Utility of Exercise-Induced Zero TBI Sign in Patients on Maintenance Hemodialysis

Kazuo Tsuyuki, CVT, PhD,1 Kenji Kohno, PhD,1 Kunio Ebine, MD, PhD,2 Susumu Tamura, MD, PhD,2 Yasuhiro Ohzeki, MD, PhD,2 Toshifumi Murase, MD,2 Takehiro Ohara, MD, PhD,3 Yujin Kunugi, MD,3 Fumihiko Iida, MT,4 Yoshie Mochizuki, MT,4 Mutsumi Sorimachi, CE, BS,1,5 and Shinichi Watanabe, PhD5

It is uncertain whether exercise-induced zero toe brachial index sign (e-ZETS) is beneficial to prevent advanced perfusion disturbance in maintenance hemodialysis (HD) patients. In HD patients, we compared the clinical findings and prognoses among 22 toes in a resting zero toe brachial index sign (r-ZETS) group, 22 toes in an e-ZETS group, and 63 toes in a non-e-ZETS group. The hemodynamics of the lower extremities in the e-ZETS group is intermediate between the r-ZETS and non-e-ZETS groups. As the result of a 36-month follow-up observation, the r-ZETS avoidance rate was significantly lower in the e-ZETS group (63.6%; P < 0.001) than the non-e-ZETS group (98.4%), showing that it was difficult to avoid advanced perfusion disturbance. The e-ZETS in HD patients may appear before r-ZETS, being beneficial as a predictor for advanced perfusion disturbance. (This is a translation of J Jpn Coll Angiol 2015; 55: 125–129.)

Keyword: peripheral arterial disease, critical limb ischemia, hemodialysis, toe brachial pressure index, exercise

Introduction

The great toe in humans is particularly important in daily life, playing a central role in maintaining the standing posture and producing a driving force in walking. However, patients on maintenance hemodialysis (HD patients) sometimes undergo great toe amputation due to critical limb ischemia (CLI), resulting in a marked decrease in the activity of daily life.1 CLI is often treated by revascularization, when revascularization is not indicated, perfusion disorders should be diagnosed as early as possible, and efforts should be made to prevent CLI. Since CLI is closely associated with a poor prognosis, even earlier diagnosis is required.

As a diagnostic method for perfusion disorders at the toe level, the ratio of the toe to brachial blood pressure (toe brachial pressure index: TBI) is widely used. Matsui et al.2) called the state not allowing TBI measurement “the zero TBI sign,” and reported that this sign is a good parameter indicating severe perfusion disorders of the toe. This zero TBI sign (resting zero TBI sign: r-ZETS) represents a state in which the toe pressure is below 40 mmHg as the measurement threshold of automatic devices for blood pressure measurement. Findings such as ischemic resting pain, ulceration, or gangrene in addition to such a hemodynamic state lead to CLI. Therefore, r-ZETS is an important factor for the diagnosis of CLI, and measurement for its detection is indispensable.

However, in terms of early diagnosis and treatment, measurement for r-ZETS detection is not performed at an appropriate timing. In daily clinical practice, regular TBI measurements are important for the early diagnosis of “the condition as the gateway to severe perfusion disorders including CLI.” However, there is no clear TBI cut-off value indicating this condition.

In HD patients, the complication rate of severe perfusion disorders is high, and CLI sometimes suddenly develops in the absence of intermittent claudication. Therefore, it is necessary to detect objective signs indicating the gateway to severe perfusion disorders including CLI and take active preventive measures. We speculated that the exercise-induced zero TBI sign (e-ZETS) can
Exercise TBI measurement
On a non-HD day, immediately after 1-minute walking using a treadmill (Series, 2000, Marquette Electronics) at a speed of 2.4 km/h with a slope of 12%, the TBI was measured using a manual mode in the supine position. For this measurement, pressure was applied to the cuff around the toe within 15 seconds after the walking, and measurement was performed at 2-minute intervals for 10 minutes. However, in terms of safety, the walking speed was reduced to 2.0 km/h in patients aged ≥70 years or showing decreased left ventricular function or decreased walking ability.

During the exercise TBI measurement, 12-lead ECG records were monitored using a cardiac assessment system for exercise testing (CASE 8000, Marquette Electronics). Walking was discontinued when one of the following symptoms appeared: 1) horizontal or downsloping ST depression of 0.1 mV compared with the resting ST at 80 m/sec after the J point; 2) abnormal blood pressure responses (systolic pressure ≥250 mmHg, diastolic pressure ≥120 mmHg); 3) dangerous or potentially dangerous arrhythmias; 4) the maximum heart rate obtained using the equation “220 – age”; 5) difficulty in walking due to lower limb pain, and 6) symptoms of the cardiopulmonary or neurological system.

Definition of e-ZETS
When all the following criteria were fulfilled, the e-ZETS was considered to be present: 1) Measurement was performed with an automatic device for blood pressure and
PVR using the oscillometric method; 2) The resting TBI could be measured; 3) The PVR of the toe became flat immediately after walking; 4) The PVR of the toe that once became flat after walking gradually reappeared with the time course (Fig. 1).

**Outcome survey**
The 85 toes examined by exercise TBI measurement were classified into 22 with and 63 without e-ZETS, and outcomes were prospectively observed. The observation period was 36 months, and the endpoint was the appearance of r-ZETS.

**Statistical analysis**
Each factor was expressed as the mean value ± SD. Between two independent groups, differences in the mean value were analyzed using the unpaired t-test, and the ratio was analyzed using the χ² test. Among multiple groups, differences in the mean value were analyzed using one-way analysis of variance, and the ratio was analyzed using the χ² test and r × k contingency table (Pearson type), but when 0 is included in N (sample number), the G test (likelihood ratio test) was used. Outcomes were analyzed using the Kaplan-Meier method and the Logrank test (Stat Mate IV). P < 0.05 was regarded as significant.

**Results**

**Incidence of r-ZETS**
Of the 156 patients, 15 (9.6%) showed r-ZETS (Table 2), consisting of 8 (5.1%) with this sign in the single foot and 7 (4.5%) with this sign in the both feet.

**Incidence of e-ZETS**
Of the 45 patients who underwent exercise TBI measurement, 14 (31.1%) showed e-ZETS (Table 2), consisting of

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**Fig. 1** Exercise-induced zero TBI sign (e-ZETS). Toe pressure disappeared after walking; and reappeared sometime after walking. TBI: toe brachial pressure index

**Table 2** Four kinds of measurements for PAD in HD patients

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Number of patients</th>
<th>Number of positive tests</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI below 0.9</td>
<td>156</td>
<td>32</td>
<td>20.5</td>
</tr>
<tr>
<td>TBI below 0.6</td>
<td>156</td>
<td>74</td>
<td>47.4</td>
</tr>
<tr>
<td>r-ZETS</td>
<td>156</td>
<td>15</td>
<td>9.6</td>
</tr>
<tr>
<td>e-ZETS</td>
<td>45</td>
<td>14</td>
<td>31.1</td>
</tr>
</tbody>
</table>

ABI: ankle-brachial pressure index; TBI: toe brachial pressure index; r-ZETS: resting zero TBI sign; e-ZETS: exercise-induced zero TBI sign; HD: hemodialysis; PAD: peripheral arterial disease
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Clinical findings
Hemodynamics in the lower limbs, symptoms, and skin lesions were compared among the 22 toes showing r-ZETS (r-ZETS group), 22 showing e-ZETS (e-ZETS group), and 63 without e-ZETS (non-e-ZETS group) (Table 3).

The ABI was significantly lower in the r-ZETS and e-ZETS groups than in the non-e-ZETS group, but did not differ between the former two groups. The TBI and toe systolic pressure significantly differed among the three groups (p < 0.001 or p < 0.01). The resting TBI in the e-ZETS group was ≥ 0.6 in 9 toes and < 0.6 in the other 13 toes.

The incidences of intermittent claudication, coldness, and numbness were highest in the r-ZETS group, followed in order by the e-ZETS group and non-e-ZETS group (p < 0.001). The incidence of cyanosis was high in the r-ZETS group (p < 0.01), but the incidence of ischemic resting pain, ulceration, or gangrene did not significantly differ among the groups.

Outcomes in toes showing e-ZETS
As a result of a 36-month follow-up survey, progression to the r-ZETS was observed in 8 (36.4%) of the 22 toes in the e-ZETS group, including 3 (13.6%) with CLI. In the non-e-ZETS group, 1 (1.6%) of the 63 toes showed progression to the r-ZETS. The r-ZETS avoidance rate significantly differed (p <0.001) between the e-ZETS and non-e-ZETS groups (Fig. 2).

Discussion
r-ZETS in HD patients
Okamoto et al.6) reported peripheral arterial disease (PAD) showing an ABI <0.9 in 20.0% of HD patients. In our study, the ABI was <0.9 in 20.5% of the HD patients, which was similar to the percentage reported by Okamoto et al. In our study, the r-ZETS as another parameter for the detection of PAD was observed in 9.6%. These results suggest the presence of severe perfusion disorder (toe pressure <40 mmHg) in about 50% of patients with PAD as a complication of HD.

In the r-ZETS group, cyanosis was present in 27.3% while the incidences of ischemic resting pain, ulceration, or gangrene were low, and gangrene was not observed. Thus, although HD outpatients with the r-ZETS may partly include those with CLI, most of them may have severe perfusion disorder in the pre-CLI stage without lower limb symptoms and tissue defects.

Clinical importance of the e-ZETS
This study confirmed the phenomenon of the appearance of the r-ZETS after 1-minute walking in HD patients, i.e.,

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Comparison of clinical findings among the three stages of zero TBI sign in HD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r-ZETS group</td>
</tr>
<tr>
<td>Number of limbs</td>
<td>22</td>
</tr>
<tr>
<td>ABI</td>
<td>0.99 ± 0.31*</td>
</tr>
<tr>
<td>TBI</td>
<td>Zero sign**</td>
</tr>
<tr>
<td>Toe pressure</td>
<td>Zero sign**</td>
</tr>
<tr>
<td>Intermittent claudication (limbs)</td>
<td>13 (59.1)</td>
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<tr>
<td>Coldness (limbs)</td>
<td>16 (72.7)</td>
</tr>
<tr>
<td>Numbness (limbs)</td>
<td>11 (50.0)</td>
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<tr>
<td>Cyanosis (limbs)</td>
<td>6 (27.3)</td>
</tr>
<tr>
<td>Resting pain (limbs)</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Ulcer (limbs)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Gangrene (limbs)</td>
<td>0</td>
</tr>
</tbody>
</table>

ABI: ankle-brachial pressure index; TBI: toe-brachial pressure index; r-ZETS: resting zero TBI sign; e-ZETS: exercise-induced zero TBI sign; %: p < 0.001; *: p < 0.01 (comparison with Non-e-ZETS group); **: p < 0.001 (comparison with r-ZETS group); HD: hemodialysis

Fig. 2 Comparison of resting zero TBI sign (r-ZETS) free survival between the e-ZETS and non-e-ZETS groups in HD patients. While 1.6% of patients developed r-ZETS for 36 months in the non-e-ZETS group, 36.4% of cases progressed to r-ZETS for 36 months in the e-ZETS group. TBI: toe-brachial pressure index; r-ZETS: resting zero TBI sign; e-ZETS: exercise-induced zero TBI sign; HD: hemodialysis
the existence of the e-ZETS, and also was the first to clarify that its incidence was 31.1%. These results suggest that the r-ZETS as severe perfusion disorder is present in about 10% of HD patients, and toe perfusion disorder that is not manifested by routine TBI measurement is present in about three times as high as this percentage.

The TBI in the non-e-ZETS group was in the normal range, but that in the e-ZETS group (0.58) was slightly lower than the normal range. Ohtake et al.\(^7\) described that the desirable cut-off value for diagnosing PAD using the TBI in HD patients is 0.6, and recommended a cut-off value of 0.25 for detecting CLI. Their study suggests that the e-ZETS is mild perfusion disorder and a hemodynamic state far from CLI. This is supported by the absence of cyanosis, ischemic resting pain, ulceration, or gangrene in the e-ZETS group.

However, progression to the r-ZETS during a 36-month follow-up period was observed only in 1.6% in the non-e-ZETS group but in 36.4% in the e-ZETS group, and the latter included toes showing CLI. Based on these results, the e-ZETS observed in HD patients may be an adequate marker showing that perfusion disorders is mild at present but can progress to severe perfusion disorders in the near future. In daily clinical practice, the prediction of severe perfusion disorders in the future by regular TBI measurements is required, but there is no definite TBI cut-off value as its gateway. In terms of this, the e-ZETS may be the gateway to severe perfusion disorders including CLI because of the high incidence of progression to the r-ZETS within 36 months after the e-ZETS. Therefore, the evaluation of the e-ZETS can be the evaluation of latent perfusion disorders of the toe, and is useful for predicting the development of the r-ZETS and CLI.

**Limitations and problems of this study**
The number of patients in whom outcomes were evaluated was small in this study. In the future, evaluation in additional cases is necessary.

**Conclusion**
The e-ZETS is useful for predicting severe perfusion disorders of the toe.

**Disclosure Statement**
The first author and co-authors have no conflicts of interest.

**References**