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Pulsatile stress correlates with (micro-)albuminuria in renal transplant recipients

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Summary

Pulsatile stress is defined as product of pulse pressure (PP) and heart rate (HR) and is largely regulated by arterial stiffness in general and specifically with reference to patients with renal insufficiency by sympathetic nerve activity. Direct effects of the pulsatile stress on heart, coronary system and ultimately cardiovascular survival have been documented whereas no data exist relating to renal transplant patients. We analysed the relation of macrocirculatory disturbance to microcirculatory defects in 92 renal transplant recipients. Therefore, we investigated aortic stiffness by carotid-femoral pulse wave velocity (PWV), pulsatile stress and albuminuria. Pulsatile stress, not PWV was associated with the extent of albuminuria ($r = 0.29$; $P < 0.01$ and $r = 0.06$; $P = 0.6$ respectively), which was confirmed in multivariate stepwise regression analysis ($P = 0.008$). Dividing the data in tertiles of pulsatile stress revealed an eightfold increased risk for microalbuminuria and 12.2-fold increased risk for macroalbuminuria comparing upper with lower tertile of pulsatile stress. Pulsatile stress, not PWV correlates with albuminuria and predicts the degree of albuminuria in renal transplant recipients. Therefore, pulsatile stress reflects an easy and cost-effective marker for renal microcirculatory defects in renal transplant patients.

Introduction

Stiffening of arterial walls results in an increased systolic (SBP) and a decreased diastolic (DBP) blood pressure (BP) and, thus, in a high pulse pressure (PP) [1]. Thus, the extent of the PP is directly related to the degree of arterial stiffness which is best determined by carotid-femoral pulse wave velocity (C-F PWV) [2]. Moreover, the reduced distensibility of muscular arteries can increase PP. In this context, enhanced sympathetic nerve activity can play an important role [3].

The action of high PP is not restricted to the large arteries; simultaneously the stress for the microcirculation is enlarged as it is the task of the small arteries to dampen the pressure oscillations to transform the pulsatile flow into steady-flow required for oxygen supply. The combination of high pulse pressure and reduced dampening from pulsatile to steady-flow has been widely evidenced to be deleterious for the heart. In contrast, downstream consequences, for example in the kidneys, have been poorly investigated. A reduced renal dampening has been observed in diabetes mellitus and systolic hypertension, both microvascular diseases in the elderly subjects. In these circumstances, an association with defective dampening and proteinuria was the key observation. However, in renal transplant patients, no investigations have been performed so far.

Kidney transplantation is characterized by a loss of graft function over time. This functional deterioration is a major cause for renal graft failure, and characterized by microvascular defects such as glomerulopathy and vasculopathy. These histomorphologic patterns are associated

with (micro-) albuminuria [4]. As origin of the graft damage, ischemia/reperfusion, surgical trauma, and alloantigen-related factors have been identified. Moreover, immunosuppression can induce microcirculatory damage [5] and sympathetic hyperreactivity has been described in muscular arteries of transplant patients [6]. Therefore, transplant recipients deal with additional factors potentially influencing the dampening of the pulsatile stress on its way into the microvascular bed. Moreover, the transplanted kidney has a relatively high intrarenal flow at rest during both systole and diastole, the diffusion of pulsatility may occur very close to the renal microcirculation of the graft. In this context, the renal damage may be even further extended by an excessive pulsatile stress in combination with microcirculatory damage.

We hypothesize that pulsatile stress is a good marker for cardiovascular-related albuminuria in renal transplant patients. Furthermore, it may be more preferable to PWV as it additionally reflects sympathetic activity and does not require additional measures as pulsatile stress is determined by pulse pressure and heart rate. Therefore we investigated the relations of pulsatile stress as determined by brachial PP × heart rate, aortic stiffness by PWV, and microcirculatory damage in a cohort of renal transplant recipients.

Methods

Populations

Renal transplant recipients were recruited from the nephrologic outpatient clinic of the Klinikum rechts der Isar der Technischen Universität München from August, 2007 to March, 2008. The protocol was approved by the local ethics committee, and all patients gave written informed consent. Inclusion criteria were stable graft function with a minimum duration of functioning grafts of 3 months. Exclusion criteria were an acute rejection period in the past 3 months, apparent *de novo* disease of the transplant or apparent recurrence of the original disease in the transplant. Furthermore, we excluded patients with major cardiovascular events such as myocardial infarction and cerebrovascular events such as stroke during the last year.

Ninety-two patients, 47.8% of whom were males, with a mean age of 49.9 ± 12.9 years, were included into this study. The average time after transplantation was 36.8 ± 47.6 months. All of these patients were treated with calcineurin inhibitors, 66 (71.7%) received tacrolimus and 26 (28.3%) cyclosporine. Age, BMI, graft age and gender were comparable for these two groups. There were no significant differences in blood pressure, lipid profiles, fasting blood glucose, serum creatinine and C-F PWV between them (data not shown). Some 25% of patients of the tacrolimus group and 46.2% of the cyclosporine group were treated with statins ($P < 0.05$).

Blood samples and morning spot urine were collected for biological measurements according to the recommendations of the American and European clinical practice guidelines – K-DOQI (http://www.kidney.org/professionals/kdoqi/guidelines.cfm).

Estimated glomerular filtration rate and albuminuria

The estimated glomerular filtration rate (eGFR) based on the Modification of Diet in Renal Disease (MDRD) equation. MDRD was used to determine the degree of renal function [eGFR (ml/min/1.73 m^2) = 186 × (serum Cr (mg/dL)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.212 if black)]. Albumin-creatinine ratios (ACRs) were calculated from morning spot urine. ACRs deviated from normal distribution and were log-transformed (logACR). Microalbuminuria was defined as ACR ≥30 mg/g creatinine and <300 mg/g creatinine. Macroalbuminuria was defined as ACR ≥300 mg/g creatinine. Information about cardiovascular factors and drug uses were obtained from medical records.

Pulse wave velocity and pulsatile stress

Carotid-Femoral pulse wave velocity (C-F PWV) was assessed by sensitive transducers and the results were analysed using the Complior program (Complior, Artech Medical, Pantin, France). First, patients rested in the supine position for 5 min. Brachial blood pressure was measured by an oscillometric device (Omron, Japan). Pressure-sensitive sensors were placed on the right carotid, radial and femoral arteries. The distance between two sites (carotid-radius, carotid-femoral) was estimated automatically according to the body height of the patients. The time difference was determined from the delay of starting phase of the first wave between carotid and another site (foot-to-foot method). PWV was calculated by dividing the distance by the time difference. Heart rate (HR) was obtained simultaneously. At least 10 signals were obtained twice and averaged to the results. In the case of an intra-patient variance of more than 10 %, a third measurement was performed. Data were collected by a single trained observer. The intra-observer repeatability coefficient for carotid-femoral (C-F) PWV was 0.90 and for carotid-radius (C-R) PWV was 0.83.

Pulsatile stress (PPxHR) was computed by multiplying brachial pulse pressure (PP) by heart rate (HR).

Statistical analysis

Statistics were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA). Variables with skewed distributions were logarithmically transformed. Descriptive

statistics were used to evaluate the total population. Comparisons of characteristics among pulsatile stress tertiles were analysed by ANOVA and chi-squared test. The tendency between pulsatile stress and different levels of albuminuria was performed by ANOVA test.

Simple univariate correlation was used to investigate the relationships between hemodynamic parameters such as PWV and pulsatile stress, renal function parameters, such as ACR, and other anthropometric, biological, and therapeutic variables. All of the variables with significant correlations to PWV and ACR, and those theoretically related to these parameters, were retained in multivariate stepwise regressions to identify those independent determinants to these parameters. The value of pulsatile stress (mean = 3995.5) was too large when compared with logACR (mean = 1.80), so we divided it by 100 and then put into regression analysis for logACR. Multinomial logistics regression with stepwise selection of variables was used to observe the significantly independent predictors for albuminuria. Normal was labeled as 1 and considered as the comparing reference, microalbuminuria labeled as 2 and macroalbuminuria as 3. A value of $P \leq 0.05$ was considered as significant. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Table 1. Characteristics of total population.

Parameters	Transplant recipients
n	92
Age, year	49.9 ± 12.9
Gender (M/F)	44/48
BMI, kg/m^2	25.0 ± 3.90
Time after transplantation, m	36.8 ± 47.6
Glycemia, mmol/l	99.1 ± 24.8
Serum creatinine, μmol/l	165.7 ± 91.0
eGFR, ml/min/1.73 m^2	43.4 ± 18.0
LogACR	1.80 ± 0.73
Total cholesterol, mmol/l	219.5 ± 55.4
Low-density lipoprotein, mmol/l	125.0 ± 39.3
High-density lipoprotein, mmol/l	59.4 ± 17.4
Triglycerides, mmol/l	230.5 ± 148.8
Systolic BP, mmHg	142.7 ± 22.0
Diastolic BP, mmHg	80.2 ± 11.4
Pulse pressure, mmHg	62.6 ± 17.6
MAP, mmHg	101.0 ± 13.3
Heart rate, bpm	64.1 ± 11.4
C-F PWV, m/s	9.12 ± 2.17
C-R PWV, m/s	8.98 ± 1.57
Hypertension, %	78.3
Diabetes, %	28.3
Cardiovascular events, %	5.4

BMI, body mass index; eGFR, estimated glomerular filtration rate; LogACR, log-transformed albumin-creatinine ratio; MAP, mean arterial pressure; C-F PWV, carotid-femoral pulse wave velocity; C-R PWV, carotid-radius pulse wave velocity.

Results

Patient characteristics

The anthropometric, biological, and clinical parameters of the cohort are presented in Table 1. Median ACR (original) was 61.0 (25th percentile: 21.0, 75th percentile: 133.5).

LogACR correlated with pulsatile stress ($r = 0.29$; $P < 0.01$), but not with PWV ($r = 0.06$; $P = 0.6$; Fig. 1). These results remained after adjustment for age, gender and BMI for pulsatile stress ($r = 0.29$; $P < 0.01$) as for PWV ($r = 0.07$; $P = 0.6$).

The characteristics of the participants categorized according to tertiles of pulsatile stress are given in Table 2. Comparing the different subgroups, age, logACR, systolic BP, pulse pressure, mean arterial pressure (MAP), heart rate and C-F PWV increased from the lower to the upper third. In addition, male, dyslipidemic and albuminuric patients were more likely to have higher pulsatile stress. A significant and positive correlation between pulsatile stress and total cholesterol and low-density cholesterol ($r = 0.29$; $P = 0.01$ and $r = 0.32$; $P = 0.01$) was observed. After adjustment for incidence of dyslipidemia and statins use, the relationships still existed with $r = 0.34$ and $r = 0.31$ respectively.

In this study, 26 diabetic patients participated; 10 with pre- and 16 with post-transplant diabetes. Patients with post-transplant diabetes had significantly longer-lasting transplants (5.8 ± 5.6 months vs. 28.8 ± 22.8 months). However, age, BMI, glycemia, eGFR, albuminuria, MAP, PWV and pulsatile stress did not differ significantly between pre- and post-transplant diabetes.

Albuminuria and aortic stiffness

There was no significant correlation between C-F PWV and logACR and the different levels of albuminuria (normal; microalbuminuria; macroalbuminuria; Fig. 2) in the univariate analysis ($P = 0.25$; $P = 0.38$ respectively). Dividing patients according to the level of stiffness (C-F PWV: <10 m/s; 10–12 m/s; >12 m/s), did not result in differences either ($P = 0.07$). No relation was established between C-R PWV and LogACR ($P = 0.82$). Renin-angiotensin system (RAS) blockers, which were used as renoprotective antihypertensive agents, did not affect microalbuminuria ($r = 0.06$, $P = 0.70$).

In the multivariate analysis of C-F PWV, factors such as age, heart rate, male gender and mean arterial pressure were independent predictors, with total explaining of 62.5% of the variance (Table 3). LogACR and eGFR did not reach statistical significance similar to diabetes

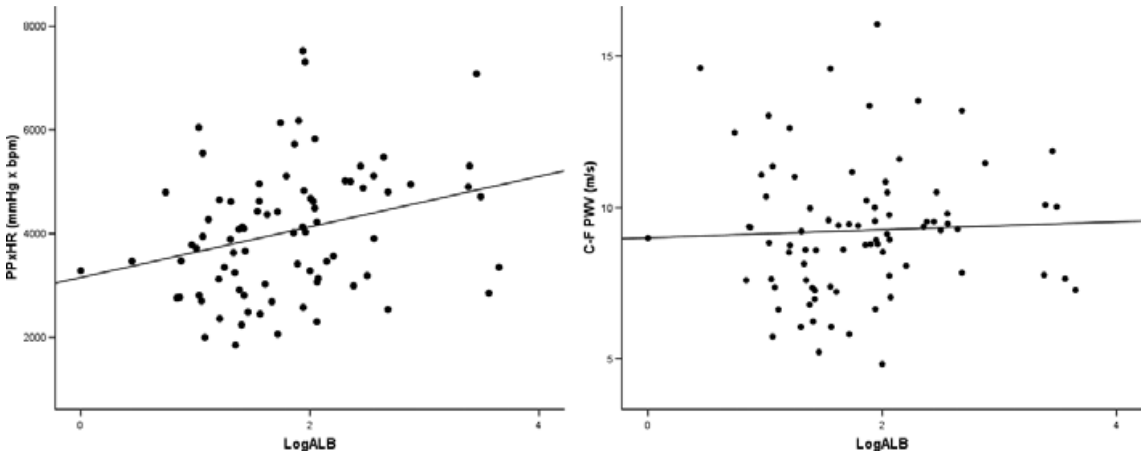

Figure 1 Correlation between pulse pressure, C-F PWV and albumin-creatinine ratio (ACR). Values for were log-transformed (logACR) because of skewed distribution. LogACR correlated with pulsatile stress ($r = 0.29$; $P < 0.01$), but not with PWV ($r = 0.06$; $P = 0.6$). These results remained after adjustment for age, gender and BMI for pulsatile stress ($r = 0.29$; $P < 0.01$) as for PWV ($r = 0.07$; $P = 0.6$).

($\beta = 0.04$, $P = 0.51$) and RAS-blockade ($\beta = 0.09$, $P = 0.22$) had no influence on pulsatility. Meanwhile, different immunosuppressive drugs, time after transplantation and history of acute rejection did not predict C-F PWV (data not shown).

Albuminuria and pulsatile stress

On univariate analysis, LogACR correlated with eGFR, pulsatile stress, calcium channel blocker (CCB), pulse pressure, hematocrit and white blood cell ($P < 0.05$). In

Table 2. Comparison of characteristics according to tertiles of pulsatile stress.

	Pulsatile stress			
Parameters	<3350 ($n = 29$)	3350–4615 ($n = 32$)	>4615 ($n = 31$)	*P* value
Age, year	44.5 ± 11.7	51.8 ± 14.4	53.0 ± 11.0	0.021
Male, %	41.4	34.4	67.7	0.021
BMI, kg/m^2	25.5 ± 4.42	24.8 ± 3.46	24.7 ± 3.91	–
Graft age, month	27.0 ± 25.1	39.6 ± 49.6	42.3 ± 59.5	–
Glycemia, mmol/l	94.1 ± 14.0	97.8 ± 20.6	100.5 ± 35.1	–
Serum creatinine, μmol/l	151.5 ± 82.4	164.3 ± 86.3	180.4 ± 103.1	–
eGFR, ml/min/1.73 m^2	47.9 ± 16.7	40.9 ± 18.2	41.7 ± 18.7	–
LogACR	1.61 ± 0.69	1.61 ± 0.63	2.16 ± 0.74	0.004
Total cholesterol/high-density lipoprotein	3.64 ± 1.13	4.33 ± 1.47	4.03 ± 1.52	–
Systolic BP, mmHg	125.4 ± 15.6	139.8 ± 12.5	161.9 ± 19.8	<0.001
Diastolic BP, mmHg	76.7 ± 10.7	80.2 ± 10.2	83.4 ± 12.4	–
Pulse pressure, mmHg	48.7 ± 10.1	59.7 ± 7.93	78.5 ± 17.8	<0.001
MAP, mmHg	92.9 ± 11.6	100.1 ± 10.3	109.6 ± 12.8	<0.001
Heart rate, bpm	55.9 ± 7.02	65.5 ± 6.53	70.4 ± 14.1	<0.001
C-F PWV, m/s	7.83 ± 1.32	8.87 ± 2.05	10.7 ± 2.01	<0.001
C-R PWV, m/s	8.69 ± 1.59	8.83 ± 1.56	9.45 ± 1.52	–
Diabetes, %	24.1	25.0	35.5	–
Albumunuria, %	48.1	48.1	85.7	0.004
Numbers of antihypertensive drugs	1.72 ± 1.19	1.84 ± 0.99	1.87 ± 1.02	–
Patients with ACEI, %	41.4	40.6	45.2	–
Patients with CCB, %	34.5	46.9	51.6	–
Patients with statins, %	41.4	31.3	22.6	–
Cardiovascular events, *n*	1	2	2	–

BMI, body mass index; eGFR, estimated glomerular filtration rate; LogACR, log-transformed albumin-creatinine ratio ; MAP, mean arterial pressure; C-F PWV, carotid-femoral pulse wave velocity; C-R PWV, carotid-radius pulse wave velocity; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium-channel blockers.

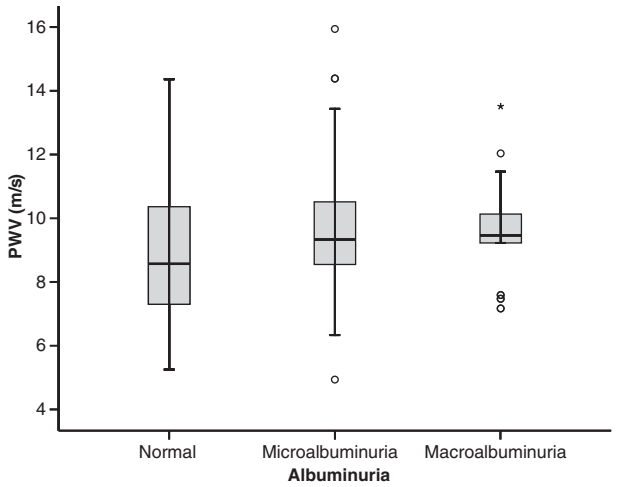

Figure 2 Box plot of carotid-femoral pulse wave velocity (C-F PWV) in the renal transplant recipients, and different levels of albuminuria as the classification variable. Boxes represent median, 75th percentile and 25th percentile. Upper whisker represents 75th percentile + 1.5 IQR (interquartile range, i.e. 50% of the distribution); lower whisker 25th percentile-1.5IQR. Outliers label with circle.

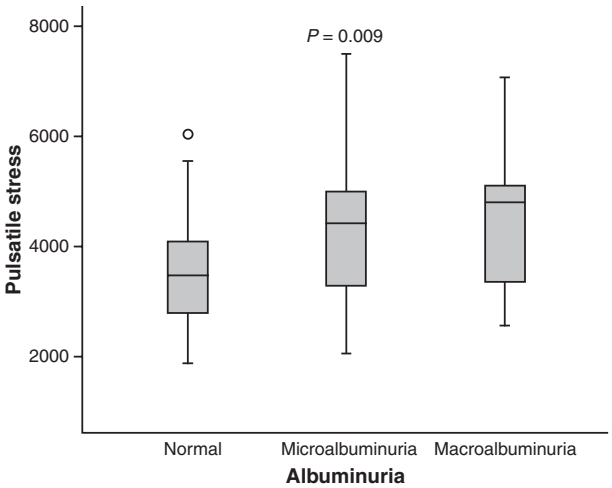

Figure 3 Box plot of pulsatile stress in the renal transplant recipients, and different levels of albuminuria as the classification variable. Boxes represent median, 75th percentile and 25th percentile. Upper whisker represents 75th percentile + 1.5 IQR (interquartile range, i.e. 50% of the distribution); lower whisker 25th percentile-1.5IQR. Outliers label with circle.

Table 3. Multivariate stepwise regression analysis for aortic stiffness.

Parameters	In/Out	R^2 increment	β-coefficient ± SE	*P* value
Dependent variable: C-F PWV				
Age (year)	IN	0.289	0.076 ± 0.012	<0.001
Heart rate (bpm)	IN	0.130	0.058 ± 0.014	<0.001
Mean arterial pressure (mmHg)	IN	0.110	0.052 ± 0.013	<0.001
Gender (1 = male, 0 = female)	IN	0.061	1.174 ± 0.335	0.001
Beta1 receptor blocker (1 = yes, 0 = no)	IN	0.035	–0.843 ± 0.330	0.01
Acute rejection (1 = yes, 0 = no)	OUT	–	–	–
LogACR	OUT	–	–	–
eGFR (ml/min/1.73 m^2)	OUT	–	–	–
Total variance explained R^2 = 0.625	*F* ratio = 23.3 (*P* < 0.001)			

Table 4. Multivariate stepwise regression analysis for logalbumin-creatinine ratio (LogACR).

Parameters	In/Out	R^2 increment	β-coefficient ± SE	*P* value
Dependent variable: LogACR				
eGFR (ml/min/1.73 m^2)	IN	0.119	–0.015 ± 0.005	0.002
Pulsatile stress*	IN	0.081	0.017 ± 0.006	0.008
C-F PWV (m/s)	OUT	–	–	–
Total variance explained R^2 = 0.178	*F* ratio = 9.12 (*P* < 0.001)			

*Pulsatile stress was divided by 100.

the multivariate analysis, only eGFR and pulsatile stress were independent determinants for logACR with pulsatile stress explaining 11.9% of the variance and total explaining 17.8% (Table 4). A significant, positive, and independent linear regression between pulsatile stress and different levels of albuminuria was found ($P < 0.01$; Fig. 3). Different immunosuppressive drugs and graft age did not impact on the changes of LogACR.

In the next step, we tried to explore risk factors for albuminuria by stepwise logistic analysis. Only eGFR and

Table 5. ORs of albuminuria analysed by stepwise logistics regression.

Parameters	Odds ratio	95% CI	*P* value
Microalbuminuria			
eGFR	0.958	0.921–0.997	0.03
Pulsatile stress tertiles			
<3350	0.125	0.026–0.602	0.01
3350–4615	0.122	0.025–0.595	0.009
>4615*	1.0	1.0	1.0
Macroalbuminuria			
eGFR	0.915	0.865–0.967	0.002
Pulsatile stress tertiles			
<3350	0.082	0.011–0.607	0.01
3350–4615	0.029	0.003–0.267	0.002
>4615*	1.0	1.0	1.0

*Patients in this category served as reference.

pulsatile stress tertiles could predict the incidence of albuminuria (Table 5). Participants with higher eGFR were less likely to have microalbuminuria (OR = 0.96; $P = 0.03$) and macroalbuminuria (OR = 0.92; $P = 0.002$). Compared with patients in the upper third of pulsatile stress, the possibility for patients in the lower third to have microalbuminuria was 12.5% ($P = 0.01$) and to have macroalbuminuria was 8.2% ($P = 0.01$). Thus, patients in the upper third had eightfold risk of microalbuminuria and 12.2-fold risk of macroalbuminuria when compared with patients in the lower third.

Discussion

This study demonstrated that pulsatile stress is associated with microcirculatory damage in renal grafts. By contrast, elevated aortic stiffness was not associated with the microcirculatory damage.

(Micro-)albuminuria is an accepted marker for microcirculatory damage [7,8]. Loss of transplant function is predominantly characterized by the histomorphologic pattern of vasculopathy and glomerulopathy, resulting in albuminuria [5,9]. Conversely, reduction of albuminuria in high-risk patients reduced rates of death, myocardial infarction and stroke [10,11].

Our major finding was that the extent of microcirculatory damage indicated by albuminuria can be partially explained by the individual magnitude of pulsatile stress on the arterial wall per unit time. Therefore, graft survival may directly be affected by the extent of pulsatile stress. This is in conformity with the predictive value of pulsatile stress in context with cardiovascular complications as evidenced in a general French population [12] as well as in renal graft recipients [13].

Pulsatile stress distorts the arterial wall, thereby promoting arteriosclerosis [14]. Moreover, transplanted kidneys receive a relatively high intrarenal flow at rest during both systole and diastole [14]. Thus, the dampening of the pulsatile flow down to steady-flow needed for the oxygen supply may occur very close to the renal microcirculation of the graft [14]. Continuously enhanced pulsatility down to microcirculatory level may thus distort resistance arteries, which can directly influence intraglomerular pressure and flow conditions [15,16].

In this context, it is of interest to note that the level of aortic stiffness alone did not predict the microcirculatory damage. Thus, structural damage accumulating in stiffness, which is one major aspect for the determination of pulse pressure, [17] may alone not be relevant for the determination of the microcirculatory damage. Other parameters may be needed, such as increased sympathetic activity which accelerates heart rate [18] which in turn results in amplification of the pulse pressure between aorta and brachial artery [12]. Interestingly, the autonomic nervous system is often enhanced in renal transplant recipients [19,20], in particular in muscular arteries of transplant recipients. In subtotally nephrectomized rats [21] and diabetic patients [22] a sympathoplegic therapy using moxonidine reduced microalbuminuria. Thus, in renal transplant patients with high pulsatile stress a reduction of sympathetic nerve activity may be an option to protect the microcirculation and therewith long-term graft function.

Our findings suggest pulsatile stress as marker for cardiovascular-related albuminuria. As the determination of pulsatile stress is based on blood pressure and heart rate and does not require extra measures, it represents an easy and cost-effective tool.

In summary, this study demonstrated that pulsatile stress correlates with microcirculatory damage in renal transplant recipients. By contrast aortic stiffness is not associated with albuminuria in this cohort. We suggest that pulsatile stress is an easy and cost-effective marker for cardiovascular-related microcirculatory damage.

Authorship

MB: wrote the paper, designed research/study, analyzed data. CRP: performed research/study. MR: collected data. MVE: collected data. DS: collected data. JL: designed research/study, analyzed data. UH: designed research/study, analyzed data.

References

1. Willum-Hansen T, Staessen JA, Torp-Pedersen C, *et al.* Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation* 2006; **113**: 664.

2. Laurent S, Cockcroft J, Van Bortel L, *et al.* Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; **27**: 2588.
3. Hausberg M, Kosch M, Harmelink P, *et al.* Sympathetic nerve activity in end-stage renal disease. *Circulation* 2002; **106**: 1974.
4. Amer H, Fidler ME, Myslak M, *et al.* Proteinuria after kidney transplantation, relationship to allograft histology and survival. *Am J Transplant* 2007; **7**: 2748.
5. Halimi JM, Buchler M, Al-Najjar A, *et al.* Urinary albumin excretion and the risk of graft loss and death in proteinuric and non-proteinuric renal transplant recipients. *Am J Transplant* 2007; **7**: 618.
6. Kosch M, Barenbrock M, Kisters K, Rahn KH, Hausberg M. Relationship between muscle sympathetic nerve activity and large artery mechanical vessel wall properties in renal transplant patients. *J Hypertens* 2002; **20**: 501.
7. Hillege HL, Fidler V, Diercks GF, *et al.* Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002; **106**: 1777.
8. Arnlov J, Evans JC, Meigs JB, *et al.* Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. *Circulation* 2005; **112**: 969.
9. Halimi JM, Matthias B, Al-Najjar A, *et al.* Respective predictive role of urinary albumin excretion and nonalbumin proteinuria on graft loss and death in renal transplant recipients. *Am J Transplant* 2007; **7**: 2775.
10. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; **342**: 145.
11. Wilmer WA, Rovin BH, Hebert CJ, Rao SV, Kumor K, Hebert LA. Management of glomerular proteinuria: a commentary. *J Am Soc Nephrol* 2003; **14**: 3217.
12. Thomas F, Bean K, Provost JC, Guize L, Benetos A. Combined effects of heart rate and pulse pressure on cardiovascular mortality according to age. *J Hypertens* 2001; **19**: 863.
13. Bahous SA, Stephan A, Barakat W, Blacher J, Asmar R, Safar ME. Aortic pulse wave velocity in renal transplant patients. *Kidney Int* 2004; **66**: 1486.
14. Safar ME, Lacolley P. Disturbance of macro- and microcirculation: relations with pulse pressure and cardiac organ damage. *Am J Physiol Heart Circ Physiol* 2007; **293**: H1.
15. Vedovato M, Lepore G, Coracina A, *et al.* Effect of sodium intake on blood pressure and albuminuria in Type 2 diabetic patients: the role of insulin resistance. *Diabetologia* 2004; **47**: 300.
16. Rajapakse NW, De Miguel C, Das S, Mattson DL. Exogenous L-arginine ameliorates angiotensin II-induced hypertension and renal damage in rats. *Hypertension* 2008; **52**: 1084.
17. Drukteinis JS, Roman MJ, Fabsitz RR, *et al.* Cardiac and systemic hemodynamic characteristics of hypertension and prehypertension in adolescents and young adults: the Strong Heart Study. *Circulation* 2007; **115**: 221.
18. Chen CH, Nevo E, Fetics B, *et al.* Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. *Circulation* 1997; **95**: 1827.
19. Guizar-Mendoza JM, Amador-Licona N, Lozada EE, *et al.* Left ventricular mass and heart sympathetic activity after renal transplantation in children and young adults. *Pediatr Nephrol* 2006; **21**: 1413.
20. Krespi PG, Makris TK, Hatzizacharias AN, *et al.* Moxonidine effect on microalbuminuria, thrombomodulin, and plasminogen activator inhibitor-1 levels in patients with essential hypertension. *Cardiovasc Drugs Ther* 1998; **12**: 463.
21. Amann K, Rump LC, Simonaviciene A, *et al.* Effects of low dose sympathetic inhibition on glomerulosclerosis and albuminuria in subtotally nephrectomized rats. *J Am Soc Nephrol* 2000; **11**: 1469.
22. Strojek K, Grzeszczak W, Gorska J, Leschinger MI, Ritz E. Lowering of microalbuminuria in diabetic patients by a sympathicoplegic agent: novel approach to prevent progression of diabetic nephropathy? *J Am Soc Nephrol* 2001; **12**: 602.