Basic Electrophysiologic Mechanisms of Sudden Cardiac Death Caused by Acute Myocardial Ischemia and Infarction

Andrew L. Wit, PhD

KEYWORDS

• Ischemia • Action potentials • Gap junctions • Reentry

KEY POINTS

- Ischemia causes increased $[K^+]_o$ that depolarizes the resting potential.
- Ischemia causes reduction in phase 0 depolarization.
- Ischemia causes gap junction uncoupling.
- Slowing of conduction and conduction block lead to formation of reentrant circuits.
- Flow of injury currents cause arrhythmias.

INTRODUCTION

Sudden cardiac death has traditionally been defined as "the unexpected natural death from a cardiac cause within a short period, usually $\leq$1 hour from the onset of symptoms in a person without any prior conditions that would appear fatal."[1,2] A rapid death of this kind is often a result of cardiac arrhythmias, although a significant number of deaths are unwitnessed. Up to 80% of individuals who suffer sudden cardiac death have coronary artery disease.[1] Approximately 20% of patients who survive cardiac arrest develop transmural myocardial infarction. Transient myocardial ischemia caused by coronary vasospasm or unstable platelet thrombi also play a role in precipitating fatal arrhythmias.[1]

Myocardial ischemia, whether transient or long lasting, resulting in myocardial infarction causes changes in the electrical properties of myocardial cells. Experimental laboratory studies on animal models buttressed by clinical observations and studies during the past 50 years have established that all ventricular arrhythmias associated with myocardial ischemia and infarction do not have the same electrophysiologic mechanisms. Rather, arrhythmias can be subdivided into acute, subacute, and chronic phases according to their time of occurrence in relation to the ischemic event, for example, a coronary artery occlusion.[3,4] In the experimental laboratory, the time of onset of ischemia is controlled and, therefore, well-documented as compared with clinical arrhythmias where, sometimes, the time of onset of ischemia may be uncertain. Therefore, much of the information concerning these electrophysiologic mechanisms comes from experimental models of ischemic arrhythmias and sudden death.[3,4] In this brief review, some of the basic effects of ischemia on cardiac cells and how these effects lead to fatal ventricular arrhythmias, in particular ventricular fibrillation (VF), are described although the experimental models and methods of original data collection are not. Rather, the experimental results are presented in the form of a narrative that provides

Department of Pharmacology, College of Physicians and Surgeons of Columbia University, 630 West 168th Street, New York, NY 10032, USA
E-mail address: alw4@cumc.columbia.edu

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a summary of current concepts of the mechanisms of sudden death in acute ischemia. For more complete reviews the reader is referred to references.[3–5]

THE ACUTE PHASE OF MYOCARDIAL ISCHEMIA AND INFARCTION

The term acute phase of myocardial ischemia refers to events occurring within the first 2 to 4 hours after the sudden reduction of blood flow through a coronary artery. In many individuals who develop VF outside the hospital, collapse occurs almost instantly (within 1 minute) after the onset of symptoms manifested as chest pain or dyspnea,[6,7] indicating that if the onset of symptoms can be equated with the onset of ischemia, ischemia need only to exist for a short time to induce arrhythmias. This proposed relationship between transient ischemia and arrhythmias has been corroborated by studies in patients with transient coronary artery spasm in whom ventricular arrhythmias, including VF, occur within minutes after the beginning of electrocardiographic signs of myocardial ischemia caused by the spasm.[8] Arrhythmias can result both from transient ischemia during ST segment changes and from reperfusion (after return of the ST segment to normal). When coronary artery occlusion is not transient but persists (because of, for example, occlusive thrombi or long-lasting spasm), ischemic cells become irreversibly damaged and myocardial infarction results. The incidence of ventricular arrhythmias during the acute phase of myocardial infarction is higher than for transient ischemic episodes, although it varies widely in different reports (for a review see reference[9]).

It is generally accepted that the occurrence of lethal arrhythmias is the result of the interplay between substrate, trigger, and modulating factors. The electrophysiologic changes brought about by acute ischemia directly on cardiac muscle cells creates the substrate. Arrhythmias in the setting of acute ischemia or infarction are more likely to become manifest in the presence of appropriate triggers, such as changes in autonomic nerve activity, heart rate, and so on. Modulating factors, such as the activity of the sympathetic nervous system, electrolyte disturbances (eg, low serum potassium levels),[10] or impaired left ventricular function may modify both the substrate and the trigger. The description that follows focuses on the substrate changes caused by acute ischemia.

Effects of Ischemia on Ventricular Muscle Substrate Electrophysiology

Myocardial ischemia that results from coronary artery occlusion has a profound effect on the electrophysiologic properties of cardiac cells resulting from a number of factors in the ischemic environment. Extracellular [K^+] is initially elevated, along with hypoxia, a low pH, no substrates, high P_{CO_2}, and accumulation of substances such as lysophosphoglycerides and catecholamines. Each may have an influence on ion channels and the various combinations may exert effects that are not predictable from the action of each substance alone.[3–5]

Within a few minutes after coronary artery occlusion, the amplitude, upstroke velocity, and duration of ventricular muscle action potentials normally supplied by that artery, decrease along with the depolarization of the resting membrane potential (**Fig. 1**, lines 5–9 min of occlusion). After a reduction to resting membrane potentials from a normal value of approximately −80 mV, to around −60 to −65 mV, the cells become unresponsive (see **Fig. 1**, lines 11–13 min of occlusion).[11,12] The phase of unresponsiveness is transient: with maintained coronary occlusion, transmembrane potentials can again be recorded in previously unresponsive cells after about 15 to 30 minutes. The action potentials at that time are abnormal in that they have a short duration, a low amplitude, and a reduced upstroke velocity, yet they are able to propagate. After 40 to 60 minutes, these action potentials disappear and the cells in the center of the ischemic zone become inexcitable.

The changes in resting membrane potential and inward and outward currents during the action potential lead to alterations in conduction, refractoriness and impulse initiation, all of which contribute to the occurrence of ventricular arrhythmias. In addition to changes in these active membrane properties, passive electrical properties are changed as well, and these changes also influence propagation in ischemic myocardium and contribute to arrhythmogenesis (the mechanisms are described elsewhere in this article).

The dramatic changes in electrical activity are rapidly reversible within 20 to 30 minutes if occlusion is transient, owing to readmission of oxygen and nutrients and the washout of substances accumulated in the extracellular space. Rapid reversal of electrical changes cannot occur after prolonged periods of occlusion beyond 20 to 30 minutes.

Resting membrane potential

Cells in the ischemic region depolarize within minutes after coronary artery occlusion from normal values of around −80 mV to between −65 and −60 mV.[11–13] The decrease in resting potential is linked at least partly to alterations in distribution