Assessment of No-Reflow Phenomenon by Myocardial Blush Grade and Pulsed Wave Tissue Doppler Imaging in Patients with Acute Coronary Syndrome

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ABSTRACT

Background: No-reflow phenomenon is a complication of myocardial revascularization and it is associated with a worse prognosis. Materials and Methods: A prospective study was carried out enrolling patients with acute myocardial infarction (64 patients, 49 male and 15 female, median age 64.9 ± 10.61 years), both STEMI and NSTEMI, who underwent myocardial revascularization with percutaneous coronary intervention (PCI). TIMI flow and Myocardial Blush Grade (MBG) were assessed at baseline (T0), in addition to tissue Doppler imaging (TDI) and electrocardiogram. Cardiological evaluation was also performed at T1 (one month after PCI) and T2 (every year after revascularization for a mean follow-up of 24.9 months ± 6.93 months). Patients were divided into two groups on the basis of MBG. Results: In the present study, we found at T1 a significant association between MBG and dyslipidemia (P = 0.038) and NYHA class and MBG (P = 0.040), among clinical variables and cardiovascular risk factors. Moreover, a statistically significant relationship was observed between MBG and a new echocardiographic index of systolic and diastolic dysfunction, the EAS index measured with tissue Doppler imaging (P = 0.013). At T2, the EAS parameter was also significantly impaired in patients with reduced MBG, compared to patients with normal MBG (P = 0.003). Conclusions: This study demonstrates that the combined evaluation of systolic and diastolic dysfunction by EAS index, according to the literature, could detect a subclinical ventricular dysfunction due to a perfusion defect. Therefore, EAS index could be a useful parameter to be measured in the follow-up of patients undergoing revascularization.

Key Words: Acute myocardial infarction, myocardial perfusion, myocardial blush grade, no reflow, tissue doppler imaging

INTRODUCTION

Coronary recanalization does not always lead to effective myocardial tissue reperfusion: This phenomenon is known as no-reflow.[1] No-reflow is associated with poor prognosis, being related to adverse left ventricular remodeling, heart failure, and an increased risk of arrhythmias and mortality.[2] Therefore, it is very important to identify and prevent this phenomenon. The aim of our study was to investigate whether Tissue Doppler Imaging (TDI), classically used to study systolic and diastolic function, could give indirect information about myocardial perfusion assessed by Myocardial Blush Grade (MBG) as reference method. We also wanted to assess if the data obtained from TDI provide prognostic information.

MATERIALS AND METHODS

Characteristics of patients

This study was designed and conducted as a prospective study, enrolling patients with acute myocardial infarction (AMI), both ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction. All patients were classified as AMI based on the typical electrocardiographic and clinical features. The study flowchart is depicted in Figure 1. The study was approved by the institutional review board, and all patients provided written informed consent.

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(NSTEMI) (64 patients, 49 males and 15 females; mean age 64.9 ± 10.61 years), subjected to myocardial revascularization with percutaneous coronary intervention (PCI). The most common cardiovascular risk factors in this population were hypertension, dyslipidemia, family history, and smoking [Table 1]. Inclusion criteria were: A typical chest pain lasting ≥30 minutes in medical history, ST-segment elevation >0.2 mV in at least two contiguous leads, or ST-segment depression of at least 1 mV or T inversion in at least two leads; TIMI flow grade 0 or 1 of the culprit vessel in the baseline angiogram; treatment with primary PCI for STEMI patients or urgent/early invasive strategy for NSTEMI patients; successful epicardial reperfusion assessed by TIMI flow grade 2 (suboptimal result) and 3 (optimal result). Patients with inadequate acoustic window were excluded. Myocardial reperfusion was performed in all patients at baseline (T0) in agreement with the recent ESC guidelines. [3,4] Coronary flow and microvascular perfusion (TIMI and MBG) were assessed during coronary angiography at baseline in addition to ECG and echocardiogram. We defined the basal TIMI before PCI, according to the TIMI group grading system. [5] After revascularization, we re-evaluated the final TIMI: An optimal procedural success was defined as TIMI-3 flow in the culprit vessel, while suboptimal result was defined as TIMI-2. At the end of the angiography, MBG was assessed according to Van’t Hof and Gibson’s methods. [6,7] MBG ≥2 was considered as normal; MBG ≤1 was considered as reduced. According to MBG, patients were divided into two groups, those with normal blush (A group) and those with reduced blush (B group). Clinical and echocardiographic variables and adverse cardiovascular events were related to the myocardial blush categories. Furthermore, cardiological evaluation including ECG and transthoracic echocardiography with tissue Doppler imaging was made one month (T1) and every year (T2) after revascularization for a mean follow-up of 24.9 months ± 6.93 months. Table 2 and Table 3 describe the angiographic and echocardiographic data at T0. Adverse cardiac events (such as reinfarction, need of new revascularization procedures, and new onset/worsening signs or symptoms of heart failure) were assessed during follow-up. Before revascularization, all patients received lysine acetylsalicylate 250 mg i.v., an initial bolus of unfractionated heparin 70 U/kg (or low-molecular-weight heparin s.c., or fondaparinux, for NSTEMI patients), and additional boluses during the procedure in order to achieve aPTT values <250 s; clopidogrel loading dose of 300 or 600 mg orally, or ticagrelor 180 mg, or prasugrel 60 mg; GP IIB/IIIa inhibitors according to clinical, laboratory, and instrumental characteristics of patients. Furthermore, after the acute phase, patients received clopidogrel 75 mg/day, ticagrelor 90 mg b.i.d., or prasugrel 10 mg for 12 months and aspirin 100 mg/day indefinitely. Standard echocardiographic evaluation with TDI was performed in all patients. Systolic and diastolic parameters of cardiac function were assessed. We measured left ventricular ejection fraction (LVEF) by a modified biplane Simpson’s method, chamber dimensions, peak early filling (E-wave) and late diastolic filling (A-wave) velocities, the E/A ratio, and deceleration time (DT) of early filling velocity using the apical view to record the mitral inflow pattern. Peak systolic velocity (S-wave), early diastolic (E’-wave) and late diastolic (A’-wave) velocities were measured by placing a sample volume at the septal side of the mitral annulus with TDI. We also calculated the ratios E/E’ and E’/A’.

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Table 1: Baseline characteristics of the study population

| Characteristic          | Study sample (n = 64) |
|-------------------------|-----------------------|
| Age (Mean±SD)           | 64.9±10.61            |
| Male, n (%)             | 49 (76.6)             |
| STEMI, n (%)            | 37 (57.8)             |
| NSTEMI, n (%)           | 27 (42.2)             |
| Smoking, n (%)          | 21 (32.8)             |
| Dyslipidemia, n (%)     | 37 (57.8)             |
| Diabetes mellitus, n (%)| 13 (20.3)             |
| Family history, n (%)   | 23 (35.9)             |
| Hypertension, n (%)     | 49 (76.6)             |
| Obesity, n (%)          | 18 (28.1)             |

Table 2: Angiographic characteristics of the study population

| Characteristic         | Value          |
|------------------------|----------------|
| LAD as culprit vessel (%) | 54.69          |
| Cx as culprit vessel (%)        | 17.19          |
| RCA as culprit vessel (%)        | 28.13          |
| MBG in LAD (Mean±SD)    | 1.69±0.60      |
| MBG in Cx (Mean±SD)     | 1.60±0.69      |
| MBG in RCA (Mean±SD)    | 1.83±0.65      |
| 1-vessel CAD (%)        | 65.63          |
| 2-vessel CAD (%)        | 26.56          |
| 3-vessel CAD (%)        | 7.81           |

LAD = Left anterior descending artery, Cx = Circumflex artery, RCA = Right coronary artery, CAD = Coronary artery disease.

Table 3: Echocardiographic parameters of the study population

| Parameter       | Mean ± SD          |
|-----------------|--------------------|
| LVEDV (ml)      | 90.72±15.76        |
| LVEF (%)        | 53.17±7.41         |
| E/A             | 1.03±0.4           |
| E/E’            | 10.29±4.73         |
| E-wave (cm/s)   | 7.94±2.78          |
| A’-wave (cm/s)  | 10.20±2.37         |
| S-wave (cm/s)   | 8.23±1.77          |
| EAS index       | 0.10±0.05          |

LVEDV = Left ventricular end-diastolic volume.
(A’ × S) (EAS index) as measures of LV filling pressures and systo-diastolic function, respectively. The S-wave was considered as normal if ≥8 cm/s and pathological if <8 cm/s. According to guidelines,[8] diastolic dysfunction was defined as follows:

1. Grade I (mild diastolic dysfunction): E/A ratio is <0.8, DT is >200 ms, IVRT is ≥100 ms, annular E’ is <8 cm/s and E/E’ ratio is <8 (septal and lateral);
2. Grade II (moderate diastolic dysfunction): E/A ratio is 0.8-1.5 (pseudonormal) and decreases by ≥50% during the Valsalva maneuver, E/E’ (average) ratio is 9-14, and E’ is <8 cm/s;
3. Grade III (severe diastolic dysfunction): E/A ratio is ≥2, DT is <160 ms, IVRT is ≤60 ms and septal E/E’ is ≥15 (average).

An E/E’ ratio ≤8 suggested normal LV filling pressures, whereas patients with E/E’ ≥15 were classified as having elevated filling pressures. In the range of E/E’ of 9-14, adjunctive measurements were applied.[8] EAS index was measured as ratio of E’/(A’ × S). It is an index of combined systolic and diastolic function. There are still no cut-off parameters in literature for this ratio.

### Statistical analysis

Continuous variables were expressed as mean ± SD and Student’s t-test was used to compare variables between the two groups (normal MBG and reduced MBG). On the other hand, categorical variables were expressed as percentages and were analyzed using the chi-square (χ²) test. Statistical analyses were performed with MedCalc software. Multiple regression was used to detect the variables independently associated with reduced MBG. The correlation between data was calculated using Pearson’s correlation coefficient. A P < 0.05 was considered statistically significant.

### RESULTS

In our study, after PCI, a normal MBG was found in 43 (67.2%) of 64 patients (A group), while 21 (32.8%) showed a reduced MBG (B group). The relationship between MBG and clinical variables, and between MBG and echocardiographic variables at 1 month (T1) is showed in Table 4. Among clinical variables and cardiovascular risk factors, dyslipidemia and New York Heart Association (NYHA) class showed an association with MBG. In particular, there was a statistically significant difference between dyslipidemic patients with normal MBG (n = 21/43) and dyslipidemic patients with reduced MBG (n = 16/21, P = 0.038). Similarly, a statistically significant difference was found between patients with NYHA class >1 and normal MBG (n = 19/43) and in patients with NYHA class >1 and reduced MBG (n = 15/21, P = 0.040). The mean ejection fraction of the study population was preserved.

Among echocardiographic parameters, a statistically significant relationship was observed between MBG and systo-diastolic dysfunction, measured by a new echocardiographic parameter, the EAS index (P = 0.013). In addition, 40 patients (30 patients with normal MBG and 10 with reduced MBG) were evaluated during a mean follow-up of 24.9 months ± 6.93 months. The following adverse cardiovascular events were described: Four reinfarctions and need of new revascularization procedures in four cases. We also assessed the relationship between MBG and clinical variables and between MBG and echocardiographic variables during the midterm follow-up as shown in Table 5. Patients with reduced MBG did not show more adverse events than patients with normal blush, although a trend toward significance (P = 0.068) was observed. During the follow up, patients with reduced MBG continued to have statistically significant lower EAS values (P = 0.003). Pearson’s correlation coefficient showed a significant association between EAS index and MBG. Specifically, MBG worsened as EAS index increased (r = −0.356, P = 0.028).

### DISCUSSION

Over the years, considerable efforts have been made to improve the outcome of patients with acute coronary syndrome (ACS). The primary aim of reperfusion therapy is not only the restoration of blood flow in the
epicardial coronary artery but also the complete and sustained reperfusion of myocardial tissue, thus limiting the extension of myocardial necrosis.\[9\] In this category of patients, the rapid recognition of symptoms and timely access to revascularization do not always achieve an effective reperfusion, a condition known as no-reflow.\[1\] This term refers to a microvascular obstruction and reduced myocardial flow after opening an occluded artery, because of microcirculatory injury.\[10\] The proportion of patients who receive an optimal myocardial reperfusion after PCI is approximately 35%.\[11\] Several studies have shown that no-reflow has a strong negative prognostic impact, thus negating the potential benefit of PCI.\[2,9\] Indeed, patients with no-reflow show a higher prevalence of post-infarction complications (e.g., arrhythmias, pericardial effusion, cardiac tamponade, early congestive heart failure), adverse LV remodeling, and mortality.\[2\] Therefore, it is important to know and prevent this phenomenon. Despite the well-established diagnostic accuracy of myocardial contrast echocardiography (MCE) in the assessment of myocardial perfusion, MBG is still widely used in clinical practice. MBG is an index that evaluates the opacification of coronary microcirculation and its clearance after a contrast injection. As known from literature data, MBG is a predictor of adverse prognosis and it has a strong negative impact on outcome: In a population of 777 patients, Van’t Hof et al. have demonstrated that MBG assessed immediately after PCI is related to the infarct size and predicts LV function and long-term mortality.\[11\] Other studies have shown that despite TIMI 3 flow restoration in the infarct-related artery (IRA), patients with MBG 0-1 had a higher risk of LV remodeling at 6 months than patients with effective myocardial reperfusion (MBG 2-3).\[12,13\]

Furthermore, a reduced MBG was significantly associated with the development of symptoms of heart failure and cardiovascular adverse events.\[14\] In our study, patients with reduced MBG did not show a higher rate of adverse events than patients with normal MBG, although a trend toward significance was observed probably because of the small sample size. The enrolment of a larger number of patients would maybe confirm the literature. Because of the well-known prognostic implications, an evaluation of MBG is needed in patients with ACS undergoing revascularization. In our study, we found a relationship between MBG and EAS index measured by TDI at the site of mitral annulus. Pulsed Wave (PW) TDI is characterized by easy accessibility and reproducibility, and it is widely used and validated in literature to study cardiac function by analyzing myocardial velocities.\[15,16\] Assuming that a perfusion defect results in subclinical systolic or diastolic dysfunction, measurement of TDI parameters E’, A’, and S-waves could provide indirect information about myocardial perfusion.

Previous studies have only partly stressed the relationship between the non-invasive echocardiographic approach and MBG as an invasive method for estimating myocardial perfusion. In 2008, Streb et al. compared the values of MCE, MBG, and TDI in the assessment of micro circulation in 39 patients with first AMI of the anterior wall, whereas none of the MCE parameters showed significant correlation with perfusion assessed by MBG. On the other hand, the presence of impaired contractile function by TDI better reflected myocardial perfusion than MCE did.\[17\] In patients with MBG 0-1 who underwent left anterior descending (LAD) artery revascularization after AMI, Abdel-Wahab et al. demonstrated a significant deterioration of systolic TDI parameters in the infarct-related segments at the mitral annular level.\[18\] EAS is a new index derived from TDI that reflects combined systolic and diastolic performances. It is known that S-wave reduction provides information on impaired cardiac function and increased E'/A' ratio is associated with increased mortality. LV dysfunction assessed by a combined index (EAS index) of systolic and diastolic performances is an independent predictor of death in the general population, and it is superior to other echocardiographic parameters.\[19\] Recently, in patients with significant LV dysfunction, EAS index has been considered as an independent predictor of NYHA functional class, and it has been also associated with cardiac mortality and hospitalization for heart failure.\[20\]

In our study, we did not observe a significant association either between MBG and systolic function assessed by S-wave or between MBG and diastolic function evaluated by E’-wave and E/A ratio. However, the combined

### Table 5: MBG analysis, clinical and echocardiographic variables during the medium-term follow-up

| Parameters                  | Normal MBG (n = 30) (%) | Reduced MBG (n = 10) (%) | P-value |
|-----------------------------|-------------------------|--------------------------|---------|
| Family history              | 36.67                   | 20                       | 0.329   |
| Smoking                     | 33.33                   | 40                       | 0.702   |
| Hypertension                | 80                      | 80                       | 1.00    |
| Diabetes mellitus           | 23.33                   | 20                       | 0.827   |
| Obesity                     | 40                      | 20                       | 0.251   |
| Dyslipidemia                | 50                      | 70                       | 0.271   |
| NYHA class                  | 56.67                   | 50                       | 0.714   |
| Adverse events              | 13.33                   | 40                       | 0.068   |
| LVEDV (ml)                  | 98.07±32.89             | 89.20±11.58              | 0.215   |
| LVEF (%)                    | 52.53±8.26              | 49.8±6.25                | 0.284   |
| E’-wave (cm/s)              | 9.69±2.21               | 9.00±1.41                | 0.266   |
| A’-wave (cm/s)              | 11.82±2.55              | 13.4±1.78                | 0.043   |
| S-wave (cm/s)               | 10.38±2.13              | 10.90±1.37               | 0.383   |
| E/A                         | 0.91±0.34               | 0.85±0.31                | 0.835   |
| E‘/E’                       | 7.39±1.88               | 7.71±2.42                | 0.714   |
| EAS index                   | 0.08±0.03               | 0.06±0.01                | 0.003   |
measurement of systolic and diastolic dysfunction by EAS index showed that this parameter was significantly impaired in patients with reduced MBG compared to that in those with normal blush with either a monthly or a medium term follow-up. Our study does not claim to identify an index of impaired regional perfusion in EAS but rather a sensitive parameter that could unmask a precocious myocardial dysfunction that could be related to perfusion defects in patients who underwent revascularization. The advantages of this parameter are that it is very simple, it is derived from transmitral Doppler and tissue Doppler at the site of mitral annulus, and it does not require specific software and new generation equipments that are not often widely available. However, like all Doppler-derived techniques, it is influenced by angle dependence and therefore, it could not provide regional information.

Limitations

The most important limitation of this study is its small sample size. Therefore, larger studies are needed to validate our results. Moreover, we included patients with AMI in different sites. As a result, the study population is not homogeneous. Furthermore, we are conscious that EAS index is a global index of cardiac function and therefore, it cannot provide regional information about perfusion but it unmasks a precocious systo-diastolic myocardial suffering.

CONCLUSIONS

In our study, a significant relationship was found between EAS index and MBG. Thus, EAS index could be used to suspect perfusion defect in patients who underwent revascularization, although this is an index of global systo-diastolic function and does not provide regional information. Moreover, it could be speculated the utility of this index in patients with cardiovascular risk factors and unknown coronary artery disease. This procedure could also be useful in case of chest pain, unmodified ECG, and normal levels of cardiac biomarkers. To confirm our data, further studies are needed.

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