REVIEW

Heart rhythm disorders and myocardial remodeling in patients with ST-segment elevation acute myocardial infarction

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Abstract: Acute myocardial infarction is a potential life threatening disease spread all over the world. The continuing progress of medical and interventional therapies requires a comprehensive understanding of the underlying pathophysiology. Moreover, the potential development of heart failure or/and arrhythmias in either acute or chronic setting, demand a deep knowledge of their molecular mechanisms in order to provide adequate treatments. This review aims to summarize the current data regarding the etiopathogenesis of acute myocardial infarction and the heart rhythm disorders associated with this clinical condition.
Keywords: acute myocardial infarction, inflammation, arrhythmias, heart rhythm disorders.

Rezumat: Infarctul miocardic acut este o afecțiune amenințătoare de viață, larg răspândită în întreaga lume. Progresul terapiilor medicale și intervenționale necesită o bună înțelegere a fiziopatologiei de bază. Mai mult decât atât, dezvoltarea potențială a insuficienței cardiace sau / și a aritmiilor, fie în cadru acut sau cronic, necesită o cunoaștere profundă a mecanismelor moleculare pentru a oferi tratamente adecvate. Această revizuire își propune să rezume date actuale privind etiopatogeneza infarctului miocardic acut și a tulburărilor de ritm cardiac asociate aceastei afecțiuni.
Cuvinte cheie: infarct miocardic acut, inflamație, aritmii, tulburări de ritm cardiac.

INTRODUCTION

ST-segment elevation acute myocardial infarction (STEMI), the most severe form of ischemic heart disease, is one of the leading causes of mortality in the world. This patient population usually dies from either heart rhythm disorders or heart failure[1,2]. The exact underlying pathophysiology of the acute myocardial infarction (AMI) has not been fully understood yet. However, recent data have brought to the spotlight the role of inflammation in the development and further evolution of this severe pathology[3]. This review synthesizes the current knowledge in what concerns the pathophysiology of AMI and the subsequent heart rhythm disorders, as well as possible future perspectives.

ACUTE MYOCARDIAL INFARCTION

According to the Fourth Universal Definition, type I ST-segment elevation acute myocardial infarction results from a complicated atherosclerotic coronary plaque leading to occlusion or subocclusion of the involved artery[1].

The subsequent ischemia leads to myocardial interstitial edema and even necrosis whenever the coronary blood flow is not timely restored. However, even effective percutaneous coronary intervention (PCI) performed in the therapeutic window with complete blood flow restoration has the potential to induce myocardial damage due to the reperfusion injury[4,5].

Recent data have shown that large epicardial vessels are not the only responsible for the tissue injury in STEMI. A microvascular obstruction (MVO) is found

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in most of the cases. Moreover, in a significant proportion of subjects, MVO leads to intramyocardial hemorrhage, associated with high risk of complications and adverse outcome[6–12].

Short and long term prognosis is also linked to infarct location, size, and collateral circulation. They appear to be major determinants of the left ventricular (LV) adverse remodeling and cardiac arrhythmias[4,13-16].

ROLE OF INFLAMMATION

Current data suggest a complex relationship between inflammation and cardiac remodeling, respectively arrhythmogenesis[17-20].

Inflammation holds a key role in tissue healing. Its involvement in the preclinical phase and post reperfusion evolution of patients with STEMI has been extensively evaluated in recent studies. Apparently, the same inflammatory mechanisms responsible for tissue healing, if not adequately controlled, have the potential to induce adverse ventricular remodeling. The rapid complement cascade activation subsequent to the ischemic injury stimulates different pathways signaling tissue damage. Further activation of the nuclear factor-kB and inflammasomes provides essential elements of the cytokine response to AMI. Moreover, the embolisation of inflammatory material from unstable plaques into the distal microcirculation before reperfusion therapy may represents another potential source of inflammatory triggers[3,21-24].

In STEMI, hours to days before the clinical onset, the fresh thrombus is unstable and may embolise into the distal microcirculation, generating pre procedural MVO and/or interstitial inflammatory injury. Additionally, the significant recruitment of neutrophils and the production of cytokines, chemokines and other proinflammatory stimuli during the ischemia-reperfusion process is involved in the development of microvascular dysfunction[11]. The irreversible microvascular damage and subsequent intramyocardial hemorrhage leads to iron deposition within the myocardium[25].

However, local inflammation is only one of the multiple mechanisms involved in arrhythmogenesis. Systemic inflammation also appears to play a significant role through a variety of direct and indirect pathways such as:

- induction of ischemic heart disease
- myocardial dysfunction
- cytokine effect
- activation of systemic coagulation response
- bacterial components (endotoxins)[17-20]

In the setting of either acute or chronic myocardial ischemia, the electrical vulnerability results from the interaction between the injured myocardium (with altered electrophysiological properties) and the particular biohumoral "atmosphere". The later is characterized by sympathetic activation, high level of catecholamine, metabolic residues and proinflamatory elements (such as CRP, IL-1, IL-6, IL-8, TNF-α, etc)[18,20,26-28]

Severe systemic inflammation has the potential to induce myocardial dysfunction, a well-known arrhythmogenic trigger. Increased wall stress and proinflamatory cytokines (as mentioned above) appear to promote heart rhythm disorders in arrhythmia-prone patients (with STEMI, cardiomyopathy, etc), possibly by reducing the arrhythmogenic threshold[18,20,29,30].

Moreover, proinflamatory cytokines influence both coagulation and fibrinolytic systems promoting the proper environment for arrhythmia development. On the other hand, a number of hemostatic markers are associated with new-onset atrial fibrillation supporting the hypothesis that endothelial dysfunction and oxidative stress are potential indirect arrhythmogenic mechanisms[31-33].

Despite recent advances, the underlying pathophysiology of infarction-related arrhythmias is not fully understood and further studies are needed.

Table 1. Heart rhythm disorders associated with acute myocardial infarction.

Supraventricular arrhythmias	Ventricular arrhythmias	Conduction abnormalities
Sinus tachycardia	Premature Ventricular Contractions	Atrioventricular Blocks (first, second and third degree)
Sinus bradycardia	Accelerated Idioventricular Rhythm	Intraventricular Blocks (left anterior fascicular block, right bundle branch block, left bundle branch block)
Atrial fibrillation	Sustained/Non-sustained Ventricular Tachycardia	
Atrial flutter	Ventricular Fibrillation	
Premature atrial contractions		
Paroxysmal supraventricular tachycardia		
Accelerated junctional rhythms		
Junctional bradycardia		

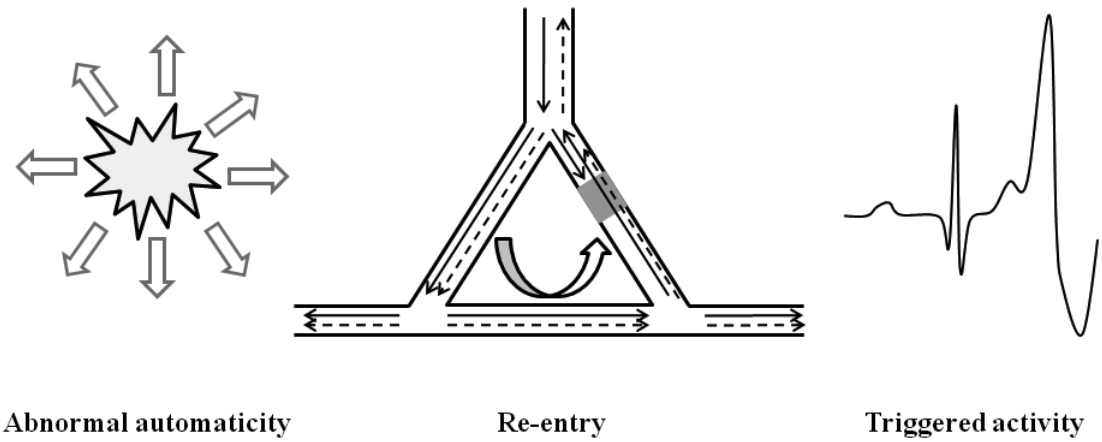

Figure 1. Arrhythmia mechanisms in patients with acute myocardial infarction: Abnormal automaticity – Spontaneous depolarization outside the sinoatrial node. Re-entry - Wave fronts travelling around an area of unidirectional block and reexcitement of previously activated cardiomyocytes (unidirectional block – grey area). Triggered activity - Oscillations in membrane voltage induced by one or more preceding action potentials.

HEART RHYTHM DISORDERS

During AMI, local and systemic conditions provide a suitable environment for a variety of rhythm and conduction disorders as shown in Table I[34,35]. The complex interaction between the arrhythmogenic triggers and the proarrhythmic substrate supports any of the classical arrhythmogenic mechanisms: abnormal automaticity, triggered activity and re-entry (Figure 1)[26,36,37].

Supraventricular arrhythmias

With the exception of sinus bradycardia / tachycardia and atrial fibrillation / flutter, all other supraventricular arrhythmias are uncommon during myocardial infarction[34,35].

Spontaneous activity of the sinoatrial node is under neurogenic (parasympathetic and sympathetic nervous system) or hormonal control, but a direct modulation of ionic currents by metabolic inhibition is also possible[36].

Sinus bradycardia is usually present in the first 24 hours of inferior AMI due to increased vagal tone. Uncommonly, it can be found in case of ischemia of the sinoatrial (SA) node, as a reperfusion arrhythmia or after medication[38,39].

Sinus tachycardia develops soon after symptoms onset and is more common in anterior AMI, usually with impaired LV, reflecting the degree of sympathetic activation[40,41].

Atrial fibrillation appears usually within the first 72 hours in patients with AMI and significant comorbidities. It has a complex ethiopathogenesis involving atrial dysfunction (atrial ischemia/infarction or atrial stretching), ischemia of the SA and atrioventricular (AV) node, increased sympathetic tone, local and systemic inflammation as well as iatrogenic factors[42,43].

Ventricular arrhythmias

Premature ventricular complexes (PVCs), ventricular tachycardia (VT) and ventricular fibrillation (VF) are common in the peri-infarct period. They result from the interaction between the proarrhythmic substrate, modulating factors and arrhythmogenic triggers[44–46].

Acute ischemia leads to myocardial damage with subsequent alteration of the electrophysiological properties of the myocardial fiber acting as arrhythmogenic substrate. Changes in the action and resting potential of the membrane subsequent to altered transmembrane ionic flow lead to abnormal conduction, refractoriness and automaticity of the myocyte[26,36]. Delayed conduction through a damaged myocardium (as potential substrates for ventricular arrhythmias (VA) re-entry) can be assessed noninvasively using ventricular late potentials (VLPs). They consist of the presence of electrical activity after the end of the standard QRS complex (Figure 2)[47].

Electrolytic imbalance (hypopotasemia, hypomagnesaemia), ongoing ischemia, impaired left ventricular (LV) function and generalized autonomic dysfunction (increased sympathetic activity associated with high levels of catecholamines) are the modulating factors[4,15,16,48].

Myocardial stretch short-circuits and injury currents in the border zone, Ca^{2+} overload in either Purkinje fibers or cardiomyocytes as well as variations in cardiac cycle length act as arrhythmia triggers[26,36].

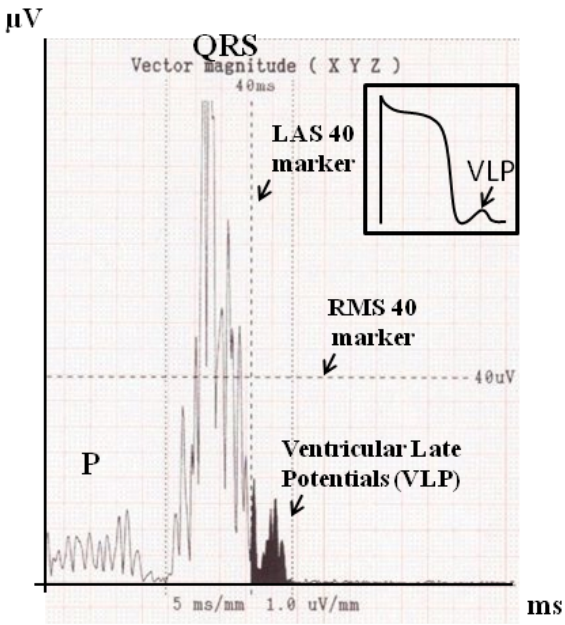

Figure 2. Assessment of the ventricular late potentials using Signal Averaged ECG (3 parameters (average values) derived from multiple beats): filtered QRS duration >114ms; LAS 40 (=low amplitude (<40 µV) signal duration) > 38ms; RMS 40 (=root mean square voltage of the terminal QRS (last 40ms) <20µV. Noise should be minimal (standard deviation of the TP segment <1 µV).

VA in the context of myocardial infarction is the result of the interplay between different events such as ischemia, necrosis, reperfusion, healing, scar formation and autonomic changes. They are responsible for the development and perpetuation of the arrhythmia[4,15].

Underlying mechanisms of the VA vary with time and have different prognostic implications.

In the early phase, the electrical vulnerability manifests as either polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF). Experimental data showed that arrhythmias occurring in the first 2 to 10 minutes after coronary occlusion, also called phase 1a VA, have re-entry as dominant mechanism while abnormal automaticity could play a minor role. Rhythm disorders that develop from 10 to 30 minutes after coronary occlusion, also called phase 1b VA, have re-entry as well as abnormal automaticity as likely dominant mechanism[36,49].

Delayed VAs usually occurs from 6 to 48h from STEMI onset. Their dominant mechanism is abnormal automaticity. Triggered activity (due to delayed afterdepolarization) and a combination of abnormal automaticity and re-entry are also possible. The most frequent VA are PVCs, non-sustained VT and accelerated idioventricular rhythm (AIVR)[50,51].

The time period between the early and delayed phase is characterized by the presence of rare PVCs due to abnormal automaticity[26,52,36].

VA in some patients is considered to be related to reperfusion, which can be either spontaneous or as a result of medical intervention (thrombolysis or percutaneous coronary intervention). Triggered activity is the dominant mechanism. The typical example is AIVR (which is neither sensitive nor specific for effective reperfusion)[26,36,56-60].

CONDUCTION ABNORMALITIES

The most common electrical conduction disorders encountered in AMI are summarized in Table 1. They are the consequence of autonomic imbalance (increased vagal tone) or ischemia/infarction affecting the electrical conduction system.

Conduction abnormalities associated with inferior infarction are more common and can develop from presentation up to days. They usually have a benign course.

Those associated with anterior infarction are less common. They are related to the extent of myocardial damage and have prognosis value[61-63].

Perspectives

A comprehensive understanding of the ethiopathogenesis of a certain disease is a prerequisite for the development of effective therapies. It allows addressing specific targets or particular pathways.

Despite the plethora of medical and interventional therapies available, a significant number of patients with STEMI develop heart failure and sudden cardiac death[3]. The reason why this subgroup has a negative prognosis is still under debate. Preventing adverse cardiac remodeling could reduce the incidence of heart failure and cardiac arrhythmias, with direct impact on survival and quality of life.

The involvement of inflammation as key mechanism, in the genesis of both AMI (with subsequent cardiac remodeling) and cardiac arrhythmias offers new therapeutic perspectives. Several anti-inflammatory drugs that have been tested over time (steroids, non-steroidal anti-inflammatory drugs, colchicines, cytokine blockers and modulators)[22,24,64-66]. Despite some encouraging results, none have entered daily clinical practice, supporting the need for further research.

Conflict of interest: none declared.

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