Independent and incremental prognostic value of left ventricular ejection fraction determined by stress gated rubidium 82 PET imaging in patients with known or suspected coronary artery disease

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Background. **Whether left ventricular ejection fraction (EF) obtained by gated rubidium 82 positron emission tomography (PET) myocardial imaging can identify patients at risk for future cardiac events is unclear.**

Methods and Results. **Consecutive patients with known or suspected coronary artery disease who underwent dipyridamole stress gated Rb-82 PET imaging were evaluated. Scoring of perfusion was accomplished by use of a 17-segment model. EF was automatically generated. Patients were stratified based on summed stress scores (SSSs) (0-3, 4-8, or >8) and stress EF (>50%, 40%-49%, or <40%). All-cause mortality was determined by use of the Social Security Death Index. Of 1,441 patients, 132 (9.2%) died during mean follow-up of 2.7 ± 0.8 years. Annualized mortality rates across SSS groups were 2.4% for SSS of 0 to 3, 4.1% for SSS of 4 to 8, and 6.9% for SSS greater than 8 ($P < .001$). Similarly, annualized mortality rates were 2.4%, 6.2%, and 9.2% for the group with EF greater than 50%, group with EF of 40% to 49%, and group with EF lower than 40%, respectively ($P < .001$). On multivariate analysis, the addition of EF to clinical and perfusion variables significantly increased the global χ^2 (73.3 to 107.7, $P < .001$). Integration of EF with SSS significantly enhanced risk stratification.**

Conclusion. **EF assessed by stress gated Rb-82 PET imaging provides independent and incremental prognostic information and, hence, should be routinely incorporated in risk assessment. (J Nucl Cardiol 2008;15:745-53.)**

Key Words: Rubidium radioisotopes • radionuclide imaging • positron emission tomography • exercise test • vasodilator agents • coronary arteriosclerosis • left ventricular function • prognosis • risk assessment

Left ventricular ejection fraction (EF), a major determinant of long-term survival in patients with known or suspected coronary artery disease (CAD),[1-3] can be accurately and reproducibly quantitated during electrocardiography (ECG)–gated single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI).[4,5] Because its quantification during SPECT imaging provides incremental prognostic information compared with perfusion assessment alone for stratifying individuals into various levels of cardiac risk,[6-9] it has become routine to acquire both perfusion and function information within a single session.[10]

Compared with SPECT, positron emission tomography (PET) provides higher-quality perfusion images because of enhanced spatial resolution, improved count density, and superior attenuation correction.[11-13] Rubidium 82 PET MPI, in particular, has a higher sensitivity and specificity than SPECT for diagnosing CAD.[12,14-16] Although the ability of PET perfusion to identify patients at risk for future cardiac events has been documented in a small number of studies,[17,18] none have yet determined

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whether information on function adds to the modality's ability for risk stratification. The goal of this study was to assess whether EF measurements determined by gated Rb-82 PET MPI provide incremental prognostic value beyond perfusion data in patients with known or suspected CAD.

METHODS

Study Population

Consecutive patients with known or suspected CAD who underwent dipyridamole stress gated Rb-82 PET MPI between September 1, 2002, and December 31, 2005, were identified through electronic databases at Hartford Hospital (Hartford, Conn) and Saint Luke's Mid America Heart Institute (Kansas City, Mo). Eligible patients were excluded only if ECG gating was not possible or if the gated component of the study was technically compromised (typically <5% of all studies). Valvular disease and dilated cardiomyopathy were not specified as exclusion criteria. Approval for the study was obtained from the Institutional Review Boards of Hartford Hospital and Saint Luke's Hospital of Kansas City.

Rb-82 PET MPI Protocol

Hartford Hospital protocol. A Discovery LS PET/computed tomography (CT) scanner (GE Healthcare, Waukesha, Wis) was used for all patients undergoing imaging at Hartford Hospital. After a scout CT scan for positioning, a 17-second transmission was performed over the thorax for attenuation correction. Rb-82 (40-60 mCi) was then administered intravenously over a period of 30 seconds, with rest images acquired for 5 minutes after a delay of 105 to 135 seconds. Pharmacologic stress was achieved with the infusion of dipyridamole (0.56 mg/kg over a period of 4 minutes) and followed by an Rb-82 injection 4 minutes after its completion. Stress scans were finally obtained by use of the same protocol as in rest imaging. All acquisitions occurred in 2-dimensional gated mode (septa extended) with simultaneous evaluation of perfusion and function.

Saint Luke's Mid America Heart Institute protocol. All studies were performed on an ACCEL PET scanner (CTI, Knoxville, Tenn). This protocol involved a 4-minute scout transmission scan (germanium 68 rotating line sources) for both patient positioning and attenuation correction. Thereafter 40 to 60 mCi of Rb-82 was infused over a period of 30 seconds. After a 90-second delay for blood pool clearance, 2-dimensional rest images (septa extended) were acquired for a total acquisition time of 5 minutes. The detector septa were then retracted for 3-dimensional acquisition and Rb-82 infused once more. After a 150-second delay, a 3-minute ECG-gated acquisition was performed to assess resting cardiac function. Patients were then stressed with intravenous dipyridamole for 4 minutes (0.56 mg/kg) and scanned via the same protocol and parameters used for rest imaging.

In both laboratories, studies were corrected for emission/transmission misalignment by use of the ImagenPro software application (Cardiovascular Imaging Technologies, Kansas City, Mo). Images were reconstructed with ordered-subset expectation maximization (6 iterations, 8 subsets) and post-filtered with a 3-dimensional isotropic Butterworth noise filter before reorientation to the short- and long-axis images. The resulting images were ultimately displayed in the AutoQuant environment (Cedars-Sinai Medical Center, Los Angeles, Calif) for interpretation and quantitation.

Rb-82 PET Image Interpretation

Myocardial perfusion and function were interpreted without clinical data during daily clinical reading sessions by a consensus of 2 or more experienced readers using standardized myocardial segmentation and nomenclature. Visual scoring of perfusion images was accomplished by means of a 17- or 20-segment model. Patients from Mid America Heart Institute were initially scored according to a 20-segment model and later converted to a 17-segment score by determining the equivalent percentage of myocardial involvement.[19] Hartford Hospital patients were scored from the outset by use of a 17-segment model.

Left ventricular perfusion in each segment was graded according to a 5-point scale (0, normal uptake; 1, mildly reduced uptake; 2, moderately reduced uptake; 3, severely reduced uptake, and 4, no uptake). A global summed stress score (SSS) and summed rest score (SRS) were derived by adding together the segment scores for stress and rest images, respectively. A summed difference score (SDS), reflecting the presence and amount of ischemia, was calculated by subtracting the SRS from the SSS. For analysis, patients were stratified by SSS based on cutoff values (0, 1-3, 4-8, 9-13, and >13). An SSS of 4 or greater represented abnormal stress perfusion, whereas an SDS of 2 or greater signified ischemia.

Stress and rest EFs were determined by use of AutoQuant software.[20-22] EF reserve was calculated as the difference between the stress and rest EFs. Patients were arbitrarily stratified into groups according to stress EF (≥60%, 50%-59%, 40%-49%, 30%-39%, and <30%).

Patient Follow-Up

The primary endpoint of all-cause mortality was assessed by the Social Security Death Index (SSDI).[23] The SSDI is a large database containing vital information for individuals whose deaths have been reported to the US Social Security Administration. It is available as a free online database that is searchable by a person's name, social security number, birth date, death date, and last location of residence. For our study, the SSDI was queried to identify those patients in our population who had died during follow-up. The length of time to follow-up (ascertainment of vital status) ranged from 11 months to 4.4 years; 93% of patients had follow-up for longer than 18 months, whereas 80% of patients had follow-up for 2 years or longer. Patients not identified as dead through the SSDI were considered to be alive at the time of follow-up.