



# Acute Myocarditis

## - Unusual Causes of HF -

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성균관대의대 순환기내과  
삼성서울병원, 심장 혈관 센터

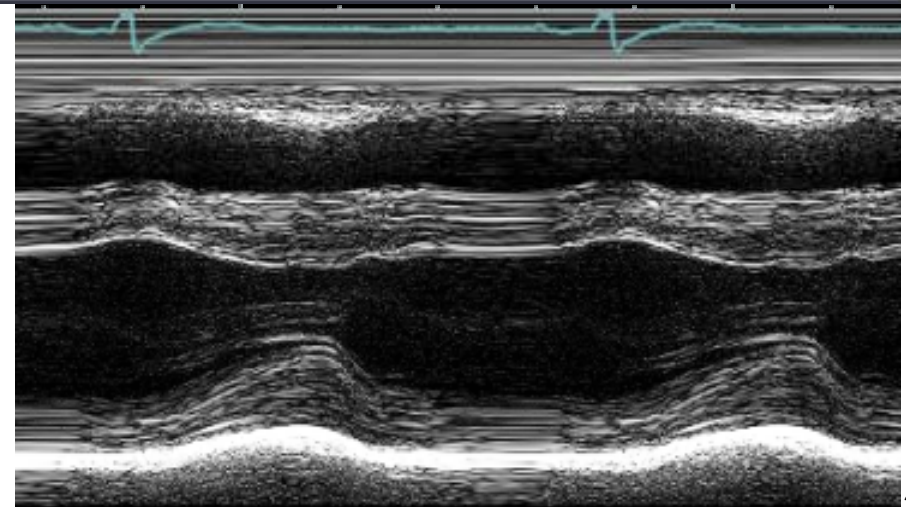
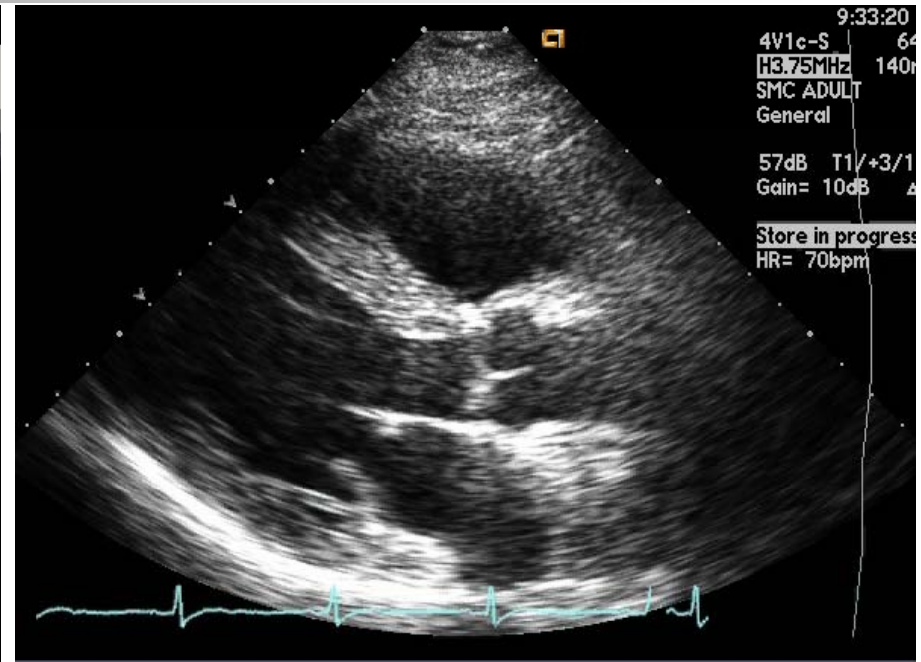
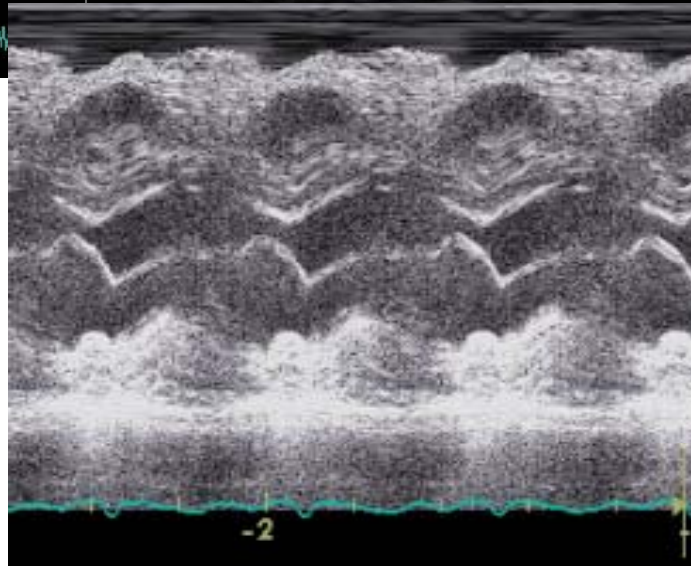
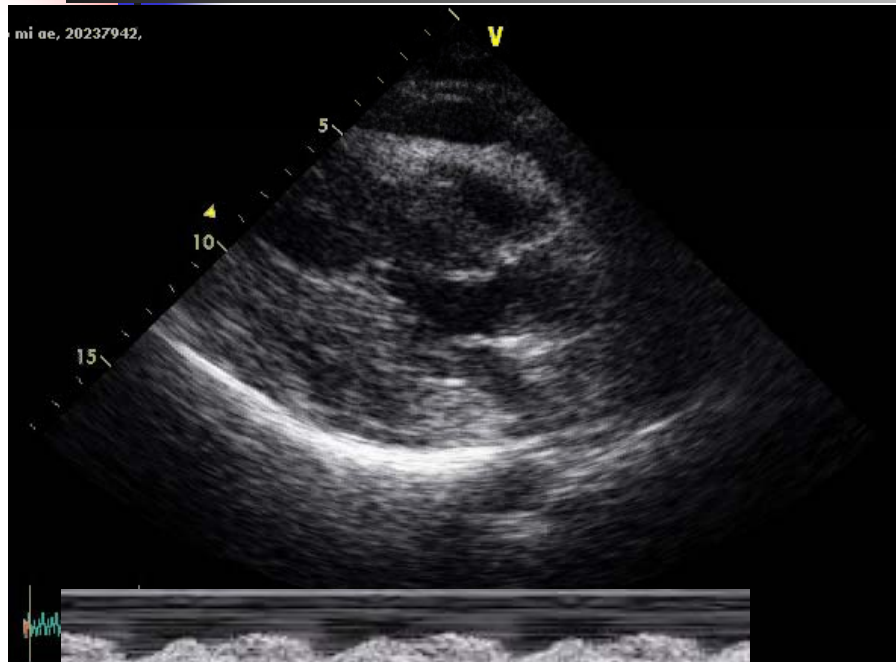
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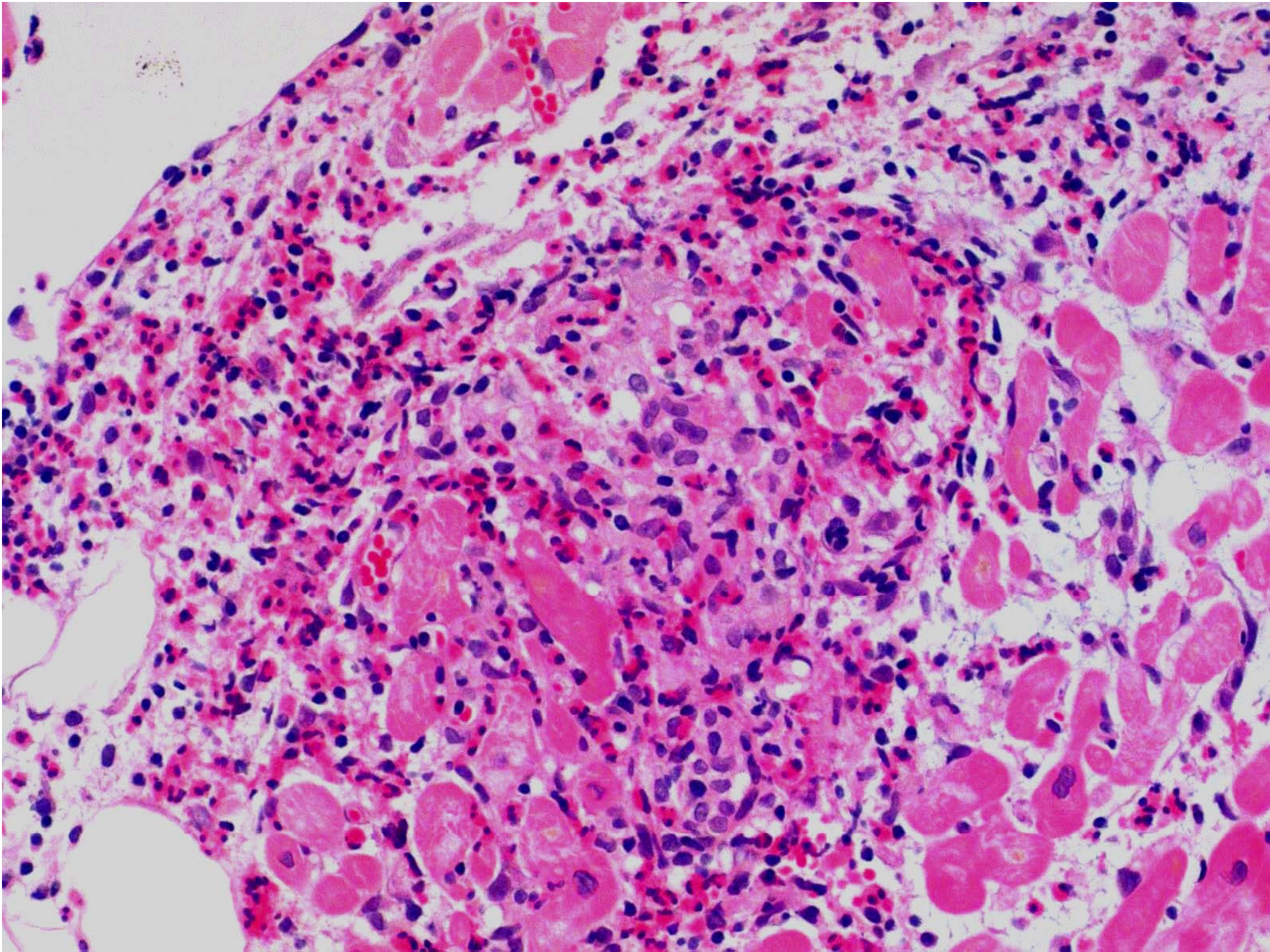
## Case Summary – initial presentation

CC) Palpitation and DOE for 5 days

- 39세 여자
- Local 입원하여 심초음파 상 pericardial effusion cardia tamponade 소견으로 전원
  - 심전도: 동성 빈맥, low voltage
  - 심초음파도) pericardial effusion-심낭 천자 10 cc

# Echocardiography



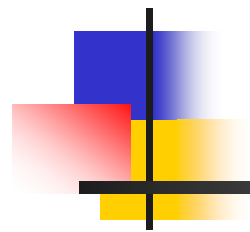


# Laboratory Findings

	08/03	08/16
	Day 1	Day 14
BP	90/60	110/80
LVID s/d	Moderate pericardial effusion with tamponade physiology	30/53
EF		68%
WBC	12110	8000
Eosinophils	5.0%	20%(1690)
Total IgE	220 (0-200)	
CK-MB/Tnl	17.71/2.6	2.82/0.911
NT-proBNP	11408	188

No specific medication  
Except pericardiocentesis  
/ 퇴원시 Pd 30 mg

Losartan  
Carvedilol



# Myocarditis; Inflammatory Heart Disease

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Department of Medicine,  
Sungkyunkwan University School of Medicine,  
Eun-Seok Jeon, MD, PhD

# Definition of Myocarditis

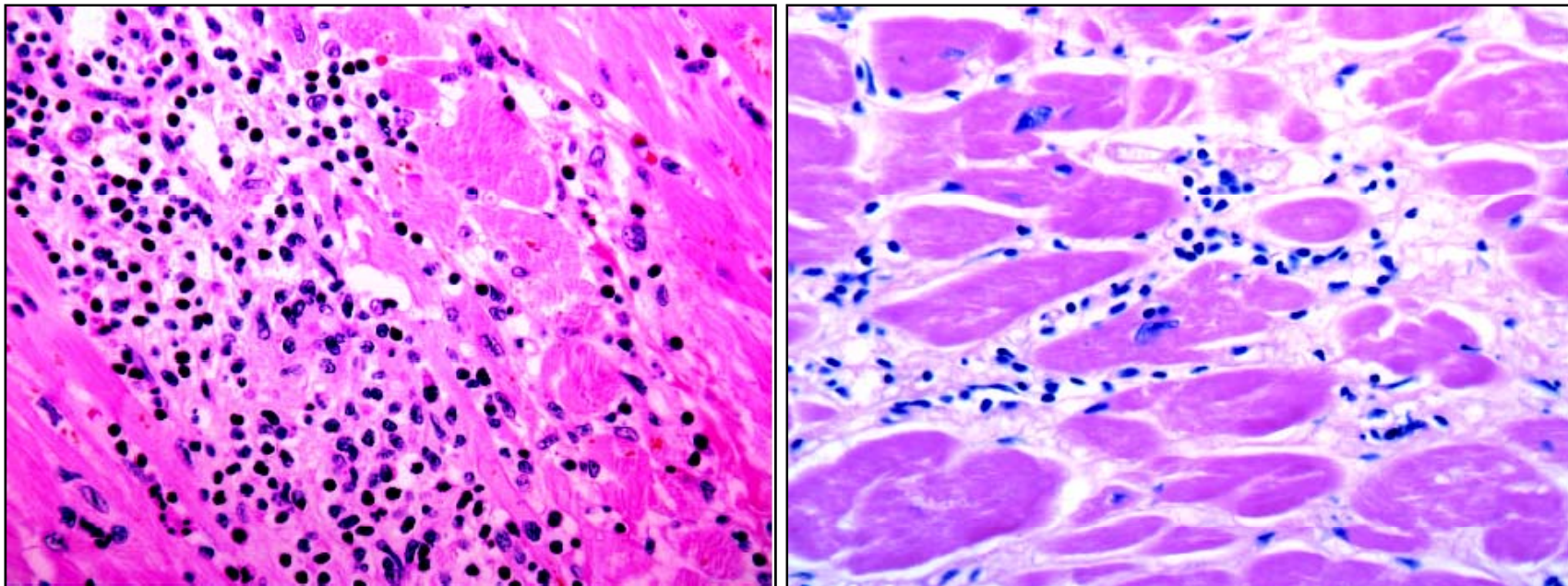
- an **INFLAMMATION INFILTRATE** and by **INJURY** to the adjacent myocardial cell that is not typical of **INFARCTION**
- Despite clear-cut definition, Classification, diagnosis and treatment continue to debate.
- Dallas Criteria (1986)
  - inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocardium not typical of the ischemic damage associated with coronary artery disease

# Dallas Criteria

- Inflammations
  - Active vs borderline
  - inflammation cell infiltration with or w/o myocardial necrosis or injury
- Inflammatory infiltrates;
  - lymphocytic, eosinophilic, granulomatous
- Amount of inflammation
  - Mild, moderate, severe
- Distribution of inflammation
  - Focal, confluent, diffuse

# Dallas Criteria

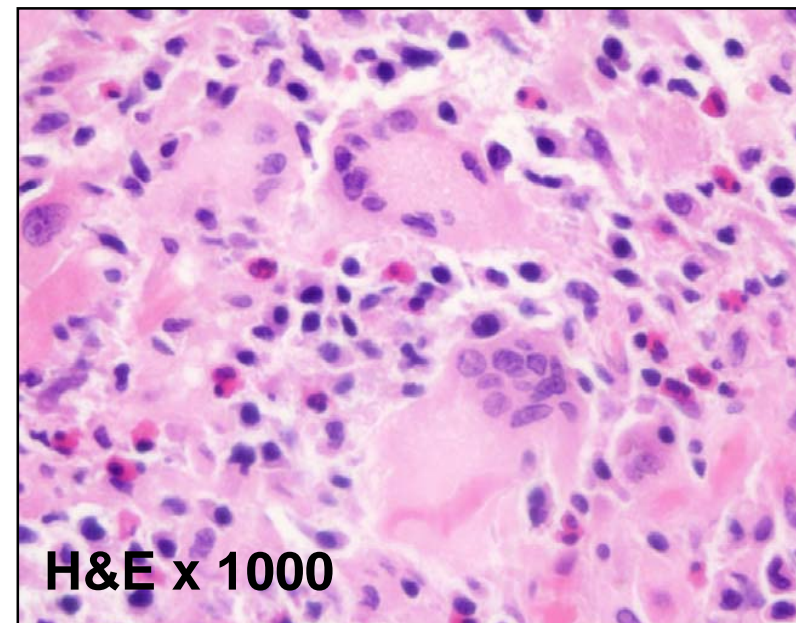
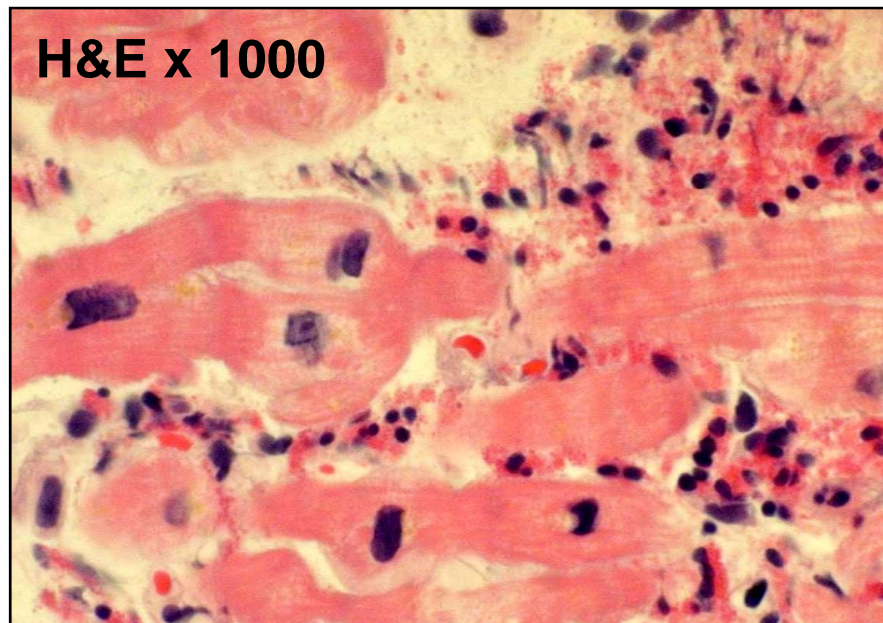
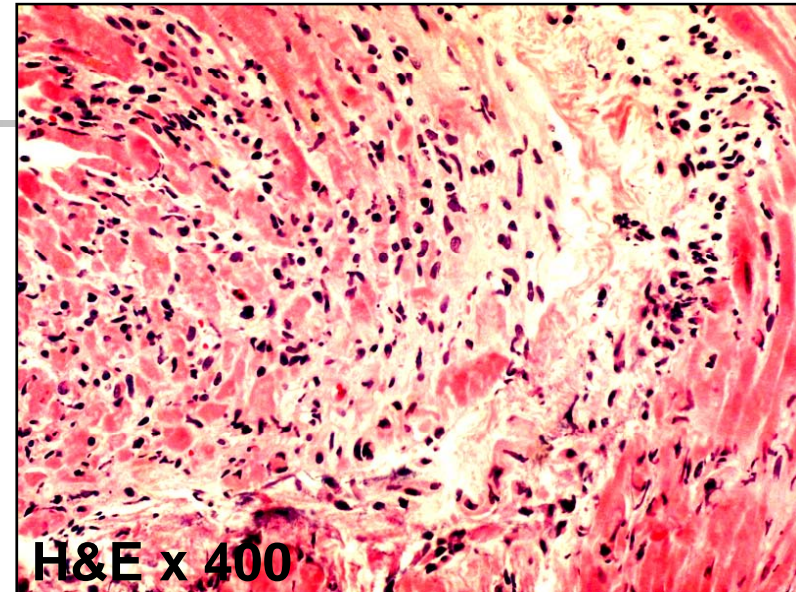
- Inflammations
  - Active vs borderline
  - inflammation cell infiltration with or w/o myocardial necrosis or injury

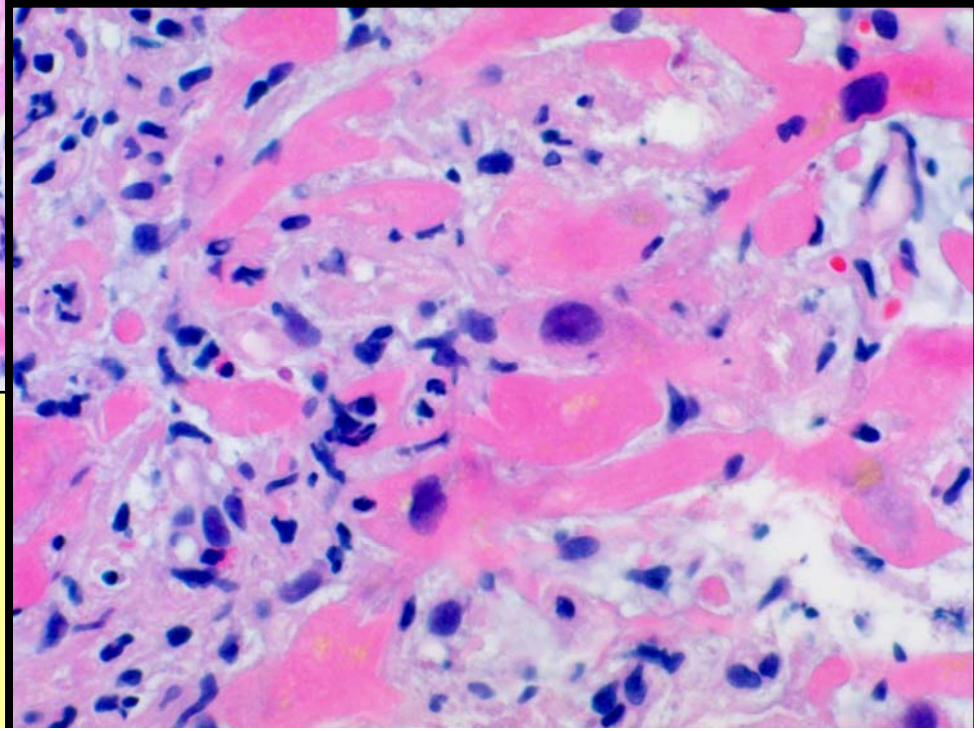
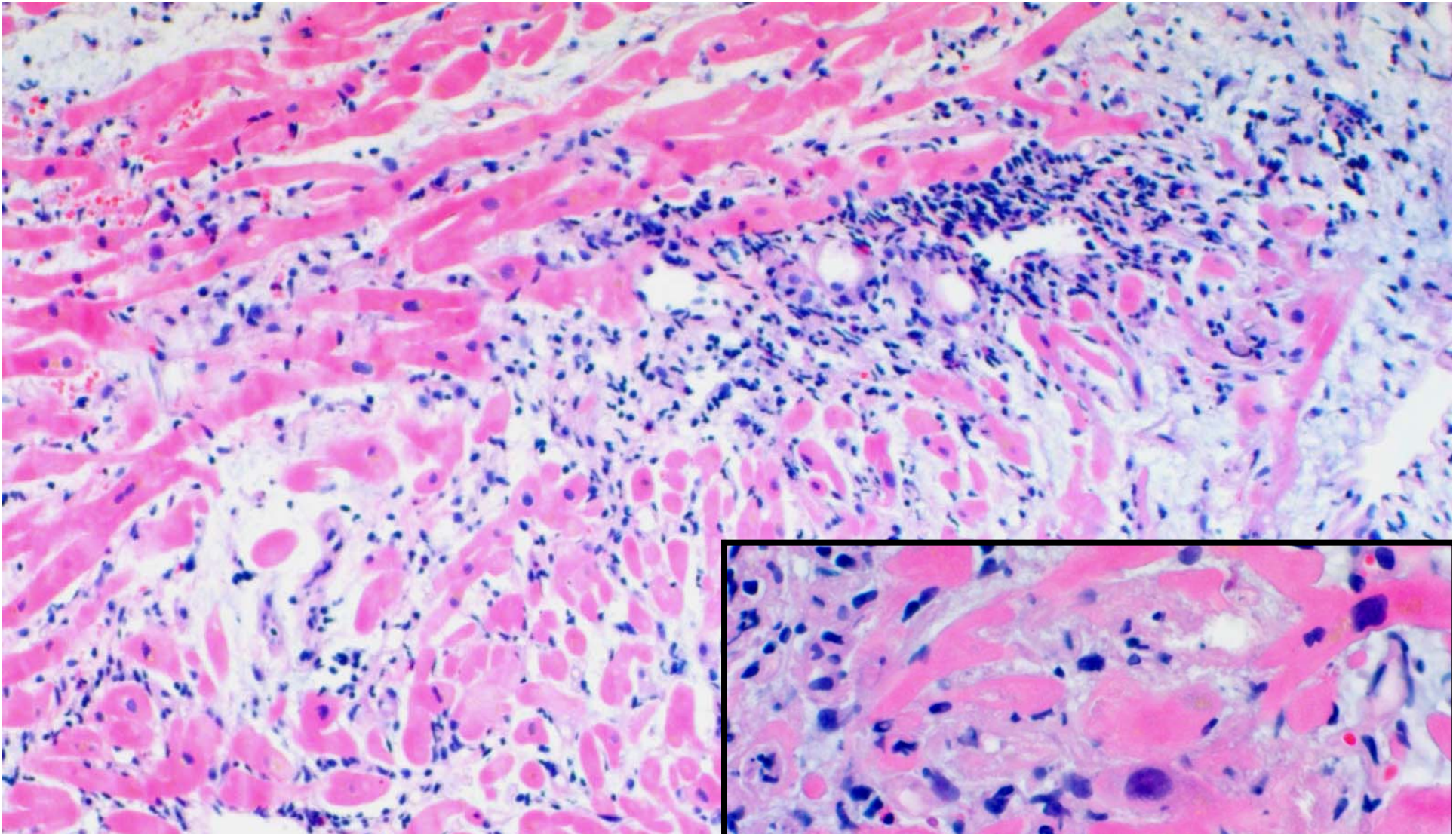


# Dallas Criteria

## Inflammatory infiltrates

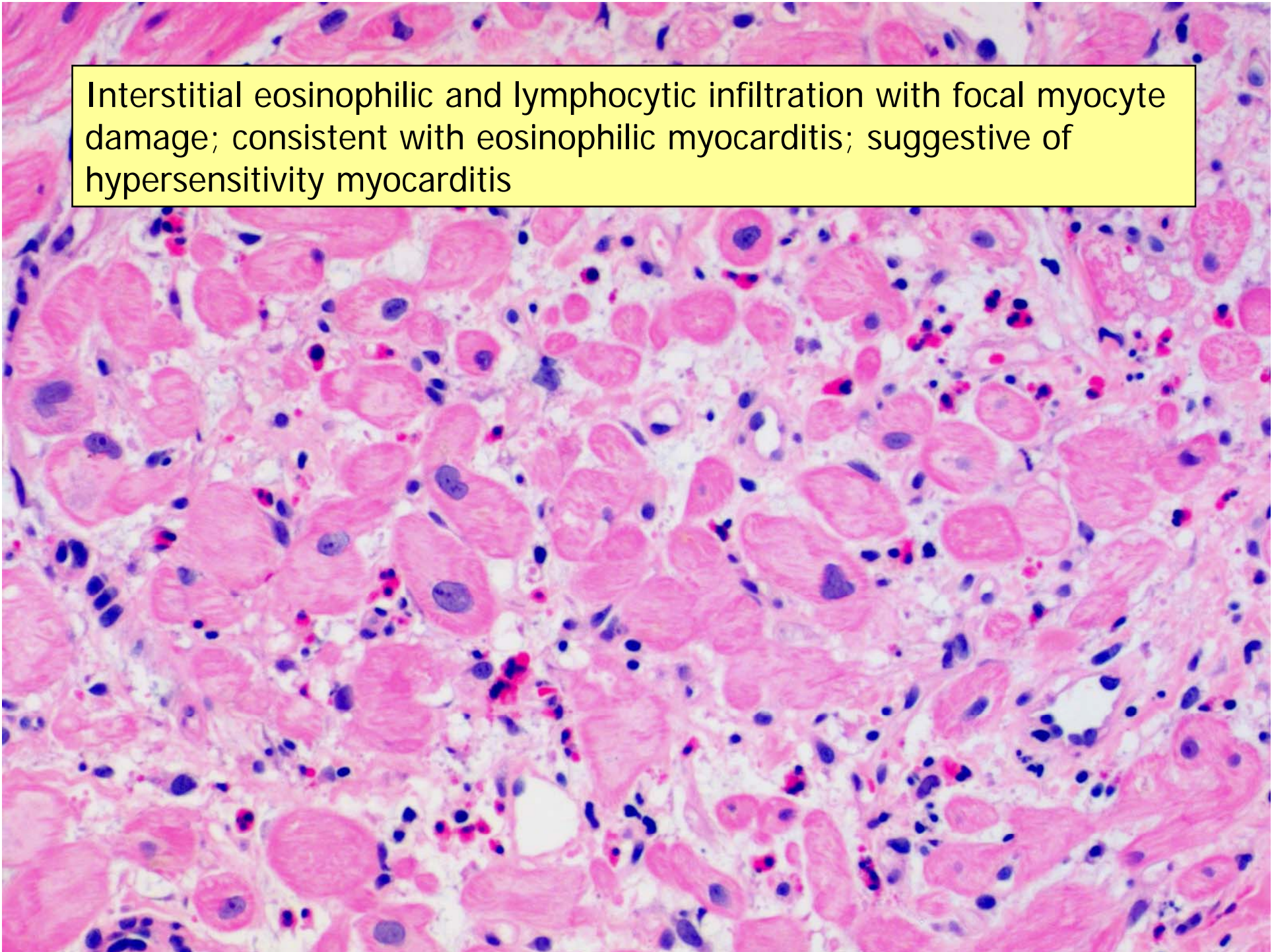
- lymphocytic
- eosinophilic
- granulomatous

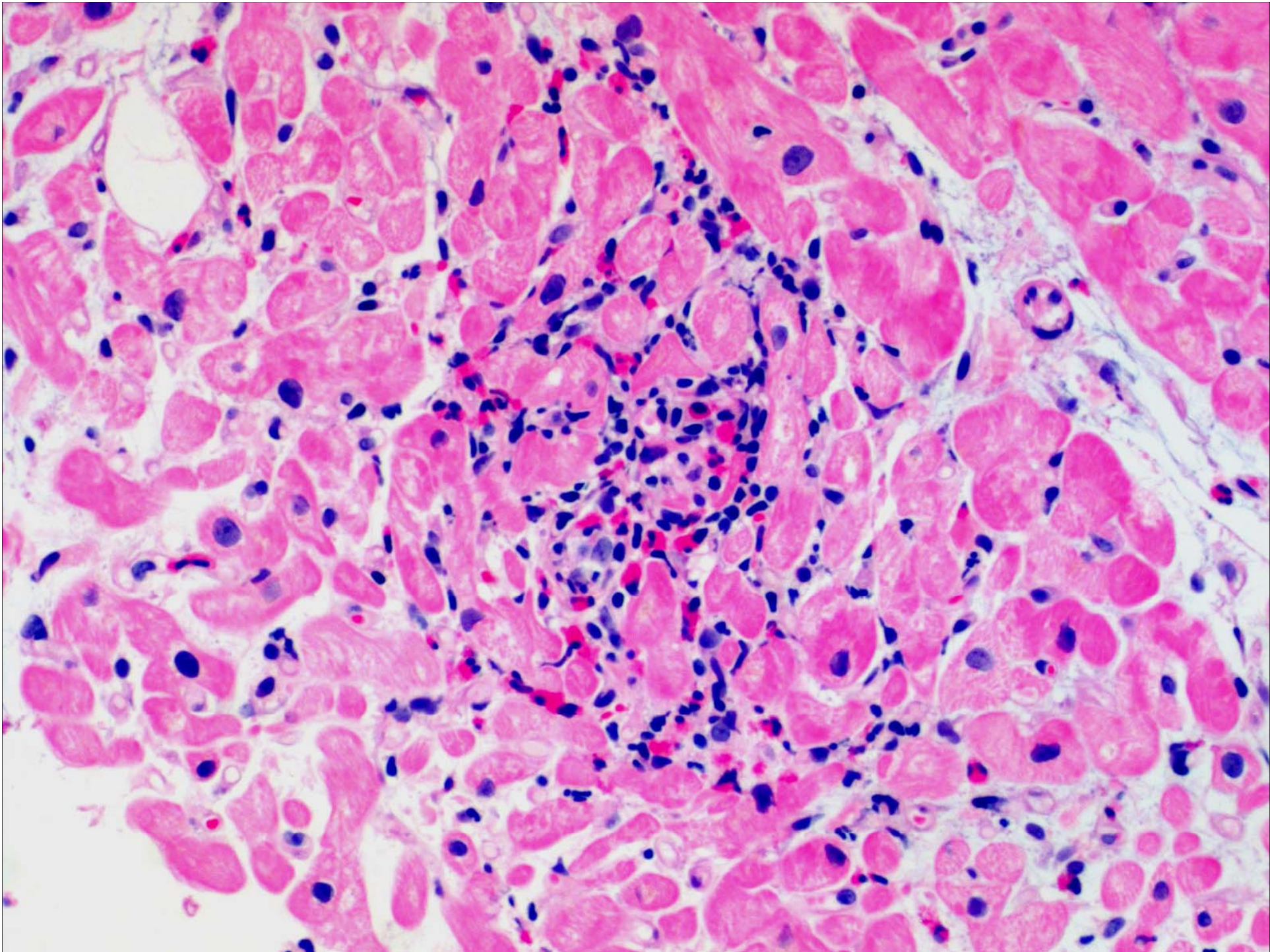


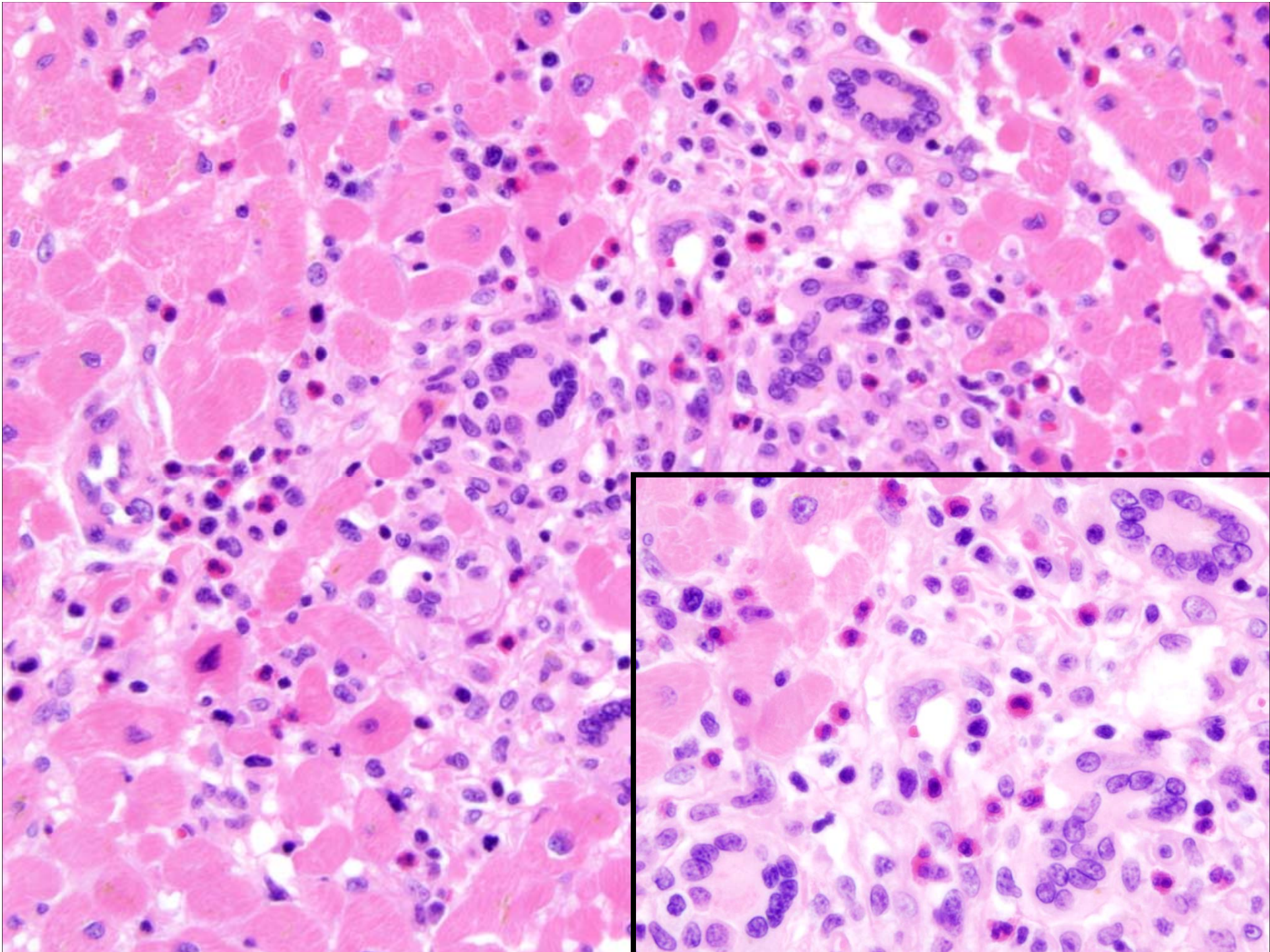


Biopsy at day 5 : Patchy interstitial and perivascular lymphoplasmacytic cell infiltration with multifocal myocyte damage; consistent with lymphocytic myocarditis

Interstitial eosinophilic and lymphocytic infiltration with focal myocyte damage; consistent with eosinophilic myocarditis; suggestive of hypersensitivity myocarditis







# Etiologic Agents of Myocarditis

## Infectious Agents

### Virus

**Coxsackievirus(A,B)**

**Adenovirus**

**HIV**

**HCV**

### Bacteria :

mycobacterial / streptococcal

mycoplasma pneumoniae

Treponema pallidum

**Metazoa** : Trichinosis,  
Echinococcosis

**Protozoa** : **Trypanozoma cruzi**

**Fungus** : Aspergillosis, Candidiasis ....

## Toxic Agents

**Anthracyclines**

**Catecholamines**

Interleukin-2

Cocaine

## Hypersensitivity

sulfonamide

cephalosporin

**diuretics/digoxin**

**TCA**

**dobutamine**

## Immunological Syndromes

Chug-Strauss

infl bowel dis

Sarcoidosis

diabetes

Sarcoidosis

SLE

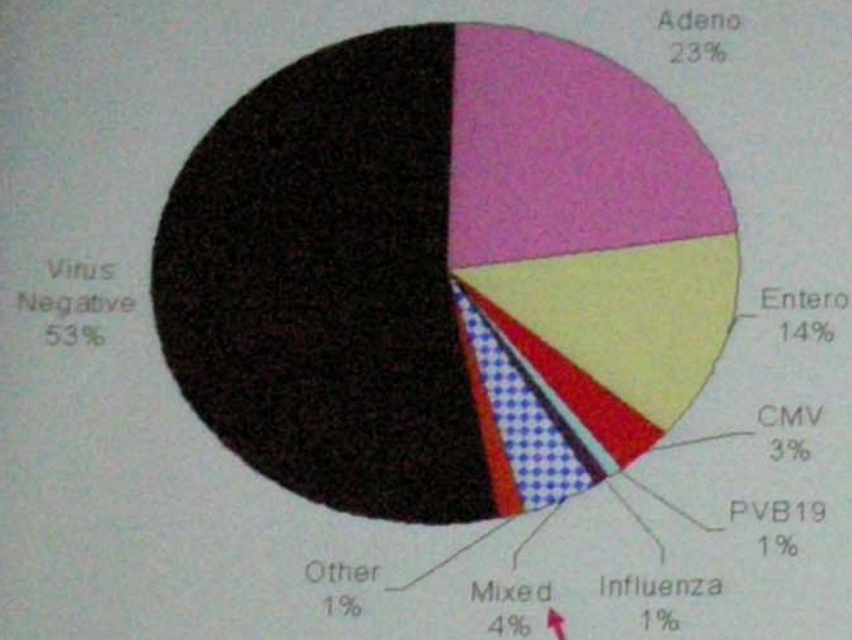
Takayasu's

Thyrotoxicosis

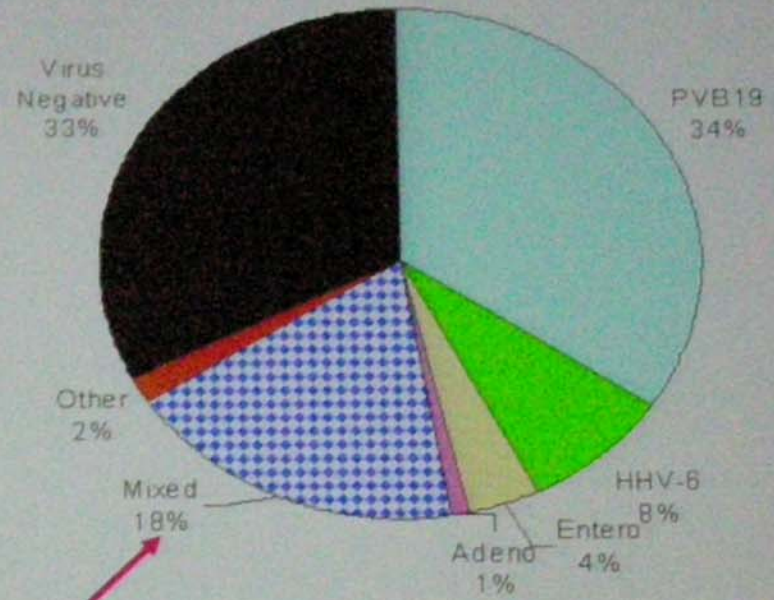
Wegener's

PSS / MCTD

Baylor



Berlin

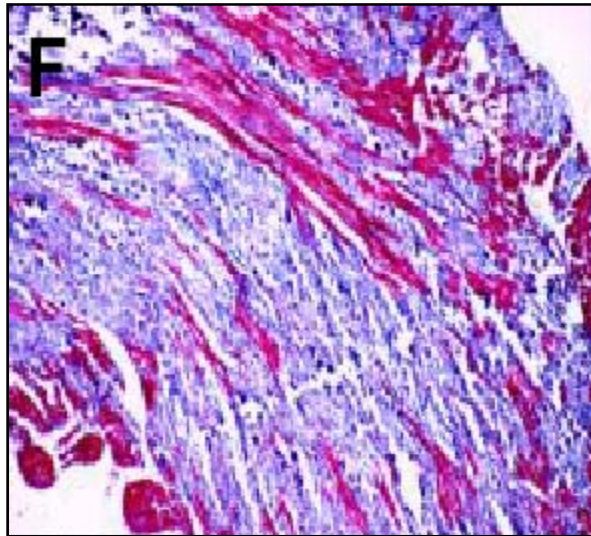
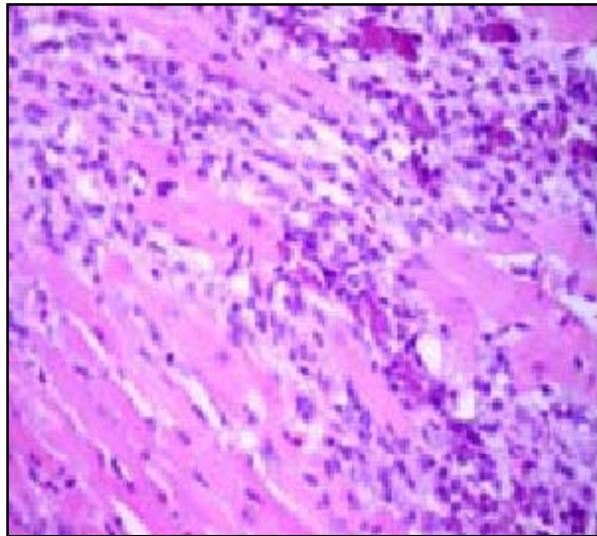
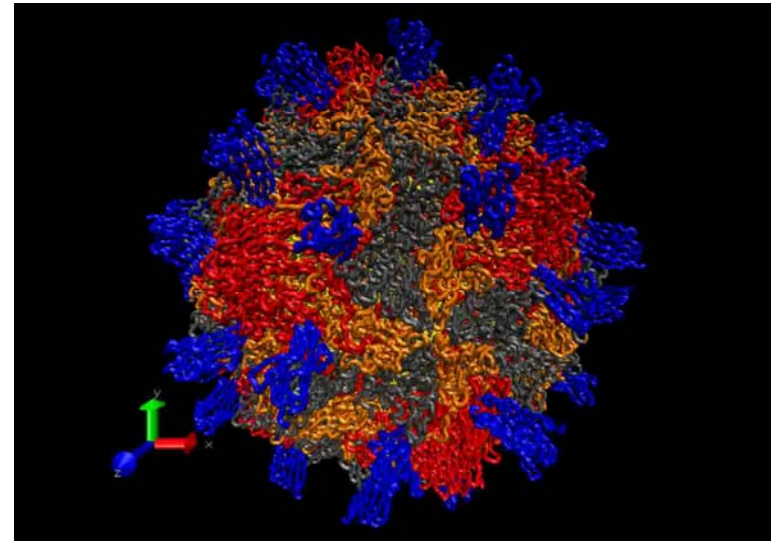


Japan

Hepatitis C Virus  
21%-33%

# Coxsackievirus Type B3 (CVB3)

- 7.4 Kb ssRNA picornavirus
- highly cardiotropic
- induces myocarditis
- progress to cardiomyopathy



# Diagnostic evaluation

## 1. Endomyocardial biopsy

## 2. Cardiac biomarkers

- Troponin I; sensitivity 34%, specificity 89%
- CK, CK-MB; low predictive value

## 3. Immunologic Approaches

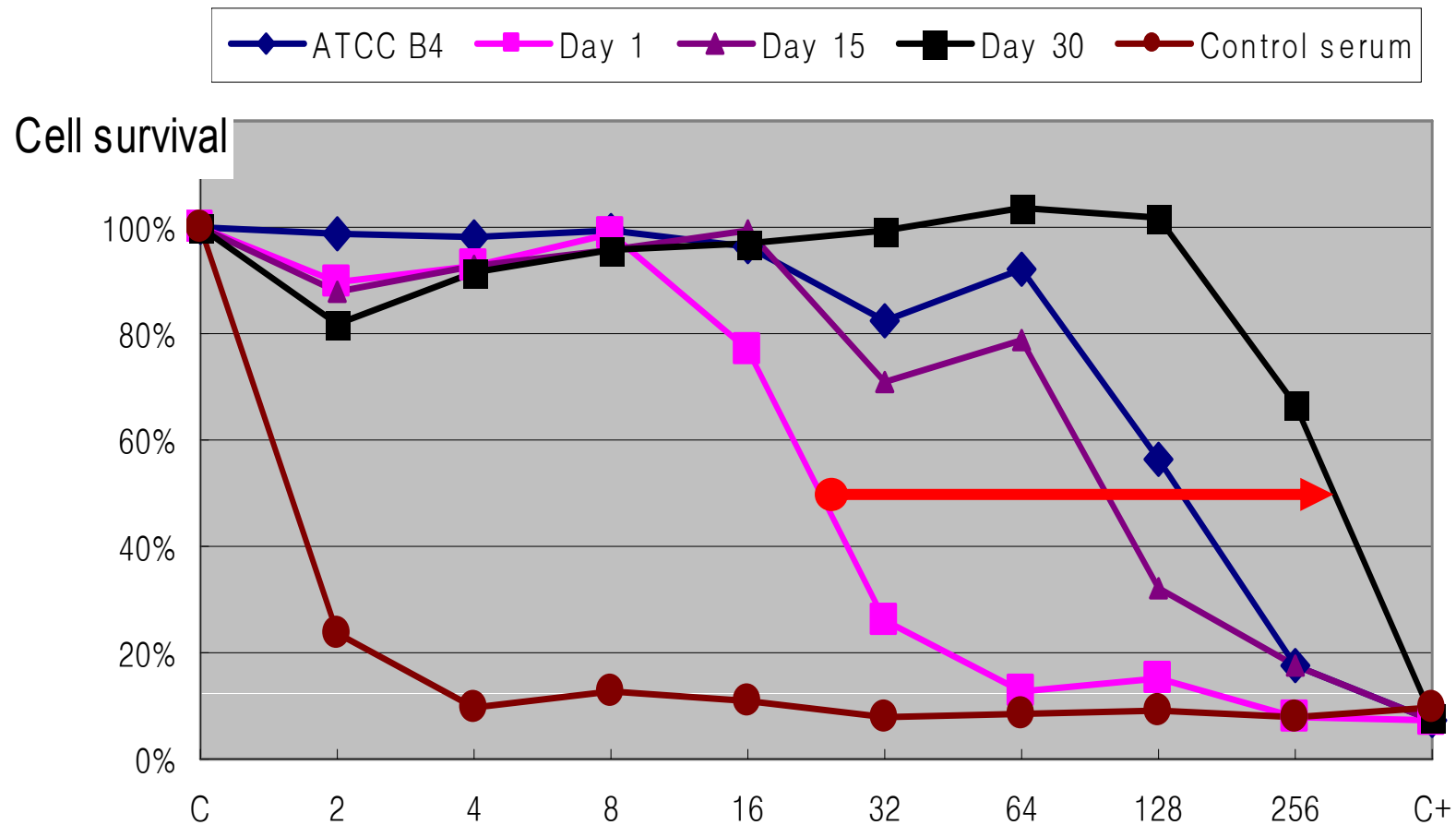
- Immunohistochemical staining for Lc
- MHC expression – chronic for of myocarditis

## 4. Myocardial imaging

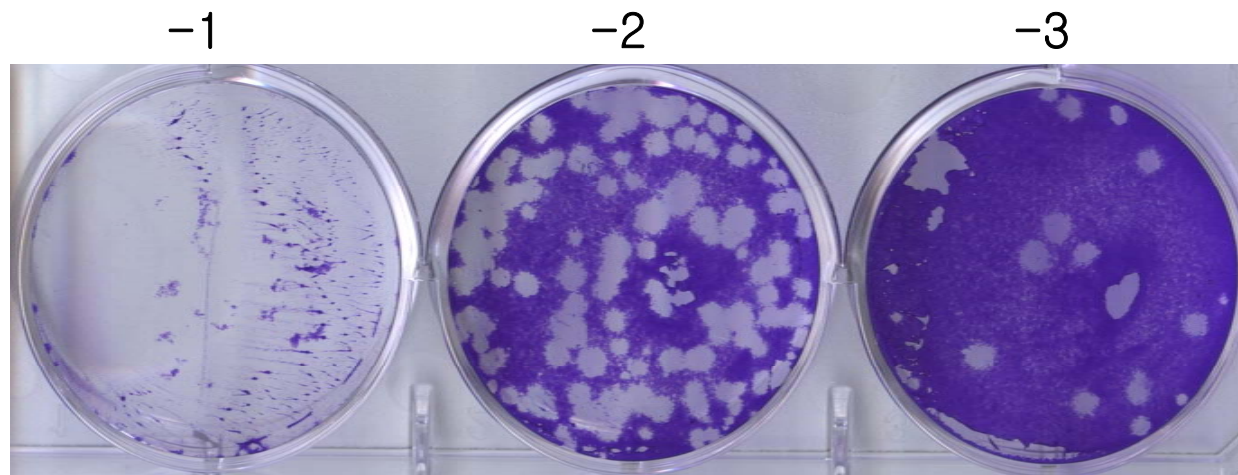
# Endomyocardial Biopsy

- Histological myocarditis in 25% of samples
- >5 biopsies, two thirds are (+)
- For accurate Dx, Needs >17 samples in >80% of patients
- Agreement of 7 pathologists in 16 DCM specimen
  - Fibrosis (25-69%) , Hypertrophy (19-88%)
  - Nuclear changes (31-94%), LC counts on HPF (0-38%)
- Myocarditis associated with
  - HIV/AIDS, ischemia,
  - Inflammations- sarcoidosis, SLE etc...
  - **Otherwise primary (postviral)**

# Neutralization test with serial sera

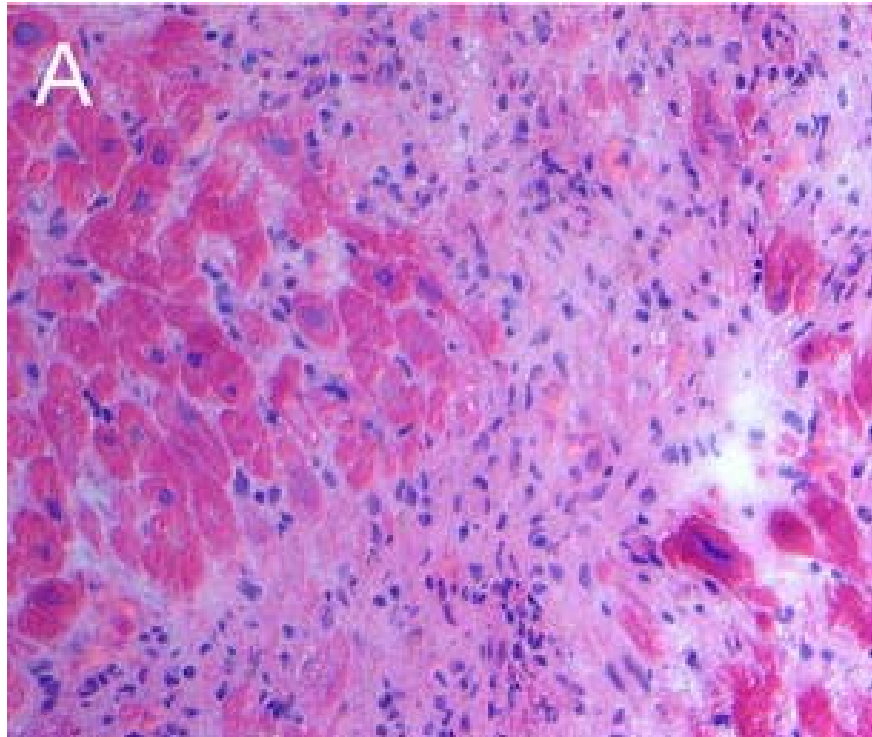


# PFU assay from tissue with HeLa

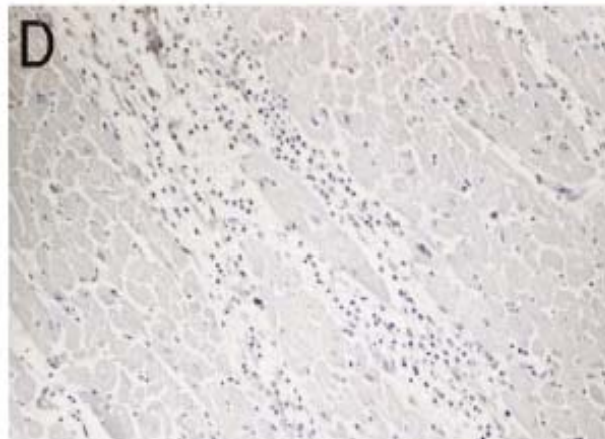
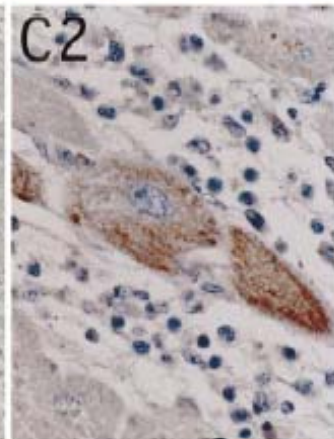
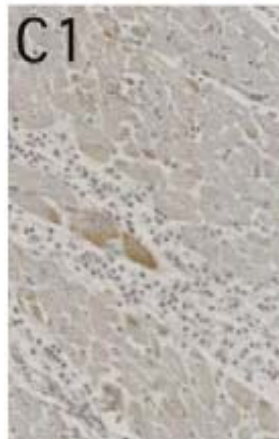
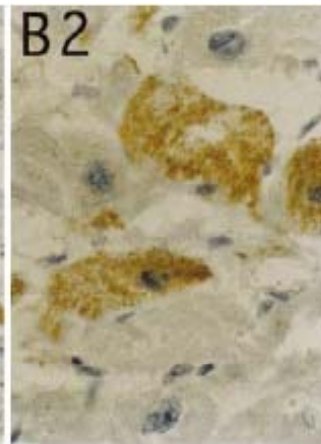
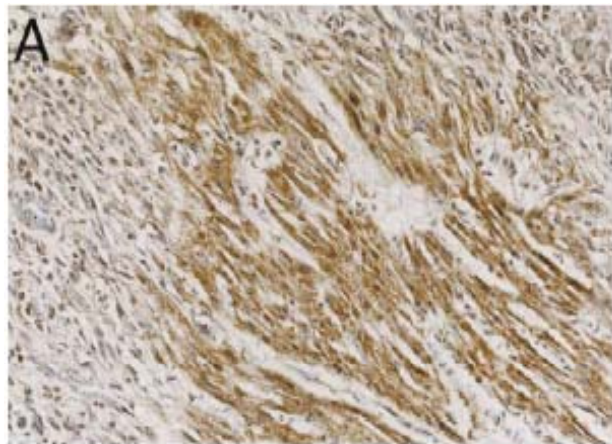


Viable virus was isolated from frozen left atrial tissue at day 1.  
The final concentration of virus was  $1.5 \times 10^4$  PFU/ml

# Detection of enteroviral Genome by *in situ Hybridization* in CVB2 myocarditis



# Detection of enteroviral capsid protein VP1 by immunohistochemistry



A : fatal myocarditis

B : D-CMP

C: Chronic myocarditis

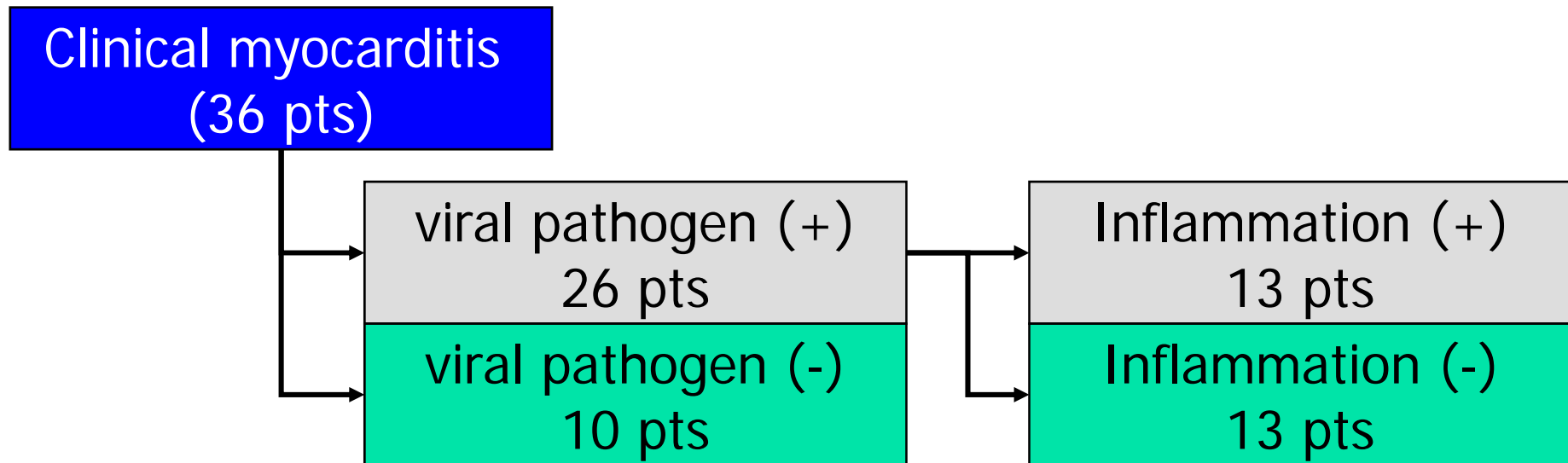
D : Negative control  
with IgG2a

x200 : A, B1, C1, D

x600 : B2, C2

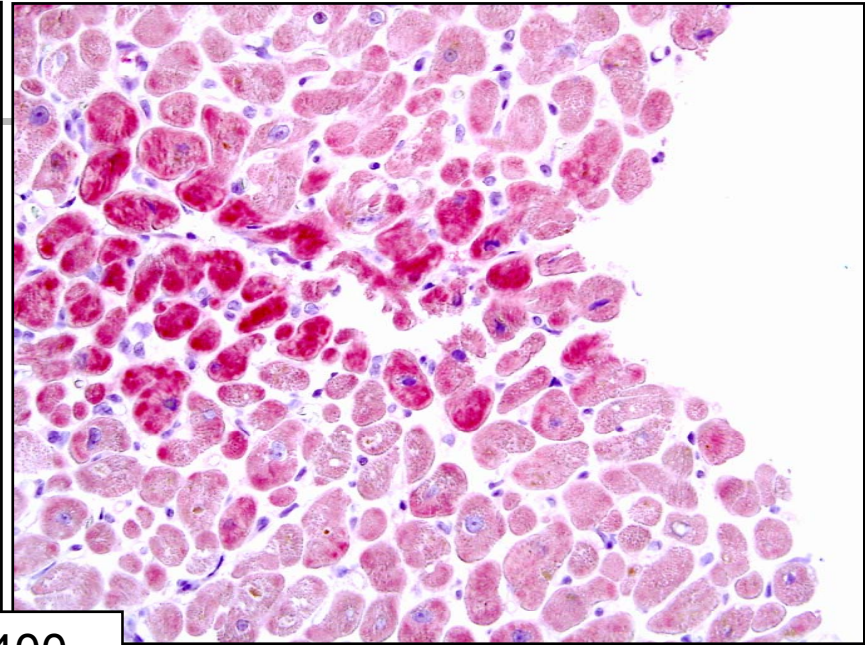
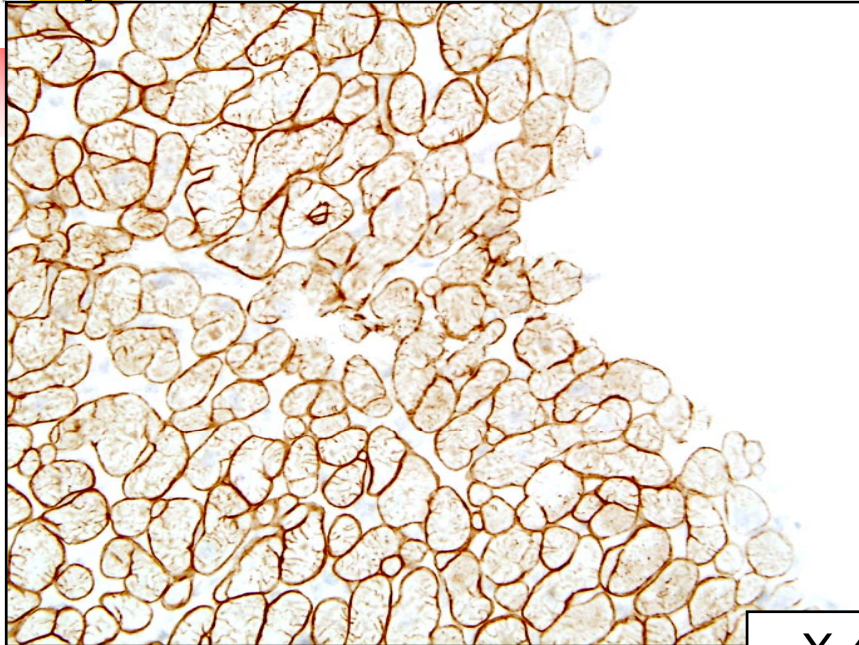
# Virus without inflammation

- Virus can exist in the myocardium (even in a replicative form) in the absence of myocardial inflammation adequate to meet Dallas criteria.

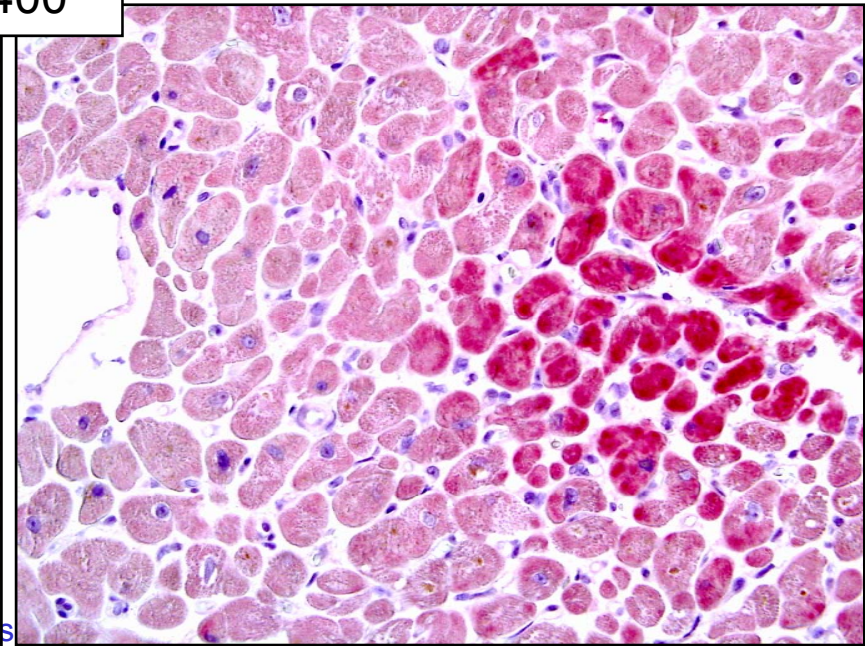
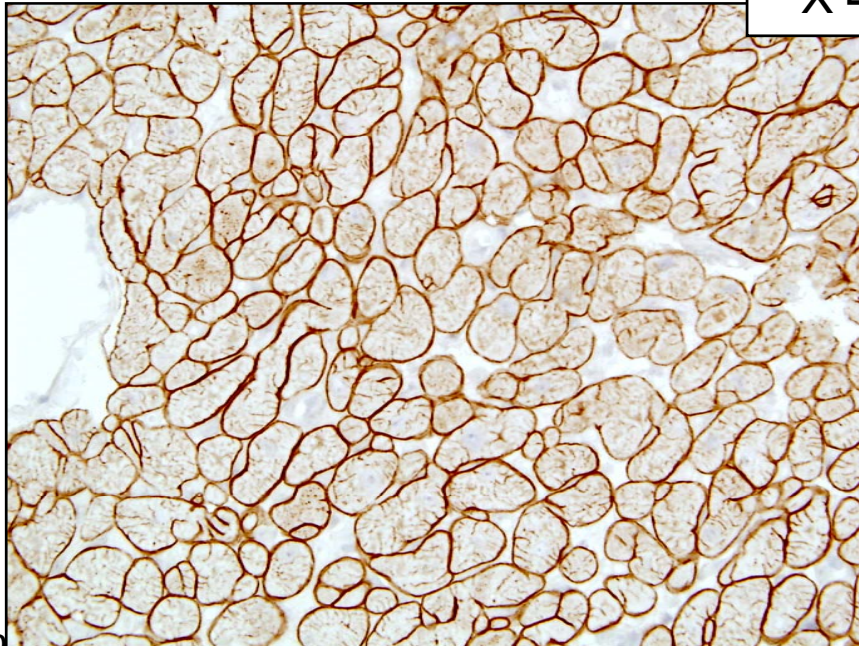


# Dystrophin

# Enteroviral VP1

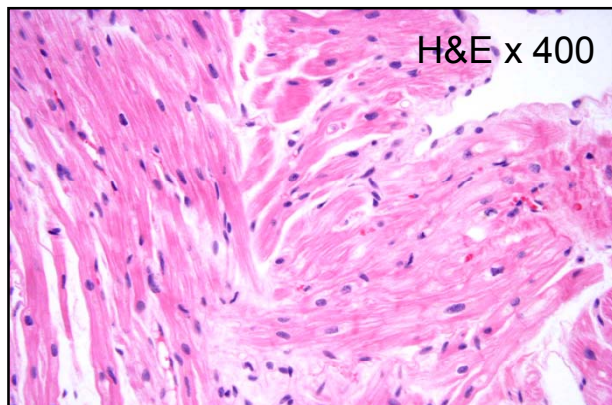


X 400

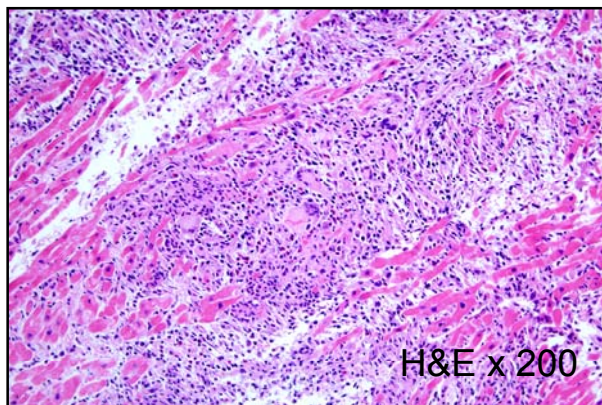


# Pathologic findings

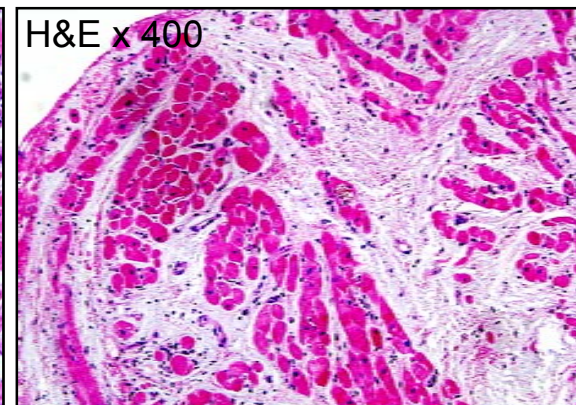
- Inflammation and fibrosis depends on the timing of biopsy



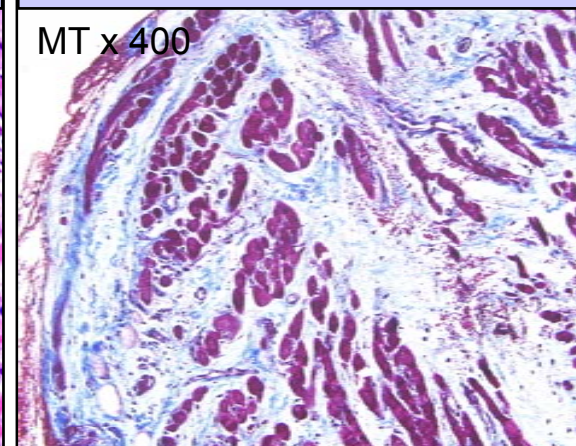
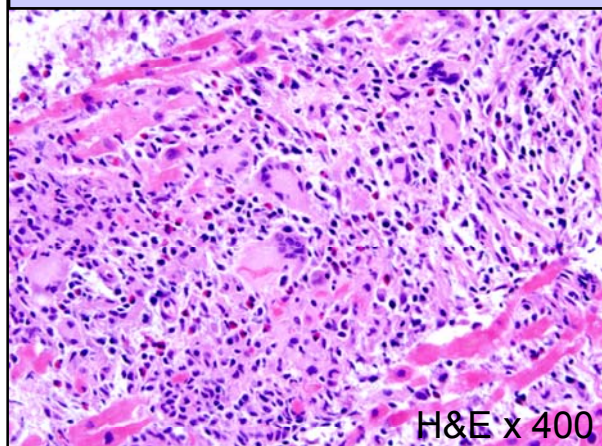
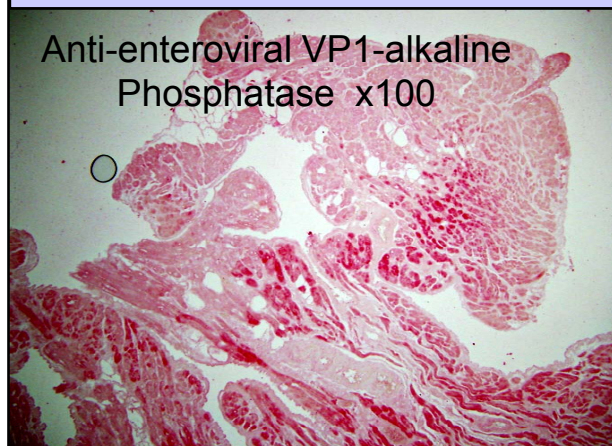
At day 1 in patients 1



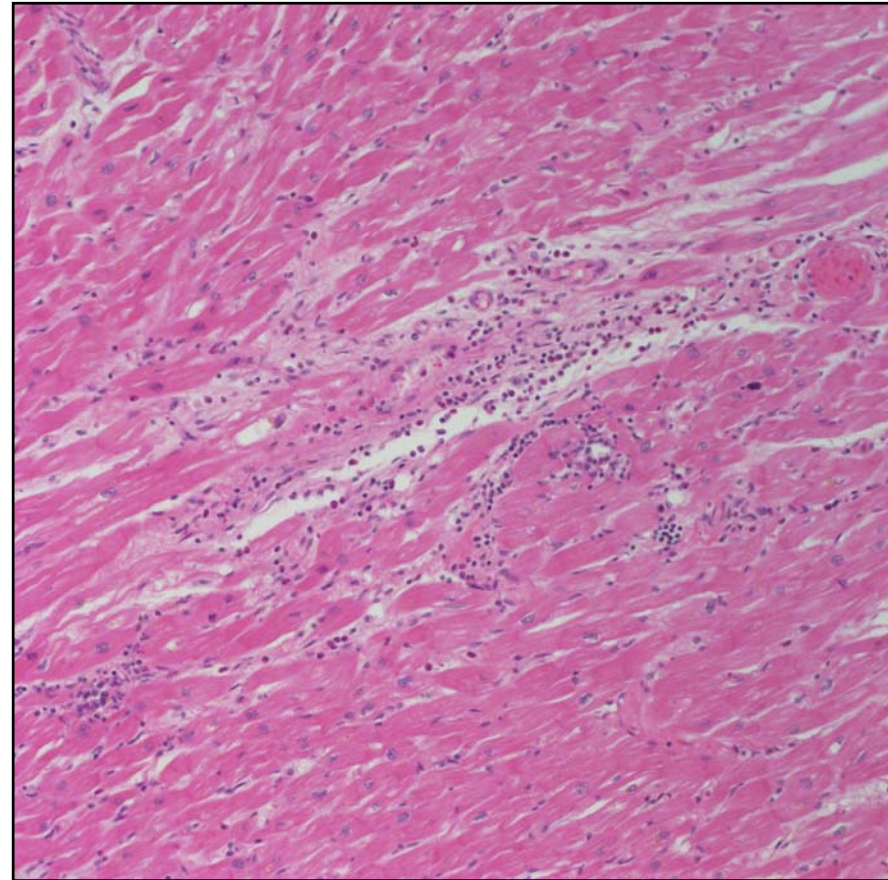
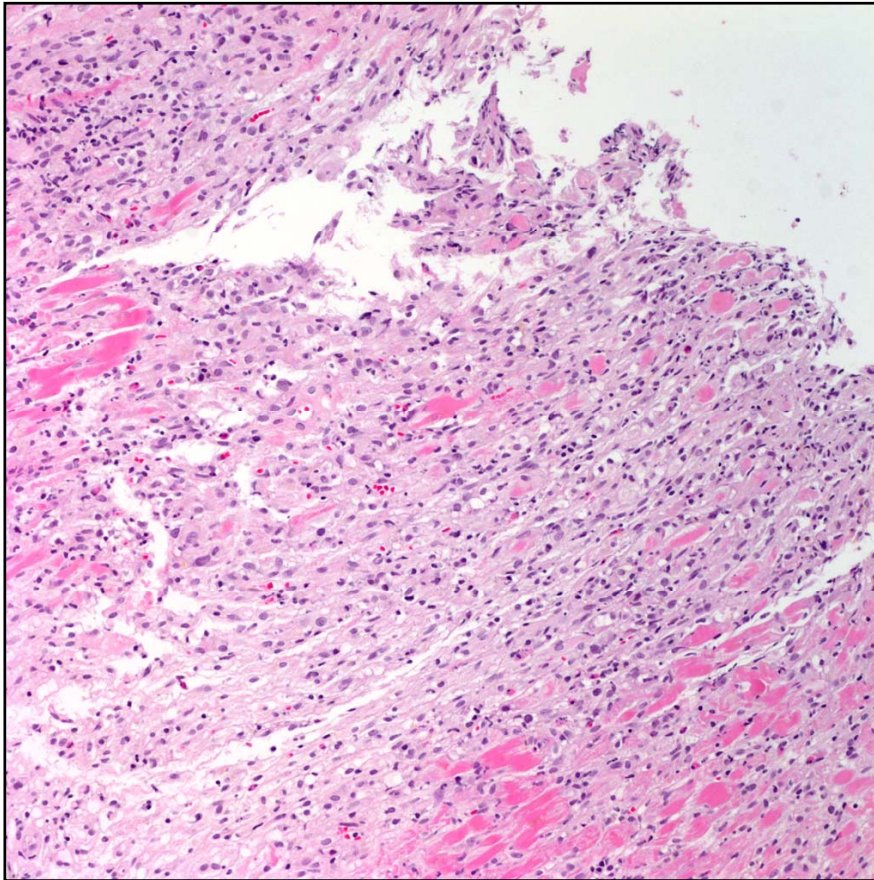
At day 5 in patients 6



At day 25 in patients 2



## Endomyocardial biopsy: Day 7 vs Day 24

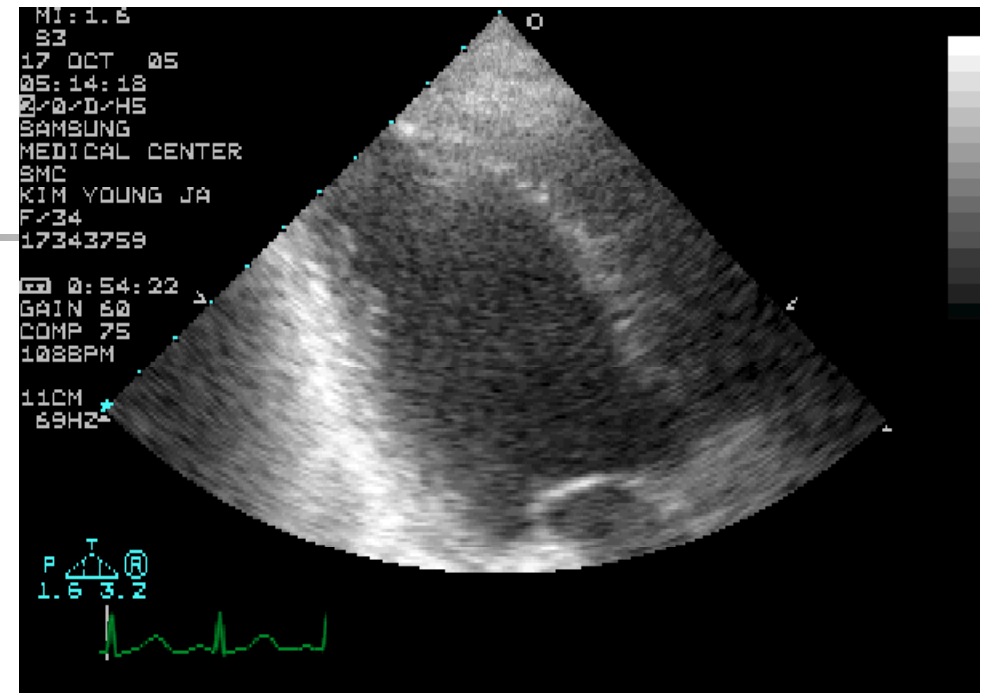


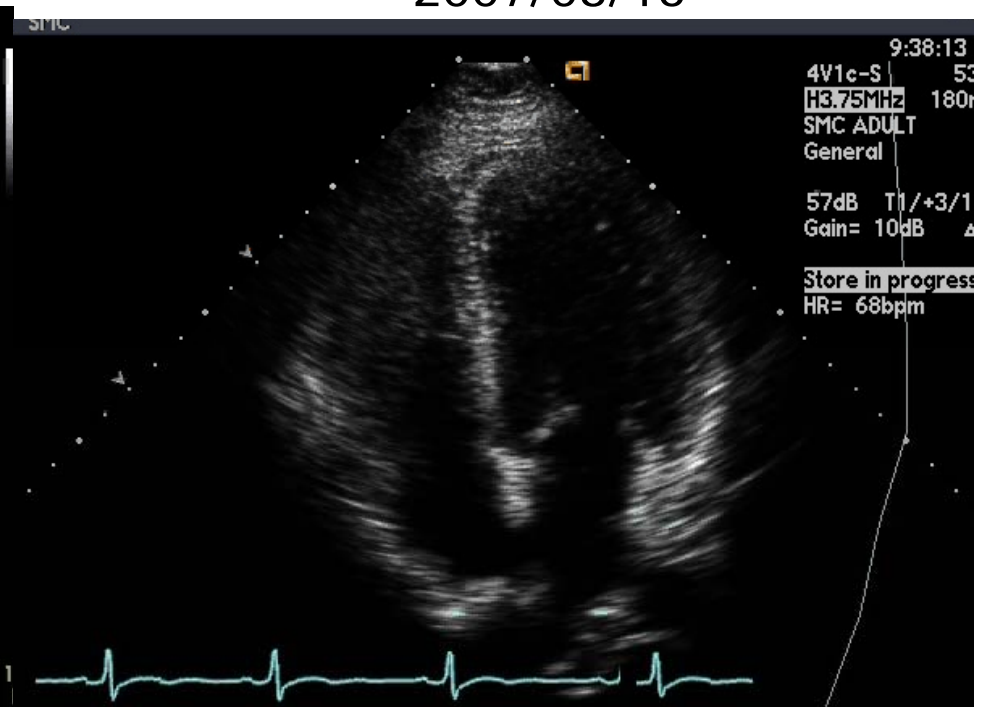
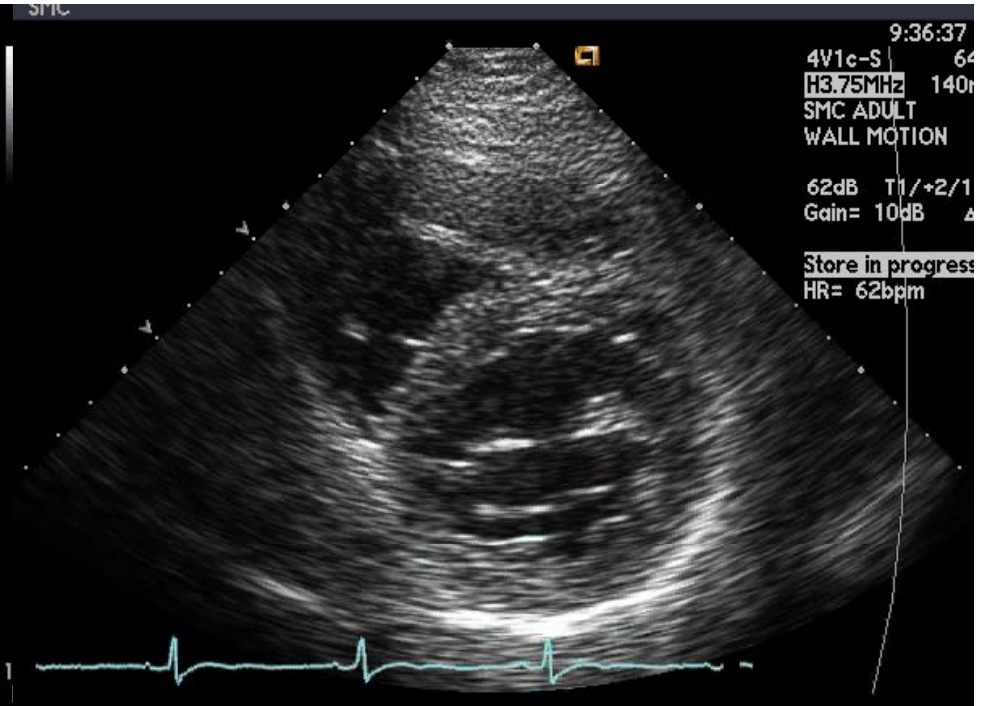
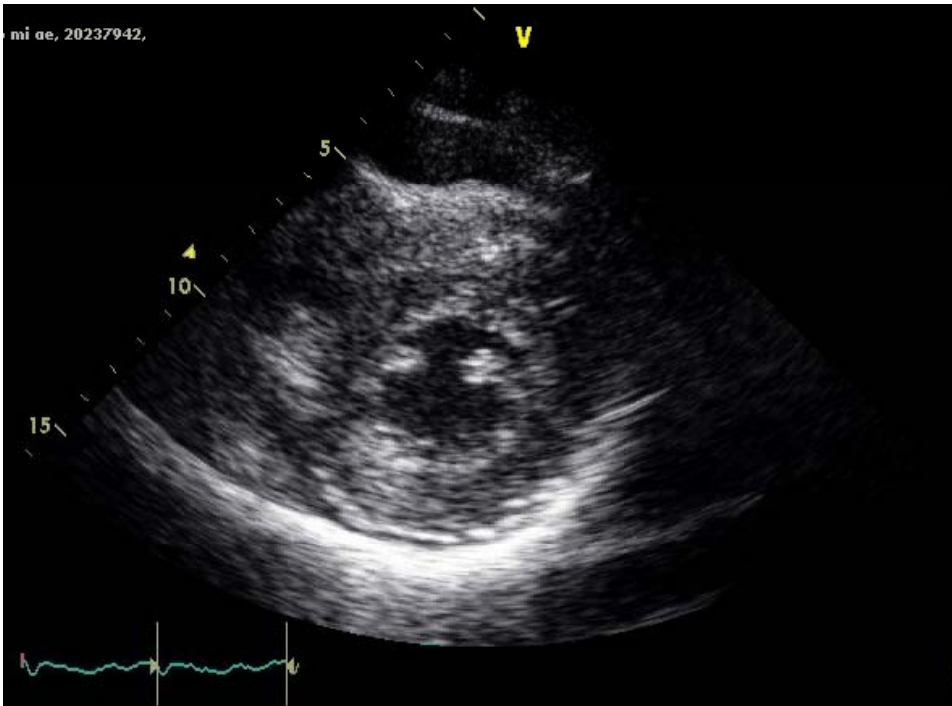
X 200

# Diagnosis

## 4. Myocardial imaging

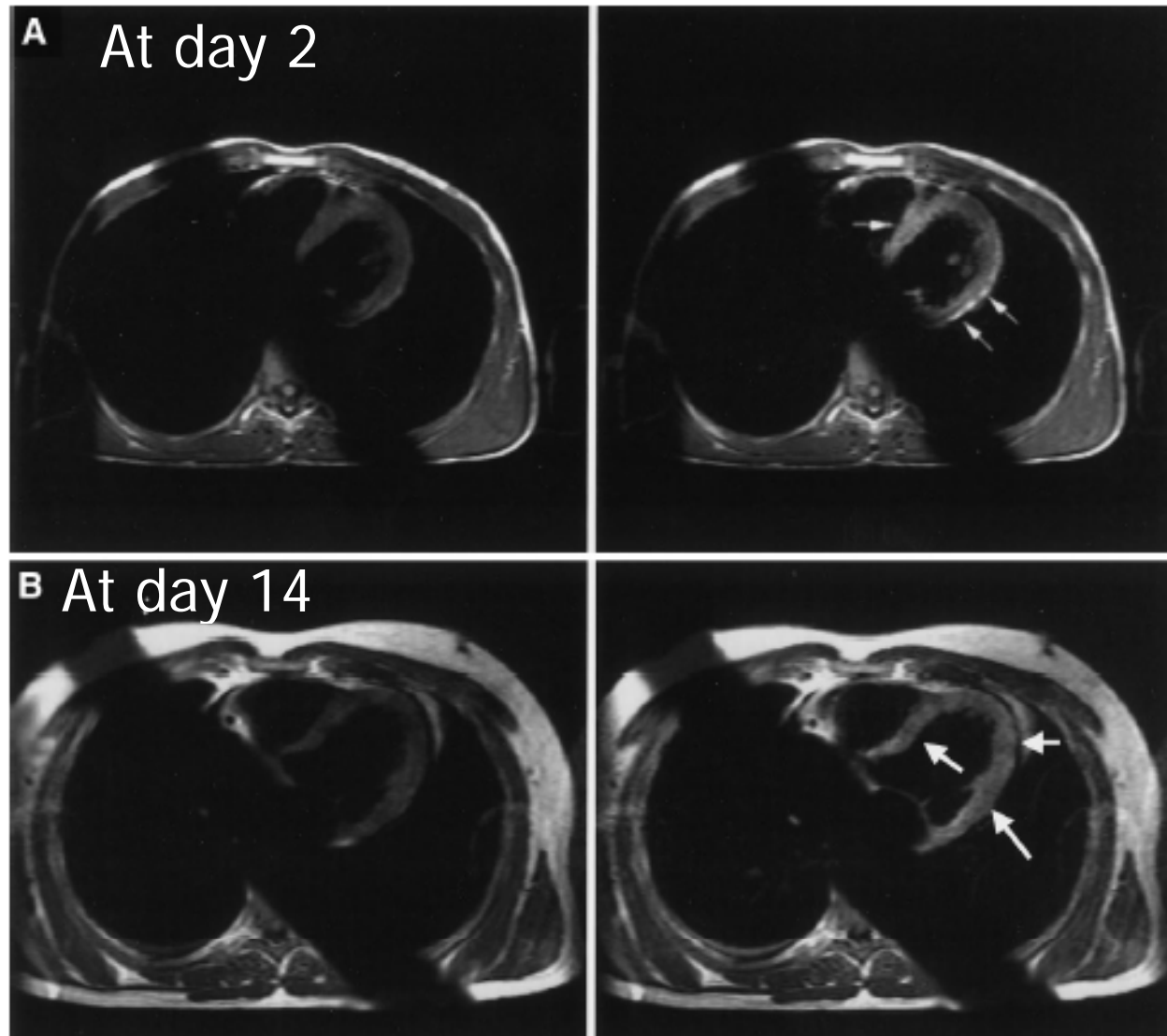
- Echocardiography
- RI imaging
  - Gallium scan for inflammation
  - In111 labeled anti-myosin RI scan for necrosis
- Contrast enhanced MRI





# Diagnostic evaluation

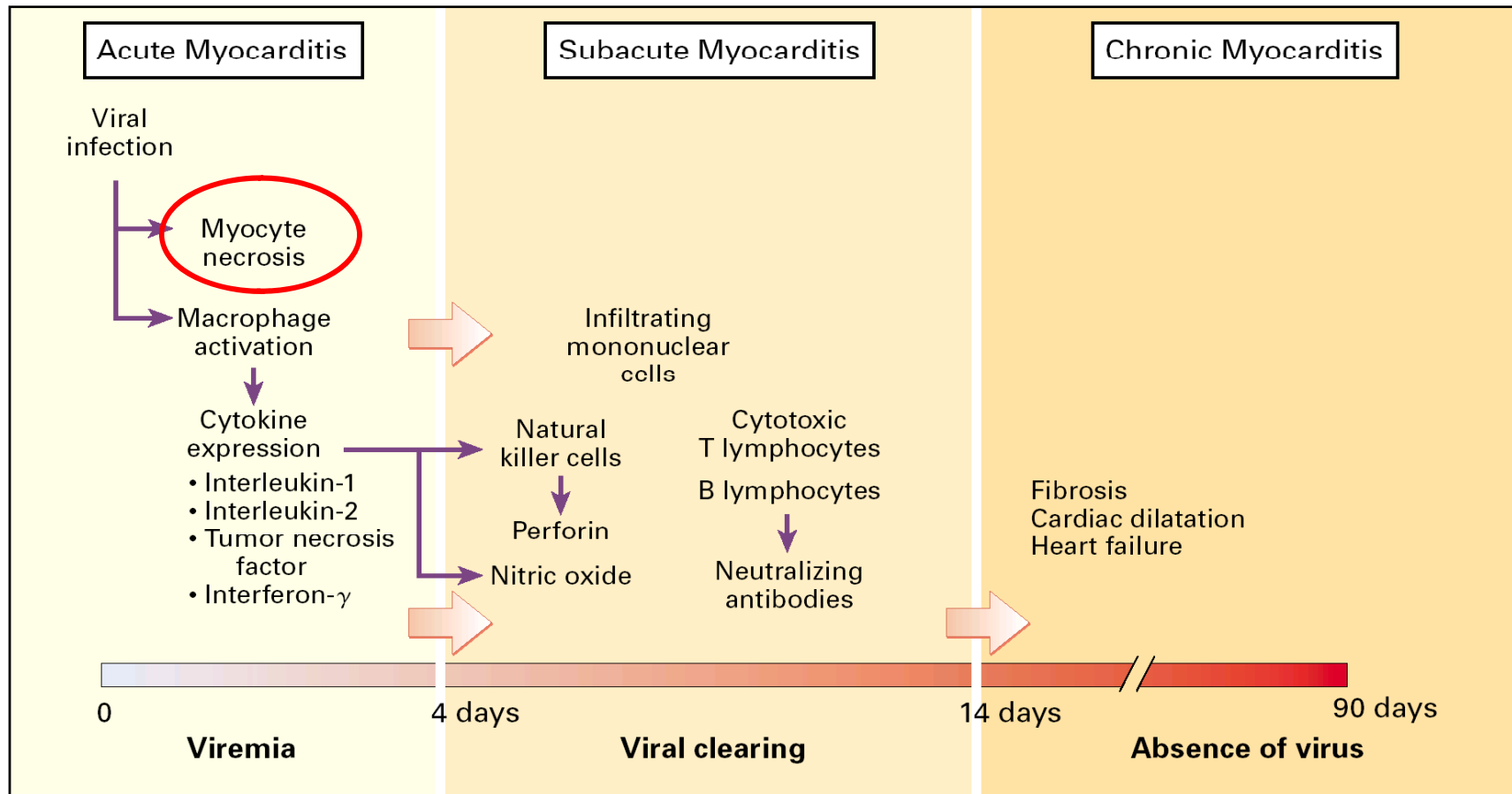
Contrast  
enhanced  
MRI



# Host Responses after Viral Infection

- Viremia (Acute phase)
  - within 3 hour to day 3
  - maximum virus titer in Heart : day 3-4 to day 7-10
- Inflammation (Subacute phase)
  - from day 3, peak day 5-10
  - mononuclear cell infiltration : macrophage, NK cell
  - cytotoxic T lymphocytes : 7-14 days
- Serum Ab titer
  - IgM from day 2, peak day 4
  - IgG from day 6, peak day 15

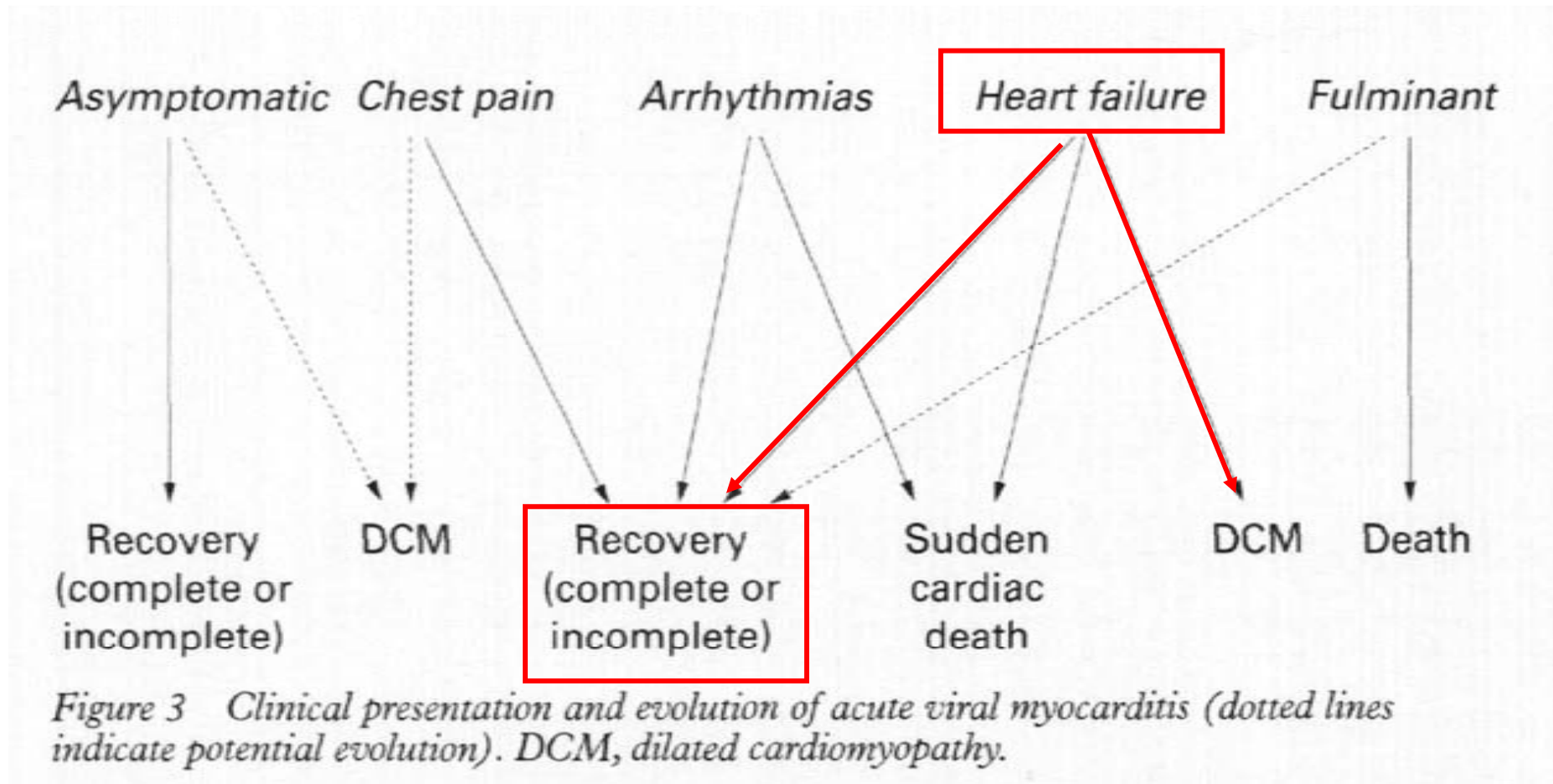
# Time Course of Viral Myocarditis



**Figure 2.** Time Course of Experimental Viral Myocarditis in Mice.

Adapted from Kawai<sup>11</sup> with the permission of the publisher. The timeline is not drawn to scale.

# Clinical Presentation & Evolution



# Types and causes of AHF

Acute de novo HF

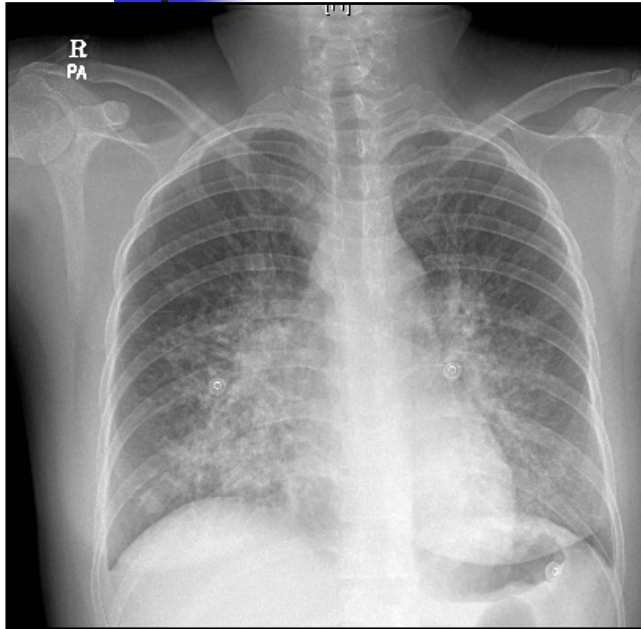
- Myocardial infarction
- Arrhythmia
- Valve destruction
- Myocarditis
- Hypertension crisis
- Cardiac surgery

Decompensated chronic HF

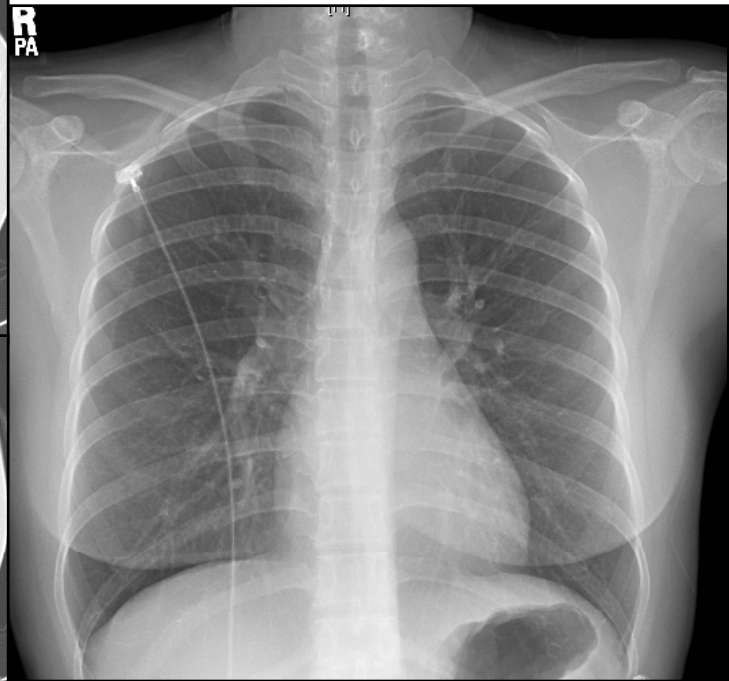
- Myocardial ischemia
- Arrhythmia
- Malcompliance
- Infections
- Salt overload
- Hypertension

Pulmonary edema  
Low CO HF  
(Congestion)  
Cardiogenic shock

# Chest PA

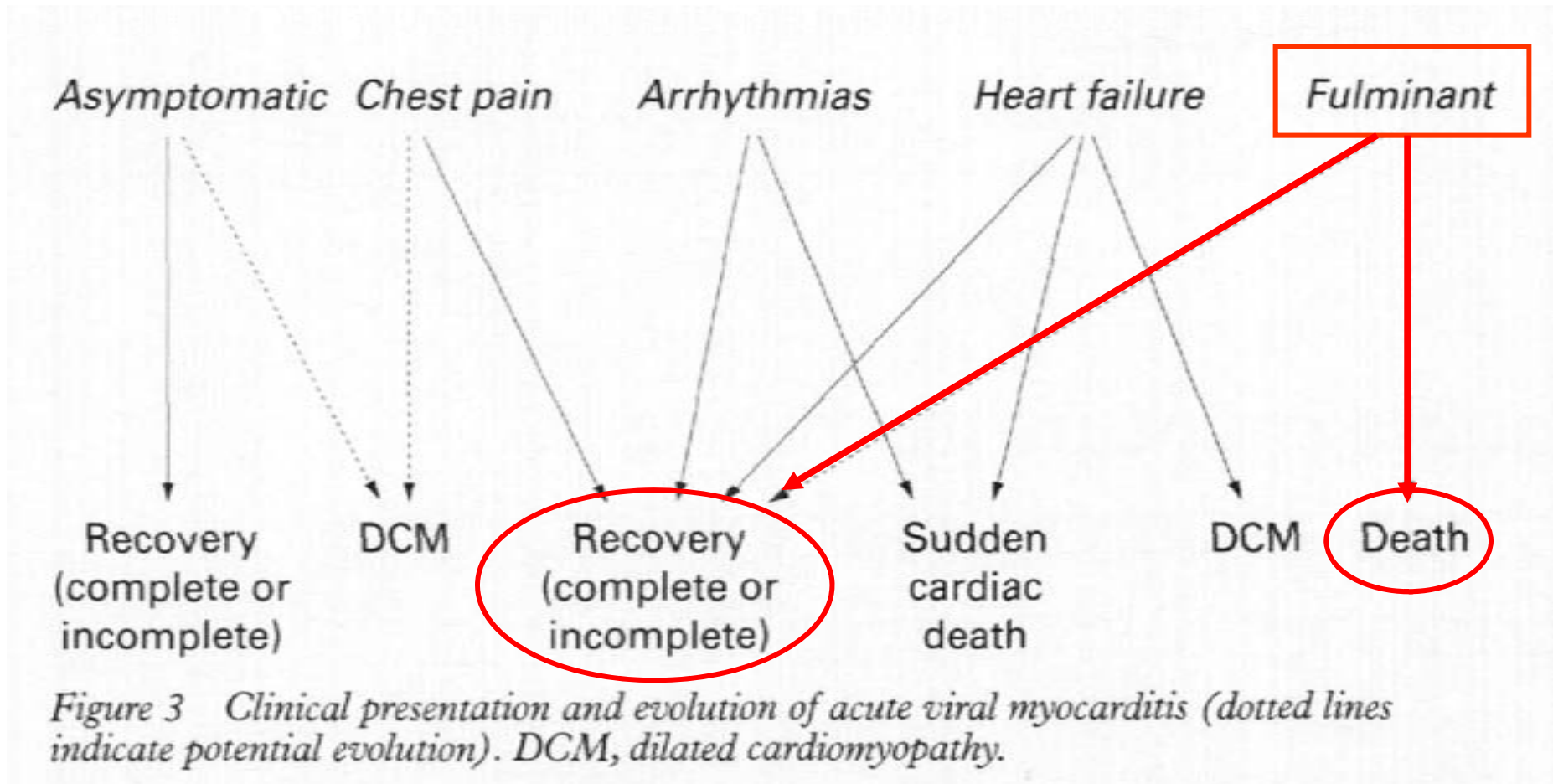


At day 1



At day 10

# Clinical Presentation & Evolution



# Definition of FM

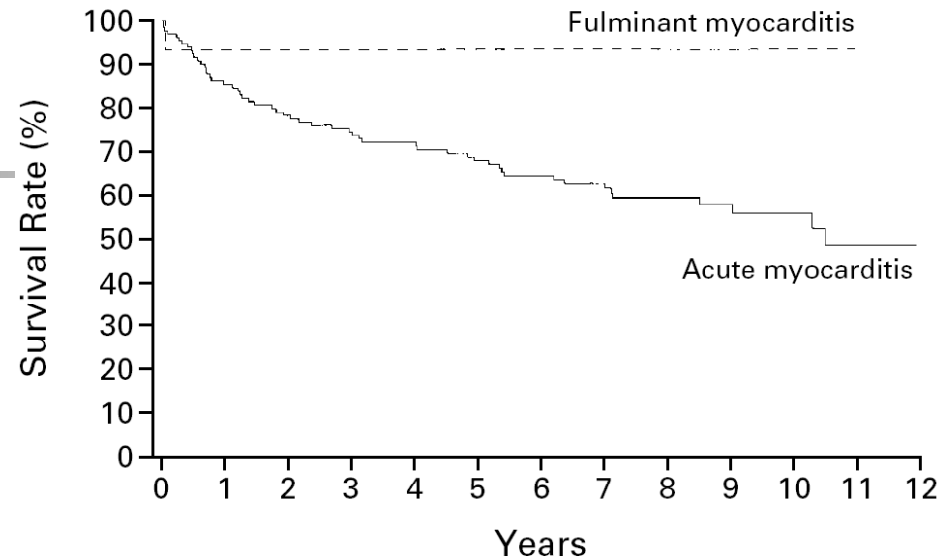
- Lieberman (JACC 1991;18:1617)

Patients with FM become acutely ill after a distinct viral prodrome, have severe cardiovascular compromise, multiple foci of **active myocarditis** by histologic study and ventricular dysfunction that **either resolves spontaneously or results in death.**

# Definition of FM

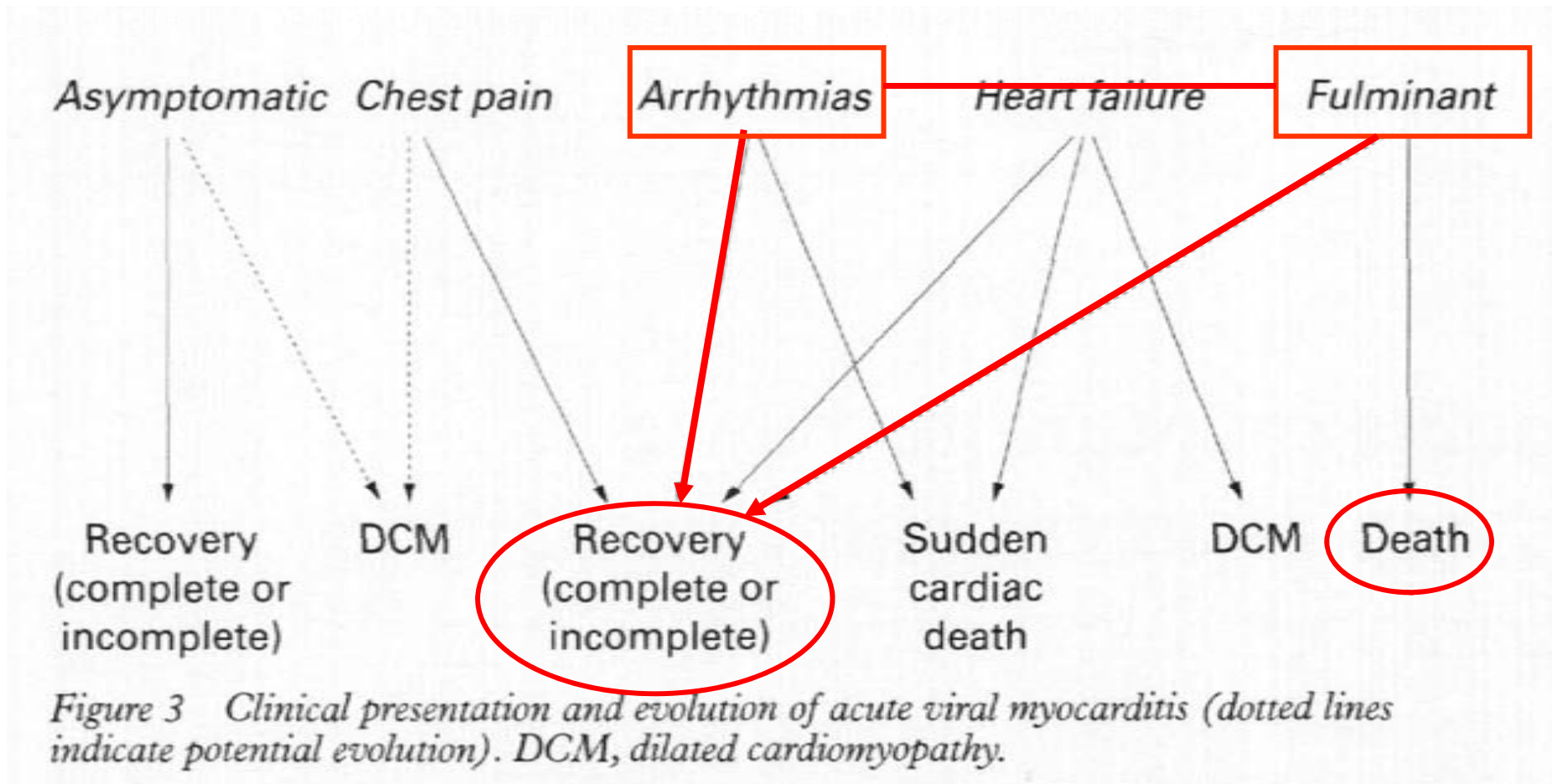
- McCarthy (NEJM 2000;342:690) : FM should have
  1. severe hemodynamic compromise requiring  
>5 mg of dopamine or dobutamine /kg/min) or LVAD
  2. histopathologically borderline or active myocarditis
  3. at least two of the following clinical features
    - 1) fever
    - 2) distinct onset of symptoms of heart failure (fatigue, dyspnea on exertion or at rest, or edema that could be dated specifically to a one-to-two-day period)
    - 3) history consistent with the presence of a viral illness within the two weeks before hospitalization

## FM has different clinical Manifestations



- **Better Survival Rate** ( Lieberman EB 1991, JACC )
  - Though more severely ill at presentation.
  - More likely to recover left ventricular function than acute myocarditis.
- **Excellent long-term prognosis** (McCarthy RE III et al. NEJM 2000)
  - Fulminant: non-fulminant = 93 % : 45 %
  - Aggressive hemodynamic support is warranted.

# Clinical Presentation & Evolution

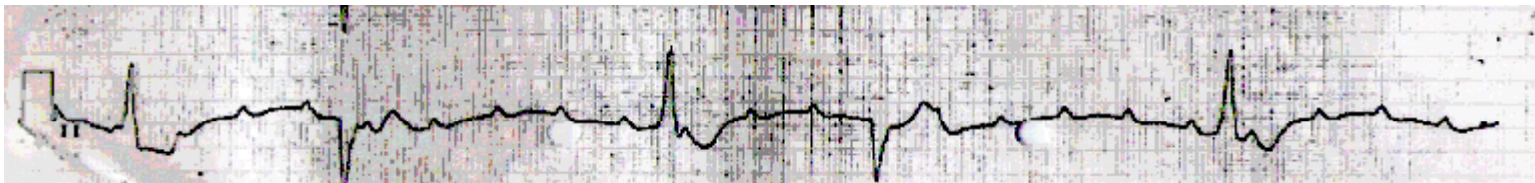


## Case Summary – initial presentation

- A 14-year-old boy was admitted with anterior chest pain for a day.
- Three days earlier, he had had flu-like symptoms.
- The patient had a positive troponin I ( 49.97 ng/ml) result and an elevated level of CK-MB (98.27 ng/ml)
- A coronary angiogram showed no thrombus and no clinically significant stenosis.

## Case Summary – Hospital course

- His ejection fraction at ER was over 50%
- Eight hours after admission, complete AV block was developed and IV isoproterenol was started for heart rate control.
- After then, various ventricular arrhythmias were developed and treated with DC version.
- Shock and urine output decreased and treated with dopamine and dobutamine.
- He was transferred to SMC after temporary pacemaker insertion and with amiodarone infusion (day 0).



## Case Summary – Hospital course

- Ventilation support were started due to hypoxia.
- At day 1, shock and pulmonary edema progressed , and urine output was decreased and EF was < 20%.

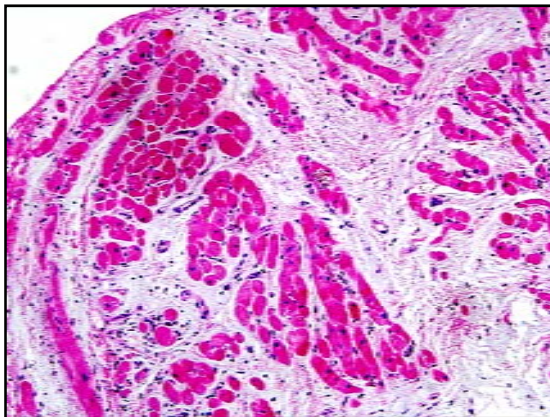
■ Mechanical circulatory support was started with EBS (Terumo, CAPIOX SP101, Tokyo, Japan). Urine output and BP were maintained with EBS and inotropics.

### CPS: Continuous flow

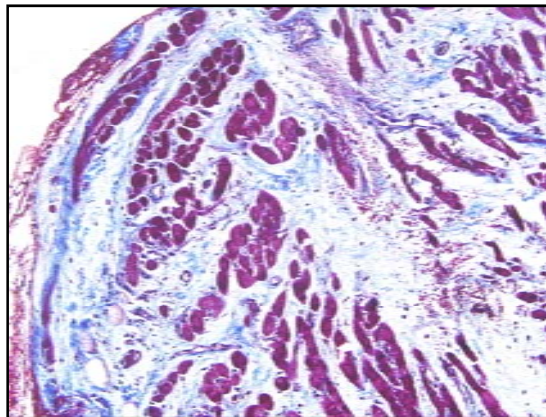


## Case Summary – Hospital course

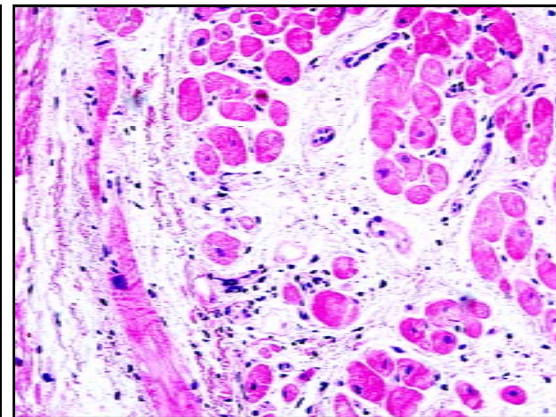
- After 56 hours of mechanical support with EBS, left-ventricular-wall motion was restored and her ejection fraction was 45 % on echocardiography.
- The EBS was removed and he was discharged at hospital day 17 without any symptoms of heart failure.



H&E x 200



MT x 200



H&E x 400

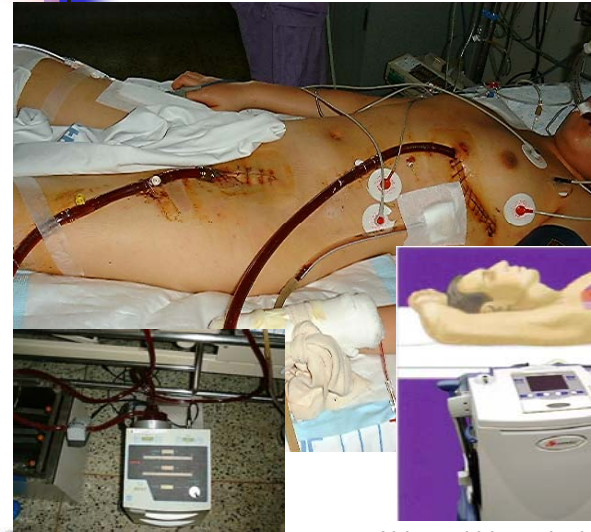
# Indications for Device support

1. Cardiogenic Shock
2. Heart failure dependent on intravenous inotropic support
3. Outpatients with symptomatic heart failure functional class IV
4. Uncontrolled ventricular arrhythmia
5. Cardiac allograft dysfunction and/or cardiac allograft vasculopathy
6. Fulminant myocarditis

## Circulatory Assist Device

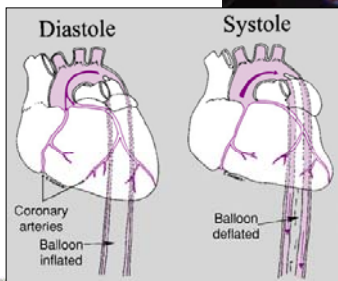
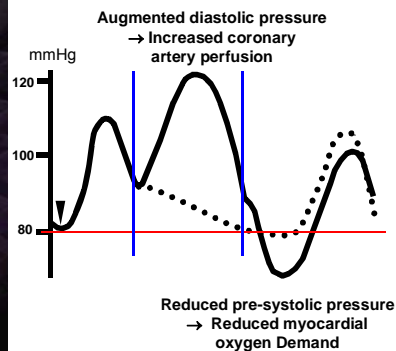
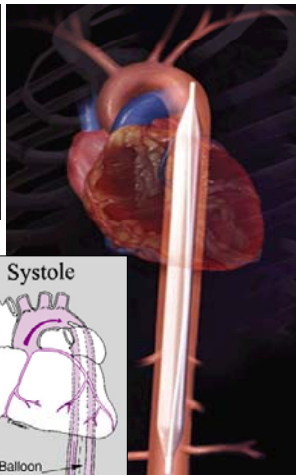
- Counterpulsation device (IABP)
- Ventricular assist device (VAD)
- Cardiopulmonary assist device (CPS)

## Ventricular Assistant Device



Abiomed biventricular system (BVS) 5000i.

## Intra-aortic balloon pump



## CPS: Continuous flow

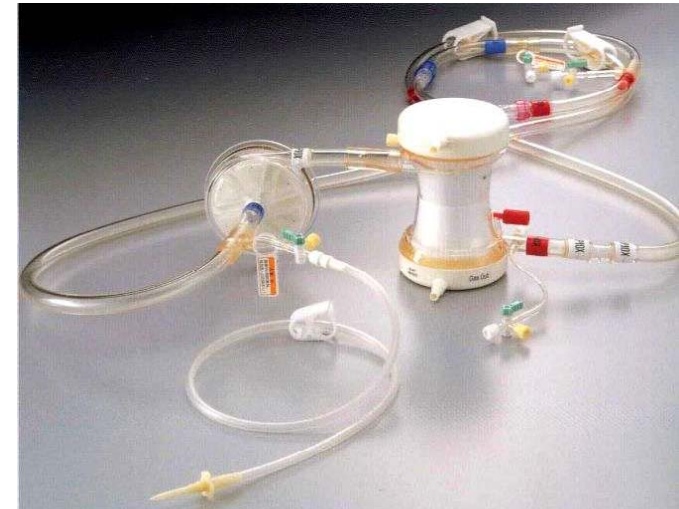
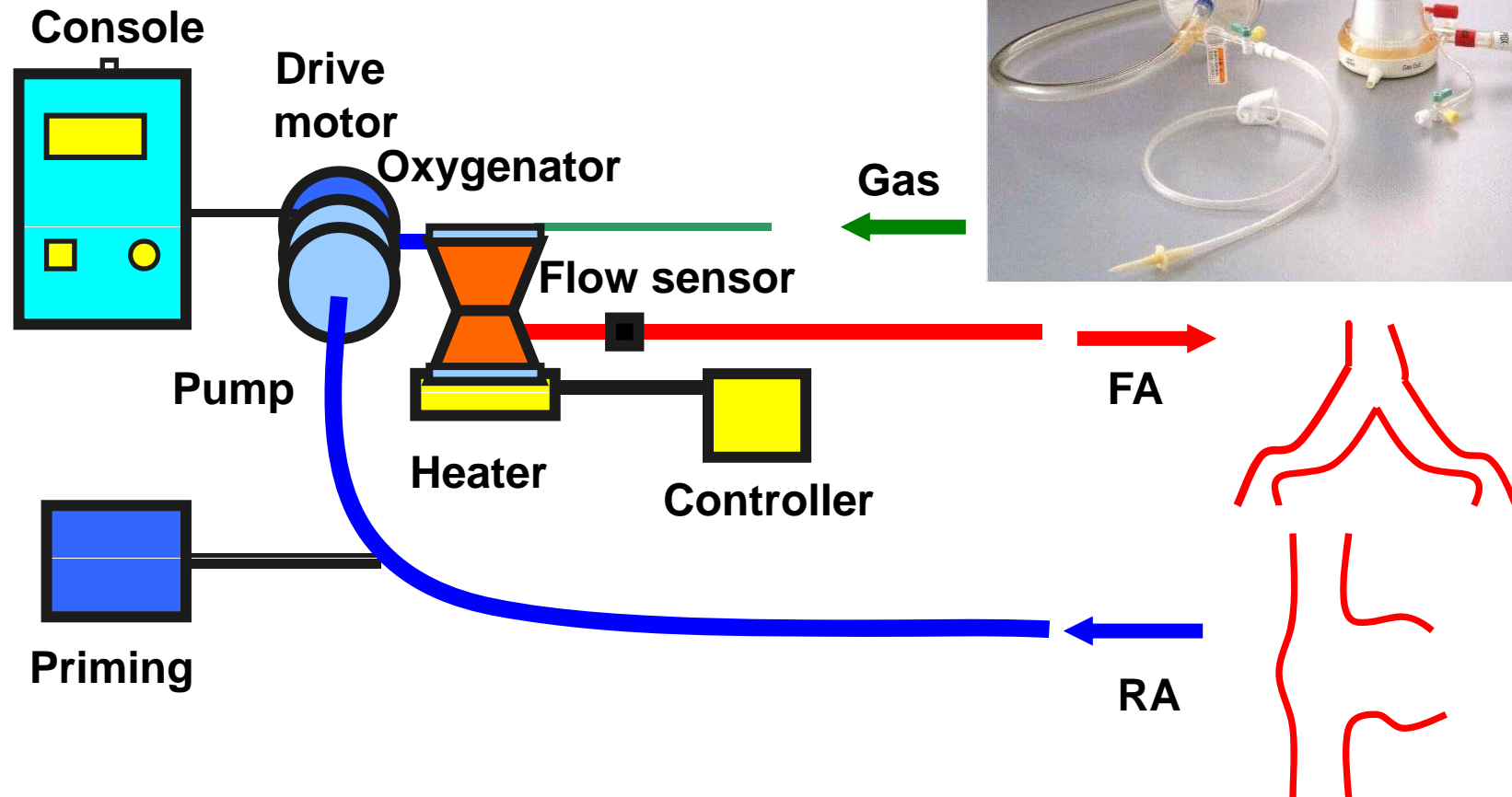


# Contraindications of PCPS

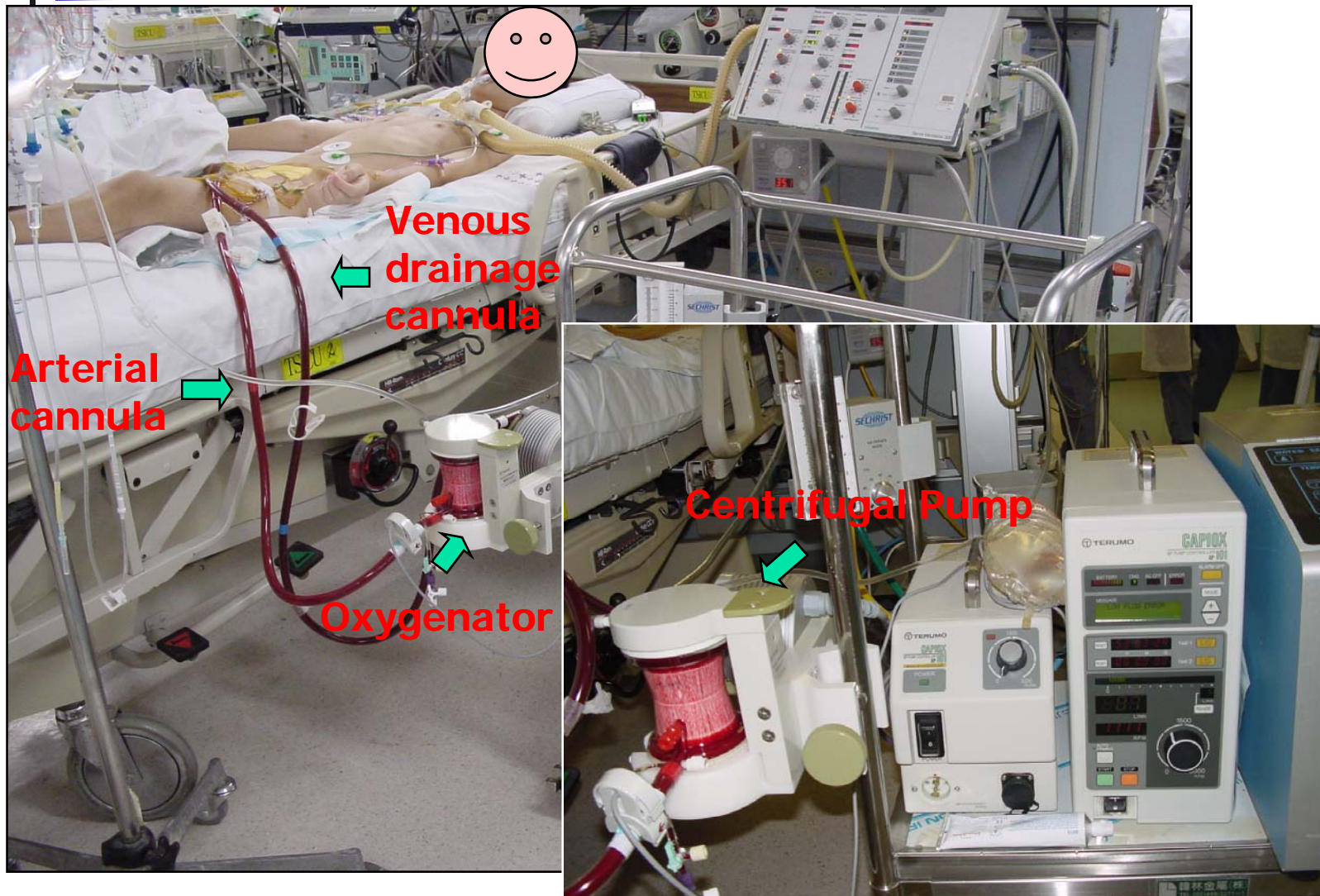
1. Significant AR
2. Severe peripheral artery disease
3. Bleeding diathesis
4. Recent CVA or head trauma
5. Irreversible or end-stage underlying illness

# Emergency Bypass System ( EBS<sup>®</sup>, Terumo, Japan )

- Quick / Compact / Simple / Safe



# EBS continuous flow



# Benefits of mechanical support

1. Decrease cardiac strain and work load
2. Increase subendocardial blood flow
3. Normalize histologic changes
  - fiber orientation
  - Cardiac hypertrophy
  - Decrease myocyte wavy fibers and contraction-band necrosis
4. Decrease chamber size
5. Increase mitochondria energy metabolism
6. Inactivation of neurohumoral factors (RAAS, Sympathetic nervous system)



# Therapeutic Guideline of Fulminant Myocarditis

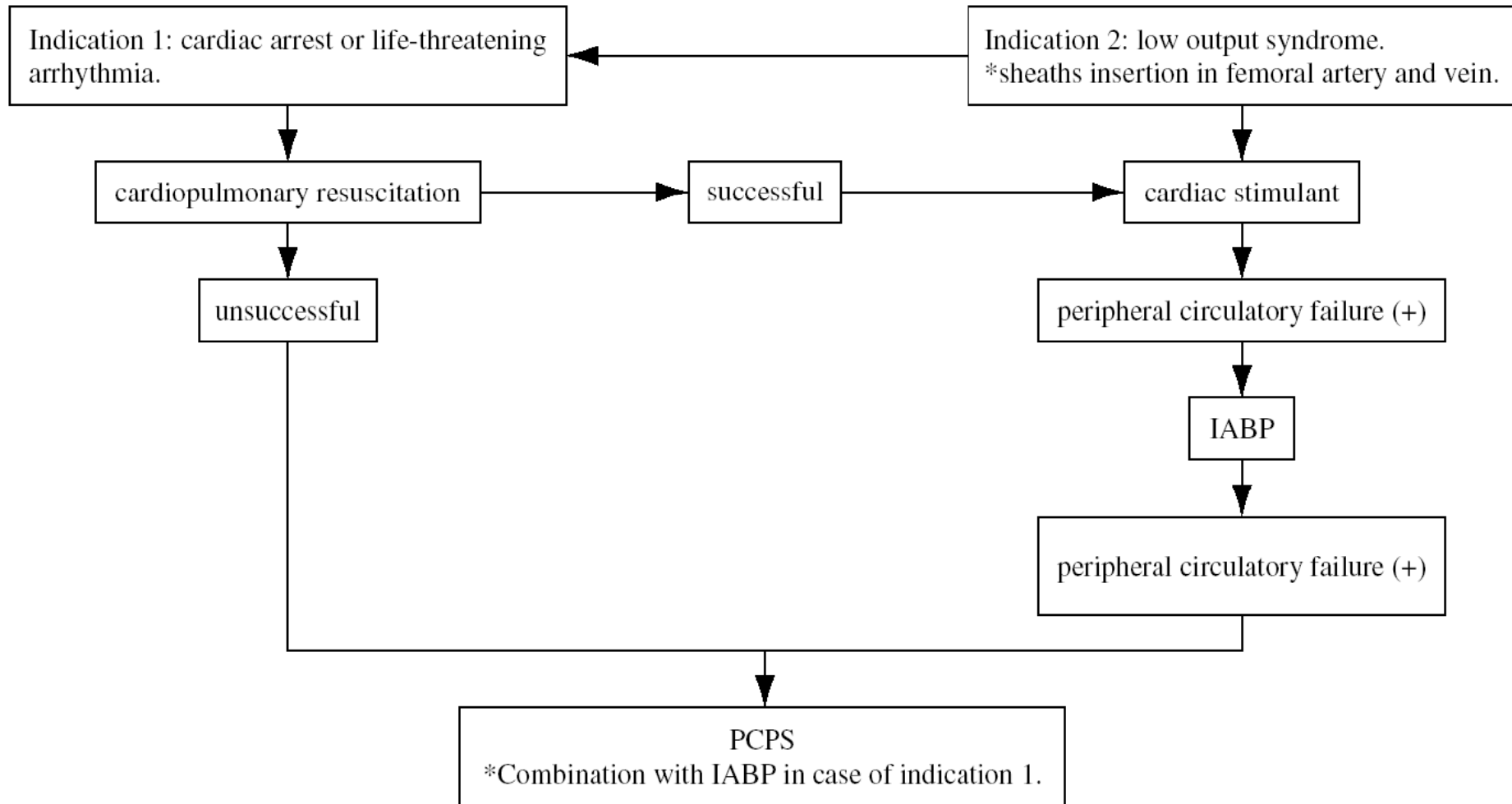
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## **National Survey of Fulminant Myocarditis in Japan — Therapeutic Guidelines and Long-Term Prognosis of Using Percutaneous Cardiopulmonary Support for Fulminant Myocarditis (Special Report From a Scientific Committee) —**

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Naoyoshi Aoyama, MD; Tohru Izumi, MD; Katsuhiko Hiramori, MD;  
Mitsuaki Isobe, MD; Masatoshi Kawana, MD; Michiaki Hiroe, MD;  
Hitoshi Hishida, MD; Yasushi Kitaura, MD; Tsutomu Imaizumi, MD;  
and Japanese Investigators of Fulminant Myocarditis

# Guidelines of PCPS for acute fulminate myocarditis (1)



# Guidelines of PCPS for acute fulminate myocarditis (2)

- (1) adjustment of initial flow rate: 3.0–3.5 L/min.
- (2) adjustment of flow rate: the lowest flow rate without peripheral circulatory failure by referring to the indicators of circulatory failure.
- (3) reconstruction of leg circulation: bypassing the dorsalis pedis or posterior tibial artery and arterial inflow catheter.
- (4) activated clotting time (ACT): adjustment to 200–300 s (heparin binding PCPS: 150–200 s).

## Markers of management

### Indicators of circulatory failure

- (1) pH, BE
- (2) SVO<sub>2</sub>
- (3) LA
- (4) TB (or AKBR)
- (5) Blood biochemistry
- (6) Urinary amount

### Indicators of cardiac function

- (1) Wall motion
- (2) EF, %FS
- (3) Ejection time
- (4) ETCO<sub>2</sub>
- (5) CI

## Course of management

- (1) adjustment of flow rate: the lowest flow rate without peripheral circulatory failure by referring to the indicators of circulatory failure.
- (2) reduction of flow rate: trial reducing the flow rate according to improvement of the indicators of cardiac function.

# Guidelines of PCPS for acute fulminate myocarditis (3)

## Prevention of complications

- (1) MOF or advancement of peripheral circulatory failure: increase of flow rate, CHF, nafamostat, ulinastatin.
- (2) circulatory disturbances of the legs: previous sheath insertion, preventive bypassing, relaxation, incision and amputation.
- (3) bleeding: adjustment to ACT 150–200s by prescribing nafamostat mesilate, hemostasis, blood transfusion (maintain above Hb 10 g/dl and plt  $5.0 \times 10^4$   $\mu$ l).
- (4) hemolysis: haptoglobin, transfusion against failure of venous outflow catheter.
- (5) infection: antibiotics, detection and removal of the focus.
- (6) hyperkalaemia: detection and removal of the origin, CHF, GI therapy.
- (7) failure of venous outflow catheter: check tip-position, transfusion.



## The standard for stopping PCPS

The following conditions are satisfied at flow rate of 1.0L/min.

### Markers of circulatory failure

- (1) Arterial blood gas analysis: no metabolic acidosis
- (2)  $SVO_2 > 60\%$
- (3) LA: normal
- (4) TB (without hemolysis)  $< 3.0$  mg/dl (or AKBR: normal)
- (5) Blood biochemistry: recovery from organic failure

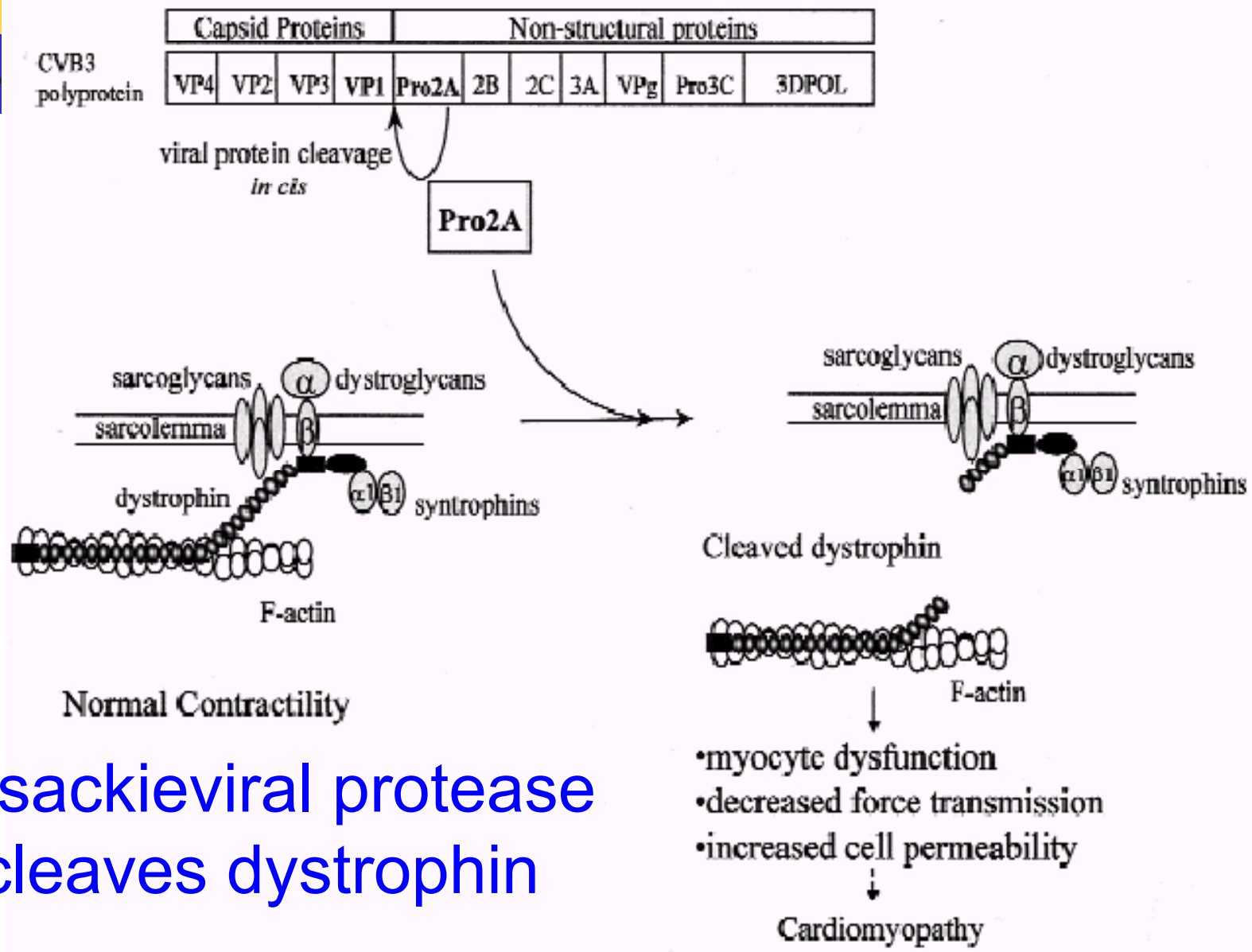
### Markers of cardiac function

- (1) Wall motion: improvement
- (2) EF, %FS: improvement
- (3) Ejection time  $> 200$  ms
- (4)  $ETCO_2 = PaCO_2$
- (5)  $CI > 2.0$  L  $\cdot$  min<sup>-1</sup>  $\cdot$  m<sup>-2</sup>

# Factors Influencing Prognosis

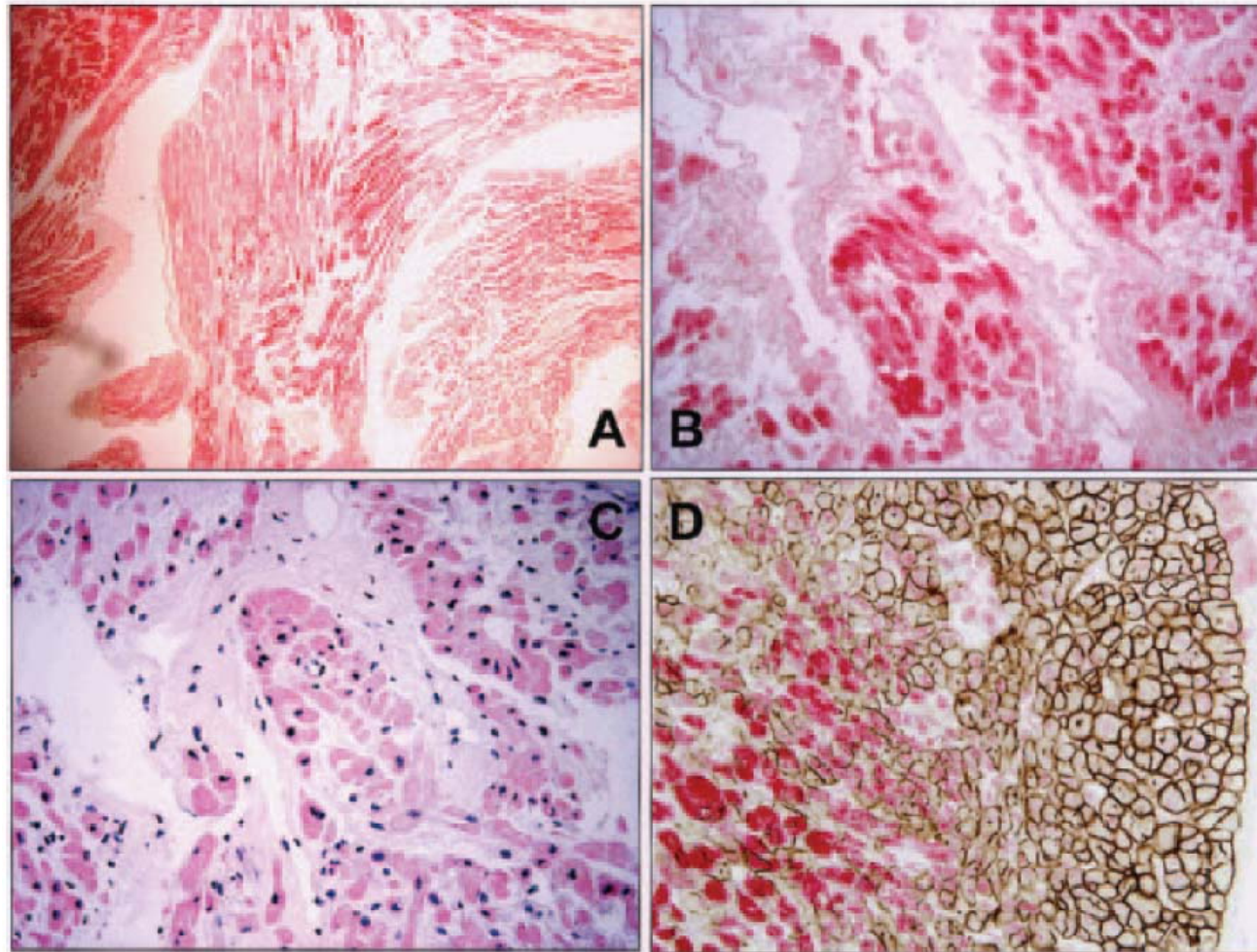
- Important factors concerning the prognosis were
  - 1) the severity and grade of cardiac and renal dysfunction
  - 2) the adjusted support flow rate to enable recovery from circulatory failure
  - 3) prevention of circulatory disturbances of the legs and multiple organ failure directly associated with PCPS.
- Long-term prognosis of patients treated with PCPS
  1. the readmission rate was 10%
  2. the exacerbation rate was 3.3%
  3. mortality was 10% during the average follow-up period of 962 days.

Optimal management of the mechanical cardiopulmonary support and curative treatment for the myocarditis further improve the outcome of this disease.



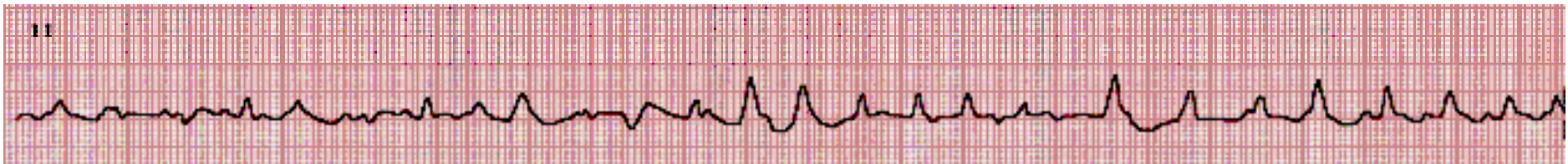
# Coxsackieviral protease 2A cleaves dystrophin

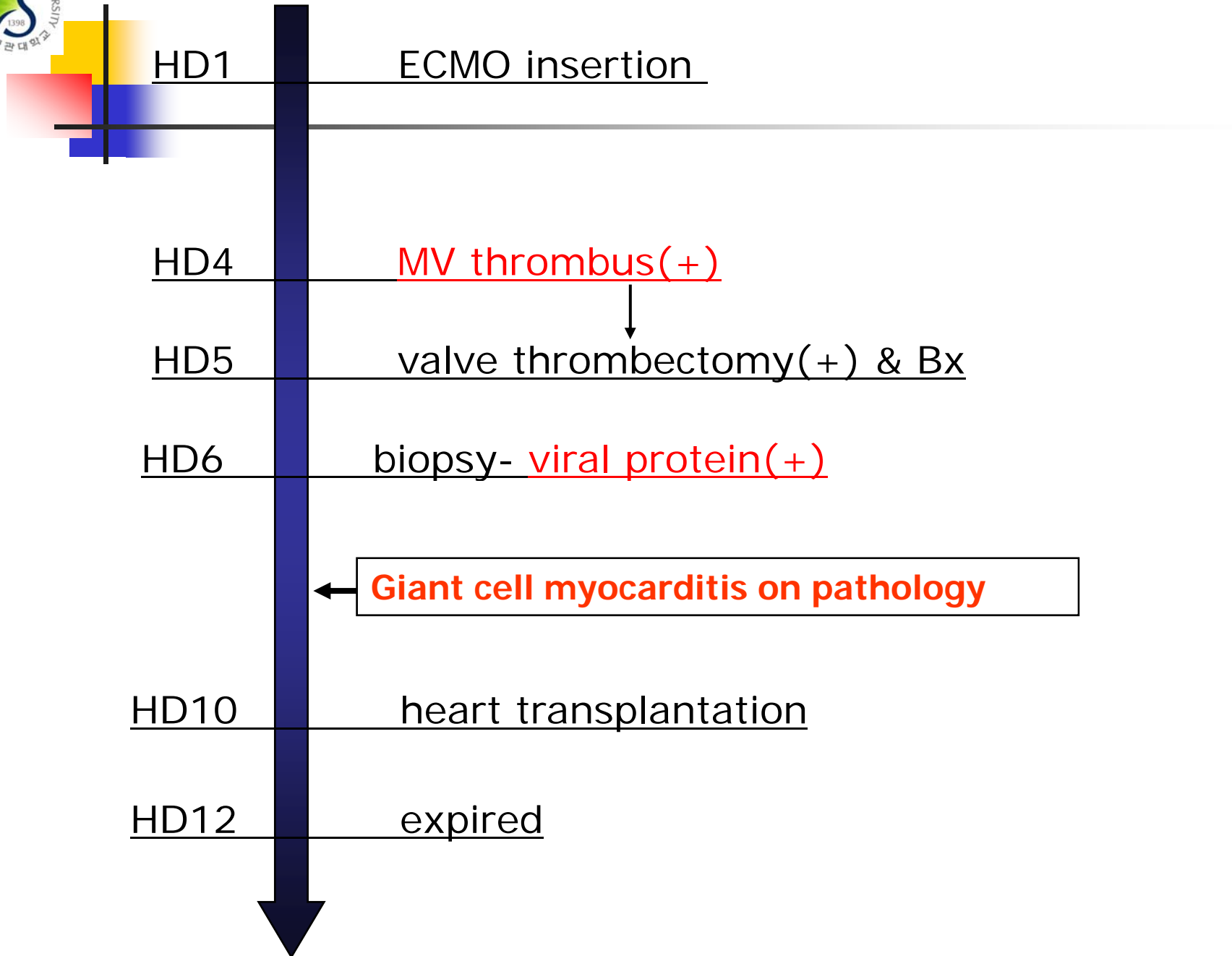
Serial histological and immunohistochemical analyses of left appendage showed the enteroviral VP1 capsid proteins over the entire heart (A, day 1, 100; B, day 6, 400), with scant lymphocytes observed at day 5. C, Hematoxylin and eosin stain, 400. Focal areas of myocardium displayed a loss of the sarcolemmal staining pattern for dystrophin using antidystrophin Ab (NCLDYSA) that colocalized with enteroviral capsid protein (D, merged image for serial sections, 200).



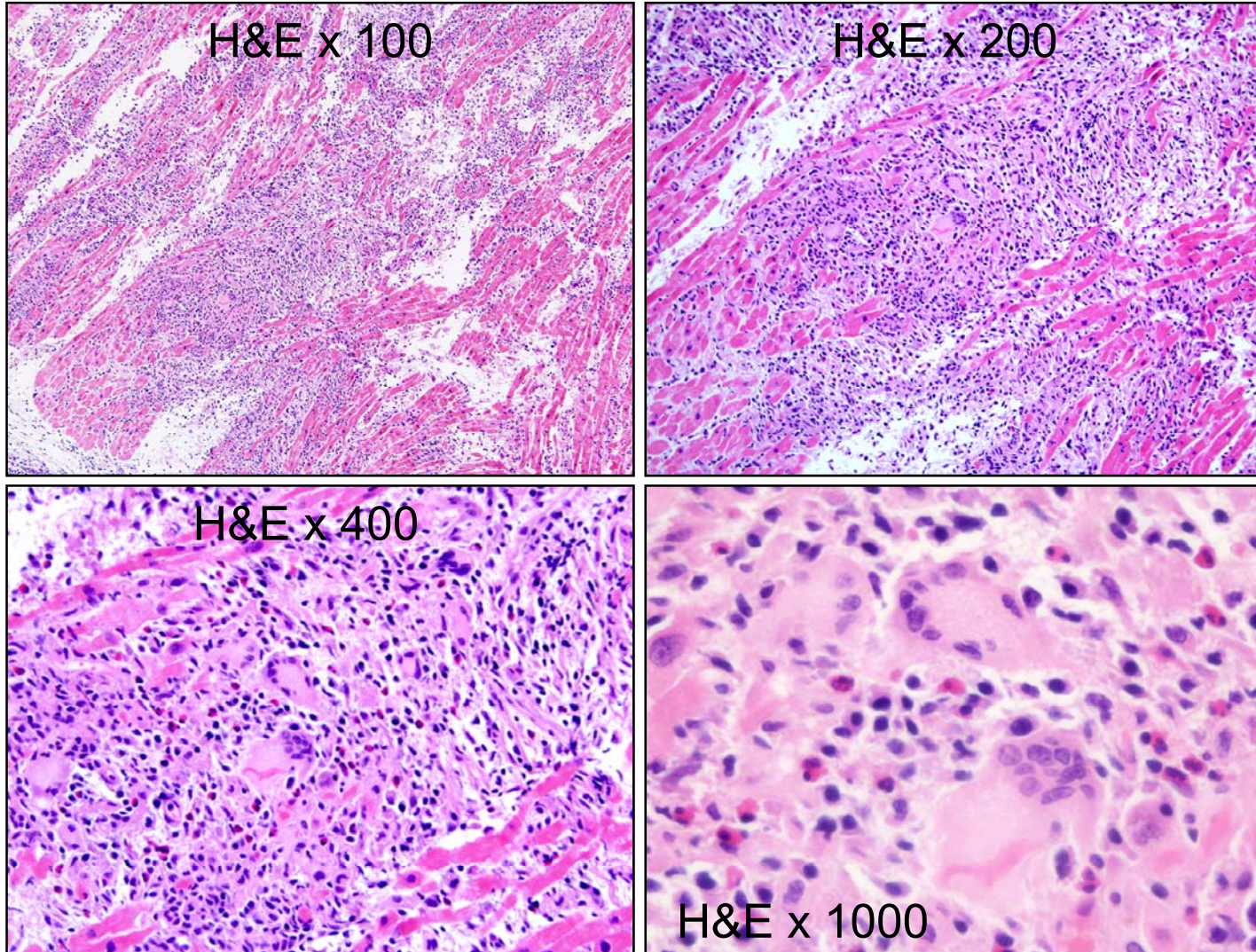
# Case Summary (F/39)

- CC) Syncope
- **2WA, fever for 5 days → 4 DA, chest discomfort, palpitation, dizziness (+) → syncope → ER**
- EKG: ant ST elevation / Cardiac enzyme ↑ / ant wall-hypokinesia  
→ r/o anterior STEMI로 CAG시행했으나 정상
- **CAG 시행 중에 VT(polymorphic) with shock 발생**
- Cardioversion & Mg replacement시행 Refractory VT → SMC ER transfer

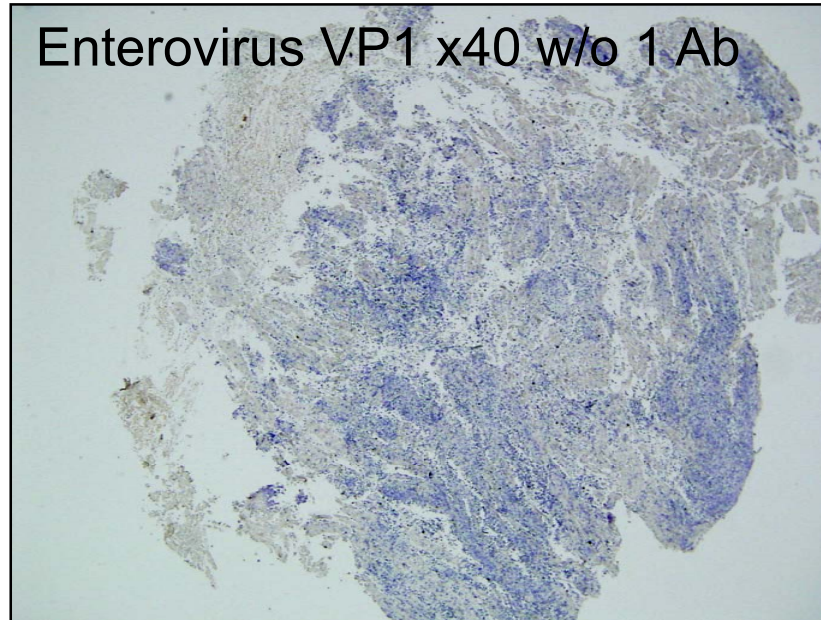
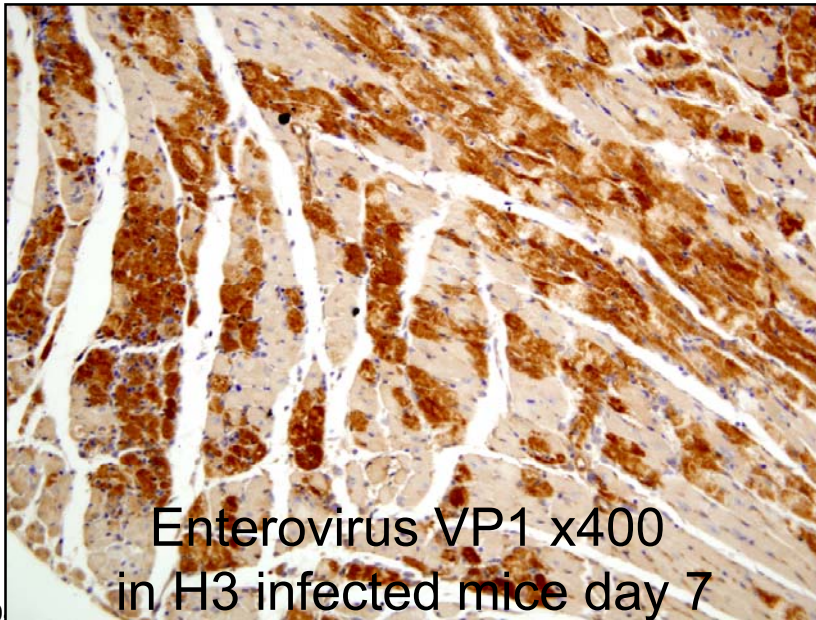
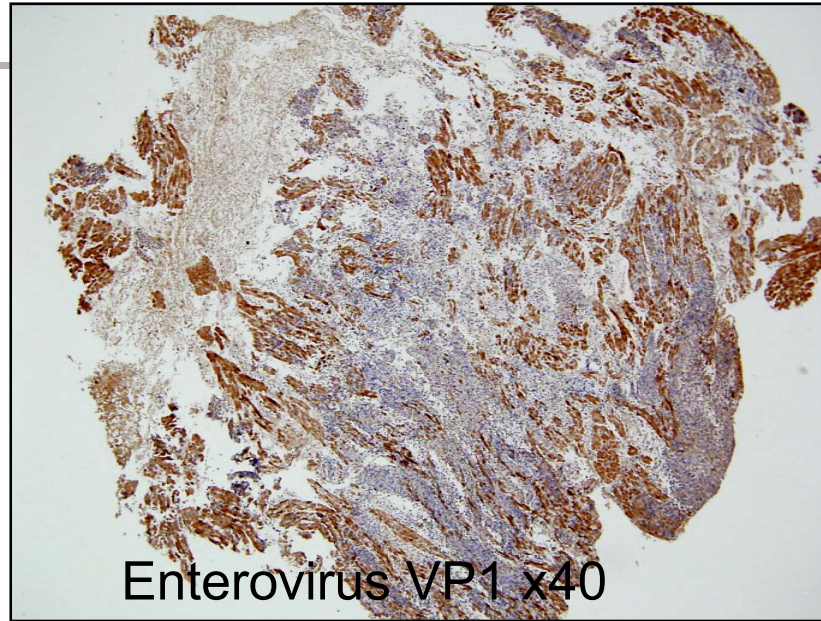
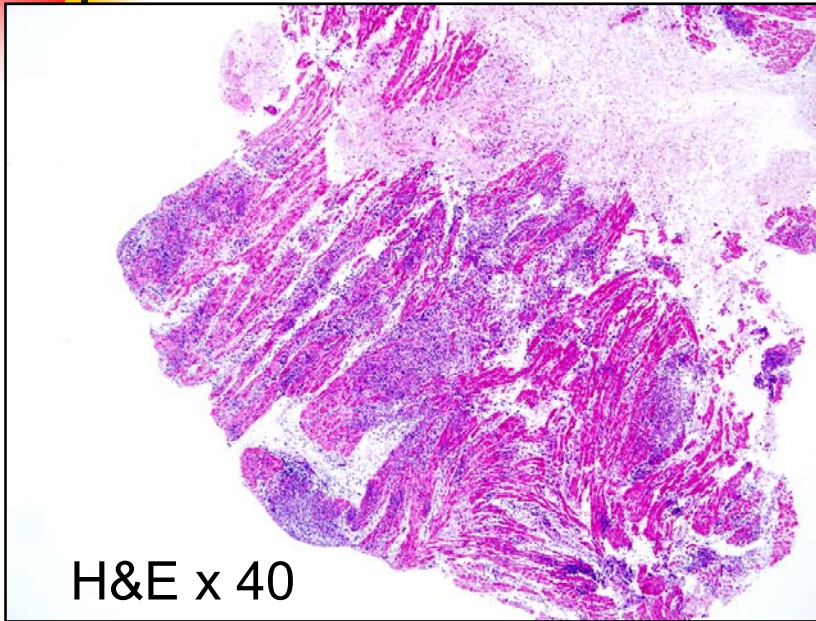




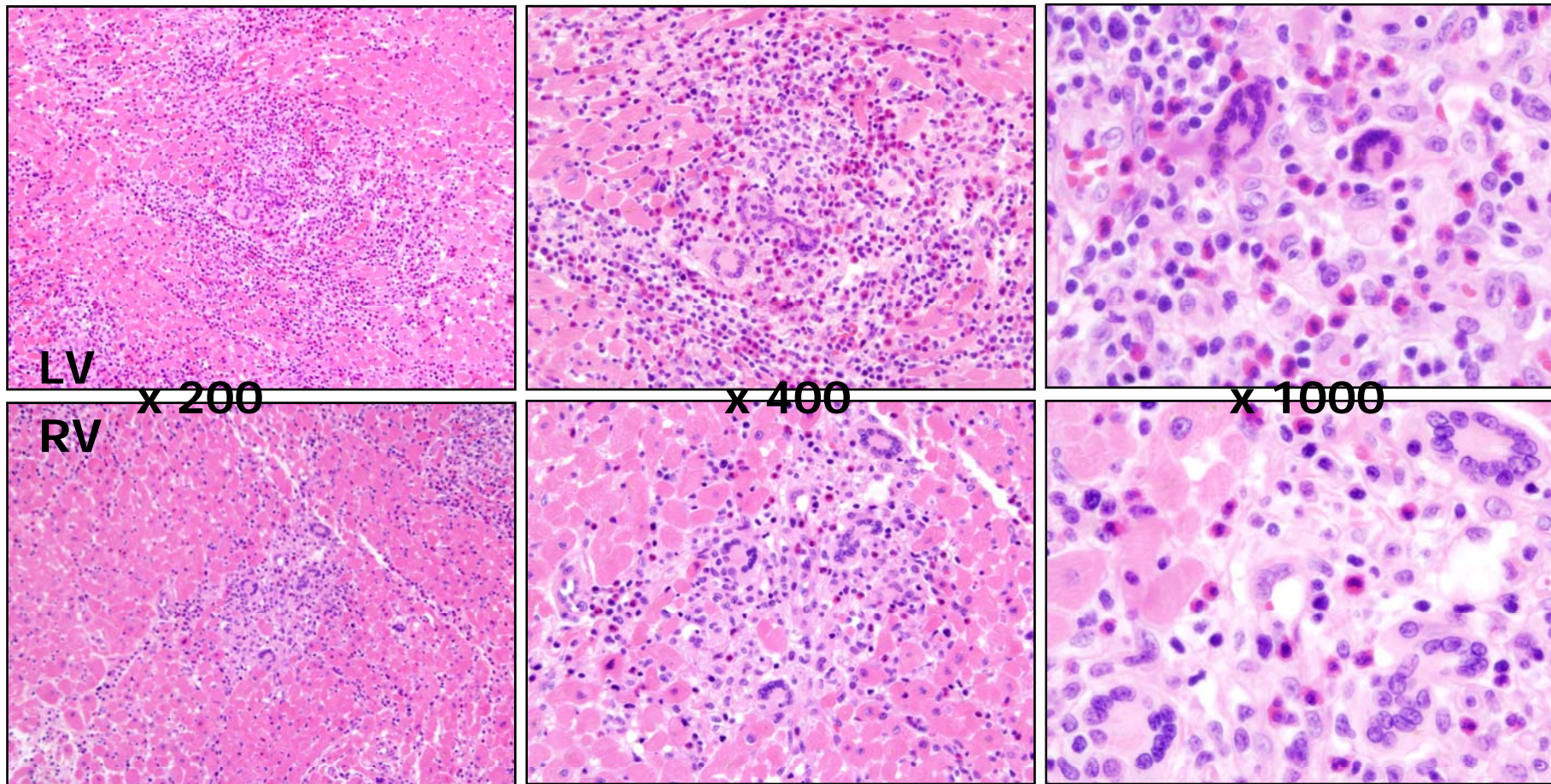
## Endomyocardial biopsy findings done at hospital day 5



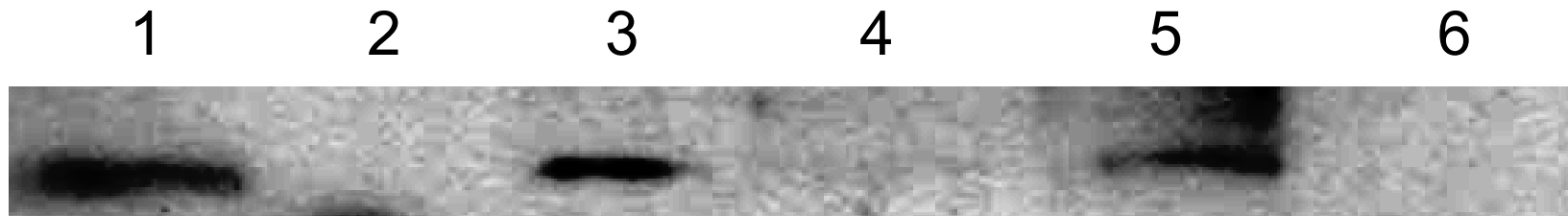
# Endomyocardial biopsy findings done at hospital day 5



# Pathology of explanted heart (day 10)



# Viral Capsid protein VP0 Western blot



**Lane 1 : H3 infected mouse heart at day 3**

**Lane 2 : Control mouse heart**

**Lane 3 : LA**

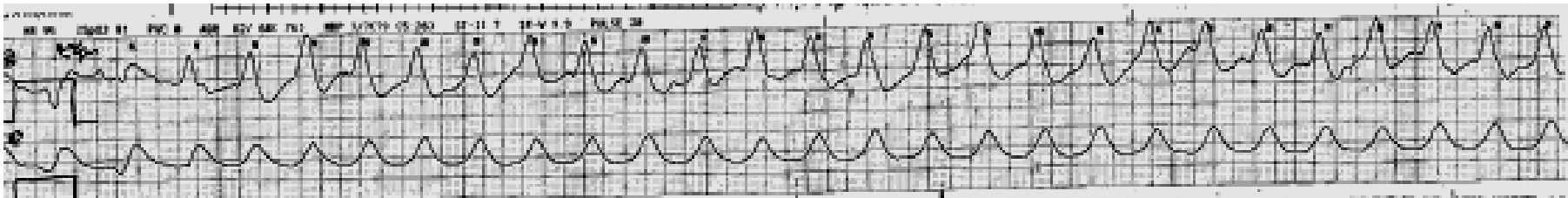
**Lane 4: LV**

**Lane 5 : RA**

**Lane 6 : RV**

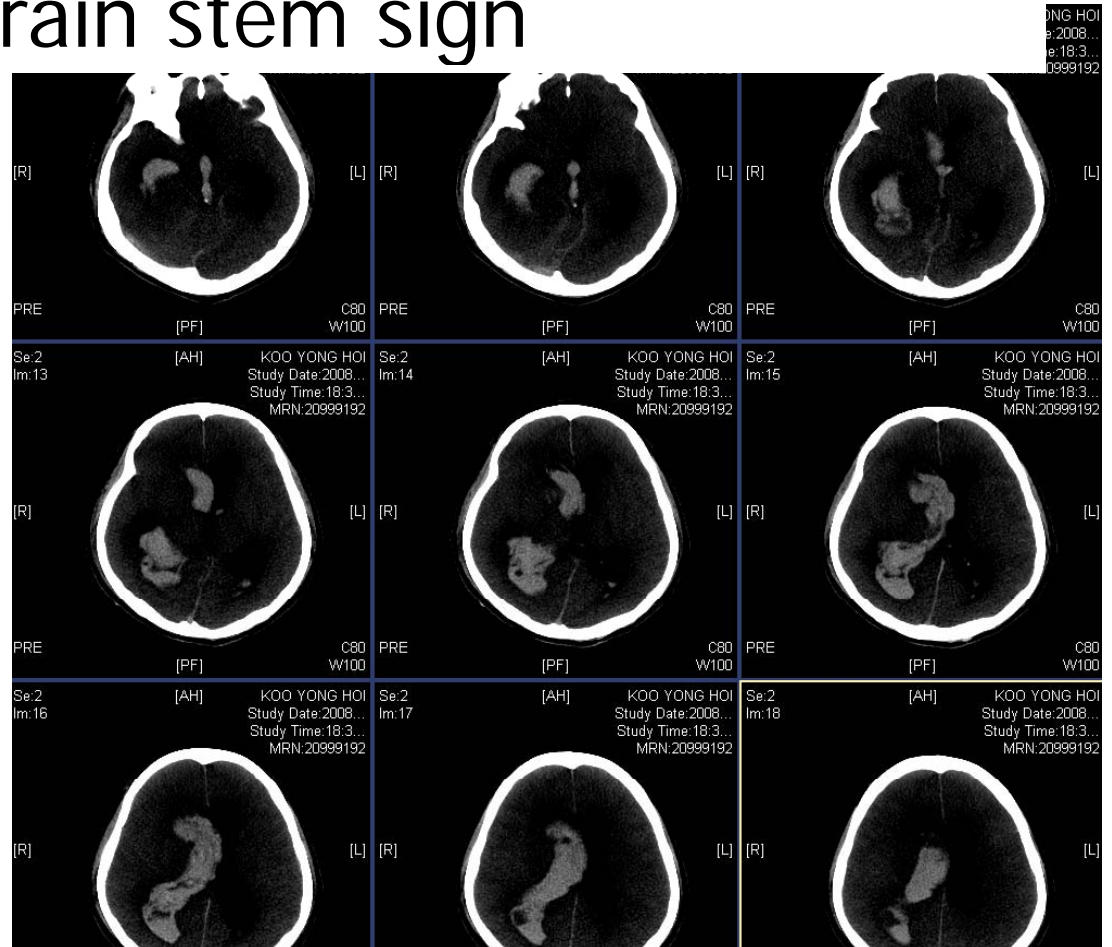
## Case Summary (M/37)

- 1WA chest pain 발생한 후 감기몸살 같은 증상(열, 근육통, 등) 있어 며칠간 일을 거르고 self medication
- 08.2.4. Sx aggravation되어 순천 성가롤로병원 방문
  - wide QRS, AV dissociation on EKG / CAG: normal
- 08.2.5. Hypotension 발생하여 SMC ER refer
  - BP 60/40, altered mentality
  - intubation and PCPS insertion 후 CCU adm

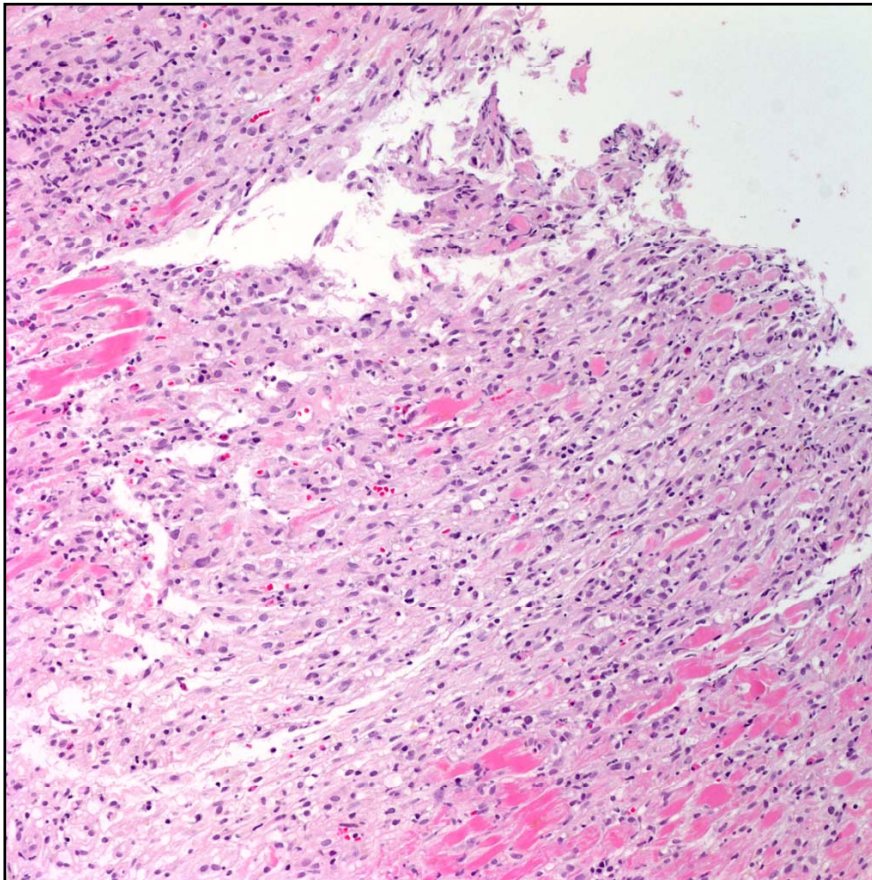


# Case Summary – Hospital course

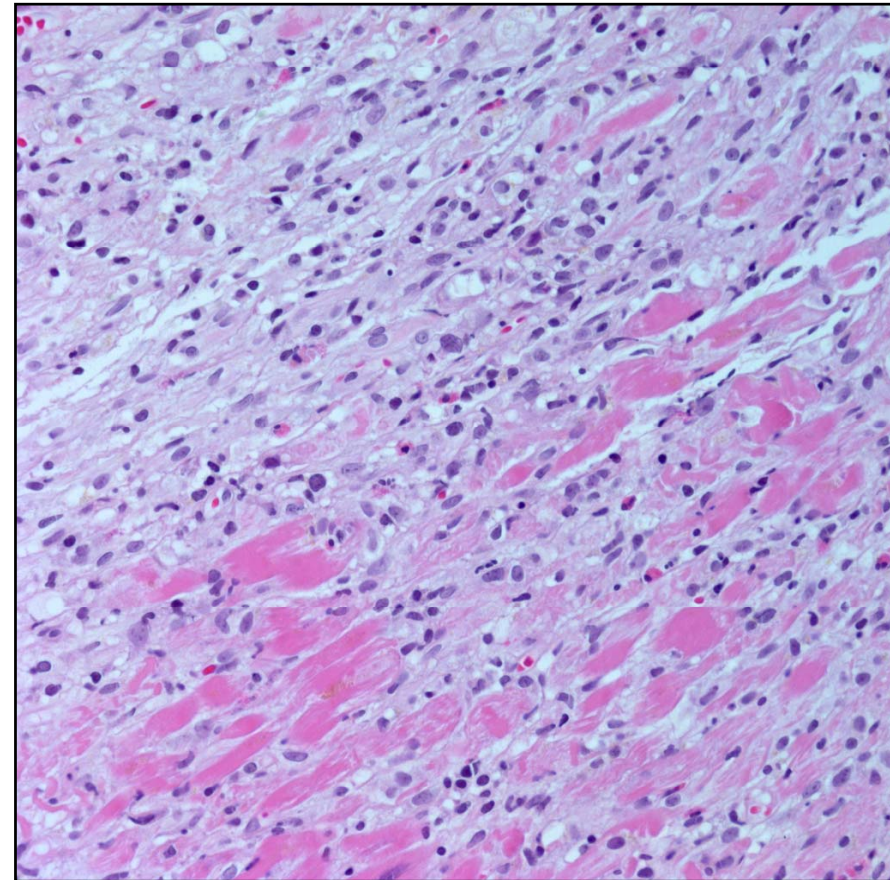
- Ventilation support were started due to hypoxia.
- At day 1, ECMO inserted.
- At HD 23, Loss of brain stem sign



## Endomyocardial biopsy findings done at hospital day 8 (H&E)

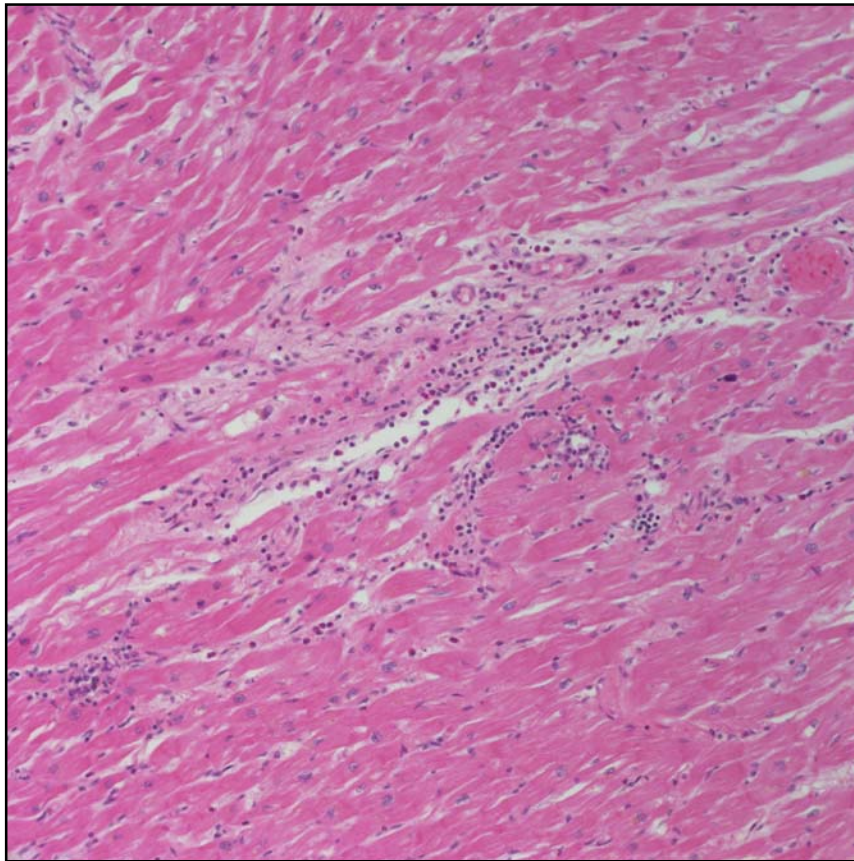


X 200

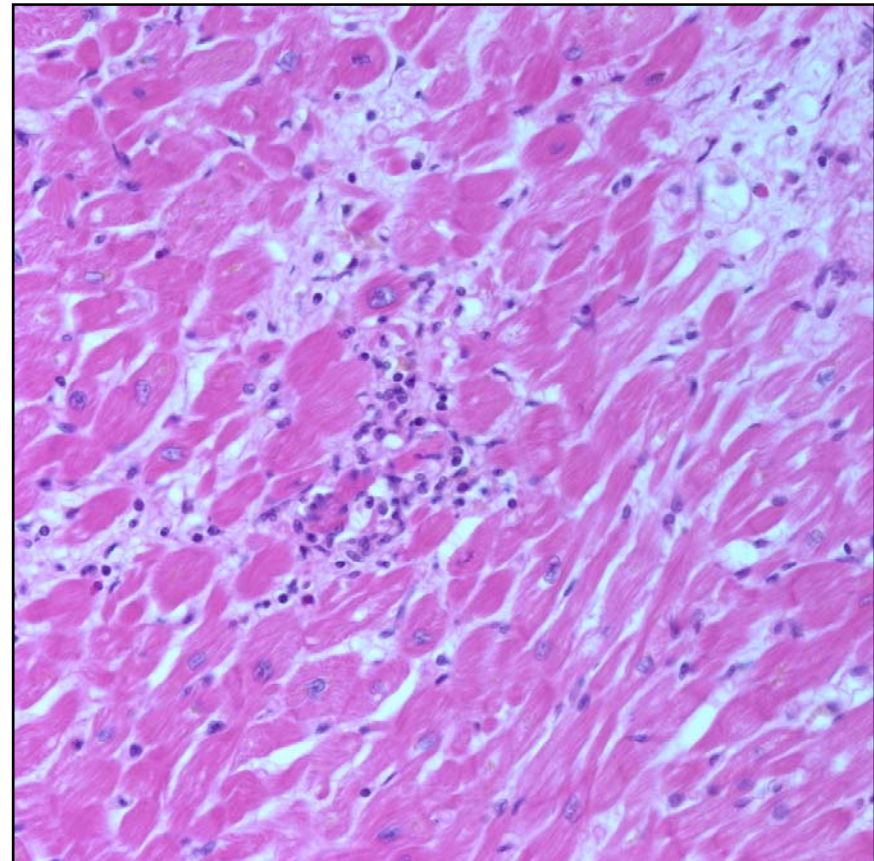


X 400

## Autopsy findings at day 24 (H&E)

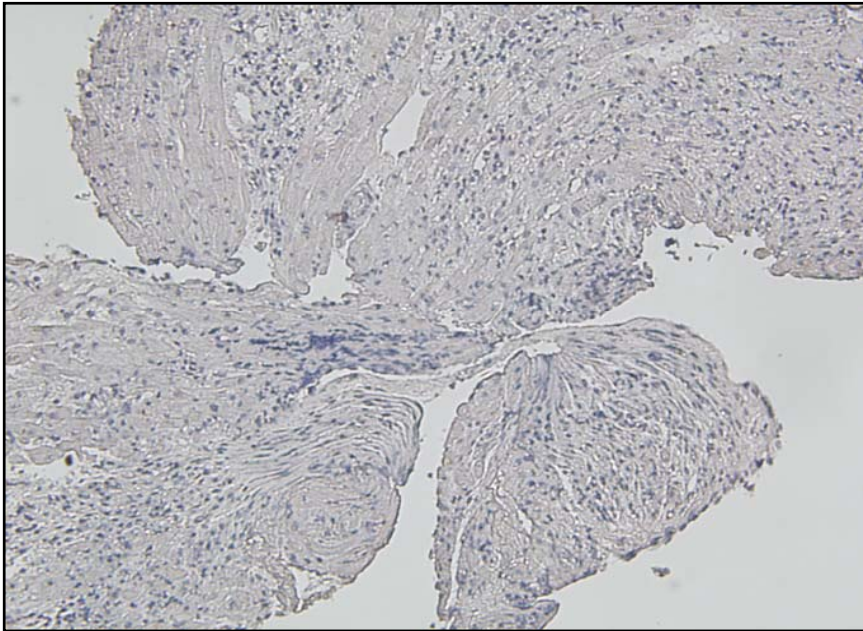


X 200

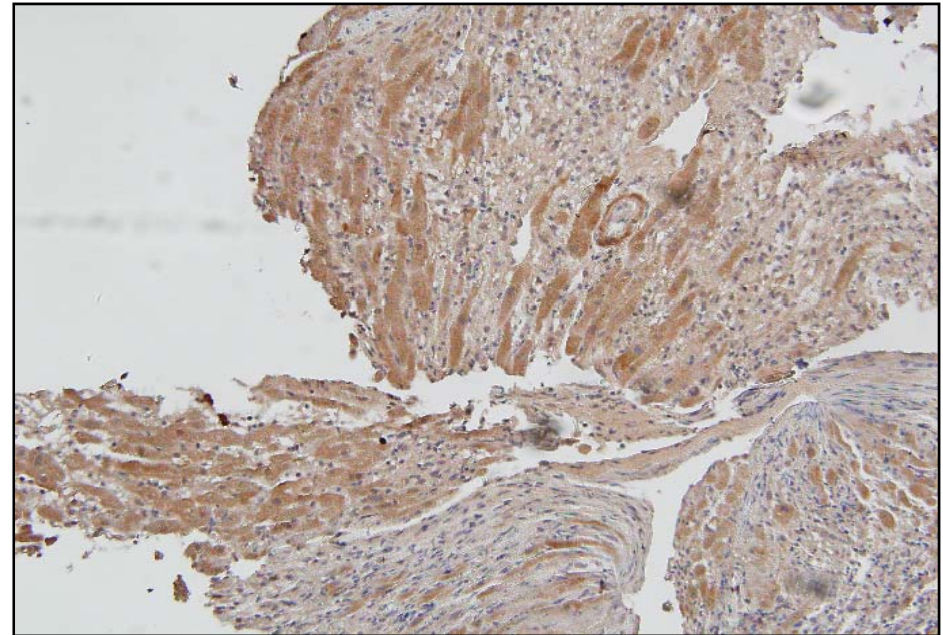


X 400

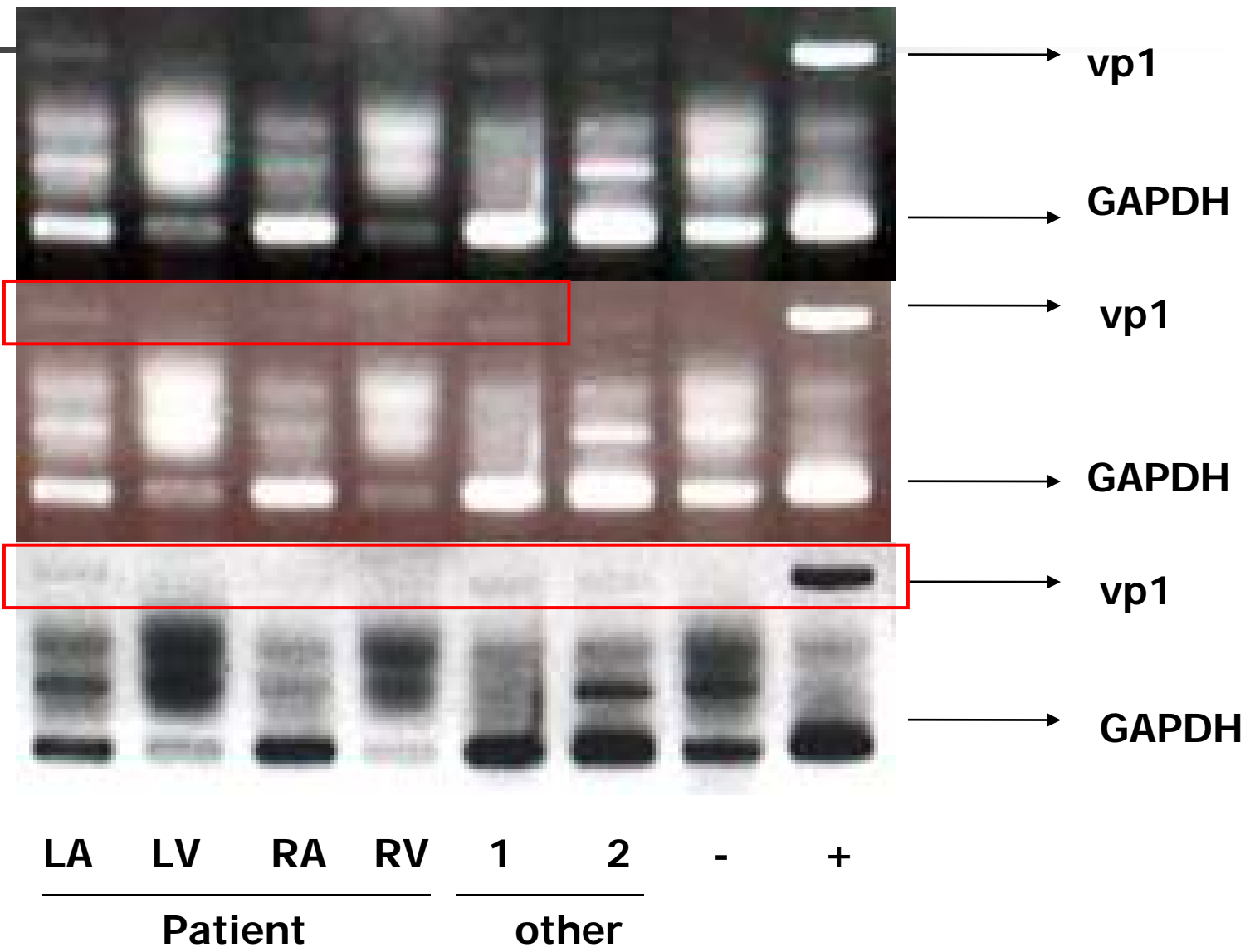
# Immunohistochemistry with enteroviral VP1 Ab at day 8



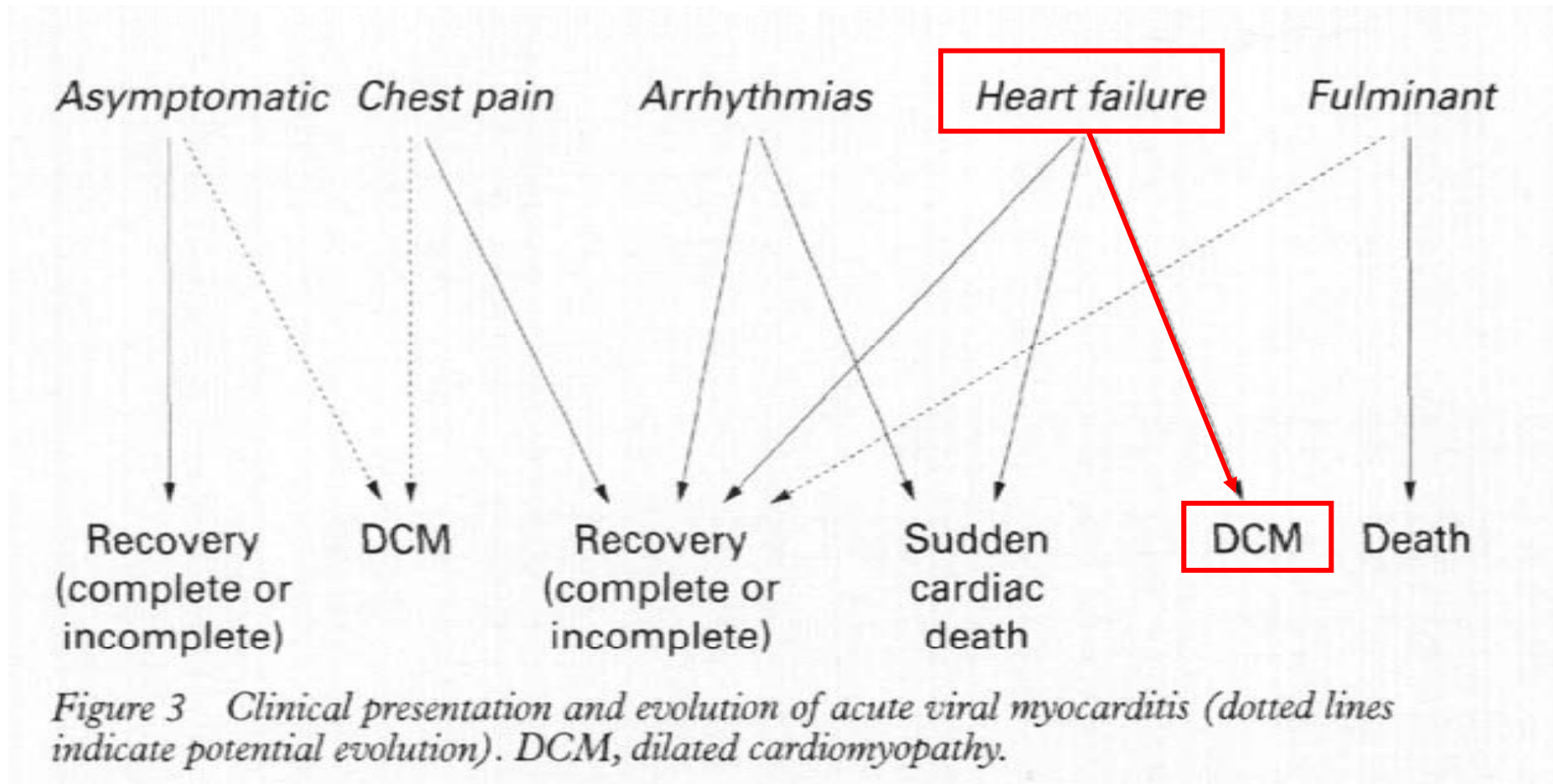
X 200 without Ab



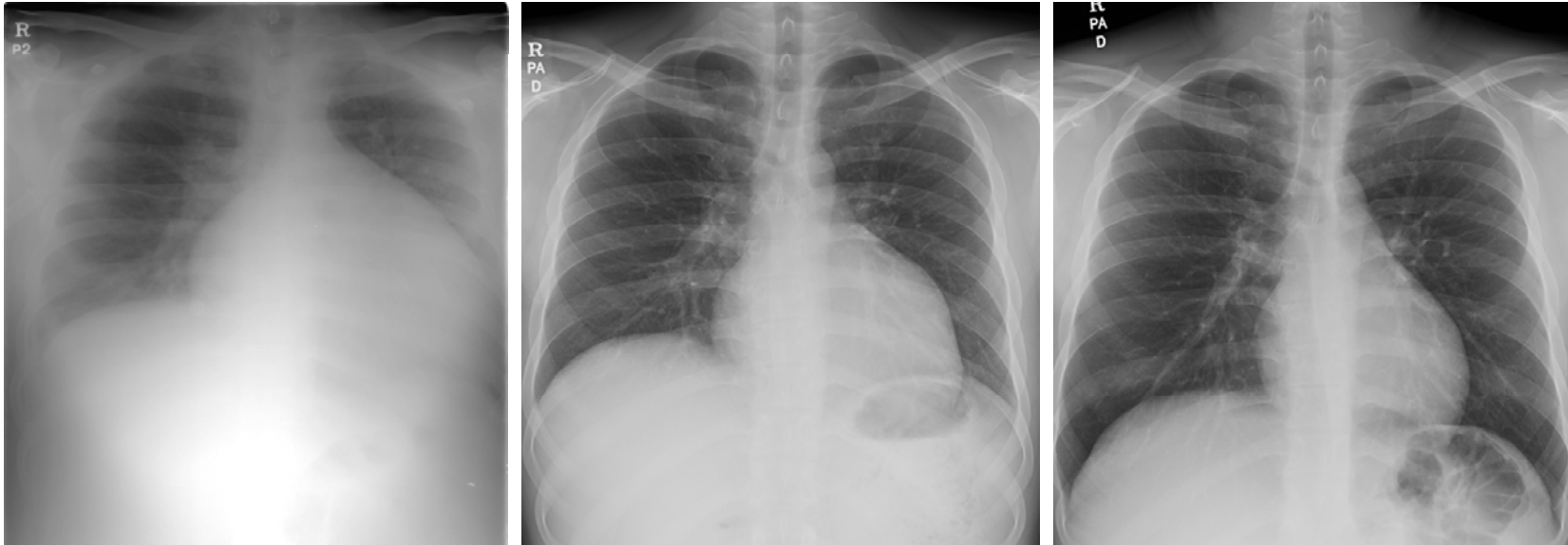
X 200 with Ab



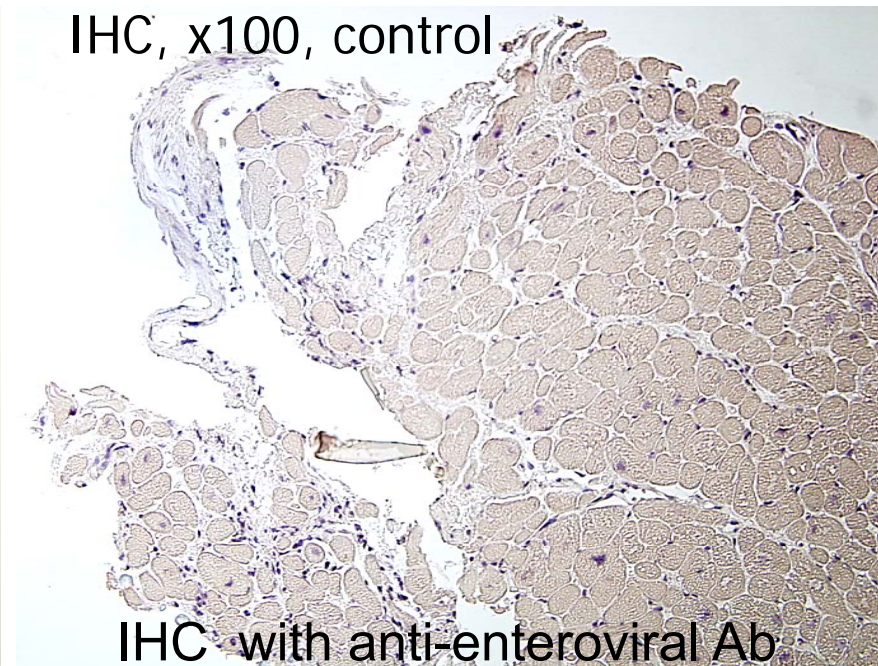
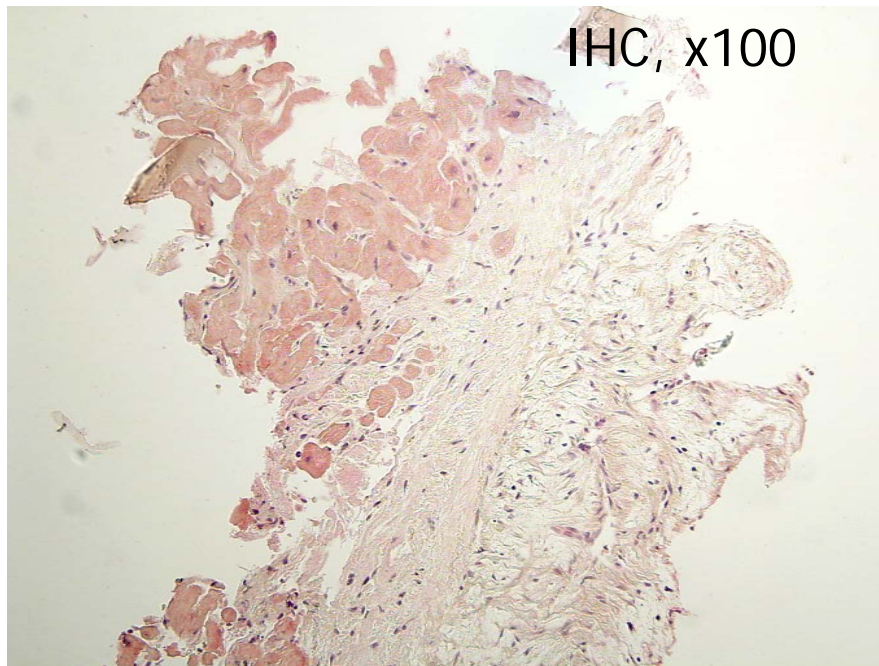
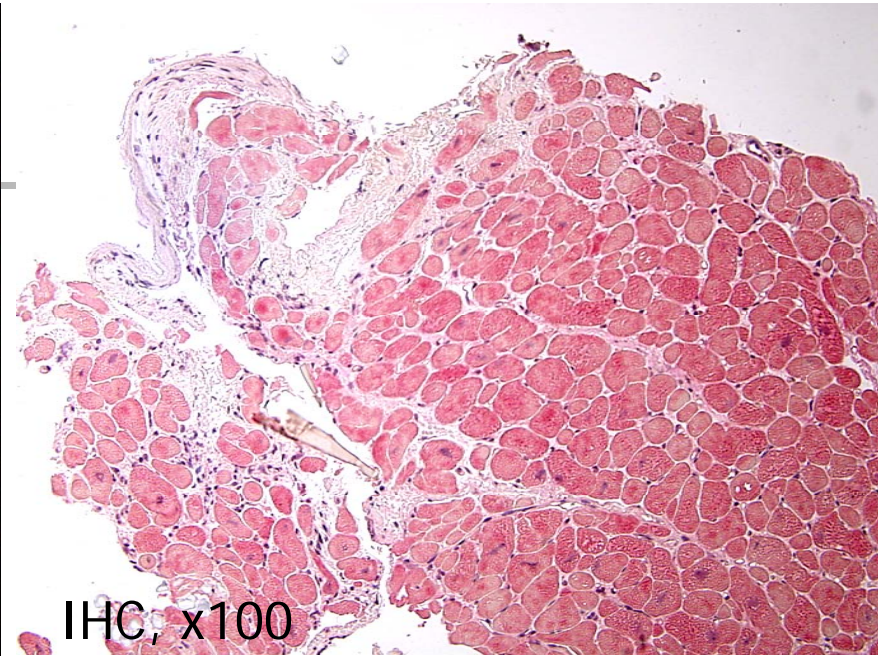
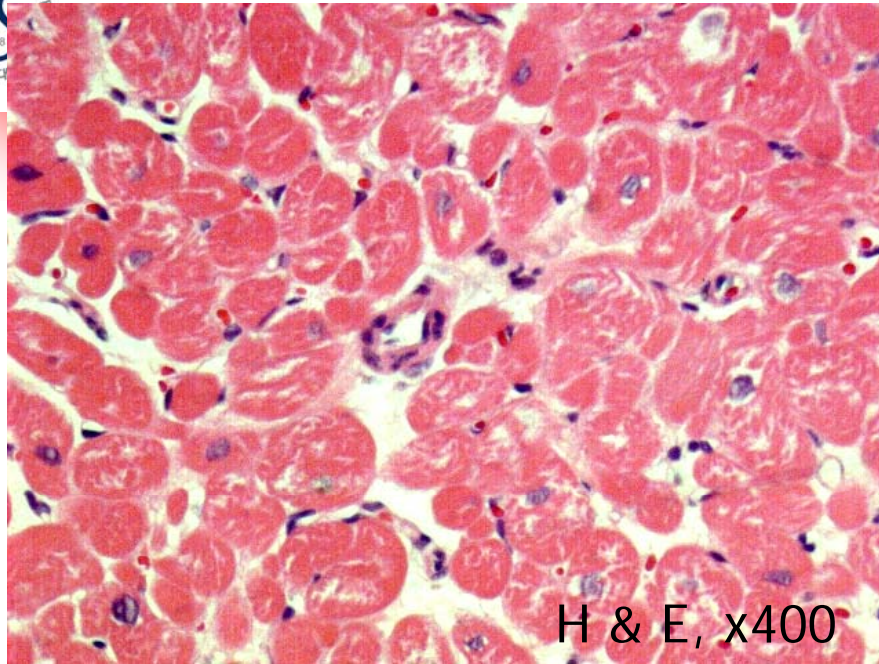
# Clinical Presentation & Evolution



# Laboratory findings



	3/22	4/4	5/19	10/06
LV	74/81	76/81	74/82	46/62
EF(%)	18	14	19.6	44.9
LA	57	52	54	36
NT-proBNP	2254	2089	1680	5.0



## Persistent Viral Infection in Chronic Phase

### ■ Clinical Evidences

- Viral gemones (+) in DCMP : CVB3, CMV, Adeno, HCV

### ■ Experimental Evidence

- EMC genome (+) 80 days after infection  
(Matsumori, Circulation 1996:94)
- Replication defective cDNA of CVB3  
(Wessely, Circulation 1998:98)
- Transgenic animal with replication defective CVB3 cDNA  
(Wessely, J Clin Invest 1998:102)

# Prognosis and viral RNA

1. JACC 1995;25:1170
  - Better TPL free survival rate in CVB3 (+) than (-) in heart (95% vs 55%)
2. Circulation 1994;89:2582
  - Actuarial survival at 24 months  
→ RNA(+) vs (-) = 92 vs 68%
3. Circulation 2003;107:857
  - In LC myocarditis, immunosuppressive non-responder → 85% had viral genome

# Immune Models of Myocarditis

- **Autoimmune Model**

Rat or mice immunized with myosin

(Kodama, Circ Res 75: 1994)

- **Cell mediated Model : SCID mice**

Adoptive transfer of immunized Lc

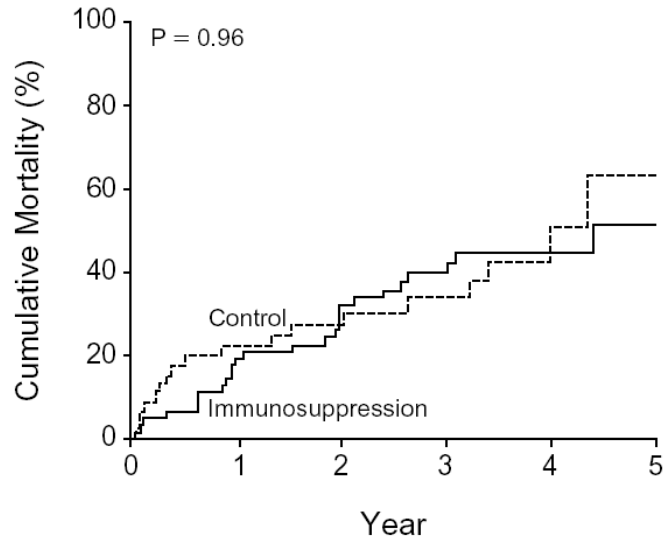
Human Lc transfer of to SCID mice

(Schwimmbeck, Circ Res 75: 1994)

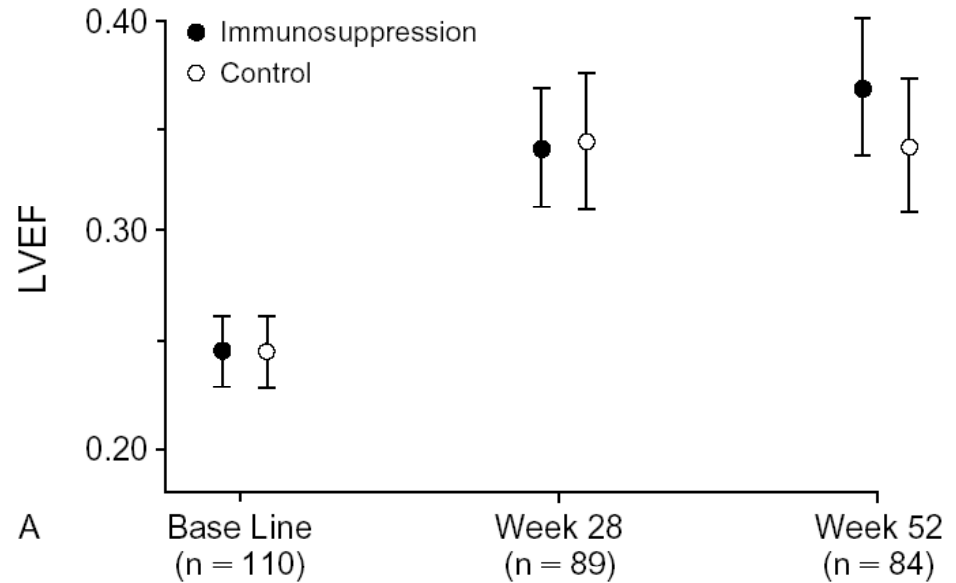
# Myocarditis Treatment Trial

- Inclusion Criteria
  - CHF not d/t VHD, CAD
  - LVEF <45% by RI angio
  - Symptom duration < 2 years
  
- Patients enrolled : 2233 pts (Oct. 1986 - 1990)
  
- Endomyocardial biopsy : 214(10%) pts - final 111 pts
  
- Drugs : Azathioprine + Prednisolone for 6 months  
Cyclosporine + Prednisolone for 6 months

# Myocarditis Treatment Trial



Immuno-suppression	64	49	37	23	12	0
Control	47	32	23	16	6	0



- Results : **No significant effects** of immunosuppression on NYHA FC, LVEF, Survival, PWP, LV dimension

# Treatment

1. Supportive care
  - Hemodynamic stabilization
2. ACC/AHA guideline for LV dysfunction
  - $\beta$ -adrenergic blocker / ACEI for all
  - Aldosterone antagonist in NYHA FC III-IV
3. Immunosuppressive agents

# Immunosuppression in myocarditis

		Supportive care	Immuno-suppressive agents	Intravenous immunoglobulin	Interferon
Fulminant		yes	?	?	?
Eosinophilic		yes	yes	?	?
Giant cell		yes	yes	Yes	?
Lymphocytic	Virus(+)	yes	?	?	+
	Virus(-)	yes	?	?	?

# Acknowledgement

- ▶ Samsung Medical Center
  - ▶ 권기영 교수(해부병리)
  - ▶ 윤수현 / 송현미 / 주은선
- ▶ University California, San Diego

Byung-Kwan Lim

Kirk Knowlton

