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Original Investigation

# Aortic Stiffness, Ambulatory Blood Pressure, and Predictors of Response to Antihypertensive Therapy in Hemodialysis

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**Background:** Arterial stiffness is associated with elevated blood pressure (BP), but it is unclear whether it also makes hypertension more resistant to treatment. Among hypertensive dialysis patients, this study investigated whether aortic stiffness determines ambulatory BP and predicts its improvement with therapy.

**Study Design:** Post hoc analysis of the Hypertension in Hemodialysis Patients Treated With Atenolol or Lisinopril (HDPAL) trial.

**Settings & Participants:** 179 hypertensive hemodialysis patients with echocardiographic left ventricular hypertrophy.

**Predictor:** Baseline aortic pulse wave velocity (PWV).

**Outcome:** Baseline and treatment-induced change in 44-hour ambulatory BP at 3, 6, and 12 months.

**Measurements:** Aortic PWV was assessed with an echocardiographic-Doppler technique (ACUSON Cypress, Siemens Medical), and 44-hour interdialytic ambulatory BP monitoring was performed with a Spacelabs 90207 monitor.

**Results:** Mean baseline aortic PWV was 7.6 ± 2.7 (SD) m/s. Overall treatment-induced changes in ambulatory systolic BP (SBP) were −15.6 ± 20.4, −18.9 ± 22.5, and −20.0 ± 19.7 mm Hg at 3, 6, and 12 months. Changes in SBP were no different among tertiles of baseline PWV. Aortic PWV was associated directly with baseline ambulatory SBP and pulse pressure (PP) and inversely with diastolic BP (DBP). After adjustment for several cardiovascular risk factors, each 1-m/s higher PWV was associated with 1.34−mm Hg higher baseline SBP ($\beta = 1.34 \pm 0.46$; $P = 0.004$) and 1.02−mm Hg higher PP ($\beta = 1.02 \pm 0.33$; $P = 0.002$), whereas the association with DBP was no longer significant. Baseline PWV did not predict treatment-induced changes in SBP (Wald test, $P = 0.3$) and DBP (Wald test, $P = 0.7$), but was a predictor of an overall improvement in PP during follow-up (Wald test, $P = 0.03$).

**Limitations:** Observational design; predominantly black patients were studied.

**Conclusions:** Because aortic PWV is not a predictor of treatment-induced change in ambulatory BP among hypertensive dialysis patients, it indicates that among these patients, hypertension can be controlled successfully regardless of aortic stiffness.

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***INDEX WORDS:*** Antihypertensive treatment; ambulatory blood pressure; BP control; pulse wave velocity (PWV); aortic stiffness; arteriosclerosis; hemodialysis (HD); renal replacement therapy (RRT); echocardiographic left ventricular hypertrophy; Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril (HDPAL) trial.

Among people with end-stage renal disease receiving maintenance hemodialysis therapy, hypertension is highly prevalent and difficult to treat.[1] Elevated blood pressure (BP), particularly when recorded outside of the dialysis unit with the use of ambulatory BP monitoring (ABPM), is related directly to cardiovascular morbidity and mortality.[2,3] Although volume control remains a fundamental strategy to control BP,[4] administration of antihypertensive drugs often is required and may confer cardiovascular protection.[5,6]

Aortic pulse wave velocity (PWV) is a marker of long-term structural alterations in the arterial wall reflecting the arteriosclerotic process. The arteriosclerotic process is accelerated in people on dialysis therapy compared to the typical age-mediated arterial stiffening observed in other high-risk groups.[7] Given that arteriosclerosis mediates isolated systolic hypertension, left ventricular hypertrophy, subendocardial hypoperfusion, and downstream heart failure, it is not surprising that aortic PWV is a strong predictor of cardiovascular morbidity and mortality.[8-10] Prior observations from our group have suggested that aortic PWV is an important determinant of ambulatory systolic BP (SBP) and pulse pressure (PP).[11] Because aortic stiffness is difficult to modify, it is possible that

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individuals on dialysis therapy with poor aortic compliance also may experience more-difficult-to-control hypertension. However, this notion has never been examined among people treated by dialysis.

Accordingly, among dialysis patients participating in the Hypertension in Hemodialysis Patients Treated With Atenolol or Lisinopril (HDPAL) trial, the aims of this study were to: (1) confirm whether baseline aortic PWV is a determinant of baseline 44-hour interdialytic ambulatory BP, (2) explore whether PWV is a predictor of response to antihypertensive therapy, and (3) establish whether these effects are independent from other known cardiovascular risk factors. Because PWV is difficult to modify, we reasoned that if PWV was not a predictor of response to measures to reduce BP (including antihypertensive therapy), it would provide evidence that the presence of heightened aortic stiffness in dialysis patients does not preclude the achievement of adequate BP control.

## METHODS

### Study Design

The design of the HDPAL trial has been published in detail.[12] Briefly, 200 adult hemodialysis patients with hypertension confirmed by 44-hour interdialytic ABPM and echocardiographic left ventricular hypertrophy who were receiving standard thrice-weekly hemodialysis therapy for at least 3 months were the participants in this 12-month randomized trial. After a 3-week run-in washout period, eligible patients were randomly assigned in a 1:1 ratio to receive open-label either atenolol, 25 mg, or lisinopril, 10 mg, both administered 3 times a week after dialysis. Monthly monitored home BP was targeted to <140/90 mm Hg by dose titration of the randomly assigned drug, add-on administration of other antihypertensive drugs, probing dry weight, reducing dialysate sodium concentration, and encouraging adherence to dialysis treatment. In particular, the initial drug doses were doubled every 2 to 4 weeks up to a maximum dose of 100 mg 3 times weekly for atenolol and 40 mg 3 times weekly for lisinopril, respectively. In case home BP remained uncontrolled, either felodipine or amlodipine, 10 mg, once daily was added, followed by other antihypertensive drugs.

Informed written consent was obtained from each patient, and the protocol was approved by the Institutional Review Board of Indiana University and the Research and Development Committee of the Roudebush VA Medical Center, Indianapolis, IN. The HDPAL trial was registered at www.ClinicalTrials.gov (study number: NCT00582114).

### Measurements

#### *Aortic PWV*

Aortic PWV measurement was performed through direct visualization of the descending aorta with the use of an echocardiographic-Doppler technique (ACUSON Cypress; Siemens Medical).[13] Flow pulse was recorded by continuous Doppler from the root of the left subclavian artery and just proximal to the bifurcation of the abdominal aorta with a simultaneous electrocardiogram recording. Length of the descending aorta was estimated by measuring the body surface distance from the suprasternal notch to the recording site of aortic signal (near the umbilicus). Time elapsed from the peak of the R wave to the foot of the systolic impulse was recorded over 6 beats. The length of the descending aorta divided by the difference between transit times was calculated to yield aortic PWV.[13]

#### *Ambulatory BP Monitoring*

ABPM was performed after the midweek dialysis session for 44 hours during the entire interdialytic period. A cuff of appropriate size was fitted to the contralateral arm from that currently used for dialysis access and ambulatory BPs were recorded every 20 minutes during the daytime period (6:00 AM to 10:00 PM) and every 30 minutes during the night-time period (10:00 PM to 6:00 AM) with a 90207 monitor (Spacelabs Medical). Measurements were used in the analysis only if >80% of recordings were valid with no more than 2 nonconsecutive day hours (6:00 AM to 10:00 PM) with fewer than 2 valid measurements and no more than 1 night hour (10:00 PM to 6:00 AM) without valid recording, following standard recommendations for ABPM.[14] All patients were instructed to maintain their usual daily activities during the recording period. Ambulatory BP was measured at the baseline evaluation and repeated at 3, 6, and 12 months after drug assignment.

### Outcome and Predictor Variables

Outcome variables included mean 44-hour interdialytic ambulatory SBP, diastolic BP (DBP), and PP at baseline and at 3, 6, and 12 months of follow-up. The primary predictor variables were baseline aortic PWV, visits, and their interaction terms, as explained in the next section.

### Statistical Analysis

Continuous variables were presented as mean ± standard deviation, and categorical variables, as absolute frequency and percentage. In order to evaluate differences in baseline characteristics in ambulatory BP levels, the study population was divided into tertiles according to baseline aortic PWV. Comparison of demographic, clinical, and hemodynamic parameters between PWV subgroups was performed with regression analysis for continuous variables and $\chi^2$ test for categorical variables.

We used a linear mixed model with fixed and random effects. Maximal likelihood estimates were used to estimate marginal mean values. The outcome variable was mean 44-hour ambulatory SBP. To investigate the association of baseline aortic stiffness with baseline and treatment-induced changes in 44-hour interdialytic ambulatory BP at 3, 6, and 12 months, we used visits (at 0, 3, 6, and 12 months) as indicator variables. The independent fixed predictors were visit (as indicator variable), PWV (as continuous variable), and the interaction of the 2 terms. The random intercept component was the subject, and random slopes, the visits. Similar models were fitted for the outcomes of mean ambulatory DBP and PP.

To evaluate the effect of PWV on ambulatory BP, we first fitted a model without PWV. This model had as an explanatory variable only visits at 0, 3, 6, and 12 months. We then added PWV to this model and tested the 2 nested models using a likelihood ratio test. Next we added the interaction term of PWV × visit to the model. To evaluate the independent contribution of PWV × visit, the nested models were evaluated again using the likelihood ratio test.

Subsequently, adjustments for the following parameters were made: age, sex, race (black or nonblack), smoking status, presence of diabetes, dialysis vintage (natural log transformed to approximate a normal distribution), history of previous cardiovascular disease (defined as stroke, myocardial infarction, coronary revascularization, and hospitalized congestive cardiac failure), and treatment arm (atenolol or lisinopril).

Statistical analysis was performed with Stata, version 11.2 (StataCorp LP). A 2-sided $P < 0.05$ was considered statistically significant.

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