Prognostic Value of Normal Perfusion but Impaired Left Ventricular Function in the Diabetic Heart on Quantitative Gated Myocardial Perfusion SPECT

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Abstract

Purpose This study aimed at identifying the predictive parameters on quantitative gated myocardial perfusion single-photon emission computed tomography (QG-SPECT) in diabetic patients with normal perfusion but impaired function.

Methods Among the 533 consecutive diabetic patients, 379 patients with normal perfusion on rest Tl-201/dipyridamole-stress Tc-99m sestamibi Gated SPECT were enrolled. Patients were grouped into those with normal post-stress left ventricular function (Group I) and those with impaired function (EF <50 or impaired regional wall motion, Group II). We investigated cardiac events and cause of death by chart review and telephone interview. Survival analysis and Cox proportional hazard model analysis were performed.

Results Between the Group I and II, cardiac events as well as chest pain symptoms, smoking, diabetic complications were significantly different ($P < 0.05$). On survival analysis, event free survival rate in Group II was significantly lower than in Group I ($P = 0.016$). In univariate Cox proportional hazard analysis on overall cardiac event, Group (II over I), diabetic nephropathy, summed motion score (SMS), summed systolic thickening score (STS), numbers of abnormal segmental wall motion and systolic thickening predicted more cardiac events ($P < 0.05$). Multivariate analysis showed that STS was the only independent predictor cardiac event.

Conclusion The functional parameter, especially summed systolic thickening score on QG-SPECT had prognostic values, despite normal perfusion, in predicting cardiac events in diabetic patients, and QG-SPECT provides clinically useful risk stratification in diabetic patients with normal perfusion.

Keywords Gated myocardial SPECT (Gated SPECT) · Diabetes mellitus · Summed systolic thickening score · Prognostic value

Introduction

Diabetes mellitus is a major risk for cardiovascular disease. Diabetic patients develop premature coronary artery disease (CAD) but are often without symptoms. Their heart diseases are often undetected until in an advanced stage. Both non-coronary heart disease and CAD cause heart failure in diabetics, and diabetic patients have a higher incidence of myocardial infarction (MI) and cardiac death than their non-diabetic counterparts. Identifying patients at risk for cardiac events is valuable in deciding the appropriate treatment and in preventing the occurrence of cardiac events [1–4].

Myocardial perfusion single-photon emission computed tomography (SPECT) is well-known to provide ischemic, metabolic, and prognostic information in not only research but clinical data of general and specific conditions, especially diabetes, even though new image modalities such as fluorine-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET)/magnetic resonance imaging (MRI) and optical imaging studies are widely investigated [5–19]. Information on perfusion such as the greater degree, extent and reversibility of perfusion defect on SPECT, are related directly to patient's adverse outcome. Left ventricular functional data provided by gating on gated myocardial perfusion SPECT (Gated SPECT)

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are post-stress ejection fraction (EF), left ventricular volume, wall motion and wall thickening. Post-stress left ventricular EF and end-systolic volume (ESV) were known to provide incremental information over perfusion and clinical data in predicting cardiac events as well as the cardiac hard events (cardiac death or MI) [7]. In patients with or without diabetes, normal perfusion predicts benign prognosis [8–10, 14]. However, symptomatic patients with diabetes mellitus and normal stress SPECT had a significantly higher 2-year cardiac event rate than that of patients without diabetes [9].

A report by Giri et al. [14] revealed that normal perfusion in diabetic patients did not guarantee the event-less outcome after adjustment for clinical variables and stress perfusion status. We need to stratify the risks of diabetic patients with normal myocardial perfusion using Gated SPECT. Myocardial function on Gated SPECT can be quantified in an automatic, and so robust, fashion on quantitative gated SPECT (QG-SPECT) [15]. In diabetic patients, it is needed to define factors affecting different prognostic values of functional parameters on QG-SPECT. The aim of this study was to identify the predictive parameters on QG-SPECT in diabetic patients with normal perfusion who were suspected to have CAD.

Materials and Methods

Study Population

We identified 533 consecutive diabetic patients with normal perfusion who underwent rest Tl-201/dipyridamole-stress Tc-99m sestamibi (MIBI) dual isotope Gated SPECT between January 1, 1997 and June 30, 2000 at a University Hospital in Seoul, Korea. All the patients with already-known CAD and a few patients inappropriate for quantitative gated analysis were excluded ($n=154$), which left 379 patients. These patients were grouped into patients with normal post-stress left ventricular function (Group I) and patients with impaired function (EF<50 or impaired regional wall motion, Group II).

Image Acquisition

Dual isotope-separate acquisition myocardial perfusion SPECT was performed in all patients. Thallium-201 (Tl-201, 111 MBq) was injected intravenously at rest, and SPECT imaging was performed. After this acquisition, 925 MBq of Tc-99m MIBI was injected after dipyridamole stress and 1 h later, gated Tc-99m-MIBI SPECT was performed. For gating, 16 frames of data per the averaged cardiac cycle were acquired with a 40 % window centered over the 140-keV photopeak using a dual-head gamma camera (Vertex; ADAC Laboratories, Milpitas, CA, USA). Gated post-stress SPECT images were re-organized to make

ungated SPECT. Filtered back-projection was performed on the projection images of ungated rest/stress SPECT to make transaxial images using a Butterworth low-pass filter of order 5 and cutoff frequency 0.25 cycles/pixel for Tl-201 rest images, and of order 2.5 and cutoff frequency 0.3 for Tc-99m MIBI stress images. No attenuation or scatter correction was done. Gated post-stress SPECT was also reconstructed similarly.

Quantitative Analysis of Gated Tc-99m MIBI SPECT

Gated SPECT tomograms were reconstructed and reoriented using AutoQUANT software (ADAC Laboratories, Milpitas, CA, USA). When automatic reconstruction or reorientation failed, reconstruction limits and axes were assigned manually. Using that software, left ventricular end-diastolic volume (EDV), ESV, and EF were calculated on post-stress SPECT images. In each of the 20 segments (Fig. 1), the number of abnormal segmental wall motion and systolic thickening, and summed score of abnormal segmental wall motion (SMS) and abnormal segmental systolic thickening score (STS) were also acquired. Segmental wall motion was graded according on a five-grade system (0 through 4) and systolic thickening was graded using a four-grade system (0 through 3) as previously described [15]. On Gated SPECT, EF>50 % regarded as normal left ventricular function, EF of 30–50 % as moderate dysfunction, and EF<30 % as severe [16].

Patient Follow-up

Patient follow-up duration was at least 1 year. We investigated cardiac events and cause of death by chart review and telephone interview. A total of 282 patients were enrolled in the Group I, and 97 in the Group II. Of these patients, 42 were lost to follow-up. Finally, 337 patients were followed up for 32 ± 12 months.

Fig. 1 Myocardium was divided into 20 segments. The apex was divided into two segments, and apical, mid and basal regions were divided each into six segments. Segments were classified to five wall locations

Pretest Likelihood of Coronary Artery Disease

Pretest likelihood of CAD was estimated using a nomogram in a given patient following the initial assessment, using the patient's age, sex, pain type, previous history of MI, presence of electrocardiographic ST-T wave changes, and risk factors including smoking, hyperlipidemia, and diabetes mellitus [17]. Subsequently, patients were divided into those with low pretest (<15 %), intermediate pretest (15–85 %), and high pretest (>85 %) probabilities of CAD.

Statistical Analysis

All continuous variables were expressed as means $\pm$ SD. The mean differences for continuous variables were compared using the Student *t*-test. Comparisons between Groups were performed using the chi-square test for categorical variables. A value of $P < 0.05$ was considered statistically significant.

Kaplan-Meier survival analysis was performed for the time to cardiac events. Survival curves were compared by the log rank test. A value of $P < 0.05$ for parameters in univariate analysis was required for entry into the multivariate analysis. The final model included only significantly independent variables ($P < 0.05$). Receiver-operator characteristics (ROC) curve analysis was performed to define thresholds for STS: this analysis provided optimal sensitivity and specificity in predicting overall cardiac event and hard cardiac events. Kaplan-Meier survival analysis was again performed using STS thresholds.

The Cox proportional hazard regression model was used to assess the incremental prognostic value of tested parameters. Multivariate analysis was performed in a stepwise fashion. At each step, variables were entered using the forward Wald method using SPSS (Version 10.0; SPSS, Chicago, IL, USA).

Results

Patient Characteristics

The historical and clinical data of the 379 patients in this study, including the 42 persons lost to follow-up, are listed in Table 1. Overall cardiac events in the total patient population developed at a rate of 4.7 %. Cardiac death and nonfatal MI occurred at 0.7 % of the total population per year for the follow-up period. The percent of male, smoking patients and diabetic complications in Group II was higher than in Group I. Age, hypertension, hypercholesterolemia, and pretest likelihood of CAD did not show a difference between Group I and II. Cardiac events were observed more often in the Group II ($P < 0.05$).

All the quantitative functional data in the Group II were worse in comparison of those of Group I ($P < 0.05$, Table 2).

Kaplan-Meier Survival Analysis: Stratification by Group

Figure 2 shows cumulative survival curves in diabetic patients with normal perfusion stratified by Groups. Patients with an EF < 50 % or with a visually abnormal regional wall motion (Group II) were at a high risk for cardiac events. The log rank statistic was 5.81 and the *P* value was 0.016.

Prediction of Overall and Hard Cardiac Events

All quantitative data of Gated SPECT and clinical parameters were included in univariate and multivariate Cox proportional hazard regression analysis for prediction of cardiac events (Table 3). In univariate Cox proportional hazard analysis on the overall cardiac events, Groups, diabetic nephropathy, SMS, STS, numbers of abnormal segmental wall motion and systolic thickening affected cardiac events significantly ($P < 0.05$). On the cardiac hard events, univariate predictors were Groups, EDV, ESV, EF, STS, numbers of abnormal segmental systolic thickening.

Multivariate analysis showed that only STS was independent variable for the prediction of cardiac events ($P < 0.004$) and cardiac hard event ($P < 0.003$).

Kaplan-Meier Survival Analysis: Stratification by Segmental Systolic Thickening Score

Based on ROC curves, optimal threshold for the prediction of both overall and hard cardiac events were STS < 8.5. This threshold yielded moderate sensitivity and high specificity for the prediction of cardiac events. Figure 3 showed that cumulative survival curve stratified by STS < 8.5 and STS $\geq$ 8.5. An STS below 8.5 identified patients with low overall and hard cardiac events.

Discussion

Most previous studies have demonstrated that myocardial perfusion SPECT provided statistically incremental prognostic value for the prediction of cardiac events in the general population [5–10]. Patients had intermediate event rates if stress perfusion was mildly abnormal, but relatively high event rates if stress perfusion was moderately or severely abnormal. However, the annual cardiac hard event rate was below 1 %, if patients had a normal stress perfusion though they had a high pre-test likelihood of CAD [10]. Gated myocardial perfusion SPECT reveals functional abnormality as well as perfusion status in patients with suspected CAD and provides useful information after surgical treatment such as coronary artery bypass grafting (CABG) [11]. Gated SPECT gave definitive incremental prognostic value for prediction of cardiac events by yielding left ventricular EF and ESV [7].

Table 1 Patient Characteristics

Parameter	Total	Group I	Group II	P value
Patients	379	282	97	
Age (years)	61±9	62±10	60±8	0.195
Male	184 (49.5 %)	115 (40.8 %)	69 (71.1 %)	< 0.0001
Symptoms				
Typical angina	43 (11.3 %)	38 (13.5 %)	5 (5.2 %)	0.005
Atypical angina	121 (31.9 %)	97 (34.4 %)	24 (24.7 %)	0.005
Asymptomatic	215 (56.7 %)	147 (52.1 %)	68 (70.1 %)	0.005
Hypertension	214 (56.5 %)	151 (53.5 %)	63 (64.9 %)	0.051
Smoking	88 (23.2 %)	53 (21.5 %)	35 (46.1 %)	< 0.0001
Hypercholesterolemia	59 (15.6 %)	42 (15.4 %)	17 (17.5 %)	0.621
Pretest likelihood of CAD	0.48±0.27	0.47±0.28	0.52±0.24	0.077
Retinopathy	201 (53.0 %)	130 (49.4 %)	71 (75.5 %)	< 0.0001
Neuropathy	145 (38.3 %)	86 (32.8 %)	59 (63.4 %)	< 0.0001
Nephropathy	157 (41.4 %)	94 (35.6 %)	63 (67.7 %)	< 0.0001
Cardiac event	18 (4.7 %)	9 (3.2 %)	9 (9.3 %)	0.015
Hard event	6 (1.8 %)	2 (0.8 %)	4 (4.7 %)	0.047

CAD coronary artery disease

Several studies have focused on diabetic patients [12–14]. Investigations for both diabetic and non-diabetic patients found that myocardial perfusion SPECT was valuable for risk stratification, and management was necessary for perfusion abnormalities in diabetic patients. Diabetic patients seemed to show worse outcomes and looked plagued with more adverse cardiac events, affecting both survival and hard-event-free survival. However, adjustment with clinical and stress myocardial perfusion on SPECT revealed that diabetic patients behaved similarly to non-diabetic patients [14]. Only the difference between diabetic and non-diabetic patients lay in a population with normal stress myocardial perfusion on SPECT. How to identify the diabetic patients with adverse outcomes has become a clinical problem now. Furthermore, asymptomatic diabetic patients can meet inducible ischemia. One interesting study by Wackers et al. [20], which was

named DIAD (the detection of ischemia in asymptomatic diabetes), was performed for evaluating these patients. In this study, enrolled subjects showed more silent myocardial ischemia. Intensive treatment came to resolution of ischemia. The DIAD study [21–23] suggested that even patients with intermediate/high baseline cardiovascular risk had low annual cardiac event if asymptomatic, and in this case routine SPECT did not alter the event rate.

In asymptomatic diabetic patients, the results of SPECT can be varied. Our study was performed in diabetic patients with normal perfusion and showed that the annual cardiac hard event rate was 0.7 % (4.2 % per the entire period of follow-up). This is similar to the previous reports [12–14]. However, simple grouping of the diabetic patients into normal

Table 2 Analyses of LV Function Assessed with the Automated Program

Parameter	Group I	Group II	P value
EDV (ml)	78±26	133±51	< 0.0001
ESV (ml)	48±18	95±42	< 0.0001
EF (%)	64±9	44±12	0.004
No. of abnormal segmental WMs	2.1±2.8	9.4±5.3	< 0.0001
SMS	3.7±5.9	19.5±14.2	< 0.0001
Mean of SMS	0.9±0.9	1.9±0.6	< 0.0001
No. of abnormal segmental WTs	1.5±2.4	9.1±6.0	< 0.0001
STS	2.3±3.8	14.9±10.9	< 0.0001
Mean of STS	0.8±0.8	1.5±0.5	< 0.0001

EDV end-diastolic volume, ESV end-systolic volume, EF ejection fraction, No. number, WM wall motion, SMS segmental wall motion score, WT systolic wall thickening, STS segmental systolic thickening score

Fig. 2 Cumulative survival with stratification by impaired LV function. Patients who had an EF<50 % or with a visually abnormal regional wall motion (Group II) were at a high risk for a cardiac event in comparison with Group I

Table 3 Multivariate Cox regression Analysis for Prediction of Overall and Hard Cardiac Events

Variables	Overall cardiac event		Hard cardiac event	
	Chi-square	P value	Chi-square	P value
Grouping	...	NS	...	NS
Nephropathy	...	NS	...	NS
EDV	...	NS	...	NS
ESV	...	NS	...	NS
EF	...	NS	...	NS
SMS	...	NS	...	NS
No. of abnormal segmental WMs	...	NS	...	NS
STS	8.291	0.004	8.832	0.003
No. of abnormal segmental WTs	...	NS	...	NS

EDV end-diastolic volume, *ESV* end-systolic volume, *EF* ejection fraction, *SMS* segmental wall motion score, *WM* wall motion, *STS* segmental systolic thickening score, *WT* systolic wall thickening, *NS* not significant

or abnormal left ventricular function enabled the differential prediction of cardiac event rates (3.2 % vs 9.3 %). Functional abnormality was bound for scrutiny for their predictive values in diabetic patients, especially when the stress myocardial perfusion was normal on Gated SPECT. QG-SPECT made it possible to assess segmental systolic thickening and wall motion as well as perfusion automatically and quantitatively, which are useful in various clinical situations. We already know that quantification of Gated SPECT is feasible, objective, robust and clinically relevant [15]. As was expected because we grouped the patients into normal perfusion with normal function and with abnormal function, QG-SPECT

showed every parameter on quantitative measurement of myocardial function was differential between Group I and II. For comparison of EF, it was larger in Group I than Group II. One thing we should consider to analyze this finding was that there were more female patients in Group I and the partial volume effect due to the small-sized heart of older women with low body weight might cause falsely high EF, which might affect the parameters of QG-SPECT. This is one limitation of this study.

Overall event-free and hard-event-free survival could be predicted by the several relevant parameters on QG-SPECT. Functional parameters such as EF and ventricular volumes were more likely to predict cardiac hard events; however, summed systolic thickening score on QG-SPECT was the only independent predictor of overall and hard cardiac events. Thickening score might represent the perfusion-contraction uncoupling on QG-SPECT. Normal perfusion after dipyridamole stress, also evaluated both by visual and automatic quantification, refuses the possibility of severe CAD. Abnormal thickening of sizable myocardium despite normal perfusion indicates that these patients have mechanical derangement possibly by metabolic derangements. Bravo et al. [24] reported that due to cardiovascular autonomic neuropathy, heart rate response to stress is diminished in patients with diabetes with normal SPECT imaging as in our study. Functional maladaptation of the diabetic heart lay beneath this disclosure of normal perfusion but impaired left ventricular function and needed appropriate treatment, whether primary or secondary prevention in this group of patients.

Wackers and Zaret [25] emphasized that we should know when, how and which asymptomatic patients should be screened. Though we did not address this important question in our retrospective study, we demonstrated clearly that diabetic patients with normal stress perfusion with impaired left ventricular function had a worse cardiac outcome. Whether this abnormality of myocardial function derives from subclinical CAD or diabetic small vessel disease, understanding of pathophysiology and appropriate selection of treatment are strongly recommended.

As Wackers and Zaret [25] emphasized in their editorial to Giri and colleagues [14] report, there is the real need for defining the factors responsible for altered prognostic value of normal myocardial perfusion in diabetic patients. Until now, few studies have evaluated the prognostic value of contractile dysfunction on nuclear testing in a diabetic population with normal stress perfusion.

Some of diabetic patients without evidence of ischemic, hypertensive, or valvular heart disease may still develop cardiac dysfunction and congestive heart failure, resulting in cardiac event [4, 26]. Sakamoto et al. [27] suggested that impairment of myocardial free fatty acid metabolism rather than small vessel abnormalities in the myocardium was responsible for modest left ventricular dysfunction in patients with diabetes and no evidence of CAD. Nagaya et al. [28]

Fig. 3 Cumulative survival with stratification by cutoff value of 8.5 in STS. Based on ROC curves, the optimal threshold for the prediction of both overall and hard cardiac events was $STS < 8.5$. An STS below 8.5 identified patients with low overall and hard cardiac events. *STS* segmental systolic thickening score

demonstrated that systolic dysfunction in a hypertrophied right ventricle was related to impaired regional fatty acid uptake. Systolic contractile dysfunction in diabetic patients without CAD may be related to impaired myocardial metabolism. Whether metabolic derangement or endothelial dysfunction was the cause of this functional abnormality in normally perfused myocardium in diabetic patients warrants further investigation.

In our study, survival analyses using the QG-SPECT variables have shown that functional data including segmental systolic thickening were powerful predictors for cardiac events in diabetic patients with a normal scan. Based on the result of our study, we concluded that the functional data, especially systolic thickening score, on quantitative gated SPECT provided significant incremental prognostic information over that provided by historical, clinical, physiological variables and normal perfusion status in diabetic patients without evidence of previous CAD. This could be a clinically useful risk stratification for a subset of patients who need closer observation or possible medical treatment or interventional approach.

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Conflicts of interest None.

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