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CASE REPORT

# Predictive Factors of Abnormal Circadian Blood Pressure Profile in Recipients of Kidney Transplantation

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**ABSTRACT**

*Arterial hypertension (HT) plays an important role and is a major factor in the occurrence and progression of chronic graft nephropathy. We evaluated 24-hour blood pressure (BP) profile in kidney transplant patients to identify factors predictive of abnormal circadian BP profile. BP was measured over a period of 24 hours using a noninvasive automatic device (EC-3H / ABPM) in 40 renal transplant patients (mean age = 37.2±12.2 years, M = 30, mean serum creatinine = 2.0±1.4 mg/dl). They were under the triple immunosuppressive therapy (CsA / Ts + Aza / MMF + PDN). 35 recipients (87.5%) had a non-dipper BP profile, with nocturnal values which fell by less than 10% from the daytime BP values. The other 5 containers (12.5%) had normal dipper BP, with lower nighttime values by more than 10% of the daytime BP values. 17/40 recipients (42.5%) had nocturnal BP values higher than daily rates (extreme non-dipper). In none of the patients there has been excessive dipper profile (low nighttime values over 20% less than the diurnal BP). There were no statistically significant differences between the dipper and non-dipper recipients profile in terms of age, gender, creatinine, mean systolic BP (SBP) and daytime SBP, short-term variability in BP and pulse pressure ($p>0.05$). Factors predictive of a non-dipper BP profile were elevated median 24h BP, median 24 systolic and diastolic blood pressure (DBP), diurnal, nocturnal and 24h pulse rate ($p<0.05$).*

*In conclusion, the absence of normal nocturnal BP lower values was relatively frequent (87.5%) in renal allograft recipients. In many studied patients nocturnal BP values were higher than the diurnal ones.*

**Keywords**: hypertension, kidney, transplantation

## INTRODUCTION

HTA is the main factor involved in the development of non-immune chronic graft nephropathy. Post-transplant renal hypertension is mainly renin-dependent and is a common cause of chronic rejection, as well as kidney native renal artery stenosis, baseline disease relapse on the renal graft or the maintenance of the immunosuppressive medication (cyclosporine, tacrolimus). Post-transplant renal hypertension contributes significantly to increased risk of cardiovascular

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death in both children and adults. Initially there was a debate regarding the effect of hypertension on renal allograft survival. Recently, it was shown that there is a significant negative correlation between systolic and diastolic blood pressure levels and long-term graft survival. The negative effect of systolic blood pressure was present even if the diastolic blood pressure was less than 90 mmHg.

The prevalence of hypertension is of 75-80% in transplanted kidney patients in the immediate cyclosporine post-transplant period, while in the same pre-cyclosporine period prevalence was 45-50%.

Factors causing post-transplant renal hypertension can be endogenous and exogenous to the graft. Renal hypertension is multifactorial and usually these patients have more than one cause of hypertension. During the immediate post-transplant period, the positive balance of sodium and water, acute tubular necrosis, acute obstruction of the ureter, acute rejection and hypercalcemia have been incriminated as causes of hypertension. After the first period after transplant hypertension may be determined by immunosuppressive treatments with corticosteroids, cyclosporine and tacrolimus, as well as by chronic rejection and chronic graft nephropathy. ❑

## THE PURPOSE OF THE STUDY

We evaluated 24-hour BP profile in renal allograft recipients to identify abnormal circadian BP profile as a negative predictive factor in these patients. A prospective study was conducted during the 1 January 2014 - 1 July 2015 period, within the Department of Nephrology, Fundeni Clinical Institute and Department of Internal Medicine – Nephrology, Fundeni Hospital, "Carol Davila" University of Medicine and Pharmacy, Bucharest. ❑

## MATERIAL AND METHOD

It was conducted a prospective assessment of BP circadian profile in renal graft recipients. BP was measured over a period of 24 hours by means of a non-invasive automatic Holter EC-3H / ABPM (Ambulatory Blood pressure Monitoring) system.

Criteria for inclusion in the study were: functional renal graft recipients (creatinine <6 mg/dL), and the blood pressure registered for more than 80% during the 24 hour period. Recordings were made in the early (<6 months) post-transplant period. Antihypertensive treatment at the time of registration was continued as before the study.

Demographic variables, clinical and biological data and the data recorded by the ABPM device were compared in order to determine factors predictive of abnormal circadian BP profile in this population. ❑

## STUDY POPULATION

The study included male and female patients aged 18 years or more with the diagnosis of end-stage renal disease, who were in the alternate program renal function by renal transplant. We evaluated 24-hour BP profile using a combined EC-3H / ABPM device.

### Criteria for inclusion in the study

- Patients with end-stage renal disease, who were in the alternate program renal function by renal transplant
- Age over 18;
- Allowance by the patient's informed consent.

### Exclusion criteria from the study:

- Refusal of patients to be monitored;
- Less than 80% of ABPM records / patient valid. ❑

## METHOD

### Data collection

For each eligible patient, after obtaining informed consent, an individual questionnaire was completed. A detailed anamnesis and all the available documents were noted, as well as a complete clinical examination. Office BP values and the BP values by monitoring BP over 24 hours were recorded.

### Individual Questionnaire

The individual questionnaire contained the following data:

- Demographic data: age and sex
- Etiology of the kidney chronic disease
- Complete history of kidney disease and renal alternate program: the age at which the disease has been diagnosed and the age when renal transplantation

was performed; There were noted the alternate renal methods used before kidney transplantation and their duration.
- History of cardiovascular disease: coronary heart disease (stable angina, angioplasty myocardial revascularization with or without stent or coronary artery bypass graft surgery), the presence of hypertrophy of the left ventricle (LVH), arrhythmia and conduction disorders, presence of signs and symptoms of congestive heart failure.

## Tracking Sheet

Tracking Sheet done to achieve this study included clinical, biochemical data and specific patient usual alternate program renal function. Also it included data and functional imaging investigations: electrocardiogram, echocardiography and parameters of blood pressure monitoring 24-hour ABPM.
- Anthropometric parameters measured under standardized conditions: height (m), weight (kg), waist circumference (cm). The body mass index – (BMI) was calculated. Characterization of patients according to BMI was performed as recommended by the National Heart, Lung and Blood Institute, US: patient underweight: BMI <18, normal weight: BMI = 18.5 to 24.9; overweight: BMI = 25 to 29.9; obesity: BMI >30
- Office BP was measured under standardized conditions According to the values obtained patients were classified according to the Guidelines of the European Society of Cardiology and European Society of Hypertension on hypertension management (Table 1).
- Cardiac auscultation.
- Diuresis / 24h in renal transplant patients, residual diuresis in predialysis and 24 h diuresis for patients in peritoneal dialysis and hemodialysis programs. This was done with the assistance of the personnel of medical care in the departments.
- Usual blood tests such as: blood count, urea, creatinine, uric acid, albumin, potassium.
- Serum lipidogram: total cholesterol, LDL cholesterol, HDL - cholesterol, triglycerides and calculating total cholesterol / HDL cholesterol.
- Fasting glycemia.
- Inflammation parameters: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and serum fibrinogen
- Nutritional status: anthropometric measurements, determination of serum albumin and SGA (Subjective Global Assessment) questionnaire.
- Phospho-calcium metabolism parameters: serum calcium, phosphate, intact parathyroid hormone serum levels (iPTH) and calculating Ca x P product.
- Resting electrocardiogram (EKG). We determined manually heart rate, electrical axis of the heart, PQ and QT intervals, QTc and we highlighted terminal phase ischemo-lesional disorders and arrhythmias.
- Echocardiographic parameters. Echocardiographic investigation was conducted with the support of colleagues from Cardiology Institute "CC Iliescu".
- ABPM parameters were recorded and calculated using the combined Holter EC-3H / ABPM monitoring unit. This is a compact, lightweight instrument capable of storing the ECG and TA routes for 24 hours (or even 48-72 hours). Standard, the patient wears the device for 24 hours, carrying out its normal activities and maintains the recorder during sleep. After 24 hours of recording, the camera stops recording automatically and stored device data are transferred to a computer software. Here they are examined and, if necessary, amended by a specialist (medical examiners).

| Category | Blood pressure systolic (mmHg) | | Blood pressure dyastolic (mmHg) |
|---|---|---|---|
| Optimal | <120 | and | <80 |
| Normal | 120-129 | and/or | 80-84 |
| Normal hight | 130-139 | and/or | 85-89 |
| | Hypertension | | |
| Grade I | 140-159 | and/or | 90-99 |
| Grade II | 160-179 | and/or | 100-109 |
| Grade III | ≥180 | and/or | ≥110 |
| Isolated systolic hypertension | ≥140 | and | <90 |

**TABLE 1.** Classification of hypertension.

Source: Adaptated from „2013 ESH/ESC Guidelines for the management of arterial hypertension".

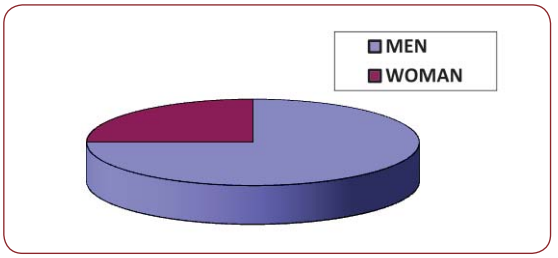


**FIGURE 1.** Sex distribution in renal transplant patients group.

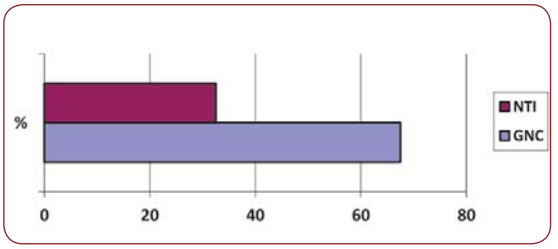


**FIGURE 2.** In the control group etiology of renal disease - kidney transplant recipients.

## Statistical analysis

We interpret the data collected for each patient using SPSS 16.0 statistical analysis system for Windows (IBM Corporation, USA). Data from individual questionnaires and tracking records were stored electronically in an SPSS file and subsequently processed statistically.

We performed statistical analysis establishing the mean, median and standard deviations for continuous Gaussian distribution parameters and we used numbers or percentages for batch parameters (6).

| Parameters | Mean values, minimum, maximum, standard deviation | | |
|---|---|---|---|
| **Values BP/24h (mmHg)** | | | |
| BP medial | 106.4 | 83.2-139.3 | 13.7 |
| BP systolic | 141.1 | 113-171.7 | 16.6 |
| BP dyastolic | 113.2 | 65.5-123.1 | 89.6 |
| **Values BP/ active period** | | | |
| BP medial | 106.9 | 81.8-132.1 | 12.4 |
| BP systolic | 140.2 | 106.6-164.6 | 15.0 |
| BP dyastolic | 89.5 | 65.8-115.9 | 11.9 |
| **Values BP/ passive period** | | | |
| BP medial | 105.9 | 79.4-152.1 | 18.1 |
| BP systolic | 141.1 | 103.7-184.7 | 21.2 |
| BP dyastolic | 86.1 | 61.14-136.8 | 20.9 |
| **PP medial/24h (mmHg)** | 51.7 | 36.6-74.7 | 9.4 |
| **Mean heart rate /24 h (b/min)** | 83.1 | 65.2+-109.7 | 10.9 |

**TABLE 2.** Assessment BP profile 24 hours in transplanted kidney patients.

We achieved statistical significance using test interpretation One-Sample T Test ($p < 0.05$ = statistically significant). ❑

# RESULTS

## Demographic characteristics of patients

We have included in this group 40 transplanted kidney patients with the transplant performed at least one month before (average age = 37.2±12.2 years, M = 30/40 – Figure 1). Mean serum creatinine was 2.0±1.4 mg/dl. They were in triple immunosuppressive therapy: tacrolimus or cyclosporine, mycophenolate mofetil or azathioprine and prednisone (CSA / Ts + Aza / MMF + PDN). Basic Kidney disease was represented by glomerulopathies in 27/40 patients (67.5%) and chronic tubulointerstitial nephropathy in 13/40 patients (32.5%) (Figure 2).

ABPM data are presented in Table 2.

## Circadian BP profile of renal graft recipients

24 hours ABPM allowed for each patient to describe the circadian BP profile. Standard literature describes 4 types of profile:

- BP dipper profile is defined by nocturnal BP values at least 10% less than the TA during the day;
- Excessive dipper profile reflects nocturnal BP values 20% lower than BP values recorded during the day;
- BP non-dipper profile is defined by nocturnal BP values lower than the daytime with less than 10%;
- Extreme non-dipper profile is defined when BP values are higher during the night than during the day.

The dipper profile is the normal one. All other circadian profiles, excessive dipper, non-dipper and excessive non-dipper are pathological (12).

We obtained the following ABPM profiles of the patients included in the study:

- 5/40 patients, representing a rate of 12.5% of transplanted patients had a dipper BP profile;
- No patient was excessive dipper;
- 35/40 patients, representing a rate of 87.5% in the group of kidney transplant recipients presented a BP non-dipper profile over 24h;

- 42.5% of renal transplant patients (17/40 patients) have registered a non-dipper extreme profile, represented by nocturnal BP values higher than BP values recorded during the day (Figure 3).

## Predictive factors circadian profile of BP in renal allograft recipients

Demographic variables, clinical and biological data and ABPM device recorded data were compared in order to determine factors predictive of abnormal circadian BP profile in this population. There were no statistically significant differences between recipients profile dipper and non-dipper in terms of age, gender, etiology of renal disease (chronic glomerulonephritis vs chronic tubule-interstitial nephropathy), age of kidney disease, age of HT, the creatinine and proteinuria (Table 3).

Regarding ABPM parameters, there were no statistically significant differences between recipients profile dipper and non-dipper in terms of the mean and daytime SBP, short-term variability in BP and pulse pressure ($p > 0.05$). Factors predictive of the non-dipper profile were elevated median 24 hours BP, median systolic and diastolic 24 h BP and the diurnal, nocturnal and 24 hours pulse rate($p < 0.05$) (Table 4, Table 5). ❑

| Parameters | Profil dipper | Profil nondipper | P |
|---|---|---|---|
| Demographic: | | | |
| - Age (years) | 41.2±16.5 | 36.7±11.7 | 0.44 |
| - Sex (M/F) | 26/35 | 4/5 | 0.8 |
| - Etiology of kidney disease CNG/PNC | 23/35 | 4/5 | 0.9 |
| - Kidney disease age (years) | 3.8±1.3 | 4.2±0.9 | 0.35 |
| - BP age (years) | 3.6±1.5 | 3.8±1.2 | 0.73 |
| Biological Data: | | | |
| - creatinine | 2.7±2.2 | 1,9±1,24 | 0,30 |
| - proteinuria | 0.4±0.5 | 0.5±1.4 | 0.60 |

**TABLE 3.** Predictors of abnormal circadian BP profile in renal transplant recipients – analyze of demographic, clinical and biological data.

## DISCUSSION

The normal BP values measurements (in the office, home and ABPM) have been defined since 2003.

## What is the normal circadian BP profile?

Under normal circumstances, there are lower BP levels during night due to the shrinking influence of the sympathetic nervous system. The sympathetic tone decreases during sleep, to get back into action in the morning when the patient wakes up.

Consequently, normal blood pressure values are peaking during the day to drop off the following night. In the early morning blood pressure values begin to rise rapidly until they reach the values of the day. This phenomenon, which develops in a very short interval, is of particular importance because it is a period which increases the risk of cardiovascular and cerebrovascular events (13).

Besides these values circadian normal, healthy patients have other changes in blood pressure: TA is higher during their business pe-

| Parameters | Profil dipper | Profil nondipper | P |
|---|---|---|---|
| ABPM Data: Values BP/24h | | | |
| - Mean BP | 95.1±6.4 | 107.1±13.8 | **0.04** |
| - SBP | 131.8±14.4 | 142.5±16.6 | 0.18 |
| - DBP | 76.8±3.6 | 91.4±13.0 | **0.01** |
| Values BP/passive period | | | |
| - Mean BP | 85.0±6.1 | 108.9±17.2 | **0.004** |
| - SBP | 119.5±13.4 | 144.3±20.4 | **0.01** |
| - DBP | 67.8±3.6 | 88.8±21.1 | **0.03** |

**TABLE 4.** Predictive factors for an abnormal circadian BP profile in renal transplant recipients.

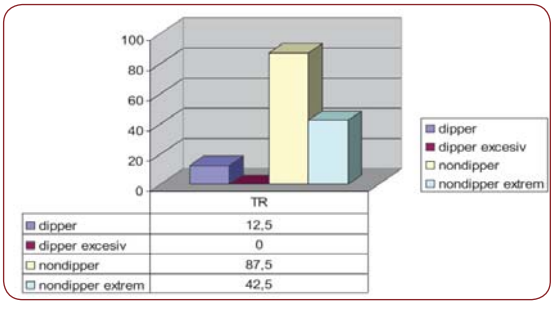


**FIGURE 3.** Circadian profile of BP in renal allograft recipients.

| Parameters | Profil dipper | Profil nondipper | P |
|---|---|---|---|
| ABPM Data: PP values | | | |
| - Average PP | 55.1±13.1 | 51.2±8.9 | 0.3 |
| - Average PP/day | 56.1±13.2 | 50.4±8.4 | 0.1 |
| - PP Medium/night | 51.8±11.9 | 53.4±10.9 | 0.7 |
| HR Values | | | |
| - HR average | 73,2±4,7 | 84.6±10.8 | **0.002** |
| - Average HR/day | 77,9±4,6 | 89.6±11.9 | **0.04** |
| - Average HR/night | 63,9±4,6 | 75.7±11.6 | **0.03** |

**TABLE 5.** Predictors of abnormal circadian BP profile in renal transplant.

| BP measurement | BPS (mmHg) | BPD (mmHg) |
|---|---|---|
| Office | 140 | 90 |
| Home | 135 | 85 |
| ABPM | 125 | 80 |

**TABLE 6.** Target values for BP therapy in different types of BP measurements.

Source: adapted from "European Society of Hypertension, Guidelines, 2003."

| Normal values ABPM | BPS (mmHg) | BPD (mmHg) |
|---|---|---|
| BP medial/24 ore | 130 | 80 |
| BP average daytime | 135 | 85 |
| BP average night time | 120 | 70 |

**TABLE 7.** Normal values by ABPM.

Source: Adapted from ESH/ESC Guidelines for Management of Arterial Hypertension, 2013

riod than at home; the biggest values are those recorded during exercise or during stress periods (13).

Opinions on normal blood pressure values vary. BP values may be influenced by associated pathological conditions (target organ damage, diabetes etc.).

(Values are expressed as mean and standard deviation. SBP - systolic blood pressure; DBP - diastolic blood pressure; SBP load - load systolic pressure, measured as a percentage of values above 140 mm Hg values). Considering the assessment of hypertensive patients according to pathological conditions associated "the 7th Committee for the prevention, detection, evaluation and treatment of hypertension" (JNC 7) recommends the target values in patients with cardiovascular risk than or patients with various diseases associated with diabetes, cardiovascular disease or in patients with the target organ damage are displayed in Table 9. The signs of damage of target organs are: heart involvement (left ventricular hypertrophy), cerebral circulation (fundus examination), systemic circulation (atherosclerotic plaques), kidneys (creatinine, proteinuria). Also, the guidelines specify target values necessary for prevention of progression of renal damage.

ABPM is non-invasive, with no side effects and tolerated by chronic renal patients. The method can be used in patients with renal graft, does not require immunosuppressive medication discontinuation or modification. ABPM is complementary method to ECG and cardiac ultrasound to assess risk status for cardiovascular morbidity and mortality in chronic renal patients, including renal transplant patients.

| AGE (years) | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 |
|---|---|---|---|---|---|---|
| BPS-24h | 122 +/- 9 | 121 +/- 8 | 120 +/- 10 | 124 +/- 12 | 127 +/- 12 | 133 +/- 16 |
| BPS diurnal | 125 +/- 10 | 125 +/- 9 | 124 +/- 11 | 127 +/- 12 | 130 +/- 12 | 137 +/- 17 |
| BPD-24h | 67 +/- 7 | 71 +/- 5 | 73 +/- 7 | 75 +/- 7 | 75 +/- 4 | 69 +/- 9 |
| BPD diurnal | 70 +/- 8 | 74 +/- 5 | 75 +/- 8 | 77 +/- 7 | 77 +/- 5 | 71 +/- 9 |
| SBP load | 9 +/- 14 | 8 +/- 11 | 8 +/- 10 | 13 +/- 16 | 18 +/- 19 | 25 +/- 20 |

**TABLE 8.** Normal parameters of BP by age and circadian conditions determined by ABPM.

Source: Adapted from: Zachariach PK, Sheps SG, Bailey KR, et al. Ambulatory blood pressure and blood pressure load in normal subjects. Am J Hypertens 1989.

| Category patients investigated | BPS (mmHg) | BPD (mmHg) |
|---|---|---|
| Patients with low cardiovascular risk | 140 | 90 |
| Various pathological conditions associated:<br>• Diabetes;<br>• Clinically overt cardiovascular disease;<br>• Target organ damage:<br>- left ventricular hypertrophy;<br>- atherosclerotic plaque;<br>- slight increases in serum creatinine;<br>- microalbuminuria;<br>- changes detected in fundus examination. | 130 | 85 |
| Target values obtained for the prevention of progression of kidney disease | 125 | 75 |

**TABLE 9.** Target BP values obtained by ABPM in patients with comorbidities.

Source: Adapted from "The 7th Committee for the prevention, detection, evaluation and treatment of hypertension" (JNC 7).

In our study group of renal transplant patients, the average values of systolic BP were over the target. The average diastolic pressure was also above the normal. The absence of normal nocturnal BP variation was frequent (87.5%) in renal allograft recipients.

In conclusion, in our study group of renal transplant recipients have a non-dipper BP profile in most cases (87.5%). This may contribute to an accelerate progression of the transplanted renal disease.

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