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Clinical Significance of Reverse Redistribution Phenomenon for ^{201}Tl Scintigraphy in Nonischemic Disease

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Abstract: The reverse redistribution phenomenon (RR) on ^{201}Tl SPECT has been focused mainly on ischemic improvement regions after reperfusion therapy or vasospastic angina pectoris. However, RR analysis has not been used in the context of non-ischemic disease. The aim of this study was to evaluate the clinical role of RR on ^{201}Tl SPECT in patients without a history of myocardial ischemia. We retrospectively enrolled 86 patients showing RR by myocardial perfusion SPECT and studied 75 other patients as a control group. For quantitative analysis, each ^{201}Tl SPECT polar map was divided into 13 segments. Differences between the RR and control group were assessed with respect to patient characteristics and cardiac event-free survival using the Kaplan-Meier method. RR was detected frequently in the inferoposterior wall, septal portion of the anterior wall, and septum. The two groups showed significant differences in rates of heart failure ($P < 0.01$), hypertrophic cardiomyopathy ($P < 0.05$), and wall motion abnormality ($P < 0.05$), but not in the rate of event occurrence. The study demonstrated that RR on ^{201}Tl SPECT could indicate the existence of myocardial damage; however, it would not be a factor that determines the prognosis.

Key words: nuclear cardiology, reverse redistribution, Thallium-201, SPECT, myocardial perfusion

Introduction

^{201}Tl has been widely used for myocardial perfusion scintigraphy in the clinical setting since the 1970s. ^{201}Tl has several advantages over the 99mTc-labeled agent including ease of use by a single administration and its usefulness for myocardial viability evaluation. ^{201}Tl reverse redistribution (RR) was defined as either normal exercise perfusion and defective redistribution or an exercise defect worsened at redistribution. Although initially many studies were conducted on ischemic improvement regions after acute coronary syndrome (ACS)[1-3], RR is sometimes noted even in patients not undergoing reperfusion therapy as part of their daily treatment.

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Recently, RR was also associated with vasospastic angina pectoris (VAP) and non-ischemic diseases[4–6]. However, to the best of our knowledge, there has been no unified study on the value of RR analysis. This study thus evaluated the clinical significance of the RR phenomenon on ^{201}Tl scintigraphy in patients without a history of myocardial ischemia.

Material and Methods

^{201}Tl myocardial perfusion SPECT was performed in patients without a history of ischemic heart disease and with no obvious signs of ischemia as diagnosed by medical examination performed between January 2000 and August 2008. For this study, we included 86 patients based on the following criteria: (1) to exclude the influence of ischemia due to stenosis of a coronary artery, we studied patients not showing reduced blood flow in stress images; (2) to exclude artefactual influence, we studied patients showing decreased uptake across at least 2 of 13 segments in the rest images. We also studied 75 patients as a control group. These patients had no history of ischemic heart disease and showed normal perfusion in stress myocardial scintigraphy performed between March 2005 and May 2005. The data presented herein corresponds to consecutive data from both groups.

Results are expressed as mean ± SD for continuous variables and as percentages of the total number of patients for categorical variables. Significance between the groups was determined by unpaired Student's t-test for continuous variables and by the chi-square test for categorical variables. If data were not distributed normally, the Wilcoxon signed-rank test was used. Kaplan-Meier analysis and long-rank tests were used to compare the event-free survival rates. Probability levels less than 0.05 were considered statistically significant.

Patients were followed up after the stress myocardial scintigraphy, using the following three items as endpoints: (1) reduced blood flow on stress scintigraphy; (2) cardiac events requiring hospitalization or PCI; and, (3) cardiac death. The longest follow-up period for cardiac death is 96 months.

Cardiac scintigraphy was performed in a large rotating field-view gamma camera (ECAM、Siemens, USA) with low-energy, high-resolution, parallel-hole collimators. Each dataset was acquired over a 180° semicircular arc extending from the right anterior oblique to left posterior oblique position. After fasting, the patients underwent stress by exercise loading or pharmacological loading, and then 110 MBq of ^{201}Tl (Nihon Medi-Physics, Nishinomiya, Japan or Fuji Film RI Pharma, Tokyo, Japan) was intravenously injected. MPS was performed within 10 minutes of the tracer injection (Stress image). Rest images for assessment of myocardial viability were obtained four hours after the stress images.

The exercise stress studies used the symptom-limited supine ergometer exercise test, performed by starting the exercise at 25 W and increasing it by 25 W every 3 min. In exercise-stressed patients, the endpoint of the test was determined by five items as follows: ① shortness of breath or fatigue; ② decreased blood pressure; ③ target heart rate (85% of predicted maximum heart rate; (220−age) ×0.85); ④ ST change on ECG; and, ⑤ high maximum blood pressure over 230 mmHg.

The pharmacological stress study used three kinds of vasodilators : adenosine ; ATP : 0.15 mg / kg / min, dypilidamole : 0.56 mg / kg, or dobutamine : 340 μg / kg.

The polar map shown in Fig. 1 was adopted to evaluate the images, and two clinical specialists in nuclear medicine conducted the visual evaluations.

Results

The different stress methods used in this study are detailed in Table 1. There were no significant differences in the number of patients undergoing the exercise stress and pharmacological stress test between groups. All the exercise-stressed patients satisfied at least one of the five endpoints (Table 2). In both groups, item ① (shortness of breath or fatigue) was most frequent, followed by item ③ (target heart rate).

On ECG, no case revealed ST elevation at aVR, and the ST depression affected a wide region over six leads in all cases including controls. No patient in the RR group showed

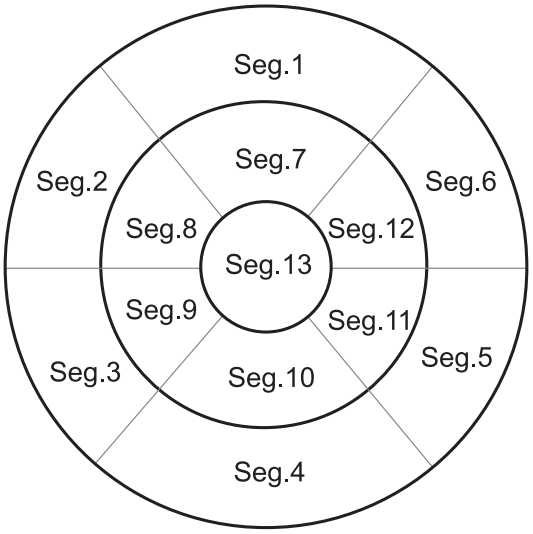

Fig. 1. Schematic polar map of the left ventricular myocardium divided into 13 segments.

Table 1. Number of patients with given type of stress for each patient group

	Control group	RR group	
exercise	56	67	
adenosine	0	6	
ATP	11	10	
dipyridamole	2	2	
dobutamine	5	1	
Exercise : pharmacological	56:18	67:19	P=0.608

Table 2. Number of patients with various exercise stress tes end-points for each patient group

	control group	RR group
① shortness of breath or fatigue	40 (71.4%)	48 (73.8%)
② blood pressure decrease	0	3 (4.6%)
③ target heart rate	15 (26.8%)	11 (16.9%)
④ ST change on ECG	1 (1.8%)	0
⑤ high maximum blood pressure	0	3 (4.6%)
Total	56	65

Table 3. Regional perfusion abnormality identified by visual inspection in 86 patients

Segment	number of cases	percentage
1	16	18.6
2	0	0
3	1	1.2
4	41	47.7
5	13	15.1
6	9.3	8
7	28	32.6
8	1	1.2
9	2	2.4
10	35	40.7
11	6	7
12	0	0
13	27	31.4

marked ST changes.

In 20 (76.9%) of the 26 cases showing both RR and abnormal wall motion, an overlap of the occurrence region was found.

Distributions of the regions in which the RR phenomenon was observed are shown in Table 3. Frequent manifestation of RR was found in Seg. 4 (41 patients, 47.7%), Seg.10 (35 patients, 40.7%), Seg. 7 (28 patients, 32.6%), and Seg. 13 (27 patients, 31.4%). Conversely, there were sites that showed a low incidence, namely Seg. 2 and Seg. 12 (0 patient), Seg. 3 and Seg. 8 (1 patient −1.2%), and Seg. 9 (2 patients −2.4%).

The baseline characteristics for both groups are shown in Table 4. Wilcoxon tests were conducted for BMI, blood pressure, RBC, uric acid, and creatinine, all of which showed a non-

Table 4. Patient characteristics

	Control group	number	RR group	number	P value
Age	67.7 ± 10.1	75	64.1 ± 14.3	86	0.076
Male	34 (45.3%)	75	50 (58.1%)	86	0.105
BMI	23.2 ± 3.2	75	24.0 ± 4.1	81	0.349
RBC	416.9 ± 58.2	65	411.9 ± 54.7	80	0.716
Uric Acid (mg / dL)	5.80 ± 1.66	65	5.85 ± 1.53	80	0.935
Creatinine	0.903 ± 0.828	66	1.417 ± 2.348	80	0.208
Systolic BP	135.7 ± 18.0	71	137.9 ± 24.2	84	0.74
Diastolic BP	77.3 ± 13.3	71	78.8 ± 14.2	86	0.874
Smoker	24 (36.4%)	66	27 (36.5%)	74	0.987
DM	13 (17.6%)	74	22 (27.5%)	80	0.142
Dyslipidemia	50 (70.4%)	71	44 (59.5%)	74	0.167
VAP	6 (8.0%)	75	3 (3.5%)	86	0.214
DCM	0 (0%)	75	3 (3.5%)	86	0.103
HCM	3 (4.0%)	75	12 (14.0%)	86	0.048
Heart failure	3 (4.0%)	75	15 (17.4%)	86	0.007
Bundle branch block	9 (11.7%)	75	8 (9.3%)	86	0.578
Arrhythmia	19 (25.3%)	75	10 (36.0%)	86	0.143
Af	8 (10.7%)	75	13 (15.1%)	86	0.403
abnormal wall motion	12 (16.0%)	75	26 (30.2%)	86	0.034
EF	65.1 ± 12.1%	75	61.5 ± 15.0%	86	0.092

(BMI=body mass index, DM=diabetes mellitus, DCM=dilated cardiomyopathy, HCM=hypertrophic cardiomyopathy, Af=atrial fibrillation, EF=ejection fraction)

normal distribution. No significant differences were found between the groups in sex, weight, blood pressure, blood findings (red cell count, uric acid, creatinine level), history of metabolic disorders (diabetes, hyperlipidemia), arrhythmia (af, others), VAP, and the presence of abnormal electrocardiogram.

Heart failure occurred more frequently in the RR group than in the control group (17.4% vs. 4.0%), and the incidence of hypertrophic cardiomyopathy (HCM) was also significantly higher in the RR group than in controls (36.0% vs. 4.0%). As for dilated cardiomyopathy (DCM), there were no significant differences between the RR and control group in the low incidence rates. Functional analysis of the thallium scintigraphy indicated a significantly higher incidence of wall motion abnormality in the RR group than in controls, and no significant difference in

EF between the groups. There were no significant differences in the presence of abnormal electrocardiogram.

Average observation period during the follow-up was 55.6 ± 30.3 months for the RR group and 59.8 ± 29.9 months for the control group. Cardiac events occurred in 13 patients in the control group and in 17 patients in the RR group, as detailed in Table 5. One patient in the RR group died of chronic heart failure after 11 months of follow-up. Cumulative event-free curves were calculated by the Kaplan-Meier method, and compared by the log-rank test. There were no significant differences in the event occurrence rate between the groups (P=0.38) (Fig. 2).

Table 5. The number of cases, separated by cause, for a heart event that was an endpoint for follow up in the two groups

Cardiac Events		
	Control group	RR group
Ischemic change at exercise	3	7
Admission due to heart failure	6	4
ACS (death)	3 (0)	5 (1)
Admission due to VAP	1	0
Admission due to Af	0	1
Mean observation period (month)	59.8 ± 29.9	55.6 ± 30.3

(ACS=acute coronary syndrome, VAP=vasospastic angina pectoris, Af=atrial fibrillation)

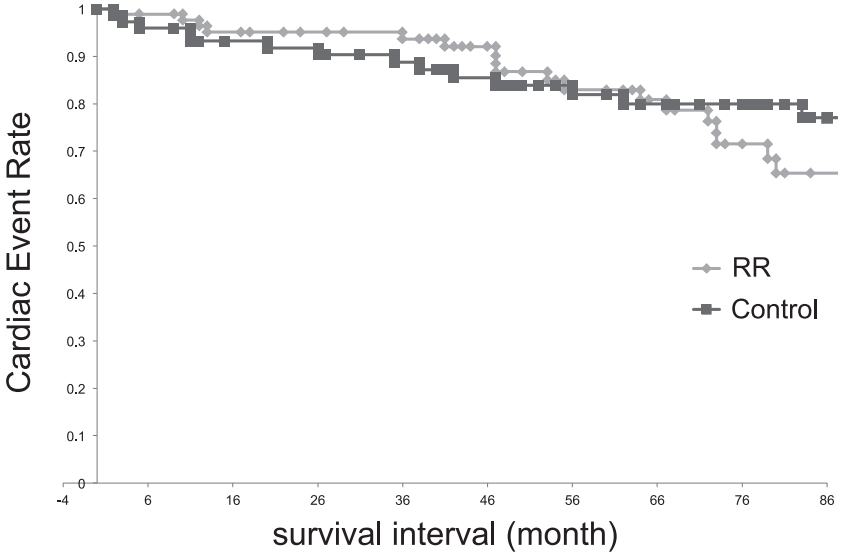

Fig. 2. Kaplan-Meier event-free survival curves for RR group and control group.

Discussion

The inflow of ^{201}Tl is associated with blood flow from the terminal branch of the coronary artery and cellular oxygen metabolism, whereas the outflow of ^{201}Tl is associated with cellular metabolism and membrane integrity. Causes of reduced uptake in the ^{201}Tl RR phenomenon at rest include myocardial stunning, reduced electrolytic concentration gradient through the cell membrane, and interstitial edema. Reports of RR since the 1990s frequently involved RR after reperfusion therapy for acute coronary syndrome, thus it seems that ischemia-induced dysfunction in metabolism or the cell membrane persists after improved blood flow[7]. Also, improvements in wall motion are known to lag behind the blood flow improvement, which is necessary for functional recovery, and it has been documented that lesions with delayed or incomplete functional improvement occur in sites away from those where infarction is complete[1,8]. On the other hand, RR phenomenon has also been attributed to an artifact, such as possible signal attenuation due to the breast, diaphragm, or obesity[4,7].

Subsequently, a high occurrence rate of RR for vasospastic angina was also reported. According to Xiang *et al*[4], the sensitivity of RR to VAP was 100% and the specificity was 63%. Although there was no significant correlation between the history of VAP and the incidence of RR in this patient group, it does not refute the association between active VAP and RR. Other similar reports cite manifestations of RR in myocardial bridging[5] and collagen disease[6], both of which are considered as stunning involved in ischemia, and similar to VAP as a phenomenon.

With regard to HCM, a significant acceleration in the regional myocardial washout rate in the thickened part as well as the non-thickened part was reported in the 1990s[9]. That study showed normal uptake in the inferior wall that had no thickening in two HCM patients with ^{123}I-labeled 15-(p-iodophenyl)-3R,S-methyl pentadecanoic acid (^{123}I-BMIPP), and reduced uptake in both the early phase and the late phase with ^{201}Tl, suggesting the possibility of myocardial damage in the non-thickened part[10]. Sugihara *et al*[11] also found that just as RR was observed in 81.8% of HCM patients by imaging in 30 minutes and 180 minutes after stress with the 99mTc-labeled agent, RR also often appeared in the anterior wall, posterior wall, and a part of the septum. The cause of such a phenomenon has been attributed to structural abnormality such as fibrosis of the myocardium[12] that decreases the mechanism by which energy is transferred to the cell membrane, which in turn accelerates the clearance of ^{99m}Tc-tetrofosmin.

As noted above, the reduced potency due to endothelial damage of the peripheral artery or the coronary artery was implicated to cause the high sensitivity of RR to VAP[13,14]. There are various papers on such disease conditions caused by dysfunction of the myocardial microcirculation, including Syndrome X[15], arteriosclerosis[16], diabetic hypertension[17], and hyperthyroidism[18]. In this study the rate of occurrence between the history of heart failure and the manifestation of RR was significantly correlated.

A significant correlation between the history of heart failure and the manifestation of RR was found in this study, and indeed, various factors can be involved in the onset of heart failure. It

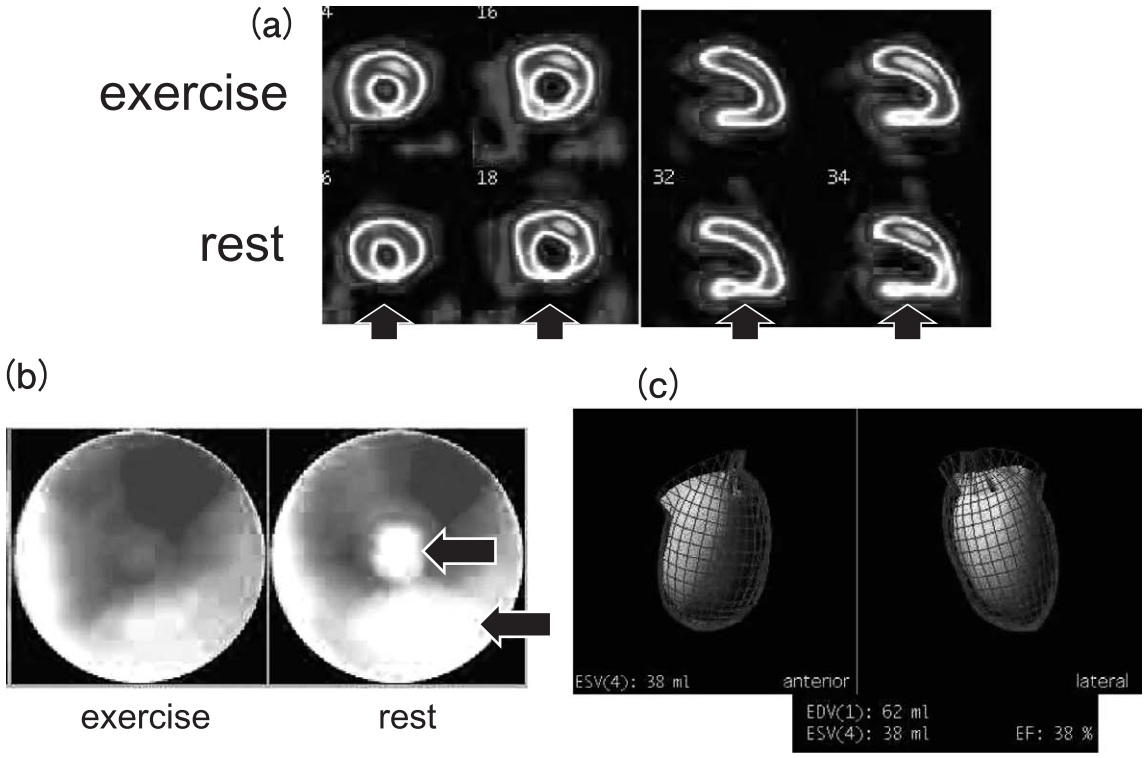

Fig. 3. An 84-year-old female : Patient with chronic heart failure and HCM (a) SPECT image (b) Bull's eye display. Reduced blood flow is maintained under stress, and reduced uptake in the posterior inferior wall is observed at rest (→). Wall thickening is shown in the septal anterior wall. (c) QGS analysis: reduced circumferential wall motion was observed with a marked decrease in cardiac output.

is therefore possible that as different diseases cause heart failure, RR with peripheral-vascular endothelial dysfunction appears[6].

Ohte *et al*[19] reported in 1995 that significantly reduced fluorodeoxyglucose (FDG) uptake in FDG-PET and reduced wall motions were found in the RR regions. Additionally, the incidence of RR phenomenon was significantly higher in the group with reduced wall motion than in those patients without reduced wall motion[20]. These findings suggest that a reduction in myocardial metabolism and function appears in regions where the blood flow is maintained. Although all of these are findings after reperfusion therapy for infarction or regarding locations of ischemia, significantly decreased wall motion that was consistent with the RR regions was also found in this study. Thus, it is likely that RR observed in our study reflected myocardial damage similar to that shown in ischemic heart disease.

In our cases, most RR phenomena were observed in the anterior and inferolateral wall, although our data showed no such tendency compared to previous literature and building a hypothesis remains difficult. The anterior wall is the most susceptible region in the heart for ischemic change, because of the large blood supply present there and the frequency of ischemia in myocardial diseases such as HCM and cardiac sarcoidosis. With regard to the inferoposterior wall, occasionally we observe less ischemic accumulation at this site in patients with DCM or

chronic heart failure. Superiority of the parasympathetic nerve system at this site thus has the possibility to be related to RR, because the sympathetic nerve increases the amount of blood flow. In summary, it remains difficult to explain the locality of RR phenomena, and it is likely that a combination of factors is involved, as mentioned above.

RR appearing after the ischemia reperfusion therapy has been observed during the functional improvement process[3], which suggests a good prognosis[1], and this study suggested that the manifestation of RR in a nonischemic lesion indicates some kind of myocardial damage requiring attention. However, this study found no significant differences in the subsequent incidence of cardiac events between the RR group without ischemia and the control group. Therefore, although some type of myocardial damage is assumed in RR, its clinical impact seems minimal.

In order to exclude artifacts, we removed narrow RR phenomena observed in only one segment in this study. Therefore, as cases that could have damage in localized myocardium were excluded, the sensitivity of RR may be increased in a study on the use of SPECT-CT or the combined use of prone images. Furthermore, as the prevalence of each cardiac disease is not high, a larger-scale study will be necessary to closely examine the relationship between such diseases and RR.

In conclusion, RR observed in patients without myocardial ischemia on thallium scintigraphy could be taken to indicate myocardial damage. However, RR will not be a prognostic determinant since no differences were found in the subsequent rates of cardiac events.

Conflict of interest

The authors declare that they have no conflict of interest.

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