Wortmannin abolishes the protective effect of simvastatin against the ischaemia and reperfusion-induced ventricular arrhythmias in the anaesthetized canine

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In a previous study we have shown that a single dose of simvastatin markedly reduced the severity of ventricular arrhythmias that resulted from a 25 min ischaemia and reperfusion (I/R) in anaesthetized dogs. This protection seems to involve the generation of nitric oxide (NO) via the activation of NO synthase (NOS), since the antiarrhythmic effect of simvastatin was abolished by L-NAME. The signaling pathways, which are involved in the rapid activation of NOS by simvastatin, are however, not fully elucidated; some studies have suggested that the stimulation of the PI3/Akt pathway may play a role. Thus, the present study has now examined whether this signaling pathway has an importance in the acute antiarrhythmic effect of simvastatin.

Mongrel dogs, anaesthetized with chloralose and urethane (i.v.) were subjected to a 25 min occlusion of the left anterior descending (LAD) coronary artery, which was followed in some cases by reperfusion. The control animals were infused either with the solvent of simvastatin (C1; n=16) or DMSO (the solvent of wortmannin; C2; n=11). In three other groups simvastatin (S; 0.1 mg/kg; n=15) and wortmannin a selective inhibitor of phosphatidyl-inositol-3-kinase (W; 1.5 mg/kg; n=10) were administered alone or together (W+S; n=9) in slow intracoronary injection just prior to the occlusion. The severity of ischaemia (degree of inhomogeneity of electrical activation, epicardial ST-segment) and of arrhythmias, as well as the plasma NOx levels in blood samples taken from the coronary sinus were assessed. The activity of eNOS was determined by Western blot, the tissue superoxide production was evaluated by dihydroethidium fluorescence staining using confocal microscopy. Compared with controls (C1+C2), simvastatin significantly decreased the number of VPBs (272 ± 73 vs. 94 ± 25) and episodes of VT (4.7 ± 1.6 vs. 0.3 ± 0.2), the incidence of VT (76% vs. 20%) and VF (28% vs. 0%) during the occlusion, and increased survival following reperfusion (17% vs 38%). This protective effect of simvastatin was abolished in the presence of wortmannin (VPBs: 257 ± 113, VT episodes: 4.6 ± 2.2, VT and VF%: 67% and 83%, survival: 17%). Simvastatin also enhanced eNOS activity and preserved NO bioavailability during occlusion and reduced superoxide production following reperfusion. We conclude from these results that the antiarrhythmic effect of simvastatin is due to an increased NO bioavailability resulting from the rapid activation of eNOS via the activation of the PI3K/Akt signaling pathway.