Surgical Repair of Coarctation of the Aorta and the Spinal Cord

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

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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 temperature, respectively, with aortic occlusion for 10 minutes at 37°C producing paresis, and 15 minutes at 37°C producing permanent paralysis.

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% FiO2 ACC for varying durations (3-11 min) at varying body temp (33-36°C)
Hemodynamics and ABG
Locomotor behavior
Histology
Table 1. Summary of Surgical Parameters and Group Sizes

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

LSA = left subclavian artery; MAP = mean arterial pressure.
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.
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
33°C

< 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

A.

- **mild impairment**
  - 1. cervical
  - 2. sacral

- **severe impairment**
  - 3.
  - 4.
  - 5.
  - 6.

Legend:
- grey = white matter
- green = spared gray matter
- red = frank lesion / necrotic tissue

B1.

- Volume (mm$^3$) ± SEM
- < 7.5 min
- 7.5 min mild
- 7.5 min severe

B2.

- area (mm$^2$) ± SEM
- Distance (μm, rostral to caudal)

- < 7.5 min
- 7.5 min mild
- 7.5 min severe
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, 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
Dorsal somatic branch (prelaminar branch) with dural branches

Anterior spinal artery

Anterior central artery

Nutrient vessels

Aorta

Intercostal artery (segmental artery)

Posterior branch

Radiculomedullary artery

Anterior branch

Muscular branch

Ganglionic branch

Posterior spinal arteries

Posterior trunk (post-central branch)

Anterior radiculomedullary artery

Posterior radiculomedullary artery

Posterior plexiform network
Jonas RA. Comprehensive Surgical Management of Congenital Heart Disease. 2004. 1st Ed.
Adult with Congenital Coarctation
10 month old Infant with Congenital Coarctation

Near infrared spectroscopy monitoring during pediatric aortic coarctation repair

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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 (rSO2) 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 rSO2 during aortic coarctation repair for three pediatric age groups (neonates, infants <1 year, and children >1 year). Two site [cerebral (rSO2-C) and somatic thoracodorsal (rSO2-


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

sd, standard deviation.
Distal Somatic NIRS during ACC
SSEP Lowest Amplitude

![Box plot showing SSEP Lowest Amplitude across Pre-ACC, During ACC, and Post-ACC phases.](image)

- **Pre-ACC**
- **During ACC**
- **Post-ACC**

**Statistical Significance:**
- † $P < .05$
- * $P < .01$
Cell death occurs 15-45 min after loss of SSEPs

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>Clonus bilateral LE</td>
</tr>
<tr>
<td>2</td>
<td>Normal</td>
<td>Clonus bilateral LE</td>
</tr>
<tr>
<td>3</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
<td>Esotropia</td>
</tr>
<tr>
<td>5</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
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 Ila**

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

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

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\textsuperscript{f}The Congenital Heart Institute of Florida, All Children’s Hospital, University of South Florida College of Medicine, Saint Petersburg and Tampa, Fla
Reviewed STS Database for Coarctation Repair 2006-2010

<table>
<thead>
<tr>
<th>Repair technique</th>
<th>Frequency, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-to-end anastomosis</td>
<td>820/2474 (33.1)</td>
</tr>
<tr>
<td>Extended end-to-end anastomosis</td>
<td>1385/2474 (56.0)</td>
</tr>
<tr>
<td>Subclavian flap repair</td>
<td>85/2474 (3.4)</td>
</tr>
<tr>
<td>Patch aortoplasty</td>
<td>104/2474 (4.2)</td>
</tr>
<tr>
<td>Interposition graft</td>
<td>70/2474 (2.8)</td>
</tr>
<tr>
<td>Other</td>
<td>10/2474 (0.4)</td>
</tr>
<tr>
<td>Variable</td>
<td>Overall</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>n</td>
<td>5025</td>
</tr>
<tr>
<td>In-hospital mortality, n/N (%)</td>
<td>119/5025 (2.4)</td>
</tr>
<tr>
<td>LOS, d; mean ± SD (median)</td>
<td>14 ± 22 (7)</td>
</tr>
<tr>
<td>Any complication, n/N (%)</td>
<td>1816/5025 (36)</td>
</tr>
<tr>
<td>Acidosis, n/N (%)</td>
<td>81/4052 (2)</td>
</tr>
<tr>
<td>Cardiac arrest, n/N (%)</td>
<td>62/5025 (1.2)</td>
</tr>
<tr>
<td>Chylothorax, n/N (%)</td>
<td>165/5025 (3.3)</td>
</tr>
<tr>
<td>PERD, n/N (%)</td>
<td>98/5025 (2)</td>
</tr>
<tr>
<td>RLN injury, n/N (%)</td>
<td>176/5025 (3.5)</td>
</tr>
<tr>
<td>Phrenic nerve/paralyzed diaphragm</td>
<td>47/5025 (0.9)</td>
</tr>
<tr>
<td>Unplanned cardiac reoperation, n/N (%)</td>
<td>33/973 (3.4)</td>
</tr>
<tr>
<td>Unplanned readmission within 30 d, n/N (%)</td>
<td>36/973 (3.7)</td>
</tr>
<tr>
<td>Spinal cord injury, n/N (%)†</td>
<td>0/973 (0)</td>
</tr>
<tr>
<td>Mechanical ventilator support, n/N (%)</td>
<td>253/5025 (5)</td>
</tr>
</tbody>
</table>

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
Pro Football

Seau Suffered From Brain Disease

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.
Anesthesia-induced Neurotoxicity

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?
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”

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