes the layer of arterial wall involved, with adventitial disease being the rarest, intimal disease accounting for < 10% of cases, and the majority due to medial layer disease, which being the most common type is subject to subclassification (Slovut and Olin, 2004). Over 80% of cases of medial layer disease are due to fibroplasia, with the remainder due to perimedial fibroplasia and medial hyperplasia. As open surgical intervention for FMD has been eclipsed by percutaneous intervention, restricting access to tissue samples, there is limited clinical utility in considering patient outcomes in relation to this classification. One

Table 213.2 Frequency of presenting signs and symptoms in fibromuscular disease

Presenting symptom or sign	Percentage of patients
Neurological presentations	
Headache	52
Pulsatile tinnitus	28
Dizziness	26
Cervical bruit	22
Neck pain	22
Cervical artery dissection	12
Transient ischaemic attack	9
Stoke	7
Amaurosis fugax	5
Horner syndrome	5
Abdominal presentations	
Flank or abdominal pain	16
Postprandial abdominal pain	8
Renal artery dissection	3
Mesenteric ischaemia	1
Cardiovascular presentations	
Hypertension	64
Chest pain or dyspnoea	16
Claudication	5
Myocardial infarction	2

Data adapted from the first 447 patients recruited to the United States Registry for Fibromuscular Dysplasia (Olin et al., 2012). Signs and symptoms are those experienced by the patient prior to diagnosis of fibromuscular disease.

Box 213.1 Signs and symptoms that may alert the clinician to a possible diagnosis of fibromuscular disease

- Onset of hypertension before 35 years of age
- Resistant hypertension
- Epigastric bruit in the presence of hypertension
- Cervical bruit in patient aged < 60 years
- Pulsatile tinnitus
- Serve recurrent headaches (especially migrainous)
- Transient ischaemic attack or stroke in patient aged < 60 years
- Peripheral artery dissection (carotid, vertebral, renal)
- Aneurysm in a visceral or intracranial vessel
- Aortic aneurysm in patient aged < 60 years
- Subarachnoid haemorrhage
- Renal infarction.

Adapted from Olin (2012).

exception may be medial fibroplasia, which accounts for the vast majority of cases. Here the non-inflammatory pathology involves areas of thinning of the intima and media of the vessel wall with loss of the elastic lamina, changes that lead to aneurysm formation. These areas alternate with localized regions of fibrotic narrowing leading to the classical 'string-of-beads' angiographic appearance (Kincaid et al., 1968) (Fig. 213.2). Other histological patterns, however, do not relate to a specific angiographic appearance (Savard et al., 2012). Consequently a simplified classification system has recently been proposed. In this patients are divided into those with a multifocal or a single focal RAS due to FMD. In addition to simplifying reporting, this system may also aid identification of patients likely to receive blood pressure benefit from revascularization with cure of hypertension achieved in 54% of patients with a single focal lesion compared to 26% with multifocal disease (Savard et al., 2012). This difference in outcome may relate to the fact that the effects of multiple stenoses on renal haemodynamics are more difficult to estimate than that of a single stenosis, but also raises the possibility of two different disease states (Olin, 2012).

Atherosclerotic renovascular disease

Hypertension

The interplay between renovascular hypertension and essential hypertension makes any assessment of the presenting characteristics of hypertension related to ARVD challenging. In a series of 161 patients found to have severe hypertension at time of presentation to an Emergency Room, 8.1% were found to have evidence of significant RAS (Börgel et al., 2010). Here patients had a blood pressure of at least 180 mmHg systolic and/or 100 mmHg diastolic, a mean age of 66 years, and were taking on average two different classes of antihypertensive medications. This prevalent figure does not meaningfully differ from that described where asymptomatic patients aged > 65 years with a mean blood pressure of 135/72 mmHg have been screened for incidental RAS (Hansen et al., 2002). In one single-centre study of 249 patients investigated for ARVD no difference in the prevalence of hypertension or severe hypertension was identified between patients found to have normal or abnormal renal vessels (Shurrab et al., 2001). This finding has been duplicated in a retrospective analysis of 434 patients who underwent diagnostic Duplex ultrasonography where RAS was suspected due to the presence of hypertension (Davis et al., 2009). In this study systolic blood pressure did not differ between patients with a positive or a negative study with a mean value of 158 mmHg in each group. Diastolic blood pressure was lower in patients found to have significant renal artery disease (83 mmHg vs 90 mmHg, $P < 0.001$), presumably reflecting greater arterial stiffness with widened pulse pressure, and these patients had a non-significant trend towards taking more antihypertensive medications (2.7 vs 2.4, $P = 0.07$). As such, there are no data to support a threshold blood pressure value above which the presence of RAS becomes more probable. Potentially this may partly relate to the high burden of impaired ventricular function observed in patients with ARVD (Wright et al., 2009).

Resistant hypertension

The presence of resistant hypertension, defined as blood pressure that remains above target despite the use of three different classes of antihypertensive medications (Calhoun et al., 2008), does not appear to be a reliable indicator of the presence of atherosclerotic

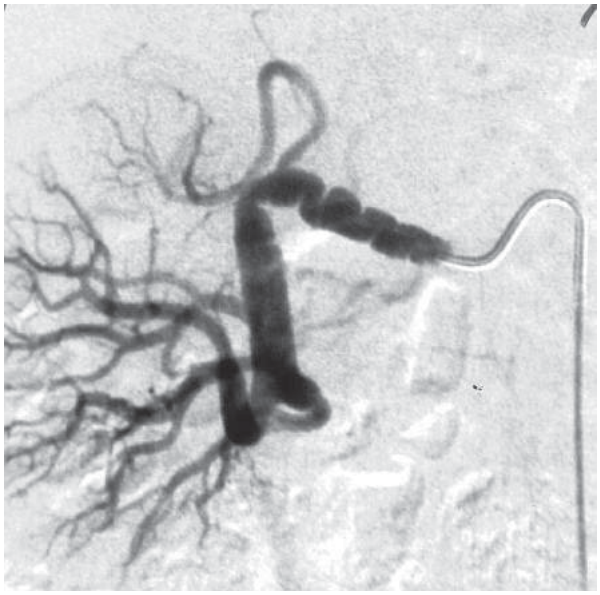

Fig. 213.2 Intra-arterial digital subtraction angiogram demonstrating medial fibroplasia giving rise to the classical 'string-of-beads' appearance in fibromuscular disease.
Image supplied by Dr Alastair Cowie, Salford Royal Hospital, Salford, UK.

RAS. In a series of 837 patients screened for RAS during coronary angiography, 55% of patients with normal renal arteries had resistant hypertension at the time of study compared to 28% of patients with a stenosis < 50% and 8% of patients with a stenosis of > 50% (Buller et al., 2004).

Age of onset of hypertension

Given that development of atherosclerotic disease is a natural part of the ageing process, it is intuitive that the proportion of patients with ARVD as a cause of secondary hypertension may increase with age. In a study of 2880 patients investigated for secondary hypertension, 185 out of 1026 (18%) patients aged 50–69 years had an identified cause of secondary hypertension compared to 172 of 1178 (14%) patients aged 30–49 years. In the younger patient group, 15% of cases of secondary hypertension were due to renovascular hypertension compared to 23% in the older patient group, although presumably some cases in the younger group were due to non-atherosclerotic causes (Streeten et al., 1992). This is comparable to more recent data that suggest 17% of patients aged > 65 years will have a secondary cause of hypertension with ARVD being the most common cause (Viera and Neutze, 2010). However, precise differentiation of 'true' renovascular hypertension, that consequent upon a RAS lesion, from essential hypertension can be very difficult as > 90% of ARVD patients will have long-standing hypertension. This is borne out by the lack of success in blood pressure control in the clinical trials.

Vascular bruits

The presence of abdominal or flank bruits has for a long time been suggested as a clinical marker for the presence of ARVD (Simon, 1972). However, early series suggested the absence of this may be better suited to ruling out renal artery disease with a sensitivity of 55% and specificity of 88% (Svetkey et al., 1990). Latterly, practice has evolved to considering bruits as part of a pattern of disease. In a study in which patients undergoing diagnostic coronary angiography were screened for atherosclerotic RAS, the presence of an abdominal bruit was considered as a composite marker of vascular disease in conjunction with previous stroke and symptomatic peripheral vascular disease (Harding et al., 1992). Although this marker was strongly associated with the existence of RAS it is likely that the other vascular pathologies dominated the association. In another study comparing patients with CKD investigated for RAS, the presence of a vascular bruit formed part of a three-point scoring system along with asymmetric kidney size and other vascular disease (Shurrab et al., 2001). Here a greater proportion of patients found to have stenosis had two of the three markers (46% vs 23%), and where the triad was present there was very good discrimination between those who went on to have a positive and a negative test (19% vs 3%).

Renal parameters

The end-organ effects of RAS are discussed in detail in Chapter 212.

Estimated glomerular filtration rate

Although patients with more severe RAS typically have a lower level of renal function than those with less severe stenosis (Buller et al., 2004), this is not very useful diagnostically. In a long-term single-centre study of 1435 patients screened for RAS at the time of coronary angiography, mean estimated GFR values did not significantly differ between those without stenosis, 68 mL/min/1.73 m^2, and those with > 50% stenosis, 66 mL/min/1.73 m^2 (Safak et al., 2013).

Proteinuria

Due to the frequent coexistence of essential hypertension and diabetes mellitus with ARVD, use of proteinuria as a diagnostic marker is complicated. Level of proteinuria and degree of stenosis are not correlated (Makanjuola et al., 1999). Although nephrotic levels of urine protein loss have been described in patients with RAS (Halimi et al., 2000), this is in the absence of biopsy data to rule out other potential causes.

Cardiovascular disease associations

Atheromatous disease

As noted previously, ARVD is strongly associated with other cardiovascular diseases. Between 11% and 15% of patients undergoing diagnostic coronary angiography have atherosclerotic RAS > 50% (Harding et al., 1992; Weber-Mzell et al., 2002; M. G. Cohen et al., 2005) with the probability of identifying renal disease increasing with the burden of coronary artery disease, reduction in GFR, and presence of diabetes mellitus. In the same studies, pre-existing hypertension was associated with an increased probability of RAS being identified and with greater proportions of patients with higher degrees of stenosis being hypertensive (M. G. Cohen et al., 2005). In this study of 843 patients undergoing combined cardiac catheterization and abdominal aortography, 62% of patients with RAS < 50% had a history of hypertension compared to 79% of patients with a stenosis > 50% and 82% of patients with a stenosis > 75%. A high prevalence of ARVD has been described in patients with aorto-iliac disease. Significant RAS can be found in 38% of patients with abdominal aortic aneurysm, 33% of patients with aorto-occlusive disease, and 39–45% of patients with peripheral vascular disease (Olin et al., 1990; Missouris et al., 1994). Significant RAS is reported in fewer patients with cerebrovascular disease, with 22% of patients with carotid artery stenosis (defined as peak systolic velocity > 200 cm/s) and 10% of patients with stroke having

Table 213.3 Associations between systemic macrovascular disease and atherosclerotic renal artery stenosis

	Proportion of patients with ARVD (%)	Adjusted odds ratio (95% confidence interval) for ARVD
Coronary artery disease	11–15	2.5 (2.3–2.6)[a]
Cerebrovascular disease	15–22	1.6 (1.5–1.7)[a]
Peripheral vascular disease	39–45	4.0 (3.7–4.2)[a]
Abdominal aortic aneurysm	38	3.4 (1.9–2.9)[a]

ARVD = atherosclerotic renovascular disease.

[a] $P < 0.0001$

Percentages are the reported proportions of patients with, for example, cerebrovascular disease who can be shown to have concomitant atherosclerotic renal artery stenosis. Adjusted odds ratio described the relative risk for ARVD in a patient with versus a patient without, for example, cerebrovascular disease (adjusted for age, gender, ethnicity, chronic kidney disease, diabetes mellitus and other major cardiovascular co-morbidities). Odds ratios adapted from Kalra et al. (2005).

significant RAS on angiography (Kawarada et al., 2007). Table 213.3 describes the prevalence and risk for coexistent ARVD for a range of systemic vascular pathologies (Kalra et al., 2005).

The studies noted above have described the prevalence of undiagnosed RAS in populations with other vascular pathologies. Predictably this relationship extends in both directions, with a high co-morbid burden observed in patients with ARVD. In randomized trials of percutaneous revascularization in ARVD, approximately 50% of patients have a history of coronary artery disease, 40–50% a history of peripheral vascular disease, and 18–30% a history of cerebrovascular disease or stoke (ASTRAL Investigators et al., 2009; Bax et al., 2009; Kalra et al., 2009).

Cardiac structural disease

Less than 5% of patients with ARVD have normal cardiac structure and/or function (Wright et al., 2005). Although perturbations in ventricular structure and function are frequently observed in CKD (Park et al., 2012), these changes appear to be more marked in CKD patients with RAS, with significantly higher proportions of patients having left ventricular hypertrophy and significantly higher left ventricular mass measurements (Wright et al., 2005). When echocardiographic changes are compared between patients with renovascular and essential hypertension, patients with RAS have more adverse markers, with greater reductions in fractional shortening and greater degrees of left ventricular dilatation and septal hypertrophy (Vensel et al., 1986) as well as a higher left ventricular mass (Rizzoni et al., 1998). Between 30% and 50% of patients with congestive cardiac failure can be found to have significant atherosclerotic RAS (MacDowall et al., 1998; de Silva et al., 2007), and clinical evidence of heart failure is present in 30% of patients with ARVD (Kane et al., 2010). Despite this, symptoms of congestive heart failure are not independently associated with an increased probability of having diagnosed ARVD (Kalra et al., 2005).

Flash pulmonary oedema

Flash pulmonary oedema (FPO) is a term used to describe dramatic presentations of acute decompensated heart failure associated with excess activity of the renin–angiotensin–aldosterone system (Rimoldi et al., 2009). Up to 10% of patients with ARVD will present with FPO (Pickering et al., 1988), with an in-hospital mortality in excess of 7% (Parissis et al., 2010). However, significant RAS is not the sole cause of FPO. In a series of 20 patients presenting in this manner, the prevalence of RAS was 45%, with the majority of these patients having significant bilateral disease (McMahon et al., 2010). Other conditions that can cause FPO include severe acute mitral regurgitation (Piérard and Lancellotti, 2004), loss of diurnal blood pressure

Table 213.4 Modified diagnostic criteria for Takayasu's arteritis

Major criteria		Minor criteria clinical criteria		Minor angiographic criteria	
1 month of typical signs or symptoms	Limb claudication, loss of pulses, > 10 mmHg left to right difference in systolic blood pressure, fever, neck pain, transient visual loss or blurred vision, dyspnoea, palpitations	High erythrocyte sedimentation rate	> 20 mm/hour	Pulmonary artery lesion	Lobar or segmental occlusion, stenosis, aneurysm, or luminal irregularity
Right mid subclavian lesion	Most severe stenosis or occlusion present in the mid portion from the point 1 cm proximal to the vertebral artery orifice	Carotid artery tenderness	Can be unilateral or bilateral	Left mid common carotid lesion	Presence of the most severe stenosis or occlusion in the mid portion, of 5 cm in length from the point 2 cm distal to its orifice
Left mid subclavian lesion	Most severe stenosis or occlusion present in the mid portion from the right vertebral artery to the point 3 cm distal to orifice determined by angiography	Hypertension	Systolic blood pressure persistently raised > 149 mmHg (brachial) or > 160 mmHg popliteal	Distal brachiocephalic trunk lesion	Presence of the most severe stenosis or occlusion in the distal third
		Aortic regurgitation	Demonstrated by echocardiography or angiography	Descending thoracic aortic lesion	Narrowing, dilatation, aneurysm, or irregularity. Not tortuosity
				Abdominal aorta lesion	Narrowing, dilatation, aneurysm or irregularity

variation (Haider et al., 2003; Rimoldi et al., 2009), obstructive sleep apnoea (Chaudhary et al., 1982), and coronary artery disease (Kelly, 2001). However, given the potential clinical benefits associated with renal artery revascularization in patients presenting with FPO (Kane et al., 2010; van den Berg et al., 2012) we would advocate consideration of renal artery imaging in all patients with this presentation.

Intolerance of renin–angiotensin blockade

Intolerance of renin–angiotensin blockade (defined as rise in serum creatinine of 12% to 25% from baseline following initiation of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), or direct renin inhibitors) has historically been considered a feature of ARVD (Zucchelli, 2002) with the *British National Formulary* advising caution in the use of these agent in patients with known or suspected renovascular disease (Joint Formulary Committee, 2013). The practical utility of this approach is limited as expert opinion suggests that a rise in serum creatinine of up to 25% may be considered acceptable following initiation of ACEIs or ARBs (D. L. Cohen and Townsend, 2008). A prospective single-centre study undertook investigation for RAS in 50 ACEI treated patients who presented with rapidly deteriorating renal function (> 25% increase in serum creatinine over a 3-month period). In these data, a significant stenosis was observed in 52% of patients (Onuigbo and Onuigbo, 2008). Other observational data have shown that angiotensin blockade can be safely deployed in the majority of patients with ARVD, even in patients with bilateral RAS (Chrysochou et al., 2012). As such, a rise in serum creatinine following initiation of ACEI or ARB therapy cannot be presumed to have either a high sensitivity or specificity for the presence of RAS.

Takayasu disease

Clinical presentation depends upon the phase of disease. In the acute phase, symptomatology is typically constitutional and non-specific with arthralgia, fever, and malaise the most commonly reported symptoms (Shelhamer et al., 1985). During the chronic, pulseless phase, symptoms and signs of diffuse arterial disease are present with claudication, mesenteric ischaemia, and diffuse bruits commonly reported. The modified diagnostic criteria for Takayasu arteritis are described in Table 213.4 (B. K. Sharma et al., 1995), with the presence of either two major, one major and two minor, or four minor criteria offering a sensitivity of 92% and a specificity of 95% for the diagnosis (Hoffman, 1996).

Takayasu's is also mentioned under the heading of vasculitis in Chapter 159.

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CHAPTER 214

Renal artery stenosis: diagnosis

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Introduction

Figure 214.1 summarizes our suggested diagnostic approach.

Screening tests

Marked asymmetry in kidney length (> 1.5 cm disparity) has been associated with renal artery stenosis, but other conditions can lead to asymmetric kidneys (Neild et al., 2004) and < 20% of patients with severe unilateral renal artery stenosis have a significant difference in their kidney sizes (Cohen et al., 2005). Equally, should bilateral renal artery disease exist then both kidneys may atrophy equally. As atrophy probably indicates a reduced chance of functional recover after revascularization (Cheung et al., 2010), screening for kidney asymmetry is unlikely to be a valuable way of improving outcomes in this disease.

Although only limited validation studies have been performed (Krijnen et al., 2005), the use of readily available clinical information appears to be both sensitive and specific in determining the probability of significant renal artery stenosis (Krijnen et al., 1998) (Table 214.1). Using this tool, which assigns risk scores in relation to smoking status for a given age, gender, serum creatinine, cholesterol, body mass index, and other clinical findings, a total score of 11 equates to a 25% probability of diagnosing renal artery stenosis, a total of 13 a 50% probability, and a total of 15 a 75% probability of renal artery stenosis.

Diagnostic tests

Digital subtraction angiography

Intra-arterial renal digital subtraction angiography (often referred to as intra-arterial angiography) is considered the gold standard investigation to which other techniques for the assessment of renal artery stenosis are compared. This, however, is rarely a first-line investigation due to reasons of cost (van Helvoort-Postulart et al.,

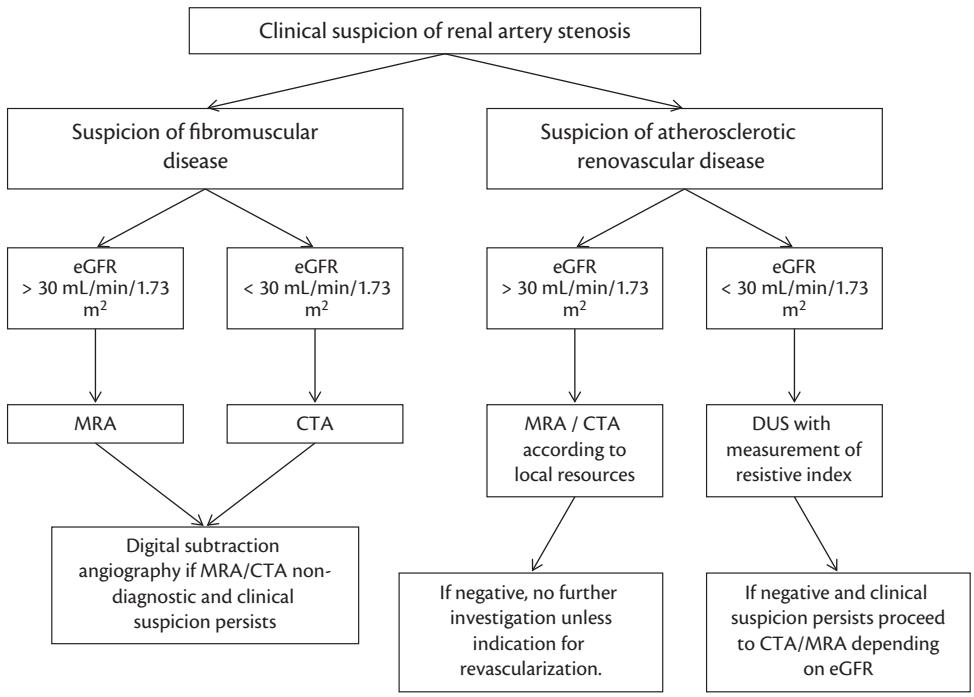

Fig. 214.1 Suggested diagnostic algorithm where clinical suspicion for renal artery stenosis exists. CTA = computed tomography angiography; DUS = duplex ultrasound; eGFR = estimated glomerular filtration rate; MRA = magnetic resonance angiography.

Table 214.1 Scoring system for likelihood of renal artery stenosis from Krijnen et al., 1998

Predictor	Score	
	Never smoked	Former or current smoker
Age:		
20 years	0	3
30 years	1	4
40 years	2	4
50 years	3	5
60 years	4	5
70 years	5	6
Female	2	2
Presence of sign or symptom (femoral or carotid bruit; angina; claudication; prior myocardial infarction, cerebrovascular event, or vascular surgery)	1	1
Onset of hypertension within 2 years	1	1
Body mass index > 25 kg/m^2	2	2
Presence of abdominal bruit	3	3
Serum creatinine:		
40 μmol/L	0	0
60 μmol/L	1	1
80 μmol/L	2	2
100 μmol/L	3	3
150 μmol/L	6	6
200 μmol/L	9	9
Serum cholesterol > 6.5 mmol/L or prescribed lipid-lowering therapy	1	1

Sum total score. In this population 11 equated to 25% probability, 13 to 50% probability, 15 to 75% probability.

2006) and risk of complications, including arterial dissection (Waugh and Sacharias, 1992; Young et al., 2002), acute kidney injury due to contrast injury (though this risk may be mitigated by use of lower contrast volumes and iso-osmolar agents) (Karlsberg et al., 2010), and death (Waugh and Sacharias, 1992). Furthermore, intra-arterial angiography provides only two-dimensional images and inter-observer agreement for detection of significant stenosis is imperfect, ranging from 0.65 to 0.78 (Vasbinder et al. 2004). The calculation used for estimation of degree of stenosis following angiographic assessment is as follows:

$$\%\ \text{stenosis} = \frac{\text{minimum lumen diameter}}{\text{reference vessel diameter}} \times 100$$

A potential advantage of invasive angiography is the opportunity to measure the pressure gradient across the stenosis, with current views suggesting that haemodynamic significance is associated with trans-lesional gradients in excess of 20 mmHg (Hirsch et al., 2006). A body of data suggest that use of pressure gradient measures performed at the time of interventional angiography may identify the patients in whom target blood pressures will be achieved following intervention (Mitchell et al., 2007; Leesar et al., 2009). A study of 53 consecutive patients undergoing renal artery revascularization to treat hypertension found that a dopamine-induced hyperaemic gradient in excess of 48 mmHg may be an important threshold value, with an area under the curve of 0.75 (95% confidence interval 0.61–0.88) for a > 20 mmHg reduction in systolic blood pressure following revascularization (Mangiacapra et al., 2010). It should be noted, however, that all of these data consider only patients with mild renal impairment with average baseline creatinine values of approximately 100 μmol/L and no study has considered a medical control group.

A final consideration is the opportunity to perform screening angiography for renal artery disease during other diagnostic or angiographic procedures—cynically called 'drive-by' angiography. Justification for this approach comes from the frequent coexistence of renal artery stenosis with peripheral (Olin et al., 1990; Valentine et al., 1993) and coronary arterial disease (Harding et al., 1992). Although imaging of renal vessels following coronary angiography requires only a small extra volume of contrast and does not increase procedural morbidity or mortality (Rihal et al., 2002), it is unlikely to significantly alter management (Kumbhani et al., 2011). As such, our position on opportunistic renal angiography stands in opposition to previous American guidelines that support this practice where there is a suspicion of concomitant renal artery disease (White et al., 2006).

Computed tomography angiography

Computed tomography angiography (CTA) is a widely available tool in which overlapping transaxial images are obtained during delivery of a timed bolus of iodinated contrast (Krumme and Blum, 1998) (Fig. 214.2). Modern scanners permit identification of vessels as small as 0.5 mm (Luboldt et al., 1999) and the speed of image capture allows all data to be obtained in a single breath hold, eliminating artefact from respiratory movement (Rubin et al., 1994). Compared to intra-arterial angiography, CTA has an overall sensitivity and specificity of 94% and 93% respectively for the detection of renal artery stenosis (Zhang et al., 2009) and when directly compared to magnetic resonance imaging (MRI) in patients with renal impairment it is a more accurate test (Eriksson et al., 2010). Despite this, the ostial calcification commonly found in atherosclerotic renovascular disease (Tolkin et al., 2009) can make interpretation of CTA images challenging (van Straten et al., 2003) and reduces inter-observer agreement (Vasbinder et al., 2004). Importantly, CTA studies reporting the highest sensitivity and specificity values for diagnosis of renal artery stenosis have focused on patients with atheromatous disease. When significant numbers of patients with fibromuscular disease are included the reported sensitivity falls to 64% (Vasbinder et al., 2004), reflecting the reduced accuracy of CTA in describing distal arterial segments (Galanski et al., 1994).

CT and the risk of contrast-induced nephropathy are further discussed in Chapter 11.

Magnetic resonance angiography

The high level of soft tissue contrast provided by MRI makes it an excellent tool for visualizing the kidneys especially with the increased availability of high-field scanners and use of diffusion-weighted

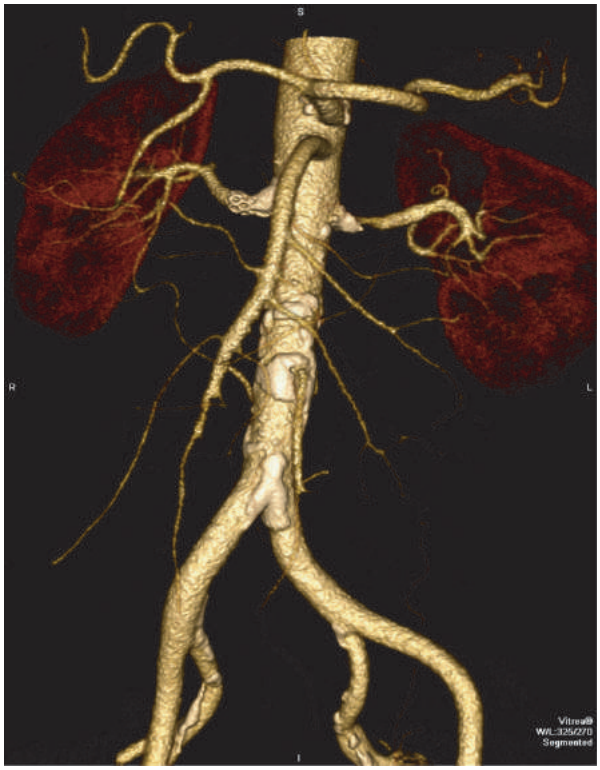

Fig. 214.2 Reconstructed CT angiogram in treated atherosclerotic renovascular disease. The left renal artery is patent and the right renal artery is patent following percutaneous stenting.

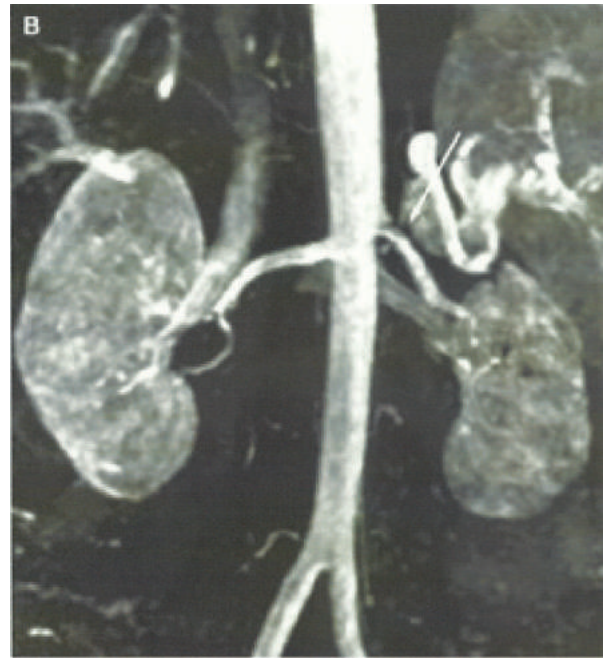

Fig. 214.3 Magnetic resonance angiogram demonstrating left-sided ostial stenosis.
Image supplied by Dr James Lay, Royal Bolton Hospital, Bolton, UK.

techniques (Artunc et al., 2011). Early methods to detect renal artery stenosis with MRI by flow visualization, using time of flight or phase contrast sequences were susceptible to artefact due to the long acquisition times (Tan et al., 2002). These methods have been superseded by magnetic resonance angiography (MRA) performed using gadolinium as a paramagnetic contrast agent (Prince et al., 1993) (Fig. 214.3; further described in Chapter 15). This technique allows sequences to be performed in a single breath hold and allows visualization of the renal arteries independent of flow effects (Snidow et al., 1996), consequently increasing specificity and positive predictive value (Tan et al. 2002). Compared to intra-arterial angiography, gadolinium enhanced MRA has a sensitivity of 96% and specificity of 93% for the diagnosis of renal artery stenosis (Zhang et al. 2009). However, in the setting of mild to moderate renal impairment MRA is less sensitive and specific than CTA (Eriksson et al., 2010) and, especially at lower levels of stenosis, can overestimate the degree of luminal loss (Patel et al., 2005).

MRA may also be less useful in diagnosis of non-atheromatous renal artery disease. Where comparison has been made between MRA and digital subtraction angiography images in patients with known fibromuscular disease, MRA had high sensitivity and specificity for identification of aneurysmal changes (sensitivity 100%, specificity 93%) and a string-of-beads appearance (sensitivity 95%, specificity 93%), but appeared less suited to identifying stenoses (sensitivity 68%, specificity 94%) (Willoteaux et al. 2006).

The risks of nephrogenic systemic fibrosis (NSF) after administration of gadolinium-containing contrast media for MRA are discussed in Chapter 15.

Colour duplex ultrasonography

Colour duplex ultrasonography (described in Chapter 13) permits both assessment of the main renal artery and assessment of the intrarenal arteries. Due to the non-invasive nature of the technique, the lack of ionizing radiation or contrast, the wide availability of equipment, and (in the presence of a single renal artery) the high sensitivity and specificity offered (Hansen et al., 1990), this is seen by many as the ideal tool with which to diagnose renal artery stenosis. However, full assessment is operator dependent and can be time-consuming (Spyridopoulos et al., 2010). The quicker indirect method that assesses intrarenal arterial waveforms in the main renal artery searching for evidence of the 'tardus-parvus' phenomenon is the least sensitive and specific method (de Oliveira et al., 2000), likely due to variation in arterial compliance modulating this finding (Halpern et al., 1995).

Use of direct Doppler parameters significantly increases sensitivity and specificity with measurement of the renal:aortic ratio (Drieghe et al., 2008) and renal:renal ratio (Chain et al., 2006) offering a greater degree of discrimination than the oft quoted parameter of a peak systolic velocity > 200 cm/s with associated post-stenotic turbulence (Baumgartner and Lerman, 2011). These measures are best suited to the diagnosis of atherosclerotic renovascular disease, where the majority of stenoses are single and ostial (Cicuto et al., 1981; Kaatee et al., 1996). Where the pattern of stenotic disease in the artery is irregular, such as in vasculitic or fibromuscular causes, all of these measures have reduced utility (Li et al., 2006). Ultrasound studies can fail due to obese body habitus or distended bowel gas pattern, however it is likely that the widely quoted failure rates of 10–20% are overestimates if appropriate bowel preparation is offered.

Assessment of the intrarenal intralobar arteries to calculate the renal resistive index has been suggested to improve the diagnostic

accuracy of duplex ultrasound in the diagnosis of unilateral renal artery stenoses (Zeller et al., 2001).

$$\text{Renal resistive index} = \frac{\text{peak systolic velocity} - \text{end diastolic velocity}}{\text{peak systolic velocity}}$$

However, renal resistive index can be modulated by other factors, including age, presence of renal parenchymal disease (Zeller et al., 2008), and heart rate (Mostbeck et al., 1990). Consequently current practice does not advocate the use of threshold values of renal resistive index for the diagnosis of renal artery stenosis. Instead a comparative approach is used, with a side-to-side difference of > 0.05 in resistive index being the most commonly adopted parameter. This has a sensitivity and specificity of at least 77% and 94% for the diagnosis of > 70% stenosis (Schwerk et al., 1994; Zeller et al., 2001).

Initial enthusiasm for widespread adoption of measurement of resistive index to guide decisions regarding the need for revascularization followed publication of a retrospective study of 131 patients. In these data, a resistive index > 0.8 appeared to identify patients who would not receive a benefit in renal function or blood pressure control following revascularization (Radermacher et al., 2001). Subsequent studies failed to validate this finding (Zeller et al., 2003; Krumme and Hollenbeck, 2007; Rocha-Singh et al., 2008) and it is uncertain as to whether the original data considered the stenotic or non-stenotic kidney (Krumme, 2006).

Novel ultrasound methodologies

Limited hilar analysis measuring acceleration time has been proposed as a method by which ultrasonographic evaluation of renal artery stenosis may be simplified (Nazzal et al., 1997), but this technique lacks both sensitivity and specificity (Motew et al., 2000). Intravascular ultrasound using blood flow velocity measurement to assess distal vascular disease has been assessed, but the invasive nature of this technique limits its use to research settings (Slovut et al., 2006) even though it is widely applied in cardiology.

Captopril renography

Captopril renography only offers high levels of diagnostic sensitivity and specificity where there is preserved renal function and a unilateral stenosis. The overall results of this test are inferior to CTA and MRA and it is now rarely used in routine clinical practice (Vasbinder et al., 2001).

Novel MRI techniques

The first two require high-field-strength scanners (3-Tesla and above) and are currently only used in a research setting.

Blood oxygen level-dependent magnetic resonance imaging

Blood oxygen level-dependent magnetic resonance imaging (BOLD-MRI) (Fig. 214.4), exploits the fact that deoxyhaemoglobin is paramagnetic and oxyhaemoglobin diamagnetic (Pauling and Coryell, 1936). Paramagnetic substances cause microscopic variations in the local magnetic field and consequently impact the MRI signal (Ogawa et al., 1990). This signal loss can be measured and utilized to provide a measure of renal tissue deoxyhaemoglobin, representative of ischaemia and quantified by an R2* value (Prasad et al., 1996). Human data suggest that BOLD-MRI may be able to identify kidneys in which tissue oxygenation is preserved despite significant stenosis (Textor et al., 2008) and that combining these data with isotopic glomerular filtration rate (GFR) measurements may select patients in whom renal function may improve following revascularization (Chrysochou et al. 2012). Although these data are promising, further studies are required to better understand the effects of other disease states and medications on R2* measurements (Warner et al., 2011).

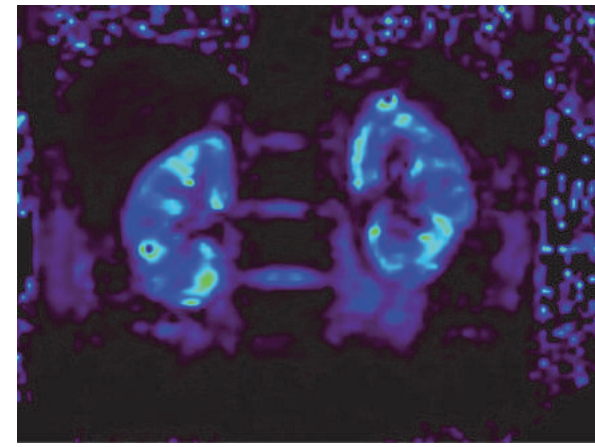

Fig. 214.4 Blood oxygen level-dependent magnetic resonance imaging in atherosclerotic renovascular disease. Dark blue and purple areas represent regions of increasing hypoxaemia.
Image supplied by Dr Constantina Chrysochou, Salford Royal Hospital, Salford, UK.

Arterial spin labelling

Arterial spin labelling uses magnetically labelled endogenous blood water as a tracer (Williams et al., 1992). Currently most published data have utilized this technique to assess renal perfusion (Kiefer et al., 2009; Artz et al., 2011); however, in a single small study, arterial spin labelling has been shown to be able to reliably identify renal artery stenosis > 70% (Fenchel et al., 2006). With very recent data suggesting this method could be adapted to estimate single-kidney GFR (He et al., 2014) there is potential for this approach to describe both structural and functional renal parameters in the future.

Non-contrast magnetic resonance imaging

Unlike BOLD-MRI and arterial spin labelling, non-contrast MRI can be performed using more widely available 1.5-Tesla scanners. Inversion pulses are applied during imaging to increase contrast between areas of static and non-static magnetization thus enhancing the appearance of the blood signal (Herborn et al., 2006). Use of non-contrast MRI provides results generally comparable to CTA (Pei et al., 2012) and contrast-enhanced MRI (Angeretti et al., 2013) in identifying the existence of a stenosis but can provide false-positive results and may overestimate degree of luminal loss (Braidy et al., 2012).

Laboratory tests

The widespread availability of improved diagnostic imaging has rendered biochemical assessments of possible renovascular hypertension far less important.

Renin

At population level, elevated plasma renin levels are associated with increased risk for cardiovascular death (Alderman et al., 2011).

Although it is intuitive and true that plasma renin activity may be particularly increased in patients with renal artery disease (Pickering, 1991), this observation is of limited value as systemic renin levels often decrease over time and elevated levels do not distinguish renal artery stenosis from other causes of hypertension (Rosner, 2001). Although renin measurements made in relation to administration of captopril are more sensitive for identification of renal artery stenosis, the specificity of this approach is low at 55% (Muller et al., 1986). Direct measurement of renal vein renin levels by cannulation of the inferior vena cava and comparison between left and right sides was investigated as an approach to select patients who would receive a blood pressure benefit from revascularization. Although 90% of patients with a ratio of > 1.5 between stenosed and non-stenosed organs saw a blood pressure benefit, > 60% of patients with a 'negative' test also received benefit (Rosner, 2001) limiting any clinical utility.

Other markers of cardiovascular risk

As the majority of cases of renovascular hypertension relate to atherosclerotic renovascular disease (ARVD), assessment of lipid profile is appropriate. Recent advances in the understanding of the pathogenesis of atherosclerosis have highlighted the role of inflammation, often measured by highly sensitive C-reactive protein (hs-CRP) (Ross, 1999), with increased levels predictive of worse outcome (Ridker et al., 2008). Although increased levels of hs-CRP are observed in patients with ARVD compared to non-atherosclerotic controls (Hommels et al., 2005), the presence of ARVD does not increase the value of hs-CRP in predicting major adverse cardiovascular events (Schlager et al., 2009). As such, measurement of hs-CRP offers meaning in relation to overall prognosis, but not specifically in relation to ARVD.

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CHAPTER 215

Renal artery stenosis: management and outcome

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Fibromuscular disease

Prognosis

Few data exist to describe blood pressure or renal functional prognosis in patients with known fibromuscular disease (FMD). In cases of incidental diagnosis in normotensive patients, a greater proportion will develop hypertension compared to a normotensive non-FMD population (Cragg et al., 1989). Risk for end-organ damage depends upon vascular bed involvement and is therefore poorly described. Cases of renal infarction exist in the literature (Niizuma et al., 2005; Van den Driessche et al., 2010) but overall FMD is not thought to cause progressive loss of renal artery patency (Plouin et al., 2007). The risk of a cerebrovascular event may be increased when cranial vessels are affected, with between 15% and 18% of patients with cervical or vertebral artery dissection having evidence of FMD in the damaged vessel (Dzielińska et al., 2007).

Treatment

The primary goal of therapy in FMD is to control blood pressure with the treatment decision being between an interventional or pharmacological approach. Historically, revascularization has been the preferred method although the reported rate of hypertension cure is highly variable, ranging from 14% to 79% (Slovut and Olin 2004) and there are no randomized trial data comparing patient outcome with pharmacological approaches. A meta-regression analysis of 47 angioplasty studies in FMD has shown that probability of blood pressure cure reduces with increasing patient age (odds ratio (OR) of cure for every 10-year increase 0.48 (0.4–0.6), $P < 0.001$) and duration of hypertension (OR of cure for every 5-year increase 0.39 (0.2–0.7), $P = 0.005$) (Trinquart et al., 2010). This finding may represent a greater proportion of older patients having concomitant essential hypertension. As such, revascularization is mainly recommended for younger patients in whom FMD is diagnosed at the time of hypertension onset (Olin and Sealove, 2011), or in those with malignant hypertension, severe bilateral disease, or threatened renal function (Plouin et al., 2007). In other cases, expert opinion suggests pharmacological treatment with angiotensin blockade and low-dose aspirin as first-line therapy (Plouin et al., 2007; Olin and Sealove, 2011). Fig. 215.1 summarizes a potential management pathway for newly diagnosed FMD.

Atherosclerotic renovascular disease

Prognosis

Blood pressure

Although newly diagnosed renal artery stenosis has a clear cross-sectional association with hypertension, the fact that we are only able to observe patients with known atherosclerotic renovascular disease (ARVD) (who are therefore under treatment) limits our ability to describe the natural history of blood pressure in this condition. In a long-term descriptive study of 171 patients with ARVD over a period of up to 9 years, mean initial blood pressure was 137/78 mmHg compared with a mean last follow-up value of 130/76 mmHg, although changes in medication number and dosage were not reported (Safak et al., 2013). It is likely that for patients in whom blood pressure does increase over time this is a result of a reduced glomerular filtration rate (GFR) rather than worsened renal haemodynamic status (Ruilope 2011).

Renal progression

Progression of renal artery stenosis

In the current era of pharmacotherapy, significant progression of the degree of stenosis in ARVD is unusual. In data from the 1980 and 1990s collected prior to widespread use of statin therapy, increased lumen loss was seen in 35% of patients 3 years after diagnosis, 44% at 4 years, and 51% at 5 years, with 16% of patients progressing to renal artery occlusion (Schreiber et al., 1984; Caps et al., 1998). More recent data from a retrospective study of 79 patients with ARVD, 40 of whom were treated with a statin, found evidence of increased stenosis at 2 years in 6% of statin-treated patients compared to 30% of non-statin-treated patients (Cheung et al., 2007). This is supported by prospective data in which two studies of renal arteries in free-living Canadian patients were undertaken at an interval of 8 years. Here no patients with > 60% stenosis in the first study progressed to occlusive renal disease with an annualized rate

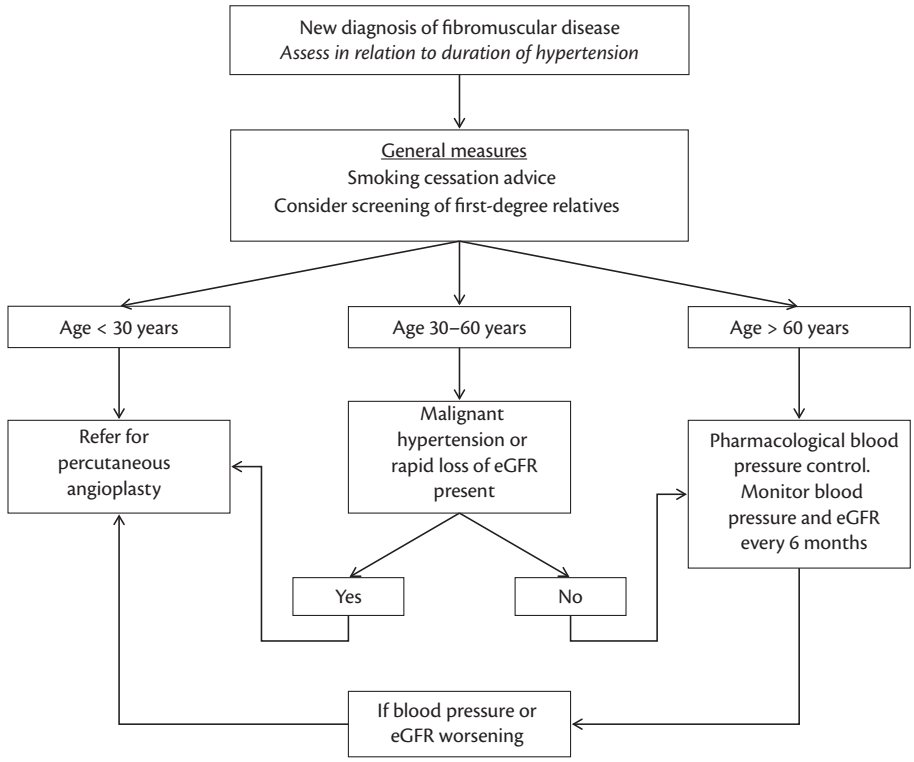

Fig. 215.1 Suggested management algorithm for patients with a new diagnosis of fibromuscular disease. eGFR = estimated glomerular filtration rate.

of only 1.3% of patients per year demonstrating significant change in stenosis burden (Pearce et al., 2006).

Progression of renal dysfunction

Discussion of renal functional loss in ARVD is covered in greater detail in Chapter 212. Accurate estimation of loss of function in ARVD is challenging, firstly because most data are based on measurement of estimated and not isotopic glomerular filtration rate, and secondly because renal artery stenosis is often an asymmetric disease. Compensatory hypertrophy of the non-stenosed kidney may balance reductions in the function of a diseased organ (Miyamori et al., 1986) and when GFR loss is halted, this may represent complete loss of function in a stenosed organ with stable contralateral function (Textor 2011). As such, it is not surprising that in a series of 541 iothalamate GFR measurements in 254 ARVD patients, estimated GFR (eGFR) values were < 45% sensitive for identifying a 20% changes in iothalamate GFR (Madder et al., 2011).

Where rate of change in renal function has been studied it is apparent that ARVD does not cause more rapid loss of function than other causes of chronic kidney disease (CKD). In the 806 patients studied in the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial, the average rate of loss of eGFR was 1–2 mL/min/1.73 m^2 per year (ASTRAL Investigators et al., 2009). In the same study, approximately 4% per year of patients reached end-stage kidney disease (ESKD) over a median follow-up period of 34 months. Over a comparable time period, ARVD was defined as the primary cause of ESKD in approximately 5% of incident dialysis patients in the United States (Guo et al., 2006). The rate of ESKD due to ARVD appears to be falling. In a single-centre epidemiology study, 3.5% of ARVD patients diagnosed between 1995 and 2000 progressed to ESKD compared to 2.3% of those diagnosed between 2000 and 2005 (Chrysochou and Kalra, 2009).

Mortality

Overall mortality

The risk for death associated with ARVD has fallen over the last decade but still far outweighs the risk for progression to ESKD (Kalra et al., 2005). Improved medical treatment of risk factors is the most probable cause for reduced mortality rates; however, there are no comparative data available within a single population. Prior to 2001, annual mortality in patients with ARVD in the United States was 16% compared to 6% in the non-ARVD population (Kalra et al., 2005). The most recent trial data, analysed in 2008, describe an 8% annual mortality rate (ASTRAL Investigators et al., 2009). Despite this reduction, risk for death in ARVD remains elevated and more in line with the 11% annual mortality observed in prevalent dialysis patients in the United Kingdom than the 2% mortality rate in comparably aged general population patients. Cardiovascular events are the leading cause of mortality in ARVD, accounting for 42% of deaths (ASTRAL Investigators et al., 2009). Whilst this is very consistent with the increased cardiovascular risk in general CKD patients (Tonelli 2006), where 41% of patients with CKD stages 3–5 die from a cardiovascular cause (Hoefield et al., 2010), distribution between age groups may vary. In CKD, the relative risk for vascular death is highest in younger patients (Foley et al., 1998). As patients with ARVD tend to be more elderly, it can be postulated that the existence of this condition marks a heavy burden of systemic atheroma and risk for cardiovascular death independent of renal function.

In dialysis patients, conflicting data exist regarding the prognostic implications of ARVD. In a single-centre study of 683 dialysis

patients performed between 1989 and 1992, patients with renovascular disease had a significantly increased mortality risk compared to patients with polycystic kidney disease, interstitial nephritis, or glomerulonephritis as the primary cause of renal failure (Mailloux et al., 1994). In contrast, analysis of > 146,000 haemodialysis patients captured in United States registry data between 1996 and 2001 noted a reduced risk for death in patients with ARVD compared to patients with other causes of ESKD (Guo et al., 2006). These data infer that the 9% of patients with a diagnosis of renal artery stenosis had increased risks for developing coronary artery disease, congestive heart failure, and peripheral vascular disease, but a reduced risk for all-cause mortality (hazard ratio (HR) 0.94 (0.92–0.96), P < 0.001). This unexpected finding may relate to some form of survivor bias and requires further study.

Mortality associated with other known macrovascular disease

As a patient's atheromatous burden increases, risk for death is further elevated. In patients with extrarenal disease screened for ARVD, the presence of a significant renal artery stenosis is associated with an increased mortality risk. In patients with coronary artery disease, concomitant ARVD is associated with a 1.5 times increased risk for death (Conlon et al., 2001). In patients with peripheral vascular disease who have ARVD, the risk increase is almost threefold (Amighi et al., 2009). In patients with known ARVD where other vascular disease is sought, the same pattern exists. A series of 95 patients with significant ARVD followed for a 50-month period noted a 22% mortality in ARVD patients with no other major macrovascular disease, a 37% mortality in those who also had peripheral vascular disease, a 55% mortality in those with coronary artery disease, and a 64% mortality in those with both peripheral and coronary arterial disease in addition to ARVD (Shurrab et al., 2003).

Prognostic factors associated with risk for death

Risk for death in ARVD is presumably influenced by similar factors to those related to risk in other causes of CKD. In addition to the effects of extrarenal vascular disease discussed above, an increased mortality risk is observed in patients with disordered renal parameters. A single-centre series of 229 patients with atherosclerotic renal artery stenosis > 50% described a significantly increased risk for death associated with an eGFR < 25 mL/min/1.73 m^2 (relative risk 4.4 (1.6–11.9), P = 0.004) (Cheung et al., 2002). Other data from the same centre have noted an increased risk for death associated with proteinuria >1 g/24 hours, although the magnitude of risk is not described (Chrysochou et al., 2009).

Medical therapy

Despite numerous studies comparing medical therapy with revascularization in ARVD, and annual mortality having fallen from 16% to 8% (Kalra et al., 2005; ASTRAL Investigators et al., 2009), what constitutes optimal medical therapy is poorly defined. Treatment is prioritized to modify vascular risk factors. In addition to lifestyle interventions such as smoking cessation and rigorous control of glycaemia in diabetic patients, blood pressure control must be optimized and consideration given to the use of antiplatelet and lipid-lowering medications. Fig. 215.2 outlines a suggested treatment algorithm.

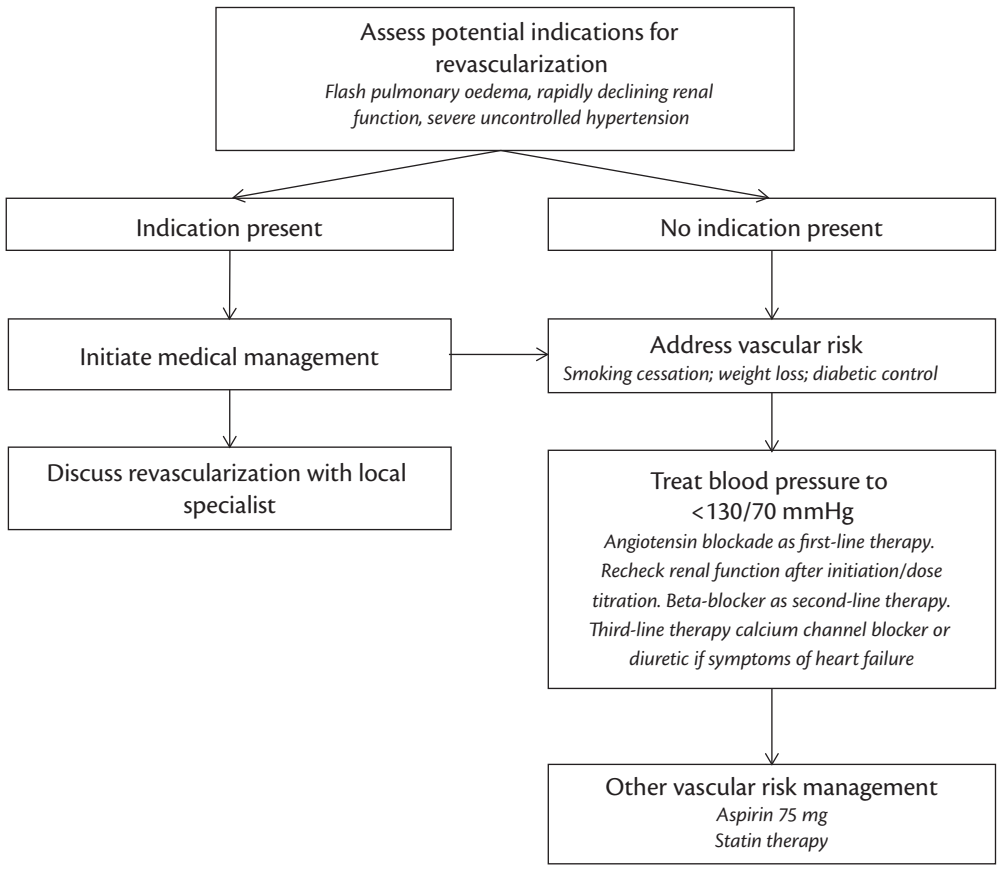

Fig. 215.2 Suggested management algorithm for patients with atherosclerotic renovascular disease. See text for explanation of differences from standard CKD protocols.

Angiotensin blockade

Angiotensin blockade is considered first-line therapy in CKD due to benefits on rate of loss of renal function exceeding what might be expected by the reduction in blood pressure alone (Jafar et al., 2001). Historically there has been underuse of these agents in patients with renal artery stenosis due to concerns regarding reduced glomerular filtration pressure (Bart et al., 1997). Whilst a reduction in GFR can be precipitated by initiation of angiotensin blockade in ARVD, there may be other reasons (Table 215.1) and in any event reductions in GFR can be reversed upon withdrawal of the agent (van de Ven et al., 1998).

Current data suggest that angiotensin blockade is better tolerated in ARVD then is generally believed. In a series of 36 patients with ARVD (26 revascularized, 10 medically managed), use of angiotensin blockade was not associated with a reduction in eGFR over a median follow-up period of 88 months (Sofroniadou et al., 2012). Another observational study has described 71 patients, not prescribed angiotensin blockade, in whom renal artery stenosis had been diagnosed following an increase in serum creatinine with initiation of angiotensin blockade (Chrysochou et al., 2012). Forty of these patients were subsequently recommenced on angiotensin blockade (13 following revascularization), without detriment to renal function. ARVD patients prescribed these agents do, however, have an increased risk for hospitalization with acute kidney injury during intercurrent illnesses (HR 1.87 (1.05–3.33), P = 0.04). This is lower than the risk associated with loop diuretics (HR 1.98 (1.01–3.88), P = 0.04) (Hackam et al., 2008).

Angiotensin blockade may be considered first-line therapy in ARVD due to significant reductions in risk for death and non-fatal cardiovascular events with two studies describing an almost 50% risk reduction for mortality associated with these agents (Hackam et al., 2008; Chrysochou et al., 2012). The mechanism of this risk reduction is uncertain, but recent data from porcine models suggest angiotensin blockade may reduce renal fibrosis and aid preservation of the microvasculature (Zhang et al., 2013) and effects upon myocardial structure and function are likely to be important. There are no data to support the use of dual angiotensin blockade in ARVD.

Table 215.1 Causes of reduced renal function after initiation of angiotensin blockade

Causes of reduction in glomerular filtration rate associated with use of angiotensin blockade	
Inadequate renal perfusion	Reduced cardiac output or systemic vascular resistance
Hypovolaemia	
Concurrent use of vasoconstrictor agents	Non-steroidal anti-inflammatory drugs
	Ciclosporin
Renal vascular disease	Bilateral renal artery stenosis or stenosis to single functioning kidney
	Afferent arteriolar disease
	Diffuse small vessel atherosclerosis without focal ostial stenosis

Settings in which a reduction in glomerular filtration rate may be due to a cause other than angiotensin blockage.

Adapted from Schoolwerth et al. (2001).

Beta blockade

In addition to excess renin–angiotensin–aldosterone activity, patients with renal artery stenosis have sympathetic overactivity and elevated serum noradrenaline concentrations (Johansson et al., 2000). In conjunction, the arterial baroreflex response to elevated sympathetic activity is reset upwards and becomes less sensitive (Grassi et al., 1998). Survival benefits associated with beta blockade are well described in essential hypertension, congestive heart failure, and following myocardial infarction (Chobanian et al., 2003; Antman et al., 2008), phenotypes all commonly observed in the context of renal artery disease. There are no data to suggest that beta blockade results in better blood pressure control in the setting of renovascular hypertension. Indeed the American Society of Hypertension defines pairing of a beta blocker with angiotensin blockade as a relatively ineffective combination to treat hypertension (Gradman et al., 2010). However, in a series of 40 patients undergoing medical treatment for atherosclerotic renal artery stenosis, use of beta blockers as second-line therapy was associated with a greater proportion of patients exhibiting stabilization in degree of stenosis compared to those using calcium channel blockers or dual angiotensin blockade (75% vs 54% vs 50%) (Cianci et al., 2011). Other data suggest a potential benefit in renal function in revascularized patients treated with nebivolol in addition to angiotensin blockade post procedure (Duranay et al., 2010). Given the relationship between renal function and blood pressure and degree of renal artery stenosis and blood pressure, these data would argue for a second-line role for beta-blockade.

Other antihypertensive medications

Due to the salt and water retention caused by excess activity of the renin–angiotensin–aldosterone system, a mechanistic argument for the use of diuretic therapy can be made for patients with ARVD. Use of these agents is considered key in the management of resistant hypertension (Myat et al., 2012). Although diuretics are one of the least well tolerated classes of antihypertensive, tolerability is improved when used in combination with other agents (Gradman et al., 2010). In addition, diuretics result in a fully additive blood pressure reduction when used as part of a combined management strategy (Chrysant 1994). Specific data regarding the use of diuretics in ARVD is anticipated from the Cardiovascular Outcomes in Renal Artery Lesions Study (CORAL) in which diuretics are specified as second-line therapy (Cooper et al., 2006). Calcium channel blockers result in an additive blood pressure reduction when combined with all classes of antihypertensive medications other than alpha blockers (Gradman et al., 2010). Few specific data exist regarding their use in ARVD.

Antiplatelet medications

Antiplatelet therapy is accepted as a standard treatment in ARVD due to the significant extrarenal burden of atheroma (Colyer and Cooper, 2011). In chronic stable disease, there are no data to compare outcome between different classes of antiplatelet agents. In CKD, aspirin therapy is generally considered efficacious and safe (Jardine et al., 2010), although debate is ongoing (Palmer et al., 2012). Despite this uncertainty, aspirin is seen as a first-line treatment due to the reduced activity and increased bleeding risk

observed in CKD patients prescribed clopidogrel (Best et al., 2008). Current research into antiplatelet therapy in ARVD is focused on optimal treatment (Cooper et al., 2008; Kanjwal et al., 2010) around time of percutaneous revascularization.

Statin therapy

Statin therapy is a rational choice in ARVD given the burden of systemic atherosclerotic vascular disease and the associations between these agents and reduced rates of loss of renal function (Shah et al., 2005; Huskey et al., 2009) and cardiovascular events in CKD patients (Baigent et al., 2011). In addition to this, statins retard progressive loss of renal luminal diameter (Cheung et al., 2007) and are associated with reduced renal fibrosis in pig models of atherosclerotic renal artery stenosis (Chade et al., 2008). Risk for death and ESKD associated with statin therapy was analysed in a cohort of 104 ARVD patients in which hyperlipidaemia patients (N = 68, mean cholesterol 5.2 mmol/L) were treated with a statin and patients without hyperlipidaemia (N = 36, mean cholesterol 4.7 mmol/L) were not. In this study, statin treated patients had a reduced risk for ESKD (HR 0.2 (0.1–0.6), P = 0.006) and death (HR 0.13 (0.04–0.4), P = 0.001) (V. S. Silva et al., 2008). A similar reduction in risk for death has been described in revascularized patients (HR 0.71 (0.53–0.95), P = 0.02) (Bates et al., 2007). In a series of 91 patients who underwent percutaneous renal artery angioplasty and stenting, statin use significantly associated with a reduced risk for re-stenosis (HR 0.35 (0.16–0.74), P = 0.006) (Corriere et al., 2009).

Renal revascularization

Surgical revascularization for ARVD has effectively been consigned to history, at least in cases without complicated anatomy, as percutaneous intervention has been shown to produce comparable angiographic results (Weibull et al., 1993) without suffering the 10% mortality rate described with open reconstruction (Modrall et al., 2008). Standard practice is now accepted to be percutaneous angioplasty with bare metal stenting (PTRAS), with stents significantly reducing rate of restenosis compared to angioplasty alone (Zeller et al., 2003; van de Ven et al., 1999) Although PTRAS is considered relatively safe in expert hands, around 2–3% of patients suffer a serious complication such as major haemorrhage or dissection, whereas less serious complications such as a transient deterioration in renal function or groin haematoma may occur in around 10% of cases (Leertouwer et al., 2000). In light of these procedural risks, it is important to determine which patients are most likely to benefit from revascularization procedures and to perform them on this select cohort rather than unselectively in all patients with ARVD.

Historical registry data indicate that revascularization procedures were performed in around 16% of cases of ARVD (Kalra et al., 2005), although this figure has fallen markedly in light of negative trials into PTRAS according to UK National Health Service hospital episode statistics. It is still unclear which patients are being revascularized. Whilst published trials have considered change in blood pressure and renal function as primary end-points, with death and cardiovascular events as secondary end-points, international guidelines consider presentation with flash pulmonary oedema, refractory hypertension and progressive CKD as the major indications for renal artery stenting (Hirsch et al., 2006).

Almost all would agree that PTRAS is indicated in patients presenting with high-risk clinical presentations of ARVD such as flash pulmonary oedema, oligo-anuric acute kidney injury or rapidly declining renal function. Arguments have also been advanced to support PTRAS to enable the institution of ACE-inhibitors (Goldsmith et al., 2000) or to treat chronic heart failure (Kane et al., 2010).

Randomised trials of revascularization in ARVD

Although some case studies showed a trend towards reduced rates of decline in renal function following endovascular revascularization procedures (Harden et al., 1997; Watson et al., 2000) others were less convincing (Isles et al., 1999; Dejani et al., 2000). Beutler *et al.* were only able to demonstrate benefit in those with declining renal function pre-intervention (Beutler et al., 2001). The uncertainty and conflicting findings of these series paved the way for a series of randomised control trials of revascularization in ARVD.

Prior to the landmark Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) study four randomised control trials had compared percutaneous renal artery revascularization with medical therapy in patients with ARVD (Plouin et al., 1998; van Jaarsveld et al., 2000; Webster et al., 1998; Bax et al., 2009) Renal function varied from normal to moderate CKD and hypertension was present. These trials were relatively small and short, and the three earlier studies looked at angioplasty rather than stent insertion and were inadequately powered to assess major functional outcomes. A later meta-analysis of the three early trials (n=210) showed that although there was no benefit in blood pressure at six months, there was a greater mean improvement in systolic blood pressure in those who underwent angioplasty (Ives et al., 2003). The Dutch led Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function (STAR) study was published just prior to ASTRAL. A high proportion of patients randomized to stenting did not receive the procedure and no differences were observed in terms of blood pressure control or renal function (Bax et al., 2009).

In ASTRAL (ASTRAL Investigators et al., 2009) 806 patients with ARVD (average 76% stenosis) were randomized to either medical therapy alone or medical therapy plus endovascular revascularization. Median follow up was 33.2 months. There was no difference in the primary endpoint of change in renal function between the groups. Similarly, blood pressure fell equally and there was no difference in cardiovascular events or mortality between the two groups.

The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial (Cooper et al., 2014) randomized 947 patients with average eGFR 58 ml/min/m^2 and evaluated stenoses more methodically by central laboratory assessment of images and measuring trans-lesional gradients. Again it found no difference in the primary composite outcome made up of adverse renal and cardiovascular consequences. There was an almost (but not quite) significant, small reduction in blood pressure from stenting.

Although there have been a number of methodological criticisms of these studies it is hard to argue with their overall conclusions. It is difficult to justify the risks of endovascular revascularization in patients presenting with stable ARVD when there is seemingly so little benefit to be gained from the procedure (Herrmann et al., 2015).

Trials of percutaneous revascularization for hypertension

Despite numerous non-randomized series reporting blood pressure improvement following PTRA or PTRAS, none of the six published

randomized trials comparing medical therapy with percutaneous revascularization have shown superiority of this approach compared to optimal medical therapy.

ASTRAL and CORAL showed no or minimal significant benefit on blood pressure, but only the two oldest randomized trials comparing percutaneous revascularization with medical therapy for ARVD have considered change in blood pressure as their primary endpoint. Both of these studies, the Scottish and Newcastle Renal Artery Stenosis Collaborative Group (SNRASCG) (Webster et al., 1998) and the Essai Multicentrique Medicaments vs. Angioplastie (EMMA) (Plouin et al., 1998), utilized PTRA not PTRAS as they were undertaken before renal artery stenting had been introduced and they were also performed prior to angiotensin blockade being an established therapy. As such, their data cannot be compared to current practice.

More recent studies using PTRAS that have focused on mortality, cardiovascular events, and change in renal function as primary endpoints have also presented data on blood pressure outcomes (van Jaarsveld et al., 2000; ASTRAL Investigators et al., 2009; Bax et al., 2009; Marcantoni et al., 2012). Although all of these studies have limitations of either small patient numbers, possible selection bias, or limited follow-up time (Ritchie et al., 2012), they are all consistent in describing no advantage in terms of achieved blood pressure control between treatment groups. A summary of blood pressure outcome data from these studies is presented in Table 215.2. In a 2011 meta-analysis of published data, this finding was validated, with no significant difference found in the weighted mean difference in blood pressure between revascularized and medically managed patients (Kumbhani et al., 2011). With 806 patients randomized, the ASTRAL study had the greatest bearing on this result (ASTRAL Investigators et al., 2009). Here baseline blood pressure was 152/76 mmHg in the medial therapy group and 149/76 mmHg in the revascularization group. With the exception of a greater reduction in systolic blood pressure at 3 months in the PTRAS group, no significant difference in blood pressure control between groups was observed at follow-up points (1 year 148/75 mmHg vs 146/73 mmHg; 5 years 141/70 mmHg vs 141/73 mmHg).

In the Dutch Renal Artery Stenosis Intervention Study Group (DRASTIC) which included 106 patients with ARVD, a reduction in medication burden was noted throughout the follow-up period in the revascularization group (van Jaarsveld et al., 2000). At baseline the medical group patients were each prescribed 3.2 and the revascularization group 3.3 antihypertensive agents. At 3 months the number of medications in the revascularization group had fallen to 2.1, with a further reduction to 1.9 agents per patient at 12 months, with no change in the mean number of antihypertensive agents prescribed to patients in the medical therapy group. Although this finding was not replicated in the Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and Impaired Renal Function (STAR) trial (Bax et al., 2009), this finding has been replicated in a meta-analysis with a weighted mean difference of −0.26 (95% confidence inetrval −0.39 to −0.13) medications in revascularized patients (Kumbhani et al., 2011). Although this finding is often interpreted as supporting revascularization for cases of renovascular hypertension, the clinical relevance can be questioned and a fractional reduction in medication burden may not sufficiently offset the potential risks of revascularization.

Novel markers and interventions

Brain natriuretic peptide

Brain natriuretic peptide (BNP) is a neurohormone with diuretic and natriuretic properties, predominantly produced by the myocardium (Maisel et al., 2008). Although originally recognized to be released in response to stretch of myocardial fibres, it has since been shown that release can occur independently of this in renal artery stenosis to counterbalance the salt and water retaining effects of activation of the renin–angiotensin–aldosterone system (Wolf et al., 2001). In a series of 40 patients investigated for suspected renovascular hypertension, a pre-test BNP of > 600 pg/mL had 80% sensitivity and 95% specificity for a positive angiogram (Wongpraparut et al., 2013). Another study in which 61 male patients with known ARVD >50% were prospectively followed with repeated BNP measurements did not demonstrate an overall increase in BNP level from the baseline median of 210 pg/mL (Zhu et al., 2013). However, in these data patients in whom BNP level rose to > 450 pg/mL had an increased risk (HR 5.1 (1.3–20.7), P = 0.02) for fatal and non-fatal cardiovascular events over a mean follow-up period of 25 ± 12 months.

Other studies have considered the viability of BNP to predict blood pressure response after renal artery angioplasty and stenting. An initial series of 27 patients with refractory hypertension and without echocardiographic evidence of congestive cardiac failure found a beneficial blood pressure effect in a significantly greater proportion of patients with BNP > 80pg/mL (77% vs 0% P < 0.001) (J. A. Silva et al., 2005). A subsequent study of 120 patients with blood pressure >140/90 mmHg (measured by 24-hour monitor) demonstrated a similar trend. Here BNP > 50 pg/mL prior to percutaneous revascularization associated with a significantly increased probability of blood pressure improvement following intervention (OR 4.0 (1.2–13.2), P = 0.02) (Staub et al., 2010). Most recently, however, in a series of 165 patients with atherosclerotic renal artery stenosis and BNP measurements performed prior to revascularization, no significant correlation was observed between BNP level and post-procedure change in blood pressure (Jaff et al., 2012). Although this latter study was of patients in whom an initial revascularization procedure had been unsuccessful, and neither considered BNP as a categorical variable nor addressed possible confounding effects of heart failure, it serves as a relevant reminder of the diversity of outcomes observed within the renal artery stenosis population.

Hibernating parenchyma

The term ‘hibernating parenchyma’ was first coined by Tuttle (Tuttle, 2002) and aims to distinguish those kidneys that have suffered irreversible parenchymal damage from those that may improve with revascularization. An ability to identify those with ‘hibernating parenchyma’ would distinguish which patients should benefit from revascularization from those that are irreparably damaged. Two techniques are mentioned here but prospective studies are needed to test them.

Cheung et al. looked at parenchymal volume assessed by MR-perfusion imaging and also performed isotopic single kidney GFRs in 50 patients with >50% RAS who underwent revascularization plus medical therapy or medical therapy alone. In this study a disproportionately high ratio of parenchymal volume to single kidney GFR was predictive of improvement in GFR post revascularization (Cheung et al., 2010).

Blood oxygen level dependent (BOLD) MRI detects changes in tissue deoxyhaemoglobin, assessed by R2*. Animal studies have shown that BOLD imaging reliably detects changes in intra-renal oxygenation with varying degrees of reduction in renal blood flow (Juillard et al. 2004). A clinical study of 28 patients demonstrated that high R2* signal to single kidney GFR was predictive of improvement in renal function following revascularization, thereby suggesting that BOLD imaging, just like volume to GFR assessment, may provide a way of detecting 'hibernating parenchyma' (Chrysochou, Mendichovszky, et al. 2012b).

Brachytherapy

Intravascular brachytherapy directly delivers gamma radiation to reduce cell division and induce smooth muscle apoptosis (Waksman et al., 1995). This technique was originally proposed as a means to limit or treat re-stenosis by inhibiting neointimal formation (Mintz et al., 2000) following angioplasty and stenting. Studies of this technique have only considered small patient numbers and data regarding possible blood pressure benefits of brachytherapy are inconsistent (Lekston et al., 2008; Lekston et al., 2009) and have only been compared against angioplasty without stenting.

Renal artery denervation

Early hope that renal sympathetic denervation might be a simple intervention for resistant hypertension (discussed in Chapter 217) does not seem to have been borne out. In these studies there were no reports of patients developing renal artery stenosis following intervention (Rippy et al., 2011), case reports of this complication have emerged (Kaltenbach et al., 2012). No data exist regarding the efficacy of this intervention in patients with renal artery stenosis, and previous stenting is a contraindication to the procedure. Due to the reductions in renal norepinephrine spillover following denervation, this may be a technique worthy of consideration in an ARVD cohort when trials in the non-CKD non-ARVD population are concluded (Kandzari et al., 2012).

Soluble CD40 ligand

The proximal tubular epithelium expresses a CD40 receptor, activation of which is associated with increased interstitial inflammation (Starke et al., 2007; H. Li and Nord, 2009), and inhibition of which is associated with less severe renal injury in mouse models of CKD (Kairaitis et al., 2003). Soluble CD40 ligand (sCD40L) is released by activated platelets, with increased levels found in patients with atherosclerosis (Haller et al., 2011), and is the main activator of CD40 (Antoniades et al., 2009). In atherosclerotic renal artery stenosis sCD40L levels are not significantly correlated with blood pressure, but are positively associated with loss of renal function over a 1-year follow-up period (Haller et al., 2013).

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is an endothelial specific growth factor expressed within the kidney by tubular epithelial cells and glomerular podocytes. The main function of VEGF is to trigger capillary growth and proliferation in response to regional hypoxia and vascular injury (Schrijvers et al., 2004). In swine models of renal artery stenosis, intrarenal infusion of VEGF is associated with preservation of microvascular density and renal blood flow and reduced interstitial fibrosis (Iliescu et al., 2010; Chade and Kelsen, 2012). No data yet exist to describe this intervention in a model of atherosclerosis and with an overlapping relationship existing between angiogenesis and inflammation, long-term results are required (Reinders et al., 2006). Interest also exists regarding blockade of the endothelin-A receptor, which may preserve renal structure via upregulation of VEGF (Kelsen et al., 2011)

Endothelial progenitor cells

Endothelial progenitor cells (EPCs) are precursors to angiogenesis and though typically produced by bone marrow they may also be produced by the kidneys in the setting of renal artery stenosis (Fadini et al., 2005), complementing EPC homing signals produced by ischaemic kidneys (Chade et al., 2010). Numbers and function of EPCs, however, reduce as renal impairment becomes established (Choi et al., 2004). In porcine models of renal artery stenosis, administration of EPCs acts to preserve renal microvascular structure (Chade et al., 2009), with statin therapy reducing EPC apoptosis (Lavi et al., 2010).

Takayasu disease

The treatment for renal artery stenosis secondary to Takayasu disease depends on both the type and the phase of disease. In the acute inflammatory phase, immunosuppressive therapy is appropriate (Chapter 160). However, most cases of renovascular hypertension due to vasculitis relate to the chronic pulseless phase of Takayasu's arteritis, treatment options for this are considered here.

The majority of series in which interventional treatment of renovascular hypertension secondary to Takayasu arteritis has been attempted have used percutaneous transluminal angioplasty without stenting. Technical success rates of between 62% and 95% are reported (S. Kumar et al., 1989; Sharma et al., 1998) with good clinical results. In the largest published series of attempted revascularization procedures in 62 patients, cure of hypertension was achieved in 14 patients and significantly improved blood pressure and/or reduction in medication burden in 45 patients, with a mean blood pressure reduction of 45/29 mmHg (Sharma et al., 1998). Following intervention of renal artery stenosis due to Takayasu's arteritis, re-stenosis rates of 25% over a 3–4-year follow-up period are been consistently described (Tyagi et al., 1993; A. A. Kumar et al., 2003). Patients with ostial disease and limited angiographic success at the time of first procedure are at the highest risk (Sharma et al., 1996).

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CHAPTER 216

Malignant hypertension

Caroline Whitworth and Stewart Fleming

Introduction

There is no accepted definition of what constitutes malignant hypertension (MH) and no specific histological finding on pathology. MH constitutes a collection of typical clinical and pathological features. The term 'accelerated phase' hypertension or pre-malignant hypertension was previously applied to patients with severe hypertension and grade III hypertensive retinopathy, but as there is no other difference in clinical features or outcome, it has been accepted that MH encompasses patients with both grades III and IV retinopathy (Ahmed et al., 1986). Clinical and pathological features were first described by Volhard and Fahr in 1914. The term malignant hypertension was used to describe a syndrome of severe hypertension and a characteristic retinitis with universal poor prognosis (Keith et al., 1928). Early case series documented the natural history of MH and estimated a 1% risk of hypertensives developing MH, with almost 100% mortality in 1 year in the era before widespread and effective treatment of hypertension existed (Keith et al., 1928; Kincaid-Smith et al., 1958). The current prevalence is not well known but MH remains a significant problem in some developing countries and is an important but avoidable cause of chronic kidney disease (CKD) and end-stage renal disease. Investigation of patients presenting with MH tends to reveal underlying contributory factors such as CKD of varying aetiologies and secondary hypertension (Gudbrandsson et al., 1979).

Clinical features

The clinical features (Table 216.1) vary and may be modified by pre-existing CKD or hypertension. A classical presentation is of a younger patient, with a previous history of hypertension in about 53% of cases (van den Born et al., 2005), developing a rising blood pressure accompanied by an initial diuresis and natriuresis which may manifest as nocturia or polyuria and weight loss. As renal impairment develops, this will change to a phase of impaired excretion of salt and water leading to peripheral oedema. Hypertensive encephalopathy may develop with initial lethargy or altered mental state, confusion, and coma but may present with signs of stroke or cortical visual loss in up to 30%. Grade III or IV hypertensive retinopathy is present (Beutler and Koomans, 1997). Around 20–40% of patients may require renal support during the acute phase (van den Born et al., 2005).

Posterior reversible encephalopathy syndrome (PRES) is seen in patients with MH (Deguchi et al., 2012) as well as eclampsia (Arora et al., 2001), systemic inflammatory response syndromes (SIRS), and post solid-organ transplantation with calcineurin phosphatase inhibitors. In MH, blood pressure may exceed the auto-regulatory limit (mean arterial pressure > 150–160 mmHg), but this is not required for development of PRES. A common feature is an acute rise in diastolic blood pressure prior to onset but PRES can occur in the absence of hypertension (Wright et al., 2012). Similar to the picture within the kidneys, cerebral and magnetic resonance angiography has demonstrated alternating focal vasoconstriction and vasodilatation or 'string-of-beads' appearance. Putative mechanisms include failed autoregulation, endothelial injury, vasoconstriction, and hypoperfusion (Bartynski, 2008a, 2008b) (Fig. 216.1).

Thrombotic microangiopathy (TMA) describes the appearances of thrombosis leading to microvascular occlusion, thrombocytopenia, and microangiopathic haemolytic anaemia leading to ischaemia and infarction particularly of the kidney and brain. It is a feature of MH, as well as other conditions—diarrhea-associated haemolytic uraemic syndrome (HUS), atypical HUS, eclampsia, pre-eclampsia, HELLP syndrome, scleroderma renal crisis, systemic lupus erythematosus (SLE), antiphospholipid syndrome, post-renal transplant acute vascular rejection, and MH (Barbour et al., 2012). Microangiopathic haemolysis appears more commonly in black patients presenting with MH and tends to be associated with a more severe presentation marked by poorer renal function (higher creatinine, increased urinary protein excretion) and higher systolic blood pressure, but they seem less likely to develop cerebral complications such as PRES or cerebral infarction (Sevitt et al., 1973; van den Born et al., 2005). Microangiopathic haemolysis signifies endothelial damage and thrombosis occurring within the microvasculature leading to direct red cell trauma through abnormal shear stresses. Patients with recent, but treated, MH show abnormalities of haemostasis in keeping with intravascular coagulation but at levels not significantly different to hypertensive patients with similar levels of blood pressure and renal dysfunction (Isles et al., 1984). The relationship between renal dysfunction and degree of microangiopathic haemolysis led to the suggestion that the principal site of red cell fragmentation is within the kidney and was demonstrated in animal studies though damage to arterioles with fibrin and platelet thrombi affects many organs (Venkatachalam et al., 1968).

Cardiac features vary at diagnosis of MH. Cardiac involvement can be relatively acute leading to symptoms and signs of left ventricular dilatation, failure, and pulmonary oedema. The duration of pre-existing hypertension is likely to be a more important factor in generating left ventricular hypertrophy (LVH). Patients presenting with MH with no known pre-existing diagnosis or short duration of hypertension tend not to have LVH. Significant diastolic dysfunction and left atrial enlargement are relatively common irrespective of whether there is a pre-existing history of hypertension (Shapiro and Beevers, 1983). Animal models have shown fibrinoid necrosis of myocardial arterioles together with micro-scarring of the myocardium (Collidge et al., 2004)

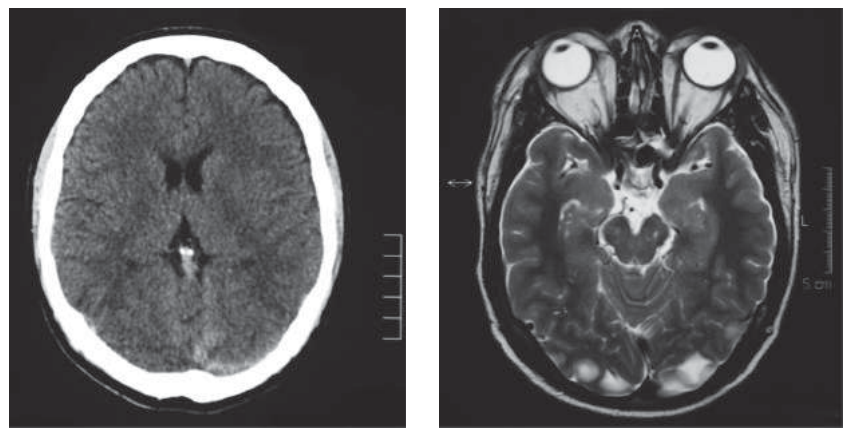
Table 216.1 Clinical symptoms, signs, and relevant investigation findings in patients with malignant hypertension. Where indicated, percentages indicate the proportion of patients who typically demonstrate the features described

Symptoms	Signs	Investigations
Headache, lethargy, fatigue, altered mental state, confusion.	Elevated blood pressure	Computed tomography or magnetic resonance imaging evidence of PRES—white matter changes in the posterior regions of the brain
Coma	Neurological signs, including stroke or encephalopathy (30%)	Cerebral infarcts
Altered vision—blurred vision, scotomata	Grade III or IV retinopathy (haemorrhages, exudates with or without papilloedema)	Left ventricular strain pattern on ECG
Shortness of breath and reduced exercise tolerance. NYHA class III or IV heart failure (30%)	Pulmonary oedema (30%)	Echo evidence of diastolic dysfunction.
Nausea, vomiting, anorexia, abdominal pain	Intravascular volume depletion (early) or extracellular volume expansion (late)	Impaired renal function in majority (80%)
Nocturia, polyuria then oliguria	Pallor	Macrolbuminuria (54%) ± microhematuria
Epistaxis		Microangiopathic haemolysis—anaemia, elevated lactate dehydrogenase, reduced platelets, schistocytes, reduced haptoglobin

Risk factors for developing malignant hypertension

Transition to MH can occur in pre-existing hypertension from all causes. The age distribution curve for patients presenting with MH is shifted to the left compared to that for essential hypertension (Kincaid-Smith et al., 1958); it was not uncommon in children in the past to present with MH (Pickering, 1971), and it still remains an issue in developing countries (Kumar et al., 1996). Essential hypertension is still the most common predisposing condition. Other causes of secondary hypertension are well described: renal artery stenosis—both atherovascular and fibromuscular dysplasia, phaechromocytoma, Conn syndrome, primary renal diseases including glomerulonephritides, reflux nephropathy, and large vessel vasculitides such as polyarteritis nodosa and aorto-aortitis (Kumar et al., 1996). Case reports exist of MH complicating SLE, antiphospholipid syndrome (Thomas et al., 2010), acute humoral rejection with associated thrombotic microangiopathy (Wyatt et al., 2005), and scleroderma renal crisis coexisting with a renal artery stenosis (Morris et al., 1994). However, many of these conditions which are associated with a thrombotic microangiopathy show common clinical features and pathologies with MH and this can lead to diagnostic uncertainty (Barbour et al., 2012).

It is evident that MH is increased in populations where detection and sustained control of hypertension is more difficult due to social, economic, or cultural factors. Increased rates of MH are seen in black hypertensive populations, but this may in part be due to delayed presentation, genetic differences, or differing pathogenesis (Pitcock et al., 1976; Patel et al., 1990; Lip et al., 1995; van den Born et al., 2006). Essential hypertension, complicated by MH in the majority, was reported as the commonest cause of CKD (van Rensberg et al., 2010) and end-stage renal disease in black South Africans accepted onto a dialysis or transplant programme (Veriava et al., 1990). It is a significant problem in other black populations (Rostand et al., 1982; Veriava et al., 1990; James et al., 1995). Increased risk of ESRD attributed to hypertension in black patients



CT scan MRI

Fig. 216.1 Typical computed tomography and magnetic resonance appearance of PRES in malignant hypertension.

may be due to other factors such as genetic differences (Freedman and Sedor, 2008) such as the *APOL1* gene (see Chapter 341) as well as MH.

Discontinuing antihypertensive medications (Patel et al., 1990), smoking history (Tuomilehto et al., 1982), previous oral contraceptive use (Hodsman et al., 1982), and past history of hypertension in pregnancy (Lip et al., 1995) have all been linked with an increased risk of MH. Drugs which can acutely increase blood pressure such as amitryptilline, monoamine-oxidase inhibitors, ecstacy, and cocaine have been reported to cause MH.

Animal models have demonstrated that a rising blood pressure, and a rapid rate of rise, may be more critical than absolute blood pressure levels in inducing transition to MH (Whitworth et al., 1995). This may be due to protective remodelling of the vasculature in response to more slowly rising blood pressure.

Pathogenesis

A key question still exists as to what makes malignant hypertension develop from a pre-existing 'stable' hypertension. The majority of animal models show evidence of intrarenal renin–angiotensin system (RAS) activation around the period of transition to a malignant phase of the hypertension (Lohmeier et al., 1984; Whitworth et al., 1995). A 'pre-malignant phase' of natriuresis and a resulting relative negative sodium balance may, through inducing relative renal hypoperfusion and reduced sodium delivery to the macula densa, lead to a further activation of the RAS and a vicious cycle (see Fig. 216.2). Endothelial damage, microvascular thrombi, myo-intimal proliferation also contribute to reduced luminal diameter and reduced renal blood flow. This will further drive activation of the intrarenal RAS. A renal ablation model demonstrated injury typical of MH in response to increased blood pressure due to loss of vascular autoregulation and vasodilatation (Bidani et al., 1994). A systemic dysfunction of vascular autoregulation may be part of the picture but this has not been conclusively demonstrated. Endothelial dysfunction is evident during MH and persists even after effective treatment. Within the kidney, development of MH is associated with elevated plasma endothelin 1 concentrations (Yoshida et al., 1994); while transition from benign hypertension to MH results in increased ET-1 expression in a rat model of MH. However, treatment with a combined ET_A and ET_B receptor antagonist, bosentan, had no effect on blood pressure and did not prevent transition to MH (Whitworth et al., 1995). Elevated circulating levels of the leukocyte adhesion molecule P-selectin, VCAM (vascular cell adhesion molecule) and von Willebrand factor are seen in patients with MH compared with other forms of hypertension, but these are also increased in TTP and sepsis syndromes (Verhaar et al., 1998).

The local, intrarenal RAS is important during the transition to malignant hypertension (Fleming, 2000). In the TGR(mRen2)27 rat on an Edinburgh Sprague-Dawley background, MH develops in 73% of animals as opposed to 1% on a Hanover background. The endocrine renin originates from the mouse transgene and there is suppression of the rat juxtaglomerular renin. During the transition to malignant hypertension the natriuresis leads to re-expression of rat renin in the juxtaglomerular apparatus (JGA) immediately prior to the development of malignant vascular injury (Whitworth et al., 1994). Furthermore non-hypotensive doses of angiotensin-converting enzyme (ACE) inhibition in this model suppresses renal tissue but not systemic angiotensin II generation and protects from the development of MH (Montgomery et al., 1998). A double transgenic (for human renin and angiotensinogen genes) rat model has shown that local generation of angiotensin II stimulated production of reactive oxygen species and nuclear factor kappa B upregulation (Muller et al., 2000). In this model, there is increased endothelial expression of adhesion molecules including

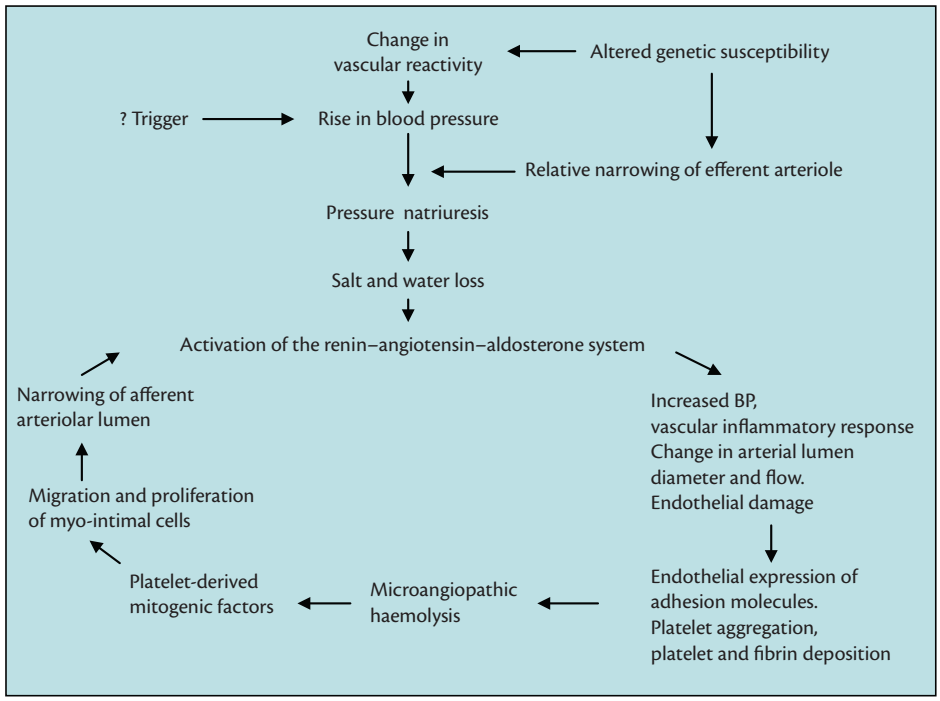


Fig. 216.2 Schematic of changes within the nephron perpetuating a vicious cycle in malignant hypertension.

ICAM-1 and VCAM-1 and their corresponding ligands, which indicate an inflammatory response may be associated with progress to malignant vascular injury (Mervaala et al., 1999).

Further support for the role of the local RAS comes from the two-kidney, one-clip model. In these rats the hypertension which occurs is dependent on renin production from the ischaemic clipped kidney, JGA renin in the unclipped kidney is suppressed. When MH supervenes there is renin production in the JGA of the unclipped kidney and it is only this kidney which shows malignant vascular injury (Mohring et al., 1971, 1976). Similar changes have been seen in patients with renal artery stenosis.

Differences in susceptibility may be influenced by genetic differences. The transgenic rat TGRmRen2 model of MH demonstrates increased susceptibility occurring as result of inheritance of certain genetic markers for both the *ACE* gene and angiotensin receptor *At1* genes (Kantachuvesiri et al., 1999). In humans, there is some evidence that possession of the D allele of the *ACE* genotype is found more frequently in individuals who have developed MH (Mayer et al., 2002), whereas a point mutation of the angiotensinogen gene was not found to be linked to MH (Stefansson et al., 2000).

Pathology

Grossly, the kidney in MH shows small petechial haemorrhages and infarcts. The kidney may be of normal size or slightly oedematous. If there has been preceding hypertension or primary renal disease there may be associated changes including cortical atrophy and scarring.

The most important morphological changes affect the interlobular arteries and afferent arterioles occasionally extending into the glomerular tuft. The two characteristic features of malignant vascular injury are fibrinoid necrosis and endarteritis proliferans. In the former, seen primarily in the afferent arterioles, there is necrosis of the smooth muscle cells of the vascular media often involving the entire thickness of the vessel wall. The lesion can be either concentric or eccentric and is focal in distribution. The endothelium overlying the necrotic smooth muscle is often viable but shows cellular swelling; however, in many cases it is also necrotic. The necrotic medial smooth muscle is replaced by extensive fibrin. The fibrin appears as an intense uniform and slightly granular eosinophilia (Fig. 216.3A). Fibrin is visualized using a variety of special histological stains. Using Martius scarlet blue, the fibrin stains an intense scarlet colour with collagen and other extracellular matrix proteins stain blue (Fig. 216.3B). As an alternative, used by many pathologists, fibrin can be seen as deep red in a Masson's trichrome. Fibrinoid necrosis is most frequently seen in afferent arterioles but can involve interlobular arteries. Segmental glomerular lesions of tuft necrosis and fibrin deposition may be seen less commonly than the arteriolar lesions. Fibrinoid necrosis heals by fibrous replacement of the arterial wall, with a consequent loss of haemodynamic control. Affected blood vessels may be seen in late renal biopsies showing as focal irregular scarring of the wall.

The lesion of endarteritis proliferans is a concentric proliferation typically affecting the interlobular artery and leading to a narrowing of the arterial lumen and a so-called onion skin appearance (Fig. 216.4). It is best seen in those arteries which by chance have been cut in cross-section. Layers of plump spindle cells within a mucoid and oedematous stroma replace the intima and occlude the lumen. There is disruption of the vascular media. Fragmented red blood cells may be seen in the vessel wall. When vascular occlusion has occurred there is re-canalization giving rise to nodular plexiform lesions of endothelium and stromal spindle cells.

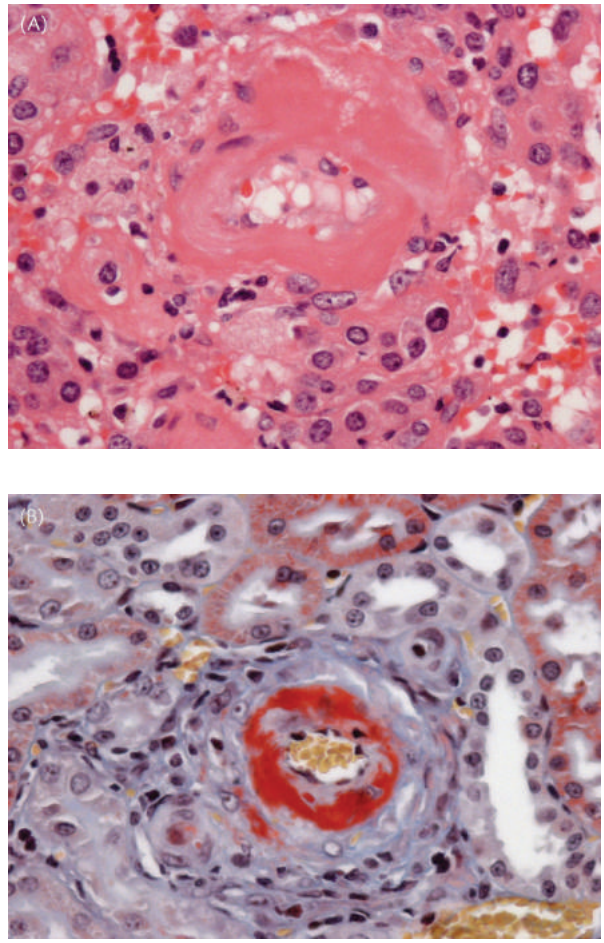


Fig. 216.3 In malignant hypertension, fibrinoid necrosis is seen as a granular eosinophilia replacing the medial smooth muscle in the wall of interlobular arteries (A). Confirmation of the presence of fibrin rests on the demonstration of an intense scarlet staining of the vessel wall in a Martius scarlet blue-stained section (B). Note that the overlying endothelium remains viable.

In the acute phase, glomeruli show collapse and shrinkage of the glomerular tuft secondary to reduced glomerular perfusion. There may be thickening of the glomerular capillary wall and this feature becomes more prominent with time since the onset of the malignant hypertension.

Tubules show acute injury with flattening of the epithelium, epithelial cell vacuolation, and the presence of cellular debris and red blood cells in the lumen. These changes are accompanied by interstitial oedema but no significant inflammatory infiltrate.

Immunofluorescence staining may reveal fibrin deposited within areas of fibrinoid necrosis. There may also be trapping of immunoglobulin (Ig)-M and C3 within these lesions. Immune complex components deposited in the glomeruli should raise the possibility of a preceding glomerular disease.

Electron microscopic examination shows the accumulation of flocculent material in the subendothelial space of the glomerular capillary wall. There may be fragmentation and duplication or thickening of the glomerular basement membrane.

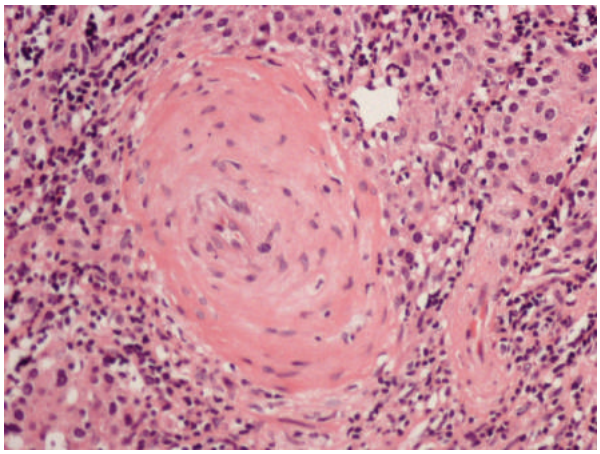


Fig. 216.4 There is a concentric fibromyxoid proliferation of the intima and media of interlobular arteries in endarteritis proliferans. The lumen shows extreme narrowing and red blood cells are leaking into the vessel wall.

A significant proportion of cases of MH are triggered by a primary renal disease. MH appears to be a particular feature of HIV-associated glomerulonephritis. It is also seen complicating hepatitis C-associated glomerular disease, idiopathic mesangiocapillary glomerulonephritis, lupus nephropathy, and membranous nephropathy. It is important to recognize the coexistence of the morphological changes of these various pathologies for accurate diagnosis and clinical management.

The morphological changes of malignant vascular injury occur indistinguishably in MH, scleroderma (see Chapter 165), haemolytic uraemic syndrome or thrombotic thrombocytopaenic purpura (see Chapter 174), and post-partum acute kidney injury (see Chapter 297). Several studies have attempted to identify pathological features which may be used to separate these conditions but none are convincing.

Fibrinoid necrosis and endarteritis proliferans resolve over time leading to irregular fibrosis of the arteriole wall and luminal narrowing. There is an associated loss of smooth muscle cells and elastic fibres from the vascular media. The end result of this process is marked fibrous narrowing of the interlobular arteries, increased peripheral resistance, and glomerular ischaemia. These vessels now lack the elasticity and smooth muscle to control vascular tone and blood flow thus limiting the autoregulatory potential of the renal microcirculation.

Although most interest has focused on the morphology of MH in the kidney, similar changes of malignant vascular injury may be seen in other tissues. There is fibrinoid necrosis and endarteritis proliferans affecting the small intramyocardial arterioles giving rise to microinfarction of the myocardium. Post-mortem examination of heart shows small areas of scarring scattered throughout the left ventricular wall in late cases. The brain shows some additional specific pathology. There is generalized cerebral oedema with necrosis of small arteries. Small intracerebral haemorrhages are common and are found most frequently in the pons and basal ganglia.

Treatment

The impact of a natriuretic phase causing a phase of relative sodium depletion and RAS activation is important in that it deserves attention and correction independent of measures to control blood pressure. Early case studies describe the impact of correcting sodium depletion with sodium loading which resulted in either a fall in blood pressure or a better response to antihypertensive agents (Kincaid-Smith, 1973; Orth and Ritz, 1975). Treatment strategies which avoid promoting sodium depletion (avoiding diuretic therapy) are theoretically attractive but need to be balanced by clinical review as salt and water retention is a common secondary consequence from deteriorating renal function.

There is consensus that in the absence of critical target organ damage such as arterial dissection or hypertensive encephalopathy a gradual reduction in blood pressure over 24–48 hours or even several days is sufficient (Varon and Marik, 2003). Too rapid a reduction in blood pressure increases the risk of myocardial or cerebral hypoperfusion and watershed infarcts. Impaired cerebral vascular autoregulation will increase the risk of this. For this reason, some authors (Webster et al., 1993) have advocated avoiding parenteral antihypertensive therapy or RAS blockade during the initial treatment of MH, but a recent consensus report suggests options for parenteral therapy in a monitored high-dependency setting.

In a hypertensive emergency where there is evidence of target organ damage, reduction of mean arterial pressure by no more than 25% should occur within minutes to 1 hour and thereafter further reduction on blood pressure to 160/100–110 mmHg should be aimed for within the next 2–6 hours (Chobanian et al., 2004). In the absence of trial data, numerous agents have been tried. Beta antagonists, labetalol, calcium channel antagonists, thiazide diuretics, and vasodilators (hydralazine, sodium nitroprusside) are commonly used. Others have supported cautious use of short-acting ACE inhibition early in the treatment regimen (Saragoca et al., 1983; Guerin and Berthoux, 1990; Watanabe et al., 1998). It is perhaps curious that the clinical practice for management of MH has largely diverged from that of scleroderma renal crisis where escalating blockade of the RAS is more strongly supported (Penn et al., 2007).

Our recommendation for treating MH would be to correct volume depletion if present, initiate parenteral therapy with close monitoring, using IV labetalol or other suitable alternative based on the patient's clinical status, and aim to reduce mean arterial pressure by up to 25% in the first 2 hours. Thereafter we would recommend cautious introduction of low dose RAS blockade and titrate with other agents—parenteral or oral to achieve ongoing gradual reduction in blood pressure over a further 24–48 hours.

Outcomes

Early studies reported a very poor outcome of patients with untreated MH, with up to 80% dead within 2 years (Keith et al., 1939; Kincaid-Smith et al., 1958). Five-year survival rates have improved for treated MH from 20–40% in the 1950–1970 era (Bulpitt, 1982), to 72% in the period from 1976 to 1987 (Guerin and Berthoux, 1990), and to 91% for patients diagnosed between 1997 and 2006 (Lane et al., 2009). Access to effective antihypertensive therapy or renal replacement therapy is clearly important and contributes to era effects, but also to poorer outcomes in developing countries or in patients with more limited access to such support due to lack of insurance. In more recent times, the largest cohort of MH patients followed up come from the West Birmingham Malignant Hypertension Study (Lip et al., 1995; Shantsila et al., 2012) where data suggested that the poorest outcomes were in black patients. The main causes of death are listed in Table 216.2.

Table 216.2 Data demonstrating overall mortality, cause of death, and proportion of patients with malignant hypertension requiring renal replacement therapy

	1995 study	2012 study
	Follow-up median 2.75 years	Follow-up median 7 years
Proportion dead by end of follow-up period	40%	56%
Proportion on dialysis	3.2%	22%
Cause of death		
Chronic kidney disease	38%	33%
Cardiovascular disorders	21.4%	21%
Cerebrovascular disease	23.8%	19%
Other causes	4%	5%
Cause of death unknown	11.1%	22%

1995 study data from Lip et al. (1995).

2012 study data from Lane et al. (2009) and Shantsila et al. (2012).

There is evidence of persisting vascular dysfunction in treated malignant hypertension; circulating endothelial cells and endothelial progenitor cells are markers of endothelial damage and are increased compared to healthy normotensive controls and treated hypertensives (Boos et al., 2007; Shantsila et al., 2011). Increased stiffness of vascular walls and cardiac ventricular walls occur as a consequence of smooth muscle cell and cardiomyocyte hyperplasia, hypertrophy, and increased collagen deposition. Reduced myocardial perfusion is seen. The severity appears to be comparable between previously treated MH patients and treated hypertensives (Shantsila et al., 2011, 2012).

Published case series report that approximately 50% of patients presenting with MH on a background of presumed essential hypertension will see a progressive deterioration in renal function despite treatment. Patients with progressive renal impairment tend to have reduced median survival. Better blood pressure control is a factor in preventing decline in renal function (Lip et al., 1997; Amraoui et al., 2012). There are many reported cases of patients requiring dialysis, but recovering sufficient renal function to become independent of renal replacement therapy (Yaqoob et al., 1991). Both the probability of survival and of not requiring renal replacement therapy appear to be improved if there is neurological involvement on admission (Guerin and Berthoux, 1990).

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CHAPTER 217

Resistant hypertension

Iain M. MacIntyre and David J. Webb

Introduction and epidemiology

Treatment-resistant hypertension (TRH) is defined as the failure to achieve a blood pressure target of < 140/90 mmHg (< 130/80 mmHg in patients with chronic kidney disease or diabetes mellitus) in patients with hypertension, despite adherence to a treatment regimen of at least three antihypertensive medications at optimal tolerated doses and which ideally should include a diuretic (Calhoun et al., 2008). The term can be used to identify patients with difficult-to-treat hypertension, who might benefit from specialist investigation and/or treatment.

The exact prevalence of TRH is unknown. However, estimates can be derived from retrospective, cross-sectional population studies. A large Spanish study of 68,000 patients found the prevalence of TRH was 12% based on office blood-pressure analysis, though this fell to 8% following ambulatory monitoring (de la Sierra et al., 2011). Similarly, post hoc analysis of the National Health and Nutrition Examination Survey (NHANES) dataset suggests that up to 13% of all US adults being treated for hypertension could be classified as having TRH (Persell, 2011). Risk factors for TRH include obesity, older age, chronic kidney disease, and diabetes (Box 217.1).

The long-term prognosis of individuals with TRH has not been adequately determined. However, indirect evidence suggests that prolonged, poorly controlled blood pressure has a poor outcome. A recent retrospective cohort study suggested that patients with TRH were almost 50% more likely to have an adverse cardiovascular event over a 3.5-year period than patients with controlled hypertension (Daugherty et al., 2012).

Investigation

Before a diagnosis of TRH can be made, pseudo-resistant hypertension must be excluded. This is the apparent failure to control blood pressure in a patient receiving treatment who does not actually have TRH. Commonly, pseudo-resistance arises due to (a) non-adherence to treatment, (b) suboptimal antihypertensive regimen and/or clinical 'inertia', (c) poor blood pressure monitoring technique, or (d) the 'white coat' effect.

Poor adherence to treatment is an important cause of pseudo-resistance. Up to 40% of newly diagnosed hypertensive patients will discontinue their medications during the first year, with rather less being compliant over a 10-year period (Mazzaglia et al., 2005; Van Wijk et al., 2005). Poor adherence may have a number of causes, including side effects, complicated dosing schedules, pill burden, poor doctor–patient relationship, poor understanding or acceptance of the need for treatment, and medication cost. The clinician should make every effort to engage with the patient and keep their medication regimen as simple as possible. Clinical 'inertia', defined as an office visit at which no therapeutic move was made to lower the blood pressure of a patient with uncontrolled hypertension, is very common, occurring in up to 80% of clinic visits (O'Connor, 2003). The clinician should always ensure the patient is receiving an optimal antihypertensive regimen with appropriate follow-up and titration of medications. For patients in whom non-adherence to medication is thought to be an issue, 'directly observed therapy' clinics may be of benefit. Patients are asked to consume their medications under observation in the clinic and then blood pressure monitoring is performed over the subsequent 6–24 hours. A significant response to the medication would obviously call compliance into question.

Improper office blood-pressure measurement technique is another common cause for pseudo-resistant hypertension. Frequent mistakes include failure to allow the patient to sit quietly for a minimum of 5 minutes prior to blood pressure recordings, use of a single blood-pressure measurement, and the use of a cuff that is too small for the arm. 'White-coat' hypertension refers to the condition in which blood pressure is elevated in the office following repeated visits but normal in the community using either ambulatory or home blood-pressure monitoring. It should be suspected particularly in those patients seen in clinic who have no evidence of end-organ damage despite repeated office recordings of significant hypertension. All patients should have ambulatory or home blood-pressure monitoring before a diagnosis of TRH is made. Furthermore, particularly in those > 70 years of age, the presence of significantly calcified brachial and radial arteries can result in substantial overestimation of intra-arterial blood pressure, so-called pseudo-hypertension, and should be considered in patients who report symptoms of postural hypotension despite ongoing high office blood-pressure readings (Kleman et al., 2013).

In those diagnosed with true TRH the next step is for the clinician to consider possible modifiable causes (Box 217.2). Secondary causes of hypertension are more common in patients with TRH, accounting for at least 5–10% of cases (Yakovlevitch and Black, 1991; Garg et al., 2005) and should be excluded. Primary hyperaldosteronism is now recognized as one of the most common causes of TRH, being found in approximately 10% of patients (Douma et al., 2008), so testing for primary hyperaldosteronism should be considered. Other common causes include obstructive sleep apnoea, renal artery stenosis, and parenchymal renal disease. In most cases, however, the aetiology of truly TRH is multifactorial and treatment will be aimed at multiple targets.

Treatment

Treatment of patients with TRH includes appropriate lifestyle change, withdrawal or minimization of offending drugs

Box 217.1 Patient characteristics associated with resistant hypertension

- Older age: especially > 75 years
- High baseline blood pressure
- Obesity
- Atherosclerotic vascular disease
- Diabetes mellitus
- Chronic kidney disease
- Excessive dietary sodium intake
- Ethnicity (black).

(see Box 217.2), and the use of effective multidrug and device therapy. Patients who are overweight or obese should lose weight, all patients should undertake regular exercise, and alcohol should be taken only in moderation. Particular importance should be placed on salt reduction, aiming for an intake of < 100 mEq of sodium/day (< 6 g sodium chloride/day) (Agarwal, 2012).

Drug therapy

Patients defined as having TRH will already be receiving, or will not have tolerated, three different antihypertensive agents. Ideally, this combination (known as 'ACD') should contain an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) ('A'), a calcium channel blocker ('C'), and a thiazide-like diuretic ('D').

Salt and associated water retention appears to play a significant role in the development of TRH. Optimizing diuretic therapy by increasing the dose, or switching to a long-acting thiazide-like diuretic such as chlortalidone or indapamide, may be of benefit. Loop diuretics should be considered in patients with renal impairment.

The use of low-dose spironolactone (25 mg once daily increased to 50 mg once daily) or eplerenone is now suggested as a suitable fourth-line agent in patients with TRH (NICE, 2011; Mancia et al., 2013). The success of these medications may be accounted for by the elevated aldosterone levels frequently found in these patients, either through undetected primary hyperaldosteronism or because aldosterone secretion escapes the early reduction associated with renin–angiotensin system blockade.

Other drugs, such as β-blockers, α-blockers, centrally acting agents such as moxonidine, or potent vasodilators, including hydralazine or minoxidil, may be considered in the multiple drug approach, depending on the clinical circumstances. The only combination of drugs that cannot be recommended on the basis of trial results is the addition of a second agent to block the renin–angiotensin system, with evidence of increased renal failure with the combination of ACEI + ARB or ARB + renin inhibitor (Mann et al., 2008; Parving et al., 2012).

Interventional approaches

There has been recent interest in non-pharmacological therapies to treat TRH, particularly renal sympathetic denervation and baroreflex activation therapy.

Box 217.2 Modifiable factors contributing to resistant hypertension

Secondary cause of hypertension

- Primary hyperaldosteronism
- Renal parenchymal disease
- Obstructive sleep apnoea
- Renal artery stenosis
- Cushing syndrome
- Thyroid disease
- Coarctation of the aorta
- Phaeochromocytoma.

Volume overload

- High sodium intake
- Inadequate diuretic therapy
- Progressive renal insufficiency.

Drug-induced hypertension

- Non-steroidal anti-inflammatory drugs
- Corticosteroids
- Contraceptive hormones
- Ciclosporin and tacrolimus
- Erythropoietin
- Sympathomimetic agents
- Liquorice
- Herbal compounds (ephedra, bitter orange)
- Illicit drugs—cocaine, amphetamines, etc.

Lifestyle factors

- Excessive alcohol intake
- Obesity.

Renal denervation

Efferent sympathetic nervous outflow to the kidney stimulates renin release, increases tubular sodium reabsorption, and reduces renal blood flow. Furthermore, afferent sympathetic signals from the kidney contribute to neurogenic elevation of blood pressure. In the first half of the twentieth century, surgical total thoracic sympathectomy was a treatment for severe hypertension, and was highly effective in lowering blood pressure. However, the procedure was invasive and carried significant morbidity, including orthostatic hypotension, sphincter incontinence, and sexual dysfunction. By the 1960s it was abandoned as antihypertensive pharmacotherapy advanced rapidly.

In 2009, a non-randomized, proof of concept study (SYMPLICITY HNT-1) showed that local renal sympathetic denervation using catheter-based radiofrequency spiral ablation to the wall of each renal artery was feasible (Krum et al., 2009). Forty-five patients with a diagnosis of TRH were enrolled, with primary

end-points being office blood-pressure and safety outcomes at 12 months. Blood pressure fell significantly from a mean blood pressure of 177/101 mmHg to 150/84 mmHg at 12 months. Only two complications occurred: a renal artery dissection occurring pre-ablation and treated successfully with stent insertion and the development of a femoral pseudoaneurysm treated non-surgically. A randomized study (SYMPLICITY HTN-2) followed on from this, randomizing 106 patients with TRH to radiofrequency ablation (N = 52) or non-sham control (N = 54) (Symplicity HTN-2 Investigators et al., 2010). At 6 months there was a mean difference of 33/11 mmHg in office blood pressure between control and treatment group. No significant safety concerns were reported. These studies were encouraging. However, they were limited by small study size and the lack of a placebo control. Moreover, the long-term effects on renal artery structure remain unknown. The SYMPLICITY HTN-3 study (Bhatt et al., 2014) aimed to answer some of these key questions. It was a prospective, single-blind, randomized, sham-controlled study in patients with THR. A total of 535 patients underwent randomization with 364 undergoing renal denervation and 171 undergoing a sham procedure. Importantly, this study used change in 24-hour ambulatory blood pressure as its primary endpoint, thus reducing the effect of white coat hypertension on the results. Disappointingly, at the end of the study there was no significant difference in blood pressure reduction between the groups. These results confirm the crucial importance of blinded placebo-controlled studies in hypertension, as well as the use of ambulatory blood pressure monitoring. They also indicate that renal denervation should only be used in the clinical trial setting, if at all.

Baroreflex activation therapy

The concept behind baroreflex activation therapy is that electrical stimulation of the afferent nerves of the carotid sinus is interpreted by the brain as a rise in blood pressure. This leads to a reduction in sympathetic outflow to counteract the perceived blood pressure increase. Electrical stimulation of the carotid sinus baroreceptor via electrodes implanted in the perivascular space around the carotid sinus has been shown to lower blood pressure with reductions in blood pressure averaging 21/12 mmHg. However, with up to 25% of patients suffering a procedural adverse event, the safety of this procedure remains unclear (Scheffers et al., 2010; Bisognano et al., 2011).

Future directions

Studies examining the best treatment options for patients with TRH are ongoing. The British Hypertension Society PATHWAY study is currently in the process of recruiting patient with TRH, and examining which antihypertensive agent should be used as fourth-line therapy in this patient group and whether blood renin concentration may predict the best treatment.

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CHAPTER 218

The hypertensive child

Wolfgang Rascher

Measuring blood pressure in children

Reliable measurement of blood pressure in infants and children requires procedures different from those used in adults. Detection of the pulse by auscultation, as in conventional sphygmomanometry, is often difficult in infants and children < 3 years of age. This may be because the blood vessels do not transmit sufficient energy for the Korotkoff sounds to be audible with an ordinary stethoscope: the mistake of applying excessive pressure with the stethoscope on the cubital artery is common.

The width of the cuff bladder is crucial to achieving correct readings of blood pressure. If very small cuffs are used, inappropriately high pressures are often recorded; with very large cuffs the recorded pressures are relatively low. The largest cuff that can be comfortably applied should be used, and its inflatable part (the bladder) should cover at least two-thirds of the circumference of the upper arm (Table 218.1).

The appearance of the first Korotkoff sound should be used as a criterion for measurement of the systolic blood pressure and phase 5 should be used to indicate diastolic blood pressure (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004; Lurbe et al., 2009). If the value of phase 5 is close to 0, the measurement should be repeated: if the second measurement gives a similar value, phase 4 should be used.

Measurement of arterial blood pressure with Doppler ultrasound or oscillometric devices is particularly valuable for the detection of arterial hypertension in neonates and small infants. Doppler ultrasound devices only measure systolic pressure reliably. Recently, Doppler blood pressure has been tested in ambulatory settings and recommended for home monitoring of infants and children (Clothier et al., 2012). Oscillometry measures mean arterial blood pressure from the point of maximum oscillation and both systolic and diastolic pressure are calculated from the relationship between the oscillations. The method is convenient, becomes more and more popular and is independent of the observer. However, there are important limitations that have to be considered.

For a particular device (Dinamap Model 8100, Critikon, Tampa, FL, USA) blood pressure recordings were reported to be 10 mmHg on average higher as obtained by auscultation (Park et al., 2001). Using the SpaceLabs 90217 oscillometric device (SpaceLabs Healthcare, Issaquah, Washington, USA) average systolic blood pressure was 8.7 mmHg and average diastolic blood pressure 5.7 mmHg higher in a cohort of 235 children and adolescents with chronic kidney disease (age 1–16 years) compared with auscultation (Flynn et al., 2012). With other devices (Datascope Accutor Plus (Datascope Corp., Fairfield, NJ, USA)), a good correlation between the two methods has been shown (Kulaga et al., 2012).

Independent of the accuracy of blood pressure devices a single casual blood pressure is poorly reproducible also with auscultation, particularly in children and irrespective of the method of blood pressure measurement, multiple blood pressure readings are important to estimate the average blood pressure level of the child. In this context, oscillometry is more convenient than auscultation. These methods are not interchangeable and require device-specific reference values.

Technological advances have enabled non-invasive, repetitive measurement of blood pressure over 24 hours in individuals performing their normal activities. This technique is useful for the evaluation of arterial hypertension (Sorof and Portman, 2001; Lurbe and Redon, 2002). In the paediatric age group, oscillometric ambulatory blood pressure monitors are being used almost exclusively. Ambulatory monitoring is able to identify a considerable proportion of the children who have high blood pressure in the clinic but a normal mean ambulatory blood pressure elsewhere ('white-coat hypertension') (Sorof and Portman, 2000). White-coat hypertension is obviously a pre-hypertensvie state, since signs of end-organ damage can be found (Stabouli et al., 2005; Kavey et al., 2007). Ambulatory blood pressure measurement also detects children and adolescents with masked hypertension, having normal blood pressure readings in the office and average high value elsewhere (Matsuoka and Awazu, 2004; Stabouli et al., 2005).

Systolic and diastolic blood pressures follow a typical circadian rhythm, values being 15–25% lower at night than during the day. Therefore, mean blood pressure should be calculated separately for the day and the night. Ambulatory blood pressure monitoring has the advantage when evaluating nocturnal blood pressure, which is particularly increased in renal hypertensive patients (Sorof and Portman, 2001; Acosta and McNiece, 2008). It appears to be the best method to monitor children with renal diseases for hypertension and has been recommended to monitor the risk and to guide the treatment of hypertension in children with chronic kidney disease (Samuels et al., 2012).

Blood pressure standards

A marked increase in average blood pressure with age in childhood and adolescence is one aspect of normal growth and development. Combined data from several studies as references for random (casual) blood pressure have been published from studies in the United States (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004). These tables for blood pressure in children were published taken into account both age and height percentiles (Table 218.2). However, these tables are rather difficult to use in

Table 218.1 Recommended sizes of blood pressure cuff bladders

Age	Width and length size
Newborn	4 × 8 cm
Infant	6 × 12 cm
Child	9 × 18 cm
Small adult	10 × 24 cm
Adult	13 × 30 cm
Large adult	16 × 42 cm

According to National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004) and Lurbe et al. (2009).

daily practice, but have been included in the European guidelines (Lurbe et al., 2009). For practical reasons, the figures presented by the International Pediatric Nephrology Association (IPNA), having been adapted from these tables, can be used (Table 218.3) and Fig. 218.1.

Normative oscillometrically derived blood pressures have been reported in very low-birth-weight infants (Tan, 1988), during the first 5 years of life (Park and Menard, 1989) in small cohorts and compared to centiles obtained by auscultation in children (Park et al., 2005). Recently normative oscillometric blood pressure centiles were obtained in large cohorts of healthy children and adolescents (Jackson et al., 2007; Munkhaugen et al., 2008; Túri et al., 2008; Neuhauser et al., 2011; Kulaga et al., 2012). The differences in the blood pressure centiles may be caused at least in part by the inclusion or exclusion of overweight and obese children. The centiles from Germany and Poland were obtained from the largest cohorts, but German centile started with an age of 3 and the values from Poland with school age (Neuhauser et al., 2011; Kulaga et al., 2012). German oscillometric blood pressure reference values and Polish auscultatory reference values were calculated as the mean of the first and second measurement. The Polish OLAF study discarded the first reading and the mean of the second and third was used. This might explain the small differences in the blood pressure centiles. For practical reasons the tables from Germany (German Health Interview and Examination Survey for Children and Adolescents (KiGGS) study) should be used, since they have been obtained from a large and nationally representative sample, cover a wide age range, and have eliminated adipose and obese participants (Table 218.4).

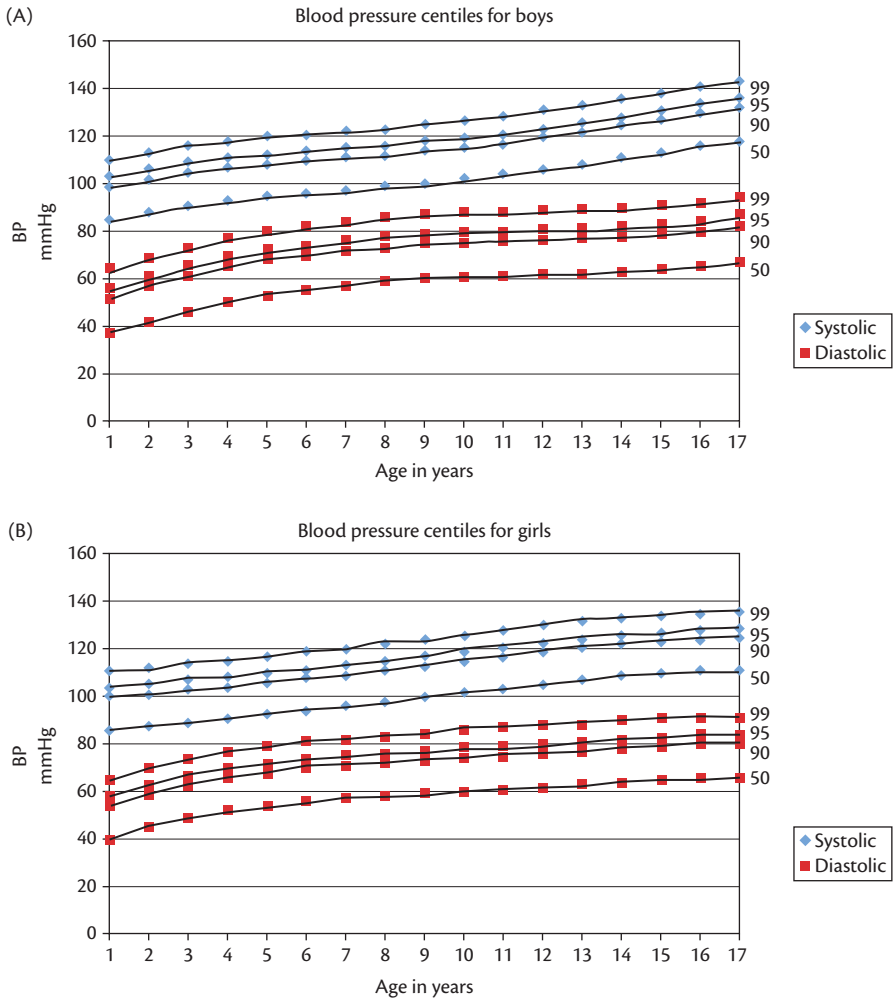

Fig. 218.1 Simplified graph of normal blood pressure ranges in children, from US data (<http://www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm>). Note that taller children have higher average blood pressures. Centile values shown are for 50th height centile: average BPs vary by ± 3–5 mmHg for 5th–95th height centiles (so range typically varies 6–10 mmHg for height at any age) (See Tables 218.2, 218.3).

Table 218.2A Blood pressure references (casual blood pressure by auscultation) for boys by age and height percentiles

		Systolic (mmHg) percentile of height							Diastolic (mmHg) percentile of height						
Age (years)	**BP percentile**	**5th**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**	**5th**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**
1	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91

Table 218.2A Continued

		Systolic (mmHg) percentile of height							Diastolic (mmHg) percentile of height						
Age (years)	**BP percentile**	**5th**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**	**5th**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**
14	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP = blood pressure.

Modified from Task Force on High Blood Pressure in Children and Adolescents (from Lurbe et al., 2009).

Table 218.2B Blood pressure references (casual blood pressure by auscultation) for girls by age and height percentiles

		Systolic (mmHg) percentile of height							Diastolic (mmHg) percentile of height						
Age (years)	**BP percentile**	**5th**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**	**5th**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**
1	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77

(*continued*)

Table 218.2B Continued

		Systolic (mmHg) percentile of height							Diastolic (mmHg) percentile of height						
Age (years)	**BP percentile**	**5th**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**	**5th**	**10th**	**25th**	**50th**	**75th**	**90th**	**95th**
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP = blood pressure.

Modified from Task Force on High Blood Pressure in Children and Adolescents (from Lurbe et al., 2009).

Reference values for ambulatory blood pressure monitoring of children and adolescents have been reported in a cohort of 1141 children and adolescents (Soergel et al., 1997). Using a modern statistical approach the data were recalculated and yielded more reference values (Wühl et al., 2002) (Table 218.5).

Home blood pressure measurement has a considerable potential to monitor blood pressure levels of children and adolescents with hypertension (Stergiou et al., 2009) and reference values from a cohort of 767 are available (Stergiou et al., 2007) (Table 218.6).

Definition and classification of hypertension in children

Criteria for the diagnosis of hypertension in adults are not applicable to children. A value of 140/90 mmHg for random (casual) blood pressure and 135/85 mmHg for daytime ambulatory blood pressure has been generally accepted as the upper limit of normal in adults, and this might also be true for adolescents. However, recommendations based on epidemiological and clinical studies define normal

Table 218.3A Blood pressure levels in boys by age and height

Age (years)	BP percentile		Systolic BP (mmHg)							Diastolic BP (mmHg)						
			5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
2	Height (cm)		81.1	82.4	84.5	86.9	89.2	91.4	92.6	81.1	82.4	84.5	86.9	89.2	94.4	92.6
	Normal	50th Pc.	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	High-normal	90th Pc.	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	Stage 1 HT	95th Pc.	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	Stage 2 HT	99th Pc. +5 mmHg	114	115	116	118	120	122	122	71	72	73	74	75	76	76
3	Height (cm)		89.2	90.5	92.7	95.3	97.9	100.4	101.9	89.2	90.5	92.7	95.3	97.9	100.4	101,9
	Normal	50th Pc.	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	High-normal	90th Pc.	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	Stage 1 HT	95th Pc.	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	Stage 2 HT	99th Pc. +5 mmHg	116	117	119	121	123	124	125	76	76	77	78	79	80	80
4	Height (cm)		96.5	97.1	99.7	102.5	105.4	108.0	109.5	96.5	97.1	99.7	102.5	105.4	108.0	109.5
	Normal	50th Pc.	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	High-normal	90th Pc.	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	Stage 1 HT	95th Pc.	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	Stage 2 HT	99th Pc. +5 mmHg	118	119	121	123	125	126	127	79	80	81	82	83	83	84
5	Height (cm)		101.5	103.2	106.0	109.2	112.3	115.1	116.8	101.5	103.2	106.0	109.2	112.3	115.1	116.8
	Normal	50th Pc.	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	High-normal	90th Pc.	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	Stage 1 HT	95th Pc.	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	Stage 2 HT	99th Pc. +5 mmHg	120	121	123	125	126	128	128	82	83	84	85	86	86	87
6	Height (cm)		107.3	109.2	112.2	115.7	119.1	122.1	123.9	107.3	109.2	112.2	115.7	119.1	122.1	123.9
	Normal	50th Pc.	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	High-normal	90th Pc.	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	Stage 1 HT	95th Pc.	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	Stage 2 HT	99th Pc. +5 mmHg	121	122	124	126	128	129	130	85	85	86	87	88	89	89
7	Height (cm)		113.2	115.1	118.4	122.0	125.7	129.0	131.0	113.2	115.1	118.4	122.0	125.7	129.0	131.0
	Normal	50th Pc.	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	High-normal	90th Pc.	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	Stage 1 HT	95th Pc.	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	Stage 2 HT	99th Pc. +5 mmHg	122	123	125	127	129	130	131	87	87	88	89	90	91	91
8	Height (cm)		118.8	120.8	124.3	128.1	132.1	135.7	137.8	118.8	120.8	124.3	128.1	132.1	135.7	137.8
	Normal	50th Pc.	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	High-normal	90th Pc.	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	Stage 1 HT	95th Pc.	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	Stage 2 HT	99th Pc. +5 mmHg	124	125	127	128	130	132	132	88	89	90	91	92	92	93

(*continued*)

Table 218.3A Continued

Age (years)	BP percentile		Systolic BP (mmHg)							Diastolic BP (mmHg)						
			5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
9	Height (cm)		123.8	126.0	129.6	133.7	137.9	141.8	144.1	123.8	126.0	129.6	133.7	137.9	141.8	144.1
	Normal	50th Pc.	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	High-normal	90th Pc.	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	Stage 1 HT	95th Pc.	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	Stage 2 HT	99th Pc. +5 mmHg	125	126	128	130	132	133	134	89	90	91	92	93	93	94
10	Height (cm)		128.2	130.5	134.4	138.8	143.3	147.4	149.0	128.2	130.5	134.4	138.8	143.3	147.4	149.0
	Normal	50th Pc.	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	High-normal	90th Pc.	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	Stage 1 HT	95th Pc.	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	Stage 2 HT	99th Pc. +5 mmHg	127	128	130	132	133	135	135	90	91	91	93	93	94	95
11	Height (cm)		132.4	134.9	139.0	143.7	148.5	152.9	155.6	132.4	134.9	139.0	143.7	148.5	152.9	155.6
	Normal	50th Pc.	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	High-normal	90th Pc.	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	Stage 1 HT	95th Pc.	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	Stage 2 HT	99th Pc. +5 mmHg	129	130	132	134	135	137	137	91	91	92	93	94	95	95
12	Height (cm)		137.3	139.9	144.3	149.3	154.4	159.0	161.9	137.3	139.9	144.3	149.3	154.4	159.0	161.9
	Normal	50th Pc.	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	High-normal	90th Pc.	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	Stage 1 HT	95th Pc.	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	Stage 2 HT	99th Pc. +5 mmHg	131	132	134	136	138	139	140	91	92	93	94	95	95	96
13	Height (cm)		143.6	146.4	151.1	156.4	161.7	166.6	169.5	143.6	146.4	151.1	156.4	161.7	166.6	169.5
	Normal	50th Pc.	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	High-normal	90th Pc.	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	Stage 1 HT	95th Pc.	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	Stage 2 HT	99th Pc. +5 mmHg	133	135	136	138	140	141	142	92	92	93	94	95	96	96
14	Height (cm)		150.5	153.6	158.7	164.1	169.5	174.2	177.0	150.5	153.6	158.7	164.1	169.5	174.2	177.0
	Normal	50th Pc.	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	High-normal	90th Pc.	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	Stage 1 HT	95th Pc.	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	Stage 2 HT	99th Pc. +5 mmHg	136	137	139	141	143	144	145	92	93	94	95	96	97	97
15	Height (cm)		156.7	159.8	164.8	170.1	175.3	179.8	182.4	156.7	159.8	164.8	170.1	175.3	179.8	182.4
	Normal	50th Pc.	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	High-normal	90th Pc.	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	Stage 1 HT	95th Pc.	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	Stage 2 HT	99th Pc. +5 mmHg	139	140	141	143	145	147	147	93	94	95	96	97	98	98

(*continued*)

Table 218.3A Continued

Age (years)	BP percentile		Systolic BP (mmHg)							Diastolic BP (mmHg)						
			5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
16	Height (cm)		160.8	163.7	168.5	173.6	178.6	182.9	185.5	160.8	163.7	168.5	173.6	178.6	182.9	185.5
	Normal	50th Pc.	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	High-normal	90th Pc.	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	Stage 1 HT	95th Pc.	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	Stage 2 HT	99th Pc. +5 mmHg	141	142	144	146	148	149	150	95	95	96	97	98	99	99
17	Height (cm)		163.1	165.8	170.4	175.3	180.2	184.5	187.0	163.1	165.8	170.4	175.3	180.2	184.5	187.0
	Normal	50th Pc.	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	High-normal	90th Pc.	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	Stage 1 HT	95th Pc.	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	Stage 2 HT	99th Pc. +5 mmHg	144	145	146	148	150	151	152	97	98	98	99	100	101	102

HT = hypertension; Pc. = percentile.

From the International Pediatric Nephrology Association (IPNA) 2011. updated January 2012 (<http://www.pediatrichypertension.org>).

Table 218.3B Blood pressure levels in girls by age and height

Age (years)	BP percentile		Systolic BP (mmHg)							Diastolic BP (mmHg)						
			5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
2	Height (cm)		79.6	80.9	83.0	85.4	87.7	89.9	91.1	79.6	80.9	83.0	85.4	87.7	89.9	91.1
	Normal	50th Pc.	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	High-normal	90th Pc.	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	Stage 1 HT	95th Pc.	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	Stage 2 HT	99th Pc. +5 mmHg	114	115	116	117	119	120	121	74	74	75	75	76	77	77
3	Height (cm)		87.8	89.2	91.6	94.2	96.9	99.3	100.8	87.8	89.2	91.6	94.2	96.9	99.3	100.8
	Normal	50th Pc.	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	High-normal	90th Pc.	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	Stage 1 HT	95th Pc.	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	Stage 2 HT	99th Pc. +5 mmHg	116	116	118	119	120	121	122	78	78	79	79	80	81	81
4	Height (cm)		94.0	95.6	98.1	101.0	104.0	106.8	108.4	94.0	95.6	98.1	101.0	104.0	106.8	108.4
	Normal	50th Pc.	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	High-normal	90th Pc.	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	Stage 1 HT	95th Pc.	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	Stage 2 HT	99th Pc. +5 mmHg	117	118	119	120	122	123	124	81	81	81	82	83	84	84
5	Height (cm)		100.4	102.0	104.8	108.0	111.2	114.3	116.1	100.4	102.0	104.8	108.0	111.2	114.3	116.1
	Normal	50th Pc.	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	High-normal	90th Pc.	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	Stage 1 HT	95th Pc.	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	Stage 2 HT	99th Pc. +5 mmHg	119	119	121	122	123	125	125	83	83	84	84	85	86	86

(*continued*)

Table 218.3B Continued

Age (years)	BP percentile		Systolic BP (mmHg)							Diastolic BP (mmHg)						
			5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
6	Height (cm)		106.9	108.6	111.6	115.0	118.6	121.9	123.9	106.9	108.6	111.6	115.0	118.6	121.9	123.9
	Normal	50th Pc.	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	High-normal	90th Pc.	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	Stage 1 HT	95th Pc.	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	Stage 2 HT	99th Pc. +5 mmHg	120	121	122	124	125	126	127	85	85	85	86	87	88	88
7	Height (cm)		113.1	114.9	118.1	121.8	125.6	129.1	131.3	113.1	114.9	118.1	121.8	125.6	129.1	131.3
	Normal	50th Pc.	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	High-normal	90th Pc.	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	Stage 1 HT	95th Pc.	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	Stage 2 HT	99th Pc. +5 mmHg	122	123	124	125	127	128	129	86	86	87	87	88	89	89
8	Height (cm)		118.5	120.5	123.9	127.8	131.9	135.6	137.9	118.5	120.5	123.9	127.8	131.9	135.6	137.9
	Normal	50th Pc.	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	High-normal	90th Pc.	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	Stage 1 HT	95th Pc.	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	Stage 2 HT	99th Pc. +5 mmHg	124	125	126	127	128	130	130	87	87	88	88	89	90	91
9	Height (cm)		123.2	125.3	129.0	133.1	137.4	141.4	143.8	123.2	125.3	129.0	133.1	137.4	141.4	143.8
	Normal	50th Pc.	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	High-normal	90th Pc.	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	Stage 1 HT	95th Pc.	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	Stage 2 HT	99th Pc. +5 mmHg	126	126	128	129	130	132	132	88	88	89	89	90	91	92
10	Height (cm)		127.5	129.8	133.7	138.2	142.8	147.0	149.6	127.5	129.8	133.7	138.2	142.8	147.0	149.6
	Normal	50th Pc.	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	High-normal	90th Pc.	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	Stage 1 HT	95th Pc.	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	Stage 2 HT	99th Pc. +5 mmHg	128	128	130	131	132	134	134	89	89	90	91	91	92	93
11	Height (cm)		132.4	135.0	139.4	144.3	149.2	153.7	156.4	132.4	135.0	139.4	144.3	149.2	153.7	156.4
	Normal	50th Pc.	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	High-normal	90th Pc.	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	Stage 1 HT	95th Pc.	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	Stage 2 HT	99th Pc. +5 mmHg	130	130	131	133	134	135	136	90	90	91	92	92	93	94
12	Height (cm)		139.2	142.0	146.5	151.5	156.4	160.8	163.5	139.2	142.0	146.5	151.5	156.4	160.8	163.5
	Normal	50th Pc.	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	High-normal	90th Pc.	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	Stage 1 HT	95th Pc.	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	Stage 2 HT	99th Pc. +5 mmHg	132	132	133	135	136	137	138	91	91	92	93	93	94	95
13	Height (cm)		145.9	148.4	152.7	157.3	162.0	166.1	168.6	145.9	148.4	152.7	157.3	162.0	166.1	168.6
	Normal	50th Pc.	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	High-normal	90th Pc.	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	Stage 1 HT	95th Pc.	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	Stage 2 HT	99th Pc. +5 mmHg	133	134	135	137	138	139	140	92	92	93	94	94	95	96

(*continued*)

Table 218.3B Continued

Age (years)	BP percentile		Systolic BP (mmHg)							Diastolic BP (mmHg)						
			5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
14	Height (cm)		149.7	152.1	156.0	160.5	164.9	168.9	171.3	149.7	152.1	156.0	160.5	164.9	168.9	171.3
	Normal	50th Pc.	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	High-normal	90th Pc.	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	Stage 1 HT	95th Pc.	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	Stage 2 HT	99th Pc. +5 mmHg	135	136	137	138	140	141	141	93	93	94	95	95	96	97
15	Height (cm)		151.3	153.6	157.5	161.9	166.3	170.2	172.6	151.3	153.6	157.5	161.9	166.3	170.2	172.6
	Normal	50th Pc.	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	High-normal	90th Pc.	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	Stage 1 HT	95th Pc.	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	Stage 2 HT	99th Pc. +5 mmHg	136	137	138	139	141	142	143	94	94	95	96	96	97	98
16	Height (cm)		151.9	154.3	158.2	162.6	166.9	170.9	173.2	151.9	154.3	158.2	162.6	166.9	170.9	173.2
	Normal	50th Pc.	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	High-normal	90th Pc.	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	Stage 1 HT	95th Pc.	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	Stage 2 HT	99th Pc. +5 mmHg	137	138	139	140	142	143	144	95	95	95	96	97	98	98
17	Height (cm)		152.3	154.6	158.6	162.9	167.3	171.2	173.6	152.3	154.6	158.6	162.9	167.3	171.2	173.6
	Normal	50th Pc.	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	High-normal	90th Pc.	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	Stage 1 HT	95th Pc.	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	Stage 2 HT	99th Pc. +5 mmHg	138	138	139	141	142	143	144	95	95	96	96	97	98	98

HT = hypertension; Pc. = percentile.

From the International Pediatric Nephrology Association (IPNA) 2011, updated January 2012. (<http://www.pediatrichypertension.org>).

blood pressure of < 130/85 mmHg as normal and values in the range 130–139/85–89 mmHg as high normal (European Society of Hypertension – European Society of Cardiology Guidelines Committee, 2003). The range of 'normal' blood pressure in children and adolescents is uncertain, but recently European guidelines recommended that normal blood pressure are values below the 90th percentile, and high normal values range between the 90th and 95th percentile (Lurbe et al., 2009). Thus, hypertension in children is defined as the persistence of blood pressure above the 95th percentile. Values above this, if confirmed by two further examinations, are compatible with the diagnosis of hypertension (Table 218.7). In children and adolescents for casual office blood pressure measurement by auscultation the reference centiles from Table 218.3 should be used, if blood pressure were taken by an oscillometric device centiles of Table 218.4 are helpful.

Determinants and causes of blood pressure elevation in childhood

The tendency of blood pressure to 'track', that is, to remain within a given age-related percentile over long periods of time, is less pronounced in children than in adults. But tracking of systolic blood pressure has been clearly demonstrated in a 15-year follow-up population-based family study in Finland (Fuentes et al., 2002). Thus, children with elevated blood pressure are more likely to become hypertensive adults (Vos et al., 2003). Other determinants of blood pressure in children include heart rate, gender, race, degree of biological maturation, social class, environmental changes, genetic factors, ethnicity, patient's body mass index (BMI), and familial aggregation. Family history is important to identify children at risk for hypertension (van den Elzen et al., 2004)

The increase in childhood obesity during the last 10–20 years is clearly associated with an elevation of blood pressure in children, the relevance of obesity-related hypertension, and early cardiovascular risk (Flynn, 2013). Furthermore, prenatal programming, the intrauterine milieu, intrauterine growth retardation, premature birth, and infant feeding have an impact on later hypertension (Ingelfinger and Nuyt, 2012; and see Chapter 138).

Essential or primary hypertension is caused by an interaction of multiple genes and environmental events (Ingelfinger, 2006). Molecular genetic techniques with candidate gene and linkage analysis have been introduced to elucidate the genetic basis of hereditary hypertension. Monogenetic forms of hereditary hypertension have been identified (New et al., 2005; Garovic et al., 2006). Liddle syndrome is caused by constitutive activation of the renal epithelial sodium channel due to mutation in the gamma subunit or by a mutation truncating the carboxy terminus of the gamma subunit of this channel. Patients with glucocorticoid-remediable

Table 218.4A Blood pressure references (casual blood pressure by oscillometry) for boys by age and height percentiles

Age (years)	Height (cm)	SBP (mm Hg)				DBP (mm Hg)			
		50th percentile (median)	90th percentile	95th percentile	99th percentile	50th percentile (median)	90th percentile	95th percentile	99th percentile
3	95	96	106	109	115	58	66	69	73
	96	96	106	109	115	58	67	69	74
	98	96	106	109	116	58	67	69	74
	101	96	107	110	116	59	67	70	75
	104	97	107	110	117	59	68	70	75
	106	97	107	111	117	59	68	71	75
	108	97	108	111	117	59	68	71	76
4	101	96	106	109	115	58	67	69	74
	103	96	106	109	115	58	67	69	74
	105	96	106	110	116	59	67	70	74
	108	97	107	110	116	59	68	70	75
	111	97	107	110	117	60	68	71	75
	114	98	108	111	117	60	69	71	76
	115	98	108	111	118	60	69	71	76
5	107	96	106	109	115	59	67	70	74
	109	97	106	109	116	59	67	70	74
	111	97	107	110	116	59	68	70	75
	115	97	107	110	117	60	68	71	75
	118	98	108	111	117	60	69	71	76
	121	98	108	112	118	60	69	71	76
	123	99	109	112	118	61	69	72	76
6	113	97	107	110	116	60	68	70	75
	115	97	107	110	116	60	68	70	75
	118	98	108	111	117	60	68	71	75
	121	98	108	111	117	60	69	71	76
	125	99	109	112	118	61	69	72	76
	128	100	109	113	119	61	70	72	77
	130	100	110	113	119	61	70	72	77
7	119	98	108	111	117	60	69	71	75
	121	98	108	111	117	61	69	71	76
	124	99	109	112	118	61	69	71	76
	128	100	110	113	119	61	70	72	76
	131	100	110	113	119	62	70	72	77
	135	101	111	114	120	62	70	73	77
	137	101	111	114	121	62	71	73	77
8	124	99	109	112	118	61	69	72	76
	126	100	109	113	119	61	70	72	76
	130	100	110	113	119	62	70	72	77

(*continued*)

Table 218.4A Continued

Age (years)	Height (cm)	SBP (mm Hg)				DBP (mm Hg)			
		50th percentile (median)	90th percentile	95th percentile	99th percentile	50th percentile (median)	90th percentile	95th percentile	99th percentile
	134	101	111	114	120	62	70	73	77
	138	102	112	115	121	62	71	73	78
	141	102	113	116	122	63	71	73	78
	143	103	113	116	122	63	71	74	78
9	129	100	111	114	120	62	70	73	77
	131	101	111	114	120	62	70	73	77
	135	102	112	115	121	62	71	73	78
	139	102	113	116	122	63	71	74	78
	143	103	114	117	123	63	72	74	79
	147	104	114	118	124	63	72	74	79
	149	104	115	118	125	64	72	75	79
10	133	102	112	115	122	63	71	74	78
	136	102	113	116	122	63	71	74	78
	140	103	114	117	123	63	72	74	79
	144	104	115	118	124	64	72	75	79
	149	105	116	119	126	64	73	75	80
	153	106	117	120	127	64	73	75	80
	155	106	117	121	127	65	73	76	80
11	137	103	114	117	124	64	72	75	79
	140	104	115	118	125	64	73	75	80
	144	105	116	119	126	64	73	75	80
	149	106	117	120	127	65	73	76	80
	154	107	118	122	128	65	74	76	81
	159	108	119	123	130	65	74	77	81
	162	109	120	123	130	66	74	77	82
12	142	105	117	120	127	65	74	76	81
	145	106	117	121	128	65	74	76	81
	150	107	119	122	129	65	74	77	81
	155	109	120	123	131	66	75	77	82
	161	110	121	125	132	66	75	77	82
	166	111	123	126	133	66	75	78	83
	169	112	123	127	134	67	76	78	83
13	149	108	120	123	131	66	75	77	82
	152	109	121	124	132	66	75	78	82
	157	110	122	126	133	66	75	78	83
	163	112	124	127	135	67	76	78	83
	169	113	125	129	137	67	76	79	84

(*continued*)

Table 218.4A Continued

Age (years)	Height (cm)	SBP (mm Hg)				DBP (mm Hg)			
		50th percentile (median)	90th percentile	95th percentile	99th percentile	50th percentile (median)	90th percentile	95th percentile	99th percentile
	174	114	127	130	138	67	77	79	84
	177	115	127	131	139	68	77	79	84
14	157	111	124	128	135	67	76	79	84
	160	112	125	128	136	67	76	79	84
	165	113	126	130	138	68	77	79	84
	170	115	128	132	140	68	77	80	85
	176	116	129	133	141	68	78	80	85
	181	118	131	135	143	69	78	81	86
	184	118	131	135	144	69	78	81	86
15	163	115	128	132	140	68	78	80	85
	165	115	128	132	141	68	78	80	85
	170	117	130	134	142	69	78	81	86
	175	118	131	135	144	69	79	81	86
	180	119	133	137	146	69	79	82	87
	185	120	134	138	147	70	79	82	87
	187	121	135	139	148	70	80	82	87
16	166	117	131	135	144	69	79	82	87
	169	118	132	136	145	70	79	82	87
	173	119	133	137	146	70	80	82	87
	178	120	134	139	148	70	80	83	88
	182	122	136	140	149	71	80	83	88
	186	123	137	142	151	71	81	84	89
	189	124	138	142	152	71	81	84	89
17	167	119	134	138	147	71	80	83	88
	170	120	135	139	148	71	81	83	89
	174	121	136	141	150	71	81	84	89
	179	123	137	142	151	72	81	84	90
	183	124	139	144	153	72	82	85	90
	187	125	140	145	154	72	82	85	90
	189	126	141	146	155	72	82	85	91

Height in centimeters for each age represents the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentile. The height percentiles are derived from the overall KiGGS population and are representative for Germany 2003–2006. Blood pressure percentiles apply exactly for the midpoint of each age group (e.g. 3 years 6 months old) and can be applied to all children of that age.

From Neuhauser et al. (2011).

aldosteronism (GRA) possess chimeric gene duplications arising from unequal crossing-over, fusing regulatory sequences of steroid 11 β-hydroxylase to coding sequences of aldosterone synthase. These chimeric genes are specific for GRA and explain the biochemistry, physiology, and genetics of this form of hypertension.

Transient hypertension

Renal diseases predominate as a cause of transient acute hypertension: such children may suffer from acute glomerulonephritis, Henoch–Schönlein nephritis, haemolytic uraemic syndrome, or acute kidney injury of any cause. The increase in blood pressure under these circumstances is mainly caused by sodium and water retention; however, under certain conditions, such as renal ischaemia or arteriolar damage, vasoconstrictor mechanisms, including the renin–angiotensin and sympathetic nervous systems, also contribute.

Iatrogenic hypertension may develop during therapy with steroids.

Table 218.4B Blood pressure references (casual blood pressure by oscillometry) for girls by age and height percentiles

Age (years)	Height (cm)	SBP (mmHg)				DBP (mmHg)			
		50th percentile (median)	90th percentile	95th percentile	99th percentile	50th percentile (median)	90th percentile	95th percentile	99th percentile
3	94	95	105	108	114	58	67	70	74
	95	96	105	108	114	59	67	70	75
	97	96	106	109	115	59	68	70	75
	100	97	106	109	115	59	68	71	75
	102	97	107	110	116	60	69	71	76
	105	98	108	111	116	60	69	71	76
	106	98	108	111	117	60	69	72	77
4	100	95	105	108	114	59	68	70	75
	102	96	106	109	114	59	68	70	75
	104	96	106	109	115	59	68	71	75
	107	97	107	110	116	60	69	71	76
	110	98	108	111	117	60	69	71	76
	113	98	108	111	117	60	69	72	76
	114	99	109	112	118	61	69	72	77
5	107	96	106	109	115	60	68	70	75
	108	96	106	109	115	60	68	71	75
	111	97	107	110	116	60	69	71	76
	114	98	108	111	117	60	69	71	76
	117	99	109	112	118	61	69	72	76
	120	99	109	113	119	61	70	72	77
	122	100	110	113	119	61	70	72	77
6	112	97	107	110	116	60	69	71	75
	114	97	107	110	116	60	69	71	76
	117	98	108	111	117	61	69	71	76
	121	99	109	112	118	61	69	72	76
	124	100	110	113	119	61	70	72	77
	127	101	111	114	120	62	70	73	77
	129	101	111	114	121	62	70	73	77
7	118	98	108	111	117	61	69	71	76
	120	98	109	112	118	61	69	72	76
	123	99	109	113	119	61	70	72	76
	127	100	110	114	120	62	70	72	77
	130	101	112	115	121	62	70	73	77
	133	102	112	116	122	62	71	73	78
	135	102	113	116	122	63	71	73	78
8	123	99	109	113	119	62	70	72	76
	125	100	110	113	119	62	70	72	77
	128	101	111	114	120	62	70	73	77

(*continued*)

Table 218.4B Continued

Age (years)	Height (cm)	SBP (mmHg)				DBP (mmHg)			
		50th percentile (median)	90th percentile	95th percentile	99th percentile	50th percentile (median)	90th percentile	95th percentile	99th percentile
	132	102	112	115	121	62	71	73	77
	136	103	113	116	123	63	71	73	78
	140	104	114	117	124	63	71	74	78
	142	104	115	118	124	63	72	74	79
9	128	101	111	114	120	62	70	73	77
	130	101	112	115	121	63	71	73	77
	134	102	113	116	122	63	71	73	78
	138	103	114	117	123	63	71	74	78
	142	104	115	118	125	64	72	74	79
	146	105	116	120	126	64	72	75	79
	149	106	117	120	127	64	72	75	79
10	133	103	113	116	122	63	71	74	78
	136	103	114	117	123	63	72	74	78
	140	104	115	118	124	64	72	74	79
	144	105	116	119	126	64	72	75	79
	149	106	117	121	127	64	73	75	79
	153	107	118	122	128	65	73	75	80
	155	108	119	123	129	65	73	76	80
11	140	105	115	119	125	64	72	74	79
	142	105	116	119	126	64	72	75	79
	146	106	117	120	127	64	73	75	79
	151	107	118	122	128	65	73	75	80
	156	109	120	123	130	65	73	76	80
	160	110	121	124	131	65	74	76	81
	162	110	121	125	132	66	74	76	81
12	146	107	118	121	128	65	73	75	80
	149	107	118	122	128	65	73	76	80
	153	108	119	123	129	65	74	76	80
	157	109	121	124	131	66	74	76	81
	162	110	122	125	132	66	74	77	81
	166	111	123	126	133	66	75	77	82
	168	112	123	127	134	66	75	77	82
13	150	108	120	123	130	66	74	76	81
	153	109	120	124	130	66	74	77	81
	157	110	121	125	131	66	75	77	82
	161	111	122	126	132	67	75	77	82
	166	112	123	127	133	67	75	78	82
	170	113	124	128	135	67	76	78	83

(*continued*)

Table 218.4B Continued

Age (years)	Height (cm)	SBP (mmHg)				DBP (mmHg)			
		50th percentile (median)	90th percentile	95th percentile	99th percentile	50th percentile (median)	90th percentile	95th percentile	99th percentile
	172	113	125	128	135	67	76	78	83
14	153	110	121	125	131	67	75	78	82
	156	110	122	125	132	67	75	78	82
	159	111	122	126	133	67	76	78	83
	164	112	123	127	134	67	76	79	83
	168	113	124	128	135	68	77	79	84
	172	113	125	129	136	68	77	79	84
	174	114	126	129	136	68	77	80	84
15	155	111	122	126	133	68	76	79	83
	157	111	123	126	133	68	77	79	84
	161	112	123	127	134	68	77	79	84
	165	113	124	128	135	68	77	80	84
	169	113	125	129	135	69	78	80	85
	173	114	126	129	136	69	78	81	85
	176	114	126	130	137	69	78	81	86
16	155	112	124	127	134	69	78	80	85
	157	112	124	127	134	69	78	80	85
	161	113	124	128	135	69	78	81	85
	165	113	125	129	135	70	79	81	86
	170	114	126	129	136	70	79	81	86
	174	115	126	130	137	70	79	82	87
	176	115	127	130	137	70	79	82	87
17	155	113	125	128	135	70	79	81	86
	157	113	125	129	135	70	79	82	87
	161	114	125	129	136	70	79	82	87
	166	114	126	129	136	71	80	82	87
	170	115	126	130	137	71	80	83	88
	174	115	127	130	137	71	81	83	88
	176	115	127	131	138	71	81	83	88

Height in centimetres for each age represents the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentile. The height percentiles are derived from the overall KiGGS population and are representative for Germany 2003–2006. Blood pressure percentiles apply exactly for the midpoint of each age group (e.g. 3 years 6 months old) and can be applied to all children of that age.

From Neuhauser et al. (2011).

Chronic sustained hypertension

The main causes of chronic hypertension in childhood are summarized in Box 218.1. Whereas in neonates and young infants coarctation of the aorta and renovascular disease predominate, renal disease is very likely in older infants, children, and adolescents. Since coarctation of the aorta at the isthmus is nowadays surgically corrected within the neonatal period, this cause of arterial hypertension is decreasing. Hypertension often occurs in adolescent and adults after repair of coarctation of the aorta (Pedersen et al., 2011). Rarely stenosis of the abdominal aorta causes sustained and curable hypertension (Fig. 218.2). Four different renal causes of persistent renal hypertension can be distinguished: diseases of the renal parenchyma, diseases of renal vessels (renovascular hypertension), chronic renal failure, and post-transplant hypertension.

Diseases of renal parenchyma

Chronic glomerulonephritis is one of the most frequent causes of hypertension in children as in adults (Box 218.1). Reduced

Table 218.5A Systolic and diastolic ambulatory blood pressure (systolic/diastolic in mmHg) reference values by age

	Boys						Girls					
	Day			Night			Day			Night		
Age (years)	75th	90th	95th	75th	90th	95th	75th	90th	95th	75th	90th	95th
5	116/76	120/79	123/81	99/59	103/62	106/65	114/77	118/80	121/82	100/61	105/66	108/69
6	116/76	121/79	124/81	100/59	105/63	108/66	115/77	120/80	122/82	101/61	106/65	110/68
7	117/76	122/80	125/82	101/60	106/64	110/67	116/77	121/80	123/82	102/60	107/65	111/67
8	117/76	122/80	125/82	102/60	108/64	111/67	117/76	122/80	124/82	103/60	108/64	112/67
9	118/76	123/80	126/82	103/60	109/64	112/67	118/76	122/80	125/82	103/59	109/64	112/67
10	119/76	124/80	127/82	104/60	110/64	113/67	119/76	123/79	126/81	104/59	110/64	113/67
11	121/76	126/80	129/82	105/60	111/64	115/67	120/76	124/79	127/81	105/59	110/63	114/66
12	123/76	128/80	132/82	107/60	113/64	116/67	121/76	125/80	128/82	105/59	110/63	114/66
13	126/76	131/80	135/82	109/60	115/64	119/67	122/77	126/80	129/82	106/59	111/63	114/66
14	129/77	134/80	138/82	112/61	118/64	121/67	123/77	127/80	130/82	106/59	111/63	114/65
15	132/77	137/81	141/83	114/61	120/64	123/66	124/77	128/80	130/82	107/59	111/63	114/65
16	135/78	140/81	144/84	117/61	123/64	126/66	124/77	129/80	131/82	107/59	111/63	114/65

Data from Wühl et al. (2002).

capacity to excrete sodium and water contribute to the pressure elevation, as well as reduced renal perfusion with subsequent activation of pressor systems. Failure to suppress vasoconstrictor hormones despite volume expansion has been implicated as a hypertensive mechanism, particularly in patients with glomerular diseases. The causes of chronic glomerulonephritis include focal segmental glomerulosclerosis and membranoproliferative glomerulonephritis.

Table 218.5B Systolic and diastolic ambulatory blood pressure (systolic/diastolic in mmHg) reference values by height

	Boys						Girls					
	Day			Night			Day			Night		
Height (cm)	75th	90th	95th	75th	90th	95th	75th	90th	95th	75th	90th	95th
120	116/77	122/80	125/82	99/58	103/61	106/63	114/77	118/80	120/82	99/60	103/63	106/65
125	117/76	122/80	125/82	100/58	105/61	108/63	115/77	119/80	121/82	100/60	104/63	107/66
130	117/76	122/80	126/82	101/59	106/62	110/64	116/76	120/80	122/82	101/59	106/63	108/66
135	117/76	123/80	126/82	102/59	108/63	111/65	116/76	120/80	123/82	102/59	107/63	109/66
140	118/76	123/80	126/82	104/60	109/63	113/65	117/76	121/80	124/82	103/59	108/63	110/66
145	119/76	124/79	127/81	105/60	111/64	114/66	118/76	123/80	125/82	103/59	109/63	112/66
150	120/76	125/79	128/81	106/60	112/64	116/66	119/76	124/80	127/82	104/59	110/63	113/66
155	122/76	127/79	130/81	107/60	113/64	117/66	121/76	125/80	128/82	106/59	111/63	114/66
160	124/76	129/79	133/81	108/60	114/64	118/66	122/76	126/80	129/82	106/59	111/63	114/66
165	126/76	132/80	135/82	110/60	116/64	119/66	123/77	127/80	130/82	107/59	112/63	114/66
170	128/77	134/80	138/82	112/61	117/64	121/66	124/77	128/80	131/82	108/61	112/67	115/71
175	130/77	136/81	140/83	113/61	119/64	122/66	125/78	129/81	131/82	109/59	113/63	115/66
180	132/77	138/81	142/83	115/61	120/64	124/66	N/A	N/A	N/A	N/A	N/A	N/A
185	134/78	140/81	144/84	116/61	122/64	125/66	N/A	N/A	N/A	N/A	N/A	N/A

Data from Wühl et al. (2002).

Table 218.6 Systolic and diastolic home blood pressure reference

	Boys			Girls		
Height (cm)	**N**	**50th**	**95th**	**N**	**50th**	**95th**
120–129	23	105/64	119/76	36	101/64	119/74
130–139	51	108/64	121/77	51	103/64	120/76
140–149	39	110/65	125/77	61	105/65	122/77
150–159	41	112/65	126/78	71	108/66	123/77
160–169	45	115/65	128/78	148	110/66	124/78
170–179	91	117/66	132/78	46	112/66	125/79
180–189	57	121/67	134/79	7	114/67	128/80

The 95th percentile is the proposed threshold for home hypertension.

Data from Stergiou et al. (2007).

One important cause of renal hypertension in childhood is pyelonephritic scarring, which results from vesicoureteric reflux combined with urinary tract infection in early life (reflux nephropathy; see Chapter 355). With improved diagnosis and early treatment of acute pyelonephritis in infants and children the number of children with significant renal scarring and subsequent arterial hypertension has decreased substantially. Some children are born with a congenital disorder of renal development mimicking reflux nephropathy.

In haemolytic uraemic syndrome (see Chapter 174), the occurrence of hypertension is related to the type of histological lesion. Severe hypertension is present if microangiopathy has affected medium-sized branches of the renal arteries. This vascular form of haemolytic uraemic syndrome occurs most frequently in older children; the glomerular form of microangiopathy mainly affects infants, in whom hypertension is rare and seldom severe. Hypertension appears to be a considerable long-term problem in 9% of children with non-familiar haemolytic uraemic syndrome (Rosales et al., 2012).

Polycystic kidneys (see Chapter 305), an important cause of severe hypertension, are seen mainly in infants with the autosomal recessive form of polycystic kidney disease (Dell, 2011). Insufficient control of blood pressure rather than renal failure was often associated with illness and death. Hypertension is often more severe in the first years of life than later, and may spontaneously return to normal. Polycystic kidney disease may be associated as 'contiguous gene syndrome' with other congenital anomalies, such as tuberous sclerosis (Boehm et al., 2007). In children with an autosomal dominant form of polycystic kidney disease glomerular, hyperfiltraton is an early marker for a more severe progression (Helal et al., 2011).

Table 218.7 Definition and classification of hypertension in children and adolescents

Class	SBP and/or DBP percentile
Normal	<90th
High-normal	>90th to <95th >120/80 even if below 90th percentile in adolescents
Stage 1 hypertension	>95th percentile to the 99th percentile plus 5 mmHg
Stage 2 hypertension	>99th percentile plus 5 mmHg

From Lurbe et al. (2009).

Box 218.1 Causes of chronic hypertension in childhood

1. Renal

- Diseases of the renal parenchyma
- Chronic glomerulonephritis (e.g. focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, systemic diseases like lupus, Henoch–Schönlein nephritis)
- Reflux nephropathy (segmental renal scars)
- Obstructive uropathy
- Polycystic kidney disease
- Renal dysplasia (seldom)
- Haemolytic uraemic syndrome
- Chronic renal failure
- Renovascular disease
- Renal artery stenosis (fibromuscular dysplasia, neurofibromatosis)
- Anomalies of the renal artery (aneurysms, thrombosis, arteriovenous fistula)
- Arteritis
- Renal tumours
- Wilms tumour
- Haemangioperiocytoma
- Hamartoma.

2. Coarctation of aorta

- Thoracic
- Abdominal.

3. Endocrine

- Catecholamine excess
- Phaeochromocytoma
- Neuroblastoma
- Corticoid excess
- Congenital adrenal hyperplasia
- Conn syndrome
- Cushing syndrome
- Low renin states
- Apparent mineralocorticoid excess (AME)
- Glucocorticoid remediable aldosteronism (GRA).

4. Primary hypertension.

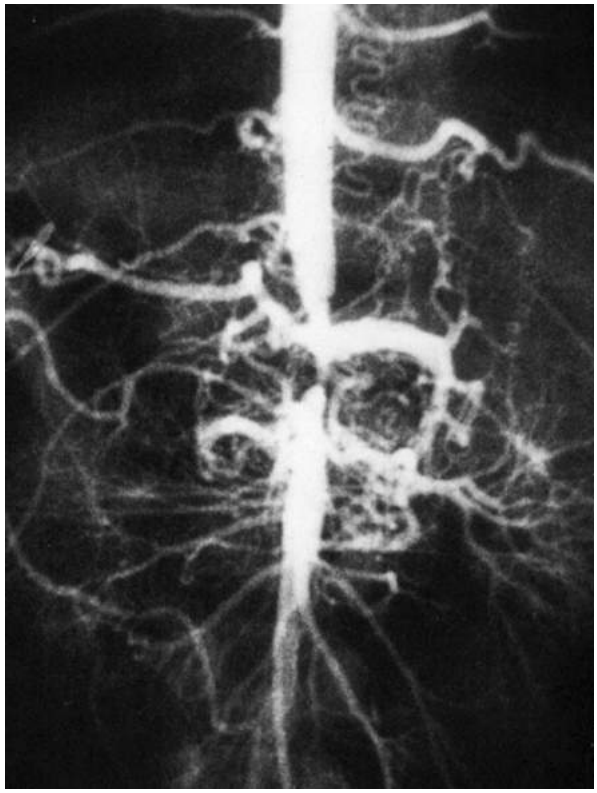

Fig. 218.2 Flush aortography in a 4-month-old girl with coarctation of the abdominal aorta, demonstrating extensive narrowing of that vessel.

Renovascular hypertension

Diseases of the renal vessels resulting from lesions that cause unilateral or bilateral impairment of blood flow to kidneys (see Chapter 213) are far rarer than diseases of the renal parenchyma (Box 218.2), accounting for about 10% of cases of secondary hypertension in children.

Renovascular disorders can generally be distinguished as those which are localized at the renal hilum and those occurring within the smaller vessels of the kidney (intrarenal) (Box 218.2).

Renal arterial stenosis is the most common cause of renovascular hypertension: approximately one-third to one-half of children has fibromuscular dysplasia (Estepa et al., 2001), the cause of which is unknown. Stenosis of the renal artery, associated with neurofibromatosis, is usually caused by intimal proliferation, which closely resembles fibromuscular dysplasia histologically (Figs 218.3 and 218.4). It is, therefore, essential to exclude neurofibromatosis in every child patient with renal artery stenosis.

The renal artery may be compressed by a tumour, fibrous bands, haematoma, or surgical intervention. Other causes of renovascular hypertension in children include renal arterial aneurysm, arteriovenous fistula, renal arterial disruption, and arterial trauma. In neonates, the causes include renal arterial thrombosis. Renovascular hypertension in children has been reported in vascular malformation syndromes, such as the Klippel–Trénaunay syndrome or Moyamoya disease. Patients with Turner syndrome and Alagille syndrome have vascular anomalies and are at risk for development of hypertension (Nathwani et al., 2000a, 2000b; Salem et al., 2012).

Box 218.2 Renovascular causes of hypertension in childhood

- Hilar compression by tumours of the kidney, adrenals, etc.
- Stenosis of the renal artery and its main branches
- Fibromuscular dysplasia, vascular neurofibromatosis, aneurysm, embolism, thrombosis (newborns), arteritis (Takayasu disease)
- Coarctation of the abdominal aorta
- Stenosis of the small arteries (intrarenal changes)
- Aneurysm (congenital, acquired, e.g. after renal biopsy)
- Irradiation nephritis, haemolytic uraemic syndrome, general vascular disease: periarteritis nodosa, vasculitis, etc.
- Vascular malformation (e.g. Klippel–Trénaunay syndrome).

Chronic renal failure and renal transplantation

Sustained hypertension frequently occurs in children with chronic renal failure, who are routinely treated by dialysis and renal transplantation (Flynn et al., 2008). The frequency of hypertension in chronic renal failure varies considerably in relation to the stage of renal impairment, the primary disease, and the treatment given. In the early stage of renal insufficiency, patients with glomerular diseases, segmental renal scars, and polycystic kidney disease usually have moderate to severe hypertension, whereas in the end stage only a few patients do not show elevation of blood pressure. These patients suffer primarily from tubular or interstitial diseases or from renal hypoplasia (e.g. oligomega-nephronic dysplasia), or have congenital malformations of the urinary tract.

After successful renal transplantation, hypertension occurs frequently in children. Up to 100% of the children are hypertensive during the first post-transplant week, when volume expansion by intravenous electrolytes commonly increases blood pressure. Acute rejection crises, treated with high-dose steroids, are also an important cause of transient increases in blood pressure. Patients with stable graft function have a lesser incidence of hypertension than

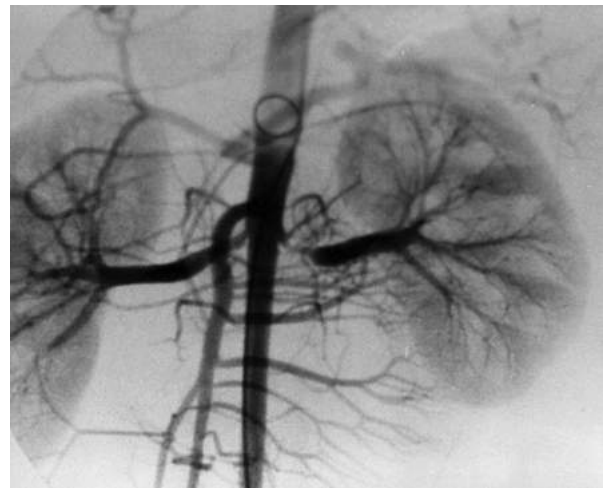

Fig. 218.3 Angiography showing stenosis of the left renal artery due to fibromuscular dysplasia in an 11-year-old girl.

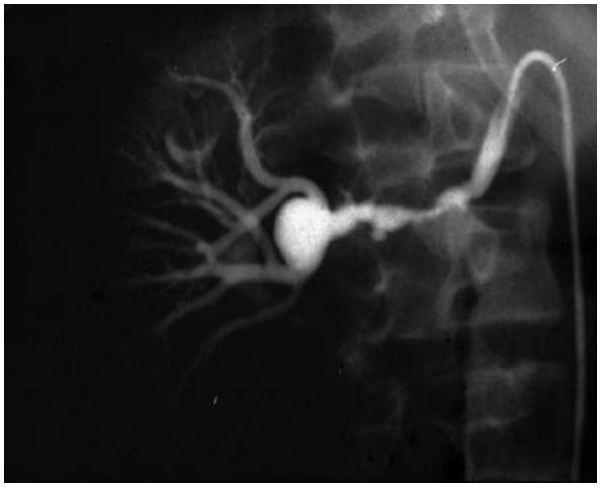

Fig. 218.4 Selective angiography of the right renal artery showing stenosis and poststenotic aneurysm in a 14-year-old boy with neurofibromatosis.

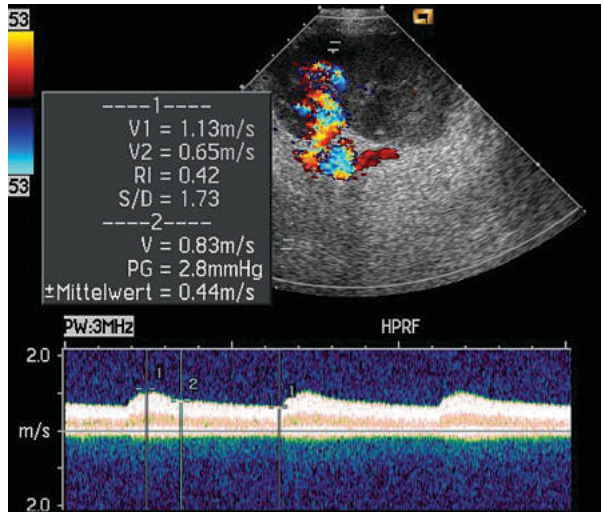

Fig. 218.5 Colour-aided and Doppler renal ultrasound in a 15-year-old kidney transplanted patient. The segmental artery showed increased systolic and particularly diastolic flow with significantly reduced resistance index demonstrating stenosis of a segmental renal artery.

those with chronic rejection. Renal arterial stenosis may result from insufficient suturing during the creation of the anastomosis, damage of the intima during removal or perfusion of the donor kidney, disproportion between the calibre of the transplanted renal artery and the recipient vessels, or from immunological reactions. From the clinical point of view, stenosis sometimes resembles acute rejection. There is a close relation between the underlying primary renal disease and the occurrence of hypertension. Children whose primary disease is glomerulonephritis are more likely to develop severe hypertension after renal transplantation than those with other nephropathies.

Clinical presentation

Even severe hypertension often occurs without any clinical symptoms. Physical signs are frequently minimal and often misinterpreted, unless blood pressure is recorded. Presenting features differ with age. During infancy, congestive heart failure, respiratory distress, failure to thrive, vomiting, irritability, and convulsions are the most common features. Headache, nausea, vomiting, polydipsia, polyuria, visual problems, irritability, tiredness, cardiac failure, facial palsy, epistaxis, and growth retardation are characteristic features in older children. The underlying disease accounts for many of the symptoms observed in the hypertensive child: nausea, tiredness, or polyuria might be related to underlying renal disease and not to specific hypertensive symptoms.

In children suffering from phaeochromocytoma, palpitations, sweating, and pallor might be characteristic, but these symptoms sometimes occur with other causes of hypertension. Conditions suggesting increased risk of hypertension in infants are abdominal mass (polycystic kidney disease, neuroblastoma, Wilms tumour), neurofibromatosis, failure to grow, indwelling umbilical arterial catheter, administration of glucocorticoids and/or ACTH, Turner syndrome, Cushing syndrome, Williams syndrome, aortic coarctation, unexplained cardiac failure, and unexplained seizures.

Physical examination may reveal signs associated with the specific underlying cause of hypertension, for example, weak pulses or differences in blood pressure between the upper and lower limbs in coarctation of the aorta, café-au-lait skin patches or other features of neurofibromatosis with renal arterial disease, and abdominal masses in polycystic kidney disease. Signs and symptoms of cardiomegaly, hypertensive retinopathy, or several neurological features are particularly important, since they indicate long-standing hypertension.

Diagnostic approach

The extent to which investigation of hypertension is justified depends on its severity and persistence, and the circumstances under which it is detected. The diagnostic strategy is clearly different for mild hypertension identified incidentally in an asymptomatic child and severe hypertension observed in a symptomatic patient. In mild forms of persistent hypertension, the family history should be taken, together with a careful history on the use of drugs. In stage 1 the investigation should include urinalysis, blood cell count, blood chemistry, and abdominal ultrasonography with flow measurement (Fig. 218.5; (Box 218.3).

Apart from the routine biochemical profile, some measures of end-organ damage should be included. Two-dimensional echocardiography is useful in identifying left ventricular hypertrophy.

Box 218.3 Primary investigation of the child with moderate to severe forms of hypertension

- Urinalysis (cells, protein)
- Blood cell count
- Serum chemistry (electrolytes, creatinine, urea, uric acid)
- Fasting plasma glucose, triglycerides, and cholesterol
- Plasma renin activity
- Abdominal ultrasound including Doppler sonography of the kidneys
- Fundoscopy
- Echocardiography.

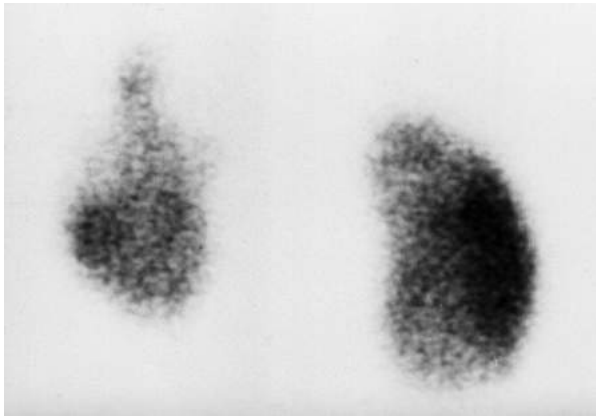

Fig. 218.6 ^{99m}Tc dimercaptosuccinic acid static scan in a 10-year-old girl with vesicoureteric reflux demonstrating reduced isotope uptake in the upper pole of the left kidney indicating upper-pole scarring; a previous renal ultrasound examination looked normal.

Bearing in mind the distribution frequency of secondary forms of hypertension, some form of renal imaging is mandatory and a combination of abdominal ultrasonography and ^{99m}Tc dimercaptosuccinic acid static scanning is very useful. The latter method is a marker of renal parenchyma, the bound isotope reflecting the functioning proximal tubular mass, and is reportedly a very sensitive method for detecting segmental parenchymal scars and ischaemic areas due to renal vascular disease. The ^{99m}Tc dimercaptosuccinic acid scan also detects small or poorly functioning kidneys and provides information on differential renal function (Fig. 218.6). Abdominal ultrasonography detects tumours of the adrenal gland and the kidneys, and is also very valuable in the diagnosis of cystic renal diseases, renal calculi, dilatation of the collecting system, presence of a duplex system, ureterocoele, and a thickened bladder

Box 218.4 Supplementary investigation in the hypertensive child

In cases of suspected renal aetiology

- Glomerular filtration rate
- Colour-aided Doppler and duplex ultrasonography
- Magnetic resonance imaging in case of suspected renal artery stenosis
- Voiding cystourethrography
- ^{99m}Tc mercaptoacetyltriglycine (dynamic) scan of the kidney
- Renal angiography or digital subtraction angiography
- Renin sampling from renal veins and vena cava
- Renal biopsy.

In cases of suspected endocrine aetiology

Plasma catecholamines and metanephrines

- If high:
  - ^{123m}I iodobenzylguanidine (MIBG) scan
  - Vena cava sampling of catecholamines
  - Magnetic resonance imaging
  - Angiography
  - Plasma renin
  - Plasma aldosterone
- If high:
  - Urine mineralocorticoids
  - Dexamethasone suppression
  - Adrenal scintigraphy

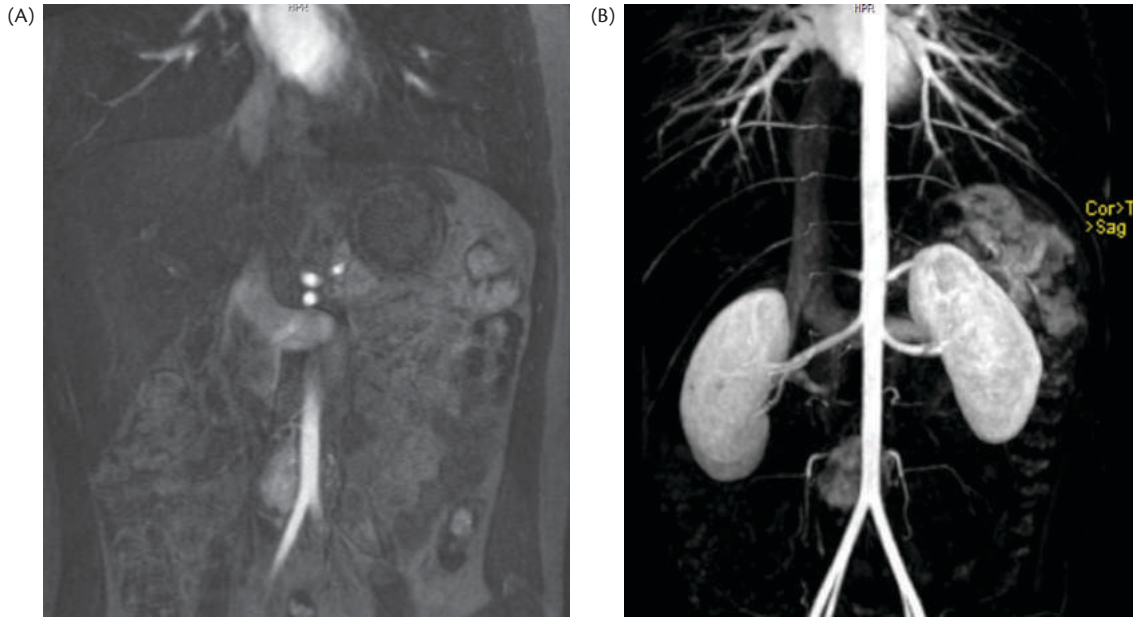

Fig. 218.7 Conventional magnetic resonance imaging in a 15-year-old boy with suspected phaeochromocytoma. The rounded mass above the bifurcation of the aorta may indicate the catecholamine producing tumour (A). The magnetic resonance angiography clearly detects a definite rounded mass as phaeochromocytoma of the Zuckerkandl organ (B). After operative removal of the mass, the biochemical and clinical signs of the disease disappeared.

- If low:
  - Urine mineralocorticoids
  - Other plasma mineralocorticoids
  - Cortisol response to ACTH or dexamethasone
  - Molecular genetic studies when genetic forms of hypertension are probable after biochemical screening.

In cases of suspected cardiovascular aetiology

- Echocardiography
- Cardiac magnetic resonance imaging
- Angiography or digital subtraction angiography

wall. Since it does not show the degree of renal function it has to be combined with other forms of renal imaging. Colour-aided Doppler and duplex sonography have been successfully used for vascular imaging in children with hypertension. Further selected studies are indicated, if any of the investigations mentioned above reveals an abnormality, or if hypertension is severe (Box 218.4). This should include rare cases of childhood hypertension (Grinsell and Norwood, 2009). Non-invasive studies (magnetic resonance angiography or three-dimensional computed tomography) are able to define the anatomy of the renal vasculature and may serve as screening method and have replaced selective angiography for the diagnosis of renal artery stenosis (Katayama et al., 2000; Leder and Nelson, 2001). Magnetic resonance imaging (Fig. 218.7) is also helpful in detecting phaeochromocytoma.

Further information

For further information see the International Pediatric Hypertension Association's website: <http://pediatrichypertension.org/>

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CHAPTER 219

Treatment of hypertension in children

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Introduction

In primary hypertension, drug treatment should be carefully considered after non-pharmacological intervention has failed. Various interventions, such as reduction of dietary sodium chloride intake, reduction of body weight in obese children and adolescents, and dynamic exercises, have been recommended, although the therapeutic success of non-pharmacological intervention is so far not sufficiently established. Drug treatment is indicated if blood pressure continues to increase.

Factors other than blood pressure that influence the decision to begin drug treatment include a family history of early complications of hypertension (renal failure, stroke, heart disease), target organ involvement (cardiac enlargement, left ventricular hypertrophy, retinal vascular changes), and the presence of other risk factors for coronary heart disease.

Surgical treatment of coarctation of the aorta, tumours (e.g. phaeochromocytoma, neuroblastoma), and renovascular hypertension often lowers the blood pressure to normal. Surgical management is also possible in unilateral hydronephrosis, nephrolithiasis, and in rare cases of peripheral renal arterial stenosis or segmental renal scars where the blood pressure can occasionally be returned to normal by polar resection. Following surgery, it often takes weeks or months before the blood pressure becomes completely normal after discontinuation of antihypertensive therapy. In the majority of children with renal hypertension, treatment is based on the long-term administration of antihypertensive drugs.

Antihypertensive agents in children

Pharmacological treatment of hypertension in children was based more on individual experience than on evidence-based studies. The legislation changes in the United States to promote clinical trials to improve paediatric drug treatment (Food and Drug Administration Modernization Act, 1997; Best Pharmaceuticals for Children Act, 2002) have led to clinical trial with antihypertensive agents in children and to approval of some of these drugs. The EU Regulation of Medicinal Products for Paediatric Use (EU Regulation 1901/2006/EC) will further stimulate clinical trials and approval of antihypertensive drugs in the paediatric population. Adequate dose recommendations based on careful dose-finding studies in various age groups of paediatric patients are still rare as well as age-appropriate drug formulations. Recently 45 observational and randomized clinical trials with antihypertensive agents in children and adolescents have been excellently reviewed (Meyers and Siu, 2011). A clear dose–relationship for only three drugs (enalapril, lisinopril, losartan) has been shown (Benjamin et al., 2008).

The target blood pressure in children with hypertension and chronic renal failure has been evaluated in a large prospective trial with valid end points (50% decline in glomerular filtration rate (GFR) or progression to end-stage renal disease (ESRD) over a period of 5 years) (ESCAPE Trial Group, 2009). Strict control of blood pressure is able to slow the progression of renal failure. In this trial, 29.9% of the patients in the intensified blood-pressure control with ramipril reached the end point (50% GFR loss or progression to ESRD) compared to 41.7% of patients with a conventional blood-pressure target.

In general, blood pressure should be lowered below the 90th age–sex and height-specific percentile in children with arterial hypertension. In those with underlying chronic kidney disease, target blood pressure should be below the 75th percentile in children without and in those with proteinuria below the 50th percentile (Lurbe et al., 2009). This 50th percentile is also true for children with diabetes mellitus type 1. The corresponding targets for adolescents and adults are 130/80 mmHg with a renal disease without proteinuria and a target blood pressure below 120/75 mmHg in case of proteinuria.

Dosages of antihypertensive agents in childhood based on clinical trials and published experience (Table 219.1) and the indications, contraindications, and side effects are listed in Table 219.2).

Angiotensin-converting enzyme inhibitors

Captoril was the first angiotensin-converting enzyme inhibitor (ACEI) used successfully in children with severe renal hypertension. However, in newborns and small infants, cerebral and renal complications have been reported, which occurred if the initial dose was too high. This age group requires substantially lower doses per unit body surface than older infants and children for the control of hypertension. In order to prevent a rapid decrease in blood pressure following the first dose of captopril, a low dose of 0.2 mg/kg (in newborns, 0.05 mg/kg) should be given. If this dose is tolerated, the dose can be increased rapidly, to 1–2 mg/kg per day if necessary. Long-term treatment should not exceed 2–3 mg/kg per day, or 150 mg in adolescents, although higher doses have been recommended. Because of multiple dosing per day, captopril is no longer the drug of choice.

Table 219.1 Dosage of oral antihypertensive agents in children and adolescents

	Paediatric indication for hypertension (USA)	Paediatric label for hypertension (EU) (Germany)	Age group	Initial dose	Maximum dose	Dosage interval
Angiotensin-converting enzyme inhibitors						
Captopril			Premature to > term ≤ 7 days	0.01 mg/kg/dose	0.5 mg/kg/day	8–12 hours
			Term neonates > 7 days	0.05–0.1 mg/kg/dose	0.5 mg/kg/day	8–12 hours
		Yes	Infants	0.15–0.3 mg/kg/dose	6 mg/kg/day	8–12 hours
			Children	0.3–0.5 mg/kg/dose	6 mg/kg/day	8–12 hours
			Older children	6.25–12.5 mg/dose	6 mg/kg/day	8–12 hours
			Adolescents	12.5–25 mg/dose	450 mg/day	8–12 hours
Enalapril	Age 6–16 years		Neonates	0.1 mg/kg/day	0.5 mg/kg/day	24 hours
			Infants and children	0.1 mg/kg/day	0.5 mg/kg/day	24 hours
		> 6 years	Adolescents	2.5–5 mg/day	40 mg/day	24 hours
Lisinopril	Age ≥6 years		Infants and children < 6 years	0.1 mg/kg/dose	0.5 mg/kg/day	24 hours
			Children ≥ 6 years	0.07 mg/kg/dose (max. 5 mg/dose)	>0.61 mg/kg or 40 mg/day	24 hours
Fosinopril	Age 6–16 years		Children > 50 kg	5–10 mg/day	40 mg/day	24 hours
Angiotensin receptor blockers						
Losartan	Age ≥ 6 years	> 6 years	Children 6–16 years	0.7 mg/kg/dose or 50 mg/day	100 mg/day	24 hours
Valsartan	Age 6–16 years	> 6 years	Children 6–16 years	1.3 mg/kg/dose or 40 mg/day	160 mg/day	24 hours
Irbesartan			Children 6–12 years	75 mg/day	150 mg/day	24 hours
Candesartan	Age 1–16 years		Children 1–5 years	0.2 mg/kg/day	0.4 mg/kg/day	12–24 hours
			Children 6–17 years, <50 kg	4–8 mg/day	16 mg/day	12–24 hours
			Children 6–17 years, >50 kg	8–16 mg/day	32 mg/day	12–24 hours
Olmesartan	Age 6–12 years		Children 1–5 years, ≥50	0.3 mg/kg/day	0.6 mg/kg/day	24 hours
			Children 6–16 years, 20–35 kg	10 mg/day	20 mg/day	24 hours
			Children ≥35 kg	20 mg/day	40 mg/day	24 hours
Calcium channel antagonists						
Amlodipine	Age ≥6 years		Children 6–17 years	2.5 mg/day	10 mg/day	24 hours
Nifedipine extended release	No		Children	0.25–0.5 mg/kg/day	3 mg/kg/day up to 120 mg/day	8–12 hours
			Adolescent	30 mg/day	120 mg/day	
Isradipine	No		Children	0.05–0.15 mg/kg/dose	0.8 mg/kg/day up to 20 mg/d	6–8 hours
Felodipine	No		Children	0.1 mg/kg/d or 2.5 mg/d	0.6 mg/kg/day or 10 mg/d	12–24 hours
Beta-receptor antagonists						
Propranolol	Yes		Children and adolescents 1–17 years	1 mg/kg/day	4 mg/kg/day up to 640 mg/day	8–12 hours
Metoprolol immediate release	Age ≥ 6 years		Children and adolescents 1–17 years	1 mg/kg/day	6 mg/kg/day up to 200 mg/day	12 hours

(*continued*)

Table 219.1 Continued

	Paediatric indication for hypertension (USA)	Paediatric label for hypertension (EU) (Germany)	Age group	Initial dose	Maximum dose	Dosage interval
extended release			Children ≥ 6 years	1 mg/kg/day	2 mg/kg/day or 200 mg/day	24 hours
		> 6 years (Germany)		23,75 mg/day	95 mg/day	24 hours
Diuretics						
Hydrochlorothiazide	No			0.25 mg/kg/day	1 mg/kg/day	24 hours
Chlorthalidone			Children 5–12 years	0.5 mg/kg/48 hours	1.7 mg/kg/48 hours	24–48 hours
			Children 12–18 years	25 mg/day	50 mg/day	24–48 hours
Furosemide	No		Only in renal insufficiency	0.5 mg/kg/day	5 mg/kg/day	8–12 hours
Others						
Clonidine	No		Children	0.005 mg/kg/day	0.3 mg/kg/day	8–12 hours
Hydralazine	No		Children	1 mg/kg/day	10 mg/kg/day	12 hours
Minoxidil	Yes		Children <12 years	0.1–0.2 mg/kg/day	50 mg/day	12 hours
			Adolescents > 12 years	5 mg/day	100 mg/day	12 hours

Enalapril is a pro-drug that must be metabolically converted to enalaprilat. Peak serum concentration occurred at 3–4 hours after oral administration. The longer plasma half-life of 12 hours is an advantage to improve compliance. Since enalapril is excreted by the kidneys, dosage should be reduced in patients with renal failure. As with captopril, approximately one-third of enalaprilat is cleared during haemodialysis. Enalapril is licensed in children > 6 years of age with hypertension.

Ramipril has also been used in children (Soergel et al., 2000), but no adequate dose-finding study has been performed. On the other hand, good outcome data are available (ESCAPE Trial Group, 2009).

Angiotensin receptor 1 antagonists

Antagonizing the angiotensin II receptor 1 is highly effective to lower blood pressure and safe in children with arterial hypertension and a variety of angiotensin receptor 1 antagonists have been studied in children including losartan, valsartan, irbesartan, candesartan, and olmesartan, but only losartan and valsartan are licensed for children > 6 years of age.

Table 219.2 Indications, contraindications, and side effects of antihypertensive agents

	Indication	Contraindication	Side effects
Angiotensin-converting enzyme inhibitors	Diabetes mellitus, progressive renal disease	Renal artery stenosis, GFR increase, pregnancy	Skin rashes, taste disturbances, cough, hyperkalaemia
Angiotensin II receptor antagonists	Diabetes mellitus, progressive renal disease	Renal artery stenosis, GFR increase, pregnancy	Skin rashes, taste disturbances, angio-oedema, hyperkalaemia
Beta-adrenergic antagonists		Asthma, concurrent diabetes mellitus	Bradycardia and bronchoconstriction
Calcium channel blockers			Gastrointestinal disturbances, constipation, oedema of the legs, gingival hyperplasia
Centrally acting alpha-adrenergic antagonists (clonidine)	Tachycardia		Sedation, bradycardia,
Loop diuretics (frusemide)	Only when GFR < 30 mL/min/m²		Hypokalaemia, hypercalciuria
Thiazide diuretics (hydrochlorothiazide)		GFR < 30 mL/min/m²	Hypokalaemia, hyperuricaemia, impairment of glucose tolerance, disturbances of lipid metabolism
Vasodilators (minoxidil, hydralazine			Induce tachycardia, salt and water retention, hypertrichosis

Table 219.3 Rational combination of antihypertensive drugs

Two drugs	ACEI (or angiotensin II receptor blocker) + diuretic
	ACEI (or angiotensin II receptor blocker) + calcium channel blocker
	Diuretic + ACEI (or angiotensin II receptor blocker)
Three drugs	ACEI (or angiotensin II receptor blocker) + diuretic + beta blocker
	ACEI (or angiotensin II receptor blocker) + diuretic + calcium channel blocker
	ACEI (or angiotensin II receptor blocker) + diuretic + clonidine
	Diuretic + beta blocker + vasodilator (ACEI or angiotensin II receptor blocker or calcium channel blocker or hydralazine or minoxidil)
	Diuretic + clonidine + vasodilator (ACEI or angiotensin II receptor blocker or calcium channel blocker or hydralazine or minoxidil)

Beta-adrenergic blockers

Propranolol is effective and safe and doses up to 16 mg/kg per day are tolerated without significant side effects. It is not clearly established whether an increase in dosage to > 5 mg/kg per day has any further blood pressure-lowering effects, although this might be possible, since bioavailability varies between 20% and 50% due to a high first-pass metabolism in the liver.

Cardioselective beta-adrenergic blockers have been recommended. Atenolol is eliminated via the kidney and has a longer half-life than propranolol; a single morning dose is therefore sufficient. Metoprolol is metabolized within the liver and dose reduction during renal insufficiency is not required (1–4 mg/kg per day). Extended-release metoprolol is licenced for children in Europe > 6 years of age.

Calcium antagonists

Oral nifedipine has been shown to reduce blood pressure effectively and safely in paediatric hypertensive emergencies. The doses used ranges between 0.25 and 0.5 mg/kg per day. Slow-release preparations of nifedipine have been used as vasodilators to treat sustained renal hypertension in children in Germany, although this experience has not yet been reported in print. The dose used ranges between 0.5 and 2.0 mg/kg per day. The drug has been replaced by amlodipine (0.06–0.3 mg/kg/day).

Diuretics

Paediatric experience has been reported with hydrochlorothiazide and chlorthalidone. Chlorthalidone has a longer half-life and the dose interval is 24 or 48 hours. Increasing the dose of thiazides affects blood pressure only marginally, but may be associated with increased incidence and severity of side effects. Loop diuretics such as frusemide are essential in children with advanced chronic renal failure. In contrast to the thiazide diuretics, frusemide induces calcium excretion and nephrocalcinosis.

Other drugs

Hydralazine and minoxidil have been used as vasodilators, but have limited use. Clonidine lowers sympathetic outflow via central alpha-2 adrenergic stimulation. Clonidine is indicated if beta blockers are contraindicated. The alpha-1 adrenergic blocker prazosin does not affect presynaptic 1 receptors, as do phentolamine and phenoxybenzamine. The alpha blockers are indicated pre- and perioperatively in patients with phaeochromocytoma.

Approach to the treatment of children with antihypertensive agents

The management of children with chronically elevated blood pressure starts with low doses of a given drug and slowly reaches therapeutically effective levels. Treatment should be started with ACEIs. Very high-dose monotherapy should be avoided because of side effects and a combination of two or more antihypertensive drugs should be used initially. Combination therapy should follow a rational approach (Table 219.3).

Hypertensive emergencies with clinical signs of hypertensive encephalopathy or of pulmonary oedema require immediate therapy (Adelman et al., 2000). Oral nifedipine at a dose of 0.25–0.5 mg/kg is efficient (Yiu et al., 2004). If there is insufficient response within 15 minutes marked tachycardia may occur, which points to sympathetic stimulation, and therefore clonidine in a dose of 2–6 micrograms/kg is indicated, given either subcutaneously, intramuscularly, or slowly intravenously. The use of diazoxide (2–6 mg/kg) is established in childhood hypertension, but no longer recommended as a first-line drug, since bolus injection may be associated with a precipitous reduction in blood pressure to hypotensive levels. In states of fluid retention, frusemide (2–7 mg/kg intravenously) should be combined. If there is no satisfactory response to the drugs discussed above, sodium nitroprusside (0.5–8 micrograms/kg per min.) should be administered as a continuous infusion with the patient under constant surveillance. The infusion rate must be continuously adjusted to the changes in blood pressure. Thiocyanate levels should be monitored. In terminal renal failure, fluid removal by dialysis may be the only way to control hypertension.

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