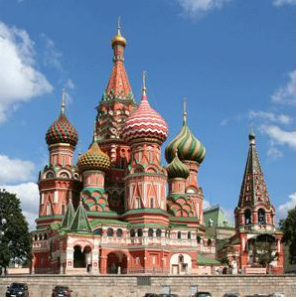
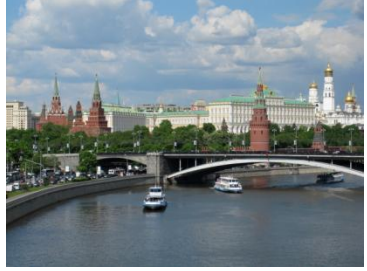
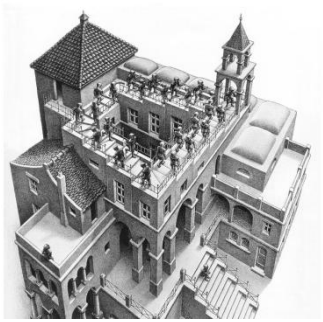


Moskow, May 25TH 2012



Brain-heart interactions



Kees H. Polderman, internist/intensivist

Medical director, Neurocritical Care Unit

University of Pittsburgh Medical Center

UPMC | University of Pittsburgh Medical Center

☺ My aim today is to get you to look at a few things that you may take for granted in a slightly different way.

Why do we need special consideration of hemodynamics in patients with brain injury?

- Arrhythmia's and electrolyte disorders, blood pressure problems (unwanted hyper- or hypotension) all occur very frequently in patients with brain injury…
- Brain injured patients have a MUCH LOWER TOLERANCE for such events than "regular" patients!
- It is of key importance to prevent excesses and "maintain homeostasis" in brain-injured patients.


THE
PERFECT STORM

Animal data overwhelmingly show that the injured brain does not tolerate:

- Hypo- & hypertension; hypo- and hypoperfusion (hypoperfusion worse)
- Hypoxia and hyperoxia (hypoxia worse)
- Hypocarbia & hypercarbia
- Fever
- Hypoglycemia & hyperglycemia
- Other disturbances of homeostasis: electrolyte disorders (Na, Mg, K, P etc), others?
- Others?

Animal data overwhelmingly show that the injured brain does not tolerate:

- Hypo- & hypertension; hypo- and hypoperfusion (hypoperfusion worse)
- Hypoxia and hyperoxia (hypoxia worse)
- Hypocarbia & hypercarbia
- Fever
- Hypoglycemia & hyperglycemia
- Other disturbances of homeostasis: electrolyte disorders (Na, Mg, K, P etc), others?
- Others?

Animal data overwhelmingly show that the injured brain does not tolerate:

- Hypo- & hypertension; hypo- and hypoperfusion (hypoperfusion worse)
- Hypoxia and hyperoxia (hypoxia worse)
- Hypocarbia & hypercarbia
- Fever
- Hypoglycemia & hyperglycemia
- Other disturbances of homeostasis: electrolyte disorders (Na, Mg, K, P etc), others?
- Others?

Animal data overwhelmingly show that the injured brain does not tolerate:

- Hypo- & hypertension; hypo- and hypoperfusion (hypoperfusion worse)
- Hypoxia and hyperoxia (hypoxia worse)
- Hypocarbia & hypercarbia
- Fever
- Hypoglycemia & hyperglycemia
- Other disturbances of homeostasis: electrolyte disorders (Na, Mg, K, P etc), others?
- Others?

Animal data overwhelmingly show that the injured brain does not tolerate:

- Hypo- & hypertension; hypo- and hypoperfusion (hypoperfusion worse)
- **Hypoxia and hyperoxia (hypoxia worse)**
- Hypocarbia & hypercarbia……?
- Fever
- Hypoglycemia & Hyperglycemia
- Other disturbances of homeostasis: electrolyte disorders (Na, Mg, K, P etc), others?
- Others?

Association Between Arterial Hyperoxia Following Resuscitation From Cardiac Arrest and In-Hospital Mortality

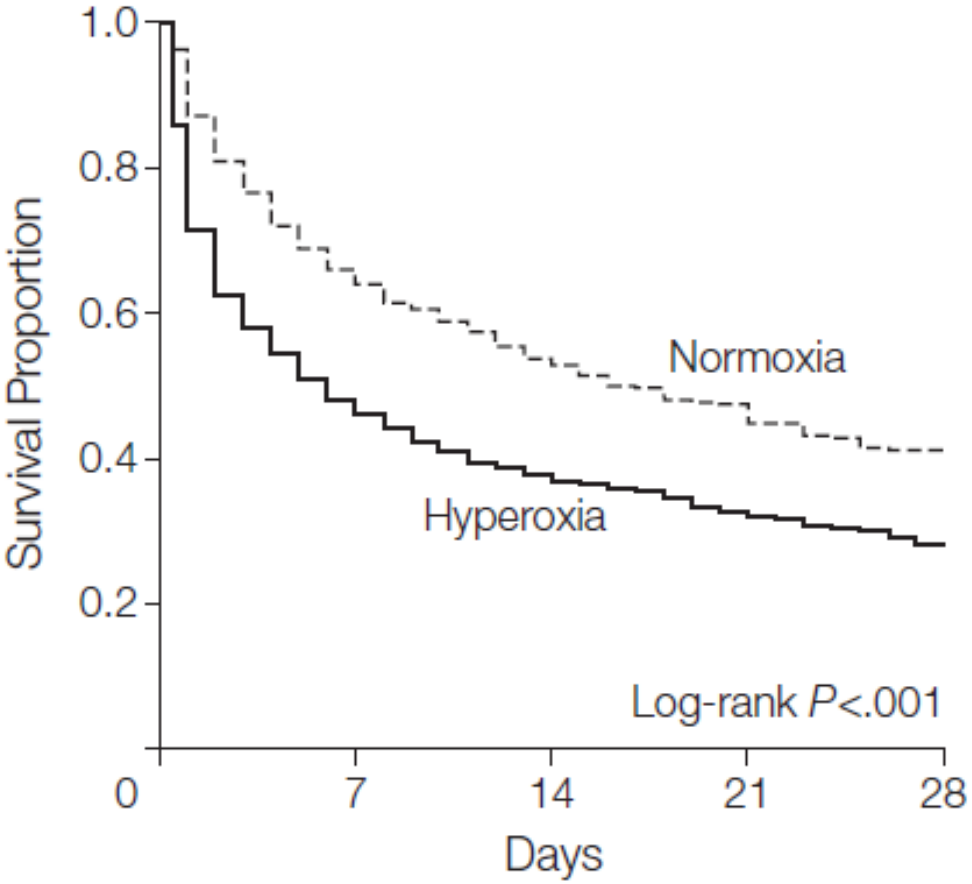
J. Hope Kilgannon, MD
Alan E. Jones, MD
Nathan I. Shapiro, MD, MPH
Mark G. Angelos, MD
Barry Milcarek, PhD
Krystal Hunter, MBA
Joseph E. Parrillo, MD
Stephen Trzeciak, MD, MPH
for the Emergency Medicine Shock Research Network (EMShockNet) Investigators

JAMA. 2010;303(21):2165-2171

N= 6326 patients

- Hyperoxia (PaO2/FiO2 ≥300) was seen in 1156 (18%)
- Hypoxia (PaO2/FiO2 ≤60) was seen in 3999 patient 63%
- 1171 (19%) had normoxia

Figure. In-Hospital Death Between Hyperoxia and Normoxia



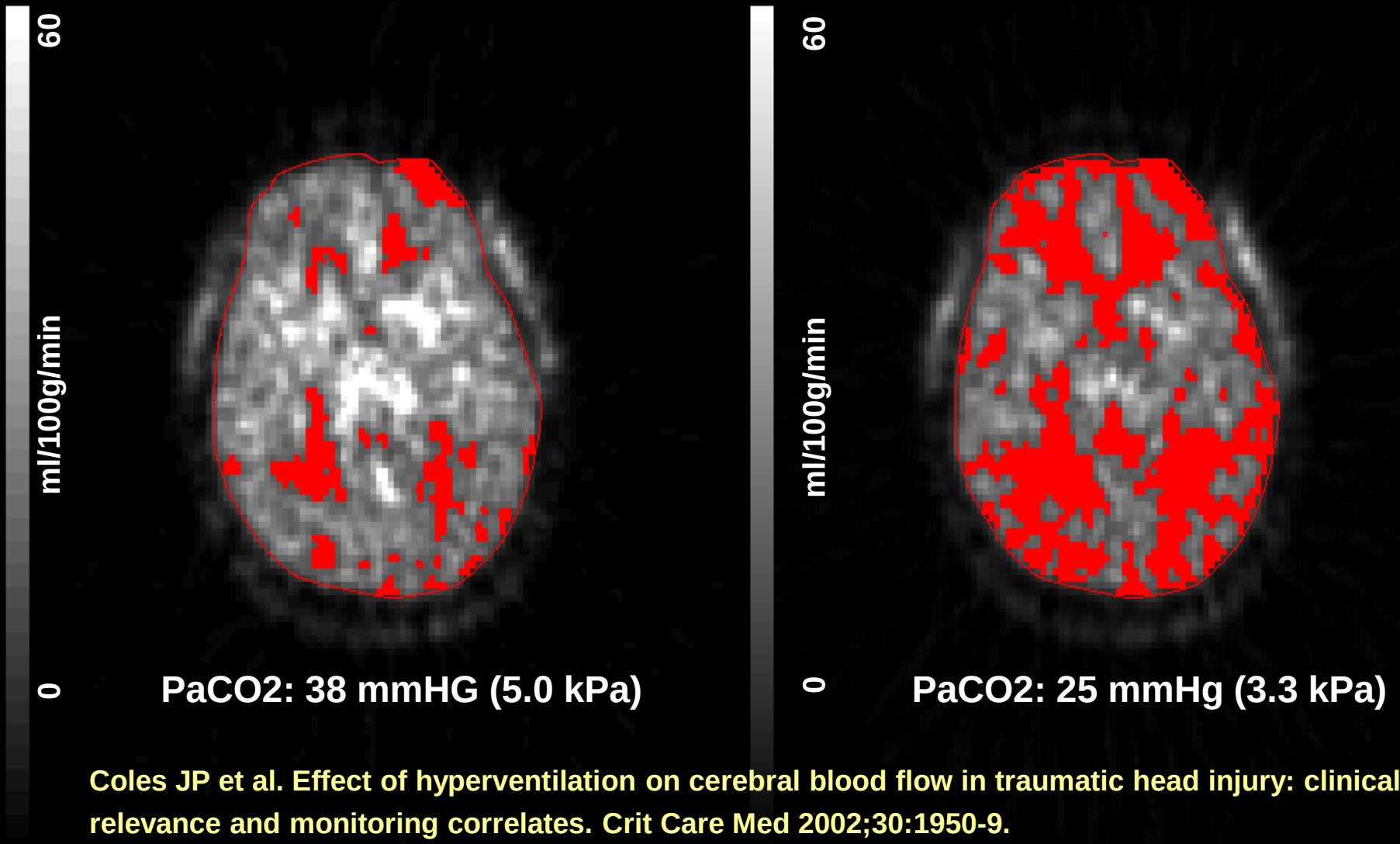
No. at risk					
Normoxia	1171	514	236	129	83
Hyperoxia	1156	406	211	115	70

Animal data overwhelmingly show that the injured brain does not tolerate:

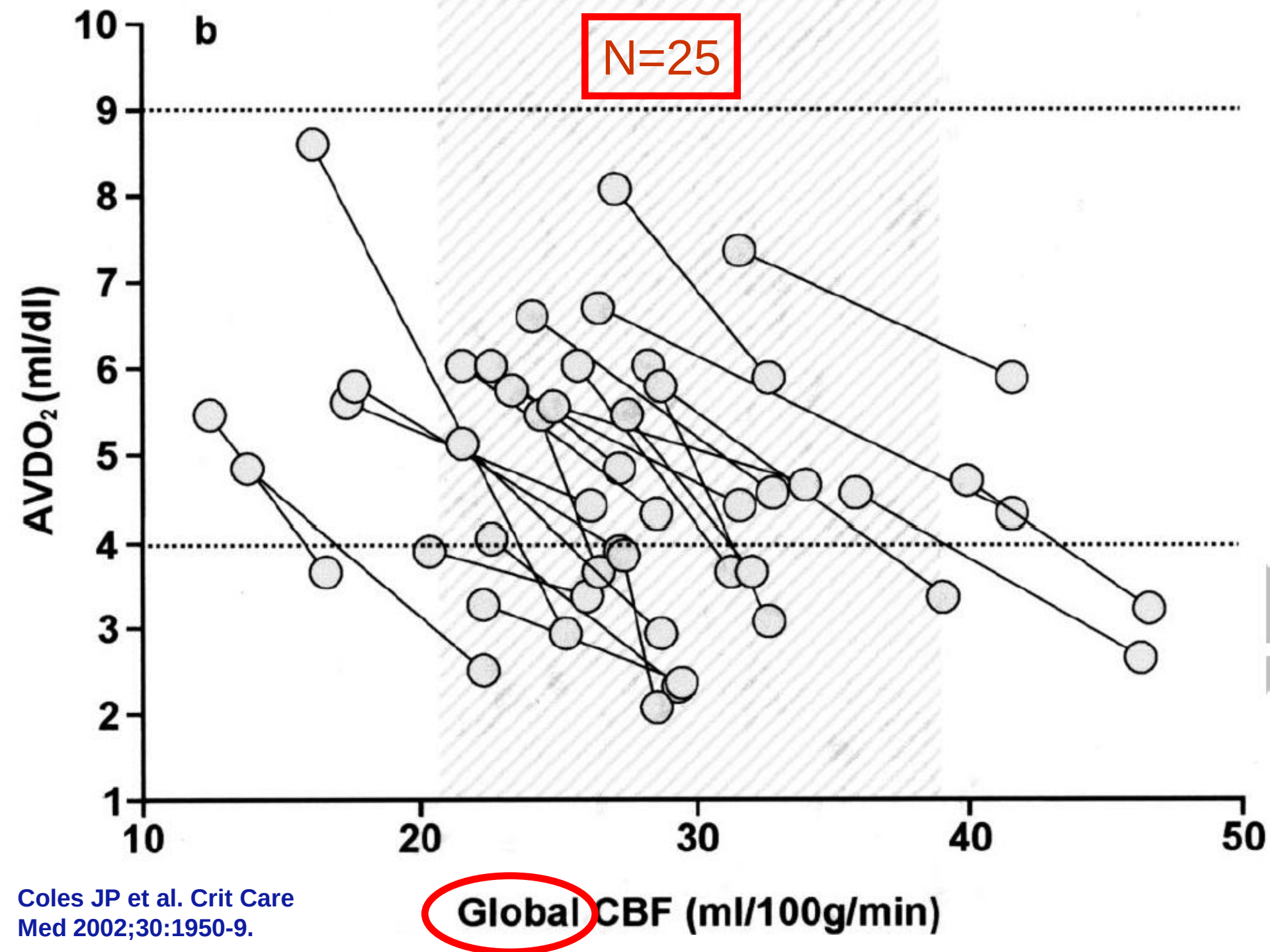
- Hypo- & hypertension; hypo- and hypoperfusion (hypoperfusion worse)
- Hypoxia and hyperoxia (hypoxia worse)
- Fever
- Hypoglycemia & Hyperglycemia
- Other disturbances of homeostasis: electrolyte disorders (Na, Mg, K, P etc), others?
- **Hypocarbia & hypercarbia……?**
- Others?

Acute head injury (6 hrs post impact)

Areas in red show regions with rCBF ≤ 20 ml/100g/min)



Coles JP et al. Effect of hyperventilation on cerebral blood flow in traumatic head injury: clinical relevance and monitoring correlates. Crit Care Med 2002;30:1950-9.



Coles JP et al. Crit Care Med 2002;30:1950-9.

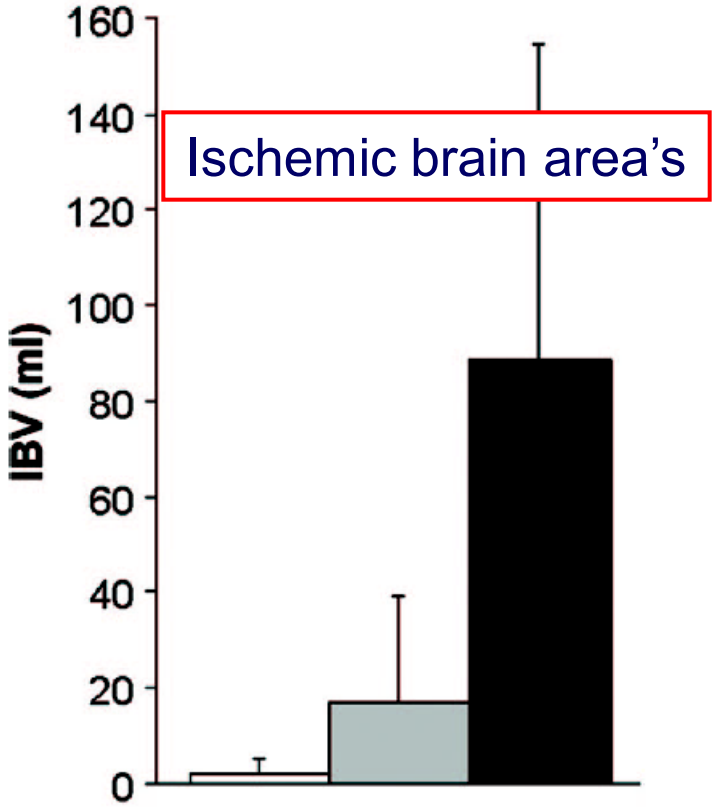


Figure 4. Estimation of ischemic brain volume (*IBV*). Mean + SD ischemic brain volumes in controls (*white*) and in head-injured patients at relative normocapnia (*gray*; mean $Paco_2$ 36 torr [4.8 kPa]) and after hyperventilation (*black*; mean $Paco_2$ 29 torr [3.9 kPa]). $*p < .0001$, paired *t*-test for comparison between normocapnic and hypocapnic values.

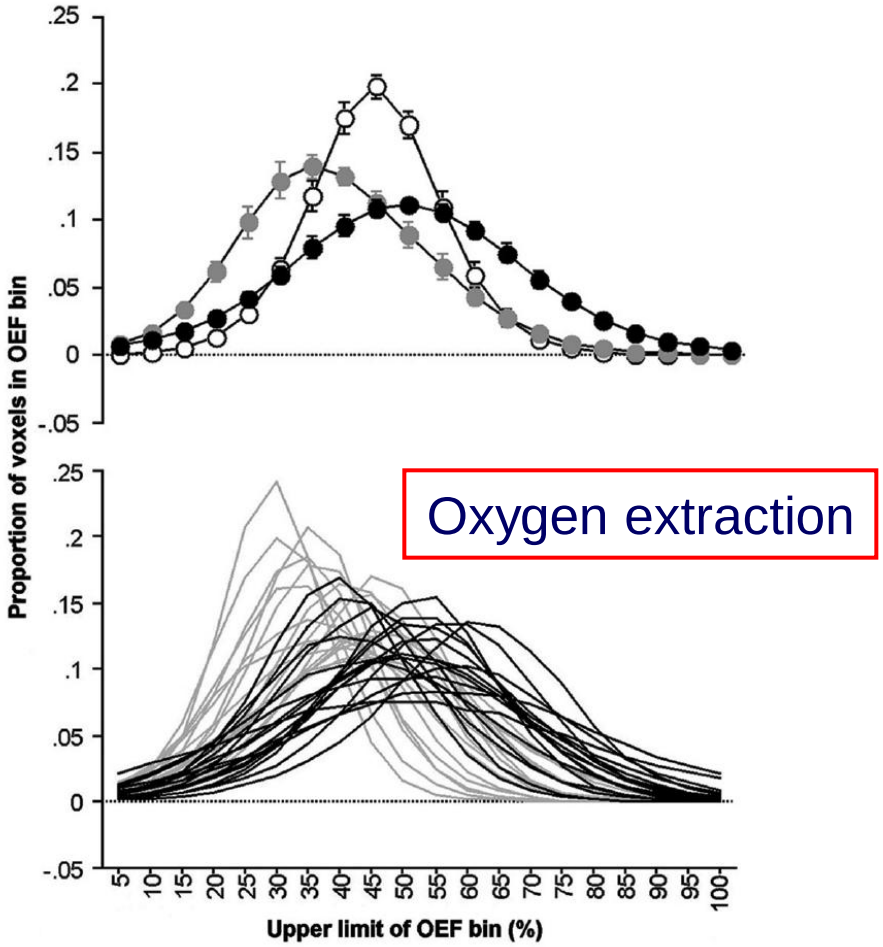


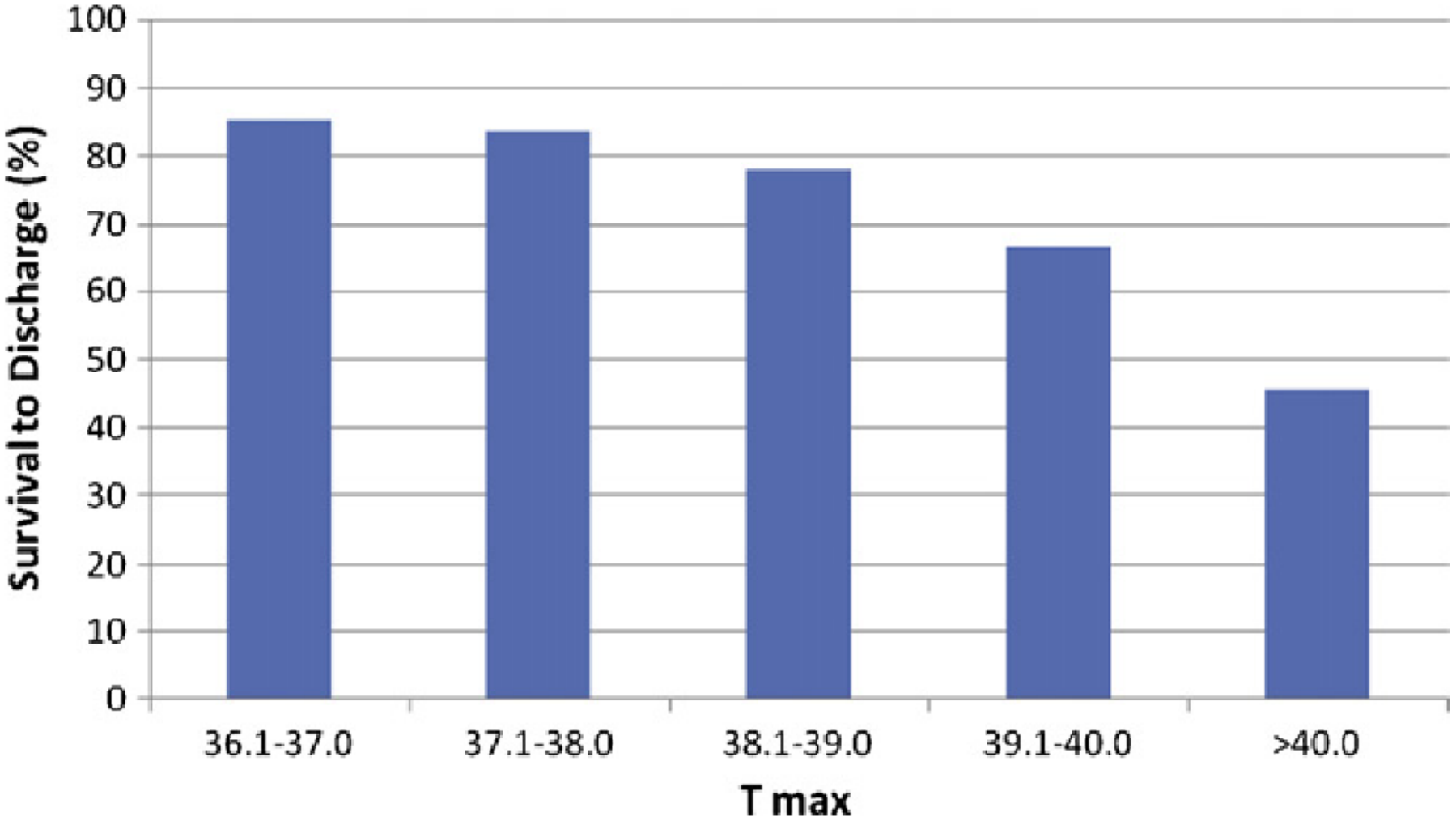
Figure 3. Oxygen extraction fraction (*OEF*) histograms. *Top*, mean ± SE OEF histograms (showing proportion of voxels in each OEF bin) in ten controls (*white*) and in 18 patients following head injury, at relative normocapnia (*gray*; mean $Paco_2$ 36 torr [4.8 kPa]) and after hyperventilation (*black*; mean $Paco_2$ 29 torr [3.9 kPa]). *Bottom*, individual patient OEF histograms at normocapnia (*gray*) and following hyperventilation (*black*). Note the rightward shift of the curves with an increase in the number of voxels with critically high OEF values.

Coles JP et al. Crit Care Med 2007;35:568-78.

Animal data overwhelmingly show that the injured brain does not tolerate:

- Hypo- & hypertension; hypo- and hypoperfusion (hypoperfusion worse)
- Hypoxia and hyperoxia (hypoxia worse)
- Hypocarbia & hypercarbia
- Fever
- Hypoglycemia & hyperglycemia
- Other disturbances of homeostasis: electrolyte disorders (Na, Mg, K, P etc), others?
- Others?

Fever following in-hospital cardiac arrest (IHCA):

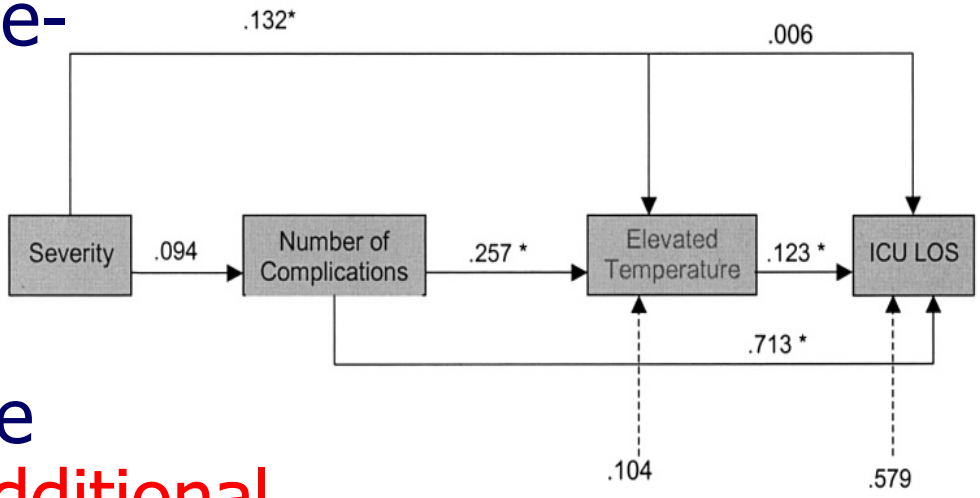


Suffoletto B et al. Resuscitation 2009; 80:1365-70.

Fever in *a mixed neuro-ICU:*

Diringer M et al. Crit Care Med 2004; 32;1489-93

- 4,295 patients with LOS >1 day
- Elevated body temperature was associated with a dose-dependent:
  - ICU & Hospital LOS
  - Mortality rate



- Elevated body temperature was associated with 3.2 additional ICU days and 4.3 additional hospital days
- ICU LOS was predicted by the number of complications and elevated body temperature

Diringer M et al. Crit Care Med 2004; 32;1489-93

Animal data overwhelmingly show that the injured brain does not tolerate:

- Hypo- & hypertension; hypo- and hypoperfusion (hypoperfusion worse)
- Hypoxia and hyperoxia (hypoxia worse)
- Hypocarbia & hypercarbia
- Fever
- Hypoglycemia & hyperglycemia
- Other disturbances of homeostasis: **electrolyte disorders** (**Na**, Mg, K, P etc), others?
- Others?

Mortality after Hospitalization with Mild, Moderate, and Severe Hyponatremia

Sushrut S. Waikar, MD, MPH,[a] David B. Mount, MD,[a,b] Gary C. Curhan, MD, ScD[a]

[a]*Renal Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass;* [b]*Renal Division, VA Boston Healthcare System, Boston, Mass.*

N=98 411 patients

THE AMERICAN JOURNAL of MEDICINE®

Table 1 Prevalence of Hyponatremia, Uncorrected and Corrected for Glucose Concentration

	Sodium Concentration (mEq/L)						
	135-144	<135	130-134	125-129	120-124	<120	% Misclassified*
Initial value during admission, n (%)	81,031 (82.3%)	14,290 (14.5%)	11,853 (12.0%)	1856 (1.9%)	415 (0.4%)	166 (0.2%)	—
Hillier[10] (2-piece linear regression), n (%)†	82,377 (83.7%)	12,562 (12.8%)	10,469 (10.6%)	1591 (1.6%)	353 (0.4%)	149 (0.2%)	12.1%
Hillier[10] (linear regression), n (%)‡	83,423 (84.8%)	11,615 (11.8%)	9671 (9.8%)	1472 (1.5%)	328 (0.3%)	144 (0.1%)	18.7%
Katz,[11] n (%)§	82,574 (83.9%)	12,617 (12.8%)	10,513 (10.7%)	1601 (1.6%)	353 (0.4%)	150 (0.2%)	11.7%

Waikar SS et al. Am J Med 2009;122:857-865

Table 3 Mortality in Patients with and without Hyponatremia

	Sodium Concentration (mEq/L)					
	135-144 (n = 82,377)	<135 (n = 12,562)	130-134 (n = 10,469)	125-129 (n = 1591)	120-124 (n = 353)	<120 (n = 149)
Crude in-hospital mortality (%)	2.4	5.4	4.8	8.9	8.5	6.7
Age-adjusted	1 (ref)	2.08 (1.90-2.28)	1.87 (1.69-2.07)	3.20 (2.67-3.83)	2.93 (2.00-4.28)	2.24 (1.17-4.28)
Age, sex, D-CI-adjusted	1 (ref)	1.88 (1.72-2.06)	1.69 (1.53-1.87)	2.88 (2.40-3.45)	2.56 (1.74-3.77)	2.29 (1.19-4.42)
Multivariable-adjusted	1 (ref)	1.47 (1.33-1.62)	1.37 (1.23-1.52)	2.01 (1.64-2.45)	1.67 (1.09-2.56)	1.46 (0.73-2.91)
Crude 1-year mortality (%)	11.7	21.4	19.8	28.5	33.1	22.2
Age-adjusted	1 (ref)	1.65 (1.57-1.73)	1.58 (1.50-1.68)	1.88 (1.68-2.11)	2.31 (1.87-2.86)	1.29 (0.86-1.95)
Age, sex, D-CI-adjusted	1 (ref)	1.51 (1.44-1.59)	1.45 (1.37-1.53)	1.76 (1.57-1.97)	2.13 (1.72-2.63)	1.42 (0.94-2.14)
Multivariable-adjusted	1 (ref)	1.38 (1.32-1.46)	1.35 (1.28-1.43)	1.53 (1.36-1.71)	1.78 (1.44-2.21)	1.03 (0.68-1.56)
Crude 5-year mortality (%)	42.3	54.8	53.6	61.0	60.6	59.7
Age-adjusted	1 (ref)	1.42 (1.37-1.46)	1.39 (1.34-1.44)	1.55 (1.43-1.68)	1.59 (1.35-1.87)	1.34 (1.04-1.72)
Age, sex, D-CI adjusted	1 (ref)	1.34 (1.30-1.39)	1.31 (1.26-1.36)	1.50 (1.38-1.62)	1.53 (1.30-1.80)	1.31 (1.12-1.86)
Multivariable-adjusted	1 (ref)	1.25 (1.21-1.30)	1.24 (1.19-1.29)	1.33 (1.23-1.44)	1.29 (1.09-1.53)	1.09 (0.84-1.41)

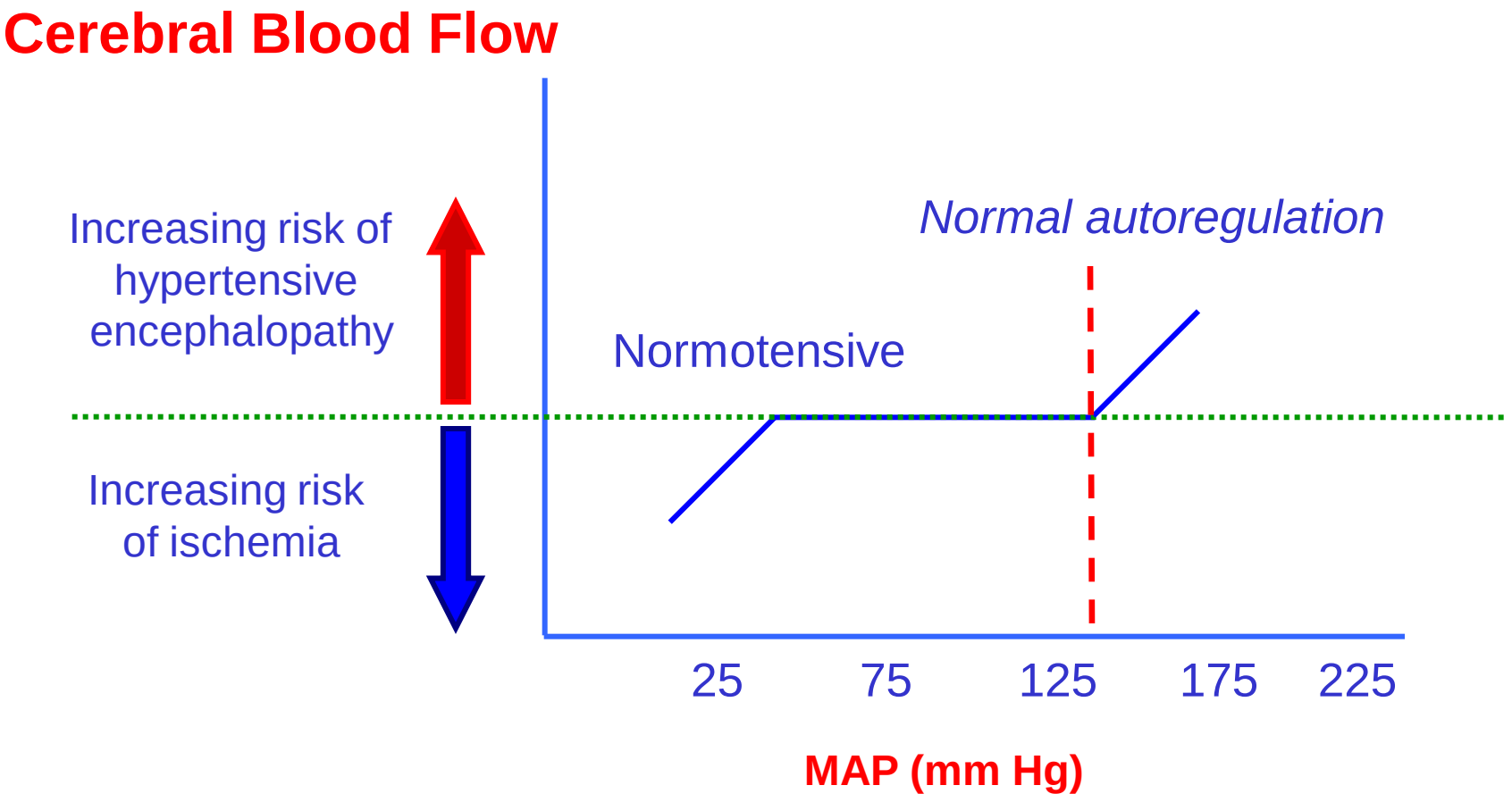
Sodium values corrected for admission glucose. Multivariable models adjusted for age, sex, Deyo-Charlson Index (D-CI), and individual diagnoses (acute myocardial infarction, congestive heart failure, sepsis, metastatic cancer, pneumonia, chronic kidney disease, liver disease, gastrointestinal bleeding, syndrome of inappropriate antidiuretic hormone, volume depletion).

Waikar SS et al. Am J Med 2009;122:857-865

What about blood pressure and arrhythmia's??

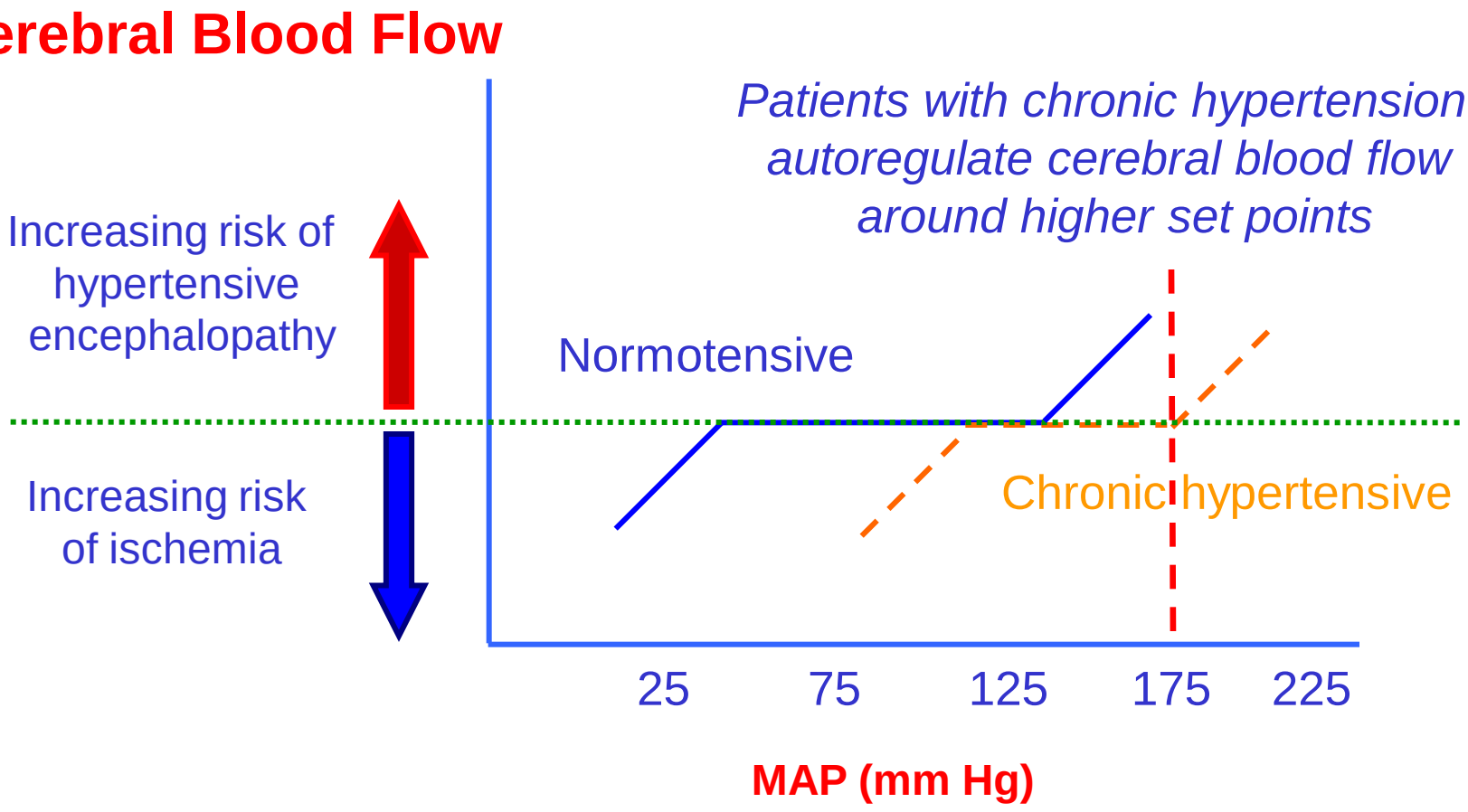
Before we look at the clinical data, we need to deal with the concept of cerebral autoregulation.

The concept of cerebral autoregulation



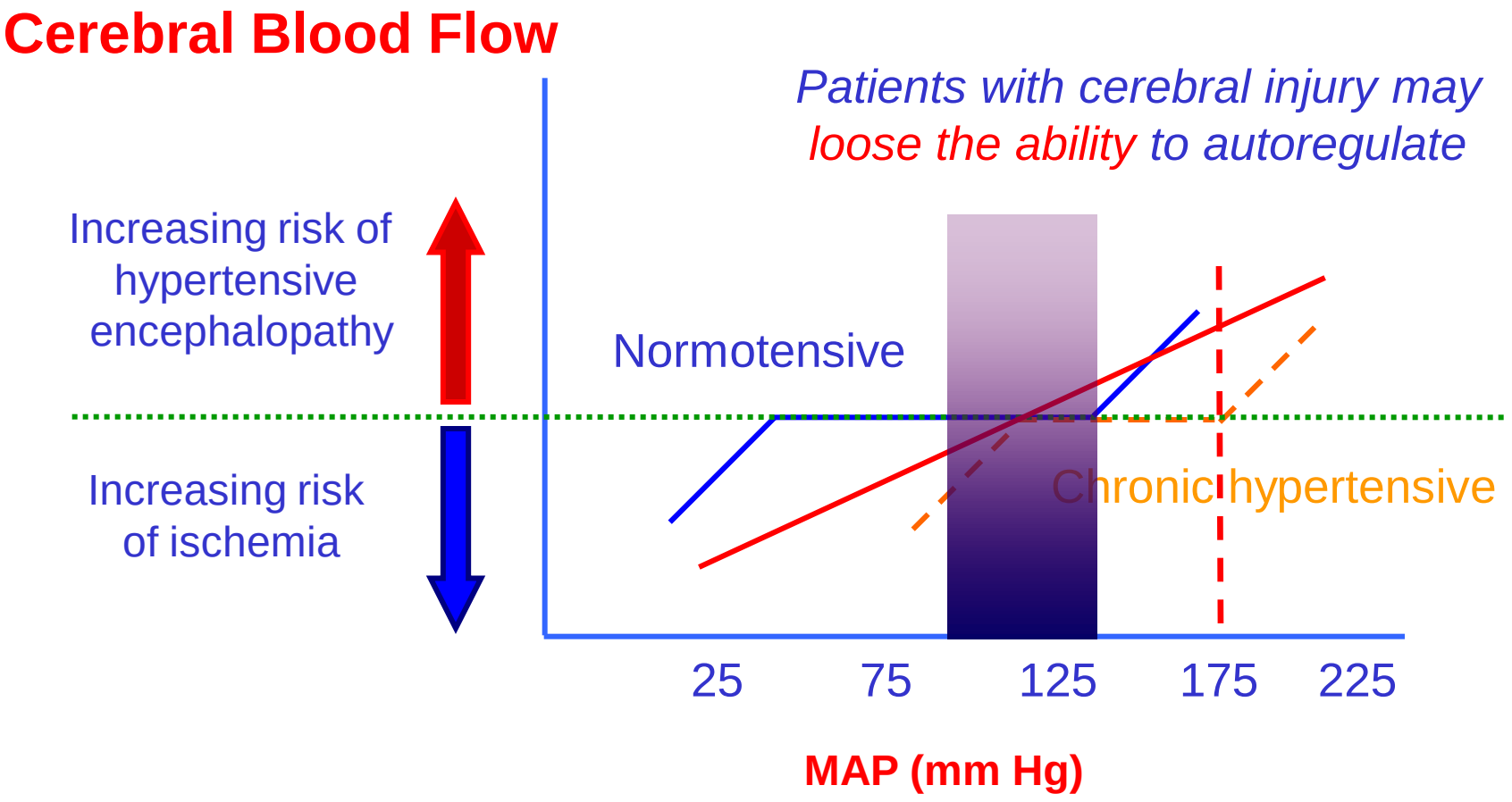
Adapted from: Varon J, Marik PE. Chest 2000; 118:214-227.

The concept of cerebral autoregulation



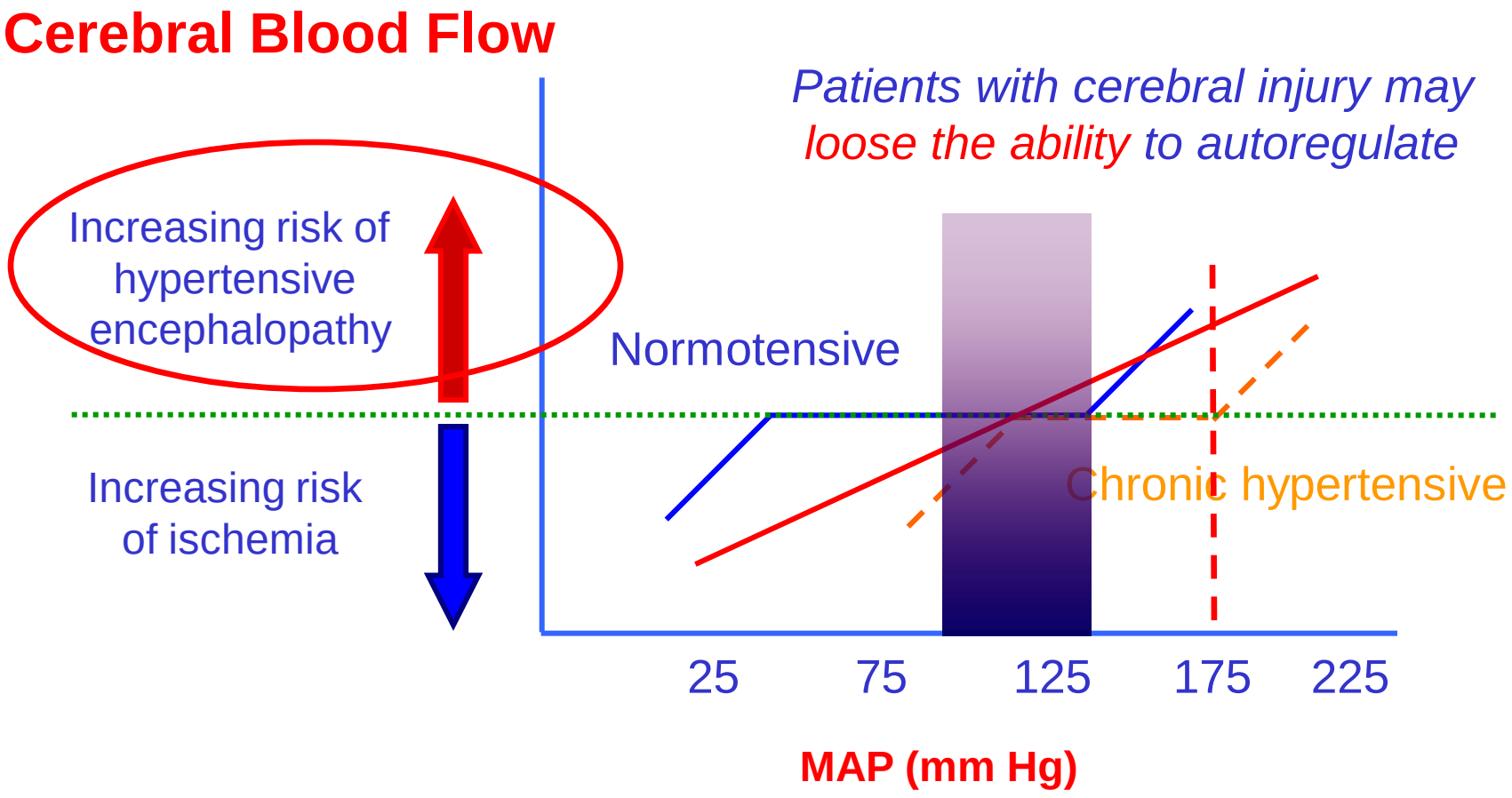
Adapted from: Varon J, Marik PE. Chest 2000; 118:214-227.

The concept of cerebral autoregulation



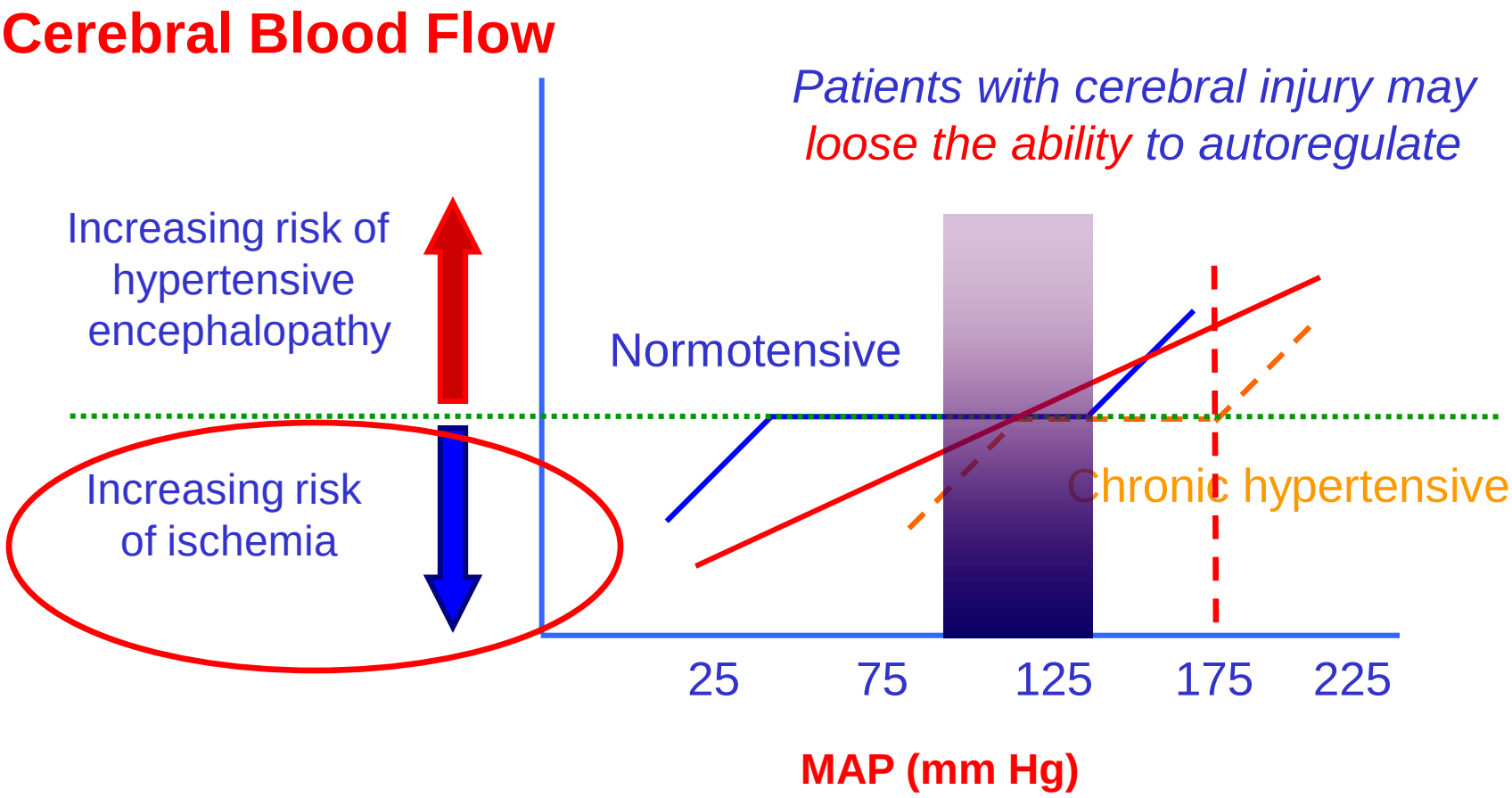
Adapted from: Varon J, Marik PE. Chest 2000; 118:214-227.

The concept of cerebral autoregulation



Adapted from: Varon J, Marik PE. Chest 2000; 118:214-227.

The concept of cerebral autoregulation



Adapted from: Varon J, Marik PE. Chest 2000; 118:214-227.

The concept of cerebral autoregulation

- So, both too low *and* too high blood pressures can be harmful.
- This applies even to non brain-injured patients, but they have a wider “margin”.
- Less margin in brain-injured patients….
- Especially if they loose their cerebral autoregulation
- Especially in injured area’s of the brain; injured area’s appear to be more susceptible to hypo- and hypertension!

Brain injury frequently leads to a wide range of medical complications:

- Myocardial dysfunction (SAH, ICH, TBI, AIS)
- Arrhythmia's/tachycardia (SAH, TBI, others?)
- Electrolyte disorders (SAH, TBI)
- Vagal nerve dysfunction leading to immune dysfunction, myocardial dysfunction and arrhythmia's (TBI, others?)
- Etc.

Cardiac complications of SAH: "Stunned myocardium"

- Elevations of cardiac troponins and/or the myocardial fraction of creatine phosphokinase (CPK-MB) (occur in 20-30% of patients with SAH)
- Linked to: high sympathetic activity ("catecholamine storm"), and also vagal activity.
  Higher risk in patients with: Hunt-Hess score >2, female sex, high BMI, high left ventricular mass, lower systolic blood pressure, higher heart rate, EKG changes, higher doses of vasoactive medication
- Elevated levels of troponins predict left ventricular dysfunction in patients with SAH (more sensitive than CK-MB)

Tung P et al. Stroke 2004;35:548-51; Deibert E et al. J Neurosurg 2003;98:741-6; Kawahara E et al. Circ J 2003;67:753-6; Kono T et al. J Am Coll Cardiol 1994;24:636-40; Parekh N et al. J Am Coll Cardiol 2000;36:1328-35; Mayer SA et al. Neurology 1994;44:815-20.

JACC Vol. 24, No. 3
September 1994:636–40

Left Ventricular Wall Motion Abnormalities in Patients With Subarachnoid Hemorrhage: Neurogenic Stunned Myocardium

TATSUJI KONO, MD, HIROSHI MORITA, MD, TOSHIHIKO KUROIWA, MD, HARUHIKO ONAKA, MD, HIROYUKI TAKATSUKA, MD, AKIRA FUJIWARA, MD

Osaka, Japan

Conclusions. **These findings suggest that patients with subarachnoid hemorrhage and ST segment elevation may demonstrate transient corresponding regional wall motion abnormalities. The mechanism of neurogenic stunned myocardium was not clearly elucidated in the present study.**

(J Am Coll Cardiol 1994;24:636–40)

"Stunned myocardium" due to sudden catecholamine release?

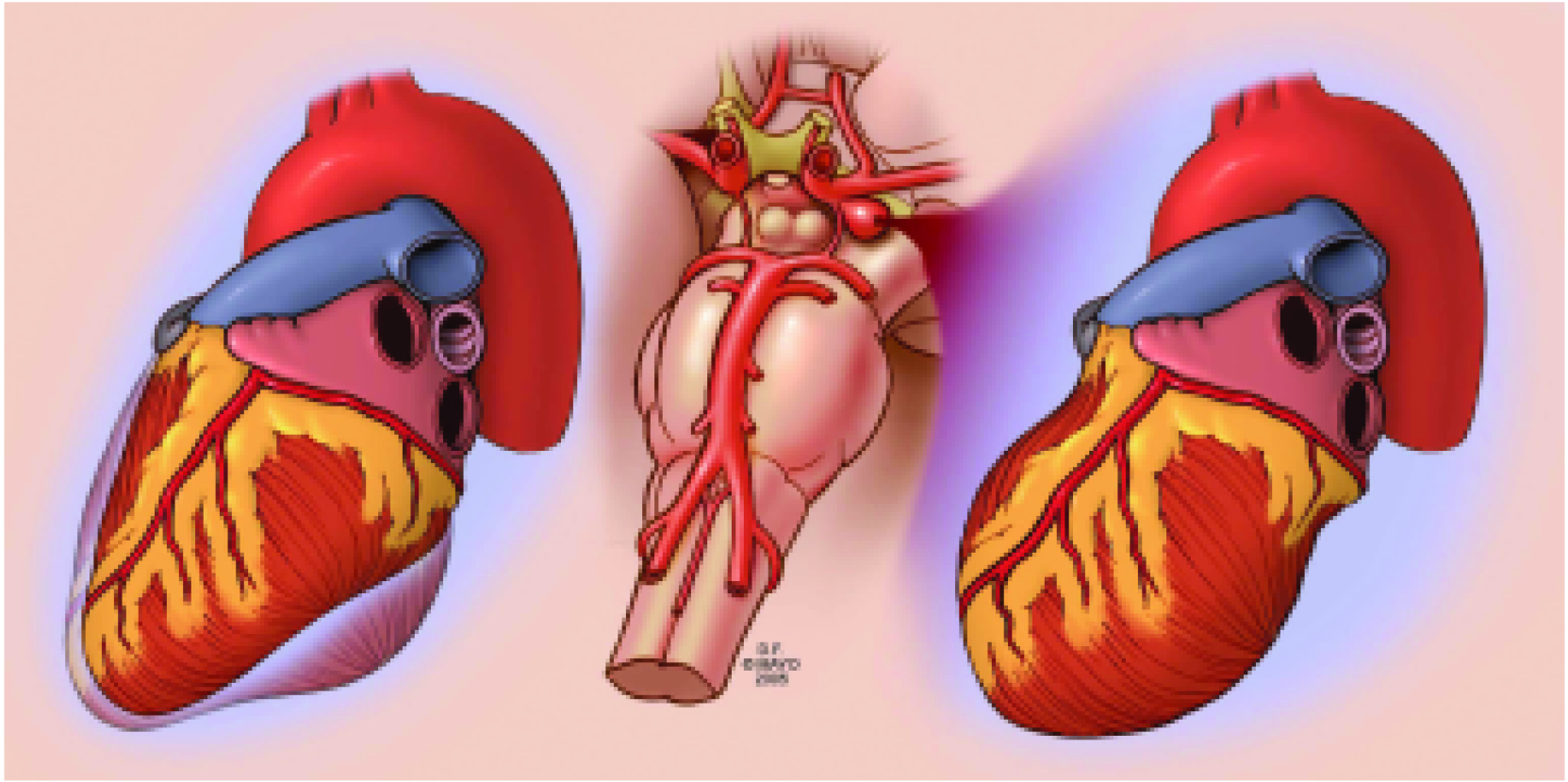


FIG. 2. Illustration of the heart depicting a normal *(left)* and abnormal *(right)* cardiac contraction. After aneurysmal SAH, the cardiac contraction becomes abnormal, with apical and midventricle akinesia consistent with tako-tsubo cardiomyopathy.

Lee VH et al. J Neurosurgery 2006; 105:264–270.

FIG. 1. Photograph illustrating a tako-tsubo, a Japanese octopus catcher pot, which is strung by rope from Japanese fishing boats. Anachoresis (living in crevices and holes) is typical behavior of octopuses. Photograph by Sarah H. Lee.

Lee VH et al. J Neurosurgery 2006; 105:264–270.

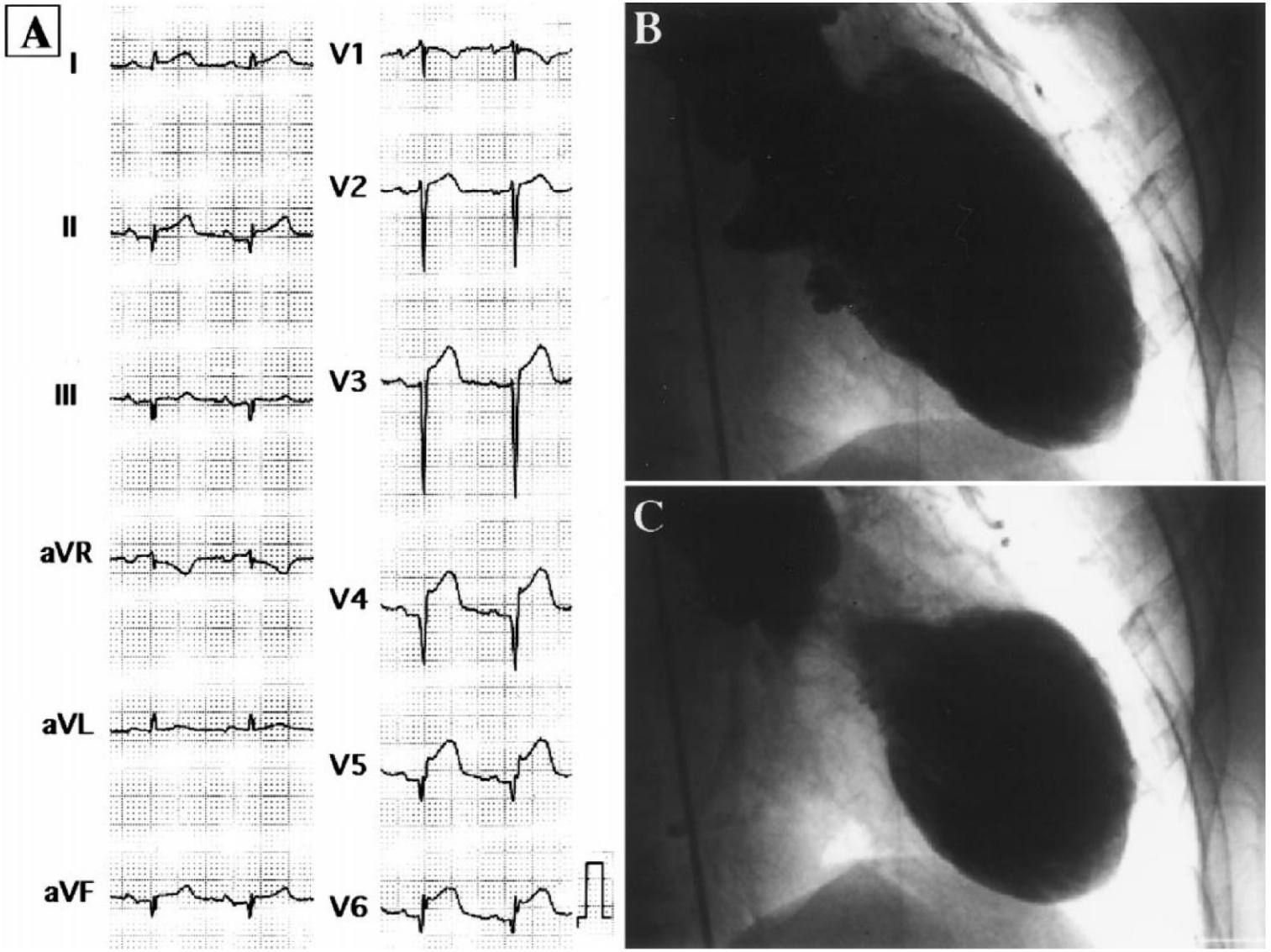


Figure 1. ECG on admission, showing abnormal Q waves and ST-segment elevation (A). Left ventriculograms in right anterior oblique view of end diastole (B) and end systole (C) show global akinesis with aneurysm formation.

Ohtsuka T et al. Circulation 2000;101;2122-2124.

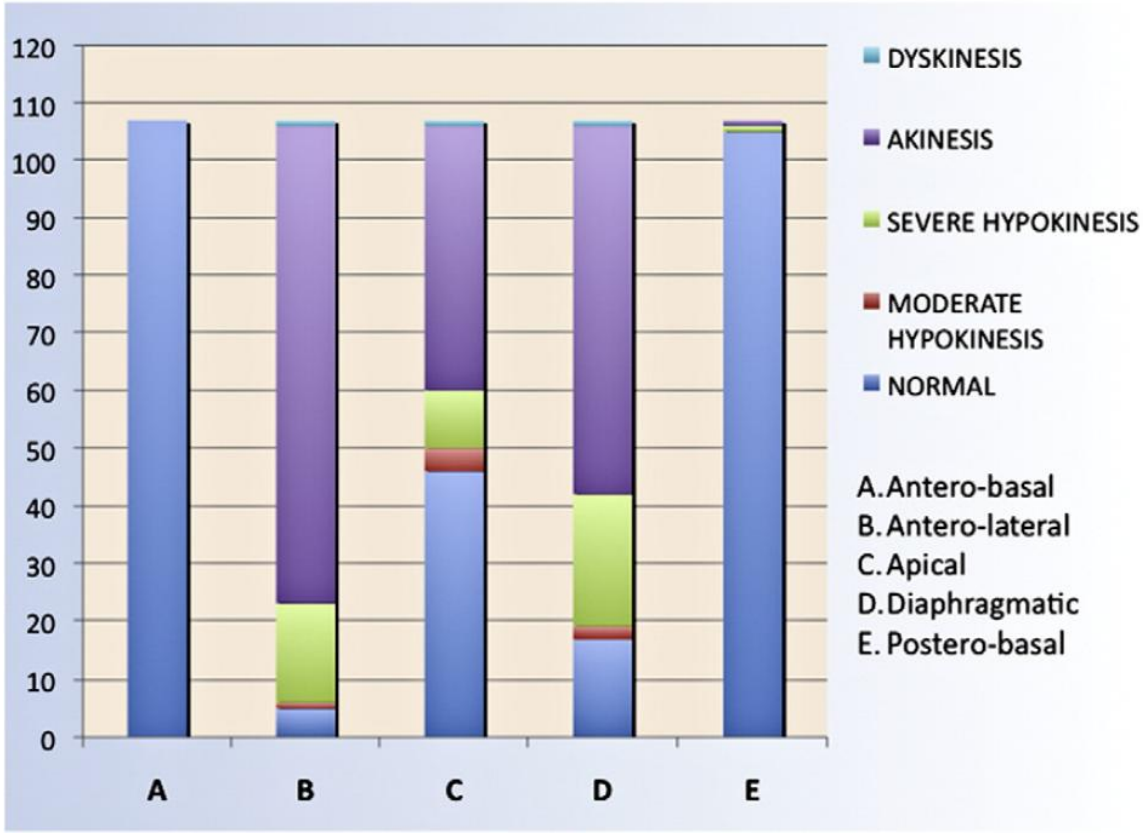
Not always typical....

Stress cardiomyopathy: Clinical and ventriculographic characteristics in 107 North American subjects

Nishith K. Singh [a,b,*], Syeda Rumman [a,b], Frank L. Mikell [a,b,c], Nasaraiah Nallamothu [a,b,c], Chandhiran Rangaswamy [a,b,c]

[a] *Department of Internal Medicine, Southern Illinois University School of Medicine, Springfield, IL, USA*
[b] *Division of Cardiology, Southern Illinois University School of Medicine, Springfield, IL, USA*
[c] *Prairie Cardiovascular Consultants, Springfield, IL, USA*

Received 27 July 2008; accepted 4 December 2008
Available online 19 January 2009



Stress cardiomyopathy: Clinical and ventriculographic characteristics in 107 North American subjects

Nishith K. Singh [a,b,*], Syeda Rumman [a,b], Frank L. Mikell [a,b,c], Nasaraiah Nallamothu [a,b,c], Chandhiran Rangaswamy [a,b,c]

[a] Department of Internal Medicine, Southern Illinois University School of Medicine, Springfield, IL, USA
[b] Division of Cardiology, Southern Illinois University School of Medicine, Springfield, IL, USA
[c] Prairie Cardiovascular Consultants, Springfield, IL, USA

Received 27 July 2008; accepted 4 December 2008
Available online 19 January 2009

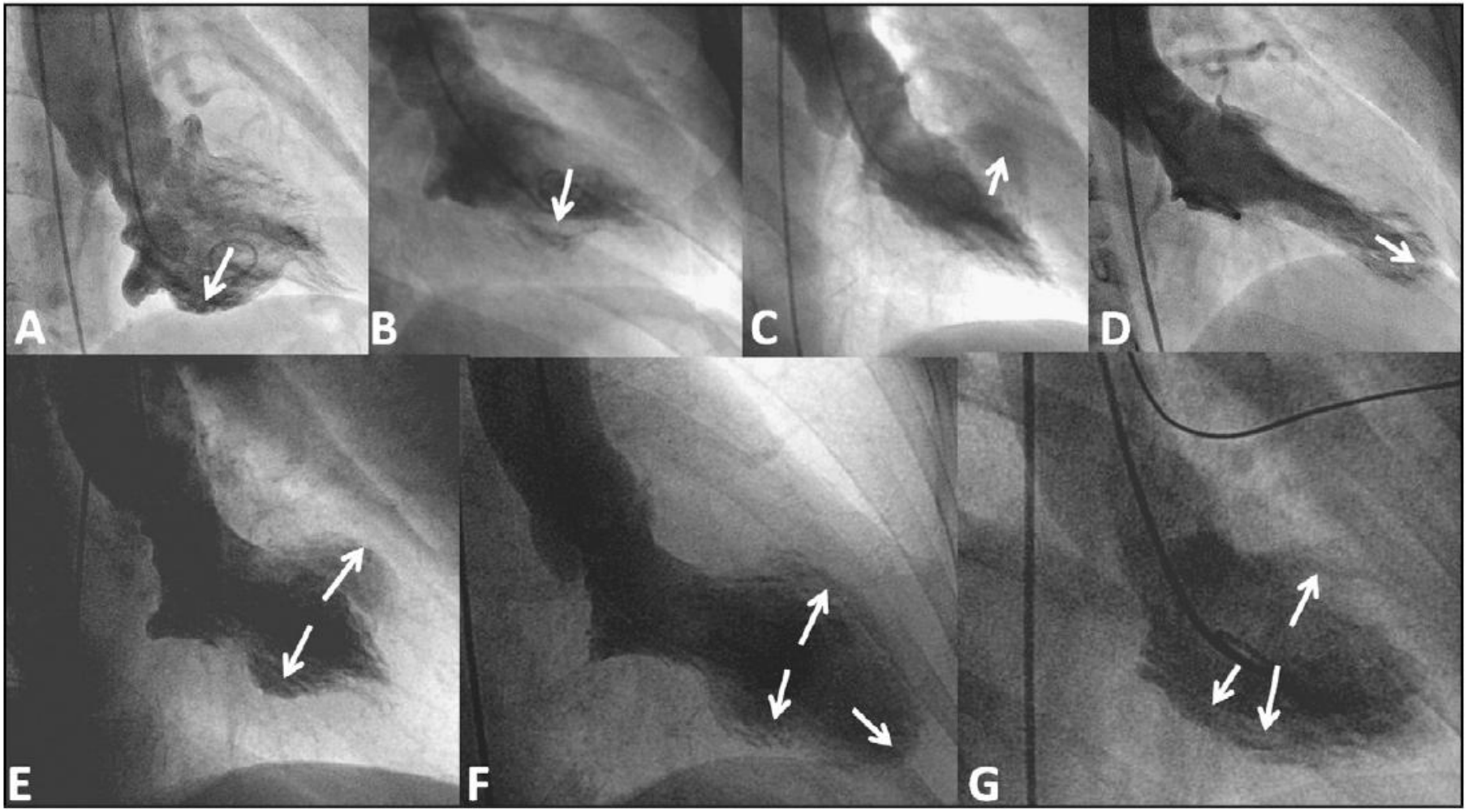


Fig. 1. End-systolic configurations of left ventricle in RAO view showing A = postero-basal, B = diaphragmatic, C = antero-lateral, D = localized apical, E = mid-ventricular, F = apico-mid-ventricular or classical or tako-tsubo, and G = postero-basal + mid-ventricular ballooning variants of stress cardiomyopathy. Arrows point towards dysfunctional segments. See text for details. RAO = right anterior oblique.

Not just in SAH....

Neurogenic stunned myocardium after acute hydrocephalus

Report of 2 cases

Hydrocephalus.....

Jeremiah Johnson, M.D.,[1] John Ragheb, M.D.,[1] Ruchira Garg, M.D.,[2] William Patten, M.D.,[3] David I. Sandberg, M.D.,[1] and Sanjiv Bhatia, M.D.[1]

[1]Division of Pediatric Neurosurgery, University of Miami Miller School of Medicine; and Departments of [2]Cardiology and [3]Critical Care, Miami Children's Hospital, Miami, Florida

J Neurosurg Pediatrics 5:428–433, 2010

Seizures.....

HIGH LIGHT

Postictal neurogenic stunned myocardium

Abstract—Neurogenic left ventricular dysfunction is a recognized complication of subarachnoid hemorrhage, but this condition has not been reported after seizure activity. The authors present two cases of neurogenic stunned myocardium after convulsive seizures, suggesting that ictal activity can lead to sympathetically mediated cardiac injury.

NEUROLOGY 2005;64:1977–1978

Peter S. Chin, MD; Kelley R. Branch, MD; and Kyra J. Becker, MD

neurocritical care society Neurocrit Care (2009) 11:395–397
DOI 10.1007/s12028-009-9279-8

PRACTICAL PEARL

Guillain-Barré Syndrome....

One Thing Leads to Another: GBS Complicated by PRES and Takotsubo Cardiomyopathy

Jennifer E. Fugate · Eelco F. Wijdicks ·
Gautam Kumar · Alejandro A. Rabinstein

Neurogenic stunned myocardium following hemorrhagic cerebral contusion

Cerebral contusion.....

Dirk Deleu, MD, FRCP, *Marie-Anne Kettern,* MD, *Yolande Hanssens,* PharmD, *Suresh Kumar,* MD, *Khalid Salim,* MD, *Francisco Miyares,* MD.

Saudi Med J 2007; Vol. 28 (2): 283-285

Relation between stress cardiomyopathy and hemorrhagic stroke

Nicolas Mansencal *, Roland N'Guetta, Julien Desperramons, Olivier Dubourg

Pôle Radio-Cardio-Vasculaire, Université de Versailles-Saint Quentin, Ambroise Paré Hospital, Assistance Publique-Hôpitaux de Paris, Centre de référence des Maladies Cardiaques Héréditaires, Boulogne, France

Hemorrhagic stroke.....

Stunned Myocardium following Ischemic Stroke

Case Report

Vasco Dias Sofia Cabral Ana Meireles Catarina Gomes Nuno Antunes
Miguel Vieira Luísa Caiado Severo Torres

Department of Cardiology, Santo António General Hospital, Oporto Hospital Center, Largo Prof. Abel Salazar, Porto, Portugal

Cardiology 2009;113:287–290
DOI: 10.1159/000205963

Ischemic stroke.....

Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 55, No. 3, 2010
ISSN 0735-1097/10/$36.00
doi:10.1016/j.jacc.2009.08.050

IMAGES IN CARDIOLOGY

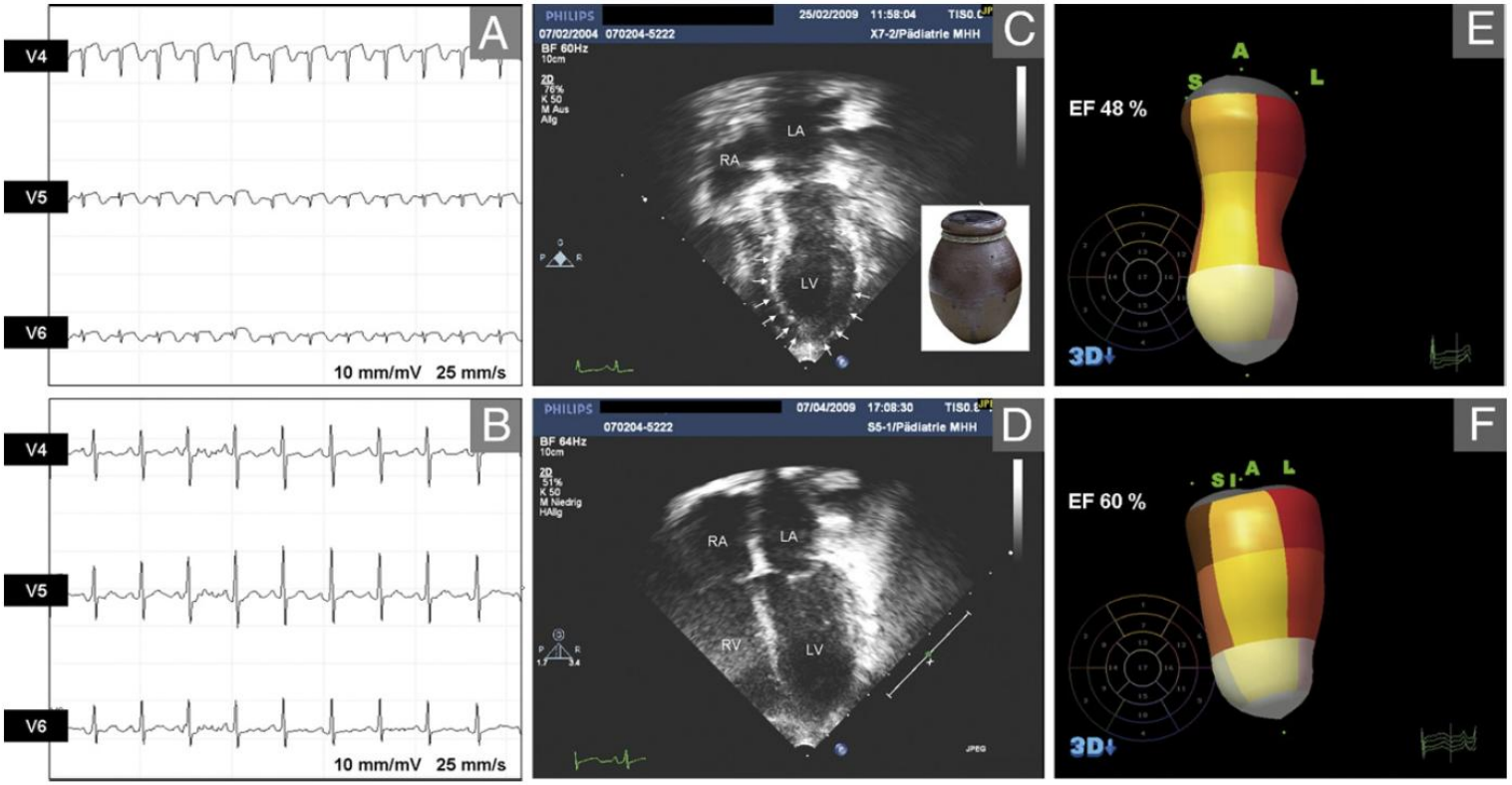
Takotsubo Cardiomyopathy in a 2-Year-Old Girl

3-Dimensional Visualization of Reversible Left Ventricular Dysfunction

Stephan Schoof, MD, Harald Bertram, MD, PHD, Dagmar Hohmann, MD, Thomas Jack, MD, Armin Wessel, MD, PHD, T. Mesud Yelbuz, MD, PHD

Hannover, Germany

Regardless of age...



Not only in brain injury....

European Heart Journal Advance Access published December 18, 2010

European Heart Journal
doi:10.1093/eurheartj/ehq456

REVIEW

Frontiers in cardiovascular medicine

Troponin elevation in coronary vs. non-coronary disease

S. Agewall[1]*, E. Giannitsis[3], T. Jernberg[2], and H. Katus[3]

Table 2 Reasons for acutely elevated troponins

Acute coronary syndrome
Acute heart failure
Pulmonary embolism
Stroke
Acute aortic dissection
Tachyarrhythmias
Hypotension / Shock
Sepsis
ARDS
Perimyocarditis
Endocarditis
Tako-tsubo cardiomyopathy
Radiofrequency catheter ablation
Cardiac contusion
Strenuous exercise
Sympathomimetic drugs
Chemotherapy

Agewall S et al.
Eur Heart J 2011;32:404-11.

"Stunned myocardium" due to sudden catecholamine release?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 10, 2005 VOL. 352 NO. 6

Neurohumoral Features of Myocardial Stunning Due to Sudden Emotional Stress

Ilan S. Wittstein, M.D., David R. Thiemann, M.D., Joao A.C. Lima, M.D., Kenneth L. Baughman, M.D., Steven P. Schulman, M.D., Gary Gerstenblith, M.D., Katherine C. Wu, M.D., Jeffrey J. Rade, M.D., Trinity J. Bivalacqua, M.D., Ph.D., and Hunter C. Champion, M.D., Ph.D.

CONCLUSIONS

Emotional stress can precipitate severe, reversible left ventricular dysfunction in patients without coronary disease. Exaggerated sympathetic stimulation is probably central to the cause of this syndrome.

Table 1. Clinical Characteristics of 19 Patients with Stress Cardiomyopathy on Admission.*

Patient No.	Age	Sex	Race or Ethnic Origin	Coronary Risk Factors	Emotional Stressor	Clinical Presentation			
						Time after Symptom Onset†	Heart Rate	MAP	Symptoms
	yr					*hr*	*beats/min*	*mm Hg*	
1	62	F	B	HTN, smoking	Mother's death	12	71	96	Chest pain
2	63	F	AA	HTN, Chol	Car accident	1	86	52	Heart failure; hypotension
3	48	F	W	HTN, Chol, smoking	Surprise reunion	4	85	88	Chest pain
4	60	F	W	HTN	Surprise party	2	109	53	Chest pain; hypotension (IABP)
5	66	F	W	HTN, FH	Father's death	5	65	91	Chest pain
6	77	F	W	HTN, FH	Husband's death	6	106	98	Chest pain
7	52	F	W	Smoking	Friend's death	2	92	50	Chest pain; hypotension (IABP)
8	52	F	W	HTN	Father's death	5	88	93	Chest pain
9	32	F	W	Chol, FH	Mother's death	1	74	90	Chest pain
10	61	F	W	Chol	Fear of procedure	1	108	45	Chest pain; shock (IABP)
11	66	F	W	Smoking	Fierce argument	2	66	109	Chest pain
12	87	F	W	HTN, Chol, DM	Friend's death	1	99	75	Chest pain
13	69	M	W	HTN, Chol	Court appearance	2	81	73	Chest pain
14	50	F	W	None	Fear of choking	2	84	100	Chest pain; heart failure
15	71	F	W	None	Public speaking	1	67	108	Chest pain
16	76	F	W	HTN, DM, smoking	Husband's death	2	109	101	Chest pain
17	65	F	W	HTN, Chol, smoking	Armed robbery	2	95	91	Chest pain
18	71	F	W	HTN	Son's death	6	70	66	Chest pain; VF
19	27	F	A	None	Tragic news	3	64	52	Chest pain; hypotension

* MAP denotes mean arterial pressure, B Bermudan, HTN hypertension, AA African American, Chol hypercholesterolemia, W white, IABP intraaortic balloon pump, FH family history, DM diabetes mellitus, VF ventricular fibrillation, and A African.

N Engl J Med 2005;352:539-48.

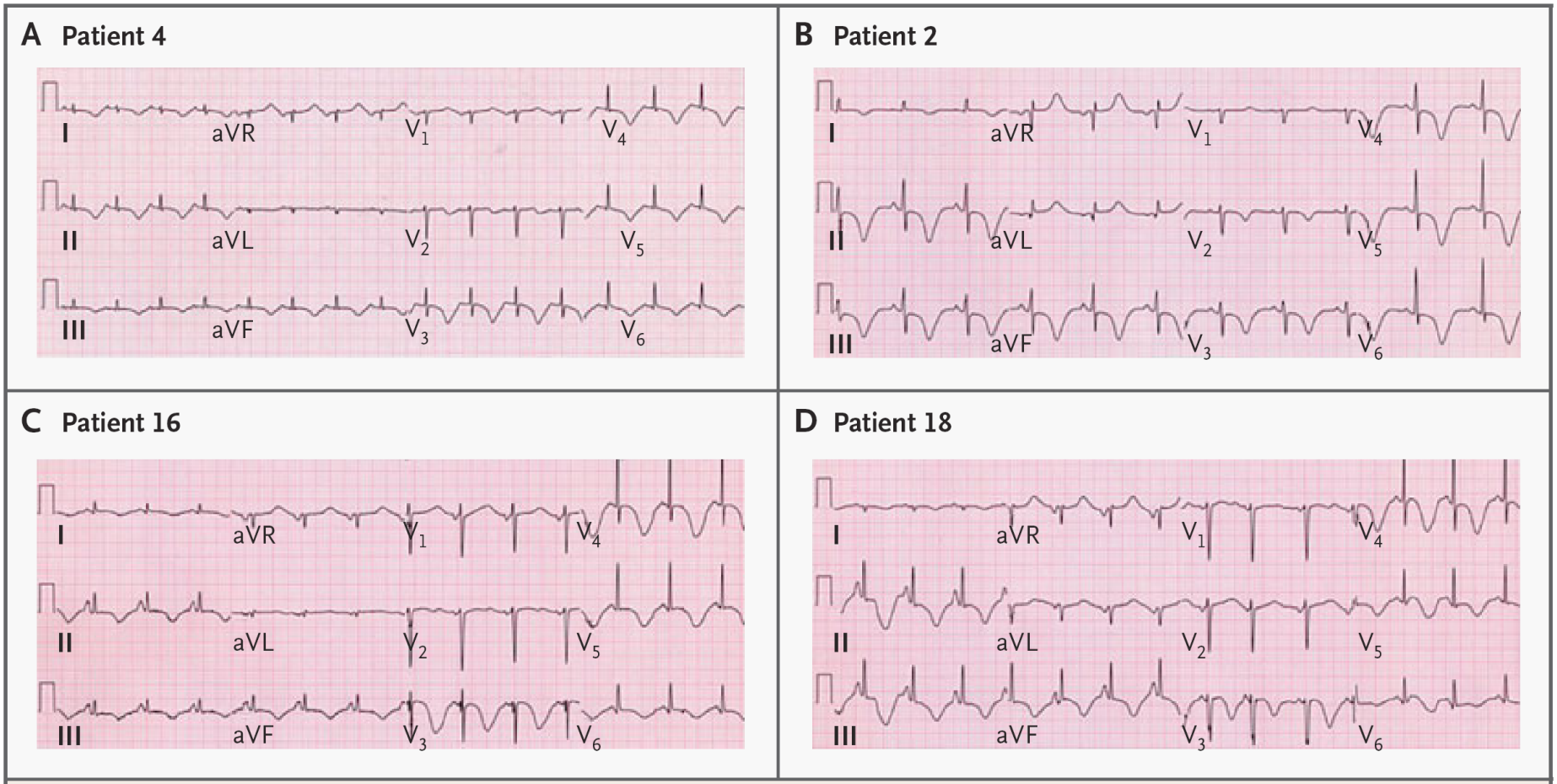


Figure 1. Typical Electrocardiograms Obtained 24 to 48 Hours after Presentation in Four Patients with Stress Cardiomyopathy.

Marked prolongation of the QT interval and diffuse symmetric T-wave inversion are present in all four electrocardiograms. Loss of R-wave progression in leads V_1, V_2, and V_3 is also evident in Panels C and D.

N Engl J Med 2005;352:539-48.

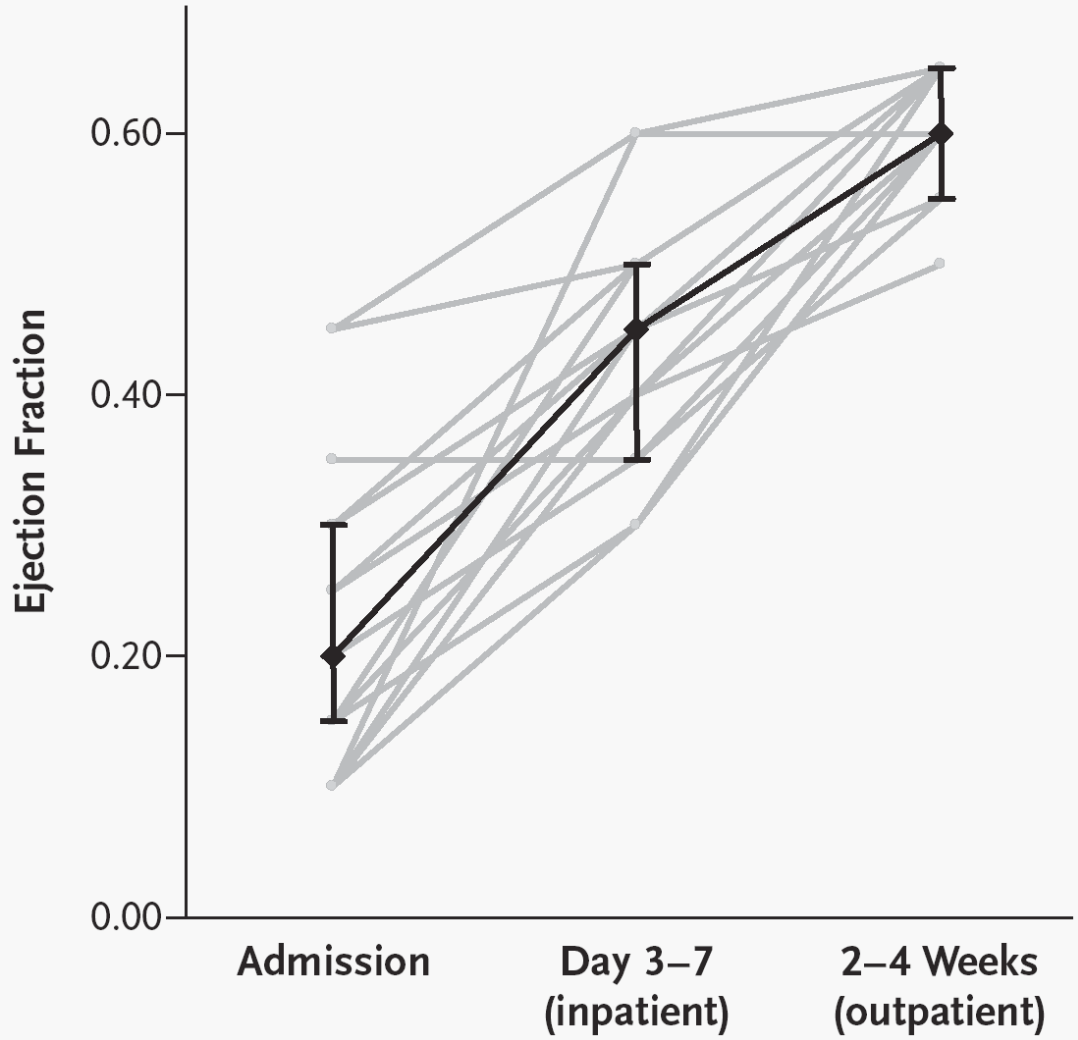


Figure 2. Serial Echocardiographic Assessment of the Ejection Fraction in 19 Patients with Stress Cardiomyopathy.

N Engl J Med 2005;352:539-48.

If this is all reversible, does this affect outcome?

neurocritical care society Neurocrit Care (2010) 13:359–365
DOI 10.1007/s12028-010-9447-x

ORIGINAL ARTICLE

Left Ventricular Dysfunction and Cerebral Infarction from Vasospasm After Subarachnoid Hemorrhage

Richard E. Temes · Elena Tessitore · J. Michael Schmidt · Andrew M. Naidech · Andres Fernandez · Noeleen D. Ostapkovich · Jennifer A. Frontera · Katja E. Wartenberg · Marco R. Di Tullio · Neeraj Badjatia · E. Sander Connolly · Stephan A. Mayer · Augusto Parra

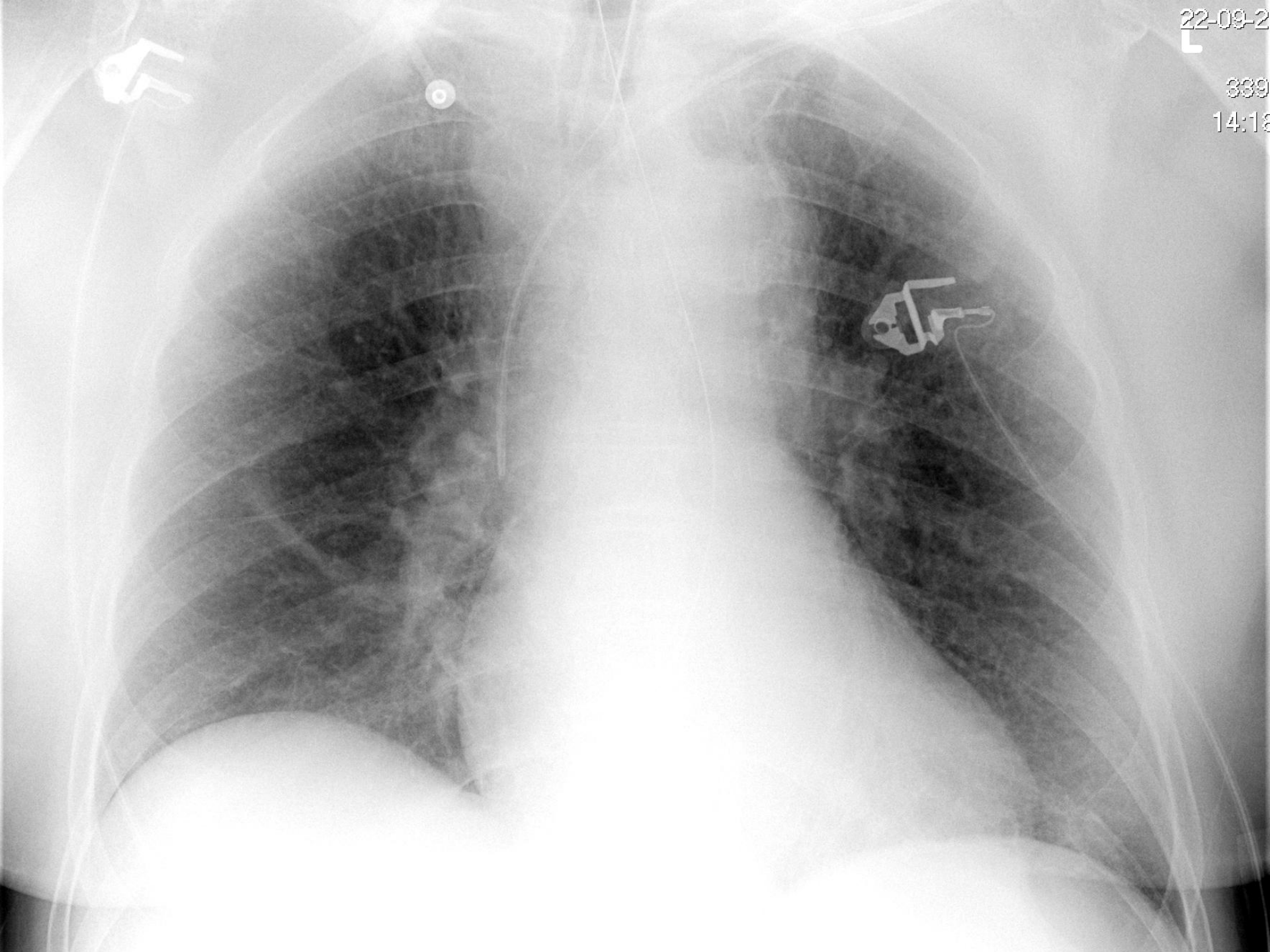
neurocritical care society Neurocrit Care (2010) 13:359–365
DOI 10.1007/s12028-010-9447-x

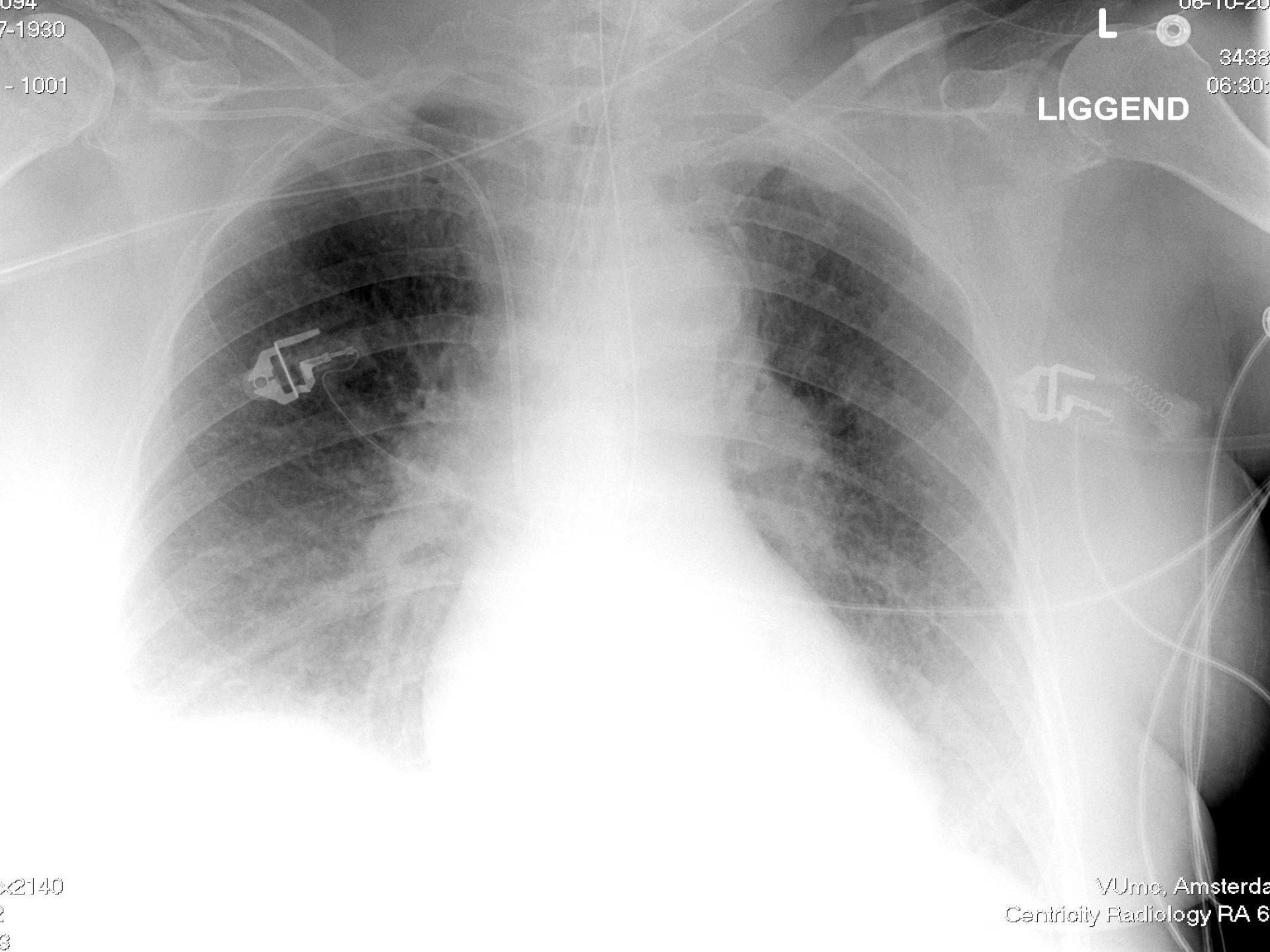
ORIGINAL ARTICLE

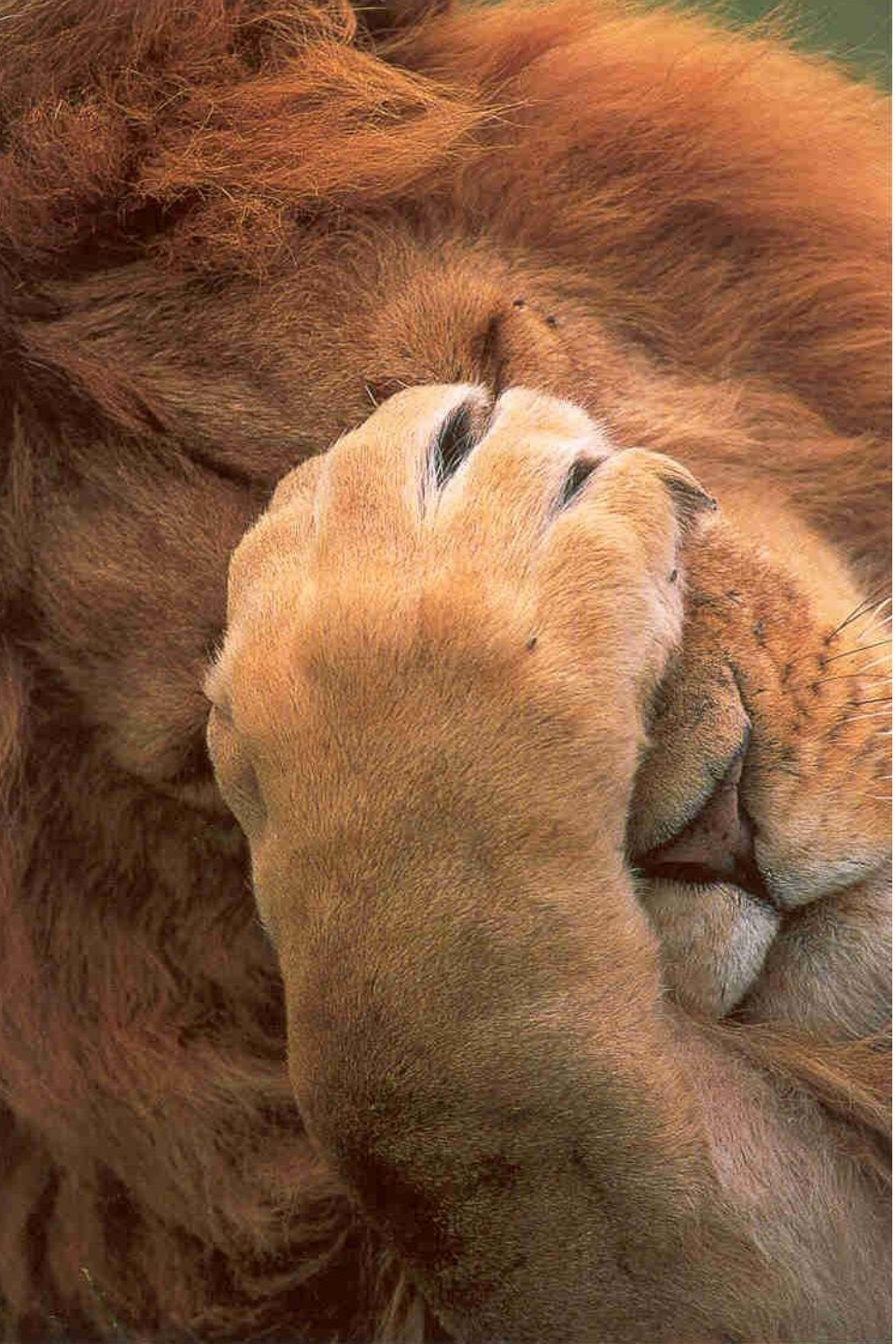
Left Ventricular Dysfunction and Cerebral Infarction from Vasospasm After Subarachnoid Hemorrhage

	LV ejection fraction		*P*
	≥40% ($N = 106$)	<40% ($N = 13$)	
Cerebrovascular events			
Cerebral infarction from vasospasm (%)	13	39	**0.034**
Any cerebral infarction (%)	45	77	**0.040**
Symptomatic vasospasm (%)	25	31	0.74
Cardiovascular events			
LV thrombus (%)	2	15	0.06
Hypotension <90 mmHg requiring pressors (%)	26	77	**0.001**
Pulmonary edema (%)	31	77	**0.002**
Cardiac arrhythmia (%)	12	15	0.67
Functional outcome[a]			
15-day mRS ≥4 (%)	69	85	0.34
Length of stay			
Median ICU stay (days)	11	15	**0.006**
Median hospital stay (days)	18	28	**0.033**

“Triple H” therapy for SAH....


22-09-2
339
14:18


L
LIGGEND

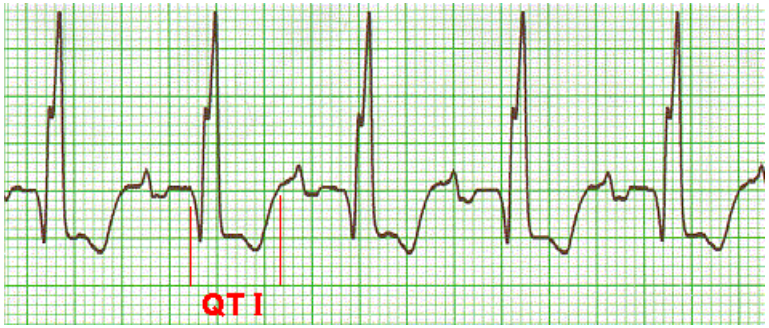


Many of the treatments we administer to protect the brain can make the “medical” situation worse!

Cardiac complications:

EKG changes & Arrhythmia's

- Occur in ±90% (!) of patients with SAH
- Especially in the first 48 hours after hemorrhage
- Most frequent EKG abnormalities:
  - Prolongation of the QTc interval (associated with higher mortality, especially in the presence of hypokalemia, defined as K <3.5)
  - ST depression
  - ST elevation
  - Inverted T waves



Lanzino G J Neurosurg Anesthesiol 1994; 6:156-62; DiPasquale G et al. Am J Cardiol 1987; 59:596-600; Mayer SA et al. J Neurosurg 1995;83:889-96.

The hyperadrenergic syndrome.....

- Tachycardia, hypertension, arrhythmia's....
- Occurs frequently in SAH, but also in TBI, ischemic stroke, ICH, and other types of neurologic injury.

Tracey KJ. J Clin Invest 2007;117:289-96

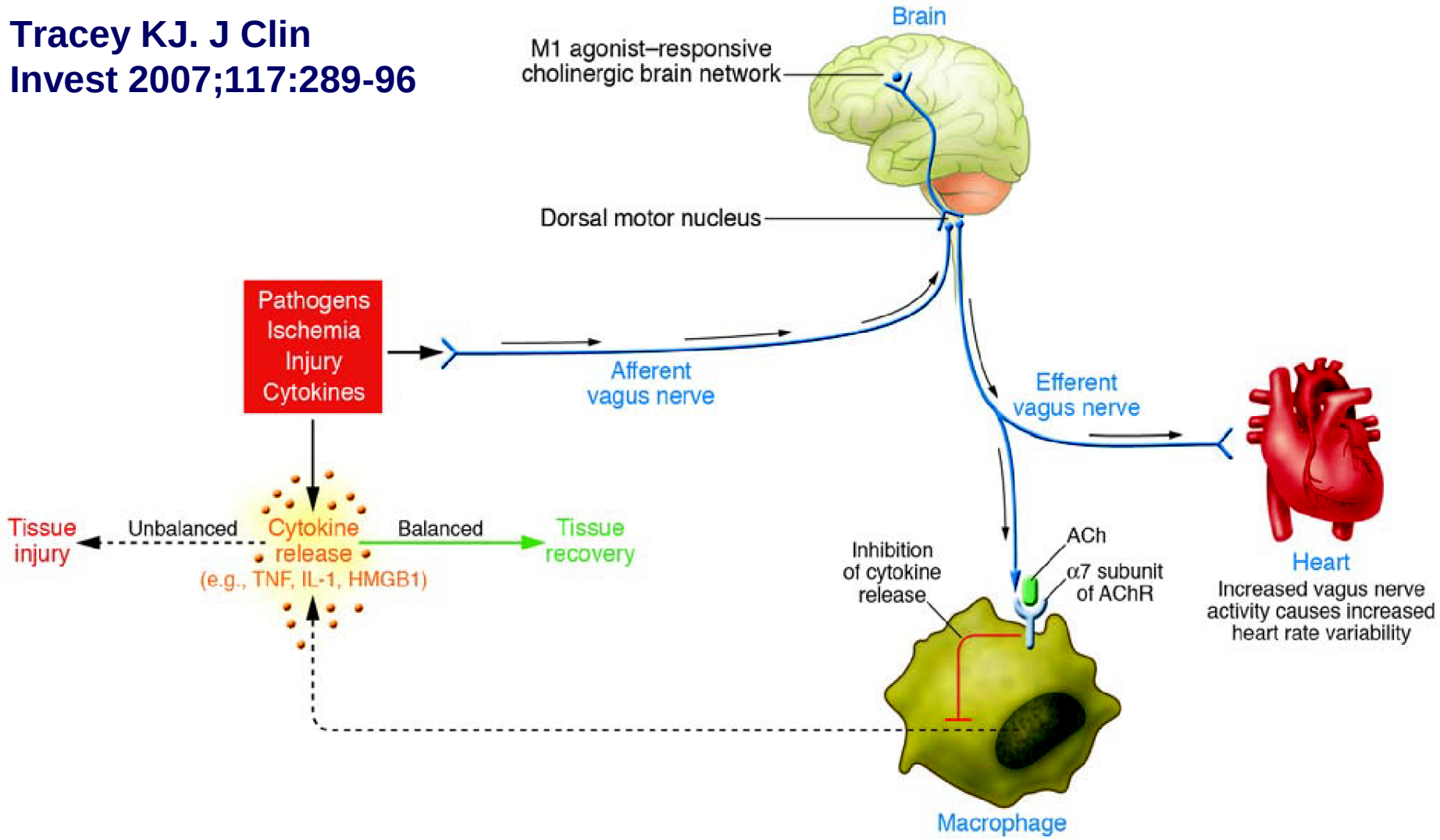
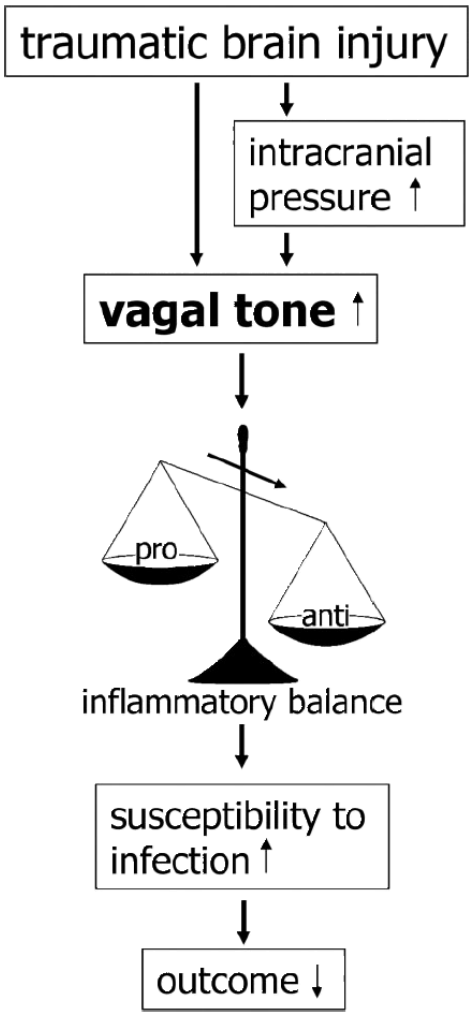


Figure 2

Wiring of the cholinergic antiinflammatory pathway, which balances cytokine production. Pathogens as well as ischemia and other forms of injury activate cytokine production, which normally restores health. If the cytokine response is unbalanced or excessive, however, then these same mediators can cause disease. Efferent signals from the vagus nerve, which can be controlled by brain networks, inhibit cytokine production via pathways dependent on the $\alpha 7$ subunit of the AChR on macrophages and other cells. Efferent vagus nerve activity also increases instantaneous heart rate variability. A cholinergic brain network that is responsive to M1 agonists can increase the activity of the cholinergic antiinflammatory pathway and also increase instantaneous heart rate variability. Afferent signals carried in the vagus nerve can activate an efferent response that inhibits cytokine release, termed the *inflammatory reflex*.

Figure Traumatic brain injury and vagal activity



Traumatic brain injury increases vagal tone directly or as a result of elevated intracranial pressure. Subsequently, vagal activity attenuates inflammation via the cholinergic anti-inflammatory pathway. As a result, susceptibility toward infections increases, resulting in worse outcome.

Kox M et al. Neurology 2008;70:48085

Can also be triggered by elective surgical procedures…

- Mainly cardiac surgery and (to a lesser extent) neurosurgery

Can also be triggered by elective surgical procedures…

- The incidence of atrial fibrillation after CABG is 16–40%, and even higher after combined CABG & valvular surgery (36–63%).
- Mortality after cardiac surgery is increased in both patients who present for cardiac surgery in atrial fibrillation, or who develop post-operative atrial fibrillation.

Kaireviciute D et al. Eur Heart J 2009; 30:410–425; Passannante AN. Curr Opinon in Anesthesiol 2011;24:58–63; Filardo G et al. Circ Cardiovasc Qual Outcomes 2009; 2:164–169; Bramer S et al. Eur J Cardiothorac Surg 2010; 38:373–379; Bramer S et al. Ann Thorac Surg 2010; 90:443–449; Schulenberg R et al. Ann Thorac Surg 2010; 89:738–744. El-Chami MF et al. J Am Coll Cardiol 2010;55:1370–1376; Kalavrouziotis D et al. Eur J Cardiothorac Surg 2009; 36:293–299.

Perioperative hypertension and tachycardia:

- Perioperative hypertension after neurosurgery is common; 54 - 91% in various studies.
- Associated tachycardia is common; arrhythmia's less frequent (new onset AF in 2% of elective and 8% of emergent cases.[1]
- Hypertension generally begins within 10 minutes of completion of surgery and lasts up to 4 hours.[2]
- Linked to significant increase in risk of ICH.[2]
- Associated with cerebral hyperemia - with increased risk for cerebral edema, and risk of ICH.[3]
- There is some evidence that early administration of antihypertensives can reduce this risk.[4]

1. Bilota F et al. Anesthesia 2009; 64:503-9
2. Basali A. Anesthesiology 2000; 93:48-54
3. Grillo P, et al. Anesth Analg 2003; 96:1145-9
4. Barron HV et al. Am J Cardiol 2000; 85:294-8.

Relation between Perioperative Hypertension and Intracranial Hemorrhage after Craniotomy

Ayman Basali, M.D., Edward J. Mascha, M.S.,† Iain Kalfas, M.D.,‡ Armin Schubert, M.D., M.B.A.§*

Anesthesiology
2000; 93:48–54

Table 2. Univariate Group Comparisons with Respect to the Incidence of Hypertension

	ICH Group (n = 69)	Control Group (n = 138)	*P* Value
Preoperative hypertension	23/68 (34%)	32/135 (24%)	0.10
Intraoperative hypertension	39/63 (62%)	42/125 (34%)	<0.001
Emergence hypertension	18/65 (28%)	15/130 (12%)	0.005
Early postoperative hypertension*	42/68 (62%)	35/136 (26%)	<0.001

* First 12 h after surgery but before intracranial hemorrhage (ICH).

Table 3. Incidence of Intraoperative Hypertension by History of Preoperative Hypertension

Preoperative Hypertension	ICH Group	Control Group
Yes	56.5% (12/23)	53.1% (17/32)
No	54.3% (25/46)	28.1% (19/103)*

* $P < 0.05$ *versus* preoperatively hypertensive controls and both intracranial hemorrhage (ICH) groups stratified by preoperative hypertension.

Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland

Anaesthesia, 2009, **64**, pages 503–507 doi:10.1111/j.1365-2044.2008.05833.x

Risk index for peri-operative atrial fibrillation in patients undergoing open intracranial neurosurgical procedures

F. Bilotta,[1] F. Pizzichetta,[1] L. Fiorani,[2] F. P. Paoloni,[3] R. Delfini[4] and G. Rosa[1]

1 Department of Anaesthesiology, Critical Care and Pain Medicine, ''La Sapienza'' University of Rome, 2 Department of Cardiology, Ospedale S. Andrea, Rome, 3 GIMEMA data centre, Rome, 4 Department of Neurosurgery, ''La Sapienza'' University of Rome, Rome, Italy

N=2020 patients

Most patients with SAH excluded!

Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland
Anaesthesia, 2009, **64**, pages 503–507 doi:10.1111/j.1365-2044.2008.05833.x

Risk index for peri-operative atrial fibrillation in patients undergoing open intracranial neurosurgical procedures

Table 4 Incidence of atrial fibrillation. Patients undergoing elective and emergency intracranial procedures who presented in sinus rhythm or developed new onset atrial fibrillation in the postoperative period.

Type of procedure	Sinus rhythm	Atrial fibrillation
Elective; number (%)	1449 (94)	33 (2.1)
Emergency; number (%)	408 (85)	37 (7.7)

Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland
Anaesthesia, 2009, **64**, pages 503–507 doi:10.1111/j.1365-2044.2008.05833.x

Risk index for peri-operative atrial fibrillation in patients undergoing open intracranial neurosurgical procedures

Table 3 Prevalence of pre-operative atrial fibrillation. Patients with sinus rhythm and with pre-operative atrial fibrillation undergoing elective and emergency intracranial procedures.

Type of procedure	Sinus rhythm	Atrial fibrillation
Elective; number (%)	1449 (94)	58 (3.7)
Emergency; number (%)	408 (85)	35 (7.2)

More reasons why arrhythmia's and hypertension are common in brain injury and after surgery..

If patients have underlying cardiovascular issues (e.g., sick sinus syndrome), this will cause problems if and when they develop other major events that put them in the ICU; e.g.,

- Trauma
- SAH
- Major surgery
- Etc. etc. etc.

And, surgery and staying in the ICU cause cardiovascular stress and psychological stress;

The patient may have pain; and any underlying psychiatric issues will become apparent.

More reasons why arrhythmia's and hypertension are common in brain injury and after surgery..

- Many of our treatments can cause electrolyte disorders, which may lead to arrhythmia's....
  - Vasoactive drugs: especially dopamine, but also norepinephrine and perhaps others;
  - Antibiotics such as pipracillin
  - Induced hypothermia
  - Etc. etc.
- Tubular dysfunction occurs in almost all ICU patients
- Etc. etc.

Causes of hypomagnesaemia

Decreased intake

- Malnutrition
- Parenteral nutrition
- Diarrhoea
- Malabsorption
- NG tube

Miscellaneous

- Pancreatitis
- Dialysis
- Alcohol-abuse
- Endocine:
  - Hyperparathyroidism
  - Hypothyroidism
  - Hyperaldosteronism
  - Excessive lactation
- Refeeding
- Hypothermia
- Intracellular shift
- Exchange transfusion
- Acute intermittent porphyria

Excessive loss

Renal loss:

- Diuretics (including osmotic diuretics)
- Diuretic phase ATN
- Hypercalcaemic states
- Tubular dysfunction
- RTA
- Hypokalemia

Drugs:

- Gentamicin, tobramycin, other aminoglycosides
- Carbenicillin
- Cis-platinum, methotrexate
- Amfotericin-B
- Foscarnet
- Pentamidine
- Polymycin B
- Ticarcillin

Here we practice only evidence-based medicine!!

What about clinical evidence??

Does hypertension *independently* predict adverse outcome in brain injury?

- **In intracranial bleeding?**
- **In ischemic stroke?**
- **After neurovascular interventions?**
- **After neurosurgical interventions?**
- **In subarachnoid haemorrhage?**

- **In post-hypoxic injury?**
- **In TBI?**
- **In other diseases associated with high intracranial pressure (liver failure, meningitis, encephalitis, etc.?**

Does hypertension *independently* predict adverse outcome in brain injury?

- **In intracranial bleeding? Yes.**
- **In ischemic stroke? Yes.**
- **After neurovascular interventions? Yes.**
- **After neurosurgical interventions? Yes.**
- **In subarachnoid haemorrhage? Yes in unsecured aneurysms; thereafter no.....?**
- **In post-hypoxic injury? No (not studied)**
- **In TBI? Yes...?**
- **In other diseases associated with high intracranial pressure (liver failure, meningitis, encephalitis, etc.? No (not studied).**

Relation between Perioperative Hypertension and Intracranial Hemorrhage after Craniotomy

Ayman Basali, M.D., Edward J. Mascha, M.S.,† Iain Kalfas, M.D.,‡ Armin Schubert, M.D., M.B.A.§*

Anesthesiology
2000; 93:48–54

Table 2. Univariate Group Comparisons with Respect to the Incidence of Hypertension

	ICH Group (n = 69)	Control Group (n = 138)	*P* Value
Preoperative hypertension	23/68 (34%)	32/135 (24%)	0.10
Intraoperative hypertension	39/63 (62%)	42/125 (34%)	<0.001
Emergence hypertension	18/65 (28%)	15/130 (12%)	0.005
Early postoperative hypertension*	42/68 (62%)	35/136 (26%)	<0.001

* First 12 h after surgery but before intracranial hemorrhage (ICH).

Table 3. Incidence of Intraoperative Hypertension by History of Preoperative Hypertension

Preoperative Hypertension	ICH Group	Control Group
Yes	56.5% (12/23)	53.1% (17/32)
No	54.3% (25/46)	28.1% (19/103)*

* $P < 0.05$ *versus* preoperatively hypertensive controls and both intracranial hemorrhage (ICH) groups stratified by preoperative hypertension.

Presenting Blood Pressure in Traumatic Brain Injury: A Bimodal Distribution of Death

Syed Nabeel Zafar, MBBS, MPH, Frederick H. Millham, MD, Yuchiao Chang, PhD, Karim Fikry, MD, Hasan B. Alam, MD, David R. King, MD, George C. Velmahos, MD, PhD, MSEd, and Marc A. de Moya, MD

(*J Trauma*. 2011;XX: 000–000)

N=7238 patients

TABLE 2. Summary Measures for Patients With TBI in Different Blood Pressure Categories

Variable	EDSBP <120	EDSBP (120–140)	EDSBP ≥140	*p*
Mortality (%)	21	9	19	<0.001*
Mean length of stay†	5.0	4.9	6.6	<0.001‡
Mean days on ventilator†	1.1	0.9	1.5	<0.001‡
Mean days in ICU†	2.1	2.2	3.0	<0.001‡

* χ^2 test.
† Of survivors.
‡ One-way analysis of variance.

Presenting Blood Pressure in Traumatic Brain Injury: A Bimodal Distribution of Death

Syed Nabeel Zafar, MBBS, MPH, Frederick H. Millham, MD, Yuchiao Chang, PhD, Karim Fikry, MD, Hasan B. Alam, MD, David R. King, MD, George C. Velmahos, MD, PhD, MSEd, and Marc A. de Moya, MD

(*J Trauma*. 2011;XX: 000–000)

N=7238 patients

Conclusions: Mortality in moderate to severe TBI has a bimodal distribution. Like hypotension, hypertension at hospital admission seems to be associated with increased mortality in TBI, even after controlling for other factors.

What about interventions to lower (or increase) blood pressure?

Ongoing studies in patients with ICH:

Two ongoing studies are evaluating the effect on outcomes of reducing BP to specified target levels:

- Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH). This study has three treatment groups: goal to reduce and maintain SBP for 24 hours from onset of symptoms to 170–200 mm Hg, 140–170 mm Hg, and 110–140 mm Hg, respectively.
- Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT)

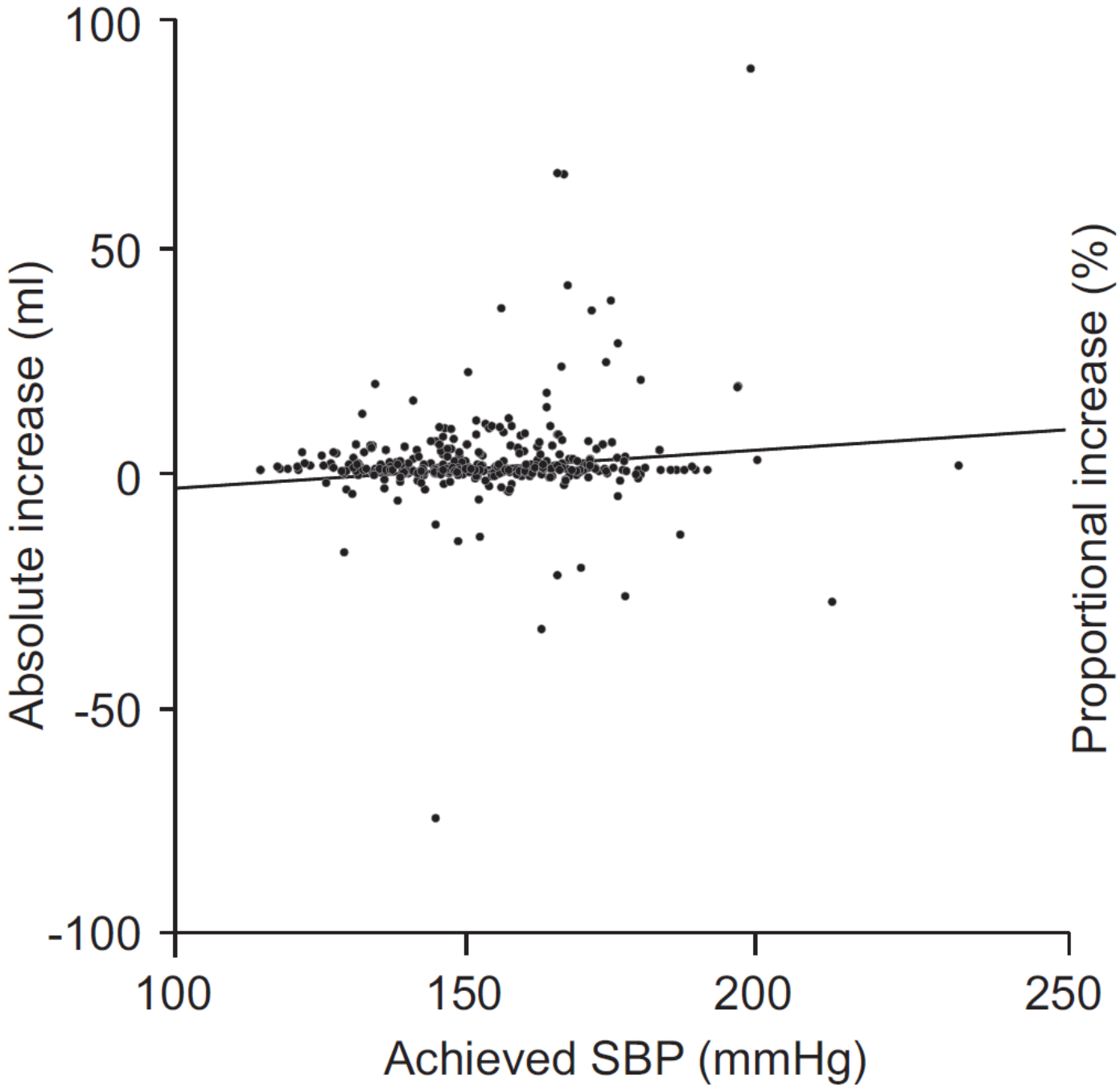
Lower Treatment Blood Pressure Is Associated With Greatest Reduction in Hematoma Growth After Acute Intracerebral Hemorrhage

Hisatomi Arima, Craig S. Anderson, Ji Guang Wang, Yining Huang, Emma Heeley, Bruce Neal, Mark Woodward, Christian Skulina, Mark W. Parsons, Bin Peng, Qing Ling Tao, Yue Chun Li, Jian Dong Jiang, Li Wen Tai, Jin Li Zhang, En Xu, Yan Cheng, Lewis B. Morgenstern, John Chalmers, for the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial Investigators

Hypertension. 2010;56:852-858.

Inclusion:

- Spontaneous ICH and elevated SBP (150–220 mm Hg)
- Early intensive BP-lowering therapy vs. standard strategy (1999 AHA guidelines)
- Intensive group: target SBP 140 mm Hg within 1 hour of randomization, maintained for 7 days.
- Treatment discontinued if SBP decreased to 130 mm Hg.
- **N=404** patients enrolled


100
50
0
-50
-100
Absolute increase (ml)
Proportional increase (%)
100
150
200
250
Achieved SBP (mmHg)

Lower Treatment Blood Pressure Is Associated With Greatest Reduction in Hematoma Growth After Acute Intracerebral Hemorrhage

Hisatomi Arima, Craig S. Anderson, Ji Guang Wang, Yining Huang, Emma Heeley, Bruce Neal, Mark Woodward, Christian Skulina, Mark W. Parsons, Bin Peng, Qing Ling Tao, Yue Chun Li, Jian Dong Jiang, Li Wen Tai, Jin Li Zhang, En Xu, Yan Cheng, Lewis B. Morgenstern, John Chalmers, for the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial Investigators

Hypertension. 2010;56:852-858.

Results:

- Mean hematoma growth 22.6% lower in the intensive treatment group (13.7% vs. 36.3%, 95% CI: -0.6% to +44.5%; p=0.06) after adjusting for initial hematoma volume and time from ICH to CT scan.
- **8%** absolute risk reduction in "substantial" hematoma growth (>33% or 12.5 mL) (95% CI -1% to +17%; p = 0.05) in low BP group (15% vs. 23%); relative risk reduction **36%.**

BUT, on the other hand….

Antihypertensive treatment of acute cerebral hemorrhage*

Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) investigators

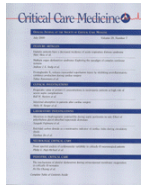


Table 6. End points observed within subjects according to SBP target tier

Characteristics	First Tier, SBP 170–200 mm Hg, n = 18	Second Tier, SBP 140–170 mm Hg, n = 20	Third Tier, SBP 110–140 mm Hg, n = 22
Treatment failure	0	0	9 (41%)
N (%) with SAE within 72 hrs	0	1 (5%)	3 (14%)
N (%) with neurologic deterioration within 24 hrs	1 (6%)	2 (10%)	4 (18%)
N (%) with symptomatic hematoma expansion	0	1 (5%)	4 (18%)
N (%) with asymptomatic hematoma expansion	6 (33%)	2 (10%)	3 (14%)
N (%) with in-hospital mortality	2 (11%)	1 (5%)	1 (4 %)
N (%) with 3-mo mortality	3 (17%)	2 (10%)	5 (23%)
1-mo favorable outcome, mRS 0–2	4 (3 missing)	6 (3 missing)	4 (2 missing)
3-mo favorable outcome, mRS 0–2	8 (3 missing)	9 (4 missing)	7 (2 missing)

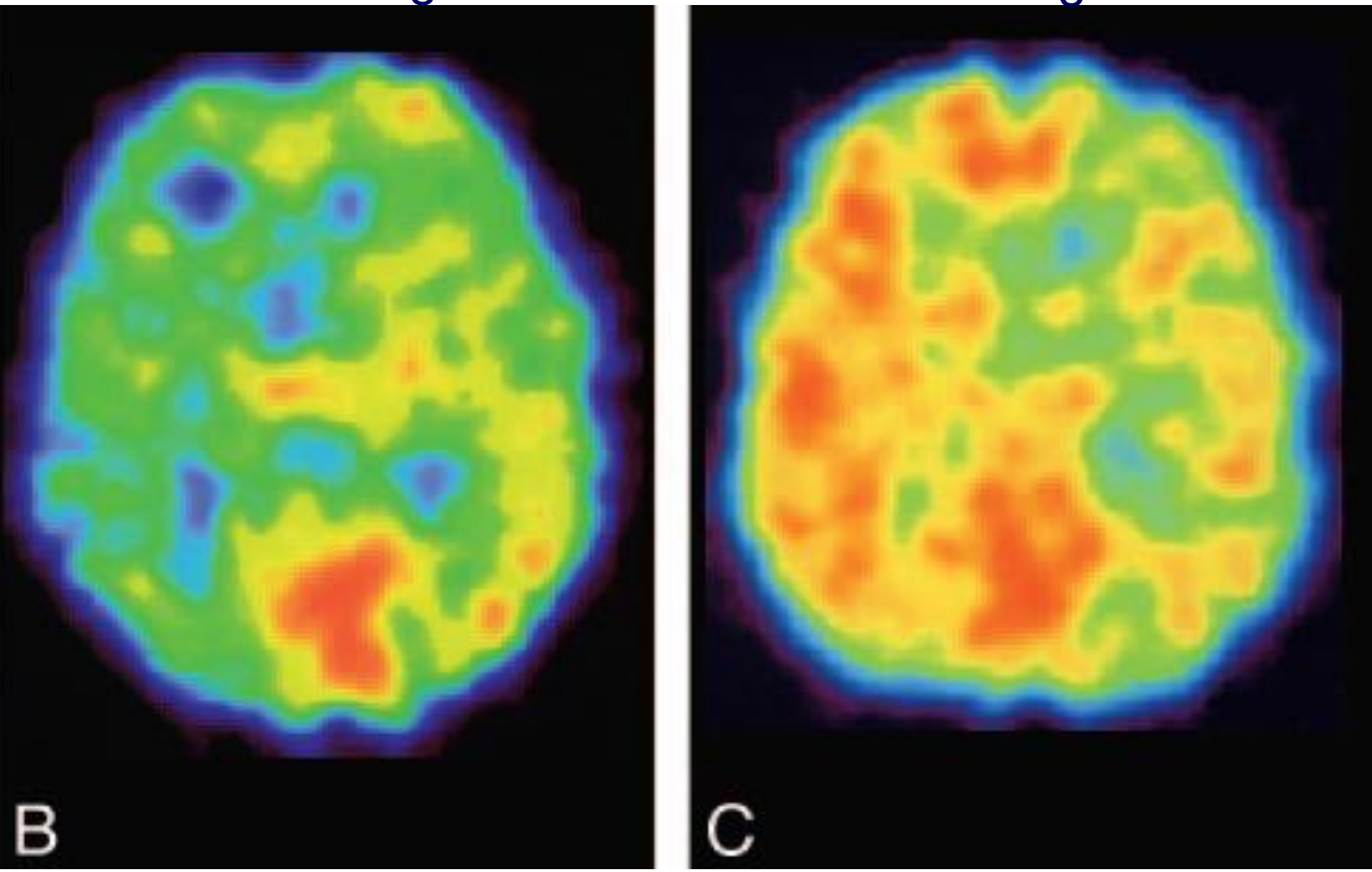
SBP, systolic blood pressue; SAE, serious adverse event; mRS, modified Rankin score.

What about interventions to lower (or increase) blood pressure?

- **In intracranial bleeding? Yes.**
- **In ischemic stroke? Yes.**
- **After neurovascular interventions? Yes.**
- **After neurosurgical interventions? Yes.**
- **In subarachnoid haemorrhage? Yes in unsecured aneurysms; thereafter no.....?**
- **In post-hypoxic injury? No (not studied)**
- **In TBI? Yes....?**
- **In other diseases associated with high intracranial pressure (liver failure, meningitis, encephalitis, etc.? No (not studied).**

R ICA stenosis (85%) before stenting

R ICA stenosis (85%) after stenting



Fukuda T et al. Am J Neuroradiol 2007;28:737– 42

Cerebral hyperperfusion syndrome

Walther N K A van Mook, Roger J M W Rennenberg, Geert Willem Schurink, Robert Jan van Oostenbrugge, Werner H Mess, Paul A M Hofman, Peter W de Leeuw

Lancet Neurol **2005; 4: 877–88**

Panel 1: Summary of revascularisation procedures causing CHS

Carotid endarterectomy[8]
Aorto-carotid surgery[9]
Extracranial-intracranial bypass[10]
Carotid stenting[11]
Carotid percutaneous transluminal angioplasty [9]
Percutaneous transluminal angioplasty of the vertebral artery[12]
Percutaneous transluminal angioplasty of the middle cerebral artery[13]
Percutaneous transluminal angioplasty of the brachiocephalic arteries[9]
Percutaneous transluminal angioplasty/stent of the subclavian artery[12]
Resection right temporo-occipital arteriovenous malformation with ipsilateral middle and posterior cerebral arterial supply[14]
Clipping of giant internal carotid artery aneurysm[15]
Carotid-subclavian bypass[16]
Innominate endarterectomy[17]
Dural arteriovenous fistula embolisation[18]

van Mook WN et al. Lancet Neurol 2005;4:877-88

	Design	Intervention	Patients/ interventions	Definition of hyperperfusion (syndrome)	Patients with hyperperfusion	Patients with CHS
Sundt[8]	Retrospective	CEA	1145	Regional cerebral blood flow >100%	Not reported	22/1145=1·9%
Reigel[24]	Restrospective	CEA	2439	Unilateral headche, seizures and transient neurological deficit during the postoperative period after CEA	Not reported	10/2439=0·4%
Piepgras[25]	Retrospective	CEA	2362	>100% increase in baseline cerebral blood flow	274/2362=11·6%	12/2362=0·5%
Nicholas[26]	Retrospective	CEA	2331	Ocular blood flow ipsilateral to the CEA exceeding a level considered to be within normal limits (=mean+3 SD, =4·12 mL/min)	12/2331=0·5%	5/2331=0·2%
Sbarigia[27]	Prospective	CEA	36	Unilateral head, eye or facepain, contralateral seizures, delayed intracerebral haemorrhage	3/36=8·3%	3/36=8·3%
Jansen[28]	Prospective	CEA	130	Not reported	Not reported	2/130=1·5%
Jorgensen[20]	Prospective	CEA	95	Symptoms related to excessive increases in cerebral blood flow	Not reported	18/95=18·9%
Chambers[29]	Prospective	CEA	35/40	Transient increase in velocity of at least 20% relative to steady state 1 month after CEA	16/40=40%	1/35=2·9%
Jansen[30]	Retrospective	CEA	233	Not reported	Not reported	17/233=7·3%
Breen[31]	Retrospective	CEA	184	Not reported	Not reported	5/184=2·7%
Spencer[32]	Retrospective	CEA	500	Persistance of MCA velocities >1·5 times values before cross clamping during shunting or after final release of carotid cross clamps, without adequate corrective measures	73/500=15% (MCAV>2×pre-clamp MCAV)	8/500=1·6 %*
Gosetti[33]	Retrospective	CEA	198/178	Mean blood velocity >100% of basal value	Not reported	12/198=6·1%
Dalman[34]	Case cohort	CEA	688	>100% increase peak blood flow velocities; 100% increase of Gosling pulsatility indices	62/688=9%	7/688=1·1%
Meyers[35]	Retrospective	PTA craniocervical arteries	140	Clinical and radiographic signs of hyperperfusion	Not reported	7/140=5%
Dunne[36]	Retrospective	CEA	30	Flow exceeding 1000 cm/s, or three times the velocity 24 h before surgery	6/30=20%	1/30=3·3%
Keunen[37]	Retrospective	CEA	55	Change of blood flow velocity >100% of preoperative value	5/55=9·1%	1/55=1·8 %
Beard[38]	Prospective	CEA	300	Cerebral oedema due to increased cerebral perfusion	Not reported	4/300=1·3%
Hosoda[39]	Prospective	CEA	26	CBF increase ⩾100%	2/26=7·7%	2/26=7·7%
Nielsen[40]	Prospective	CEA	61	Symptoms occurring some days after surgery accompanied by hypertension and seizures	100% directly postoperative	2/61=3·3%
Hingoran [41]	Retrospective	CEA	444	Hypertension, headaches, seizures, intraparechymal bleeding, oedema, herniation and death	Not reported	2/444=0·5%
Ogasawara[42]	Prospective	CEA	50	CBF increase of ⩾100% compared with preoperative values	6/50=12%	1/50=2%
Naylor[4]	Prospective	CEA	949	Not reported	3/8 if MCAV >100% following clamping and after 3	8/949=0·8%
Ogasawara[23]	Prospective	CEA	55	CBF increase of ⩾100% compared with preoperative values	8/55=14·5%	2/55=3·6%
Hosoda[43]	Prospective	CEA	41	CBF increase ⩾100%	5/41=12·2%	4/41=9·8%
Ascher[44]	Retrospective	CEA	404	Severe unilateral postoperative headache ipsilateral to the site of endarterectomy, seizures, of stroke, accompanied by increased ipsilateral ICA flow (100%) compared with intraoperative values	Not reported	9/404=2·2%
Coutts[45]	Retrospective	CEA/CAS	129/44	Neurological deficit that occurred after cerebral vascularisation and was localised ipsilateral to the treated artery, not related to thromboemolism	Not reported	4/129=3·1%/ 3/44=6·8%
Fujimoto[46]	Prospective	CEA	95	Probable hyperperfusion syndrome was diagnosed if the patient demonstrated a focal seizure, temporary deterioration of consciousness level with remarkably abnormal speech and conduct for 6 h after stopping propofol sedation, development of focal neurological signs, such as motor weakness, or intracranial haemorrhage, on CT	Not reported	12/95=12·6 %
Yoshimoto[47]	Prospective	CEA	18	Not reported.	7/18=38·9%	2/18=11·1%
Karapanayiotides[48]	Retrospective	CEA	388	Transient neurological deficits associated with a migraine-like headache, seizures, and intracerebral haemorrhage	Not reported	5/388=1·3%
Wagner[49]	Retrospective	CEA	1602	Severe headaches that significantly prolonged the patients hospitalisation, new-onset seizures or intracranial haemorrhage that developed after completion of the endarterectomy	Not reported	6/1602=0·4%
Ogasawara[50]	Prospective	CEA	67	CBF increase of ⩾100 % compared with preoperative values	7/67=10·4%	2/67 3·0%

*Hyperperfusion sometimes in combination with other causal factors. CEA=carotid endarterectomy; PTA=percutaneous transluminal angioplasty.

Table: Overview of studies on CHS

Incidence
0.4 – 18.9%

van Mook WN et al. Lancet Neurol 2005;4:877-88

Table I. Incidence of hyperperfusion, cerebral hyperperfusion syndrome, and intracranial hemorrhage after carotid endarterectomy in the reviewed series from 2003 to 2008

Author	*Year*	*Patients (n)*	*Definition of hyperperfusion/CHS*	*Patients with hyperperfusion (%)*	*Patients with CHS (%)*	*Patients with ICH (%)*
Ogasawara[47]	2007	1596	Acute neurological deteriorati		30/1596 (1.9%)	6/1596 (0.4%)
Maltezos[65]	2007	100	in the immediate		14/100 (14%)	n.r.
Wagner[84]	2005	1602	postoperative period		6/1602 (0.4%)	3/1602 (0.2%)
Karapanayiotides[24]	2005	388			5/388 (1.3%)	4/388 (1%)
Fujimoto[73]	2004	95			12/95 (13%)	n.r
Coutts[3]	2003	129			4/129 (3.1%)	1/129 (0.8%)
Fukuda[71]	2007	70	CBF increase of 100% compared with preoperative values assessed by PWI	7/70 (10%)	2/70 (2.8%)	n.r.
Ogasawara [15]	2005	67	CBF increase >100%, compared with preoperative values measuring BFV in MCA by TCD or assessed by SPECT images	7/67 (10.4%)	2/67 (3%)	n.r.
Hosoda[18]	2003	41	CBF increase >100%, compared	4/41 (9.8%)	n.r.	0%
Yoshimoto[19]	2005	18	with preoperative values	7/18 (11%)	2/18 (11%)	n.d.
Suga[20]	2007	90	assessed by SPECT images	12/90 (13%)	2/90 (2.2%)	n.d.
Komoribayashi[75]	2006	89		10/89 (11%)	2/89 (2.2%)	n.d.
Ascher[21]	2003	404	Severe ipsilateral headache, seizures Increased ipsilateral ICA volume flow (>100%) compared with intraoperative values measured by TCD	n.r.	9/404 (2.2%)	n.d.
Total		4689		47/375 (12.5%)	90/4648 (1.9%)	14/3756 (0.37%)

Incidence
0.4 – 14%
Avg. 1.9%

BFV, Blood flow velocity; *CEA*, carotid endarterectomy; *CHS*, cerebral hyperperfusion syndrome; *ICA*, intracranial artery; *ICH*, intracranial hemorrhage; *MCA*, middle cerebral artery; *n.d.*, not determined; *n.r.*, not reported; *PWI*, perfusion-weighted magnetic resonance imaging; *SPECT*, single-photon emission computed tomography; *TCD*, transcranial Doppler.

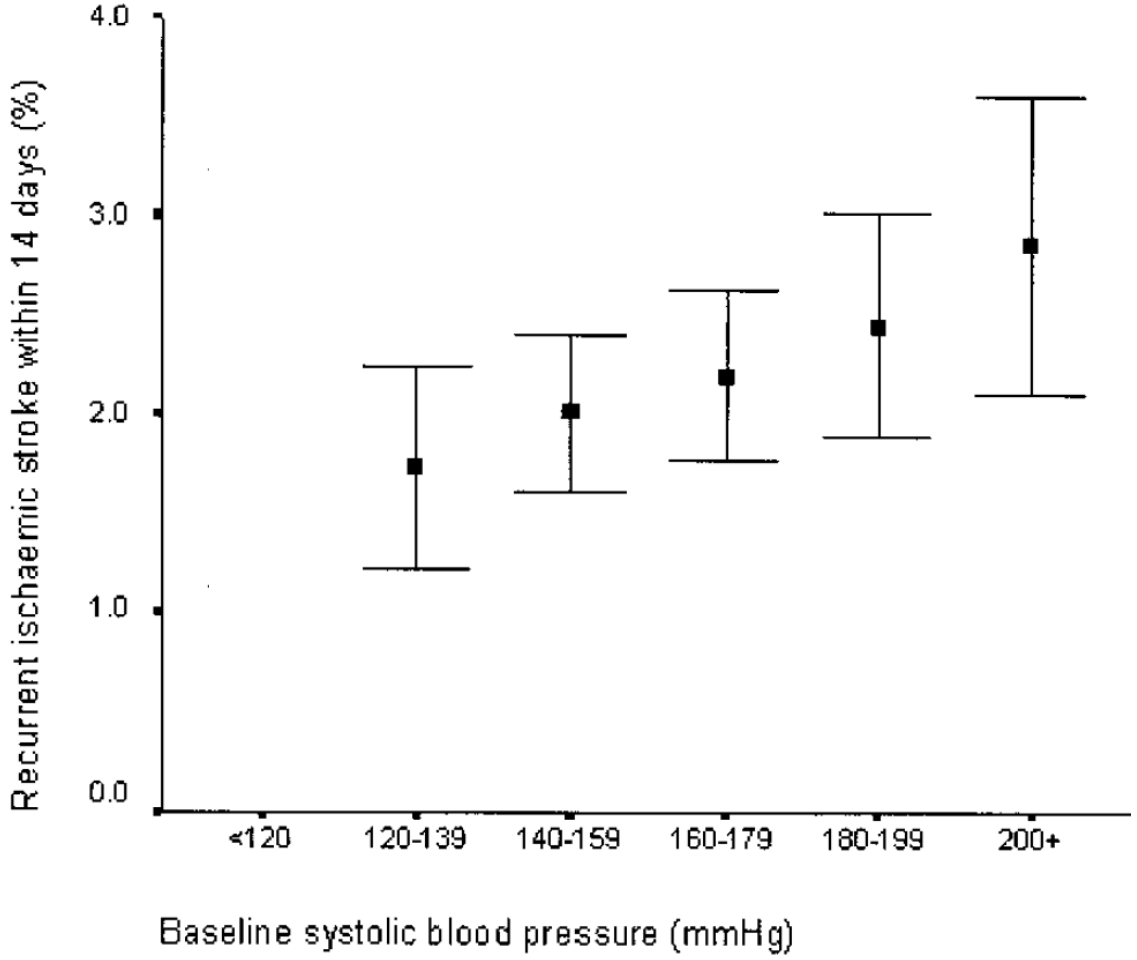
Konstantinos G et al. J Vasc Surg 2009;49:1060-8

Does hypertension *independently* predict adverse outcome in brain injury?

- **In intracranial bleeding? Yes.**
- **In Stroke? Yes.**
- **After neurovascular interventions? Yes.**
- **In subarachnoid haemorrhage? Yes in unsecured aneurysms; thereafter no...?**
- **In post-hypoxic injury? No (not studied)**
- **In TBI? No....?**
- **In other diseases associated with high intracranial pressure (liver failure, meningitis, encephalitis, etc.? No (not studied).**

Blood Pressure and Clinical Outcomes in the International Stroke Trial

Jo Leonardi-Bee, MSc; Philip M.W. Bath, FRCP; Stephen J. Phillips, FRCPC; Peter A.G. Sandercock, FRCP; for the IST Collaborative Group



N= 17398 patients

Does *hypo* tension independently predict adverse outcome in brain injury?

- **In intracranial bleeding? Yes (?)**
- **In Stroke? Yes!**
- **After neurovascular interventions? Yes.**
- **After neurovascular interventions? Yes.**
- **In subarachnoid haemorrhage? Not studied..**
- **In post-hypoxic injury? Yes..?**
- **In TBI? Yes?**
- **In other diseases associated with high intracranial pressure (liver failure, meningitis, encephalitis, etc.? Yes/not studied**

Hypotension predicts adverse outcome in TBI:

- **Fearnside MR et al. Br J Neurosurg 1993; 7:267-79 (adult patients)**
- **Chesnut RM et al. J Trauma 1993; 34:216-22 (adult patients)**
- **Vavilala MS et al. J Trauma 2003; 55:1039-44 (paediatric patients)**
- **Ducrocq SC et al. Pediatr Crit Care Med 2006; 7:461-7 (paediatric patients)**

Hypotension predicts adverse outcome in TBI:

- **Fearnside MR et al. Br J Neurosurg 1993; 7:267-79 (adult patients)**
- **Single episode of hypotension is associated with ↑↑morbidity and doubling of mortality**

Presenting Blood Pressure in Traumatic Brain Injury: A Bimodal Distribution of Death

Syed Nabeel Zafar, MBBS, MPH, Frederick H. Millham, MD, Yuchiao Chang, PhD, Karim Fikry, MD, Hasan B. Alam, MD, David R. King, MD, George C. Velmahos, MD, PhD, MSEd, and Marc A. de Moya, MD

(*J Trauma*. 2011;XX: 000–000)

N=7238 patients

TABLE 2. Summary Measures for Patients With TBI in Different Blood Pressure Categories

Variable	EDSBP <120	EDSBP (120–140)	EDSBP ≥140	*p*
Mortality (%)	21	9	19	<0.001*
Mean length of stay†	5.0	4.9	6.6	<0.001‡
Mean days on ventilator†	1.1	0.9	1.5	<0.001‡
Mean days in ICU†	2.1	2.2	3.0	<0.001‡

* χ^2 test.
† Of survivors.
‡ One-way analysis of variance.

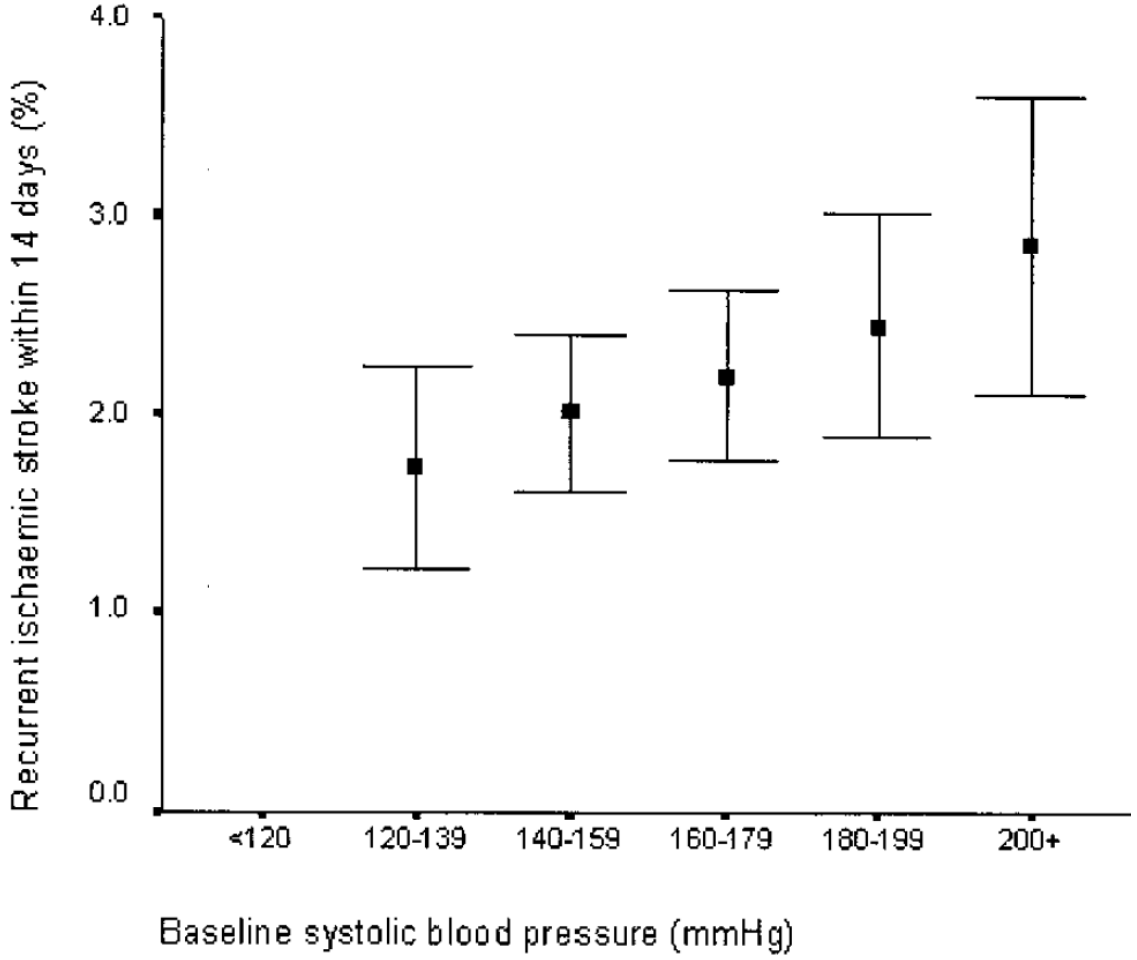
Hypotension predicts adverse outcome in stroke.

- **Hypotensive episodes also associated with adverse outcome in stroke**

Martin DR et al. Ann Emerg Med 1993; 22:917 [abstract]; Spivey et al. Ann Emerg Med 1991; 20:453 [abstract]; Mullner M et al. Stroke 1996; 27:59-62.

Blood Pressure and Clinical Outcomes in the International Stroke Trial

Jo Leonardi-Bee, MSc; Philip M.W. Bath, FRCP; Stephen J. Phillips, FRCPC; Peter A.G. Sandercock, FRCP; for the IST Collaborative Group

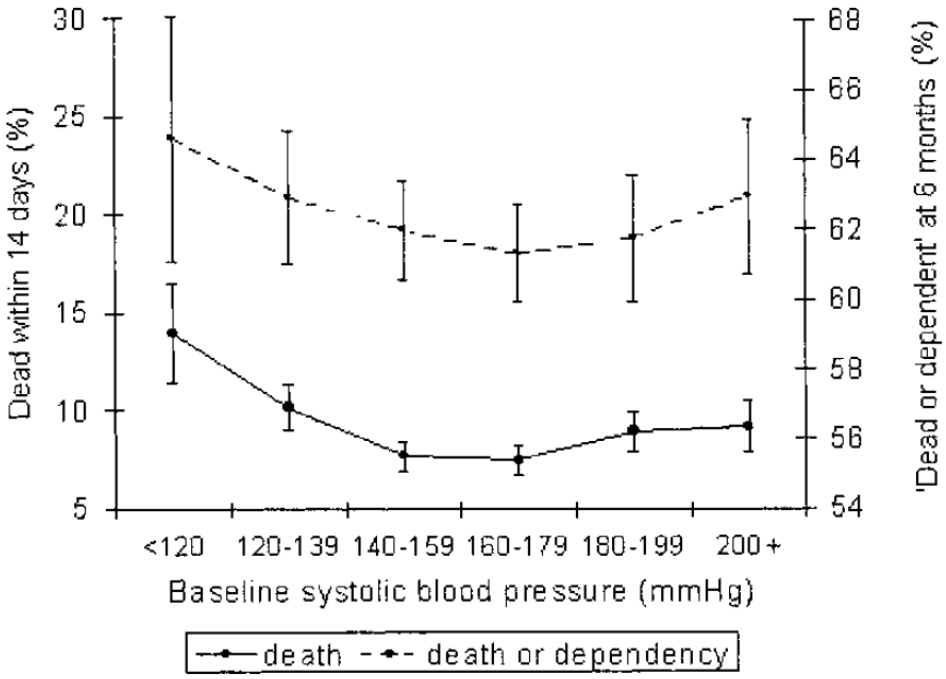


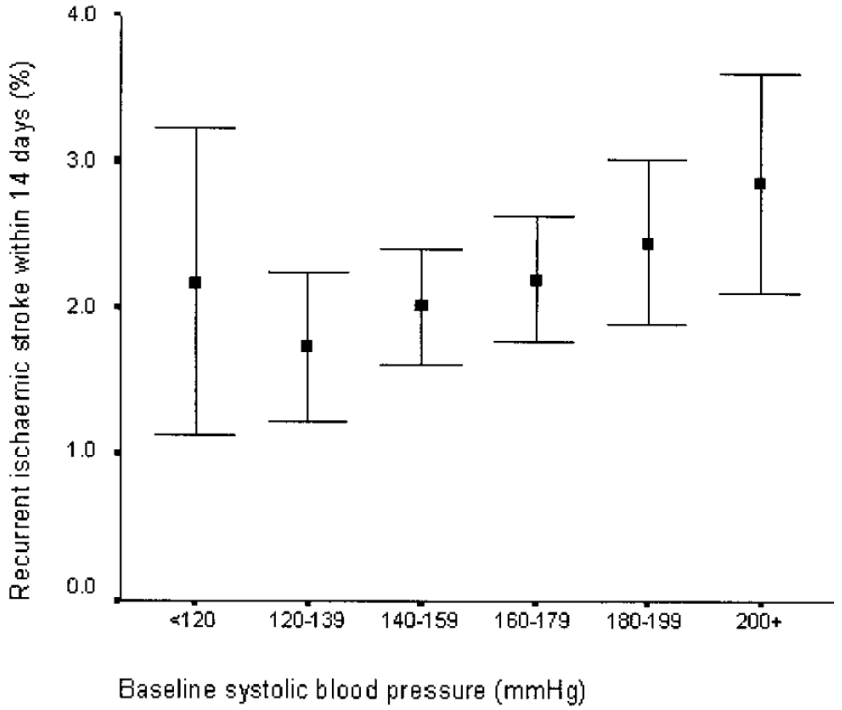
N= 17398 patients

Blood Pressure and Clinical Outcomes in the International Stroke Trial

Jo Leonardi-Bee, MSc; Philip M.W. Bath, FRCP; Stephen J. Phillips, FRCPC; Peter A.G. Sandercock, FRCP; for the IST Collaborative Group

Results—A U-shaped relationship was found between baseline SBP and both early death and late death or dependency: early death increased by 17.9% for every 10 mm Hg below 150 mm Hg ($P<0.0001$) and by 3.8% for every 10 mm Hg above 150 mm Hg ($P=0.016$). The rate of recurrent ischemic stroke within 14 days increased by 4.2% for every 10–mm Hg increase in SBP ($P=0.023$); this association was present in both fatal and nonfatal recurrence.



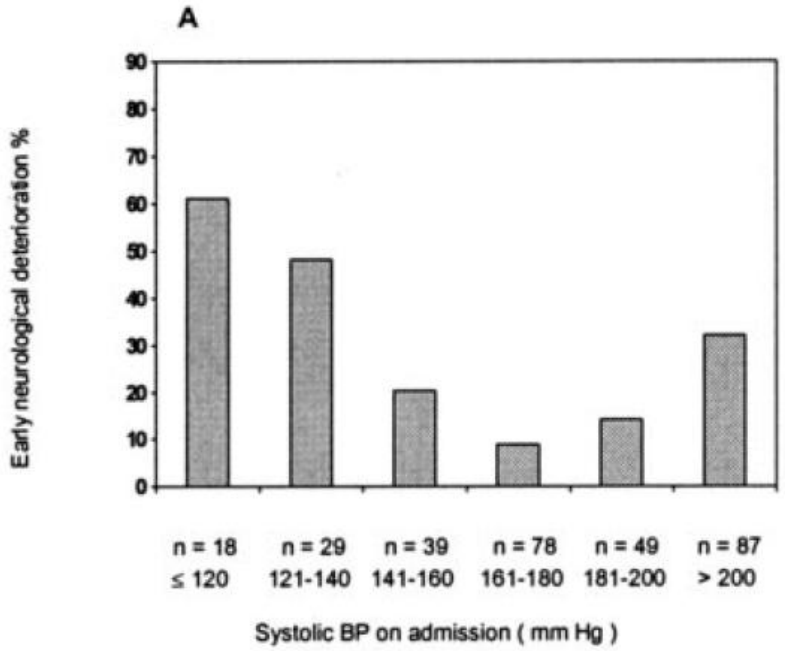


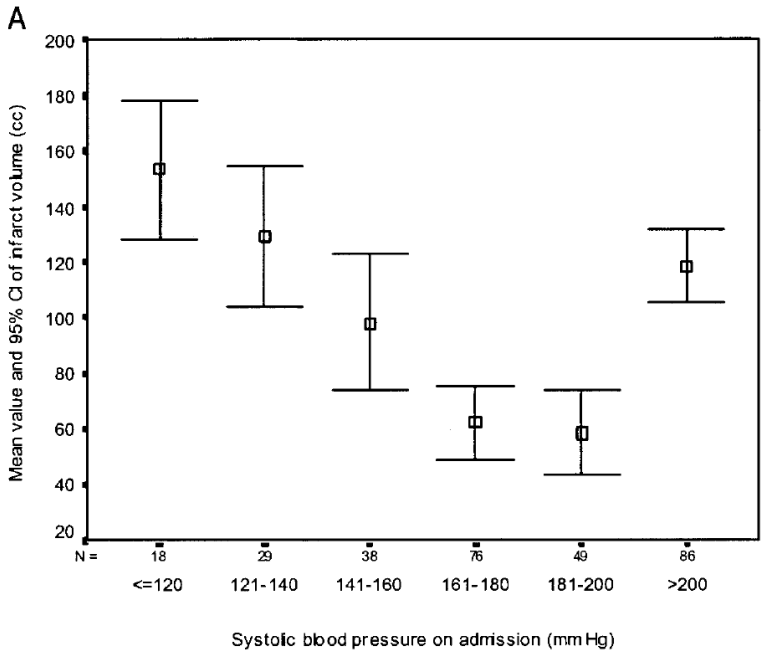
N= 17398 patients

Blood Pressure Decrease During the Acute Phase of Ischemic Stroke Is Associated With Brain Injury and Poor Stroke Outcome

José Castillo, MD, PhD; Rogelio Leira, MD, PhD; María M. García, MD, PhD;
Joaquín Serena, MD, PhD; Miguel Blanco, MD, PhD; Antoni Dávalos, MD, PhD

(*Stroke*. 2004;35:520-527.)





N= 304 patients

SO, hypertension is bad, but hypotension is worse!!

Blood pressure treatment in acute ischemic stroke: a review of studies and recommendations

George Ntaios[a], Philip Bath[b] and Patrik Michel[a]

Current Opinion in Neurology 2010, 23:46–52

Recent findings

We found 34 observational studies (33 470 patients), with results being inconsistent among the studies; most studies reported a negative association between increased levels of BP and clinical outcome, whereas a few studies showed clinical improvement with higher BP levels, clinical deterioration with decreased BP, or no association at all. Similarly, the conclusions drawn by the 18 intervention studies included in this review (1637 patients) were also heterogeneous. Very recent clinical data suggest a possible beneficial effect of early treatment with some antihypertensives on late clinical outcome.

Blood pressure treatment in acute ischemic stroke: a review of studies and recommendations

George Ntaios[a], Philip Bath[b] and Patrik Michel[a]

- 34 observational studies (n = 33470 patients)
- 18 intervention studies (n = 1637 patients)

Ntaios G et al. Current Opinion in Neurology 2010, 23:46–52

Blood pressure treatment in acute ischemic stroke: a review of studies and recommendations

George Ntaios[a], Philip Bath[b] and Patrik Michel[a]

- 34 observational studies (n = 33470 patients)
- 18 intervention studies (n = 1637 patients)

- Most studies reported a negative association between increased blood pressure and clinical outcome.
- However, some studies showed clinical improvement with higher blood pressure levels and clinical deterioration with decreased blood pressure;
- While yet other studies showed no association at all.

Ntaios G et al. Current Opinion in Neurology 2010, 23:46–52

Blood pressure treatment in acute ischemic stroke: a review of studies and recommendations

George Ntaios[a], Philip Bath[b] and Patrik Michel[a]

Current Opinion in Neurology 2010, 23:46–52

Conclusion

There is still considerable controversy regarding the proper management of BP in the setting of acute ischemic stroke, since the results of observational and intervention studies have been inconsistent.

It is unclear whether the presence of elevated BP during the initial phase of acute ischemic stroke has a protective, detrimental or no effect on clinical outcome.

Ntaios G et al. Current Opinion in Neurology 2010, 23:46–52

STROKE PRECIPITATED BY MODERATE BLOOD PRESSURE REDUCTION

Glenn M. Fischberg, MD, Edward Lozano, MD, Kumar Rajamani, MD, Sebastian Ameriso, MD, and Mark J. Fisher, MD

The Journal of Emergency Medicine, Vol. 19, No. 4, pp. 339–346, 2000

Table 1. Patient Summaries

Patient No.	Age (yrs)	Neurological Presentation	Baseline BP	Antihypertensive Drugs	Post-treatment BP	% MAP Change*	Outcome
1	60	Nausea and vertigo	220/120	Nifedipine (sublingual)	168/86	26%	stroke
2	63	Lightheadedness and headache	180/110	Felodipine (oral)	160/80	18%	stroke
3	58	Resolved TIA	190/120	Nifedipine (oral)	128/80	33%	stroke
4	49	Resolved TIA	174/114	Labetalol (intravenous)	154/88	18%	stroke
5	60	Asymptomatic	170/100	Nifedipine (sublingual)	120/88	20%	stroke
6	30	Asymptomatic	280/120	Triamterene/HCTZ, Nifedipine, captopril, hydralazine (all oral)	160/85	36%	bilateral retinal infarctions

*Mean MAP fall of 25 ± 7.7%.
BP, blood pressure; MAP, mean artrial pressure; TIA, transient ischemic attack.

STROKE PRECIPITATED BY MODERATE BLOOD PRESSURE REDUCTION

Glenn M. Fischberg, MD, Edward Lozano, MD, Kumar Rajamani, MD, Sebastian Ameriso, MD, and Mark J. Fisher, MD

The Journal of Emergency Medicine, Vol. 19, No. 4, pp. 339–346, 2000

Table 2. Published Series of Acute Stroke in the Setting of Blood Pressure Treatment

Author (year)	Number of Patients	Decline in MAP (mmHg) Mean (±SD)	Initial Neurological Condition
1) Graham (1975)[23]	2	81 ± 9	asymptomatic
2) Jackson et al. (1976)[24]	6	45 ± 25	asymptomatic
3) Kumar et al. (1979)[25]	1	200	headache, dizziness
4) Ledingham et al. (1979)[26]	10	92 ± 23	asymptomatic
5) Britton (1980)[5]	6	141 ± 43	mild ischemic strokes
6) Nobile-Orasio et al. (1981)[27]	2	Unknown	asymptomatic
7) Lavin (1986)[6]	2	75 ± 35	mild ischemic strokes
8) Schwartz et al. (1990)[28]	2*	69 ± 8	mild ischemic stroke
9) Present series (2000)	6	37 ± 16	mild ischemic symptoms, TIA, asymptomatic

*Two events in the same patient separated by 9 months.
MAP, mean artial pressure;TIA, transient ischemic attack.

Does Perioperative Systolic Blood Pressure Variability Predict Mortality After Cardiac Surgery? An Exploratory Analysis of the ECLIPSE trials

Solomon Aronson, MD,* Cornelius M. Dyke, MD,† Jerrold H. Levy, MD,‡ Albert T. Cheung, MD,§ Philip D. Lumb, MB, BS,‖ Edwin G. Avery, MD,¶ Ming-yi Hu, PhD,# and Mark F. Newman, MD*

CONCLUSIONS: Perioperative blood pressure variability is associated with 30-day mortality in cardiac surgical patients, proportionate to the extent of SBP excursions outside the range of 75 to 135 mm Hg intraoperatively and 85 to 145 mm Hg pre- and postoperatively. Predicted mortality was greater for high-risk patients than for low-risk patients. (Anesth Analg 2011;113:19–30)

Table 2. Procedural Characteristics (All ECLIPSE Studies, Pooled mITT Populations)

Perioperative procedure type	Total no. of patients (n = 1512)
CABG	960 (63.5)
MIDCAB	0 (0.0)
OPCAB	205 (13.6)
Valve replacement	158 (10.4)
Valve repair	34 (2.2)
Combination	151 (10.0)
Surgery not classified	3 (0.2)
No surgery	1 (0.1)

Table 3. Summary of Odds Ratios of AUC (per 60 mm Hg × min/h) for 30-Day Mortality by Blood Pressure Range

SBP range (mm Hg)	*P* value	Odds ratio	95% Confidence interval	
			Lower limit	Upper limit
65–135 intraop 75–145 pre- and postop	0.0707	1.142	0.989	1.319
75–135 intraop 85–145 pre- and postop	0.0082	1.160	1.039	1.295
85–135 intraop 95–145 pre- and postop	0.0005	1.180	1.076	1.295
95–135 intraop 105–145 pre- and postop	<0.0001	1.153	1.074	1.238
105–135 intraop 115–145 pre- and postop	<0.0001	1.105	1.053	1.160

AUC = area under the curve; SBP = systolic blood pressure; intraop = intraoperative; pre- and postop = preoperative and postoperative.

Table 4. Multiple Logistic Regression Analysis on Risk Variables for 30-Day Mortality (All ECLIPSE Studies, Pooled mITT Populations)

Variable	*P* value	Odds ratio	95% Confidence interval	
			Lower limit	Upper limit
Age (y)	0.0008	1.065	1.027	1.104
History of COPD[a]	0.0117	2.515	1.228	5.150
Preoperative SCr ≥1.2 mg/dL[a]	0.0028	2.678	1.405	5.105
Preoperative hemoglobin (g/dL)	0.0076	0.802	0.682	0.943
Preoperative SBP >160 mm Hg or DBP >105 mm Hg[a]	0.0185	2.419	1.160	5.045
Additional procedures during index surgical procedure[a]	0.0111	2.332	1.214	4.480
Surgery duration (h)	<0.0001	1.534	1.258	1.872
AUC (per 60 mm Hg × min/h)[b]	0.0082	1.160	1.039	1.295

mITT = modified intent-to-treat; COPD = chronic obstructive pulmonary disease; SCr = serum creatinine; SBP = systolic blood pressure; DBP = diastolic blood pressure; AUC = area under the curve.

[a] Binary variable compared on the basis of yes versus no.

[b] AUC was derived from the SBP range of 75–135 mm Hg intraoperatively and 85–145 mm Hg pre- and postoperatively.

Aronson S et al. Anesthesia Analgesia 2011;113:19-30

Clinical practices, complications, and mortality in neurological patients with acute severe hypertension: The Studying the Treatment of Acute hyperTension registry

Stephan A. Mayer, MD; Pedro Kurtz, MD; Allison Wyman, MS; Gene Y. Sung, MD; Alan S. Multz, MD; Joseph Varon, MD; Christopher B. Granger, MD; Kurt Kleinschmidt, MD; Marc Lapointe, PharmD; W. Frank Peacock, MD; Jason N. Katz, MD, MHS; Joel M. Gore, MD; Brian O'Neil, MD; Frederick A. Anderson, MD; on behalf of the STAT Investigators

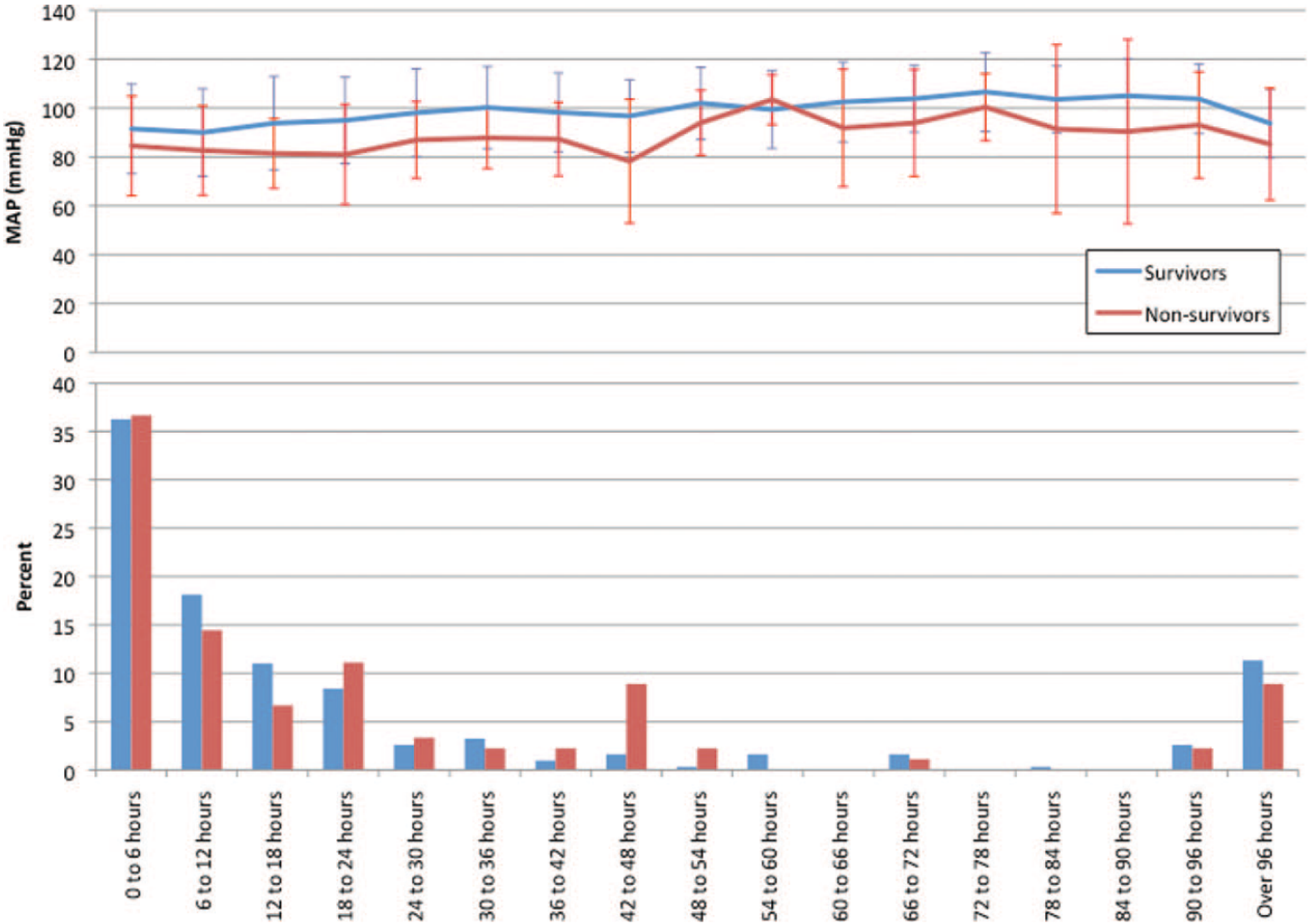


Figure 1. Level and timing of lowest-recorded mean arterial blood pressure (*MAP*) in survivors vs. nonsurvivors. Regardless of mortality status, lowest-recorded blood pressure occurred most frequently within the first 6 hrs of admission. "Percent" in *bottom panel* refers to the % of dead or alive patients.

Mayer SA et al. Crit Care Med 2011;39:2330-36

Table 6. Multivariable analysis of predictors of mortality at 90 days (n = 360)

Predictors of Mortality	Adjusted Odds Ratio	95% Confidence Interval	Wald Chi-Square
Non-BP-Related Variables			
Age (per 10 yrs)	1.876	**1.466–2.402**	**24.9**
Cardiac history	2.140	**1.076–4.256**	**4.7**
Admission glucose (per 10 mg/dL)	1.034	0.993–1.075	2.7
Admitting diagnosis of intracranial hemorrhage	1.486	0.801–2.756	1.6
Glasgow coma score (per 1 unit)	0.739	**0.685–0.798**	**60.2**
BP-Related Variables			
Hours to target BP	0.967	0.931–1.003	3.2
Lowest recorded systolic BP (per 10 mm Hg)	0.729	**0.626–0.848**	**16.8**
Lowest recorded diastolic BP (per 10 mm Hg)	0.675	**0.535–0.853**	**10.9**
Excessive hypotension from intravenous hypertension treatment[a]	2.221	0.668–7.387	1.7
Recurrent severe acute hypertension with intravenous treatment	0.362	**0.194–0.678**	**10.1**

Mayer SA et al. Crit Care Med 2011;39:2330-36

Clinical practices, complications, and mortality in neurological patients with acute severe hypertension: The Studying the Treatment of Acute hyperTension registry

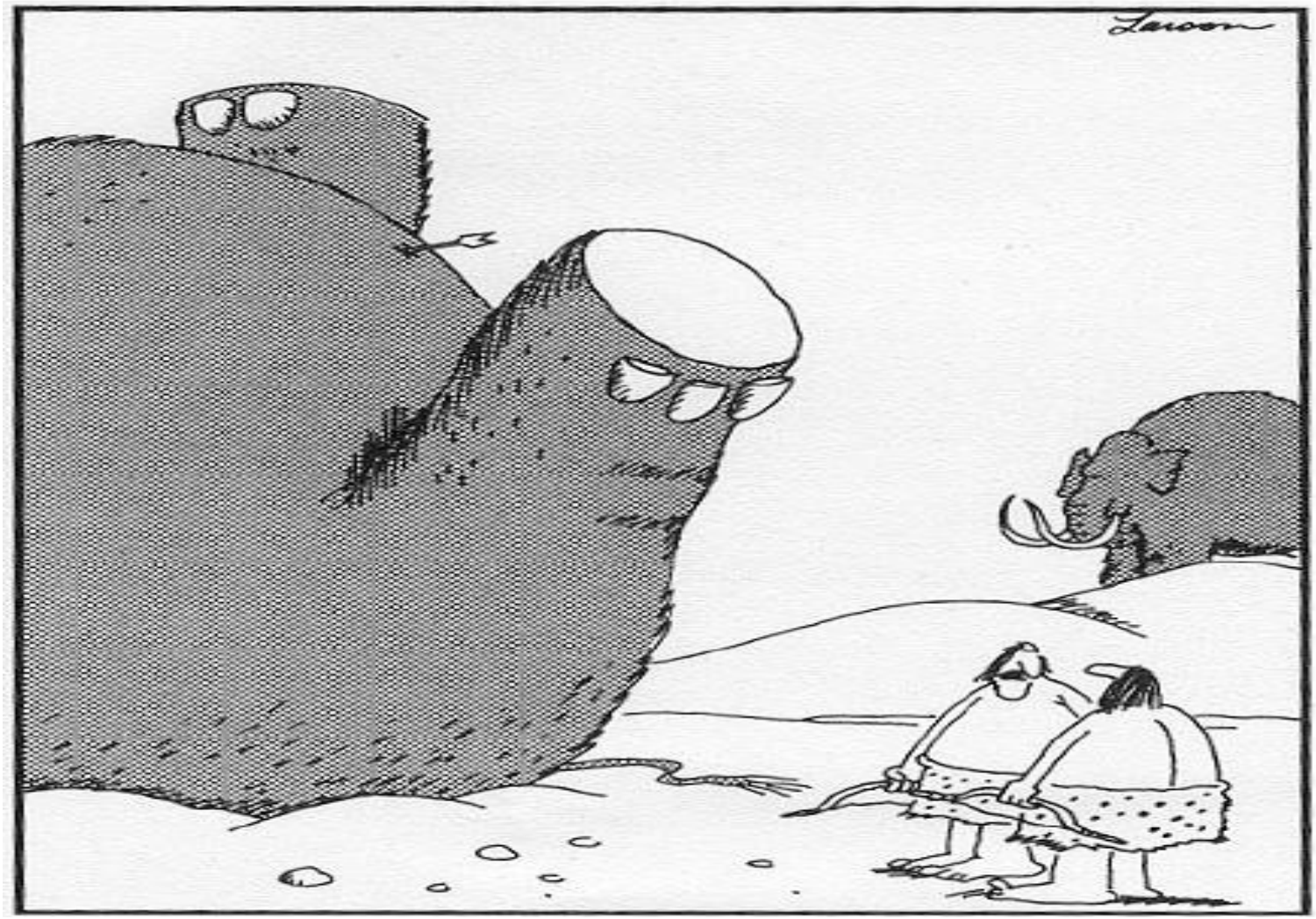
Stephan A. Mayer, MD; Pedro Kurtz, MD; Allison Wyman, MS; Gene Y. Sung, MD; Alan S. Multz, MD; Joseph Varon, MD; Christopher B. Granger, MD; Kurt Kleinschmidt, MD; Marc Lapointe, PharmD; W. Frank Peacock, MD; Jason N. Katz, MD, MHS; Joel M. Gore, MD; Brian O'Neil, MD; Frederick A. Anderson, MD; on behalf of the STAT Investigators

Conclusion: **Neurologic emergencies account for approximately 30% of hospitalized patients with severe acute hypertension, and the majority of those who die. Mortality in hypertensive neurologic patients is associated with lower minimum blood pressure values, less rebound hypertension, and a higher frequency of neurologic deterioration. Excessive blood pressure reduction may contribute to poor outcome after severe brain injury.**


順 路
THIS WAY

The solution??

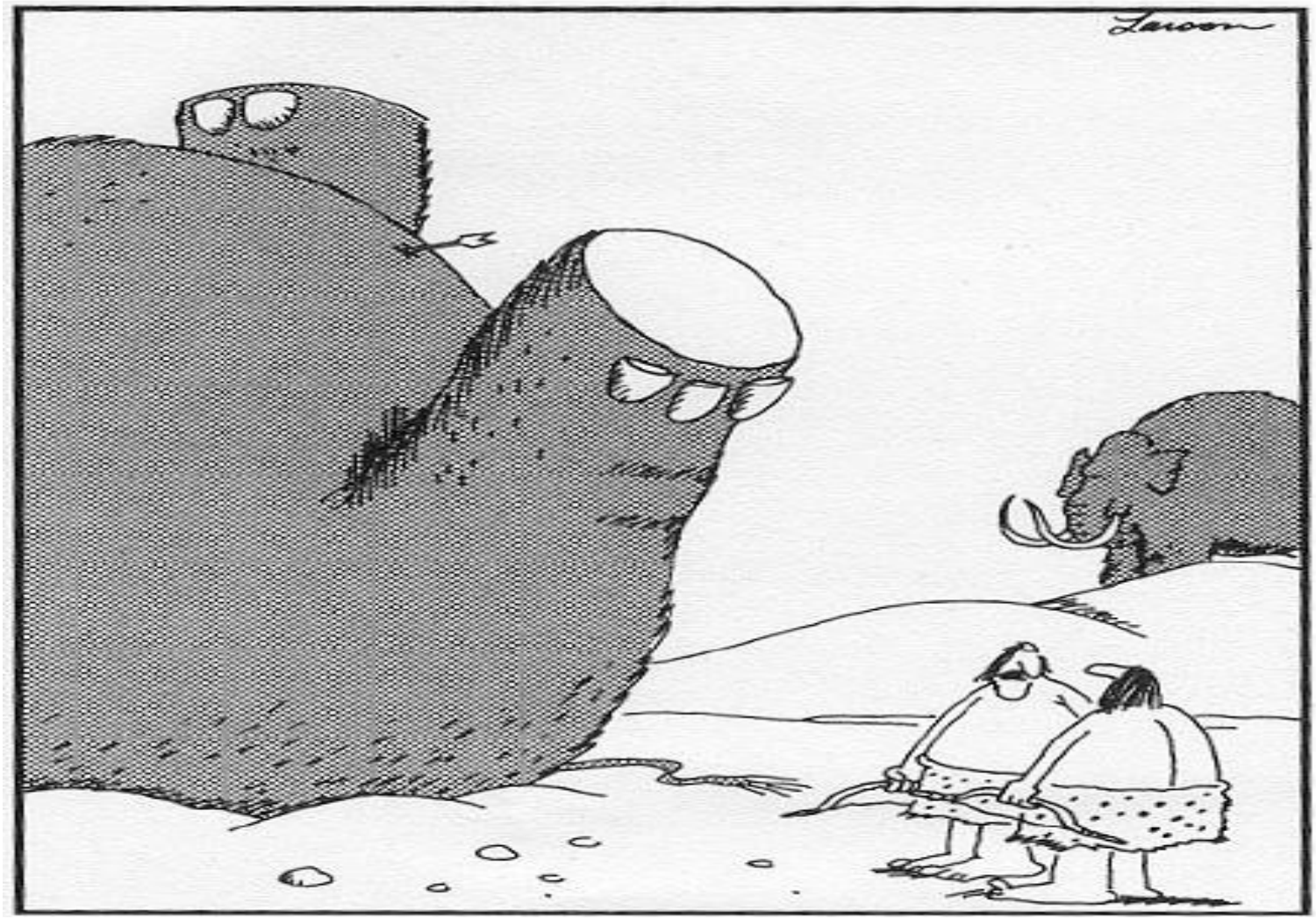
We need to get things just right!



“We should write that spot down”

The solution??

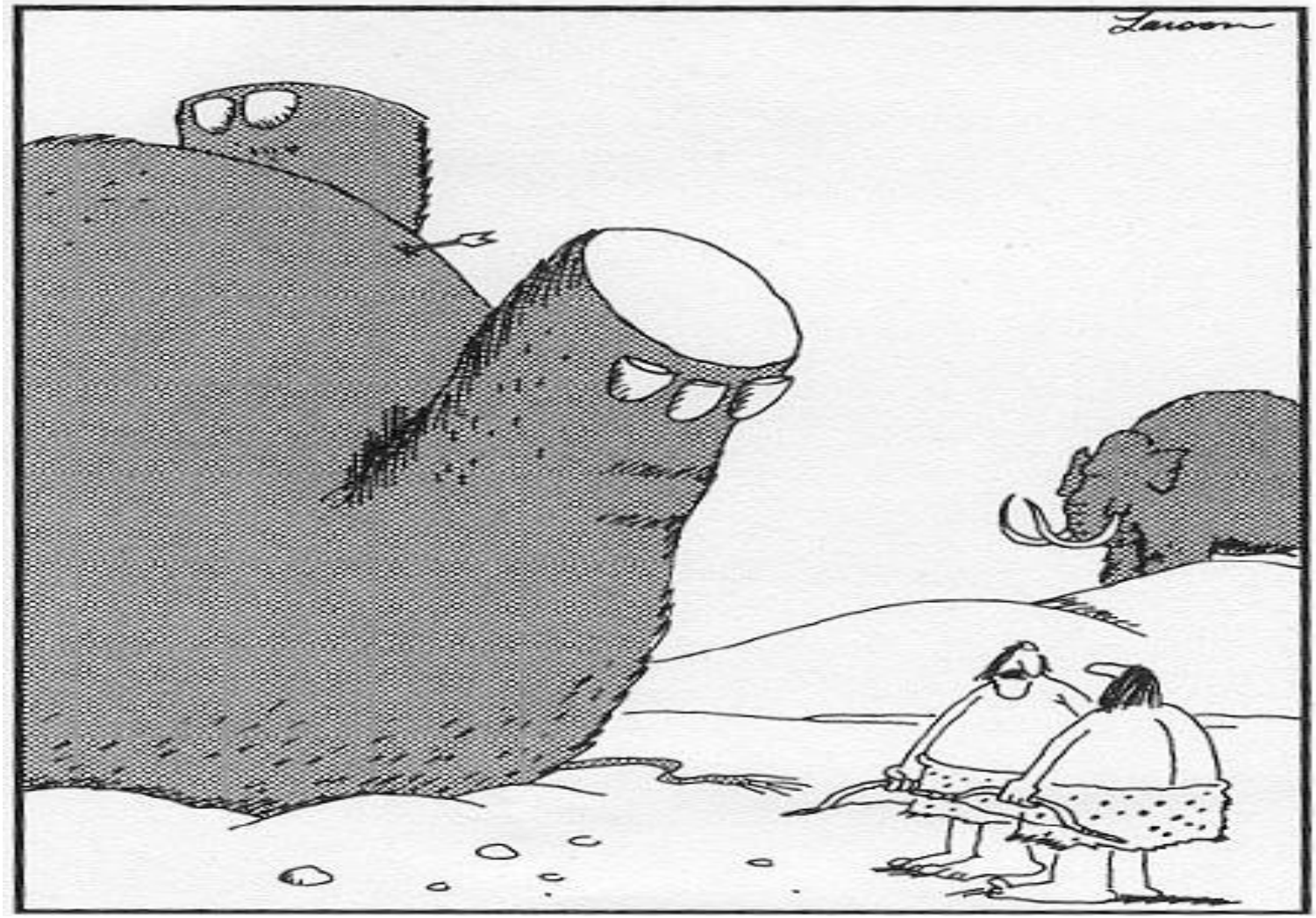
Appropriate use and dosage of antihypertensives.



“We should write that spot down”

The solution??

Applies not just to antihypertensives, but to all aspects of (neuro)ICU care.



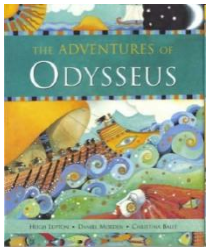
“We should write that spot down”

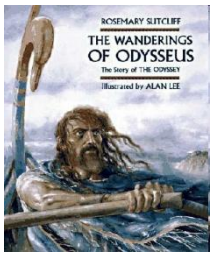
Primum non nocere.....

(first, do no harm...)

Primum non nocere.....

(first, do no harm...)





- **That is why I like using short-acting agents in critically ill patients, especially when I am manoeuvring between Scylla en Charybdis…**
  - **Remifentanyl or fentanyl rather than morphine..**
  - **Propofol rather than benzodiazepines..**
  - **For some arrhythmia's, Esmolol rather than Diltizem, Labetolol or Amiodarone…**
  - **For blood pressure, depending on the desired reduction of blood pressure and heart rate: clevidipine and esmolol rather than nicardipine, hydralazine etc..**

When to use which drug???

- **Depends on situation, risk of overshoot, severity of hypertension, presence of tachy/bradycardia, etc.**

The ECLIPSE Trials: Comparative Studies of Clevidipine to Nitroglycerin, Sodium Nitroprusside, and Nicardipine for Acute Hypertension Treatment in Cardiac Surgery Patients

(Anesth Analg 2008;107:1110–21)

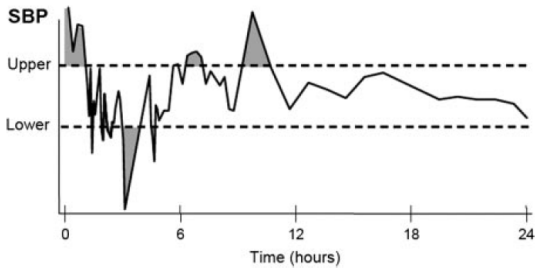


Figure 1. Schematic illustration of the AUC calculation for an individual patient from the ECLIPSE trial. $AUC_{SBP\text{-}D}$ captures the magnitude and duration of arterial blood pressure (BP) excursions outside the predefined systolic BP (SBP) ranges (65–135 mm Hg intraoperatively, 75–145 mm Hg pre- and postoperatively).

N=1512 patients

RESULTS: There was no difference in the incidence of myocardial infarction, stroke or renal dysfunction for CLV-treated patients compared with the other treatment groups. There was no difference in mortality rates between the CLV, NTG or NIC groups. Mortality was significantly higher, though, for SNP-treated patients compared with CLV-treated patients ($P = 0.04$). CLV was more effective compared with NTG ($P = 0.0006$) or SNP ($P = 0.003$) in maintaining BP within the prespecified BP range. CLV was equivalent to NIC in keeping patients within a prespecified BP range; however, when BP range was narrowed, CLV was associated with fewer BP excursions beyond these BP limits compared with NIC.

Aronson S. et al. Anesth Analg 2008;107:1110-21

Beneficial effects of adrenergic blockade in patients with subarachnoid haemorrhage

BRITISH MEDICAL JOURNAL VOLUME 284 5 JUNE 1982

P WALTER, G NEIL-DWYER, J M CRUICKSHANK

N=39 patients

TABLE IV—*Neurological results in all patients with aneurysm at four weeks according to sex*

	Treated	Control
Women:		
Good result	24	15
Poor result	11 (4 deaths)	19 (11 deaths)
Men:		
Good result	8	7
Poor result	9 (6 deaths)	9 (3 deaths)

Beta-blockade rather than alpha-blockade appears to be the useful component. A randomised, blind extension of the present study using long-acting propranolol and placebo has shown a significant ($p=0.026$) decrease in deaths and significantly ($p=0.003$) fewer poor results in the treatment group.

Beta-Adrenergic Blockade and Traumatic Brain Injury: Protective?

Thomas J. Schroeppel, MD, Peter E. Fischer, MD, MS, Ben L. Zarzaur, MD, MPH, Louis J. Magnotti, MD, L. Paige Clement, PharmD, Timothy C. Fabian, MD, and Martin A. Croce, MD

(*J Trauma.* 2010;69: 776–782)

N=2601 patients

TABLE 3. Results of Multivariable Logistic Regression Analysis in Blunt TBI Patients Admitted From 2003 to 2007

	Adjusted OR	CI	*p*
BB	0.347	0.246–0.490	<0.0001
Age	1.049	1.041–1.058	<0.0001
ISS	1.055	1.042–1.069	<0.0001
GCS	0.789	0.765–0.814	<0.0001
Transfusions	1.509	1.107–2.056	0.009

Beta-Adrenergic Blockade and Traumatic Brain Injury: Protective?

Thomas J. Schroeppel, MD, Peter E. Fischer, MD, MS, Ben L. Zarzaur, MD, MPH, Louis J. Magnotti, MD, L. Paige Clement, PharmD, Timothy C. Fabian, MD, and Martin A. Croce, MD

(*J Trauma.* 2010;69: 776–782)

Conclusions: BB are associated with significantly reduced mortality in patients with TBI. This simple, inexpensive intervention may have a profound effect on mortality in this population of injured patients and requires further prospective study.

Effect of propranolol and phentolamine on myocardial necrosis after subarachnoid haemorrhage

G NEIL-DWYER, P WALTER, J M CRUICKSHANK, B DOSHI, P O'GORMAN

British Medical Journal, 1978, **2**, 990-992

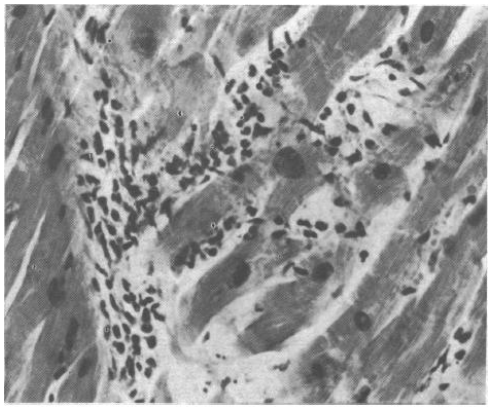


FIG 2—Necrotic muscle fibre in heart with interstitial inflammatory cell infiltration. (Haematoxylin and eosin. ×160)

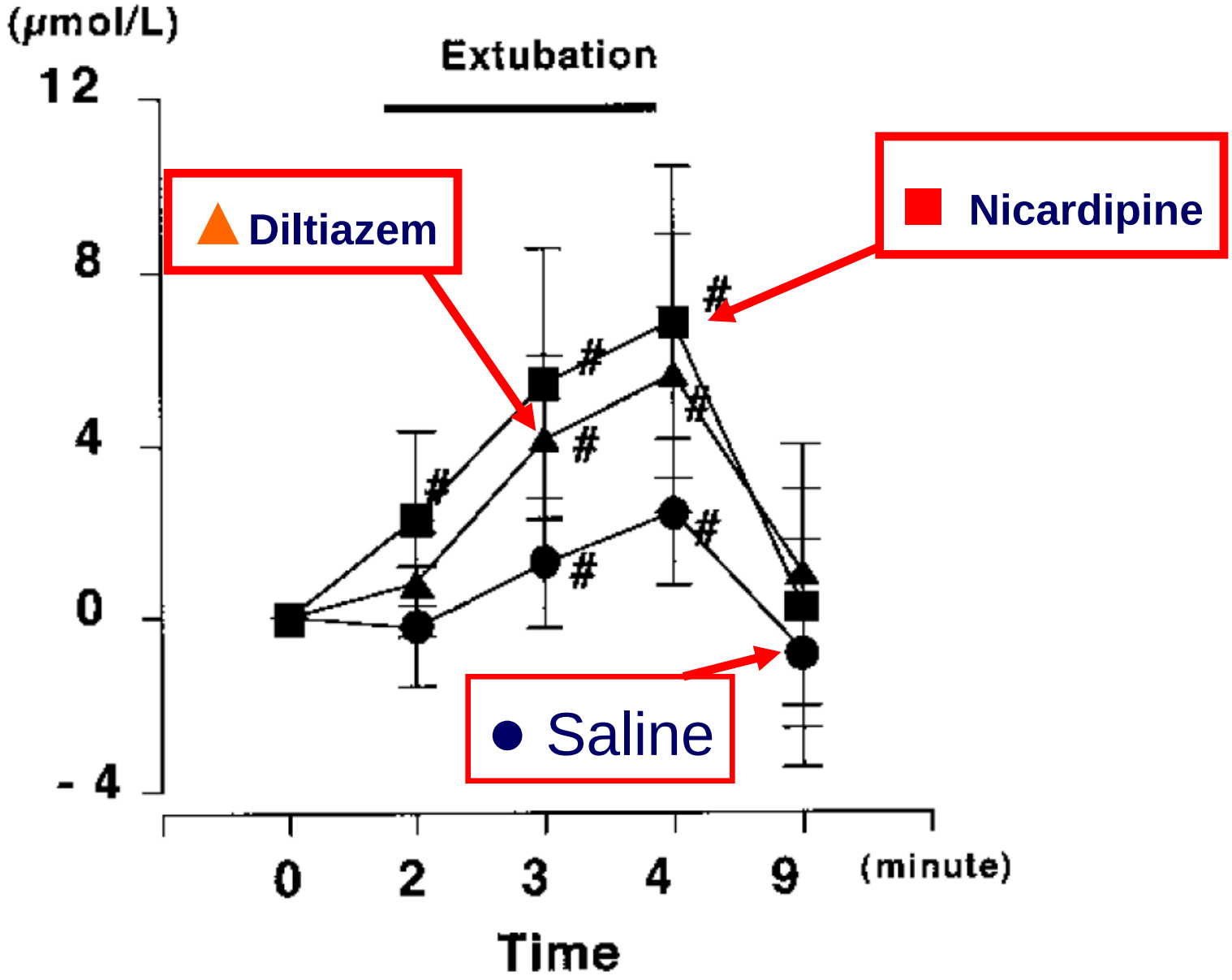
TABLE II—*Clinical details and findings at necropsy in 12 patients who died*

	Propranolol 80 mg eight-hourly by mouth + phentolamine 20 mg three-hourly by mouth	Placebo
Mean pulse rate (beats/min)	65·0 ± 2·2	80·9 ± 6·7
Mean blood pressure (mm Hg)	143 ± 3·0/84 ± 2·6	140 ± 7·1/83 ± 3·7
Appearance of ECG	Entirely normal in 3 patients; in remaining 3, ECGs taken on day 1 were abnormal and all subsequent ECGs normal. Abnormalities were peaked P, S-T, peaked T, and large U waves	All ECGs of 5 patients were abnormal. In remaining patient 1 of 4 ECGs was abnormal. Abnormalities included short P-R interval, peaked P wave, depressed S-Ts, flat or inverted T waves, and large U waves
Mean 24-hour urinary catecholamine excretion rates (and ranges)*	Adrenaline 281·0 ± 122·6 (23-564) nmol/24 h Noradrenaline 959 ± 409·4 (143-2156) nmol/24 h Metadrenaline 3·1 ± 0·26 (1·3-5·9) μmol/24 h HMMA 38·5 ± 8·1 (17-116) μmol/24 h	503·0 ± 85·2 (246-752) nmol/24 h 912·4 ± 687·6 (49-6345) nmol/24 h 2·2 ± 1·2 (0·1-8·0) μmol/24 h 28·7 ± 4·0 (11-39) μmol/24 h
Disease of coronary arteri	2 patients had no atheroma or occlusion; 4 had mild atheroma and no occlusion	2 patients had no atheroma or occlusion; 4 had mild atheroma and no occlusion
Appearance of left ventricular myocardium	No lesions	2 patients had focal necrotic lesions of muscle fibres; 4 had focal necrotic lesions with inflammatory cell infiltration
Appearance of hypothalamus	All had hypothalamic lesions—perivascular haemorrhage and endothelial oedema with cuffing by polymorphonuclear leucocytes	5 had lesions similar to those in treated group; 1 had a complete hypothalamic infarct

HMMA = 3-Methoxy-4-hydroxymandelic acid.
*Normal ranges: adrenaline 0-275 nmol/24 h; noradrenaline 110-1100 nmol/24 h; metadrenaline 0-4·0 μmol/24 h; HMMA 10-35 μmol/24 h.
Conversion: SI to traditional units—Adrenaline: 1 nmol/24 h ≈ 0·18 μg/24 h. Noradrenaline: 1 nmol/24 h ≈ 0·17 μg/24 h. Metadrenaline: 1 μmol/24 h ≈ 0·18 mg/24 h. HMMA: 1 μmol/24 h ≈ 0·2 mg/24 h.

When to use which drug???

- **Depends on situation, risk of overshoot, severity of hypertension, presence of tachy/bradycardia, etc.**



Changes in cerebral [HbO_2]

Morimoto Y et al.
Anesth Analg 2000; 91:347-52

When to use which drug???

- **So, if the brain is hypoperfused a calcium channel blocker would probably be a good choice!**

Esmolol Blunts the Cerebral Blood Flow Velocity Increase During Emergence from Anesthesia in Neurosurgical Patients

Philippe Grillo, MD*, Nicolas Bruder, MD*, Pascal Auquier, MD†, Daniel Pellissier, MD*, and François Gouin, MD*

*Département d'Anesthésie-Réanimation and †Service de Santé Publique et de Biostatistiques, Marseille, France

Cerebral hyperemia has been demonstrated during emergence from anesthesia in neurosurgical patients, but its mechanism is speculative. We performed this study to test the hypothesis that this could be attributed to sympathetic overactivity. Thirty neurosurgical patients were included in a prospective, randomized, double-blinded study comparing esmolol, a short-acting β-blocker, and a placebo. Esmolol ($0.3\ mg \cdot kg^{-1} \cdot min^{-1}$) was infused from the end of anesthesia to 15 min after extubation. Cerebral blood flow velocity (CBFV), mean arterial blood pressure, and heart rate were recorded before anesthesia, during anesthesia after surgery, at extubation, and 5–60 min after extubation. Cardiac output (COe) was estimated by using an esophageal Doppler from anesthesia to 60 min after extubation. CBFV, COe, and heart rate were significantly lower in the esmolol group. Mean arterial blood pressure was comparable between the groups. There was no correlation between CBFV and COe at any time point during the study. In conclusion, esmolol blunted the CBFV increase during emergence, confirming that sympathetic overactivity contributes to cerebral hyperemia during neurosurgical recovery.

(Anesth Analg 2003;96:1145–9)

Grillo P, et al. Anesthesia & Analgesia, 96(4):1145-9, 2003

Esmolol Blunts the Cerebral Blood Flow Velocity Increase During Emergence from Anesthesia in Neurosurgical Patients

Philippe Grillo, MD*, Nicolas Bruder, MD*, Pascal Auquier, MD†, Daniel Pellissier, MD*, and François Gouin, MD*

*Département d'Anesthésie-Réanimation and †Service de Santé Publique et de Biostatistiques, Marseille, France

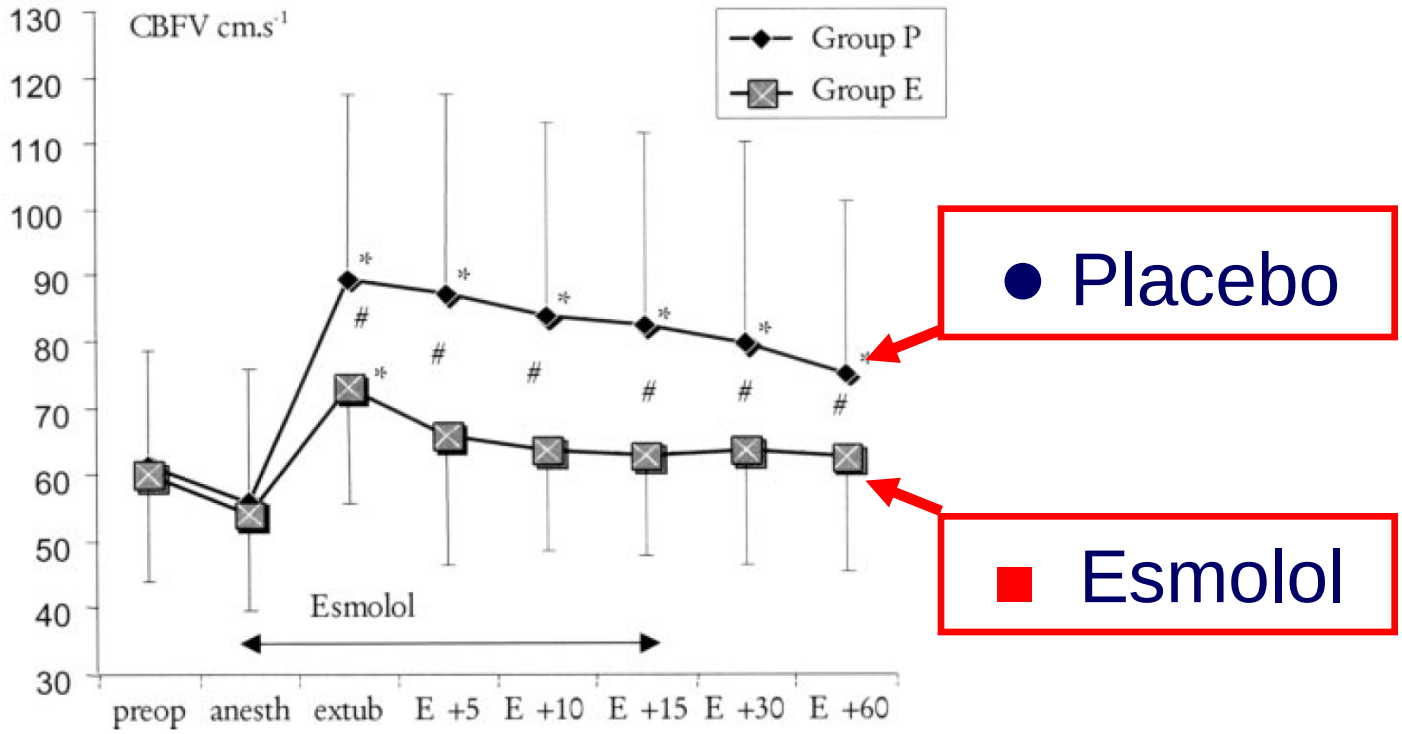


Figure 1. Middle cerebral artery blood flow velocity (CBFV) before anesthesia (preop), during anesthesia (anesth), at extubation (extub), and 5–60 min after extubation (E + 5' to E + 60') in Group P (placebo) and Group E (esmolol) (mean ± SD). *$P < 0.05$ compared with preoperative (preop) value. #$P < 0.05$ statistically significant between groups.

Grillo P, et al.
Anesth Analg 2003; 96:1145-9

When to use which drug???

- **But in situations of hyperperfusion a beta blocker might be better.**

When to use which drug???

- **Depends on situation, risk of overshoot, severity of hypertension, presence of tachy/bradycardia, etc.**

Case 1

- **A patient has undergone posterior fusion surgery. His case was complicated by bleeding from his surgical wound. He was taken back to theater, received anesthesia with propofol and remifentanyl. A small arterial bleeder was located and coagulated, a small hematoma was drained. Propofol and remifentanyl are stopped, patient is taken back to the ICU.**

Case 1

- **A patient has undergone posterior fusion surgery. His case was complicated by bleeding from his surgical wound. He was taken back to theater, received anesthesia with propofol and remifentanyl. A small arterial bleeder was located and coagulated, a small hematoma was drained. Propofol and remifentanyl are stopped, patient is taken back to the ICU.**
- **He is still intubated. He is highly agitated. His blood pressure is 188/105, heart rate 128 BPM, sinus rhythm.**
- **You are asked to see this patient because of his tachycardia and hypertension.**

Case 1

What would you recommend?

- **Give a bolus dose of 5 mg of metoprolol IV**
- **Start a Diltiazem drip 0.25 mg/kg/min bolus dose over 2 minutes and drip at 10 mg/hr**
- **Give an Esmolol bolus of 5 mg and start a drip at 50 mcgr/kg/min**
- **Nothing at this time; the patient is in sinus rhythm and the blood pressure is acceptable**
- **Sedate the patient with Propofol or a benzodiazepine**
- **Give 5 mg of Haloperidol to treat delirium**
- **Give 100 microgram of Fentanyl**

Case 1

What would you recommend?

- **Give a bolus dose of 5 mg of metoprolol IV**
- **Start a Diltiazem drip 0.25 mg/kg/min bolus dose over 2 minutes and drip at 10 mg/hr**
- **Give an Esmolol bolus of 5 mg and start a drip at 50 mcgr/kg/min**
- **Nothing at this time; the patient is in sinus rhythm and the blood pressure is acceptable**
- **Sedate the patient with Propofol or a benzodiazepine**
- **Give 5 mg of ~~Haloperidol~~ to treat delirium**
- **Give 100 microgram of Fentanyl**

PAIN

Can be a source of amusement

Don’t forget the basics!

No antihypertensives if pain is not (sufficiently) controlled)...!

And remember:

Pain + sedation = Delirium!

Conclusions:

The injured brain seems to be far less tolerant of disturbances in homeostasis in general

So, getting the basics of ICU care and ED care right is even more important in patients with cerebral injury.

Conclusions:

We need to do everything we normally do, except: We need to do even better!

Conclusions:

We need to do everything we normally do, except: We need to do even better!

- Avoid even brief episodes of hypoxia
- Avoid even brief episodes of hypotension
- Avoid excessive hypertension
- Avoid hyperventilation and hypoventilation
- Avoid metabolic disorders
- Avoid fever…
- (and consider specific effects of various drugs on the injured brain…….)

Conclusions:

- In unstable patients who can tolerate neither hypertension no hypotension, there is a strong case for use of short-acting agents such as esmolol and clevidipine
- Titrate to a target, individualized!
- Many patients with acute brain injury, especially (but not only!!) SAH, develop arrhythmia's and myocardial dysfunction ("Hyperadrenergic state"); there is some evidence that treating this with beta-blockers improves outcome.

Does it all matter???

Does it all matter???

Trends in head injury outcome from 1989 to 2003 and the effect of neurosurgical care: an observational study

H C Patel, O Bouamra, M Woodford, A T King, D W Yates, F E Lecky, on behalf of the Trauma Audit and Research Network

Lancet 2005; 366: 1538–44

Findings Patients with head injury (n=22 216) had a ten-fold higher mortality and showed less improvement in the adjusted odds of death since 1989 than did patients without head injury (n=154 231). 2305 (33%) of patients with severe head injury (presenting between 1996 and 2003) were treated only in non-neurosurgical centres; such treatment was associated with a 26% increase in mortality and a 2·15-fold increase (95% CI 1·77–2·60) in the odds of death adjusted for case mix compared with patients treated at a neurosurgical centre.

26% increase in mortality and a 2·15-fold increase (95% CI 1·77–2·60) in the odds of death

Trends in head injury outcome from 1989 to 2003 and the effect of neurosurgical care: an observational study

H C Patel, O Bouamra, M Woodford, A T King, D W Yates, F E Lecky, on behalf of the Trauma Audit and Research Network

Lancet 2005; 366: 1538–44

	All SHI patients n=6921 (age 16–65)	
	Neurosurgical centres	Non–neurosurgical centres
Number of patients	4616	2305
Age (years, median, IQR)	28 (16–48)	34 (20–58)
Male (%, 95% CI)	3448 (75%, 73–76)	1642 (71%, 69–73)
ISS (median, IQR)	25 (18–33)	26 (18–35)
GCS (median, IQR)	3 (3–6)	4 (3–6)
Isolated head injury (95% CI)	2054 (44%, 43–46)	899 (39%, 37–41)
SBP <90 mm Hg (95% CI)	383 (8%, 8–9)	434 (19%, 17–20)
Transferred (95% CI)	2665 (58%, 56–59)	302 (13%, 12–14)
Deaths (95% CI)	1624 (35%, 34–37)	1406 (61%, 59–63)
Isolated, non-surgical SHI n=894 (age 16–65)		
Number of patients	552	342
Age (years, median, IQR)	33 (23–47)	31 (22–46)
ISS (median, IQR)	16 (10–25)	16 (10–25)
GCS (median, IQR)	4 (3–7)	5 (3–7)
SBP <90 mm Hg (%, 95% CI)	21 (4%, 2–5)	29 (9%, 6–12)
Patients transferred (%, 95% CI)	311 (56%, 52–60)	23 (7%, 4–9)
Deaths (%, 95% CI)	142 (26%, 22–29)	118 (34%, 29–40)

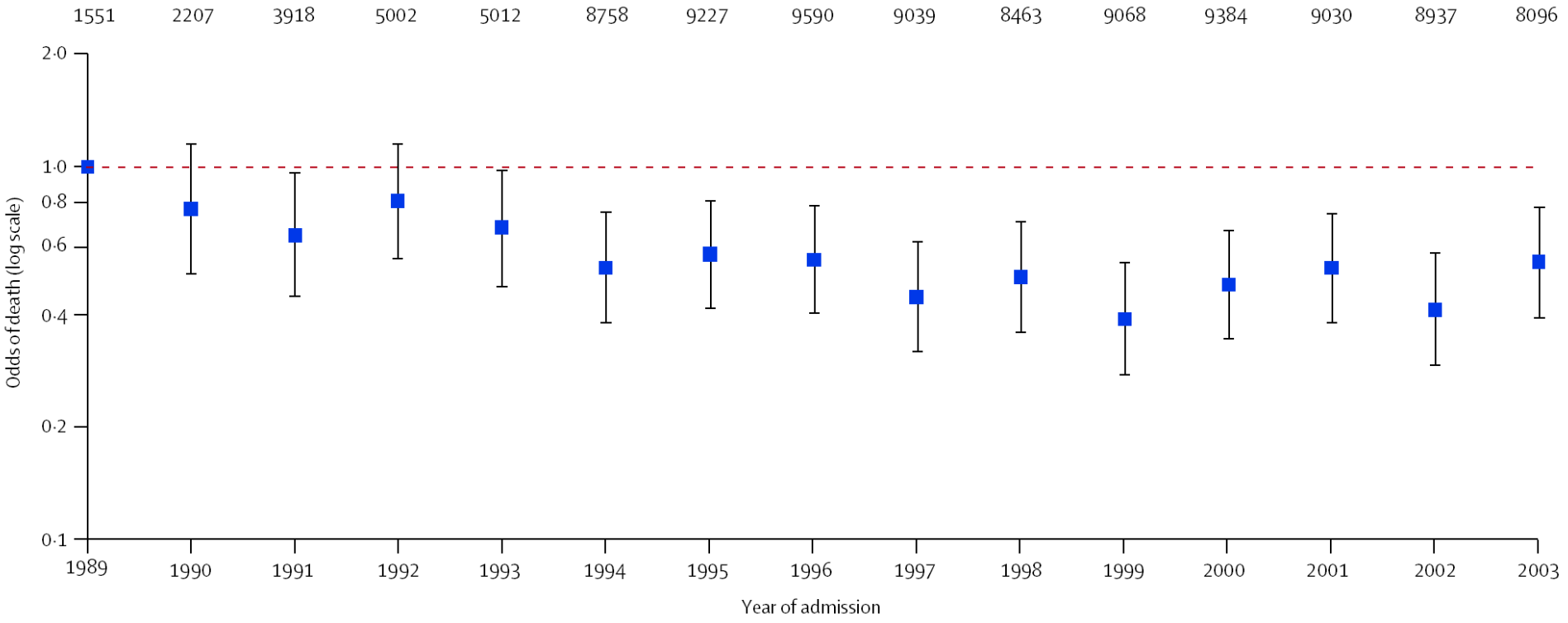
SHI=severe head injury. GCS=Glasgow coma score. SBP=systolic blood pressure.

Table 2: **Patient characteristics after severe head injury according to treatment centre**

Trends in head injury outcome from 1989 to 2003 and the effect of neurosurgical care: an observational study

H C Patel, O Bouamra, M Woodford, A T King, D W Yates, F E Lecky, on behalf of the Trauma Audit and Research Network

Lancet 2005; 366: 1538–44



Does it all matter???

Yes; we can (and should!) do better.

And never forget that in brain injury, prevention is always better than cure…

As is demonstrated by this short film.

And never forget that in brain injury, prevention is always better than cure…

As is demonstrated by this short film.

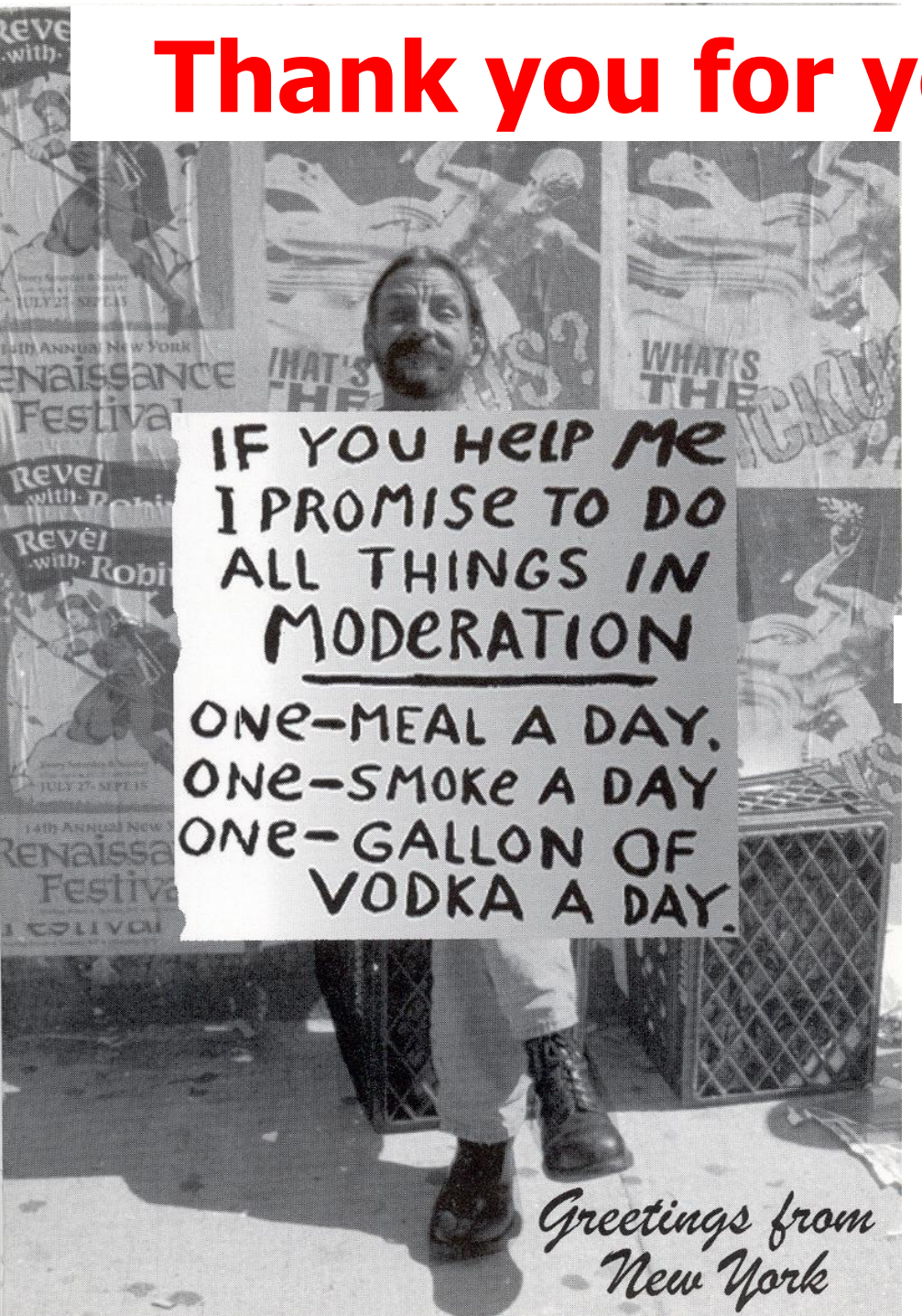
Показал ролик на котором антилопа бежала по саванне и треснулась головой в дерево, под которым отдыхали львы

This unfortunate patient not only suffered severe brain injury, but chose a very bad place to do it....

This unfortunate patient not only suffered severe brain injury, but chose a very bad place to do it....

Make sure that your hospital is not one of those places!!

Thank you for your attention!



PoldermanKH@UPMC.edu