“The very essence of cardiovascular practice is the early detection of heart failure”
Sir Thomas Lewis, 1933

I have no relevant financial disclosures or conflicts
I will not be discussing off label use of pharmaceutical agents or devices
Objectives

To discuss available treatment strategies for advanced cardiothoracic disease

To discuss patient factors that effect these options
A clinical syndrome of sodium and water retention leading to breathlessness caused by neurohormonal activation in the setting of cardiac disease. No reference to ejection fraction or systolic function. Nothing about etiology.

Symptoms result from:
- Increased filling pressures with relaxation
- Inadequate rise cardiac output with exercise
- Reduced resting cardiac output
Burden of Heart Failure

Annually in US

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Incidence</th>
<th>Primary Mortality</th>
<th>Hospital admissions</th>
<th>Re-Hospital &lt;30d</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,100,000</td>
<td>&gt;650,000</td>
<td>55,000</td>
<td>&gt;1,000,000</td>
<td>25%</td>
<td>$39 billion</td>
</tr>
</tbody>
</table>

50% of people who have heart failure die within 5 years of diagnosis

200,000 people have Stage D HF with >70% annual mortality

It is the leading cause of hospitalization for those >65 yo with a 22% annual mortality following the first hospitalization

Death is 6-9x more common than general population

Mortality greater than AIDS, lung, prostate and breast cancer combined

Adler et al, Circ 2009; Thome et al, Circ 2006
Heart failure (preferred over congestive heart failure)

Symptoms of dyspnea and fatigue

Inability to meet the metabolic demands of the body, or having to do so with elevated filling pressures

<table>
<thead>
<tr>
<th>EF (%)</th>
<th>EF ≤ 40</th>
<th>41-49</th>
<th>≥ 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFrEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFpEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFpEF borderline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFpEF improved (from HFrEF)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Preserved LVEF (cut off has varied from LVEF 40-55%; normal LVEF=>=55%)

Absence of significant valvular, pericardial and ischemic heart disease
ACC/AHA HF Stages

**At Risk for Heart Failure**

**Stage A**
At high risk for HF but without structural heart disease or symptoms of HF.

*Example: Patients with:
- Hypertension
- Atherosclerotic disease
- Diabetes
- Metabolic syndrome
- Patients using cardiotoxins
- With HFx CM

**Stage B**
Structural heart disease but without symptoms of HF.

*Example: Patients with:
- Previous MI
- LV remodeling including LVH and low EF
- Asymptomatic valvular disease

**Stage C**
Structural heart disease with prior or current symptoms of HF.

*Example: Patients with:
- Known structural heart disease and
- Shortness of breath and fatigue, reduced exercise tolerance

**Heart Failure**

**Stage D**
Refractory HF requiring specialized interventions.

*Example: Patients who have marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)

**Therapy Goals**
- Treat hypertension
- Encourage smoking cessation
- Treat lipid disorders
- Encourage regular exercise
- Discourage alcohol intake, illicit drug use
- Control metabolic syndrome

**Drugs**
- ACEI or ARB in appropriate patients (see text)
- Beta-blockers
- Devices in Selected Patients
- Implantable defibrillators

**Therapy Goals**
- All measures under stages A and B
- Dietary salt restriction
- Drugs for Routine Use
- Diuretic for fluid retention
- ACEI
- Beta-blockers

**Drugs in Selected Patients**
- Aldosterone antagonist
- ARBs
- Digitalis
- Hydralazine/nitrates
- Devices in Selected Patients
- Biventricular pacing
- Implantable defibrillators

**Therapy Goals**
- Appropriate measures under stages A, B, C
- Decision re: appropriate level of care

**Options**
- Compassionate end-of-life care/hospice
- Extraordinary measures
- Heart transplant
- Chronic inotropes
- Permanent mechanical support
- Experimental surgery or drugs
ACC/AHA HF Stages

At Risk for Heart Failure

**Stage A**
At high risk for HF but without structural heart disease or symptoms of HF.

- **e.g.: Patients with:**
  - hypertension
  - atherosclerotic disease
  - diabetes
  - metabolic syndrome
  - or
  - Patients using cardiotoxins
  - with HFx CM

**Therapy Goals**
- Treat hypertension
- Encourage smoking cessation
- Treat lipid disorders
- Encourage regular exercise
- Discourage alcohol intake, illicit drug use
- Control metabolic syndrome

**Drugs**
- ACEI or ARB in appropriate patients
- (see text)

**Development of Symptoms of HF**

**Stage B**
Structural heart disease but without symptoms of HF.

- **e.g.: Patients with:**
  - previous MI
  - LV remodeling including LVH and low EF
  - asymptomatic valvular disease

**Therapy Goals**
- All measures under stage A and B
- Dietary salt restriction
- Drugs for Routine Use
- Diuretic for fluid retention
- ACEI
- Beta-blockers

**Devices in Selected Patients**
- Implantable defibrillators

**Stage C**
Structural heart disease with prior or current symptoms of HF.

- **e.g.: Patients with:**
  - known structural heart disease
  - and
  - shortness of breath
  - and fatigue
  - reduced exercise tolerance

**Therapy Goals**
- All measures under stages A and B
- Dietary salt restriction
- Drugs for Routine Use
- Diuretic for fluid retention
- ACEI
- Beta-blockers

**Devices in Selected Patients**
- Implantable defibrillators
- Biventricular pacing

**Stage D**
Refractory HF requiring specialized interventions.

- **e.g.: Patients** who have marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)

**Therapy Goals**
- Appropriate measures under stages A, B, C
- Decision re: appropriate level of care

**Options**
- Compassionate end-of-life care/hospice
- Extraordinary measures
- Heart transplant
- Chronic inotropes
- Permanent mechanical support
- Experimental surgery or drugs
NYHA Functional Classification

Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina.

Class II: Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.

Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.

Class IV: Unable to carry on any physical activity without discomfort. Symptoms present at rest. With any physical activity, symptoms increase.

Refractory HF requiring specialized interventions

Patients who have marked symptoms at rest despite maximal medical therapy

All medical therapies AND Mechanical assist devices, Heart Transplantation, Continuous IV inotropic infusions for palliation Hospice

The median survival for heart failure patients 2.1 years

Men

- Normal EF: 31%
- Borderline EF: 42%
- Reduced EF: 27%

Women

- Normal EF: 67%
- Borderline EF: 23%
- Reduced EF: 10%

Cardiovascular Health Study
Etiology of HF

- Ischemic heart disease
- Hypertension
- Valvular heart disease
- Cardiomyopathies
  - Dilated
  - Arrhythmic (typically tachycardia)
  - Familial
- Congenital heart disease

Risks also:
  - Alcohol, obesity, diabetes, thyroid disease, infections
Patients with HF often do not understand their disease prognosis.

Cognitive deficits affect the ability to understand and self manage.
Comorbidities contribute, cardiorenal, hepatic congestion, encephalopathy.

Defects are in functional domains – visual- spatial, insight.

There is often no clearly defined terminal phase to direct conversations.

Survival time vs. quality of life.
Time to prepare for things, get affairs in order.

Maclver et al. JLHT 27:2008
Murks, CM, Fedson SF – unpublished data
Lewis et al. JHLT 2001
Survival Differences: EF

Worse survival associated with lower EF, renal dysfunction, hospital admission

Systolic HFrEF
EF < 40%
Contractile dysfunction

“Diastolic” HFpEF
EF >40%
Relaxation/compliance dysfunction
Trajectory of (systolic) Heart Failure

Allen et al. Circ 2012
Trajectory of (systolic) Heart Failure

- Transplant – normalcy with gradual decline
- Mechanical Support
- Palliative Care
- Continuous inotropes
- MCS with complications
- Traditional Care
OPTIONS FOR STAGE D
Therapeutic Options Stage D

Severe Heart Failure
Aggressive therapies
Likelihood of death < 12 months

Lack of Absolute Contraindications
Significant comorbidities
Malignancies

Relative Contraindications
(Renal failure, PVD)

Mechanical Circulatory Support

Experimental / Alternative Therapies
Hospice/Palliative Care

Transplant Candidate
Cardiopulmonary stress testing

Invasive/non invasive measurement of Cardiac Output – poor predictors of symptoms, exercise capacity, prognosis and need for transplantation

<table>
<thead>
<tr>
<th>Study</th>
<th>pVO2 (ml/kg/min)</th>
<th>Outcomes (mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mancini et al Circ 1991</td>
<td>$&lt; 14$ candidate for OHT</td>
<td>52% 1 yr</td>
</tr>
<tr>
<td></td>
<td>$&lt;14$ not candidate for OHT</td>
<td>68% 2 yr</td>
</tr>
<tr>
<td></td>
<td>$&gt;14$ too well for OHT</td>
<td>16% 2 year</td>
</tr>
<tr>
<td>Szlachcic et al AJC 1985</td>
<td>$&lt;10$</td>
<td>77% 1 yr</td>
</tr>
<tr>
<td></td>
<td>$&gt;10$</td>
<td>21% 1 yr</td>
</tr>
<tr>
<td>Likoff et al AJC 1987</td>
<td>$&lt;13$</td>
<td>64% 1 yr</td>
</tr>
<tr>
<td></td>
<td>$&gt;13$</td>
<td>85% 1 yr</td>
</tr>
<tr>
<td>Stelken et al JACC 1996</td>
<td>$\leq 50%$ predicted</td>
<td>26% 1 yr</td>
</tr>
<tr>
<td></td>
<td>$&gt; 50%$ predicted</td>
<td>57% 2 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2% 1yr, 10% 2 yr</td>
</tr>
</tbody>
</table>
All cause mortality
Peak O2 still discriminatory
Consider different cut-point – given improved survival with beta blockers (12ml/kg/min)

Excessive ventilatory response (ie VE/VCO2 slope of ≥ 35) = mortality rate similar to peak VO2 of ≤ 10 ml/kg/min (whole population)

O’Neill et al, Circ 2005
Corra et al, Chest 2004
PA Hypertension, PVR
Predictive for morbidity and eligibility in Transplant AND LVAD

Response to vasodilator therapy (transplant)
PCWP < 16mmHg – 83 % 1yr survival 83% v. 38% without response to vasodilator testing
Donor RV does not tolerate PASP 55-60mmHg
RV failure, graft dysfunction, death

Much PA HTN is reactive, or secondary to elevated PCWP
Vasodilator testing for responsiveness – residual PVR of 2.5 WU increases transplant mortality
Transplant Survival by PVR (Tx 1/03 – 6/11)

1-<3 vs. 3-<5: p = 0.0006
No other pair-wise comparisons were significant at p < 0.05

JHLT. 2013 Oct; 32(10): 951-964
RV Failure post LVAD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC (95% CI)</th>
<th>*p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV failure risk score</td>
<td>0.73 (0.65–0.81)</td>
<td>—</td>
</tr>
<tr>
<td>Severe RV failure on echocardiograph</td>
<td>0.59 (0.51–0.68)</td>
<td>0.004</td>
</tr>
<tr>
<td>RVSWI</td>
<td>0.63 (0.55–0.72)</td>
<td>0.011</td>
</tr>
<tr>
<td>PVR</td>
<td>0.50 (0.41–0.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TPG</td>
<td>0.56 (0.48–0.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PA systolic pressure</td>
<td>0.59 (0.51–0.68)</td>
<td>0.017</td>
</tr>
<tr>
<td>RA pressure</td>
<td>0.53 (0.44–0.61)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CVP:PCWP > 0.63

PAC = SV/PASP-PADP

PASP-PADP/CVP = PAPI

**Figure 3** Kaplan–Meier curves for 6-month survival stratified by a hemodynamic profile of indexed pulmonary arterial compliance (PACi) and the ratio of central venous pressure to pulmonary capillary wedge pressure (CVP:PCWP).
Transplant (and LVAD) Evaluation

Look for co-morbidities that effect survival and quality of life

Pulmonary limitation – O2 dependence, - PFTs

Vascular disease (cerebral, arterial) – Carotid duplex, ABI, Eval for AAA

Infectious Disease –
- HIV – relative contraindication
- Hep B/C – relative without OLT
- EBV – risk for PTLD
- CMV – risk for primary, reactivation
- TB – risk for reactivation
- RPR – needs treatment

Renal Disease –
- Risk for renal failure
- SPEP/UPEP in addition

Cancer Screening –
- Age and risk appropriate
- Colonoscopy
- PSA
- Mammography
- PAP
- High Res CT for smokers

Dental – abscess, oral lesions (cancer)

Anticipated risks/needs –
- Homocysteine, G6PD
Indications for LVAD

Class IV heart failure unresponsive to Optimal Medical Management for at least 60 of last 90 days
LVEF < 25%
Functional limitation VO2 <12 ml/kg/min, or inotrope dependence
Appropriate size (BSA 1.5m2)

Intention:
Destination Therapy (DT)
Bridge to … Transplantation (BTT)

Type:
Durable – longevity, ambulatory
Temporary – months of support, +/- ambulatory, often only in hospital

LVADs are restorative – not reversing the course of heart failure changing the trajectory of demise and symptoms (similar to hemodialysis)
They are also life sustaining and life prolonging at times
**Candidacy – for Options**

**TRANSPLANT**
- VO2 ≤ 14 ml/kg/min (12 on ββ)
- Age ≤ 70 years
- BMI ≤ 35 kg/m²
- Cancer – if likelihood of recurrence is low, negative metastatic work up (No time period stated)
- No significant other co morbidities that are not managed (renal ftn, diabetes)
- Appropriate psychosocial evaluation – no substance abuse

**LVAD**
- Class IV HF unresponsive to OMM for at least 60 of last 90 days
- LVEF < 25%
- Functional limitation VO2 <12 ml/kg/min, or inotrope dependence
- Appropriate size (BSA 1.5m²)
Psychosocial Evaluation

Often overlooked in the setting of complex medical diseases

Cognitive dysfunction in HF patients
   Need to assess ability of patient to care for/manage transplant, medical adjustments

Depression/substance abuse
   PTSD (present in up to 11% of transplant candidates related to ICD shocks)
Smoking and Transplantation

Effects medical outcome

Thoracic selection criteria uses personal behaviors, compliance, alcohol, drug use, morbid obesity more than abdominal selection committees

Consequence of tobacco/marijuana use
Medical outcomes of malignancy, all cause mortality

Patient’s right to self-injurious behaviors

“Sin tax”

Is nicotine addiction a medical condition that warrants treatment?
Which Choice, What Patient
Transplant Numbers

Waiting list 121,422
Active waiting 78,002

Jan-Nov 2015
Total transplants 28,211
Donors 13,708

Transplants Jan 1, 1988-Nov 30, 2015

<table>
<thead>
<tr>
<th>Organ</th>
<th>Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>384,691</td>
</tr>
<tr>
<td>Liver</td>
<td>139,371</td>
</tr>
<tr>
<td>Pancreas</td>
<td>8,110</td>
</tr>
<tr>
<td>Kidney / Pancreas</td>
<td>21,262</td>
</tr>
<tr>
<td>Heart</td>
<td>62,267</td>
</tr>
<tr>
<td>Lung</td>
<td>30,822</td>
</tr>
<tr>
<td>Heart / Lung</td>
<td>1,181</td>
</tr>
<tr>
<td>Intestine</td>
<td>2,644</td>
</tr>
<tr>
<td>Total</td>
<td>650,348</td>
</tr>
</tbody>
</table>

Puerto Rico (Region 3) | Washington, DC (Region 2)

Learn more about each region:
- Region 1
- Region 2
- Region 3
- Region 4
- Region 5
- Region 6
- Region 7
- Region 8
- Region 9
- Region 10
- Region 11

Unos.org; accessed Feb 17, 2016
Equity

Fairness/Impartiality
Access to transplant centers (listing at multiple centers)
Geographic – local, regional or national (country)
Physician ignorance
Insurance contracts
freedom from bias
Which Choice, What Patient

Medical considerations – the patient (candidate)
Not everyone is a transplant or MCS candidate

Cancer – moving target on issues of prostate cancer, non-melanomatous skin cancers

   Age – how old is too old?
      Physiologic age

Mechanical Circulatory support – anticipated complications
   Organic brain disease, infections
   Colonic, Urologic pathology
   RV function

Who can best use an organ or pump? Potential?
Heart Transplant Survival
(1/1982 – 6/2013)

Median survival = 11 years
Median survival conditional on surviving 1st year = 13 years

N = 112,521
N at risk at 30 years = 16

JHLT. 2015 Oct; 34(10): 1244-1254
Autonomy of persons is the ethical basis for consent
HF – cognitive impairment, (even when on VAD)

Exchange of one set of medical problems for another
DM, infection, PTLD and other cancers
Bleeding, CVA, infection, life with a “toaster”
Increase arrhythmia, less dyspnea

Primary of First Person consent – as distinguished from surrogate decision making/ or substituted judgment for MCS
Can you submit patients to life shortening drugs for non-life extending transplantation?

What will MCS outcomes need to be?

    Should age be considered in outcome expectations?

Are transplants going to be the option for those who cannot have a VAD?

Palliative inotropes
Sensitized Patients

Occurs from interaction of host (recipient) with non-self antigens

Previous transplant (most robust way of exposure to antigens)

Pregnancy (especially multiple paternity)

Blood transfusions – PRBC, pooled products, platelets

Composite tissue (congenital repairs, bioprosthetic valves)

Mechanical circulatory support (LVADs) – membrane exposure

Additional Risks

Hemodialysis

Viral infections (CMV)

Panel Reactive antibody (PRA) - % of cells from a panel of random donor against which a recipient’s serum reacts

>10% = sensitized

>80% = highly sensitized

>30% may necessitate aggressive desensitization protocols
### Interagency Registry for Mechanically Assisted Circulatory Support

<table>
<thead>
<tr>
<th>Level</th>
<th>Clinical Status</th>
<th>Colloquially</th>
<th>Expected survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Critical Cardiogenic Shock</td>
<td><em>Crash and Burn</em></td>
<td>hours</td>
</tr>
<tr>
<td>2</td>
<td>Progressive decline on Inotopes</td>
<td><em>Sliding on inotropes</em></td>
<td>1-7 days</td>
</tr>
<tr>
<td>3</td>
<td>Stable, inotrope dependant</td>
<td><em>Dependant Stability</em></td>
<td>weeks</td>
</tr>
<tr>
<td>4</td>
<td>Resting symptoms on Oral therapy</td>
<td><em>Frequent flyer</em></td>
<td>Weeks to few months</td>
</tr>
<tr>
<td>5</td>
<td>Exertion intolerant</td>
<td><em>Housebound</em></td>
<td>Weeks to months</td>
</tr>
<tr>
<td>6</td>
<td>Exertion limited</td>
<td><em>Walking wounded</em></td>
<td>months</td>
</tr>
<tr>
<td>7</td>
<td>Advanced NYHA III(b)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ideal implantation is INTERMACS 3-5
VAD implantable device
  Decreased cardiac workload
  Increases systemic circulation and tissue perfusion
  Decreases Preload

left (LVAD), right (RVAD) ventricle, or both (BiVAD)

External driveline to battery/comptroller
Electrical power 24 hours
No MRI, no Swimming
**Good, Bad (Life with an LVAD)**

LVAD opportunity for “restoring life”

Improvement in multiple measures of quality of life – 6MWT, KCCQ, NYHA

Fewer than 50% of VAD implanted as a Bridge are transplanted

---

- **Bleeding** – intracranial, GI, epistaxis, GU
- **Thrombosis of LVAD**
- **Hemolysis**
- **Infections** – driveline infections, bacteremia
- **Recurrent Heart failure (RV failure)**
LVAD Survival

Jorde et al. JACC 2014
Palliative Options

Palliative care – organized system of treatments to reduce symptoms of disease rather than alter prognosis

Applicable to anyone with a life-limiting or life-style limiting illness at any stage

Emphasis on Quality of Life
Based on NEED rather than prognosis or life-expectancy

The technology of LVADs can improve the “short wretched lives” of patients as a palliative option for destination patients

Destination Therapy has great potential for palliation
   Also with great potential for complications with extreme morbidity and mortality
Inotropes

Westaby and Poole-Wilson, BMJ 2007
Rizzieri et al. Phil, Ethics, Hum in Med 2008
Inotropes as Palliation

Inotropes improve symptoms
50% dead from pump failure by 12 months

No significant difference between Dobutamine or Milrinone

Nauman D and Hershberger R. Curr Hrt Faril Rep 2007
Gorodeski et al. Circ Heart Failure 2009; Hauptman AHJ 2006
Heart Failure associated with significant morbidity and mortality
Most patients are unaware of this risk

Average heart transplantation survival is now greater than 12 year
LVAD provide durable (5 years +) support
Inotropes improve quality of life, but shortened duration

Decision based on
Medical comorbidities
Right heart hemodynamics
Ability to tolerate anticoagulation
Insurance coverage/Social support
Patient preference
Progressive myocardial dysfunction

<table>
<thead>
<tr>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
</table>

↓Cardiac output
↓Stroke volume

Systemic perfusion

Hypotension

↓Coronary Perfusion pressure

Ischemia

Compensatory vasoconstriction

↑LVEDP
Pulmonary congestion

Hypoxemia

Progressive myocardial dysfunction

DEATH

Modified from Reynolds HR, Hochman JS Circulation 2008; 117