Mechanisms of Action of Esmolol as a Cardioprotective Agent: $^7$Li$^+$ and $^{87}$Rb$^+$ Magnetic Resonance Spectroscopy Studies on Na$^+$ and K$^+$ Kinetics in the Isolated Rat Heart.

Mauricio Ede MD, Bozena Kuzio MSc., Bo Xiang DDS and Roxanne Deslauriers, PhD.
Institute for Biodiagnostics, National Research Council Canada - Winnipeg, MB, Canada

Purpose
The purpose of this study was to examine the effects of the ultra-short acting beta-blocker Esmolol on transmembrane ionic homeostasis of Na$^+$ and K$^+$ ions when used as a cardioprotective agent during normothermic cardiac surgery.

Introduction
Extracorporeal circulation (total cardiopulmonary bypass, CPB) and hyperkalemic cardioplegia are associated with neurological, respiratory, renal and hematological disturbances following cardiac surgery. Surgeons are now beginning to perform routine and uncomplicated procedures without CPB and hyperkalemic cardioplegic arrest$^{1,2}$. Due to its ultra-short acting characteristics, Esmolol may be the drug of choice for use under these conditions. We have used $^{87}$Rb$^+$ and Li$^+$ MR Spectroscopy (as congeners of K$^+$ and Na$^+$, respectively) to examine the effects of Esmolol arrest in isolated, buffer-perfused rat hearts.

Methods
Thirty-nine animals were used in a modified Langendorff isolated rat heart preparation placed inside the bore of a 360 MHz (8.7 T) magnet. Spectral and functional data were acquired pre-arrest, during arrest, and a 30-minute recovery period. Rubidium (n=20) spectra were acquired at 117.84 MHz, 90° pulse=60 μs; recycle time 14 ms, 10240 scans per spectrum. A total of 32 spectra were acquired for each experiment (loading + washout) with “dry mode” perfusion$^3$. Lithium (n=19) spectra were acquired using the same broadband probe operating at 139.93 MHz. The repetition time was 2.2 s (60° pulse), 52 scans were accumulated for a time resolution of ~2 minutes per spectrum. These were chosen to increase the contribution from the intracellular Li$^+$ signal and decrease the contribution from the extracellular and bath signals$^4$.

Results
$^{87}$Rb$^+$ MRS data: Esmolol did not affect the uptake of Rb$^+$: ($k_{\text{Esmolol}} = 0.032 \pm 0.014 \text{ vs. } k_{\text{control}} = 0.036 \pm 0.008, p=0.184$), but significantly reduced Rb$^+$ efflux (30-40%) during washout ($k_{\text{Esmolol}} = 0.025 \pm 0.007 \text{ vs. } k_{\text{control}} = 0.036 \pm 0.009, p=0.0101$; Figure 1), suggesting an effect on K$^+$ channels.

Li$^+$ MRS data: Lithium efflux was significantly inhibited during washout, suggesting Na$^+$ channel block in both Esmolol and potassium-arrested hearts (62% and 57% respectively, Figure 2). The rate constants of the Esmolol group (n=15) differed significantly from those of controls (p<0.001, n=19) but not from those of the K$^+$-arrested hearts (p=0.32, n=4).

Discussion
We have previously demonstrated the potential for Esmolol to be used as a cardioprotective agent$^6$. Esmolol has been used as an agent to reduce rate and motion of the heart during minimally invasive procedures with promising results$^7$. Its effects, however, at the subcellular level were not established. In this study we present evidence suggesting that Esmolol produces cardiac arrest through mechanisms other than simple β–blockade. Our data is consistent with blockade of K$^+$ and Na$^+$ channels. These effects however, appear to be non-specific and further investigation is required to define unambiguously the alterations caused by Esmolol infusion on channels/currents during the action-potential cycle in the heart.

References

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Figure 1. Average kinetic curves expressed as peak intensities relative to the reference over time of Rb$^+$ uptake and washout in control (n=5) and Esmolol-arrested (n=15) hearts. A 30-40% inhibition of Rb$^+$ efflux was found during washout.

Figure 2. Averages of calculated rate constants (k) for Li$^+$ efflux for control (n=19), Esmolol (n=15) and potassium (n=4) arrested hearts. Efflux was significantly inhibited in both the Esmolol and potassium groups relative to control, but not from each other.