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Research Article

Effectiveness of Myocardial Contrast Echocardiography Quantitative Analysis during Adenosine Stress versus Visual Analysis before Percutaneous Therapy in Acute Coronary Pain: A Coronary Artery TIMI Grading Comparing Study

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The study aim was to compare two different stress echocardiography interpretation techniques based on the correlation with thrombosis in myocardial infarction (TIMI) flow grading from acute coronary syndrome (ACS) patients. Forty-one patients with suspected ACS were studied before diagnostic coronary angiography with myocardial contrast echocardiography (MCE) at rest and at stress. The correlation of visual interpretation of MCE and TIMI flow grade was significant. The quantitative analysis (myocardial perfusion parameters: A, β, and $A \times \beta$) and TIMI flow grade were significant. MCE visual interpretation and TIMI flow grade had a high degree of agreement, on diagnosing myocardial perfusion abnormality. If one considers TIMI flow grade <3 as abnormal, MCE visual interpretation at rest had 73.1% accuracy with 58.2% sensitivity and 84.2% specificity and at stress had 80.4% accuracy with 76.6% sensitivity and 83.3% specificity. The MCE quantitative analysis has better accuracy with 100% of agreement with different level of TIMI flow grading. MCE quantitative analysis at stress has showed a direct correlation with TIMI flow grade, more significant than the visual interpretation technique. Further studies could measure the clinical relevance of this more objective approach to managing acute coronary syndrome patient before percutaneous coronary intervention (PCI).

1. Introduction

Acute myocardial infarction (AMI) is one of the major problems influencing public health, and PCI is one of the most effective method to reduce myocardial ischemia, ventricular remodeling and restore myocardial functions after AMI [1]. TIMI flow grade was at first related to a postthrombosis's coronary flow status measured by coronary angiography, where a totally obstructed flow receive grade 0 and a totally opened artery grade 3 [2]. Nowadays these flow grading is applied in others circumstances, supporting clinical decisions about PCI and making TIMI risk one of reference standards in ACS clinical management [3, 4].

Despite the clinical role of coronary flow in the prediction of myocardial ischemia, coronary angiography power of visualization is restricted to blood vessels with diameter >100 μm, which is not so accurate for collateral vessels and capillaries assessment, consequently not accurate for myocardial perfusion data.

Recently, the confirmation of myocardial microvascular integrity before PCI procedure becomes one of important concerns to achieve better survival and functional recovery of myocardium [5], and myocardial contrast-enhanced echocardiography (MCE) can assess the myocardial blood volume changes at stress using adenosine for accurately and securely evaluating of myocardial microvascular perfusion in a real-time manner. This technique, which became more popular in clinical practice [6, 7], detects contrast microbubble at the capillary level within the myocardium and, thus, has the potential to assess tissue viability and the duration of the contrast effects [8].

MCE has been used for the determination of functional relevance of coronary stenoses of intermediate angiographic severity and is at least equivalent to single-photon emission computed tomography (SPECT) in microvascular disease and ACS evaluation, with a tendency toward higher sensitivity [9, 10].

Otherwise, MCE has a great advantage as a bedside technique and can be used early in patients presenting with acute heart failure to rapidly assess left ventricular (LV) function (regional and global) and perfusion (rest and stress) [11, 12].

There is no research data comparing TIMI flow grade with MCE perfusion in acute patients, neither comparing a quantitative and a visual MCE analysis for this purpose. So the objective of the study is to validate MCE as a useful tool for predict coronary flow dysfunctions and determinate which MCE analysis technique is more accurate.

2. Methods

2.1. Patients. The study was conducted during the period of March to December 2008, consisted of 41 patients (34 men, 36–69 years old and mean age 54 ± 10.8) who were diagnosed as acute coronary syndrome (ACS) highly elected for a PCI treatment. From the final population, 30 patients had acute myocardial infarction (AMI) confirmed. Diagnosis of ACS and AMI was based on the criteria by International Society of Cardiology and World Health Organization.

All patients underwent rest and hyperemic stress real-time myocardial contrast echocardiography (RT-MCE) before coronary angiography (CAG). All the diseases arteries had stents implanted with the blood flow of each reached 3 in TIMI flow grade after PCI. Baseline characteristics of the patients are listed in Table 1. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University, and all of the patients provided written informed consent forms before their enrollment in the study.

2.2. Contrast Agent Administration. The contrast agent Sonovue (BRACCO Imaging B. V., Switzerland) is a suspension of microbubbles whose active product is sulphur hexafluoride, an innocuous gas eliminated through the respiratory system. The product is presented in the form of particles that activate when added to a saline solution and shaken vigorously for 30 seconds. A total amount of 2 mL was administered intravenously using an infusion pump at the rate of 1 mL/min. Then, 5 mL saline solution was added at the same rate. No adverse effects occurred in using the contrast agent.

2.3. Hyperemic Stress. Adenosine was the clinical stress agent preferred due to the efficient vasodilatation effect, the rapid effect and short half-life, and the modest chronotropic and inotropic effects. When resting RT MCE cine loops had been captured, adenosine was administered intravenously at a rate of 140 g/kg/min for up to 6 minutes. After 2.5 minutes of infusion, destruction-replenishment sequences were repeated in all apical views. Heart rate and rhythm were monitored continuously, and blood pressure and 12-lead electrocardiogram recorded every minute. All patients underwent the examinations in the research protocol, and no side effects occurred during these procedures.

Table 1: Demographic and clinical characteristics of 41 patients.

Variable	Value
Age (years)	54 ±10.8
Men	34 (82.9%)
Previous coronary angioplasty	0
Previous coronary bypass	0
Hypertension (*n*)	26 (63.4%)
Diabetes mellitus (*n*)	15 (36.6%)
Smokers (*n*)	28 (68.3%)
AMI	30
ACS	11
Diseased arteries	44
Left anterior descending	22 (50.0%)
Left circumflex coronary artery	7 (15.9%)
Right coronary artery	15 (34.1%)
Single-vessel disease	28
Multivessel disease	8
TIMI flow of diseased arteries before PCI <3	40 (90.9%)
TIMI flow of diseased arteries after PCI <3	0
Left ventricular ejection fraction (%)	47 ± 5
Left ventricular end diastolic volume (mL)	129 ± 41
Left ventricular end systolic volume (mL)	66 ± 32

Data presented as mean ± SD, unless otherwise noted; data in parentheses are percentages.
TIMI: thrombolysis in myocardial infarction; AMI: acute myocardial infarction; ACS: acute coronary syndrome.

2.4. Echocardiographic Image Acquisition. Echocardiography was performed within 48 hours before PCI, using a Philips iE 33 unit with S5 sound, the transmitting and receiving frequency was 1.8 MHz and 3.6 MHz, respectively. RT-MCE was performed using the technique of power modulation with the angiographic mode, which used a combination of low (0.08) and high (1.7) mechanical indexes. After obtaining an adequate acoustic window, the depth was adjusted so that only the left ventricle filled the image sector. The gain was adjusted to the limit until we began to see tissue noise. Then the contrast agent was infused as above. When a good signal was seen in the myocardium, a high (1.7) mechanical index impulse was given to destroy the contrast agent. Soon after, a low (0.08) mechanical index of RT-MCE was switched on, the myocardial contrast replenishment was visualized. Images of the apical 2-, 3-, and 4-chamber views were acquired for up to 15 cardiac cycles after the flash sequence was obtained and stored for offline evaluation later.

2.5. Assessment of RT-MCE. The MCE data of rest and stress cine loops were transferred to an offline computer workstation for analysis using Q-Lab (version 6.0, Philips Ultrasound) and performed by two independent researchers; both blinded to the results of CAG. The myocardial segments from the apical 2-, 3- and 4-chamber views were divided into 16 segments according to the standard segmentation scheme recommended by American Society of Echocardiography (ASE) [13]. Malm's et al. method [14] was adopted on analyzing the relationship between myocardial segments and CA. There were three segments (the basal, the middle, and the apical) within each wall of the anterior, inferior in apical 2-chamber, anterior interventricular septum and post in apical 3- chamber, and lateral and post interventricular septum in apical 4- chamber. Totally, 646 segments were analyzed among 41 patients. For qualitative analysis of myocardial perfusion the visual interpretation was used considering the degree of perfusion: the uniform distribution of contrast scored 1, no uniform scored 0.5, and no visualization scored 0. The quantitative analysis region of interest (ROI, $5\,\text{mm} \times 5\,\text{mm}$) was placed in the middle of each myocardial segment by using Qlab software quantitatively analyzing the reperfusion curve of real-time acoustic radiography. The mean value of three measurements was taken for the parameters in each region (Figure 1). Plots of contrast intensity versus time were constructed and fitted to an exponential function, $y = A(1 - e - \beta t)$ [15]. The plateau of signal intensity (A) and the slope of maximum signal intensity rise (β) were measured, and the product of $A \times \beta$ was computed. Then the mean value of A, β, and $A \times \beta$ in each segment was calculated. A, β, and $A \times \beta$ represent myocardial blood volume, myocardial blood flow velocity, and myocardial blood flow, respectively. The segmental MCE parameters and their vasodilator reserves (stress-rest ratios) were recorded, named for A-reserve (stress A/rest A), β-reserve (stress β/rest β), and $A \times \beta$-reserve (stress $A \times \beta$/rest $A \times \beta$) [16].

2.6. Coronary Angiography. Selective coronary angiography on device INNOVA 2000 (GE, USA) was performed in all patients within 48 hours of the MCE. An independent experienced observer blinded to the MCE data analyzed the coronary angiograms. The coronary TIMI flow grading was expressed, using digital substation angiography, which was equipped with the function of image counting. AMI and ACS results underwent TIMI flow grading according to TIMI study group [2].

2.7. Reproducibility of the Measurements. The visual interpretation scoring and quantitative assessment of blood flow parameters were conducted by two doctors blindly. We randomly selected 50 segments of the patients to assess the inter- and intra-observer agreement.

2.8. Statistical Analysis. Categorical variables were expressed as number (%) of myocardial segments and quantitative variables as mean ± standard deviation (SD). The comparisons for categorical data were performed by Wilcoxon signed ranks test and consistency test by *Kappa*. Univariate ANOVA or Welch tests that are similar to ANOVA were used for quantitative data. The Dunnett's *T3* test was used for comparison between any two groups [17]. Spearman-rank correlation was used to analyze the correlation between visual interpretation perfusion score, perfusion parameters and TIMI flow grade. Inter- and intra-observer reproducibility of ordered variables agreement was assessed by *Kappa* [18]. For quantitative variables, interclass correlation coefficient (ICC) was used with reproducibility considered perfect if the ICC was between 0.81 and 1.0. The statistical analysis was done using the Statistical Package for Social Sciences, version 13.0 for windows (SPSS, Inc., Chicago, IL, USA). All results were considered to be statistically significant when the P value was less than 0.05.

3. Results

3.1. Coronary Angiography. From 41 patients that underwent coronary angiography, 36 were elected for PCI, 28 had single-vessel disease, and 8 were multivessel. The blood flow of coronary artery was determined by the TIMI flow grade classification. There are 8 vessels in TIMI flow grade 0. There are 12 vessels in TIMI flow grade 1. There are 20 vessels in TIMI flow grade 2. There are 4 vessels in TIMI flow grade 3. All the diseases arteries (36 patients) had stents implanted with the blood flow of each reached 3 in TIMI flow grade after PCI.

3.2. RT-MCE Assessments before PCI. In the 41 patients, 123 vessels were selected. A total of 656 myocardial segments from the apical 2-, 3-, and 4-chamber views were imaged. 89 non-analyzable segments comprising 41 basal segments. 567 segments were analyzable and had clear images being used for MCE qualitative and quantitative analysis at rest and at stress. 271 segments were fed by the diseased arteries, in which 198 by LAD, 28 by LCx and 45 by RCA.

3.3. Visual Interpretation (Qualitative Analysis). The number of myocardial segments analysed by MCE in each TIMI flow grade were shown in Tables 2 and 3 (rest and stress). There was a positive correlation between MCE and TIMI flow grade ($rs = 0.691$, P values <0.001) at rest. There was a positive correlation between MCE and TIMI flow grade ($rs = 0.738$, P values <0.001) at stress. On diagnosing myocardial perfusion abnormality, MCE at rest and at stress had a high degree of agreement comparing with TIMI flow grade (*Kappa* = 0.687, P values <0.001) and (*Kappa* = 0.827, P values <0.001).

3.4. Quantitative RT-MCE Assessment. The results of myocardial perfusion parameters (A, β, and $A \times \beta$) before PCI at rest and at stress were shown in Table 4.

The differences in A, β, and $A \times \beta$ values at rest between any of two groups were different and statistically significant ($W = 382.13$, 192.61, and 450.96 resp., P values <0.001). These results also apply to the stress group ($W = 499.64$, 318.15, and 601.17 resp., P values <0.001). A, β, and $A \times \beta$

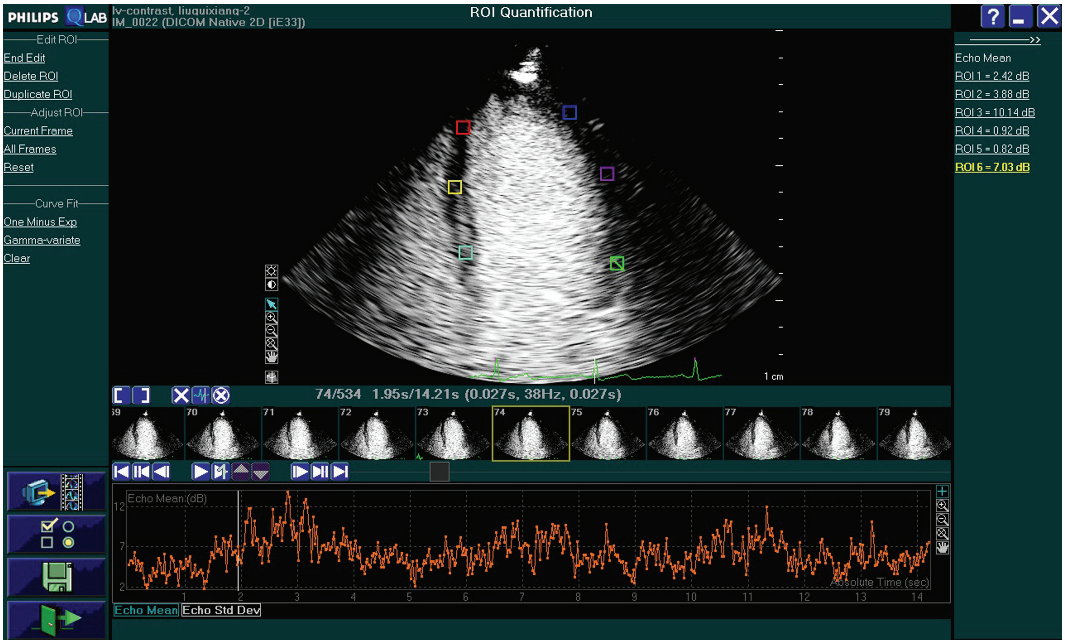

Figure 1: Region of interest (ROI, 5 mm × 5 mm) was placed in the middle of the six myocardial segments, and the ROI was tracked manually to assure its center position in each segment. The reperfusion curves of acoustic contrast intensity versus time were constructed automatically with QLab software. The specific values of signal intensity peak (A), the slope of slope of curve (β), and perfusion volume ($A \times \beta$) were acquired.

Table 2: MCE visual interpretation at rest among TIMI flow grades before PCI n (%).

MCE visual interpretation	TIMI flow grades			
	Grade 0	Grade 1	Grade 2	Grade 3
0	31 (64.6)	9 (11.7)	8 (6.7)	9 (2.8)
0.5	10 (20.8)	46 (59.7)	38 (31.9)	42 (13.0)
1	7 (14.6)	22 (28.6)	73 (61.3)	272 (84.2)
Total	48	77	119	323

TIMI: thrombolysis in myocardial infarction trial; PCI: percutaneous coronary intervention.
MCE visual interpretation at rest and TIMI flow grade correlated positively, $rs = 0.691$, $P < .001$.
PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction trial.
Grades 0, 1, and 2 were abnormal, grade 3 was normal for TIMI grade. MCE Visual Interpretation 0 and 0.5 were abnormal, and 1 was normal for MCE Visual Interpretation.
On diagnosing myocardial perfusion abnormality TIMI flow grade and MCE Visual Interpretation at rest had a high degree of agreement, *Kappa* = .687, $P < .001$.

Table 3: MCE visual interpretation among at stress TIMI flow grades before PCI n (%).

MCE visual interpretation	TIMI flow grades			
	Grade 0	Grade 1	Grade 2	Grade 3
0	41 (85.4)	26 (33.8)	14 (11.8)	10 (3.1)
0.5	6 (12.5)	44 (57.1)	56 (47.1)	44 (13.6)
1	1 (2.1)	7 (9.1)	49 (41.2)	269 (83.3)
Total	48	77	119	323

TIMI, thrombolysis in myocardial infarction trial; PCI, percutaneous coronary intervention.
MCE Visual Interpretation at stress and TIMI flow grade correlated positively, $rs = 0.738$, $P < .001$.
PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction trial.
Grades 0, 1, and 2 were abnormal, grade 3 was normal for TIMI grade. MCE Visual Interpretation 0 and 0.5 were abnormal, and 1 was normal for MCE Visual Interpretation.
On diagnosing myocardial perfusion abnormality TIMI flow grade and MCE Visual Interpretation at stress had a completely consistent, *Kappa* = .827, $P < .001$.

values at rest and at stress increased linearly with the TIMI flow grading, and the means of the parameters correlated with TIMI flow grade ($rs = 0.741$, 0.528, and 0.715 for A, β, and $A \times \beta$, P values <0.001, and $rs = 0.872$, 0.767 and 0.845 for A, β, and $A \times \beta$, P values <0.001, resp.).

If one considers TIMI grade <1 is abnormal, MCE Visual Interpretation (at rest/at stress) had 72.0%/65.5% accuracy with 85.4%/97.9% sensitivity and 70.7%/62.6% specificity respectively. If one considers TIMI grade <2 is abnormal, MCE Visual Interpretation (at rest/at stress) had 77.7%/76.7% accuracy with 76.8%/93.6% sensitivity and 78.1%/71.9% specificity, respectively. If one considers TIMI grade <3 is abnormal, MCE Visual Interpretation (at rest/at stress) had 73.1%/80.4% accuracy with 58.2%/76.6% sensitivity and 84.2%/83.3% specificity, respectively (see Table 5).

The correlation between the trend of A-reserve, β-reserve, $A \times \beta$-reserve, and TIMI grade are shown in Figure 2.

3.5. Reproducibility of the Measurements. For MCE visual interpretation, a high degree of intraobserver agreement (*Kappa* = 0.79, $P = 0.08$) and interobserver agreement

Table 4: Comparison of myocardial perfusion parameters at rest and stress among TIMI flow grades.

Myocardial perfusion parameters	TIMI flow grades					
	Grade 0	Grade 1	Grade 2	Grade 3	W^*	P
A (db):						
rest	$1.06 \pm 0.02^{*\S\dagger}$	$3.17 \pm 0.08^{*\S}$	$4.49 \pm 0.32^{*}$	5.29 ± 0.47	382.13	.000
stress	$1.01 \pm 0.06^{*\S\dagger}$	$3.09 \pm 0.11^{*\S}$	$4.83 \pm 0.09^{*}$	$5.71 \pm 0.53^{*}$	499.64	.000
β (s−1):						
rest	$0.13 \pm 0.02^{*\S\dagger}$	$0.17 \pm 0.03^{*\S}$	$0.24 \pm 0.03^{*}$	0.28 ± 0.01	192.61	.000
stress	$0.11 \pm 0.06^{*\S\dagger}$	$0.23 \pm 0.05^{*\S\#}$	$0.57 \pm 0.04^{*\#}$	$0.71 \pm 0.09^{*}$	318.15	.000
A × β (db/S):						
rest	$0.14 \pm 0.01^{*\S\dagger}$	$0.54 \pm 0.03^{*\S}$	$1.08 \pm 0.02^{*}$	1.39 ± 0.04	450.96	.000
stress	$0.11 \pm 0.01^{*\S\dagger}$	$0.71 \pm 0.01^{*\S\#}$	$2.75 \pm 0.09^{*\#}$	$4.05 \pm 0.11^{*}$	601.17	.000
A-reserve	$0.95 \pm 0.08^{*\S\dagger}$	$0.98 \pm 0.07^{*\S}$	$1.08 \pm 0.07^{*}$	1.09 ± 0.05	452.14	.000
β-reserve	$0.85 \pm 0.02^{*\S\dagger}$	$1.36 \pm 0.02^{*\S}$	$2.37 \pm 0.03^{*}$	2.54 ± 0.05	267.82	.000
A × β-reserve	$0.79 \pm 0.02^{*\S\dagger}$	$1.31 \pm 0.03^{*\S}$	$2.55 \pm 0.06^{*}$	3.11 ± 0.05	539.74	.000

A: indicates myocardial blood volume; β: myocardial blood flow velocity; A × β: myocardial blood flow; A-reserve: stress A/rest A; β-reserve: stress β/rest β; A × β-reserve: stress A × β/rest A × β; TIMI: thrombolysis in myocardial infarction trial.
The correlation between the means of A, β, and A × β at rest and TIMI grade reached significant ($rs = 0.741$, 0.528, and 0.715, resp., P values <.001).
The correlation between the means of A, β, and A × β at stress and TIMI grade reached significant ($rs = 0.872$, 0.767, and 0.845 for A, β, and A × β, resp., P values <.001).
$^*P < .001$ versus TIMI grade 3.
$^\S P < .001$ versus TIMI grade 2.
$^\dagger P < .001$ versus TIMI grade 1.
$^\# P < .001$ versus parameter in rest.
*Welch tests.

Table 5: Accuracy, sensitivity, and specificity of abnormal in MCE Visual Interpretation at rest and stress with different TIMI flow grades as abnormal (%).

TIMI flow grades	Accuracy	Sensitivity	Specificity
Grade <1:			
rest	72.0	85.4	70.7
stress	65.6	97.9	62.6
Grade <2:			
rest	77.7	76.8	78.1
stress	76.7	93.6	71.9
Grade <3:			
rest	73.1	58.2	84.2
stress	80.4	76.6	83.3

TIMI: thrombolysis in myocardial infarction trial.
TIMI grade <1, grade 0 was abnormal, grades 1, 2, and 3 were normal for TIMI grade. TIMI grade <2, grades 0 and 1 were abnormal, grades 2 and 3 were normal for TIMI grade. TIMI Grade <3, grades 0, 1, and 2 were abnormal, grade 3 was normal for TIMI grade.

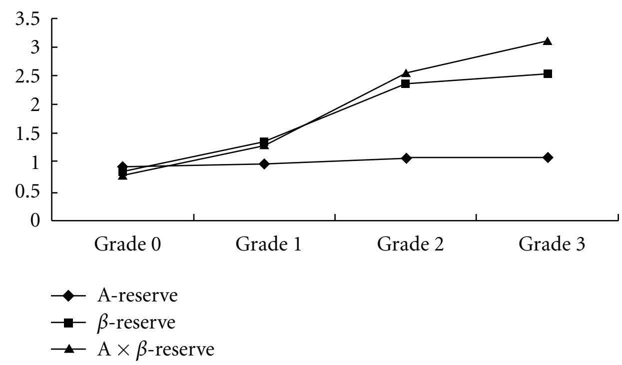

Figure 2: Trend of intergroup reserve of MEC parameters among groups of each coronary artery TIMI grade.

Table 6: Reproducibility of quantitative assessment of myocardial perfusion parameters.

	A	β	A × β
Intraobserver r_i	0.950	0.820	0.873
Interobserver r_i	0.950	0.869	0.851

($Kappa = 0.76$, $P = 0.09$) was observed. The intraobserver reproducibility of A, β, and $A \times \beta$ was perfect. The ICCs were 0.950, 0.820, and 0.873 for, A, β, and $A \times \beta$, respectively. The interobserver agreement was perfect for A, and $A \times \beta$, with ICCs being 0.950, 0.869, and 0.851 for A, β, and $A \times \beta$, respectively (Table 6).

4. Discussion

The results of visual interpretation and parametric quantification of MCE and TIMI flow grade were not totally similar and the correlation was quite different. Using MCE visual interpretation scoring method, the changes in cardiac imaging can be directly observed with unaided eyes, and the PCI preoperative microcirculation status can be preliminarily evaluated. The results of MCE visual interpretation at rest and stress had a positive correlation with TIMI flow grade. It indicated that visual interpretation could reflect myocardial perfusion and TIMI flow grade as well. However, the results of the quantitative analysis from our study expressed by the myocardial perfusion parameters (A, β, and $A \times \beta$) can directly reflect the status of blood perfusion and coronary TIMI flow grade even more accurate and precise than visual analysis.

With the help of this parametric quantification, this could overcome the limitations of visualization and part of operator dependency bias.

Malm's et al. [14] study demonstrate that the importance of quantitative assessment of RT-MCE by myocardial perfusion parameters β (velocity) and $A \times \beta$ (Volume $\times$ velocity) has more influence in prediction of coronary artery stenosis. In the mean time, study from Li et al. [19] showed that when there were no collateral circulation patencies, β, and $A \times \beta$ decreased with the aggravation of coronary artery stenosis. Through quantitative analysis of myocardial perfusion parameters, we observed that β and $A \times \beta$ value increased at rest and being more exponential at stress to TIMI flow grading level reaching at least 1–3 folds. It also indicated that perfusion injury became severe with the decrease of β value (velocity) more accentually, confirming the importance of pathophysiology of steal phenomenon from coronary artery flow, more evident at stress.

Even though TIMI flow grade and MCE focused on different ways to look at the same physiopathology, the epicardical coronary tree flow had a great concordance with myocardial flow measured by MCE, inferring that in acute patients TIMI's grading still has a good accuracy as a perfusion-deficit predictor. However, there were two patients where TIMI grade was abnormal and MCE was normal, possibly because collateral microcirculation takes place in those patients. There were no data that supports a conservative treatment for then, despite clinical evidence that percutaneous interventions without myocardial ischemia leads to a worst prognostic tendency [20, 21].

For the ACS patients screening before PCI, the MCE technique could raise more necessary evidence for clinician in evaluating the status of myocardial perfusion give the data of possible improvements of preoperative myocardial microvascular perfusion and also filtering case for correct treatment choice.

In conclusion, MCE parametric quantification had a positively correlation with TIMI flow grading and can qualitatively and quantitatively assess the myocardial perfusion more accurately than the visual one. The technique of MCE can work as a beneficial tool aiding before coronary angiography to predict TIMI risk and help clinical decision.

5. Limitations

The limitations of the study include no data about MCE side effects and the level of acceptability by the patients and the absent of traditional perfusion gold standards, like fractional flow reserve (FFR) or Rubidium nuclear imaging.

The improvements of the myocardial perfusion has not been further investigated by conducting follow-up visits 3–6 months after the surgery, which will be improved in the future studies.

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