Anesthésie en boucle fermée: Mythe ou réalité?

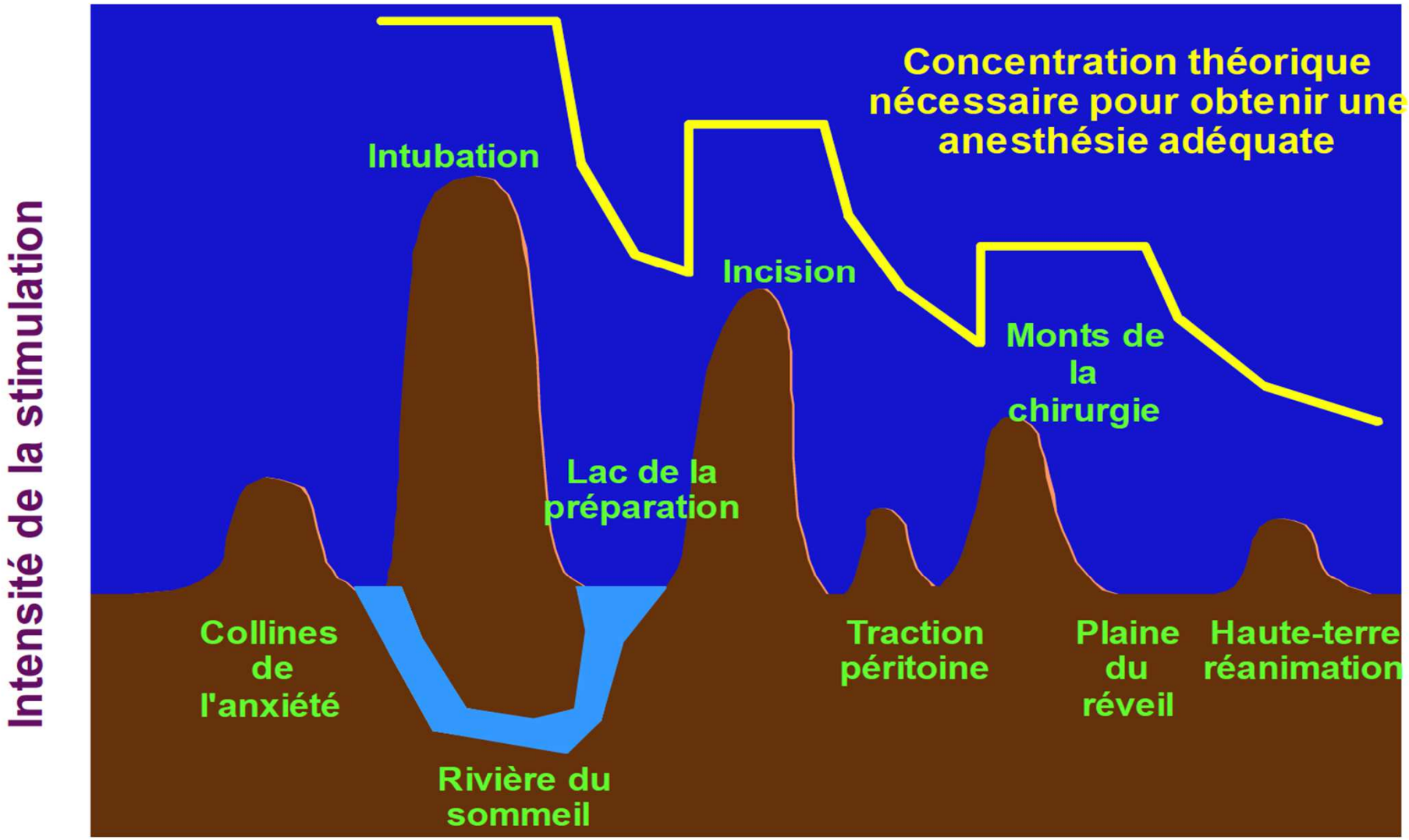
Cédrick ZAOUTER, MD,MSc
Service d'Aneshtésie et Réanimation II,
CHU de Bordeaux, France.

C·H·U
Hôpitaux de Bordeaux

PLAN

- Limites de l'AIVOC
- Solutions pour répondre à ces limites
- Les intérêts de ces solutions
- Boucle fermée - Mythe ou réalité?

AIVOC


Intensité de la stimulation
Concentration théorique nécessaire pour obtenir une anesthésie adéquate
Intubation
Incision
Monts de la chirurgie
Lac de la préparation
Collines de l'anxiété
Rivière du sommeil
Traction péritoine
Plaine du réveil
Haute-terre réanimation

LIMITES de l'AIVOC

- Model Obsolete*
- Vigilance/Fatigue**
- Charge de travail***

*: Kuizenga, Curr Opin Anesthesiol 2016
**: Giacalone, EJA 2016
***: Dussaussoy JCMC 2014

Quelles solutions ?

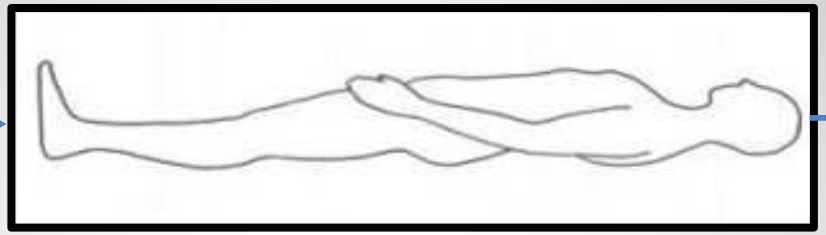
Boucle fermée: La solution

- Les systèmes de contrôle physiologique emploient des boucles fermées:
  → Thermorégulation
- Dans notre quotidien:
  → Thermostat

Cruise control

Patten BC, Odum EP. The cybernetic nature of ecosystems. Am Nat 1981;118:886–95

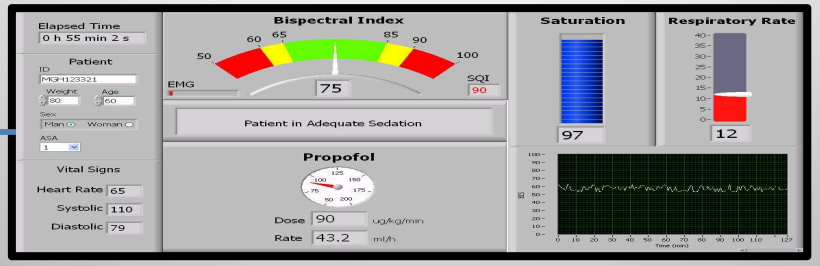
Closed Loop System - CLS



Patient sous anesthésie

Perfusion de propofol

Index Bispectral



System de contrôle

CLS for propofol is feasible

- Premiers essais dans les années ‘50*
  - Zaouter C et al. JCMC 2016
- Faisable pour l’entretien
  - Struys MM, et al. Anesthesiology 2001; 95:6
- Faisable pour l’induction et l’entretien
  - Ngai liu, et al. Anesthesiology 2006; 104:686
- Faisable pour des chirurgie complexe
  - Zaouter C. et al A&A février 2017
- Faisable pour patients très fragile avec comorbidités+++
  - Zaouter C. et al A&A février 2017

Liu N.

Double boucle: une seule variable

Remifentanil et propofol guidés par le BIS.

Les stimuli peropératoires douloureux provoquent l'activation corticale et, par conséquent, les valeurs du BIS augmentent

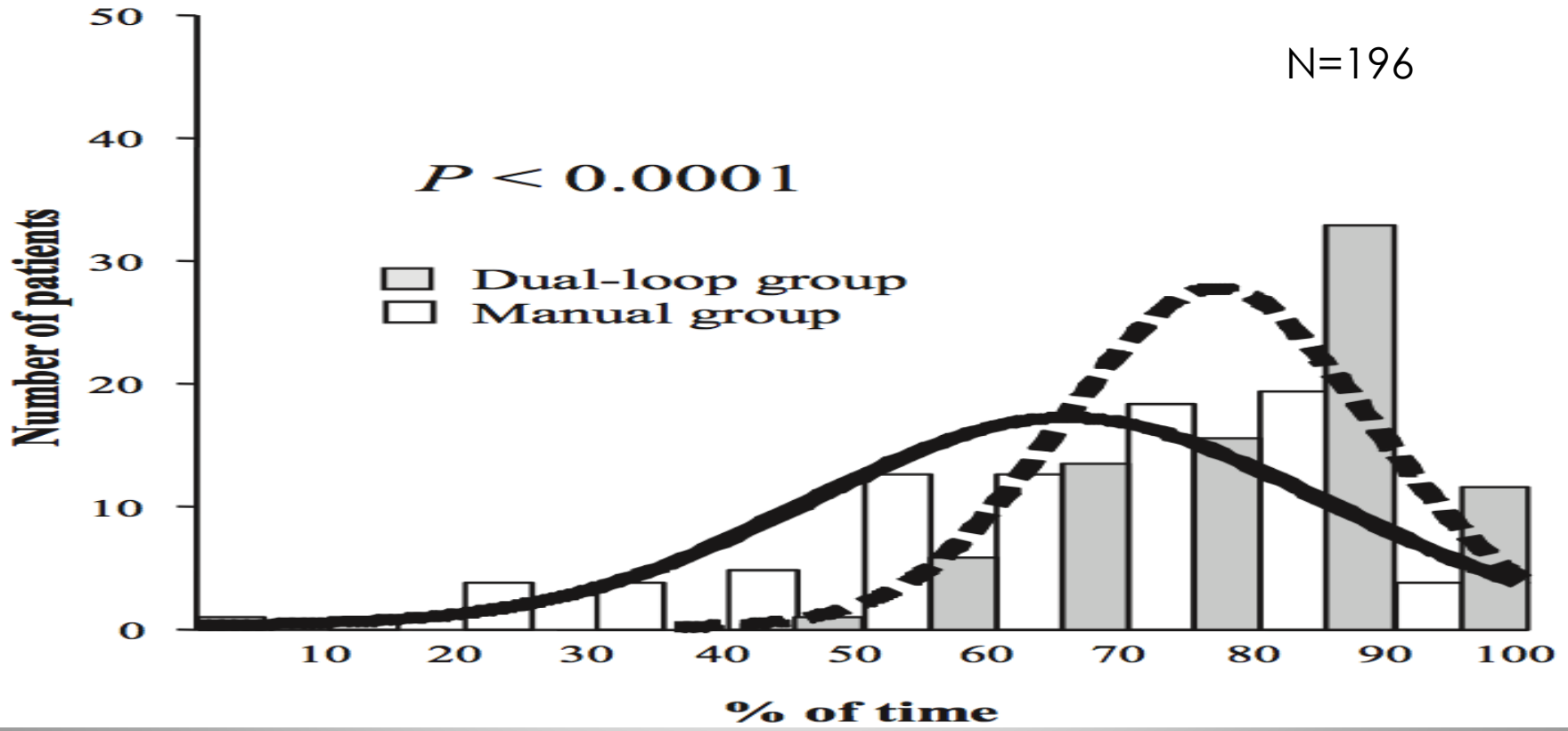
1- Petites oscillations: remifentanil
2- Grandes oscillations: remifentanil + propofol

Liu N. Anesth Analg, 2011 vol. 112 (3) pp. 546-557

Liu N.

Double boucle: une seule variable

Remifentanil and propofol guided via BIS monitoring.

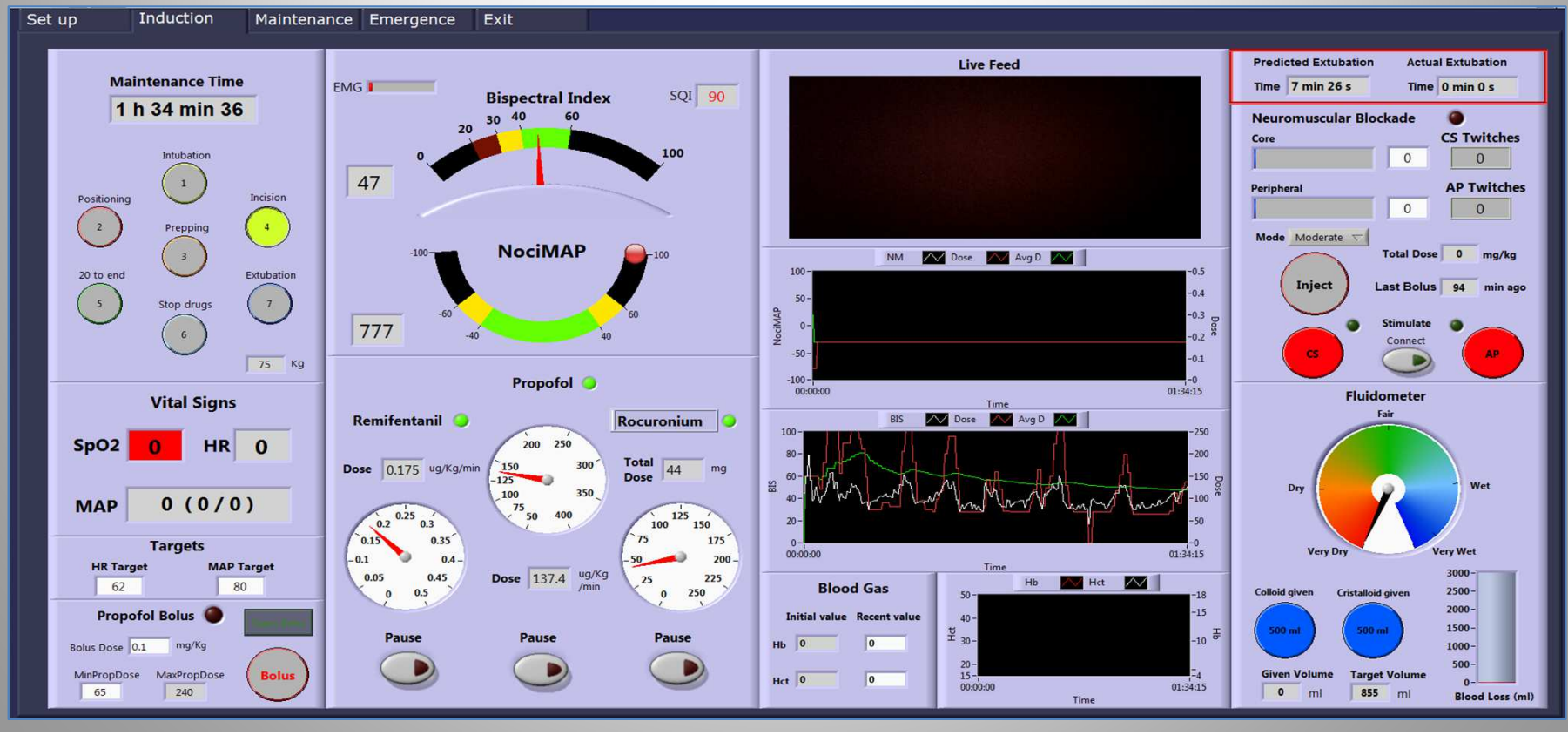


Liu N. Anesth Analg, 2011 vol. 112 (3) pp. 546-557

Hemmerling T.

McSleepy™

- 3 seringues électriques
- 3 variables contrôlées



Analgoscore

TABLE I.
RULES FOR SCORE DETERMINATION

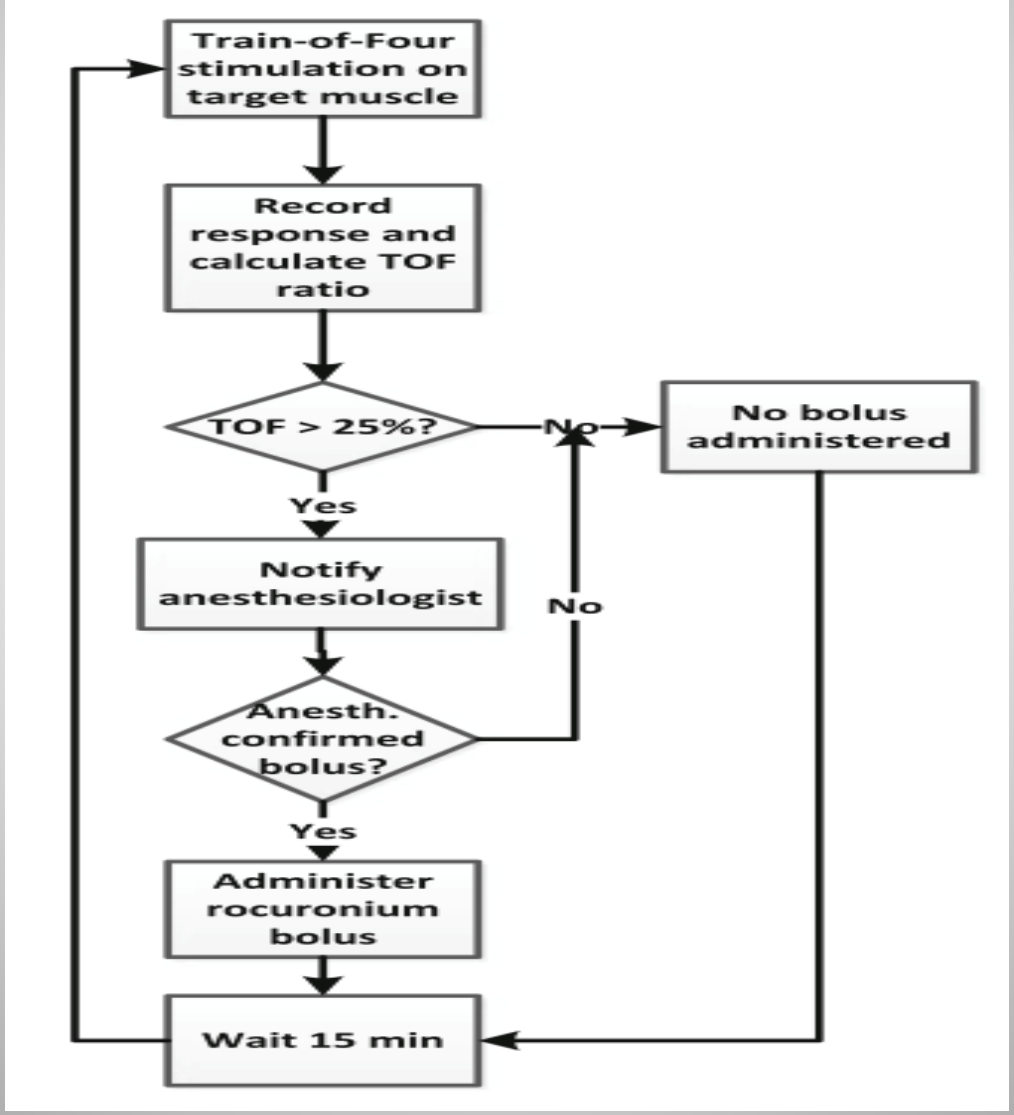
MAP / HR	<20%	<15%	<10%	<5%	MAP	>5%	>10%	>15%	>20%
<35%	-9	-8	-6	-5	-4	Vagal Reaction			
<25%	-8	-7	-5	-4	-3				
<15%	-6	-5	-4	-3	-2				
<10%	-5	-4	-3	-1	-1				
HR	-4	-3	-2	-1	0	1	2	3	4
>10%	Hypotension caused by volume depletion				1	1	3	4	5
>15%					2	3	4	5	6
>25%					3	4	6	7	8
>35%					4	5	6	8	9

MAP = mean arterial pressure; HR = heart rate

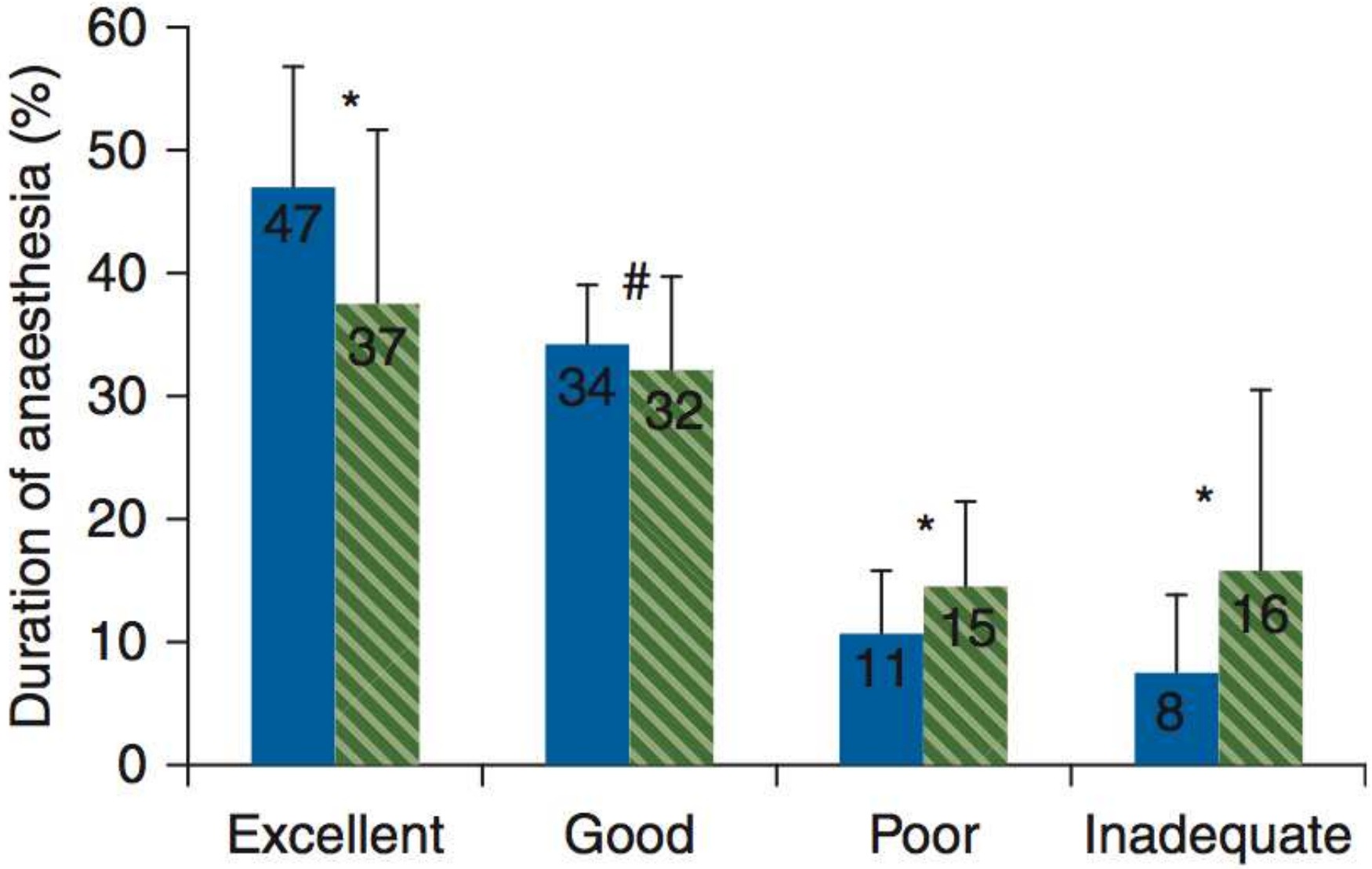
Analgoscore

Analgoscore™	Infusion Modification	CF
-9 to -2	No infusion	
-1,0, 1	No change	1
2	↑20%	1.2
3	↑30%	1.3
4	↑40%	1.4
5	↑50%	1.5
6	↑60%	1.6
7	↑70%	1.7
8	↑80%	1.8
9	↑90%	1.9

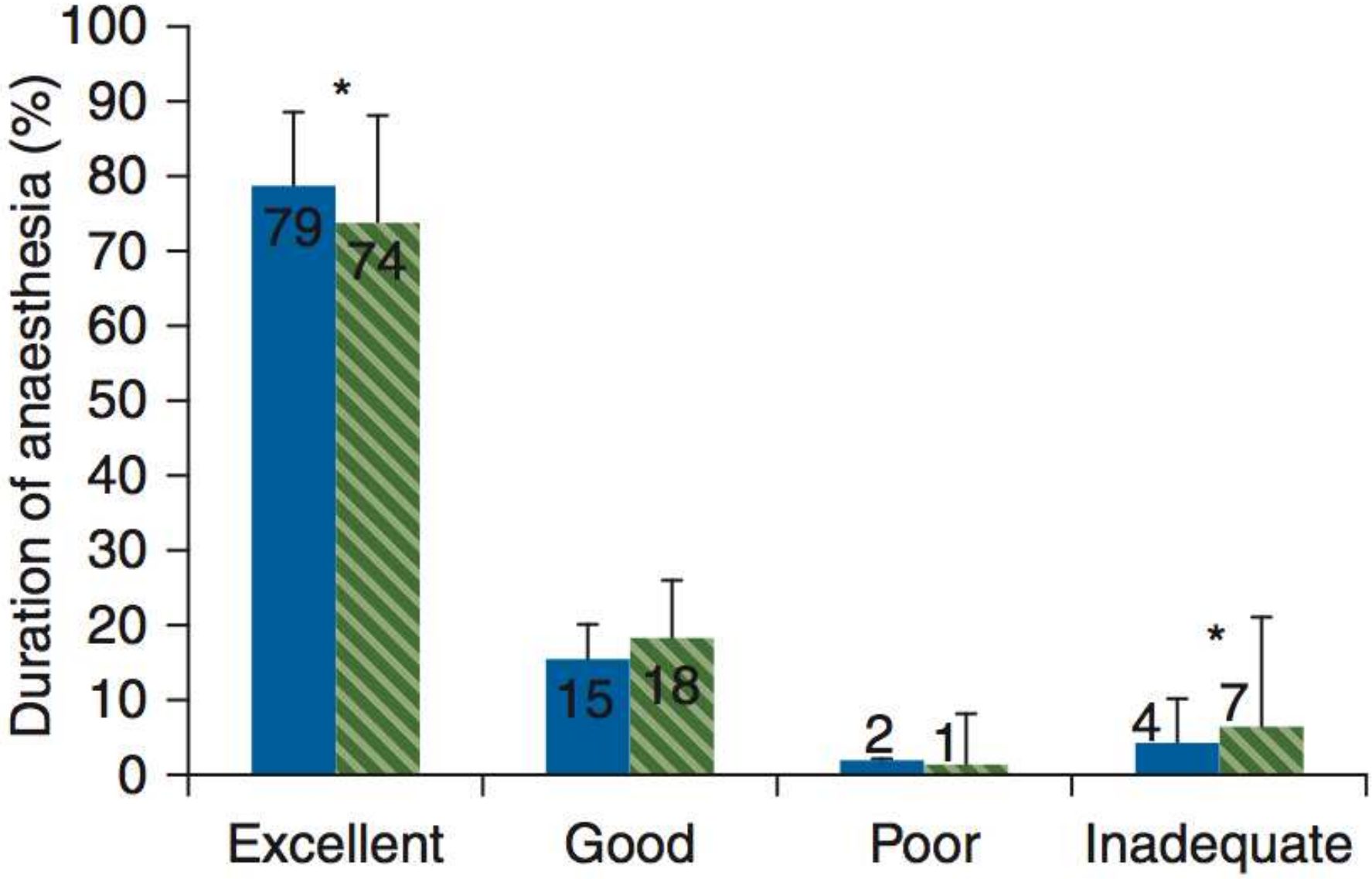
Boucle du curare



Performance de la sédation



Performance de l'analgésie



Que disent les meta-analyses?

Study or Subgroup	Manual Mean	Manual SD	Manual Total	Closed-loop Mean	Closed-loop SD	Closed-loop Total	Weight	Mean Difference IV, Random, 99% CI
Agarawal J [10]	12.1	3.3	22	6.8	2.2	22	12.4%	5.30 [3.12, 7.48]
De Smet T [11]	24.1	8	20	11.5	4	20	8.9%	12.60 [7.45, 17.75]
Hemmerling TM [13]	15.7	7.4	20	9.1	1.9	20	9.8%	6.60 [2.20, 11.00]
Hemmerling TM [14]	15.4	10.4	93	11	2.6	93	11.7%	4.40 [1.54, 7.26]
Liu N [15]	18	11.9	35	12	8.9	35	7.5%	6.00 [-0.47, 12.47]
Liu N [16]	15	5.5	98	11.4	4.3	98	12.7%	3.60 [1.78, 5.42]
Liu Y [18]	11.7	4.1	90	10.1	3	90	13.0%	1.60 [0.22, 2.98]
Puri GD [21]	18	7.4	121	10	1.5	121	12.7%	8.00 [6.23, 9.77]
Puri GD [20]	16	5.3	20	9.4	1.8	20	11.3%	6.60 [3.38, 9.82]
Total (99% CI)			**519**			**519**	**100.0%**	**5.82 [3.17, 8.46]**

Heterogeneity: $Tau^2 = 7.80$; $Chi^2 = 78.88$, df = 8 ($P < 0.00001$); $I^2 = 90\%$
Test for overall effect: $Z = 5.67$ ($P < 0.00001$)

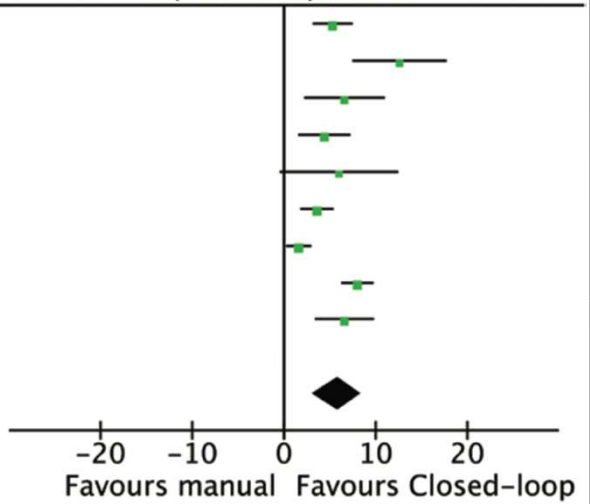


Figure 4. Forest plot of the median absolute performance errors. CI indicates confidence interval.

Study or Subgroup	Manual Mean	Manual SD	Manual Total	Closed-loop Mean	Closed-loop SD	Closed-loop Total	Weight	Mean Difference IV, Random, 99% CI
Liu N [15]	43	40	98	26	11	98	25.4%	17.00 [6.21, 27.79]
Liu N [16]	50	62	90	21	8	90	21.9%	29.00 [12.03, 45.97]
Liu Y [18]	27.2	15.3	90	22.2	8.5	90	27.9%	5.00 [0.25, 9.75]
Puri GD [20]	51	50.4	121	24	8.1	121	24.8%	27.00 [15.05, 38.95]
Total (99% CI)			**399**			**399**	**100.0%**	**18.77 [2.28, 35.25]**

Heterogeneity: $Tau^2 = 143.56$; $Chi^2 = 31.81$, df = 3 ($P < 0.00001$); $I^2 = 91\%$
Test for overall effect: $Z = 2.93$ ($P = 0.003$)

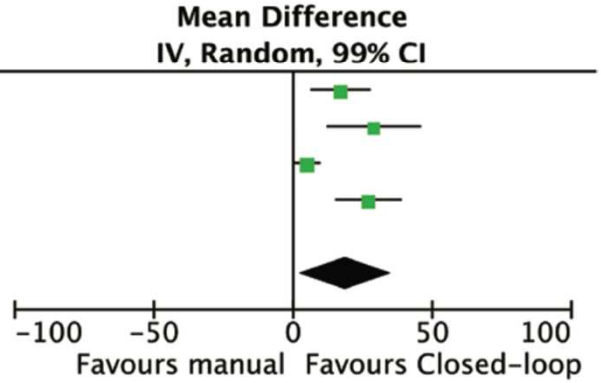


Figure 5. Forest plot of the Global Scores. CI indicates confidence interval.

- Pasin A&A 2017

Que disent les meta-analyses?

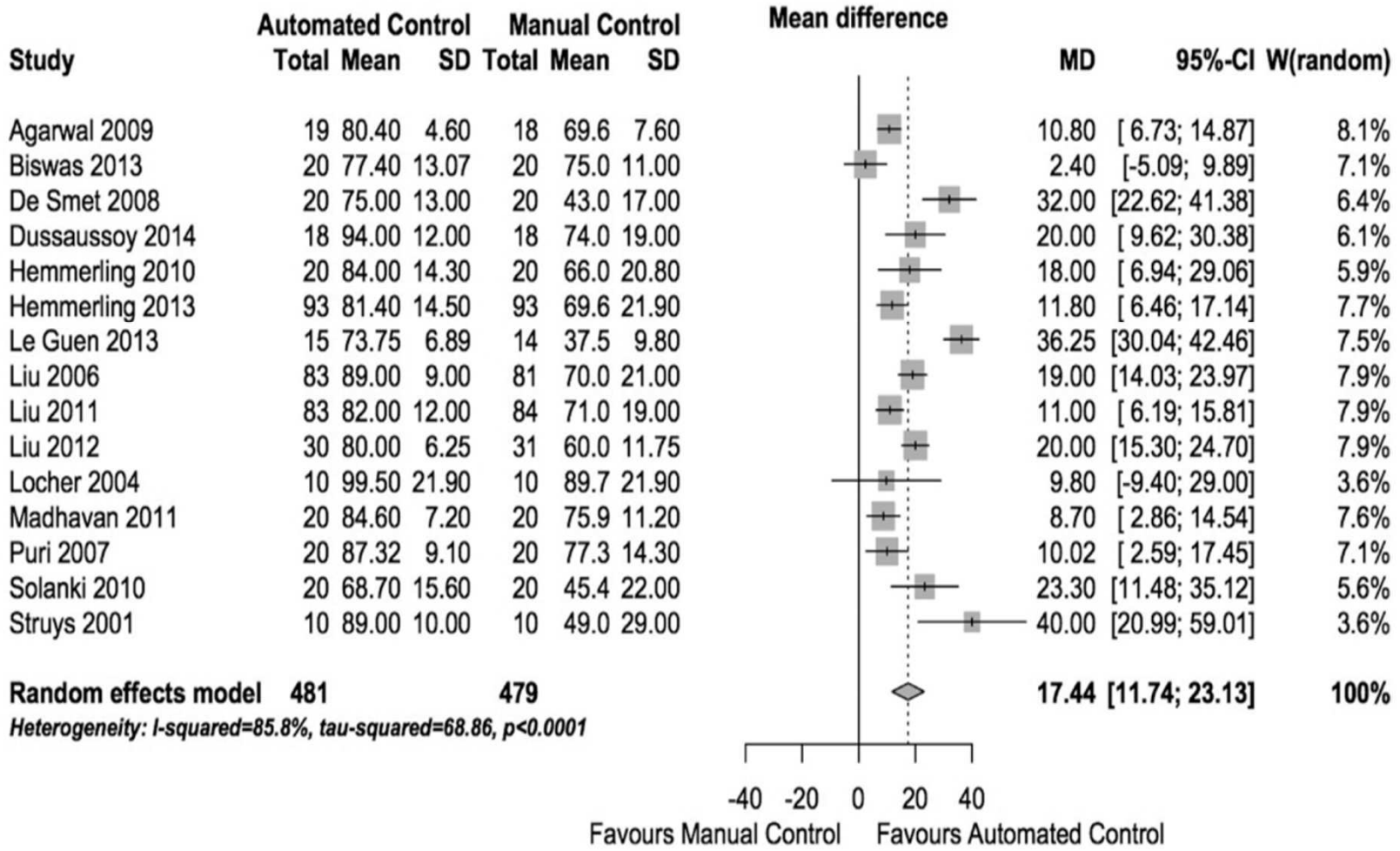


Figure 2. Forest plot presenting the percentage of time a given target (bispectral index or SE) was maintained within the desired range in closed-loop delivery systems (automated control) in comparison with manual control. The diamond represents the pooled results while the horizontal line represents the 95% confidence interval (CI).

- Hemmerling A&A 2017

Quels intérêts?

Avantages du système

- Réduction de la charge de travail*
  → Permet de se concentrer sur des taches
  Qui nécessite une intelligence humaine
  (Saignement – interprétation des GDS)

⇑ Sécurité

- Control d'un paramètre avec plus de précision
  → Pas distraction = Pas d'erreur humaine

⇑ Sécurité

*: Dussaussoy JCMC 2014
**: Zaouter A&A 2016

→ maintien des valeurs BIS entre 40 et 60 plus précis

BIS <45 a été associé à des prognostics défavorable chez les ***personnes âgées***, chez les ***patients atteints de cancer*** et pendant la ***chirurgie cardiaque***.

Cela souligne l'importance des systèmes en boucle fermée sur le devenir des patients

Leslie K. Anesth Analg 2010;110:816
Lindholm ML. Anesth Analg 2009;108:508
Kertai MD. Anesthesiology 2010;112:1116
Radtke BJA 2013; 110: i98

Monk TG. Anesth Analg 2005;100:4
Sessler DI. Anesthesiology 2012;116:1195
Watson PL. Crit Care Med 2008;36:3171
Chan MT J Neurosur Anesthesiol 2013; 25:33

Anaesthetics activity : still growing ?

C Dadure et coll., *SFAR* 2012; F Clergue et coll. *Anesthesiology* 1999; F Hatton et coll. Ann Fr Anesth Reanim 1983

Rate of Anaesthetics :

- 1980 : 6.6 per 100 population
- 1996 : 13.5 per 100 population
- 2010 : 17.8 per 100 population

	1980	1996	2010
Density (Anaesthetist per 100'000 population)	5.1	14.4	16.2
Cases / year / anaesthetist	1302	946	1219

with the courtesy of S Pontone

Mythe ou réalité?

Sur le marché? Concert-CL

https://french.alibaba.com/product-detail/closed-loop

Sur le marché? Concert-CL

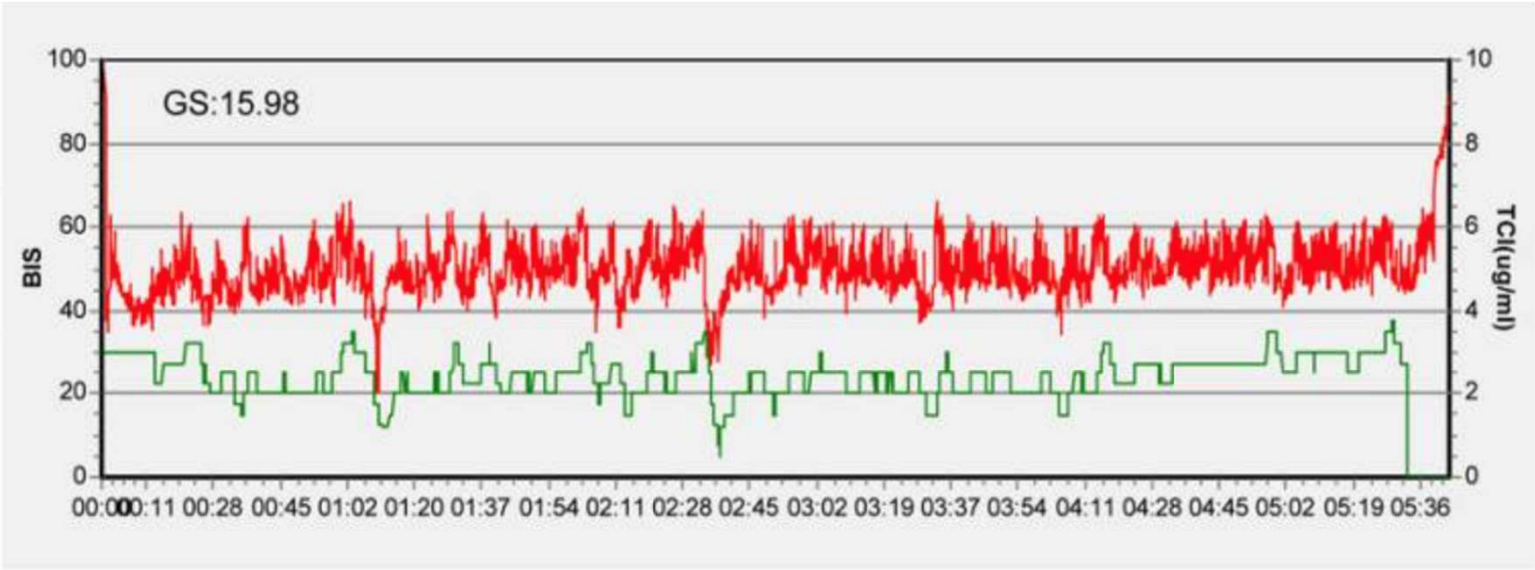
https://french.alibaba.com/product-detail/closed-loop

Sur le marché? Concert-CL

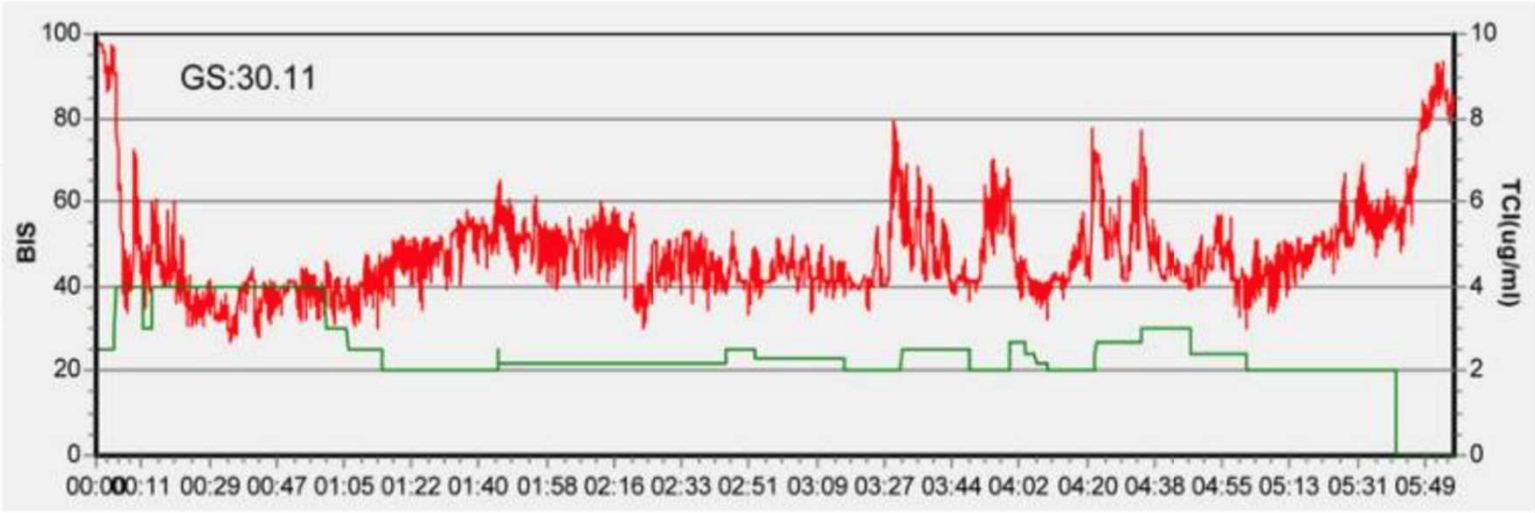
https://french.alibaba.com/product-detail/closed-loop

Sur le marché? Concert-CL

A sample result in closed-loop group



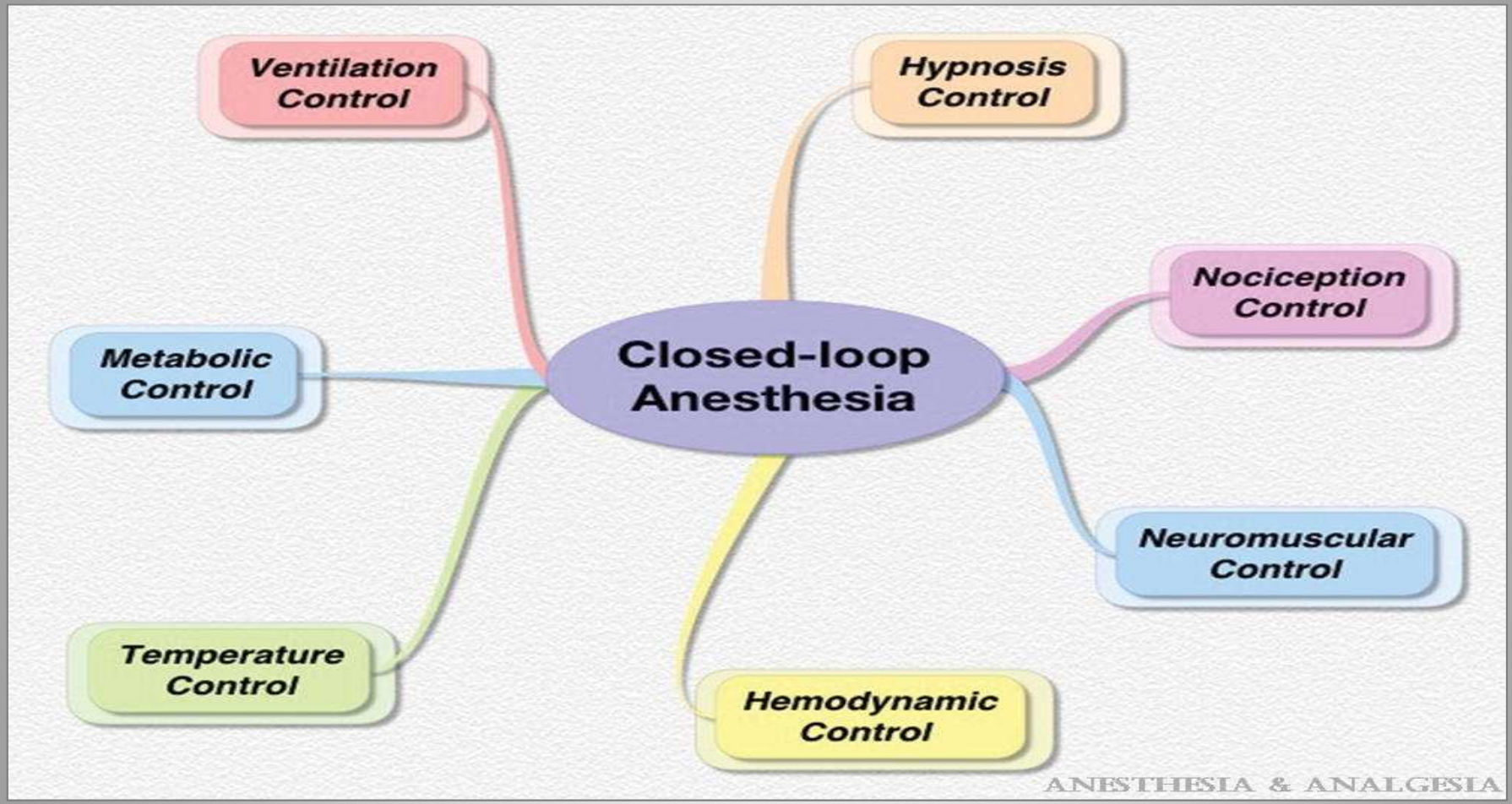
A sample result in open-loop group



Liu Y, PlosOne 2015

Perspectives

Dumont, Guy A. Anesthesia & Analgesia. 117(5):1130-1138, November 2013.



Rinehart J. Crit Care 2011;15:R278
Rinehart J. Anesth Analg 2013;117:1110–8
Rinehart J. Anesth Analg 2013;117:1119–29

Conclusion

L'automatisation de l'anesthésie est non seulement faisable mais permet une ***meilleur qualité d'administration*** des drogues associé à une ***réduction de la charge de travail***.

Leurs introduction dans la pratique clinique quotidienne est ***irrépressible*** et n'est qu'une question de temps.

The Future of Anesthesia: Will we be replaced by robots?

The answer is **NO**

- Anesthesiologists should not fear this development but drive it.
- Anesthesiologist will work hand in hand with robots to provide best patient care

The aim is to provide equal quality and performance any place, any time!

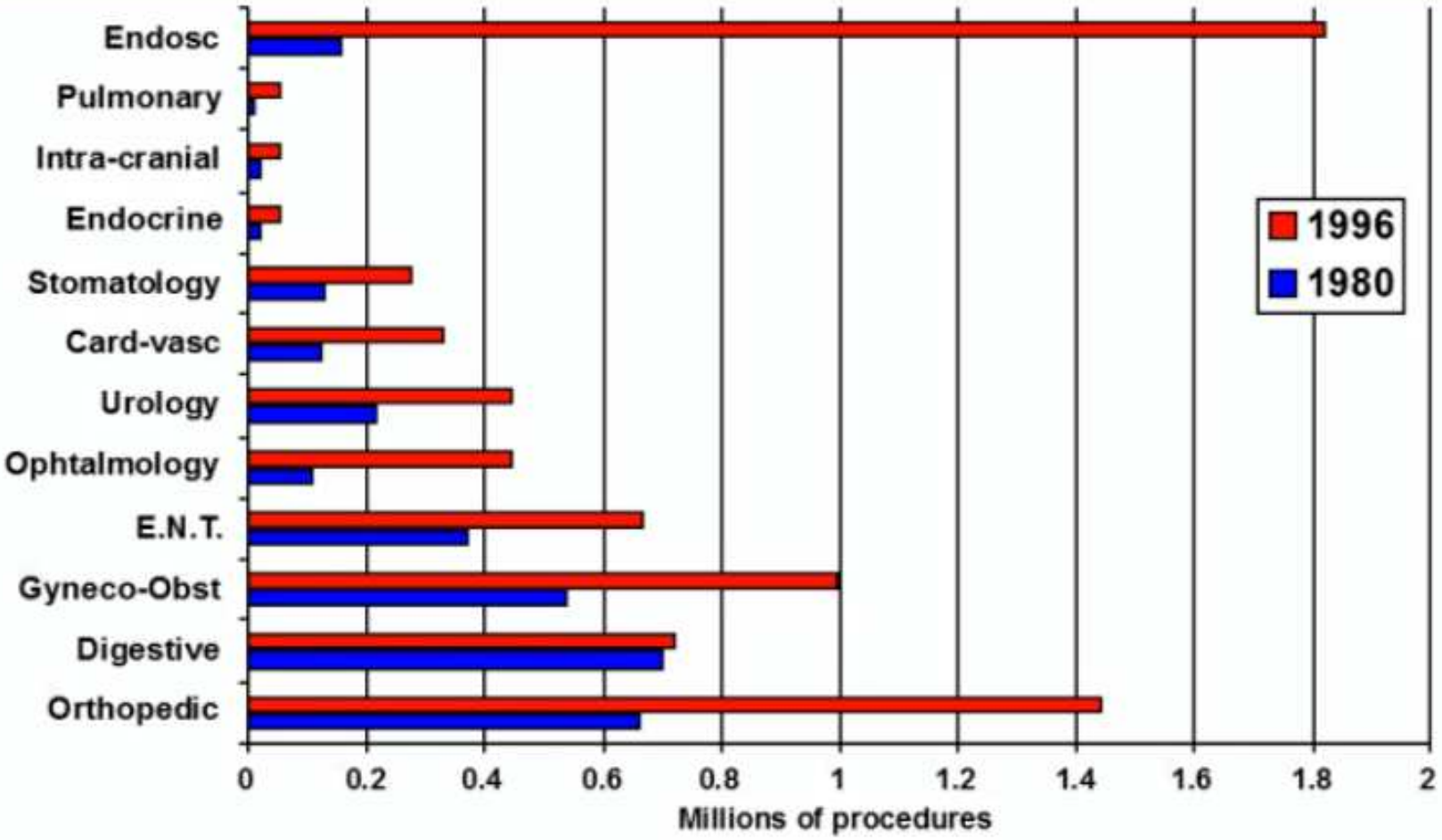
Robotic/Automatic drug delivery

1. **Proportional-integral-differential (PID)**
   - Simple and versatile: most used one.
   - Not appropriate when:
     - there is a significant delay of the controller feedback
     - dealing with a system encompassing multi-variable
2. **Based Adaptative/predictive (predictive self-adaptative)**
   - More complex → tailored to specific application
   - Minimize future output errors
3. **Intelligent control: fuzzy logic – expert systems**
   - Control of process that defy accurate mathematical description

* Lan JY, Abbod MF, Yeh RG, Fan SZ, Shieh JS.
Review: intelligent modeling and control in anesthesia. J Med Biol Eng 2012;32:293–308

A huge increase in the number of anaesthetics

Procedures associated with anaesthesia (France : 1980-1996)



F Clergue et al. Anesthesiology 1999

Liu N.

Double boucle: une seule variable

Remifentanil and propofol guided via M-entropy monitoring.

State entropy (SE)
SE is a surrogate measure of hypnotic depth
frontal electroencephalogram activity range of 0.8 –32Hz
Response entropy (RE)
electroencephalogram & electromyogram
frequency range of 0.8 – 47Hz = pain

Liu N. Anesthesiology 2012; 116:286–95

Liu N.

Double boucle: une seule variable

Remifentanil and propofol guided via M-entropy monitoring.

	Manual (n = 31)	Dual-loop (n = 30)	*P* Value
$SE_{<40}$	37 [14–62]	16 [5–32]	0.029
$SE_{>60}$	5 [1–7]	7 [2–9]	0.21
$SE_{40–60}$	60 [35–82]	80 [60–85]	0.046
SE_{PE}	−14 [−20– (−4)]	−6 [−12– (−1)]	0.014
SE_{MDPE}	−16 [−24– (−10)]	−8 [−12– (−4)]	0.016
SE_{MDAPE}	18 [14–26]	12 [10–18]	0.022
SE_{Wobble}	8 [6–10]	8 [8–14]	0.40
$SE_{Global\ Score}$	44 [25–110]	25 [19–53]	0.043
SR	7 (23)	4 (13)	0.51

	Manual (n = 31)	Dual-loop (n = 30)	*P* Value
$RE_{<40}$	23 [6–46]	12 [3–26]	0.12
$RE_{>60}$	10 [4–13]	11 [6–15]	0.38
$RE_{40–60}$	67 [42–84]	79 [57–84]	0.21
RE_{PE}	−7 [−15–1]	−1 [−7–4]	0.09
RE_{MDPE}	−10 [−18– (−2)]	−2 [−10–1]	0.11
RE_{MDAPE}	16 [10–26]	13 [10–19]	0.18
RE_{Wobble}	10 [8–12]	10 [8–14]	0.95
$RE_{Global\ Score}$	39 [24–91]	30 [22–63]	0.25

Liu N. Anesthesiology 2012; 116:286–95

Independent Predictors of One-year Mortality

"Multivariate modeling identified three significant predictors of mortality: patient comorbidity, cumulative deep hypnotic time (Bispectral Index < 45) and intraoperative systolic hypotension."

Predictor	Relative Risk [95% CI]	P Value
Charlson Comorbidity Score *(3+ vs 0-2)*	16.116 [10.110 – 33.717]	<0.0001
Cumulative Deep Hypnotic Time (BIS < 45) *(per hour)*	1.244 [1.062-1.441]	0.0121
Hypotension SBP < 80 mm Hg *(per minute)*	1.036 [1.006-1.066]	0.0125

c-statistic: 0.847, $p < 0.001$

Monk et al. Anesth Analg 2005

Poor Outcome with "Deep Anesthesia"

Monk et al (Anesthesia & Analgesia 2005)
- "Anesthetic management and one-year mortality after noncardiac surgery" A&A 2005
- **Hazard ratio (HR) 1.24** for Year 1

Lindholm et al (Anesthesia & Analgesia 2009)
- "Mortality within two years after surgery in relation to low intraoperative BIS values and pre-existing malignant disease" A&A 2009
- **Hazard ratio (HR) 1.13** (1.01-1.27) for Year 1 and 1.18 (1.08-1.29) for year 2

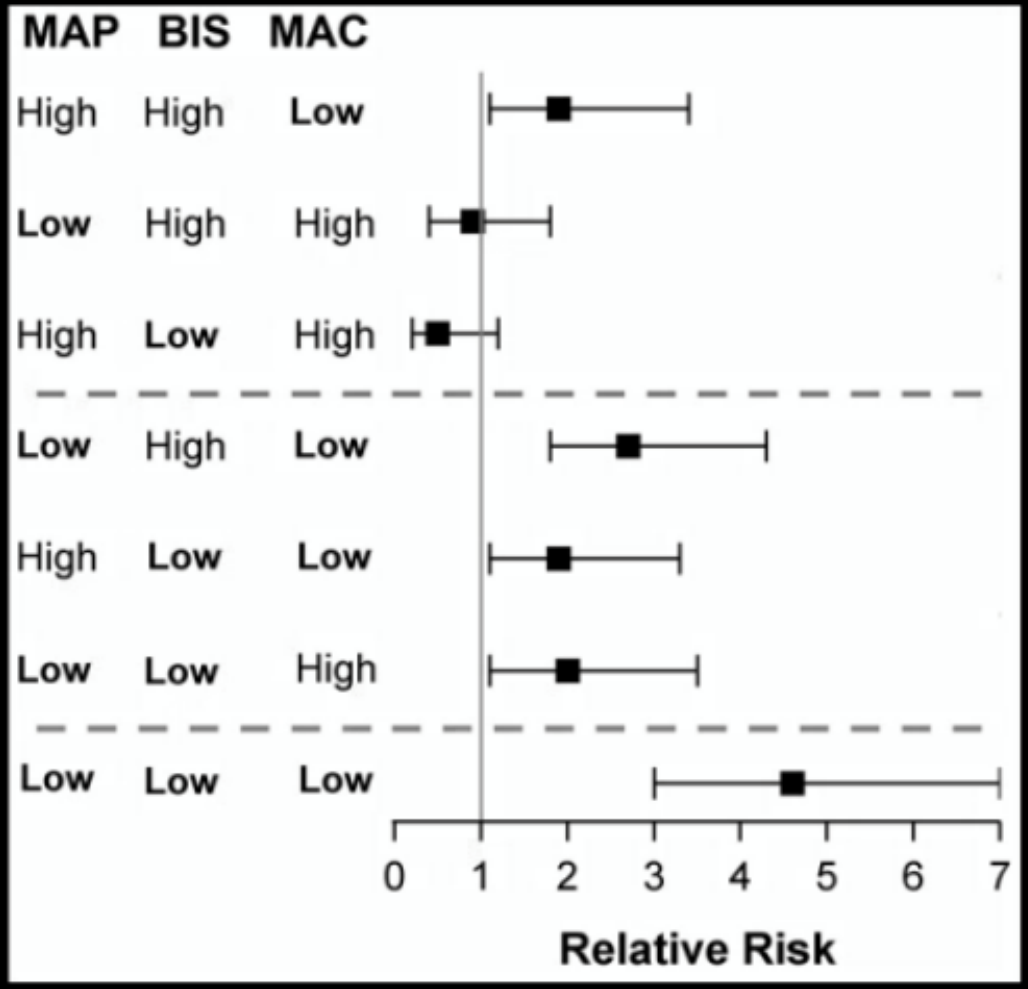
Searleman et al (ASA Meeting 2008)
- "Deep Hypnotic Time and One-Year Mortality in Non-Cardiac and Cardiac Surgical Patients" 2008 ASA A-1
- **Hazard ratio (HR) 1.25** (1.13 to 1.37) for Year 1

Watson et al (Critical Care Medicine 2009)
- "Presence of EEG suppression in critically ill patients is associated with increased mortality" CCM In Press
- **Hazard ratio (HR) 2.04** (1.12-3.70) for 6-month endpoint

Karri S et al (Society of Cardiac Anesthesia 2009)
- Deeper Level Of Anesthesia Is Associated With Adverse Neurological Outcomes In Cardiac Surgical Patients; ANESTH ANALG 2009; 108(SCA Suppl);1-104
- **Hazard ratio (HR) 3.67** for neurological morbidity

Leslie et al (TIVA/TCI Congress 2009)
- Prospective/Randomized: *Avoidance of Deep Anesthesia* (BIS<45 for 5 min) results in *lower mortality* compared to standard practice.

Double & Triple Lows, Risk Adjusted



M Sessler Cleveland Hospital A&A 2010

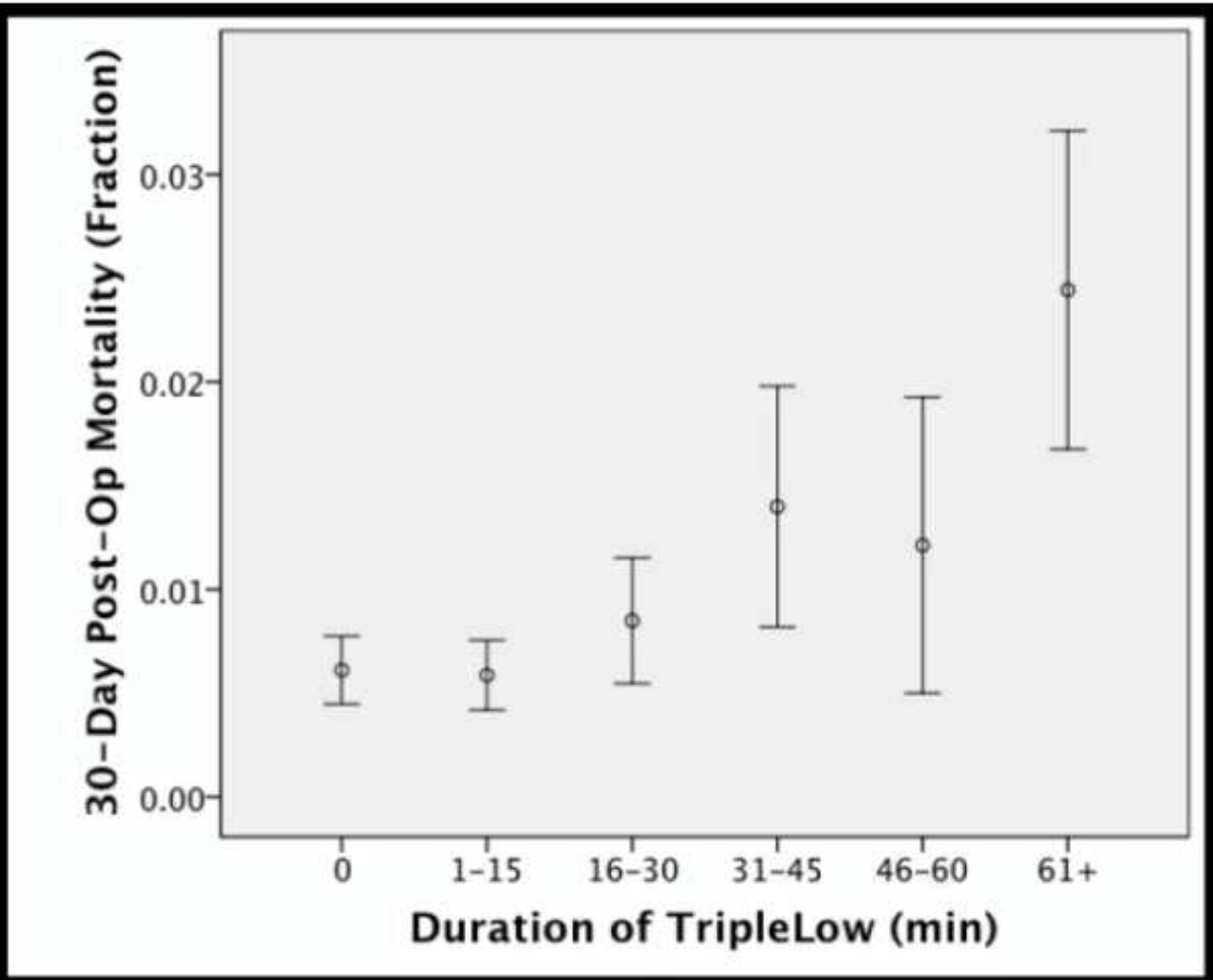
30-Day Mortality

Thresholds:

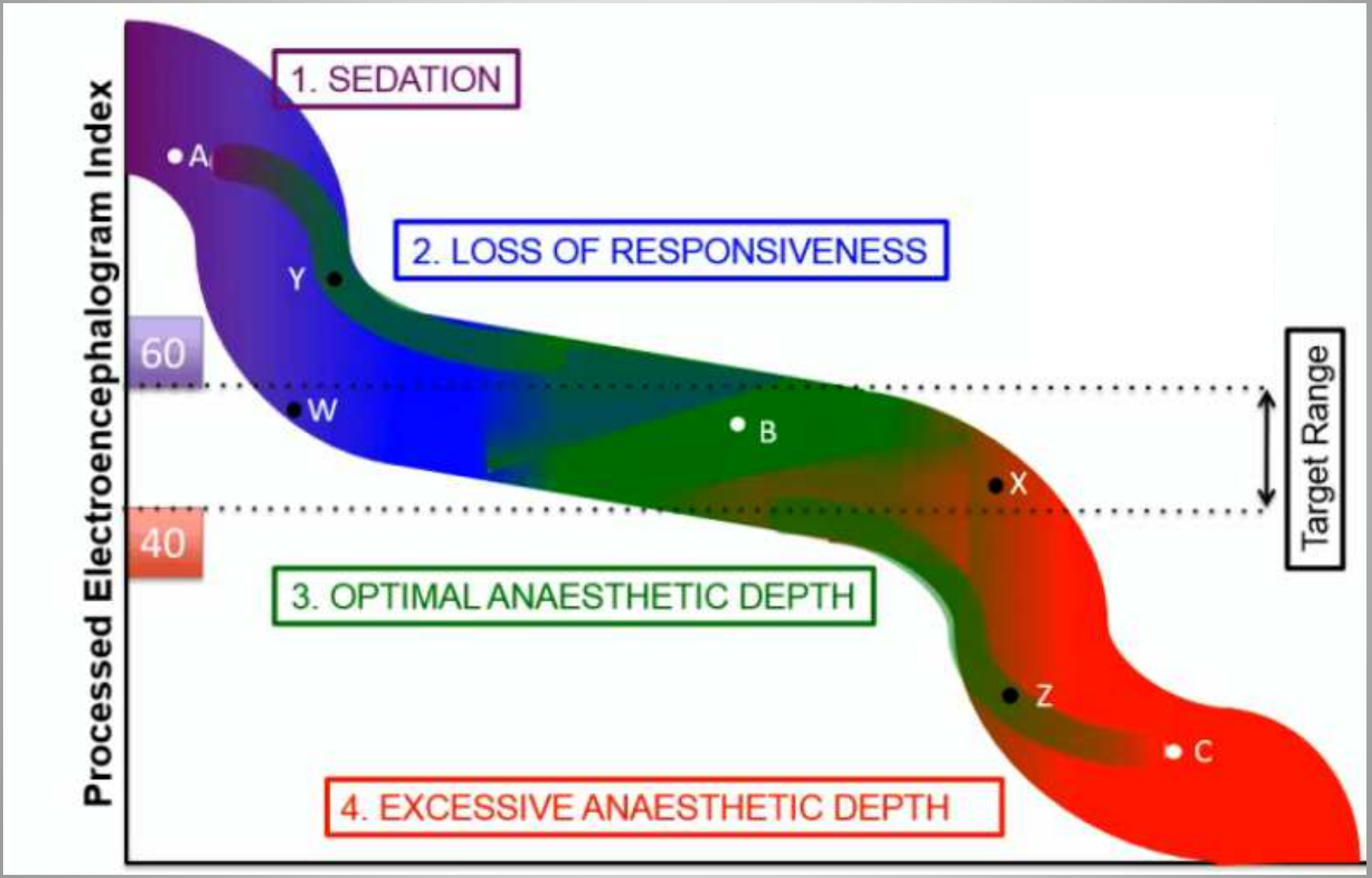
MAP <75 mmHG

MAC < 0.8

BIS <45



Individual response variation to BIS



What are the solutions ?

Tele aplication For GA

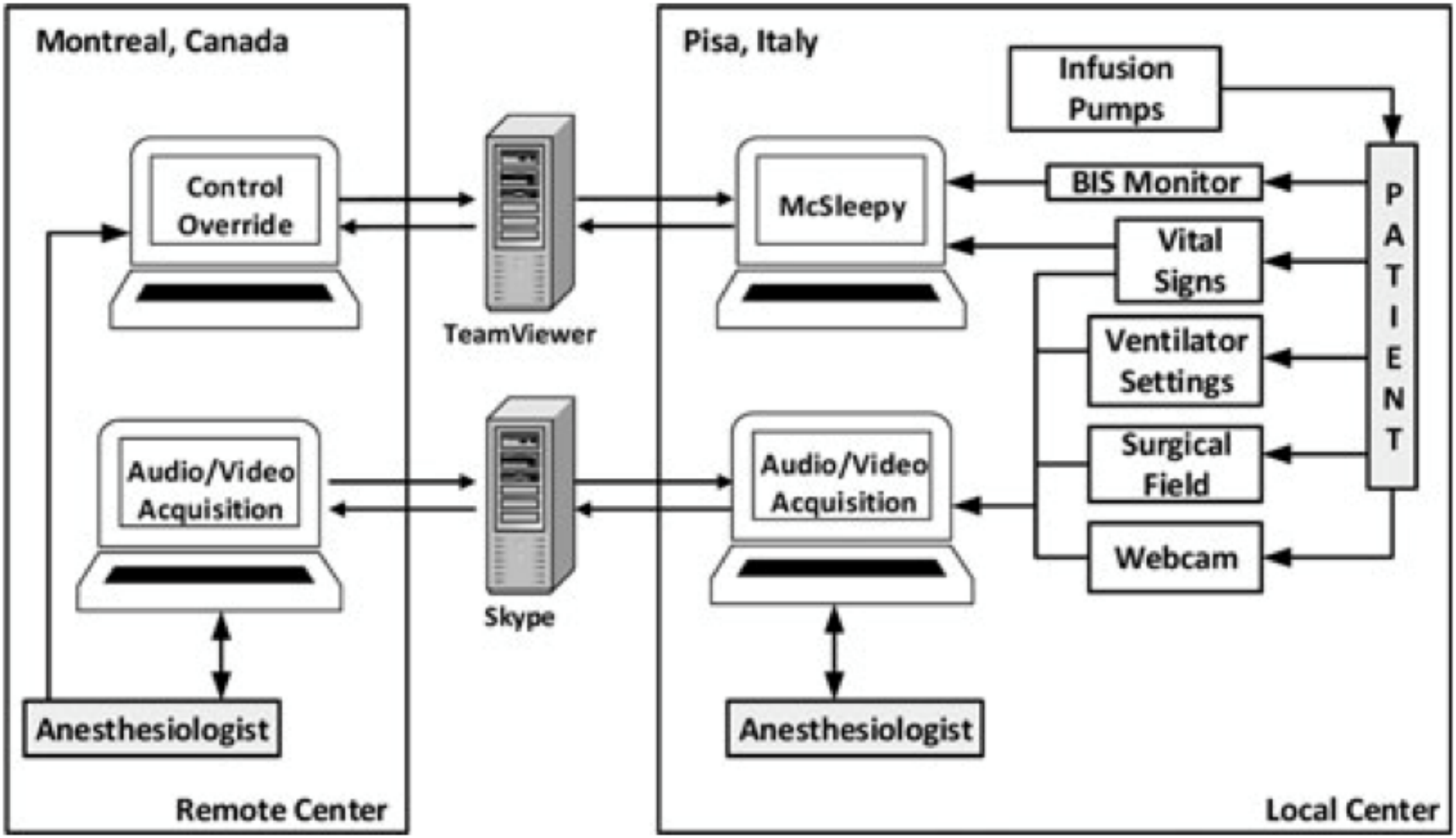
McSleepy™

- The first world tele-anesthesia was performed on August 30, 2010, using the **McSleepy™**.

Automated control of all 3 components of anesthesia:

- ✓ BIS monitor
- ✓ Analgesia monitor (NociMAP™)
- ✓ Muscle relaxation (Phonomyography)

TELE - APLICATION



What about sedation

Where anaesthesiologists are in short supply, the gap may be filled by training a greater number of nurse anaesthetists. If not, it is possible that alternative solutions would be sought outside anaesthesia, as is presently the case for sedation in gastrointestinal endoscopy.

Vargo JJ, Gastroenterology 2009; 137:2161 – 2167.

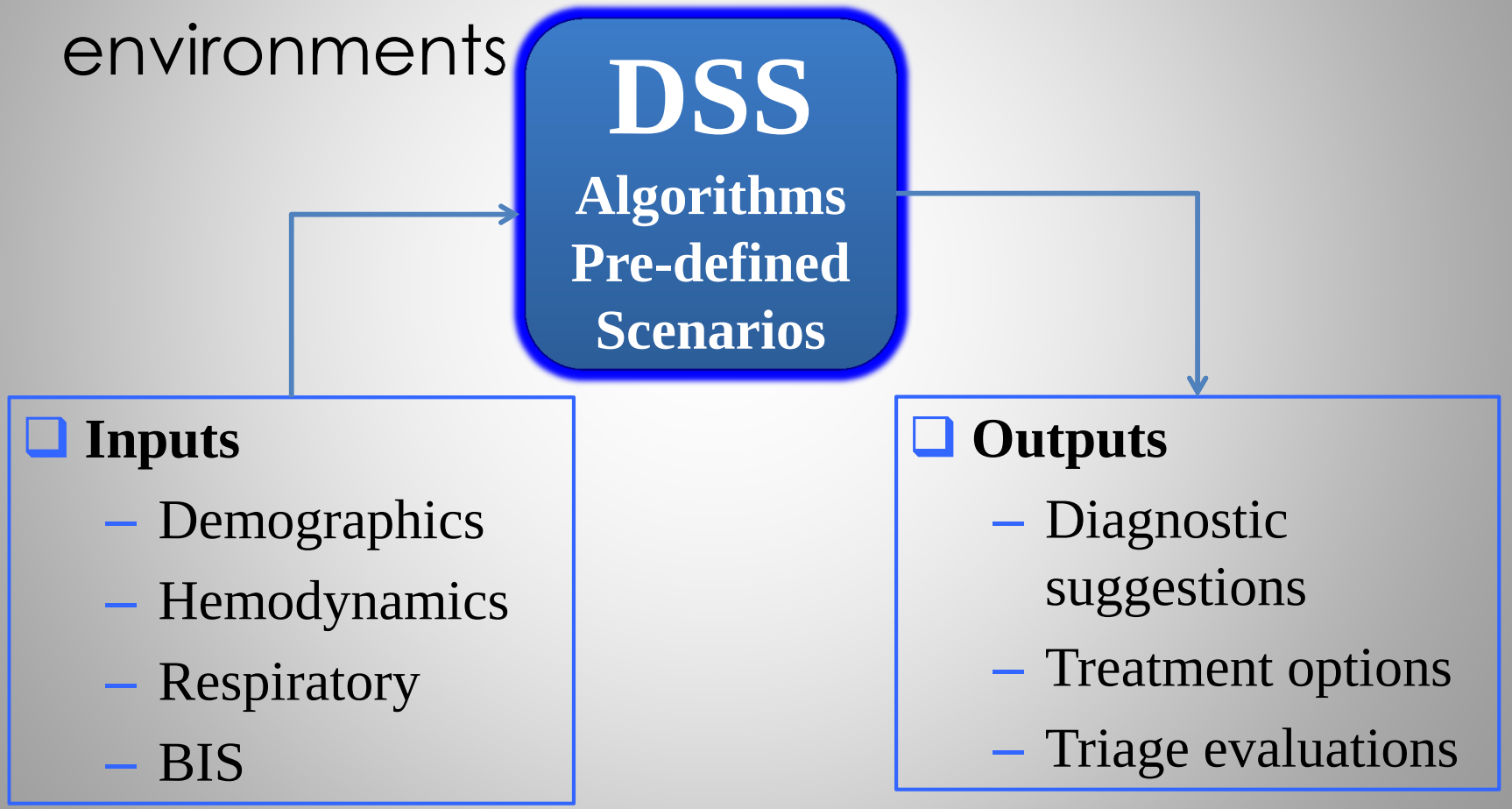
What else can be done

- Smart Monitoring and Control Systems
  - Closed Loop system; Has three elements:
    1. Data Acquisition
    2. Controller (Computer)
    3. Actuator
  - Decision-Support:
    1. Data collection and algorithmic analysis
    2. Presents diagnostic and therapeutic suggestions to operator

Hemmerling. Curr opp in anesth vol. 22 (6) pp. 757-63

Decision Support System (DSS)

- Aid decision-making in multi-tasking environments



Hemmerling. Automated anesthesia. Curr Opin Anaesthesiol, 2009

Effects of Computerized Clinical Decision Support Systems on Practitioner Performance and Patient Outcomes

A Systematic Review

- Diagnosis
- Disease Management
- Prevetion
- Drugs administration

DSS → Improve practitioner performance

Garg et al. JAMA (2005) vol. 293 (10) pp. 1223-38

Pharmacological Robots

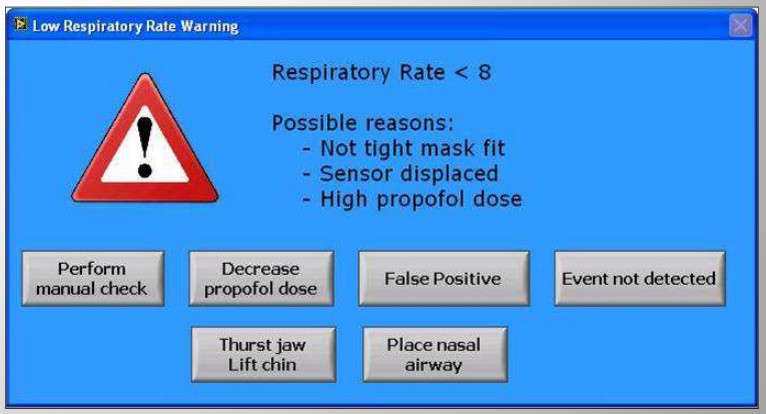
HSS- Hybrid Sedation System

- HSS is an hybrid closed loop sedation system which integrates a decision support system for controlled sedation.

'*HSS*' – A NOVEL HYBRID SYSTEM FOR CONSCIOUS SEDATION

Thomas Hemmerling, MSc, MD; E Arbeid; L Tang; S Cyr; M Wehbe; C Zaouter
Dept. of Anesthesiology, McGill University, ITAG Laboratory, Montreal, Canada

HSS interface

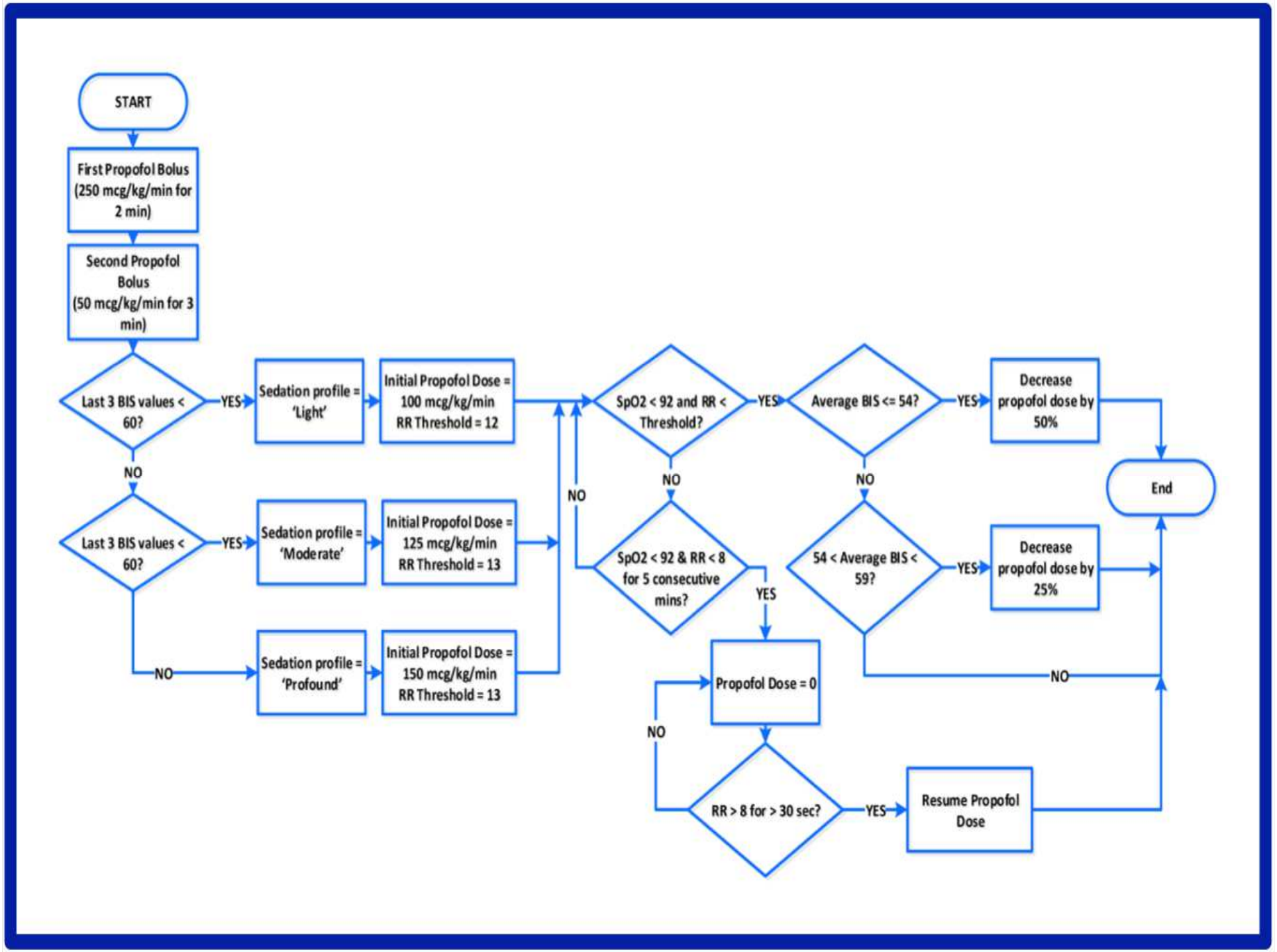


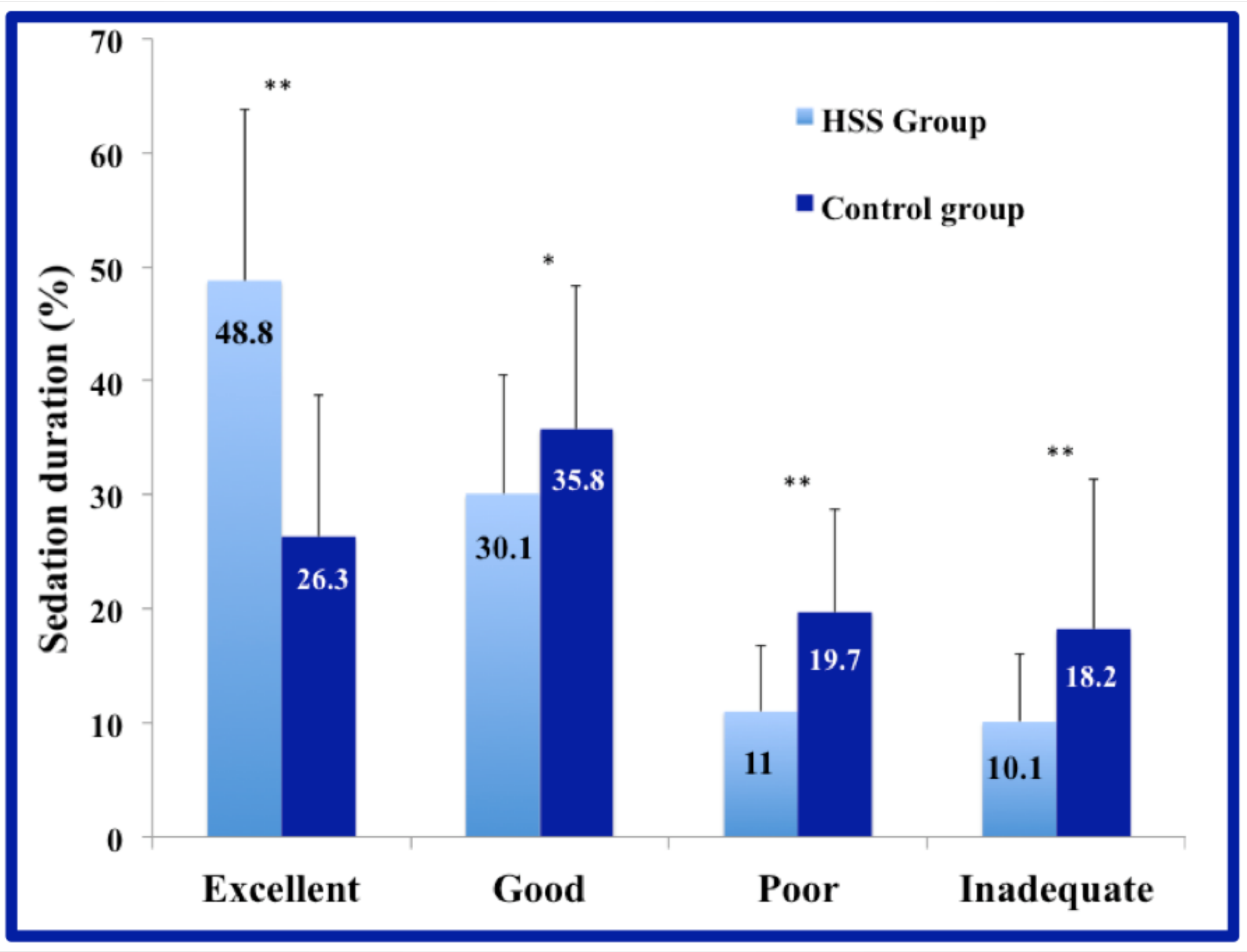
Pop – up menu for critical events

Hybrid Sedation System

- BIS value of 65 as the sedation target
- Rational of 65:
  - profound sedation state: confort
  - avoiding any abrupt movement

Johansen JW. *Best practice & Research.Clinical anaesthesiology.*2006;20(1):81
Glass PS. 1997;86(4):836-847
Liu J,*Anesthesia & analgesia.* Jan!1997;84(1):185-189.
Kearse LA, *Anesthesiology.* Jan 1998;88(1):25-34.


START
First Propofol Bolus (250 mcg/kg/min for 2 min)
Second Propofol Bolus (50 mcg/kg/min for 3 min)
Last 3 BIS values < 60?
YES
Sedation profile = 'Light'
Initial Propofol Dose = 100 mcg/kg/min RR Threshold = 12
NO
Last 3 BIS values < 60?
YES
Sedation profile = 'Moderate'
Initial Propofol Dose = 125 mcg/kg/min RR Threshold = 13
NO
Sedation profile = 'Profound'
Initial Propofol Dose = 150 mcg/kg/min RR Threshold = 13
NO
SpO2 < 92 and RR < Threshold?
YES
Average BIS <= 54?
YES
Decrease propofol dose by 50%
NO
SpO2 < 92 & RR < 8 for 5 consecutive mins?
YES
Propofol Dose = 0
NO
RR > 8 for > 30 sec?
YES
Resume Propofol Dose
NO
54 < Average BIS < 59?
YES
Decrease propofol dose by 25%
NO
End


70
60
50
40
30
20
10
0
Sedation duration (%)
HSS Group
Control group
**
*
**
**
48.8
26.3
30.1
35.8
11
19.7
10.1
18.2
Excellent
Good
Poor
Inadequate

Intraoperative sedation management and awake time

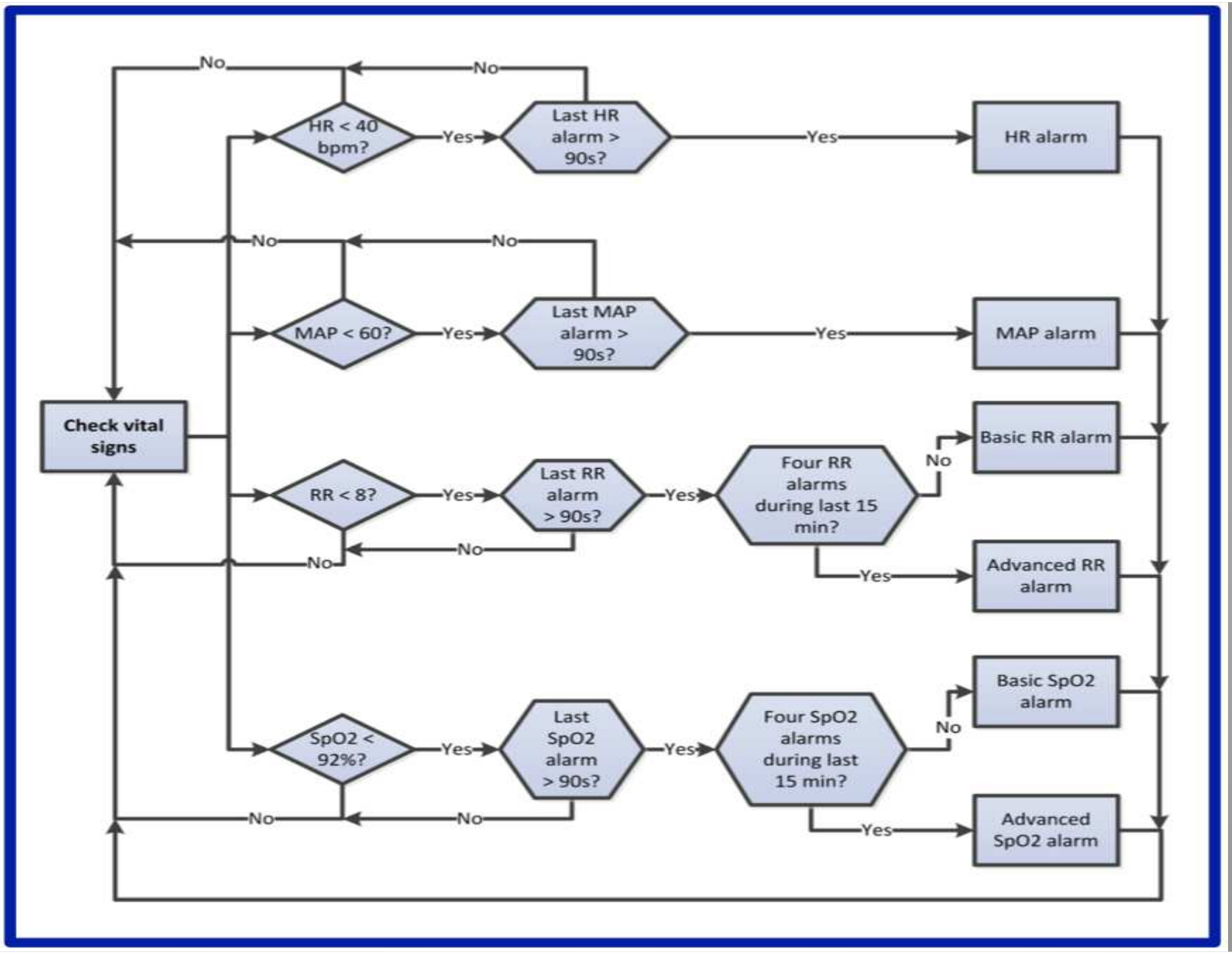
	HSS-Group (n=75)	Control Group (n=75)	P
Median propofol dose (mg)	87.1±38.5	68.7±22.3	**0.001***
Dose change/hour	22.2±4.6	4.7±2.9	**<0.0001***
Awake time/hour (min)	4.7±10.0	13.7±13.8	**<0.0001***

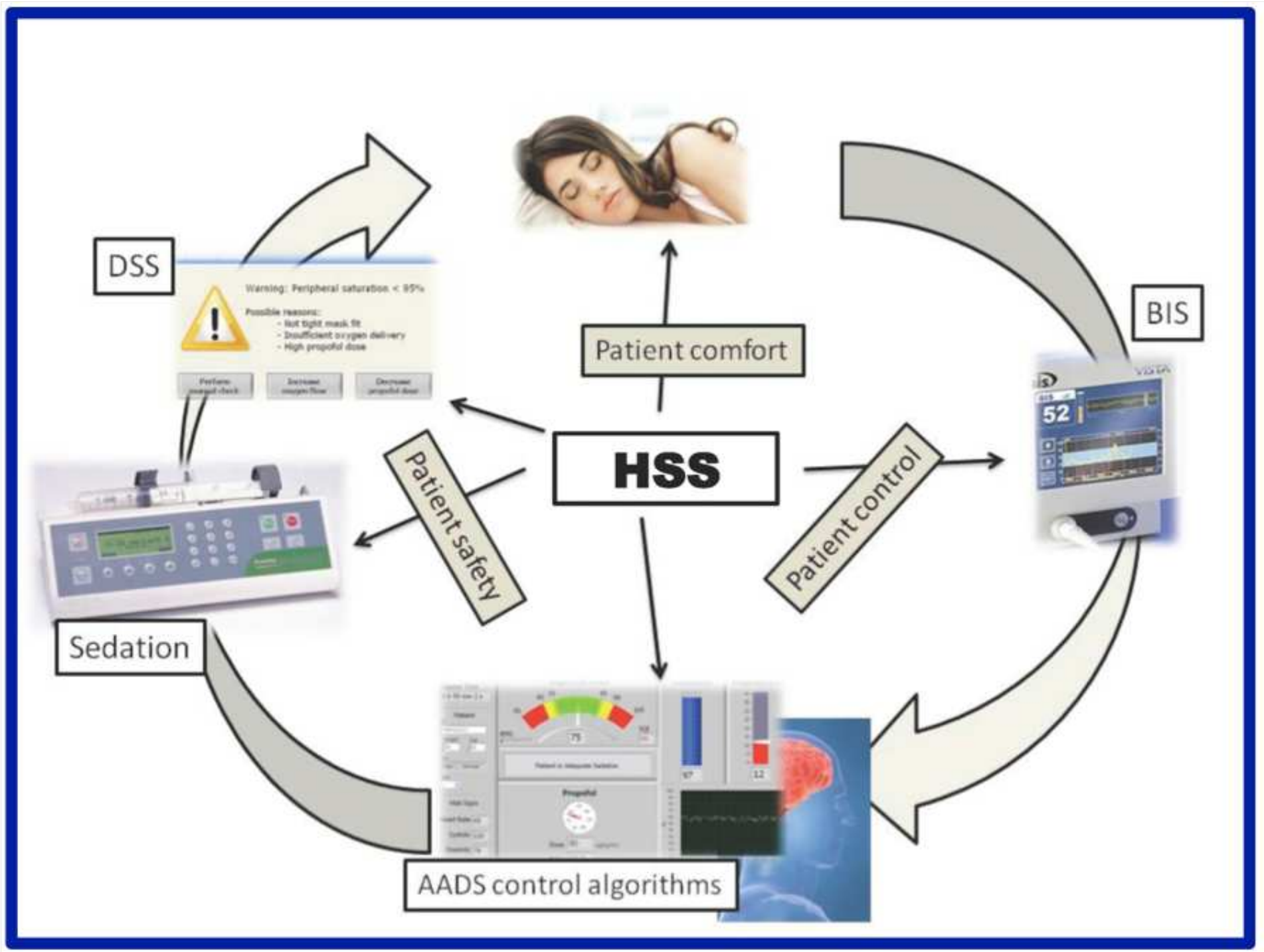
Clinical Performance

Sedation time (%)	HSS-Group (n=75)	Control Group (n=75)	P
BIS<55	14.0±9.3	21.8±20.2	**0.003***
BIS<60	23.2±11.6	29.0±23.2	0,059
BIS>75	16.6±9.9	31.8±24.5	**<0.0001***
BIS>80	7.1±6.7	14.8±15.6	**<0.0001***

Control Performance

	HSS-Group (n=75)	Control Group (n=75)	P
MDPE	2.4±5.0	4.9±13.4	NS
MDAPE	10.8±4.0	18.0±5.4	**<0.0001***
Wobble	9.4±3.6	11.7±5.2	**0.001***
Divergence	-0.11±0.13	-0.06±0.11	**0.02***
GPI	131.9±151.3	23.4±23.2	**<0.0001***


Check vital signs
HR < 40 bpm?
Yes
Last HR alarm > 90s?
Yes
HR alarm
No
No
MAP < 60?
Yes
Last MAP alarm > 90s?
Yes
MAP alarm
No
No
RR < 8?
Yes
Last RR alarm > 90s?
Yes
Four RR alarms during last 15 min?
No
Basic RR alarm
Yes
Advanced RR alarm
No
No
SpO2 < 92%?
Yes
Last SpO2 alarm > 90s?
Yes
Four SpO2 alarms during last 15 min?
No
Basic SpO2 alarm
Yes
Advanced SpO2 alarm
No
No


DSS
Warning: Peripheral saturation < 95%
Possible reasons:
- Not tight mask fit
- Insufficient oxygen delivery
- High propofol dose
Patient comfort
BIS
HSS
Patient safety
Patient control
Sedation
AADS control algorithms