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Renal transplant blood flow in patients with acute tubular necrosis

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Background. *Since there are contradictions in data, this study was aimed to investigate the quantity of renal transplant blood flow in patients affected by acute tubular necrosis (ATN).*

Subjects and methods. *During the four year period, 179 examinations were performed in 60 patients (31 female, 29 male, median age 37 years, range 11-62 years, 42 cadaveric and 18 living related transplants, median follow-up 21 months) using Tc-99m-pertechnetate and I-131-OIH. Renal blood flow was calculated from the first-pass time activity curves generated over the kidney and aorta and expressed as a percentage of cardiac output (RBF/CO).*

Results. *In 53 examinations of the patients with ATN, the mean RBF/CO was significantly lower than in 60 examinations of patients with normal graft function (6.5 % ± 3.4 %, 11.4 % ± 3.4 %, respectively, $p = 9.6 \times 10^{-12}$), and similar to the mean values of 49 examinations with acute rejection (AR) and 17 examinations with the combination of ATN and AR (7.3 % ± 3.4 %, 5.8 % ± 2.5 %, respectively, $p > 0.05$). In the patients with ATN, mean RBF/COs were significantly related to creatinin serum (CS) value (CS < 500 μmol/l - 8.0 % ± 3.0 %, CS > 1000 μmol/l - 5.2 % ± 2.2 %, $p < 0.05$) and to I-131 OIH renogram patterns (some OIH excretion from renal parenchyma during the examination - 7.0 % ± 3.5 %, no excretion - 5.1 % ± 2.2 %, $p < 0.05$).*

Conclusions. *Renal transplant blood flow is clearly diminished in ATN, similarly as in AR, and significantly related to the graft function.*

Key words: kidney transplantation; kidney tubular necrosis, acute, kidney-blood supply-radionuclide imaging; quantitative analysis; graft rejection

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Introduction

Radionuclide methods, as non-invasive procedures, are very useful in detection of many complications, which affect renal transplants. It is necessary to study both renal perfusion and function to differentiate post-transplant complications.[1,2]

Acute tubular necrosis (ATN) is present in the majority of cadaveric transplanted kidneys, but only infrequently in transplants from living related donors. It arises in the immediate post-transplant period and usually resolves without therapy. The major pathologic changes in ATN are caused by ischemic damage to the kidney, which usually arises from prolonged ischemia caused by harvesting and implanting of the kidney or by reaction to X-ray contrast media.

Renal blood flow (RBF) in patients with ATN has been shown to be associated equally with both good and compromised perfusion and it has been usually described as "relatively good", always assumed better than in acute rejection (AR).[1-6]

Since the data are contradictory, the aim of our study was to investigate the quantity of renal transplant blood flow in patients affected by ATN.

Subjects and methods

Patients

During the four year period, 179 examinations were performed in 60 patients (31 female, 29 male, median age 37 years, range 11-62 years). Forty-two patients received the kidney from cadavers and 18 from living related donors. Median follow-up was 21 months (range 1-45 months). A baseline examination with Tc-99m pertechnetate (perfusion) and I-131-OIH (function) was performed in all patients within 48 hours of transplantation and additional examinations during post-transplant period in the patients in whom the transplant function impairment was suspected. All patients were treated with antirejection therapy.

Diagnostic criteria

All examinations were classified by the following diagnostic criteria:

A. Acute tubular necrosis (ATN)
1. Delayed and prolonged peak of the OIH renogram.
2. No sings and symptoms of rejection on the day of the examination and within the following week.
3. Clinical and OIH renographic improvement after supportive therapy only.

B. Acute rejection (AR)
1. Signs and symptoms of AR (graft tenderness, pyrexia, rising serum creatinine level or decrease in the creatinine clearance).
2. Evidence of rejection confirmed by biopsy (when available).
3. Clinical improvement after specific treatment for acute graft rejection.

C. Acute tubular necrosis complicated with acute rejection (ATN+AR)
1. Criteria A+B.

D. Normal functioning graft
1. Good urine production of at least 150 ml/h.
2. Serum creatinine level not more than 130 μmol/l.
3. No sings and symptoms of rejection on the day of the examination and within the following week.
4. Normal appearance of OIH renogram.

Radionuclide studies

The perfusion and subsequent dynamic graft scintigraphy were performed using 555 MBq of Tc-99m-pertechnetate and 8 MBq of I-131-OIH.

Tc-99m-pertechnetate was injected rapidly as a compact bolus. A gamma camera with low energy parallel collimator was used for

data acquisition. Flow images were collected at a frame rate of 1 per sec for 60 sec.

Pre- and post-dose syringe counts were measured on collimated gamma camera's face as 10 sec static frames for measuring the net injected dose. Dead time correction was performed as described previously.[7]

The distance between an anterior abdominal wall marker and the center of the transplanted kidney was obtained on a lateral view for depth correction factor measuring.

The dynamic examination with I-131-OIH was performed immediately after perfusion study using medium energy collimator and a frame rate of 1 per minute for 20 minutes for data acquisition.

Data analysis

The well known method for measuring RBF as a percentage of cardiac output (CO) was applied on blood flow studies.[8,9] One region of interest was placed around the kidney and three along the course of the abdominal aorta. Each aortic curve was corrected for recirculation using a gamma fit, integrated and multiplied by the ratio of the maximum upslope of the integrated gamma function aortic curve. The obtained curve represents the renal curve that would be recorded if the Tc-99m-pertechnetate was totally trapped in the vascular bed of the kidney on the first pass.

RBF as a fraction of CO was finally calculated from the formula:

$$RBF/CO = \frac{gk \times A \times DCF \times 100}{ga \times D}$$

where RBF/CO = RBF as a percentage of CO; gk = maximum upslope of the renal curve; ga = maximum upslope of the integrated aortic curve; A = plateau of the integrated aortic curve (cts/sec); D = net injected dose (cts/sec); DCF = depth correction factor ($e^{\mu x}$); m = Tc-99m soft tissue linear attenuation coefficient (0.153 cm^{-1}).

A final RBF/CO value was expressed as an average value of three estimates from three aortic ROIs.

Statistical analysis

Comparative testing of more than two variables at a time was performed by the Kruskal-Wallis analysis of variance. Differences were considered significant if the respective probability values were less than 0.05. Testing of Kruskal-Wallis sub-groups was conducted by the Mann-Whitney-U test. The t - test was used for testing the differences between the two variables.

A summary statistics, including mean values, standard deviations, and minimal and maximal values was run on all data sets.

Results

According to our diagnostic criteria 42 patients (33 cadaveric and 9 living related transplantations) were affected with ATN in the immediate post-transplant period.

In 53 examinations of the patients with ATN, the mean RBF/CO value was significantly lower than in 60 examinations of the patients with normal graft function (6.5% ± 3.4%, 11.4% ± 3.4%, respectively; $p = 9.6 \times 10^{-12}$; Mann-Whitney-U test), but similar to the mean RBF/CO values of 49 examinations of the patients with AR and 17 examinations of the patients with the combination of ATN and AR (7.3 % ± 3.4 %, 5.8 % ± 2.5 %, respectively; $p > 0.05$; Mann-Whitney-U test). These data are summarized in Table 1.

In patients with ATN, mean RBF/CO values were significantly related to the creatinine serum (CS) level and to OIH renogram patterns, as shown by the first examinations after transplantation. The mean RBF/CO was 5.2 % ± 2.2 % in nine examinations with CS > 1000 µmol/l and 5.3 % ± 3.2 % in 20 examinations with CS between 501 and 1000 µmol/l,

Table 1. Mean RBF/CO values, standard deviations and ranges in patients with normal graft function, ATN, AR, and ATN + AR

Diagnosis	Mean RBF/CO (%)	Standard deviation (%)	Range (%)	Number of examinations
ATN	6.5	3.4	1.4 - 19.2	53
AR	7.3	3.4	1.2 - 16.1	49
ATN + AR	5.8	2.5	1.9 - 13.2	17
Normal	11.4*	3.4	6.4 - 21.1	60

* significantly different from all other mean values (Kruskal-Wallis analysis of variance, $p = 4.8 \times 10^{-14}$).

as a contrary to higher RBF/CO values in 13 examinations with CS less than 500 µmol/l (8.0 % ± 3.0 %; p = 0.044; Kruskal-Wallis analysis of variance; Table 2).

Table 2. Mean RBF/CO values, standard deviations and ranges in patients with ATN according to creatinin serum values (CS)

CS (µmol/l)	Mean RBF/CO (%)	Standard deviation (%)	Range (%)	Number of examinations
< 500	8.0*°	3.0	5.6-14.3	13
501-1000	5.3*	3.2	1.5-12.2	20
> 1000	5.2°	2.2	1.4-8.5	9

* p = 0.034; ° p = 0.025 (Mann-Whitney-U test)

Some excretion of OIH from renal parenchyma during 22 I-131-OIH examinations was accompanied with better renal blood flow (RBF/CO = 7.0 % ± 3.5 %) in comparison with 20 cases without any hippuran excretion (RBF/CO = 5.1 % ± 2.2 %; p < 0.05, t-test).

In 13 patients affected with ATN graft function recovered and became normal in the second examination after transplantation. This improvement was followed with the mean RBF/CO rise of 5.4 % ± 3.4 % (range -0.2 % - 13.6 %). Only one patient did not show any flow improvement (Table 3.).

Discussion

At our department, we routinely use Tc-99 pertechnetate for assessing renal transplant perfusion. Since the renal handling of Tc-99m-DTPA, Tc-99m-MAG3 and I-123-OIH interferes on the downslope of the first-pass curve, these pharmaceuticals may be less useful in poorly or non-functioning kidneys. Tc-99-pertechnetate is preferable for simple routine studies because of its low price, high vascular transit and low kidney radiation.[10] At the same time, we perform quantitative analysis of the transplant blood flow which is based on the principle of fractionation of cardiac output. This method depends minimally on bolus shape and is applicable with any recirculating gamma emitting tracer.[8,9,11]

The major pathologic changes in ATN are caused by prolonged ischemia, which usually arises during harvesting and implanting of the kidney. ATN is present in the majority of cadaveric kidneys and, in most cases, it will resolve without therapy in few weeks following the transplantation. Histologically, there is dilatation of the proximal as well as distal convoluted tubules lined by degenerative flattened or necrotic epithelial cells and there is disruption of the basement membrane. The glomeruli and vasculature are spared.[5]

In nuclear medicine literature, RBF in patients affected by ATN was described variously, from good and satisfactory to compromised.[1-6] The situation is somewhat clearer when renal function is being assessed by tubular agents. With tubular agents (I-131 or I-123-OIH and Tc-99m-MAG_3), the most prominent finding in ATN is delayed transit

Table 3. RBF/CO changes in patients with normalization of renal transplant function after ATN.

Patient	First examination (ATN) RBF/CO (%)	Second examination (normal) RBF/CO (%)
1	14.3	19.0
2	6.5	8.8
3	3.0	7.6
4	7.5	21.1
5	1.6	8.7
6	6.6	6.4
7	4.1	12.2
8	9.5	11.7
9	12.2	16.8
10	7.4	11.4
11	6.4	13.4
12	5.7	11.8
13	1.8	7.6

with delayed T-max in severe cases without activity excreted into the bladder.

According to our results, RBF in renal transplant recipients with ATN is clearly diminished, on average amounting to more than 50 % of RBF in normal studies (6.5 % ± 3.4 %, 11.4 % ± 3.4 %, respectively). We did not observed any significant difference in the blood flow between ATN and AR (6.5 % ± 3.4 %, 7.3 % ± 3.4 %, respectively), what means that differentiation between these two post-transplant complications is not possible with RBF/CO values. With RBF/CO values both complications are obviously separated from normal functioning transplants.

Higher RBF/CO values in patients with lower CS values and in patients with some excretion of OIH during renography confirm the relation between the renal blood flow and transplants' function. Normalization of the renal function in 13 patients with ATN was accompanied with notable RBF improvement in 12 patients indicating a possible prognostic role of RBF/CO in the graft function recovery from ATN.

Conclusions

In conclusion, renal transplant blood flow is clearly diminished in ATN, similar as in AR, and significantly related to the graft function, which means that RBF/CO value could potentially serve as a prognostic factor in the graft function recovery from ATN.

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