Endothelial Dysfunction Is Associated with Cognitive Impairment of Elderly Cardiovascular Disease Patients
A Reactive Hyperemia-Peripheral Arterial Tonometry Study

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Summary
Cognitive impairment is frequently represented in elderly patients with cardiovascular disease (CVD); yet, the mechanism is uncertain. Recent studies have suggested the association between the vascular endothelial dysfunction and cognitive impairment. The aim of this study was to clarify the association between endothelial dysfunction and cognitive impairment in elderly patients with CVD.

A total of 80 elderly patients (>70 years old) with CVD were included. Patients who had already pharmacologically intervened for cognitive impairment were excluded. The endothelial dysfunction was assessed by the reactive hyperemia-peripheral arterial tonometry (RH-PAT). Cognitive impairment was diagnosed by the Mini-Mental state examination.

The RH-PAT index was significantly lower in cognitive impairment (median 1.60 [interquartile range (IQR) 1.34 to 1.89], n = 51) as compared with non-cognitive impairment (median 1.75 [IQR 1.55 to 2.30], n = 29, P = 0.005). By a multivariate analysis, the RH-PAT index was independently associated with cognitive impairment (odds ratio: 0.89; 95% confidence interval: 0.81 to 0.97; per 0.1, P = 0.044). In the receiver-operating characteristic analysis, the best cut-off of the RH-PAT index to identify cognitive impairment was 1.65 (area under the curve 0.67; P = 0.011) with limited the sensitivity (63%) and specificity (66%).

A lower RH-PAT index was significantly associated with the presence of cognitive impairment in elderly CVD patients. Further studies are required to clarify the mechanism and the causal relationship between the endothelial dysfunction and cognitive impairment in patients with CVD.

Key words: Endothelial function, Reactive hyperemia-peripheral arterial tonometry index, Cognitive function

Cognitive impairment is a major comorbidity in elderly patients with cardiovascular disease (CVD) due to the common risk factors, including atrial fibrillation,11 lower left ventricular ejection fraction (LVEF),2 and heart failure2 in addition to the conventional risk factors for atherosclerosis.4,5 The presence of cognitive impairment may disturb the optimal management of CVD and worsen the clinical course.5,6 However, the causal relationship between cognitive impairment and CVD still remains unclear.

Recently, several studies have suggested the association between vascular endothelial dysfunction and cognitive impairment.5,9 In particular, the value of the reactive hyperemia-peripheral arterial tonometry (RH-PAT) has been demonstrated to represent the status of systemic atherosclerosis including micro vascular disease,10 vasospastic artery disease,11 thrombus formation,12 and peripheral arterial disease.13 Therefore, in the present study, we aimed to clarify 1) the association between the endothelial dysfunction evaluated by RH-PAT and the presence of cognitive impairment, and 2) the diagnostic potential of RH-PAT to identify cognitive impairment in patients with CVD.

Methods

Study population: This is a cross-sectional observational study conducted between October 2015 and June 2016 in cardiac rehabilitation center of Kitasato University East Hospital. A total of consecutive 101 CVD patients who planned to initiate cardiac rehabilitation were enrolled. CVD included ischemic heart disease (myocardial infarc-
tion, angina pectoris and vasospastic angina), atrial fibrillation and heart failure. After excluding patients with < 70 years old (n = 15), dementia (Diagnostic and Statistical Manual of Mental Disorder Fourth Edition (DSM-IV) criteria) with pharmacological therapy (n = 4) and denial (n = 2), 80 patients were finally included in this study. The Human Research Committee of Kitasato University School of Medicine approved the study protocol. All the subjects provided written informed consent.

**Assessment of endothelial function:** The endothelial function was evaluated by RH-PAT (EndoPAT2000; Itamar Medical, Caesarea, Israel).\(^{14,15}\) On the day of visit, the patients were not allowed any caffeine-containing drinks or tobacco consumption. Before measurement, the patients were asked to rest for 10 minutes. In line with previous studies, we applied 10 minutes’ rest before the measurement.\(^{16,17}\) Using a fingertip peripheral arterial tonometry device, we measured the digital pulse amplitude in the supine position of the patients for 5 minutes at baseline and after a reactive hyperemia induced by a 5-minute forearm cuff occlusion. RH-PAT was measured in fasting condition. The data were digitized and were computed automatically with Endo-PAT2000 software. The digital RH-PAT index, representing the endothelial function, was defined as the ratio of the mean post-deflation signal (in the 90 to 120-s post-deflation interval) to the baseline signal in the hyperemic finger and was normalized by the same ratio in the contra-lateral finger and was multiplied by a baseline correction factor, as calculated by the Endo-PAT 2000 software. An independent clinical psychologist, who was blinded to the outcomes of the cognitive function performed the RH-PAT evaluation.

**Assessment of cognitive function:** The Mini-mental state examination (MMSE), a widely used quantified assessment of cognitive state, was used to evaluate the cognitive function.\(^{26}\) The MMSE included the evaluation of orientation, registration, attention, memory, and the ability to name, follow verbal and written commands, write a sentence, and copy a complex figure. The MMSE scores range from 0 to 30, with a lower score indicating lower cognitive impairment. Cognitive impairment was defined as the MMSE score ≤ 26 according to previous studies\(^ {2,19} \) among several definitions because this study focused on mild cognitive impairment in addition to moderate and severe cognitive impairment. An independent clinical psychologist, who was blinded to the outcomes of the endothelial function, performed the MMSE evaluation.

**Definition:** Hypertension was defined as arterial blood pressure > 140/90 mmHg or taking antihypertensive medication. Dyslipidemia was defined as high-density lipoprotein cholesterol < 40 mg/dL, low-density lipoprotein cholesterol > 140 mg/dL, or triglycerides > 150 mg/dL or taking medication for dyslipidemia. Diabetes mellitus was defined as symptoms of diabetes plus casual plasma glucose concentration > 200 mg/dL, fasting plasma glucose concentration > 126 mg/dL, 2hours plasma glucose concentration > 200 mg/dL during 75 g oral glucose tolerance test, or taking medication for diabetes mellitus. Current smoking was defined as smoking habit within 1 year. The endothelial function, cognitive function, laboratory data, and clinical information were obtained on the same day.

**Statistical analysis:** The continuous variables with normal distribution were expressed as mean ± standard deviation (SD), whereas the median value with interquartile range (IQR) was reported when the data was not normally distributed. The continuous variables were analyzed by the t test or the Mann-Whitney U test. The categorical variables were reported as count (%) and were analyzed by the chi-square test. A multivariate regression analysis was performed to identify the factors for the presence of cognitive impairment within variables with P < 0.05 in the univariate logistic regression analysis. The receiver-operating characteristics (ROC) curves were constructed with the RH-PAT index. To predict cognitive impairment, the area under the curve (AUC), sensitivity, and specificity were calculated. The best cut-off value of the RH-PAT index was identified by maximizing the sum of sensitivity and specificity. Statistical significance was defined as P < 0.05. JMP 9.0 version (SAS Institute, Cary, North Carolina, USA) was used to perform all the statistical analyses.

**Results**

**Clinical characteristics:** Among 80 elderly patients with CVD, the number of patients with normal cognitive function and cognitive impairment was 29 patients (36.3%) and 51 patients (63.7%), respectively. Table I describes the baseline clinical characteristics according to the status of cognitive impairment. Except for Hemoglobin A1c (HbA1c) and left ventricular ejection fraction (LVEF) on echocardiography, all the clinical characteristics were similar between the two groups.

**RH-PAT indexes and cognitive functions:** The RH-PAT indexes were compared between the two groups (Figure 1). The index in the cognitive impairment patients (median 1.60 [IQR 1.34 to 1.89]) were significantly lower than that in the non-cognitive impairment patients (median 1.75 [IQR 1.55 to 2.30], P = 0.005). The MMSE score was positively correlated with the RH-PAT index (r = 0.236, P = 0.035) (Figure 2).

**RH-PAT indexes and presence of cognitive impairment:** The univariate analysis showed that LVEF (OR 0.90; 95% confidential interval (CI) 0.83 to 0.97; per 1%; P = 0.004), HbA1c (OR 1.08; 95% CI 1.01-1.18; per 0.1%, P = 0.014), and the RH-PAT index (OR 0.89; 95% CI 0.81 to 0.97; per 0.1; P = 0.006) were independently associated with the presence of cognitive impairment (Table II). The multivariate analysis demonstrated that the LVEF (OR 0.91; 95% CI 0.83 to 0.98; P = 0.032), and the RH-PAT index (OR 0.89; 95% CI 0.82 to 0.99; P = 0.044) were independently associated with the presence of cognitive impairment (Table III).

**ROC analysis for RH-PAT index to detect cognitive impairment:** The ROC curve was constructed to assess the ability of the RH-PAT index to detect cognitive impairment. The AUC for the detection of cognitive impairment was 0.67 (95% CI: 0.54 to 0.78; P = 0.011) of the RH-PAT index (Figure 3). The best cut-off of the RH-PAT index for the detection of cognitive impairment was 1.65, and the sensitivity and specificity was 63% and 66%, respectively.
The main findings of this study include: 1) Compared with non-cognitive impairment, the RH-PAT index was significantly lower in patients with cognitive impairment. 2) The RH-PAT index was independently associated with the presence of cognitive impairment. 3) The potential of RH-PAT to detect cognitive impairment in patients with CVD was limited.

Several previous studies have demonstrated that the cognitive function is impaired in most CVD patients by the increased platelet activity, enhanced thrombogenicity, or decreased cardiac function via so-called “heart-brain continuum”. It is suggested that the early diagnosis and therapeutic intervention of cognitive impairment is a key to preventing secondary CV events in patients with CVD. O’Donnell, et al. reported the significant relationship between impaired cognitive impairment and the higher rate of CV events in patients with increased CV risk. They mentioned their poor self-medication status and insufficient therapeutic intervention for CV risk factors as the cause of the increased CV events. In the present study, around one third of the patients had impaired cognitive function, which is relatively larger than that reported in previous reports about the general elderly population. This difference might be due to the higher prevalence of impaired cognitive function in CVD patients. Although further studies are still required to clarify whether the therapeutic intervention for cognitive impairment could decrease CV events, several recent studies have demonstrated that the comprehensive approach, including appropriate diet, continuous exercise, cognitive training, and the routine assessment of cardiovascular risk contributes to the improvement of or the maintenance of the cognitive function. In addition, recent reports have suggested the importance of therapeutic intervention for cognitive impairment in the early stage to effectively improve or preserve the cognitive function.

The present study demonstrated that endothelial dysfunction was independently associated with the presence of cognitive impairment. This means that the assessment of the endothelial function might contribute to the screening of cognitive impairment in CVD patients. In fact, it is practically impossible to assess the cognitive function of CVD patients in daily cardiology clinic. Therefore, the simple and practical methodology of cognitive impairment screening has been required. The theoretical relationship between endothelial dysfunction and cognitive impairment...
is still unclear, whereas the common risk factors exist. It has been reported that mild glucose intolerance, excessive salt intake, lack of regular exercise, estrogen deficiency, and depression status in addition to conventional CVD risk factors lead to endothelial dysfunction. In addition, those factors might impair the cognitive function through the disturbance of the cerebral microcirculation via decreased nitric oxide synthesis, prostacyclin, tissue plasminogen activator, and shear stress. In particular, those factors might interactively deteriorate the status of the endothelial function in CVD patients. Furthermore, the deceased cardiac function affects the cognitive impairment in CVD patients as we identified the decreased LVEF as an independent factor. Although the difference of the LVEF in patients with and without cognitive impairment appeared insubstantial in the present study, a previous study demonstrated that a lower LVEF affected the cognitive dysfunction. Several previous studies suggested the cerebral hypoperfusion with the consequent reduction of the circulating volume and relative hypotension with the combination of reduced cerebral auto-regulation as the cause of cognitive impairment, in addition to the hypercoagulable state. Although, in general, the most influential factor on cognitive function is age, the association was not demonstrated in the present study. This might be due to the specific cohort of this study with CVD and age >70 years old. In the present study, the prevalence of hypertension seems to be negatively correlated with impaired cognitive function. However, due to the presence of CVD in all the patients, both of the groups had very high prevalence of hypertension. Thus, the apparent difference might have no significant impact. There was a statistical difference in HbA1c between the two groups, though the prevalence of diabetes was comparable in the present study. The reason for this discrepancy may be due to the difference between the clinical diagnosis and the present disease status.

Among several devices that can be used to assess the endothelial function, RH-PAT is a promising tool due to its practical utility. The endothelial function is simply evaluated by finger arterial pulse wave amplitude in RH-PAT, and the status of the autonomic nervous activation reflects the measured index. In addition, compared with flow mediated dilation (FMD), RH-PAT requires shorter time for the measurement, thus, we applied it in the present study. Although some studies reported the feasibility

![Figure 1](image1.png)

**Figure 1.** The RH-PAT index and cognitive function. The RH-PAT index was significantly lower in cognitive impairment (median 1.60 [interquartile range (IQR) 1.34-1.89], n = 51) than in non-cognitive impairment (median 1.75 [IQR 1.55-2.30], n = 29, P = 0.005). The RH-PAT index indicates the Reactive hyperemia-peripheral arterial tonometry index.

![Figure 2](image2.png)

**Figure 2.** Correlation of the MMSE score with the RH-PAT index. The MMSE score was positively correlated with the RH-PAT index. The MMSE, Mini-mental state examination. The RH-PAT index indicates Reactive hyperemia-peripheral arterial tonometry index.
Table II. Univariate Analysis for the Presence of Cognitive Impairment

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per year</td>
<td>1.00</td>
<td>0.91-1.11</td>
<td>0.955</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.87</td>
<td>0.34-2.21</td>
<td>0.775</td>
</tr>
<tr>
<td>Body mass index, per kg/m²</td>
<td>0.96</td>
<td>0.84-1.10</td>
<td>0.545</td>
</tr>
<tr>
<td>sBP, per mmHg</td>
<td>4.99</td>
<td>0.66-43.09</td>
<td>0.118</td>
</tr>
<tr>
<td>dBP, per mmHg</td>
<td>2.12</td>
<td>0.23-20.52</td>
<td>0.503</td>
</tr>
<tr>
<td>HR, per/minute</td>
<td>0.28</td>
<td>0.02-2.94</td>
<td>0.296</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.92</td>
<td>0.17-1.47</td>
<td>0.222</td>
</tr>
<tr>
<td>History of PCI and/or PTA</td>
<td>1.83</td>
<td>0.71-4.92</td>
<td>0.213</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.11</td>
<td>0.42-3.04</td>
<td>0.833</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.33</td>
<td>0.02-2.18</td>
<td>0.272</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.64</td>
<td>0.48-5.51</td>
<td>0.423</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.11</td>
<td>0.42-3.04</td>
<td>0.833</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.19</td>
<td>0.15-7.58</td>
<td>0.858</td>
</tr>
<tr>
<td>Education, per year</td>
<td>0.82</td>
<td>0.63-1.04</td>
<td>0.105</td>
</tr>
<tr>
<td>ARB/ACEI</td>
<td>0.69</td>
<td>0.27-1.73</td>
<td>0.427</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>1.47</td>
<td>0.59-3.76</td>
<td>0.408</td>
</tr>
<tr>
<td>Statin</td>
<td>1.39</td>
<td>0.47-3.96</td>
<td>0.546</td>
</tr>
<tr>
<td>Anticoagulant therapy</td>
<td>1.92</td>
<td>0.59-7.48</td>
<td>0.285</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>1.15</td>
<td>0.45-2.97</td>
<td>0.776</td>
</tr>
<tr>
<td>HbA1c, per 0.1%</td>
<td>1.08</td>
<td>1.01-1.18</td>
<td>0.014</td>
</tr>
<tr>
<td>LDL-C, per mg/dL</td>
<td>1.01</td>
<td>0.99-1.03</td>
<td>0.300</td>
</tr>
<tr>
<td>HDL-C, per mg/dL</td>
<td>1.00</td>
<td>0.96-1.03</td>
<td>0.777</td>
</tr>
<tr>
<td>BNP, per pg/mL</td>
<td>1.01</td>
<td>1.00-1.02</td>
<td>0.212</td>
</tr>
<tr>
<td>Mean PWV, per cm/second</td>
<td>1.00</td>
<td>0.99-1.00</td>
<td>0.116</td>
</tr>
<tr>
<td>LVEF, per 1%</td>
<td>0.90</td>
<td>0.83-0.97</td>
<td>0.004</td>
</tr>
<tr>
<td>RH-PAT index, per 0.1</td>
<td>0.89</td>
<td>0.81-0.97</td>
<td>0.006</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval; sBP, systolic blood pressure; dBP, diastolic blood pressure; HR, heart rate; PCI, percutaneous coronary intervention; PTA, percutaneous transluminal angioplasty; ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; LDL-C, low-density-lipoprotein cholesterol; HDL-C, high-density-lipoprotein cholesterol; BNP, brain natriuretic peptide; PWV, pulse wave velocity; LVEF, left ventricular ejection fraction; and RH-PAT, reactive hyperemia-peripheral arterial tonometry.

Table III. Multivariate Analysis for the Presence of Cognitive Impairment

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, per 1%</td>
<td>0.91</td>
<td>0.83-0.98</td>
<td>0.032</td>
</tr>
<tr>
<td>HbA1c, per 0.1%</td>
<td>1.06</td>
<td>1.00-1.16</td>
<td>0.062</td>
</tr>
<tr>
<td>RH-PAT index, per 0.1</td>
<td>0.90</td>
<td>0.82-0.99</td>
<td>0.044</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; and RH-PAT, reactive hyperemia-peripheral arterial tonometry.
CVD. Thus, the interpretation of the results needs to be done cautiously. Third, there was not a complete removal of the potential confounding factors which might affect the RH-PAT index (e.g., temperature, time, season). Fourth, the RH-PAT index might vary among the CVD types. Fifth, the results might change if the different cut-off of the MMSE was applied. Sixth, we have no data concerning the diagnosis of dementia in these patients. However, a previous report has described the cognitive impairment in CVD patients as being mainly due to vascular dementia, although the cognitive impairment in the general population was mainly due to Alzheimer disease.\(^6\)\(^7\) It might be a tough theme to clarify if the endothelial function in patients with Alzheimer disease without CVD/risk factors is impaired or not due to the following two reasons. First, usually, most Alzheimer patients have CVD risk factors.\(^5\) Second, cognitive function of Alzheimer disease is partly impaired by CVD risk factors.\(^5\) Lastly, the findings of this observational study did not clarify the causal relationships between the endothelial dysfunction and cognitive impairment.

In conclusion, a lower RH-PAT index was significantly associated with the presence of cognitive impairment in elderly CVD patients. Further studies are required to clarify the mechanism and causal relationship between endothelial dysfunction and cognitive impairment in patients with CVD.

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Disclosures

Conflicts of interest: None.

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