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**The effect of pre-existing HLA sensitization on the renal allograft
function according to angionephroscintigraphy results**

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An important role in assessing the transplanted kidney function recovery and diagnosing posttransplant complications belongs to angionephroscintigraphy allowing a qualitative and quantitative assessment of renal perfusion, filtration, and excretion.

The aim of the study was to evaluate and monitor the allograft function after cadaveric kidney transplantation by using angionephroscintigraphy with ^{99m}Tc-Pentatech and studying the obtained results in relation to pre-existing HLA sensitization.

We analyzed the results of radionuclide tests of 55 patients in the early postoperative period in time from 5 days to 3 months after transplantation. In most patients, the higher was the blood anti-HLA antibody levels in the recipient before the kidney transplantation, the more pronounced decrease in the function was noted in them according to angionephroscintigraphy results. In the treatment of patients with a primary allograft function, the function of the transplanted kidney had gradually

improved by the 3–4th week, reaching normal values in a number of parameters. In patients with a delayed allograft function, only partial recovery of function was observed after 3–4 weeks. In that case, when a high level of preexisting anti-HLA antibodies had been noted, an abrupt decline in perfusion typical for an acute rejection crisis, and the filtration impairment were seen, often there was an impaired excretion, indicating a concomitant severe ischemic injury of the kidney or acute tubular necrosis.

Thus, angionephroscintigraphy enables to assess the recovery of the graft function thanks to a separate evaluation of the function components, and in combination with the test for preexisting anti-HLA antibodies, helps to make a differential diagnosis of an acute rejection crisis and acute tubular necrosis allowing the choice of an adequate treatment tactics.

Keywords: angionephroscintigraphy, kidney transplantation, renal allograft function, HLA sensitization

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AI – accumulation index

MFI – mean fluorescence intensity

ARC – acute rejection crisis

PI – perfusion index

ATN – acute tubular necrosis

RPh – radiopharmaceutical

CKAT – cadaveric kidney

ROIs – regions of interest

allotransplantation

EI – excretion index

Angionephroscintigraphy allows a qualitative and quantitative assessment of renal perfusion, filtration, and excretion [1–3], which plays an

important role in assessing the recovery function of the transplanted kidney and diagnosing posttransplant complications [4, 5]. At the same time, the absence of adverse reactions to the radiopharmaceutical (RPh), a low radiation dose, and a high reproducibility of results are essential.

As a rule, glomerulotropic RPh (^{99m}Tc -DTPA, or ^{99m}Tc -Pentatech, a Russian-manufactured analogue filtered by renal glomeruli) or tubulotropic RPhs (^{123}I - hippurate and ^{99m}Tc -MAG3 secreted in the proximal tubules) are used to evaluate the renal graft function. None of these drugs has any essential advantages over the others, but in repeated studies it is recommended to use one and the same RPh [6, 7]. A wide experience has been gained in the world practice in using the radionuclide method in kidney transplantation, which provides important information to solve such problems as acute tubular necrosis (ATN), acute rejection crisis (ARC), vascular complications, urinary tract damage, and urinary leakage, and also to perform long-term monitoring of renal graft function while the patient being on immunosuppression therapy [8, 9]. Nevertheless, we have found no published studies in the available literature that would have investigated the relationship between the graft functional abnormalities detected by angioneuroscintigraphy in the posttransplant period and the pre-existing HLA-sensitization of a recipient; and this encouraged us to publish our study.

The objective was to assess and monitor the allograft function after cadaveric kidney transplantation by using the results of angioneuroscintigraphy with ^{99m}Tc -Pentatech and to investigate the relationship of the obtained data with pre-existing HLA sensitization level.

Material and methods

The results of the radionuclide assay performed in 55 patients (33 women, 22 men) in the early postoperative period in time from 5 days to 3 months after cadaveric kidney allotransplantation (CKAT) were analyzed. The mean age of the patients was 46.4 ± 14.3 years old (from 19 to 72 years). Depending on the transplanted kidney function, the patients were distributed into two groups. The first group consisted of 36 (65.5%) recipients with primary graft function (the function recovery within 24-48 hours); the second group included 19 (34.5%) recipients with delayed graft function. In each group, the recipients were allocated into subgroups (a, b, c) depending on the presence and level of pre-existing anti-HLA antibodies (Fig. 1).

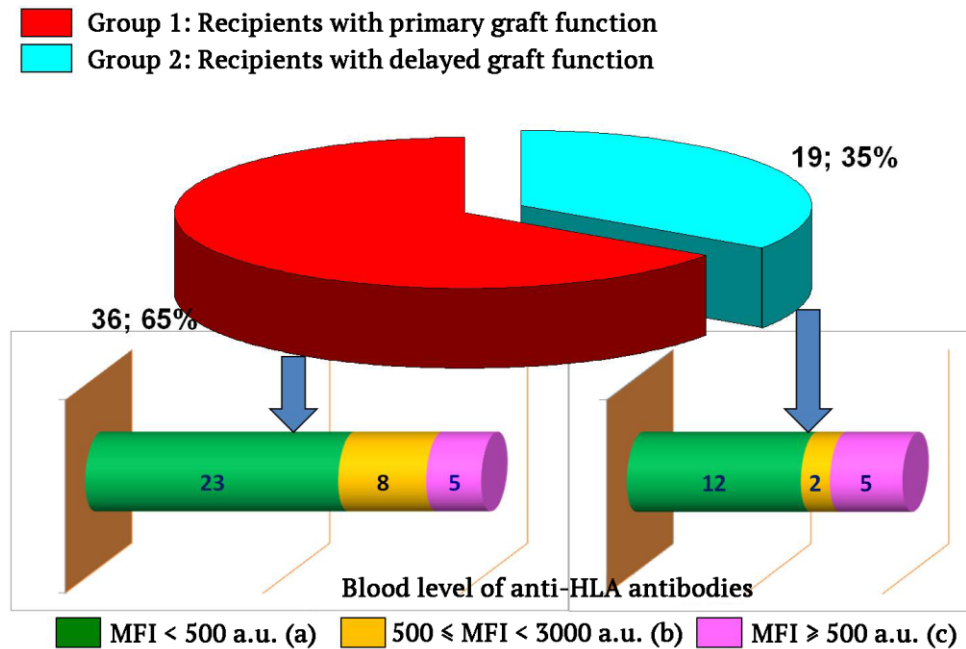


Fig.1. Recipient allocation in groups

The anti-HLA antibody levels in recipient blood were detected just prior to transplantation by multiplexed assay on the Luminex platform using LabScreen kits (One Lambda, USA). Serum reactivity was assessed by the fluorescence signal; the result was qualified as negative sensitization at mean

fluorescence intensity (MFI) not exceeding 500 a.u., as a moderate HLA sensitization level at MFI values of 500-3000 a.u., and as a high HLA sensitization level at MFI over 3000 a.u. [10].

Dynamic angioneuroscintigraphy was performed on Infinia II gamma camera (GE, US) using glomerulotropic radiopharmaceutical ^{99m}Tc -Pentatech (i.v. bolus, 130 - 170 MBq, radiation dose of 0.6-0.9 mSv); a front view was taken with a large field of view detector, the patient lying in a horizontal position. A two-stage recording mode in the matrix of 128 x 128 pxls was applied: 1) the vascular phase of 60 seconds (1 image/s); 2) the parenchymal phase of 20 minutes (1 image/20 s) for evaluation of filtration and excretion. When processing the results, the regions of interest (ROIs) were chosen: the allograft, iliac artery, inferolateral background, and the bladder, with further producing the time-activity curves and subsequent subtraction of the background curve normalized to the area of the ROI over the kidney.

In order to distinguish between the various impaired components of the kidney function, which is especially important for monitoring, we analyzed the type of the curve (renogram) over the allograft and the quantitative variables calculated when estimating the functional curves produced for the selected ROIs.

The perfusion was assessed quantitatively by the curves plotted for the vascular phase for one minute of the study. For this, the Hilson's perfusion index (PI) (A.J.W. Hilson, 1978) [11] was calculated as the ratio of the areas under the area-normalized curves constructed for the iliac artery and for the kidney during the arterial phase, i.e. from the start of the elevation to the peak of the curve from iliac artery. Based on the results of

angionephroscintigraphy in patients with normal filtration and excretion values, PI did not normally exceed 150 for the transplanted kidney.

The filtration and excretion were assessed visually by the renogram type (afunctional, isostenuric, obturational, parenchymal curve types), by the duration of RPh retention in the kidney parenchyma, the delayed RPh entry into the bladder, or by the lack of visualization. With the renogram of the parenchymal type, the traditional parameters [12, 13] were calculated: the time of maximum accumulation (T_{\max} , 3-5 minutes being the norm); the RPh half-life ($T_{1/2}$, no more than 18 minutes for normal kidneys, under 30 minutes for a graft), the glomerular filtration rate (total GFR should be 110-130 ml/min for normal kidneys, and half as low for a graft), time of RPh entering the urinary bladder (T_{ub} , normally being equal to or less than 5 minutes).

To obtain the most complete information about the function, as well as to evaluate the isostenuric and obturational curves, some additional parameters were developed and used: the filtration index (FI) as the increment of the curve amplitude in the ascending part of the filtration segment within 2-3 minutes (normally over 18); the RPh accumulation index (AI) in the organ parenchyma (the ratio of kidney/background accumulation) on the peak of the curve (the norm being over 3) and at minute 20 (the norm being over 1.7); the excretion index (EI) defined as the RPh accumulation ratio of kidney/bladder at 20 minutes (the normal one should be over 3).

Dynamic angionephroscintigraphy was performed 1 to 4 times, depending on the graft function and the presence of complications. For simplicity and clarity, the quantitative values of all the radionuclide study results obtained for each patient were included in the table being a part of the medical report (Fig.2-9). The results were analyzed using the STATISTICA

software package to determine the statistical characteristics of the parameters and the statistical significance of their differences in the nonparametric Mann-Whitney test.

Study results

According to angioneuroscintigraphy results, the majority of patients (21 of 23; 91.3%) with the primary graft function without pre-existing anti-HLA antibodies in blood (MFI less than 500 a.u.) (comprising subgroup 1a: n=23 [63.9%] of 36 recipients) demonstrated a sufficient or slightly reduced perfusion with the PI normalized by day 20-40. Initially, the curves over the allograft area were of the parenchymal type; there was a moderately impaired filtration manifested in the reduction of GFR and FI that increased by day 20 (by 40-50% of the initial values); that was accompanied by the AI and EI increases. The excretion significantly improved, which was manifested in a decrease of $T_{1/2}$. The bladder was visualized from the 5th-6th minute (Fig. 2). According to clinical data, the number of complications in this subgroup was minimal (in 2 patients only) in the form of ARC and ATN.

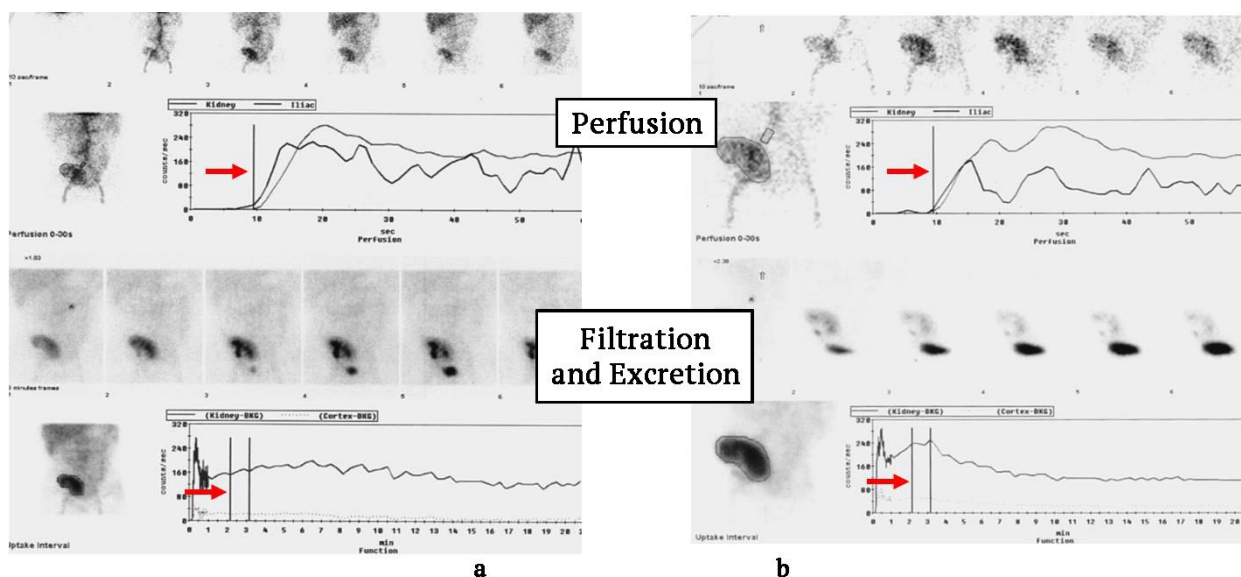


Fig. 2. Normalization of angioneuroscintigraphy parameters of patient B., 58 years old, (subgroup 1a) for 30 days: at posttransplant day 10 (a) and posttransplant day 41 (b). The arrows indicate the calculation intervals for PI (the first 60 seconds) and FI (2-3 minutes)

Day after CKAT	Renogram type	PI	FI	T _{MAX}	T _{1/2}	AI _{peak}	AI ₂₀	EI	T _{ub}	GFR
10th	Parenchymal	200.00	11.17	6.30	37.00	4.94	3.88	0.84	8	33.30
41st	Parenchymal	114.36	20.71	3.15	30.60	8.15	4.55	2.55	4	53.39

At the same time, two patients without pre-existing anti-HLA antibodies and with a satisfactory blood supply demonstrated significant impairments of filtration and excretion, and the renogram above the kidney region was different from the parenchymal type. In one case, the assay performed on day 26 after CKAT yielded the obturational type curve over the region of the transplanted kidney. There was an uncompromised perfusion (PI = 154.5), but a significantly decreased filtration and an abruptly decreased excretory function were observed. In the other case with slightly reduced perfusion (PI = 190), the curve over the kidney region was of isostenuric type, abruptly decreased filtration and excretion were noted.

The data suggested the presence of severe ischemic injury and ATN development.

Among HLA-sensitized patients with MFI in the range of 500-3000 a.u. and the primary graft function (subgroup 1b; n=8 [22.2%] of 36 recipients), 7 of 8 examined patients had the parenchymal type renogram on day 9-10 after CKAT, the filtration and excretion of the graft were reduced; 3 of them had a significantly decreased blood flow: PI exceeded 200, reaching 400 in one case (the risk of ARC). In the course of treatment, all parameters gradually improved, reaching the normal values by the 20-35th day.

Only in one patient of the subgroup, the renogram kept isostenuric type on day 10, and later on day 19 after CKAT; a slight improvement in all quantitative indices had been recorded by day 19: PI decreased from 208 to 160 (showing the improvement), FI and GFR slightly increased, the time of RPh entering the bladder (T_{ub}) reduced. The parenchymal renogram type had restored and all the parameters had reached normal values by day 90 only (Fig. 3). That clinical case was consistent with severe ischemic graft injury or ATN, which required a prolonged pharmacological therapy that gave a positive effect.

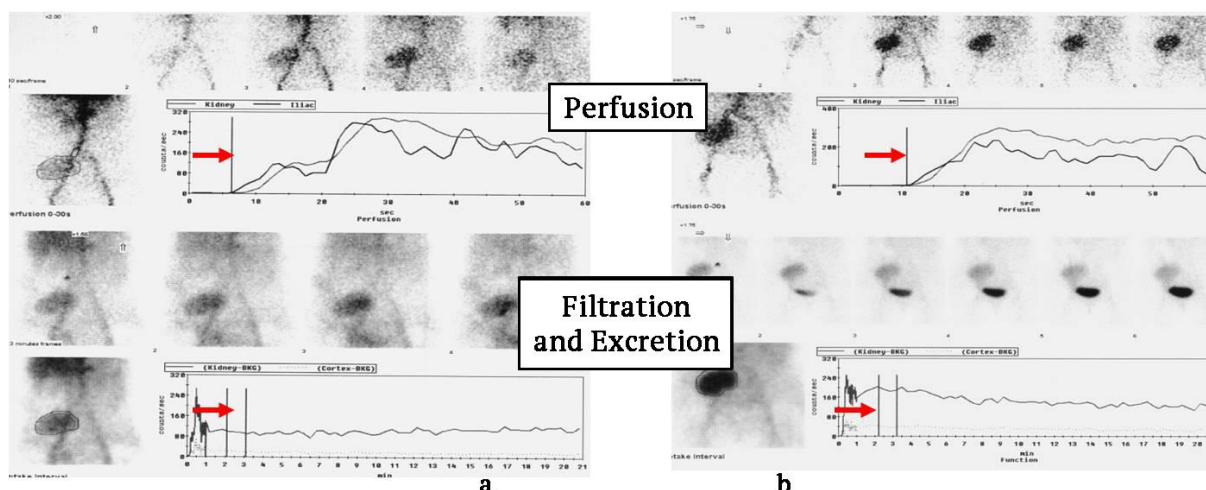


Fig. 3. Normalization of angioneuroscintigraphy parameters of patient N., 66 years old, (subgroup 1b) for 90 days: at posttransplant day 10 (a) and at 3 months after transplantation (b). The arrows indicate the calculation intervals for PI (the first 60 seconds) and FI (2-3 minutes)

Day after CKAT	Renogram type	PI	FI	T _{MAX}	T _{1/2}	AI _{peak}	AI ₂₀	EI	T _{ub}	GFR
10th	Isostenuric	208.00	4.42	20.00	abs	abs	2.30	0.76	16	8.35
90th	Parenchymal	126.00	16.33	3.50	23.10	4.19	3.26	1.56	5	30.29

In patients with a primary graft function and a high HLA sensitization level (MFI over 3000 a.u.) (subgroup 1c; n=5 [13.9%] of 36 recipients), the scintigraphy made on day 7-11 after CKAT demonstrated the parenchymal renogram type and the reduction of all functional components: perfusion, filtration, and excretion that had gradually improved only by day 30-60. In that subgroup of patients with impaired graft perfusion and a high HLA-sensitization level, the ARC episodes were recorded more frequently (in 3 out of 5 patients) than in the other two subgroups of Group 1.

The more difficult for diagnosis and making the treatment plan were the patients with delayed graft function (Group 2). Those patients without anti-HLA antibodies in blood (MFI lower 500 a.u.) (subgroup 2a; n=12 [63.2%] of 19 recipients) were examined in the period from day 6 to 60 after CKAT. In most cases, they were studied 2-3 times. The first study showed a

parenchymal type of the curves in 6 (50%) patients, other patients with a severely impaired function had isostenuric or obturational renogram types. At the same time, in all the patients, filtration and excretion were reduced to a greater extent than in Group 1. At repeated studies, all of them showed an insignificant improvement of all graft function components. The exception was a patient in whom all the parameters had deteriorated by day 24, the renogram acquired an obturational type with an abruptly decreased filtration, which suggested the ATN development (Fig. 4). The outcome renograms were of obturational type in 3 recipients, of isostenuric type in 2 others having either preserved or slightly reduced perfusion, abruptly impaired filtration and excretion, which was also typical for ischemic injury of the graft or ATN.

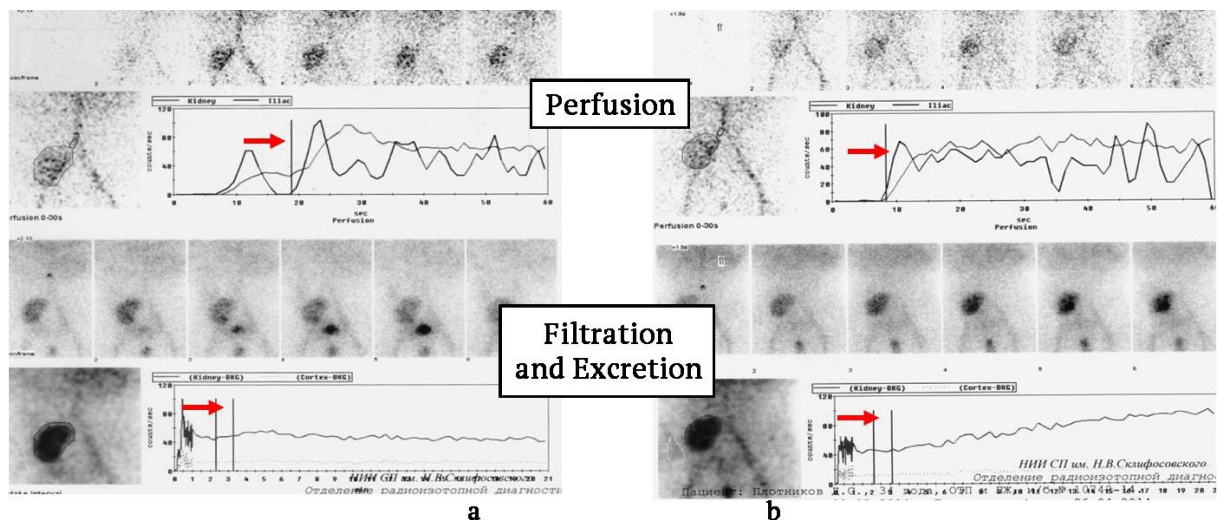


Fig. 4. Angionephrosцинтиграфия of patient P, 34 years old, (subgroup 2a) who developed acute tubular necrosis: deteriorated filtration and excretion with satisfactory perfusion at posttransplant day 12 (a) and day 24 (b). The arrows indicate the calculation intervals for PI (the first 60 seconds) and FI (2-3 minutes)

Day after CKAT	Renogram type	PI	FI	T _{max}	T _{1/2}	AI _{peak}	AI ₂₀	EI	T _{ub}	GFR
12th	Parenchymal	130.09	4.41	5.50	98.70	3.62	3.07	0.79	5	12.52
24th	Obturatoral	135.00	2.74	20.50	abs	abs	3.67	0.17	19	6.18

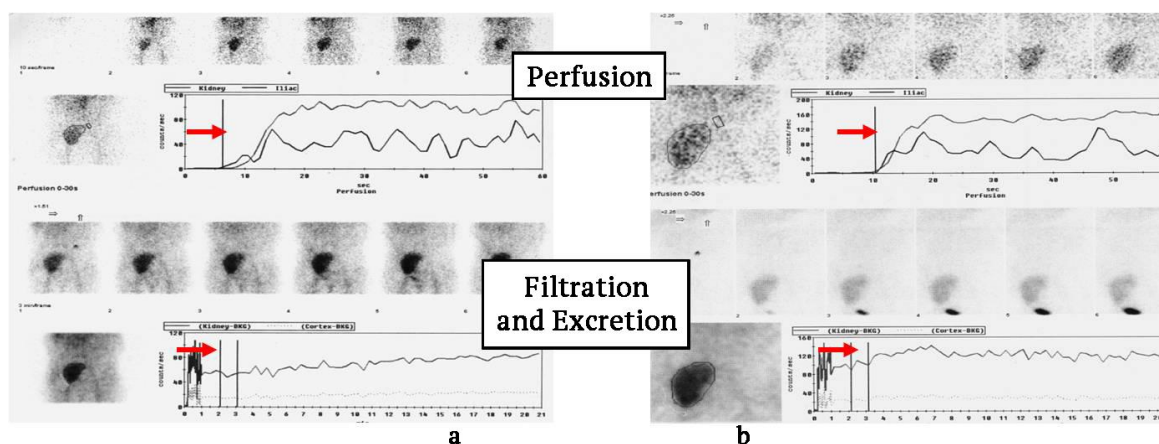


Fig. 5. Ischemic injury of the graft. Recovery of impaired filtration and excretion with initially normal perfusion in patient M., 48 years old, (subgroup 2a) at posttransplant days 18 (a) and 30 (b). The arrows indicate the calculation intervals for PI (the first 60 seconds) and FI (2-3 minutes)

Day after CKAT	Renogram type	PI	FI	T _{max}	T _{1/2}	AI _{peak}	AI ₂₀	EI	T _{ub}	GFR
18th	Isostenuric	126.00	2.59	abs	abs	abs	2.47	0.14	12	12.30
30th	Parenchymal	128.00	7.02	6.64	105.45	3.16	2.95	1.12	5	19.59

In those patients, the graft function had partially restored by day 18-30, which was accompanied by an increased RPh accumulation in kidney, an increased EI parameter; the renograms acquired a parenchymal type, but all parameters reflecting perfusion, filtration, and excretion remained significantly reduced (Fig. 5).

A female patient from 2a subgroup was examined on day 17 after CKAT, the renogram kept an afunctional type with the perfusion being satisfactory, which suggested a severe tubular dysfunction that slightly improved on day 29; an incomplete recovery of kidney function was observed on day 43. At the same time, the renogram remained isostenuric, however, the quantitative parameters of GFR and AI improved (Fig. 6).

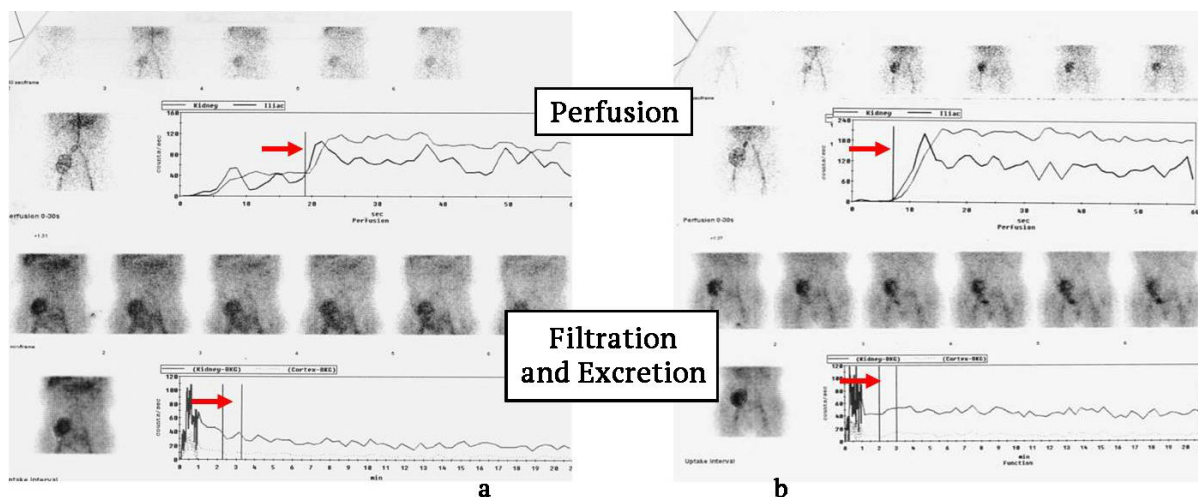


Fig. 6. Angionephrosintigraphy of patient K. (subgroup 2a) with tubular dysfunction at days 17 (a) and 29 (b) after transplantation: uncompromised perfusion (within the normal range) and a moderate recovery of initially abruptly impaired filtration and excretion

Day after CKAT	Renogram type	PI	FI	T _{max}	T _{1/2}	AI _{peak}	AI ₂₀	EI	T _{ub}	GFR
17th	Afunctional	163.00	abs	abs	abs	abs	1.50	0.29	abs	1.00
29th	Isostenuric	136.00	6.60	abs	abs	1.89	1.69	0.81	11	5.46
43rd	Parenchymal	163.00	7.53	1.36	45.73	2.12	1.87	0.80	7	12.33

In the subgroup of HLA-sensitized patients with MFI ranging from 500-3000 a.u. who showed a delayed graft function recovery (subgroup 2b), 2 patients were examined. In one of them, the scintigraphy was performed on days 6 and 10: the curves in both cases were of the parenchymal type with abruptly reduced perfusion that could serve as a sign of ARC development. By day 10, there was an improvement in all parameters: perfusion became normal, PI decreased from 208 to 122, FI and GFR increased, T_{1/2} and the time of RPh entering the bladder decreased. A repeated scintigraphy performed in the other recipient on day 17 after CKAT demonstrated an abruptly impaired perfusion and an isostenuric type of renogram with severely impaired filtration and excretion parameters. The diagnosis of acute rejection crisis was confirmed and the pulse therapy was

performed. At a repeated examination after 45 days, the completely restored perfusion and graft function were seen (the renogram turned into the parenchymal type), all quantitative parameters returned to normal values (Fig. 7).

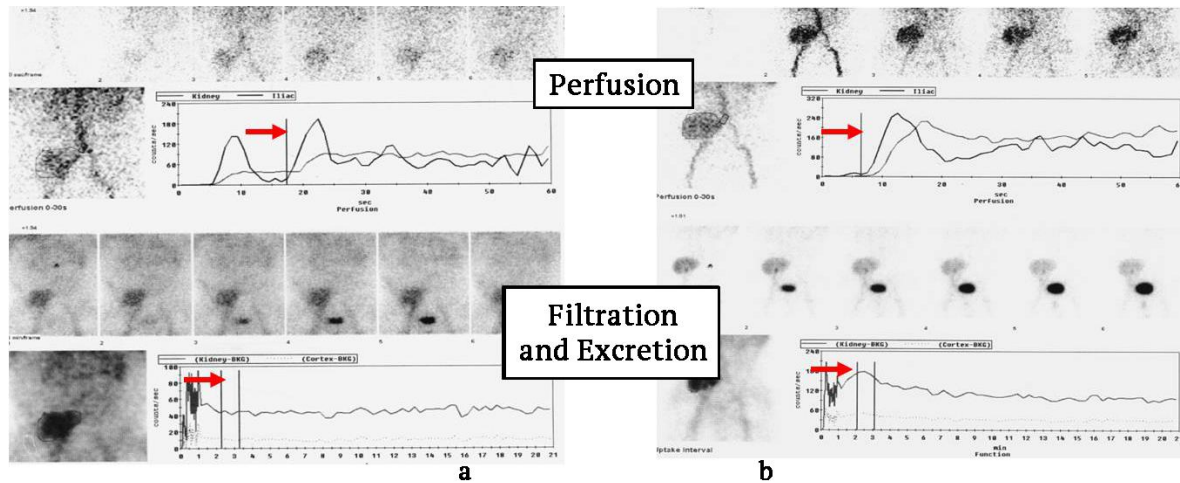


Fig. 7. Angionephrosциigraphy of patient Ch., 57 years old, (subgroup 2b) with the signs of graft rejection at posttransplant day 17 (isostenuric renogram, abruptly decreased perfusion) and at posttransplant day 75 (b): marked positive dynamics with significant improvement of all functional renal components

Day after CKAT	Renogram type	PI	FI	T _{max}	T1/2	AI _{peak}	AI ₂₀	EI	T _{ub}	GFR
17th	Isostenuric	328.00	abs	abs	abs	3.13	2.60	0.70	7	5.05
75th	Parenchymal	250.00	24.66	2.50	44.00	4.03	2.68	2.08	3	30.00

In the most severe, highly HLA-sensitized patients with MFI over 3000 a.u. and a delayed graft function recovery (subgroup 2c; n=5 [26.3%] of 19 recipients), the examination performed on day 7-10 demonstrated an abruptly reduced perfusion down to the absent RPh accumulation in the graft in the vascular phase in the patients with rejection episodes. The afunctional or isostenuric types of renogram were accompanied by a high extrarenal background and the abruptly decreased perfusion and filtration indices, the slowing down of T1/2 as a result of severe ischemic allograft nephropathy.

ATN signs with rejection episodes were observed in all patients of that subgroup. The moderately positive dynamics due to some improvements in GFR and excretion rates, according to angionephroscentigraphy results, was seen only by day 30. With a prolonged recovery of the graft function, all the indices remained markedly reduced (Fig. 8 and 9).

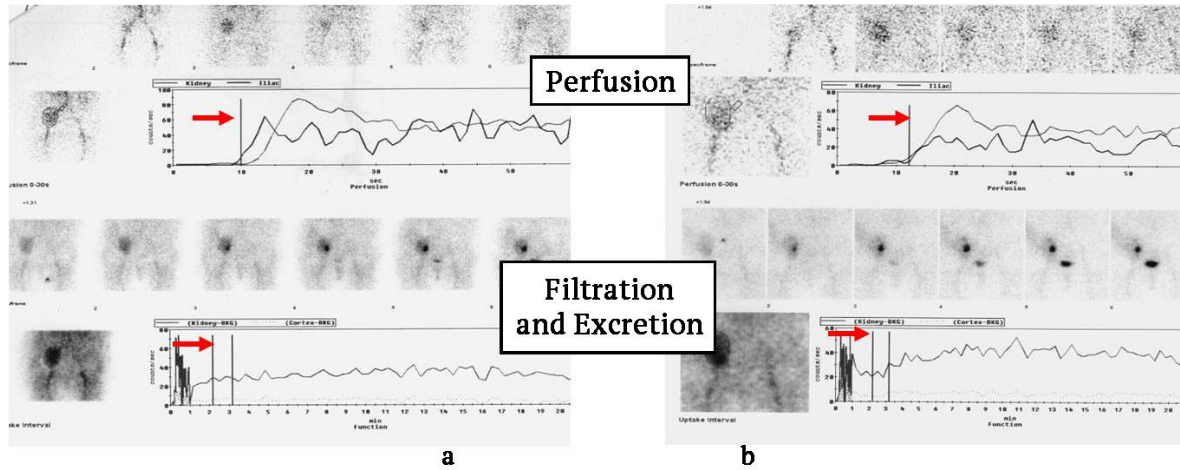


Fig. 8. Angionephroscentigraphy of patient Z., 54 years old, (subgroup 2c) with the signs of a severe ischemic injury and abrupt perfusion disorder (the risk of rejection) at days 30 (a) and 53 (b) after transplantation: recovery of perfusion, a moderate improvement in filtration and excretion in dynamics

Day after CKAT	Renogram type	PI	FI	T _{max}	T _{1/2}	AI _{peak}	AI ₂₀	EI	T _{ub}	GFR
30th	Isostenuric	280.00	6.82	14.00	29.00	2.18	2.02	0.41	13	1.88
53rd	Parenchymal	174.00	9.15	10.88	75.00	3.50	3.55	0.85	9	2.37

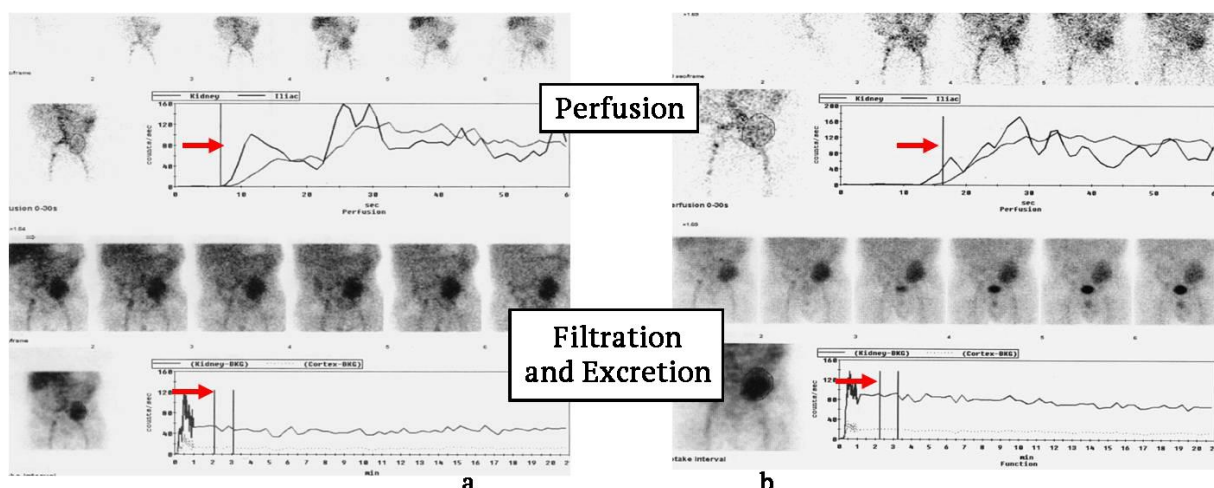


Fig. 9. Angioneuroscintigraphy of patient K., 44 years old, (subgroup 2c): an abrupt decrease in perfusion at days 12 (a) and 36 (b); rejection episodes with severe ischemic injury of the graft; a slightly improved filtration and excretion at re-evaluation

Day after CKAT	Renogram type	PI	FI	T _{MAX}	T _{1/2}	AI _{peak}	AI ₂₀	EI	T _{ub}	GFR
12th	Isostenuric	376.00	6.06	abs	abs	2.66	2.61	0.30	abs	11.17
36th	Parenchymal	268.00	6.11	5.12	58.00	3.95	3.30	0.67	6	25.31

When comparing the mean values of the main angioneuroscintigraphy parameters characterizing perfusion (PI) and filtration (FI) of the renal graft according to the results obtained within 7-12 days after CKAT, the statistically significant differences ($p < 0.05$) were found between the patients of subgroup 1a and all other subgroups by using the Mann-Whitney test, except subgroup 2b because of its small number of patients. For $T_{1/2}$, the statistically significant differences ($p < 0.05$) were found between the recipients of subgroup 1a and subgroups 2a and 2c. The results of studies performed after 20 days from CKAT demonstrated a statistically significant difference ($p < 0.05$) in all the studied parameters when comparing the patients of subgroups 1a and 2c. It is somewhat premature to make a conclusion about the statistical significance of the differences in all available parameters between all patient subgroups with

different HLA sensitization levels, since all the subgroups are small, except for 1a; however, there was a clear tendency to a correlation between the sensitization level and the changes in the scintigraphy results characterizing perfusion (PI), filtration (FI), and excretion ($T_{1/2}$) (Fig. 10 and 11).

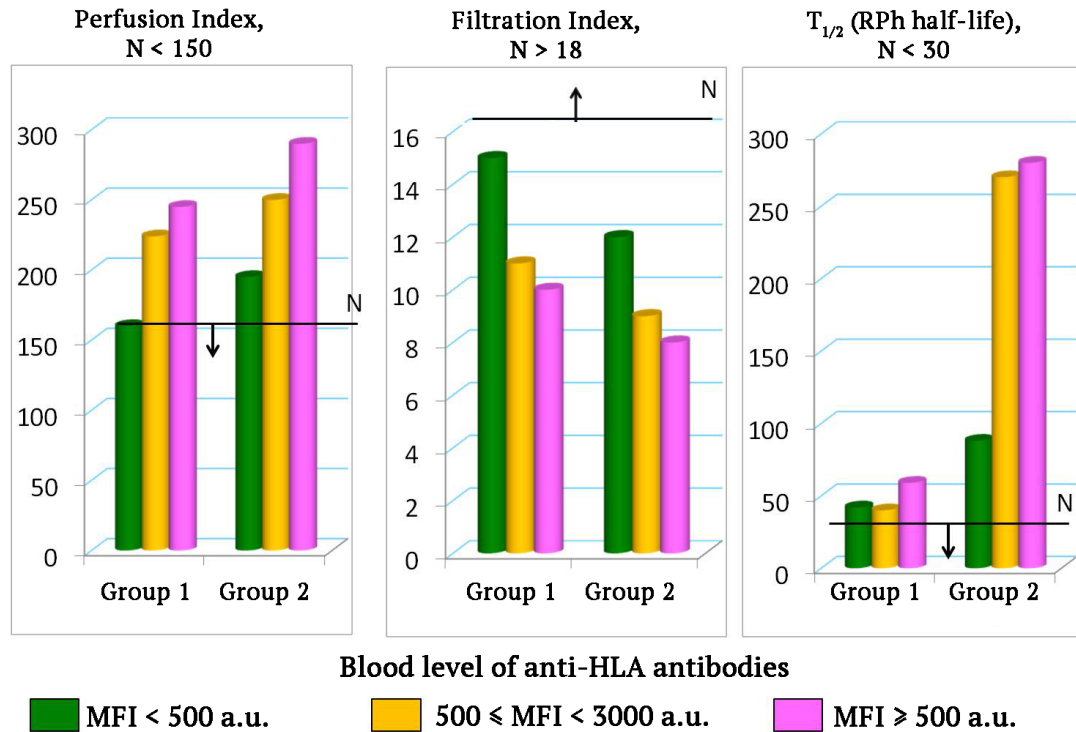


Fig. 10. The main angioscintigraphy parameters at days 7-12 after transplantation in subgroups.

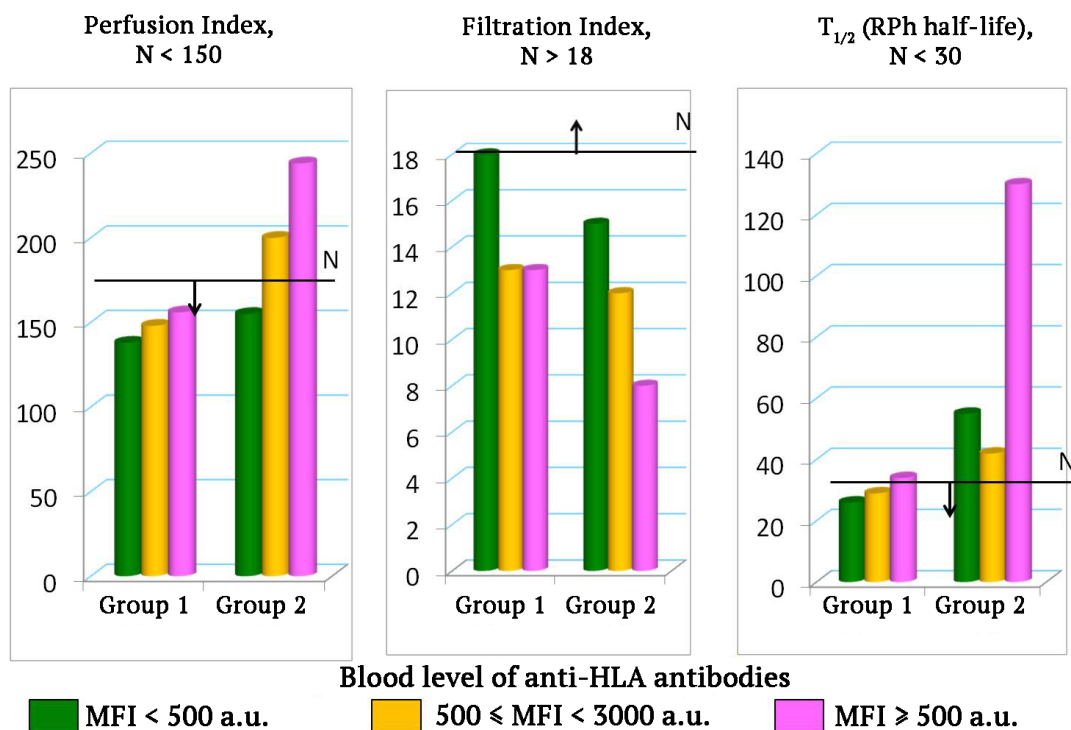


Fig. 11. The main angioscintigraphy parameters at days 20-30 after transplantation in subgroups.

Angioneuroscintigraphy, being an informative method of studying the function and hemodynamics of the kidneys in patients after CKAT, enables to assess the graft function recovery by a separate evaluation of the functional components, as well as to make a long-term monitoring of the renal graft function by conducting a number of repeated studies in a patient receiving an immunosuppression therapy with nephrotoxic drugs: calcineurin inhibitors (tacrolimus, cyclosporine). Angioneuroscintigraphy in combination with the detection of pre-existing anti-HLA antibody levels helps in the differentiated diagnosis of ARC and ATN, which allows to identify the excretion impairments being indicative of concomitant severe ischemic renal injury (ATN) complicated by rejection crisis and the adverse effects of nephrotoxic drugs, and to select an adequate therapeutic tactics.

Conclusions

1. In the majority of patients (91.3%) with the primary allograft function, without pre-existing HLA sensitization (MFI <500 a.u.), the angioneuroscintigraphy showed a normal or slightly decreased blood flow with moderately reduced filtration and excretion, which improved rapidly and fully normalized by the 3-4th week of follow-up.

2. In all HLA-sensitized patients with primary allograft function, all kidney function parameters were initially lowered. Meanwhile, the higher was the pre-transplant anti-HLA antibody level in the recipient blood, the more pronounced decrease of the renal function was found at angioneuroscintigraphy. In the course of treatment, the transplanted kidney function had gradually improved with a number of parameters reaching normal values by week 3-4 of follow-up.

3. In the patients with delayed graft function, the scintigraphy data suggested a marked functional impairment, and the higher was the pre-transplant HLA sensitization level of the patient, the more significant was the reduction of filtration and excretion due to tubular dysfunction. Partial recovery of the function in response to pharmacological therapy was observed after 3-4 weeks, mainly due to the improvement of GFR and excretion.

4. In the patients with a delayed allograft function and a high level of pre-existing anti-HLA antibodies (MFI > 3000 a.u.), an abrupt reduction in perfusion typical for ARC, and an impaired filtration were noted initially, the latter gradually improving (within 30 days) as the perfusion recovered. In the same group of patients, an impaired excretion was frequent indicating concomitant severe ischemic injury of the kidneys or ATN.

Conflict of interests. Authors declare no conflict of interest.

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