



# Arrhythmia and metabolism

**Danielle Feuvray**  
UMR CNRS 8078 & Université Paris-Sud XI, France

Correspondence: Professor Danielle Feuvray, CNRS UMR 8078 & Université Paris-Sud XI,  
Marie Lannelongue Hospital, 92350 Le Plessis Robinson, France.  
E-mail: danielle.feuvray@ibaic.u-psud.fr

The observation that plasma free fatty acid concentrations are increased during and immediately after myocardial infarction was made several decades ago [1]. Clinical observations showed that plasma free fatty acid concentrations greater than those that could bind to the two primary affinity-binding sites on albumin were associated with an increase in the incidence of ventricular arrhythmias during myocardial infarction [2]. Subsequently, it was proposed that certain arrhythmias have a metabolic basis [3]. The oxygen-wasting effects of increased provision of free fatty acids to the acutely ischemic myocardium were found to be augmented by impairment of the uptake or utilization of glucose [4]. These early findings led to the views that provision of glucose is "good" [5] and that the presence of increased circulating free fatty acid concentrations is "bad" [3] for the ischemic myocardium.

During ischemia,  $\beta$ -oxidation of long-chain fatty acids in mitochondria is inhibited and there is an intracellular accumulation of metabolites such as long-chain acyl carnitine and acyl coenzyme A. The metabolites that accumulate during ischemia-reperfusion may, indirectly, lead to ionic disturbances; in particular, they may alter both sodium and calcium homeostasis and contribute to electrical dysfunction. Increases in intracellular sodium ( $\text{Na}^+_i$ ), which have been demonstrated during ischemia-reperfusion [6], may indeed have functional and proarrhythmogenic consequences [7], because increases in  $\text{Na}^+_i$  in turn generate  $\text{Ca}^{2+}$  loading via reverse  $\text{Na}^+-\text{Ca}^{2+}$  exchange. Interestingly, it has been shown that trimetazidine, which inhibits fatty acid oxidation in the heart [8], also significantly reduces the increase in  $\text{Na}^+_i$  during ischemia and early reperfusion [6]. The most plausible underlying mechanisms for the gain in  $\text{Na}^+_i$  during ischemia are a decrease in  $\text{Na}^+$  extrusion via  $\text{Na}^+/\text{K}^+$ -ATPase or an influx of  $\text{Na}^+$  via  $\text{Na}^+-\text{H}^+$  exchange and the voltage-

gated  $\text{Na}^+$  channel, or both.  $\text{Na}^+-\text{H}^+$  exchange activity may be rapidly inhibited by extracellular acidosis during total ischemia, which suggests that voltage-gated  $\text{Na}^+$  channels may have a significant role as mediators of ischemic  $\text{Na}^+$  loading [9]. A large proportion of these channels become rapidly non-recruitable in ischemic tissues after resting membrane potential depolarization, and action potentials initially shorten and subsequently cease with exhaustion of cellular ATP.  $\text{Na}^+$  influx continues, however, through non-inactivated voltage-gated sodium channels, giving rise to persistent window currents [10,11]. Moreover, the slowly inactivating component of the  $\text{Na}^+$  current also increases substantially during ischemia, amplifying  $\text{Na}^+$  influx [11,12]. In this context, it has been shown that long-chain acyl carnitine, which accumulates in the cell membrane during ischemia, markedly increases the slowly inactivating component of the  $\text{Na}^+$  current [12]. Experimental data also indicate that acyl carnitine, like ouabain, produces a reversible inhibition of the  $\text{Na}^+/\text{K}^+$  pump current [13] and thereby a decrease in  $\text{Na}^+$  extrusion. Therefore, specific myocardial metabolic modulation such as with trimetazidine, which limits the accumulation of long-chain acyl carnitine during ischemia [14], may well limit the increase in  $\text{Na}^+_i$  via slowly inactivating the sodium channels and causing a relative increase in  $\text{Na}^+/\text{K}^+$  pump function. This would be particularly important in reducing ionic disturbances and the susceptibility of the myocardium to malignant arrhythmogenic events.

The experimental evidence summarized above probably represents only a few aspects of the fascinating machinery that may underlie the metabolic signals of arrhythmia. This issue of *Heart and Metabolism* will highlight the importance of metabolic disturbances, associated either with an imbalance of metabolic substrates or, as most recently reported, with genetic mutations that can alter the function of a key

regulatory enzyme of cardiac energy metabolism [15] and downstream effectors such as cardiac ion channels [16] and, possibly, other ion transporters. ■

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