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Regional renal blood flow in normal and disease states

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Abstract Renal function is intimately dependent on renal blood flow. Alterations in either total or regional renal blood flow have major consequences for renal function. Through homeostatic mechanisms the kidneys are able to maintain relatively stable rates of flow over a wide range of perfusion pressures. A combination of neural, endocrine, exocrine and autocrine signals serve to regulate renal blood flow at both local and systemic levels. Alterations in the balance of these systems occur in the presence of certain pathophysiological conditions and an understanding of the subsequent changes in regional renal blood flow distribution aids in the understanding of the associated changes in renal function. The regulation and distribution of regional blood flow and the effects of surgical and pathophysiological conditions on these factors are reviewed.

Key words Regional renal blood flow
Ureteric obstruction · Nephrectomy · Ischaemia
Prostaglandin · Angiotensin

The kidney plays a pivotal role in the homeostatic maintenance of the internal environment. It regulates not only the concentration of metabolic waste products but also the volume, osmolarity, acid base status and ionic composition of the extracellular fluid. These functions are mediated via two interdependent regulatory systems which govern the rate at which the glomerulus filters blood passing through the glomerular tuft and control the rate at which solutes are secreted and reabsorbed along the tubular structures. The quality and regional distribution of renal blood flow is important in this regard.

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Renal vascular anatomy

The main renal artery branches to form several interlobar arteries, which in turn give rise to a series of arcuate arteries, which pass along the boundary between the cortex and the medulla (Fig. 1). Multiple interlobular arteries arise from the arcuate arteries passing outwards through the medulla to the capsule. It is from these interlobular vessels that the afferent arterioles supplying the glomerular capillaries arise. The glomerular capillaries, which represent the site of renal filtration, in turn drain into efferent arterioles. This unique arrangement constitutes a portal system, since all other capillary systems in the body drain directly into venules.

The efferent arterioles in the outer two-thirds of the cortex branch into a second dense capillary network surrounding the cortical tubular elements known as the pritubular capillaries. The efferent arterioles in the inner third of the cortex, in addition to giving rise to a small number of peritubular capillaries, also give rise to the vasa recta. These capillaries follow a hairpin course deep into the medulla where they lie adjacent to the loops of Henle and the collecting tubules before returning to the cortex (Fig. 2). Both the vasa recta and peritubular capillaries eventually drain into the renal vein and back to the general circulation [4].

Renal blood flow and renal function

The relationship between renal function and systemic haemodynamics is unique. The kidneys receive between 20 and 25% of the total cardiac output (5 l/day) although their combined weight is less than 1% of total body weight. This high renal blood flow has a dual function. It serves primarily to provide blood for filtration since an adequate glomerular blood supply is necessary if the normal excretory function of the kidney is to be maintained. In addition the renal circulation provides oxygen and nu-

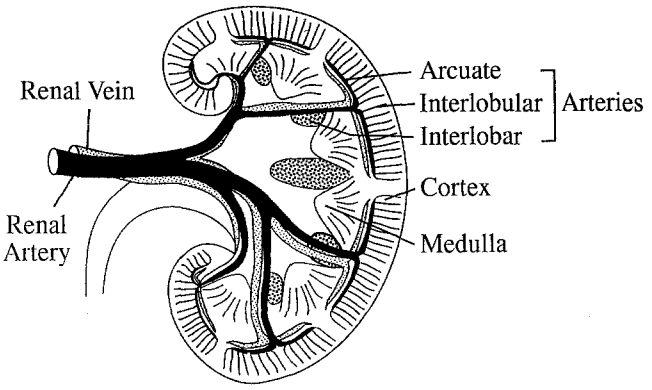

Fig. 1 Pattern of distribution of the renal vessels within the kidney

trients to the renal parenchyma. For this reason alterations in renal blood flow may lead not only to changes in function due to tissue ischaemia but also as a direct consequence to changes in glomerular filtration. The kidney does not remain passive in this relationship but rather reacts to alterations in systemic haemodynamics and in turn interacts with the systemic regulatory mechanisms in order to maintain total and regional renal blood flow at a level consistent with optimal renal function.

Total renal blood flow is normally measured by determination of the renal clearance rate of para-aminohippuric acid (PAH). In man total renal blood flow has been estimated at approximately 1.1 l/min, which is equal to a total daily renal blood flow of 1640 l/day. The kidneys require this phenomenal daily blood flow in order to achieve their primary function of regulation of the internal environment via the delicate balance of filtration and selective reabsorption of plasma constituents which results in urine production. The primary force driving renal filtration is the mean glomerular capillary pressure. Mean glomerular capillary pressure is usually around 50 mmHg or approximately half of the mean systemic arterial pressure. This level is considerably higher than that found in capillaries in other regions, due in the main to the fact that the afferent arterioles leading to the glomeruli are wider and therefore offer less resistance to flow. This positive filtration pressure is opposed by a combination of the capsular hydrostatic pressure and the osmotic gradient across Bowman's capsule, resulting in a final positive filtration pressure of approximately 10 mmHg. As a consequence of these forces the entire body plasma volume is filtered over 60 times/day. Of this volume 99% is subsequently reabsorbed into the peritubular capillaries.

The kidneys maintain a relatively constant renal blood flow over a range of perfusion pressures. This is achieved via a renal autoregulatory mechanism, as the result of which the resistance to flow increases with increases in perfusion pressure maintaining both renal blood flow and glomerular filtration rate at a constant level over a range of mean arterial pressures from 90 to 200 mmHg. There appears to be two elements responsible for mediation of this dynamic regulation, a slow component provided by tubuloglomerular feedback and a faster component that is most likely an intrinsic vascular myogenic mechanism [25]. If the kidney is placed under stress, due to changes in blood flow, the glomerular filtration rate is maintained by a combination of renal autoregulation, sympathetic nervous tone, the juxtaglomerular apparatus secretory activity and endogenous prostaglandin production [26].

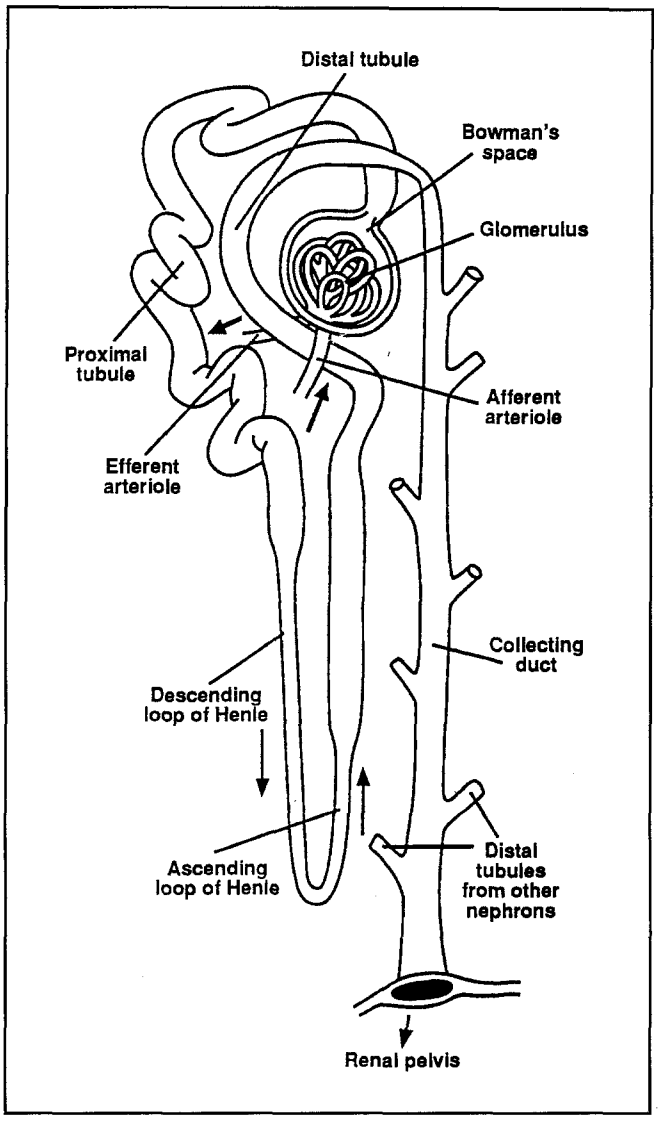

Fig. 2 Structure of the glomerulus

Renal autoregulation is independent of hormonal or neurological influences and is thought to be primarily due to a combination of afferent and efferent arteriolar vasoconstrictor activity [59]. An increase in wall tension, occurring as a consequence of an increase in mean arteriolar pressure, results in an increase in afferent arteriolar tone thereby increasing the resistance to flow and thus keeping the glomerular filtration rate constant despite the change in the perfusion pressure. Conversely a decrease in mean systemic arterial pressure leads to a constriction of the efferent arterioles and hence to an increase in outflow resistance from the glomerulus, again keeping the glomerular filtration constant. Further fine regulation of

blood flow in individual glomeruli may be provided by the tubuloglomerular feedback mechanism in response to the glomerular filtration rate in that glomerulus [23]. This tubuloglomerular feedback loop is mediated by the detection of alterations in chloride ion concentration by the macula densa. Changes in the Cl^- ion composition of the tubular fluid in the region of the macula densa result in alterations in the glomerular haemodynamics of that nephron. Thus as the rate of flow through the ascending limb of the loop of Henle and first part of the distal tubule increases, so glomerular filtration in the same nephron decreases and conversely a decrease in flow increases the glomerular filtration rate. These changes in the glomerular filtration rate are achieved by either constriction or dilatation of the afferent arterioles. The sensitivity of this mechanism appears to be increased when the extracellular fluid volume is decreased and decreased when the extracellular fluid volume is expanded.

Regional distribution of flow

The regional distribution of renal blood flow within the kidney can be determined using a number of techniques. Clearance techniques and electromagnetic flow cytometry give only a single value for renal blood flow. Micropuncture methods, while providing better resolution, are invasive and to not allow precise identification of the anatomical region being studied. The reference microsphere sample technique [30] is presently the most widely used method for measuring the regional distribution of renal blood flow. This technique allows focal measurements to be performed but there is a conflict between the resolution of this technique and the number of microspheres necessary in each sample for statistical accuracy [72]. In addition axial streaming of beads may influence the pattern of flow density, particularly with a larger microsphere. A number of newer modalities used to measure renal blood flow, including positron emission tomography, computed tomography and magnetic resonance imaging, provide a higher degree of spatial resolution than was previously available [40]. More recently the technique of quantitative autoradiography, previously used to measure cerebral and gastrointestinal blood flow [28, 57], has been applied to the measurement of renal blood flow [17]. This new technique has the advantage of allowing the measurement of blood flow in a precisely defined anatomical location with a resolution of 100 μm.

There is some degree of variation in the exact figures for regional flow provided by these different methods of measurement, but there is an overall concordance in terms of the magnitude and pattern of regional distribution.

More than 90% of blood entering the kidney goes to supply the renal cortex, resulting in a cortical perfusion rate of between 500 and 850 ml/min per 100 g tissue depending on the technique used, while the remainder serves to supply the capsule and the renal adipose tissue. There does not appear to be any significant difference in the flow to polar and central regions of the cortex, with a flow to the polar region of 875 ± 57 ml/min per 100 g tissue compared with 926 ± 71 ml/min per 100 g tissue in the central region of the cortex [17]. The overall volume of blood passing from the cortex to the medulla is significantly reduced as a result of a loss of plasma volume due to filtration in the glomeruli. Measurement of medullary blood flow reveals a flow rate of between 100 and 250 ml/min per 100 mg tissue in the outer medulla and 20–45 ml/min per 100 g tissue in the inner medulla. As previously observed in the cortex, there does not appear to be any difference in flow between the polar and central regions of the outer medulla, with recorded flow rates of 246 ± 11 and 272 ± 16 ml/min per 100 g tissue respectively [17].

The low flow rate in the inner medulla, obtained using the different techniques, presents some problems of interpretation. This arises as a result of the vascular anatomy in this region. It has been suggested that countercurrent exchange between the descending and ascending vasa recta may result in an underestimation of flow using the currently available techniques, since there is no accurate definition of effective blood flow in tissues where countercurrent exchange mechanisms are present. Although these limitations may result in an underestimation of "true" absolute medullary blood flow, it does not prevent comparative studies from being performed [41].

Regulation of renal blood flow

Renin, an acid protease, is released from the juxtaglomerular apparatus in response to sodium depletion and alterations in circulating volume. Renin releases the decapeptide angiotensin I by cleavage of the α_2-globulin angiotensinogen. Angiotensin I is rapidly converted to angiotensin II by the plasma-converting enzyme kinase II. The primary concern of the renin/angiotensin system is regulation of body fluid and sodium concentration. Angiotensin II is a very potent arteriolar constrictor and a weak venoconstrictor and, as such, is in part responsible for maintenance of systemic blood pressure. In addition angiotensin II has a direct action on intrarenal flow, eliciting vasoconstriction in efferent arterioles at a lower concentration than that required to cause vasoconstriction in afferent arterioles (Fig. 3).

Angiotensin II has been shown to cause a dose-related increase in blood pressure and a reduction in cortical perfusion [11, 27, 61]. The blood flow to the glomeruli of the juxtamedullary region is only slightly decreased, however [61], and the papillary perfusion rate is completely unaltered [11, 27], It has been suggested that this differential regulation of blood flow throughout the kidney may be mediated via localised differences in prostaglandin concentration and sensitivity [61]. However, there is also evidence to suggest that these respones may be independent of prostaglandins, bradykinin, renal perfusion pressure and endothelial-derived relaxing factor (EDRF) [27].

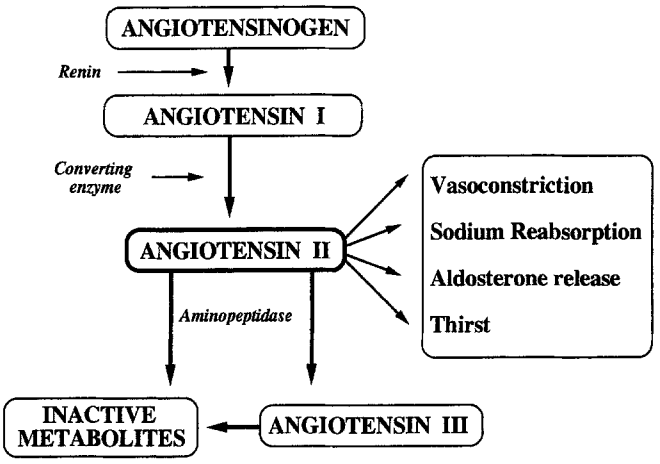

Fig. 3 Renin-angiotensin system

The endocrine hormone atrial natriuretic peptide [ANP-(99-126)] is produced by cardiac atrial cells in response to increased effective circulating volume. The increase in circulating volume results in stretching of the cardiac atrium due to increased venous return. Among the actions of ANP are vasodilatation, a reduction in vasopressin release, naturesis and diuresis. The latter effect is thought to be due in part to dilatation of the intrarenal vasculature. ANP tends to redistribute the renal blood flow towards the outer cortex and this may contribute to its natriuretic action. Decreased collecting tube Na^+ reabsorption could in part be a consequence of increased medullary blood flow and a reduced corticomedullary solute gradient. Receptors for ANP are located in glomeruli and other areas of the renal vasculature [9] and high doses of ANP increase glomerular filtration [18]. It is of note, however, that elevated concentrations of ANP within the physiological range that cause a naturesis may do so without detectable effects on the glomerular filtration rate and renal blood flow [6]. In addition, although atriopeptin can increase medullary blood flow, the exact relationship between changes in blood flow and the increase in urine flow or in sodium secretion remains controversial [54]. It has been suggested that atriopeptin exerts insufficient effect on the renal vasculature to cause natriuresis unless plasma levels become quite high. A further natriuretic peptide, urodilantin [ANP-(95-126)], with a similar structure and range of activities has been isolated from the urine. It is synthesised within the kidney. Urodilantin is found in the urine but not in the plasma and has a natriuretic potency similar to that of ANP [19]. ANP also antagonises the renal vasoconstricting actions of norepinephrine by dilating the afferent arterioles [33].

Endothelin is a potent vasoconstrictor peptide, synthesised by vascular endothelial cells, whose actions are thought to be mediated via leukotrienes [16]. Systemic administration of endothelin causes a transient fall in blood pressure followed by a sustained increase [42, 73]. In the kidney, the vasoconstrictive actions of endothelin lead to an increase in renal resistance and a reduction in vessel diameters within the renal vascular bed, with a 70% reduction in glomerular blood flow [16]. The exact physiological role of endothelin in the regulation of regional renal blood flow remains to be determined.

Stimulation of the renal nerves causes a marked decrease in renal blood flow. The renal sympathetic innervation is connected primarily to the afferent renal arterioles and it is thought that their effect is mediated by α_1-adrenergic receptors and to a lesser extent postsynaptic α_2-adrenergic receptors. There is some tonic discharge in the renal nerves at rest in both animals and humans. Mild stimulation of the renal nerves leads to a reduction in the blood flow to the superficial nephrons and increases the blood flow to the juxtamedullary nephrons, which in turn leads to sodium retention. Some of these effects may be mediated indirectly via the release of renin and the secondary production of angiotensin as a result of direct renal nerve stimulation acting primarily via β_1-adrenergic receptors at the juxtaglomerular apparatus.

Renal vasoconstriction can occur in response to a decreased discharge in the baroreceptor nerves, which occurs in response to a fall in systemic blood pressure [68]. Hypoxia is also a stimulus for renal vasoconstriction, but only when arterial pO_2 falls to less than 50% of its normal level. The response is mediated via chemoreceptors which stimulate the vasomotor centre to produce renal vasoconstriction when the renal nerves are intact. Catecholamines, which are released in response to stress, constrict the renal vessels. Low doses of adrenaline and noradrenaline have a greater effect on the efferent than the afferent arterioles so that glomerular capillary pressure and consequently the glomerular filtration rate are maintained while renal blood flow is decreased; large doses, however, depress the glomerular filtration rate. This differential effect on renal blood flow and glomerular filtration is utilised in the use of low-dose (1 μg/kg per min) dopamine to protect the kidneys during episodes of shock or sepsis, in which generalised vasoconstriction in response to alterations in the systemic circulation might otherwise have led to ischaemic renal damage [44]. Decreases in renal blood flow have also been observed during exercise and to a lesser extent on rising from the supine to the standing position.

PGE_1 and PGE_2 are both vasodilators and are produced by the kidney in increased amounts when the renal perfusion is threatened. The pharmacological inhibition of renal prostaglandin synthesis has no effect on renal blood flow in normal individuals but can lead to large falls in renal blood flow in individuals who have vasoconstrictor stimuli to the kidney, such as occur when effective circulating volume is decreased. In addition renal prostaglandins appear to modulate the alterations in renal medullary haemodynamics which are observed in response to changes in renal perfusion pressure. Indeed, an intact renal prostaglandin system is necessary for the full expression of the medullary haemodynamics and natriuretic responses which normally occur as a consequence of increases in renal perfusion pressure [55].

The antivasconstrictor role of the renal prostaglandins is a cortical effect, with PGE_1 being the most important. Hence, decreased effective circulating volume leads to increased cortical prostaglandin synthesis. Thromboxane A_2 unlike other prostanoids is a vasoconstrictor. Normally only small quantities of thromboxane A_2 are produced but its synthesis increases following prolonged ureteric obstruction and thus may be responsible for reducing the blood flow to the ineffective, obstructed kidney by inducing renal vasoconstriction [50].

When the effective circulating volume is decreased, blood pressure is maintained by increasing sympathetic nervous activity. This causes vasoconstriction in most parts of the body, including the kidney, but with the exception of the brain. Thus the sympathetic nerves to the afferent renal arterioles can override the autoregulatory mechanism and lower the renal blood flow. Vasoconstrictor stimuli to the kidney, however, lead to increased renal cortical synthesis of vasodilator prostaglandins (PGE_1 and PGE_2) so that generally the renal blood flow remains adequate for glomerular filtration since efferent arteriolar vasoconstriction occurs to maintain filtration pressure, unless the mean blood pressure falls below 80 mmHg. Below this level the renal blood flow falls dramatically, renal function is impaired and unless there is a prompt restoration of the effective circulating volume there is danger of acute renal failure. In severe volume depletion the stimulus for renal vasoconstriction is so intense that the renal blood flow may not be restored by measures to restore the circulatory volume and permanent renal failure may occur due to anoxia and necrosis.

Fifteen percent of nephrons have long loops of Henle which pass into the medulla (juxtaglomerular nephrons), while 85% have short loops which barely reach the medulla (cortical nephrons). There is evidence that in rats on a low-sodium diet filtration is reduced in cortical nephrons and increased in juxtaglomerular nephrons. Conversely filtration in cortical nephrons is increased and in juxtaglomerular nephrons is reduced on a high-sodium diet. The high-sodium diet presents the need to excrete sodium and hence the distribution of the filtration could be directed to the superficial (short loop of Henle) nephrons and vice versa on a low-sodium diet. It is possible that this distribution of blood flow to the two types of nephrons according to the need for sodium excretion or sodium conservation may be mediated by the intrarenal haemodynamic actions of angiotensin II although this remains a controversial topic [61]. In addition bacterial pyrogens are recognised as a cause of renal vasodilatation and a high-protein diet increases renal blood flow.

In most organs and tissues of the body the main purpose of the blood supply is to provide O_2 and remove CO_2 and other products of metabolism. The O_2 consumption of the human kidney is about 18 ml/min. The renal cortex receives far more O_2 than it requires, so that arteriovenous O_2 differences are only 1–2%. This occurs because a high renal blood supply exists to maintain the glomerular filtration rate. In addition, there is evidence to suggest that there is significant juxtaglomerular shunting of oxygen within the juxtaglomerular vasculature. This most likely occurs between the interlobular vessels, which are arranged in a countercurrent fashion and represent quantitatively the largest area of contact between the arterial and venous systems within the renal cortex [58]. Surprisingly if the renal blood flow is reduced, the arteriovenous O_2 difference does not increase until the cortical flow is down to about 150 ml/min per 100 mg tissue. This is because the blood flow determines the rate of filtration and more than 50% of the O_2 consumption is used for sodium reabsorption. So if the filtration rate is reduced reabsorption can occur at a lower rate and O_2 consumption is also reduced.

In spite of very high blood supply the medullary blood supply is no more than adequate for the supply of oxygen to the medullary cells because the vasa recta arrangement causes oxygen to short circuit the loops of Henle. O_2 and CO_2 undergo countercurrent exchange in the vasa recta so that the vasa recta are rather inefficient suppliers of O_2 and removers of CO_2.

Effect of pathophysiological conditions on regional renal blood flow

There are a variety of pathophysiological conditions which alter intrarenal haemodynamics and may thus compromise renal function. Nephrectomy, ureteric obstruction, renal artery stenosis, diabetes and ischaemia and reperfusion injury are among the most important of these.

Nephrectomy

Renal excretory function is divided equally between the two kidneys, assuming normal function. Nephrectomy leads to a sudden decrease in excretory capacity. This in turn initiates a compensatory process which results in hypertrophy of the remnant kidney and a progressive improvement following the acute reduction in renal excretory function. Within 3–4 months these alterations may restore the renal mass to up to 80% of normal and enhance the glomerular filtration capacity of the remnant kidney particularly in younger individuals [53]. Removal of renal tissue has been shown to cause development of proteinuria and eventual glomerular sclerosis. Injury to remnant glomeruli has been attributed to adaptive alterations in glomerular haemodynamics function, including increases in capillary pressure and flow [46]. The reduction in renal mass is associated with an increase in the production of vasodilating prostaglandins and a consequent rise in renal blood flow. At the same time there is a degree of impairment of the autoregulatory system and an increase in the activity of the renin-angiotensin system. It is thought that impaired autoregulation increases the vulnerability to hypertensive glomerular injury possibly by permitting the transmission of coexistent systemic hypertension to the glomerular capillaries [7, 8].

There is strong evidence to suggest that vasodilating prostaglandins mediate some, if not all, of the haemodynamic changes observed in the rat remnant kidney model. It has been reported that reducing the dietary protein intake, thereby decreasing the production of vasodilating prostaglandins [12], attenuates renal vasodilation, improves renal autoregulatory ability and decreases the activity of the renin-angiotensin system [7]. An alternative hypothesis suggests that, although prostaglandin production may impair renal autoregulation, it is not responsible for its mediation, nor is it responsible for the mediation of the renin-angiotensin system in the remnant kidney of the rat. It is thought rather that prostaglandin-independent mediators of altered calcium entry or kinetics in the preglomerular vasculature and in juxtaglomerular apparatus cells of remnant kidneys are responsible for the impairment of renal autoregulation and increased renin secretion [22].

Renal ablation can affect, or be affected by, existing renal pathologies. Nephron loss in the nephrotic kidney can cause increased remnant nephron protein excretion, independent of the primary disease process. It has been found that the increased protein excretion cannot be accounted for by glomerular haemodynamic changes alone [46] and therefore must reflect further injury to the glomerular capillary wall. It has been suggested that glomerular capillary wall damage may be exacerbated when injured glomeruli are forced to undergo compensatory hypertrophy. Studies in normal rats subjected to renal ablation show that epithelial cell hypertrophy is a component of remnant glomerular hypertrophy [52]. Deranged growth of damaged epithelial cells can thus account for further impairment of the permeability barrier in remnant glomeruli of nephrotic rats exposed to renal ablation [46].

Five-sixths nephrectomy (unilateral total nephrectomy with contralateral partial nephrectomy, preserving a one-third kidney remnant) can inhibit deterioration of renal function, and renal tubular damage, due to mercury chloride-induced acute renal failure. A moderate inhibitory effect was also noted with uninephrectomy [62]. The mechanisms involved cannot be completely explained by either hypertrophy or acceleration of intracellular energy metabolism and it is thought that intrarenal redistribution of blood flow may play an important role.

Ureteric obstruction

Numerous authors have demonstrated that obstructive renal failure is associated with profound alterations in renal blood flow. The renal damage associated with urinary blockage is the result of a sequence of pathophysiological events initiated by outflow obstruction. Both partial and complete ureteric obstruction are associated ultimately with a reduction in renal blood flow, which may lead eventually to renal insufficiency of ischaemic aetiology [65].

Following ureteric obstruction, there is a temporary elevation, followed by a sustained reduction in the perfusion of the ipsilateral kidney [3, 29, 31, 37, 51, 65] and a compensatory increase in the perfusion of the contralateral kidney [34, 65]. These changes in total renal blood flow are accompanied by alterations in intrarenal flow, characterised by a shunting of flow from the outer to the inner cortical zones [3, 13, 21, 29, 56, 70].

Partial ureteric obstruction significantly decreases blood flow to the ipsilateral kidney (51 vs. 26%) and increases blood flow to the contralateral kidney (49 vs. 74%). In the ipsilateral kidney there is a decrease in outer cortical blood flow (57 vs. 76%) and a concomitant increase in inner cortical blood flow (35 vs. 18%). A similar, if somewhat less marked, shunting of blood from the outer to the inner cortex is seen in the contralateral kidney [21].

The exact aetiology of the changes remains to be elucidated but a number of mechanisms have been identified. The transient increase in renal blood flow following obstruction is due to decreased afferent arteriolar tone and a fall in renal vascular resistance. This effect is mediated by the release of vasoactive hormones and may persist for up to 3 h. Prostaglandins are thought to be primarily responsible for this increase in blood flow and may also mediate increased renin secretion [60]. A rise in histamine concentration following acute ureteral obstruction is known to abolish the vasodilation [2]. Renal vasoconstriction occurs approximately 4 h after the onset of obstruction and there is a concurrent rise in the synthesis of thromboxane A_2, which is thought to mediate this change [50]. Several reports have demonstrated an increase in the release of renin by obstructed kidneys, indicating that angiotensin II may be the humoral mediator of vasoconstriction [47, 66]. Support for this concept is provided by the observation that the administration of converting enzyme inhibitors results in improved renal function following the release of complete ureteric obstruction in rats [56, 71]. Changes in the levels of prostaglandin have also been observed following ureteric obstruction [39, 50]. Synthesis of the vasoconstrictive prostaglandin thromboxane A_2 and the vasodilatory prostaglandins PGE_2 and PGI_2 are all increased during ureteric obstruction and the final haemodynamic effect is a result of interaction of these vasoactive agents [39].

The onset of obstructive uropathy is associated with early dilatation of the proximal and distal tubules. This dilatation is rapidly followed by cortical thinning and proximal tubular atrophy. From recent studies it has become clear that changes in renal function cannot be accounted for by increased pressure alone, as these changes are short lived, with a return to normal values as the collecting system progressively dilates. Tubular atrophy and cortical thinning, however, continue to progress for a further 4 weeks, despite renal pressure returning to normal levels [65].

In an animal model of partial ureteric obstruction, relief of obstruction after 4 weeks did not restore the renal circulation to its pre-obstructive profile [21]. In the same model relief of obstruction did lead to a significant

improvement in glomerular filtration [35]. This difference may occur as a consequence of a divergence in the distribution pattern of renal blood flow and glomerular filtration following ureteric obstruction. The distribution of blood flow and glomerular filtration are significantly different following the release of complete obstruction [24, 70], with perfusion being more markedly decreased in the outer cortex and filtration most significantly impaired in the inner cortex. Thus the relief of obstruction may lead to an improvement in filtration without restoration of intrarenal blood flow to its pre-obstruction profile. Animals obstructed for 1, 2 or 3 weeks have permanently decreased renal function to approximately one-half, one-third and one-sixth of normal, respectively. If captopril is administered during the obstructive period there is a marked decrease in loss of renal function to only 40% of control at 1 week, 50% at 2 weeks and 50% at 3 weeks [45].

Renal artery stenosis

Renal artery stenosis is well established as a cause of hypertension, ischaemia and renal impairment. The role of the kidney in the pathophysiology of hypertension was first suggested in 1834, when Goldblatt and his co-workers demonstrated that decreased renal perfusion caused hypertension in dogs, and that restoration of renal blood flow cured that hypertension [20]. Either one or both renal arteries may be occluded. If one is affected, ipsilateral renin production is high while sodium excretion and urine production are low. Contralateral renin production is low. Peripheral renin activity is initially elevated and anti-angiotensin therapy is effective. Progressively the renin levels decrease; hypertension, however, remains responsive to angiotension blockade. Finally, plasma volume becomes expanded and hypertension becomes unresponsive to anti-angiotensin agents. If both kidneys are involved and there is no normal contralateral kidney, systemic renin and its production is low, but the plasma volume is expanded and there is hypertension. There is poor responsiveness to inhibition of the renin-angiotensin system [68].

Greater than 95% of renal artery stenosis is secondary to either atherosclerosis or one of the fibromuscular dysplasias. Atherosclerosis is the most important common cause of renovascular hypertension. Both renal arteries are involved in approximately 50% of cases. Fibromuscular dysplasia accounts for the majority of significant non-atherosclerotic renal artery stenosis. These diseases are classified best according to the portion of the arterial wall that appears to be abnormal under the light microscope [68].

The earliest histological change associated with renal ischaemia due to stenosis is a progressive loss of glomerular volume. Progressive degrees of ischaemia result in the appearance of areas with tubular atrophy, interstitial fibrosis and arteriolar thickening. There are reports that these changes are reversible [38]. Glomerular hyalinisation only occurs at severe degrees of ischaemia and is the last change noted prior to infarction of the kidney. The changing renal haemodynamics have been well documented [48]. There is a progressive loss of glomerular volume with increasing degrees of ischaemia; with more severe ischaemia glomerular architecture becomes disrupted, uncoiling the glomerular vascular tuft and exposing blind-ending vessels. This may eventually lead to glomerular hyalinisation. Progressive ischaemia results in only a slight compensatory increase in blood flow to the contralateral kidney [48]. This increase in flow is uniformly distributed to all regions. In contrast, on the ischaemic side there is a redistribution of regional blood flow with increasing ischaemia. A higher percentage of overall renal blood flow is shunted to the medulla relative to the outer cortex. Medullary blood flow is therefore conserved relative to the cortex, though absolute blood flow to the medulla is slightly decreased. This redistribution of blood flow undoubtedly influences glomerular filtration and tubular reabsorption and presumably plays an important role in the regulation of sodium filtration, reabsorption and excretion.

The interrelation of renal artery disease and hypertension/ischaemia is mediated by the renin-angiotensin-aldosterone system, which regulates vascular tone and plasma volume. As mentioned previously, renin secretion is stimulated by decreased perfusion pressure, decreased sodium load, decreased sodium concentration, β-sympathetic outflow and a number of prostaglandins. Through a series of enzymatic steps renin leads to the production of angiotensin II. The actions of angiotensin II are potent arteriolar and weak venous vasoconstriction, direct sodium-retaining effect in the ascending portion of the loop of Henle and stimulation of aldosterone production. Aldosterone, a steroid hormone produced by the adrenal zona glomerulosa, increases plasma volume by stimulating sodium retention. There are two available agents to contravene the renin-angiotensin system: saralasin, a competitive angiotensin II antagonist with weak agonist activity, and captopril, a converting enzyme inhibitor without agonist activity [68].

It is widely accepted that revascularisation of the ischaemic malfunctioning kidney, with restoration of renal function, is possible and preferable to nephrectomy in many cases [38, 44]. Preservation of all potentially functional renal parenchyma is worthwhile, but inappropriate revascularisation of an unsalvageable kidney may be hazardous to a patient who might be managed effectively by simple nephrectomy or no treatment [48]. There is considerable controversy with regard to the factors that are of prognostic value to the surgeon when considering a revascularisation procedure. It has been established that the time interval between occlusion and operation is not of prognostic significance [49]. Nephron viability can be maintained by arterial perfusion pressures which are so low that glomerular filtration does not occur; in man subfiltration pressures are provided by a rich collateral circulation that develops within hours after total occlusion of the renal artery. Neither is the size of the kidney of significant prognostic value. Histological changes,

particularly changes involving the glomerular architecture observed on pre-operative or intra-operative renal biopsies, are used by some to predict which kidneys are salvageable [38].

Diabetes

Increased pressure in the microvasculature, such as in the glomerular capillaries, resulting from decreased vascular resistance and associated increased blood flow, may play an important role in diabetes [74]. Autoregulation of the renal blood flow is impaired and glomerular filtration rate and renal blood flow are increased after the onset of poorly controlled diabetes in both humans and animals. Subsequently glomerular filtration and renal blood flow fall below normal levels as a result of mesangial hypertrophy and renal failure ensues [43]. This increase in the glomerular filtration rate occurs as a consequence of an imbalance between afferent and efferent arteriolar resistance, which leads to increased glomerular capillary hydraulic pressure, rather than an increase in blood flow per se.

Recent studies have demonstrated that the increased renal vascular permeability for albumin associated with diabetes is due to increased metabolism of glucose to sorbitol and is prevented by inhibitors of aldose reductase [67]. Basement membrane thickening of glomerular capillaries in rats and dogs has also been associated with increased metabolism of glucose and galactose to their respective polyols, sorbitol and galactitol [32]. Moreover, increased glomerular filtration rate and proteinuria in diabetic rats are reduced by inhibitors of aldose reductase [5]. Although there is little firm evidence as yet to establish a relationship between blood flow changes in diabetes and increased polyol metabolism, renal blood flow has been reported to be increased by acute elevations in glucose levels [10]. Finally, recent studies indicate that in diabetic rats blood flow is increased in tissues that are sites of vascular disease in humans with diabetes and that these blood flow changes and increases in vascular albumin permeation and glomerular filtration rate are prevented by inhibitors of aldose reductase [64].

The pathophysiological significance of the decrease in vascular resistance, and the associated increase in blood flow in diabetes, is that arterial pressure will be transmitted further downstream into terminal arterioles and capillaries. An increase in microvascular pressure would tend to increase the rate of vascular permeation of plasma constituents that normally permeate the microvasculature without any change in the permeability characteristics of the vessel wall per se.

Protein consumption, prostaglandin metabolism and ANP have been reported to modulate both the renal haemodynamic and structural changes associated with diabetes. The nature of the metabolic and hormonal imbalances, however, that initiate diabetes-induced haemodynamic changes in the kidney remains unclear [64].

Ischaemia-reperfusion

A characteristic series of changes occurs in the kidney after a significant period of ischaemia followed by reperfusion. A marked decrease in glomerular filtration and inner medullary blood flow is seen, with relative preservation of cortical and total renal blood flow. Ten minutes after reperfusion, the peritubular capillary of the inner stripe of the outer medullary becomes packed with red blood cells [69]. This capillary sludging gives rise to a dark discoloration at the corticomedullary junction. This is a consistent feature of the post-ischaemic, unprotected kidney and is known as the "blue line" phenomenon [15]. It has been shown that post-ischaemic renal failure is associated with this medullary perfusion defect [1, 63]. The lesion, which is caused by red blood cells being trapped in the peritubular capillaries of the inner stripe of the outer medulla, may be prevented in animal models by sodium bicarbonate treatment [15, 36].

Ischaemia results in an influx of calcium into the cell with activation of phospholipase, which degrades the lipid bilayer of the cell membrane and further increases its permeability. Continued action of the phospholipases results in membrane disruption. Toxic lipid by-products from membrane degeneration also potentiate further membrane destruction. There is a disruption on mitochondrial respiration, lack of energy production and increased free radical production, as intracellular calcium increases and diffuses into the mitochondria; all of these combine to destroy the membrane further. Not only may the membrane be destroyed by these mechanisms during the ischaemic period but its destruction may also be enhanced when the ischaemia is corrected and reperfusion is established since calcium in conjunction with free radicals injures mitochondria and reduces cellular respiration.

Under the normal conditions of respiration limited quantities of free radicals are produced by the oxidation of nicotinamide adenine dinucleotide phosphate (reduced form NADPH) to nicotinamide adenine dinucleotide phosphate (NADP). Their concentration is kept at a minimum by naturally occurring free radical scavengers. In the presence of limited oxygen supply, however, mitochondria are required to increase their workload and the production of free radicals markedly increases. Free radicals induce lipid peroxidation and in the presence of calcium cause mitochondrial dysfunction.

The most significant free radical production, however, occurs following the re-introduction of oxygen which occurs as a result of reperfusion. In the presence of ischaemia, regeneration of ATP is limited and hypoxanthine accumulates as a consequence of the degradation of high-energy phosphates (ATP) to AMP and subsequently to hypoxanthine. During reperfusion the hypoxanthine is converted to xanthine by xanthine oxidase and this results in oxygen free radical generation [44]. The excessive generation of oxygen free radicals may lead to cell swelling, increased capillary permeability and medullary hyperaemia [36].

Toxic levels of ammonia accumulate in the kidney and renal vein during ischaemia; these are produced by the action of the glutaminase enzyme system in the tubular cells at the corticomedullary junction. This enzyme converts glutamine to glutamic acid, leading to the production of free ammonia. During ischaemia, glutaminase is not initially inhibited and production of ammonia continues, leading to toxic levels. Ammonia is nephrotoxic, causing inhibition of renal uptake of oxygen and *p*-aminohippuric acid and reducing creatinine clearance. Urinary alkalinisation inhibits the main part of the glutaminase enzyme system and therefore prevents potentially toxic effects of ammonia accumulation during ischaemia [14, 36].

Conclusion

Renal regulation and regional distribution of renal blood flow form an essential part of the body's homeostatic processes. Interruption of normal renal function has wide-ranging effects beyond the direct consequences on the renal parenchyma. Indeed the consequences of either partial renal damage or surgical obstructive or ischaemic events directly affecting one kidney are not simply limited to that kidney but may also involve the contralateral organ and other body systems, as a result of hormonal and neurally mediated responses. Reversal of the renal insult does not always lead to a full restoration of normal renal function.

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