The role of parameters of arterial stiffness to prognose cardivascular survival in haemodialysis patients: determinants and therapeutic options

Ph.D. Thesis

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Introduction

In the population of patients with end-stage renal disease (ESRD) structural and functional alterations and calcification in the large arteries begin early, facilitating a 20 to 30 times higher rate of cardiovascular (CV) mortality than in the age-matched general population. CV mortality is responsible for 45% of all-cause mortality in this population. It is therefore of prudent importance to study the predisposing risk factors of CV mortality; especially those that are unique to ESRD such as vascular calcification that affects both the intima as well as the media of the arteries. Prospective studies demonstrated that the association between calcification of large arteries and increased risk of CV morbidity and mortality in this population is independent of classical CV risk factors.

The presence of structural changes induced by vascular calcification in ESRD patients is a strong promoter of arterial wall stiffening. Increased aortic wall stiffness has emerged as an independent predictor of all-cause and CV mortality in this population. For a given stroke volume, stiffer aortic wall (decreased compliance) would lead to form a higher amplitude of the forward traveling pulse wave. This, combined with a faster return of the reflected pressure wave from the periphery (a.k.a. augmentation), would result in increased central pulse pressure, increasing thereby cardiac afterload, and decreasing diastolic coronary circulation. While increased cardiac afterload leads to increased oxygen demand, the result of decreased coronary artery circulation is decreased oxygen supply. This discrepancy between oxygen demand and supply is a major cause of the cardiac complications of arterial stiffness which leads to increased CV morbidity and mortality in the ESRD population.

Arterial stiffness is described by several parameters, among which four are widely used (carotid-femoral pulse wave velocity: PWV, carotid augmentation index: AI, central (carotid) pulse pressure: CPP and carotid to brachial pulse pressure amplification: AMP). Previous studies used separate cohorts to evaluate the prognostic value of these parameters in ESRD, where more than one parameter was rarely considered, and the time of measurements in relation to the dialysis procedure was not standardized. The relative prognostic value of these parameters has not previously been evaluated in one cohort, therefore it is not known which of them is the best at prognosing CV events, and when the measurements are to be performed in relation to the dialysis procedure.

Progressive arterial calcification and consequent arterial stiffening present a clinically relevant situation: decreasing or at least attenuating arterial calcification may possibly lead to better arterial wall compliance and hence patient outcome. It is therefore clinically sound to evaluate drug induced influences on the progression of arterial stiffness in this population. In January 2005, sevelamer - an oral phosphate binder - became available in Hungary for the treatment of hyperphosphatemia in ESRD. Sevelamer decreases arterial calcification but its effect on aortic stiffness has not previously been evaluated.

Assessment of arterial stiffness is increasingly used in the everyday clinical management of patients. Devices that are validated and suited for clinical use are needed for this purpose but clinicians and researchers still report difficulties in selecting the most appropriate methodology for their specific use. A well validated device is essential to determine parameters of arterial stiffness; non-validated parameters lead to false conclusions on the relationship between examined factors and outcome. Recently a new oscillometric device (Arteriograph) has been developed and marketed to measure arterial stiffness, but

its device- and prognostic validity in high risk ESRD patients has not previously been evaluated.

Objectives

During my work my specific objectives were to determine:

1. which of the widely used four parameters of arterial stiffness (PWV, AI, CPP and AMP) is the best at predicting CV mortality in ESRD patients on HD assessed in one cohort,
2. whether the timing of measurement, in relation to the dialysis procedure, influences the predictive ability of the measured parameters,
3. whether treatment with sevelamer improves aortic arterial stiffness in a prospective observational study using concomitant controls and an appropriate follow-up period,,
4. whether the effect of sevelamer on aortic stiffness in this population is linked to bone turnover or/and inhibitors of vascular calcification,
5. the validity of the oscillometric Arteriograph device in measuring arterial stiffness parameters compared to the reference tonometric PulsePen device in ESRD patients on HD,
6. and whether, parameters assessed by the Arteriograph device have similar prognostic value in predicting survival in ESRD patients on HD compared to those measured by PulsePen.

Patients and methods

ERDS patients on chronic HD (>3 months on HD) at two dialysis units of the B. Braun Avitum Nephrological Network were invited to participate (n = 126) in the three studies. Among them 28 patients declined participation leaving 98 patients for inclusion into the projected studies. All patients received thrice-weekly HD for 4 hour duration using a dialysate calcium concentration of 1.50 mmol/L, a bicarbonate bath and a polysulphone membrane. Baseline demographic and clinical data were gathered by chart review, and laboratory parameters were measured prior to a midweek dialysis at the time of arterial stiffness assessment.

My research is built on three studies which were performed in the cohort above. The ***first*** (n = 98) is a prospective follow-up study, where patients were followed for a median of 29 (range 1–35) months to examine the ability of parameters of arterial stiffness to predict CV mortality. Stiffness parameters (PWV, AI, CPP, AMP) were measured using the validated PulsePen tonometer (DiaTecne, Milan, Italy) before and after a midweek dialysis session with the patient in the supine position. Follow-up was censored at the time of death from CV or non-CV causes, transplantation, transfer to another unit or at the end of follow-up on February 29, 2008. Primary outcome measure was death from a CV event; CV mortality was defined as sudden cardiac death, death related to myocardial infarction, arrhythmia, heart failure or stroke as assessed by the attending physician at the dialysis center.

Thirteen patients, who started sevelamer treatment, were involved in the ***second study*** to examine the effect of sevelamer on central arterial stiffness. Thirteen control patients paired to those treated with sevelamer were also selected from the same dialysis units matched for age, sex, presence of diabetes, and

dialysis duration who continued on their previous calcium carbonate phosphate binder treatment. During follow-up, eventually all but one sevelamer treated patient received 4800 mg of sevelamer. Other medications, including antihypertensive drugs and active vitamin-D treatment, were at the discretion of the treating physician. Laboratory and arterial stiffness parameters (PWV, AI) where determined at the start and at the end of follow-up. Patients (n = 26) were followed for 10.8 (±2.3) months and the primary outcome was the change in PWV in the two groups.

The ***third study*** 92 patients (n = 92) were involved to test the validity of the Arteriograph device (TensioMed, Budapest, Hungary) in measuring parameters of arterial stiffness (PWV, AI) compared to those measured by the validated PulsePen device. During the study PWV and AI were measured both by the reference PulsePen as well as the tested Arteriograph devices before a midweek dialysis treatment in the supine position. The order of measurements (PulsePen or Arteriograph) was randomly chosen. After this patients were followed for a median of 29 (range 1–35) months. Follow-up was censored at the time of death from CV and non-CV causes, transplantation, transfer toother unit or at the end of follow-up on February 29, 2008. The outcome measure was death from a CV event; CV mortality was defined as in the first study.

In all studies, blood pressure and heart rate was recorded by the validated BpTru device (VSM Medtech, Vancouver, B.C., Canada) with two sequential measurements averaged manually. Carotid tonometric measurements were performed on the side contralateral to the fistula or tunneled jugular line. The same sides were used to obtain femoral pressure waves.

PulsePen device measures the time difference between the R wave of the ECG and the 'foot' of the pulse pressure wave – obtained sequentially above the carotid and the femoral arteries using a handheld tonometer – to calculate pulse transit time between these two sites. By using surface tape measurements pulse wave travel distance was assessed and then used to calculate PWV with the PulsePen software. AI was measured after automatic identification of the inflection point on the averaged carotid pulse signal by the software. CPP was determined by measuring the amplitude of the averaged carotid signal after calibration of the carotid curve to the brachial mean and diastolic blood pressures. AMP was the ratio of brachial and carotid pulse pressures.

Arteriograph device calculates PWV_A and AI_A by contour analysis of the averaged oscillometric pressure curve registered by the cuff on the upper arm. The forward and reflected waves are identified on this pressure curve, detected during the heart cycle, by the Arteriograph software. The time difference between the beginning of the two waves is related to the distance from the jugular notch to the symphysis, resulting in the calculated PWV_A in m/s. AI_A corresponds to the pressure difference between the amplitude of the two waves in relation to the pulse pressure without applying a transfer function.

The SAS statistical package version 6.11 (SAS Institute, Cary, NC, U.S.A.) was used for the main analyses in all three studies. Continuous variables are presented as mean (standard deviation) or, in case of evidence against normal distribution, as median (interquartile range), and categorical variables are presented as n (%). P-values with a two-sided α of 0.05 were considered statistically significant. Hazard ratios are presented with their 95% confidence intervals in parentheses.

In the first study, log-rank tests and Cox proportional hazards regression analyses were used to assess the relationship of arterial stiffness parameters with CV mortality. Hazard ratios were adjusted for age, diabetes and the presence of established CV disease. Stiffness parameters that showed a significant association with CV mortality in univariate models were finally considered in the same adjusted model.

In the second study, baseline variables between sevelamer-treated and control patients were compared by Student's t test for independent samples for continuous variables with normal distribution, by the Wilcoxon rank-sum test for continuous variables with a non-normal distribution, and by Fisher's exact test for categorical variables. The main analysis consisted of comparing the changes of variables during follow-up between sevelamer-treated and control groups by Student's t test for independent samples and by the Wilcoxon rank sum test. We also performed multivariate linear regression analyses with the change in PWV as the dependent variable.

In the third study, we used Pearson's correlation analysis between readings of the test Arteriograph and reference PulsePen devices. Second, we analyzed the readings according to the method proposed by Bland and Altman. To assess prognostic validity, PWV and AI readings obtained by each device were analyzed by log-rank tests using tertiles of the respective parameters and also by Cox proportional hazard regression using the data as continuous variables and adjusted for age, diabetes and established CV diseases.

Results

In the ***first study*** {n = 98, mean age: 63.4 (14.4) years, male: 61 % and dialysis time: median 29.6 (12.4-48.6) months} the most frequent causes for renal disease were vascular-tubulointerstitial disorders (including hypertension: 39%), diabetes mellitus (33%) and glomerulonephritis (13%). During follow-up, 40 patients died (mortality rate 20.7/100 patient-years) of which 25 were due to CV causes. Heart rate, central and brachial systolic and diastolic blood pressures were significantly higher immediately after dialysis ($p \leq 0.001$ in all cases). CPP and brachial pulse pressures were also higher, but the differences were not statistically significant ($p = 0.064$ and 0.187, respectively). At the end of dialysis, PWV increased and AI decreased significantly ($p = 0.009$ and 0.033, respectively), while AMP did not show a significant change ($p = 0.247$).

In separate univariate Cox proportional hazards models, pre- and postdialysis PWV, predialysis CPP (but not postdialysis) and predialysis AMP values (but not postdialysis) were related to CV mortality. AI was not related to outcome, irrespective of the timing of the measurement. After adjustments for age, diabetes and established CV disease, pre- and postdialysis PWV and predialysis AMP remained significantly related to CV mortality. When included in the same adjusted model, both predialysis PWV and AMP remained significantly associated with CV survival [hazard ratios for 1 m/s higher PWV and 10% lower AMP were 1.23 (1.07–1.42) and 1.39 (1.02–1.89), respectively].

In the ***second study*** mean age in the sevelamer-treated and control subjects was 54.7 (8.7) and 54.0 (9.3) years, male percentage was 76.9 and 76.9 %, median of dialysis time was 38.2 (35.5) and 23.9 (32.3) months, respectively. By the end of follow-up, PWV decreased by 0.83 (2.27) m/s in sevelamer-treated patients

while it increased by 0.93 (1.88) m/s in those continuing previous therapy (p=0.042). The direction of changes of AI was similar to that of PWV, although between-group comparison did not reach the level of statistical significance (p=0.105). Time-averaged PO4 values decreased significantly during sevelamer treatment, and this change was statistically significant when compared with that in controls (p=0.008). Total cholesterol decreased by 0.36 (0.69) mmol/L in patients treated with sevelamer, and it increased by 0.27 (0.67) mmol/L in controls (p=0.040). Bone turnover at baseline was higher in patients started on sevelamer, but changes in β-crosslaps and osteocalcin levels were not significant and not different between groups during follow-up. There were no significant differences between groups in fetuin-A, matrix GLA protein, osteoprotegerin, and soluble RANKL levels either at baseline or at the end of follow-up.

In multivariate linear regression models baseline PWV was significantly associated with baseline CRP (p=0.008), systolic blood pressure (p=0.011), time-averaged phosphorus levels (p=0.042), and the presence of CV disease (p=0.033) (total r^2=0.625). Change in PWV during follow-up was associated with baseline CRP (p=0.034), sevelamer treatment (p=0.042), diabetes (p=0.004), and baseline heart rate (p=0.016) (total r^2=0.608).

In the ***third study*** the mean age of patients was 62.4 (13.7) years, 61.9 % of them were male and the median of dialysis time was 29.5 (12.2-48.9) months. Mean AI values measured with Arteriograph were significantly lower than those obtained by PulsePen {2.2 (25.6) % vs. 23.0 (12.1)%, p <0.001}. Mean PWV values measured by Arteriograph were also significantly lower compared to those measured by PulsePen {9.9 (2.2) m/s vs. 11.1 (3.1) m/s, p < 0.01}. Comparison of the AI values measured by the two methods showed statistically significant linear

correlation (R = 0.527, p <0.001). There was, however, no significant correlation between the PWV values measured by the two devices(R = 0.174, p = 0.097).

During follow-up, 36 of the 92 patients died (mortality rate 19.5/100 patient-years) of whom 21 died due to CV causes. In separate log-rank tests, only increasing tertiles of PWV_P (measured by PulsePen), but not those of PWV_A (measured by Arteriograph), AI_P (measured by PulsePen) or AI_A (measured by Arteriograph) were related to CV mortality (log-rank p values 0.008, 0.135, 0.431, 0.243, respectively). Results were similar in adjusted Cox-proportional hazard regression where data were considered as continuous variables: only increasing PWV_P, but not PWV_A, AI_P or AI_A were related to CV mortality (HRs associated with 1 m/s increase in PWV 1.29 [1.11–1.51] and 0.84 [0.62–1.14] and with 1% increase in AI 1.01 [0.96–1.05], 0.98 [0.96–1.01], respectively).

Conclusions

1. Among different parameters of arterial stiffness, PWV is consistently related to CV mortality in ESRD patients on HD. Measuring AMP before dialysis seems to add further prognostic information on the risk of CV mortality. Parameters of arterial stiffness that depend more on the timing and amount of wave reflection (AI, CPP) do not seem to be useful to prognose CV mortality in this population.
2. As opposed to AMP, the ability of PWV to prognoses CV mortality is not influenced by the timing of measurement in relation to the dialysis procedure.
3. Treatment with sevelamer is associated with improvement in aortic stiffness in ESRD patients on HD.
4. The effect of Sevelamer on arterial stiffness is not associated with changes in parameters of bone turnover or/and serum levels of inhibitors of vascular calcification. Change in CRP level, as a nontraditional CV risk factor in the ESRD, seems to provide a plausible explanation for the mechanism how sevelamer effects aortic PWV.
5. Compared to the reference PulsePen device, the tested Arteriograph device does not seem to be appropriate to determine parameters of arterial stiffness in ESRD patients on HD.
6. PWV, as measured by the Arteriograph device, can not be used to assess risk of cardiovascular mortality in ESRD patients on HD.

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