Angina Relief by Ranolazine Identifies False-Negative SPECT Myocardial Perfusion Scans in Patients with Coronary Disease Demonstrated by Coronary Angiography

Gary L. Murray, MD, FACC, FSCAI, FASNC, FICA¹

¹ Director Medical Research, Heart and Vascular Institute, Germantown, Tennessee

Address for correspondence Gary L. Murray, MD, FACC, FSCAI, FASNC, FICA, Heart and Vascular Institute, Germantown, 7205 Wolf River Blvd., TN 38138 (e-mail: drglmurray@hotmail.com).

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Abstract

Normal myocardial perfusion imaging (MPI) reduces intermediate- or high-risk pretest probability patients to low- or intermediate-risk posttest probability, respectively, for coronary disease (CD). Since ranolazine (RAN) relieves only angina, anginal patients with normal MPI whose angina is relieved by RAN present a significant dilemma. The purpose of this retrospective chart review was to confirm the impression that coronary angiography (CA) is indicated in patients whose class 3 to 4 angina is relieved by RAN, but have normal myocardial single-photon emission computed tomography (SPECT) MPIs. Charts of patients with stable class 3 to 4 angina (typical and atypical) and normal MPIs (left ventricular ejection fraction [LVEF] $\geq 50\%$ and segmental score = 0) were reviewed. CA was done on all the patients with complete angina relief taking RAN, as well as nonresponders whose anginal etiology could not be explained. Stenoses were considered flow-restrictive when more than 70% diameter stenosis is observed by quantitative CA, or, when 50 to 70%, fractional flow reserve (FFR) measured ≤ 0.80 . RAN relieved angina in 36 of 54 (67%) patients. Of the known cases, 25 of these 36 (69%) had 43 stenoses $\geq 50\%$ (mean = 66%): 15 (60%) had 1 vessel disease; 9 (36%) had multivessel disease; 18 (72%) had left anterior descending (LAD) disease; 1 (4%) had left main disease. Twenty one of 43 (49%) stenoses were $> 70\%$; 22 (51%) stenoses were 50 to 70% and required FFR measurement. Twenty nine of 43 stenoses (67%) were considered flow-restrictive in 18 of these 25 (72%) patients. Eight RAN nonresponders with no explanation for angina had no CD at CA. RAN angina relief is invaluable in identifying falsely negative SPECT MPI, and 50% of these patients have flow-restrictive stenoses.

Keywords

- ▶ ranolazine
- ▶ coronary disease
- ▶ angina
- ▶ myocardial SPECT perfusion
- ▶ cardiac catheterization
- ▶ fractional flow reserve

Myocardial perfusion imaging (MPI) for diagnosing coronary disease (CD) carries a class 1 recommendation for patients unable to exercise or who have uninterpretable electrocardiograms, and a class 2a recommendation in patients with an intermediate- or high-risk pretest probability of ischemic heart disease (IHD).¹ However, the sensitivity of MPI single-photon emission computed tomography (SPECT) varies from 83% (and as low as 60–76%) for single vessel disease, to 95% for triple vessel disease,^{2,3} with a specificity of 77%.

Consequently, a significant number of IHD patients are missed on SPECT MPI. Since our practice elected to use RAN in moderate-to-high risk IHD-probability patients with stable class 3 to 4 angina based upon its specificity for angina relief and superiority to β -blockers and calcium-channel blockers,⁴ we were impressed that a relatively high percentage of the normal SPECT MPI, but RAN-responsive patients had, when performed, positive CAs, and, therefore, undertook a retrospective case review.

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Methods

A retrospective chart review of patients, who presented at the Heart and Vascular Institute between June 2012 and January 2013, with stable class 3 to 4 angina (40% typical, 60% atypical), was considered to be at moderate- (72%) to high- (28%) risk pretest probability for IHD, with normal SPECT MPI (left ventricular ejection fraction [LVEF] $\geq 50\%$ and a segmental score = 0) performed. Patients had been given 500 mg RAN p.o. bid for 3 days, then 1,000 mg p.o. bid for up to 2 weeks. If RAN completely relieved angina, cardiac angiography (CA) was performed; if not, the patients were referred back to their primary care physician (PCP) for further evaluation. If no etiology for angina was found, CA was done. Antianginal medications were held 24 hours before MPI. For exercise SPECT MPI, 10-mCi technetium (99mTc) tetrofosmin were given intravenously (IV) at rest; 20 to 40 minutes thereafter, SPECT images were acquired under a double-headed gamma camera with high-resolution collimation. At peak exercise (all patients reached target heart rate), 30 mCi of 99mTc tetrofosmin were injected IV, stress images were acquired 20 to 40 minutes later in a 64×64 matrix, with 64 projections, 20 second stops, and 8 frames per cycle with a 20% window centered on the 140 keV photopeak of 99mTc. The stress study was gated to evaluate regional wall motion and calculate LVEF. Resting images were acquired in the same 64×64 matrix, with 64 projections, and 20 second stops. Data was reconstructed in the short, horizontal long, vertical long axis views, and tomographic slices were generated. For

pharmacologic stress, 0.4 mg regadenoson was given IV, and 1 minute later 30 mCi 99mTc tetrofosmin was injected. Gating was performed 60 minute thereafter. Polar maps were divided into 20 segments. CA was performed with coronary diameter stenosis measured by quantitative analysis (Siemens). Using the most severe stenosis of orthogonal views, CD was defined as $\geq 50\%$ diameter stenosis. All 50 to 70% stenoses had FFR measured (off ranolazine) during up to a 3-minute infusion of adenosine at $140 \mu\text{g/kg/min}$, adenosine being discontinued when FFR reached ≤ 0.80 . When FFR was ≤ 0.80 (5), or diameter stenosis was more than 70%, stenoses were considered flow-restrictive, and percutaneous coronary intervention (PCI) was considered. Appropriate informed consent was obtained for each procedure described above.

Statistics

Fisher exact test of statistical significance was used to analyze the independence of the relatively small sample sizes in the 2×2 contingency tables derived from the RAN- versus non-RAN-responsive columns of ►Table 1. Statistical significance was accepted at $p = 0.05$.

Results

►Table 1 describes the patients' demographics. Comparison of RAN-responders to RAN-unresponsive patients revealed a few differences. There were more males in the RAN-

Table 1 Patient demographics ($N = 54$)

RAN responsive ($n = 36$)		RAN unresponsive ($n = 18$)	p Value
Age (mean)	63	62	–
Gender	17M, 19F	4M, 14F	0.14
PHx			
CD	11 (30%) ^a	2 (11%) ^a	0.18
Hyperlipidemia	23 (64%)	15 (83%)	0.21
Hypertension	21 (58%)	12 (67%)	1.00
Diabetes	13 (36%)	7 (39%)	0.77
FH ⁺	19 (53%)	11 (61%)	0.57
Smoker	7 (19%)	4 (22%)	1.00
β Blocker	12 (33%)	5 (28%)	0.76
CC Blocker	10 (28%)	5 (28%)	1.00
PAD	2 (6%)	1 (6%)	1.00
Angina	15 (42%)	6 (33%)	0.77
Atypical angina	21 (58%)	12 (67%)	0.02
Pretest probability CD			
Intermediate	23 (64%)	16 (89%)	0.10
High	13 (36%)	2 (11%)	0.10

Abbreviations: β , beta; CC Blocker, calcium-channel blocker; CD, coronary disease; FH, family history; PAD, peripheral arterial disease; PHx, patient.

^aAll CD patients both groups prior revascularized.

responsive group (47 vs. 22% of RAN-nonresponders), more RAN-responders had a history of CD (30 vs. 11% of RAN-nonresponders, all CD patients in both groups having been previously completely revascularized), and RAN-responders had a higher pretest probability of CD, although the majority in both the groups were considered intermediate-pretest probability. However, the p values for these differences were not significant in this sample size. The only significant difference found was that more RAN-unresponsive patients had atypical angina (67 vs. 58%). Ages, risk factors for CD, and medical management were similar, with 56 to 61% of patients taking β -blockers or calcium-channel blockers. RAN was added to this regimen when the patient's angina was not relieved.

Of 54 patients with stable class 3 to 4 angina, whose charts were reviewed, 36 (67%) had complete angina relief by RAN; 25 of those (69%) who responded to RAN had 43 stenoses $\geq 50\%$ (mean 66%, range 50–99%), shown in **Table 2** (coronary angiographic results) and **Fig. 1** (management strategy). Of the stenoses, 31 (72%) were proximal, and 18 (42%) involved the LAD. Of these 18, 12 (67%) were with proximal LAD stenoses. One patient of the 25 with CAD (4%) had a 75% distal left main stenosis. Twenty-nine (67%) of the 43 stenoses were considered flow-restrictive: 21 with at least 70% diameter stenosis (mean stenosis 82%), with 8 of the remaining 22 (36%) intermediate stenoses having FFRs ≤ 0.80 .^{5,6} CA resulted in 15 of these 36 patients (42%, 7 with typical angina,

8 with atypical angina) receiving 24 stents, 10 of which were placed in the LAD. Two patients with flow-restrictive stenoses were treated medically, and the patient with 75% distal left main stenosis (85% mid right coronary artery [RCA] and proximal obtuse marginal stenoses were also found) was referred for coronary bypass surgery (CABG).

Patients with angina relief by RAN, who had no CD, or nonflow-restrictive CD, had a mean left ventricular end diastolic pressure (LVEDP) of 20 mm Hg. Two patients had LAD myocardial bridges with FFRs 0.82 and 0.87.

The 18 of our 54 patients (33%) who were not relieved from angina by RAN were referred back to their PCP for noncardiac evaluation. In 8 of them (44%), no cause of angina was found; consequently, all 8 patients were referred for CA (2 males, 6 females), none of whom had CD. Their mean LVEDP was 17 mm Hg.

Discussion

99mTc tetrofosmin SPECT MPI has a sensitivity for CD of 66 to 95%, with sensitivities for LAD, RCA, and left circumflex (LCX) disease of 71 to 78%, 73 to 76%, and 61 to 66%, respectively.^{7,8} Therefore, when patients with intermediate- or high-risk pretest probability of CD⁹ have normal MPI, their posttest probability of IHD is reduced to low or intermediate, respectively. All patients in this report had normal MPI. The 11 of the 36 patients with RAN-relieved angina (31%) had exercise MPI (all achieving target HR), while 25 (69%) underwent regadenoson MPI. The long-term prognosis of a normal exercise tetrofosmin SPECT MPI is excellent,¹⁰ with 60% of the patients free of cardiac death, nonfatal myocardial infarction (MI), or revascularization at 10 years. Similarly, following normal adenosine tetrofosmin SPECT MPI, the annualized death rate is as low as 0.6%, although higher in patients ≥ 75 years of age.¹¹ However, one study showed that the 10-year mortality after normal adenosine SPECT MPI versus normal exercise SPECT MPI is substantially higher.¹² Hence, although normal SPECT MPI generally carries a good prognosis, no study has reported the prognosis in patients with falsely normal SPECT MPI, that is, flow-restrictive stenoses as calibrated by FFR. RAN's ability to ferret out false-negative SPECT MPI could improve the good prognosis of normal-SPECT MPI studies.

The FAME 2 trial⁶ was halted prematurely because FFR guided PCI plus best medical therapy had a better prognosis than best medical therapy alone, as in the COURAGE trial,¹³ driven by fewer urgent revascularizations triggered by MI or ischemia shown on electrocardiography. Therefore, patients with normal MPI but flow-restrictive CD, reasonably, might be expected to have a better prognosis if PCI were performed. Angina relief by RAN identifies these patients, since 18 patients had 29 flow-restrictive stenoses, whereas none of the patients unresponsive to RAN had CD (**Fig. 1**).

With normal SPECT MPIs, the decision to perform PCI (FAME 2) or aggressively medically manage patients (COURAGE) depends upon the degree of symptom relief and the coronary anatomy. Inadequate symptom relief, single or multivessel CD involving the proximal LAD,¹⁴ and left main

Table 2 Cardiac catheterization findings in RAN-responsive patients (N = 36)

CD+	25(69%, mean stenosis 66%, range 50–99%)
1V LAD	9 (36%)
2V LAD	5 (20%)
3V	4 (16%)
LM	1 (4%)
1V NLAD	6 (24%)
Myocardial Bridge	2 (6%)
21/43(49%) Stenoses not requiring FFR: mean stenosis 82%	
FFR done	22/43 (51%) stenoses
FFR ≤ 0.80 (mean 0.73)	8/22 (36%)
24 Stents (15 patients)^a	
Vessel stented	
LAD	61% (39% proximal, 22% mid)
LCX	22% (80% proximal, 20% distal)
RCA	17% (99% proximal)
Stent diameter (mean)	2.7 mm
Stent length (mean)	17 mm

Abbreviations: CD, coronary disease; FFR, fractional flow reserve; LAD, left anterior descending artery; LCX, left circumflex; LM, left main; NLAD, non-left anterior descending artery; RCA, right coronary artery; V, vessel.

^aTwo patients treated medically, and one referred for coronary bypass.

Fig. 1 Management of 54 patients with angina given a ranolazine trial. CMVD, coronary microvascular dysfunction; FFR, fractional flow reserve.

disease favor PCI provided the SYNTAX (synergy between PCI with Taxus and cardiac surgery) score is low.

Approximately, 70% of RAN-responsive patients had no prior PCI, CABG, or CA showing $\geq 50\%$ stenosis. Low-risk SPECT MPI findings ($< 5\%$ ischemic myocardium) carry an appropriate use score of 4 (uncertain) in these symptomatic patients for performing diagnostic catheterization.¹⁵ In the 30% of RAN-responsive patients with a past history of CD, low-risk noninvasive findings carry an appropriate use score of 6 (uncertain) with limiting symptoms, such as class 3 to 4

angina as experienced by our patients. Our results suggest catheterization in RAN-responsive patients is reasonably appropriate, as 50% of these patients had at least one flow-restrictive coronary stenosis.

In the author's experience, when clinical suspicion of symptomatic IHD remains after normal SPECT MPI, obtaining precertification for CA has been extremely difficult. However, upon appeal of denial, when the patient's complete anginal relief by RAN was mentioned, the procedure was always approved once it was pointed out that RAN chest pain relief

is specific for angina, and that RAN is superior to β -blocker or calcium-channel blocker therapy for angina relief.⁴

CA identified LAD disease in 18 of 36 (50%) (**►Table 2**) RAN-responsive patients, 13 flow-restrictive stenoses being stented in 11 patients, 4 of whom had multivessel stents deployed. Four non-LAD single-vessel patients were stented, two in the RCA as well as in the LCX. The patient with left main, multivessel disease was referred for CABG. The remaining two patients with flow-restrictive stenoses were treated medically. Ultimately, 24 of the 29 flow-restrictive stenoses (83%) were stented (**►Fig. 1**).

CA was deemed necessary because patients had stable, but limiting class 3 to 4 angina despite β -blocker $\pm$ calcium-channel blocker therapy in 62%. In the remaining 38% of patients not taking a β -blocker $\pm$ calcium-channel blocker, catheterization was done for diagnostic purposes, to determine the etiology of the RAN response or the possibility of CD in RAN-unresponsive patients who had no noncardiac cause of their angina diagnosed. PCI was considered appropriate even in 1 or 2 vessel CD involving the proximal LAD with low-risk MPI with no or minimal antianginal medical therapy.¹⁴ PCI was done to improve outcomes (fewer urgent revascularizations compared with best medical therapy as in the COURAGE trial) in all 15 patients stented in accordance with the FAME 2 trial.⁶ Patients without LM or proximal LAD disease who achieved good symptom control could have been managed as per the COURAGE trial.¹³

All stented patients with multivessel disease had a SYNTAX score ≤ 22 ,¹⁶ thereby favoring PCI over CABG surgery for revascularization.

Two of 36 RAN-relieved patients (6%) had myocardial bridges with FFRs of 0.82 and 0.87. FFR measurement and management of myocardial bridges remain controversial,^{17,18} and both the patients are angina-free on RAN.

Eighteen of the 54 patients (33%) did not respond to RAN, and a noncardiac source of anginal pain was found in 10 (56%), typically gastrointestinal. The remaining 8 patients had catheterization for diagnostic purposes, no CD being found (**►Fig. 1**). However, LVEDP averaged 17 mm Hg in these patients. Of the 11 of 36 (31%) patients whose angina responded to RAN but no CD was found, the mean LVEDP was 20 mm Hg. These findings suggest coronary microvascular dysfunction as the cause of angina,^{19–22} with RAN relieving symptoms in 11 of these 19 patients (58%).

Limitations

We used the same day low-dose rest/high-dose stress 99mTc tetrofosmin protocol, which reduces stress defect contrast, as roughly 15% of the radioactivity during stress imaging comes from the preexisting resting myocardial radioactivity. However, our strict definition of normal MPI likely minimizes this drawback; it is unlikely that we missed enough small defects to affect our results. Our laboratory has a sensitivity of 83% and a specificity of 79% for diagnosing CD, consistent with published values.^{2,3} Furthermore, this definition of normal takes subjectivity out of the MPI interpretation, just as our using quantitative angiography to measure diameter stenosis

(Siemens) eliminated subjectivity in grading stenosis severity. Most centers use dual-isotope MPI (rest Tl-201, stress 99mTc sestamibi/tetrofosmin). Kamínek et al study²³ found no significant difference in the sensitivity, specificity, and diagnostic accuracy for detection of IHD between the dual isotope and 2 day tetrofosmin protocols, and the sensitivity of same day 99mTc-tetrofosmin imaging for detecting CD is the same as with the 2 day protocol.²⁴

Conclusions

When SPECT MPI is normal in patients with stable class 3 to 4 angina, angina relief with a short trial of RAN identifies patients likely to have flow-restrictive CD. Patients considered with low probability for CD after a negative-stress SPECT MPI should be considered with moderate probability for CD if RAN-responsive; correspondingly, post MPI moderate CD probability subjects should be considered high probability for CD if RAN-responsive, since 18 of 36 (50%) RAN-responsive patients had flow-restrictive CD at CA. Another two RAN responders had myocardial bridges. The remaining RAN-responsive patients could suffer from coronary microvascular dysfunction; low coronary flow (velocity) reserve absent flow-restrictive CD would be consistent with this. RAN nonresponders are highly unlikely to have epicardial CD as the cause of their chest pain, confirming the SPECT MPI results.

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Disclosure

None.

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