Heart failure with preserved ejection fraction
Focus on exercise and the endothelium

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Jacqueline Bernheim Prize Lecture
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Heart failure

Heart Failure - Preserved Ejection Fraction

- Symptom: Exercise intolerance
- Symptom: Shortness of breath
- Symptom: Swollen legs
- Prognosis: 75% mortality over 5 years
- Incidence: 50% of HF and ↑
- Treatment: None

Heart Failure - Reduced Ejection Fraction

- Symptom: Exercise intolerance
- Symptom: Shortness of breath
- Symptom: Swollen legs
- Prognosis: 75% mortality over 5 years
- Incidence: 50% of HF and ↓
- Treatment: 8 drug classes, several devices
HFpEF pathophysiology

Endothelial dysfunction

Cardiac factors

Non-cardiac factors

EXERCISE INTOLERANCE

Gevaert et al, Front Physiol 2019
Cardiac-endothelial interaction in HFpEF

• Comorbidities
  • Ageing
  • Overweight/Obesity
  • Diabetes
  • Hypertension
  • Renal failure
  • Iron deficiency

• Inflammation

• Endothelial dysfunction

• Cardiomyocyte stiffness

• Fibrosis

• Diastolic dysfunction

Gevaert et al, Front Physiol 2019 - Paulus & Tschoepe, JACC 2013
Clinical endothelial function in HFpEF

• Conflicting studies: normal or impaired endothelial function?

Exercise training in HFpEF

The only therapy to

• Improve exercise capacity (peak VO₂)

[Diagram showing favor of exercise over control]

• Improve quality of life

[Diagram showing favor of exercise over control]

Kitzman 2010
Edelmann 2011
Smart 2012
Kitzman 2013

Gray 2004
Kitzman 2010
Edelmann 2011
Smart 2012
Kitzman 2013
Not clear how exercise increases peak VO$_2$ in HFpEF

VO$_2$ = Cardiac output • Peripheral O$_2$ extraction

Lung O$_2$ → Muscle

• Training improves vascular function
  • HFrEF
  • Coronary artery disease
  • Healthy (most)

• HFpEF: large to medium vessel function NOT improved

Gevaert et al, Ox Med Cell Longev 2017
Aims and outline

Part I
- Effect of exercise on vascular function and repair in HFpEF

Part II
- Comorbidities and endothelial dysfunction in HFpEF

Part III
- Predicting the response to exercise in HFpEF

Endothelium
- ↑ Inflammation
- ↑ Dysfunction
- ↓ Repair

Exercise intolerance
- Cardiac factors
- Non-cardiac factors

Comorbidities
- Ageing
- Metabolic syndrome
- Anaemia & iron deficiency
  ...

EXERCISE
Vascular function measurement

Before and after
- A single maximal exercise
- 3 months of exercise training
Single maximal exercise

• Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Healthy (n=26)</th>
<th>HFpEF (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>73 ± 6</td>
<td>74 ± 7</td>
</tr>
<tr>
<td>Gender (%F)</td>
<td>61.5</td>
<td>61.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.3 (23.1-28.0)</td>
<td>29.1 * (26.8-32.9)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>0.0</td>
<td>30.8 *</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>7.7</td>
<td>76.9 *</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>0.0</td>
<td>84.6 *</td>
</tr>
<tr>
<td>GFR (mL/min/1.73m²)</td>
<td>82.0 (73.8-86.8)</td>
<td>63.2 * (50.4-83.0)</td>
</tr>
</tbody>
</table>

• Exercise capacity

![Peak VO₂ (mL/kg/min)](p<0.001)

* *p<0.05 vs Healthy

Gevaert et al, Eur J Heart Fail 2019
HFpEF patients have microvascular endothelial dysfunction

PAT

Reactive Hyperemia Index

* p<0.05 vs Healthy

Gevaert et al, Eur J Heart Fail 2019

* Endothelium

Exercise intolerance

Exercise
A single maximal exercise does not influence microvascular function in HFpEF

PAT

**PAT Ratio**

- Healthy
- HFpEF

**Time (minutes)**

- p=0.002
- p=0.99

Reactive Hyperemia Index

**Reactive Hyperemia Index**

- Healthy
- HFpEF

**Before exercise**

- p-group = 0.048
- p-time = 0.733
- p-interaction = 0.013

**After exercise**

* p<0.05 vs Healthy

Gevaert et al, Eur J Heart Fail 2019
Endothelial repair

• Endothelial progenitor cells (EPC)
  • ↓ in HF, ↑ by exercise

• Angiogenic T lymphocytes (TA)
  • Effect of HF, exercise mainly functional
EPC and TA are lower in HFpEF, indicating deficient endothelial repair

**EPC**
- **Healthy**
- **HFpEF**

**TA**
- **Healthy**
- **HFpEF**

*TA levels higher in patients with*
- Better exercise capacity
- Fewer symptoms (NYHA)

*EPC and TA are lower in HFpEF, indicating deficient endothelial repair*

**Gevaert et al, Eur J Heart Fail 2019**

*p<0.05 vs Healthy*
A single maximal exercise recruits TA in HFpEF

TA levels higher in patients with
• Better exercise capacity
• Fewer symptoms (NYHA)

*p<0.05 vs Healthy
Gevaert et al, Eur J Heart Fail 2019
Effect of three months exercise training on vascular function in HFpEF

OptimEx trial, n=176 HFpEF patiënts
Conclusions I

• HFpEF patients have microvascular endothelial dysfunction and deficient endothelial repair

• Exercise acutely recruits TA, but does not influence endothelial function

• Exercise training does not influence vascular function and repair
Part II – Comorbidities and endothelial dysfunction in HFpEF

Endothelium
↑ Inflammation
↑ Dysfunction
↓ Repair

Comorbidities
Ageing
Metabolic syndrome
Anaemia & iron deficiency
...
Heterogeneity of HFpEF population

• Same symptoms, similar hearts, but different comorbidities
• ‘Phenotypes’

F, Hypertension, overweight, chronic kidney disease
M, Coronary artery disease, diabetes
F, Atrial fibrillation, iron deficiency

• Different vascular function?
Machine learning

• Agglomerative hierarchical clustering
• SIMILAR subjects grouped WITHIN cluster
• DISSIMILAR subjects grouped in DIFFERENT clusters
Microvascular function differs between HFpEF phenotypes

- Cluster 3 > 1 > 2
- Could explain discrepant studies

Gevaert et al, American College of Cardiology 2019
Animal study

• Senescence-accelerated mouse (SAM)
  • Premature ageing (6 mo)
  • Diastolic dysfunction (6 mo)
  • Endothelial dysfunction (6 mo)

• Senescence-resistant mouse (CON)
  • Normal ageing
  • No cardiovascular disease

Gevaert et al, Circ Heart Fail 2017
SAM-WD mice have HFpEF

- Preserved ejection fraction
- Diastolic dysfunction

![Image of ultrasound scans with Endothelium and Comorbidites](image.png)

Gevaert et al, Circ Heart Fail 2017

* p<0.05 vs CON, † p<0.05 vs SAM, ‡ p<0.05 vs CON-WD
§ p<0.05 vs 8w, || p<0.05 vs 16w

- CON – EF 58%
- CON-WD – EF 61%
- SAM – EF 63%
- SAM-WD – EF 65%
SAM-WD mice have HFpEF

- Structural heart disease
- Elevated natriuretic peptides
- Signs of heart failure

Gevaert et al, Circ Heart Fail 2017
SAM have endothelial dysfunction, SAM-WD also endothelial inflammation

* p<0.05 vs CON, † p<0.05 vs SAM

Gevaert et al, Circ Heart Fail 2017
Cellular senescence of the endothelium in SAM-WD mice

* p<0.05 vs CON, † p<0.05 vs SAM
§ p<0.05 vs 8w, || p<0.05 vs 16w

Acetyl-p53
CD31
DAPI

Gevaert et al, Circ Heart Fail 2017
Conclusions II

• When feeding WD to ageing mice, endothelial inflammation and endothelial senescence ensue, and HFpEF develops

• Different phenotypes can be discerned among HFpEF patients, based on comorbidities

• Microvascular function is different between these phenotypes
Discussion & future prospects

• What causes peak VO$_2$ to increase after exercise training in HFpEF?
  • It’s not vascular function
  • It might be skeletal muscle?

• Endothelial senescence as therapeutic target?
  • Neuregulin-1 has effect on endothelial senescence (Shakeri et al, Cardiovasc Res ‘18)

• Influence of phenotypes
  • On animal studies – different models, different results
  • On clinical studies – therapy, inclusion criteria
  • Iron deficiency!
Thank you for your attention!
Prix scientifique
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Wetenschappelijke prijs

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vooruitgang door onderzoek

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progresser par la recherche

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JACQUELINE BERNHEIM PRIZE

- Award from Foundation for Cardiac Surgery
- Since 1998

Completed fundamental or clinical research work

- **Field**
  - Cardiology
  - Cardiovascular Surgery
  - Thoracic Organ Transplant

- **Candidates**
  - Younger than 40
  - Member of a Belgian University Institution

- **Amount**
  - 25,000 €

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