Myocarditis and dilated cardiomyopathy

Diagnosis and management

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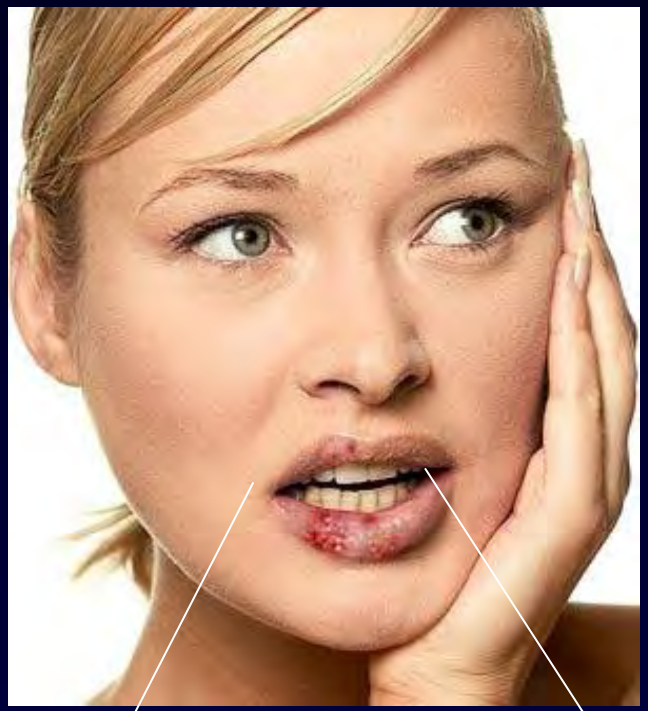
- Viral myocarditis
- Dilated cardiomyopathy
- Diagnosis
- Treatment

What is viral myocarditis?
"Sleeping" viruses → Injury

Herpesvirus

Δ Immunogenetic background

Δ Environment
- Additional virus
- Illness



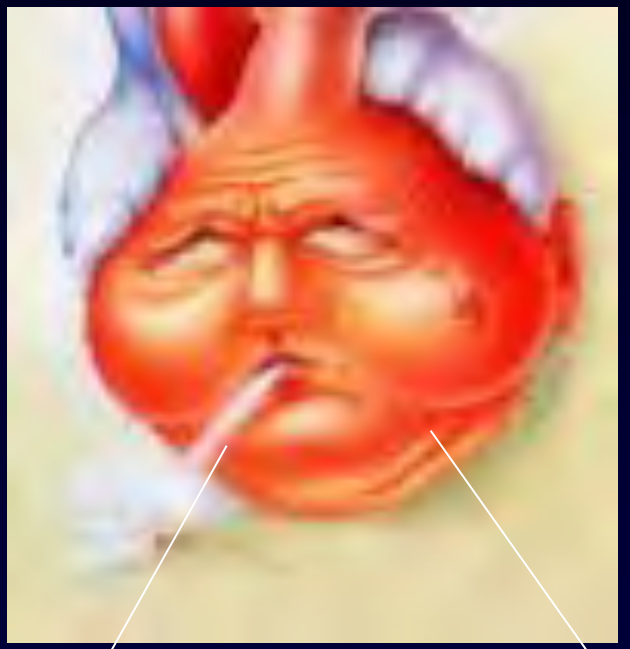
What is a viral myocarditis... cough of the heart !

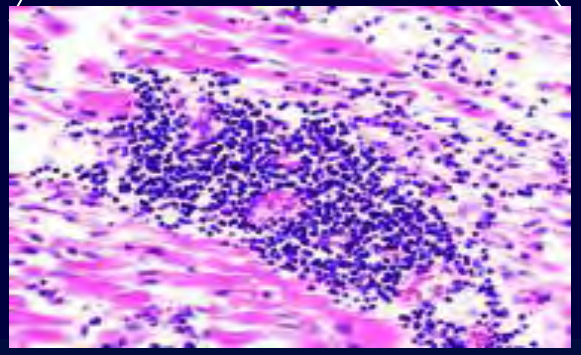
Herpesvirus
Parvovirus
Epstein BV
Enterovirus

→

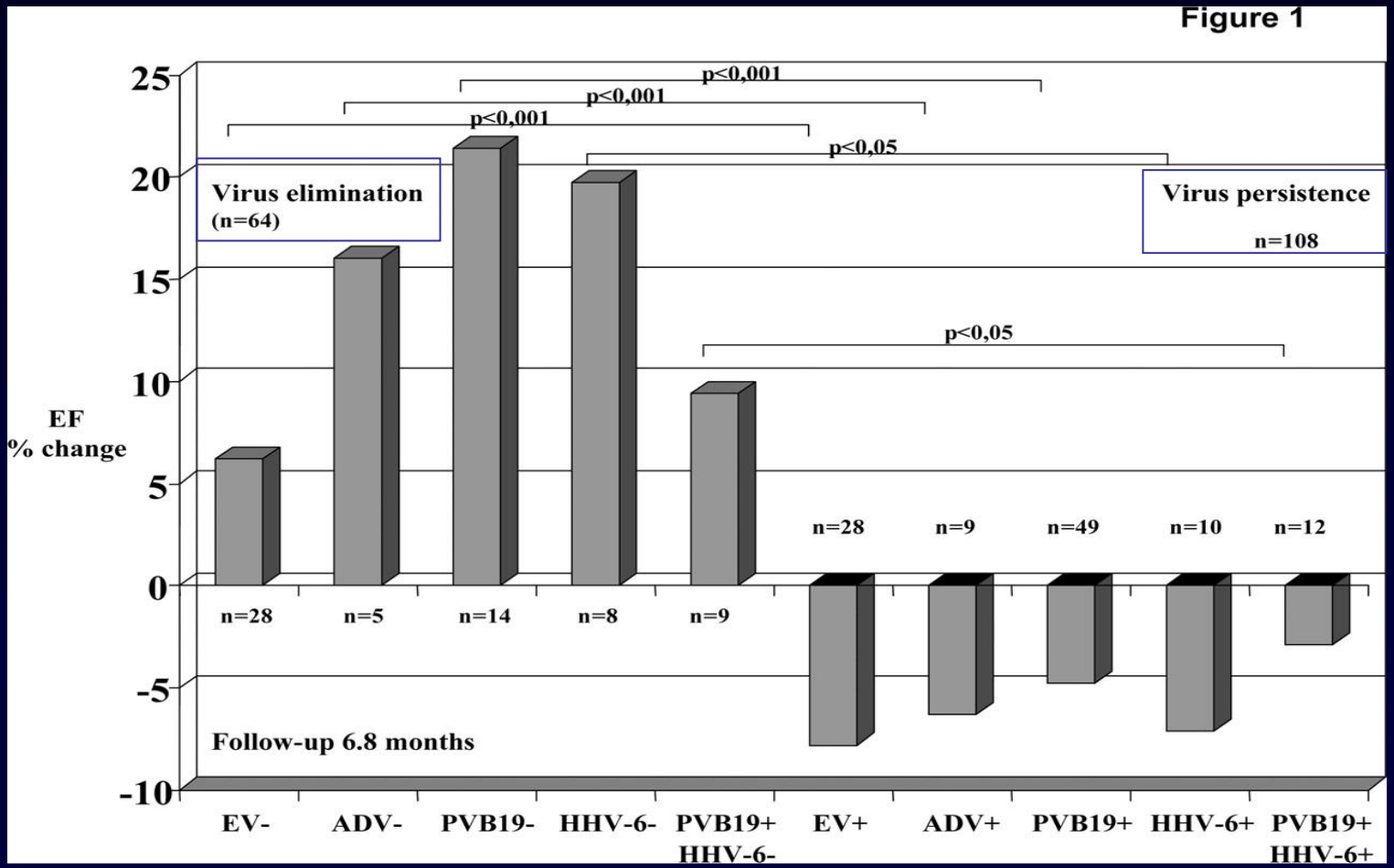
Δ Immunogenetic background

Δ Environment
- Additional virus
- Heart failure





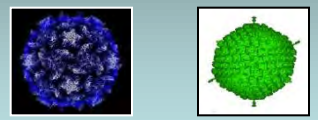
Virus persistence 6 months after acute myocarditis relates to heart failure



Kuhl, Circulation 2005

Viral myocarditis

Parvovirus, Enterovirusses, Adenovirus, EBV, HHV6



Asymptomatic

Cough of the heart

Acute myocarditis

Genetic background
Environment

Genetic background
Environment

20 %

…. % ? (0.1-5 %)

Idiopathic(dilated)CMP

- Viral myocarditis
- Dilated cardiomyopathy
- Diagnosis
- Treatment

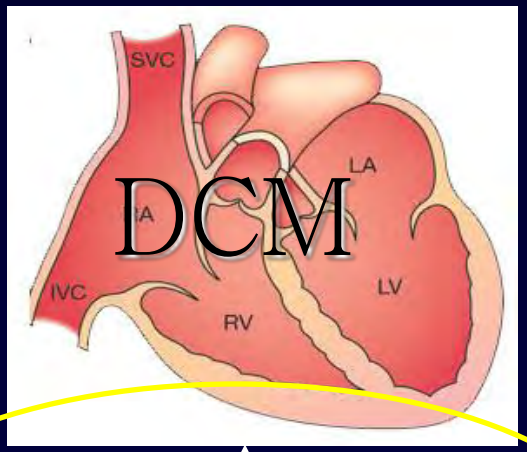
Idiopathic cardiomyopathies (DCM)

Non-ischemic, non-valvular, non-hypertrophic CMPs

Gene mutations

Metabolic Δ

Structural Δ



Inflammatory Δ

Viruses

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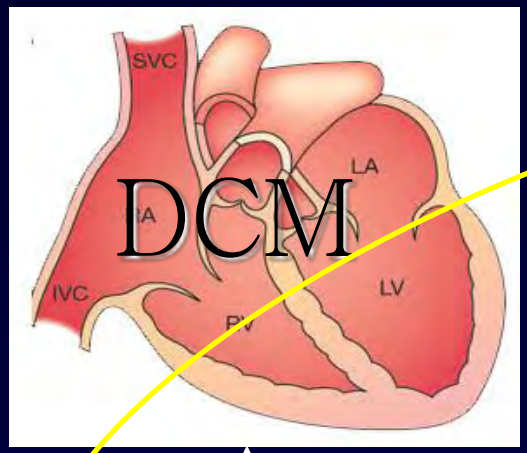


Inflammatory Δ

Viruses

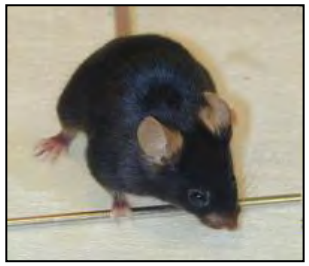
Immunogenetic background

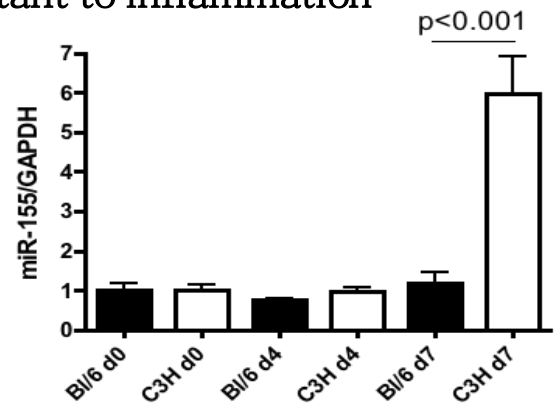
Increased microRNA-155 expression during Coxsackievirus-B3 induced myocarditis

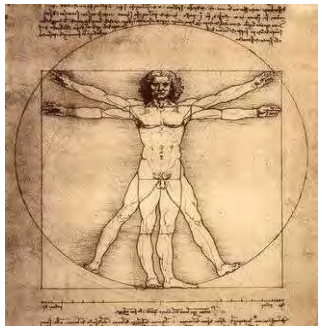
MicroRNA-array analysis in mice and human

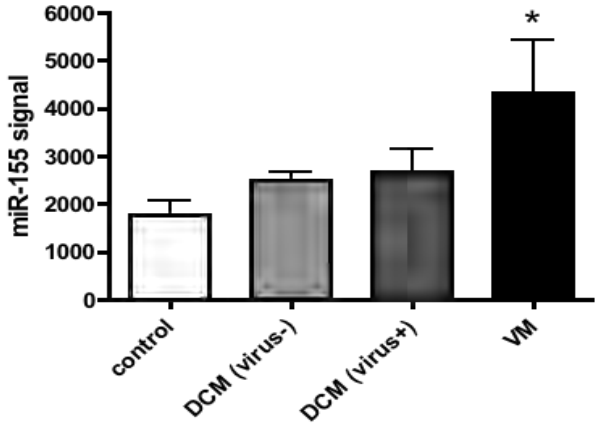
C3h=susceptible to inflammation

B6= resistant to inflammation

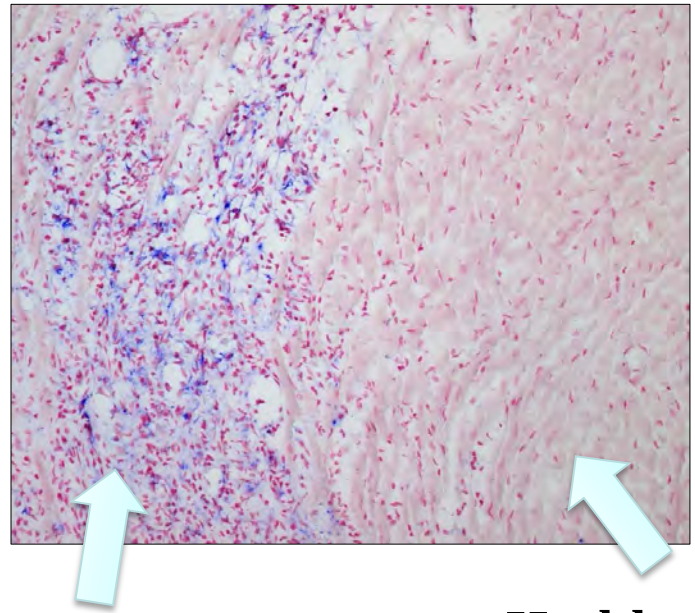








In situ hybridisation of miR-155



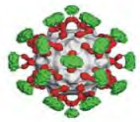
Infiltrate

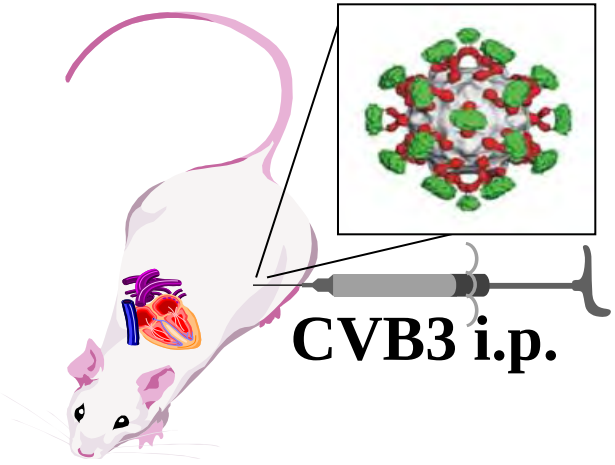
Healthy myocardium

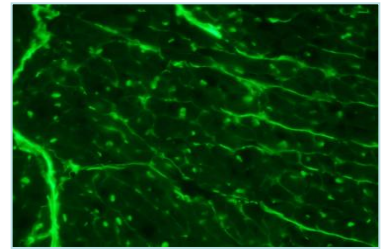
LNA-antimiRNA-155 reduces acute cardiac inflammation during viral myocarditis

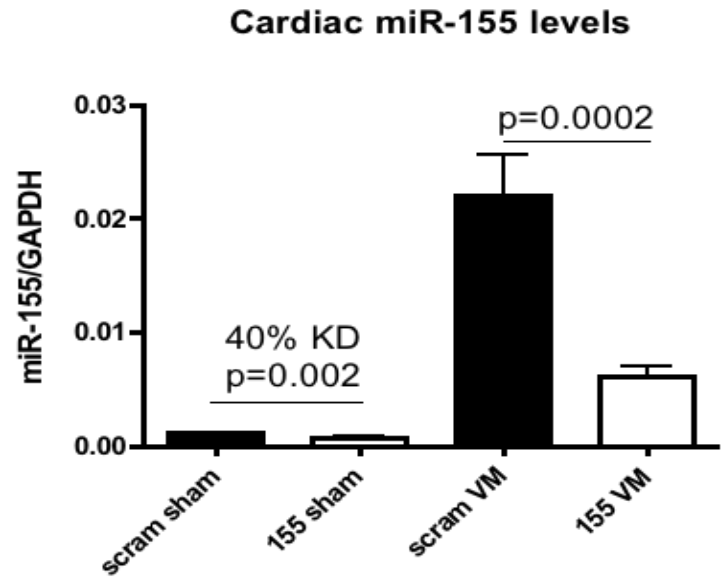
Locked Nucleic Acid (LNA) anti-miR-155, *25mg/kg iv.*

day 0 CVB3 — **day 1** LNA#1 — **day 4** LNA#2 — **day 6** LNA#3 — **day 7** sacrifice









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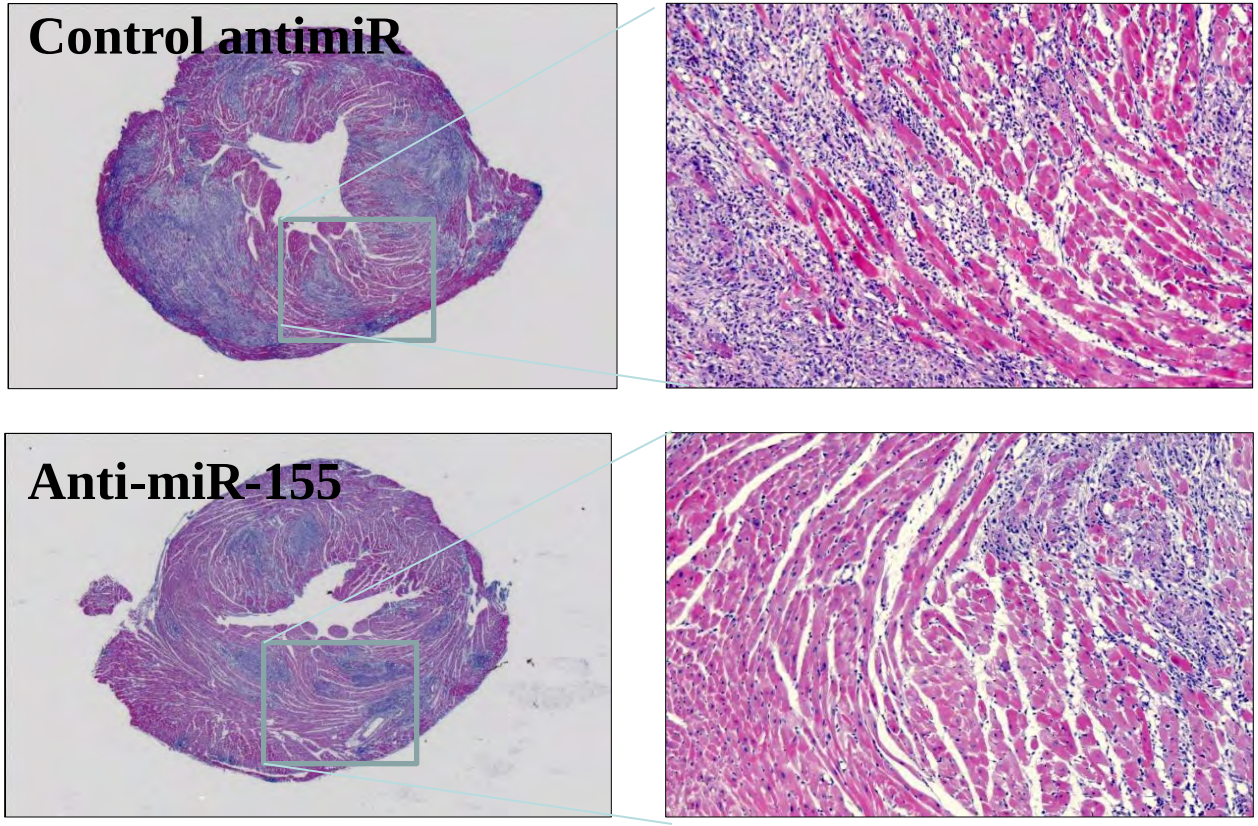
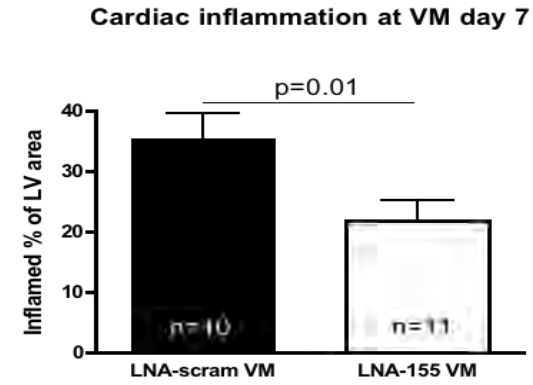
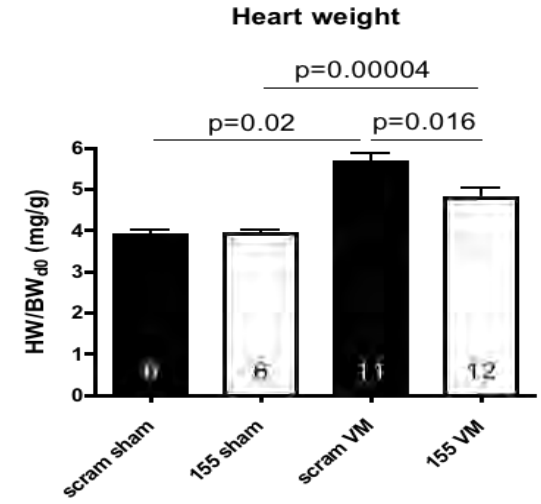






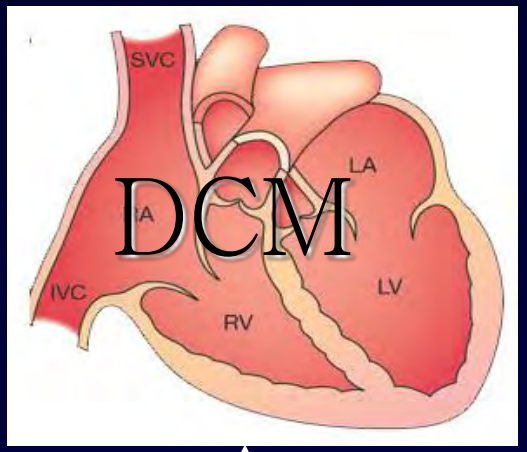
Idiopathic cardiomyopathies (DCM)

Non-ischemic, non-valvular, non-hypertrophic CMPs

Gene mutations

Metabolic Δ

Structural Δ



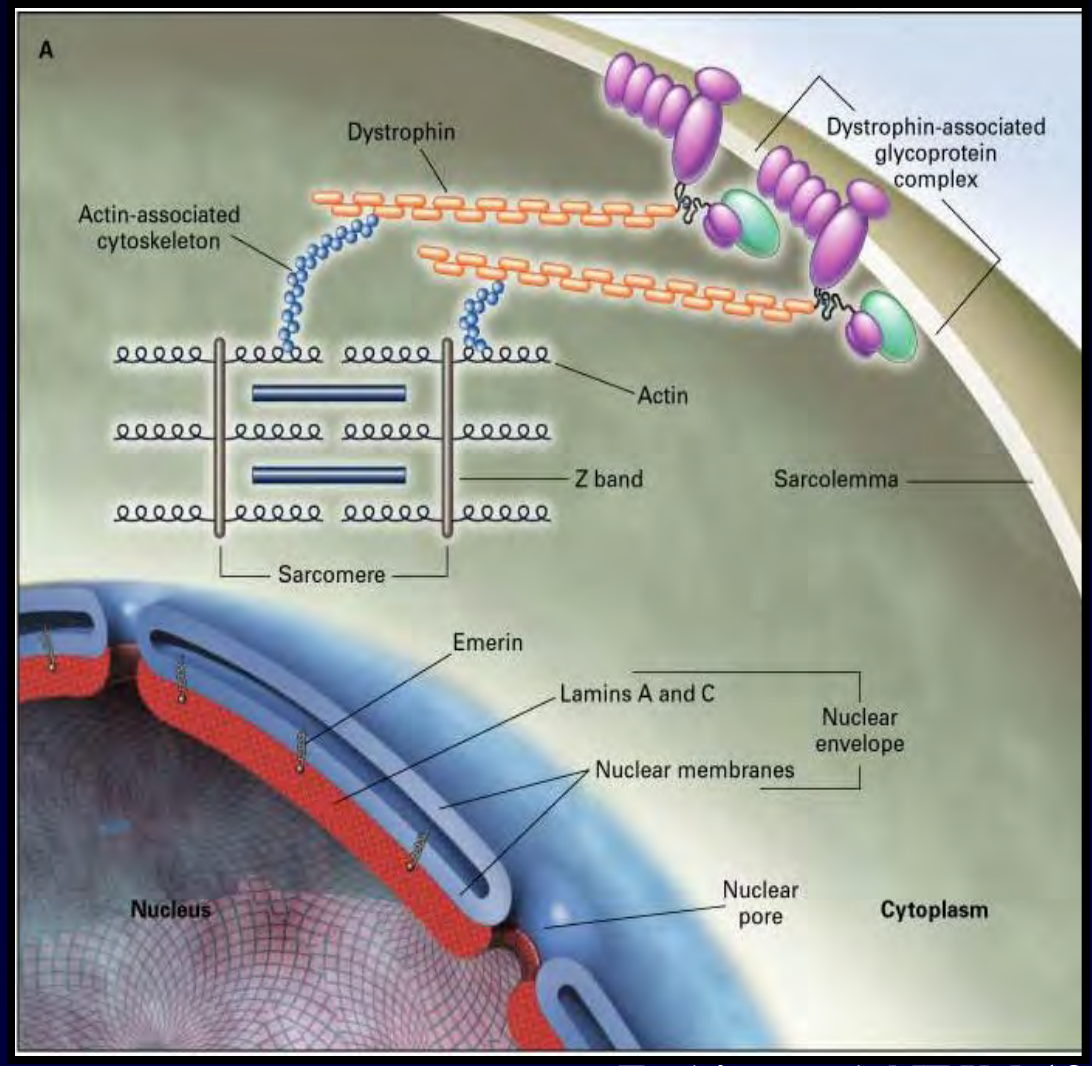
Inflammatory Δ

Viruses

Gene mutations in idiopathic dilated cardiomyopathy

GENES

Lamin A/C
δ-sarcoglycan
Dystrophin
Desmin
Vinculin
Titin
Troponin-T
α-tropomyosin
ß-myosin heavy chain
Actin
Phospholamban
Mitochondrial DNA mutations



Fatkin, et al. NEJM 1999

The 80 % gap of DCM

- Hypertrophic CMP & gene mutation
  - 80 (-90 %) % with proven mutation
  - 10-20 % gap
- >< Dilated CMP & gene mutations
  - 20 -(50?) % proven mutations
  - 80 % gap → cause ??

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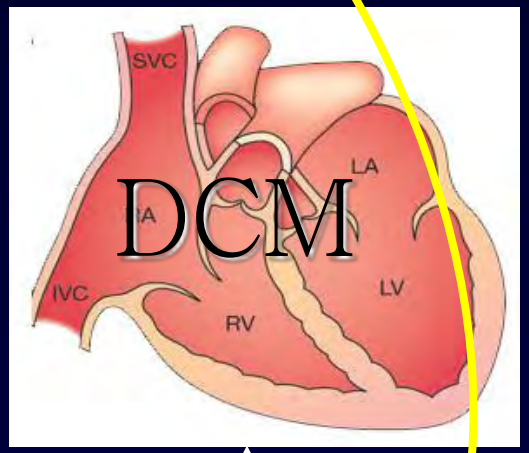


Inflammatory Δ

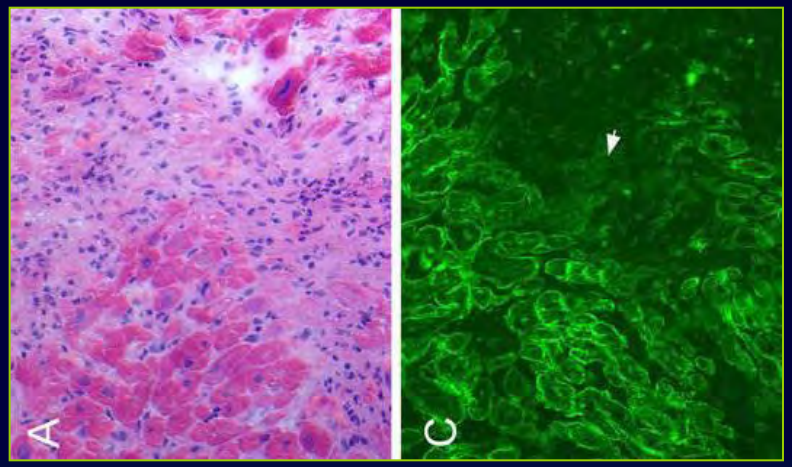
Viruses

Patient, female, 34 years old

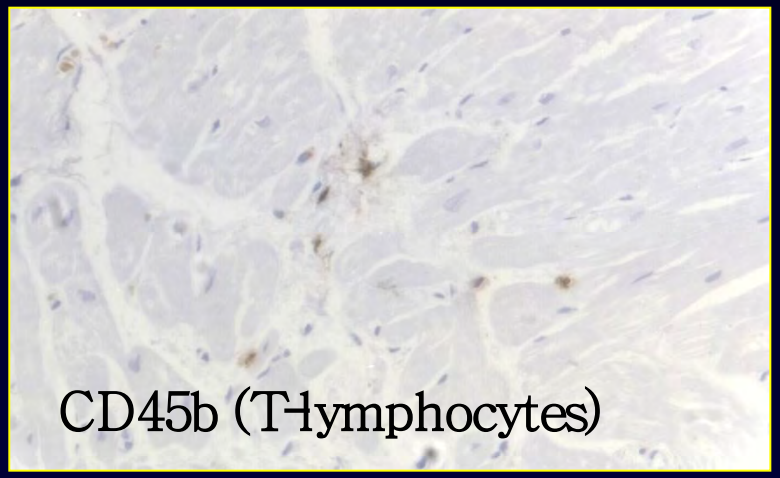
- Becker disease: dystrophin abnormality
  - Normal cardiac function 3 months before
- Flue like symptoms, followed by severe dyspnoe
  - Echocardiography:
    - Severe cardiac dysfunction (EF 15 %)
    - Cardiac dilatation (EDD 68 mm)
  - Cardiac biopsies: Epstein Barr virus (820 copies/µg DNA)

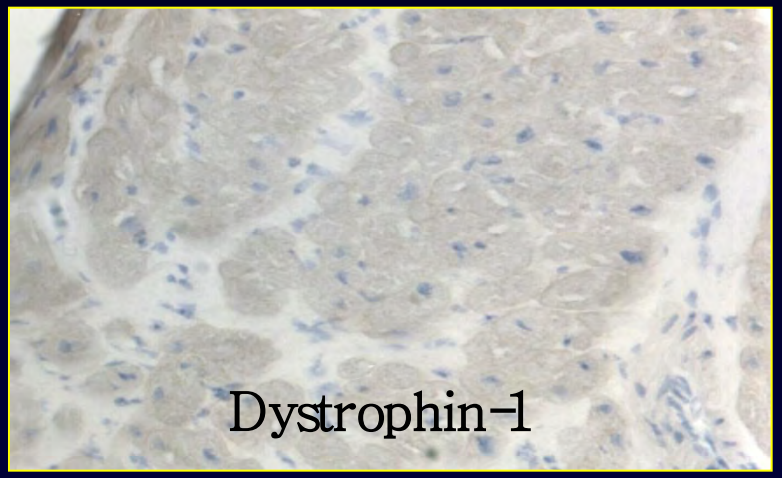
Link between hereditary and viral cardiomyopathies

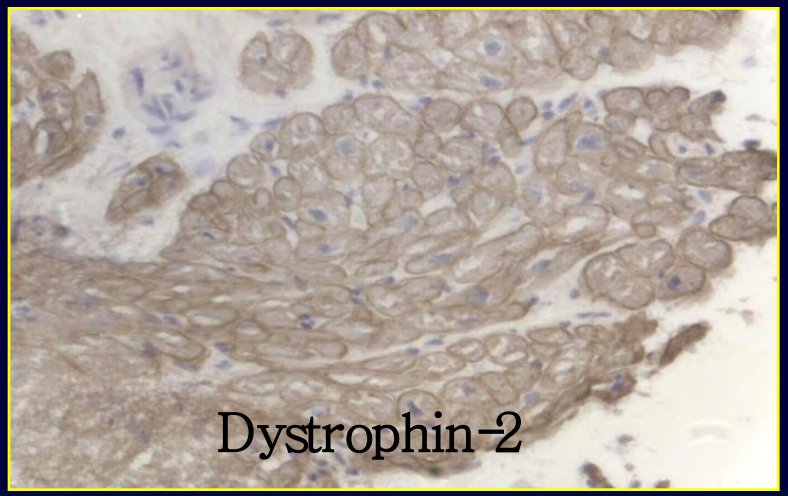
- Viral protease cleaves dystrophin
  - disruption of the dystrophin–glycoprotein complex
  - similar to hereditary abnormalities in dystrophin expression

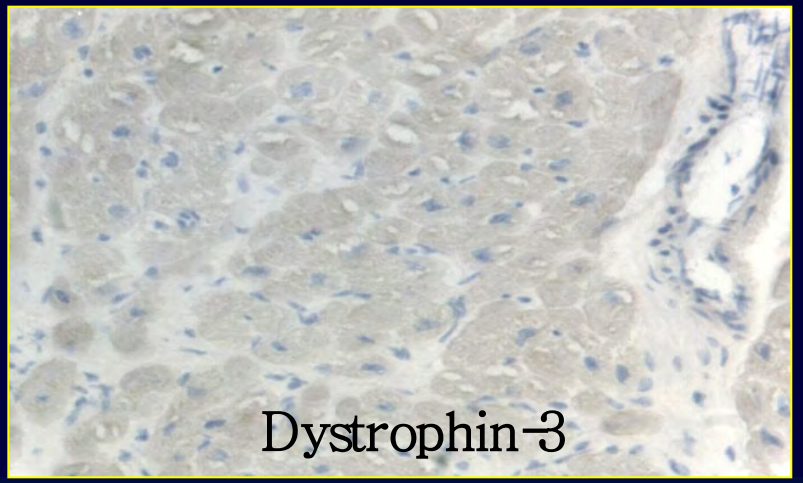


Patient, male, 34 years old
Cardiac biopsies: EBV↑ + inflammation↑

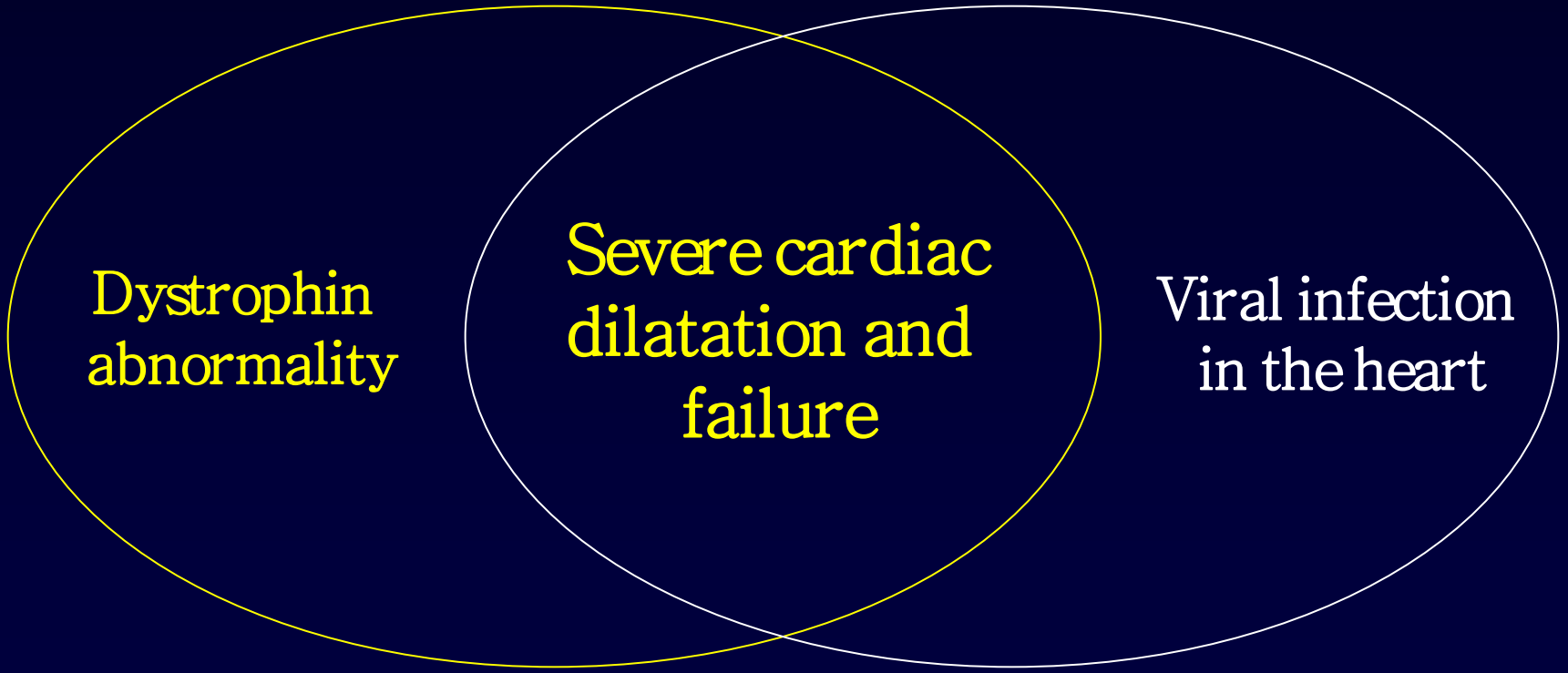








Viral cardiac infection and genetic predisposition



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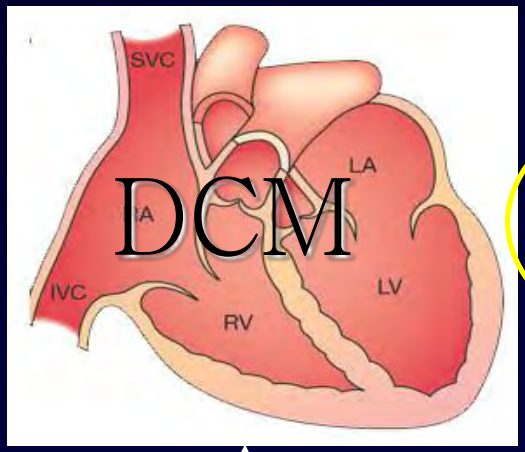


Inflammatory Δ

Viruses

Autoimmune diseases

- Cardiac involvement in systemic diseases:
  - Churg-Strauss: 30-60 %
  - Sarcoidosis: 5-30 %
  - Other systemic diseases: 2-20 %
- History: systemic complaints
- Blood: inflammation & T-cell activation
  - Neopterine
  - Soluble-IL2 receptor
  - ANF and CRP

Female 32 yr

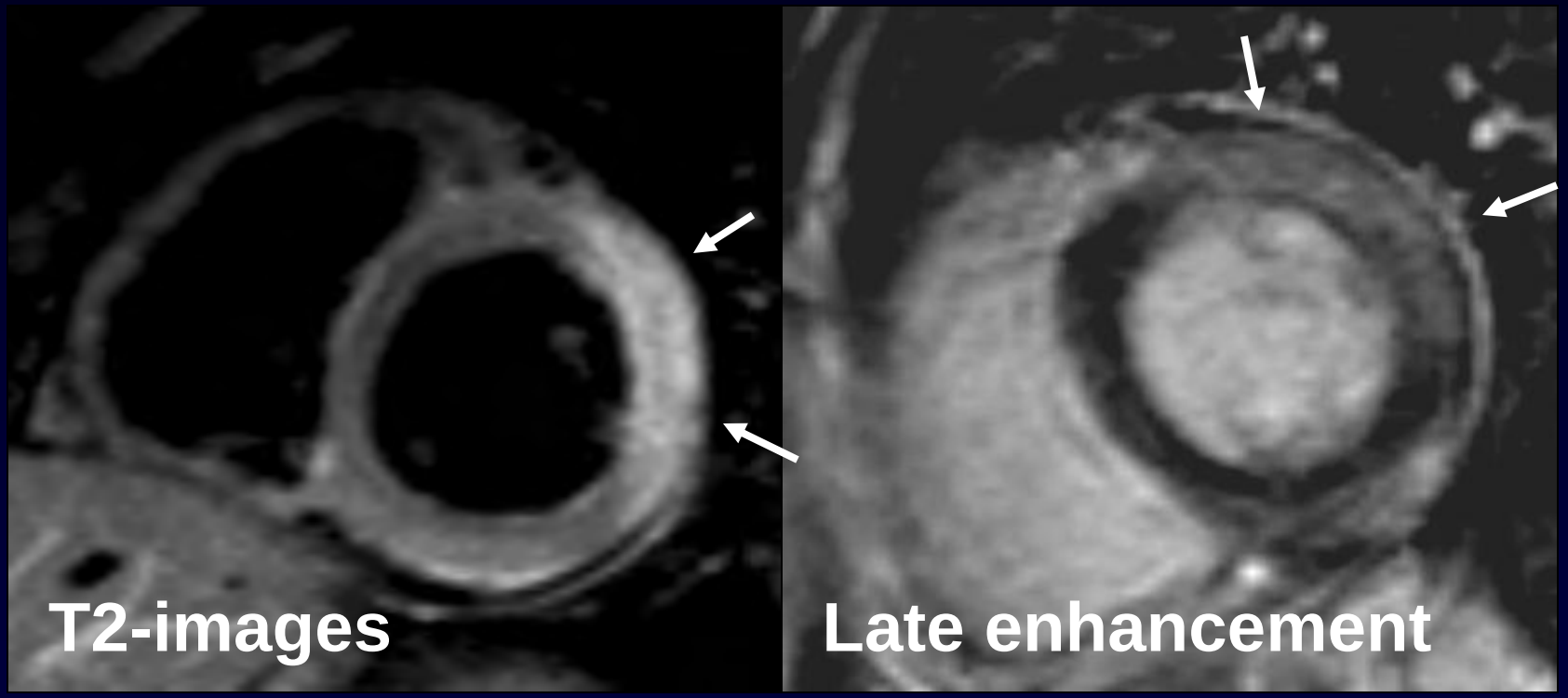
- Prior medical history: none

- Presented to the first heart aid with chest pains
  - Flu-like symptoms 2 weeks prior to admission
  - Progressive position dependant chest pain

Female, 32 y

- Physical: no fever, HD stable
- Biochemistry:
  - TnT 0.67µg/L,
  - CRP 136 mg/L, WBC 19 .10^9/L , soluble IL2-rec↑↑
- Echocardiogram:
  - slightly depressed LV function (EF 51%),
  - no pericardial effusion,
  - normal left ventricular dimensions

CMR



- T2-weighted: increased signal intensity anteriorly and laterally of the left ventricle
- Late enhancement: focal transmural hyperenhancement basal-lateral of the left ventricle

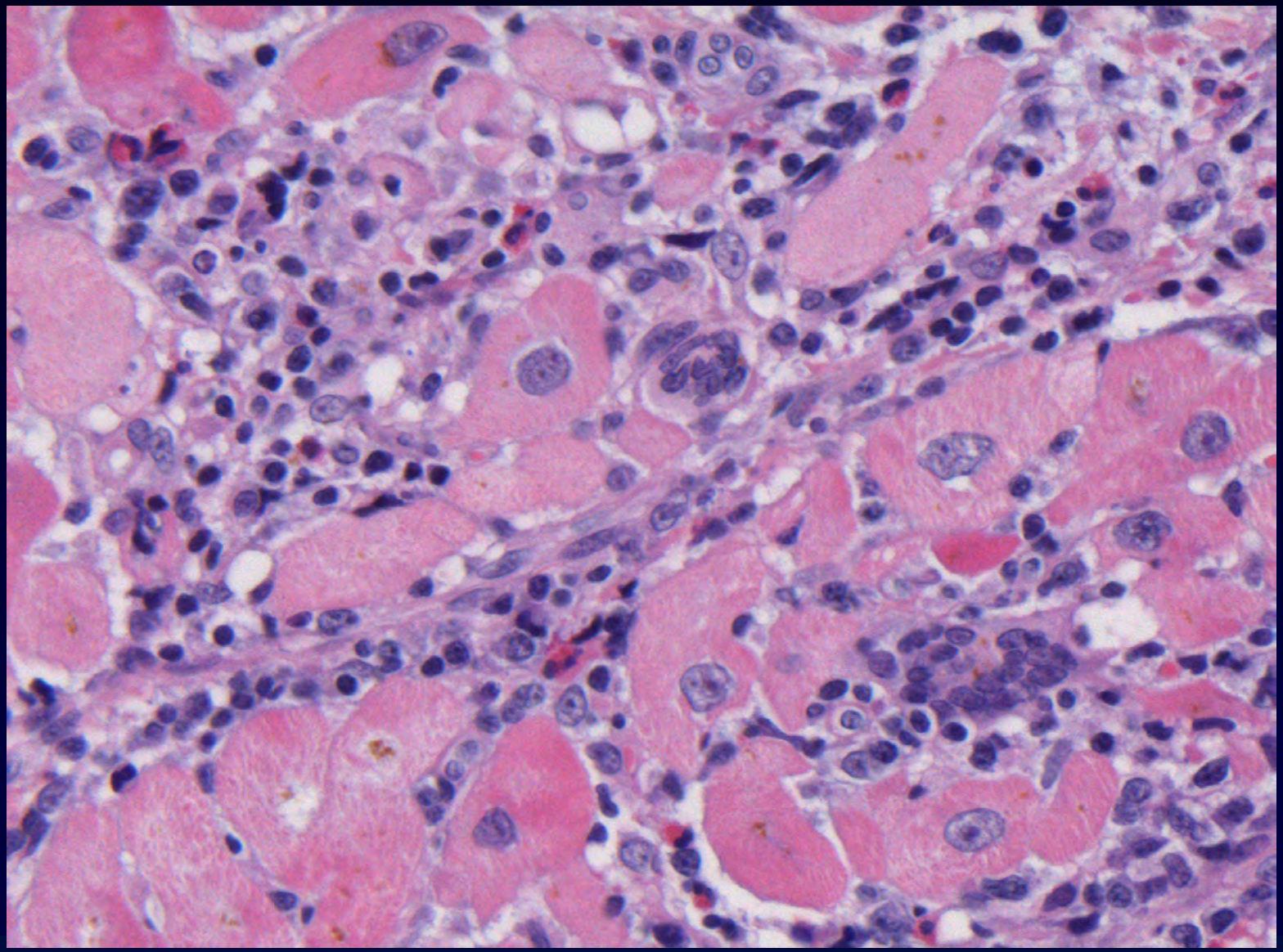
Female, 32y

- LV dysfunction deteriorated
- Endomyocardial biopsies:
  - Viral PCR:
    - Parvovirus B19 pos (2184 copies mcg/DNA)
    - EBV, HHV6, ADV and EV negative
  - Histology
    - Increased CD3/CD45 positive lymphocytes

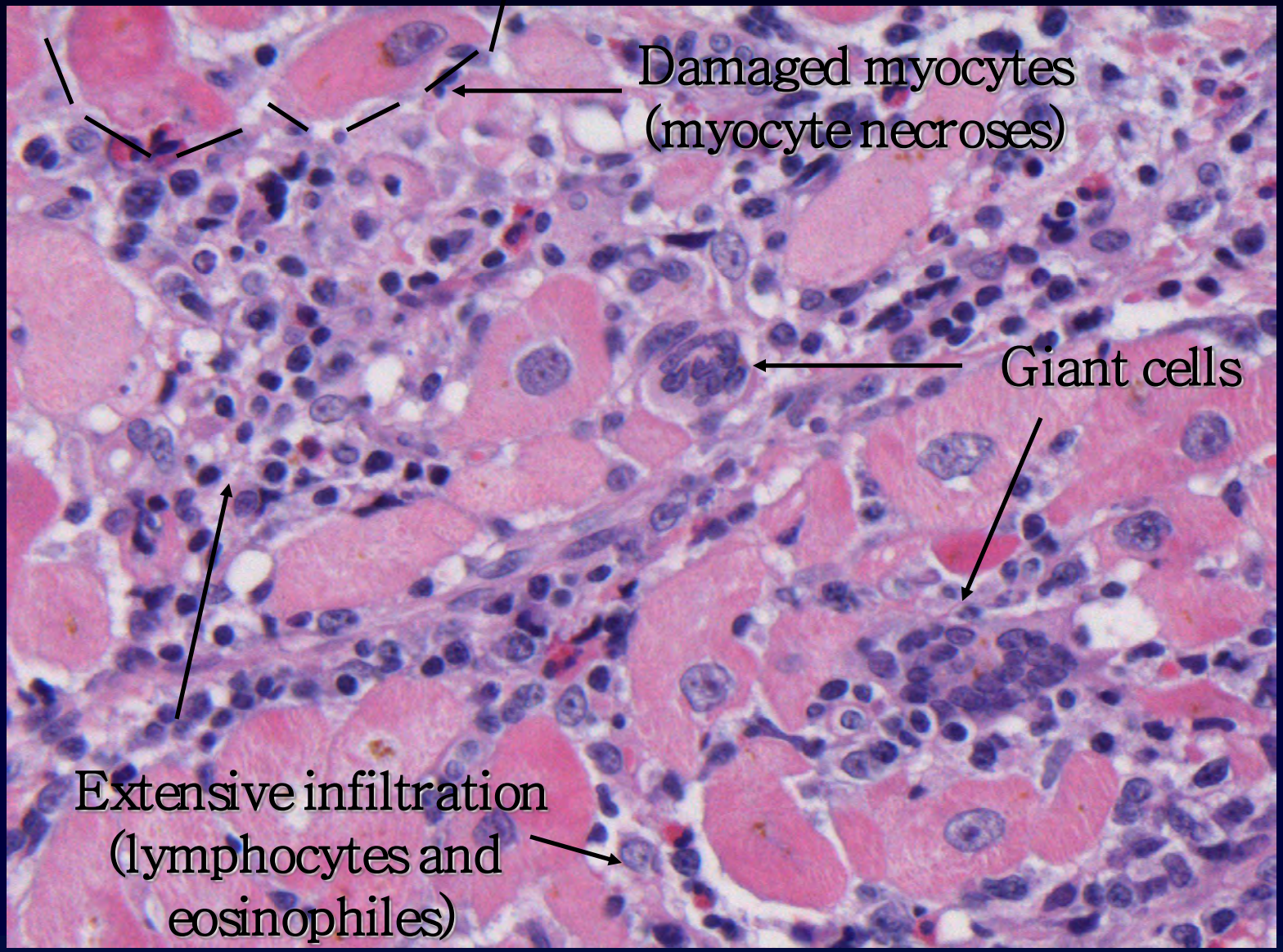
Female, 32 years

- Despite aggressive immunomodulatory (IVIG 2gr/kg) and immunosuppressive (prednisone 50mg/day iv) therapy
- Cardiac function declined
- Ultimately requiring a left ventricular assist device → cardiac transplantation

Cardiac biopsies at LVAD



Cardiac biopsies at LVAD



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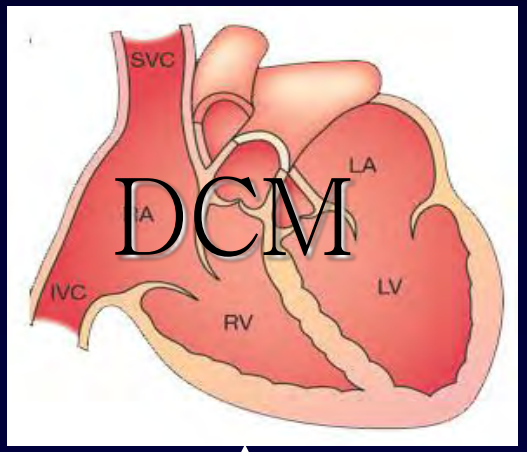


Inflammatory Δ

Viruses

Metabolic and toxic causes

- Metabolic triggers
  - Metabolic syndrome: obesity /diabetes/ hypertension
  - Fabry disease
- Toxic triggers:
  - Ethyl (reversible)
  - Drugs (cocaine)
  - Chemotherapy (anthracyclines)

Male, 45 years

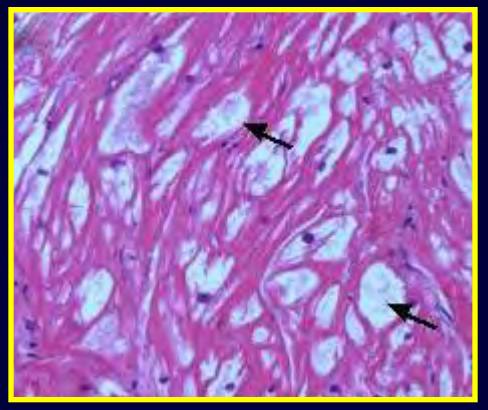
- Idiopathic CMP
  - Slight hypertrophy
  - EF 35 %
  - EDD 58 mm
- Non-sustained VT
- Cardiac oedema
- Minor renal dysfunction

CMR: T2 and LE

Male, 45 years

- Idiopathic CMP
  - Slight hypertrophy
  - EF 35 %
  - EDD 58 mm
- Non-sustained VT
- Oedema at MRI
- Cardiac biopsies:
  - Motten eaten myocytes
  - Sfingolipid accumulation
- α-galactosidase deficiency

CMR: T2 and LE



Cardiac biopsies

- Viral myocarditis
- Dilated cardiomyopathy
- Diagnosis
- Treatment

How to diagnose…

- History
- Signs and symptoms
- Blood studies
- ECG
- Echo
- CMR
- Biopsies

Myocarditis

- History
  - Often flu-like symptoms days-weeks prior to cardiac symptoms
- Signs and symptoms
  - Diverse: from malaise, atypical chest discomfort, heart failure to idiopathic ventricular arrhythmias.

History in DCM

- Systemic symptoms (inflammation/metabolic)
  - Joints, skin, gastro-intestinal, fatigue
- Familial history (genetic?)
  - Premature heart disease, sudden death, neurological diseases
- Toxic causes
  - Drugs, alcohol, chemotherapy
- Metabolic
  - Diabetes, hypertension, obesity

How to diagnose…

- History
- Signs and symptoms
- ECG
- Blood studies
- Echo
- CMR
- Biopsies

How to diagnose…

- History
- Signs and symptoms
- ECG
- Blood studies
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- CMR
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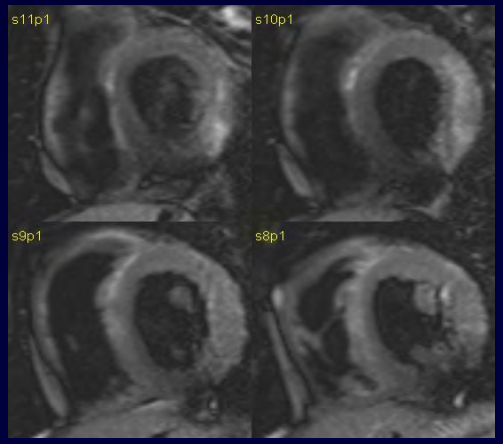
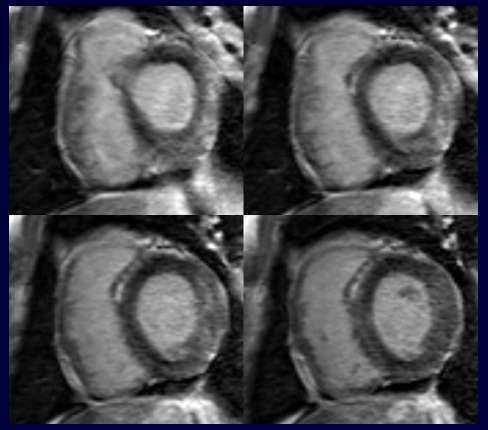
CMR in acute myocarditis

- Acuut
  - T2W: (+) oedema
  - LE: (+) injury
    - Focal, subbepicardiaal
    - posterolateraal



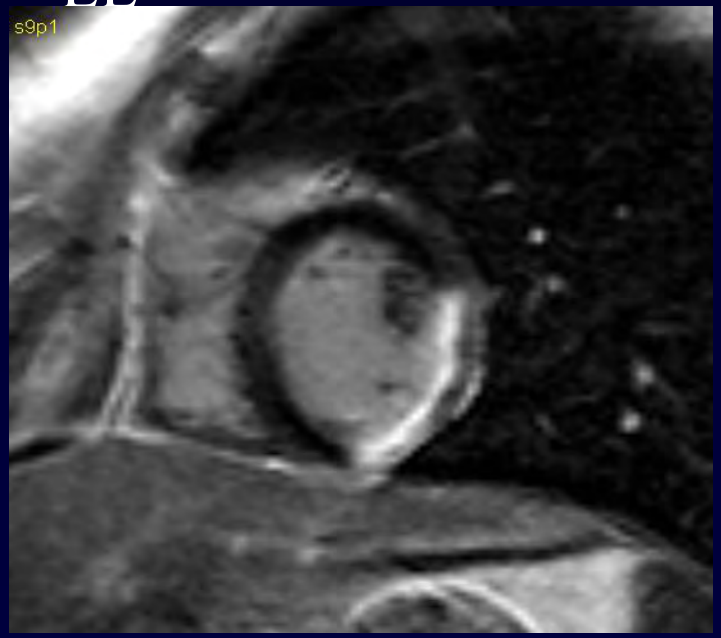
- Follow-up
  - T2W: (-)
  - LE: (+) injury/fibrosis



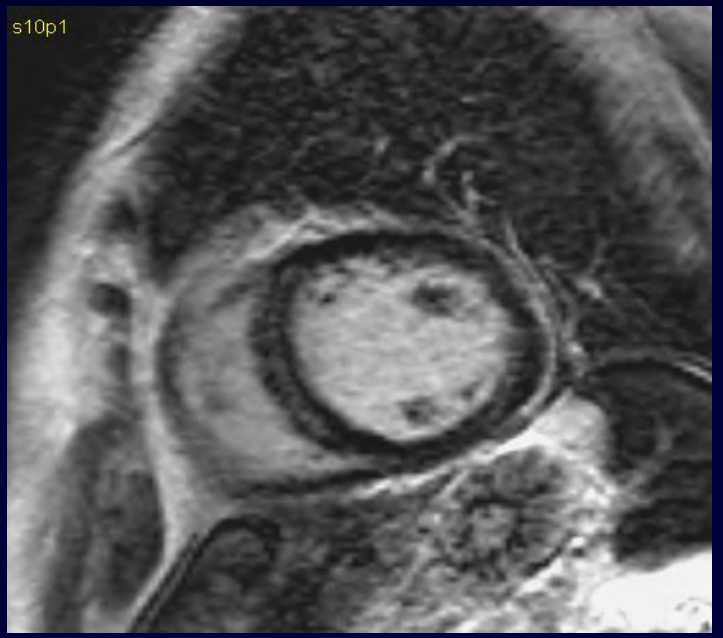
De Cobelli et al. *JACC* 2006;47: 1649-54

CMR in DCM

- Ischemic
  - Subendocardial/transmural LE



- DCM, non-ischemic/valvular
  - midwall or subepicardial LE



How to diagnose…

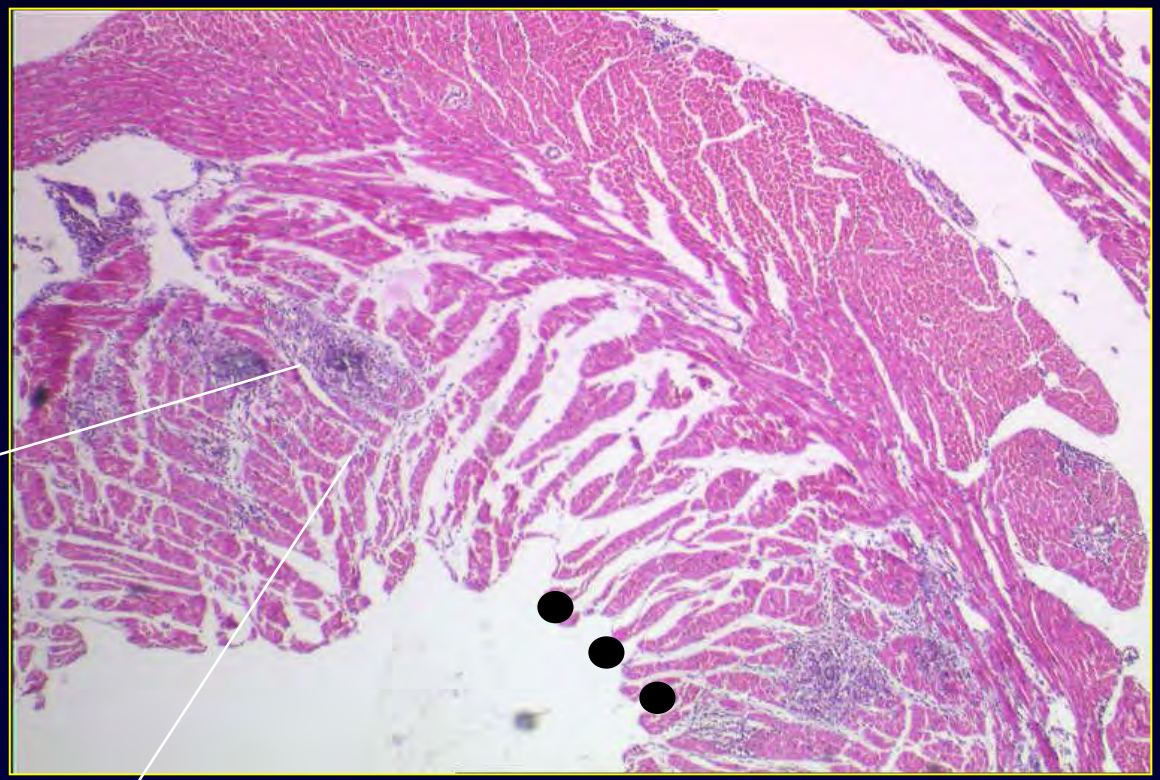
- History
- Signs and symptoms
- ECG
- Blood studies
- Echo
- CMR
- Biopsies

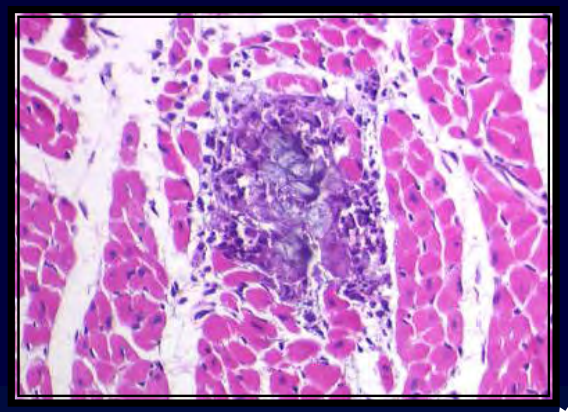
Biopsies

Death of Dallas criteria

(Baughman et al, Circulation, Jan 2006: p593)

- Pro: standardised
- Contra:
  - Poor sensitivity
  - Poor specificity



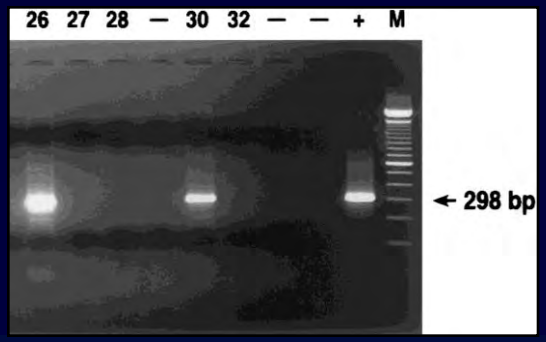


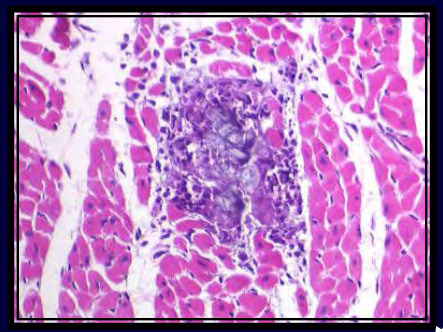
Virus: diffuse
Inflammation: focal

Biopsies

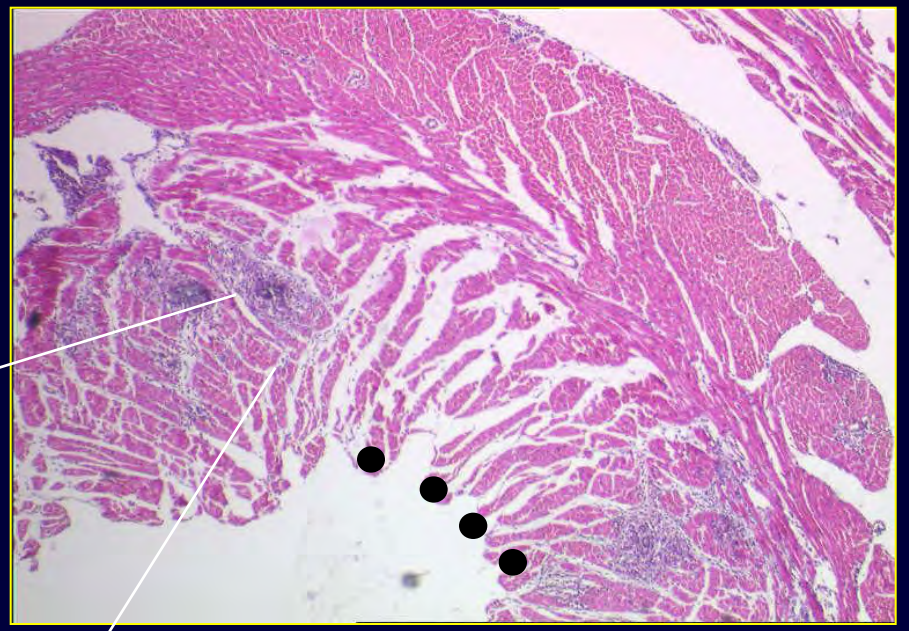
Quantitative RNA/DNA

- Viral rt-PCR in biopsies
  - Pro:
    - High sensitivity
    - High specificity
  - Contra:
    - Invasive (biospies)





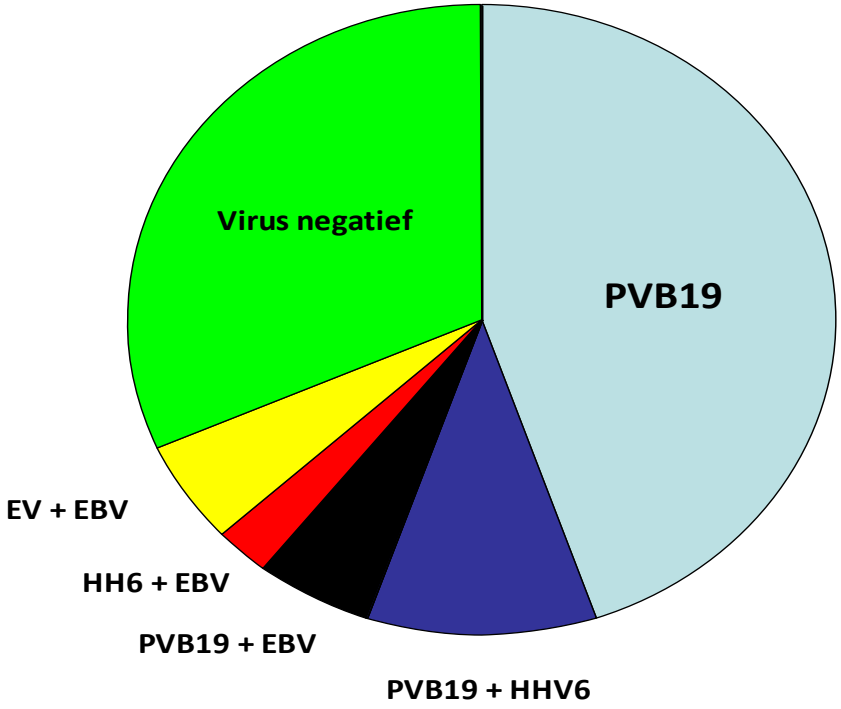
Enterovirus (coxsackie, echovirus), Parvovirus B19, Adenovirus, EBV, HHV6



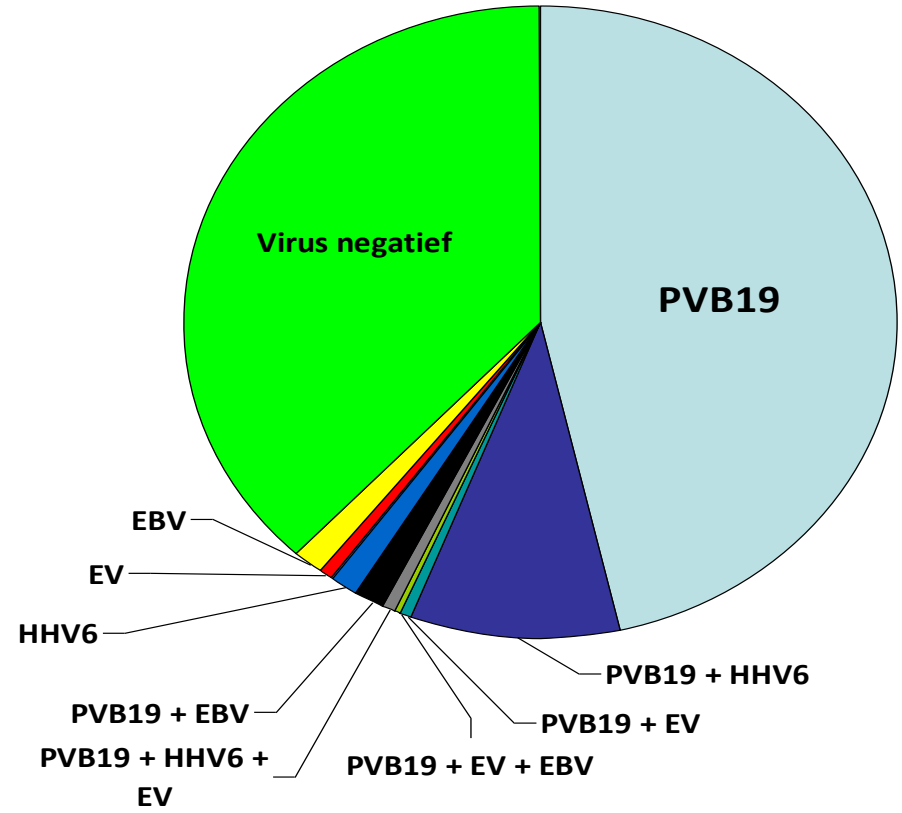
Virus: diffuse
Inflammation: focal

Virus presence in myocarditis vs. idiopathic cardiomyopathy

Myocarditis
(n=20/35)

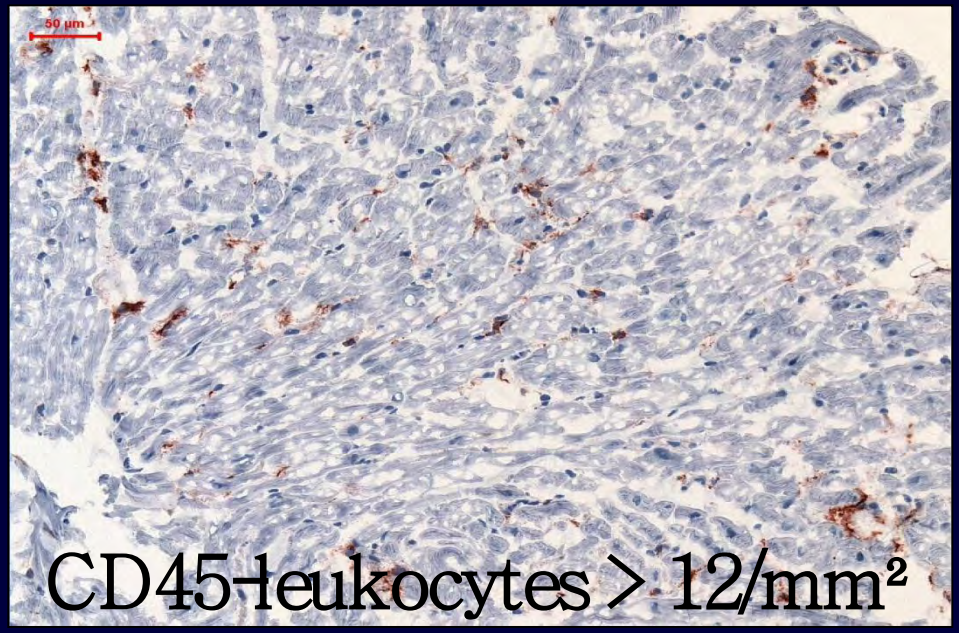


Idiopathic CMP
(n=315)

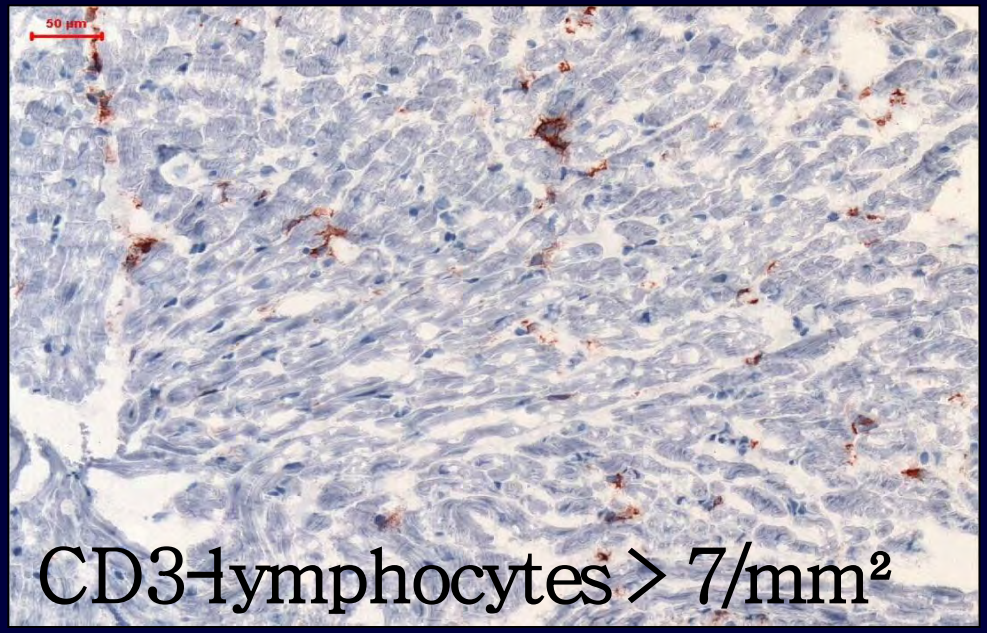


Inflammatory cell staining in biopsies

- Increased inflammation ?
  - Systemic disease (history ?, blood ?)
  - Virus presence ?



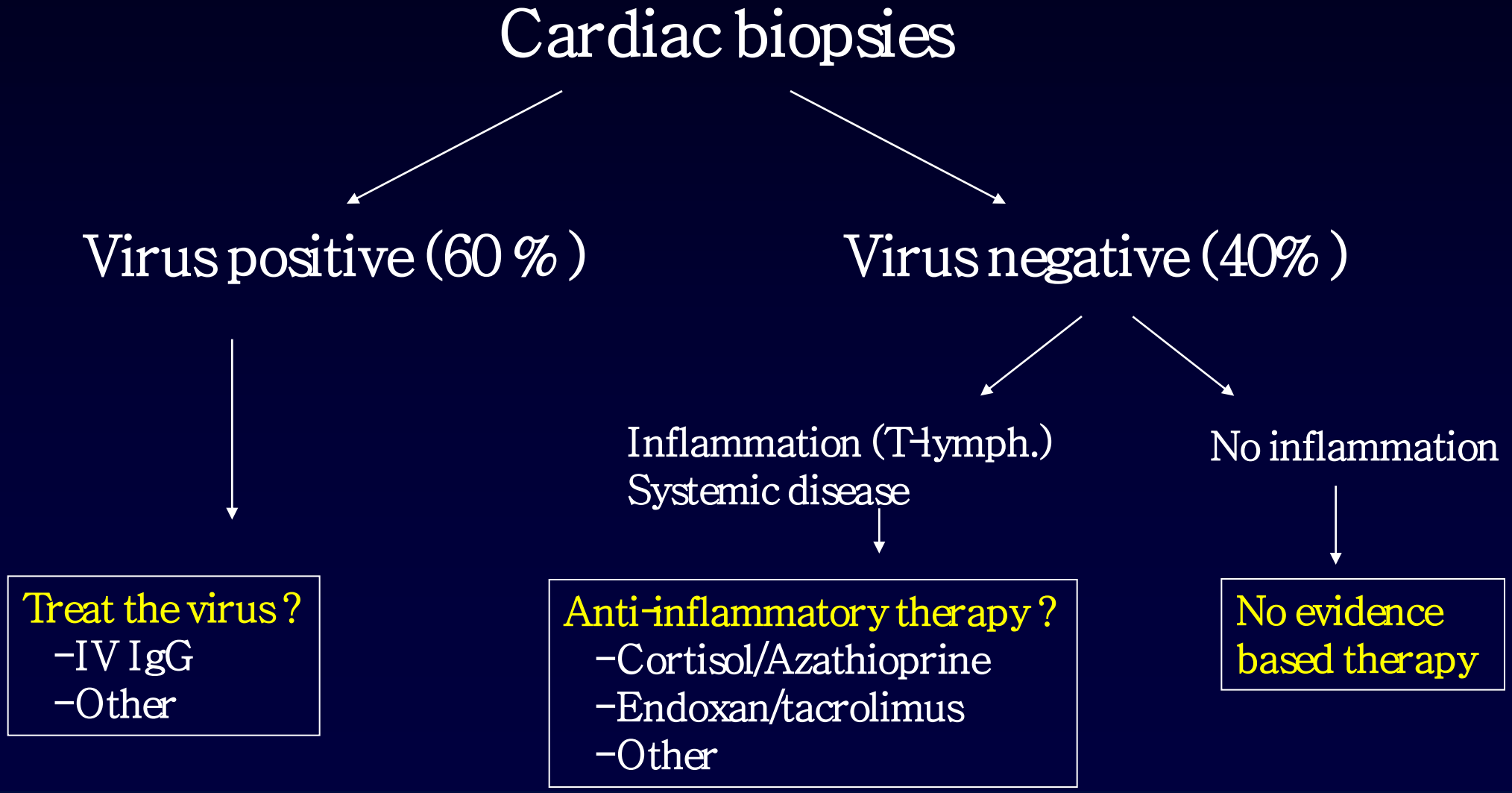
CD45-leukocytes > 12/mm²



CD3-lymphocytes > 7/mm²

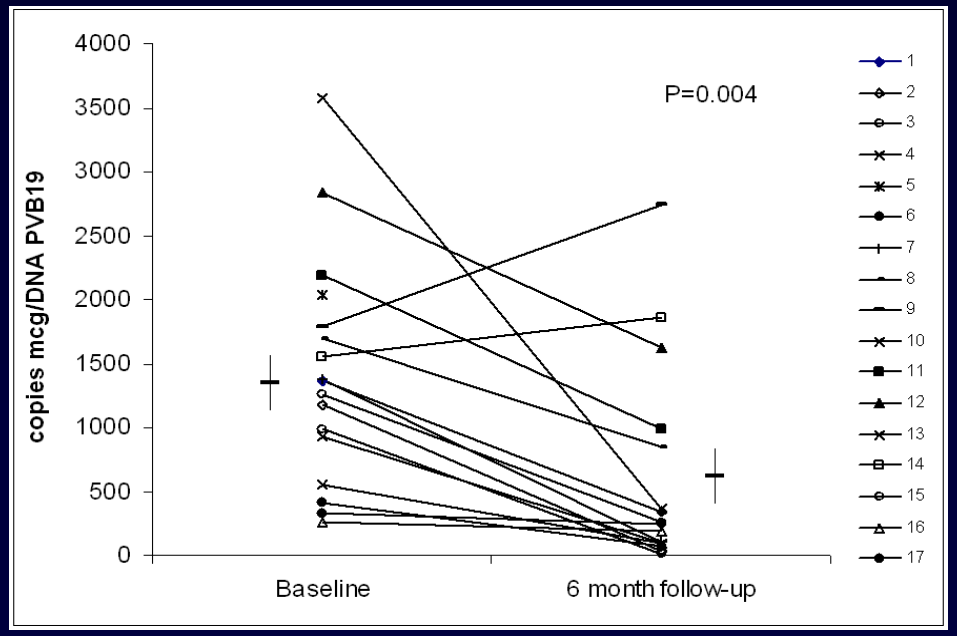
- Viral myocarditis
- Dilated cardiomyopathy
- Diagnosis
- Treatment

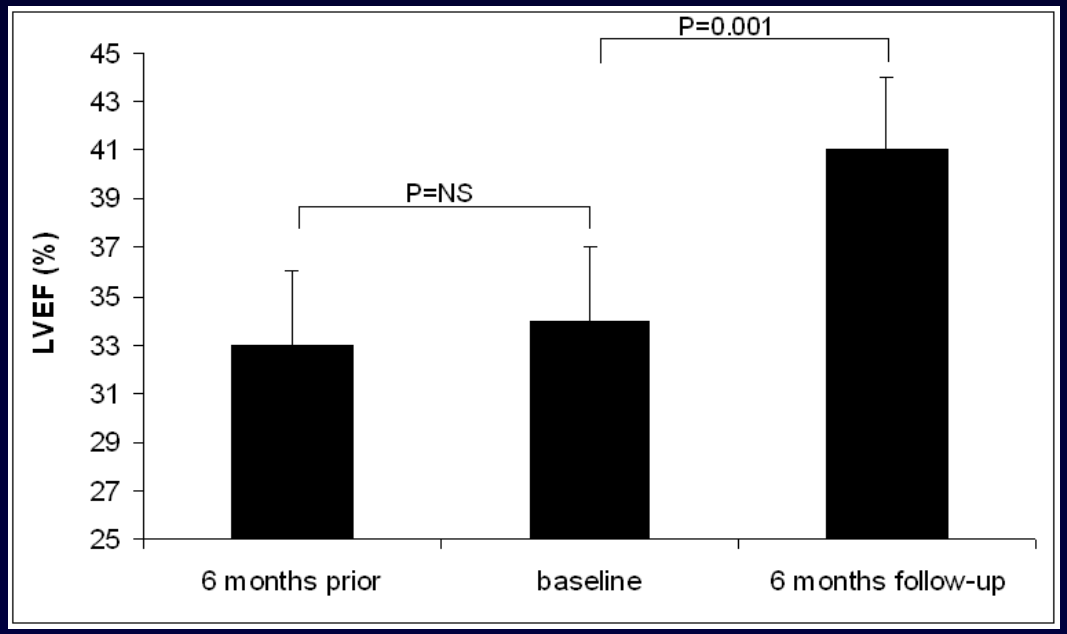
Treatment: idiopathic cardiomyopathy/myocardits ?



Intravenous immunoglobulins for the treatment of PVB19-related CMP

- Randomized single centre clinical trial since 2010 (n=54)
- Based upon pilot data:
  - 2g/kg iv immunoglobulins
  - DCM, EF<45 %
  - > 6 months duration/standard HF therapy
  - PVB19> 250 copies/µg DNA





Dennert et al. AVT 2010

Urgent need for refined diagnosis/ treatment !

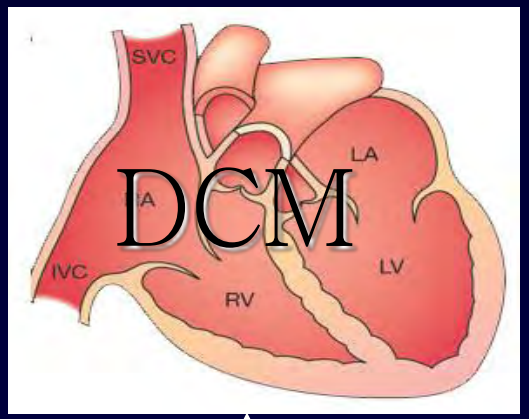
→ International diagnostic protocols & databases

→ New clinical trials

Gene mutations

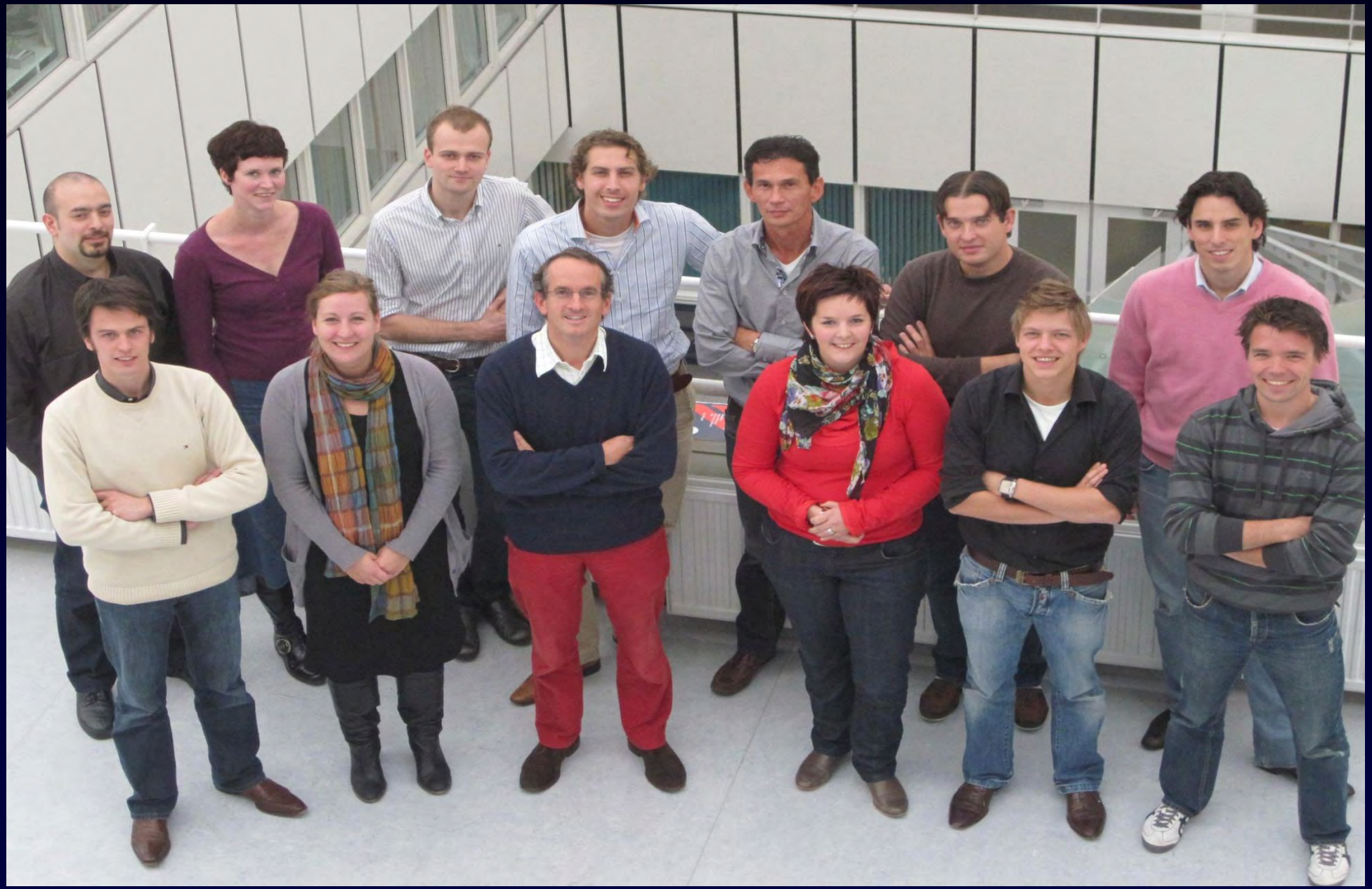
Metabolic Δ

Structural Δ



Inflammatory Δ

Viruses



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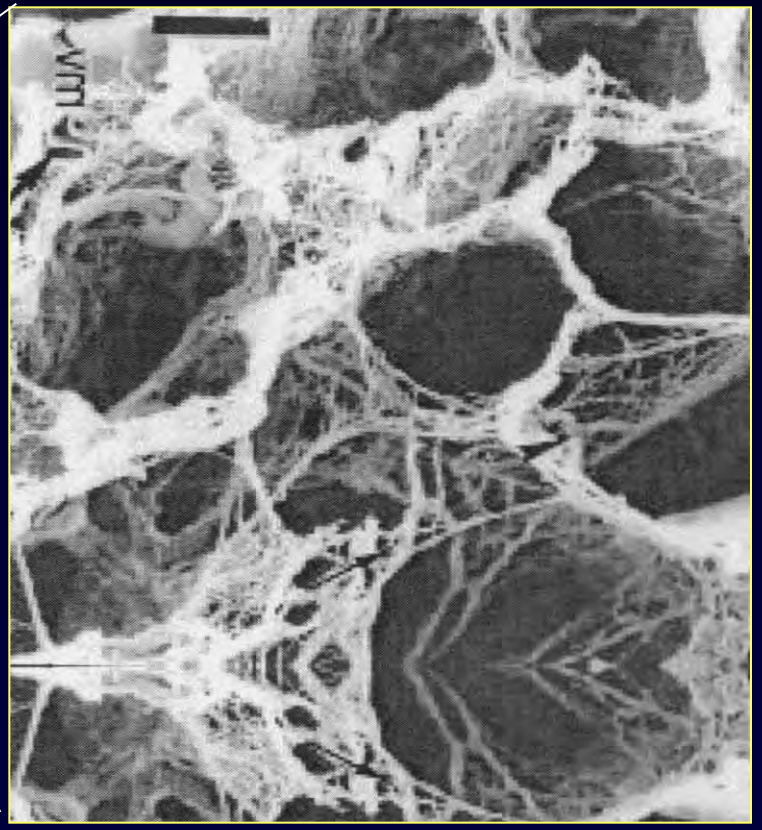
ICIN The Netherlands Heart Institute

NWO Nederlandse Organisatie voor Wetenschappelijk Onderzoek

funded by the Netherlands Heart Foundation

FWO VLAANDEREN

Gezond bindweefsel belet ontsteking!



- Functie van het hart
- Cement in het hart
- **Belet ontsteking!!**
  - Mechanische barriere
  - Cytokines

Afweersysteem in hart: bindweefsel!!

AFBRAAK
Metalloproteinasen

- Afbraak van bindweefsel
- Verhoogde ontsteking

OPBOUW
Thrombospondins/SPARC

- Verstevigt het bindweefsel
- Verminderde ontsteking

⊕ Hartfalen ⊖

***Heymans*, Circulation.** 2006;114:565
Schellings J. Exp. Med. 2009

MMP-inhibition

- Myocardial infarction
  - Inflammation blunted

    →Hypertrophy reduced

    →Cardiac rupture prevented

    →Cardiac dilatation reduced
- Hypertension

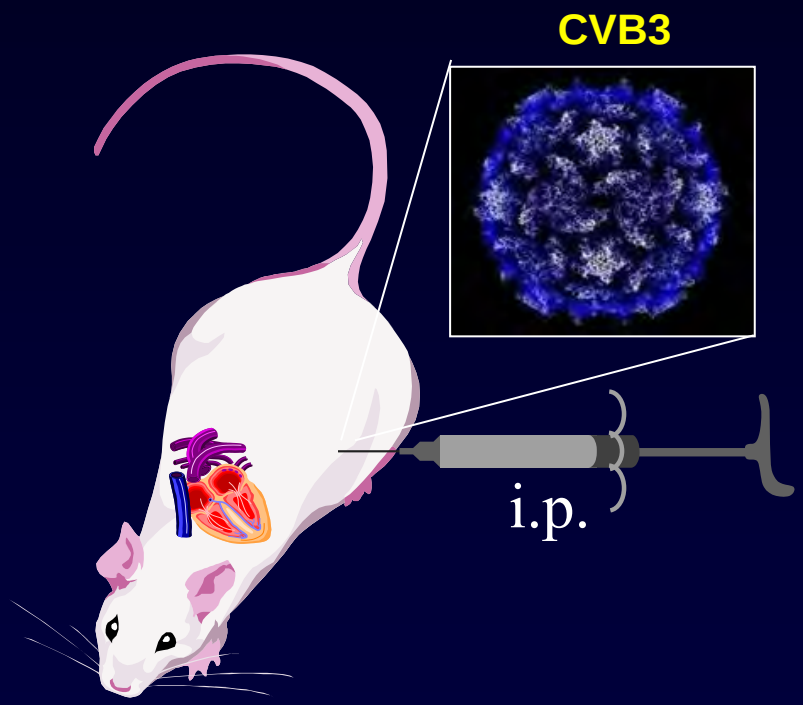
  →LV dilatation reduced

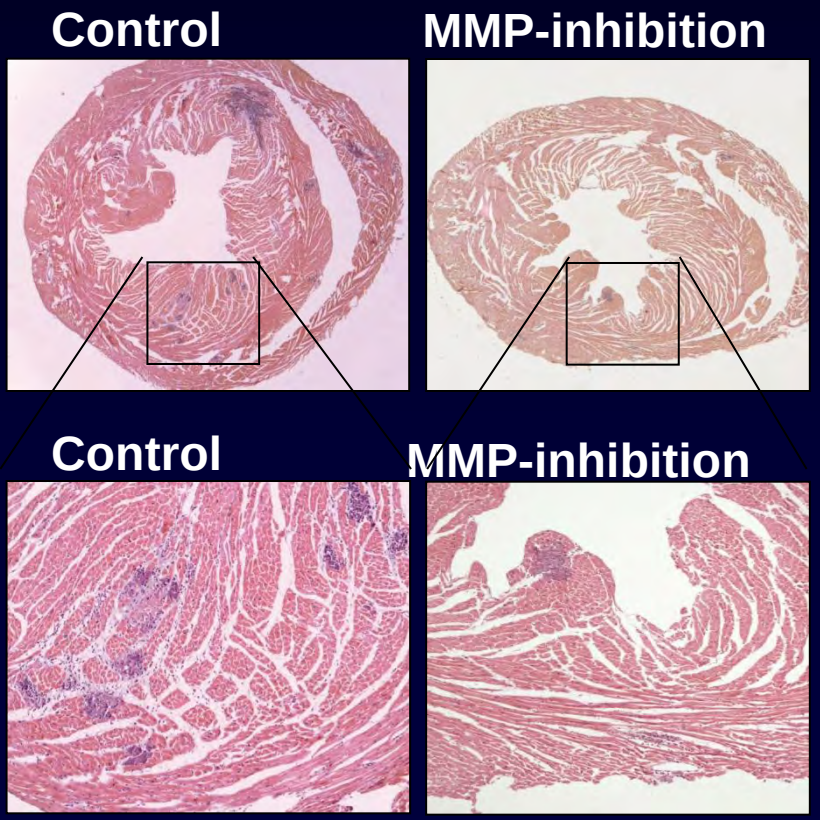
  →LV function preserved

Heymans S., *Nature Med*, 1999
Ducharme A., *J. Clin. Invest,* 2000
Hayashidani S, *Am J Physiol Heart Circ Physiol 2003.*
Matsumura, S, *J. Clin. Inv.*, 2005

Heymans S., *Am. J. Pathol*, 2005
Heymans S.., *Circulation*, 2005

Inhibite van collageen afbreek voorkomt virale schade door ontsteking





Number of inflammatory foci per grid

10 ± 1.2 3.9 ± 1.3

Heymans S., Pauschinger et al, *Circulation, 2006*

Bench to bedside:
Toegenomen MMP-9 in een patiënt met virale myocarditis

- Male, 20 years, acute fulminant myocarditis
- Echo: EF 20 %, EDD 64 mm
- Cardiac biopsies: Epstein-Barr virus: 1750 copies/µg