Use of Plasma Biomarkers to Test Frailty in Geriatric Trauma Patients

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Grant Sponsors

Emergency Nurses Association
Friends of Yuma
Goals

Goals of the study were to determine if a new plasma biomarker of oxidative stress could be related to:

1. Redox status in patients who have experienced traumatic injury as well as healthy community-dwellers

2. Outcomes of patients who have experienced trauma

3. Frailty measured by established frailty scales in healthy community-dwellers can be correlated to ORP
Background

• Physically injured elder adults present challenges in the emergent injury phase

• Oxidative stress contributes to cellular deterioration

• Can leads to a decrease in physiological reserve
Why Study This Topic

• Acutely aware as far back as 2008 that elders who make up increasing percentage of all trauma patients did not fare as well as younger cohorts

• EAST Practice Guidelines first published in 2006 offered few operational guidelines

• Over 26% of trauma patients at my institution were over age 65 and numbers were predicted to grow those numbers have grown to 37% in last 7 years

• A deeper understanding was needed as to when “elderly” begins physiologically

Improving Outcomes for Frail Elders Who Have Experienced Physical Trauma

- Existing literature has focused on predicting outcomes not on seeking to understand why some experience poor outcomes

- Understanding the mechanisms may improve the care plans

- Frailty is a common syndrome encountered that is characterized by a decrease in biological reserves
Concept of Frailty

• Frailty is a state of vulnerability due to an accumulation of physical deficits in the physiological systems during a lifetime.

• This influences the way an individual weathers the health transition. The acute trauma injury tips the frailty scale from a chronic condition to an acute component of the transition from health to illness.

• This cumulative decline depletes homeostatic reserves until a stressor (an acute trauma injury) triggers a disproportionate change in health status. Thus, frailty’s cumulative effects are that the more individuals have wrong with them, the more likely they are to be frail.

Current Approaches to Assessing Frailty

• Multiple assessment tools

• Two most commonly used FFP and the FI

• In 2012, at the Gerontological Society Meeting, 13 additional tools were introduced

• Limited for injured because most are time consuming and also primary care for office visits

• Requires self-reporting

• Injuries can preclude testing such as gait or dynamometer/Primary care visits may also preclude extensive testing
### Statistical Groups Based on Frailty Assessment Scores

<table>
<thead>
<tr>
<th>Frailty Assessment</th>
<th>Score associated with “Not Frail”</th>
<th>Score associated with “Frail”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fried Frailty Phenotype (FFP)</td>
<td>0</td>
<td>$\geq 3$</td>
</tr>
<tr>
<td>Frailty Index (FI)</td>
<td>0</td>
<td>$\geq 47$</td>
</tr>
<tr>
<td>CSHA Clinical Frailty Scale (CSHA Scale)</td>
<td>$\leq 3$</td>
<td>$\geq 4$</td>
</tr>
<tr>
<td>FRAIL Scale (FS)</td>
<td>$\leq 1$</td>
<td>$\geq 3$</td>
</tr>
</tbody>
</table>


Tools Used in This Study

- Current Approaches to Accessing Frailty
  - Fried Frailty Phenotype (FFP)
  - Frailty Index (FI)
  - CSHA Clinical Frailty Scale (CSHA Scale)
  - FRAIL Scale (FS)

The CSHA Clinical Frailty Scale

1 Very fit — robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age
2 Well — without active disease, but less fit than people in category 1
3 Well, with treated comorbid disease — disease symptoms are well controlled compared with those in category 4
4 Apparently vulnerable — although not frankly dependent, these people commonly complain of being “slowed up” or have disease symptoms
5 Mildly frail — with limited dependence on others for instrumental activities of daily living
6 Moderately frail — help is needed with both instrumental and non-instrumental activities of daily living
7 Severely frail — completely dependent on others for the activities of daily living, or terminally ill

Current Methods for Evaluating Oxidative Stress

- Rely on detecting levels of individual byproducts of oxidative damage
- Determine the total levels of activity of individual antioxidant enzymes

Oxidative Reduction Potential as an Aggregate Marker of Oxidative Stress

• Imbalances in ORP are the result of an increased production of ROS/RNS and a decrease in levels of antioxidants

• ORP is a comprehensive measure of redox status without looking for a particular molecule

• ORP does not require processing, purification or isolation of a specific biomarker

• ORP reflects changes in redox status under conditions in which modifications of individual targets are not detected
Two Distinct Elements to ORP

- **Static ORP (sORP)** is the working potential between the electrode and a reference electrode with no driving current which is proportional to the balance of reductants and oxidants
  - sORP is the "classically" termed ORP in which the standard potential between a working electrode and a reference electrode is measured as current (millivolts, mV)

- **Capacity ORP (cORP)** is a measure of antioxidant reserves available in the body’s system
  - cORP is a measure of antioxidant reserve available in the body’s circulation that is obtained when a plasma sample is oxidized with a small increasing linear electrical current in a titration manner and is measured in microcoulombs (µC)

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Lower ORP Example

Normal Levels/or Equilibrium

+ Hydrogen peroxide ($\text{H}_2\text{O}_2$)
+ Hydroxyl radical (HO)
+ Nitrogen oxide (NO)
+++ Ascorbic acid (vitamin C)
+++ Glutathione
+++ Tocopherol (vitamin E)
+++ Beta-carotene

Key:
+ Lower
+++ Higher
Balance of oxidant and antioxidants

Figure 4-1

Figure 4-2

Figure 4-3

Capacity ORP Reported in microCoulombs ($\mu$C)
Higher ORP Example

Abnormal/ High for Radicals
Low Antioxidant

+ +++ Hydrogen peroxide (H$_2$O$_2$)
+ +++ Hydroxyl radical (HO)
+ ++ Nitrogen oxide (NO)
+ + Ascorbic acid (vitamin C)
+ + Glutathione
+ + Tocopherol (vitamin E)
+ + Beta-carotene

Key:

+ Lower
+++ Higher

Balance of oxidant and antioxidants
Low cORP has below normal antioxidant reserves
Practicality

- Easy to use
- Low costs $ 5-7/per test
- Can be used anywhere
- No risk of cross contamination with single use strip
Methodology
Samples

• Injured Patients
  • N=93

• Healthy Participants
  • N=93
### Trauma Patient Demographics, ORP Values, and Outcomes

<table>
<thead>
<tr>
<th>Value</th>
<th>N=93</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>75.9 (7.40)</td>
</tr>
<tr>
<td>Gender/Female, variable (%)</td>
<td>51 (54.80%)</td>
</tr>
<tr>
<td>Gender/Male, variable (%)</td>
<td>42 (45.20%)</td>
</tr>
<tr>
<td>History of smoking, variable (%)</td>
<td>9 (9.70%)</td>
</tr>
<tr>
<td>Diabetes, variable (%)</td>
<td>18 (19.40%)</td>
</tr>
<tr>
<td>Statin use, variable (%)</td>
<td>36 (38.70%)</td>
</tr>
<tr>
<td>Consumes any alcohol, variable (%)</td>
<td>28 (30.10%)</td>
</tr>
<tr>
<td>Vitamin use, variable (%)</td>
<td>18 (19.50%)</td>
</tr>
<tr>
<td>Any alcohol on arrival, variable (%)</td>
<td>3 (3.20%)</td>
</tr>
<tr>
<td>ISS, mean (SD)</td>
<td>9.50 (4.90)</td>
</tr>
<tr>
<td><strong>ORP values</strong></td>
<td></td>
</tr>
<tr>
<td>sORP, mV, mean (SD)</td>
<td>111.65 (26.60)</td>
</tr>
<tr>
<td>sORP, mV, median (range)</td>
<td>106.20 (64 – 206)</td>
</tr>
<tr>
<td>cORP, μC, mean (SD)</td>
<td>0.71 (0.92)</td>
</tr>
<tr>
<td>cORP, μC, median (range)</td>
<td>0.40 (0.10 – 7.50)</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>LOS, days mean (SD)*</td>
<td>5.50 (4.70)</td>
</tr>
<tr>
<td><strong>Disposition</strong></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>36 (38.70%)</td>
</tr>
<tr>
<td>SNF/Rehab</td>
<td>56 (62%)</td>
</tr>
<tr>
<td>Expired</td>
<td>1 (1.10%)</td>
</tr>
</tbody>
</table>

Note. SD = Standard Deviation *LOS Range = 1-32 days
Aim 1

- **Aim 1**: To determine plasma sORP and cORP values in hospitalized and physically injured elder adults as a function of age, gender and Injury Severity Score (ISS).

- **Hypothesis 1A** postulated that sORP would be elevated, and that cORP would be decreased with increasing age. **Hypothesis 1B** postulated that females would have a higher sORP and a lower cORP compared to males. **Hypothesis 1C** predicted that a higher Injury Severity Score (ISS) would be positively associated with sORP and negatively associated with cORP.
Aim 1 Results

• Age

• Gender

• ISS

• Not found to be significantly correlated with either sORP or cORP
Aim 2

• **Aim 2**: To determine the relationship between plasma sORP and cORP and the traditional oxidative burden variables (use of statins, alcohol, vitamins, tobacco and diabetes) as well as to hospital length of stay (LOS) and discharge outcomes in hospitalized physically injured elder patients.

• **Hypothesis 2A** is that the use of alcohol, statins, tobacco and presence of diabetes would be associated with a higher sORP and a lower cORP. We also hypothesized that vitamin use should positively impact both with sORP and cORP. **Hypothesis 2B** postulated that length of stay (LOS) would be positively correlated with sORP and negatively correlated with cORP. **Hypothesis 2C** was that sORP and cORP would vary according to disposition after a hospital stay such that those discharged to a skill nursing facility would have a higher sORP and a lower cORP than those discharged to home.
Aim 2 Results

• 2A difference in sORP and cORP values
  – sORP did not differ with statins, alcohol, or vitamins
  – Smoking history had higher sORP 134.58 vs. 109.10 mV; $t=2.9$, $p=0.004$
  – Diabetic history had higher sORP 123.48 vs. 109 mV; $t=2.12$, $p=0.04$
Aim 2 Results

- 2B There was no difference between with LOS with sORP or cORP

  - Post hoc analysis by primary diagnosis did demonstrate that patients with chest injuries have a 9.2 day LOS vs. overall mean of 5.5 days
Aim 2 Results

• 2C No significant differences were detected
Healthy Participants Recruitment Procedures

**Pre-Study Visit and Recruitment**

1. Population identified in Injury Prevention Class
2. A pre-visit to the class by the Principle Investigator one to two weeks prior to the planned data collection date is completed to explain the study including inclusion and exclusion criteria and answer questions.

**Day of Study**

1. Re-introduction of topic
2. Consents obtained from each participant
3. Participants are logged and identified with sequential number codes
4. Assessment with four frailty tools:
   a. Frail Phenotype,
   b. Frail Scale,
   c. Frailty Index, and
   d. CHAS Scale;
5. Blood collection
6. Strength tests:
   a. arm grip strength with the dynamometer
   b. TUG (timed get up and go).

**Study Log will have sticker created for each consent, frailty tool and blood samples that are completed.**

**Handling of samples – transported via cooler to research lab immediately following draw**

**Handling at lab site – plasma will be obtained from whole blood and processed by aliquot of plasma and stored (80c) for later analysis of plasma ORP.**
## Healthy Participants Demographics, ORP Values and Frailty Scores

<table>
<thead>
<tr>
<th>Variable</th>
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<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age, years, mean (SD)</td>
<td>75.90 (7.40)</td>
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<tr>
<td>Gender/Female, variable (%)</td>
<td>50 (53.80%)</td>
</tr>
<tr>
<td>Gender/Male, variable (%)</td>
<td>43 (46.20%)</td>
</tr>
<tr>
<td>History of smoking, variable (%)</td>
<td>3 (3.20%)</td>
</tr>
<tr>
<td>Diabetes, variable (%)</td>
<td>10 (10.80%)</td>
</tr>
<tr>
<td>Statin use, variable (%)</td>
<td>44 (47.30%)</td>
</tr>
<tr>
<td>Consumes any alcohol, variable (%)</td>
<td>54 (58.00%)</td>
</tr>
<tr>
<td>&gt;10 alcoholic drinks/week, variable (%)</td>
<td>10 (10.80%)</td>
</tr>
<tr>
<td>Drinks per week, mean (SD)</td>
<td>3.60 (5.20)</td>
</tr>
<tr>
<td>Vitamin use, variable (%)</td>
<td>4 (51.60%)</td>
</tr>
<tr>
<td><strong>ORP Values</strong></td>
<td></td>
</tr>
<tr>
<td>sORP, mV, mean (SD)</td>
<td>105.10 (23.60)</td>
</tr>
<tr>
<td>sORP, mV, median (range)</td>
<td>103.20 (74.30 – 166.70)</td>
</tr>
<tr>
<td>cORP, μC, mean (SD)</td>
<td>0.95 (0.86)</td>
</tr>
<tr>
<td>cORP, μC, median (range)</td>
<td>0.75 (0.12 – 4.69)</td>
</tr>
<tr>
<td><strong>Frailty Scores</strong></td>
<td></td>
</tr>
<tr>
<td>Fried Frailty Phenotype (FFP), mean (SD)</td>
<td>2.40 (1.50)</td>
</tr>
<tr>
<td>Frailty Index (FI), mean (SD)</td>
<td>0.08 (0.06)</td>
</tr>
<tr>
<td>CSHA Clinical Frailty Scale (CSHA Scale), mean (SD)</td>
<td>1.90 (0.93)</td>
</tr>
<tr>
<td>FRAIL Scale (FS), mean (SD)</td>
<td>0.34 (0.76)</td>
</tr>
</tbody>
</table>

Note. SD = Standard Deviation
Aim 3

• **Aim 3**: To determine if plasma sORP and cORP in healthy, community-dwelling elder adults correlates with the results of the validated frailty assessments scale scores and traditional oxidative burden variables.

• **Hypothesis 3A** was that the plasma sORP and cORP would correlate with the results of the frailty assessment scale scores on the four different frailty assessment tools. **Hypothesis 3B** was that sORP and cORP would correlate with or vary as a function of the traditional oxidative burden variable.
Aim 3 Results

• The first significant finding was that there was a negative association between cORP and the CHSA scale and a positive association between sORP indicating that there is increase in frailty as there is decrease in antioxidant capacity
The CSHA Clinical Frailty Scale

1. Very fit — robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age.
2. Well — without active disease, but less fit than people in category 1.
3. Well, with treated comorbid disease — disease symptoms are well controlled compared with those in category 4.
4. Apparently vulnerable — although not frankly dependent, these people commonly complain of being “slowed up” or have disease symptoms.
5. Mildly frail — with limited dependence on others for instrumental activities of daily living.
6. Moderately frail — help is needed with both instrumental and non-instrumental activities of daily living.
7. Severely frail — completely dependent on others for the activities of daily living, or terminally ill.

Strengths

• ORP can be utilized to evaluate oxidative stress

• Minimally invasive

• Requires small sample volume

• Adequately powered for effective size
Limitations

• Single institution

• Concept of ORP is new with no established values to distinguish “high or low levels”
Implications for Nursing Practice

• ORP testing can be incorporated into injury prevention activities

• ORP testing is easy to use and low cost

• The Model of Frailty and Acute Trauma (MFAT) can be further tested with geriatric trauma patients using the CSHA Scale in combination with ORP biomarkers
Conclusions

• Providing care to injured elders can be challenging

• Use of the CSHA Scale to determine frailty in correlation with the use of the plasma biomarker ORP can be a good first start to further develop clinical protocols

• Smoking and diabetes also were identified as potential risk factors that contribute to oxidative stress suggesting a loss of redundancy in physiological systems
THANK YOU!
Bibliography

Bibliography cont.

Bibliography cont.


