Vascular homeostasis and disease progression in chronic kidney disease

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Background: Vascular disease is unfortunately an asymptomatic process that is responsible for a variety of organ damages such as chronic kidney disease (CKD). Present therapeutic strategy in CKD which is usually initiated at the late stage of CKD fails to enhance renal perfusion or restore function.

Objective: To summarize the mechanism of vascular homeostasis in different stages of CKD to explain the present therapeutic failure. Furthermore, the authors propose an innovative strategy to restore effectively renal perfusion and function in CKD.

Results: Altered vascular homeostasis with impaired vascular repair is observed in late stage of CKD and would explain the present therapeutic failure. However, an adequate vascular repair is observed in early stage of CKD, which would provide an alternative innovative approach to restore renal function in this early stage under environment favorable for renal angiogenesis and regeneration.

Conclusion: A restoration of renal perfusion and function can be accomplished in early stage of CKD with multidrug vasodilators.

Keywords: Early therapeutic strategy, enhanced renal perfusion, renal angiogenesis, vascular homeostasis, vascular repair.
earlier stage of CKD may be an alternative approach to effectively enhance renal perfusion and restore renal function in CKD patients.

In this article, we firstly summarize the mechanism of vascular homeostasis in different stages of CKD to explain the present therapeutic failure, and then propose an innovative strategy to effectively restore renal perfusion and function in CKD.

**A balance state of vascular homeostasis**

Vascular injury is usually influenced by a variety of circulating toxins derived from metabolic products such as oxidative stress [9-14], glycation end-product, lipid [15], pro-inflammatory cytokine [16], etc. These circulating toxins induce vascular injury and subsequently a detachment of endothelial cell into the circulation [17, 18]. This, in turn, would trigger the vascular repair by recruiting the endothelial progenitor cell to the site of vascular injury, in order to induce proliferation of endothelial cell to replace for the endothelial cell loss [19]. In this process under normal circumstance, it requires an adequate amount of vascular endothelial growth factor (VEGF), which normally activates through the VEGF receptor 1 (VEGFR1) receptor, by which it induces coupling of endothelial nitric oxide synthesis (eNOS), and eventually enhances nitric oxide production [20]. In addition, angiopoietin-1 is required [21] for the angiogenesis and maturation of the endothelial cell (Fig. 1).

**An altered vascular homeostasis in late stage of CKD**

Accumulating evidence renders support that treatment under present common practice, which is usually initiated at the late stage of CKD, cannot improve renal perfusion or restore renal function. Such information implies that the mechanism of vascular repair is likely to be impaired. Indeed, such view is supported by a study by Furtakul N and Futrakul P [19] regarding the mechanism of vascular repair in the late stage of CKD.

There are multiple defects in the mechanism of vascular repair. With respect to the endothelial progenitor cell (EPC) [22], it has been demonstrated that the number of EPC is markedly depleted [15]. Such depleted number of EPC would impair the proliferation of endothelial cells. All the angiogenic factors, namely angiopoietin-1, VEGF, and VEGFR1, are markedly deficient. In addition, all the antiangiogenic factors, namely angiopoietin-2, and KDR (VEGF2) receptor, are abnormally elevated. Therefore, both defective VEGF and VEGFR1 would prohibit the activation through the classical pathway of VEGFR1. Instead, due to the abnormally elevated KDR receptor, VEGF would alternately activate through the pathological KDR receptor, by which it cannot induce coupling of eNOS, and eventually is unable to enhance NO production [23, 24]. Impaired endothelial cell proliferation and impaired NO production would impair the vascular repair and angiogenesis.

![Fig. 1 Normal vascular homeostasis.](image)
To complicate the situation further, the abnormally elevated angiopoietin-2 [25] would induce a progressive proliferation of vascular smooth muscle cells, which leads to a progressive narrowing of vascular lumen, and eventually a progressive reduction in vascular perfusion. A progressive reduction of peritubular capillary flow has been observed as the disease severity progresses under conventional therapy (inadequate vasodilator) [26]. Such findings explain the present therapeutic strategic failure initiated at the late stage under common practice, which is unable to improve renal perfusion, and instead induce a progressive reduction in renal supply to the kidney (Fig. 2).

An innovative strategy to restore renal function in early stage of CKD

An interesting question relevant to the therapeutic strategy is whether a therapeutic strategy towards renal restoration in CKD plausible. To access to this crucial issue, it is mandatory to solve the two crucial issues relevant to the present therapeutic practice failure: 1) the inappropriate therapeutic target, and 2) the treatment at the late stage of CKD.

With respect to the first issue, the present therapeutic target aiming at suppression of proteinuria, or controlling of blood pressure although is beneficial, but indeed not perfect. We, as well as many others, have experienced that many CKD patients under well-suppressed proteinuria or well-controlled blood pressure still progress to the end-stage renal disease. Such therapeutic failure implies that the present therapeutic strategy does not correct the mechanism of renal disease progression.

Accumulating evidence renders support that renal microvascular disease is the crucial determinant inducing renal disease progression [27]. In this regard, a correlation between renal microvascular disease and the development of tubulointerstitial fibrosis has been repeatedly demonstrated [28-33]. Several important notions are as follows: 1) Renal microvascular disease is reflected by hemodynamic maladjustment and peritubular capillary flow reduction [34, 35]. 2) Peritubular capillary flow reduction usually precedes the development of tubulointerstitial fibrosis [36]. 3) Tubulointerstitial fibrosis has been substantiated only in CKD patients associated with a reduction in peritubular capillary flow.

A correlation between peritubular capillary flow reduction and tubulointerstitial fibrosis is noted as: the lower the peritubular capillary flow and the higher the magnitude of tubulointerstitial fibrosis. A CKD patient with normal peritubular capillary flow does not develop tubulointerstitial fibrosis. It has been noted that the reduction in peritubular capillary flow becomes progressively decreased as the disease severity progresses. This would lead to chronic ischemic injury to the tubulointerstitium, finally inducing tubulointerstitial fibrosis. Therefore, correction of the hemodynamic maladjustment and improvement of peritubular capillary flow with multidrug vasodilators such as angiotensin converting enzyme (ACE) inhibitor, All receptor blocker, and calcium channel blocker resulting in improving renal function, would be the appropriate target for therapeutic intervention [37-42].

With respect to the second issue, relevant to the proper timing to initiate the treatment, the treatment for CKD patients should be initiated at the early stage under the environment favorable for renal regeneration. This view is supported by a recent study by Futrakul N et al. [43] which demonstrated an adequate function in vascular repair which is reflected by clinical restoration of renal perfusion and function following vasodilators initiated only at early stage of CKD. Indeed, treatment of nephrotic patients with focal segmental glomerulosclerosis and type 2 diabetic patients the early stage (normoalbuminuria) can improve the renal perfusion and function [37-41] (Fig. 3).

In conclusion, a therapeutic strategy towards restoration of renal function can be accomplished in the early stage of CKD patients by implementing a sensitive diagnostic marker such as fractional excretion of magnesium or actual creatinine clearance determination, to screen for the early stage of CKD. This is important since the common diagnostic markers under common practice such as determination of serum creatinine and microalbuminuria fails to do so [44-46].

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The authors declare no conflict of interest.
Fig. 2 Altered vascular homeostasis in late stage of CKD.

Fig. 3 Improved renal perfusion and function with vasodilators in the early stage of CKD.

References
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