The Future of Cardiac Biomarkers

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Nothing
to declare
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The Sun, The Sea…and CME!

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First, the Good News

ED physicians are...

...94.7% sensitive...

...74% specific...

...in identifying patients who were subsequently diagnosed with ACS within 30 days of ED visit.

Christenson et al. CMAJ 2004;170:1803
What We Have Now

- Myoglobin
- CK-MB
- CTnI
- CTnT
- BNP
- NT-proBNP
- LDH(?)
Emergency Medicine

What We Have Now

- Myoglobin
- CK-MB
- CTnI
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- LDH(?)

All require myocyte necrosis or dysfunction before turning positive.
What We Need Will...

detect myocardial ischemia with or without necrosis

not be elevated if other organs ischemic

rise & fall rapidly after ischemia

perform reliably

be simple to use

have turnaround time <60 min
Upstream biomarkers like...
...proinflammatory cytokines
...cellular adhesion molecules
...acute-phase reactants
...plaque destabilization biomarker
...plaque rupture biomarker
...prenecrosis ischemia biomarker
“A cynic is not merely one who reads bitter lessons from the past, he is one who is prematurely disappointed in the future.”

Sydney J. Harris
1917 – 1986
“Strong Association”

No correlation with...
...sensitivity
...specificity
...accuracy
...usefulness
“Independent Predictor”

- Means if patients matched in all other parameters, **group** with abnormal test results will have more outcome events than **group** with normal test results.
Predictors & Associations

Does not mean:

- “Your test is negative, you can go home now.”
- “Your test is positive, you need to stay and have more studies.”
- **No value** in making diagnostic or therapeutic decisions
Negative Predictive Value

- Probability of no disease among patients with a negative test

\[ \text{NPV} = \frac{\text{TN}}{\text{TN} + \text{FN}} \]

- Denominator is number of patients who test negative

- So if disease prevalence low…
**Negative Predictive Value**

- NPV does **not** tell you test value
- If disease prevalence 5%, coin flip has NPV = 95%
- If disease prevalence 85%, coin flip has PPV = 85%
Positive screening test referred to receive verification of diagnosis by “gold standard”

Example: treadmill stress test
- Cardiologist’s office: sensitivity 70%, specificity 70%
- Family practitioner’s office: sensitivity 40%, specificity 85%
Sanford Guide says: “80% of cat bites get infected”

Do you have a cat??

Dog bite: self-referral because of wound size, rabies worry, etc.

Cat bite: “It’s infected”

Headache in oncologist’s office
"This Test May Be Useful..."

- Consider this an incomplete sentence
- It should say, “This test may or may not be useful.”
Need POEM, Not DOE

Randomize ED Patients with CP

Experimental: New Test

Control: Standard Tests

Outcomes: Morbidity, Mortality, Admissions, Length of Stay, Cost
Order of Battle

Proinflammatory Cytokines → Plaque Destabilization

Plaque Rupture → Acute Phase Reactant

Ischemia → Necrosis
The Future

IMA
PAPP-A
MPO
MMP-9
FFAu
PIGF
sCD40L
Macrophages infiltrate coronary artery plaque causing unstable lesions with thin fibrous cap

Macrophages secrete matrix metalloproteinases (MMPs) and metal-independent myeloperoxidase (MPO)
Plaque Destabilization

- MMPs and MPO degrade collagen layer that prevents atheroma erosion or rupture
- Plaque infiltrated by macrophages has thin fibrous cap vulnerable to erosion or rupture
Shoulder regions of coronary artery lesions particularly vulnerable
- Point of highest shear stress of arterial blood
Matrix Metalloproteinase-9

- Normally protective, limits and stabilizes plaque growth
- Heavy concentration at vulnerable location ("shoulder")
- MMP-9 values related to future cardiovascular death
But MMP-9 levels lowered by…

...renin-angiotensin system
...aspirin
...atorvastatin
...doxycycline

Outcome studies: ongoing
Myeloperoxidase

- Hemoprotein stored in azurophilic granules of PMNs and macrophages
- Released into extracellular fluid and general circulation during inflammatory conditions
Myeloperoxidase

- Makes snot green and phlegm yellow
Myeloperoxidase

- Catalyzes conversion of chloride + H₂O₂ = hypochlorite
- WBC MPO activity significantly associated with presence of CAD
Myeloperoxidase

- Neutrophil activation not induced by ischemia
- So MPO is marker of plaque instability, not myocyte damage
- But...not specific to cardiac disease: present in infectious, inflammatory, infiltrative process
Destabilization: Conclusion

- Won’t be specific: serve more as markers of inflammation
- May not be sensitive: levels lowered by many factors
- Not as accurate as a clinician
- Not ready for prime time
Plaque Rupture

Formation of Platelet Thrombus

Fissure and Rupture of Plaque
Plaque Rupture

- Soluble CD40 ligand
- Placental growth factor
- Pregnancy-associated plasma protein A
Soluble CD40 Ligand

- CD40 ligand rapidly up-regulated in fresh thrombus
- >95% of circulating CD40L derived from platelets
- Associated with increased risk of cardiovascular events in apparently healthy women
Soluble CD40 Ligand

- Chronic elevations possible due to shedding into plasma from unstable atherosclerotic plaque
- Reduced levels from statins, glitazones, glycoprotein IIb/IIIa inhibitors, clopidogrel
Placental Growth Factor

- PIGF stimulates angiogenesis
- Activates Vascular Endothelial Growth Factor (VEGF)
- Angiogenesis improves circulation
Placental Growth Factor

- VEGF plays essential role in both physiologic and pathologic angiogenesis
- PlGF restricted to pathologic conditions
  - Key role in atheroma expansion
  - Upregulated in ischemic myocardium
Placental Growth Factor

- Powerful *independent predictor* of adverse cardiac events in both high-risk ACS and in undifferentiated ED population
- Does not correlate with troponin levels: possible complementary prognostic information?
Placental Growth Factor

- Downside: >5% of patients with negative PlGF experience a cardiac event within 30 days
- CTnT more powerful independent predictor
PAPP-A

- Pregnancy-associated plasma protein A
- Zinc-binding matrix metalloproteinase (MMP)
- Abundantly expressed in eroded and ruptured plaques, lower in stable plaques
PAPP-A

- Release: timing not defined
- Increased circulating levels in hypercholesterolemia and coronary atherosclerosis, even in asymptomatic patients
- *May* serve as marker for total lipid burden
Rupture: Conclusion

- Kinetics still being worked out
- Sensitivity / specificity to be determined
- Not as accurate as a clinician
Pre-Necrosis Ischemia

- Unbound Free Fatty Acids
- Whole Blood Choline and Plasma Choline
- Ischemia-Modified Albumin
Unbound Free Fatty Acids

- Most FFAs bound to albumin
- FFAu = soluble FFA
- Positive correlation between FFAu and cTnI at presentation
- Independent of plaque rupture: not ↑ after cocaine, trauma
WBCHO & PLCHO

- Whole blood choline
- Plasma choline
WBCHO & PLCHO

- Both ↑ rapidly after stimulation of phospholipase D in plaque destabilization / tissue ischemia
- PLD key in destabilizing plaque
- Choline released into plasma, then taken up by RBCs
For Acute Myocardial Infarction:
Sensitivity 40.5%
Specificity 78.7%

For Unstable Angina:
Sensitivity 86.4%
Specificity 86.2%

Danne O et al. Am J Cardiol. 2003;91(9):1060
Ischemia-Modified Albumin

- Albumin’s capacity to bind with cobalt is reduced during myocardial ischemia.
- IMA rises within minutes of ischemia, stays up for 6 to 12 hours, normal within 24 hours.
Ischemia-Modified Albumin

But also found in patients with...

...some cancers
...some infections
...liver disease
...end-stage renal disease
...brain ischemia
Ischemia-Modified Albumin

- Levels inhibited by endogenous lactate production
  - Limits usefulness in DKA, sepsis, renal failure, other causes of increased lactic acid
- Not elevated immediately after marathon run, rise 24 – 48 hours later (latent GI ischemia?)
Ischemia-Modified Albumin

In study with 63% prevalence ACS
Sensitivity: ~80%  PPV: 72%
Specificity: ~45%  NPV: 59%

“IMA, ECG, and cTnI combined identified 95% of...ischemic heart disease.”

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...74% specific...
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“... (studies reach the) interesting and illogical conclusion... that a test... demonstrably less sensitive, less specific and less accurate than clinical practice will somehow improve our diagnostic accuracy.”

Grant Innes – January, 2006
Predicting the Future

We’ll order a ‘panel’ containing...
...inflammatory marker
...platelet aggregation marker
...ischemia marker
...necrosis marker
...hemodynamic marker
...or two
Predicting the Future

…and probably drive the sensitivity up above 99% to “rule out ACS”

…but we’ll be stuck with a HUGE number of false positives which we’ll be required to justify in some manner.
“It is a basic principle of diagnostic testing that adding tests together increases sensitivity, even if the tests have no diagnostic value.”

Is A New Era Dawning??
Conclusions

“A statistically significant association is sufficient to publish a paper, but it doesn’t help make a diagnosis... It may be true that a new era is dawning, but that faint pink glow on the horizon isn’t bright enough to guide us anywhere yet.”

Grant Innes – January, 2006
Thank you for your time and attention