ENERGY-METABOLIC ASPECTS OF ISCHEMIA AND PRE-TREATMENT: STUDIES IN PORCINE MYOCARDIUM

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I Ahlström K, Biber B, Åberg A, Waldenström A, Ronquist G, Abrahamsson P, Strandén P, Johansson G, Haney MF.
Metabolic responses in ischemic myocardium after inhalation of carbon monoxide.
Acta Anaesthesiologica Scandinavica 2009; 53(8): 1036-42.

II Ahlström K, Biber B, Åberg AM, Abrahamsson P, Johansson G, Ronquist G, Waldenström A, Haney MF.
Exogenous carbon monoxide does not affect cell membrane energy availability assessed by sarcolemmal calcium fluxes during myocardial ischaemia-reperfusion in the pig.
European Journal of Anaesthesiology 2011; 28(5): 356-62.

III Åberg AM, Ahlström K, Abrahamsson P, Waldenström A, Ronquist G, Hauck P, Johansson G, Biber B, Haney M.
Ischaemic pre-conditioning means an increased adenosine metabolism with decreased glycolytic flow in ischaemic pig myocardium.
Acta Anaesthesiologica Scandinavica 2010; 54(10): 1257-64.

IV Katarina Ahlström, Björn Biber, Anna-Maja Åberg, Anders Waldenström, Gunnar Ronquist, Pernilla Abrahamsson, Göran Johansson, Heléne Seeman-Lodding, Michael Haney.
Adenosine utilization as a substrate for glycolysis during myocardial ischemia after ischemic preconditioning is dependent on intact purine nucleoside phosphorylase activity.
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Energy-Metabolic Aspects of Ischemia and Pre-treatment: Studies in Porcine Myocardium

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Abstract
The focus of this thesis is to clarify mechanisms involved in protective pre-treatment of ischemia by carbon monoxide (CO) and ischemic preconditioning (IP), so that new protective therapies can be designed. This is studied in heart muscle, where the clinical gain would ultimately be to be able to prolong the period during a threatened myocardial infarction where permanent injury can be prevented. The aim is to elucidate energy metabolic relations as a basis for temporary metabolic adaptation to threatened injury in heart muscle, with focus on the biological relevance of this mechanism. All studies were conducted in an open-chest, anesthetized pig model using microdialysis sampling in the heart wall to identify metabolic conditions.

Methods: In anesthetized approximately 40 kg pigs, regional myocardial ischemia was produced by transient snare-ligation of a branch of the left anterior descending coronary artery. Microdialysis catheters were used for local sampling of interstitial fluid in the ischemic area. In Studies 1 and 2, CO was administered before prolonged ischemia in a clinically relevant dose (5% increase in carboxyhemoglobin). In Study 2, $^{45}Ca^{2+}$ was administered locally by microperfusate to ischemic myocardium with $^{45}Ca^{2+}$ recovery used as a marker for intracellular calcium overload during ischemia. Myocardial injury markers glycerol and glutamate (and taurine in Studies 3 and 4) were measured in microdialysate. In Studies 3 and 4, IP was performed by 4 brief transient cycles of coronary occlusion and reperfusion before a prolonged index ischemic episode was performed. In Study 3, ^{14}C-marked adenosine was administered locally via microdialysis catheters in the heart muscle wall, and when this was metabolized during ischemia as an energy source, it was detected as ^{14}C-marked lactate. In Study 4, a water-soluble purine nucleoside phosphorylase inhibitor was administered locally to heart muscle via microdialysis which was treated by IP before an index ischemia. Metabolic markers of glycolysis were measured serially before and during ischemia for Studies 1-4. Radio-labelled markers were analyzed using liquid chromatography and scintigraphy.

Results: Study 1 results showed clear signs of metabolic advantage as far as glycolytic markers related to CO during myocardial ischemia. Study 2 results demonstrated no apparent energy metabolic advantage including for $^{45}Ca^{2+}$ recovery and no diminishment of injury markers related to the single tested carbon monoxide dose during ischemia. Study 3 showed that IP led to enhanced radio-marked adenosine consumption as an energy-metabolic substrate, and that glycolytic flow (as less glucose consumption and lactate formation) was slower in IP-treated heart muscle. Study 4 showed that local purine nucleoside phosphorylase blockade inhibits adenosine utilization as an energy-metabolic substrate during ischemia, but this did not have an effect on glycolysis or injury markers during prolonged ischemia after IP.

Conclusions: From Studies 1 and 2, we concluded that CO in this dose could show effects on glycolysis during ischemia but does not seem to confer cell protection during ischemia or early reperfusion, though CO protective effects in other doses or time frames cannot be ruled out. From Study 3 we concluded that there may be an immediate energy-metabolic explanation for why more IP-treated cells survive during prolonged ischemia. From Study 4 we concluded that experimental purine nucleoside phosphorylase blockade appears to allow interruption of IP-related adenosine utilization as an energy-metabolic substrate during prolonged ischemia without obvious effects on glycolysis, and that this requires further study to test if adenosine as an energy resource during ischemia is associated with protection during infarction.

Key words: myocardial ischemia, preconditioning, carbon monoxide, adenosine

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