# Closed-loop Control of Perioperative Hypotension



## Hōpital Erasme

#### Alexandre JOOSTEN, MD PhD Department of Anesthesiology Bicètre & Paul Brousse Hospital



# **Conflicts of Interest**

## **Consultant for:**

- Edwards Lifesciences
- Aguettant
- Fresenius Kabi
- Baxter
- Getinge

## **Research Fundings:**

- Fresenius Kabi
- Edwards Lifesciences
- European Society of Intensive Care Medicine
- Belgium Society of Anesthesiology
- Biospectal

# Paul Brousse

- 5 Operating rooms
- 240 liver resection per year
- 60 Pancreatic surgery per year
- 175 Liver Transplant per year 3rd largest in Europe



#### Henri Bismuth





Chairman: Rene Adam





### APHP: The greatest university hospital in Europe

- > 39 hospitals
- > 100,000 professionals
- Connected to 5 medical universities and 17 nursing schools
- > 1st biomedical research center in Europe
- > 69 rare disease reference centers
- An operating budget of 7.5 billion euros

## AP-HP:

- > 10 millions of patients
- > 200 000 surgeries/ year
- > 1250 transplants / year



 We must delve into the roots of the past to discern the bearing branches of our future »

**Jules Verne** 1828 - 1905





# 



British Journal of Anaesthesia **110** (5): 758–63 (2013) Advance Access publication 10 March 2013 · doi:10.1093/bja/aes498

## Transcontinental anaesthesia: a pilot study

T. M. Hemmerling<sup>1\*</sup>, E. Arbeid<sup>1</sup>, M. Wehbe<sup>1</sup>, S. Cyr<sup>1</sup>, F. Giunta<sup>2</sup> and C. Zaouter<sup>2</sup>

 The transcontinental approach was performed in order to deliver a proof of concept in a setting without specific Internet set-up other than standard Internet communication. Globally, there is a severe lack of specialists and specialist treatment in medicine, especially in anaesthesia, for example, only nine anaesthesiologists are available in Rwanda for a population of more than 10 million.<sup>19</sup> But even in highly industrialized countries such as Canada, a significant population lives in remote regions away from tertiary healthcare centres. Teleanaesthesia could help to overcome the shortage of specialists in remote areas, and it can potentially reduce travel costs and improve patients' accessibility to professional consultations and treatments.

2013

In conclusion, distant preoperative assessment and distant control of anaesthesia are feasible via standard means of Internet communication.





# Our Vision:

"Helping to reduce the number of preventable deaths in hospitals is a pledge that I made. My personal goal goes beyond: Improving Acute Care with technologies and services that lead to therapy assistance and ultimately to hospital automation."

Stefan Dräger, Chairman and CEO (2018)

We envision a future where human capabilities to deliver patient care in high acuity environments are enhanced by interoperability. Medical devices will be connected as systems and interact with one another, enabling new clinical applications in a safe and secure network. These new clinical applications include decision-supporting technologies, remote control capabilities or automated processes.



## On the Cutting Edge of O.R. Safety and Design



## **Driving Medical Device Interoperability**

Perseus AS

in Hospitals with Connected Technologies

## From Heroism to Safe Design

## Leveraging Technology

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 healthcare information ecosystem with integrated technologies that support the clinician's work, provide safety nets, and improve productivity." Anesthesiology 2014

# **Closed Loop System**



Closed Loop" is a generic term which has no specific meaning Briefly, a closed-loop system is a system wherein a controller monitors one or multiple variables and adjusts one or more interventions using a feedback process. The term is most often applied to automated systems.

## "Physiology" is based on Closed Loop controls



## "Life" is based on Closed Loop controls

## Thermostat



## Cruise control









# NEWS Self-driving Audi to drive from California to New York



# **Closed Loop Systems in Medicine?**



# Closed-loop drug delivery: A Novel idea?

Trans Am Soc Artif Intern Organs. 1981;27:241-5.

Blood glucose control by closed loop insulin delivery during coronary artery bypass surgery.

Kuntschen F, Galletti PM, Hahn C.

IEEE Trans Biomed Eng. 1981 Jun;28(6):475-9.

A microcomputer-based fluid infusion system for the resuscitation of burn patients.

Bowman RJ, Westenskow DR.

Crit Care Med. 1982 Dec;10(12):831-4.

The need for closed-loop therapy.

## Medically relevant articles with « closed-loop » in title by year





# **Toolbox Family**

# 19982002200420062008





# **TOOLBOX 2004**

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# **TOOLBOX Patent ULB**

#### Computer-controlled intravenous drug delivery system

#### Dec 21, 2004

The present invention relates to a system for computer-aided intravenous delivery of anesthetics and/or other drugs to a patient, wherein said system comprises an Infusion Controller that delivers an amount of drug(s) to a patient; possibly a DataLogger Controller with one or more Sensors adapted so as to be coupled to a patient and to generate signals reflecting one or more health conditions or statuses of the patient; a Communication Controller connected with the infusion pumps and/or monitors; a Session Controller that carries out the modeling of anesthesia procedures and is arranged to run a first procedure and to dynamically adapt said first procedure and/or select and run a second procedure based upon one or more of said sensors' output and/or observation from a physician; a Graphic User Interface to display different views of the system and to accept user input; a set of interfaces used to link the Infusion, Datalogger and Session Controllers to views displayed by the Graphical User Interface; a Processor or Infusion Session Manager that integrates the Graphic User Interface, the Infusion Controller, the DataLogger Controller, the Communication Controller and the Session Controller and that steers drug delivery, wherein the system contains a set of configurable written procedures to steer intravenous anesthetic drug delivery and/or other drug delivery, whereby said procedures have been adapted to the type of surgical action and/or therapy, adapted to the patient's physical condition, and adapted to the type of drugs, tools and theoretical models used. The system of the present invention finds its use among others in intravenous anesthesia (IVA) and in cancer therapy.

Patent number: 9597448 Assignee: <u>Université Libre de</u> Bruxelles (Brussels) Inventors: <u>Luc Barvais</u> (Wemmel), <u>Eddy</u> <u>Coussaert</u> (Waterloo)

## Perioperative Hypotension is

## 1) FREQUENT 2) MULTIFACTORIAL ETIOLOGY

Vasodilation (anesthetic drugs, deep anesthesia) Intravascular hypovolemia (bleeding) Low cardiac output (bradycardia or low stroke volume) High intraoperative pressure (mechanical ventilation) Impairment baroreflex regulation

# DIFFERENT MECHANISMS MAP = (CO x SVR) + CVP

## DECREASE in SVR and/or CO

#### Loss of vascular tone

- Sedation
- Anesthetic drugs
- Inflammation
- Spinal anesthesia
- Associated treatment

## Abnormal vascular tone

- Age
- Diabete
- Etc...

# Cardiac dysfunction

- RV dysfunction
- Pulmonary hypertension
- etc...

#### Acute hypovolemia

- Bleeding
- Excessive fluid loss
- Surgical clamping



# Numerous Large Database Analyses

# Low Blood Pressure during surgery Postoperative Organ Injury

(AMI and AKI)

## **Hypotension and Outcomes**

BJA	British Journal of Anaesthesia, 121 (4): 706–721 (2018) doi: 10.1016/j.bja.2018.04.036		
	Intensive Care Med (2018) 44:811-822 https://doi.org/10.1007/s00134-018-5224-7		
Anaesthesia 2018 Original Art	8, 73, 1223-1228 REVIEW		
_		018) 68–73	
-	Journal of Clinical Anesthesia 75 (2021) 110516	ceDirect	-112 
ELSEVIER	Contents lists available at ScienceDirect	sour Clinical Augestresic	CARDIOLOGY
	Perioperative Medicine		
	ORIGINAL CLINICAL RESEARCH REPORT		

#### Original Contribution

healthcare resor

Wolf H. Stapelfeldt, FRCA, FRCPC, FFICI Mitali Stevens, Phan

PhE

\*Department of Anesthesiology <sup>†</sup>Department of Anesthesiolog

<sup>‡</sup>Department of Epidemiology

## Association of **POPEN** Intraoperative Hypotension Is Associated With Adverse Clinical Outcomes After Noncardiac Surgery

Anne Gregory, MD, MSc, FRCPC,\* Wolf H. Stapelfeldt, MD,† Ashish K. Khanna, MD, FCCP, FCCM,‡§ Nathan J. Smischney, MD, MSc, II Isabel J. Boero, MD, MS, Qinyu Chen, MS, Mitali Stevens, PharmD, BCPS,# and Andrew D. Shaw, MB. FRCPC\*.\*\*

опеснь, опеснь, нешегана <sup>§</sup>Department of Cardiothoracic Surgery, Radboud University, Nijmegen, Nether <sup>1</sup>Department of Anesthesiology, Vrije Universiteit University Medical Center, Amsterdan \*Department of Anesthesiology, Radboud University, Nijmegen, Netherland \*\*Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, Nether

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<sup>a</sup> Department of Anesthesiology, Nanjing Drum Tower Hospital, Medical College of Nanjing University, Nanjing 210008, China <sup>b</sup> Department of Neurology, The First Affiliated Hospital of Chongging Medical University, Chongging Key Laboratory of Neurology, Chongging 400016, China

K. Maheshwari,<sup>1</sup> A. Turan,<sup>1</sup> G. Mao,<sup>2</sup> D. Yang,<sup>2</sup> A. K. Niazi A. Kurz<sup>o</sup>

# IN ICU



#### RESEARCH ARTICLE

Hypotension and a positive fluid balance are associated with delirium in patients with shock

Duc Nam Nguyen<sup>1</sup>\*, Luc Huyghens<sup>1</sup>, Jose Parra<sup>2</sup>, Johan Schiettecatte<sup>3</sup>, Johan Smitz<sup>3</sup>, Jean-Louis Vincent<sup>4</sup>

 Observational Study
 > Anesth Analg. 2021 May 1;132(5):1410-1420.

 doi: 10.1213/ANE.000000000005374.

#### Postoperative Hypotension and Adverse Clinical Outcomes in Patients Without Intraoperative Hypotension, After Noncardiac Surgery

Ashish K Khanna <sup>1</sup> <sup>2</sup>, Andrew D Shaw <sup>3</sup> <sup>4</sup>, Wolf H Stapelfeldt <sup>5</sup>, Isabel J Boero <sup>6</sup>, Qinyu Chen Mitali Stevens <sup>7</sup>, Anne Gregory <sup>3</sup>, Nathan J Smischney <sup>8</sup>

#### Association Between Mean Arterial Pressure and Acute Kidney Injury and a Composite of Myocardial Injury and Mortality in Postoperative Critically III Patients: A Retrospective Cohort Analysis

Ashish K. Khanna, MD, FCCP, FCCM<sup>1,2</sup>; Kamal Maheshwari, MD, MPH<sup>3</sup>; Guangmei Mao, MS<sup>3,4</sup>; Liu Liu, MS<sup>3,4</sup>; Silvia E. Perez-Protto, MD<sup>3</sup>; Praneeta Chodavarapu, MD<sup>3</sup>; Yehoshua N. Schacham, MD<sup>3</sup>; Daniel I. Sessler, MD<sup>3</sup>

Intensive Care Med (2018) 44:857-867 https://doi.org/10.1007/s00134-018-5218-5

#### ORIGINAL

CrossMark

#### The relationship between ICU hypotension and in-hospital mortality and morbidity in septic patients

Kamal Maheshwari<sup>1,7\*</sup>, Brian H. Nathanson<sup>2</sup>, Sibyl H. Munson<sup>3</sup>, Victor Khangulov<sup>3</sup>, Mitali Stevens<sup>4</sup>, Hussain Badani<sup>3</sup>, Ashish K. Khanna<sup>5</sup> and Daniel I. Sessler<sup>6</sup>

Vincent et al. Ann. Intensive Care (2018) 8:107 https://doi.org/10.1186/s13613-018-0448-9

O Annals of Intensive Care

#### RESEARCH

#### Open Access



Mean arterial pressure and mortality in patients with distributive shock: a retrospective analysis of the MIMIC-III database

Jean-Louis Vincent<sup>1\*</sup>, Nathan D. Nielsen<sup>2</sup>, Nathan I. Shapiro<sup>3</sup>, Margaret E. Gerbasi<sup>4</sup>, Aaron Grossman<sup>5</sup>, Robin Doroff<sup>5</sup>, Feng Zeng<sup>6</sup>, Paul J. Young<sup>7</sup> and James A. Russell<sup>8</sup>

Crit Care Med 2019

#### ANESTHESIOLOGY 2020 September







Postoperative Hypotension after Noncardiac Surgery: Association with Myocardial Injury

Volume 133 Number 3 anesthesiology.org

Margallan .....

Later St. ...

COLUMN TO THE

The Journal of the American Society of Anesthesiologists, Inc.

Intraoperative Hypotension and Acute Kidney Injury

Low Mean Arterial Pressure during Cardiopulmonary Bypass Is Associated with an Increased Risk of Stroke

September 2018

Perfusion

2 PA mmHg 🖄 10/10

Volume 129, Number 3 ISSN 0003-3022

hesiologists, Inc. • anesthesiology.org

#### Relationship between Intraoperative Mean Arterial Pressure and Clinical Outcomes after Noncardiac Surgery

#### Toward an Empirical Definition of Hypotension

Michael Walsh, M.D.,\* Philip J. Devereaux, M.D., Ph.D.,† Amit X. Garg, M.D., Ph.D.,‡ Andrea Kurz, M.D.,§ Alparslan Turan, M.D., || Reitze N. Rodseth, M.D.,# Jacek Cywinski, M.D.,\*\* Lehana Thabane, Ph.D.,†† Daniel I. Sessler, M.D.‡‡ Anesthesiology 2013; 119:507-15



Fig. 3. Predicted probability of (A) acute kidney injury and (B) myocardial injury by lowest mean arterial pressure (MAP) experienced during surgery.

## **AKI and MI by lowest MAP**

# <u>INJURY</u>= Minutes MAP < 55 mmHg



Time spent with a MAP < 55 mmHg during noncardiac surgery is independently associated with an increased risk of AKI & MI

Notably, any amount of time at a MAP < 55 mmHg was associated with adverse outcomes

Joosten et al. BMC Anesthesiology (2021) 21:12 https://doi.org/10.1186/s12871-020-01228-y

## **BMC** Anesthesiology

#### **RESEARCH ARTICLE**

#### **Open Access**

Intraoperative hypotension during liver transplant surgery is associated with postoperative acute kidney injury: a historical cohort study



Joosten et al, BMC ANESTHESIOLOGY 2021





# 1) Hypnosis drugs administration

Anesthesiology. 2012 Feb;116(2):286-95. doi: 10.1097/ALN.0b013e318242ad4f.

Feasibility of closed-loop titration of propofol and remifentanil guided by the spectral M-Entropy monitor.

Liu N<sup>1</sup>, Le Guen M, Benabbes-Lambert F, Chazot T, Trillat B, Sessler DI, Fischler M.

J Clin Monit Comput. 2019 Jul 20. doi: 10.1007/s10877-019-00360-6. [Epub ahead of print]

Behavior of a dual closed-loop controller of propofol and remifentanil guided by the bispectral index for postoperative sedation of adult cardiac surgery patients: a preliminary open study.

Squara P<sup>1</sup>, Chazot T<sup>2,3</sup>, Auboin G<sup>2,3</sup>, Fischler M<sup>4,5</sup>, Dreyfus JF<sup>6</sup>, Le Guen M<sup>2,3</sup>, Liu N<sup>2,3,7</sup>.

Minerva Anestesiol. 2018 Apr;84(4):437-446. doi: 10.23736/S0375-9393.17.11915-2. Epub 2017 Dec 13.

Effects of closed-loop intravenous anesthesia guided by Bispectral Index in adult patients on emergence delirium: a randomized controlled study.

Cotoia A<sup>1</sup>, Mirabella L<sup>2</sup>, Beck R<sup>2</sup>, Matrella P<sup>2</sup>, Assenzo V<sup>3,4,5</sup>, Chazot T<sup>3,4</sup>, Cinnella G<sup>2</sup>, Liu N<sup>3,4,5</sup>, Dambrosio M<sup>2</sup>.

Intensive Care Med. 2013 Mar;39(3):454-62. doi: 10.1007/s00134-012-2762-2. Epub 2012 Dec 6.

Automated sedation outperforms manual administration of propofol and remifentanil in critically ill patients with deep sedation: a randomized phase II trial.

Le Guen M<sup>1</sup>, Liu N, Bourgeois E, Chazot T, Sessler DI, Rouby JJ, Fischler M.

Anesth Analq. 2011 Mar;112(3):546-57. doi: 10.1213/ANE.0b013e318205680b. Epub 2011 Jan 13.

Closed-loop coadministration of propofol and remifentanil guided by bispectral index: a randomized multicenter study.

Liu N<sup>1</sup>, Chazot T, Hamada S, Landais A, Boichut N, Dussaussoy C, Trillat B, Beydon L, Samain E, Sessler DI, Fischler M.

#### Anesthesiology. 2006 Apr;104(4):686-95.

Titration of propofol for anesthetic induction and maintenance guided by the bispectral index: closed-loop versus manual control: a prospective, randomized, multicenter study.

Liu N<sup>1</sup>, Chazot T, Genty A, Landais A, Restoux A, McGee K, Laloë PA, Trillat B, Barvais L, Fischler M.



#### **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) Better maintains a given target within a selected range

2) Decreases overshooting or undershooting of a given target

# Potential benefits of closed-loop systems

- Automation of previously manual tasks
- Improvement in stability of the controlled parameters
- Monitor and analyze more frequently
- The closed-loop is not distractible from its task
- Its algorithm is perfectly repeatable
- Allow anesthesiologist to focus on higher clinical tasks and decisions
- Areas left for human being: Elaboration, Creation and management of unique situation
### On the market



### Concert CL

### Neurowave CL



### Medsteer, Paris

### 2) Analgesic drug administration

Conf Proc IEEE Eng Med Biol Soc. 2018 Jul;2018:506-509. doi: 10.1109/EMBC.2018.8512330.

#### Closed-loop administration of analgesic drugs based on heart rate variability analysis.

De Jonckheere J, Jeanne M, Keribedj A, Delecroix M, Logier R.



## 3) Fluid administration

British Journal of Anaesthesia Page 1 of 10 doi:10.1093/bja/aeu452

#### Variability in practice and factors predictive of total crystalloid administration during abdominal surgery: retrospective two-centre analysis

M. Lilot<sup>1,2</sup>, J. M. Ehrenfeld<sup>3</sup>, C. Lee<sup>1</sup>, B. Harrington<sup>1</sup>, M. Cannesson<sup>1</sup> and J. Rinehart<sup>1\*</sup>

### Perioperative Fluid Utilization Variability and Association With Outcomes

Considerations for Enhanced Recovery Efforts in Sample US Surgical Populations

British Journal of Anaesthesia 114 (5): 717–21 (2015) Advance Access publication 19 March 2015 · doi:10.1093/bja/aev067

Perioperative fluid management: science, art or random chaos?

G. Minto<sup>1,2</sup> and M. G. Mythen<sup>3,4,\*</sup>

#### **Critical** Care

#### RESEARCH

#### **Open Access**



Antonio Messina<sup>1,2\*</sup><sup>®</sup>, Chiara Robba<sup>3,4</sup>, Lorenzo Calabrò<sup>1</sup>, Daniel Zambelli<sup>1</sup>, Francesca Iannuzzi<sup>4</sup>, Edoardo Molinari<sup>4</sup>, Silvia Scarano<sup>4</sup>, Denise Battaglini<sup>4</sup>, Marta Baggiani<sup>5</sup>, Giacomo De Mattei<sup>6</sup>, Laura Saderi<sup>7</sup>, Giovanni Sotgiu<sup>7</sup>, Paolo Pelosi<sup>3,4</sup> and Maurizio Cecconi<sup>1,2</sup>

### **Conclusions** GDT strategy reduces postoperative complications

Effect of a Perioperative, Cardiac Output-Guided Hemodynamic Therapy Algorithm on Outcomes Following Major Gastrointestinal Surgery A Randomized Clinical Trial and Systematic Review

-Multicenter RCT
> largest study in the field
-734 medium to high-risk
patients
-Primary outcome: composite
of postoperative complications
& mortality

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(RR, 0.80;

P = .04).

Editorial

Perioperative goal directed therapy: Evidence and compliance are two sides of the same coin

A. Joosten <sup>a, b</sup> , J. Ri	nehart <sup>a</sup> , M. (	Cannesson <sup>a,</sup>	📥 - 🔽	
Mortality at 180 days	7.7%	11.6%	0.08	assumed to expense outcome as
ΙΔΝΛΔ®				had been allocate alternative group 95% Cl. 0.61-0.99

### **Compliance is a huge problem**



### **Compliance is linked to poor patient's outcomes**

#### Adherence to the Enhanced Recovery After Surgery Protocol and Outcomes After Colorectal Cancer Surgery

Ulf O. Gustafsson, MD, PhD; Jonatan Hausel, MD; Anders Thorell, MD, PhD; Olle Ljungqvist, MD, PhD; Mattias Soop, MD, PhD; Jonas Nygren, MD, PhD; for the Enhanced Recovery After Surgery Study Group



**Figure 3.** Association between adherence to the enhanced recovery after surgery protocol and postoperative outcomes. \*Statistically significant at P < .05.

Eight years of experience with Enhanced Recovery After Surgery in patients with colon cancer: Impact of measures to improve adherence

Nathalie Bakker, MD,<sup>a,b,c</sup> Hamit Cakir, MD,<sup>a</sup> H. J. Doodeman, MSc,<sup>a,b</sup> and A. P. J. Houdijk, MD, PhD,<sup>a,b,c</sup> Alkmaar and Amsterdam, The Netherlands



adherence (%)

BJA

British Journal of Anaesthesia, 115 (4): 560-8 (2015)

doi: 10.1093/bja/aev105 Advance Access Publication Date: 29 April 2015 Clinical Practice

#### CLINICAL PRACTICE

## Enhanced recovery from surgery in the UK: an audit of the enhanced recovery partnership programme 2009–2012<sup>+</sup>

J. C. Simpson<sup>1</sup>, S. R. Moonesinghe<sup>1,2</sup>, M. P. W. Grocott<sup>1,2,3</sup>, M. Kuper<sup>4</sup>, A. McMeeking<sup>5</sup>, C. M. Oliver<sup>1,2</sup>, M. J. Galsworthy<sup>1,2</sup>, and M. G. Mythen<sup>1,\*</sup> on behalf of the National Enhanced Recovery Partnership Advisory Board<sup>‡</sup>

### Need > 80% compliance with pathways to see most improved outcomes



### DEPARTMENT OF ANESTHESIOLOGY & PERIOPERATIVE CARE SCHOOL OF MEDICINE

STAIR 31

UNIVERSITY of CALIFORNIA • IRVINE





#### Q core Sapphire Pump



### Extensive pre-clinical evaluation from 2011-2013

#### Society for Technology in Anesthesia

Section Editor: Maxime Cannesson

#### **Closed-Loop Fluid Resuscitation: Robustness Against** Weight and Cardiac Contractility Variations

Joseph Rinehart, MD,\* Christine Lee, BS,\* Maxime Cannesson, MD, PhD,\* and Guy Dumont, PhD†

Rinehart et al. Critical Care 2011, 15:R278 http://ccforum.com/content/15/6/R278



**Open Access** 

#### RESEARCH

Evaluation of a novel closed-loop fluidadministration system based on dynamic predictors of fluid responsiveness: an *in silico* simulation study

Joseph Rinehart<sup>1</sup>, Brenton Alexander<sup>1</sup>, Yannick Le Manach<sup>2,3</sup>, Christoph K Hofer<sup>4</sup>, Benoit Tavernier<sup>5</sup>, Zeev N Kain<sup>1</sup> and Maxime Cannesson<sup>1\*</sup>

Journal of Cardiothoracic and Vascular Anesthesia, Vol 26, No 5 (October), 2012: pp 933-939

Intraoperative Stroke Volume Optimization Using Stroke Volume, Arterial Pressure, and Heart Rate: Closed-Loop (Learning Intravenous Resuscitator) Versus Anesthesiologists

Joseph Rinehart, MD, Elena Chung, MD, Cecilia Canales, MPH, and Maxime Cannesson, MD, PhD

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

Ann Fr Anesth Reanim. 2014 Mar;33(3):e35-41. doi: 10.1016/j.annfar.2013.11.016. Epub 2013 Dec 27.

#### First closed-loop goal directed fluid therapy during surgery: a pilot study.

Rinehart J<sup>1</sup>, Le Manach Y<sup>2</sup>, Douiri H<sup>3</sup>, Lee C<sup>1</sup>, Lilot M<sup>1</sup>, Le K<sup>1</sup>, Canales C<sup>1</sup>, Cannesson M<sup>4</sup>.

Rinehart et al. Critical Care (2015) 19:94 DOI 10.1186/s13054-015-0827-7

#### RESEARCH



#### **Open Access**

Closed-loop assisted versus manual goal-directed fluid therapy during high-risk abdominal surgery: a case–control study with propensity matching





#### **RINEHART et al, Crit Care 2015**



#### **BRUGMANN HOSPITAL**

### ERASME HOSPITAL



## The primary outcome: compliance to GDFT protocol = percentage of case time where SVV was ≤ 12%



**Figure 4 Goal-directed fluid therapy compliance by group.** Box plots for the manual and closed-loop assisted groups, including outliers, are shown. The closed-loop assistance not only improved mean compliance to goal-directed fluid therapy (GDT) principles but also substantially reduced the variability in compliance within the group (manual group compliance standard deviation (SD) =14%, closed-loop group compliance SD =6%). Asterisks represent outliers, dot represent extreme outliers.

This system may help providers maintain high compliance to GDFT protocols.



#### **ORIGINAL ARTICLE**

Implementation of closed-loop-assisted intra-operative goal-directed fluid therapy during major abdominal surgery

A case-control study with propensity matching

Objective : Assess the impact of our closed-loop system in patients undergoing major abdominal surgery at Erasme hospital without a GDFT programme

**Primary outcome**: Intraoperative net fluid balance

Secondary outcomes: Composite of major & minor complications and LOS

Joosten et al, EJA 2018

### **Time Series Analysis**





## 4) Vasopressor administration

### **Current Practice**

Blood pressure variability in surgical and intensive care patients: Is there a potential for closed-loop vasopressor administration?

Joseph Rinehart<sup>a</sup>, Michael Ma<sup>a</sup>, Michael David Calderon<sup>a</sup>, Aurelie Bardaji<sup>b</sup>, Reda Hafiane<sup>b</sup>, Philippe Van der Linden<sup>c</sup>, Alexandre Joosten<sup>b,d,\*</sup>

- > 800 critically ill patients in the ICU
- > > 2,500 high-risk surgical patients (major surgery)
- under continuous norepinephrine infusion (2014-2017)





### **OR and ICU Patients spent:**

48.8% with a MAP [60- 80] mmHg 11.2% with MAP < 60 mmHg 40% with MAP > 80 mmHg

- 1) Blood pressure management is suboptimal
- 2) There is room for improvement in the BP management of OR and ICU patients receiving vasopressor therapy
- 3) There may be a need for more accurate and timely titration

### 7 research groups: Experimental research

#### **Physician-Directed Versus Computerized Closed-Loop Control of Blood Pressure Using Phenylephrine in a** Swine Model

Nicole Ribeiro Margues, MD,\* William E. Whitehead, PhD,\* Upendar R. Kallu, PhD,† USA Michael P. Kinsky, MD,\* Joe S. Funston, MD,\* Taoufik Wassar, PhD,† Muzna N. Khan, MS,\* Mindy Milosch, MD,\* Daniel Jupiter, PhD,<sup>‡</sup> Karolos Grigoriadis, PhD,<sup>†</sup> and George C. Kramer, PhD<sup>\*</sup>

Closed-loop double-vasopressor automated system to treat hypotension during spinal anaesthesia for caesarean section: a preliminary study

A. T. H. Sia, H. S. Tan, B. L. Sng

#### Singapore

First published:28 September 2012 | https://doi.org/10.1111/anae.12000 | Cited by: 21

#### RESEARCH

#### Open Access CrossMark

Performance of closed-loop resuscitation of haemorrhagic shock with fluid alone or in combination with norepinephrine: an experimental study

Nicolas Libert<sup>1,2</sup>, Guillaume Chenegros<sup>3</sup>, Anatole Harrois<sup>1,4</sup>, Nathalie Baudry<sup>1</sup>, Gilles Cordurie<sup>3</sup>, Ryad Benosman<sup>3</sup>, Eric Vicaut<sup>1,5</sup> and Jacques Duranteau<sup>1,4\*</sup><sup>o</sup> France

Uemura et al. BMC Anesthesiology (2017) 17:145 DOI 10.1186/s12871-017-0437-9

**BMC** Anesthesiology

#### **TECHNICAL ADVANCE**

**Open Access** ( CrossMark

Computer-controlled closed-loop drug infusion system for automated hemodynamic resuscitation in endotoxininduced shock JAPAN

Kazunori Uemura<sup>\*</sup>, Toru Kawada, Can Zheng, Meihua Li and Masaru Sugimachi

**Closed-Loop Feedback Computer-Controlled Phenylephrine for Maintenance of Blood Pressure During Spinal Anesthesia for Cesarean Delivery: A Randomized Trial Comparing Automated Boluses Versus Infusion** 

Warwick D. Ngan Kee, MD, FANZCA, FHKCA,\* Yuk-Ho Tam, BSc, MPhil,\* Kim S. Khaw, MD, FRCA, FHKCA,\* Floria F. Ng, RN, BASc,\* and Shara W. Y. Lee, PhD+

#### Closed-loop regulation of arterial pressure after acute brain death

Kristian Soltesz<sup>1</sup> · Trygve Sjöberg<sup>2</sup> · Tomas Jansson<sup>3</sup> · Rolf Johansson<sup>1</sup> · Anders Robertsson<sup>1</sup> · Audrius Paskevicius<sup>2</sup> · Quiming Liao<sup>2</sup> · Guangqi Qin<sup>2</sup> · Stig Steen<sup>2</sup>



China

### **Pre-clinical evaluation**

CrossMark

#### In Silico studies

### In Vivo study

Journal of Clinical Monitoring and Computing

--- February 2018, Volume 32, <u>Issue 1</u>, pp 5–11 | <u>Cite as</u>

Feasibility of automated titration of vasopressor infusions using a novel closed-loop controller

Journal of Clinical Monitoring and Computing https://doi.org/10.1007/s10877-018-0234-0

**ORIGINAL RESEARCH** 

Closed-loop vasopressor control: in-silico study of robustness against pharmacodynamic variability PERIOPERATIVE MEDICINE

### ANESTHESIOLOGY

Automated Titration of Vasopressor Infusion Using a Closed-loop Controller

*In Vivo* Feasibility Study Using a Swine Model

Joosten et al, ANESTHESIOLOGY 2019



## Experimental model of induced normovolemic hypotensive episodes (4 episodes of 30 min each < serum nitroprusside)





Closed-Loop vs. Unmanaged Vasodilation

110

Closed-Loop vs. Unmanaged Vasodilation



## **Clinical studies in the Operating room?**

#### KK Women's & Children's Hospital, Singapore





Peri-operative medicine, critical care and pain

#### Original Article 🔒 Free Access

Closed-loop double-vasopressor automated system to treat hypotension during spinal anaesthesia for caesarean section: a preliminary study

A. T. H. Sia, H. S. Tan, B. L. Sng

First published:28 September 2012 | https://doi.org/10.1111/anae.12000 | Cited by: 21



#### Original Article 🙃 Free Access

Closed-loop double-vasopressor automated system vs manual bolus vasopressor to treat hypotension during spinal anaesthesia for caesarean section: a randomised controlled trial

B. L. Sng, H. S. Tan, A. T. H. Sia

First published: 20 November 2013 | https://doi.org/10.1111/anae.12460 | Cited by: 29

#### **Chinese University of Hong Kong**

J Clin Monit Comput (2017) 31:617–623 DOI 10.1007/s10877-016-9883-z



ORIGINAL RESEARCH

Performance of a closed-loop feedback computer-controlled infusion system for maintaining blood pressure during spinal anaesthesia for caesarean section: a randomized controlled comparison of norepinephrine versus phenylephrine

Warwick D. Ngan Kee $^1\cdot$  Kim S. Khaw $^1\cdot$ Yuk-Ho $\mathrm{Tam}^1\cdot\mathrm{Floria}$  F. Ng $^1\cdot$ Shara W. Lee $^2$ 

Closed-Loop Feedback Computer-Controlled Phenylephrine for Maintenance of Blood Pressure During Spinal Anesthesia for Cesarean Delivery: A Randomized Trial Comparing Automated Boluses Versus Infusion

Warwick D. Ngan Kee, MD, FANZCA, FHKCA,\* Yuk-Ho Tam, BSc, MPhil,\* (Anesth Analg 2017;125:117–23) Kim S. Khaw, MD, FRCA, FHKCA,\* Floria F. Ng, RN, BASc,\* and Shara W. Y. Lee, PhD†

# Low-risk patients (C-Section-spinal Anesthesia) Ephedrine and/or Phenylephrine



### 1) High-risk patients (under general anesthesia)

### 2) Norepinephrine infusion

BJA

British Journal of Anaesthesia, 123 (4): 430–438 (2019)

doi: 10.1016/j.bja.2019.04.064 Advance Access Publication Date: 27 June 2019 Cardiovascular

Feasibility of closed-loop titration of norepinephrine infusion in patients undergoing moderate- and high-risk surgery

#### 20 patients

**2.6 %** of case time under-target (Hypotension)

2.4% of case time over-target (Hypertension)

Joosten et al, BJA 2019

### Aorto-Bifemoral Bypass Surgery



ERASME Hospital Brussels BELGIUM

### TARGET MAP at 70mmHg ± 5 mmHg

### 0% case time with a MAP < 65 mmHg



Closed-Loop Control of Vasopressor Administration in Patients Undergoing Cardiac Revascularization Surgery



Joosten et al J Cardiothorac Vasc Anesth. 2020


# ROBOTIC CARDIAC SURGERY



# ON-PUMP CARDIAC SURGERY



Feasibility of computer-assisted vasopressor infusion using continuous non-invasive blood pressure monitoring in high-risk patients undergoing renal transplant surgery



# Neuro embolization of cerebral aneurysm





## Mean Arterial Pressure - Manual versus Closed-Loop Management



Mean Arterial Pressure in Neurotrauma Over First 11 Hours



### CLINICAL INVESTIGATION

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



### Joosten et al, BJA 2020

ORIGINAL CLINICAL RESEARCH REPORT

## Control of Postoperative Hypotension Using a Closed-Loop System for Norepinephrine Infusion in Patients After Cardiac Surgery: A Randomized Trial

**40 patients:** RCT (manual vs automated adjustments of noradrenaline)

Primary objective: % postop stud period with a MAP < 65 mmHg







Desebbe et al, A&A 2022



## **Mean Arterial Pressure in All Cases**



Hours

# « COMAT » study Control MAP Brain Injury Patients





### Violin plots of distributions





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# Rodent model of haemorrhagic shock

Libert et al. Ann. Intensive Care (2018) 8:89 https://doi.org/10.1186/s13613-018-0436-0

### O Annals of Intensive Care

#### RESEARCH





## Performance of closed-loop resuscitation of haemorrhagic shock with fluid alone or in combination with norepinephrine: an experimental study

Nicolas Libert<sup>1,2</sup>, Guillaume Chenegros<sup>3</sup>, Anatole Harrois<sup>1,4</sup>, Nathalie Baudry<sup>1</sup>, Gilles Cordurie<sup>3</sup>, Ryad Benosman<sup>3</sup>, Eric Vicaut<sup>1,5</sup> and Jacques Duranteau<sup>1,4\*</sup><sup>®</sup>

# Pig model of haemorrhagic shock

Journal of Clinical Monitoring and Computing https://doi.org/10.1007/s10877-020-00542-7

ORIGINAL RESEARCH



Performance of closed-loop resuscitation in a pig model of haemorrhagic shock with fluid alone or in combination with norepinephrine, a pilot study

Nicolas Libert<sup>1,2</sup> · Guillaume Chenegros<sup>3</sup> · Anatole Harrois<sup>1,4</sup> · Nathalie Baudry<sup>1</sup> · Benoit Decante<sup>5</sup> · Gilles Cordurie<sup>3</sup> · Ryad Benosman<sup>3</sup> · Olaf Mercier<sup>6,7</sup> · Eric Vicaut<sup>1,8</sup> · Jacques Duranteau<sup>1,4</sup>

# ANESTHESIOLOGY

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



Joosten et al, ANESTHESIOLOGY 2021

FIGURE 1

#### Computer-assisted Goal Directed Therapy protocol





Closed-loop vasopressor controller

> Infusion pump for noradrenaline administration

largest.

## Heatmap of Mean Arterial Pressure Error & Stroke Volume Index in All Cases by Group



Stroke Volume Index

A&A 2016 Dec 15;7(12):260-265

### CASE REPORT

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



### Joosten et al, A&A 2016

Section Editor: Maxime Cannesson
BRIEF REPORT

Feasibility of Fully Automated Hypnosis, Analgesia, and Fluid Management Using 2 Independent Closed-Loop Systems During Major Vascular Surgery: A Pilot Study



### Joosten et al, A&A 2019

# Impact on patient outcome

#### EDITORIALS

### PERIOPERATIVE MEDICINE

# ANESTHESIOLOGY

Anesthetic Management Using Multiple Closedloop Systems and Delayed Neurocognitive Recovery

A Randomized Controlled Trial

## **Robots Will Perform Anesthesia in the Near Future**

Thomas M. Hemmerling, M.D., D.E.A.A.





- Background:
- Cognitive changes after anesthesia concern.
- We tested the hypothesis that, in automated management of anesthe
   ventilation using three independent
   variables.
- Methods:
- Single-center, patient-and-evalua
- -90 patients having non-cardiac sub-
- -Primary outcome was a change in Assessment)
- -Secondary outcomes: battery of months post-surgery



### Figure 1

Preoperative (DAY-1)	Postoperative day 3-7 (POD# 3-7)	Postoperative day 90 (POD# 90)
<ul> <li>✓ Edmonton Frailty score</li> <li>✓ QoR-15</li> <li>✓ EQ-5D-5L</li> </ul>	✓ QoR-15	✓ EQ-5D-5L
✓ MoCA test	✓ MoCA test	✓ MoCA test
<ul> <li>✓ Episodic memory (Free and Cued Selective Reminding Test)</li> </ul>	<ul> <li>✓ Episodic memory (Free and Cued Selective Reminding Test)</li> </ul>	<ul> <li>✓ Episodic memory (Free and Cued Selective Reminding Test)</li> </ul>
<ul> <li>✓ Working memory (Forward and Backward digit spans)</li> </ul>	<ul> <li>✓ Working memory (Forward and Backward digit spans)</li> </ul>	<ul> <li>✓ Working memory (Forward and Backward digit spans)</li> </ul>
✓ Executive function (Stroop test)	✓ Executive function (Stroop test)	✓ Executive function (Stroop test)

TO Surgery T1 T	.5
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Evaluation Follow-Up Time (Weeks)

 Automated anesthetic management using the combination of 3 controllers outperforms manual control and may have an impact on delayed neurocognitive recovery.

✓ However, given the study design, it is not possible to determine the relative contribution of each controller on the cognition score























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1. Vasopressor Setup

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# Self-driving Uber kills Arizona woman in first fatal crash involving pedestrian

Tempe police said car was in autonomous mode at the time of the crash and that the vehicle hit a woman who later died at a hospital







#### **Dr. JOOSTEN** Guardian 2.93 Assembly v.1.0.7211.17416 -× dpc Monitor Bad Data Setup Alarms Vital signs outside nominal ranges; auto mode disabled Silence Norepinephrine Rate Locked: 7.4 mcg/min 16 mcg/ml concentration 0 A Drip Limits (mcg/min) 8 **Rate Locked** 25 to O MAP: 0 -Target 8 SBP MAP 75 Repinephrine 7.4 mcg/min Chemyx (3) Mode Running Rate 466 ul/min Hubb Total In 23.65 Change Vol Rem. 26.34 EV-1000 (12) HR 0 0/0 (0) BP SV 0 Continuous 0 SW

Journal of Clinical Monitoring and Computing https://doi.org/10.1007/s10877-020-00642-4

#### **ORIGINAL RESEARCH**



## Detection of arterial pressure waveform error using machine learning trained algorithms

Joseph Rinehart<sup>1,4</sup> · Jia Tang<sup>1</sup> · Jennifer Nam<sup>1</sup> · Sophie Sha<sup>1</sup> · Paulette Mensah<sup>1</sup> · Hailey Maxwell<sup>1</sup> · Michael-David Calderon<sup>1</sup> · Michael Ma<sup>1</sup> · Alexandre Joosten<sup>2,3</sup>

Received: 30 June 2020 / Accepted: 29 December 2020

Prospective Clinical Evaluation of a Machine-Learning Trained Algorithm for Detection of Arterial Pressure Transducer Drop

Joseph Rinehart MD <sup>1</sup>, Nicholas Pham, Deena Khoury BS, Ishita Srivastava, Paulette Mensah BS<sup>1</sup>, Hailey Maxwell BM <sup>1</sup>, Sophie Shah MD <sup>1</sup>, Michael Ma BS <sup>1</sup>, Alexandre Joosten MD PhD <sup>2,3</sup>

The Washington Post

#### The Switch

## 'We are convinced the machine can do better than human anesthesiologists'





The iControl-RP, which fully automates anesthesia for operations, stands on the right. On the left are traditional anesthesia monitors that would be used by a human doctor. UNIVERSITY OF BRITISH COLUMBIA PHOTO





## We still need a good Anesthetist!

Technology-enhanced simulation training in health care professions education is associated with large effects for outcomes of knowledge, skills, and behaviors! JAMA

### Pilots complained about autopilot issues with Boeing jets involved in two deadly crashes

#### 'DON'T SINK! DON'T SINK!'

By Andrew J. Hawkins | @andyjayhawk | Mar 13, 2019, 12:32pm EDT



"Pilots aren't being adequately trained on the autopilot system".