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H(2) mediates cardioprotection via involvements of K(ATP) channels and permeability transition pores of mitochondria in dogs

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Abstract

Purpose: Inhalation of hydrogen (H(2)) gas has been shown to limit infarct size following ischemia-reperfusion injury in rat hearts. However, H(2) gas-induced cardioprotection has not been tested in large animals and the precise cellular mechanism of protection has not been elucidated. We investigated whether opening of mitochondrial ATP-sensitive K+ channels (mK(ATP)) and subsequent inhibition of mitochondrial permeability transition pores (mPTP) mediates the infarct size-limiting effect of H(2) gas in canine hearts.

Methods: The left anterior descending coronary artery of beagle dogs was occluded for 90 min followed by reperfusion for 6 h. Either 1.3% H(2) or control gas was inhaled from 10 min prior to start of reperfusion until 1 h of reperfusion, in the presence or absence of either 5-hydroxydecanoate (5-HD; a selective mK(ATP) blocker), or atractyloside (Atr; a mPTP opener).

Results: Systemic hemodynamic parameters did not differ among the groups. Nevertheless, H(2) gas inhalation reduced infarct size normalized by risk area (20.6±2.8% vs. control gas 44.0±2.0%; $p<0.001$), and administration of either 5-HD or Atr abolished the infarct size-limiting effect of H(2) gas (42.0±2.2% with 5-HD and 45.1±2.7% with Atr; both $p<0.001$ vs. H(2) group). Neither Atr nor 5-HD affected infarct size per se. Among all groups, NAD content and the number of apoptotic and 8-OHdG positive cells was not significantly different, indicating that the cardioprotection afforded by H(2) was not due to anti-oxidative actions or effects on the NADH dehydrogenase pathway.

Conclusions: Inhalation of H(2) gas reduces infarct size in canine hearts via opening of mitochondrial K(ATP) channels followed by inhibition of mPTP. H(2) gas may provide an effective adjunct strategy in patients with acute myocardial infarction receiving reperfusion therapy.

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