Challenges in Anticoagulation During MCS

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Speaker Disclosure: Member, Scientific Advisory Council, Haemonetics Inc
Learning Objectives

• Recognize the common thrombotic and hemorrhagic complications associated with MCS devices
• Recognize approaches and evolution of antithrombotic therapy
• Identify the limitations of coagulation assays used to monitor and adjust UFH
Cedars-Sinai Implants 1st
SynCardia Total Artificial Heart
to Bridge Mother of Three to
Second Heart Transplant

39-Year-Old Michelle Johnson Waiting for
Matching Donor Heart at Home with Her Children
Using the Freedom® Portable Driver

SynCardia Systems, Inc., manufacturer of the world’s
first and only FDA, Health Canada and CE (Europe)
approved Total Artificial Heart, said today that Cedars-
Sinai Medical Center in Los Angeles has discharged its
first patient to be implanted with the SynCardia
temporary Total Artificial Heart. Michelle Johnson, 39,
left the hospital to wait for a matching donor heart at
home using the Freedom® portable driver to power
her Total Artificial Heart.
Continuous –Flow (VAD Adults)

• The most common **cause of death** is a neurologic event (Ref 1).
• **Device thrombosis** rate for **HeartMate II** (HMII) LVAD: 8.4% of implanted devices at 3 months (Ref 2) and 6% of implanted devices at 6 months (Ref 3)*
• **Pump thrombosis rate for HVAD**: in the Heart Ware bridge to transplant (BTT) trial database: 8.1% of implanted patients, requiring exchange, in 4.2% (Ref 4)*
• 28.7% of patients with the **Heart Ware** HVAD experienced one or more **strokes** over 2 years (Ref 5)
• **Heart Mate 3** – Momentum 3 trial (HMII versus HM3 6-months outcome) (Ref 6)
  ➢ Pump thrombosis HM3 - 0.7% versus HMII- 7.7%
  ➢ No difference in stroke or bleeding
• *The FDA has recently issued a safety communication regarding both devices, however the net benefits of both devices are generally accepted to outweigh the risks in the group of patients with stage D heart failure (Ref 7)
Continuous –Flow (VAD Adults)

- **Thrombosis risk factors (Ref 8):**
  - Non mechanical
    - intensity of antithrombotic therapy
    - blood pressure management
    - status of AV opening after LVAD implantation
  - Mechanical
    - type of the material used in the inflow cannula
    - surgical implantation techniques

- **Bleeding risk factors**
  - GI bleed in up to 30% of patients (Ref 9)
    - acquired VWS (type 2a)- 20-30%
    - Arteriovenous malformations (AVM) of GI
VAD Anticoagulation Challenges

- Current VAD antithrombotic therapy: **UFH, VKA and Aspirin**
- Because of high rate of early postoperative bleed some centers eliminated the use of UFH and reduced intensity of VKA
- These practices were related to increase in pump thrombosis (from 2.2% to 8.4%) (Ref 3,10)

- The PREVENtion of HMII Pump thrombosis trial (Ref 10) was designed to evaluate the incidence of pump thrombosis (overall rate 2.9% at 3 months and 4.8% at 6 months) using close adherence to a standardized clinical guidelines:
  1. Surgical techniques during implantation
  2. Anticoagulation and antiplatelet management (UFH bridging)
  3. Pump speed management (>9000 revolutions/min)
  4. Blood pressure management
- Rate of pump thrombosis with full adherence to 1-3 criteria 1.9% vs 8.9% with non adherence (Ref 11)

- Overall bleeding incidence 45% at 6 months (Ref 11)
Pediatric VADs

- Berlin Heart EXCOR – pulsatile flow VAD
- Standardized approach to antithrombotic therapy (Ref 12)
- Major bleed in 50% of patients (only 24% were related to anticoagulation)
- Stroke 29% (only 9% related to anticoagulation)
- Both bleeding and clotting events occurred early in the time course
- Only 40% of coagulation monitoring assay were in the protocol – specified target range

- The anticoagulation strategy – Edmonton Protocol (Ref 12)
  - TEG is used to adjust UFH
  - Dipyridamole is initiated at 48 hours
  - Aspirin twice daily monitored by TEG PM
  - Warfarin Goal INR 2.7-3.7
Utility of Hypercoagulable Work-up in Predicting Post-Operative Complications in Total Artificial Heart (TAH) Implant Patients at Cedars-Sinai Medical Center

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Non-Event</th>
<th>Clotters</th>
<th>Bleeders</th>
<th>Association w/ Event (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Short-Term Device</td>
<td>3:1 days (1-6 days) = 7/23 patients (30.4%)</td>
<td>3 days (1-5 days) = 3/6 patients (50%)</td>
<td>4 days (3-5 days) = 2/14 patients (14%)</td>
<td>N</td>
</tr>
<tr>
<td>Pump Time (minutes)</td>
<td>188 (108-243)</td>
<td>185 (156-322)</td>
<td>175 (108-257)</td>
<td>N</td>
</tr>
<tr>
<td>INTERMAC Profile (patients)</td>
<td>I:8 II:7 III:2 IV:2 N/A:4</td>
<td>I:3 II:0 III:1 IV:2 N/A:0</td>
<td>I:2 II:7 III:0 IV:2 N/A:0</td>
<td>N</td>
</tr>
<tr>
<td>BMI</td>
<td>25.7 (19.5-40.2)</td>
<td>26.7 (22.8-31.7)</td>
<td>26 (19.2-38.7)</td>
<td>N</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>N/A</td>
<td>Not elevated Median: 113/64</td>
<td>N/A</td>
<td>N</td>
</tr>
<tr>
<td>Hx DM (patients)</td>
<td>6/23 (26%)</td>
<td>2/6 (33%)</td>
<td>4/14 (29%)</td>
<td>N</td>
</tr>
<tr>
<td>INR at event time</td>
<td>N/A</td>
<td>1.3 (1.2-1.8)</td>
<td>1.4 (1.1-2.1)</td>
<td>Y = Clotters N = Bleeders</td>
</tr>
<tr>
<td>LDH (patients)</td>
<td>N/A</td>
<td>Elevated: 3 Not available: 3</td>
<td>N/A</td>
<td>N</td>
</tr>
<tr>
<td>Active Infection (patients)</td>
<td>8/23 (35%) *Within 30 days 4/6 (67%) *Around time of implantation 5/14 (36%) *Around time of implantation</td>
<td>Y—High rate of post-operative infection overall (40%)</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>HIT</td>
<td>19/23 negative 7 not tested</td>
<td>0/6 negative 11/14 negative 3 not tested</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>#Days on device</td>
<td>196 (5-931)</td>
<td>27 (10-68)</td>
<td>88 (12-511)</td>
<td>36 (25-95)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thrombophilia Work-up</th>
<th>Non-event Group</th>
<th>Clotters</th>
<th>Bleeders</th>
<th>Association with Event (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus Antiocoagulant (patients)</td>
<td>Pos*: 11/23 (48%)</td>
<td>Pos: 26 (33%)</td>
<td>Pos: 3/14 (21%)</td>
<td>N</td>
</tr>
<tr>
<td>Neg: 6/23 (28%)</td>
<td>N/A: 6</td>
<td>N/A: 6</td>
<td>N/A: 6</td>
<td>N</td>
</tr>
<tr>
<td>Antiphospholipid Antibodies (patients)</td>
<td>Pos: 5 (22%)</td>
<td>Pos: 4 (26%)</td>
<td>Pos: 4 (26%)</td>
<td>N</td>
</tr>
<tr>
<td>Other patients</td>
<td>FVL pos: 1</td>
<td>FVL pos: 1</td>
<td>Low ATIII: 1</td>
<td>N</td>
</tr>
</tbody>
</table>

1. Thrombotic events occurred on **average 5.5 days** after implantation; **Bleeding events** - **7.5 days** after, indicating a necessity for early adequate anticoagulation therapy.

2. Comprehensive pre-operative hemostasis workup did not reveal inherited thrombophilia risk factors associated with adverse events.

3. Of all hypercoagulable work-up, lupus anticoagulant (LA) appears to be the most important factor, as it can interfere anticoagulation management.

4. Infection may contribute to the incidence of clotting and bleeding events.

5. Baseline TEG (CI) can identify patients who would be at risk for post-device implantation events.

6. This study supports a targeted, rather than comprehensive, pre-operative screening work-up, that would also include baseline TEG analysis.

Abstract presented at 2018 ISHLT, Nice
MCSD Anticoagulation Challenges

• In the setting of risk of early device thrombosis (VAD) or TE (TAH), bridging protocols during the perioperative period and the way we monitor anticoagulation may need revision.

• The need for anticoagulation varies widely among patients with CF-LVADs, and the standard “one-size fits all” anticoagulation protocols cannot be employed.
Role of Thromboelastography Platelet Mapping and International Normalized Ratio in Defining “Normocoagulability” During Anticoagulation for Mechanical Circulatory Support Devices: A Pilot Retrospective Study

<table>
<thead>
<tr>
<th>MEAN</th>
<th>CLOT (N=13)</th>
<th>NON-CLOT (N=87)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAH (N=28)</td>
<td>HMII (N=30)</td>
<td>HW (N=23)</td>
</tr>
<tr>
<td>SP</td>
<td>5.67</td>
<td>7.19</td>
<td>5.74</td>
</tr>
<tr>
<td>R</td>
<td>6.11</td>
<td>7.53</td>
<td>6.43</td>
</tr>
<tr>
<td>INR</td>
<td>2.4</td>
<td>2.40</td>
<td>2.20</td>
</tr>
<tr>
<td>Δ (SP-R)</td>
<td>0.44</td>
<td>0.34</td>
<td>0.69</td>
</tr>
<tr>
<td>α</td>
<td>76.09</td>
<td>73.29</td>
<td>71.91</td>
</tr>
<tr>
<td>MA</td>
<td>75.91</td>
<td>72.43</td>
<td>71.51</td>
</tr>
<tr>
<td>G</td>
<td>16.38</td>
<td>14.69</td>
<td>13.05</td>
</tr>
<tr>
<td>Cl (1 to 3)</td>
<td>2.92</td>
<td>1.14</td>
<td>1.74</td>
</tr>
<tr>
<td>MA-AA</td>
<td>50.53</td>
<td>48.82</td>
<td>45.59</td>
</tr>
<tr>
<td>MA-ADP</td>
<td>63.57</td>
<td>61.68</td>
<td>52.94</td>
</tr>
</tbody>
</table>

Anticoagulation Therapy

- **Heparin Starting Time:**
  - POD 1-3 without IV bolus dose
  - or after chest closure & based on observed chest tube (CT) drainage: < 30mL/hr, X 12hrs
  - or CXR shows no blood accumulation.

- **Starting Dose:** 2 - 5 Units/kg/hr via continuous IV infusion

- **Therapeutic Goal:**
  - Target Heparin level 0.11- 0.27 units/ml or aPTT 40-60 sec

- **Monitoring Parameters:**
  - Thrombocytopenia after Post op Day #4 → (HIT panel)
  - ATIII deficiency:
    - if there is no/minimal aPTT/heparin level/TEG changes after 2 consecutive blood draws
    - If level <60% (80-120 %), consider transfusion with 1 unit of FFP
    - For severe deficiency consult hem/onc for potential use of ATIII concentrate
    - Check TEG/INR, correlate with Coagulation Consultative Service
Conclusion:

• Levels of aPTT were disproportionally prolonged or normal relative to the corresponding heparin assay levels in MCSD patients irrespective of the type of device or INTERMACS profiles.

• Lupus anticoagulant, concurrent warfarin administration as well as high fibrinogen or factor VIII level may falsely prolong or shorten aPTT causing overestimation or underestimation of heparin dose.

• Concurrent use of aPTT and heparin assay to guide heparin therapy may be misleading. The heparin assay appears to be more reliable than aPTT in patients with MCSDs.

• The ideal level of anticoagulation should be individually tailored.

• Target values of heparin assay level between 0.15 IU/ml to 0.3 IU/ml appears to be safe for bridging using low intensity heparin dose.

Abstract presented at ISHLT annual meeting, 2017
Clot lifespan model (CLSM) of hemostasis

- CLSM is a TEG based approach that utilizes a standard clotting and fibrinolytic stimuli to assess clot growth and disintegration via changes in clot resistance.
Vitamin K antagonists (VKA, e.g. warfarin) are the anticoagulants of choice for LVAD patients.

Titration to keep patients within target international normalized ratio (INR) goal is challenging and labor-intensive.

The novel oral anticoagulant (DOAC) dabigatran was therefore tested in a randomized, pilot, single center study against VKA in addition to aspirin for long-term anticoagulation.*

The trial was stopped early due to increased thrombotic events (pump thrombus and transient ischemic attack) in the dabigatran arm.

Just as DOACs are contra-indicated in mechanical heart valves based on the RE-ALIGN trial **, they should be avoided in LVAD patients until further data are obtained.


ECMO Challenges in Anticoagulation: Heparin
Case 1 ACT & aPTT Discrepancy

- 64 yo female with severe pulmonary HTN was placed on VA ECMO as a bridge to IV pulmonary vasodilators
- ACT 165 sec (therapeutic levels are clinically determined)
- aPTT 139 sec (65-117 sec for 0.3-0.7 IU/ML UFH level)
- Heparin drip unchanged
- Patient developed large ICH and care was withdrawn
### Possibilities

<table>
<thead>
<tr>
<th>Possibilities</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT can be affected by factor deficiency &amp; LA</td>
<td>LA positive</td>
</tr>
<tr>
<td>Supratherapeutic UFH ?</td>
<td>Therapeutic</td>
</tr>
<tr>
<td>Patient on ECMO may develop acquired VWS</td>
<td>0.36 IU/MI with aPTT of 162 sec</td>
</tr>
<tr>
<td>Additional bleeding risk factors ?</td>
<td>6 % HMWM ( &gt;14 %)</td>
</tr>
<tr>
<td></td>
<td>PT 17.6 ( VII – 43%)</td>
</tr>
<tr>
<td></td>
<td>Aspirin 325 mg</td>
</tr>
<tr>
<td></td>
<td>Platelets 53 K</td>
</tr>
</tbody>
</table>

### Summary:
- Platelet dysfunction (thrombocytopenia, aspirin, HMWM loss) – bleeding risk factor
- Discordant aPTT due to Lupus Anticoagulant Presence
Case 2: Subtherapeutic ACT, bleeding

- Call from ICU NP: 35 YO, Trauma patient on ECMO had significant bleeding, but because of subtherapeutic ACT and surgeon request dose was increased

CK -72 min (5-10 min)
CKH 7.7 min
Case 2 : Additional Work Up

Interpretation :
- Supratherapeutic Heparin
- Platelet function inhibition
- Thrombocytopenia (64K)
- HMWM Loss (5% activity)

<table>
<thead>
<tr>
<th></th>
<th>401 12/12/2017 0842</th>
<th>400 12/12/2017 0920</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PTT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial Thromboplas...</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PROTIME W/ INR</strong></td>
<td>&gt; 200 * ↑</td>
<td></td>
</tr>
<tr>
<td>Prothrombin Time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>COAG FACTOR ACTIVITY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High MW vWF Multimers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate MW vWF...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low MW vWF Multimers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombin III A...</td>
<td></td>
<td></td>
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<tr>
<td>vWF Ag</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Von Willebrand MUL...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vWF Activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>COAG OTHER</strong></td>
<td>169 *</td>
<td></td>
</tr>
<tr>
<td>Activated Clotting...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEG Prf Mapping He...</td>
<td></td>
<td>SEE PATH REPORT... *</td>
</tr>
<tr>
<td><strong>HEPARIN STUDIES</strong></td>
<td>1.34 * ↑</td>
<td></td>
</tr>
<tr>
<td>Heparin Urification...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td>Specimen</td>
<td>What may affect assay</td>
</tr>
<tr>
<td>---------------------</td>
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<td>-----------------------</td>
</tr>
</tbody>
</table>
| aPTT                | Citrated plasma | Lupus Anticoagulant (>)
|                     |               | Factor deficiency (>)
|                     |               | Underfilled tube (>)
|                     |               | AT deficiency |
| UFH Level (anti Xa) | Citrated plasma | AT deficiency ( < 60%)
|                     |               | ➢ If the test uses patient’s own AT III and patient is AT deficient, this assay will underestimate heparin amount, however may represent the actual degree of anticoagulation of the patient
|                     |               | Differential clearance of heparin fractions can cause discordant results
|                     |               | ➢ HMW cleared faster; retained LMW fractions measured by heparin assay, but have little effect on aPTT
|                     |               | Significant bilirubinemia and hemolysis |
| ACT 180-220 sec     | Whole blood   | Values are **device-specific** even if the same activator is used
|                     |               | Varies based on heparin-dependent (heparin responsiveness/resistance) and heparin-independent (hemodilution, hypothermia, platelet count, race) factors
|                     |               | ACT is also affected by concomitant administration of other antithrombotic agents (abciximab, aprotinin (Celite-ACT)) |
| VEA (TEG,ROTEM)     | Whole blood   | Shows physiologic effect of UFH |
High-Molecular-Weight von Willebrand Factor Multimer Loss and Bleeding Complications in Patients on Short Term MCS

* Abstract presented at ASAIO, Chicago 2017, Manuscript accepted by JECT, 2018

Conclusion

• Despite providing improved survival and quality of life, the current MCS technology is not “hemocompatible”
• Both bleeding and thrombotic complications are multifactorial
• Novel approached to anticoagulation are warranted
• The need for anticoagulation varies widely among patients and devices, and the standard “one-size fits all” anticoagulation protocols cannot be employed
• It is useful to have a standardized protocol to start antithrombotic management that is than tailored to the individual patient
• Dedicated team of experienced providers needed to manage patients with MCS devices


Thank You