Renal Perfusion and Disease Progression

RAJANEE SENSIRIVATANA, M.D.*,
PORNCHAI KINGWATANAKUL, M.D.*,
PRASIT FUTRAKUL, M.D.*

Abstract

The pathogenetic concept of renal hyperperfusion and hyperfiltration in inducing glomerular pathology and disease progression documented in the renal ablation model in experimental animals to mimic renal disease with reduced nephron mass has recently been challenged. In contrast to the above, the intrarenal hemodynamic study in a variety of chronic glomerulonephropathies reveals a unique characteristic of renal hypoperfusion rather than hyperperfusion. This is associated with an elevated renal arteriolar resistance and reductions in renal plasma flow and peritubular capillary blood flow. The magnitude of reduction in peritubular capillary blood flow is inversely proportional to the degree of tubulointerstitial disease and tubular dysfunction. A progressive reduction in the vascular space due to nonvascular expansion with disease progression supports the concept of hypoperfusion of a whole kidney as well as a single nephron. In accordance with the renal ablation model and early diabetes mellitus, a similar hypoperfusion pattern is also subsequently observed in the chronic stage of renal ablation model in animals and late diabetic nephropathy. The disparity between the hyperperfusion and hypoperfusion in inducing renal disease progression can be enlightened by the Noble Truth of Lord Buddha stating "The Middle Tract is The Balance of Nature". Further support of this conceptual view of renal hypoperfusion as a determinant of tubulointerstitial disease and disease progression is in accordance with the therapeutic benefit with an enhanced-renal-perfusion formula per se in a variety of chronic glomerulonephropathies.

Key Word : Hemodynamics, Peritubular Capillary Blood Flow, Tubulointerstitial Disease

The correlation between tubulointerstitial disease and renal functional decline in patients suffering from a variety of chronic glomerulonephritides has been demonstrated for over two decades[1,2]. Despite this fact, the precise pathogenetic mechanism as to which would be the crucial determinant

* Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

of tubulointerstitial disease still remains unsettled. However, much accumulative evidence renders support that the key answer to this issue is likely to be hemodynamically mediated. In this regard, the conceptual view of hyperperfusion and hyperfiltration inducing renal disease progression derived from the experimental model of renal ablation in animals in an attempt to mimic a clinical setting of renal disease with reduced nephron mass, has been widely accepted[3,4]. The intrarenal hemodynamics characteristic of this experimental model reveals a high renal plasma flow (hyperperfusion) and glomerular filtration rate (hyperfiltration), a normal or elevated intraglomerular hydrostatic pressure and a low renal arteriolar resistance[3-5]. The question which remains to be established is whether the hemodynamic pattern of hyperperfusion observed in this animal model is also applicable to a variety of clinical settings of chronic glomerulonephritides in humans? A few clinical disorders with a hemodynamic pattern similar to the hyperperfusion of the renal ablation model has been observed in the early stage of diabetes mellitus, unilateral nephrectomy and renal transplant recipients receiving a kidney from a pediatric donor[5-8]. It is, therefore, the general belief that a nephron under such hyperperfusion of a whole kidney as well as of a single nephron would likely incriminate in the development of intraglomerular hypertension and, thus, subsequently exert further a significantly hemodynamic impact upon the histopathologic hallmarks of disease progression namely glomerulosclerosis and extracellular matrix expansion commonly encountered in the chronic stage of diabetic nephropathy and renal ablation model in animals[9-12]. This hemodynamic concept of hyperperfusion also implicates that the peritubular capillary blood flow supplying the tubulointerstitial compartment would also be hyperperfused. Therefore, such a hyperperfused peritubular capillary blood flow is believed to be responsible for the subsequent development in the later stage of tubulointerstitial disease.

The preceding conceptual view of hyperperfusion inducing renal disease progression has led to a general acceptance that this model is likely to be extrapolated to other clinical settings of chronic glomerulonephropathies.

It, thus, appears that this specific issue which has never been specifically proven, still remains to be established. That the remaining unsolved issue has encouraged us as well as others to approach such a problem by means of an intrarenal hemodynamic study. The information gathered from such a study in a wide spectrum of clinical settings of human renal diseases revealed a strikingly contrast hemodynamic pattern than that observed in the renal ablation model and early stage of diabetes mellitus.

Intrarenal hemodynamic study in renal disease : Perfusion modulates structure and function.

In accordance with the preceding context, we performed a hemodynamic study by the previously described method[13,14] in a variety of human clinical renal diseases. In brief, there are 2 patterns of hemodynamic characteristics which distinguish one with normal renal perfusion from the other with low renal perfusion.

In the first category associated with normal perfusion, the hemodynamic characteristics reveal a normal vascular function expressed by normal renal plasma flow, peritubular capillary blood flow and normal of both afferent and efferent arteriolar resistances. (Fig. 1) The presence of normal perfusion is likely to modulate the normal structure and function of the nephronal compartments[15]. In the presence of normal renal plasma flow, the glomerular function appears to be intact and expresses as normal glomerular filtration rate, normal ultrafiltration coefficient of the glomerulus and normal intraglomerular hydrostatic pressure. In addition, the glomerular structure also shows no or low evidence of disease progression such as glomerulosclerosis and it is usually associated with a benign clinical course. Similarly, the normal peritubular capillary blood flow also modulates the normal function and structure of the tubulointerstitial compartment. In the presence of normal peritubular capillary blood flow, the tubular function appears to be intact and expresses as (1) a normal tubular transport which is reflected by a normal fractional excretion of filtered solutes, (2) a normal maximal concentration and (3) a normal acidification. This normal tubular function also reflects the normal structure of the tubulointerstitial compartment or absence of tubulointerstitial disease. All of these findings indicate that the glomerular endothelium is functionally intact[16].

In the second category associated with a low renal perfusion such as that observed in the clinical settings of nephrosis associated with focal segmental glomerulosclerosis, nephrosis associated with membranoproliferative glomerulonephritis, IgA glo-

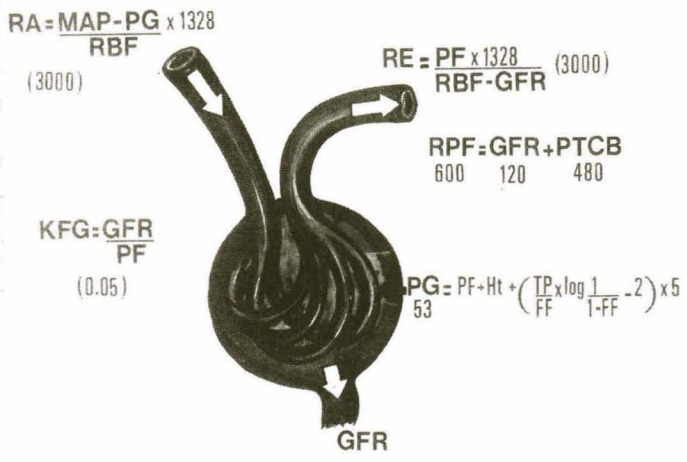

Fig. 1. Intrarenal hemodynamics in balanced state with normal perfusion. RA = afferent arteriolar resistance, dyne.s.cm^{-5}, MAP = mean arterial pressure, mmHg. PG = intraglomerular hydrostatic prpessure, mmHg, RE = efferent arteriolar resistance, dyne.s.cm^{-5}, PF = effective filtration pressure assumed to be 35 mmHg in normotensive and 40 mmHg in hypertensive, RBF = renal blood flow, ml/sec/1.73 m^2, KFG = ultrafiltration coefficient of glomerulus, ml/sec/mmHg, TP = total plasma protein, FF = filtration fraction. figures in parentheses represent normal values.

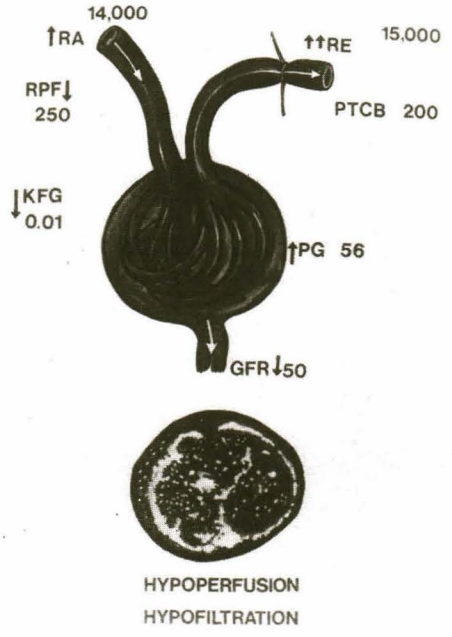

Fig. 2. Intrarenal hemodynamics in chronic glomerulonephropathies, RA = afferent arteriolar resistance, RE = efferent arteriolar resistance, RPF = renal plasma flow, PTCB = peritubular capillary blood flow, KFG = ultrafiltration coefficient of glomerulus, PG = intraglomerular hydrostatic pressure GFR = glomerular filtration rate, ↑ = elevated, ↓ = decreased

merulonephropathy, hemolytic uremic syndrome, the late stage of diabetic nephropathy, antiglomerular basement membrane disease, lupus nephritis, crescentic glomerulonephritis, a variety of chronic glomerulonephropathies and reflux nephropathy, there are usually associated functional and structural alterations of the nephronal compartments which are characterized by (1) a vascular dysfunction expressed by a low renal plasma flow and low peritubular capillary blood flow and elevation of both afferent and efferent arteriolar resistance (Fig. 2) (2) a glomerular dysfunction expressed by a low glomerular filtration rate, low ultrafiltration coefficient of the glomerulus and elevated intraglomerular hydrostatic pressure (intraglomerular hypertension) and a greater incidence of glomerulosclerosis and (3) a tubular dysfunction expressed as a transport defect which is reflected by enhanced fractional excretion of filtered solutes, a maximal concentration defect and acidification defect, and an increased incidence of tubulointerstitial fibrosis[16-19]. The preceding intrarenal hemodynamic findings documented in a variety of human clinical settings of renal disease revealed 3 important remarks that are distinctly contrast to that observed in the renal ablation model in animals. Firstly, with the exception of that observed in the early stage of diabetes mellitus, the intrarenal hemodynamics observed in the early stage of renal disease such as in minimal-change, steroid-sensitive nephrosis, revealed mainly a normal range of renal plasma flow and peritubular capillary blood flow and did not encounter a stage of hyperperfusion. Secondly, the intrarenal hemodynamics documented in the clinical settings of glomerulonephropathies associated with renal disease progression always reveal a characteristic pattern of renal hypoperfusion. In fact, the intrarenal hemodynamics characteristic of hyperperfusion have never been

observed even in the very early stage of the chronic form of glomerulonephropathy such as nephrosis associated with focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, crescentic glomerulonephritis, lupus nephritis and IgA nephropathy. This observation would raise an intriguing issue as to whether a state of hyperperfusion is essential to the subsequent development of renal disease progression in the chronic form of renal disease. The intrarenal hemodynamic information gathered in over 500 determinations for the past 20 years in the majority of renal diseases with the exception of diabetes mellitus does not support the conceptual view of hyperperfusion. It is likely that this specific issue remains to be further clarified. Thirdly, a very interesting issue needing to be addressed is whether a single nephron under total renal hypoperfusion associated with chronic glomerulonephropathy is either hypoperfused or hyperperfused? Although there is no direct answer to this, indirect evidence can be derived from a morphometric analysis in a variety of chronic glomerulonephropathies in which there is general agreement that the vascular component or the ratio between the vascular and nonvascular components is reduced regardless of the size of the glomerulus[18-23]. The reduction in vascular component or space is due to either the encroachment of the vascular space externally by an extracellular matrix expansion and cell proliferation, and internally by an intraluminal coagulation and altered hemorheology. This prudent informative evidence derived from the morphometric analysis seems to correlate with the marked elevation in renal arteriolar resistance and low plasma flow observed in chronic glomerulonephritis[8,15, 16,24]. A 6- to 10-fold increase in renal arteriolar resistance (normal value 2,700 dyn.s.cm^{-5}) in the presence of low perfusion speaks against the concept of hyperperfusion of a single nephron. Therefore, the proposed hemodynamic pattern of hyperperfusion of a single nephron in an experimental model of renal ablation in animals with the characteristic increase in renal plasma flow and low renal arteriolar resistance is unlikely to be applicable to human clinical settings of chronic glomerulonephritis with reduced nephron mass. The plausible explanation for such a difference between the two models is likely based on the difference in fundamental structure and function of the glomerular endothelium. In fact, the hyperperfused state recognized in the early course of the renal ablation model is the natural response of an intact endothelium to a high blood flow with a respective increase in the release of endothelium-dependent vasodilators, whereas, the hypoperfused state associated with chronic glomerulonephritis is the abnormal response of the dysfunctioning endothelium to the low flow state with an inadequate release of the endothelium dependent vasodilators[16]. Further observation in the chronic stage of renal ablation models in animals and late stage of diabetic nephropathy also revealed a hemodynamic pattern of hypoperfusion similar to that observed in chronic glomerulonephritis.

The precise mechanism responsible for the progressive loss of renal perfusion in the renal ablation model or the early stage of diabetes mellitus is likely to be explained on the hemodynamic basis. One of the general observations under this circumstance is that there is an increased metabolism under such extraordinary high fluid shear stress and a concomitantly increased production of reactive oxygen radicals. The endothelium in the chronic stage under continuous exposure to the supra high fluid shear stress is likely to dysfunction and thereby express altered endothelial surface phenotypes with upregulations of growth factors, vasoactive mediators, adhesion molecules and reactive oxygen radicals[25,26]. Two substantial pieces of evidence support this view. Firstly, there is a greater increase in the cellular metabolism after resection by which a great quantity of reactive oxygen radicals is produced[27, 28]. This high concentration of reactive oxygen radicals is believed to be the important trigger inducing the subsequent injury to the glomerular endothelium as well as increasing the renal arteriolar resistance by upregulating the vasoconstrictors. Secondly, the rapid growth of the nonvascular component of the renal mass after resection is likely to progressively reduce the vascular space by external encroachment of the vascular wall due to cell proliferation and extracellular matrix expansion as a result of upregulating the growth factor. These preceding views are well illustrated by the sequential morphometric analyses of the glomerulus in the chronic stage in animals with subtotal nephrectomy[9] and by the subsequent assessment of intrarenal hemodynamics which revealed a progressive increase in renal arteriolar resistance, intraglomerular hypertension and reductions in glomerular filtration rate, renal plasma

flow and peritubular capillary blood flow[29]. A similar hemodynamic alteration associated with the hyperglycemic state is likely to progressively induce an endothelial dysfunction along the course of diabetic nephropathy[10,12]. Therefore, the hyperperfused state observed early in the course of human diabetic nephropathy and renal ablation model in animals can subsequently be converted later in the course into the hypoperfused state with characteristic loss of renal structure and function. The disparity between these two conceptual views is likely to be explained by the wisdom derived from the "NOBLE TRUTH OF LORD BUDDHA" stating that "The middle tract is the balance of nature" which means that any deviation in blood perfusion from the natural balance, either too high or too low, is unnatural and indeed harmful.

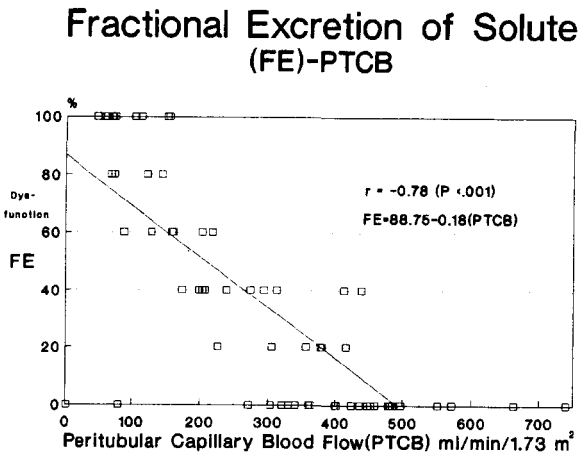

Fig. 3. Linear regression analysis illustrates the peritubular capillary blood flow (PTCB) correlates negatively with the degree of tubular transport defect expressed by fractional excretion (FE) of solute.

Peritubular capillary blood flow determines the function and structure of tubulointerstitial compartment.

It has been observed that the peritubular capillary blood flow in the normal or balanced state is usually associated with normal function and structure of the tubulointerstitial compartment. By linear regression analysis, the normal peritubular capillary blood flow is likely to maintain the normal tubular transport expressed by normal fractional excretion of filtered solutes. With the progression of renal disease, there is a progressive reduction in peritubular capillary blood flow and a progressive increase in tubular transport defect expressed by increase in percentage of dysfunction of FE solute. (Fig. 3) This progressive reduction in peritubular capillary blood flow also correlates inversely with the intensity of tubulointerstitial fibrosis. This view has recently been supported by the elegant demonstration by Bohle et al that the postglomerular capillary space correlates negatively with the cortical interstitial volume and serum creatinine level[31].

The consistently observed reduction in peritubular capillary blood flow is due to multiple factors namely a total reduction in renal plasma flow secondary to glomerular endothelial dysfunction, a glomerular pathology obstacle to blood flow and a preferential constriction at the efferent arteriole[15, 16,30]. In the presence of glomerular endothelial dysfunction, the reduction in peritubular capillary blood flow to a critical level is likely to be a progressive and a self-perpetuating event. In accordance with the Poiseuille-Hagen relationship, this conceptual view can be explained by the *in vitro* study of molecular aspects of signal tranduction of shear stress on the endothelial cell[25]. Under a low flow condition, the endothelial cell expresses its phenotypes with upregulation of vasoconstrictors, growth factors, adhesion molecules, procoagulant tissue factors, inhibitors to plasminogen activators and to tissue metalloproteinase[25,32-39]. In the presence of dysfunctioning glomerular and peritubular capillary endothelium, these mediators released are likely to be greatly amplified and persistent. The continuous release of these pathogenetic mediators would culminate in the progressive reduction in vascular space by external encroachment of the vascular wall due to extracellular matrix expansion and cell proliferation secondary to the enhanced growth factors and by intraluminal obstacle to blood flow due to intravascular coagulation secondary to the release of adhesion molecules and procoagulant proteins [16]. This concept of progressive reduction in renal perfusion has been well substantiated in all forms of chronic glomerulonephritides associated with tubulointerstitial disease. The severity of tubulointerstitial disease is inversely proportional to the magnitude of reduction in peritubular capillary blood flow[40]. It is consistently observed that in patients with chronic glomerulonephritis and severe tubulointerstitial

disease, the peritubular capillary blood flow is usually less than 200 ml/min/1.73 m^2 (normal 480 ml/min/1.73 m^2). Beyond this critical point, there is usually an accelerated rate of renal disease progression. (Fig. 3) These patients are usually refractory to conventional treatment (prednisolone ± cyclophosphamide) and eventually enter into end-stage renal disease.

What is then the cause-and-effect relationship between the reduction in peritubular capillary blood flow and the development of tubulointerstitial disease ? In this regard, there is evidence from both a clinical setting in humans as well as experimental ischemic injury in animals to support that the reduction in peritubular capillary blood flow is likely to be the primary trigger of tubulointerstitial disease. In humans with minimal-change and IgM steroid-resistant nephrosis, there was a reduction in peritubular capillary blood flow for quite some time before the detection of tubulointerstitial disease and tubular dysfunction[41]. In the experimental setting of renal artery occlusion in animals, the ischemic insult per se subsequently induced a tubulointerstitial lesion which mimicked human glomerulonephropathy[42]. In this essence, the ischemic insult is likely to exert a profound effect upon the tubular epithelium by upregulating the tubular-derived cytokines, growth factors, vasoactive mediators, adhesion molecules, reactive oxygen metabolites and translocating the integrins from the basolateral to the apical region[43]. In addition, other triggers such as filtered macromolecular protein, lipid, free iron, intraluminal cast, ammonia and complements can also induce additional damage to the tubular epithelium[44]. Taken together, these preceding triggers would perturb the phospholipid component of the cell membrane with subsequent breakdown of arachidonic acid and increase in intracytosolic calcium[45]. The preceding event is indirectly supported by the demonstration of a hypermetabolic state, depletion of cellular high energy ATP, reduction in ATPase activity and increase in reactive oxygen species encountered in a condition mimicking remnant nephron exposed to the ischemic insult[27]. The releases of chemoattractant proteins, adhesion molecules and MHC class are responsible for the infiltration of immunologic T lymphocytes and macrophages. The activation of procoagulant phenotype expression on the surface of macrophage in conjunction with the leakage of plasma constituents from the abnormally ischemic permeable vascular wall into the interstitium, would activate the extrinsic coagulation pathway with subsequent fibrin formation, activation of fibroblast and extracellular matrix expansion[46-50]. These multifactorial interplays would synergistically act in concert and induce cell degeneration, proliferation and extracellular matrix expansion with subsequent encroachment of the functioning peritubular capillary network. In fact, obliteration of postglomerular capillary network has previously been implicated [31,51]. It is also our general impression that there is a progressive loss of peritubular capillary blood which correlates with the increment in severity of tubulointerstitial disease.

A new therapeutic strategy aiming to enhanced renal perfusion.

This preceding concept of hemodynamically mediated tubulointerstitial disease is further substantiated by the therapeutic modalities. Therapeutic failure in preventing disease progression in patients with a variety of chronic glomerulonephritides has consistently been observed under conventional therapy (prednisolone and cyclophosphamide)[15,52-54]. In contrast, functional improvement can be achieved by a variety of therapeutic agents aiming to improve a peritubular capillary blood flow[14-16,30,40,41,55-62]. Improvement in hemodynamics and function can be substantiated following the enhanced renal perfusion formula. This therapeutic response can be eludicated even in severe cases of nephrosis associated with focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis and chronic glomerulonephritis with a severe degree of functional impairment[15, 24,30,63]. It is of notion that many of these patients have previously been quoted as refractory to treatment and pending on future renal replacement therapy. Improvement in peritubular capillary blood flow gradually minimizes the magnitude of tubular dysfunction of which is observed in the enhanced-renal-perfusion therapy per se. Inasmuch as this therapeutic maneuver encompasses multiple therapeutic agents with diversified pharmacologic actions, the therapeutic achievement observed in our study as well as by other investigators simply implies that the improvement in renal perfusion by vasodilatory agents may be part of the several mechanisms of action simultaneously interplaying namely (1) cytoprotective and antiproliferative actions by preventing the increment in cytosolic calcium of which its action is shared by the antiplatelet agent,

calcium channel blocker and angiotension converting enzyme inhibitor (2) correction of altered hemorheology by anticoagulant and antiplatelet agent and (3) increase in effective circulatory blood volume by hydration.

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เลือดหล่อเลี้ยงไตกับการทำลายไต

รัชนี เซ็นศิริวัฒนา, พ.บ.,*
พรชัย กิ่งวัฒนสกุล, พ.บ., ประสิทธิ์ ฟูตระกูล, พ.บ.**

ภาวะเลือดหล่อเลี้ยงไตเกิน (renal hyperperfusion) และการกรองที่เพิ่มผิดปกติ (hyperfiltration) เป็นกลไกสำคัญที่ทำลายไตในสัตว์ทดลองที่ทำให้เกิดภาวะไตวาย การศึกษาโลหิตพลศาสตร์ของเลือดที่หล่อเลี้ยงไตในโรคไตอักเสบเรื้อรังชนิดต่าง ๆ ในคนกลับพบภาวะเลือดหล่อเลี้ยงไตพร่องทั้งสิ้น โดยมีการพร่องของ renal plasma flow, peritubular capillary blood flow ขณะที่ความต้านทานใน arteriolar สูงผิดปกติ ปริมาณของ peritubular capillary blood flow สัมพันธ์ในลักษณะผกผันกับการตายของเนื้อไตส่วน tubulointerstitium และการทำงานของไตส่วนหิวบูล (tubular function)

ความผิดปกติชนิดภาวะเลือดหล่อเลี้ยงไตเกินที่พบในสัตว์ทดลองระยะแรกที่ทำให้เกิดภาวะไตวาย หรือในผู้ป่วยเบาหวานระยะแรก จะเปลี่ยนลักษณะเป็นชนิดเลือดหล่อเลี้ยงไตพร่องพร้อมกับการตายของเนื้อไตในระยะหลังของโรค ความผิดปกติทางโลหิตพลศาสตร์ของเลือดหล่อเลี้ยงไตทั้งชนิดเลือดหล่อเลี้ยงไตพร่องหรือมากเกินไป ล้วนทำให้เกิดโรคเป็นลักษณะสัจจธรรม มิชฌิมาปฏิปทา ของพระพุทธองค์

การรักษาป้องกันการตายของเนื้อไตสามารถกระทำได้โดยการใช้ยาออกฤทธิ์ขยายหลอดเลือด และแก้ไขความผิดปกติของเลือดเพื่อเพิ่มปริมาณเลือดหล่อเลี้ยงไต

คำสำคัญ : เลือดหล่อเลี้ยงไต, เลือดหล่อเลี้ยงไตส่วนท่อไต, การตายของเนื้อไตส่วนท่อไต

* ภาควิชากุมารเวชศาสตร์, คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, กรุงเทพ ฯ 10330