

15 YEARS OF CPPOPT

(FROM 'ART' TO 'TARGET')

Cambridge seminar

January 2017

Marcel Aries

CONTENT

45 MIN HISTORY

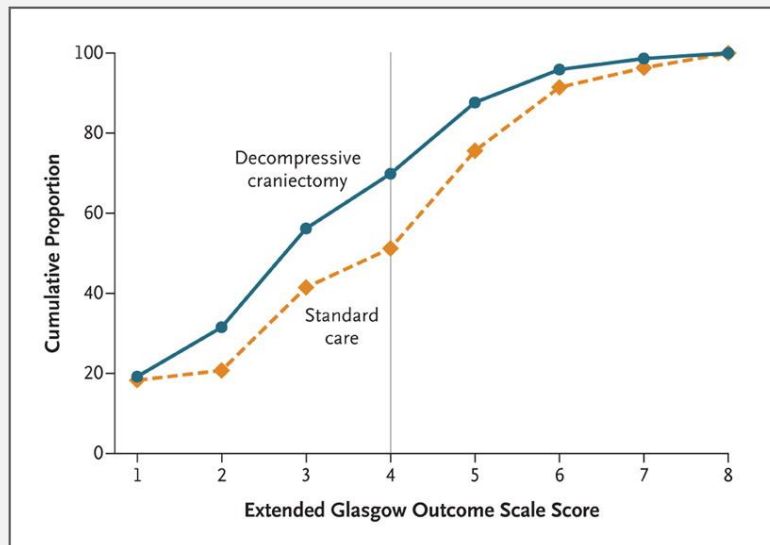
- Traumatic Brain Injury
- CPPopt studies
 - Adults
 - Main results
 - Some comments

15 MIN (NEAR) FUTURE

- Intervention study
- Recent (hard) work for that

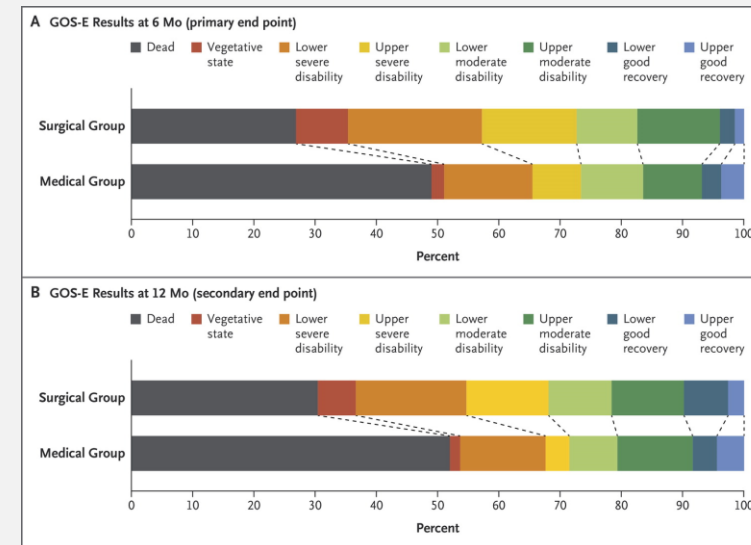
2002-2017: TBI

2002



Start DECRA

END 2016



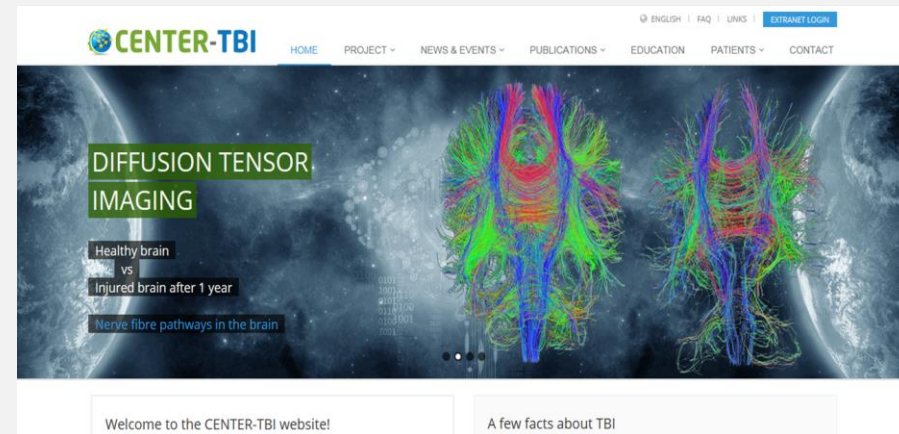
Results of RESCUE ICP

RETHINKING IDEAS

2002-2017

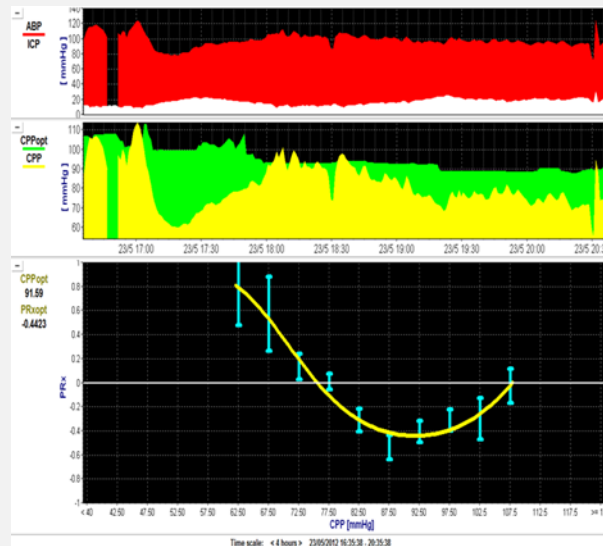


CENTER TBI



INDIVIDUALISED TREATMENT

OPTIMAL CPP



2002-2017

- ‘Preparation phase’
- ‘Magic bullet’/ ‘Holy grail’ ?
- Small and careful steps
 - ICP monitoring
 - Feasibility and safety study
- Offline → online analysis → recommendation
- Software challenge

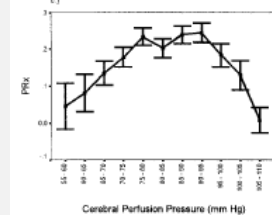
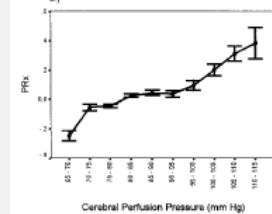
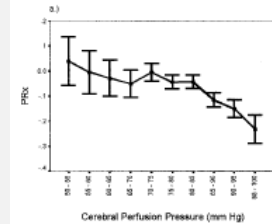
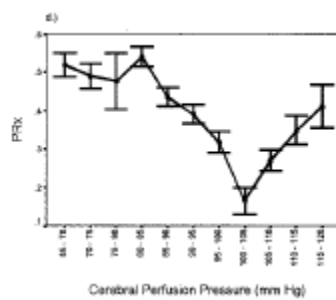
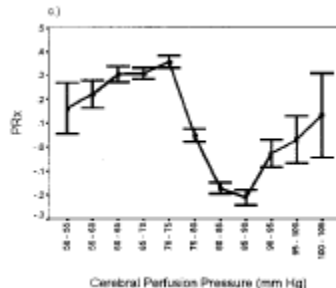
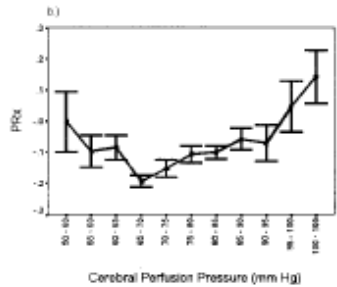
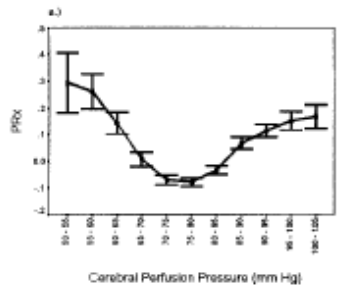
HISTORY



2002: marriage of.....

STEINER ET AL. (2002)

PRx for CPPopt determination



- PRx-CPP plot whole recordings
- 60% U shape
- < and > CPPopt related to poor outcome
- Visual determination

2006-2008

CONFIRMATION OF CPPOPT AND RELATION WITH OUTCOME

- Balestreri et al. NCC 2006
- Jaeger et al. CCM 2006
- Zweifel et al. Neurosurg focus 2008

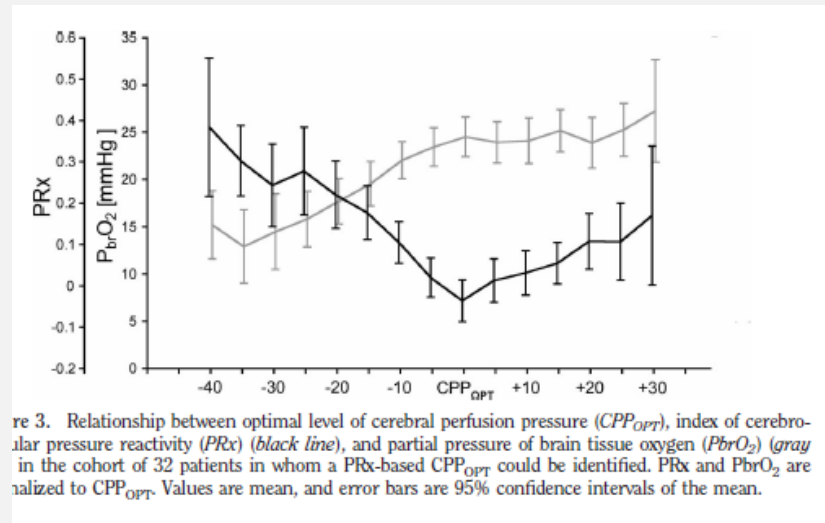
COMMENTS

- Focus on PRx
 - Decompression
 - Therapeutic hypothermia
- Relationship with outcome
 - $CPP > CPP_{opt}$ AND $CPP < CPP_{opt}$
- 'Proof of concept'
 - Correlation PRx - ORx
 - Correlation PRx - PBtio2

JAEGER ET AL. 2010

CPPOPT AND BREAKPOINT OF PBTiO2

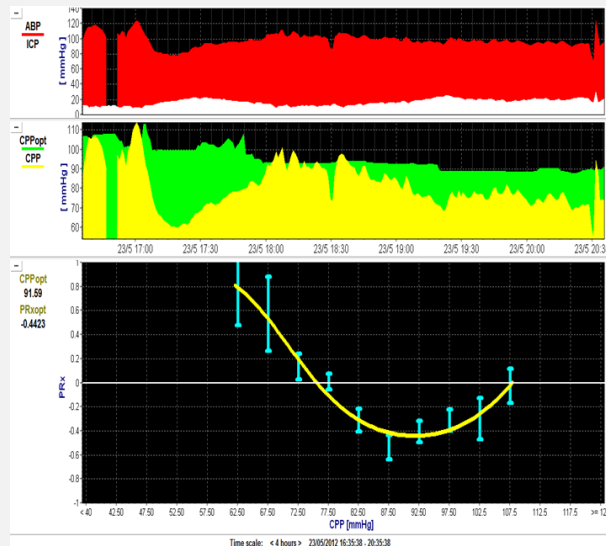
COMMENTS



- 'Proof of concept'
- N=38
- Whole recording
- PBTiO2 not targeted?
- Park et al. 2016
- Difficult 'proof of concept'
 - Difficult to measure
 - Local
 - Many contributing factors

ARIES ET AL. (2012)

AUTOMATED CALCULATION OF CPPOPT



COMMENTS

- Automated
- Relationship with outcome
 - No correction for covariates
- 60% of monitoring time a value
- Only 70% (somehow) U-shaped
- High CPPopt values (80)
- Autoregulation status

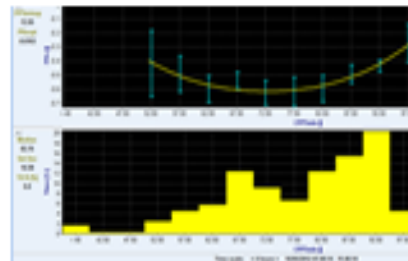
WEERSINK ET AL. (2014)

REASONS FOR CPPOPT ABSENCE

Main conclusions

1. Results show an association between absence of CPPopt and the following physiological and clinical variables:

- * absence of ABP slow waves
- * impaired autoregulation
- * status after decompressive craniectomy
- * not applying muscle paralytics
- * light or moderate sedation
- * high vasopressor use

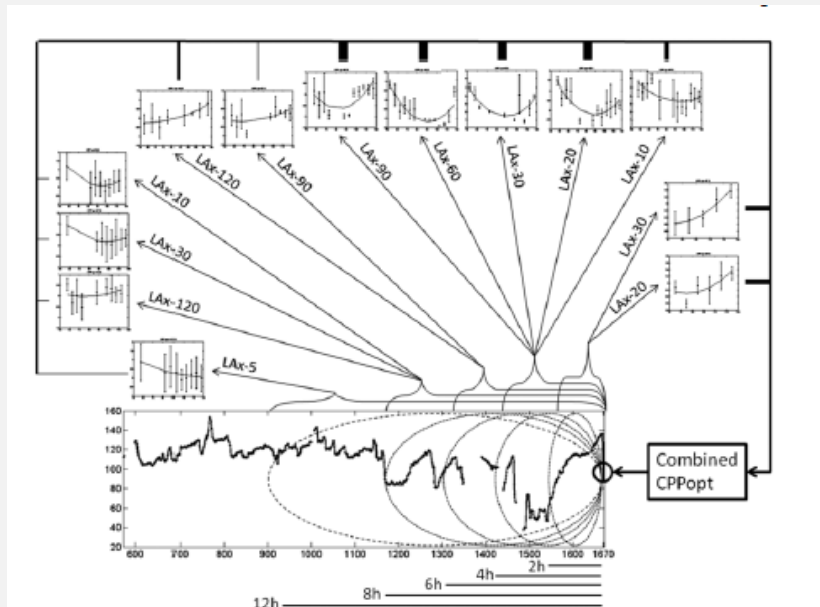


COMMENTS

- Absence CPPopt?
- Did we incorporate results into CPPopt calculation?
 - ‘PRx range to exclude curve’
 - ‘Multi-window approach’ (confounders)
- Exclude sec decompression patients
- (Threshold for power of slow ABP waves)
- (Confounders)
 - PP Ventilation
 - CVP
 - CO₂

DEPREITERE ET AL. (2013 + 2014)

CPPOPT CALCULATION IN LEUVEN



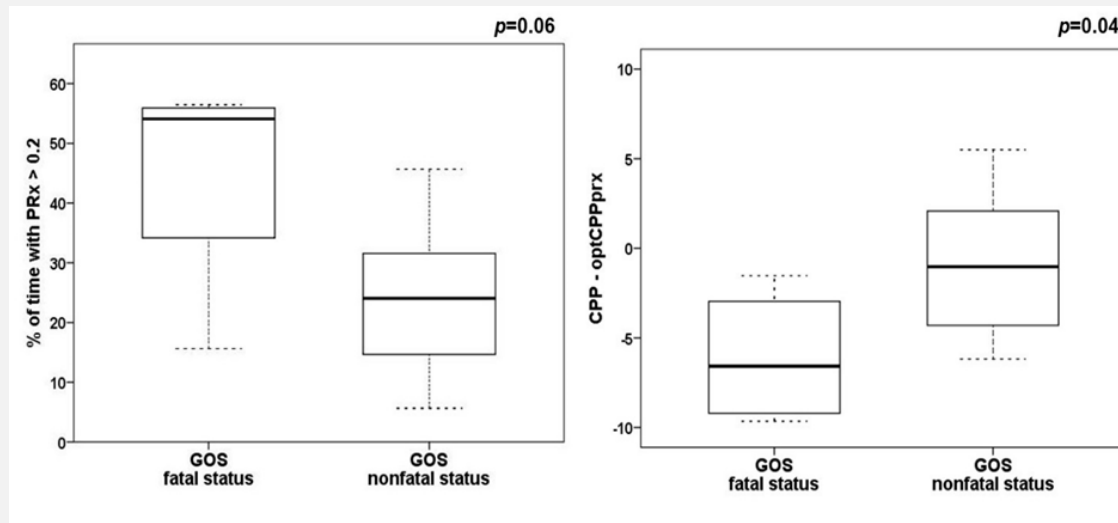
COMMENTS

- N=180
- CPPopt 95% of monitoring time
- LAX
- Averaged CPPopt
 - 1-24 hrs
 - Weighted (fit/low LAX)
- Independent relationship with outcome
 - CRASH covariates

DIAS ET AL. (2015)

CPPOPT GUIDED MANAGEMENT AT THE BEDSIDE

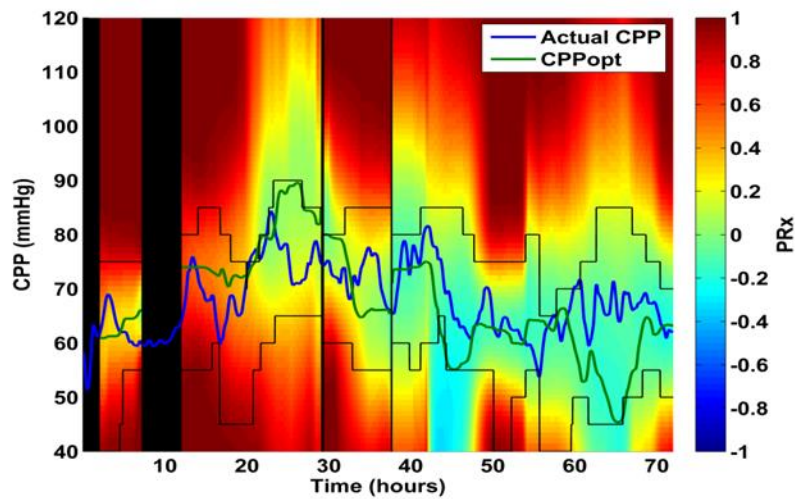
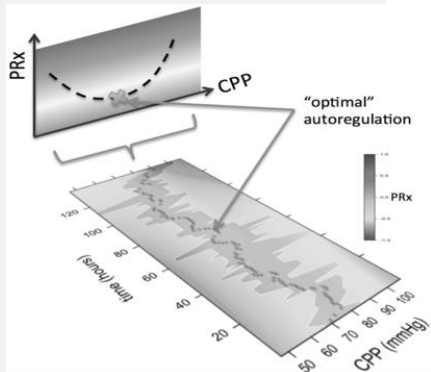
COMMENTS



- N=18
- CPPopt guided patients!
- CPPopt 59% of time available
- CPP 86 mmHg
- Hypoperfusion?

WESSELINK ET AL. (2016)

VISUALISATION OF CPPOPT



COMMENTS

- Difficult to repeat in different TBI pts
- (time) patterns?
 - How often interventions?
- Needs further exploration
 - With what kind of question?
- Preliminary version ICM+

UNFINISHED STUDIES (I)

RETROSPECTIVE MULTICENTER CPPOPT STUDY[†]

- Multivariate day-by-day analysis of CPPopt after TBI
- The CPPopt Multicenter Study Group (n=10)
- **Conclusion:** These retrospective multicenter data show that there is heterogeneity between centers when the association between PRx and derived CPPopt and outcome is considered. However, deviation of CPPopt was significantly correlated with poor outcome in the whole cohort after correction for known prognostic variables.

COMMENTS

- Different interpretations of TBI protocols
- CPPopt 60% of time
- Independent relationship with outcome
- CPPopt follows CPP (!)
- Intervention study
 - 3 centres
 - Zeroing ICP/CPP

[†] Boston abstract ICP 2016

UNFINISHED STUDIES (2)

CPPOPT IN SCANDINAVIA ²

- CPPopt calculation in Groningen, Cambridge and Uppsala
- Effects of different TBI treatment protocols on CPPopt calculation numbers

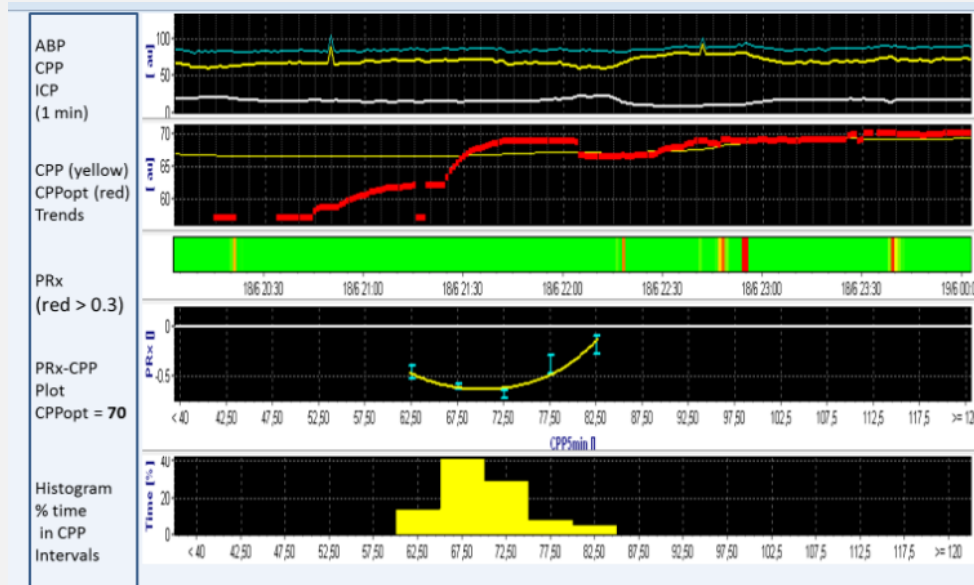
COMMENTS

- CPPopt calculation in ODIN software
- CPP = same..... (80)
- Results to come
- Intervention study
 - Medical ethical

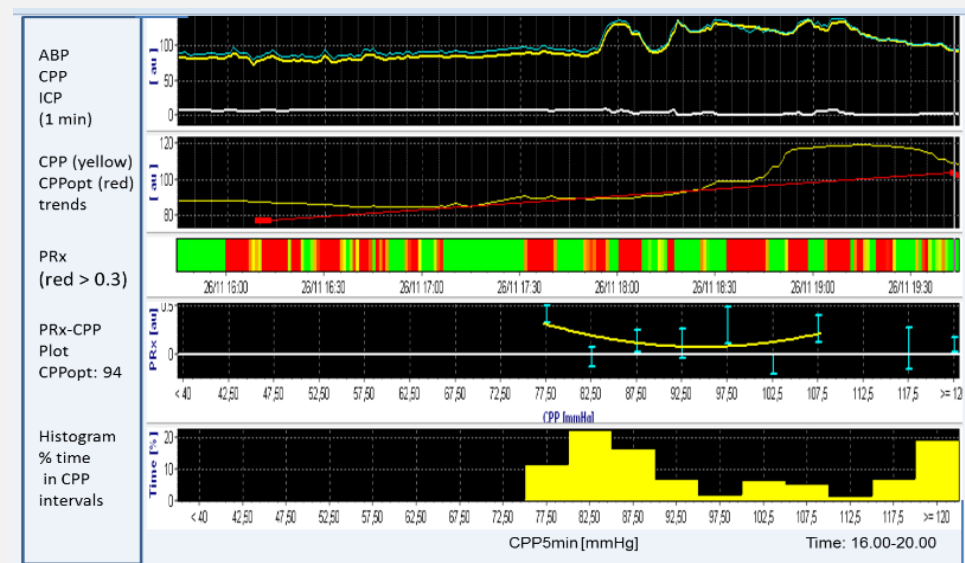
²Work in progress

DIFFICULT TO PUBLISH STUDY

FACE VALIDITY OF CPPOPT



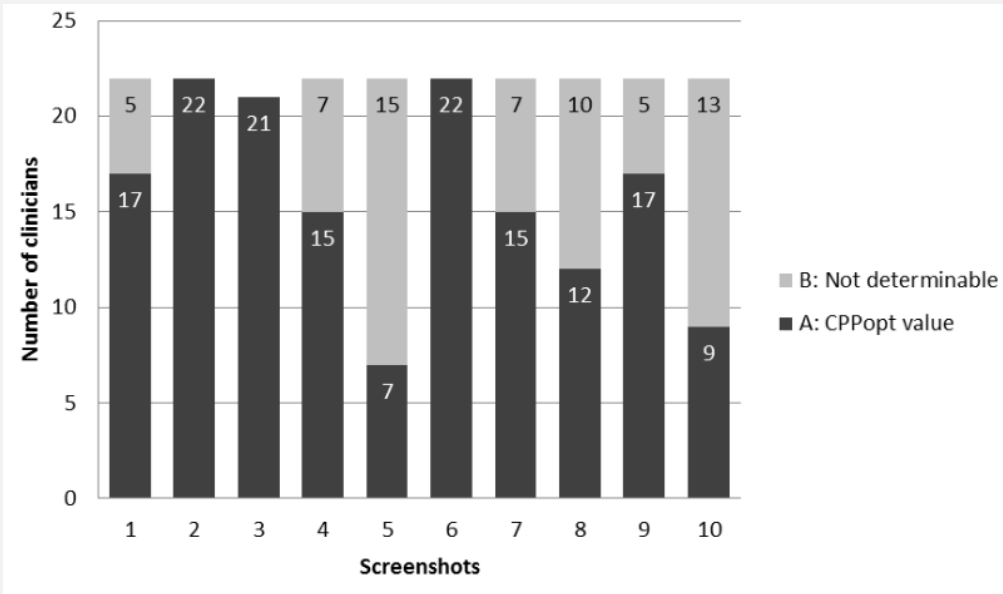
FACE VALIDITY OF CPPOPT



Thanks to Romy

DIFFICULT TO PUBLISH

FACE VALIDITY OF CPPOPT

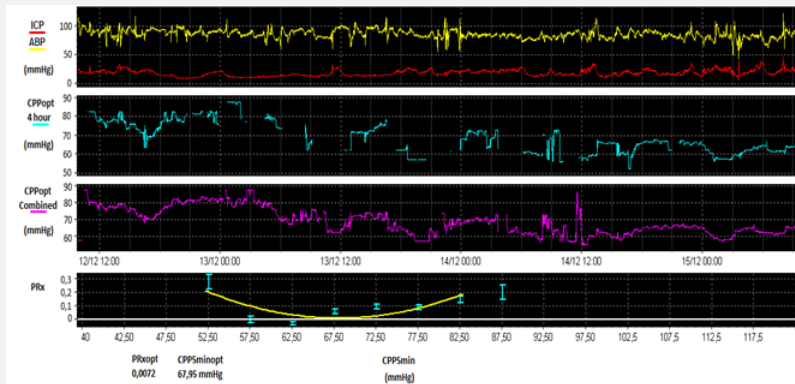


COMMENTS

- N= 25 reviewers
- 3 screenshots 'CPPopt' not determinable
- Intervention study
 - 'Reliability/stability' score: too difficult
 - Averaging/smoothing
 - Display PRx-CPP curve

X. LIU ET AL. (IN PRESS)

FINDINGS



Function options

Function: **OptimalValueflex**

Missing Data Limit [%]	50
Number of bins	16
Minimum bin value	40
Maximum bin value	120
Minimum bin data count [%]	2
Minimum included data [%]	50.00
Minimum Y span	0.2
Concave	<input type="checkbox"/>
Need not include 'best'	<input type="checkbox"/>
Use error weighting	<input checked="" type="checkbox"/>
Enforce Y range	<input checked="" type="checkbox"/>
Enforce Y region - Min	-0.3
Enforce Y region - Max	0.6
Output value type	Optimal X
Min Calc Period	7200
Step	500
Multwindow Treatment	Weighted Average
Window Weight Exp	0.5
Fit Error Weight Exp	1
Use full fit error	<input type="checkbox"/>
Non-parabolic window weight	0.1

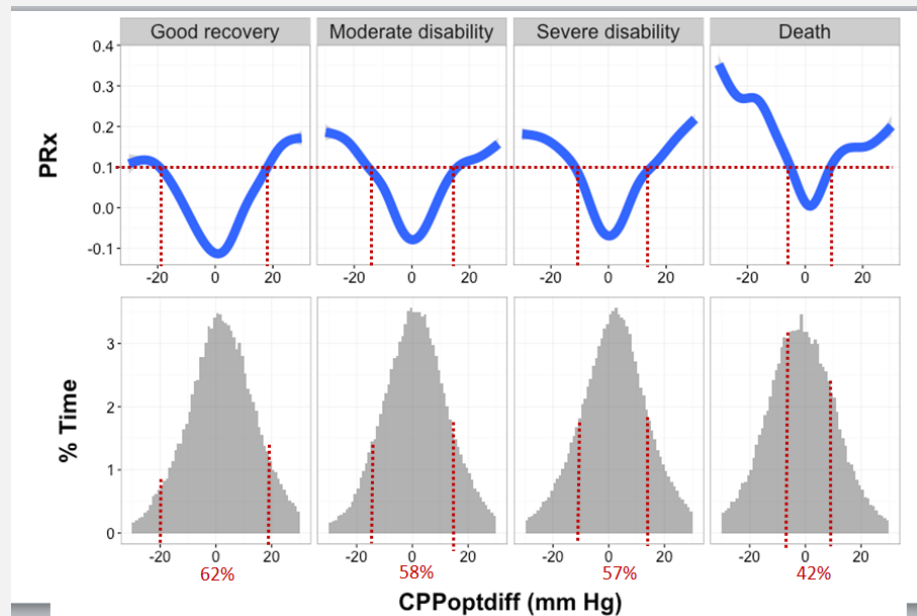
OK Cancel

COMMENTS

- CPPopt yield \approx 100%
- Multiwindow (2-8 hrs)
- Weighting
- Improved variability
- Relationship with outcome
- Intervention study
 - Make choices
 - Legenda !

DONNELLY ET AL. (IN PREP)

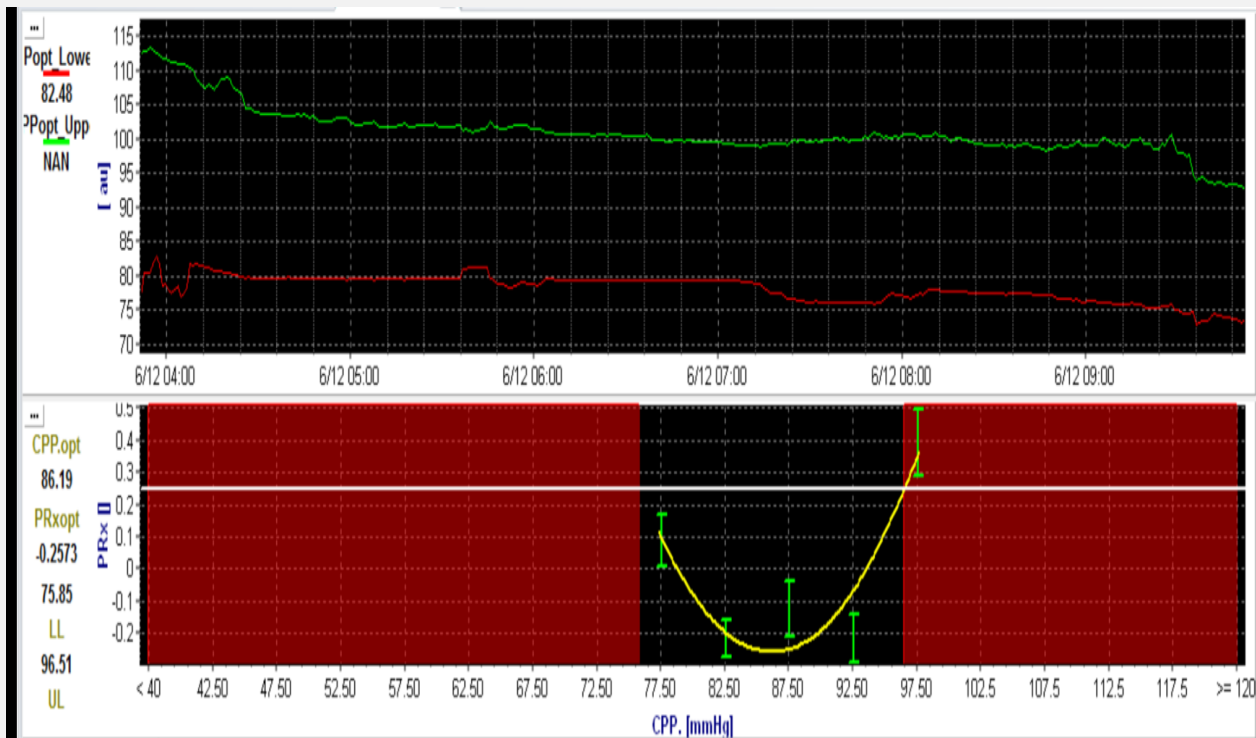
FINDINGS



FINDINGS

- Take into account
 - CPP-CPPopt difference
 - Autoregulation status
 - Theshold voor PRx?
- Relationship with outcome

DONELLY ET AL. (IN PREP)



COMMENTS

- Automated feature
- Feeds the (oscillating!) discussion
 - Clinical application of CPPopt?
 - Share this information?
- Intervention study
 - Too early

2002-2017

ACHIEVEMENTS

- Nice concept
 - PRx
 - CPPopt
 - Relationship with outcome
 - Tackled many problems
- Good (flexible) infrastructure
- Good network/team
 - Scientists/clinicians
- TBI: 31 publications

QUESTIONS (SMALL STEPS)

- How does CPPopt behave prospectively?
- Is it safe?
- How do clinicians behave?
- What is good outcome parameter (proof)?

FUTURE: 3 CENTER RANDOMIZED INTERVENTION STUDY

FEASIBILITY AND SAFETY STUDY



Covering 5 days after admission

GOGITATE

COGiTATE

CPPOpt Guided Therapy: Assessment of Target Effectiveness

CPP treatment arm

- CPP: 60-70 mmHg
- No CA information is displayed

CPPopt treatment arm

- Target the CPPopt
- CA information is provided
- CPP > 50 and < 100

In common

- ICP < 22 protocol
- Review every 4 hours (3x review by research team)
- Clinicians might decide/choose different CPP targets
- Simple CPP treatment protocol

N = 30

N = 30

AFTER (BLOCK) RANDOMIZATION

CPP ARM

- Start 60-70 mmHg
- Review after 4 hours (60-70), regular 6dd
- ICM+ display:
 - ICP/CPP
 - Other cerebral monitoring

CPPOPT ARM

- Start 60-70 mmHg
- Review after 4 hours (CPPopt), regular 6dd
- ICM+:
 - ICP/CPP
 - PRx
 - PRx-CPP error bar (6 hr)
 - CPPopt number + trend (multiwindow + weighted) + CPP 5 min trend
 - Other cerebral monitoring
- CPP > 50 and < 100
- If no CPPopt: clinical target

4 HOURLY REVIEW

ALERT

CPPopt Intervention group

CPP	64.2
CPPopt	91.4

Review Patient

Additional charts are available in the ICM+ pages.

Question 1. Do you follow the CPPopt target?

Other target:

Question 2. If no, please specify why you not follow the CPPopt target?

Other:

Question 3. Are you planning to start an intervention for targeting CPPopt?

Question 4. If yes, please specify which intervention you start?

Other:

ALERT

CPPopt Intervention group

CPP	76.6
CPPopt	46.5

Review Patient

Additional charts are available in the ICM+ pages.

Question 1. Do you follow the CPPopt target?

Other target:

Question 2. If no, please specify why you not follow the CPPopt target?

Other:

Question 3. Are you planning to start an intervention for targeting CPPopt?

Question 4. If yes, please specify which intervention you start?

Other:

Thanks to Jeanette and Manuel

TREATMENT (LOCAL) PROTOCOL

CPP target	ICP	Action	Interventions
↑	> 20 mmHg	Decrease ICP	ICH treatment ↑
↑	< 20 mmHg	Increase ABP	Fluids Vasopressor ↑ (as per clinician)
↓	> 20 mmHg	Decrease ABP	Vasopressor ↓
↓	< 20 mmHg	Decrease ABP	Vasopressor ↓

OUTCOMES

MAIN PRIMARY (FEASIBLE)

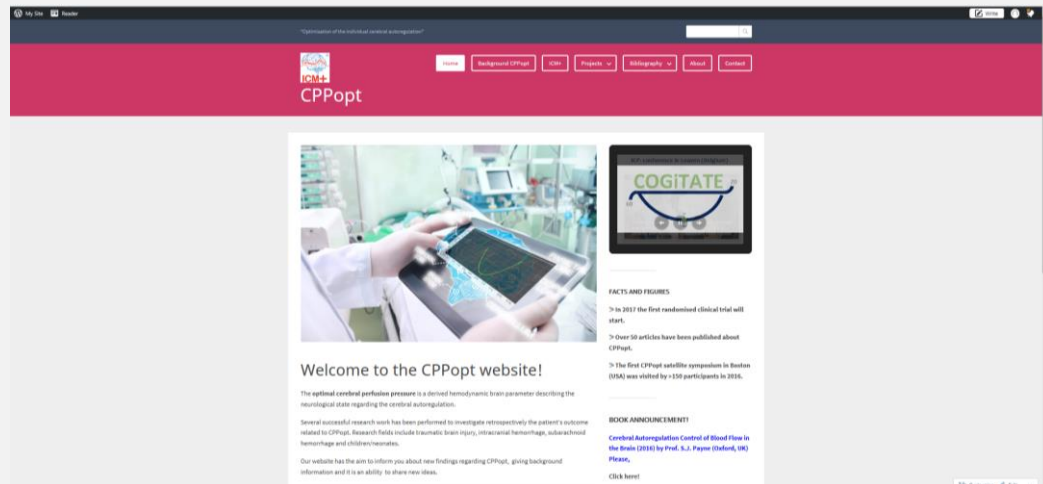
- Percentage of time CPP is within 5 mmHg of CPP_{opt}
- During first 5 days

MAIN SECONDARY (SAFE)

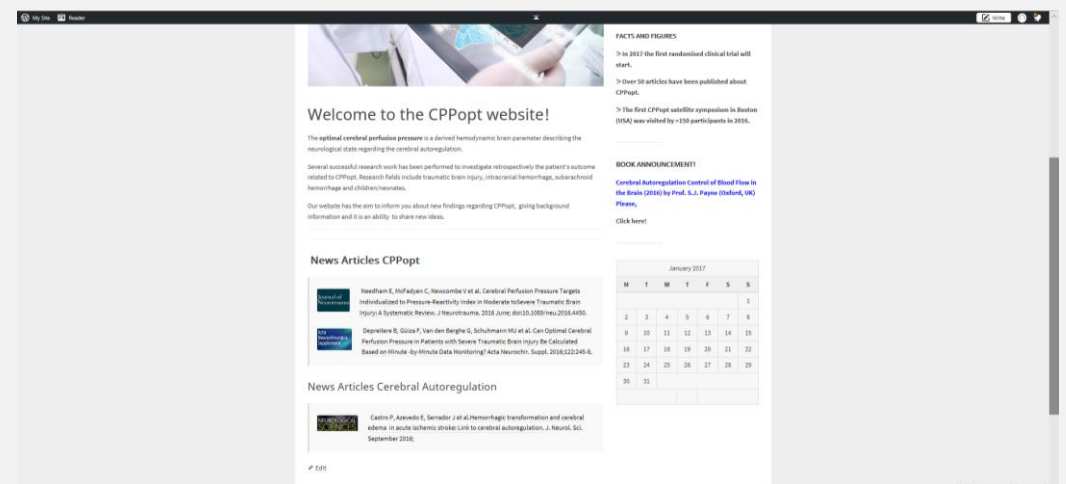
- Average treatment intensity level score (TIL) score (> 3 points)
- Many different secondary outcomes
 - Organ damage
 - Physiological parameters
 - Adherence to monitoring protocol
 - Outcome at 6 months

COMMUNICATION

WEBSITE



WEBSITE

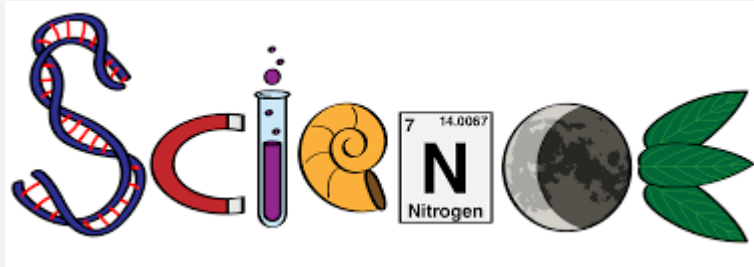


Thanks to Jeanette

- Explanation of CPPopt options
- Powerpoints, etc
- Studies

SUMMARY

SCIENTISTS



CLINICIANS



Thank you all!!!

UNCERTAINTIES

- Whole recordings



- 'Up-to-date' (4 hr)



- "Up-to-date" (2-10 hr)

- CPPopt



- CPPopt 'safe' range



- CPP Lower Limit of Reactivity (LLR)

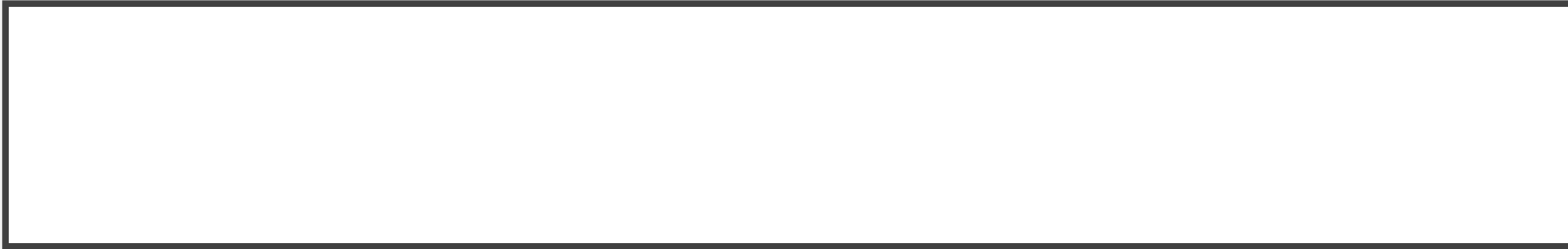
- CPP Upper Limit of Reactivity (ULR)



- CPPopt + SD

- JD

- JT



- Current proposal
 - Pragmatic
 - 6dd revision (3dd by team)
 - CPPopt target vs Control
 - CPP 50-100
 - Feasible
 - adherence
 - Closer to CPPopt
 - Safety
- How will it look like?
 - 4 hour review
 - Review charts (CPPopt)
- Medical ethical
- Website