Association of cerebral blood flow with the development of cardiac death or urgent heart transplantation in patients with systolic heart failure

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Aims

Although cerebral blood flow (CBF) is known to be low in patients with advanced systolic heart failure (HF), little is known of the prognostic significance of this observation. We investigated whether CBF might be associated with the development of adverse outcomes in systolic HF, and whether it might provide prognostic information in addition to that provided by exercise tests.

Methods and results

We performed a prospective observational study involving 224 systolic HF patients (left ventricular ejection fraction ≤35%). The study endpoint was the occurrence of cardiac death or urgent heart transplantation. Global CBF was measured using radionuclide angiography. Clinical, biochemical, echocardiographic, and exercise data were also obtained. During follow-up (median 36 months), 52 patients experienced death or urgent transplantation. Multivariable analysis showed that global CBF, the minute ventilation/carbon dioxide production (VE/VCO₂) slope, New York Heart Association functional class ≥III, symptom duration ≥12 months, serum sodium, and serum creatinine were associated with the development of the endpoint. Patients with a CBF <35.4 mL/min/100 g were at increased risk of death or urgent transplantation (hazard ratio = 2.47; 95% confidence interval, 1.35–4.52). The addition of global CBF to a prognostic model including the VE/VCO₂ slope increased the C-index for the prediction of adverse outcomes with borderline significance.

Conclusion

Cerebral blood flow was associated with the development of long-term outcomes in systolic HF, and therefore may be useful in identifying patients suitable for heart transplantation. This finding is especially relevant for patients in whom exercise tests may not be performed sufficiently.

Keywords

Cerebral blood flow • Systolic heart failure • Prognosis • Heart transplantation

Introduction

Identifying predictors of survival in patients with systolic heart failure (HF) is an area of intense investigation. Numerous biomarkers such as serum sodium, creatinine, haemoglobin, and B-type natriuretic peptide (BNP) levels have been used to identify patients at risk. Their abnormal findings are prevalent in HF patients. But the robust evidence that any single biomarker is solely helpful in predicting prognosis is still lacking. Some demographic variables such as age, resting heart rate, blood pressure, and body mass index (BMI) are established as a good prognosticator. However, they are also commonly combined for the prediction of survival. The existence of multiple HF models composed of diverse determinants indicates the lack of a single powerful tool for predicting survival.
Peak oxygen consumption rate (peak VO2) has been the single best predictor of survival in HF patients. This parameter is measured using a cardiopulmonary exercise test (CPET), and is used in the selection of heart transplant recipients. However, CPET results can be affected by comorbidities such as pulmonary or musculoskeletal disease. In addition, advanced age or chronic disuse of the extremity muscles can affect CPET results. Moreover, although an issue of debate, exercise may increase the risk of myocardial infarction and sudden cardiac death. Hence, physicians and HF patients may be reluctant to use a CPET for determining the need for heart transplantation. Identification of a novel powerful prognostic indicator that does not involve exercise would be highly clinically advantageous.

Previous animal and human studies have shown that chronic low cardiac output is associated with a reduction in cerebral blood flow (CBF). We have also shown that global CBF at rest is low in the cardiac output is associated with a reduction in cerebral blood flow highly clinically advantageous. A single researcher blinded to patient clinical information analysed radionuclide angiography images.

Methods

Study population

From December 2002 to August 2008, 233 patients with systolic HF (left ventricular ejection fraction, LVEF ≤ 35% on transthoracic echocardiography) were prospectively enrolled in hospital or from the outpatient department at the Asan Medical Center. The study excluded patients with a history of cerebrovascular disease or cognitive dysfunction such as dementia or myocardial infarction during the previous 3 months. Of these 233 patients, 8 were incidentally found to have cerebrovascular disease when performing brain MR angiography and one had an insufficient radionuclide angiographic view, which was not enough to obtain CBF (an overlap of pulmonary artery on aorta). Thus, 224 patients were analysed in the present study. The patients had a mean age of 45.3 ± 12.3 years (range: 15–69 years), and 173 were male. All study subjects provided informed consent, and the study was approved by the review board of the Asan Medical Center.

Clinical and laboratory evaluation

At enrolment, demographic and clinical data including the duration of symptoms and the New York Heart Association (NYHA) functional class were obtained, and a blood sample was taken for laboratory tests. Serum BNP levels were determined from whole blood samples taken just prior to hospital discharge or during a visit to the outpatient department when patients were in a stable condition. B-type natriuretic peptide concentration was determined using the ADVIA Centaur® CP immunoassay System (Siemens Medical Solution Diagnostics, Tarrytown, NY, USA).

Global cerebral blood flow

Radionuclide angiography was performed immediately after the intravenous injection of a bolus of 740 MBq (20 mCi) technetium-99m ethyl cysteinate dimer. Scanning was done using a dual-head gamma camera (ECAM+, Siemens Medical Systems, Hoffman Estates, IL, USA) fitted with low-energy, high-resolution, parallel-hole collimators. Anterior planar images were acquired through the passage of the tracer from the aortic arch to the brain in a 128 × 128 matrix (magnification × 1.0) for 120 s at 1 s intervals. Regions of interest were manually drawn over the aortic arch and bilateral cerebral hemispheres. Time–activity curves in those regions of interest were plotted, and the mean hemispheric brain perfusion index was determined and converted to global CBF as previously described. A single researcher blinded to patient clinical information analysed radionuclide angiography images.

Cardiopulmonary exercise tests

Cardiopulmonary exercise tests were performed after inclusion. One hundred and sixteen patients (51.8% of total patients) underwent a CPET using bicycle ergometry (MedGraphics, Cardiopulmonary Diagnostic Systems, St Paul, MN, USA). The decision to undertake a CPET was based on the patient’s clinical condition. The CPET was performed by two investigators blinded to the clinical information and test results such as CBF. During testing, the electrocardiogram was continuously monitored and blood pressure was recorded every 2 min. A ramp protocol was used, in which the workload was increased stepwise by 10 W per minute. The exercise test was terminated when the patient’s ability to exercise became limited by symptoms or an oxygen plateau was attained.Expired gas was collected and analysed using a computerized system (MedGraphics, Cardiopulmonary Diagnostic). The equipment was calibrated with reference gas before each test. The CPET was used to determine peak VO2, carbon dioxide production (VCO2), minute ventilation (VE), anaerobic threshold (AT), and resting/peak heart rate. Ventilatory variables were acquired breath-by-breath and averaged over 10 s intervals. The peak VO2 was defined as the greatest 15 s average oxygen consumption. The VE/VCO2 slope was determined using linear regression analysis of VE and VCO2 responses throughout exercise. The AT was determined using the V-slope method and expressed as a percentage of the predicted measure.

Transthoracic echocardiography

Comprehensive two-dimensional and colour Doppler echocardiographic evaluation was performed in all patients before exercise tests and CBF examinations. Cardiac chamber volumes and LVEF were measured using the modified Simpson method. Early mitral velocity (E), late mitral velocity (A), E/A ratio, and deceleration time were obtained using a transmitral Doppler beam from the apical four-chamber view. Early diastolic mitral annular velocity (E') was assessed using a tissue Doppler image, and the E/E' ratio was calculated for assessing LV diastolic function. Mitral and tricuspid regurgitation were graded from 0 to +4, depending on the spatial extent of the colour flow jet area expressed as a percentage of each atrial area. The peak pressure gradient of tricuspid regurgitation was calculated using the continuous wave Doppler technique. Two investigators who were blinded to the clinical information and test results performed the examination and analysed the results.

Follow-up and study endpoint

Clinical follow-up was usually performed either at outpatient clinic visits every 3 months or by telephone interviews. The study endpoint was a composite variable of cardiac death (death suddenly from cardiac causes or from pump failure) or urgent heart transplantation [United Network for Organ Sharing (UNOS) status 1]. The National Vital
Statistics death file was used to confirm mortality during follow-up. Patients who received elective transplantation were censored on their transplantation date. All survivors were followed for a minimum of 12 months, and the median follow-up duration was 36 months (inter-quartile range: 17–53 months, actual range: 12–81 months).

**Statistical analysis**

All values are expressed as mean ± standard deviation (continuous variables) or as counts and percentages (categorical variables). Continuous variables were compared using t-test or Mann–Whitney U test, and categorical variables were compared using $\chi^2$ statistics or Fisher’s exact tests. To examine the association between variables and the development of the endpoint, univariate analyses were performed separately for each variable using Cox proportional hazards models. The variables for univariate analyses included the clinical parameters showing a difference between the groups with and without an event or the previously well-known HF prognostic factors. Variables with a probability value of ≤0.20 in univariate analyses were candidates for multivariable Cox proportional hazards models. Multivariable analysis was performed for CBF population (224 patients). Subgroup of CBF population was CPET population in which 116 patients (51.8% of CBF population) underwent a CPET using bicycle ergometry. The final multivariable model on CBF population was constructed using the following model formula: [NYHA ≥ III] + [symptom ≥ 12 months] + [CBF] + [serum sodium] + [serum creatinine] + [exercise] + [I(exercise = 1) × VE/VCO2], where exercise is coded as 0 and 1 for whether the CPET was performed or not and I(·) is an indicator function. If a patient is not included in CPET population, (exercise = 1) × VE/VCO2 is coded as 0. Hazard ratios (HRs) of variables were represented as effects on CBF population except for the VE/VCO2 slope variable. The hazard ratio of the VE/VCO2 slope was represented as effects on patients who underwent the CPET (CPET population). The correct functional form of continuous variables was examined by the method of Therneau, who suggested plotting the martingale residuals from a null model.16 A backward elimination process was used to develop the final multivariable model, and adjusted HRs with 95% confidence intervals (CIs) were calculated. Proportional hazards assumptions were assessed using the log-log survival plot and the test.

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**Table 1  Baseline clinical characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total patients ($n = 224$)</th>
<th>Death/HTPL ($n = 52$)</th>
<th>No event ($n = 172$)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>45.3 ± 12.3</td>
<td>48.0 ± 12.2</td>
<td>44.5 ± 12.3</td>
<td>0.071</td>
</tr>
<tr>
<td>Male</td>
<td>173 (77.2)</td>
<td>43 (82.7)</td>
<td>130 (75.6)</td>
<td>0.284</td>
</tr>
<tr>
<td>Resting heart rate, b.p.m.</td>
<td>82.8 ± 20.5</td>
<td>82.9 ± 24.7</td>
<td>82.8 ± 19.2</td>
<td>0.978</td>
</tr>
<tr>
<td>Mean BP, mmHg</td>
<td>78.5 ± 12.8</td>
<td>76.6 ± 9.7</td>
<td>79.1 ± 13.6</td>
<td>0.145</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.2 ± 3.8</td>
<td>22.1 ± 2.6</td>
<td>23.6 ± 4.1</td>
<td>0.003</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>114.6 ± 30.0</td>
<td>121.4 ± 30.7</td>
<td>112.6 ± 29.6</td>
<td>0.073</td>
</tr>
<tr>
<td>NYHA class ≥ III</td>
<td>106 (47.3)</td>
<td>32 (61.5)</td>
<td>74 (43.0)</td>
<td>0.013</td>
</tr>
<tr>
<td>Symptom duration ≥ 12 months</td>
<td>100 (44.6)</td>
<td>32 (61.5)</td>
<td>68 (39.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>20 (8.9)</td>
<td>8 (15.4)</td>
<td>12 (7.0)</td>
<td>0.092</td>
</tr>
<tr>
<td>Diabetes</td>
<td>32 (14.3)</td>
<td>9 (17.3)</td>
<td>23 (13.4)</td>
<td>0.477</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42 (18.8)</td>
<td>8 (15.4)</td>
<td>34 (19.8)</td>
<td>0.478</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>26 (11.6)</td>
<td>9 (17.3)</td>
<td>17 (9.9)</td>
<td>0.143</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>64 (28.6)</td>
<td>23 (44.2)</td>
<td>41 (23.8)</td>
<td>0.008</td>
</tr>
<tr>
<td>ICD/CRT-ICD</td>
<td>8 (3.6)</td>
<td>1 (1.9)</td>
<td>7 (4.1)</td>
<td>0.685</td>
</tr>
</tbody>
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**Aetiology**

<table>
<thead>
<tr>
<th></th>
<th>Total patients ($n = 224$)</th>
<th>Death/HTPL ($n = 52$)</th>
<th>No event ($n = 172$)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated CMP</td>
<td>151 (67.4)</td>
<td>36 (69.2)</td>
<td>115 (66.9)</td>
<td>0.749</td>
</tr>
<tr>
<td>Ischaemic CMP</td>
<td>36 (16.1)</td>
<td>9 (17.3)</td>
<td>27 (15.7)</td>
<td>0.782</td>
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<tr>
<td>Hypertensive CMP</td>
<td>5 (2.2)</td>
<td>1 (1.9)</td>
<td>4 (2.3)</td>
<td>0.671</td>
</tr>
<tr>
<td>Others</td>
<td>32 (14.3)</td>
<td>6 (11.5)</td>
<td>26 (15.1)</td>
<td>0.518</td>
</tr>
</tbody>
</table>

**Medication**

<table>
<thead>
<tr>
<th></th>
<th>Total patients ($n = 224$)</th>
<th>Death/HTPL ($n = 52$)</th>
<th>No event ($n = 172$)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-inhibitors or ARBs</td>
<td>220 (98.2)</td>
<td>50 (96.2)</td>
<td>170 (98.8)</td>
<td>0.231</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>98 (43.8)</td>
<td>21 (40.4)</td>
<td>77 (44.8)</td>
<td>0.577</td>
</tr>
<tr>
<td>Digoxin</td>
<td>212 (94.6)</td>
<td>50 (96.2)</td>
<td>164 (95.3)</td>
<td>0.579</td>
</tr>
<tr>
<td>Diuretics</td>
<td>214 (95.5)</td>
<td>50 (96.2)</td>
<td>164 (95.3)</td>
<td>0.579</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>128 (57.1)</td>
<td>33 (63.5)</td>
<td>95 (55.2)</td>
<td>0.293</td>
</tr>
<tr>
<td>Nitrates</td>
<td>138 (61.6)</td>
<td>33 (63.5)</td>
<td>105 (61.0)</td>
<td>0.637</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>63 (28.1)</td>
<td>18 (34.6)</td>
<td>45 (26.2)</td>
<td>0.235</td>
</tr>
<tr>
<td>Anti-platelet agent</td>
<td>34 (15.2)</td>
<td>12 (23.1)</td>
<td>22 (12.8)</td>
<td>0.070</td>
</tr>
<tr>
<td>Anti-arrhythmic agent</td>
<td>22 (9.8)</td>
<td>7 (13.5)</td>
<td>15 (8.7)</td>
<td>0.314</td>
</tr>
</tbody>
</table>

Values represent number (percentages) or mean ± SD. Endpoint, cardiac death or urgent transplantation. CBF, cerebral blood flow; HTPL, urgent heart transplantation; NYHA, New York Heart Association; ICD/CRT, intracardiac defibrillator/cardiac resynchronization therapy; CMP, cardiomyopathy; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.
were confirmed using Schoenfeld’s tests, and no relevant violations were found.

As mentioned in the introduction, CPET results can be affected by comorbidities, advanced age, or chronic disuse of the extremity muscles, and exercise may increase the risk of myocardial infarction and sudden cardiac death. So the CPET population can show selection bias such as less severe symptoms. However, despite the existence of possible selection bias, we performed multivariable analysis on CPET population in order to investigate whether CBF might also be associated with the development of adverse outcomes in the subgroup. In addition, the sensitivity analysis was also performed for the case of a missing VE/VCO₂ slope in the multivariable analysis. In other words, the median, minimum, and maximum values of the non-missing VE/VCO₂ slope were used as substitutes of missing values (Supplementary material online, Table S3).

A time-dependent receiver-operating characteristic (ROC) curve analysis was used to assess the cut-off point of global CBF or the VE/VCO₂ slope for predicting cardiac death or urgent transplantation within 2 years after enrolment. The optimal cut-off was defined as the value with the maximal sum of sensitivity and specificity. Freedom from cardiac death or urgent transplantation was estimated by the Kaplan–Meier method and compared by the log-rank test. The C-index was used to evaluate whether CBF could provide prognostic information additional to that derived from exercise parameters. The reported 95% CI for the difference was obtained through bootstrap with the percentile method (1000 replicates).

All reported P-values are two-sided, and P-values < 0.05 were considered to indicate statistical significance. SAS software, version 9.1 (SAS Institute, Cary, NC, USA), and the R programming language with survivalROC library were used for statistical analysis.

### Results

Among CBF population (n = 224), the study endpoint was reached in 52 patients (23.2%); this included cardiac death in 38 patients and urgent heart transplantation in 14 patients. A further 10 patients underwent elective heart transplantation. The characteristics of patients who experienced cardiac death or urgent heart transplantation, and in whom the endpoint was met (group with an event), and those who did not (group without an event) are shown in Table 1. Both groups were similar in terms of age, gender ratio, mean blood pressure, comorbidities, HF aetiology, and medications. The group with an event had a higher NYHA functional class, longer duration of HF symptoms, and higher incidence of prior atrial fibrillation than those without an event.

Global CBF was lower in the group with an event compared with those without an event (35.0 ± 4.3 vs. 40.1 ± 5.4 mL/min/100 g, P < 0.001) (Table 2). All patients had marked systolic LV dysfunction (mean LVEF: 22.0 ± 7.7%). Echocardiographic parameters were similar in both groups, with the exception of deceleration time and pulmonary artery systolic pressure. Moreover, differences were found in serum sodium, serum creatinine, and BNP levels.

The characteristics of patients with or without the CPET performed are shown in Supplementary material online, Tables S1 and S2. Among patients with the CPET (CPET population, n = 116), 21 patients (18.1%) developed the endpoint—cardiac death in 12 patients and urgent heart transplantation in 9 patients. Only the VE/VCO₂ slope among exercise parameters differed between the groups with or without an event (42.6 ± 11.0 vs.

### Table 2 Results of global cerebral blood flow, echocardiography, and laboratory tests

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total patients (n = 224)</th>
<th>Death/HTPL (n = 52)</th>
<th>No event (n = 172)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global CBF, mL/min/100 g</td>
<td>38.9 ± 5.6</td>
<td>35.0 ± 4.3</td>
<td>40.1 ± 5.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Echocardiographic parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVIDs, mm</td>
<td>62.2 ± 11.5</td>
<td>64.7 ± 13.8</td>
<td>61.5 ± 10.7</td>
<td>0.076</td>
</tr>
<tr>
<td>LVIDd, mm</td>
<td>71.3 ± 10.9</td>
<td>74.1 ± 13.4</td>
<td>70.5 ± 9.9</td>
<td>0.074</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>22.0 ± 7.7</td>
<td>21.8 ± 8.4</td>
<td>22.1 ± 7.5</td>
<td>0.817</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>136.3 ± 45.3</td>
<td>124.8 ± 40.2</td>
<td>140.2 ± 46.4</td>
<td>0.044</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>2.3 ± 1.4</td>
<td>2.6 ± 1.0</td>
<td>2.3 ± 1.5</td>
<td>0.157</td>
</tr>
<tr>
<td>E/E’ ratio</td>
<td>21.2 ± 10.3</td>
<td>23.0 ± 11.3</td>
<td>20.7 ± 9.9</td>
<td>0.273</td>
</tr>
<tr>
<td>MR ≥ grade 3</td>
<td>117 (52.2)</td>
<td>33 (63.5)</td>
<td>84 (48.8)</td>
<td>0.060</td>
</tr>
<tr>
<td>PASP, mmHg</td>
<td>38.1 ± 15.1</td>
<td>44.5 ± 14.5</td>
<td>36.1 ± 14.7</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Laboratory examination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin, g/dL</td>
<td>14.0 ± 1.9</td>
<td>13.6 ± 2.0</td>
<td>14.1 ± 1.9</td>
<td>0.110</td>
</tr>
<tr>
<td>Serum sodium, mmol/L</td>
<td>137.2 ± 4.5</td>
<td>135.1 ± 5.6</td>
<td>137.8 ± 3.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.1 ± 0.4</td>
<td>1.2 ± 0.6</td>
<td>1.0 ± 0.3</td>
<td>0.024</td>
</tr>
<tr>
<td>Serum BNP*, pg/mL</td>
<td>382 (198–675)</td>
<td>578.5 (396–1513)</td>
<td>327 (147–574)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values represent number (percentages) or mean ± SD. Endpoint, cardiac death or urgent transplantation; HTPL, urgent heart transplantation; CBF, cerebral blood flow; LVIDs/d, left ventricular internal dimension at systolic/diastolic phase; LVEF, left ventricular ejection fraction; E, early mitral velocity; A, late mitral velocity; E’, early mitral annular velocity; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; BNP, B-type natriuretic peptide.

*Median (inter-quartile range).
Univariate analysis showed that BMI, NYHA functional class \( \geq \) III, symptom duration \( \geq \) 12 months, history of atrial fibrillation, global CBF, LV chamber dimensions, deceleration time, haemoglobin, serum sodium, serum creatinine, and \( \log_2(\text{BNP}) \) levels were associ-
ated with the development of the study endpoint (Table 3). Among CPET population, peak VO₂ (HR = 0.91; 95% CI, 0.83–0.99, P = 0.037), VE/VCO₂ slope (HR = 1.12; 95% CI, 1.08–1.16, P < 0.001), and peak heart rate (HR = 0.83; 95% CI, 0.72–0.96, P = 0.015) were also found to be associated with cardiac death or urgent transplantation.

Multivariable analysis showed that NYHA functional class ≥III, symptom duration ≥12 months, global CBF, serum sodium, serum creatinine, and VE/VCO₂ slope among CPET population were associated with cardiac death or urgent transplantation (Table 4). In the multivariable analysis on CPET population, only global CBF and the VE/VCO₂ slope were associated with the development of cardiac death or urgent heart transplantation (Table 5). HRs and CIs of CBF and the VE/VCO₂ slope from CPET population showed similar values and directivities compared with those of CBF population.

Time-dependent ROC analysis showed that the best cut-off value for predicting cardiac death or urgent transplantation within 2 years after study enrolment was 35.4 mL/min/100 g for the global CBF, which showed a sensitivity of 86% and a specificity of 61%, and 35 for the VE/VCO₂ slope, which showed a sensitivity of 92% and a specificity of 73% (Figure 1). The global CBF cut-off value demonstrated more obvious risk stratification for the risk of cardiac death or urgent transplantation (HR = 2.47; 95% CI, 1.35–4.52 for CBF of <35.4 mL/min/100 g; Supplementary material online, Table S4).

Kaplan–Meier curve showed that patients with CBF of <35.4 mL/min/100 g developed more long-term adverse

Figure 1 Time-dependent receiver-operating characteristic curves testing the diagnostic value of global cerebral blood flow (CBF, A) from cerebral blood flow population (n = 224) and the minute ventilation/carbon dioxide production (VE/VCO₂) slope (B) from cardiopulmonary exercise test (CPET) population (n = 116) in predicting cardiac death or urgent heart transplantation within 2 years in systolic heart failure patients.

Figure 2 Kaplan–Meier curves for outcomes in patients with systolic heart failure according to cerebral blood flow (CBF) with cut-off values of 35.4 mL/min/100 g.
outcomes (higher rates of cardiac death or urgent heart transplantation) than patients with CBF of $\geq 35.4$ mL/min/100 g (Figure 2).

We investigated whether the inclusion of global CBF data would enhance the predictive accuracy of a model that incorporated exercise data. We found that the C-index increased from 0.826 to 0.837 for predicting the occurrence of cardiac death or urgent transplantation when the global CBF value was included in a prognostic model that used the VE/VCO$_2$ slope data. However, this increase could not reach the statistical difference (difference = 0.011; 95% CI, −0.003 to 0.040).

**Discussion**

The present prospective observational study demonstrated that global CBF measured using radionuclide angiography was associated with cardiac death or urgent heart transplantation in patients with systolic HF. In addition, global CBF data provided further prognostic information in addition to that provided by exercise test results. To our knowledge, this study is the first to investigate global CBF as a prognostic surrogate.

The present findings indicate that global CBF may be useful for determining the prognosis of systolic HF patients, and in the selection of heart transplantation candidates. Moreover, the study indicates that global CBF measurement may provide supplementary prognostic information in advanced HF patients who are not able to perform a CPET.

**The development of cerebral hypoperfusion in systolic heart failure**

Normal CBF is $\sim 50$ mL/min/100 g and is usually maintained by autoregulation of brain vessels with changes in mean blood pressures over a wide range.$^{10,11}$ Compensatory mechanisms operate to protect brain perfusion during marked depression of cardiac output. In general, patients with HF are believed to have normal CBF because of the redistribution of blood flow towards the vital organs. However, previous studies have demonstrated that prolonged low cardiac output resulted in decreased CBF despite the compensatory mechanisms.$^{9,10}$

The reasons why brain vessel autoregulation is impaired in advanced HF patients are yet to be determined. Because myocardial performance deteriorates in HF, the sympathetic and the renin–angiotensin systems are activated to maintain systemic perfusion pressure. However, this enhanced neurohormonal system may increase vascular resistance within the brain and lead to decreased CBF. This scenario is supported by studies showing that inhibition of the renin–angiotensin system augmented CBF in HF patients.$^{19,20}$ However, the findings of the present study argue against this being the sole mechanism because we found that the groups with/without an event were similar in terms of angiotensin-converting enzyme-inhibitor and angiotensin II receptor blocker use.

A previous report indicated the beneficial effects of phosphodiesterase inhibitors, which increase intracellular adenosine monophosphate levels in cerebral vessels, on cerebral vasodilation in HF patients, suggesting the importance of endogenous vasoactive molecules.$^{21}$ Furthermore, we previously reported that some cerebral metabolites might be associated with CBF reduction in HF.$^{22}$ Regardless of the mechanism, CBF reduction seems to reflect the chronicity of low cardiac output. This is supported by previous findings showing that decreased CBF in HF was related to disease duration,$^{11}$ and that acute modulation of cardiac output had little effect on CBF.$^{21,23}$

Cerebral blood flow is not influenced by abrupt changes in cardiac output, which makes it more attractive as a prognostic indicator than other haemodynamic parameters that are likely to change frequently in the setting of medical treatment affecting cardiac output. Our finding that a long duration of HF symptoms was associated with survival also supports the contention that global CBF (indicative of disease duration) would be a good prognostic surrogate in patients with systolic HF.

**Cerebral blood flow as a complementary predictor of prognosis in patients with systolic heart failure**

Peak VO$_2$ has been considered the best indicator for assessing functional capacity and for predicting HF. Mancini et al. proposed a peak VO$_2$ cut-off of 14 mL/kg/min when assessing the risk of mortality.$^{24}$ This threshold is accepted as an indicator for heart transplantation in current practice. However, peak VO$_2$ depends on subject effort and peripheral function, and the prognosis may be inaccurate if these are compromised.$^{25}$ Moreover, peak VO$_2$ is of limited prognostic value in the ‘grey zone’ of 10–18 mL/kg/min.$^{26}$

Recent studies showed the prognostic importance of respiratory gas exchange variables obtained during CPET, such as the VE/VCO$_2$ slope. The increased slope gradient can predict the risk of mortality, hospitalization, and other outcomes more powerfully than peak VO$_2$. Our data showed that the VE/VCO$_2$ slope was independently associated with survival. However, there are also some limitations when using the VE/VCO$_2$ slope as a predictor because it can be affected by acute hyperventilation from anxiety in the early phase of exercise and by lactic acidosis when exercise becomes excessive.$^{29}$

The CPET may not be helpful in all systolic HF patients. Chronic HF itself induces exercise intolerance leading to suboptimal exercise during the test. Maximal cardiac output is impaired up to 50% in HF because of only a small increase of stroke volume during exercise.$^5$ This central haemodynamic abnormality is not the sole cause of exercise intolerance in HF. Peripheral limitations such as reduced muscle mass due to chronic disuse and enhanced ergoreflex activity have been considered other mechanisms of developing exercise intolerance. Chronotropic incompetence is also the important contributor to exercise intolerance, especially in patients with pacemaker implants. Moreover, reduced respiratory muscle endurance or increased pulmonary artery pressure limited the use of the CPET, not to mention patients with pulmonary disorders such as chronic obstructive pulmonary disease or bronchial asthma.

Another concern of physicians and patients is the safety of the CPET. Studies demonstrating CPET safety have used small
sample sizes in selected populations. Moreover, lethal ventricular arrhythmia was reported to be associated with significant LV dysfunction. Recently, a large multicentre prospective study investigating the safety of exercise training in patients with chronic HF (the HF-ACTION trial) reported that regular exercise training was safe, and CPET was found to be safe in a sub-study including this patient cohort. However, those study subjects were medically stable, and only ~1% were of NYHA functional class IV. The safety of using the CPET in HF patients who are not medically stable remains undetermined.

The outstanding issues surrounding CPET suitability and safety further highlight the advantage of using CBF data in prognostic evaluation of advanced systolic HF patients. Radionuclide angiography can be performed even in patients who have limited ability to exercise. Because of small amount of radioligand and short scan time, it seems to be relatively safe even in patients with NYHA class IV.

We found that CBF of \( \leq 35.4 \text{ mL/min/100 g} \) had a relatively good accuracy for predicting adverse outcomes within 2 years as shown in the VE/VCO\(_2\) slope of \( \geq 35 \) (Figure 1). The addition of global CBF data to a model using the VE/VCO\(_2\) slope data increased the C-index although the increase could not reach the statistical difference. This finding suggests that combining global CBF data with exercise data is likely to improve prognostic accuracy and assist in selecting candidates for heart transplantation.

**Study limitations**

First, the study subjects were relatively young and the majority was men. Moreover, the number of patients with ischaemic cardiomyopathy was low. Most of the patients were referred to our institute as possible candidates of heart transplantation. In South Korea, the main aetiology of transplantation is dilated cardiomyopathy, not ischaemic cardiomyopathy. This will explain the difference of the study population compared with that of previous HF trials. Furthermore, only ~44% of patients were on a \( \beta \)-blocker. The reason for the low usage of \( \beta \)-blocker was that it was not yet started in some patients newly diagnosed with HF, and discontinued in others owing to their severely decompensated condition. However, further investigation would be needed about the question that global CBF might have prognostic implications for the patients with currently more prevalent aetiologies and more optimal therapy.

Second, not all patients underwent the CPET, and non-application of the test was not based on criteria determined prior to study enrolment. In the real world, it is not easy to decide to perform the CPET in patients hospitalized for acute decompensated HF. Actually some of the patients were not recovered from the decompensated condition, and underwent heart transplantation. This low rate of exercise testing is our study limitation. To overcome this weak point, we performed the multivariable analysis twice on both total population (CBF population) and its subgroup (CPET population). If we analysed only CPET population, there might be a chance to select patients with less severe symptoms and relatively stable conditions. As shown in Supplementary material online, Tables S1 and S2, clinical and laboratory characteristics of the two groups were not the same. And subsequent reduction of the development of adverse outcomes would affect the results that global CBF may be associated with them as a bias. Therefore, when we analysed CBF population, we added the variable, in the statistical analysis, whether exercise testing was performed or not, to enable an adjustment for bias. In this analysis, six variables including global CBF and the VE/VCO\(_2\) slope were meaningful (Table 4). In the multivariable analysis on CPET population, only CBF and the VE/VCO\(_2\) slope were the common significant variables. But other significant variables in total population were not significant in CPET subgroups (Table 5). It might be due to a selection bias and smaller number of patients. Moreover, we also performed the sensitivity analysis for the case of a missing VE/VCO\(_2\) slope in the multivariable analysis (Supplementary material online, Table S3). When we substituted the missing values with the median, minimum, and maximum values of the non-missing VE/VCO\(_2\) slope, global CBF was still associated with the development of adverse outcomes irrespective of the VE/VCO\(_2\) slope. According to these series of analyses, we concluded that global CBF was independently associated with the development of adverse outcomes.

Third, the study measured global CBF, including both hemispheres rather than regional CBF. Regional CBF is known to be associated with cognitive dysfunction, which is another prognostic determinant in systolic HF patients. It may be useful for future studies to examine the relationship between global CBF and regional CBF.

Fourth, a brain MRI/CT scan was not performed in all patients. Only 81 patients (34.8% of the 233 screened patients) underwent brain MR angiography and 8 patients (9.9%) were found to have cerebrovascular disease. Even if we precluded the patients with a history of cerebrovascular disease or dementia, the effect of silent ischaemia on CBF measurement might not be excluded. In addition, we did not check up the presence of depression at enrolment, which is known to be related to adverse cardiac events. Despite little evidence that depression is associated with decreased CBF in patients with HF, it may be a possible confounder of our results.

Finally, in the present study, we suggested the cut-off value of 35.4 mL/min/100 g to predict adverse outcomes. This value offers us a more straightforward and convenient criterion for prognosis prediction. However, the cut-off value might vary with study population and methods used to measure CBF. Thus, the simple use of the cut-off value should be cautious and the validity should be evaluated in further investigation.

**Conclusions**

Global CBF was found to be independently associated with cardiac death or urgent transplantation in systolic HF patients. This finding is particularly relevant for patients who cannot undergo exercise testing due to poor medical condition. Inclusion of global CBF data improved the predictive power of a model using exercise data only with borderline significance. These findings suggest that global CBF data may assist in identifying advanced systolic HF patients who require urgent transplantation.

**Supplementary material**

Supplementary material is available at European Heart Journal online.
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References