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REPERFUSION ARRHYTHMIAS IN ACUTE MYOCARDIAL INFARCTION

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Abstract:
Reperfusion arrhythmias (RA) are quite a common complication of procedures aimed at restoration of coronary blood flow (percutaneous coronary interventions (PCI), thrombolysis, and aortocoronary bypass grafting). Known risk factors for RA are infarct size, duration and severity of ischemia, reperfusion rate, heart rate, extracellular potassium concentration, and the presence of congestive heart failure or left ventricular hypertrophy. Treatment of RA should be aimed primarily at improving the microcirculation of the reperfusion zone by using various groups of drugs, including direct anticoagulants, beta-blockers, and ACE inhibitors. The class III antiarrhythmic drugs, cardioversion, and radiofrequency ablation are used to eliminate arrhythmias.

Keywords: *reperfusion, myocardial infarction, arrhythmia, endothelial dysfunction, percutaneous coronary intervention.*

INTRODUCTION

When restoring blood circulation in the coronary vessels during myocardial infarction after balloon angioplasty, stenting, or thrombolysis, heart rhythm disturbances often occur that are difficult to treat, and effective methods for preventing these arrhythmias have not yet been proposed [1,2]. Today, myocardial reperfusion injuries are associated with complications of operations to restore blood flow in the infarct-related artery [2].

Early reperfusion is necessary for myocardial survival during acute myocardial infarction. Reperfusion of ischemic myocardial tissue using fibrinolysis or percutaneous coronary intervention (PCI) is critical to reduce infarct size and improve outcomes. On the other hand, reperfusion is called a double-edged sword because it can lead to additional myocardial damage beyond that caused by ischemia alone [3].

RA is often characterized by premature ventricular contractions with prolonged complex intervals and rapid idioventricular rhythms that begin within the first 20 minutes after reperfusion [5].

Numerous studies have been conducted to determine the time course of reperfusion arrhythmias. Traditionally, accelerated idioventricular rhythm (AIVR) is considered a marker of reperfusion. However, reperfusion may reveal any arrhythmia (or lack of arrhythmia); conversely, AIVR can occur without reperfusion [6].

Some studies have mentioned that these arrhythmias may be caused by ongoing myocardial cell damage and ischemia. Some RAs resolve spontaneously and do not require treatment, but others may be associated with circulatory collapse and require immediate treatment [7]. R. Ilia et al. defined it as IVVR, ventricular tachycardia, or multiple premature ventricular complexes occurring within the first minute after balloon inflation. H. Bonnemeier et al. defined it as an arrhythmia occurring within twenty-four hours after PCI [8,9]. C.J. Terkelsen et al [8] defined it as any predefined arrhythmia occurring within 90 minutes of cardiac intervention. The European Heart Rhythm Association (EAHR) has defined reperfusion arrhythmia as an arrhythmia that occurs during or in the first minutes after restoration of coronary blood flow [10].

PATHOPHYSIOLOGY

Reperfusion of previously ischemic tissue removes extracellular electrolytes and uses the H+/Na+ exchanger to correct intracellular acidosis, resulting in increased intracellular sodium concentration. Due to ongoing adenosine triphosphate (ATP) deficiency, regulation of intracellular sodium concentration by Na+/K+ ATPase is insufficient, and an inverted Na+/Ca2+ exchanger takes over, leading to intracellular calcium overload [11]. Reperfusion enhances the release of intracellular calcium by activating the renin-angiotensin system, which releases angiotensin II, which, in combination with catecholamines released during ischemia and reperfusion, leads to additional release of intracellular calcium. In addition, reperfusion-induced generation of reactive oxygen species (ROS) is largely associated with excess calcium through damage to the sarcoplasmic reticulum. When reactive oxygen species and free fatty acids combine and alpha-1 adrenergic receptors are stimulated, it also results in calcium overload through interaction with catecholamines. [12].

Under stressful conditions, large amounts of ROS are produced. During ischemia, xanthine oxidase is formed, as well as hypoxanthine. After reperfusion,

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oxygen reacts with xanthine oxidase and hypoxanthine to generate ROS. Neutrophils are a significant source of ROS at the site of reperfusion, both directly and through stimulation by nicotinamide adenine dinucleotide phosphate [13].

Neutrophils are found at the border of ischemic tissue. The accumulation of neutrophils in nonperfused myocardium is associated with slow infiltration into the risk zone during the first 12-24 hours after ischemia, reaches a peak after 2-4 days, and is most pronounced near the border zone of infarction. However, the accumulation of neutrophils accelerates and increases in the reperfused myocardium, and their concentration is higher in the subendocardial layer than in the subepicardial layer [14].

The opening of the mitochondrial permeability transition pore (MPT) due to excess ROS and intracellular calcium overload is already recognized as a major step in reperfusion injury. [14]. Because of the inhibitory effect of acidosis on the pore, the modest increase in intracellular calcium and ROS produced during ischemia is not sufficient to open the pore. After reperfusion, acidosis disappears, and ROS and intracellular calcium increase, which leads to the opening of PPPm. Opening of the PPPm channel results in the influx of additional molecules, increasing the osmotic load and leading to mitochondrial swelling in addition to an increase in ROS and intracellular calcium. The swelling ultimately leads to mitochondrial rupture and the release of apoptotic proteins [15].

In addition, cleavage of PPPm and intracellular calcium overload cause uncoupling of oxidative phosphorylation. Uncoupling oxidative phosphorylation induces apoptosis through ATP hydrolysis, which activates degradative enzymes [16]. Finally, intracellular calcium overload can lead to myocyte hypercontracture. Excessive hypercontracture can cause myocytes to detach from tight junctions, causing damage to the sarcolemmal membranes of adjacent cells and cytoskeletal elements, ultimately leading to apoptosis. On histological examination, this appears as necrosis of the contractile band. [16].

Within a few seconds after ischemia, significant metabolic changes occur: high-energy phosphates are hydrolyzed, intracellular pH decreases due to the initiation of the anaerobic process of glycolysis, and extracellular potassium levels increase. As the membrane's resting potential approaches the excitation threshold, the rate of electrical conduction increases. In addition, acidosis increases cytosolic calcium, which promotes early and late depolarization. In addition, ischemia dephosphorylates connexin-43 intermediates, disrupting electrical communication between cells. Finally, sympathetic activation causes calcium release from the sarcoplasmic reticulum and lipolysis, increasing circulating levels of free fatty acids and predisposing to arrhythmia [16]. Arrhythmia during ischemia may be due to autonomic imbalance associated with vagal hyperactivity during the first few hours of myocardial ischemia, resulting in a transient slowing of atrioventricular conduction (AVC). Myocardial ischemia and necrosis can cause immediate disruption or irreversible damage to the AVB system, resulting in a new bundle branch block (BBB) or worsening of existing high-grade symptomatic AVB [17]. On the other hand, ischemia can induce ventricular arrhythmias such as ventricular tachycardia (VT) or ventricular fibrillation (VF) in proarrhythmic myocardial cells or tissues [18].

Although the pathophysiology of reperfusion arrhythmias is not fully understood, some underlying events are well established. One of them is delay after depolarization (DAP). DAP is the most common cause of reperfusion arrhythmias. It is caused by excess intracellular calcium. When the depolarizing current threshold is exceeded, a spontaneous action potential occurs. It is worth noting that this action potential can generate a postpotential, which leads to self-sustaining cyclic activity. [19].

Reperfusion in patients with AMI leads to an increase in the concentration of intracellular Ca2+, normalization of the concentration of extracellular K+, and restoration of the duration of the action potential. These changes, but even in this case are not uniform, expressing the spatial heterogeneity of the restoration of regional blood flow in the ischemic zone. This leads to dissipation of refractoriness, resulting in the formation of a reentry substrate. [19].

In the inferior wall, infarction may manifest as transient bradycardia and hypotension due to reflex activation of the Bezold-Jarisch reflex (bradycardia, vasodilation, and hypotension), since reperfusion provokes receptors located in the inferior wall of the left ventricle. Multiple reperfusion mechanisms can increase susceptibility to atrial fibrillation (AF), providing either a substrate or trigger for this arrhythmia. AF can be caused by hemodynamic changes such as pulmonary capillary pressure and left atrial pressure. The frequency of reperfusion arrhythmias depends on:

- Early reperfusion: The earlier reperfusion begins, the greater the likelihood of reperfusion arrhythmias. As a result, reperfusion occurs more frequently with the use of prehospital thrombolytics than with the use of in-hospital thrombolytics.
- Reperfusion rate: The faster reperfusion occurs, the more often reperfusion arrhythmias occur. As a result, in acute coronary syndrome (ACS), PCI is more

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often associated with reperfusion arrhythmias than fibrinolytics. [20].

TREATMENT

As mentioned previously, most reperfusion arrhythmias resolve spontaneously, but some cause significant hemodynamic changes and require treatment.

Electrical cardioversion/defibrillation. If life-threatening ventricular arrhythmias associated with ACS persist despite optimal revascularization, electrical cardioversion/defibrillation should be considered first. Additionally, in atrial arrhythmias such as AF, adverse hemodynamic consequences can rapidly worsen symptoms. If cardiac output decreases and hemodynamic destabilization, cardioversion should be performed immediately to restore sinus rhythm [17]. In addition, antiarrhythmic drugs are also used, including beta-blockers (BBs). BBs reduce heart rate. Beneficial effects include a decrease in automaticity, which reduces the likelihood of ventricular fibrillation and allows, to a certain extent, to prevention of fatal arrhythmias in the acute stage of myocardial infarction; The antiarrhythmic activity of β-blockers is based on their ability to eliminate adrenergic effects on the heart, while 1) the heart rate decreases, the automaticity of the sinus node, AV node and His-Purkinje system, atria and ventricles decreases 2) the duration of the action potential and refractory period decreases in the His-Purkinje system 3) the conductivity of the AV node worsens and the duration of the effective refractory period of the AV node increases; PQ interval prolongs For VT or VF, it should be prescribed as first-line therapy. A beta-blocker should be used with caution in patients with bradycardia or significant right coronary artery ischemia. [20]. Amiodarone is a drug with predominant class III activity and can treat recurrent VT and VF refractory to a beta blocker. In addition to this main effect, amiodarone affects the function of Na+ and Ca2+ channels and has weak beta-blocking properties. The primary antiarrhythmic effect of amiodarone is facilitated by prolongation of the refractory period and suppression of reentry. However, there is also a decrease in automaticity. Along with beta-blockers, amiodarone should be considered for the suppression and prevention of recurrent arrhythmias [17]. Lidocaine may be used along with amiodarone. Lidocaine is a Class IB antiarrhythmic drug that blocks fast sodium channels responsible for rapid phase 0 depolarization. Because calcium currents regulate phase 0 activity in spontaneously depolarizing nodal tissue, class I drugs do not directly affect sinoatrial or AV node features. Na+ blockade generally reduces conduction velocity in atrial and ventricular tissues, which may be effective in reducing reentry tachyarrhythmias. However, this may occur due to an increase in the number of afterdepolarizations and polymorphic VTs. Lidocaine therapy after cardiac arrest and successful resuscitation has been shown to have significant benefits on both recurrent ventricular arrhythmias (VAs) and survival. [21].

Radiofrequency ablation. Catheter ablation for the treatment of VA in the acute phase is not routinely performed. Success in the acute phase is about 70%, but in unstable patients, there is a 3 percent periprocedural mortality rate. Ablation is mainly performed subendocardially and in the border zone. The targets are re-entrant circuits in heterogeneous myocardium, as well as post-depolarization and automatic foci formed by Purkinje fibers. If frequent PVCs appear, activation mapping can be performed. If PSGs occur less frequently, pace mapping can be performed on previously recorded PSGs. This patient population is often hemodynamically unstable, and the complexity of the procedure requires that it be performed in high-volume centers by experienced electrophysiologists using 3D electroanatomical mapping systems and advanced supportive care [11].

Mechanical circulation. VA support is a common condition after myocardial infarction, complicated by cardiogenic shock and the need for inotropes. Inotropes may aggravate VA, but their dosage can be reduced if mechanical support is used. In addition to assisting with revascularization procedures, mechanical support can help maintain adequate cardiac output. The most commonly used device is the intra-aortic balloon pump (IABP). This counterpulsation device reduces afterload, increases diastolic coronary perfusion, and increases cardiac output. IABN has been used to improve outcomes after primary PCI in high-risk patients by increasing coronary flow reserve, reducing preload and afterload, and increasing systemic pressure. Prophylactic use of IABN in high-risk patients may reduce the likelihood of VF, especially in patients with cardiogenic shock. However, it cannot provide support for VF, whereas other forms of mechanical support can, such as ECMO (extracorporeal membrane oxygenation) [21].

Angiotensin-converting enzyme (ACE) inhibitors, unlike many other vasodilators, generally do not cause reflex tachycardia. At the same time, there is an increase in the concentration of bradykinin (an active vasodilator). As a result of a complex mechanism of vasodilatory action, ACE inhibitors also dilate venous vessels, and therefore reduce the return of blood to the heart (preload) and pressure in the pulmonary circulation. By reducing the formation of angiotensin II

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not only in the blood plasma but also, for example, in the heart, ACE inhibitors prevent the progression of left ventricular dilatation (its remodeling) and cause the reverse development of myocardial hypertrophy. Drugs in this group increase the volumetric velocity of coronary blood flow and reduce the tension of the ventricular walls, can have an antiarrhythmic effect associated with the effect on trophic processes in the myocardium, an increase in the content of potassium and magnesium ions in the blood, a decrease in the content of

In recent years, increasing evidence has emerged supporting the role of statins in preventing reperfusion injury, independent of their lipid-lowering effects. Statins also inhibit the activation and extravasation of neutrophils, which can cause acute heart failure during reperfusion. Statins also have a beneficial effect on endothelial and cardiac contractile dysfunction caused by ischemia/reperfusion. Further clinical studies appear to be indicative. [22].

Clinical consequences of reperfusion arrhythmias in reperfusion injury

The fundamental mechanism described above shows that reperfusion arrhythmias are caused by intracellular calcium excess. Likewise, excess intracellular calcium plays a critical role in catastrophic cell death caused by reperfusion injury. Thus, reperfusion arrhythmias and fatal reperfusion injury are likely two separate results of the same mechanism.

CONCLUSION

Reperfusion arrhythmia occurs immediately or within the first minutes after restoration of coronary blood flow. AIVR is the most common reperfusion arrhythmia. Reperfusion arrhythmia is one of the spectrum of reperfusion injury. Delay after depolarization and reentry often causes reperfusion arrhythmias. Numerous studies have shown that reperfusion arrhythmias are not related to coronary blood flow. Cardioversion/defibrillation, antiarrhythmic drugs, cardiac pacing, radiofrequency ablation, and mechanical circulatory support are used to treat reperfusion arrhythmias. Treatment of reperfusion arrhythmias may be helpful in this process but requires additional research.

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