Serum Cortisol as a Useful Predictor of Cardiac Events in Patients With Chronic Heart Failure
The Impact of Oxidative Stress

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Background—The pathophysiological role of cortisol, which binds to the mineralocorticoid receptor with an affinity equal to that of aldosterone (ALD), may be influenced by oxidative stress in patients with chronic heart failure. We evaluated cardiac event prediction using cortisol levels in chronic heart failure, in comparison with ALD, adrenocorticotropic hormone, and brain natriuretic peptide (BNP), and the impact of oxidative stress.

Methods and Results—We measured the plasma levels of biomarkers such as BNP, ALD, adrenocorticotropic hormone, serum cortisol, and oxidized low-density lipoprotein (oxLDL), a biomarker of oxidative stress, in 319 consecutive symptomatic patients with chronic heart failure, and we followed these patients for a mean period of 33 months. During the follow-up period, 29 patients had cardiac events (death or hospitalization). Plasma levels of BNP, ALD, adrenocorticotropic hormone, oxLDL, and serum cortisol (16.8±1.8 µg/dL versus 12.4±0.3 µg/dL, P=0.01) were significantly higher in patients with cardiac events than in those without cardiac events. On stepwise multivariate analyses, high levels of BNP (P=0.0003), renin (P=0.002), cortisol (P=0.02), and oxLDL (P=0.002) were independent predictors of cardiac events, but ALD and adrenocorticotropic hormone levels were not. In patients with serum cortisol ≥12.5 µg/dL, the hazard ratio of cardiac events in patients with oxLDL ≥12 U/mL was 3.5 compared with that in patients with oxLDL <12 U/mL (P=0.008).

Conclusions—These findings indicate that serum cortisol levels were a complementary and incremental cardiac event risk predictor in combination with BNP in patients with chronic heart failure and that cardiac event prediction based on cortisol levels was influenced by oxidative stress. (Circ Heart Fail. 2009;2:608-615.)

Key Words: cortisol ■ aldosterone ■ BNP ■ oxidative stress ■ cardiac events ■ prognosis ■ heart failure

Suppression of increases in the renin-angiotensin-aldosterone (ALD) system is a cornerstone in the management of patients with chronic heart failure (CHF), and monitoring the renin-angiotensin-aldosterone system activity might be useful for assessing CHF severity and response to therapy.1–6 Higher plasma ALD concentrations were associated with increased mortality and rehospitalization rates.4,5,7 A previous report suggested that mineralocorticoid receptor (MR) antagonist decreased brain natriuretic peptide (BNP) and improved left ventricular remodeling.8 In Randomized Aldactone Evaluation Study and Eplerenone Heart Failure Efficacy and Survival Study, MR antagonist improved survival and lowered hospitalization in patients with severe CHF and post-myocardial infarction.9,10

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MR binds mineralocorticoids and glucocorticoids with equal affinity.11,12 Circulating glucocorticoid concentrations are 100- to 1000-fold higher in plasma compared with those of ALD and thus, in principle, would be expected to preferentially occupy the MR. However, the enzyme 11β-hydroxysteroid dehydrogenase type 2, which converts cortisol to the non-MR–binding metabolite cortisone, allows ALD to selectively bind and activate MR.13–15 MR is expressed in the heart16 and is upregulated in CHF.17,18 However, 11β-hydroxysteroid dehydrogenase type 2 levels in the heart are almost negligible. Therefore, it has been proposed that cardiac MRs are occupied by cortisol rather than by ALD.18–20 However, cortisol usually acts as an MR antagonist in the kidney and the heart.21,22 If an intracellular redox state changes with tissue damage and generation of reactive oxygen species in CHF, cortisol may act as MR agonist like ALD.18–20,23 However, the usefulness of predicting cardiac events based on cortisol levels, which may also bind and activate the MR, remains unclear. Güder et al24 reported that higher serum levels of both cortisol and ALD were indepen-

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dent predictors of increased mortality risk in patients with CHF. However, they did not evaluate BNP, adrenocorticotropin hormone (ACTH), and a biomarker of oxidative stress.

This study evaluated the cardiac events prediction based on serum cortisol levels in patients with CHF in comparison with that based on ALD and ACTH, which stimulates the secretion of ALD and cortisol, and in combination with BNP, which is a well-established prognostic predictor. Furthermore, we assessed the impact of oxidative stress on the prognostic role of cortisol, which has been reported in relation to cortisol-MR complex activation.18–20,23

Methods

Patients

The study population was drawn from 520 consecutive symptomatic patients with CHF admitted to our hospital between 2003 and 2008 for management of CHF. Among these patients, the study population consisted of 319 consecutive patients with CHF under cardiac catheterization for clinical indication several days after the management of CHF. We prospectively followed up these patients for a mean period of 33 months, and cardiac events were defined as cardiac death (including sudden death) or hospitalization for CHF. Patients with acute myocardial infarction, congenital heart disease, renal failure (serum creatinine >2.5 mg/dL), or malignancy were excluded. New York Heart Association functional class was evaluated on the day of cardiac catheterization. Informed consent was obtained from each patient for participation in the study, according to a protocol approved by the institutional Committee on Human Investigation.

Study Protocol

All patients underwent cardiac catheterization. Hemodynamic measurements and blood samples for measuring the plasma levels of neurohumoral factors (ie, BNP, norepinephrine [NE], plasma renin concentration [PRC], angiotensin II and ALD, ACTH, oxidized low-density lipoprotein [oxLDL], and serum levels of cortisol), sodium, creatinine and other laboratory data were collected from a peripheral vein before the procedure after at least 20 minutes of supine bed rest. Blood was centrifuged at 4°C, and then, the plasma was frozen in aliquots and stored at −30°C until assay. The plasma levels of BNP, NE, PRC, angiotensin II, and ALD were measured as previously reported.25 The plasma oxLDL levels were measured by specific immunoradiometric assay using a commercial kit (Kyowa Medex, Tokyo, Japan), as previously reported.25,26 The serum cortisol levels and plasma ACTH levels were measured using a commercial radioimmunoassay kit (SRL, Tokyo, Japan). Left ventriculography was performed using contrast medium or radioisotope after hemodynamic measurements and blood sampling. Oxidative stress was estimated by oxLDL.25 and oxLDL ≥12 U/mL was defined as positive, as previously reported.26 This cutoff level was calculated by receiver operating characteristics analysis to detect cardiac events. The attending physicians were unaware of the neurohumoral data.

Statistical Analysis

All results are expressed as mean±SEM. Categorical variables were presented by frequency counts and percentages, and intergroup comparisons were analyzed by χ² test. Univariate analyses were performed using Student t test. Because BNP, NE, PRC, angiotensin II, ALD, ACTH, and cortisol levels were not normally distributed, differences between the groups were detected by Mann–Whitney U test, with 2-tailed P values <0.05. Variables with nonnormal distribution were transformed logarithmically before linear regression analysis. Associations between serum cortisol levels and measurement variables were examined through Pearson's correlation coefficient and linear regression. Multivariate linear regression analyses were performed to examine the independent correlates of log-transformed cortisol levels, including baseline variables that were associated with cortisol levels at P values <0.10 on univariate analysis. The β-coefficients were standardized regression coefficients. The prediction of cardiac events was tested by Cox proportional hazards regression analysis with categorized variables dichotomized at the cutoff levels. The cutoff level was defined by the maximal point of (sensitivity+specificity) on receiver operating characteristics analysis. Multivariate Cox proportional hazards analyses were performed as stepwise regressions, and the main models were adjusted by variables that were considered traditional risk factors for mortality in CHF and that were associated with cardiac events at P values <0.10 on univariate analysis in this study. Kaplan–Meier analysis was performed on the cumulative rates of cardiac event-free status in patients with CHF divided into 2 groups based on cutoff levels of BNP, NE, PRC, ALD, and cortisol, and differences between the cardiac event-free curves were analyzed by log-rank test. The cardiac event prediction utility of the combination of cortisol and BNP and oxLDL was analyzed by Cox proportional hazards regression analysis. A P value <0.05 was considered significant.

Results

Clinical Characteristics

Patients were divided into 2 groups: with and without cardiac events (Table 1). Twenty-nine patients had cardiac events (17 patients died because of worsening heart failure or sudden death and 12 patients were admitted to hospital for decompensated heart failure) during the mean follow-up period of 33 months. Neurohumoral data such as BNP, NE, PRC, angiotensin II, ALD, ACTH, cortisol, and oxLDL levels were significantly higher in patients with cardiac events than in those without cardiac events.

Univariate and Multivariate Predictors of Cardiac Events

Patients with CHF were divided into 2 groups based on cutoff levels for each variable calculated by receiver operating characteristics analysis to detect cardiac events, and cardiac event prediction was evaluated by Cox proportional regression analysis (Table 2). The cutoff level was determined as 187 pg/mL for BNP, giving a sensitivity of 65.5% and a specificity of 67.2%; 378 pg/mL for NE, giving a sensitivity of 65.5% and a specificity of 66.5%; 54 pg/mL for PRC, giving a sensitivity of 69% and a specificity of 72.8%; 89 pg/mL for ALD, giving a sensitivity of 58.6% and a specificity of 77.7%; and 12.5 pg/dL for cortisol, giving a sensitivity of 82.8% and a specificity of 52.1%. Kaplan–Meier analysis was performed on the cumulative rates of cardiac event-free status in patients with CHF divided into 2 groups based on cutoff levels of BNP, NE, PRC, ALD, and cortisol. Patients with higher plasma BNP, NE, PRC, ALD, and cortisol showed a high risk of cardiac events (Figure 1).

On stepwise multivariate analyses, only high levels of plasma BNP (P=0.0003), PRC (P=0.002), serum cortisol (P=0.02), and oxLDL (P=0.002) were significant independent predictors of cardiac events, but plasma ALD and ACTH levels were not (Table 2). Hazard ratios (HRs) of cardiac events for neurohumoral factors adjusted for age, sex, and body mass index (BMI) were shown in Figure 2.

Cardiac Event Prediction Stratified by the Combination of BNP and Cortisol

Patients were stratified into 4 groups based on cutoff levels of the combination of BNP and cortisol (Figure 3). Compared
Table 1. Clinical and Hemodynamic Characteristics of Patients With CHF

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients (n=319)</th>
<th>Cardiac Events (+) (n=29)</th>
<th>Cardiac Events (-) (n=290)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.8±0.6</td>
<td>64.2±2.7</td>
<td>66.0±0.6</td>
<td>0.42</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>244/75</td>
<td>25/4</td>
<td>219/71</td>
<td>0.29</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.9±0.2</td>
<td>22.2±1.1</td>
<td>23.0±0.2</td>
<td>0.27</td>
</tr>
<tr>
<td>Etiology, IHD</td>
<td>185 (58)</td>
<td>12 (41.4)</td>
<td>173 (59.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>NYHA, II/III/IV</td>
<td>211/74/34</td>
<td>12/6/9</td>
<td>199/66/25</td>
<td>0.0004</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>79.8±1.5</td>
<td>79.1±3.1</td>
<td>79.9±1.6</td>
<td>0.88</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>11.2±0.4</td>
<td>17.3±1.8</td>
<td>10.6±0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>2.81±0.04</td>
<td>2.53±0.13</td>
<td>2.84±0.04</td>
<td>0.03</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>46.7±0.7</td>
<td>38.3±2.2</td>
<td>47.5±0.7</td>
<td>0.0002</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>214.2±15.4 (119)</td>
<td>534.4±105.3 (285)</td>
<td>182.1±11.9 (110.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NE, pg/mL</td>
<td>381.2±12.3 (326)</td>
<td>559.8±60.2 (529)</td>
<td>365.2±11.8 (322)</td>
<td>0.005</td>
</tr>
<tr>
<td>PRC, pg/mL</td>
<td>113.1±15.2 (24.5)</td>
<td>464.4±109.2 (310)</td>
<td>77.6±10.7 (23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Angiotensin II, pg/mL</td>
<td>20.4±2.1 (9)</td>
<td>30.1±8.2 (18.5)</td>
<td>19.5±2.1 (9)</td>
<td>0.01</td>
</tr>
<tr>
<td>ALD, pg/mL</td>
<td>70.8±3.2 (56.7)</td>
<td>117.3±16.9 (98)</td>
<td>66.1±3.0 (55)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Cortisol, µg/dL</td>
<td>12.8±0.3 (12.5)</td>
<td>16.8±1.8 (14.8)</td>
<td>12.4±0.3 (11.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>ACTH, pg/mL</td>
<td>31.9±1.9 (24.7)</td>
<td>36.5±4.7 (32.5)</td>
<td>31.6±2.0 (23.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.9±0.1</td>
<td>12.5±0.4</td>
<td>12.9±0.1</td>
<td>0.27</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.00±0.02</td>
<td>1.15±0.1</td>
<td>0.99±0.02</td>
<td>0.009</td>
</tr>
<tr>
<td>oxLDL, unit/mL</td>
<td>13.7±0.5</td>
<td>17.6±2.0</td>
<td>13.2±0.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Treatments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>129 (40.4)</td>
<td>20 (69)</td>
<td>109 (37.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>134 (42)</td>
<td>21 (72.4)</td>
<td>134 (46.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>254 (79.6)</td>
<td>24 (82.6)</td>
<td>230 (79.3)</td>
<td>0.84</td>
</tr>
<tr>
<td>β-blocker</td>
<td>158 (49.5)</td>
<td>18 (62.1)</td>
<td>140 (48.3)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Data are presented as mean±SE (median) or n (%). IHD indicates ischemic heart disease; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

with patients who had low levels of both BNP and cortisol, patients with high levels of both variables had a 15.5-fold higher cardiac event risk (P=0.0003). Furthermore, in patients with plasma BNP ≥187 pg/mL, the HR of cardiac events in patients with serum cortisol ≥12.5 µg/dL was 3.4 compared with that in patients with serum cortisol <12.5 µg/dL (P=0.04).

Influence of Oxidative Stress
Patients were further stratified into 4 groups based on cutoff levels of the combination of cortisol and oxLDL (Figure 4). Among patients with serum cortisol ≥12.5 µg/dL, none of the patients with oxLDL <12 U/mL showed significant prediction of cardiac events compared with patients with serum cortisol <12.5 µg/dL. However, in patients with serum cortisol ≥12.5 µg/dL, the HR of cardiac events in patients with oxLDL ≥12 U/mL was 3.5 compared with that in patients with oxLDL <12 U/mL (P=0.008).

Univariate and Multivariate Linear Regression Model of Serum Log Cortisol
On univariate analysis, 11 clinical, neurohumoral, and hemodynamic variables were significant predictors of high serum log cortisol (Table 3). On stepwise multivariate analyses, 3 parameters such as plasma levels of NE, ALD, and ACTH were significant independent predictors.

Effect of Spironolactone
Spironolactone was more frequently prescribed for patients with cardiac events than for those without cardiac events (Table 1), probably because patients receiving spironolactone had more severe CHF. The mean dose of spironolactone did not differ significantly between patients with and without cardiac events (26.9±2.4 mg/d versus 25.8±1.6 mg/d, P=0.76). Plasma ALD levels were significantly higher in patients receiving spironolactone than in those not receiving spironolactone (93.8±6.1 pg/mL versus 55.2±2.9 pg/mL, P<0.0001), and serum cortisol levels were slightly higher in patients receiving spironolactone than in those not receiving spironolactone (13.4±0.6 µg/dL versus 12.4±0.4 µg/dL, P=0.18), but the difference was not significant. Furthermore, intake of spironolactone was significantly associated with plasma ALD levels (r=0.315, P<0.0001) but not with cortisol levels (r=0.08, P=0.18). Moreover, spironolactone administration to patients was a significant predictor of
cardiac events on univariate analysis ($P=0.002$) but not on multivariate analysis.

**Discussion**

**MR Activation by Cortisol**

Cortisol usually acts as an MR antagonist in the kidney and the heart.21,22 Funder19,20,23 indicated that if an intracellular redox state changes with tissue damage and generation of reactive oxygen species, cortisol may act as an MR agonist like ALD. In patients with CHF, intracellular nicotinamide adenine dinucleotide phosphate oxidase is activated and generation of reactive oxygen species is increased in cardiomyocytes,27 and then, cortisol may act as an MR agonist under those conditions. In this study, high serum cortisol was an independent predictor of cardiac events. However, there was no significant difference in the prediction of cardiac events between patients with high cortisol and low oxidative stress and those in whom both variables were low ($P=0.13$), and only patients with high levels of both cortisol and oxidative stress showed a significantly higher risk of cardiac events ($P=0.008$; Figure 4). These findings suggested that oxidative stress was required for cortisol to be a cardiac event predictor and might provide one explanation of the phenomenon that oxidative stress activates the cortisol-MR complex as an MR agonist and that serum cortisol levels had a cardiac event prediction value.

Moreover, in this study, there was a close correlation between serum cortisol levels and plasma ACTH levels (Table 3), which are considered a nonspecific indicator of stress, and these levels were higher in patients with cardiac events than in those without cardiac events. Both cortisol and ACTH levels were significant predictors of cardiac events on univariate analysis (Table 2). However, on multivariate analysis, only serum cortisol levels were an independent predictor of cardiac events, but plasma ACTH levels were not (Figure 2), suggesting that cortisol is not only a nonspecific indicator of stress but may also increase the risk of cardiac events by acting as an MR agonist.

**Predictor of Cardiac Events**

In this study, BNP and PRC were significant independent predictors of cardiac events in patients with CHF, consistent with previous reports.3,5,6,28,29 Furthermore, this study indicated that serum cortisol levels were an independent predictor of cardiac events even after adjusting for traditional risk factors, but plasma ALD levels were not (Figure 2), which was not consistent with the findings from a previous study.24 The prognostic importance of BNP, a biomarker of ventricular wall stress,29 has been confirmed by many clinical studies, as previously reported.8,28,30,31 Although patients with CHF with higher ALD levels showed a high risk of cardiac events (Figure 1) and ALD levels were positively associated with cardiac event risk with a HR of 4.08 (95% CI, 1.36 to 12.2) for the highest versus lowest quartile of ALD (data not shown) in this study, the prognostic role of ALD remains controversial because many factors, including therapy for heart failure, influence the plasma levels of that marker. Especially, MR blockers may increase plasma ALD levels,32,33 and actually, plasma ALD levels were significantly higher in patients receiving spironolactone than in those not receiving spironolactone in this study. Therefore, plasma ALD levels may not be appropriate for assessing renin-angiotensin-aldosterone system activity in patients with CHF receiving standard therapy.

In the Randomized Aldactone Evaluation Study and the Eplerenone Heart Failure Efficacy and Survival Study, aldactone...
though MR antagonist reduced mortality and the rate of sudden death in patients with severe CHF and postmyocardial infarction, ALD levels were within the normal range and salt status was unremarkable. Moreover, Nagata et al reported that MR blockade resulted in the attenuation of left ventricular hypertrophy and failure, without an antihypertensive effect, in rats with low-ALD hypertension. Cortisol, which manifests the same affinity for the MR as ALD, has been described as one explanation for the activation of MR in previous reports.

The cause or effect of the prognostic impact of high cortisol remains unknown in this study; however, combined measurements of BNP and cortisol may be useful for monitoring patients with CHF (Figure 3). Further studies are needed to determine whether serial measurements of cortisol provide useful information for the management of patients with CHF.

### Correlation With Serum Cortisol Levels

Higher cortisol levels have been reported in acute heart failure and CHF with cardiac cachexia, but those levels in patients with CHF remain unclear. Certainly, mean serum cortisol levels were almost within the normal range in this study population, but Güder et al suggested that normal circulating cortisol concentrations may be sufficient to occupy cardiac MR. In this study, serum cortisol levels were positively correlated with pulmonary capillary wedge pressure and NE and negatively correlated with left ventricular ejection fraction and cardiac index (Table 3), suggesting that serum cortisol levels may reflect worse hemodynamic parameters and systemic sympathetic nerve activity.

![Figure 1](image-url)  
Figure 1. Kaplan–Meier event-free curves for patients with CHF divided into 2 groups based on cutoff levels of BNP (A), NE (B), PRC (C), ALD (D), and cortisol (E).

![Figure 2](image-url)  
Figure 2. HRs of cardiac events. Estimates were adjusted for age, sex, and body mass index. The square shows the HRs and 95% CIs for cardiac events, with patients stratified according to subgroups prespecified in the statistical analysis plan.
activity in CHF because cortisol is considered a nonspecific indicator of stress.

Furthermore, in this study, serum cortisol levels were correlated with plasma ALD levels (Table 3). The mechanism of cortisol secretion is mainly regulated by ACTH. Alternatively, ACTH is one of the mechanisms involved in ALD secretion, thus there would be a positive correlation between serum cortisol and plasma ALD in this study. Actually, serum ACTH levels were positively correlated with plasma ALD ($r=0.379, P=0.0001$) and serum cortisol ($r=0.597, P=0.0001$) in this study.

Figure 3. A, Kaplan-Meier event-free curves for patients with CHF stratified into 4 groups based on cutoff levels of the combination of BNP and cortisol. B, Usefulness of cardiac event prediction using a combination of plasma brain BNP levels and serum cortisol levels. HR for comparison with the referent (ie, “cortisol low-BNP low”): for “cortisol low-BNP high,” 4.6 ($P=0.05$); for “cortisol high-BNP low,” 4.8 ($P=0.04$); for “cortisol high-BNP high,” 15.5 ($P=0.0003$). Interaction ($\times$) ($P=0.725$).

Figure 4. A, Kaplan-Meier event-free curves for patients with CHF stratified into 4 groups based on cutoff levels of the combination of serum cortisol and plasma oxLDL, a biomarker of oxidative stress. B, Usefulness of cardiac event prediction using a combination of serum cortisol levels and plasma oxLDL. HR for comparison with the referent (ie, “cortisol low-oxLDL low”): for “cortisol low-oxLDL high,” 3.6 ($P=0.25$); for “cortisol high-oxLDL low,” 5.2 ($P=0.13$); for “cortisol high-oxLDL high,” 18.4 ($P=0.004$). Interaction ($\times$) ($P=0.976$).
Table 3. Univariate and Multivariate Predictors of Serum Cortisol Levels in Patients With CHF

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate Correlation Coefficients</th>
<th>P</th>
<th>Multivariate β-Coefficients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>-0.227</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, male = 1</td>
<td>0.197</td>
<td>0.0004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA, III/IV = 1</td>
<td>0.128</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>0.1</td>
<td>0.07</td>
<td></td>
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<tr>
<td>PCWP, mm Hg</td>
<td>0.217</td>
<td>0.0001</td>
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</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>-0.01</td>
<td>0.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>-0.174</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log BNP, pg/mL</td>
<td>0.029</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log norepinephrine, pg/mL</td>
<td>0.151</td>
<td>0.007</td>
<td>0.116</td>
<td>0.02</td>
</tr>
<tr>
<td>Log PRC, pg/mL</td>
<td>0.158</td>
<td>0.005</td>
<td></td>
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</tr>
<tr>
<td>Log angiotensin II, pg/mL</td>
<td>0.169</td>
<td>0.003</td>
<td></td>
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</tr>
<tr>
<td>Log ALD, pg/mL</td>
<td>0.415</td>
<td>&lt;0.0001</td>
<td>0.162</td>
<td>0.004</td>
</tr>
<tr>
<td>Log ACTH, pg/mL</td>
<td>0.597</td>
<td>&lt;0.0001</td>
<td>0.512</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>0.147</td>
<td>0.01</td>
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<tr>
<td>Creatinine, mg/dL</td>
<td>0.031</td>
<td>0.58</td>
<td></td>
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<tr>
<td>oxLDL, unit/mL</td>
<td>0.023</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

β-coefficients indicates standardized regression coefficients; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; LVEF, left ventricular ejection fraction.

Study Limitation

Several limitations should be noted in the interpretation of these results. First, this study was performed as a single-center study analyzing a small number of subjects, and only a small number of cardiac events occurred. Therefore, it might be insufficient to determine independent predictors by multivariate analyses. A larger study is warranted to confirm the prediction of cardiac events based on serum cortisol levels in patients with CHF.

Second, serum cortisol levels show changes throughout the day. Although blood samples for measuring the serum cortisol levels were collected between 9:00 AM and 12:00 PM in all patients in this study, the best time to collect samples for the prediction of cardiac events remains unclear. Further studies are needed to clarify this problem.

Conclusions

In conclusion, serum cortisol levels were a complementary and incremental cardiac event risk predictor in combination with BNP in patients with CHF, and cardiac event prediction based on cortisol levels was influenced by oxidative stress.

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

Our research shows, for the first time, that cardiac event prediction based on cortisol levels is influenced by oxidative stress. Mineralocorticoid receptor (MR) antagonist improved survival and reduced hospitalization in patients with severe chronic heart failure and postmyocardial infarction in the Randomized Aldactone Evaluation Study and Eplerenone Heart Failure Efficacy and Survival Study trials. However, in these trials, plasma aldosterone levels were within the normal range in most patients, raising a question of what the MR antagonist was actually blocking to have such a beneficial effect. Recently, it has been proposed that cardiac MRs are occupied by cortisol rather than by aldosterone because cortisol manifests the same affinity for MR like aldosterone. However, cortisol usually acts as an MR agonist in heart. Funder et al indicated that if the intracellular redox state changes with tissue damage and generation of reactive oxygen species, cortisol may act as an MR agonist like aldosterone. In this study, high serum cortisol levels were an independent predictor of cardiac events. However, there was no significant difference in the prediction of cardiac events between patients with high cortisol and low oxidative stress and those in whom both variables were low, and only patients who had high levels of both cortisol and oxidative stress showed a significantly higher cardiac event risk. In conclusion, the cardiac event prediction value based on cortisol levels was significant only in patients with chronic heart failure with higher levels of oxidative stress, and a clinical outcome that confirmed part of hypothesis derived from the basic experiments by Funder et al might be obtained.
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