IS THERE AN OPTIMAL ARTERIAL PRESSURE LEVEL IN PATIENTS WITH END-STAGE CHRONIC RENAL FAILURE BEFORE AND AFTER KIDNEY TRANSPLANTATION?

UDC 616.12–008.331.1+616.61–008–002.2–089.87
Received 5.12.2013

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Arterial hypertension occurs in 100% cases of end-stage chronic renal failure (ESCRF). It significantly worsens ESCRF and provokes cardiovascular complications. The presence of uncontrolled arterial hypertension after kidney transplantation becomes a determining factor deteriorating the prognosis of patients.

The aim of the investigation was to define the changes of arterial pressure (AP) in patients with end-stage chronic renal failure before and after kidney transplantation, along with antihypertensive therapy, and determine the most safe arterial pressure levels, with the kidney continuing its optimal functioning.

Materials and Methods. The study involved 31 patients (16 male, 15 female patients), who underwent kidney transplantation for ESCRF. The study included the kidney functioning monitoring for a month after the transplantation (5 examinations), and the analysis of hemodynamic, biochemical indices, with transplant function definition. With the aim of achieving optimal AP before and after kidney transplantation, we actively titrated antihypertensive medicinal preparations and studied the functional state of a transplant.

Results. Arterial hypertension was diagnosed in 100% of patients before transplantation; its level decreasing, on average, to the next lower order. In early postoperative period on day 7±1 the patients' systolic AP decreased from 159.4±13.2/98.7±5.6 to 137.1±9.4/84.8±8.1 mm Hg ($p<0.001$), and by the time of discharge its level averaged 127.9±9.2/81.1±6.9 mm Hg. Before hospitalization the patients took on average 1.9±0.2 basic medications, on discharge — 2.9±0.1. The indices of creatinine and urea levels, glomerular filtration rate (GFR) and proteinuria consistently normalized. Postoperative intensity of systemic AP decrease had no effect on GFR levels in patients with ESCRF: GFR insignificantly increased in higher systolic AP: $R^2=0.082$; $p=0.09$; $R'^2=0.083$; $p=0.23$. A month after kidney transplantation AP level appeared to be optimal in the range of 115–130 mm Hg, and with such AP values GFR indices significantly grew ($R^2=0.25$; $p=0.035$; $R'^2=0.3$; $p=0.027$). Diastolic AP level had no significant effect on transplant function.

Conclusion. In 100% cases, ESCRF patients have a syndrome of II or III degree arterial hypertension. After kidney transplantation there is an independent AP increase by one-two AP increase degrees. Intensive AP decrease in ESCRF patients before transplantation results in GFR decline. After transplantation there is GFR increase with an active decrease of systolic AP in the range of 115–130 mm Hg.

Key words: kidney transplantation; end-stage chronic renal failure; arterial hypertension; glomerular filtration rate; antihypertensive therapy.

Hypertension syndrome is a common manifestation of end-stage chronic renal failure (ESCRF) [1, 2]. High arterial pressure (AP) level is an independent risk factor of cardiovascular complication in ESCRF patients [3]. The presence of uncontrolled AP results in progressive renal failure in patients with renal disorders [4, 5].

The study of AP level dynamics in patients after kidney transplantation is still provoking interest [6, 7], since AP increase after transplantation is certain to have an effect on transplant state and continue to destroy progressively target organs. In 1988 B.L. Kasiske et al. for the first time showed that the presence of arterial hypertension (AH) in ESCRF patients after renal transplantation increases the risk of cardiovascular complications: as early as four years after transplantation its level grows by 3–4 times compared with the population of patients with renal disorders without AH [8]. In the structure of death rate after kidney transplantation, cardiovascular causes associated with high AP level amount to 55–70% [9, 10]. Transplant damage due to high AP level

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becomes an independent risk factor of cardiovascular complications [10] and incompetence of a transplanted kidney concerning rejection or quicker development of renal failure.

The latest studies on large samplings have shown the presence of AP over 130/80 mm Hg to be an independent factor of both cardiovascular complications and organ rejection syndrome [11]. The study [12] has found that AP of a recipient after renal transplantation being over 160/100 mm Hg increases the risk of cardiovascular and non-cardiovascular complications more than twofold.

Some researchers show systemic AP level after kidney transplantation to grow within 7–14 days that can be considered as essential hypertension formation or early transplant rejection [13–15]. Current stratification theory of risk factors considers the summing of variable and invariable risk factors when making a prognosis of a patient included in cardiorenal continuum. The presence of uncontrolled AH becomes a determining factor, which worsens the prognosis of patients after renal transplantation.

The aim of the investigation was to define the changes of arterial pressure in patients with end-stage chronic renal failure before and after kidney transplantation, along with antihypertensive therapy, and determine the most safe arterial pressure levels, with the kidney continuing its optimal functioning.

Materials and Methods. The study involved 31 patients (16 male and 15 female patients) who underwent kidney transplantation for ESCRF. Patients` age ranged within 22–60 years (mean age — 33.0±8.7 years). The main etiological causes of ESCRF were the following: in 78.2% cases (n=25) — chronic glomerulonephritis, in 6.3% (n=2) — chronic tubulo-intestitial nephritis. Rare causes were chronic calculous pyelonephritis — in 3.1% patients (n=1), polycystic kidneys — in 6.2% (n=2) and congenital urinary abnormalities — in 3.1% (n=1).

Before transplantation the patients were in an inpatient department for no more than two days. On the average, the patients were discharged from hospital after effective renal transplantation on day 33.0±8.6.

The study complies with the declaration of Helsinki (adopted in June, 1964 (Helsinki, Finland) and revised in October, 2000 (Edinburg, Scotland)). Written informed consent was obtained from all patients.

Study design. Every patient involved in the study was examined on admission, intraoperatively, on day 7±1 after surgery, on day 20±1 after renal transplantation, and when being discharged from hospital, if the length of a recipient's hospital stay appeared to be more than three weeks. Each time, AP and heart rate were measured thrice, as well as mean values were calculated.

The study design also included the determination of creatinine, urea, uric acid, proteinuria levels, calculation of glomerular filtration rate (GFR) according to Cockroft–Gault formula [16, 17].

Renal blood flow was studied concurrently. Renal blood flow of a transplanted kidney was dynamically controlled using Doppler sonography (USDG) on the first postoperative day, and daily within two weeks, then — once in three days, and in case a recipient was stable — once a week before discharge from hospital.

For the purposes of the most effective AP reduction, first line antihypertensive drugs in average therapy doses were used both before and after renal transplantation. In case non-effective AP control persisted (the study specified target AP level — under 140/90 mm Hg) the number of medications increased due to second line antihypertensive drugs.

Mathematical analysis. The findings were statistically processed using software and statistical packages. To determine significant differences between the groups we used Student t-test, dispersion analysis ANOVA (in case of parametric value distribution) and chi square test (for nonparametric value distribution).

For regression analysis between parametric variables we used linear (R^2) and square regression ($R^{\wedge 2}$) models. Determination coefficient was used as the criterion determining constraint force of variables in the described model. Hypothesis test results were considered significant if $p<0.05$.

Results and Discussion. AH was diagnosed in all patients before kidney transplantation. Its duration averaged 12.9±8.1 years. Due to the fact that the main reason for renal transplantation was diagnosed chronic glomerulonephritis, it can be expected that the major part of patients had secondary renal hypertension. Although all patients during the pre-hospital period took antihypertensive medications, most patients (90.3%, n=28) had uncontrolled AP levels. None patients in the sample had optimal AP levels.

Other risk factors deteriorating patients` prognosis were smoking, overweight or obesity, dislipidemy. One in three men with ESCRF smoked, there were no smoking women. Overweight was found in six patients and I stage obesity — in two of them. Dislipidemy was revealed in 30% patients; meanwhile in all patients low-density lipoprotein cholesterol was over 3.0 mmol/L.

On admission average systolic AP (SAP) was 159.4±13.7 mm Hg, average diastolic AP (DAP) was 98.7±5.6 mm Hg. Average HR in a study group was close to tachycardia – 78.6±9.9 per minute (Table 1).

In an early postoperative period – on day 7±1 — SAP decreased from 159.4±13.2 to 137.1±9.4 mm Hg ($p<0.001$). During the following examinations the SAP decrease was found to have linear character: by the fourth visit (20±1 day) it dropped to 132.6±7.7 with active titration of antihypertensive drugs ($p<0.001$) and by the time of discharge — to 127.9±9.2 mm Hg ($p<0.001$).

Less expressed regularity was observed for DAP levels. On day 7±1 after operation DAP was 84.8± 8.1 mm Hg, and did not differ from its values in the moment just before the surgery ($p=0.99$). On day 20±1 after kidney transplantation there was statistically

Table 1

The dynamics of SAP- and DAP-levels in patients during kidney transplantation

Parameter	1. On admission	2. Intraoperative	3. On day 7±1	4. On day 20±1	5. On day 33±8.6
SAP, mm Hg	159.4±13.7	127.7±9.2	137.1±9.4 p_{2-3}<0.001	132.6±7.7 p_{3-4}<0.001	127.9±9.2 p_{4-5}<0.001
DAP, mm Hg	98.7±5.6	83.5±9.9	84.8±8.1 p_{2-3}=0.99	85.8±9.6 p_{3-4}=0.69	81.1±6.9 p_{4-5}=0.046
HR, per minute	78.6±9.9	73.6±7.8	70.1±4.2 p_{2-3}=0.02	67.3±5.4 p_{3-4}=0.01	63.6+6.8 p_{4-5}<0.001
The number of drugs	1.9±0.2 p_{1-5}<0.0001	2.1±0.3 p_{2-3}=0.03	1.8±0.3 p_{2-3}<0.001	2.5±0.3 p_{3-4}<0.001	2.9±0.1 p_{4-5}<0.001

insignificant DAP elevation up to 85.8±9.6 mm Hg (p=0.64). By the time of discharge DAP level dropped up to 81.1±6.9 mm Hg, and appeared to be statistically significant compared to DAP level during the fourth visit (day 20±1) (p=0.046) as well as the DAP level on admission (p<0.001).

Heart rate reached the normal value much more quickly compared with SAP and DAP levels. Its value became normal as early as on day 7±1 — 70.1±4.2 per minute and by the moment of discharge reached relative bradycardia — 63.6±6.8 per minute (See Table 1).

We analyzed the dynamics of AP increase after transplantation to determine how systemic AP level is resistant to antihypertensive therapy in a postoperative period (Fig. 1).

The following fact attracts attention: none of the patients in a pre-hospital stage had an effective AP control. We can assume that renal hypertension is resistant to antihypertensive therapy, however the number of medications (1.9±0.2 drugs) taken at a pre-hospital stage indicates an inadequate antihypertensive therapy that underlies the involvement of target organs. On 7±1 day after surgery none of the patients with transplanted kidney had AP increase to III degree AH. This period was remarkable for the redistribution of the patients by AP increase degree compared to hypertension indices in a pre-hospital period: the portion of II degree AH patients decreased (up to 29.0%; p=0.56), the number of I degree AH patients increased (up to 48.4%; p=0.45), and there was formed the sampling of patients with normal AP (up to 22.6%; p=0.12). AP normalized in patients taking an invariable dose of antihypertensive drugs, having slightly increased preoperative AP, whose hypertension duration did not exceed seven years.

On the back of the changed antihypertensive therapy within the following three weeks (visit — discharge day) 67.7% test subjects had normal AP (under 140/90 mm Hg). The differences appeared to be highly significant as compared with the periods of days 7±1 and 20±1 (p<0.001). When being discharged from hospital the rest of the patients had AP level consistent with degree I AH that was also highly significant in comparison with the mentioned periods (p<0.001).

AP normalization among the treatment group patients with transplanted kidney became possible only after active titration of antihypertensive drugs. Before hospitalization the patients took on average 1.9±0.2 basic medications that turned out to be ineffective in relation to AP control in patients with ESCRF. Over the period of preparation for surgery or immediately after the operation, the number of medications significantly grew, but by day 7±1 the number of antihypertensive drugs was significantly reduced, concurrently with an independent AP decrease after transplantation. The findings give evidence of the termination of renal hypertension associated with terminal renal failure. Further AP dynamics showed that effective AP control needs significant increase of the number of antihypertensive drugs (to 2.9±0.1 on day 33±8.6) that subsequently enabled to achieve effective AP control in most recipients. AP re-growth on day 7±1 corrected by the increased number of antihypertensive drugs

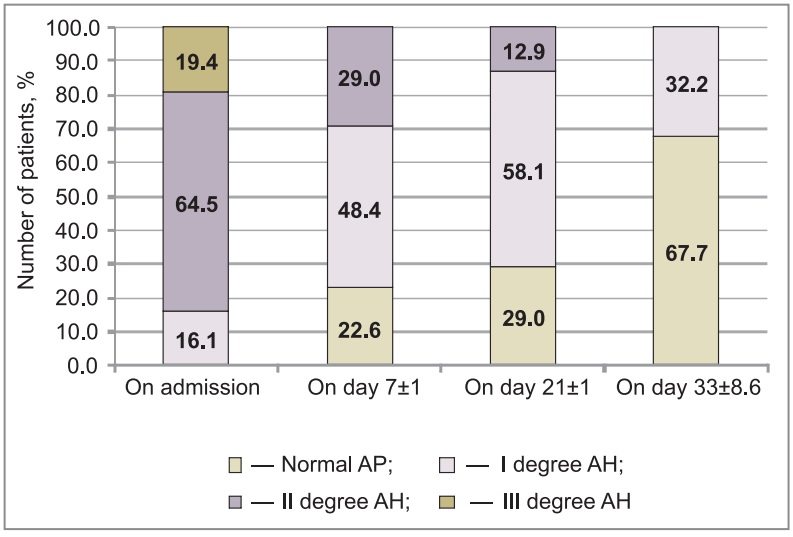

Fig. 1. AP level dynamics in patients before and after renal transplantation

Table 2

Main parameters of renal function in patients before and after kidney transplantation

Parameter	1. On admission	2. Intraoperative	3. On day 7±1	4. On day 20±1	5. On day 33±8.6
Urea, mmol/L	18.5±6.0 p_{1-5}<0.0001	12.7±5.9 p_{2-3}=0.03	11.8±6.5 p_{2-3}=0.26	10.3±5.9 p_{3-4}=0.09	8.5±2.0 p_{4-5}=0.001
Creatinine, μmol/L	753.7±290.3 p_{1-5}<0.0001	572.0±180.5 p_{2-3}=0.02	317.2±192.2 p_{2-3}<0.001	138.7±78.4 p_{3-4}<0.001	113.0±39.8 p_{4-5}<0.001
GFR, ml/min	10.89±4.66 p_{1-5}<0.0001	17.52±8.34 p_{2-3}=0.03	29.16±11.90 p_{2-3}<0.001	59.42±23.8 p_{3-4}<0.001	65.48±20.03 p_{4-5}=0.001
Proteinuria, g/L	0.78±0.41 p_{1-5}<0.0001	0.57±0.39 p_{2-3}=0.03	0.35±0.3 p_{2-3}=0.01	0.19±0.27 p_{3-4}=0.03	0.15±0.27 p_{4-5}=0.001

was related to the adaptation transplant function in a recipient, and an active beginning of glucocorticosteroid and immunosuppressive therapy.

During the research the dynamics of main parameters of renal function before and after transplantation (Table 2) was analyzed. On 7±1 postoperative day urea level dropped to 11.8±6.5 mmol/L in comparison with the similar preoperative parameter (p=0.26) and in 20±1 days it was 10.3±5.9 mmol/L (p=0.09). Significant decrease of urea level was found on admission, when its value dropped to 8.5±2.0 mmol/L (p=0.001). The similar tendency was discovered for creatinine level change. On day 7±1 after operation creatinine level was 317.2±192.2 μmol/L, which turned out statistically lower than before operation (p<0.001). By day 20±1 after operation creatinine level continued decreasing significantly and reached 138.7±78.4 μmol/L (p<0.001) and by the moment of discharge this parameter was close to the upper normal value and was 113.0±39.8 μmol/L (p<0.001).

GFR (glomerular filtration rate) was analyzed according to Cockroft–Gault formula, because during the first 6–12 months following the transplantation this formula has more accurate findings [16, 17]. According to the received data on day 7±1 after kidney transplantation 95.3% of patients were found to have GFR decrease. During this period mean value is 29.16±11.90 ml/min that is statistically higher (p<0.001) than before operation. Every following examination the GFR value continued increasing linearly and amounted to 59.42±23.80 ml/min on day 21±1 after operation (p<0.001). In this period 100% of patients had higher GFR in comparison with its value on admission. By the time of discharge the parameter increased up to 65.48±20.03 ml/min (p<0.001).

The surveillance over proteinuria level during all the study period showed the patients had a significant decrease of protein level. The most intensive drop was found 33±8.6 days after transplantation: proteinuria level in patients decreased to 0.15±0.27 g/L (p=0.001). Only 38.7% of patients had proteinuria that is significantly lower than that before surgery — 96.7% (p<0.001).

Consequently, after successful kidney transplantation, basic biochemical indices of its function (GFR, creatinine and urea level, proteinuria) significantly improve what results from adequate transplant functioning.

Since 100% patients in ESCRF had AH, and the study stated the dynamics of AP levels depending on medication growth, we analyzed the change of GFR levels in patients after transplantation due to the intensity of AP level decrease (Fig. 2). In the pre-operative period the indices of lower levels of systemic AP had no effect on GFR in ESCRF patients (R^2=0.082; p=0.09; $R^{\wedge 2}$=0.083; p=0.23). GFR indices were found to be higher in higher SAD level, though GFR ranged from 5 to 10 ml/min. This may be due to the fact that in ESCRF the number of functioning glomeruli is so small that more intense systemic hypertension is required, which stimulates glomerular function only due to intraglomerular pressure increase. On the other hand, systemic AP decrease results in glomerular circulation improverishment and decreased excretory activity. In ESCRF the decrease of systemic AP aims only at preventing the damage of target organs involved in cardiovascular AH continuum rather than at preserving a dying kidney.

The study of GFR level changes depending on the intensity of AP level decrease after kidney transplantation revealed the following regularity: the lower systemic AP level, the more effective the transplant's function is. The findings showed SAD level in the range of 115–130 mm Hg to be optimal for transplant functioning. A month after transplantation GFR was established to be significantly much higher (R^2=0.25; p=0.035; $R^{\wedge 2}$=0.3; p=0.027) if SAD is 115–130 mm Hg. In addition, DAD level in the range of 70–90 mm Hg was found to have no significant effect on GFR indices.

So, the AP control in patients with terminal chronic nephrotonia is necessary only for the purpose of prevention of target-organ damage (heart, brain, aorta, etc.), the change of AP level has no effect on affected kidney function. After transplantation AP increase should be more aggressive, than the achievement of target AP level — this enables to ensure high efficiency of transplant and other target-organs. One should pay

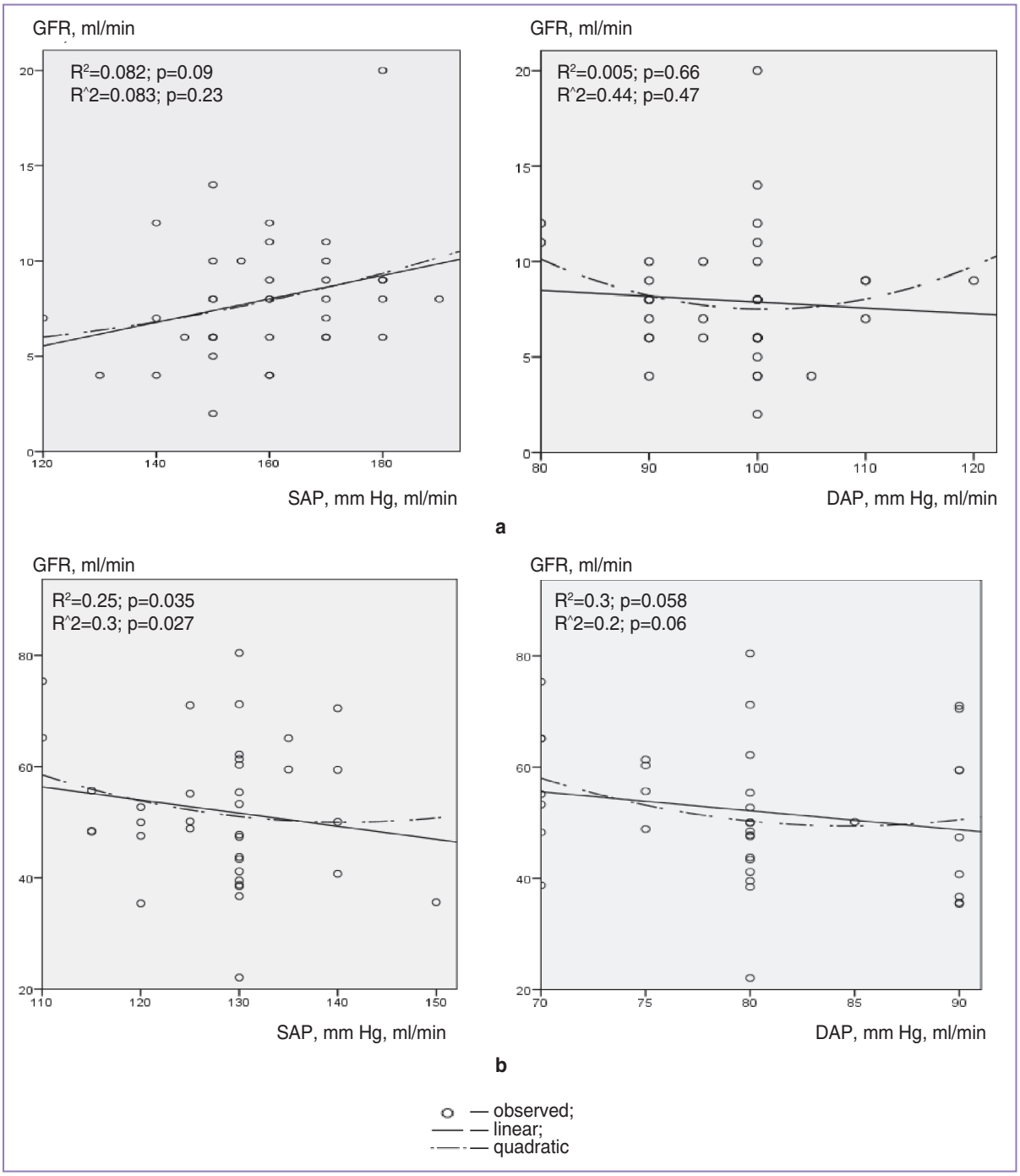

Fig. 2. GFR dynamics depending on systemic AP level before (*a*) and 33±8.6 days after (*b*) renal transplantation

attention to the fact that drug hypotension (AP level is lower than 115/70 mm Hg) results in deterioration of normal transplant function.

Conclusion. 100% patients with end-stage chronic renal failure have II and III degree arterial hypertension syndrome. Before kidney transplantation AP decrease in such patients results in glomerular filtration rate reduction, therefore there is no active AP control in these patients in real clinical practice.

After kidney transplantation there is an independent AP decrease within one degree. But at the same time to achieve target AP it is necessary to take on average 2.9±0.1 antihypertensive drugs at standard doses that enables to reach effective AP control in two out of three patients within a month after the operation. More effective use of antihypertensive therapy in patients after renal transplantation leads to glomerular filtration rate increase.

Study Funding and Conflict of Interests. The study was not supported by any funds, and the authors have no conflict of interest to disclose.

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