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Pulse Wave Velocity Predicts Mortality in Renal Transplant Patients

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Abstract

Background: Measuring arterial stiffness using pulse wave velocity (PWV) has become an important tool to assess vascular function and cardiovascular mortality. For subject with hypertension, end-stage renal disease and diabetes, PWV has been shown to predict cardiovascular and all-cause mortality. We hypothesize that PWV would also predict mortality in subjects who have undergone kidney transplantation.

Methods: A cohort of 330 patients with renal transplantation was studied with a mean age at entry 51.4 ± 0.75 years. Mean follow-up was 3.8 years (± 0.7 years); 16 deaths occurred during follow-up. At entry, together with standard clinical and biochemical parameters, PWV was determined from pressure tracing over carotid and femoral arteries.

Results: With increasing PWV, there was a significant increase in age, systolic blood pressure and pulse pressure. In addition, subjects with higher PWV also exhibited more frequently the presence of coronary heart disease. On the basis of Cox analyses, PWV and systolic blood pressure emerged as predictors of all-cause mortality.

Conclusion: These results provide evidence that PWV is a strong predictor of all-cause mortality in the population of renal transplant recipients.

Key words: Pulse Wave Velocity, Arterial Stiffness, Renal Transplantation, Mortality

Introduction

Measuring arterial stiffness has become a major tool for assessing arterial function and cardiovascular mortality [1]. In particular, pulse wave velocity (PWV) has been proposed to be a clinically useful stiffness marker due to its non-invasiveness and ease of use [2]. PWV not only reflects the overall atherosclerotic burden of the arterial tree but has also been shown to predict cardiovascular mortality in hypertension [3, 4], end-stage renal disease [5, 6], and diabetes mellitus [6, 7].

Another population with high cardiovascular risk includes subjects who have undergone kidney transplantation. To date, only few studies have investigated arterial function in kidney transplant recipients, and little is known about the predictive value of PWV in this population. Therefore, we hypothesize that PWV may also predict mortality in this group of patients. In the present study, we evaluated the predictive value of PWV in 330 kidney transplant patients.

Material, Methods and Statistics

Study Population

In this longitudinal study, 330 subjects with stable renal transplantation were recruited from our renal transplant outpatient clinic [8]. Height and weight were measured, and body mass index (BMI) was calculated as weight to height squared. Laboratory measurements were measured with commercially available kits in our central laboratory. The study was performed in accordance with the principles laid down in the Declaration of Helsinki.

Hemodynamic Measurements

Measurements were performed in a quiet, temperature-controlled room after 10 minutes, in a supine position according to the recommendations for user procedures of clinical applications of arterial stiffness, task force III [9], using the SphygmoCor device (AtCor Medical, Sydney, Australia). Blood pressure and heart rate (mean of three readings) were measured with an automatic upper-arm oscillometric device (Omron *705IT*, Omron Medizintechnik, Mannheim, Germany). Pulse pressure (PP) was calculated by subtracting diastolic (DBP) from systolic blood pressure (SBP).

Aortic pulse wave velocity (PWV) was calculated from sequentially recorded pressure waveforms of the carotid and femoral artery as reported previously by our group [10, 11]. With a simultaneous ECG recording of the R-wave as reference, the integral software calculated the pulse wave transit time. Anatomical measurements of the distance between the carotid and femoral artery were made on the surface of the body. The distance between carotid artery recording site and the suprasternal notch was subtracted from the distance from the suprasternal notch over the umbilicus to the femoral artery recording site [12]. PWV [m x s^{-1}] was calculated as ratio between the distance travelled by the pulse wave and pulse transmission time.

Statistical Analysis

The outcome events studied was all-cause mortality. Survival curves were estimated by the Kaplan-Meier

product-limit method. Prognostic factors of survival were identified by use of logistic regression analysis and the Cox proportional hazards regression model. The cohort was divided into 3 groups according to the PWV < 7.5 m/s in the lower third, between 7.5 and 10.0 in the second third, and >10.0 in the upper third. Variables were considered to be prognostic when they were found to be statistically significant ($P<0.05$) in the logistic regression or the Cox proportional hazards regression models of all-cause mortality.

$P < 0.05$ was considered statistically significant. Data are expressed as mean ± SD. Statistical analysis was performed using GraphPad Prism 4.0 for MS Windows (GraphPad Software, Inc., San Diego, CA, U.S.A.).

Results

The characteristics of the cohort population in total and according to tertiles of PWV are displayed in Table 1. With increasing PWV, there was a significant increase in age, systolic blood pressure and pulse pressure. In addition, subjects with higher PWV also exhibited more frequently the presence of coronary heart disease (Table 1).

Mean follow-up was 3.87 years (± 0.7 years); during this period, 16 deaths were recorded. According to the Cox analysis, the significant covariates retained by the model were PWV and SBP (Table 2). Figure 1 shows the probabilities of all-cause survival as a function of PWV values. Comparisons between survival curves were highly significant with better survival for those with lower PWV.

Discussion

In the present study, we showed for the first time that PWV predicts all-cause mortaliy in renal transplant patients. We focused our analysis on all-cause mortality since only 16 deaths occurred during the mean follow-up time of 3.8 years. After renal transplantation, cardiovascular complications remain common, but a large number of patients also dies from infectious and tumoural diseases [13]. Therefore, it was unclear, whether PWV would predict mortality in this population. In the present study we could show that PWV

Table 1. Characteristics [mean ± SEM] of the study population at inclusion according to tertiles of PWV. CHD, coronary heart disease; AOD, arterial occlusive disease.

Parameter	Total (n = 330)	PWV < 7.5 (n = 138)	PWV > 7.5 < 10 (n = 99)	PWV > 10 (n = 93)	P, ANOVA
Age [years]	51.4 ± 0.75	44.4 ± 12.9	51.6 ± 10.8	61.6 ± 10.7	< 0.0001
Gender (male/female)	168/162	65/73	49/50	54/39	0.250
Body mass index [kg/m2]	25.3 ± 4.3	25.0 ± 4.5	25.8 ± 4.5	25.2 ± 3.6	0.366
Hypertension	N = 298	N = 120	N = 98	N = 91	0.076
History of CHD	N = 79	N = 18	N = 26	N = 35	< 0.0001
History of AOD	N = 26	N = 5	N = 10	N = 11	0.082
Cholesterol [mg/dl]	213 ± 41	208 ± 46	218 ± 38	215 ± 36	0.247
Triglycerides [mg/dl]	187 ± 113	184 ± 109	194 ± 117	184 ± 115	0.262
Glucose [mg/dl]	108 ± 32	102 ± 31	108 ± 29	118 ± 36	0.0006
Systolic blood pressure [mmHg]	149 ± 20	142 ± 20	152 ± 20	157 ± 19	< 0.0001
Diastolic blood pressure [mmHg]	83 ± 11	83 ± 11	83 ± 9	81 ± 18	0.372
Pulse pressure [mmHg]	67 ± 18	59 ± 15	69 ± 17	76 ± 18	< 0.0001
Heart rate [b.p.m.]	67 ± 13	66 ± 12	68 ± 12	67 ± 15	0.473
Pulse wave velocity [m/s]	9.1 ± 3.3	6.2 ± 0.8	8.5 ± 0.8	13.1 ± 2.9	< 0.0001

Table 2. Proportional Hazards Regression Analysis of All-Cause Mortality. SBP, systolic blood pressure; CHD, coronary heart disease.

Parameter	Regression Coefficient	SE	z Value	P
PWV	0.066	0.024	2.704	0.0055
Age	-0.006	0.006	-1.038	0.3083
SBP	-0.007	0.003	-2.048	0.0406
Glucose	-0.001	0.002	-0.273	0.7846
CHD	0.138	0.152	0.912	0.3620

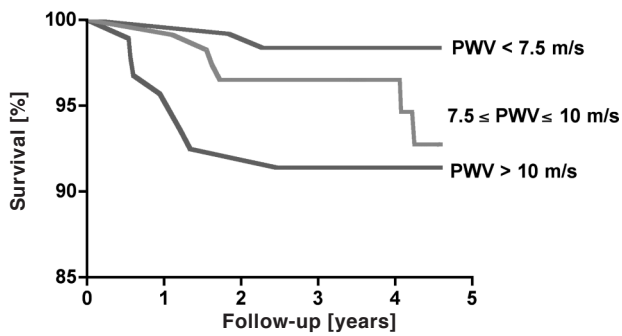

Fig. 1. Probabilities of overall survival in study population according to level of PWV divided into tertiles. Comparisons between survival curves were statistically significant (P = 0.047).

predicts mortality in renal transplant patients even during a relatively short follow-up period of 3.8 years. These results are consistent with previous reports showing the strong predictive value of PWV in populations of hypertensives [3, 4], patients with end-stage renal disease [5, 6], and diabetes mellitus [6, 7].

Hemodynamically, stiffening of the aortic tree results in characteristic changes of the blood pressure pattern [2]. Aortic stiffening leads to a rise of systolic and a fall of diastolic blood pressure resulting in a widening of the pulse pressure. Results from our study are consistent with such hemodynamic concept in that subjects with higher PWV also exhibited higher systolic blood pressure and pulse pressures as a consequence of arterial stiffening.

Several other studies have investigated stiffness markers in renal transplant patients. Bahous et al. followed up 106 transplant subjects, and found that tobacco consumption and acute renal rejection influence aortic stiffness as measured by PWV [14]. Two other studies have investigated the effect of renal transplantation on arterial stiffness, and demonstrated that renal transplantation improved PWV and augmentation index in subjects who underwent renal transplantation [15, 16]. Recently, Schwenger et al. showed in a cohort of 76 kidney allograft patients that PWV, pulse pressure, and intima-media-thickness are independent determinants of the resistance index, a strong predictor of kidney allograft survival [17]. Our data on 330 renal transplant recipients extend these associations between stiffness markers, cardiovascular risk factors and renal disease to the predictive value of stiffness markes in this patient population.

In addition to PWV also systolic blood pressure predicted mortality. Hypertension in renal transplant recipients can originate from different sources including marginal renal function, use of immune suppressive drugs, and renal artery stenosis. Despite the inhomogeneous pathogenesis of arterial hypertension in renal transplant patients, this classical cardiovascular risk factor predicts mortality in renal transplant patients.

Clinical Implication

The results of the present study show that the classical marker of arterial stiffness PWV predicts mortality in renal transplantation. Stiffness markers are increasingly used in population studies to evaluate cardiovascular morbidity and mortality. Our data suggest, that also in renal transplant subjects stiffness markers may be used as tools for the prediction of all-cause mortality. Even though it is very likely, further studies are required to evaluate the predictive value of PWV for cardiovascular mortality.

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