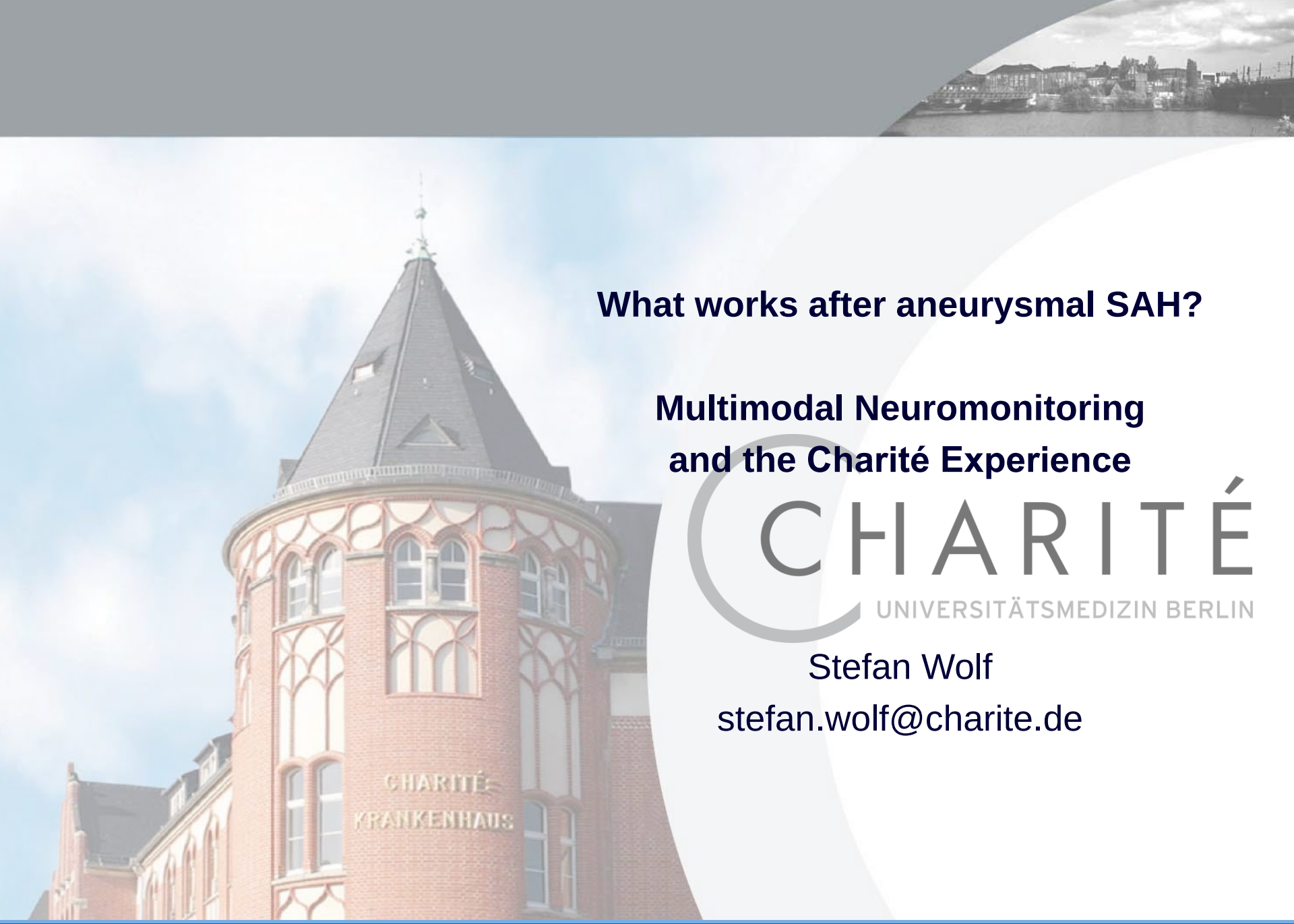


What works after aneurysmal SAH?

Multimodal Neuromonitoring and the Charité Experience

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

Stefan Wolf
stefan.wolf@charite.de

Outline

- Most important tip
- What does work: Nimodipine
- Are Raumedic and Licox probes different?
- Evicence for $p_{bt}O_2$ monitoring
- How to influence a low $p_{bt}O_2$ reading
- What may work: lumbar drains


Use dedicated software
for recording
multimodal monitoring data
at the bedside!

Nimodipine

- Relevant work: The British Nimotop Trial
- Randomized multicenter (four sites) trial
- Nimotop 6 x 60 mg / d for 21 days vs Placebo

Pickard, BMJ 1989

Nimotop: The British Nimotop Trial

TABLE I—*Demographic data on and indices of severity of initial subarachnoid haemorrhage in patients treated with nimodipine or placebo. Values are numbers of patients unless stated otherwise*

	Patients taking nimodipine (n=278)	Patients taking placebo (n=276)
Mean (SD) age (years)	46 (13)	48 (12)
Men	114	107
Women	164	169
Alcohol abuse	12	5
Diabetes mellitus	4	3
Chronic airways disease	5	7
Peripheral vascular disease		2
Smoker (>10 cigarettes/day)	120	143
Clinical grade:		
I	8	12
II	168	159
III	76	72
IV	19	25
V	7	8
Initial computed tomography	273	276

Pickard, BMJ 1989

Nimotop: The British Nimotop Trial

TABLE I—*Demographic data on and indices of severity of initial subarachnoid haemorrhage in patients treated with nimodipine or placebo. Values are numbers of patients unless stated otherwise*

	Patients taking nimodipine (n=278)	Patients taking placebo (n=276)
Time from ictus to angiography (days)	5·5	5·1
Aneurysm:		
Proved	187	181
Multiple	40	29
Carotid	68	54
Anterior cerebral	81	83
Middle cerebral	54	49
Posterior circulation	20	15
Spasm present	54	46
Operations:		
No	165	154
Time from ictus to operation (days) range)	10·8 (2-60)	11·3 (2-116)

Pickard, BMJ 1989

Nimotop: The British Nimotop Trial

TABLE II—*Effect of nimodipine on incidence of cerebral infarction and outcome after subarachnoid haemorrhage. Values are numbers (percentages) of patients unless stated otherwise*

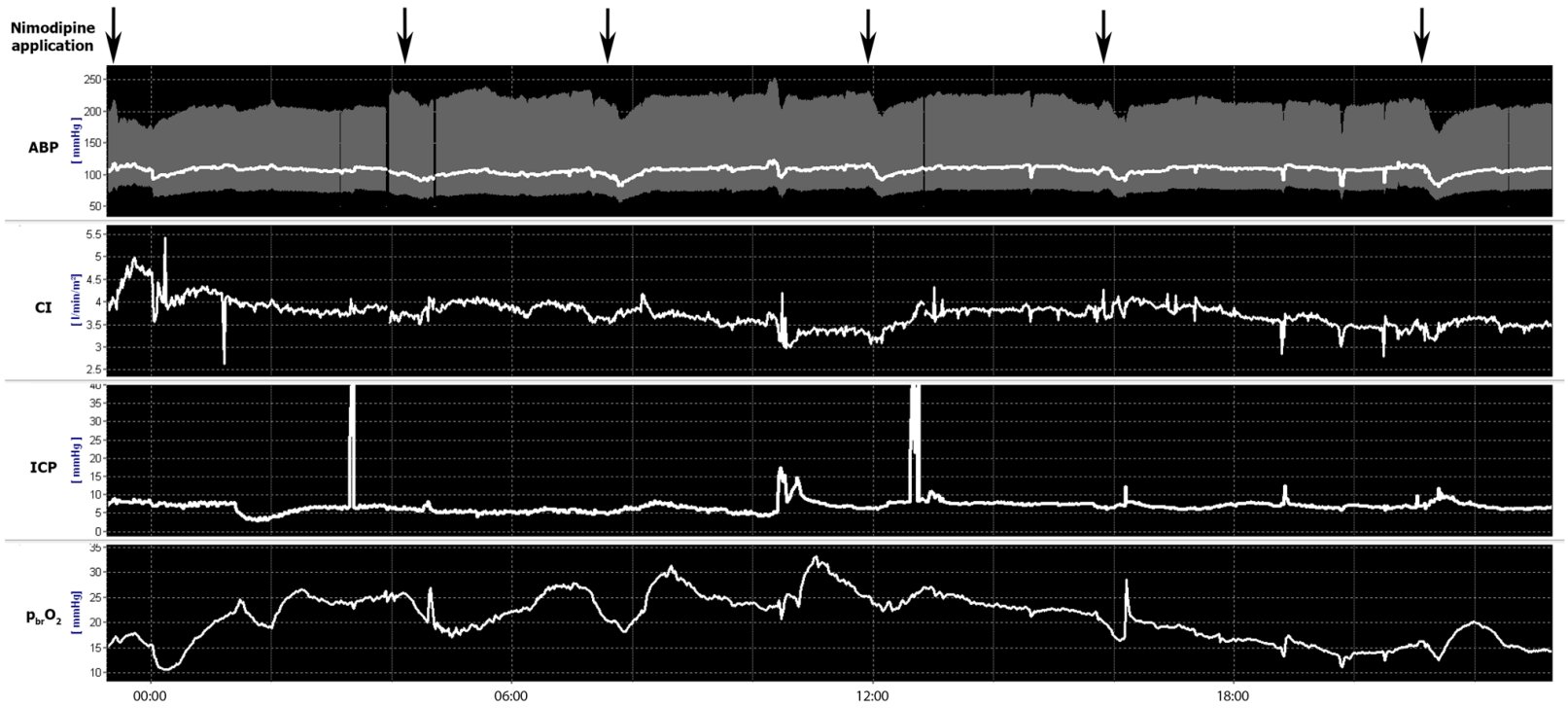
	Patients taking nimodipine (n=278)	Patients taking placebo (n=276)	Relative reduction (%)	95% Confidence interval	Significance (p value)
Cerebral infarct	61 (22)	92 (33)	34	13 to 50	0·003 (χ^2= 8·99; df=1)
Poor outcome	55 (20)	91 (33)	40	20 to 55	<0·001 (χ^2=12·41; df=1)
Rebleed	25 (9)	38 (14)	35	−5 to 59	0·077 (χ^2= 3·13; df=1)

„ In Glasgow, the prevalence of reported alcohol abuse was lowest (2%) …“

„ The protocol allowed for adjustment of dose if hypotension occured, but this was not found to be necessary …“

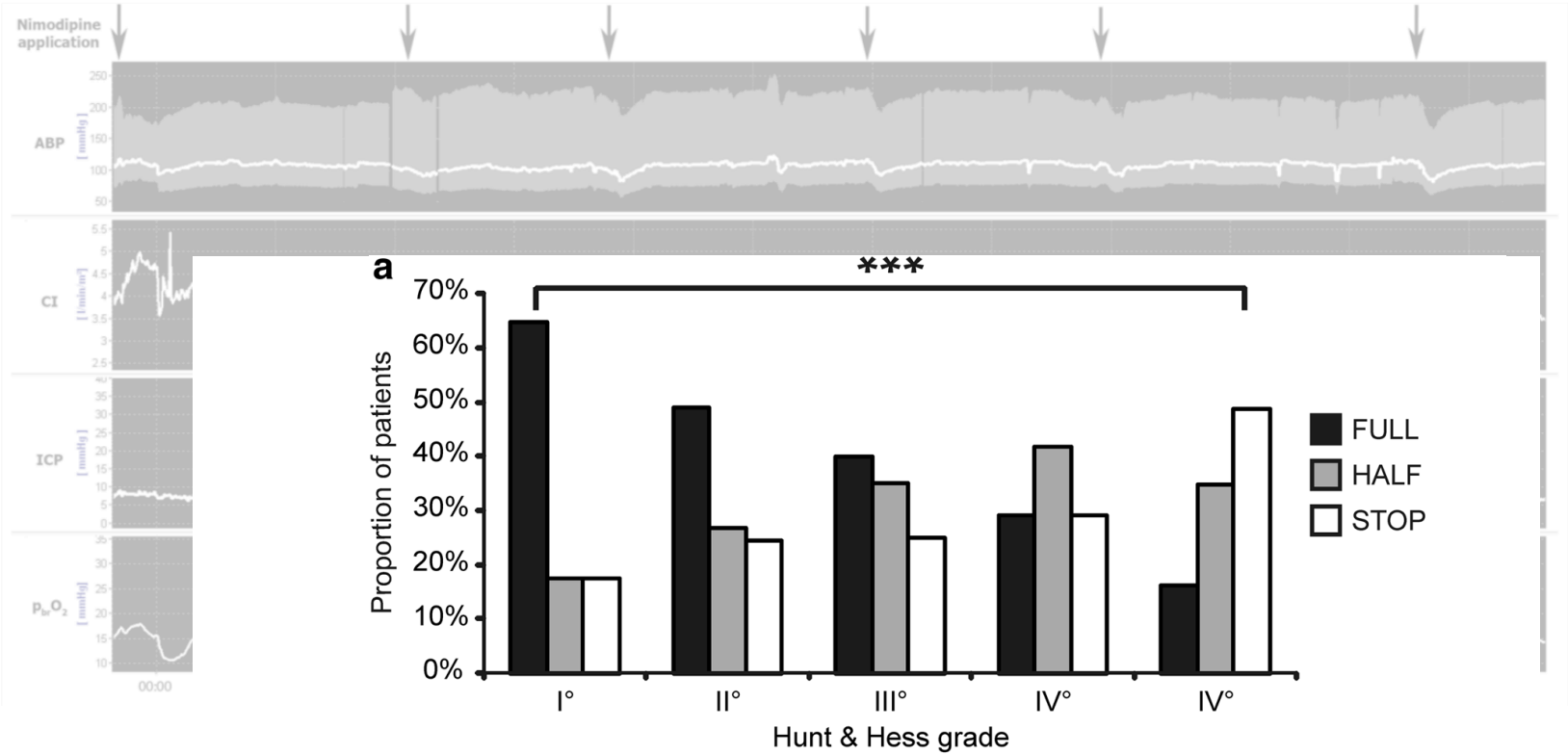
Pickard, BMJ 1989

Nimotop: mean arterial blood pressure drops



Sandow, Neurocritical Care 2016

Nimotop: mean arterial blood pressure drops



retrospective analysis, 270 SAH patients

Sandow, Neurocritical Care 2016

Nimotop: mean arterial blood pressure drops

Table 3 Risk factors for unfavorable clinical outcome (mRS >2)

	Univariate		Multivariate	
	OR (95 % CI)	*p*	OR (95 % CI)	*p*
Age	1.036 (1.008, 1.066)	**0.015**	1.040 (1.007, 1.076)	**0.022**
Male sex	0.764 (0.371, 1.535)	0.456	1.094 (0.466, 2.551)	0.835
Hunt & Hess grade	1.780 (1.417, 2.272)	**≤0.001**	1.652 (1.221, 2.279)	**0.002**
Fisher grade	1.739 (1.118, 2.832)	**0.019**	0.891 (0.498, 1.621)	0.700
Angiographic vasospasm	3.021 (1.337, 7.532)	**0.012**	2.392 (0.942, 6.582)	0.076
Nimodipine dosage	0.862 (0.789, 0.937)	**≤0.001**	0.895 (0.809, 0.987)	**0.029**
Norepinephrine dosage	1.564 (1.216, 2.054)	**≤0.001**	1.081 (0.794, 1.486)	0.623

- Nimodipine dose is important
- If in doubt, increase noradrenalin and keep nimodipine dose
- iv.- nimodipine shows no advantage compared to oral

Sandow, Neurocritical Care 2016

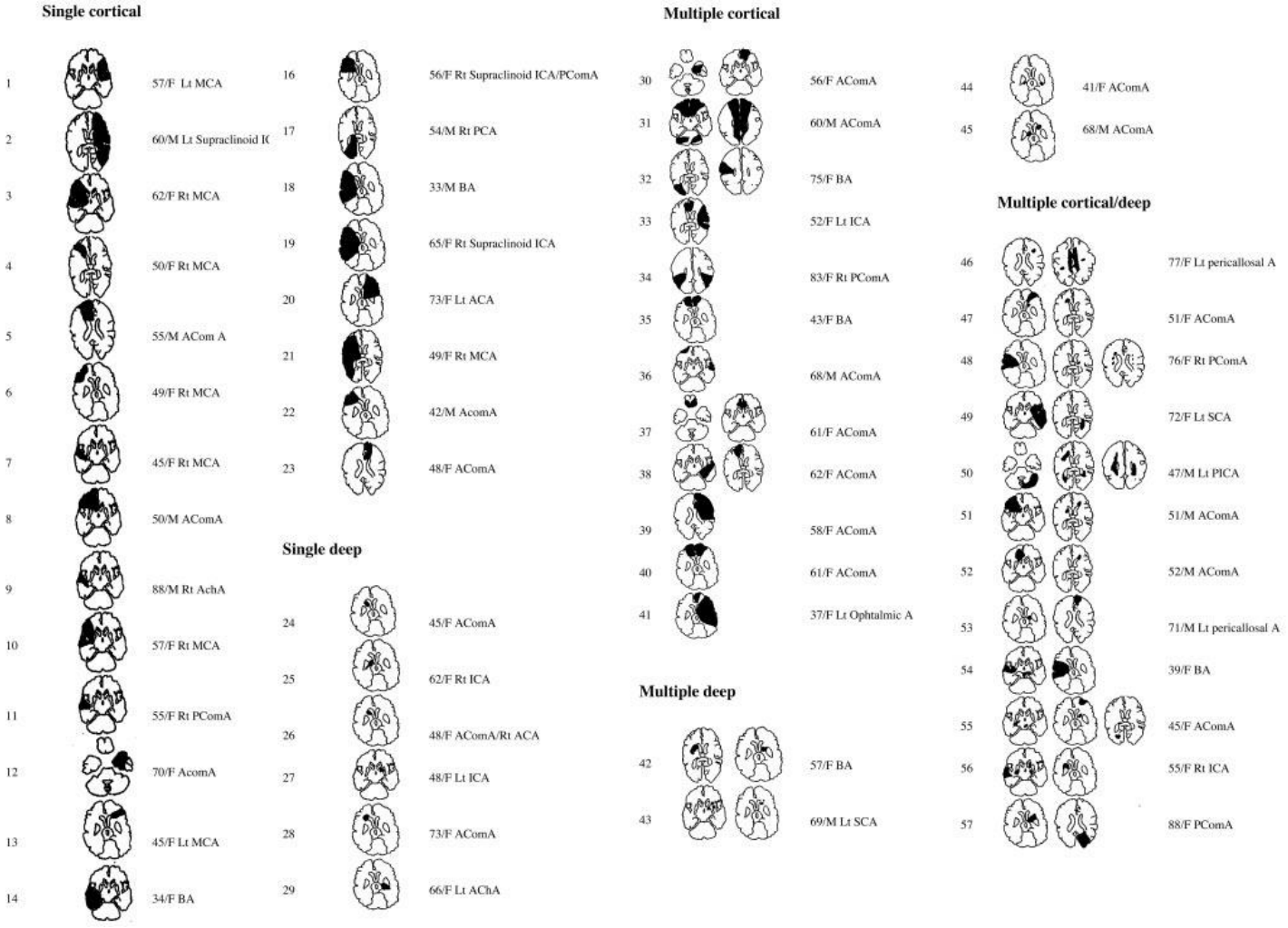
Monitoring after SAH – what, when and for whom

All patients: clinical exam

Poor grade patients:

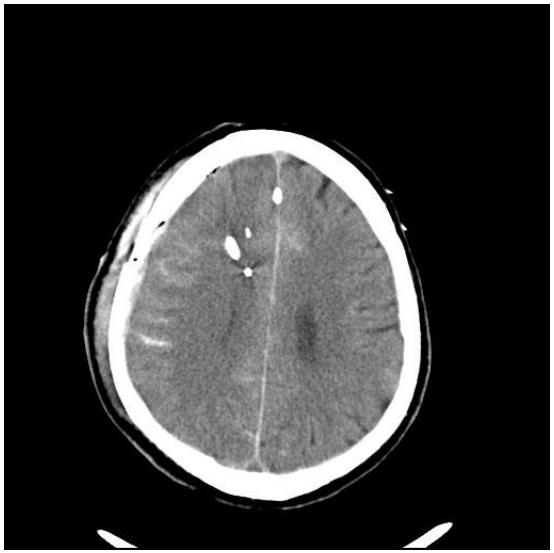
- TCD
- CT angiography, CT perfusion give spatial resolution
- $p_{bt}O_2$ for temporal resolution

What do infarctions look like after SAH?

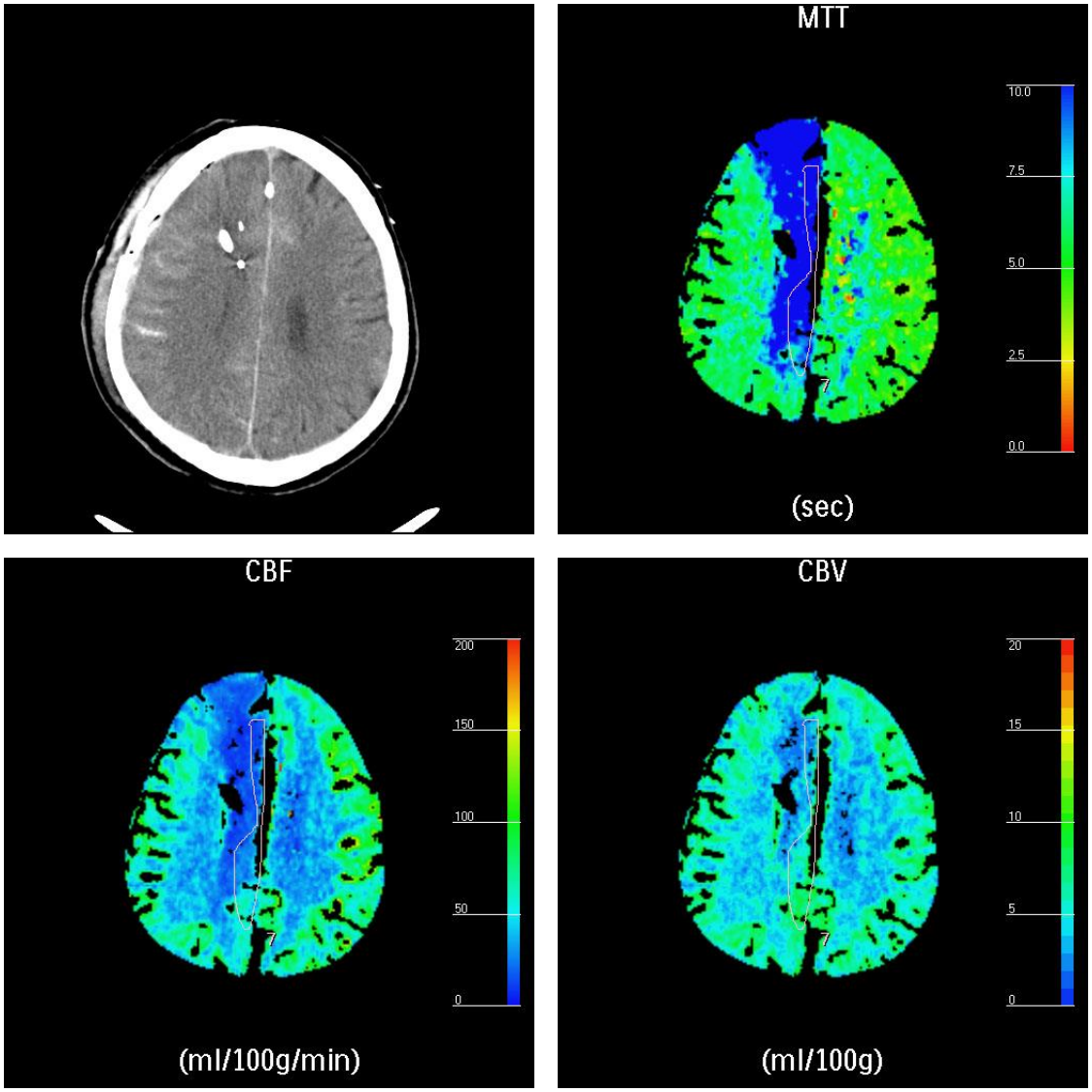


Rabinstein et al, Stroke 2005

Probe implantation in the ACA territory

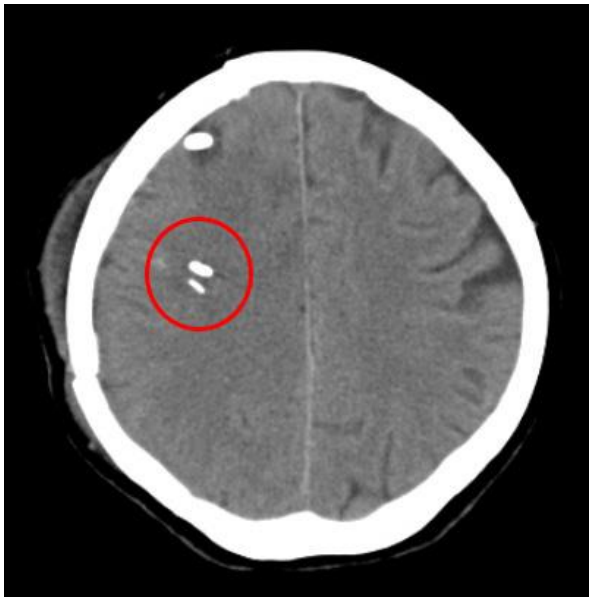


Implantation in the ACA territory – CT perfusion



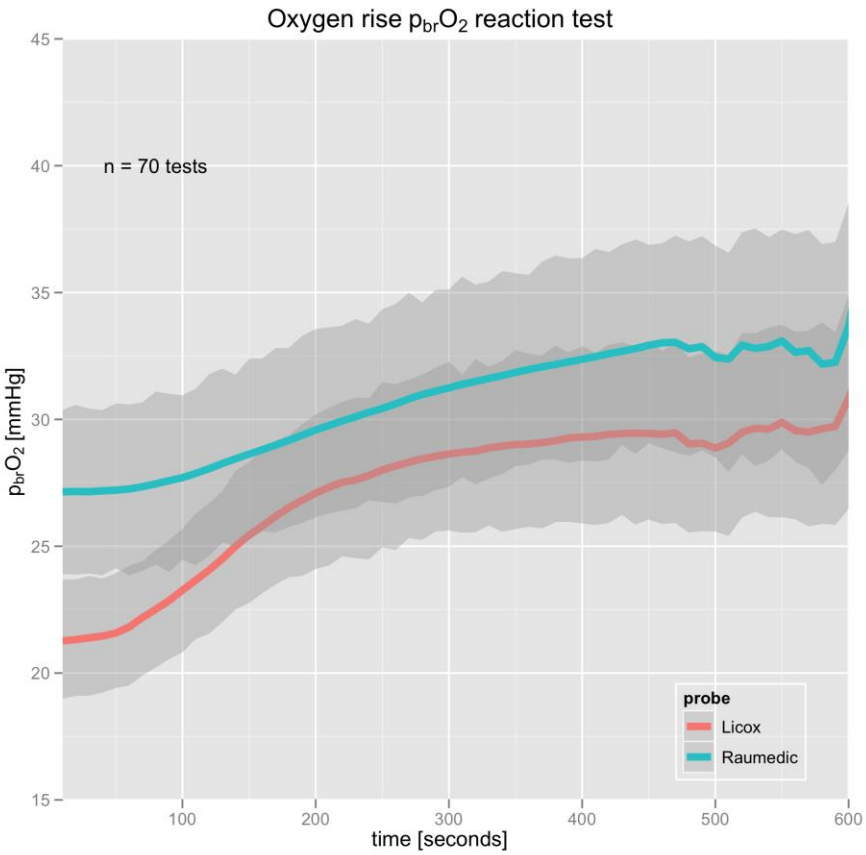
Are Licox- and Raumedic probes comparable?

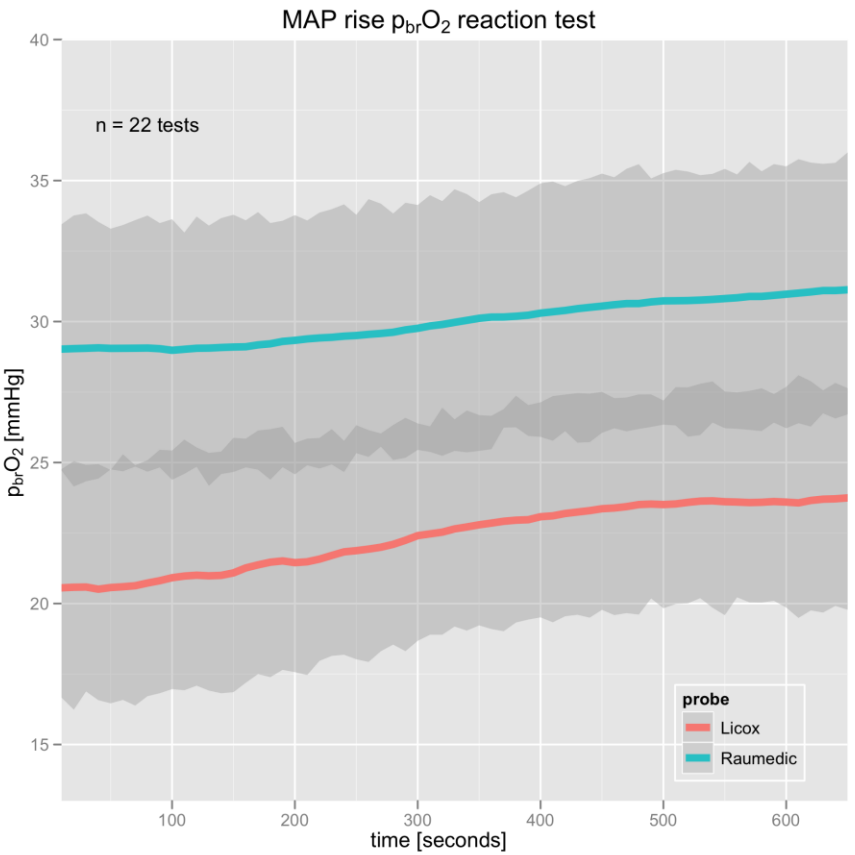
- Eleven Patients (TBI, SAH) with a Licox and a Raumedic $p_{bt}O_2$ probe implanted in *tissue-at-risk*
- Measurement on average for 8.2 days
- Interventions with MAP und F_iO_2 rise
- Comparison of random samples with one hour latency



Dengler et al, ICM 2011
Dengler et al, Neurocrit Care 2012
Wolf, Acta NCH supp 2011

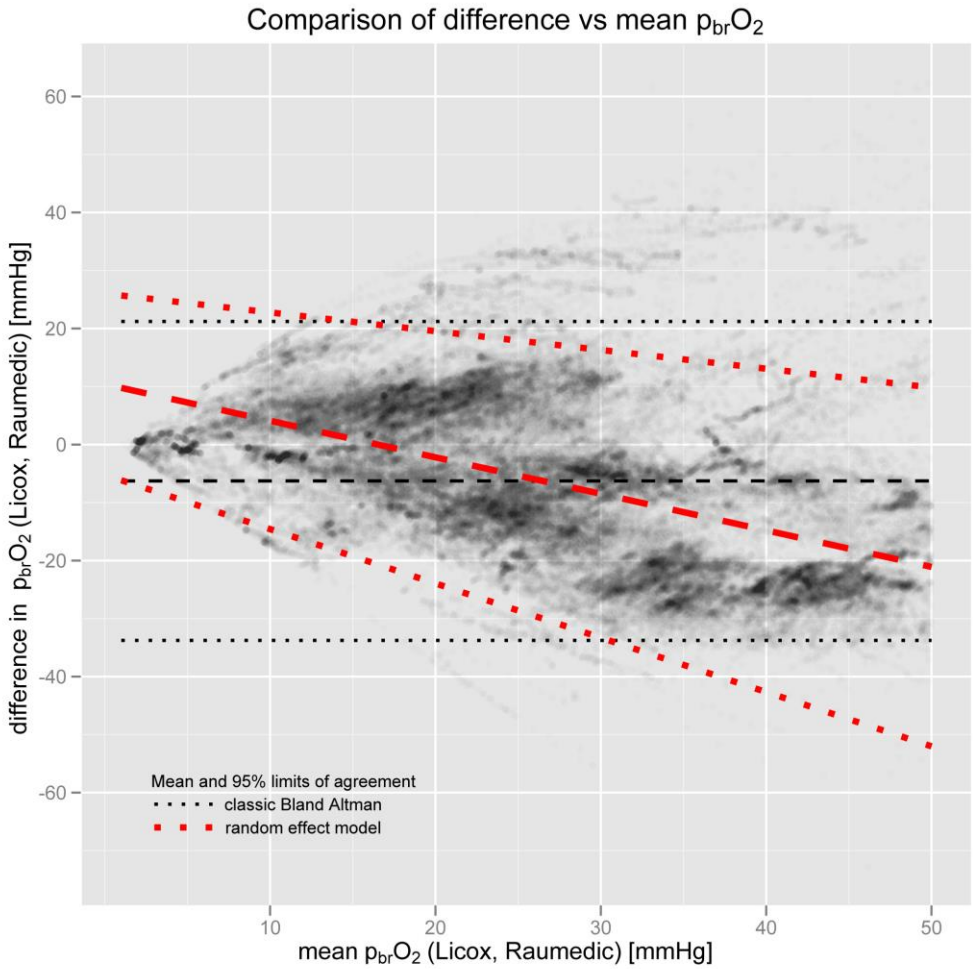
Intervention tests for Licox- and Raumedic- $p_{bt}O_2$ probes





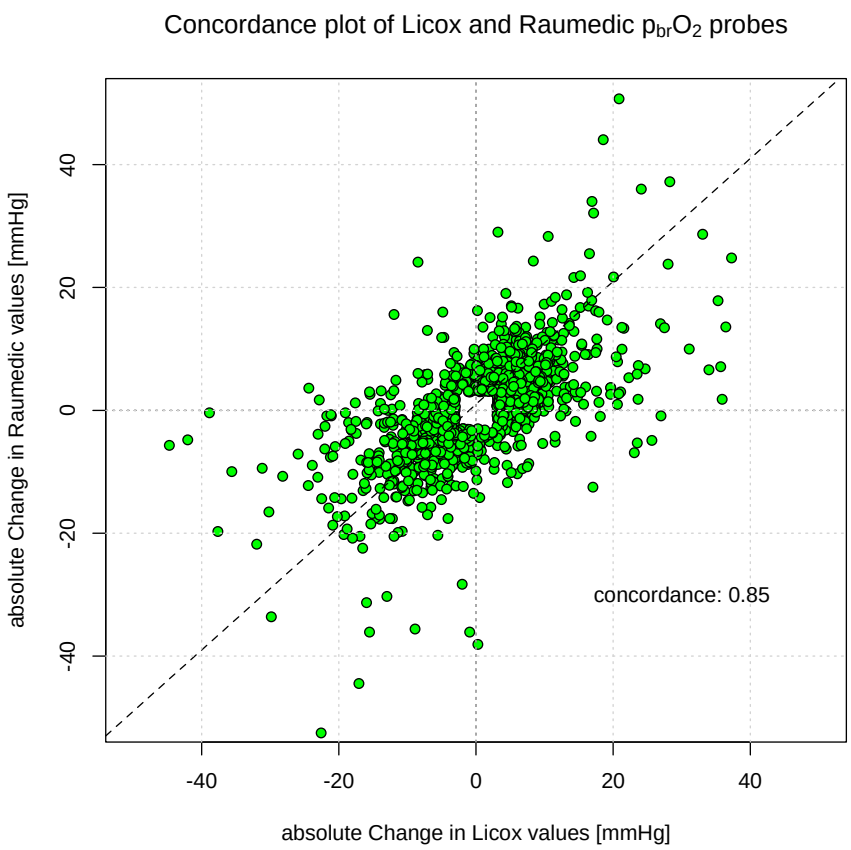
Dengler et al, ICM 2011

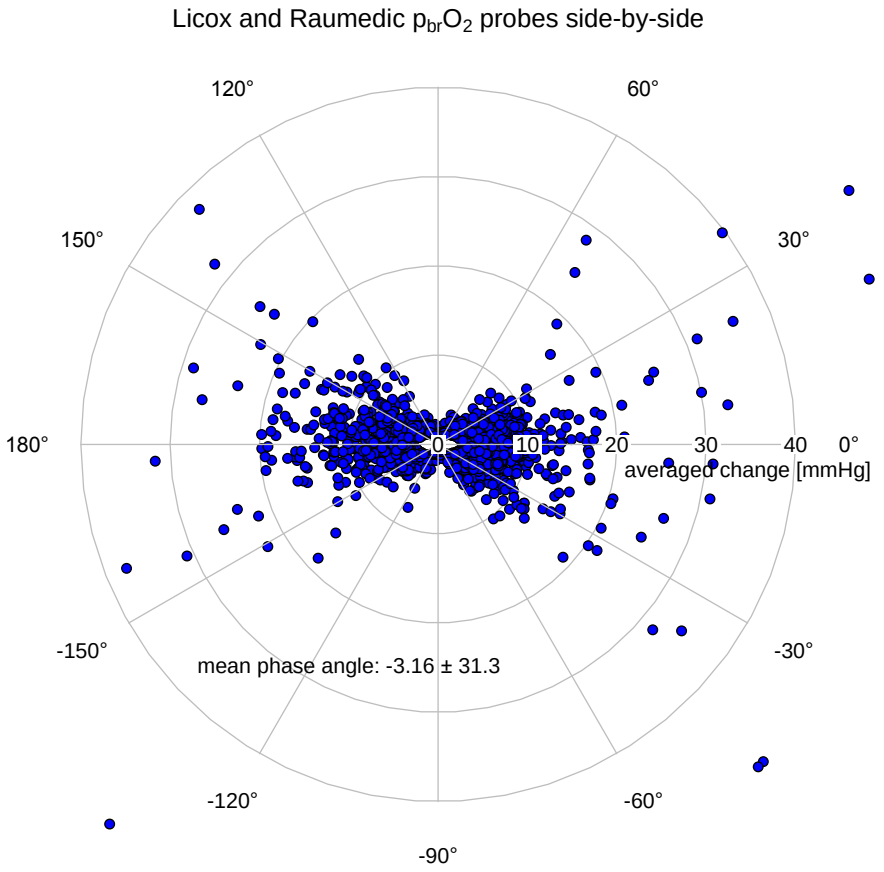
Licox- and Raumedic- $p_{br}O_2$ probes – pooled data



Wolf, Acta NCH supp 2012

Licox- and Raumedic – $p_{br}O_2$ – probes: trend data



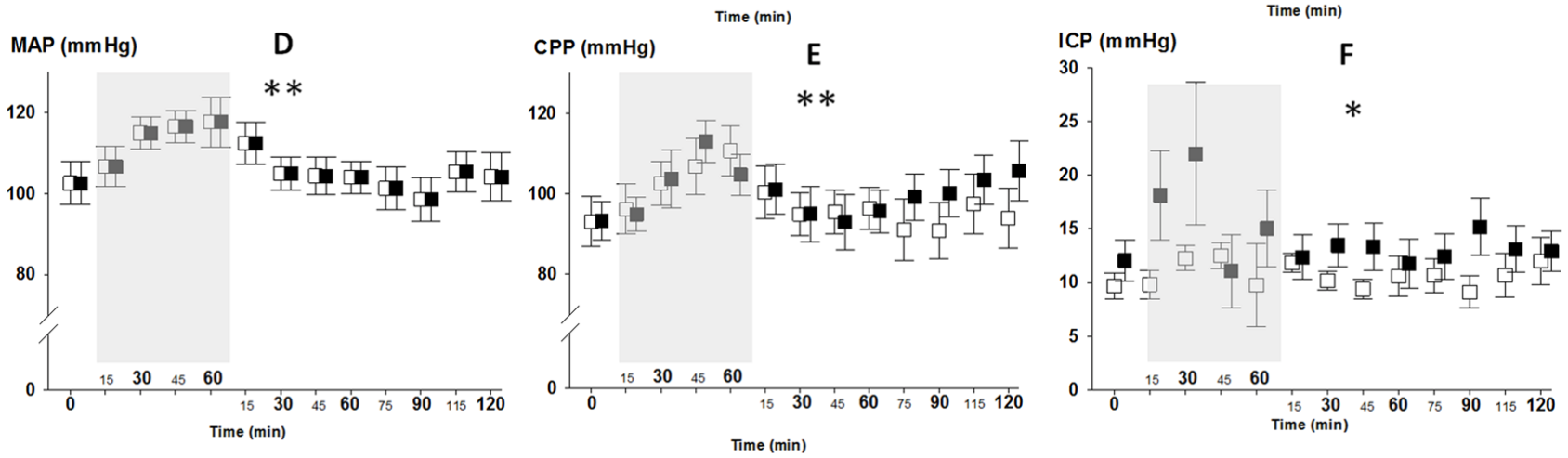


Trends of both probes correlate well

Differences of absolute values: most likely tissue heterogeneity

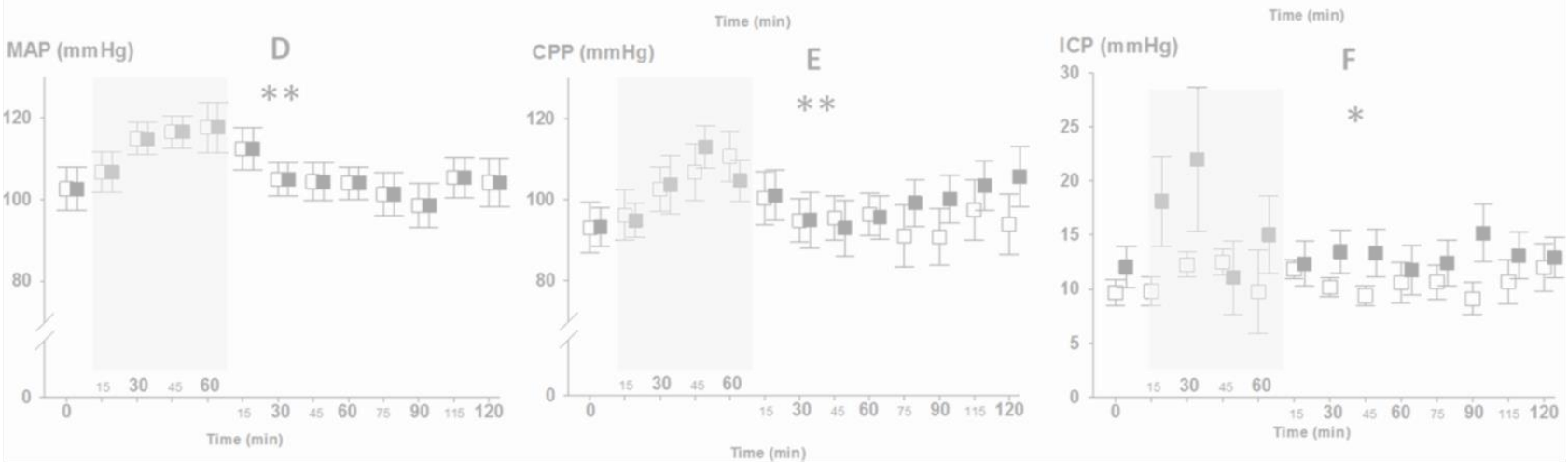
still unpublished

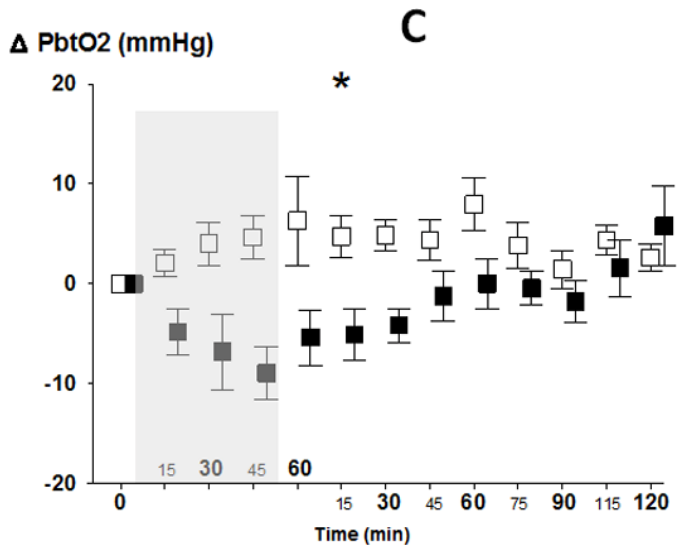
Weaning of mechanical ventilation after aneurysmal SAH

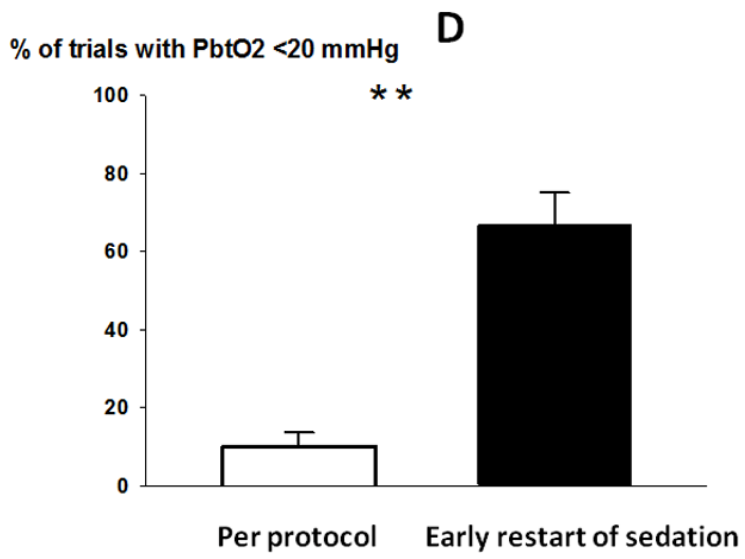


Helbok, Crit Care 2012

Weaning of mechanical ventilation after aneurysmal SAH

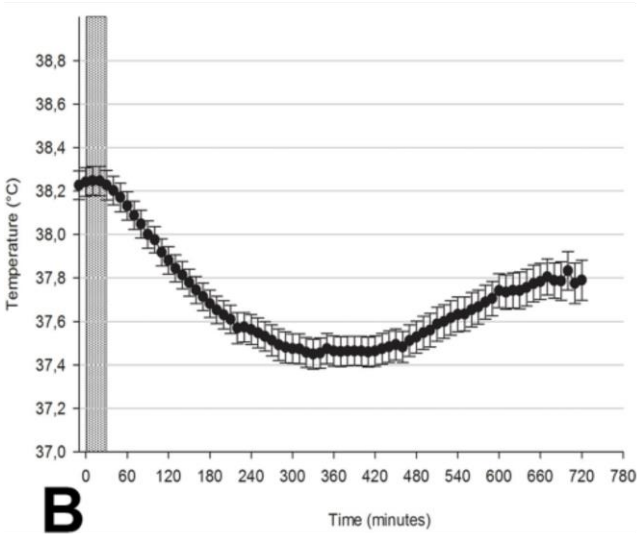






Helbok, Crit Care 2012

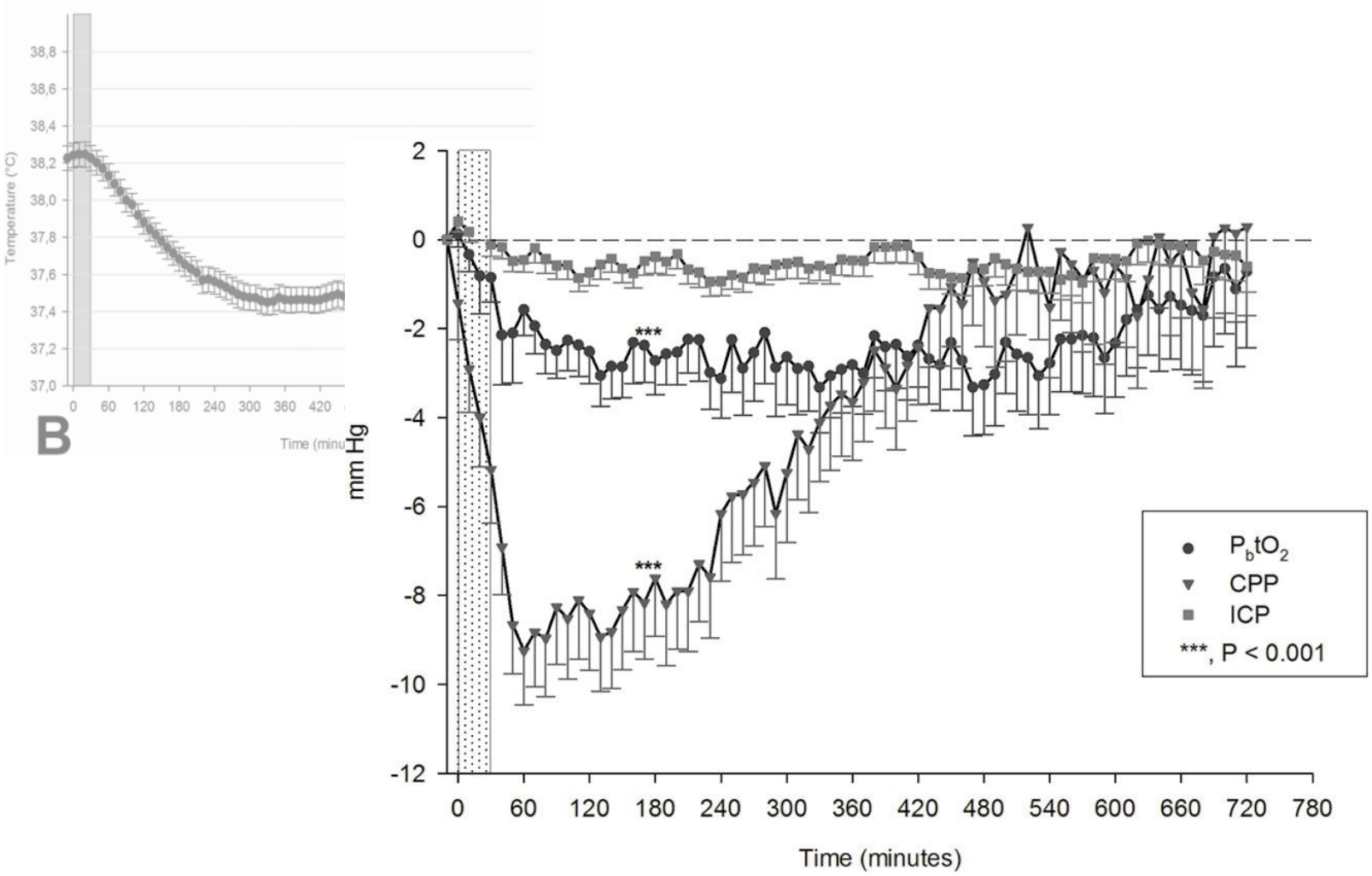
Decrease fever burden!



22 patients with aneurysmal SAH

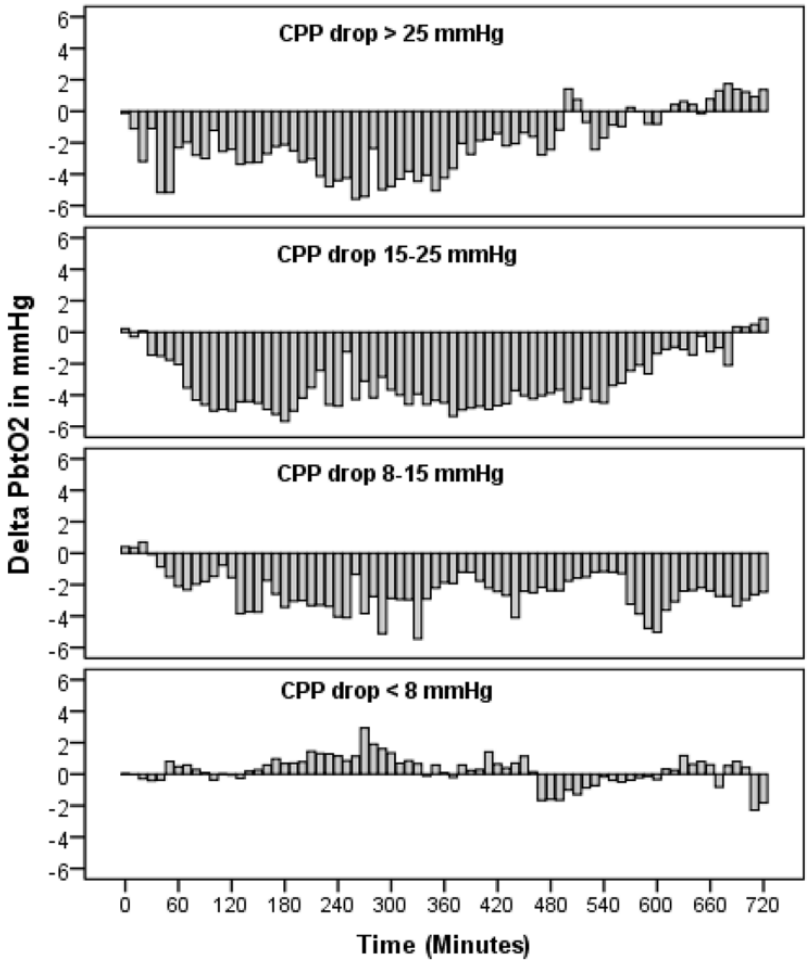
Schiefecker, Crit Care 2013

Decrease fever – but be aware of side effects!



Schiefecker, Crit Care 2013

CPP loss due to fever treatment and effect on $p_{br}O_2$



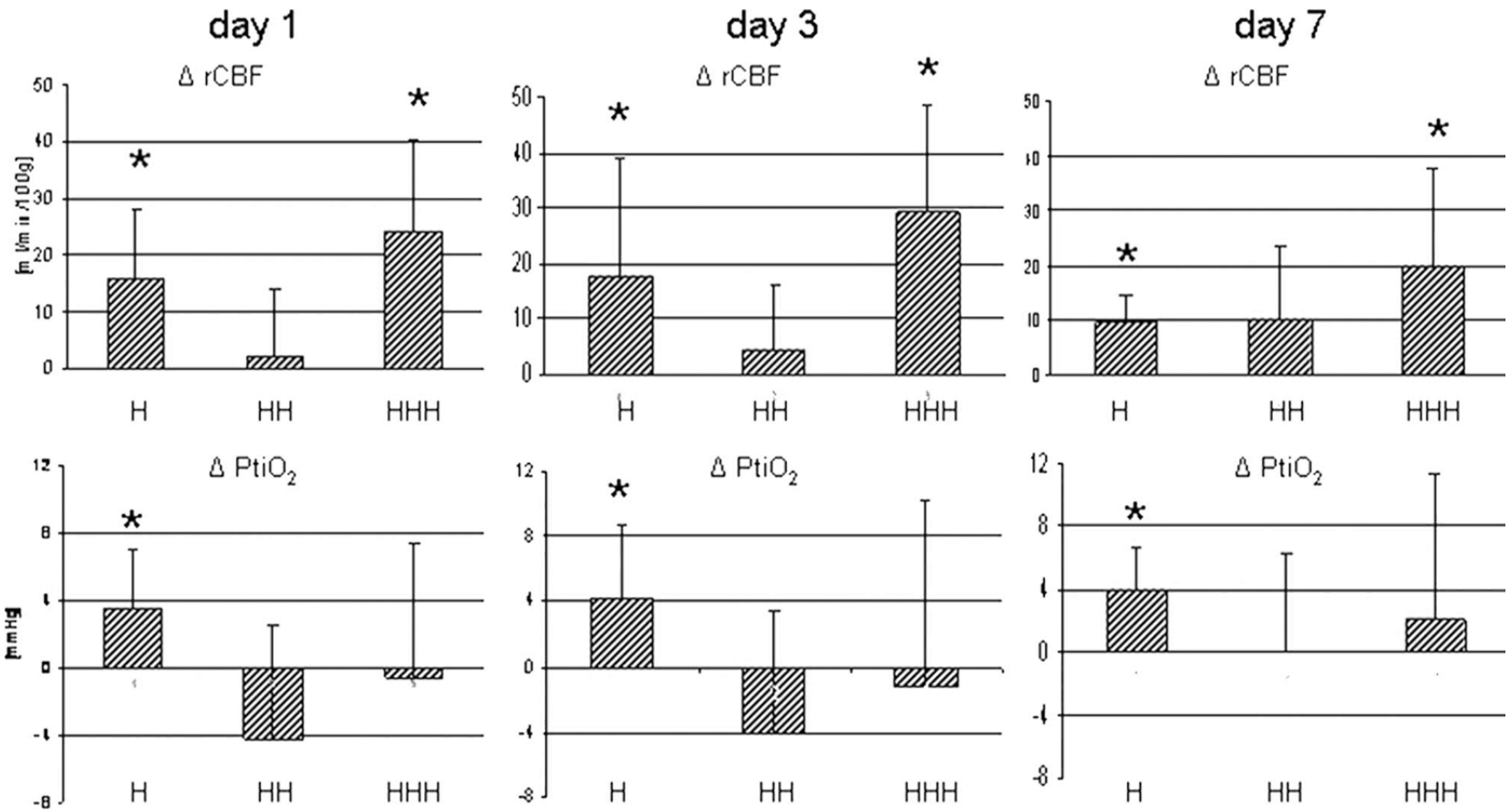
$p_{br}O_2$ < 20 mmHg:

mRS 1-4: 32 ± 9% monitoring time
mRS 5,6: 66% ± 12% monitoring time

$p < 0.05$

Schiefecker, Crit Care 2013

Monitoring of hyperdynamic therapy – rCBF and $p_{bt}O_2$



Muench, Crit Care Med 2007

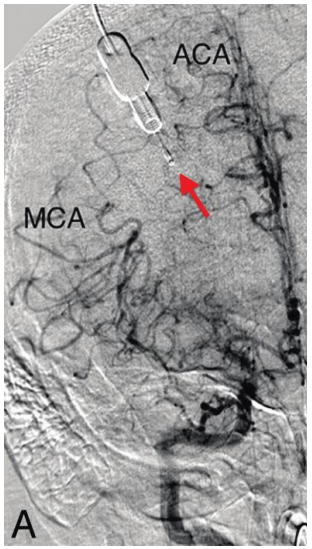
Conclusions from Münch et al, CCM 2007:

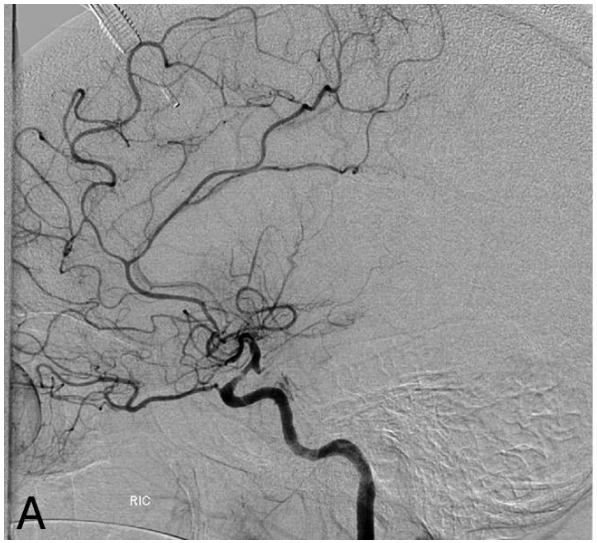
- Not all components of HHH therapy are equally effective
- Hypervolemia does not seem to improve cerebral perfusion and seems to worsen $p_{br}O_2$

But:

- ***No*** vasospasm in rCBF measurements on day 7, but in 6 of 10 patients angiographically
- Hemedex rCBF is a promising technology, but has validity problems
- Very unrealistic MAP and volume parameters
  (RR_{mean} 140 mmHg, very high ITBVI (mean 1123 ml/kg/m²),
  cardiac output weakly documented,
  unclear duration of intervention

Endovascular vasospasm therapy

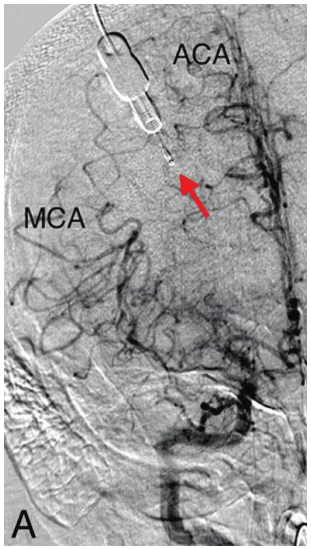


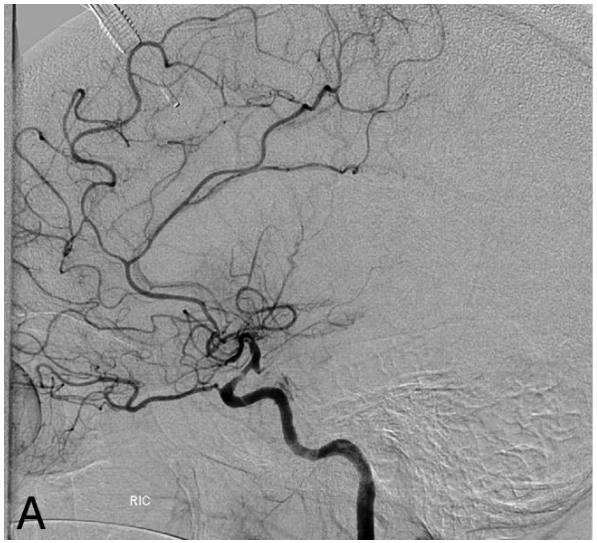


8 patients with aneurysmal SAH and $p_{bt}O_2$ monitoring
Routine screening for vasospasm with TCD, PCT, CTA
Endovascular therapy with i.a.-verapamil

Deshajes, AJNR 2012

Endovascular vasospasm therapy





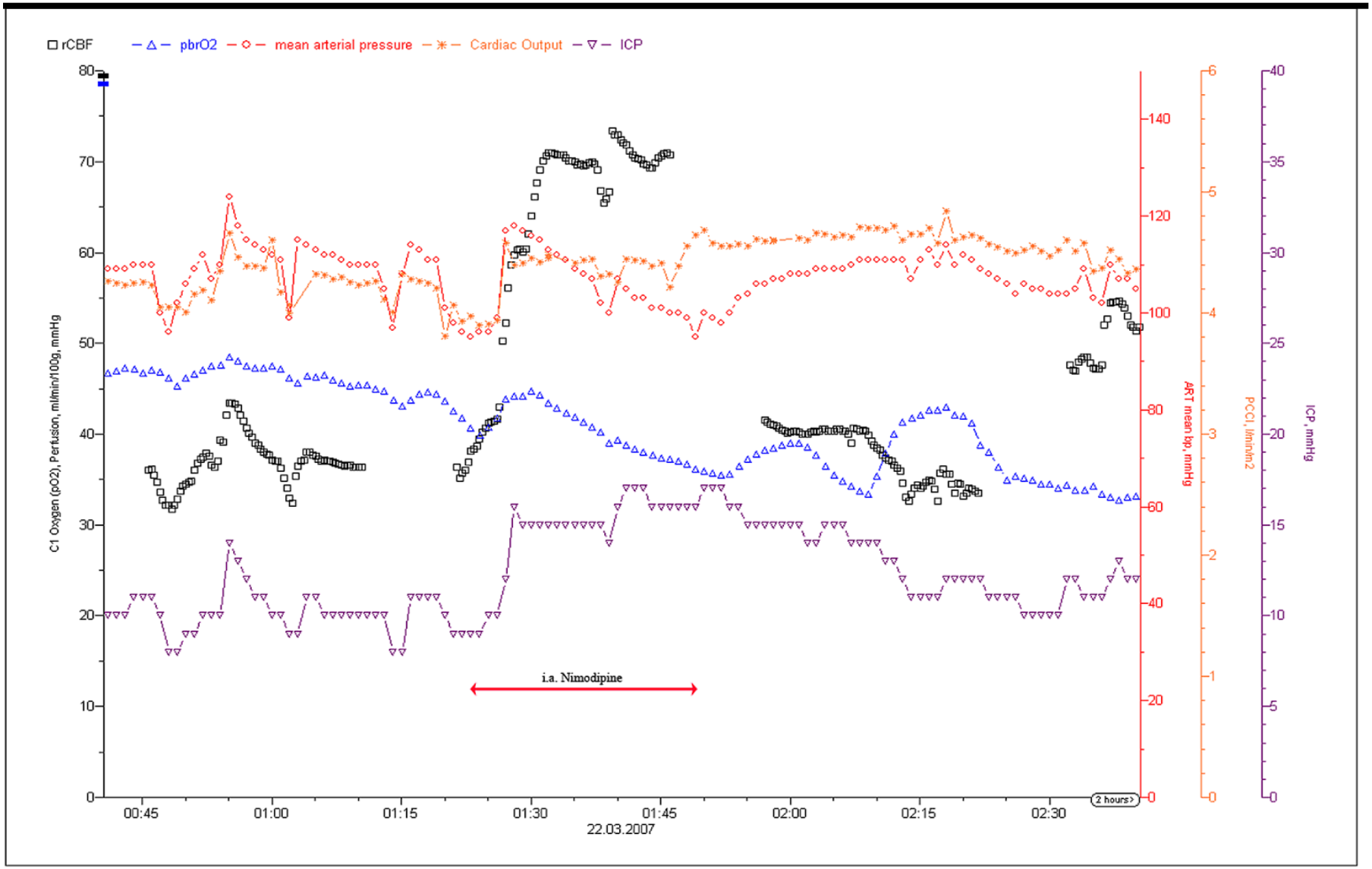
Mild-to-moderate and moderate-to-severe group physiologic parameters before and after spasmolytic therapy along with percentage improvement in PbO_2 after spasmolytic therapy

Vasospasm Severity	Timing	PbO_2[a] (mm Hg ± SE)	CPP[b] (mm Hg ± SE)	ICP[b] (mm Hg ± SE)	SaO_2[b] (mm Hg ± SE)	FIO_2[b] (mm Hg ± SE)	% PbO_2 Improvement
Mild-mod	Prespasmolysis	35.2 ± 3.1	110.9 ± 3.5	5.4 ± 2.2	99.6 ± 0.3	55.7 ± 3.5	14
	Postspasmolysis	40.3 ± 3.1	107.9 ± 4.0	4.6 ± 1.0	99.5 ± 0.3	55.5 ± 4.1	
Mod-sev	Prespasmolysis	27.3 ± 3.1	116.7 ± 3.8	5.8 ± 1.3	99.8 ± 0.2	57.5 ± 6.1	40
	Postspasmolysis	38.4 ± 3.2	113.9 ± 4.4	7.8 ± 1.9	99.2 ± 0.5	57.0 ± 6.1	

Note:—Mild-mod indicates mild-moderate; Mod-sev, moderate-severe.
[a] Statistical significance ($P \leq .05$).
[b] No statistical significance ($P > .05$).

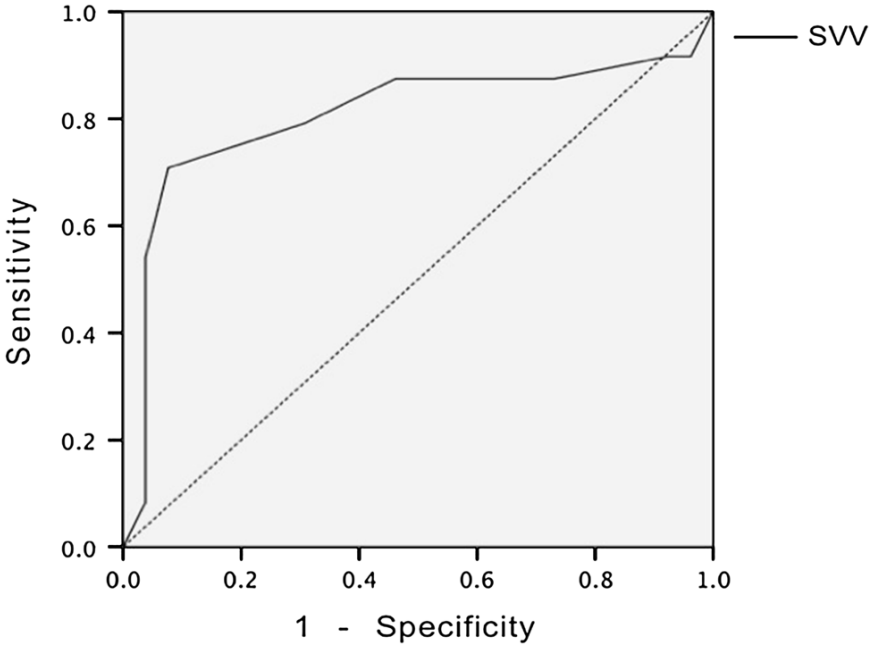
Deshajes, AJNR 2012

Endovascular vasospasm therapy II

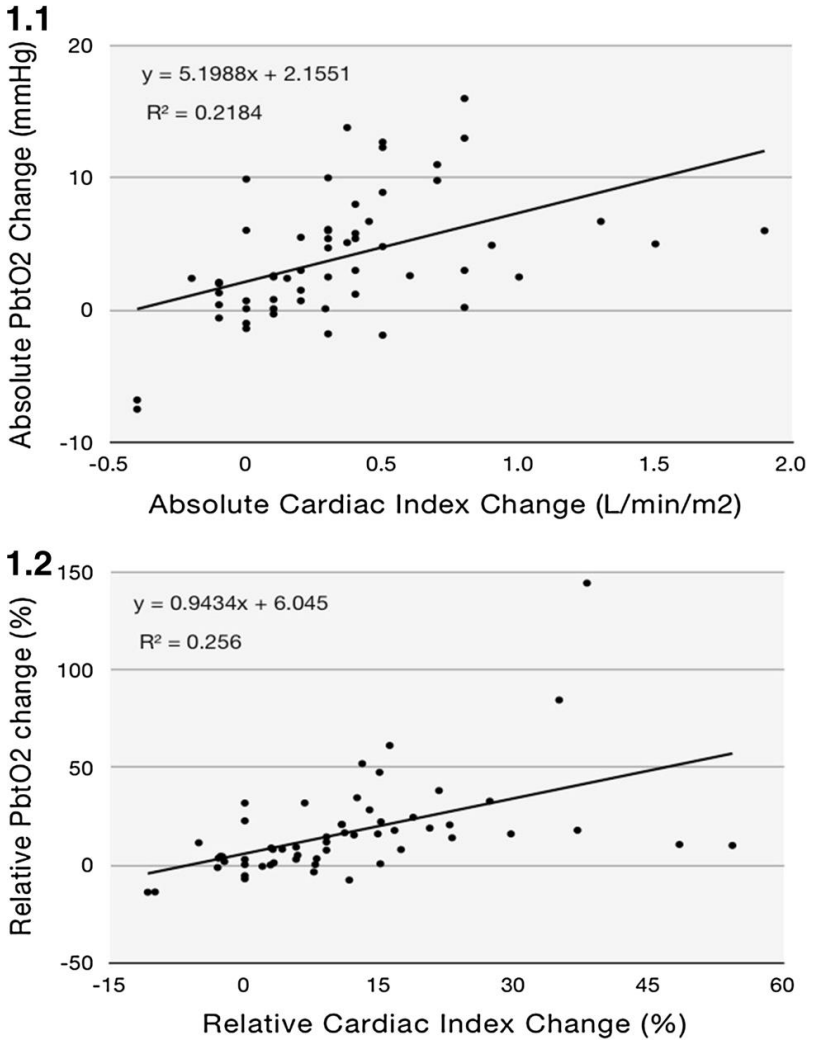


Wolf et al., Neurocrit Care 2010

Volume status, cardiac output and $p_{bt}O_2$

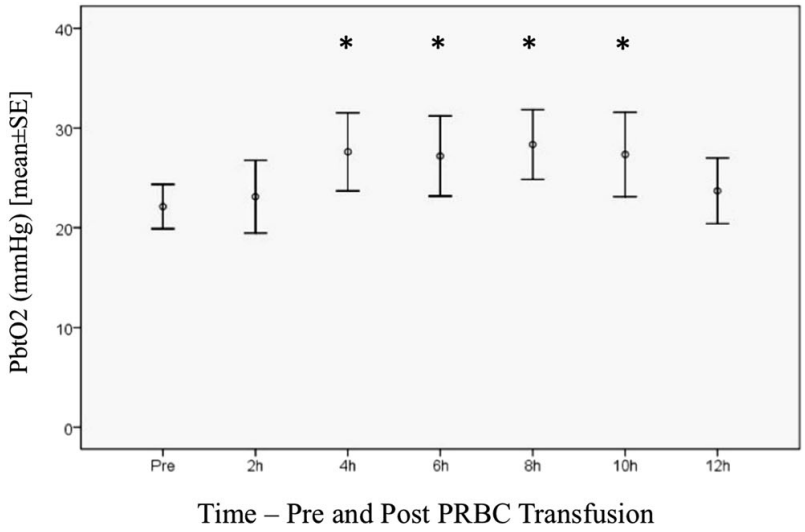


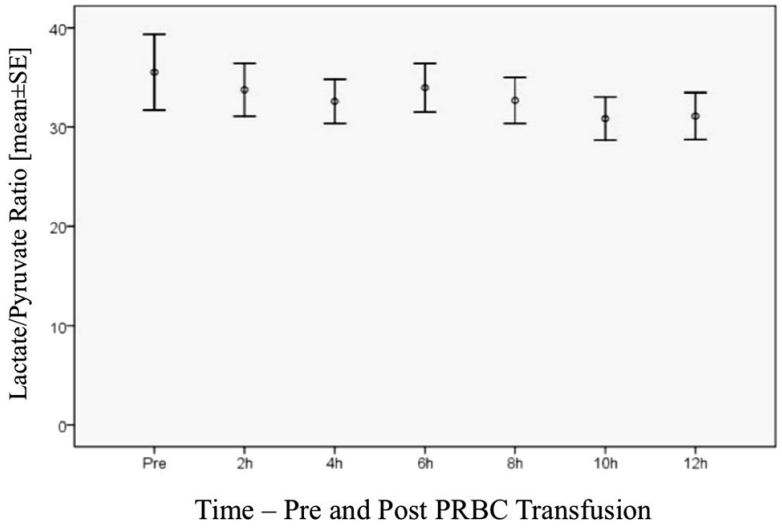
75 volume challenge tests in 10 patients with aSAH and disturbed autoregulation



Kurtz, Neurocrit Care 2014

Transfusion?

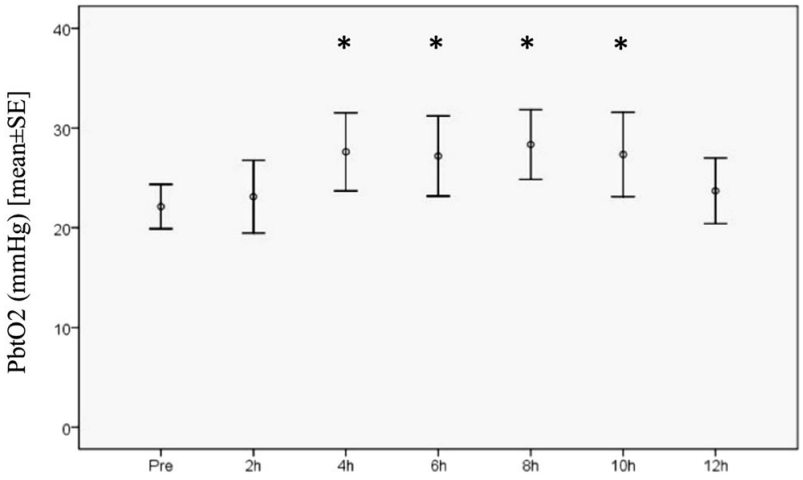




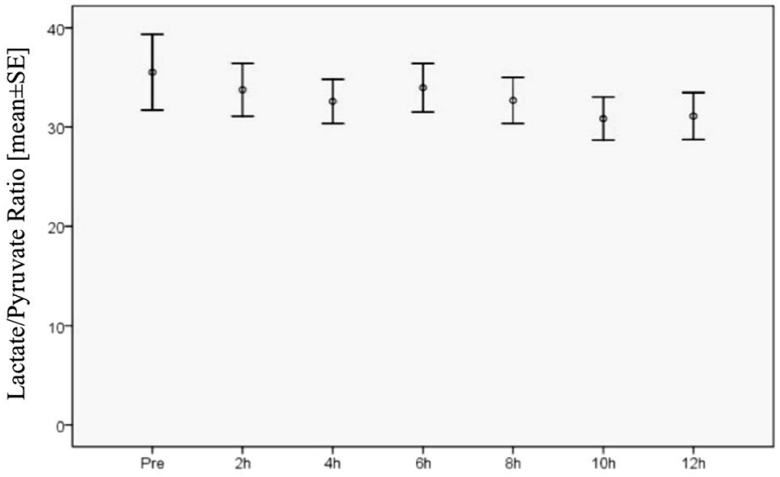
15 patients with aneurysmal SAH
Target Hb 8 g/dl unless evidence for ischemia

Kurtz, Neurocrit Care 2015

Transfusion



Time – Pre and Post PRBC Transfusion



Time – Pre and Post PRBC Transfusion

Table 2 Changes in $PbtO_2$

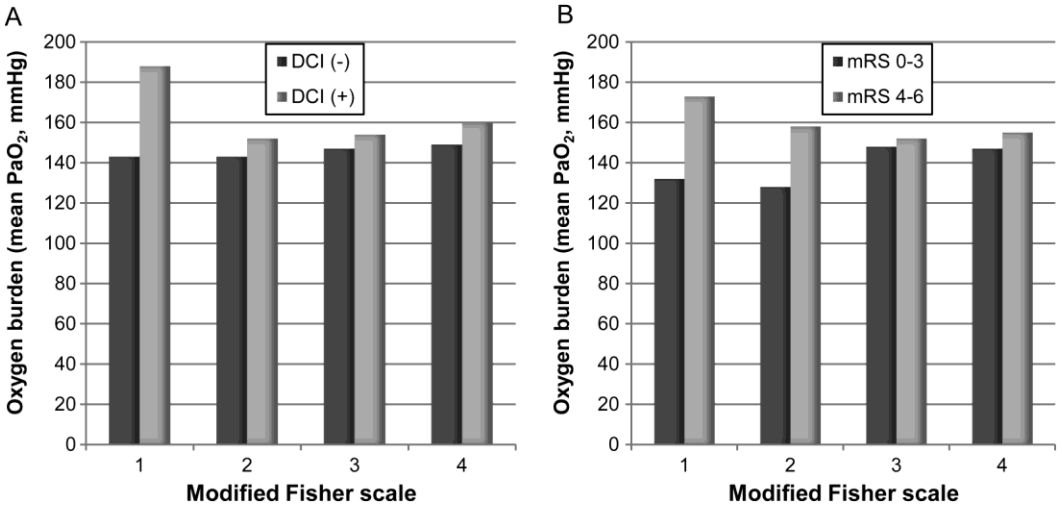
Variables	Univariate			Multiivariate		
	Coefficient	95 % CI	*P*	Coefficient	95 % CI	*P*
Δ Hemoglobin (g/dL)	2.20	0.91–3.49	0.001	1.39	0.09–2.69	0.036
Δ Cerebral perfusion pressure (mmHg)	0.11	0.11–0.12	<0.001	0.11	0.05–0.17	<0.001
Δ LPR	−0.31	−0.53–(−0.09)	0.006	−0.201	−0.36–(−0.04)	0.014
Δ End-tidal CO_2 (mmHg)	0.64	−0.76–2.04	0.37			
Δ SO_2 (%)	2.13	2.13–2.13	<0.001	0.128	−1.07–1.33	0.84
Baseline PO_2 (mmHg)	−0.12	−0.44–0.02	0.447			
Baseline FiO_2 (%)	−3.77	−15.55–8.01	0.53			
Baseline PCO_2 (mmHg)	−0.21	−0.54–0.12	0.21			

Univariate and multivariate linear regression models using GEE

Transfusions improve $p_{bt}O_2$, but no clear effect on metabolism

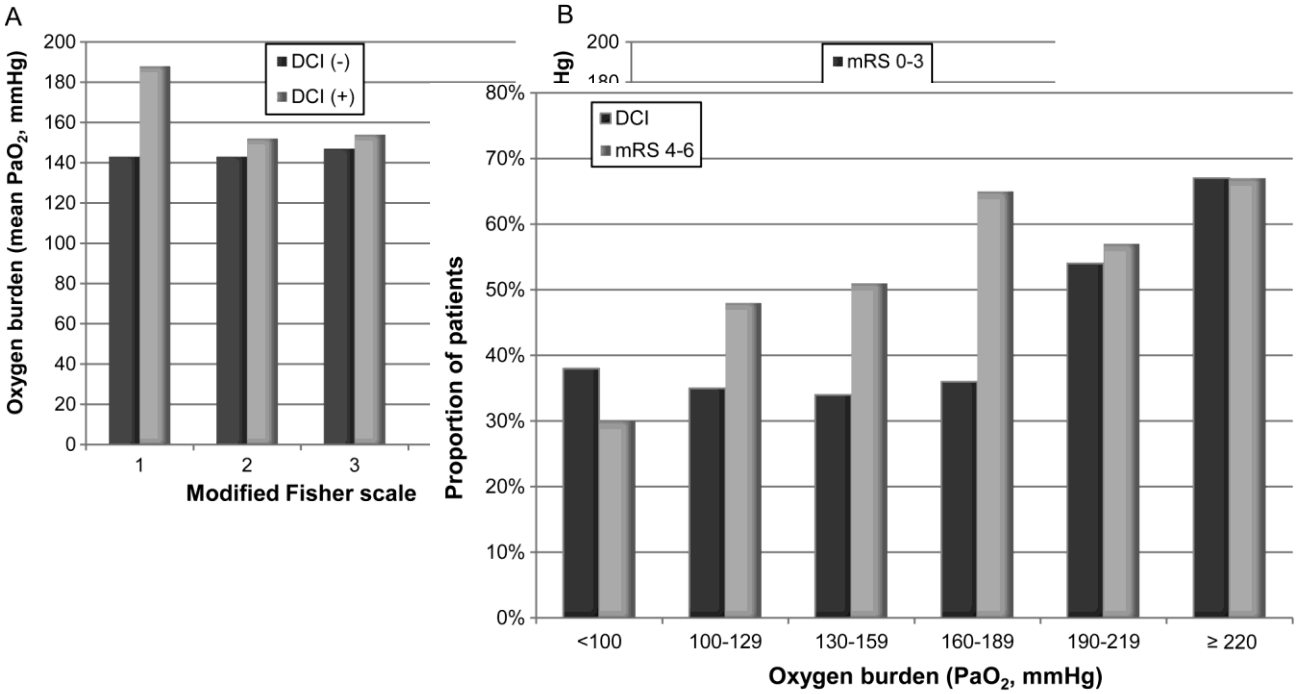
Kurtz, Neurocrit Care 2015

Oxygen – friend or foe?



Jeon et al, JNNP 2014

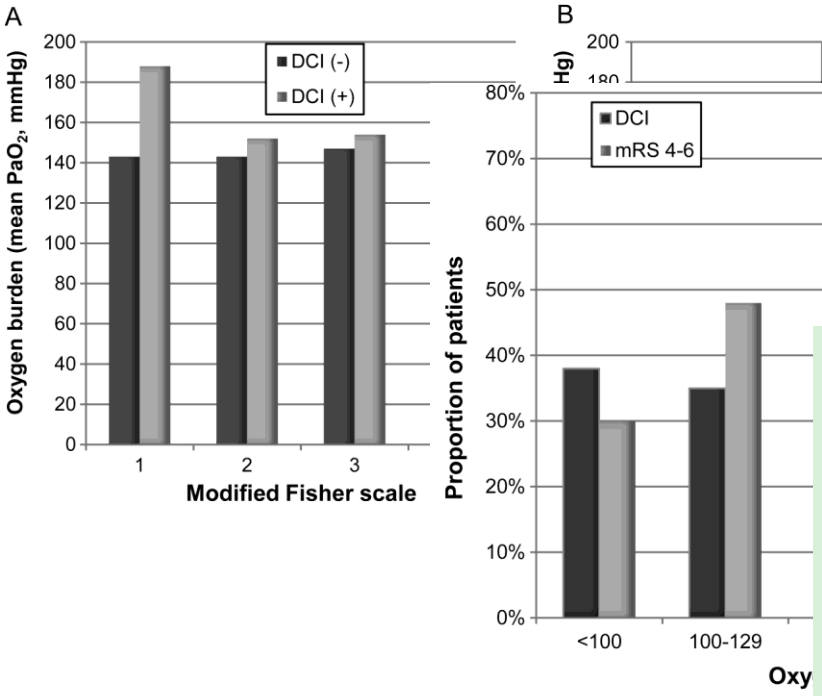
Oxygen – friend or foe?



No. of patients						
DCI (-)	8	44	55	32	12	4
DCI (+)	5	24	28	18	14	8
mRS 0-3	7	29	33	13	9	3
mRS 4-6	3	27	35	25	12	6

Jeon et al, JNNP 2014

Oxygen – friend or foe?



No. of patients		
DCI (-)	8	44
DCI (+)	5	24
mRS 0-3	7	29
mRS 4-6	3	27

Table 3 Factors associated with poor outcome

	Univariable analysis OR (95% CI)	Multivariable analysis OR (95% CI)
Age, years	1.04 (1.02 to 1.06)	1.05 (1.02 to 1.08)
Hunt–Hess grade	1.78 (1.31 to 2.43)	1.74 (1.13 to 2.68)
Aneurysm size, mm	1.08 (1.02 to 1.15)	1.08 (1.01 to 1.16)
APACHE II score	1.07 (1.03 to 1.12)	
Rebleeding	3.07 (1.31 to 7.22)	3.06 (1.09 to 8.64)
Global cerebral oedema, follow-up CT	3.26 (1.66 to 6.42)	
Pneumonia and/or pulmonary oedema	2.48 (1.35 to 4.58)	
Sepsis	2.39 (1.14 to 5.03)	
Exposure to hyperoxia	1.78 (0.92 to 3.44)	2.30 (1.03 to 5.12)

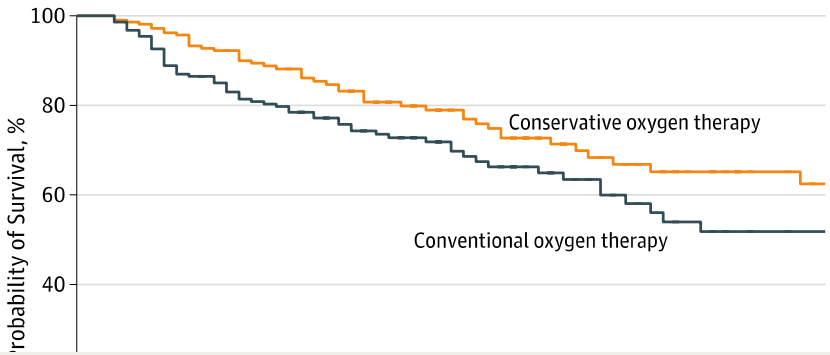
APACHE II, Acute Physiology and Chronic Health Evaluation II.

Only systemic, no tissue oxygenation monitoring in this study

Jeon et al, JNNP 2014

Increasing F_iO_2? - The Oxygen ICU study

Figure 2. Probability of Survival From Study Inclusion (Day 0) Through Day 60 for Patients in the Conservative and Conventional Oxygen Strategy Groups



	Oxygen Therapy, No. (%)			
	Conservative (n = 216)	Conventional (n = 218)	Absolute Risk Reduction (95% CI)	*P* Value
Primary outcome				
ICU mortality	25 (11.6)	44 (20.2)	0.086 (0.017-0.150)	.01
Secondary outcomes				
Shock	8 (3.7)	23 (10.6)	0.068 (0.020-0.120)	.006
Liver failure	4 (1.9)	14 (6.4)	0.046 (0.008-0.088)	.02
Bacteremia	11 (5.1)	22 (10.1)	0.050 (0.000-0.090)	.049

p_aO_2 70-100 mmHg
(= conservative)

vs.

p_aO_2 100-150 mmHg
(= conventional)

Patients discharged alive from the hospital were considered to have survived, and their median follow-up was 22 days for the conservative group (interquartile range, 13-37) and 24 days for the conventional group (interquartile range, 15-35).

Girardis, Jama 2016

$p_{br}O_2$ and outcome after SAH

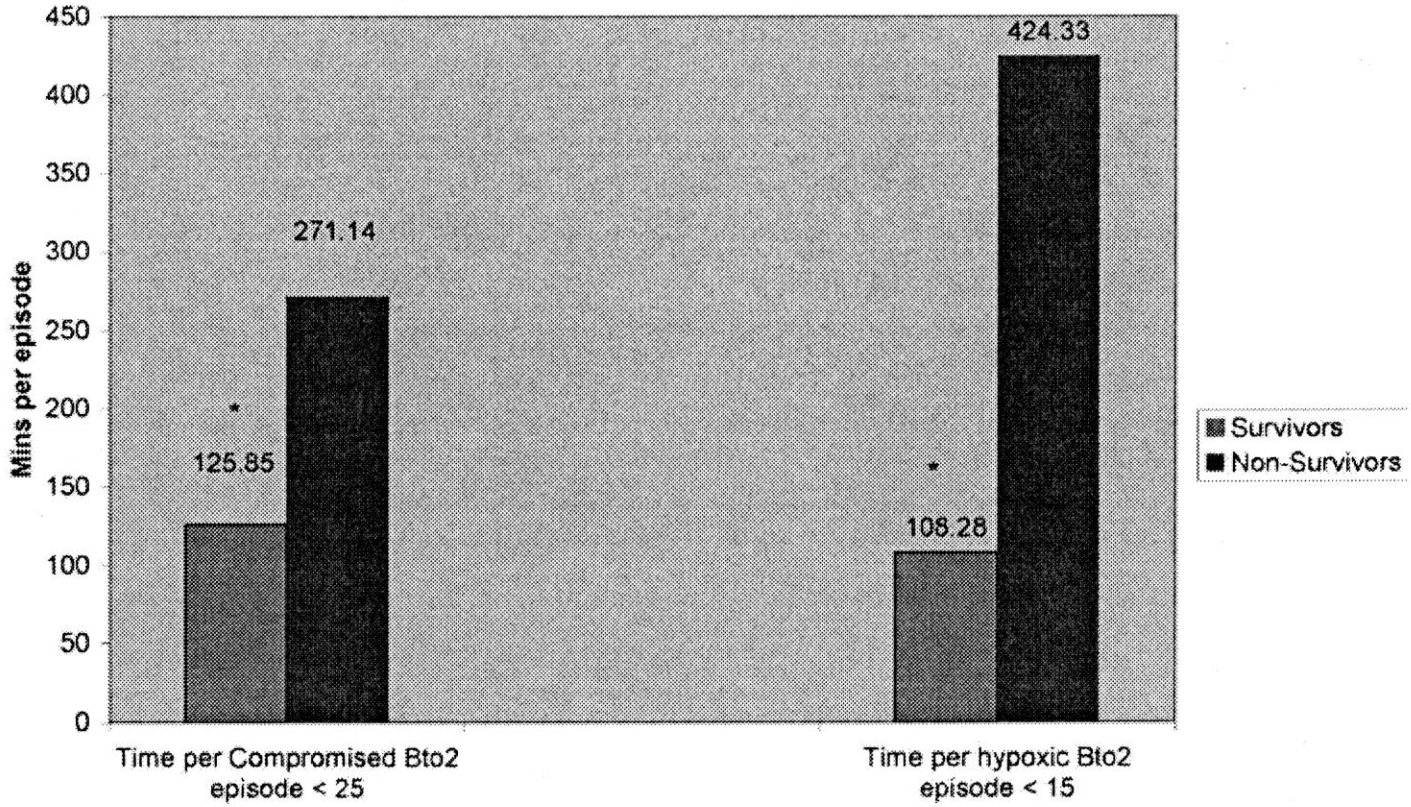
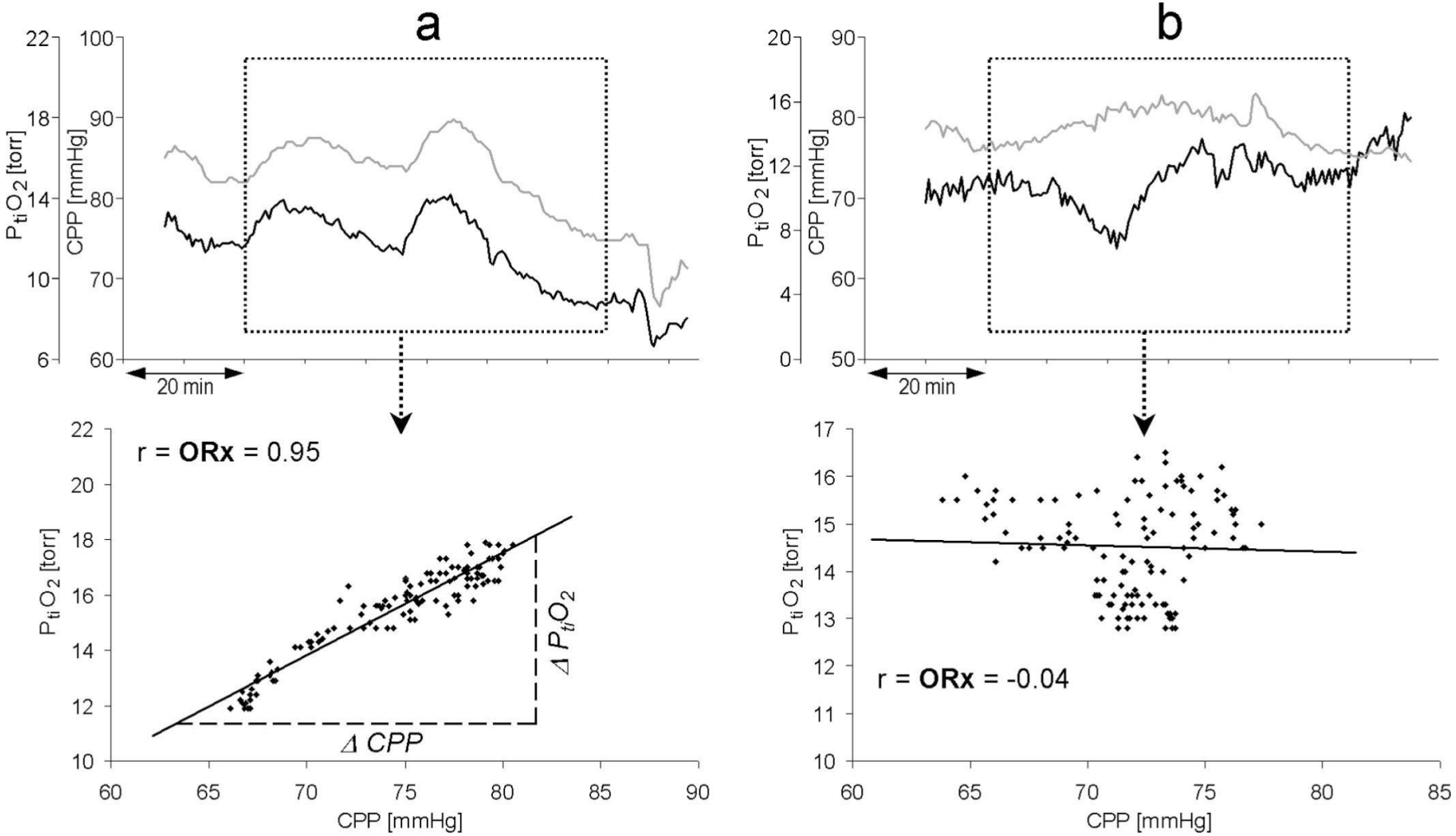


FIG. 2. Histogram illustrating relationship between survival after SAH and mean time of compromised cerebral oxygenation (< 25 mm Hg) and cerebral hypoxia (< 15 mm Hg). *p < 0.05.

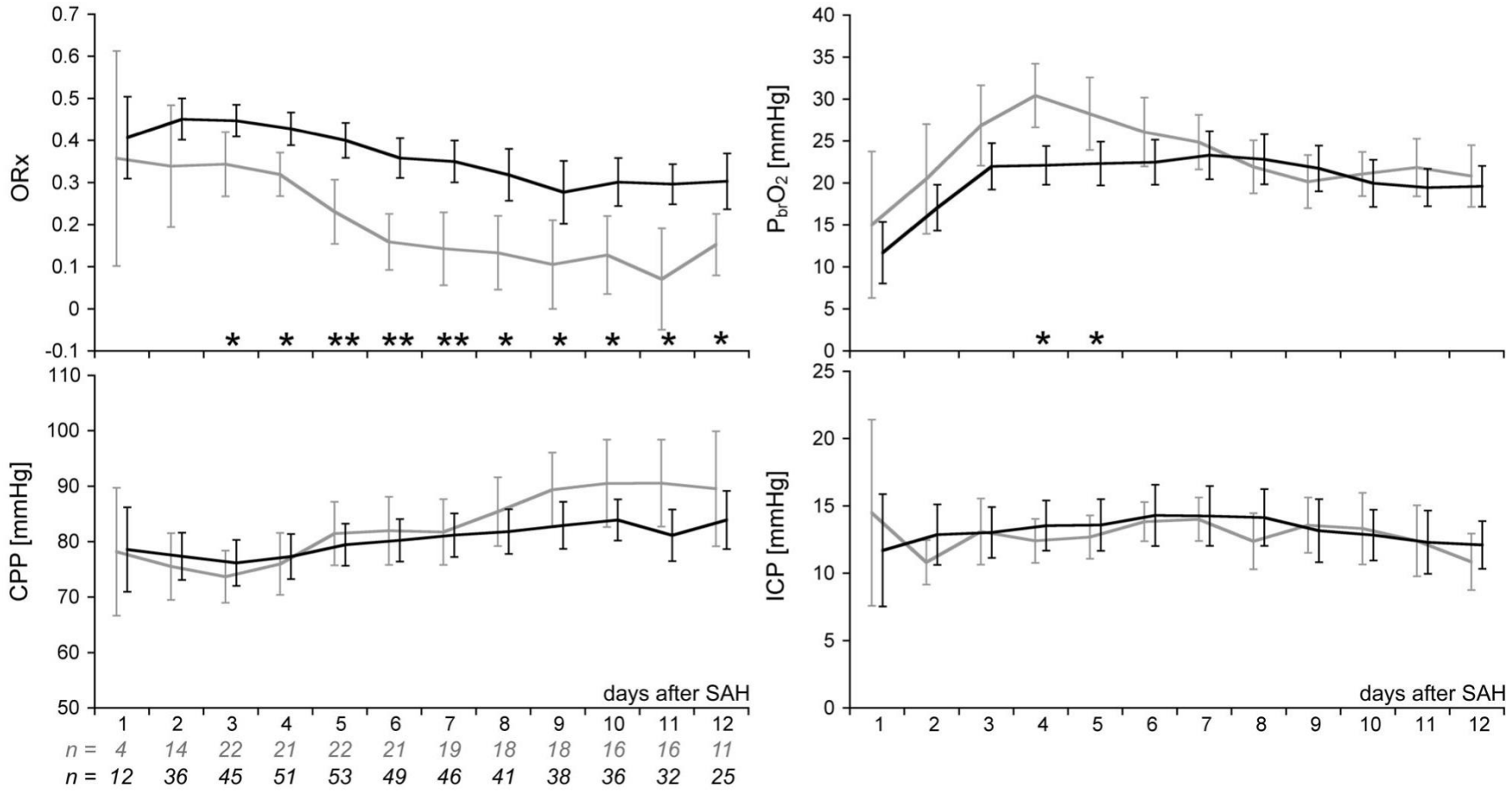
Ramakrishna, JNS 2008

Determination of the *Oxygen Reactivity Index* ORx



Jaeger, CCM 2006

ORx, ICP, CPP und $p_{br}O_2$ vs outcome after SAH



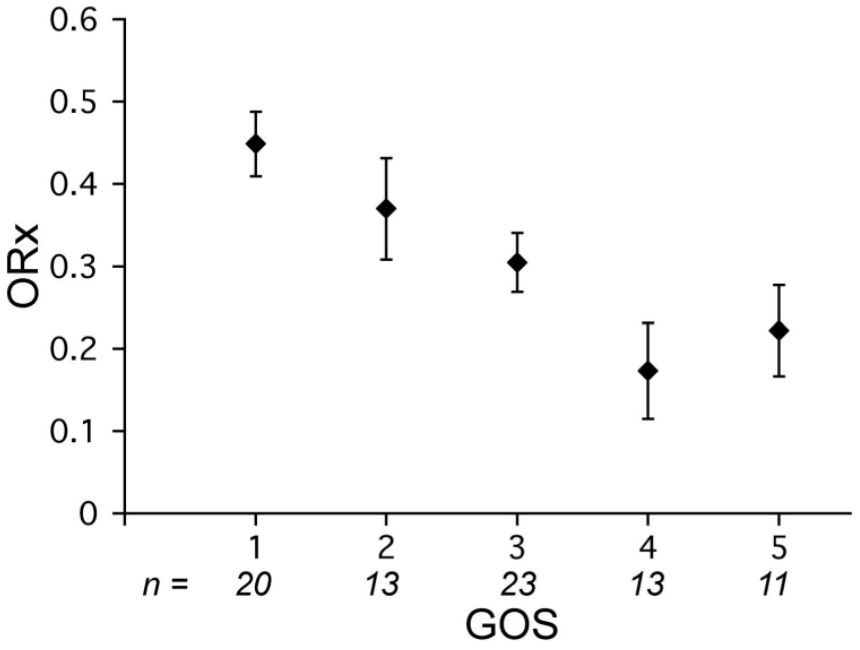
Jaeger, Stroke 2012

Outcome after SAH – prognostic factors from multimodal monitoring

Table 2. Neuromonitoring Characteristics of Favorable (GOS 4–5) and Unfavorable (GOS 1–3) Outcome Groups*

Variable	Favorable (n=24)	Unfavorable (n=56)	*P* Value
ORx	0.19 (±0.10)	0.37 (±0.11)	<0.001
CPP, mm Hg	83.5 (±13.8)	80.4 (±11.6)	0.70
$P_{br}O_2$, mm Hg	24.9 (±6.6)	21.8 (±6.3)	0.048
ICP, mm Hg	12.7 (±3.6)	13.4 (±6.0)	0.98
Start of monitoring after SAH, h	50.8 (±40.9)	47.8 (±36.5)	0.55
End of monitoring after SAH, h	240.8 (±68.9)	236.0 (±64.4)	0.62
Time of valid monitoring, h	164.8 (±55.5)	164.8 (±61.9)	0.90

Values are mean±SD; *P* for Mann-Whitney *U* test.



Jaeger, Stroke 2012

Cerebro-spinal fluid after SAH

Klimo et al, JNS 2004

Lumbar drainage after clipping

Outcome	Group		p Value
	LD	Control	
no. of patients	81	86	
primary measure			
clinical vasospasm (%)	14 (17)	44 (51)	<0.001
angioplasty/papaverine (%)	14 (17)	39 (45)	0.001
vasospasm-related infarction (%)	6 (7)	23 (27)	0.008
disposition (%)			0.002
home	44 (54)	22 (25)	
inpatient rehabilitation	26 (32)	41 (48)	
extended care facility	9 (11)	19 (22)	
death	2 (3)	4 (5)	
GOS score (%)*			<0.001
1	2 (3)	4 (5)	
2	0	4 (5)	
3	13 (16)	31 (40)	
4	8 (10)	12 (15)	
5	56 (71)	27 (35)	
secondary measure			
LOS (mean no. of days)			
ICU	13	16	0.0077
hospital	17	21	0.0014
shunt (%)	19 (24)	28 (36)	0.145

Klimo et al, JNS 2004

Data on lumbar drains after aneurysmal SAH

- Published retrospective works are in favor of lumbar drains

But….

- Patient distribution not fairly balanced between treatment groups
- Retrospective design
- No data on the amount of drainage (5-10-… ml/h)
- Long term outcome not documented

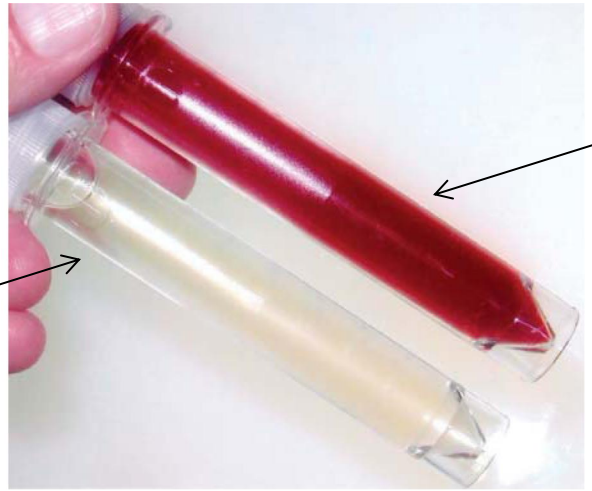
- Prospective data not supportive
  - predominantly good grade patients
    (in contrast to more poor-grade patients in retrospective trials)
  - underpowered for effect size
    (Al-Tamimi et al, Stroke 2012)

Wolf, S.: Curr Op Crit Care 2015

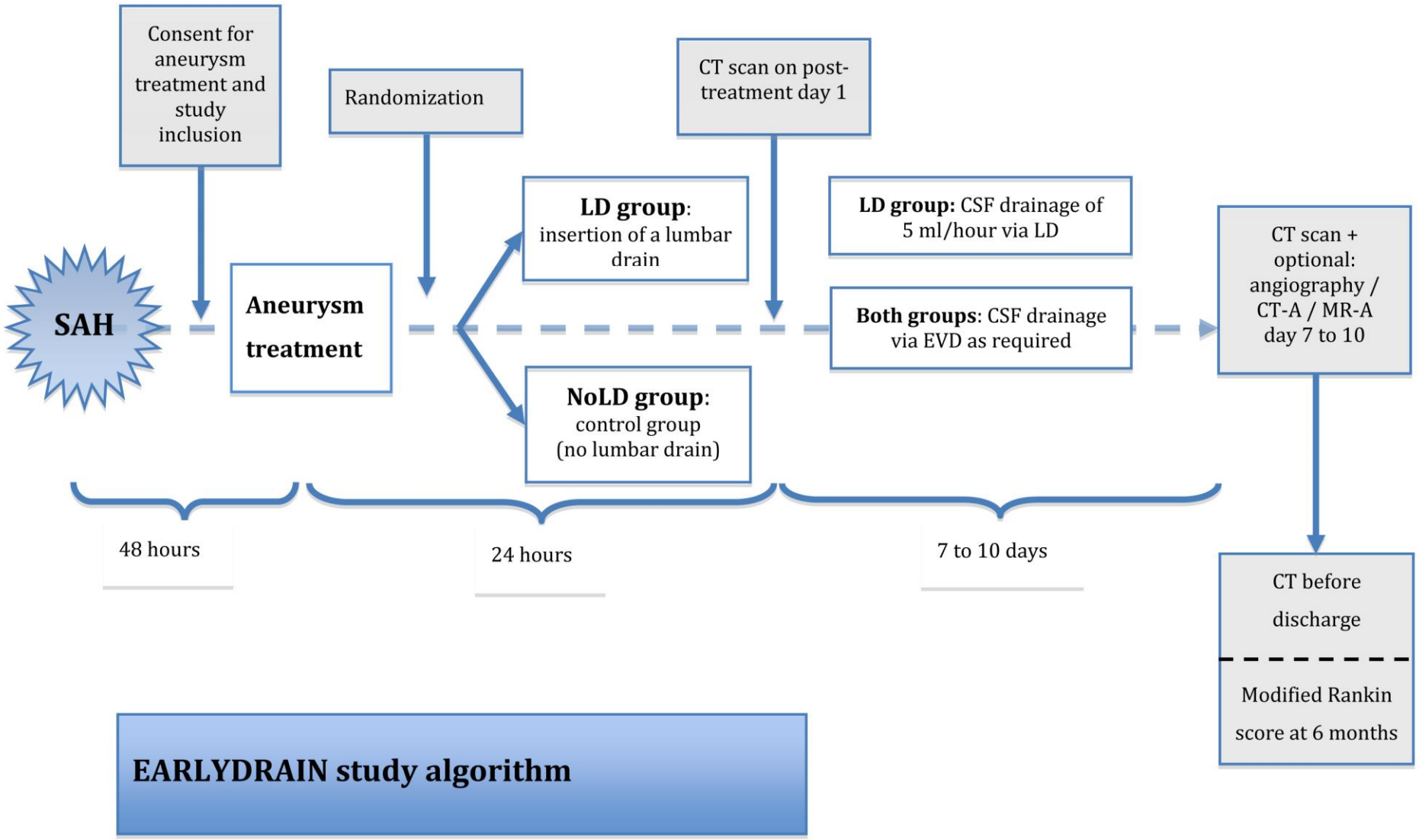
EARLYDRAIN – questions asked

Does an early lumbar CSF drainage improve clinical outcome after aneurysmal subarachnoid hemorrhage?

Does the early lumbar CSF drainage decrease the incidence of cerebral vasospasm after aneurysmal SAH?



Bardutzky et al., Trials 2011



Bardutzky et al., Trials 2011

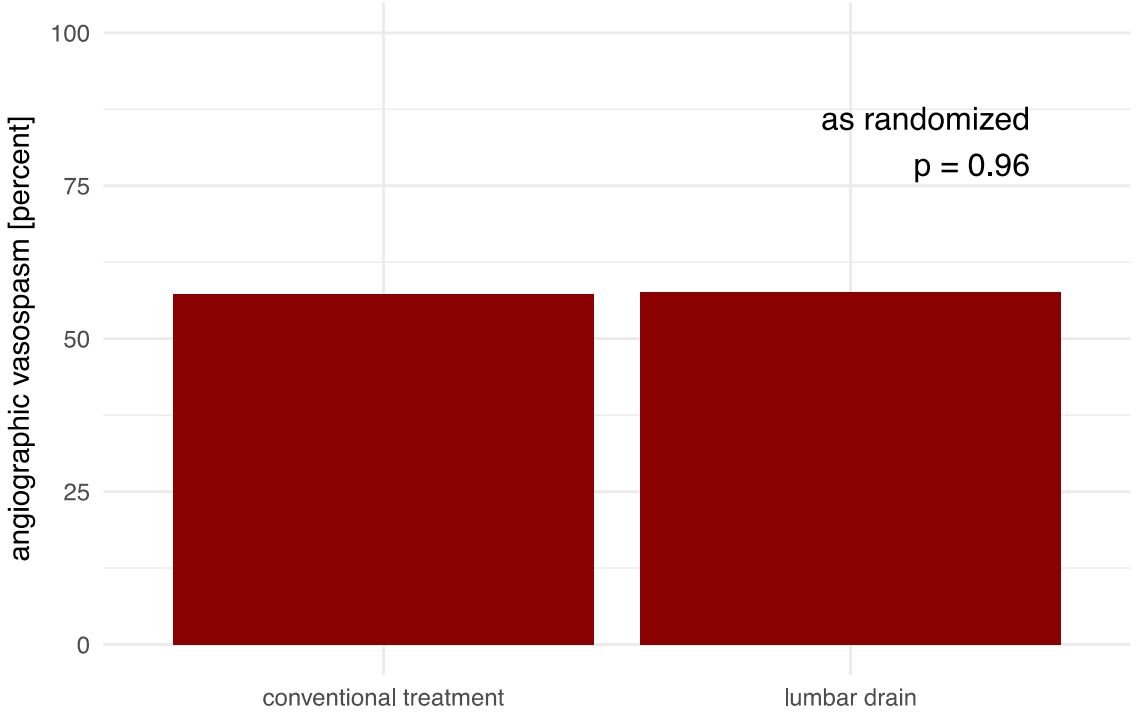
Patient characteristics I – *"as randomized"* data

	LD	No LD
N	145 (100%)	145 (100%)
Age	54 (48 - 63)	56 (47 - 65)
female Sex	98 (68%)	99 (68%)
Hunt-Hess grade		
1	28 (19%)	25 (17%)
2	41 (28%)	29 (20%)
3	25 (17%)	34 (23%)
4	20 (14%)	24 (17%)
5	30 (21%)	33 (23%)
missing data	1 (1%)	0 (0%)

Patient characteristics II – *"as randomized"* data

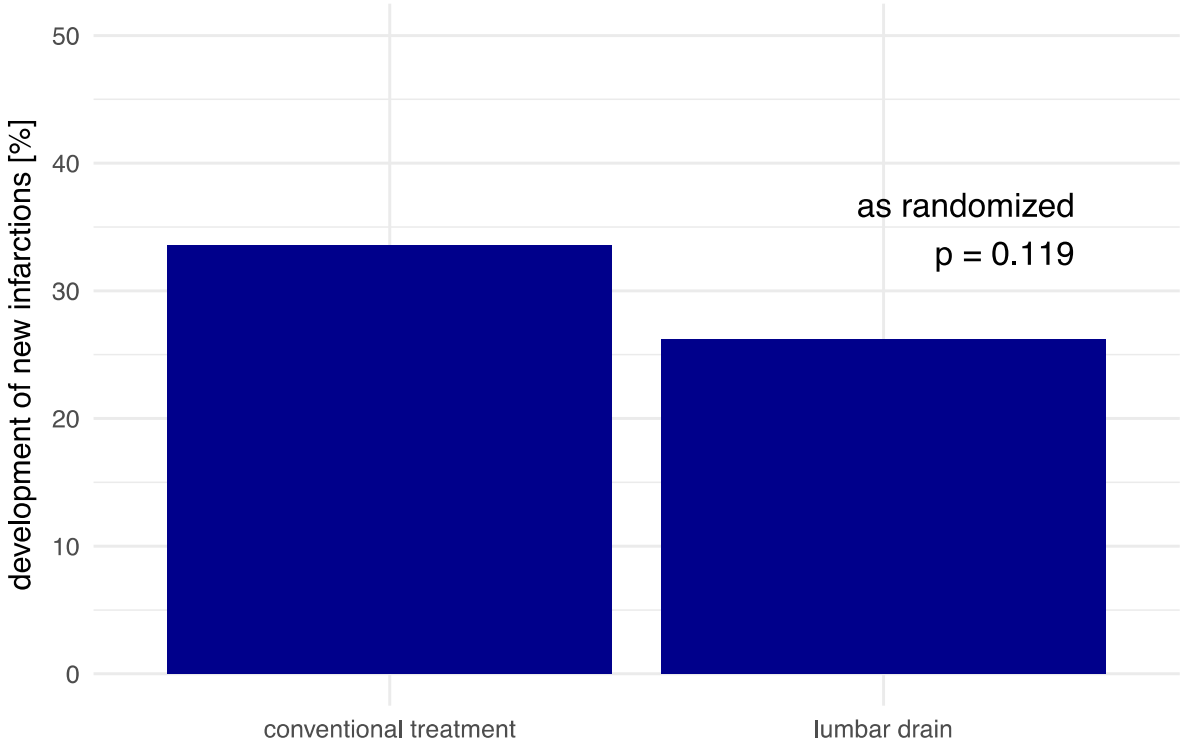
	LD	No LD
modified Fisher grade		
2 – thin SAH	6 (4%)	2 (1%)
3a – thick SAH w/o IVH	30 (21%)	47 (32%)
3b – thick SAH with IVH	53 (37%)	45 (31%)
4a – SAH + ICH w/o IV	18 (12%)	11 (8%)
4b – SAH + ICH with IVH	37 (26%)	40 (28%)
missing data	1 (1%)	0 (0%)
Number of Aneurysms		
1	100 (69%)	113 (78%)
2	33 (23%)	21 (14%)
3	8 (6%)	6 (4%)
>3	4 (3%)	5 (3%)
Aneurysm treatment		
clipping	77 (53%)	70 (48%)
coiling	65 (45%)	73 (50%)
missing data	3 (2%)	2 (1%)

Secondary endpoint: angiographic vasospasm (“as randomized” data)



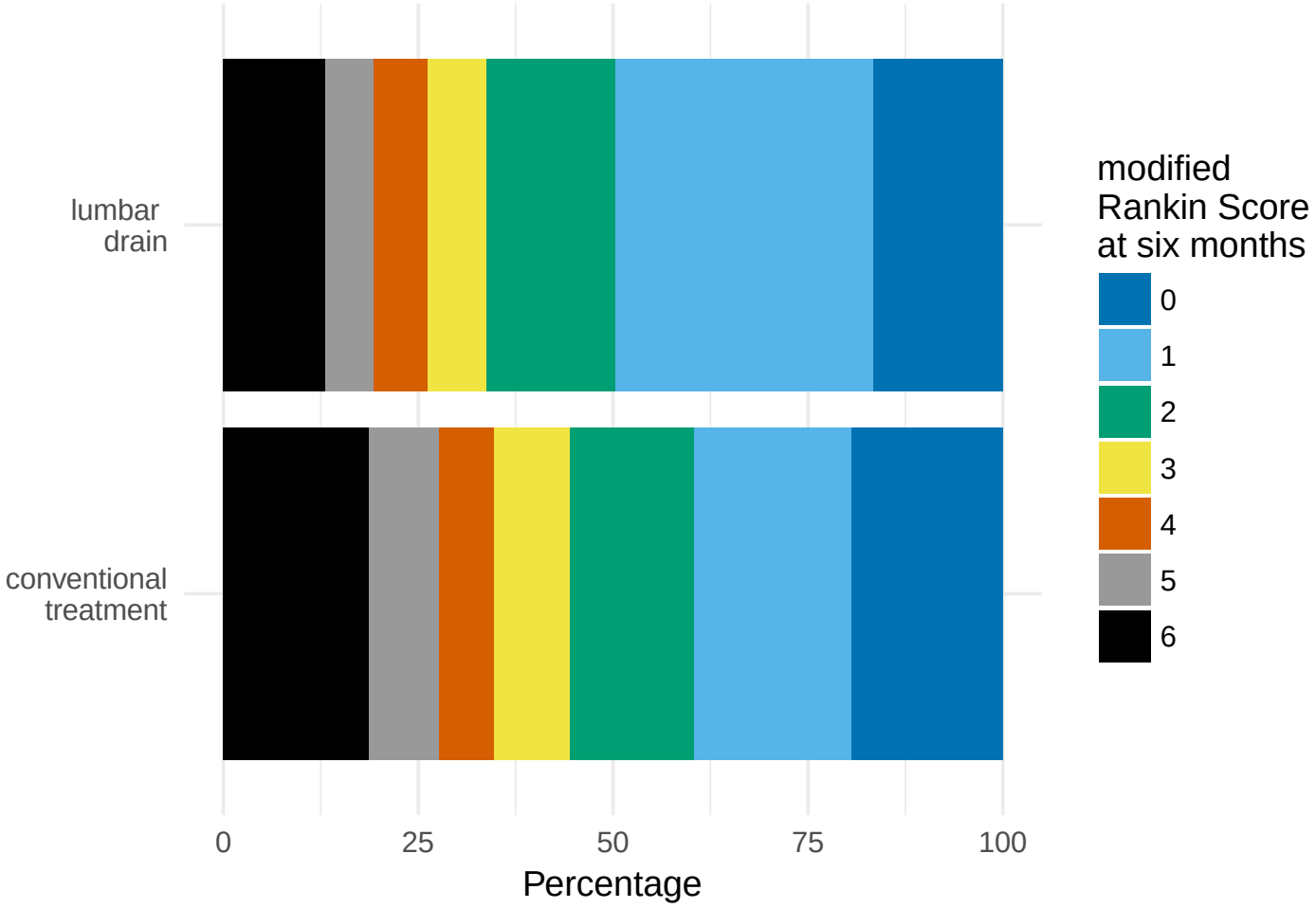
Rate of angiographic vasospasm: 57%
CTA or DSA (6% MR angiography) on clinical suspicion or as routine on day 7-10

Secondary endpoint: new infarction at discharge (“as randomized” data)



Overall rate of new infarction: 30%

Outcome – "*as randomized*" data



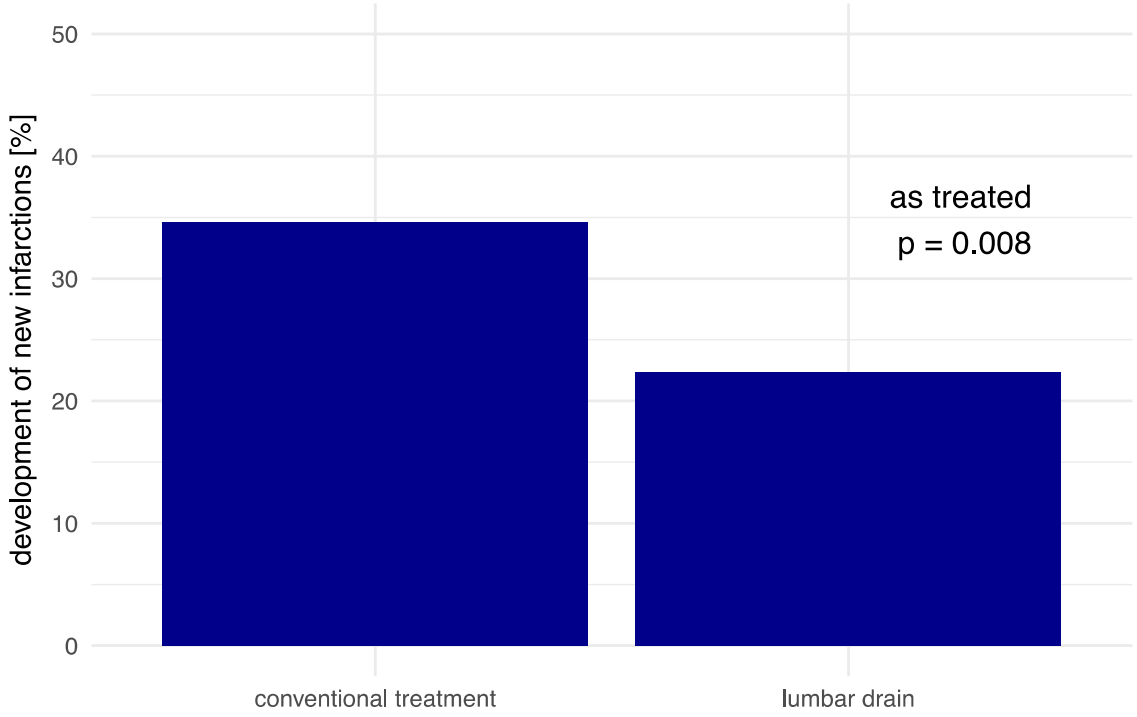
6-months outcome data from 289 patients

Why is there a difference between "*as randomized*" vs "*as treated*"?

Main reasons for protocol deviations were (decreasing order):

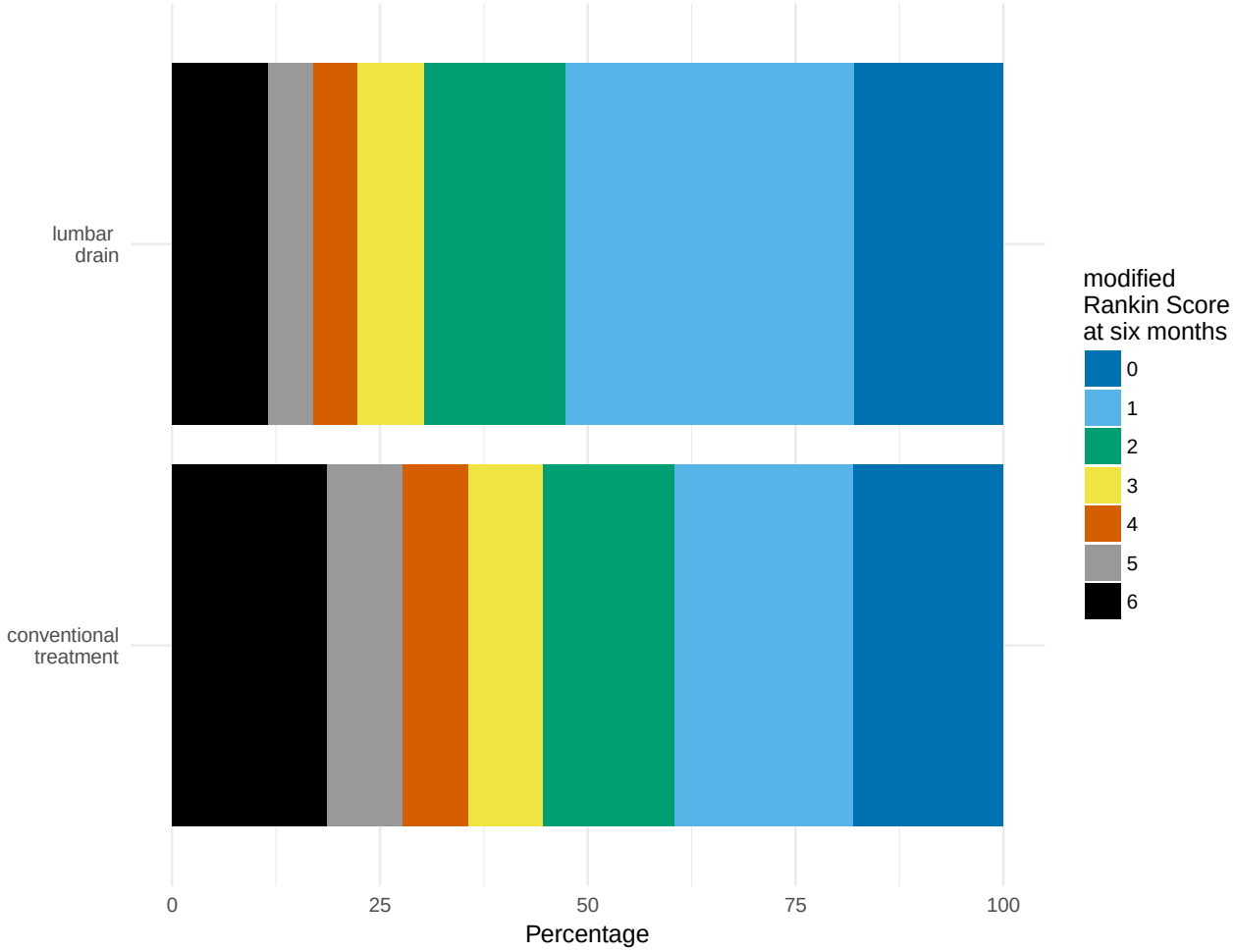
- Hardware failure
- Safety concerns in the LD group
- Requirement of full anticoagulation after coiling
  (therefore no placement of LD possible)
- Assignment error
- Request of the consulting neurologist for treatment with a lumbar drain

Secondary endpoint: new infarction at discharge ("*as treated*" data)



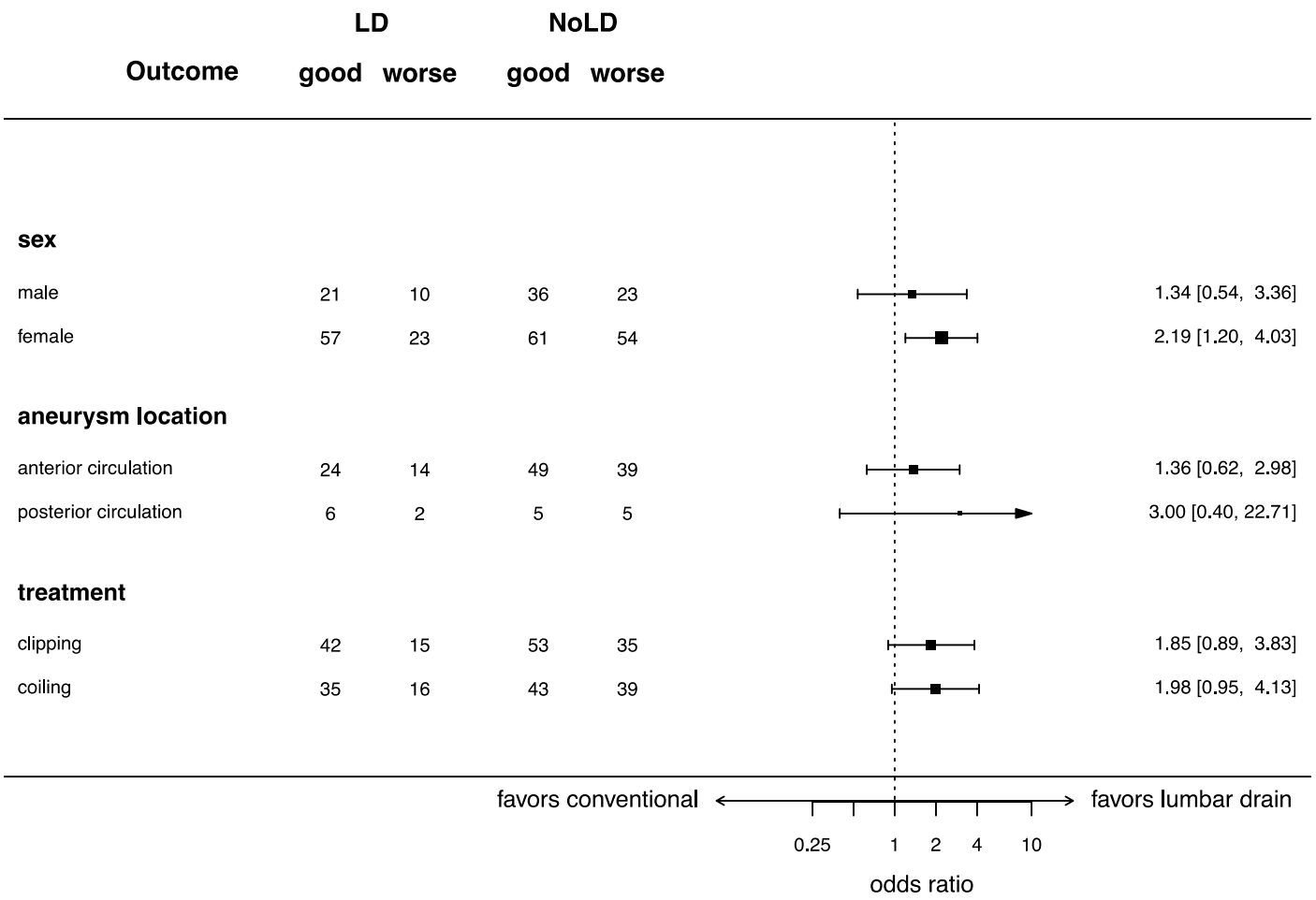
Overall rate of new infarction: 30%

Outcome – *"as treated" data*



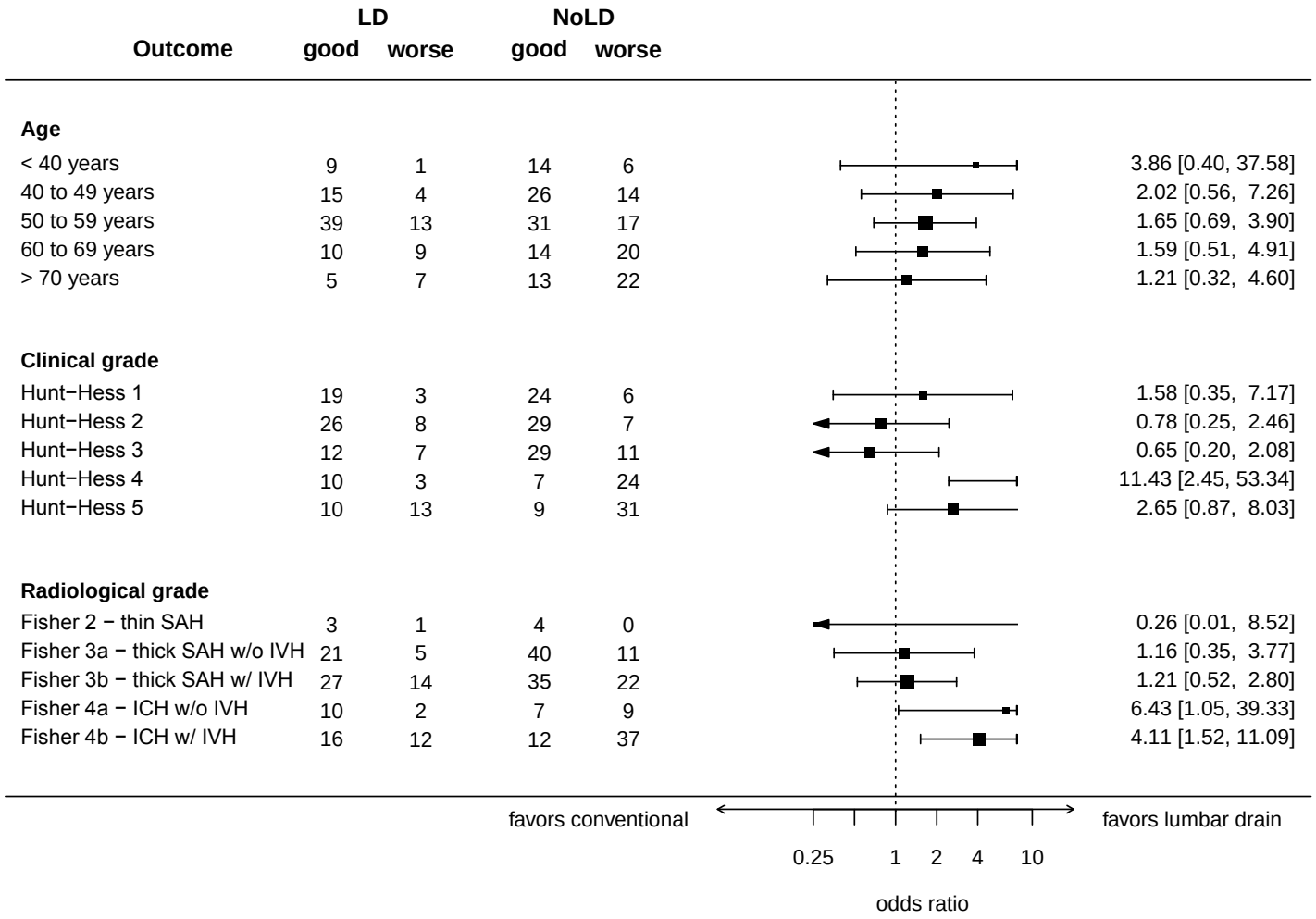
6-months outcome data from 289 patients

Who may benefit? (subgroup analysis – *"as treated" data)*



based on 6-months outcome data from 289 patients
good outcome: mRS 0, 1 or 2

Who may benefit? (subgroup analysis – *"as treated" data)*



based on 6-months outcome data from 289 patients
good outcome: mRS 0, 1 or 2

Summary – ICU treatment after aneurysmal SAH

- Nimodipine: still in use, class I evidence

- Monitoring: may facilitate recognition of unfortunate effects in poor-grade patients
- Use dedicated software for data acquisition
- Combine different methods (= *multimodal monitoring*), or a second $p_{bt}O_2$ probe
- Perfusion CT is your friend. Repeat it!

- Lumbar drains: promising in younger, more severely affected patients

- $p_{bt}O_2$ monitoring: *number needed to treat* unknown so far
  (= *we need further research – please listen, dear* RAUMEDIC *people!*)

just in case: stefan.wolf@charite.de