Cardiomyopathies

Dilated cardiomyopathy:
idiopathic, ischemic and others

Regina Ribeiras M.D., FESC
Hospital de Santa Cruz
Carnaxide, Portugal
Dilated Cardiomyopathy (DCM)

“A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of:
coronary artery disease,
hypertension,
valvular disease and congenital heart disease, sufficient to cause the observed myocardial abnormality.”
DCM phenotype: LV remodeling

- LVEDd >117% may precede
- systolic dysfunction EF% <45% /FS<25%
- LV spherical dilatation
- Normal or reduced wall thickness

“a progressive” disease along time
DCM phenotype: LV remodeling

- No regional WMAbn
- Mechanical Dyssynchrony
- RV involvement
- 4 chambers dilatation
- MV Regurgitation (functional)
Regional wall motion abnormalities (RWMab)

- Ischemic DCM - coronary distribution (can be faint in extreme LV remodelling)

- iDCM – some “regionality” – basal posterolateral segments relatively preserved systolic function

- Friedrich’s ataxia - posterior wall motion abnormality

- Takotsubo - apical hypokinesia/akinesia with preservation of the basal segments
- Radiation – RWMab
Functional Mitral Regurgitation

“incomplete closure of normal MV leaflets”

- Secondary MR to DCM
  - apical tenting,
  - annular dilatation, and
  - ventricular dyssynchrony.
Magnetic Resonance Imaging: DELAYED ENHANCEMENT

**Ischemic**
- subendocardial
- transmural

**Non-Ischemic**
- Mid-wall
- Epicardial
- Global endocardial

Ischemic Patterns (GLE)
- Idiopathic Dilated Cardiomyopathy
- Hypertrophic Cardiomyopathy
- Myocarditis
- Right ventricular pressure overload (e.g., congenital heart disease, pulmonary HTN)
- Sarcoïdosis
- Myocarditis
- Anderson-Fabry
- Chagas Disease

Non-Ischemic patterns (GLE):
- Idiopathic Dilated Cardiomyopathy
- Hypertrophic Cardiomyopathy
- Myocarditis
- Right ventricular pressure overload (e.g., congenital heart disease, pulmonary HTN)
- Sarcoïdosis
- Myocarditis
- Anderson-Fabry
- Chagas Disease

- Amyloidosis
- Systemic Sclerosis
- Post cardiac transplantation
ISCHEMIC  Non-ISCHEMIC  No-LGE

Ananthasubramaniam R et al. Heart Fail Rev Dec10
Illes L et al JACC 11, 57:821
### Diagnostic criteria for DCM

1. Left ventricular ejection fraction < 0.45 (> 2SD) and/or fractional shortening < 25% (> 2SD), as ascertained by echocardiography, radionuclide scanning or angiography and
2. Left ventricular end-diastolic diameter > 117% of the predicted value corrected for age and body surface area, which corresponds to 2SD of the predicted normal limit ± 5% or using the formula: $\left(45.3 \times (\text{BSA})^{1/3} - (0.03 \times \text{age}) - 7.2\right) \pm 12\%$

### Exclusion criteria, which can lead to phenocopies

- Systemic arterial hypertension (> 160/100 mmHg documented and confirmed at repeated measurements and/or evidence of target-organ disease)
- Coronary heart disease (obstruction > 50% of the luminal diameter in a major branch)
- History of chronic excess alcohol consumption, with remission of heart failure after 6 months of abstinence
- Clinical, sustained and rapid supraventricular arrhythmias
- Systemic diseases
- Pericardial diseases
- Congenital heart disease
- Cor pulmonale

---

Mestroni et al. EHJ 1999; 20:93  
Classification of the cardiomyopathies: a position statement from the European Society of Cardiology working group on myocardial and pericardial diseases

“specific morphological and functional phenotypes”
more > 35% (40-60%) of cases of DCM have a genetic etiology (a monogenic familial disease)  

Mode of inheritance: autosomal (33 genes); X-Linked (2)  

variable penetrance = 80% in families with an autosomal dominant pattern of transmission (which is the most frequent mode of inheritance)  

the clinical manifestation of the disease appears to be typically age-dependent  

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20 yrs</td>
<td>10 %</td>
</tr>
<tr>
<td>20-30 yrs</td>
<td>34 %</td>
</tr>
<tr>
<td>30-40 yrs</td>
<td>60 %</td>
</tr>
<tr>
<td>&gt;40 yrs</td>
<td>90 %</td>
</tr>
</tbody>
</table>


The Genetic Bases of Cardiomyopathies

<table>
<thead>
<tr>
<th>DCM Gene</th>
<th>Locus</th>
<th>Inheritance</th>
<th>Associated Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-myosin heavy chain</td>
<td>14q12</td>
<td>Autosomal dom.</td>
<td></td>
</tr>
<tr>
<td>Actin</td>
<td>15q14</td>
<td>Id</td>
<td></td>
</tr>
<tr>
<td>Troponin T</td>
<td>1p32</td>
<td>Id</td>
<td></td>
</tr>
<tr>
<td>Alpha-tropomyosin</td>
<td>15q22.1</td>
<td>Id</td>
<td></td>
</tr>
<tr>
<td>Titin</td>
<td>2q24.3</td>
<td>Id</td>
<td></td>
</tr>
<tr>
<td>Muscle LIM protein</td>
<td>11p15.1</td>
<td>Id</td>
<td></td>
</tr>
<tr>
<td>Telethonin</td>
<td>17q12</td>
<td>Id</td>
<td></td>
</tr>
<tr>
<td>Dystrophin</td>
<td>Xp21</td>
<td>X linked</td>
<td></td>
</tr>
<tr>
<td>Desmin</td>
<td>2q35</td>
<td>Autosomal dom.</td>
<td></td>
</tr>
<tr>
<td>Metavinculin</td>
<td>1q21</td>
<td>Id</td>
<td></td>
</tr>
<tr>
<td>Beta-sarcoglycan</td>
<td>4q12</td>
<td>Id</td>
<td></td>
</tr>
<tr>
<td>Delta-sarcoglycan</td>
<td>5q33</td>
<td>Id</td>
<td></td>
</tr>
<tr>
<td>Taffazin</td>
<td>Xq28</td>
<td>X linked</td>
<td></td>
</tr>
<tr>
<td>Lamin A/C</td>
<td>1q21</td>
<td>Autosomal dom.</td>
<td></td>
</tr>
</tbody>
</table>

The phenotype is highly heterogeneous
- Isolated
- Syndromic

Sarcomeric proteins
- Cytoskeleton proteins
- Proteins of the nuclear membrane
  - "cardioLaminopathies"
LMNA gene mutations

Need for Early Diagnosis
Probands and mutated healthy persons

- early indications for ICD implantation so as to prevent SCD and provide a possible bridge to heart transplantation in end stage HF.
- ICD implantation in patients who are candidates for pacemaker implantation due to AVBlock
- low dynamic noncompetitive sport activity

malignant disease:

- high rates of malignant arrhythmias even with mild LV-DCM phenotype
- (HF / high risk of SCD before the onset of HF).

Fatkin D et al. NEJM 1999;341:1715-24
Pasotti, et al. JACC 2008;52:1250
1st: TAKE A **3-4 generation FAMILY HISTORY**

2nd: If Positive (>1 family member affected)

*ECHO screening of first-degree relatives*

3rd: Consider GENETIC TESTING: check for

phenotypic "red flags"

for high-risk mutations (Lamin A/C)
4th: Genetic testing

Identification probands and family members

Combination of DCM and AVBlock

Co-existent myopathy (EDMD2 or variable myopathy) and increased serum creatine phosphokinase levels, especially if AVBlock,

• Clinical and Genetic Issues in Familial Dilated Cardiomyopathy: Hershberger and Siegfried. JACC 2011;57:1641–9
5th: **ECHO Screening of first degree relatives**

In **Asymptomatic Relatives of a proband** (genotype-phenotype patient)
- isolated LVE – 20%
- mild contractile impairment (dFS) - 6%
- DCM - histological and immunohistochemical changes similar to those with established disease – 3%

*Necessity of ECHOCardiographic Serial Assessment over a lengthy FUP*

For *pre-clinical Dx*

Based on the observed incidence and risk for progression

- DCM have a significant medium-term risk for disease progression
- Progression to DCM - occurred in 13 (10%) relatives with LVE or dFS versus 3 (1.3%) healthy relatives

Pre-Clinical diagnosis

Early Detection of Structural Abnormalities

“subjects with negative DCM-phenotype in a Familial-DCM kindred warrant rescreening for disease detection (examination, ECG and echocardiography) every 3 to 5 years”

Because ..... Age-dependency and early treatment by ACE-inhibitors or beta-blockers could limit the progression of the disease once detected
A. progressive reduction in circumferential strain (CS) for each stratum (Groups B to E)
B. ALL control subjects have CS higher -16%, and no DMD subjects have CS better than -16%.
Non-Familial **DCM** (Disease sub-type)

- Myocarditis (infective/toxic/immune)
- Kawasaki disease
- **Eosinophilic** (Churg Strauss syndrome)
- Viral persistence
- **Drugs** (ephedra, anthracyclines, trastuzumab, cyclofosfamide)
- Pregnancy
- Endocrine
- **Nutritional** — thiamine, carnitine, selenium, hypophosphataemia, hypocalcaemia
- Tachycardiomyopathy
- Alcohol
specific associated features
(spontaneous echo contrast thrombus ...)
( anticoagulant Rx )
Out of 41 patients (mean age 47 ± 9 years), 10 (25%) developed Trastuzumab mediated cardiomyopathy (CM).

As early as 3 months:
- The lateral S' between the normal cohort and the CM group differed significantly (9.1 ± 1.6 cm/s and 6.4 ± 0.6 cm/s, p<0.05).
- Peak global longitudinal and radial strain decreased in the CM group.

Left ventricular ejection fraction (LVEF) decreased (10% below 55%) at 6 months of follow-up in all 10 patients.

Fallah-Rad N. et al, JACC 2011;57:2263
Trastuzumab mediated CM

25% patients (10/41)

<table>
<thead>
<tr>
<th>Echo Variables</th>
<th>Cut-Off Value</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>S’ (cm/s)</td>
<td>0.60</td>
<td>0.93 (0.59, 0.99)</td>
<td>0.99</td>
<td>0.96</td>
<td>0.98</td>
</tr>
<tr>
<td>Longitudinal Strain (%)</td>
<td>2.00</td>
<td>0.79 (0.51, 0.96)</td>
<td>0.82</td>
<td>0.60</td>
<td>0.92</td>
</tr>
<tr>
<td>Radial Strain (%)</td>
<td>0.80</td>
<td>0.86 (0.57, 0.98)</td>
<td>0.81</td>
<td>0.60</td>
<td>0.95</td>
</tr>
</tbody>
</table>

- cardiac biomarkers did not predict the development of cardiac dysfunction
- TVI and strain imaging were able to detect preclinical changes in LV function, prior to conventional changes in LVEF

prophylactic administration of cardioprotective agents (ACEi ; BB)
Echocardiographic FUP
During Trastuzumab Therapy under ACEi + BB; NYHA II

after Trastuzumab suspension under ACEi + BB

GLS -9%

GLS -20%
Dilated Cardiomyopathy

Clinical courses are heterogeneous under medical therapy (ACEI and/or BB)

- Rapidly progressive course, high mortality rates, need for inotropic/LVAD and TX.
- Response to medical therapy (reverse remodelling) - 50%
- Healing courses – 16% (acute myocarditis; peripartum DCM)

8 Year: Transplant free survival (under medical therapy)
94% - normalized LVEF
83% - NYHA class I-II and LVEF >40%
64% - NYHA class I-II and LVEF ≤40%
31% - NYHA III-IV

Sugrue et al Ann Inter Med 1992, 117
Heart Failure - Therapeutic Management

“aetiology-independent”

Starting Stage B (structural heart disease / No signs or symptoms of HF)

- Beta blockers / ACE inhibitors / ARB / diuretics

- Cardiac Ressynchronization Therapy; MV surgery; LVAD; Cardiac Tx

Early intervention:

1. Accurate and Early diagnosis
2. Identification of modifiable prognostic factors:
   - dysynchony
   - MV regurgitation
DCM – LV assessment

**Diagnostic criteria:**

- **accurate Chamber Dimensions, indexed to BSA**
- **LV Dilatation**
  - LV end-diastolic dimension >117% predicted value corrected for age and body surface area (2 SD+5%)
  - Henry equation: \((45.3 \times \text{BSA})^{1/3} - (0.03 \times \text{age}) - 7.2) \pm 12\%\)

- **Global Systolic LV function**
  - Ejection fraction (EF) <45%, and/or a fractional shortening <25\%
accurate chamber dimensions/volumes, indexed to BSA
Global Systolic LV function
Left ventricular volume measurement with echocardiography: a comparison of left ventricular opacification, three-dimensional echocardiography, or both with magnetic resonance imaging

<table>
<thead>
<tr>
<th>EDV (207 ± 79 mL)</th>
<th>ESV (117 ± 71 mL)</th>
<th>EF (47 ± 13 %)</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>-41 ± 21</td>
<td>-22 ± 18</td>
<td>-2 ± 4</td>
<td>NC-2DE</td>
</tr>
<tr>
<td>-18 ± 19</td>
<td>-8 ± 16</td>
<td>-2 ± 4</td>
<td>CE-2DE</td>
</tr>
<tr>
<td>-15 ± 18</td>
<td>-9 ± 12</td>
<td>0 ± 3</td>
<td>NC-3DE</td>
</tr>
<tr>
<td>-6 ± 14</td>
<td>-3 ± 10</td>
<td>0 ± 3</td>
<td>CE-3DE</td>
</tr>
</tbody>
</table>

LV volumes and LVEF using 2D speckle-tracking

- 2DSTE – underestimation of LVEDV and LVEF (mean 8%) (higher LVESV)
- smaller inter-observer variability in LV volumes and LVEF

Identification of a Structural and Functional Abnormality

Echocardiography Assessment

Class I (Level of Evidence C)

LV: numerical estimate of EF, dimensions/volumes, wall thickness, chamber geometry & regional wall motion.

RV: size and systolic performance

Atrial size: LA dimensions and/or volumes

Valves: exclude primary valve disease secondary valve changes (MR/TR)

Noninvasive hemodynamic data:

- Stroke volume
- LV filling and left atrial pressure
- Systolic pulmonary artery pressure and central venous pressure

2009 ACCF/AHA Heart Failure Guidelines
<table>
<thead>
<tr>
<th>Prognostic indicator</th>
<th>Key echocardiographic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV size and systolic function</td>
<td>Ejection fraction (sphericity)</td>
</tr>
<tr>
<td>LV diastolic function</td>
<td>Moderate (pseudonormal) or severe (restrictive filling) ; E/e´ &gt;15</td>
</tr>
<tr>
<td>Filling pressures</td>
<td>TAPSE &lt;14mm</td>
</tr>
<tr>
<td>Right ventricular function</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Tricuspid regurgitation velocity &gt;40mmHg</td>
</tr>
<tr>
<td>Left atrial size</td>
<td>Left atrial volume index (&gt;68ml/m2)</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>Presence, severity, mechanism &gt;0,20cm²</td>
</tr>
<tr>
<td>Contractile reserve</td>
<td>Dobutamine stress echo</td>
</tr>
</tbody>
</table>

The additive prognostic value of “filling pressure” evaluation

LV ejection fraction ≤40%;

Hillis et al. JACC 2004;43:360–367
the additive prognostic value of “LA volume”

3.8 times higher risk of an adverse outcome

Moller et al Circulation.2003107:2207
Beinart JACC 2004;44:327
Right ventricular function in patients with preserved and reduced ejection fraction heart failure

It is related to the severity of LV dysfunction and biventricular involvement in the disease process rather than secondary to pulmonary hypertension.


Quantification of right ventricular function

- tricuspid annular proximal systolic excursion (TAPSE) < 14mm (adverse prognosis)


The prevalence of RV systolic dysfunction in reduced EF%-HF:

- RV FAC = 63%
- TAM = 76%
- TV Sm = 73%
## Myocardial Fibrosis: GDE (MRI)

Positive hyperenhancement = visually defined as >2 standard deviations of the signal intensity of the non-enhanced myocardium.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Threshold Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ejection fraction, %</td>
<td>&lt;32</td>
</tr>
<tr>
<td>LV TDI S-wave, cm/s</td>
<td>&lt;5</td>
</tr>
<tr>
<td>dP/dt of mitral regurgitation jet, mm Hg/s</td>
<td>&lt;600</td>
</tr>
<tr>
<td>Right ventricular TDI S-wave, cm/s</td>
<td>&lt;11.5</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>&lt;150</td>
</tr>
<tr>
<td>E/Ea</td>
<td>&gt;15</td>
</tr>
<tr>
<td>Ischemic mitral regurgitation, EROA, mm²</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Pulmonary pressure, mm Hg</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Circumferential strain, %</td>
<td>≥−10.7</td>
</tr>
</tbody>
</table>
Iles et al. J Am Coll Cardiol 2011;57:821–8

103 Pts  Median follow-up - 573 days

LGE + :
100% ICM (n= 42)
51%  NICM (n = 61)
Global 2-Dimensional Strain as a New Prognosticator in Patients With Heart Failure

(J Am Coll Cardiol 2009;54:618–24)
Group A: Endocardial and midmyocardial scarring

Group B: Epicardial and midmyocardial scarring

Group C: Transmural scarring

M.M. Kansal et al. EHJ of Cardiovascular Imaging Journal of Echocardiography, 2012: 43-49
Cardiac Resynchronization Therapy

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Patient population</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-P/CRT-D is recommended to reduce morbidity and mortality (^d)</td>
<td>NYHA function class III/IV LVEF ≤35%, QRS ≥120 ms, SR Optimal medical therapy Class IV patients should be ambulatory (^e)</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

Better Selection – *adjunctive to QRS* !

1. Exclude: Residual ischemia
   Non-Functional Mitral Regurgitation

2. Identify Mechanical Dyssynchrony

3. Contractile reserve; Scar burden / Viability

NonResponse 30-40%
Stress Echo: contractil reserve
Inducible “septal flash“
• Severe delayed LV wall – guide to the best lead location

Ypenburg et al, JACC 2008;52:1402–9

Death, cardiac transplantation or hospitalization for heart failure

Log-rank p-value 0.022

Discordant LV lead position
Concordant LV lead position

Follow-up (months)

<table>
<thead>
<tr>
<th>ts at risk</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>244</td>
<td>224</td>
<td>156</td>
<td>88</td>
<td>34</td>
</tr>
</tbody>
</table>

• Device Optimization (AV intervals)

Gorcsan III JASE 2008; 21

1. E and A Waves Separated
2. Termination of A after QRS onset or Mitral Closure Click Aligned With End of A and QRS Complex.
CONCLUSIONS:

1. DCM is the most common cardiomyopathy, occurring primarily due to genetic defects or secondarily as a consequence of multiple factors. The differential diagnosis remains quite broad since many pathologies can present as DCM so multiimaging is frequently needed.

2. From a clinical point of view, the most important is to differentiate between familiar-DCM, and non-familiar DCM, since genetic testing has to be done specially in the high-risk genetic-DCM (LaminA/C).

3. Early intervention based upon accurate diagnosis remains the mainstay of pharmacologic treatment which is independent of the aetiology and may prevent disease progression and its complications.

4. Echo-imaging is a powerful tool for Diagnosis and DDx (DCM-phenocopies) identification of associated cardiac abnormalities such as valve disease highlight features requiring specific therapeutic management (thrombus) identify prognostic markers and guiding therapy (CRT; MV repair).
Dilated cardiomyopathy