Association of Ventricular Ectopy with Nuclear Scintigraphic Perfusion Defects during Dipyridamole Stress Testing

DAVID L. RABIN, M.D., AMJAD ALI, M.D., JOHN T. BARRON, M.D., PH.D.

Section of Cardiology, Department of Medicine and Department of Radiology and Nuclear Medicine, Rush Medical College, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois, USA

Summary

Background and hypothesis: No information is available regarding the significance of ventricular ectopic activity induced during dipyridamole nuclear scintigraphic stress testing. This study tested the hypothesis that dipyridamole-induced ventricular ectopy predicts a thallium-201 or technetium-99m sestamibi perfusion defect.

Methods: A group of 186 consecutive patients with premature ventricular contractions and/or couplets occurring during dipyridamole stress testing (ventricular tachycardia did not occur) was compared with a control group of 194 patients without ventricular ectopy during dipyridamole stress testing.

Results: The results indicated that ventricular ectopy induced during dipyridamole infusion occurred more frequently in patients demonstrating either a fixed or reversible perfusion defect on scintigraphic imaging ($p < 0.01$). The higher frequency of perfusion defects in this group of patients was attributable to a higher frequency of "fixed" compared with "reversible" defects ($p < 0.05$). This finding is consistent with the additional observation that ventricular ectopy induced by dipyridamole was associated with the presence of Q waves on the resting ECG ($p < 0.05$). The positive and negative predictive values of the presence of ventricular ectopy in predicting a fixed myocardial perfusion defect were 59 and 54%, respectively.

Conclusions: Ventricular ectopy induced during dipyridamole infusion suggests the presence of a fixed myocardial perfusion defect.

Key words: dipyridamole, stress testing, ventricular ectopy, nuclear scintigraphy, myocardial perfusion

Introduction

The significance of ventricular arrhythmias in cardiac stress testing has been controversial. Ventricular ectopic activity (VEA), specifically isolated premature ventricular contractions (PVCs), couplets, and nonsustained ventricular tachycardia are common during stress testing, yet their association with coronary artery disease (CAD) and prognostic importance is unclear.^{1,2} Early work indicated that VEA during treadmill stress testing was suggestive of CAD, though not diagnostic.³ Subsequent studies indicated that although VEA with concomitant ischemic changes was associated with CAD, VEA alone was more likely associated with either dilated cardiomyopathy or no cardiac disease at all.⁴ Califf *et al.*⁵ examined the prognostic value of PVCs, couplets, and ventricular tachycardia in patients undergoing exercise stress testing. They reported a higher prevalence of significant coronary disease, triple-vessel disease, and left ventricular dysfunction in patients with than without exercise-induced ventricular ectopy. They also observed that those patients with VEA during exercise were at increased risk for cardiac death. This risk, however, was primarily attributable to the association of VEA with left ventricular dysfunction.

No information is available regarding the significance of VEA induced during dipyridamole nuclear scintigraphic stress testing, a noninvasive diagnostic modality commonly used to assess the presence of CAD in patients unable to exercise. In a review of the safety of intravenous dipyridamole thallium stress testing, Ranhosky *et al.*⁶ reported ventricular extrasystoles occurring in 5.2% of 3,911 patients. Two case reports^{7,8} describe episodes of ventricular fibrillation and ventricular tachycardia occurring during dipyridamole testing in patients with CAD. Other than these studies, a systematic examination of the significance of VEA induced during dipyridamole stress testing has not been performed. This is the subject of the present investigation. We tested the hypothesis that dipyridamole-induced VEA predicts a 201-thallium or 99m technetium-sestamibi (MIBI) perfusion defect.

Address for reprints:

John T. Barron, M.D., Ph.D.
Director, Stress Testing Laboratory
Rush-Presbyterian-St. Luke's Medical Center
1653 West Congress Parkway
Chicago, IL 60612, USA

Received: July 22, 1997

Accepted with revision: December 11, 1997

Methods

The study population consisted of 380 patients without VEA on resting, prestress electrocardiograms who were about to undergo dipyridamole stress testing. A group of 186 consecutive patients with PVCs and/or couplets occurring during dipyridamole stress testing (ventricular tachycardia or three or more consecutive ectopic beats did not occur) was compared with a control group of 194 patients without VEA during dipyridamole stress testing. Intravenous dipyridamole stress testing was carried out according to a standard protocol.⁹ Dipyridamole was infused at a rate of 0.56 mg/kg over 4 min. Adjunctive straight leg-raising exercise was then initiated when possible to reduce side effects and improve image quality. The isotope was injected 3 min after completion of infusion. Aminophylline (75 mg) was injected intravenously thereafter to eliminate any adverse reaction. A positive stress was defined as either a fixed or reversible perfusion defect seen on nuclear scintigraphic imaging. Studies with the reverse redistribution phenomenon or studies that were deemed equivocal were excluded from our analysis because of the uncertain nature of these results.¹⁰

Results

The association of VEA with scintigraphic myocardial perfusion defects is given in Table I. In the group of patients with VEA, 128 scans demonstrated a myocardial perfusion defect (73 with a reversible defect) and 58 scans were normal (without defect). In the group of VEA, there were 109 scans with perfusion defects (71 with a reversible defect, 38 with a fixed defect) and 38 normal scans (Table I).

An analysis of the results (Table I) indicated that VEA induced during dipyridamole infusion occurred significantly more frequently in patients demonstrating either a fixed or reversible perfusion defect on scintigraphic imaging ($p < 0.01$). It is important to note that 9 of the 12 patients who demonstrated ventricular couplets had positive scintigraphic studies. The positive and negative predictive values of the presence of ectopy in predicting perfusion abnormalities were 54 and 59%, respectively. Further analyses of the data indicated that the higher frequency of perfusion defects seen in patients with dipyridamole-induced VEA was primarily attributable to a higher frequency of "fixed" defects compared with "reversible" perfusion defects in these patients (Table II). Therefore, the positive and negative predictive values of the presence of VEA in predicting a fixed myocardial perfusion defect were 59 and 54%, respectively.

Table III gives the association of other demographic and clinical variables with VEA induced by dipyridamole. The variables selected were male gender, age greater or less than 65 years, presence of Q waves on the electrocardiogram (ECG) indicative of prior myocardial infarction, significant ST-segment depression during dipyridamole infusion, a drop in blood pressure > 15 mmHg, and the development of angina. There was no significant difference in the number of men ver-

TABLE I Scintigraphic perfusion defects and ventricular ectopy

		Nuclear perfusion images	
		No defect	Defect present
DP-induced VEA	Absent		
	(control)	85	109
	Present	58	128

$p < 0.01$ by X^2 test.

Abbreviations: DP = dipyridamole, VEA = ventricular ectopic activity.

TABLE II Fixed and reversible scintigraphic defects and ventricular ectopy

		Nuclear perfusion images	
		No defect	Defect present
DP-induced VEA	Absent		
	(control)	Fixed 38	Reversible 71
	Present	55	73

$p < 0.05$ by X^2 test.

Abbreviations as in Table I.

TABLE III Association of clinical variables with dipyridamole-induced ventricular ectopy

Variable	p Value (Pearson X^2)
Age	0.001
Male sex	0.120
Q waves	0.046
ST depression ≥ 0.1 mV	0.198
Hypotension ≥ 15 mmHg	0.690
Angina	0.942

sus women in either group. In the group of patients with VEA there were 94 men and 92 women; in the group of patients without VEA there were 98 men and 96 women. The patients with VEA during dipyridamole infusion were older (70 ± 10 years vs. 63 ± 13 years, $p < 0.001$). Of the variables listed in Table III, age > 65 years and the presence of Q waves on the ECG were significant univariate predictors of VEA during dipyridamole infusion.

Discussion

This is the first study to examine the significance of ventricular ectopy induced during dipyridamole stress testing. An association between VEA and perfusion defects on scintigraphic imaging was demonstrated. Ventricular ectopy activity occurred more frequently to some extent in subjects with "fixed" defects when compared with subjects with "rever-

sible" defects or no perfusion defects at all. This finding is consistent with the additional observation that VEA induced by dipyridamole was significantly associated with the presence of Q waves on the resting ECG.

The mechanism by which VEA could be induced by dipyridamole is unknown. Dipyridamole has not been reported to exert direct arrhythmogenic effects on the myocardium. In fact, dipyridamole has been reported in one study to terminate ventricular tachycardia of nonischemic etiology.¹¹ It is tempting to speculate that dipyridamole induced ischemia within the zone of previous infarct or in the peri-infarct region. Myocardial ischemia induced by dipyridamole is thought to be due to redistribution of blood flow from the endocardium to epicardial layers in a segment of myocardium subtended by a stenotic epicardial coronary artery as a consequence of the reduced flow reserve of the stenotic artery. An area of viable myocardium adjacent to or within a zone of previous infarction may be especially vulnerable to ischemia mediated by dipyridamole, since the blood supply to this watershed region may be severely limited. Other plausible explanations for dipyridamole-induced ectopy in the setting of myocardial scarring and/or ischemia may also be proposed, and more investigations are needed to establish the mechanism. In any case, the results of our study addresses a question frequently encountered by physicians when interpreting the ECG response during dipyridamole infusion.

Limitations of the Study

The occurrence of ventricular ectopy may be random, regardless of the presence or absence of underlying structural heart disease. The probability of detecting ventricular ectopy increases as the period of ECG monitoring increases. The ECG monitoring period during the infusion of dipyridamole exceeded that in which the prestress baseline ECG was obtained. Therefore, some patients who were categorized as having no VEA on the prestress ECG, but who demonstrated VEA during the infusion of dipyridamole, may have had VEA in the baseline state had the prestress monitoring period been extended. Such patients would have been entered into the analysis incorrectly. On the other hand, there may have been patients with ambient ventricular ectopy, detected on the prestress ECG, which might have increased with dipyridamole infusion, causing them to be excluded from the analysis. Other patients with no structural heart disease or scintigraphic perfusion defect and no VEA provokable by dipyridamole might also have been excluded from the analysis because of ambient

VEA detected on the prestress ECG. In any case, the monitoring period for the prestress baseline ECG and the period for dipyridamole infusion were identical for both groups of patients in this study. This would tend to limit the erroneous categorizations of patients into the two groups.

Acknowledgment

The authors thank Diane Grayer for typing the manuscript.

References

1. Udall JA, Ellestad MH: Predictive implications of ventricular premature contractions associated with treadmill stress testing. *Circulation* 1977;56:985-989
2. Sami M, Chaitman B, Fisher L, Holmes D, Fray D, Alderman E: Significance of exercise induced ventricular arrhythmia in stable coronary artery disease: A coronary artery surgery study project. *Am J Cardiol* 1984;54:1182-1188
3. McHenry PI, Fisch C, Jordan J, Corya B: Cardiac arrhythmias observed during maximal treadmill exercise testing in clinically normal men. *Am J Cardiol* 1972;29:331-336
4. Helfant RH, Pine R, Kabde V, Banka VS: Exercise related ventricular premature complexes in coronary heart disease: Correlations with ischemia and angiographic severity. *Ann Intern Med* 1974;80:589-592
5. Califf RM, McKinnis RA, McNeer F, Harrell FE Jr, Lee KL, Pryor DB, Waugh RA, Harris PJ, Rosati RA, Wagner GS: Prognostic value of ventricular arrhythmias associated with treadmill exercise testing in patients studied with cardiac catheterization for suspected ischemic heart disease. *J Am Coll Cardiol* 1983;2:1060-1067
6. Ranhosky A, Kempthorne-Rawson J, and the Intravenous Dipyridamole Thallium Imaging Group: The safety of intravenous dipyridamole thallium myocardial perfusion imaging. *Circulation* 1990;81:1205-1209
7. Egloff P, Douard JL, Broustet JP: Trouble du rythme ventriculaire grave d'origine ischémique au cours d'une scintigraphie au dipyridamole. *Arch Mal Coeur* 1991;84:861-863
8. Bayliss J, Pearson M, Sutton GC: Ventricular dysrhythmias following intravenous dipyridamole during "stress" myocardial imaging. *Br J Radiol* 1983;56:686
9. Beller GA: Pharmacologic stress imaging. *J Am Med Assoc* 1991;265:633-638
10. Silberstein EB, DeVries DF: Reverse redistribution phenomenon in thallium-201 stress tests: Angiographic correlation and clinical significance. *J Nucl Med* 1985;26:707-710
11. Kobayashi Y, Kikushima S, Tanno K, Kurano K, Baba T, Katagiri T: Sustained left ventricular tachycardia terminated by dipyridamole: Cyclic AMP-mediated triggered activity as a possible mechanism. *Pace* 1994;17:377-385