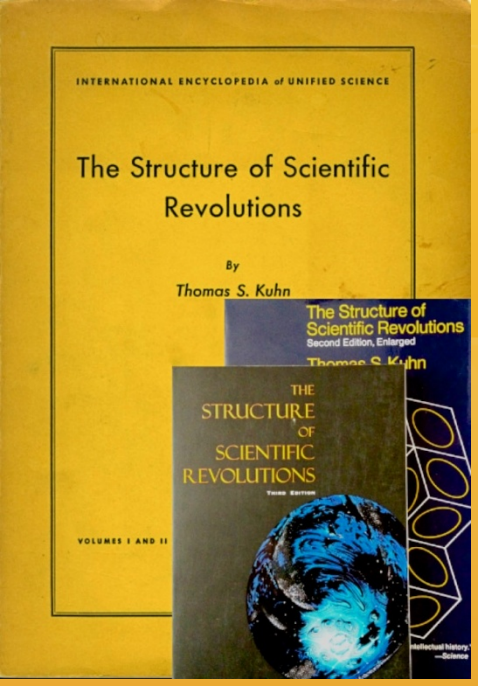
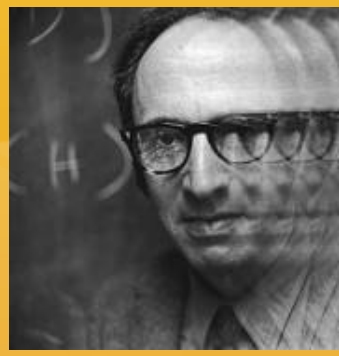


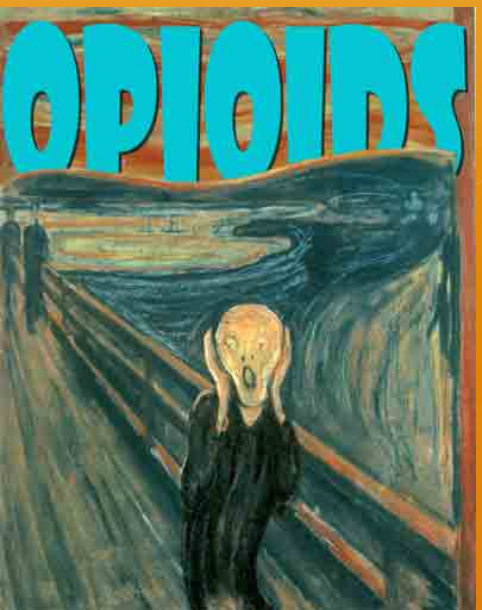
Non-opiate surgical anesthesia A Paradigm Shift?



Jan P Mulier, MD PhD

Dep of anaesthesiology Sint Jan Bruges, Belgium

In collaboration with M DeKock UCLeuven.



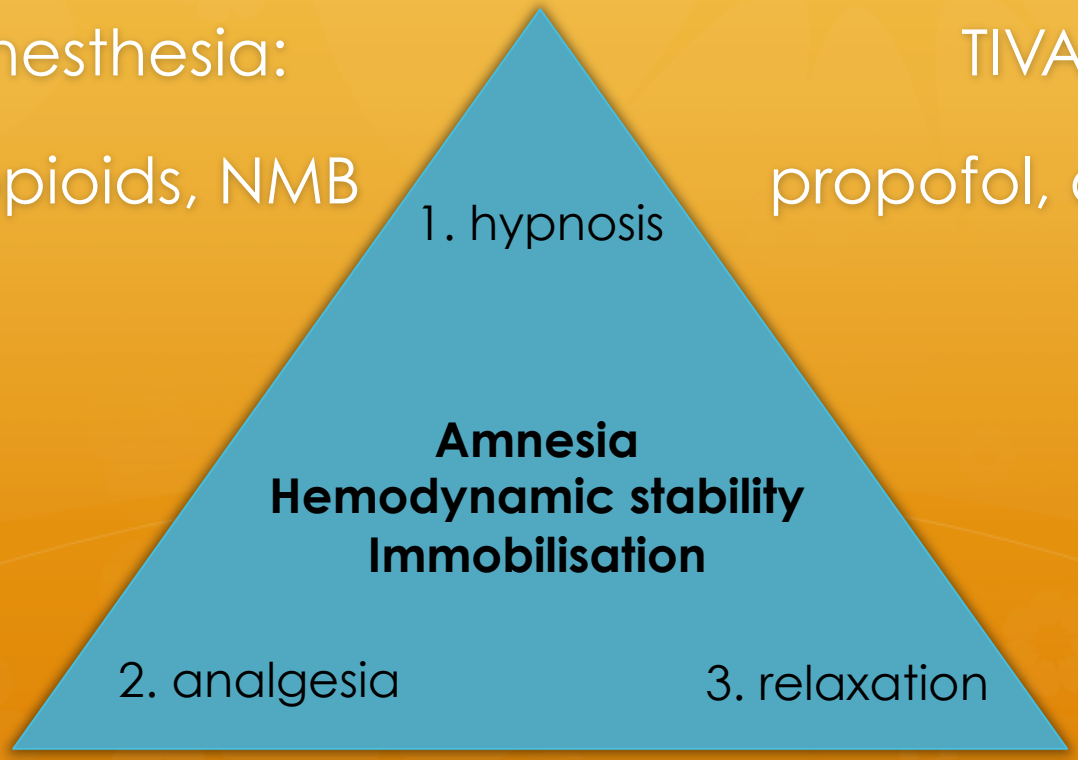
We learned that we need 1. 2. 3.

Balanced anesthesia:

Inhalation, opioids, NMB

TIVA:

propofol, opioids, NMB

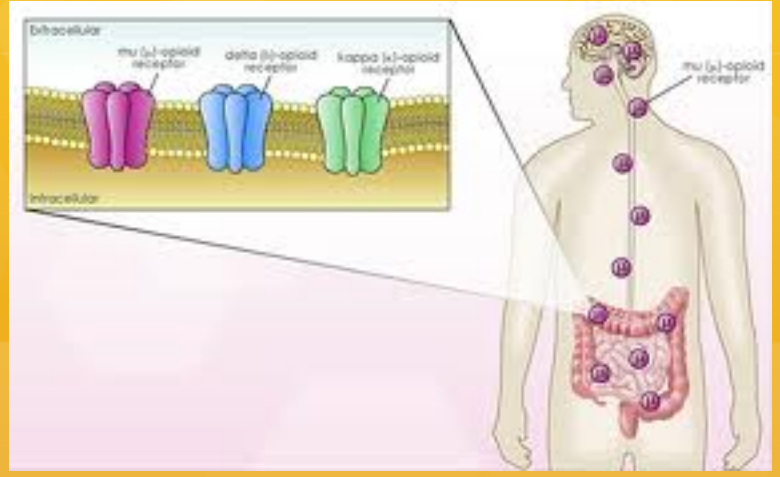


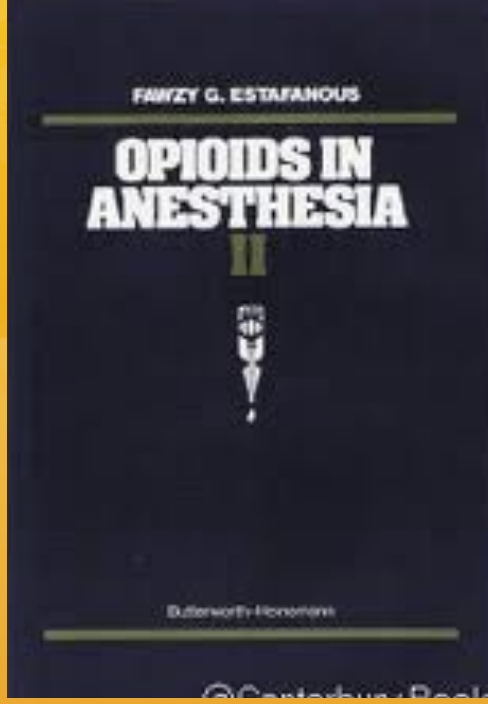
Do we need analgesia to achieve hemodyn stability?
Analgesia is against pain, but pain is impossible if asleep.

Question 1: Why have opioids been introduced from 1960

1. Better analgesia during surgery
2. Less awareness with high dose opioids
3. Better hemodynamic stability
4. Less hypotension
5. Less drop in cardiac output
6. Better cardiac oxygen supply/demand equilibrium

Dr Paul Janssens, 1926 - 2003





A paradigm took place, 50 years ago:

1960 Dr P Janssens invented synthetic opiates; it changed anesthesia forever from inhalation to balanced anesthesia with opioids

- Perfect suppression of sympathetic system in balanced anesthesia
  - Without cardiovascular collaps or histamine release.
- High doses possible having hypnotic effects, relaxant effects?
  - Neurolept anesthesia; stress free anesthesia; sedation; locoregional ..

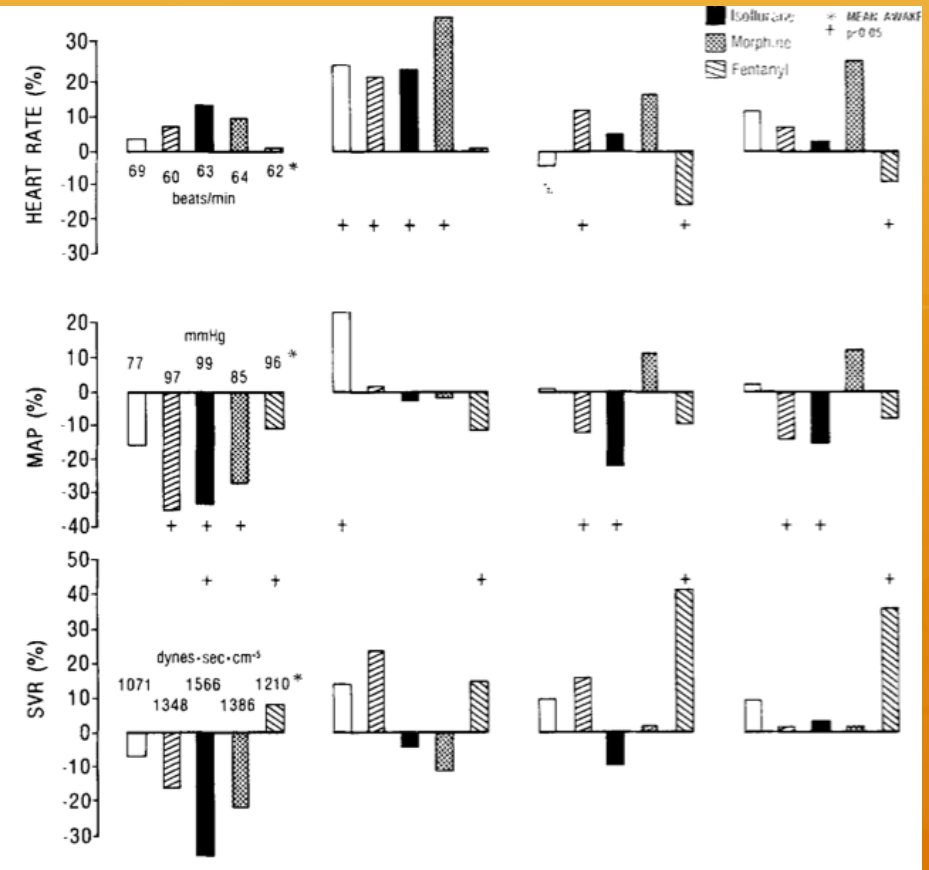
Why was opioid anesthesia successful?

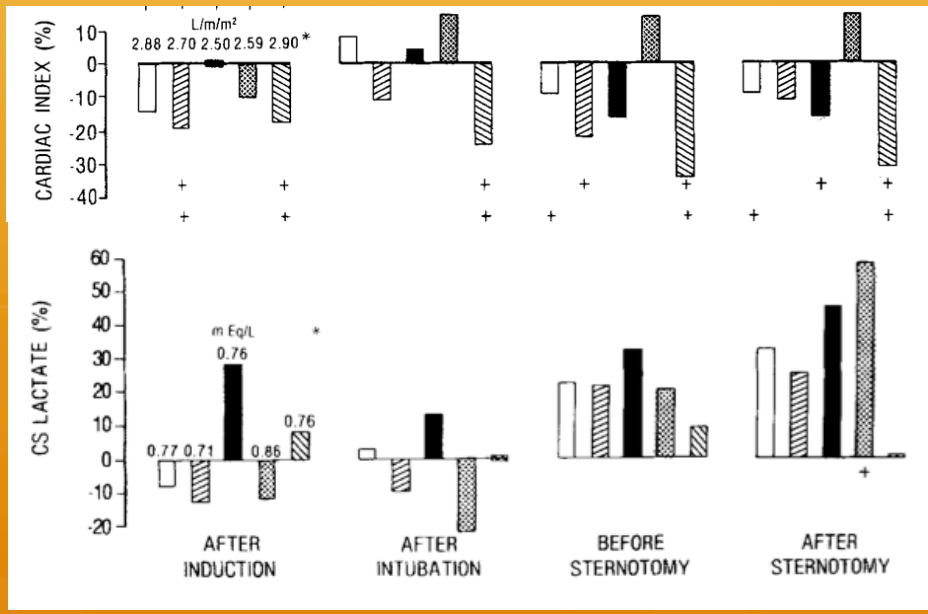
Fentanyl:

Decrease in cardiac output; Increase in SVR,
Slight decrease in HR – MAP and stable!

No lactate production

Moffitt E The Coronary Circulation and Myocardial Oxygenation in Coronary Artery Disease: Effects of Anesthesia Anesth-Analg 1986;65:395-410



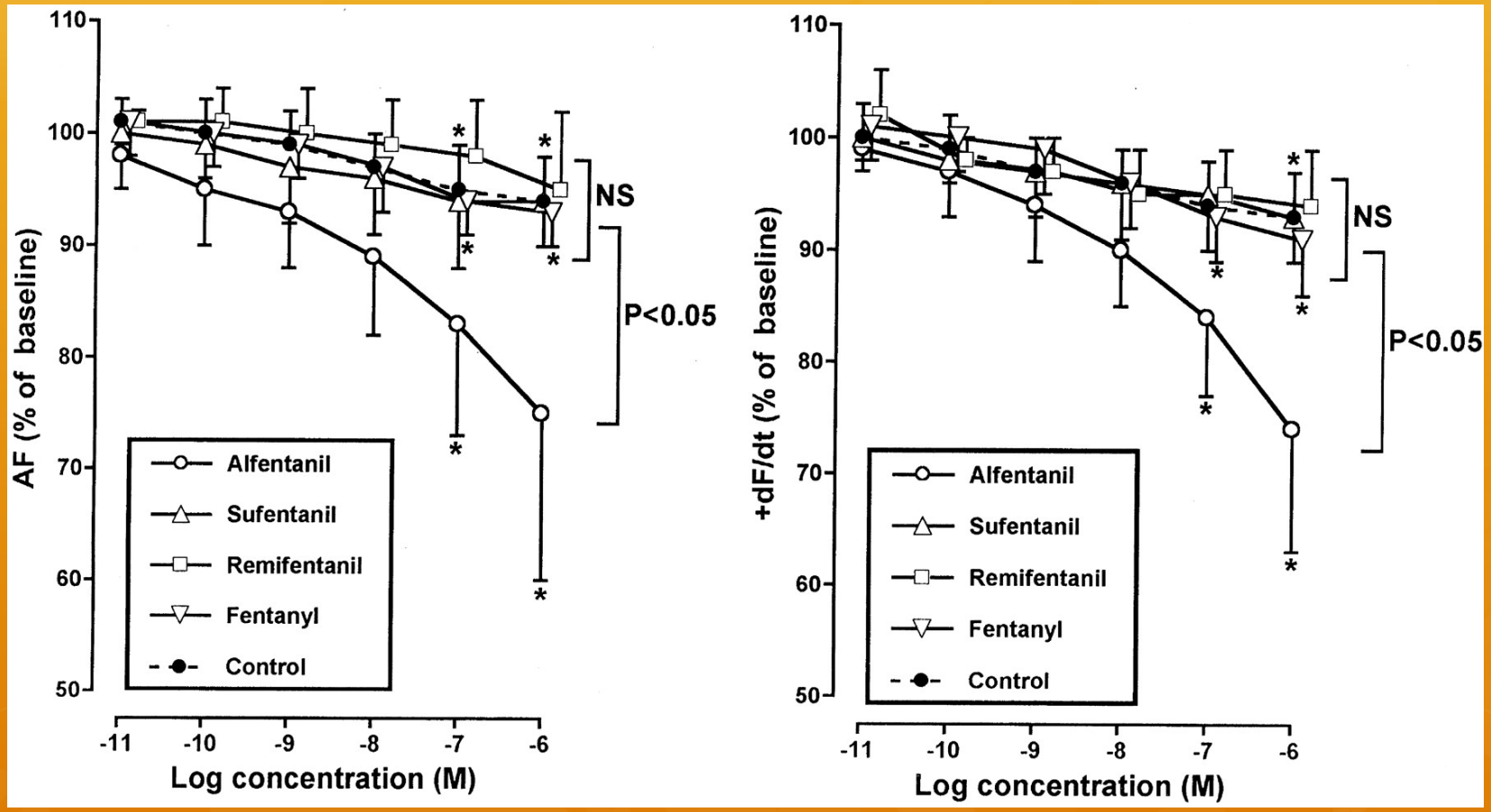


CHANGES FROM AWAKE STATE

Halothane
Enflurane
Isoflurane
Morphine
Fentanyl
* MEAN AWAKE LEVELS
+ p<0.05

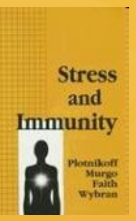
But
No negative inotropic effects of opioids
(except alfentanyl)

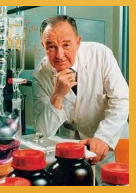
Effect of alfentanil, fentanyl, sufentanil, and remifentanil on maximum isometric active force (left panel) and the peak of the positive force derivative (right panel)



Hanouz J et al. Anesth Analg 2001;93:543-549

Why a new Paradigm today?





1. **Immuno suppression by opioids?**

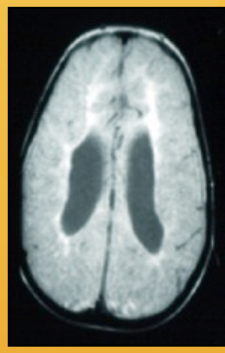
Wybran J. Suggestive evidence for receptors for morphine and methionine-enkephalin on normal human blood T lymphocytes. J Immunol. **1979**;123:1068-70

1992 Dr Paul Janssens invented Remifentanyl but refused to market Remifentanyl and sold it to Beecham afraid of unknown long-lasting effects of opioids…

Sacerdote P. Non-analgesic effects of opioids: mechanisms and potential clinical relevance of opioid-induced immunodepression. Curr Pharm Des. **2012**;18(37):6034-42.

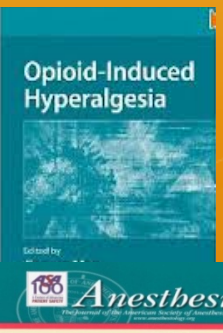
- **Morphine decreases natural and acquired immunity**, both directly and indirectly via the activation of central receptors.
- the immunological effects of opioid are receiving considerable attention because of concerns that opioid-induced changes in the immune system **may affect the outcome of surgery** or of variety of disease processes, **including bacterial and viral infections and cancer**.
- The impact of the opioid-mediated immune effects could be particularly **dangerous in selective vulnerable populations**, such as the elderly or immunocompromised patients.
- Choosing **anesthetic drugs without an effect on immune responses** may be an important consideration in anesthesia.

Why a new Paradigm today?

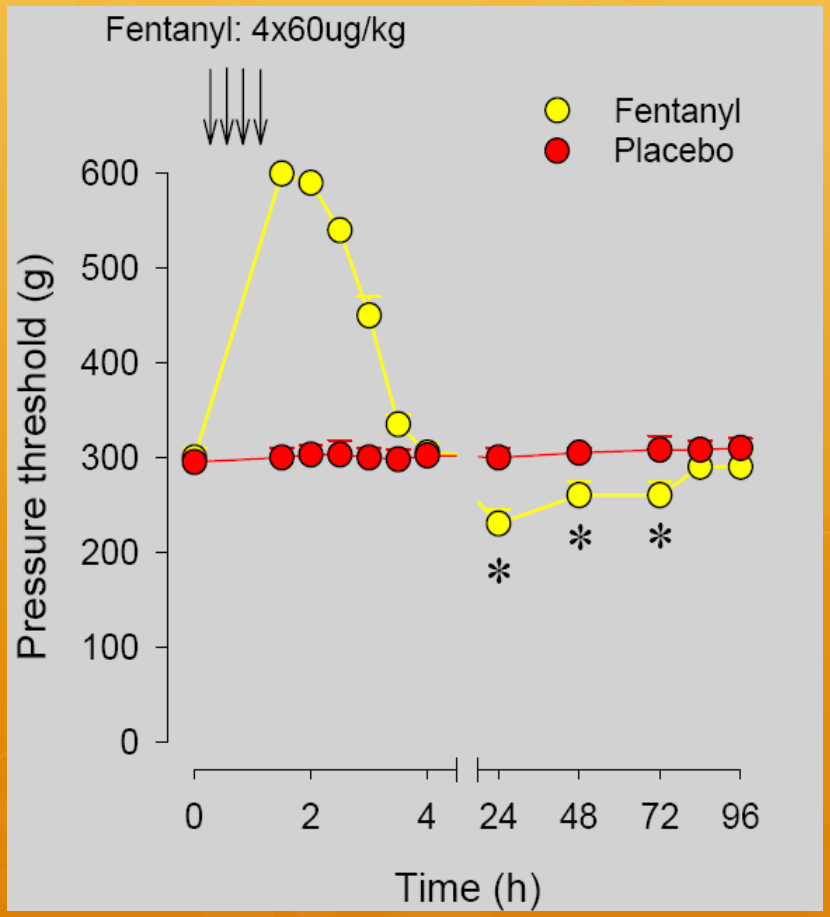


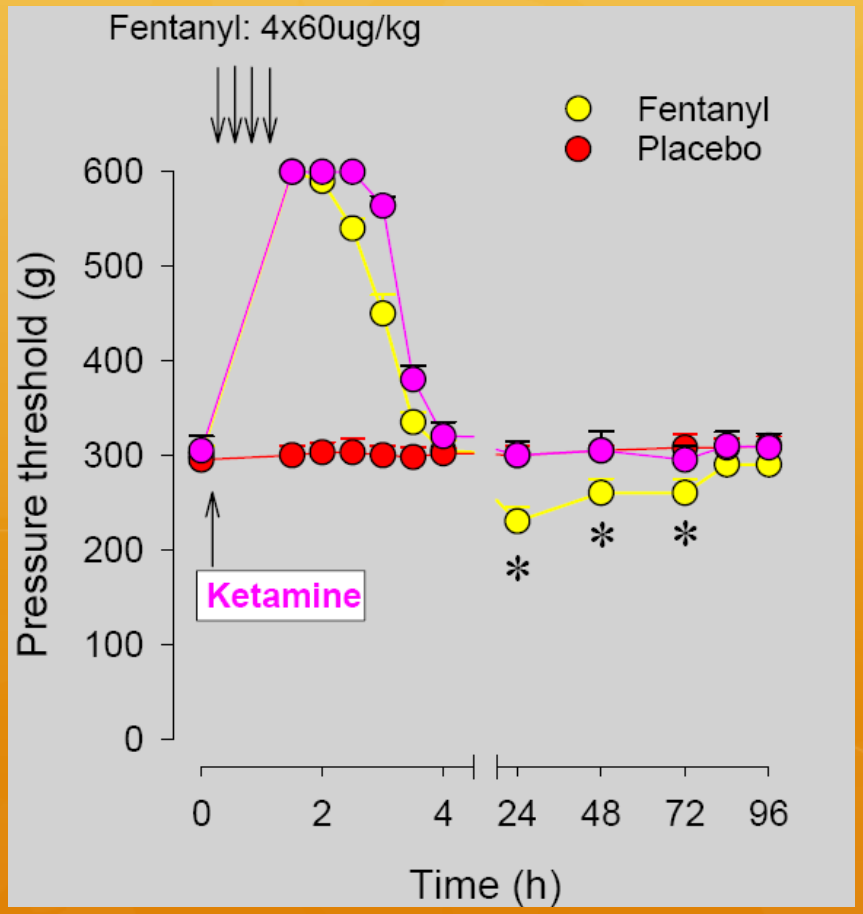
2. Fentanyl induces fixed **neurologic sequels?** (Periventricular Leucomalacia)
   - *Neonatal outcome and prolonged analgesia in neonates. Anand et al. Arch Pediat Adolesc Med 1999; 153: 331-8*

3. **Opioids induced hyperalgesia?**: Patients receiving opioids become *more sensitive to pain.*
   - Opioids are *short lasting analgesics* and *long during hyperalgesics by upregulation of compensatory pronociceptive pathways*
   - Angst MS. Opioid-induced hyperalgesia: a qualitative systematic review. Anesthesiology. 2006;104:570-87



Acute hyperalgesia after isolated exposure





Celerier et al, Anes 2000

Angst (charts)

What do we need, peri-op?

Per operative we need:

- Hypnosis; hemodynamic stability; immobilisation
  - high dose **opioids were the simplest** method to reduce hypnotics; to keep **stable hemodynamics** and to block breathing
  - In very high dose no other drugs needed?
  - therefore we thought we needed **analgetics** and made them the third cornerstone of anesthesia

Post operative we need:

- Analgesia, no hypnosis, no muscle relaxation:
  - low dose opioids not always enough (due to high dose addiction per op)
    - Use PCIA PCEA … local, locoregional addition
  - avoid opioids side effects post operative: multimodal analgetics

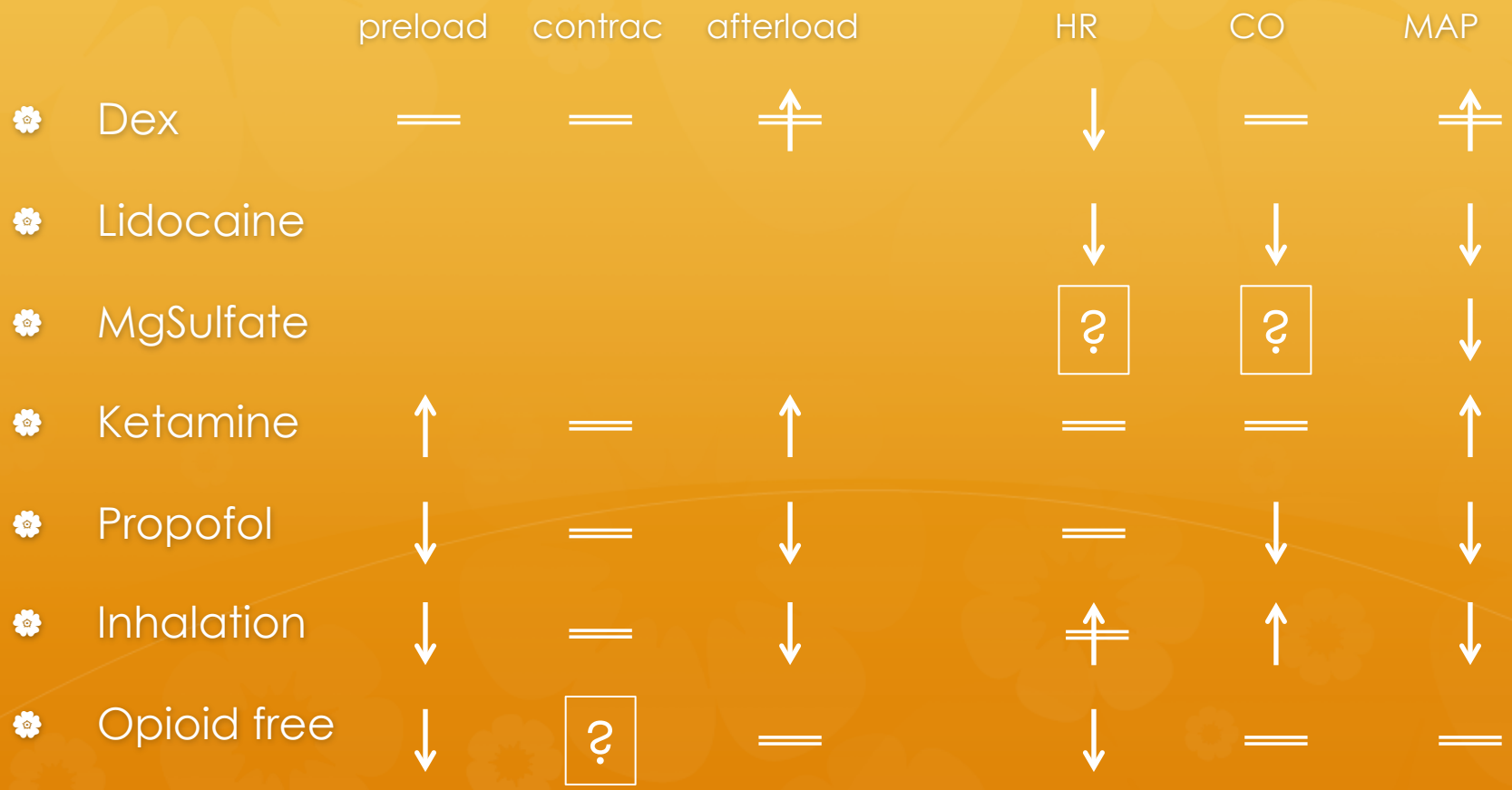
Question 2: How to avoid opioids

1. Measure BIS to ensure that a higher dose of inhalation anesthetics is sufficient.
2. Use different non opioid analgetics during surgery.
3. Use central and peripheral blockers of the sympathetic system.
4. Use vasodilators and beta blockers to stabilize the hemodynamic system.

How to avoid opioids?

- Direct sympathetic block central - peripheral
  - Clonidine, Dexmedetomidine, B blockers
- Indirect block of sympathetic effects
  - Nicardipine, lidocaine, Mg sulfate, inhalation vapor
- Multimodal analgetics (non opoids) loading up per operative to be active when waking up.
  - low dose ketamine, dexmedetomidine, lidocaine, diclofenac, paracetamol
- Epidural, plexus and local infiltration block
- Spinal anesthesia with higher sympathical nerve block. Epidural block.

Hemodynamic stability possible?



Case report 2005: Morbid obesity using dexmedetomidine without narcotics

- 433 kg morbidly obese patient with obstructive sleep apnea and pulmonary hypertension.
- 0.5 MAC inhalation. A continuous infusion of dexmedetomidine (0.7 ug/kg/h) per operative and a low infusion rate first postoperative day.
- 48 mg morphine by PCA first day with dex
- 148 mg morphine by PCA second day without dex.

Hofer R. Anesthesia for a patient with morbid obesity using dex-medetomidine without narcotics. Can J Anaesth. 2005; 52: 176-80.


Anesthesia for a patient with morbid obesity using dexmedetomidine without narcotics

[L'anesthésie chez un patient obèse morbide avec la dexmédétomidine sans narcotiques]

Roger E. Hofer MD,* Juraj Sprung MD PhD,* Michael G. Sarr MD,† Denise J. Wedel MD*

Purpose: To describe the anesthetic management of a patient with extreme obesity undergoing bariatric surgery whose intraoperative narcotic management was entirely substituted with dexmedetomidine.

Clinical features: We describe a 433-kg morbidly obese patient with obstructive sleep apnea and pulmonary hypertension who underwent Roux-en-Y gastric bypass. Because of the concern that

Objectif : *Décrire la démarche anesthésique utilisée chez un patient atteint d'obésité morbide devant subir un pontage gastrique. Les narcotiques peropératoires ont été entièrement remplacés par la dexmédétomidine.*

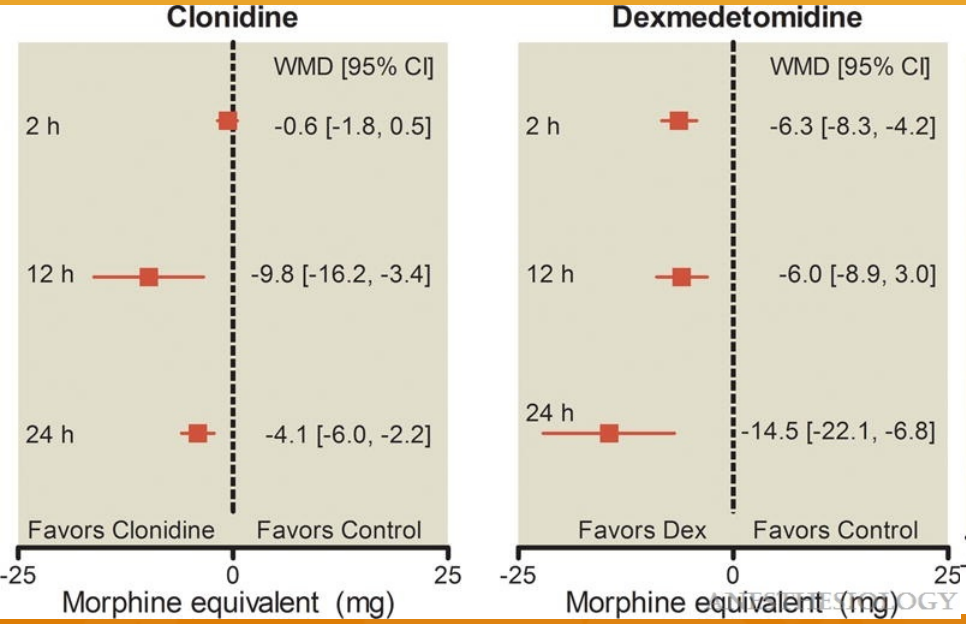
Éléments cliniques : *Le patient pesait 433 kg, présentait une apnée du sommeil obstructive et de l'hypertension pulmonaire. Il devait subir un pontage gastrique de Roux-en-Y. Inquiets de causer une*

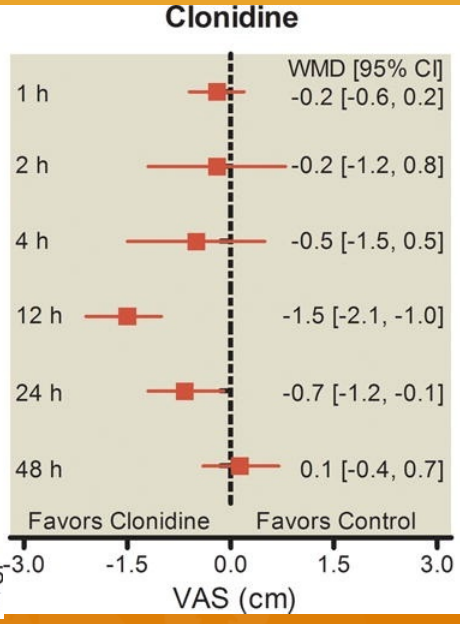
Effect of clonidine-dexmedetomidine on post-op opioid use

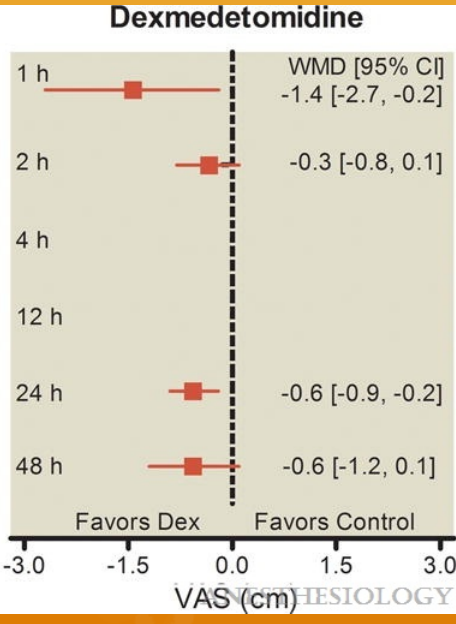
- Blaudszun G. Anesthesiology 2012 ; 116: 1312-22 Effect of systemic alpha2 agonists on post operative morphine consumption and pain intensity. Review and meta analysis.

Morphine post OP

VAS post OP



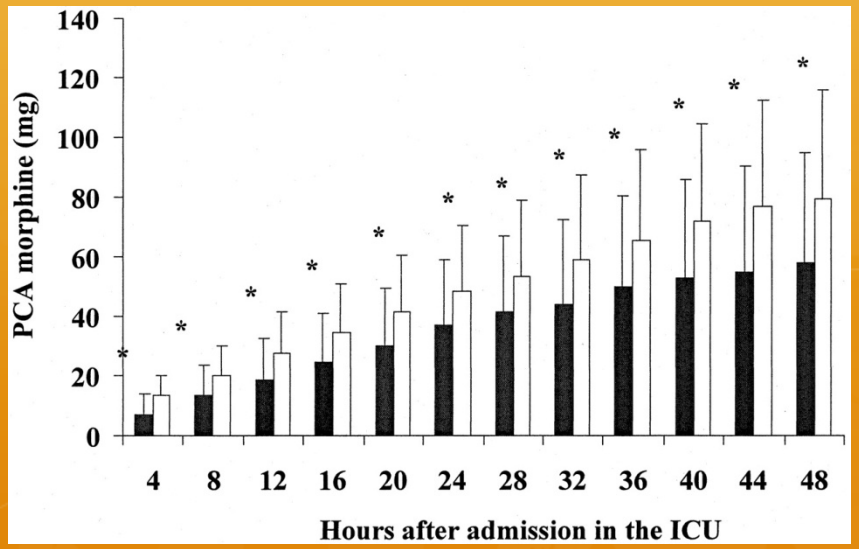




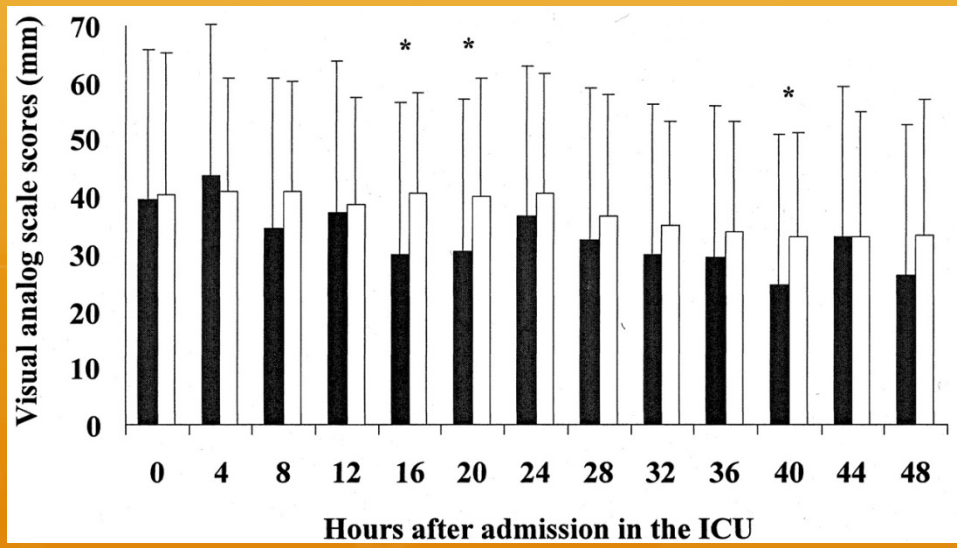
Effect of ketamine on post-operative opioid use

- Bell RF Perioperative Ketamine for acute post operative pain. the cochrane library 2010; 11

Cumulative postoperative patient-controlled analgesia (PCA) morphine consumption.



Visual analog scale score at mobilization during the 48-h study.

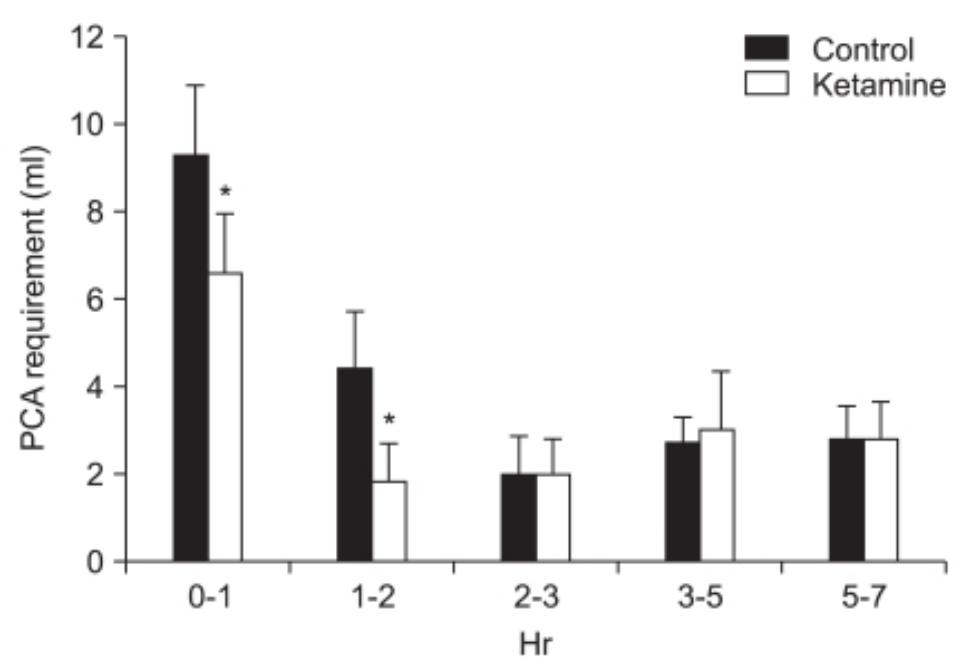


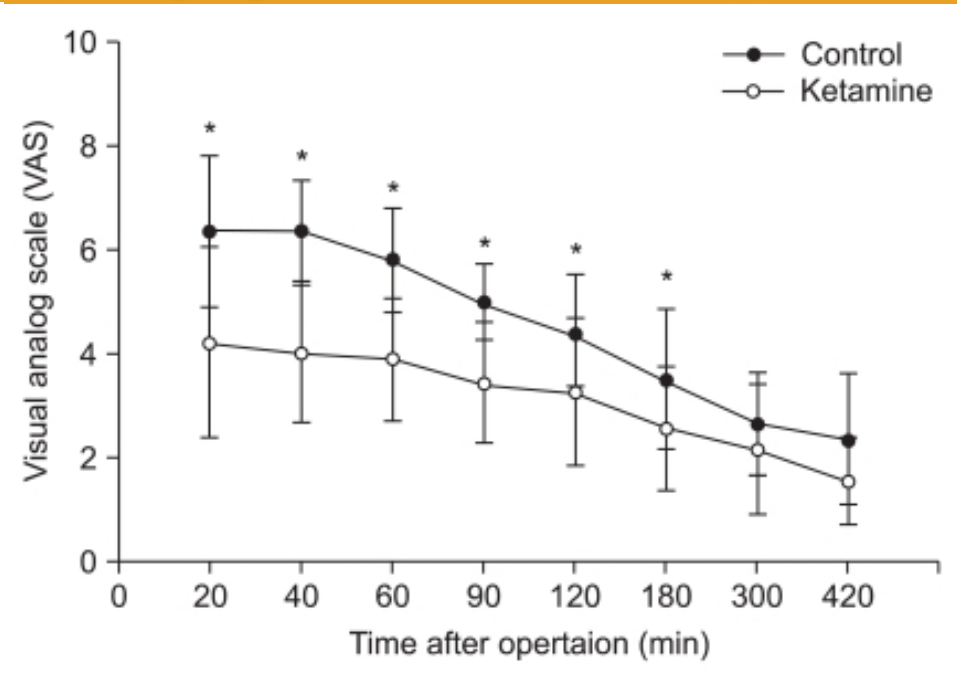
Ketamine per op
Placebo per op

Guillou N et al. Anesth Analg 2003;97:843-847

Ketamine reduces opioid induced hyperalgesia

- Boo Hwi Hong Effects of intraoperative low dose ketamine on remifentanil-induced hyperalgesia in gynecologic surgery with sevoflurane anesthesia. Korean J Anesthesiol. 2011; 61: 238.
- Same dose of remifentanyl with ketamine 25 mg vs without ketamine
- Ketamine 0,3 mg/kg followed by 3 ug/kg/min





Effect of Mgsulfate on per-op opioids

- Kogler The analgesic effect of magnesium sulfate in patients undergoing thoracotomyJ Acta Clin Croat. 2009;48:19-26.

Thoracotomy patients received Fentanyl as required and 30-50 mg/kg MgSO4 followed by continuous infusion of 500 mg/h or placebo.

Fentanyl consumption during the operation was significantly lower in the Mg treated group versus placebo.

Effect of lidocaine on post-op opioid use

- McCarthy G. Drugs. 2010;70:1149-63. **Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials.**
- 33% reduction vs placebo in opioid consumption postoperative.
  - when the lidocaine infusion was maintained for 1 hour
- 83% reduction vs placebo in opioid consumption postoperative.
  - when the lidocaine infusion was maintained for 24 hours.
- earlier return of bowel function, allowing for earlier rehabilitation and shorter duration of hospital stay. Duration of hospital stay was reduced by an average of 1.1 days in the lidocaine-treated patients.
- intravenous lidocaine did not result in toxicity or clinically adverse events.

Steroids revival for post op analgesia?

- Massera G. Indications for steroid anesthesia.

Acta Anaesthesiol. 1959;10:541-9

- Tiippana E. Effect of paracetamol and coxib with or without dexamethasone after laparoscopic cholecystectomy.

Acta Anaesthesiol Scand. 2008;52:673-80

Conclusion

- Many studies show reduction in opioid use per operative and post operative if a drug is added.

If these drugs are combined in a multimodal approach is it possible to avoid all opioids per operative???

Marc de Kock (UCL Belgium) achieved this already several years before Dexmedetomidine became available in Europe using high dose clonidine –low dose ketamine and esmolol.

Question 3: how should you start opioid free?

1. Reduce long acting opioids first and switch to short acting opioids like remifentanyl.
2. Load your patient with long acting opioids up per operative and reduce first your post operative opioids.
3. Reduce gradual your opioids per operative while combining a multimodal approach.
4. Add non opioid analgetics per operative first and measure your post operative opioid need.

How should you start OFA?

1. Stop remifentanyl infusions, use only 10 ug sufentanil at induction. Measure anesthesia depth, blood pressure, HR; give low dose opioids before extubation.
2. add an alpha agonist (central direct sympathetic block)
   - Clonidine, 150 - 300 ug at induction dexmedetomidine infusion 0,5 – 1 ug/kg/h after induction,
3. keep peripheral B blocker as escape if tachycard
4. Indirect block of sympathetic effects
   - lidocaine bolus before induction,
   - increase to 1,5 MAC inhalation vapor,
   - Keep Nicardipine or other vasodilator as escape
5. start non opioid analgetics per operative
   - Low dose ketamine 10 – 20 mg,
   - Diclofenac, keterolac or parecoxib
   - Paracetamol, dexamethasone, droperidol (PONV?).
6. Epidural, plexus and local infiltration block of pain nerves

How to monitor anesthesia depth during opioid free anesthesia?

- Ketamine given at a hypnotic dosis of 1,5 mg/kg rises the BIS value. (we give ketamine in OFA dosis of 0,25 mg/kg IBW far below an hypnotic dosis.)
  - Wu CC. EEG-bispectral index changes with ketamine versus thiamylal induction of anesthesia. Acta Anaesthesiol Sin. 2001;39:11-5.
- BIS values are elevated by a bolus dose of isoproterenol, ketamine, neostigmine or sugammadex above 60 % while patients have no recall.
  - Dahaba AA. Effect of sugammadex or neostigmine neuromuscular block reversal on bispectral index monitoring of propofol/ remifentanil anaesthesia. Br J Anaesth. 2012 Apr;108(4):602-6
  - Matthews R. Isoproterenol induced elevated bispectral indexes while undergoing radiofrequency ablation. AANA J. 2006;74:193-5

No risk for awareness if you keep BIS below 60% during OFA.

Protocol Sint Jan Brugge

- Three drugs (Dex 200ug, Ket 50 mg, Lid 300 mg, add H20 to 20 ml) given at 1 ml/10 kg IBW and followed by 1 ml/10 kg IBW/h adapt to HR/MAP
  - Dexmedetomidine 0,5 to 1 ug/kg IBW followed by 0,5 to 1 ug/kg IBW/h
  - Ketamine 0,125 to 0,25 mg/kg followed by 0,125 to 0,25 mg/kg IBW/h
  - Lidocaine 1,5 mg/kg IBW followed by 1,5 to 3 mg/kg IBW/h
- MgSulfate 40 mg/kg IBW followed by 10 mg/kg IBW/h
- Propofol is given at 2,5 mg/kg IBW followed by inhalation anesthesia at 0,8 – 1,0 MAC with BIS around 40%.
- Rocuronium 0,6 – 1 mg/kg IBW followed by infusion 1 mg/kg IBW/h and based on TOF PTC (if NMB is needed).
- Have metoprolate and nicardipine available when tachycard or hypertensive.
- Wound infiltration with local anesthetics, reduce total dose.

Post operative analgesia

- non steroidal anti-inflammatory agents
  - Paracetamol 2 gr loading 1 gr/6h
  - Diclofenac 150 mg loading, 2x75 mg/day
  - Or Keterolac 40 mg loading, 3 x 10 mg/day
- Local wound infiltration (calculate toxic dose!)
- and choice between
  - give low dose morphine or
  - keep infusion of sympathicolytica (ket dex lido Mg) at low dose without deep sedation
    - Ketamine 0,05 mg/kg/h
    - Lidocaine 1 mg/kg/h
    - Mgsulfate 10 mg/kg/h
    - Dexmedetomidine 0,1 – 0,2 ug/kg/h

Example of a recent live case

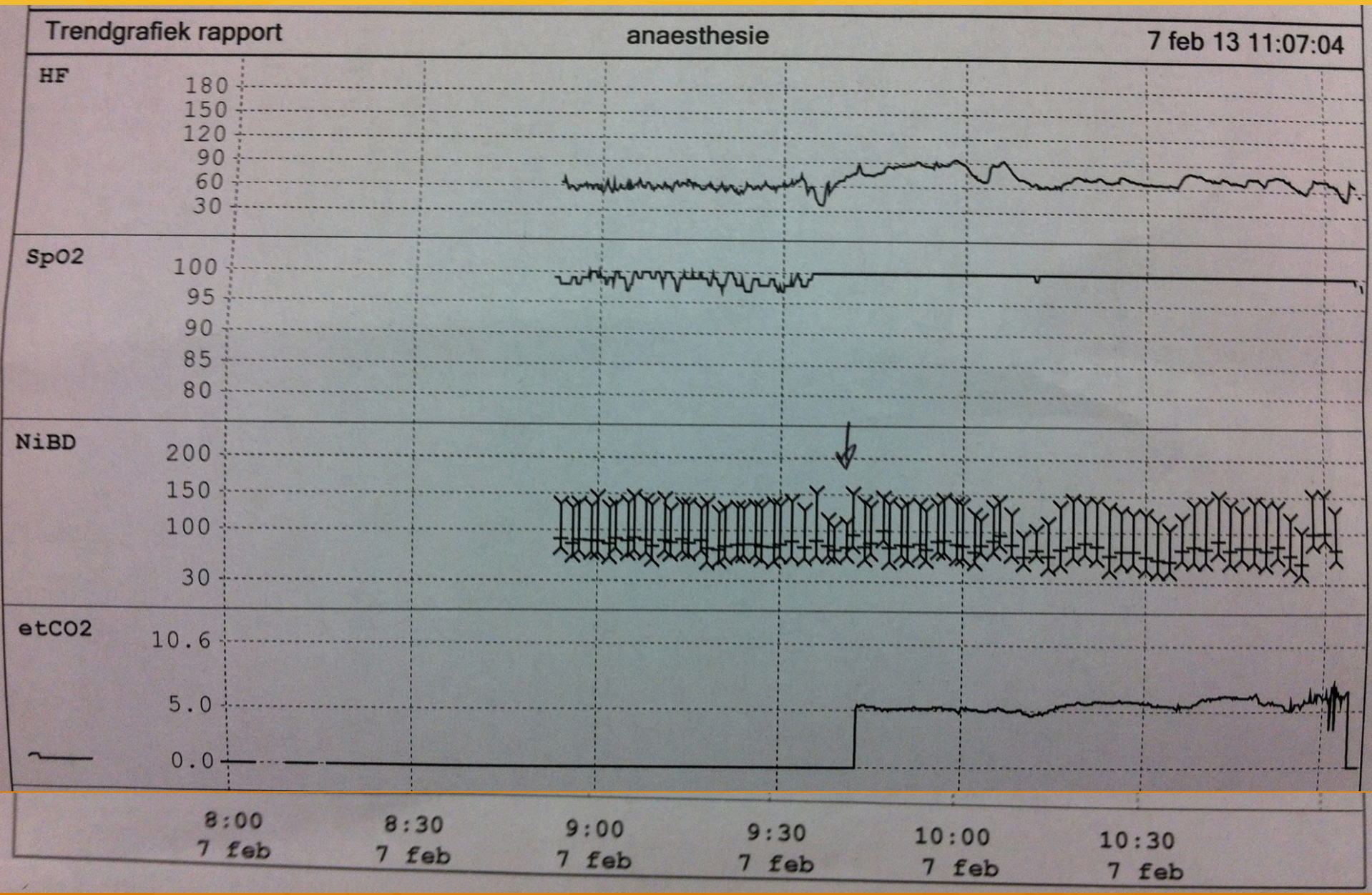
- 9:40 anesthesia induction and intubation when TOF = 0 and BIS = 40. (80 mg Roc) PTC was still 20. 20 mg rocuronium and continuous infusion at 2 mg/kg IBW/h followed by 1 mg/kg IBW/h and 0,5 mg/kg IBW/h: infused Roc: 78,1 mg

Ketamine: 35 mg; Lidocaine: 210 mg; Dexmedetomidine: 140 ug; Rocuronium: 158,1 mg; desflurane 0,8 MAC; paracetamol 3 gr.

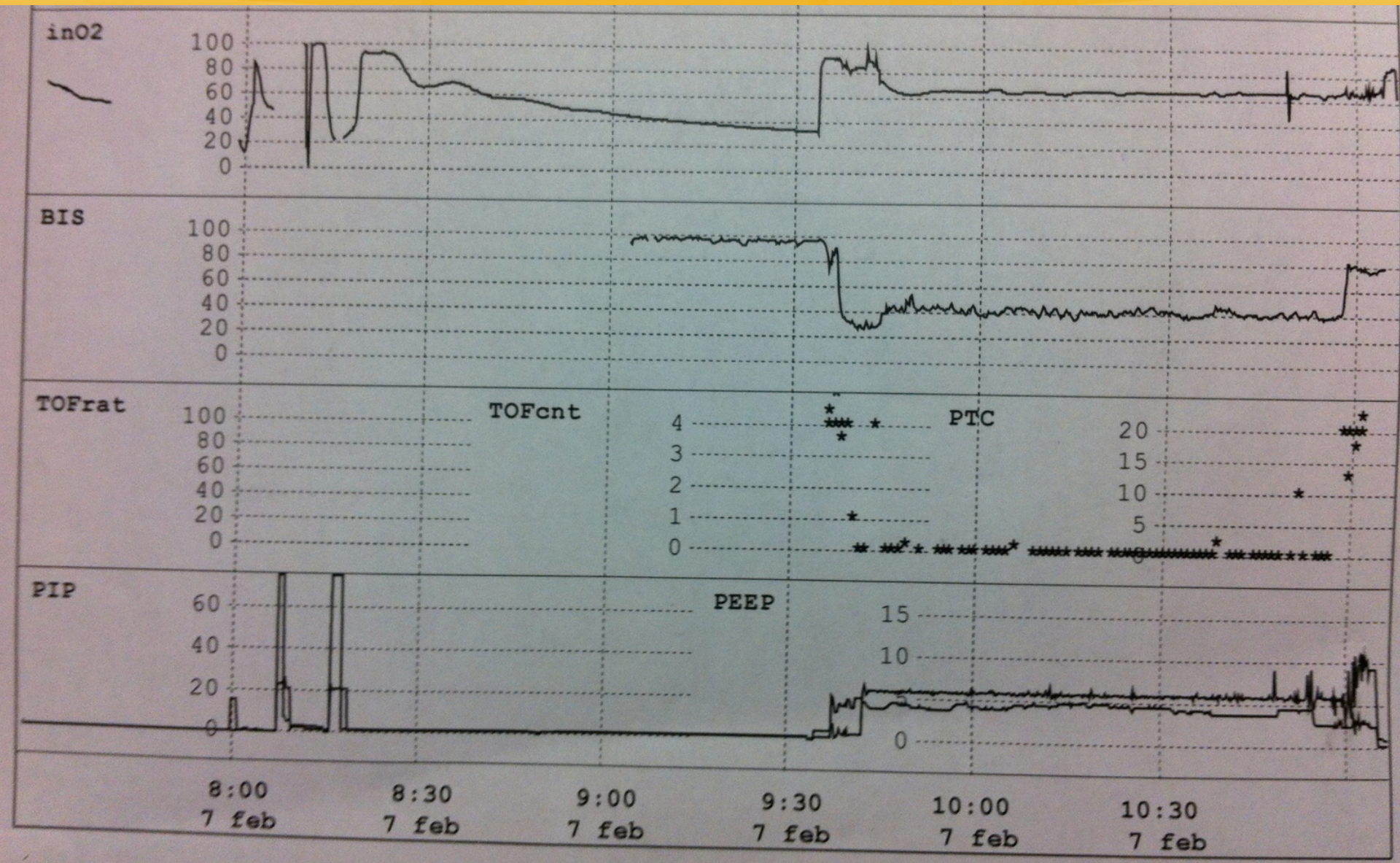
- 10:00 incision: insufflation of abdomen and APVR calculation.
- 11:16 Lap Roux and Y gastric bypass procedure.
- 10:45 Roc infusion stop
- 10:55 last surgical stitch: stop dexmedetomidine infusion.
- 10:57 PTC 4 and 600 mg Sugammadex given
- 11:01 TOF = 100 % BIS rose to 77% (not awake!) and stop desflurane.
- 11:06 patient awake when called, extubation.
- 11:08 patient full awake, no pain, feels happy to hear that operation is finished and had sufficient force to move himself painfree in bed at 11:14.

Patient video

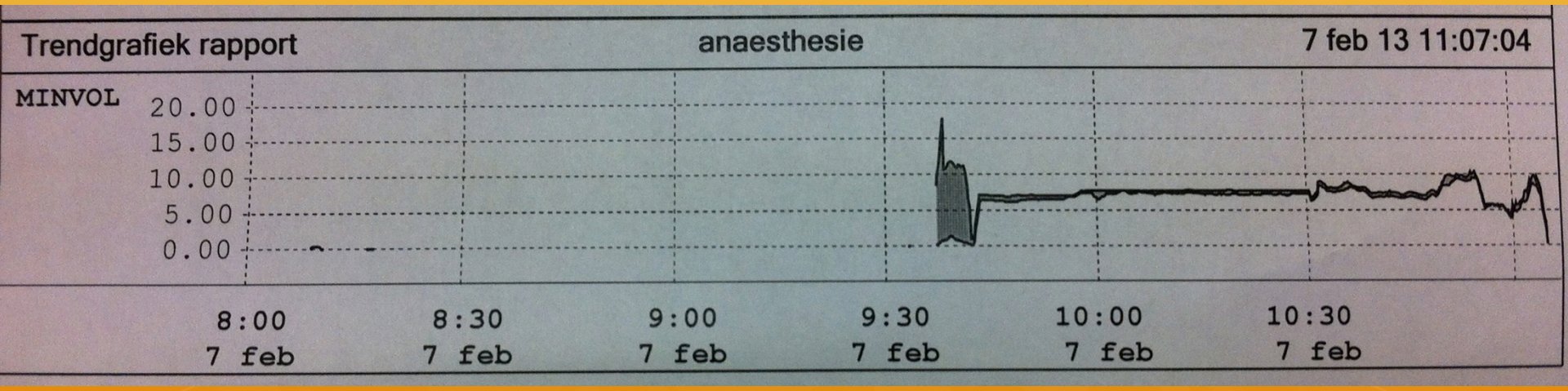
HR, Sat, NIBP, etCO2



02%, BIS, TOF, PTC, airw pres



Peak airway pressures in mmHg



Good indications for OFA

- Obese patients and patients with obstructive sleep apnea syndrome (OSAS),
- COPD, asthma, respiratory insufficiency.
- Acute and chronic opioid addiction.
  - Sufficient analgesia preferential with non-opioids is essential also in long-term abstinence to avoid relapses.
  - Huxtable 2011, Bryson 2010, Rundshagen 2010, Jage 2006, Stromer 2013
    - If heroine addict: substitution
    - If alcohol: use clonidine/benzo
    - If cocaine, amphetamines: avoid stress and craving
- Allergy, anaphylaxis for opioids? Histamine release.
  - Fentanyl-associated anaphylaxis (Fukuda 1986, Fischer 1991, Cummings 2007, Tomar 2012, Baldo B Anaesth Intensive Care 2012; 40: 216)
- Hyperalgesia problems. Is frequent but you have to ask.
- Complex regional pain syndromes (CRPS)
  - Causalgia, Suddeck's atrophy, Raynaud syndrome and reflex sympathetic dystrophy.
- Chronic Fatigue and Immune Dysfunction Syndrome?
  - Avoid histamine release, ponv prevention, Mg and K extra,
- Oncologic surgery?
  - Being pain free and stress free more important than immunosupression by morphine? Pro –contra opoids.
    - Imani B Morphine use in cancer surgery Front pharmacol 2011; 2: 46

Contra indications for OFA

- Allergy to one of the drugs.
- Acute Ischemic problems due to coronary stenosis.
- Controlled hypotension with need for dry surgical field by a low cardiac output.
- Relative contra indication
  - disorders of autonomic failure better known as orthostatic hypotension (Multiple System Atrophy).

Today paradigm shift to OFA

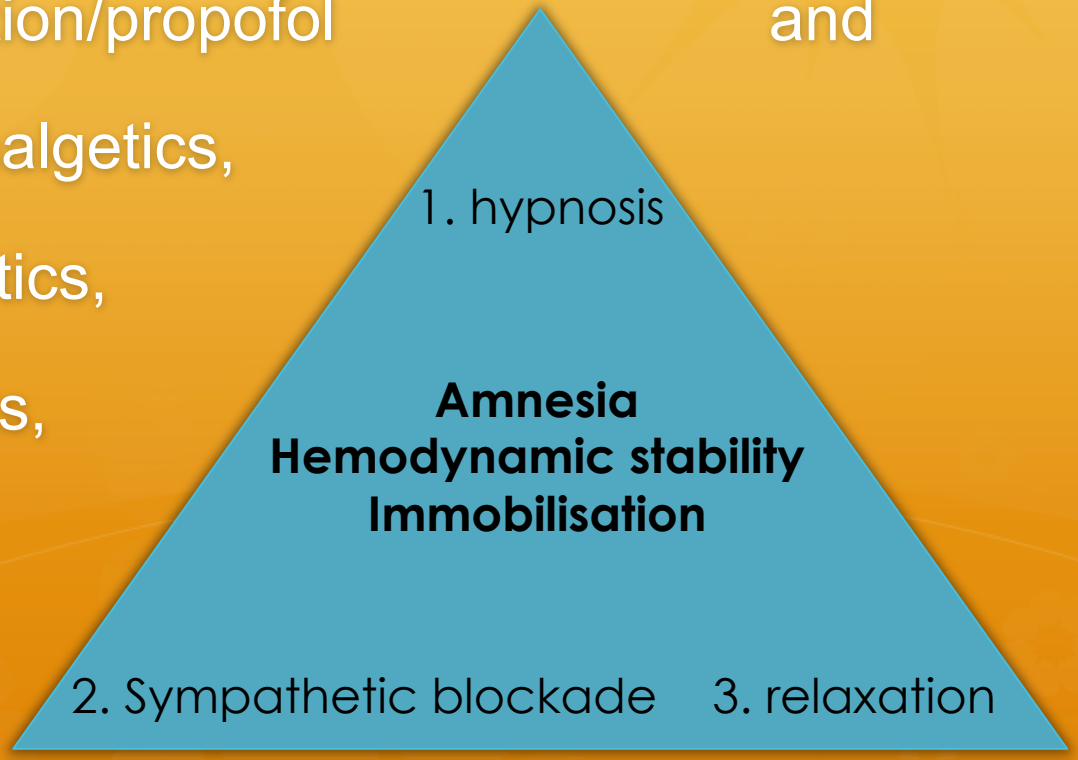
OFA: Inhalation/propofol and

non opioid analgetics,

local anesthetics,

alpha agonists,

B blockers



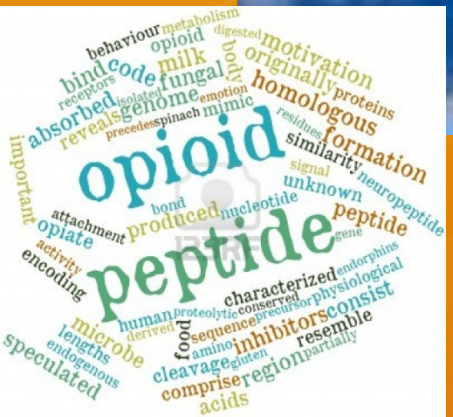
No analgesia is needed during anesthesia
We need sympathetic stability to avoid organ dysfunction or damage

OFA

- Is possible.
- Is an alternative for opioid anesthesia!
- Is better for a selective group of patients!!
- Might be better for most patients?

the future of anesthesia and a paradigmshift?

More research is needed before becoming evidence based. Try it slowly and listen to your patients.



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