Prognostic value of Rb-82 positron emission tomography myocardial perfusion imaging in coronary artery bypass patients

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Received 11 October 2013; accepted after revision 19 November 2013; online publish-ahead-of-print 29 January 2014

Aims
We sought to determine the prognostic value of positron emission tomography (PET) myocardial perfusion imaging (MPI) in patients with prior coronary artery bypass graft (CABG) surgery. PET MPI has recently been shown to provide incremental risk stratification for patients with suspected coronary artery disease (CAD), but the prognostic utility of PET MPI in CABG patients has not been well studied.

Methods and results
A multi-centre PET registry of 7061 patients who underwent Rb-82 PET MPI from four participating centres was screened. Nine hundred and fifty-three CABG patients were identified and their images were analysed. Outcomes of all-cause mortality and cardiac death were collected. With a mean follow-up of 2.4 ± 1.4 years, 128 (13.4%) all-cause deaths and 44 (4.6%) cardiac deaths were observed. Multivariable analyses, adjusted for clinical variables, demonstrated that the summed stress score (SSS) was a significant independent predictor of both all-cause mortality [HR: 1.60 (per 1 category increase in SSS); 95% CI: 1.34–1.92; P < 0.001] and cardiac death (HR: 1.80; 95% CI: 1.33, 2.44; P < 0.001). The receiver-operator characteristic (ROC) curves showed that the addition of SSS increased the area under the curve (AUC) from 0.645 to 0.693 (P = 0.014) for all-cause mortality, and from 0.612 to 0.704 (P = 0.027) for cardiac death. SSS also improved the net reclassification improvement (NRI) for all-cause mortality (category-free NRI = 0.422; 95% CI: 0.240–0.603; P < 0.001) and cardiac death (category-free NRI = 0.552; 95% CI: 0.268–0.836; P < 0.001).

Conclusions
PET MPI provides independent and incremental prognostic value to clinical variables in predicting all-cause mortality and cardiac death in CABG patients.

Keywords
Coronary artery bypass graft • Positron emission tomography • Myocardial perfusion imaging • Rubidium-82 • Prognosis • All-cause mortality • Cardiac death

Introduction
Coronary artery bypass graft (CABG) surgery is performed to reduce patient symptoms and improve patient survival. However, progression of disease in native coronary arteries and the development of disease in bypass grafts can result in significant morbidity and mortality post-CABG. Patients with prior CABG have high rates of major adverse cardiac events (MACEs) and/or mortality compared with those without prior CABG. Thus, the stratification and management of CABG patients remains clinically important.

Positron emission tomography (PET) myocardial perfusion imaging (MPI) is an accurate non-invasive tool for assessing myocardial perfusion and myocardial blood flow, and has emerged as a useful tool for patients with suspected coronary artery disease (CAD).
Specifically, the use of Rb-82 PET MPI has largely expanded in clinical practice and its prognostic value has previously been studied. Recently, results from a large multi-centre PET registry suggested that Rb-82 PET has an incremental value for risk estimation compared with traditional risk factors. Though the prognostic value of PET MPI has primarily been studied in patients with suspected CAD, the incremental value of PET specifically in CABG patients requires investigation.

We sought to determine the potential incremental value of PET MPI in patients with prior CABG.

Methods

Study population

Between January 2000 and July 2009, a total of 7061 patients from four participating centres underwent pharmacological stress Rb-82 MPI and were entered into a PET registry. Of these, 953 patients with prior CABG were identified and included in this analysis. Baseline clinical characteristics were collected as per site-specific protocols. Risk factors were based on historical information and were verified by medical records whenever possible. This study was approved by the institutional review board at each participating centre.

MPI methods

Each patient underwent Rb-82 MPI using a dedicated or hybrid PET/computed tomography (CT) scanner using site-specific protocols. From PET MPI images, the SSS, summed rest score (SRS), and summed difference score (SDS) were computed by dividing by 68 and multiplying by 100 based on visual scoring in three sites or generated by software in one site as described above and multiplied by 100 to obtain a percentage. Patients were stratified according to percent left ventricular SSS categories (four categories: 0; 0.1–9.9; 10–19.9; ≥20%).

Outcome measures

The primary outcome measure of all-cause mortality was available at all four participating centres. Since cardiac death was available at three of the four centres, cardiac death was used as a secondary outcome. The ascertainment of death was conducted by trained study coordinators supervised by the site clinical investigators. Telephone contact with the patients with scripted patient interviews, electronic medical records, or other source documents (i.e. patient’s medical record, verbal confirmation by the patient’s primary care physician, or review of death certificates) were used for death confirmation. At all US sites, the National Death Index was applied for confirmatory purposes.

Statistical analyses

Statistical analyses were performed using the IBM SPSS Statistics 20 (Armonk, NY, USA) and SAS 9.2 (NC), and statistical significance was defined as $P < 0.05$. Continuous variables are presented as means and standard deviations, and categorical variables are presented as frequencies with percentages.

Univariable Cox regression models were used to evaluate the association between clinical and/or PET measures with death outcomes. Risk-adjusted analyses were conducted using multivariable Cox regression models to examine the prognostic value of PET measures adjusted for clinical variables, and the adjusted survival curves were plotted. Model over-fitting was considered, and the proportional hazards assumption was met in every case. The incremental value of PET measures was calculated by defining the clinical predictors model followed by the addition of PET measures and compared using the likelihood ratio tests. The receiver-operator characteristic (ROC) curves were generated using the multivariable logistic models. The area under the ROC curves [95% confidence intervals (CIs)] was compared to evaluate the discrimination ability of PET measures over clinical predictors to predict death outcomes. Additionally, a category-free net risk reclassification improvement (NRI) was calculated to assess the improvement of reclassification using the PET measures. The warranty period (i.e. time to cardiac death rate ≥1%) of a normal PET scan was also calculated using the adjusted survival curve for cardiac death.

Cox models of all-cause mortality

A total of 953 subjects with prior CABG were analysed for the primary outcome of all-cause mortality (Table 1). Follow-up was available for all patients and the mean follow-up time was $2.4 \pm 1.4$ years.

All-cause mortality was observed in 128 subjects (13.4%). Univariable Cox regression analysis showed that patients who died were older, had a lower BMI, and had a lower prevalence of dyslipidaemia and angina/dyspnoea (Table 2). PET MPI measures (SSS, SRS, and SDS) were higher in patients who died compared with those who were alive (Table 2). The risk-adjusted analysis for all-cause mortality included the following clinical predictors of age, female, BMI, diabetes mellitus (DM), dyslipidaemia, hypertension, smoker, and angina/dyspnoea. The Cox multivariable model adjusted for clinical variables demonstrated that SSS was a significant independent predictor of all-cause mortality.
Table 2  Univariable and multivariable analyses for all-cause mortality (n = 953)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariable</th>
<th>Multivariable</th>
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<tbody>
<tr>
<td></td>
<td>No death, n = 825</td>
<td>Death, n = 128</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>69.1 ± 10.8</td>
<td>72.0 ± 10.4</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>240 (29.1)</td>
<td>38 (29.7)</td>
</tr>
<tr>
<td>Body mass index (per unit increase in kg/m²)</td>
<td>29.0 ± 5.8</td>
<td>27.3 ± 6.4</td>
</tr>
<tr>
<td>Cardiac risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>330 (40.0)</td>
<td>58 (45.3)</td>
</tr>
<tr>
<td>Dyslipidaemia (%)</td>
<td>667 (80.8)</td>
<td>91 (71.0)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>622 (75.4)</td>
<td>96 (75.0)</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>160 (19.4)</td>
<td>23 (18.0)</td>
</tr>
<tr>
<td>Angina and/or Dyspnoea (%)</td>
<td>569 (69.0)</td>
<td>76 (59.4)</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>365 (44.4)</td>
<td>65 (50.8)</td>
</tr>
<tr>
<td>PET parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summed stress score (per % increase)</td>
<td>11.7 ± 12.6</td>
<td>18.1 ± 15.1</td>
</tr>
<tr>
<td>Summed rest score (per % increase)</td>
<td>5.9 ± 8.8</td>
<td>11.1 ± 11.9</td>
</tr>
<tr>
<td>Summed difference score (per % increase)</td>
<td>5.8 ± 8.2</td>
<td>7.0 ± 9.4</td>
</tr>
<tr>
<td>Summed stress score categories</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>147 (17.8)</td>
<td>8 (6.25)</td>
</tr>
<tr>
<td>0.1–9.9%</td>
<td>321 (38.9)</td>
<td>41 (32.0)</td>
</tr>
<tr>
<td>10–19.9%</td>
<td>174 (21.1)</td>
<td>24 (18.8)</td>
</tr>
<tr>
<td>≥20%</td>
<td>183 (22.2)</td>
<td>55 (43.0)</td>
</tr>
</tbody>
</table>

Cox models of cardiac death

Of the 953 CABG patients, 805 (84.5%) had cardiac death information and were included in a secondary analysis. Cardiac death occurred in 44 subjects (5.2%). Patients who had cardiac death were older, had a higher prevalence of DM, and had lower prevalence of dyslipidaemia and angina/dyspnoea (Table 3). Similar to all-cause mortality, PET measures (SSS, SRS, and SDS) were higher in patients who suffered cardiac death (Table 3). The Cox multivariable model adjusted for clinical variables demonstrated that SSS was also a significant independent predictor of cardiac death (HR: 1.80, 95% CI: 1.33, 2.44; P < 0.001; Table 3). The addition of prior MI in the Cox multivariable model led to similar findings for SSS (HR: 1.82, 95% CI: 1.32, 2.49; P < 0.001). The relative HR for cardiac death were 0.92 (95% CI: 0.29, 2.95; P = 0.892), 2.18 (95% CI: 0.68, 6.95; P = 0.189), and 3.84 (95% CI: 1.31, 11.23; P = 0.014) for patients with 0.1–9.9, 10–19.9, and ≥20% SSS, respectively, compared with patients with normal SSS (Table 3 and Figure 2). The annual cardiac death rates were 0.87, 1.00, 3.37, and 5.08% for subjects with SSS: 0, 0.1–9.9, 10–19.9, and ≥20%, respectively. The warranty period (i.e. time to cardiac death rate ≥1%) of a normal PET scan in CABG patients was estimated at 1.33 years.

Receiver-operator characteristic curves

Receiver-operator characteristic (ROC) curves were created to evaluate the incremental value of PET MPI over the clinical predictors for all-cause death (Figure 3) and cardiac death (Figure 4). For all-cause death, the area under the curve (AUC) for clinical variables was 0.645.
(95% CI: 0.594, 0.695) and increased to 0.693 (95% CI: 0.645, 0.742; P = 0.014) when SSS categories were added (Figure 3). For cardiac death, the addition of SSS categories to clinical variables increased the AUC to 0.704 (95% CI: 0.622, 0.786; P = 0.027) from 0.612 (95% CI: 0.527, 0.696) (Figure 4).

**Net risk reclassification improvement**

Using the category-free NRI analysis, the addition of SSS categories to the clinical model led to a statistically significant improvement in risk reclassification (NRI: 0.422; 95% CI: 0.240–0.603, P < 0.001) for all-cause mortality (Table 4).

**Discussion**

To our knowledge, this is the first study to demonstrate the independent and incremental prognostic value of PET MPI in CABG.
patients. Our findings suggest that SSS measured by Rb-82 PET MPI in CABG patients has prognostic value and is incremental to clinical predictors. Using ROC models, the addition of SSS to clinical predictors resulted in an increase of the AUCs for both all-cause mortality and cardiac death. Additionally, SSS led to a significant risk reclassification for all-cause mortality and cardiac death.

There is growing single-centre and multi-centre evidence supporting the prognostic value of PET MPI. In an early study, Marwick examined cardiac outcomes (cardiac death, MI, unstable angina, and late revascularization) of 685 patients who underwent Rb-82 PET stress MPI, and showed that patients with normal scans had a higher event-free survival compared with patients with abnormal scans. This was subsequently confirmed in 629 patients with normal PET MPI, which showed that normal Rb-82 PET MPI has a very low annual event rate for cardiac death, non-fatal MI, or revascularization and that the rates of cardiac death and non-fatal MI increased with the severity of Rb-82 PET stress MPI results. The prognostic value of PET appears to be preserved even in association with exercise and dobutamine stress.

As well, other PET measures such as ejection fraction (EF) and myocardial flow reserve (MFR) were an independent predictor of events. Prognostic value of MFR (measured by N-13 ammonia PET) has been shown to be a better predictor than resting left ventricular ejection fraction (LVEF) and relative MPI. These studies suggest that quantitative MBF using Rb-82 PET MPI could improve risk stratification. Future studies examining the incremental value of MFR over SSS in CABG patients are needed.

In our large multi-centre registry, of which the current report is a subset analysis, Dorbala et al. showed that patients with severely abnormal stress PET MPI had an increased risk of cardiac death (about five-fold increase) compared with those who had a normal stress PET MPI. Our findings are consistent with those obtained from the aforementioned analyses, and given that CABG patients without perfusion defects were at low risk as evidenced by an annual cardiac death rate of <1% (0.87%), this study confirms the prognostic value of PET MPI in CABG patients.

The prognostic value of other modalities has been documented in the CABG population showing that the number of protected coronary territories predicted MACE and all-cause death. Recently, complete pre-operative echocardiography has been reported to provide incremental value over traditional risk scores in identifying patients at high risk of mortality following CABG. The prognostic value of SPECT MPI has been well established and can detect graft disease in CABG, its prognostic value in CABG patients has not been robustly studied. Our findings support those of previous studies in CABG patients, but emphasize that the risk among CABG patients varies and can be further stratified using PET MPI. The benefit of one non-invasive modality over another remains to be determined.

Though counter-intuitive, dyslipidaemia, BMI, angina/dyspnoea, female gender, and/or hypertension were associated with lower all-cause mortality and cardiac death. These results are likely explained by treatment bias with more aggressive medical therapy (i.e. treatment for dyslipidaemia or hypertension) in those patients with greater co-morbidities. The lower mortality rates observed in patients with greater BMI could also be due to the obesity paradox.

**Limitation**

In our study cohort, clinical variables such as heart failure, symptoms, atrial fibrillation, medications, time from CABG, and graft type (arterial or venous) were unavailable and therefore could not be assessed within the clinical model. This may limit the generalizability of our results. However, traditional clinical variables such as age, sex, DM, BMI, dyslipidaemia, hypertension, smoking, and angina/dyspnoea were used. LVEF was available for 423 of the 953 CABG patients (44.4%). Cox regression analyses were conducted in this subset of CABG patients with LVEF. The incorporation of LVEF into the clinical model did not provide incremental value to SSS for all-cause mortality and was likely due to the small sample size. Similarly, LVEF could not be assessed as a predictor of cardiac death due to the small number of events. The prognostic value of SDS was not demonstrated in our study. However, in a multivariable Cox model adjusted for clinical variables (including prior MI), a trend towards predicting both all-cause mortality (HR: 1.02, 95% CI: 1.00, 1.04; $P = 0.078$) and cardiac death (HR: 1.03; 95% CI: 1.00–1.06; $P = 0.056$) was observed for SDS. This may be related to a population bias, whereby revascularization may have been driven by the PET results and ischaemia thus altering the outcomes of patients with significant SDS scores.

MACE was not systematically collected at all centres, but cardiac death was available for 805 patients and confirmed the findings of
the primary outcome measure. This is the largest PET prognosis study in CAGB patients, but confirmation in a larger population is needed.

Conclusions

We demonstrate that the use of PET MPI provides incremental value over clinical predictors in predicting all-cause mortality and cardiac death in CAGB patients. Further studies using a larger CAGB cohort are needed to confirm our results.

References