Cardioprotective effects of amlodipine in the ischemic-reperfused heart

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4/0/15307

Amlodipine is a dihydropyridine calcium entry–blocking agent characterized as having a slow onset and relatively long duration of action with minimal effects on cardiac electrophysiology and myocardial contractility.

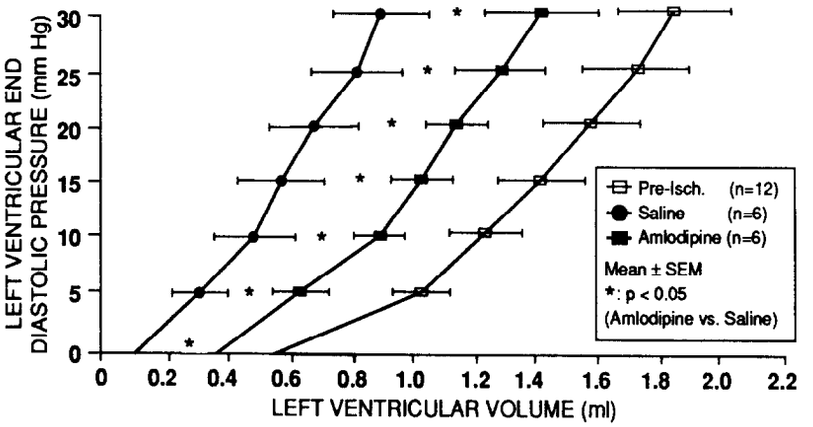

Fig. 1. Left ventricular compliance in the cat-isolated heart before and after being subjected to 60 minutes of global ischemia followed by reperfusion for 60 minutes. Pretreatment with amlodipine resulted in a preservation of compliance compared with nontreated control hearts (compare middle graph with that to the far left).

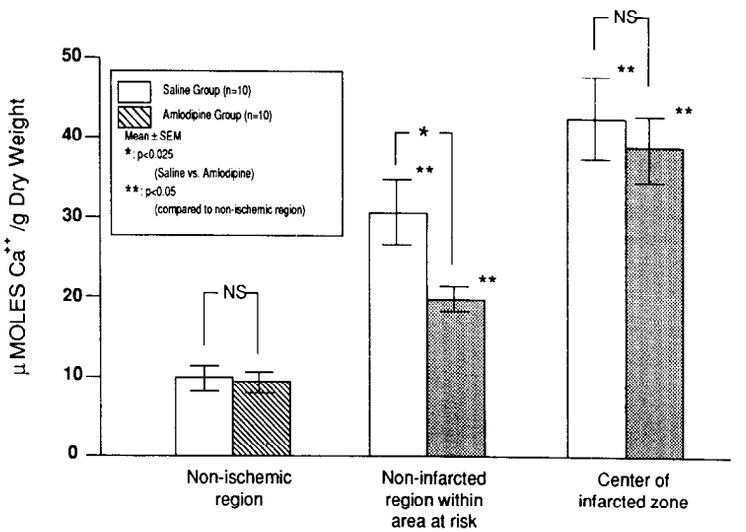

Fig. 2. Tissue concentration of calcium ion in the canine heart after 90 minutes of regional ischemia followed by 6 hours of reperfusion. Amlodipine reduced the calcium content in the noninfarcted tissue within the risk region.

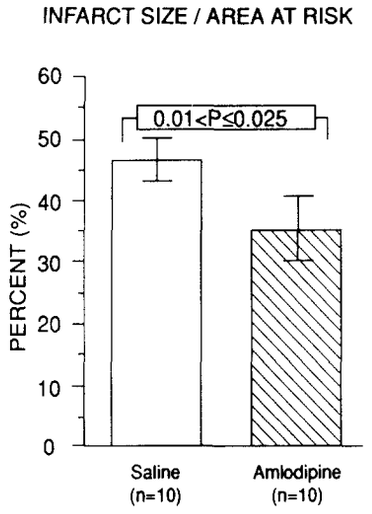

Fig. 3. Infarct size in the canine heart. The left circumflex coronary artery was occluded for 90 minutes followed by 6 hours of reperfusion. Infarct size was assessed by the triphenyltertazolium staining method. Pretreatment with intravenous amlodipine, 150 μg/kg given 15 minutes before reperfusion, resulted in a significant decrease in the size of the ultimate infarct. Size of the risk regions in the two groups of animals did not differ.

The protective effect of amlodipine was studied in isolated, blood-perfused cat hearts made globally ischemic for 60 minutes followed by reperfusion for 60 minutes. Ischemia-induced alterations of left ventricular–developed pressure and compliance were monitored. In 11 control and seven amlodipine-treated hearts, amlodipine produced significant decreases in coronary vascular resistance, as assessed by changes in perfusion pressure (120 ± 1 to 100 ± 4 mm Hg) and myocardial oxygen consumption (6.2 ± 0.4 to 4.4 ± 0.4 ml oxygen/min/100 gm). Amlodipine administered before the onset of global ischemia decreased the development of ischemic contracture as reflected by a progressive increase in resting left ventricular diastolic pressure (Fig. 1). The return of contractile function 60 minutes after reperfusion was improved significantly in the amlodipine-treated group compared with controls, and there was better maintenance of the tissue concentrations of Na^+, Ca^{2+}, and K^+ (Fig. 2).

A canine model of regional myocardial ischemia (90 minutes) followed by 6 hours of reperfusion was used to assess the cardioprotective effects of amlodipine, 150 μg/kg, administered 15 minutes before reperfusion. Infarct size, expressed as a percentage of the area at risk, was significantly smaller in the amlodipine-treated group ($n = 10$) compared with the control group ($n = 10$) (34.5% ± 3.8% vs 45.9% ± 2.8%, $p = 0.027$) (Fig. 3). Risk region size did not differ between groups, and both groups were comparable with respect to hemodynamic parameters of heart rate, blood pressure, rate pressure product, and total blood flow in the left circumflex coronary artery.

We conclude that amlodipine reduces myocardial ischemic injury by mechanism(s) that may involve a reduction in myocardial oxygen demand, as well as by positively influencing transmembrane Ca^{2+} fluxes during ischemia and reperfusion.