Reverse Redistribution Phenomenon In Patients With Normal Coronary Epicardial Arteries And Its Relationship To Systolic Left Ventricular Dysfunction

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Citation

Abstract

Background: Among the different imaging patterns found in myocardial perfusion imaging, the true significance of the reverse redistribution remains a controversial subject.

Objective: The objective of this study was to evaluate the prevalence of reverse redistribution and its relation to left ventricular systolic function among a cohort of patients who underwent coronary angiography and scintigraphic study

Methods: We retrospectively analyzed the data of patients with normal coronary arteries on angiography and who had a scintigraphic study.

Results: There were 42 patients who had normal coronaries on coronary angiography and had a scintigraphic study; 16 (38.1%) had reverse redistribution pattern. Patients with reverse redistribution pattern showed higher prevalence of myocardial infarction (31 vs. 7.7%) and diabetes mellitus type 2 (50 vs. 23%) than those who did not show the pattern. Subjects with severe reverse redistribution had lower left ventricular ejection fractions (43.3 ± 1.5% vs. 61.5 ± 15.4%) than subjects without it.

Conclusion: Among patients undergoing coronary angiography and Tc99 Sestamibi myocardial perfusion scintigraphy, severe reverse redistribution was associated with lower left ventricular ejection fraction

INTRODUCTION

Scintigraphy has a important role in the study of ischemic heart disease; nevertheless, there are cases without obstructive coronary lesions where its results are non-conclusive, especially regarding the so called reverse redistribution (RR) perfusion defects. [1, 2]

Among the described perfusion patterns, RR is the least characterized; it is not clear if it represents reversible ischemia. Its prognostic value is unknown, many investigators consider that RR is not clinically significant, does not require further investigation or treatment. [2]

Reverse redistribution pattern is said to exist when images acquired after exercise or pharmacologic stress show normalization or regression of a perfusion defect compared to the redistribution or rest images obtained afterwards.

This kind of pattern is frequently observed among patients with ischemic heart disease (history of myocardial infarction, treated by thrombolysis or myocardial revascularization procedures), and it is probably explained by a higher-than-normal blood flow with an accelerated wash-out of the radionuclide in non-infarcted tissue around the reperfusion areas. An alternative explanation is thallium harnessing in the expanded interstitial compartment of the

reperfused area with faster wash-out.[3] Altered myocardial thallium uptake can be secondary to an inadequate perfusion as well as to metabolic abnormalities that compromise potassium transfer across the cell membrane.[4]

In studies performed with MIBI (although RR is strictly inexact because MIBI have not redistribution, however the term has been used in the same way) RR was observed in high risk areas among patients with acute myocardial infarction (MI) and preserved left ventricular function.[5] Choe et al. [6] found that RR correlated to acute non-transmural MI detected by means of myocardial contrast echocardiogram.

The present study was designed to determine the association between reverse redistribution as a scintigraphic perfusion (with MIBI) defect and left ventricle dysfunction.

METHODS

STUDY POPULATION

The data of all patients referred for coronary angiography and that showed no epicardiac coronary lesions from January 1999 to April 2004 were retrospectively reviewed and followed-up until August 30th 2004.

Patients older than 18 years, who had normal epicardial coronary arteries (no lesions or lumen narrowing equal or less than 25% of the angiographic image) and had a myocardial perfusion imaging test were included in the study. Patients with incomplete data, hypertrophic or dilated cardiomyopathy, valve heart disease, pericardiac disease, and myocardial infarction or characteristic unstable angina within the 6 months previous to the study were excluded.

CARDIAC SCINTIGRAPHY

Patients included in this study had a cardiac perfusion imaging test with a stress and rest phase obtained with a Siemens Multispect 2HD/HD gamma-camera with two rectangular detectors with 59 photomultipliers each, a rotatory system (gantry) and a high resolution multipurpose collimator. Images were obtained through an anterior 180° arch with 6° intervals, 40 seconds per image, beginning 60 minutes after the rest dose and after a lipid-rich snack to stimulate hepato-billiary elimination of the administered radio-isotope. Technetium 99m Sestamibi was administered in all studies. Rest images were obtained 60 minutes after the injection of 10 mCi (371 Mbq) of Tc 99m Sestamibi. Two hours later stress images were obtained after stress induced with intravenous dipyridamole at a 0.142 mg/Kg/min four-minute infusion. After three minutes of completion of dipyridamole infusion, 25 mCi of Tc99M Sestamibi (927 Mbq) were administered. Every patient was encouraged to have a lipid-rich snack in order to stimulate billiary emptying.

Images were obtained and processed without attenuation correction, evaluated and interpreted by two blinded experts in nuclear imaging and nuclear cardiology. Both of them did the interpretation according to the American Society of Nuclear Cardiology guidelines.

As before was emphasized in our cases RR was considered present when images acquired after exercise show normalization of a perfusion defect observed on rest images

Any reduction in the radio-isotope uptake detected by visual semi-quantitative inspection located to any of the following territories: anterior, septal, apical, inferior, posterior or lateral, was considered as an evidence of a perfusion defect. Images were analyzed on a segment-by-segment basis in the three main coronary artery distribution territories. A stress perfusion imaging score was established as follows: 0= normal, 1= mild hypoperfusion, 2=moderate hypoperfusion, 3= severe hypoperfusion. Stress/rest images were compared segment by segment and a score was also assigned to rest perfusion defects as follows: 0= No defect, 1= completely reversible, 2= partially reversible, 3= fixed or irreversible.

According to previously described scores, segments were described as:

Normal: without defects or changes in perfusion; Reversible: a reduction in radio-nuclide uptake between stress and rest images; Reverse redistribution: better radio-nuclide uptake in stress images when compared to the rest one's; Fixed: defects without any changes between stress and rest images.

A twenty-segment interpretation model was used: six in the apical segment, six in the mid-ventricle and 6 in basal segments. Apex was divided in two. This was done in order to assign every segment to the distribution of the three main coronary arteries according to the next scheme:

- Inferior, posterior and posterolateral to the right coronary artery

- Anterior, anteroseptal and anterolateral for the anterior descending artery

- Lateral and posterolateral to the left circumflex artery.

- The apex was assigned to the territory of the artery that showed adjacent defects.

An average of affected territories was calculated for each patient and the involved coronary artery was identified. Subjects were classified with diabetes based on World Health Organization's criteria for oral glucose tolerance test. [7] Patients with story of chest pain with increased cardiac enzyme concentrations grater to than twice the upper limit of normal occurring without the subsequent development of new Q waves on the 12 lead electrocardiogram was considered nonQ wave myocardial infarction opposition to cases with ST segment elevations of 1 mm in two contiguous leads that were considered ST elevation myocardial infarction [8]

Ejection fraction was determined using echocardiogram and/or radionuclide ventriculography

STATISTICAL ANALYSIS

Continuous variables are presented as means ± standard deviation and categorical as number and percentage. Categorical variables were analyzed by exact Fisher's test or Chi-square. The number and severity of the segments with abnormalities was compared with unpaired Student's T-test. A p value <0.05 was considered statistically significant.

RESULTS

Fifty-five patients with normal coronary arteries were found but only 42 had a scintigraphy. They were followed for 33.8±21.7 months, with age range of 29 to 83 years and mean of 59±11.5 years. Twenty five were women (59.5%) and 17 were men (40.5%). Coronary angiography was performed in 14 patients (33.3%) because of typical angina, in 17 (40.5%) because of atypical angina and 11 (26.2%) because of other conditions different from chest pain.

Among the 42 patients analyzed, 16 (38.1%) had RR in at least one of the myocardial segments. Table 1 shows differences regarding the frequency of co-morbidities and LV ejection fraction of patients with RR and those who did not have it. Statistically significant difference was found regarding prevalence of previous MI, which was higher among patients with RR. Prevalence of diabetes mellitus was also higher among these subjects, although it did not reach statistical significance, and ejection fraction did not show any differences between both groups.

Figure 1

Table 1: Co-morbidities, primary events and left ventricular fraction related reverse redistribution.

Variables	Reverse redistribution		P
	Yes n =16	No n = 26	
Age (years)*	59±14.3	59.5±9.4	NS
BMI (kg/m²)*	28.5±5.6	29.0±5.1	NS
Sex (F/M), n (%)	7 (43.7) /9 (56.3)	18 (69.2)/8 (30.8)	NS
Diabetes Mellitus, % (n)	50.0 (8)	23.1 (6)	0.07
Arterial hypertension, % (n)	75,0 (12)	57.7 (15)	NS
Hypercholesterolemia, % (n)	80.0 (20)	65.4 (17)	NS
Heart failure, % (n)	18.8 (3)	11.5 (3)	NS
Stroke history, % (n)	6.34 (1)	7.7 (2)	NS
Peripheral arterial failure , % (n)	0	7.7 (2)	NS
Previous Myocardial infarction, % (n)	31.1 (5)	7.7 (2)	0.047
COPD/ Asthma, % (n)	12.5 (2)	7.7 (2)	NS
Smoker, % (n)	31.3 (5)	34.6 (9)	NS
Stable Angina, % (n)	18.8 (3)	42.3 (11)	NS
Unstable angina, % (n)	6.3 (1)	3.8 (1)	NS
Stroke, % (n)	6.3 (1)	0	NS
Ejection fraction (%)*	57.2± 19.9	61.1±12.7	NS

* Mean ± standard deviation; COPD: Chronic Obstructive Pulmonary Disease; NS = non significant

Considering the possibility that severe RR could be related to abnormalities in myocardial function, an analysis was performed comparing subjects with severe RR (>2 in a 1 to 3 severity score) showed in Table 2.

Figure 2

Table 2: Co-morbidities, primary results and left ventricular ejection fraction in severe reverse redistribution
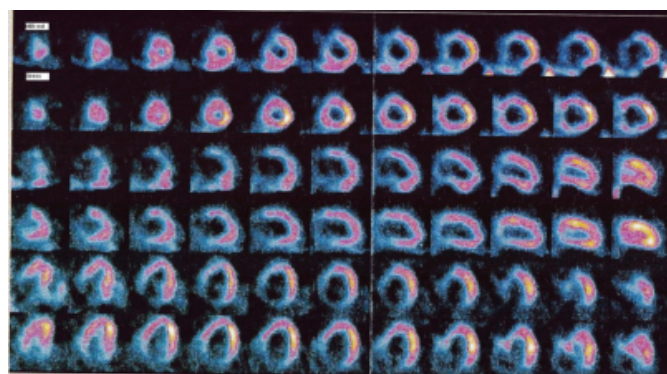
Variables	Severe reverse redistribution		
	Yes n = 6	No n = 36	p
Age, (years)*	65±12.4	58.1%±11.1	NS
BMI, (kg/m²)*	30.2±7.3	28.6±4.9	NS
Sex (F/M), n (%)	3 (50)/3 (50)	22 (61.1)/14 (38.9)	NS
Diabetes Mellitus, n (%)	83.3% (5)	25.0% (9)	0.01
Arterial hypertension, n (%)	66.7% (4)	63.9% (23)	NS
Hypercholesterolemia, n (%)	50.0% (3)	61.1% (22)	NS
Heart failure, n (%)	16.7% (1)	13.9% (5)	NS
Stroke History, n (%)	0	8.3% (3)	NS
Peripheral arterial failure, n (%)	0	5.6% (2)	NS
Previous Myocardial infarction, n (%)	33.3% (2)	13.9% (5)	NS
COPD / Asthma, n (%)	16.7% (1)	8.3% (3)	NS
Smoker, n (%)	16.7% (1)	36.1% (13)	NS
Stable Angina, n (%)	16.7% (1)	36.1% (13)	NS
Unstable Angina, n (%)	0	5.6% (2)	NS
Stroke, n (%)	0	2.8% (1)	NS
Ejection fraction, (%)*	43.3± 1.5	61.5±15.3	<0.05

* Mean ± standard deviation; COPD: Chronic Obstructive Pulmonary Disease, NS = non significant.

In patients with severe RR, the left ventricle ejection fraction (LVEF) was significantly lower when compared to those that did not show such a pattern. When a 45% LVEF cut point was considered, 50% of these patients had RR, compared to 8.7% of those with higher LVEF (p<0.05). This difference was independent from MI history. Patients with RR had significantly higher DM2 frequency.

Figure 3

Figure 1: Cardiac perfusion imaging (Tc 99m Sestamibi) rest /stress test showing a severe reverse redistribution: better radio-nuclide uptake in stress images when compared to the rest one's in anteroseptal and inferior myocardial segments.

DISCUSSION

Among perfusion defects, reverse redistribution is the less well characterized, and there is controversy about its origin being endothelial dysfunction or ischemia. For many researchers, RR does not need any more screening or intervention.[2]

Patients with a history of MI treated by thrombolysis o percutaneous revascularization show frequently a RR pattern that could be the consequence of a higher-than-normal blood flow and accelerated radio-nuclide wash out in the non-infarcted tissue surrounding the reperfusion areas. Another explanation could be an expanded thallium uptake in the expanded interstitial compartment of the reperfused area with a faster wash-out.[3, 4] Thallium uptake abnormalities could be secondary either to an abnormal myocardial perfusion or to metabolic abnormalities that compromise potassium transport across the cell membrane.[4]

In 1981, Hecht et al [9] described perfusion abnormalities compatible with RR in 7% of their scintigraphic studies, and 85% of them were related to severe coronary artery disease, mainly total luminal obstructions higher than 90%. Even if the mechanism for RR to occur has not been clearly defined, it has been related to the presence of ischemic myocardium adjacent to the region where this phenomenon happens, that is, a combination of scar and viable tissue. Only in 1% of cases (3 out of 300) there was no angiographic evidence of coronary artery occlusion. Tanasescu et al. [10] demonstrated that two thirds of their patients had obstructions higher than 75% although the rest of them had normal coronary arteries. In other words, even if RR was not a manifestation of ischemia, it was considered a marker of significant coronary disease.

The regions with RR and higher thallium uptake on re-injection images were associated to an absence of electrocardiographic or functional findings suggesting myocardial necrosis such as Q wave, dyskinesia, or akynesia of the ventricular wall and non-conclusive or normal patterns on 18-Fluorodeoxyglucose (FDG) imaging through positron emitting tomography (PET scan) in those regions. On the other hand, the areas that did not take-up thallium in re-injection were associated to Q waves, severely compromised wall motion, reduced 18-FDG uptake and blood flow by PET. It was concluded that RR frequently represents viable myocardium critically dependent on collateral blood flow.[11]

A logistic regression analysis showed that severe RR was an independent prognostic factor for subsequent adverse

cardiovascular events and a depressed left ventricular function as another bad prognosis factor. [12]

In studies performed with MIBI, RR was observed in high risk areas among patients with acute MI and preserved left ventricular function.[5] Choe et al.[6] found that RR correlated to acute non-transmural MI detected by means of myocardial contrast echocardiogram.

Weiss et al. demonstrated that RR occurred in regions that had evidence of viable myocardium after reperfusion. Besides, they found an enhancement in regional wall motion in areas with RR ten days after reperfusion and it lasted for at least 1 to 8 weeks after MI.3

Reverse redistribution has been described in 24 to 75% of cases after a recent MI treated in a conservative way or with thrombolysis. It has been related to the presence of a permeable MI-related vessel and subjacent viable myocardium. This could explain that 70% of segments with RR were related to the infarction area, and only 30% out of it.

Sugihara et al.[13] found RR with Tecnetium-99m/tetrophosmin among patients treated with successful angioplasty. Segments with RR showed preserved function one month after PCTA; this was interpreted as recoverable myocardium in MI regions. They also found RR with Tecnetium-99m/tetrophosmin more frequently among patients with hypertrophic cardiomyopathy, especially in early images after exercise. This was interpreted as a disorder in Tecnetium-99m/tetrophosmin uptake because of myocite metabolic dysfunction.[14]

In the present study, a higher incidence (38.1%) of RR was found when compared to other series (13%),[13,14,15] and aside from its severity it was more frequent among diabetics and individuals with a previous MI, as it has been previously established.[5]

Some works have mentioned that RR is related to the presence of viable myocardium,[9] even if, depending on its severity, it can be associated to bad prognosis and depressed ventricular function.[12] In the cases of the present study, the latter was most frequently associated to diabetes, a population well known for endothelial dysfunction and coronary syndromes that can induce heart failure, although it has been suggested that dysfunctional segments with this RR pattern can still show some recovery on dobutamine or nitroglycerin administration.[13]

The higher rate of RR was observed among patients with compromised left ventricular function independent of the jeopardized coronary territory, even when adjustments were done for MI history. It could be speculated that RR could reflect functional, sub-clinical resting changes that appear earlier than obstructive angiographic coronary lesions. Stress-induced hyperemia, physical or pharmacological, could reverse those abnormalities in resting states through coronary reserve flow not at all effected and thus could preclude symptoms, may be for long periods. Nevertheless, those perfusion abnormalities on the long term could represent inability to maintain adequate ventricular function and thus represent a prognostic factor considering its association with left ventricular dysfunction. Therefore, the presence of RR should be evaluated in patients with congestive heart failure since the frequency of the perfusion abnormalities is related to left ventricle dysfunction as observed in the present series.

STUDY LIMITATIONS

This is a retrospective study in a small population of a tertiary level referral center where a high proportion of other metabolic illnesses, and thud it could not reflect the real occurrence of these events in a general population. Nonetheless, because of technical and logistic reasons, there are fewer possibilities for such a study to be performed in a different center since Nuclear Cardiology services are not widely available, as hemodynamic or angiography facilities.

CONCLUSION

Severe reverse redistribution in patients with normal epicardial coronary arteries is associated with higher prevalence of diabetes mellitus and lower left ventricular ejection fraction

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References

1. Beller GA, Zares BL. Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. Circulation 2000;101:1465-78
2. Pieri P. How do you deal with the reverse redistribution pattern? Is it a clinically relevant issue? J Nucl Cardiol 2000;7:402-4.
3. Weiss AT, Maddani J, Lew A, Shan P, et al. Reverse redistribution of thallium 201: a sign of nontransmural myocardial infarction with patency of the infarct related coronary artery. J Am Coll Cardiol 1986;7:61-7

4. Poole-Wilson. Potassium and the heart. Clinics in Endocrinology and Met 1984; 13:249-68

5. Itagane H, Otsuka M, Yamagishi H, et al. Estimation of myocardial viability and clinical significance of reverse redistribution in resting Tc99 sestamibi SPECT in patients with acute myocardial infarction. J Cardiol 1997;30:179-88

6. Choe W, Kwan J, Kim S. Reverse redistribution revisited with myocardial contrast echocardiography. Ann Nucl Med 1998;12:287-92.

7. Alberti KG, Zimmet PZ. Definition diagnosis and classification of diabetes mellitus and its complocations. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998; 15:539-553.

8. S J Maynard, G O Scott, J W Riddell, A A J Adgey. Management of acute coronary síndromes. BMJ 2000;321:220-3

9. Hecht H, Hopkins J, Rose J, Blumfield D, Wong M. Reverse redistribution: worsening of thallium 201 myocardial images from exercise to redistribution. Radiology 1981; 140:177-181.

10. Tanasescu D. Apparent worsening of Thallium 201 myocardial defects during redistribution -what does it mean? J Nucl Med 1979;20:688.

11. Marin Neto J, Dilsizian V, Arrighi J, Freedman N, et al. Thallium reinjection demonstrates viable myocardium in regions with reverse redistribution. Circulation 1993; 88:1736-45.

12. Dey M, Souffer R. Reverse redistribution on planar thallium scintigraphy: relationship to resting thallium uptake and long-term outcome. Eur J Nucl Med 1995; 22:237-42.

13. Sugihara H, Nakagawa T, Yamashita E, et al. Reverse redistribution of Tc-99m-tetrofosmin in patients with acute myocardial infarction. Ann Nucl Med 1999;3:43-7.

14. Sugihara H, Taniguchi Y, Kinoshita N, et al. Reverse redistribution of Tc-99m tetrofosmin in exercise myocardial SPECT in patients with hypertrophic cardiomyopathy. Ann Nucl Med. 1998;12:287-92.

15. Fragasso G, Rossetti E, Dosio F, Gianolli L et al. High prevalence of the thallium 201 reverse redistribution phenomenon in patients with syndrome X. Eur Heart J 1996;17:1482-87.

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