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 to 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 mortality 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).
Acknowledgements: We would like to thank Petra Höhner for her help in recruiting patients. We would also like to thank Christa Sittartz for her technical assistance.

Sources of Funding: This study was supported, in part, by grants from the intramural research fund (IFORES) and the Jackstädt foundation.

Conflict of Interest/Disclosure: None.

The results of the present study show that the classical marker of arterial stiffness PWV predicts mortality in renal transplantation. Stiffness markers are increasing used in population studies to evaluate 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 increasing 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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Received: March 30, 2010 / Accepted: June 18, 2010

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