Fractional Flow Reserve Value of Reverse Redistribution in 201-Thallium Stress Scintigraphy

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Abstract:

Background: Reverse redistribution (RR) is a unique finding in Thallium-201 chloride (\(^{201}\)TlCl) stress scintigraphy, but there is no established notion of its mechanism. We hypothesized that RR enhances blood flow in the RR area and that the fractional flow reserve (FFR) is low in the RR area if there is decreased microvascular resistance. We aimed to clarify the mechanism of RR by comparing FFR with \(^{201}\)TlCl stress scintigraphy. Methods and Results: This single-center retrospective study enrolled forty consecutive patients who underwent both FFR and stress/rest \(^{201}\)TlCl stress scintigraphy between April 2012 and April 2016. A total of 11 patients were excluded due to the following reasons: percutaneous coronary intervention performed between FFR and scintigraphy (n = 1), unreliable FFR value (n = 1), and severe coronary artery stenosis (n = 5). Finally, 29 patients were analyzed. Each coronary territory was classified into three groups according to the value of summed difference score (SDS): control (SDS = 0; n = 6), redistribution (SDS ≥ 1; n = 12), and RR (SDS ≤ -1; n = 11) regions. The FFR values among the 3 groups were compared using Kruskal-Wallis test. The redistribution region as well as the RR region showed significantly lower FFR value than the control region (control; 0.93 vs. redistribution; 0.85, P = 0.03, vs. RR; 0.85, P = 0.03). Conclusions: The RR region had significantly lower FFR value than the control region. Reduced microvascular resistance due to the increased collateral wash-out may be one of the mechanisms of RR.

Key words: Scintigraphy, Reverse redistribution, Fractional flow reserve, Coronary artery disease

Introduction

Thallium-201 chloride (\(^{201}\)TlCl) scintigraphy can assess regional myocardial perfusion noninvasively\(^6\). The major clinical application of myocardial perfusion imaging is for the detection of coronary artery disease (CAD)\(^5\). Comparison of both stress and resting phases can detect functional ischemia\(^5\), and these results may serve as a prognostic marker in patients with confirmed or suspected CAD\(^5\). Redistribution refers to a decline of radioisotope uptake in a certain area during the stress phase, which recovers in the resting phase. Redistribution suggests myocardial viability progressing to ischemic state with CAD\(^5\). Meanwhile, reverse redistribution (RR) is a unique finding in \(^{201}\)TlCl stress scintigraphy, and is manifested by the following: normal or slightly decreased uptake in the stress phase and paradoxically decreased uptake in the delayed phase in the same segment\(^7\). Previous studies\(^6\)\(^7\) have revealed that RR is involved with a variety of coronary artery diseases\(^6\)\(^7\), mainly in the ischemic improvement area after reperfusion therapy or vasospastic angina pectoris. The remaining theories include the chronic totally occluded coronary artery, multiple coronary vessel stenosis, and stenosis at its distal site with collateral blood supply. Although the mechanisms of RR have been
Figure 1. Flowchart of study enrollment. FFR, fractional flow reserve; PCI, percutaneous coronary index; SDS, summed difference score.

**Inclusion**

\[ N = 40 \]
Both of stress scintigraphy and FFR were performed between April 2012 to April 2016

**Exclusion**

\[ N = 11 \]
1. PCI performed between stress scintigraphy and FFR
2. Unstable FFR value because of drifting
3. Severe organic stenosis (angiographic stenosis ≥ 90%)

**Eligible for analysis**

\[ N = 29 \]

| SDS = 0 | SDS ≥ 1 |
|---------|---------|
| N = 6   | N = 12  |
| Control | Redistribution |

| SDS ≤ 1 |
|---------|
| N = 11  |
| Reverse redistribution |

**Discussion**

Discuss the implications of the findings in the context of reverse redistribution and fractional flow reserve. Highlight the significance of the study's outcomes and their potential impact on clinical practice.

**Conclusion**

Summarize the main findings and their implications. Emphasize the importance of reverse redistribution in understanding coronary flow dynamics and the potential benefits of using FFR in such scenarios.

**References**

Cite relevant studies and clinical guidelines that support the study's findings.

**Supplementary Material**

Include any additional data or results that support the conclusions drawn in the main text.

**Author Contributions**

State the roles of each author in the study, including data collection, analysis, and interpretation.

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Disclose any funding sources and their role in the study's design, conduct, or dissemination.

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**Materials and Methods**

**Participants**

This retrospective observational study was conducted at a single center. Consecutive patients who underwent both the FFR and stress/rest \(^{201}\)TlCl stress scintigraphy between April 2012 and April 2016 were potentially eligible for this study.

Forty patients underwent \(^{201}\)TlCl stress scintigraphy and FFR during the study period. Among them, 1 patient who underwent percutaneous coronary intervention (PCI) between FFR and scintigraphy, 5 patients with an unreliable FFR value because of drifting, and 5 patients with severe organic stenosis (angiographic stenosis ≥ 90%) were excluded. Finally, 29 coronary territories in 29 patients were included in the analysis (Figure 1).

The Ethics Committee at Tomishiro Central Hospital, Okinawa, Japan, approved the study protocol and waived the requirement of obtaining informed consent from the patients because of the study design’s retrospective nature. This study was performed with full adherence to the Japanese ethical guidelines. A poster in the hospital illustrated the outline and objectives of the study, which was easily visible to all enrolled patients. Moreover, the patients could freely access the information via e-mail and could withdraw their participation without any consequence.

**Data Collection**

The clinical research coordinators collected demographic data, procedural data, and \(^{201}\)TlCl stress scintigraphy findings from the hospital’s computerized patient charts, retrospectively.

**Fractional Flow Reserve**

The primary outcome of this study was the FFR value. FFR was measured by the pressure wire crossing the target lesion with or without adenosine infusion at 0.15 mg/kg/min for 4 minutes. FFR was the minimum fraction of the mean arterial pressure at the distal lesion site to that of the ostium.
at the coronary artery during 4 minutes\textsuperscript{17}. If the FFR value was unstable, the adenosine infusion rate was set at 0.18 mg/kg/min.

**Scintigraphy**

\textsuperscript{\textit{\textsuperscript{201}Tl}}Cl scintigraphy was performed using an e.cam scanner (Signature, Siemens, Muenchen, Germany). The patients were instructed to fast for at least 4 h and to abstain from caffeine-containing products for at least 24 h before the scan. The protocol involved stress imaging, followed by redistribution imaging 3 to 4 hours later. The loading stress included (1) pharmacological stress by adenosine (120 μg/kg/min) for 5 minutes or (2) exercise prior to the \textsuperscript{\textit{\textsuperscript{201}Tl}}Cl injection. The exercise goal was the target heart rate, which was calculated as 85% of the predicted maximum heart rate (220 - age)\textsuperscript{15,16}.

At 3 minutes after adenosine triphosphate infusion or peak exercise, 74 MBq of \textsuperscript{\textit{\textsuperscript{201}Tl}}Cl was injected intravenously, and the patient was asked to continue exercising for an additional 2 minutes. Immediately after the stress test, single photon emission computed tomography (SPECT) acquisition was performed in the supine position. The collimator was set to Cardio high-sensitivity, with a matrix size of 256 × 256 and an enlargement factor of 1.0. Subsequent to the collimator test, SPECT was conducted with the following settings: matrix size of 64 × 64 and a magnification factor of 1.45. The imaging time was 15 minutes, and the angle of the two detectors was 76°. The mode was step and shoot. Each heartbeat was divided into 16 gate collections\textsuperscript{185}.

**Semi-quantitative Scoring Analysis**

Semi-quantitative scoring was performed on a cross-section of the heart using dedicated software (Cardiobull, Fujifilm RI Pharma, Ltd., Tokyo, Japan). The accumulation of the left ventricle was divided into 17 segments. The stress scores of 0, 1, 2, 3, and 4 represented normal, slight, mild, moderate, and severely abnormal, respectively, in the stress phase. The total summed stress score (SSS) was obtained from the 17 segments. The summed rest score (SRS) was obtained similarly in the delayed phase. The summed difference score (SDS) was calculated by subtracting the SRS from the SSS. A positive value of SDS indicated functional ischemia in a specific area supplied by a coronary vessel. Zero SDS indicated a normal condition. A negative value of SDS suggested a more depressed re-uptake in the delayed phase than in the stress phase\textsuperscript{17}. The scores of 17 segments reflected the perfusion area provided by the left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA); segments 1, 2, 7, 8, 13, 14, and 17 were related to the LAD perfusion area, segments 5, 6, 11, 12, and 16 were included in the LCX perfusion area, and segments 3, 4, 9, 10, and 15 concerned the RCA perfusion area (Figure 2).

We designated the coronary artery examined by the pressure wire to obtain FFR value as the target coronary artery. Each target coronary artery territory was classified into the following three groups according to the value of SDS: control (SDS = 0), redistribution (SDS ≥ 1), and RR (SDS ≤ -1), regions (Figure 3; Figure 3 shows each representative scintigraphy finding).

Based on the \textsuperscript{\textit{\textsuperscript{201}Tl}}Cl stress scintigraphy findings, 29 coronary territories were divided into the following groups: 6 as the control group, 12 as the redistribution group, and 11 as
Table 1. Baseline characteristics, stress scintigraphy findings, and fractional flow reserve value

|                        | Overall | Control (SDS = 0) | Redistribution (SDS ≥ 1) | Reverse redistribution (SDS ≤ -1) | P value |
|------------------------|---------|-------------------|--------------------------|-----------------------------------|---------|
|                        | n = 29  | n = 6             | n = 12                   | n = 11                            |         |
| Age, years             | 69 ± 8  | 68 ± 9            | 67 ± 10                  | 73 ± 5                            | 0.22    |
| Female                 | 7/29 (24) | 2/6 (33)       | 3/12 (25)               | 2/11 (18)                         | 0.86    |
| Diabetes mellitus, n (%) | 13/29 (45) | 2/6 (33)    | 4/12 (33)               | 7/11 (64)                         | 0.28    |
| Dyslipidemia, n (%)    | 12/29 (41) | 1/6 (17)      | 8/12 (67)               | 3/11 (27)                         | 0.062   |
| Hypertension, n (%)    | 23/29 (79) | 6/6 (100)     | 9/12 (75)               | 8/11 (73)                         | 0.37    |
| LVEF, %                | 70 [61, 76] | 72 [70, 74]  | 62 [49, 65]             | 76 [74, 78]                       | 0.033   |
| Stress for the scintigraphy |          |                  |                          |                                   |         |
| Drug (adenosine)       | 19/29 (66) | 4/6 (67)      | 7/12 (58)               | 8/11 (73)                         | 0.88    |
| Exercise               | 10/29 (35) | 2/6 (33)      | 5/12 (42)               | 3/11 (27)                         |         |
| Interval between examinations, days† | -5 [-36, 184] | -2 [37, 217] | -3 [-19, 190]           | -12 [-133, 106]                   | 0.55    |
| Medication, n (%)      |          |                  |                          |                                   |         |
| ACE-I or ARB           | 21/29 (72) | 5/6 (83)      | 8/12 (67)               | 8/11 (73)                         | 0.87    |
| Beta blocker           | 11/29 (38) | 2/6 (33)      | 5/12 (42)               | 4/11 (36)                         | >0.99   |
| Calcium blocker        | 10/29 (35) | 4/6 (67)      | 3/12 (25)               | 3/11 (27)                         | 0.21    |
| Statin                 | 20/29 (69) | 5/6 (83)      | 10/12 (83)              | 5/11 (46)                         | 0.17    |
| Nicorandil             | 15/29 (52) | 5/6 (83)      | 7/12 (58)               | 3/11 (27)                         | 0.081   |
| Anti-platelet drug     | 22/29 (76) | 5/6 (83)      | 9/12 (75)               | 8/11 (73)                         | 0.88    |
| Anticoagulant          | 2/29 (6.9) | 1/6 (17)      | 0/12 (0)                | 1/11 (9.1)                        | 0.39    |
| Target coronary artery, n (%) | 21/29 (72) | 3/6 (50)      | 9/12 (75)               | 9/11 (82)                         | 0.11    |
| Left anterior descending artery | 4/29 (14) | 0/6 (0)      | 2/12 (17)               | 2/11 (18)                         |         |
| Right coronary artery  | 4/29 (14) | 3/6 (50)      | 1/12 (8.3)              | 0/11 (0)                          |         |
| Stress scintigraphy |          |                  |                          |                                   |         |
| SSS                    | 4 [2, 6] | 3 [1, 4]       | 7 [5, 10]               | 3 [2, 4]                          | 0.026   |
| SRS                    | 4 [2, 7] | 3 [1, 8]       | 4 [2, 5]                | 6 [3, 8]                          | 0.38    |
| SDS                    | 1 [1, 3] | 1 [3, 1]       | 4 [2, 5]*               | -1 [-3, -1]**                      | <0.001  |
| SSS in the target coronary artery territory | 2 [1, 3] | 0 [0, 2]   | 3 [2, 4]                | 2 [1, 3]                          | 0.076   |
| SRS in the target coronary artery territory | 1 [1, 4] | 0 [0, 2]   | 1 [1, 2]                | 4 [2, 6]                          | 0.03    |
| SDS in the target coronary artery territory | 0 [-1, 1] | 0 [0, 0]   | 2 [1, 2]**              | -1 [-3, -1]**                      | <0.001  |
| Coronary angiography |          |                  |                          |                                   |         |
| The number of coronary vessels with ≥75% angiographic stenosis    | 4/29 (14) | 2/6 (33)      | 1/12 (8)                 | 1/11 (9.1)                        | 0.25    |
| 1 vessel               | 11/29 (38) | 4/6 (67)      | 3/12 (25)               | 4/11 (36)                         |         |
| 2 vessels              | 8/29 (28) | 0/6 (0)       | 4/12 (33)               | 4/11 (36)                         |         |
| 3 vessels              | 6/29 (21) | 0/6 (0)       | 4/12 (33)               | 2/11 (18)                         |         |
| ≥75% angiographic stenosis in the target coronary artery | 21/29 (72) | 3/6 (50)      | 10/12 (83)              | 8/11 (73)                         | 0.37    |
| Quantitative coronary angiography |          |                  |                          |                                   |         |
| Reference diameter, mm | 2.50 [2.26, 2.85] | 2.83 [2.41, 2.85] | 2.42 [2.26, 2.50] | 2.64 [2.23, 2.83] | 0.53 |
| % diameter stenosis, % | 50 [40, 55] | 52 [51, 54]   | 46 [30, 52]             | 52 [43, 57]                       | 0.26    |
| Minimal lesion diameter, mm | 1.34 [1.16, 1.54] | 1.36 [1.16, 1.52] | 1.46 [1.16, 1.60] | 1.27 [1.19, 1.38] | 0.51 |
| Stenotic segment length, mm | 9.43 [6.52, 12.85] | 9.12 [8.05, 10.10] | 10.56 [8.80, 13.63] | 9.43 [6.48, 12.50] | 0.82 |

LVEF, left ventricular ejection fraction; SDS, summed difference score; SRS, summed rest score; SSS, summed stress score.†The interval is days from fractional flow reserve to stress scintigraphy. Asterisks denote statistical significance compared to the control group; *, P < 0.05; **, P < 0.01; ***, P < 0.001.

the RR group (Figure 1).

**Quantitative Coronary Angiography**

Quantitative coronary angiography (QCA) was performed using the CASS 5.9.2 (Pie Medical Instruments, Maastricht, The Netherlands) by an experienced interventional cardiologist and a medical radiology technician.

**Statistical Analysis**

Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), whereas categorical variables were represented by the number and percentage. To assess the baseline characteristics, continuous variables were analyzed by one-way analysis of variance or Kruskal-Wallis test with Holm’s test for multiple comparisons. Fisher’s exact test was used for the categorical variables.

All statistical analyses were performed with R 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria), EZR1.23 (Saitama Medical Center, Jichi Medical University).
Results

Baseline Characteristics

Table 1 summarizes the baseline characteristics of patients with control, redistribution, and redistribution regions according to the $^{201}$TI Cl stress scintigraphy findings. There were no significant differences in age, gender, diabetes mellitus, and hypertension among the three groups. Old myocardial infarction had not been documented, and angiographic coronary collateral was not observed in our study population. There was a trend towards less nicorandil use in the RR group, but the difference was not statistically significant.

$^{201}$TI Cl Stress Scintigraphy

SSS in the redistribution group was significantly greater than that in the RR group (redistribution, 7 [5, 10] vs. RR, 3 [2, 4], P = 0.032; Table 1). There was no significant difference in SRS among the three groups (P = 0.38). SDS of the control group was smaller than that of the redistribution group (control, 1 [-1, 3] vs. redistribution, 4 [2, 5], P = 0.019), while SDS in RR group was lower (control, 1 [-1, 3] vs. redistribution, -1 [-3, -1], P < 0.001).

There was no significant difference in the SSS and the SRS of the target coronary territory among the groups. Compared to the target coronary artery territory’s SDS in the control group, the target coronary artery territory’s SDS in the redistribution group was greater (control, 0 [0, 0] vs. redistribution, 2 [1, 2], P = 0.001), while the target coronary territory’s SDS in the RR group was lower (control, 0 [-0, 0] vs. redistribution, -1 [-3, -1], P = 0.001).

Fractional Flow Reserve

FFR values were 0.93 [0.89, 0.95], 0.85 [0.79, 0.86], and 0.83 [0.80, 0.84] in the control, redistribution, and RR groups, respectively. Compared to the control region, the redistribution and RR regions showed significantly lower FFR values (P for the three-group comparison = 0.011; control vs. redistribution, P = 0.03; control vs. RR, P = 0.03; Figure 4).

Discussion

In this study, we compared the FFR value with the $^{201}$TI Cl stress scintigraphy findings to confirm enhanced wash-out in the RR region. Our results revealed that RR was associated with a low FFR value, even in the absence of severe angiographic organic stenosis.

RR might be associated with the imbalance of coronary blood flow between RR-related and RR-unrelated areas$^{5-10}$. FFR is defined as the ratio of maximum flow in the presence of stenosis to the normal maximum flow during pharmacological vasodilation$^{11}$. The concept of FFR is explained in Figure 4. Coronary pressure in the non-stenotic coronary vessel should be maintained across the epicardial coronary artery (Figure 5A) and the distal coronary artery without significant decline compared to the central aortic pressure.

When a central stenosis exists, the FFR value is low, owing to the reduced coronary flow at the distal site of the severe organic stenosis (Figure 5B, redistribution group). The FFR value in the RR region was lower despite the absence of angiographic severe organic stenosis in this study. Recent studies reported that not only central stenosis but also distal microvascular resistance in the coronary artery flow determine the value of FFR$^{21, 22}$. When high microvascular resistance is present, FFR might be preserved even with the presence of organic coronary stenosis (Figure 5C, control group). In contrast, the value of FFR should be low when microvascular resistance is low. In the RR region, no collateral blood supply was found angiographically. Lower FFR value without severe organic stenosis suggests that there may be a microvascular collateral blood supply that could not be found angiographically. Myocardial damage subsequent to microvascular dysfunction is related to hypertension, obesity, insulin resistance, diabetes mellitus, aging, and female gen-
Figure 5. The concept of stenotic vascular resistance, microvascular resistance, and collateral flow in the measurement of fractional flow reserve. FFR, fractional flow reserve; Qp, hyperemic myocardial flow; QN, normal hyperemic myocardial flow.

der24-27]. We believe that myocardial damage at the microvascular level induces coronary collateral circulation in the microvascular bed in RR (Figure 5D, reverse redistribution group). In our study population, the RR group had 7/11 (64%) patients with diabetes mellitus, which is not statistically significant but reflects a trend of the high prevalence of this condition in these relatively elderly patients compared to other groups. Poor-glycemic control, especially, large blood glucose fluctuations, promotes microvascular dysfunction, which may ultimately lead to myocardial ischemia and damage. Long-standing myocardial ischemia at the microvascular level may induce the development of microvascular collaterals (Figure 5D). Furthermore, our data shows that the RR group exhibited a tendency towards less nicorandil use than the control group. Thus, it might be considered that non-use of nicorandil is linked to RR28. Nicorandil may improve microvascular dysfunction in diabetic patients25,29, and might be beneficial for patients with poor glycemic control or glucose fluctuations. It is recommended that cardiologists and nuclear radiologists be aware of the possibility of myocardial damage subsequent to microvascular dysfunction and the underlying conditions related to microvascular dysfunction, which cause collateral vessel development.

There are several methodological limitations in this study. First, the study was retrospective in nature and was conducted at a single center. Moreover, the study’s sample size was small, partly because the study focused on patients with RR derived from the 201TlCl stress scintigraphy. Second, both adenosine and exercise stress scintigraphy were performed, which might have affected the scintigraphy findings. Third, the small sample size may mean that the study is statistically underpowered and may have overlooked factors influencing FFR subsequent to microvascular dysfunction. Aging and female sex has been reported to be associated with microvascular dysfunction29,30,31; there were no significant differences in either factor among the groups. Further assessment of microvascular resistance using pressures wire to determine the mechanism of RR is warranted in a well-designed prospective study in the future.
Conclusions

The RR region in 123I-Tl stress scintigraphy had a lower FFR value compared to the normal perfusion area. Microvascular resistance due to the increased collateral washout may be one of the mechanisms of RR.

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Conflicts of Interest

The authors declare no conflict of interest.

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