

## Brief communication (Original)

# Restoration of renal perfusion and function in chronic kidney disease

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**Background:** Present treatment with vasodilators usually initiated at the late stage of chronic kidney disease (CKD) fails to restore renal perfusion and function. This may be due to impaired mechanism of nitric oxide production, while the mechanism of vascular repair appears to be adequately functional in the early stage of CKD.

**Objective:** Investigate restoration of renal perfusion and function in CKD patients by implementing vasodilators treatment at the early stage of CKD.

**Methods:** Vasodilators treatment was implemented in 65 CKD patients (33 males and 32 females) at the early stage of CKD. The patients aged 28-71 years old, and were associated with mildly impaired renal function (mean creatinine clearance:  $83 \pm 21$  mL/min/1.73m<sup>2</sup>, fractional excretion of magnesium (FE Mg):  $4 \pm 2\%$  vs. normal  $1.6 \pm 0.6\%$ , total urinary protein:  $85 \pm 12$  mg/day, renal plasma flow (RPF):  $459 \pm 59$  mL/min/1.73m<sup>2</sup>, glomerular filtration rate (GFR):  $84 \pm 25$  mL/min/1.73m<sup>2</sup>, peritubular capillary flow (PTCF):  $332$  mL/min/1.73m<sup>2</sup>). Treatment included vasodilators as follows, angiotensin converting enzyme inhibitor (ACEI) 5-20 mg/day, angiotensin II receptor blockers (ARB) 40-80 mg/day, and calcium channel blocker 5-10 mg/day for 12-24 months.

**Results:** Following the treatment, actual creatinine clearance rose to  $101 \pm 23$  mL/min/1.73m<sup>2</sup>, and FE Mg and total urinary protein declined to  $3 \pm 2\%$  and  $46 \pm 7$  mg/day, respectively. RPF, GFR and PTCF significantly rose to  $513 \pm 90$  mL/min/1.73m<sup>2</sup>,  $99 \pm 33$  mL/min/1.73m<sup>2</sup> and  $413 \pm 73$  mL/min/1.73m<sup>2</sup>, respectively.

**Conclusion:** Treatment with vasodilators at the early stage of CKD could restore renal perfusion and function.

**Keywords:** Chronic kidney disease, creatinine clearance, FE Mg, vascular repair, vasodilators, renal hemodynamics

It has been a general consensus that renal microvascular disease is crucial to induce chronic ischemia and renal disease progression [1, 2]. Present therapeutic strategy of chronic kidney disease (CKD) with vasodilators fails to prevent the progression of renal disease towards end-stage renal failure. Treatment in general has been initiated at a rather late stage due to the insensitiveness of the available diagnostic marker such as serum creatinine determination. This usually becomes abnormal only when the creatinine clearance drops to fifty percent level [3-6].

Vasodilators are used to enhance renal perfusion and function. These are usually ineffective in the late stage of CKD, due to the impaired mechanism of vascular repair. Recently, we demonstrated that

angiogenic factors, such as vascular endothelial growth factor (VEGF), angiopoietin 1 and VEGF receptor 1, are defective in the late stage CKD in both type 2 diabetes and non-diabetic CKD [7, 8]. In contrast, anti-angiogenic factors, such as VEGF receptor 2 and angiopoietin 2, are abnormally elevated [9-11]. In the presence of defective angiogenic factors, VEGF would impair the phosphatidylinositol 3-kinase/protein kinase Akt phosphorylation through defective VEGF receptor 1, uncoupling of endothelial nitric oxide synthase, and impair nitric oxide (NO) production. Impaired NO production in conjunction with defective endothelial progenitor cell and angiopoietin 1 would incriminate in impaired vascular repair [12]. Failure to enhance NO production explains the therapeutic resistance to vasodilator treatment in the late stage CKD.

In the presence of abnormally elevated anti-angiogenic factors, VEGF would excessively activate the Akt phosphorylation through NO-independent

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pathway, by which it would abnormally induce an excessive immature endothelial cell proliferation. This abnormal endothelial cell is due to defective angiopoietin 1 which impair endothelial cell maturation [13], in conjunction with the abnormally elevated angiopoietin 2 which destabilizes the endothelial cell and also induces endothelial cell apoptosis [14]. Increased angiotensin II is also noted in CKD. This would activate a progressive vascular smooth muscle cell proliferation, a thickening of vascular wall, a narrowing of vascular lumen and eventually a progressive reduction in peritubular capillary flow supplying the tubulointerstitium. Collectively, these would induce a progressive vascular disease and chronic ischemia to the tubulointerstitium.

In contrast to the above finding, the mechanism of vascular repair observed in the early stage of CKD appears to be adequately functional [15]. In this regard, normal levels of VEGF and VEGF receptor 1 would activate the classical or angiogenic pathway (VEGF → VEGF receptor 1), induce coupling of endothelial NO synthase, and enhance NO production. This implies that the mechanism of vascular repair is vulnerable to enhance renal perfusion and renal regeneration in early stage of CKD.

In this study, we set up a therapeutic implementation to correct the chronic ischemic environment with vasodilators in the early stage of CKD.

### Subjects and methods

The present study was a prospective, randomized uncontrolled trial. The study was approved by the Ethics Committee of Faculty of Medicine, Chulalongkorn University. Sixty-five patients associated with CKD stages 1-2 were recruited from

plasma flow (RPF), or peritubular capillary flow (PTCF).

The therapeutic strategy aimed to improve renal perfusion and to restore renal function at the early stage of CKD with vasodilators as follows. ACEI (Enaril): 5-20 mg/day, ARB (Telmisartan) 40-80 mg/day, or (Losartan) 50-100 mg/day, calcium channel blocker 5-10 mg/day, antioxidants (such as vitamin C) 1000-2000 mg/day, and vitamin E 400-800 units/day. All patients were advised to drink water *ad lib* (3000 mL/day).

These patients compiled well with the study and recommendation. The renal functions were repeated at regular intervals thereafter.

### Renal function study

Renal function study was performed under 10-hour urinary collection. No diuretic was administered during or within 24 hours before the test. Briefly, after a regular supper, no additional food except drinking water *ad lib* was allowed. The patients were instructed to void at 7pm., and the urine was totally collected from 7pm. to 5am. Clotted blood from venipuncture was drawn at the end of the test for analysis of creatinine and magnesium levels. Urine samples were analyzed as blood samples by the Renal Metabolic Laboratory Unit, King Chulalongkorn Memorial Hospital. For analysis of creatinine and magnesium, we used the methods described by Faulkner and King, and Atomic Absorption Spectrophotometer (model 1100 G, Perkin Elmer, Norwalk, USA), respectively. A reflection of tubulointerstitial fibrosis was derived from the determination of FE Mg which was calculated through the formula:

$$\text{FE Mg} = \frac{\text{urine magnesium}}{\text{plasma magnesium}} \times \frac{\text{plasma creatinine}}{\text{urine creatinine}} \times 100\%$$

King Chulalongkorn Memorial Hospital. Here, CKD was defined by i) the presence of tubulointerstitial fibrosis, indirectly reflected by the abnormally elevated fractional excretion of magnesium (FE Mg), which has previously been demonstrated to correlate directly with the magnitude of tubulointerstitial fibrosis [16], ii) a decline in measured creatinine clearance, and iii) a renal ischemia characterized by a reduction in renal

### Intrarenal hemodynamic study

Simultaneous assessments of effective RPF using <sup>131</sup>I-labeled orthoiodohippuric acid (hippuran) and of glomerular filtration rate (GFR) using <sup>99m</sup>Tc-labeled diethylene triamine penta-acetic acid (DTPA) were determined by the previously described method [17]. The PTCF is derived from the subtraction of GFR from RPF and is in mL/min/1.73m<sup>2</sup>.

### Statistics

All data were expressed as means  $\pm$  Standard deviation (SD). Comparison of the sample mean of two quantitative variables was determined by the paired student t test. P values below 0.05 were considered significantly different.

### Results

Results of restoration of renal perfusion and function with vasodilators in 65 CKD patients are shown in **Table 1**. We note that significant improvements in renal function as well as renal hemodynamic studies were documented following vasodilators treatment in the early stage of CKD.

### Discussion

We showed that the conventional diagnostic marker such as serum creatinine determination in the early stage of CKD patients was not significantly different from the control, as indicated in **Table 1**. However, this early stage of CKD could be recognized by 1) measured creatinine clearance which was significantly impaired, 2) FE Mg was doubling the normal value, which reflects the presence of tubulointerstitial disease, and 3) the presence of renal ischemia which was reflected by the reduction in RPF and PTCF. Treatment at this early stage of CKD

with vasodilators could restore renal perfusion. This supports the vascular homeostasis studied in the early stage of CKD that the mechanism of vascular repair produces an adequate amount of NO and sufficiently responds to vasodilator treatment. This view is further substantiated by our recent study [18], where an improved vascular repair could be accomplished in the early stage of CKD following a restoration of renal perfusion in response to vasodilator. Increased PTCF would correct the chronic ischemic state of the tubulointerstitial structure. Improvement in PTCF would inhibit the process of tubulointerstitial fibrosis which is reflected by the regression of FE Mg value following the treatment, that is, an indication of renal regeneration [16]. This view is supported by the increments in both creatinine clearance and glomerular filtration rate.

In conclusion, therapeutic treatment with vasodilators in the early stage of CKD would be an innovative strategy to effectively prevent the development of end-stage renal disease.

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**Table 1.** Restoration of renal perfusion and function with vasodilators in the early stage of chronic kidney disease.

	Pre-treatment	P-value	Post-treatment	Normal
<b>Renal function</b>				
Serum creatinine (mg/day)	1 $\pm$ 0.3	<0.001	0.9 $\pm$ 0.2	$\leq$ 1
Creatinine clearance (mL/min/1.73m <sup>2</sup> )	83 $\pm$ 21	<0.001	101 $\pm$ 23	120
Fractional excretion of Mg (FE Mg %)	4 $\pm$ 2	<0.05	3 $\pm$ 2	1.6 $\pm$ 0.6
Urinary protein (mg/day)	85 $\pm$ 12	<0.01	46 $\pm$ 7	<30
<b>Hemodynamics</b>				
Renal plasma flow (mL/min/1.73m <sup>2</sup> )	419 $\pm$ 59	0.001	513 $\pm$ 90	605 $\pm$ 29
Glomerular filtration rate (mL/min/1.73m <sup>2</sup> )	84 $\pm$ 25	<0.05	99 $\pm$ 33	119 $\pm$ 15
Peritubular capillary flow (mL/min/1.73m <sup>2</sup> )	332 $\pm$ 49	0.001	413 $\pm$ 73	485 $\pm$ 39
Mean arterial pressure mmHg	87 $\pm$ 10	<0.01	81 $\pm$ 8	$\leq$ 83

Data were expressed as means $\pm$ SD.

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