CONTEMPORARY REVIEW

Postrepolarization refractoriness in acute ischemia and after antiarrhythmic drug administration: Action potential duration is not always an index of the refractory period

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Action potential duration is widely used as a measure of refractory period in ischemia. Although the end of repolarization closely corresponds to the end of refractoriness in the well-perfused, well-oxygenated myocardium, it is no longer true for the ischemic myocardium, in which the recovery of excitability lags behind full repolarization. The purpose the study was to review this phenomenon of postrepolarization refractoriness during ischemia and after application of various antiarrhythmic drugs. The findings showed that although postrepolarization refractoriness is profoundly proarrhythmic during ischemia, it may protect the heart from reentrant arrhythmias in the absence of depolarization of the resting membrane. An increase in postrepolarization refractoriness induced by sodium-channel–blocking drugs may exert an antifibrillatory action.

KEYWORDS Ischemia; Dispersion of refractoriness; Graded responses; Dispersion of repolarization; Antiarrhythmic drugs; Action potential duration

ABBREVIATIONS APD = action potential duration; **ERP** = effective refractory period; **PRR** = postrepolarization refractoriness; **VF** = ventricular fibrillation

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Introduction

Changes in myocardial excitability are mainly mediated through the conformational changes in the cardiac sodium channel. After being activated, the channel enters its open state and current flows down the electrochemical gradient, normally leading to a depolarization and to the upstroke of the cardiac action potential. The maximum upstroke velocity (dV/dt_{max}) of the action potential is a determinant of conduction velocity. After full activation, inactivation of the channel follows. Only after full repolarization of the action potential the channel enters the resting state again, from which a new activation may occur. These processes are time and voltage dependent. Under normal conditions, the channel recovers from inexcitability as soon as the resting membrane potential has been regained; the end of the refractory period then coincides with the end of repolarization.

Thus, action potential duration (APD) is widely used as a measure of the refractory period, also during acute myocardial ischemia. For example, in a recent article[1] of Heart*Rhythm*, dispersion of APD was measured in globally ischemic hearts. It was stated that " . . . an enhanced dispersion for repolarization is now well known to act as a substrate for arrhythmogenesis."[1] Another group of authors attributed the increased arrhythmogenesis in myocardial ischemia to the dispersion of repolarization across the border and discusses its relation with the dispersion of refractoriness.[2] Although the end of repolarization closely corresponds to the end of refractoriness in the well-perfused, well-oxygenated myocardium,[3,4] it is no longer true for the ischemic myocardium, in which the recovery of excitability lags behind full repolarization. Dispersion of repolarization then markedly underestimates the heterogeneity in refractoriness. The objective of this article was to review this phenomenon of postrepolarization refractoriness (PRR).

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PRR during ischemia

In 1974, Gettes and Reuter[5] studied the recovery kinetics of dV/dt_{max} of the transmembrane potentials of isolated myocardial and Purkinje fibers in control conditions and during superfusion with solutions having an elevated potassium concentration, which depolarized the resting membrane. When the resting membrane potential was more negative than −80 mV, the time constant of recovery of dV/dt_{max} after full repolarization was <20 ms. When the resting membrane potential was between −65 and −60 mV, this value increased to >100 ms. Gettes and Reuter predicted that this would occur in ischemia, since it was known at that

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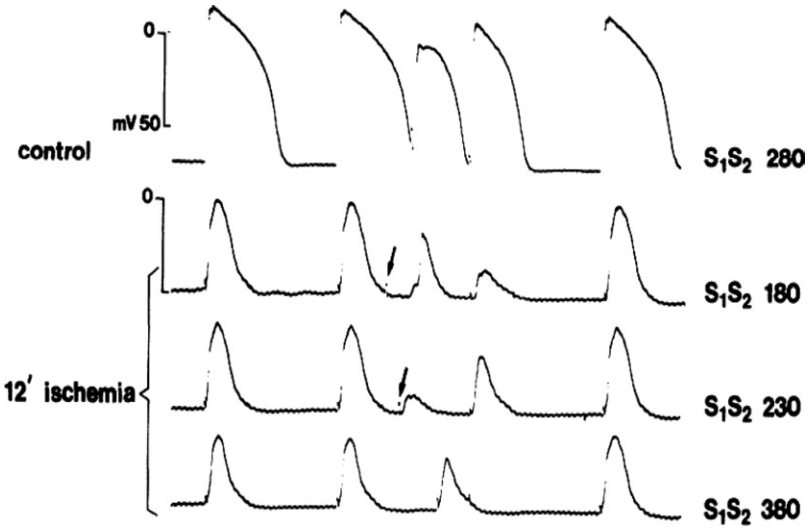

Figure 1 Postrepolarization refractoriness in acute myocardial ischemia. Transmembrane potentials from the intact porcine heart were recorded with floating microelectrodes. After the completion of repolarization, the upstroke of the premature action potential is lower than that of the action potential in response to the last basic stimulus. Before full recovery there is a long period with graded responses. See text for details. Reproduced with permission from Downar et al[8].

time that ischemic cells lose potassium and that potassium accumulates in the extracellular space.[6,7]

Figure 1 shows an example of PRR in the ischemic zone of a Langendorff perfused porcine heart, 12 minutes after the occlusion of the left anterior descending coronary artery.[8] Floating microelectrodes were used to record transmembrane potentials. Basic and premature stimuli were delivered within 1 mm of the microelectrode. In control conditions, the recovery of excitability closely followed repolarization. After 12 minutes of regional ischemia, premature stimuli elicited graded responses over a wide range of coupling intervals, from 230 ms, which hardly produced any response, to 380 ms, which still failed to produce an action potential comparable in amplitude to the basic response.

The fact that during ischemia the heart responded to a premature stimulus that was 100 ms shorter than in the control condition, but with a latency of >100 ms between stimulus and local response, indicates that the refractory period elsewhere in the ischemic zone had decreased to a value shorter than that in the preischemic control condition. In the outer border zone close to the normal zone, there is a small rim of several hundreds of micrometers where anoxia coexists with a normal extracellular potassium concentration. In the remainder of the ischemic zone, oxygen is absent and a large degree of dispersion of extracellular potassium concentrations exists.[9] As a consequence, action potentials with high amplitudes and short durations ("anoxic" action potentials) can be recorded in the "anoxic" zone in which the level of extracellular potassium is only mildly elevated. In regions closer to the central ischemic zone with higher extracellular potassium levels, action potentials with small amplitudes and low upstroke velocity are found ("ischemic" action potentials). Anoxic cells with an extracellular potassium concentration between 6 and 9 mM have short refractory periods, and anoxic cells with extracellular potassium concentrations >9 mM exhibit PRR. This inhomogeneity forms the basis for reentrant arrhythmias.[10]

The threshold for the excitation of the depressed myocardium in the central ischemic zone is also increased. As a consequence, very high stimulus intensities are usually applied in the ischemic tissue when refractoriness is being measured (see also below). This may lead to the paradoxical situation in which the applied current is capable of exciting tissue distant from the site of stimulus application without causing excitation of tissue under the stimulus electrode(s). We deduce that the excited site of Figure 1 (second trace) is remote from the site of stimulation and that it is located in the anoxic-but-normokalemic border zone in which the refractory period is shorter than normal. The premature activation wave supposedly traveled around the area of block and arrived after a time delay when the tissue has regained excitability.

Figure 2 shows the relation between APD and refractory period in the central ischemic zone (blue lines) and in the border zone (red lines) close to the normal myocardium in a Langendorff-perfused porcine heart.[11] After about 6 minutes of ischemia, the APDs of both the central ischemic zone and the border zone have decreased to the same degree. However, because of PRR in the central zone, the difference in refractory periods amounts to >100 ms.

In a study in humans, monophasic action potentials and refractory periods were recorded simultaneously from a single left ventricular epicardial site in patients undergoing coronary artery surgery during cardiopulmonary bypass.[12] A 3-minute period of global ischemia was created by cross-clamping the aorta at 37°C. The refractory period was determined by using the extrastimulus technique at 4 or 2 times the preischemic diastolic threshold (groups 1 and 2: 15 and 11 patients, respectively). During ischemia, APD decreased similarly in both groups (Figure 3A). Over the same time the effective refractory period (ERP) prolonged (Figure 3B), resulting in rapidly increasing disparity between APD and ERP (PRR; Figure 3C). Before ischemia there was a good correlation between ERP and APD that was lost as early as 1 minute of ischemia when APD decreased and ERP increased.