ABSTRACT OF PhD DISSERTATION

Cardiovascular ATP-sensitive potassium channels

Experimental and clinical studies

Ulrik Markus Mortensen

This PhD dissertation was accepted by the Faculty of Health Sciences of the University of Aarhus, and defended on May 10, 2004.
Tutors: Jens Erik Nielsen-Kudsk and Torsten Toftegaard Nielsen.
Correspondence: Ulrik Markus Mortensen, Vilh. Kyhns Allé 1, DK-8270 Højbjerg.


ABSTRACT
Sulfonylurea drugs stimulate endogenous insulin secretion by blockade of ATP-sensitive potassium channels in pancreatic beta cells. These drugs are widely used in the treatment of type 2 diabetes. However, as ATP-sensitive potassium channels also exist in cardiomyocytes and coronary and peripheral arterial vascular smooth muscle cells, sulfonylurea drug usage in theory may cause unwanted cardiovascular side effects. The purpose of the PhD project was to investigate this issue.

In the first study, we assessed the effect of glibenclamide treatment on the coronary flow reserve induced by stimulation with adenosine or dipyridamole in closed-chest anaesthetized pigs. Glibenclamide had no effect on the resting blood flow, but reduced the coronary hyperaemia and the coronary flow reserve stimulated by adenosine or dipyridamole. This interaction may possibly interfere with the validity of adenosine- and dipyridamole-dependent tests for coronary artery disease in type 2 diabetic patients treated with glibenclamide and motivates further studies in patients undergoing myocardial perfusion imaging with adenosine stimulation.

In the second study, we investigated electrocardiographic ST segment changes during coronary occlusion following ischaemic preconditioning in closed-chest anaesthetized pigs. We found that ischaemic preconditioning reduced the size of the myocardial infarction compared to control animals. Following ischaemic preconditioning, the electrocardiographic changes during renewed coronary occlusion consisted of an early phase of reduced ST segment elevation and a late phase of increased ST segment elevation. Thus, the ST segment shifts induced by ischaemic preconditioning were dynamic and critically time-dependent. The late phase of increased ST segment elevation despite presence of a protected myocardial state may possibly indicate opening of ATP-sensitive potassium channels and merits further studies using pharmacological modulators of ATP-sensitive potassium channels.

In the third study, we used a double blind, randomized crossover set-up in order to examine the effect of placebo or a single oral dose of glibenclamide on walking distance in non-diabetic patients with intermittent claudication. Compared to placebo, glibenclamide had no effect on neither the maximal and pain-free walking distances nor the ankle systolic blood pressure.