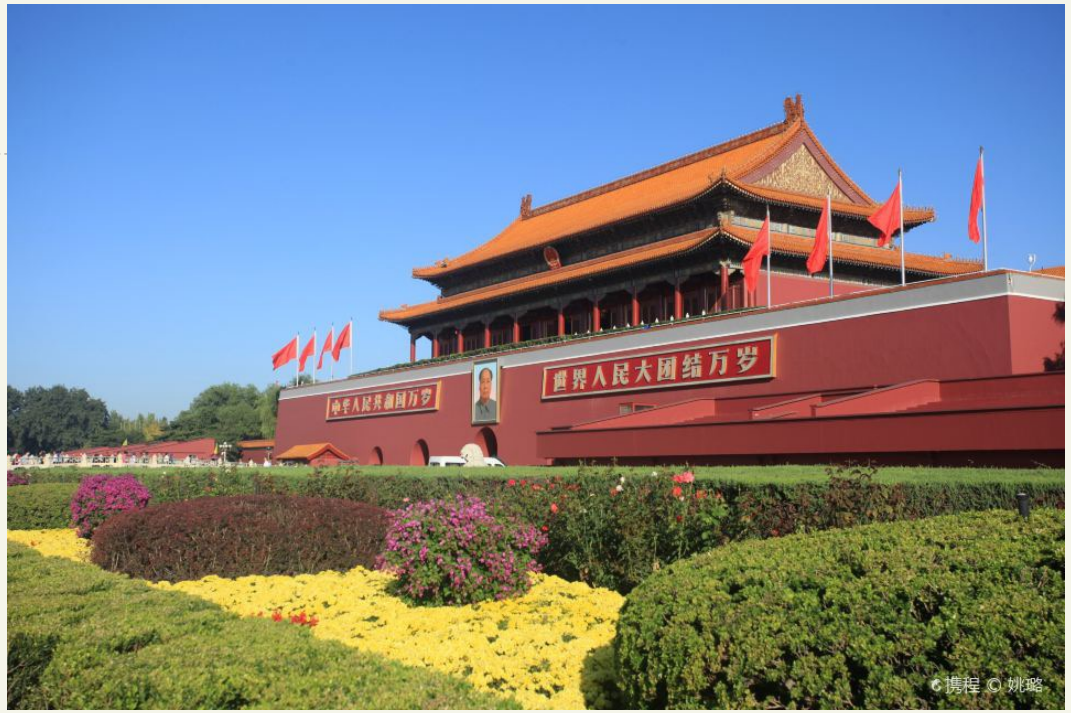
Tianjin Medical University General Hospital

Clinical Application of New Opioid Anesthetic

Guolin Wang



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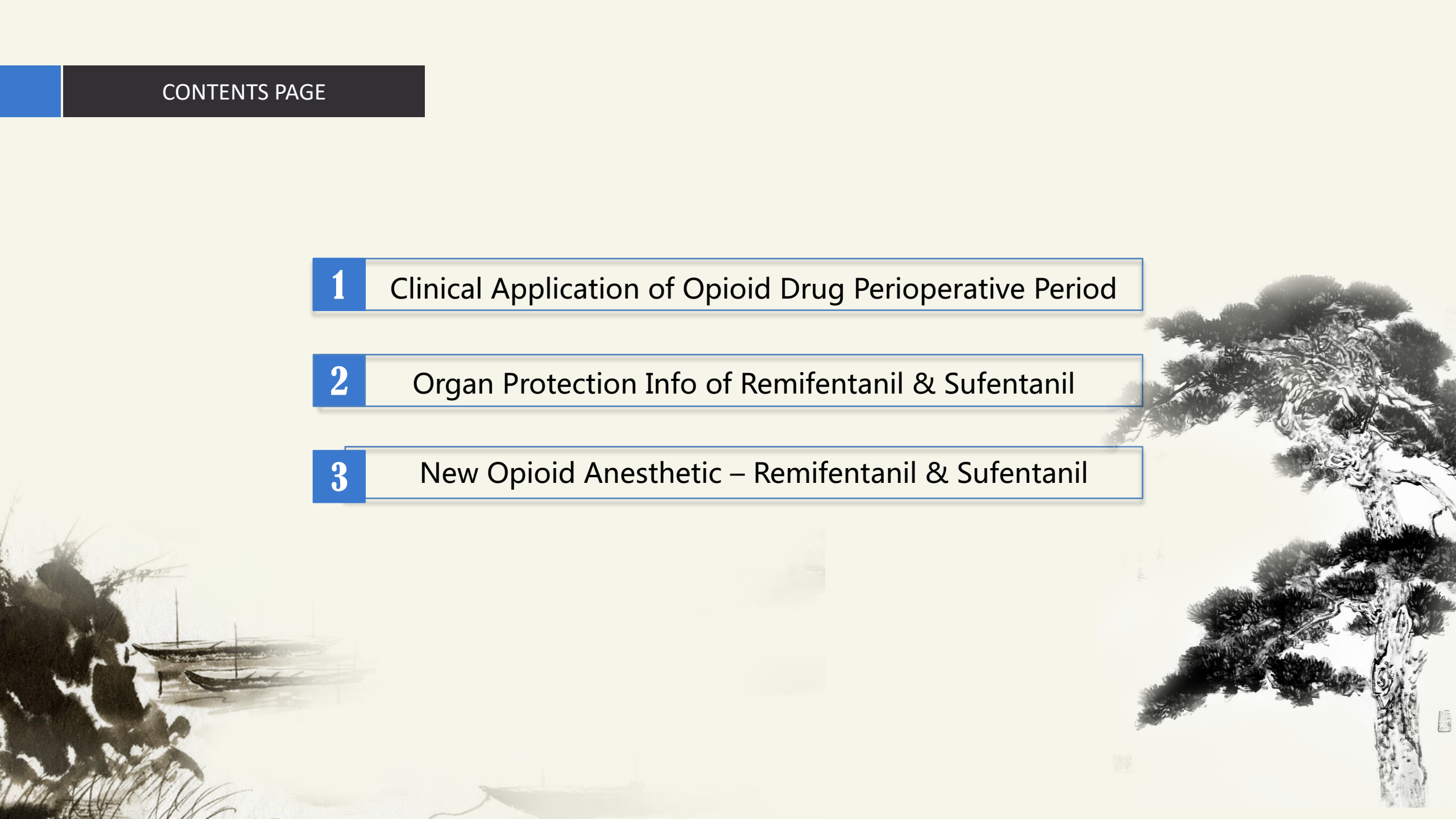
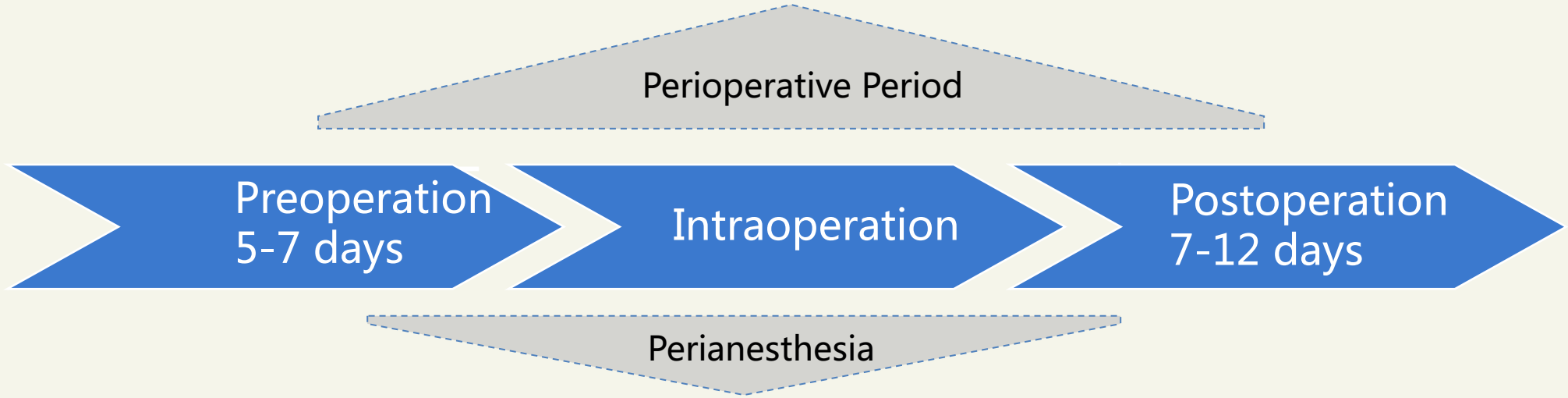


TRANSITION PAGE

Perioperative Period Clinical Application of Opioid Anesthetic

1.1 Perioperative Period

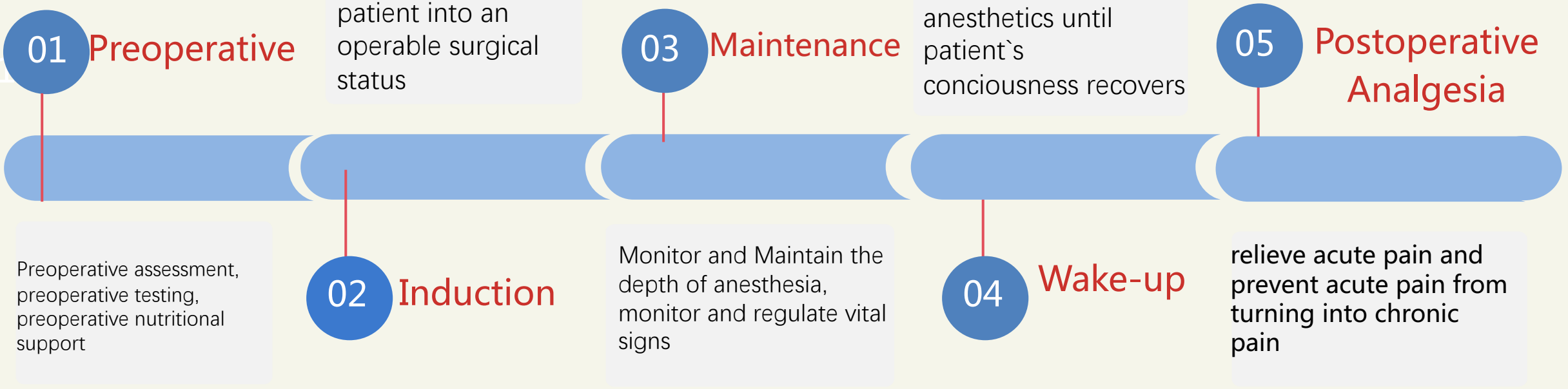
Definition： the time period of a patient's surgical procedure. It commonly includes ward admission, anesthesia, surgery, and recovery. Perioperative may refer to the three phases of surgery: preoperative, intraoperative, and postoperative .



The time period of 1-2 days preoperation, intraoperation and 1-2 postoperation.

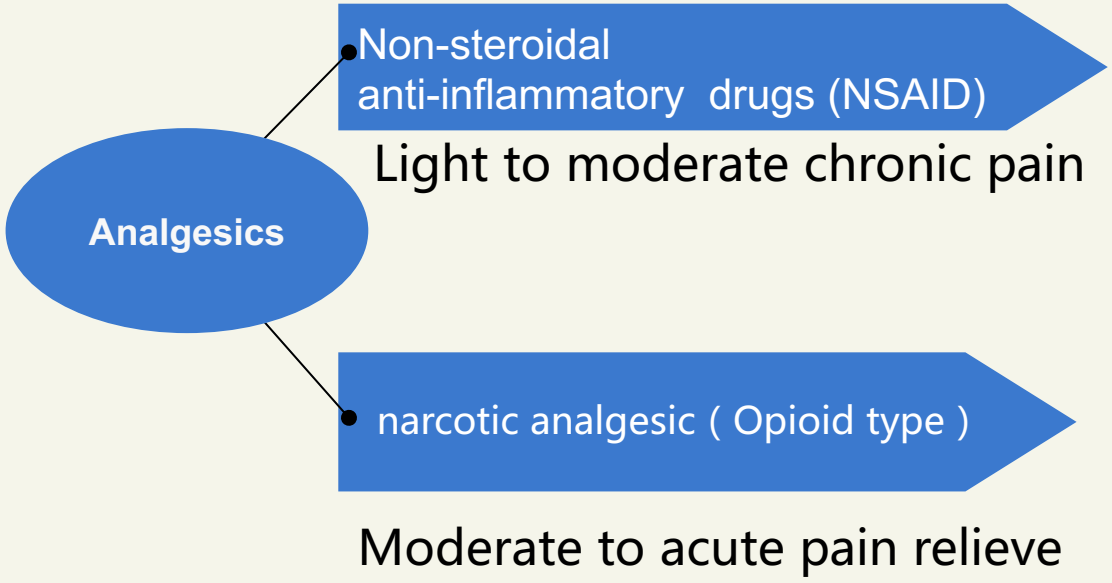
1.1 Perioperative Period

Phases of General Anesthesia



The four elements of general anesthesia are sedation, analgesia, muscle relaxation and reflex inhibition.
The principle is to prevent the patient from being uncomfortable and without adverse reactions, so that the patient can smoothly enter into the anesthesia status (given sedative + analgesic + muscle relaxant).

1.2 Analgesic for Perioperative period



Opioid Drugs

Potency	Drug	Value
Strong	Sufentanil	*1000*
	Remifentanil	*100-200*
	Fentanyl	*100-200*
	Alfentanil	*40-50*
	Hydromorphone	*8-10*
	Butorphanol	*4-6*
Moderate	Methadone	*1.5*
	Morphine	*1*
	Nalbuphine	*0.5-0.8*
	Pentazocine	*0.3*
Weak	Codeine	*0.2*
	Pethidine	*0.1*
Very Weak	Allyl prarone	*0.07-0.1*
	Tramadol	*0.05-0.07*

Opioid drugs are main analgesics for perioperation period!

Brunton，The Pharmacological Basis of Therapeutics.Pub date: 23 Aug 2005.

Analgesia Methods

General analgesia

Oral
Muscle injection
Intravenous

Local analgesia

local infiltration
Peripheral nerve block
Epidural injection

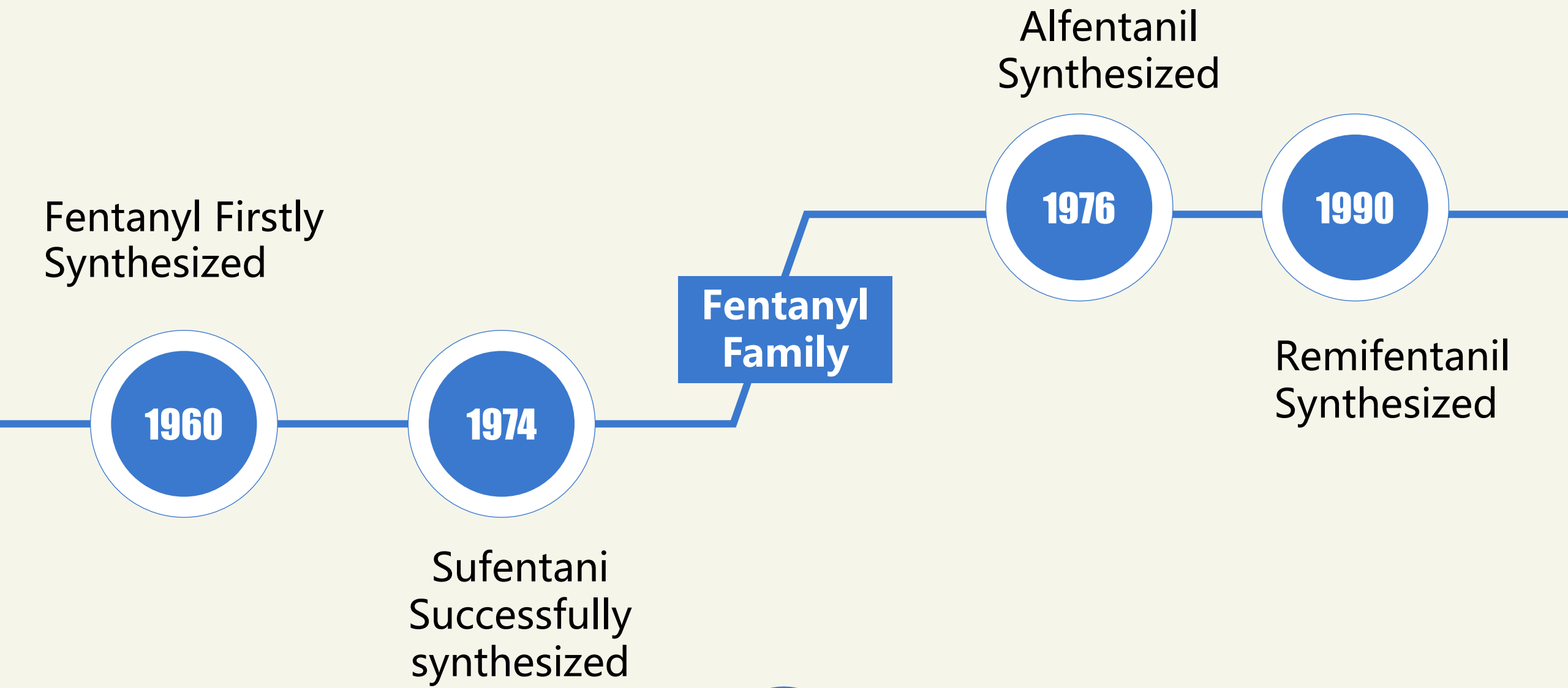
Self-control analgesia

PCIA
PCEA
PCSA
PCRA

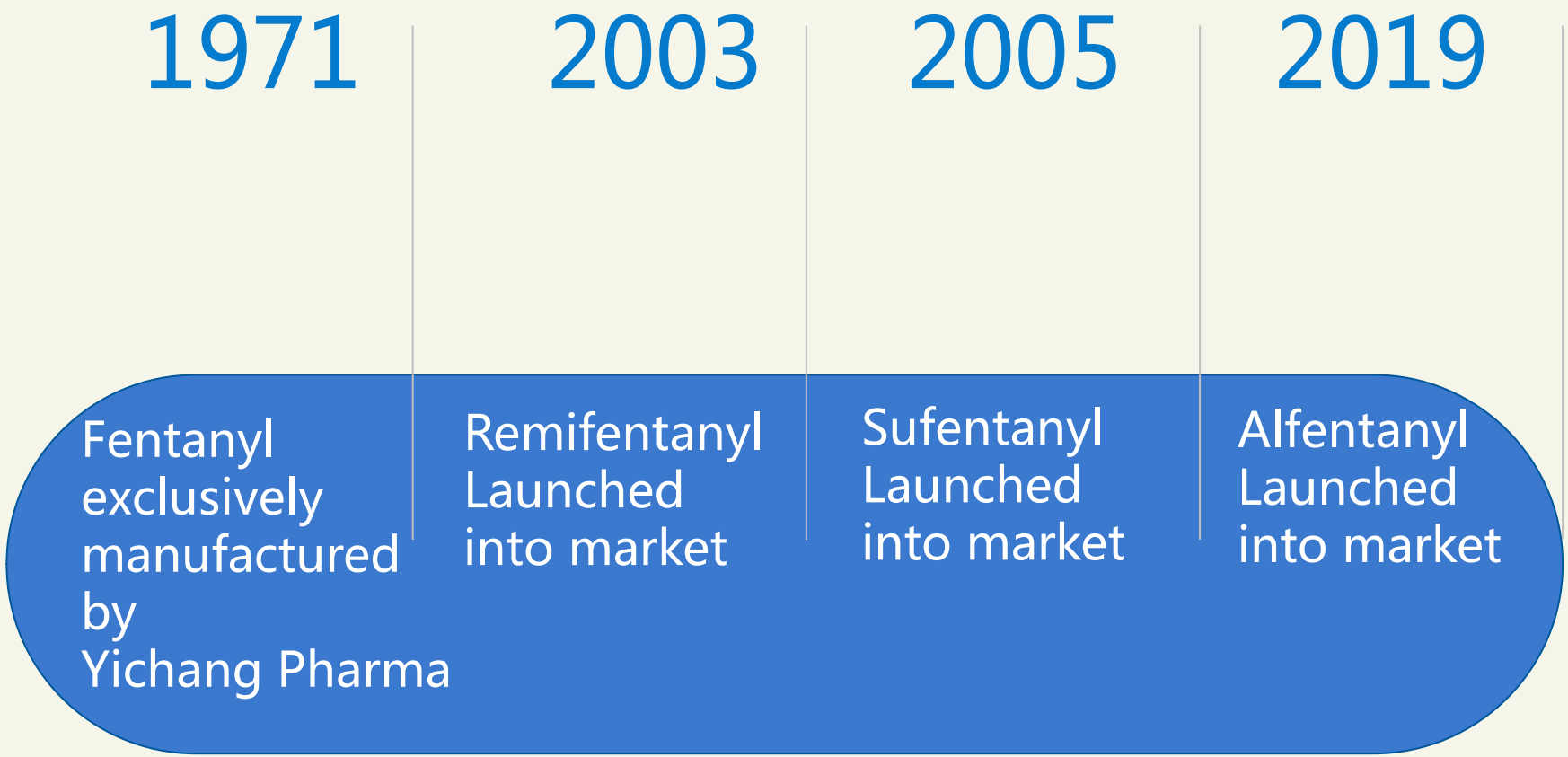
Multi-mode analgesia

Multi-drug delivery
Multi-method delivery

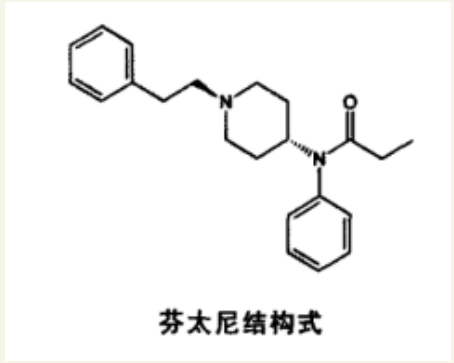
1.3 Fentanyl Family



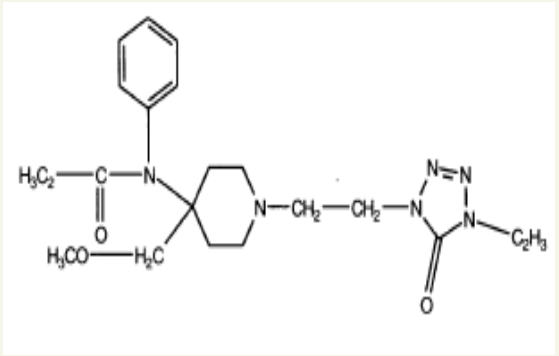
1.3 Fentanyl Family Marketed in China



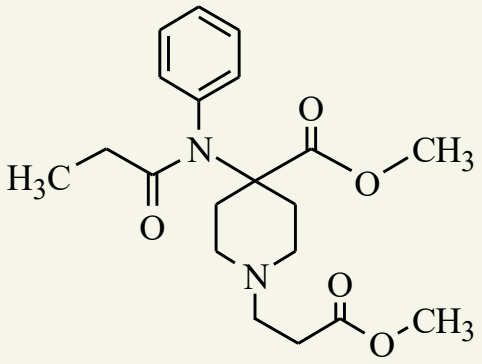
1.3 Fentanyl Family



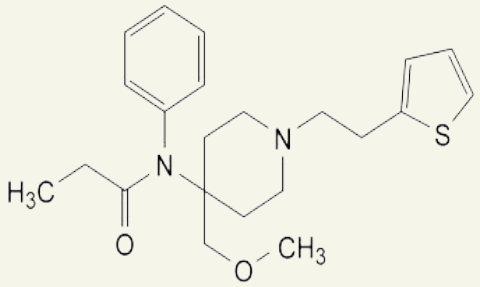
芬太尼结构式



Alfentanil



Remifentanil



Sufentanil

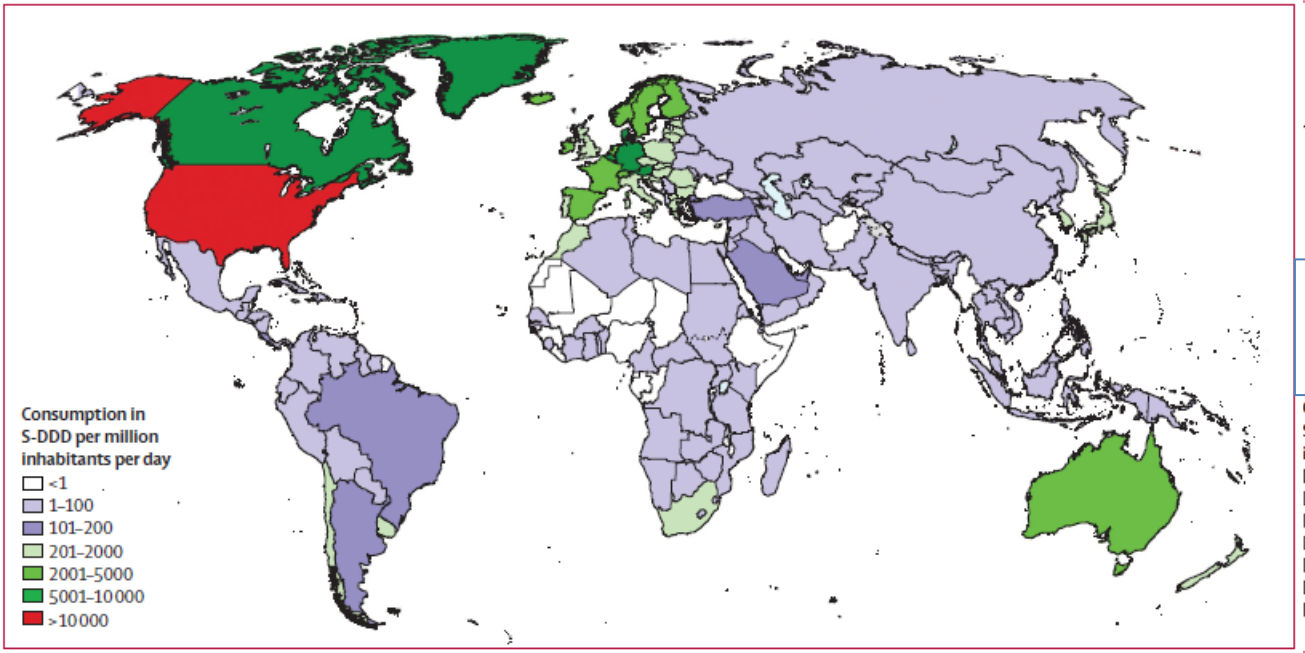
Types and characteristics of opioids receptor

Receptor	function
μ (μ_1)	To create analgesia and sedation on spinal cord
(μ_2)	Adverse events such as respiratory depression, apnea , addiction, illusion , etc.
κ	Analgesia and sedation on spinal cord, diuresis, dysphoria
δ	Antidepressant effects, convulsant effects , analgesia
σ	Anxiety, depression, appetite,
ε	release of met-enkephalin

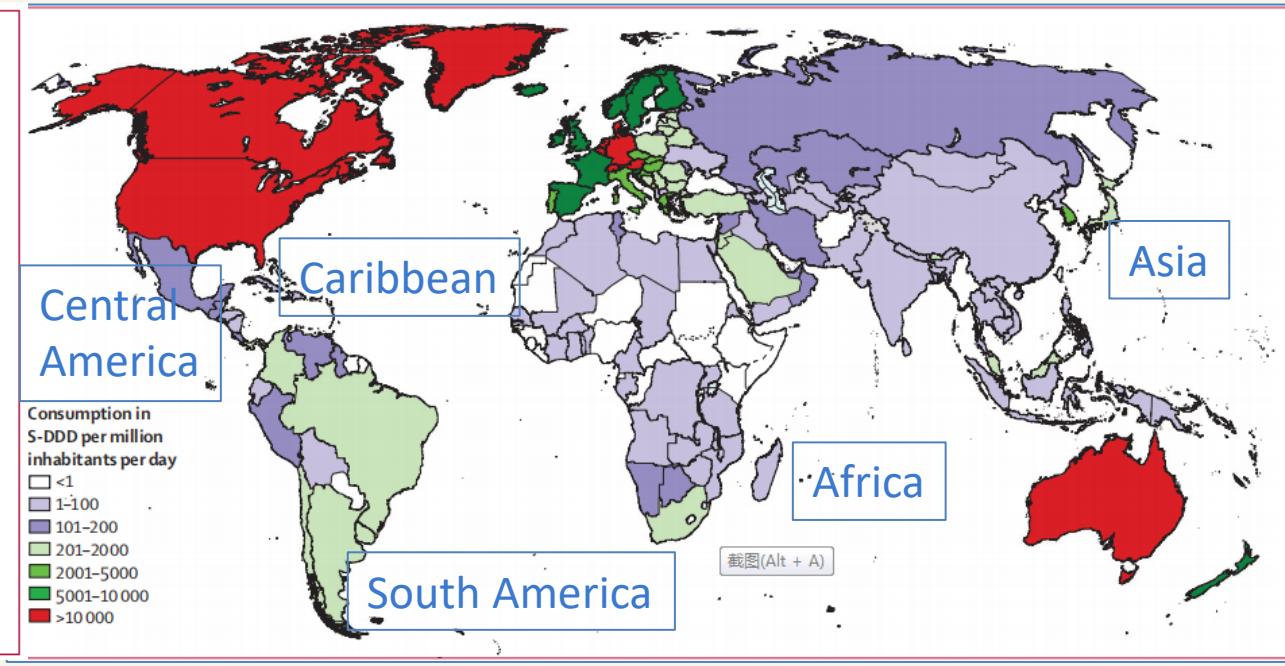
Climcal PharmacokInetics 8: 422-446 (1983)

1.4 Opioid Drug Application Status

2001–03



2011–2013

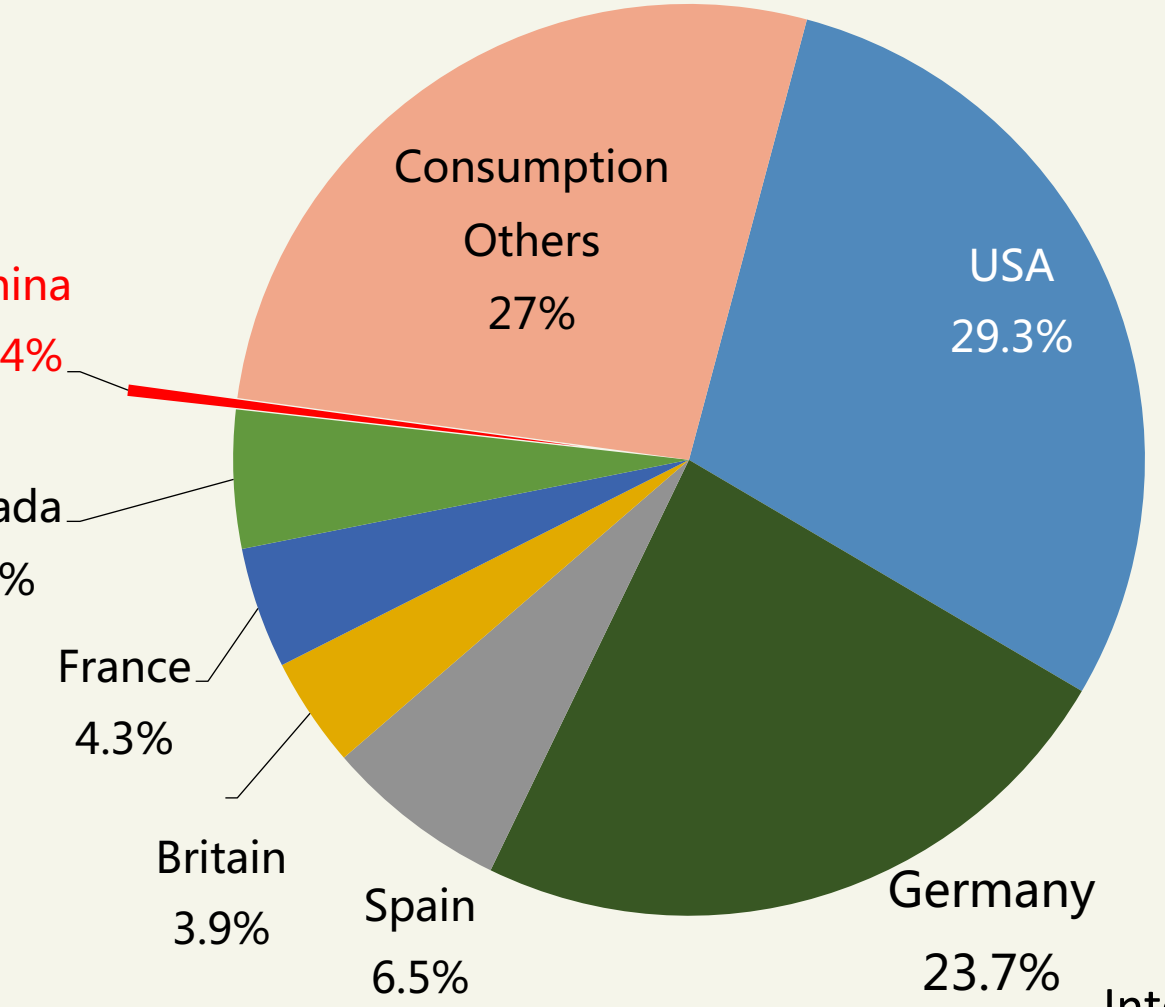


Mean availability of opioids for pain management

Use of opioid analgesics has increased, but remains low in Africa, Asia, Central America, the Caribbean, South America, and eastern and southeastern Europe.

Berterame D S. Lancet, 2016, 387(10028):1644-1656.

1.4 Opioid Drug Application Status



Fentanyl consumption

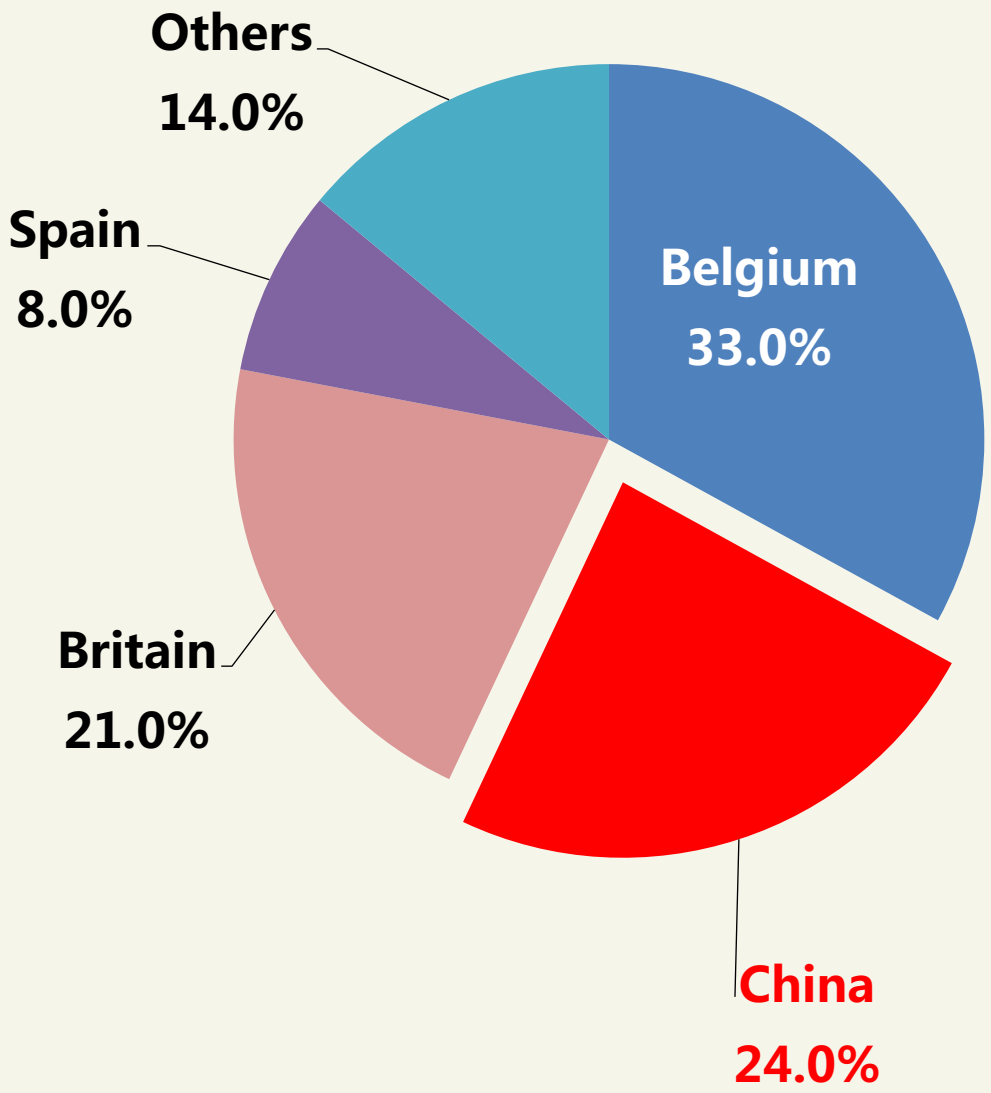
Of 2015 is 1600kg all over the world.

USA consumed 468.8kg, takes 29.3%.

China consumed 6.2kg, takes 0.4%.

International Narcotics Control Board （INCB）Report 2016

1.4 Opioid Drug Application Status



Remifentanil consumption

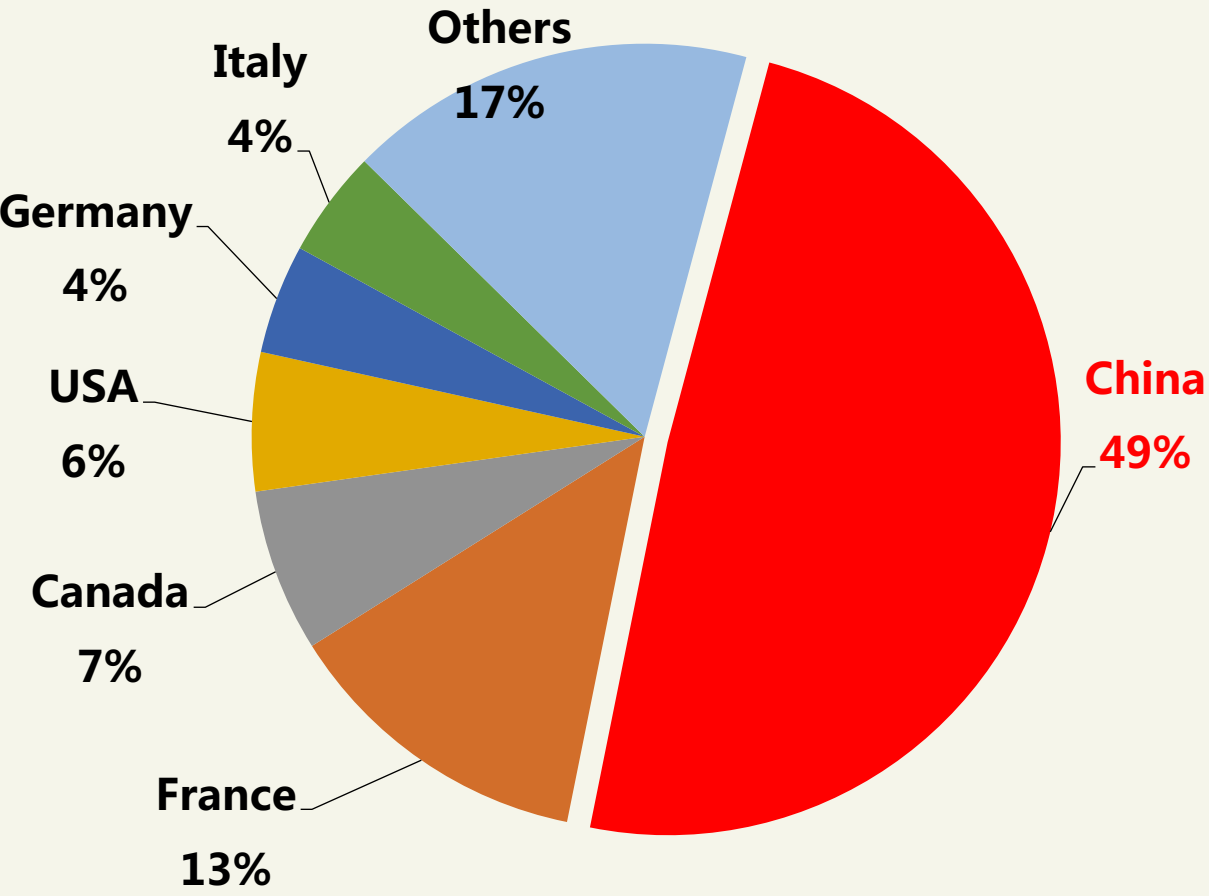
Of 2015 is 73kg all over the world.

Belgium consumed 24kg, takes 33%.

China ranked No.2, takes 24%.

International Narcotics Control Board（INCB）Report 2016

1.4 Opioid Drug Consumption



Sufentanil consumption

Of 2015 is 3kg all over the world.

China consumed 1.47kg, takes 49%.

France ranked No.2, takes 13%.

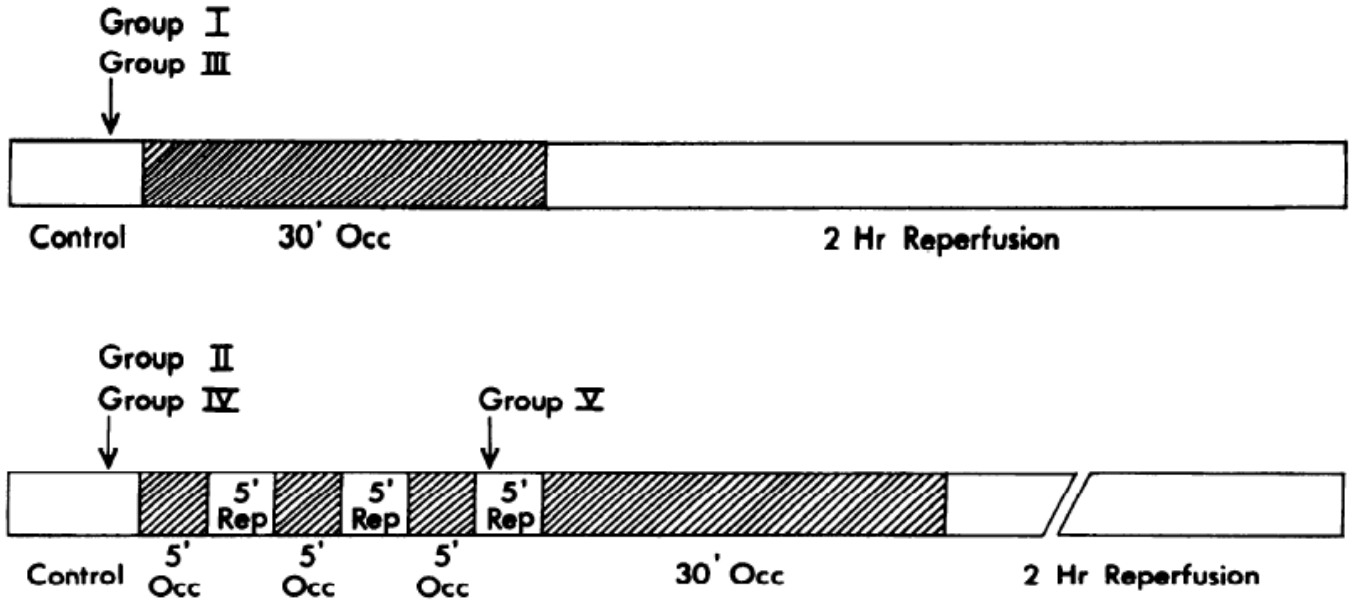
International Narcotics Control Board（INCB）Report 2016

TRANSITION PAGE

Organ Protection of Remifentanil and Sufentanil

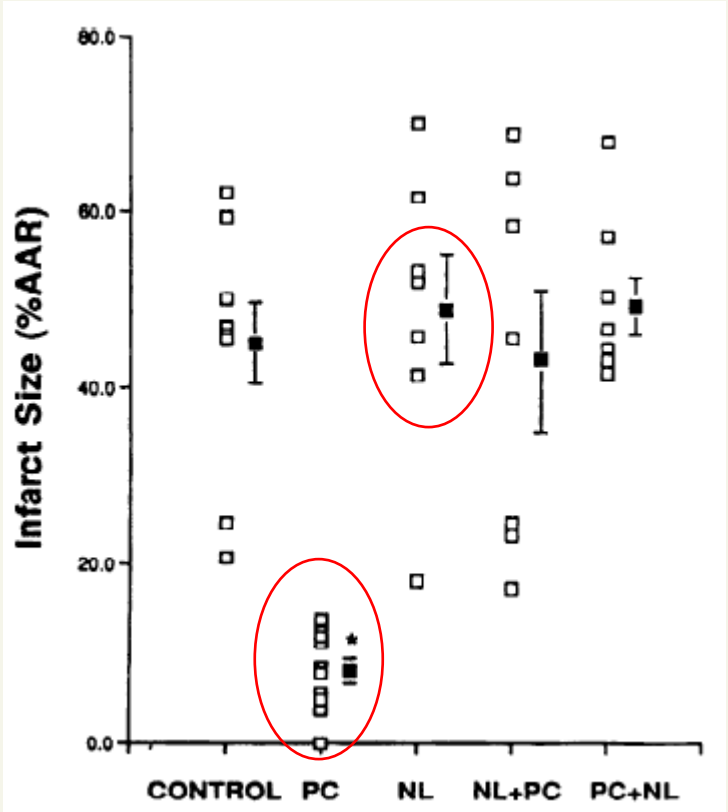
2.1 Discovery of Organ Protection by Opioid Drug

In 1995, Schultz discovered that opioid drug preconditioning has protective effects on cardiac ischemic.



Group Ⅰ : Control Saline
Group Ⅱ : PC
Group Ⅲ : NL (3mg/kg)
Group Ⅳ : NL (3mg/kg) + PC
Group Ⅴ : PC + NL (3mg/kg)

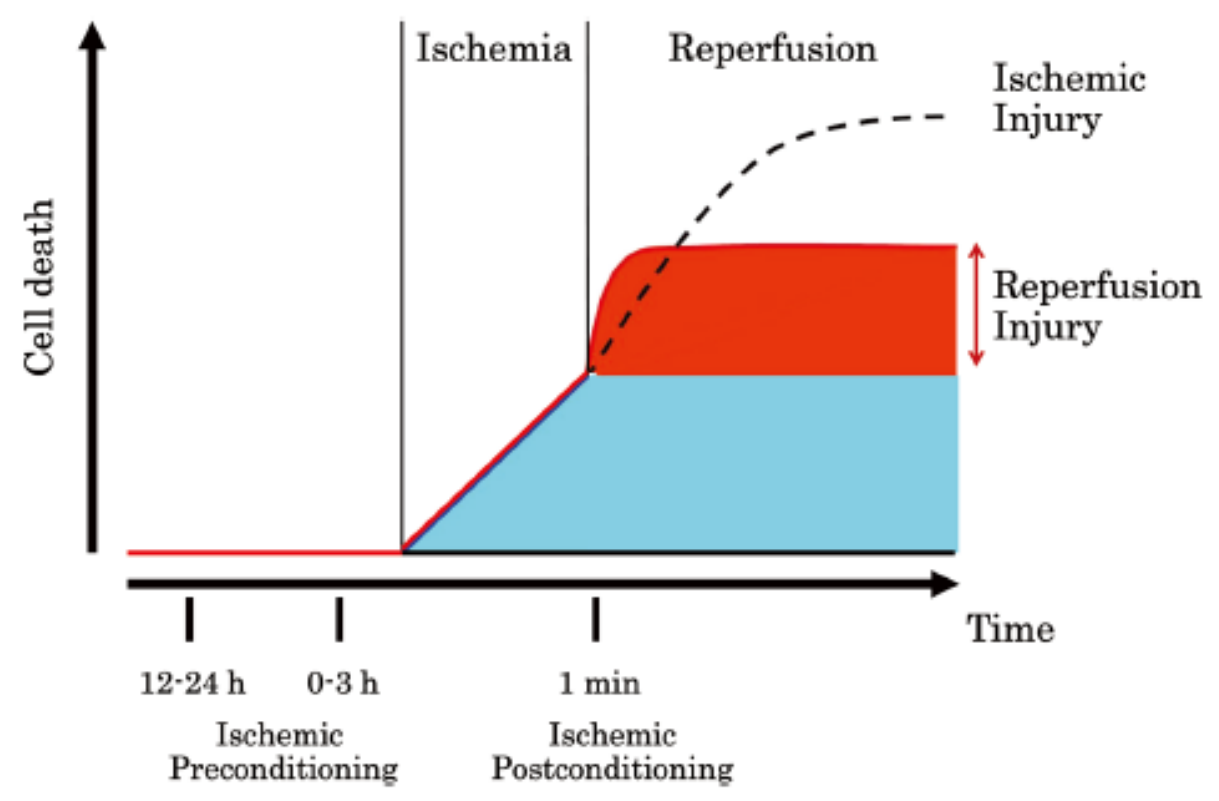
Fig. 1. Protocol bar indicating procedure of ischemic preconditioning (PC) study. NL, naloxone; Occ, occlusion; Rep, reperfusion.



Naloxone treatment before or immediately after PC abolished this protective effect

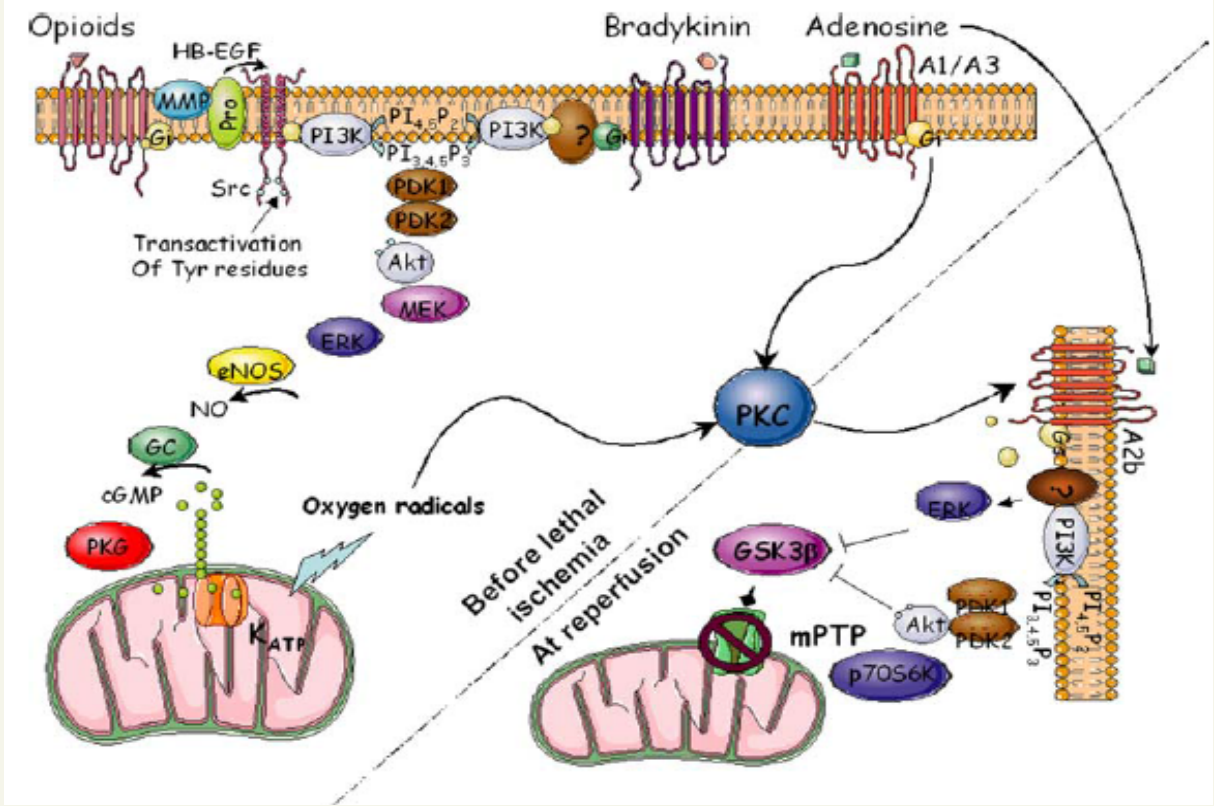
Schultz JJ. Am J Physiol. 1995;268:H2157-61

2.1 Discovery of Organ Protection by Opioid Drug



Myocardial ischemia/reperfusion (IR) injury and ischemic conditioning

Minamino T. Circulation，2012;76:1074-1082



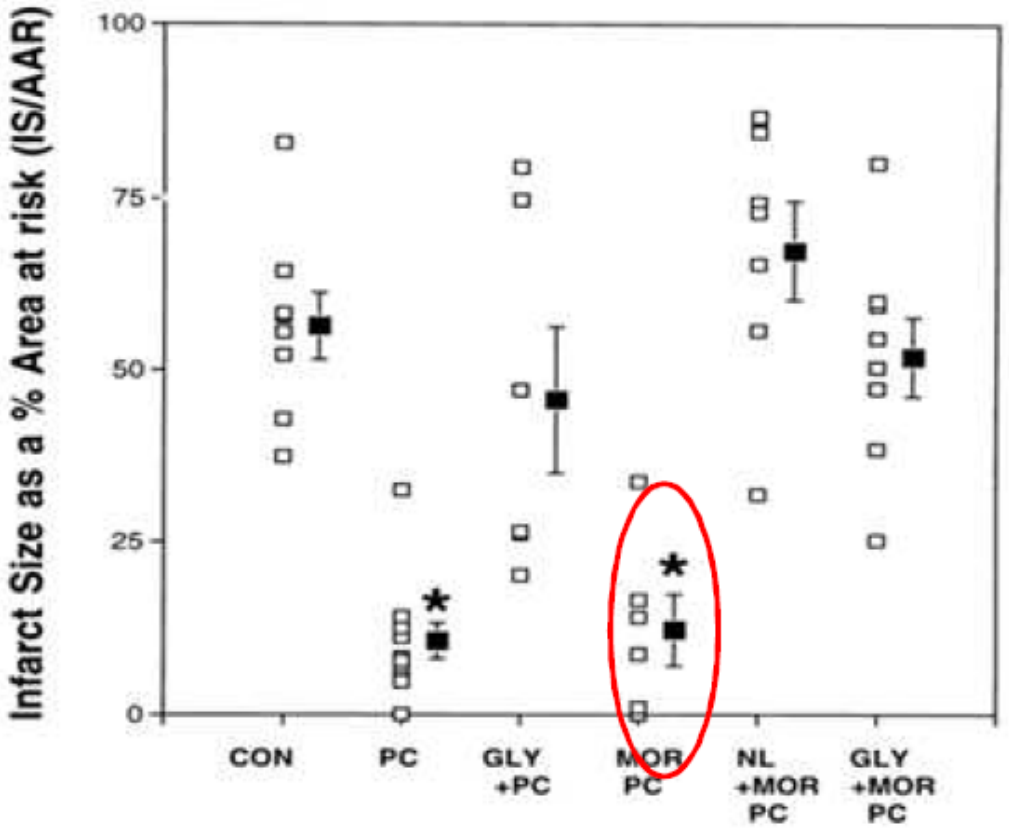
Signaling pathways involved in triggering the preconditioned state prior to the ischemic insult (events above the dividing line) and those that mediate protection in the first minutes of reperfusion (events below the dividing line).

Downey, J. M et al. Ann N Y Acad Sci，2008;1123:187-96

2.1 Discovery of Organ Protective Effects by Opioid Drug

Morphine Mimics the Cardioprotective Effect of Ischemic Preconditioning via a Glibenclamide-Sensitive Mechanism in the Rat Heart

Schultz, Jo El J.; Hsu, Anna K.; Gross, Garrett J.



PC : ischemic PC (group)
GLY : glibenclamide , a KATP channel antagonist,
MOR : morphine , a nonselective opioid receptor antagonist
NL : naloxone

In 1996, Schultz researched in anesthetized thoracotomy rats, 30 min for ischemia and then reperfusion for 120 min to simulate ischemic preconditioning to give morphine 100 μg/kg (total dose 300 μg/kg), and found that morphine can simulate ischemic preconditioning. The protective effect reduces the infarct area after cardiac ischemia.

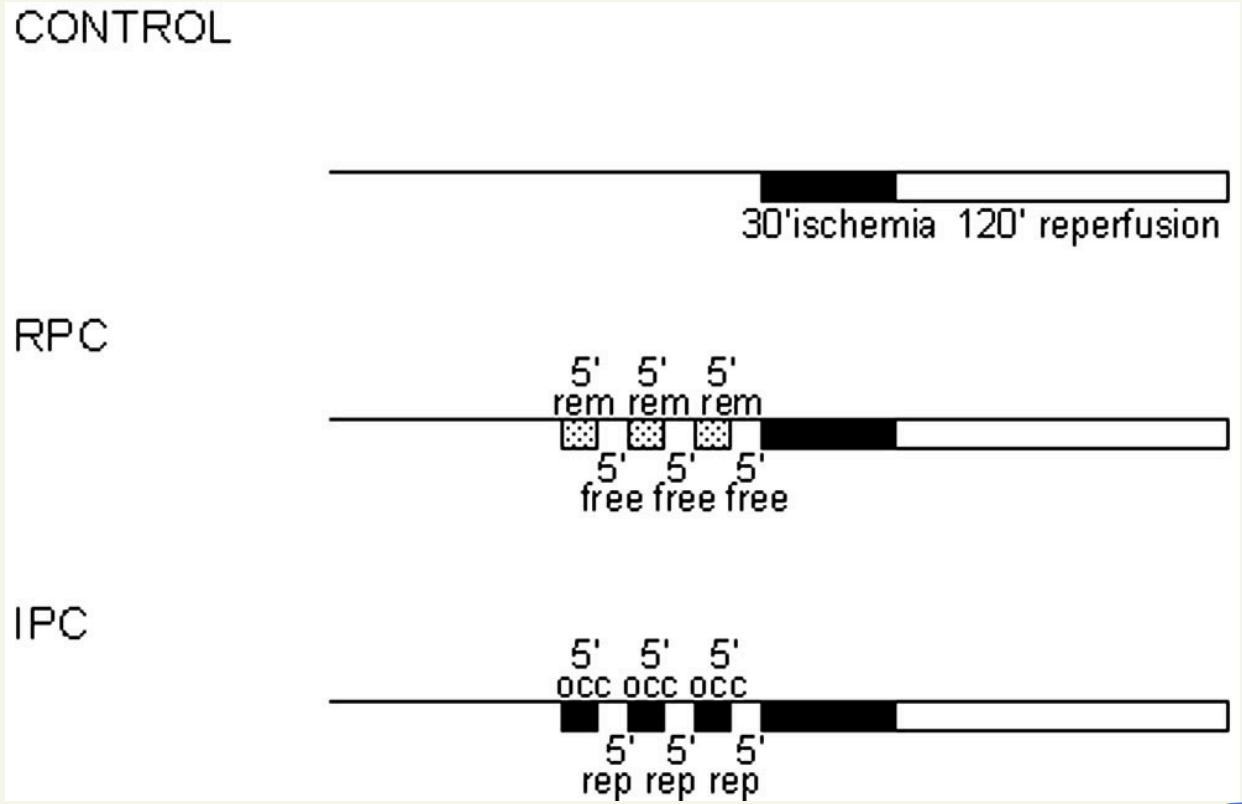
Schultz JJ. Circulation Research. 1996;78:1100-1104.

2.2 Heart – Organ Protective Effects of Remifentanil

Anesthesiology 2004; 101:918–23

Remifentanil Preconditioning Protects against Ischemic Injury in the Intact Rat Heart

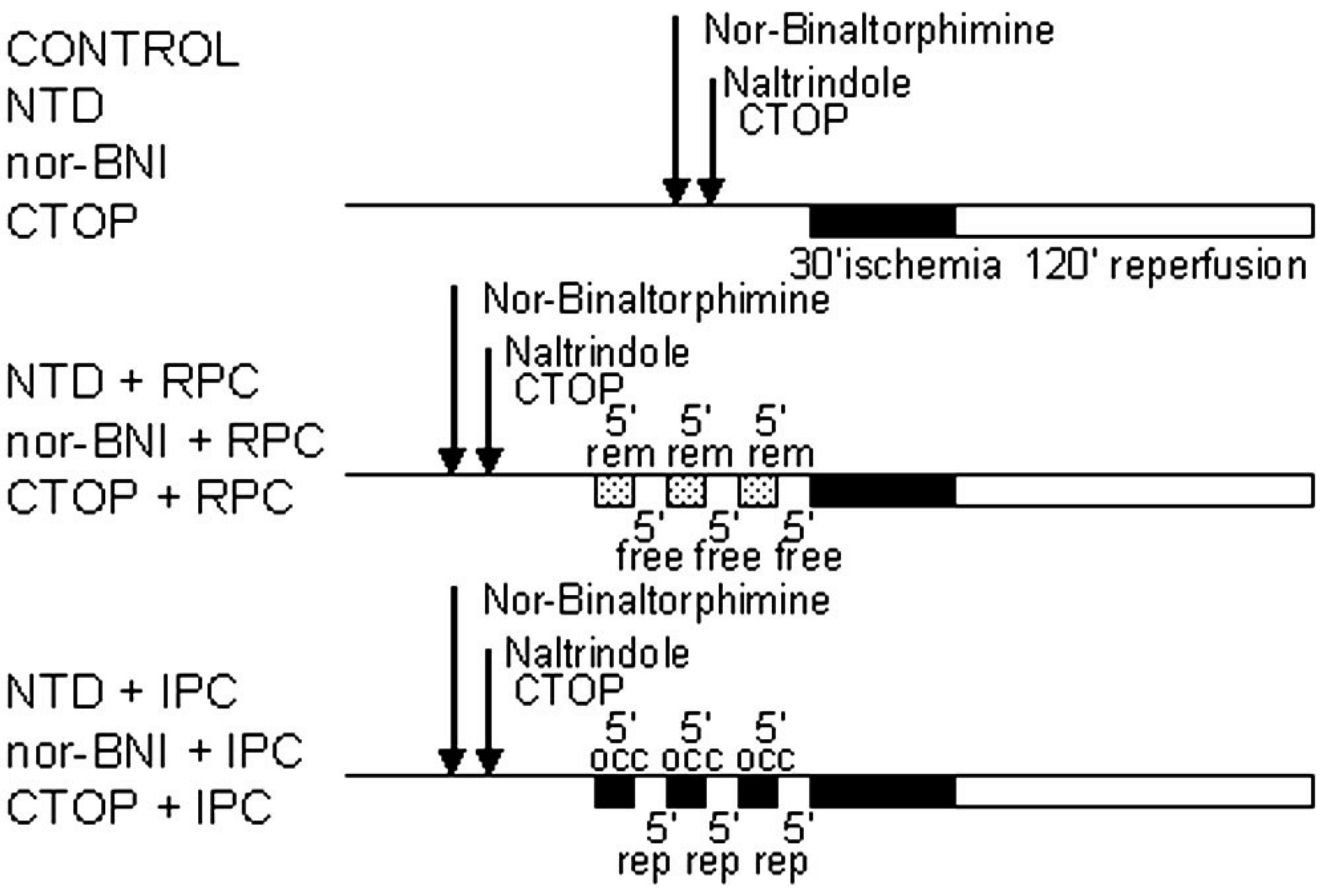
Ye Zhang M.D., Michael G. Irwin M.B., Ch.B., M.D., F.R.C.A., F.H.K.A.M.,† Tak Ming Wong, Ph.D.‡*



Male SD rats :
All group hearts were subject to 30 min of occlusion and120 min of reperfusion. Before ischemia, **ischemic preconditioning**(**IPC**) hearts were subject to three 5-min cycles of occlusion interspersed with 5 min of reperfusion, whereas **remifentanil preconditioning** (**RPC**) hearts were subject to three 5-min cycles of infusion of remifentanil (**0.2, 0.6, 2, 6, or 20 μg•kg^{-1}•min^{-1}**)interspersed with 5min drug-free periods.
Occ : occlusion ofthe left coronary artery;
rep : reperfusion;
rem : infusion of remifentanil,
free : drug-free periods.

Anesthesiology 2004; 101:918–23

2.2 Heart – Organ Protective Effects of Remifentanil



1.Control (CON, saline vehicle).

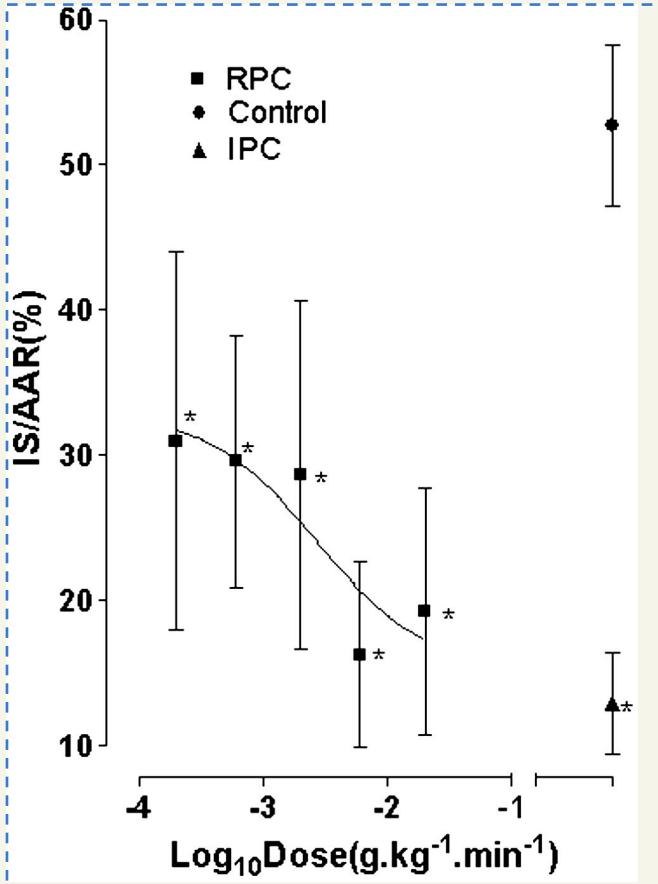
2. Naltrindole10 (**NTD, a selective δ-OR antagonist**) 5mg/kg intravenously 10 min before ischemia.

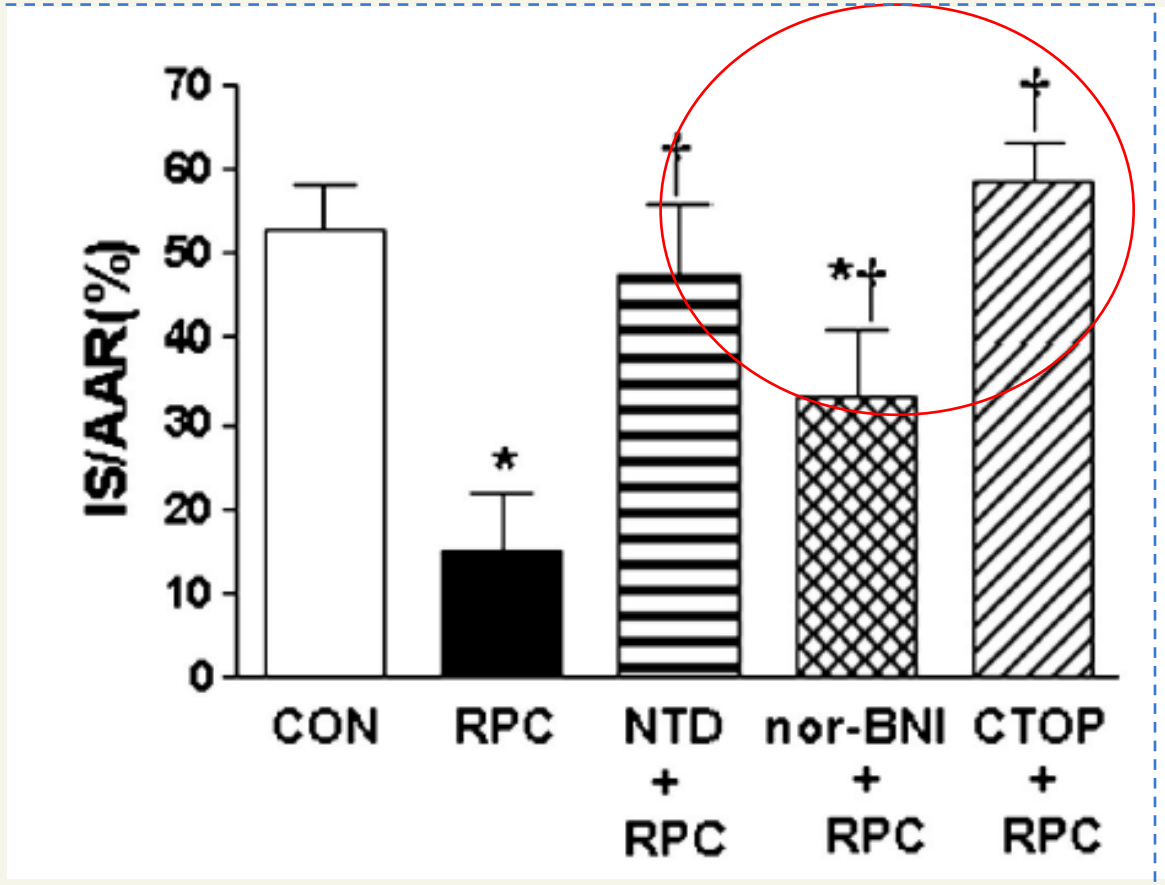
3. Nor-binaltorphimine11 (**nor-BNI, a κ-OR selective antagonist**) ,5 mg/kg intravenously 15 min before ischemia.

4. **CTOP: a μ-OR selective antagonist**, 1 mg/kg intravenously 10min before ischemia

Anesthesiology 2004; 101:918–23

2.2 Heart – Organ Protective Effects of Remifentanil





Results: There was a dose-related reduction in infarct size/area at risk after treatment with remifentanil that was similar to that seen with ischemic preconditioning. This effect was prevented or significantly attenuated by coadministration of a μ, κ, or δ-opioid antagonist.

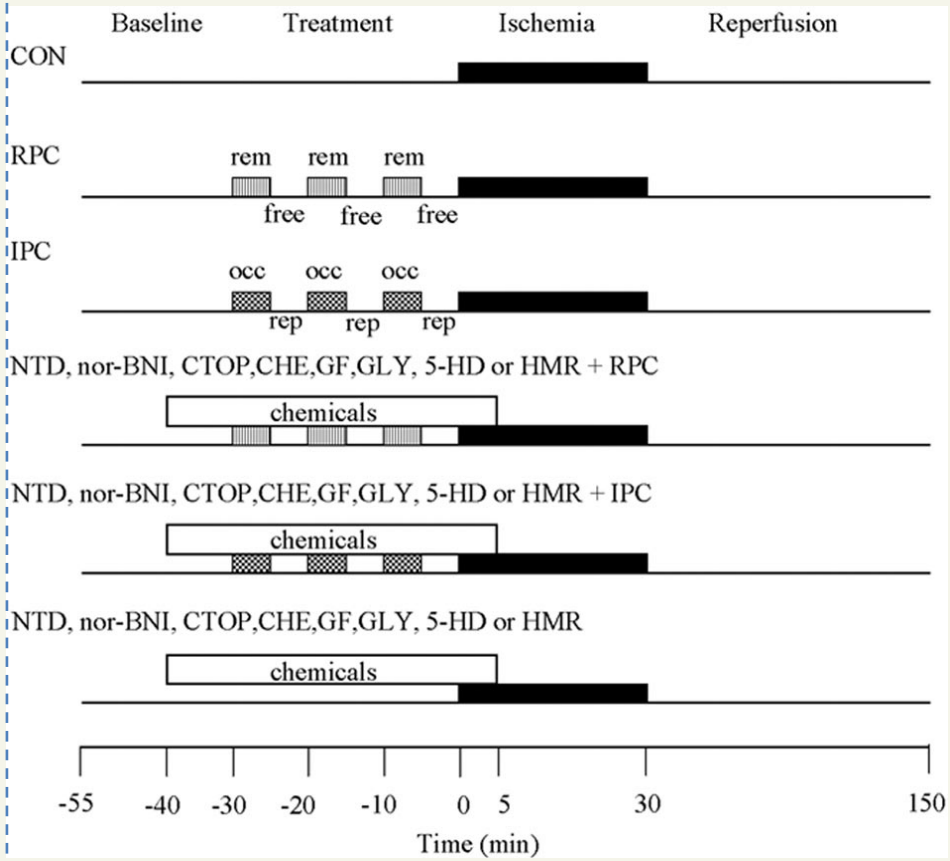
Anesthesiology 2004; 101:918–23

2.2 Heart – Organ Protective Effects of Remifentanil

Anesthesiology 2005; 102:371–8

Remifentanil Preconditioning Confers Cardioprotection via Cardiac κ- and δ-Opioid Receptors

Ye Zhang, M.D., Michael G. Irwin, M.B., Ch.B., M.D., F.R.C.A., F.H.K.A.M.,† Tak Ming Wong, Ph.D.,‡ Mai Chen, Ph.D.,§ Chun-Mei Cao, Ph.D.§*



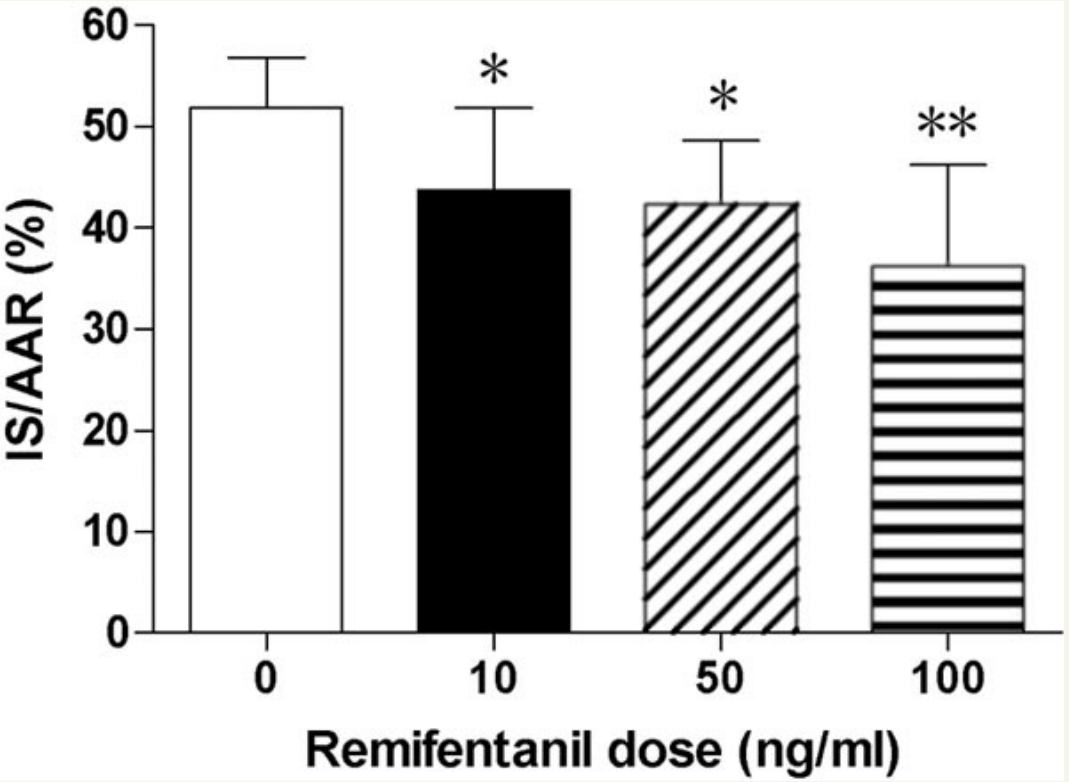
The heart of male Sprague-Dawley rats was removed immediately

- **Chelerythrine（CHE）and GF109203X（GF):** both protein kinase C inhibitors
- **5-Hydroxydecanoate（5-HD）**:a selective mitochondrial KATP channel blocker
- **glibenclamide (GLY):** Adenosine triphosphate–sensitive potassium channel blocker
- **HMR-1098** :a selective inhibitor of the sarcolemmal KATP channel

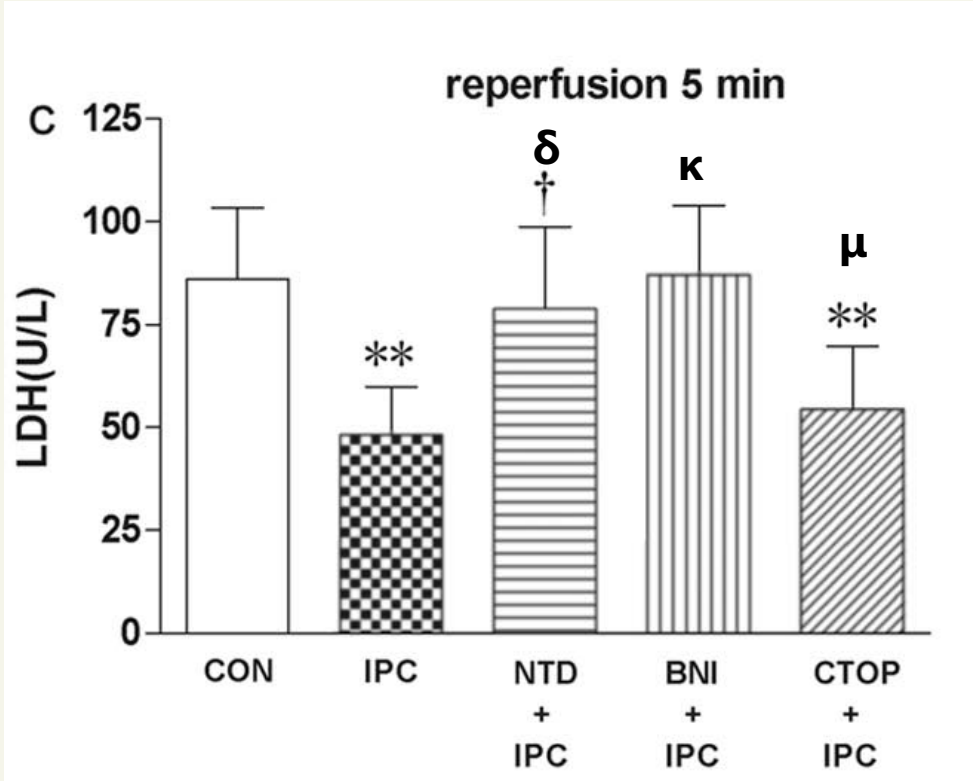
Anesthesiology 2005; 102:371–8

2.2 Heart – Organ Protective Effects of Remifentanil

Cardiac κ- and δ- but not μ-ORs mediate the cardioprotection produced by remifentanil preconditioning .



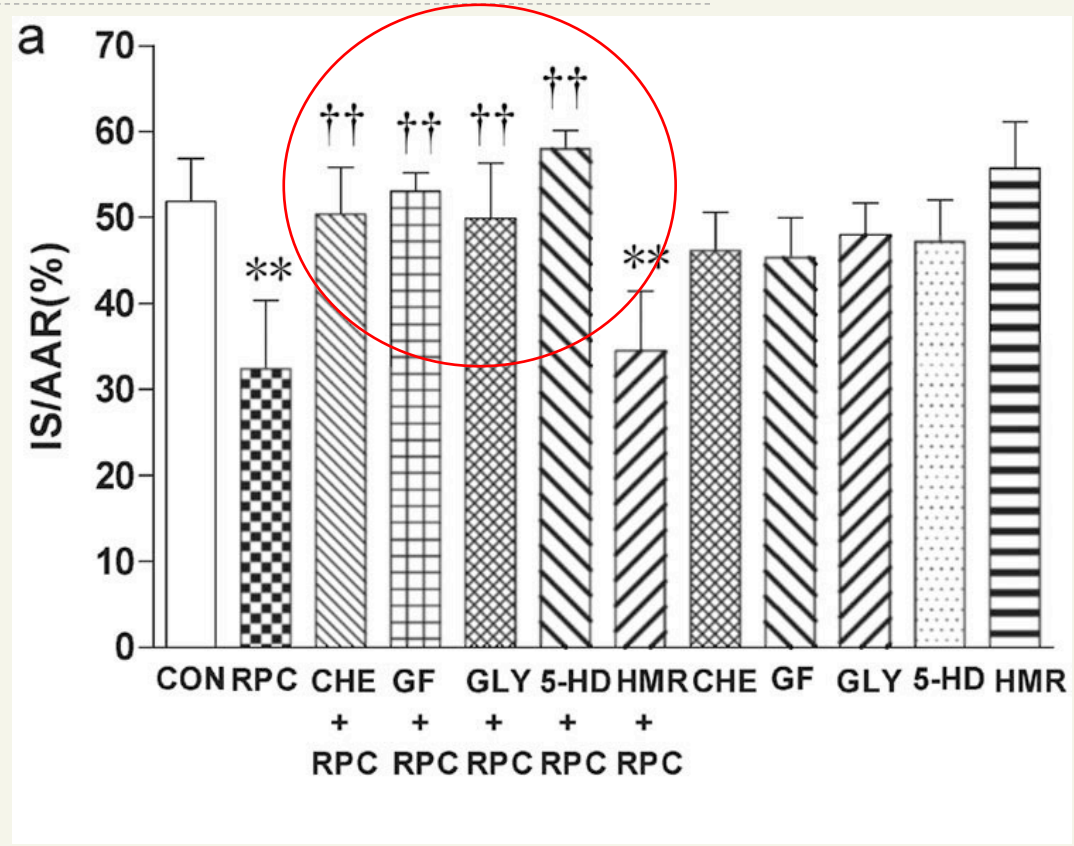
Effect of remifentanil preconditioning on infarct size, as a percentage of the area at risk (IS/AAR), concentration dependently

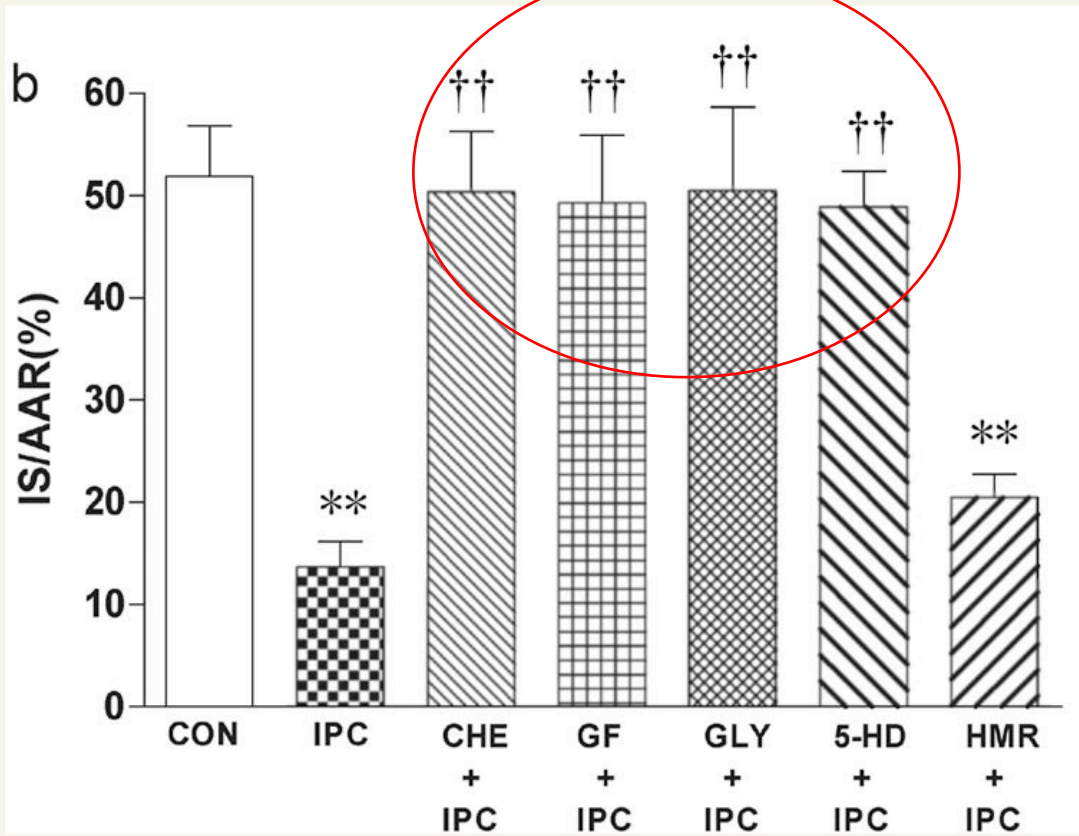


The effect of opioid antagonists on remifentanil preconditioning (RPC) or ischemic preconditioning (IPC). Lactate dehydrogenase (LDH) release in rat hearts

Anesthesiology 2005; 102:371–8

2.2 Heart – Organ Protective Effects of Remifentanil





Results：

- Both protein kinase C inhibitors abolished the effects of RPC or ischemic preconditioning
- 5-Hydroxydecanoate(a selective mitochondrial KATP channel blocker) also abolished the cardioprotection of RPC and IPC,
- HMR-1098 (a selective inhibitor of the sarcolemmal KATP channel) did not.

Anesthesiology 2005; 102:371–8

2.2 Brain – Organ Protective Effects of Remifentanil Preconditioning

Protective effects of remifentanil preconditioning on cerebral injury during pump-assisted coronary artery bypass graft

T.Z. Zhang, J. Zhou, Q. Jin, Y.J. Sun, Y.G. Diao, Y.N. Zhang and Z. Zhang

Department of Anaesthesiology, General Hospital of Shenyang Military Region, Shenyang City, Liaoning Province, China

40 patients are divided into 4 groups, R1, R2, and R3 and Control Group. Remifentanil (0.6, 1.2, and 1.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was respectively administered by intravenous infusion in the R1, R2, and R3 groups 30 min after anesthesia induction, and the remifentanil preconditioning was accomplished by intravenous infusion for 5 min, which was repeated three times at 5 min intervals. After the preconditioning, the operation was initiated.

Zhang T Z, Zhou J, Jin Q, et al. [J]. Genetics and Molecular Research, 2014, 13(3): 7658-7665.

2.2 Cerebral Injury – Organ Protective Effects of Remifentanil Preconditioning

Index	Group	T_0	T_1	T_2	T_3
S-100β protein (μg/L)	C group	0.104 ± 0.003	0.250 ± 0.061*	1.289 ± 0.194#	1.417 ± 0.193#
	R_1 group	0.096 ± 0.003	0.213 ± 0.043*	1.244 ± 0.142#	1.346 ± 0.144#
	R_2 group	0.102 ± 0.004	0.232 ± 0.091*	1.184 ± 0.183#	1.333 ± 0.171#
	R_3 group	0.100 ± 0.003	0.246 ± 0.046*	0.918 ± 0.187#Δ	1.079 ± 0.150#Δ
SOD (U/mL)	C group	111 ± 13	101 ± 9*	80 ± 5#	69 ± 7#
	R_1 group	111 ± 13	104 ± 15*	81 ± 7#	73 ± 7#
	R_2 group	110 ± 15	101 ± 14*	82 ± 10#	74 ± 9#
	R_3 group	106 ± 10	100 ± 9*	90 ± 6#Δ	83 ± 8#Δ
MDA (nmol/mL)	C group	4.8 ± 1.0	6.5 ± 1.4*	10.8 ± 1. 7#	12.5 ± 1.8#
	R_1 group	4.5 ± 1.2	6.3 ± 1.8*	10.9 ± 1.7#	12.4 ± 1.8#
	R_2 group	4.8 ± 1.3	6.4 ± 1.3*	10.6 ± 1.8#	12.8 ± 1.7#
	R_3 group	4.7 ± 1.0	6.3 ± 1.2*	8.7 ± 1.5#Δ	10.4 ± 1.4#Δ

*$P < 0.05$, #$P < 0.01$ *vs* T_0 time point, Δ$P < 0.05$ *vs* group C. Data are reported as means ± SD.

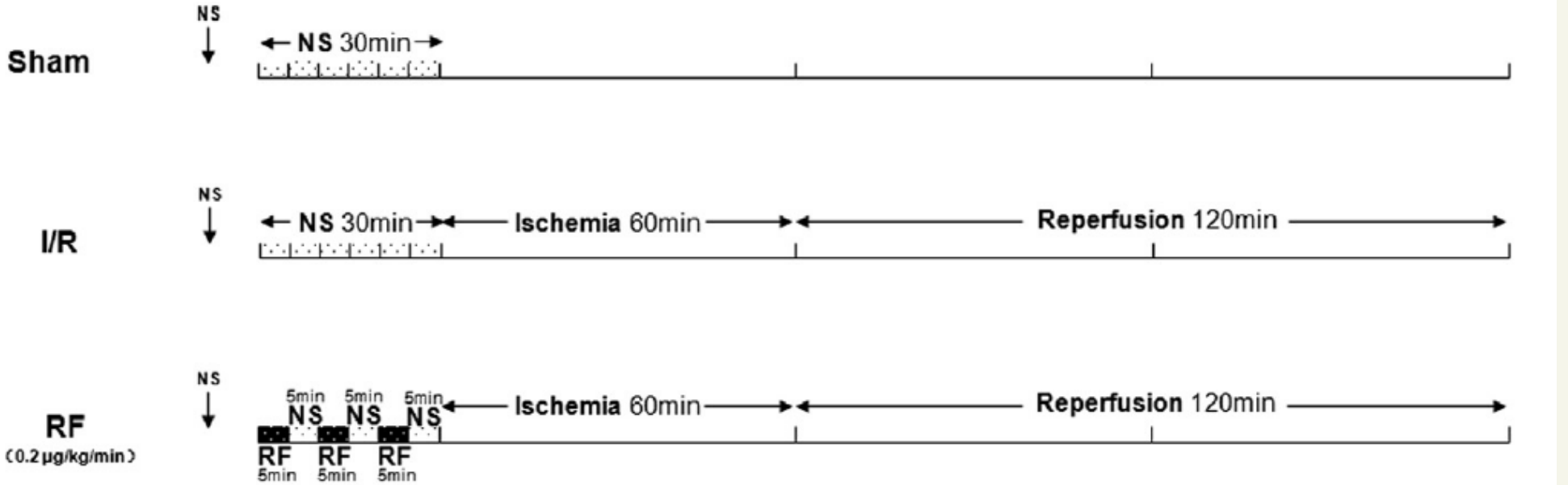
The remifentanil preconditioning at 1.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ decreased S-100β protein and the MDA concentration ,and increased plasma SOD activity.

Zhang T Z, Zhou J, Jin Q, et al. [J]. Genetics and Molecular Research, 2014, 13(3): 7658-7665.

2.2 Small Intestine – Organ Protective Effects of Remifentanil

Remifentanil preconditioning protects the small intestine against ischemia/reperfusion injury via intestinal δ- and μ-opioid receptors

Jian-Tong Shen, MD, Yun-Sheng Li, MD, Zhi-Qiu Xia, MD, Shi-Hong Wen, MD, Xi Yao, MD,



NS, normal saline;

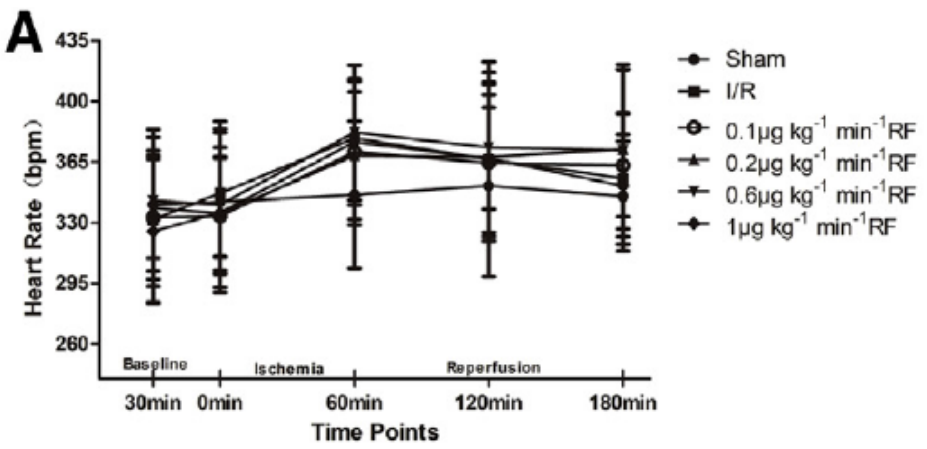
RF, remifentanil;

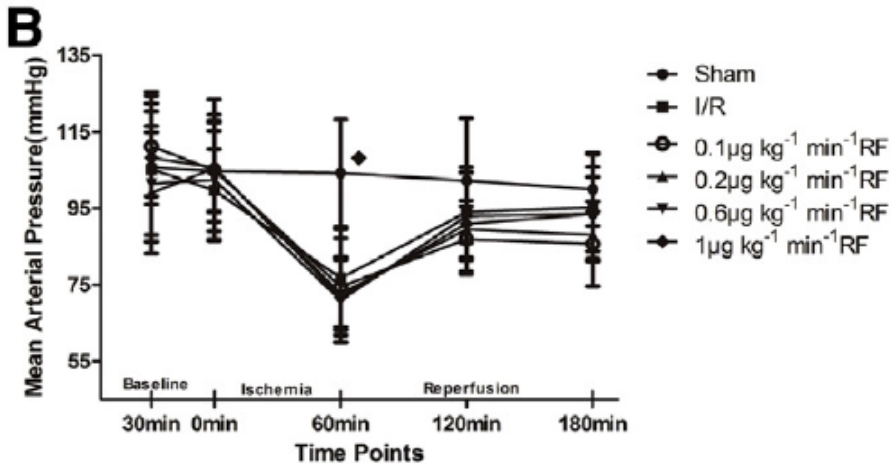
$0.1\mu g\ kg^{-1}\ min^{-1}$RF
$0.2\mu g\ kg^{-1}\ min^{-1}$RF
$0.6\mu g\ kg^{-1}\ min^{-1}$RF
$1\mu g\ kg^{-1}\ min^{-1}$RF

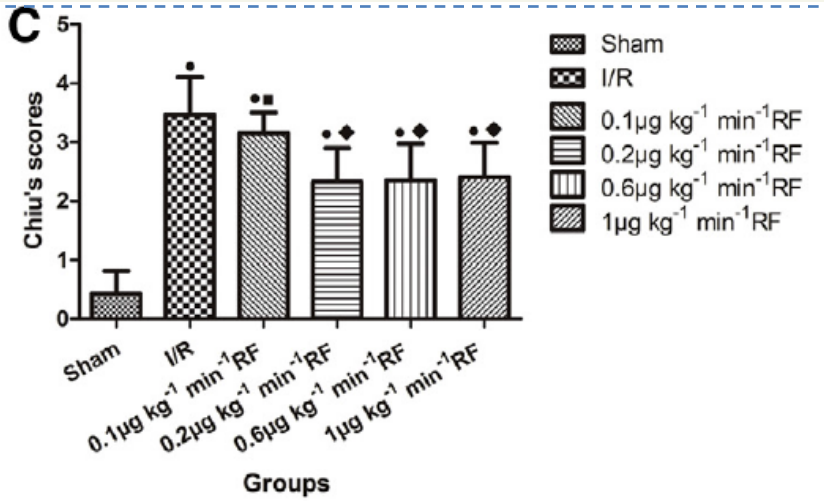
Surgery 2016;159:548-59.

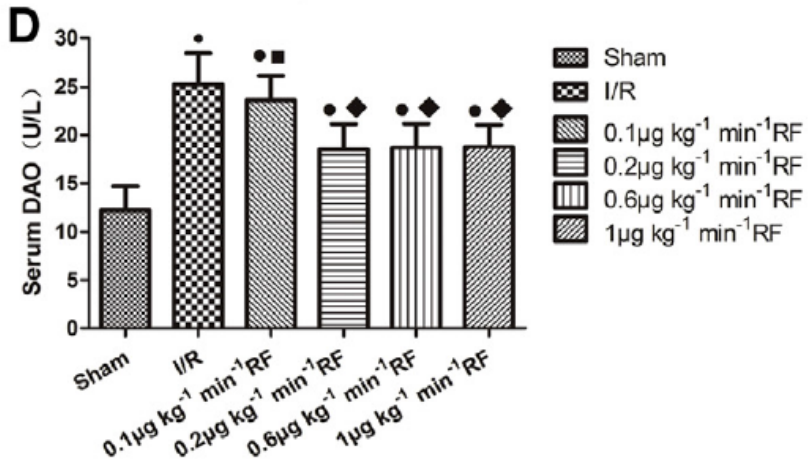
2.2 Small Intestine – Organ Protective Effects of Remifentanil

Effects of different doses of remifentanil preconditioning on HR (A), MAP (B), and intestinal I/R-induced intestinal injury (C–J) in vivo.





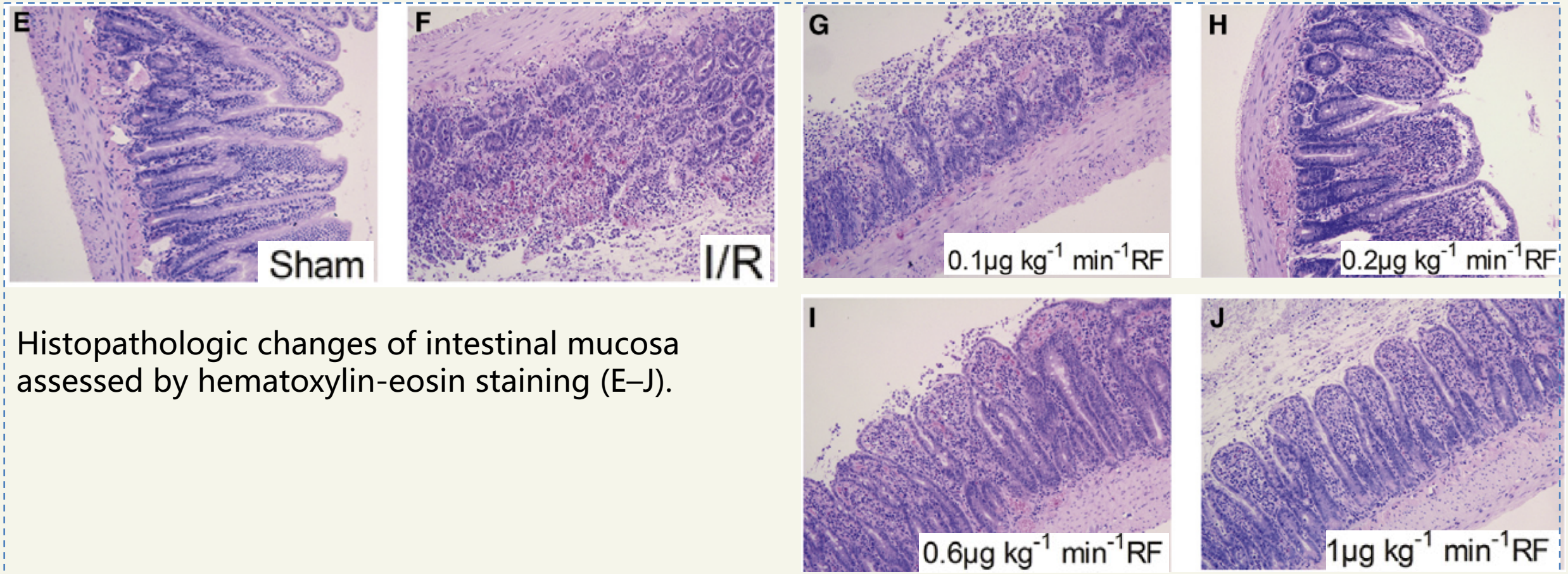




- Intestinal I/R induced obvious intestinal injury as evidenced by increases in the Chiu score, serum diamine oxidase activity,
- Remifentanil reconditioning significantly improved these changes

Surgery 2016;159:548-59.

2.2 Small Intestine – Organ Protective Effects of Remifentanil



Histopathologic changes of intestinal mucosa assessed by hematoxylin-eosin staining (E–J).

- In the I/R group (F), severe edema ofmucosal villi and injury of intestinal glands accompanied with infiltration of inflammatory cells were observed
- **Remifentanil preconditioning protect the small intestine from intestinal I/R injury**

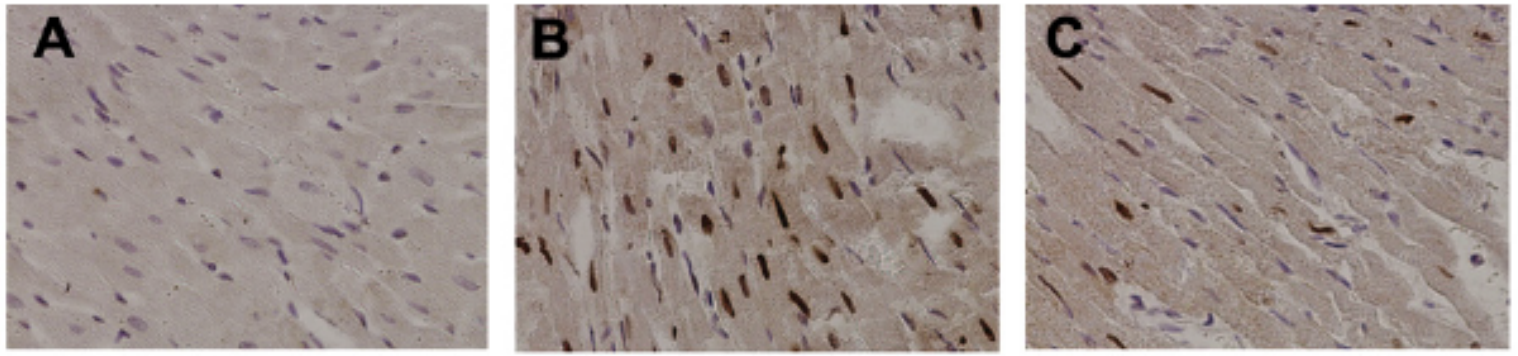
Surgery 2016;159:548-59.

2.3 Myocardium - Organ Protective Effects of Sufentanil

Sufentanil postconditioning protects the myocardium from ischemia-reperfusion via PI3K/Akt-GSK-3β pathway

Qiao-ling Wu, PhD,[a] Tu Shen, MD,[b] Hong Ma, MD, PhD,[a] and Jun-ke Wang, MD, PhD[a,]*

[a] *Anesthesiology Department, First Hospital Affiliated With China Medical University, Shenyang, China*
[b] *Anesthesiology Department, First Hospital Affiliated With Liaoning Medical College, Jinzhou, China*



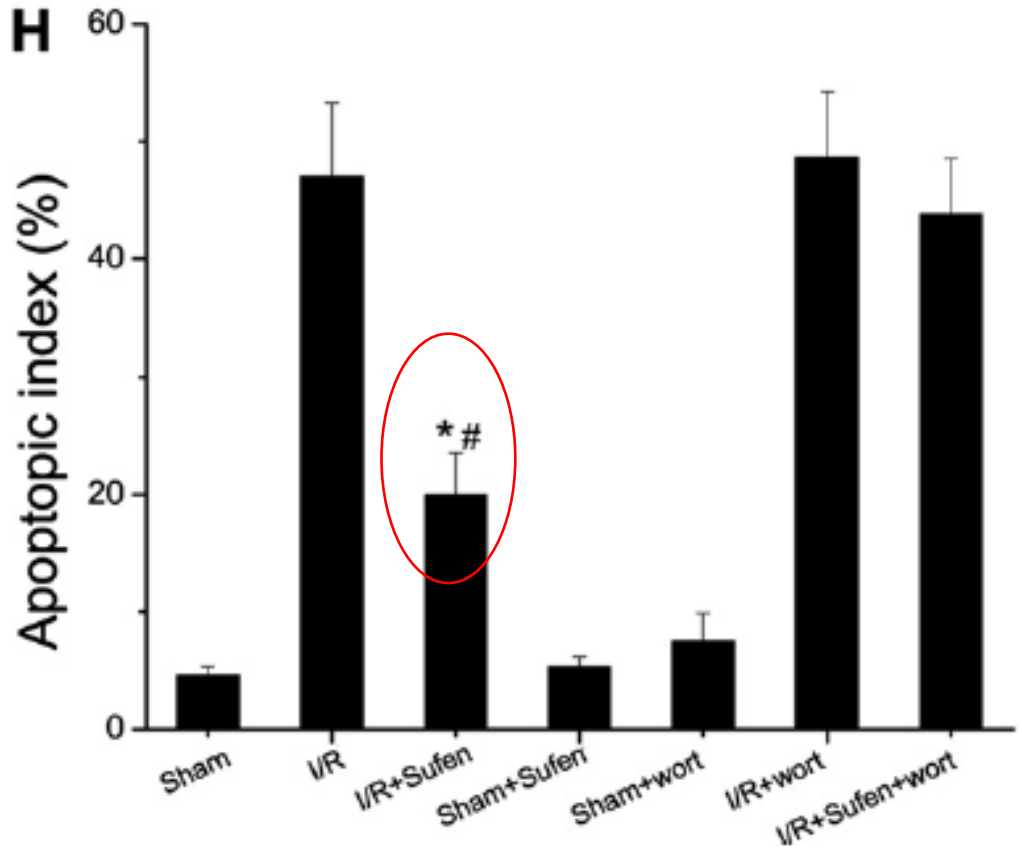
Sprague-Dawley rats

TUNEL staining (magnification 3400).
(A) Sham group.
(B) I/R group.
(C) I/R+sufen (3 μg/kg)group.

Sufentanil postconditioning can induce myocardial protection

Journal of surgical research 178(2012)563-570

2.3 Myocardium - Organ Protective Effects of Sufentanil



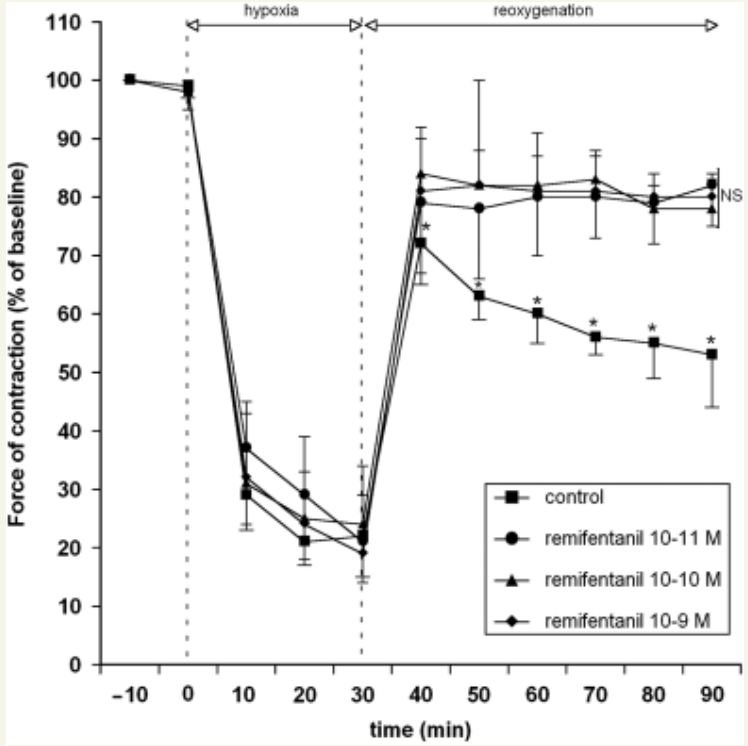
The apoptotic index of cardiomyocytes was significantly reduced with sufentanil treatment (20.0%) compared with the I/R group (47.0% ; $P < 0.05$).

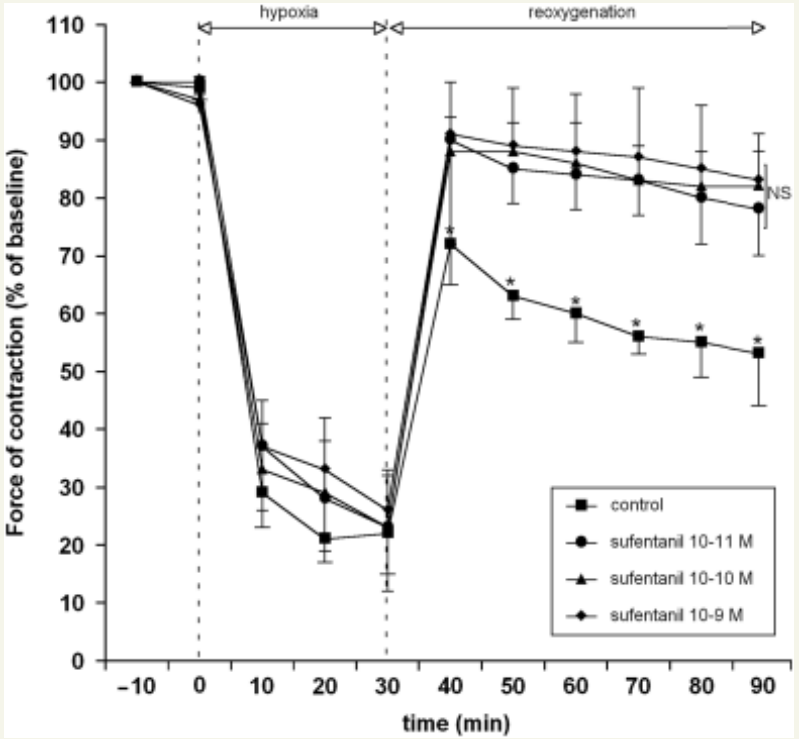
Journal of surgical research 178(2012)563-570

2.3 Myocardium - Organ Protective Effects of Sufentanil

Continuous administration of remifentanil and sufentanil induces cardioprotection in human myocardium, *in vitro*

S. Lemoine[1], L. Zhu[1], M. Massetti[2], J.-L. Gérard[1,3] and J.-L. Hanouz[1,3]





- isolated human right atrial trabeculae
- Remifentanil : 10^{-11}, 10^{-10}, 10^{-9}M
- sufentanil : 10^{-11}, 10^{-10}, 10^{-9}M

Remifentanil sufentanil & cardioprotection : Remifentanil and sufentanil enhanced the recovery of FoC as compared with the control group

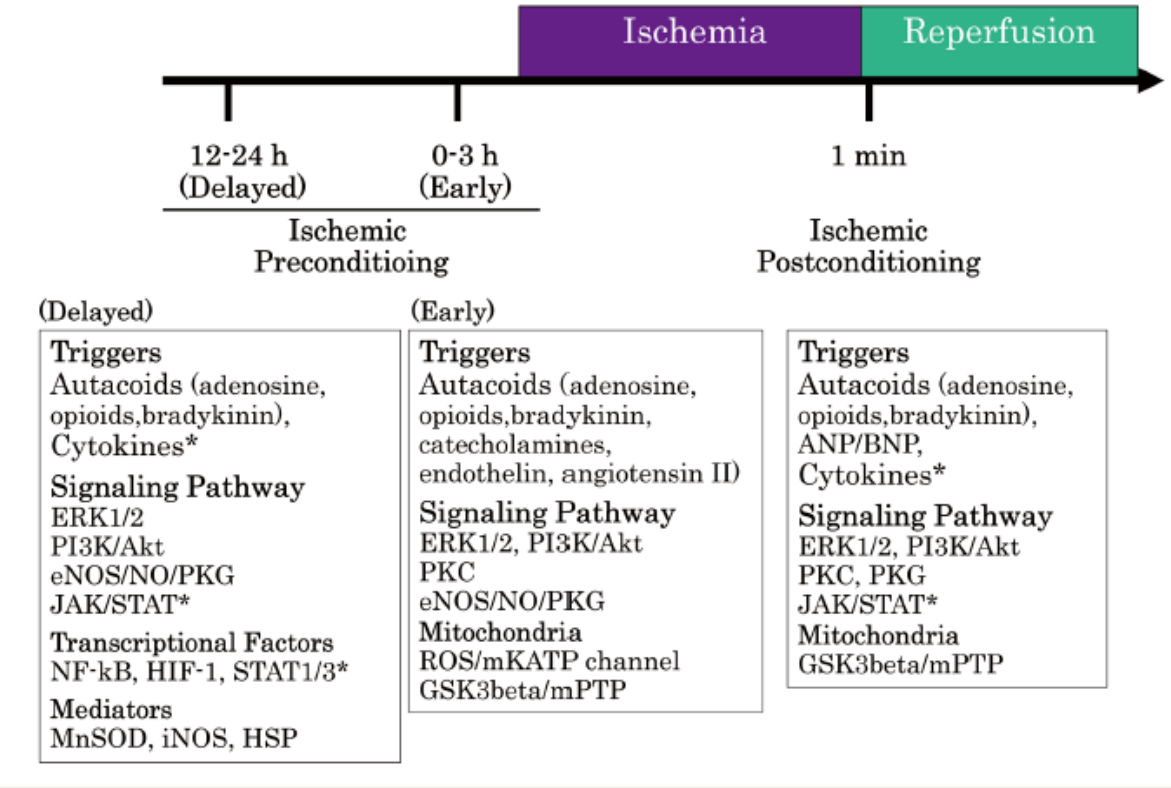
Acta Anaesthesiol Scand 2011; 55: 758–764

2.4 Summary - Organ Protective Effects

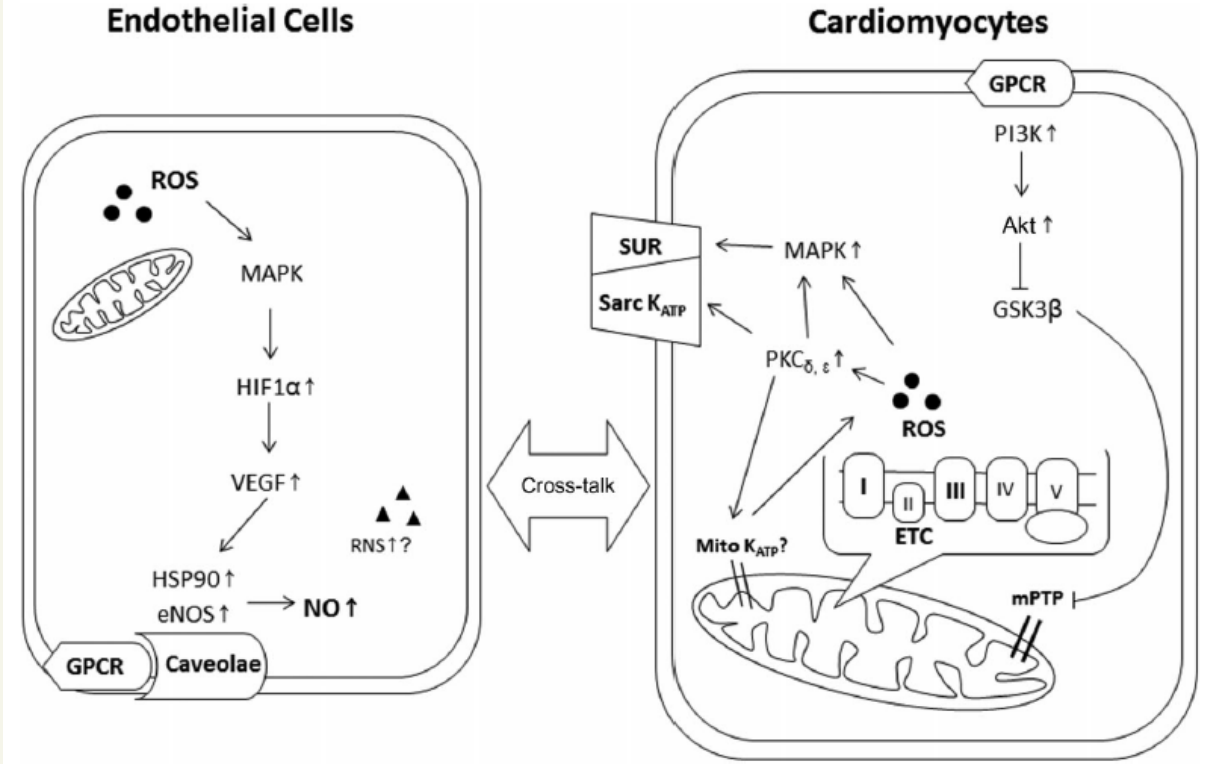
Drug	Dose	Organ	experimental subject
morphine	300μg/kg	heart	Male Wistar rats
remifentanil	0.2, 0.6, 2, 6, or 20 μg·kg^{-1}·min^{-1}*15min	heart	Sprague-Dawley rats
remifentanil	0.6, 1.2, and 1.8 μg·kg^{-1}·min^{-1}*15min	brain	patients
remifentanil	1 μg·kg^{-1}·min^{-1}*15min	small intestine	Sprague-Dawley rats
sufentanil	3 μg/kg	heart	Sprague-Dawley rats
remifentanil sufentanil	Remifentanil：2.7 ng/ml Sufentanil：2.6 ng/ml	right atrial trabeculae	patient

2.4 Summary - Organ Protective Effects

mechanism



(Delayed)	(Early)	
Triggers Autacoids (adenosine, opioids,bradykinin), Cytokines* **Signaling Pathway** ERK1/2 PI3K/Akt eNOS/NO/PKG JAK/STAT* **Transcriptional Factors** NF-kB, HIF-1, STAT1/3* **Mediators** MnSOD, iNOS, HSP	**Triggers** Autacoids (adenosine, opioids,bradykinin, catecholamines, endothelin, angiotensin II) **Signaling Pathway** ERK1/2, PI3K/Akt PKC eNOS/NO/PKG **Mitochondria** ROS/mKATP channel GSK3beta/mPTP	**Triggers** Autacoids (adenosine, opioids,bradykinin), ANP/BNP, Cytokines* **Signaling Pathway** ERK1/2, PI3K/Akt PKC, PKG JAK/STAT* **Mitochondria** GSK3beta/mPTP



Key elements of the pathways activated in anaesthetic-induced protection. Several autacoids play an essential role in "early" ischemic preconditioning. Upon binding to their respective receptors, autacoids activate intracellular signaling pathways.

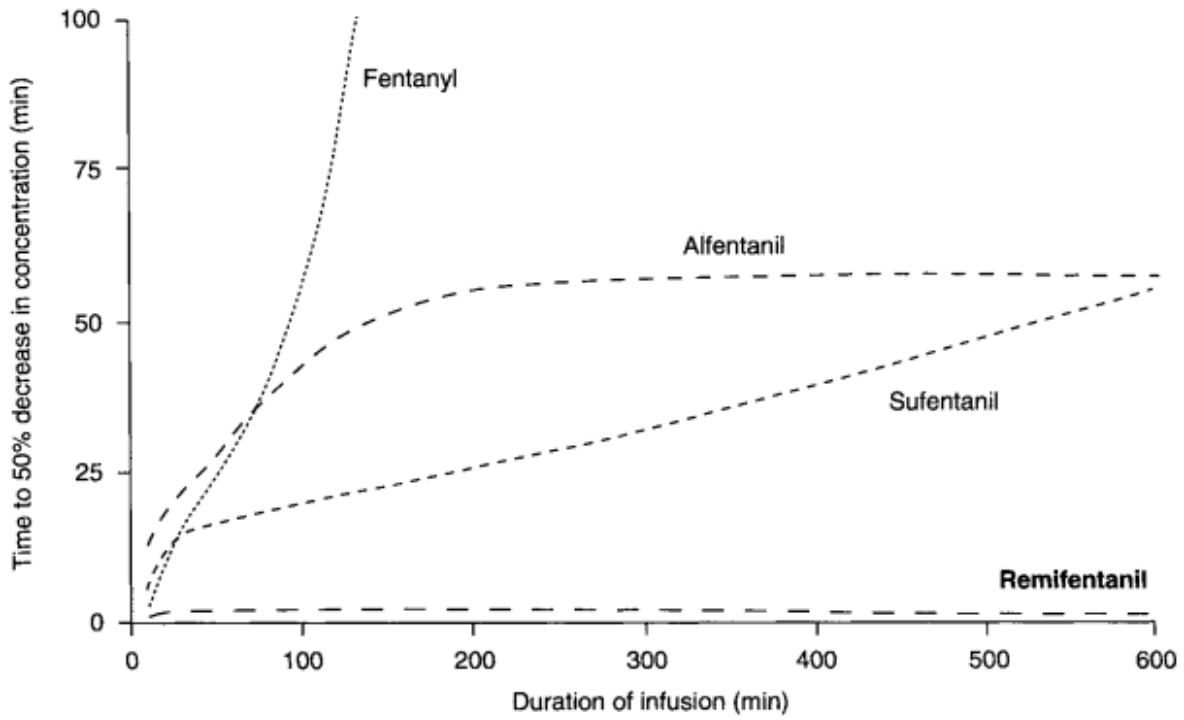
Circ J 2012;76: 1074 – 1082)
British Journal of Pharmacology (2015) 172 2051–2061

TRANSITION PAGE

New Opioid Anesthetic Remifentanil & Sufentanil

3.1 Clinical Application of Remifentanil & Sufentnail

Opioid anesthetics used for general anesthesia can not only reduce adverse reactions, but maintain stable anesthesia and reduce other combined anesthetics.
Remifentanil is often used for anesthesia maintainance and Sufentanil is the ideal analgesic.



- Drug accumulation will take place after long time infusion.
- Remifentanil has no accumulation issue even after 600 mins continuous infusion.

Clin. Pharmacokinet. 29 (2): 80-94, 1995

Proper usage of Remifentnail reduces death rate in operations

Effects of Remifentanil on In-Hospital Mortality and Length of Stay Following Clipping of Intracranial Aneurysm: A Propensity Score-matched Analysis

Kanji Uchida, MD, PhD, Hideo Yasunaga, MD, PhD,† Masahiko Sumitani, MD, PhD,* Hiromasa Horiguchi, PhD,‡ Kiyohide Fushimi, MD, PhD,§ and Yoshitsugu Yamada, MD, PhD**

It`s been researched that in brain tumor excision operations, patients group of Remifentanil has much lower death rate and shorter length of stay in hospital than the group of fentanyl.

The research includes 2760 patients, 1380 patients in Group of Remifentanil, 1380 patients in Group of Fentanyl.

Uchida K, Yasunaga H, Sumitani M, et al. [J]. Journal of neurosurgical anesthesiology, 2014, 26(4): 291-298.

In the study, the research results suggest that

Remifentanil is an independent factor in reducing mortality

	Remifentanil and Fentanyl (n = 1380)	Fentanyl Alone (n = 1380)	*P*
In-hospital death (n [%])			
Overall	58 (4.2)	106 (7.7)	< 0.001
Diagnosis and consciousness level			
Ruptured ICA with JCS grade 0	3/232 (1.3)	11/213 (5.2)	0.019
Ruptured ICA with JCS grade 1	19/234 (8.1)	20/229 (8.1)	0.812
Ruptured ICA with JCS grade 2	14/176 (8.0)	25/184 (13.6)	0.086
Ruptured ICA with JCS grade 3	22/186 (11.8)	49/216 (22.7)	0.004
Unruptured ICA	0/552 (0)	1/538 (0.2)	0.311

The results of a large number of experiment data shows that the mortality rate was 4.2% in the fentanyl + remifentanil group and 7.7% in the fentanyl group. There was a significant difference in mortality between the two groups. Remifentanil is an independent factor in reducing hospital mortality (odds ratio = 0.52; 95% confidence interval, 0.37-0.74; P < 0.001).

Uchida K, Yasunaga H, Sumitani M, et al. [J]. Journal of neurosurgical anesthesiology, 2014, 26(4): 291-298.

3.1 Clinical Application of Remifentanil & Sufentnail

Combination with sufentanil and remifentanil

Table 1: Patient demographics.

	C group ($N = 39$)	S group ($N = 39$)	P
Age (years)	40 ± 11	40 ± 13	0.802
Height (cm)	158 ± 6	160 ± 5	0.078
Weight (kg)	58 ± 9	59 ± 9	0.705
Smoking (pack × years)	0	0	—
Hx of motion sickness	1	4	0.358
Hx of PONV	0	0	—
Remifentanil (μg)	3891 ± 1581	3613 ± 976	0.352
Propofol (mg)	791 ± 375	721 ± 288	0.356
Anaesthesia time (min)	170 ± 61	156 ± 37	0.224
Surgery time (min)	137 ± 65	122 ± 36	0.210
Recovery time (min)	14 ± 4	15 ± 10	0.646
Surgical procedures			
Ovarian cystectomy	19	24	0.255
Uterine myomectomy	3	2	0.644
Vaginal hysterectomy	17	13	0.352

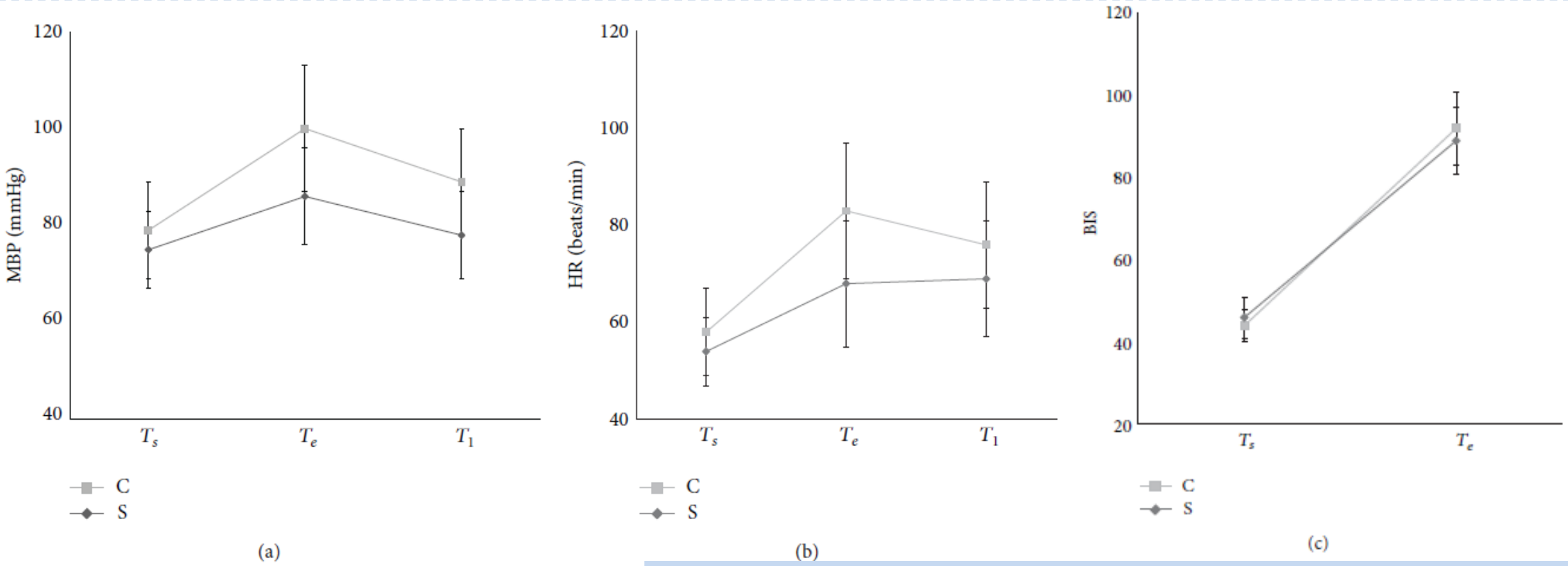
The Effect of Sufentanil Administration on Remifentanil-Based Anaesthesia during Laparoscopic Gynaecological Surgery: A Double-Blind Randomized Controlled Trial

Ilsoon Son,[1] Chung-Sik Oh,[1] Jae Won Choi,[1] and Seong-Hyop Kim[1,2]

- **C group**: normal saline group:
  remifentanil TCI: 10 ng·mL^{-1} + saline
- **S group**: sufentanil group :
  remifentanil TCI: 10 ng·mL^{-1} +sufentanil 0.15 ng·mL^{-1}
- Maintained until extubation

The Scientific World Journal Volume 2014, Article ID 701329

3.1 Clinical Application of Remifentanil & Sufentnail



Ts : at initiation of sufentanil (S group) or normal saline (C group) administration

Te : after extubation;

T_1, : on arrival to the postanaesthetic care unit.

Sufentanil administration before concluding remifentanil anaesthesia improved postoperative hyperalgesia and achieved haemodynamic stability at extubation

The Scientific World Journal Volume 2014, Article ID 701329

3.1 Clinical Application of Remifentanil & Sufentnail

Table 3: Postoperative pain based on visual analogue scale (VAS) and postoperative nausea and vomiting (PONV).

	C group ($N = 39$)	S group ($N = 39$)	P
T1			
VAS	48 ± 9	21 ± 11	0.000
PONV incidence	6	1	0.108
PONV scale	0.2 ± 0.6	0.0 ± 0.2	0.048
Analgesic	13	0	0.000
Antiemetic	3	0	0.240
T1-T2			
VAS	50 ± 8	27 ± 10	0.000
PONV incidence	4	5	1.000
PONV scale	0.2 ± 0.5	0.2 ± 0.6	0.712
Analgesic	7	0	0.012
Antiemetic	2	2	1.000
T2-T3			
VAS	35 ± 8	19 ± 8	0.000
PONV incidence	15	12	0.475
PONV scale	0.6 ± 1.1	0.6 ± 0.9	0.719
Analgesic	3	0	0.240
Antiemetic	3	2	1.000
Rhodes index	3.4 ± 5.3	2.9 ± 5.4	0.613
T3-T4			
VAS	24 ± 8	24 ± 6	0.743
PONV incidence	3	2	1.000
PONV scale	0.1 ± 0.4	0.1 ± 0.2	0.629
Analgesic	0	0	—
Antiemetic	1	0	1.000
Rhodes index	0.5 ± 2.0	0.2 ± 0.9	0.471
T4-T5			
VAS	16 ± 6	15 ± 4	0.606
PONV incidence	2	0	0.494
PONV scale	0.1 ± 0.4	0.0 ± 0.0	0.155
Analgesic	0	0	—
Antiemetic	0	0	—
Rhodes index	0.3 ± 1.2	0.00 ± 0.00	0.155

Table 3: Postoperative pain based on visual analogue scale (VAS) and postoperative nausea and vomiting (PONV).

Sufentanil administration before concluding remifentanil anaesthesia didn't delay recovery or increase PONV during laparoscopic gynaecological surgery.

The Scientific World Journal Volume 2014, Article ID 701329

3.1 Clinical Application of Remifentanil & Sufentnail

PCA

Patient-controlled analgesia after coronary bypass: Remifentanil or sufentanil?

Seyed Mostafa Alavi[1], Seyed Mohammadmehran Ghoreishi[1],

Table 1. Characteristics of 249 patients undergoing coronary artery bypass.

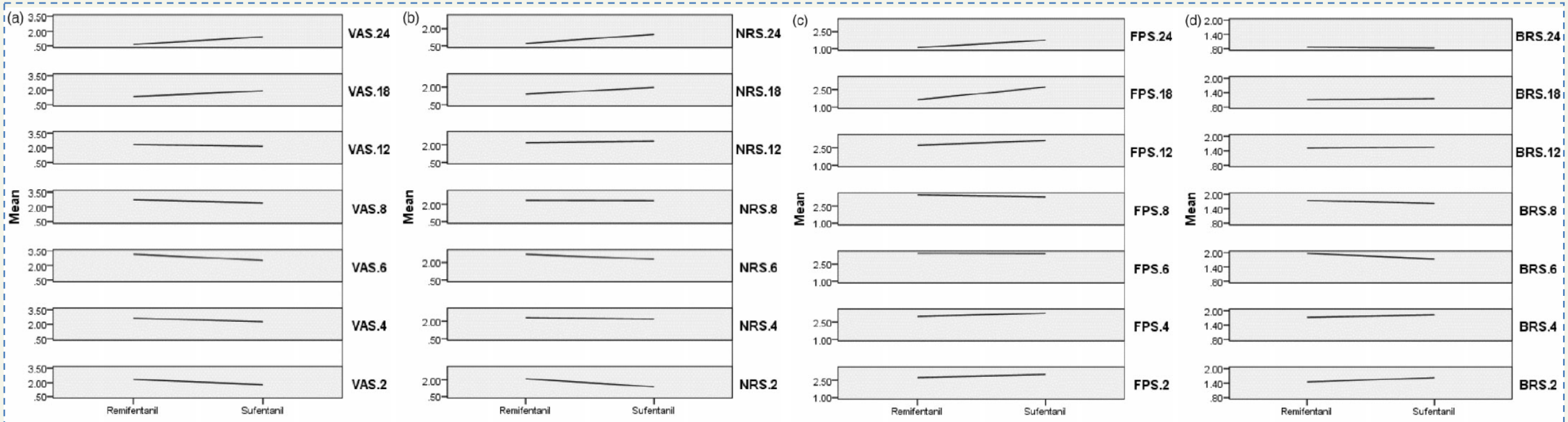
Variable	Remifentanil group	Sufentanil group	*p* value
No. of patients	76	173	
Age (years)	56.22 ± 13.92	56.75 ± 13.30	0.77
Body mass index ($kg\,m^{-2}$)	26.02 ± 3.02	25.89 ± 3.01	0.33
Sex (M/F)	54 (71%)/22 (29%)	123 (71%)/50 (29%)	0.94
Diabetes mellitus	22 (29%)	56 (32%)	0.62
Ejection fraction	45.45% ± 11.37%	45.05% ± 9.29%	0.77
Aortic crossclamp time (min)	54.52 ± 27.81	58.61 ± 35.70	0.41
Cardiopulmonary bypass time (min)	100.56 ± 44.52	95.54 ± 41.64	0.43
Operative time (min)	255.72 ± 75.50	245.17 ± 61.77	0.39

Patients in one group (R-PCA) received remifentanil
25 μg/mL administered via the intravenous
PCA infusion pump at 5mL/h

Patients in one group(S-PCA) received sufentanil 2 μg/mL administered via the PCA infusion pump at 4mL/h

Asian Cardiovascular & Thoracic Annals 2014,Vol. 22(6) 694–699

3.1 Clinical Application of Remifentanil & Sufentnail



Mean pain intensity in the 2 groups based on the 4 pain rating scales.
(a) VAS: Visual Analog Scale;
(b) NRS: Numeric RatingScale;
(c) FPS: Faces Pain Scale;
(d) BRS: Behavior Rating Scale.

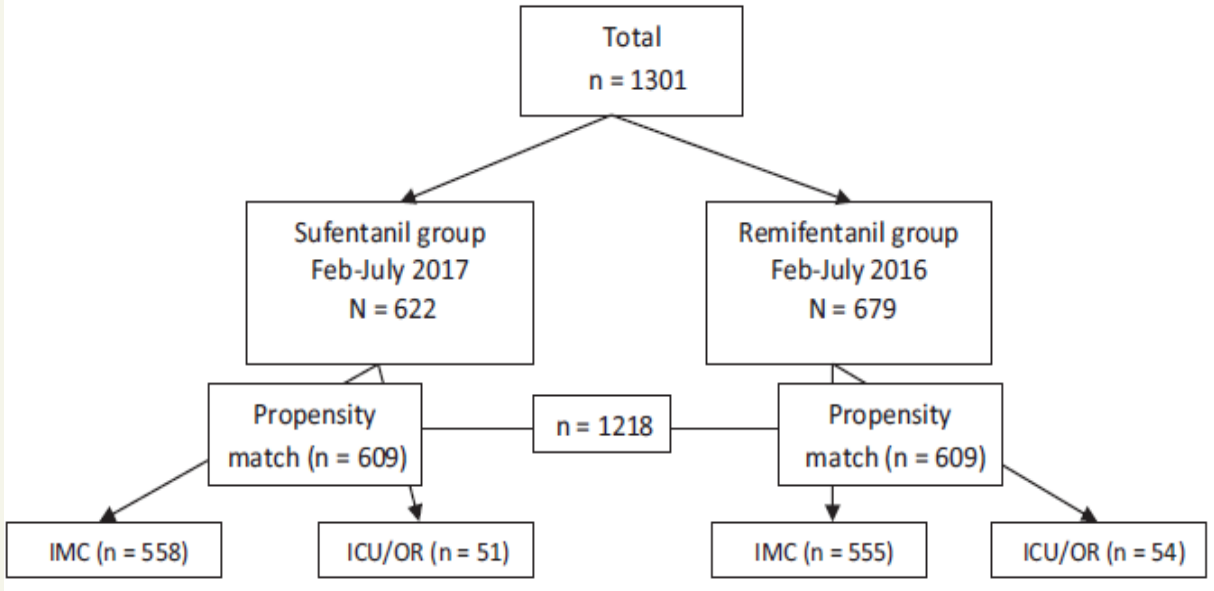
- Both remifentanil and sufentanil patient-controlled analgesia can provide acceptable analgesia after coronary artery bypass.
- The difference between their efficacies was inconspicuous until 24 h postoperatively. Remifentanil seems to result in better pain relief at 24 h postoperatively.

Asian Cardiovascular & Thoracic Annals 2014,Vol. 22(6) 694–699

FTA

A comparison of sufentanil vs. remifentanil in fast-track cardiac surgery patients*

W. Z. A. Zakhary,[1] E. W. Turton,[1] A. Flo Forner,[1] K. von Aspern,[2] M. A. Borger[3] and J. K. Ender[4]



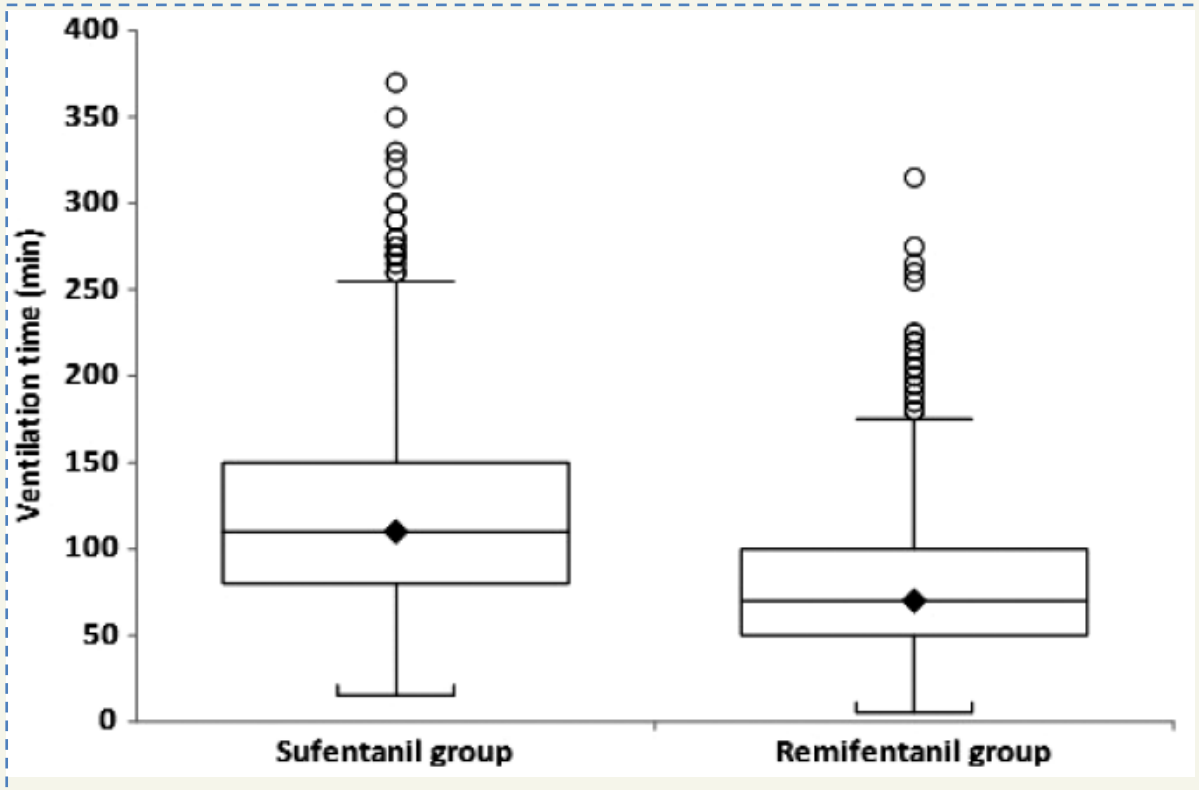
Study flowchart for patients included in the study.
IMC： intermediate care unit;
ICU： intensive care unit;
OR：operatingroom

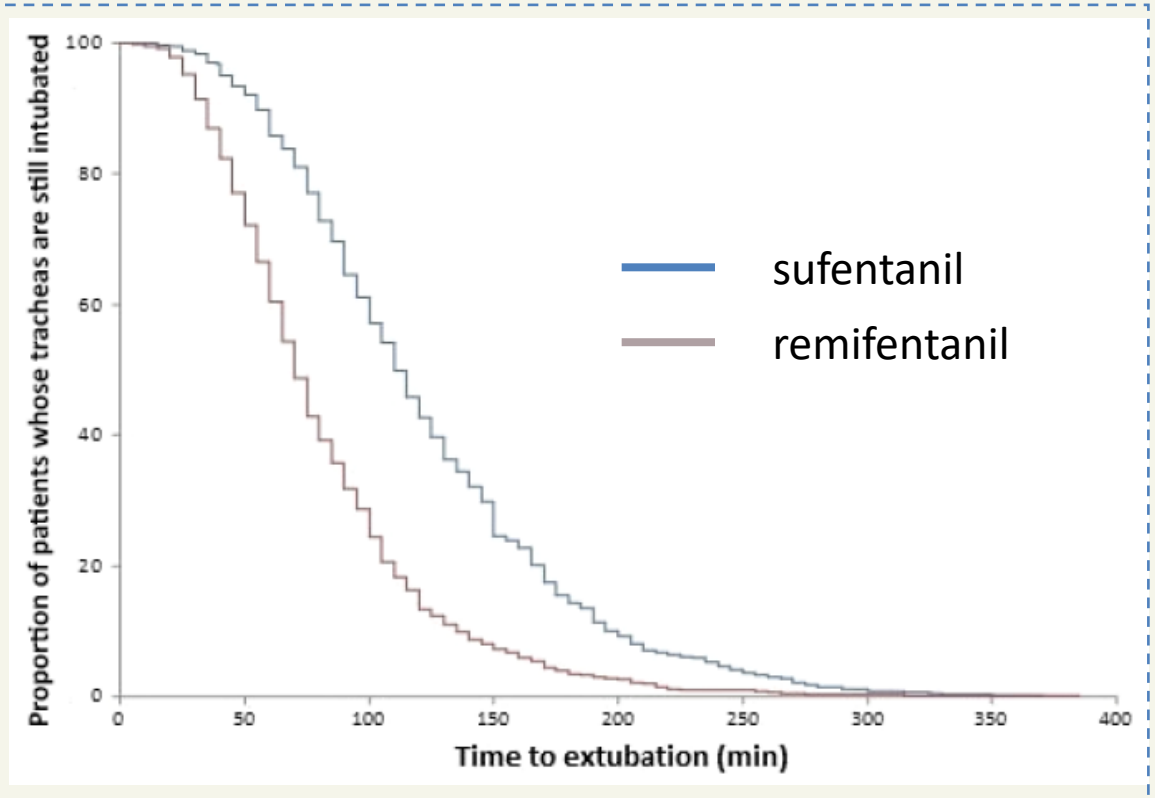
- Induction ：fentanyl 200 μg and propofol 1–2 $mg.kg^{-1}$.
- Maintenance：

Drug	until sternotomy	until and during bypass	until chest closure
sufentanil	1 $\mu g.kg^{-1}.h^{-1}$	0.5 $\mu g.kg^{-1}.h^{-1}$	0.25$\mu g.kg^{-1}.h^{-1}$
remifentanil		0.2-0.3 $\mu g.kg^{-1}.min^{-1}$	

Anaesthesia 2019, 74, 602–608

3.1 Clinical Application of Remifentanil & Sufentnail





- The sufentanil group had a significantly longer mean (SD) ventilation time compared with the remifentanil group;
- Remifentanil was more effective in reducing time to tracheal extubation

Anaesthesia 2019, 74, 602–608

3.1 Clinical Application of Remifentanil & Sufentnail

Table 3 Postoperative outcome parameters for patients included in the study. Values are median (IQR [range]), mean (SD) or number (proportion).

	Sufentanil group	Remifentanil group	p value	95%CI of the difference
Ventilation time; min	110 (80–150 [15–370])	70 (50–100 [5–315])	<0.001	36.3 to 48.3
RA-LOS; min	277 (78)	263 (78)	0.002	5.09 to 22.6
IMC-LOS; h	65.1 (64.0)	68.7 (78.2)	0.364	−11.90 to 4.37
Hospital length of stay; d	14.1 (6.1)	15.5 (8.8)	0.020	−2.22 to −0.50
VAS pain score	1.5 (1.2)	2.4 (1.5)	<0.001	N/A
Piritramide requirement; mg	2.6 (4.7)	18.9 (7.3)	<0.001	−17.0 to −15.5
In- RA PCA requirement	11 (1.8%)	17 (2.7%)	0.339	N/A
Out- RA PCA requirement	62 (10.1%)	55 (9.0%)	0.559	N/A

RA, recovery area; IMC, intermediate care unit; LOS, length of stay; PCA, patient-controlled analgesia; VAS, visual analogue scale.

Table 4 Postoperative complications for patients included in the study. Values are number (proportion).

	Sufentanil group	Remifentanil group	p value
Fast-track failure	51 (8.3%)	54 (8.8%)	0.760
Tracheal re-intubation	3 (0.4%)	5 (0.8%)	0.725
Postoperative nausea and vomiting	95 (15.5%)	92 (15.1%)	0.873
Postoperative delirium (Nu-DESC ≥ 2)	9 (1.8%)a	8 (2.4%)[b]	0.721
Deaths	1 (0.2%)	4 (0.6%)	0.374

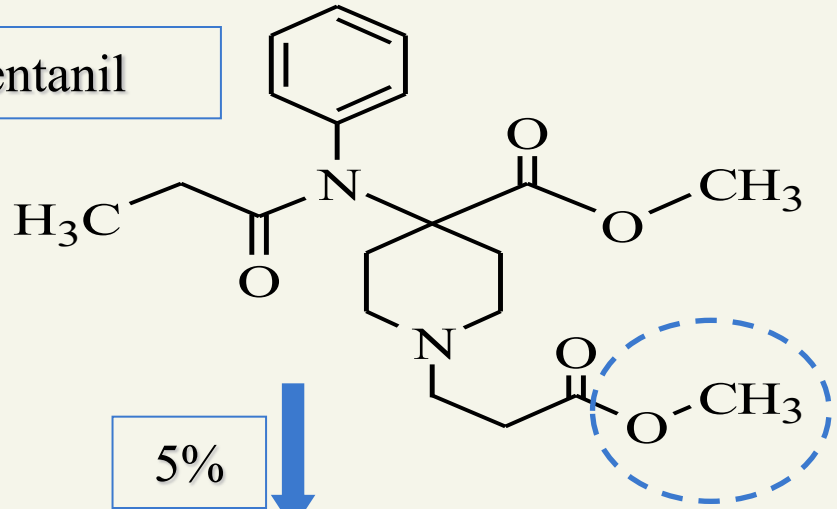
Nu-DESC, nursing delirium screening scale.

- The sufentanil group had a longer mean (SD) length of stay in the recovery area
- The sufentanil group had a lower mean (SD) visual analogue pain score than the remifentanil group
- there was an increased requirement for postoperative analgesia when remifentanil was used.

Anaesthesia 2019, 74, 602–608

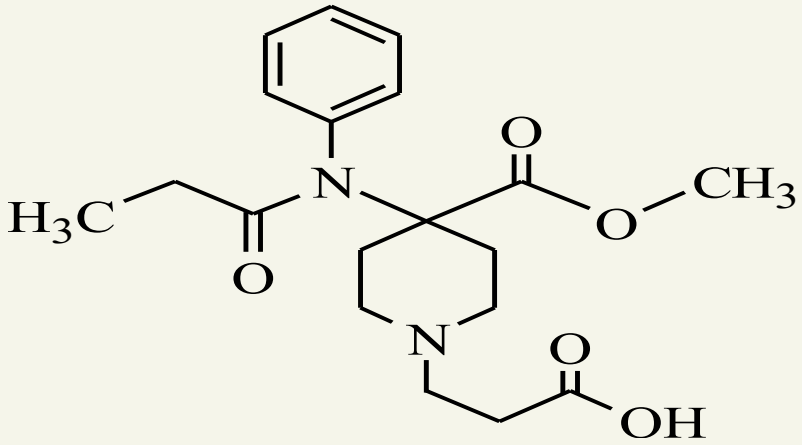
3.2 Remifentanil & Sufentainil Summary

Remifentanil



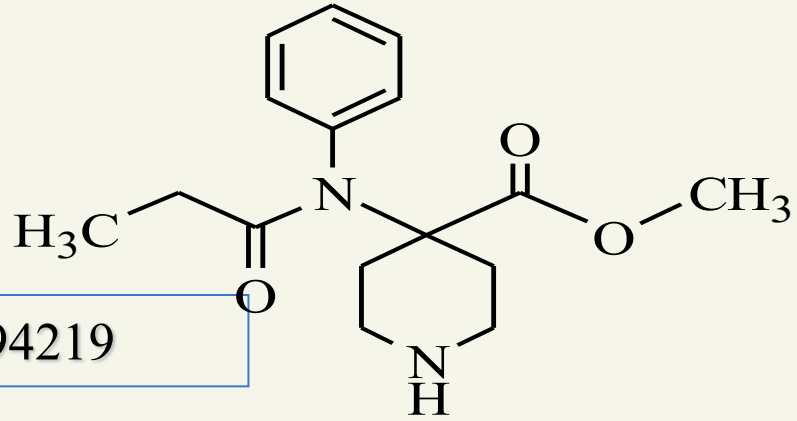
95%

Unlike Fentanyl is metabolized by liver and kidney, Remifentanil is metabolized by non-specific esteres in blood.



GI-90291 Remifentanil Acid

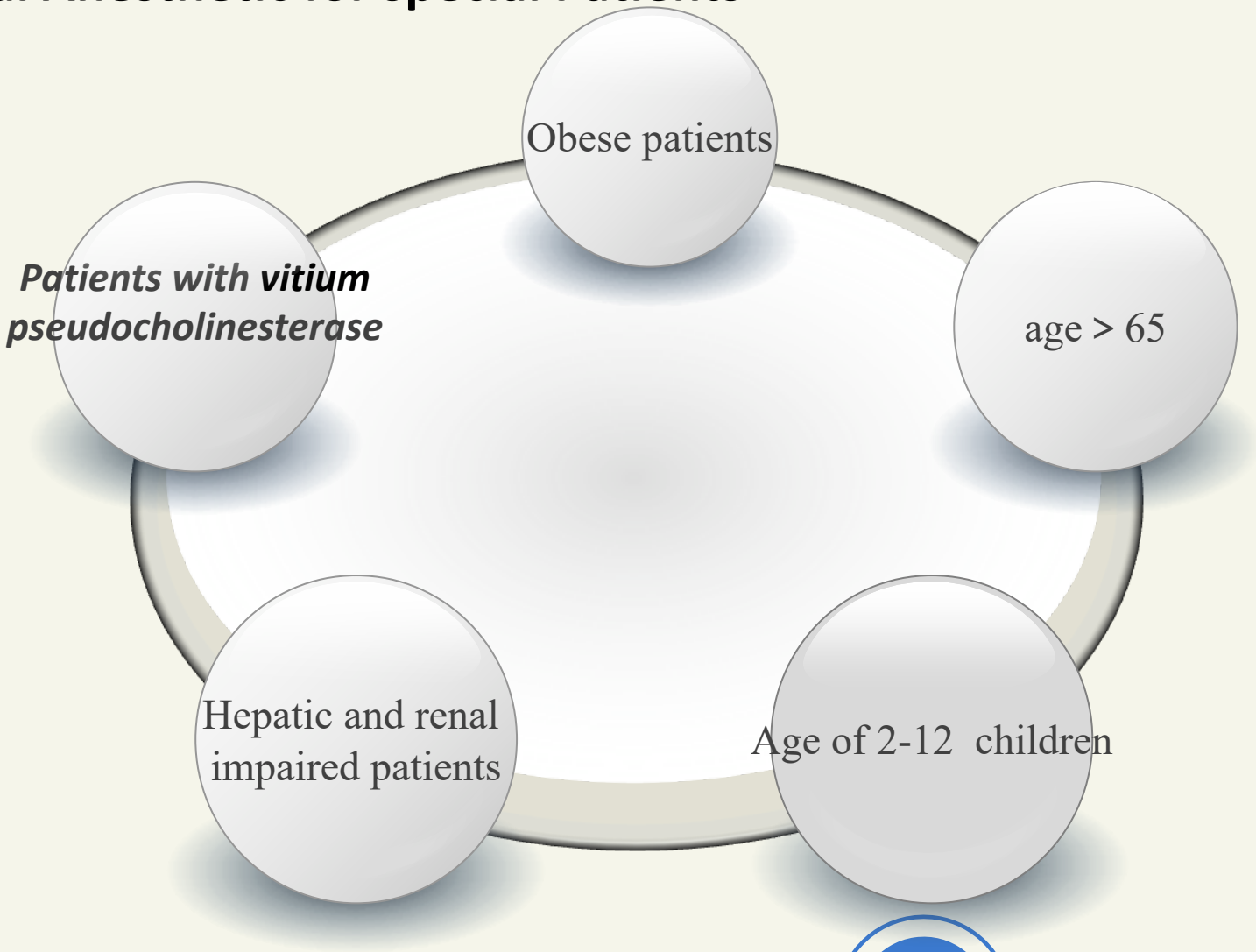
5%



GI-94219

—— Anesthesiology,1991;74:53-63

Ideal Anesthetic for special Patients



◆The metabolism is not related to the patients weight, age, pseudocholinesterase activity, kidney and liver function,

◆so it is the first choice of anesthetics for special patients including obese patient, old patients, children, Hepatic and renal Impaired patient and patients with vitium pseudocholinesterase.

——Anesth Analg, 2002;95:1305-1307.
—— Eur J Anaesthesiol, 2002;19:839-840.

3.2 Remifentanil Summary

Brief Introduction

【Generic Name】 Remifentanil HCL for Injection

【Ingredient】 Remifentanil HCL

【Excipient】 Glycine

【Identification】 This product presents loose white or similar white colour

【Indication】 This product is indicated as an analgesic agent for intravenous administration

【Package】 glass-made vials for injection

1mg 5 vials/ box

2mg 5 vials/ box

5mg 2 vials/ box

【Storage】2-25℃ and protect from light, do not freeze or refrigerate

【Shelf Life】18 months

Characters

Short-Acting	Rapid onset 1 to 2 mins, rapid offset within 5-10 mins with rapid recovery.
No Accumulation	Rapidly metabolized by nonspecific blood and tissue esterases.
Rapid Recovery	Rapid recovery with earlier discharge from the operating room for outpatients.
Coordinated Sedation	When coordinated with other sedation drugs intraoperatively , it may reduce the usage of sedation drugs.
Organ Protection	Can be used in patients with hepatic or renal impairment

3.2 Remifentanil Summary

瑞捷®

注射用盐酸瑞芬太尼

Remifentanil Hydrochloride For Injection

Rapid on-set & off-set for awakening ;
Suitable for TCI pump, infusion pump ;
No accumulation for liver and kidney ;
Ideal analgesic for special patients ;

Notice:

This product should not be administered into the same IV tubing with blood product, such as blood, serum, blood plasma.

Remifentanil can penatrate through placenta and cause neonate respiratory depression.

- **General anesthesia maintainance : 0.1-1μg/kg/min ;**
- **TCI pump infusion:**
  Target plasma concentration 6ng/L, which equals TCI:2ng/ml≈ 0.07μg/kg/min

3.2 Sufentainil Summary

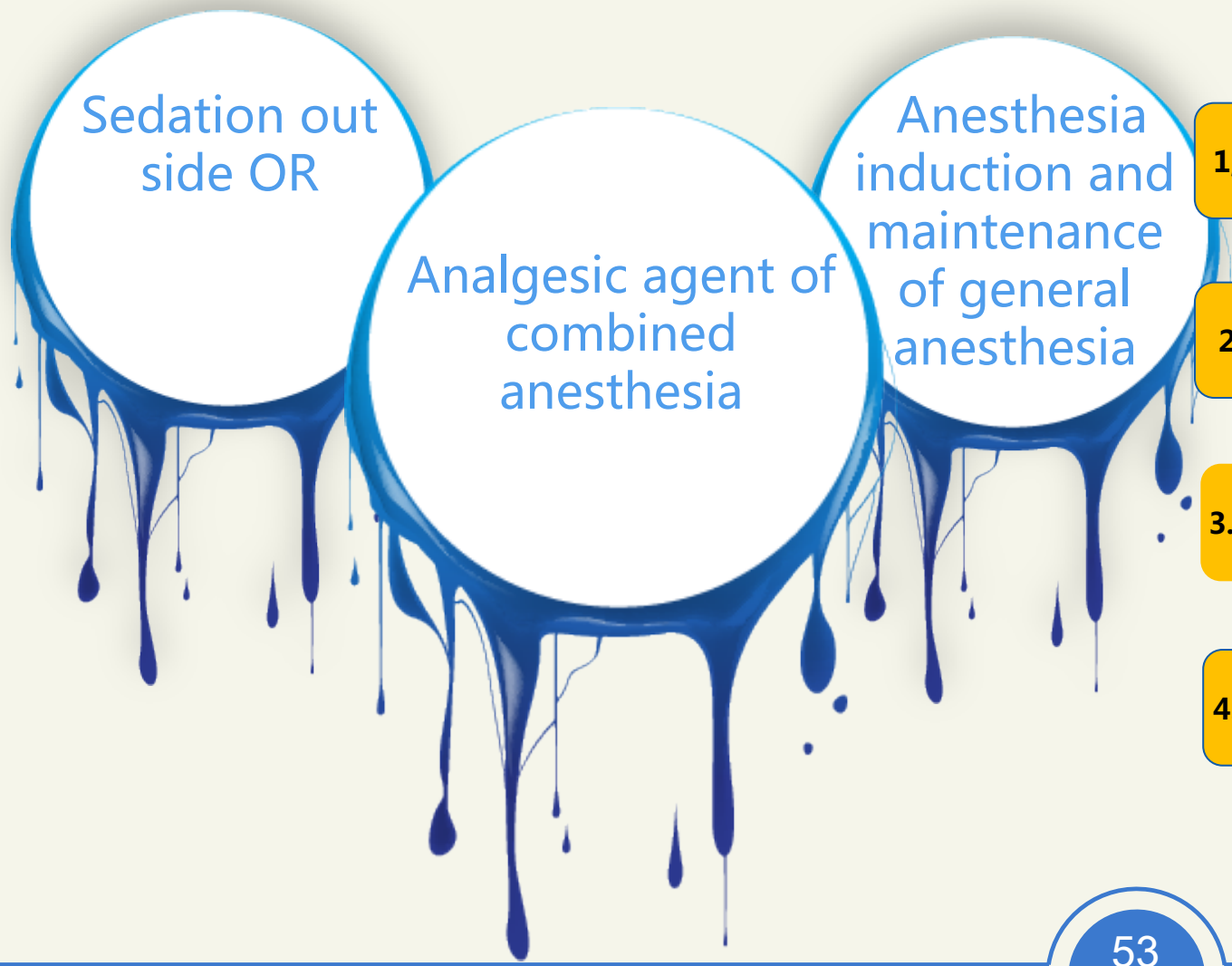
Pharmacodynamics index

	Morphine	Fentanyl	Sufentanil
Type	μ , κ	μ	μ
on-set time (min)	-	2-3	1.3-3
Peak time (min)	20	5-8	3-5
effect period (min)	3-4h	25-30	25-50
Equal dose	10	0.1	0.01
Analgesic potency	1	100	1000
Therapeutic window(LD50/ED50)	70-90	277	25211

Journal of Clinical Anesthesia (2016) 32, 300–312

3.2 Remifentanil & Sufentainil Summary

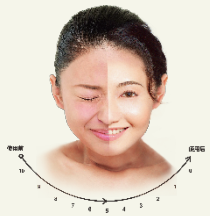
Indications



Characters

1,potent and lasting	High potency , long lasting , effectively reduce pain and complications for severe trauma patients
2. safe and comfort	Wide range of application, safe and less adverse reactions, high satisfaction
3.Inhibition of stress	Effectively inhibits patient's stress response, improve patient compliance。
4.synergistic sedation	synergistic effect, reduce sedatives and hypnotic drug dosage.

3.2 Remifentanil & Sufentainil Summary



人福舒芬®
枸橼酸舒芬太尼注射液
Sufentanil Citrate Injection

Sufentanil is 800-1000 times potent as Morphine, with therapeutic index of 26716. One of the safest analgesic in market.

PCIA： loading dose 0.15-0.25μg/kg，background dose0.03-0.05μg/(kg·h)，
Bolus0.5ml，the flow rate 2ml/h，lockout time 15min；
Cardiothoracic Operation：0.08-0.1 μg/(kg·h)；

PCEA：background dose2ml/h，Bolus 3ml， lockout time 15-30min ；
Gynecologic operation：0.4μg/ml sufentanil+0.125% Ropivacaine
Major abdominal surgery.：0.75μg/ml sufentanil+0.2% Ropivacaine
Joint Replacement：1.25μg/ml sufentanil+0.125%ropivacaine

3.3 Side effects of opioid analgesic and solution

Adverse reactions :

- PONV
- OIH
- Respiratory depression
- Addiction
- Tumor recurrance
- Urinary retention
- Somnolence

Opioids: keeping the good, eliminating the bad

The challenge at the moment is to maintain the analgesic effect, meanwhile, prevent the side effect.

Puig S.Nature Medicine, 2017, 23(3):272.

3.3 Side effects of opioid analgesic and solution

Proper use of opioid drug can reduce adverse reactions

Opioids are the most effective analgesic drugs.The proper use of opioids is safe, unlike other analgesic drugs, opioids is of no organ toxicity; NSAIDs and para-acetyl Aminophenol produces severe gastrointestinal for liver.

Adverse reactions of opioid drug can be reduced by decreasing bolus dose, lower infusion rate, longer infusion period.

OPIOID CONSIDERATIONS IN PAIN TREATMENT

Despite important advances in pain treatment, opioids remain the most potent class of analgesic medications available. They relieve most types of pain, are widely available, and are generally safe when used appropriately. Unlike some other analgesics, opioids do not cause organ toxicity when used appropriately; in contrast, NSAIDs and acetaminophen can cause serious gastric, hepatic, and renal toxicities, which are responsible for 15.3 deaths per 100,000 users per year (Lanas et al., 2005; Nourjah et al., 2006). However, opioids may be misused by indi-

prone to falls. Common adverse reactions with opioids use include:

- constipation, nausea and vomiting;
- sedation;
- impaired judgement;
- impaired psychomotor function;
- respiratory depression.

With all opioids, these can be limited by using lower starting doses, longer dose intervals, and slow titration; however, constipation, nausea, and vomiting often require prophylaxis or therapy.

The use of more than one analgesic modality (i.e., multimodal analgesia) to achieve effective pain control while minimizing the side effects of opioids that delay discharge has become the standard of care in ERAS protocols.

Savage SR, et al. Addict Sci Clin Pract. 2008;4(2):4-25.
Pergolizzi J, et al. Pain Pract. 2008;8(4):287-313.

M. Tan et al.Can J Anesth/J Can Anesth (2015) 62:203–218
Paul F.et al.Anesth Analg 2007;1041380–96

3.3 Side effects of opioid analgesic and solution - OIH

Opioid-induced pain sensitization（OIH, opioid-induced Hyperalgesia）

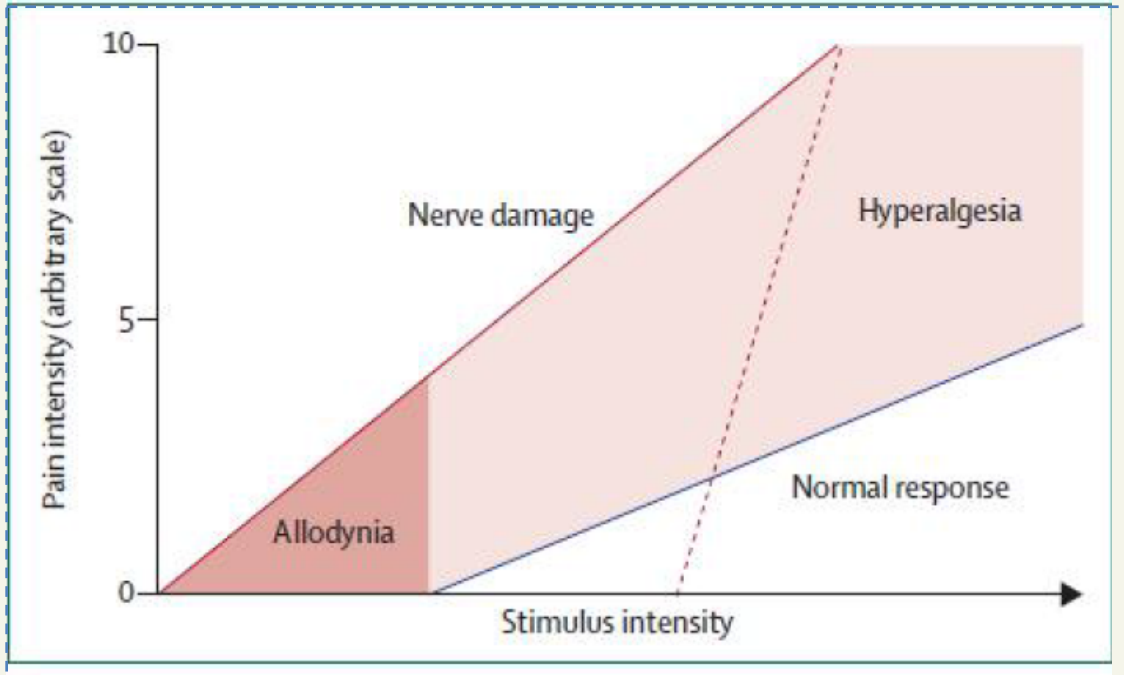


Figure 1: Stimulus–response function illustrating allodynia and hyperalgesia following nerve damage

Opioids can trigger central sensitization and induce hyperalgesia, known as opioid-induced hyperalgesia, which are widely recognized complication of opioid therapy. This phenomenon has been confirmed by numerous clinical observations and basic researches.

OIH：
Sensitization of nociceptive pathways, enhancement of pain sensitization

OIH The core of prevention: combined medication, advanced analgesia combined with opioid drugs, especially notice that pre-administration of alternative analgesics before the ending of surgery , and postoperative analgesia combined with anti-inflammatory analgesics.

Lancet Neurol. 2014 Sep;13(9):924-35.

3.3 Side effects of opioid analgesic and solution - PONV

Opioid-induced PONV is μ receptor-mediated stimulation of the chemosensory region of the lower brainstem.

The solution for PONV should be based on multi-analgesic combination.

Complementary analgesic mechanisms (acting on different receptors or different sites related to analgesia)
Additional analgesic enhancement without synergistic
Side effects add-up or even less side effects.

Use antiemetics, such as ondansetron and tropisetron.

Use of the mixed agonist–antagonist nalbuphine in opioid based analgesia

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KEYWORDS
Kappa-receptor;
Mu-receptor;
Nalbuphine; Mixed agonist–antagonist;
Opioid side effects

Summary Opiate analgesics provide effective pain relief and are widely used for control of mild to severe pain. The well-known side effects of the mu-agonist opioids, including pruritis, nausea/emesis, constipation, urinary retention, respiratory depression, excessive sedation, and the development of tolerance and dependence, are occasionally problematic. Here we review use of the mixed opioid agonist–antagonist nalbuphine in opioid analgesia with a view to its potential advantages. Used as the sole opioid analgesic, it can satisfactorily cover mild to moderate pain with a low incidence of the common opioid side effects. With care, it can be used concurrently with the more commonly employed mu-opioid agonists (e.g. morphine, hydromorphone, fentanyl), yielding good analgesia while simultaneously decreasing the incidence and severity of mu-agonist side effects. This paper provides information sufficient to enable the practitioner to determine whether nalbuphine might be a useful addition to his/her pharmacopoeia.

3.3 **Side effect of Opioid analgesics - Tumor recurrance**

Two articles in Anesth Analg 2010 reported the connection between analgesics and tumor recurrance

Do Intraoperative Analgesics Influence Breast Cancer Recurrence After Mastectomy? A Retrospective Analysis

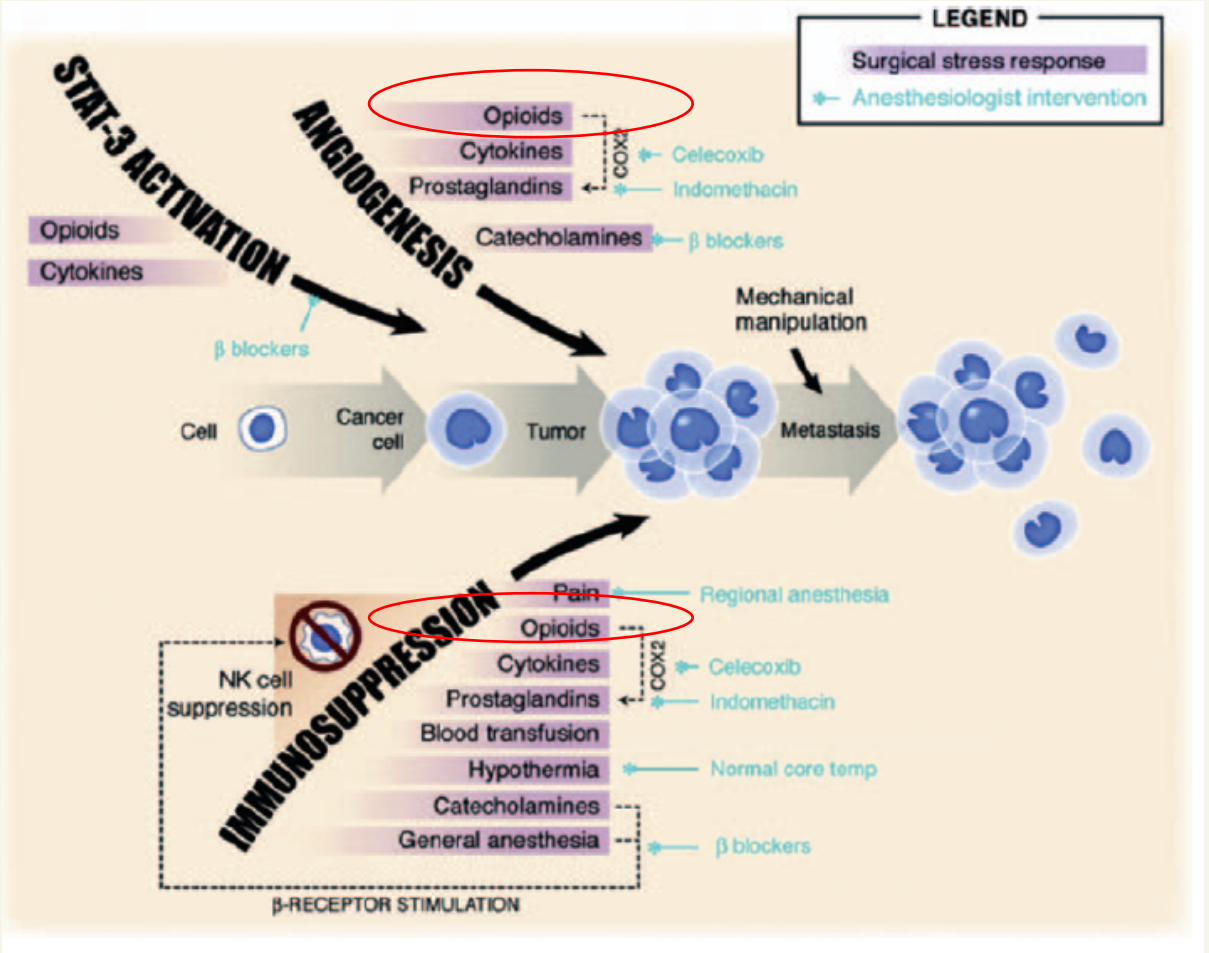
Patrice Forget, MD,* Julie Vandenhende, MD,* Martine Berliere, MD, PhD,† Jean-Pascal Machiels, MD, PhD,‡ Benoît Nussbaum, MD,* Catherine Legrand, PhD,§ and Marc De Kock, MD, PhD*

REVIEW ARTICLE

CME

The Role of the Perioperative Period in Recurrence After Cancer Surgery

Antje Gottschalk, MD,*† Sonal Sharma, MD,* Justin Ford, MD,* Marcel E. Durieux, MD, PhD,* and Mohamed Tiouririne, MD*



Anesth Analg 2010;110:1630–5
Anesth Analg 2010;110:1636 –43

3.3 **Side effect of Opioid analgesics - Tumor recurrance**

Table 1. Overview of Reported Anesthetic Effects on Tumor Genesis and Recurrence

Surgical stress response and cancer
Stress and surgical excision of the primary tumor can promote tumor metastasis[4,11]

Neuroendocrine system
General anesthesia accompanied by surgical stress may suppress immunity, presumably by directly affecting the immune system or activating the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system[19]

Inflammatory system
Promotion of cancer progression through immunosuppression via cytokines, chemokines, prostaglandins, COX[30]

Pain
Suppression of NK cell activity[31,32] and promotion of tumor development in animals[33]

Opioids
Opioids inhibit cellular and humoral immune function in humans[36]
Morphine inhibits spontaneous and cytokine-enhanced NK cell cytotoxicity[35–37]
In contrast, IV fentanyl increases NK cell cytotoxicity and circulating CD16(+) lymphocytes in humans[41]
Opioid-induced promotion and stimulation of angiogenesis[39]

***β*-adrenergic blockade**
β-blocker (nadolol) and a prostaglandin synthesis inhibitor (indomethacin) attenuated the metastasis-promoting effects of surgery when used alone or in combination[11]

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- Opioid-induced promotion and stimulation of angiogenesis

Anesth Analg 2010;110:1636 –43

3.3 **Side effect of Opioid analgesics - Tumor recurrance and solution**

Surgery for Cancer: A Trigger for Metastases

Samer Tohme, Richard L Simmons, and Allan Tsung

DOI: 10.1158/0008-5472.CAN-16-1536 Published April 2017 Check for updates

Surgery is a crucial intervention and provides a chance of cure for patients with cancer. The perioperative period is characterized by an increased risk for accelerated growth of micrometastatic disease and increased formation of new metastatic foci. The true impact for cancer patients remains unclear. This review summarizes the often fragmentary clinical and experimental evidence supporting the role of surgery and inflammation as potential triggers for disease recurrence. Surgery induces increased shedding of cancer cells into the circulation, suppresses antitumor immunity allowing circulating cells to survive, upregulates adhesion molecules in target organs, recruits immune cells capable of entrapping tumor cells, and induces changes in the target tissue and in the cancer cells themselves to enhance migration and invasion to establish at the target site. Surgical trauma induces local and systemic inflammatory responses that can also contribute to the accelerated growth of residual and micrometastatic disease. Furthermore, we address the role of perioperative factors, including anesthesia, transfusions, hypothermia, and postoperative complications, as probable deleterious factors contributing to early recurrence. Through the admittedly limited understanding of these processes, we will attempt to provide suggestions for potential new therapeutic approaches to target the protumorigenic perioperative window and ultimately improve long-term oncological outcomes. *Cancer Res; 77(7); 1548–52.* ©2017 AACR.

- Surgical intervention, for the purpose of cure, but might "trigger" tumor metastasis.
- Surgical infestation of tumor tissue, traumatic hemorrhage and inflammatory response can directly lead to and trigger the "metastasis". Other factors that may trigger tumor metastasis during perioperative period are anesthesia, blood transfusion, hypothermia, postoperative complications, etc.
- **The effect of opioid drugs on the tumor during the perioperative period is the minimal among all factors.**
- **More attention should be paid to the impact of cancer treatment on the use of opioids of tumor progression. At present, adequate analgesia should still be the main treatment strategy.**

WELCOM TO TIANJIN!

Thank You