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Amphiphilic Lipid Metabolism and Ventricular Arrhythmias

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12.1 INTRODUCTION

Sudden death associated with coronary artery disease results primarily from disturbances in cardiac rhythm culminating in ventricular fibrillation (Armstrong et al., 1972). During the past decade, the electrophysiological derangements induced by ischaemia have been characterised and several arrhythmogenic mechanisms proposed to explain the high incidence of ventricular fibrillation coincident with an ischaemic insult.

12.2 THE ELECTROPHYSIOLOGICAL DERANGEMENTS CHARACTERISTIC OF EARLY ISCHAEMIA

Ventricular dysrhythmias after coronary occlusion in experimental animals occur during three distinct phases. The earliest (phase 1), which begins within minutes and persists for approximately 30 min, may be analogous to the malignant, pre-hospital phase of acute myocardial infarction. Arrhythmias appearing 12-24 h later (phase 2) or days to weeks after acute myocardial infarction (phase 3) appear to depend upon different electrophysiological alterations and hence different arrhythmogenic mechanisms (Corr and Sobel, 1979). The primary focus of this discussion will be those derangements responsible for the early phase 1 ventricular arrhythmias.

Early phase 1 malignant arrhythmias appear to result from sustained re-entry within ventricular muscle. Thus, extracellular electrograms recorded from ischaemic segments in vivo demonstrate delays in excitation, prolonged electrical activity, fractionation of the waveform and significant reduction of waveform amplitude (Scherlag et al., 1974; Bigger et al., 1977; Penkoske et al., 1978). In addition, intracellular transmembrane potentials recorded in vivo from ischaemic regions
manifest prompt reduction of resting membrane potential, amplitude, $V_{\text{max}}$ of phase 0 and action potential duration (Downar et al., 1977a; Russell et al., 1977; Akiyama, 1981). Fractionation of the action potential and also shortening of refractory period and post-repolarisation refractoriness occur as well, resulting in increased disparity of refractoriness (see chapter 4). The appearance of ventricular fibrillation during the interval soon after the onset of ischaemia has been correlated not only with a delay in activation of the epicardial ischaemic zone persisting beyond the duration of inscription of the T-wave on the surface electrocardiogram (Williams et al., 1974) but also with the appearance of electrical alternans in the intracellular action potentials, probably reflecting intermittent variation of regional refractoriness. Other evidence (Scherlag et al., 1974) implicating re-entry as opposed to enhanced ventricular automaticity as a probable mechanism underlying phase 1 ventricular dysrhythmias includes the following: (1) exacerbation by high right atrial electrical pacing; (2) a slow idioventricular escape rate; (3) inhibition of arrhythmia by efferent vagal nerve stimulation; and (4) absence of enhanced automaticity in vitro in Purkinje cells isolated from ischaemic regions.

Despite each of these findings, specific re-entrant pathways responsible for early phase 1 arrhythmias have not been delineated.

Recently, data implicating two different types of arrhythmogenic mechanisms during phase 1 ventricular arrhythmias have been obtained (Janse et al., 1980, and chapter 4). Findings suggesting that ventricular ectopic activity which initiates ventricular tachycardia or fibrillation is not due to a re-entrant mechanism include the observations that the earliest activation occurs in the normal zone adjacent to the ischaemic border zone and that activation of Purkinje fibres precedes activation in myocardial segments. However, the maintenance of ventricular tachycardia or ventricular fibrillation appears to depend upon both macro and micro re-entrant circuits through the ischaemic regions (Janse et al., 1980, and chapter 4).

Possible electrophysiological mechanisms responsible for initiation of earliest activation in the normal region include current flow from ischaemic to normal regions due to delayed activation of ischaemic regions and hence earlier repolarisation in normal zones. Others include enhancement of phase 4 diastolic depolarisation in Purkinje fibres by depolarising electrotonic current or induction of abnormal types of automaticity, including oscillatory activity at reduced resting membrane potentials due to disparities in the magnitude of depolarisation in ischaemic compared to non-ischaemic regions. Thus, the early phase 1 ventricular arrhythmias may be initiated by alterations in current flow across the ischaemic border sufficient to prematurely excite normal regions. Maintenance of ventricular tachycardia or fibrillation may involve a perpetuation of this early excitation through re-entrant circuits involving slowed conduction and variable refractoriness in ischaemic regions.

In addition to induction of ventricular arrhythmias by sustained occlusion, a rapid onset-ventricular arrhythmia occurs after reperfusion of ischaemic regions and is associated with a high incidence of ventricular fibrillation. Arrhythmias induced by reperfusion may play an important role in the aetiology of sudden cardiac death since relief of coronary spasm may occur spontaneously (Oliva and