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Evaluating the Outcome of Percutaneous Transluminal Angioplasty in Renal Graft Artery Stenosis Using the Areas under the Time Curve of Glomerular Filtration Rate and Blood Pressure

J. STŘÍBRNÁ, O. SCHÜCK, J.H. PEREGRIN, D. KRAJÍČKOVÁ, J. SKIBOVÁ

Institute for Clinical and Experimental Medicine, Prague, Czech Republic

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Summary

The benefit of percutaneous transluminal angioplasty (PTA) of transplant renal artery stenosis for ischemic nephropathy may be adversely affected by rejection or other complications. As a result, assessment of the effect of PTA on renal function or blood pressure is often difficult. In this paper, we evaluated the effect of PTA using the method of integrated glomerular filtration rate (GFR) based upon the area under the curve over a follow-up period (AUC_{0-t}), to express the level of GFR in a simple manner despite its significant fluctuations. A similar procedure was used to evaluate mean arterial pressure (MAP). The method was employed to assess the outcome in 20 individuals before PTA, and 1, 3, 6, 9 and 12 months after PTA. In eight cases, rejection was detected while there was one case of glomerulonephritis in the graft during the follow-up period. Evaluation $(AUC_{Ccr})_{0-12}$ related to the integrated pre-PTA value of C_{cr} $[(C_{cr})_0 \times 12]$ revealed a rise in GFR by more than 20 % in 65 % of cases. No improvement was observed in seven individuals with post-PTA complications. When assessing the integrated value of MAP, success of PTA (a reduction by at least 10 %) was found in 85 % of cases. No significant correlation was found between the relative changes of integrated GFR and MAP. Our data suggest that evaluation of the integrated value of GFR or MAP on the basis of AUC_{0-t} allows to characterize, in a simple manner, the level of graft function and MAP throughout the follow-up period in individual cases. Furthermore, it may provide additional information on the average values obtained at different time intervals after the therapeutic procedure.

Key words

Renal artery graft stenosis • Angioplasty • Graft function • Blood Pressure • integrated GFR and MAP

Introduction

In recent years, percutaneous transluminal angioplasty (PTA) has been indicated in patients with renal artery stenosis, primarily to preserve the function of the ischemic kidney. This indication is particularly urgent in patients with a single functional kidney or with a renal transplant. It is often difficult to evaluate the outcome of

Fax+4202 24920590
E-mail: physres@biomed.cas.cz http://www.lf2.cuni.cz/physiolres/physiolres.htm

PTA of transplant renal artery stenosis as the level of graft function may be affected not only by improved hemodynamics but, also adversely by complications, with rejection being the most frequent. Complications occurring during the post-PTA period may result in fluctuations of graft function and the evaluation of the impact of PTA on GFR may be difficult.

Until now no uniform criteria have been developed for evaluating the effect of PTA on graft function. The parameters usually assessed include the changes in serum creatinine concentration (S_{cr}). Some studies (Greenstein *et al.* 1987, Thomas *et al.* 1992, Raynauld *et al.* 1994) estimated the statistical significance of the changes in mean S_{cr} of the whole group after PTA compared with baseline values. Other authors define the success of PTA as a reduction in S_{cr} by at least 20 % (Krajíčková *et al.* 1998), while others by a mere 15 % (Fauchald *et al.* 1992). Similarly, diverse criteria have been employed to evaluate the effect of PTA on blood pressure. The required decrease varies from 15 % (de Meyer *et al.* 1989, Sankari *et al.* 1996) to 10 % (Fauchald *et al.* 1992, Krajíčková *et al.* 1998), with a reduction in the number of antihypertensive agents required. With all this in mind, it is not easy to compare the results of individual studies.

Our research was designed to enable an interpretation and more specifically the effect of PTA on graft function by monitoring the level of function over a follow-up period (one year in our study) using the area under the curve (AUC) delineated by the time course of the glomerular filtration rate (GFR). This calculation allows us to express, in a simple manner, glomerular function despite its fluctuations (Schück 1998). The effect of PTA on blood pressure was evaluated using the same approach.

Patients and Methods

We evaluated 20 kidney graft recipients with transplant renal artery stenosis who had undergone technically successful PTA. The group included 8 women and 12 men with a mean age of 37.6±10.2 years. Angioplasty was performed at a mean 15.9±13.9 months post-transplant. All subjects were cadaveric renal graft recipients; five had a second transplant and three had repeated PTA because of restenosis. Immunosuppression included prednisone (10-15 mg/day), azathioprine (1.0-1.5 mg/kg/day) combined with cyclosporin A (CsA) in 13 individuals (65 %). CsA doses were adjusted so as to maintain its blood levels within the range of 300-500 ng/ml. Blood levels were determined using RIA with non-specific monoclonal antibody (Cyclosporin RIA kit Imunotech). Details of angiography and the technique of PTA were reported in a previous paper (Krajíčková *et al.* 1998).

All individuals were indicated for PTA because of hypertension up to a hypertensive crisis associated in 11 (55%) patients with deteriorating graft function. Two individuals had temporarily been on dialysis prior to PTA (because of graft failure); in one of them this was associated with recurrent pulmonary edema. All patients were on antihypertensive therapy. Before PTA, they were taking an average of three drugs (1-4); this number was reduced to two (0-3) antihypertensive drugs.

The post-PTA course was complicated by *de novo* glomerulonephritis involving the graft in one case, and by rejection in another 8 individuals. In all these cases, graft biopsy was performed and the diagnosis was based on histology. Its treatment involved the administration of methylprednisolone (in pulse doses of 500-1000 mg/day).

Creatinine clearance (C_{cr}) was measured before PTA and 6 and 12 months after this procedure in all patients. Moreover, additional 2-3 determinations were performed at months 1 or 3, or 9 after PTA. The measured values of C_{cr} were used to calculate the area under the curve (AUC_{Ccr}) Creatinine clearance (C_{cr}) was established on the basis of 24-hour urine collection and related to 1.73 m^2 of body surface area. Creatinine levels in the blood and urine were determined on Hitachi 704 and 712 autoanalyzers. Significant improvement in C_{cr} was defined as a rise by at least 20 % compared to the baseline (pre-PTA levels).

Blood pressure was repeatedly measured three times by a cuff mercury sphygmomanometer in the sitting position. For evaluation, mean arterial pressure (MAP) was calculated as diastolic blood pressure plus 1/3 of the systolic-diastolic difference. Our definition of significant improvement was a decrease in MAP by at least 10 % of the baseline value.

The changes in C_{cr} and MAP were assessed using two methods: 1) the conventional method based on estimating the mean values of C_{cr} or MAP as established at defined intervals after PTA and 2) evaluation of the area under the curve (AUC) over the follow-up period. Details of the latter method were described in our previous paper (Schück 1998, Schück *et al.* 1998). AUC was calculated using the trapezoid method.

The *t*-test with Holm's correction and linear regression analysis were used for statistical evaluation.

Results

The mean values, standard deviations and range of C_{Cr} in the group of 20 renal transplant recipients before PTA and 1, 3, 6, 9 and 12 months after PTA are shown in Table 1 which also gives the averages, S.D. and the range of AUC over the follow-up period, i.e. $(AUC_{Ccr})_{0\text{-}12}$. Table 2 presents the mean values ± S.D. and the range of MAP before PTA and at the same time intervals after PTA. This table also gives the averages ± S.D. and the range of $(AUC_{MAP})_{0\text{-}12}$. It is evident from Table 1 that the rise in average C_{cr} established at 6 months after PTA was significantly higher ($p<0.01$) compared with the baseline. However, the average C_{cr} at 12 months after PTA was not significantly different from the baseline. The average MAP was significantly decreased at all time intervals after PTA (Table 2).

Table 1. Creatinine clearance (Ccr) before and after PTA of transplant renal artery stenosis.

	C_{cr0}	C_{cr1}	C_{cr3}	C_{cr6} (ml/s)	C_{cr9}	C_{cr12}	$AUC_{0\text{-}12}$ (ml . months/s)
Average	0.64	0.80	0.80	0.89**	0.80	0.78	10.56
S.D.	0.24	0.33	0.34	0.42	0.36	0.40	5.03
Range	0.13-1.02	0.32-1.64	0.26-1.58	0.23-1.81	0.26-1.54	0.11-1.32	3.3-22.6

*$(C_{cr})_0$ – baseline before PTA, $(C_{cr})_{1\text{-}12}$ – 1, 3, 6, 9 and 12 months after PTA, $AUC_{0\text{-}12}$ – the integrated Ccr within the follow-up period. Statistical significance of C_{cr} post-PTA vs $(C_{cr})_0$, **$p<0.01$.*

Table 2. Mean arterial pressure (MAP) before and after PTA of transplant renal artery stenosis.

	MAP_0	MAP_1	MAP_3 (mm Hg)	MAP_6	MAP_9	MAP_{12}	$AUC_{0\text{-}12}$ (mm Hg . months)
Average	132	109***	110***	109***	110***	107***	1393
S.D.	11	11	9	10	10	10	192
Range	107-159	86-129	95-126	93-126	93-126	93-133	1173-1971

*MAP_0 – baseline before PTA, $(MAPs)_{1\text{-}12}$ – 1,3,6,9 and 12 months after PTA, $AUC_{0\text{-}12}$ – the integrated MAP within the follow-up period. Statistical significance of MAP post-PTA vs MAP_0, **$p<0.001$.*

Evaluation of the effect of PTA on graft function throughout the 12-month period after PTA, using a method based upon the area under the curve $(AUC_{Ccr})_{0\text{-}12}$ related to integrated $(C_{Cr})_0$ [$(C_{cr})_0$ x 12] is shown in Figure 1. This figure is arranged so as to be divided into two parts by a straight line. The position of the straight line gives the values of AUC_{Ccr} that would have been established if C_{cr} had remained stable at baseline levels $(C_{cr})_0$ throughout the follow-up period (or if a transient increase were countered by a quantitatively identical decrease). The points located above the straight line identify cases whereby integrated C_{cr} during the follow-up period were higher than integrated $(C_{cr})_0$ values, whereas points below the straight line identify patients in whom integrated C_{cr} after PTA were lower than integrated $(C_{cr})_0$. The patients experiencing rejection after PTA are marked with a circle. The patient with glomerulonephritis involving the graft is identified by a square.

It is evident from Figure 1 that the points identifying patients with rejection are usually close to the straight line. However, in occasional cases, improvement in C_{cr} (far enough from the straight line) was seen even in patients with a complicated course after PTA. An

explanation for these findings is that the complications did not produce a prolonged marked decline in graft function offsetting the initial improvement of C_{cr}. In 13 cases (65 %), the relative change in integrated C_{cr} was higher than 20 %. These 13 individuals include 11 patients with an uncomplicated course after PTA and two patients with rejection which, however, did not set in until the last month of the follow-up period thereby not affecting the final evaluation.

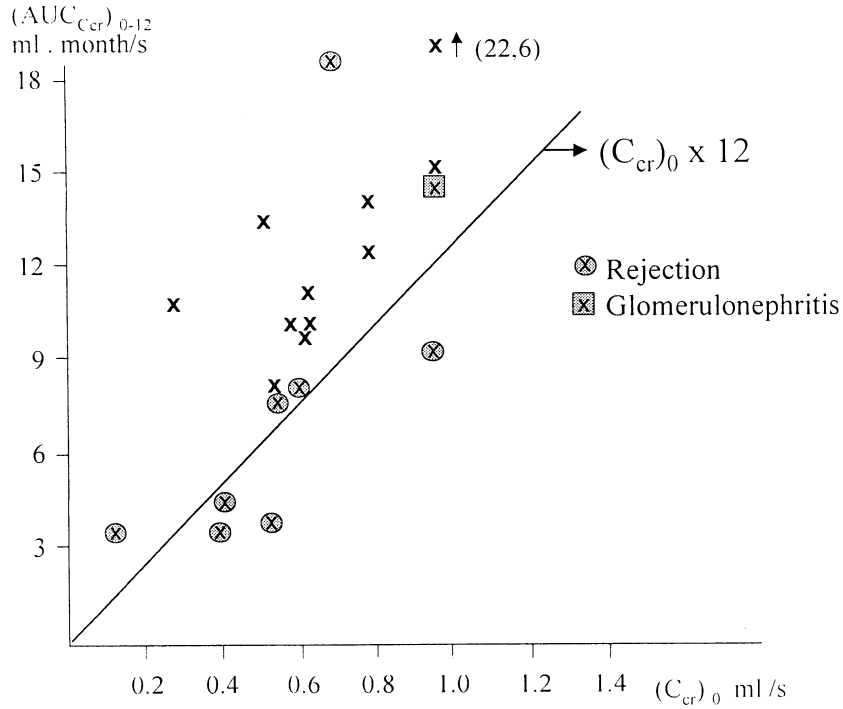

Fig. 1. *The relationship between creatinine clearance (C_{cr}) before PTA [$(C_{cr})_0$] and (AUC_{Ccr})$_{0-12}$ in individual cases. The straight line shows the product of $(C_{cr})_0$ x 12 (the area that would be delineated if C_{cr} throughout the follow-up period were stable at baseline). Points in circles identify individuals experiencing rejection during the follow-up while the point in a square identifies a patient developing glomerulonephritis in the graft.*

Figure 2 shows changes in integrated MAP after PTA. The dividing line is defined by AUC corresponding to $(MAP)_0$ x 12 which is the value of the area that would have been delineated if MAP throughout the follow-up period had been stable at baseline. It is evident from Figure 2 that most points are below the straight line, including 6 individuals developing complications during the follow-up. A position below the straight line identifies individuals with MAP improvement. Out of the 4 points above the straight line (increase in MAP), two identify patients with rejection and one individual with glomerulonephritis involving the graft.

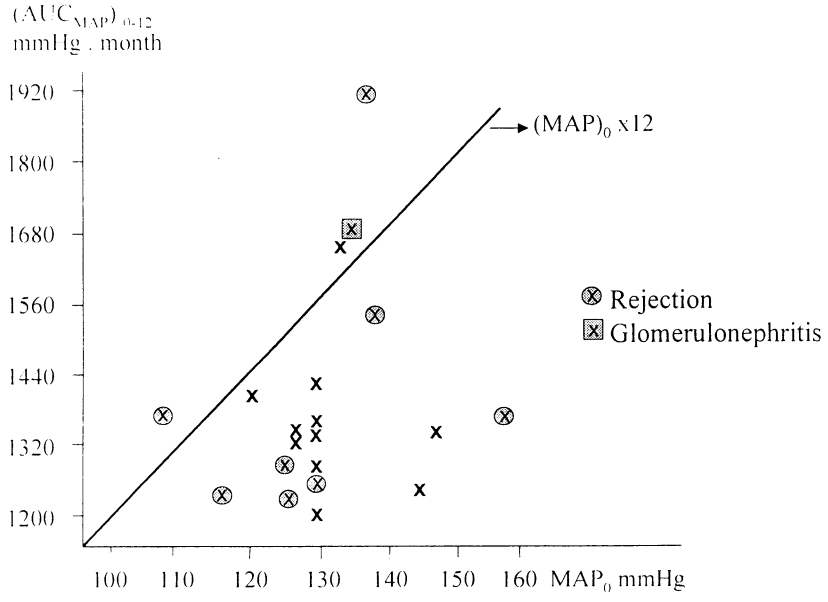

Fig. 2. *The relationship between mean arterial pressure (MAP) before PTA [$(MAP)_0$] and (AUC_{MAP})$_{0-12}$ in individual cases. The straight line shows the product of MAP_0 x 12 (the area that would be delineated if MAP throughout the follow-up period were stable at baseline). For symbols, see Figure 1.*

Figure 3 shows the relationship between the changes in $(AUC_{Ccr})_{0\text{-}12}$ and changes in $(AUC_{MAP})_{0\text{-}12}$ related to the integrated baseline values. It indicates that, in 17 patients (85 %), the decrease in integrated MAP was greater than 10 %. It is also evident from this figure that no significant correlation was found between the relative changes in integrated C_{cr} and MAP.

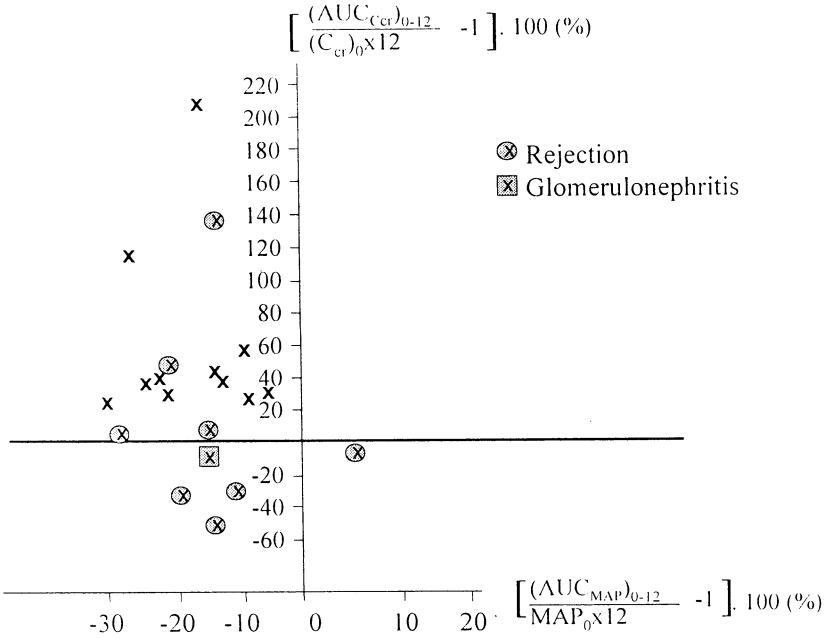

Fig. 3. *The relationship between the changes in integrated C_{cr} $[(AUC_{Ccr})_{0\text{-}12}]$ and MAP $[(AUC_{MAP})_{0\text{-}12}]$, expressed in percentage of integrated baseline values $[(C_{Cr})_0 \times 12, MAP_0 \times 12]$. For symbols, see legends to Figure 1.*

Discussion

Assessment of the outcome of PTA on graft function using the conventional approach (Table 1) clearly shows the beneficial effect of PTA manifested by a significant rise in C_{cr} at month 6 of the follow-up; however, this rise was only transient. At the end of the follow-up (month 12 after PTA), no demonstrable difference could be seen in the average C_{cr} compared with the baseline. The initial significant rise in GFR was affected adversely during follow-up by the onset of complications in nine out of the 20 cases. Some authors likewise did not demonstrate significant alterations in graft function, as evaluated by serum creatinine concentration (Greenstein *et al.* 1987, Thomas *et al.* 1992). This clearly indicates that, when comparing the significance of the difference between the mean pre- and post-PTA values, a key role is played by the time interval over which the outcome of PTA is assessed. The conventional method of assessment does not identify the time course of GFR in individual cases and does not allow to establish the contributions of rejection or other complications in the outcome of PTA.

However, when using the method of integrated values $(AUC)_{0\text{-}12}$, we were able to demonstrate (after evaluatiion of the whole follow-up period) that GFR (as compared with the baseline) increased in 16 patients (Fig. 1) out of which an increase by the required 20 % was present in 13 out of the 20 patients (65 %). It is also easy to identify (Fig. 3) the patients in whom PTA failed to rise GFR (stabilization of function in four and a decline in three cases). In all these seven patients, the cause of failure was a complication (rejection or glomerulonephritis involving the graft).

Our data showing a beneficial effect of PTA on GFR, evaluated by the calculation of area under the curve in transplant patients, are consistent with the results reported by Fauchald *et al.* (1992) who, using the conventional method of evaluation, demonstrated improved graft function after PTA in 14 out of 21 renal transplant recipients (65 %). Their criterion of success was a decrease in S_{cr} by 15 % only, and the follow-up period was in average 24 months with a wide range (6-78 months). In a number of patients, follow-up was discontinued for complications, their individual data are fairly difficult to identify. In another study, Sankari *et al.* (1996) demonstrated a benefit of PTA in transplant renal artery stenosis on renal function (S_{cr}) in 11 out of 16 (69 %) patients. However, the stabilization of graft function was also included as a criterion for the success of PTA. Improvement of serum creatinine level by at least 20 % of baseline values was observed in less than

40 % of the group. The follow-up period with a wide range (6-74 months) was discontinued with the onset of complications.

In agreement with literary data (Greenstein *et al.* 1992, Steiner *et al.* 1995, Sankari *et al.* 1996, Krajíčková *et al.* 1998), we can confirm that the PTA is more successful in the therapy of hypertension than in graft function improvement. When using the conventional method of evaluation, mean MAP declined significantly at all the time intervals (Table 2); in most cases, this was accompanied by a reduction in number of antihypertensive agents. The integrated values of $(AUC_{MAP})_{0\text{-}12}$ after PTA decreased by more than 10 % compared to the baseline in 17 out of the 20 individuals (85 %). The success in hypertension control was observed not only in patients with an uncomplicated course, but even in most cases with rejection and in the case of glomerulonephritis involving the graft. No correlation was demonstrated between the ultimate effects of PTA on C_{Cr} and MAP (Fig. 3). This finding can be explained by different mechanisms by which hypoperfusion of the kidney with renal artery stenosis activates the factors which raise blood pressure and deteriorate renal function (Textor 1993).

Conclusions

GFR changes after PTA of renal graft artery stenosis very often exhibit significant fluctuations because of interference with rejection or other complications. For these reasons, the evaluation of PTA effect on GFR may be difficult. The present results and their analysis support the assumption that the evaluation of the effect of PTA on GFR and MAP on the basis of their integrated values may provide useful additional information on the conventional method (based upon the analysis of average values and S.D. of the follow-up parameters at defined time intervals after PTA). This is because it takes into account irregular fluctuations of GFR within the entire follow-up period. Furthermore, the evaluation of the results on the basis of integrated values allows to characterize, in a simple manner, the effect of PTA in individual patients.

The present results indicate that the beneficial effect of PTA on GFR in patients with renal graft artery stenosis, which is usually abolished by rejection, although this complication need not exclude the beneficial effect of PTA on MAP.

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Reprint requests

J. Stříbrná, M.D., D.Sc., Institute for Clinical and Experimental Medicine, Vídeňská 1958/9, 140 21 Prague 4, Czech Republic. Fax: 61363168