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# Impact of Anemia on Aortic Pulse Wave Velocity in Hemodialysis Patients

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**Key Words**
Anemia · Aortic pulse wave velocity · Hemodialysis

**Abstract**
***Background:*** Recent studies indicate an increased mortality of anemic patients with renal failure when near-normal hemoglobin levels are aimed for by treatment with erythropoiesis stimulating agents. Aortic pulse wave velocity (aPWV) is a strong predictor of all-cause and cardiovascular mortality in patients with end-stage renal disease. The relationships between aPWV, hemoglobin levels and erythropoiesis stimulating agent dosage have not been evaluated to date. ***Methods:*** In 75 patients, aPWV was measured by applanation tonometry. Associations of aPWV and a broad range of clinical, laboratory and therapeutic parameters were determined by stepwise linear regression analysis. ***Results:*** aPWV was positively correlated to age ($r = 0.55$, $p < 0.001$), whereas the association with hemoglobin was significant, but negative ($r = -0.31$, $p = 0.01$). Multivariate analysis determined age ($\beta = 0.513$, $p < 0.001$), mean blood pressure ($\beta = 0.255$, $p = 0.01$), the presence of heart failure ($\beta = 0.188$, $p = 0.03$), hemoglobin ($\beta = -0.226$, $p = 0.01$), daily calcium load ($\beta = -0.230$, $p = 0.01$) and the presence of diabetes mellitus ($\beta = 0.179$, $p = 0.04$) to have a significant and independent influence on aPWV. ***Conclusions:*** This study demonstrates that in hemodialysis patients, aPWV is significantly but negatively associated with the serum hemoglobin concentration, even after multiple adjustments for other covariates.



## Introduction

The incidence of cardiovascular events is increased even in patients with early stages of renal disease and excessive mortality and morbidity has been reported after the initiation of renal replacement therapy [1–4].

Disorders of divalent ion metabolism unique to chronic kidney disease (CKD) likely contribute to this process [5–7]. Abnormalities of phosphate and calcium homeostasis are, along with other factors [8–10], associated with large-artery and coronary calcifications [11–14], the presence and extent of which are linked to mortality [11, 15]. Aortic media calcification is a major determinant of arterial stiffness [16], which can be assessed reliably by the noninvasive measurement of aortic pulse wave velocity (aPWV) [17]. aPWV is recognized as a strong and independent predictor for all-cause and cardiovascular mortality in patients with end-stage renal disease (ESRD) undergoing hemodialysis [18–21], as well as in the general population and hypertensive subjects [22, 23].

Anemia is another frequent complication of CKD and also has been associated with morbidity and mortality. Comparable to studies in patients with CKD [24], observational studies in patients on hemodialysis indicate that higher hemoglobin values may decrease the risk of death or hospitalization [25–27] as well as improve quality of life and cognitive function [28, 29]. On the contrary, large interventional trials and a recent meta-analysis [30] found consistent trends towards an increased risk in CKD and ESRD patients when near-normal hemoglobin values

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were aimed for by treating patients with erythropoiesis stimulating agents (ESAs) [31–33].

The mechanisms through which anemia may influence cardiovascular remodeling in ESRD are not completely understood. A strong correlation between aPWV and markers of endothelial damage attributed to anemia has been previously reported [34]. However, to the best of our knowledge, the association between aPWV, hemoglobin levels and ESA dosage in patients on chronic hemodialysis has not been investigated to date. Furthermore, a broad range of other parameters was evaluated for their power to predict aPWV.

## Patients and Methods

*Subjects*

aPWV was measured in 75 subjects treated in 2 dialysis units (56 in the Innsbruck Dialysis Training Center and 19 in the General Public Hospital of St. Josef Braunau). Patients with a history of renal transplantation were excluded because this has been shown to massively affect aortic stiffness [35], as were patients with atrial fibrillation, which creates difficulties in obtaining appropriate and reproducible measurements. Subjects were studied without discontinuation of any medication. Sixty-one patients were regularly receiving ESA therapy. Characteristics of the study population are detailed in table 1. The study was approved by the ethical committee of the Innsbruck Medical University.

*Data Collection*

Laboratory parameters were obtained from computerized clinical documentation systems. To account for variability, mean values were calculated over a 6-month period preceding the measurement for serum phosphate, calcium, parathyroid hormone, Kt/V, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and C-reactive protein (CRP) concentrations. CRP values exceeding 10 mg/dl were excluded as they are considered highly suggestive of an intermittent acute inflammatory process. BMI was calculated as the dry weight divided by the square of body height, with dry weight defined as the mean value of 3 measurements of the postdialytic body weight before the long dialysis interval. In clinical routine, the assessment of the dry weight of each patient is based on clinical parameters and re-evaluated weekly. Daily calcium load imposed by oral phosphate binders was defined as the prescribed dose of calcium carbonate per day at the time of aPWV measurement. Vitamin D (oral calcitriol or alphacalcidol) and sevelamer therapy were coded as binary variables. ESA therapy, i.e. epoetin alpha, epoetin beta and darbepoetin alpha, was documented as dose (IU) per body weight (kg) per week. For this purpose, darbepoetin dosages were adapted to the other formulations using a dose conversion ratio of 200:1. Furthermore, the amount of ESA (IU per kg body weight per week) divided by the achieved hemoglobin level (g/dl) was computed as an indicator of ESA responsiveness (ESA/Hb) [36–38].

Comorbid conditions were identified from the patient records and defined as follows: coronary heart disease = history of myocardial infarction, angina pectoris, coronary artery angioplasty or coronary artery bypass graft; peripheral artery disease = history of Fontaine Stage II, III or IV; congestive heart failure (CHF) = history of hospital admission due to nonpneumopathological dyspnea; cerebrovascular disease = history of

**Table 1.** Patient characteristics

| | |
|---|---|
| *Demographic data* | |
| Number of patients | 75 |
| Gender, male/female | 44/31 |
| Age, years | 64.4 ± 15.8 |
| BMI | 25.3 ± 4.5 |
| Waist/hip ratio | 1.01 ± 0.07 |
| Current smokers | 14 (19) |
| Ever smokers | 34 (45) |
| Pack-years | 0.0 (0–120)* |
| Dialysis vintage, months | 26 (1–200)* |
| Residual diuresis, <0.5/0.5–1/>1 liters/day | 44/14/10 |
| Dialysate calcium, 1.25/1.5/1.75 mmol/l | 40/28/6 |
| Years since 1st diagnosis of CKD | 5.0 (3–50)* |
| *Comorbidities* | |
| Diabetes mellitus | 26 (35) |
| Years since diagnosis of diabetes mellitus | 20.6 ± 11.5 |
| Presence of coronary heart disease | 27 (36) |
| Presence of peripheral artery disease | 26 (35) |
| Presence of cerebrovascular disease | 18 (24) |
| Presence of congestive heart failure | 15 (20) |
| *Laboratory parameters* | |
| Serum calcium, mmol/l | 2.2 ± 0.1 |
| Serum phosphate, mmol/l | 1.7 ± 0.4 |
| Serum parathyroid hormone, pg/ml | 326.1 ± 192.1 |
| Serum total cholesterol, mg/dl | 171 ± 41 |
| Serum LDL cholesterol, mg/dl | 92 ± 35 |
| Serum HDL cholesterol, mg/dl | 45 ± 13 |
| HbA1c, % | 6.7 ± 1.2 |
| Kt/V | 1.4 ± 0.2 |
| Hemoglobin, g/dl | 11.4 ± 1.1 |
| Serum ferritin, ng/ml | 326 ± 299 |
| Albumin, g/dl | 4.0 ± 0.4 |
| Serum CRP, mg/dl | 0.88 (0.1–9.8)* |
| *Therapeutic parameters* | |
| ESA dose, $IU \cdot kg^{-1} \cdot week^{-1}$ | 51.8 (0–413.2)* |
| ESA/Hb, $IU \cdot dl \cdot kg^{-1} \cdot week^{-1} \cdot g^{-1}$ | 4.9 (0–40.8)* |
| Daily phosphate binder calcium load, g/day | 0.0 (0–3.0)* |
| Sevelamer | 29 (39) |
| Antihypertensive therapy | 58 (77) |
| Lipid-lowering therapy | 20 (27) |
| Vitamin D administration | 21 (28) |

Values are n (%), mean ± SD or median (range).

* For all non-normally distributed variables, median and range are given. LDL = Low-density lipoprotein; HDL = high-density lipoprotein; CRP = C-reactive protein.

**Table 2.** Hemodynamic measurements

| | |
|---|---|
| aPWV, m/s | 11.4 ± 3.6 |
| Heart rate, beats/min | 69 ± 9.8 |
| Systolic blood pressure, mm Hg | 142 ± 23 |
| Diastolic blood pressure, mm Hg | 77 ± 12 |
| MBP, mm Hg | 99 ± 14 |
| Pulse pressure, mm Hg | 64 ± 19 |

**Table 3.** Correlation coefficients (Pearson) of aPWV with continuous variables

| | r | p[1] |
|---|---|---|
| Age, years | 0.55 | <0.001 |
| Waist/hip ratio | 0.38 | 0.01 |
| MBP, mm Hg | 0.26 | 0.02 |
| Pulse pressure, mm Hg | 0.55 | <0.001 |
| SBP, mm Hg | 0.46 | <0.001 |
| Hemoglobin, g/dl | –0.31 | 0.01 |
| Daily calcium load, g/day | –0.31* | 0.01 |

* Spearman's rho.
[1] Only significant results are presented.

stroke or transitory ischemic attack; and diabetes mellitus (DM) = history of diabetes type I or II, use of a hypoglycemic agent or insulin.

Data regarding former and current nicotine consumption, residual diuresis, time from the 1st diagnosis of CKD and dialysis vintage, and, when applicable, time since the diagnosis of DM was documented as reported by the patient.

*Hemodynamic Measurements*

All measurements were performed before the dialysis session after a long interval in a calm environment with the patient in the supine position after 5 minutes of supine rest. Brachial systolic pressure (SBP) and diastolic pressure (DBP) were calculated as the mean values of a minimum of 3 measurements taken at least 3 minutes apart on the nonfistula arm using a validated sphygmomanometer (HEM-780-D; Omron, Kyoto, Japan). Mean blood pressure (MBP) was calculated as DBP + [(SBP – DBP)/3] and pulse pressure was calculated as SBP – DBP. aPWV was determined by sequential applanation tonometry at the carotid and femoral arteries using a SphygmoCor device (AtCor Medical, Sydney, NSW, Australia) and a handheld high-fidelity micromanometer (SPC-301; Millar Instruments, Houston, Tex., USA). The foot of the pressure wave was identified by the application of the intersecting tangents method. The total transit distance was defined as the difference of the surface distances between the suprasternal notch and each recording site. Data were processed using specialized software (SphygmoCor CVMS Version 8.0, AtCor Medical).

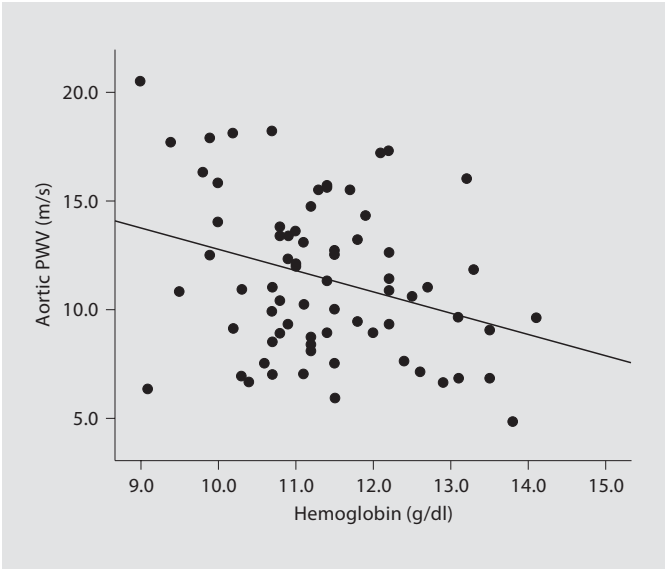


**Fig. 1.** Inverse relationship between aPWV and hemoglobin concentrations.

*Statistical Analyses*

Patient characteristics are presented as absolute frequencies and as mean values ± SD, respectively. Normal distribution of the data was assessed using the Kolmogorov-Smirnov test. To evaluate the associations of aPWV and continuous variables, Pearson's correlation coefficient, and where appropriate, Spearman's correlation coefficients were computed. aPWV was compared between groups of dichotomized variables and nominally scaled variables using nonparametric tests to account for variances in group size (Mann-Whitney U tests and Kruskal-Wallis tests for nominally scaled variables). To identify independent predictors of aPWV, variables that showed a significant relationship to aPWV in bivariate analyses were entered into a stepwise linear regression model. Statistical analysis was performed with SPSS version 16.0 for Windows. The level of significance was set to 0.05.

## Results

The results of the hemodynamic measurements are listed in table 2. aPWV ranged from 4.8 to 20.5 m/s (median 11.0 m/s).

*Bivariate Analyses*

All significant associations between aPWV and the continuous variables are shown in table 3. Of note, aPWV had a strong positive linear association with age, whereas the relationship with hemoglobin was significant but negative (fig. 1). The correlations with all other continu-

**Table 4.** Stepwise linear regression model for aPWV as a dependent variable

| Independent variables | β | p | Sequential adjusted $R^2$ |
|---|---|---|---|
| Age | 0.513 | <0.001 | 0.277 |
| Brachial MBP | 0.255 | 0.01 | 0.414 |
| CHF | 0.188 | 0.03 | 0.463 |
| Hemoglobin | –0.226 | 0.01 | 0.503 |
| Daily calcium load | –0.230 | 0.01 | 0.548 |
| DM | 0.179 | 0.04 | 0.570 |

ous variables (heart rate, dry weight, body height, BMI, years since diagnosis of CKD or DM, hemodialysis vintage, cigarette abuse in pack-years and concentrations of serum calcium, phosphate, parathyroid hormone, total cholesterol, LDL, HDL, ferritin, HbA1c, albumin and CRP, as well as Kt/V) were not significant (data not shown). aPWV, in particular, did not appear to vary across the range of ESA therapy dosage (0–413 IU/kg/week) or ESA/Hb, respectively.

Values of aPWV were significantly higher in patients with DM ($p < 0.001$), presence of CHF ($p = 0.04$), presence of coronary heart disease ($p = 0.04$) and presence of peripheral artery disease ($p < 0.001$). Patients receiving vitamin D therapy showed a strong trend towards a higher aPWV ($p = 0.05$) whereas patients receiving sevelamer hydrochloride had a significantly lower aPWV ($p = 0.02$). Comparisons of aPWV with all other binary and nominally scaled variables, namely gender, current smoker, ever smoker, residual diuresis, dialysate calcium, presence of cerebrovascular disease, antihypertensive therapy, lipid-lowering therapy and vitamin D administration, showed no significant differences.

*Multivariate Analyses*

For multivariate analyses, all parameters with a significant association or difference in mean value in the bivariate analyses were considered. Among brachial pressure measurements, MBP was favored over SBP and pulse pressure, because peripheral MBP provides a substantially equivalent estimate of aortic MBP [39] and MBP was considered the best surrogate of the mean arterial distending pressure. After stepwise linear regression analysis, age, brachial MBP, CHF/DM history, serum hemoglobin concentration and total calcium load remained in the model (table 4), predicting approximately 58% of the variance of aPWV.

## Discussion

Stiffening of the central arteries begins to increase in early renal dysfunction and progresses through all stages of CKD as glomerular filtration deteriorates [40]. Associations between measures of increased central arterial stiffness and comorbid conditions in ESRD populations have previously been reported [20, 21]. This study demonstrates that in hemodialysis patients, aPWV is, even after multiple adjustments for other covariates, independently and negatively associated with the serum hemoglobin concentration.

Patient age was the most important single parameter predicting aPWV in our study. This association has also been described by others in the general population [41–43]. In the presence of each coronary and peripheral arterial disease, aPWV was significantly higher, but neither of these conditions remained significant after multivariate analysis. In addition, aPWV was higher in diabetic patients and to a relatively small extent, DM also contributed significantly to the variance of aPWV in multilinear regression. Advanced glycation end products may be a reason for this influence of the presence of DM on the prediction of aPWV [44]. The development of CHF in ESRD patients may be attributed to numerous factors, but aortic stiffness is likely to play a major role in its pathogenesis through the elevation of SBP and pulse pressure, early return of wave reflections and subsequent left ventricular hypertrophy and altered coronary perfusion [45, 46]. We consistently observed a strong relationship between aPWV and an estimate of advanced CHF, which was defined as a history of hospital admission due to nonpneumopathological dyspnea. Conditions such as acute exacerbations of chronic asthma/chronic obstructive pulmonary disease, pneumonia or acute respiratory distress syndrome were ruled out to be the cause for hospitalization. However, dyspnea could be a possible result of both a weakness in myocardial contraction and/or a preload excess due to volume overload, as we did not differentiate between these pathophysiological pathways. Furthermore, anemia is a well-established predisposing factor for the development of CHF; however, the influence of the hemoglobin concentration on aPWV remained significant even when adjusted for CHF (table 4).

aPWV is considered a strong risk marker and possibly even a risk factor for all-cause and cardiovascular mortality in hemodialysis patients, with higher aPWV values indicating shorter survival [18–21]. Therefore, the negative association of aPWV and hemoglobin values ob-

served in our study (fig. 1) deserves special attention. In several retrospective analyses [25–27], lower hemoglobin levels in patients with CKD were associated with poorer survival. In contrast, 3 prospective randomized controlled trials [31–33] found at least trends towards an increased mortality in CKD as well as ESRD patients when near-normal hemoglobin levels were aimed for with ESA treatment. Several hypotheses have been put forward to explain these somewhat conflicting results. Some authors argued for a direct 'toxic' effect of hemoglobin, while others speculated that high doses of ESAs per se might be dangerous. In the study by Besarab et al. [31], mortality was lower when higher hemoglobin levels were actually achieved regardless of the target level. Nonetheless, total mortality still was higher in the near-normal target value group. These data suggest that ESA hyporesponsiveness might either lead to the administration of excessively high and thus toxic ESA doses, or simply might identify patients with a poor prognosis due to other concomitant risk factors like a chronic inflammatory condition [47]. In our study, higher hemoglobin levels were associated with a lower aPWV, making, at least in this respect, a direct deleterious effect of higher hemoglobin unlikely. We were, however, unable to find an association between aPWV and the administered ESA dose or ESA/Hb as an index of ESA responsiveness.

The dilation and wall hypertrophy of the major arteries commonly observed in dialysis patients have traditionally been proposed to be partly caused by chronic blood flow and volume overload as a consequence of anemia (via a compensatory increase in cardiac output), arteriovenous shunts and overhydration [34, 48]. Recent investigations, however, emphasize the role of shear stress, which, in parallel to whole blood viscosity, is in fact reduced in dialysis patients due to anemia [34, 49, 50]. The impairment of the physiological maintenance of shear stress is reflected by elevated concentrations of endothelial microparticles, which are released from cells upon apoptosis. Furthermore, endothelial microparticle concentrations were strongly and positively correlated to aPWV, suggesting that anemia could play an indirect role in the pathogenesis in the endothelial and arterial dysfunctions in patients with ESRD [34]. The observed impact of anemia on aPWV in the present study may well reflect structural arterial alterations as a consequence of reduced shear stress. However, our study design precludes causative conclusions as, for example, a survivor bias (patients with higher hemoglobin levels and high aPWV might die earlier) might strongly interfere with our results.

Patients treated with the noncalcium phosphate binder sevelamer hydrochloride had significantly lower aPWV values even though a treatment indication bias might have been present (vide infra), supporting previous studies that have demonstrated that the use of sevelamer reduced the progression of coronary and aortic calcification [51, 52] and mortality [53]. However, the serum phosphate concentrations in patients treated exclusively with sevelamer (mean 1.82 mmol/l, SD 0.47), exclusively with calcium carbonate (mean 1.78 mmol/l, SD 0.42), a combination of both (mean 1.70 mmol/l, SD 0.34) and without a phosphate-binding therapy (mean 1.66 mmol/l, SD 0.40) were compared and no significant difference could be found ($p = 0.65$, tested by ANOVA).

Interestingly, daily calcium load had a negative association with aPWV even though mostly positive associations of calcium intake and arterial calcifications in patients undergoing hemodialysis were reported previously. Guerin et al. [16] found that the calcium dose prescribed as a phosphate binder was positively and independently associated with a score of arterial calcifications which was measured by sonography in the common carotid artery, the abdominal aorta, the iliofemoral axis and the lower extremities. Similarly, Goodman et al. [14] reported that patients with coronary artery calcifications had a daily ingested amount of calcium as a phosphate-binding agent nearly twice as high as those without. London et al. [11] observed that higher doses of calcium-based phosphate binders were prescribed in dialysis patients with arterial media and intima calcifications as measured by radiograms of the pelvis and thigh. In our opinion, the negative relationship of calcium load and aPWV in the current study is most likely caused by an indication bias. The decision to treat patients with calcium carbonate or calcium-free phosphate binders was made by the treating physicians based on the suggestions made in the K/DOQI guidelines and, accordingly, the prescription of calcium carbonate was restricted to patients without vascular calcification or soft tissue calcification [54, 55]. Thus, patients with these conditions and likely increased arterial stiffness have zero calcium load values, whereas relatively healthy patients with low aPWV likely have high calcium load values. The apparent association may be explained by this confounding indication.

aPWV values of patients receiving vitamin D therapy, on the contrary, tended to be higher, but as therapy indications, concomitant calcimimetic therapy and measurements of serum concentrations of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin $D_3$ were not included in the analysis, benefical vascular effects of vitamin D supple-

mentation cannot be excluded. Both daily calcium load and vitamin D administration were tested for a possible confounding effect in multivariate analysis, but neither variable showed a significant contribution. This, however, might well be due to the low patient number involved.

As possible pathogenetic links between parathyroid overfunction and anemia have been discussed previously [56, 57], hemoglobin and parathyroid hormone levels were tested for correlations, but did not show a significant relationship.

Chronic inflammation is one of the determinants of vascular pathology in dialysis patients; however, the effect of acute massive elevations of CRP is much less clear. We therefore excluded short-lasting leaps of CRP concentrations above 10 mg/dl from the calculation of the average CRP values over 6 months for each patient. Our patient population, however, had only modestly elevated median CRP values (median 0.88, range 0.1–9.8 mg/dl) and, thus, our ability to detect a significant effect of CRP on aPWV might have been limited.

Antihypertensive therapy modalities were assessed in a subanalysis (data not shown). These parameters involved very small patient numbers and/or showed a strong dependency on blood pressure. Thus, neither variable provided a significant contribution in the linear regression model. The differentiation of antihypertensive drug treatment was therefore not included in our analysis.

## Conclusions

In hemodialysis patients, aPWV is significantly and negatively associated with the serum hemoglobin concentration, even after multiple adjustments for other covariates. Stepwise linear regression determined brachial MBP, presence of CHF, daily calcium load and presence of DM to have a significant influence on aPWV, which was otherwise independent of a broad range of clinical, laboratory and therapeutic parameters. Further studies are needed to elucidate the effects of anemia treatment in ESRD.

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