Comparison of Active Renin Concentration and Plasma Renin Activity as a Prognostic Predictor in Patients With Heart Failure

Takayoshi Tsutamoto, MD; Hiroshi Sakai, MD; Toshinari Tanaka, MD; Masanori Fujii, MD; Takashi Yamamoto, MD; Atsuyuki Wada, MD; Masato Ohnishi, MD; Minoru Horie, MD

Background Plasma renin activity (PRA) may be limited to angiotensinogen levels, which decrease in patients with heart failure (HF) because of liver congestion. Methods and Results To evaluate whether the plasma active renin concentration (ARC) is a more useful prognostic predictor than PRA, the plasma levels of ARC, PRA, angiotensin II, aldosterone, brain natriuretic peptide (BNP), norepinephrine, and hemodynamic parameters were measured in 214 consecutive HF patients who were already taking angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB). Median follow-up period was 1,197 days. Of the clinical variables, including pulmonary capillary wedge pressure, right atrial pressure, left ventricular ejection fraction, and neurohumoral factors, only high plasma levels of log ARC (p<0.0001) and log BNP (p=0.0009), but not log PRA, were significant independent prognostic predictors. Log ARC/PRA ratio was significantly higher in nonsurvivors than in survivors. Log ARC/PRA significantly correlated with pulmonary capillary wedge pressure (r=0.305, p<0.0001), right atrial pressure (r=0.222, p=0.0011), and log BNP (r=0.242, p=0.0004). Conclusions Plasma ARC is superior to PRA and a high plasma ARC is an independent prognostic predictor in HF patients who are already receiving ACEI or ARB. (Circ J 2007; 71: 915–921) Key Words: Active renin concentration; Angiotensin II; Brain natriuretic peptide; Heart failure; Prognosis

Support of an increase in the renin–angiotensin system (RAS) is a cornerstone in the management of heart failure (HF) patients and monitoring of RAS activity might be useful for assessing HF severity and response to therapy.1-7 Angiotensin-converting enzyme inhibitors (ACEI) leads to an increase in plasma renin activity (PRA) because of a lack of negative feedback.3,8 This increase in PRA may contribute to an increase in the plasma angiotensin II (AngII) level, despite ACEI therapy. In such patients, plasma AngII concentrations may be useful for prognostication.6 Patients who cannot tolerate ACEI should receive angiotensin-receptor blockers (ARB), because either ACEI or ARB is recommended for the management of HF. However, plasma AngII levels are increased after administration of ARB9,10 so the prognostic value of plasma AngII concentrations may be masked during ARB treatment.

A recent study has shown that PRA has an independent prognostic impact, despite ACEI therapy, in outpatients with stable HF;7 however, PRA is determined by radioimmunological measurement of angiotensin I generated from angiotensinogen during in vitro incubation with plasma renin. Therefore, determination is limited to angiotensinogen levels, which may be decreased in HF.11-13 In addition, ARC is thought to be more reproducible between and within laboratories because the coefficients of variations are lower with ARC assays than with PRA assays.14,15 We hypothesized that the plasma ARC level is preferable to PRA for evaluation of HF severity, but it has not been elucidated whether this is the case in comparison with PRA in HF patients who are receiving ACEI or ARB.

The present study was designed to assess whether plasma ARC concentrations provide prognostic information that is additional to that obtained from clinical, hemodynamic and biochemical variables such as brain natriuretic peptide (BNP), PRA, AngII, aldosterone (ALD), and norepinephrine (NE), which are previously recognized as associated with a high mortality in HF patients receiving ACEI or ARB.

Methods

Patients

The study population was drawn from 312 consecutive symptomatic HF patients admitted to hospital between 1998 and 2004 for management of HF, despite a history of standard therapy with ACEI or ARB. Of these 312 patients, the study population consisted of 214 patients with left ventricular dysfunction (left ventricular ejection fraction <45%) who underwent cardiac catheterization several days after management of HF. Patients with acute myocardial infarction, hypertrophic cardiomyopathy, aortic stenosis, congenital heart disease, renal failure (serum creatinine >2.0 mg/dl), or malignancy were excluded. New York Heart Association functional class was evaluated on the day of cardiac catheterization. Informed consent was given by all
patients for participation in the study, according to a protocol approved by the institutional Committee on Human Investigation.

**Study Protocol**

All patients were premedicated with an oral dose of diazepam (5 mg) and right-sided cardiac catheterization was performed with a 7F Swan-Ganz catheter. Hemodynamic measurements and blood sampling from the pulmonary artery were performed after at least 20 min of supine bed rest.

Blood was centrifuged at 4°C, and the plasma was frozen in aliquots and stored at –30°C until assay. The plasma ARC level was measured by a specific and sensitive immunoradiometric assay kit (SRL, Tokyo, Japan) and the intra- and interassay coefficients of variation were 1.4% (n=10) at 74 pg/ml and 3.1% (n=10) at 27 pg/ml, respectively.

PRA was measured by a specific and sensitive radioimmunoassay kit (SRL, Tokyo, Japan) and the intra- and interassay coefficients of variation were 8.2% (n=8) at 2.0 ng·ml⁻¹·h⁻¹ and 7.0% 2.2 ng·ml⁻¹·h⁻¹ (n=8), respectively. The plasma levels of BNP, Aldosterone, RA, CI, and mean blood pressure were measured as previously reported. Blood samples for measurement of serum sodium and creatinine were also collected from the venous side after at least 20 min of supine bed rest.

**Statistical Analysis**

All results are expressed as the mean ± SEM. Categorical data were compared against a chi-square distribution. Univariate analyses were performed using Student’s t-test. Because BNP, PRA and ARC levels were not normally distributed, differences between the groups were detected by Wilcoxon rank-sum test with 2-tailed p-values <0.05, and log BNP, log PRA and log ARC were used in correlations and regression models. The prognostic value of the variables was tested in a Cox proportional hazards regression analysis. The sensitivity and the specificity of ARC and PRA for predicting mortality were determined, and receiver operating characteristics curves were constructed. Kaplan-Meier analysis was performed on the cumulative rates of survival in patients with HF stratified into 2 groups based on cut-off levels of ARC and BNP, and the differences between survival curves were analyzed by log-rank test. A value of p<0.05 was considered significant.

**Results**

**Patient Characteristics (Table 1)**

Patients were divided into 2 groups according to the median value of ARC/PRA: ARC/PRA <10 (group I) and
Active Renin Concentration and Prognosis in HF

ARC/PRA >10 (group II). Thirty-eight patients died during the median follow-up period of 1,197 days. Mortality rate, plasma BNP level, and pulmonary capillary wedge pressure were significantly higher and mean blood pressure significantly lower in group II than in group I. Patients in group II showed a poor prognosis in comparison with group I in Kaplan-Meier survival analysis (Fig 1).

ACEI was used more often in group I than in group II, whereas ARB was used more often in group II than in group I. Neurohumoral data (ie, BNP, NE, ALD, AngII, PRA and ARC) were significantly higher in nonsurvivors than in survivors (Fig 2).

Relation Between Plasma ARC and PRA

There was a significant correlation between the log ARC and log PRA (r=0.910, p<0.0001), with some exceptions. Among 11 patients with a higher ARC, as supposed by the value of PRA for 95% confidence interval of the regression survival analysis, the log plasma renin activity (PRA) and the log plasma active renin concentration (ARC) in patients with chronic heart failure. (○) Survivors (●) non-survivors. Dotted lines show the 95% confidence interval.

Fig 1. Kaplan-Meier survival curves for 2 groups stratified by the median value of active renin concentration (ARC)/plasma renin activity (PRA).

Fig 2. Comparisons of brain natriuretic peptide (BNP), plasma renin activity (PRA), plasma active renin concentration (ARC), and the ratio of ARC/PRA between survivors and non-survivors. The box defines the interquartile range with the median indicated by the crossbar. Median values are shown before log transformation.

Fig 3. Relationship between the log plasma renin activity (PRA) and the log plasma active renin concentration (ARC) in patients with chronic heart failure. (○) Survivors (●) non-survivors. Dotted lines show the 95% confidence interval.
line (Fig 3), 8 patients (73%) were nonsurvivors. The log ARC/PRA ratio was significantly higher in nonsurvivors than in survivors (Fig 2). The log ARC/PRA significantly correlated with pulmonary capillary wedge pressure (r=0.305, p<0.0001), right atrial pressure (r=0.222, p=0.0011), and log BNP (r=0.242, p=0.0004).

**Univariate and Multivariate Predictors of Mortality**

In the stepwise multivariate analyses, only high levels of plasma log ARC (p<0.0001) and log BNP (p=0.0009), but not log PRA, were significant independent predictors (Table 2). Receiver operating characteristics analysis to detect prognosis is shown in Fig 4. The curves showed a slightly greater area under the curve for plasma ARC than for PRA. The cut-off level was determined as 78 pg/ml for ARC and 15 ng·ml⁻¹·h⁻¹ for PRA, giving a sensitivity of 76% and specificity of 71% for ARC, and a sensitivity of 55% and specificity of 72% for PRA. The cut-off level was determined as 93 pg/ml for BNP, giving a sensitivity of 81% and specificity of 54%.

**Kaplan-Meier Lifetime Analysis**

Kaplan-Meier analysis was performed on the cumulative rates of survival in patients with HF stratified into 2 groups based on cut-off levels of ARC and BNP, and patients with high plasma ARC and BNP had poor prognosis (Fig 5). The patients were stratified into 4 groups based on cut-off levels of ARC and BNP (Fig 6). The hazard ratio of patients with plasma BNP >93 pg/ml and ARC >78 pg/ml was 5.5 (95% confidence interval, 2.24–13.52) compared with those with plasma BNP >93 pg/ml and ARC <78 pg/ml for cardiac death (p=0.0002).

**Univariate and Multivariate Linear Model of Plasma Log ARC (Table 3)**

In the univariate analyses, 12 clinical, neurohumoral and hemodynamic variables were significant predictors of high plasma log ARC. In the stepwise multivariate analyses, 7

---

**Table 2** Univariate and Multivariate Predictors of Mortality in 214 Patients With Heart Failure

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate p value</th>
<th>Multivariate p value</th>
<th>chi-square</th>
<th>chi-square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.553</td>
<td>0.216</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male=1, female=0)</td>
<td>0.468</td>
<td>0.493</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI (yes=1, no=0)</td>
<td>0.012</td>
<td>0.912</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class (III/IV=1, I/II=0)</td>
<td>18.394</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic etiology (yes=1, no=0)</td>
<td>19.14</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>1.52</td>
<td>0.217</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum sodium</td>
<td>9.681</td>
<td>0.0019</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log BNP (pg/ml)</td>
<td>20.86</td>
<td>&lt;0.0001</td>
<td>10.997</td>
<td>0.0009</td>
</tr>
<tr>
<td>Log PRA (ng·ml⁻¹·h⁻¹)</td>
<td>13.806</td>
<td>0.0002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log ARC (pg/ml)</td>
<td>30.943</td>
<td>&lt;0.0001</td>
<td>15.473</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Angiotensin II (pg/ml)</td>
<td>13.534</td>
<td>0.0002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone (pg/ml)</td>
<td>8.83</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>26.345</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA (mmHg)</td>
<td>7.489</td>
<td>0.0062</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI (ml·min⁻¹·m⁻²)</td>
<td>2.678</td>
<td>0.101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>12.189</td>
<td>0.0005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>18.742</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>14.879</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
Fig. 5. Kaplan-Meier survival curves for heart failure patients already receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers stratified into 2 groups based on cut-off levels of plasma active renin concentration (ARC) and brain natriuretic peptide (BNP).

Fig. 6. Kaplan-Meier survival curves for heart failure patients already receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers stratified into 4 groups based on cut-off levels of plasma active renin concentration (ARC) and brain natriuretic peptide (BNP).

Table 3 Univariate and Multivariate Linear Model of Plasma Log ARC

<table>
<thead>
<tr>
<th></th>
<th>Univariate correlation coefficient</th>
<th>p value</th>
<th>Multivariate coefficient (SE)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>−0.322</td>
<td>&lt;0.0001</td>
<td>−0.015 (0.003)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (male=1, female=0)</td>
<td>0.085</td>
<td>0.215</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class (III/IV=1, I/II=0)</td>
<td>0.251</td>
<td>0.0002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum sodium</td>
<td>−0.494</td>
<td>&lt;0.0001</td>
<td>−0.058 (0.009)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log BNP (pg/ml)</td>
<td>0.184</td>
<td>0.069</td>
<td>−0.183 (0.086)</td>
<td>0.034</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>0.428</td>
<td>&lt;0.0001</td>
<td>0.001 (0.0002)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>−0.625</td>
<td>&lt;0.0001</td>
<td>−0.019 (0.002)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CI (ml·min⁻¹·m⁻²)</td>
<td>−0.185</td>
<td>0.0065</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>0.270</td>
<td>&lt;0.0001</td>
<td>0.017 (0.005)</td>
<td>0.0019</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>−0.432</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretics (yes=1, no=0)</td>
<td>0.398</td>
<td>&lt;0.0001</td>
<td>0.299 (0.074)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACEI (yes=1, no=0)</td>
<td>−0.128</td>
<td>0.0625</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker (yes=1, no=0)</td>
<td>0.076</td>
<td>0.269</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
parameters such as age, serum sodium level, mean blood pressure, pulmonary capillary wedge pressure, plasma levels of NE and BNP and the use of loop diuretics were significant independent predictors.

Discussion

The prognosis of HF patients remains poor despite treatment with ACEI or ARB. This study shows, for the first time, that plasma ARC is superior to PRA in predicting survival and that a high plasma ARC is associated with higher mortality despite ACEI or ARB therapy in patients with HF. High ARC, the upper stream of the RAS, reflects the resetting of this system — the most important determinant of disease progression. And this may explain why, despite ACEI or ARB therapy, many patients continue to show HF symptoms and poor outcome. Moreover, patients with high ARC, despite ACEI or ARB therapy, had lower mean blood pressure and higher plasma NE, suggesting that hypotension and baroreflex may play a role in the rebound of ARC, probably as a compensatory mechanism. In addition, patients with high ARC have a greater use of loop diuretics, lower serum sodium and higher pulmonary capillary wedge pressure, also suggesting that these patients are in a more severe stage.

Few data are available for the relative, independent contributions of each individual neurohumoral factors to predicting outcome in HF by direct comparison in the same population. In the present study, plasma levels of BNP and ARC were independent prognostic predictors in 214 HF patients, despite therapy with ACEI (77%), ARB (25%), ß-blockers (64%) and spironolactone (44%). Our findings are consistent with the recent finding from the Val-HeFT trial that PRA and plasma BNP at baseline have an independent prognostic impact despite therapy with ACEI (93%), ß-blockers (35%) and spironolactone (5%) in approximately 4,000 stable outpatients with systolic left ventricular dysfunction.

In the present study, we measured plasma ARC for comparison with PRA in patients who were hospitalized for management of HF caused by systolic left ventricular dysfunction. The ratio of ARC/PRA was significantly higher in nonsurvivors than in survivors (Fig 2) and among 11 patients with a higher ARC, as supposed by the value of PRA, 8 patients (73%) died (Fig 3), suggesting (1) that plasma angiotensinogen levels were decreased and (2) the usefulness of the measurement of ARC in patients who are hospitalized for HF.

Active renin, produced and secreted by the myoepithelial cells of the glomerular afferent arteriole, contributes to angiotensin generation in blood and tissue sites. Local RAS in the heart is often invoked to explain the beneficial effects of ACEI or ARB therapy. Most of the components of RAS are generated in the heart, but renin in the heart is mainly derived from the kidney. It is now generally agreed that the renin found in most tissues is taken up from circulation and is of renal origin. Therefore, the plasma level of ARC, which is well correlated with renin in cardiac tissue, may play an important role in the local synthesis of angiotensin in human heart, especially in HF patients, because cardiac chymase, which is insensitive to ACEI, increases in HF and promotes cardiac remodeling. Renin/prorenin receptors have been recently identified in the human heart and cardiac renin/prorenin mainly derived from the kidney may contribute to the development of cardiac fibrosis and cardiac damage with or without AngII formation. Although we did not measure prorenin in the present study, high plasma levels of renin/prorenin may have had a causal impact on the progression of congestive HF.

The prognostic importance of BNP, a biomarker of ventricular wall stress, has been confirmed by many clinical studies, including our findings. However, the prognostic role of the parameters of RAS such as renin, AngII and ALD remain controversial because many factors, including therapy for HF, influence the plasma levels of these markers. Plasma AngII concentrations have been reported as useful for predicting prognosis, despite ACEI therapy, but in the present study it was not a prognostic predictor probably because of increased AngII after ARB therapy. Anti-ALD drugs may also increase plasma ALD levels.

Therefore, the AngII and ALD levels may not be appropriate for assessing RAS activity in HF patients receiving standard therapy. The cause or effect of the prognostic impact of high ARC remains unknown in the present study; combined measurements of BNP and ARC may be useful for monitoring HF patients (Fig 6). However, further studies are required to assess whether the use of BNP and ARC to guide management improves the outcomes for HF patients.

Study Limitations

We did not measure the plasma angiotensinogen level and there were a small number of deaths in this study. However, hemodynamic measurements were performed and the patients were followed for a long-term period. The impact of ACEI or ARB on PRA is controversial in HF. Previous studies showed that there was no difference of PRA between ACEI and ARB therapy in patients with HF. In the present study, ACEI were used more often in group I than in group II, whereas ARB were used more often in group II than in group I, suggesting that there may be a different effect of these drugs on ARC (ARC/PRA). However, this study was not randomized control study and further studies are needed to clarify this problem.

A new, orally effective renin inhibitor has been reported as effective as ARB in lowering blood pressure in hypertensive patients and is also useful for the treatment of HF. Taken together with the prognostic value of PRA in stable HF patients in the Val-HeFT study and the plasma ARC levels in the present patients who were hospitalized for worsening HF, renin inhibitor treatment may have a potential therapeutic benefit in the management of HF.

In conclusion, the plasma ARC level is superior to that of PRA for evaluating HF severity, and a high plasma ARC is an independent prognostic predictor in HF patients who are already receiving ACEI or ARB. High ARC, the upper stream of RAS, may reflect stimulation of the RAS system in blood and tissue and the severity of HF, despite therapy with ACEI or ARB.

Acknowledgments

We thank Ms Aoi Murata for her excellent technical assistance. We also thank Mr Daniel Mrquez for his assistance with the manuscript. This study was supported by a Grant-in-Aid for Scientific Research in Japan.

References


Circulation Journal Vol. 71, June 2007