Prognostic value of treadmill exercise and dobutamine stress positron emission tomography

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BACKGROUND: Although positron emission tomography (PET) is routinely performed using vasodilator stress, exercise and dobutamine stress are available alternatives. Evidence suggests that vasodilator PET myocardial perfusion imaging (MPI) has prognostic value, but the prognostic value of treadmill exercise and dobutamine PET MPI is unknown.

OBJECTIVE: To determine the potential prognostic value of nonvasodilator stress PET MPI.

METHODS: Patients underwent treadmill exercise or dobutamine PET MPI. Images were assessed qualitatively and semiquantitatively. PET results were categorized as normal (summed stress score [SSS] of less than 4), abnormal (SSS of 4 or greater) or inconclusive (SSS of less than 4 and submaximal peak stress heart rate). Patient follow-up (cardiac death, nonfatal myocardial infarction [MI] and/or late revascularization) was performed.

RESULTS: Of the 124 patients (mean follow-up period of 2.3±1.6 years), 46 patients (37%) had a normal study, 15 patients (12%) had an inconclusive study and 63 (51%) had an abnormal PET. Patients with a normal PET had no deaths or nonfatal MI. One patient with a normal PET underwent late revascularization (annual event rate of 1.7%). Patients with an abnormal PET had 15 cardiac events (one cardiac death, four nonfatal MIs and 10 late revascularizations), with an annual event rate of 13.0% (P=0.002).

CONCLUSIONS: Although small, the present study suggests that defects seen on PET myocardial perfusion, resulting from stressors (treadmill exercise and dobutamine) that increase myocardial oxygen demand, may have prognostic value.

Key Words: Coronary artery disease; Dobutamine; Positron emission tomography; Prognosis; Treadmill exercise

Myocardial perfusion imaging (MPI) using single-photon emission tomography (SPECT) is a highly useful noninvasive modality for the detection and risk stratification of patients with documented or suspected coronary artery disease (CAD). Compared with SPECT, vasodilator stress positron emission tomography (PET) MPI appears to have superior sensitivity and specificity for the detection of CAD (1-4) and there is mounting evidence that vasodilator stress PET MPI also has prognostic value (5-8). Though less commonly used, treadmill exercise and dobutamine are available stressors used with PET MPI, but data supporting their use with PET are limited (2,3,9-11). The evidence supporting the diagnostic and prognostic value of treadmill exercise and dobutamine PET MPI is similarly limited. The objective of the present study was to evaluate the prognostic value of myocardial demand perfusion defects measured by treadmill exercise and dobutamine PET MPI.

METHODS

Patients

All patients who underwent treadmill exercise or dobutamine PET between January 2001 and October 2006, and consented to the University

La valeur pronostique des exercices sur tapis roulant et de la tomographie par émission de positrons avec un stress de dobutamine

HISTORIQUE : Même si la tomographie par émission de positrons (TÉP) est souvent utilisée avec un stress vasodilatateur, il est aussi possible d'utiliser l'exercice et le stress de dobutamine. Selon les données probantes, l'imagerie de perfusion myocardique (IPM) par TÉP avec un stress vasodilatateur a une valeur pronostique, mais on ne connaît pas celle de l'exercice sur tapis roulant et de l'IPM par TÉP avec un stress de dobutamine.

OBJECTIF : Déterminer la valeur pronostique potentielle de l'IPM par TÉP avec un stress vasodilatateur.

MÉTHODOLOGIE : Les patients ont fait des exercices sur tapis roulant ou subi une IPM par TÉP avec un stress de dobutamine. Les images ont été évaluées de manière qualitative et semi-quantitative. Les résultats de la TÉP ont été classés comme normaux (résultat global de l'épreuve d'effort [RGÉE] inférieur à 4), anormaux (RGÉE d'au moins 4) ou non concluants (RGÉE inférieur à 4 et fréquence cardiaque de pointe sous-maximale). On a procédé au suivi des patients (décès cardiaque, infarctus du myocarde non fatal [IM] ou revascularisation tardive).

RÉSULTATS : Des 124 patients (suivi moyen de 2,3±1,6 ans), 46 patients (37 %) ont eu une étude normale, 15 (12 %), une étude non concluante et 63 (51 %), une TÉP anormale. Parmi les patients dont la TÉP était normale, on n'a pas constaté de décès ou d'IM non fatal. Un patient dont la TÉP était normale a subi une revascularisation tardive (taux annuel d'événement de 1,7 %). Les patients dont la TÉP était anormale ont présenté 15 événements cardiaques (un décès cardiaque, quatre IM non fatals et 10 revascularisations tardives), ainsi qu'un taux d'événements annuel de 13,0 % (P=0,002).

CONCLUSIONS : Même si l'échantillonnage était petit, la présente étude laisse supposer que les déficiences de la perfusion myocardique par TÉP, résultant d'événements stressants (exercice sur tapis roulant et dobutamine) qui accroissent la demande en oxygène myocardique, pourraient avoir une valeur pronostique.

of Ottawa Heart Institute (Ottawa, Ontario) PET registry were included in the present prospective study. All patients had either documented CAD or an intermediate-to-high pretest probability for CAD (5,6). Patients who underwent dobutamine PET had a contraindication to vasodilator stress. Patients who did not give informed consent or refused to participate in the PET registry were excluded. The study was approved by the University of Ottawa Heart Institute Human Research Ethics Board.

PET imaging

The PET images were acquired with an ECAT ART scanner (Siemens/CTI PET Systems, USA). The imaging protocol was previously described (10,11). In brief, a cesium-137 singles transmission scan was acquired for patient positioning and for attenuation correction. Nitrogen 13 (N-13) ammonia (10 mCi) or rubidium 82 (Rb-82) (10 mCi to 20 mCi) was injected at rest and with stress. Static images were created by summing 17 min (N-13 ammonia) or 7.5 min (Rb-82) of emission data. An 8 min (N-13 ammonia) or 4 min (Rb-82) transmission scan was acquired following stress for attenuation correction (10,11).

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TABLE 1
Patient characteristics

Characteristic	Normal PET (n=46)	Abnormal PET (n=63)	P
Age, years	60.4±11.1	62.0±11.1	NS
Men, n (%)	24 (52.2)	53 (84.1)	<0.001
Follow-up time, years	2.7±1.6	2.1±1.6	NS
BMI, kg/m ²	31.7±9.6	27.8±5.7	<0.02
Cardiac risk factors, n (%)			
Smoking history	30 (65.2)	47 (74.6)	NS
Hypertension	33 (71.7)	39 (61.9)	NS
Diabetes	7 (15.2)	10 (15.9)	NS
Dyslipidemia	27 (58.7)	51 (81.0)	<0.02
Family history of CAD	17 (37.0)	23 (36.5)	NS
Cardiac medications, n (%)			
ASA	28 (60.9)	45 (71.4)	NS
Beta-blocker	16 (35.6)	31 (49.2)	NS
ACE-I	19 (42.2)	39 (61.9)	NS
Statin	23 (50.0)	45 (71.4)	<0.03
Medical history, n (%)			
MI	9 (19.6)	41 (65.1)	<0.001
PCI	8 (17.4)	28 (44.4)	<0.01
CABG	3 (6.5)	15 (23.8)	<0.02

*Data presented as mean ± SD unless otherwise indicated. ACE-I Angiotensin-converting enzyme inhibitor; ASA Acetylsalicylic acid; BMI Body mass index; CABG Coronary artery bypass graft surgery; CAD Coronary artery disease; MI Myocardial infarction; NS Nonsignificant; PET Positron emission tomography; PCI Percutaneous coronary intervention

Exercise stress testing

The Bruce protocol was used for the treadmill exercise protocol. Age-predicted maximal heart rate (APMHR) was estimated by subtracting age from 220; 85% of the APMHR or greater was targeted (12). The electrocardiogram was monitored continuously, and the heart rate (HR) and blood pressure were measured every 3 min. During the final 1.5 min of peak exercise, the patient received Rb-82 or N-13 ammonia. On completion of the treadmill exercise, the patient was repositioned in the PET scanner for emission data acquisition and transmission imaging.

Dobutamine stress

Dobutamine infusion was initiated (5 µg/kg/min) and doubled every 3 min until the target HR was achieved or to a dose of 40 µg/kg/min. If the target HR was not achieved with 40 µg/kg/min of dobutamine, either dobutamine was increased to 50 µg/kg/min, or 0.6 mg to 1.0 mg of atropine was administered to achieve the target HR (13). Rb-82 or N-13 ammonia was administered at peak stress while the peak HR was sustained for 1 min.

Electrocardiogram and image analysis

Ischemic ST segment depression was defined as 1 mm or greater horizontal or downsloping ST segment depression at the J point and persisting for 80 ms or 1.5 mm or greater upsloping depression at 80 ms beyond the J point (14). For HRs of 135 beats/min or greater, ST segment measurements were performed at 60 ms beyond the J point (14).

The PET images were assessed qualitatively by two expert observers blinded to the modality of stress and using a 17-segment model and a five-point grading system (0 indicates normal radiotracer uptake, 1 indicates mildly reduced uptake, 2 indicates moderately reduced uptake, 3 indicates severely reduced uptake and 4 indicates absence of radiotracer uptake). The summed stress score (SSS), summed rest score and summed difference score (SDS) were calculated (15,16). An abnormal scan was defined as an SSS of 4 or greater, a normal scan was defined as an SSS of less than 4 with a peak stress HR at 85% of the APMHR or greater, and an inconclusive study was defined as an SSS

TABLE 2
Treadmill exercise data

Parameter	Normal PET (n=19)	Abnormal PET (n=51)	P
Exercise duration, min	9.1±3.2	7.9±1.8	NS
ST segment changes, n (%)	9 (47.4)	35 (68.6)	NS
Chest pain, n (%)	4 (21.1)	18 (35.3)	NS
Rest heart rate, beats/min	63.8±9.0	65.6±11.6	NS
Stress heart rate, beats/min	151.7±13.5	149.4±22.4	NS
Rest blood pressure, mmHg			
Systolic	144.7±20.8	143.7±18.1	NS
Diastolic	79.7±10.4	80.9±10.0	NS
Stress blood pressure, mmHg			
Systolic	188.8±28.5	184.0±32.6	NS
Diastolic	88.6±11.3	89.2±12.9	NS
Summed stress score	1.3±1.1	11.4±6.9	<0.001

Data presented as mean ± SD unless otherwise indicated. NS Nonsignificant; PET Positron emission tomography

of less than 4 and a peak stress HR of less than 85% of the APMHR.

Outcomes

The primary outcome measure was the composite end point of cardiac death and nonfatal myocardial infarction (MI), and the secondary outcome measure was the composite of cardiac death, nonfatal MI and late revascularization (defined as revascularization that occurred 90 days or more after PET MPI). An excellent patient follow-up rate was achieved (97.6%). Patient-reported events were confirmed with hospital records, autopsy reports or correspondence with the patient's attending physicians.

Statistical analysis

Statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc, USA), and statistical significance was defined as $P < 0.05$. Continuous variables are presented as means and SDs, and categorical variables are presented as frequencies with percentages. The Wilcoxon rank-sum test was used to compare continuous variables, and Fisher's exact tests were used for categorical variables.

The prognostic value of SSS for unadjusted hard event (cardiac death and nonfatal MI) and total cardiac event (cardiac death, nonfatal MI and late revascularization) rates were assessed. All unadjusted comparisons of event rates were based on survival analysis log-rank tests. The annual event rates (AERs) were calculated by dividing the two-year Kaplan-Meier event rates by 2. The unadjusted survival, free from cardiac events, was also described with Kaplan-Meier curves.

RESULTS

A total of 124 patients underwent treadmill exercise N-13 ammonia PET (n=26), treadmill exercise Rb-82 PET (n=54) and dobutamine (n=44) Rb-82 PET MPI. Excluding the 15 patients with an inconclusive PET MPI (SSS of less than 4 and submaximal peak HR), the study population comprised 109 patients (70 exercise and 39 dobutamine). Forty-six patients had a normal PET MPI and 63 patients had an abnormal scan. The mean follow-up time of the study population was 2.3±1.6 years. Patient characteristics and stress parameters of the patients with a normal and abnormal PET MPI were compared (Tables 1 to 3).

Using a univariate analysis to compare patients with and without cardiac events, an abnormal PET appeared to be the strongest predictor of patient outcome (Table 4). Thus, prognostic analysis was performed based on PET MPI results.

Of the 46 patients with a normal PET MPI, none had cardiac death or nonfatal MI, but one patient underwent late revascularization (Table 5). The AER for the composite end point of cardiac death, nonfatal MI and late revascularization was 1.7% in the population with a

TABLE 3
Dobutamine data

Parameter	Normal PET (n=27)	Abnormal PET (n=12)	P
ST segment changes, n (%)	8 (29.6)	6 (50.0)	NS
Chest pain, n (%)	12 (44.4)	5 (41.7)	NS
Rest heart rate, beats/min	75.7±19.3	69.0±13.6	NS
Stress heart rate, beats/min	154.0±8.9	141.0±15.6	<0.01
Rest blood pressure, mmHg			
Systolic	139.5±36.3	127.4±45.2	NS
Diastolic	76.6±9.3	81.3±24.8	NS
Stress blood pressure, mmHg			
Systolic	148.8±25.6	151.6±52.9	NS
Diastolic	75.4±14.3	79.3±14.3	NS
Summed stress score	0.6±1.0	15.0±7.3	<0.001

Data presented as mean ± SD unless otherwise indicated. NS Nonsignificant; PET Positron emission tomography

normal PET MPI. Patients with an abnormal PET MPI had a total of 15 cardiac events (one death, four nonfatal MIs and 10 late revascularizations), with an AER for cardiac death and nonfatal MI of 5.4% and for the composite end point of cardiac death, nonfatal MI and late revascularization of 13.0% (Table 5). Unadjusted survival free from hard events (cardiac death and nonfatal MI) and total cardiac events (cardiac death, nonfatal MI and late revascularization) were significantly different between the patients with a normal and abnormal PET MPI ($P=0.047$ and $P=0.002$, respectively) (Figures 1 and 2).

Early revascularization (occurring within 90 days of PET MPI scan), which is traditionally driven by the results of the PET MPI, was not included in the preliminary analysis. A total of six early revascularizations occurred in the patients with an abnormal PET MPI (exercise, $n=5$; dobutamine, $n=1$) and one early revascularization occurred in a patient with a normal exercise PET MPI. Because patients with 'normal' PET MPIs should not require revascularization, early revascularization in the normal PET MPI group may be considered a significant cardiac event. Further review revealed that the patient had a 'normal PET MPI' with an SSS of less than 4, but had an SDS equal to 3, reflecting the presence of significant myocardial ischemia. Because the primary outcome measure was a composite of cardiac death and nonfatal MI, this patient did not affect the primary outcome measure results. If this patient had been included in the analysis of the secondary outcome measures, the statistically significant difference between the normal and abnormal groups would have been maintained ($P=0.006$). None of the patients who underwent early revascularization had cardiac events at follow-up.

Of the 15 patients with an inconclusive PET MPI, one patient with a history of myocardial infarction (an SSS of 1 and an SDS of 1) had a cardiac death. The remaining 14 patients had no cardiac events.

DISCUSSION

The diagnostic and prognostic value of exercise and vasodilator SPECT MPI has been well established (16-19). Patients with a normal exercise and vasodilator SPECT MPI have very low rates of cardiac death or nonfatal MI (0.7% to 1% per year). However, events increase proportionally with higher SSS (20-22). Although dobutamine SPECT MPI has been studied less, it is an accepted modality for the detection of CAD in patients who may have contraindications to exercise and vasodilator stress (23,24). Such contraindications include inability to exercise, advanced atrioventricular blocks, reactive airway disease and allergy to dipyridamole or adenosine. The development of specific adenosine 2A agonists may play a future role in these patients, but until they are widely available, dobutamine remains a viable cost-effective alternative.

Although it is usually well tolerated, dobutamine has infrequent significant adverse effects including hypertension, hypotension and arrhythmia. In our study, there were no significant adverse events associated with either dobutamine or treadmill exercise.

TABLE 4
Baseline characteristics of patients with and without cardiac events

Characteristic	Patients with an event (n=16)	Patients with no events (n=93)	P
Age, years, mean ± SD	58.0±10.2	61.9±11.2	NS
Men, n (%)	13 (81.3)	64 (68.8)	NS
BMI, kg/m ² , mean ± SD	28.9±4.9	29.6±8.2	NS
Cardiac risk factors, n (%)			
Smoking history	12 (75.0)	65 (69.9)	NS
Hypertension	9 (56.3)	63 (67.7)	NS
Diabetes	4 (25.0)	13 (14.0)	NS
Dyslipidemia	14 (87.5)	64 (68.8)	NS
Family history of CAD	7 (43.8)	33 (35.5)	NS
Medical history, n (%)			
Myocardial infarction	10 (62.5)	40 (43.0)	NS
PCI	5 (31.3)	31 (33.3)	NS
CABG	4 (25.0)	14 (15.1)	NS
Summed stress score, n (%)			
Normal	1 (6.3)	45 (48.4)	
Abnormal	15 (93.8)	48 (51.6)	0.002

BMI Body mass index; CABG Coronary artery bypass graft surgery; CAD Coronary artery disease; NS Nonsignificant; PCI Percutaneous coronary intervention

Although dobutamine SPECT, treadmill exercise and dobutamine PET are available, their prognostic value has not been well studied (25). By comparison, treadmill exercise SPECT and dobutamine stress echocardiography have been established as accurate modalities for the diagnosis and risk stratification of patients (26-31). The prognostic value of exercise SPECT and dobutamine stress echocardiography cannot be inferred on exercise and dobutamine PET, and requires further evaluation.

The diagnostic accuracy of vasodilator stress PET has been well studied (1,2,32-34) and there is mounting evidence that vasodilator PET has prognostic value (5-8). Although treadmill exercise Rb-82 and N-13 ammonia PET MPI, as well as dobutamine PET, are feasible and available in patients with contraindications to vasodilator stress, the prognostic value of such tests has not been well studied (10,11,35). The results of the present study demonstrate the potential prognostic value of PET myocardial perfusion defects induced by stressors that increase myocardial demand.

A major determinant of prognosis in CAD is the SSS, measured by SPECT and PET MPI, which reflects total myocardial ischemia and scarring. In adjusted survival models, Yoshinaga et al (5) demonstrated that dipyridamole stress Rb-82 PET SSS was the strongest predictor of total cardiac events. Similarly, our unadjusted survival analysis showed that the SSS detected with treadmill exercise and dobutamine stress PET MPI had a statistically significant prognostic value.

Although exercise PET and dobutamine PET are alternatives to vasodilator stress, it is equally important to demonstrate that their prognostic value is similar to currently available techniques. Our study reveals the potential prognostic value of exercise and dobutamine PET, but larger studies are required to confirm these results. The AER (1.7%) for cardiac death, nonfatal MI and late revascularization in the present study's normal population appears high, but is likely related to the single event (revascularization) in our small sample size. The AER (13.0%) in the abnormal population is consistent with previously published SPECT and PET data.

Limitations

The prognosis of exercise and dobutamine PET was not assessed individually because of the small population sample size and low event rate. Unlike vasodilator stressors, both exercise and dobutamine cause increases in myocardial oxygen demand with resultant 'demand ischemia' and thus were analyzed together in the present study. Larger studies are required to assess the prognostic value of each modality independently.

TABLE 5
Rate of cardiac events

PET MPI result	n	Death, n (%)	Nonfatal MI, n (%)	Late revascularization, n (%)	Death/nonfatal MI, n (%)	Death/nonfatal MI AER, %	Total events, n (%)	Total events AER, %
Normal	46	0 (0)	0 (0)	1 (2.2)	0 (0)	0	1 (2.2)	1.7
Abnormal	63	1 (1.6)	4 (6.4)	10 (15.9)	5 (7.9)	5.4	15 (23.8)	13.0
Log-rank test P		0.350	0.079	0.014	0.047		0.002	

AER Annual event rate; MI Myocardial infarction; MPI Myocardial perfusion imaging; PET Positron emission tomography

Figure 1 Unadjusted survival, free from hard cardiac events (cardiac death and nonfatal myocardial infarction [MI]), as a function of summed stress score on positron emission tomography myocardial perfusion imaging

Also, the small sample size and low event rate prevented our ability to perform a multivariable analysis to stratify the sample according to other prognostic parameters such as age, sex, history of CAD and modality of stress (exercise versus dobutamine). As well, the effects of medical therapy cannot be accounted for. Large studies have demonstrated the incremental value of MPI over traditional clinical parameters but, given our study size, only one variable – SSS – could be assessed.

CONCLUSION

Myocardial demand perfusion defects detected with treadmill exercise and dobutamine PET may have prognostic value in patients with

Figure 2 Unadjusted survival, free from total cardiac events (cardiac death, nonfatal myocardial infarction and late revascularization), as a function of summed stress score on positron emission tomography myocardial perfusion imaging

documented or suspected CAD. The results of the present study require confirmation with a larger-scale study.

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