Amniotic Fluid Embolism

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AFE: Attack of the KILLER Platelets
Murder-Suicide
AFE

- Rare; 1:8,000 births, 500 cases/yr
- 2nd direct cause maternal death
  - 10% direct maternal deaths
- Old: mortality rate 40-80%
- New: mortality rate 20-30%
• Only humans get AFE
• Amount of embolized material is usually small
• Thus, chemical mediators must cause AFE lethality
Traditional Definition of AFE

- Three groups of symptoms
  - Hypotension or cardiac arrest
  - Dyspnea, cyanosis, respir arrest
  - Consumptive coagulopathy
- Occurs peripartum
Other Sx of AFE

- Fetal distress, uterine atony
- Decorticate posturing, restlessness, confusion
Timing of AFE

- During labor – 70%
- After C/S – 19%
- After vaginal delivery – 11% – 8 +/- 8 min after delivery
- Ruptured membranes – 78%
Risk Factors for AFE

• Placenta previa – OR 30
• Preeclampsia – OR 7
• C/S or forceps – OR 5
• Any trauma or instrumentation of uterus or cervix
• Labor induction
Initial Cardiac Rhythm

- PEA – 24%
- Bradycardia – 22%
- Asystole – 13%
- Ventricular tach/fib – 17%
- Undescribed/normal – 24%
After the CPR…

- Consumptive coagulopathy
  - Very low fibrinogen
  - Very low platelet count
  - Very high fibrin split products
  - Prolonged PT, aPTT
Outcome

• Maternal
  – 39% survival
  – 15% neuro-intact survival

• Fetuses *in utero* at time of AFE
  – 79% survival
  – 50% neuro-intact survival
Autopsy Findings

- Amniotic fluid, fetal nRBC’s and squames, trophoblastic material
- All also seen in healthy pts
- Autopsy may be negative
How does this material get into the maternal circulation?
Myometrial biopsy during C/S
68 healthy patients
Formalin, H&E stain
Most specimens had some blood vessels filled with fetal squames, hair, fibrin, platelet thrombi
If amniotic fluid ends up in the veins of most parturients, why do 7,999 of 8,000 parturients NOT have AFE symptoms?
Case Reports
AFE Patient #1

- 41 yo G8P3 39 wks, labor induction, 10 cm
- Dyspnea, SpO2 80%, cardiac arrest
- Forceps delivery, 31 min ACLS
- Atropine 1mg, Ondansetron 8mg, Ketorolac 30mg (A-OK)
- Pulse and stable vital signs (with pressor support) within 2 min
- Echo: RV dilation. DIC 1 hr later.
- Survived with minor neuro deficits
Patient 1

Traditional CPR: 0-31 minutes

A-OK

Persistent Pulse & Perfusion after A-OK

MINUTES

Pulse

140
120
100
80
60
40
20
0

0 3 6 9 12 15 18 21 24 27 30 33
AFE Patient #2

- 28 yo G2P1 39 wks, elective c/s, uterine incision
- Tachypnea, restlessness, gasp, decerebrate posturing, apnea, pulseless electrical activity
- Intubated, chest compression, epinephrine 1mg, vasopressin 40 units with brief weak pulse, no BP
  - Atropine 0.8mg, Ondansetron 4mg, Ketorolac 30mg (A-OK) at minute 5
- Strong pulse and BP 105/80 within 1 min
- No further cardiac meds needed
- Echo: RV dilation. DIC 1 hr later.
- Survived neurologically intact
Why were these resuscitations successful?
Pathophysiology of pulmonary embolism
(clot, marrow, fat, beads)
in any mammal
(rat, rabbit, dog)
Initial Pathophys of PE

- Just-barely-lethal amount of material embolized into pulm arteries (blood clot, marrow, fat, microspheres)
- Platelets degranulate
- Thromboxane, serotonin cause intense pulm vasoconstriction, stimulate vagal reflex
- Peripheral vasodilation, bradycardia are the final lethal events
Platelets
• Rabbit, marrow, prePE
• Control, platelet depletion, vagotomy, 5-HT3 blocker, vagal stimulation
• Platelet depletion prevented CV changes, death
Thromboxane
Dog, blood clot, prePE
Placebo, imidazole, indomethacin, PgI2
Dead space, shunt, CI improved with any of the treatments
Dead space correlated with TxB2 (r=0.79)
Figure 7. A significant relation exists between TxB₂ and V_D/V_T (P < 0.001). Data from control and PGI₂ groups are plotted before the PGI₂ infusion was started.
Term pregnant amniotic fluid increases platelet thromboxane production.

• Platelets + Thrombin + Arachadonic acid = Thromboxane

• Adding 15-17 wk amniotic fluid did not increase thromboxane production

• Adding term pregnant amniotic fluid doubled thromboxane production
Serootonin
Figure 1. A schematic summarizing the actions of peripheral 5-HT receptors on the cardiovascular system. The reported ability of 5-HT₁B-receptor activation to cause release of NO has been omitted because it is not clear how a decrease in cAMP causes NO. (−) represents inhibition.
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Agonists</th>
<th>Antagonists</th>
<th>Localization</th>
<th>Cardiovascular effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT}_{1B/1D}</td>
<td>Sumatriptan</td>
<td>GR127935</td>
<td>Sympathetic ganglia and postganglionic sympathetic nerve terminals</td>
<td>Reduce sympathetic drive (i.e. reduction in noradrenaline release to the heart and vasculature)</td>
</tr>
<tr>
<td>5-HT}_{1B}</td>
<td>CP-93–129 (in rats)</td>
<td>GR 55562</td>
<td>Vascular smooth muscle</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>5-HT}_{1D}</td>
<td>PNU-109291</td>
<td>BRL15572</td>
<td>Yet to be distinguish from 5-HT}_{1B/1D} sites</td>
<td></td>
</tr>
<tr>
<td>5-HT}_{2A}</td>
<td>DOI</td>
<td>MDL 100907</td>
<td>Vascular smooth muscle</td>
<td>Vasoconstriction, platelet aggregation and direct tachycardia in rats Adrenaline release from the adrenal medulla?</td>
</tr>
<tr>
<td>5-HT}_{2B}</td>
<td>BW723C86</td>
<td>RS 127445</td>
<td>Vascular endothelium</td>
<td>Release of NO, thus, vasodilation</td>
</tr>
<tr>
<td>5-HT}_{3}</td>
<td>PBG</td>
<td>Granisetron</td>
<td>Vagal afferent terminals in the lungs and heart</td>
<td>Reflex bradycardia and hypotension Rabbit heart where it causes the release of noradrenaline from sympathetic terminals</td>
</tr>
<tr>
<td>5-HT}_{4}</td>
<td>BMIU4</td>
<td>GR113808</td>
<td>Human, pig atrium, rats with CHF</td>
<td>Tachycardia (positive chronotropism) and increase in atrial force (positive iontropy) Dilation</td>
</tr>
<tr>
<td>5-HT}_{5A/5B}</td>
<td>None</td>
<td>None. SB-269970 does have good affinity, but is also a 5-HT}_{7} antagonist</td>
<td>Postganglionic sympathetic nerve terminals?</td>
<td>Reduce sympathetic drive (i.e. reduction in noradrenaline release, to the heart and vasculature?)</td>
</tr>
<tr>
<td>5-HT}_{7}</td>
<td>None. 5-CT is often used, but it shows poor selectivity Newer agonists are AS19 and LP44, but their selectivity is not clear</td>
<td>SB-269970 (also has affinity for 5-HT}_{5A/5B})</td>
<td>Vascular smooth muscle</td>
<td>Vasodilation Tachycardia in cats</td>
</tr>
</tbody>
</table>

*?* denotes that there is uncertainty with this information.
About half of the vagal afferent terminals in the lung and the heart are serotonergic, not cholinergic.
• Rabbit, microspheres, prePE
• Control, vagotomy, 5-HT3 blocker, indomethacin
• All Tx prevented tachypnea
• Indomethacin best protection against cardiovascular changes
Fig. 1. Graphical representation of the percentage change in respiratory rate produced by embolization (Sephadex G-25 beads, 1 mg min⁻¹, i.v.) in control (○), vagotomized (●), MDL 72222 (640 μg kg⁻¹, i.v.)-pre-treated (△) and indomethacin (5 mg kg⁻¹, i.v.)-pre-treated rabbits (▲). The figure shows the mean ± 1 standard error of five observations (four in the case of vagotomy).
Serotonin-Induced Vagal Stimulation
• Rabbit, marrow, prePE
• Control, platelet depletion, vagotomy, 5-HT3 blocker, vagal stimulation
• Platelet depletion prevented CV changes, death
• Vagotomy prevented SBP decrease, death, no effect on PAP
• 5-HT3 antagonist = vagotomy
• Vagal stimulation caused severe SBP decrease and death
Treatment with an NSAID plus a serotonin blocker
• Rabbit, blood clot, prePE
• Control, methysergide, aspirin, both
• BP decrease: 40% control, 30% methysergide, 18% aspirin, 8% both
• Mortality: 55% control, 9% methysergide, 0% aspirin and both
Animal Pulmonary Embolism Events

- Embolism
- Platelet activation and degranulation
- Pulmonary hypertension due to serotonin and thromboxane
- Systemic hypotension and bradycardia due to reflex vagal stimulation
- Death
Cardiopulmonary Effects of AFE
Figure 3–3 TEE four-chamber view. Drawing (left) and echocardiographic image (right) in a TEE four-chamber view is obtained from a high TEE position with the multiplane probe at 0° rotation. In this view the apparent apex may actually represent a segment of the anterior wall because of foreshortening of the long axis of the ventricle.

Short Axis View

Diastole

Systole

Diastole

Diastole-Pressure Overload
10 min into AFE
After 1 hr CPB
Fatal case

MEASUREMENTS NOT POSSIBLE.
Fatal case
TEE findings in AFE

• Right ventricle
  – Massively dilated
  – Akinetic

• Left ventricle
  – Very small
  – Normal contractility
Successful Treatments

• Inhaled prostacyclin
• Inhaled NO
• RV assist device
• ECMO
• Cardiopulmonary bypass
AFE
Coagulopathy
24 samples of human AF added to human platelets
Irreversible platelet aggregation
Cause: free Type 1 collagen in AF
• 31 elective C/S pts
• TEG with venous blood and autologous amniotic fluid
• R time significantly decreased
• TEG-ReoPro: increased platelet activation, no fibrinolysis
• Surfactant acts like thromboplastin
• Cells in amniotic fluid (AF) externalize tissue factor
• Cells in AF directly activate factor X and prothrombin
• AF also has anticoagulants
AFE patients have high blood levels of tissue factor.
Don’t use rVIIa!

- rVIIa works by binding to tissue factor and immediately forming a clot
- Tissue factor is supposed to be in bleeding tissues, not in blood stream
- AFE pts have high blood levels of tissue factor
- Major organ, bld vessel clots possible
• rVIIa used in 16 AFE pts 2003-9
  – Full recovery in 12%, 50% died
• 28 AFE pts 2003-9 needing surgery to control bleeding
  – Full recovery in 61%, 25% died
• P<0.05 for full recovery
Most of the rVIIa patients had death or severe residual disability from thrombosis.

Most of the control patients lived with minimal disability. Deaths were due to unstoppable hemorrhage.
Conditions that look like AFE
Collagen Matrix Embolism

- 18 yo woman, 13-level spinal fusion
- 2 gm collagen powder, 10,000 IU bovine thrombin in 20 mL saline injected into a pedicle hole
- Cardiac arrest, coagulopathy
- Difficult CPR, neuro-intact survival
Figure 3. Postoperative chest computed tomography.
<table>
<thead>
<tr>
<th>Laboratory value</th>
<th>pH</th>
<th>Paco₂ (mm Hg)</th>
<th>Pao₂ (mm Hg)</th>
<th>HCO₂ (mEq/L)</th>
<th>Base excess</th>
<th>Hematocrit (%)</th>
<th>Platelets (1000/μL)</th>
<th>INR</th>
<th>PTT (s)</th>
<th>Fibrinogen (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39</td>
<td>332</td>
<td>1.0</td>
<td>30.7</td>
<td></td>
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<tr>
<td>Intraoperative preevent</td>
<td>7.44</td>
<td>42</td>
<td>404</td>
<td>22</td>
<td>0</td>
<td>25</td>
<td>204</td>
<td>1.3</td>
<td>41.6</td>
<td>202</td>
</tr>
<tr>
<td>Intraoperative postevent</td>
<td>7.02</td>
<td>56</td>
<td>328</td>
<td>15</td>
<td>−16</td>
<td>28</td>
<td>11</td>
<td>3.2</td>
<td>&gt;100</td>
<td>51</td>
</tr>
</tbody>
</table>

INR = international normalized ratio; PTT = partial thromboplastin time.
Ketorolac 30mg
Ondansetron 8 mg
Ketorolac 30 mg
Decompression Sickness (DCS) (‘The Bends’)

(The Bends)
Platelets and neutrophils aggregate and activate on IV bubbles, decreasing the platelet count and forming particles that cause tissue injury and neurologic deficits.
Fall in blood platelet count in rats with lethal, neurologic, and no DCS after decompression


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Percent Decrease in Platelet Count After Decompression in a Rat Model


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Mortality after DCS:
- Control: 71%
- Heparin: 70%
- ASA: 50%
- Clopidogrel: 5%
Human Endotoxemia

- Almost-normal 18-30 yo humans volunteer to have an arterial line, IV’s, etc. and then receive 2 ng endotoxin IV.
- Tachycardia, mild biventricular failure, fever, chills, rigors for the next 6 hours.
- Researchers and ICU nurses watch.
- All studies funded by NIH.
Table 1

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th></th>
<th>Patient 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Time interval (min)*</td>
<td>Pre-AFE:</td>
<td>20</td>
<td>Pre-AFE:</td>
<td>142</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.2</td>
<td>8.7</td>
<td>8.1</td>
<td>3.7</td>
</tr>
<tr>
<td>Platelets (/cumm)</td>
<td>293,000</td>
<td>100,000</td>
<td>471,000</td>
<td>165,000</td>
</tr>
<tr>
<td>Leukocytes (/cumm)</td>
<td>7,700</td>
<td>9,700#</td>
<td>5,600</td>
<td>6,900</td>
</tr>
<tr>
<td>Monocytes (/cumm)</td>
<td>900</td>
<td>200#</td>
<td>900</td>
<td>400</td>
</tr>
<tr>
<td>Lymphocytes (/cumm)</td>
<td>1,200</td>
<td>1,600#</td>
<td>1,900</td>
<td>400</td>
</tr>
<tr>
<td>Prothrombin time (s)</td>
<td>-</td>
<td>24.6</td>
<td>-</td>
<td>23.2</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>-</td>
<td>2.28</td>
<td>-</td>
<td>2.1</td>
</tr>
<tr>
<td>Partial thromboplastin time (s)</td>
<td>-</td>
<td>55.5</td>
<td>-</td>
<td>54.1</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>-</td>
<td>&lt;100</td>
<td>-</td>
<td>119</td>
</tr>
<tr>
<td>D-dimer (mg/L)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&gt;4</td>
</tr>
</tbody>
</table>

AFE=amniotic fluid embolism, cumm=cubic millimeter. *Time interval is the time from the first amniotic fluid embolism symptom until the first post-event blood was sent for analysis. No blood products were administered before the first post-event blood was drawn. #These three laboratory values were drawn 130 minutes after the first amniotic fluid embolism symptom.
Could AFE be diagnosed based on the pattern of WBC changes?
Unanswered Questions about AFE
1. What causes AFE?
Good question.

A better question:

Are AFE symptoms severe because of the embolized material or because of the physiology of pregnancy?
Reversible Cerebral Vasoconstrictive Syndrome

- Anyone could get this disease, but
- 81% of all patients are women
- 9% of patients are pregnant women
- Do high estrogen levels make profound vasoconstrictive syndromes worse?
2. Can the coagulopathy be treated without making the hemorrhage worse?
A-OK does not prevent AFE coagulopathy. Eptifibatide (Integrilin) might stop the platelet activation but seems like a bad idea.
3. If platelet activation is the problem, do platelet transfusions make AFE patients better or worse?
Do platelet transfusions just throw fuel on the fire?
4. Is there a way to improve AFE neurologic outcomes?
Outcome

- Maternal
  - 39% survival
  - 15% neuro-intact survival

- Fetuses *in utero* at time of AFE
  - 79% survival
  - 50% neuro-intact survival
So far, 5 AFE patients, 2 collagen matrix embolus patients, and 2 methyl methacrylate embolus patients have been treated with A-OK. All had good neurologic outcomes.
5. Does ondansetron alone provide sufficient vagolysis, or is atropine helpful?
Forget the Fatalism!
A-OK Protocol

- Atropine 1 mg for vagolysis (needed?)
- Ondansetron 8 mg to block serotonin receptors and for vagolysis
- Ketorolac 30 mg to block thromboxane production
- Off-label recommendations
How I Treat AFE

- Organize the CPR if needed
- A-OK: atropine 1mg, ondansetron 8mg IV, ketorolac 30mg
- Deliver the fetus stat. Don’t wait until the code is over!
- Decide if CPB useful; call early
Treat the R heart failure!

- TEE or TTE if available
- Vasopressin, dobutamine, milrinone
- Diuretics
- Inhaled PGI2 or NO
- CPB or RVAD if needed
Treat the coagulopathy!

- Aggressive blood product support, including cryoprecipitate
- Avoid rVIIa
Why is AFE so lethal?

• Standard CPR is not tailored for acute right heart failure due to pulmonary vasoconstriction
• Knowledge about chemical mediators of PE hasn’t changed therapy……..yet
A-OK Protocol: Proposed Mechanism

- **KETOROLAC**
- **THROMBOXANE**
- **PULMONARY VASO-CONSTRICCION**
- **SEROTONIN**
- **VAGAL REFLEX**
- **ATROPINE**
- **ONDANSETRON**
- **BRADYCARDIA AND PERIPHERAL VASODILATION**

Amniotic fluid triggers platelet aggregation in pulmonary vasculature.