Nephroprotective therapy features for partial nephrectomy

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Summary.
The article presents data on nephroprotective therapy for the surgical treatment of the patients with kidney tumors. Among the mechanisms involved in the formation of nephrosclerosis, a key role is played by angiotensin II. Normalization of blood pressure is essential to prevent nephrosclerosis (both primary and secondary) and the removal of intraglomerular hypertension. This explains the importance of the use of drugs that block the renin-angiotensin system in these patients. The article presents data on the efficacy of drugs for nephroprotective therapy because inhibitors antgiotenzin converting factor, pentoxifylline, mannitol and low molecular weight heparin in patients after kidney resection, diabetic and nondiabetic nephropathy.
Keywords: nephroprotective therapy, chronic renal failure, the renin-angiotensin system.

A promising direction in improving organ preservation during surgical treatment the patients with renal cell carcinoma is the using of local ischemia and additional methods of preventing its consequences, which may lead to decreased renal function.

The methods of nephrosclerosis prevention are: adequate hydration, maintenance of normal blood pressure and nephroprotective therapy that improves microcirculation in the kidneys, maintains optimal renal perfusion and prevent vasospasm in kidney during ischemia.

The kidney is a major organ for damaging in hypertension. Patients with cancer, diabetes and the elderly are particularly at risk for the presence kidney dysfunction. This makes it relevant not only to the use of renal protection drugs - renin-angiotensin system with microalbuminuria and proteinuria, but administering the drugs with dual route of elimination to prevent the possible accumulation.

Nephroprotective therapy is a set of different measures, including medication, diet and lifestyle modifications which is aimed for preventive renal function or deceleration rate of decline regardless of the underlying disease. It prevents or inhibits the development of chronic renal failure, leading to death and need kidney dialysis and kidney transplant. During decreasing intraglomerular

hyperfiltration, the activity of renin, angiotensin II, aldosterone and also for decresing the proteinuria it is recommended the blockade of the renin-angiotensin-aldosterone system (RAAS), which is achieved by regular and long-term (life) inhibitors, angiotensin-converting enzyme (ACE) inhibitors or angiotensin AT1-receptor or angiotensin renin block against. The action of these drugs promotes the renal protection by reducing intraglomerular hypertension and nephrosclerosis.

During the first 30 days after surgery there is a significant increase the concentration of biogenic amines vasoconstrictor (epinephrine, norepinephrine) in kidney due to the relative scarcity of vasodilator biogenic amines (eg, dopamine), which suggests a possible violation of the organ of vascular tone with the phenomenon of tissue hypoperfusion and hypoxia. Such changes are less pronounced and persistent after partial nephrectomy than after nephrectomy. This indicates on the better condition of microcirculation in organs and tissues after partial nephrectomy compared with nephrectomy.

One of the central problems in modern nephrology is the question of the mechanism of progression of chronic kidney disease. The ending of this process is the development of chronic renal failure (CRF). Now do not question the fact that CRF is an inevitable and natural outcome of almost all of nephropathy.

CRF syndrome is the consequience of irreversible decline in kidney function due to a significant (not less than 30%) reduction of the number of active nephrons.

Chronic kidney disease (CKD) will inevitably lead to the progression of chronic renal failure due to gradual sclerosis of renal tissue. Therefore, reducing the rate of development of renal failure can only be achieved by studying of nephrosclerosis and developing the effective methods its prevention. The stydying of the issue, was started in the 70's and demonstrated that the basis of the developing and progression of nephrosclerosis is the aggregate effect of the cellular and molecular mechanisms, which are complex processes of tissue repairing in response to damage.

Vrenner B. M. and Anderson S. made hypothesis which explain the renal role in the development of hypertension due to decrease the number of functioning nephrons, which may be congenital or acquired as a result of chronic illness or surgery. The reducing of number of nephrons lead to an increase in blood volume and blood pressure (BP). Renal sodium retention and increased blood pressure elevate the glomerular capillary pressure and sclerosis. Reducing the mass of existing nephrons (ITD) leads to adaptive, functional and structural changes of the remaining functioning nephrons with the outcome of progressive glomerular and

nephrosclerosis [5, 7]. Adaptive hemodynamic changes result in a chain of interrelated changes: stress and tension of the glomerular capillary walls, the violation of its integrity and permeability, the formation of microthrombi and microaneurysms. This contributes to endothelial dysfunction, the damage of the glomerular epithelial, denudation of the basement membrane. As a consequence, there is a transudation of macromolecules in the mesangium and in the cavity of the capsule Shumlyanskogo-Bowman, which leads to overload and dysfunction of mesangial cells and tubular epithelium with increased production of cytokines and growth factors (they currently have a key role) and ends the formation of glomerulosclerosis and tubulointerstitial fibrosis [7, 11]. Kidney damage due to high blood pressure is a result of pathological changes in the renal arteries of small caliber called primary nephrosclerosis. Secondary nephrosclerosis develops because of kidney disease, such as glomerulonephritis, polycystic, obstructive diseases and other early diagnosis of hypertension and its insistence on treatment are essential components of preservation of renal function in patients with nephrological diseases.

In addition to blood pressure reduction, it is important to prevent the nephrosclerosis (both primary and secondary) to reduce intraglomerular hypertension. It is considered that the severity of kidney disease is dependent on the pressure in the glomerulus and the degree of glomerular hypertrophy than on the level of systemic blood pressure. Antihypertensive drugs that can reduce intraglomerular hypertension have a more significant nephroprotective effect than those that do not affect renal hemodynamics. The reduction of proteinuria has also nephroprotective effect. Deterioration of renal function occurs more rapidly in patients with severe proteinuria. On the contrary, its reduction at the beginning of antihypertensive therapy is a predictor of a more favorable course of renal disease in the future. The MDRD study (The Modification of Diet in Renal Disease) showed that in patients with proteinuria, less than 1 g per day, the best outcome (the least progression of glomerular filtration rate) is observed in blood pressure less then 130/80 mm Hg and in patients with proteinuria equal to or greater than 1 g per day - with BP less125/75 mm Hg. In this regard, there were recommendations of WHO (1999) on the need for a more aggressive reduction of blood pressure (<125/75 mm Hg) in patients with renal disease and proteinuria 1 g/ day than in patients with renal disease and proteinuria less 1 g/day or without (130/80 mm Hg) [40, 41].

In addition, it was proven good nephroprotective effect of ACE inhibitors (lisinopril). It has been shown with randomized, double-blind, placebo-controlled trial which was attended by 530 patients with diabetes mellitus (DM) I type in the

age of 20-59 years with normoalbuminuria or microalbuminuria. According to the study, lisinopril decrease the progression of kidney disease in patients with diabetes type I with normal blood pressure and microalbuminuria. The greatest effect was observed in patients with microalbuminuria. The results of this study also showed that lisinopril does not increase the risk of hypoglycemia in insulin-dependent diabetes [37].

Relationship between glomerular hypertrophy and sclerosis also noted by A.Fogo in other kidney damage, arising, in diabetes or hypoxia. The data obtained have allowed the author to express the idea that increasing the size of the glomerulus is a sign of growth factors, stimulating hypertrophy and increased accumulation of extracellular matrix in it, which is a substrate of glomerulosclerosis [33, 35]. A. Fogo suggests that the stimulus that promote the growth of glomeruli and glomerulosclerosis include: 1) loss of renal mass and 2) a high proteinuria or high intake of salt and 3) the effect of a number of neurotransmitters and hormones such as growth hormone, insulin-like growth factor, androgens , glucocorticoids and vasoactive molecules (angiotensin II, endothelin) [34, 35].

An another mechanism of stimulation fibrosing risk factors and cytokines is considered the hypoxia.

According to L.C. Fine et al. [30] the entire chain of events occurring in advanced renal disease can not be explained only by the hemodynamic adaptive changes. Therefore, without denying the importance of adaptive hemodynamic mechanisms they offer what is called a unifying "hypoxic" the hypothesis that the primary driver of fibrogenesis in the kidney is chronic hypoxia. According to the authors of this hypothesis the death of the renal parenchyma inevitably accompanies ischemia arising from the neglect and atrophy of the tubules and the peritubular capillary bed. It directly promotes fibrogenesis in the interstitium and in the glomerulus and these processes are in addition to those that are associated with hyperperfusion and hyperfiltration. The authors also suggest that the specific to the reduction of the MEN (the mass of existing nephrons) the increase of intraglomerular pressure plays an important role not only in the initiation of reverse osmosis, but also through its transmission to the efferent arterioles and then to the interstitium leading to further damage and loss of the remaining nephrons. The significance of hypoxia in the formation of nephrosclerosis L.C. Fine et al. confirm their own data demonstrating stimulation under the influence of ischemia profibrosing production of cytokines and growth factors in cell culture and mezangiocites tubular epithelium [30].

Now it is out of question the suggestion that independ on the triggers the increased production of a number of mediators of cellular response cytokines and growth factors such as transforming growth factor (TGF-pi), platelet derived growth factor (PDGF), fibroblast growth factor (TCP), insulin-like growth factor 1 (IGF1) and others are the basis for the development of glomerulosclerosis and tubulointerstitial fibrosis [24-27].

In a chain of the events that initiate and sustain the process of nephrosclerosis the important role was given to angiotensin II (Ang II) [8, 12] - the main effector of the renin-angiotensin system (RAS). His intrarenal concentration thousands of times greater than the level in the blood.

Hemodynamic effects of Ang II is manifested by stimulation of vascular tone and efferent arterioles supporting the glomerular filtration in the nephron and develops intraglomerular hypertension and hyperfiltration.

Nongemodinamic effect of Ang II is a potent inducer of growth factors play an important role in the proliferation of vascular smooth muscle cells and mesengial glomeruli [12].

Numerous studies have proven a key role of Ang II in the initiation and progression of nephrosclerosis. It were the basis for developing a strategy of nephroprotection based on pharmacological inhibition of intrarenal RAS. RAS inhibition is a recognized as "gold standard" of therapy aimed to reducing the progression of CKD in an advanced stage [2, 3]. In the majority of cases it is used the two groups of drugs: blockers angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers kAng II (ARB). Inhibition of intrarenal RAS may be accompanied by an acute increase in blood creatinine. This occurs due to the reduction in glomerular filtration as to the expected weakening of constrictor influence Ang II on efferent arterioles. This effect is one of the main components of the ACE nephroprotective effect. The CF reduction (approximately in 30%) did not require discontinuation of therapy. After 30 days of treatment renal hemodynamics stabilized at a new level and the CF is usually returned to the original values. It should be keep in mind that ACE inhibitors are prescribed in chronic renal failure not as an antihypertensive therapy, but as inhibition of progression nephrofibrosis. Nephroprotective effect in taking ACE inhibitors due to lower intraglomerular hypertension have increased glomerular filtration rate, increased natriuresis and decrease potassium, reduce proteinuria, increase urine output [8].

In patients with non-diabetic renal disease the ACF inhibitor are the basis therapy of renal protection. It was proven in several studies. In a study of REIN (Ramipril Efficacy in Nephropathy) [28] in patients with chronic diffuse diseases of the kidney, with moderate chronic renal failure were treated with ACE inhibitors

had a slower rate of progression of chronic renal failure (decreased glomerular filtration rate 0,55 ml/min per month in the group which was treated with ACE inhibitors compared with 0,88 ml/min per month in the placebo group. In the group with severe proteinuria (more than 3 g/day) the effect of ACE inhibitors was extremily pronounced. The study AIPRI (Angiotensin-converting enzyme Inhibition in Progressive Renal Insufficiency) [5, 15] demonstrated the ability of ACE inhibitors in patients with non-diabetic renal disease and moderate renal insufficiency (creatinine clearance less than 50 ml / min) to inhibit the development of chronic renal failure and to prolong the predialysis period. It was found that treatment with ACE inhibitors helps prolonged the period of predialysis chronic renal failure by an average of 4 years. In particular 3 years of therapy of the terminal renal failure has been ascertained only 31 of the 300 patients of the group, while in the control group by that time it has developed in 57 of 283 patients. After 6 years of treatment nearly half of patients in the control group (102 of 283) were in need of renal replacement therapy, whereas in the experimental group these patients were less than half as much (79 of 300) [29].

The administation of ACE inhibitors according to an analysis of 10 randomized studies in patients with non-diabetic kidney disease allows compared to other antihypertensive drug therapy groups to reduce the risk of developing end-stage renal failure by 30% [5]. Effectivness of ACE inhibitors in patients with diabetic nephropathy have been proven in studies ACEi-I Trial and MICRO-HOPE [36]. In a study of ACEi-I Trial [8] was used captopril in over 4 years in patients with diabetes mellitus type 1 that gave the reduction the rate of progression of chronic renal failure in 2 times. Renal protective effect of ACE inhibitors was independent on the blood pressure reduction. The use of ACE inhibitors during the 4,5 years of the study MICRO-HOPE (Microalbuminuria, Cardiovascular and Renal Outcomes in the Heart Outcomes Prevention Evaluation) [14, 36] reduced the risk of proteinuretic stage of diabetic nephropathy by 24%. The study EUCLID in the group with initial microalbuminuria ACEI therapy within 2 years decreased by 50% compared with placebo, the rate of excretion of albumin. In the group with normoalbuminuria albumin excretion rate differed slightly. According to S. Lambert [14], the administering of perindopril for 3 years reduced albuminuria from 60 to 12 mg/day. According to a meta-analysis conducted by R. Bretzel in patients with diabetic nephropathy, ACE inhibitors are superior to other drug groups on the degree of reduction in proteinuria and blood pressure, yielding to these indicators only combination therapy, in other wards, the use of ACE inhibitors in patients with diabetes may dramatically reduce the progression of renal dysfunction [10, 15].

The search the ways to address the mechanisms of progression of nephrosclerosis led to the creation the new direction in the treatment of renal

protection, the possibility of that in the last ten years have increased significantly. Now we can talk about five of these methods, the influence of which on the progression of nephrosclerosis was proven or studied: 1) ACE, 2) Low molecular weight heparins (LMWH), 3) Pentoxifylline, 4) lipid-lowering drugs and 5) mannitol.

Low molecular weight heparins in nephrology practice is used not only due to their ability to inhibit the process of intravascular (including intraglomerular) coagulation they have a diuretic, natriyuretic, antihypertensive and lipid-lowering effects. In addition, they reduce proteinuria, reduce mesangial cell proliferation [12].

For the improvement of the rheological properties of blood in patients with diabetic nephropathy the preference is given to the pentoxifylline (Trental), because it not only improves the microcirculation and inhibits transforming growth factor-β, but demonstated the fibrotic changes in the kidney. It may be used for a long time without any risk of serious side effects (oral dose is 300-500 mg/day) depending on the height and weight of the patient. Pentoxifylline in a relatively short time has got a wide popularity as an effective tool for the treatment of peripheral circulatory disorders caused by atherosclerosis [30], diabetes and inflammation [16] as well as for the treatment of pathological conditions associated with a deficiency of blood supply [26]. Pentoxifylline improves microcirculation in the tissues primarily by increasing elasticity (deformability) and reducing the aggregation activity of erythrocytes [36], reducing the viscosity [16, 19] and improve the flow of blood [29]. The vasodilation effect of the drug is less pronounced and is manifested mainly in the spastic vessels (skin effect). This effect distinguishes the pentoxifylline from the most vasodilating drugs that are capable to produce so-called "steal syndrome" due to unfavorable redistribution of blood flow in the ischemic area. Pentoxifylline has the unique ability to increase the plasticity of the cell membrane of red blood cells, allowing them to penetrate into the vessels with altered clearance (reduced diameter) and improve the blood supply to the tissues, especially during hypoxia [3]. During the decreasing of the blood flow velocity in the microvasculature part it is increased the ability of red blood cells to aggregate. Pentoxifylline inhibits the aggregation of red blood cells, facilitates their entry into the extravascular channel, that increases the tissue oxygenation.

In patients with hyperlipidemia, lipid-lowering drugs reduce the deposition of lipids in the kidneys with subsequent reduction of the proliferation of mesangial cells and slowing hardening of the kidney tissue. Statins reduce cholesterol

synthesis in the liver - lovastatin (Mevacor), flyuvastatin (Lescol). Numerous experimental studies confirmed the beneficial effect of statins in various nephropathies, but clinical observations in this area are scarce. Mannitol reduces the damage of the tubules in the kidneys in a sharp drop filtration. During intraoperative administration manitol maintains optimal renal perfusion and prevents cortical vasoconstriction during renal artery clamping. It provides increased fluid excretion after perfusion, reduces renal vascular resistance and increases the blood flow in them, removes nephrotoxins [32, 33].

During a relatively short ischemic time kidney nephron wall are unpermeable to mannitol, but prolonged ischemia with the development of acute tubular necrosis or high concentrations of nephrotoxic substances that damage the tubular epithelium, gradually reduced the selective permeability of the nephron walls to water molecules, making the use of osmodiuretics ineffective. As mentioned before, mannitol has certain properties of vasodilator. Indeed, the application of medium and low-dose mannitol (<200 mg per day or <400 mg per 48 hours), mannitol causes marked dilation of the arteries and arterioles of the kidneys. While there is a significant increase in renal blood flow, especially in the medulla, are particularly sensitive to ischemia. The mechanism of this phenomenon seems to be associated with mannitol-induced increase in the production of prostaglandins in renal medullary tissue [31 - 33]. Manitol reduces damage of the tubules of the kidneys in an acute droping filtration (in patients with shocks, burns, sepsis, peritonitis, osteomyelitis, in which the drug improves renal blood flow) and severe poisoning hemolytic poisons (precipitation of proteins, hemoglobin-risk of blockage of the renal tubules and anuria).

The ACE-inhibitors have pronounced nephroprotective effect in patients after the kidney resection and hypertension. It manifests as in a decreasing in proteinuria and slowing of decline in glomerular filtration, as well as the later appearance of morphological changes (signs of glomerulosclerosis). The main mechanism of renal protection with ACE-inhibitors is a reducing the hydrostatic pressure in the glomerulus, due to a decrease of efferent arteriolar tone. This prevents protein hyperfiltration and the appearance of morphological changes due to intraglomerular hypertension. Afferent arteriolar tone is also reduced, although to a lesser extent than the efferent. Due to dilation of blood vessels the renal blood flow is not getting worse, despite the reduction in systemic blood pressure [11].

Thus, from the presented date it can be concluded that the use of ACE-inhibitors slows the progression of nephrosclerosis after partial nephrectomy. Do not always the use of monotherapy with ACE-inhibitors can achieve the target

value. The effectiveness of the administration other drugs that control blood pressure and slow the progression of nephrosclerosis is under study. The adequate hydration, maintaining a normal blood pressure and nephroprotective therapy can reduce the level of renal insufficiency. Nephroprotective therapy has cardioprotectiveeffect and allows to slow the progression of nephrosclerosis and the development of cardiovascular disease. Nephroprotective therapy reduces the cost of treatment complications and end-stage renal failure. Given the existing evidence, the inclusion of ACE-inhibitors and other drugs in the treatment program of the patients today must become a regular tool, regardless of their effect on blood pressure.

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