The iron link in the vicious circle of heart failure

Peter van der Meer
Prevalence and definition of anaemia

Anaemia is common in patients with chronic heart failure

Prevalence 14–79%

Prevalence of anaemia depends on:

- Severity of HF
- Definition of anaemia
  - WHO definition:  
    - male <13.0 g/dL (8.1 mmol/L)
    - female <12.0 g/dL (7.5 mmol/L)
Anaemia and mortality

34 studies included

- 150,000 patients
- 37.8% had anaemia
- Odds ratio: 1.96 [1.74–2.21, p<0.001]
- Adjusted HR: 1.46 [1.26–1.69, p<0.001]
- Similar outcome in systolic/diastolic HF
Possible aetiologies of anaemia in heart failure

- Bone marrow failure
  - Westenbrink EJHF 2010
  - Ruifrok J Mol Med 2011

- Renal failure
  - EPO production
    - Westenbrink EHJ 2007
    - Belonje Circ 2010

- Medication
  - ACE-inhibitors
    - vd Meer Circ 2005

- Inflammation
  - Kleijn Heart 2012

- Blood loss
  - Anticoagulation

- Iron deficiency
  - Jankowska EHJ 2011

- Fluid retention
  - Hemodilution
    - Westenbrink EHJ 2007

van der Meer P. Eur Heart J 2004;25:285–91
Definition of iron deficiency

• Absolute ID
  – Depletion of iron available in the circulation (bound to transferrin) and iron stores (ferritin in the liver and iron in the RES)
  – Caused by chronic blood loss

  Strict: Ferritin < 30 µg/L
  FAIR-HF: Ferritin < 100 µg/L
  Nephro: Ferritin < 100 µg/L

• Functional ID
  – Depletion of iron available in the circulation (bound to transferrin) but not iron stores
  – Caused by inflammation induced by elevated hepcidin levels

  Strict: Ferritin < 30-99 µg/L when TSAT < 20%
  FAIR-HF: Ferritin < 100-299 µg/L when TSAT < 20%
  Nephro: TSAT < 20%
# Ferritin: Storage iron

<table>
<thead>
<tr>
<th>Parameter measured</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage iron(^1) (serum ferritin)</td>
<td>• The most useful indirect estimate of body iron stores(^2)</td>
<td>• Normal or high ferritin does not exclude functional ID or absolute ID(^3)</td>
</tr>
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<td></td>
<td>• In healthy individuals, serum ferritin correlated with body iron stores(^2)</td>
<td>• Gender differences (normally lower in women)(^1)</td>
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<td>• Acute-phase reactant(^1)</td>
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<td>• Can be elevated by concomitant inflammatory conditions, infection, malignancy or liver disease(^2,3)</td>
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## TSAT: Circulation iron

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<th>Limitations</th>
</tr>
</thead>
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<tr>
<td>• Amount of iron available for erythropoiesis&lt;sup&gt;1&lt;/sup&gt;</td>
<td>• Absence (or near absence) of stainable iron in bone marrow correlates with TSAT &lt;20%&lt;sup&gt;2&lt;/sup&gt;</td>
<td>• Marked diurnal variation&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>• TSAT = serum iron divided by total iron binding capacity (amount of transferrin) x 100&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td>• Transferrin is an acute-phase reactant&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>• Influenced by inflammation, malnutrition and chronic disease&lt;sup&gt;2&lt;/sup&gt;</td>
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<sup>1</sup> Macdougall IC. Curr Opin Nephrol Hyperten 1994;3:620–5

Transferrin
Iron deficiency is a common cause of anaemia

- A population-based cohort of patients with new-onset HF
  - n=12,065
- Anaemia identified in 17% of patients who tended to be:
  - older
  - female
  - hypertensive
  - chronically renal insufficient
- ID is the cause in 21% of patients with anaemia

![Bar chart showing the causes of anaemia](chart.png)

Iron deficiency is common in heart failure
Bone marrow biopsy “the golden standard”

- Patients with anaemia and advanced chronic HF
  - n=37
  - NYHA: IV
  - LVEF: 22%
  - Ferritin: 113 ng/mL
- Bone-marrow biopsy confirmed ID in 73% (27/37) of patients
- MCV, MCHb and serum ferritin concentration significantly lower in patients with ID compared with patients without ID

![Graph showing percentage of patients with different types of anaemia](image-url)
Prevalence of iron deficiency in large cohort

Iron deficiency and/or anemia

- NYHA class I-IV
- 1506 patients
- 86% were HFrEF
- ID: Ferritin < 100 µg/L or ferritin 100-299 µg/L when TSAT <20%
- Anemia WHO criteria

50% of HF patients are iron deficient

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Iron deficiency increases with severity of HF

Iron deficiency and/or anemia stratified by NYHA functional class

Frequency (%)

NYHA I (n = 121)
NYHA II (n = 577)
NYHA III (n = 712)
NYHA IV (n = 96)

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Mechanism of iron deficiency in HF

FPN=ferroportin; HFE=hemochromatosis; HJV=haemojuvelin; RBC=red blood cell; TFR=transferrin receptor

Effect of iron deficiency anemia on cardiac structure

A

Hemoglobin (g/dL)

1week 4weeks 12weeks 20weeks

* * * *

B

4weeks 12weeks 20weeks

Control IDA Control IDA

12weeks 20weeks

E

LVW/TL (mm)

1week 4weeks 12weeks 20weeks

* *

F

E

Fibrosis area (%)

4weeks 12weeks 20weeks

*
Iron deficiency is associated with reduced exercise capacity

- Iron deficiency defined as serum ferritin <100μg/L, or serum ferritin 100–300μg/L with TSAT <20%
- Anaemia defined as haemoglobin level <12g/dL in women and <13g/dL in men

- 443 patients with stable systolic CHF
- age 54 ± 10 years,
- males 90%,
- LV ejection fraction 26 ± 7%,
- NYHA: I/II/III/IV 49/188/180/26)

Impact of iron deficiency on exercise intolerance

IRON DEFICIENCY (ID)

HAEMATOPOIETIC TISSUES (ERYTHROCYTES, IMMUNE CELLS, PLATELETS)

Anaemia

↓ Oxygen carrying capacity (↓Hb)

Symptoms related to reduced O₂ transportation (↓ Maximal performance)

NON-HAEMATOPOIETIC TISSUES (MYOCARDIUM, ADIPOSE TISSUE, LIVER, KIDNEYS, BRAIN)

↓ Oxygen storage (myoglobin)
  ↓ Tissue oxidative capacity
  ↓ Energetic efficiency
  Anaerobic metabolism
  Mitochondrial dysfunction

Symptoms related to Tissue ID (↓ Endurance)

EXERCISE INTOLERANCE
### Predictor of iron deficiency

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Female vs. male</td>
<td>1.85 (1.45 - 2.35)</td>
<td>&lt; 0.001</td>
<td>1.67 (1.17 - 2.31)</td>
<td>0.005</td>
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<tr>
<td>NYHA functional class</td>
<td></td>
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<tr>
<td>III vs. I/II</td>
<td>1.73 (1.41 - 2.14)</td>
<td>&lt; 0.001</td>
<td>1.61 (1.25 - 2.11)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IV vs. I/II</td>
<td>2.07 (1.34 - 3.20)</td>
<td>0.001</td>
<td>1.80 (1.02 - 3.20)</td>
<td>0.022</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anemia, yes vs. no*</td>
<td>2.06 (1.63 - 2.61)</td>
<td>&lt; 0.001</td>
<td>1.68 (1.20 - 2.38)</td>
<td>0.033</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
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<tr>
<td>MCV, per 1 fl †</td>
<td>0.99 (0.98 - 0.99)</td>
<td>0.001</td>
<td>0.99 (0.98 - 0.99)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NT-proBNP, per 1 log pg/mL</td>
<td>1.21 (1.12 - 1.32)</td>
<td>&lt; 0.001</td>
<td>1.15 (1.05 - 1.34)</td>
<td>0.010</td>
</tr>
</tbody>
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Iron deficiency associated with adverse clinical outcome

HR 1.44; 95% CI 1.16 - 1.81; p = 0.001

P = 0.001

Numbers at risk:

<table>
<thead>
<tr>
<th></th>
<th>ID absent</th>
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<td></td>
<td>753</td>
<td>386</td>
<td>104</td>
<td>63</td>
<td>40</td>
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<tr>
<td>ID present</td>
<td>753</td>
<td>343</td>
<td>100</td>
<td>49</td>
<td>33</td>
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CONCLUSIONS

• Iron deficiency and anaemia are both commonly observed comorbidities in HF
• Iron deficiency is observed in almost 50% of HF patients
• Iron deficiency relates to a reduced exercise tolerance
• Iron deficiency is associated with a substantial higher mortality risk