

APPAC 2011



POSTCONDITIONING

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de Mulhouse



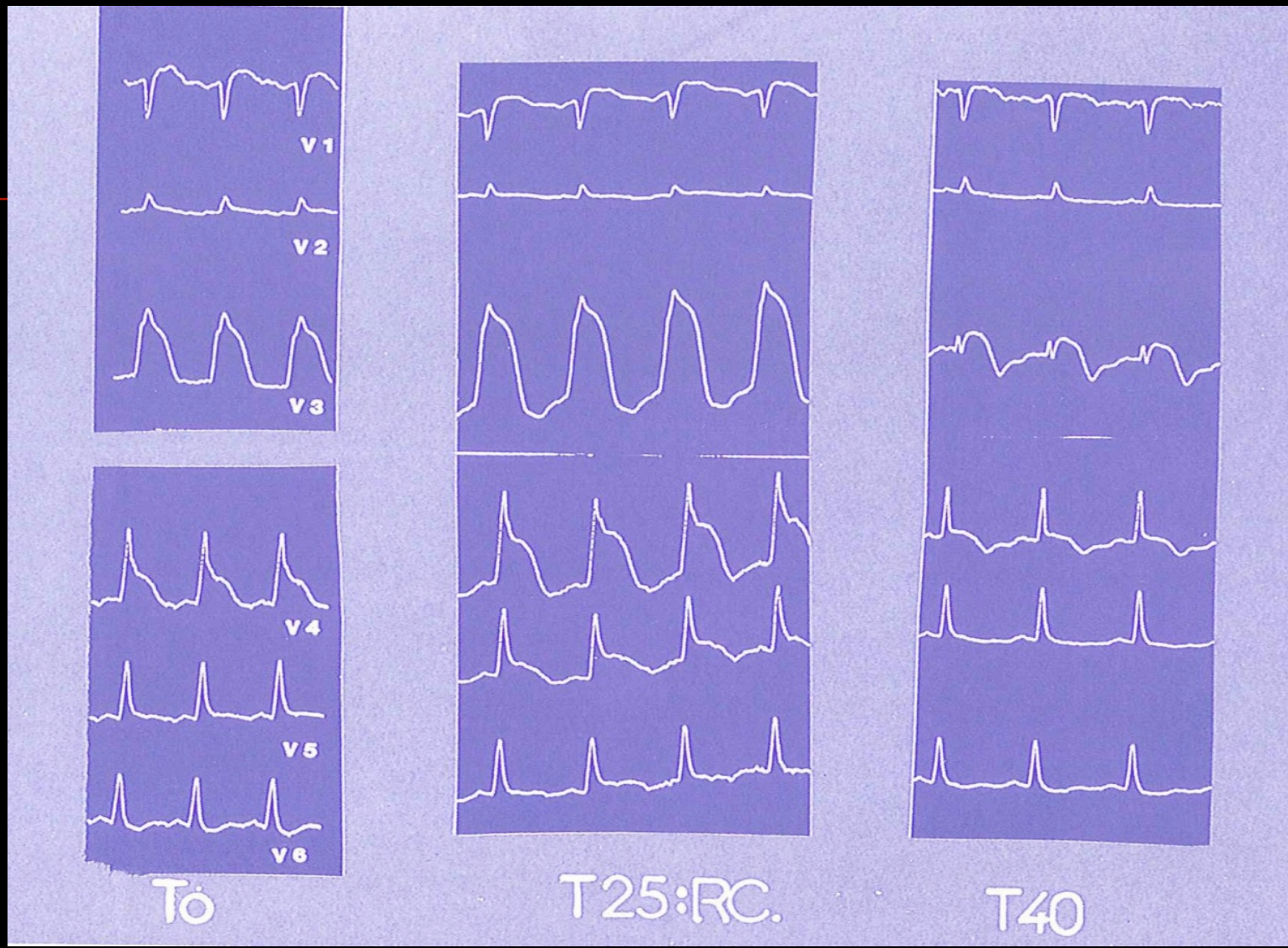
PREAMBULE

- Braunwald E Kloner RA

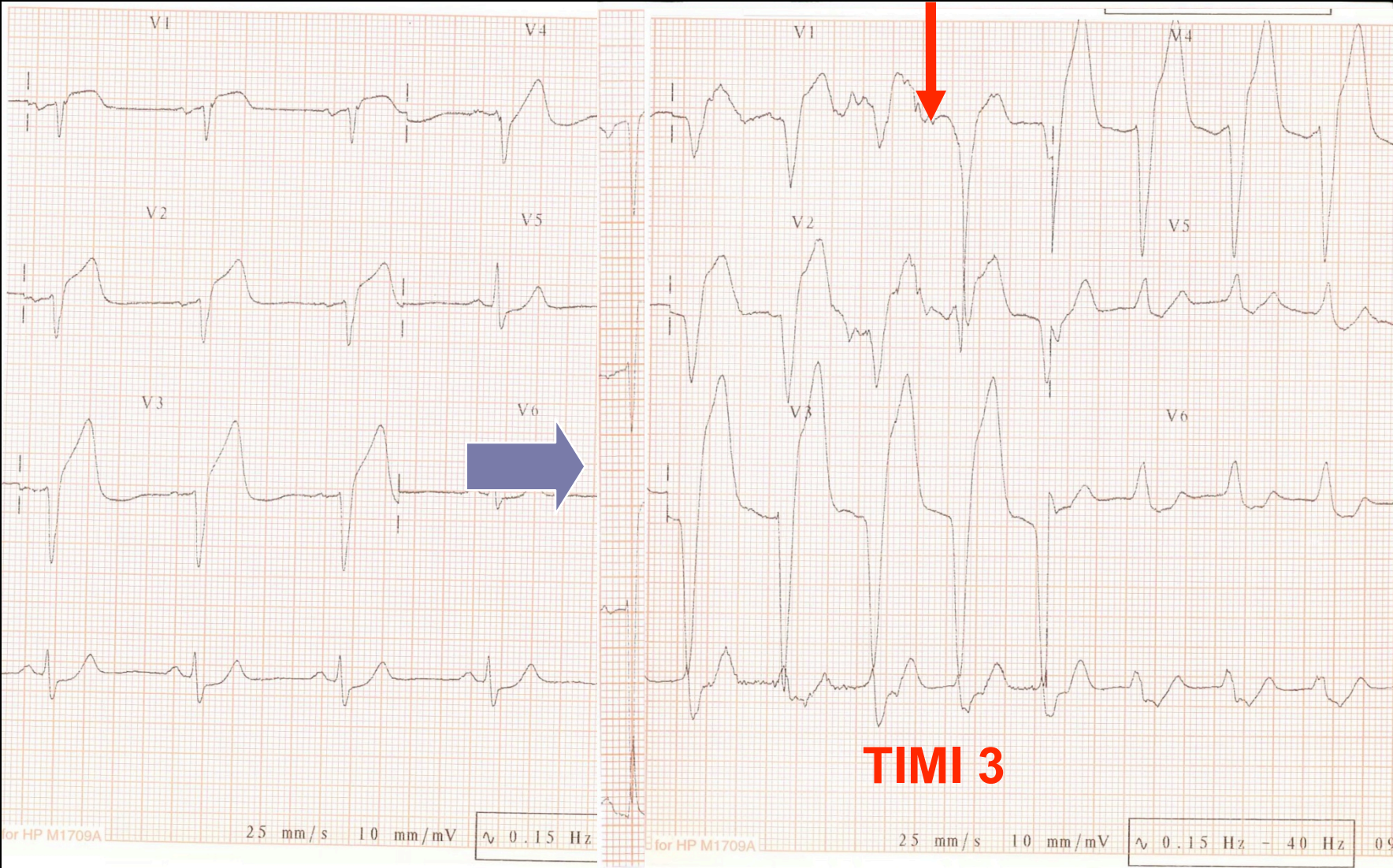
- **Myocardial Reperfusion :**

- **A Double-Edged Sword ?**

- J Clin Invest 1985 ; 76 : 1713-9



VERY ACUTE CHEST PAIN



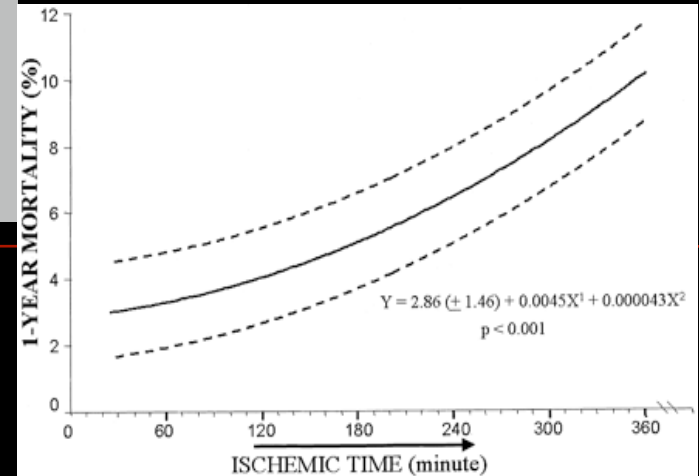
Background

•NEW PARADIGM

•**Early** reopening of the Infarct Related Artery is **needed** to save myocardium : « **Time is Muscle** »

•**BUT !!**

•**Reperfusion Injury** is now an accepted deleterious phenomenon

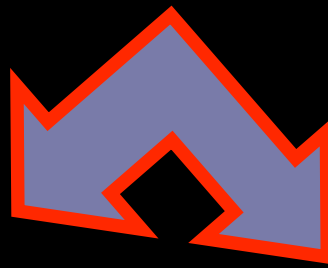


Acute coronary Occlusion



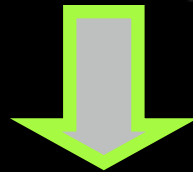
Localized Myocardial Ischemia

Too Late Reopening



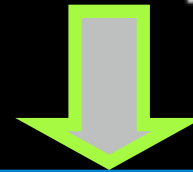
Early Reopening

Irreversible Injured Cells



No Salvage

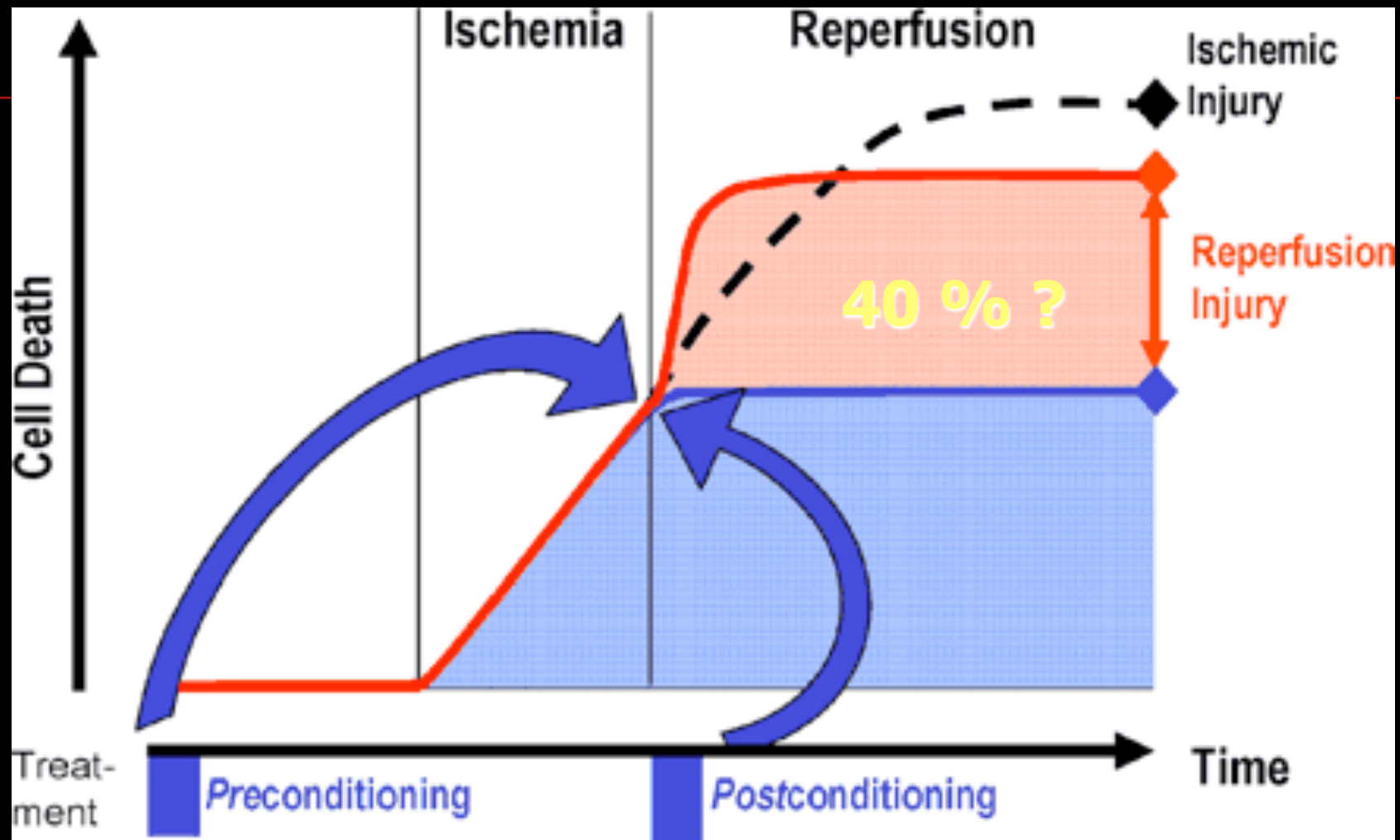
Reversible Injured Cells



Salvage +

Death of Viable Cells





Selon D Garcia-Dorado

-
- **TIME TO TAKE MYOCARDIAL REPERFUSION INJURY SERIOUSLY**
 - **Experimental studies indicate that this form of myocardial injury accounts for up to 50 % of the final size of the infarct !!!**

■ Hausenloy DJ , Yellon DM NEJM **2008** ; 359 : 518-9

-
- **NO-REFLOW** : non adequate myocardial perfusion despite TIMI 3
 - **CARDIOMYOCYTE** : Viable Cells are Killed due to Oncosis , Apoptosis and Autophagy (?) linked to Reoxygenation , Oxygen Free Radical Burst , Calcium Overload

-
- LE **POSTCONDITIONNEMENT**
S'INSCRIT DANS LES TENTATIVES DE
PREVENTION DES LESIONS DE
REPERFUSION

■ **What is PostConditioning?**

■ How does it Work ?

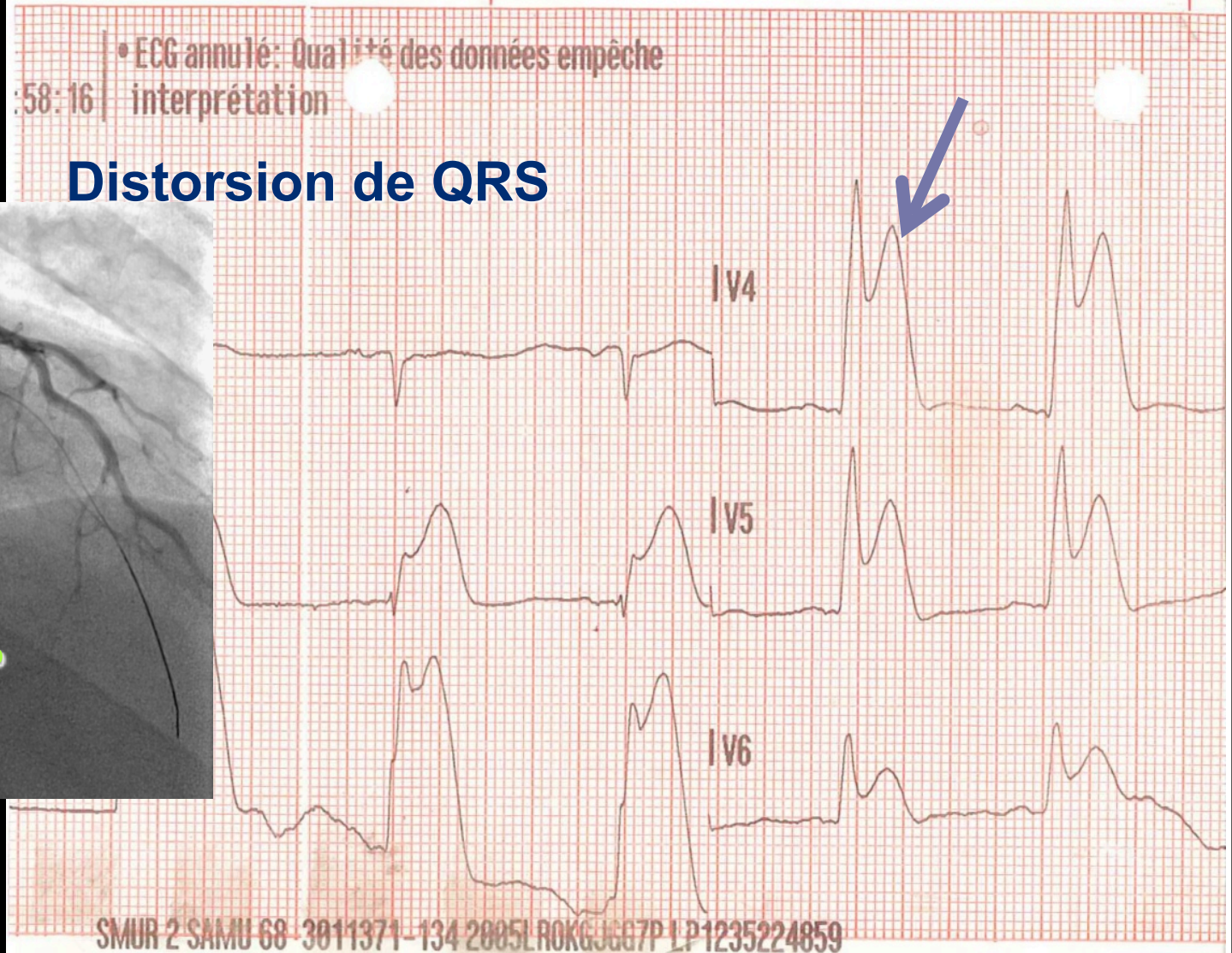
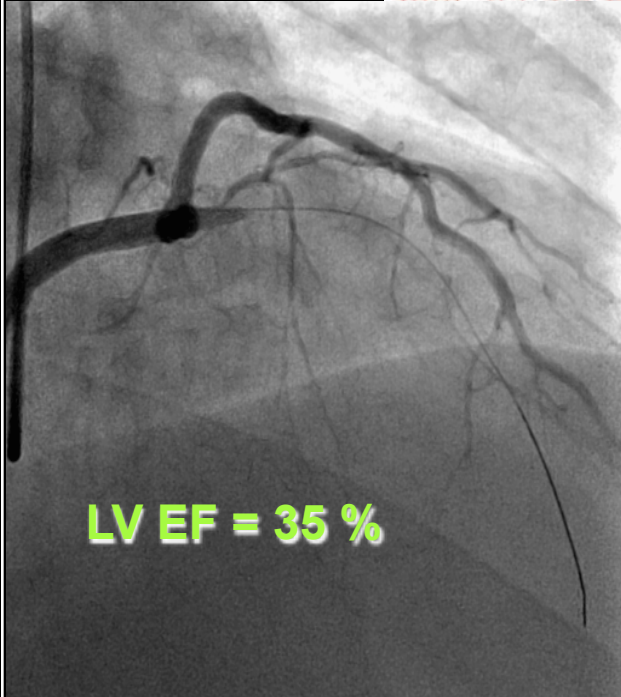
■ Does-it Work in Humans ?

■ PostConditioning or Thrombus Aspiration ?

-
- **Modified** Technique of **Myocardial Reperfusion** in Acute Myocardial (PCI)
 - **Progressive**
 - To **Improve** Myocardial Salvage

• ECG annulé: Qualité des données empêche
:58:16 | interprétation

Distorsion de QRS

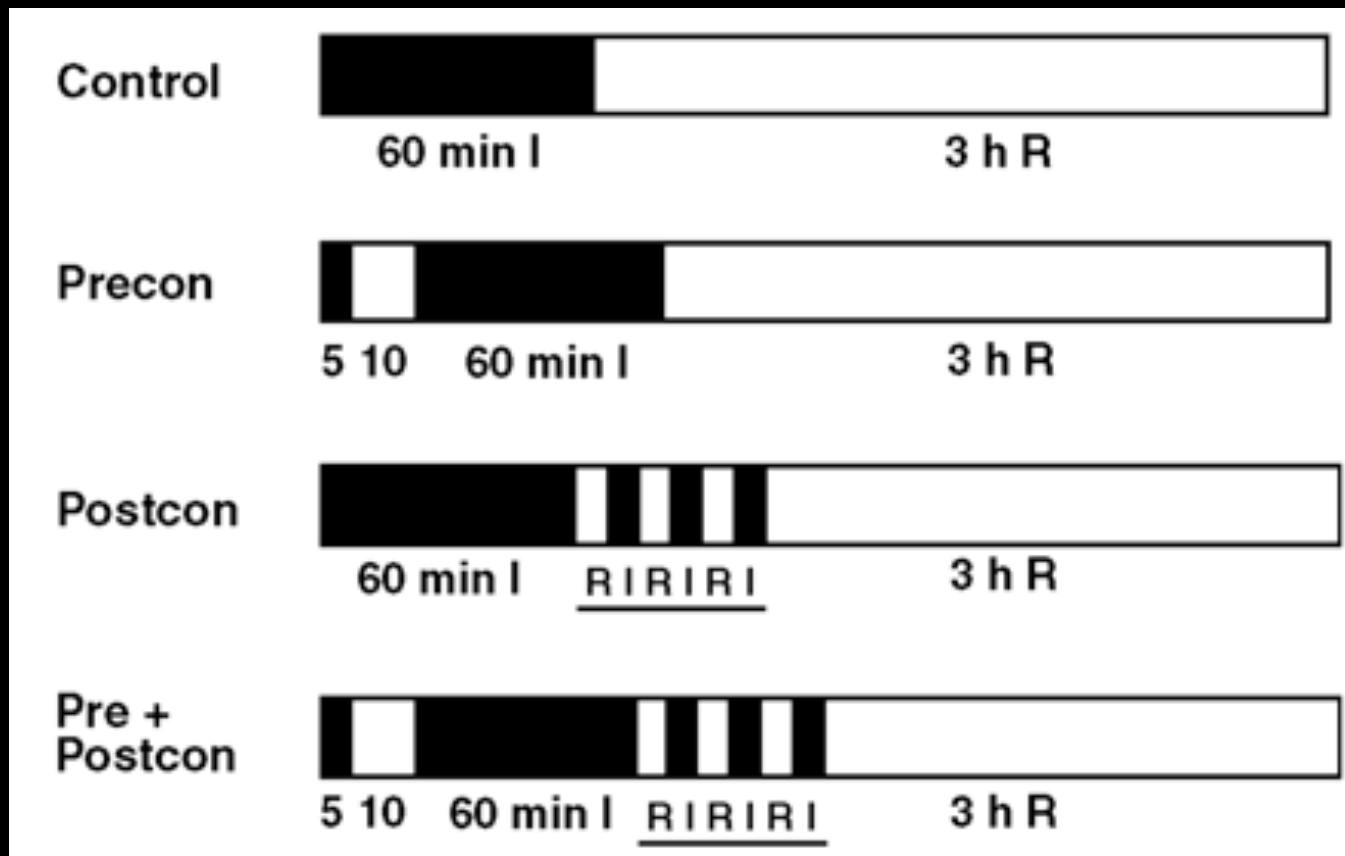


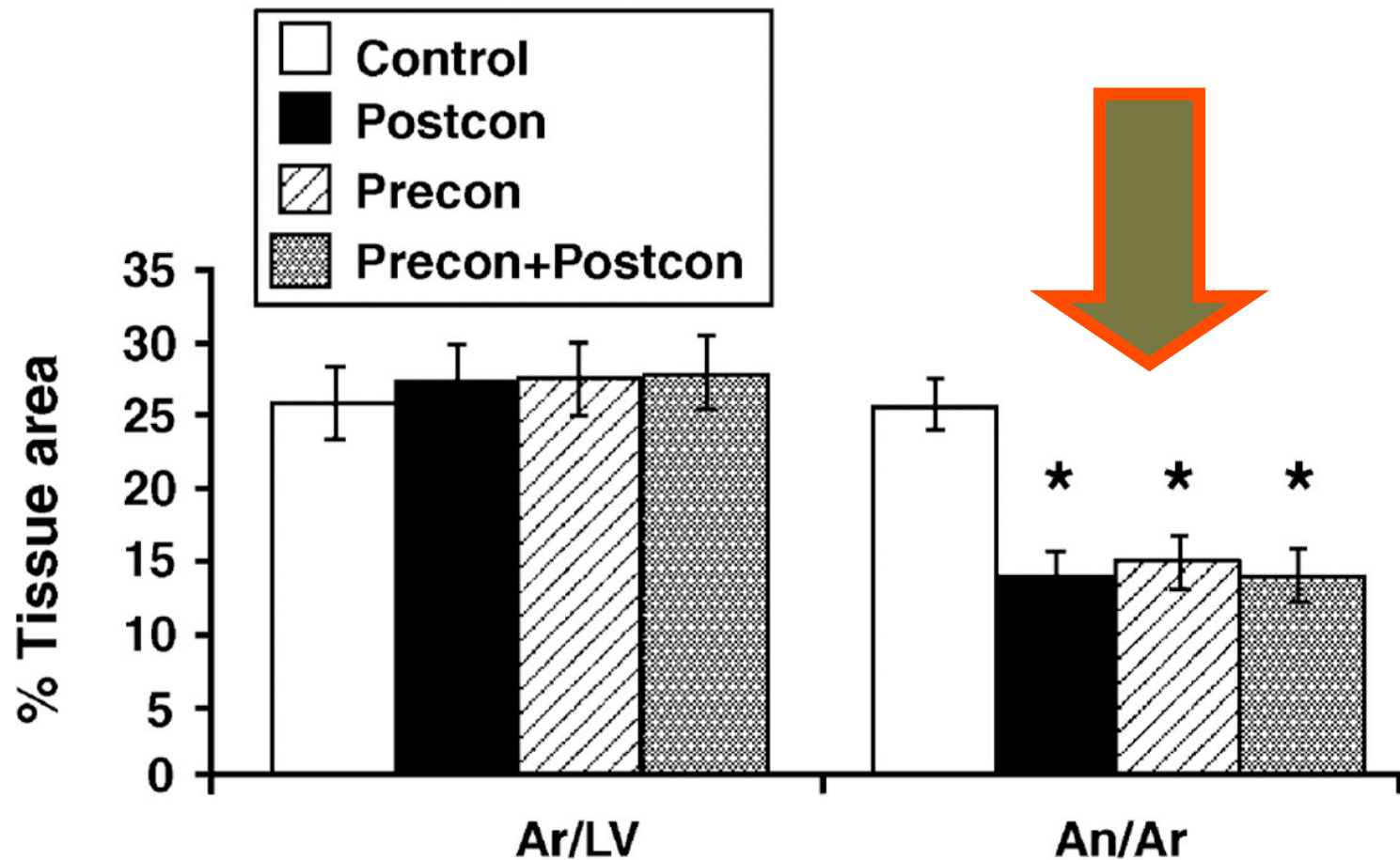
POSTCONDITIONING

- Intermittent Reperfusion or
- « Stuttering Reperfusion »
- Several cycles of **closing and opening** the infarct related artery
- **Immediately** after Angiography
- TIMI 0 or 1 flow

FORM OF CONTROLLED REPERFUSION

POSTCONDITIONING

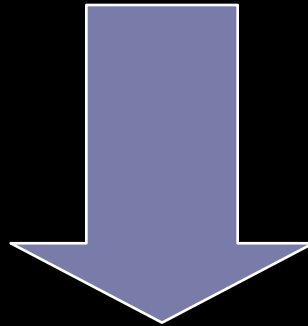




-
- What is PostConditioning?
 - **How does it Work ?**
 - Does-it Work in Humans ?
 - PostConditioning or Thrombus Aspiration ?

The CELL KILLER

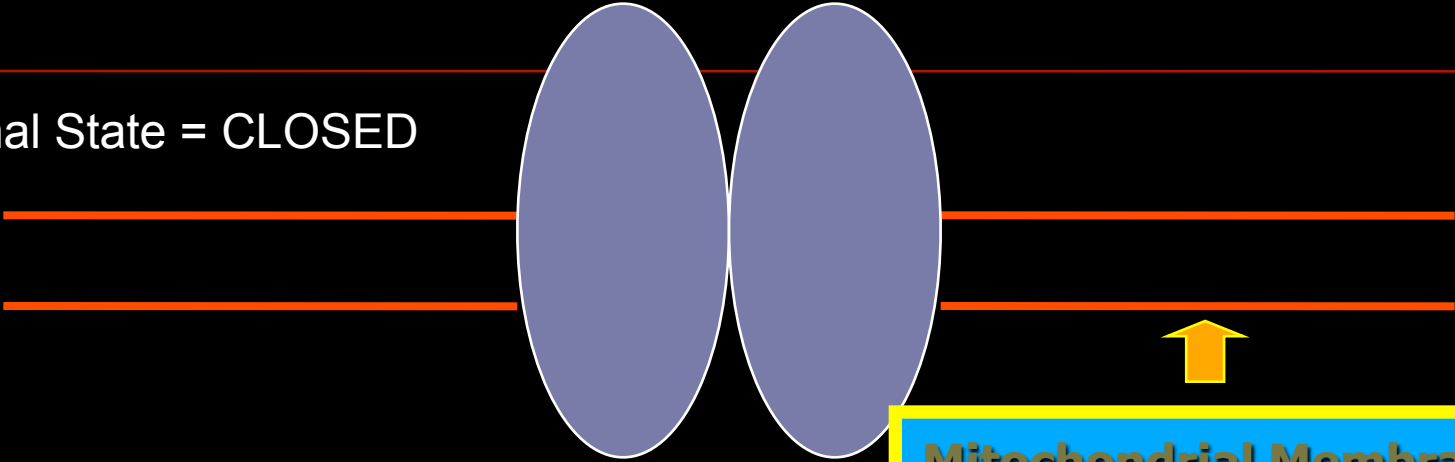
- The « Death Pore »



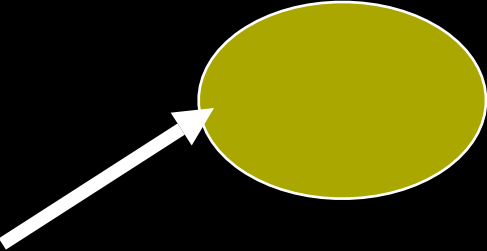
MITOCHONDRIAL MEMBRANE PERMEABILIZATION

Mitochondrial Transition Permeability Pore

Normal State = CLOSED

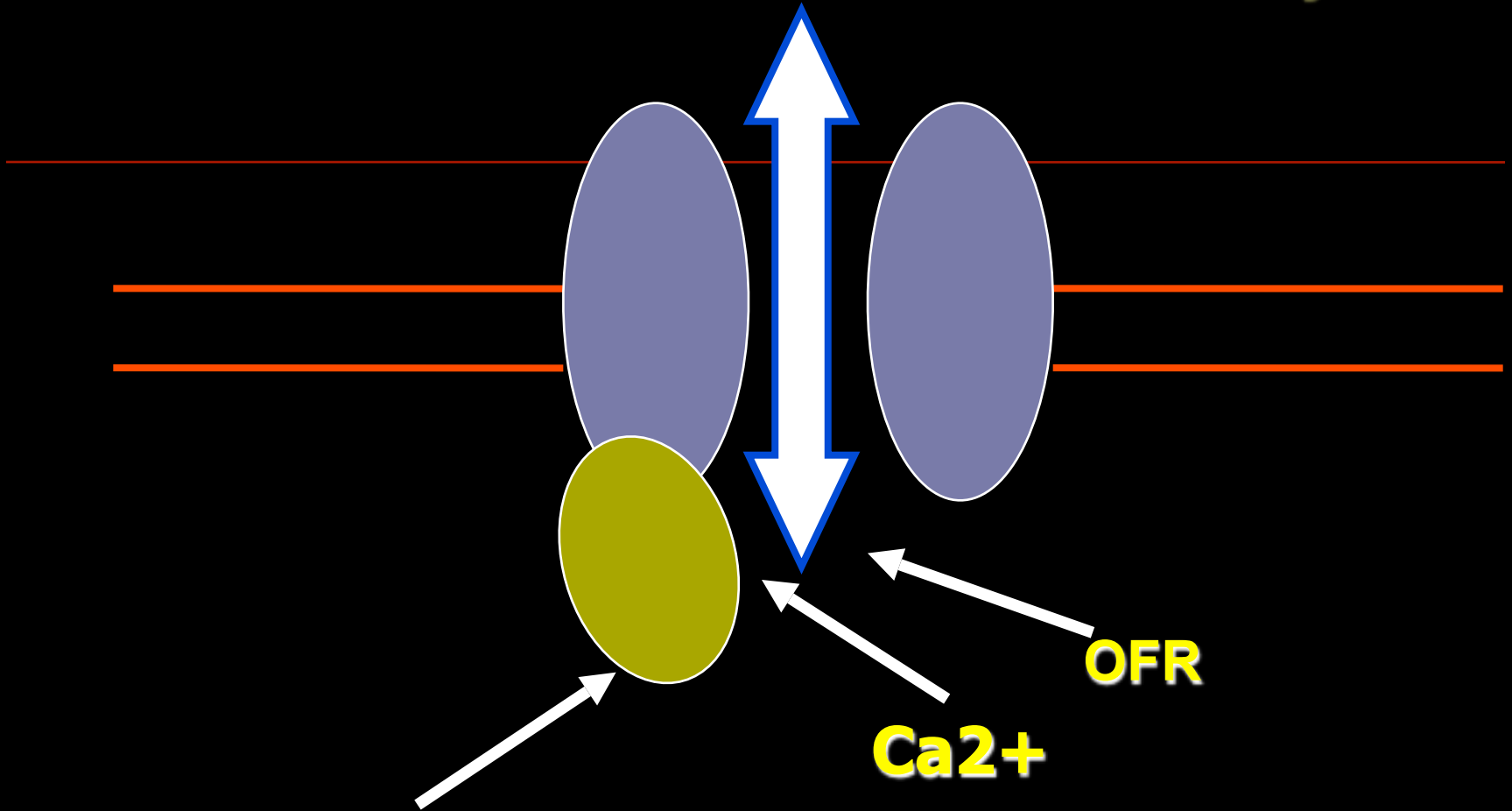


Mitochondrial Membrane



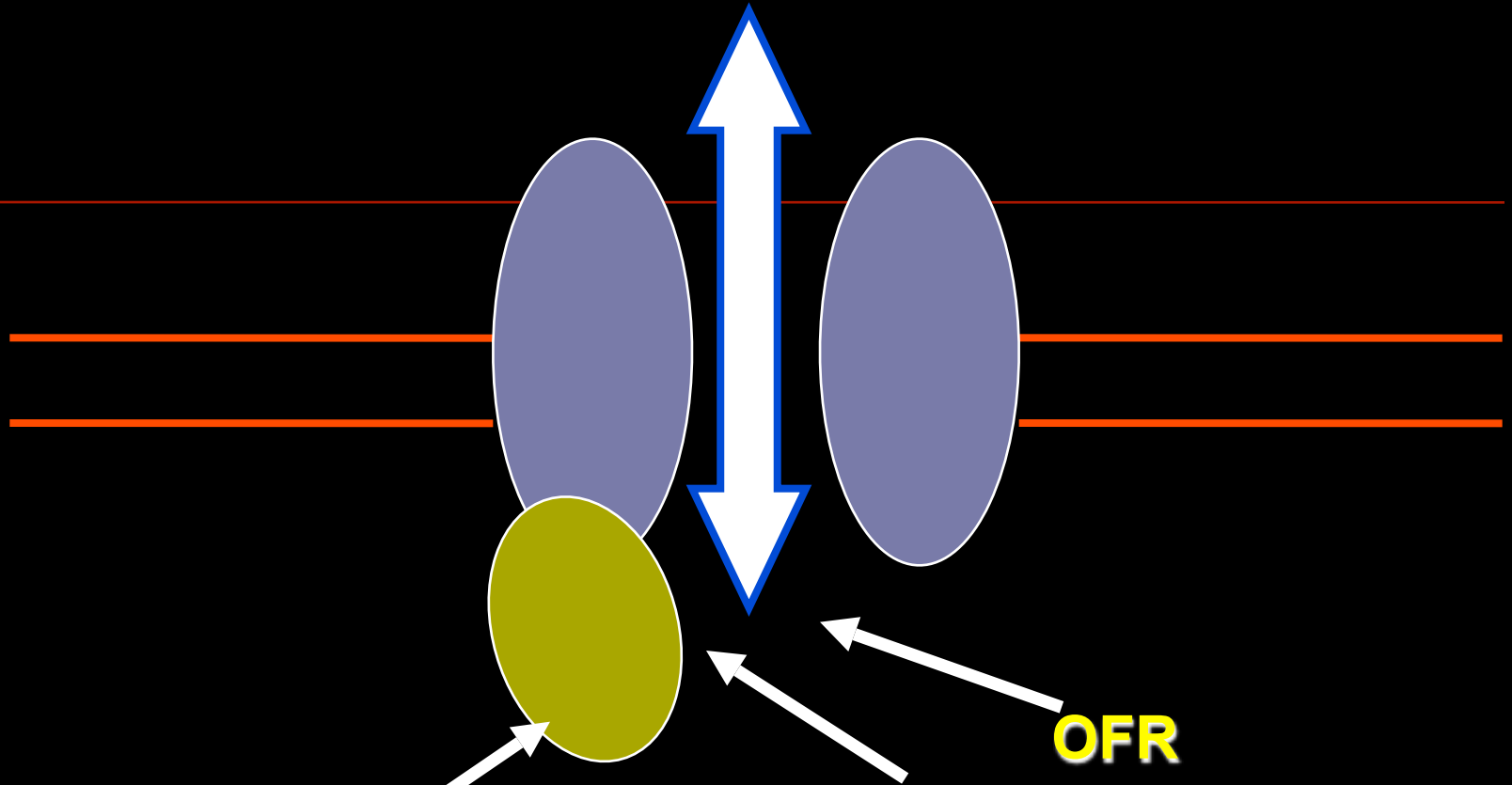
CYCLOPHILINE D

Mitochondrial Transition Permeability Pore



CYCLOPHILINE D

Mitochondrial Permeability Transition Pore



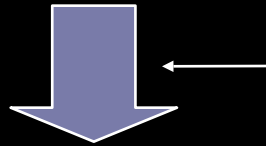
CYCLOPHILINE D

SWELLING = ONCOSIS

**CYTOCHROME c RELEASE =
APOPTOSIS**

Mitochondrial Permeability Transition Pore

CLOSED STATE



REPERFUSION

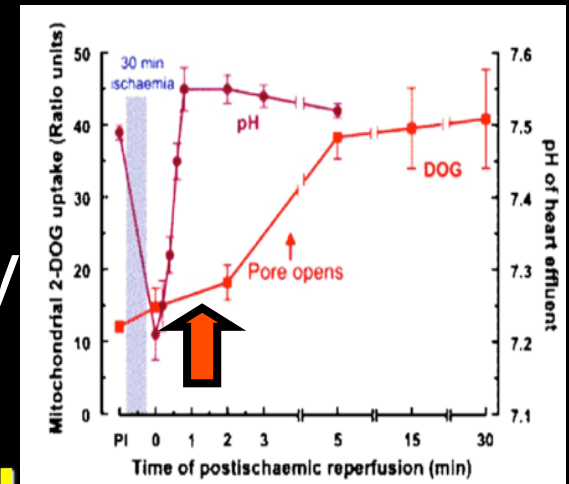
OPENED STATE

ACIDOSIS THEORY

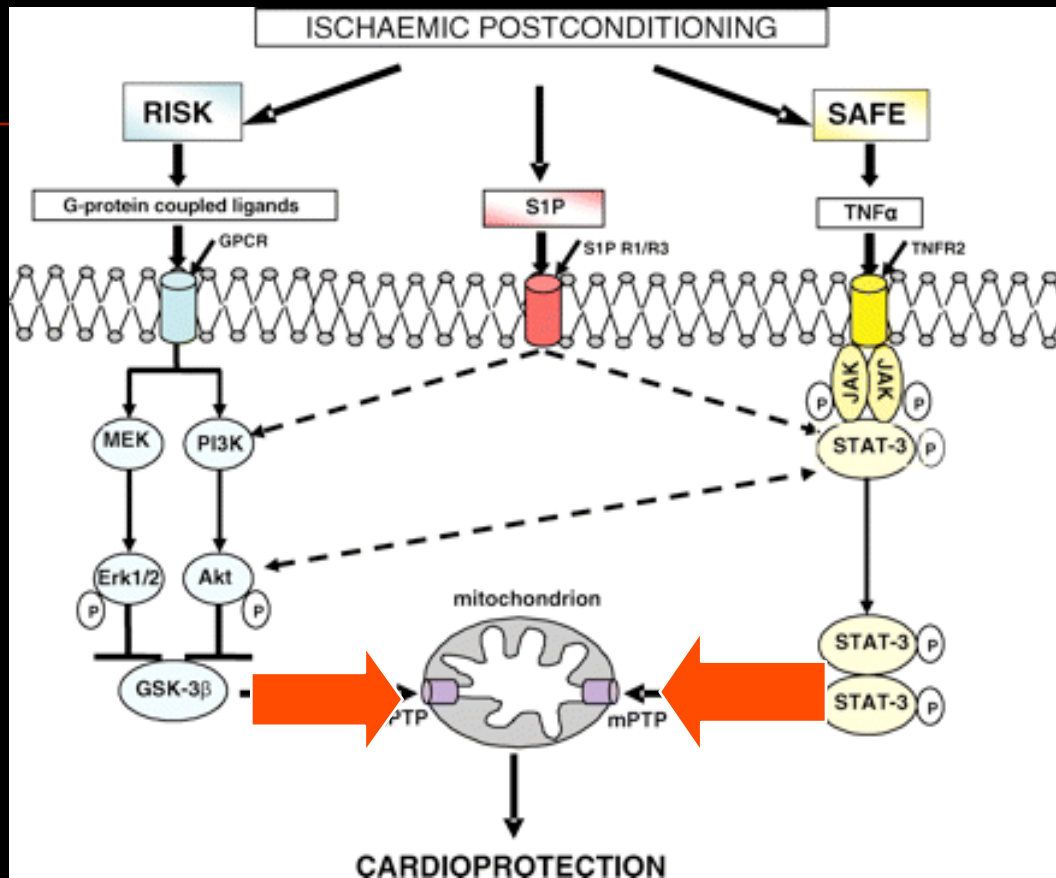
- During Ischemia Acidosis **Closes mPTP**

- Reperfusion **Opens** It Quickly

- PostConditioning **Slows Acidosis Correction** and Maintains mPTP Closed



SALVAGE KINASES CASCADES



INITIATION

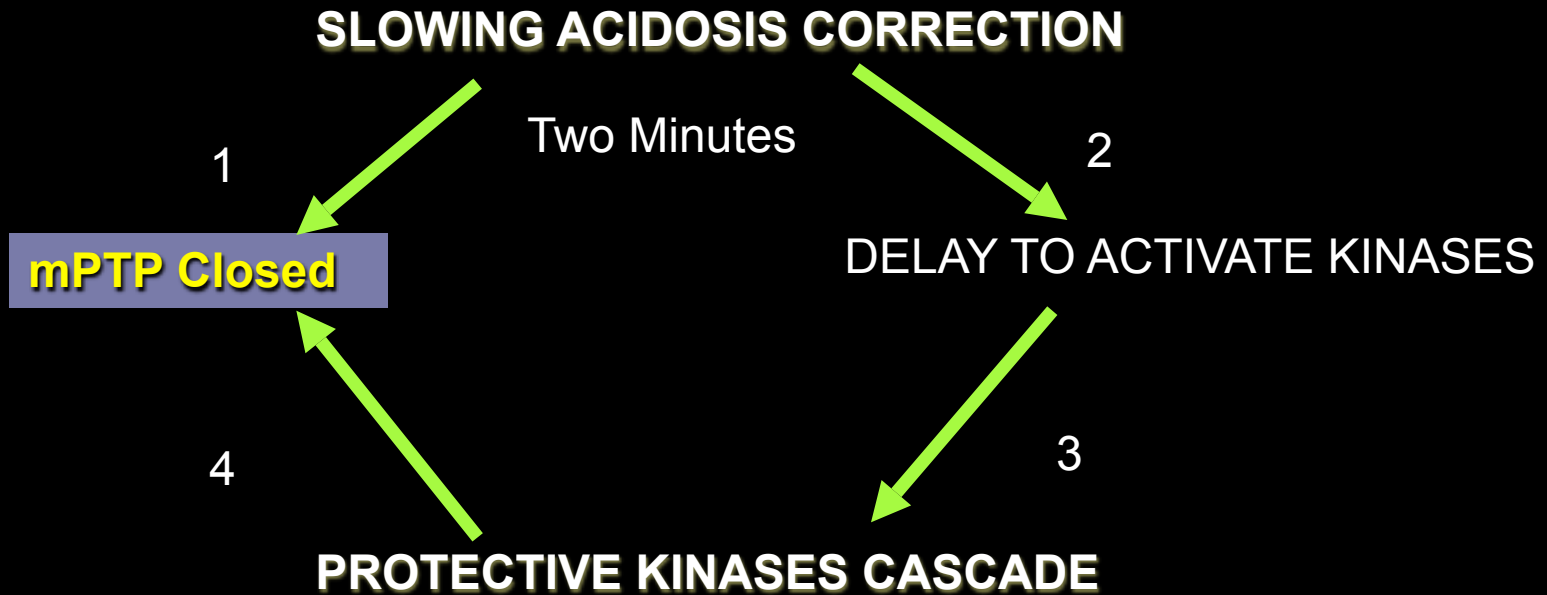


KINASES CASCADES



M. M.

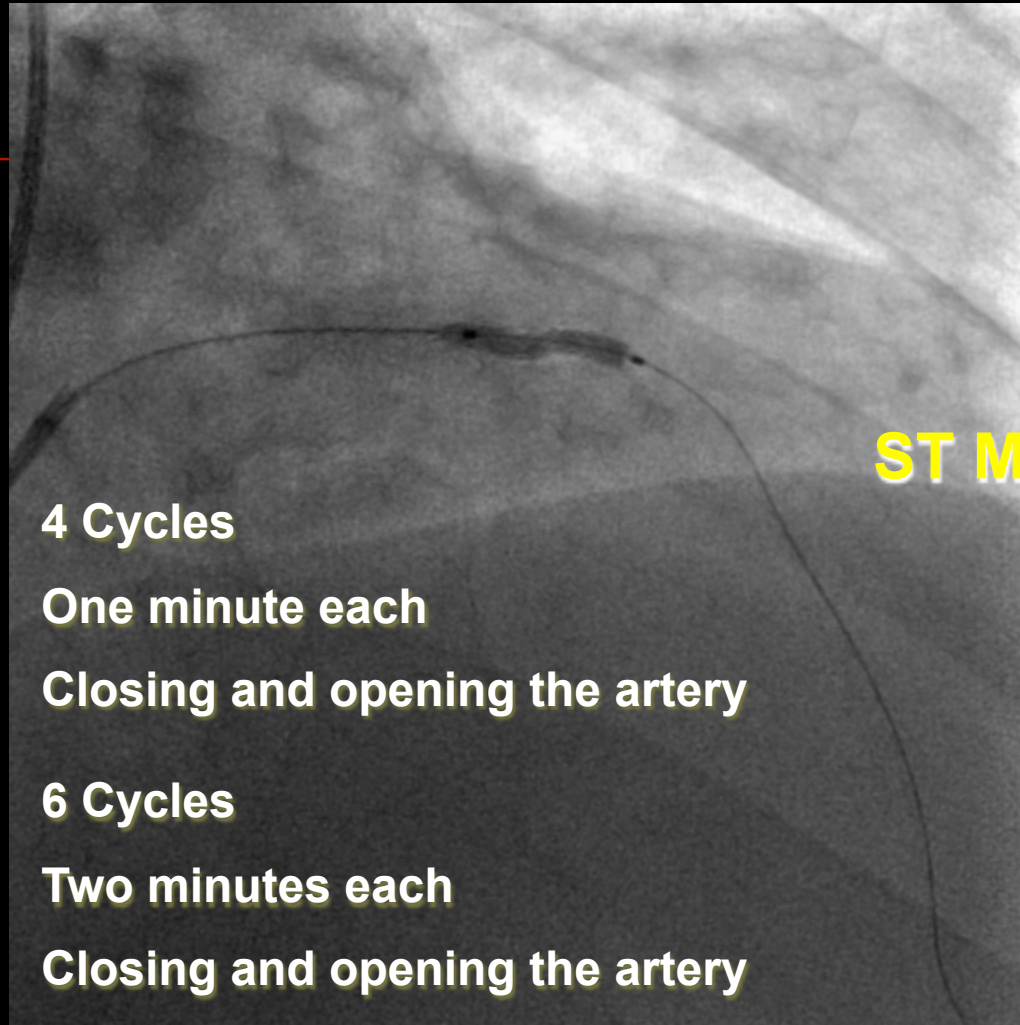
LINK BETWEEN BOTH THEORIES



-
- **POSTCONDITIONING PREVENTS THE OPENING OF THE DEATH PORE**
 - **Slowing Acidosis Correction**
 - **GIVING TIME TO CELLS FOR INSTALLING THEIR DEFENCE STRATEGY**

-
- What is PostConditioning?
 - How does it Work ?
 - **Does-it Work in Humans ?**
 - PostConditioning or Thrombus Aspiration ?

To Prevent Massive Reoxygenation



ST Monitoring ?

4 Cycles

One minute each

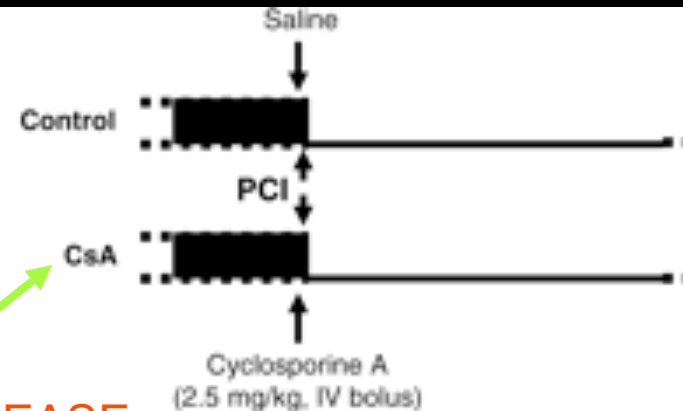
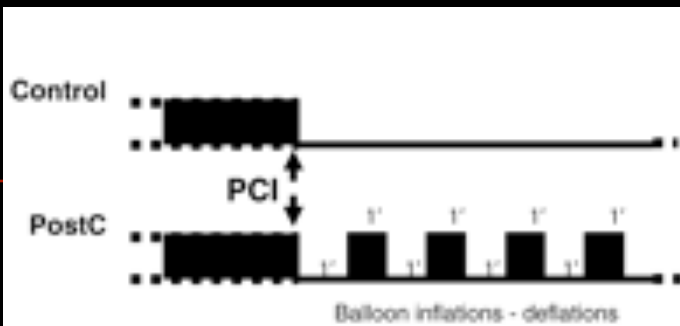
Closing and opening the artery

6 Cycles

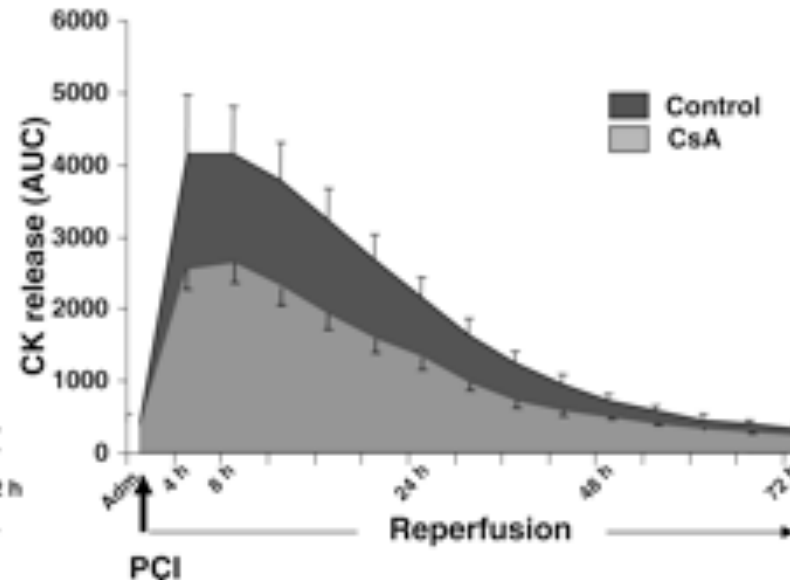
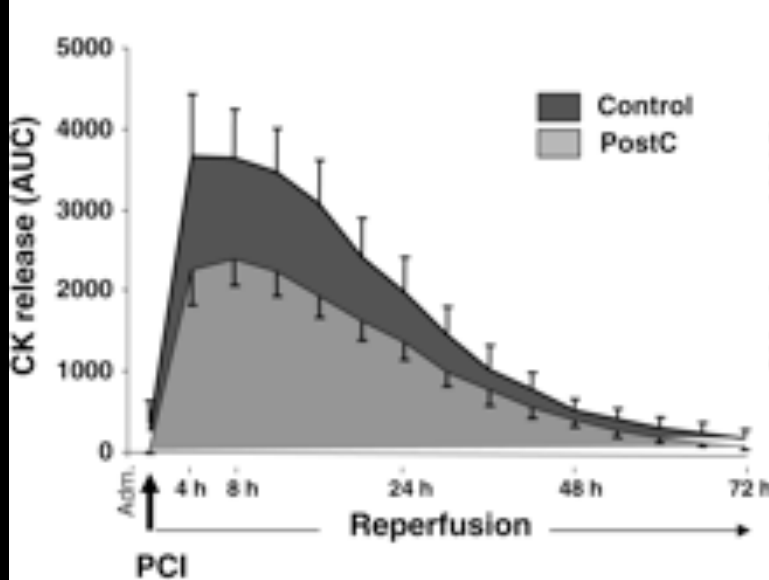
Two minutes each

Closing and opening the artery

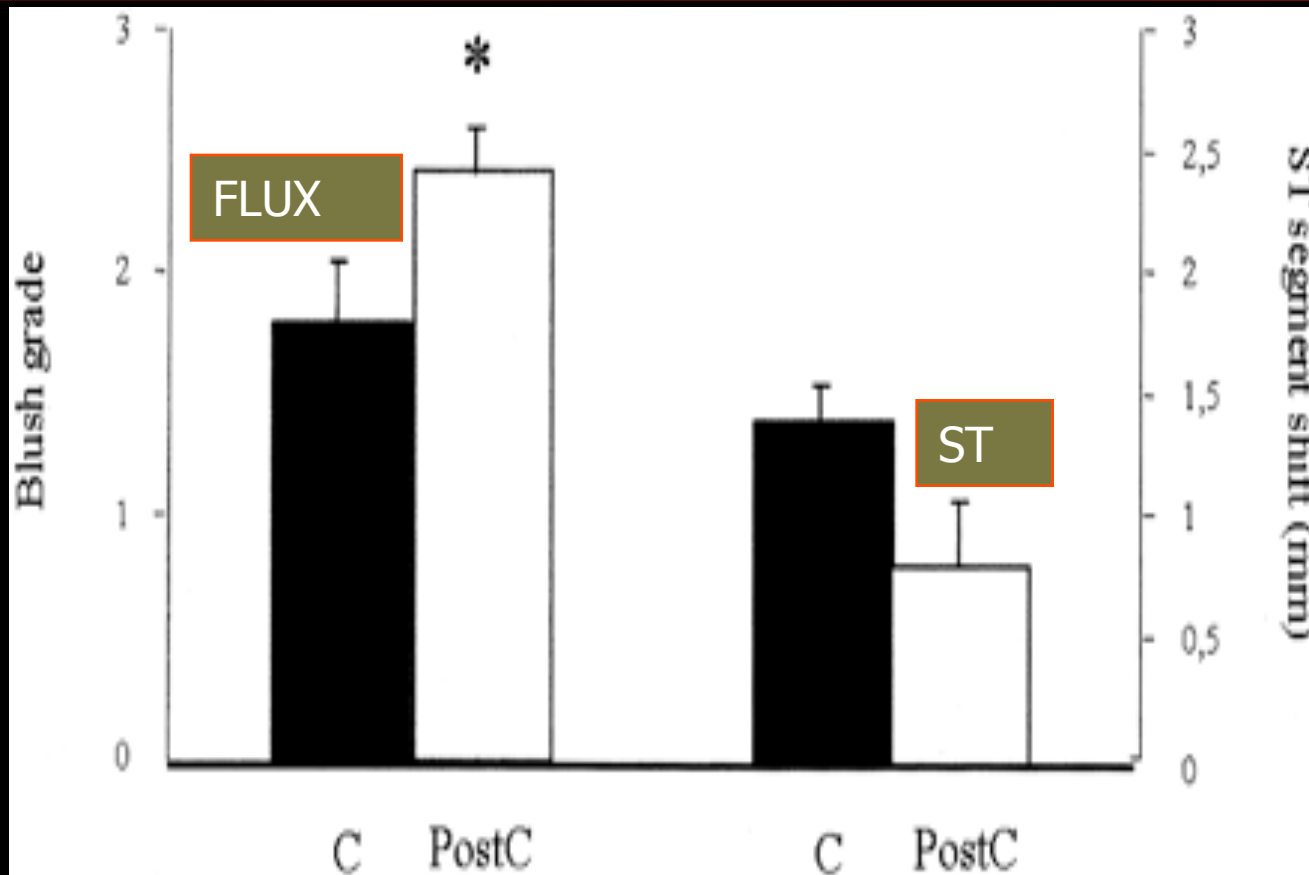
OR ?



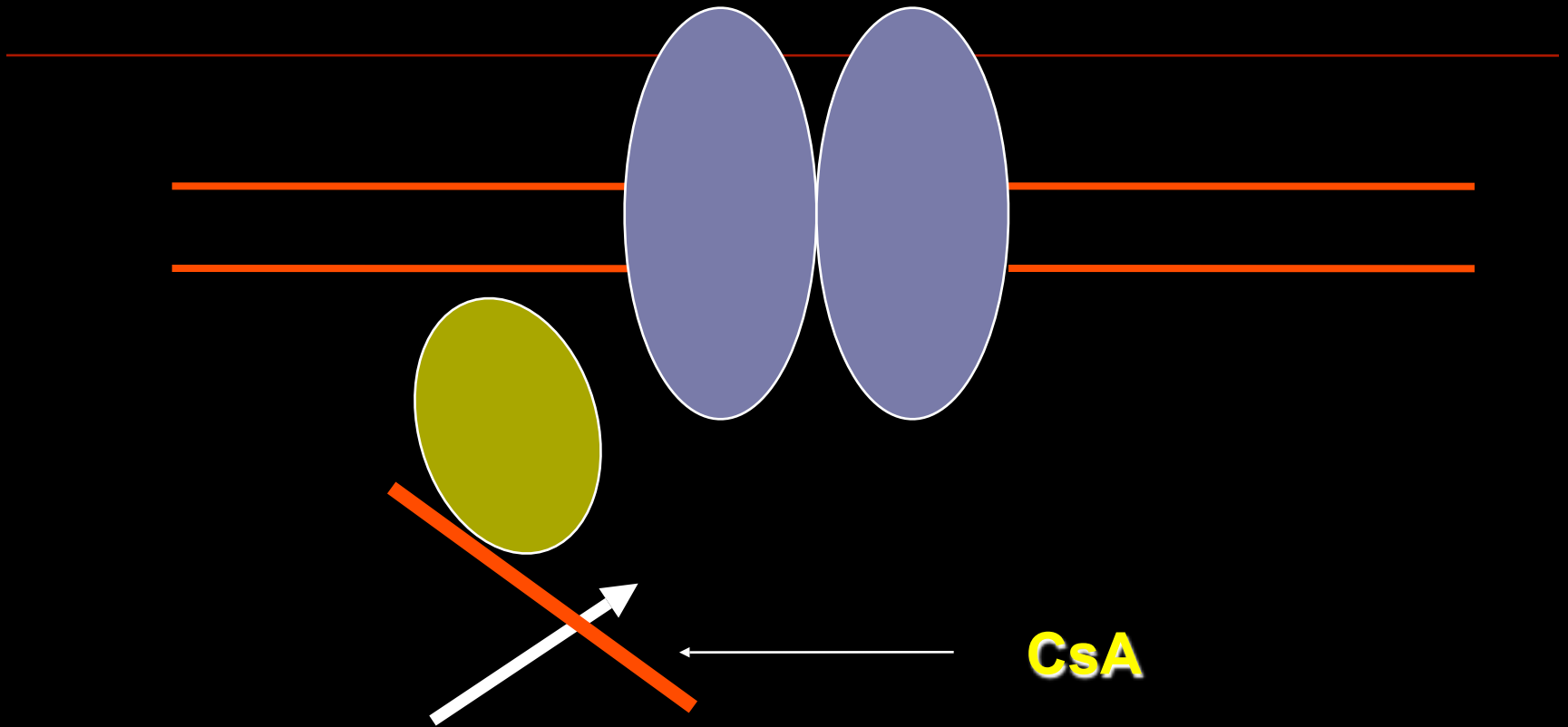
MINUS 40 % RELEASE



No-Reflow



Mitochondrial Transition Permeability Pore



CYCLOPHILINE D

Cyclosporine

- Pharmacological PostConditioning

CIRCUS Study

- Does **C**yclosporine **ImpR**ove **C**linical **oU**tcome in **S**T elevation myocardial infarction patients

Multicenter European Trial - M Ovize – Lyon

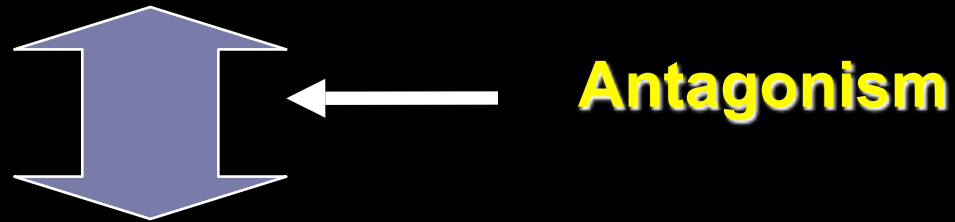
800 Patients

-
- What is PostConditioning?
 - How does it Work ?
 - Does-it Work in Humans ?
 - **PostC or Thr. Asp. or Thr.Disl ?**

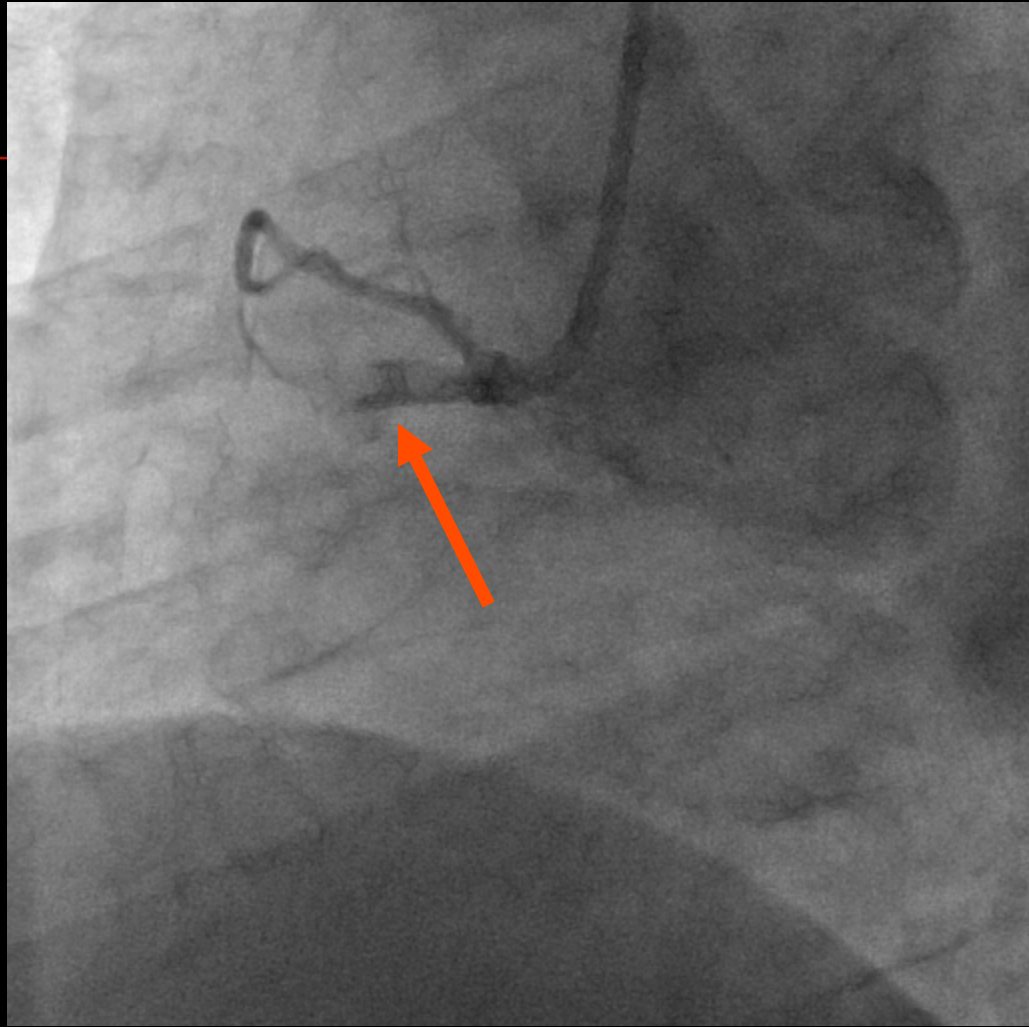
Export

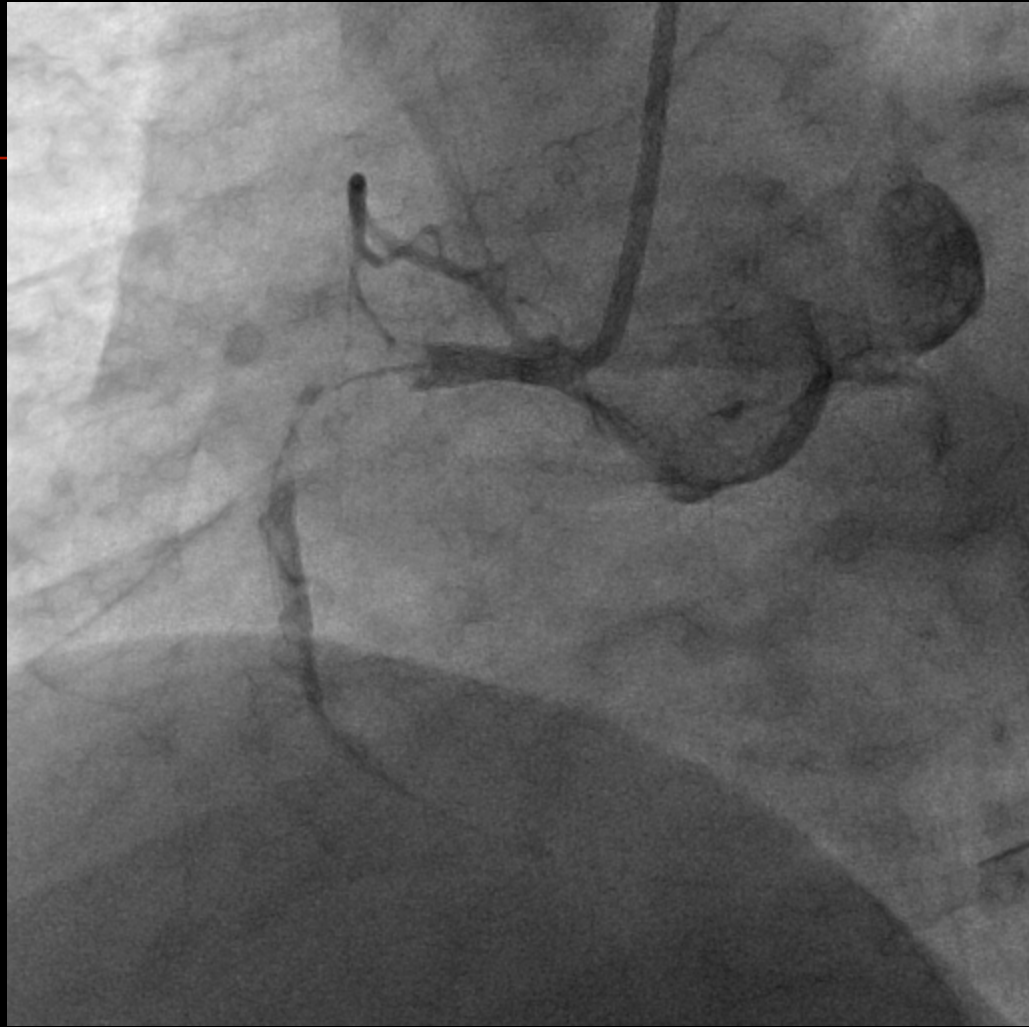
Clearway

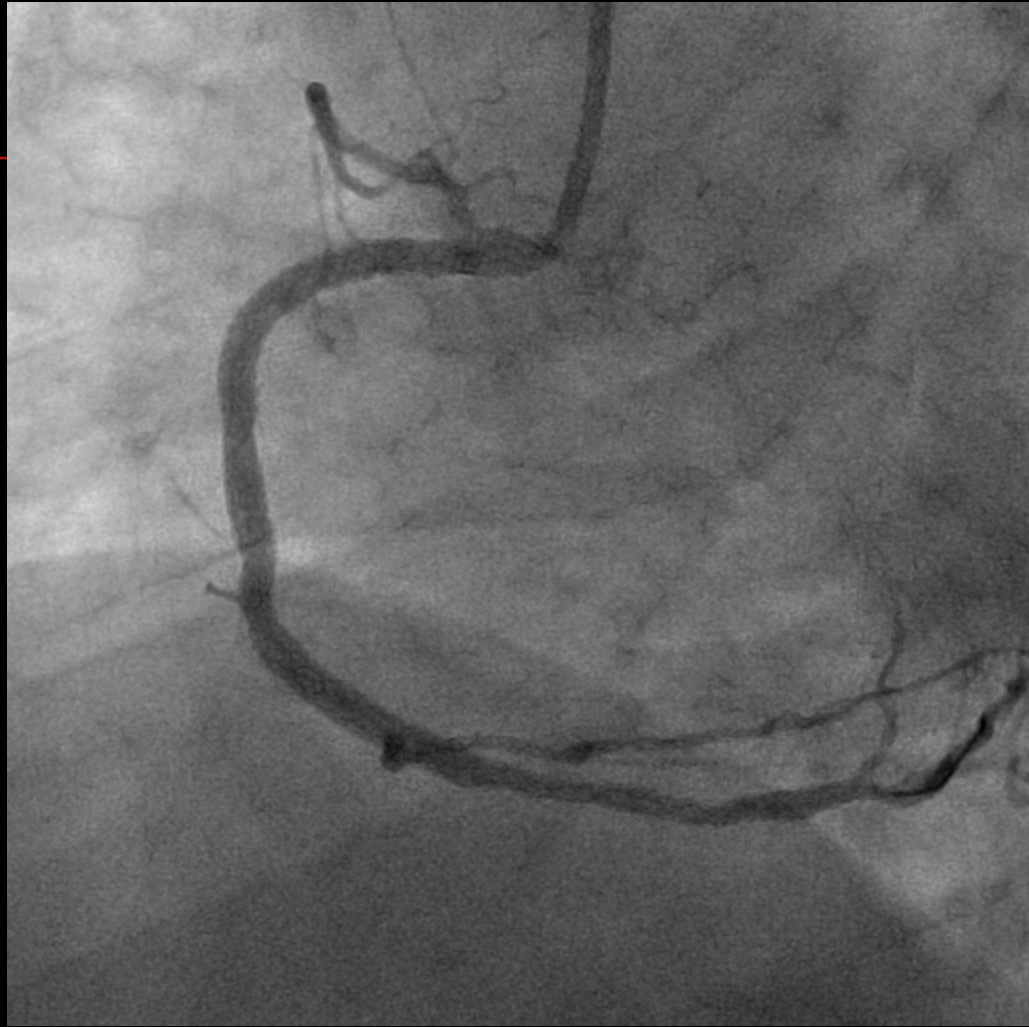
-
- **PostConditioning** is a Progressive Reperfusion



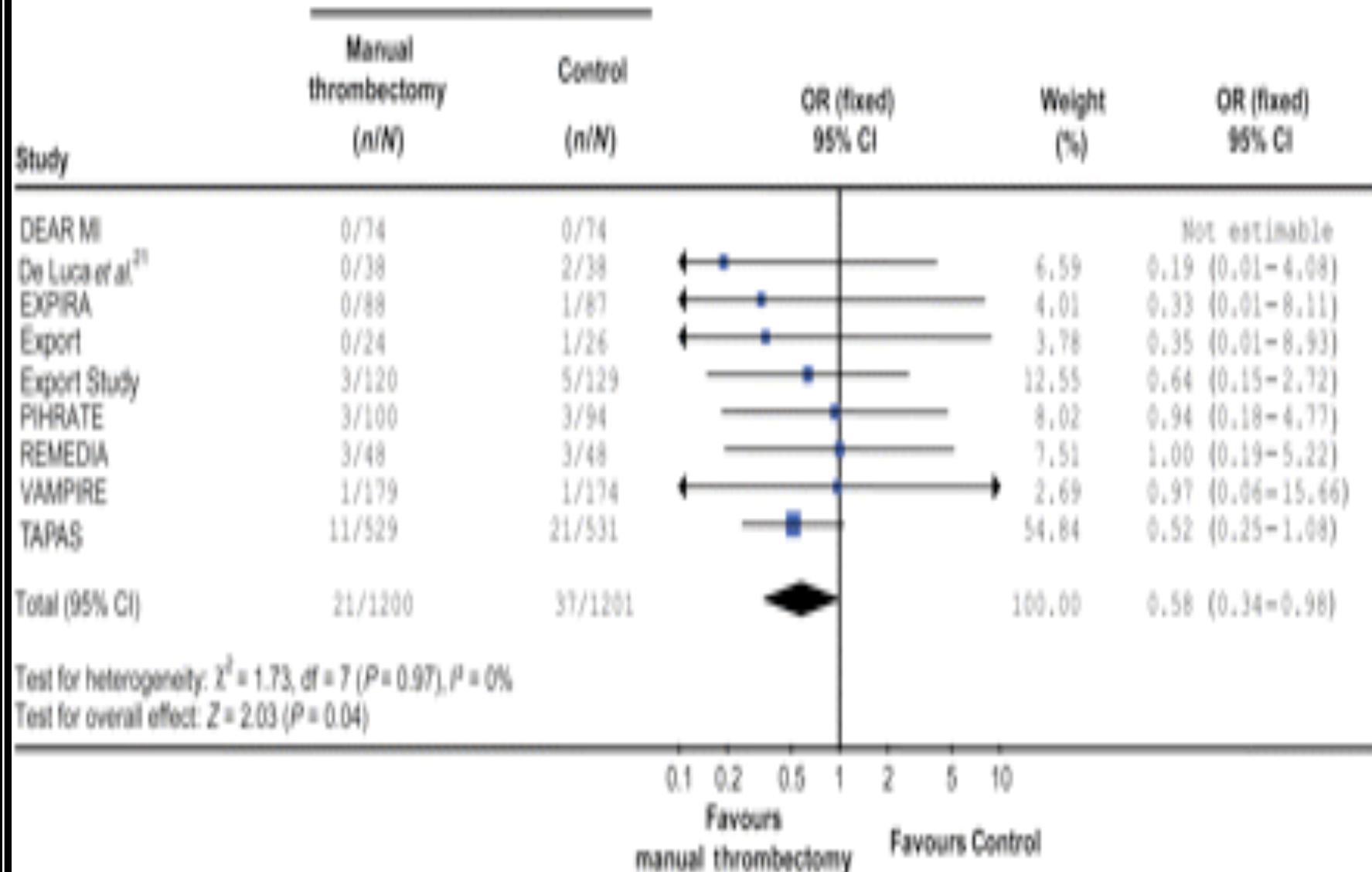
- **Thrombus Aspiration** results in a Few Seconds in TIMI 3 Flow



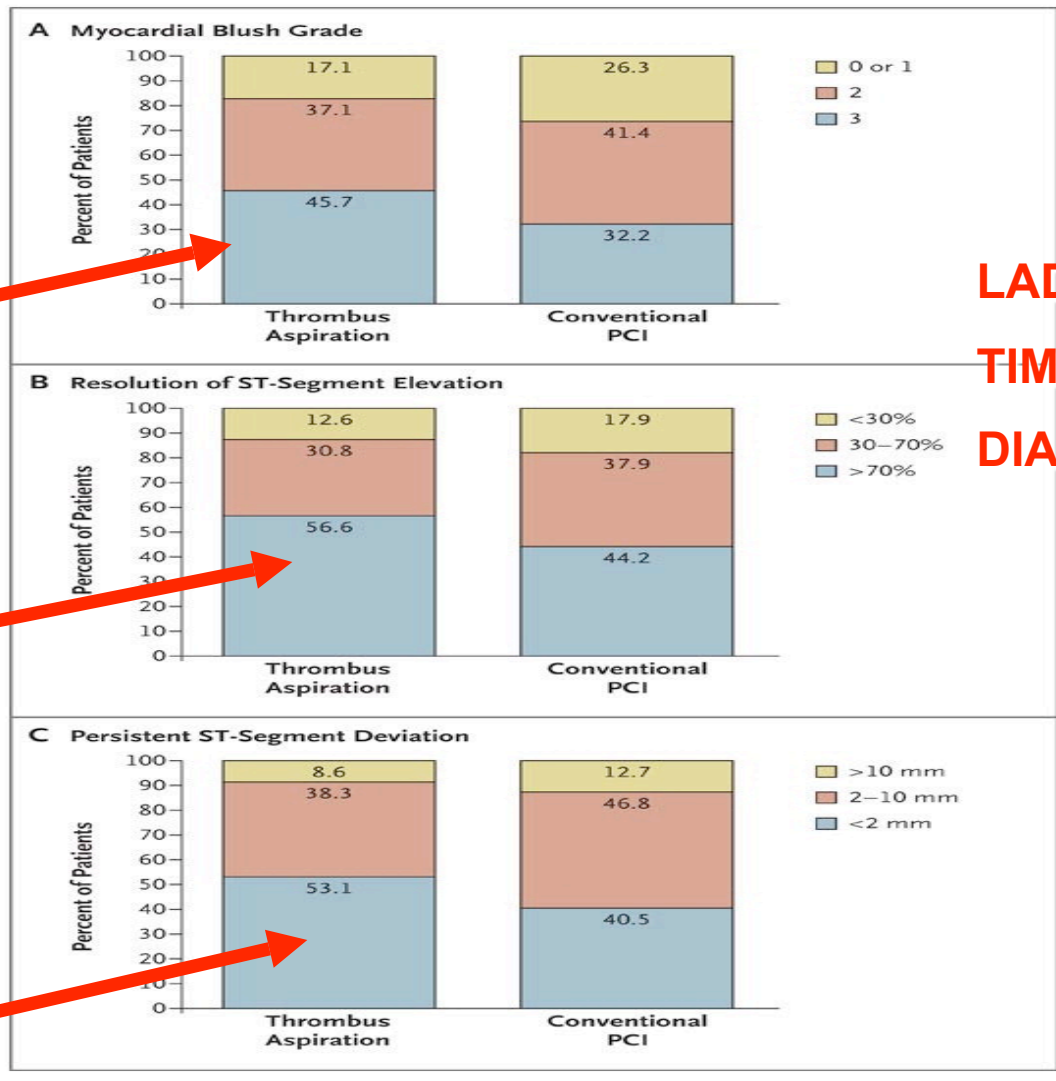




30-Day mortality



TAPAS



48 %

57 %

53 %

LAD = 43 %

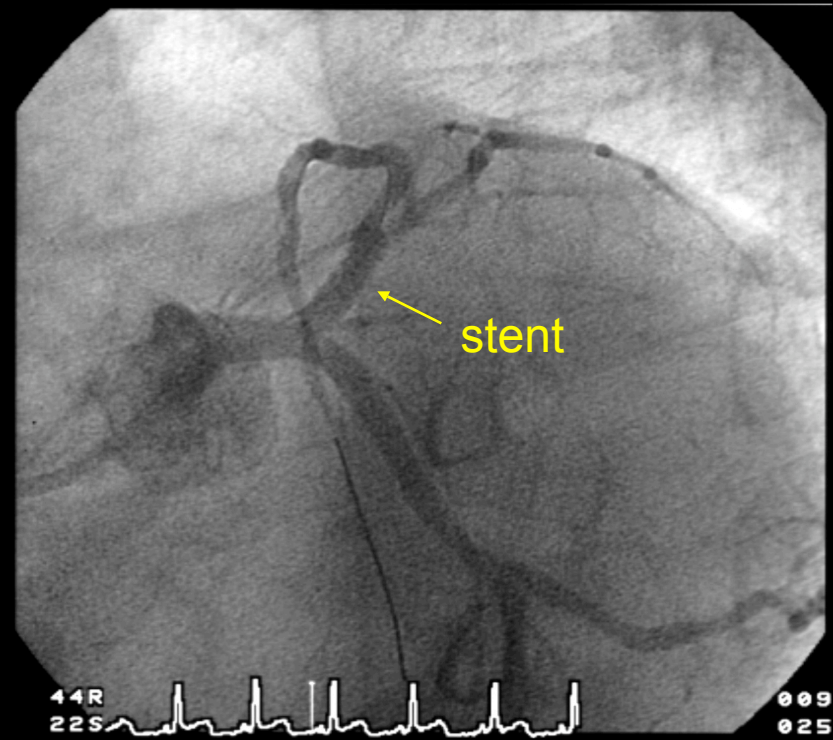
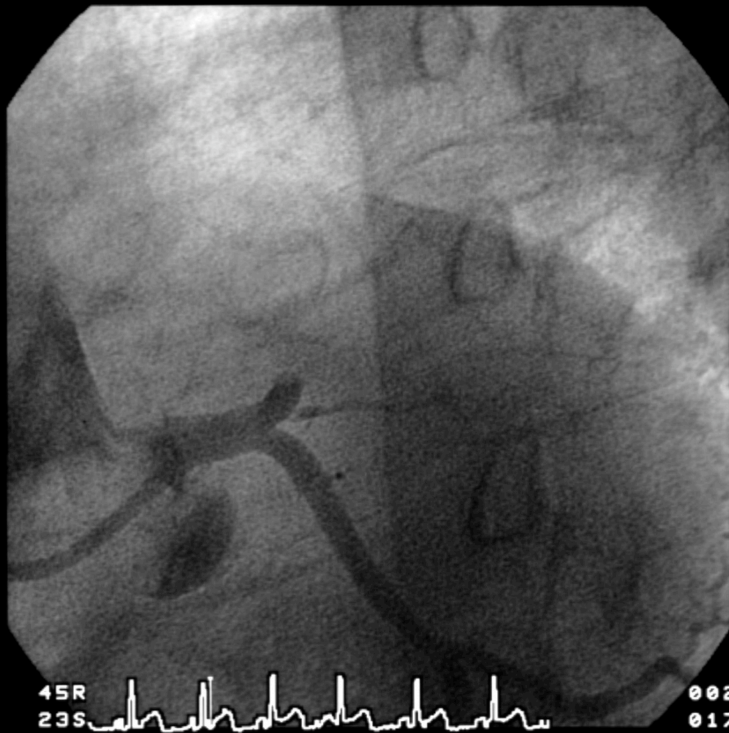
TIMI 0,1 = 55%

DIABETES = 11%

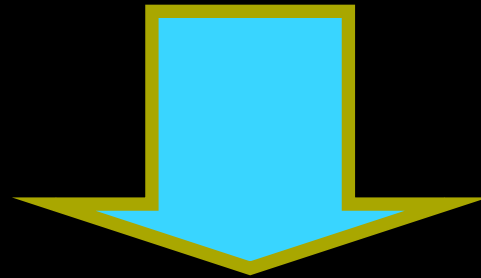
« We Have a Dream »

- Pharmacological Protection Before Infarct Related Artery Reopening (CsA)
- Thrombus Aspiration
- Clearway  PostC + Thrombus

■ OFF – ON PCI !!



« OFF-ON » PCI : THE END !!



CONTROLLED REPERFUSION

LES AUTRES PROTECTIONS

- **Préconditionnement**
- **Postconditionnement**
- **Conditionnement à Distance**
- **« Remote Conditioning »**

■ « **CARDIAC PROTECTION TAKES OFF** »

- Piper HM , Garcia-Dorado D
- Cardiovasc Res 2009 ; 83 : 163-4



THANK

YOU

-
- What is PostConditioning?
 - How does it Work in Experimental Conditions ?
 - Does-it Work in Humans ?
 - PostConditioning or Thrombus Aspiration ?