

## Value of Excess Pressure Integral for Predicting 15-Year All-Cause and Cardiovascular Mortalities in End-Stage Renal Disease Patients

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**Background**—The excess pressure integral (XSPI), derived from analysis of the arterial pressure curve, may be a significant predictor of cardiovascular events in high-risk patients. We comprehensively investigated the prognostic value of XSPI for predicting long-term mortality in end-stage renal disease patients undergoing regular hemodialysis.

**Methods and Results**—A total of 267 uremic patients (50.2% female; mean age  $54.2 \pm 14.9$  years) receiving regular hemodialysis for more than 6 months were enrolled. Cardiovascular parameters were obtained by echocardiography and applanation tonometry. Calibrated carotid arterial pressure waveforms were analyzed according to the wave-transmission and reservoir-wave theories. Multivariable Cox proportional hazard models were constructed to account for age, sex, diabetes mellitus, albumin, body mass index, and hemodialysis treatment adequacy. Incremental utility of the parameters to risk stratification was assessed by net reclassification improvement. During a median follow-up of 15.3 years, 124 deaths (46.4%) incurred. Baseline XSPI was significantly predictive of all-cause (hazard ratio per 1 SD 1.4, 95% confidence interval 1.15–1.70,  $P=0.0006$ ) and cardiovascular mortalities (1.47, 1.18–1.84,  $P=0.0006$ ) after accounting for the covariates. The addition of XSPI to the base prognostic model significantly improved prediction of both all-cause mortality (net reclassification improvement=0.1549,  $P=0.0012$ ) and cardiovascular mortality (net reclassification improvement=0.1535,  $P=0.0033$ ). XSPI was superior to carotid-pulse wave velocity, forward and backward wave amplitudes, and left ventricular ejection fraction in consideration of overall independent and incremental prognostics values.

**Conclusions**—In end-stage renal disease patients undergoing regular hemodialysis, XSPI was significantly predictive of long-term mortality and demonstrated an incremental value to conventional prognostic factors. (*J Am Heart Assoc.* 2017;6:e006701. DOI: 10.1161/JAHA.117.006701.)

**Key Words:** cardiovascular mortality • hemodynamics • prognosis • reservoir-pressure analysis • uremia

The prevalence of end-stage renal disease (ESRD) patients is rising globally.<sup>1</sup> Although the facilities and techniques for dialysis have improved substantially, the mortality remains high.<sup>2,3</sup> The disproportionately elevated cardiovascular morbidity and mortality in ESRD patients undergoing dialysis cannot be fully explained by the traditional cardiovascular risk factors such as aging, hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking.<sup>4</sup> Consequently, increasing attention

presently is paid to the emerging prognostic factors to improve the risk stratification and identify the targeted therapies for ESRD patients.<sup>5</sup> Among the first of these efforts, arterial factors, including arterial stiffness<sup>6,7</sup> and arterial wave reflection,<sup>8</sup> have been identified as useful prognostic factors for cardiovascular outcomes in hemodialysis patients. Therefore, high blood pressure (BP) and hemodynamic overload are widely accepted as the main contributing factors to the left

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Accompanying Tables S1 and S2 are available at <http://jaha.ahajournals.org/content/6/12/e006701/DC1/embed/inline-supplementary-material-1.pdf>

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Received May 17, 2017; accepted October 13, 2017.

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## Clinical Perspective

### What Is New?

- We found that the excess pressure integral (XSPI) derived from the reservoir-wave analysis significantly associated with long-term mortality and demonstrated incremental prognostic value compared to conventional factors in end-stage renal disease patients undergoing regular hemodialysis.
- The prognostic value of XSPI was superior to those of conventional arterial stiffness and wave reflection parameters. XSPI remained significant in a subgroup of patients who had attained dry weight and normotension during regular hemodialysis when conventional arterial stiffness and wave reflection parameters might have lost their predictive power.

### What Are the Clinical Implications?

- Arterial factors may play an important role in the outcomes of end-stage renal disease patients, even when normotension and ideal dry weight are achieved.
- XSPI may represent both the wave-related component of the arterial pressure and the excess work exerted by the left ventricle during a cardiac cycle and therefore the result of the interaction between the individual mechanical properties of the left ventricle and systemic circulation.
- The significance and incremental value of XSPI for the prediction of long-term mortalities may implicate the potential for risk stratification and clinical management of end-stage renal disease patients undergoing regular hemodialysis.

ventricular hypertrophy,<sup>9</sup> left ventricular dysfunction,<sup>10</sup> and increased cardiovascular events and mortality in these patients.<sup>11</sup> However, in hemodialysis patients who had attained normotension without antihypertensive medications, only left ventricular ejection fraction (LVEF) but none of the arterial factors was the independent predictor for all-cause and cardiovascular mortalities.<sup>12</sup>

Recently, Tyberg et al proposed the reservoir-excess pressure approach,<sup>13</sup> which separates the measured arterial pressure into reservoir and excess-pressure components.<sup>14</sup> The latter, excess pressure integral (XSPI), has been identified as a novel indicator of cardiovascular dysfunction for predicting cardiovascular events in the treated hypertensive individuals,<sup>15-17</sup> and high-risk<sup>18</sup> and stable heart failure patients.<sup>19</sup> However, whether XSPI represents aortic wave propagation and reflection<sup>14</sup> or the unnecessary work exerted by the ventricle in each cardiac cycle<sup>17</sup> or both remains to be determined.

We hypothesized that XSPI may represent both the wave-related component of the arterial pressure and the excess ventricular workload. In “dry” ESRD patients, where

conventional arterial factors of arterial stiffness and wave reflection may become less important, XSPI may be particularly useful in risk stratification. Therefore, in the present study, we comprehensively investigated the prognostic value of XSPI for predicting long-term mortality in ESRD patients undergoing regular hemodialysis.

## Methods

### Study Population

This was a retrospective cohort study with a study population constructed of eligible subjects who had participated in our previous studies investigating the cardiovascular hemodynamics of hemodialysis patients.<sup>12,20-22</sup> Every participant had provided a written informed consent approved by the institutional review board of Taipei Veterans General Hospital. Patients were eligible for inclusion in the study if they were older than 18 years of age and had received regular maintenance hemodialysis for more than 6 months. Patients with acute disease or any history of myocardial infarction, heart failure, or significant valvular heart disease were excluded. All participants received a comprehensive cardiovascular examination with blood tests on the nondialysis day of midweek.<sup>7</sup>

The eligible hemodialysis population consisted of 268 patients treated at Taipei Veterans General Hospital, a nearby community hospital, and 8 local dialysis centers during the period of January 1998 through December 2005. One patient was excluded due to the presence of atrial fibrillation and heart failure history. Thus, 267 hemodialysis patients (133 men, 134 women) with a mean age of  $54.2 \pm 14.9$  years were included in the final analysis, and 42 patients (15.8%) had diabetes mellitus. (Table 1).

### Hemodialysis Procedures

The ESRD patients received a 4-hour dialysis session thrice-weekly using 1.6 m<sup>2</sup> surface area dialyzers with bicarbonate-based dialysate ([Na<sup>+</sup>]=140 mEq/L, [HCO<sub>3</sub><sup>-</sup>]=39 mEq/L, [K<sup>+</sup>]=2.0 mEq/L, [Ca<sup>2+</sup>]=3.0 mEq/L, and [Mg<sup>2+</sup>]=1.0 mEq/L). In addition to baseline echocardiographic and vascular examinations, the patients were assessed via meticulous physical examinations, chest x-ray, and extra echocardiography for adjustment of fluid status during the follow-up period. Dry weight was defined as proposed by Charra et al.<sup>23</sup> If symptoms and signs of fluid overload were noted, the exceeded volume was ultrafiltered during the dialysis session or via additional sessions. All patients were treated with subcutaneous recombinant erythropoietin (Eprex, Janssen-Cilag, Schaffhausen, Switzerland) at a mean dosage of 20 000 U per month with the aim of keeping their hematocrit level up to 30% according to the National Health Insurance guideline.<sup>12,21,22</sup>

**Table 1.** Characteristics of Study Population

	All (N=267)	Dead (N=124)	Alive (N=143)	P Value
Age, y	54.2±14.9	61.2±14.1	48.1±12.8	<0.001
Men, %	49.8	48.4	51.1	0.664
Diabetes mellitus, %	15.8	28.5	4.9	<0.001
Body mass index, kg/m <sup>2</sup>	22.8±3.5	23.3±3.4	22.4±3.5	0.024
Albumin, mmol/L	4.1±0.4	4.0±0.4	4.2±0.3	<0.001
Hematocrit, %	30.0±4.3	29.6±3.8	30.4±4.7	0.141
Total cholesterol, mmol/L	189.0±49.5	195.3±54.1	183.7±44.9	0.071
Kt/V, L/min	1.53±0.29	1.51±0.29	1.54±0.28	0.543
Central venous pressure, cm H <sub>2</sub> O	6.4±2.4	6.3±2.2	6.5±2.5	0.44
Brachial SBP, mm Hg	126.9±29.8	130.9±30.9	123.4±28.6	0.041
Brachial DBP, mm Hg	75.5±17.1	75.5±16.9	75.5±17.4	0.984
Brachial PP, mm Hg	57.4±18.9	61.4±21.2	53.9±15.9	0.002
Central SBP, mm Hg	120.6±26.9	124.2±27.1	117.4±26.4	0.038
Central PP, mm Hg	44.6±15.7	48.2±17.4	41.5±13.4	<0.001
MAP, mm Hg	94.6±20.3	96.0±20.2	93.5±20.4	0.314
Heart rate, bpm	74.5±12.9	76.1±12.6	73.1±13.0	0.056
Conventional cardiovascular parameters				
LVEF, %	57±11	54±12	59±9	0.002
PWV, cm/s	1069±460	1259±500	901±345	<0.001
Pf, mm Hg	35.2±10.7	37.5±11.9	33.1±9.1	<0.001
Pb, mm Hg	18.0±7.3	19.3±7.8	16.9±6.7	0.007
Arterial reservoir function				
XSPI, mm Hg-s	11.2±5.3	12.8±6.0	9.8±4.2	<0.001
Average oscillatory work/average total work*	0.16±0.06	0.17±0.07	0.14±0.05	0.006

DBP indicates diastolic blood pressure; Kt/V, hemodialysis treatment adequacy; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; Pb, backward wave amplitude; Pf, forward pressure amplitude; PP, pulse pressure; PWV, carotid-femoral pulse wave velocity; SBP, systolic blood pressure; XSPI, excess pressure integral.

\*Available in 180 patients.

## Uremia-Related Modulators and Laboratory Evaluation

Blood tests and other clinical biochemistry data including albumin and cholesterol were obtained by averages of 2-month data before patients' entry. Hemoglobin and hematocrit were measured by CELLDYNE 1400 (Abbot Laboratories, Abbott Park, IL). The adequacy of hemodialysis dosage (Kt/V) was indexed by the formula dialyzer clearance of urea × dialysis time/volume of distribution of urea.

## BP Measurements

Supine BP right before each dialysis session was measured with an oscillometric BP monitor. Readings from 25 consecutive dialysis sessions before the cardiovascular examination were averaged as predialysis BP of the baseline data. On the

day of the cardiovascular examination, supine brachial artery systolic and diastolic BPs were measured with an oscillometric device. Pulse pressure was the difference between systolic and diastolic BP. Mean arterial pressure was diastolic BP plus one third pulse pressure.

## Echocardiographic Evaluation

Echocardiographic examinations were conducted using a multifrequency transducer incorporated in a SONOS 5500 echocardiograph (Hewlett Packard, Inc, Agilent Technologies, Andover, MA). LVEF was calculated from 2-dimensional echocardiographic volume calculations using the biplane method of disks summation (modified Simpson rule), according to the recommendations from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.<sup>24</sup> Left ventricular outflow tract diameter from a

parasternal long-axis view and pulsed Doppler from an apical 5-chamber view were available in a subgroup of 180 patients. All measurements of the ultrasonography-based parameters were conducted 4 times, and the results were averaged.

## Arterial Tonometric Evaluation

### Arterial Stiffness

Applanation tonometry was performed with a pencil-type tonometer incorporating a high-fidelity strain-gauge transducer in a 7-mm-diameter flat tip (SPC-350, Millar Instruments Inc, Houston, TX).<sup>25</sup> Carotid-femoral pulse wave velocity (PWV) was measured by recording pulse waves at the right common carotid artery and right femoral artery sequentially using tonometry and a simultaneous ECG.<sup>25</sup>

### Forward Wave and Wave Reflection

Right common carotid artery pressure waveforms were registered and digitized<sup>26,27</sup> and then ensemble averaged.<sup>28</sup> Brachial mean arterial pressure and diastolic BP were used to calibrate the averaged carotid pressure waveform. The calibrated carotid pressure waveforms from all patients were batch-analyzed with custom-designed software on a commercial software package (Matlab<sup>®</sup>; version 4.2 and 7.0, The MathWorks, Inc, Natick, MA). Based on the wave-transmission theory, the central arterial pressure is composed of a forward traveling wave and a backward traveling reflection wave. The calibrated carotid pressure waveform was therefore separated into forward and reflected components based on the triangulation method<sup>29</sup> to obtain the magnitudes of the forward wave (Pf) and backward wave (Pb).<sup>29,30</sup>

### Reservoir Pressure and Excess Pressure

In the reservoir-wave analysis, the central arterial pressure is presumed to be the instantaneous sum of a pressure associated with the compliance and aortic blood volume (reservoir pressure) plus a pressure due to the wave's propagation characteristics (excess pressure).<sup>13</sup> Reservoir pressure is thought to vary temporally in the same pattern throughout the aorta and large elastic arteries, with a time lag depending on the location and wave propagation characteristics of the arteries.<sup>31</sup> In the present study, reservoir pressure was calculated from the calibrated carotid pressure waveform. XSPI was obtained from reservoir-wave analysis. Details of the calculations of parameters of reservoir pressure are presented in our previous studies.<sup>16,19</sup>

### Average Oscillatory Work Analysis

To understand whether XSPI represents unnecessary work that does not contribute any net flow to end organs, we

conducted an analysis of average oscillatory work in a subgroup of 180 patients with available Doppler-derived aortic flow waveforms. Average oscillatory work is associated with pulsatile pressure and flow, and it does not result in net flow to end organs over the cardiac cycle. The carotid pressure waveforms and aortic flow waveforms were subjected to Fourier transform. The first 15 harmonics were chosen for energy calculation, and the average oscillatory work was calculated as the sum of 15 products of pressure and flow moduli of the same harmonics over the period of 1 cardiac cycle. The average total hydraulic work was calculated as the integral of carotid pressure times aortic flow over 1 cardiac cycle. The ratio of average oscillatory work/average total work was considered as an index of the excess ventricular work.

## Patient Follow-Up

The dates and causes of death for the expired patients were confirmed via telephone contact with the relatives of the patients, review of hospital charts and death certificates, and linkage of our database with the National Death Registry. Cardiovascular deaths were identified with *International Classification of Disease, Ninth Revision (ICD-9)*, codes 390 to 459. Patients who did not appear in the National Death Registry on the censoring date were all confirmed to be survivors on census date by direct telephone contacts.

## Statistical Analysis

Data are expressed as percentage for categorical variables and mean±standard deviation for continuous variables. Between-group comparisons were performed by 2-sample t test for continuous variables and by chi-squared test for categorical variables. Correlations between parameters were evaluated by using Pearson correlation coefficient and linear regression analysis. Prognostic values of XSPI and conventional cardiovascular function parameters, including LVEF, PWV, Pf, and Pb, were evaluated with the multivariable Cox proportional hazard regression adjusting for variables of a base model of age, sex, diabetes mellitus, albumin, body mass index, and hemodialysis treatment adequacy. The 6 covariates were selected according to clinical significance (sex, dialyzer clearance of urea×dialysis time/volume of distribution of urea) and statistical significance (age, diabetes mellitus, albumin, and body mass index) (Table 1). Time-interaction terms for all covariates had been added to the multivariable models, and none of the interaction terms were significant. Comparisons between XSPI and other cardiovascular parameters in the prediction of mortalities were performed by using the multivariable Cox regression models and adjusting for the base model. Incremental values of XSPI and other

cardiovascular parameters to the base model were evaluated by using net reclassification improvement.<sup>32-34</sup> The performance characteristics of the base models and then the models after the addition of XSPI were evaluated by using likelihood ratio test to compare the goodness of fit and the Akaike Information Criterion (AIC) for model comparisons.<sup>35</sup> The area under the curve from the receiver-operating characteristic (ROC) curves were used for model discrimination,<sup>32</sup> the survival-adapted Hosmer-Lemeshow  $\chi^2$  statistic for model calibration,<sup>36</sup> and a  $P < 0.05$  for the  $\chi^2$  statistic suggests that the model is not well calibrated.

Survival curves were plotted using the Kaplan-Meier method and assessed using the log-rank test. The prognostic value of XSPI was further investigated in a subgroup of patients who had attained dry weight and normotension during regular hemodialysis.

All statistical analyses were conducted using SAS<sup>®</sup> 9.4 software. Values of two-tailed  $P < 0.05$  were considered as statistically significant. Bonferroni correction was applied for multiple comparisons.

## Results

### Baseline Characteristics of ESRD Patients

The baseline characteristics of the study patients are shown in Table 1. During a median follow-up of 15.3 years (0.2-17.3 years), there were 124 deaths (46.4%), including 92 cardiovascular-related deaths (34.5%). Patients with fatal events were older than the survivors, had a higher proportion of type 2 diabetes mellitus, higher body mass index, and lower albumin levels. Patients with fatal events had significantly higher brachial and carotid systolic BP and pulse pressure, lower LVEF, faster PWV, higher Pf and Pb, and higher XSPI (Table 1). In patients with available noninvasive aortic flow data ( $n=180$ ), the ratio of average oscillatory work over average total work was significantly higher in those with fatal events (Table 1).

### Hemodynamic Determinants of XSPI

XSPI significantly correlated with Pf ( $r=0.62$ ,  $P < 0.0001$ ), Pb ( $r=0.51$ ,  $P < 0.0001$ ), ratio of average oscillatory work/average total work ( $r=0.50$ ,  $P < 0.0001$ ), and PWV ( $r=0.39$ ,  $P < 0.0001$ ) (Table S1). To understand the biophysical perspective of XSPI, we conducted a linear regression analysis in patients with available noninvasive aortic flow data ( $n=180$ ). The result showed that Pf (standardized beta=0.38468,  $P=0.0001$ ) and the ratio of average oscillatory work/average total work (standardized beta=0.20979,  $P=0.0033$ ) were significant independent determinants of XSPI (Table 2).

**Table 2.** Determinants of XSPI by Multivariable Linear Regression ( $n=180$ )

	Standardized $\beta$	Standard Error	t Value	P Value
Age	0.09205	0.02252	1.46	0.146
Sex	-0.0776	0.66328	-1.29	0.1974
PWV	0.01581	0.00082	0.22	0.8276
Pf	0.38468	0.05203	3.88	0.0001
Pb	0.14905	0.06557	1.67	0.0963
Average oscillatory work/average total work	0.20979	6.34788	2.98	0.0033

Pb indicates backward wave amplitude; Pf, forward pressure amplitude; PWV, carotid-femoral pulse wave velocity; XSPI, excess pressure integral.

### Prognostic Values of XSPI and Conventional Cardiovascular Parameters

We constructed a base risk prediction multivariable Cox regression model with age, sex, diabetes mellitus, albumin, body mass index, and hemodialysis treatment adequacy. There was no effect modification by sex. As shown in Table 3, among the cardiovascular parameters, only LVEF, PWV, and XSPI separately could predict all-cause and cardiovascular mortalities in the multivariable Cox regression analyses incorporating the base risk prediction model (Table 3). When a significance level of 0.0083 for Bonferroni corrected  $P$  value was applied, only XSPI was a significant predictor of mortalities. XSPI remained significantly independently predictive of both all-cause mortality and cardiovascular mortality when PWV, Pf, the ratio of average oscillatory work/average total work, or was added to the model (Table 4).

The Kaplan-Meier survival curves clearly demonstrated that a high XSPI was significantly associated with a high long-term all-cause (Figure Panel A) and cardiovascular (Figure Panel B) mortality, in comparison to a low XSPI.

The incremental risk prediction values of XSPI and the conventional cardiovascular parameters were individually examined by analyzing the categorical net reclassification improvement with the base risk prediction Cox model. For all-cause mortality, Pf ( $P=0.0098$ ), LVEF ( $P=0.0077$ ), the ratio of average oscillatory work/average total work ( $P=0.0427$ ), and XSPI ( $P=0.0012$ ) resulted in significant net improvement; for cardiovascular mortality, only the ratio of average oscillatory work/average total work ( $P=0.0098$ ) and XSPI ( $P=0.0033$ ) showed incremental utility (Table 5). When a significance level of 0.01 for Bonferroni corrected  $P$  value was applied, only XSPI had an incremental value for both all-cause and cardiovascular mortalities.

The area under the ROC curve for the prediction of cardiovascular mortality was 0.779 (95% confidence interval

**Table 3.** Standardized Hazard Ratios for Predicting All-Cause and Cardiovascular Mortality in Multivariable Cox Models

	All-Cause Mortality					Cardiovascular Mortality				
	Hazard Ratio, Per SD	95% Confidence Intervals		$\chi^2$	P Value	Hazard Ratio, Per SD	95% Confidence Intervals		$\chi^2$	P Value
LVEF	0.74	0.60	0.91	8.2169	0.0042	0.70	0.55	0.88	9.078	0.0026
PWV	1.24	1.01	1.54	4.0657	0.0438	1.29	1.02	1.63	4.6244	0.0315
Pf	1.31	1.03	1.66	4.8108	0.0283	1.23	0.95	1.60	2.4762	0.1156
Pb	1.17	0.86	1.59	0.9719	0.3242	1.10	0.78	1.53	0.2902	0.5901
XSPI	1.40	1.15	1.70	11.6767	0.0006	1.47	1.18	1.84	11.9177	0.0006
Average oscillatory work/average total work*	1.13	0.89	1.44	1.0532	0.3048	1.37	1.05	1.79	5.4318	0.0198

Base model included age, sex, diabetes mellitus, albumin, body mass index, and hemodialysis treatment adequacy. Significance level for *P* value after Bonferroni correction for multiple comparisons=0.0083. LVEF indicates left ventricular ejection fraction; Pb, backward wave amplitudes; Pf, forward pressure amplitude; PWV, carotid-femoral pulse wave velocity; XSPI, excess pressure integral.

\*Available in 180 patients.

0.709-0.848) using the base model and increased to 0.790 (95% confidence interval 0.722-0.858) with the addition of XSPI (Table 6). *P* values of the survival-adapted Hosmer-Lemeshow  $\chi^2$  statistic were all >0.05 for the base model with or without XSPI, indicating good calibration for both models (Table 6). Both the Akaike Information Criterion and the likelihood ratio test suggested a better model performance when XSPI was added into the base model (Table 6).

### Subgroup Analysis

We have previously reported in 145 hemodialysis patients (Table S2) who had attained normotension without

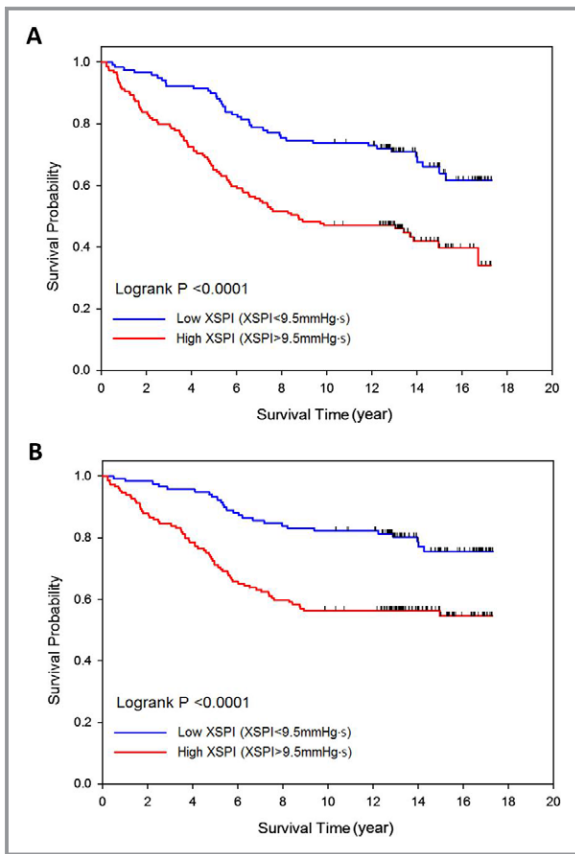
antihypertensive medications, only LVEF but not PWV or carotid augmentation index was independently predictive of all-cause and cardiovascular mortalities during  $72.6 \pm 28.5$  months' follow-up.<sup>12</sup> The 145 normotensive ESRD patients were included in the present study, and they had lower brachial and central pulse pressure, PWV, Pf, Pb, and XSPI in comparison to the full sample. As shown in the multivariable Cox models in Table 7, LVEF was no longer a significant predictor of mortalities in the extended follow-up. PWV, Pf, Pb, and the ratio of average oscillatory work/average total work were not significant predictors of all-cause mortality. In contrast, XSPI was a significant predictor of all-cause mortality (*P*=0.036) and cardiovascular mortality

**Table 4.** Multivariable Cox Regression Models for Comparisons Between XSPI and Other Cardiovascular Parameters in the Prediction of Mortalities

Parameter	All-Cause Mortality		Cardiovascular Mortality	
	HR (95% CI)	P Value	HR (95% CI)	P Value
<b>Model 1</b>				
XSPI	1.33 (1.07-1.64)	0.0103	1.38 (1.08-1.77)	0.0105
PWV	1.10 (0.86-1.40)	0.4444	1.12 (0.85-1.47)	0.4186
<b>Model 2</b>				
XSPI	1.41 (1.08-1.84)	0.0124	1.64 (1.20-2.24)	0.002
Pf	0.99 (0.71-1.38)	0.9556	0.84 (0.58-1.21)	0.3381
<b>Model 3</b>				
XSPI	1.51 (1.14-1.98)	0.0035	1.51 (1.11-2.05)	0.009
Average oscillatory work/average total work*	0.93 (0.71-1.24)	0.6295	1.14 (0.84-1.56)	0.3937
<b>Model 4</b>				
XSPI	1.34 (1.10-1.63)	0.0037	1.41 (1.13-1.76)	0.0025
LVEF	0.78 (0.63-0.97)	0.0223	0.73 (0.57-0.93)	0.0113

Base model included age, sex, diabetes mellitus, albumin, body mass index, and hemodialysis treatment adequacy. CI indicates confidence interval; HR, hazard ratio per 1 standard deviation; LVEF, left ventricular ejection fraction; Pf, forward pressure amplitude; PWV, carotid-femoral pulse wave velocity; XSPI, excess pressure integral.

\*Available in 180 patients.



**Figure.** A, Kaplan-Meier curves for subgroups with high and low excess pressure integral (XSPI), showing a significant difference in all-cause mortality in hemodialysis patients who had achieved ideal dry weight. B, Kaplan-Meier curves for subgroups with high and low XSPI, showing a significant difference in cardiovascular mortality in hemodialysis patients who had achieved ideal dry weight.

( $P=0.004$ ). When a significance level of 0.0083 for Bonferroni-corrected  $P$  value was applied, XSPI remained a significant predictor of cardiovascular mortality (Table 7).

## Discussion

The present study comprehensively investigated the values of XSPI and several conventional cardiovascular parameters for predicting long-term all-cause and cardiovascular mortalities in ESRD patients. In ESRD patients undergoing regular hemodialysis, XSPI may represent both the wave-related component of the arterial pressure and the excess work exerted by left ventricle during a cardiac cycle. The present study clearly demonstrated that the prognostic value of XSPI was superior to those of conventional arterial stiffness and wave reflection parameters. Only XSPI consistently demonstrated a significant and incremental prognostic value for long-term all-cause and cardiovascular mortalities over a base risk prediction model. The prognostic value of XSPI remained

significant in a subgroup of patients who had attained dry weight and normotension during regular hemodialysis when conventional arterial stiffness and wave reflection parameters might have lost their predictive power.

High BP is a major determinant of deranged cardiovascular structure and function and an independent predictor of cardiovascular risk in the uremic patients.<sup>26</sup> It is conceivable that hemodialysis patients with normal BP had a relatively favorable prognosis.<sup>12,37</sup> In ESRD patients who had already attained normotension by hemodialysis, reduced LVEF but not arterial function parameters was an independent predictor for both all-cause and cardiovascular mortalities.<sup>12</sup> We had reasoned that the arterial factors might have been improved substantially by BP reduction associated with the attainment of patients' ideal dry weight.<sup>12</sup> The present study expanded the previous study population, prolonged the follow-up period, and employed the reservoir-wave theory to reanalyze the arterial function. We found that XSPI may play an important role in the long-term outcomes in patients with ESRD, particularly in the normotensive hemodialysis patients. These novel findings may have important clinical implications for the management of hemodialysis patients.

## Risk Stratification for Uremic Patients

In comparison with the risk prediction of subjects with chronic kidney disease,<sup>38,39</sup> there have been few studies systematically investigating the prognostic factors and proposing the risk prediction models for uremic patients. It may be due to the poor prognosis of ESRD patients. However, with the improvement of facilities and techniques for dialysis, the prognosis of ESRD patients has been improved substantially.<sup>2,3</sup> Currently, the mortality risk of this growing population is primarily estimated with their comorbidities, such as the USRDS (US Renal Data System) index<sup>40</sup> and Taiwan index.<sup>41</sup> Because cardiovascular events are the major cause of morbidity and mortality for ESRD patients, it is reasonable that cardiovascular functional parameters should carry important prognostic values beyond the comorbidities.

## Conventional Cardiovascular Functional Parameters

Reduced LVEF has been associated with adverse cardiovascular events in ESRD patients.<sup>42</sup> In agreement with previous studies,<sup>12,43</sup> we also demonstrated that a reduced LVEF was an independent predictor for both all-cause and cardiovascular mortalities in hemodialysis patients.<sup>12</sup>

In ESRD patients with suboptimal volume status, conventional arterial functional parameters such as arterial stiffness<sup>6</sup>

**Table 5.** The Net Reclassification Improvement of the Cardiovascular Parameters When Added to the Base Risk Prediction Cox Model

	Event NRI	No Event NRI	Overall NRI	Upper CI	Lower CI	P Value
All-cause mortality						
PWV	0.0282	0.0350	0.0632	0.1381	−0.0118	0.0985
Pf	0.0426	0.0588	0.1014	0.1783	0.0244	0.0098
LVEF	0.0421	0.0909	0.1330	0.2308	0.0352	0.0077
XSPI	0.1053	0.0496	0.1549	0.2486	0.0611	0.0012
Average oscillatory work/average total work*	0.0645	0.0241	0.0886	0.1743	0.0029	0.0427
Cardiovascular mortality						
PWV	0.0423	0.0282	0.0704	0.1509	−0.0100	0.0863
Pf	−0.0282	0.0423	0.0141	0.0946	−0.0664	0.7316
LVEF	0.0432	0.0327	0.0759	0.1773	−0.0256	0.1429
XSPI	0.0845	0.0690	0.1535	0.2559	0.0511	0.0033
Average oscillatory work/average total work*	0.0851	0.0918	0.1769	0.3112	0.0427	0.0098

Significance level for *P* value after Bonferroni correction for multiple comparisons=0.01. The subjects were classified by the base risk prediction Cox model incorporating parameters of age, sex, diabetes mellitus, albumin, body mass index, and hemodialysis treatment adequacy into low, middle, and high risk for all-cause mortality (cutoff points 0.19 and 0.78, portions of the study population) and cardiovascular mortality (cutoff points 0.15 and 0.75). CI indicates confidence interval; LVEF, left ventricular ejection fraction; NRI, net reclassification improvement; Pf, forward pressure amplitude; PWV, carotid-femoral pulse wave velocity; XSPI, excess pressure integral.

\*Available in 180 patients.

and wave reflection<sup>8</sup> have been recognized as important prognosticators. However, measures of arterial function are closely related to the volume status of hemodialysis patients,<sup>22</sup> and the predictive values could be attenuated by attaining ideal dry weight or comorbidities.<sup>12,44</sup> Such speculations are partly supported by the findings of the present study; we observed that PWV was an independent predictor of all-cause and cardiovascular mortalities in the whole study population (Table 3) but not in the normotensive subgroup (Table 7).

### Why May XSPI Be Linked to Mortality?

According to the reservoir-wave theory, the arterial pressure waveform is composed of a reservoir pressure and an excess pressure; the latter is the summative result of wave propagation and reflection, and XSPI is simply its integral.<sup>14</sup> Based on the understanding that the arterial system functions as a wave and a reservoir system, left ventricular stroke work is utilized primarily in 2 categories: (1) as a potential energy (indexed by reservoir pressure integral), stored by extending the elastic

**Table 6.** Performance of the Prognostic Models With and Without XSPI

	Model Fit			Model Discrimination	Model Calibration
	Likelihood Ratio Test Statistics		AIC	AUC (95% CI)	P Value of H-LGOF Test
	−2 Log L	P Value*			
All-cause mortality					
Base model <sup>†</sup>	894.5		906.5	0.782 (0.718-0.845)	0.3522
Base model+XSPI <sup>†</sup>	883.5	0.0009	897.5	0.788 (0.725-0.851)	0.3042
Cardiovascular mortality					
Base model <sup>†</sup>	666		678	0.779 (0.709-0.848)	0.0672
Base model+XSPI <sup>†</sup>	654.4	0.0007	668.4	0.790 (0.722-0.858)	0.2627

Base model included age, sex, diabetes mellitus, albumin, body mass index, and hemodialysis treatment adequacy. AIC indicates Akaike Information Criteria; AUC, area under curve from the receiver-operating characteristic curve; CI, confidence interval; H-LGOF, Hosmer-Lemeshow goodness-of-fit test; XSPI, excess pressure integral;  $\chi^2$ , chi-squared statistics for the Hosmer and Lemeshow goodness-of-fit test. −2 Log L=−2 log likelihood estimation.

\*Likelihood ratio test was used to compare the goodness of fit of the base model with or without the addition of XSPI.

<sup>†</sup>P-value of prediction model <0.0001.



**Table 7.** Standardized Hazard Ratios for Predicting All-Cause and Cardiovascular Mortality in Multivariable Cox Models in the 145 Hemodialysis Patients<sup>12</sup> Who Had Attained Normotension Without Antihypertensive Medications (n=145)

	All-Cause Mortality					Cardiovascular Mortality				
	Hazard Ratio, Per SD	95% CI		$\chi^2$	P Value	Hazard Ratio, Per SD	95% CI		$\chi^2$	P Value
LVEF	0.84	0.62	1.12	1.4157	0.2341	0.81	0.59	1.12	1.5738	0.2097
PWV	1.02	0.77	1.33	0.0109	0.9167	1.23	0.95	1.59	2.3652	0.1241
Pf	1.24	0.91	1.68	1.9087	0.1671	1.57	1.14	2.16	7.6431	0.0057
Pb	0.84	0.61	1.154	1.1662	0.2802	1.07	0.76	1.50	0.1339	0.7144
XSPI	1.29	1.02	1.64	4.3963	0.036	1.44	1.12	1.85	8.2943	0.004
Average oscillatory work/average total work	1.20	0.84	1.70	1.0027	0.3167	1.62	1.09	2.40	5.8055	0.016

Base model included age, sex, diabetes mellitus, albumin, body mass index, and hemodialysis treatment adequacy. Significance level for *P* value after Bonferroni correction for multiple comparisons=0.0083. CI indicates confidence interval; LVEF, left ventricular ejection fraction; Pb, backward wave amplitudes; Pf, forward pressure amplitude; PWV, carotid-femoral pulse wave velocity; SD, standard deviation; XSPI, excess pressure integral.

artery during charging the aortic reservoir in systole and recovered during diastole through the recoil of elastic artery that continues to push blood to vital organs; and (2) as a wave energy (indexed by XSPI), transmitting blood and energy to periphery; this energy is dissipative and unrecoverable.

In the present study, XSPI was significantly independently associated with Pf, a major component of the pressure wave, and the ratio of average oscillatory work/average total work, an index of excess work exerted by the left ventricle that does not contribute any net flow to end organs. Pf had a significant independent and incremental predictive value for all-cause mortality (Tables 3 and 5), indicating the adverse effect of high wave energy on long-term outcomes. On the other hand, the significant and incrementally predictive value for cardiovascular mortality associated with the ratio of average oscillatory work/average total work (Tables 3, 5, and 7) may support the concept that the load of the unnecessary or wasted ventricular work is adversely associated with long-term outcomes. From a biophysical perspective, the average oscillatory work consists of all wave energy and part of the potential energy of the reservoir-wave analysis. Therefore, the energy of wave propagation and reflection should contribute substantially to the excess ventricular workload. Because XSPI apparently outperformed both Pf and the ratio of average oscillatory work/average total work, our results may support the idea that XSPI represents both the wave-related component of the arterial pressure and the excess work exerted by the left ventricle during a cardiac cycle. Moreover, this may also suggest that XSPI is the result of the interaction between the individual mechanical properties of the left ventricle and systemic circulation. PWV is considered a purely mechanical factor of the systemic circulation. Because XSPI outperformed PWV in the present study, this may further suggest that a parameter of pure systemic circulation is not sufficient to describe the cardiovascular risk in ESRD patients undergoing regular hemodialysis.

### Potential Limitations of the Present Study

Interpretation of the findings of this study should be done with the acknowledgment of our study limitations. First, it was a retrospective cohort study, and data on some potential confounding factors, such as natriuretic peptide measures, were not collected, and the aortic flow data required for the calculation of the ratio of average oscillatory work/average total work were not available in all patients. Second, although data on all-cause mortality were robust due to the robustness of the National Death Registry and the confirmation of all survivors by direct telephone contacts, the data on cardiovascular mortality might be less reliable. Third, the study population primarily comprised Taiwanese of Chinese decent, which may restrict the generalizability of our study findings.

### Perspectives

Arterial factors play an important role in the outcomes of ESRD patients, even when normotension and ideal dry weight are achieved. XSPI, easily derived from the reservoir pressure analysis on a noninvasively recorded central pressure waveform, has been proved to be a novel indicator of cardiovascular events and end-organ damage in the hypertensive,<sup>15-17</sup> high-risk,<sup>18</sup> and stable heart failure patients.<sup>19</sup> The present study extended the utility of XSPI in ESRD patients undergoing regular hemodialysis. The significance and incremental value of XSPI for the prediction of long-term mortalities may implicate the potential for risk stratification and clinical management of patients with ESRD. Future research is needed to translate this novel finding into clinical practice guidelines.

### Acknowledgments

We are especially grateful to Prof Kim H. Parker for providing the Matlab function to conduct the reservoir-wave analysis.

## Sources of Funding

This work was supported in part by grants from the Ministry of Science and Technology (MOST 104-2314-B-010-060 and MOST 106-2314-B-010-043), intramural grants from the Taipei Veterans General Hospital (grants V104C-140, V105C-073, and V106C-098), Research and Development contract NO1-AG-1-2118, grants from the Ministry of Health and Welfare (MOHW106-TDU-B-211-113001), and Taipei Veterans General Hospital-National Yang-Ming University Excellent Physician Scientists Cultivation Program, No. 105-Y-B-056.

## Disclosures

None.

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# **Supplemental Material**

**Table S1.** Correlation matrix of the cardiovascular parameters.

	XSPI	Average oscillatory work/average total work	PWV	Pf	Pb	LVEF
XSPI	1	0.50139 <0.0001	0.39431 <0.0001	0.62434 <0.0001	0.51824 <0.0001	-0.11569 0.059
Average oscillatory work/average total work	0.50139 <0.0001	1	0.29986 <0.0001	0.57461 <0.0001	0.36525 <0.0001	-0.17358 0.0198
PWV	0.39431 <0.0001	0.29986 <0.0001	1	0.47145 <0.0001	0.52213 <0.0001	-0.23894 <0.0001
Pf	0.62434 <0.0001	0.57461 <0.0001	0.47145 <0.0001	1	0.72452 <0.0001	-0.0264 0.6693
Pb	0.51824 <0.0001	0.36525 <0.0001	0.52213 <0.0001	0.72452 <0.0001	1	-0.10961 0.0754
LVEF	-0.11569 0.059	-0.17358 0.0198	-0.23894 <0.0001	-0.0264 0.6693	-0.10961 0.0754	1

LVEF = left ventricular ejection fraction; Pb = backward wave amplitudes; Pf = forward pressure amplitude; PWV = pulse wave velocity; XSPI = excess pressure integral.

**Table S2.** Characteristics of the normotensive population.

	All (N=155)	Dead (N=63)	Alive (N=92)	P value
Age, years	55.3±14.8	64.6±12.0	48.9±13.1	<0.001
Men, %	54.2	54.0	54.4	0.963
Diabetes mellitus, %	10.3	19.1	4.4	0.003
Body mass index, kg/m <sup>2</sup>	23.2±3.3	23.5±3.0	23.0±3.5	0.349
Albumin, mmol/L	4.1±0.4	4.0±0.4	4.2±0.3	0.022
Hematocrit, %	30.9±4.3	30.3±3.8	31.3±4.6	0.172
Total cholesterol, mmol/L	188.8±45.2	192.2±44.3	186.5±45.9	0.466
Kt/v, L/min	1.51±0.29	1.46±0.24	1.54±0.32	0.104
Central venous pressure, cmH <sub>2</sub> O	6.2±2.1	5.8±1.8	6.4±2.3	0.053
Brachial SBP, mmHg	112.6±18.2	112.7±18.7	112.4±17.9	0.916
Brachial DBP, mmHg	65.5±11.8	64.9±11.5	65.9±12.1	0.596

Brachial PP, mmHg	47.0±11.1	47.8±13.1	46.5±9.5	0.487
Central SBP, mmHg	102.3±16.7	103.5±17.6	101.4±16.0	0.429
Central PP, mmHg	36.3±9.9	38.2±12.1	35.0±7.8	0.07
Mean BP, mmHg	81.2±13.3	80.9±12.9	81.4±13.6	0.79
Heart rate, bpm	75.0±13.6	75.6±12.9	74.5±14.1	0.622
<i>Conventional parameters</i>				
LVEF, %	59±10	57±12	60±8	0.062
<i>Arterial parameters</i>				
PWV, cm/s	919±350	1075±393	810±270	<0.001
Pf, mmHg	31.1±8.4	32.2±9.7	30.4±7.4	0.211
Pb, mmHg	13.9±4.7	14.5±5.4	13.5±4.0	0.186
<i>Arterial reservoir function</i>				
XSPI, mmHg·s	9.9±4.5	11.4±5.4	8.8±3.4	<0.001
Average oscillatory	0.15±0.06	0.17±0.07	0.14±0.05	0.05

work/average total work

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DBP = diastolic BP; Kt/v = hemodialysis treatment adequacy; LVEF = left ventricular ejection fraction; Pb = backward wave amplitudes; Pf = forward pressure amplitude; PP = pulse pressure; PWV = pulse wave velocity; SBP = systolic BP; XSPI = excess pressure integral.