Closed Loop Anesthesia

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UCLA

Conflicts of Interest

Consultant for:
Edwards Lifesciences
Masimo Corp.

Shareholder:
Sironis
Perceptive Medical

Research Support:
Masimo Corp
Edwards Lifesciences

Outline

- Introduction
- Feedback Control / Closed Loop / Automation
- Examples of Closed Loop Systems in Anesthesia
- The Challenges Ahead

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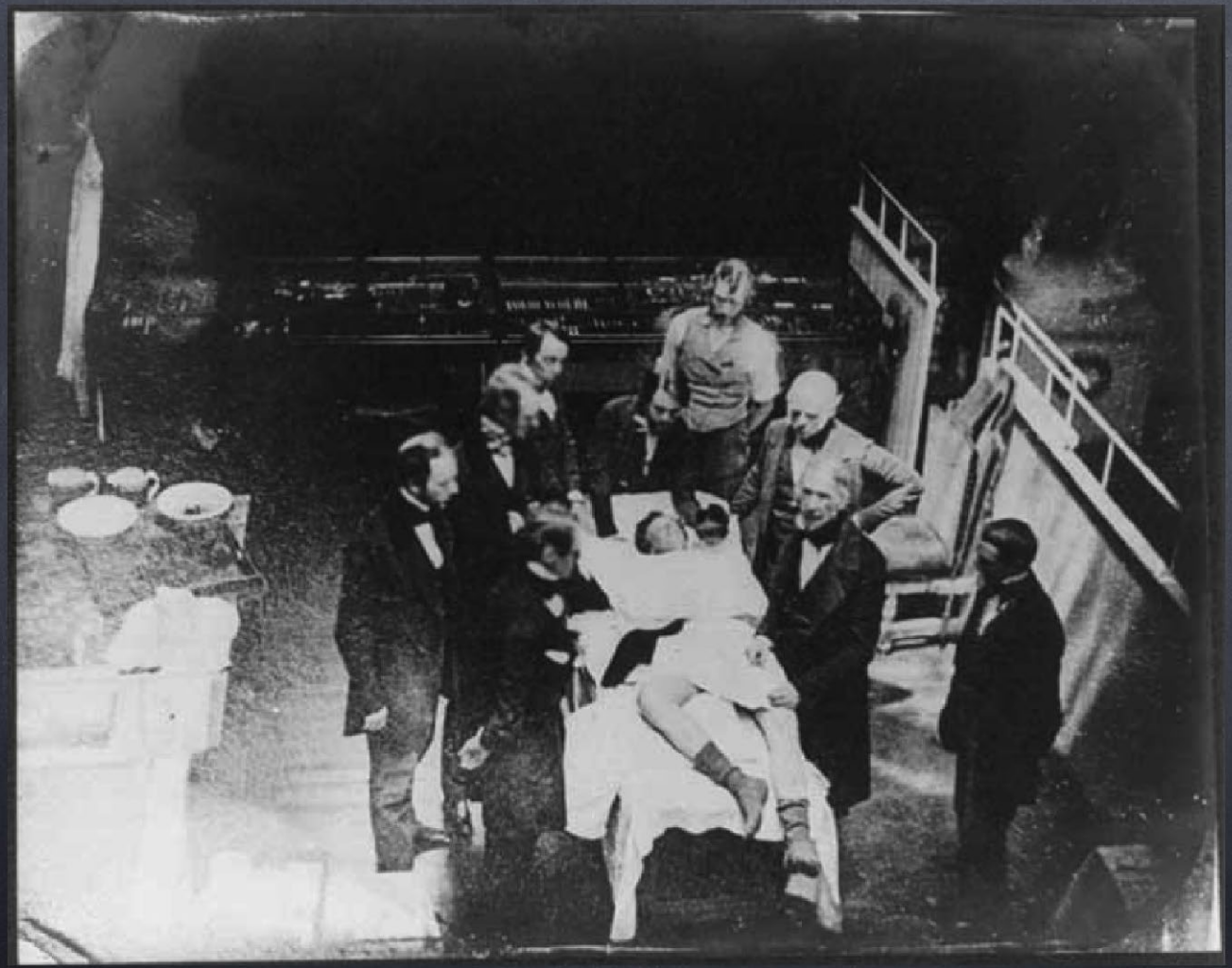


THE OPEN MIND

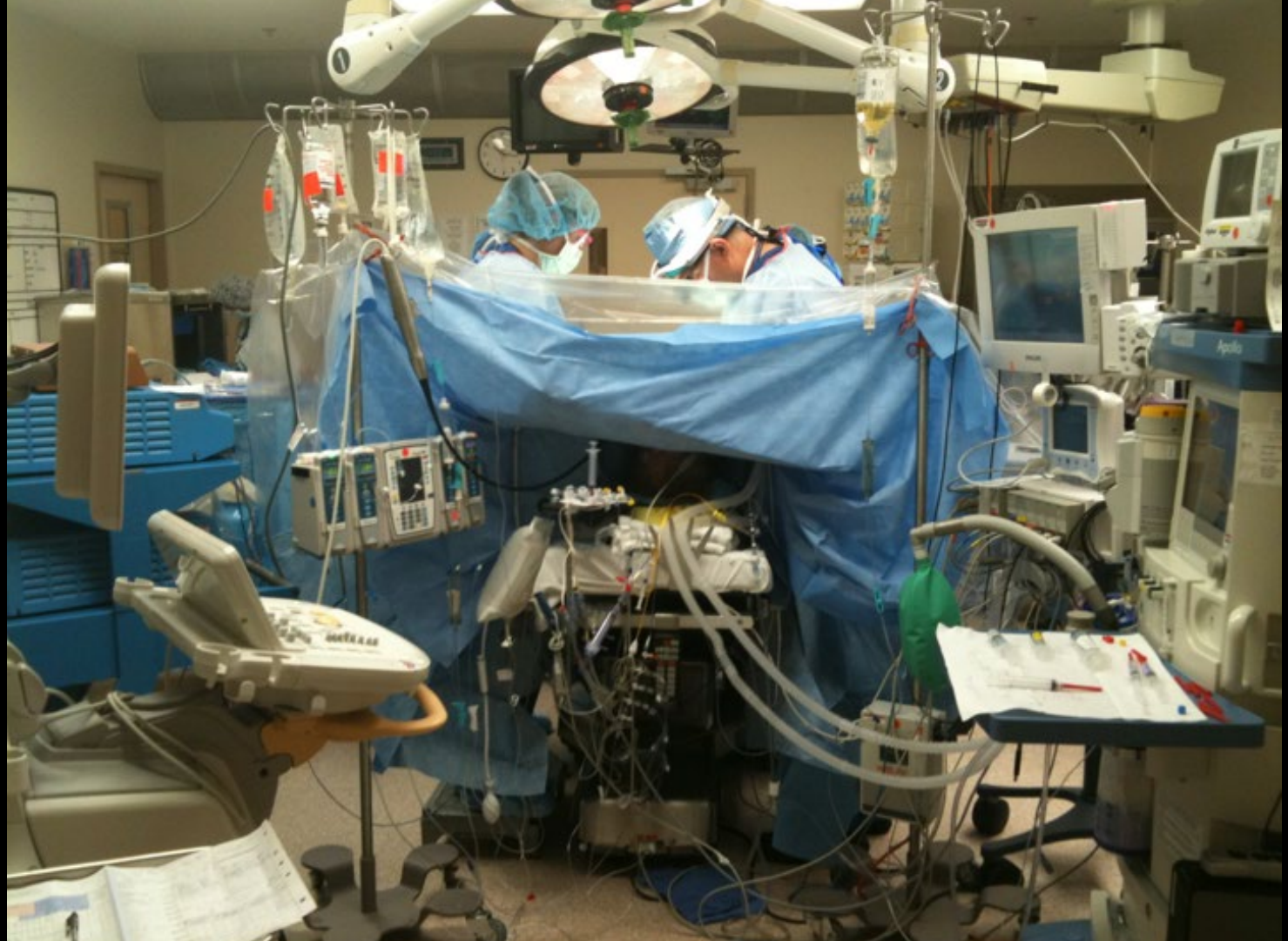
A Century of Technology in *Anesthesia & Analgesia*

Jane S. Moon, MD, and Maxime Cannesson, MD, PhD

A&A 2022

In operating rooms of the future technical equipment probably will include a device by means of which the pulse may be counted with the aid of electronics and a beam of light may be projected on a scale on the operating room wall, so that any interested person in the room can immediately see exactly what the pulse rate is. The same means can be used for showing the blood pressure and also the degree of anoxemia or need for oxygen. A permanent record could even be made. At the moment, the proposal sounds complicated, but if the method were once in use, it would soon become part of everyday life and the anesthesiologist and surgeon would wonder how they got along without it.

—John S. Lundy, MD.
Factors that influenced the development of anesthesiology.
Anesth Analg. 1946;25:38–43.

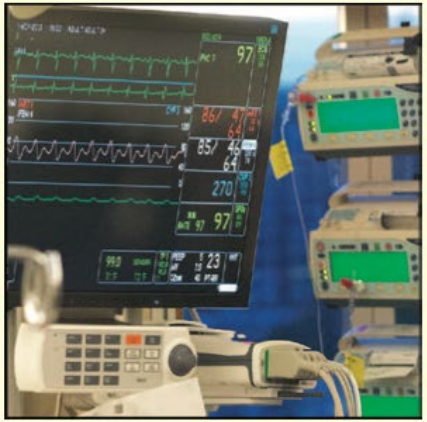


From Heroism to Safe Design

Leveraging Technology

Anesthesiology 2014

Peter J. Pronovost, M.D., Ph.D., George W. Bo-Linn, M.D., M.H.A., Adam Sapirstein, M.D.



"To improve patient safety and productivity, patients and clinicians need a health-care information ecosystem with integrated technologies that support the clinician's work, provide safety nets, and improve productivity."

Critical Care December 2005 Vol 9 No 6 Pinsky and Payen

Review

Functional hemodynamic monitoring

Michael R Pinsky[1] and Didier Payen[2]

‘Finally, no monitoring tool, no matter how accurate, by itself has improved patient outcome’

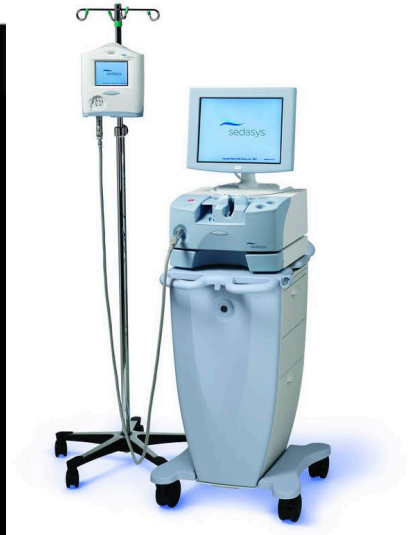
BUSINESS

J&J to Stop Selling Automated Sedation System Sedasys

Poor sales from a product that was opposed by anesthesiologists

By JONATHAN D. ROCKOFF
March 14, 2016 5:08 p.m. ET

1 COMMENTS

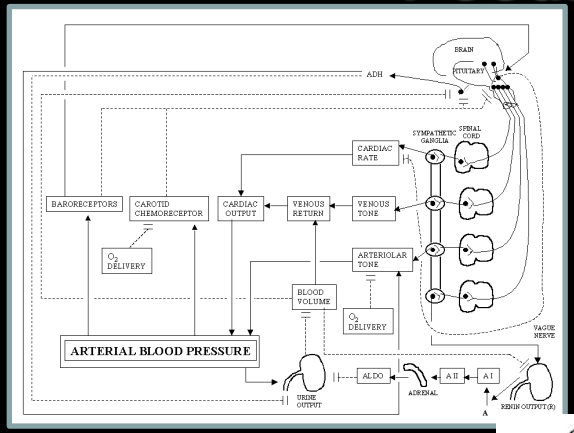


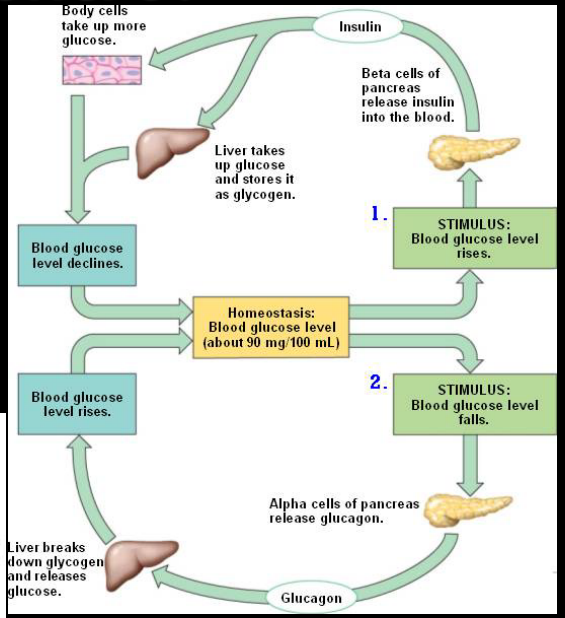
Outline

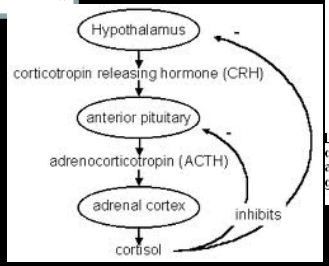
- Introduction
- **Feedback Control / Closed Loop / Automation**
- Examples of Closed Loop Systems in Anesthesia
- The Challenges Ahead

Biology / Physiology

Feedback Control







- "Closed Loop" is a **generic term** with no specific meaning
- **"Physiology"** and "Life" are **based on Closed Loop** controls
- The specificity is in the **Sensor** and in the **Controller**

Closed Loop Systems are Everywhere

- AC
- Cruise Control (speed regulators in modern cars)
- Electric Oven
- Elevators
- ….

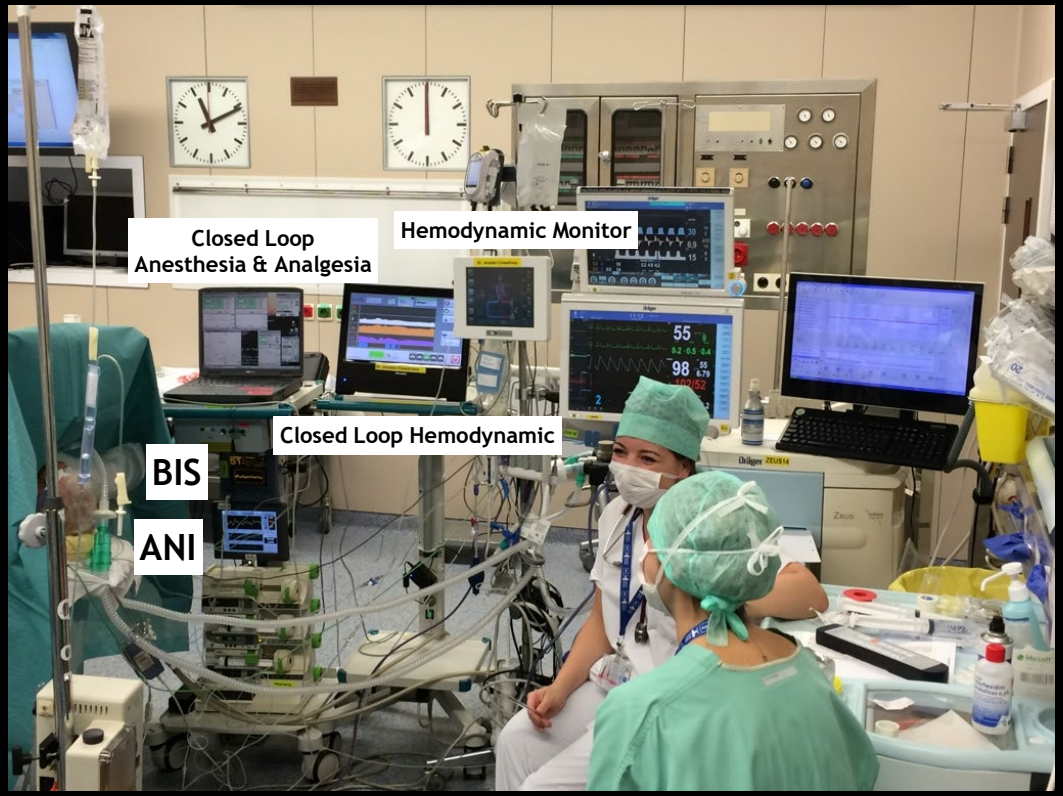
Air conditioning

The main unit pumps cool air throughout the house, the temperature is monitored by sensors in the home, and this data is then compared to the settings on the thermostat and used to increase or decrease the cooling so that the temperature hovers near the set point. While it would be possible to manually adjust the flow rate, the odds are that you would commonly overshoot or undershoot your desired temperature and the system would require many adjustments every hour to even modestly approximate the performance the automatic controller easily achieves.

Fully Automated Anesthesia and Fluid Management Using Multiple Physiologic Closed-Loop Systems in a Patient Undergoing High-Risk Surgery

Alexandre Joosten, MD,* Amélie Delaporte, MD,* Maxime Cannesson, MD, PhD,† Joseph Rinehart, MD,‡ Jean Philippe Dewilde, MD,§ Luc Van Obbergh, MD, PhD,* and Luc Barvais, MD, PhD*

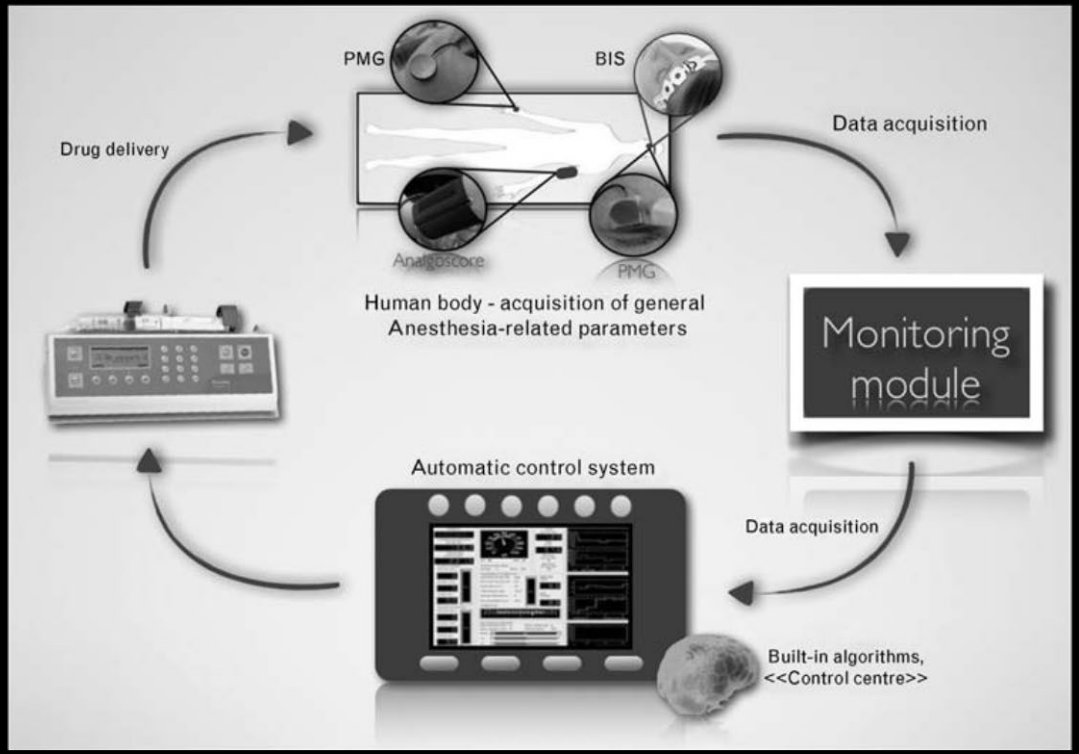
Automated delivery of anesthesia guided by processed electroencephalogram monitoring using a closed-loop system is no longer a novel concept. However, combining multiple independent physiologic closed-loop systems together has never been documented before. The purpose of this case report was to evaluate the feasibility of automated anesthesia and fluid management based on a combination of physiological variables (bispectral index, stroke volume, and stroke volume variations) using 2 independent closed-loop systems. (A&A Case Reports. 2016;XXX:00–00.)



Anesthesia Analgesia 2016

The Future
Closed Loop

Automated anesthesia
Thomas M. Hemmerling



Hemmerling TM. *Curr Opin Anaesthesiol* 2009

Technology, Computing, and Simulation
Section Editor: Maxime Cannesson
SPECIAL ARTICLE

Regulatory Considerations for Physiological Closed-Loop Controlled Medical Devices Used for Automated Critical Care: Food and Drug Administration Workshop Discussion Topics

Bahram Parvinian, MS,*† Christopher Scully, PhD,† Hanniebey Wiyor, PhD,* Allison Kumar, BS,‡ and Sandy Weininger, PhD†

PCLC: Physiological Closed Loop Control

Table 3. Concept of Level of Automation Applied to an Example of a Physiological Closed-Loop Controlled Medical Device

Medical Device LOA	Task	Example Neonatal Oxygen Therapy
1	Manual therapy. All decisions pertaining to care of the patient as related to a specific therapy are made by the clinician. The device does not provide decisions nor does it provide recommendations	Clinician determines oxygen therapy is needed. Makes F_{IO_2} adjustment for a hypoxemic patient based on vital signs, Spo_2 monitor, and overall status of the patient. Clinician decides when to wean
2	Partial automation. Clinician determines the type of therapy that is needed, determines the input target/range. The device actuates automatically to keep the patient on target or within the prescribed range. All set points are determined by clinician	Clinician determines the patient needs oxygen therapy, inputs the prescribed range of Spo_2 between 90% and 95%. Device senses Spo_2 of 80% and increases F_{IO_2} by 50% automatically to keep the patient Spo_2 between 90% and 95% as determined by clinician. Clinician decides when to wean
3	High automation. The clinician determines the type of therapy that is needed and prescribes the first target range or set point. Device actuates to keep the patient within target prescribed range but determines and adjusts the subsequent set points automatically. Clinician will have override capabilities to assume manual care at any time	Clinician determines the patient needs oxygen therapy. Device senses Spo_2 of 80% and increases F_{IO_2} by 50% autonomously to keep the patient Spo_2 between 90% and 95% as determined by the device algorithm. The clinician decides when and how to wean
4	Full automation. Device determines type of therapy. Determines the set points and course of oxygen delivery as well as initiation and rate of weaning. Clinician will have override capabilities to assume manual care at any time	Device determines oxygen therapy is needed and autonomously delivers oxygen to keep Spo_2 within a range of 90%–95% as determined by device. The device determines when and how the patient is going to be weaned from oxygen. Clinician can always intervene

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A Novel Two-Dimensional Echocardiographic Image Analysis System Using Artificial Intelligence-Learned Pattern Recognition for Rapid Automated Ejection Fraction

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Dennis M. McNamara, MD, FACC,* Shobhit Madan, MD,† Joan M. Lacomis, MD,†
John Gorcsan III, MD, FACC*

Pittsburgh, Pennsylvania

Objectives We sought to test the hypothesis that a novel 2-dimensional echocardiographic image analysis system using artificial intelligence-learned pattern recognition can rapidly and reproducibly calculate ejection fraction (EF).

Background Echocardiographic EF by manual tracing is time consuming, and visual assessment is inherently subjective.

Methods We studied 218 patients (72 female), including 165 with abnormal left ventricular (LV) function. Auto EF incorporated a database trained on >10,000 human EF tracings to automatically locate and track the LV endocardium from routine grayscale digital cineloops and calculate EF in 15 s. Auto EF results were independently compared with manually traced biplane Simpson's rule, visual EF, and magnetic resonance imaging (MRI) in a subset.

Results Auto EF was possible in 200 (92%) of consecutive patients, of which 77% were completely automated and 23% required manual editing. Auto EF correlated well with manual EF ($r = 0.98$; 6% limits of agreement) and required less time per patient (48 ± 26 s vs. 102 ± 21 s; $p < 0.01$). Auto EF correlated well with visual EF by expert readers ($r = 0.96$; $p < 0.001$), but interobserver variability was greater ($3.4 \pm 2.9\%$ vs. $9.8 \pm 5.7\%$, respectively; $p < 0.001$). Visual EF was less accurate by novice readers ($r = 0.82$; 19% limits of agreement) and improved with trainee-operated Auto EF ($r = 0.96$; 7% limits of agreement). Auto EF also correlated with MRI EF ($n = 21$) ($r = 0.95$; 12% limits of agreement), but underestimated absolute volumes ($r = 0.95$; bias of -36 ± 27 ml overall).

Conclusions Auto EF can automatically calculate EF similarly to results by manual biplane Simpson's rule and MRI, with less variability than visual EF, and has clinical potential. (J Am Coll Cardiol 2007;49:217–26) © 2007 by the American College of Cardiology Foundation

Two-dimensional (2D) echocardiography is widely used clinically to assess left ventricular (LV) ejection fraction (EF) (1–5). Because EF has become an important criterion for pharmacologic, defibrillator, and resynchronization therapy, an accurate and reproducible EF has become increasingly important (1,6–10). Recent advances in 3-dimensional echocardiography have improved the accuracy of LV volumes and EF (11–13); however, 2D imaging currently remains most widely used in mainstream clinical practice (14). Because previous automated EF approaches were affected by gain-dependence and endocardial dropout (15–20), quantitative EF usually requires manual endocardial tracing of end-diastolic and end-systolic frames, which requires experience and may be time consuming. Consequently, visual estimation of EF is most popular in clinical practice, even though it is inherently subjective (21–25). A new approach applied to routine 2D images, known as Auto EF, has been developed using artificial intelligence-learned pattern recognition programming trained on several thousand human endocardial tracings to mimic steps such as bridging gaps in endocardial dropout and excluding papillary muscles. The objectives of this study were to test the hypotheses that Auto EF can: 1) rapidly and reproducibly calculate EF similar to results by manually traced biplane Simpson's rule; 2) perform with less variability than visual EF by expert readers; 3) perform more accurately than visual

From the *Cardiovascular Institute and †Department of Radiology, University of Pittsburgh, Pittsburgh, Pennsylvania. Dr. Gorcsan was supported in part by National Institutes of Health award K24 HL04503-01. Dr. Cannesson was a recipient of a grant from the Médaille d'Or des Hospices Civils de Lyon Program at the Claude Bernard University of Lyon, France.

Manuscript received April 10, 2006; revised manuscript received August 17, 2006, accepted August 21, 2006.

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John Gorcsan III, MD, FACC*

- Step 1: Creating Database (Memory)
  Expert manual tracing of > 10,000 LV 4 ch and 2 ch views
- Step 2: Identifying LV cavity (Pattern recognition)
- Step 3: Tracing the endocardial border (Sensor)
- Step 4: Tracking the LV border (Processor)
- Step 5: Calculating LV volumes and EF (Processor)

Cannesson et al. *J Am Coll Cardiol* 2007

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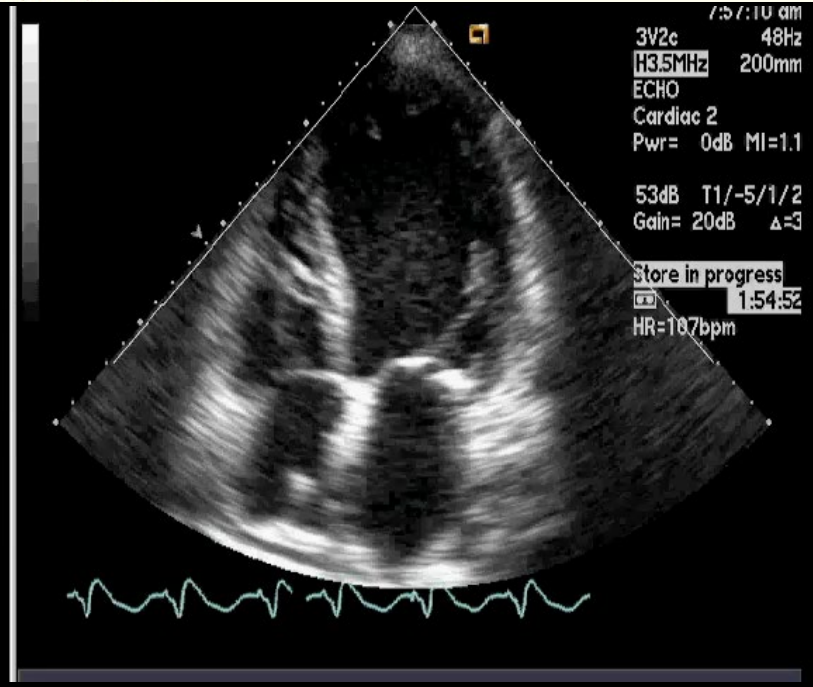

Cannesson et al. *J Am Coll Cardiol* 2007

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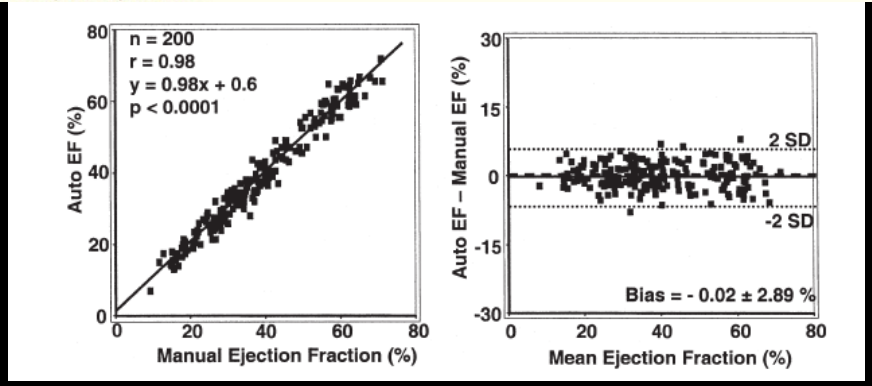

R 1

Cannesson et al. *J Am Coll Cardiol* 2007

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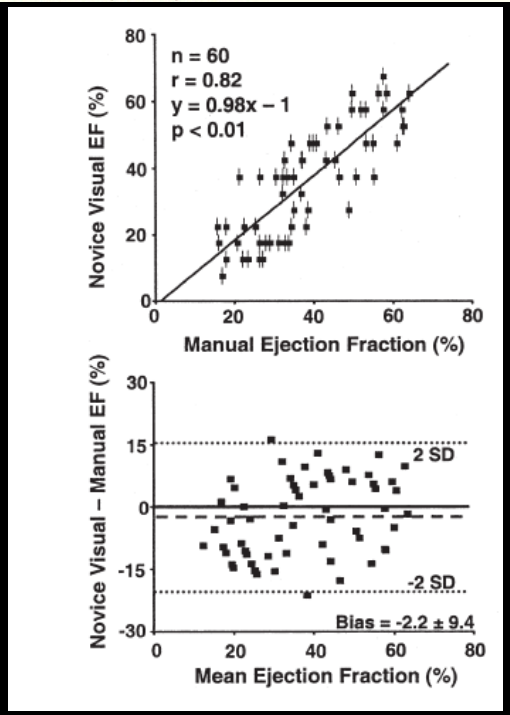
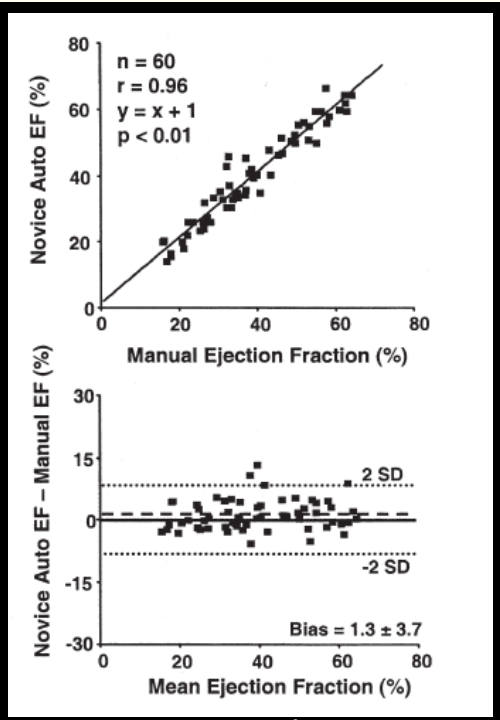




R 2

Cannesson et al. *J Am Coll Cardiol* 2007

Outline

- Introduction
- Feedback Control / Closed Loop / Automation
- Basics of Automation
- Examples of Automated Systems in Anesthesia
- The Challenges Ahead

ELECTROENCEPHALOGRAPHICALLY CONTROLLED ANESTHESIA IN ABDOMINAL SURGERY

CHARLES W. MAYO, M.D.
REGINALD G. BICKFORD, M.B.
and
ALBERT FAULCONER Jr., M.D.
Rochester, Minn.

JAMA®
The Journal of the American Medical Association

1950, 144 (13)

50 patients, ETHER
"Major Surgical procedures
varying age, both sexes
Without untoward effect "

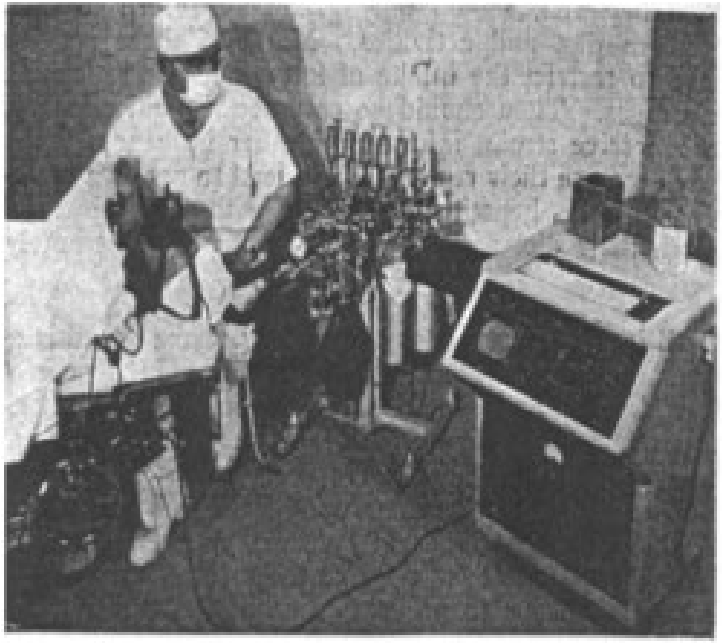
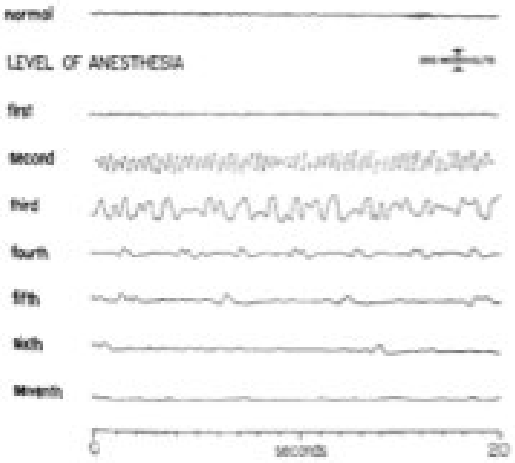


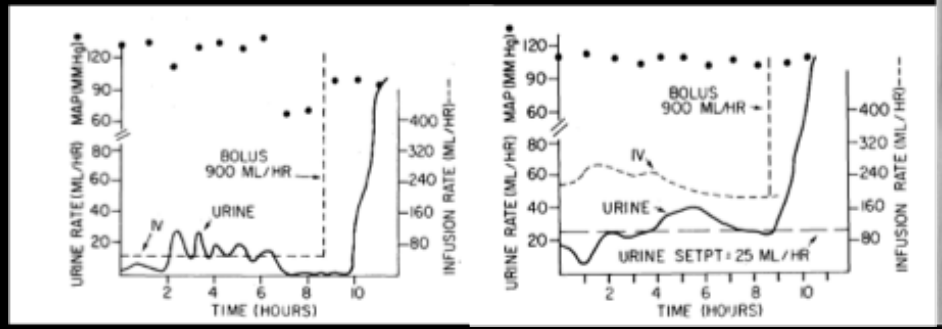
Fig. 2.—Automatic administration of ether.



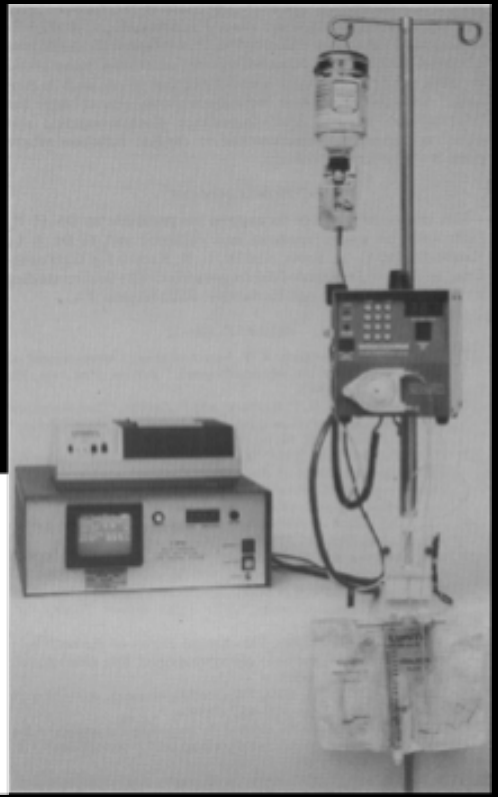
A Microcomputer-Based Fluid Infusion System for the Resuscitation of Burn Patients

R. J. BOWMAN AND D. R. WESTENSKOW

burn and trauma patients. The FIDAC system provides real-time measurement of infused fluid and urine output, the display and routine recording of fluid balance parameters, and closed-loop control of fluid resuscitation. The system has been evaluated through a series of animal tests and is currently in clinical use at the University of Utah Medical Center Intermountain Burn Unit.

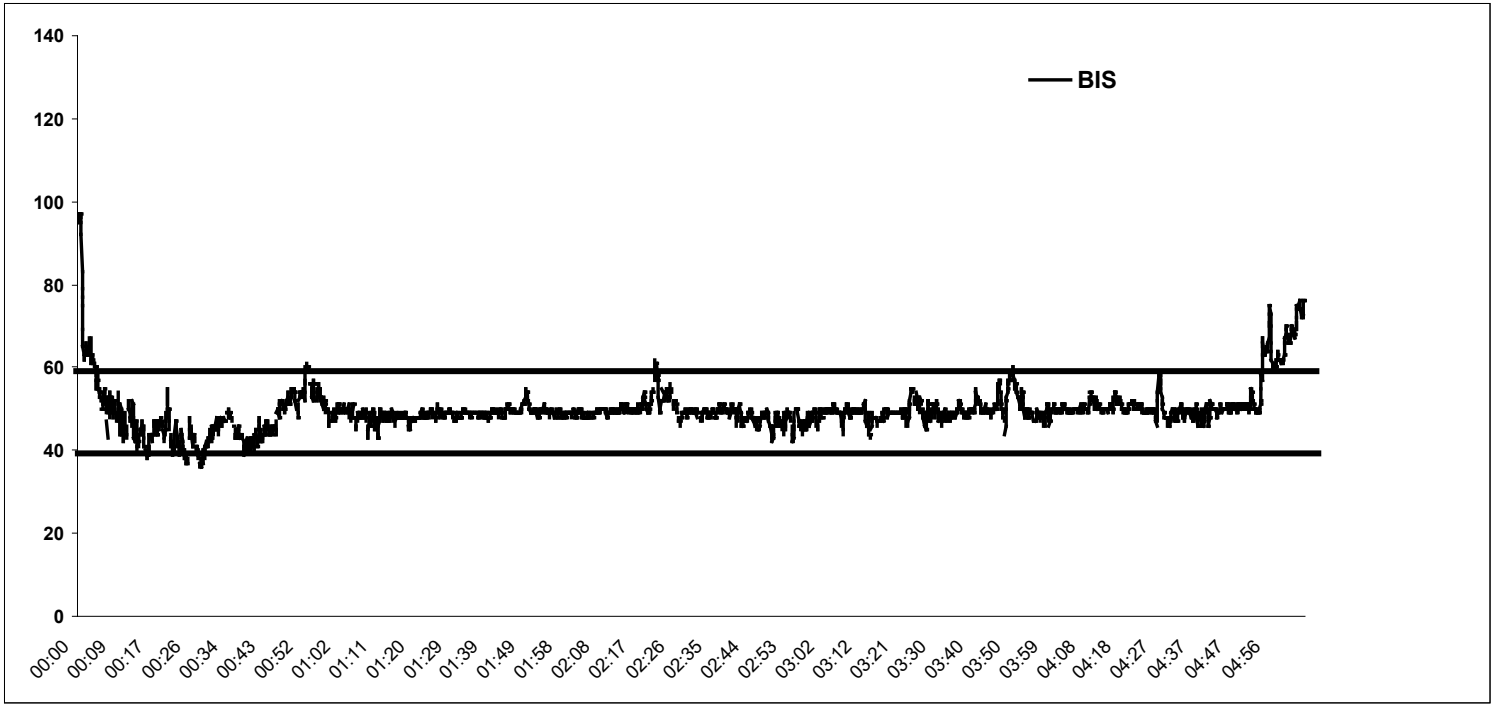


Control CL



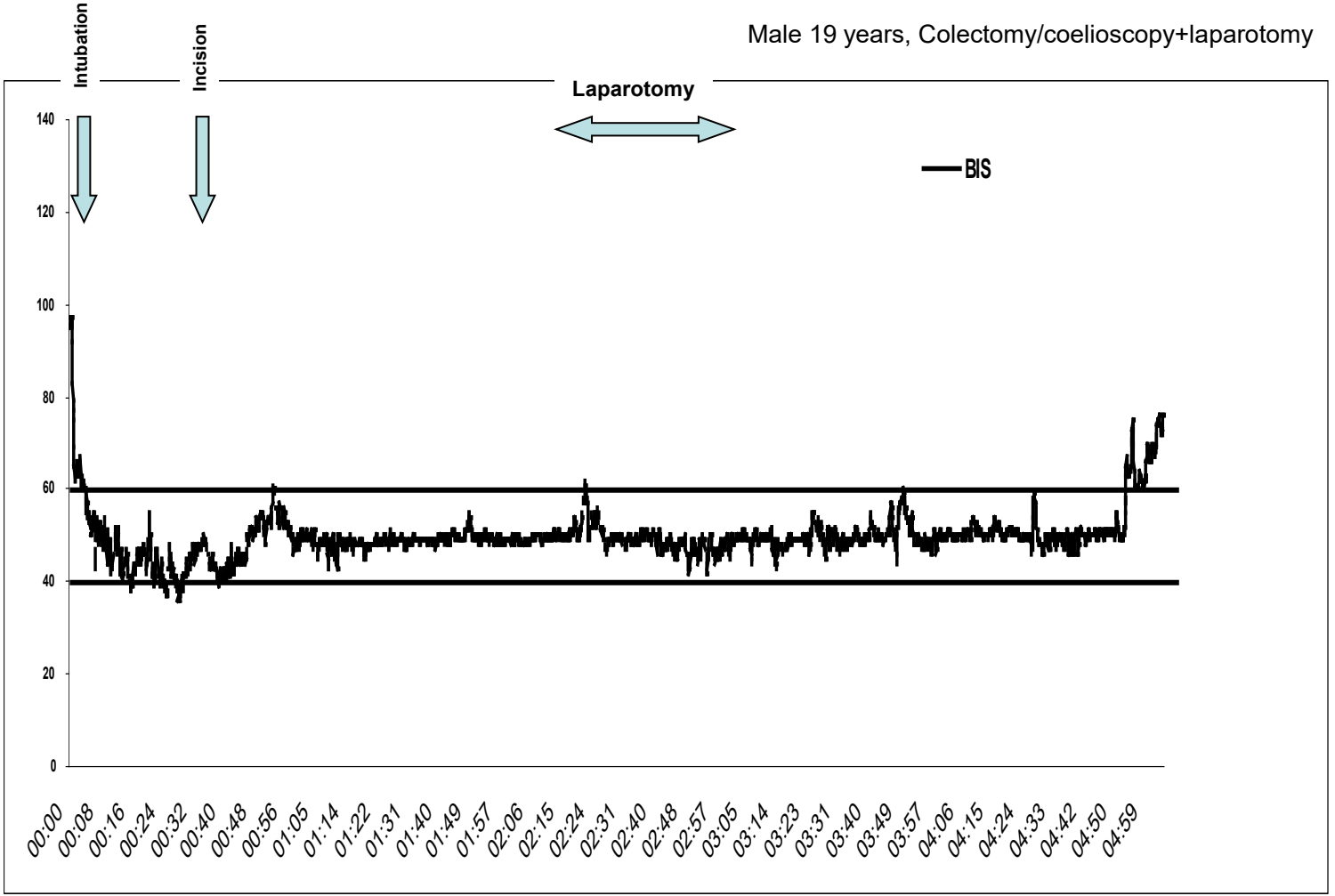
Depth of Anesthesia

Male 19 years, Colectomy/coelioscopy+laparotomy



Courtesy Dr Ngai Liu – Hoch Hospital, Paris France

Male 19 years, Colectomy/coelioscopy+laparotomy



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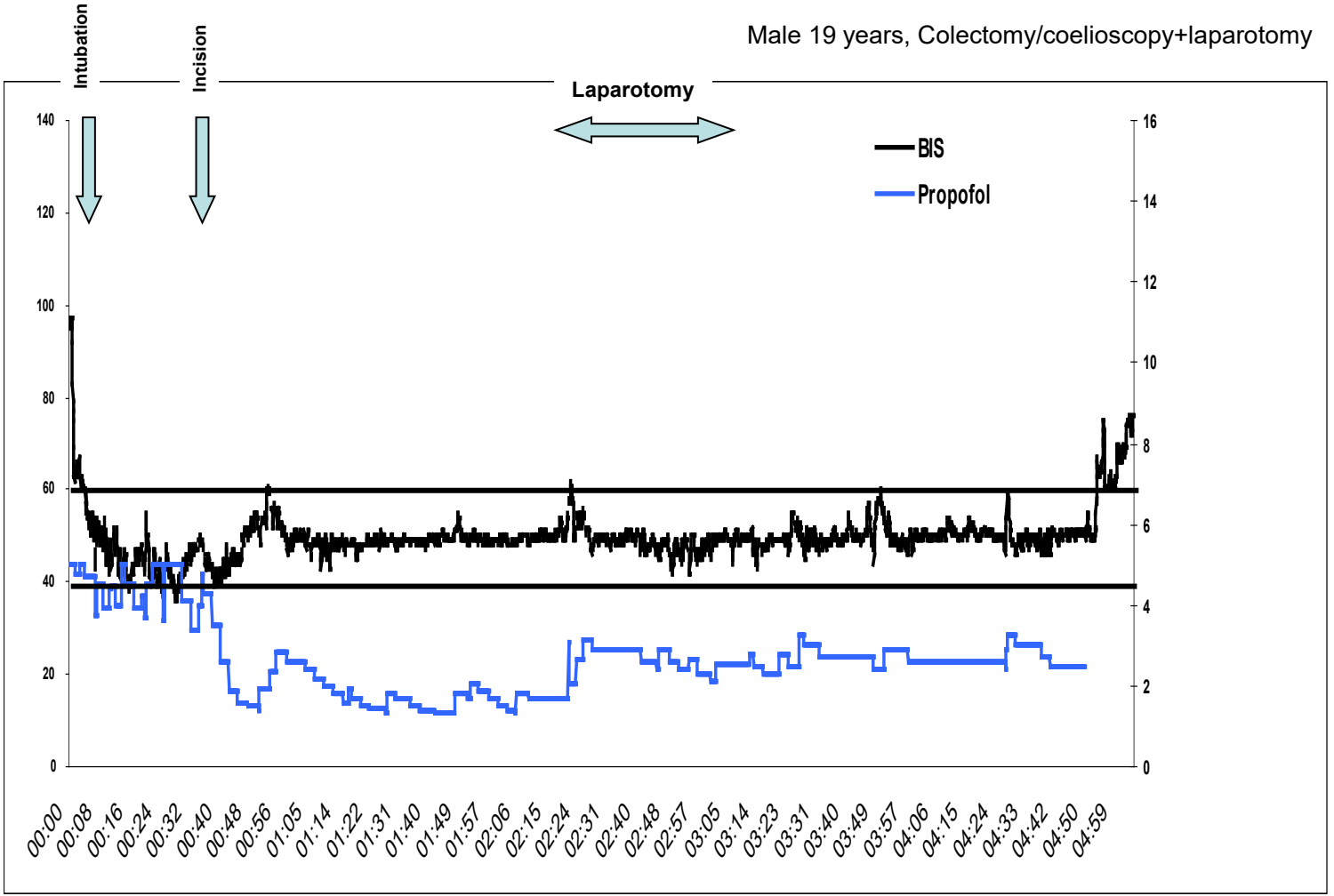

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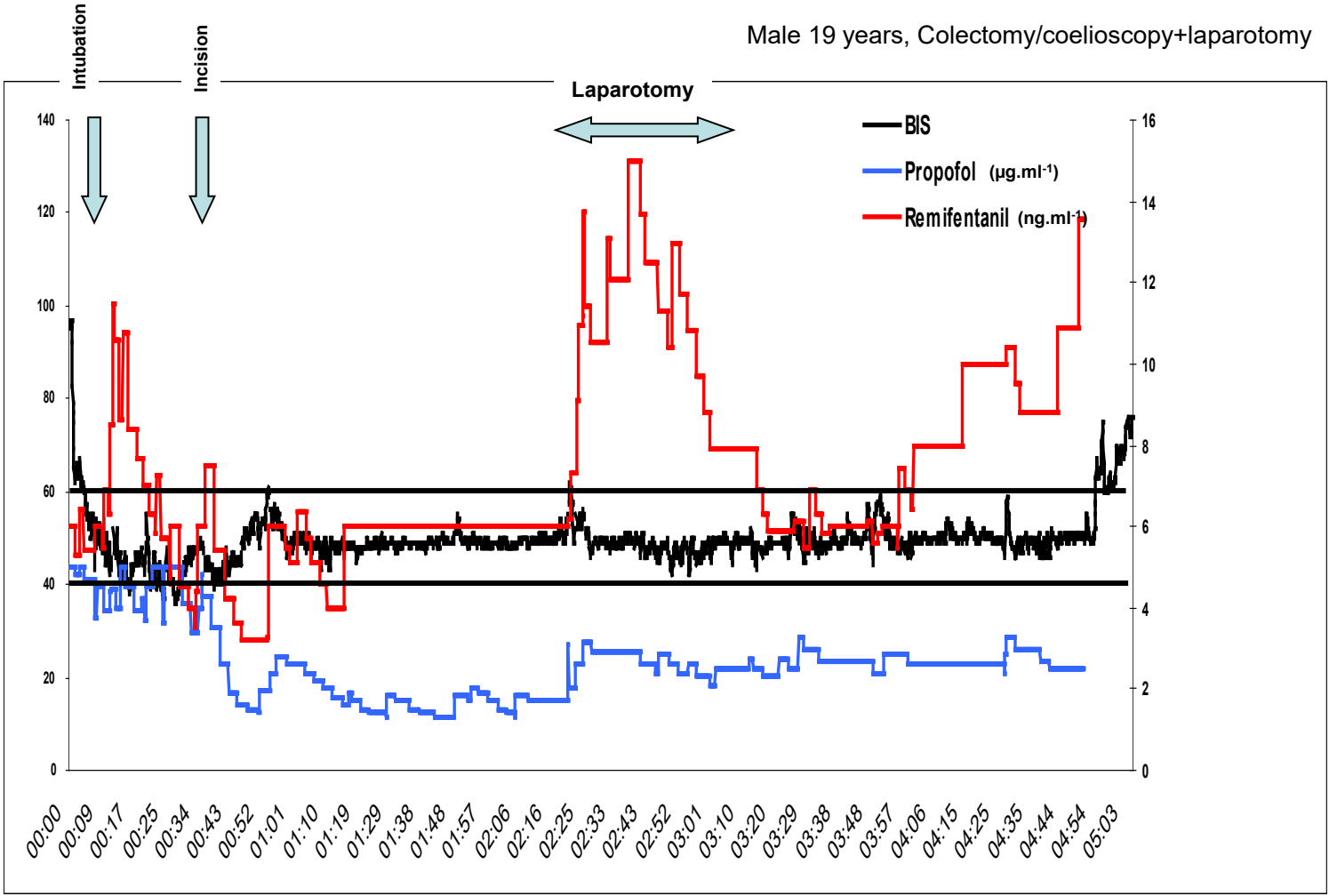


Courtesy Dr Ngai Liu – Hoch Hospital, Paris France

Society for Technology in Anesthesia

Section Editor: **Maxime Cannesson**

A Multicenter Evaluation of a Closed-Loop Anesthesia Delivery System: A Randomized Controlled Trial

Goverdhan D. Puri, MD, PhD,* Preethy J. Mathew, MD,* Indranil Biswas, MD,* Amitabh Dutta, MD,† Jayashree Sood, PGDHHM, FFARCS, MD, MBBS, FICA,† Satinder Gombar, MD,‡ Sanjeev Palta, MD,‡ Morup Tsering, MD,§ P. L. Gautam, MD,‖ Aveek Jayant, MD, DM,* Inderjeet Arora, MSc,* Vishal Bajaj, MD,¶ T. S. Punia, MD,¶ and Gurjit Singh, MSc#

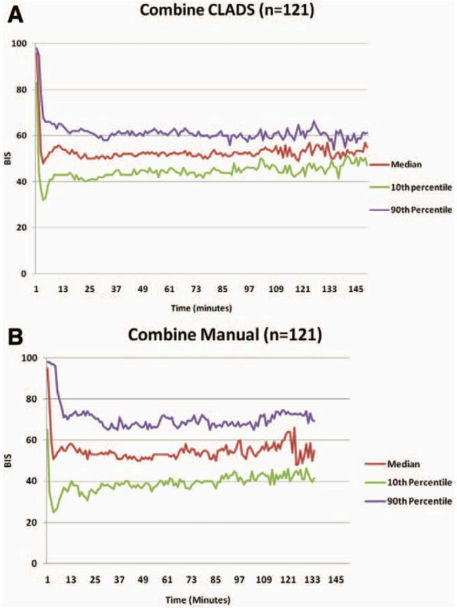


Figure 2. A, BIS values during anesthesia in CLADS group. B, BIS values during anesthesia in manual group. Data are represented as median values (red line) with 10th (green line) and 90th percentiles (blue line). BIS = Bispectral Index; CLADS = closed-loop anesthesia delivery system.

Table 2. Induction Characteristics

	CLADS group (*N* = 121)	Manual group (*N* = 121)	*P*	WMWodds	95% confidence interval of WMWodds
Propofol induction dose (mg/kg)	1.4 (1.2, 1.8)	1.8 (1.6, 2.2)	<0.0001*	2.71	1.99–3.86
Induction time (seconds)	160 (125, 213)	105 (55, 150)	<0.0001*	2.39	1.75–3.44
Minimal BIS at induction	42 (37, 47)	37 (30, 43)	0.0003*	1.74	1.29–2.41
Maximal BIS after intubation	62 (57, 68)	62 (51, 70)	0.5577	1.51	1.21–2.07
Minimal MAP during induction	90 (76, 96)	89 (78, 100)	0.6059	1.08	0.805–1.45

Values in median (interquartile range).
CLADS = closed-loop anesthesia delivery system; WMWodds = Wilcoxon Mann-Whitney odds measure; BIS = Bispectral Index; MAP = mean arterial pressure.
*$P < 0.05$, Mann-Whitney *U* test.

Table 3. Performance Characteristics, Recovery Parameters, and Hemodynamic Stability

	CLADS group (*N* = 121)	Manual group (*N* = 121)	*P*	WMWodds	95% confidence interval of WMWodds
% time BIS within ±10 of target BIS	82 (76, 89)	61 (41, 74)	<0.0001*	5.15	3.65–8.09
% of time BIS >60	10.28 (6.157, 16.536)	15.66 (4.589, 33.685)	0.0049*	1.53	1.13–2.11
% of time BIS <30	0 (0,0)	0.33 (0.0, 3.875)	<0.0001*	2.97	2.302–3.97
Median absolute performance error (MDAPE)	10 (10, 12)	18 (14, 24)	<0.0001*	6.48	4.57–10.36
Wobble	9 (8, 10)	10 (8, 14)	0.0009*	1.64	1.22–2.26
Global score	24 (19,30)	51 (31, 99)	<0.0001*	6.04	4.26–9.63
% time heart rate ±25% of baseline	95 (87, 99)	90 (75, 98)	0.0031*	1.56	1.17–2.13
% time mean arterial pressure ±25% baseline	92 (86, 96)	89 (79, 97)	0.0411*	1.36	1.01–1.84
Total propofol consumption (mg/kg/h)	5.4 (4.5, 6.7)	5.3 (4.3, 6.9)	0.5698	1.09	0.81–1.47
Fentanyl Consumption (μg/kg)	3 (2.8, 3.7)	3 (2.7, 3.5)	0.3367	1.15	0.86–1.55
Obeying time from propofol stop(min)	8.0 (6, 10.5)	8.0 (6, 12)	0.2108	1.20	0.89–1.62
Extubation time from stopping propofol (min)	8.0 (7, 11)	9.0 (7, 12)	0.3579	1.15	0.86–1.54

The values are median (1st quartile, 3rd quartile).
CLADS = closed-loop anesthesia delivery system; WMWodds = Wilcoxon Mann-Whitney odds measure; BIS = Bispectral Index.
*$P < 0.05$, Mann-Whitney *U* test.

ANESTHESIA & ANALGESIA

2017

META-ANALYSIS

SYSTEMATIC REVIEW ARTICLE

Closed-Loop Delivery Systems Versus Manually Controlled Administration of Total IV Anesthesia: A Meta-analysis of Randomized Clinical Trials

Laura Pasin, MD, Pasquale Nardelli, MD, Margherita Pintaudi, MD, Massimiliano Greco, MD, Massimo Zambon, MD, Luca Cabrini, MD, and Alberto Zangrillo, MD

Anesthetic Clinical Pharmacology

Anesthetic Clinical Pharmacology Section Editor: **Ken B. Johnson**
Preclinical Pharmacology Section Editor: **Markus W. Hollmann**

SYSTEMATIC REVIEW ARTICLE

Clinical Performance and Safety of Closed-Loop Systems: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Etrusca Brogi, MD,* Shantale Cyr, PhD,† Roy Kazan, MD, MSc,‡ Francesco Giunta, MD,* and Thomas M. Hemmerling, MSc, MD, DEAA†‡

Closed-loop systems (CLS), when compared to human management:

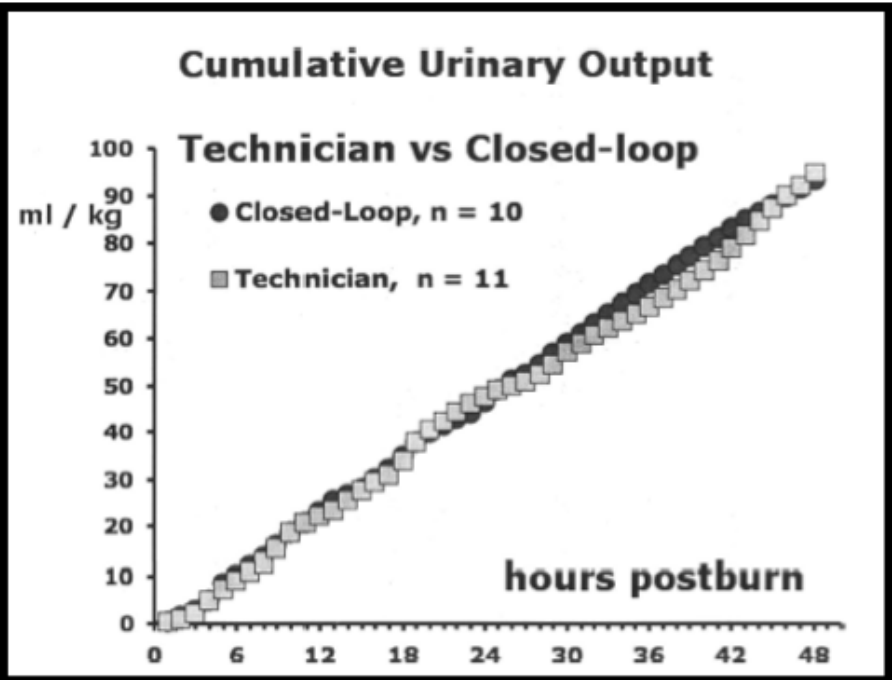
1) More Stable Anesthesia / More frequent adjustements

2) Less Overshoot / Undershoot

Fluid Management

Closed-Loop and Decision-Assist Resuscitation of Burn Patients

Jose Salinas, PhD, Guy Drew, BS, James Gallagher, MD, Leopoldo C. Cancio, MD, Steven E. Wolf, MD, Charles E. Wade, PhD, John B. Holcomb, MD, FACS, David N. Herndon, MD, and George C. Kramer, PhD



The Journal of TRAUMA® *Injury, Infection, and Critical Care* 2008

Closed-Loop and Decision-Assist Resuscitation of Burn Patients

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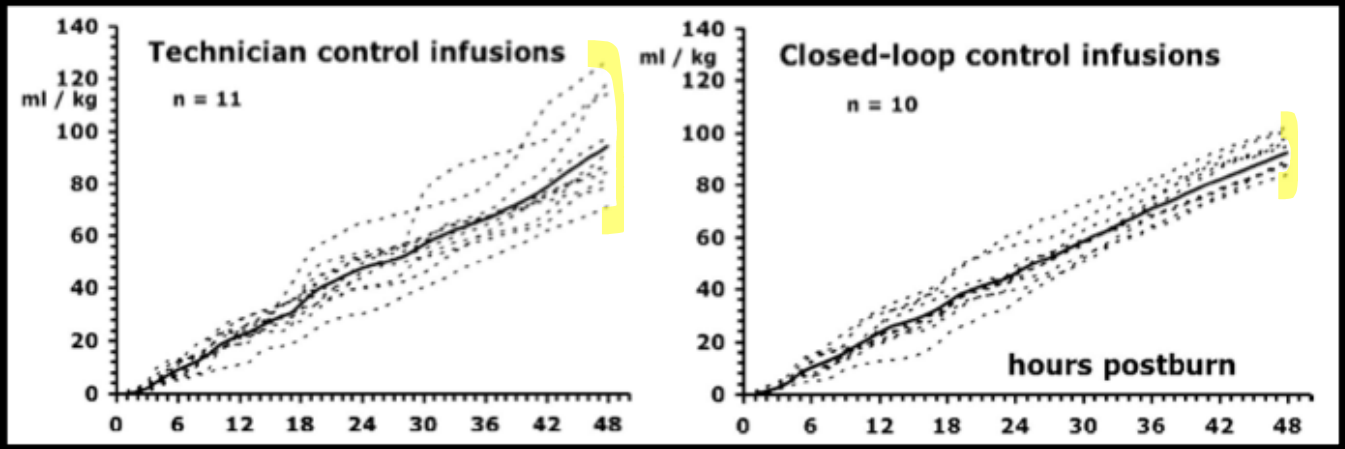


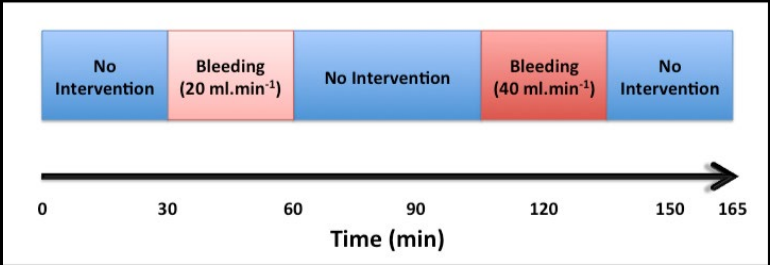
Based on Urine output

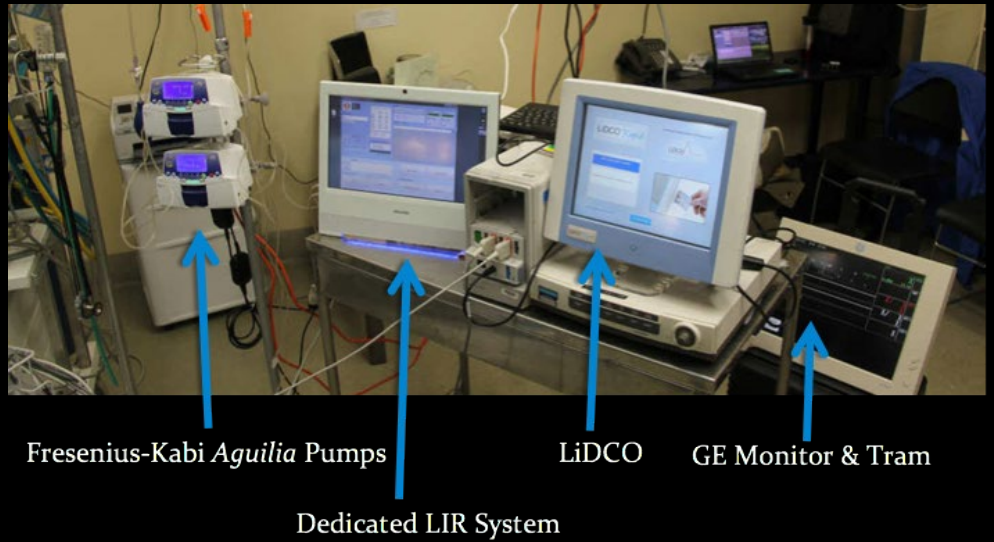
The Journal of **TRAUMA**® *Injury, Infection, and Critical Care* **2008**

Closed-Loop Fluid Administration Compared to Anesthesiologist Management for Hemodynamic Optimization and Resuscitation During Surgery: An In Vivo Study

Joseph Rinehart, Christine Lee, Cecila Canales, Allen Kong, Zeev Kain, Maxime Cannesson

Anesthesia Analgesia 2013





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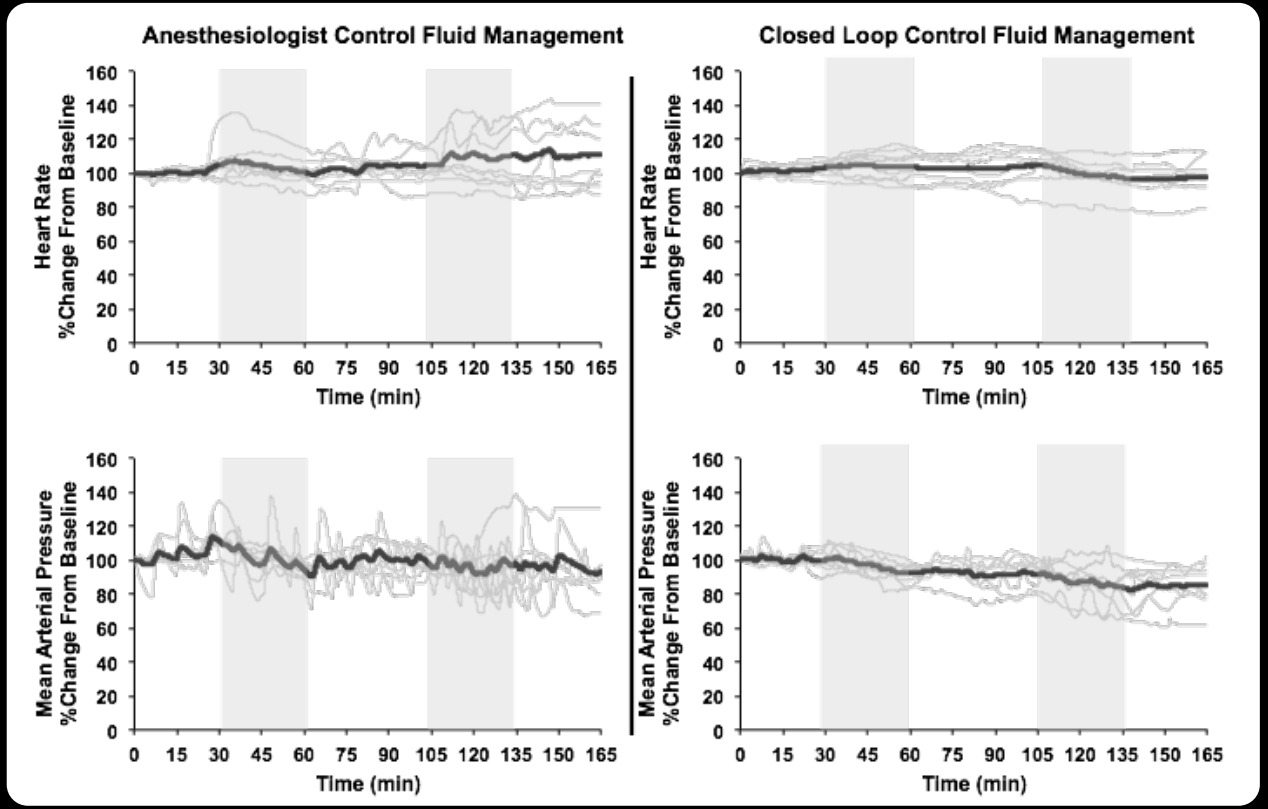

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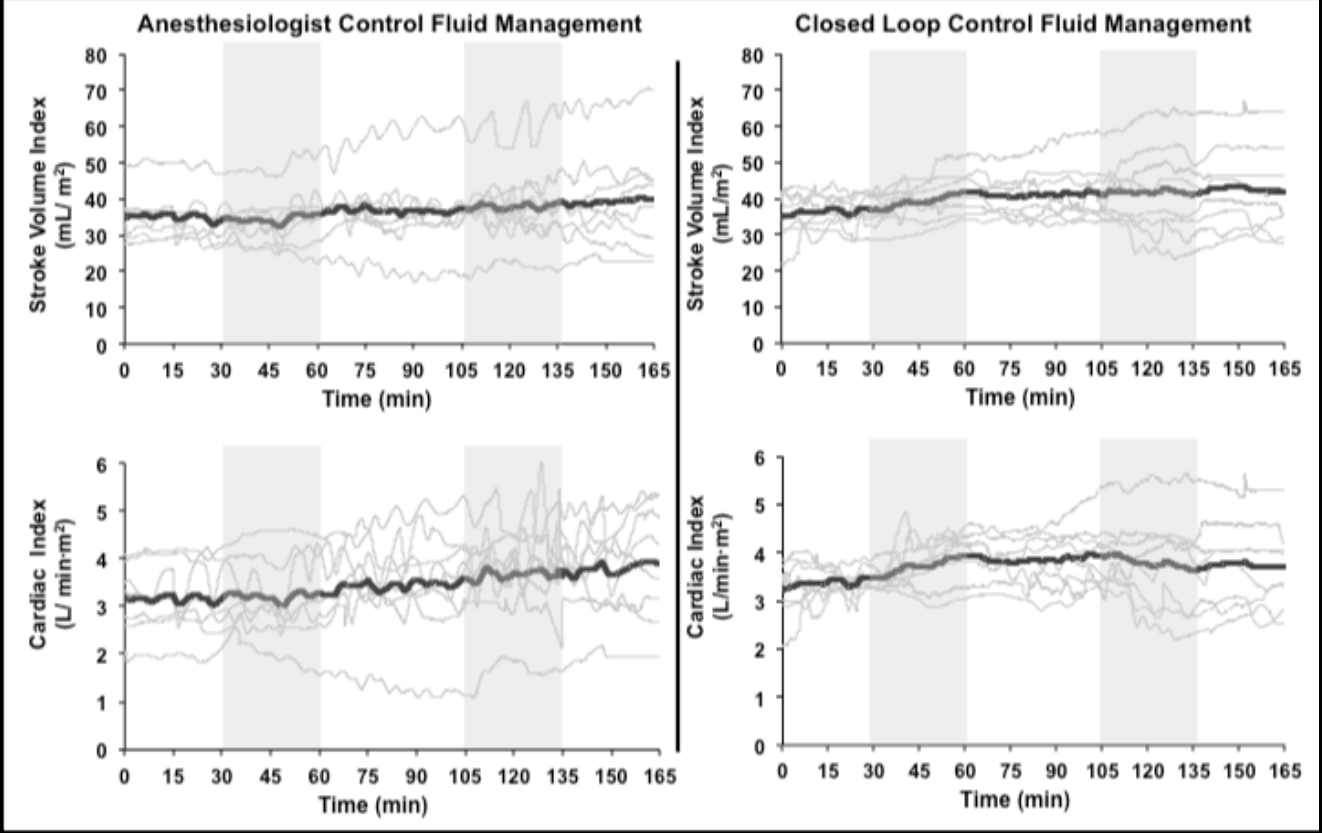


ANESTHESIOLOGY

Assisted Fluid Management Software Guidance for Intraoperative Fluid Administration

Kamal Maheshwari, M.D., M.P.H., Gaurav Malhotra, M.D., Xiaodong Bao, M.D., Ph.D., Peiman Lahsaei, M.D., William R. Hand, M.D., Neal W. Fleming, M.D., Ph.D., Davinder Ramsingh, M.D., Miriam M. Treggiari, M.D., Ph.D., M.P.H., Daniel I. Sessler, M.D., Timothy E. Miller, M.B.Ch.B., on behalf of the Assisted Fluid Management Study Team*

ANESTHESIOLOGY 2021; XXX:00–00

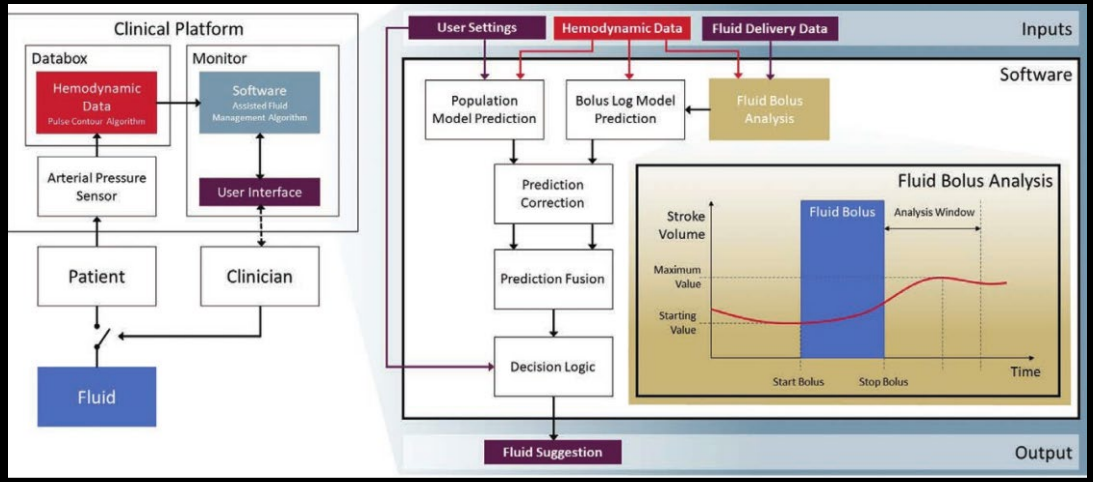
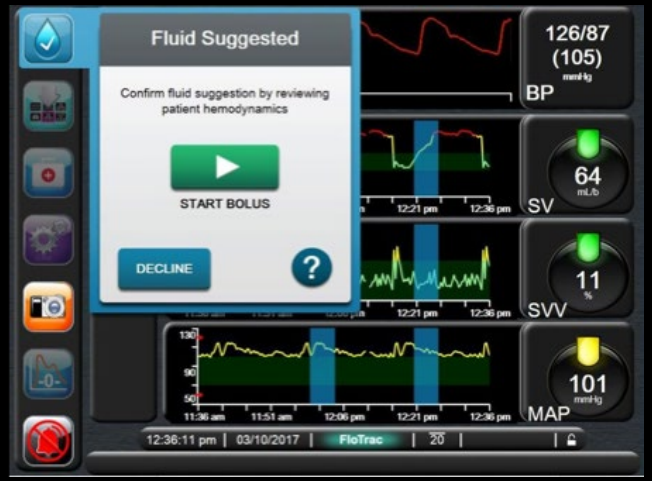


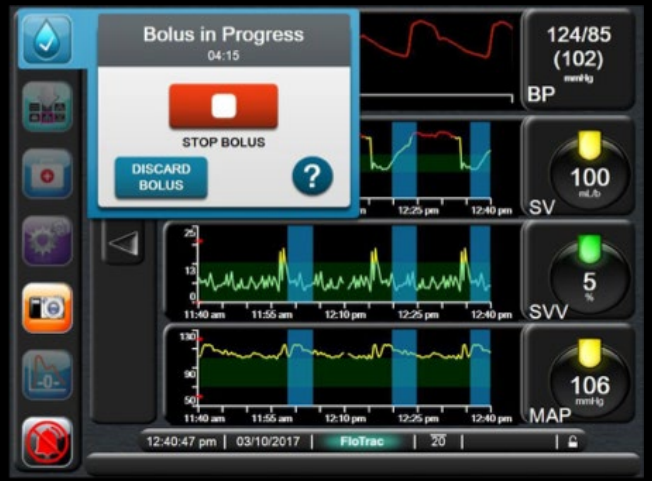
Table 3. Primary Analysis, Stroke Volume Change in Response to a Fluid Bolus

Bolus Category	Software-Prompt: Test* (n = 741)	Software-Prompt: Recommended* (n = 424)	Clinician Initiated† (n = 508)
Analyzed boluses			
Total bolus volume delivered, ml	170 ± 84 150 (100, 500)	190 ± 81 200 (100, 500)	218 ± 97 200 (100, 500)
Resulting change in stroke volume, %	16 ± 26‡ 11 (−26, 361)	14 ± 14‡ 11 (−16, 80)	8 ± 12 7 (−26, 134)
Primary effectiveness endpoint at event level			
Mean response, % (97.5% bootstrapped CI)	60 (58, 63)	66 (62, 70)§	41 (38, 44)§
No. of boluses/subjects	741/278	424/143§	508§
Selected fluid strategy‖			
10%	4 (32%)	9 (40%)	6 (30%)
15%	76 (56%)	88 (67%)	72 (36%)
20%	19 (143%)	3 (13%)	22 (114%)

Conclusions: Fluid boluses recommended by the software resulted in desired SV increases more often, and with greater absolute SV increase, than clinician-initiated boluses. Automated assessment of fluid responsiveness may help clinicians optimize intraoperative fluid management during noncardiac surgery.

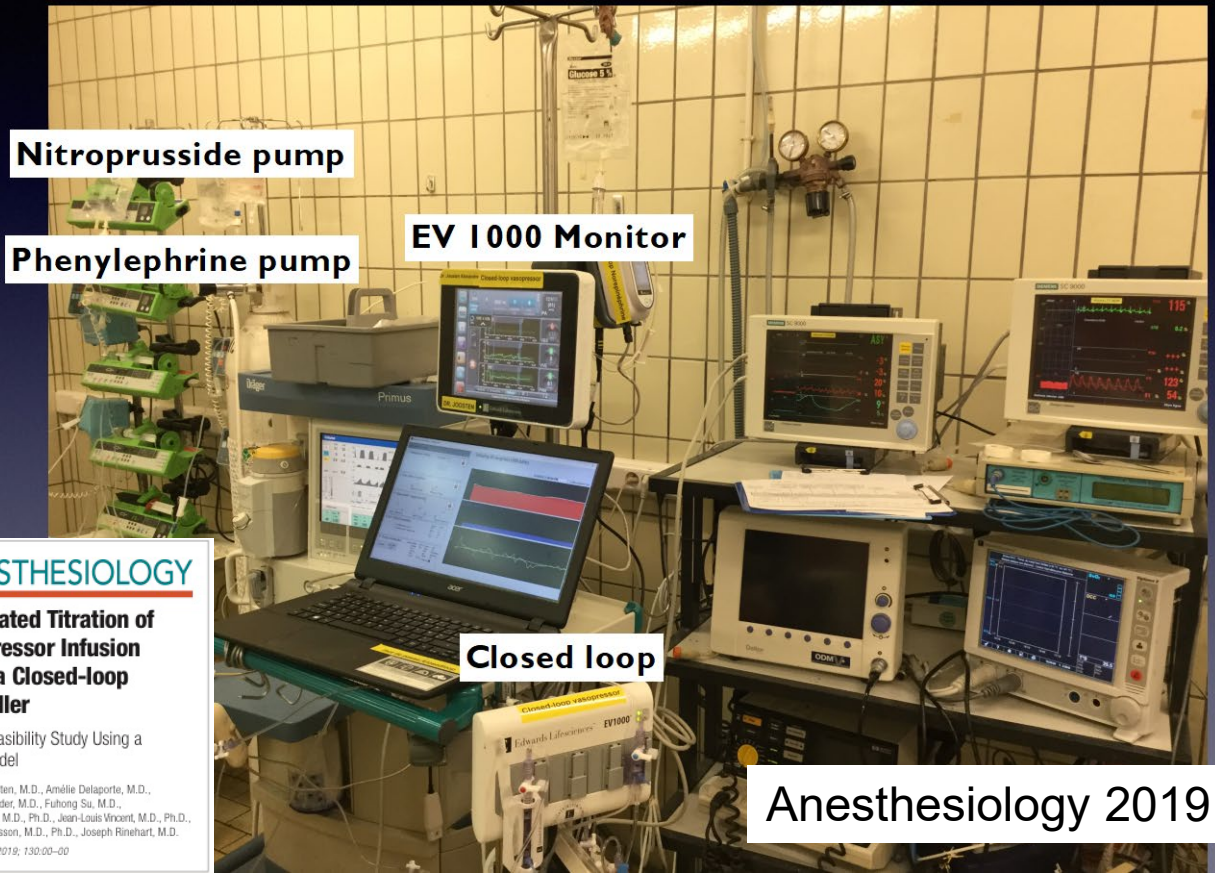
Assisted Fluid Management (AFM) Software





Vasopressors

Closed Loop Blood Pressure and Phenylephrine



ANESTHESIOLOGY

Automated Titration of Vasopressor Infusion Using a Closed-loop Controller

In Vivo Feasibility Study Using a Swine Model

Alexandre Joosten, M.D., Amélie Delaporte, M.D., Brenton Alexander, M.D., Fuhong Su, M.D., Jacques Creteur, M.D., Ph.D., Jean-Louis Vincent, M.D., Ph.D., Maxime Cannesson, M.D., Ph.D., Joseph Rinehart, M.D.

ANESTHESIOLOGY 2019; 130:00–00

ANESTHESIOLOGY

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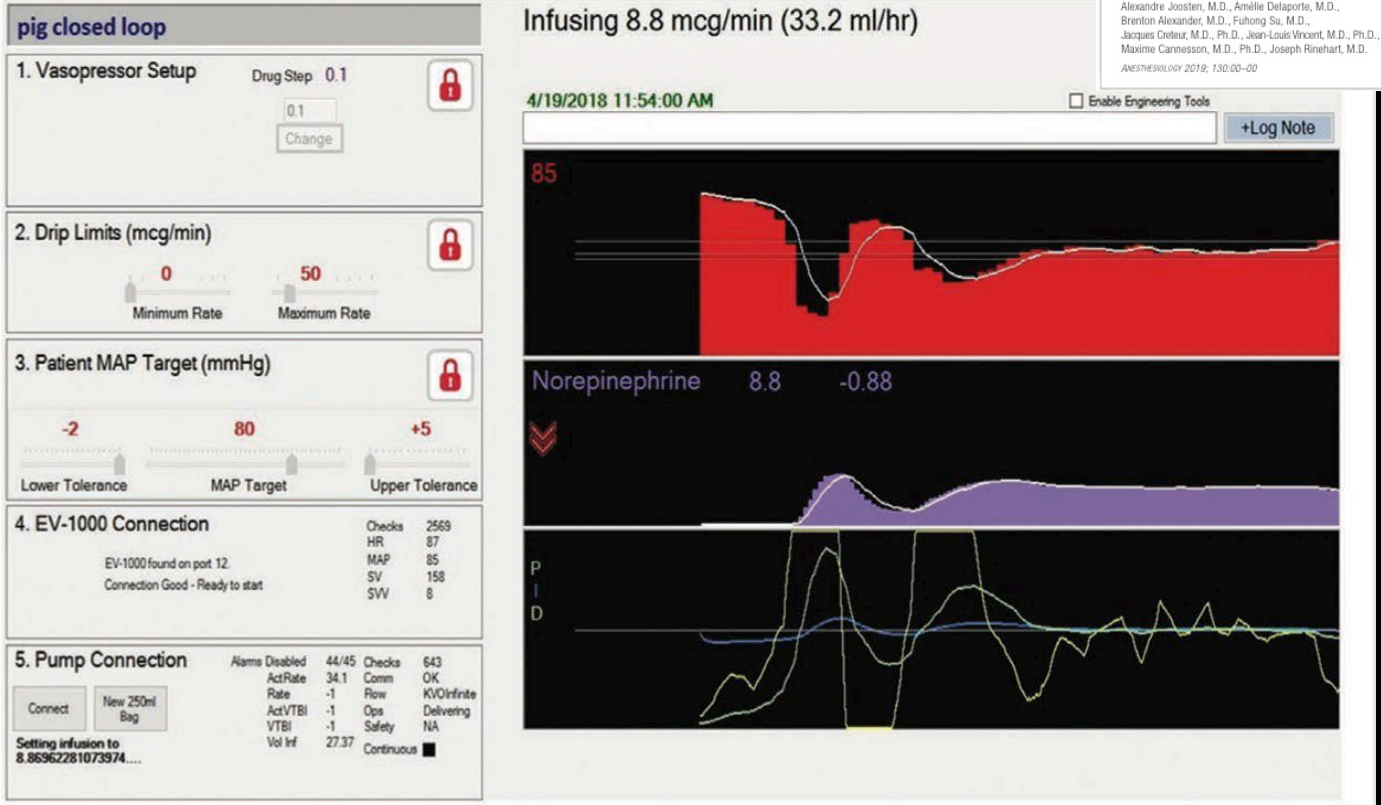
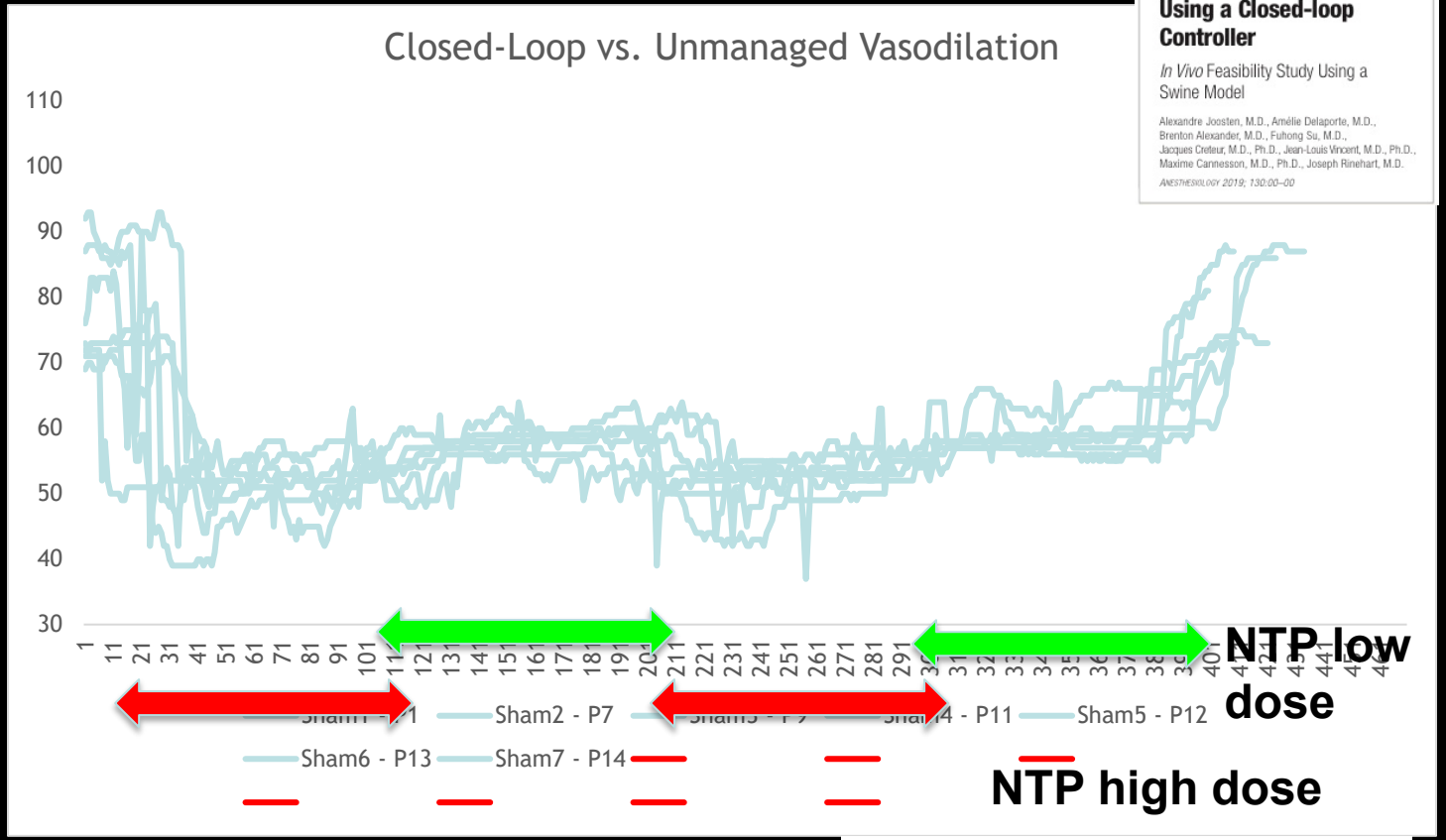
ANESTHESIOLOGY 2019; 130:00–00





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ANESTHESIOLOGY 2019; 130:00–00

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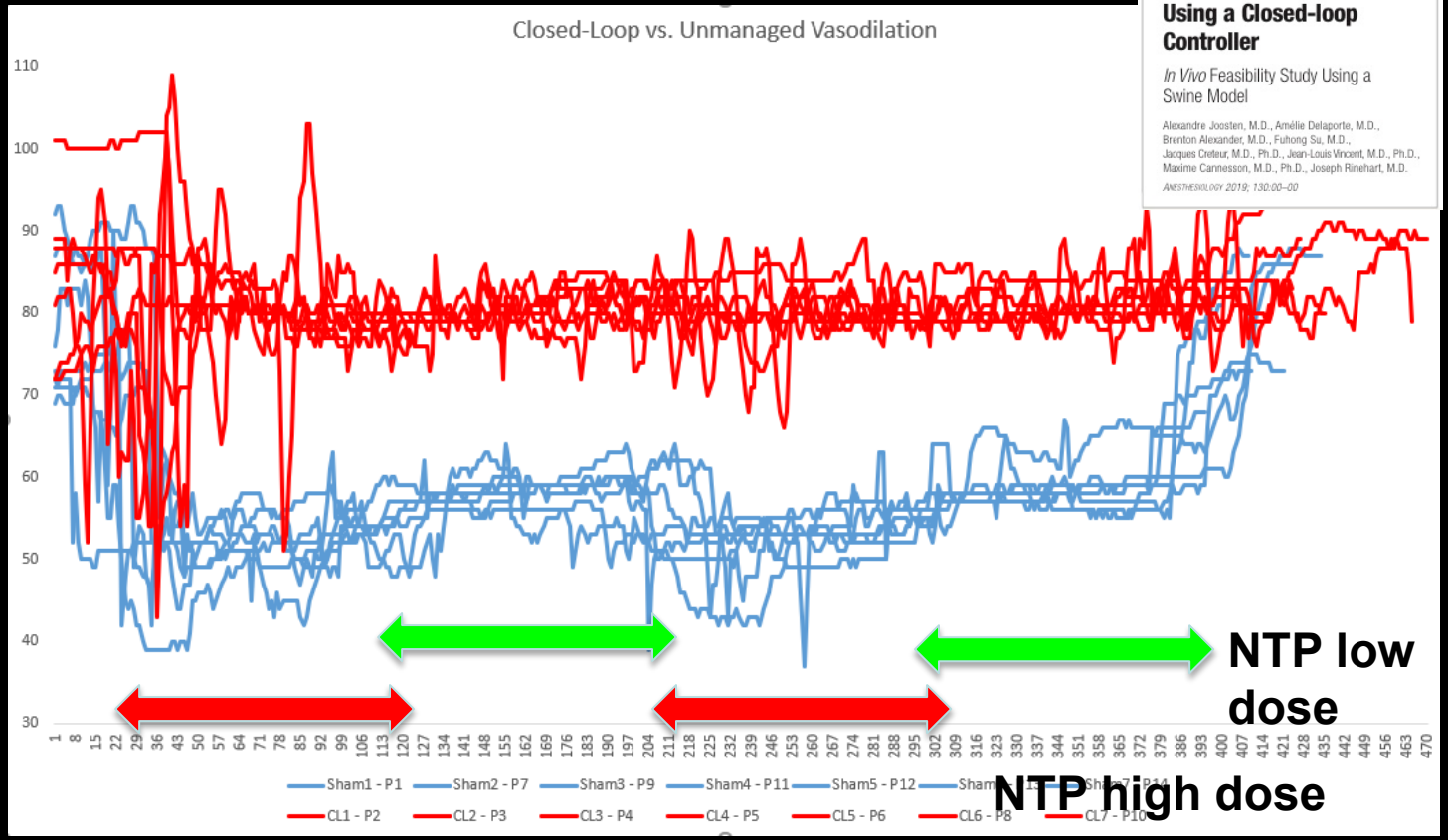

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Anesthesiology 2019

BJA

British Journal of Anaesthesia, 126 (1): 210–218 (2021)

doi: 10.1016/j.bja.2020.08.051
Advance Access Publication Date: 8 October 2020
Critical Care

Automated closed-loop *versus* manually controlled norepinephrine infusion in patients undergoing intermediate- to high-risk abdominal surgery: a randomised controlled trial

Alexandre Joosten[1,2,*], Dragos Chirnoaga[1], Philippe Van der Linden[3], Luc Barvais[1], Brenton Alexander[4], Jacques Duranteau[2], Jean-Louis Vincent[5], Maxime Cannesson[6] and Joseph Rinehart[7]

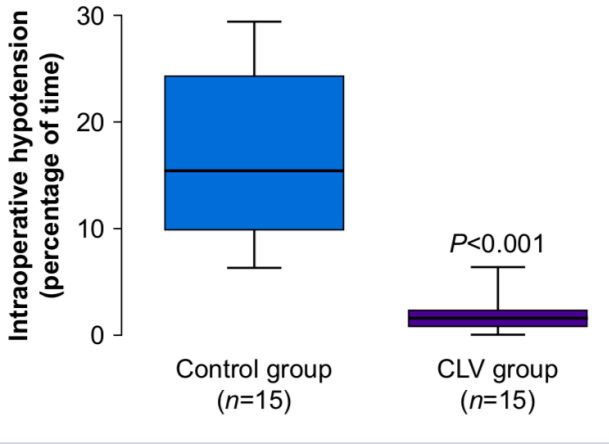
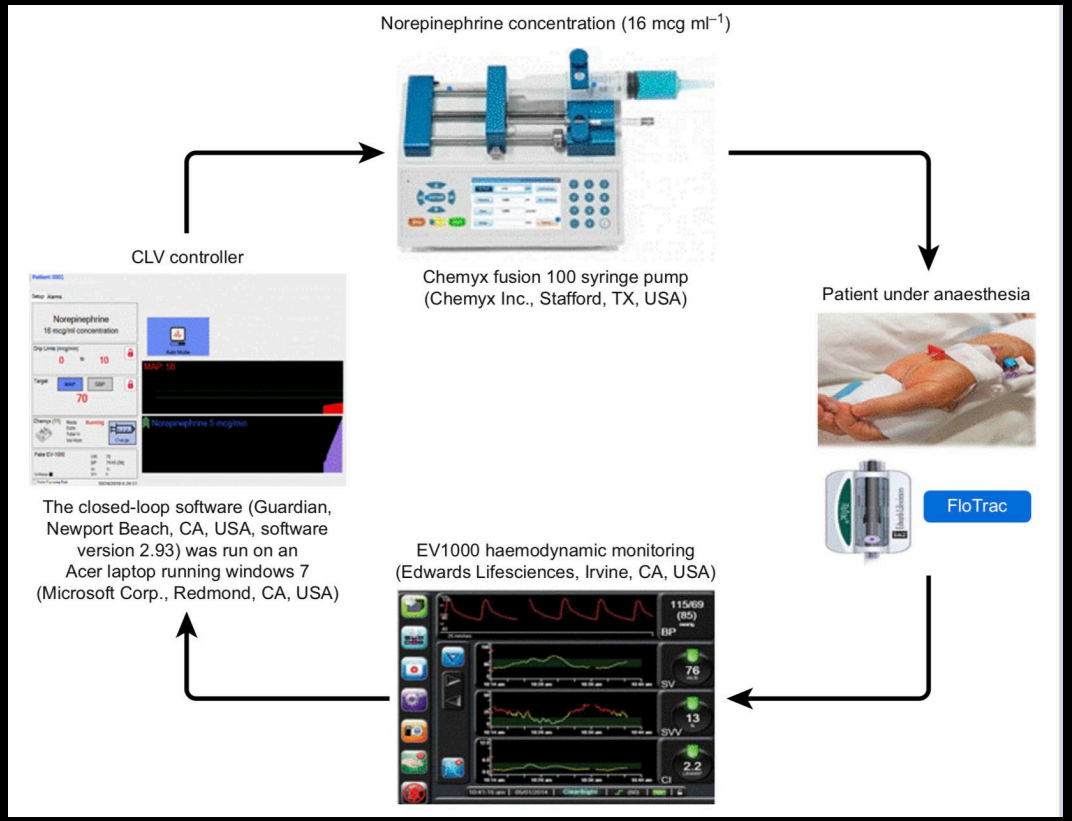
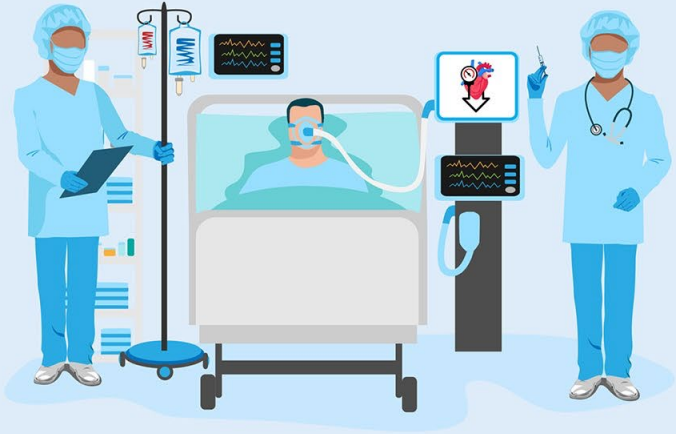


Fig 3. Primary outcome representation. Box plot shows the incidence of intraoperative hypotension (defined as MAP <90% of patient's baseline MAP value) in the two groups. CLV, closed-loop vasopressor.



Closed-Loop System of Vasopressor Infusion Post Cardiac Surgery

Currently, vasopressor infusions for managing hypotension post-surgery are adjusted manually



A novel closed-loop vasopressor (CLV) has been developed by physicians

Can the CLV replace manual titration?

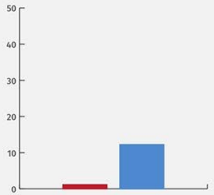
Randomized trial of 42 patients after cardiac surgery

Norepinephrine infusion

- CLV system
- Two-hour study period
- Manual (control)

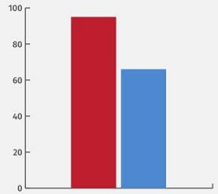
Mean arterial pressure measured

% of time with hypotension (MAP <65 mmHg)



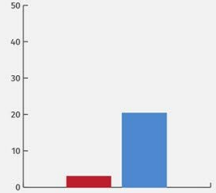
CLV - 1.4% | Control - 12.5%

% of time with MAP 65-75 mmHg



CLV - 95% | Control - 66%

% of time with MAP >75 mmHg



CLV - 3.2% | Control - 20.6%

Closed-loop vasopressor is an efficient system to control post-operative hypotension in patients with cardiac surgeries

Control of Postoperative Hypotension using a Closed-loop System for Norepinephrine. Infusion in Patients after Cardiac. Surgery: A Randomized Trial

Joosten et al. (2021)

ANESTHESIOLOGY

Computer-assisted Individualized Hemodynamic Management Reduces Intraoperative Hypotension in Intermediate- and High-risk Surgery: A Randomized Controlled Trial

Alexandre Joosten, M.D., Ph.D., Joseph Rinehart, M.D., Philippe Van der Linden, M.D., Ph.D., Brenton Alexander, M.D., Christophe Penna, M.D., Ph.D., Jacques De Montblanc, M.D., Maxime Cannesson, M.D., Ph.D., Jean-Louis Vincent, M.D., Ph.D., Eric Vicaut, M.D., Ph.D., Jacques Duranteau, M.D., Ph.D.

Anesthesiology 2021; 135:258–72

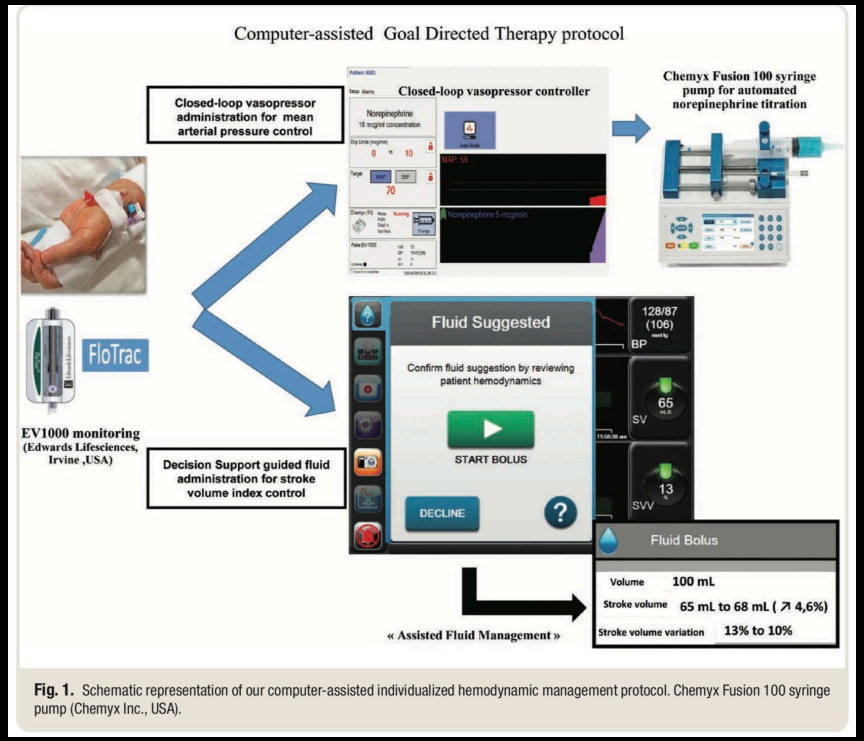
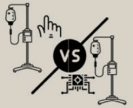


Fig. 1. Schematic representation of our computer-assisted individualized hemodynamic management protocol. Chemyx Fusion 100 syringe pump (Chemyx Inc., USA).

Computer-assisted Individualized Hemodynamic Management Reduces Intraoperative Hypotension in Intermediate- and High-risk Surgery

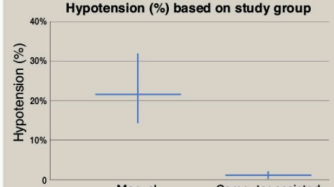
Single-center single-blinded parallel two-arm prospective randomized controlled trial in 38 patients



Hypothesis: Computer-assisted individualized hemodynamic management can reduce intraoperative hypotension

	Manual Goal-directed	Computer-assisted
Norepinephrine titration	Manual	Closed-loop
Mini-fluid challenge	Manual	Decision-support assistance

- **Norepinephrine goal**: MAP within 10% of baseline
- **Fluid goal**: Maximize SV Index



Computer-assisted individualized vasopressor and fluid titration reduced intraoperative hypotension compared to a manually controlled goal-directed approach

Joosten A, *et al.* ANESTHESIOLOGY, 2021.

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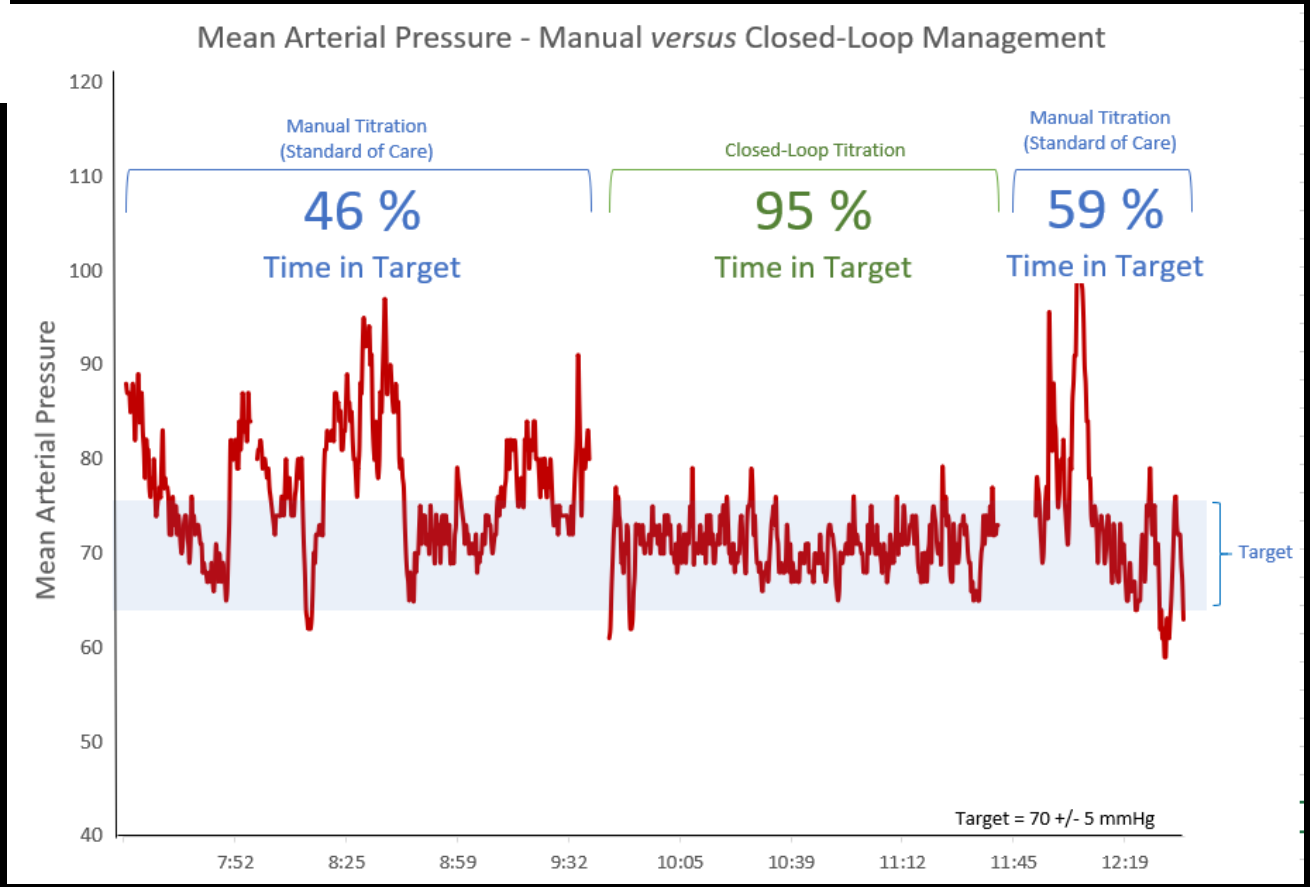
Closed Loop Vasopressor Use in ICU
Erasme Hospital, Brussels, Belgium



Hôpital Erasme

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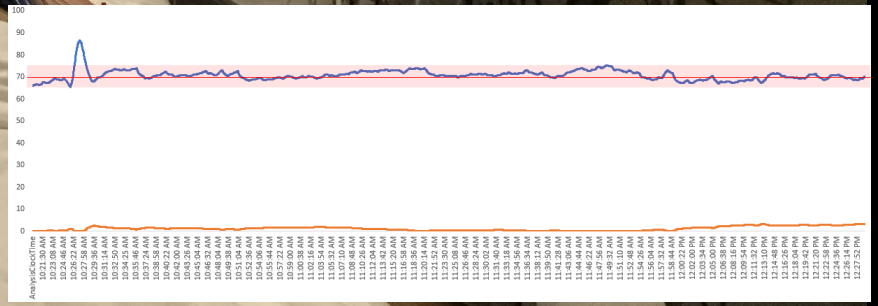

Integration

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2020
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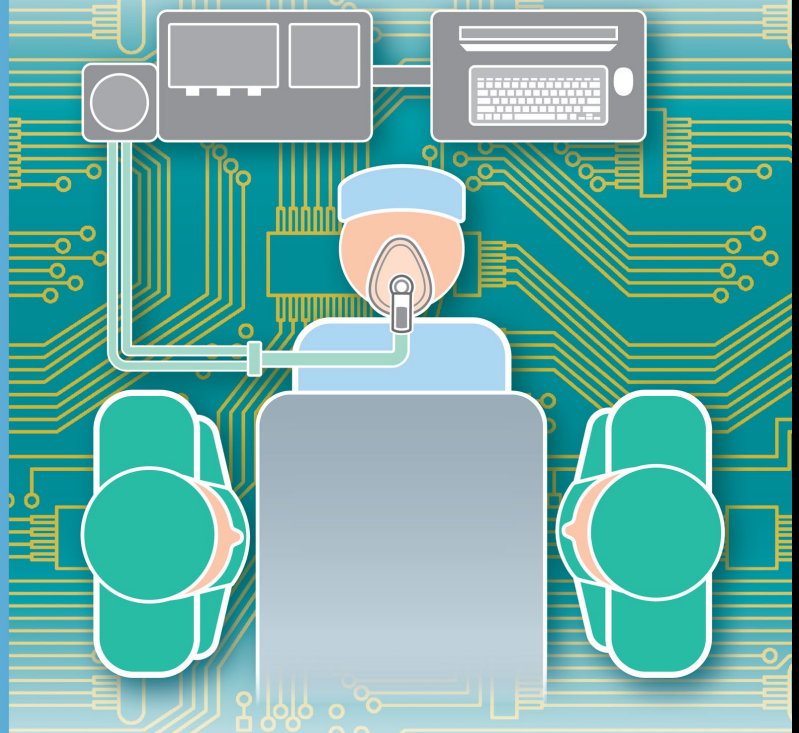

Robotic Anesthesia Will Be Available Soon

Volume 132
Number 2
anesthesiology.org

The Journal of the American Society of Anesthesiologists, Inc.

ANESTHESIOLOGY

Anesthetic Management Using Multiple Closed-loop Systems and Delayed Neurocognitive Recovery

A Randomized Controlled Trial

Alexandre Joosten, M.D., Ph.D., Joseph Rinehart, M.D., Aurélie Bardaji, M.D., Philippe Van der Linden, M.D., Ph.D., Vincent Jame, M.D., Luc Van Obbergh, M.D., Ph.D., Brenton Alexander, M.D., Maxime Cannesson, M.D., Ph.D., Susana Vacas, M.D., Ph.D., Ngai Liu, M.D., Ph.D., Hichem Slama, Ph.D., Luc Barvais, M.D., Ph.D.

ANESTHESIOLOGY 2020; 132:253–66

Preoperative (DAY-1)	Postoperative day 3-7 (POD# 3-7)	Postoperative day 90 (POD# 90)
✓ Edmonton Frailty score		
✓ Quality of Recovery	✓ Quality of Recovery	
✓ Quality of Life		✓ Quality of Life
✓ MoCA test	✓ MoCA test	✓ MoCA test
✓ Episodic memory (Free and Cued Selective Reminding Test)	✓ Episodic memory (Free and Cued Selective Reminding Test)	✓ Episodic memory (Free and Cued Selective Reminding Test)
✓ Working memory (Forward and Backward digit spans)	✓ Working memory (Forward and Backward digit spans)	✓ Working memory (Forward and Backward digit spans)
✓ Executive function (Stroop test)	✓ Executive function (Stroop test)	✓ Executive function (Stroop test)

ANESTHESIOLOGY

Anesthetic Management Using Multiple Closed-loop Systems and Delayed Neurocognitive Recovery

A Randomized Controlled Trial

Alexandre Joosten, M.D., Ph.D., Joseph Rinehart, M.D., Aurélie Bardaji, M.D., Philippe Van der Linden, M.D., Ph.D., Vincent Jame, M.D., Luc Van Obbergh, M.D., Ph.D., Brenton Alexander, M.D., Maxime Cannesson, M.D., Ph.D., Susana Vacas, M.D., Ph.D., Ngai Liu, M.D., Ph.D., Hichem Slama, Ph.D., Luc Barvais, M.D., Ph.D.

Anesthesiology 2020; 132:253–66

Variables	Control Group (N = 44)	Closed-loop Group (N = 45)	Point Estimate (95% CI)	*P* Value
Anesthesia duration (min)	265 ± 144	274 ± 101	9 (–44 to 62)	0.732
Surgery duration (min)	177 [117 to 267]	203 [139 to 300]	23 (–19 to 62)	0.313
Crystalloid volume (ml)	2,000 [1,000 to 2,483]	900 [688 to 1,210]	–950 (–1,209 to –600)	**< 0.001**
Colloid volume (ml)	0 [0 to 0]	700 [400 to 1500]	600 (400 to 900)	**< 0.001**
Blood component transfusion (%)				
Packed red blood cells	1 (2.3)	1 (2.2)		> 0.999
Fresh frozen plasma	0	0		> 0.999
Platelets	0	0		> 0.999
Total IN (ml)	2,000 [1,500 to 2,688]	1,600 [1,011 to 2,610]	–225 (–600 to 192)	0.299
Urine output (ml)	300 [150 to 488]	330 [238 to 500]	75 (–25 to 150)	0.152
Estimated blood loss (ml)	150 [50 to 488]	250 [100 to 725]	50 (0 to 200)	0.202
Total OUT (ml)	535 [255 to 1,015]	780 [400 to 1,300]	200 (0 to 430)	0.063
Fluid balance (ml)	1,250 [850 to 1,888]	875 [488 to 1380]	–350 (–650 to –50)	**0.028**
Epinephrine (mg)	0 [0 to 0]	0 [0 to 15]	0 (0 to 2)	0.109
Phenylephrine (µg)	0 [0 to 0]	0 [0 to 0]		> 0.999
Patients under norepinephrine (%)	11 (25)	12 (27)	1.7 (–17 to 20)	0.857
Patients under any kind of vasopressor agents, n (%)	28 (64)	31 (69)	5 (–14 to 25)	0.600
Percentage case time with Bispectral Index [40 to 60] (%)	56 [38 to 75]	84 [74 to 89]	22 (14 to 31)	**< 0.001**
Percentage case time with Bispectral Index < 40 (%)	29 [12 to 50]	10 [3 to 19]	–18 (–28 to –9)	**< 0.001**
Percentage case time with Bispectral Index > 60 (%)	7 [1 to 13]	3 [2 to 8]	–2 (–5 to 0)	0.128
Number of episode with suppression ratio > 10 > 1 min	0 [0 to 1]	0 [0 to 0]	0 (0 to 0)	0.707
Intraoperative heart rate (beats/min)	65 [59 to 74]	68 [63 to 76]	4 (0 to 8)	0.094
Intraoperative mean arterial pressure (mmHg)	90 [82 to 95]	84 [78 to 94]	–4 (–8 to 1)	0.130
Percentage case time with MAP < 60 mmHg	0.8 [0 to 3.6]	1.0 [0 to 3.2]	0 (–0.5 to 0.4)	0.703
Number of effect site propofol modifications per hour	5 [3 to 8]	24 [18 to 32]	18 (15 to 22)	**< 0.001**
Number of effect site remifentanil modifications per hour	4 [2 to 5]	24 [21 to 30]	21 (19 to 22)	**< 0.001**
Total propofol consumption (mg · kg^{-1} · h^{-1})	4.4 [3.3 to 5.5]	3.8 [3.0 to 4.5]	–0.71 (–1.37 to –0.05)	**0.033**
Total remifentanil consumption (µg · kg^{-1} · min^{-1})	0.12 ± 0.05	0.14 ± 0.04	0.02 (0.01 to 0.04)	**0.012**
24-h morphine consumption (mg)	4 [2 to 10]	4 [2 to 8]	–0.5 (–4.0 to 0.0)	0.313
Mean tidal volume (ml · kg^{-1})	6.6 [6.1 to 6.9]	6.9 [6.7 to 7.1]	0.31 (0.08 to 0.52)	**0.012**
Percentage case time with end-tidal carbon dioxide [32 to 38] mmHg (%)	48 [21 to 80]	80 [56 to 92]	20.5 (5.5 to 37.6)	**0.004**
Percentage case time with end-tidal carbon dioxide < 32 mmHg (%)	24 [5 to 54]	8 [3 to 30]	–8 (–23 to 0)	**0.037**
Percentage case time with end-tidal carbon dioxide > 38 mmHg (%)	2.2 [0.5 to 12.8]	4.3 [1.1 to 7.7]	0.4 (–1.2 to 2.1)	0.537
Total number of ventilation parameters modifications	3 [2 to 5]	13 [3 to 33]	6 (1 to 18)	**0.001**

Data are listed as number and percentage (%), or mean ± SD for continuous variables that were normally distributed or median [25th to 75th percentiles] if not normally distributed. Point estimates for group differences were estimated for Mann–Whitney U test as the median difference in the set of values representing all differences in pairings between the two groups. Bold indicates significant results with *P* value < 0.05. IN includes all fluid and blood products received during surgery. OUT includes estimated blood loss and urine output.

MAP, mean arterial pressure.

Outline

- Introduction
- Feedback Control / Closed Loop / Automation
- Examples of Closed Loop Systems in Anesthesia
- The Challenges Ahead

To Err is human…

Regulatory Challenges Facing Closed-Loop Anesthetic Drug Infusion Devices

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Table 1 Potential benefits of a closed-loop anesthesia delivery system

More consistent drug administration
Less interpatient variability
Less over- and underdosing
Faster control of unexpected arousal (less awareness by patient during surgery)
Smaller quantities of drug used
Faster recovery of the patient
Better hemodynamic control
Less hypotension during induction of anesthesia

Technology, Computing, and Simulation

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SPECIAL ARTICLE

Regulatory Considerations for Physiological Closed-Loop Controlled Medical Devices Used for Automated Critical Care: Food and Drug Administration Workshop Discussion Topics

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Table 2. Regulatory Considerations for Design, Development, and Preclinical Evaluation of PCLC Medical Devices Used in Critical Care Environments

Sensor considerations
- Sensor validity and how accurately the sensed quantity represents the controlled variable. For example, if end-tidal anesthetic agent is being measured as feedback and surrogate quantity to adjust anesthetic gas concentration in the blood ultimately brain, consider providing a clinically robust justification for validity of this surrogate
- Characterizing sensor latency and potential detrimental effects on controller stability and inadequate therapy delivery
- Sensor robustness which may be thought of as the sensor's continuous valid performance in face of patient variabilities/uncertainties
- Sensor reliability and resilience which may be defined as valid performance of the sensor in face of environmental uncertainties. For example in case of automated anesthesia delivery based on EEG-derived sensors, consider the effect of concomitant drugs (eg, neuromuscular blockers), motion artifact, and surgical disturbance (eg, electrocautery artifact) on the sensed depth of hypnosis

Controller design considerations
- Quantifying various types of uncertainties including but not limited to dynamic uncertainty imposed by inter and intra patient variability for the purpose of controller design
- Establishing a criteria for model selection and model optimality in design based on clinical context of use
- Pitfalls (eg, lack of established methods to determine stability and robustness) that may hamper system analysis and evaluation
- Potential additional validation activities that may ensue as a result of model-free design approach (eg, extensive simulation studies)
- Verifiable and structured methodologies for control system tuning during the design stage
- Designing the system with particular attention to nonlinearities in the whole system (eg, actuator saturation, plant, and sensor nonlinear behavior) which may result in system instability and failure
- Control algorithm conformity to the drug label

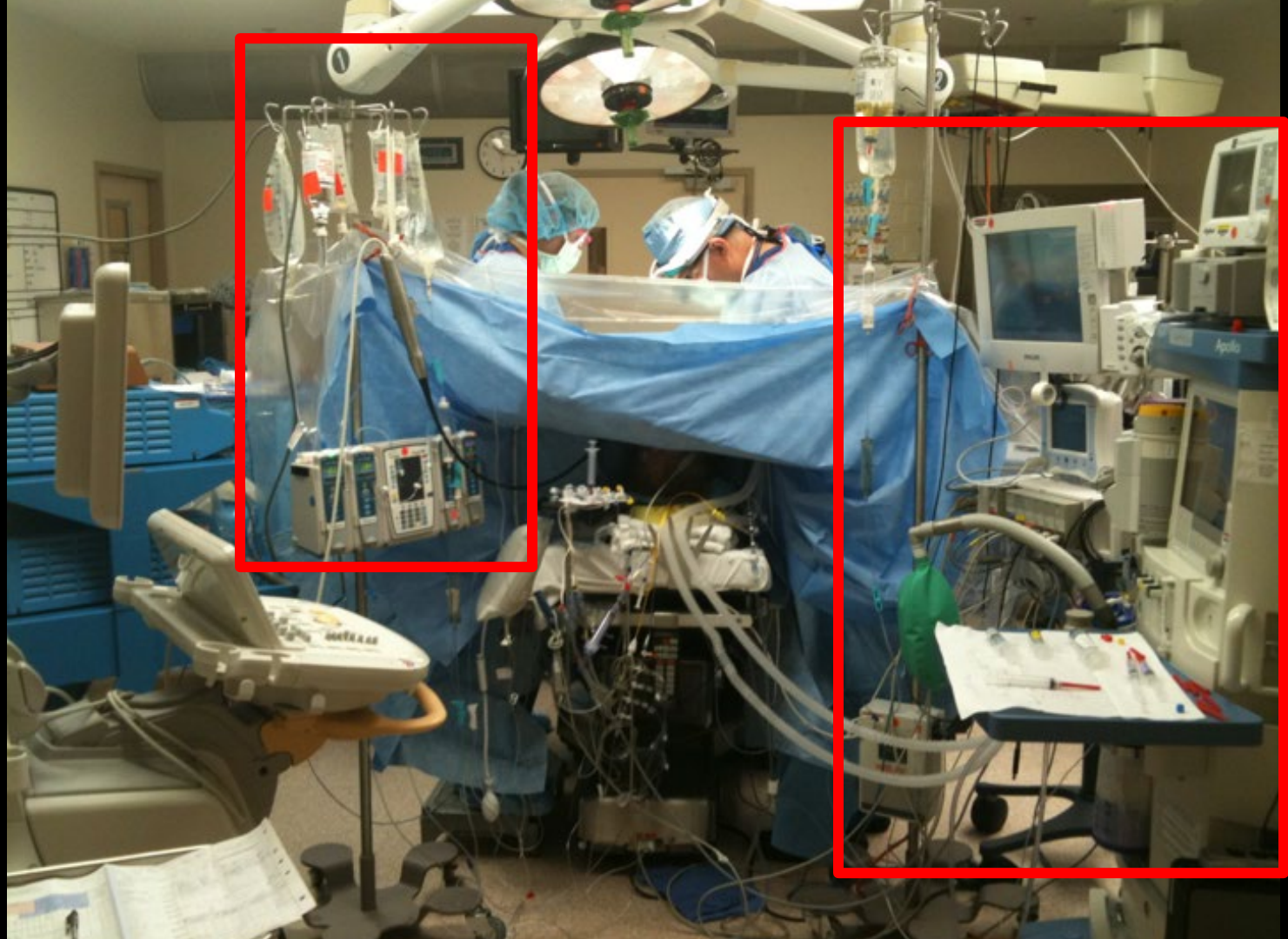
Clinical use considerations
- Relation between clinical outcomes and sensed/controlled variable(s) and the criteria that make a control variable appropriate for PCLC applications should be considered
- User interface design to provide operational transparency to the clinical users especially for device output is an important consideration
- Physical controls and display elements to improve user perception, cognition, and responses
- Information that needs to be conveyed to the user when reverting to an open-loop or completely manual control such that the state of the patient and previous delivered therapy is clear for the operator
- Specific environments of use (ie, hospital versus en route transport) may affect the interface design and how the PCLC medical device is used
- Design features to allow a clinician to recognize if a patient may not be responsive, or response changes, to therapy controlled by PCLC medical device
- The limitation of PCLC medical device in terms of delivering therapy based on a single sensor as compared with manual care where multiple factors are considered by the user
- System complexity and the training needed to ensure safe device use
- Including instruction for use language to enhance operational transparency and to create a mental model for the user of the PCLC medical device

Usability/human factors considerations
- Clinical setting, use scenarios, and potential for infrequent but critical events should be considered
- Simulator based training approaches may be leveraged to evaluate safety and assess human–automation interactions
- Depending on the level of automation, analysis techniques for identifying hazards such as overreliance and complacency may need to be considered
- Evaluating the effectiveness of any risk mitigation strategies for automation-induced hazards such as overreliance and/or complacency
- Language in the instruction for use should increase understanding and transparency of the controller operation

Implementation considerations
- Interoperability of system components such as pumps and sensors should be considered
- Implementing safety features and fallback modes for system fail-safe operation
- The need for data capture to allow forensic data and failure root cause analysis

Preclinical evaluation considerations
- Aiming to assess the performance of the whole system (controller, device components, patient, use environment)
- Analytical, bench computational (eg, in silico and hardware-in-the-loop), and animal testing or combination of these testing methods
- Analytical approaches for nonclinical assessment may depend on controller design (eg, knowledge-based; proportional, integral, and derivative; model-predictive control)
- Providing evidence of safe system performance (eg, stability) during inter and intra patient variability and disturbances that can be expected clinically
- Verifying functionality of fault detection and fallback modes
- Verification, validation, and uncertainty quantification of computational physiological models used for in silico and hardware-in-the-loop evaluation studies
- Animal testing needs to consider physiological and anatomical differences between animal model and human. Consider establishing clinical relevance of the animal model

Future challenges and considerations
- Development of standardized terminology in an effort to reduce the gap between expertise domains
- Development of recognized consensus standards on system performance metrics
- The relation between levels of autonomy and the benefit/risk profile design, risk mitigation strategy, and evaluation of a PCLC medical device
- Framework for establishing sensor validity criteria is an important consideration that may help in identifying safer sensors for PCLC medical devices
- Establishing a framework for identifying validation methods, extent of validation, and credibility of computational models used for design and evaluation of PCLC medical devices. This may be achieved by cross collaborative efforts between industry, academia and FDA



The Dangers of AI in Medicine

Technological Risks	Algorithmic bias and unrepresentative and / or inacurate data Cybersecurity
Ethical Risks	Equity and Inclusion Data Privacy and Security Right to access
Legal Risks	Liability and accountability
Professional Risks	Automation and Unem[illegible] Ethics of labor unions Medical Education and AI Patients physicians relationship and Humanistic medicine
Human / Machine Interface	Building trust in AI / Black [illegible] Risk Homeostasis Automation bias and complacency Error underreporting Interpretable and explainable AI


Technology, Computing, and Simulation

SPECIAL ARTICLE

Science Without Conscience Is but the Ruin of the Soul: The Ethics of Big Data and Artificial Intelligence in Perioperative Medicine

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