**Pharmacology of Cardioprotection**

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**Introduction**

Protection of the heart against ischemia is a difficult task, as is reflected by the variety of biochemical and pharmacologic approaches evaluated in the past and by the many controversial experimental and clinical data reported in this field [1–7]. The intention of this contribution is not to consider any of these procedures in detail, but rather to outline in brief the most promising interventions used in this kind of study (which will be discussed in detail in later contributions).

Before undertaking such a discussion it is necessary to reconsider very briefly those steps of the infarction process which might eventually be susceptible to therapeutic interventions (Fig. 1). The basic events involved in the transition from ischemia to infarction include a restriction of oxygen and substrate delivery, and

![Sequence of major events diagram]

**Potentially useful interventions**

- Improvement of collateral flow
- Reduction of cardiac work
- Metabolic support
- Antagonism of potentially harmful mediators

**Pharmacological tools**

- Vasodilators
- Aggregation inhibitors
- Beta-adrenergic blockers
- Vasodilators
- GIK-Solution
- Beta-adrenergic blockers
- Calcium antagonists
- Thromboxane antagonists
- Prostacyclin analogues
- Radical scavengers
- Antiinflammatory drugs

*Fig. 1. Synopsis of the sequence of events in myocardial ischemia and of potentially useful therapeutic interventions (GIK glucose-insulin-potassium)*

H. Schmutzler et al. (eds.), *Limitation of Infarct Size*  
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Ischemia-induced changes in myocardial calcium and related processes

Fig. 2. Schematic diagram of the ischemia-induced changes in myocardial calcium turnover and related processes

an impaired washout of metabolites, which finally lead to the formation of potentially harmful mediators and activators of cell degradation [1–3, 7–9]. The initial process depletes the ischemic myocardium of ATP and activates anaerobic metabolism, causing production of lactate and protons, which are then accumulated, causing intracellular acidosis and probably deleterious enzyme activation.

Special attention has focused recently on the role of Ca ions [5, 8, 10–12] which accumulate as a result of several mechanisms such as: (a) increased inward current through potential-operated channels in partially depolarized cell membranes; (b) inhibition of the outward transport mechanisms; and (c) release from intracellular stores. The resulting cytosolic Ca overload is supposed to be an important feature of irreversible cell damage by triggering the activation of proteases and lipases and the release of potentially harmful mediators. These processes together contribute to membrane destruction which is seen as the critical event in irreversible cell damage – it determines the “point of no return” (Fig. 2).

Only the initial changes of this complex sequence of events are reversible, but as the duration or severity of ischemia increases, and the cellular integrity is destroyed, the injury becomes irreversible [2, 7, 8, 13, 14]. Therefore, the whole concept of myocardial protection is crucially dependent both on the endogenous rate of evolution from severely ischemic to irreversibly injured myocardium, which is different in any particular experimental or clinical setting, and on the timing of