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Effects of a Combination of Acidosis, Lactate, and Lysophosphatidylcholine on Action Potentials and Ionic Currents in Guinea Pig Ventricular Myocytes

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Summary: The aim of this study was to determine the electrophysiological effects of a combination of factors that are of importance during myocardial ischaemia, i.e., acidosis, lactate, and lysophosphatidylcholine, in ventricular myocytes. Intracellular microelectrode techniques were used to record action potential and ionic currents in ventricular myocytes before, during, and after a 30 min exposure to a salt solution that was acidotic (pH 6.8), and contained lactate (10 m*M*) and lysophosphatidylcholine (5 μ*M*). Single ventricular myocytes were dissociated enzymatically from guinea pig hearts, and perfused with either normal or modified physiological salt solution. Combined acidosis, lactate, and lysophosphatidylcholine resulted in a reduction in the resting membrane potential and maximum rate of depolarisation of phase 0, and flattening of the plateau but prolongation of the action potential duration at 90% repolarisation. Automatic activity was also induced in about one-third of the cells studied. Under voltage-clamp conditions, this combination of factors reduced the peak inward calcium current, on repolarisation after a depolarising step, reduced the steady-state outward current, and reduced the delayed rectifier current, measured as the tail current at the end of a depolarising clamp step. In some cells, a transient inward current was induced by the modified salt solution. It is concluded that the characteristic alterations in action potential characteristics induced by a combination of acidosis, lactate, and lysophosphatidylcholine are likely to result from reductions in the inward Ca current and the background and delayed rectifier K current. **Key Words:** Myocardial ischaemia—Arrhythmias—Acidosis—Lactate—Lysophosphatidylcholine—Action potentials—Membrane currents.

Myocardial ischaemia induces marked electrophysiological derangements in cardiac tissue that provide the substrate for the onset of potentially life-threatening arrhythmias. These electrophysiological derangements are extremely diverse in nature and vary with time after coronary artery occlusion. Within the first few moments of occlusion, there is a lengthening of the action potential followed by a shortening (1), but by 1 h postocclusion a progressive lengthening in the action potential duration of both Purkinje cells and surviving ventricular muscle cells is observed (2,3). In addition to these alterations in action potential duration, the resting membrane potential, maximum rate of depolarisation of phase 0, and action potential amplitude are all decreased (1–3). Intracellular microelectrode studies of the ionic mechanisms that may underlie these ischaemia-induced changes are hampered by the fact that it is impossible to simulate in vitro all of the biochemical and ionic changes that occur during myocardial ischaemia.

In vivo myocardial ischaemia is a complex entity involving hypoxia, substrate deprivation, metabolical alterations, and also intracellular and/or extracellular accumulation of ions and metabolic wastes such as lactate and lysophosphoglycerides (4). Three of these factors, namely hypoxia, acidosis, and high extracellular K^+, are commonly used to simulate the electrophysiological changes that occur during the peak of the arrhythmias that develop within 30 min after coronary artery occlusion when the action potential is abbreviated (5,6). As there

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