Autonomic monitoring

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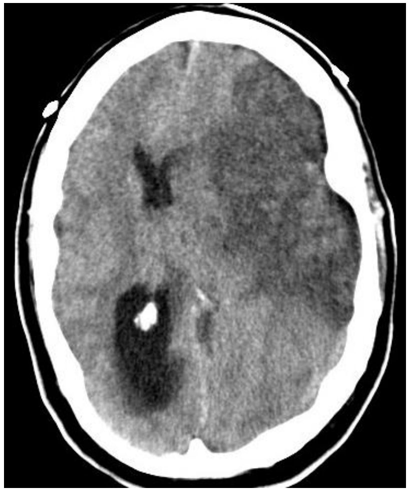
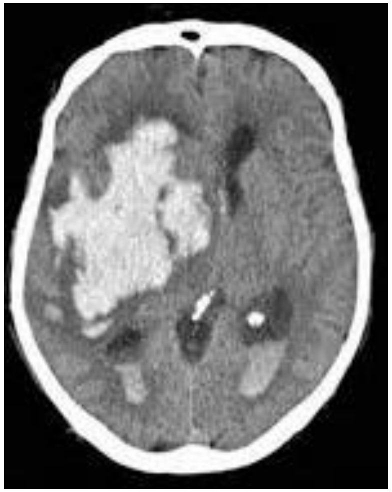
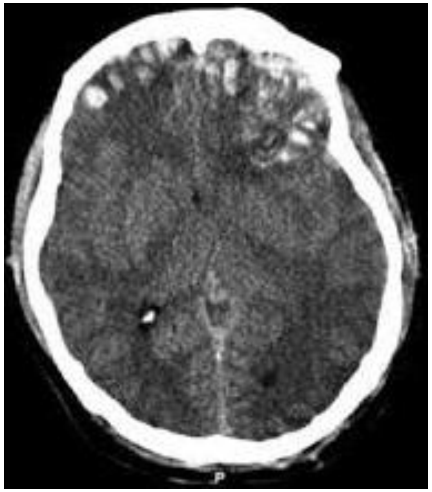
Agenda

- Meaning of ANS in acute brain injury
- Studies using ICM+ for autonomic assessment

Types of brain injury

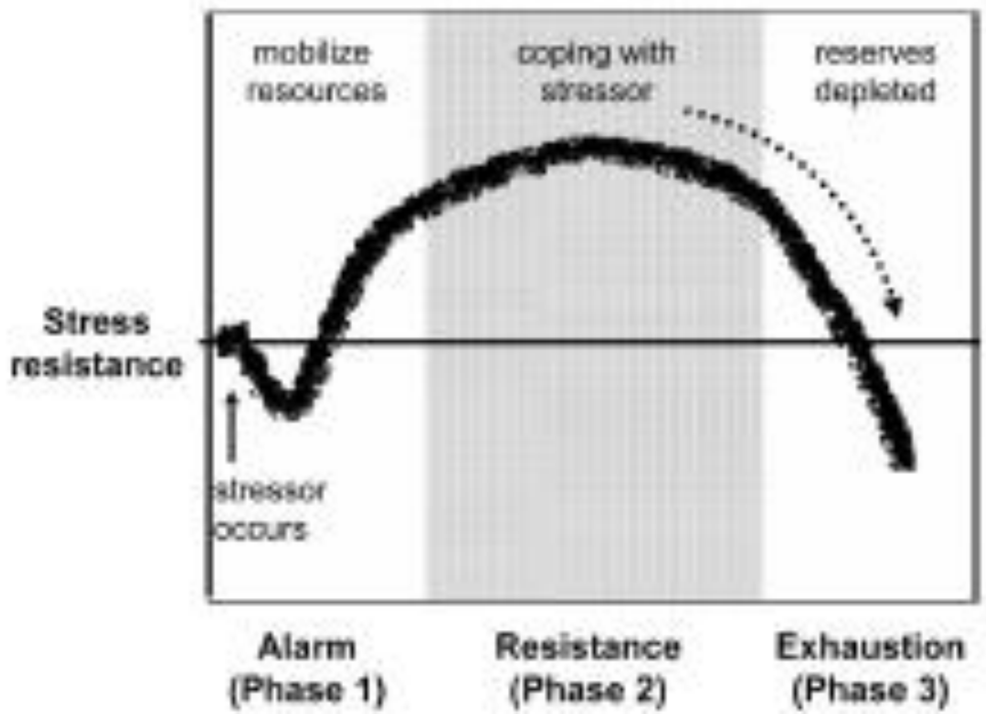
Ischemic stroke	ICH +/- IVH	SAH	TBI
			

Stress and stress-reaction

• Stress is everything what disturbs or endangers *homeostasis*

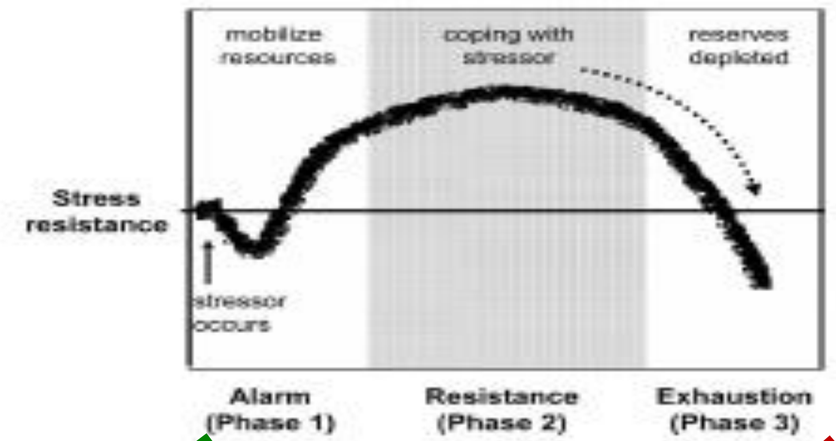
• ANS, hypothalamic-pituitary-adrenal axis, cardiovascular, metabolic, and immune systems try to maintain "stability through change"

•Adaptive stress-reaction
•Maladaptive stress-reaction



Brame, CCM 2010

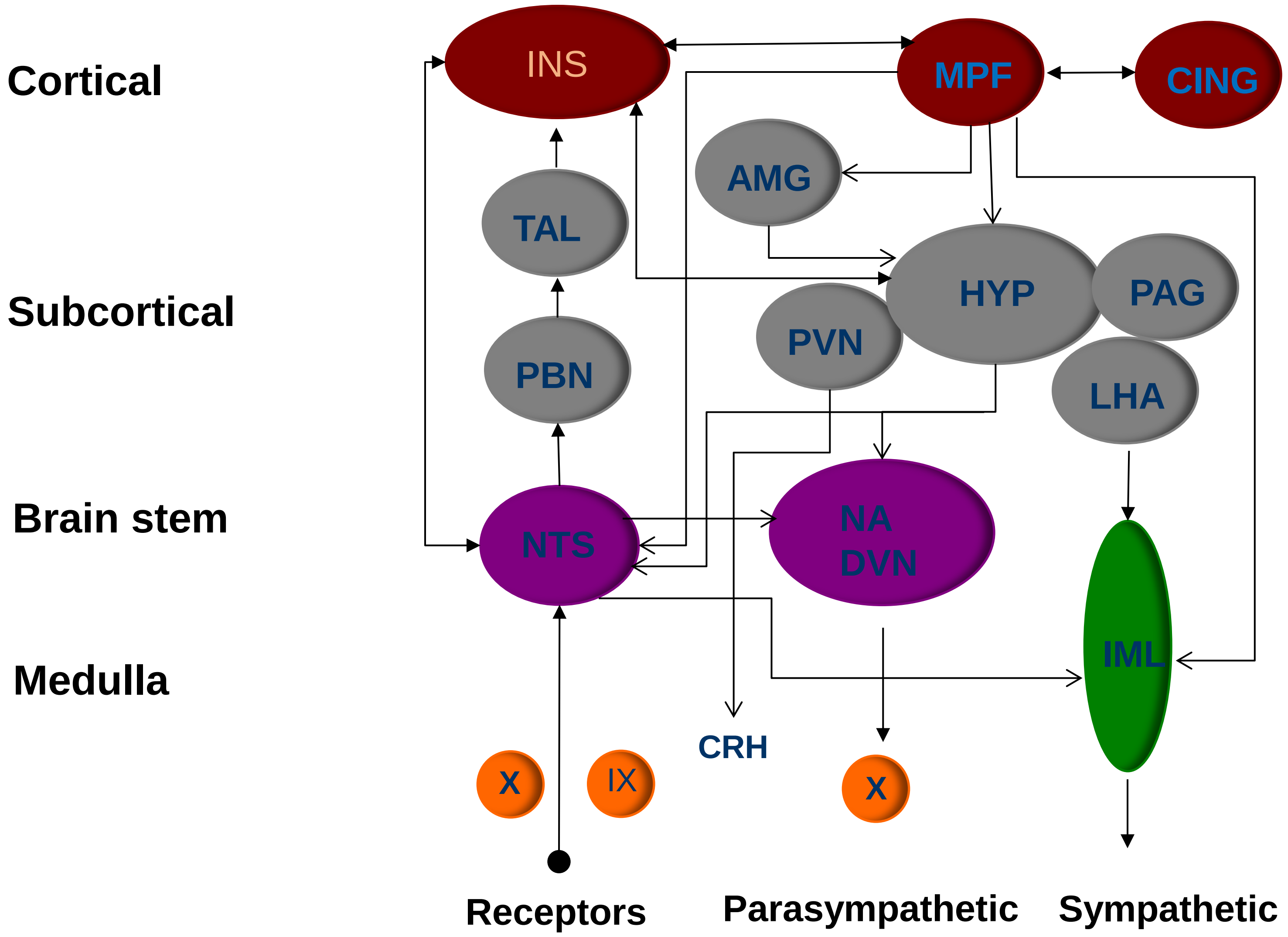
Stress response: a major contributor to harm



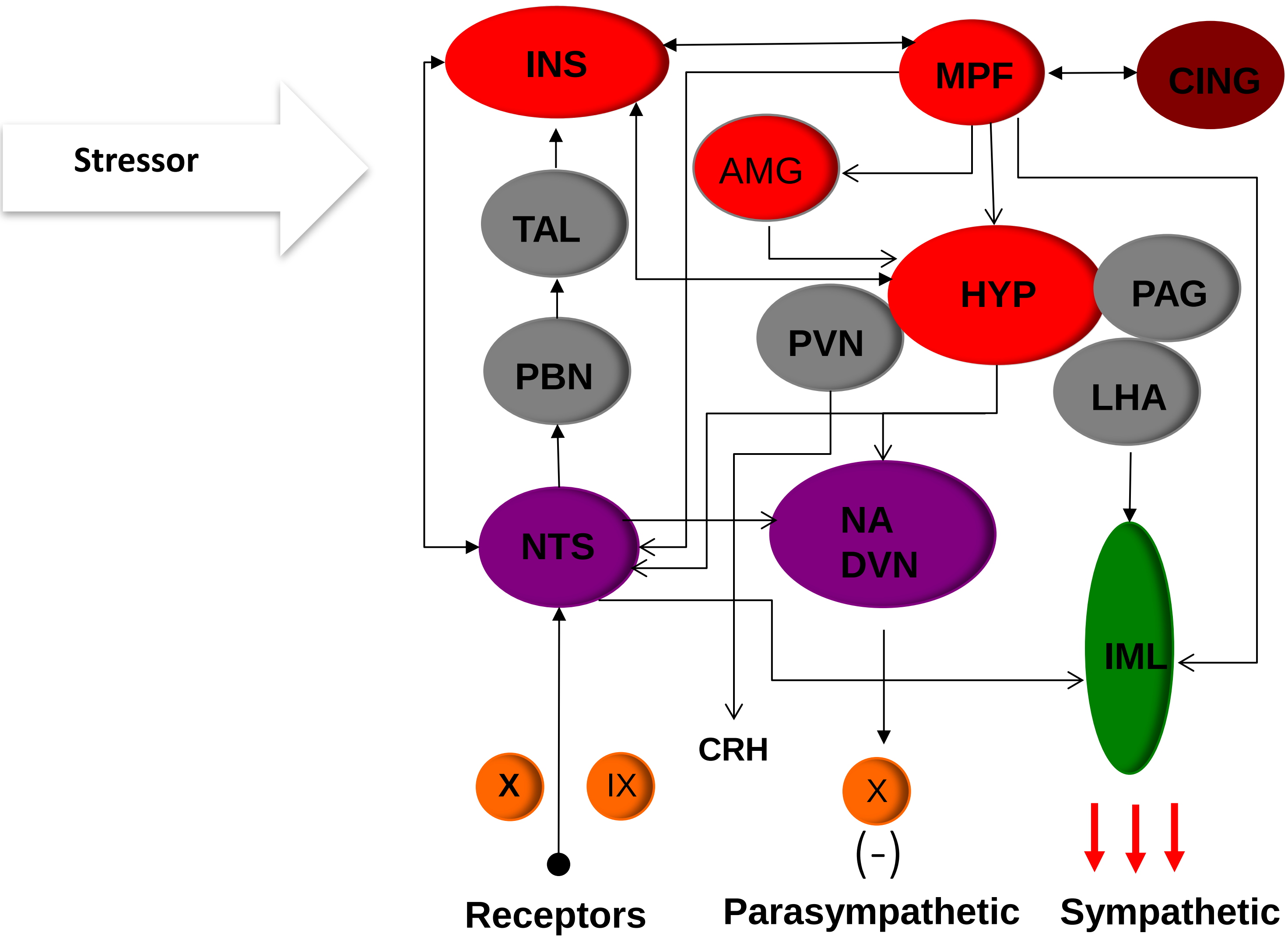
Fight-or-flight-or-freeze reaction
Adrenaline, Cortisole ↑
Glycogenolysis
Blood pressure centralisation
BP, HF ↑
Bronchodilation
Leu, Tr ↑
Thrombogenisity ↑

Arrhytmiae
Myocardial necrosis
Endothelial dysfunction
Insulin resistance, hyperglycemia
Immunodepression
Catabolism, end-organ damage
SIRS, MODS

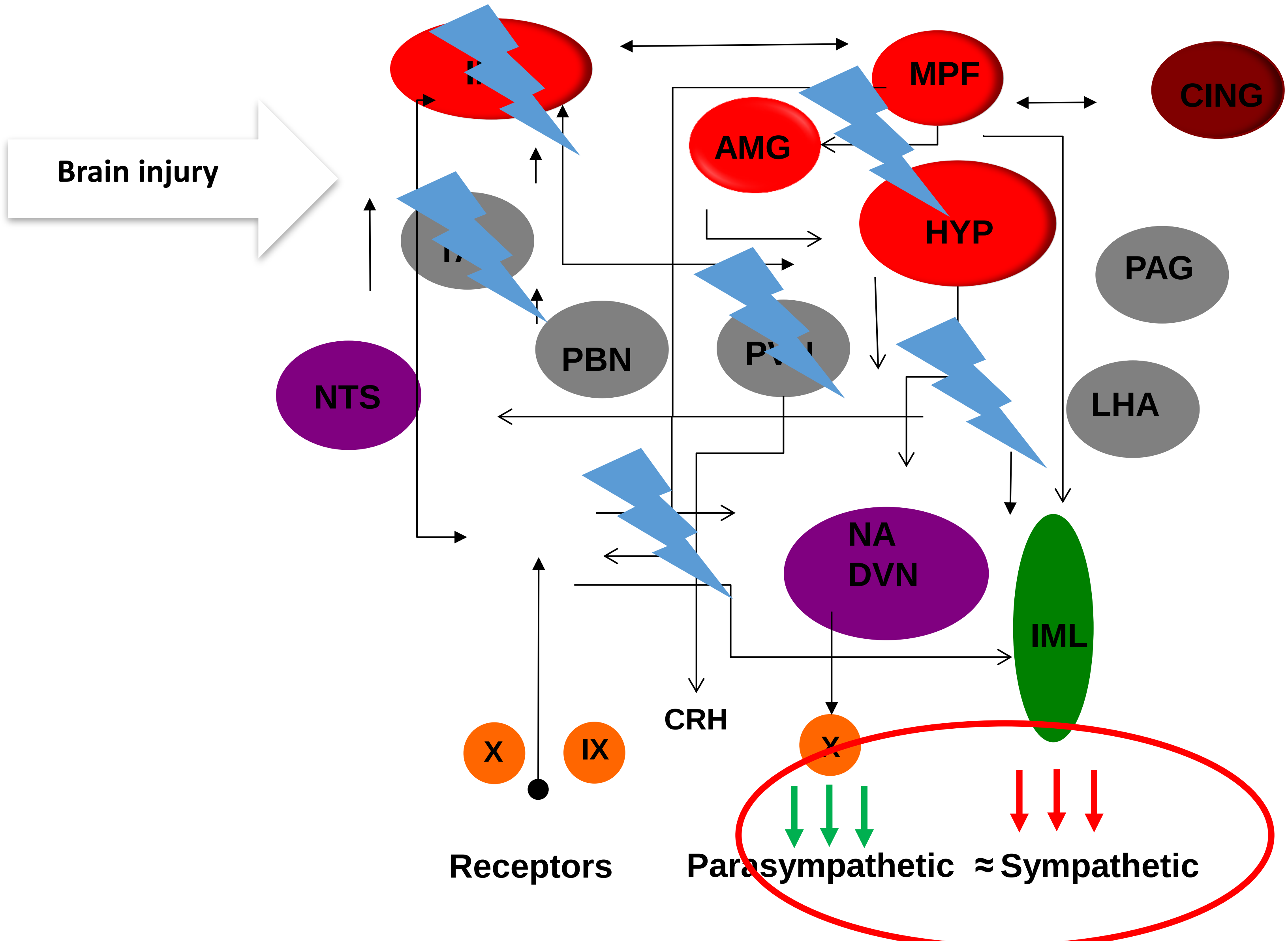
Central autonomic network



Central autonomic network

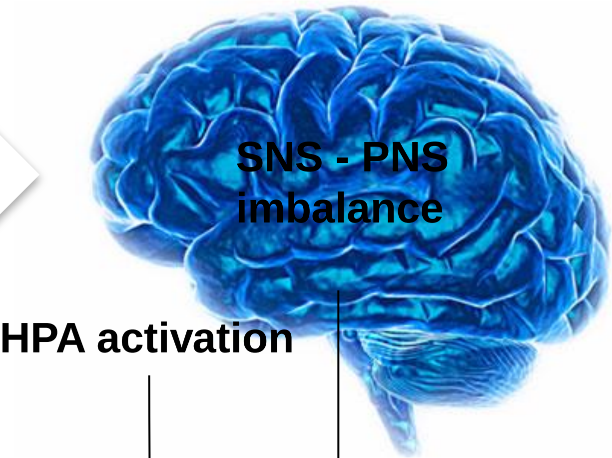


Central autonomic network



Central autonomic disconnection syndrome

Brain injury



HPA activation

Acute-phase response

↑catecholamines, ↑cortisol, ↑ TNFα, ↑ NPY, ↑ IL1, ↑ IL6 ↑ IL10, insuline resistency, ↑ Glu

Ly-Apoptosis
Th1->Th2 cytokines
↓NK activity
↓ Macrophage activity

Immunusupression

Contraction band necrosis
Myocytolysis
Cross-band formation
Subendocardial hemorrhage

Myocardial damage

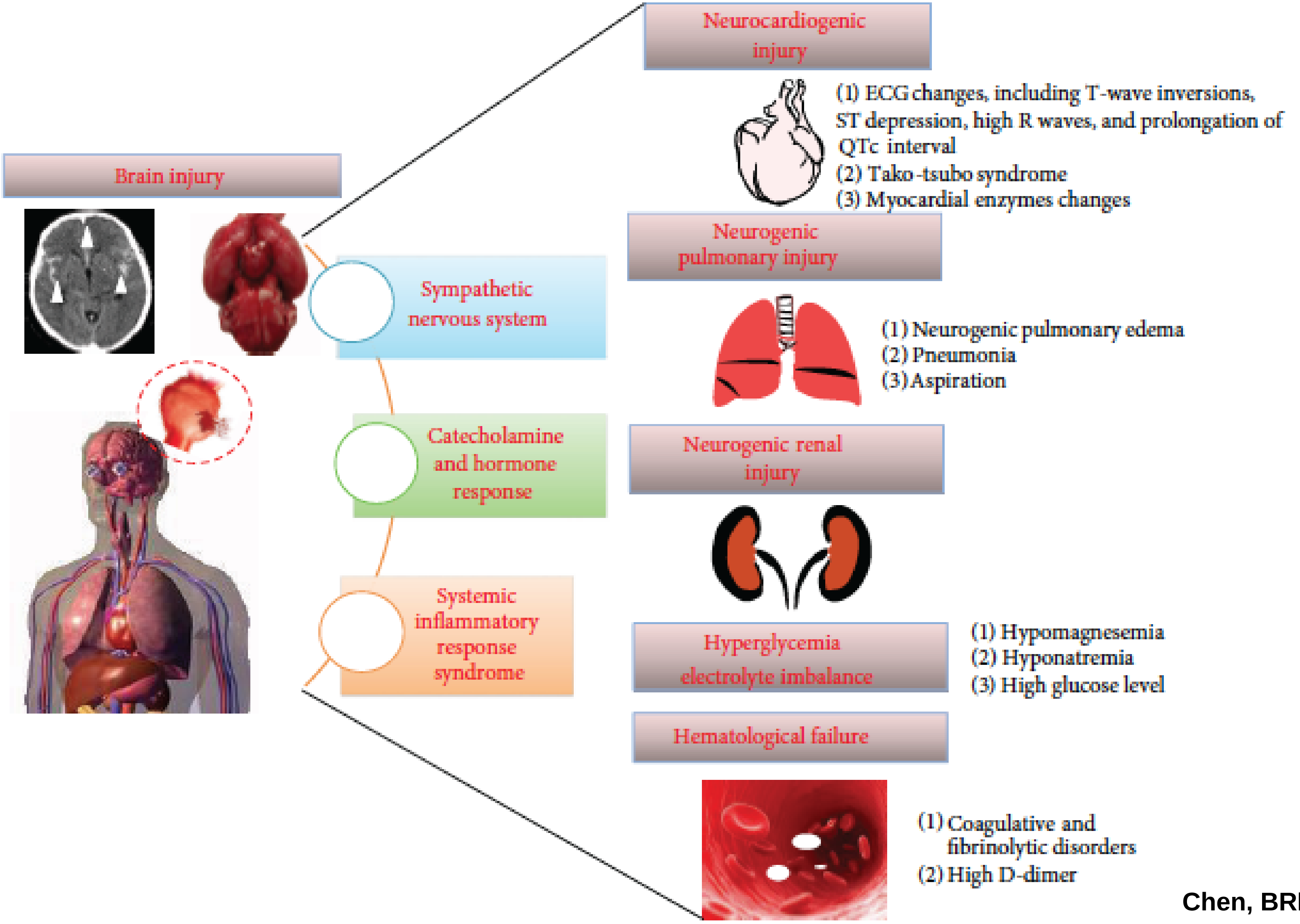
IL 6, syst. immfl.
↑ Vessel permeability
Second hit

NPE

Hypoperfusion
↑ Permeability
Endotoxin
Loc. autonomic Dysreg.

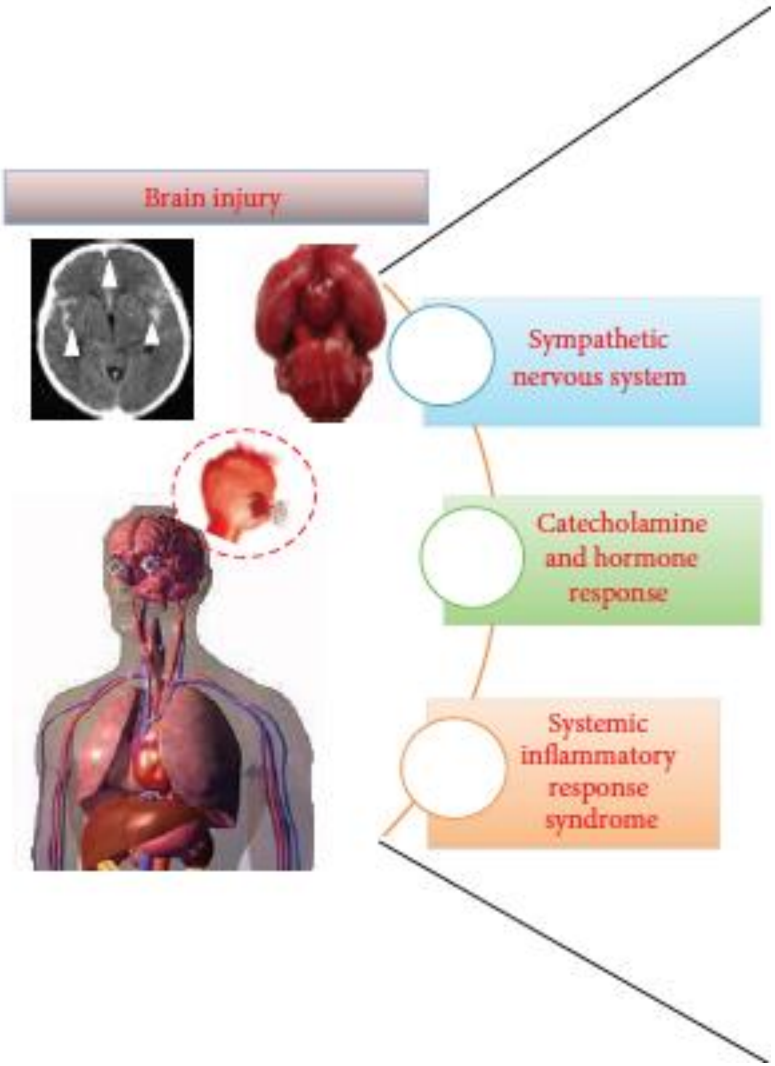
Colon paralysis

Extracerebral effects



Chen, BRI, 2014

Cerebral effects (secondary brain injury)



Vasocontriction
↑ Permeability
Microthrombosis
Hyperglycemia
BBB breakdown

Spleen Tr, systemic IL-1,IL-6, IL-12, TNFalfa
Local inflammation

Immunosupression
Post-stroke autoimune response
Autoimmune inflammation

Hypoperfusion
Baroreflex failure
Impaired autoregulation
Impaired CBF

Surrogates of autonomic activity

cardiac derived
HRV
(SDNN, RMSSD
HF, LF, HF/LF, VLF powers)
BRS
Decelaration capacity
HR turbulence
QT-variability index

HPA derived
AVP, CRH
Cortisol
Catecholamines
Degradation products
Orexin, Urocortins
Copeptin

IS, ICH, IVH, SAB, TBI, GBS, SIRS, MODS, acute MI, HF

↓ Outcome and ↑Mortality
90 days, 6 month, 1 year, 5 years

HRV and BRS in brain injury

IS Colivicchi 2005, Hilz 2011

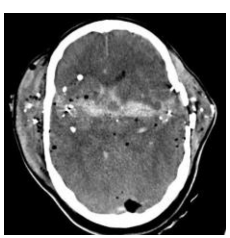
↓ HF pow
↑ LF pow
↑ LF/HF
↓ BRS

ICH Sykora 2008, Sykora 2018

↑ HF pow
↓ LF pow
↓ LF/HF
↓ BRS

SAH Chiu 2012, Chen 2016, Nasr 2018

↑ HF pow
↓ LF pow
↓ LF/HF
↓ BRS



TBI Sykora 2016, Henden 2014, Biswas 2000

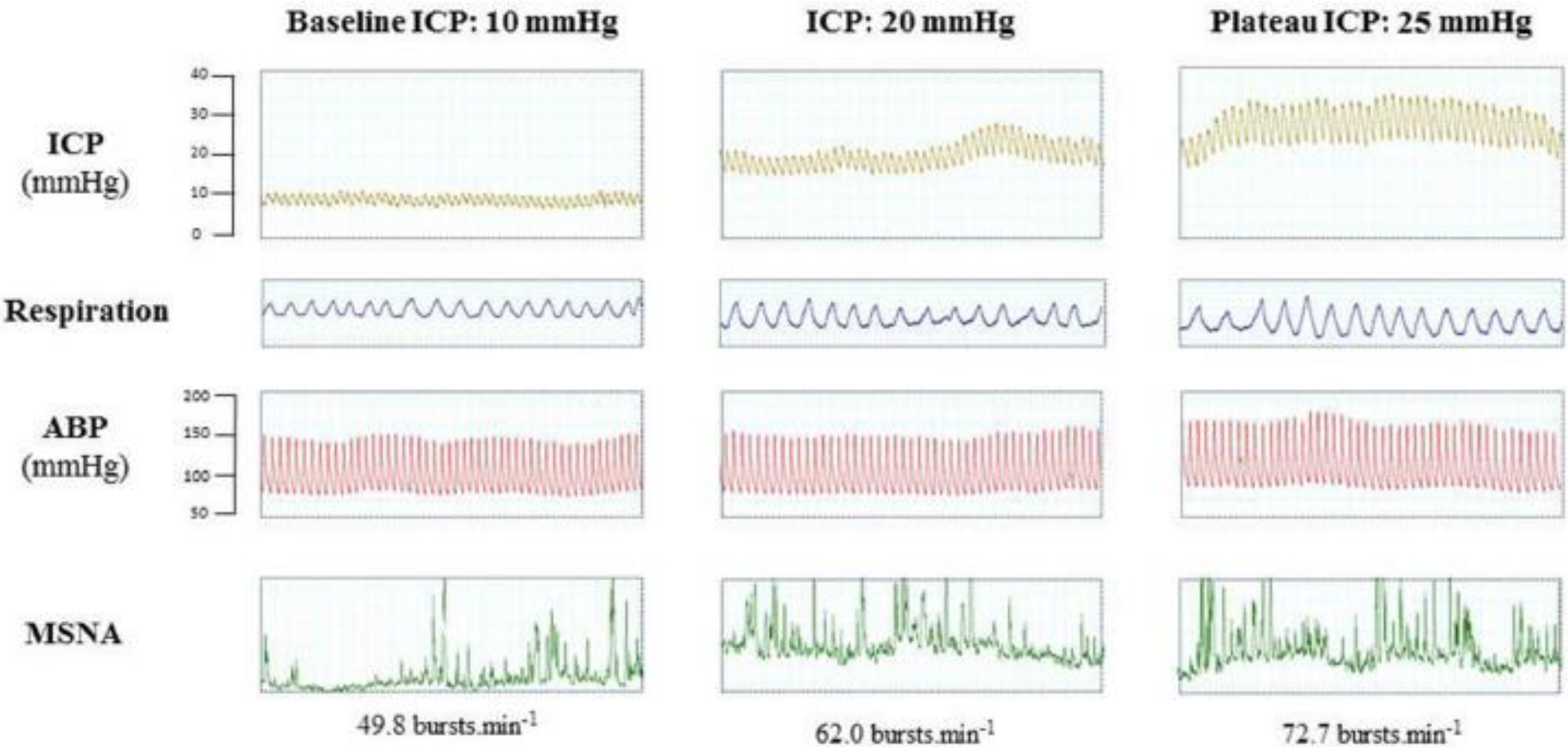
↓(↑) HF pow
↓(↑) LF pow
↑(↓) LF/HF
↓ BRS

↓ Outcome and ↑Mortality

Autonomic impairment influences outcome

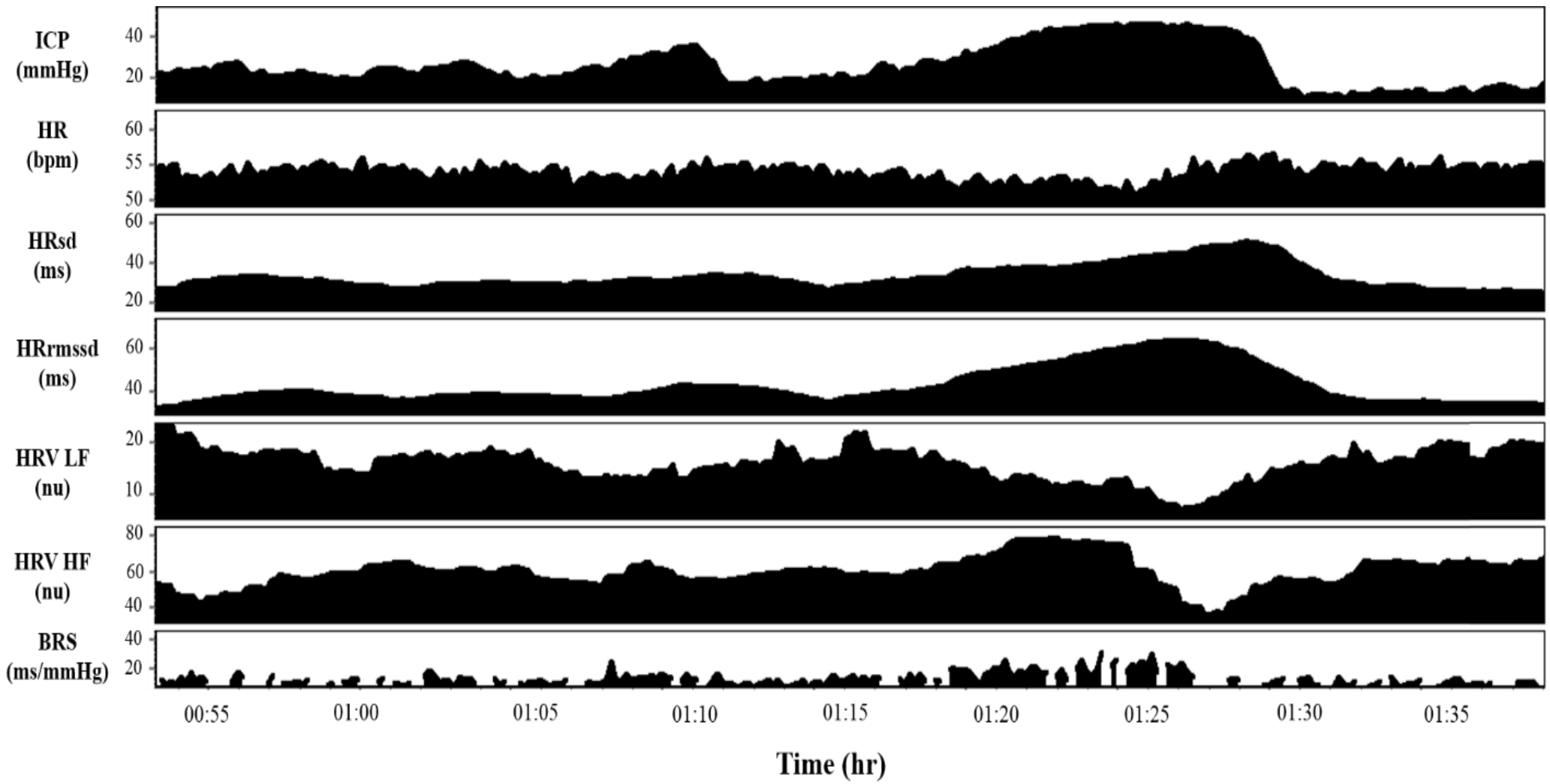
- Cardiac complications und susceptibility to sudden death
- Boost of brain edema und BBB damage
- Blood pressure derrangements und cerebral hypoperfusion
- Stress hyperglycemia
- Immunosupression / Infections

Sympathetic activity in ICP



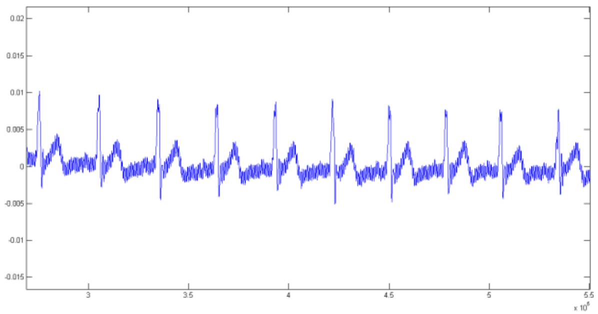
Schmidt, Fro Physiol, 2018

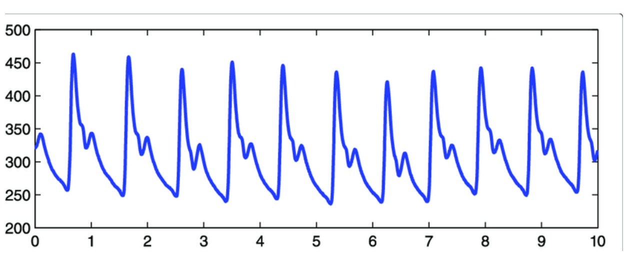
Baroreflex sensitivity in ICP



Tymko, CAN, 2018

Autonomic assessment



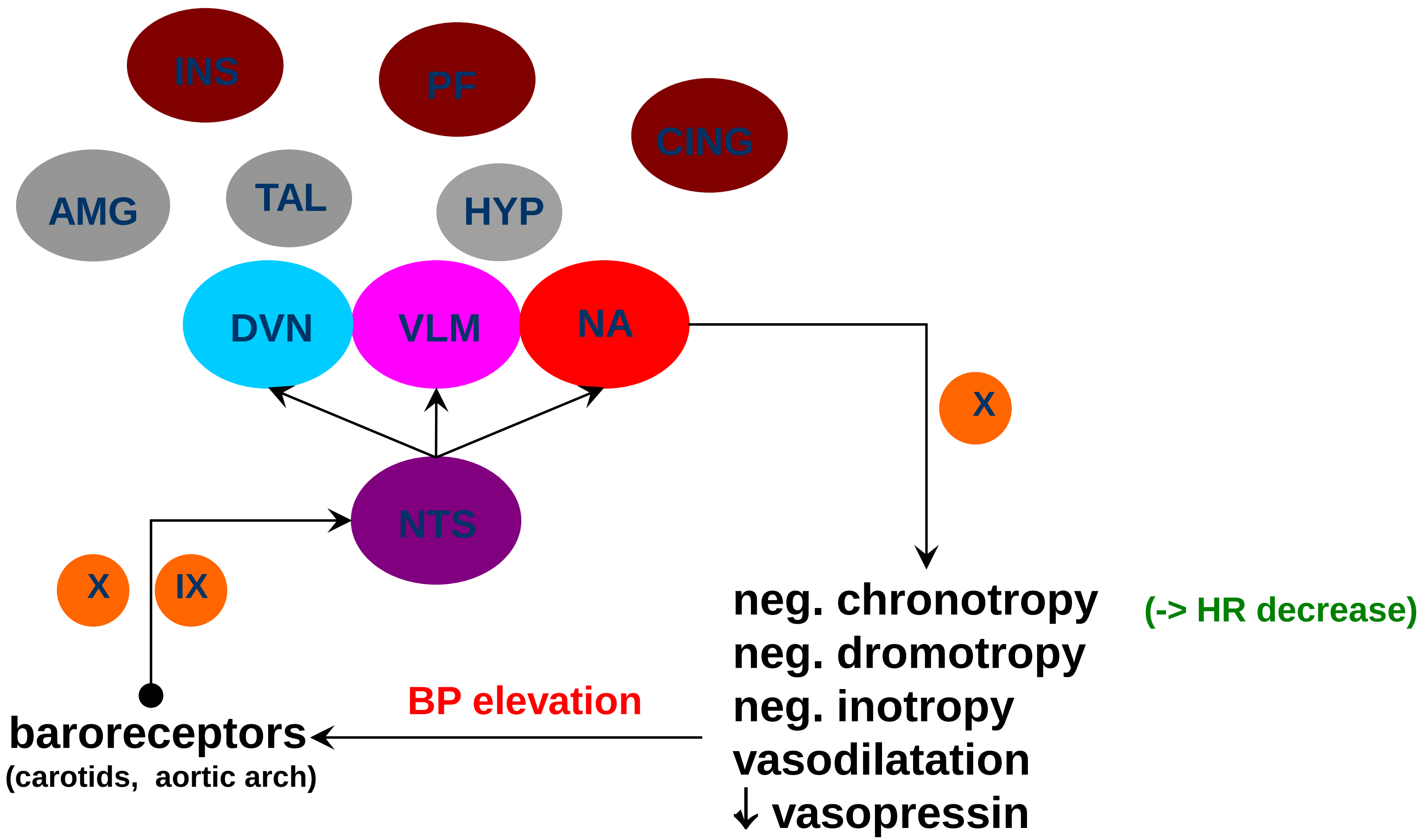


ICM+
peak detection
ectopics removal
spectral analysis
cross-correlation
moving window

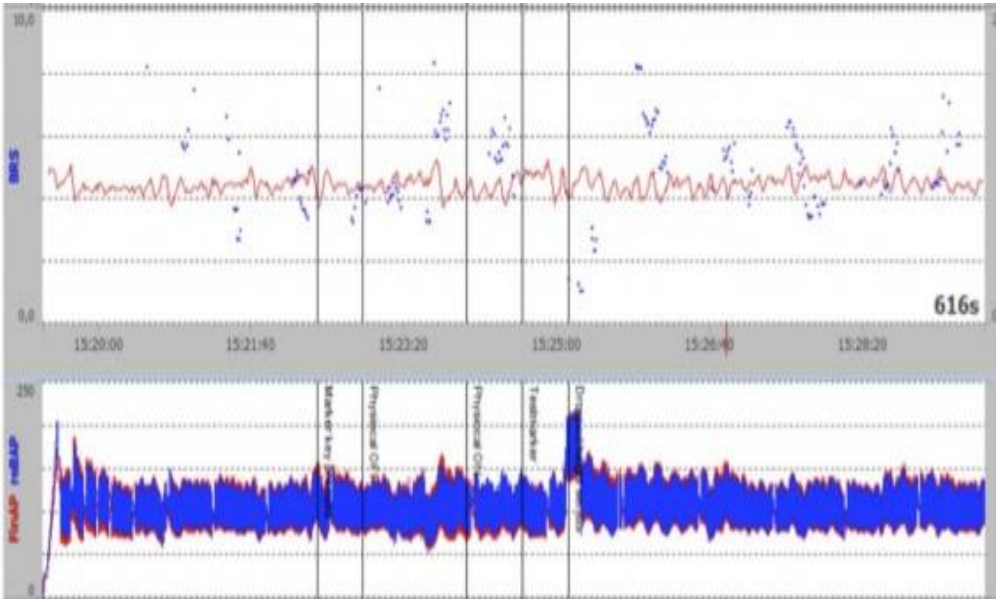
HRV variability
HF, LF, VLF powers
LF/HF ratio

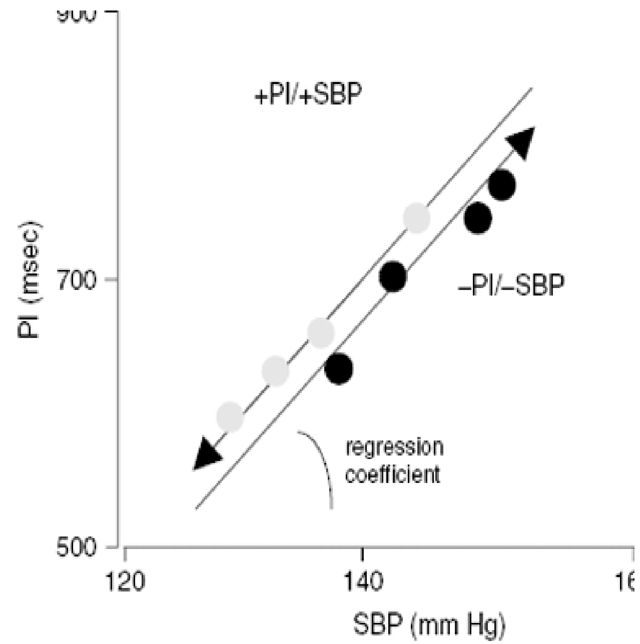
xBRS

Baroreflex - physiology



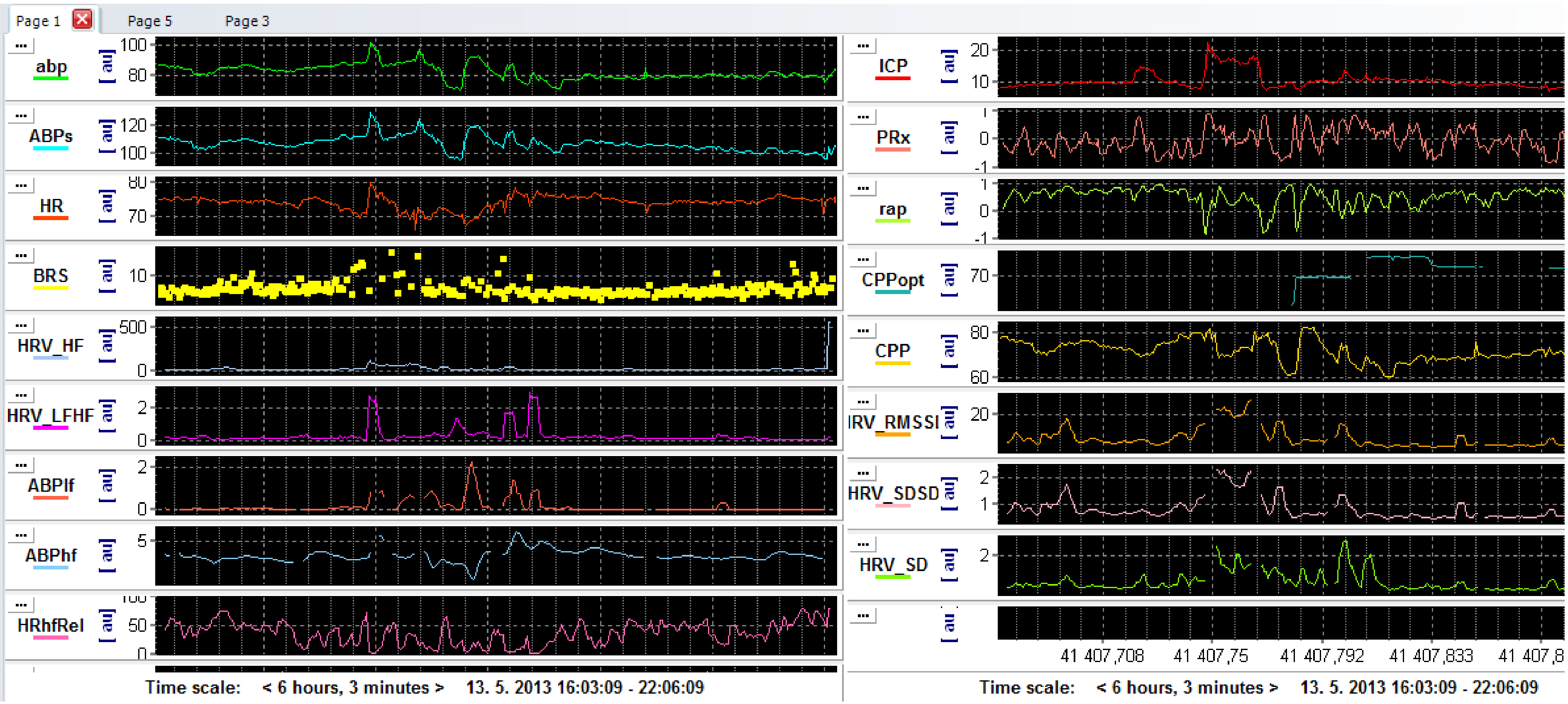
Baroreflex sensitivity (xBRS) im ICM+®



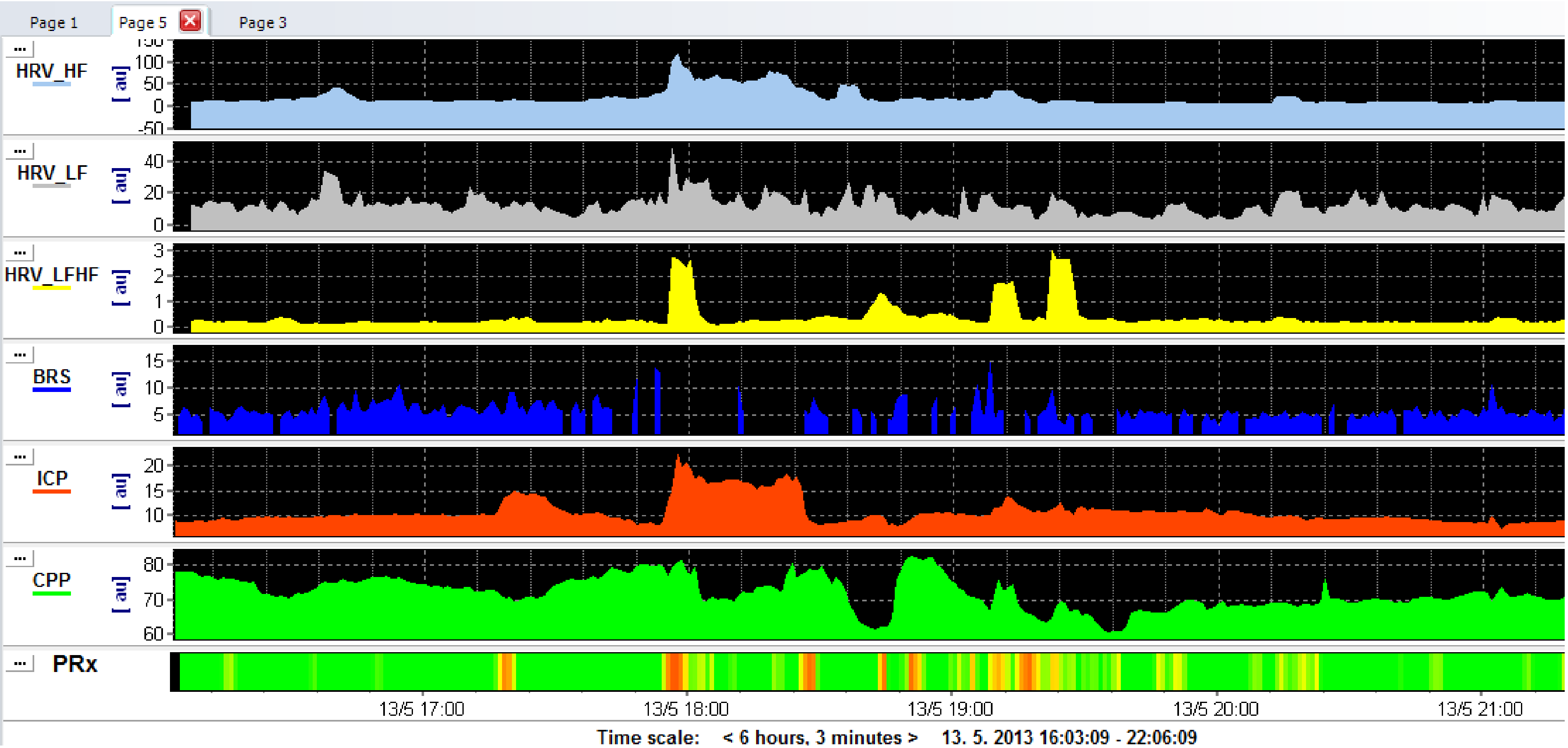


The slope of the linear regression between 10s series of RR intervals and 10s series of systolic BP is calculated. The RR window is shifted against the systolic BP in stepwise manner and the highest correlation is reported, if it fulfills the criteria outlined below. Valid BRS value is returned only if the correlation coefficient is significant at $p<0.01$, and if no irregular beats (ectopics) are detected by the software. The BRS is updated every 10s and expressed in ms/mmHg

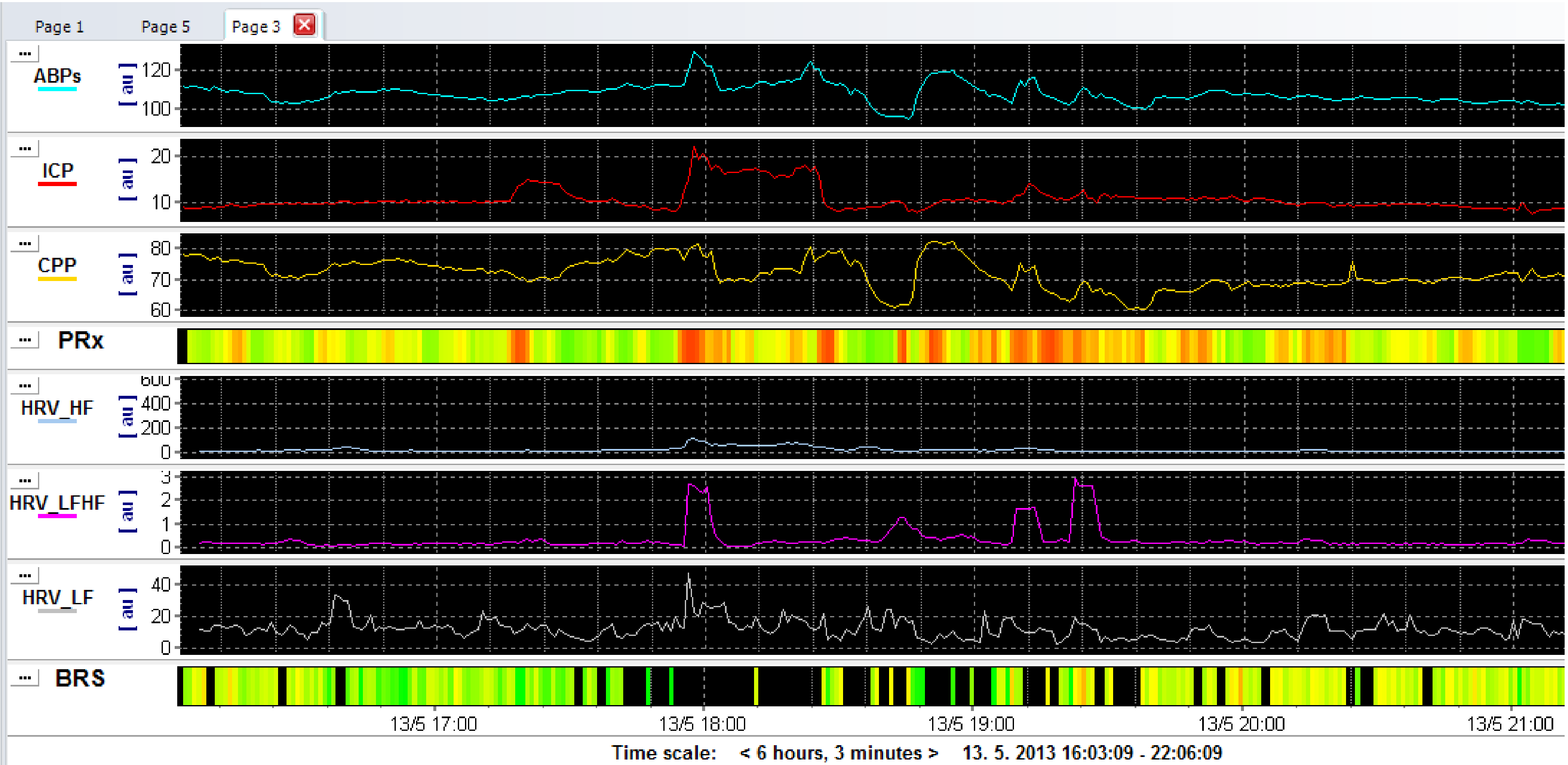
Baroreflex sensitivity (xBRS) im ICM+®



Baroreflex sensitivity (xBRS) im ICM+®



Baroreflex sensitivity (xBRS) im ICM+®



Autonomic Impairment in Severe Traumatic Brain Injury: A Multimodal Neuromonitoring Study

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Peter Hutchinson, BSc (hons), MBBS, PhD, FRCS (Surg Neurol)[1];
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Baroreflex Impairment After Subarachnoid Hemorrhage Is Associated With Unfavorable Outcome

Nathalie Nasr, MD, PhD; Rita Gaio, PhD; Marek Czosnyka, PhD; Karol Budohoski, PhD;
Xiuyun Liu, PhD; Joseph Donnelly, PhD; Marek Sykora, MD, PhD;
Peter Kirkpatrick, MD, FMedSci; Anne Pavy-Le Traon, MD, PhD; Christina Haubrich, MD, PhD;
Vincent Larrue, MD; Peter Smielewski, PhD

Heart rate variability is associated with outcome in spontaneous intracerebral hemorrhage

Jozef Szabo [a], Peter Smielewski [b], Marek Czosnyka [b], Stanislava Jakubicek [c], Stefan Krebs [d],
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Autonomic Impairment in Severe Traumatic Brain Injury: A Multimodal Neuromonitoring Study

- Monocentric, non-randomised comparison
- Cambridge TBI database , n=327, 2003-2009
- Severe TBI, sedated, with ICP monitoring
- xBRS every 10s and HRV every 300s with ICM+

- Adjustment for ICP, CPP und autoregulation (PRx)
- Mortality und Outcome GOS at 6 months

Sykora, CCM, 2016

Autonomic Impairment in Severe Traumatic Brain Injury: A Multimodal Neuromonitoring Study

TABLE 1. Comparison of Clinical and Autonomic Variables Between Traumatic Brain Injury Survivors and Nonsurvivors at 6 Months

Variable	Survivors, $n = 201$	Nonsurvivors, $n = 61$	p
Age (yr), median (range; IQR)	33 (16–76; 23)	44 (18–76; 32)	< 0.001
Glasgow Coma Scale, median (range; IQR)	7 (3–15)	5 (3–14)	0.072
Intracranial pressure, mm Hg, median (range; IQR)	15.8 (4.5–29.0; 5.6)	17.6 (3.0–50.9; 9.7)	0.002
Cerebral perfusion pressure, mmHg, median (range; IQR)	77.7 (57.7–100.1; 6.6)	74.2 (56.2–102.1; 11.6)	0.002
Pressure reactivity index, median (range; IQR)	0.05 (−0.29–0.70; 0.20)	0.14 (−0.30–0.70; 0.23)	0.002
Baroreflex sensitivity, ms/mm Hg, median (range; IQR)	6.6 (1.6–18.8; 4.2)	5.1 (1.3–18.7; 4.0)	0.026
HF power, ms^2, median (range; IQR)	160.0 (9.9–1853.9; 285.4)	115.0 (6.2–1840.3; 212.1)	0.024
HF relative power, median (range; IQR)	25.8 (5.0–65.4; 17.5)	33.4 (6.6–81.8; 22.3)	< 0.001
LF-to-HF ratio, median (range; IQR)	1.6 (0.2–8.3; 1.3)	1.0 (0.0–8.8; 1.2)	< 0.001
LF power, ms^2, median (range; IQR)	598 (9–133; 927, 1,883)	748 (1–41; 628, 2,291)	0.833
LF relative power, median (range; IQR)	22.1 (7.7–39.5; 7.5)	19.9 (2.6–45.7; 12.1)	0.137
Heart rate variability total power, ms^2, median (range; IQR)	2,551 (90–250; 617, 3 ,802)	2,169 (56–66; 197; 4,228)	0.701

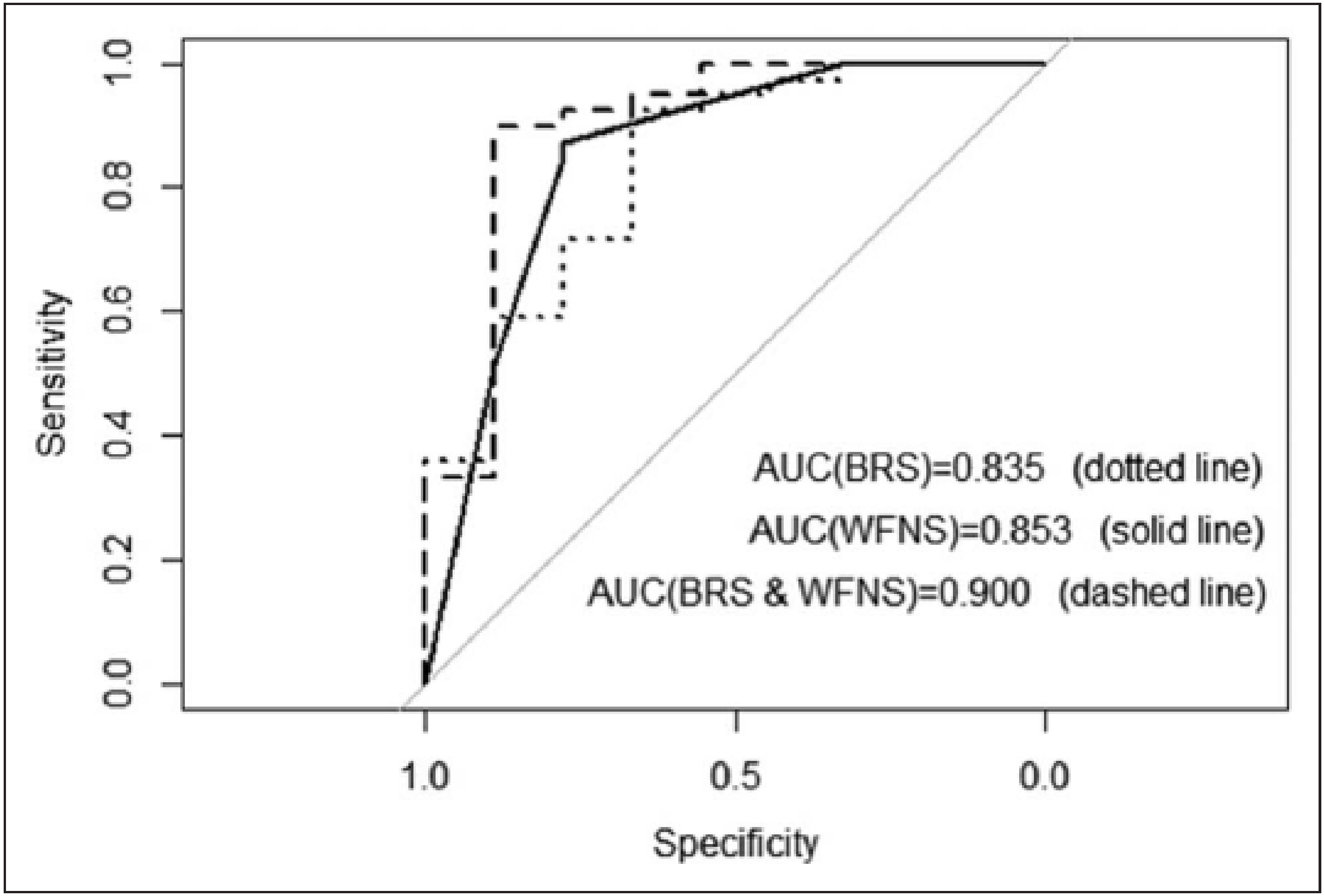
IQR = interquartile range, HF = high frequency, LF = low frequency.

Sykora, CCM, 2016

Variable	Adj OR	95% CI	*p*
Model for mortality			
BRS, ms/mm Hg	0.888	0.801–0.984	0.024
HF relative power, ms^2	1.046	1.019–1.074	0.001
Age (yr)	1.073	1.046–1.101	< 0.001
Admission GCS	0.800	0.713–0.899	< 0.001
ICP, mm Hg	1.140	1.062–1.225	< 0.001
PRx	11.927	1.559–91.254	0.017
Model for poor outcome			
BRS, ms/mm Hg	0.887	0.804–0.978	0.016
HF relative power, ms^2	1.041	1.015–1.068	0.002
Age (yr)	1.068	1.043–1.095	< 0.001
Admission GCS	0.802	0.718–0.897	< 0.001
ICP, mm Hg	1.132	1.058–1.211	< 0.001
PRx	7.317	1.041–51.420	0.045
Model for unfavorable outcome			
BRS, ms/mm Hg	1.027	1.003–1.051	0.030
HF relative power, ms^2	0.999	0.998–1.000	0.061
Age (yr)	1.058	1.037–1.080	< 0.001
Admission GCS	0.811	0.741–0.888	< 0.001
ICP, mm Hg	1.079	1.017–1.144	0.012

Sykora, CCM, 2016

Baroreflex Impairment After Subarachnoid Hemorrhage Is Associated With Unfavorable Outcome



Nasr, Stroke, 2018

Heart rate variability is associated with outcome in spontaneous intracerebral hemorrhage

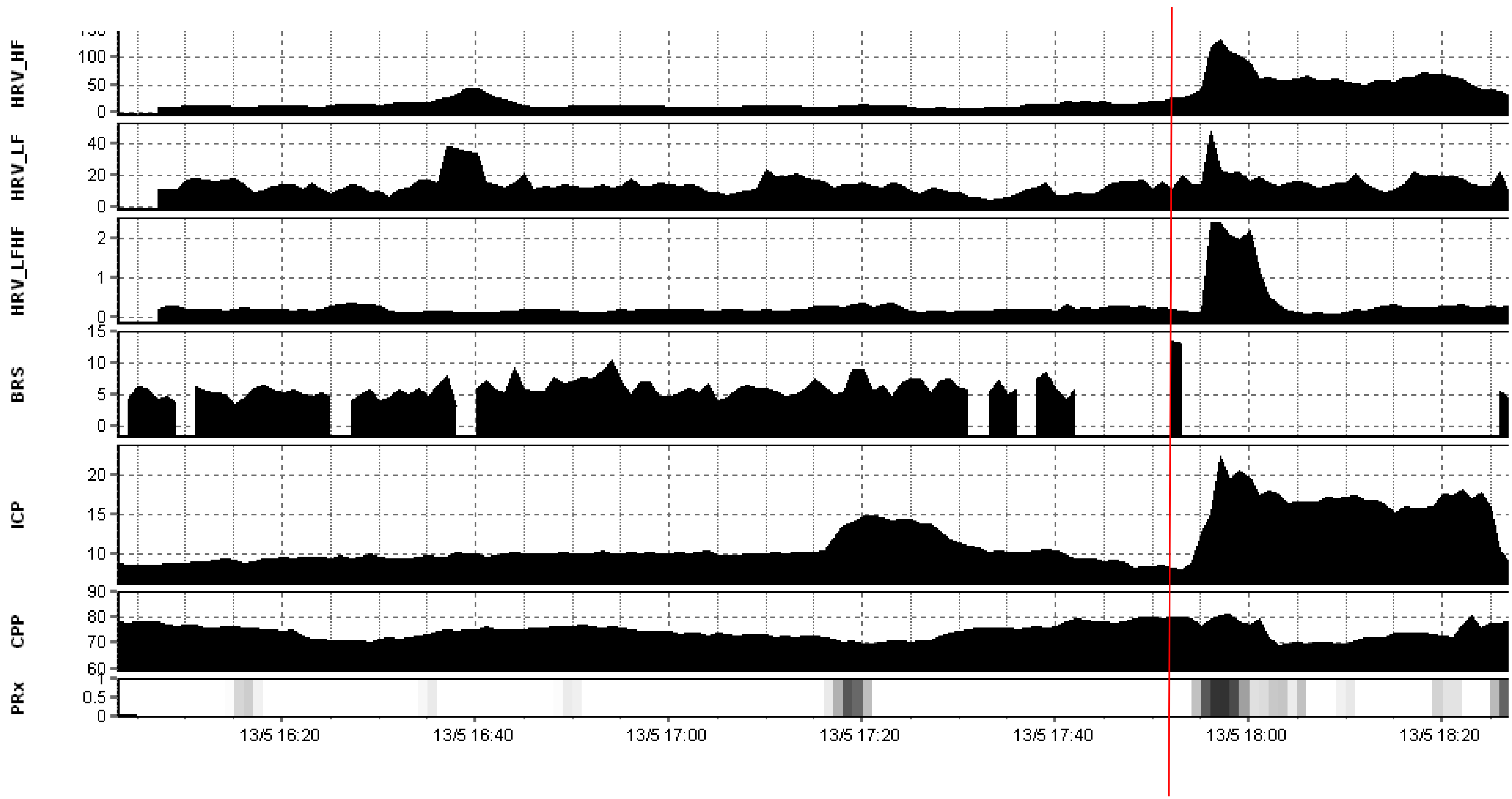
Variable	mRS 0–3 at 3 months	mRS 4–6 at 3 months	P
Age mean (range, SD)	59.5 (17–86, 20)	62.2 (34–84, 21)	0.8
Admission NIHSS, median (range, IQR)	5 (1–34, 13)	28 (6–34, 21)	<0.001
Hemorrhage volume median (range, IQR)	14 (1–102, 34)	50 (7–234, 84)	<0.001
Intraventricular extension n (%)	8 (34.8)	18 (75)	0.008
Admission glucose mg/d, median (range, IQR)	113 (89–162, 26)	154 (95–327, 40)	<0.001
HF power, total, ms^2, median (range, IQR)	118 (16–22,588, 263)	55 (5–7458, 343)	0.04
HF power, normalized median (range, IQR)	21 (11–60, 16)	34 (15–83, 16)	0.01
LF power, total, ms^2 median (range, IQR)	162 (10–19,060, 262)	24 (2–4704, 178)	0.004
LF power, normalized median (range, IQR)	24 (10–52, 11)	16 (4–46, 14)	0.01
LF/HF ratio median (range, IQR)	1.2 (0.3–4.1, 1)	0.6 (0.05–3, 0.5)	0.003

Variable	Alive at 3 months	Dead at 3 months	P
Age mean (range, SD)	61.3 (17–86, 18)	60.2 (42–84, 13)	0.6
Admission NIHSS, median (range, IQR)	10 (1–34, 18)	34 (11–34, 21)	0.008
Hemorrhage volume median (range, IQR)	36 (1–202, 50)	50 (10–234, 94)	0.03
Intraventricular extension n (%)	15 (43)	11 (92)	0.006
Admission glucose mg/d, median (range, IQR)	124 (89–300, 45)	150 (95–327, 232)	0.04
HF power, total, ms^2, median (range, IQR)	118 (5–22,588, 338)	34 (6–923, 62)	0.01
HF power, normalized median (range, IQR)	27 (11–83, 19)	39 (20–80, 27)	0.04
LF power, total, ms^2 median (range, IQR)	153 (2–19,057, 314)	16 (2–283, 22)	0.001
LF power, normalized median (range, IQR)	22 (5–52, 12)	15 (4–37, 10)	0.006
LF/HF ratio median (range, IQR)	0.8 (0.1–4.1, 1)	0.4 (0.05–1, 0.6)	0.02

Szabo, JCC, 2018

BARMHERZIGE BRÜDER
KRANKENHAUS WIEN

Future directions – monitoring time trends



Future directions – examining therapies

- BB reduce infarct size and mortality in stroke models (Savitz 2000)
- Pre-stroke BB may have positive outcome effects (n=111, Laowattana 2007)
- BB reduce edema in ICH (Sansing 2011)
- Pre-injury BB reduce stunned myocardium in SAH (Liang 2013)
- BB reduce tissue injury markers and inflammation in SAH (Kawaguchi 2010)
- BB reduce edema in TBI models (Liu 1995)
- Pre-injury BB have positive outcome effects in TBI (Mohseni 2014)
- Post-injury BB have positive outcome effects in TBI

(meta-analysis, n=4782, adjusted OR 0.35; 95 % CI 0.27-0.45, Alali 2014)

Thank you for your attention