Cardiac Update
2016-2017

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Learning Objectives
• Pharmacology for cardiac procedures
• TAVR: What's the latest?
• New procedures you may be doing
• Atrial Fibrillation- Is it rate or rhythm?
• Blood transfusion- What's the limit? What can we add?
• Grab Bag of info

Pharmacology
• Cardiac Anesthesia
  – Definition of polypharmacy
  – Neurocognitive outcomes
  – Aging population
  – Fast track patients
• Do we make a difference?
  – CPB times
  – Embolic CVA
  – Transfusions

Dexmedetomidine Use
• Several prior studies showing improved outcomes in cardiac surgery
  – Mortality: In house, 30d, 1 yr
  – Neurologic : Delirium
  – Renal outcomes
• Recent publications in non-cardiac surgery
  – Reduced delirium post op in elderly patients
  – Safety in sedation of elderly with cognitive impairments

Dexmedetomidine versus Propofol Sedation Reduces Delirium after Cardiac Surgery
A Randomized Controlled Trial

Anesthesiology 2016; 124:362-8`
• Prospective, randomized, controlled trial of Dex vs Propofol
• Addressed heterogeneity of data on delirium
• Delirium as primary outcome
• 185 patients randomized
**Study Methods**

- Patients > 60 yo with elective complex surgery
- Patients >70 yo with CABG or single valve surgery
- Standardized anesthetic
  - Midazolam limited to 0.05 mg/kg max
- Sedation initiated on ICU arrival
  - Dex bolus + infusion – not DC’ed on extubation
- Ventilation > 24 hrs: Dex converted to propofol
- Multimodal analgesia

**Results**

<table>
<thead>
<tr>
<th>Study aftermaths</th>
<th>Dexmedetomidine Group</th>
<th>Propofol Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>74 (70-79)</td>
<td>74.5 (70-79)</td>
<td>0.92</td>
</tr>
<tr>
<td>Mean duration of ICU stay (d)</td>
<td>2 (1-5)</td>
<td>2 (1-5)</td>
<td>0.61</td>
</tr>
<tr>
<td>Mean APACHE II score (n)</td>
<td>2 (1-5)</td>
<td>3 (1-7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean SOFA score (n)</td>
<td>2 (1-5)</td>
<td>3 (1-7)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Summary**

- Post Op Delirium (POD)
  - Dex 17.5% vs Prop 31.5%
- Duration of delirium (median days)
  - Dex 2d vs Prop 3d
- Hospital LOS (median days)
  - Dex 7.5 vs Prop 10
- Delirium related hours
  - 450 vs 1200 (ICU) and 532 vs 888 (floor) for Dex vs Prop

**Methodology**

- Univariate and multivariate regression analysis
  - Demographic, therapeutic, and clinical outcome variables
- Propensity score
  - Likelihood of a patient receiving Dex
- Dex group: More CRF, CHF, lipid lowering agents
  - Less urgent surgery, CVD and lower BMI
  - Shorter CPB, X-clamp times, less IABP use

**Take Away Message**

- Data consistent with prior studies
  - Same dataset as previously published work
- Improved in hospital and 30d mortality benefit
  - 1 year mortality benefit did not persist in elderly
- Decreased stroke risk
- Decreased delirium
  - Very low rates of delirium reported in this study
• Randomized controlled trial, 2 hospitals
• Isolated CABG in native chest
• TIVA vs volatile anesthetic maintenance
• 900 patients randomized 2012-2014

Details

• Volatile group
  – Allowed for propofol during induction (38% without propofol)
  – Fentanyl, sevoflurane, cisatricurium intermittent bolus
• TIVA group
  – Propofol gtt, fentanyl intermittent, and cisatricurium
• No benzodiazepines or etomidate use reported in either

Conclusions

• Largest randomized trial of volatile vs TIV anesthetic
• Decreased post-op TroponinT
• Decreased proBNP
• Decreased hospital LOS
• Increased biomarkers and LOS if propofol was used during induction in
  – Trend towards mortality benefit at all points

Simple Answer

• There was no difference!
• Primary Outcome: Prolonged ICU stay or 30d mortality
  – Trend towards Sevo better for prolonged ICU stay
• Clinically irrelevant cTnT and Cr elevation with Sevo
• Cost Analysis:
  – Sevo: $41 (Canadian $)
  – Iso: $5
Etomidate

- The story continues….
- Known adrenocortical insufficiency with single doses
  - Clinically relevant?
- Periop concerns for hemodynamic instability and infection
- Potential modulation of inflammation
  - Increased IL-6 and without commensatory anti-inflammatory
- Authors question relationship for atrial fibrillation
  - A Fib admittedly multifactorial

Conclusions

- Atrial fibrillation rates no different
- ICU and hospital LOS also the same
- Secondary outcomes
  - Increased RBC use with etomidate
  - Trend towards increased FFP and platelets
- Limitations
  - Observational trial
  - Selection bias

TAVR – Long term followup

- TAVR implantation > 5 yrs ago (5-14 yrs) in 2002-2011
- 2 centers
- Cribier Edwards, Edwards SAPIEN, SAPIEN XT valves
- 704 TAVI cases, 378 with long term followup
- Degeneration
  - Mean gradient ≥ 20mmHg without endocarditis
  - Moderate AI
TAVR followup

- Valve types
  - C-E: 14.3%, Edwards Sapien 49.7%, Sapien XT 36%
- Access Route
  - Transfemoral 68.5%, Transapical 28.7%
- Median Survival Time: 51 months (4 yrs, 3 mo)
- Approximately 50% degeneration at 8 years
  - CRF strongest correlation with degeneration
  - About 2/3 AI and 1/3 AS

Long Term TAVR follow up

Original Article
Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients
Martin B. Leon, M.D., Craig R. Smith, et al. for the PARTNER 2 Investigators

In a randomized trial involving more than 2000 patients, transcatheter aortic-valve replacement was noninferior to surgical replacement in the primary end point of death from any cause or disabling stroke at 2 years.

Take Away Points

- TAVR non-inferior to surgery in intermediate risk patients
- Valve gradients were lower in TAVR than SAVR
- Paravalvular leaks greater with TAVR than SAVR
  - Moderate-Severe PVL with Hazard Ratio 2.85
- TAVR had lower bleeding risks, atrial fibrillation, AKI
- Length of Stay
  - ICU 2 vs 4 days – favoring TAVR
  - Hospital 6 vs 9 days – favoring TAVR
Have you ever seen a passive CT surgeon?  They will not go away quietly

Sutureless Valve Technology

- Percutaneous biologic prostheses that require less than 3 sutures
- Still require Aortic x-clamp and CPB
- Diseased valve removed and prosthesis implants under direct vision
- CPB and x-clamp times reported are approximately half of STS averages
- Reduced PVL vs TAVR

SUAVR Data

- SUAVR vs Conventional AVR (C-AVR)
  - Outcomes differences yet to be reported
  - Consistently significant CPB and X-clamp times across studies
  - Shorter LOS and potential cost benefit
- 1 randomized trial of SUAVR vs C-AVR
  - Shorter x-clamp times, similar CPB
  - No differences in early outcomes
  - Improved mean gradient in SUAVR

TAVI vs SUAVR

- Meta-analysis of TAVI vs SUAVR
- Primary outcomes paravalvular leak, short, and intermediate mortality
- 6 studies met inclusion criteria
- Compared TAVI to SUAVR via propensity score matching

Mortality

Hospital LOS

Pacemaker

Mild PVL

Moderate-Severe

Any PVL
TAVR Anesthetic Implications and safety

- General anesthesia initially preferred choice
  - Airway management
  - Immobility during deployment
  - TEE guidance
  - Duration of initial procedures
  - Learning curve for the room

- Safety, cost containment, neurological outcomes
  - MAC as an alternative

Secondary analysis from observational and prospective OBSERVANT trial
- Multicenter trial in Italy 2010-2012
- 1494 patients undergoing transfemoral TAVR
- Propensity score matching 310 pairs of MAC vs GA

Methods
- Sapien XT (Edwards Life-Science, Irvine, CA)
- CoreValve (Medtronic, Minneapolis, MN)
- Primary Endpoint: All cause mortality
- Secondary Endpoint: Adverse events
- Propensity score matching
- MAC 1137 (76.1%) vs GA 357 (23.9%)

Results
- No primary end point differences
- Severe paravalvular leak in 2 MAC patients, 0 in GA
- 3 year survival the same
- No methodology for MAC
- No commentary on intra-procedure adverse events

Anesthetic plan
- TAVI-GA
  - Oral midazolam
  - Propofol 3mg/kg/hr (50 mcg/kg/min)
  - Remifentanil 0.2 mcg/kg/min

- TAVI-S
  - Oral midazolam
  - Propofol 1 mg/kg/hr (16.7 mcg/kg/min)
  - Remifentanil 0.03 mcg/kg/min

Comparison of sedation and general anaesthesia for transcatheter aortic valve implantation on cerebral oxygen saturation and neurocognitive outcome

<table>
<thead>
<tr>
<th>Method</th>
<th>sedation</th>
<th>General anaesthesia</th>
<th>n</th>
<th>Cerebral oxygen saturation</th>
<th>Neurocognitive outcomes</th>
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<tr>
<td>Transcatheter</td>
<td>68%</td>
<td>64%</td>
<td>62</td>
<td>76%</td>
<td>78%</td>
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<tr>
<td>Sapien XT</td>
<td>68%</td>
<td>64%</td>
<td>62</td>
<td>76%</td>
<td>78%</td>
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<tr>
<td>CoreValve</td>
<td>68%</td>
<td>64%</td>
<td>62</td>
<td>76%</td>
<td>78%</td>
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</table>

INSERT Trial – single center, balanced randomization
- Transfemoral Medtronic CoreValve™ in 68 patients
- Evaluated cerebral desaturations in sedation vs GA - NIRS
- Secondary look at neurocognitive outcomes
Results

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<th>Variable</th>
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<td>PaCO2</td>
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<td>SBP</td>
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<td>MAP</td>
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<tr>
<td>HR</td>
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</table>

Discussion

- No statistical difference in cerebral desaturation
- No differences in neurocognitive testing
- High rate of adverse events
  - Primarily respiratory ~ 20% required BMV
  - Hypercarbia/respiratory acidosis – during procedure
  - Hypoxia
- No obvious safety concerns related to anesthetic choice

Blood Gas Analysis

Anesthetic Plan

- **MAC**
  - Dexmedetomidine load: 1mcg/kg over 10-15 min
  - Infusion 0.2-0.7 mcg/kg/hr
  - Fentanyl 25 mcg bolus PRN
  - 1% lidocaine at catheter site

- **GA**
  - Etomidate 0.2-0.6 mg/kg
  - NMB
  - Sevoflurane

Retrospective, case controlled study- single health system
- 65 patients undergoing TAVR with Medtronic CoreValve™
- GA (n=21) or MAC (n=44) was utilized
- Hospital LOS, morbidity and mortality data reviewed
Conclusions

• No significant outcomes differences
• Underpowered to detect significant differences
• During learning curve phase of institution
• Comorbid CAD more likely to get GA
  – Also more likely to get transfusions
• No risks or benefits between anesthetic choice

New Devices coming to you

• Atrial Fibrillation Occlusion devices
• Only 30-50% of Atrial fibrillation patients treated with AC
  – 5 fold increased risk of CVA with Afib
  – AC reduces risk only 60% with 1-3% increased bleeding
  – Left Atrial Appendage – site of thrombus in 90% in AF
• Left Atrial Appendage Occlusion Devices
  – Catheter based delivery system with self expanding occluder
  – Trans-septal Puncture required

WATCHMAN Device

• Boston Scientific, Marlborough, MA
• Only device with FDA approval in the US
• Central Nickel-titanium with 10 fixation anchors
• European Society of Cardiology Guidelines
  – 2012 - Class IIb (LOE B) recommendation for patients at high risk of stroke but contraindication to AC
• Indications for AC currently based on CHA2DS2-VASc

Contraindications

• Presence of ASD or PFO closure device
• Inability to tolerate warfarin, ASA, or clopidogrel
  – ASA/warfarin used for 45 days post procedure
  – 45 d – 6 mo: ASA/clopidogrel
  – 6 mo+ ASA Monotherapy
  – Endocarditis prophylaxis initial 6 mos

Outcomes Data

• PROTECT AF
  – Efficacy endpoint of stroke, CV death, embolic event
    • 2.3/100 vs 3.8/100 events compared to warfarin
• PREVAIL
  – Endpoint of ischemic stroke prevention
    • Non-inferior to warfarin therapy

Homes DR Jr. J Am Coll Cardiol 64:1-12, 2014

http://www.watchman.com/how-watchman-device-works.html
**TEE guided procedure**

- Identify contraindications to procedure
- Aid fluoro guided direction of device
- Identify size, morphology, # of lobes relative to ostium
- Rapid recognition of procedural complications
  - Pericardial effusions

**TEE Assessment**

- LAA measured ostium, depth
  - ME 4C: 0-20°, 45-60°, ME 2C: 90°, ME LAX: 120-135°
  - 0° and 135° may show largest ostial diameter

**Atrial Fibrillation**

- 20-50% incidence post cardiac surgery
- Increased rates of
  - Death
  - Complications
  - Cost of hospitalization
- Non-surgical Patients: AFFIRM trial*
  - No advantage to rhythm control vs rate control

*NEJM 2002;347:1825-33.

**Methodology**

- Rate Control Group (n=255)
  - Medications to control HR <100
  - Could be converted if provider thought necessary for hemodynamics or symptoms
- Rhythm Control (n=250)
  - Amiodarone +/- rate controls agents for 24-48 hrs
  - DCCV recommended at that time for failure to convert
  - Amiodarone continued for 60 days unless side effects
- Pts DC’ed home in rate control or after amio load

- Cardiothoracic Surgical Trials Network (CTSN), 23 sites
- CABG, Valve repair, bioprosthetic valve replacement
- 2109 patients enrolled
- 695 (33%) developed atrial fibrillation
Outcomes

- Primary
  - Total hospital days within 60 days of randomization
- Secondary
  - Days to DC from randomization
  - Need for readmission
  - Need for PPM
  - Other adverse events

Atrial Fibrillation Results

Discussion

- 10x size of previous trials
- ~25% non-adherence to trial outline
  - Multiple crossovers reflecting clinical practice
- No primary end point differences – hospital days
  - Readmission rate still 28% - 1/5 for Atrial Fib issues
- Rhythm control achieved more SR faster
- Overall in total study participants
  - 85% in SR by discharge
  - 95% by 6 mo

Take Home Points

- No measurable differences
- Rate control avoids toxic side effects of amio
  - At a cost of slower onset to rhythm control
  - More Anti-coagulation
- Most deviations from rhythm control group were amio toxicity side effects
- Continue to practice clinical bedside medicine

Results

- Circulatory d/o, trauma, neoplasm, GI bleed
  - 67% of all patients
- Average of 2 units RBC per patient
- Mortality 9.1% vs 8.7% in new vs old blood units
- Sub-group analysis of high risk patients with no difference
  - Includes CT surgery – 1 institution excluded
Practice Guidelines

- **Recommendation 1**
  - Threshold of 7 g/dL for hospitalized adult patients
  - 8 g/dL for those undergoing orthopedic or cardiac surgery
  - Or those with pre-existing cardiac conditions

- **Recommendation 2**
  - Patients should receive any unit of RBC within standard issue dates
  - There is no benefit to fresher blood

Future Research

- Single center retrospective analysis
- 2 surgical teams with different thresholds for transfusion
- Restrictive < 8 g/dL or Liberal < 10 g/dL
- 74 patients studied over 1 year undergoing aortic surgery with DHCA

Table 4: Perioperative Mortality and Complications Compared Between the 2 Groups of Patients

| Group | Mortality (%) | Stroke (%) | MI (%) | Pulmonary Edema (%) | Sepsis (%) | Acute renal failure (%) | Major complications (%) 
|-------|--------------|------------|--------|---------------------|-----------|------------------------|-------------------------
| Group A | 3.1          | 1.2        | 3.6    | 5.1                 | 0.8       | 2.3                    | 12.3                    |
| Group B | 3.2          | 1.4        | 3.8    | 6.1                 | 0.7       | 2.5                    | 13.2                    |

Future Research

- No significant differences in M&M between groups
- Restrictive group did receive more PCC
- Limitations
  - Retrospective
  - Small sample size

Over 50 Years of Fibrinogen Concentrate

- The first license granted for fibrinogen concentrate was in Brazil in March 1963
  - Was available prior in unregulated forms
- 1985 – Pasteurization step added for viral inactivation
  - 3 million grams have been used since
  - Available as Haemcomplettan® or RiaSTAP® (US version)
Fibrinogen Concentrate

- During major bleeding events, fibrinogen is the first clotting factor to reach critically low levels
- 1/23,300 cases of thrombotic events in post-marketing surveillance
- Purification of recombinant fibrinogen was completed in 1993
- Multiple clinical trials underway to investigate its use in major bleeding

REPLACE Trial

Randomized evaluation of fibrinogen vs placebo in complex cardiovascular surgery (REPLACE): a double-blind phase III study of haemostatic therapy

Methodology

- Phase III, multinational, multi-center, randomized, double blinded trial in 2012-2014
- Post heparin reversal bleeding 60-250 g in 5 minutes
- FCH concentrates given to target FIBTEM maximal clot firmness (MCF) of 22mm
- Standard transfusion algorithm followed if bleeding continued
- 68% adherence rate in transfusion algorithm

Outcomes

- End Points: total allogenic units transfused in 24 hours
  - RBC, FFP, and platelets
- Secondary Endpoints
  - Individual unit types transfused
  - Need for reoperation
  - Mortality
  - Plasma fibrinogen (Clauss assay)
  - MCF – FIBTEM assay using ROTEM device

Data

- Primary outcome
  - Increased RBC and FFP use with FCH
- Secondary outcomes
  - Increased fibrinogen levels and MCF target achieved
  - No differences in periop bleeding between groups
- Wide variability between centers
• 304 assessed for eligibility
• 52 enrolled
• Double blind, randomized, placebo controlled trial
• Fibrinogen did not influence bleeding

• 89 Bilateral Lung Transplant (BLT) for patients with cystic fibrosis over 6 years
• Excluded pre-op ECMO, redo transplants, ex vivo lung reconditioning, and multiorgan transplants
• CPB was used if required
<table>
<thead>
<tr>
<th>Classification / Definition</th>
<th>Indication of the end of maturation/maturity change</th>
<th>5 5' group (mg/kg)</th>
<th>6 6' group (mg/kg)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deuterium added to a single lower limb fibroblast monolayer</td>
<td>Tissue viability of cells at 72 h post-treatment</td>
<td>10.22 ± 0.01</td>
<td>10.33 ± 0.02</td>
<td>0.06</td>
</tr>
<tr>
<td>Site of the fibroblast monolayer on the chitosan film</td>
<td>Tissue viability of cells at 72 h post-treatment</td>
<td>10.23 ± 0.01</td>
<td>10.34 ± 0.02</td>
<td>0.05</td>
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<tr>
<td>Site of the fibroblast monolayer on the chitosan film</td>
<td>Tissue viability of cells at 72 h post-treatment</td>
<td>10.24 ± 0.01</td>
<td>10.35 ± 0.02</td>
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<tr>
<td>Strain of the fibroblast monolayer on the chitosan film</td>
<td>Tissue viability of cells at 72 h post-treatment</td>
<td>10.25 ± 0.01</td>
<td>10.36 ± 0.02</td>
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<td>10.26 ± 0.01</td>
<td>10.37 ± 0.02</td>
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