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ORIGINAL ARTICLE

A new systolic parameter defined as the ratio of brachial pre-ejection period to brachial ejection time predicts overall and cardiovascular mortality in hemodialysis patients

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Impaired left ventricular systolic function is an important cause of mortality in hemodialysis patients. An increase in the ratio of pre-ejection period (PEP) to ejection time (ET) is associated with a decrease in left ventricular systolic function. Brachial PEP (bPEP) and brachial ET (bET) can be automatically determined from an ankle-brachial index (ABI)-form device. The aim of this study was to investigate whether bPEP/bET was a useful predictor for overall and cardiovascular mortality in hemodialysis patients. We enrolled 212 hemodialysis patients in one regional hospital. The bPEP and bET were measured using an ABI-form device. The mean follow-up period was 28.3 ± 5.7 months. The relative mortality risk was analyzed by Cox-regression methods. Twenty-two deaths were recorded in 212 patients (10.4%). In a multivariate analysis, the bPEP/bET (hazard ratio [HR], 1.055; *P*=0.047) and serum creatinine level (*P*=0.029) were positively and negatively associated with overall mortality, respectively. In addition, increased bPEP/bET (HR, 1.080; *P*=0.017), increased fasting glucose (*P*=0.046) and decreased serum creatinine level (*P*=0.004) were independent predictors for cardiovascular mortality. Our findings show that bPEP/bET, a surrogate of left ventricular systolic function, is a useful predictor for overall and cardiovascular mortality in hemodialysis patients. Screening hemodialysis patients by means of bPEP/bET may help to identify a high-risk group for increased mortality.
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Keywords: brachial ejection time; brachial pre-ejection period; cardiovascular mortality; hemodialysis; overall mortality

INTRODUCTION

End-stage renal disease is an increasing worldwide public health problem associated with increased morbidity and mortality.[1,2] Cardiovascular disease is the leading cause of mortality in hemodialysis patients. Systolic time intervals are an established noninvasive technique for the quantitative assessment of cardiac performance and remain valuable for clinical application.[3] Prolonged pre-ejection period (PEP) and shortened ejection time (ET) have been reported to be significantly correlated with decreased left ventricular systolic function.[3–5] A high correlation ($r=-0.90$) between PEP/ET and left ventricular ejection fraction has been shown in patients with a wide variety of heart disease.[4] However, PEP and ET are frequently obtained from echocardiography, which may preclude their application in evaluating left ventricular systolic function if echocardiography is not available. A clinical device, ankle-brachial index (ABI)-form (Colin VP1000, Komaki, Japan), has been developed to automatically and simultaneously measure blood pressures in both arms and ankles and record pulse waves of the brachial and posterior tibial arteries, using an automated oscillometric method. Using this device, we can easily and automatically calculate the brachial PEP (bPEP) and brachial ET (bET) by analyzing the signals of ECG, phonocardiogram and brachial pressure volume waveform.[6,7] Recently, we have shown bPEP/bET to have significant correlation with left ventricular ejection fraction and it is a useful parameter in prediction of impaired left ventricular systolic function.[6] However, no study has evaluated the relationship between bPEP/bET and clinical outcome in hemodialysis patients. The aim of this study was to investigate whether bPEP/bET was a useful predictor of overall and cardiovascular mortality in patients receiving hemodialysis.

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METHODS

Study patients and design

The study was conducted at one dialysis clinic in a regional hospital in Taiwan. All routine hemodialysis patients in this hospital were included except 6 patients refusing ABI-form device examinations, 4 patients with atrial fibrillation and 13 patients with inadequate image visualization. Ultimately, 212 patients (95 males and 117 females) formed our study group. There was no patient with complete left bundle branch block in this study. The protocol was approved by our Institutional Review Board and all enrolled patients gave written, informed consent.

Hemodialysis

All patients underwent routine hemodialysis three times a week using a Toray 321 machine (Toray Medical Company, Tokyo, Japan). Each hemodialysis session was performed for 3–4 h using a dialyzer with a blood flow rate of 250–300 ml min^{-1} and dialysate flow of 500 ml min^{-1}.

Assessment of bPEP, bET, ABI and brachial-ankle pulse wave velocity

The values of bPEP and bET were measured 10–30 min before hemodialysis. The bPEP and bET were measured using an ABI-form device, which automatically and simultaneously measures blood pressures in both arms and ankles using an oscillometric method.[7–9] Occlusion and monitoring cuffs were placed tightly around the upper arm without blood access and both sides of the lower extremities in the supine position. The bET was automatically measured from the foot to the dicrotic notch (equivalent to the incisure on the downstroke of the aortic pressure wave contour produced by the closure of the aortic valve) of the pulse volume waveform. Total electromechanical systolic interval (QS_2) was measured from the onset of the QRS complex on the ECG to the first high-frequency vibrations of the aortic component of the second heart sound on the phonocardiogram. The bPEP was also automatically calculated by subtracting the bET from the QS_2 (Figure 1). In this study, the bPEP and bET were obtained from the right and left brachia in 168 and 44 patients, respectively. The values of ABI and brachial-ankle pulse wave velocity were also measured, and the measurement method has been reported and validated in earlier studies.[7–9]

Collection of demographic, medical and laboratory data

Demographic and medical data, including age, gender, smoking history (ever *vs.* never) and comorbid conditions, were obtained from medical records and interviews with patients. The body mass index was calculated as the ratio of weight in kilograms divided by the square of height in meters. Laboratory data were measured from fasting blood samples using an autoanalyzer (COBAS Integra 400; Roche Diagnostics GmbH, Mannheim, Germany). High-sensitivity C-reactive protein (Dade Behring Marburg GmbH, Marburg, Germany) was measured by commercially available kits. Serum intact parathyroid hormone (PTH) concentration was evaluated using a commercially available two-sided immunoradiometric assay (CIS bio international, France). Blood samples were obtained within 1 month of enrollment. Kt/V was evaluated monthly as a marker of dialysis efficiency and was determined according to the Gotch procedure.[10] In addition, information regarding patient medications including aspirin, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB) and HMG-CoA reductase inhibitors (statins) during the study period was obtained from medical records.

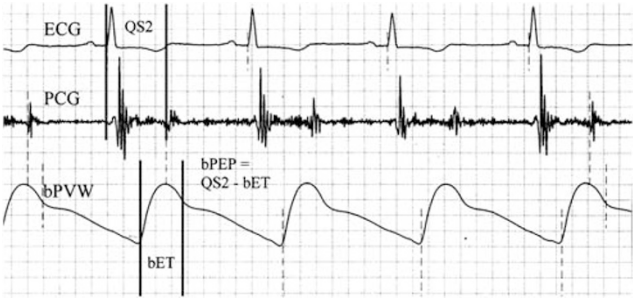

Figure 1 The brachial ejection time (bET) was automatically measured from the foot to the dicrotic notch of the brachial pulse volume waveform (bPVW). Total electromechanical systolic interval (QS_2) was measured from the onset of the QRS complex on the ECG to the first high-frequency vibrations of the aortic component of the second heart sound on the phonocardiogram (PCG). The brachial pre-ejection period (bPEP) was also automatically calculated by subtracting the bET from the QS_2.

Statistical analysis

Statistical analysis was performed using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are expressed as percentages or means ± s.d. The differences between groups were checked by χ^2 test for categorical variables or by independent *t*-test for continuous variables. The relationship between two continuous variables was assessed by a bivariate correlation method (Pearson's correlation). Time to death and covariates of risk factors were modeled using the Cox proportional hazards model. Age, gender and significant variables in the univariate analysis were further analyzed by multivariate analysis. A *P*-value <0.05 was considered significant.

RESULTS

The clinical characteristics of study patients are shown in Table 1. The mean age of the 212 patients was 59.3 ± 13.1 years. The bPEP/bET was 0.35 ± 0.08. The prevalence of heart failure was 17.0%. The differences between patients in terms of survival *vs.* mortality were shown in Table 2. Compared with survival-group patients, patients in the mortality group were significantly associated with shorter duration of hemodialysis, higher prevalence of a history of coronary artery disease, higher bPEP/bET and lower creatinine and PTH levels. In addition, patients in the mortality group had a higher percentage of having received aspirin or ACEI and/or ARB therapy.

We performed further analysis to identify the determinants of duration of hemodialysis and found that age ($r=-0.172$; $P=0.012$) was negatively correlated with the duration of hemodialysis. In addition, patients with diabetes mellitus ($P<0.001$) and hypertension ($P=0.020$) had shorter durations of dialysis.

In addition, the use of aspirin or ACEI and/or ARB was more frequent among patients with coronary artery disease (26.7% *vs.* 6.6%, $P<0.001$; 31.7% *vs.* 15.2%; $P=0.007$, respectively). Patients with diabetes mellitus and hypertension had a higher percentage of having received statins and ACEI and/or ARB therapy, respectively (39.0% *vs.* 22.5%; $P=0.010$; 27.3% *vs.* 1.6%, $P<0.001$).

The mean follow-up period was 28.3 ± 5.7 months. During the period of follow-up, 22 deaths were recorded in these 212 patients (10.4%), including fatal cardiovascular events ($n=15$), malignancy ($n=3$), infectious disease ($n=2$), gastrointestinal bleeding ($n=1$) and others ($n=1$). Table 3 shows a Cox proportional hazards-regression analysis for overall mortality. The univariate regression analysis shows that the hazard ratio (HR) of the bPEP/bET was 1.051 (95% confidence interval, 1.005–1.100; $P=0.030$). In addition, other variables including the presence of coronary artery disease, short duration of hemodialysis, increased fasting glucose, decreased serum creatinine level and the use of aspirin or ACEI and/or ARB were associated with a significant increase in overall mortality. In the multivariate analysis, the bPEP/bET (HR, 1.055; 95% confidence interval, 1.001–1.112; $P=0.047$) was positively associated with and serum creatinine level (HR, 0.733; $P=0.029$) was negatively associated with overall mortality.

Fifteen cardiovascular deaths were documented during the follow-up period, including heart failure ($n=8$), myocardial infarction ($n=4$), cerebral infarction ($n=2$) and ventricular fibrillation ($n=1$). A Cox proportional hazards-regression analysis for cardiovascular mortality

Table 1 The characteristics of the study patients

Characteristics	*All patients (n=212)*
Age (year)	59.3 ± 13.1
Male gender (%)	44.8
Duration of dialysis (month)	74.7 ± 47.8
Smoking history (%)	25.5
Diabetes mellitus (%)	39.2
Hypertension (%)	71.2
Coronary artery disease (%)	28.8
Cerebrovascular disease (%)	9.4
Systolic BP (mm Hg)	145.5 ± 25.1
Diastolic BP (mm Hg)	79.3 ± 15.4
Pulse pressure (mm Hg)	66.2 ± 17.3
Body mass index (kg m^{-2})	23.9 ± 3.6
ABI < 0.9 (%)	13.6
baPWV (cm s^{-1})	1917.5 ± 543.7
bPEP (ms)	97.1 ± 18.7
bET (ms)	284.0 ± 29.1
bPEP/bET	0.35 ± 0.08
Laboratory parameters	
Albumin (g per 100 ml)	3.8 ± 0.3
Fasting glucose (mg per 100 ml)	120.4 ± 55.2
Triglyceride (mg per 100 ml)	171.4 ± 129.0
Cholesterol (mg per 100 ml)	184.0 ± 41.9
HDL cholesterol (mg per 100 ml)	46.5 ± 14.7
LDL cholesterol (mg per 100 ml)	88.0 ± 26.5
Creatinine (mg per 100 ml)	10.3 ± 2.3
Hematocrit (%)	30.7 ± 3.3
Calcium (mg per 100 ml)	9.8 ± 0.8
Phosphate (mg per 100 ml)	4.9 ± 1.2
Uric acid (mg per 100 ml)	7.6 ± 1.5
PTH (pg ml^{-1})	501.6 ± 429.2
hsCRP (mg l^{-1})	0.8 ± 1.6
Kt/V	1.3 ± 0.2
Cardiothoracic ratio > 50%	44.8
Medications	
Aspirin use (%)	12.3
ACEI and/or ARB use (%)	19.8
Statins use (%)	28.8

Abbreviations: ABI, ankle-brachial index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; bPEP, brachial pre-ejection period; bET, brachial ejection time; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PTH, parathyroid hormone.

Table 2 Comparison of baseline characteristics between patients with survival and mortality

Characteristics	*Patients with survival (n=190)*	*Patients with mortality (n=22)*	P
Age (year)	58.9 ± 13.2	63.3 ± 11.6	0.130
Male gender (%)	44.7	45.5	0.949
Duration of dialysis (month)	77.0 ± 48.7	55.2 ± 34.2	0.043
Smoking history (%)	24.2	36.4	0.216
Diabetes mellitus (%)	37.4	54.5	0.118
Hypertension (%)	70.0	81.8	0.246
Coronary artery disease (%)	25.8	54.5	0.005
Cerebrovascular disease (%)	8.4	18.2	0.137
Systolic BP (mm Hg)	145.97 ± 24.4	142.2 ± 30.7	0.517
Diastolic BP (mm Hg)	79.8 ± 14.6	75.7 ± 21.1	0.387
Pulse pressure (mm Hg)	66.1 ± 17.6	66.6 ± 14.6	0.918
Body mass index (kg m^{-2})	23.9 ± 3.6	23.0 ± 3.9	0.293
ABI < 0.9 (%)	13.2	22.7	0.223
baPWV (cm s^{-1})	1912.4 ± 540.7	1961.2 ± 580.6	0.691
bPEP (ms)	96.4 ± 18.4	102.4 ± 21.4	0.161
bET (ms)	284.9 ± 28.9	275.4 ± 29.5	0.146
bPEP/bET	0.34 ± 0.08	0.38 ± 0.11	0.034
Laboratory parameters			
Albumin (g per 100 ml)	3.8 ± 0.3	3.8 ± 0.4	0.190
Fasting glucose (mg per 100 ml)	117.9 ± 52.6	145.4 ± 73.0	0.124
Triglyceride (mg per 100 ml)	173.6 ± 132.5	152.6 ± 93.2	0.469
Cholesterol (mg per 100 ml)	185.3 ± 41.5	173.0 ± 44.3	0.192
HDL cholesterol (mg per 100 ml)	45.6 ± 16.2	46.5 ± 14.6	0.801
LDL cholesterol (mg per 100 ml)	88.9 ± 27.1	79.0 ± 17.7	0.121
Creatinine (mg per 100 ml)	10.4 ± 2.2	9.0 ± 2.7	0.005
Hematocrit (%)	30.6 ± 3.3	31.4 ± 3.7	0.297
Calcium (mg per 100 ml)	9.8 ± 0.9	9.7 ± 0.9	0.724
Phosphate (mg per 100 ml)	4.9 ± 1.2	4.8 ± 1.2	0.887
Uric acid (mg per 100 ml)	7.7 ± 1.6	7.3 ± 1.2	0.303
PTH (pg ml^{-1})	520.5 ± 440.6	330.7 ± 256.4	0.006
hsCRP (mg l^{-1})	0.7 ± 1.5	1.2 ± 2.0	0.262
Kt/V	1.3 ± 0.2	1.3 ± 0.3	0.922
Cardiothoracic ratio > 50%	44.2	50.0	0.605
Medications			
Aspirin use (%)	10.6	27.3	0.024
ACEI and/or ARB use (%)	18.0	36.4	0.041
Statins use (%)	30.7	13.6	0.135

Abbreviations: ABI, ankle-brachial index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; bPEP, brachial pre-ejection period; bET, brachial ejection time; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PTH, parathyroid hormone.

is shown in Table 4. In the multivariate analysis, increased bPEP/bET (HR, 1.080; P=0.017), increased fasting glucose (HR, 1.007; P=0.046) and decreased serum creatinine level (HR, 0.610; P=0.004) were independent predictors for cardiovascular mortality.

Fifteen patients were New York Heart Association class III and IV, and 21 patients were New York Heart Association class I and II. We performed further forward multivariate analysis after including congestive heart failure as a variable and found that the presence of congestive heart failure (HR, 7.798; P<0.001 and HR, 10.255; P<0.001, respectively) and increased bPEP/bET (HR, 1.056; P=0.029 and HR, 1.063; P=0.017, respectively) were independent predictors of overall and cardiovascular mortality.

We further performed survival analysis after excluding the value of serum creatinine and found that there was still an independent association between bPEP/bET and both overall and cardiovascular mortality (HR, 1.065; P=0.022 and HR, 1.105; P=0.002, respectively). In addition, there was no significant correlation between bPEP/bET and serum creatinine level (r=0.107; P=0.120).

Reproducibility

The mean percentage errors for bPEP, bET and bPEP/bET measurement (3.6 ± 3.6, 2.0 ± 1.5 and 4.2 ± 4.4%, respectively) have been reported in our earlier study.[6]

Table 3 Predictors for overall mortality using Cox proportional hazards model

	Univariate		*Multivariate*	
Parameter	*Hazard ratios (95% CI)*	P	*Hazard ratios (95% CI)*	P
Age (per 1 year)	1.025 (0.992–1.060)	0.144	0.997 (0.949–1.048)	0.919
Male *vs.* female	1.035 (0.447–2.395)	0.936	1.573 (0.528–4.686)	0.416
Duration of dialysis (per 1 month)	0.987 (0.974–0.999)	0.041	0.987 (0.771–1.003)	0.107
Smoking (ever *vs.* never)	1.755 (0.736–4.185)	0.204	—	—
Diabetes mellitus	1.998 (0.863–4.624)	0.106	—	—
Hypertension	1.899 (0.642–5.610)	0.246	—	—
Coronary artery disease	3.221 (1.392–7.457)	0.006	2.690 (0.938–7.714)	0.066
Cerebrovascular disease	2.335 (0.790–6.903)	0.125	—	—
Systolic BP (per 1 mm Hg)	0.994 (0.978–1.011)	0.510	—	—
Diastolic BP (per 1 mm Hg)	0.983 (0.958–1.010)	0.215	—	—
Pulse pressure (per 1 mm Hg)	1.002 (0.978–1.026)	0.900	—	—
Body mass index (per 1 $kg\,m^{-2}$)	0.933 (0.816–1.067)	0.311	—	—
ABI < 0.9 (*vs.* $\geqslant 0.9$)	1.941 (0.716–5.262)	0.192	—	—
baPWV (per 1 $cm\,s^{-1}$)	1.000 (0.999–1.001)	0.658	—	—
bPEP (per 1 ms)	1.015 (0.994–1.036)	0.157	—	—
bET (per 1 ms)	0.989 (0.975–1.004)	0.145	—	—
bPEP/bET (per 0.01)	1.051 (1.005–1.100)	0.030	1.055 (1.001–1.112)	0.047
Laboratory parameters				
Albumin (per 1 g per 100 ml)	0.402 (0.109–1.479)	0.171	—	—
Fasting glucose (per 1 mg per 100 ml)	1.006 (1.001–1.011)	0.026	1.004 (0.997–1.010)	0.259
Triglyceride (per 1 mg per 100 ml)	0.999 (0.995–1.003)	0.497	—	—
Cholesterol (per 1 mg per 100 ml)	0.992 (0.980–1.004)	0.191	—	—
HDL cholesterol (per 1 mg per 100 ml)	0.995 (0.964–1.028)	0.779	—	—
LDL cholesterol (per 1 mg per 100 ml)	0.985 (0.967–1.004)	0.125	—	—
Creatinine (per 1 mg per 100 ml)	0.740 (0.600–0.912)	0.005	0.733 (0.555–0.968)	0.029
Hematocrit (per 1%)	1.069 (0.950–1.203)	0.269	—	—
Calcium (per 1 mg per 100 ml)	0.908 (0.543–1.519)	0.714	—	—
Phosphate (per 1 mg per 100 ml)	0.986 (0.691–1.407)	0.939	—	—
Uric acid (per 1 mg per 100 ml)	0.864 (0.648–1.151)	0.318	—	—
PTH (per 1 $pg\,ml^{-1}$)	0.999 (0.997–1.000)	0.061	—	—
hsCRP (per 1 $mg\,l^{-1}$)	1.124 (0.961–1.314)	0.144	—	—
Kt/V (per 1.0)	0.868 (0.153–4.931)	0.873	—	—
Cardiothoracic ratio $>50\%$	1.268 (0.550–2.925)	0.577	—	—
Medications				
Aspirin use	2.863 (1.120–7.319)	0.028	1.375 (0.349–5.427)	0.649
ACEI and/or ARB use	2.529 (1.061–6.029)	0.036	2.087 (0.741–5.879)	0.164
Statins use	0.376 (0.111–1.269)	0.115	—	—

Abbreviations: ABI, ankle-brachial index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; bPEP, brachial pre-ejection period; bET, brachial ejection time; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PTH, parathyroid hormone.
Values express as hazard ratios and 95% CI.

DISCUSSION

In this study, we evaluated the predictors for overall and cardiovascular mortality in 212 patients receiving hemodialysis. We found that the bPEP/bET obtained from the ABI-form device could predict overall and cardiovascular mortality. Therefore, the bPEP/bET might be a useful predictor for overall and cardiovascular mortality among hemodialysis patients, even after including congestive heart failure as a variable.

The prolongation of PEP may be caused by a diminished rate of left ventricular pressure rise during isovolumic contraction.[3] Increased PEP usually occurred when heart function decreased.[5] The duration of ET reflects both the velocity and the extent of fiber shortening. In left ventricular decompensation, the extent of fiber shortening is decreased, so a shortened ET is usually noted.[4] As heart function impairment usually prolongs PEP and shortens ET, the ratio of PEP to ET may enhance the diagnostic value for the identification of left ventricular dysfunction. Our recent study showed that bPEP, bET and bPEP/bET had a significant correlation with left ventricular ejection fraction and bPEP/bET had a higher accuracy in prediction of left ventricular ejection fraction $<50\%$ than bPEP and bET.[6] In this study, although bPEP and bET were not predictors of overall and cardiovascular mortality, the bPEP/bET was helpful in the prediction of overall and cardiovascular mortality. Therefore, bPEP/bET may be a useful survival parameter in patients with hemodialysis. This may imply that

Table 4 Predictors for cardiovascular mortality using Cox proportional hazards model

	Univariate		*Multivariate*	
Parameter	*Hazard ratios (95% CI)*	P	*Hazard ratios (95% CI)*	P
Age (per 1 year)	1.021 (0.981–1.063)	0.303	0.988 (0.927–1.053)	0.712
Male *vs.* female	1.086 (0.394–2.996)	0.873	2.067 (0.519–8.238)	0.303
Duration of dialysis (per 1 month)	0.989 (0.974–1.003)	0.129	—	—
Smoking (ever *vs.* never)	2.670 (0.968–7.365)	0.058	—	—
Diabetes mellitus	2.493 (0.887–7.005)	0.083	—	—
Hypertension	2.743 (0.619–12.158)	0.184	—	—
Coronary artery disease	3.993 (1.421–11.220)	0.009	3.507 (0.903–13.613)	0.070
Cerebrovascular disease	3.791 (1.207–11.912)	0.023	1.302 (0.214–7.922)	0.775
Systolic BP (per 1 mm Hg)	0.997 (0.977–1.018)	0.781	—	—
Diastolic BP (per 1 mm Hg)	0.984 (0.953–1.016)	0.310	—	—
Pulse pressure (per 1 mm Hg)	1.007 (0.980–1.035)	0.631	—	—
Body mass index (per 1 $kg\,m^{-2}$)	0.976 (0.832–1.144)	0.763	—	—
ABI < 0.9 (*vs.* $\geqslant 0.9$)	2.399 (0.764–7.536)	0.134	—	—
baPWV (per 1 $cm\,s^{-1}$)	1.000 (0.999–1.001)	0.691	—	—
bPEP (per 1 ms)	1.023 (0.999–1.048)	0.058	—	—
bET (per 1 ms)	0.985 (0.968–1.003)	0.102	—	—
bPEP/bET (per 0.01)	1.073 (1.020–1.128)	0.006	1.080 (1.014–1.150)	0.017
Laboratory parameters				
Albumin (per 1 g per 100 ml)	0.535 (0.102–2.810)	0.460	—	—
Fasting glucose (per 1 mg per 100 ml)	1.007 (1.002–1.013)	0.008	1.007 (1.000–1.014)	0.046
Triglyceride (per 1 mg per 100 ml)	1.000 (0.995–1.004)	0.847	—	—
Cholesterol (per 1 mg per 100 ml)	0.991 (0.977–1.066)	0.248	—	—
HDL cholesterol (per 1 mg per 100 ml)	0.996 (0.959–1.035)	0.856	—	—
LDL cholesterol (per 1 mg per 100 ml)	0.986 (0.964–1.008)	0.216	—	—
Creatinine (per 1 mg per 100 ml)	0.704 (0.544–0.911)	0.008	0.610 (0.433–0.858)	0.004
Hematocrit (per 1%)	1.084 (0.942–1.248)	0.260	—	—
Calcium (per 1 mg per 100 ml)	0.888 (0.475–1.657)	0.708	—	—
Phosphate (per 1 mg per 100 ml)	1.287 (0.874–1.894)	0.202	—	—
Uric acid (per 1 mg per 100 ml)	0.882 (0.625–1.246)	0.476	—	—
PTH (per 1 $pg\,ml^{-1}$)	0.998 (0.996–1.000)	0.071	—	—
hsCRP (per 1 $mg\,l^{-1}$)	1.119 (0.922–1.358)	0.256	—	—
Kt/V (per 1.0)	0.336 (0.040–2.836)	0.317	—	—
Cardiothoracic ratio $> 50\%$	1.108 (0.402–3.056)	0.843	—	—
Medications				
Aspirin use	1.887 (0.532–6.688)	0.326	—	—
ACEI and/or ARB use	2.949 (1.050–8.287)	0.040	2.361 (0.626–8.898)	0.204
Statins use	0.368 (0.083–1.633)	0.189	—	—

Abbreviations: ABI, ankle-brachial index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; bPEP, brachial pre-ejection period; bET, brachial ejection time; CI, confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PTH, parathyroid hormone.
Values express as hazard ratios and 95% CI.

patients with left ventricular systolic dysfunction, indicated by increased bPEP/bET, may be a high-risk group for increased mortality in hemodialysis patients.

Our study subjects were selected from a population of patients receiving regular hemodialysis and their overall health might, therefore, be relatively stable. Therefore, impaired left ventricular systolic function, instead of coronary artery disease, cerebrovascular disease, diabetes or hypertension, might be the chief cause of mortality among these stable patients.[11,12] Hence, an increase of bPEP/bET, which indicated a decrease in left ventricular systolic function, was a predictor of mortality. However, coronary artery disease, cerebrovascular disease, diabetes and hypertension could not predict mortality independently in this study.

This study revealed that creatinine and PTH levels were lower in patients in the mortality group than in patients in the survival group. Furthermore, after multivariate analysis, serum creatinine level was still associated with overall and cardiovascular mortality. Traditional-risk factors, such as high blood pressure, obesity and hypercholesterolemia, have an important function in the cardiovascular mortality of the general population. Recently, the concept of reverse epidemiology has been raised, suggesting that low body mass index, low blood pressure, hypocholesterolemia, low low-density lipoprotein cholesterol and low homocysteine level are associated with high cardiovascular mortality and total mortality in dialysis patients.[13–15] Similar reverse epidemiologic observations have also been found for serum creatinine and PTH levels.[13,16,17] Reduced intake of calcium, phosphorous and

protein might lead to low serum creatinine and PTH levels, which usually reflect poor nutritional status and might contribute to high mortality.[13,18] In this study, patients in the mortality group had lower creatinine and PTH levels and their serum creatinine level was a predictor of overall and cardiovascular mortality (HR, 0.733; $P=0.029$ and HR, 0.610; $P=0.004$, respectively) in multivariate analysis. Therefore, malnutrition, as indicated by the low serum creatinine and PTH levels, might have a function in increased mortality in this study.

A long duration of hemodialysis has been reported to be associated with increased mortality in patients with end-stage renal disease,[19] which might be explained by the vascular calcification caused by alterations in the metabolism of calcium, phosphate and PTH, inflammatory alterations, oxidative stress or hyperhomocysteinemia.[20,21] Our study showed that patients in the mortality group had shorter hemodialysis duration than survival-group patients did. We further analyzed the determinants of duration of hemodialysis and found that age was negatively correlated with duration of hemodialysis and patients with diabetes mellitus and hypertension had a shorter duration of hemodialysis, which might explain the inconsistent results of earlier studies.[22] Furthermore, duration of dialysis was not significantly associated with overall mortality after the multivariate Cox-regression analysis. Thus, duration of hemodialysis was not a major determinant of overall mortality in this study.

Statins, ACEI, ARB and aspirin have been shown to reduce neointimal proliferation and vascular inflammation.[23–26] Hemodialysis patients are usually prescribed many of these medications for cardiovascular causes. In this study, patients in the mortality group had a higher percentage of having received aspirin or ACEI and/or ARB therapy. Further analysis found that the use of aspirin or ACEI and/or ARB was more frequent among patients with coronary artery disease (26.7 *vs.* 6.6%, $P<0.001$ and 31.7 *vs.* 15.2%; $P=0.007$, respectively), which might partially explain the greater use of aspirin or ACEI and/or ARB in our patients in the mortality group. Furthermore, the use of aspirin or ACEI and/or ARB was not significantly associated with overall mortality after multivariate Cox-regression analysis. Thus, treatment with aspirin or ACEI and/or ARB was not a major determinant of overall mortality in this study.

The measurement of bPEP and bET may be influenced by hemodialysis.[27,28] To avoid interference from hemodialysis in this study, bPEP and bET were measured before hemodialysis in all study subjects. In addition, because of ethical reasons, bPEP and bET were only measured on the arm, without blood access. Hence, in this study, the bPEP and bET were obtained from the right and left brachium in 168 and 44 patients, respectively. The bET represented the ET of the left ventricle. Therefore, bET should be unchanged whether it was obtained from the right or the left brachium. The bPEP was calculated by subtracting the bET from the QS_2, so it should be also unchanged whether it was measured from the right or the left brachium. Hence, bPEP/bET is likely to be unchanged when obtained from the right or left brachium.

There were several limitations to this study. The study subjects were enrolled from only one regional hospital and the selection of patients was relatively restricted. Therefore, generality of the results was limited. In addition, we did not further validate our finding with invasive methodology or noninvasive echocardiographic parameters.

In conclusion, our results show that bPEP/bET, a surrogate of left ventricular systolic function, obtained from the ABI-form device can predict overall and cardiovascular mortality in patients with hemodialysis. Screening hemodialysis patients by means of bPEP/bET may help to identify a high-risk group for increased mortality.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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