

Ossabaw swine with an impaired function AMP kinase mutation exhibit no preconditioning to myocardial ischemia

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**Background:** Myocardial ischemia activates a major metabolic regulator, AMP kinase (AMPK), which affects the electrocardiogram (ECG). Preconditioning is the phenomenon whereby brief ischemic episodes render the heart more resistant to subsequent ischemic injury. The increase in time to reach adverse ECG criteria upon consecutive episodes of coronary occlusion-induced ischemia is a measure of preconditioning in humans. We hypothesized that AMPK mutants will not exhibit preconditioning in contrast to the wild-type swine.

**Methods:** Ossabaw miniature swine with a spontaneous point mutation Valine199→Isoleucine in the AMPK  $\gamma$ 3 subunit were compared to wild-type swine with the Valine199. Balloon occlusion of the circumflex artery induced ischemia and was verified by angiography. The occlusion was released once any of several ECG criteria were met: ST elevation of 5 mm, QRS widening greater than 50%, 1 premature ventricular contraction, or reaching the occlusion time limit of 15 minutes. A recovery period allowed ST elevation to return to the isoelectric point before beginning the next occlusion.

**Results:** Young AMPK mutants ( $3.1 \pm 0.5$  years, N=3) showed no increase in time to ECG ischemic criteria for 3 consecutive occlusions (mean = 4.3, 3.8, 4.3 minutes). In contrast, young wild-type swine withstood consecutive occlusions for 4.4, 8.8, and 15 minutes, thereby showing preconditioning. One aged (9 years) wild-type pig showed tolerance to ischemia by surpassing the 15-minute time limit without reaching ECG criteria while one aged (9 years) AMPK mutant tolerated ischemia even less than the young mutants. The oldest wild-type pig (14 years) failed to precondition.

**Conclusion:** Our data support the hypothesis that preconditioning to myocardial ischemia occurs in young wild-type, but not AMPK mutant pigs. Aging further decreased ischemic tolerance of AMPK mutants and impaired preconditioning in wild-type pigs. Future studies are needed to clarify the age-dependence of ischemic preconditioning and tolerance in the Ossabaw swine model.