Annals of Nuclear Medicine (2003. Dec) 17(8):717-723.

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ABSTRACT

Objectives: The purpose of this study was to validate a new quantitative index of salvaged myocardial mass calculated from Tc-99m tetrofosmin SPECT for evaluating the therapeutic effect of emergent reperfusion therapy in acute myocardial infarction (AMI).

Methods: Tc-99m tetrofosmin SPECT was performed before and after emergent percutaneous transluminal coronary angioplasty (PTCA) in eight patients with AMI. In the pre-PTCA study, Tc-99m tetrofosmin was injected before emergent PTCA. Two weeks after the PTCA, post-PTCA study was performed. As a quantitative index of salvaged myocardial mass, salvaged myocardial volume (SMV) was defined as the difference of myocardial functional volume between the SPECT studies before and after the PTCA. To investigate the clinical significance of SMV, SMV was compared with the grade of therapeutic efficacy determined visually from pre- and post-PTCA SPECT images and clinical parameters, namely peak creatine phosphokinase level (pCK) and the time from the onset of the AMI to reperfusion (RPT).

Results: SMV showed a significant correlation with the visual grade of therapeutic efficacy ($r = 0.737$, $P < 0.037$) and a trend toward significant correlation with pCK ($r = -0.622$, $P < 0.1$). SMVs in early- and late-reperfusion groups (RPT $\leqq$ 6 hr and RPT > 6 hr) were 30.0 ± 14.0 and -6.2 ± 25.5 ml, showing a greater mean SMV value in the early-reperfusion group ($P < 0.07$).

Conclusion: SMV could be used as a quantitative index of salvaged myocardial mass for evaluating the therapeutic effect of emergent reperfusion therapy.

Key words:

Tc-99m Tetrofosmin, salvaged myocardium, PTCA, AMI

INTRODUCTION

Percutaneous transluminal coronary angioplasty (PTCA) and intracoronary thrombolytic therapy have been performed as aggressive reperfusion therapies for acute myocardial infarction (AMI). Both therapies can improve the fate of ischemic myocardium surrounding the infarct core, leading to consequent improvements in left ventricular function and long-term survival[1-5]. According to previous studies, clinical outcomes of these therapies are similar[5], but some authors suggested that PTCA could be more effective than thrombolytic therapy in treating underlying arteriographic stenoses[4]. To discuss the strategy for treating AMI, evaluation of the efficacy of reperfusion therapies has become an important issue recently. To resolve this issue, there are several kinds of conventional methods including electrocardiography (ECG) and echocardiography, which are often performed under exercise or pharmacological stress, and the measurement of serum cardiac markers such as creatine phosphokinase (CK)[1, 6-11]. These methods, however, cannot always fully disclose the underlying cardiac functional status and pathological changes. For example, the presence of conduction disturbances might hinder correct ECG diagnosis in exercise stress test, while echocardiography tends to underestimate cardiac function[12]. Peak blood creatine phosphokinase level (pCK) cannot provide any information regarding the location of the damaged myocardium, and its level tends to depend on the sampling time after the onset.

In view of these facts, single photon emission computed tomography (SPECT) with myocardial perfusion agents is a better choice for evaluating reperfusion therapy because it is noninvasive and can give correct information regarding infarcted area and viable myocardial mass. Some authors reported that the findings of myocardial perfusion SPECT were significantly correlated with the pathological infarct size[13]. Furthermore, the recent advent of labeling kits for Tc-99m labeled myocardial perfusion agents such as

Tc-99m tetrofosmin has enabled emergent SPECT examination for evaluating the risk area in patients with AMI. To date, several studies regarding the use of Tc-99m labeled myocardial perfusion agents in reperfusion therapies were reported[5, 10, 14-17]. These studies, however, employed qualitative or semiquantitative methods based on the visual scoring or profile curves for the image analysis. For more objective and quantitative SPECT evaluation of infarcted myocardium, we introduced a new quantitative index of salvaged myocardial volume (SMV), which was based on the functional myocardial volume calculated from the SPECT images taken before and after reperfusion therapy. In this feasibility study, the clinical significance of SMV was investigated using data from eight patients with AMI.

MATERIALS AND METHODS

Subjects

The subjects consisted of eight patients (five men, three women; mean age, 60 ± 12 years old) who were admitted to the Sapporo-Higashi Tokushukai Hospital with AMI. The diagnoses were based on ECG, echocardiography, and clinical symptoms such as severe typical chest pain lasting for at least 30 minutes. After the admission, culprit arteries were confirmed by coronary angiography (CAG) and urgent PTCA was performed. No patient had any history of previous myocardial infarction or other cardiac diseases. All the patients and their families provided written informed consent to participate in this study.

Radiopharmaceutical

Tc-99m tetrofosmin was prepared using a kit vial (Myoview®,

Nihon-Mediphysics, Nishinomiya, Japan) and Tc-99m pertechnetate freshly eluted from a Tc-99m generator (Meditech®, Nihon-Mediphysics, Nishinomiya, Japan). Tc-99m labeling of tetrofosmin was performed immediately after the angiographic confirmation of coronary artery stenoses and the decision to perform urgent revascularization.

Imaging protocol

Tc-99m tetrofosmin (740 MBq) was injected intravenously before urgent PTCA. About 6 hours after the PTCA, SPECT data acquisition was performed to obtain images reflecting the risk area before PTCA using a rotating dual-headed digital gamma camera system equipped with low-energy high-resolution collimators (GCA 7200, Toshiba, Tokyo, Japan). The in-plane spatial resolution of this system was 20 mm FWHM in the air. Sixty-four projections over 360-degree were recorded in a 64 x 64 matrix with an acquisition time of 25 seconds per each projection, using an energy window of 10% centered at 140 KeV. Two weeks after the first SPECT, the follow-up SPECT after PTCA was performed using the same acquisition parameters as used in the first SPECT study.

SPECT image reconstruction was performed on a dedicated data processing unit (GMS-5500DI, Toshiba, Japan). Standard filtered back-projection algorithm without attenuation and scatter correction was chosen. A ramp filter was used after preprocessing with a Butterworth filter (order 8, cutoff-frequency 0.42 cycle/cm) to reconstruct transaxial images with 6.9 mm thickness. Oblique sections including short-axial slices with 1-pixel thickness were then generated by pixel reorientation.

Calculation of myocardial perfusion volume and salvaged myocardial volume

Myocardial perfusion volume (MPV) was defined as a functional volume that

was calculated by integrating the voxels whose counts were greater than 50% of the maximum voxel count in the myocardium. Using short-axial images, a circular region of interest (ROI) surrounding whole left ventricular myocardium was drawn with a freehand technique. After confirming that all the left ventricular myocardial slices were within the ROI, the maximum voxel count in the myocardium was determined. Based on the maximum voxel count, MPV was calculated. SMV was defined as a volume calculated by subtracting MPV after PTCA from that before PTCA.

Clinical significance of MPV and SMV

To clarify the clinical significance of MPV and SMV, relationships of MPV to myocardial perfusion and culprit artery were investigated. MPV and SMV were compared with the results of visual evaluation of the SPECT images. Relationships of SMV to the clinical parameters related to the infarct size, such as pCK and time from the onset of AMI to reperfusion (RPT), were also investigated.

Relationships of MPV to myocardial perfusion and culprit artery

To investigate the relationship of MPV to myocardial perfusion, MPV was compared with relative myocardial uptake of Tc-99m tetrofosmin on a segment basis, using both pre- and post-PTCA SPECT data. Left ventricular myocardium was divided into four segments (anterior, septal, inferior, and lateral segments) based on the four equal sector regions of interest radially placed on a short-axial plane. Mean segmental myocardial uptake was calculated by dividing mean voxel count of a segment by the maximum voxel count of the whole myocardium. Segmental MPV was determined by dividing whole MPV according to the four sector regions of interest. Correlation between the segmental MPV and the mean segmental uptake was examined. And to examine whether segmental decrease in MPV matched up to the territory of the culprit

artery, the subjects were divided into three groups according to their culprit arteries (LAD, RCA, and LCX). Segmental MPV from the pre-PTCA SPECT studies was compared in these three groups.

Relationships of SMV to therapeutic efficacy of PTCA

Therapeutic efficacy of PTCA was assessed visually by comparing the pre- and post-PTCA SPECT images. Improvement on SPECT images was classified into three grades by a consensus of two nuclear medicine physicians: 0, no improvement; 1, partial improvement; 2, complete improvement. Correlation between SMV and the visual grades was examined. As an index of infarct size, pCK level was also compared with SMV. Since RPT is thought to be a major factor affecting the fate of ischemic myocardium, we investigated whether RPT was related to SMV. The subjects were divided into two groups according to RPT: early-reperfusion, RPT < 6 hours; late-reperfusion, RPT > 6 hours. SMV was compared between these two groups.

Statistical analysis

For parametric and nonparametric correlation analyses, Pearson's product-moment correlation coefficient and Spearman's rank correlation coefficient were calculated with corresponding P values. To test the between-group differences, two-sample t-test was used with or without Satterthwaite's approximation depending on the equality of variances. A P value less than 0.05 was considered statistically significant. If a P value was greater than 0.05 but less than 0.1, a trend toward statistical significance was noted.

RESULTS

Patient profiles are summarized in table 1. Culprit arteries were LAD, LCX, and RCA in two, three, and three cases respectively. In all cases, urgent PTCA resulted in success without any major complications or death. RPT ranged from 1.57 to 18.25 hours. In three cases, RPT was less than 6 hours. Pre-PTCA SPECT studies could be performed without any significant interference with urgent patient care.

Relationships of MPV to myocardial perfusion and culprit artery

Whole MPV of the left ventricle calculated from pre- and post-PTCA SPECT studies ranged from 134 to 272 ml and from 123 to 244 ml. Segmental MPV calculated by dividing whole MPV according to the four sector ROIs ranged from 5.8 to 98.5 ml and from 8.1 to 87.6 ml in pre- and post-PTCA studies. On the other hand, mean segmental myocardial uptake ranged 53.4% to 73.2% and from 55.0% to 72.9% in pre- and post-PTCA studies. Segmental MPV from pre- and post-PTCA studies was plotted against corresponding segmental myocardial uptake in scatter plots (Figure 1,2). There were significant correlations between segmental MPV and segmental myocardial uptake in both pre- and post-PTCA studies ($P < 0.0007$ and $P < 0.0009$).

Mean and SD of the pre- PTCA segmental MPV in the three groups of culprit artery were expressed in bar graphs for each segment (Figure 3A-D). Segmental MPV from the pre-PTCA studies showed a decrease in the segment corresponding to the territory of the culprit artery. In the anterior, septal, inferior, and lateral segments, segmental MPV showed the minimum in the LAD, LAD, RCA, and LCX groups of culprit artery, respectively.

Relationships of SMV to therapeutic efficacy of PTCA

SMV calculated as the difference between post- and pre-PTCA MPVs ranged

from –28 to 46 ml. Grading of therapeutic efficacy of PTCA by visual comparison of pre- and post-PTCA SPECT gave the result that two, four, and two cases were graded as grade 0, 1, and 2. The mean SMVs in the corresponding visual grades were –22.3 ± 9.81, 18.7±15.0, and 35.0±15.6 ml, respectively (Figure 4). There was a significant correlation between SMV and the visual grade ($P < 0.037$).

The blood pCK level ranged from 1,090 to 7,000 U/l. The relationship of SMV to pCK was expressed in a scatter plot (Figure 5). Between blood pCK level and SMV, there was a trend toward a significant inverse correlation ($P < 0.100$).

Time from the onset of AMI to reperfusion (RPT) is summarized in table 1. In three cases, RPT was less than 6 hours. The mean SMV values of the early-reperfusion (RPT< 6 hours) and late-reperfusion groups (RPT > 6 hours) were 30.0 ± 14.0 and –6.2 ± 25.5 ml (Figure 6). There was a trend toward a significant difference between SMVs of these two groups ($P < 0.068$).

DISCUSSION

In evaluation of the therapeutic efficacy of urgent PTCA in AMI, it is desirable to obtain detailed information of the risk area that might lapse into eventual infarction unless effective intervention is implemented. Indirect methods, such as electrocardiography and echocardiography, have been playing a major role for this purpose in the routine clinical setting, although they are not sufficient. With the advent of Tc-99m myocardial perfusion agents such as Tc-99m tetrofosmin, it has become possible to grasp the extent and severity of the risk area directly from myocardial perfusion SPECT images. Quick formulation of Tc-99m labeled agents injectable on demand and relatively stable myocardial accumulation that holds myocardial perfusion

at administration have enabled immediate injection on admission and late imaging after the provision of necessary treatment. These features are essential for the use of Tc-99m labeled myocardial perfusion agents for evaluation of the risk area in AMI.

In evaluation of myocardial perfusion SPECT images, quantitative indices such as extent and severity scores based on circumferential curve profiles are useful for objective evaluation of perfusion abnormality. However, these indices depend somewhat on operator's slice selection, and do not directly reflect myocardial mass volume. According to previous studies, some authors used a polar map to evaluate the defect size in acute myocardial infarction. But, this method has difficulty evaluating the affected region. The real defect size is not reflected correctly on a polar map because the original 3-dimensional myocardial configuration can't be transformed to a 2-dimensional polar map without spatial distortion. Compared to these indices, MPV has the advantages of more objective calculation and direct reflection of absolute viable myocardial mass volume in principle. To our knowledge, there is no previous study using MPV as an objective index, and our method offers enhanced objectivity.

In calculation of MPV, the threshold percentage for myocardial boundary determination is an important factor. Some previous studies, using Tc-99m sestamibi as perfusion agents, reported that a 60% threshold is better[5]. But unfortunately, relatively few studies have commented on the use of Tc-99m tetrofosmin. A 50% threshold should theoretically be optimal if no scatter and no attenuation exist[5], and some previous studies using Tc-99m tetrofosmin adopted 50% as an appropriate threshold for evaluating myocardial viability[12, 18]. We decided the threshold regarding the above-mentioned. However, since MPV is simply determined by threshold of relative uptake, it might not reflect the severity of myocardial ischemia. In this context, mean segmental uptake, which reflects the severity of ischemia, and segmental MPV were

correlated significantly. This result indicated that MPV could reflect not only viable myocardial mass volume but also the severity of ischemia. Furthermore, segmental decrease in MPV was in good agreement with the territory of the culprit arteries. These results indicated that MPV could be used as a quantitative index of viable myocardial mass. Thus, SMV, which is the difference is MPV between pre- and post-PTCA, could be a practical quantitative index of salvaged myocardial mass volume.

In this study, pCK and RPT were used as clinical parameters that could be related to the therapeutic efficacy of PTCA. However, pCK did not show a significant correlation with SMV. According to Figure 5, one patient had a deviated SMV value. This patient had re-PTCA after this study because of restenosis. In the acquisition of post-PTCA study, although this patient had neither subjective nor objective symptoms, there is a possibility that this restenotic lesion might have affected the result. And the following reasons are also possible. Another determinant of pCK except the quantity of infarcted myocardium was the period between the onset of AMI and blood sampling. Moreover, CK includes several isozymes, some of which are not of cardiac origin. These factors might have a certain influence on the correlation between pCK and SMV.

As for RPT, it is not the only factor that determines the infarcted myocardial mass volume. Both duration and degree of ischemia could be related to infarcted myocardial mass volume. Considering these circumstances of pCK and RPT, although a significant correlation or difference was not obtained with SMV, their trends to significance could support the feasibility of SMV as a practical index of salvaged myocardial mass volume.

Limitations of the study

This study has several limitations that should be mentioned. First, the number of subjects was limited to only eight. This could influence the statistical test results. Second, attenuation and scatter corrections were not performed in reconstruction of SPECT images. This could influence the values of MPV and SMV, especially in inferior segmental ones. Third, we could not perform tests for evaluating left ventricular function and correlate functional parameters to MPV and SMV. To resolve this important issue, gated SPECT study could be useful, enabling direct comparison of left ventricular function and SMV.

CONCLUSION

This study has some limitations as mentioned above. But, compared with other indexes, MPV has an advantage from a quantitative and objective standpoint in principle. Furthermore, this study indicates that MPV and SMV are clinical meaningful indexes. In conclusion, it is possible that MPV and SMV are useful indexes for estimating viable myocardium and salvaged myocardium, respectively.

ACKNOWLEDGMENT

This study was partly supported by Nihon-Mediphysics corporation.

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LEGEND

Figure 1

This plot shows the correlation between MPV and mean percentage of uptake to maximum before the PTCA. These two parameters show a statistically significant correlation ($P < 0.0007$).

Figure 2

This plot shows the correlation between MPV and the mean percentage of uptake to maximum after the PTCA. These two parameters also show a statistically significant correlation ($P < 0.0009$).

Figure 3

These bar graphs show each correlation of MPV with the culprit artery. Figure 3A refers to the anterior segment. figure 3B to the septal segment, figure 3C to the inferior segment, and figure 3D to the lateral segment. These figures show that each segmental MPV reflected the myocardial perfusion.

Figure 4

This bar graph shows the correlation of the SMV with the visual score. These two parameters show a statistically significant correlation ($P < 0.0368$).

Figure 5

This plot shows the relationship of SMV and pCK in the blood. There is a tendency of inverse correlation ($P < 0.100$).

Figure 6

This bar graph shows the SMV in the early-reperfusion group and late-reperfusion group. SMV of the early-reperfusion group tends to have much more salvaged volume compared with late-reperfusion group ($P < 0.0680$).

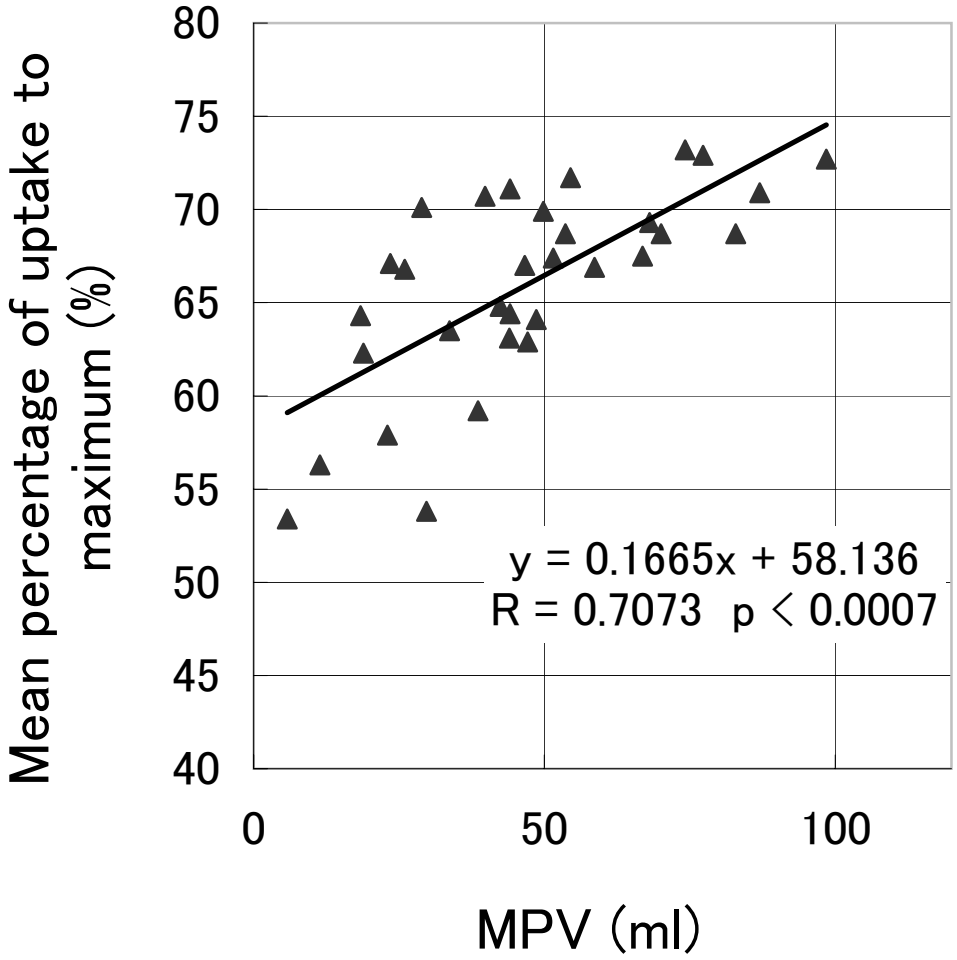
Table 1 Patient characteristics

Patient	Age	Sex	Culprit artery	RPT (h)	pCK (U/l)
No.1	64	M	LCX segment 11 ; 99%	6.88	2019
No.2	46	F	RCA segment 4AV ; 100%	4.75	2830
No.3	61	F	LAD segment 6 ; 50% segment 7 ; 100%	6.33	2001
No.4	85	F	RCA segment 1 100%	2.53	1090
No.5	60	M	LCX segment 11 ; 100%	6.83	3377
No.6	61	M	RCA segment 3 ; 100%	1.57	1553
No.7	46	M	LAD segment 6 ; 100%	6.5	6030
No.8	59	M	LCX segment 11 ; 100%	18.25	7000

Abbreviations: RPT = time from the onset of the AMI to reperfusion, pCK = peak creatine phosphokinase, RCA = right coronary artery, LAD = left anterior descending branch, LCX = left circumflex branch

The characteristics and results of reperfusion therapies were shown in this table. Percutaneous transluminal coronary angioplasty (PTCA) for these patients had been successful without death or other major complications.

Figure 1


Mean percentage of uptake to maximum (%)
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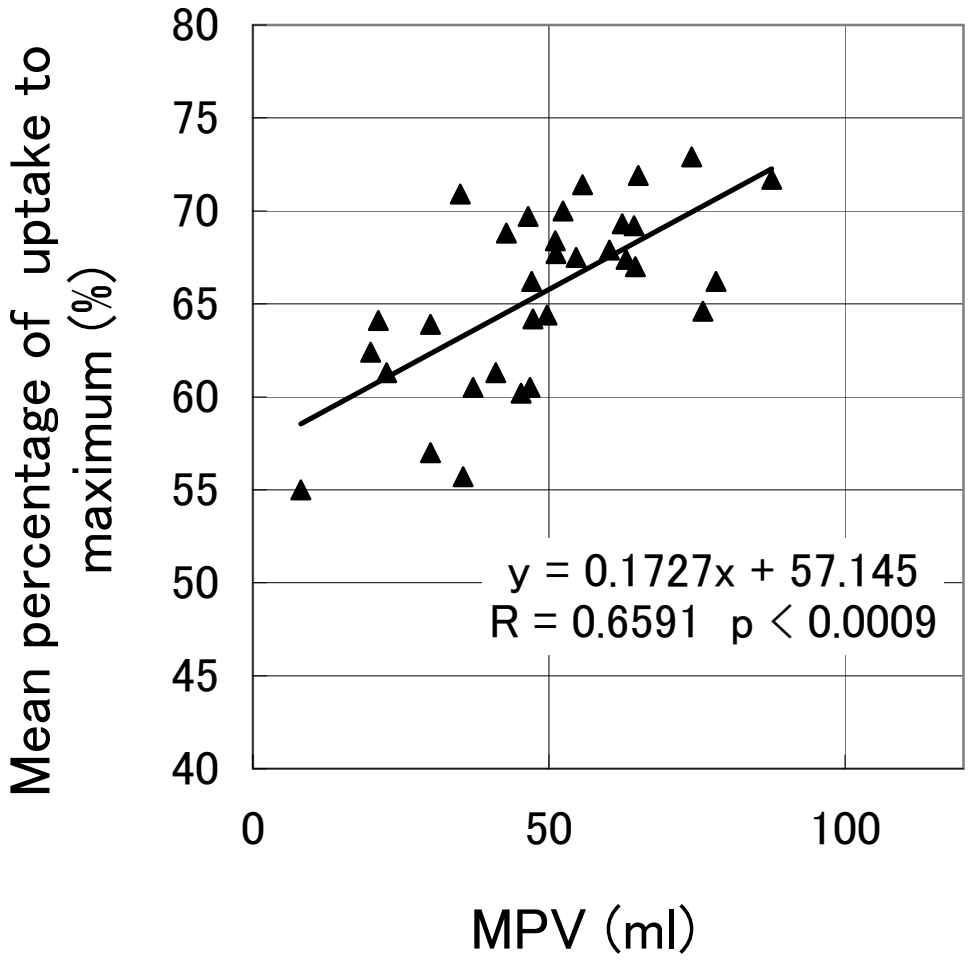
75
70
65
60
55
50
45
40
0
50
100
MPV (ml)
y = 0.1665x + 58.136
R = 0.7073 p < 0.0007

Figure 2


Mean percentage of uptake to maximum (%)
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75
70
65
60
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50
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MPV (ml)
y = 0.1727x + 57.145
R = 0.6591 p < 0.0009

Figure 3A

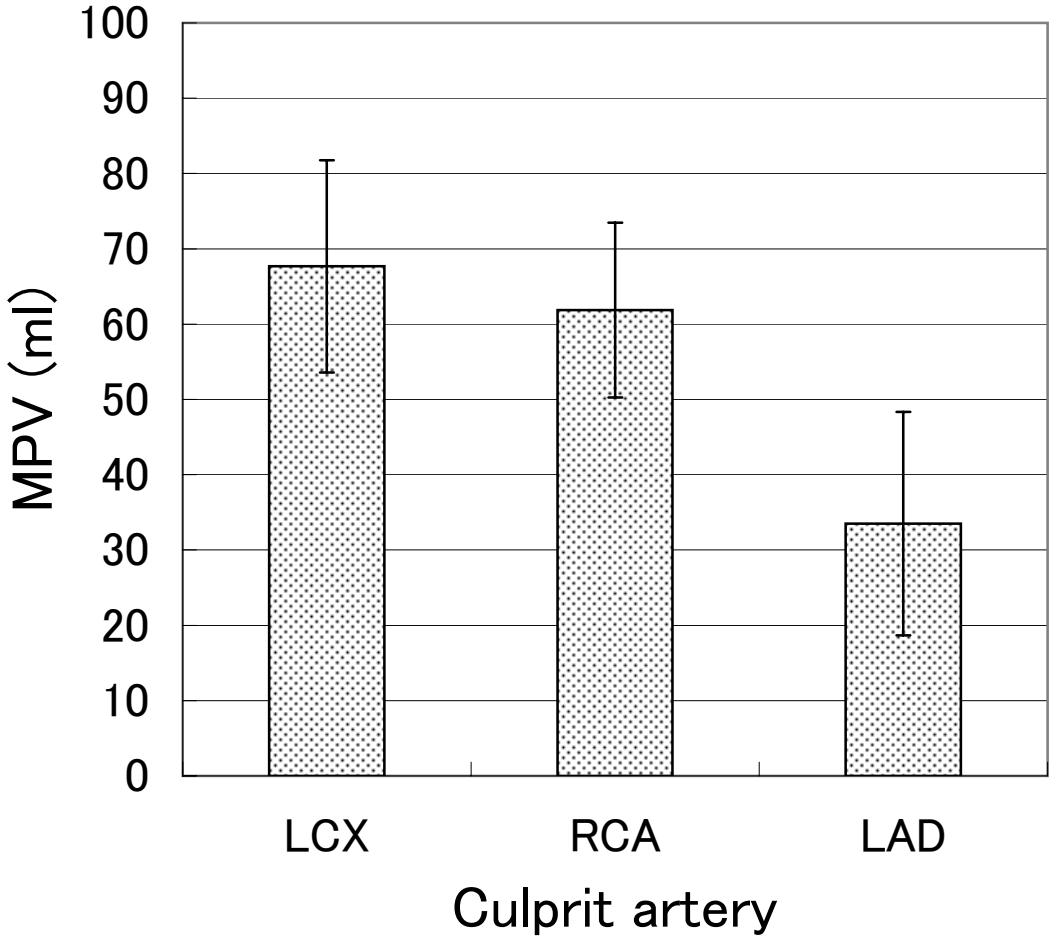


Figure 3B

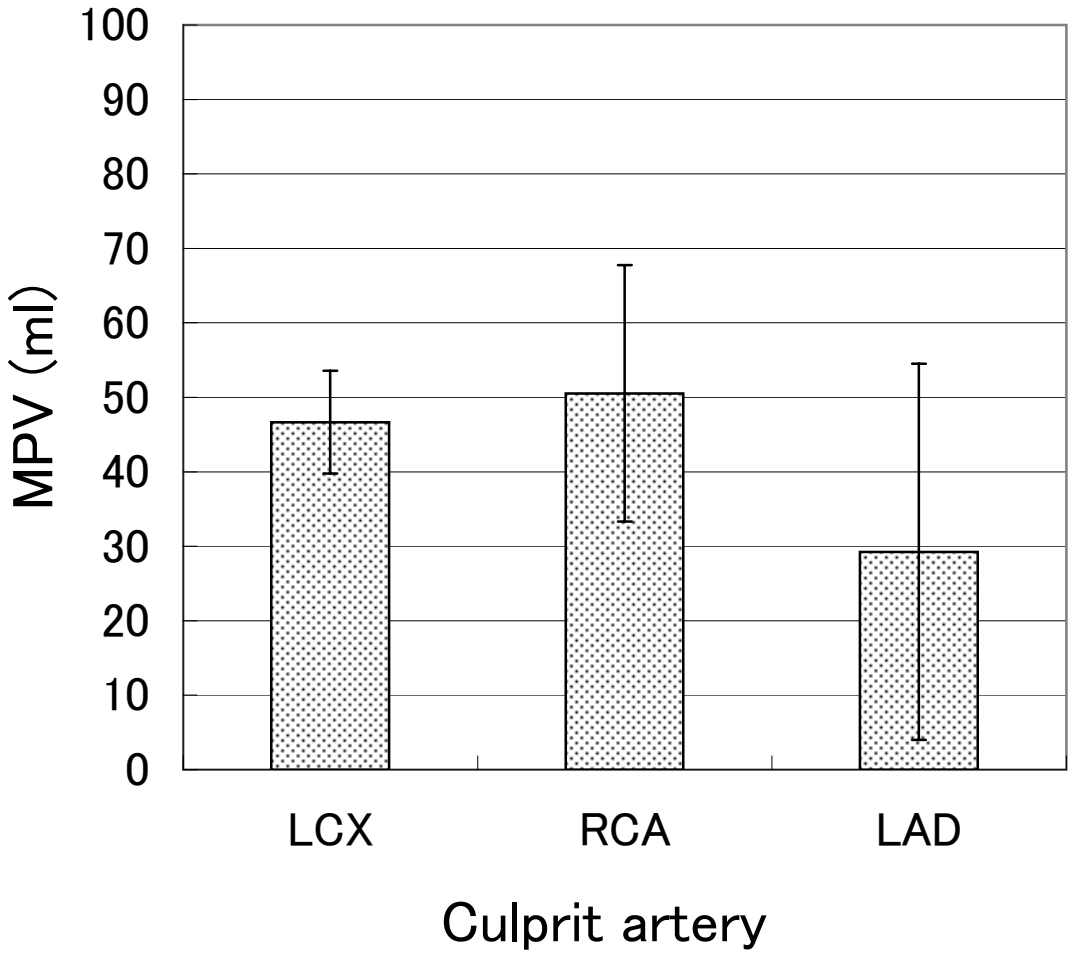
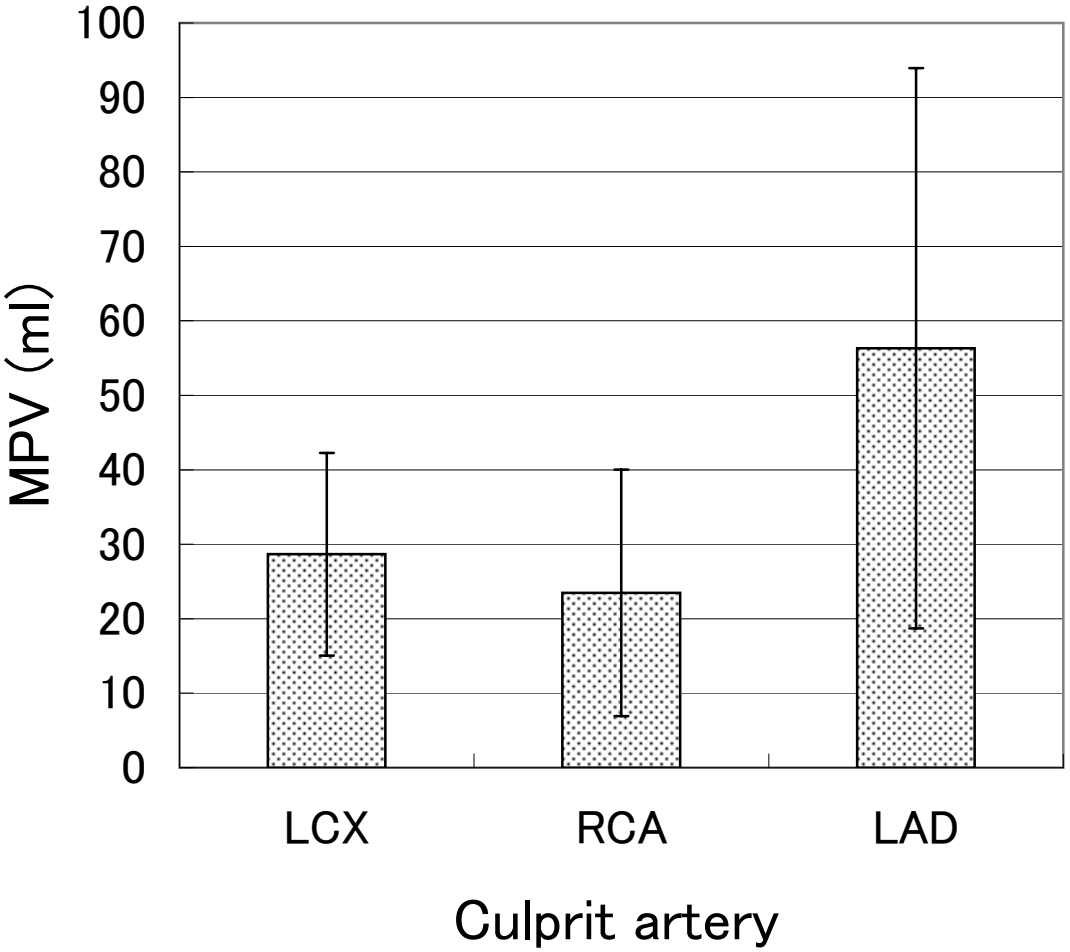


Figure 3C



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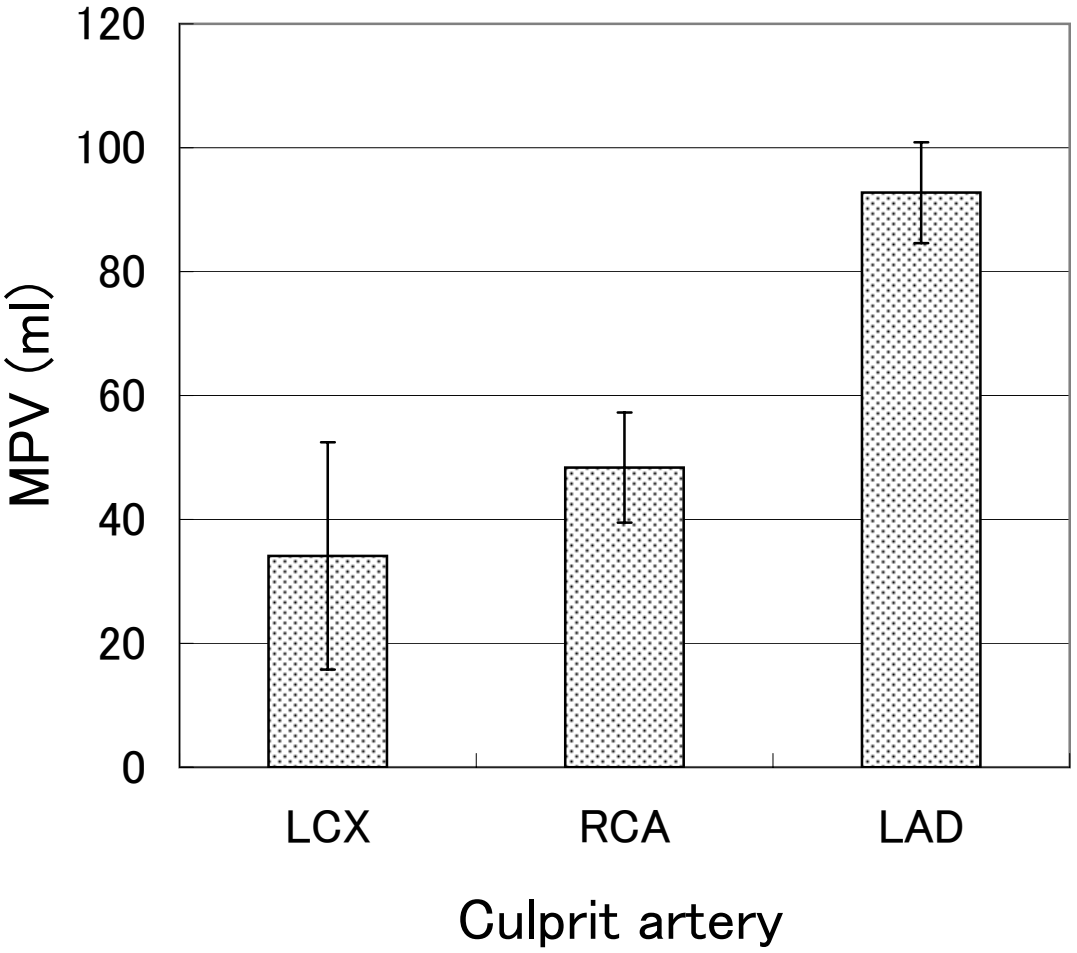


Figure 4

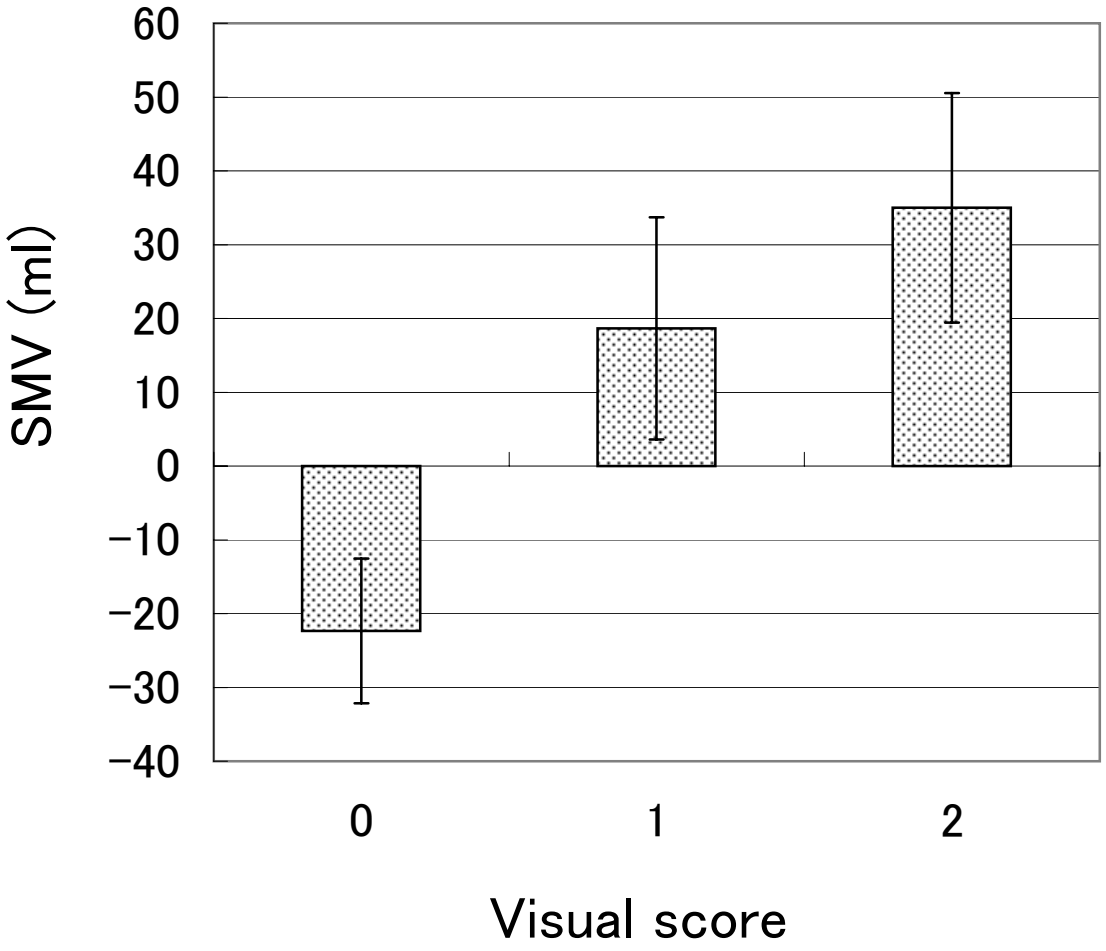
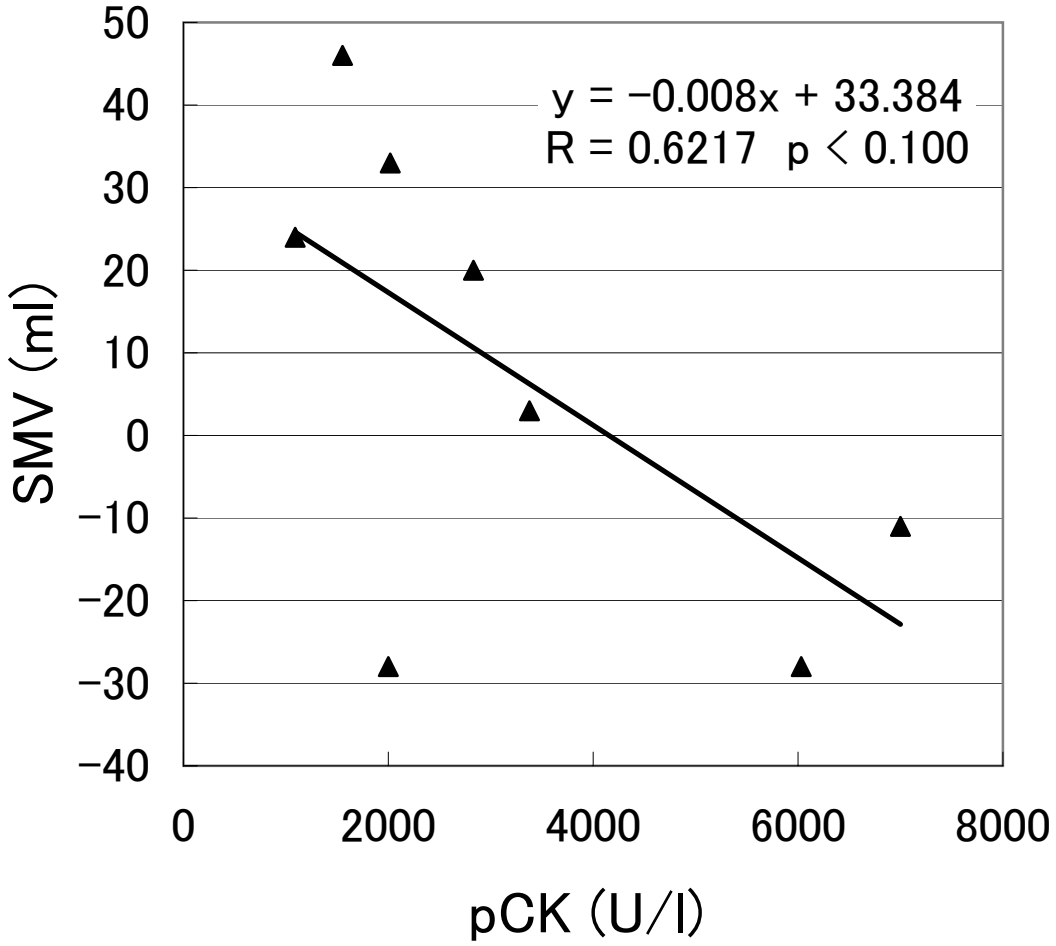


Figure 5


y = −0.008x + 33.384
R = 0.6217 p < 0.100
SMV (ml)
pCK (U/l)
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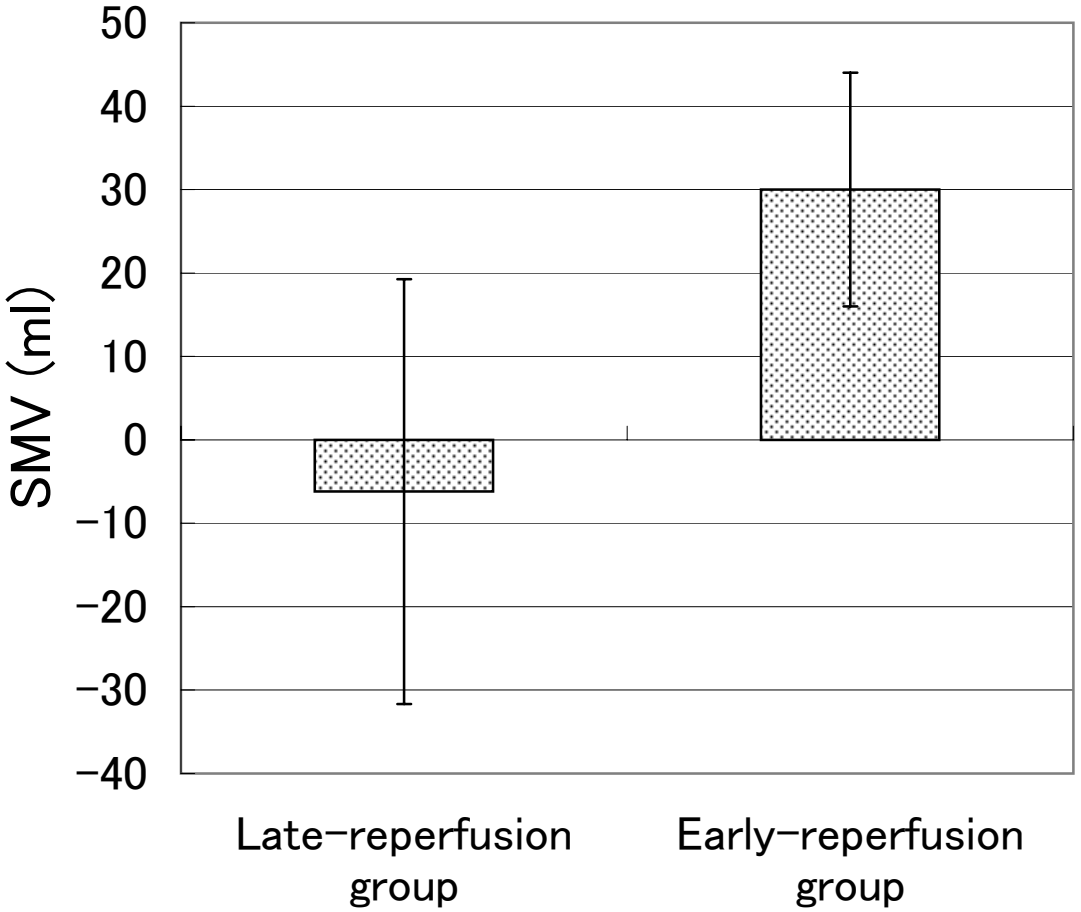
40
30
20
10
0
−10
−20
−30
−40
0
2000
4000
6000
8000

Figure 6


50
40
30
20
10
0
−10
−20
−30
−40
SMV (ml)
Late-reperfusion group
Early-reperfusion group