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CPP_{OPT} – Thoughts 16 Years After We Invented It

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Positive Korrelation von FV_m u. FV_s mit CPP
zeigt gestörte Autoregulation und ist
prognostisch ungünstig. Erste 2 Tage entscheidend

11/2/99

Monitoring of Cerebral Autoregulation in Head-Injured Patients

Marek Czosnyka, PhD; Piotr Smielewski, MSc; Peter Kirkpatrick, FRCS(NS); David K. Menon, MD, PhD; John D. Pickard, MChir, FRCS

Background and Purpose Disturbed cerebral autoregulation has been reported to correlate with an unfavorable outcome after head injury. Using transcranial Doppler ultrasonography, we investigated whether hemodynamic responses to spontaneous variations of cerebral perfusion pressure (CPP) provide reliable information on cerebral autoregulatory reserve.

Methods We studied 82 patients with head injury daily. Waveforms of intracranial pressure (ICP), arterial pressure, and transcranial Doppler flow velocity (FV) were captured during 2-hour periods. Time-averaged mean FV (FVm) and the FV during cardiac systole (FVs) were resolved. The correlation coefficient indices between FVm and CPP (Mx) and between FVs and CPP (Sx) during spontaneous fluctuations of CPP were calculated during 3-minute epochs and averaged for each investigation.

Results Mx and Sx correlated with CPP ($r=-.34$, $P=<.002$; $r=-.2$, $P=$NS, respectively), with ICP ($r=.46$, $P<.0001$; $r=.34$, $P<.003$, respectively), with admission Glasgow Coma Scale score ($r=-.34$, $P<.0025$; $r=-.38$, $P<.0008$, respectively), and with outcome after head injury ($r=.41$, $P<.0002$; $r=.48$, $P<.00009$, respectively). In patients who died, cerebral autoregulation was severely disturbed during the first 2 days after injury.

Conclusions Indices derived from spontaneous fluctuations of FV waveform and CPP describe cerebral vascular pressure reactivity. They correlate with outcome after head injury and therefore may be used to guide autoregulation-oriented intensive therapy. ***(Stroke. 1996;27:1829-1834.)***

Key Words • autoregulation • blood flow velocity • head injury • ultrasonics

Autoregulation of cerebral blood flow is important in preventing secondary insults to the injured brain.[1] Disturbed autoregulation may result in an abnormal balance between cerebral blood flow, blood volume, and the metabolic requirement of the cerebral tissues. Transient episodes of cerebral ischemia, hyperemia,[2] and/or uncontrollable increases in cerebral blood volume[3] are thought to be detrimental.

Although abnormal cerebral autoregulation is seen after head injury, the underlying mechanisms effecting this disturbance are not fully understood.[4,5] Endothelial dysfunction,[6] vasospasm,[7] and release of free radicals[8] may be involved. Accordingly, little is known regarding how to restore autoregulation. Some pursue an "autoregulation-oriented" therapy that attempts to maintain an adequate CPP[9] by pressure support and mild hypocapnia.[10] Some centers have suggested that disordered cerebral autoregulation correlates with a poor outcome.[11,12] Since the autoregulatory reserve may vary with time, reliable and repeatable clinical tests of autoregulation are essential to guide therapy.

Various methods of assessing the cerebrovascular hemodynamic reserve are available. These include tests of carbon dioxide reactivity,[4] stress tests relying on mechanical[13] or pharmacological[14] alteration of arterial pressure, and the transient hyperemic response test after carotid artery compression.[15] All may use TCD to assess the dynamic response of cerebral FV in the basal arteries to various stimuli. The averaged FV values encompass a complex array of factors, making interpretation of abnormalities difficult.[16] However, the value of TCD in head-injured patients has been facilitated by methods of continuous analysis of FV waveform. Observation of the respiratory-related fluctuations in arterial pressure and FV to assess cerebral autoregulation has been recently reported.[17] The FV pulse waveform is of particular importance, and in head-injured patients FV pulsatility correlates with the cerebral arteriovenous oxygen difference as CPP falls, which has clinical significance.[18]

In the present study we examined the possibility that continuous assessment of autoregulatory reserve can be achieved by comparing changes in FVm and FVs with spontaneous changes in CPP. We verified the hypothesis that a generous autoregulatory margin should be associated with a better outcome, and we attempted to study changes in autoregulatory reserve in time after head injury.

Subjects and Methods

Patients

Eighty-two patients (27 females, 55 males; age range, 6 to 75 years; mean age, 36 years) were admitted to Addenbrooke's Hospital suffering from head injuries with a mean GCS score of 6 (range, 3 to 13). Forty-five percent of the patients had hematomas seen on first (68%) or subsequent (32%) scans (45% extradural, 30% subdural, 25% intracerebral), of which 77% were evacuated surgically. No patients in whom bone flaps were removed were included in this study. The patients were paralyzed, sedated, and

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IT

Continuous Assessment of the Cerebral Vasomotor Reactivity in Head Injury

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Academic Neurosurgical Unit (MC, PS, PK, RJL, JDP) and Department of Anaesthesia (DM), Addenbrooke's Hospital, Cambridge, England

OBJECTIVE: Cerebrovascular vasomotor reactivity reflects changes in smooth muscle tone in the arterial wall in response to changes in transmural pressure or the concentration of carbon dioxide in blood. We investigated whether slow waves in arterial blood pressure (ABP) and intracranial pressure (ICP) may be used to derive an index that reflects the reactivity of vessels to changes in ABP.

METHODS: A method for the continuous monitoring of the association between slow spontaneous waves in ICP and arterial pressure was adopted in a group of 82 patients with head injuries. ABP, ICP, and transcranial doppler blood flow velocity in the middle cerebral artery was recorded daily (20- to 120-min time periods). A Pressure-Reactivity Index (PRx) was calculated as a moving correlation coefficient between 40 consecutive samples of values for ICP and ABP averaged for a period of 5 seconds. A moving correlation coefficient (Mean Index) between spontaneous fluctuations of mean flow velocity and cerebral perfusion pressure, which was previously reported to describe cerebral blood flow autoregulation, was also calculated.

RESULTS: A positive PRx correlated with high ICP ($r = 0.366$; $P < 0.001$), low admission Glasgow Coma Scale score ($r = 0.29$; $P < 0.01$), and poor outcome at 6 months after injury ($r = 0.48$; $P < 0.00001$). During the first 2 days after injury, PRx was positive ($P < 0.05$), although only in patients with unfavorable outcomes. The correlation between PRx and Mean Index ($r = 0.63$) was highly significant ($P < 0.000001$).

CONCLUSION: Computer analysis of slow waves in ABP and ICP is able to provide a continuous index of cerebrovascular reactivity to changes in arterial pressure, which is of prognostic significance. (Neurosurgery 41:11–19, 1997)

Key words: Autoregulation, Cerebrovascular reactivity, Head injury, Intracranial pressure, Outcome

Fluctuations observed in arterial blood pressure (ABP) usually produce a response in intracranial pressure (ICP) (13–15, 17, 19, 23). However, the temporal relationship between ABP and ICP waves is complex, and is influenced by the properties of the craniospinal fluid compartment and the cerebrovascular bed, including arterial wall compliance, muscular basal tone, and cerebrovascular resistance (6, 19). Cerebrovascular reactivity to changes in ABP describes the ability of vascular smooth muscle to change basal tone in response to variations in transmural pressure. There is a complex relation between cerebrovascular reactivity and cerebral autoregulation; these two expressions are not equivalent (3, 7). When the cerebral autoregulatory reserve nears exhaustion, cerebral blood flow becomes unstable. However, vessels may still demonstrate responses to a further reduction in perfusion pressure or changes in concentration of carbon dioxide (3, 7). Vascular responses may continue to occur outside the range of a stable cerebral blood flow, i.e., outside the limits of cerebral autoregulation (7).

Quantifying the vascular reactivity to changes in pressure, which is reported to be of prognostic importance (3, 18), without resort to artificial manipulation of the ABP, remains a challenge in clinical practice. Because natural variations in ABP occur during the cardiac cycle, several authors have suggested that vascular pressure-reactivity may be estimated from an analysis of the characteristic pulse waveforms in ABP and ICP (19, 20). Precise signal processing is necessary to achieve this in clinical practice, because the time-constant of

One Size Fits All?

Rosner MJ *et al.* J Neurosurg 83;1995:949-62

„The minimum level of CPP in this instance is greater than 70 mmHg and frequently higher, defined by **individual** circumstances that may occasionally require a level of 100 mmHg or more, but average 85 mmHg“

J Neurosurg 95:560–568, 2001

Adult respiratory distress syndrome: a complication of induced hypertension after severe head injury

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Object. The factors involved in the development of adult respiratory distress syndrome (ARDS) after severe head injury were studied. The presence of ARDS complicates the treatment of patients with severe head injury, both because hypoxia causes additional injury to the brain and because therapies that are used to protect the lungs and improve oxygenation in patients with ARDS can reduce cerebral blood flow (CBF) and increase intracranial pressure (ICP). In a recent randomized trial of two head-injury management strategies (ICP-targeted and CBF-targeted), a fivefold increase in the incidence of ARDS was observed in the CBF-targeted group.

Methods. Injury severity, physiological data, and treatment data in 18 patients in whom ARDS had developed were compared with the remaining 171 patients in the randomized trial in whom it had not developed. Logistic regression analysis was used to study the interaction of the factors that were related to the development of ARDS.

In the final exact logistic regression model, several factors were found to be significantly associated with an increased risk of ARDS: administration of epinephrine (5.7-fold increased risk), administration of dopamine in a larger than median dose (10.8-fold increased risk), and a history of drug abuse (3.1-fold increased risk).

Conclusions. Although this clinical trial was not designed to study the association of management strategy and the occurrence of ARDS, the data strongly indicated that induced hypertension in this high-risk group of patients is associated with the development of symptomatic ARDS.

Individual Optimal CPP?

- SJO_2 and TCD

  Chan KH *et al*.: The effect of changes in cerebral perfusion pressure upon middle cerebral artery blood flow velocity and jugular bulb venous oxygen saturation after severe brain injury. J Neurosurg 1992;77:55-61

- Microdialysis

  Nordstrom CH *et al*.: Assessment of the lower limit for cerebral perfusion pressure in severe head injuries by bedside monitoring of regional energy metabolism. Anesthesiology 2003;98:809-14

- Brain Tissue Oxygen

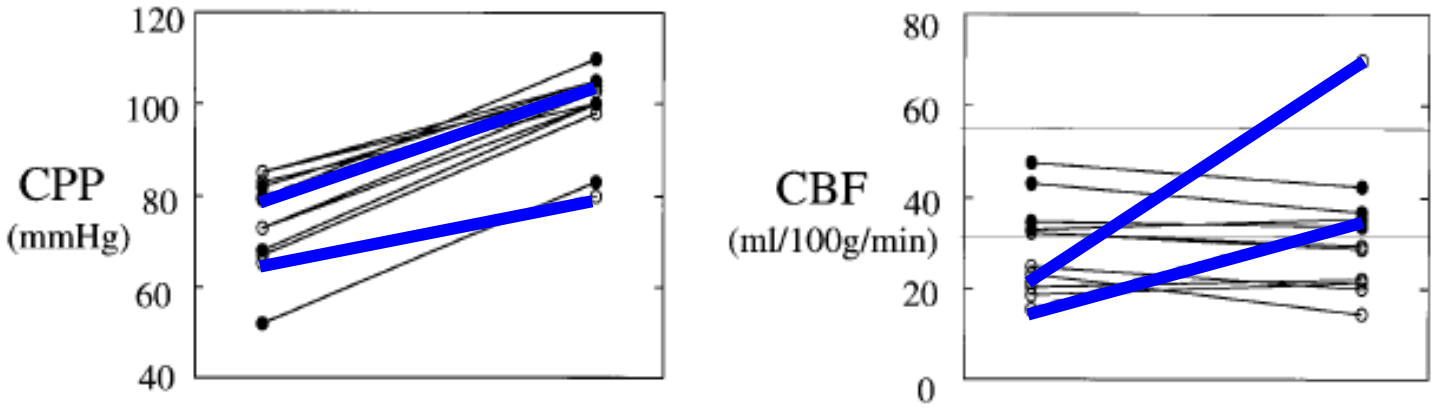
  Meixensberger J *et al*. Brain tissue oxygen guided treatment supplementing ICP/CPP therapy after traumatic brain injury. J Neurol Neurosurg Psychiatry. 2003;74:760-4

The Cambridge Hypothesis:

CPP should be kept at the CPP where an individual patient autoregulates most efficiently

Why Autoregulation?

- Cerebrovascular autoregulation will affect any CPP manipulation

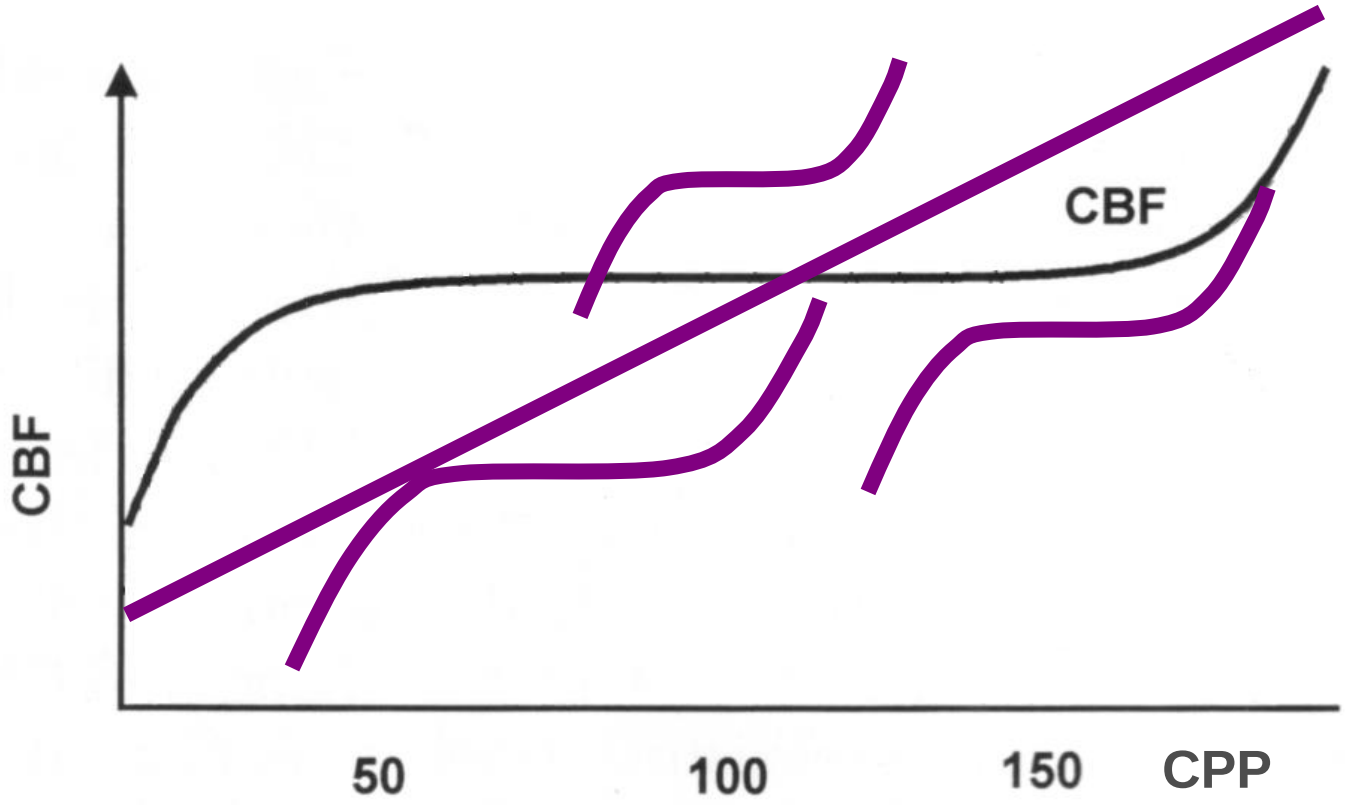


Mascia L *et al.*: Cerebral blood flow and metabolism in severe brain injury: the role of pressure autoregulation during cerebral perfusion pressure management. Intensive Care Med 2000;26:202-5

Autoregulation in Head Injury

- Protective Mechanism: Outcome better in patients with “intact” autoregulation
  - Overgaard J, Tweed WA. Cerebral circulation after head injury. 1. Cerebral blood flow and its regulation after closed head injury with emphasis on clinical correlations. J Neurosurg 1974;41:531-41
  - Lam JM, Hsiang JN, Poon WS. Monitoring of autoregulation using laser Doppler flowmetry in patients with head injury. J Neurosurg 1997;86:438-45
  - Czosnyka M, *et al*. Cerebral autoregulation following head injury. J Neurosurg 2001;95:756-63

Autoregulation in Head Injury



Requirements

- Continuous monitoring of autoregulation or cerebrovascular pressure reactivity.

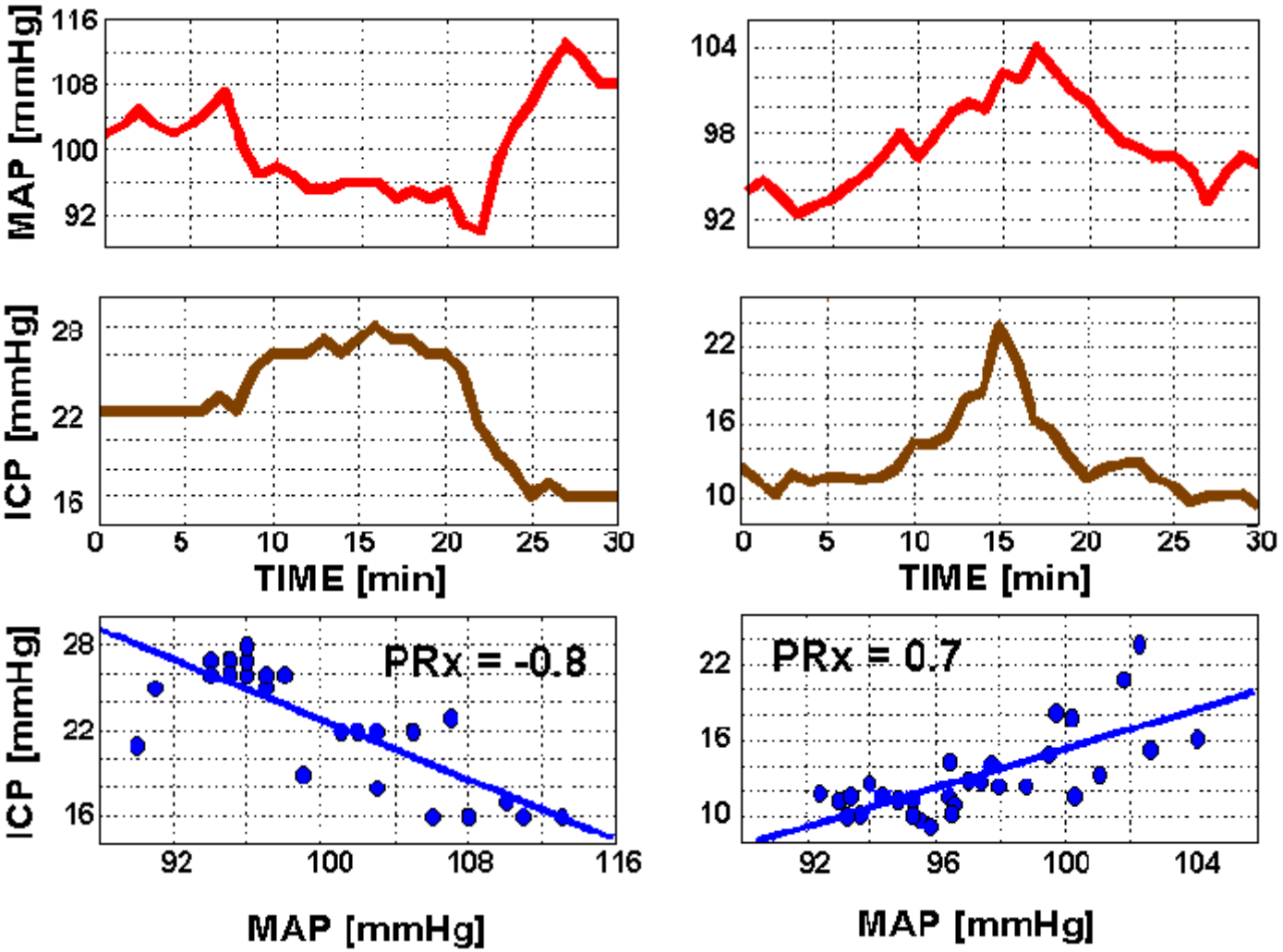
  Czosnyka M, *et al*. Monitoring of cerebral autoregulation in head-injured patients. Stroke 1996;27:1829-34

  Czosnyka M, *et al*. Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery 1997;41:11-7

  Steinmeier R, *et al*. Continuous cerebral autoregulation monitoring by cross-correlation analysis. J Neurotrauma 2002;19:1127-38

- Software to display an index of autoregulation or cerebrovascular reactivity against CPP

Pressure Reactivity Index (PRx)



Pressure Reactivity Index (PRx)

- Validated against PET CBF

  Steiner LA, *et al.* Assessment of cerebrovascular autoregulation in head-injured patients: a validation study. Stroke 2003;34:2404-9

- Correlates with outcome

  Czosnyka M, *et al*. Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery 1997;41:11-7

- Disturbed pressure reactivity is associated with low $CMRO_2$ and low OEF

  Steiner LA, *et al.* Cerebrovascular pressure reactivity is related to global cerebral oxygen metabolism after head injury. J Neurol Neurosurg Psychiatry 2003;74:765-70

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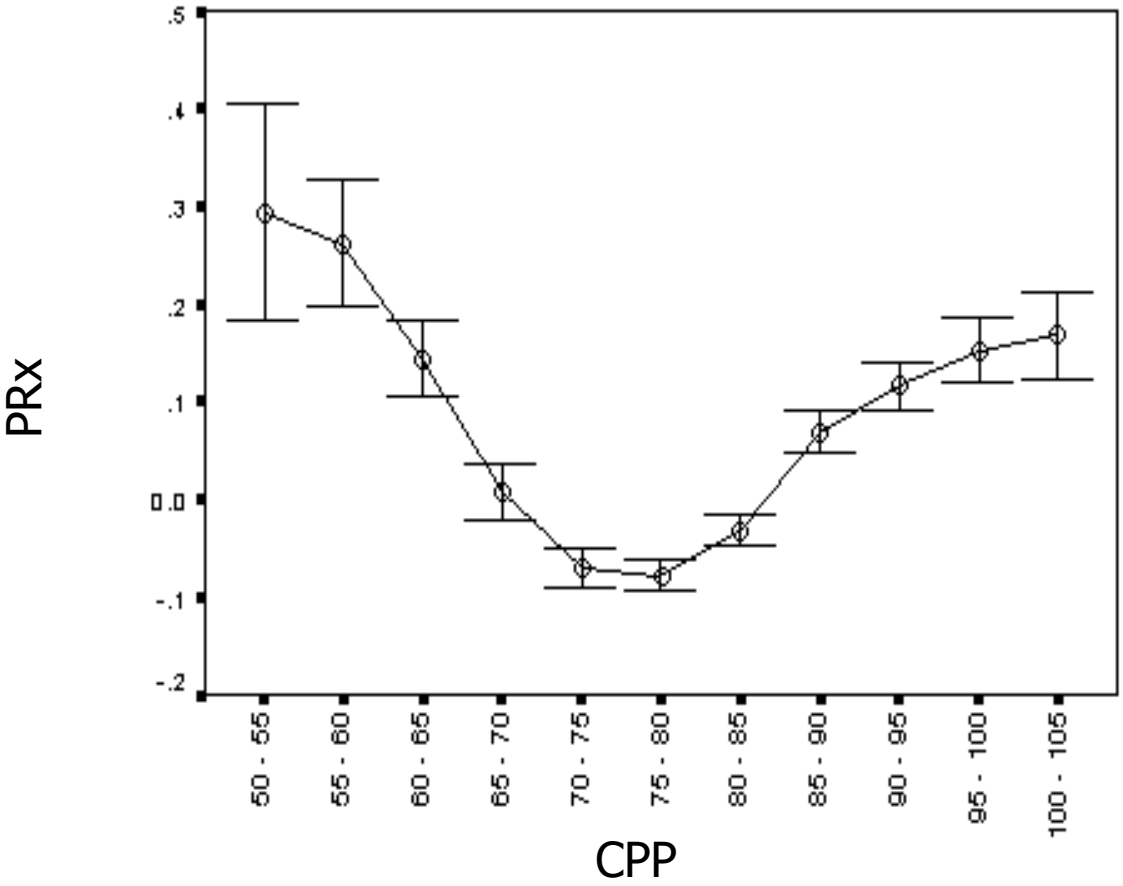
Individual Optimal CPP



Steiner LA, *et al.* Crit Care Med 2002;30:733-8

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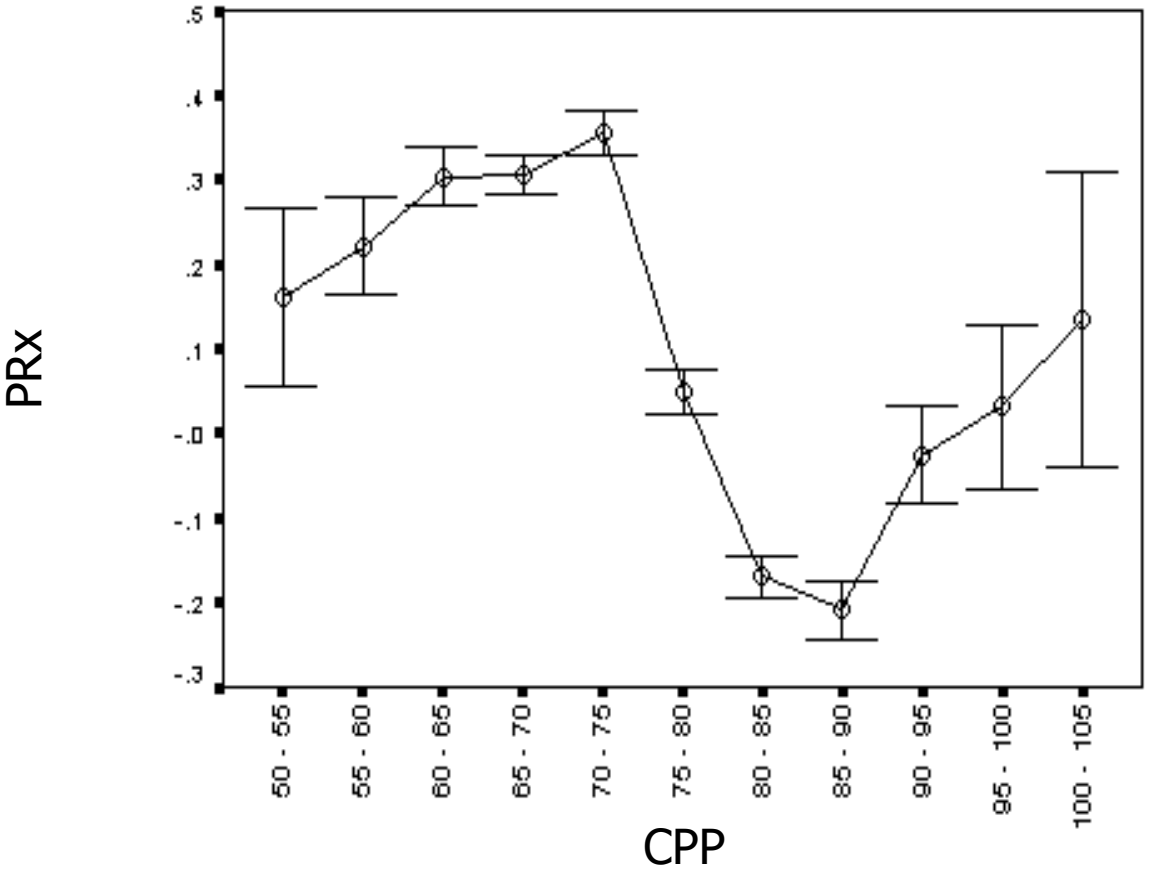
Individual Optimal CPP



Steiner LA, *et al.* Crit Care Med 2002;30:733-8

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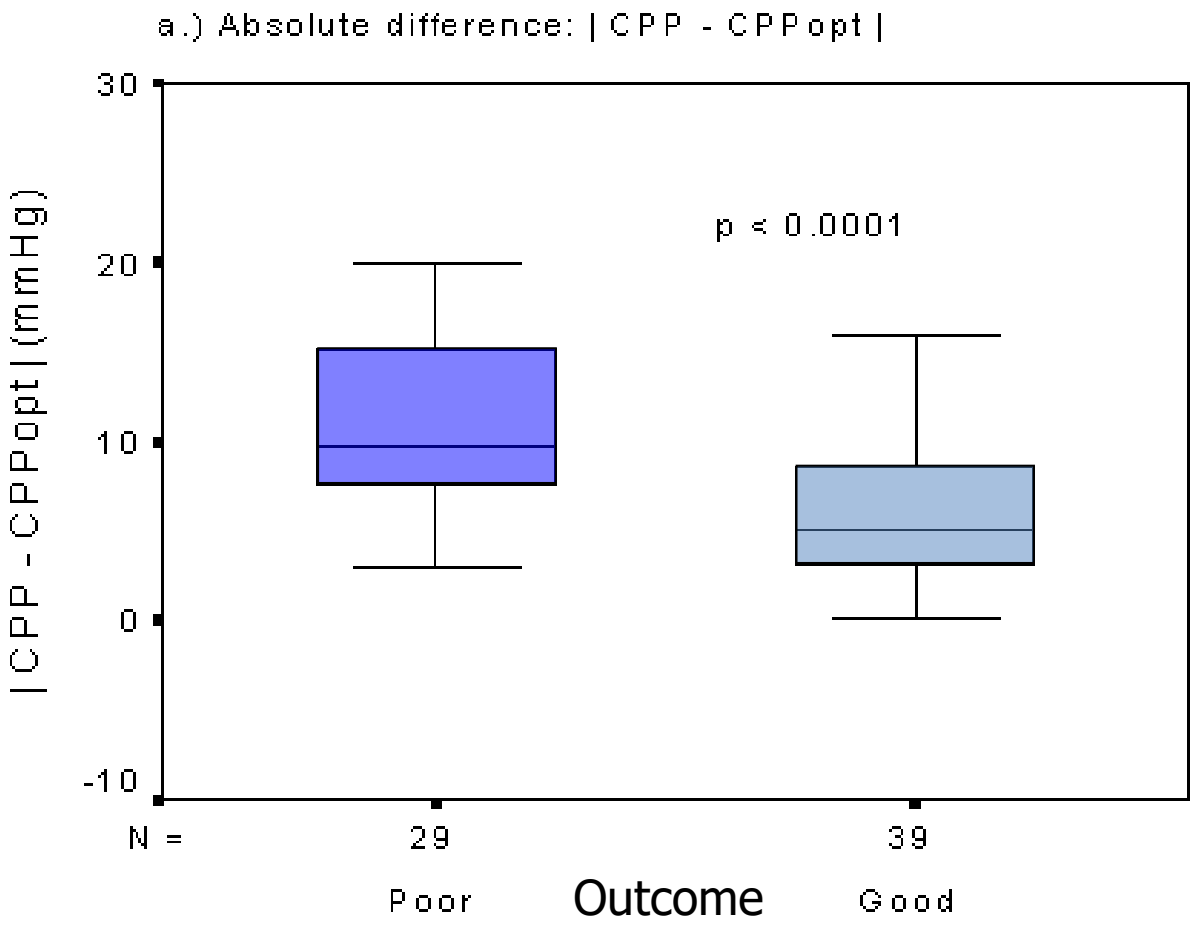
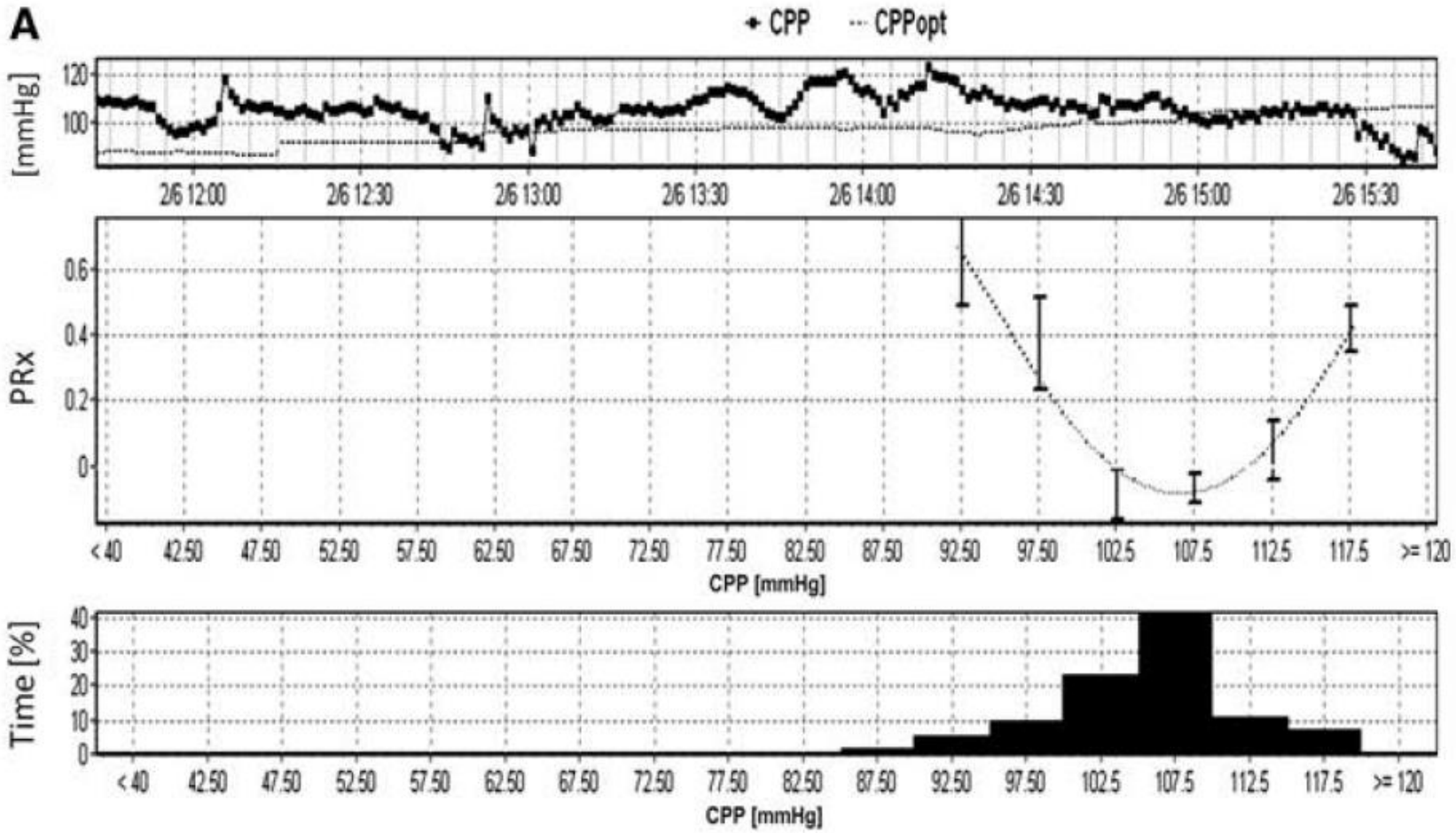
Individual Optimal CPP



Steiner LA, *et al.* Crit Care Med 2002;30:733-8



Aries MJ et al. Crit Care Med. 2012 Aug;40:2456-63

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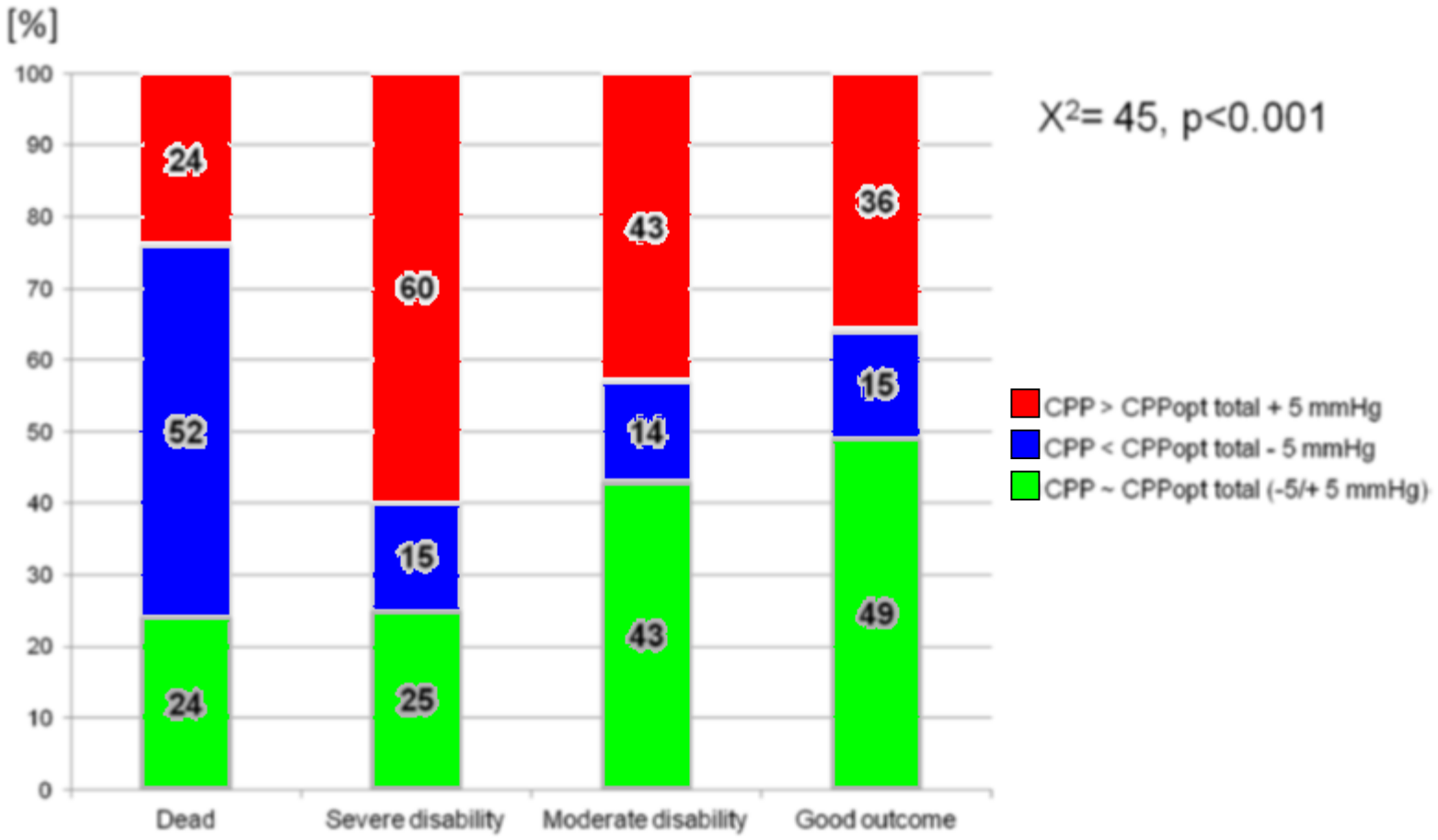
Optimal CPP



Aries MJH et al. Crit Care Med 2012;40:2456-63

Initial Conclusions

- There is retrospective evidence that an „autoregulation orientated“ approach may be beneficial in head injured patients.
- The hypothesis that CPP should be kept on the plateau of the autoregulatory curve merits further investigation.
  - We need a prospective multicentre trial!

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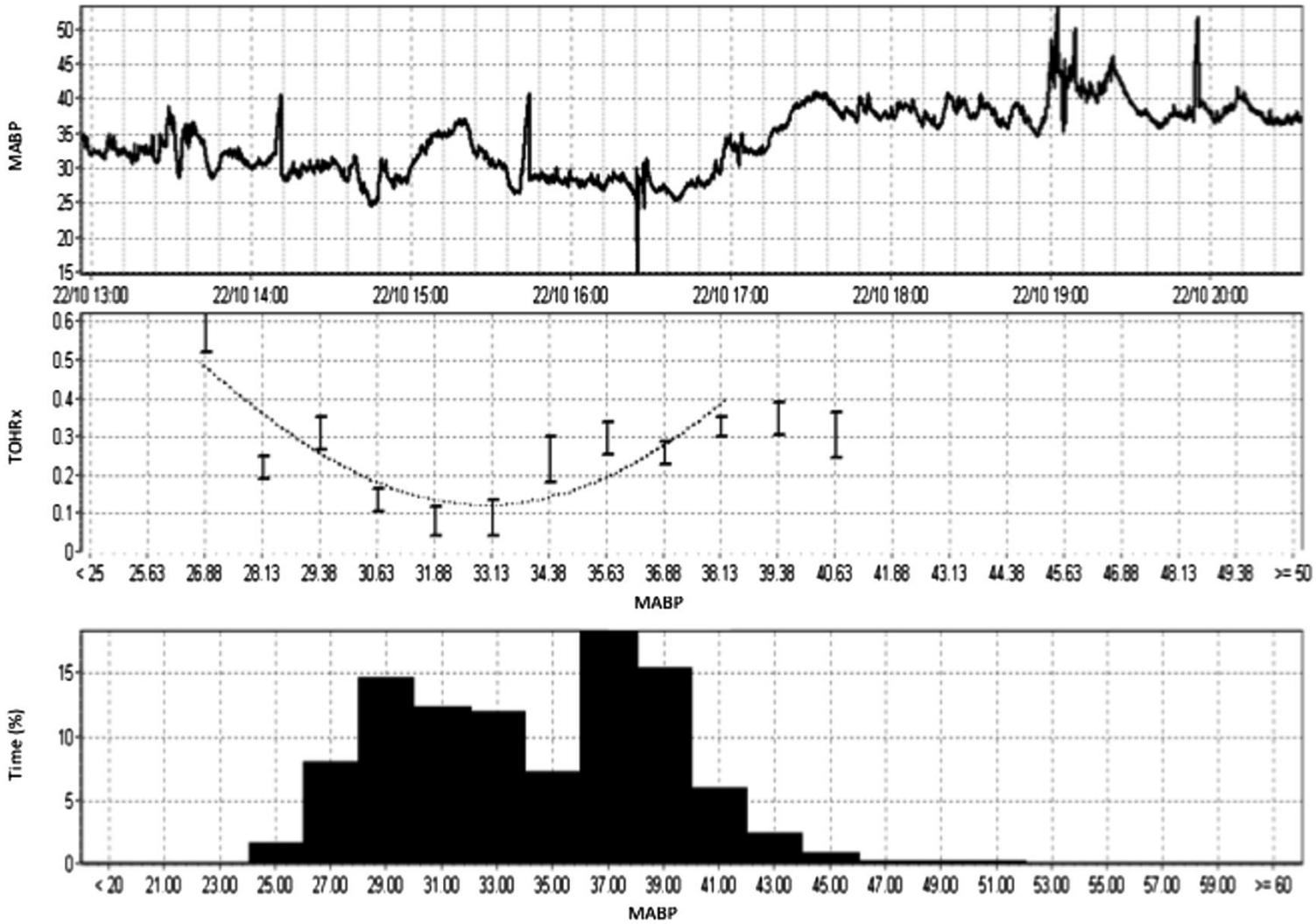
NICU? It works too!



da Costa CS et al. J Pediatr. 2015;167:86-91

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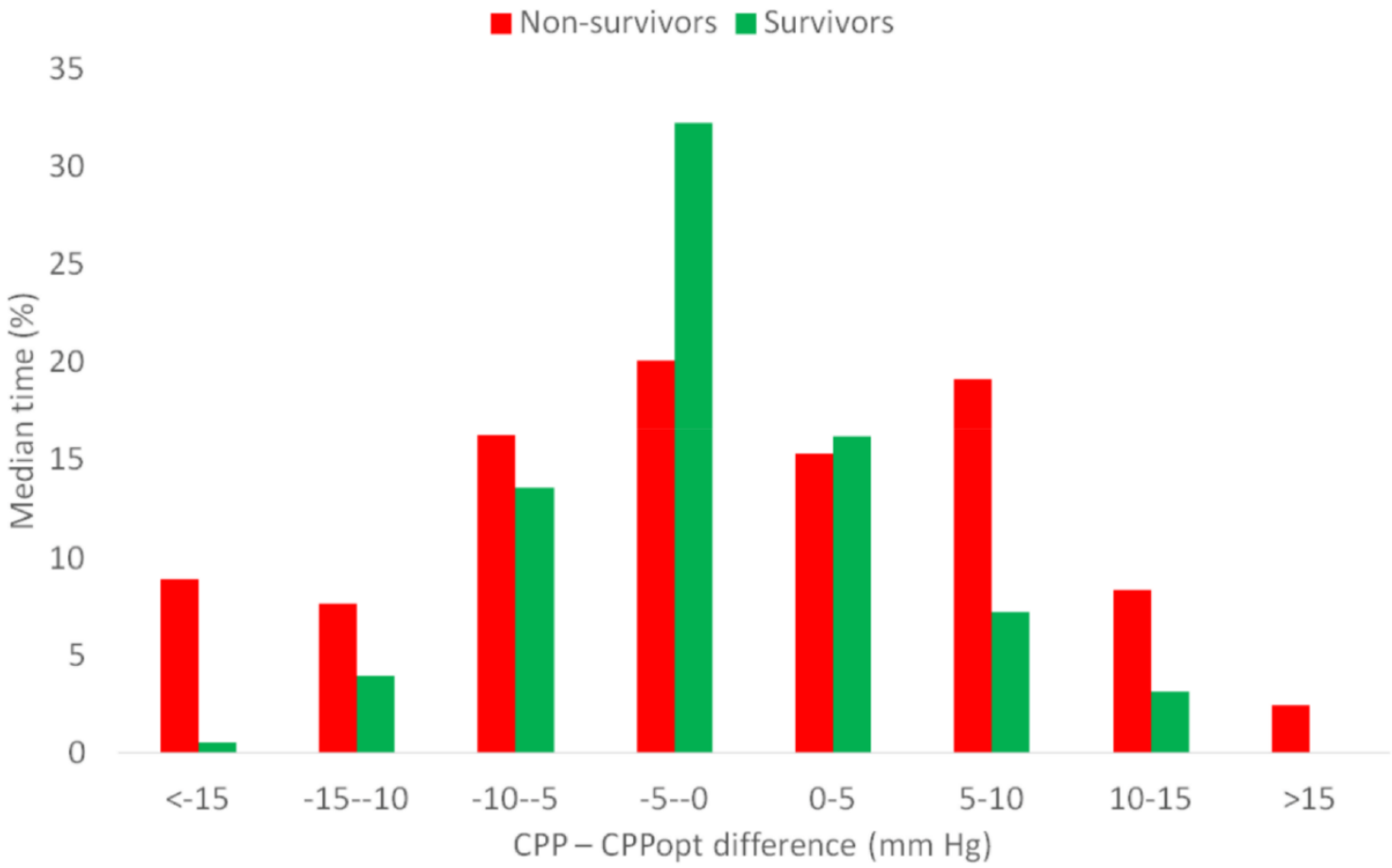
PICU? It works too!



Young AM et al. PLoS One. 2016 Mar 15;11(3):e0148817

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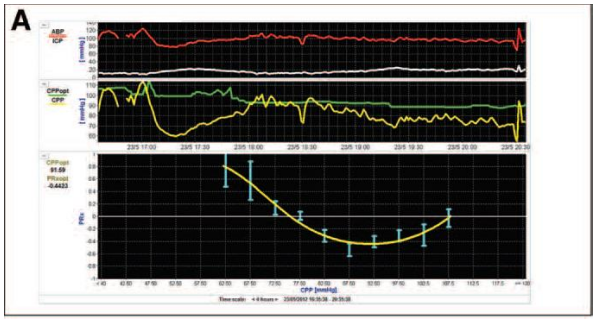
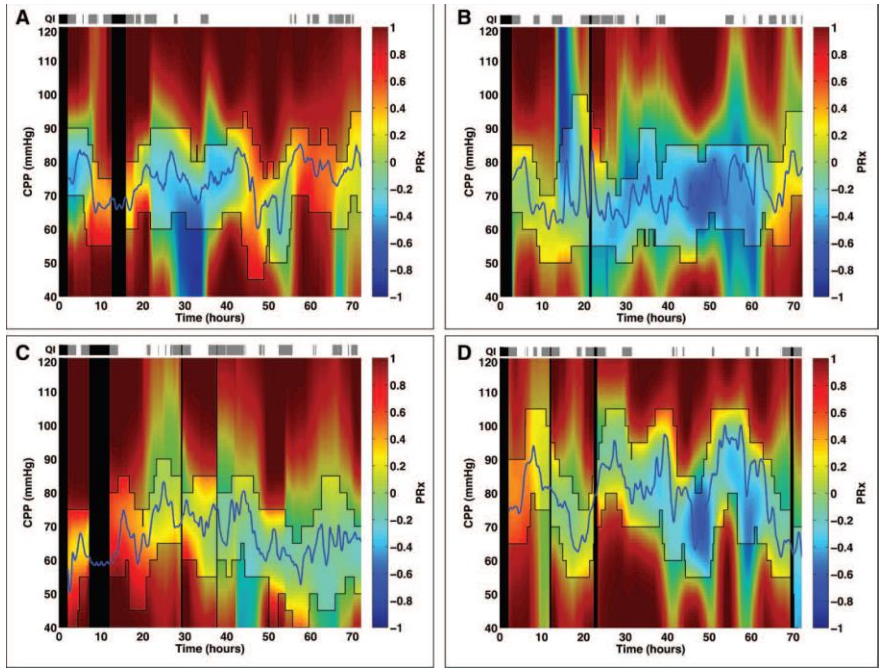
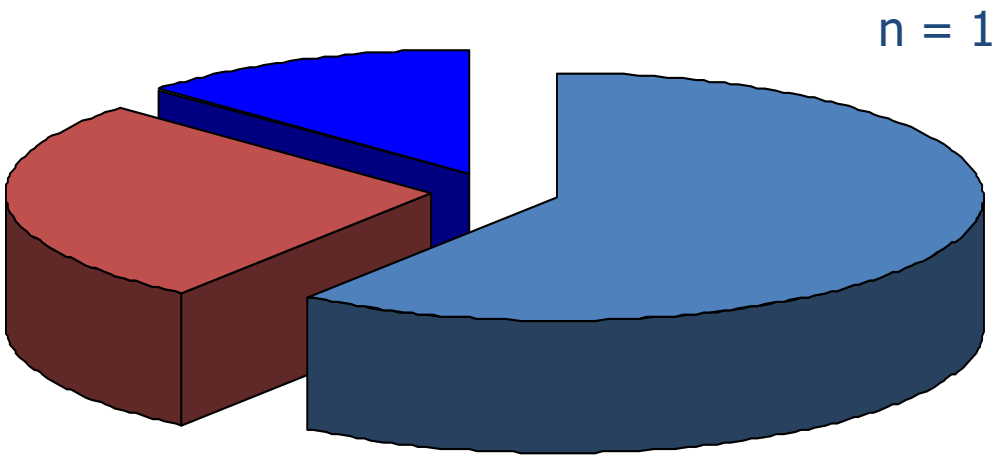
Simplify?





Aries MJ et al. Crit Care Med. 2016;44(10):e996-9

Patients without CPP_{OPT}



Steiner LA, *et al.* Crit Care Med 2002;30:733-8

"We were able to calculate CPPopt continuously during, on average, 55% of the ICP monitoring time."

Aries MJH et al. Crit Care Med 2012;40:2456-63

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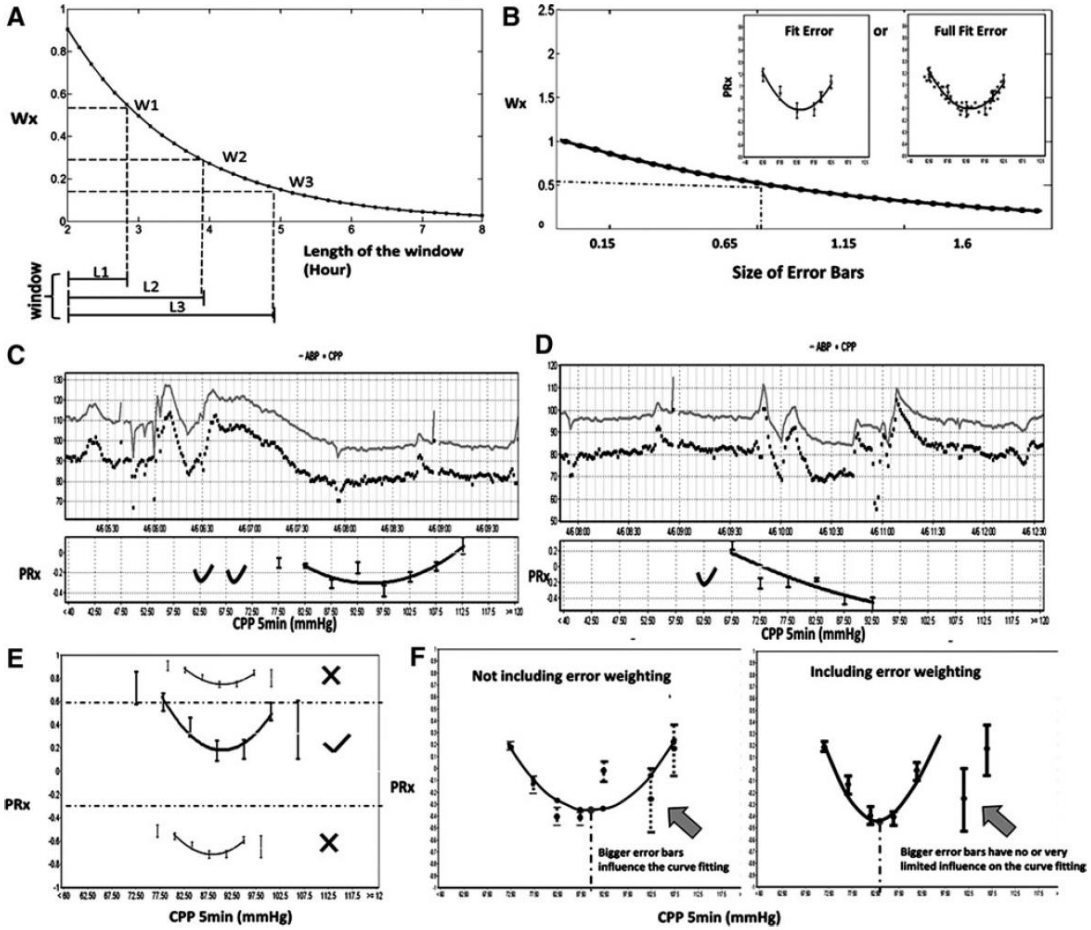
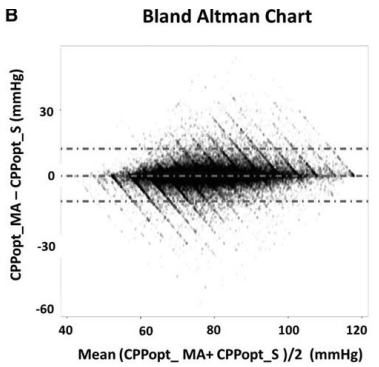
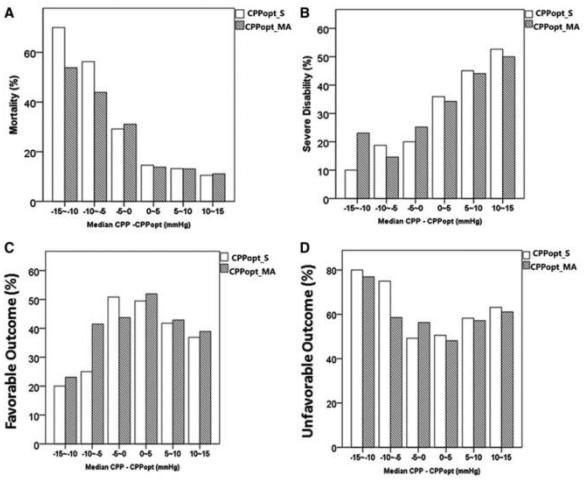
No CPP_{OPT}?







Liu X et al. J Neurotrauma 34;2017:3081–3088

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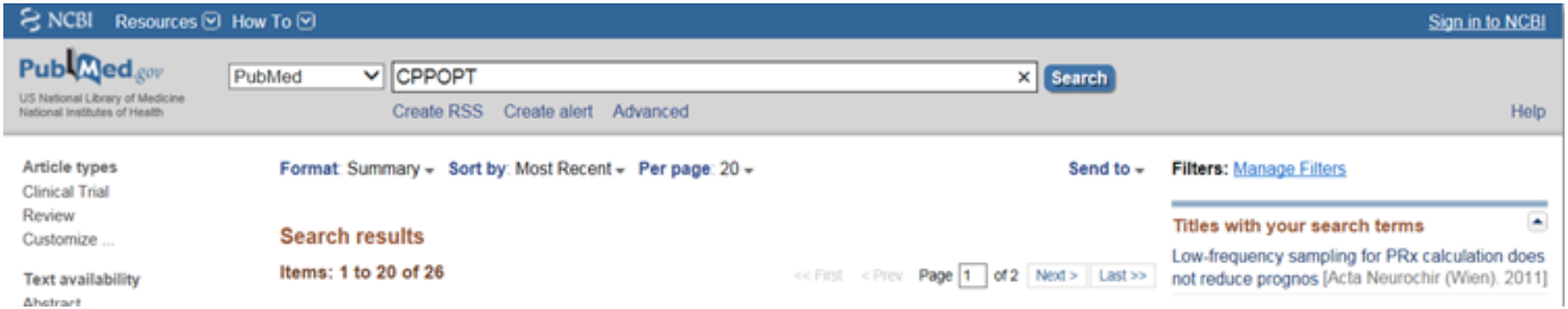
No CPP_{OPT}?

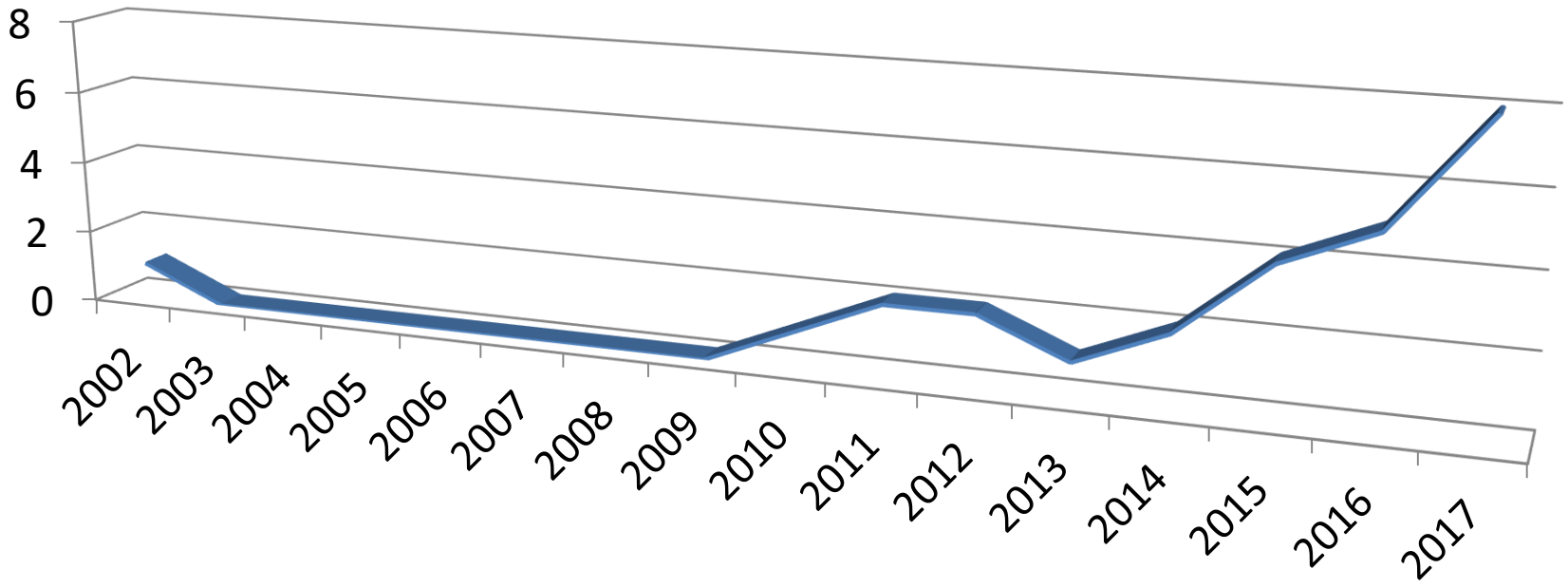
TABLE 3. THE YIELD AND STANDARD DEVIATION OF SAMPLE-TO-SAMPLE DIFFERENCES (SDD) OF OPTIMAL CEREBRAL PERFUSION PRESSURE (CPPOPT) CALCULATED USING THE SINGLE-WINDOW APPROACH (CPPOPT_S OR CPPOPT_SYE) AND USING THE MULTI-WINDOW ALGORITHM (CPPOPT_MA, CPPOPT_MAYE, CPPOPT_MW OR CPPOPT_MWYE)

Statistics	CPPopt_S	CPPopt_SYE	CPPopt_MA	CPPopt_MAYE	CPPopt_MW	CPPopt_MWYE
Yield (Mean ± SE)	50.5% ± 0.94%	46.1% ± 0.95%	94.2% ± 2.11%	92.3% ± 2.09%	94.2% ± 2.13%	92.3% ± 2.08%
SDD (Mean ± SE)	0.83 ± 0.015	0.74 ± 0.014	0.58 ± 0.015	0.61 ± 0.016	0.69 ± 0.016	0.72 ± 0.019

Liu X et al. J Neurotrauma 34;2017:3081–3088



Number of Publications



So why have we not started a multicenter randomized trial yet?

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Why?

- Why do some ideas spread faster than others
- Is 16 years a long time?

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ANNALS OF MEDICINE JULY 29, 2013 ISSUE

SLOW IDEAS

Some innovations spread fast. How do you speed the ones that don't?

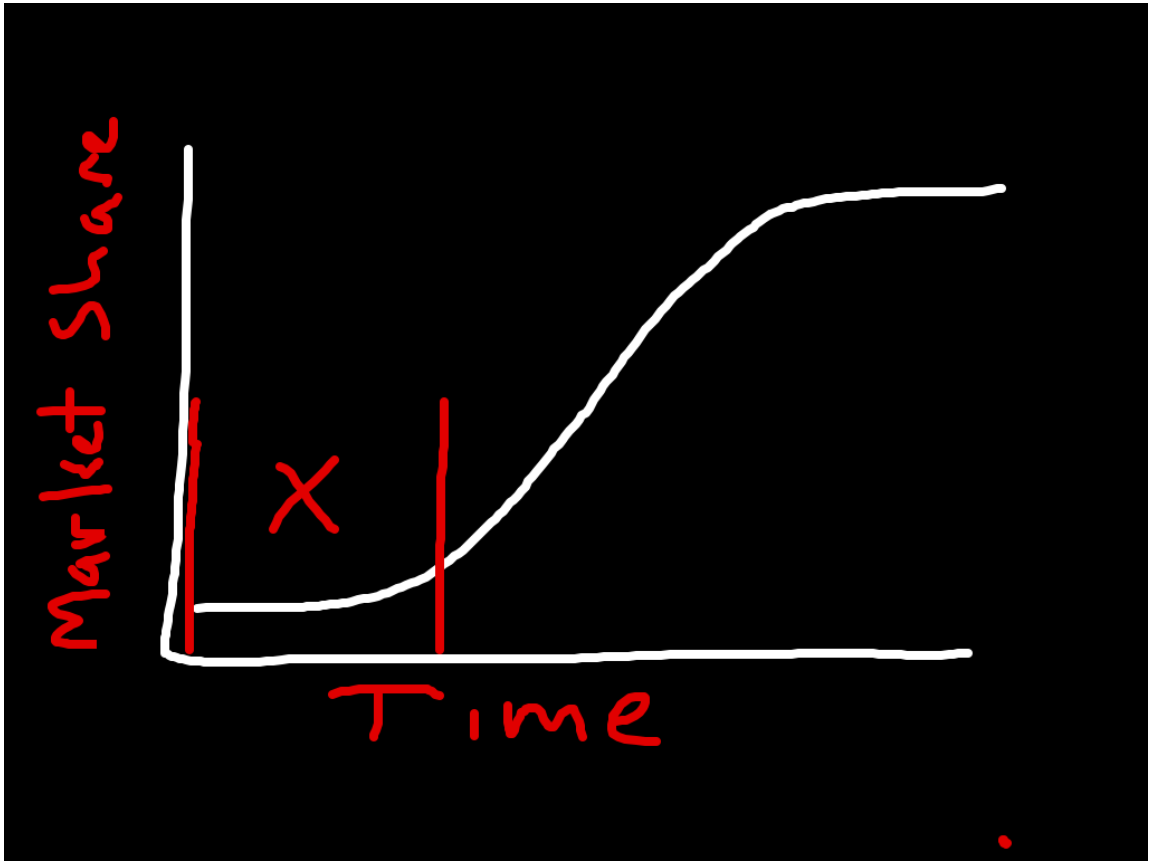
By Atul Gawande

On October 16, 1846, at Massachusetts General Hospital, Morton administered his gas through an inhaler in the mouth of a young man undergoing the excision of a tumor in his jaw. By mid-December, surgeons were administering ether to patients in Paris and London. By February, anesthesia had been used in almost all the capitals of Europe, and by June in most regions of the world.

Strikingly lower rates of sepsis and death by using carbolic acid for cleansing hands and wounds were published in a groundbreaking series of reports in The Lancet, in 1867, this antiseptic method should have spread as rapidly as anesthesia. Two decades later, hand washing was still perfunctory. Surgeons soaked their instruments in carbolic acid, but they continued to operate in black frock coats stiffened with the blood and viscera of previous operations

https://www.newyorker.com/magazine/2013/07/29/slow-ideas

The Long S-Curve of Innovation Diffusion



http://timkastelle.org/blog/2011/04/innovation-myth-ideas-spread-quickly/

The Myth of Quick Adoption

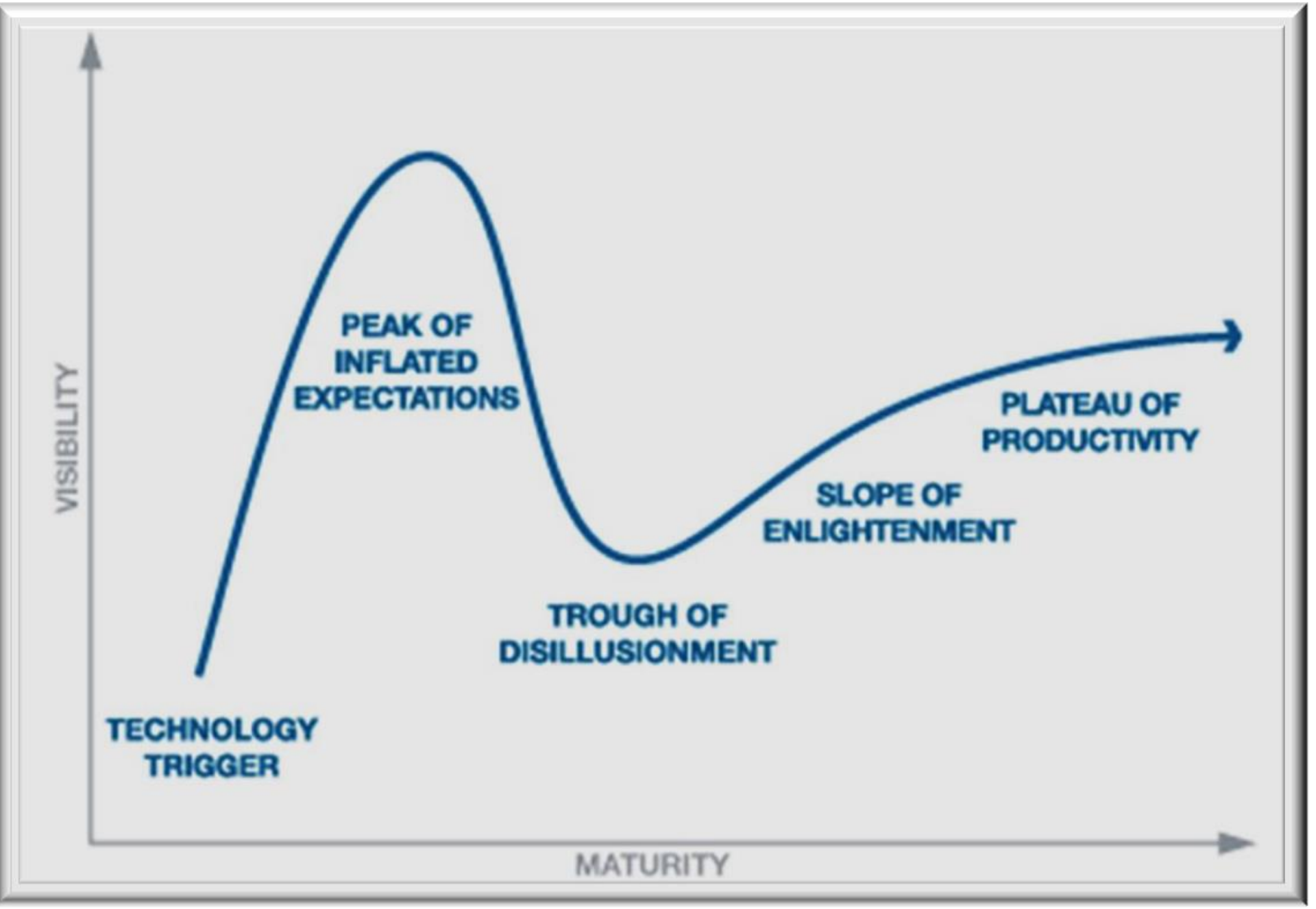
- Our tendency to dramatically underestimate the true value of X in innovation diffusion causes all kinds of problems. If we're early adopters, we expect new ideas to spread quickly. And yet, they don't. If we're threatened by new ideas, the long X can give us a false sense of security. As it becomes clear that early predictions are exaggerated, we become complacent. But eventually, once all the experimentation has been done, and people have figured out what the new ideas are really good for, and how to create value with them, the threat begins to bite.
- I'm not sure of any way to move through the innovation diffusion curve more quickly. It is by its very nature slow, experimental, unpredictable, exciting, revolutionary and wasteful. It is part of what makes innovation both exhilarating but also frustrating.
- Being aware of the myth of quick adoption is the first step towards figuring out how to deal with it.

http://timkastelle.org/blog/2011/04/innovation-myth-ideas-spread-quickly/

The Myth of Quick Adoption

- The reasons for the long X: Mainly uncertainty
- We have to figure out how to make the new idea work: the best use of a new idea is often not obvious. In fact, because we tend to think in analogies, we often get this wrong at the start
- We have to fight against the hype cycle: the long X is a direct contributor to the hype cycle. The Early Adopters get excited about the new idea, and it gets oversold. Then the people that are threatened by the new idea fight back. When it doesn't spread as quickly as expected, the excitement wanes and cynicism sets in. Eventually, though, through experimentation we figure out what the best use of the new idea will be, and at that point it is finally poised to take off.
- Most importantly, we have to figure out how to create value for people or patients with the new idea. This is the part that the Early Adopters tend to ignore – they usually like new things simply because they're new. For everyone, the new idea needs to solve a problem.

http://timkastelle.org/blog/2011/04/innovation-myth-ideas-spread-quickly/



http://avc.com/2014/09/the-bitcoin-hype-cycle/

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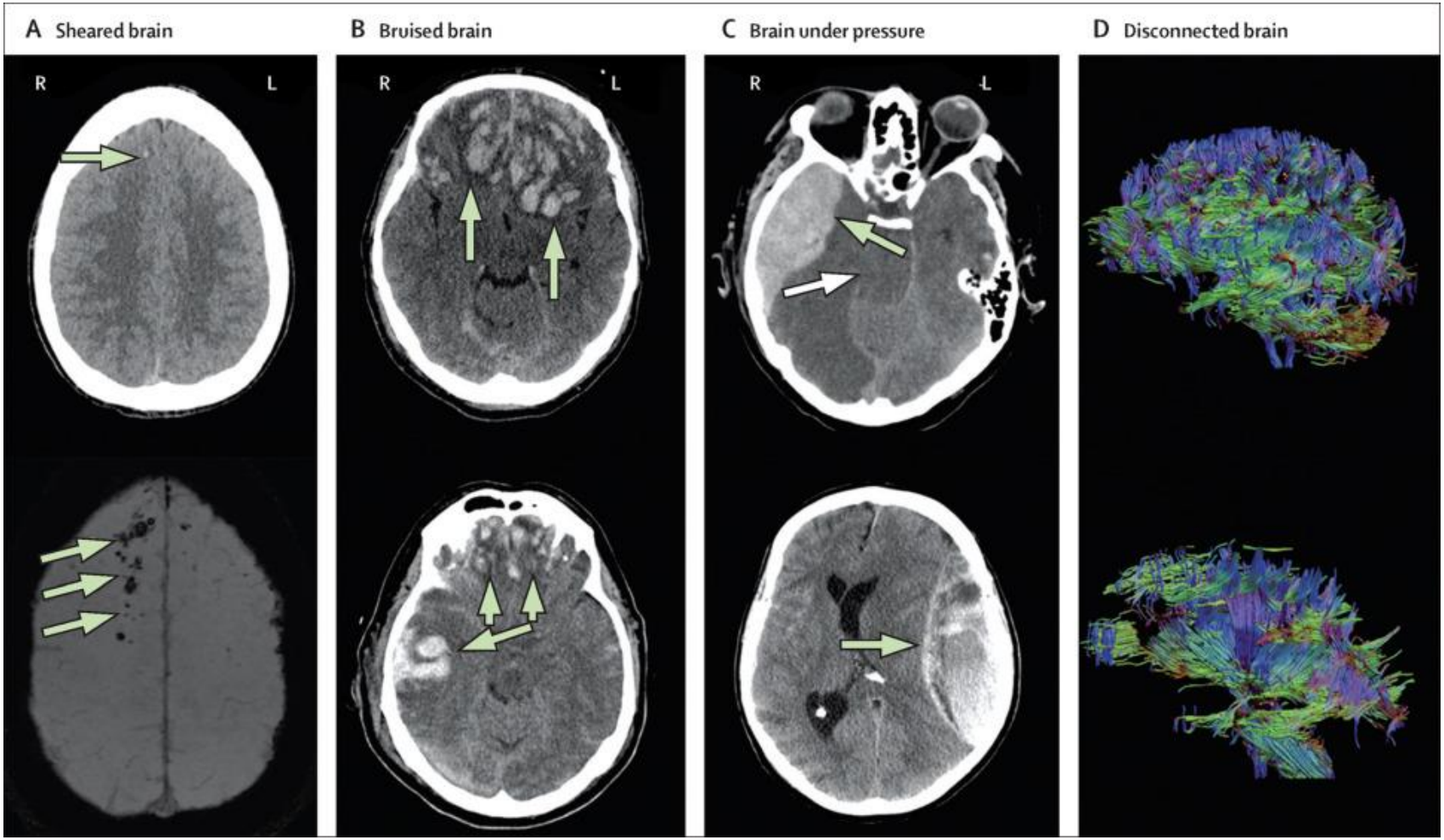
Neurocritcal Care Reality



Maas AIR, Menon DK, …, Czosnyka M, … et al. Lancet Neurol. 2017 Nov 6. [Epub ahead of print]

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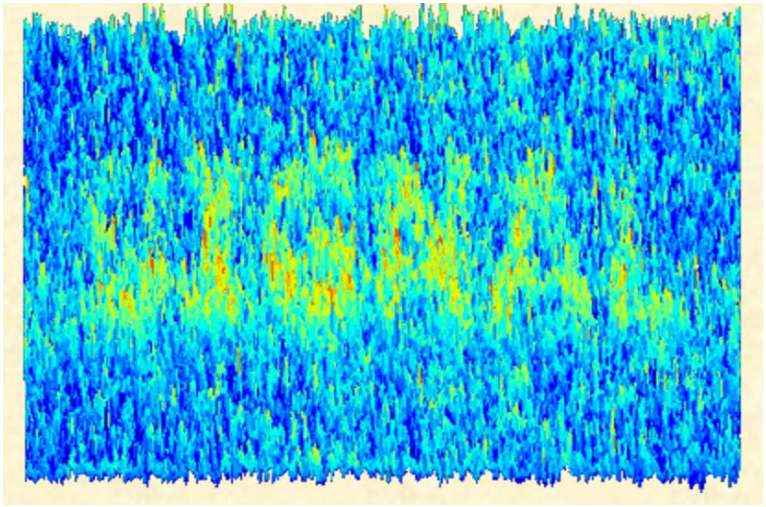
Neurocritical Care Reality



Sedation

Glycaemic Control

$PaCO_2$

CPP

ICP

Sepsis

Temperature

Trial Design

- What should the primary outcome be?
- Which intervention?
- How much effect do we expect from our intervention?
- Patient selection?
- Which units should participate?
- Ethics?

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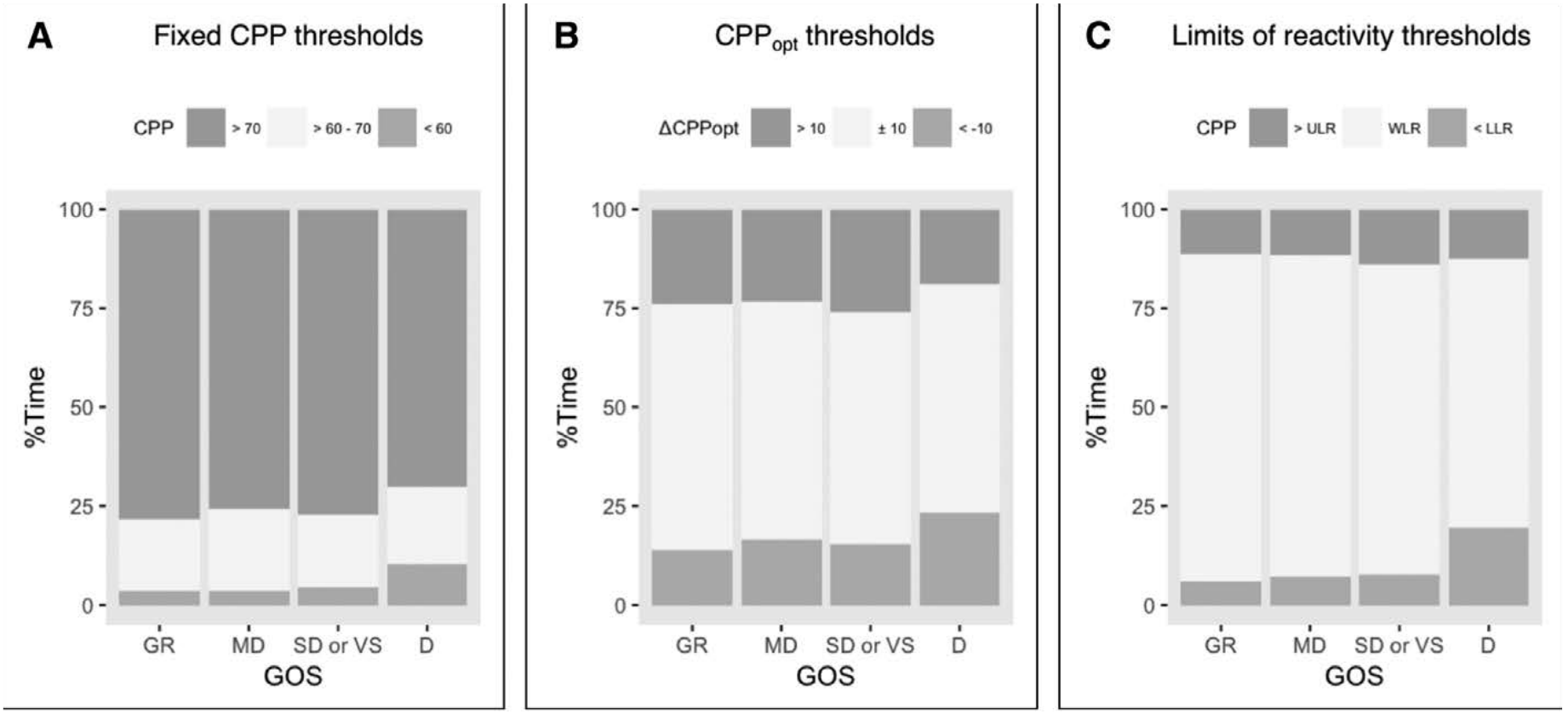
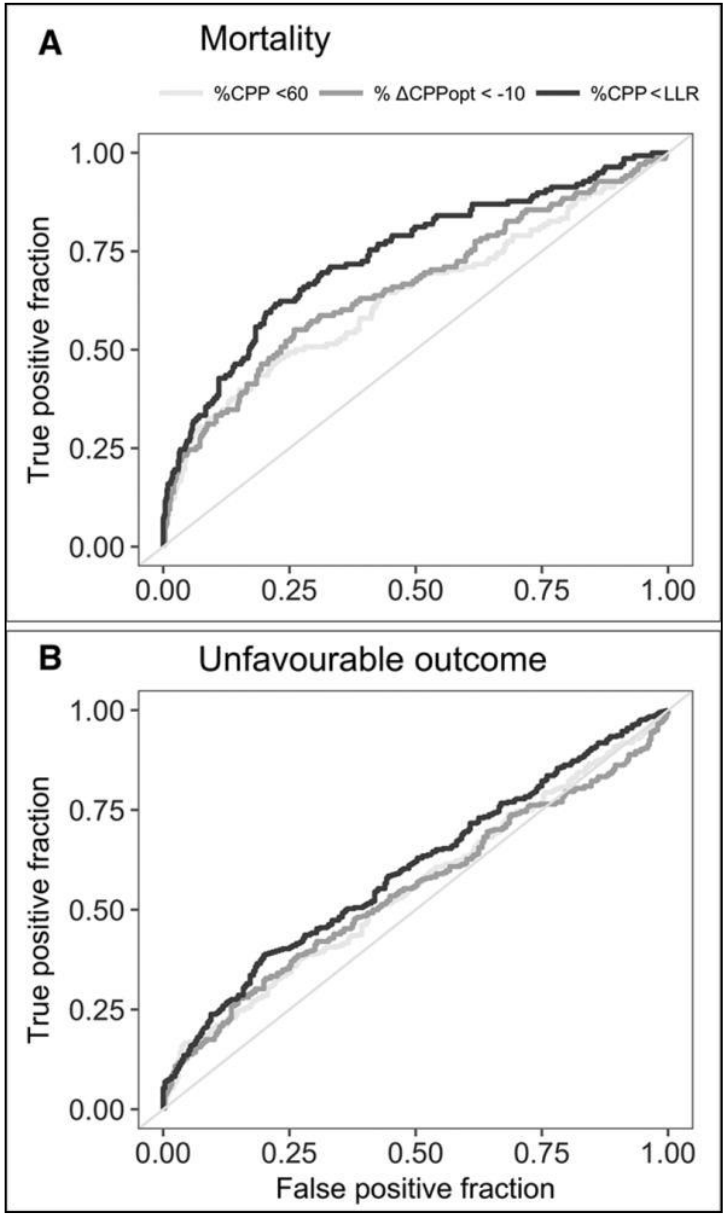
CPP_{OPT} or «Within Limits»



Donnelly J et al. Crit Care Med. 2017;45:1464-1471



Individualizing Thresholds of Cerebral Perfusion Pressure Using Estimated Limits of Autoregulation.
Donnelly, Joseph; Czosnyka, Marek; Adams, Hadie; Robba, Chiara; Steiner, Luzius; PhD, MD; Cardim, Danilo; Cabella, Brenno; Liu, Xiuyun; Ercole, Ari; PhD, FFICM; Hutchinson, Peter; John FRCS SN, PhD; Menon, David; Krishna MD, PhD; Aries, Marcel; MD, PhD; Smielewski, Peter

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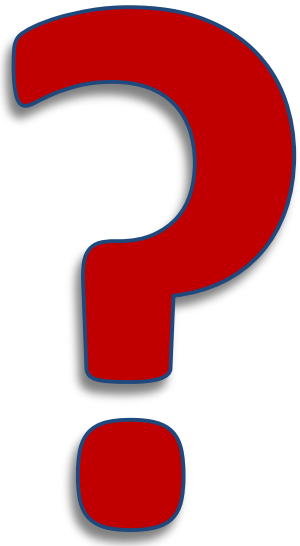
10.1097/CCM.0000000000002575

Figure 3 . Comparison of receiver operator characteristic curves for predicting mortality (A) and unfavorable outcome (B). Percentage of time with cerebral perfusion pressure (CPP) below the lower limit of reactivity (LLR) (%CPP < LLR) was the strongest predictor of mortality and unfavorable outcome. [DELTA]CPPopt = CPP - CPPopt.

Donnelly J et al. Crit Care Med. 2017;45:1464-1471



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