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Original Article

Tachycardic vs. pharmacologic stress myocardial perfusion imaging: differential implications in multi-vessel ischemia

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Abstract: Background**:** In patients unable to exercise, potential methods of induction of reversible myocardial ischemia include physiological heart rate acceleration via pacing or dobutamine infusion and asymmetric coronary vasodilatation using dipyridamole. Although their bases for induction of ischemia are widely disparate, no direct comparison of these techniques has previously been reported. Methods**:** We performed a randomised, paired comparison of dipyridamole and pacing myocardial perfusion imaging (MPI) in 28 patients in whom exercise stress imaging was precluded, comparing the detection, localisation and quantitation of ischemia. Results**:** Reversible myocardial ischemia was detected in 21 patients, concordantly in 13 ($p = 0.042$). There was a high degree of concordance ($p < 0.0001$) regarding locations of sites of ischemia. While there was a good correlation ($r = 0.74$, $p < 0.0001$) between size of total ischemic zones with dipyridamole and pacing, the magnitude of ischemia tended to be greater with dipyridamole (mean percentage of left ventricular myocardium ± SD, 9.4 ± 11.0% vs. 7.0 ± 9.0%, $p = 0.091$). Furthermore, this difference resulted from accentuation of the primary ischemic zone with dipyridamole in patients with multi-vessel ischemia (mean ± SD, 28.1 ± 21.1% vs. 18.7 ± 16.1%, $p = 0.046$). Conclusions**:** Despite major differences in mechanism(s) of induction of ischemia, dipyridamole and pacing produce similar results regarding detection, localisation and severity of ischemia. However, dipyridamole accentuates ischemia in primary (vs. secondary) ischemic zones, consistent with known induction of coronary "steal". This should be taken into account in interpretation of scan results.

Keywords: Dipyridamole, pacing, myocardial perfusion imaging, coronary "steal"

Introduction

Stress single photon emission computed tomography myocardial perfusion imaging (SPECT MPI) is the most widely used non-invasive test with high diagnostic and prognostic values for the detection and stratification of myocardial ischemia [1]. The central issue of the available stress modalities is the potential non-equivalence of ischemic stimuli: exercise, with associated tachycardia and increased myocardial oxygen demand [2], is considerably different as a stimulus for ischemia from adenosine and dipyridamole, which induce asymmetric coronary dilatation. Exercise stress MPI is the conventional first choice because important information is obtained regarding ECG changes, patient symptoms and the hemodynamic response to exercise [3, 4]. However, in patients in whom adequate levels of exercise for induction of ischemia are not possible, the optimal alternative stress method is uncertain. Available options include "physiological" tachycardia-based stress (classically via pacing but also potentially via pharmacological induction of tachycardia) and alternative pharmacological provocation via vasodilatation using adenosine or dipyridamole. Atrial pacing increases heart rate and therefore myocardial oxygen demand and coronary blood flow [5, 6], while dipyridamole induces asymmetric peripheral coronary dilatation (and thus potentially coronary "steal") through its indirect effects on adenosine kinetics [7, 8]. Thus, in theory, while inherently cumbersome and expensive, atrial pacing represents a more "physiological" basis for induction of ischemia than adenosine or dipyridamole infusion. However, to date, no systematic comparisons between these two categories of induction of ischemia have been reported.

The potential disparities between tachycardic and vasodilatory induction of ischemia extend beyond the magnitude of the ischemic stimulus:

the relative capacity of these techniques to (a) detect primary zones of ischemia (with a view to PCI) and (b) multi-vessel ischemia (as an indication for coronary artery surgery) is unknown. Therefore, the principal objective of the current study was to compare the induction of ischemia by these two stress methods in patients in whom adequate exercise was not feasible. The investigation tested the primary hypotheses that localisation and extent of induced ischemia would be independent of mode of induction. The secondary hypothesis of the study to be investigated was that the induction of single vs. multi-vessel ischemia does not vary between methods.

Materials and methods

Patient population

The study was performed in a cross section of patients with a variety of bases for reduced exercise capacity referred for stress myocardial perfusion imaging (MPI). Patients with pre-test probability of coronary artery disease (CAD) of over 5% [9] were invited to participate in the study. Those with brittle asthma, known allergy to dipyridamole, left bundle branch block, and atrial fibrillation were excluded. Any changes in cardiac status (e.g. myocardial infarct, revascularisation) or major change in general health (as determined by the investigator) between stress imaging protocols were considered withdrawal criteria. Written informed consent was obtained before the study entry. The study was approved by the Central Northern Adelaide Health Service Ethics of Human Research Committee. All patients underwent both pacing stress and dipyridamole stress SPECT MPI in random order within 2 weeks of each other. The mean time (± SD) between the 2 stress scans was 7 ± 7 (SD) days. Anti-anginal therapy was not withheld for the study, but neither medication changes nor therapeutic interventions were allowed between the two study procedures.

Right atrial pacing stress protocol

Tachycardic stress imaging was performed as previously described [10]. Using an aseptic technique, a bipolar 6F pacing catheter was inserted percutaneously into the right femoral vein under local anaesthesia and advanced into the right atrium under fluoroscopy using the Seldinger technique. A Swan-Ganz catheter was also inserted via the femoral vein for measurement of right heart pressures in all but 3 of the patients. Atrial pacing was started at 80 beats/min and increased by 10 beats/min at one minute intervals, until one of the following endpoints was achieved: maximum heart rate of > 85% MAPHR; elevation of pulmonary capillary wedge pressure to > 35 mmHg; severe chest pain; or development of atrial fibrillation or flutter. Intravenous atropine administration (300 mcg or 600 mcg) was given if atrioventricular block occurred before these endpoints were reached. When an end-point was obtained, 400 MBq of ^{99m}Tc Sestamibi (n = 25, 78%) or Tetrofosmin (n = 7, 22%) was injected via the femoral vein-sheath and flushed with 20ml normal saline. Pacing was continued for further 2 minutes and then decreased until intrinsic rhythm returned. The heart rate, blood pressure, 3-lead ECG and pulmonary capillary wedge pressure (PCWP) were monitored continuously during the stress test. The presence, intensity and character of chest pain during pacing were reported.

Dipyridamole stress protocol

Caffeine-containing products were not allowed for 24 hours before the test. A dose of 0.56 mg/kg dipyridamole was infused via a peripheral intravenous cannula for 4 minutes with the patient in the supine position. A 12-lead ECG was continuously monitored during the administration of dipyridamole. 400 MBq ^{99m}Tc Sestamibi or Tetrofosmin (same as used in pacing protocol) was injected intravenously 3 minutes after completion of the infusion, followed by 75 mg of IV aminophylline another 3 minutes later to reverse dipyridamole effects. The patient's symptoms, heart rate, blood pressure and a 12-lead ECG were recorded before, every 2 minutes during the test and repeated following aminophylline injection.

SPECT imaging protocol

A same-day stress-rest SPECT MPI protocol without supplemental exercise was utilised. The stress SPECT imaging was performed 30 minutes after the stress injection. Only on the first study day was a rest study also performed 3 hours after the stress injection. 900 MBq of the ^{99m}Tc agent was administered intravenously at rest and followed by the performance of SPECT imaging 30 minutes later. The rest images were not repeated on the second study day.

Myocardial perfusion images were acquired using a triple-headed Irix gamma camera (Philips; Cleve-

land, Ohio) with a low-energy, high-resolution collimator. 60 projections (20s/projection) were obtained over a 360° circular arc (pixel size = 3.5 mm). Filtered back projection using a Butterworth filter with a frequency cut-off of 0.22cycles/pixel was performed. Motion correction was applied if needed, but no attenuation correction or scatter subtraction was applied.

Quantitative analysis using 4D-MSPECT program

The 2 sets of stress myocardial SPECT images in comparison with same rest image were interpreted by blinded individuals for size and location of ischemic defects utilizing a quantitative software package (4D-MSPECT; the University of Michigan, USA) using a 5-point scale according to the severity of perfusion deficit (0 = normal, 1 = equivocal, 2 = abnormal, 3 = severe, 4 = absent) in comparison to the normal database in the software corresponding to patient's gender. Summed stress scores (SSS) and summed rest scores (SRS) were obtained by total score added. Summed difference scores (SDS) was created by subtracting the SRS from the SSS. The extension of perfusion defects and reversibility of each region perfused by the 3 main coronary arteries were calculated from polar maps of the deficit relative to normal database files and expressed as a percentage of that territory. A vascular territory reversible defect > 5% was interpreted as a significant ischemic region for purposes of regional ischemia localisation. Images with a total perfusion reversible defect sizes of < 3 %, 3% to 9%, and > 9% of total left ventricular myocardium were considered normal, mild, and severe reversible ischemia, respectively. These cut-off values correspond to summed difference scores (SDS) < 2, 2 ≤ SDS ≤ 7, and > 7, which were used in previous studies [11]. In order to evaluate the secondary hypothesis of the study, the "primary" ischemic region detected (if any) was defined on the basis of location of the reversible defect of maximal size. Statistical analysis of the 4D-MSPECT data was performed using the percentage extent of the left ventricular myocardium, avoiding potential changes in segmental scores if alignment between rest and stress images was not perfect.

Statistical methods

One-way ANOVA analysis was used to compare differences in hemodynamic changes during pacing and dipyridamole stress tests. Correlations between the development of clinical ischemic parameters during stress and the presence or absence of ischemia on both pacing and dipyridamole MPI were analysed using multivariate analyses. The two-tailed paired t test was used to evaluate differences in the size of total ischemic perfusion defects of the two sets of MPI images. One-way analysis of variance with the post hoc Bonferroni test for multiple comparisons was used to determine differences exist among the means of reversible defect sizes between pacing and dipyridamole in 3 coronary artery regions. Distribution of segments according to 4D-MSPECT scores as well as concordance between pacing and dipyridamole MPI for individual coronary territory ischemic detection were assessed via the Fisher exact test and compared by using Kappa statistic with 95% confidence interval (CI). A value of $p < 0.05$ was considered significant.

Results

Patient characteristics

Clinical characteristics of the study population are shown in **Table 1**. 28 patients (9 female, 32%; 19 male, 68 %; mean age 68 years old, range 46 to 86) formed the study group. All patients had undetectable serum caffeine levels (< 5 μmol/L) prior to dipyridamole stress. Mean BMI of the group was 29.1 ± 6.4. Hypercholesterolemia (79%) and hypertension (75%) were the most common cardiac risk factors in this study group, followed by previous smoking (64%), diabetes mellitus (46%) and family history of CAD (39%).

The population examined exhibited a range of factors precluding exercise stress imaging, including poor physical mobility due to leg or back pain, hip replacement, peripheral vascular disease, or leg amputation in 7 patients (25%), and/or severe shortness of breath during exercise in 15 patients (54%). Among patients with dyspnoea on mild exertion, a previous exercise MPI had been negative at a low workload in 3 cases. Four patients had known severe systolic heart failure (NYHA class III or IV), and 1 had severe lung disease. 13 (46%) patients had previous MI, 6 (21%) had previous CABG and 5 (18%) had previous PTCA. Among patients with previous MI, 5 patients (18%) had a MI within 2 weeks of enrolment into the study and were referred for post MI risk assessment. The other reasons for stress MPI were typical chest pain in 13 patients (46%), dyspnoea in 14 (50%), and preoperative assessment in 4 (14%). Six patients (21%) underwent pacing MPI in conjunction with coronary angiography in order to define

Table 1. Clinical Characteristics (BMI = body mass index, CABG = coronary artery bypass graft surgery, PTCA = percutaneous coronary angiography, MI = myocardial infarction, PVD = pulmonary vascular disease).

Clinical Characteristics		No	%
Mean Age (range)	68±10 (46 to 86)		
Female		9	32
Male		19	68
BMI	<25	8	29
	25 to 30	6	21
	>30	14	50
Cardiac history	MI	13	46
	CABG	6	21
	PTCA	5	18
Reasons for study	Chest pain: Typical	13	46
	Chest pain: Atypical	6	21
	Dyspnea	14	50
	Post MI	5	18
	Preoperative evaluation	4	14
Reasons for non-exercise stress			
Inability to exercise	Poor physical mobility	7	25
	Dyspnea on mild exertion	15	54
b) Other	In conjunction with angiogram	6	21
Cardiac risk factors	Hypertension	21	75
	Diabetes mellitus	13	46
	Hypercholesterolemia	22	79
	Smoking	18	64
	Family history	11	39

zones of reversible ischemia in the presence of multi-vessel disease. 19 (68%) patients were taking nitrates, 14 (50%) were taking calcium channel blockers, and 13 (46%) were taking β-blockers at the time of their studies.

No major complications were observed during either stress test. During pacing stress, 9 patients (32%) experienced chest pain, 6 (21%) had dyspnoea, and 13 (46%) had minor bleeding or local bruising at the femoral puncture site (4 of these 13 patients had coronary angiography immediately before the pacing stress test and among these, 1 had severe bleeding but no blood transfusion was required). One patient developed atrial fibrillation during pacing and the arrhythmia resolved 3 days after the termination of the test. The most common side effect during dipyridamole infusion was headache (39%), followed by flushing (25%), dizziness or dyspnea (11%), and palpitation (7%). All of these side effects were reversed within 2-5 minutes after the intravenous administration of aminophylline.

Hemodynamic responses during pacing and dipyridamole stress tests

There were no differences in heart rate, diastolic blood pressure and rate-pressure product (RPP) at baseline, but systolic blood pressure was significantly higher prior to pacing stress ($p = 0.018$). During pacing stress, heart rate ($p < 0.0001$), rate-pressure product ($p < 0.0001$), and PCWP ($p = 0.019$) at peak stress conditions were significantly higher compared to baseline, while there was a significant decrease in systolic blood pressure ($p = 0.048$). With dipyridamole stress, there were a significant decrease in systolic and diastolic blood pressure ($p = 0.032$ and 0.007, respectively), while heart rate increased significantly during peak stress compared to baseline ($p = 0.001$). However, the increase in rate-pressure product did not reach significance. In comparison between two stress tests, heart rate, diastolic blood pressure, and rate-pressure product (but not systolic blood pressure) increased significantly during pacing, compared to dipyridamole stress.

Clinical correlates of positivity of pacing and dipyridamole stress tests are shown in **Table 2**. In spite of a more profound increase in heart rate, systolic blood pressure, and rate-pressure product at peak pacing stress, there was no concordance between these changes and the finding of reversible ischemia with pacing MPI images. Interestingly,

Table 2. Clinical determinants of positivity of ischemia during pacing and dipyridamole stress MPI utilizing multivariate analysis (*n = 25).

	Response	B(S.E.)	p value	95% C.I.for EXP(B)	
				Lower	Upper
Pacing	Age	-0.005(0.038)	0.889	0.923	1.072
	MHR	-0.025(0.04)	0.532	0.902	1.055
	MRPP	0.000(0.000)	0.219	1.000	1.00
	SBP change	-0.019(0.021)	0.363	0.942	1.022
	PCWP change*	0.038(0.06)	0.528	0.923	1.169
Dipyridamole	Age	-0.069(0.044)	0.117	0.856	1.018
	MHR	-0.01(0.029)	0.701	0.93	1.047
	MRPP	0.0001(0.0001)	0.017	0.999	1.00
	SBP change	0.068(0.035)	0.051	1.00	1.145

increased maximum rate-pressure product (MRPP) was a significant correlate of the presence of reversible perfusion defects with dipyridamole MPI (p = 0.017). Moreover, there was a trend towards correlation between a fall in systolic blood pressure and reversible ischemia (p = 0.051). No significant correlation between the development of chest pain during both stress tests and the presence of ischemia was seen.

Detection of reversible ischemia by pacing and dipyridamole stress

Right atrial pacing MPI was normal in 9 patients (32%), showed fixed defects in 2 patients (7%) and reversible ischemia in 17 (61 %). The results for dipyridamole MPI were similar: 9 patients had normal scans, 2 had fixed defects, and 17 had reversible ischemia. Concordant results between pacing and dipyridamole MPI for presence of ischemia were seen in 13 patients, while 8 patients had discordant results (p for concordance = 0.042). Overall, 21 patients had at least one area of reversible ischemia with either pacing or dipyridamole MPI. 12 patients had multiple ischemic zones with dipyridamole (n = 8) and/or pacing (n = 9) stress.

Right atrial pacing MPI showed mild reversible defects in 8 (29%), and severe reversible defects in 9 (32%). Similar results were obtained for dipyridamole MPI: 7 had mild ischemia and 10 had severe ischemia. There was concordance between two stress tests regarding this grading of ischemic severity (Kappa value = 0.458, p value = 0.001; **Table 3**). Despite these overall results, 10 patients (35.7%) had discordant results. No patients with negative dipyridamole MPI were diagnosed with severe ischemia with pacing MPI, but one patient with normal pacing MPI had a severe reversible defect with dipyridamole MPI. In one patient, severe reversible defects were seen with dipyridamole, but only mild ischemia with pacing. Similarly, one patient with severe ischemia on the pacing MPI had only minor reversible defects with dipyridamole MPI. There was also a good correlation regarding sizes of total reversible ischemic zones by either pacing or dipyridamole MPI (r = 0.74, p < 0.0001) (**Figure 1**). However, there was a trend for more severe reversible ischemia to be induced by dipyridamole stress in comparison to pacing stress MPI. Median reversible defect size induced by dipyridamole was 9.3 ± 11.0 % of left ventricular myocardial volume, compared to 7.0 ± 9.5(%) with pacing MPI (p = 0.09). There were no significant differences in reversible defect sizes in the three coronary artery territories between the two stress methods.

Table 3. Concordance regarding extent of ischemia detected with pacing and dipyridamole (Kappa value = 0.458, p = 0.001).

Pacing MPI	Dipyridamole MPI			
	Negative	Mild	Severe	Total
Negative	7	3	1	11
Mild	4	3	1	8
Severe	0	1	8	9
Total	11	7	10	28

Given the fundamental differences in mode of induction of ischemia between dipyri-damole and pacing, it was also possible that the two methods would also vary as regards the detection of multi-vessel ischemia. Therefore, comparisons were made of reversible defect size differences between primary and secondary ischemic regions induced by pacing (δP) and dipyridamole MPI (δD) in the 12 patients with

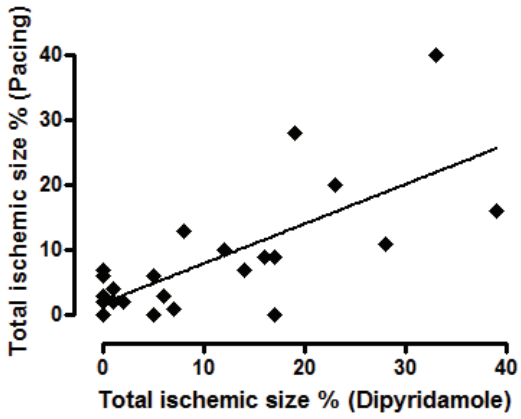

Figure 1. Correlation between total ischemic zone size with pacing and dipyridamole MPI ($r = 0.74$, $p < 0.0001$).

multiple reversible perfusion defects (either with dipyridamole or pacing). Dipyridamole significantly induced more pronounced reversible defects in primary ischemic zones, compared to pacing (46.7 ± 25.8% vs. 33.4 ± 23.6%, p = 0.05). However, there was no significant difference in ischemic sizes in secondary zones induced by dipyridamole and pacing methods (18.6 ± 19.4% vs. 14.8 ± 12.6% respectively, p = 0.4). Nevertheless, the mean difference in severity of ischemia between primary and secondary ischemic zones was more pronounced with dipyridamole than with pacing MPI (28.1 ± 21.1% vs. 18.7 ± 16.1%, p = 0.046) (**Table 4**).

Consistent results using segment by segment comparisons of the quantitative 4D-MSPECT reversibility scores (SDS) were seen. A total of 476 segments were analysed. An exact agreement between pacing and dipyridamole SDS scores was seen in 392 segments (82%), while higher scores were seen with dipyridamole MPI in 55 segments (12%), compared to 29 segments with pacing stress (6%) (Kappa value = 0.3 and p value <0.0001 for concordance).

Discussion

Detection, localisation and quantitation of inducible myocardial ischemia all are potential advantages of "physiological" evaluation of patients at cardiovascular risk. With aging and disability of the population, an increasing proportion of patients screened for inducible ischemia are unable to exercise extensively. A number of alternative methods of induction of ischemia are available, and may be categorized as primarily tachycardia/inotropy-based (e.g. dobutamine, pacing) or "steal"-based (e.g. dipyridamole, adenosine). The current comparison between pacing and dipyridamole stress MPI has revealed substantial similarities (in ischemia detection), but also potentially significant differences. The differences in physiology between pacing and dipyridamole stress are obvious and extensive. Pacing involves predominantly tachycardic stress with associated activation of the inotropic Treppe effect but can also be associated with emotional stress, so peripheral vasomotor changes may result. However, the presence of ischemia during pacing MPI was not correlated with any hemodynamic changes or the presences of either chest pain or ECG changes. Several previous studies have reported that neither ECG changes nor chest pain during pacing-induced tachycardia are reliable for the detection of CAD with a poor sensitivity of 72% and specificity of 70% [12, 13]. In contrast, dipyridamole, a pharmacological vasodilator, is used to generate segmentally hyperaemic coronary flow, creating flow heterogeneity between normal and abnormally perfused myocardium. A small fall in systolic and diastolic blood pressure (related to direct vasodilatory effect of adenosine) accompanied by a small rise in heart rate (due to reflex tachycardia) resulting in an unchanged rate-pressure product during dipyridamole (as well as adenosine) stress in patients with or without CAD is typically seen [14, 15]. Therefore, reversible perfusion defects induced by dipyridamole are not due to an increase in myocardial oxygen consumption [16, 17] and true myocardial ischemia is rare unless coronary "steal" occurs

Table 4. Comparisons of reversible defect size differences between primary and secondary ischemic regions induced by pacing (δP) and dipyridamole MPI (δD) (2-tailed paired sample T-test).

	Pacing (%)	Dipyridamole (%)	p value
Primary ischemic zones	33.4 ± 23.6	46.7 ± 25.8	0.05
Secondary ischemic zones	14.8 ± 12.6	18.6 ± 19.4	0.4
Differences between primary and secondary zones	18.7 ± 16.1	28.1 ± 21.1	0.046

[8]. In the current study, the magnitude of total reversible perfusion defects tended to be greater with dipyridamole in spite of less marked hemodynamic responses at peak stress: this again implies that the pathogenesis of dipyridamole-induced ischemia is at least in part load-independent.

There are no published data comparing the diagnostic value of atrial pacing and dipyridamole SPECT MPI for the detection of CAD. In this study, both methods were approximately equivalent for the detection of myocardial ischemia. However, while there was a good correlation between size of total ischemic zones with dipyridamole and pacing, the magnitude of ischemia tended to be greater with dipyridamole. Furthermore, this difference resulted from accentuation of the primary ischemic zone with dipyridamole in patients with multi-vessel ischemia. Therefore, although dipyridamole stress induces more reversible perfusion abnormalities, particularly in the primary ischemic zone, than pacing does, secondary ischemia in patients with multi-vessel disease may be missed with dipyridamole MPI. This underestimation may be explained by the coronary "steal" phenomenon [7]. It has been reported in a PET study that there was a significant reduction in absolute myocardial blood flow in regions with angiographically proven collateral-dependent myocardium during dipyridamole stress compared to regions without "steal" in approximately 45% patients with multi-vessel CAD [18]. Interestingly, Smart et al have previously observed that tachycardic imaging with dobutamine/atropine stress echocardiography is superior to dipyridamole MPI in detection of multi-vessel disease: these findings may have an analogous basis to those of the current study [19]. However, the results of the current study cannot be utilised to evaluate the sensitivity/specificity of either dipyridamole or pacing MPI for detection of significant fixed coronary stenoses, given that angiography was not routinely performed. It does, however, have implications as regards the accuracy of localisation of putative stenoses.

Study limitations

While this is the first reported comparison of pacing vs. dipyridamole stress MPI, it was a relatively small study and therefore the lack of statistical differences between methods in detecting ischemia may reflect type II error. Furthermore, the patients were heterogeneous as regards reason(s) for inability to exercise, and were receiving variable anti-ischemic pharmacotherapy: both of these factors may have affected outcomes. As the analysis was paired, the effect of anti-ischemic medication was minimised as no changes were allowed between the two stress studies. Also, as coronary angiography was not performed routinely anatomical correlates with physiological findings are incomplete. However, the purpose of this study was the comparison of two methods of inducing ischemia, regardless of angiographic stenosis severity (which itself may be a poor predictor of ischemic effect).

While dipyridamole is in extensive clinical use for pharmacological induction of ischemia, pacing is utilised only rarely (although may be easily utilised non-invasively in the increasing number of patients with permanent pacemakers), and dobutamine would be represented a more commonly utilized "tachycardic" stimulus. While the results for pacing and for dobutamine might have been similar, dobutamine actually represents a mixed tachycardic/vasodilator/inotropic stimulus [20, 21]. The observed differences between pacing and dipyridamole stress therefore are relevant as much related to understanding the physiology of inducible ischemia as to the choice of mode of induction.

The 4D-MSPECT quantitative program is well validated in the evaluation of perfusion defects in a single SPECT study [22]. However, as in most MPI analysis programs, stress and rest datasets are normalized to the corresponding maximal pixel count. The rest-stress comparison will lose quantitative accuracy if the maximal tracer content in a region of the rest image is relatively less than the stress image because the stress scan has been normalised to the brightest pixel in another segment. This issue should be taken into account in the case of multi-vessel disease interpretation due to a relative "balance" of ischemia, particularly in the case of dipyridamole stress MPI. Although the area of "best" perfusion may also be ischemic, it is still considered the maximal pixel count during normalisation [23]. As a result, the extent of individual ischemia in those patients is underestimated in about 40% of cases [24].

Conclusions

The results have demonstrated good concordance between pacing- and dipyridamole-induced ischemia as regards presence/absence and extent/

location of ischemia. However, when the results of individual distributions of main reversible ischemic zones were closely analysed, pacing and dipyridamole MPI correlated only moderately as regards the detection of ischemic severity. Furthermore, dipyridamole accentuates reversible perfusion defects in primary vs. secondary ischemic zones in patients with multi-vessel ischemia, consistent with known induction of coronary "steal". The fact that dipyridamole induces more marked ischemia in the primary ischemic zone in patients with multi-vessel disease should be taken into account before a patient is referred for a PTCA intervention decision, while a pacing stress MPI may be more beneficial to determine how many ischemic regions are involved.

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References

[1] Clark A, Beller G. The present role of nuclear cardiology in clinical practice. Q J Nucl Med Mol Imaging 2005; 49: 43-58.

[2] Nelson RR, Gobel FL, Jorgensen CR, Wang K, Wang Y, Taylor HL. Haemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise. Circulation 1974; 50: 1179-1189.

[3] Amanullah AM, Heo J, Iskandrian AE. Impact of exercise single-photon emission computed tomographic imaging on appropriateness of coronary revascularization. Am J Cardiol 1998; 81: 1489-1491.

[4] Poornima IG, Miller TD, Christian TF, Hodge DO, Bailey KR, Gibbons RJ. Utility of myocardial perfusion imaging in patients with low-risk treadmill scores. J Am Coll Cardiol 2004; 43: 194-199.

[5] Fuchs RM, Brinker JA, Maughan WL, Weisfeldt ML, Yin FC. Coronary flow limitation during the development of ischaemia. Effect of atrial pacing in patients with left anterior descending coronary artery disease. Am J Cardiol 1981; 48: 1029-1036.

[6] Markham R, Winniford M, Firth B. Symptomatic, electrocardiographic, metabolic, and haemodynamic alterations during pacing-induced myocardial ischaemia. Am J Cardiol 1983; 51: 1590.

[7] Demer L, Gould K, Goldstein R, Kirkeeide R. Noninvasive assessment of coronary collaterals in man by PET perfusion imaging. J Nucl Med 1990; 31: 259-270.

[8] Patterson RE, Kirk ES. Coronary steal mechanisms in dogs with one-vessel occlusion and other arteries normal. Circulation 1983; 67: 1009-1015.

[9] Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. N Engl J Med 1979; 300: 1350-1358.

[10] Stratmann H, Aker U, Vandormael M, Ischinger T, Wiens R, Kennedy H. Atrial pacing during percutaneous transluminal coronary angioplasty: results and comparison with exercise treadmill testing. Angiology 1987; 38: 663-671.

[11] Berman D, Kang X, Hayes S, Friedman J, Cohen I, Abidov A, Shaw LJ, Amanullah AM, Germano G, Hachamovitch R. Adenosine myocardial perfusion single-photon emission computed tomography in women compared with men. Impact of diabetes mellitus on incremental prognostic value and effect on patient management. J Am Coll Cardiol 2003; 41: 1125-1133.

[12] Markham RV Jr, Winniford MD, Firth BG, Nicod P, Dehmer GJ, Lewis SE, Hillis LD. Symptomatic, electrocardiographic, metabolic, and haemodynamic alterations during pacing-induced myocardial ischaemia. Am J Cardiol 1983; 51: 1589-1594.

[13] Piessens J, VanMieghem W, Kesteloot H, DeGeest H. Diagnostic value of clinical history, exercise testing and atrial pacing in patients with chest pain. Am J Cardiol 1974; 33: 351-356.

[14] Feldman R, Nichols W, Pepine C, Conti C. Acute effect of intravenous dipyridamole on regional coronary haemodynamics and metabolism. Circulation 1981; 64: 333-344.

[15] Wilson R, Wyche K, Christensen B, Zimmer S, Laxson D. Effects of adenosine on human coronary arterial circulation. Circulation 1990; 82: 1595-1606.

[16] Iskandrian A, Verani M, Heo J. Pharmacologic stress testing: Mechanism of action, haemodynamic responses, and results in detection of coronary artery disease. J Nucl Cardiol 1994; 1: 94.

[17] Zhu Y, Lee W, Botvinick E, Dae M, Chatterjee K, Danforth J, Ports T. The clinical and pathophysiologic implications of pain, ST abnormalities, and scintigraphic changes induced during dipyridamole infusion: their relationships to the peripheral haemodynamic response. Am Heart J 1988; 116: 1071-1080.

[18] Akinboboye O, Idris O, Chou R, Sciacca R, Cannon P, Bergmann S. Absolute quantitation of coronary steal induced by intravenous dipyridamole. J Am Coll Cardiol 2001; 37: 109-116.

[19] Smart SC, Bhatia A, Hellman R, Stoiber T, Krasnow A, Collier BD, Sagar KB. Dobutamine-atropine stress echocardiography and dipyrida-

mole sestamibi scintigraphy for the detection of coronary artery disease: limitations and concordance. J Am Coll Cardiol 2000; 36: 1265-1273.
[20] Meyer SL, Curry GC, Donsky MS, Twieg DB, Parkey RW, Willerson JT. Influence of dobutamine on haemodynamics and coronary blood flow in patients with and without coronary artery disease. Am J Cardiol 1976; 38: 103-108.
[21] Willerson JT, Hutton I, Watson JT, Platt MR, Templeton GH. Influence of dobutamine on regional myocardial blood flow and ventricular performance during acute and chronic myocardial ischaemia in dogs. Circulation 1976; 53: 828-833.
[22] Wolak A, Slomka PJ, Fish MB, Lorenzo S, Acampa W, Berman DS, Germano G. Quantitative myocardial-perfusion SPECT: comparison of three state-of-the-art software packages. J Nucl Cardiol 2008; 15: 27-34.
[23] Williams K, Schuster R, Williams K, Schneider C, Pokharna H. Correct spatial normalization of myocardial perfusion SPECT improves detection of multivessel coronary artery disease. J Nucl Cardiol 2003; 10: 353-360.
[24] Daou D, Delahaye N, Vilain D, Lebtahi R, Faraggi M, LeGuludec D. Identification of extensive coronary artery disease: incremental value of exercise TI-201 SPECT to clinical and stress test variables. J Nucl Cardiol 2002; 9: 161-168.