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Incidence and Predictors of Reperfusion Arrhythmia on STEMI Patients and Its Association with Infarct and Reperfusion Therapy Factors: A Cross-Sectional Study

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A B S T R A C T

Reperfusion arrhythmia was one of the markers of reperfusion in acute myocardial infarction (AMI). However, as the study developed, there were controversial findings of the meaning of reperfusion arrhythmias as a marker of successful reperfusion or persistent ischemia. The study aims to analyze the occurrence of arrhythmia in patients with STEMI undergoing reperfusion therapy with primary PCI or thrombolytic at Dr. Soetomo General Hospital Surabaya. This study is a retrospective observational study with a cross-sectional design using medical records as a data source. The occurrence of arrhythmias in patients was observed within 24 hours after the reperfusion therapy procedure. A total of 82 STEMI patients undergoing reperfusion therapy were observed (78 primary PCI and 4 thrombolytic). The total rate of reperfusion arrhythmia beyond the first 24 hours after the procedure was 54.9% (n = 45). There was no significant association for the baseline clinical characteristics of patients with the risk of reperfusion arrhythmia except for the heart rate on admission (p-value=0.003). The choice of reperfusion therapy (thrombolytic or PPCI) and time to revascularization were also not significantly associated with the occurrence of arrhythmias. Infarct characteristics, including the location and the number of blood vessels diseased, also did not have a significant relationship with the incidence of arrhythmias. Reperfusion therapy remains, resulting in a higher incidence of reperfusion arrhythmias. The incidence of reperfusion arrhythmias may be influenced by various factors. Thus, close monitoring beyond the first 24 hours after reperfusion therapy is required.

1. Introduction

ST-segment elevation myocardial infarction (STEMI) is an indicator of total occlusion of coronary arteries. Therefore, according to the guidelines for the management of acute coronary syndrome (ACS) from the Indonesian Heart Association, reperfusion or revascularization is highly indicated to restore myocardial blood flow immediately.[1] There are two options for reperfusion therapy for STEMI cases, with thrombolytic agents or mechanically using primary percutaneous coronary intervention (PPCI). Previously, reperfusion arrhythmias were thought to be one of the indicators for successful revascularization in acute myocardial infarction. The incidence of reperfusion arrhythmias has the highest frequency occurring within 24 hours of reperfusion

therapy.[2] However, controversy remains as to whether arrhythmias are a sign of successful reperfusion or a sign of ongoing myocardial cell damage and ischemia.[2–4] More importantly, another study found that arrhythmias that occurred 24 hours after the reperfusion procedure were associated with an increase in patient mortality during hospitalization.[5] Much less is known about the incidence and predictors of reperfusion arrhythmia occurring in patients with STEMI undergoing reperfusion therapy. Therefore, to have a better understanding of the occurrence of reperfusion arrhythmias, this study observes and evaluates the incidence and predictors of reperfusion arrhythmias within 24 hours of reperfusion therapy with either the primary PCI method or the thrombolytic method.

2. Methods

The study was performed cross-sectionally based on the patient's medical records from Dr. Soetomo General Hospital, Surabaya, Indonesia, between January 1st, 2019, and December 31st, 2019. The ethical review committee at Dr. Soetomo General Hospital Surabaya has approved the study. This study population included patients undergoing reperfusion therapy with thrombolytic or primary PCI for acute STEMI. All the patients diagnosed with STEMI who underwent thrombolytic therapy or primary PCI with a time from symptom onset to reperfusion therapy of less than 12 hours were included using the non-probability consecutive sampling technique. Patients with only conservative therapy (non-reperfused), patients with arrhythmia nor cardiac conduction system disorders before reperfusion therapy, patients who underwent cardiac arrest as a result of acute myocardial infarction, patients admitted with cardiogenic shock, and patients with failed thrombolytic and underwent rescue PCI were excluded from the study. Data elements, including patient age, gender, height, weight, blood pressure, heart rate, diabetes mellitus, hypertension, history of previous MI, smoking, ECG, blood glucose, urea, potassium values, type of reperfusion therapy, symptom onset time-to-reperfusion, location of STEMI, and a number of the diseased vessels were recorded. In this study, thrombolytic therapy was administered to four patients within 12 hours from the onset of symptoms using Streptokinase 1.5 IU between 30-60 minutes. The symptom onset to reperfusion time is defined as the time interval between the patient's first onset of symptoms and the start of the reperfusion procedure (thrombolytic therapy or primary PCI). STEMI localization was determined by the ECG interpretation, while the number of diseased vessels was obtained from coronary angiography records.

Early coronary angiography was performed on all patients except for four of the 82 patients who did not undergo coronary angiography because the patients received thrombolytic therapy and did not accept the coronary angiography procedure. The occurrence of arrhythmia was observed within 24 hours of the reperfusion procedure. The data was performed using a statistical package for the social sciences (SPSS) version 24 (IBM Corp., Armonk, NY). Numerical data obtained from the study were expressed as mean ± standard deviation. Categorical data were presented as percentages (%). The association between the two study groups was analyzed using the Chi-square or Fisher exact test for categorical data and the student's T-test or Mann–Whitney U test for numerical data. In all comparisons, $p < 0.05$ was considered statistically significant.

3. Results and Discussion

A total of 82 STEMI patients who underwent reperfusion therapy were enrolled in this study, and 45 (54.9%) had reperfusion arrhythmia within 24 hours after the procedure. The baseline characteristics of the subjects according to the occurrence of reperfusion arrhythmia are shown in Table 1. Most of the patients were males (79.3%), while the mean age of the patients was 53.8 years and did not differ

between groups. 39% of patients had diabetes mellitus, 48.8% had hypertension, 8.6% had a history of coronary artery disease (CAD), and 47.9% were smokers. At the time of admission, the mean systolic blood pressure of the patients was 126.6 ±24.5 mmHg. The mean heart rate of the patients was 86.9 ±17.7 beats/min, and patients with reperfusion arrhythmia had a lower heart rate (82.1 ± 16.4 beats/min vs 92.8 ± 17.6 beats/min, P < 0.05). The mean blood glucose level was 203±103.9mg/dL. The mean blood urea was 15.2±6.7 mg/dL, and the mean potassium value was 4.0±0.5 mmol/L.

The frequency distribution of reperfusion arrhythmia between procedures is presented in Figure 1. Reperfusion arrhythmia developed more commonly in patients undergoing rescue percutaneous coronary intervention than in patients who underwent thrombolytic (P=1.000). Table 2 presents the procedural details of the study. Timelines of procedure, including symptom onset to all procedures, symptom onset to thrombolytic, and symptom onset to PPCI, did not differ between groups. Table 3 shows the infarct-related characteristics of this study. Based on the ECG findings, there was no significant difference in the localization of STEMI, yet the involvement of the posterior wall was found to dominate the location of STEMI. There was no significant difference in the number of diseased vessels in those with and without reperfusion arrhythmia, but the occurrence of triple vessel disease was found more commonly in patients with reperfusion arrhythmia.

Table 1. Baseline characteristics of the subjects (n = 82).

	All patients (n = 82)	**Reperfusion arrhythmia (n = 45)**	**No reperfusion arrhythmia (n = 37)**	**p-value**
Male, n(%)	65 (79.3)	37 (82.2)	28 (75.7)	0.650
Age (y), mean ± SD	53.8 ± 10.4	52.3 ± 9.8	55.7 ± 10.9	0.137
Medical history, n (%):				
Diabetes mellitus	32 (39.0)	19 (42.2)	13 (35.1)	0.669
Hypertension	40 (48.8)	23 (51.1)	17 (45.9)	0.808
Hyperlipidemia	10 (12.2)	4 (8.9)	6 (16.2)	0.335*
Previous stroke	3 (3.7)	0	3 (8.1)	0.088*
Coronary artery disease	7 (8.6)	6 (15.4)	1 (0.03)	0.121*
Current smoker	39 (47.6)	24 (53.3)	15 (40.5)	0.351
Kidney disease	3 (3.7)	1 (2.2)	2 (5.4)	0.586*
Clinical presentation, mean ± SD				
Systolic blood pressure (mmhg)	126.6 ± 24.5	123.1 ± 26.8	130.1 ± 20.1	0.153
Heart rate (beats/min)	86.9 ± 17.7	82.1 ± 16.4	92.8 ± 17.6	0.003**
Respiratory rate	20.9 ± 2.6	20.84 ± 2.7	21 ± 2.4	0.794**
Temperature (°C)	36.4 ± 0.4	36.4 ± 0.3	36.4 ± 0.4	0.322**
Laboratory, mean ± SD:				
Blood glucose (mg/dL)	203.7 ± 103.9	212.1 ± 111.1	193.4 ± 94.9	0.493**
BUN (mg/dL)	15.2 ± 6.7	15 ± 7.4	15.4 ± 5.7	0.435**
Potassium (mmol/L)	4.0 ± 0.5	4.0 ± 0.6	4.0 ± 0.5	0.812**
Creatinine level (mg/dL)	1.2 ± 0.5	1.2 ± 0.6	1.2 ± 0.4	0.586**

Categorical data was analyzed using the Continuity Correction Chi-Square test and *Fisher Exact Chi-Square, and numerical data was analyzed using Independent T-test and **Mann Whitney.

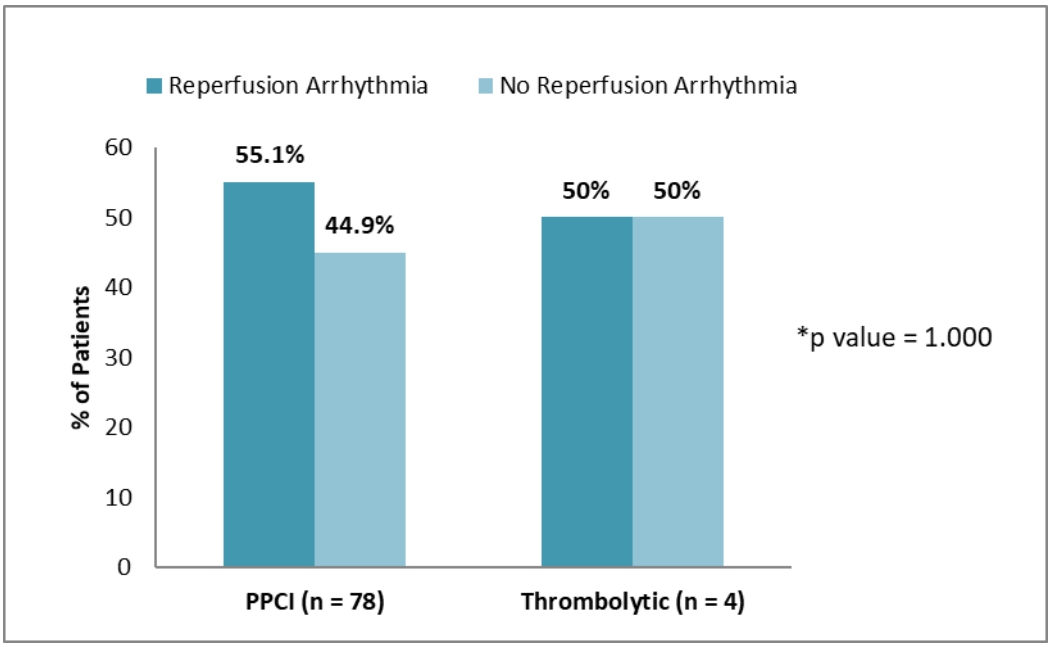

Figure 1. Frequency distribution of reperfusion arrhythmia between procedures.

Table 2. Procedural details of the subjects.

Parameter	All patients	Reperfusion arrhythmia	No reperfusion arrhythmia	p-value
Timelines of procedure (h), mean ± SD				
Symptom onset to thrombolytic	4.3 ± 1.3	4.5 ± 0	4.2 ± 1.6	0.874
Symptom onset to PPCI	6.8 ± 2.5	6.6 ± 2.1	7.1 ± 2.9	0.409
Symptom onset to all procedure	6.7 ± 2.5	6.5 ± 2.1	6.8 ± 3.0	0.596

Data analyzed by Independent T-Test.

Table 3. Infarct-related characteristics of the subjects.

Parameter	All patients	Reperfusion arrhythmia	No reperfusion arrhythmia	p-value
STEMI localization, n (%):				
Anterior	12 (14.6)	5 (11.1)	7 (18.9)	0.496
Wide anterior	12 (14.6)	7 (15.6)	5 (13.5)	1.000
Anterolateral	1 (1.2)	0 (0)	1 (2.7)	0.451*
Anteroseptal	11(13.4)	6 (13.3)	5 (13.5)	0.615*
Inferior	12 (14.6)	10 (22.2)	2 (5.4)	0.067
Inferoposterior	34 (41.5)	17 (37.8)	17 (45.9)	0.602
RV	37 (45.1)	22 (48.9)	15 (40.5)	0.594
Number of diseased vessels, n (%):				
SVD	25 (30.5)	12 (26.7)	13 (35.1)	0.557
DVD	29 (35.4)	14 (31.1)	15 (40.5)	0.847
TVD	24 (29.3)	18 (40.0)	6 (16.2)	0.256
LM disease	2 (2.5)	0 (0)	2 (5.4)	0.563*
No angiographic data	4 (4.9)	2 (4.4)	2 (5.4)	1.000*

Categorical data was analyzed by the Continuity Correction Chi-Square Test, and *Fisher Exact Chi-Square, and numerical data was analyzed by the Independent T-Test.

The primary objective of our study was to observe and analyze the occurrence of arrhythmia in patients with STEMI undergoing reperfusion therapy with primary PCI or thrombolytic. This study has four main findings. First, 54.9% of patients developed reperfusion arrhythmia after the reperfusion procedure for acute STEMI. Second, of all baseline characteristics, clinical history, and clinical presentation observed in this study, only patients' heart rate at admission had a significant association with the reperfusion arrhythmia. Third, although reperfusion arrhythmia occurred quite often in patients who underwent primary PCI and thrombolytic (respectively, 55.1% vs. 50%), there was no significant difference in the occurrence of reperfusion arrhythmia within both groups. In addition, there was also no significant association between symptom time to procedure and the occurrence of reperfusion arrhythmia. Finally, the number of diseased vessels and the location of the infarct were also not associated with reperfusion arrhythmia. In our study, reperfusion arrhythmia was found to occur in 45 people, or about 54.9 % of patients, within 24 hours of reperfusion therapy. Therefore, the incidence of reperfusion arrhythmia in our study was similar or lower than that described in other reports. In the study reported by Shah et al. in 2021, they reported that 53.6% of patients experience arrhythmias during the first 24 hours after the reperfusion procedure. Only patients who underwent PCI procedures were recorded in their study.[5] Another study conducted in India stated that arrhythmias occurred in as many as 80 people or about 78.4% of the patients. This value was higher than the results reported in our study. The higher value possibly happened because they observed the occurrence of arrhythmias within 48 hours of myocardial infarction, which is longer than our study, which only observed the occurrence of arrhythmia within 24 hours. In addition, they also included patients on conservative therapy (without reperfusion).[6]

The occurrence of reperfusion arrhythmia may better be explained by the activation of the calpain system. At the cellular level, there is an excess of intracellular Ca^{2+} levels, reactive oxygen species (ROS) production, and neutrophil accumulation, which then stimulates the activation of the calpain system, which further might induce proteolysis of myofibrillar proteins and disorganization of the tubular structure. These changes might have a role in the alteration of myocardial contractility. Changes in contractility, apoptosis, and necrosis of cardiac muscle can also occur as a result of the mechanisms.[7]

Of the overall baseline characteristics, clinical history, and clinical presentation observed, none of the variables showed a significant association with the reperfusion arrhythmias except for patients' heart rate. However, based on other previous studies, pre-procedural baseline characteristic parameters that were also observed by other researchers, including old age, male gender, low systolic and diastolic blood pressure (often related to cardiogenic shock), high and uncontrolled blood glucose levels (in both diabetic or non-diabetic patients), and potassium levels have been reported to have an association with the incidence of reperfusion arrhythmias. Furthermore, there are also other pre-procedural parameters which not observed in this study but are often reported to be strongly associated with reperfusion arrhythmias. Those are high leukocyte levels, decreased left ventricular ejection fraction (LVEF), and concentrations of cardiac biomarkers.[2,6,8,9]

Ohlow et al.[8] demonstrated that patients with a higher heart rate on admission (in this study, >100 beats/min) were reported to have an increased risk of malignant arrhythmias. The difference in mean heart rate observed in this study when compared with previous studies was thought to be a variation of the study population. Although the heart rate in the arrhythmic group was lower than the non-arrhythmic group in our study, the average heart rate in both groups is still within normal limits.

The percentage of arrhythmias within the two procedure groups did not show a statistically significant difference for procedural details. From a total of 78 samples that underwent PPCI therapy, 43 patients, or about 55.1% of them, experienced arrhythmias. On the other hand, from a total of 4 patients who underwent thrombolytic therapy, 2 of them (50%) had reperfusion arrhythmias.

An analysis by Tatli of an observational study conducted in Turkey in 2013 revealed that the incidence of reperfusion arrhythmia in primary PCI and the thrombolytic group were 83.3% and 88.7%, respectively.[3] Although our study showed a lower incidence of arrhythmia in both groups, the results reported in previous studies also showed no significant association between the two variables, which is compatible with our study. Another study conducted in Malaysia in 2020 reported that the percentage of arrhythmias in both primary PCI and thrombolytic groups were respectively 22.2% and 44.4% and the findings were also reported to have no significant association.[9]

These results suggest that reperfusion arrhythmias may occur as a result of multifactorial causes, and the choice of reperfusion therapy (PPCI or thrombolytic) has not proven to be one of them. The different results of arrhythmia incidence in all studies mentioned may suggest that although similar studies have been compared, the study design and observed endpoints are not the same between studies. For example, the result of the study conducted by Samat was limited to the detection of ventricular reperfusion arrhythmias only, which is different from our study. This can indirectly explain why the rate of arrhythmias in their study is lower than the results of current researchers.

According to the result of our study, the mean symptom time to thrombolytic with or without reperfusion arrhythmias was about 4 hours, while the mean symptom time to primary PCI had an average of 6-7 hours. On the other hand, a shorter time from symptom onset to the procedure was found in patients undergoing thrombolytic therapy, with the mean symptom time to reperfusion being about 6-7 hours. Unlike primary PCI therapy, which is recommended to be carried out within 12 hours, according to existing guidelines, thrombolytic therapy is more recommended to be performed immediately within 120 minutes after the diagnosis of STEMI is established (level of evidence IA).[10] Moreover, the PPCI procedure itself takes a longer preparation time compared to thrombolytics, which will indirectly extend the time to revascularization of patients undergoing PPCI procedures.

The average symptoms-to-all reperfusion procedures found in this study were shorter in patients with reperfusion arrhythmias than in those who were reperfusion arrhythmia-free. In line with our findings, an analysis by Cricri et al. of an observational retrospective study conducted in Switzerland demonstrated that the duration between the onset of symptoms and the procedure was significantly shorter in patients with life-threatening arrhythmias.[11] On the contrary, another study by Ohlow et al. investigated the incidence and predictors of ventricular arrhythmias (VA) in patients who underwent PCI for STEMI. On the basis of the reperfusion procedure recorded, symptom onset to balloon time of 4 hours or more was associated with a significantly higher incidence of malignant VA.[8]

Until now, reported findings from several studies about the role of symptom onset time to reperfusion and its association with the risk of experiencing reperfusion arrhythmias during the first 24 hours of hospitalization in STEMI patients undergoing reperfusion therapy are controversial. The association between these variables remains unclear as some reported data are still contradicting each other. Moreover, the possible explanations regarding these findings are still less well-established.

Methodologically, symptom onset time to reperfusion procedure may not be decent enough to be used as a determining predictor of reperfusion

arrhythmia. It seems likely that this variable has a large bias as its value depends on the patient's recall. In addition, other factors, such as the availability and accessibility of reperfusion therapy facilities, as well as policies related to the referral system, also play an important role in the duration of symptom onset time to reperfusion procedure. Therefore, in addition to being considered highly biased, symptom time to reperfusion therapy is also considered to have a low level of precision.

Our analysis demonstrated that the majority of infarcts occurred with the involvement of the inferior wall. Infarct location did not have a statistically significant association with the occurrence of reperfusion arrhythmias. Cricri et al. investigated the incidence of arrhythmia in patients with STEMI undergoing primary PCI by observing the occurrence of potentially life-threatening arrhythmias during the first 24 hours after hospital admission.[11] The researchers demonstrated that the most common arrhythmias are inferior wall arrhythmias. Although the result is not statistically significant, this result is compatible with our result.

In our population, the number of vessels involved based on coronary angiography was also observed. Although there was no statistically significant association between the number of vessels involved and the occurrence of reperfusion arrhythmia, the majority of patients with reperfusion arrhythmia were reported to have triple-vessel disease (TVD). This finding was found to be similar to those reported in other studies, including the study from Cricri et al. and Albanese et al., in which multi-vessel disease was reported to have more commonly occurred in the group with arrhythmias, although this finding was not statistically significant.[2,11] On the other hand, another study reported that multivessel disease was significantly associated with the incidence of VT and VF.[12]

This study has several limitations in the aspect of research design. The present study resides in its cross-sectional design and was conducted in a single center. The limited number of sample size included is also another major limitation of our study. A larger-scale prospective multicenter study may provide a better representation of our population.

4. Conclusion

Reperfusion arrhythmias occur frequently in STEMI patients undergoing reperfusion therapy procedures. The study also found that the patient's heart rate on admission was one of the predictors of reperfusion arrhythmias. However, these findings need to be analyzed further in a more developed study design in order to establish more insight into the occurrence of reperfusion arrhythmias. Potentially, having a better understanding of reperfusion arrhythmias, as well as their predictor factors, may improve the quality of patient care. Therefore, by performing more intensive supervision and having early intervention to address the existing predictor factors in vulnerable patients, the occurrence of clinically important reperfusion arrhythmias might be prevented.

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