Evaluation of Serial Biomarkers in Intermediate Risk Acute Pulmonary Embolism Patients

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Introduction - Pulmonary Embolism

- Major cause of morbidity and mortality in the US
- Third most common cause of cardiovascular disease after MI and stroke
- Risk stratified into low, intermediate, and high risk based on European classification system
- Management is clear in low and high risk but not in intermediate
<table>
<thead>
<tr>
<th>RISK OF DEATH WITH PULMONARY EMBOLISM</th>
<th>SHOCK OR HYPOTENSION</th>
<th>SIGNS OF RIGHT VENTRICULAR DYSFUNCTION</th>
<th>BIOMARKERS (TROPOIN AND BNP)</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>FIBRINOLYSIS</td>
</tr>
<tr>
<td>INTERMEDIATE</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>LOW</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>ANTICOAGULATION</td>
</tr>
</tbody>
</table>
Introduction

PEITHO

- No mortality benefit of thrombolysis in intermediate risk patients and increased bleeding
- 5-8% of intermediate risk patients will become hemodynamically unstable in first 24-72 hours
- This subset of patients may benefit from thrombolysis
- Need more accurate prognostication tools to identify these patients before hemodynamic collapse
- Cardiac biomarkers have been studied but at a single time point not throughout the course
Among patients with intermediate risk PE, serial measurements of biomarkers up to 72 hours after admission will help identify the subgroup of patients who progress to high risk. We predict there will be three specific patterns of biomarker evolution.

A. Elevated at diagnosis and then down trending

B. Stable level throughout admission

C. Normal level initially with rise during the hospitalization
Specific Aims

1. To characterize the temporal trends of biomarkers in the first 72 hours
   - Troponin T
   - Lactate
   - NT proBNP
   - Uric acid

2. To explore the relationship of hemodynamic instability and escalation of care with biomarker patterns
   - Hemodynamic instability is defined as
     - Persistent SBP < 90 mmHg or drop in SBP by 40 mmHg for more than 15 minutes with signs of end-organ hypoperfusion
     - Use of vasopressors to maintain adequate organ perfusion and SBP of >90 mm Hg
     - Need for cardiopulmonary resuscitation
   - Escalation of care is defined as
     - Need for systemic or catheter directed thrombolysis
     - Catheter thrombus fragmentation
     - ICU transfer/Mechanical ventilation
     - Embolectomy
     - Extracorporeal membrane oxygenation (ECMO)
Methods

- Pilot, prospective, observational study involving a cohort of patients diagnosed with intermediate risk PE
- Will measure serial biomarkers over the first 72 hours or until the patient receives fibrinolysis, whichever comes first
  - PEITHO trial suggests adverse outcomes mostly occur within this window
- Schedule for lab draws:

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Sample type</th>
<th>SOC</th>
<th>Time block from initial diagnosis</th>
<th>Total blood volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProBNP</td>
<td>Plasma</td>
<td>×</td>
<td>1 2 3 4 5 6 7</td>
<td>12 ml</td>
</tr>
<tr>
<td>Troponin T</td>
<td>Plasma</td>
<td>×</td>
<td>1 2 3 4 5 6 7</td>
<td>6 ml</td>
</tr>
<tr>
<td>Lactate</td>
<td>Plasma</td>
<td>×</td>
<td>1 2 3 4 5</td>
<td>6 ml</td>
</tr>
<tr>
<td>Uric acid</td>
<td>Serum</td>
<td>×</td>
<td>1 2 3 4 5</td>
<td>3 ml</td>
</tr>
</tbody>
</table>

*SOC= standard of care

Time block defined as:
1: 0-8 hours
2: 8-16 hours
3: 16-24 hours
4: 24-36 hours
5: 36-48 hours
6: 48-60 hours
7: 60-72 hours

*SOC= standard of care
Methods

- Since cardiac biomarkers are well studied and closely associated with right ventricular dysfunction and myocardial injury, we decided to measure these more frequently.

- Vital signs at seven specified time blocks will be considered for serial assessments.

- We plan to examine:
  - The temporal pattern of serial serum biomarker levels in shock index from first recorded vital signs (defined as ratio of HR and SBP) group <1 and >1.
  - Relation of serial biomarkers levels with shock index, SBP, and ratio of pulse oxygen saturation to fraction of inspired oxygen concentration, each separately.
  - Association of baseline serum biomarker concentration with blood pressure progression and hypotension.

  » This will be done by assigning participants into three biomarker tertile groups (low, medium, high) and categorizing serial SBP measurements into Group I (>100 mmHg), Group II (90-100 mmHg), and Group III (<90 mmHg). Two BP outcomes will then be evaluated: (1) Progression of BP by 1 or more category (2) Development of hypotension.
### Outcome Measures

**Primary**
Pattern of serial biomarker levels over 72 hours after admission (or initial diagnosis of PE) in two groups of SI (<1 and >1). Will be analyzed by several methods including peak abnormal value, time to peak, time to resolution, and AUC.

**Secondary**
1. Changes in blood pressure, heart rate, and shock index. Compare admission value with measurements taken in pre-specified time block (1-7).  
   
   **[Time frame: 72 hours]**

2. Frequency of clinical complications  
   **[Time frame: entire hospitalization]**
   - Hemodynamic decompensation
   - Respiratory deterioration (S/F ratio ≤240, RR>25, PO2/FiO2 ≤300 mm Hg on O2≥10 LPM x 15 min)
   - PE related in hospital death
   - Major bleeding (hemorrhagic stroke or drop in hemoglobin by at least 4 g/dL with or without the need for red cell transfusion)

3. Frequency of advanced treatment for PE

4. Length of hospitalization
Statistical Analyses

• Primarily descriptive and all formal statistical tests will be performed for exploratory purposes only

• Each analyte will be plotted by patient over time so we can visually identify patients with a trend in biomarker levels

• Changes over time will be explored individually, using either Pearson’s or Spearman’s correlation, wherein biomarkers’ concentration will be continuous predictor and SI, SBP, and S/F ratio will be dependent variable to calculate correlation coefficient

• Will also calculate regression (linear) coefficient if linear relationship exist in correlation analysis
Results

- **Research in progress**
- These graphs show BNP and troponin trends in a sample patient
- The rise of the biomarkers correlated with a change in hemodynamics and transfer to the ICU
- This is the pattern we predict for patients who will progress to high risk
Discussion

- Short-term goal of this project is to better understand the natural course of PE biomarkers
  - Biomarkers have been studied before but only at a single time point
  - We believe trending the biomarkers will help find patterns that will correlate with progression to high risk pulmonary embolism

- Long-term goal is to use longitudinal biomarker measurements to improve our ability to identify patients at intermediate risk who could benefit from thrombolysis or other advanced therapies
  - This will allow treatment to be more effectively targeted and improve patient outcomes
  - This will be the subject of future studies wherein if we detect implied signal, future studies can focus on prospective management trials comparing thrombolysis therapy (targeted/catheter directed or systemic vs standard of care) and has potential for integration into risk stratification algorithm
Conclusion

We believe understanding the changes in biomarker values over time will assist in designing future studies to better prognosticate and manage patients with intermediate risk PE.
References


Kucher N, Rossi E, Goldhaber SZ. Massive Pulmonary Embolism. Circulation. 2006;113:577-582


