Surgical Repair of Coarctation of the Aorta and the Spinal Cord

Richard J. Levy, M.D.
Director, Cardiac Anesthesia
Vice Chief, Division of Anesthesiology and Pain Medicine
Children's National Medical Center
Associate Professor of Anesthesiology and Critical Care Medicine, Pediatrics, and Information Systems Biology

Anesthesiology 2010; 113:880–91

Copyright © 2010, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins

A Mouse Model of Ischemic Spinal Cord Injury with Delayed Paralysis Caused by Aortic Cross-clamping

Hamdy Awad, M.D.,* Daniel P. Ankeny, Ph.D.,† Zhen Guan, M.D.,‡ Ping Wei, B.S.,‡ Dana M. McTigue, Ph.D.,§ Phillip G. Popovich, Ph.D.‖

* Assistant Professor, Department of Anesthesiology, † Research Scientist, ‡ Research Associate, § Associate Professor, ‖ Professor, Department of Neuroscience, Center for Brain and Spinal Cord Repair, The Ohio State University College of Medicine, Columbus, Ohio.

ABSTRACT

Background: Spinal cord ischemia and paralysis are devastating perioperative complications that can accompany open or endovascular repair surgery for aortic aneurysms. Here, we report on the development of a new mouse model of spinal cord ischemia with delayed paralysis induced by cross-clamping the descending aorta.

Methods: Transient aortic occlusion was produced in mice by cross-clamping the descending aorta through a lateral thoracotomy. To establish an optimal surgical procedure with limited mortality, variable cross-clamp times and core temperatures were tested between experiments.

Results: The onset of paresis or paralysis and postsurgical mortality varied as a function of cross-clamp time and core

What We Already Know about This Topic

- Spinal cord ischemia and paralysis are devastating perioperative complications that can accompany open or endovascular repair surgery for aortic aneurysms.

What This Article Tells Us That Is New

- A new mouse model of spinal cord ischemia with delayed paralysis induced by cross-clamping the descending thoracic aorta may prove useful for defining mechanisms of delayed paralysis and as a screening tool for neuroprotective therapeutics after transient cord ischemia.

Aim:
Develop a mouse model of spinal cord ischemia with delayed paralysis induced by cross-clamping the descending aorta

Methods:

Adult 7-12 week old C57Bl6 mice

Thoracotomy under general endotracheal isoflurane anesthesia with 100% FiO_2

ACC for varying durations (3-11 min) at varying body temp (33-36ºC)

Hemodynamics and ABG

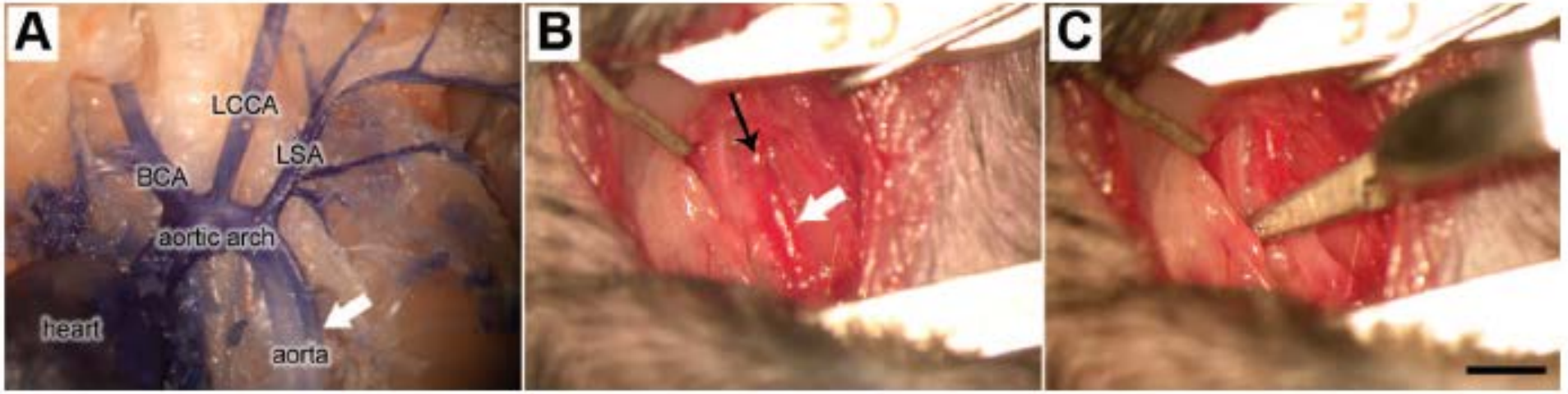
Locomotor behavior

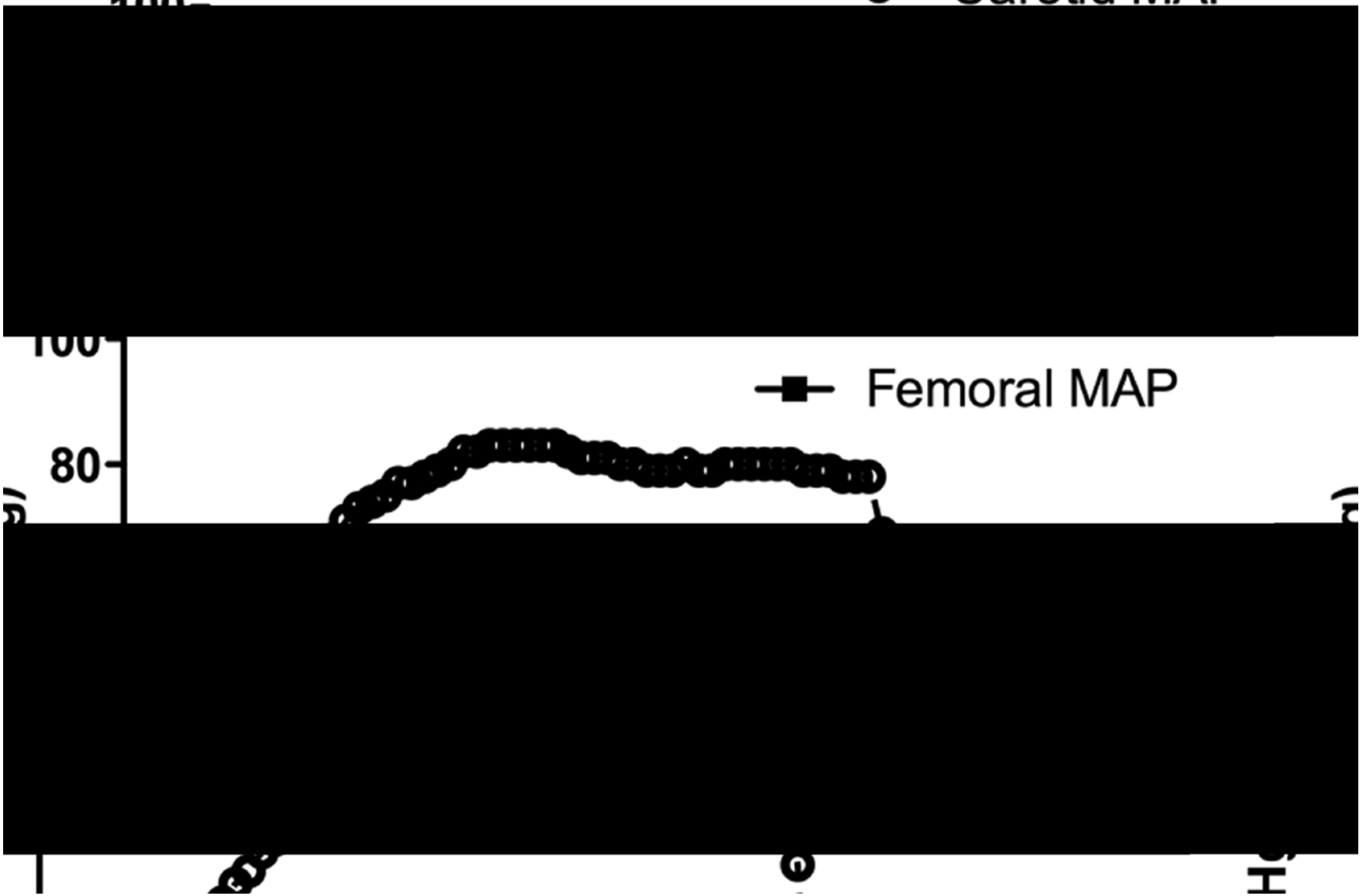
Histology

Table 1. Summary of Surgical Parameters and Group Sizes

Cross-clamp Location	Temperature, °C	Cross-clamp Time, min	n
Aortic Arch, LSA	35–36	8–11	14
Descending Thoracic Aorta	35	3–7.5	11
Descending Thoracic Aorta	35	8–11	8
Descending Thoracic Aorta	33	3–7	11
Descending Thoracic Aorta	33	7.5	29
Descending Thoracic Aorta	33	8–10	3
Descending Thoracic Aorta	33	7.5 (acute time points)	24
Descending Thoracic Aorta	33	7.5 (MAP and blood gases)	6

LSA = left subclavian artery; MAP = mean arterial pressure.


A
LCCA
LSA
BCA
aortic arch
heart
aorta
B
C


Carotid MAP
Femoral MAP
100
80

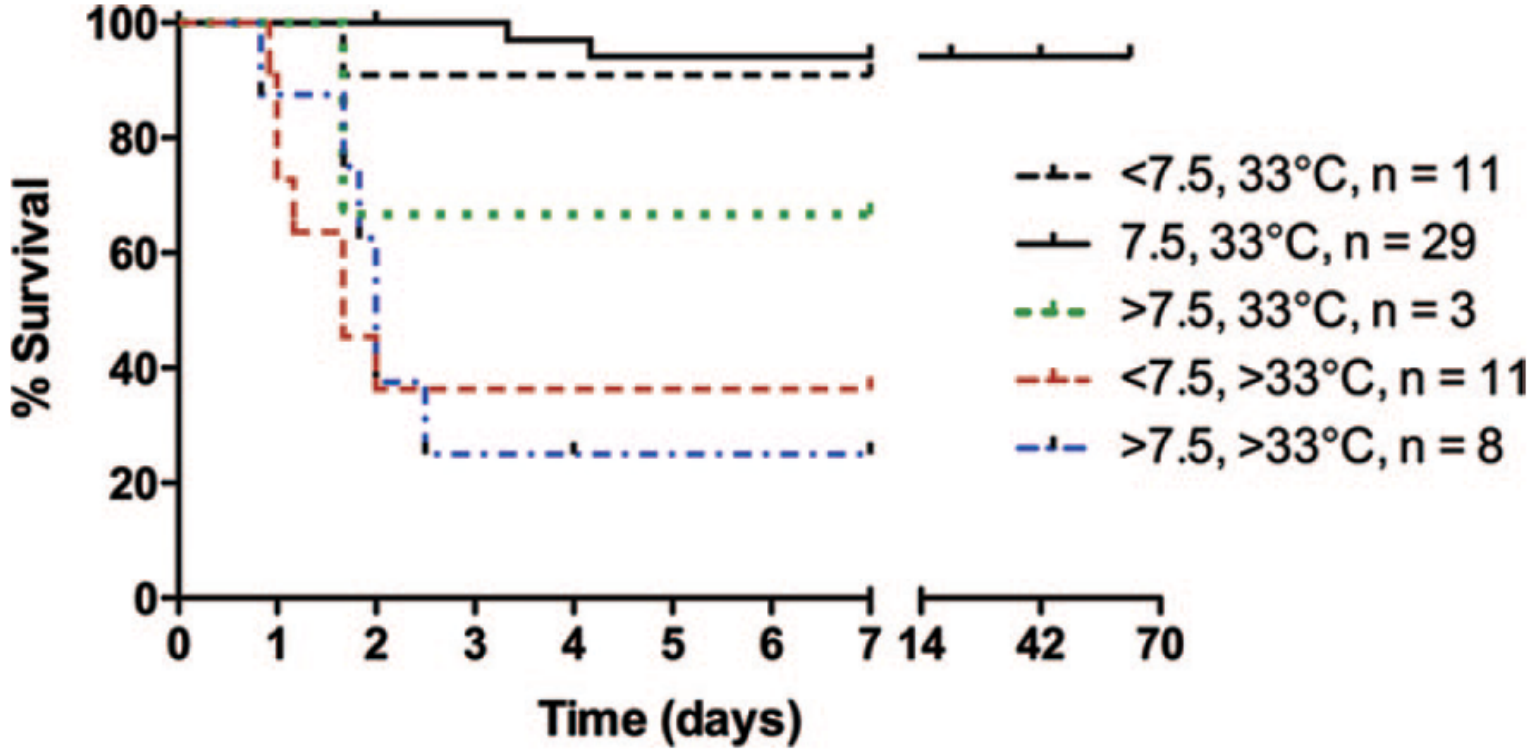


Fig. 2. Transient aortic cross-clamp (up to 7.5 min.) with systemic hypothermia (33°C) markedly improves survival. Kaplan-Meier survival curves illustrate the effects of varying intraoperative core temperature and duration of aortic cross-clamping. Survival curves were significantly different (*P* less than 0.0001), according to the Log-rank (Mantel-Cox) test.

35ºC

72% of mice with ACC for 8-11 min at 35-36ºC developed immediate paralysis

2 of the 7 remaining developed paralysis within 24 hours of ACC

33ºC

< 7.5 min ACC failed to cause paralysis
7.5 min ACC caused delayed neurologic impairment in all mice between 20-49 hours post ACC

Gait abnormalities

- toe drag, missed steps, loss of coordination, wide base, external paw rotation, trunk instability

Mild or severe (progression to paralysis)

Forelimb spared

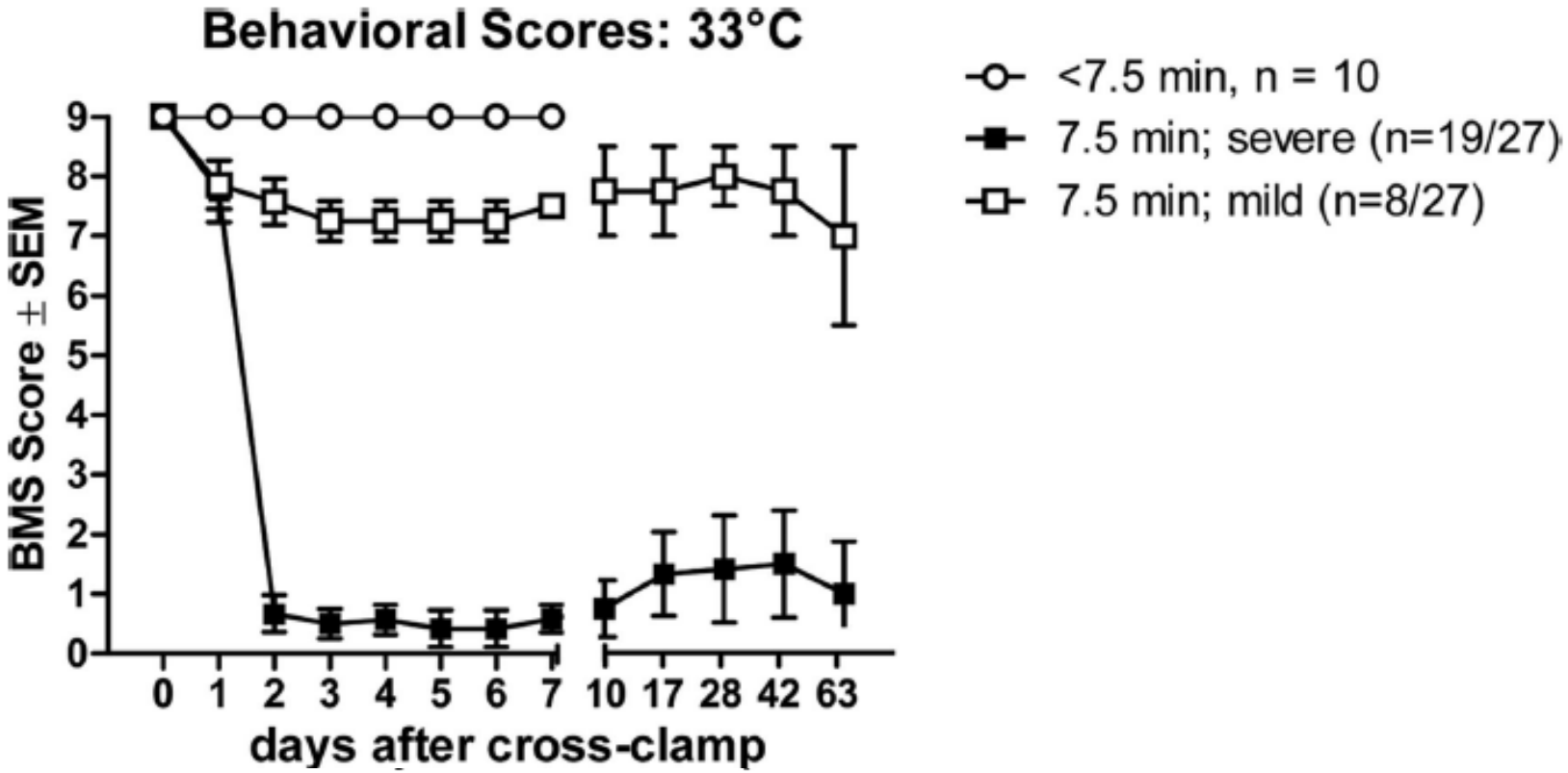


Fig. 3. Transient aortic occlusion (7.5 min) with mild systemic hypothermia (33°C) causes consistent but delayed hind limb locomotor deficits. Analysis of open-field locomotor function using the Basso Mouse Scale (BMS) reveals two functionally distinct cohorts of mice (*i.e.*, those that develop mild *vs.* severe neurological impairment). See Results for detailed description of the functional attributes that define these cohorts. Data are presented as mean (± SEM) BMS score as a function of days after ischemia/reperfusion.

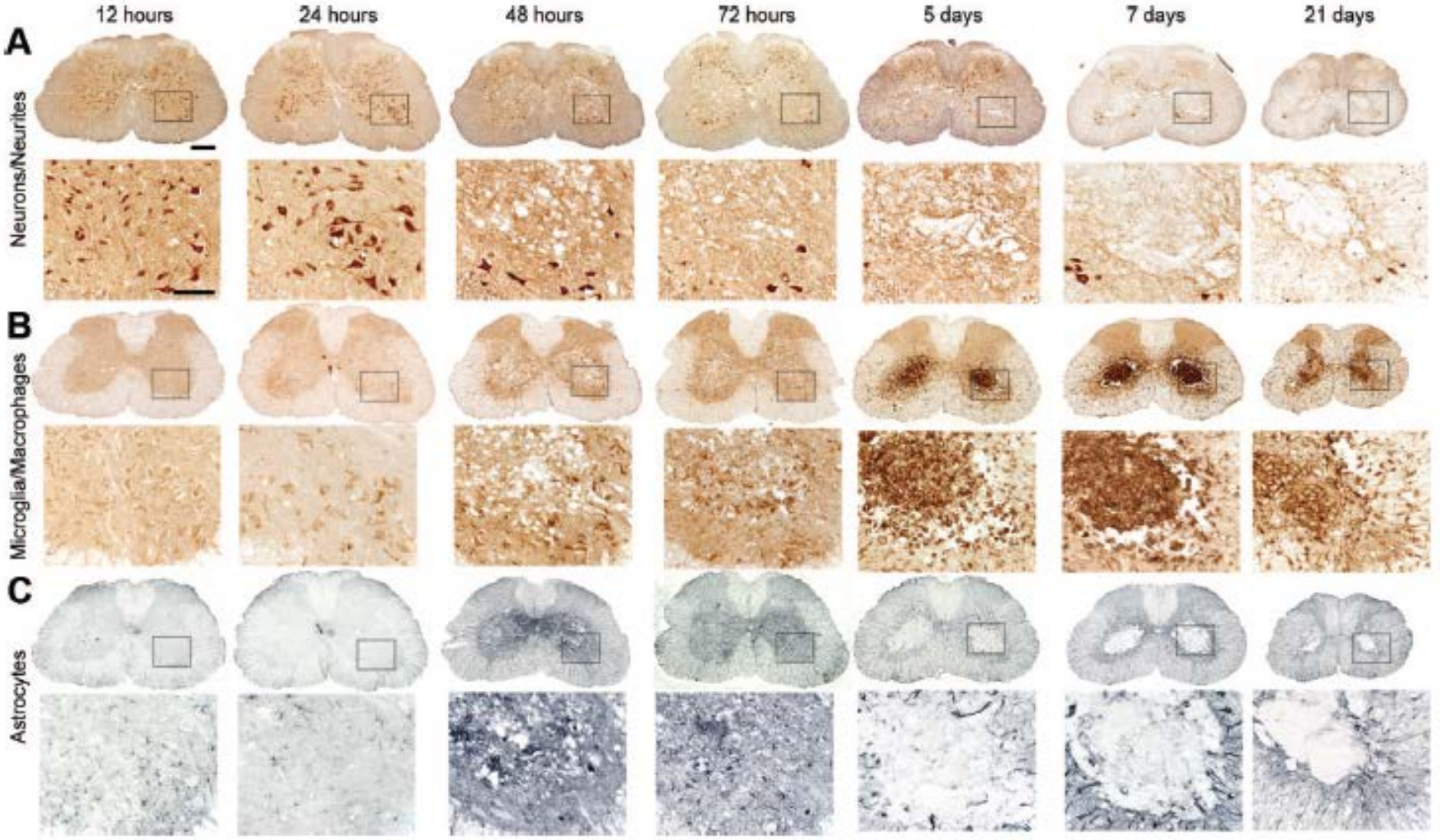
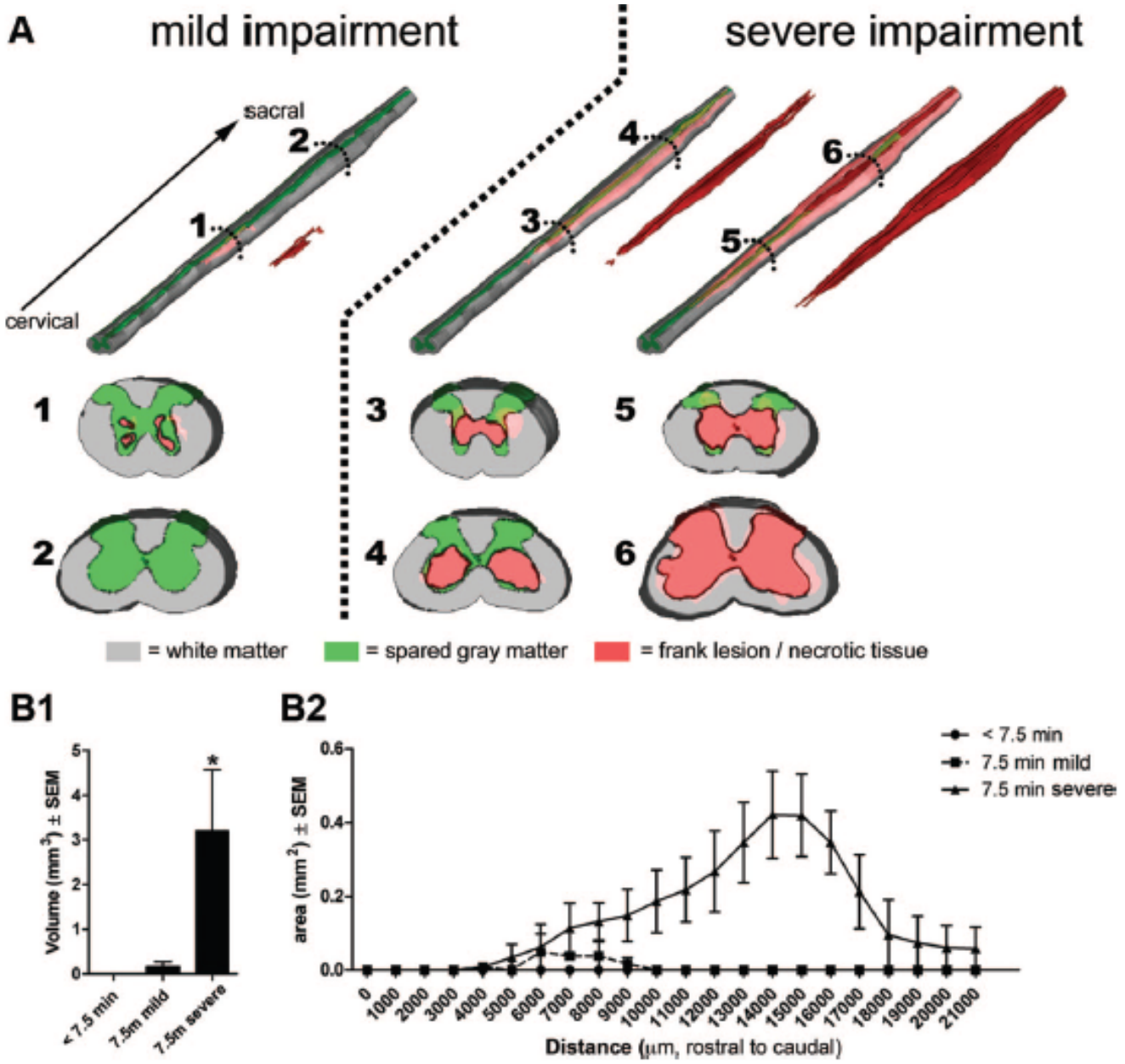


Fig. 4. Temporal sequence of intraspinal pathologic lesions in the lumbar spinal cord caused by two transient aortic cross-clamps (7.5 min) at 33°C. Representative cross-sections in series reveal time-dependent changes in neurons (*A*), microglia/macrophages (*B*), and reactive astrocytes (*C*). Note the significant spinal cord atrophy at 21 days. All sections were sampled from the ~L3–L4 spinal cord and were collected at the times indicated from a severely affected animal. An enlargement of the boxed regions is provided below each cross-section. Scale bar = 200 μm in low-magnification images and 100 μm in high-power images.

3-D Analysis of Spinal Cord Lesion



Conclusions:

Successful development of a mouse model for future investigation

Progressive necrosis, axonal degeneration, and intraspinal inflammation developed in multiple spinal cord segments between 2-7 days post ACC

Injury may be due to inflammation, excitotoxicity, oxidative stress, etc.

Recognizing subclinical pathologic conditions during or immediately after aortic repair surgery in humans is difficult because neither electromyography nor strength/sensory tests are performed routinely,[32] and most patients are discharged without reporting overt neurologic complications. This does not mean, however, that the spinal cord is not damaged or that neurologic impairment will not develop.

So what?

Does this translate to humans?

Are infants and children at risk?

Spinal Cord Blood Supply

Extrinsic circulation

Vertebral arteries

- cervical, upper thoracic cord

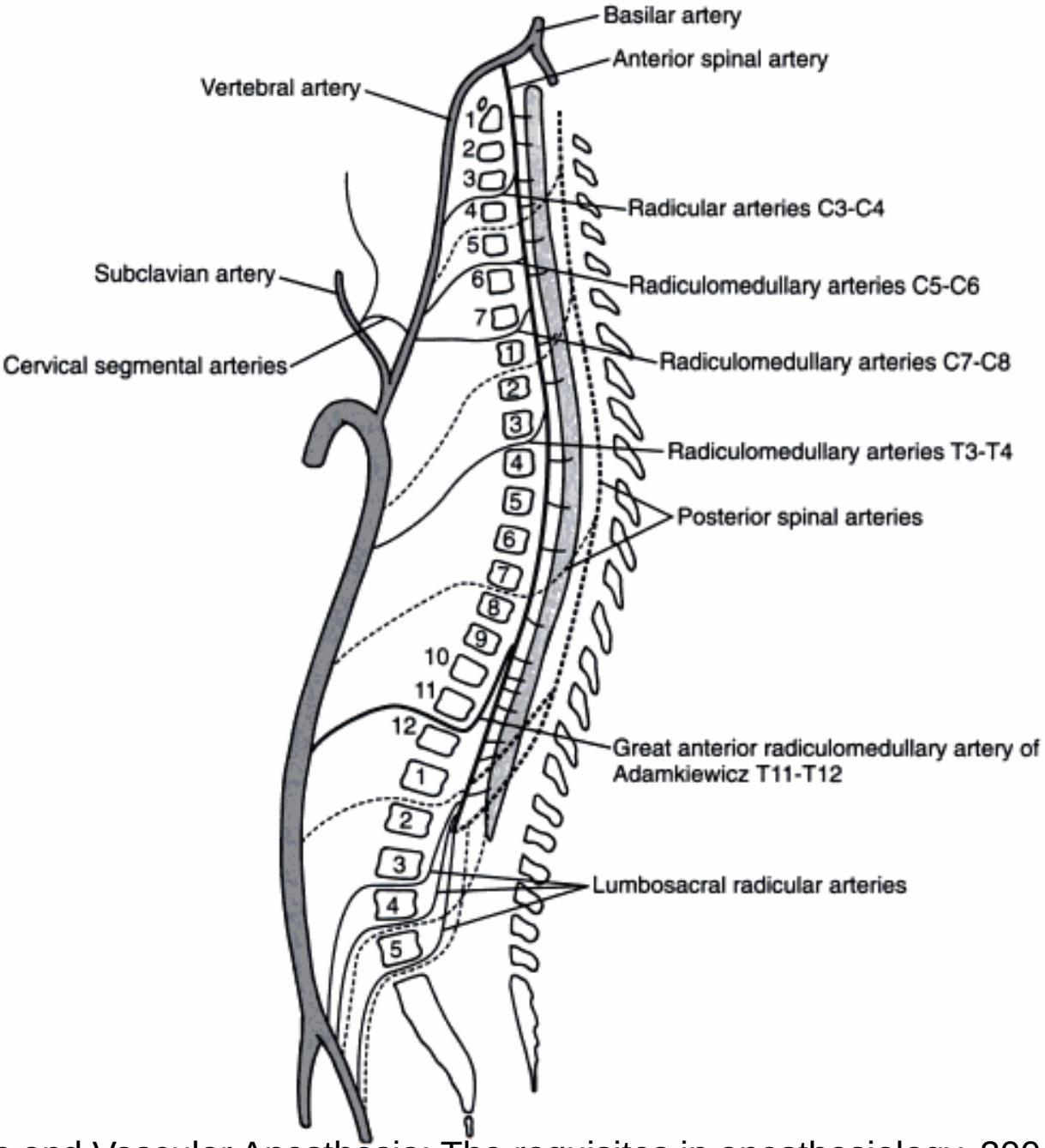
Intercostals and lumbar arteries

- midthoracic, thoracolumbar cord

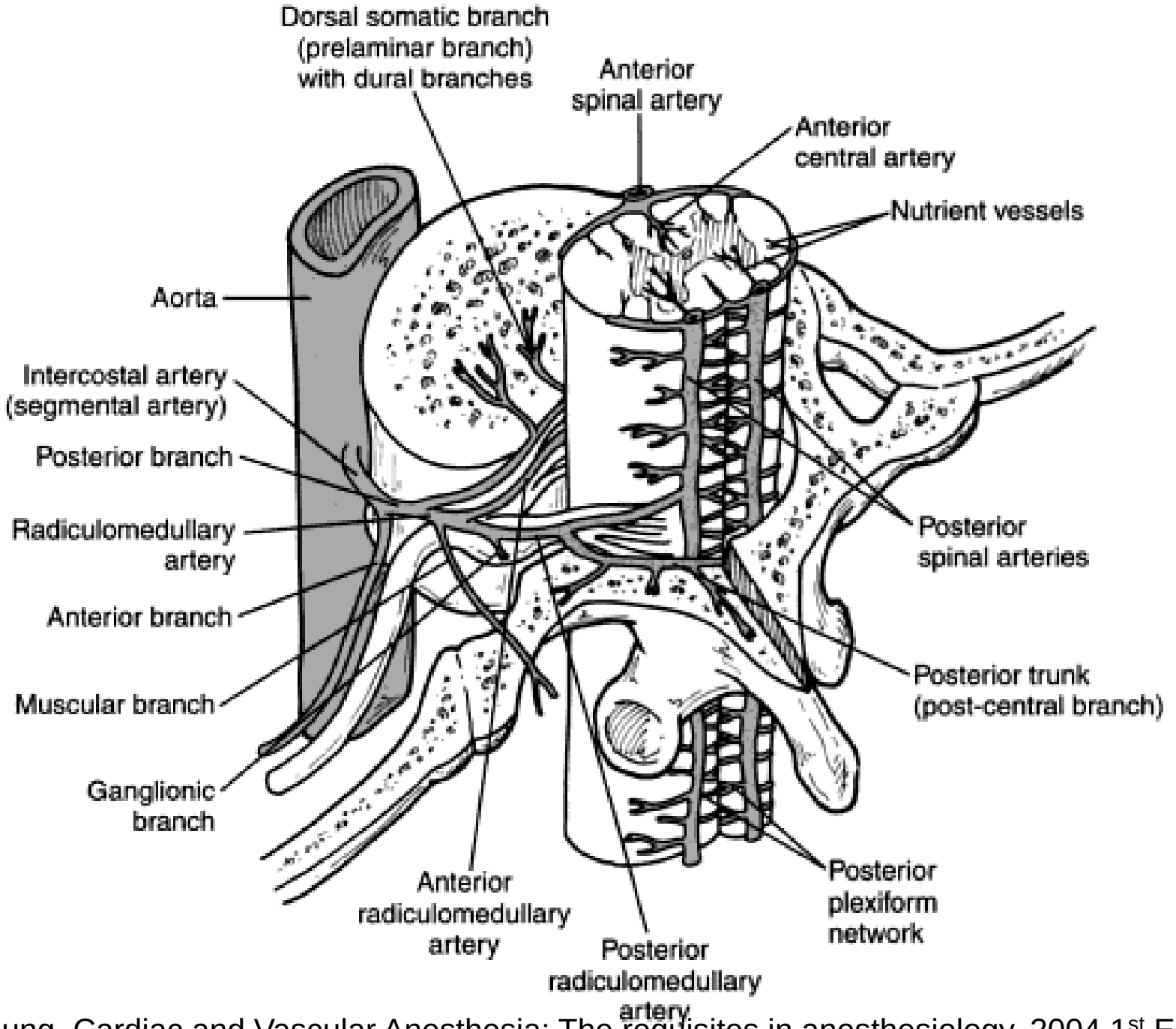
Intrinsic circulation

Anterior and posterior spinal arteries

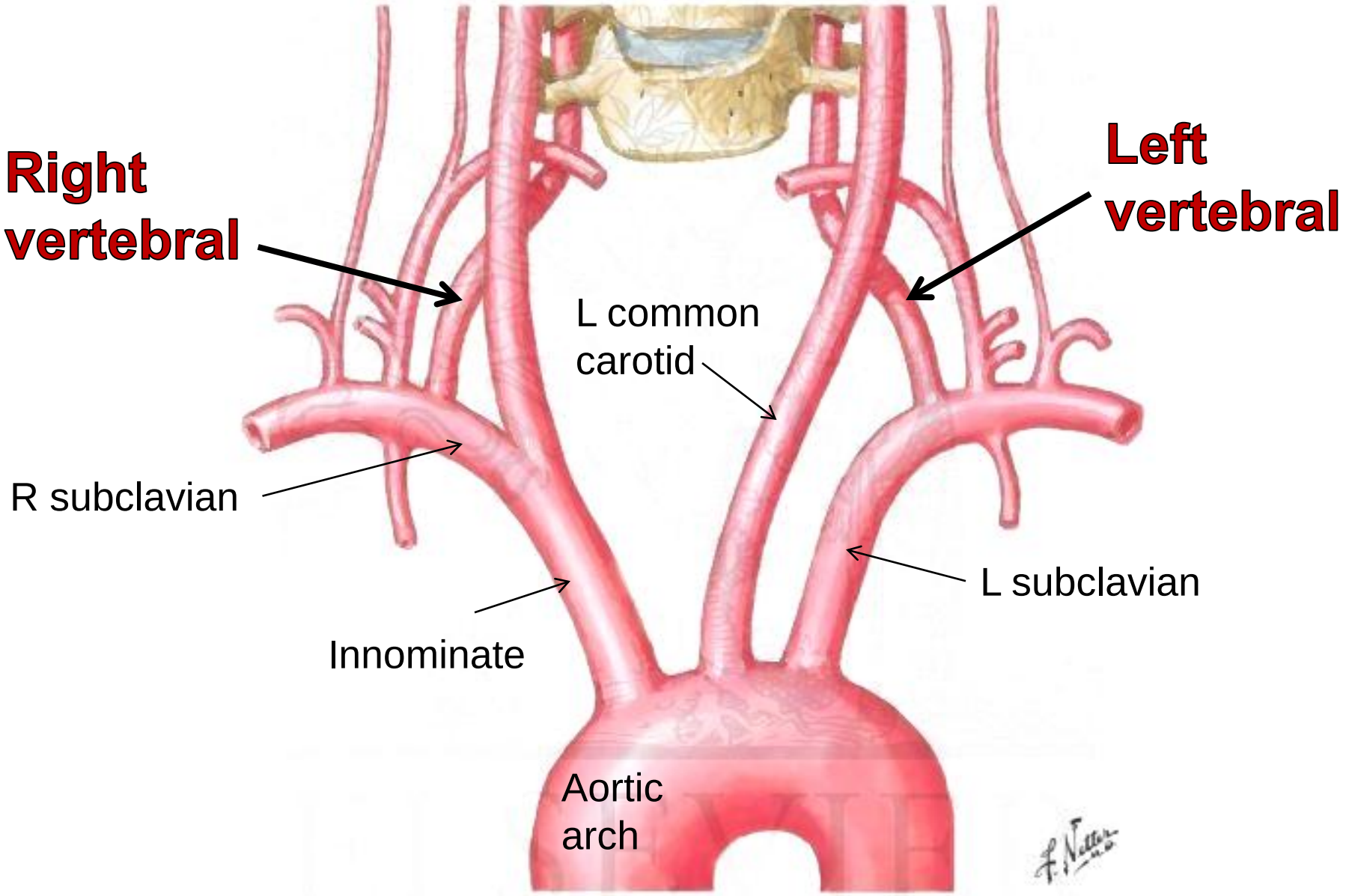
J Leung. Cardiac and Vascular Anesthesia: The requisites in anesthesiology. 2004 1st Ed



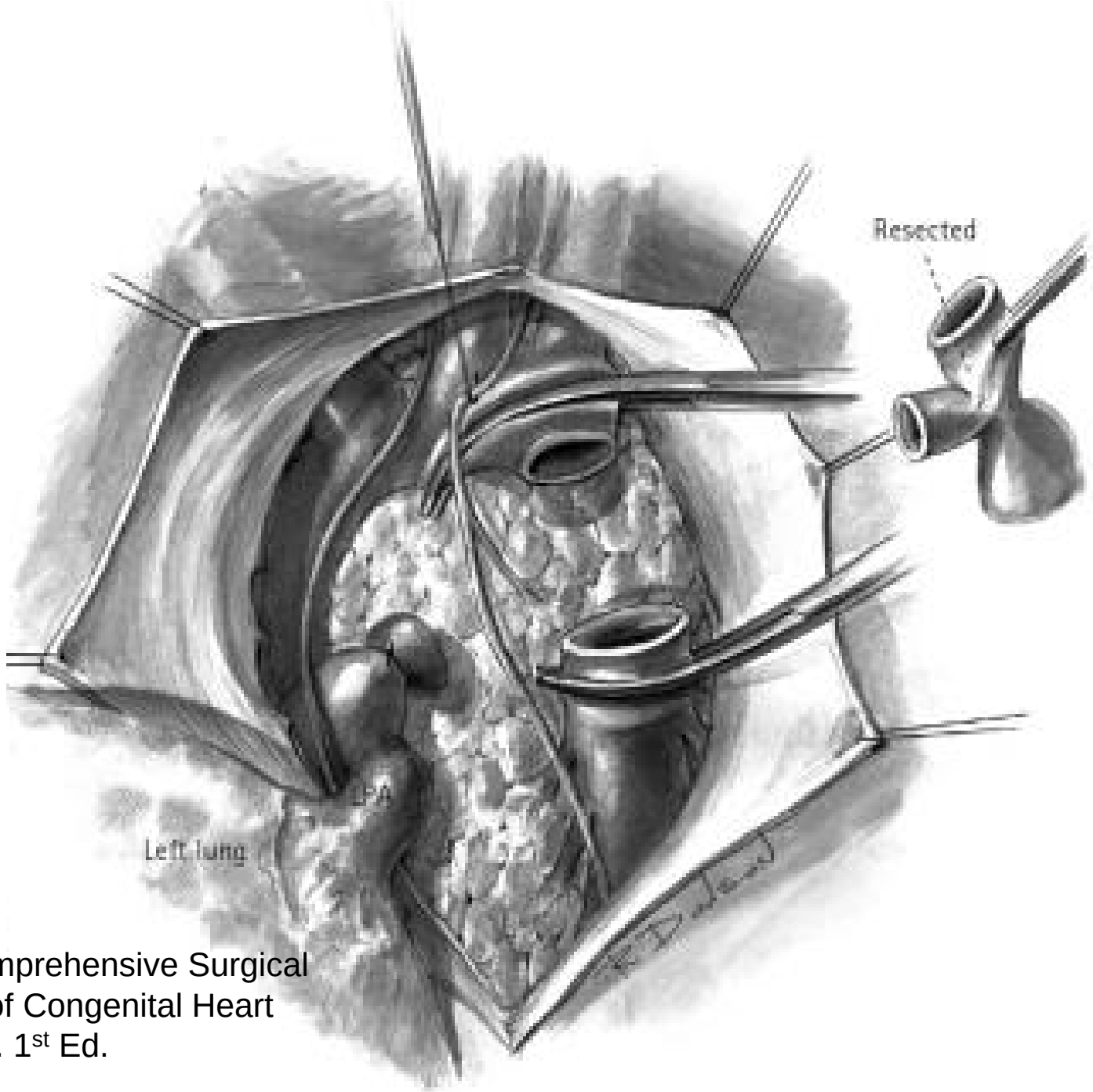
J Leung. Cardiac and Vascular Anesthesia: The requisites in anesthesiology. 2004 1st Ed



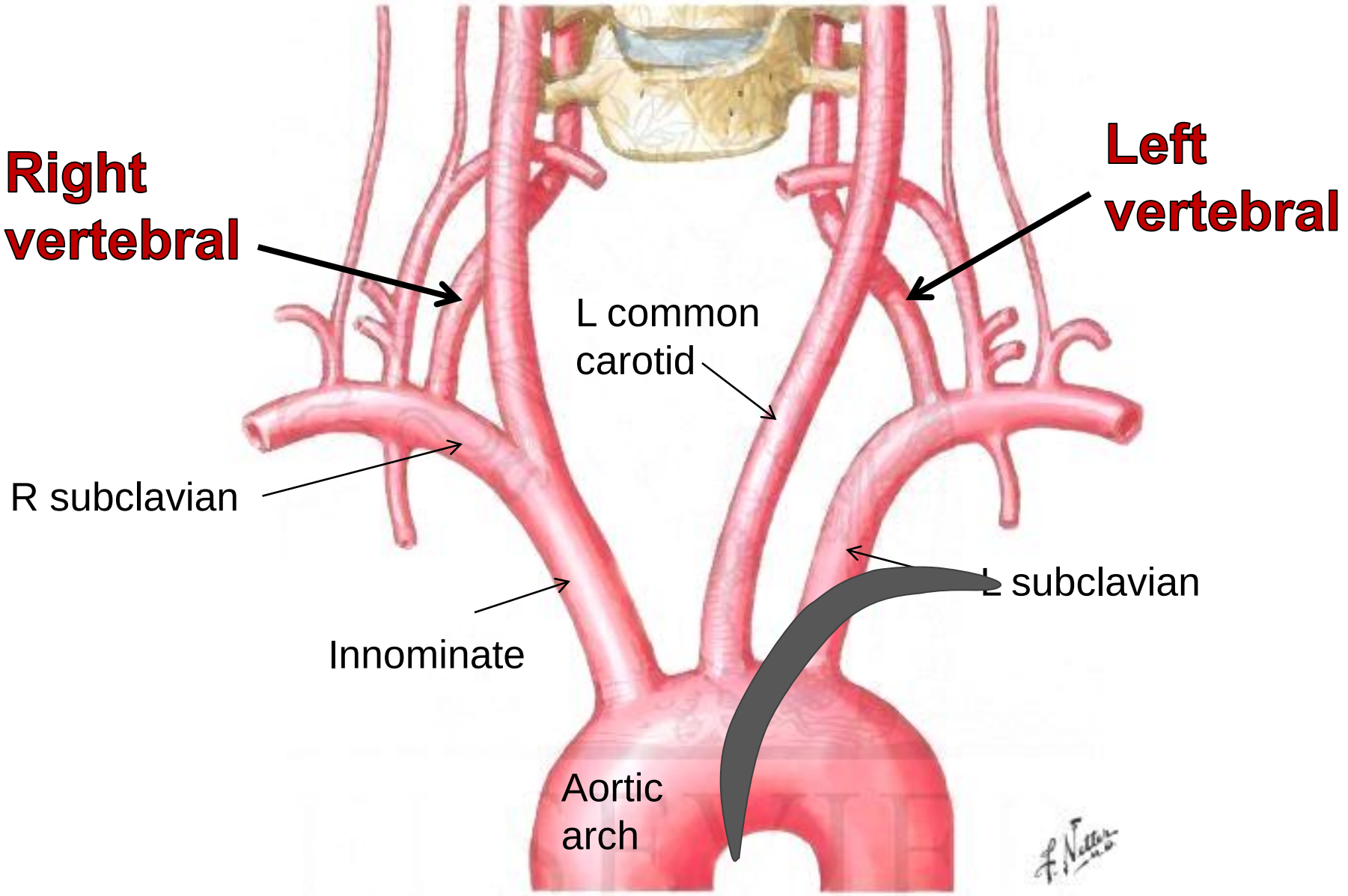
J Leung. Cardiac and Vascular Anesthesia: The requisites in anesthesiology. 2004 1st Ed



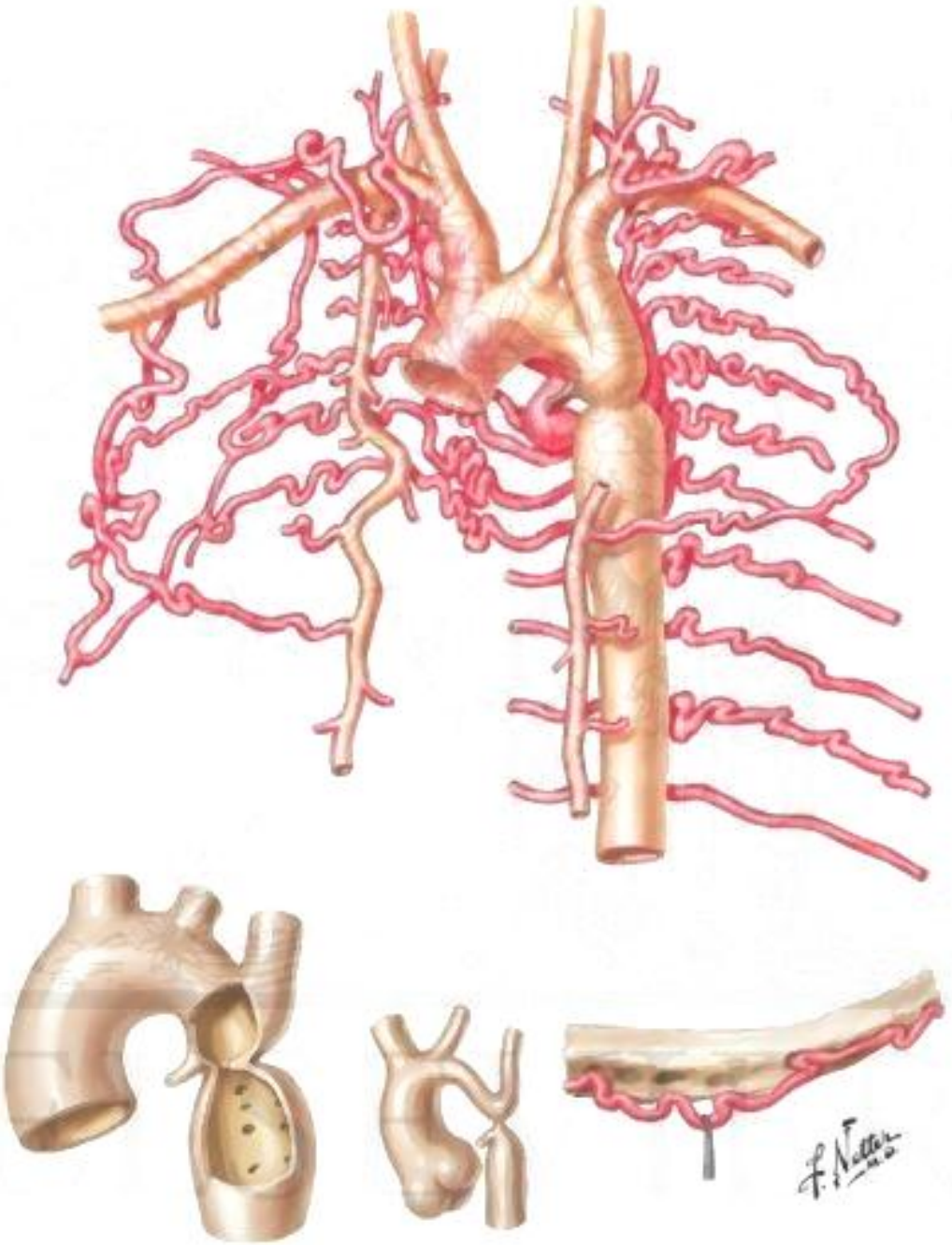
© ELSEVIER, INC. – NETTERIMAGES.COM



Jonas RA. Comprehensive Surgical Management of Congenital Heart Disease. 2004. 1st Ed.

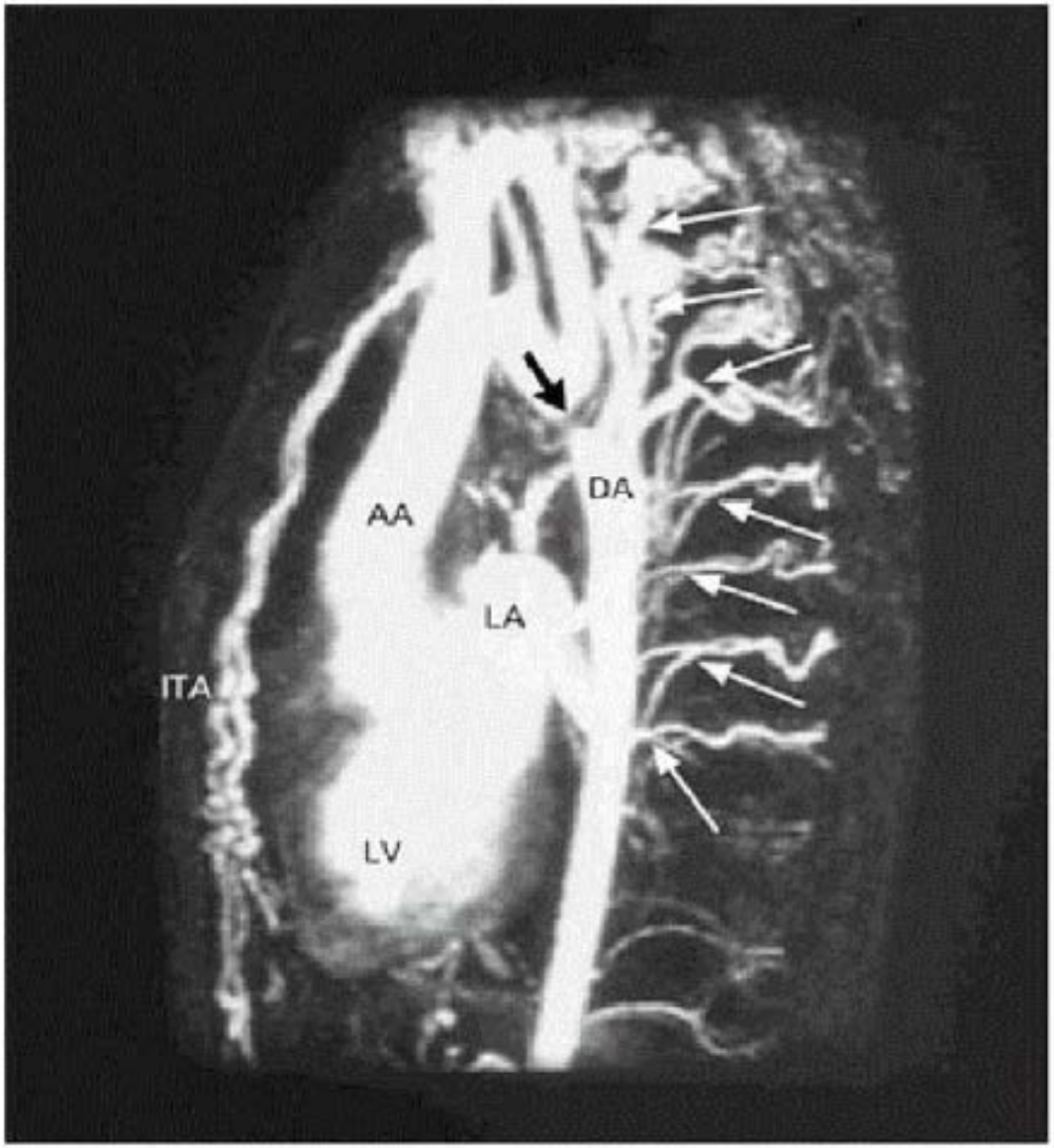


© ELSEVIER, INC. – NETTERIMAGES.COM



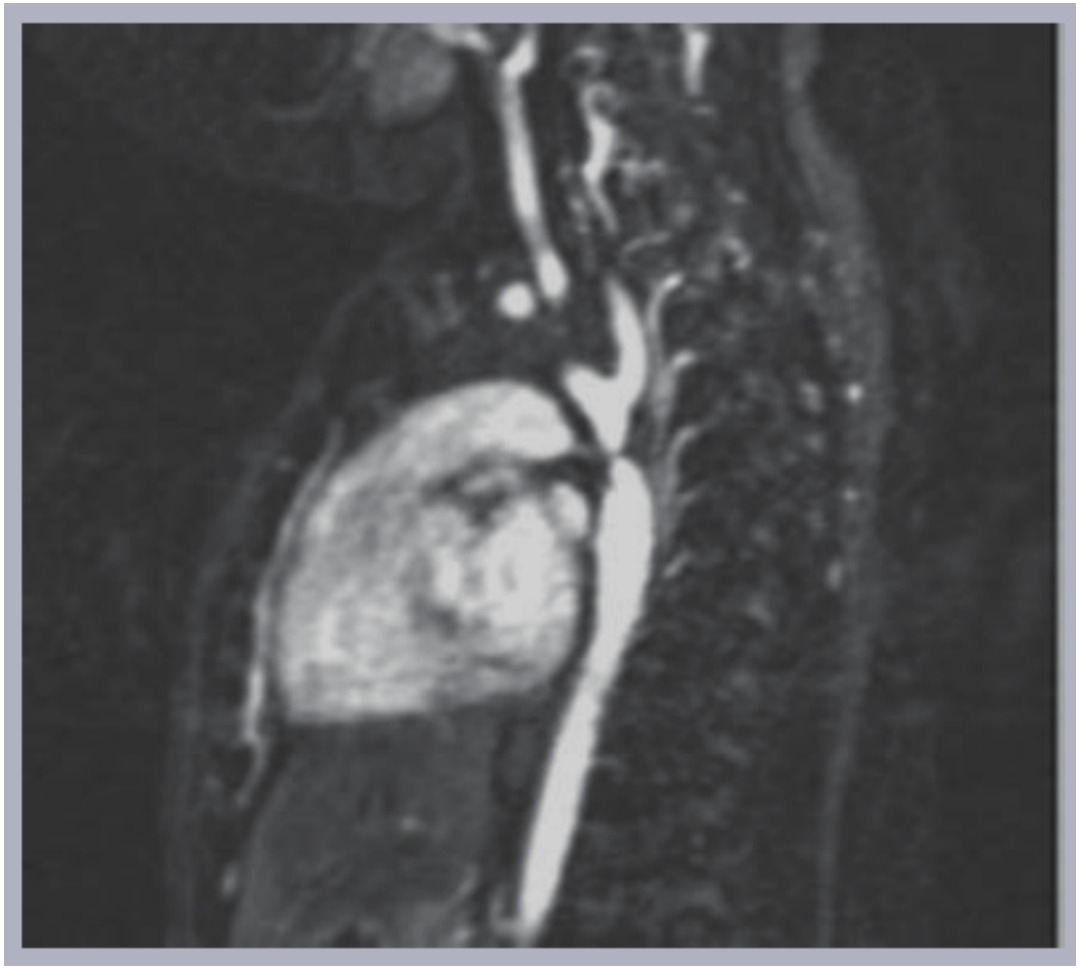
© ELSEVIER, INC. – NETTERIMAGES.COM

Adult with Congenital Coarctation



Hamdan M. J. Arab Neonatal Forum 2006; 3:5-13

10 month old Infant with Congenital Coarctation



Kenney D, Hijazi Z. Cardiology Journal, 2011.

Pediatric Anesthesia 2006 **16**: 777–781 doi:10.1111/j.1460-9592.2006.01956.x

Near infrared spectroscopy monitoring during pediatric aortic coarctation repair

RICHARD J. BERENS MCW CHW, ECKEHARD A. STUTH MCW CHW, FREDERICK A. ROBERTSON MCW CHW, ROBERT D. JAQUISS MCW CHW, GEORGE M. HOFFMAN MCW CHW, TODD J. TROSHYNSKI MCW CHW, SUSAN R. STAUDT MCW CHW, JOSEPH R. CAVA MCW CHW, JAMES S. TWEDDELL MCW CHW AND S. BERT LITWIN CHW

Medical College of Wisconsin, Children's Hospital of Wisconsin, Milwaukee, WI, USA

Summary

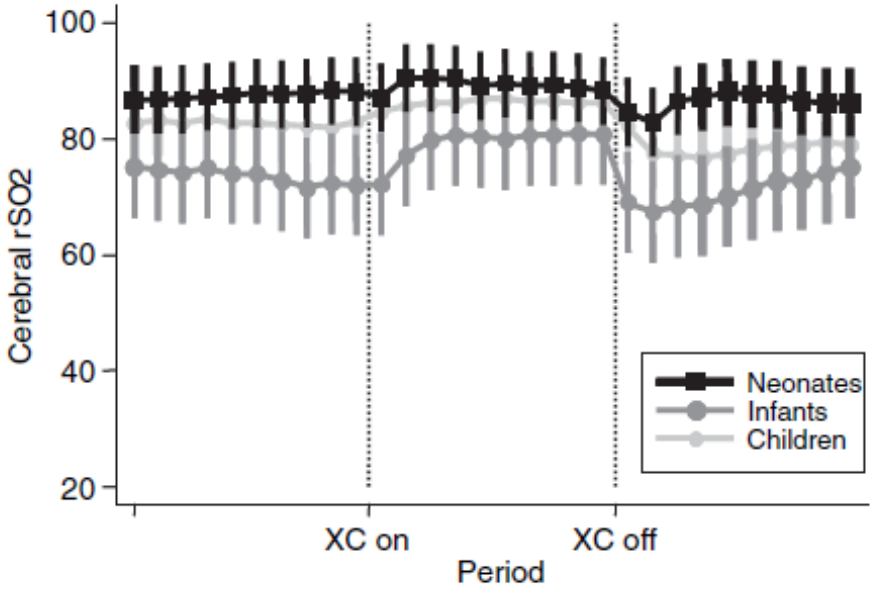
Background: Near infrared spectroscopy (NIRS) measures regional tissue oxygenation continuously and noninvasively and may allow assessment of changes in regional perfusion in real time.

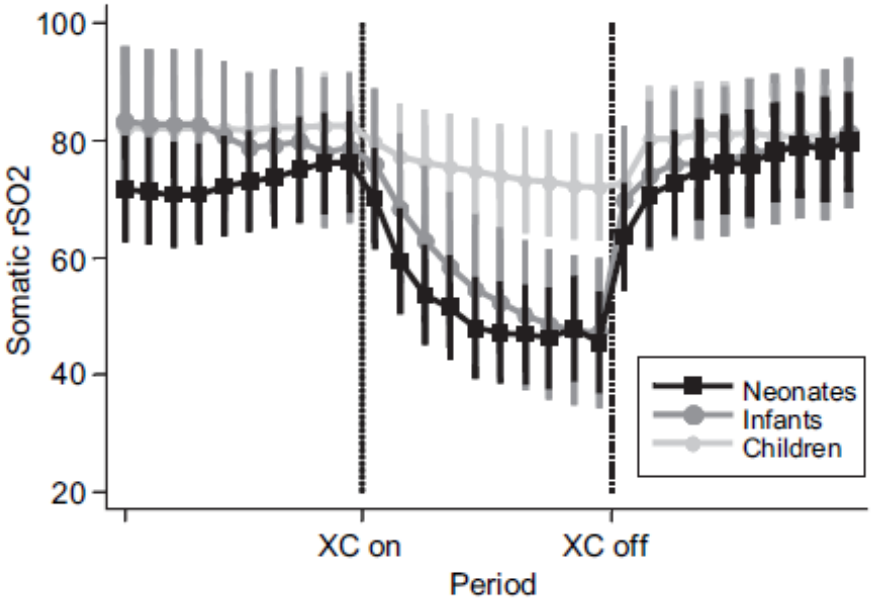
Methods: We used NIRS monitoring to track real-time changes in regional oxygenation (rSO_2) above and below the aortic cross-clamp in patients undergoing aortic coarctation repair and routinely stored these data in an operative electronic data base. This allowed us to analyze the changes in rSO_2 during aortic coarctation repair for three pediatric age groups (neonates, infants <1 year, and children >1 year).Two site [cerebral (rSO_2-C) and somatic thoracodorsal (rSO_2-

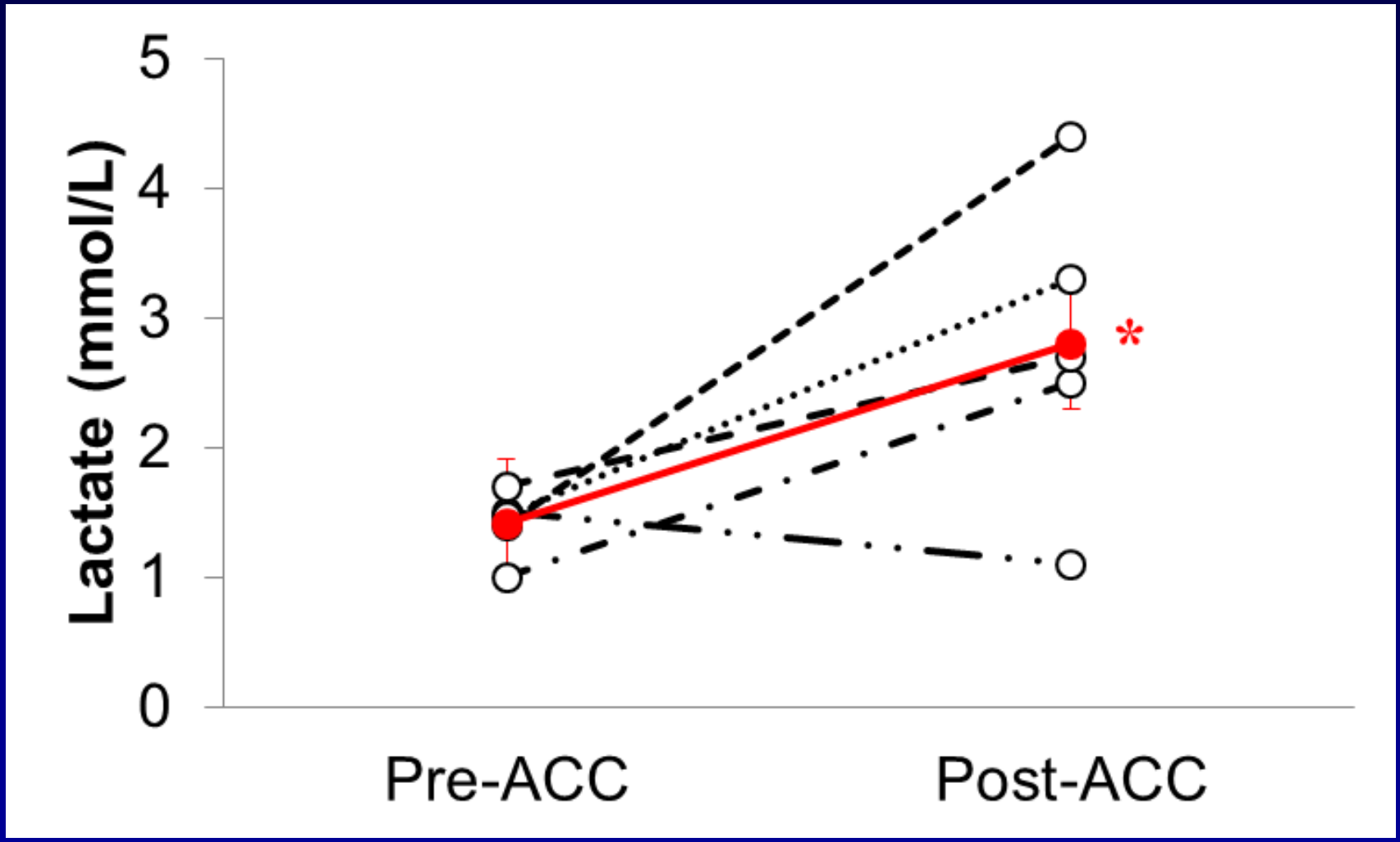
Age group	*Age median (range) in days*	*Gender female/male*	*Cross-clamp time mean (min)* ± SD	*P-value for cross-clamp time between age groups*
Neonate ($n = 11$)	6 (3–22)	2/9	16.6 ± 2.3	n.s.
Infant ($n = 5$)	62 (36–210)	3/2	17.8 ± 4.2	n.s.
Child ($n = 10$)	1410 (407–4148)	2/8	20.3 ± 5.6	n.s.

SD, standard deviation.

Distal Somatic NIRS during ACC

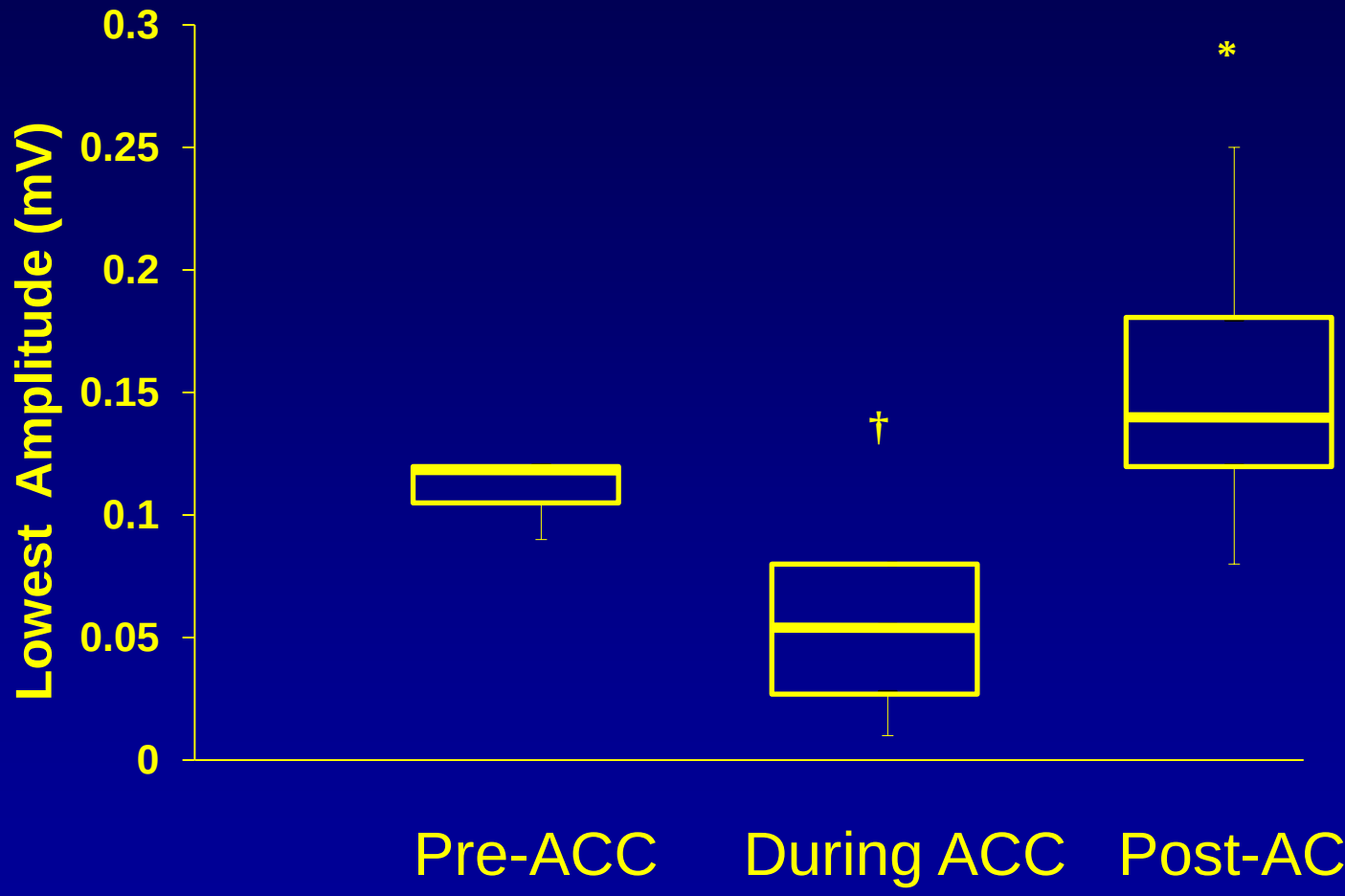






*P<.05

SSEP Lowest Amplitude



† $P < .05$

* $P < .01$

Cell death occurs 15-45 min after loss of SSEPs

Park SC, Neches WH. Neurologic Clin. 1993.

Neuro Exams

Patient	Pre	Post
1	Normal	Clonus bilateral LE
2	Normal	Clonus bilateral LE
3	Normal	Normal
4	Normal	Esotropia
5	Normal	Normal

AMERICAN COLLEGE of CARDIOLOGY FOUNDATION

American Heart Association.
Learn and Live.



ACC/AHA Pocket Guideline

Based on the 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM

Guidelines for the Diagnosis and Management of Patients With Thoracic Aortic Disease

March 2010

20.2. Recommendations for Spinal Cord Protection During Descending Aortic Open Surgical and Endovascular Repairs

Class I	1. Cerebrospinal fluid drainage is recommended as a spinal cord protective strategy in open and endovascular thoracic aortic repair for patients at high risk of spinal cord ischemic injury. *(LOE: B)*
Class IIa	1. Spinal cord perfusion pressure optimization using techniques, such as proximal aortic pressure maintenance and distal aortic perfusion, is reasonable as an integral part of the surgical, anesthetic, and perfusion strategy in open and endovascular thoracic aortic repair patients at high risk of spinal cord ischemic injury. Institutional experience is an important factor in selecting these techniques. *(LOE: B)* 2. Moderate systemic hypothermia is reasonable for protection of the spinal cord during open repairs of the descending thoracic aorta. *(LOE: B)*

Class IIb	1. Adjunctive techniques to increase the tolerance of the spinal cord to impaired perfusion may be considered during open and endovascular thoracic aortic repair for patients at high risk of spinal cord injury. These include distal perfusion, epidural irrigation with hypothermic solutions, high-dose systemic glucocorticoids, osmotic diuresis with mannitol, intrathecal papaverine, and cellular metabolic suppression with anesthetic agents. *(LOE: B)*
	2. Neurophysiological monitoring of the spinal cord (somatosensory evoked potentials or motor evoked potentials) may be considered as a strategy to detect spinal cord ischemia and to guide reimplantation of intercostal arteries and/or hemodynamic optimization to prevent or treat spinal cord ischemia. *(LOE: B)*

1972 review of 12,532 coarctation repairs

- 66 patients with spinal cord injury
- 51 paraplegia
- 0.41% incidence of paralysis

Brewer LA III, Fosburg RG, Mulder GA, Verska JJ J Thorac Cardiovasc Surg. 1972; 64:368–381.

NIH Public Access
Author Manuscript
J Thorac Cardiovasc Surg. Author manuscript; available in PMC 2013 November 24.

Published in final edited form as:
J Thorac Cardiovasc Surg. 2013 January ; 145(1): . doi:10.1016/j.jtcvs.2012.09.053.

Contemporary patterns of surgery and outcomes for aortic coarctation: An analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database

Ross M. Ungerleider, MD, MBA[a], **Sara K. Pasquali, MD**[b,c], **Karl F. Welke, MD**[d], **Amelia S. Wallace, BS**[c], **Yoshio Ootaki, MD, PhD**[a], **Michael D. Quartermain, MD**[e], **Derek A. Williams, DO**[e], and **Jeffrey P. Jacobs, MD**[f]

[a]Department of Cardiothoracic Surgery, Brenner Children's Hospital, Wake Forest Baptist Health, Winston Salem, NC

[b]Department of Pediatrics, Duke University School of Medicine, Durham, NC

[c]Duke Clinical Research Institute, Durham, NC

[d]Seattle Children's Hospital, Seattle, Wash

[e]Division of Pediatric Cardiology, Department of Pediatrics, Brenner Children's Hospital, Wake Forest Baptist Health, Winston Salem, NC

[f]The Congenital Heart Institute of Florida, All Children's Hospital, University of South Florida College of Medicine, Saint Petersburg and Tampa, Fla

NIH-PA Author Manuscript
NIH-PA Author

Reviewed STS Database for Coarctation Repair 2006-2010

Repair technique	Frequency, n/N (%)
End-to-end anastomosis	820/2474 (33.1)
Extended end-to-end anastomosis	1385/2474 (56.0)
Subclavian flap repair	85/2474 (3.4)
Patch aortoplasty	104/2474 (4.2)
Interposition graft	70/2474 (2.8)
Other	10/2474 (0.4)

Variable	Overall	C/HAA–isolated, group 1	C/HAA–VSD, group 2	C/HAA–other, group 3	*P* value
n	5025	2705	840	1480	
In-hospital mortality, n/N (%)	119/5025 (2.4)	27/2705 (1)	21/840 (2.5)	71/1480 (4.8)	<.0001
LOS, d; mean ± SD (median)	14 ± 22 (7)	9.7 ± 16.2 (5)	19.7 ± 24.3 (11)	18.6 ± 27.6 (9)	<.0001
Any complication, n/N (%)	1816/5025 (36)	666/2705 (24.6)	463/840 (55.1)	687/1480 (46.4)	<.0001
Acidosis, n/N (%) *	81/4052 (2)	21/2206 (1)	12/663 (1.8)	48/1183 (4.1)	<.0001
Cardiac arrest, n/N (%)	62/5025 (1.2)	11/2750 (0.4)	19/840 (2.3)	32/1480 (2.2)	<.0001
Chylothorax, n/N (%)	165/5025 (3.3)	56/2705 (2.1)	35/840 (4.2)	74/1480 (5)	<.0001
PERD, n/N (%)	98/5025 (2)	36/2705 (1.3)	25/840 (3)	37/1480 (2.5)	.002
RLN injury, n/N (%)	176/5025 (3.5)	42/2705 (1.6)	76/840 (9)	58/1480 (3.9)	<.0001
Phrenic nerve/paralyzed diaphragm	47/5025 (0.9)	10/2705 (0.4)	12/840 (1.4)	25/1480 (1.7)	<.0001
Unplanned cardiac reoperation, n/N (%) †	33/973 (3.4)	7/479 (1.4)	9/177 (5.1)	17/297 (5.7)	.002
Unplanned readmission within 30 d, n/N (%) †	36/973 (3.7)	12/499 (2.4)	5/177 (2.8)	19/297 (6.4)	.01
Spinal cord injury, n/N (%) †	0/973 (0)	0/499 (0)	0/177 (0)	0/297 (0)	NA
Mechanical ventilator support, n/N (%)	253/5025 (5)	64/2705 (2.4)	57/840 (6.8)	132/1480 (8.9)	<.0001

All based on total group population, unless otherwise specified.

C/HAA, Coarctation or hypoplastic aortic arch; *VSD*, ventricular septal defect; *LOS*, length of stay; *SD*, standard deviation; not applicable.

* Some complications were only coded prior to 2010, and denominator is specified.

† Some complications were only coded since 2010, and denominator is specified.

Paralysis is the most extreme outcome endpoint

The New York Times

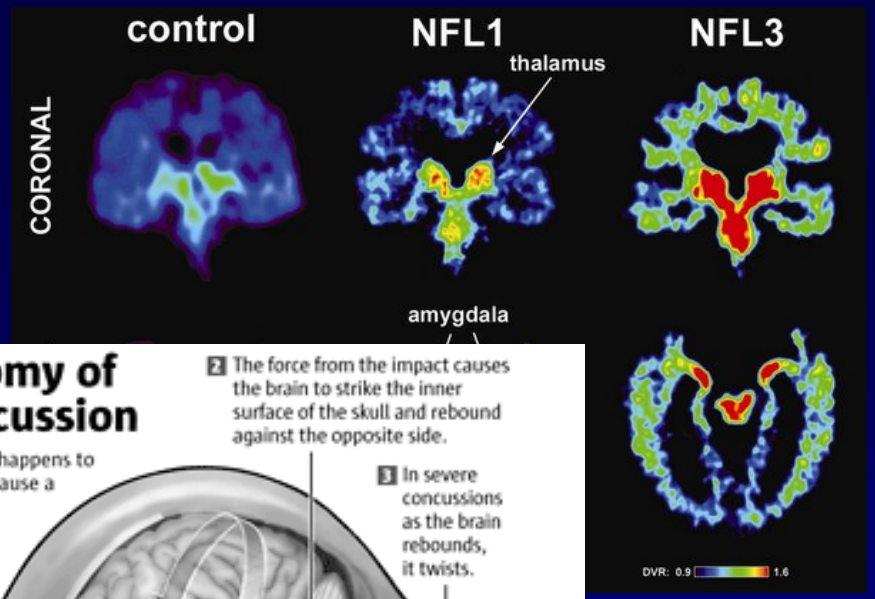
Pro Football

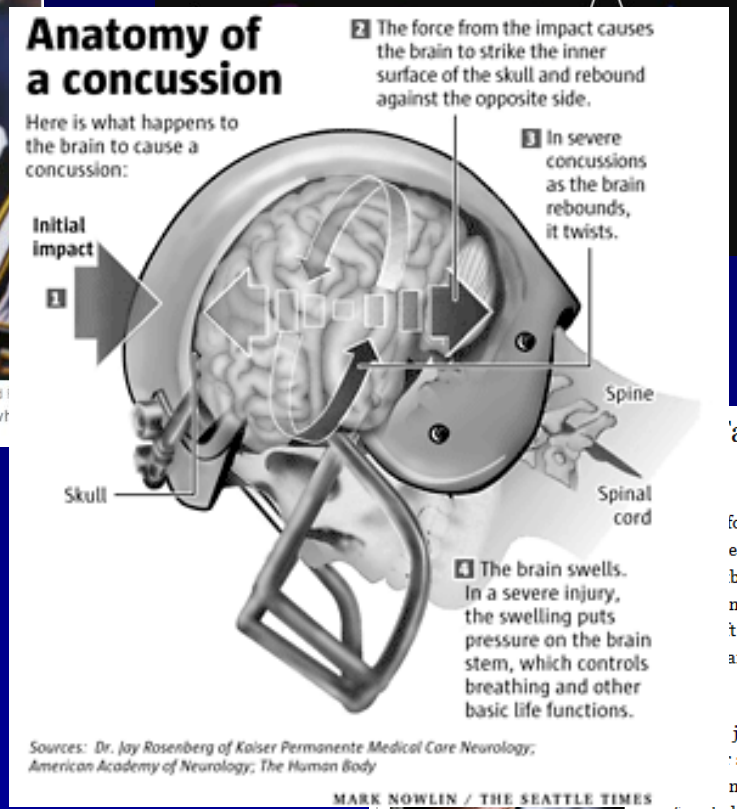
Seau Suffered From Brain Disease



Junior Seau have absor

Sandy Huffaker/Associated connected to athletes wh





THE FIFTH DOWN; Study Finds Risk of Brain Disease for N.F.L. Players

By MIKE TIERNEY
Published: September 6, 2012

A disproportionate number of men who played at least five seasons in the N.F.L. from 1959 to 1988 developed Alzheimer's disease or Lou Gehrig's disease, according to a study released Wednesday.

The findings were based on a review of death certificates by the National Institute for Occupational Safety and Health, part of the Centers for Disease Control and Prevention.

Of the 334 player deaths prior to 2008 that were inspected, Alzheimer's was an underlying or contributing factor in seven and Lou Gehrig's disease, also known as amyotrophic lateral sclerosis, in seven others. The rate for the general population is two in each category.

FACEBOOK
TWITTER
GOOGLE+
EMAIL
SHARE
PRINT
REPRINTS

3 CRITICS' CHOICE AWARDS BEST PICTURE

'amily's Ordeal

football last Sunday, a
ed on a wall over his
ball differently from most
ne, fitting for a tackle out
t pick of the Saints in 200
arly games reach halftime

jersey has its spot, but the
stops with other teams,
ny that White sometimes
confused about what order the team
came in and who the coach was.
Everywhere it was the same, though
White never played in a regular-
season game, always stopped by a
freakish injury, a newly signed playe
extended battle with the staph infect
After that, White asked the Tampa B
allocate him to N.F.L. Europe, now

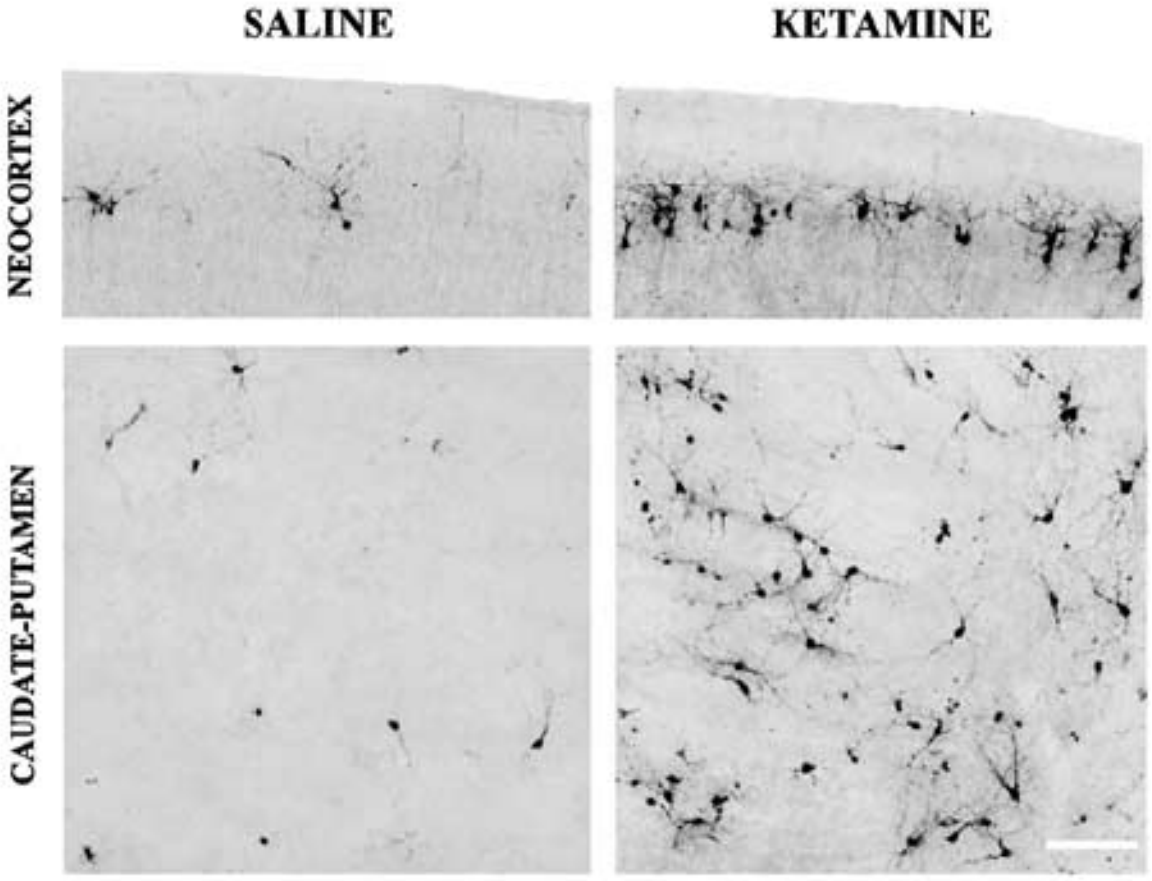
MARK NOWLIN / THE SEATTLE TIMES



Michael Mulvey for The New York Times

Mitch White, a former player for the Saints and the Buccaneers, at times loses his ability to move, talk and think. He is suing the N.F.L. over his concussion.

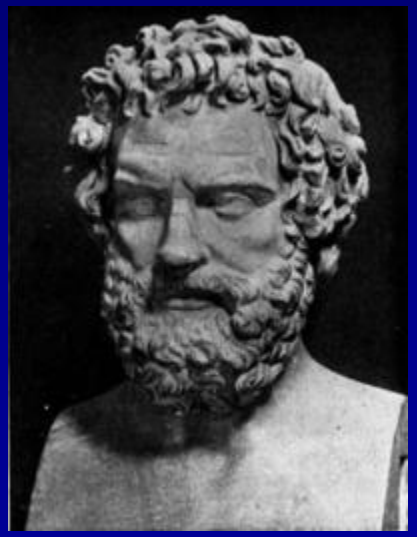
Anesthesia-induced Neurotoxicity



Young C, Jevtovic-Todorovic V, Qin YQ, Tenkova T, Wang H, Labruyere J, Olney JW. Br J Pharmacol. 2005 Sep;146(2):189-97.

No one has looked for subclinical spinal cord injury or insults other than paralysis

“Look and you will find it –
what is unsought will go undetected.”

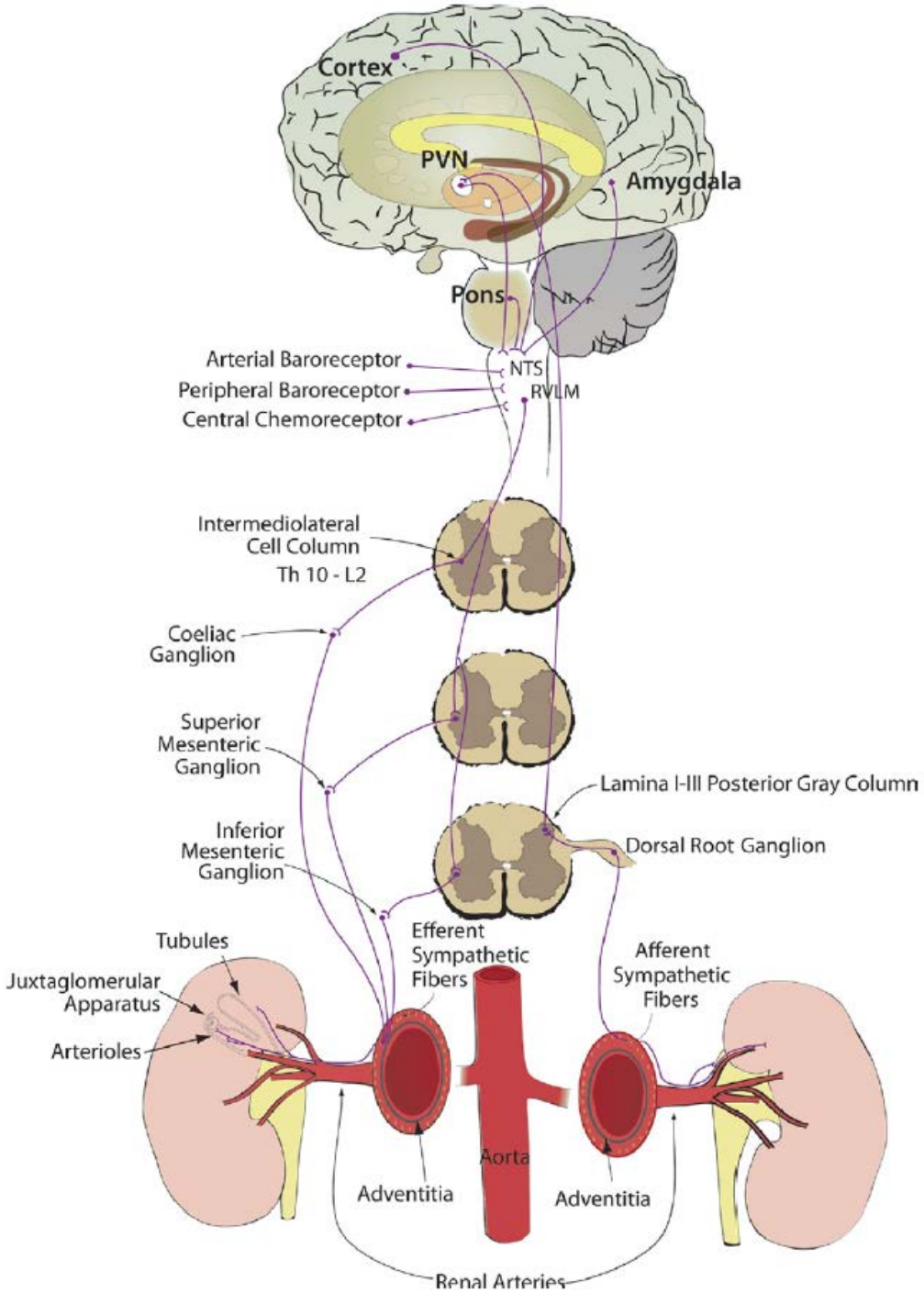


Sophocles

0496 BC – 0406 BC

Pure speculation…

How could subclinical injury in the developing spinal cord manifest?


Cortex
PVN
Amygdala
Pons
Arterial Baroreceptor
Peripheral Baroreceptor
Central Chemoreceptor
NTS
RVLM
Intermediolateral
Cell Column
Th 10 - L2
Coeliac
Ganglion
Superior
Mesenteric
Ganglion
Inferior
Mesenteric
Ganglion
Lamina I-III Posterior Gray Column
Dorsal Root Ganglion
Tubules
Juxtaglomerular
Apparatus
Arterioles
Efferent
Sympathetic
Fibers
Afferent
Sympathetic
Fibers
Aorta
Adventitia
Adventitia
Renal Arteries

Hypertension causes significant late morbidity and mortality following coarctation repair

Up to 75% of all patients undergoing coarctation repair will have systemic hypertension by 20-30 years post op

D S Celermajer, K Greaves. Heart 2002;88:113–114

119 children who underwent coarct repair between 2-3 months of age

- compared with 1034 controls
- 28% had HTN 7-16 years later
- 21% had no residual coarct disease

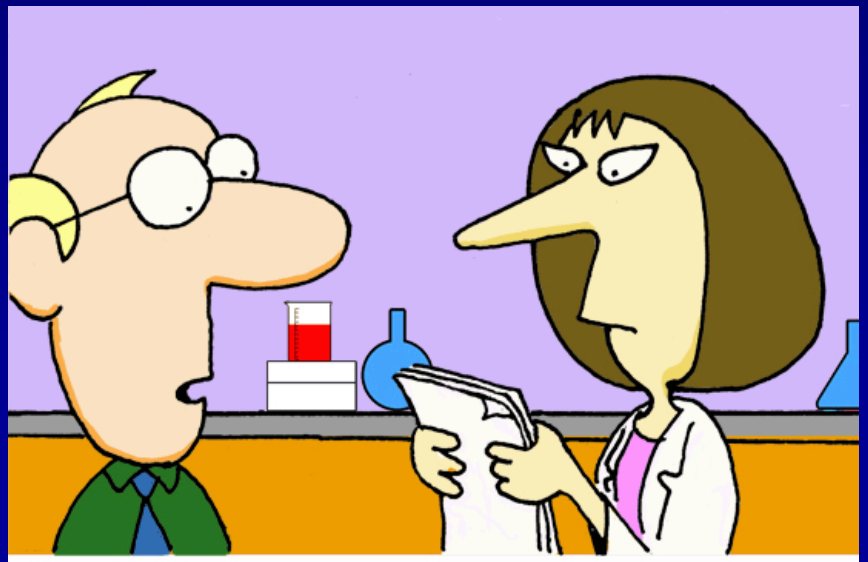
“successful repair”

O’Sullivan JJ, et al. Heart 2002;88:163–6.

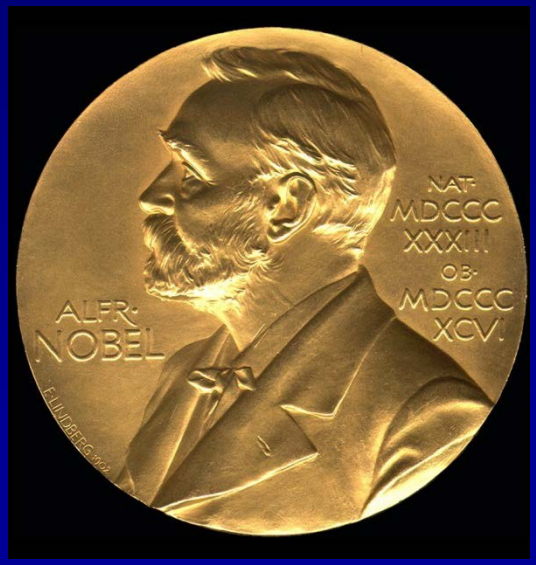
Although there are theories, the pathophysiology of hypertension following coarctation repair is unclear

This gap provides opportunity for investigation,
funding, publication, promotion, fame, and glory….





"With this much grant money, only experiment we can do is 'flip a coin'.



In reality, if physiologically significant spinal cord injury is demonstrated following ACC, then there will be an opportunity for pediatric cardiac anesthesiologists to pioneer protective measures

Anesthesia-induced neurotoxicity

Animal Studies

Mechanisms

Confirmation studies in children

Therapy and prevention

Paradigm Change

ACC-induced SCI

Animal Studies

Mechanisms

Confirmation studies in children

Therapy and prevention

Paradigm Change


" If opportunity doesn't knock, build a door."
Milton Berle