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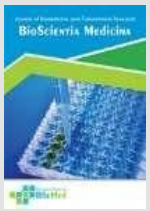

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Reperfusion Arrhythmia in Acute Myocardial Infarction

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A B S T R A C T

Management of reperfusion in acute myocardial infarction is an important component of myocardial cell survival to minimize the area experiencing infarction and improve patient clinical outcomes. However, this reperfusion also contributes to myocardial injury which is preceded by the ischemic process. One of the injuries related to the ischemia-reperfusion process in the myocardium is reperfusion arrhythmia. Reperfusion arrhythmias from several studies can begin to occur in the first minutes after restoration of obstructed coronary flow. The features of reperfusion arrhythmia can include accelerated idioventricular rhythm, ventricular tachycardia, ventricular fibrillation, and other arrhythmias. The mechanism of reperfusion arrhythmia can be excess calcium in the cells, oxidative stress due to an increase reactive oxygen species, energy metabolism disorders, and neutrophil accumulation. Excessive intracellular calcium and other mechanisms cause a delay in the depolarization of previously ischemic cells. This reperfusion arrhythmia requires special attention because it can disrupt hemodynamics and patient outcomes after reperfusion procedures. Knowledge of the mechanisms of reperfusion arrhythmias will guide clinicians to provide better management during and after reperfusion procedures.

1. Introduction

Cardiovascular disease, according to the WHO (World Heart Organization), is the main cause of death in the non-communicable disease (NCD) group and causes 17.5 million deaths or 46% of all non-communicable disease deaths, 80% of which occur in low-middle income countries, and this figure is expected to increase to 23.6 million in 2030.[1-3] Coronary heart disease (CHD) is a class of cardiovascular disease that contributes greatly to high mortality. CHD is currently more commonly used in patients who have experienced myocardial infarction, both acute and chronic.[2,3] Acute myocardial infarction can be acute myocardial infarction with ST-segment elevation (STEMI), without ST-segment elevation (Non-STEMI), and unstable angina pectoris. Acute myocardial infarction should be used when there is evidence of myocardial injury (defined as an increase in cardiac troponin values of at least one value above the 99th percentile of the upper limit of the reference value) accompanied by necrosis in a clinical condition (symptom) of myocardial ischemia.

In the STEMI management guidelines issued by the European Society of Cardiology (ESC) in 2017, reperfusion therapy is the main choice.[3] Reperfusion therapy can include administering fibrinolytic agents

and/or percutaneous coronary intervention (PCI). This treatment is given to STEMI patients with an onset of less than 12 hours. In cases that occur in the hospital coverage area with PCI facilitation, and it is estimated that the time from the first medical contact until PCI is carried out is less than 90 minutes, the first choice for reperfusion is primary PCI. If the requirements for primary PCI in reperfusion management are not met, fibrinolytic agents are given.[3] The criteria for successful reperfusion are a reduction in symptoms of chest pain, a decrease in the ST segment of more than 50% from before, electrical instability of the heart (heart rhythm disturbances in the form of ventricular tachycardia, supraventricular tachycardia, etc.), and an early increase in markers of acute myocardial infarction. One of the serious things that occurs during and after reperfusion therapy is instability of the heart's electrical activity, known as reperfusion arrhythmia.[3-5]

Reperfusion arrhythmia (RA) is included in the spectrum of ischemic/reperfusion injury to the myocardium, with several mechanisms resulting from the opening of coronary blood flow that was previously completely blocked. The mechanism for this ischemic/reperfusion injury is endothelial dysfunction resulting in vasoconstriction, activation of leukocytes and platelets, increased production of oxidants, and increased extravasation of fluid and protein. Another mechanism is an increase in intracellular calcium and mitochondrial activity, which uses oxygen as a substrate to produce reactive oxygen species (ROS), resulting in an increase in markers of oxidative damage.[5-7] Reperfusion arrhythmias can be characterized by premature ventricular beats, accelerated idioventricular rhythms, and other arrhythmias and can occur within the first 20 minutes after reperfusion to several hours after the procedure. Several studies have been carried out to determine and predict the time of occurrence of reperfusion arrhythmias but have not obtained satisfactory results. Some reperfusion arrhythmias can resolve spontaneously but can also cause hemodynamic disturbances and even death. Management of reperfusion arrhythmia depends on the type of arrhythmia that occurs and the stability of the patient's clinical condition. Measures to prevent the occurrence of reperfusion arrhythmias have been widely studied, starting from calcium-based drugs to balloon inflation stages during PCI, but there have been no satisfactory results.[7]

Reperfusion arrhythmias and underlying mechanisms

Arrhythmia is a disturbance in the frequency or rhythm of the heartbeat. Based on frequency, arrhythmias can be divided into two, namely bradyarrhythmias and tachyarrhythmias. Bradyarrhythmias have a frequency of less than 60 times per minute, while tachyarrhythmias have a frequency of more than 100 times per minute.[1] The term reperfusion arrhythmia was used first in studies of revascularization-guided thrombolytic therapy in patients with acute myocardial infarction. Electrocardiographic data, in addition to clinical and laboratory measurements, are used by clinicians to confirm vessel patency and successful myocardial reperfusion after thrombolytic therapy.[7] Several studies have been conducted to determine the definition of reperfusion arrhythmia. RA is a collection of arrhythmias in the form of accelerated idioventricular rhythm, ventricular tachycardia, and a number of premature ventricular complexes that occur in the first minutes after balloon inflation. RA is also defined as an arrhythmia that occurs before and 90 minutes after percutaneous coronary intervention is performed. RA is also defined as an arrhythmia that occurs within 24 hours after PCI. Then, the European Heart Rhythm Association Consensus defined RA as an arrhythmia that occurs during or in the early minutes after restoration of coronary blood flow from obstruction. This reperfusion arrhythmia can occur both after PCI and fibrinolytic procedures. Reperfusion arrhythmias that occurred after reperfusion with either PCI or fibrinolytics were not significantly different.[8-10]

In reperfusion arrhythmia, delayed afterdepolarizations (DADs) are likely causes based on electrophysiology. Delayed afterdepolarizations is an oscillation of the membrane potential occurring after complete repolarization of the previous action potential. As in other pathologies, DAD after reperfusion is caused by excess intracellular calcium and is further enhanced by the release of calcium by the sarcoplasmic reticulum on calcium influx into the cells. If the threshold is reached for the depolarizing current, a spontaneous action potential will occur.[9] This action potential can again induce an afterpotential that produces self-sustaining rhythmic activity. Accelerated idioventricular rhythms have features consistent with DAD-related rhythmic behavior. Additionally, intracellular calcium overload can cause reperfusion arrhythmias with uncoupling of oxidative phosphorylation, as described above. Uncoupling of oxidative phosphorylation results in a decrease in ATP concentration, inducing shortening of the action potential with closure of K^+ channels ATP.[9] The pathophysiology of reperfusion arrhythmias has not been described in detail. The pathophysiology described above suggests a process in which excess intracellular calcium is central to triggering reperfusion arrhythmias. At the same time, intracellular calcium overload is also a key component to induce cell death in fatal reperfusion injury. Therefore, it is likely that reperfusion arrhythmia and fatal reperfusion injury are not two independent processes but two different outcomes of the same process. Consequently, reperfusion arrhythmias can be seen and used as markers of lethal reperfusion injury.[9] Illustrations depicting the mechanisms of arrhythmia during ischemia and reperfusion, as well as the absence of arrhythmia during the quiescent period, are shown in Figure 1. Black areas indicate unresponsive tissue, while arrows flowing through white areas indicate slow-conducting impulses through stressed tissue.[11-15]

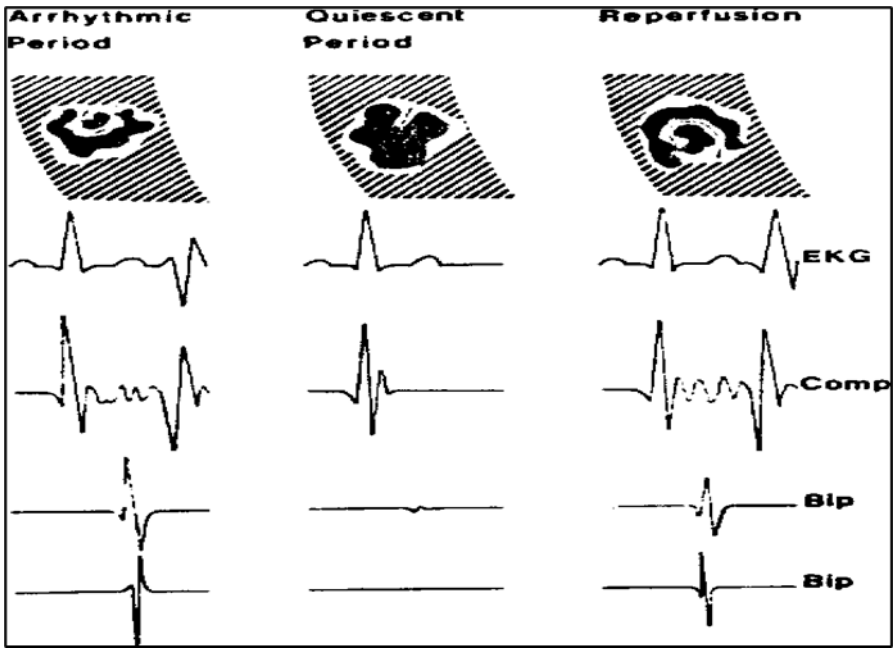

Figure 1. Illustration of arrhythmia mechanisms during ischemia and reperfusion.[15]

Several independent cohort studies have shown that ventricular reperfusion arrhythmia 'bursts' (VA bursts) are associated with clinically larger infarct sizes. Significant differences persisted in optimal epicardial and microvascular reperfusion. Research showed whether VA blasts were related to broader risk areas, but no association was found.[16-18] In a study, it was stated that there was a development of VT and VF rhythms in 3491 STEMI patients after undergoing thrombolytic therapy, and it was reported that cases

who experienced VT or VF had TIMI grade 0-2 flow. The relationship between arterial patency and coronary blood flow is displayed on coronary angiography images known as TIMI flow grade. TIMI flow analysis provides a better understanding of the relationship between arterial patency and the incidence of reperfusion arrhythmias. However, in the primary PCI group with TIMI 3, there was no statistically significant relationship (83.3% of cases) between reperfusion arrhythmia and TIMI flow grade in patients undergoing primary PCI. Reperfusion arrhythmia as an electro biomarker of reperfusion injury has rarely been reported in clinical trials focused on infarct size reduction strategies. The above-mentioned pathophysiology and clinical observations suggest that reperfusion arrhythmias could be an important early and unique marker for reperfusion injury. Thus, reperfusion arrhythmias may be an early marker of risk stratification and strategies to reduce reperfusion injury.[19,20] Reperfusion arrhythmias are usually detected within the first 48 hours after the patient receives reperfusion therapy. The study showed that at least 83.3% of patients in the primary PCI group and 88.7% of the thrombolytic group had at least one reperfusion arrhythmia. When the rates of different arrhythmic findings were examined separately, the ratios of sustained VT, nonsustained VT, VF, and AV block were similar between the two groups. However, the ratio of AIVR and AF was higher in the thrombolytic group. The incidence of AF development in AMI is approximately 5-10%, and it is known that the development of AF in AMI is usually caused by impaired left ventricular function or poor reperfusion.[21]

Diagnosis enforcement

The diagnosis of arrhythmia is mainly made through an ECG examination. Arrhythmia should be suspected in patients who complain of palpitations or an irregular heartbeat, especially if they have cardiovascular risk factors such as hypertension. In some cases of arrhythmia, especially bradyarrhythmia, patients may experience no symptoms. Arrhythmias can also cause patients to experience decreased consciousness due to syncope. Bradyarrhythmia patients report non-specific complaints, such as fatigue, shortness of breath, intolerance during activity or exercise, malaise, and chest pain. In tachyarrhythmia, patients may complain of palpitations, chest pain, dizziness, floating, and feeling weak.[19]

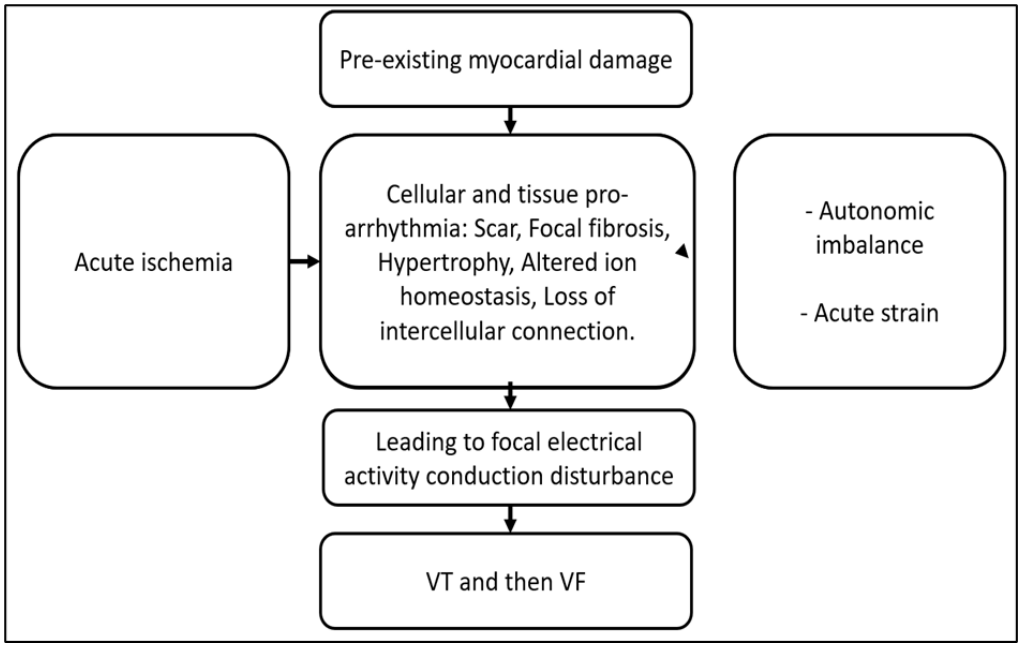

Figure 2. Scheme of arrhythmia in acute coronary syndrome.[18]

Palpitations are sensations related to increased force of heart contractions. Typically, patients have no awareness of the heartbeat because the contractile force of each beat is moderate and because the structures surrounding the heart and large blood vessels are not stretched enough to generate sensory impulses. If the left ventricle suddenly contracts more strongly, the resulting greater ejection of blood stretches the large arteries or increases the physical movement of the heart within the pericardium and can be felt by the patient. Arrhythmias are thought to produce changes in the strength of contractions associated with sudden changes in the length of the rhythm cycle and the interval between beats.[19]

Table 1. Arrhythmias in STEMI patients after primary PCI.[20]

Conduction disorders	Percentage (%)
First-degree AV Block	25% (125)
Second-degree AV Block, Mobitz I	3% (13)
Second-degree AV Block, Mobitz II	2% (9)
Third-degree AV Block	5% (24)
Right bundle branch block	8% (40)
Left bundle branch block	1% (7)
Arrhythmia	Percentage (%)
Sinus arrest (>2.5 s)	5% (23)
Sinus bradycardia <59 beats/min	28% (141)
Sinus tachycardia ≥ 100 beats/min	22% (112)
Atrial fibrillation	9% (47)
Junctional bradycardia <50 beats/ min	8% (42)
Junctional rhythm, 50-100 beats/min	8% (38)
AIVR, 50-120 beats/min	42% (210)
Nonsustained VT, > 120 beats/min	26% (129)
Sustained VT, > 120 beats/min	2% (8)
Ventricular fibrillation	2% (10)
ventricular paced rhythm	1% (7)

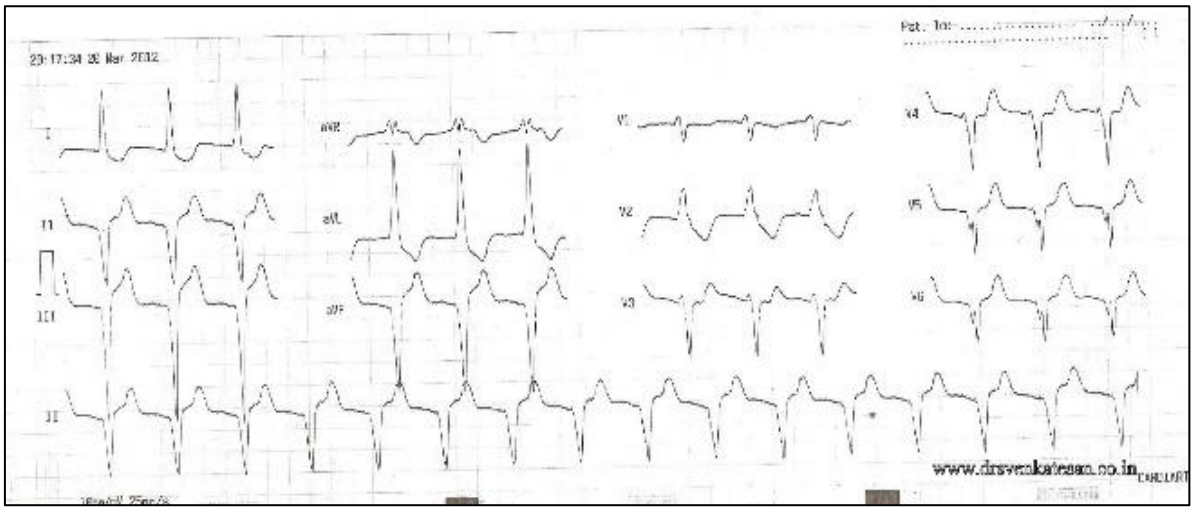

Figure 3. Accelerated idioventricular rhythm.

Electrocardiography is a supporting examination that has an important role in diagnosing arrhythmia. The ECG feature will vary depending on the type of arrhythmia experienced. For example, patients with atrial fibrillation will show ECG features in the form of irregular R-R intervals, no P waves on the ECG, and intervals between 2 atrial activations if they appear >200 ms or >300 rates per minute.[19] Ventricular tachycardia will appear on the ECG: the QRS complex widens >0.14 seconds with a pattern right bundle

branch block or >0.16 seconds with a pattern left bundle branch block. Other features include AV dissociation, RS intervals >100 ms in the precordial leads (Brugada's sign), QRS complexes with negative concordance in the precordial leads, and ventricular fusion beats.[19]

Management

Rapid restoration of blood flow to ischemic tissue is essential for optimal salvage and to reduce mortality and morbidity in patients with AMI. However, this does not prevent lethal reperfusion injury, which can reach 50% of the infarct size. Prevention and reduction of the impact of reperfusion injury requires knowledge of its pathophysiology. Various treatments and procedures have been tested, and although they differ in setting, most of them have one common feature: despite promise in preclinical trials, phase II and III clinical trials rarely prove successful.[9] Reducing excess intracellular calcium has become an important focus in the prevention of reperfusion injury in the form of animal trials for rapid Na^+/H^+ blockers, sodium channel blockers, Na^+/Ca^{2+} blockers, calcium antagonists, N-methyl-D-aspartate and ACE-I antagonists. Most studies have been conducted in mice, although rabbit, dog, and pig models have also been used. The drugs used reduce the incidence of ventricular premature beats, ventricular tachycardia, and/or ventricular fibrillation while at the same time reducing infarct size.[9-12]

Another important factor in reperfusion injury is the production of ROS. Giving ROS scavenger has been shown to reduce ventricular fibrillation and infarct size in mice and, in some cases, even ventricular tachycardia and mortality. However, in all studies, drug administration was performed before induction of ischemia, and the application of ROS scavenger in phase II and III trials did not reduce infarct size. mPTP opening is a key component in reperfusion injury induced by excess intracellular calcium and ROS. Pore/membrane blockage by cyclosporin A can reduce infarct size in animal studies.[22]

Beta-blockers have been used to reduce reperfusion injury, but results have been conflicting. This may be due to different factors, which are discussed extensively in recent reviews. Both trials focused only on ventricular fibrillation and none on other occurrences of reperfusion arrhythmias.[9] Beta-blockers work by inhibiting beta-adrenoreceptors and decreasing heart rate. Beneficial effects include decreased automaticity, possibly accompanied by reduced ventricular arrhythmias, decreased conduction velocity, and increased circuit stability re-entry. In VT or VF, it should be initiated as first-line therapy. Beta-blockers should be used with caution in patients experiencing bradycardia or significant right coronary ischemia.[22]

Amiodarone is a drug with predominant Vaughan-Williams class III activity that can treat recurrent VT and VF resistance to beta-blockers. Amiodarone works through various mechanisms, one of which is the blockade of K^+ channels (phase 3 repolarization). Along with these primary effects, amiodarone affects the function of Na^+ and Ca^{2+} channels and has weak beta-blocking properties. Amiodarone's primary anti-arrhythmic action occurs by prolonging the refractory period and suppressing re-entry. However, a decrease in automaticity was also observed. Amiodarone should be considered to suppress and prevent recurrent arrhythmia events.[22]

Lidocaine is a class IB antiarrhythmic drug that blocks fast sodium channels responsible for rapid phase 0 depolarization. Calcium currents regulate phase 0 activity in the spontaneous depolarization nodal network, so class I drugs have no direct impact on sinoatrial or AV nodal features. Na^+ blockade generally decreases conduction velocity in atrial and ventricular tissue, which may be effective in downregulating tachyarrhythmias caused by re-entry. Lidocaine after cardiac arrest and successful resuscitation has been shown to have great benefits for preventing ventricular arrhythmia (VA) recurrence and survival.[22]

Pacing overdrive can be used if such measures fail to suppress VA in the early post-MI period. The focus

can be captured and suppressed automatically, or an exit block can be achieved by refactoring the nearby myocardium. Pacemaker-induced conduction and refractory changes can terminate tachycardia induced by the re-entrant mechanism. This procedure may be used in patients with refractory VA to avoid repeat cardioversion while waiting for drug therapy to take full effect or before further revascularization or catheter ablation.[22]

All work by significantly slowing conduction. However, in ACS, this drug can worsen VT/VF. After the publication of the CAST trial, which demonstrated increased mortality in patients treated with flecainide or moricizine after MI compared with a placebo, additional studies on AAD and class I VA were largely abandoned. Consequently, this drug should not be used in ACS. Calcium channel blockers have been shown to reduce excess intracellular calcium and improve vascular flow. A retrospective study examined the effectiveness of intracoronary verapamil treatment in AMI to terminate ventricular tachyarrhythmias that occur after reperfusion. It was found that intracoronary verapamil was effective in rapidly terminating all reperfusion-induced arrhythmias except for VF. There were no significant side effects associated with intracoronary administration of verapamil, and no recurrence of arrhythmias was observed.[22] If life-threatening ventricular arrhythmias associated with ACS persist despite optimal revascularization, then cardioversion/electrical defibrillation should be considered first. In addition, the adverse hemodynamic consequences of atrial arrhythmias such as AF can rapidly worsen symptoms. If cardiac output is disturbed and hemodynamics becomes unstable, immediate cardioversion must be performed to restore sinus rhythm.[22-25]

2. Conclusion

The term reperfusion arrhythmia was used in the first study of revascularization-guided thrombolytic therapy in patients with acute myocardial infarction. Reperfusion injury is damage caused by inflammation, oxidative stress, and electronic imbalance resulting from the return of blood flow to previously ischemic tissue. Reperfusion of ischemic myocardial tissue with thrombolysis or percutaneous coronary intervention (PCI) is essential to effectively reduce infarct size and improve clinical outcomes in patients with acute myocardial infarction (AMI). The diagnosis of arrhythmia is mainly made through an ECG examination. Arrhythmia should be suspected in patients who complain of palpitations or an irregular heartbeat, especially if they have cardiovascular risk factors such as hypertension. Rapid restoration of blood flow to ischemic tissue is essential for optimal salvage and to reduce mortality and morbidity in patients with AMI. However, this does not prevent lethal reperfusion injury, which can reach 50% of the infarct size.

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