High-Sensitivity Troponin and Heart Failure: Prospects for Machine Learning to integrate Biomarkers into Clinical Practice

Alan S Maisel MD FACC
Professor of Medicine Emeritus
University of California, San Diego
Disclosures

• Co-founder Brainstorm Medical
Well- lets talk about the new high-sensitivity troponins?
HF: High-sensitivity cardiac troponin

1. What is cTn/hs-cTn
2. Hs-cTn in chronic HF
3. Hs-cTn in AHF
4. Incorporation of machine learning to integrate biomarkers and clinical care
Q1: WHICH STATEMENT IS TRUE?

A) AHF often presents with cTn↑ and thereby accompanying AMI.

B) AHF rarely presents with cTn↑

C) AHF often presents with cTn↑, which however, may have multiple causes
Famous lies throughout history

1600’s You can’t burn a witch
1700’s Night air causes pneumonia
1800’s Tomatoes will kill you
1900’s Stop that or you’ll go blind
   (my mother)
2010’s Those are just false positive troponins
   (~a bunch of very famous cardiologists)
Are they really false positives when the elevation gives you greater risk?
More troponin is worse than less troponin
Troponin & Heart Failure

• MORE troponin is worse than less troponin

![Graph showing in-hospital mortality versus troponin quartile.]

<table>
<thead>
<tr>
<th>Troponin Quartile</th>
<th>In-Hospital Mortality (%)</th>
<th>No. of Patients</th>
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<tbody>
<tr>
<td>≤0.04</td>
<td>2.0</td>
<td>11,090</td>
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<tr>
<td>&gt;0.04–0.10</td>
<td>2.7</td>
<td>10,367</td>
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<tr>
<td>&gt;0.10–0.20</td>
<td>3.4</td>
<td>9,323</td>
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<tr>
<td>&gt;0.20</td>
<td>5.3</td>
<td>9,534</td>
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</table>

Peacock et al. NEJM. 2008:358:2117
TROPONIN IS A MARKER OF MYOCARDIAL INFARCTION INJURY
cTnT/I in HF: multiple causes

Proteolysis or turnover of myocardial contractile proteins

Direct toxicity of circulating neurohormones, inflammation, infiltrative processes, etc.

Myocardial apoptosis or autophagy

Supply demand mismatch with subendocardial ischaemia

Coronary ischaemia due to epicardial CAD or endothelial dysfunction

cTnT/I: quantitative marker of cardiomyocyte injury

\[ cTnT/I: \text{structural proteins unique to the heart} \]

Cardiomyocyte injury: AMI, multiple other causes
Hs Tn Definition

<table>
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<tr>
<th>Assay designation</th>
<th>Measurable normal values below the 99th percentile, %</th>
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<tbody>
<tr>
<td>Level 4 (third generation, hs)</td>
<td>≥95</td>
</tr>
<tr>
<td>Level 3 (second generation, hs)</td>
<td>75 to &lt;95</td>
</tr>
<tr>
<td>Level 2 (first generation, hs)</td>
<td>50 to &lt;75</td>
</tr>
<tr>
<td>Level 1 (contemporary)</td>
<td>&lt;50</td>
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</table>

Hs-cTn: Quantitative marker of cardiomyocyte injury

<table>
<thead>
<tr>
<th>ng/L</th>
<th>Differential Diagnosis</th>
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<tr>
<td>10000</td>
<td><strong>Very large AMI</strong>, myocarditis</td>
</tr>
<tr>
<td>1000</td>
<td><strong>Large AMI</strong>, myocarditis, Tako-tsubo, PE, critical illness</td>
</tr>
<tr>
<td>100</td>
<td><strong>Small AMI</strong>, early large AMI, myocarditis, Tako-tsubo, PE, shock, CHF, SAB, ...</td>
</tr>
<tr>
<td>50</td>
<td><strong>Micro AMI</strong>, early large AMI, myocarditis, Tako-tsubo, PE, shock, CHF, hypertensive crisis, SAB, stable CAD...</td>
</tr>
<tr>
<td>14</td>
<td>Stable angina, CHF, LVH, subclinical heart disease, etc</td>
</tr>
<tr>
<td>10</td>
<td>Healthy individuals</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Mueller C. Eur Heart J 2014
Elevated Cardiac Troponin Value(s) >99th percentile URL

Troponin rise and/or fall

- With acute ischaemia
  - Acute myocardial infarction
    - Atherosclerosis + thrombosis
      - Type 1 MI: triggers
        - Plaque rupture
        - Plaque erosion
    - Oxygen supply and demand imbalance
      - Type 2 MI: examples
        - Severe hypertension
        - Sustained tachyarrhythmia

- Without acute ischaemia
  - Acute myocardial injury

Troponin level stable

- Without acute ischaemia
  - Chronic myocardial injury
    - Examples
      - Structural heart disease
      - Chronic kidney disease
Heart failure with troponin elevation - what are the venues

- 1. type one vs type two MI - who goes to cath
- 2. type II - who is high risk for later events (and penalties) who can go home
- 3. trop elevation and AHF
- 4. trop elevation and Afib
Hs-cTn in chronic HF

Q1: Hs-cTn↑ in chronic HF: Is ...
A) Rare (≈5%)
B) ≈50%
C) Nearly all (≈95%)
≈50% of chronic HF pts have hs-cTnT↑ (>14ng/L)

**CHRONIC HF: HS-cTn TO PREDICT DEATH**

N=9’286, 60% ischemic, 85% LVEF <40%

1. Hs-cTn in AHF

**Q2:** Hs-cTn↑ in AHF: Is ..

1. | A) Uncommon (∼20%)  
   | B) ∼50%  
   | C) Common (∼80%)
86 yo female patient presenting to the ED

- Dyspnea NYHA III-IV for 1 week, worsening today
- Restrosternal „pressure“

- BP 149/77 mmHg, SpO2 99%, RR 16/min
- JVP↑, Rales, ankle edema

- Medical history:
  - Moderate aortic stenosis. LVEF normal (6 months ago)
  - Diabetes mellitus type 2
  - Paroxysmal atrial fibrillation
86 yo female patient presenting to the ED
BNP 532 ng/l  
hs-cTnT 138 ng/l (n<14)
Q2: **What is your diagnosis?**

A) AHF + AMI

B) AHF for sure, possible AMI, need more info

C) AHF, AMI very unlikely
Q2: WHAT IS YOUR DIAGNOSIS?

A) AHF + AMI

B) AHF for sure, possible AMI, need more info

C) AHF, AMI very unlikely

0h: hs-cTnT 138 ng/l (n<14)
3h: hs-cTnT 182 ng/l
Q3: What would you do next?

A) Immediate coronary angiography

B) Immediate echo

C) Nitrates, Furosemide 40mg, Aspirin+Clopido
   angio in 1-2 days

D) Nitrates, Furosemide 40mg, non-invasive stress test
Final diagnosis

AHF, coronary + valvular heart disease

-NSTEMI (PCI)

-AS 2

-FU 6 months: o.k.

-FU 18 months: Dyspnoe, AS 3  TAVI
Biomarkers will Make bad doctors worse and good doctors better!
When a Troponin is “elevated” in the ED, many think their job is over!!

“Cards to See for Elevated Troponin”
They are not stand-alone tests
AI – Revolution in Healthcare

A.I. Shows Promise
Assisting Physicians

Will AI replace doctors? – Probably not
But doctors who use AI will replace doctors who don’t

>$4.3B invested

AI in healthcare funding hit a historic high in Q2’18
Disclosed equity funding, Q1’13 – Q2’18

Source: cbinsights.com
Definitions

• Raise your hand if you’ve been caught in the confusion of differentiating artificial intelligence (AI) vs machine learning (ML) vs deep learning (DL)...
Artificial Intelligence vs Deep Learning—sometimes the difference is clear
What is machine learning?

• Machine learning is a method of data analysis that learns from experience, enabling computers to find hidden insights without being explicitly programmed to do so.

• Machine learning analyzes data and learns from it to make decisions and predictions, and includes supervised (manual entry of data and solutions) and unsupervised learning.
AI should incorporate Biomarkers since they bring pathophysiological data that cannot otherwise be ascertained clinically.
What does AI bring to the table?

Biomarkers are great at ruling out.
Biomarkers + AI are great at ruling in!

- Replace a differential diagnostics process (ruling out) with a definitive diagnostic process (ruling in) to save time and costs.
- Get to a definitive diagnosis faster and move patients from ER to where they need to go (admit, release, cath)
- Reduce costs on unnecessary tests, procedures, and admissions
- Reduce 30-day readmission penalties
How much should you “weigh” a BNP level in the evaluation of a dyspneic patient?

Most biomarkers are continuous variables. Yet we use specific cut points for convenience. This can cause problems. For instance
My neural networks (machine learning) knows how to combine features of history, physical exam and biomarkers so that appropriate weight can be given to each variable.
Lets say your dyspneic patient has a BNP of 1000 pg/ml- must be heart failure- right?

• Hx of previous heart failure and a fever pneumonia
• Large pulmonary embolism and right heart failure
• Sepsis and AKI
BNP is 90 in a dyspnic patient- it can’t be heart failure can it?

• obesity

• Acute hypertensive pulmonary edema
Artificial intelligence (AI)

• AI uses machine learning to create layers of neural networks
• Neural networks can learn in hours what the seasoned doctor learns in lifetime
• Neural networks don’t make mistakes due to lack of sleep or bias
Discerning between Type 1 & 2 MI

- Up to 10 million chest pain ED patients a year
- 1+ million cardiac catheterizations/year
- Up to 40% of type 2’s sent to cardiac cath
- $677M = annual cost of complications of cardiac cath
- Type 2’s = 10% of all readmitted patients

Cath complications:
1. Bleeding
2. Stroke
3. Kidney failure
4. Recurrent MI
5. Coronary bypass surgery
6. Pericardial tamponade
7. Heart failure
8. Death
AI product for Chest pain in ED

AI models trained offline on private research data

94.5% accuracy! More accurate than an expert cardiologist!

Type 1 vs. 2 MI (Myocardial Infarction)
30 AI features affect type 1/2 outcome

AI features ranked by impact (diagnostic prediction)

94.5% accuracy! More accurate than an expert cardiologist!

ALL VARIABLES CAN BE OBTAINED BY HISTORY AND EMR BY THE TIME FIRST TROPOININ RESULT IS READY (OR SECOND)

No need for any extra diagnostic tests
Not more than normal statistics?

To focus on hidden data structure algorithmically and make predictions or classifications

VS

To conduct inference about sample or population parameters
30 day readmission predictor for heart failure patients
Using approximately 250 variables representing demographics, socioeconomic status, medical history, clinical symptoms, vital signs, laboratory values, and discharge interventions, machine learning algorithms were unable to predict 30-day readmission better than logistic regression.

The findings are potentially limited by a lack of many strong predictors of heart failure readmission.

*JAMA Cardiol.* 2017;2(2):204-209
Analysis of Machine Learning Techniques for Heart Failure Readmissions

Bobak J. Mortazavi, PhD; Nicholas S. Downing, MD; Emily M. Bucholz, MD, PhD; Kumar Dharmarajan, MD, MBA; Ajay Manhapra, MD; Shu-Xia Li, PhD; Sahand N. Negahban, PhD*; Harlan M. Krumholz, MD, SM*

Background—The current ability to predict readmissions in patients with heart failure is modest at best. It is unclear whether machine learning techniques that address higher dimensional, nonlinear relationships among variables would enhance prediction. We sought to compare the effectiveness of several machine learning algorithms for predicting readmissions.

Methods and Results—Using data from the Telemonitoring to Improve Heart Failure Outcomes trial, we compared the effectiveness of random forests, boosting, random forests combined hierarchically with support vector machines or logistic regression (LR), and Poisson regression against traditional LR to predict 30- and 180-day all-cause readmissions and readmissions because of heart failure. We randomly selected 50% of patients for a derivation set, and a validation set comprised the remaining patients, validated using 100 bootstrapped iterations. We compared C statistics for discrimination and distributions of observed outcomes in risk deciles for predictive range. In 30-day all-cause readmission prediction, the best performing machine learning model, random forests, provided a 17.8% improvement over LR (mean C statistics, 0.628 and 0.533, respectively). For readmissions because of heart failure, boosting improved the C statistic by 24.9% over LR (mean C statistic 0.678 and 0.543, respectively). For 30-day all-cause readmission, the observed readmission rates in the lowest and highest deciles of predicted risk with random forests (7.8% and 26.2%, respectively) showed a much wider separation than LR (14.2% and 16.4%, respectively).

Conclusions—Machine learning methods improved the prediction of readmission after hospitalization for heart failure compared with LR and provided the greatest predictive range in observed readmission rates. (Circ Cardiovasc Qual Outcomes 2016;9:666-681. doi:10.1161/CIRCQUAL Outcomes.116.001292)

25% increase in ROC
Ngal in Predicting Primary Endpoint of AKINESIS in Patients with eGFR < 60 on admission
(an increase in creatinine of 0.5 mg/dl or ≥50% or renal-replacement therapy)

Original AKINESIS Study

AI Model

Top 3 variables:
Delta uNGAL/creatinine, Peak uNGAL/creatinine and Gal3
Shortness of Breath

• 3.4 million patients visit ED annually because of shortness of breath.

*National Hospital Ambulatory Medical Care Survey: 2014 Emergency Department Summary Tables*
Biomarker panel and AI for SOB: diagnosis, medications, admit versus discharge,

- Acute MI
- AHF
- Amyloid myocarditis
- PE
- Aortic dissection
- Bacterial pneumonia

AI

- Hx and P exam
- D-dimer
- ST2
- PCT
- BNP
- Troponin
How will this play out in the ED integrating with the Medical Record
Case one B.T.  
64 yo woman with a history of hypertension and high cholesterol, who for the past 4 days has palpitations, shoulder pain and lethargy.

ED

ECG- atrial fibrillation 116 bpm
Troponin 0h 6 ng
Troponin 2h 7.0 ng

Standard Practice

Machine Learning
Standard Practice

Diagnosis was atrial fibrillation.

Rate effectively slowed to 90 bpm with beta blockers

Patient sent home on beta blocker and Rivaroxiban

That evening she collapsed and died in the bathroom

Autopsy showed complete occlusion of left anterior descending coronary artery

COULD THERE HAVE BEEN ANOTHER WAY?
**Troponin Risk Level**

**First hs-cTNI**
- 6 ng/L
- 21:32

**Second hs-cTNI**
- 7 ng/L
- 23:59

**Risk Level Type One**
- **High**
- 9

**Risk Level Type Two**
- **Low**
- 2

**Explanation:**
Atypical symptoms presentation for women due to four (4) days of symptoms, shoulder pain.

**Recommendations:**
- Admit to CCU
- Immediate anticoagulation
- Urgent coronary angiography (Cath lab)
Case two – J.L.
74 y.o. male-hx of hypertension. Now a one-week history of increasing difficulty breathing, and now chest pain this morning.

ECG - sinus tachycardia
Troponin 0h 6 ng
Troponin 2h 7ng
Creatinine 1.8

ED

Standard Practice

Machine Learning
Standard Practice

Type one MI diagnosed by ED staff

Sent to cardiac catheterization

No lesions in coronary arteries
AKA -- NOT a TYPE one MI like had been expected

12 hours later - patient developed severe kidney injury and hospitalized five days

COULD THERE HAVE BEEN ANOTHER WAY?
Troponin Risk Level

First hs-cTnI
6 ng/L  21:32

Second hs-cTnI
7 ng/L  23:59

Risk Level Type One
Low

Risk Level Type Two
High
Risk Heart Failure

Explanation:
Elevated BNP, History of heart failure, Dyspnea or minimal exertion
Dynamic troponin changes less than 20%

Recommendations:
Safe to go home after 2-23 hours:
Vital signs stable, Lungs clear, Renal function stable
Breathing improved, Patient can lie flat
Urine output More than 1 Liter, Atrial fibrillation, rate controlled

Save to EMR
HPI Generator
Printable Media
AI - A FINAL WARNING
AI = Big Eater

- AI/machine learning takes an enormous amount of data to train a deep learning model because of the vast number of parameters that must be estimated.
Garbage In Garbage Out

• Even a perfect model is limited by the quality and magnitude of signal in the dataset from which it is trained.
• Algorithm does not get better than the data.
Who is responsible?

• Although AI-based driverless cars are generally safer than human drivers, a pedestrian death due to a driverless car error caused great alarm.

• Who is responsible for the failure of healthcare management made by AI?
I'm being sued for a missed diagnosis! What do I do now?!

Sorry, buddy, comes with the job.

When handing radiology over to artificial intelligence sounds appealing.
• Identification of novel genotypes or phenotypes of heterogeneous syndromes such as HF.

• Exploration of novel factors in score systems or add hidden risk factors to existing models.

• AI will drive improved patient care because physicians will be able to interpret big data in greater depth than ever before.

• We need to use AI sufficiently to generate hypotheses, perform big data analytics, and optimize AI applications in clinical practice to bring on the era of precision CV medicine.
Will AI replace doctors?

• Probably not.
AI doesn’t want to replace ED docs - The ED is one of the last places where you can really think.

What machine and neural learning should do is make the doctor better.

In fact in the future a doctor with use of AI will make a better doctor than one without.

It is a tool.
Thank you
The Music Of Love
Laziness
Thank You!!!
Big Health Data and Artificial Intelligence: Implications in Heart Failure

Alan S Maisel MD
FACC
Professor of Medicine
Emeritus
University of California, San Diego
Type 1 vs. 2 MI

- Up to 40% of type 2’s sent to cath lab
- $677M = annual cost of complications of cardiac cath
- Type 2’s = 10% of all readmitted patients, or $57M in penalties

Cath complications:
1. Bleeding
2. Stroke
3. Kidney failure
4. Recurrent MI
5. Emergency coronary bypass surgery
6. Pericardial tamponade
7. Heart failure
8. Death
Excellent clinical performance!

94.5% separation power!

<table>
<thead>
<tr>
<th>Scorer</th>
<th>Final ensemble external validation scores +/- standard deviation</th>
</tr>
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<tbody>
<tr>
<td>GINI</td>
<td>0.8916 +/- 0.068757</td>
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<tr>
<td>MCC</td>
<td>0.80753 +/- 0.097029</td>
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<tr>
<td>F0.5</td>
<td>0.95039 +/- 0.021658</td>
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<tr>
<td>F1</td>
<td>0.9533 +/- 0.023513</td>
</tr>
<tr>
<td>F2</td>
<td>0.9777 +/- 0.011838</td>
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<tr>
<td>ACCURACY</td>
<td>0.92857 +/- 0.036008</td>
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<tr>
<td>LOGLOSS</td>
<td>0.27158 +/- 0.040945</td>
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<td>AUCPR</td>
<td>0.98104 +/- 0.012288</td>
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<tr>
<td>AUC</td>
<td>0.9458 +/- 0.034378</td>
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</table>
Let's look at our progress to date.
Discerning between Type 1 & 2 MI

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- 1+ million cardiac catheterizations/year
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5. Coronary bypass surgery
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7. Heart failure
8. Death
94.5% accuracy to discern between Type 1 and 2 MI

Cardiac biomarkers
- Troponin
- BNP
- ST2
- D-dimer