Diastolic Filling Parameters Derived from Myocardial Perfusion Imaging Can Predict Left Ventricular End-Diastolic Pressure at Subsequent Cardiac Catheterization

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Morbidity and mortality increase when diastolic dysfunction accompanies coronary artery disease (CAD). An elevated stress 201Tl lung-to-heart ratio (LHR) is a traditional marker of elevated left ventricular end-diastolic pressure (LVEDP), which adds prognostic value in CAD. Since the introduction of 99mTc-labeled agents, this valuable marker has been lost. Hence, there is only a limited ability to assess diastolic dysfunction by myocardial perfusion imaging (MPI).

Methods: Fifty-two consecutive patients with an ejection fraction of ≥45% underwent MPI and cardiac catheterization within 15 d. Peak filling rate (PFR), time to PFR (TPFR), and filling rate during the first third of diastole (1/3FR) were obtained from MPI with SPECT software. Resting 201Tl LHR was calculated manually, and LVEDP was obtained at catheterization.

Results: PFR, TPFR, and 1/3FR correlated significantly with LVEDP (r = 0.53, 0.45, and −0.45, respectively; P = 0.00005, 0.0009, and 0.0009, respectively), whereas resting 201Tl LHR did not (r = 0.10, P = 0.49). Receiver-operating-characteristic curve analysis of PFR, TPFR, and 1/3FR for detecting LVEDPs of ≥18 mm Hg showed areas under the curve of 0.83, 0.75, and 0.80, respectively. The combination of PFR and 1/3FR showed a negative predictive value of 84%, a positive predictive value of 86%, and a specificity of 94%.

Conclusion: Diastolic filling variables obtained with the SPECT software showed a significant correlation with LVEDP. PFR, TPFR, and 1/3FR were superior to resting 201Tl LHR and showed good sensitivity, specificity, and predictive power for detecting LVEDPs of ≥18 mm Hg. Hence, combining data on the presence of perfusion defects with data on diastolic impairments can be achieved by adding these variables to MPI results.

Key Words: diastole; heart failure; gated SPECT; ventricles


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had undergone both of these procedures within 15 d. All patients with an ejection fraction of \( \geq 45\% \) were included because such patients are considered to have preserved left ventricular systolic function (15). Patients were excluded if there was any significant interval clinical intervention or change in medication between MPI and cardiac catheterization, irregular rhythm, and an incomplete medical record. The study was approved by the local institutional review board.

**MPI**

All patients underwent dual-isotope MPI with 114–148 MBq of \(^{201}\)TI at rest and 925–1,110 MBq of \(^{99m}\)Tc for stress acquisition. Fifteen minutes after \(^{201}\)TI-labeled tracer injection, resting SPECT images were acquired. Sixty minutes after \(^{99m}\)Tc-labeled tracer injection, at peak stress, electrocardiogram-gated SPECT images were obtained. A fixed 90° dual-detector camera (C-cam; Siemens Medical Systems) with elliptic 180° arc (45° right anterior oblique to 45° left posterior oblique), 32 projections at 30 s per projection, and 16 frames per R–R interval was used to acquire SPECT data. The projection data were reconstructed into tomographic transaxial images by use of a filtered backprojection technique with a 3-dimensional ramp Butterworth filter (order, 4; cutoff frequency, 0.50 cycle per pixel). For data analysis, 4D-MSPECT software (University of Michigan) was applied to determine the left ventricular ejection fraction (LVEF), end-diastolic volume (EDV), and end-systolic volume. 4D-MSPECT software automatically fits the left ventricular volume curve (Fig. 1) with a fourth-order harmonic function and derives peak filling rate (PFR), time to PFR (TPFR), and filling rate during the first third of diastole (1/3FR). All diastolic measurements were obtained during stress-gated \(^{99m}\)Tc MPI.

**Resting \(^{201}\)TI LHR Calculation**

The anterior projection frame obtained during resting \(^{201}\)TI SPECT acquisition was used to calculate LHR. Fixed-size square regions of interest were drawn, one over the right lung field and the other over the myocardial wall with the highest count density. LHR was defined as mean counts per pixel in the lung regions of interest divided by mean counts per pixel in the myocardial regions of interest.

**Cardiac Catheterization**

All patients underwent left heart catheterization, coronary angiography, and left ventriculography within 15 d of MPI. A fluid-filled high-fidelity micromanometer pigtail catheter was placed in the left ventricle under fluoroscopic guidance. LVEDP was measured before and after ventriculography, and the average value was obtained. LVEDPs of \( \geq 16 \text{ mm Hg} \) are considered abnormal (15,16). We applied a more stringent criterion for abnormal LVEDPs: \( \geq 18 \text{ mm Hg} \).

**Statistical Analysis**

Numeric variables are expressed as the mean \( \pm 1 \) SD, and categoric variables are presented as numbers and percentages. The Pearson correlation was used to analyze the relationships of PFR, TPFR, 1/3FR, and resting \(^{201}\)TI LHR with LVEDP. Hotelling \( t \) tests were performed to evaluate differences between correlation coefficients (17). Receiver-operating-characteristic (ROC) curve analysis was performed with Analyse-it software (Analyse-it Software, Ltd.) to evaluate the sensitivity and specificity of different PFR, TPFR, and 1/3FR values for detecting LVEDPs of \( \geq 18 \text{ mm Hg} \). The optimal PFR, TPFR, and 1/3FR cutoff values for providing maximum accuracy were then determined. A \( P \) value of \( <0.05 \) was considered to be statistically significant.

**RESULTS**

**Demographics**

The characteristics of the study population are shown in Table 1. Fifty-two patients met all criteria. Patients were more likely to be men (58%), and the mean age of the population was 58 \( \pm 11 \) y (range, 36–85 y). The mean interval between MPI and cardiac catheterization was 8 d. All patients underwent coronary angiography, and 38 patients (73%) had CAD. Fifteen patients (29%) had diabetes, and 42 patients (81%) had hypertension. All patients had LVEFs of \( \geq 45\% \) (the mean LVEF was 54%), and the mean LVEDP was 15 mm Hg.

**4D-MSPECT Diastolic Function Parameters and LVEDP**

The association between diastolic function parameters from 16-frame gated SPECT and LVEDP is shown in Figure 2. There were significant inverse correlations between LVEDP and PFR (\( r = -0.53, P = 0.00005 \)) and between LVEDP and 1/3 FR (\( r = -0.45, P = 0.0009 \)). There was also a significant positive correlation between LVEDP and TPFR (\( r = 0.45, P = 0.0009 \)). Correlations remained significant and similar in the presence or absence of CAD (\( r = 0.42–0.57, P < 0.05 \)), except that 1/3FR did not achieve statistical significance in patients without CAD.

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**FIGURE 1.** Left ventricular diastolic filling curves derived from 4D-MSPECT. (A) Curve with normal diastolic filling parameters. (B) Curve with abnormal diastolic filling parameters. LVEDPs determined at and similar in the presence or absence of CAD.
The correlation between LVEDP and resting $^{201}$Tl LHR was not statistically significant ($r = 0.10, P = 0.49$) (Fig. 3).

Comparison of Correlation Coefficients

Hotelling $t$ test values, used for comparisons among 3 correlation coefficients (for PFR, TPFR, and 1/3FR vs. LVEDP), were not significant ($t < 1, P > 0.05$ for all). Therefore, no linear correlation with LVEDP was superior among the 3 filling parameters.

ROC Curve Analysis

The ROC curves for detecting LVEDPs of $\geq 18$ mm Hg were not statistically significant ($r = 0.10, P = 0.49$) (Fig. 3).

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These PFR, TPFR, and 1/3FR values showed sensitivities of 82%, 88%, and 82% and specificities of 80%, 63%, and 74%, respectively, for correctly identifying patients with LVEDPs of $\geq 18$ mm Hg. Each diastolic filling variable showed a positive predictive value (PPV) of $\geq 54\%$ and a negative predictive value (NPV) of $\geq 90\%$.

Hence, all diastolic filling parameters improved the ability to detect LVEDPs of $\geq 18$ mm Hg (AUCs of $\geq 0.75$). These parameters showed good sensitivity ($\geq 82\%$), but the specificity ($\geq 63\%$) and the PPV ($\geq 54\%$) were modest. The NPV of these parameters for identifying patients with LVEDPs of $< 18$ mm Hg was remarkably good ($\geq 90\%$).

After identifying these 3 variables as predictors of diastolic dysfunction, we investigated the incremental effect of the presence of more than one variable. TPFR correlated well with PFR and 1/3FR ($r = 0.32$ and $-0.64$, respectively; $P = 0.02$ and $< 0.0001$, respectively), whereas PFR did not correlate with 1/3FR ($r = 0.18, P = 0.19$). Because there was no correlation between PFR and 1/3FR, it was feasible to use these 2 parameters in combination to assess their combined predictive power for LVEDPs of $\geq 18$ mm Hg. When the results for both were above the cutoff values, PFR and 1/3FR combined showed a PPV of 86%, a sensitivity of 67%, and a specificity of 94% for detecting LVEDPs of $\geq 18$ mm Hg. Similarly, the normal values for both of these parameters showed an NPV of 84% for detecting LVEDPs of $< 18$ mm Hg. All values from the ROC curve analysis are shown in Table 2.

DISCUSSION

The predictive power of MPI for subsequent cardiac events and the severity of CAD is significantly enhanced when stress $^{201}$Tl lung uptake is added to the extent and severity of perfusion defects (4,18–20). Several studies have shown that increased stress $^{201}$Tl lung uptake correlates very well with increased left ventricular filling pressure (4–7). Elevated LVEDP is a major predictor of left ventricular diastolic dysfunction (15,16) and has been shown to be an independent predictor of future clinical heart failure events (21) and...
mortality (1,22). In these circumstances, the ability to predict an elevation of LVEDP during MPI could improve the predictive power of myocardial perfusion studies for subsequent cardiac events.

At the present time, the majority of MPI studies are performed with stress 99mTc-labeled perfusion agents. With the transition from 201Tl to 99mTc, access to stress 201Tl lung uptake data is no longer available. With the loss of stress 201Tl LHR data, few studies have assessed the utility of stress 99mTc and resting 201Tl lung uptake for predicting left ventricular filling pressure (8–10,23). Studies with 99mTc MPI have shown a very poor correlation between stress 99mTc LHR and elevated left ventricular filling pressure (9,10), probably because of the rapid washout of 99mTc from the lung during stress (24). Marcassa et al. (23) investigated the use of resting 201Tl LHR, which is quite often used with 99mTc in dual-isotope imaging. In a group of 159 consecutive patients with LVEFs of $\leq 35\%$ (mean $\pm 1$ SD, 23% $\pm 6\%$), resting 201Tl LHR had significant predictive power for subsequent cardiac events and mortality. Resting 201Tl LHR also correlated well with pulmonary capillary wedge pressure in 19 patients. This approach appeared to show some promise, especially because Patel et al. (10) showed a significant correlation between resting 201Tl LHR and stress 99mTc LHR ($r = 0.55, P < 0.01$). However, correlation coefficients for stress 99mTc LHR with LVEDP and with pulmonary capillary wedge pressure were very modest, at 0.29 and 0.34, respectively. Despite the strong correlation between resting 201Tl LHR and stress 99mTc LHR, multivariate linear regression indicated that the relationship between pulmonary capillary wedge pressure and LVEDP was significant with stress 99mTc LHR but not with resting 201Tl LHR. Given the modest correlations and the rapid washout of 99mTc, the reporting of LHR with stress 99mTc is not a common practice. LHR with resting 201Tl appears to be somewhat inferior to LHR with stress 99mTc but, more importantly, it has never been validated in a group of patients with preserved left ventricular systolic function (8,10,23).

With the improved count statistics and resolution of MPI with a 99mTc-labeled radiotracer, LVEF and wall motion can be reliably assessed during MPI (25,26). More recently, diastolic filling curves were derived from an assessment of wall motion during diastole (13,14,27,28) with 16-frame acquisitions. Studies with gated MPI have shown that PFR, TPFR, and 1/3FR can be derived and show excellent correlations with the same markers derived from radionuclide angiography (13,14). Furthermore, these diastolic function parameters have been shown to correlate well with Doppler echocardiographic variables of diastolic dysfunction (28) and with plasma B-type natriuretic peptide levels (28). 4D-MSPECT software derives the second-derivative curve from wall motion and automatically calculates PFR, TPFR, and 1/3FR. We are not aware of any studies in which 4D-MSPECT was used to assess left ventricular diastolic parameters at MPI and correlating these parameters with LVEDP at subsequent cardiac catheterization.

Three diastolic parameters measured by 4D-MSPECT showed a robust correlation with LVEDP at subsequent

![FIGURE 3. Correlation between LVEDP and resting 201Tl LHR.](image)

![FIGURE 4. ROC curve analysis for ability of PFR (A), TPFR (B), and 1/3FR (C) to detect LVEDPs of $\geq 18$ mm Hg or $< 18$ mm Hg.](image)
An inverse correlation of decreasing values for PFR and 1/3FR for identifying patients with LVEDPs of ≥18 mm Hg was observed. The use of left ventricular filling curve parameters to assess diastolic function is not helpful for patients with irregular heart rhythm because gating is disabled. Our patient population underwent MPI and cardiac catheterization within 15 d. This delay could have affected the volume status of the patients and therefore the LVEDPs measured at different time points. Despite this limitation, we found good correlations between diastolic function indices from MPI and LVEDPs. Because our study was retrospective, we relied on the accuracy of medical records. However, tracings of all LVEDP readings were manually checked, and nuclear studies were reprocessed and reanalyzed. Because the present study was a retrospective series of consecutive patients, a prospective investigation of this technique is indicated to validate its utility in predicting LVEDP at cardiac catheterization.

**CONCLUSION**

In patients with LVEFs of ≥45%, resting $^{201}$Tl LHR did not correlate significantly with LVEDP. Diastolic function parameters (PFR, TPFR, and 1/3FR) derived from 16-frame gated SPECT with 4D-MSPECT correlated significantly with LVEDP at cardiac catheterization. If the assessment of diastolic function is combined with MPI results for risk stratification, then 4D-MSPECT diastolic filling parameters are superior to resting $^{201}$Tl LHR, according to our observations. These parameters showed good sensitivity and specificity for detecting LVEDPs of ≥18 mm Hg and a good NPV for identifying patients with LVEDPs of <18 mm Hg. Combining PFR and 1/3FR can result in improved PPV (86%) and specificity (94%).
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