

Uterotonic and tocolytic agents

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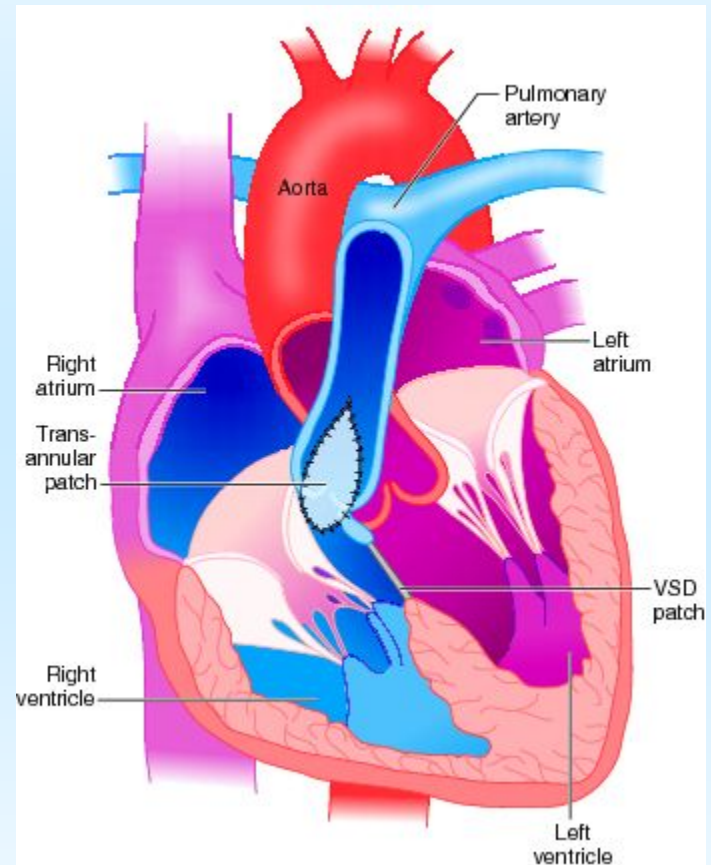
© H.S. Helbo-Hansen
Odense University Hospital
Denmark



Krusenberg 2014

Case

- 25-year-old, P0
- Repaired TOF, low risk, moderate PR
- Polyhydramniotic
- Vaginal instrumental delivery with EDA
- OT 10 IU/h ~ 17.2 $\mu\text{g/h}$
- PPH 900 ml, retained products, soft uterus
- Arrives in OR
- HR 120, BP 85/40



Uterotonic agents

Oxytocins

- Oxytocin (Syntocinon®)
- Carbetocin (Pabal®)

Ergot alkaloids

- Methylergometrine (Methergin®)

Prostaglandins

- Misoprostol (Cytotec®)
- Gemeprost (Cervagem®)
- Carboprost (Prostinfenem®)

Oxytocin - Severe cardiac complications after

Maternal death

- Pulmonary hypertension (2 cases)
- Aortic stenosis (2 cases)
- Congestive heart failure (1 case)
 - Confidential Enquiries into Maternal Deaths 1997-1999
 - JAMA 1967;200:378, Anaesthesia 1998;53:604
 - Am J Obstet Gynecol 1970;108:751

Ventricular tachycardia

- Prolonged QT-syndrome (2 cases)
 - SC Liou. Acta Anaesthesiol Sin 1998;36: 49-52

Myocardial infarction

- Healthy
 - JP Chilvers. Anaesthesia 2003;58:821-823
- Hypertrophic Obstructive Cardiomyopathy
 - JD Schmitto et al. Acta Anaesthesiol Scand 2008 ;52: 578-9

Oxytocin-receptors

- uterus



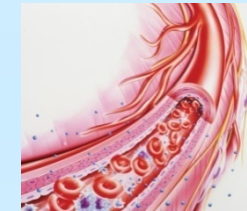
- brain



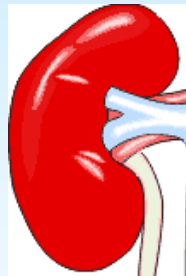
- breast



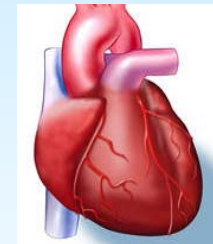
- blood vessels



- kidney



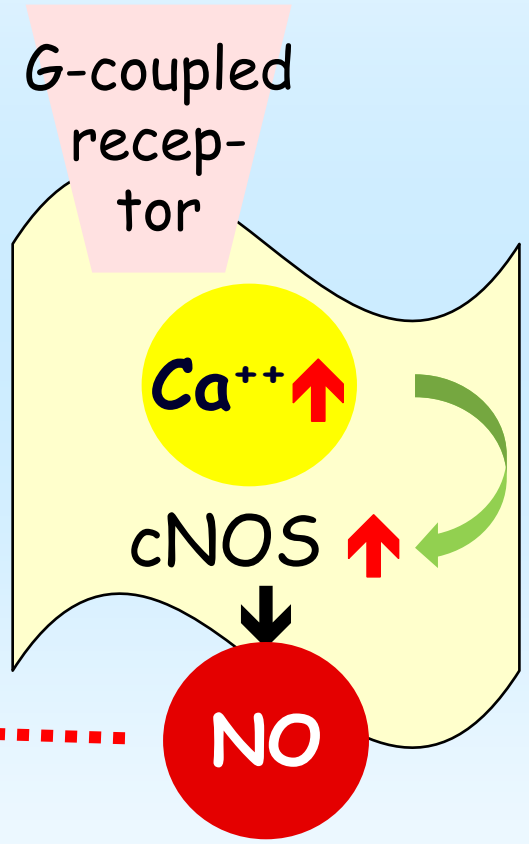
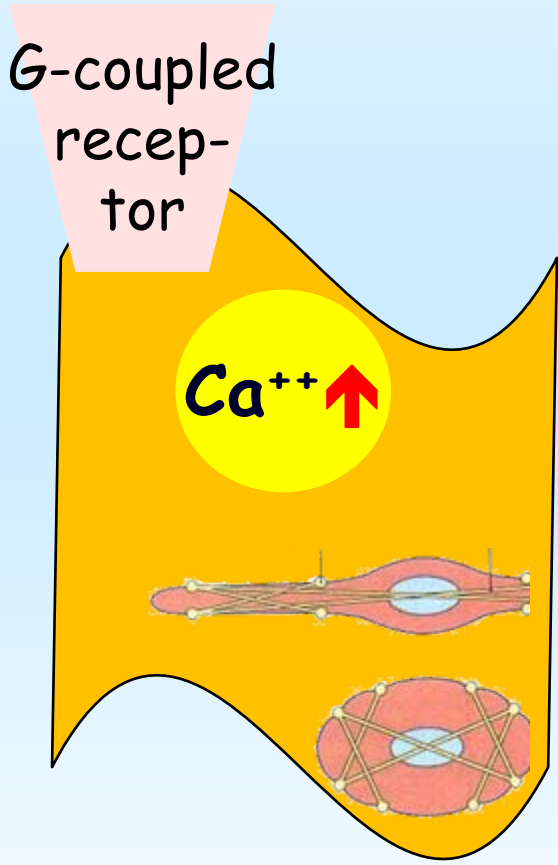
- heart



OT Receptor regulation of vascular tone

Smooth muscle cell

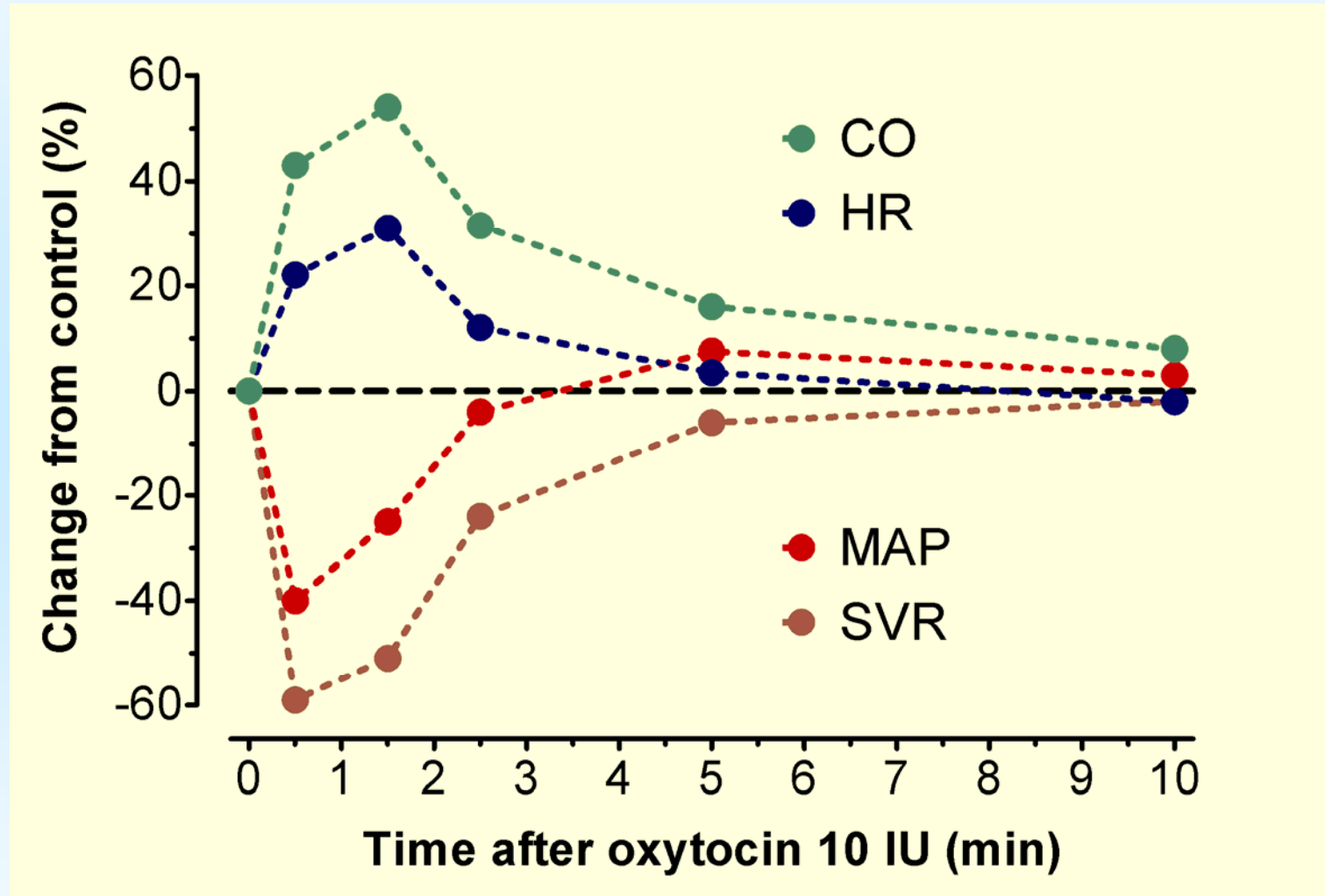
Endothelial cell



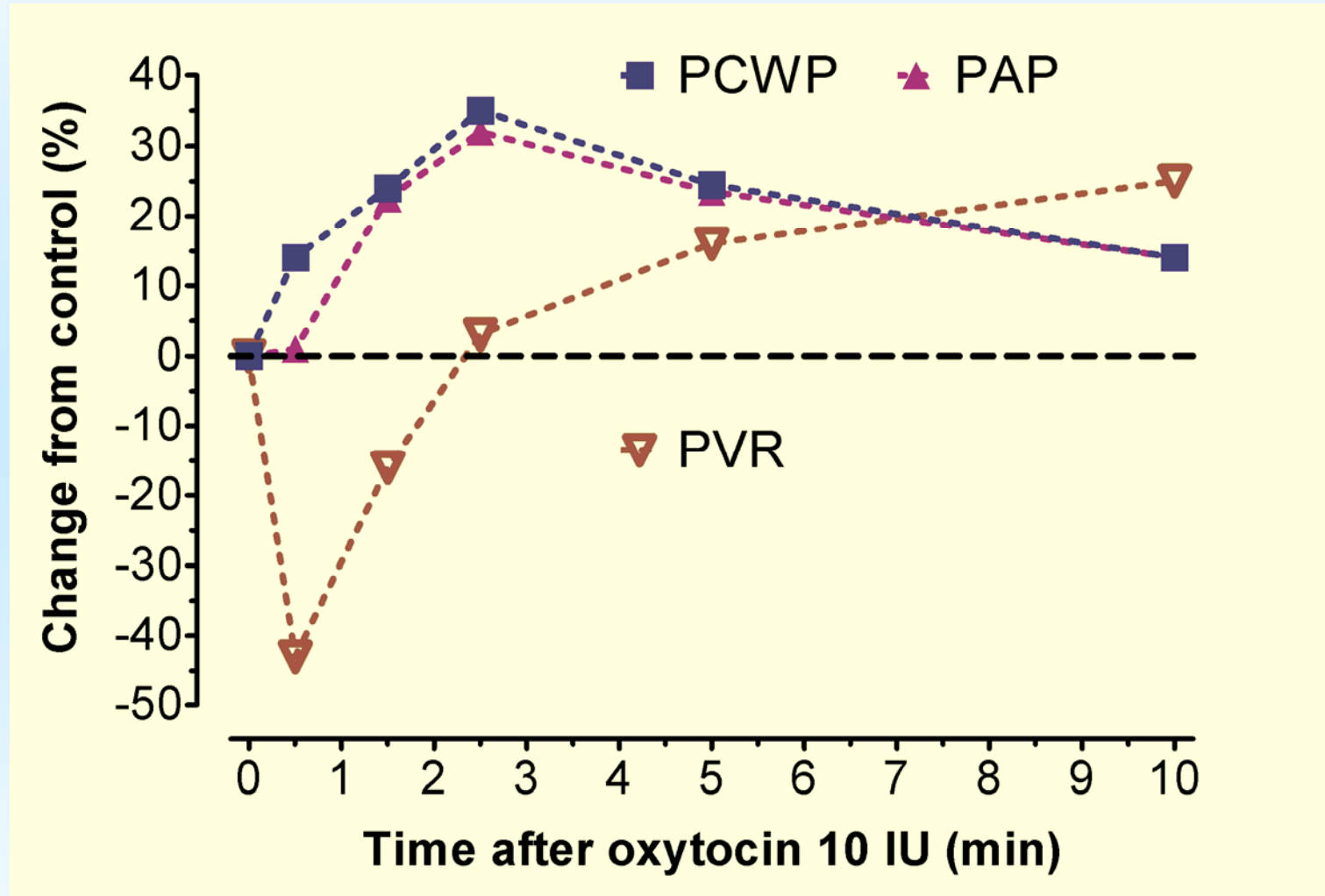
H Yazawa et al.
Br J Pharmacol 1996;117:799

M Thibonnier et al.
Endocrinology 1999;140:1301

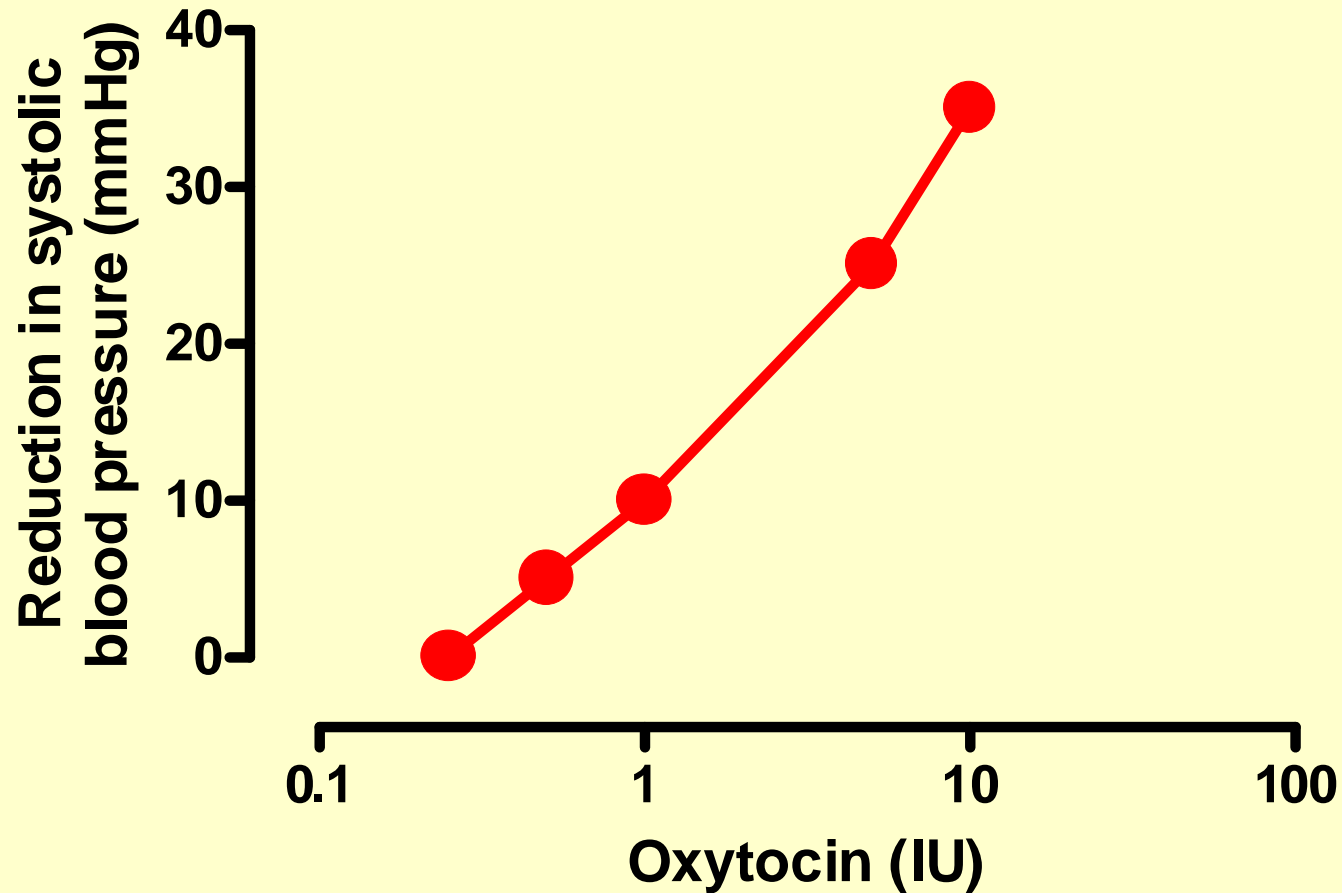
Effects on systemic circulation



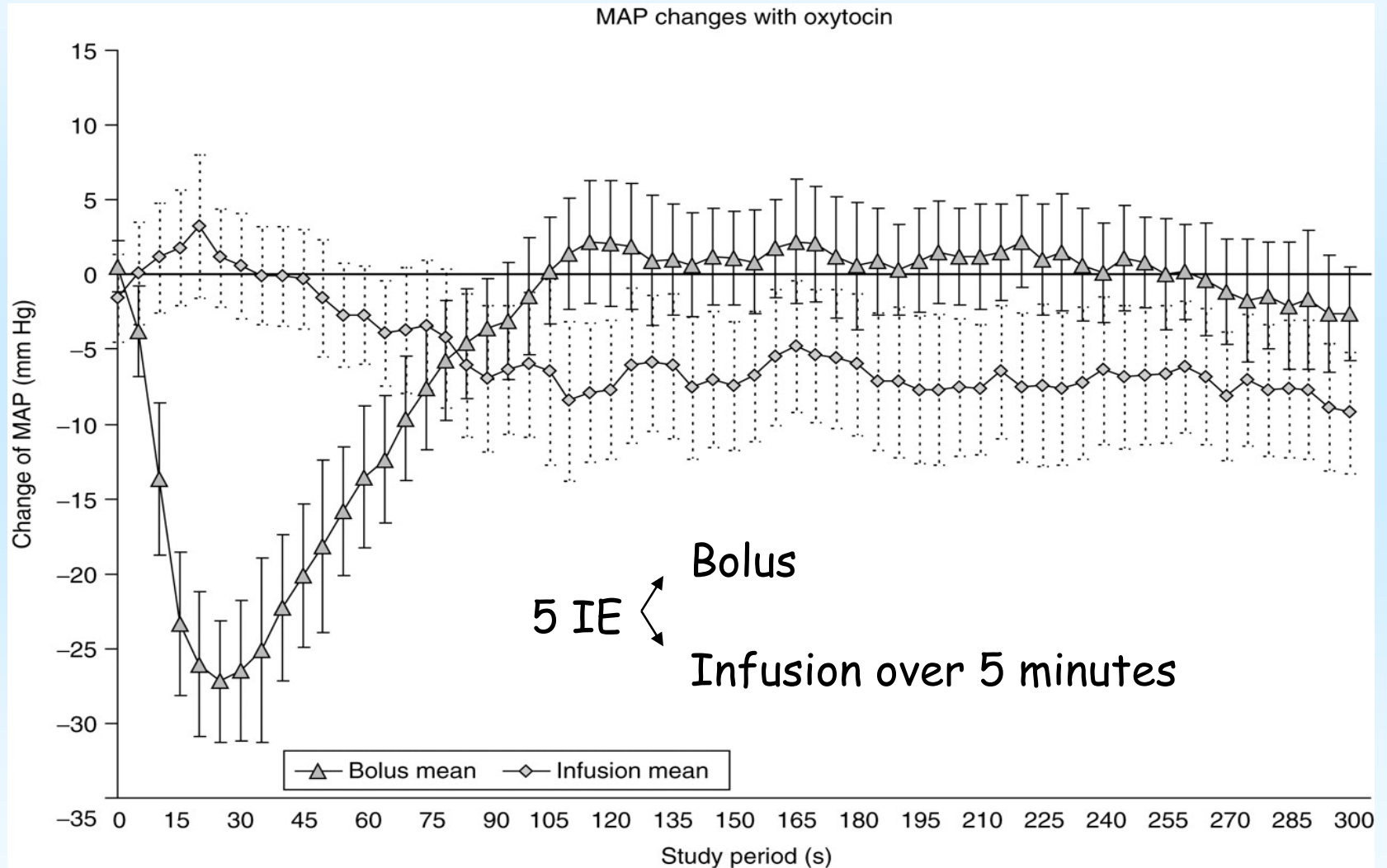
Effects on pulmonary circulation



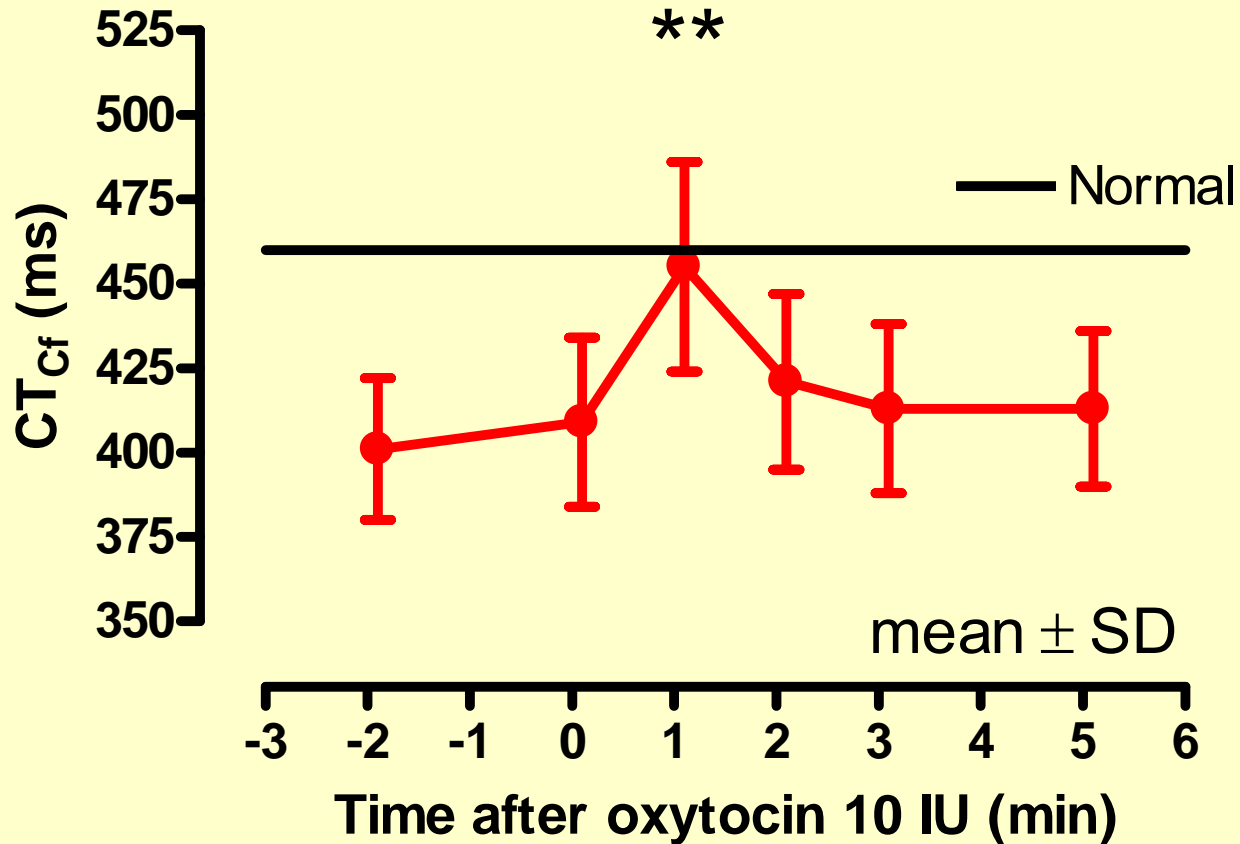
Oxytocin: dose-related decrease in blood pressure



Oxytocin bolus vs. infusion

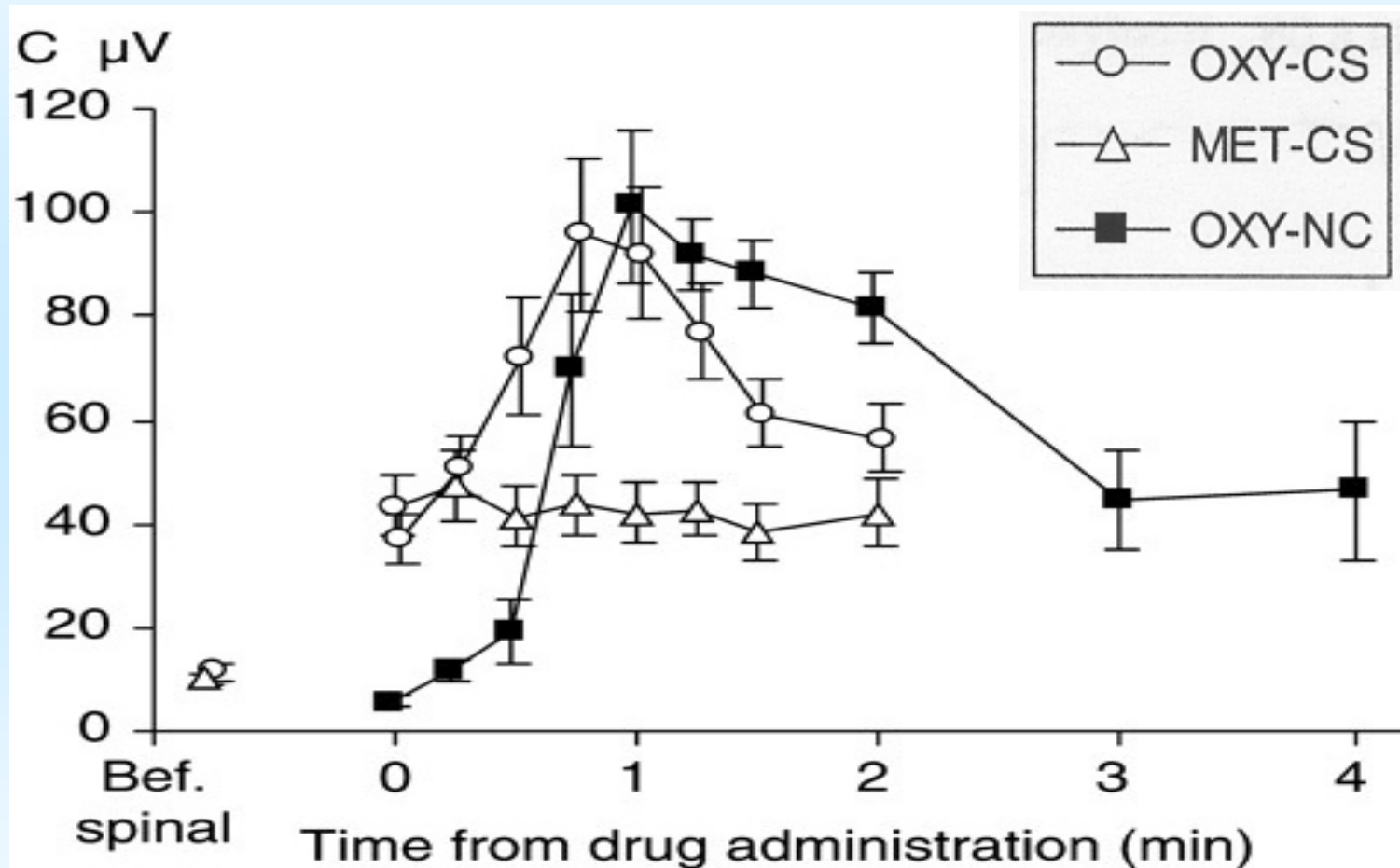


QT interval prolongation after oxytocin



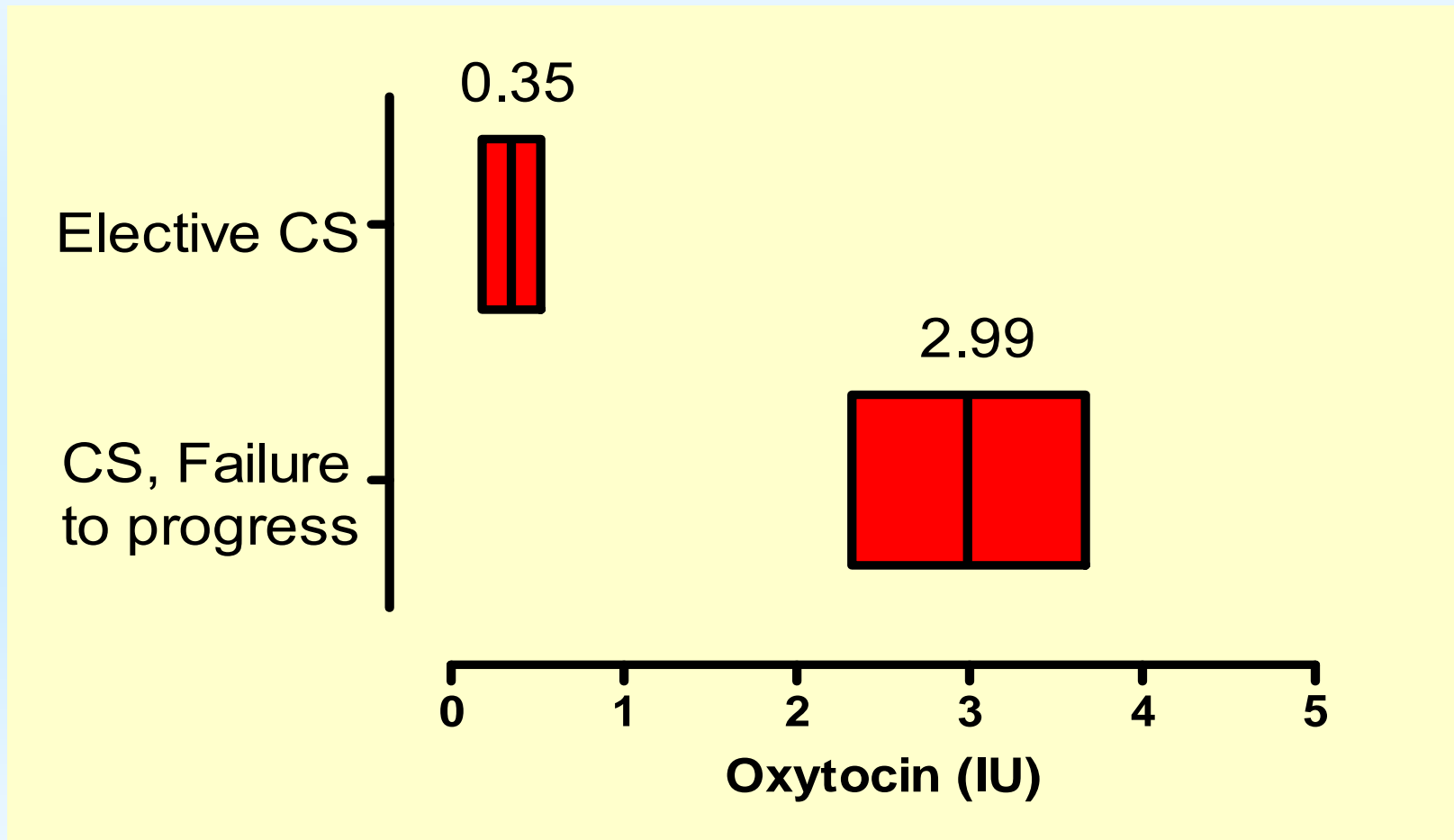
Myocardial ischaemia following 10 IE oxytocin

Spatial ST change vector magnitude (STC-VM)



Svanstrom, M. C. et al. Br. J. Anaesth. 2008 in press

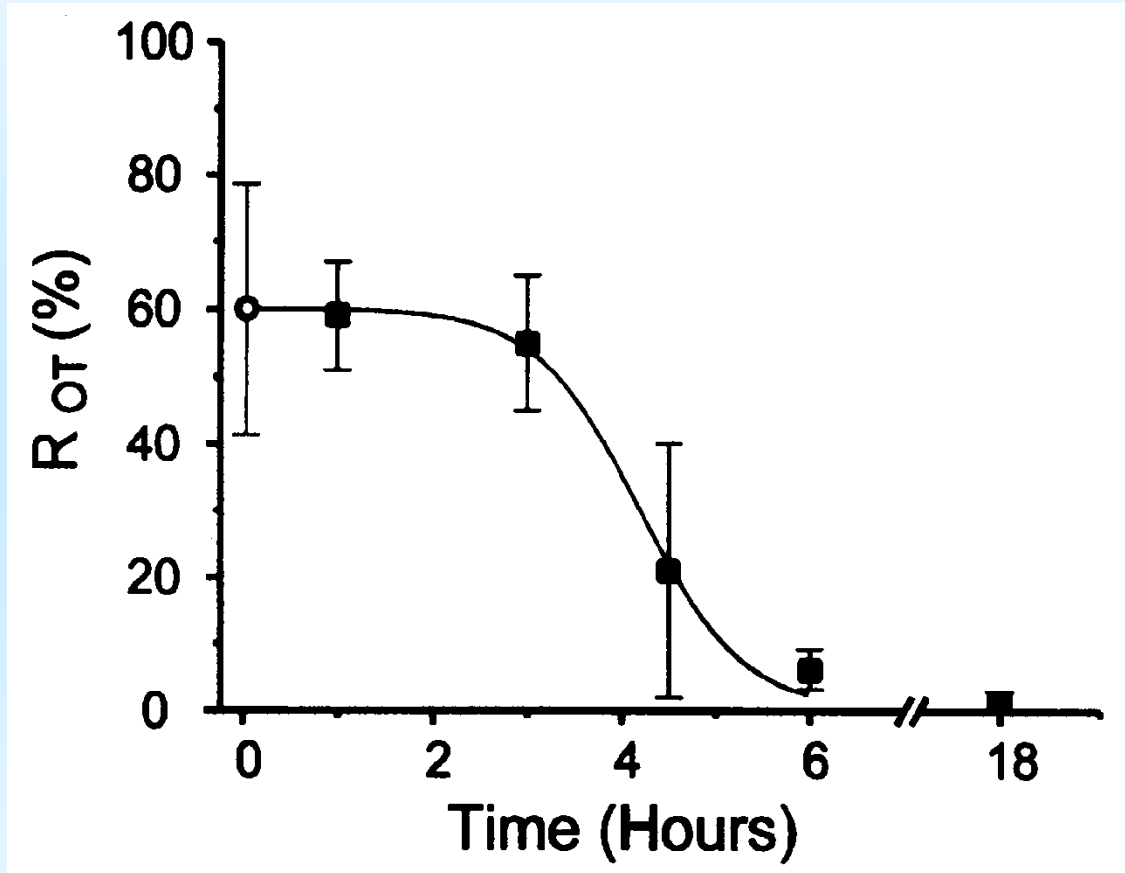
ED₉₀ (95% CI) for oxytocin at cesarean section



JCA Carvalho et al. *Obstet Gynecol* 2004; 104: 1005-10

M Balki et al. *Anesthesiology* 2005; 102 suppl. 1: SOAP A-7

Oxytocin receptor down-regulation

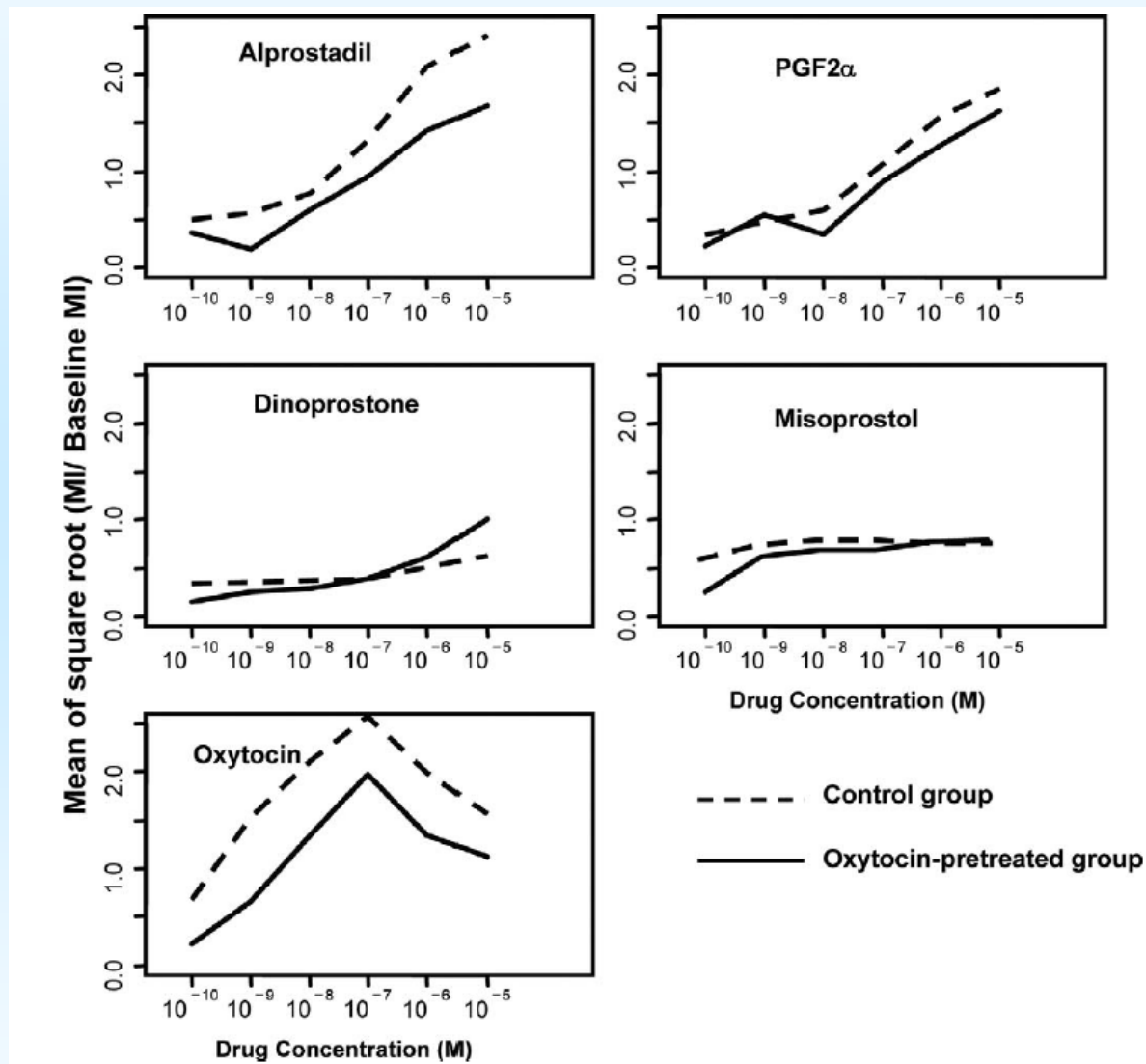


Oxytocin exposure during labor

A risk factor for PPH

Grotegut et al.
AJOG
2011;204:56e1-6

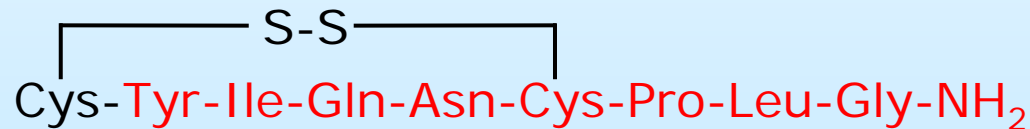
Rat Myometrium pretreated with Oxytocin



Carbetocin (Pabal[®]) An Oxytocin Analogue

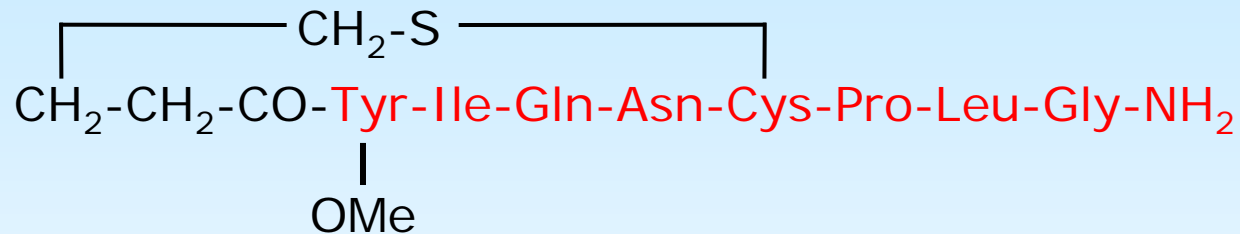
Oxytocin - Syntocinon[®]

T_{1/2} 4-5 min.



Carbetocin - Pabal[®] (oxytocin analog)

T_{1/2} 30-50 min.

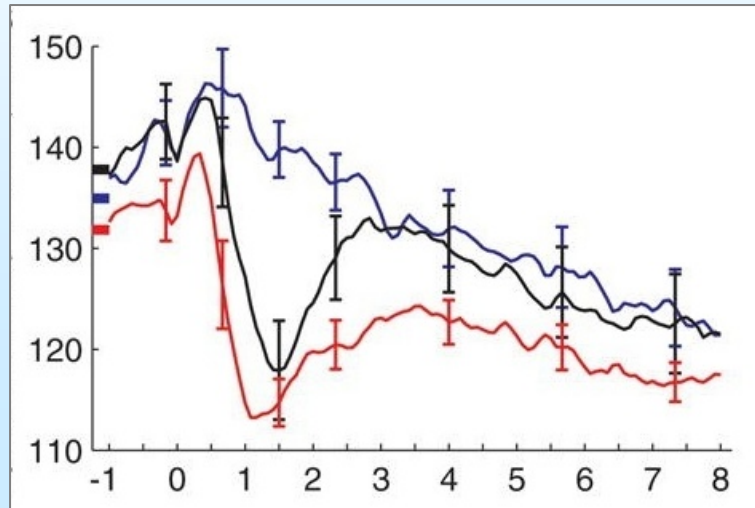


G Rydén et al. Acta Endocrinol. 1969; 61:425

G Sweeney et al. Curr Ther Research 1990; 47: 528

Carbetocin vs. Oxytocin Hemodynamics

Systolic BP
(mmHg)

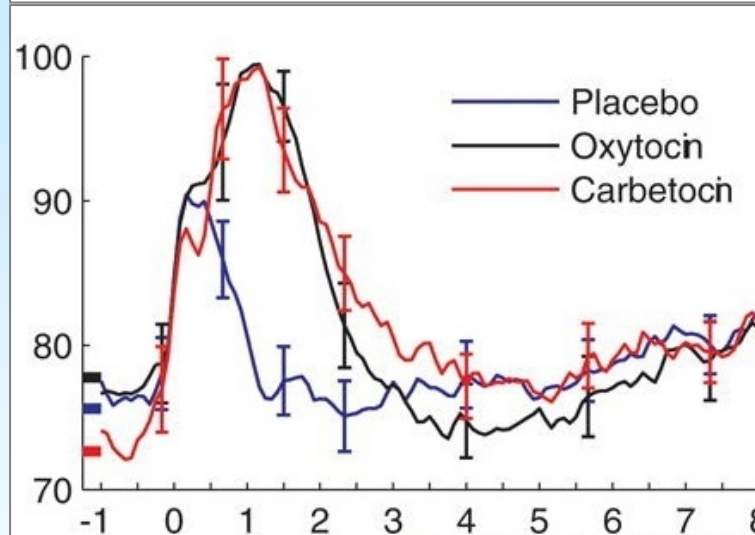


Minutes after
start of injection

Carbetocin 100 μ g
Oxytocin 5 IU

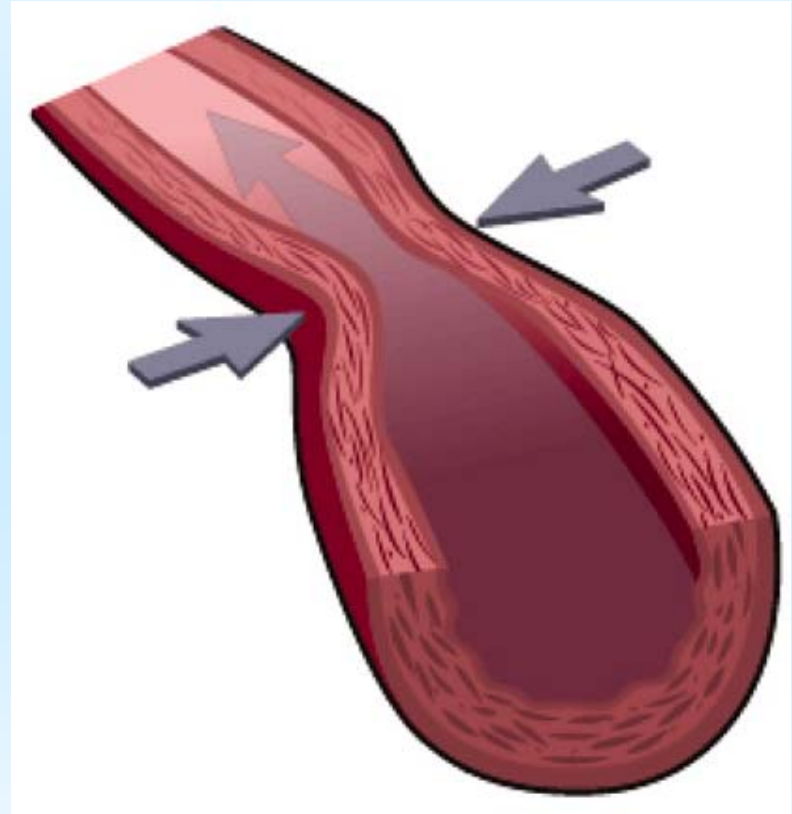
over 1 minute

HR
(per min.)

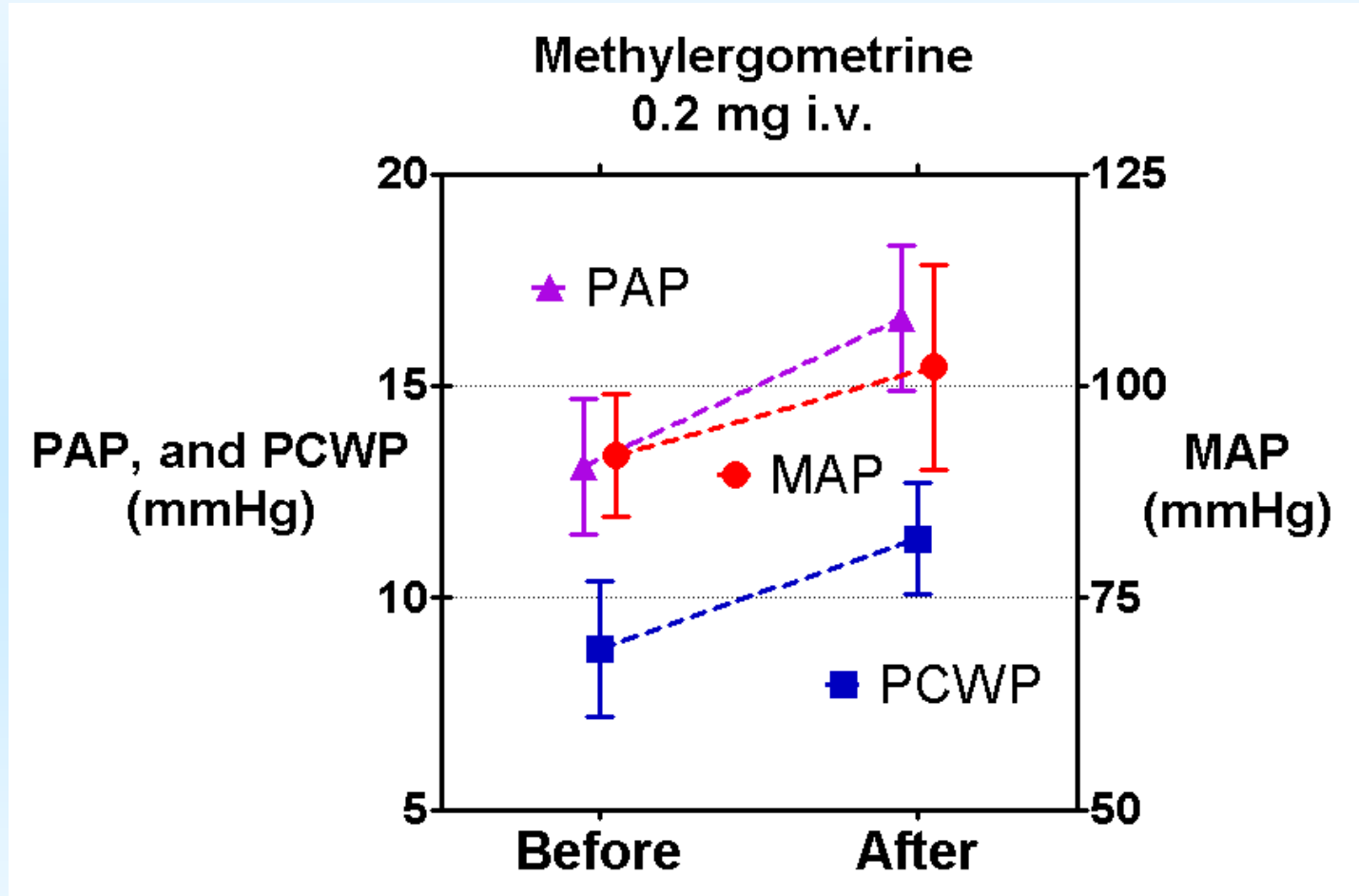


Methylergometrine (Methergine®)

- Synthetic analogue of ergonovine
- Direct constrictive action on smooth muscle
- No specific ergometrine receptor
- Interaction with:
 - 5-HT₂ (seretonegic)
 - α_1 -adrenergic,
 - dopaminergic receptors
- Dose response studies?



Effect on pulmonary and systemic blood pressures



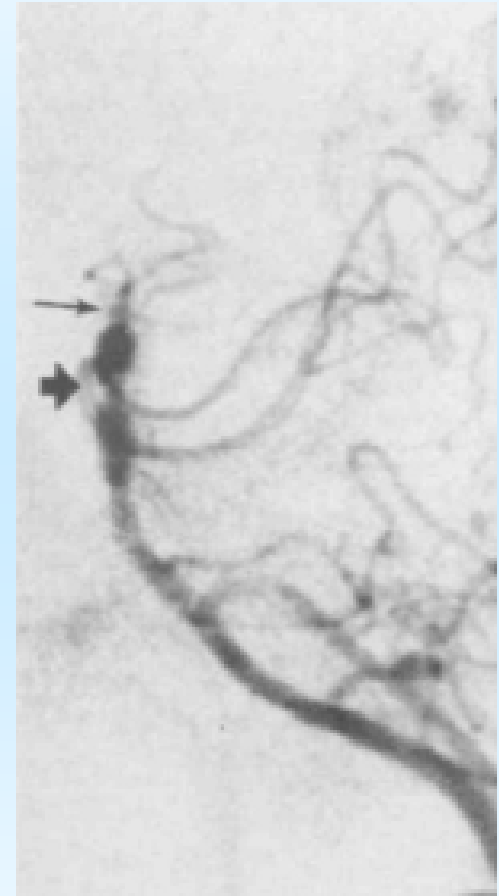
Cases #9-10

Occasional severe hypertension

- 37-year-old: pre-eclampsia → 130/100 →
ergometrine 0.5 mg → 180/120
→ eclamptic fit
- 17-year-old, normotensive → 0.2 mg
ergometrine → 190/120
→ intracerebral haemorrhage

Ergometrine

- 28-year-old, CS.
- ergometrine 0.20 mg i.v.
- severe headache
- bilateral amaurosis,
- mild confusion, normal blood pressure
- right hemisensory deficit to all modalities
- arteriography: basilar artery spasm



RCVS - Reversible Cerebral Vasoconstriction Syndrome

Postpartum cerebral angiopathy

- Increased risk post partum
- Temporal relationship with methylergometrine
- Elements
 - Segmental cerebral artery vasoconstriction
 - No evidence of aneurysmal SAH
 - Normal/near normal CSF analysis
 - Severe acute headache “thunderclap”
 - With or without neurological signs or symptoms
 - Reversibility within 12 wk

Case #: ergometrine

- 34-year-old, uterus atonic despite oxytocin
- ergometrine 0.25 mg iv
- ventricular fibrillation
- resuscitated
- intraaortic ballon pump
- spasm of LAD and circumflex
- reversed by intra-coronary nitroglycerin



Several case reports on ergometrine provoked myocardial infarction

GJ Taylor et al.	Obstet Gynecol	1985; 66: 821
JK Liao et al.	Am J Cardiol	1991; 68: 823
Y Fujiwara et al.	Jpn Heart J	1993; 34: 803
WJ Ko et al.	Int J Cardiol	1998; 63: 81
N Yaegashi et al	Int J Gynecol Obstet	1999; 64: 67
N Sutaria et al.	Heart	2000; 83: 97
HA Mousa et al.	Br J Obstet Gynecol	2000; 107: 939
BCH Tsui et al.	Anesthesiology	2001; 94: 363
Y Hayashi	Intern Med	2003;42:983
YH Lin	Acta Obstet Gynecol Scand	2005;84:1022
A De Labriolle	Cardiovasc Toxicol	
2009;9:46		

Methylergonovine and risk of Acute Coronary Syndrome and Myocardial Infarction

	Ergonovine n=139,617 (n/100,000)	Not exposed n=2,094,013 (n/100,000)	Risk difference /100,000 (95% CI)
ACS	4.3	2.4	1.81 (-1,69 to 5,32)
AMI	2.9	2.1	0,76 (-2,11 to 3,64)

- Retrospective cohort study
 - USA 2007-2011
 - 2,233,630 deliveries

Prostaglandins

PGE₁

PGE₂

PGF_{2α}

Natural

Alprostadiil

Prostivas ®

Dinoprostone

Minprostin ®

Propess ®

Prostin E2 ®

Dinoprost

Prostin F2alpha ®

Analougues

Misoprostol

Cytotec ®

Carboprost

Prostinfenem ®

Gemeprost

Cervagem ®

Sulprostone

Nalador ®

Prostaglandins

Natural

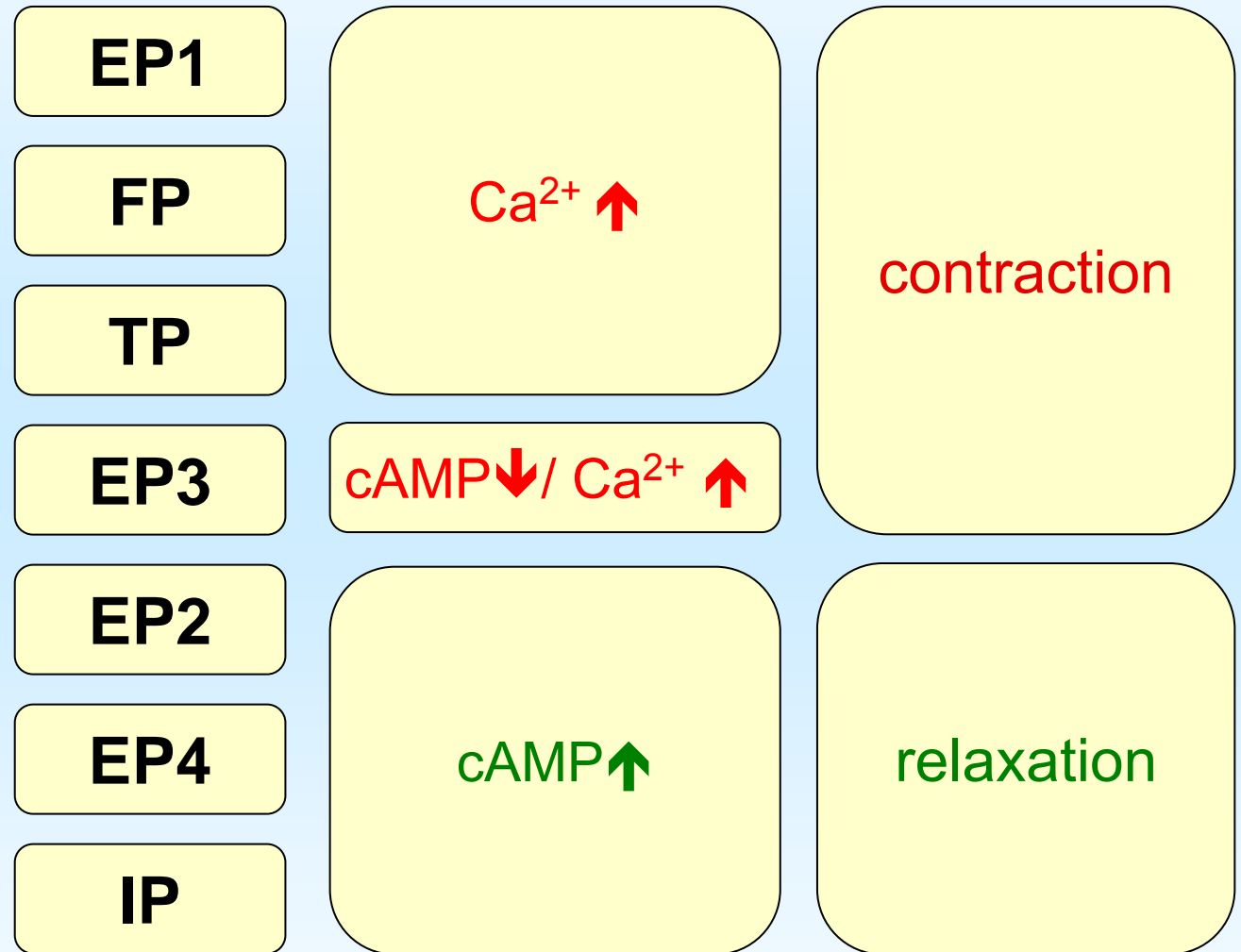
rapid
metabolism

half-life
seconds to
minutes

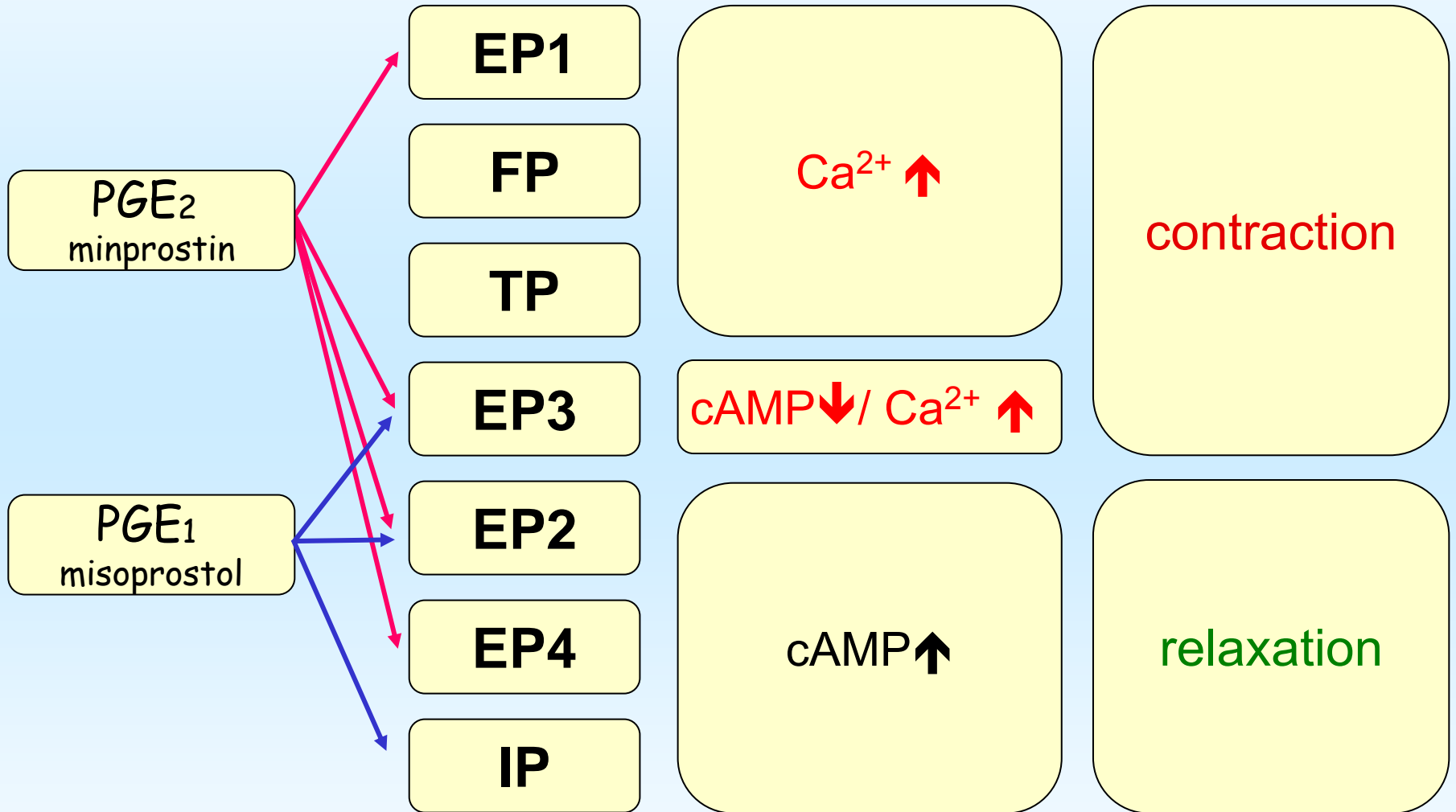
Analogues

more specific
first step in
metabolism blocked
active metabolites
longer half-life
may differ with
regard to cardio-
vascular effects

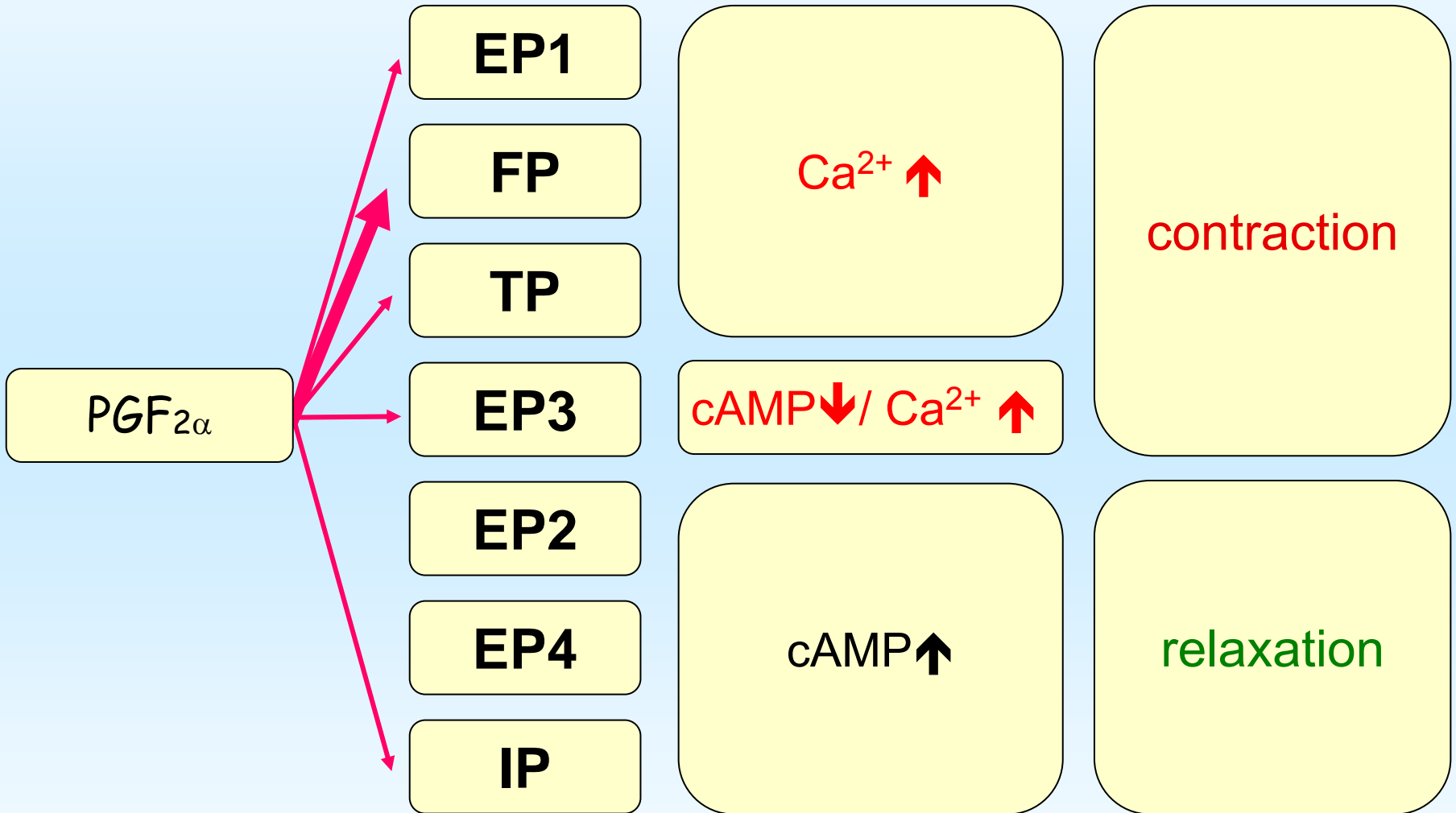
Prostanoid receptors



Prostanoid receptors



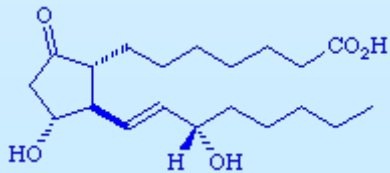
Prostanoid receptors



PGE₁

Natural PGE₁

Alprostadiil



ductus dependent
heart defects

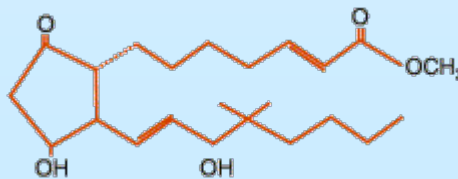
cardiomyopathy

end stage heart
failure

erectile dysfunction

PGE₁ analogues

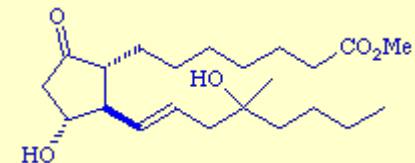
Gemeprost Cervagem®



coronary artery
spasm &
circulatory
collapse

**Largely
replaced by
misoprostol**

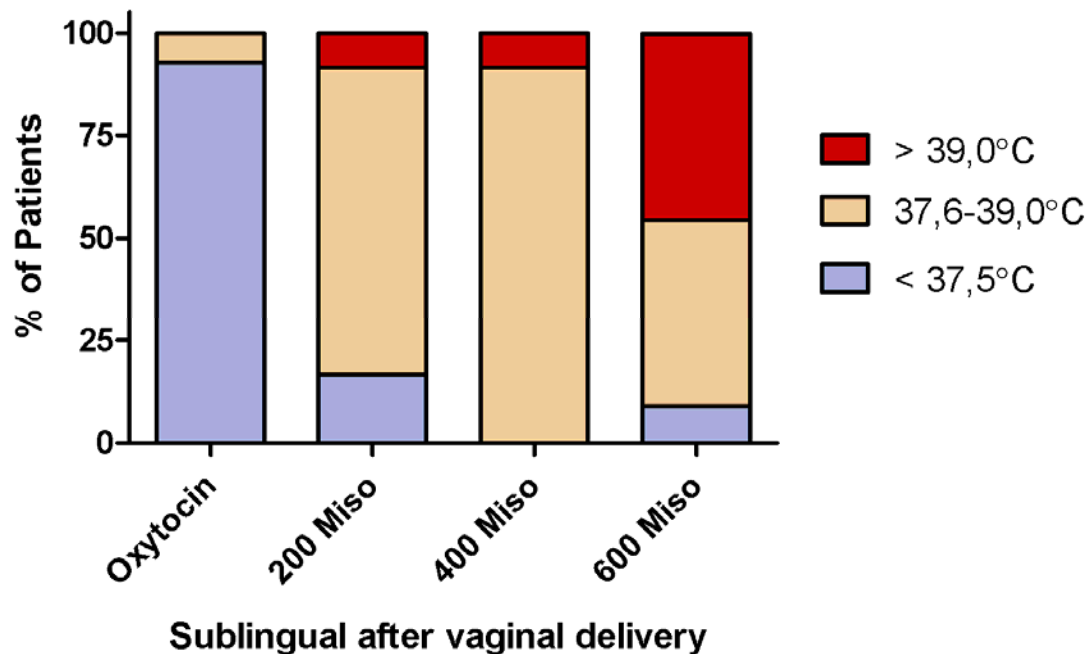
Misoprostol Cytotec®



negligible circulatory
effects

Misoprostol - Fever

- Case report: Severe hyperthermia (41.9°C)
 - Chong. Obstet Gynecol 1997;90:703,



Fever:

Usually preceded by shivering

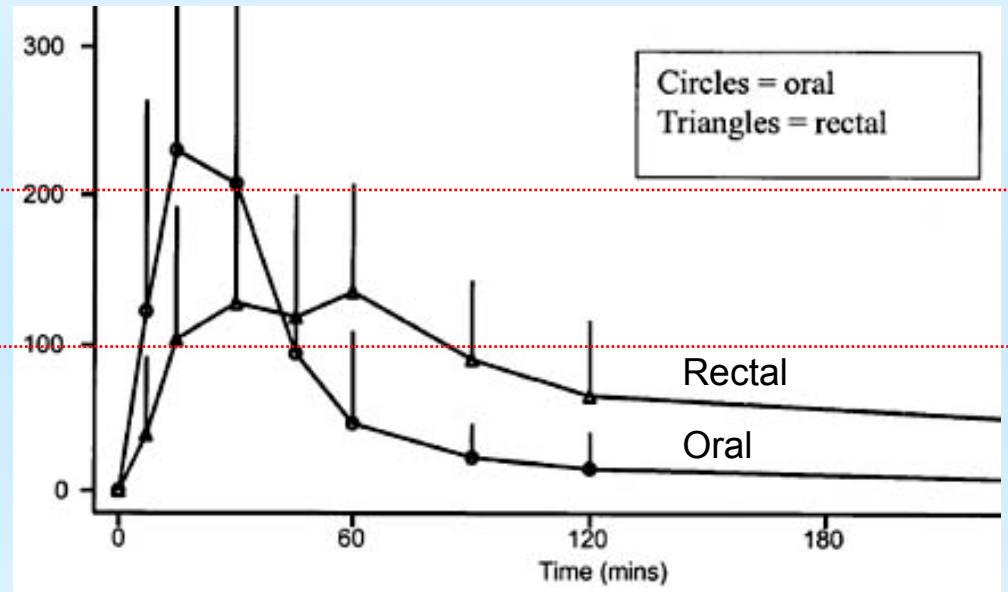
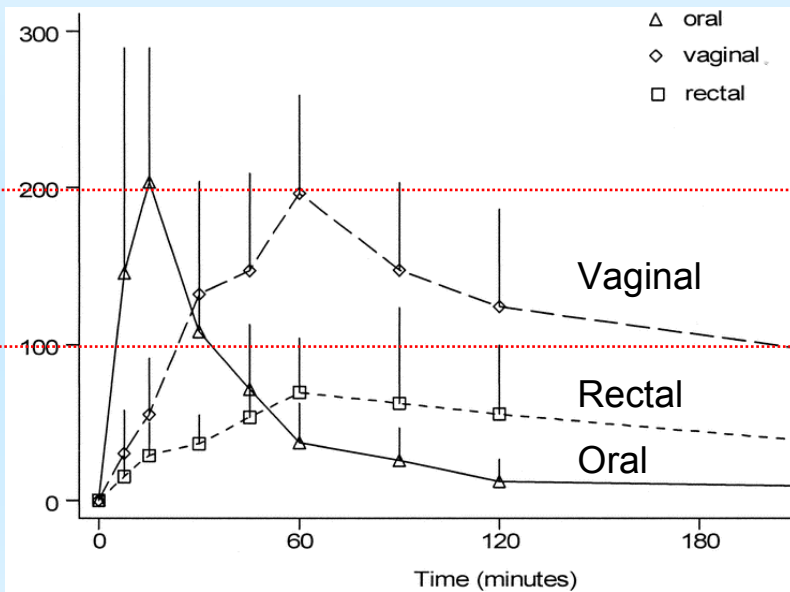
Onset less than 20 min

Peaks at 1-2 hours

Declines over 3 hours

Misoprostol Pharmacokinetics

Plasma levels (pg/ml)



Termination of pregnancy
GA 7 - 14 weeks

Vaginal delivery
GA 37 - 41 weeks

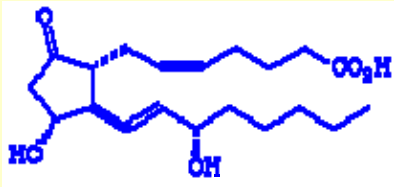
Misoprostol = Cytotec® (PGE₁ analogue)

- Misoprostol is not more effective and has more side effects than Oxytocin for PPH prophylaxis after vaginal delivery and CS.
 - » Chaudhuri Int J Obstet Gynecol 2012;116:138
 - » Conde-Agudelo et al. AJOG 2013;209:40e1-17
 - » Hua BJOG 2013;120:531
- Oxytocin infusion is more effective than Misoprostol for the treatment of primary PPH.
 - » Mousa et al. Treatment for primary PPH. Cochrane Review 2014
 - » Winikoff et al. Lancet 2010; 375: 210
- Addition of Misoprostol to Oxytocin for treatment of PPH after vaginal delivery confers no benefit.
 - » Widmer et al. Lancet 2010;375:1808
- Addition of Misoprostol to Oxytocin during caesarean section is more effective than oxytocin alone.
 - » Conde-Agudelo et al. AJOG 2013;209:40e1-17

PGE₂

Natural PGE₂

Dinoprostone (Minprostine®)



Safe doses/administration:

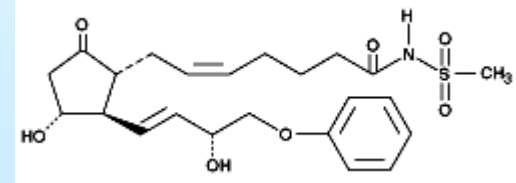
Intracervical 0.5 mg

Vaginal 2-3 mg

Reports on profound hypotension, VT and myocardial infarction with intramyometrial inj. or with larger doses

PGE₂ analogue

Sulprostone (Nalador®)



23 case reports, 4 deaths
severe hypotension
pulmonary edema
myocardial infarction
cardiac arrest

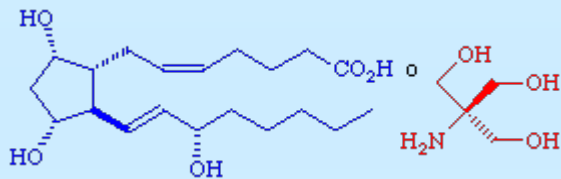
Withdrawn 1992

M Winkler. Drug Safety
1999;20:323

PGF_{2α}

Natural PGF_{2α}

Dinoprost



half-life 30 sec.

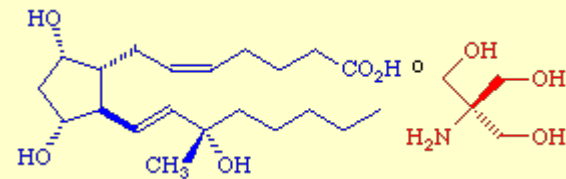
Withdrawn 2000

PGF_{2α} analogue

15-methyl PGF_{2α}

Carboprost

Prostinfenem®

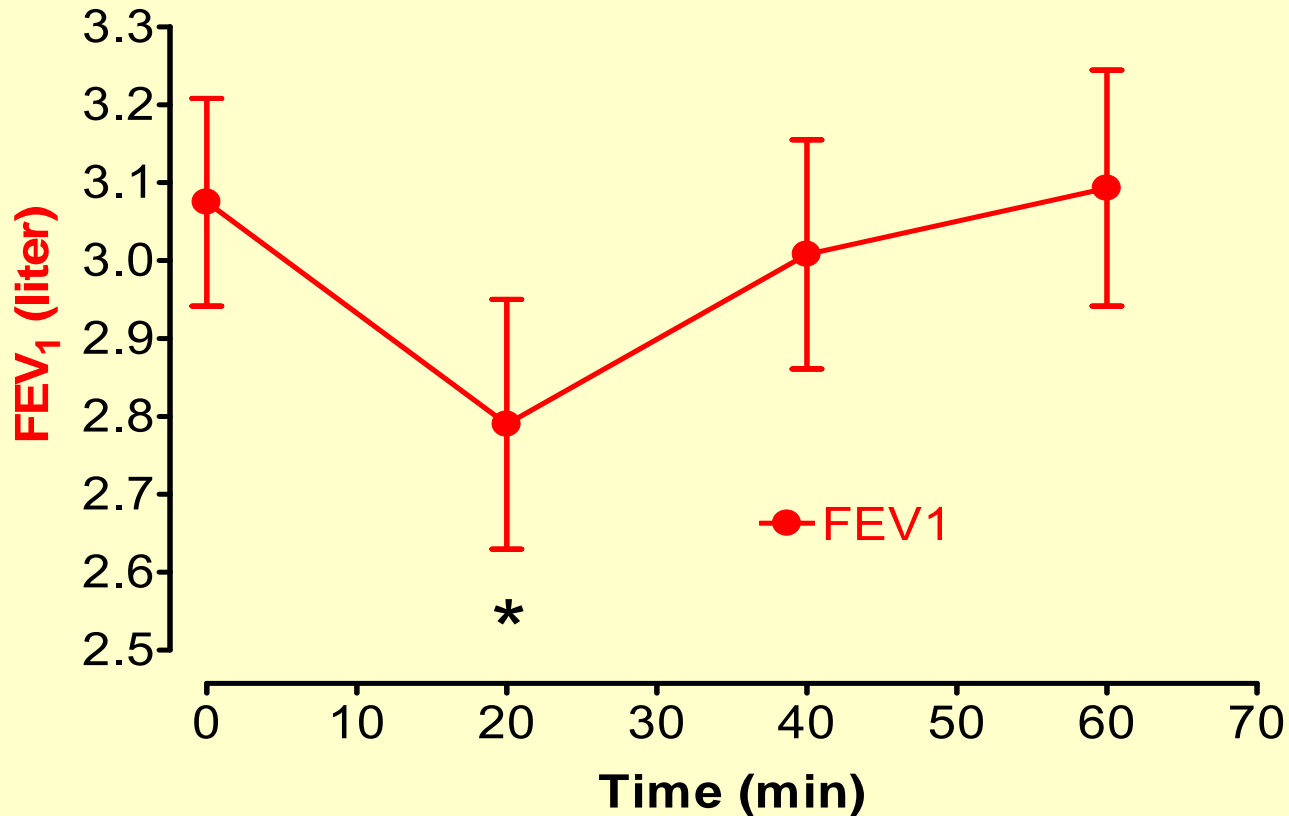


half-life 30 min.

more potent

similar pharmaco-dynamic
properties

Bronchoconstriction – 250 µg Carboprost IM



Asthmatic patients may be 8,000 times more sensitive to PGF₂ α

Heslet Andersen. Thorax 1976;31:685 & Mathé BMJ 1973;1:193

Carboprost - Bronchospasm

- 39-year-old, mild asthma, no medication
- Placental abruption → CS under GA,
- Uterine atony
- Oxytocin and ergometrine
- 250 µg x 2 with a 15 min. interval
 - Severe bronchospasm,
 - Salbutamol, aminophylline
 - ketamine, adrenaline, hydrocortisone
 - Insp. pressure 45-50 cm H₂O
 - Tidal volume 220 ml
 - PaCO₂ 26 kPa
 - 15 days in ITU



Carboprost mismatching of ventilation and perfusion

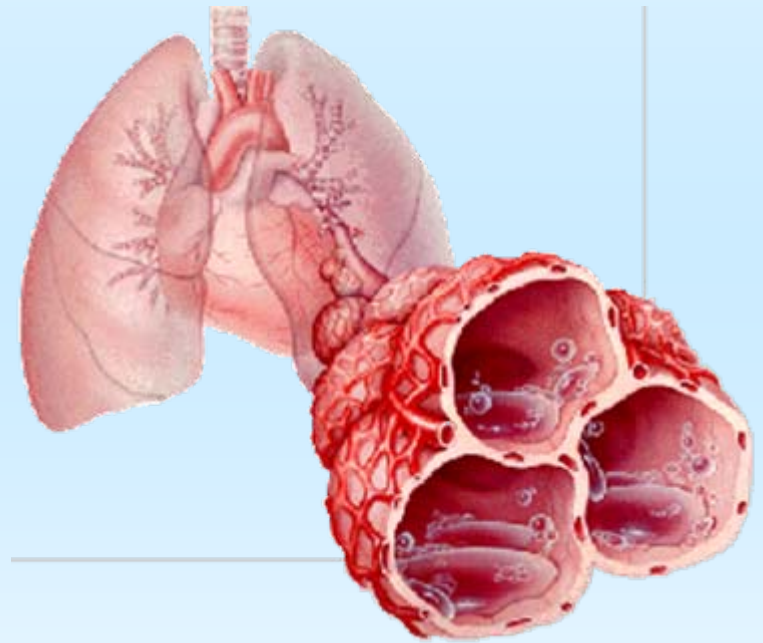
Clinically significant hypoxia
in 5 of 14 patients

- dose: 1-2 x 250 μg IM
- duration: 10-20 min
- shunt: 11-29%

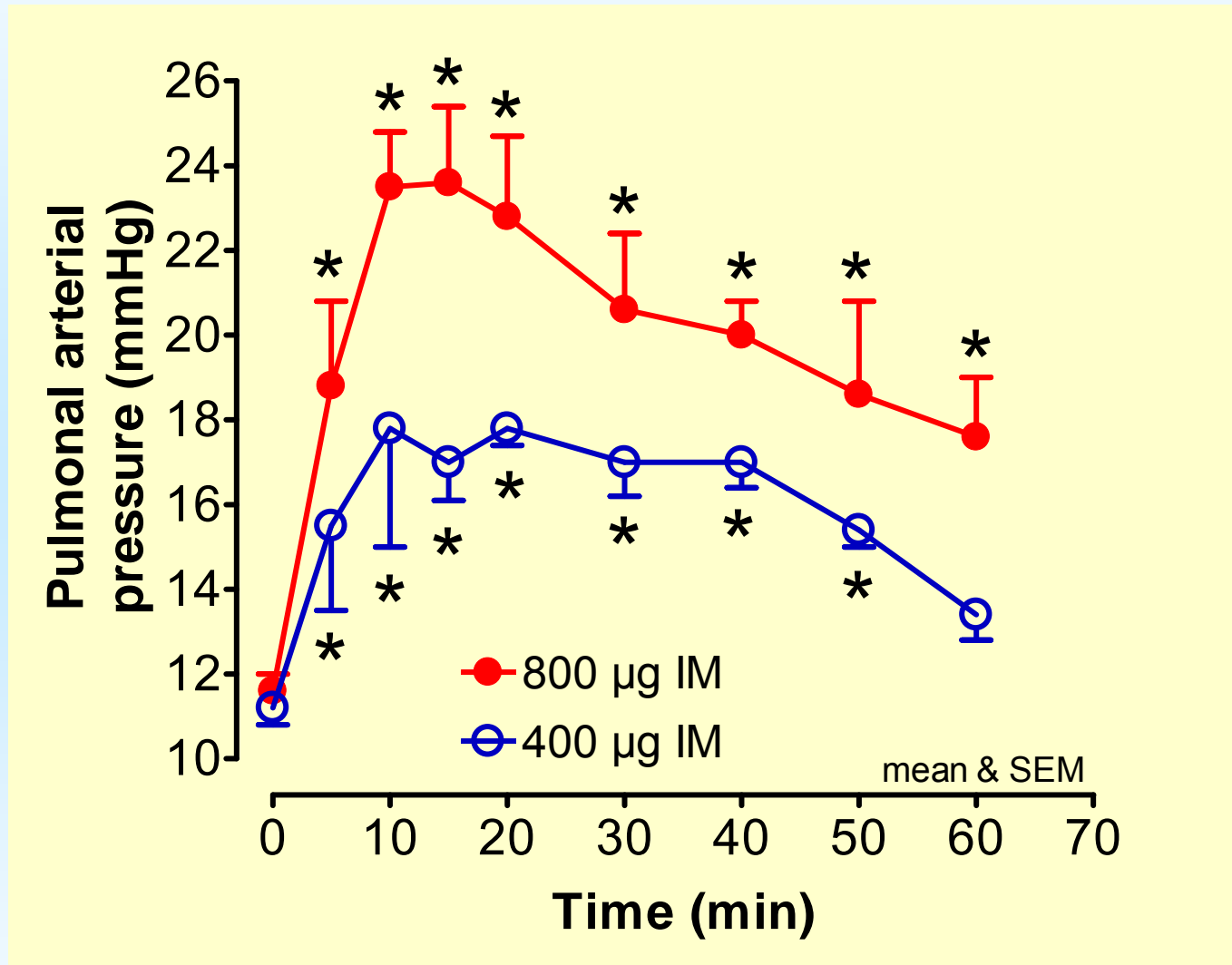


Carboprost – Pulmonary edema

- 18-year-old, CS under epidural anaesthesia
- uterine atony despite oxytocin and ergometrine
- 250 µg carboprost intramyometrially
- 5 min later:
 - SpO₂ 89%, dyspnea
 - HR 130-140
 - X-ray: pulmonary edema

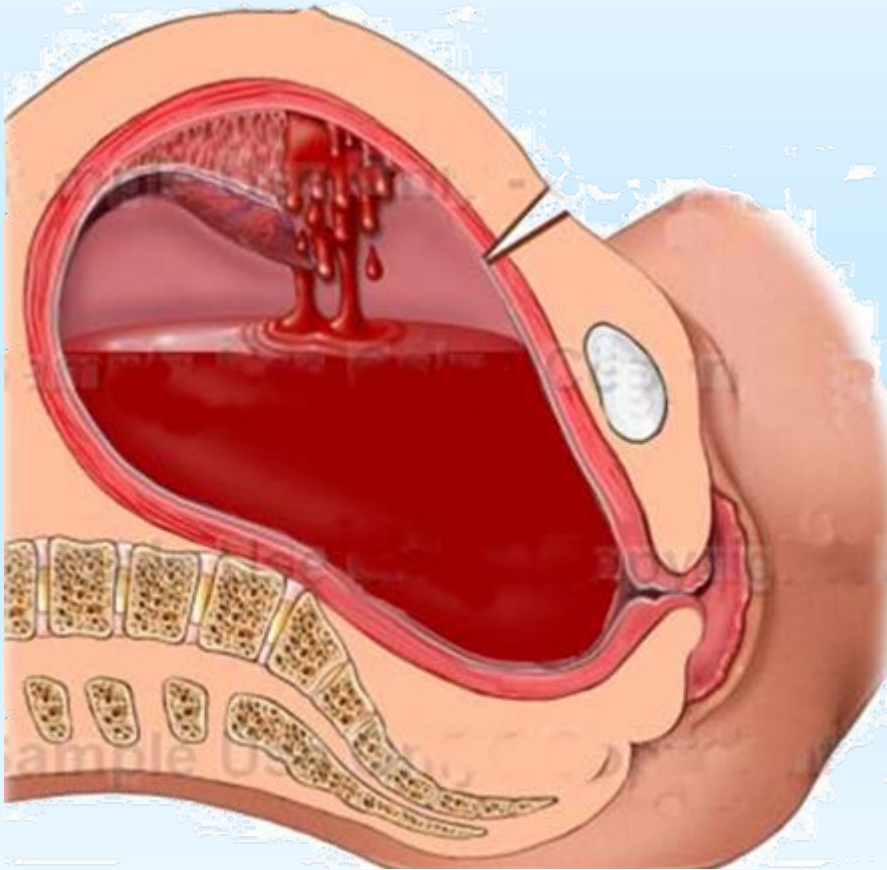


Carboprost - Pulmonal hemodynamics



PPH

Post Partum
Hemorrhage



PPH prophylaxis after Cesarean delivery

- Oxytocin bolus dose
 - Elective CS, spinal, no risk factors: 0 – 0.5 IU
 - CS in labor or with risk factors: 3 IU
 - Cardiac disease, pulm. hypertension: 0.1 IU
- Maintenance
 - Oxytocin infusion: 7,5 IU/h for 4 hours
 - (Cardiac disease 2,5 IU/h)
 - Alternatives
 - Carbetocin 100 µg (IV)
 - Misoprostol 400 µg (sublingual or rectal)

L.C. Stephens. *Anaesth Intens Care* 2012; 40: 247

M. Balki. *Anesthesia Clinics* 2014; 52: 48-66

A. Conde-Agudelo et al. *AJOG* 2013; 209: 40.e1-17

D. Leduc et al. *J Obstet Gynaecol Can* 2009; 31: 980

Treatment of PPH

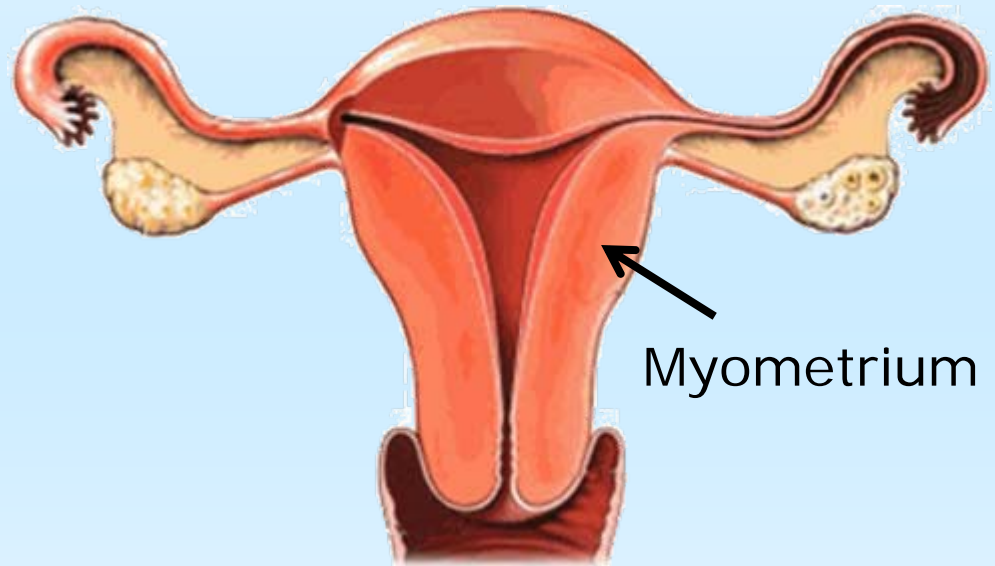
- First choice:
 - Oxytocin bolus 5 IE/5 min + infusion 7,5-15 IE/h
 - 40 IE/500 ml NaCl at 125 ml/h ~ 10IU/h
- Supplemented by:
 - Methylergometrine 0.2–0.5 mg IM/IV
 - Carboprost 250 µg IM
 - Buttino L et al. Am J Perinatal 1986;3:241
 - Misoprostol 600 µg oral or sublingual, 1000 µg rectally
 - J Blum et al. Int J Gynecol Obstet 2007;99:S202-S205

Contraindications

Oxytocin	Hypovolemic shock. Coronary artery disease, fixed CO, aortic stenosis Long QT syndrome Elevated pulmonary artery pressures
Carbetocin	Same as oxytocin + Pre-eclampsia
Methylergotamin	Pre-eclampsia. Hypertension. Coronary artery disease Peripheral vascular disease Elevated pulmonary artery pressures
Misoprostol	?
Carboprost	Asthma. Intracardiac shunting, single ventricle (Fontan circulation) Elevated pulmonary artery pressures.

Tocolytics

Drugs that
inhibit
myometrial
contractions



Intra-partum Tocolysis

Indications

- Non-reassuring FHR
- Buying time for neuraxial block
- Prolapsed cord
- Malpresentations
- During CS

Agents

- | | |
|------------------|----------------|
| • Terbutaline | cAMP ↑ |
| • Nitroglycerine | NO ↑ |
| • Atosiban | OTr antagonist |

Acute tocolysis during term labour

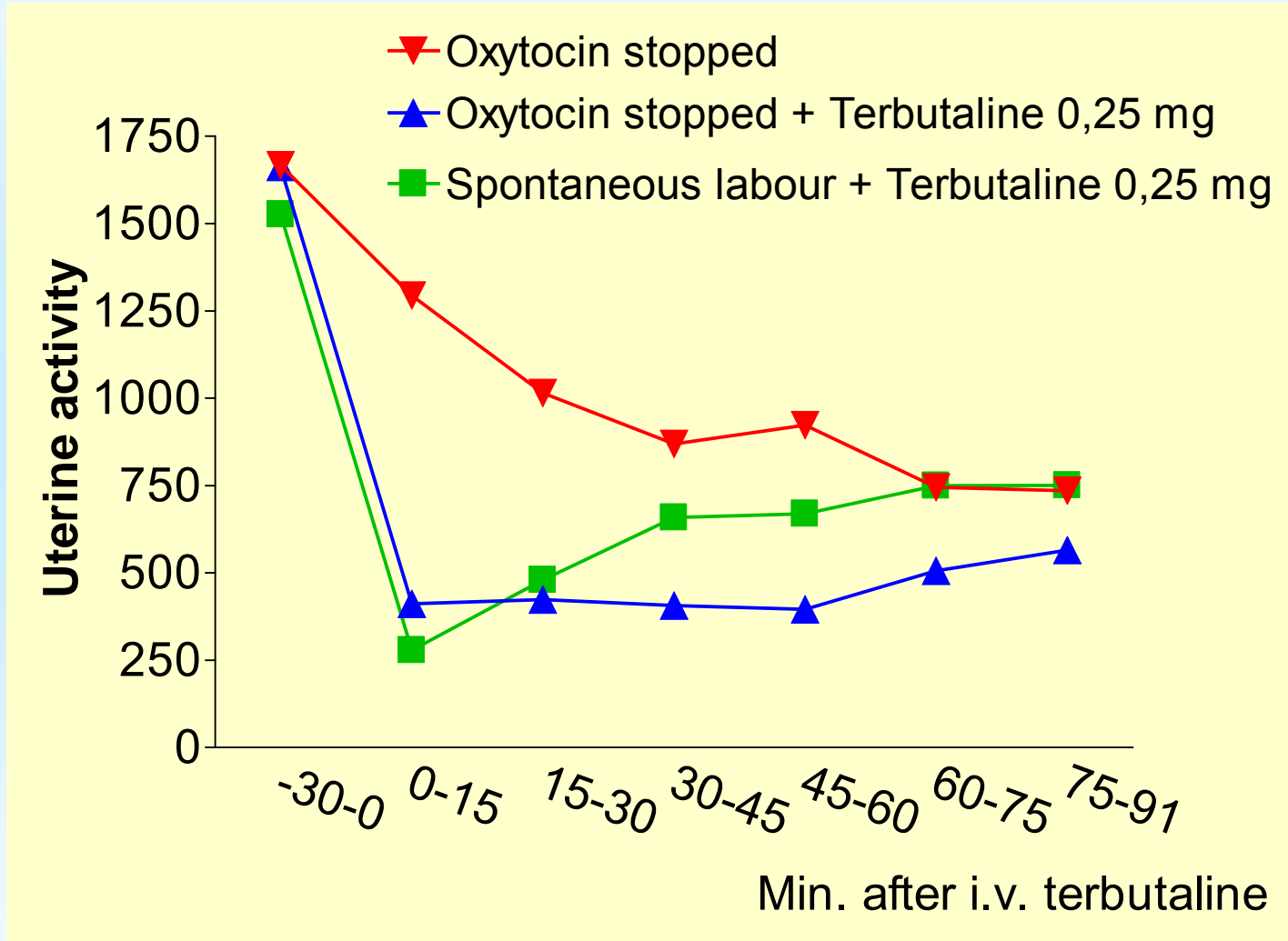
	Terbutaline 0,25 mg i.v.	Atosiban 6,75 mg i.v.	Nitroglycerine 0,25 mg i.v.
Onset	1-2 min	2 min	1 min
Duration	15 min	8 min	2 min

Ingemarsson et al.
Am J Obstet Gynecol
1985;153:865

Afschar et al.
BJOG
2004;111:316

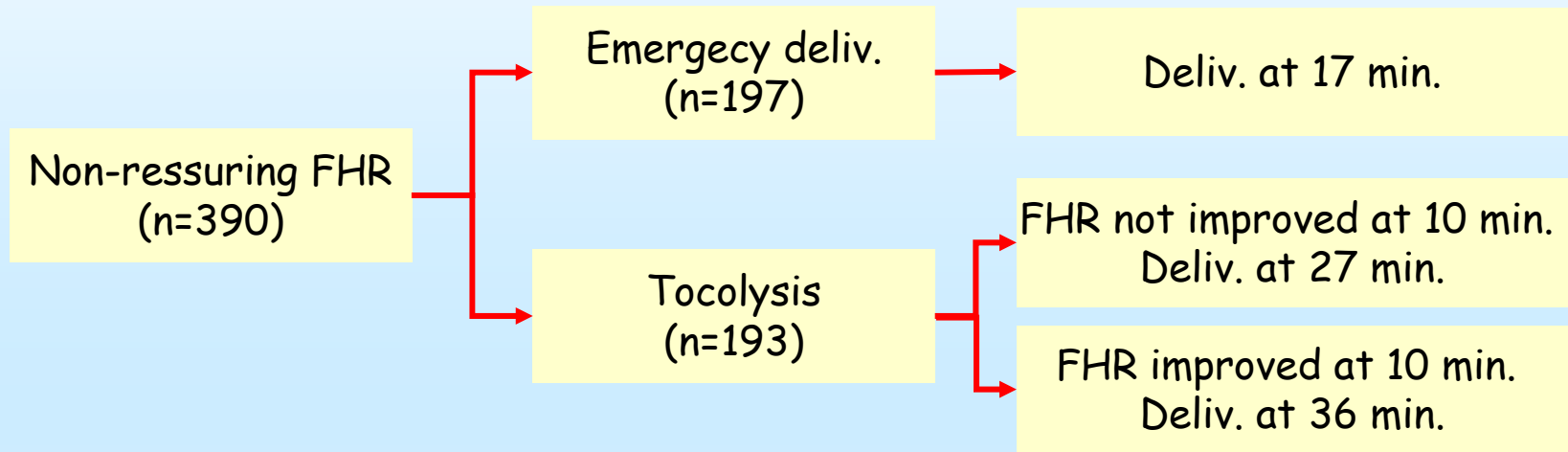
O'Grady et al.
J Perinatol
2000;1:27-33

Terbutaline 0.25 mg i.v. Effect on Uterine Activity during Term Labour



β-adrenergic tocolysis for non-reassuring FHR

Fenoterol



	Tocolysis (n=193)	Emergency delivery (n=197)	<i>P</i>
BE ≤ 12	17.1%	25.4%	0.045
NICU	8.3%	17.8%	0.005

Nitroglycerin for acute tocolysis

Positive observational studies and case reports

- **Intravenous bolus**
 - Emergency situation 250 µg i.v.
- **Repeat boluses**
 - 50-250 µg at 1-2 min. intervals
- **Side-effect**
 - Short-lived decrease in blood pressure (up to 40%)

Nitroglycerin for acute tocolysis

Positive RCT

- Retained placenta
 - 1 mg sublingually
 - Bullarbo et al Int J Obstet Gynecol 2005;91:228

Nitroglycerin for acute tocolysis

Negative RCT's

- External version –
 - 800 µg sublingually
 - H Yanny et al. BJOG 2000;107:562
 - E Bujold et al.. Am J Obstet Gynecol 2003;189:1070
- Fetal extraction during CS
 - 500 µg i.v.
 - M David Obstet Gynecol 1998;91:119
- Uterine tone during active labor
 - 3 x 800 µg sublingually
 - CS Buhimschi. Am J Obstet Gynecol 2002;187:235

Nitroglycerin Acute Tocolysis

- Inconsistent evidence
- The strongest evidence come from clinical reports detailing 346 patients
- Maternal hypotension
- No serious sequelae reported