Prognostic Value of Blood Pressure Responsiveness in Hemodialysis for Cardiovascular Mortality, Development of A New Predictive Equation

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Introduction. Cardiovascular disease is considered as the main cause of mortality and morbidity in HD-patients and AS is a fundamental cause. This study was conducted to investigate whether intradialytic BP changes can use as a surrogate clinical marker.
Methods. Fifty-one patients on maintenance hemodialysis, for at least 12 hours per week, were included in a prospective cohort study. Intradialytic BP was measured using validated automated device. PWV was performed to assess Augmentation Index (AIx) as marker of arterial stiffness. All measurements were repeated in alive individuals after 5 years of follow-up. Patients with 5% reduction of intradialytic BP were considered as HD-responsive and Several statistical analyses were employed based on responsiveness to HD.
Results. After 5-year follow-up the findings demonstrated BP response to HD was an important and independent determinant of mortality ($P < .05$). Augmentation index (AIx) ($P < .05$), heart rate ($P < .05$), and calcium phosphate product ($P < .05$) as well as log PTH ($P < .05$) were significantly different between two responsive and non-responsive to HD. Pearson's Correlation studies revealed a significant relationship between the BP response to HD and heart rate (r = 0.4, $P < .05$), LVEF (r = -0.4, $P < .05$) and PTH (r = -0.3, $P < .05$). BP response to HD and log-PTH remained significant even after age and gender adjustment ($P < .05$).
Conclusion. BP-response to HD can use as a clinical and surrogate marker of AS which is significantly associated with mortality and LVEF. Arterial stiffness and intradialytic BP can predict the changes in Ejection Fraction (EF).

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Original Paper

INTRODUCTION

Cardiovascular disease is considered as the main cause of mortality and morbidity in ESRD patients on hemodialysis. Although many traditional risk factors are related to cardiovascular disease (CVD) such as diabetes, hypertension, smoking and hypercholesterolemia, recent studied demonstrated the effect of some arterial related factors such as

Intima media thickness of carotid arteries and arterial stiffening (AS).[1] In patients with ESRD specific factors are thought to contribute to arterial stiffness such as uremia, inflammation and Ca x P abnormalities.[2,3]

It seems that AS is a fundamental cause in the cardiovascular and renal adverse outcomes in chronic kidney disease (CKD) and HD patients.[2,3] In ESRD patients AS independently plays a role in mortality prediction.[4,5] However, since ESRD patients have an alternating hemodynamic status, there is a significant limitation in the repeated measurement of AS indices such as pulse wave velocity (PWV). Moreover, expensive devices as well as the lack of experienced staff may seem as a deterrent in measuring these indices in dialysis centers. Therefore, an accessible, affordable, easy and clinical based marker is really essential to be as a surrogate marker of cardiovascular function. Given this view, our research group suggested that intradialytic blood pressure (BP) changes may be considered as a potential marker of cardiovascular mortality. Despite the direct and linear association of hypertension with cardiovascular mortality in CKD patients, BP in ESRD patients seems to have a reverse relationship in peri dialytic periods.[6] In other words, there is a paradoxical association in a way that displays a U-shape pattern.[7,8] Therefore, severe intradialytic hypotension can be harmful and associated with poor outcome while fixed or increased BP during HD may show arterial stiffness due to lack of vascular elasticity and endothelial dysfunction.[8] All in all, a different approach is needed to evaluate BP in HD-patients. A few years ago, our cross-sectional study demonstrated that patients with hemodialysis unresponsive BP (which means Mean Arterial Pressure decline less than 5% during HD) are more likely to have arterial stiffening and as a result the association of PWV and BP reduction during dialysis could partially explain the paradoxical association of BP and mortality in this population.[4,9] Moreover, a cohort study also stresses on the role of endothelial cell function on the intradialytic hypertension which leads to adverse outcome.[10] However, intradialytic BP[11] as well as BP response to dialysis[12-14] is still a less-recognized and confusing issue in clinical practice. Thus, as Devanport stated: "although BP control is a vital part in the management of the hemodialysis patients, more study is required to determine which blood pressure measurements should be used for the setting of future clinical target".[15]

In this longitudinal study, the association of "BP response to hemodialysis" with AS, echocardiographic findings and patients' outcome have been evaluated after five years of follow-up.

MATERIALS AND METHODS

Participants

In this longitudinal study from 60 patients who were on a maintenance HD in in a referral hospital, fifty-one individuals were enrolled in this 5-year follow up study. These patients were all more than 18 years of age and were on HD for more than 12 months. All patients received HD a 4h / session, 3 times /week. Patients with symptomatic cardiovascular disease, AV fistula on both arms, acute deteriorating states and any recent major trauma or patients who refused measurements were excluded. No change was administered in their current medications.

Study Design

All patients were on maintenance HD for at least 12 months and were assumed as good volume controlled. Dialysis protocol with a mean spKT/V = 1.4 /session, using bicarbonate dialysate, dialysate flow rate = 500 cc /min was applied by Fresenius B 4008 machine. BP was measured after a minimum of five minutes rest in the sitting position using a validated automated device (Omron-HBP1300). An average of three sitting BP readings taken pre- and post-HD for three consecutive HD sessions during 1 week was used to make this determination.

Patients whose mean arterial pressure (MAP) decreased by more than 5% during HD were defined as HD responsive.[4,16] The blood samples were collected before the mid-week HD session and the PVW measurements were done 30 minutes after mid-week session.

Pulse wave analysis was performed using the SphygmoCor (Sydney, Atcor Medical®,2005) to assess Augmentation Index (AIx) as a marker of AS. Two transducers

They were placed, one over the common carotid artery, and one over the femoral artery. The software automatically determined the transit time between the carotid and the femoral pulse

waves using the second derivative algorithm. The direct distance was assessed by measurement of the superficial distance between the two probes. Each measurement of PWV (m/s) was expressed as the mean of 10 consecutive cardiac cycles. Then all these hemodynamic measures were done in alive individuals after 5 years of follow-up. Similarly, Echocardiography was done at the beginning and repeated at the end of the study by Eko 7 Cardiovascular Ultrasound System (Samsung Medison©). A single observer precisely checked all measurements.

Statistical Analysis

All analyses were performed using SPSS 24.0 for Windows (SPSS Inc., Chicago, IL, USA). A two-sided $P < .05$ was considered statistically Significant.

The primary outcome was mortality, while final AS and final LVEF were assigned as the secondary outcomes. Patients with 5% reduction of MAP during dialysis were considered as HD-responsive otherwise they were called HD-non responsive.[5] Several statistical analyses were employed including t-test, chi-square, spearman correlation, and multiple regression study. The distribution of the variables was examined by the Kolmogrov-Smearnov method. Moreover, an artificial neural network model was applied with age and BP response to HD as the input, mortality as the output and 4 hidden layers, while 74 and 26% of data were randomly selected for the training and test sets respectively. Hidden layer activation function was hyperbolic tangent and the output layer activation function was softmax.

Table 1. The Basic Characteristics and Initial Evaluation of the Patients

Variable	Mean ± SD
Age, y	51.08 ± 17.10
Hb, mg/dL	11.20 ± 1.72
TG, mg/dL	141.03 ± 89.48
Cholesterol, mg/dL	138.00 ± 29.56
Albumin, g/dL	3.91 ± 0.36
PTH, pg/mL	314.62 ± 322.26
Ca, mg/dL	8.95 ± 1.12
P, mg/dL	5.73 ± 1.58
K, mmol/L	5.19 ± 0.61
Ca*P Product, mg/dL	51.67 ± 16.79
Pre-dx SBP, mmHg	126.86 ± 16.76
Post-dx SBP, mmHg	115.49 ± 13.54
KT/V	66.15 ± 8.53
UF, mL/h/Kg	1.32 ± 0.30
Ejection Fraction (%)	56.19 ± 11.20
LVDs, cm	3.68 ± 0.85
LVDd, cm	5.36 ± 0.84
IVS, cm	1.15 ± 0.18
LAD, mm	3.07 ± 0.49
Aortic Root Dimention, cm	4.05 ± 0.64
HR	79.16 ± 21.44
ΔTp	17.56 ± 4.47
ED (%)	36.22 ± 6.04
Augmentation Pressure, mmHg	8.55 ± 7.65
AIx (%)	18.22 ± 15.96
Adj. AIx (%)	22.25 ± 11.66
SEVR	154.63 ± 44.28
ESP	106.53 ± 24.82

Abbreviations: Hb, hemoglobin; TG, triglyceride; PTH, parathyroid hormone; UF, ultrafiltration rate; Pre-dx SBP, pre-dialysis systolic blood pressure; Post-dx SBP, post-dialysis systolic blood pressure; HR, heart rate; AIx, augmentation index; ED, ejection duration; LVDs, left ventricular diameter in systole; LVDd, left ventricular diameter in diastole; IVSd, interventricular septal thickness; LAD, left atrial diameter; SEVR, subendocardial viability ratio; ΔTp, round tip travel time of the reflecting pressure wave.

RESULTS

The demographic, biochemical, clinical and echocardiographic findings of HD patients are presented in Table 1. Mean age was 51.1 (± 17.1) years old with 47.1% being female. The main causes of kidney dysfunction in these patients were hypertension (31.4%), diabetes mellitus (29%), glomerulonephritis (7.8%). During the 5-year follow-up 26 individuals (51%) died, 3 (5.9%) patients underwent kidney transplantation, 17 (33%) remained alive on HD and 5 (9.8%) migrated to other cities. The comparison between the dead and alive individuals (Table 2) revealed that the dead group had an older age and greater left ventricular systolic and diastolic diameter. In addition, dead patients had a lower level of serum cholesterol and albumin. Importantly, there was a significant difference in terms of BP responsiveness between dead and alive groups. ($P < 0.05$)

After the patients being categorized based on their baseline BP-responsiveness to dialysis, the two groups of responsive and non-responsive were analyzed. Consequently, augmentation index (AIx) ($P < 0.05$), Heart rate ($p < 0.05$) and Calcium Phosphate product ($p < 0.05$) and log PTH (0.04) were significantly different between two groups. (Table 3).

The patients who were alive after 5 years of follow-up underwent reassessment. The following table shows the paired comparison for the target

Table 2. Comparison the Baseline Demographic and Clinical Variables Between the Dead and Alive Individuals

Variable	Alive (Mean ± SD)	Dead (Mean ± SD)	*P*
Gender			
Male (%)	21.7	78.3	0.01*
Female (%)	60.0	40.0	
Age, y	40.65 (12.00)	59.85 (15.67)	< .001
Hb, mg/dL	11.50 (1.95)	10.99 (1.74)	> .05
TG, mg/dL	167.82 (109.38)	121.48 (61.25)	> .05
Cholesterol, mg/dL	147.82 (25.04)	130.31 (26.13)	< .05
Albumin1, g/dL	4.05 (0.17)	3.81 (0.41)	< .05
Log PTH	2.30 (0.45)	2.31 (0.50)	> .05
Ca, mg/dL	8.66 (1.38)	9.13 (1.05)	> .05
P, mg/dL	5.48 (1.81)	5.86 (1.36)	> .05
K, mmol/L	5.16 (0.49)	5.15 (0.61)	> .05
Ca*P Product, mg^2/dL^2	48.58 (20.15)	53.54 (14.31)	> .05
KT/V	69.24 (8.13)	64.13 (8.22)	> .05
UF, mL/h/Kg	1.45 (0.29)	1.24 (0.27)	< .05
Pre-dx SBP, mmHg	121.47 (18.27)	126.92 (16.25)	> .05
Post-dx SBP, mmHg	112.35 (14.37)	114.81 (19.38)	> .05
HD-BP response, mmHg	9.12 (8.88)	13.11 (8.51)	< .05
BP change (%)	7.06 (6.30)	9.25 (5.88)	> .05
HR	78.70 (14.50)	79.38 (24.69)	> .05
ED	297.50 (45.82)	280.50 (41.82)	> .05
ED (%)	38.40 (4.80)	35.75 (7.01)	> .05
Augmentation Pressure, mmHg	9.50 (8.58)	7.44 (6.63)	> .05
AIx (%)	23.10 (14.69)	15.69 (14.28)	> .05
Adj. AIx (%)	24.90 (10.72)	21.23 (11.02)	> .05
ΔTp	16.86 (3.65)	18.26 (4.99)	> .05
SEVR	142.20 (26.53)	157.94 (56.97)	> .05
Ejection Fraction	59.94 (8.49)	53.84 (0.13)	> .05
LVDs	3.31 (0.74)	4.0 (0.90)	< .05
LVDd	4.94 (0.65)	5.68 (0.92)	< .01
IVS	1.08 (0.22)	1.18 (0.17)	> .05
LAD	2.91 (0.47)	3.16 (0.47)	> .05
Aortic Root	4.09 (0.42)	4.04 (0.75)	> .05

Abbreviations: Hb, hemoglobin; TG, triglyceride; PTH, parathyroid hormone; UF, ultrafiltration rate; Pre-dx SBP, pre-dialysis systolic blood pressure; Post-dx SBP, post-dialysis systolic blood pressure, HR, heart rate; AIx, augmentation index, Tr, tricuspid regurgitation, LVDs, end-systolic left ventricular dimension; LVDd, end-diastolic left ventricular dimension; IVSd, interventricular septal thickness; LAD, left atrial diameter; SEVR, subendocardial viability ratio; ΔTp, round tip travel time of the reflecting pressure wave.

variables. These findings demonstrated that BP response to HD and LVEF decreased while aortic root diameter and diastolic left ventricular diameter increased after 5 years of follow-up (Table 4).

Pearson's Correlation studies revealed a significant relationship between the HD-BP response and heart rate ($r = 0.4$, $P < 0.05$), LVEF ($r = -0.4$, $P < 0.05$) and PTH ($r = -0.3$, $P < 0.05$). The BP response to HD was inversely associated to Logarithm (Log) of PTH and Aortic Augmentation as shown in the Figure 1 and 2.

Since gender could play a confounding role in mortality, categorization strategy was examined i.e., males and females were analyzed separately. As a result, the dead patients in female group had a diminished BP response to HD ($P < 0.05$), compared to their male counterparts. ($P < 0.05$).

Importantly, modeling determinants of arterial stiffness demonstrated that after age-adjustment, four factors including gender, LVEF, Ca*P and HD-duration turned out to be significant and independent determinants of arterial stiffness (as defined by AIx) in this group ($P < 0.05$, $R^2 = 81\%$).

Follow-up arterial evaluation showed that three basal characteristics including BP response to HD, Ca*P product and log-PTH significantly predicted future AIx (R^2 for model = 69%, $P < 0.05$) as shown in Table 5.

Table 3. Comparison the Demographic and Clinical Variables in Two Groups Based on BP Response to Dialysis

Variable	Non-responsive (Mean ± SD)	Responsive (Mean ± SD)	*P*
Gender			
Male (%)	44	56	> .05
Female (%)	54.5	45.5	
Age, y	49.48 (16.08)	51.04 (18.36)	> .05
Hb, mg/dL	11.30 (1.65)	11.18 (1.85)	> .05
TG, mg/dL	118.17 (64.68)	167.87 (107.03)	> .05
Cholesterol, mg/dL	132.87 (29.61)	139.87 (28.33)	> .05
Albumin, g/dL	3.90 (0.36)	3.90 (0.39)	> .05
Log PTH	2.40 (0.38)	2.14 (0.46)	< .05
Ca*P Product, mg^2/dL^2	46.81 (14.68)	56.24 (18.72)	< .05
KT/V	66.73 (6.55)	65.36 (10.34)	> .05
UF, mL/h/Kg	1.32 (0.25)	1.32 (0.34)	> .05
Pre-dx SBP, mmHg	125.22 (14.34)	129.58 (19.86)	> .05
Post-dx SBP, mmHg	120.43 (11.96)	111.67 (14.70)	< .05
HR	69.75 (13.79)	84.65 (23.54)	< .05
ED (%)	34.58 (5.66)	37.41 (6.35)	> .05
Augmentation Pressure, mmHg	11.17 (6.46)	7.06 (8.46)	> .05
AIx (%)	25.17 (12.58)	13.76 (16.54)	< .05
Adj. AIx (%)	25.45 (11.64)	20.07 (12.35)	> .05
ΔTp	15.36 (2.96)	18.83 (4.72)	< .05
ESP	120.67 (25.27)	96.59 (21.47)	< .05
SEVR	168.75 (45.32)	143.82 (43.79)	> .05
Ejection Duration, s	53.50 (13.81)	58.08 (9.09)	> .05
LVDs, cm	3.78 (0.99)	3.57 (0.78)	> .05
LVDd, cm	5.53 (0.84)	5.20 (0.88)	> .05
IVSd, cm	1.15 (0.19)	1.17 (0.19)	> .05
LAD, mm	3.23 (0.51)	2.98 (0.48)	> .05
Aortic root dimensions, cm	4.35 (0.60)	4.00 (0.50)	> .05

Abbreviations: Hb, hemoglobin; TG, triglyceride; PTH, parathyroid hormone; UF, ultrafiltration rate; Pre-dx SBP, pre-dialysis systolic blood pressure; Post-dx SBP, post-dialysis systolic blood pressure; HR, heart rate; AIx, augmentation index; Tr, tricuspid regurgitation; LVDs, end-systolic left ventricular dimension; LVDd, end-diastolic left ventricular dimension; IVSd, interventricular septal thickness; LAD, left atrial diameter.

BP response to HD and log-PTH remained significant even after age and gender adjustment ($P < 0.05$). According to these findings, this study proposed the following equation as predictive score for AS in ESRD patients.

AIx = 56.62-0.60 (BP response to HD) +0.43 (Ca*P) -2.95 (logarithm of PTH)

Interestingly, the follow-up LVEF could be predicted (R^2 = 89.6%; residual men = 0.018, residual DS = 0.054) by BP response to HD, AS (ΔTp) and EF at the beginning of the study, as shown in Figure 3.

Furthermore, there was a non-linear association between LVEF and HD-responsiveness. In other words, intradialytic BP decline between 5 to 10% was associated with an improvement in LVEF, while decreasing BP greater than 10% during HD showed progressive decrease in LVEF. Therefore, the optimal range for BP changes in response to HD was 5 to 10% (Figure 4).

The applied artificial neural network (ANN) reached to 91.4% area under the curve with 2 inputs (age and BP changes in HD). The area under the curve increased to 98.5% with entering other factors. Finally, the normalized importance indices introduced age, aortic augmentation, LVEF, gender and BP response to HD as the most important determinants of mortality among HD patients (Figure 4).

DISCUSSION

In order to explore the interactive effect of BP-response to HD, AS and subsequent CVD we conducted this prospective cohort study. After 5-year follow-up the findings of this study demonstrated BP response to HD was an important and independent determinant of mortality ($P < 0.05$) and also associated with arterial stiffness, calcium

Table 4. Comparison the Clinical Variables at the Beginning of Admission and Five Years Later in Living Patients

Variables	2014	2019	*P*
Hb, mg/dL	11.50 (1.95)	11.49 (2.16)	> .05
TG, mg/dL	167.82 (109.38)	135.38 (109.38)	< .05
Cholesterol, mg/dL	147.82 (25.04)	148.41 (31.64)	> .05
Albumin, g/dL	4.05 (0.17)	4.26 (0.53)	> .05
PTH	326.62 (339.35)	254.31 (223.22)	> .05
Ca*P Product, mg^2/dL^2	48.58 (20.15)	37.63 (9.52)	< .05
Pre-dx SBP, mmHg	121.47 (18.27)	121.18 (28.04)	> .05
Post-dx SBP, mmHg	112.35 (14.37)	120.88 (34.88)	> .05
HD-BP response (%)	7.06 (6.03)	0.00 (0.19)	< .001
HR	78.70 (14.50)	79.00 (17.70)	> .05
ED (%)	38.40 (4.77)	37.40 (6.33)	> .05
Augmentation Pressure, mmHg	9.50 (8.58)	12.40 (6.19)	> .05
AIx (%)	23.10 (14.69)	29.10 (0.23)	> .05
Adj. AIx (%)	24.90 (10.72)	28.70 (13.63)	> .05
ΔTp	16.68 (3.65)	17.47 (4.70)	> .05
ESP	104.10 (30.19)	103.60 (33.03)	> .05
SEVR	142.20 (26.53)	143.00 (43.01)	> .05
EF (%)	59.94 (8.49)	54.69 (5.13)	< .001
LVDs, cm	3.31 (0.74)	3.05 (0.64)	> .05
LVDd, cm	4.94 (0.65)	4.41 (0.71)	< .05
Aortic Root Dimensions, cm	3.04 (0.71)	4.09 (0.42)	< .001

Abbreviations: Hb, hemoglobin; TG, triglyceride; PTH, parathyroid hormone; UF, ultrafiltration rate; Pre-dx SBP, pre-dialysis systolic blood pressure; Post-dx SBP, post-dialysis systolic blood pressure; HR, heart rate; AIx, augmentation index; LVDs, end-systolic left ventricular dimension; LVDd, end-diastolic left ventricular dimension; IVSd, interventricular septal thickness; LAD, left atrial diameter; SEVR, subendocardial viability ratio; ΔTp, round tip travel time of the reflecting pressure wave.

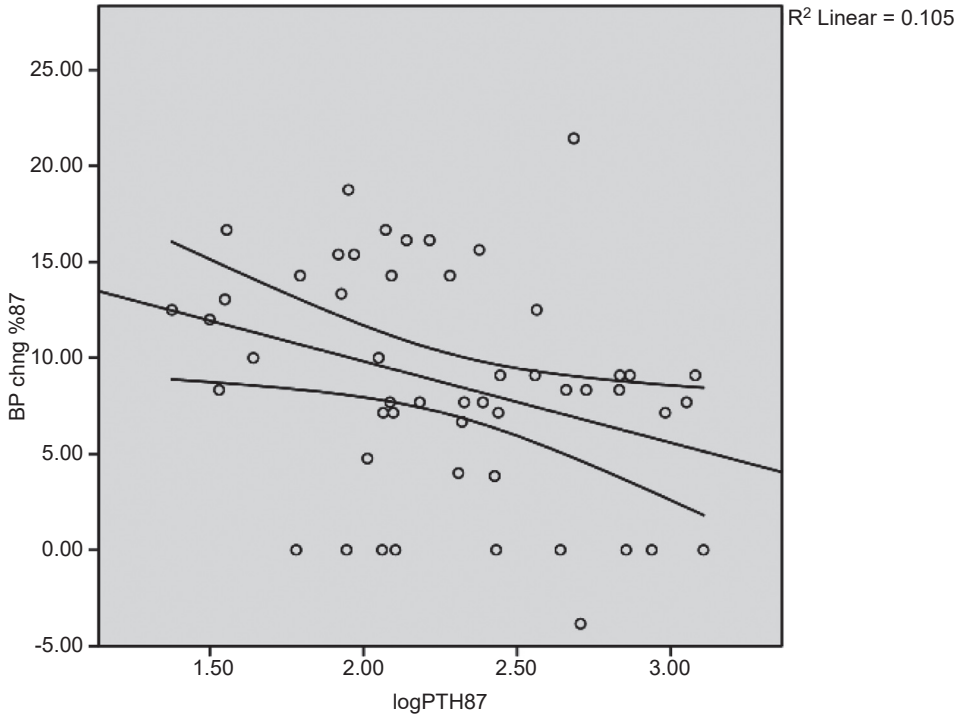

Figure 1. Relationship Between the HD-BP Response and LogPTH87

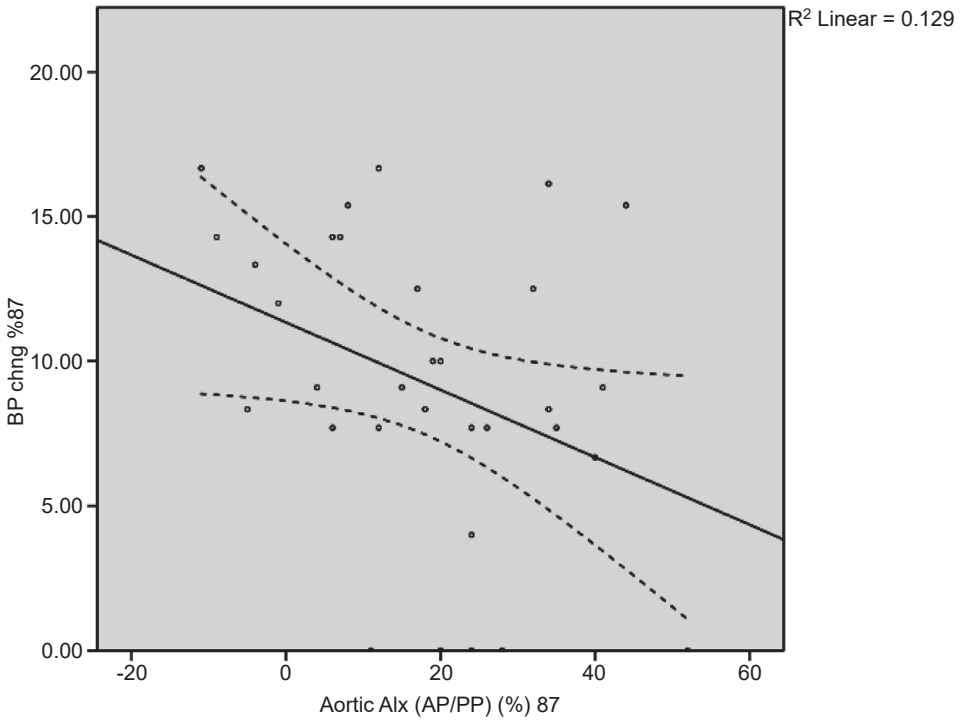

Figure 2. Relationship Between the HD-BP Response and Aortic Augmentation

Table 5. The Relationship Between Variables and ALX (Arterial Stiffness) Based on a Multiple Regression Model

Factor	B	β	t	*P*
Augmentation Index at Entry				
Age	-0.30	-0.43	-2.23	> .05
Gender	14.31	0.58	3.07	< .05
Ejection Fraction	-32.85	-0.45	-2.44	< .05
Ca*P Product	0.51	0.73	3.56	< .05
Hemodialysis Duration	0.86	0.52	2.39	< .05
Augmentation Index After Follow-up				
Ejection Fraction	70.34	0.60	1.28	> .05
Left Ventricular Diameter	-0.84	0.59	1.28	> .05
Blood Pressure Change (%)	-1.38	-0.80	-3.33	< .05
Ca*P Product	0.28	0.52	2.43	< .05
Log PTH	22.45	0.89	3.92	< .05

metabolism and left ventricular Function. This is consistent with previous study such as J Park *et al* who in a retrospective cohort revealed that slight intradialytic BP decline was associated with better survival, while increasing, as well as significant reduction in BP were associated with increased mortality.[18]

The increased risk of CVD with ESRD cannot be explained only by traditional risk factors and other non-traditional vascular-related risk factors such as AS should be considered.[6] AS measurement is a well-accepted predictor of CV mortality in HD-patient and using PWV from carotid to femoral artery is considered as a gold standard measurement of AS.[6] Thismeasurement does not only reflect the overall atherosclerotic burden of the artery, but has also been used to predict the CVD mortality in healthy people. It is evident that AS can increase systolic BP and Pulse Pressure. This incremental effect leads to the high work load of LV and subsequent LV hypertrophy as well as subendocardial ischemia due to reduced coronary perfusion.[8]

Therefore, these pathophysiological mechanisms may cause various cardiovascular events. However, an alternating hemodynamic status in HD patients

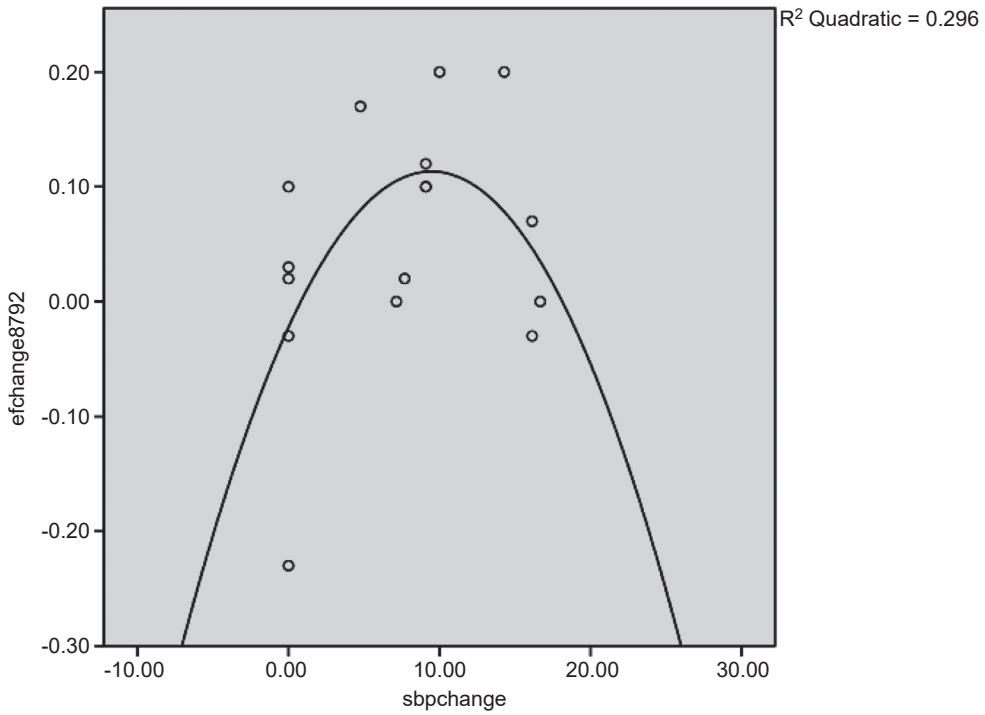

Figure 3. Relationship Between EF and the HD-BP Response

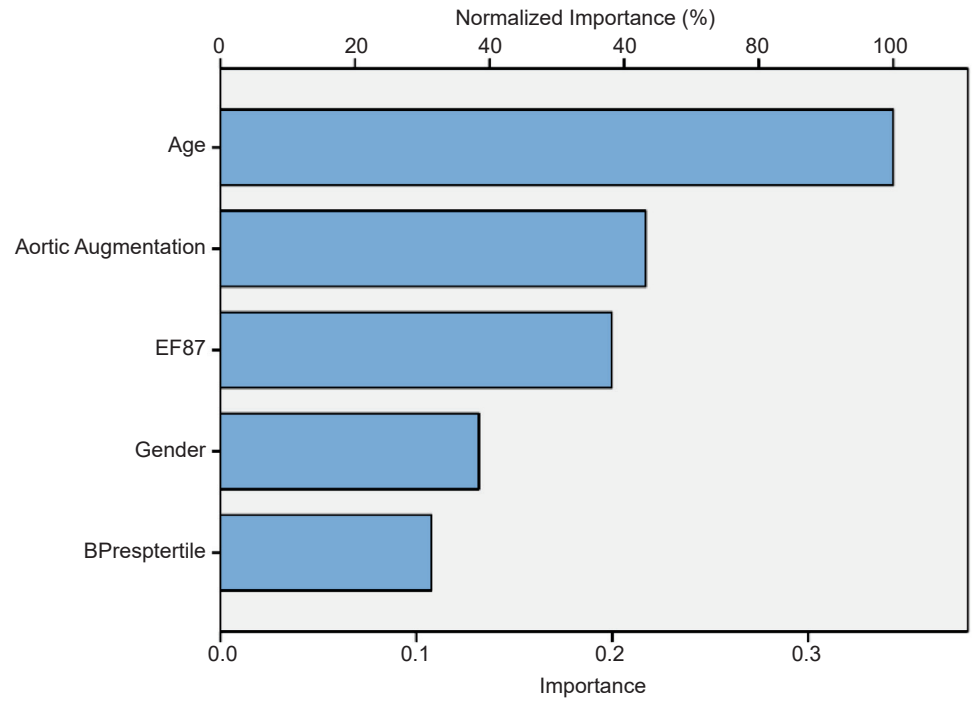

Figure 4. The Normalized Importance of the Mortality Determinant Factors in HD Patients

leads to, a significant limitation in the repeated measurement of AS indices such as pulse wave velocity (PWV).

In addition, the expensive measurement devices and expert operators might not be available in every dialysis centers. Therefore, an accessible, affordable, easy and clinical based marker is really essential to be as a surrogate marker of cardiovascular function such as BP response to HD.[5] Accumulating evidence suggest that BP decline during HD is influenced

by several factors including volume depletion, overload, ultrafiltration rate, serum osmolality, immunologic response to dialysis membrane and dialysate, as well as antihypertensive drugs and erythropoietin.[2,5] Furthermore, some hormonal mechanisms have been described for BP changes during HD,[13] while arterial stiffness plays an axial role in being responsive in HD.[5,11] While arterial stiffness is an independent predictor of mortality, the BP response to HD could be used as its surrogate marker of cardiovascular function and mortality. However, it seems that this marker is more prominent in medium risk groups compared to high-risk individuals with very non-compliant arteries (such as females vs. males or younger individuals vs. elderly).[5]

Our novel approach to the issue by artificial neural network revealed that the most important prognostic factor in mortality is BP response to HD as a new clinical marker. Since BP response to HD and log-PTH remained significant even after age and gender adjustment a new equation was proposed to predict AS. It is clear that an impaired calcium phosphate homeostasis means increased release of serum phosphate and calcium from bone, by FGF23 deficiency and hyperparathyroidism, which is responsible for decreased bone mineral density and subsequently induced vascular calcification in CKD and ESRD [20] and it is a sufficient justification for the result of this study. As a result, by using BP response to HD and adding a determined ratio of ca*p and PTH the AIx as a marker of AS can be predicted.

This study also revealed that BP response to HD and arterial stiffness can predict the future LVEF in a way that 5 to 10% reduction in BP during HD seems to be the optimal level.

The intradialytic hypotension can cause subendocardial ischemia as well as inducing significant arrythmia.[23] Therefore, LV remodeling as long-term consequence of intradialytic hypotension is predictable.[24]

J Park *et al* published a large retrospective cohort and demonstrated a significant relationship between BP response to HD and mortality.[18] Interestingly, A U-shape association was observed between the BP changes to HD and mortality, even after several stratification for the level of pre-HD BP, UF and follow-up period or after adjustment for malnutrition and time on dialysis. However, their study was criticized by its retrospective nature and systematic differences (including age, ethnicity, mortality, gender, dialysis, comorbidities, etc) between the groups that makes ambitions for any conclusion about the net and independent effects on mortality.

Although this study population does not represent the HD population, it introduces a new clinical marker that must be validated in the future studies among diverse populations. Also, a multivariate model could be presented to take all influential factors on BP response to HD into account while it is used in clinical settings.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The present study was approved by Chronic Kidney Research Center and registered in Clinicaltrial.gov with the identifier code NCT04933006. Moreover, an informed consent was taken from every participant before the enrollment.

CONFLICT OF INTEREST

None declared.

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CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The dataset gathered during the present study are available from the corresponding author on reasonable request. However, the research center should give the permission beforehand.

AUTHORS CONTRIBUTIONS

All authors contributed to the study conception

and design. Material preparation, data collection and analysis were performed by [Sara Keshtkari], [Bahareh hajibaratali],[Mostafa Shahrezaei], [Mohammad Parsa Mahjoob]. The first draft of the manuscript was written by [Sara Keshtkari]. [Nooshin dalili] and [Sadra Ashrafi] revised the manuscript carefully. [Ali Reza Khoshdel] supervised the whole project. Finally, All authors read and approved the final manuscript.

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