Chronic Heart Failure: Pathophysiology and Treatment in a nutshell and Natriuretic peptides in Heart Disease
Heart Failure

- Final common pathway for many cardiovascular diseases whose natural history results in symptomatic or asymptomatic left ventricular dysfunction
- Cardinal manifestations of heart failure include dyspnea, fatigue and fluid retention
- Risk of death is 5-10% annually in patients with mild symptoms and increases to as high as 30-40% annually in patients with advanced disease
Main causes

- Coronary artery disease
- Hypertension
- Valvular heart disease
- Cardiomyopathy
- Cor pulmonale
New classification of heart failure

- **Stage A**: Asymptomatic with no heart damage but have risk factors for heart failure
- **Stage B**: Asymptomatic but have signs of structural heart damage
- **Stage C**: Have symptoms and heart damage
- **Stage D**: Endstage disease

ACC/AHA guidelines, 2001
Types of heart failure

- Diastolic dysfunction or diastolic heart failure
- Systolic dysfunction or systolic heart failure

Inability of Heart to Pump enough Blood
- Systolic: Large dilated heart with low EF
- Diastolic: Limited by filling of heart
Factors aggravating heart failure

- Myocardial ischemia or infarct
- Dietary sodium excess
- Excess fluid intake
- Medication noncompliance
- Arrhythmias
- Intercurrent illness (e.g., infection)
- Conditions associated with increased metabolic demand (e.g., pregnancy, thyrotoxicosis)
- Administration of drug with negative inotropic properties or fluid retaining properties (e.g., NSAIDs, corticosteroids)
- Alcohol
NYHA Classification of heart failure

- Class I: No limitation of physical activity
- Class II: Slight limitation of physical activity
- Class III: Marked limitation of physical activity
- Class IV: Unable to carry out physical activity without discomfort
Compensatory changes in heart failure

- Activation of SNS
- Activation of RAS
- Increased heart rate
- Release of ADH
- Release of atrial natriuretic peptide
- Chamber enlargement
- Myocardial hypertrophy
Effects of SNS Activation in Heart Failure

- Dysfunction/death of cardiac myocytes
- Provokes myocardial ischemia
- Provokes arrhythmias
- Impairs cardiac performance

These effects are mediated via stimulation of $\beta$ and $\alpha_1$ receptors

*Am J Hypertens 1998; 11: 23S-37S*
Relation between plasma noradrenaline and mortality in patients with heart failure

Cumulative mortality (%)

Overall
p<0.0001

Noradrenaline > 900 pg/ml

Noradrenaline > 600 pg/ml and <900 pg/ml

Noradrenaline <600 pg/ml

Months

NEJM 1984; 311: 819-823
Receptor densities in human left ventricular myocardium

Scand Cardiovasc J 1998; Suppl 47:45-55
The role of angiotensin II in the progression of heart failure

Coronary artery disease

Cardiac overload

Left ventricular dysfunction

Cardiomyopathy

Arterial blood pressure

Angiotensin II

Peripheral organ blood flow

Skeletal muscle blood flow

Renal blood flow

Exercise intolerance

Oedema

Renin release

Aldosterone release

Na+ and water retention

Inotropy and hypertrophy of vascular and cardiac cells

Cardiac remodelling

Left ventricular dilation & hypertrophy

Pump failure
Approach to the Patient with Heart Failure

Assessment of LV function (echocardiogram, radionuclide ventriculogram)

EF < 40%

Assessment of volume status

Signs and symptoms of fluid retention

Diuretic (titrate to euvolemic state)

No signs and symptoms of fluid retention

ACE Inhibitor

β-blocker

Digoxin
Goals of treatment

- To improve symptoms and quality of life
- To decrease likelihood of disease progression
- To reduce the risk of death and need for hospitalisation
## Summary of drug treatment for CHF

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic LV dysfunction</th>
<th>Mild to moderate CHF</th>
<th>Moderate to severe CHF</th>
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<tbody>
<tr>
<td>ACE inhibitor</td>
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<tr>
<td>Beta blocker</td>
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<td>Digoxin</td>
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<td>Beta blocker</td>
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<td></td>
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<tr>
<td>Spironolactone</td>
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</tbody>
</table>
COPERNICUS: Effect on Mortality

22nd Congress of European Society of Cardiology, August 2000

Mortality (\%)  
- Carvedilol (n=1156): 11.4\%  
- Placebo (n=1133): 18.5\%  

35\% decrease
Carvedilol in Heart Failure

- Effective receptor-blockade approach to heart failure
- Negative inotropic effect counteracted by vasodilation
- Provides anti-proliferative, anti-arrhythmic activity and inhibition of apoptosis
- Prevents renin secretion

Dosage guidelines for Carvedilol in heart failure

Patient selection
- Stable on background medications (diuretics, digoxin and/or ACE inhibitors)
- Not in a fluid-overload state
- Not hypotensive

Before dose increase
Evaluate for
- Worsening heart failure
- Vasodilation
- Bradycardia

After each new dose initiation
- Observe for signs of dizziness or light headedness for one hour

3.125 mg bid

2 weeks

Doubled every 2 weeks

Max dose 25 mg bid (<85 kg); 50 mg bid (>85 kg)
Management of Complications

Transient worsening of heart failure (e.g. increasing dyspnea, decreasing exercise capacity)
- Increase dose of diuretic and/or ACE inhibitor
- If necessary, reduce carvedilol dose and/or prolong titration interval
- Search for other possible causes (e.g. thyroid malfunction, infection, non-compliant drug intake, excessive liquid intake, etc.)

Vasodilatory Symptoms (dizziness, light headedness, symptomatic hypotension)
- Decrease diuretic dose and, if necessary, ACE inhibitor dose
- If the cessation of both is not successful, reduce carvedilol dose and/or prolong titration interval
Bradycardia (Pulse rate below 55 beats/min)

- Check and eventually reduce digitalis dose
- If necessary, reduce carvedilol dose and/or prolong titration interval
- Withdraw carvedilol only in the event that hemodynamics are affected

Symptoms of Bronchial obstruction

- Search for other possible causes (e.g., concurrent infection, subacute pulmonary edema)
- Reduce dose of, or withdraw, carvedilol only after possible causes for symptoms have been ruled out
Asymptomatic Patients

**Enalapril** (SOLVD Prevention Trial)

Patients with EF <35%
↓ HF progression, ↓ hospitalization

**Captopril** (SAVE, GISSI-3, ISIS-4)

Post MI patients with EF <40%
↓ overall mortality, ↓ re-infarction
↓ hospitalization, ↓ HF progression
Symptomatic Patients

Hydralazine + Isosorbide dinitrate

VHeFT-I: ↓ mortality, improved functional class as compared with use of digoxin and diuretics

VHeFT-II: proved less effective than enalapril
AIRE Study demonstrated efficacy of ramipril on mortality and morbidity in CHF post-MI NYHA class I-III patients

- 2006 patients enrolled in a double-blind, randomized, placebo-controlled study
- 27% reduction in the risk of death
- 23% decrease in progression to severe / resistant heart failure

Lancet 1993; 342:821-828
ACE Inhibitors: physiologic benefits

Arteriovenous Vasodilatation

- \( \downarrow \) pulmonary arterial diastolic pressure
- \( \downarrow \) pulmonary capillary wedge pressure
- \( \downarrow \) left ventricular end-diastolic pressure
- \( \downarrow \) systemic vascular resistance
- \( \downarrow \) systemic blood pressure
- \( \downarrow \) maximal oxygen uptake (MVO\(_2\))
ACE Inhibitors: physiologic benefits

- ↑ LV function and cardiac output
- ↑ renal, coronary, cerebral blood flow
- No change in heart rate or myocardial contractility
- no neurohormonal activation
- resultant diuresis and natriuresis
ACE Inhibitors: clinical benefits

- Increases exercise capacity
- Improves functional class
- Attenuation of LV remodeling post MI
- Decrease in the progression of chronic HF
- Decreased hospitalization
- Enhanced quality of life
- Improved survival
Contraindications

- Renal artery stenosis
- Renal insufficiency (relative)
- Hyperkalemia
- Arterial hypotension
- Cough
- Angioedema

Alternatives: Hydralazine + ISDN, ARB
Guidelines to ACE Inhibitor Therapy

- All patients with symptomatic heart failure and those in functional class I with significantly reduced left ventricular function should be treated with an ACE inhibitor, unless contraindicated or not tolerated.

- ACE inhibitors should be continued indefinitely.

- It is important to titrate to the dosage regimen used in the clinical trials ... in the absence of symptoms or adverse effects on end-organ perfusion.

- In very severe heart failure, hydralazine and nitrates added to ACE inhibitor therapy can further improve cardiac output.
Diuretics

- Indicated in patients with symptoms of heart failure who have evidence of fluid retention
- Enhance response to other drugs in heart failure such as beta-blockers and ACE inhibitors
- Therapy initiated with low doses followed by increments in dosage until urine output increases and weight decreases by 0.5-1kg daily
Effect of treatment and some spontaneous recovery on cardiac and vascular function curve

Guyton AC. Textbook of Medical Physiology, 5th Ed. 1976 p343
**Digoxin**

- Enhances LV function, normalizes baroreceptor-mediated reflexes and increases cardiac output at rest and exercise.
- Recommended to improve clinical status of patients with heart failure due to LV dysfunction and should be used in conjunction with diuretics, ACE inhibitors and beta-blockers.
- Also recommended in patients with heart failure with AF.
- Digoxin initiated and maintained at a dose of 0.25 mg daily.
- Adverse effects include cardiac arrhythmias, GI symptoms and neurological complaints (eg. visual disturbances, confusion).
Anemia and Mortality in Heart Failure Patients
A Systematic Review and Meta-Analysis

Hessel F. Groenveld, MD,* James L. Januzzi, MD, FACC,† Kevin Damman, MD,* Jan van Wijngaarden, MD, PHD,‡ Hans L. Hillege, MD, PHD,* Dirk J. van Veldhuisen, MD, PHD, FACC,* Peter van der Meer, MD, PHD†

Groningen and Deventer, the Netherlands; and Boston, Massachusetts

J Am Coll Cardiol 2008;52:818–27
Results

Anemia was defined by criteria used in the original articles. Of the 153,180 CHF patients, 37.2% were anemic.

After a minimal follow-up of 6 months, 46.8% of anemic patients died compared with 29.5% of nonanemic patients. Crude mortality risk of anemia was odds ratio 1.96 (95% confidence interval: 1.74 to 2.21, \( p<0.001 \)).

Lower baseline hemoglobin values were associated with increased crude mortality rates (\( r=-0.396, \ p=0.025 \)). Adjusted hazard ratios showed an increased adjusted risk for anemia (hazard ratio 1.46 [95% confidence interval: 1.26 to 1.69, \( p<0.001 \)]). Subgroup analysis showed no significant difference between mortality risk of anemia in diastolic or systolic CHF.
Methods

A systematic literature search in MEDLINE (through November 2007) for English language articles was performed. In addition, a manual search was performed. We included cohort studies and retrospective secondary analyses of randomized controlled trials whose primary objective was to analyze the association between anemia and mortality in CHF. Of a total of 1,327 initial studies, we included 34 studies, comprising 153,180 patients.

Information on study design, patient characteristics, outcome, and potential confounders were extracted.
Conclusions

Anemia is associated with an increased risk of mortality in both systolic and diastolic CHF. Anemia should, therefore, be considered as a useful prognosticator, and therapeutic strategies aimed to increase hemoglobin levels in CHF should be investigated.

(J Am Coll Cardiol 2008;52:818–27)
<table>
<thead>
<tr>
<th>Definition of Anemia</th>
<th>Author (Ref. #)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>Elabbassi et al. (8), Maraldi et al. (11), De Silva et al. (42), Go et al. (3), Komajda et al. (10), Formiga et al. (18), Hebert et al. (25), O'Meara et al. (36), Felker et al. (13), Ralli et al. (16), Grigorian Shamagian et al. (14), Rosolova et al. (35), Gardner et al. (19), Ezekowitz et al. (24), van der Meer et al. (30), Kerzner et al. (40), Mozaffarian et al. (37), Schou et al. (17)</td>
</tr>
<tr>
<td>Hb &lt;11.5 g/dl</td>
<td>Kalra et al. (26)</td>
</tr>
<tr>
<td>Hb &lt;12.0 g/dl</td>
<td>Varadarajan et al. (6), Anand et al. (1), Szachniewicz et al. (33), Tanner et al. (32)</td>
</tr>
<tr>
<td>Hb &lt;12.3 g/dl</td>
<td>Horwich et al. (9)</td>
</tr>
<tr>
<td>Hb &lt;13.0 g/dl</td>
<td>Sharma et al. (34)</td>
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<tr>
<td>Hb &lt;11.0 g/dl in women and Hb &lt;12.0 g/dl in men</td>
<td>Maggioni et al. (Val-HeFT) (5), Maggioni et al. (IN-CHF) (5)</td>
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<tr>
<td>Hb &lt;11.5 g/dl in women and &lt;13.0 g/dl in men</td>
<td>Berry et al. (7), Newton and Squire (15)</td>
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<tr>
<td>Ht &lt;35%</td>
<td>Al-Ahmad et al. (12)</td>
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<tr>
<td>Ht ≤37%</td>
<td>Kosiborod et al. 2003 (39), McClellan et al. (38)</td>
</tr>
<tr>
<td>Ht &lt;37%</td>
<td>Terrovitis et al. (31)</td>
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<tr>
<td>Ht &lt;37% in women and &lt;40% in men</td>
<td>Kosiborod et al. 2005 (4)</td>
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<tr>
<td></td>
<td>Definitions of Systolic and Diastolic HF Used in the Original Articles</td>
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<td>----------------</td>
<td>----------------------------------------------------------------------------</td>
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<tr>
<td><strong>Systolic CHF</strong></td>
<td>Mozaffarian et al. (37), Anand et al. (1)</td>
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<td></td>
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<td>Grigorian Shamagian et al. (14)</td>
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</table>
Figure 4: Relationship Between Baseline Hemoglobin and Annual Mortality

$r = -0.396, P = 0.025$
Findings from intervention studies. Considering the increased mortality risk caused by anemia, in heart failure as well as renal failure, trials have been designed in which patients receive erythropoiesis-stimulating proteins (ESPs) to increase Hb levels. The first intervention study to address the efficacy of EPO in CHF patients was performed by Silverberg et al. in 32 patients. Correction of anemia with EPO and intravenous iron led to a significant increase in left ventricular ejection fraction and decrease in NYHA functional class, which was reflected by almost 90% reduction in the number of hospitalizations. A similar study showed that EPO treatment significantly increased peak oxygen consumption and exercise duration in patients with moderate-to-severe CHF.

Recently, 2 substantially larger multicenter phase II studies evaluated the effects of darbepoetin (a long-acting ESP) on surrogate cardiovascular end points. Treatment with darbepoetin was safe and effectively raised Hb. Moreover, it significantly improved clinical status; however, no significant improvement in exercise tolerance could be observed.
However, recently several studies showed a potentially harmful effect of ESP treatment in patients with kidney disease and malignancies. A meta-analysis in patients with cancer-associated anemia showed an increased risk in venous thromboembolism and mortality associated with recombinant EPO and darbepoetin administration.

Furthermore, concerns about the cardiovascular safety of ESP in patients with kidney disease have been raised. Two separate studies showed that patients targeted to a higher Hb level had an increased incidence of cardiovascular events. However, in these studies, no placebo groups were included. These studies were all performed in patients with severe renal failure, and only a minority of patients suffered from heart failure. Consequently, the results of the studies mentioned in the preceding text cannot be extrapolated to the CHF population.
Conclusions

Anemia is present in one-third of the CHF population and is an independent risk prognosticator for mortality in subjects so affected, irrespective of a systolic versus diastolic etiology of CHF. Further research is needed to assess the effect of correcting anemia in CHF patients.
Natriuretic Peptides: The Heart as a Secretory Organ

- Atrial stretch receptors link blood volume to renal function
- Distension of a balloon catheter in atria of dogs resulted in diuresis
  
  Henry et al (1956)

- Secretory granules discovered in the atria
  
  Kisch (1956)

- BNP was characterized by amino acid sequence and DNA clones
  
  Jamieson and Palade (1964)
Enzymatic Cleaving of proBNP

proBNP
(aa1 - aa108)

NT-proBNP
(aa1 - aa76)

BNP
(aa77 - aa108)
Physiology of receptors and elimination of BNP

Natriuretic Peptide A Receptor

Neutral endopeptidase

BNP

cGMP
Physiologic effects of BNP

Venous, arterial and coronary vasodilatation

HEMODYNAMIC

CARDIAC INDEX

Preload
Afterload
PCWP
Dyspnoea

CARDIAC

Lusitropic effect
No increase in HR
Not proarrhythmic

SYMPATHETIC AND NEUROHORMONAL SYSTEMS

NATRIURESIS DIURESIS

Fluid volume
Preload
Diuretic usage

RENAL

Aldosterone
Endothelin
Norepinephrine

Fluid volume
Preload
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SYMPATHETIC AND NEUROHORMONAL SYSTEMS

NATRIURESIS DIURESIS

Fluid volume
Preload
Diuretic usage

RENAL

Aldosterone
Endothelin
Norepinephrine
Introduction

The heart is an extremely efficient and resilient pump, but is also an important endocrine organ that functions together with other physiological systems to control fluid volume.

The natriuretic peptides are natural antagonists for the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS).

BNP Consensus Panel 2004. Congestive Heart Failure 2004; 10(5)
Physiologic purpose of BNP

The main physiological function of the natriuretic peptides is homeostasis and protection of the cardiovascular and other systems from the effects of volume overload.

BNP Consensus Panel 2004. Congestive Heart Failure 2004; 10(5)
BNP Elevations- not only with left HF

Right sided heart failure

- Cor pulmonale: 200-500 pg/mL
- Primary pulmonary hypertension: 200-500 pg/mL
- Acute pulmonary embolism: 150-500 pg/mL

Non heart failure elevations

- Acute coronary syndromes: 40 - 400 pg/mL
- Acute myocardial infarction: 40 - >1300 pg/mL
- End-stage renal disease: 80 - >1300 pg/mL
BNP is a *specific marker* of cardiac disease. Its level is augmented in any condition involving myocardial stress.

It does not point to the specific cause of heart strain.
BNP or NT-proBNP level is augmented in any condition involving myocardial stress.

- Contusion
- Cardiac infarction
- Pulmonary embolism
- Fluid overload
- Cor Pulmonale
- Cardiac ischemia
- Pressure overload
- Toxins
- CHF
- CHF or NT-proBNP level is augmented in any condition involving myocardial stress.
Elevated levels of BNP and NT-proBNP in heart failure: A diagnostic opportunity

The BNP and NT-proBNP are established assays used to diagnose and rule out HF in the emergency room.

Their negative predictive value is > 95%, and the assays are incorporated in diagnostic algorithms.
BNP level increases following volume or pressure load on the myocardium or a portion of it regardless of cause.

BNP is the cardiac stress hormone and a specific marker of cardiac disease.

It does not point to the specific cause of heart strain.
Elevated levels of BNP and NT-proBNP in heart failure

A diagnostic opportunity
Chronic heart failure: magnitude of the problem
Diastolic heart failure: Elevated Natriuretic peptide

The left ventricle is markedly thickened in this patient with severe hypertension that was untreated for years.

The myocardial fibers have undergone hypertrophy.
Accuracy of BNP in Detection of Left Ventricular Systolic Dysfunction

<table>
<thead>
<tr>
<th>Group</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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<tbody>
<tr>
<td>Participants aged 25 - 74</td>
<td>77</td>
<td>87</td>
<td>16</td>
<td>97.5</td>
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<td>All study participants</td>
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<tr>
<td>Participants w/ Ischemic</td>
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<td>76</td>
<td>30</td>
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</table>

NPV = \( \frac{\text{TN}}{\text{TN} + \text{FN}} \)

BNP Concentration for the degree of CHF Severity

Mild (n=27): 186 ± 22 pg/mL
Moderate (n=34): 791 ± 165 pg/mL
Severe (n=36): 2013 ± 266 pg/mL

Relationship of BNP and NYHA Classification

- **Class I**: BNP = 167.5 pg/mL
- **Class II**: BNP = 396.5 pg/mL
- **Class III**: BNP = 678.6 pg/mL
- **Class IV**: BNP = 977.7 pg/mL

Triage® BNP package insert. Data on File at Biosite Diagnostics Inc.
Baseline BNP and Mortality in HF: Val-HeFT Study

Survival vs Month

Q1 <41
Q2 41-97
Q3 97-238
Q4 >238

RR 95% CI
1.0
1.47 (1.15-1.89)
2.27 (1.80-2.86)
3.95 (3.18-4.92)

P<0.0001

Heart Failure Diagnostic Algorithm

Patient with dyspnea or other CHF signs/symptoms

- History
- Physical Exam
- ECG

Diagnostic for CHF

CHF Management (echocardiography, if not done previously)

Non-Diagnostic

BNP Blood Test

Positive

CHF Management (echocardiography, if not done previously)

Negative

Evaluate for non-CHF etiologies (echocardiography usually not indicated)

BNP Assay May Also Help Guide Rx
Patient presenting with dyspnea

Physical examination, chest x-ray, ECG, BNP level

- BNP <100 pg/mL: CHF very unlikely (2%)
- BNP 100-400 pg/mL: Baseline LV dysfunction, underlying cor pulmonale or acute pulmonary embolism?
  - Yes: Possible exacerbation of CHF (25%)
  - No: CHF likely (75%)
- BNP > 400 pg/mL: CHF very likely (95%)

מחלקת האינטגרת הקידוקליוגרפי בישראל

הפפטיד הגרעיניים הודוריים (Brain-type Natriuretic Peptide): שימושם אפשרים ברפואת הלב

שם המודל
מכונת הלב, מכונת רפואה חלל חיצונית עד הפנים פנסית

דב פרימקר
מכונת הלב, מכונת רפואה עלית חימום שיבא

הקדמה

הפפטידי הגרעיניים הודוריים הם הרבמטונים המפורסמים 입יהتجار商报 על כל מפרטים עלéfono של חלב משתייה, אואת את כלلكביש הלוברוניה את מחצית והכחולכיים וה הקרובים למות分彩ים

พอינו אתיליגני. בשער האחורי והחמרפוסומ, לון, מחקר זה בדיך הודמים ב.setStatus hakkליים והארבות

של הפפטידי הגרעיניים הודוריים. ביניהן עבידות זה באטfiltrולוגית אחר אפשריהות השמיים של הרפואת בויהר
BNP for EValuation in the Emergency Room (BNP4EVER): Assessing the acutely dyspneic patient in the emergency room

Dr. Shmuel Meyel, Dr. Avi Shotton - Medical Center, Dr. Gilad Ashcar,
Dr. Felix Feinstein, Dr. Morrieitah Medvedovsky - Malra, Dr.
Gborah Rostock - Medical Department
Aim of study

To evaluate the effect of the NT-proBNP test performed in central lab on admission rate of patients presenting to the ED with dyspnea, and on the accuracy of diagnosis of AHF in the patients admitted to medical departments.

In addition, we intended to assess the impact of correct diagnosis on mortality and event-free survival following index admission.
BNP4EVER Study design

n = 246 visits

רמנזיה

נבדקים בחמר מיון בשל קוצר נשימה מסיבה לא ידועה

הערכת דיוק האבחנה בחדר המיון והערך המוסף של בדיקת NT-proBNP

n = 485 patients or 517 ER visits

Randomization

ק買って באבחנהひとつיה

קלינית ועל אישוף卧 피

אבחנה, בדיקה גופנית, בדיקות עזר

n = 271 visits

 thước proBNP

 girlfriends

n = 271 visits

 Interstate proBNP

הערצות דיק האבחנה בחדר המיון והערך המוסף של בדיקת NT-proBNP ב”מ ובאפשוז

s = 246 visits

Kernel proBNP
### Age-stratified cutpoints for the diagnosis of CHF

<table>
<thead>
<tr>
<th>Patient age</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>&lt; 300</td>
<td>300-450</td>
<td>&gt; 450</td>
</tr>
<tr>
<td>50-75</td>
<td>&lt; 300</td>
<td>300-900</td>
<td>&gt; 900</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>&lt; 300</td>
<td>300-1800</td>
<td>&gt; 1800</td>
</tr>
</tbody>
</table>

**Interpretation**
- CHF is unlikely
- Acute CHF less likely, alternative causes must be considered
- Acute CHF likely, Consider confounding factors

Januzzi JL. JACC 2005;45:140 Suppl A
Study population

Hillel Yaffe Medical Center (10/05-3/07): 386 patients and 416 referrals to the ER. Assaf Harofeh Medical Center (3/06-1/07): 99 patients with 101 referrals to the ER.

Overall, 484 patients and 517 presentations to the ER. 261 Females (74.4±12.4, median-72), and 249 males (70.5±13.4, median-77)
Results

Percentage of patients discharged home from ER and admitted according to blinding status in all groups

There was a significant difference between but not within groups. The central lab NT-proBNP assay did not affect admission rate.
BNP4EVER Study

#Patients in each group

<table>
<thead>
<tr>
<th>Group</th>
<th>#Patients</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF unlikely</td>
<td>84</td>
<td>17%</td>
</tr>
<tr>
<td>CHF less likely</td>
<td>123</td>
<td>24%</td>
</tr>
<tr>
<td>CHF very likely</td>
<td>302</td>
<td>59%</td>
</tr>
</tbody>
</table>

ER diagnosis of HF

<table>
<thead>
<tr>
<th>Group</th>
<th>ER diagnosis of HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF unlikely</td>
<td>18%</td>
</tr>
<tr>
<td>CHF less likely</td>
<td>54.5%</td>
</tr>
<tr>
<td>CHF very likely</td>
<td>75%</td>
</tr>
</tbody>
</table>

Admission rate

<table>
<thead>
<tr>
<th>Group</th>
<th>Admission rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF unlikely</td>
<td>74%</td>
</tr>
<tr>
<td>CHF less likely</td>
<td>88.6%</td>
</tr>
<tr>
<td>CHF very likely</td>
<td>96.3%</td>
</tr>
</tbody>
</table>

Discharge Dx of HF

<table>
<thead>
<tr>
<th>Group</th>
<th>Discharge Dx of HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF unlikely</td>
<td>10.8%</td>
</tr>
<tr>
<td>CHF less likely</td>
<td>24%</td>
</tr>
<tr>
<td>CHF very likely</td>
<td>66%</td>
</tr>
</tbody>
</table>
BNP4EVER Study

Age-stratified NT-proBNP cutpoints

- CHF unlikely
  - %ER diagnosis of CHF: 18.0
  - Admission rate: 74.0
  - %Hospital Diagnosis of CHF: 11.0

- CHF less likely
  - %ER diagnosis of CHF: 54.5
  - Admission rate: 88.6
  - %Hospital Diagnosis of CHF: 24.0

- CHF very likely
  - %ER diagnosis of CHF: 75.0
  - Admission rate: 96.3
  - %Hospital Diagnosis of CHF: 66.0
The pro-BNP test improved, despite test assimilation period, the accuracy of acute heart failure diagnostic on discharge in patients admitted for clinically significant dyspnea.
Survival in all study patients according to ASC group
Life table analysis of mortality in HF-likely HYMC patients (group C): No difference according to blinding or final diagnosis of HF.
NT-proBNP levels in HF patients (group C) according to median value

![Graph showing survival over time with NT-proBNP levels as a factor.](image-url)
Survival in HF-likely patients (group C) with NT-proBNP < 5000 (A) and > 5000 pg/ml (B) according to discharge diagnosis

HF-diagnosed patients
HF-undiagnosed patients

P = 0.05
<table>
<thead>
<tr>
<th>Study group</th>
<th>N</th>
<th>NT-proBNP Mean ±SE</th>
<th>Survival 21 Months%</th>
<th>BB%</th>
<th>Treatment intensity Mean ± std Median</th>
<th>AA%</th>
<th>Treatment intensity mean ± std (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinded</td>
<td>151</td>
<td>5168 (2901-11807) / 8695 ± 723.4</td>
<td>54</td>
<td>32</td>
<td>1.44 ± 0.55 (1.0)</td>
<td>55.0</td>
<td>1.88 ± 0.56 (2.0)</td>
</tr>
<tr>
<td>Unblinded</td>
<td>140</td>
<td>4114 (2433, 8212) / 9337 ± 637.7</td>
<td>57</td>
<td>14.4</td>
<td>1.71 ± 0.73 (2.0)</td>
<td>50.5</td>
<td>1.92 ± 0.61 (2.0)</td>
</tr>
<tr>
<td>Patients undiagnosed as AHF</td>
<td>97</td>
<td>5168 (2901-11807) / 6970 ± 714 *</td>
<td>57</td>
<td>14.4</td>
<td>1.71 ± 0.73 (2.0)</td>
<td>50.5</td>
<td>1.92 ± 0.61 (2.0)</td>
</tr>
<tr>
<td>Patients diagnosed as AHF</td>
<td>192</td>
<td>6149 (2930-12,456) / 2825 ±160</td>
<td>59</td>
<td>40.1</td>
<td>1.49 ± 0.62 (1.0)</td>
<td>59.9</td>
<td>1.98 ± 0.55 (2.0)</td>
</tr>
<tr>
<td>NT-proBNP &lt; median undiagnosed as AHF</td>
<td>55</td>
<td>2780 (1149-3878) / 2891 ± 116</td>
<td>58</td>
<td>9.1</td>
<td>1.8 ± 0.84 (2.0)</td>
<td>56.3</td>
<td>1.94 ± 0.63 (2.0)</td>
</tr>
<tr>
<td>NT-proBNP &lt; median diagnosed as AHF</td>
<td>84</td>
<td>2897 (1092-3783) / 12398 ± 1202</td>
<td>74 *</td>
<td>31.0</td>
<td>1.5 ± 0.58 (1.5)</td>
<td>66.6</td>
<td>2.0 ± 0.47 (2.0)</td>
</tr>
<tr>
<td>NT-proBNP &gt; median undiagnosed as AHF</td>
<td>42</td>
<td>8982 (7159-14,551) / 14350 ± 865</td>
<td>55</td>
<td>21.4</td>
<td>1.67 ± 0.71 (2.0)</td>
<td>42.9</td>
<td>1.89 ± 0.58 (2.0)</td>
</tr>
<tr>
<td>NT-proBNP &gt; median diagnosed as AHF</td>
<td>108</td>
<td>11517 (7723-17,585)</td>
<td>46</td>
<td>47.2</td>
<td>1.47 ± 0.65 (1.0)</td>
<td>54.7</td>
<td>1.97 ± 0.62 (2.0)</td>
</tr>
</tbody>
</table>

*p=0.019
Conclusions

- The NT-proBNP test did not affect ER admission rate.

(2) The NT-proBNP test improved the accuracy of the diagnosis of AHF on discharge.

(3) Accurate diagnosis based on the NT-proBNP resulted in improved mid-term (20 months) overall mortality in patients with < 5000 pg/ml, but not in those with > 5000 pg/ml.

(4) Undertreatment and treatment effect.