The Endocrine and Neurohormonal Dysregulation in Heart Failure.

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Argentina

No potential conflicts of interest
Heart Failure Pathophysiology

A complex multiorgan disease

Excess Neurohormonal Activation

Multiple Endocrine Deficiency
Heart Failure Pathophysiology

A complex multiorgan disease

Multiple Endocrine Deficiency

✓ Insulin Resistance
✓ Thyroid hormone
✓ Anabolic Hormones
  ✓ Growth hormone
    ✓ Insulin-like growth factor 1
✓ Anabolic steroids
  ✓ Testosterone
  ✓ DHEA
Insulin Resistance and Heart Failure

Incidence of Heart Failure

Prognostic Significance

Cumulative Survival (%)

Incidence, Cases/1000 Person-years at Risk

Quartiles of Clamp Glucose Disposal Rate (mg/kg body weight per min)

Ingelsson et al. JAMA 2005;294:334

Doehner et al. JACC 2005; 46:1019
Swan et al JACC 1997 30:527

Witteles et al JACC 2004; 44:78

Insulin Resistance and Heart Failure

Heart Failure and Insulin Resistance
Heart Failure

Sympathetic Activity

↓Tissue perfusion

Insulin Resistance

Intracellular ↓Glucose ↑FFA

Energetic Deficit
Myocardial Damage

Coronary disease

Hypertension

Pathophysiological link
Insulin Resistance and Heart Failure Inflammatory Mechanisms

Insulin Resistance

Adipose Tissue

Inflammatory Mediators

- Tumor Necrosis Factor
- Interferon $\gamma$
- C-RP
- Interleuquina 6
- Adiponectin
- Resistin

Heart Failure
Energetic Consequences of Insulin Resistance

Witteles Jacc 2008; 51:93-102
Heart Failure

Sympathetic Activity

↓ Tissue perfusion

Insulin Resistance

Intracellular ↓ Glucose ↑ FFA

Energetic Deficit Myocardial Damage

Coronary disease

Hypertension

Pathophysiological link
**Insulin Resistance and Heart Failure**

**A potential therapeutic target**

<table>
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<th>Diabetic Medications</th>
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<tr>
<td>✅ Metformin</td>
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<td>✅ TZD (Increase risk of heart failure?)</td>
</tr>
<tr>
<td>✅ Incretin System (GLP-1 DPP4 (-) )</td>
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<th>Metabolic Modulators</th>
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<tbody>
<tr>
<td>✅ Trimetazidine</td>
</tr>
</tbody>
</table>
Metformin vs Other Treatments
All Cause Hospital Admissions at one year

<table>
<thead>
<tr>
<th>Study</th>
<th>(Treatment</th>
<th>Control)</th>
<th>Odds ratio</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eurich 2005</td>
<td>537/1060</td>
<td>406/773</td>
<td>29.7</td>
<td>0.93(0.77-1.12)</td>
</tr>
<tr>
<td>Masoudi 2005</td>
<td>1265/1861</td>
<td>8702/12069</td>
<td>70.3</td>
<td>0.82(0.74-0.91)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2921</td>
<td>12842</td>
<td>100</td>
<td>0.85(0.76-0.95)</td>
</tr>
</tbody>
</table>

*Eurich D et al. BJM 2007;335:497*
Insulin Resistance and Heart Failure

A potential therapeutic target

Diabetic Medications
- Metformin
- TZD (Increase risk of heart failure?)
- Incretin System (GLP-1 DPP4 (-))

Metabolic Modulators
- Trimetazidine
GLP-1 Infusion Metaanalysis

Study or subgroup

Halbirk et al. 2010
Sokos et al. 2006
Total (95%CI)

Mean difference IV, fixed, 95% CI

-500 -250 0 250 500
Favours control Favours experimental

Study or subgroup

Halbirk et al. 2010
Nikolaidis et al. 2004
Sokos et al. 2006
Total (95%CI)

Mean difference IV, fixed, 95% CI

-100 -50 0 50 100
Favours control Favours experimental
Insulin Resistance and Heart Failure

A potential therapeutic target

Diabetic Medications
- Metformin
- TZD (Increase risk of heart failure?)
- Incretin System (GLP-1 DPP4 (-) )

Metabolic Modulators
- Trimetazidine

At present there is not enough evidence
Low IGF-1 in HF patients

- Low IGF-1 resembles HF
- Low IGF-1 predicts HF
- Low IGF-1 in HF is associated with poor outcome

- ↓GH
- ↓ILGF-1
- ↓cardiac performance
- ↑peripheral vascular resistance
- ↓exercise capacity
## Heart Failure and Growth Factor

<table>
<thead>
<tr>
<th></th>
<th>H Failure</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broglio et al</td>
<td>135±47(n:39)</td>
<td>194±64(n:42)</td>
</tr>
<tr>
<td>Anker et al</td>
<td>124±9(n:21)</td>
<td>151±9(n:26)</td>
</tr>
<tr>
<td>Al-Obaidi et al</td>
<td>121±18(n:12)</td>
<td>108±15(n:21)</td>
</tr>
<tr>
<td>Anwar et al</td>
<td>83±5(n:60)</td>
<td>95±5(n:103)</td>
</tr>
<tr>
<td>Saeki et al</td>
<td>101±34(n:18)</td>
<td>173 ±27(n:15)</td>
</tr>
<tr>
<td>Konteleon et al</td>
<td>124± 49(n:23)</td>
<td>236± 66(n:23)</td>
</tr>
<tr>
<td>Mankowska et al</td>
<td>208±(n:183)</td>
<td>299(n:366)</td>
</tr>
<tr>
<td>Weighted mean</td>
<td><strong>168</strong></td>
<td><strong>236</strong></td>
</tr>
</tbody>
</table>

No trial with GH or IGF-1 in HF demostated beneficial effects.
Hypothyroidism in Heart Failure

- 31 cases with Low T3 and Normal T4 and TSH
- 9 treated cases
- 6 subclinical hypothyroid cases

N: 132

Ascheim D et al Thyroid. 2002;12:511
Significance of Low $T_3$

Iervasi et al. Circulation 2003;107:708

n: 573
<table>
<thead>
<tr>
<th>Author/year</th>
<th>N</th>
<th>Drug</th>
<th>Results</th>
<th>Adv Eff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moruzzi 1994</td>
<td>10</td>
<td>T4 (1 month)</td>
<td>↓SVR ↑CO ↑LVEY ↑EXERCISE TOLERANCE</td>
<td>No</td>
</tr>
<tr>
<td>Moruzzi 1996</td>
<td>10</td>
<td>T4 (3 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamilton 1998</td>
<td>23</td>
<td>T3</td>
<td>↓SVR ↑CO</td>
<td>No</td>
</tr>
<tr>
<td>Malik 1999</td>
<td>10</td>
<td>T4</td>
<td>↑CI ↑PCWP</td>
<td>No</td>
</tr>
<tr>
<td>Iervasi 2001</td>
<td>6</td>
<td>T3</td>
<td>↓SVR ↑CO</td>
<td>No</td>
</tr>
<tr>
<td>Pingitore 2008</td>
<td>20</td>
<td>T3</td>
<td>↓NA ↓Aldosterone ↑LVEDV ↓NTproBNP</td>
<td>No</td>
</tr>
<tr>
<td>Goldman 2009</td>
<td>86</td>
<td>DITPA</td>
<td>↓SVR ↑CI</td>
<td>Poorly tolerated</td>
</tr>
</tbody>
</table>

Gerdes; Circulation 2010;122:385
Anabolic Steroids in Heart Failure

Testosterone

- Estimated free testosterone [pg/mL]
- NYHA I: P=0.0001
- NYHA II: P=0.02
- NYHA III: P=0.005
- NYHA IV: P=0.01

DHEA

- Dehydroepiandrosterone sulphate [ng/mL]
- NYHA I: P=0.0002
- NYHA II: P=0.006
- NYHA III: P=0.002
- NYHA IV: P=0.01

Testosterone and Exercise Capacity

- Study Reference
  - Caminiti 2009
  - Malkin 2006
  - Pugh 2004
  - Iliamno 2010
- Summary
  - Placebo Better
  - Testosterone Better

Jankowsa E et al.
Circulation 2006; 114:1829

Toma et al.
Circ Heart Fail. 2012;5:315
Anabolic Deficiency and Survival

Jankowsa E et al.  Circulation 2006; 114:1829
Multiple Endocrine Deficiency

Reaffirms HF is a complex multiorgan disease.

MED is:

Just a biomarker not mechanistically linked to HF.
Useful only for staging and monitoring Adaptative response. LEAVE THE STATUS QUO
Negative consequence of HF. SEARCH AND CORRECT

Possible therapeutic target, but... still, no clear evidence
Heart Failure Pathophysiology

A complex multiorgan disease

Excess Neurohormonal Activation

Multiple Endocrine Defficiency
Models of heart failure

- Cardiorenal
- Hemodynamic
- Neurohormonal
Mechanisms of heart failure

Index Event

Cardiac Dysfunction

Ventricular Remodelling

Salt and H2O retention
Vasoconstriction

Neurohormonal Activation

Structural Myocardial Damage
Neurohormonal Mechanisms in heart failure

Trigger (cardiac damage)

Vascular Underfilling

Inadequate baroreceptor and chemoreceptors response

Autonomic Imbalance

↑Sympathetic tone  ↓Parasympathetic

Counterbalance Mechanisms (protective?)

Natriuretic Peptides
Prostaglandins
Nitric Oxide

Neurohormonal Activation (compensatory and deleterious)

Catecholamines
RAAS
AVP
(irrespective of osmotic conditions)
Endothelins
Therapeutic Application of the neurohormonal model

Consensus Trial

SOLVD Treatment Trial

SOLVD Prevention Trial


p=0.001
Therapeutic Application of the neurohormonal model

Capricorn Investigators *Lancet* 2011; 357:1385-90
Clinical Application of the neurohormonal model

Neurohormonal model based Trials

Positive Trials

CONSENSUS
SOLVD
AIRE  SAVE  TRACE
RALES  EPHESUS  EMPHASIS
CHARM  ALTERNATIVE
VALHEFT
CHARM  ADDED
CIBIS II  MERIT
COPERNICUS
CAPRICORN
Combination of ACE inhibitors and Angiotensin II receptor blockers

Nesiritide in acute heart failure

Death or rehospitalization for Heart Failure at 30 days. (% pts)

- Placebo
- Nesiritide

**P = 0.31**

Hazard ratio 0.93 (95% CI 0.8-1.08)

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<td>Death</td>
<td>-0.7 (-2.1 to 0.7)</td>
<td>4.0 (-1.3 to 0.5)</td>
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<td>Rehospitalization For Heart Failure</td>
<td>10.1</td>
<td>9.4</td>
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- Placebo
- Nesiritide

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<tr>
<td>Death</td>
<td>-0.4 (-1.3 to 0.5)</td>
<td>3.6 (-1.2 to 1.0)</td>
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<tr>
<td>Rehospitalization For Heart Failure</td>
<td>6.1</td>
<td>6.0</td>
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**n = 7141**

Ascend HF Trial O'Connor et al. NEJM 2011; 365:32
Omapatrilat in heart failure

% Event free survival

Months

P:0.339

Omapatrilat

Enalapril
Tolvaptan in Heart Failure

**All-Cause Mortality**

- Proportion Surviving
- Months in Study
- Tolvaptan vs Placebo

**Cardiovascular Mortality or Heart Failure Hospitalization**

- Proportion Without Event
- Months in Study
- Tolvaptan vs Placebo

N: 4133

EVEREST Trial JAMA 2007; 297:1391
Central Sympathetic Inhibition

Moxcon Trial n:1934

Cohn et al. Eur J Heart Fail 2003;5:659

Prematurely discontinued because increased mortality.
Neurohormonal model based Trials

Positive Trials
- CONSENSUS
- SOLVD
- AIRE
- SAVE
- TRACE
- RALES
- EPHESUS
- EMPHASIS
- CHARM
- ALTERNATIVE
- VALHEFT
- CHARM ADDED
- CIBIS II
- MERIT
- COPERNICUS
- CAPRICORN

Neutral or Negative Trials
- BEST
- MOXCON
- EVEREST
- ASCEND-HF
- OVERTURE
- RITZ IV
- FIRST
- VALIANT
- ENABLE
- RECOVER
- RENAISSANCE
- RENEWAL
Although excess neurohormonal activation is harmful, some degree may be necessary.
Importance of hypotension

Pre- and posttitration daytime and nocturnal diastolic hypotensive episodes

Hypotension may be a pharmacotherapeutic ceiling

Mak et al. J Cardiac Fail 2008;14:555
Are there limits to the neurohormonal model?

- Placebo
- ACE inhibitors
- β-Blockers (except Bucindolol)
- Bucindolol
- Omapatrilat
- Endothelin Antagonists
- Moxonidine
- Angiotensin Receptor Antagonist
- Etanercept

Mehra et al. JACC 2003; 41:1606
“We must stop assuming that the body’s compensatory actions to chronic HF are harmful; we do not understand enough physiology to know why they are often needed.”
Limits of the NH blockade strategy

Pathophysiology

application

Learning

Therapy
Patagonia, Argentina