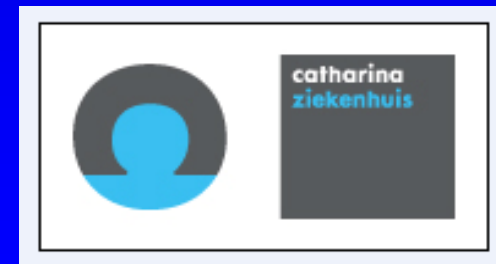


MODULE 2

THE CLINICAL ENIGMA: *RANDOMIZED TRIALS vs CLINICAL PRACTICE*



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Disclosure

All presenters have a speaker agreement with Maquet

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Key points in this presentation:

- **Why did current prospective trials with IABP not meet their endpoints**
- **The emerging science of selection of patients who *may* benefit from IABP**

IABP: CLINICAL ENIGMA:

- In some patients dramatic improvement of clinical condition by IABP
- In others no effects at all
- Many retrospective studies show benefits
- In prospective randomized studies no differences

WHY those differences?

How to select patients and clinical conditions which benefit from IABP ?

SHOCK II Trial

- 600 patients with acute MI, complicated by cardiogenic shock and planned primary PCI
- Randomized to PCI + IABP or PCI only
- Primary endpoint: 30-day mortality
- High cross-over rate in PCI only group:
 - 10% to IABP, **and** ~5 % to LVAD/Impella/etc
- Crossover rate 4 % in IABP group, due to immediate death before IABP could be started

SHOCK II Trial

High cross-over rate of 15 % in PCI only group:
10% to IABP, **and** ~5 % to LVAD/Impella/etc

- The worst patients from the control group received additional treatment which - at least at the judgement of the treating physician - was considered useful
(positive bias in favor of control group)

SHOCK – II Trial

Crossover rate 4 % in IABP group, due to *immediate death before IABP could be started*

- The patients from the “treatment” group who would have the highest profit of IABP, contributed in negative sense for the endpoint
(negative bias for the “treatment group”

SHOCK II Trial

So-called “**selective cross-over**” (NTVG 2013; 157: 2151-2155)

→ **serious bias**

If use of additional support device would have been part of primary endpoint → positive study

CRISP AMI TRIAL

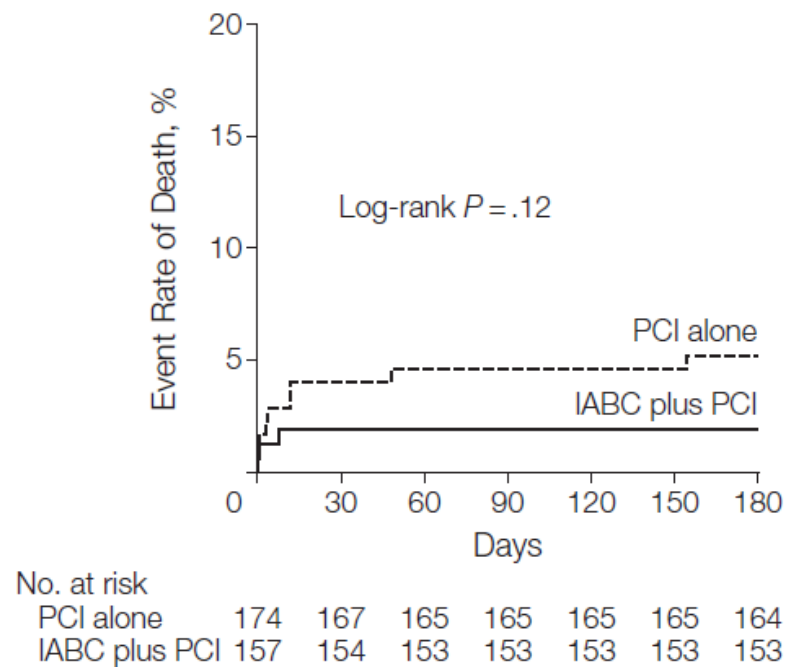


- 339 patient with STEMI \leq 6 Hours admitted for primary PCI
- 2 palpable femoral arteries
- ECG with Anterior STEMI
(*2 mm in 2 Leads or \geq 4 mm total*)
- Randomized to IABP / no IABP prior to PCI
- Endpoints:
 - Infarct size after 5 days by MRI
 - Manifest heart failure at 6 months

Outcomes of CRISP AMI

- No difference in infarct size (or any other MRI parameter)
- At 6 months
 - 3 patients IABP plus PCI died, vs. 9 patients PCI alone (strong trend)
- Significant difference in non-specified composite endpoint of death, shock or heart failure
 - 8 vs. 21 events at 6 months
 $P=0.03$

Figure 2. Event Rate of Death From 0 to 180 Days



IABP indicates intra-aortic balloon counterpulsation; PCI, percutaneous coronary intervention.

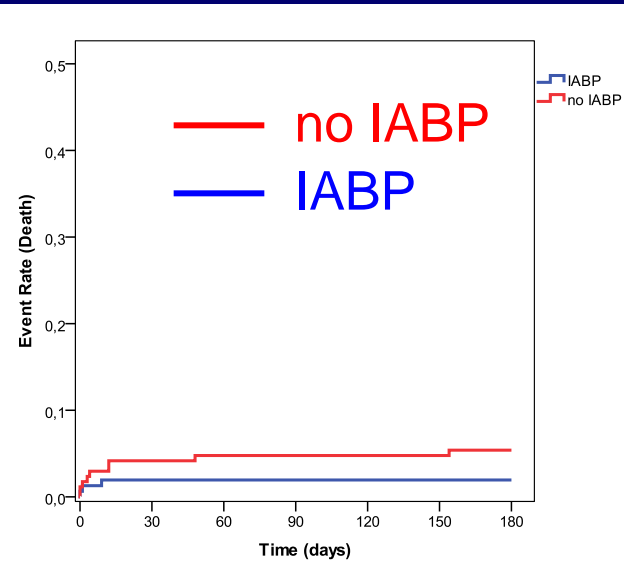
Limitations of CRISP AMI

- Inclusion criteria not “robust” enough
 - In many patients (56%) limited amount of myocardium at risk → dilution of benefit

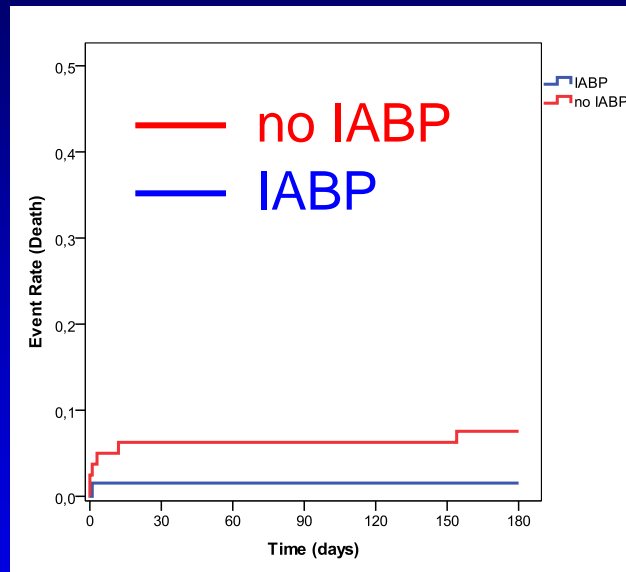
(in fact, the study was severely underpowered)
- If good “reflow” after PCI (as is the case in many patients), good outcome anyway → further dilution of benefit *(unavoidable in CRISP-AMI due to protocol)*
- High cross-over rate in PCI only group (8.5 %)



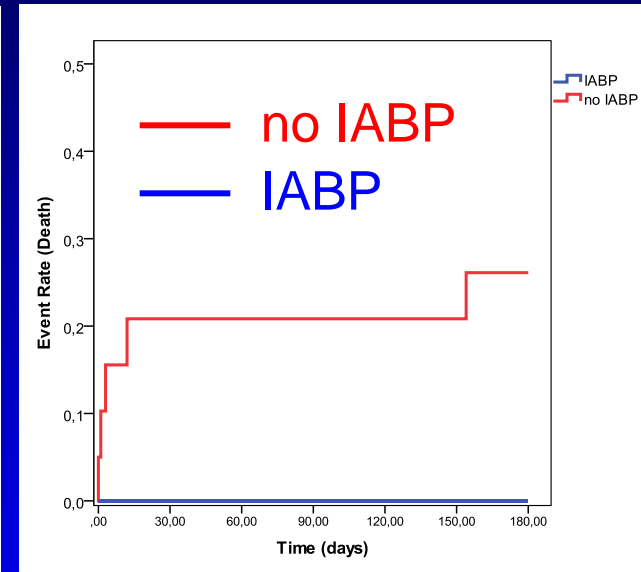
CRISP AMI: 30-day mortality



All patients (N=329)



“Large” infarction (N=146)



Persistent ischemia (N=36)

→ **IABP significantly reduced mortality in large STEMI with persistent ischemia**

Is an Intention-to-Treat analysis suitable to analyze this kind of studies?

→ **No**

Prerequisites for an Intention-to-Treat analysis:

- Double-blind study
- Large sample size
- Events relatively rare compared to sample size
- Low and *non-selective* cross-over rate

Especially if cross-over is driven by failure of the one treatment strategy, serious confounding is introduced (positive bias in favor of control group and negative bias for the “device” group is unavoidable, unless cross-over is considered as part of the primary endpoint)

Is an “as treated” analysis then suitable to analyze these kind of studies?

(as suggested by the authors of SHOCK-2)

- In case of high asymmetrical cross-over rate, the baseline characteristics of the groups change considerably
(the worst patients from the “control group” are moved to the “device” group!)
- Absence of difference in outcome in both groups, may in fact indicate superiority of one treatment !

- In the prospective RCT's to the benefits of IABP, serious negative bias and confounding was present, masking *by definition* potentially positive effects of IABP
- This is a fundamental problem in open studies in “back-to-the wall” patients with high mortality, like many other studies in Intensive Care (IC) units
- The only way to circumvent this, is to forbid cross-over or adding cross-over to the primary endpoint (*like in the SEMPER FI study*)

When does a balloon pump make sense ?

- Increase of (diastolic) perfusion pressure does **NOT** increase coronary blood flow and oxygen supply under normal physiologic circumstances
(autoregulation counteracts IABP effects)
- *In normal circumstances, cannot expect noticeable effect of IABP on coronary blood flow*
- But when autoregulation is exhausted, IABP may be expected to become effective

Coronary autoregulation is exhausted in case of:

- Low (diastolic) blood pressure (< 60 mmHg)
- Very tight (critical) stenosis
- Ongoing myocardial ischemia:
 - Acute phase of MI with no/insufficient reflow
 - Sometimes the patient after cardiac surgery

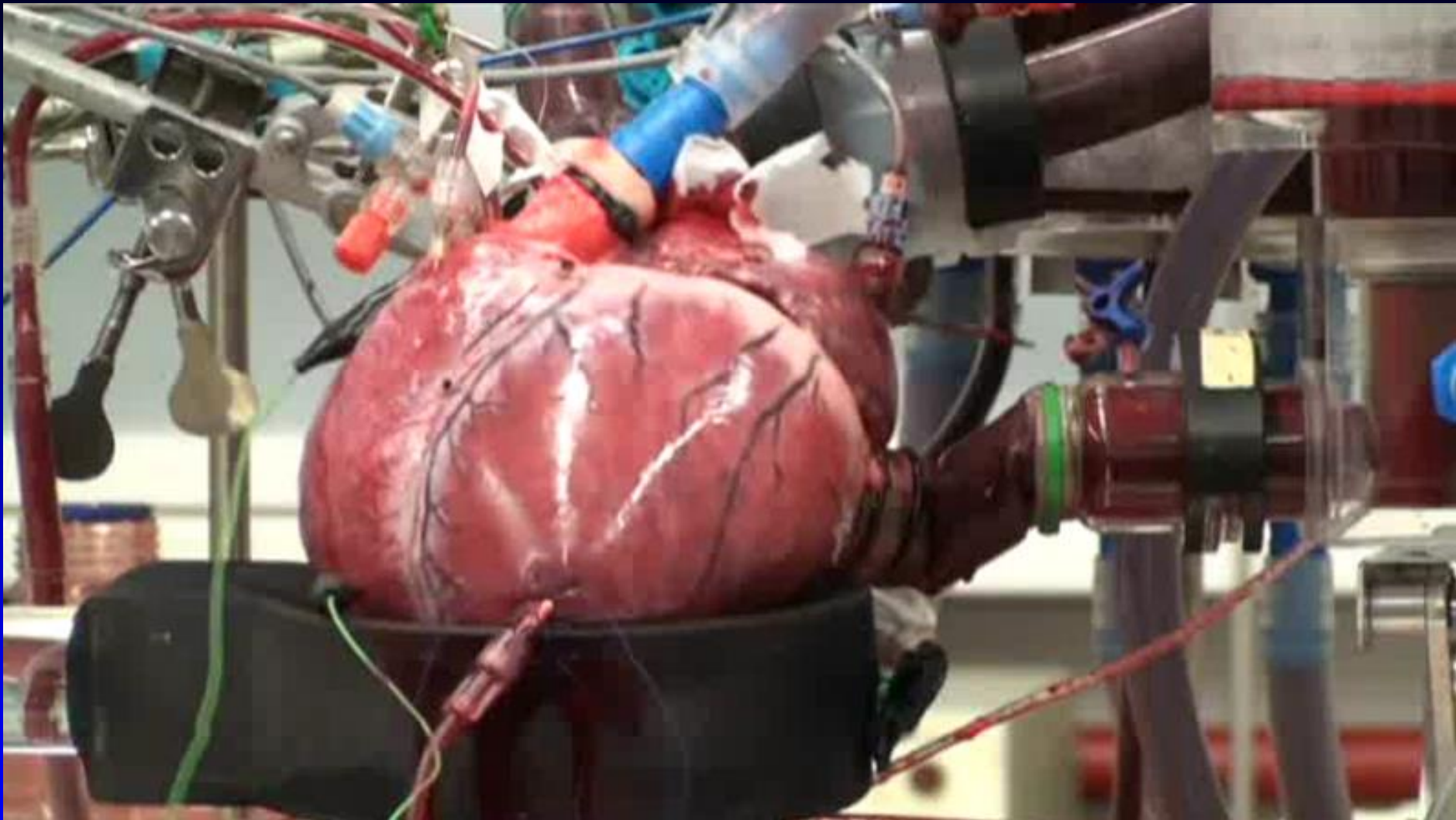
Under these circumstances, coronary blood flow is directly proportional to diastolic perfusion pressure

Large STEMI: When to Use IABP ?

Hypothesis:

IABP may be expected to be useful in patients with viable myocardium suffering from persistent ischemia despite an unobstructed coronary artery

How to validate this??



Isolated beating pig heart

Beating heart model with independent control of:

- Afterload (blood pressure)
- Preload (LA pressure)
- Contractility (dP/dt)
- Arterial oxygen saturation
- Heart rate

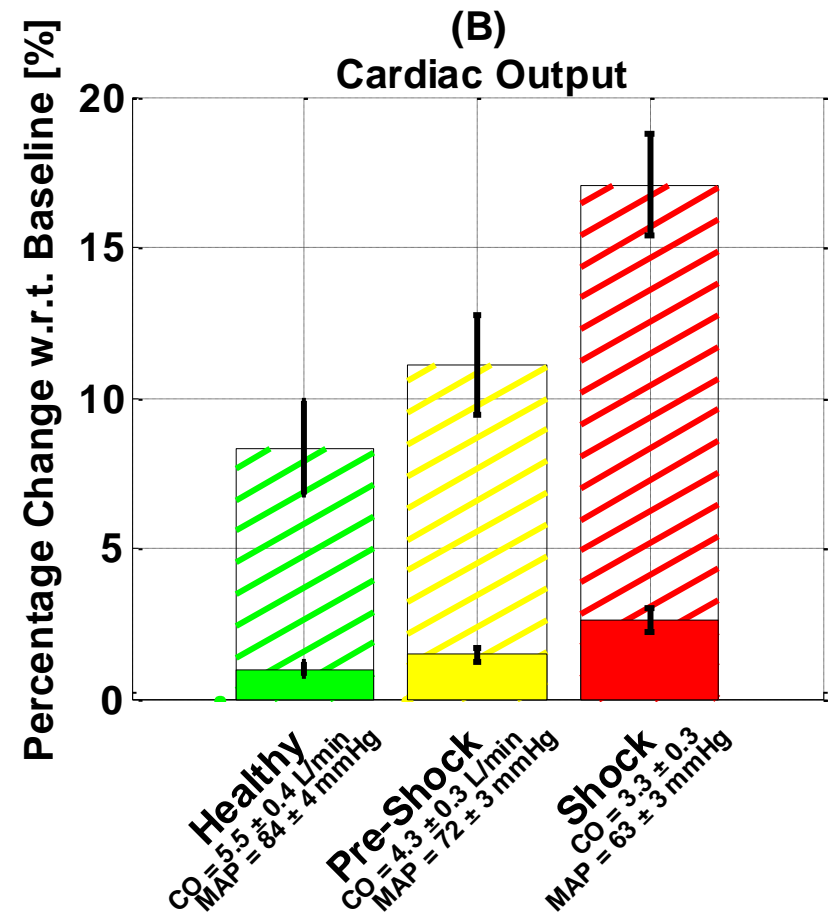
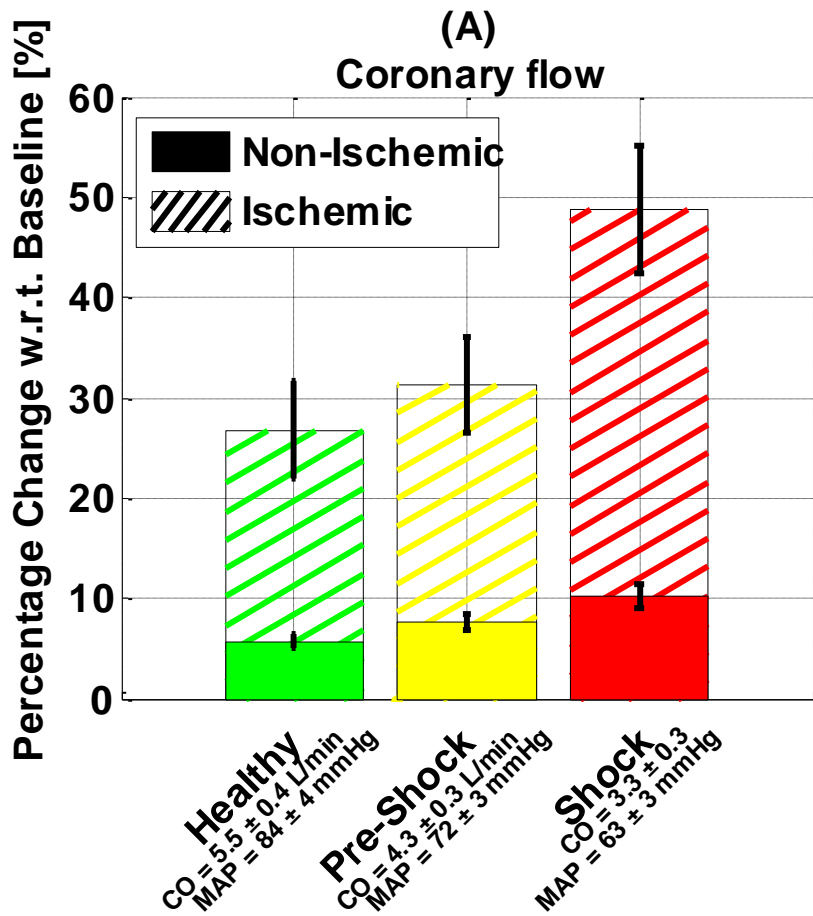
Measurement of these parameters and in addition:

- Cardiac output
- Coronary blood flow
- Myocardial oxygen consumption

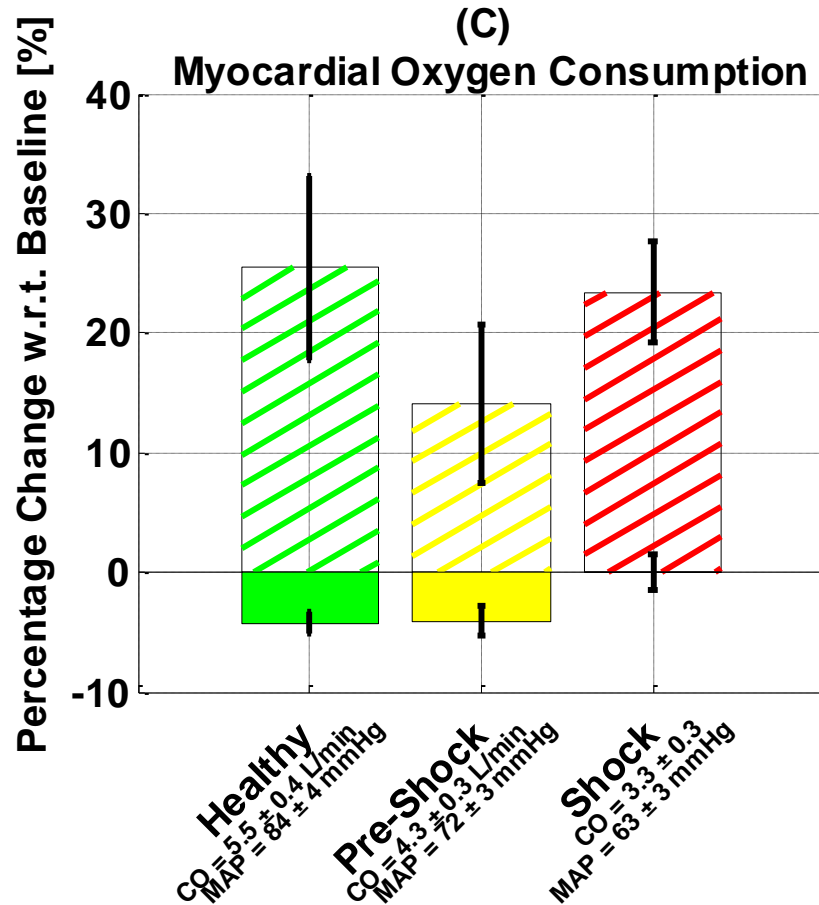
In this ex-vivo animal model :

- Autoregulation was switched off
- Pump failure / cardiogenic shock could be imitated
- *Large myocardial infarction with persistent ischemia could be induced*

Effect of IABP was tested in all these different clinical scenario's of persistent ischemia whether or not superimposed on (pre-)shock



Effects of IABP on coronary blood flow and cardiac output with and without persistent ischemia



Ongoing ischemia: IABP increases oxygen utilization
 No ischemia: IABP (mildly) decreases oxygen utilization

Conclusions:

1. Several large prospective RCT's like SHOCK II and CRISP-AMI are hampered by:
 - *Inappropriate patient selection*
 - *Inappropriate statistical analysis*

As a consequence, such trials should be considered as non-conclusive

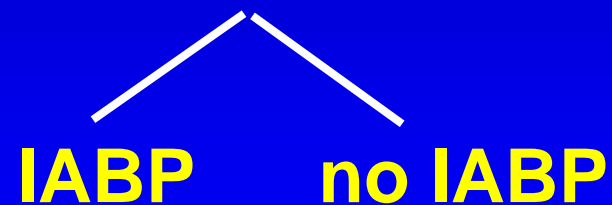
Conclusions:

2. IABP may be particularly useful in patients with viable myocardium suffering from persistent ischemia despite an unobstructed coronary artery
 - Acute STEMI, successful epicardial stenting, no-reflow
 - Cardiac surgery, good bypasses, stunning

→ SEMPER FI study

Survival in Extensive Mycocardial Infarction
with Persistent Ischemia Following IABP

- Recently started, prospective RCT in patients with large myocardial infarction (summed ST-elevation ≥ 15 mm)
- Primary PCI, ECG immediately following PCI (< 10 min)
- *If ST-resolution is $< 50\%$ → randomization 1:1*



- Endpoint: mortality at 6 months or necessity to LVAD (cross-over to IABP not permitted)

Summary

- Discussed recent clinical trials & why they apparently have not shown a clear benefit
- A model has been developed to prove the role of IABP and has shown that persistent ischemia seems to be a pre-requisite for IABP
- This is being investigated in the SEMPER FI trial