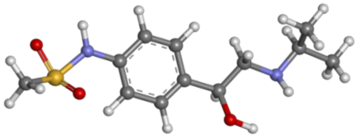

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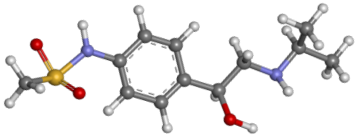


Esmolol as an adjuvant to traditional cardioplegia

Christie Zammit

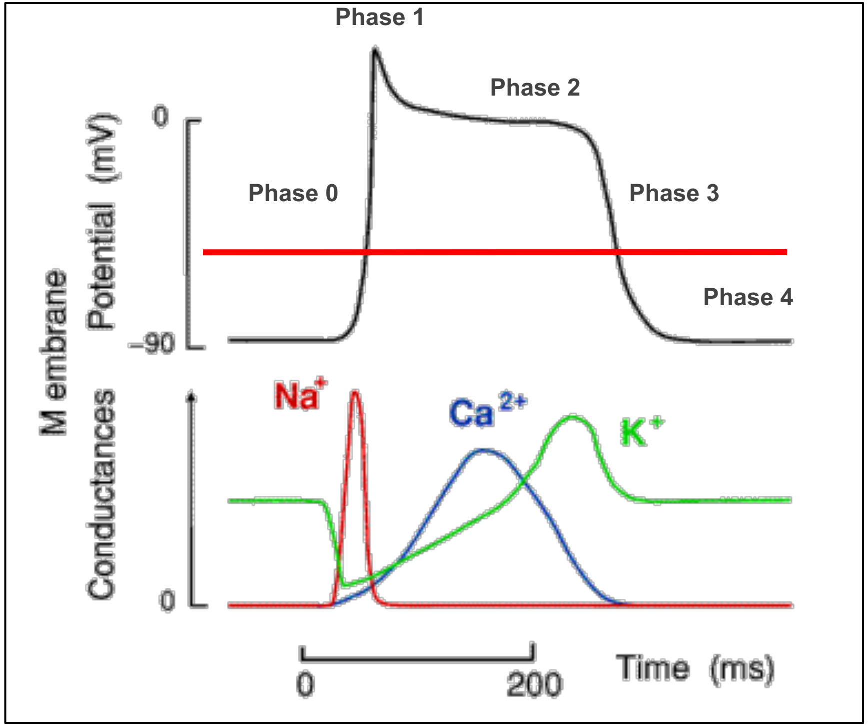
BSc, Cardiovascular Perfusion Student

Current Cardioplegia

Hyperkalemic Solutions

- K+ > 10 mEq/L
- Depolarized Arrest
    - ↑ K+ raises RMP to -65 to - 50 mV
    - Inhibits Fast Na+ Channels
    - No phase 0 of AP

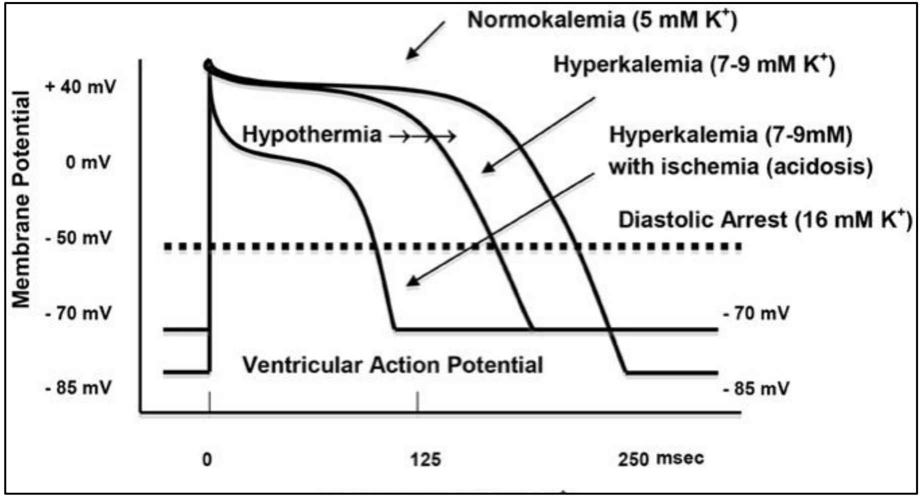
Hypothermic delivery



Myocardiocyte Action Potential

Current Cardioplegia

- More than 99% of Cardioplegia Solutions worldwide are hyperkalemic
- Gold standard of care since the 1980's
- Focus of debate has since shifted toward:
  - **Temperature** (warm vs cold)
  - **Transport vector** (blood, crystalloid)
  - **Dosing regime** (intermittent, singular continuous)



Current Cardioplegia: Drawbacks

Perioperative morbidity and mortality still remains relatively high in cardiac patients

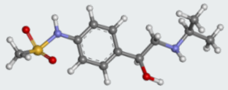
- 10% CABG → LV dysfunction
- 2-13% patients → MACE
- 20% patients → excessive bleeding
- 20-40% CABG → post-op fibrillation

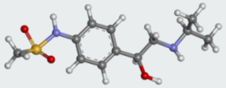
Hyperkalemic cardioplegia associated with:

- Ischemia-Reperfusion Injury
- Myocardiocyte Damage
- Myocardiocyte Death
- Post-Op Arrhythmias
- Systolic Dysfunction
- Ventricular Dysfunction
- Need for inotropic support
- Post-op myocardial stunning
- Excess catecholamines

Time to explore new potential cardioplegia adjuvants:

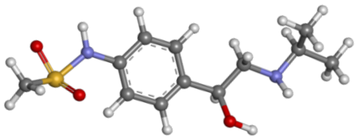
Esmolol





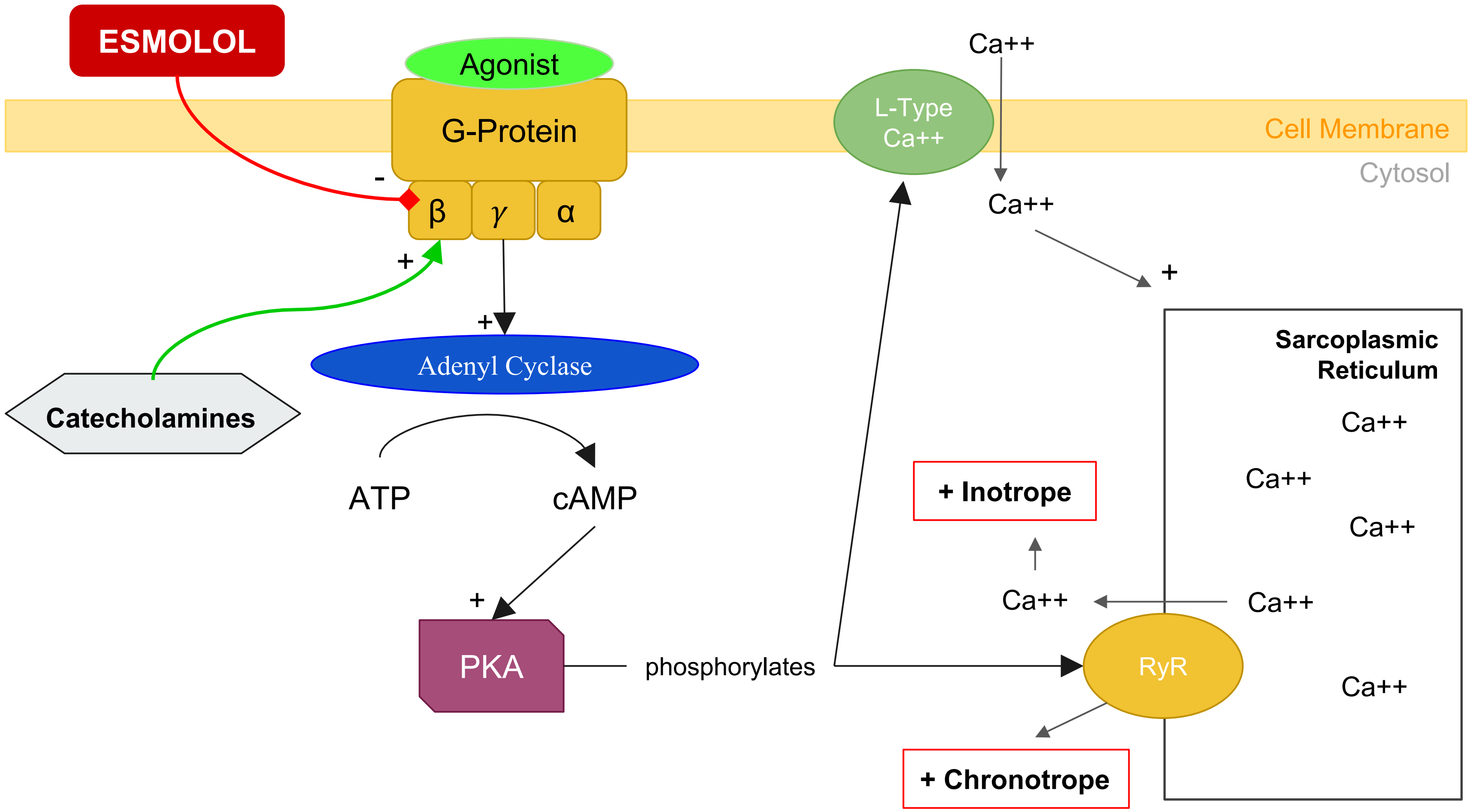
Esmolol

- β1-Adrenergic Receptor Blocker
- Negative Inotrope & Chronotrope
- Fast-acting → T ½ = 9.2 mins
  - Metabolized via RBC esterases
- Inhibits Fast-Na+ channels
- Inhibits L-type Ca++ channels
- ↓ myocyte sensitivity to catecholamines



Esmolol: Current Uses

- Antiarrhythmic agent
- Treatment for Heart Failure
- Treatment for Tachycardia & HTN
- Off-Pump CABG
- Prevention of the SNS Response

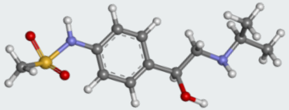

ESMOLOL
Agonist
G-Protein
Cell Membrane
Cytosol
L-Type
Ca++
Ca++
Ca++
-
β
γ
α
+
+
+
Catecholamines
Adenyl Cyclase
ATP
cAMP
+
PKA
phosphorylates
Sarcoplasmic
Reticulum
Ca++
Ca++
Ca++
+ Inotrope
Ca++
Ca++
RyR
Ca++
+ Chronotrope

Esmolol as a Cardioplegia Adjuvant

1. Decrease **Myocardiocyte Damage**
    - attenuates the O_2 supply / demand mismatch
    - decreases serum cardiac TnT

2. Decrease **Ventricular Fibrillation**

3. Decrease **Systolic Dysfunction**



1. Myocyte Damage

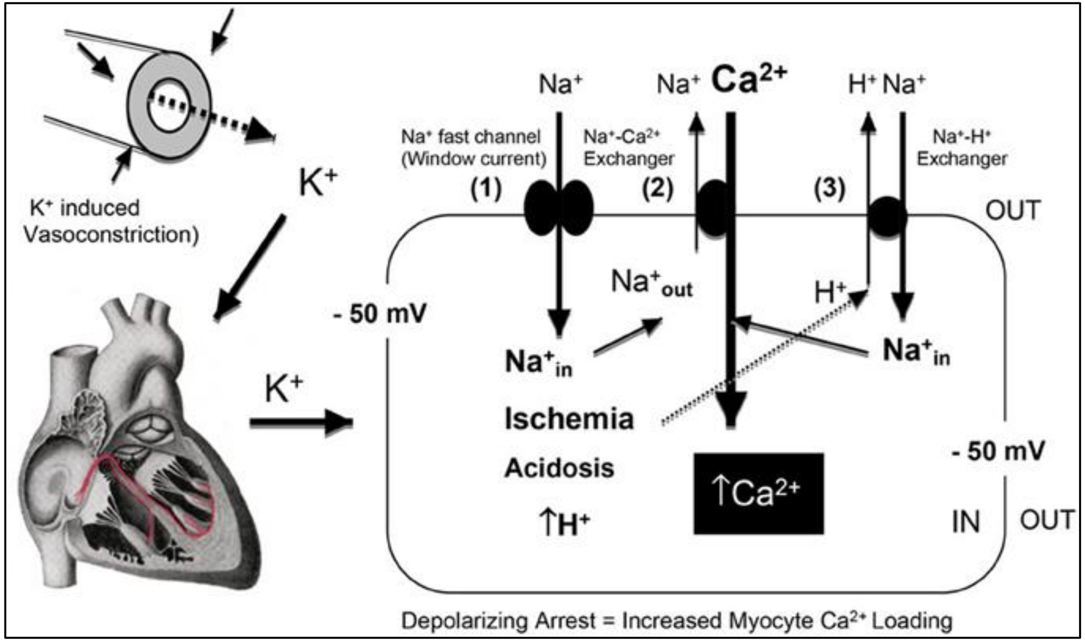
Ischemia-Reperfusion (IR) Injury

Ischemia:

- **O2 supply / demand mismatch**
- Anaerobic metabolism
- ROS metabolites
- Acidosis
- Ca++ influx

Reperfusion:

- ROS formation
- Complement activation
- mPTP opening
- Cardiomyocyte death
- Stone heart



Cardiac Troponin (Tnt)

- Biomarker of myocardial damage
  - More sensitive than CK and CK-MB
- ↑ TnT : myocardial injury
  : poorer clinical outcome
  : proportional to short and long-term mortality

Esmolol:

β1-Receptor Blocker → ++ Negative Inotropy → ↓ Myocyte O2 Consumption → ↓ O2 Mismatch & ↓ IR Injury → ↓ Cardiac Troponin (TnT)

Efficacy of esmolol as a myocardial protective agent during continuous retrograde cardioplegia. (Scorsin et al. 2003)

Control Group	Esmolol Group
N = 18	N = 23
Arresting Dose: Antegrade K+ Blood (1.2 g K+ / 2-3 mins) Subsequent Dose: Continuous Warm Retro K+ (4-6 g/ hr K+)	Arresting Dose: Antegrade Esmolol Blood (250-300 mg E/ 2-3 mins) Subsequent Dose: Continuous Warm Retro (300-600 mg/hr Esmolol)
Full Arrest	HR = 30 bpm

1° Measurement	TMO2
2° Measurement	LV EF (%), TnT

Efficacy of esmolol as a myocardial protective agent during continuous retrograde cardioplegia. (Scorsin et al. 2003)

<u>**Transmyocardial O_2 Content Gradient**</u>

$$TMO_2 = [O_2 \text{ Content in Perfusion Line}] - [O_2 \text{ Content in L Coronary Ostium}]$$

TMO_2 : used during retrograde plegia delivery

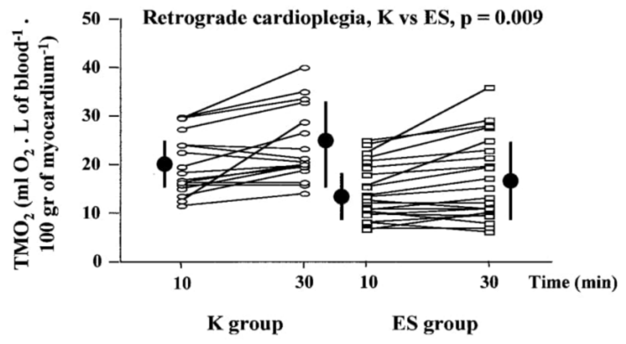
: **smaller gradient → less O_2 consumption**

→ indicates superior usage of myocardial O_2

→ attenuation of O_2 supply/demand mismatch

Efficacy of esmolol as a myocardial protective agent during continuous retrograde cardioplegia. (Scorsin et al. 2003)

- Esmolol group had significantly lower TMO2:
  - ↓ myocardial O2 consumption
  - Improved myocardial O2 usage
  - ↓ IR injury
- Plasma TnT and Ejection Fraction not significantly different between groups



Conclusion:

- Esmolol is a safe alternative to traditional hyperkalemic cardioplegia solutions
- Esmolol is capable of decreasing myocardial O2 consumption, with no signs of myocardial insult

Esmolol before cardioplegia and as a cardioplegia adjuvant reduces cardiac troponin release after cardiac surgery. (Bignami et al. 2017)

Control Group	Esmolol Group
N = 25	N = 21
HTK & Placebo	Esmolol IV Bolus before CPB (1 mg/kg) Esmolol as an HTK adjuvant (2 mg/kg)
Full Arrest	Full Arrest

1° Measurement	**Troponin** (Tn1)
2° Measurement	V-Fib, LOS Need for Inotropic Support

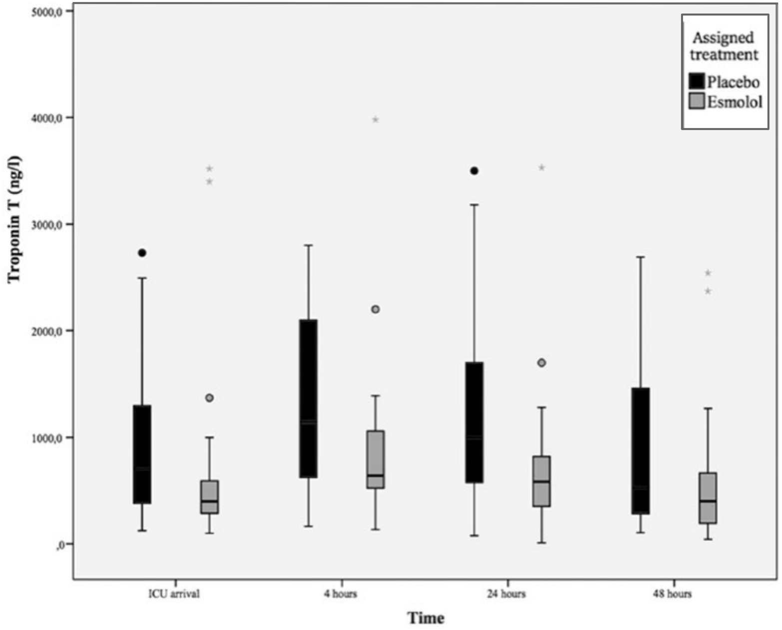
Esmolol before cardioplegia and as a cardioplegia adjuvant reduces cardiac troponin release after cardiac surgery. (Bignami et al. 2017)

Bignami et al. 2017:

- 46 % reduction in serum TnT in Esmolol pt
- Incidence of V. Fib, need for Inotropic Support and LOS not significantly different between groups

Conclusion:

- β-blockade "reduced myocardial O2 consumption to virtually zero"
- No negative postoperative clinical impacts
  - Plasma esmolol levels post-CPB negligible



Post-op TnT levels measured over time.
(Bignami et al. 2017)

A pilot study of perioperative esmolol for myocardial protection during on-pump cardiac surgery. (Liu et al. 2016)

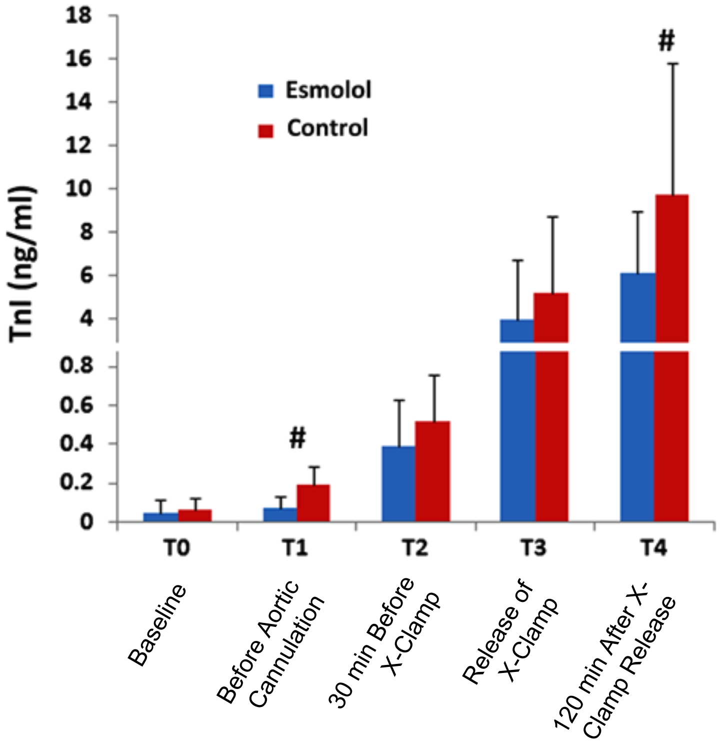
Control Group	Esmolol Group
N = 12	N = 12
K+ Cardiopelgia 0.9% Saline Placebo	Esmolol IV Infusion Before CPB (70 mcg/kg/min) K+ Cardioplegia
Full Arrest	Full Arrest

1° Measurement	**Troponin** (Tn1), CK, CK-MB
2° Measurement	HR, MAP, CVP

Liu et al. 2016:

- 61% reduction in serum TnT in Esmolol pt
- Hemodynamic parameters: MAP, HR, CVP
    - Not significantly different between groups

Serum TnT (UNITS)	Esmolol	Control	P Value
Baseline	0.048	0.064	0.282
Aortic X-Clamp	6.114 +/- 2.864	9.709 +/- 6/146	0.039
120 min After X-Clamp Removal	0.072 +/-0.058	0.188 +/- 0.094	< 0.001



2. Ventricular Fibrillation

Perioperative beta-blockers for preventing surgery-related mortality and morbidity (Review). (Blessberger et al. 2014)

Blessberger et al. concluded that β-Blockers like Esmolol prevent:

- Ventricular arrhythmias
- Supraventricular arrhythmias

Cochrane
Library

Cochrane Database of Systematic Reviews

Perioperative beta-blockers for preventing surgery-related mortality and morbidity (Review)

Blessberger H, Kammler J, Domanovits H, Schlager O, Wildner B, Azar D, Schillinger M, Wiesbauer F, Steinwender C

"According to our findings, perioperative application of beta-blockers still plays a pivotal role in cardiac surgery, as they can ***substantially reduce the high burden of supraventricular and ventricular arrhythmias in the aftermath of surgery****. Their influence on mortality, AMI, stroke, congestive heart failure, hypotension and bradycardia in this setting remains unclear."*

Effect of short-acting beta blocker on the cardiac recovery after cardiopulmonary bypass. (Sun et al. 2011)

Control Group	Esmolol Group
N = 28	N = 30
- Cardiopelgia - 0.9% Saline Placebo	- Cardioplegia - Esmolol IV Bolus (1 mg/kg) prior to X-Clamp Removal

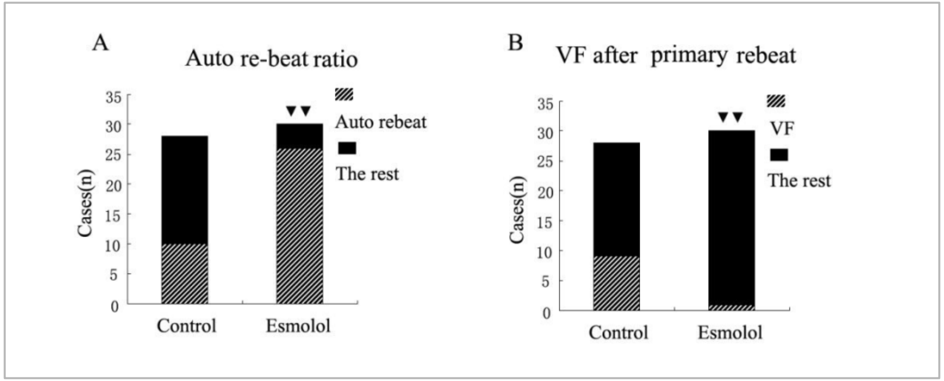
Note: did not specify type or delivery method of cardioplegia

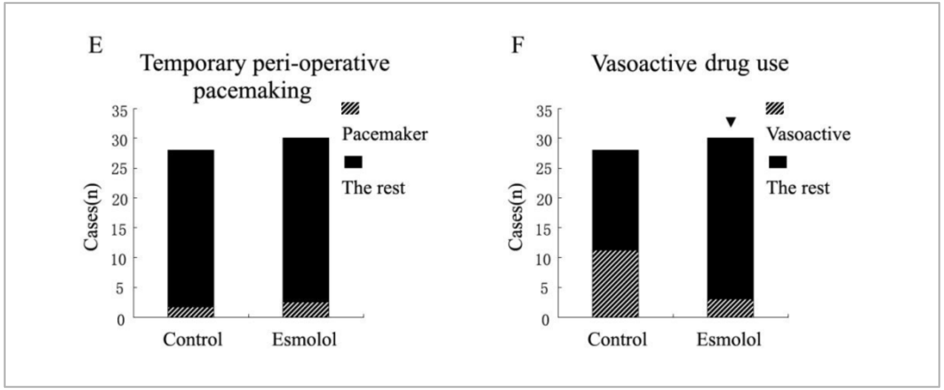
Effect of short-acting beta blocker on the cardiac recovery after cardiopulmonary bypass. (Sun et al. 2011)

Clinical Parameter	Esmolol (N = 30)	Control (N = 28)	Statistial Signif.
Automatic Re-beat	26	10	$p < 0.01$ *
V. Fib	1	9	$p = 0.005$ *
A. Fib	10	11	$p = 0.786$
Recovery Duration	4.1 +/- 1.3 min	4.4 +/- 1.5 min	$p = 0.407$
HR After Steady Re-Beat	49.9 +/- 14.6	89.6 +/- 14.9	$p < 0.001$ *
HR 10 min After Re-Beat	91.5 +/- 10.5	94.8 +/- 14.3	$p = 0.31$
Temporary Pacing	3	2	$p = 1.00$
Vasoactive Weaning	3	11	$p = 0.014$ *
Reperfusion Time	24.3 +/- 7.8	29.6 +/- 8.9	$p = 0.007$ *
Total Bypass Time	63.7 +/- 10.9	69.9 +/- 9.0	$p = 0.022$ *

Sun et al. 2011 concluded that Esmolol:

- attenuates O2 supply / demand mismatch
- ↓ incidence of ventricular arrhythmia
- ↑ auto re-beat success rate
- ↓ incidence of V. Fib after auto-rebeat
- ↓ reperfusion time





3. Systolic Dysfunction & LV Contractility

Preload Recruitable Stroke Work (PRSW)

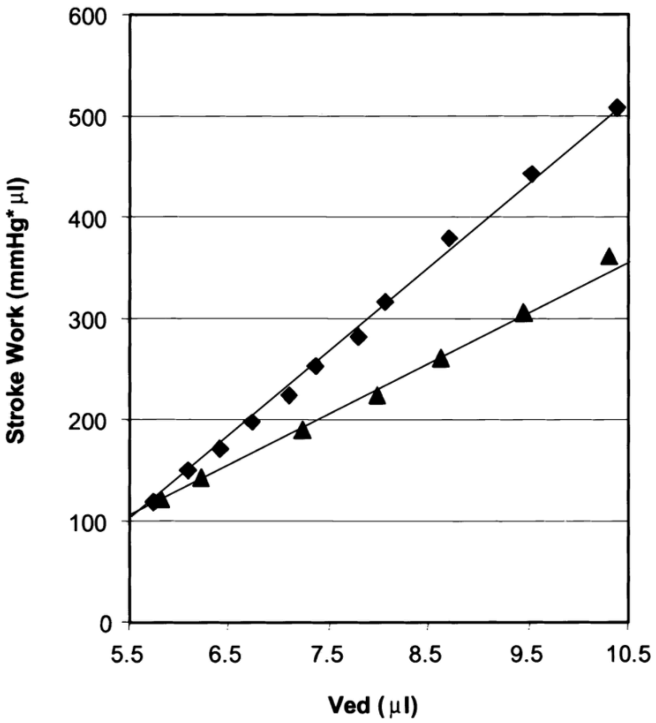
Highly linear relationship between:

Stroke Work	End-diastolic chamber volume End-diastolic segment length

PRSW : appropriate end-point for measuring myocardial contractile function

: **↑ slope = better function**

ESPVR : functional measure in isolated hearts, but not in intact subjects



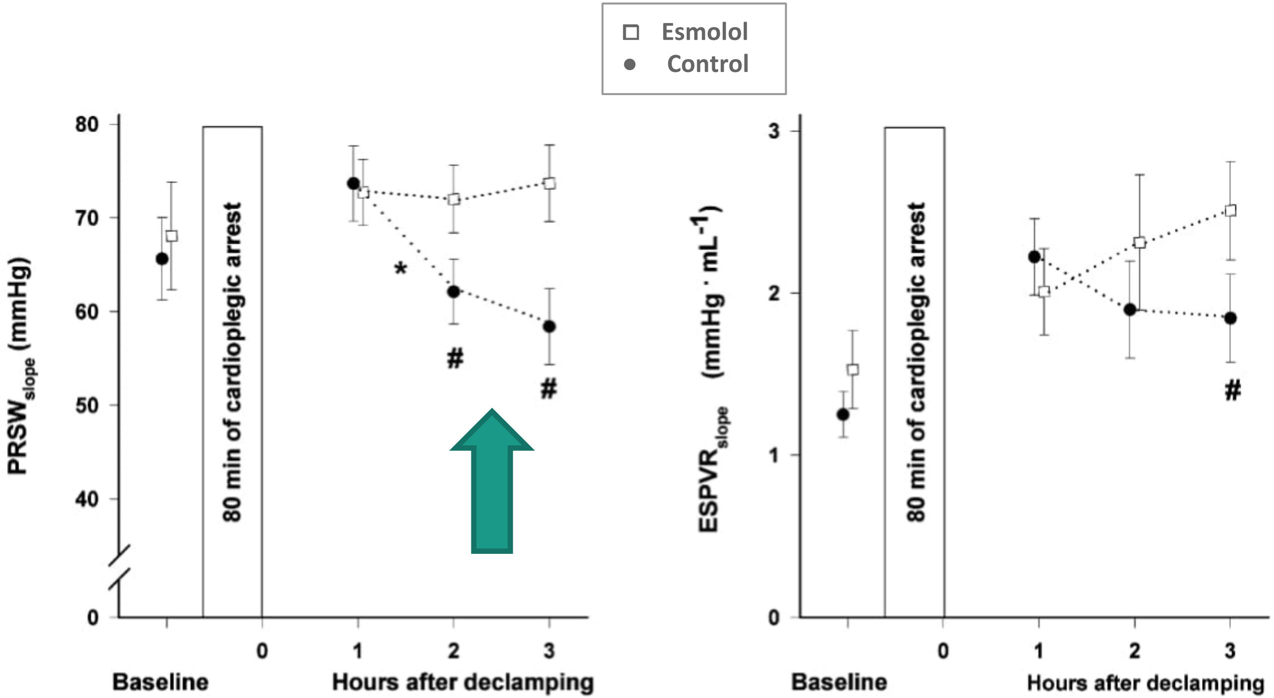
Esmolol before 80 min of cardiac arrest with oxygenated cold blood cardioplegia alleviates systolic dysfunction. An experimental study in pigs. (Fannelop et al. 2008)

Cardioplegia:

- K+, cold (12℃), blood, antegrade, intermittent

Esmolol:

- IV bolus (1 mg/kg)
- Administered before CPB



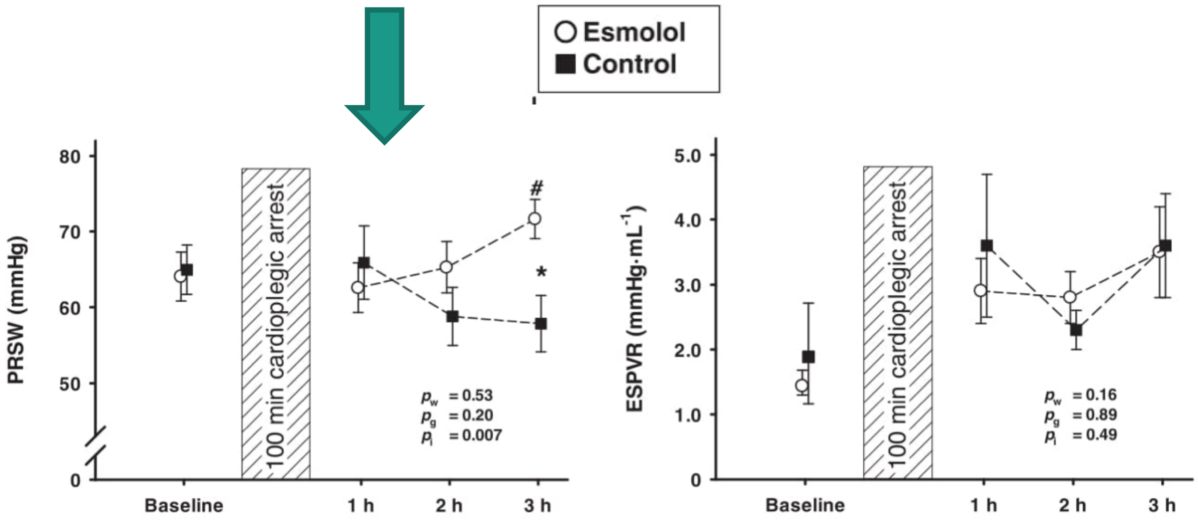
Esmolol added in repeated, cold, oxygenated blood cardioplegia improves myocardial function after cardiopulmonary bypass. (Dahle et al. 2015)

Cardioplegia:

- K+, cold (12℃), blood, antegrade, intermittent

Esmolol:

- Additive to cardioplegia (0.467 mg/kg)
- Administered throughout CPB



Myocardial function after polarizing versus depolarizing cardiac arrest with blood cardioplegia in porcine model of cardiopulmonary bypass. (Aass et al. 2015)

Esmolol / Adenosine / Magnesium

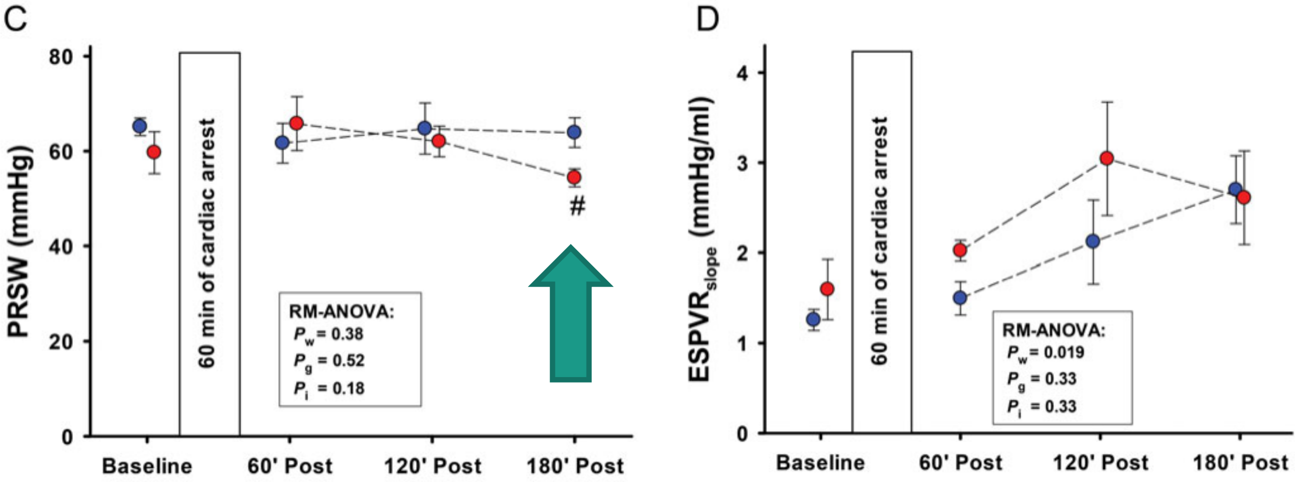
St Thomas' Hospital Cardioplegia Sln' 2

Control Cardioplegia:

- St. Thomas Solution No. 2
- Mg2+, K+, Cl-
- Cold, blood, intermittent

Esmolol Cardioplegia:

- Esmolol/Adenosine/Mg2+
- Cold, blood, intermittent



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Myocardial function after polarizing versus depolarizing cardiac arrest with blood cardioplegia in porcine model of cardiopulmonary bypass. (Aass et al. 2015)

All 3 studies concluded:

- ESPVR not capable of capturing myocardial function in intact hearts
- Esmolol groups consistently demonstrate higher post-op PRSW slopes
- High PRSW slope corresponds to superior postoperative contractility
- Esmolol confers a greater LV function postoperatively

Esmolol before 80 min of cardiac arrest with oxygenated cold blood cardioplegia alleviates systolic dysfunction. An experimental study in pigs. (Fannelop et al. 2008)

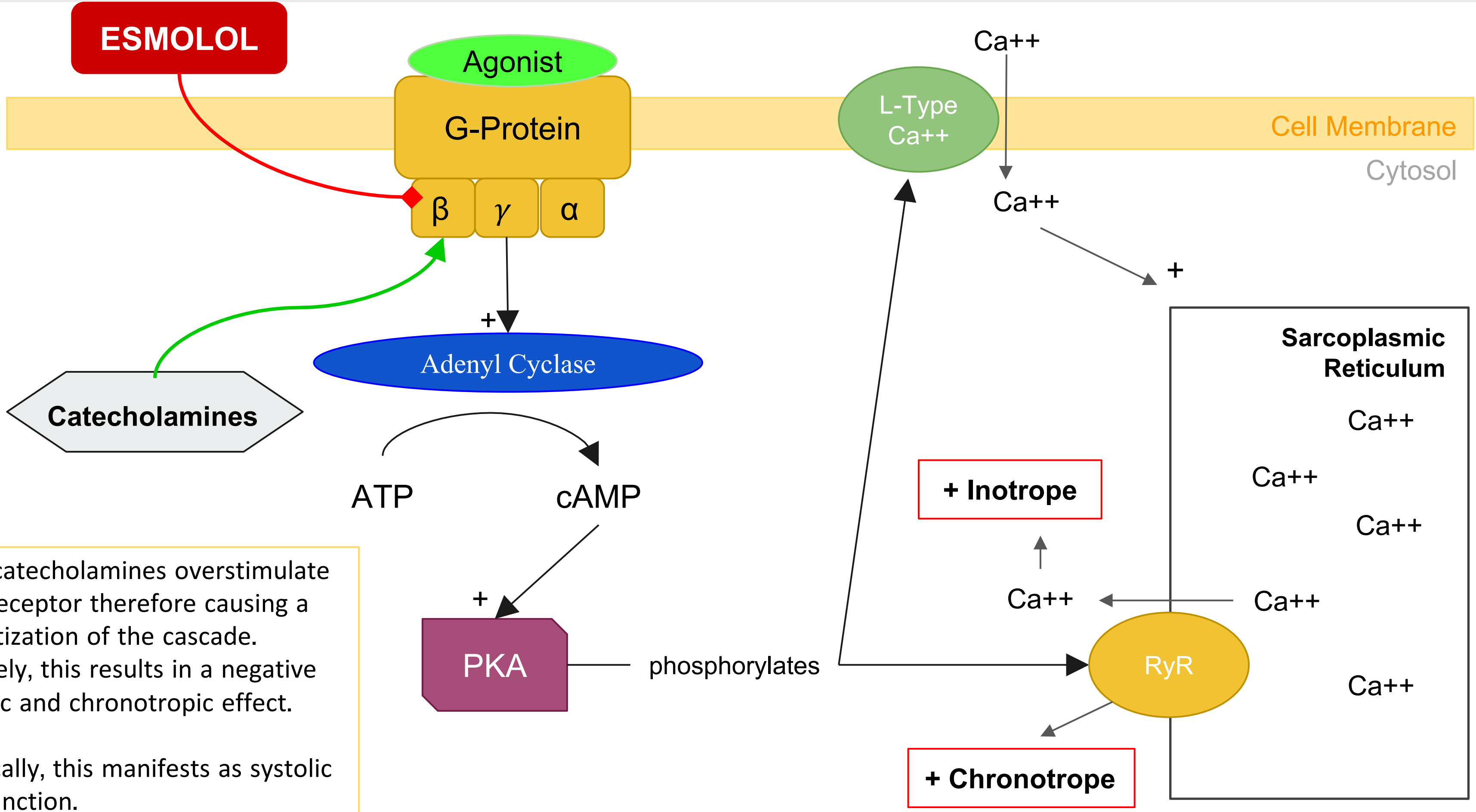
CPB is associated with excess release of catecholamines due to : Hypothermia

: Depth of anesthetic plane

: SNS response to non-physiological materials

→ Therefore, increased levels of circulating catecholamines such as Epinephrine, Norepinephrine & Dopamine on CPB

Might the excess catecholamine release be contributing to the systolic dysfunction often seen in the immediate post-operative period?



Excess catecholamines overstimulate the B-Receptor therefore causing a desensitization of the cascade. Ultimately, this results in a negative inotropic and chronotropic effect.

→ Clinically, this manifests as systolic dysfunction.

Esmolol before 80 min of cardiac arrest with oxygenated cold blood cardioplegia alleviates systolic dysfunction. An experimental study in pigs. (Fannelop et al. 2008)

- Could Esmolol attenuate the negative inotropic effect of excess catecholamines…
  - IV bolus (1 mg/kg)
  - Administered before CPB

Conclusion:

- Esmolol = ↓ cardiomyocyte sensitivity to catecholamines
- When taken before the↑ catecholamines, **Esmolol annuls the catecholamine receptor overstimulation**
  - **Esmolol prevents systolic dysfunction due to excess catecholamines**

At What Times Should We Administer Esmolol?

Ischemia-Reperfusion Injury most likely to occur:

1. Before Surgery & CPB
2. Initiation of CPB
3. “Protected“ Ischemic Periods of CPB

- Timing is key
- No consistency among current studies…

→ IV Bolus
→ IV Infusion
→ Cardioplegia Additive

→ Before CPB
→ During CPB
→ Entire Perioperative Course

Hypothesis:

- Timing will impact outcome parameters
- Administration throughout entire perioperative period = Ideal

Timing and Methods of Esmolol Administration Prior to and During Cardiopulmonary Bypass

	Scorsin	Bignami	Liu	Fannelop	Dahle	Aass	Sun
	Esmolol Administered BEFORE Bypass						
IV Bolus		X		X			
IV Infusion			X				
	Esmolol Administered DURING Bypass						
Cardioplegia	X	X			X	X	
Bolus at X-Clamp Removal							X
	Outcome Parameters						
Serum Cardiac TnT	No Δ	↓ by 46%	↓ by 62%	No Δ	No Δ	No Δ	-
Ventricular Fibrillation	-	No Δ	No Δ	-	-	-	Significant ↓
Systolic Function	-	-	-	↑	↑	↑	-

At What Times Should We Administer Esmolol?

Ischemia-Reperfusion Injury most likely to occur:

1. Before Surgery & CPB
2. Initiation of CPB
3. “Protected“ Ischemic Periods of CPB

Optimal Timing for Esmolol Administration:

1. Prior to CPB (IV)
2. During CPB (Cardioplegia)
3. At X-Clamp Removal (IV)

Conclusions:

- Safe adjuvant
- No negative hemodynamic impacts

  → due to ultra short T ½ of 9 mins

- Capable of:
  1. ↓ Myocardial Cell Damage
  2. ↓ Serum Cardiac TnT
  3. ↓ Post-op Dysrhythmias
  4. ↓ Systolic Dysfunction

Future Direction:

- Proceed with caution
- Generate a more comprehensive studies: ↑ N, RCTs
- Study esmolol timing of administration
- More clinical trials
- Talk to your anesthetists & surgeons!

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