Objectives
- Review markers for cardiovascular risk and 2013 Canadian guidelines for dyslipidemia
- Review markers for cardiac injury with a focus on troponin I and T
- Briefly review markers of cardiac function (BNP and NT-BNP)

Heart Disease
- Lifetime risk of Coronary Heart Disease
  - 49% men
  - 32% women
- Leading cause of death in both groups
- Most risk factors are modifiable
- In Canada 400,000 MI's/yr
- Also 400,000 individuals with heart failure
Heart disease begins long before the heart attack and continues after the management of the acute event.

Markers of Cardiovascular Disease

- Risk Stratification
- Acute Injury (infarction)
- Prognosis
- Treatment Guidance
- Cardiac Function
Cardiac Markers: Risk Assessment

Established:
- Raised LDL Cholesterol (Apo B, small dense LDL) or non-HDL cholesterol
- Decreased HDL Cholesterol
- Presence of Metabolic Syndrome

Secondary markers:
- Inflammatory markers (CRP, interleukins, SAA)
- Procoagulant markers (homocysteine, Lp(a), TPA, Plasminogen AI, fibrinogen)

2013 Canadian Lipid Guidelines

Who to Screen

- Men ≥ 40 years of age, and women ≥ 50 years of age or postmenopausal
- Consider earlier in ethnic groups at increased risk such as South Asians or First Nations individuals
- All patients with any of the following conditions, regardless of age:
  - Current cigarette smoking
  - Diabetes
  - Arterial hypertension
  - Family history of premature CVD
  - Family history of hyperlipidemia
  - Erectile dysfunction
  - Chronic kidney disease
  - Inflammatory disease
  - HIV infection
  - Chronic obstructive pulmonary disease
  - Clinical evidence of atherosclerosis or abdominal atheroma
  - Clinical manifestation of hyperlipidemia
  - Obesity (body mass index ≥ 37)

Modifiable risk factors for CVD

- High cholesterol (LDL)
- High blood pressure
- Diabetes
- Physical inactivity
- Smoking
- Excessive drinking
- Being overweight (difficult challenge!)
Non-modifiable risk factors

- Age
- Gender
- Family history of heart disease

The “Big” problem in NA

INTERNATIONAL DEFINITION OF THE METABOLIC SYNDROME

Central Obesity:
Men > 94 (90) cm, Women > 80 cm plus 2 of the following:
Fasting glucose > 5.6 mmol/L
Low HDL cholesterol: <1.0 mmol/L (M), <1.3 mmol/L (F)
Triglycerides > 1.7 mmol/L
Hypertension: BP >130/85 mm Hg or on medication

*People with the metabolic syndrome are at increased risk of developing diabetes mellitus and cardiovascular disease. Today >60 million N. Americans fit the def’n
The Problem of Abdominal Obesity (visceral fat)

Associated with:
- small dense LDL particles which are more atherogenic
- increased apolipoprotein B
- decreased HDL
- increased triglycerides
- hypertension
- insulin resistance

Lipid Risk Factors

- Total cholesterol / LDL cholesterol / Apo B
  - LDL-C is most important atherogenic particle
  - New guidelines now incorporate non-HDL cholesterol as a risk marker. *Advantage is that it does not require fasting.

How is LDL cholesterol commonly determined in the lab?
Apo B

- Only apoprotein on LDL (1 apo B/particle) but also found on other atherogenic particles, VLDL and IDL
- Most (but not all) studies have shown Apo B to be better as a marker of CHD than LDL-cholesterol. Non-HDL cholesterol shows good correlation with apo B.

HDL Cholesterol (Apo A-1)

- HDL-C consistently found to be a negative risk factor
- Apo A-1 questionable additional benefit over HDL-C and other risk factors

High Sensitivity C-Reactive Protein (hsCRP)

Is It a Useful Marker for Cardiovascular Disease Risk?
hsCRP

- Pentameric protein made in liver
- Function:
  - Opsonizes infectious organisms
  - Activates complement
  - Binds free DNA
  - Acute phase reactant
- Objective marker of inflammation. The progression of atherosclerosis lesions is a chronic inflammatory process.
- Ability to measure CRP at very low concentrations may potentially identify asymptomatic individuals at risk for CAD.
Limitations of CRP

- Not specific for cardiovascular disease risk
- Values >10 mg/L usually suggest active inflammation, trauma, infection, active autoimmune disease. In this case, repeat 2 to 3 weeks later
- Intra-individual day to day variability may be quite wide (Ann Clin Biochem 2002;39:85-8)
- Recent paper (NEJM, 2004; 350: 1387-97) suggests CRP contribution to risk overestimated.

Factors used in Framingham risk assessment for CVD

- Age
- Gender
- Total cholesterol
- HDL cholesterol
- Smoking status
- Systolic BP
- Presence of Diabetes

*Traditional markers account for most CVD risk
### Framingham Scoring: Men

**SUPPLEMENTARY TABLE 4A**

Estimation of 15-year risk of total cardiovascular disease in men (Framingham Heart Study)

<table>
<thead>
<tr>
<th>Points</th>
<th>Risk, %</th>
<th>Points</th>
<th>Risk, %</th>
<th>Points</th>
<th>Risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3 or less</td>
<td>&lt;1</td>
<td>5</td>
<td>3.9</td>
<td>13</td>
<td>15.6</td>
</tr>
<tr>
<td>-2</td>
<td>1.1</td>
<td>6</td>
<td>4.7</td>
<td>14</td>
<td>18.4</td>
</tr>
<tr>
<td>-1</td>
<td>1.4</td>
<td>7</td>
<td>5.6</td>
<td>15</td>
<td>21.6</td>
</tr>
<tr>
<td>0</td>
<td>1.6</td>
<td>8</td>
<td>6.7</td>
<td>16</td>
<td>23.3</td>
</tr>
<tr>
<td>1</td>
<td>1.9</td>
<td>9</td>
<td>7.8</td>
<td>17</td>
<td>28.4</td>
</tr>
<tr>
<td>2</td>
<td>2.3</td>
<td>10</td>
<td>9.4</td>
<td>18+</td>
<td>&gt;30</td>
</tr>
<tr>
<td>3</td>
<td>2.8</td>
<td>11</td>
<td>11.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3.3</td>
<td>12</td>
<td>13.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: Double the point score if individual has family history of premature CVD

### Cardiovascular Disease Risk: Men

**SUPPLEMENTARY TABLE 4B**

Cardiovascular disease risk for men

### Framingham Scoring: Women

**SUPPLEMENTARY TABLE 4A**

Estimation of 15-year risk of total cardiovascular disease in women (Framingham Heart Study)
Cardiovascular Risk: Women

### SUPPLEMENTARY INFORMATION – CONTINUED

### SUPPLEMENTARY TABLE 5B

<table>
<thead>
<tr>
<th>Points</th>
<th>Risk, %</th>
<th>Points</th>
<th>Risk, %</th>
<th>Points</th>
<th>Risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>⩽ 2 or less</td>
<td>10.0</td>
<td>7</td>
<td>3.9</td>
<td>14</td>
<td>11.7</td>
</tr>
<tr>
<td>1</td>
<td>1.2</td>
<td>8</td>
<td>4.5</td>
<td>16</td>
<td>15.9</td>
</tr>
<tr>
<td>1</td>
<td>1.5</td>
<td>9</td>
<td>5.3</td>
<td>17</td>
<td>18.51</td>
</tr>
<tr>
<td>2</td>
<td>1.7</td>
<td>10</td>
<td>6.3</td>
<td>18</td>
<td>21.5</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>11</td>
<td>7.3</td>
<td>19</td>
<td>24.8</td>
</tr>
<tr>
<td>4</td>
<td>2.4</td>
<td>12</td>
<td>8.6</td>
<td>20</td>
<td>27.5</td>
</tr>
<tr>
<td>5</td>
<td>2.8</td>
<td>13</td>
<td>10.0</td>
<td>21+</td>
<td>⩾ 30</td>
</tr>
</tbody>
</table>

---

Risk stratification

---

Treatment Goals 2013

---
Cardiac Markers: Myocardial Infarction

American AMI Facts (BT: before troponin)
- 6 million/year have AMI or UA (Acute coronary syndrome (ACS))
- 700,000 admissions to hospital/year
- 500,000 die of complications of ACS/yr
- 75,000 are misdiagnosed
- 20% of malpractice suits involve AMI
- 40% diagnosed too late for optimal treatment
- 10% inappropriately discharged
- Initial ECG not diagnostic in half of all AMI patients

Causes of Chest Pain
- Acute coronary syndrome (AMI)
- Aortic dissection
- Pericarditis
- Pulmonary embolism
- Pneumothorax
- Pneumonia
- GI problems (acid reflux)
- Musculoskeletal problems

* Chest pain accounts for 10% of all ER visits and 25% of ED admissions to inpatient units
Characteristics of an Ideal Marker for Myocardial Injury

- Be specific for myocardial injury
- Be sensitive to small injuries
- Be rapidly released following injury
- Be long enough lasting in the blood to permit delayed diagnosis

Characteristics cont’d

- Produce blood levels that are proportionate to infarct size
- Permit risk assessment
- Be technically easy to measure
- Inexpensive
- Fast TAT (POCT vs. Central lab), < 60 minutes from order (30 minutes ideal)

Biochemical Markers of Cardiac Injury (historical)

- Creatine Kinase (CK): CKMB
- Lactate dehydrogenase (LD): LD Isoenzymes
- Myoglobin
- Troponin T (TnT)
- Troponin I (Tnl)
Estimated Clinical Sensitivity & Specificity of Cardiac Markers for AMI

<table>
<thead>
<tr>
<th>Marker</th>
<th>Spec</th>
<th>Sens</th>
<th>Sens</th>
<th>Sens</th>
<th>Sens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoglobin</td>
<td>70</td>
<td>95</td>
<td>75</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CK-MB</td>
<td>95</td>
<td>90</td>
<td>95</td>
<td>98</td>
<td>50</td>
</tr>
<tr>
<td>Troponin*</td>
<td>99</td>
<td>75</td>
<td>95</td>
<td>98</td>
<td>98</td>
</tr>
</tbody>
</table>

*Note: Sensitivity on admission now approaching 90% when the lower cut-offs are used with the improved assays.

Myoglobin

- Oxygen-bearing heme protein found in the skeletal muscles and heart.
- Molecular weight 17 kDa. No tissue isoenzymes.
- Early marker of myocardial infarction (~3 h before CK-MB).
- Cleared quickly by renal filtration.
- Non-specific AMI marker. Increased in patients with skeletal muscle disease and chronic renal failure (retention).
Creatine Kinase (CK)

- Function: Cr + ATP <-> CrP + ADP
- MW = 86,000
- Structure: Dimer of 2 subunits (M or B)
- Isoenzymes: MM, MB, BB
- Tissue distribution: Skeletal muscle 99% MM, 1% MB; Heart 80% MM, 20% MB, other tissues (brain) 100% BB
- Time to peak after MI: 18 - 24 h

Causes of Increased CK

- **Myocardial diseases**
  - AMI, heart trauma, myocarditis, after heart surgery
- **Skeletal muscle diseases and injury**
  - Muscular dystrophy, rhabdomyolysis, polymyositis, IM injections, seizures, trauma, vigorous exercise
- **Miscellaneous**
  - Hypothyroidism, malignant hyperthermia, prolonged hypothermia, cerebral injury

Interpretation of CKMB Results

- CK MB determined by immunoassay and the mass amount of this enzyme is reported, not enzyme activity. (RI < 5 ug/L)
- CKMB index then determined:
  - CKMB index = CKMB/total CK X 100
  - Reference interval < 4.0
- *CKMB > 5 ug/L and index > 4 consistent with MI (myocardial damage)
Deficiencies of CKMB

- Poor sensitivity early after infarct
- Poor specificity (elevated with muscle injury)
- Detectable in normal individuals
- Rapidly cleared, may be back to normal in less than 48 hours

Troponin T and I

- Part of the thin filament of muscle
- cTnT and cTnI different cardiac specific proteins (not enzymes) involved in the contractile process of the heart
- Highly sensitive markers and specific markers of cardiac injury
- Originally considered not an early marker, however improved with increased sensitivity assays

Structure of Troponin Complex
Troponin forms in circulation

Sensitivity

- Troponin concentration in muscle tissue is high (~ 13 times higher than CKMB)
- Healthy people have no detectable Troponin (there is always some CKMB detectable). With new high sensitivity assays this is no longer the case!
Sensitivity cont’d

- We now detect a significant number of patients who are:
  - CKMB negative
  - Troponin positive
  And have no other evidence of cardiac injury

Troponin

- Time to detection: 2 - 6 hours
- Persistence in blood: 5 - 10 days
Differentiating Unstable Angina from MI with Troponin

Acute Coronary Syndrome

- No ST Elev
- Trp Neg
- Unstable Angina

- ST Elev
- Trp Pos
- Myocardial Infarction

NSTEMI QWMI

Continuing Issues for Troponin

- Lack of assay standardization
- Precision at decision level variable
- Lack of standardization between POCT and central lab tests
- Correlation between assays varies with time after MI (up to 20 fold variability between assays). This has changed too!
- Variability in decision levels between labs
- False positive results (fibrin, Ab)

Issues Confronting Standardization

- Trp circulates in multiple forms (ternary, binary, or free)
- Trp degraded by proteases from both the N and C terminal ends
- Trp molecule can be oxidized, reduced or phosphorylated changing immunoreactivity

Solution: Manufacturers must standardize reagent antibodies to bind to most well conserved epitopes and use an international ref preparation for calibration
Role for Troponin I or T in Prognosis or Directing Therapy in ACS
1. Typical rise and gradual fall of troponin above the 99th percentile reference limit with clinical evidence of myocardial ischemia and at least 1 of the following:
   a) ischemic symptoms;
   b) pathologic Q waves;
   c) ECG changes indicative of new ischemia
   d) Imaging evidence of loss of myocardium or wall motion abnormality
   e) Identification of thrombus by angio or autopsy

ESC = European Society of Cardiology; ACC = American College of Cardiology

Timing of Blood Collection Following Onset of Chest Pain

- 10 to 15% of admission values for patients with MI are normal. Single determination not adequate to rule out MI
- Recommended sample times: on admission, 3-6 h, 6-9 h, and 12 h essential.
- Options for assessing reinfarction: Remeasure Trp I at time of new event and 3-6 hours later
  *Prefer plasma rather than serum at VGH
Troponin I or T is the Standard for Myocardial Injury

- Increase generally reflects irreversible cell death (97% in cell associated with contractile fibrils).
- Increases are specific for myocardial damage not MI

Non-thrombotic Causes of Elevated TnI and T

- **Demand ischemia**: sepsis, hypotension, hypovolemia, atrial fib, left vent. hypertrophy
- **Myocardial ischemia**: coronary vasospasm, stroke, adrenergic drugs
- **Direct cardiac injury**: trauma, myocyte infiltration, chemotherapy, myocarditis, pericarditis, transplant
- **Myocardial strain**: CHF, pulmonary embolism or hypertension, emphysema, strenuous exercise
- **Chronic renal failure**
New Classification of MI

Type 1: intraluminal thrombus
Type 2: secondary to ischemic imbalance
Type 3: death due to MI before Tn results available
Type 4 and 5: MI related to cardiac operations or procedures

Type 1 versus Type 2 MI

Optimise the early identification of patients with Type 1 AMI.
Troponin and Renal Failure

- 2 yr survival in ESRD patients on dialysis 68%. Major cause of mortality is CV disease
- Trp T elevated in 1/5 to 1/3 depending on cutoff used. Degree of elevation predictive of mortality and likely reflects myocardial injury.
- Detectable Trp I found in up to 10% of renal failure patients. Presence also predictive of future cardiac events.
- Mechanism? Subclinical ischemia, pericarditis, myocarditis or simply impaired clearance of degradation products of troponin

Analytical Goals for Troponin I

- Upper reference interval should be the 99\textsuperscript{th} percentile, not the 97.5 percentile
- Analytical precision should be <10% at this decision level
- Recent study showed many of the common assays did not meet these criteria. 2nd generation assays are now meeting these criteria.

CTNI Functional Sensitivity

- Functional Sensitivity = 0.035 ng/mL
VGH TnI Comments

- TnI < 0.05: TnI result less than the 99th percentile.
- TnI >= 0.05 and < 1.0: TnI elevations below 1.0 ug/L are associated with various conditions that result in myocardial damage. Use clinical judgement to evaluate result.
- TnI >= 1.0: Consistent with myocardial damage including ACS

Risk stratification in ACS by troponin
NACB Guidelines

"Any amount of myocardial damage, as detected by cardiac troponins, implies an impaired clinical outcome for the patient"

Other Uses of Troponin

- Determination of size of infarct
- Determination of success of reperfusion
Different Assays Different Cut-offs

<table>
<thead>
<tr>
<th>Assay</th>
<th>LLD</th>
<th>99%</th>
<th>10%cv</th>
<th>ROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ab Ar</td>
<td>0.009</td>
<td>0.012</td>
<td>0.032</td>
<td>0.3</td>
</tr>
<tr>
<td>Ab Ax</td>
<td>0.02</td>
<td>0.04</td>
<td>0.16</td>
<td>0.4</td>
</tr>
<tr>
<td>iSTAT</td>
<td>0.02</td>
<td>0.08</td>
<td>0.1</td>
<td>NA</td>
</tr>
<tr>
<td>Cent</td>
<td>0.02</td>
<td>0.1</td>
<td>0.35</td>
<td>1.0</td>
</tr>
<tr>
<td>BC Ac</td>
<td>0.01</td>
<td>0.04</td>
<td>0.06</td>
<td>0.5</td>
</tr>
<tr>
<td>DB Roi</td>
<td>0.04</td>
<td>0.07</td>
<td>0.14</td>
<td>0.6-1.5</td>
</tr>
<tr>
<td>DPC I</td>
<td>0.1</td>
<td>0.2</td>
<td>0.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Vitros</td>
<td>0.02</td>
<td>0.08</td>
<td>0.12</td>
<td>0.4</td>
</tr>
<tr>
<td>RLeacs</td>
<td>0.01</td>
<td>0.01</td>
<td>0.03</td>
<td>0.1</td>
</tr>
<tr>
<td>R POC</td>
<td>0.05</td>
<td>0.05</td>
<td>NA</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Summary: Troponin and ACS

- Highly specific and sensitive for myocardial injury
- Highly predictive of adverse outcomes
- Useful for directing triaging of patients and appropriate therapeutic management

Now we have HS Troponin I and T. What to do!

Short- and Long-Term Biological Variation in Cardiac Troponin I
Measured with a High-Sensitivity Assay
Implications for Clinical Practice
Alan H.B. Wu,1* Quynh Anh Lu,2 John Todd,2 Joachim Moecks,3 and Frank Wians4

Low index of individuality (II) suggests that low level changes within an individual for TnI more important than comparison to a reference interval. Values below the 99th percentile may also be useful.
Balancing the ED Assessment...

- Missed MI vs. Over-investigation
- Hospital overcrowding vs. litigation
- Increased M&M for both
  - missed MI
  - concerned to an overcrowded ED

Recommendations for timing

- AHA guidelines:
  - 6-hr after symptom onset.

- ESC guidelines:
  - 3-hr after presentation with hs troponin

- 3rd Universal Definition of MI:
  - 3-hr after first assessment. (No comment on hs-assays)

3. New opportunities to improve clinical care with hs troponin assay use

  a) Diagnosis of UAP
  b) Cessation of investigations
  c) Sex difference cut-off values
  d) Subclinical disease
Recommendations:

- Clear, consistent reporting of results
  - ng/l rather than µg/l (9ng/l not 0.009µg/L)
  - Assay-specific cut-off values
  - Report which assay used

*With hs TnI the 99th percentile will be much lower than with the present assays and we will detect much smaller changes
Definition of HS Troponin

1. Ability to yield a valid measurement reliably in at least 50% of healthy reference population (ideally >95%)
2. The total imprecision at the 99%ile should be < 10%
3. At this point in time we are using sensitive TnI, not hs TnI. Several companies are developing these assays, however not yet released.

What new information will hsTnI or T test give us? Problems?

- Earlier detection of MI. Now we wait at least 3 – 6 hours to confirm negative events. With new assays may be able to discharge within 1 – 2 hours after ER visit if negative.
- Other consequence will be many more positive tests above the 99th %ile. Many of which will not show rise and fall of values.
- Early studies show these patients are at risk for future CV events. How to treat?
Congestive Heart Failure

A Role for BNP or NT proBNP?

Congestive heart failure (CHF)

A condition where the heart is unable to supply the body with enough oxygenated blood to accommodate the body's needs during exercise and at rest. As a result of decreased heart function, body fluids may build up in the lungs and limbs.

Etiology of CHF

- Ischemia: 69%
- Hypertension: 7%
- Idiopathic: 13%
- Other: 11%

SOLVD Registry (N=6,063)
Clinical symptoms of CHF

• Shortness of breath
• Orthopnea (difficulty breathing when lying down)
• Peripheral edema (swelling of ankles, legs, and arms)
• Pulmonary edema
• General fatigue and weakness

Diagnosis: Clinical findings plus echocardiography to determine ejection fraction (Normal 50 – 70%)

The Heart Failure Epidemic (NA data)

- 400,000 to 700,000 new cases/year
- 10 % prevalence in people >65
- ½ are asymptomatic
- 11 million office visits/year
- 3.5 million hospital admissions/year
- 250,000 deaths/year
- Annual cost +$30 billion
Causes of Congestive Heart Failure

- Atherosclerotic Ischemic Heart Disease
  - Arterial blockage and ischemia induced
  - Myocardial damage secondary to AMI
  - Ischemic cardiomyopathy
- Hypertension – results in left sided hypertrophy
- Pulmonary diseases such as Chronic obstructive pulmonary disease (COPD) and pneumonia
- Heart Valve problems (e.g. rheumatic, calcification, mitral valve regurgitation)
- Cardiomyopathy, and arrhythmias
- Anemia or other hematological disorders that require coronary compensation

New York Heart Association (NYHA) Classification System

- Healthy
- Class I: Asymptomatic
- Class II: Decreased Activity, SOB
- Class III: Decreased Activity, SOB
- Class IV: SOB at rest

BNP and CHF

Natriuretic Peptides:
Biochemistry and Physiology
Natriuretic Peptides

- There are 3 types: A (atrial), B (brain), and C - types
- The B-type now known to be primarily from ventricular myocytes
- ANP: 28 aa peptide
- BNP: 32 aa peptide
- CNP: 22 aa peptide (brain and CNS)

BNP: Physiology

- Released from cardiomyocytes, primarily ventricles, in response to stretch, volume overload, increased CVP, or LVD.
- BNP interacts with receptors on cells in blood vessels, adrenal, and kidney
- It is a potent diuretic, natriuretic, and vasorelaxant peptide
- It lowers angiotensin II, aldosterone, and endothelin-1
- It increases GFR and sodium excretion
Pharmacologic Actions of BNP

- **Hemodynamic**
  - balanced vasodilation
  - venous tone
  - arterial tone
- **Neurohumoral**
  - renin/aldosterone release
- **Renal**
  - diuresis
  - natriuresis

Synthesis & Degradation of BNP and NTproBNP

- Intracellular cleavage
  - BNP (physiologically active)
  - NT-proBNP (physiologically inactive)
- Plasma Clearance
  - T1/2: 1-2 hrs
  - Renal Filtration
- Tissue Neutral Endopeptidases
- BNP Receptors on brain, vasculature, adrenals, kidney (NPR A, B, C)

Reference Range for BNP

- Burnett et al. Unpublished data.
The “Breathing Not Proper” study methods

- 1586 patients presenting to the ED with shortness of breath
- Data recorded: history, physical exam, lab tests
- Initial assessment by ED physicians
- BNP measured
- Followup assessment: 2 cardiologists with access to all tests (echos), hospital course, response to treatment, etc.

Clinically Validated Algorithms are Being Used in Clinical Practice

BNP/NTproBNP Uses From Clinical Studies

- Correlation with other CHF Criteria
- NYHA Classification
- Echocardiography
- Diagnosis of CHF in ED patients
- Prognostic potential of BNP
- Screening
- Monitoring CHF therapy
1. Hypertrophy & Dilatation

- E.D.V

2. Sympathetic activity:

- H.R.
- V.C

Angiotensine
Aldosterone

Positive Inotropics

Diuretics

ACE inhibitors

vasodilators

Treatment of heart failure

Evolving Research Areas:
Prognosis and Prediction of Adverse Outcome in Patients with Heart Failure and Acute Coronary Syndrome

BNP in ACS

- An elevated plasma concentration of BNP (>80 pg/ml) at presentation in patients with UA and NSTEMI predicts higher short- and long-term mortality as well as new-onset CHF.
- BNP adds incremental information to cTnI for predicting death and recurrent ischemic events.
- BNP may be used for risk assessment and triaging patients with suspected ACS.

- BNP

- N.B. & water retention

- Pre-load

- After-load
BNP and Diagnosis of Heart Failure

- Diagnosis of HF difficult
- Non-specific symptoms: dyspnea, fatigue, ankle swelling
- <40% of suspected heart failure confirmed by expensive investigations.
- Grade A, level 1 evidence recommended by Canadian Cardiologists for use of BNP as test to aid in differentiation of cause of dyspnea.
  *not a stand alone test. False positive results possible

BNP and Heart Failure (cont.)

- BNP has been shown to be more accurate than clinical assessment and LVEF.
- Breathing Not Properly Multinational Study looked at 1586 ER patients with dyspnea. At decision level of 100 pg/mL diagnostic accuracy 83%. NPV at 50 pg/mL was 96%.
- Basel study (NEJM, Feb. 2004) showed BNP availability improved eval., treatment, time to discharge, and cost in ER patients
- <100 pg/mL CHF unlikely, >400 CHF likely

Possible Applications of BNP

- Recognition of cardiomyopathy
- Screening for LV dysfunction
- Screening for mild heart failure
- Identification of LV hypertrophy secondary to hypertension
- Assess severity of CHF
- Prognosis after MI
- Predict mortality in elderly
- Monitoring treatment for CHF
- Risk assessment in ACS
Problems with Interpretation of BNP
- Slight increases not specific: MI, LV hypertrophy, cardiomyopathy, renal failure, COPD, essential hypertension, pulmonary embolism, hyperthyroidism, cirrhosis with ascites, Cushing’s, Conn’s
- Levels affected by medication: ACE inhibitors, valsartan, diuretics and nitrates decrease BNP; beta blockers may increase BNP
- Test has excellent NPV but poor specificity at moderate increased levels

BNP and Risk of CVD
- Wang et al NEJM Feb. 12, 2004
- Followed >3000 pts without HF for avg of 5 years. Measured BNP and looked at risk of death, CV events, HF, atrial fib, stroke, TIA, and CHD
- BNP above 80%ile (20 pg/mL) risks were 1.62 for death, 1.76 for CV event, 1.91 for atrial fib, 1.99 for stroke or TIA, 3.07 for HF

Assays for BNP
- Biosite point of care test for BNP
- NT proBNP (Roche, Dade Behring)
- BNP (Siemens, Abbott, Beckman)
  - BNP (physiologically active form) half life 20 min. in vivo. 8 hour stability at room temp in blood.
  - NT proBNP (inactive co-secreted fragment) half life is 120 min. Stable for 72 hours at room temp. More affected by renal failure
- * Recent revelation about BNP. Not just measuring the bioactive molecule!
Class I
BNP or NT-proBNP testing can be used in the acute setting to rule out or to confirm the diagnosis of heart failure among patients presenting with ambiguous signs and symptoms. (Level of Evidence: A)

ROC CURVE ANALYSIS

PRIDE Study
BNP or NT BNP has become a standard test offered by the laboratory. It will be used for applications other than those suggested by the BC guidelines. BNP vs NT pro-BNP?

Current and Future Cardiovascular Biomarkers

- Plaque: LDL, HDL, CRP, IL-6, Priningen, TMF
- Unstable Plaque: HBP, HPO, ICAM, VCAM
- Plaque: Rasch, sCD62E, PAP, PAI-1, PLX, SMILE, D-dimer
- Tumor Necrosis: FFA, Cholin, CKMB, Myoglobin
- LV Remodeling: BNP, NT-ProBNP, MMP