Blood Pressure and Sympathetic Nerve Tone Relation during Hemodialysis may Reflect Cardiovascular Dysfunction

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Abstract

Background The blood pressure response to the rapid removal of fluid during hemodialysis is complex and the pathophysiological mechanisms underlying intradialytic hypotension are not clear and sometimes these mechanisms render dialysis difficult to continue.

Purpose We analyzed the changes in blood pressure and sympathetic nerve tone and attempted to clarify whether the dynamic pattern of this relationship reflects cardiovascular dysfunction.

Methods The dynamic pattern of sympathetic nerve activity throughout dialysis was analyzed by frequency analysis of RR intervals recorded by 24 hours Holter electrocardiography in 64 patients and 3 minutes ECG every 15 minutes during dialysis in 121 stable end-stage renal failure patients who underwent maintenance hemodialysis. Blood pressure and fluid volume removed was measured every 15-30 minutes during dialysis and the average value of the ratio of low to high frequency components (LF/HF) was calculated as an index of sympathetic nerve tone. The relationship between removed fluid volume, systolic blood pressure (Bp) and LF/HF was analyzed.

Results The patients were classified into 3 groups based on the correlation between the LF/HF and Bp as follows: positive (52 cases), inverse (54 cases), and not significant (NS; 61 cases). Eighteen patients who showed multiple arrhythmias, atrial fibrillation and other artifacts or noises were eliminated as they were inadequate for frequency analysis of RR intervals. The positive group was characterized by a hypotension-resistant response with a low LF/HF, whereas the inverse group was characterized by a hypotension-prone response with high LF/HF. These results suggest that cardiovascular dysfunction is responsible for the inverse correlation.

Conclusion Analysis of the relationship between sympathetic nerve tone and Bp is effective in predicting the existing of cardiovascular dysfunction.

Key words: haemodialysis, autonomic nerve tone, blood pressure, cardiovascular dysfunction, dialysis-induced hypotension


Introduction

Dialysis treatment of patients with end-stage renal failure (ESRF) usually involves the removal of 1.5-3 L of body fluid over a 4-h period. This may cause relative hypovolemia and in some cases it results in the lowering of blood pressure, which occasionally leads to major problems in performing dialysis treatment (1-5). Several mechanisms act to preserve blood pressure in this situation. One such mechanism involves appropriate activation of the sympathetic nervous system to induce peripheral vasoconstriction, en-

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Received for publication November 18, 2010; Accepted for publication June 27, 2011
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hance cardiac inotropic and chronotropic actions (1-4). From this perspective, several studies have been reported on the aspects of sympathetic nerve activation and hypovolemia or intradialytic hypotension (1, 4-6). However, contradictory results have been reported concerning the relationship between autonomic disturbance and hypotension (1, 4-9). On the other hand, cardiovascular dysfunction also has been suggested to concern intradialytic hypotension (10-12). However, it is difficult to differentiate by which mechanisms intradialysis hypotension is induced, though it is important to perform dialysis safety.

We analyzed the relationship between sympathetic nerve tone and systolic blood pressure (Bp) during dialysis in patients with ESRF to evaluate whether or not impaired autonomic activity or cardiovascular dysfunction is a factor in this relationship.

### Materials and Methods

#### Study population

One hundred eighty-five patients with ESRF who were receiving regular 4-hour maintenance hemodialysis 3 times a week consented to participate in this study followed by IRB. The patients, 110 men and 75 women, were aged 64.2±11.7 years (mean ± standard deviation). In those patients, 18 cases were eliminated due to the inadequacy to calculate RR interval because of frequent arrhythmias including atrial fibrillation or artifacts. Therefore 167 cases were analyzed.

Underlying diseases were chronic glomerulonephritis (46 cases), diabetic nephropathy (56 cases), polycystic kidney (11 cases), nephrosclerosis (13 cases) pregnancy-related renal disease (5 cases), hereditary disease (6 cases), nephrotic syndrome (2 cases), other diseases (9 cases) and unknown (19 cases). The duration of dialysis was 109.6±98.3 months (mean ± standard deviation).

#### Study protocol

A Holter ECG (Cardy 2, Suzuken kk, Nagoya, Japan) monitor and calorie counter (Welsupport Nipro kk, Osaka, Japan) was set immediately before hemodialysis to record the electrocardiogram (ECG) and physical activity over a 24-hour period in 64 cases, and 3 minutes ECG were recorded by digital ambulatory ECG (HCG801;Omron kk, Kyoto, Japan) in 103 cases, blood pressure and the volume of fluid removed were measured every 30 minutes. Data obtained from these recordings were evaluated by frequency analysis of the ECG RR intervals to calculate low-frequency (0.03-0.14 Hz) and high-frequency components (0.15-0.4 Hz) at 2-minute intervals. The ratio of low-frequency to high-frequency components (LF/HF) was regarded as an index of sympathetic nerve tone or sympatho-vagal balance (13, 14). The average value of the LF/HF recorded every 30 minutes was used to compare Bp during the dialysis period by linear regression analysis. The average LF/HF value was also calculated from the end of dialysis until the patient fell asleep, during sleep, and on the following morning in Holter monitoring cases. Laboratory variables such as, hematocrit, albumin, and electrolyte levels were checked before and/or after hemodialysis. Brain natriuretic peptide (BNP) was measured before hemodialysis on the day of first hemodialysis during the test week. Cardiac ultrasound tomography was performed after hemodialysis within 1 month of the test.

When premature contractions were recorded every 2 minutes, the data for this period were excluded and moving averaged values of three points were used instead of excluded data. The drugs received by patients before examination including antihypertensive drugs were continued during the examination.

#### Statistical analysis

The relationship between LF/HF and blood pressure was analyzed by linear regression analysis then we analyzed 106 patients who showed a significant relationship between LF/HF and Bp. Inter-group differences were analyzed by two-way repeated measure ANOVA, and then paired or unpaired Student’s t test and categorical data were compared by Fisher’s test or the $\chi^2$ test. p values<0.05 were considered statistically significant.

#### Results

The typical examples of analysis are shown in Fig. 1, 2. As seen in the right panel of each figure, removing in fluid volume caused a decreasing in Bp in both cases, however, LF/HF decreased in the case of Fig. 1, resulting in positive LF/HF and Bp relation as seen in the left panel of Fig. 1. On the contrary, LF/HF increased in the case of Fig. 2, resulting in an inverse LF/HF and Bp relation.

Linear regression analysis revealed 3 types of relationship between LF/HF and Bp: positive (52 cases), inverse (54 cases), and not significant (NS; 61 cases).

The background and characteristics of the positive and inverse correlation groups are shown in Table 1, 2. There were no differences in age, duration of dialysis, underlying diseases, drugs used (Table 1), body weight before and after dialysis and fluid volume removed. Serum albumin concentration, level of hematocrit, serum K and Ca were almost within the normal range, except for serum K, after dialysis in inverse group but no differences was seen between the groups (Table 2).

BNP level was higher in the inverse group but the cardiothoracic ratio (CTR) was within the normal range and did not differ between the two groups. Atrial systolic dimension, left ventricular diastolic volume, wall thickness and LVMI was large or thick in both groups but did not differ between the two groups on cardiac ultrasound tomography. Ejection fraction was normal range in both groups. Daily physical activity (amount of energy expended and walk count) was significantly higher in the positive group than that in the inverse group, and the frequency of dialysis-induced hypoten-
Figure 1. Typical example of positive group. Systolic Bp: \( \text{Bp} = 51x + 86.6 \ (r=0.827, p<0.025) \), Blood Volume Reduction and LF/HF relation: \( \text{LF/HF} = 0.21x + 1.37 \ (r=0.849, p<0.025) \), Blood Volume Reduction and Bp relation: \( \text{Bp} = 11.2x + 160 \ (r=0.837, p<0.025) \).

Figure 2. Typical example of inverse group. Blood volume reduction was induced in decreasing of systolic blood pressure and increasing in LF/HF, resulted in inverse relationship between LF/HF and systolic blood pressure as seen in right and left panel, respectively. LF/HF and Bp relation: \( \text{Bp} = -59x + 285 \ (r=0.839, p<0.025) \), Reduction of fluid volume and LF/HF relation: \( \text{LF/HF} = 0.208x + 2.67 \ (r=0.996, p<0.001) \), Reduction of fluid volume and Bp relation: \( \text{Bp} = 1.5x + 164 \ (r=0.852, p<0.001) \).

An elevation, which was defined as decreasing in Bp over 30 mmHg with some symptoms such as, fatigue, dizziness, faintness and the need of some transfusion of physiological saline to continue dialysis within 1 month of examination, was high in the inverse group (Table 2).

The changes in Bp in each group are shown in Fig. 3. There were no significant differences between groups before dialysis; however, Bp decreased gradually in the inverse group.
group, on the contrary, Bp was maintained in the positive group 15 minutes after dialysis and a significant difference was seen after 2.5 hours between the two groups (Fig. 3).

Changes in LF/HF are shown in Fig. 4. A significant increase in LF/HF was noted in the inverse group but it was unchanged or slightly decreased in the positive group through the dialysis (Fig. 4). The two-way repeated measure ANOVA showed a significant difference between the two groups with a significant interaction between time and group (p<0.001). A significant difference was also observed after 30 minutes by simple comparison in each time. The increased level was persistent throughout the next morning and a significant difference was seen between the two groups through dialysis to next day. A transient increase in

Table 1. Background of Each Group

<table>
<thead>
<tr>
<th></th>
<th>Positive group</th>
<th>Inverse group</th>
</tr>
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<tbody>
<tr>
<td>Number of cases (HCG/Holter)</td>
<td>52 (33/19)</td>
<td>54 (36/18)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.8 ± 12.6</td>
<td>65.3 ± 11.6</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>33/19</td>
<td>32/22</td>
</tr>
<tr>
<td>Duration of Dialysis (months)</td>
<td>95.1 ± 91.6</td>
<td>110.9 ± 93.4</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Diabetic Nephropathy</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Nephrosclerosis</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Pregnancy Nephropathy</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Polycystic Kidney</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Hereditary disease</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Drugs admitted
- Ca-Chanel Blocker: 41 vs 40
- Ace I+ARB: 35 vs 36
- Beta Blocker: 13 vs 14
- Anti-Arrhythmics: 7 vs 8
- α-Blocker: 12 vs 19
- Nitrate: 9 vs 15
- Diuretics: 8 vs 4
- Erythropoietin: 44 vs 48

Average value of age and duration was shown as mean ± standard deviation. No difference was seen between the two groups. AceI: Angiotensin 2 converting enzyme inhibitor, ARB: Angiotensin 2 receptor blocker

Table 2. Characteristics of Positive and Inverse Correlated Groups (1)

<table>
<thead>
<tr>
<th></th>
<th>Positive group</th>
<th>Inverse group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight before dialysis (kg)</td>
<td>55.5 ± 11.0</td>
<td>55.0 ± 10.2</td>
</tr>
<tr>
<td>after dialysis (kg)</td>
<td>52.9 ± 10.6</td>
<td>52.4 ± 9.8</td>
</tr>
<tr>
<td>Serum Albumin (mg/dL)</td>
<td>3.85 ± 0.36</td>
<td>3.86 ± 0.12</td>
</tr>
<tr>
<td>Ht before dialysis (%)</td>
<td>32.1 ± 1.7</td>
<td>33.5 ± 1.1</td>
</tr>
<tr>
<td>after dialysis (%)</td>
<td>34.7 ± 3.5</td>
<td>34.6 ± 8.3</td>
</tr>
<tr>
<td>Serum K before dialysis(mEq/L)</td>
<td>4.99 ± 0.47</td>
<td>5.2 ± 0.5</td>
</tr>
<tr>
<td>after dialysis (mEq/L)</td>
<td>3.3 ± 0.2</td>
<td>3.2 ± 0.3</td>
</tr>
<tr>
<td>Serum Ca before dialysis (mEq/L)</td>
<td>9.35 ± 0.8</td>
<td>9.8 ± 0.9</td>
</tr>
<tr>
<td>after dialysis (mEq/L)</td>
<td>9.7 ± 0.7</td>
<td>9.7 ± 0.6</td>
</tr>
<tr>
<td>BNP (μg/mL)</td>
<td>355.7 ± 392.4</td>
<td>792.9 ± 1212.8*</td>
</tr>
<tr>
<td>CTR(%)</td>
<td>47.1 ± 14.2</td>
<td>47.4 ± 15.0</td>
</tr>
<tr>
<td>LAD s</td>
<td>33.3 ± 7.2</td>
<td>38.5 ± 4.8</td>
</tr>
<tr>
<td>LVD d</td>
<td>53.2 ± 0.2</td>
<td>51.5 ± 3.8</td>
</tr>
<tr>
<td>PWTd</td>
<td>11.0 ± 1.8</td>
<td>10.9 ± 1.9</td>
</tr>
<tr>
<td>IVTd</td>
<td>11.9 ± 2.0</td>
<td>11.8 ± 2.8</td>
</tr>
<tr>
<td>EF(%)</td>
<td>70.3 ± 7.8</td>
<td>68.0 ± 9.0</td>
</tr>
<tr>
<td>LVMI</td>
<td>193.9 ± 63.9</td>
<td>190.6 ± 72.0</td>
</tr>
<tr>
<td>Daily Walk Count</td>
<td>5484 ± 3355</td>
<td>3627 ± 2539 *</td>
</tr>
<tr>
<td>Frequency of hypotension</td>
<td>0.28 ± 0.56</td>
<td>0.89 ± 1.24 *</td>
</tr>
</tbody>
</table>

*: p < 0.05, difference between positive and inverse group

Average values were shown as mean ± standard deviation. BNP: brain natriuretic peptide, CTR: Cardiotoracic ratio, LADs: Systolic left atrial dimension, LVDd: Diastolic left ventricular dimension, EF (%): Ejection fraction, LVMI: left ventricular mass index, Frequency of hypotension: frequency of dialysis-induced hypotension during the month the test was performed
**Figure 3.** Changes in systolic blood pressure during dialysis in each group. Systolic blood pressure was scarcely changed in the positive group, on the contrary, it decreased gradually in the inverse group, resulting in significant lowering from 150 min after dialysis.

**Figure 4.** Changes in LF/HF during dialysis in each group. No differences were seen between the positive and inverse group before dialysis. However, LF/HF in the inverse group increased significantly during dialysis, on the contrary, LF/HF was unchanged or slightly decreased in the positive group, resulting in a significant difference between the groups with a significant interaction between time and group (p<0.001). This increased LF/HF in the inverse group continued until the next morning (not shown in the figure).
the other hand, Rubinger et al (4) and others (10, 11) have emphasized that the dysfunction of autonomic nerve is the main mechanism of dialysis-induced hypotension. On the other hand, there appears to be abnormal large imbalance between the volumes of fluid removed and plasma refilled, which mainly affects the serum albumin concentration. Second, autonomic nerve function, which is regulating the cardiovascular system to maintain adequate blood pressure is impaired. Finally, cardiovascular function could not act appropriately in spite of normal autonomic nerve stimulation.

In the present study, we did not find any patients with abnormally low serum albumin levels and there were no intergroup differences in the serum albumin level. Levels of hematocrit, serum K and Ca before dialysis were also not different between the positive and inverse groups. These data suggest that refilling did not differ between the groups and may not account for the difference in the relationship between sympathetic nerve tone and blood pressure.

In such a condition, the other main compensatory mechanism would be the interaction between sympathetic nerve tone and cardiovascular functions. Many researchers have undertaken studies to determine which mechanism is concerned in hemodialysis-induced hypotension, however, the results are conflicting. Dysfunction of the autonomic nervous system has been observed in many patients undergoing dialysis (1, 4, 8, 9) Pelosi et al (1) and Barnas et al (15) have emphasized that the dysfunction of autonomic nerve is the main mechanism of dialysis-induced hypotension. On the other hand, Rubinger et al (4) and others (10, 11) have emphasized cardiac dysfunction and further, Cavalcanti et al (12) have emphasized the roles of both cardiac and vascular function in the induction of hemodialytic hypotension.

In those reports, hemodialysis-induced hypotensive patients were analyzed as a whole although several different conditions may be included and the characteristics of the pathophysiological condition might be masked. We first found that there are two or three kinds of characteristic relationships between Bp and LF/HF during hemodialysis in randomly selected dialysis patients in which the relationship between Bp and LF/HF was positive, inverse, and NS, assuming that this different relationship may reflect the interaction between autonomic nerves and cardiovascular function.

Detection and evaluation of the severity of autonomic nerve dysfunction is difficult and requires complex techniques with expensive instruments, however, we assumed that if autonomic nerve dysfunction may exist, any significant relationship between Bp and LF/HF is not seen, that is, a part of the NS group may include autonomic nerve dysfunction and the positive or inverse group may maintain normal autonomic nerve function.

Under such a conception, we assumed two conflicting possible mechanisms. First, the inverse group has normal autonomic nerve function with normal cardiac function, because baroreflex is the main mechanism to regulate Bp. When Bp is reduced, baroreflex of carotid pressure receptor stimulates sympathetic nerve tone and may result in an inverse relation. On the other hand, there appears to be abnormal autonomic nerve function with normal cardiac function in the positive group, because of in spite of reduce in Bp, sympathetic nerve tone was never excited.
The second explanation is that the positive group may have normal cardiovascular function with normal autonomic nerve function and the negative group may have normal autonomic nerve function with cardiovascular dysfunction. In this conception, baroreflex function acts normally, that is, a transient increase in sympathetic nerve tone by a decrease in Bp will occur to regulate Bp at an adequate level, however, sympathetic nerve tone return to a new lower basic level (16), resulting in the positive relationship. If sympathetic nerve tone is measured instantaneously, this may be shown more directly, however, in the present study we measured the average value of sympathetic nerve tone and Bp every 15 minutes, when Bp could not be maintained at adequate level, in spite of sympathetic nerve stimulated, a further increase in sympathetic nerve tone was required to maintained the Bp, resulting in the inverse relation.

We expect that the second explanation is more reasonable based on the following reasons:

First, the ESRF patients showed inappropriately enhanced sympathetic nerve tone by retention of NaCl, excess water and uremic substances (17, 18), and improving such a condition after dialysis resulted in decreasing in LF/HF in the end of dialysis.

Second, our data suggested that the possibility to cardiac failure in the inverse group, such as increased serum BNP level and lower daily physical activity with increased sympathetic nerve tone, similar condition as that defined in the guideline for heart failure in general population by the American Heart Association (AHA) (19).

Third, hemodialysis-induced hypotension was seen more frequently in the inverse group and some papers also pointed out the participant of cardiac dysfunction in intradialysis hypotension (11, 20). Although there was no direct evidence, those results strongly suggest the existence of cardiovascular dysfunction in the inverse group.

Recently, some studies have stressed that the pathophysiological behavior of autonomic nerve as evaluated by LF/HF response in dialysis showed a different pattern in same selected cases. Rubinger et al reported that LF/HF is significantly decreased during dialysis especially in unstable women compared to men (4) and Giordano et al pointed out that LF/HF increased during dialysis period in unselected patients (21). Further, Tong and Hou demonstrated that LF/HF was significantly reduced during dialysis in patients without cardiovascular disease and diabetes mellitus who may have no autonomic nerve dysfunction (22).

Those results suggest the importance of differentiation the patients with impaired autonomic nerve function from cardiovascular dysfunction or the categorization of the patients who showed various hemodynamic responses in hemodialysis in order to correctly analyze the mechanism of intradialysis hypotension (23).

Concerning the clinical significance of these results, we expect that this analysis may contribute to the determination of the existence of cardiac failure. Many patients treated by dialysis may have some cardiac disorder, such as left ventricular hypertrophy, coronary artery disease, and valvular disorder with calcification, which means that those patients suffer from heart failure at least stage A or B according to AHA guideline (19) or that they have substrate to induce heart failure. However, it is difficult to differentiate symptomatic heart failure of stages C and D from renal disease because of the main symptom of heart failure is induced by over retention of fluid and this condition are seen in dialysis patients every day. Exercise tolerance test or other stress tests are applied in the general population to determine the heart failure, however, in dialysis patients difficult to perform. We assumed that acute removal of fluid in a short period at dialysis will be regarded as a kind of stress test for evaluating cardiac reserve and the results suggest that this kind of analysis may be one type of method to express cardiac dysfunction. The early recognition of those patients relative to symptoms or asymptomatic will contribute to the protection from further progress in cardiac injury in hemodialysis patients.

Finally, we suspect that there were some patients with autonomic nerve dysfunction in the NS group, though we have no direct evidences to substantiate this suspicion.

The drugs used such as, renin-angiotensin system and vasopressin blockades, might be involved in the maintenance of blood pressure. We did not evaluate this possibility, but we noted that ACE inhibitors and angiotensin-2 receptor blockers were used by more than 50% of the patients in both groups and this did not affect the results.

Further, the complication of diabetes mellitus did not affect the results.

We conclude that analysis of the relationship between sympathetic nerve tone and blood pressure may useful as a conventional method to predict the occurrence and possible mechanism of intradialysis hypotension or cardiovascular dysfunction.

The authors state that they have no Conflict of Interest (COI).

References