

## SCA 44

**ANESTHETIC PRECONDITIONING PRESERVES MITOCHONDRIAL BIOENERGETICS**<sup>1</sup>Novalija E, <sup>2</sup>Henry M, <sup>1</sup>Kevin L, <sup>1</sup>Stowe D, <sup>1</sup>Eells J<sup>1</sup>Medical College of Wisconsin, Milwaukee, WI, USA; <sup>2</sup>Medical College of Wisconsin/Anesthesiology, Milwaukee, WI, USA

**Background:** We hypothesize that preservation of mitochondrial function is a key determinant in anesthetic preconditioning (APC) induced cardioprotection. In support of this hypothesis, we have documented preservation of ATP synthesis and attenuation of reactive oxygen species formation in mitochondria isolated from sevoflurane preconditioned hearts.<sup>1</sup> The present study examines the hypothesis that APC improves mitochondrial bioenergetics during early reperfusion.

**Methods:** Isolated guinea pig hearts were treated with two 2-min pulses of sevoflurane (APC, 0.37 mM), with or without the putative mitochondrial ATP-sensitive potassium (mKATP) channel antagonist 5-hydroxydecanoate (APC+5-HD, 5-HD) before 30 min ischemia and 120 min reperfusion. Control (CON) hearts were neither subjected to ischemia nor pharmacological treatments and ischemia/reperfusion (I/R) hearts underwent no pharmacological treatment. Global cardiac function and tissue damage were measured (n=34). In another series of experiments, using the same protocol, hearts were reperfused for only 5 min and mitochondria were isolated by differential centrifugation (n=24). Oxygen consumption was measured polarographically using a dual-channel respirometer (Model 782, Stratkelvin Instruments, Ltd., Scotland). The function of electron transport chain was examined using succinate as a substrate. State 3 respiration was initiated with the ad-

dition of 250  $\mu$ M ADP. The respiratory control ratio (RCR = State 3 respiration rate/ State 4 respiration rate) was also determined. All data expressed as mean  $\pm$  SEM (p < 0.05; \* vs. I/R).

**Results:** Brief sevoflurane exposure prior to ischemia/reperfusion preserved both ATP synthesis and mitochondrial respiration compared to hearts exposed to ischemia/reperfusion only. The rate of state 3 respiration which reflects the rate of ATP synthesis was significantly reduced in mitochondria from I/R hearts relative to mitochondria from CON hearts (77 $\pm$ 8 and 105 $\pm$ 5\*  $\mu$ moles/L/min, respectively). In mitochondria isolated from APC hearts the rate was significantly improved to 96 $\pm$ 7\*  $\mu$ moles/L/min. A corresponding improvement in the RCR in mitochondria isolated from APC hearts relative to mitochondria isolated from I/R hearts (2.3 $\pm$ 1\* and 1.3 $\pm$ .3, respectively) was also observed. This was accompanied by induced global cardiac protection manifested by improved contractile, vascular and electrical function, and decreased infarction on reperfusion. Inhibition of the mKATP channel by 5-HD antagonized each of these effects.

**Discussion:** The results indicate that preservation of mitochondrial bioenergetics by APC plays an important role in protection of cardiac function and cellular integrity during early reperfusion. They also support the involvement of the mitochondrial KATP channel in APC induced cardioprotection.

**References:** 1) Anesthesiology 98: 1155-63, 2003.

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