NEFROLOGIA. Vol. XII. Supl. 4. 1992

Endothelial and mesangial dysfunction in acute renal failure

G. H. Neild
Department of Renal Medicine, Institute of Urology and Nephrology, University College, London.

1. Introduction

There are two phases of acute renal failure (ARF) that should be distinguished: the «induction» phase as GFR falls toward zero, and the «maintenance» phase when acute tubular necrosis is established and GFR remains at zero. They need to be considered separately as different mechanisms may be involved. Therapy aimed at preventing ARF requires comprehension of the pathogenesis of the induction phase.

Although many of the mediators are still unknown there are tantalising clues. Why should volume/salt loading protect agains ARF and even more so why should volume contraction render the kidney exquisitely susceptible to further nephrotoxic insults? If physicians and surgeons could remember this and scientists understand it, established ARF would receed as a clinical problem.

In both clinical and experimental examples of ARF, a reduction in renal blood flow (RBF) leading to renal ischaemia is a major factor during the initiation of injury. The reason why oliguria persists when renal blood flow is restored is unclear. Generally in man there are many factors that summate in the induction of ARF. To date, most experimental models of acute tubular necrosis (ATN, have involved a massive single insult, which bears little relationship to the onset of ATN in man. Recently multifactorial models have been introduced which perhaps more faithfully simulate the human situation[1,2].

I will discuss vascular factors in the induction and maintenance of ARF. There are two major considerations —vascular tone and vascular pathology. Although these will be discussed separately they are closely related.

2. Physiology of the kidney

2.1. *Glomerular filtration*

When renal blood flow is decreased, effective glomerular hydrostatic pressure for filtration may be maintained by an increase in efferent arteriolar tone relative to afferent tone. If the hydrostatic pressure falls below a critical level, filtration will cease even though blood still flows through the glomerular capillary circulation. The glomerular filtration rate (GFR), depends on the total capillary surface area available for filtration, as well as the rate of plasma flow. The permeability of the GBM to crystalloids, ie. the effective hydraulic permeability (k), could in theory change in response to injury, although this can not be measured directly. However the ultrafiltration coefficient (Kf), which is the product of the total capillary surface area available for filtration and k, can be measured.

It is important to emphasise the role of Kf, since reduction in this quantity may play a vital role in the maintenance of the reduced GFR in acute renal failure. Vasoconstrictors such as angiotensin, not only increase efferent arteriolar tone but cause mesangial cell contraction which will reduce the effective capillary surface area, ie. Kf[3].

Thus, glomerular ultrafiltration is controlled by arteriolar and mesangial tone. These, in turn, are partly regulated by the juxta-glomerular apparatus (IGA) as part of the tubulo-glomerular feedback system[4].

In the maintenance phase of ARF both vascular and tubular elements play a role. RBF may be totally restored, but blood flow and pressure in the glomerulus may remain insufficient for effective glomerular filtration to occur[5-7].

2.2. *New Developments in regulation of glomerular haemodynamics*

2.2.1. Endothelium-derived relaxant factor (EDRF)

For several years it has been recognised that a number of vasodilators (such as acetylcholine, bradykinin) are endothelium-dependent[8,9]. In response to such agonists the endothelium releases an EDRF, whose biological action is virtually indistinguishable from nitric oxide (NO)[10]. NO is both a potent vasodilator and inhibitor of platelet aggregation and adhesion[11,12]. In these ways it is very similar to the endothelium-derived prostacyclin, and the two act synergistically[11]. NO is thought to have a local paracrine action, acting directly on adjacent smooth muscle cells. It

Correspondencia: Dr. G. H. Neild.
Departament of Renal Medicine.
University College, London.

is also released in response to shear stress and transmural pressure and co-ordinates blood flow in resistance vessels[13].

NO acts on vascular smooth muscle by activating guanylate cyclase which leads to a rise in intra-cellular cyclic-GMP[14]. NO is released during the metabolism of L-arginine to L-citrulline by the enzyme NO-synthase. Already two distinct types of enzyme are recognized; the first is constituitively expressed, is present in vascular endothelium and permits the release of NO in seconds, the second is induced by inflammatory cytokines (IL-1, TNF) and is present in macrophages and vascular smooth muscle. Once the latter is induced there may be sustained release of NO[15].

The renal vasculature dilates in response to endothelium-dependent vasodilators, and constricts in response to specific competitive inhibitors of NO-synthase (such as the L-arginine analogue L-NMMA), which in turn suggests that basal release of NO modulates renal vascular tone[16]. Following intravenous infusion of acetylcholine urinary levels of c-GMP increase in parallel with the haemodynamic changes and this response is blocked by L-NMMA[17].

2.2.2. Endothelium-derived constricting factors

Endothelin-1 is a 21 amino acid peptide with potent and sustained vasoconstrictor activity. Endothelin is released from endothelium in response to physiological stimuli such as hypoxia and increased transmural pressure. It is a potent constrictor of the renal vasculature. Micropuncture studies have shown that it increases the resistance of both afferent and efferent arterioles and lowers both single nephron GFR and Kf[16, 18].

2.2.3. Mesangial cell contraction

Mesangial cells are modified smooth muscle cells and contract in response to many vasoconstrictors[19-21]. They produce a number of vasoactive factors including vasodilatory prostaglandins, thromboxane A_2 and PAF. For example, mesangial cell contraction in response to angiotensin II may be difficult or impossible to demonstrate *in vitro*, until the cells are treated with a cyclooxygenase inhibitor, since the angiotensin II stimulates the release of vasodilatory prostaglandins which offsets the contraction[20]. Mesangial cells contain inducible NO-synthase and produce NO, and also have high-avidity binding sites for endothelin.

The list of compounds that cause a fall in Kf is longer than for mesangial contraction since some like parathyroid hormone and prostacyclin act by stimulating the renin-angiotensin system, i.e. induced angiotensin-mediated contraction of mesangial cells. The list of compounds causing mesangial contraction increases. Recently cyclosporin[22], adenosine[23] have been added to the leukotrienes[24] and, perhaps above all, endothelin[16].

On the other hand a number of drugs will inhibit mesangial contractility, such as isoproterenol, dopamine, atriopeptins and nitroprusside and these appear to act by raising intracellular levels of c-AMP and c-GMP[25].

2.3. *Control of Renal Blood Flow*

2.3.1. Cortical Blood Flow

The kidneys have one of of the highest blood flow rates per unit tissue mass in the body: although they represent less than 0.5 % of the body mass, they receive about 20 % of the cardiac output. In general, renal blood flow per gram of tissue declines progressively from outer to inner cortex. Glomerular density shows a similar gradient. This ensures that the outer cortical glomeruli have a large flow of plasma to filter.

The tone in the arterioles is influenced by several vasoactive systems including sympathetic nervous system, renin-angiotensin, prostaglandins and thromboxanes[26]. The role of paracrine mediators such as neuropeptides and NO[27] is still being explored.

Evidence of arteriolar reactivity has come from micropuncture studies of glomerular haemodynamics, from direct observation of vessels, and from isolated vascular segments[5, 28]. The various renal resistance vessels show quite different reactivity. Thus of constrictor agents, noradrenaline has a similar effect on interlobular arteries and both afferent and efferent arterioles, while angiotensin probably acts preferentially on the efferent arteriole[28, 29]. Of dilator agents, acetylcholine acts on all three vessels, dopamine just on the arterioles[5, 28]. More recently, vasoconstrictor effects in isolated perfused rabbit afferent arterioles have illustrated how very complex the regulation is. By perfusing arterioles with and without the glomerulus and juxtaglomerular apparatus attached, it was found that either angiotensin II or an adenosine-1 agonist could only constrict the arterioles when they were attached to the glomerulus, whereas the two together could constrict the isolated vessel[30]. In response to changes in perfusion pressure, the kidney auto-regulates both renal blood flow and GFR this auto-regulation way also be demonstrated in both denervated and isolated perfused kidneys. As will be discussed later, loss of auto-regulation is a regular feature of acute tubular necrosis. NO may have an important role to play in autoregulation. In the rabbit kidney, endothelium-dependent vasodilatation has been shown to have a heterogenous effect exerting a preferential effect of afferent glomerular arterioles and thereby maintining GFR as mean arterial blood pressure (renal perfusion pressure) falls[31]. Endothelium-*in*dependent vasodilators (prostacyclin and nitroprusside) caused equivalent dilatation of afferent and efferent arterioles so that GFR fell as mean arterial blood pressure fell[31]. This differential sensitivity of the glomerular arterioles to NO has been confirmed by others[32].

2.3.2. Medullary Blood Flow

The medullary blood supply is derived entirely from efferent arterioles of the inner cortical glomeruli[33]. These arterioles descend into the medulla and divide into the descending vasa rectae, which themselves descend in vascular bundles and at intervals leave to supply the adjacent peritubular capillary plexus. In the region of the thick ascending limb of loop of Henle the plexus is very dense.

The capillary plexus drains upwards via the ascending vasa rectae which empty into the arcuate veins at the cortico-medullary junction. Both descending and ascending vasa rectae are resistance vessels, which regulate medullary blood flow. Ascending vessels have very thin walls and are potentially very susceptible to compression by swollen tubules[33].

There are many methodological problems measuring medullary flow, but using non-diffusable indicators, such as radio-labelled albumin or red cells, or rubidium ions the medullary flow accounts on average for 10-15 % of total renal blood flow[34]. Flow in the outer cortex is approximately six-fold greater than outer medulla and twenty-fold greater than inner medulla. Auto-regulation occurs in the medulla.

In the kidney there are gradients of oxygen availability. Medullary tissue pO_2 is much lower than arterial pO_2, and in animals medullary pO_2 is in the range of 10 mmHg. The cortico-medullary gradient pO_2 is maintained by countercurrent diffusion of O_2 between arterial and venous branches of the vasa rectae[35, 36]. Indirect evidence suggests that the thick ascending limb of the loop of Henle operates on the verge of hypoxia[35].

3. Renal ischaemia —Changes in renal blood flow in response to injury

3.1. *Reduction in GFR during induction of renal failure*

3.1.1. Response to Compromised Renal Perfusion (Pre-renal Failure)

The immediate increase in renal vascular resistance in response to hypovolaemia and heart failure is mediated by massive sympathetic activity with secondary activation of the renin-antiogensin system. Although renal blood is decreased, glomerular filtration (GFR) may be preserved initially by a disproportionate rise in efferent arteriolar tone, which is mediated in particular by angiotensin. In addition the increased tone in the pre-glomerular vessels is offset by local, renal production of vasodilatory prostaglandins[37]. For these reason the use of either angiotensin-converting enzyme inhibitors or inhibitors of cyclo-oxygenase, in patients with renal hypoperfusion, may cause a precipitous decline in GFR and sometimes oliguria.

Following controlled haemorrhage, in experimental models, there is a preferential reduction in outer cortical flow, although neither the quantity nor mechanism is know[34]. This redistribution is present in denervated kidneys. When ischaemia is induced by infusion of norepinephrine or angiotensin, or by renal nerve stimulation there is no redistribution although total blood flow is reduced by 50 %; with hindsight these features may be explained by loss of NO activity in hypoxic endothelium.

Changes in sodium balance also affect regional blood flow; in summary, sodium depletion leads to a decrease in absolute and fractional outer cortical perfusion and vice versa with sodium expansion[34].

The techniques used for measuring regional perfusion all have methodological problems: those normally used are inert gas washout or the more recent freeze-dissection washout, or infusions of radio-labelled microspheres[5].

3.1.2. Regional Variations in renal perfusion leading to established renal failure

Initially, hypoperfusion leads to a relative reduction in flow to the outer cortex (physiological hypoperfusion). However when more severe, medullary blood flow is reduced and ischaemic damage to the adjacent tubules occurs[38-40]. Even so there is a disproportionate decrease in GFR compared with blood flow.

In established ATN, there is a reduction in medullary blood flow of greater than 50 % (shown by microsphere techniques, hydrogen clearance, Rb extraction) even when blood flow to the outer cortex is restored. In a recent model of blood flow following 60 minutes of renal ischaemia, measured by single-fiber laser-Doppler flowmetry, flow decreased in superficial cortex to 60 % of pre-ischaemia value and to 16 % in outer medulla. The latter was associated with marked red cell trapping. If the venous haematocrit was reduced before ischaemia, then trapping was largely avoided and the fall in medullary blood flow was not seen[41].

The precise role played by endothelial and epithelial cell swelling, rheological humoral and neural factors is unclear[5], but reviewed below.

3.1.3. Relationship of GFR to reduced blood flow and tubular injury

It is likely that this disproportionate and subsequently, sustained fall in GFR is partly due to reduction in the effective capillary surface area (Kf). Direct measurements of Kf by micro-puncture and other techniques have confirmed this in several experimental models of ATN, both ischaemic and toxic (eg. gentamicin, uranium-induced)[5, 42-44]. In a model of severe ATN, induced in the rat by high doses of mercury salts, the complete cessation of filtration was associated with normal total renal blood flow, but intense afferent arteriolar constriction and a re-

ciprocal fall in efferent tone[43], leading to an inadequate capillary pressure for filtration to occur. The mechanism is not known although angiotensin, leukotrienes[3,37,43] as well as endothelin and thromboxane can cause mesangial cell contraction, and possibly direct toxic injury to the mesangial cells may occur.

Once endothelin had been described its potential as a mediator in ARF was obvious. Subsequently, Kon and her colleagues showed that infusion of anti-endothelin antibody into a branch of a rat renal artery reduced the vasoconstriction and reduced GFR that was induced by a period of ischaemia leading to ARF[18]. Similarly, Shibouta and his colleagues found that a similar antibody could largely reverse the ARF following bilateral renal occlusion in a rat model[45]. More recently, Schrier's group have shown, in an isolated perfused rat kidney, that an endothelin antagonist can prevent the vasoconstriction and fall in GFR that ischaemia produces[46].

3.2. *Maintenance of reduced GFR in Established Renal Failure*

3.2.1. Vascular pathology

In ATN following ischaemia the mechanism of continued reduction in renal blood flow after correction of systemic pressure and volume («no re-flow» phenomenon) is unknown. In renal sections, the dark zone at the outer medulla seen in ATN is due to intense vascular congestion. Using colloidal carbon or silicon rubber casts, obstruction of the vasculature in the deep cortex and outer medulla is consistently found in experimental models.

It has been suggested that endothelial swelling prevents recovery. However endothelial swelling is patchy and transient[47], with the exception in the cortico-medullary area where it is consistent and persists[38]. In these models, vascular pathology in resistance vessels, in the form of focal and segmental arteriolar necrosis, is also seen. This is probably a consequence of the initial severe vasospasm, but may contribute to any continuing reduction in blood flow[47-49].

3.2.2. Haemodynamic considerations

In experimental ATN, loss of renal autoregulation occurs[48,49]. This may have two consequences: firstly, there may not be the expected compensatory vasodilatation following the initial ischaemia, and secondly the kidney will not be protected from any subsequent falls in perfusión pressure.

Following the induction of ATN there is a loss of endothelium-dependent vasodilatation within the kidney[50], which may explain the paradoxical vasoconstriction in response to a fall in perfusion pressure and the increased sensitivity to renal nerve stimulation which occur in ARF[50]. Brezis and his colleagues have recently shown that the co-administration of L-NMMA in their rat model of radiocontrast-induced ARF[2] exacerbates the injury[51].

Ischaemia leads to a rise in adenosine content in the kidney and adenosine may act as a potent mediator of vasoconstriction. Hypoxaemia in neonates and newborn rabbits is associated with a fall in GFR and RBF and this may be abolished by low doses of theophylline an antagonist of adenosine[52]. Although adenosine appears to play an important role in some experimental models, in the human kidney a significant density of A1 receptors is present only in the glomerulus: the presence of receptors on renal medullary species shows marked species variability[53].

During ARF, glomeruli, examined *in vitro*, are refractory to vasoconstrictors including angiotensin II, arginine vasopressin, noradrenaline[54,55].

Finally, locally produced vasoconstrictors such as thromboxane, leukotrienes and endothelin may add a further insult to a compromised microcirculation.

3.2.3. Tubular obstruction

The role of tubular obstruction in the maintenance of oliguria has provoked much debate for many years. It plays a role in some animal models, although there is less evidence for this in man[7].

Tubular cell injury, probably, has an effect by compressing capillaries as a result of the cell swelling and interstitial oedema[5,38]. Sufficient cell swelling to contribute to «no-reflow» does not occur until anoxia has persisted for some 30 to 40 minutes. Following injury, cell volume regulation is inhibited and tubular epithelial cells swell. They become more permeable to sodium, and there is a rise in intracellular calcium.

The medullary circulation is drained by the very thin walled ascending vasa rectae, which are at particular risk of obstruction due to the proximity of the damaged ascending limb of Henle[33].

4. Endothelial injury

4.1. *Is Endothelial Injury of Intravascular Coagulation Involved? There are several ways in wich one might expect endothelial injury to play a role.*

4.1.1. Ischaemia may damage the capillary endothelium. This may cause endothelial swelling and capillary obstruction. However as discussed above, there is very little evidence for this except in the medullary vessels[38,47].

4.1.2. Endothelial damage may cause platelet aggregation and thrombosis to occur. It is possible that this may also occur in the glomerular as well the tubular circulation. Unfortunately, platelets can only be identified by electron mi-

croscopy and if they are involved they are likely to have degranulated and be unrecognisable. Similarly fibrin may be very difficult to identify as the fibrinolytic capacity of the endothelium is so large than fibrin persists only when the system is overwhelmed. However, Clarkson and his colleagues consistently found, by electron microscopic examination of renal biopsies obtained during the oliguric phase, conspicuous intraglomerular deposition of fibrin and platelets consistent with intraglomerular capillary thrombosis[56]. Moreover there was often swelling of the glomerular endothelium or subendothelial deposits. These changes were found in ARF of various causes.

In attempting to address the question of the role of endothelial injury Mason and her colleagues found that neither aspirin nor heparin were able to modify medullary vascular obstruction[40]. However both pathological and functional aspects of this injury were prevented by either raising perfusion pressure or lowering blood haematocrit[40]. It has also been suggested that the red cell trapping that occurs in the capillaries of the outer medulla may be preceded by capillary leakage and haemoconcentration. In experimental models the amount of red cells trapped is directly proportional to both the length of ischaemic period and the haematocrit – and the more red cells trapped the worse the prognosis[57].

4.1.3. Sepsis may trigger off localised intravascular coagulation leading to occlusion of the capillary microcirculation and secondary endothelial damage[58]. Models of endotoxin shock can produce renal failure and thrombosis in the renal mierocireulation. Infusion of endotoxin into baboons causes ATN with endothelial cell injury which is more prominent in peri-tubular than glomerular vessels[59].

In septicaemia and septic shock, however, there is little information regarding the renal microcirculation in either man or experimental models. In a study of 47 cases of disseminated intravascular coagulation (DIC) (seen out of 115,000 consequtive hospital admissions) 19 patients developed ARF, of whom 13 had an associated sepsis. All 19 had autopsies and none had evidence of microvascular thrombosis[60].

In a model of septicaemia in sheep, the development of ARF was related to the severity of septicaemia but histological examination showed only mild tubular changes and no evidence of thrombosis[61].

4.1.4. It has been suggested that alterations in the morphology of glomerular endothelium, in particular a reduction inthe size and number of fenestrations, may play a role in the reduction of GFR and Kf[5,42]. Significant changes have been reported in a number of models; but some of these changes may be artefactual, since very careful studies in other models have shown no abnormalities[62].

References

1. Vari R, Natarajan L, Whitescarver S, Jackson B, and Ott C: Induction, prevention and mechanisms of contrast media-induced acute renal failure. *Kid Int*, 33:699-707, 1988.
2. Heyman SN, Brezis M, Reubinoff CA, Greenfeld Z, Lechene C, Epstein FH, and Rosen S: Acute renal failure with selective medullary injury in the rat. *J Clin Invest*, 82:401-412, 1988.
3. Brenner BM, Dworkin LD, and Ichikawa I: Glomerular Ultrafiltration. In: Brenner BM, Rector FC (eds.). *The Kidney*, 3rd ed. Philadelphia: W. B. Saunders, 124-144, 1986.
4. Blantz RC, and Pelayo JC: A functional role for the tubuloglomerular feedback mechanism. *Kid Int*, 25:739-746, 1984.
5. Brezis M, Rosen S, and Epstein FH: Acute renal failure. In: Brenner BM, Rector FC (eds.). *The Kidney*, 3rd ed. Philadelphia: W. B. Saunders, 735-799, 1986.
6. Levinsky NG: Pathophysiology of acute renal failure. *N Engl J Med*, 296:1453-1458, 1977.
7. Myers BD, and Moran SM: Hemodynamically mediated acute renal failure. *N Engl J Med*, 314:97-105, 1986.
8. Furchgott RF, and Zawadski JV: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature*, 288:373-376, 1980.
9. Griffith TM, Edwards DH, Lewis MJ, Newby AC, and Henderson AH: The nature of endothelium-derived vascular relaxant factor. *Nature*, 308:645-647, 1984.
10. Palmer RMJ, Ferrige AG, and Moncada S: Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature*, 327:524-526, 1987.
11. Radomski MW, Palmer RMJ, and Moncada S: The anti-aggregating properties of vascular endothelium: interactions betweeen prostacyclin and nitric oxide. *Br J Pharmac*, 92:639-646, 1987.
12. Radomski MW, Palmer RMJ, and Moncada S: Endogenous nitric oxide inhibits human platelet adhesion to vascular endothelium. *Lancet*, 2:1057-1058, 1987.
13. Griffith TM, Edwards DH, Davies RL, Harrison TJ, and Evans KT: EDRF coordinates the behaviour of vascular resistance vessels. *Nature*, 329:442-445, 1987.
14. Rapport RM, Draznin MB, and Murad F: Endothelium-dependent relaxation in rat aorta may be mediated through cyclic GMP-dependent protein phosphorylation. *Nature*, 306174-176, 1983.
15. Moncada S, and Palmer RMJ: Inhibition of the induction of nitric oxide synthase by glucocorticoids. *Trends Pharmacol Sci*, 12:130-131, 1991.
16. King AJ, and Brenner BM: Endothelium-derived vasoactive factors and the renal vasculature. *Am J Physiol*, 260:R653-R662, 1991.
17. Tolins JP, Palmer RM, Moncada S, and Raij L: Role of endothelium-derived relaxing factor in regulation of renal hemodynamic responses. *Am J Physiol*, 258:H655-H662, 1990.
18. Kon V, Yoshioka T, Fogo A, and Ichikawa I: Glomerular actions of endothelin in vivo. *J Clin Invest*, 83:1762-1766, 1989.
19. Kreisberg JI, Ventkatachalam M, and Troyer D: Contractile properties of cultured glomerular mesangial cells. *Am J Physiol*, 249:F457-F463, 1985.
20. Ausiello DA, Kreisberg JI, Roy C, and Karinnovsky MJ: Contraction of cultured glomerular cells of apparant mesangial origin after stimulation with angiotensin II and arginine vasopressin. *J Clin Invest*, 65:754-760, 1980.
21. Mene P, and Dunn MJ: Modulation of mesangial cell contraction by arachidonate metabolites. *Trans Assoc Am Physicians*, 99: 125-131, 1986.
22. Lamas S, Olivera A, Obregón L, Duque I, et al.: Cyclosporin A-induced contraction of isolated human and rat glomeruli and cultured rat mesangial cells. *Nephrol Dial Transplant*, 3:487 (Abstr.), 1988.
23. Lamas S, Olivera A, Puyol DR, and López JM: Adenosine-induced rat mesangial cell contraction: an effect mediated by the A1 receptor type. *Nephrol Dial Transplant*, 3:487 (Abstr.), 1988.
24. Simonson M, and Dunn M: Leukotriene C4 and D4 contract rat glomerular mesangial cells. *Kid Int*, 30:524-531, 1986.
25. Mene P, Dubyak G, and Dunn M: Actions and second messengers of thromboxane A2 and prostaglandins in cultured rat mesangial cells. In: Davison A (ed.). *Nephrology*. London: Bailliere Tindall, 98-106, 1988.
26. Heller J: Effect of vasoactive mediators on renal haemodynamics. *Nephrol Dial Transplant*, 2:197-204, 1987.

27. Vanhoutte PM: Endothelium: Modulator of vascular smooth-muscle tone. *N Engl J Med*, 319:512-513, 1988.
28. Edwards RM: Response of isolated renal arterioles to acetylcholine, dopamine, and bradykinin. *Am J Physiol*, 248:F183-F189, 1985.
29. Knox FG, and Granger JP: Renal hemodynamics and sodium chloride excretion. In: Klahr S, Massry SG (eds.). *Contemporary Nephrology*. New York: Plenum, 61-90, 1985.
30. Schnermann J, Weihprecht H, Lorenz JN, and Briggs JP: Vasoconstrictor effects in isolated perfused afferent arterioles of rabbit kidneys. *J Am Soc Nephrol*, 1:670 (Abstr.), 1990.
31. Cairns HS, Rogerson, ME, Westwick J, and Neild GH: Regional heterogeneity of endothelium-dependent vasodilatation in the rabbit kidney. *J Physiol*, 436:421-429, 1991.
32. Deng A, Samsell L, and Baylis C: Locally produced endothelial derived relaxing factor (EDRF) controls preglomerular (RA) arteriolar tone and the glomerular capillary ultrafiltration. *JASN*, 2:503, 1991.
33. Kriz, W: Structural organization of renal medullary circulation. *Nephron*, 31:290-295, 1982.
34. Brenner BM, Zatz R, and Ichikawa I: The renal circulations. In: Brenner BM, Rector FC (eds.). *The Kidney*, 2nd ed. Philadelphia: W. B. Saunders, 93-123, 1986.
35. Brezis M, Rosen S, Silva P, and Epstein FH: Renal ischaemia: a new perspective. *Kid Int*, 26:375-383, 1984.
36. Brezis M, Rosen S, Silva P, and Epstein FH: Selective vulnerability of the thick ascending limb to anoxia in the isolated perfused rat kidney. *J Clin Invest*, 73:182-190, 1984.
37. Ballerman BJ, Levenson DJ, and Brenner BM: Renin, angiotensin, kinins, prostaglandins, and leukotrienes. In: Brenner BM, Rector FC (eds.). *The Kidney*, 2nd ed. Philadelphia: W. B. Saunders, 281-340, 1986.
38. Frega NS, DiBona DR, Guertler B, and Leaf A: Ischaemic renal injury. *Kid Int*, 10:S17-S25, 1976.
39. Mason J, Torhorst, J, and Welsch J: Role of the medullary perfusion defect in the pathogenesis of ischaemic renal failure. *Kid Int*, 26:283-293, 1984.
40. Mason J, Welsch J, and Torhorst J: The contribution of vascular obstruction to the functional defect that follows renal ischaemia. *Kid Int*, 31:65-71, 1987.
41. Olof, P, Hellberg A, Kallskog O, and Wolgast M: Red cell trapping and postischemic renal blood flow. Differences between the cortex, outer and inner medulla. *Kid Int*, 40:625-631, 1991.
42. Gross PA, and Anderson RJ: Acute renal failure and toxic nephropathy. In: Klahr S, Massry SG (eds.). *Contemporary Nephrology*. New York: Plenum, 447, 1985.
43. Wolfert AI, Laveri LA, Reilly KM, Oken KR, and Oken DE: Glomerular hemodynamics in mercury-induced acute renal failure. *Kid Int*, 32:246-255, 1987.
44. Williams, RH, Thomas CE, Navar LG, and Evan AP: Hemodynamic and single nephron function during the maintenance phase of ischemic acute renal failure in the dog. *Kid Int*, 19:503-515, 1981.
45. Shibouta Y, Suzuki N, Shino A, Matsumoto H, Terashita ZI, Kondo K, and Nishikawa K: Pathophysiological role of endothelian in acute renal failure. *Life Sci*, 46:1611-1618, 1990.
46. Chittindana A, Chan L, Suleymanlar G, Shapiro JE, and Schrier RW: Effects of endothelin antagonist (ETA) on ischemic acute renal failure (ARF). *JASN*, 2:644, 1991.
47. Kashgarian M, Siegel NJ, Ries AL, DiMeola, HJ, and Hayslett JP: Hemodynamic aspects in development and recovery phases of experimental postischemic acute renal failure. *Kid Int*, 10:S160-S168, 1976.
48. Adams PL, Adams FF, Bell PD, and Navar LG: Impaired renal blood flow autoregulation in ischemic acute renal failure. *Kid Int*, 18: 68-76, 1980.
49. Matthys E, Patton MK, Osgood RW, Venkatachalam MA, and Stein JH: Alterations in vascular function and morphology in acute ischaemic renal failure. *Kid Int*, 23:717-724, 1983.
50. Conger JD, Robinette JB, and Schrier RW: Smooth Muscle Calcium and Endothelium-derived Relaxing Factor in the Abnormal Vascular Responses of Acute Renal Failure. *J Clin Invest*, 82:532-537, 1988.
51. Brezis M, Heyman SN, Spokes K, Epstein FH, and Rosen S: Role of nitric oxide in renal medullary oxygen balance. *J Am Soc Nephrol*, 1:438 (Abstr.), 1990.
52. Gouyon J-B, and Guignard J-P: Theophylline prevents the hypoxemia-induced renal hemodynamic changes in rabbits. *Kid Int*, 33: 1078-1083, 1988.
53. Brines ML, Weber RG, and Forrest JN: Localization of A1 adenosine receptors is markedly heterogeneous in rodent, canine and human kidney. *J Am Soc Nephrol*, 1:438 (Abstr.), 1990.
54. Wilkes BM, Caldicott WJH, Schulman G, and Hollenberg NK: Loss of the glomerular contractile response to angiotensin in rats following myohemoglobinuric acute renal failure. *Circulation Res*, 49:1190-1195, 1981.
55. Ikuma K, Honda N, Yonemura K, Ahishi K, Hishida A, and Nagase M: Glomerular refractoriness to contractile stimuli in rabbits recovering from ischemic acute renal failure. *Nephron*, 48:306-309, 1988.
56. Clarkson AR, MacDonald MK, Fuster V, et al.: Glomerular coagulation in acute ischaemic renal failure. *Quart J Med*, 39:585, 1970.
57. Olof P, Hellberg A, Bayatti A, Kallskog O, and Wolgast M: Red cell trapping after ischaemia and long-term kidney damage. Influence of haematocrit. *Kid Int*, 37:1240-1247, 1990.
58. Wardle, EN: Fibrin in renal disease: functional considerations. *Clin Nephrol*, 2:85-92, 1974.
59. Richman AV, Gerber LI, and Balis JU: Peritubular capillaries: a major target site of endotoxin-induced vascular injury in the primate kidney. *Lab Invest*, 43:327-332, 1980.
60. Mant M, and King E: Severe, Acute Disseminated Intravascular Coagulation. *Am J Med*, 67:557-563, 1979.
61. Cumming A, Driedger A, McDonald J, Lindsay R, Solez K, and Linton A: Vasoactive hormones in the renal response to systemic sepsis. *Am J Kid Dis*, XI:23-32, 1988.
62. Bulger RE, Eknoyan G, Purcell DJ, and Dobyan DC: Endothelial characteristics of glomerular capillaries in normal, mercuric chloride-induced and gentamicin-induced acute renal failure in the rat. *J Clin Invest*, 72:128-141, 1983.