Post-Stress Perfusion Abnormalities Detected on Myocardial Perfusion Single-Photon Emission Computed Tomography Predict Long-Term Mortality After Elective Abdominal Aortic Aneurysm Repair

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Background: After abdominal aortic aneurysm (AAA) repair, relatively low survival during long-term follow-up remains an unresolved issue. Stress myocardial perfusion single-photon emission computed tomography (SPECT) well predicts future mortality overall, as well as providing diagnoses of coronary artery disease. The prognostic value of myocardial SPECT findings after AAA repair, however, remains unclear.

Methods and Results: This study followed 285 patients, all undergoing preoperative pharmacologic stress myocardial perfusion SPECT to determine summed stress score (SSS), then elective AAA repair by open AAA repair or endovascular aneurysm repair. The endpoint of the study was cardiac death. The median follow-up duration was 925 days (range, 541–1,095 days). Twenty-four (8%) died during follow-up. Kaplan-Meier analysis showed that patients with SSS ≥9 had a significantly poorer prognosis than those with SSS <9 (76% vs. 93%, P=0.003). Multivariate Cox proportional hazards analysis indicated that SSS ≥9, diabetes, and chronic kidney disease ≥stage 3 could significantly and independently predict long-term cardiovascular mortality in patients after AAA repair (hazard ratio [HR], 4.2; 95% confidence interval [CI]: 1.8–9.7, P=0.001; HR, 3.0; 95% CI: 1.2–7.4, P=0.020; and HR, 4.1; 95% CI: 1.7–10.1, P=0.029, respectively).

Conclusions: Preoperative pharmacologic stress myocardial perfusion SPECT is a useful method to predict long-term cardiovascular mortality for patients undergoing elective AAA repair. (Circ J 2013; 77: 1229–1234)

Key Words: Coronary artery disease; Endovascular aneurysm repair; Open abdominal aortic aneurysm repair; Summed stress score

Elective abdominal aortic aneurysm (AAA) repair is a prophylactic operation to prevent aneurysm-related death. Patients must have an expectation of relatively long survival, taking into account the operative risk. When compared with open AAA repair (OAR), endovascular aneurysm repair (EVAR) is associated with a significant reduction of short-term morbidity and mortality.1,2 Thus, EVAR has become established as a therapeutic choice for the majority of patients with AAA.3 After successful AAA repair, independent of whether by OAR or EVAR, however, relatively reduced survival with long-term follow-up remains unresolved.4,6 Furthermore, there has been limited study reporting predictors of long-term outcome after elective AAA repair including EVAR in a Japanese population. Therefore, clarification of risks regarding long-term mortality after AAA repair is needed.

Stress myocardial perfusion single-photon emission computed tomography (SPECT) is an established tool not only to diagnose coronary artery disease (CAD) but also to predict outcome. In particular, the summed stress score (SSS), representing the extent of myocardial perfusion abnormality, can well predict future morbidity and mortality.7,8 Although many studies have shown that CAD is a risk factor after elective AAA repair, there has been limited study reporting predictors of long-term outcome after elective AAA repair including EVAR in a Japanese population. Therefore, clarification of risks regarding long-term mortality after AAA repair is needed.
repair, the definitions of CAD have differed between studies. Furthermore, to the best of our knowledge, limited reports on stress myocardial perfusion SPECT findings are available concerning prediction of long-term cardiovascular mortality after elective AAA. The aim of this study was therefore to determine risk factors, including SSS evaluated on preoperative pharmacologic stress myocardial perfusion SPECT, for cardiovascular death in Japanese patients undergoing elective AAA repair.

Methods

Patients

This study followed consecutive patients who underwent successful elective infrarenal AAA repair, by OAR or EVAR, between January 2007 and June 2011 in Nagoya University Hospital. In all patients, except for those with uncontrolled bronchial asthma, pharmacologic stress myocardial perfusion SPECT was performed within 2 months before AAA repair. The primary endpoint was cardiac death, defined as death from cardiovascular cause or sudden death. Patients were followed up for up to 3 years. The database was developed prospectively and clinical data were analyzed retrospectively. The protocol for the current study and chart reviews were approved by the institutional ethics committee.

Pharmacologic Stress Myocardial Perfusion SPECT

For the stress, adenosine triphosphate disodium was used for all patients, a dose of 720μg/kg being injected over 6 min using an infusion pump. Thallium-201 (201Tl; 111 MBq) was injected i.v. 3 min after the start of adenosine infusion. Scintigraphic images were acquired at 10 min and then 4 h after tracer injection using a 2-detector camera (Symbia-S, Siemens Japan, Tokyo, Japan or E.CAM, Toshiba, Nasu, Japan) equipped with a low-energy high-resolution parallel collimator. Images were collected over a 180° arc from 45° left anterior oblique to 45° right posterior oblique with an acquisition time of 30 s/image. Energy discrimination was provided by a 20% window centered at 70 KeV. SPECT images were transferred to a computer with 64×64 matrix size and were reconstructed from data using a data processor (e.soft, Toshiba, Nasu, Japan) combined with a Butterworth filter (order 8, cut-off frequency 0.32 cycle/pixel) and a ramp filter (order 8, cut-off frequency 0.32 cycle/pixel), without attenuation or scatter correction. SPECT slices were created relative to the anatomic axis of the left ventricle, and vertical long axis, horizontal long-axis, and short-axis were generated. The SSS from the 201TI SPECT data using a 17-segment and 5-point scoring system were calculated automatically using Heart Score View software (Nihon Medi-Physics, Tokyo, Japan). A previous report has demonstrated that defect scores calculated by this software are similar to those by visual assessments. The results were checked visually by 2 physicians (S.I. and S. Oshima) blinded to the patient details. Thresholds of % tracer uptake required to produce scores by the software were determined as previously described. We stratified the severity of CAD according to the previous literature: normal, SSS <4; mildly abnormal, SSS 4–8; moderately abnormal, SSS 9–13; and severely abnormal, SSS ≥14.

Other Definitions

Fasting blood samples were obtained from a peripheral vein in the morning before stress myocardial perfusion SPECT to evaluate renal and metabolic profiles. The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) study equation modified with the Japanese coefficient (0.741 MDRD). Left ventricular ejection fraction (LVEF) was determined on echocardiography. Hypertension was defined as systolic/diastolic blood pressure (SBP/DBP) >140/90 mmHg, or having received treatment for hypertension. Diabetes mellitus was diagnosed if patients had hemoglobin A1c ≥6.5%, a fasting plasma glucose concentra-

| Table 1. SPECT Complications and Measurements |
|---------------------------------------------|
| **n=285**                                   |
| Minor complication                          |
| Chest discomfort                            |
| 5 (2)                                       |
| Palpitation                                 |
| 2 (1)                                       |
| Flushing                                    |
| 4 (1)                                       |
| Major complication                          |
| Death                                       |
| 0                                           |
| Myocardial infarction                       |
| 0                                           |
| Cerebral infarction                         |
| 0                                           |
| Shock                                       |
| 0                                           |
| Asthma                                      |
| 0                                           |
| ECG change                                  |
| ST elevation                                |
| 0                                           |
| ST depression                               |
| 8 (3)                                       |
| Atrioventricular block                      |
| 3 (1)                                       |
| Premature ventricular contraction           |
| 5 (2)                                       |
| Supraventricular premature contraction      |
| 6 (2)                                       |
| BP (mmHg) [resting/ peak]                   |
| SBP 148±21/127±21 <0.001                    |
| DBP 77±15/68±14 <0.001                      |
| Heart rate (beats/min) [resting/ peak]      |
| 66±11/75±13 <0.001                          |

Data given as n (%) or mean±SD. BP, blood pressure; DBP, diastolic BP; ECG, electrocardiogram; SBP, systolic BP; SPECT, single-photon emission computed tomography.
SSS Predicts Mortality After AAA Repair

Results

Two hundred and eighty-five patients were eligible for the present study. Complications and measurements during preoperative pharmacologic stress myocardial perfusion SPECT are summarized in Table 1. Although several patients experienced minor complications, no major problems were encountered. The mean peak blood pressure was significantly lower than the resting blood pressure (SBP, 127±21 mmHg vs. 148±21 mmHg, P<0.001; DBP, 68±14 mmHg vs. 77±15 mmHg, P<0.001). At the same time, the mean peak heart rate was significantly higher than the resting heart rate (75±13 beats/min vs. 66±11 beats/min, P<0.001). Abnormal SPECT images were obtained for 83 patients (29%). Figure 1 shows results of pharmacologic stress myocardial perfusion SPECT. The median follow-up duration was 925 days (range, 541–1,095 days). During follow-up, 24 patients (8%) died of cardiovascular disease (sudden death, n=3; myocardial infarction, n=4; heart failure, n=6; stroke, n=4; others, n=7). Incidence of cardiac death was 6% in patients with normal SSS (≤3), 9% in those with mildly abnormal SSS (4–8), 25% in those with moderately abnormal SSS (9–13), and 24% in those with severely abnormal SSS (≥14; P=0.020). *P=0.042 for SSS 9–13 vs. SSS 0–3. †P=0.025 for SSS ≥14 vs. SSS 0–3.

Table 2. Patient Characteristics

|                | Survivors (n=261) | Cardiac death (n=24) | P-value |
|----------------|------------------|----------------------|---------|
| Age (years)    | 75±7             | 76±8                 | 0.629   |
| Male           | 217 (83)         | 22 (92)              | 0.390   |
| Clinical history |                  |                      |         |
| Hypertension   | 183 (70)         | 18 (4)               | 0.652   |
| Diabetes       | 44 (17)          | 10 (42)              | 0.006   |
| Brinkman index | 700 (0–1,085)    | 615 (0–1,117)        | 0.355   |
| COPD           | 25 (10)          | 5 (21)               | 0.153   |
| Cerebrovascular disease | 26 (10) | 2 (9)               | 1.000   |
| eGFR (ml·min⁻¹·1.73m⁻²) | 62±20 | 47±25               | 0.001   |
| CKD ≥ stage 3  | 125 (48)         | 17 (71)              | 0.034   |
| LVEF <45%      | 8 (3)            | 2 (8)                | 0.202   |
| Stress myocardial perfusion SPECT |                |                      |         |
| SSS            |                  |                      | 0.020   |
| 0–3            | 190 (72)         | 12 (50)              |         |
| 4–8            | 49 (19)          | 5 (21)               |         |
| 9–13           | 9 (3)            | 3 (13)               |         |
| ≥14            | 13 (5)           | 4 (17)               |         |

Data given as mean ± SD, median (interquartile range) or n (%).
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; EVAR, endovascular aneurysm repair; LVEF, left ventricular ejection fraction; SPECT, single-photon emission computed tomography; SSS, summed stress score.

Statistical Analysis

SPSS version 18 (SPSS, Chicago, IL, USA) was used for all statistical analyses. Shapiro-Wilk test was performed to test normal distributions. Variables with a non-normal distribution are given as median and interquartile range, and were analyzed using Mann-Whitney U-test. Variables with a normal distribution are described as mean±SD and differences were evaluated using Student unpaired or paired t-tests. Categorical variables are presented as numbers (percentages), and comparisons across 2 groups were done with a chi-square test or a Fisher exact test. The cumulative survival rates in each group were analyzed with the Kaplan-Meier method, and the differences in survival rates between groups were estimated using the log-rank method. Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated for each factor on Cox univariate analysis. Furthermore, Cox multivariate regression analysis was performed to determine independent predictors of cardiac death. Factors with P<0.10 on univariate analysis were entered into the multivariate Cox regression analysis. Statistical significance was defined as a 2-tailed P<0.05.
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Cardiac death more frequently had SSS \( \geq 9 \) than survivors, and therefore, we adopted SSS \( \geq 9 \) as a cut-off value. As a result, also in patients after AAA repair, SSS \( \geq 9 \) was a significant predictor of long-term cardiovascular mortality. In the earlier study, however, the cumulative 3-year survival rate in patients with SSS \( \geq 9 \) was \( >90\% \). Com pared to that, the present rate was very much lower, underlining the necessity for patients with SSS \( \geq 9 \) after AAA repair to be treated intensively to SSS (9–13), and 24\% in those with severely abnormal SSS (\( \geq 14 \); \( P=0.020 \)). The incidence of cardiac death in patients with moderately abnormal SSS (9–13) and that in patients with severely abnormal SSS (\( \geq 14 \)) was significantly higher than that in patients with normal SSS (\( \leq 3 \); \( P=0.042 \) and \( P=0.025 \), respectively; Figure 2). Patient characteristics are given in Table 2. The prevalences of diabetes and chronic kidney disease (CKD) \( \geq \) stage 3 in patients with cardiac death were significantly higher than in survivors (44\% vs. 10\%, 42\%; \( P=0.006 \); and 125\% vs. 17\%, 71\%; \( P=0.034 \)). Worse SSS was evident in patients with cardiac death than in survivors (\( P=0.020 \)). Kaplan-Meier analysis indicated that the cumulative 3-year survival rate was significantly lower in patients with SSS \( \geq 9 \) than in those with SSS <9 (76\% vs. 93\%, \( P=0.003 \); Figure 3). Also in patients with diabetes or CKD \( \geq \) stage 3, the cumulative 3-year survival rate was significantly lower than in those without (81\% vs. 93\%, \( P=0.001 \), and 88\% vs. 96\%, \( P=0.029 \); Figure 4). Multivariate Cox proportional hazards analysis indicated that diabetes, CKD \( \geq \) stage 3, and SSS \( \geq 9 \) were significant and independent predictors of 3-year cardiac death (HR, 4.2; 95\% CI: 1.8–9.7, \( P=0.001 \); HR, 3.0; 95\% CI: 1.2–7.4, \( P=0.020 \); and HR, 4.1; 95\% CI: 1.7–10.1, \( P=0.029 \), respectively; Table 3).

**Discussion**

In the present study we have demonstrated for the first time that preoperative pharmacologic stress myocardial perfusion SPECT is a safe and helpful method to predict long-term cardiovascular mortality after elective AAA repair in a Japanese population. Previous studies in patients undergoing stress myocardial SPECT due to suspected or known CAD showed that increased SSS, \( \geq 9 \) being a good cut-off value, is a predictor of future cardiovascular events.\(^7\) In the present study, patient with cardiac death more frequently had SSS \( \geq 9 \) than survivors, and therefore, we adopted SSS \( \geq 9 \) as a cut-off value. As a result, also in patients after AAA repair, SSS \( \geq 9 \) was a significant predictor of long-term cardiovascular mortality. In the earlier study, however, the cumulative 3-year survival rate in patients with SSS \( \geq 9 \) was \( >90\% \).\(^8\) Compared to that, the present rate was very much lower, underlining the necessity for patients with SSS \( \geq 9 \) after AAA repair to be treated intensively to
improve their prognosis. Diabetes and CKD also could significantly predict long-term cardiovascular mortality in the present study, as previously reported. 16,17 Although these diseases are well-known risk factors for CAD,18–20 the multivariate model showed that myocardial ischemia detected on pharmacologic stress myocardial perfusion SPECT could significantly and independently predict long-term cardiovascular mortality in patients after AAA repair.

Various risk prediction models for elective AAA repair have shown that CAD detected on chart review, rest electrocardiogram (ECG), and so on adversely influences outcome. 9,21,22 Exercise stress ECG is the first-line examination to detect CAD, but it causes blood pressure elevation, with the risk of unexpected AAA rupture. 23 Furthermore, the sensitivity and specificity of this test, at 70% and 66%, respectively, are not very high. 24 Coronary angiography or coronary computed tomography angiography using contrast medium are established approaches to diagnose CAD. 25,26 A reasonably high number of patients undergoing elective AAA repair, however, suffer from CKD. 27 Approximately half of the present patients had concomitant moderate to severe CKD. Therefore, it might be better to avoid use of contrast medium to prevent contrast-induced nephropathy. 27,28 In the present study, no major complications including blood pressure concerns were seen during pharmacologic stress myocardial perfusion SPECT, although heart rate elevation was observed. The sensitivity and specificity of this examination, at 87% and 73%, respectively, are relatively high. 29 Furthermore, this method does not affect renal function. Therefore, preoperative pharmacologic stress myocardial perfusion SPECT can be performed safely as a less invasive method to detect concomitant CAD in patients referred for elective AAA repair.

LVEF and left ventricular end-diastolic volumes derived from quantitative gated SPECT are reportedly powerful predictors for adverse cardiac events. 8,29 In the present study, because we used 201TI as a perfusion tracer, we did not perform quantitative gated SPECT analysis. Therefore, we did not obtain LVEF and left ventricular volumes in this way.

**Conclusion**

Preoperative pharmacologic stress myocardial perfusion SPECT is not only safe, but also a useful method to predict long-term cardiovascular mortality for patients undergoing elective AAA repair. Patients with SSS ≥9, as well as diabetes or CKD, are at high risk after elective AAA repair.

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### Disclosures

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### Table 3. Predictors for Cardiac Death: Cox Proportional Hazards Analysis

| Predictor                      | HR (95% CI) | P-value | HR (95% CI) | P-value |
|--------------------------------|-------------|---------|-------------|---------|
| Age ≥70 years                   | 3.9 (0.91–16.5) | 0.067   | 3.0 (0.69–13.1) | 0.144   |
| Male                           | 2.6 (0.60–10.9) | 0.202   |             |         |
| Hypertension                   | 1.3 (0.53–3.4) | 0.541   |             |         |
| Diabetes                       | 3.5 (1.5–7.8) | 0.001   | 4.2 (1.8–9.7) | 0.001   |
| Brinkman index ≥800            | 0.97 (0.43–2.2) | 0.943   |             |         |
| Cerebrovascular disease        | 1.0 (0.24–4.3) | 0.982   |             |         |
| CKD stage 3                    | 2.6 (1.1–6.2) | 0.029   | 3.0 (1.2–7.4) | 0.020   |
| LVEF <45%                      | 2.7 (0.64–11.6) | 0.177   |             |         |
| SSS ≥9                         | 3.5 (1.5–8.5) | 0.003   | 4.1 (1.7–10.1) | 0.002   |
| EVAR                           | 1.2 (0.53–2.6) | 0.688   |             |         |

Cardiac deaths, n=24. Multivariate model; chi-square P<0.001.

CI, confidence interval; EVAR, endovascular aneurysm repair; HR, hazard ratio. Other abbreviations as in Table 2.
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