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Spatial organization of acute myocardial ischemia

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Abstract

Introduction: Myocardial ischemia is a pathological condition initiated by supply and demand imbalance of the blood to the heart. Previous studies suggest that ischemia originates in the subendocardium, i.e., that nontransmural ischemia is limited to the subendocardium. By contrast, we hypothesized that acute myocardial ischemia is not limited to the subendocardium and sought to document its spatial distribution in an animal preparation. The goal of these experiments was to investigate the spatial organization of ischemia and its relationship to the resulting shifts in ST segment potentials during short episodes of acute ischemia.

Methods: We conducted acute ischemia studies in open-chest canines (N = 19) and swines (N = 10), which entailed creating carefully controlled ischemia using demand, supply or complete occlusion ischemia protocols and recording intramyocardial and epicardial potentials. Elevation of the potentials at 40% of the ST segment between the J-point and the peak of the T-wave (ST40%) provided the metric for local ischemia. The threshold for ischemic ST segment elevations was defined as two standard deviations away from the baseline values.

Results: The relative frequency of occurrence of acute ischemia was higher in the subendocardium (78% for canines and 94% for swines) and the mid-wall (87% for canines and 97% for swines) in comparison with the subepicardium (30% for canines and 22% for swines). In addition, acute ischemia was seen arising throughout the myocardium (distributed pattern) in 87% of the canine and 94% of the swine episodes. Alternately, acute ischemia was seen originating only in the subendocardium (subendocardial pattern) in 13% of the canine episodes and 6% of the swine episodes ($p < 0.05$).

Conclusions: Our findings suggest that the spatial distribution of acute ischemia is a complex phenomenon arising throughout the myocardial wall and is not limited to the subendocardium.
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Keywords: Spatial organization; Acute myocardial ischemia; Subepicardium; Subendocardium

Introduction

Despite a century of research and practice, the clinical accuracy of the electrocardiogram (ECG) to detect and localize myocardial ischemia remains less than satisfactory [1]. Myocardial ischemia occurs when the heart does not receive adequate oxygen-rich blood to keep up with its metabolic requirements, and severe ischemia can lead to myocardial infarction and life-threatening arrhythmias. Early and accurate detection is therefore an essential component of managing this condition. In the emergency room (ER), a resting 12-lead ECG is often recorded in patients with symptoms of angina (chest pain). However, such a single resting ECG is normal in up to 50% of patients with chronic, stable angina [2]. Far from static, ischemia is known to be a dynamic condition that reflects a changing imbalance between blood supply and metabolic demand. This dynamic behavior presents diagnostic challenges and encourages continuous monitoring, which is feasible only with a technique like the ECG. Outside the emergency room, it is natural that examination of the ECG under physical stress conditions, or exercise testing (ET), has long been in widespread clinical use. A meta-analysis (24,047 patients with interpretable resting ECG in 147 studies) found exercise ECG without imaging to have a pooled sensitivity of 68% and specificity of 77% for detection of coronary artery disease [2]. Thus, ET is characterized by poor sensitivity and specificity, limiting its diagnostic usefulness. Due to the extremely high incidence of ischemia and the many practical and economical advantages of ECG based testing, any

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improvements in this technique and the interpretation of the data it gathers will have a profound impact on clinical practice.

The most common clinical ECG marker for myocardial ischemia detection is the ST segment, that portion of the ECG time signal that lies between the QRS complex and the T-wave. Changes in the ST segment can occur within 15–30 seconds after the onset of ischemia [3] and hence represent one of the earliest markers of the condition. The ST segment represents the period when the ventricles are depolarized, i.e., the ventricular action potentials are all in the plateau phase. In a healthy heart, this means that all regions of the ventricles have approximately the same transmembrane potential and that this phase of the normal ECG is isoelectric. However, the ST segment potential can shift above (ST segment elevation) or below (ST segment depression) the baseline during myocardial ischemia, depending on the flow of what are known as "injury currents." These currents are the result of voltage gradients between normal and ischemic regions, gradients that arise because of differences between the action potentials (AP) of ischemic and normal cells that include localized shortening, diminishing amplitude, and a decrease (more positive value) in resting membrane potential. Furthermore, the change in the resting potential of ischemic cells (due to increased K^+ efflux) causes a TQ segment shift [4], whereas the shortening of AP duration due to activation of I_{KATP} channel causes the ST segment shift [5]. A change in the plateau potential to a less positive (more negative) value in the ischemic region, in addition to a shortening of its duration, will also contribute to ST segment changes. Thus, the ST segment elevation on the body surface is a combination of a TQ segment change and ST segment change. The resulting injury currents can produce an ST segment *elevation* in an extracellular or body-surface electrode if they are directed *toward* the recording electrode or ST segment *depression* if they are directed *away* from the electrode.

Classic electrocardiographic theory builds on these biophysically sound concepts with additional assumptions about the spatial distribution of healthy and ischemic tissues; however, these assumptions may be too simplified to explain both experimental and clinical observations. The historical basis for many of these assumptions lies in postmortem examinations of infarcted hearts [6] under the additional assumption that the location and extent of eventual scar and infarct zones match approximately the ischemic regions that arise acutely following onset of ischemia. Previous studies of acute ischemia were instead based on measured potentials primarily from the epicardial and endocardial surfaces [7]. While surface potentials are a reflection of intramyocardial events, it is only possible to *infer* the underlying bioelectric sources rather than measure them directly. Intramural potentials have also been measured using wick electrodes (10–40 recording sites) [8] but have been limited by low spatial resolution. With the recent development of flexible multiple electrode needles [9] we can now capture extracellular potentials throughout the ventricular wall with high spatial resolution (250 recording sites).

From these early experiments have come several elements that now make up the prevailing putative explanation for clinical observations of ST segments during acute ischemia. Central to this explanation of the spatial dynamics of ischemia is the assumption that at low grades of perfusion deficit, myocardial ischemia is localized to the subendocardium (innermost region of the heart wall) [3]. Justification for this assertion includes the notion that this region has the highest metabolic demand and is the most distal perfusion zone and hence most vulnerable [3]. Moreover, with increased stress, ischemia was thought to progress over time uniformly toward the epicardium (outermost region), eventually becoming transmural (spanning the full thickness of the heart wall). According to this theory, ischemia localized to the subendocardium would generate injury currents flowing away from the epicardial or body-surface electrodes toward the localized subendocardial ischemic region. Thus ST segment depression is thought to indicate subendocardial ischemia. Moreover, transmural ischemia would then produce injury currents flowing toward the recording electrodes located above the affected region of the heart, resulting in ST segment elevations. Many decades of clinical practice and experimental studies have shown that, indeed, superficial leads with ST segment elevation can be linked spatially to the region of ischemia and thus provide a means to localize transmural ischemia from the body surface. However, the same is not true of the ability of ST segment depression to locate nontransmural ischemia [10].

Preliminary results from our group using intramyocardial recordings do not support the assertion that nontransmural ischemia arises only in the subendocardium [11] and have motivated a comprehensive evaluation of the spatial distribution of acute ischemia based on high-resolution measurements under a range of conditions. Our goal in this study was to evaluate the conventional mechanisms for nontransmural ischemia using intramural electrodes to measure three-dimensional potential distributions in the ventricles of animals exposed to acute ischemia. We conducted a series of 29 separate experiments under a range of acute ischemia conditions using two different in situ animal models. To interpret the resulting electrograms, we assumed that localized ischemia causes localized elevations in the extracardiac ST segment potentials. We measured three-dimensional surface and transmural potential distributions under study protocols that altered both the local coronary supply and global metabolic demand.

Methods

Experimental preparation

The goal of these experiments was to detect the three-dimensional distribution of ischemia-induced shifts in ST segment potentials during the acute phase of short episodes of ischemia created by reduced coronary flow and an increased rate of contraction. We performed experiments on open-chest, intact canines and swines using multipolar intramural needle electrodes and epicardial surface electrodes. Study subjects included 29 animals: 19 purpose bred dogs and 10 adult mini pigs, following the approval from the

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