Heart Failure, Ventricular Assist Devices, and Assessment of Recovery

Robert S. George (BSc BM MRCS)
Clinical Research Fellow
Definition

1) The pathophysiological state in which the heart is unable to pump blood at a rate commensurate with the requirements of the metabolising tissues, or can do so only from an elevated filling pressure.

2) A clinical syndrome characterised by dyspnoea and fatigue, at rest or with exertion, due to structural and/or functional abnormalities of the heart.

Heart failure is not a stand alone diagnosis, there is always a cause, although in many cases the exact cause is not uncovered.
Most Common Causes of Heart Failure

• Coronary Artery Disease (36-46%)

• Hypertension — results in LV hypertrophy and increased risk of MI (10-20%)

• Cardiomyopathy
# Other Causes of Heart Failure

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
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<tr>
<td>Drugs</td>
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<td>- Anaemia</td>
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<td>- Thyrotoxicosis</td>
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<td>Pericardial disease</td>
<td>- Constrictive pericarditis</td>
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<td>- Pericardial effusion</td>
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<td>- Tamponade</td>
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<td>Primary right heart PE/COPD</td>
<td>- Pulmonary hypertension 2º</td>
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<td>- Tricuspid regurgitation</td>
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<td>Post Cardiotomy</td>
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New York Heart Association Classification

<table>
<thead>
<tr>
<th>CLASS</th>
<th>Class Description</th>
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<tr>
<td>I</td>
<td>Cardiac disease but no limitation in physical activity</td>
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<td>II</td>
<td>Slight limitation, but comfortable at rest</td>
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<td>III</td>
<td>Marked limitation, less than ordinary activity causes dyspnoea</td>
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<td>IV</td>
<td>Unable to carry out any physical activity without discomfort, symptoms often present at rest</td>
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Patients can move in either direction
# Stages of Heart Failure (ACC/AHA)

<table>
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<tr>
<th>STAGE</th>
<th>Stage Definition</th>
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</table>
| A     | High risk of developing heart failure with no symptoms / structural disorder of the heart  
Managed by reducing risk factors, patient and family education |
| B     | Structural heart disease (systolic LV dysfunction) with no symptoms  
Diagnosis is usually made when EF < 40% is found during an echo. |
| C     | Structural heart disease (i.e. known systolic heart failure) with current or past symptoms. |
| D     | End stage disease with refractory symptoms requiring special intervention (inotropes, VAD, transplantation, or Hospice) |

Patients can only progress from A → D
Scale of the Problem

• Incidence 10 per 1000 over 65 years of age
• Over 900,000 people in UK; 5 million in USA
• Prevalence 1-2% adult population
• 65,000 new cases/yr
• In 2006, costs NHS £716 million/yr (£628 million/yr in 2000)
• 1 million bed days
• 2% NHS total cost
• 5% acute medical admissions
Cost to NHS (£716 millions/yr)

- Primary care: 17
- Hospital inpatient care: 60
- Hospital day-case care: 17
- Hospital outpatient care: 9
- Outpatient investigations: 8
- Drugs: 0.07

Royal Brompton & Harefield NHS
Imperial College London
The Magdi Yacoub Institute
Heart Failure – Prognosis

• Poor prognosis
  – Worse than malignancy
  – 50% with severe heart failure die within 2 years of diagnosis
  – NYHA III/IV 40 - 60% annual mortality
  – 30-40% patients with heart failure die suddenly from lethal arrhythmias
Chronic Heart Failure

- Chronic decline in myocardial function takes place over months or years
- Physiological adaptations to chronic heart failure lead to stable “compensated” heart failure
- These short term adaptation leads to MYOCARDIAL REMODELING - the HALLMARK of Heart Failure
- Myocardial remodeling leads to further impairment of pump function and a self perpetuating cycle
- This leads to progression of heart failure until signs and symptoms become apparent
Clinical Features – Symptoms

- Dyspnoea – common symptom in general population so not specific
- Orthopnea – more specific symptom
- PND – results from nocturnal fluid redistribution
- Fatigue and lethargy
- Confusion
- Peripheral oedema
- Right hypochondrial pain (liver distension)
- Ascites
Clinical Features – Physical Signs

- May be absent in mild/mod HF
- Peripheral oedema
- Lung crackles
- Pleural effusion
- AF present in 10-50%
- Anaemia
Pathophysiology

Myocardial Injury → Fall in LV performance

Myocardial Toxicity

RAA SNS Cytokines Others

Remodelling and progressive worsening of LV function

- ANP & BNP
  • Peripheral vasoconstriction
  • Haemodynamic alterations

Morbidity and mortality

Heart Failure Symptoms

Symptoms

ANP & BNP-
**RAA system**

- Perfusion
- **SNS**
- **ADH**
- **Aldosterone**
- **Vasoconstriction**
- **Sodium Retention**

**Angiotensinogen**
- **Renin**
- **Angiotensin I**
- **ACE**
- **Angiotensin II**
  - **ADH**
  - **Aldosterone**
  - **Vasoconstriction**
  - **Sodium Retention**
  - **Sodium Retention**
Sympathetic Nervous System

- Activated in HF via baroreceptors to provide inotropic support
- Causes activation of RAA system and vasoconstriction leading to increased pre- and after-load
- Chronic activation leads to
  - myocyte hypertrophy, necrosis and apoptosis
  - down regulation of β-receptors leading to impaired responsiveness of heart to catecholamines
G-proteins and Ca^{2+} handling

- Gs stimulates AC \rightarrow \uparrow \text{intracellular cAMP} \rightarrow \text{Ca}^{2+} \text{ influx.}
- Gi inhibits

HF is associated with increase in Gi:Gs ratio

- Other alterations in calcium handling and excitation-contraction coupling are also seen in HF
Other Players

• Norpinephrine transporter
• Extracellular Matrix (MMP and TIMPs)
• Endothelial Cells (PGI$_2$ and NO)
• Fibroblasts (fibrogenesis and collagen cross-talks)
• SERCA and Phospholamban
• Cytokines – IL6, TNF$_\alpha$
• Na$^+$-Ca$^{2+}$ exchanger
Reverse Remodeling

• Can we break the vicious cycle?

• It is possible to reverse the pathological remodelling process by a combination of:
  
  • Mechanically unloading the failing left ventricle
  
  • Reversing neurohormonal dysfunction and promote reverse remodelling with drugs
  
  • Promote physiological hypertrophy of the ventricle
Treatment options for Heart Failure

**Symptomatic Heart Failure and low LV ejection fraction**

- **Angina**
  - Nitrates
  - Amlodipine
  - Nicorandil
  - Antiplatelet
  - Revascularisation

- **NYHA II-IV (Consider in all patients)**
  - ACE Inhibitor
  - B-Blocker
  - Angiotensin-receptor blocker
  - Implantable cardioverter defib

- **Atrial Fibrillation**
  - Digoxin
  - Warfarin
  - Amiodarone

- **Hypertension**
  - Spironolactone
  - Hydralazine
  - Amiodipine

**NYHA III-IV (persisting signs and symptoms)**

- Spironolactone
- Digoxin
- Cardiac resynchronisation

**NYHA IV (Intractable heart failure)**

- Transplantation
- Ventricular Assist Device
ISHLT Registry of Adult Heart Transplants Performed
Royal Brompton and Harefield Heart Transplants 1980-2006
Problems Associated with Transplantation

• Finding donor
  • 30,000 patients added on Tx waiting list
  • 3,500 die whilst waiting
• Rejection
  • Hyperacute
  • Acute
  • Chronic
• Immunosuppression
• Infection
Mechanical Circulatory Support

Indication

Deteriorating heart failure despite optimal medical therapy
Application of VAD

- Short term support (e.g. post cardiotomy – using Levitronix)
- Bridge to transplantation
- Bridge to recovery
- Long-term chronic support (Destination Therapy)
Bridge to Transplantation

- Life saving in deteriorating patients
- Improves secondary organ dysfunction for Tx
- Nutrition can be improved
- Opportunities for prospective HLA matching
- Reduces PA pressures
- Comparable survival following LVAD/ non-LVAD OCTx
REMATCH Study

- Suitability of Heart-Mate vented-electric device (first generation pulsatile device) for long term myocardial replacement in patients “ineligible” for transplantation
- 629 patients randomised to either LVAD or Medical Rx
- NYHA Class 4 > 90 days
- 20 centres USA 1998-2001
- Enrollment stopped after 92 deaths
REMATCH Study - survival

No. at Risk

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<th>Medical therapy</th>
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</table>
REMATCH Study – outcome

• Improvement in NYHA classification in LVAD patients at 1, 3, 6, 9, and 12 months.

• LVAD patients had significantly higher number of days out of hospital.

• Improvement of quality of life in LVAD patients.
Summary

• Heart failure is a syndrome

• Different pathophysiological pathways

• Trend in transplantation is declining

• Mechanical circulatory support provide an alternative to transplantation
Harefield Recovery Study

Promising results in Class IV DCM
High explantation rate – 75%
Low post-explantation mortality with preserved LV function. Survival of 90% after 6 years
HeartMate I
HeartMate II
HeartWare
Human Left Ventricular Myocytes

Inclusion Criteria

• Patients with severe heart failure with idiopathic dilated cardiomyopathy (class III and IV)

• Age 8 – 65

• Large enough for intra-peritoneal device (for HeartMate I devices) – If not other alternative devices (e.g. Jarvik 2000, HeartMate II)

• mVO2 less than 14mls / min / kg

• Ejection fraction ≤ 20%

• EDD ≥ 65mm

• Cardiac Index ≤ 1.8 l/min/m²
Pharmacological Therapy (1)

Drugs Started post operatively as tolerated:

**PHASE I**

- Digoxin 125µg OD
- Lisinopril 20mg OD
- Losartan 100mg OD
- Spironolactone 25mg OD
- Carvedilol 25mg BD
PHASE II

- **Clenbuterol** started when evidence of myocardial recovery

- Carvedilol => Bisoprolol 10 mg OD
β2- Agonist [CLENBUTEROL]

- Selective β2 receptor agonist

Promotes physiological hypertrophy
Clenbuterol & its actions

1) On skeletal muscle
   • ‘Physiological’ hypertrophy
   • Increased power – Petrou 1999, Maltin 1993
   • Faster contraction & relaxation – Petrou 2000
   • Induction of IGF1 – *Cell* 2002

2) On cardiac muscle
   • ‘Physiological’ hypertrophy – Wong 1998, Petrou 1995
   • Prevents fibrosis following banding of the aorta & PA – Hon 2001
   • Gene expression (physiological hypertrophy) – Bhavsar 2002
Recovery Algorithm

Phase I
- Digoxin
- Lisinopril
- Losartan
- Spironolactone
- Carvedilol

Evidence of recovery?
Yes → Phase II
- Clenbuterol

RECOVERED?
Yes → Explanant
No → Recovery Assessment

No → Tx Waiting List

How do we assess recovery?

1. Regular Haemodynamic measurements
2. Regular Echocardiograms
3. Regular Exercise Testing
4. Cardiac Catheterisation
5. $^{123}$I-MIBG nuclear imaging
METHODS

Device switched off / reduce speed 10 minutes after 10,000 units of intravenous heparin

- Pulsatile pumps -> hand pumping 3 times every 15 seconds to avoid blood stagnation within the pump

- Non-pulsatile pumps -> reduce the speed of the pump
  - 6000 rpm in HeartMate II
  - 1800 rpm in HeartWare
  - 6000 rpm in Jarvik2000
1) Haemodynamic Measurements

Blood pressure and heart rate

– with device on

– at 0 minute

– at 5, 10, and 15 minutes (pump off / reduced speed)

– and if tolerated after 6-minute walk (6MW)
2) Echocardiographic Measurements

Ventricular dimensions, EF, and wall thickness:

– with device on

– at 5 and 15 minutes (pump off / reduced speed)

– and if tolerated after 6-minute walk (6MW)
## Example of Serial Echocardiograms

<table>
<thead>
<tr>
<th>Date</th>
<th>9000 RPM</th>
<th>15min 6000 RPM</th>
<th>Post 6MW</th>
<th>9000 RPM</th>
<th>15min 6000 RPM</th>
<th>Post 6MW</th>
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<th>9000 RPM</th>
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<table>
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<tr>
<th>Date</th>
<th>LVSD 9400 RPM</th>
<th>15min 6000 RPM</th>
<th>Post 6MW</th>
<th>LVDD 9400 RPM</th>
<th>15min 6000 RPM</th>
<th>Post 6MW</th>
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<th>EF 9400 RPM</th>
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</table>
Echo Data

LVDD pre & post imp

LVSD pre & post imp
HArefield Recovery Protocol (HARP) – 9 US centres

- Texas Heart Institute (Drs OH Frazier/Dr Borgaev)
- Washington Hospital Centre (Dr LW Miller)
- University of Michigan (Drs F Pagani/K Aaronson)
- Ohio State University (Dr D Feldman)
- Northwestern University, Chicago (Dr J O’Connell)
- University of Pennsylvania (Dr M Jessup)
- Montefiore Hospital, New York (Dr S Maybaum)
- Cleveland Clinic
- University of Alabama
3) Exercise Testing (mVO$_2$)

When able to achieve 450 metres in 6 minute walk “off-pump / reduced speed”

mVO$_2$, $V_E/VCO_2$, exercise time

Modified Bruce Protocol

VAD on / full speed
VAD off / reduced speed after several hours
## Example of Serial mVO$_2$

<table>
<thead>
<tr>
<th>Time since explantation</th>
<th>Test protocol</th>
<th>Duration of test</th>
<th>mVO$_2$ (mls/kg/min)</th>
<th>VE/VCO$_2$</th>
<th>Reason for stopping</th>
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<tr>
<td>1.5 month</td>
<td>Full Bruce</td>
<td>6 min 20 sec</td>
<td>24.7</td>
<td>23 %</td>
<td>Fatigue</td>
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<tr>
<td>2.5 months</td>
<td>Full Bruce</td>
<td>6 minutes</td>
<td>24.4</td>
<td>26 %</td>
<td>Fatigue</td>
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<td>3.5 months</td>
<td>Full Bruce</td>
<td>7 minutes</td>
<td>26</td>
<td>26 %</td>
<td>Fatigue</td>
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<tr>
<td>5 months</td>
<td>Full Bruce</td>
<td>8 min 35 sec</td>
<td>28.8</td>
<td>26 %</td>
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<td>6 months</td>
<td>Full Bruce</td>
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<td>28.7</td>
<td>27 %</td>
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<td>9 minutes</td>
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<td>Fatigue</td>
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<td>Full Bruce</td>
<td>9 minutes</td>
<td>29.9</td>
<td>20 %</td>
<td>Fatigue</td>
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4) Cardiac Catheterisation / Blood

Right and left heart catheter

LV Biopsies : Gene chip, single cell physiology

Humoral changes – BNP, ANP, Norepinephrine
5) $^{123}$I-MIBG nuclear imaging

Early post device implantation

Pre-explantation or listing for Tx

• Early and delayed heart/mediastinum ratios
• Washout rate
Explantation Criteria

LV dimensions with device off / reduced speed

- EDD <60mm, ESD <50mm, EF >45%

LVEDP <12mmHg

Resting CI >2.8L/min/m²

mVO₂ >16ml/kg/min
“Device Cessation / Speed Reduction”

- Is it SAFE?

- Is it NECESSARY?

- Is it EFFECTIVE in ASSESSING RECOVERY?
Patient Population

• 22 patients with HeartMate I LVAD for end-stage non-ischaemic cardiomyopathy

• Enrolled in the Harefield Recovery Programme

• Time period 1998-2006
Outcome

22 patients submitted to echocardiogram and haemodynamic protocols

22 Patients

16 Patients Recovered and device Explanted

6 Patients did not recover and Tx
Results

• 207 tests were performed

• On 5 (2.4%) occasions patients could not tolerate the initial switching off the device

• No late or early thromboembolic events
Echocardiographic Measurements
Recovered Group (n=16)

132 serial echocardiograms

- All tolerated the initial switching off the device

- 8 occasions (6.1%) patients unable to complete 6-minute walk
Echocardiographic Measurements
Non-Recovered Group (n=6)

75 serial echocardiograms

- 5 occasions (6.7%) patients did not tolerate the initial switching off the device
- 12 occasions (16%) patients unable to perform 6-minute walk
- Assessment continued for 14 ± 3.8 months since implantation
Mean Arterial Blood Pressure

Mean ± S.D.

MAP (mmHg)

LVAD on
LVAD immediately off
LVAD 5 mins off
LVAD 10 mins off
LVAD 15 mins off
LVAD off Post 6MW

‡ p<0.05
Systolic Blood Pressure

<table>
<thead>
<tr>
<th>SBP (mmHg)</th>
<th>LVAD on</th>
<th>LVAD immediately off</th>
<th>LVAD 5 mins off</th>
<th>LVAD 10 mins off</th>
<th>LVAD 15 mins off</th>
<th>LVAD off Post 6MW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered</td>
<td>On</td>
<td>0mins</td>
<td>5mins</td>
<td>10mins</td>
<td>15mins</td>
<td>6MW</td>
</tr>
<tr>
<td>Non-Recovered</td>
<td>On</td>
<td>0mins</td>
<td>5mins</td>
<td>10mins</td>
<td>15mins</td>
<td>6MW</td>
</tr>
</tbody>
</table>

MEAN ± S.D.

* p<0.05
** p<0.05
Diastolic Blood Pressure

Diastolic Blood Pressure (DBP) in mmHg for patients with LVAD on and off at different time points: 0 mins, 5 mins, 10 mins, 15 mins, and post 6MW. The graph shows the mean ± standard deviation (SD) for recovered and non-recovered patients.

- On LVAD immediately off
- LVAD 5 mins off
- LVAD 10 mins off
- LVAD 15 mins off
- LVAD off Post 6MW

$p < 0.05$ indicates a statistically significant difference between the groups.
Pulse Pressure

PP (mmHg)

Recovered Non-Recovered

LVAD on
LVAD immediately off
LVAD 5 mins off
LVAD 10 mins off
LVAD 15 mins off
LVAD off Post 6MW

MEAN ± S.D.

‡‡ p<0.05
‡ p<0.05
** p<0.05
Heart Rate

“Inotropic Reserve” MEAN ± S.D.

‡ p<0.05
‡‡ p<0.05
¤ p < 0.05

“Inotropic Reserve”

LVAD on
LVAD immediately off
LVAD 5 mins off
LVAD 10 mins off
LVAD 15 mins off
LVAD off Post 6MW

HR (bpm)

Recovered

Non-Recovered

On 0mins 5mins 10mins 15mins 6MW On 0mins 5mins 10mins 15mins 6MW
Correlating MAP and HR after 6 minutes walk

**Recovery Group**

- $R = 0.254$
- $p = 0.361$

**Non-Recovery Group**

- $R = 0.932$
- $p = 0.021^*$
Ejection Fractions Measurements

* p<0.05

![Bar chart showing Ejection Fractions Measurements for LVAD on and off with different time intervals and post 6 MW.](chart.png)

- LVAD on
- LVAD 5 mins off
- LVAD 15 mins off
- LVAD off Post 6 MW
Ventricular Dimensions in Recovered Group

![Graph showing ventricular dimensions](image)

- LVAD on
- LVAD 5 mins off
- LVAD 15 mins off
- LVAD off Post 6 MW

**LVSD**
- ON
- 5 mins
- 15 mins
- 6MW

**LVDD**
- ON
- 5 mins
- 15 mins
- 6MW
Ventricular Dimensions in Non-Recovered Group

**p=0.05**

- LVAD on
- LVAD 5 mins off
- LVAD 15 mins off
- LVAD off Post 6MW

LVAD Dimensions (mm)

- LVSD
- LVDD
Total Distance Walked during 6-minute walk

<table>
<thead>
<tr>
<th>Group</th>
<th>Distance (m)</th>
<th>MEAN ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>544.30</td>
<td>*</td>
</tr>
<tr>
<td>Non-Recovery</td>
<td>418.41</td>
<td>*</td>
</tr>
</tbody>
</table>

*p=0.03
Conclusion

- Switching off the HeartMate I device is safe with no long lasting effects

- Haemodynamic and echocardiographic parameters are valuable in evaluating recovery

- Inotropic reserve appears to be a strong indicator of recovery

- MAP, PP and EF after 6MW are strong predictive factors for recovery