Δυσλειτουργία του ενδοθηλίου και καρδιακή ανεπάρκεια

Κίμων Σταματελόπουλος
Θεραπευτική Κλινική
Ιατρική Σχολή
Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών
Heart failure in numbers

- >37.7 million individuals globally
- >1 million hospitalizations annually
- Postdischarge mortality and readmission rate approximately 45% at 60 to 90 days
- In the USA, the total medical costs are expected to rise from US$20.9 billion in 2012 to $53.1 billion by 2030

Ziaeian et al. Nat Rev Cardiology 2016
Heart Failure outcomes at the community level remain suboptimal

Deaths Attributed to Heart Failure, U.S.

Hospitalization Rates for Heart Failure, Ages 45–64 Years and 65 Years and Older, U.S.

NHLBI Factbook 2012.
Need for Novel Therapeutic Targets for Heart Failure

Phase II studies
Improvement in **surrogate markers** did not consistently translate into better clinical outcomes

Phase III trials
**HFrEF**: Few therapies have produced positive results
**HFpEF**: none

**new biomarkers as therapeutic targets warrant consideration**

*Marti et al. J Am Coll Cardiol. 2012*
New Biomarkers as therapeutic targets in Heart Failure
Requirements for application in clinical practice – STEP 1

1. Biological plausibility
2. Methodology: safe, available, reproducible, cost-effective
3. Proof of concept. Do marker levels differ between subjects with and without disease?
4. Prospective validation. Independent association with survival outcomes
5. Clinical utility in risk stratification:
   a. Good discrimination between low and high risk patients (\(C\) statistics, IDI, Likelihood Ratio)
   b. Good performance in different populations (Calibration)
   c. Good reclassification performance over validated risk scores (Net Reclassification Index – NRI >9%)

ACCF/AHA Guideline 2013
Hlatsky Ma et al. Circulation 2009
New Biomarkers as therapeutic target in Heart Failure
Requirements for application in clinical practice – STEP 2

1. Novel Biomarker amenable to interventions?

2. Consider clinical trials in therapeutic interventions

ACCF/AHA Guideline 2013
Hlatsky Ma et al. Circulation 2009
Tzoulaki et al. JAMA Int Med 2013
Endothelial Function is a major mediator in cardiovascular disease

Biological plausibility

Endothelial dysfunction in HF

Failing Heart

Neurohumoral activation
Inflammatory messengers from the myocardium
Local shear forces

Increased oxidative stress and reduced NO production

Systematic and pulmonary vasoconstriction
Myocardial damage
↑ myocardial stiffness
Myocardial hypertrophy
Kidney dysfunction

Increased cytokine production and inflammation
eNOS downregulation
↑ oxidative stress

Endothelial dysfunction

Endothelium dysfunction and Acute HF

Decreased NO availability – Increased endothelin-1 and angiotensin II availability

Augmented systolic ventricular workload
- Increased arterial stiffness
- Increased endothelin-1 dependent vasoconstriction
- Increased sympathetic outflow and catecholamine release

Fluid overload
- Decreased sodium excretion in the kidney

Worsening Acute HF

Endothelium dysfunction and Chronic HF

Decreased NO availability – Increased endothelin-1 and angiotensin II availability

- Augmented systolic and ↑ left ventricular workload
- Increased arterial stiffness
- Systematic vasoconstriction
- Pulmonary hypertension and ↑ right ventricular workload
- Smooth muscle cell dysregulation
- Pulmonary vascular remodeling
- Pulmonary vasoconstriction

Fluid overload and renal dysfunction
- Decreased sodium excretion in the kidney
- Vasomotor nephropathy and cardiorenal syndrome

Left ventricular remodeling
- Decreased coronary endothelium-dependent vasodilation
- Increased cell migration and heart hypertrophy
- ↑ smooth muscle cell growth and matrix production
- ↑ myocardial stiffness

Biological plausibility

Coronary endothelial dysfunction Idiopathic Dilated Cardiomyopathy

Proof of concept

Epicardial artery endothelial function

Small coronary artery endothelial function

CSA: coronary cross-section area
CBF: coronary blood flow
C1: control

Endothelial function assessment

**Invasive assessment**

**Non-Invasive assessment**

safe, available, reproducible, cost-effective

Conduit peripheral arteries

Flow-mediation dilation (FMD)

Small peripheral arteries

Reactive hyperemia peripheral arterial tonometry (RH-PAT)

Venous occlusive plethysmography

Coretti MC et al. J Am Coll Cardiol 2002
Shah et al. Eur Heart J. 2018
Kuvin JT et al. Am Heart J 2003
Peripheral endothelial function is associated with risk factors for HF

**Methodology**

PAT and FMD provide distinct information

<table>
<thead>
<tr>
<th></th>
<th>Abnormal PAT Ratio</th>
<th>Abnormal FMD Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR* (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>1.08 (0.87–1.33)</td>
<td>1.44 (1.28–1.63)</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.41 (1.12–1.78)</td>
<td>1.30 (1.10–1.54)</td>
</tr>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td>0.71 (0.63–0.81)</td>
<td><strong>1.44 (1.33–1.56)</strong></td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.15 (1.04–1.28)</td>
<td>1.18 (1.09–1.27)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>1.30 (1.17–1.44)</td>
<td>1.18 (1.09–1.27)</td>
</tr>
<tr>
<td>Total/HDL cholesterol ratio</td>
<td>1.36 (1.22–1.51)</td>
<td>…</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>1.73 (1.28–2.34)</td>
<td>…</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.97 (1.48–2.60)</td>
<td>…</td>
</tr>
<tr>
<td>Lipid-lowering medication</td>
<td>1.43 (1.10–1.86)</td>
<td>…</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>…</td>
<td>…</td>
</tr>
</tbody>
</table>

Hamburg N et al. Hypertension 2011
Endothelial dysfunction in patients with HF with reduced EF

**Conduit artery endothelial function**

**Small artery endothelial function**

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**Klosinska M et al. European Journal of Heart Failure 2009**

**Bank et al. J Card Fail. 2000**
Endothelial dysfunction in patients with HF with **preserved** EF

**Proof of concept**

**Conduit artery endothelial function**

**Small artery endothelial function**

P=0.001

**Flow mediated dilation (%)**

- HFP EF
- Controls

**RHI**

- Non-HF
- HFNEF

P<0.001

*Marcehaux et al. J Cardiac Fail 2015*

*Akiyama et al. J Am Coll Cardiol 2012*
Endothelium dysfunction independently predicts outcome in HFrEF

**Conduit artery endothelial function**
Flow-mediated dilatation

**Small artery endothelial function**
Reactive hyperemia using strain-gauge plethysmography

Prospective validation

Meyer et al. J Am Coll Cardiol. 2005

De Berrazueta et al. Eur J Heart Fail. 2010
Endothelium dysfunction independently predicts outcome in HFrEF.
Endothelium dysfunction correctly reclassifies risk in HFpEF

### General population

<table>
<thead>
<tr>
<th>N=3026</th>
<th>Net correct reclassification %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with no incident CV event</td>
<td>52</td>
</tr>
<tr>
<td>Subjects with incident CV event</td>
<td>-23</td>
</tr>
<tr>
<td>Net reclassification improvement</td>
<td>29 %</td>
</tr>
</tbody>
</table>

FRS: Framingham risk score  
FMD: Flow-mediated dilatation

### HFpEF

<table>
<thead>
<tr>
<th>N=321</th>
<th>Net correct reclassification %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with no incident CV event</td>
<td>8.8</td>
</tr>
<tr>
<td>Subjects with incident CV event</td>
<td>10.2</td>
</tr>
<tr>
<td>Net reclassification improvement</td>
<td>19 %</td>
</tr>
</tbody>
</table>

PF5: I-PRESERVE risk score  
RHI: Digital artery Reactive Hyperemia Index

Yeboah et al. Circulation 2002  
Akiyama et al. J Am Coll Cardiol 2012
Is endothelial function amenable to interventions in HF?

PDE inhibitors, sGC stimulators, L-arginine, tetrahydrobiopterin

Physical training improves endothelial function in chronic HF

Therapeutic target

Conduit artery endothelial function

Small artery endothelial function


Dose dependent effect on FMD in Chronic HFrEF

NID: nitrate-induced dilation

Enalapril

Sildenafil


Drakos et al. J Am Cardiol 2003
Does improvement in ED lead to improvement in HF parameters?

Preservation of coronary endothelial function is related to improvement in LVEF in IDC

![Graph showing correlation between CSA, CBF, and LVEF]

- CSA: coronary cross-section area
- CBF: coronary blood flow
- C1: control

Endothelial dysfunction in heart failure (HF)

Conclusions

High prevalence and mortality despite optimal treatment

New biomarkers as therapeutic targets warrant consideration

Strict requirements for validation

Endothelial dysfunction as a new therapeutic target in HF?

Biological plausibility:
involved in multiple pathways in all types of acute and chronic HF

Proof of concept
Evidence of endothelial dysfunction in:
Conduit and small arteries
Ischemic and dilated CM
HFrEF and HFpEF

Prospective validation and Clinical utility
Prognostic value in small cohorts
Preliminary evidence for reclassification value

Therapeutic implications
Can be targeted by:
specific and non-specific drugs
Prospective validation: Large epidemiological studies to confirm ED as a biomarker for outcome prediction

Clinical utility (reclassification value): Large epidemiological studies to confirm ED in risk stratification

Which method? Which arterial network?

Normal and reference values?

Is specific therapeutic targeting beneficial for CV outcomes?

Further evaluation in randomized controlled trials
Which method?

Flow-mediation dilation (FMD)
- Operator dependent – long learning curve
- Inconsistent methodology
- Long-term technical experience
- Relatively low cost – no consumables
- Conduit arteries

Reactive hyperemia peripheral arterial tonometry (RH-PAT)
- Operator independent – short learning curve
- Consistent methodology
- Short-term technical experience
- Relatively high cost – consumables / patient
- Small digital arteries
Systematic endothelial dysfunction associated with Coronary microvascular dysfunction in HFpEF
Tetrahydrobiopterin Improves Impaired Endothelium-Dependent Forearm Vasodilation in HFrEF

L-arginine improves endothelial function in patients with HFpEF

Novel therapeutic targets

<table>
<thead>
<tr>
<th>Photoplethysmographic indices</th>
<th>Arginine (n = 13)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAT/TI, pre-ischemia:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>38.75 ± 11.52</td>
<td>0.007</td>
</tr>
<tr>
<td>2 months</td>
<td>23.32 ± 6.08</td>
<td></td>
</tr>
<tr>
<td>MAT/TI, 0–30 s post-ischemia:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>38.91 ± 9.31</td>
<td>0.005</td>
</tr>
<tr>
<td>2 months</td>
<td>21.32 ± 16.43</td>
<td></td>
</tr>
<tr>
<td>MAT/TI, 30–60 s post-ischemia:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>39.86 ± 12.47</td>
<td>0.004</td>
</tr>
<tr>
<td>2 months</td>
<td>21.32 ± 16.43</td>
<td></td>
</tr>
<tr>
<td>MAT/TI, 60–90 s post-ischemia:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>36.60 ± 11.51</td>
<td>0.004</td>
</tr>
<tr>
<td>2 months</td>
<td>18.81 ± 15.13</td>
<td></td>
</tr>
<tr>
<td>MAT/TI, 90–120 s post-ischemia:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>33.47 ± 7.67</td>
<td>0.018</td>
</tr>
<tr>
<td>2 months</td>
<td>14.74 ± 17.67</td>
<td></td>
</tr>
</tbody>
</table>

MAT: maximum amplitude time
TT: total time of the curve
L-arginine: 8g/day in two doses

Endothelium dysfunction is related with adverse CV events in CHF

Prospective validation

HFrEF and HFP EF


A: FMD > median
B: FMD < median

![Graph showing event-free survival over follow-up period (months)]
Requirements for validation of a novel therapeutic target

Candidate target

Yes

Target measurable?

Yes

Consistent and credible observational association with outcomes?

Yes

Target amenable to interventions?

Yes

Consider clinical trials

FMD is decreased in patients with HF with reduced EF

Small arteries endothelial dysfunction is an independent predictor of adverse outcome in HFrEF

Endothelial dysfunction measured by reactive hyperemia using strain-gauge plethysmography

Endothelial dysfunction in patients with severe ischemic HFrEF and adverse CV events

<table>
<thead>
<tr>
<th>Variable</th>
<th>FMD ≤4.6% (n = 41)</th>
<th>FMD &gt;4.6% (n = 41)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5 (12.1%)</td>
<td>0</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Hospitalization for chronic heart failure exacerbation</td>
<td>16 (39.0%)</td>
<td>8 (19.5%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1 (2.4%)</td>
<td>0</td>
<td>0.23</td>
</tr>
<tr>
<td>Composite adverse events</td>
<td>22 (53.6%)</td>
<td>8 (19.5%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Small artery endothelial function predicts adverse outcome in HFrEF

Maximal forearm blood flow responses to
(A) Acetylcholine 30 g/min and (B) sodium nitroprusside 10g/min

Endothelium dysfunction and mortality risk in CHF patients with reduced EF

Normal arterial structure

- In large arteries stiffness is determined by extracellular matrix components.

- Stiffness of smaller arteries and arterioles is determined by hypertrophy and smooth cell tone.

- Stiffness increases with age, cardiometabolic abnormalities and sodium intake.

Μελέτες για την προγνωστική αξία της ενδοθηλιακής λειτουργίας σε ΑΣΥΜΠΤΩΜΑΤΙΚΑ ΑΤΟΜΑ ΧΩΡΙΣ ΕΓΚΑΤΕΣΤΗΜΕΝΗ ΚΑ ΝΟΣΟ

Η FMD ΒΕΛΤΙΩΝΕΙ ΤΗΝ ΤΑΞΙΝΟΜΗΣΗ ΣΗΜΑΝΤΙΚΟΥ ΑΡΙΘΜΟΥ ΑΤΟΜΩΝ ΠΟΥ ΑΡΧΙΚΑ ΚΑΤΑΤΑΣΣΟΝΤΑΙ ΒΑΣΕΙ FRS ΣΕ ΕΝΔΙΑΜΕΣΟΥ ΚΙΝΔΥΝΟΥ

<table>
<thead>
<tr>
<th>Table 4. Reclassification of Subjects Based on FRS+FMD vs FRS Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>FRS + FMD Risk Category</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Subjects with no incident CVD event</td>
</tr>
<tr>
<td>FRS risk category</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Intermediate</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Subjects with an incident CVD event</td>
</tr>
<tr>
<td>FRS risk category</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Intermediate</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reclassified to Higher Risk</th>
<th>Reclassified to Lower Risk</th>
<th>Net Correct Reclassification, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>161</td>
<td>1644</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>74</td>
<td>-23</td>
<td></td>
</tr>
</tbody>
</table>

| Net reclassification improvement, % | 29 | <0.001 |

| Net reclassification improvement (intermediate risk only), % | 28 | <0.001 |

Yeboah J et al. CHS. Circulation. 2009
Arterial stiffness assessment

• Pulse pressure

• Pulse wave velocity and augmentation index

Bruno et al Cardiovascular Ultrasound 2014.
Arterial stiffness and HF Outcomes

- Increased arterial stiffness is associated with LV diastolic dysfunction and HF with preserved EF

- Increased PWV and augmentation index are independently associated with systolic and diastolic dysfunction

- Higher PP associated with mortality in Chronic HF and Lower PP with mortality in Acute HF

Peripheral endothelial function is associated with **risk factors for HF**

**Table 3. Age- and Sex-Adjusted Models of Pulse Amplitude**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean Baseline</th>
<th>PAT Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ (SE)</td>
<td>$P$</td>
</tr>
<tr>
<td>Age</td>
<td>0.07 (0.02)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Sex, female vs male</td>
<td>$-0.94$ (0.03)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.13 (0.02)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.08 (0.02)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.05 (0.02)</td>
<td>$0.005$</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.23 (0.02)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Total/HDL cholesterol</td>
<td>0.15 (0.02)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.13 (0.02)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>0.11 (0.02)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.52 (0.10)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.28 (0.04)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.29 (0.05)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>0.17 (0.12)</td>
<td>0.15</td>
</tr>
<tr>
<td>Hypertension treatment</td>
<td>0.29 (0.06)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Lipid-lowering treatment</td>
<td>0.30 (0.06)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Prevalent cardiovascular disease</td>
<td>0.22 (0.13)</td>
<td>0.10</td>
</tr>
</tbody>
</table>
Endothelium function assessment reclassifies patients’ risk for CVD events

<table>
<thead>
<tr>
<th>General population</th>
<th>Reclassified to Higher Risk</th>
<th>Reclassified to Lower Risk</th>
<th>Net correct reclassification %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with no incident CV event</td>
<td>161</td>
<td>1644</td>
<td>52</td>
</tr>
<tr>
<td>Subjects with incident CV event</td>
<td>32</td>
<td>74</td>
<td>-23</td>
</tr>
<tr>
<td>Net reclassification improvement</td>
<td></td>
<td></td>
<td>29 %</td>
</tr>
</tbody>
</table>

Reclassification of Subjects Based on FRS+FMD

HFpEF

reclassification index was significant after addition of the RHI (19.0%, p = 0.01) Akiyama et al. J Am Coll Cardiol 2012;

Inhibition of ACE and phosphodiesterase type 5 improves endothelial function in HF

ΔFMD%

Black bars: placebo
Dark-grey bars: Ramipril
Light-grey bars: Sildenafil
White bars: Ramipril and sildenafil

Hours post study drug

Sildenafil Enhances FMD in Chronic HF

Dose dependent effect

change in FMD (%)

1 minute 3 minute 5 minute

closed squares: placebo, open squares: sildenafil 12.5 mg, open circles: sildenafil 25 mg) and open triangles: sildenafil 50 mg

Protective Role of Carvedilol against CHF-induced endothelial cell apoptosis

Spironolactone improves endothelial vasodilator dysfunction in Chronic HF

FMD responses to acetylcholine and angiotensin after placebo (■) or spironolactone (▲) therapy.

sGC stimulator increases coronary blood flow in anaesthetized dogs

Δ Coronary blood flow mL/min

Abnormal coronary microvascular endothelial function in humans with asymptomatic LV dysfunction

Endothelial dysfunction related to disease severity in HFrEF

Mild HF: NYHA Class I and II
Severe HF: NYHA Class III and IV

FBF: forearm blood flow,
Assessed with strain-gauge plethysmography