전격성 심근염 환자에서 순환보조 장치 치료

- VAD in treatment of Fulminant Myocarditis -

성균관의대 내과학교실

삼성서울병원 심장혈관센터

전 은 석

Definition of Myocarditis

- an INFLAMMATION INFILTRATE and by INJURY to the adjacent myocardial cell that is *not typical of* INFARCTION

- 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

Etiologic Agents of Myocarditis

Infectious Agents

Virus

Coxsackievirus(A,B), HIV

Echovirus, Influenza(A,B),

Poliovirus, Herpes Simplex,

Varicella-Zoster, Rubella, Rubeola,

Epstein-Barr,Cytomegalovirus, Mumps, Vaccinia, Hepatitis B,

Bacteria : diphtheria, Neisseria ....

Metazoa : Trichinosis, Echinococcosis

Protozoa : Trypanozoma, Toxoplasma

Fungus : Aspergillosis, Cadidiasis ....

Toxic Agents

Anthracyclines

Catecholamines

Interleukin-2

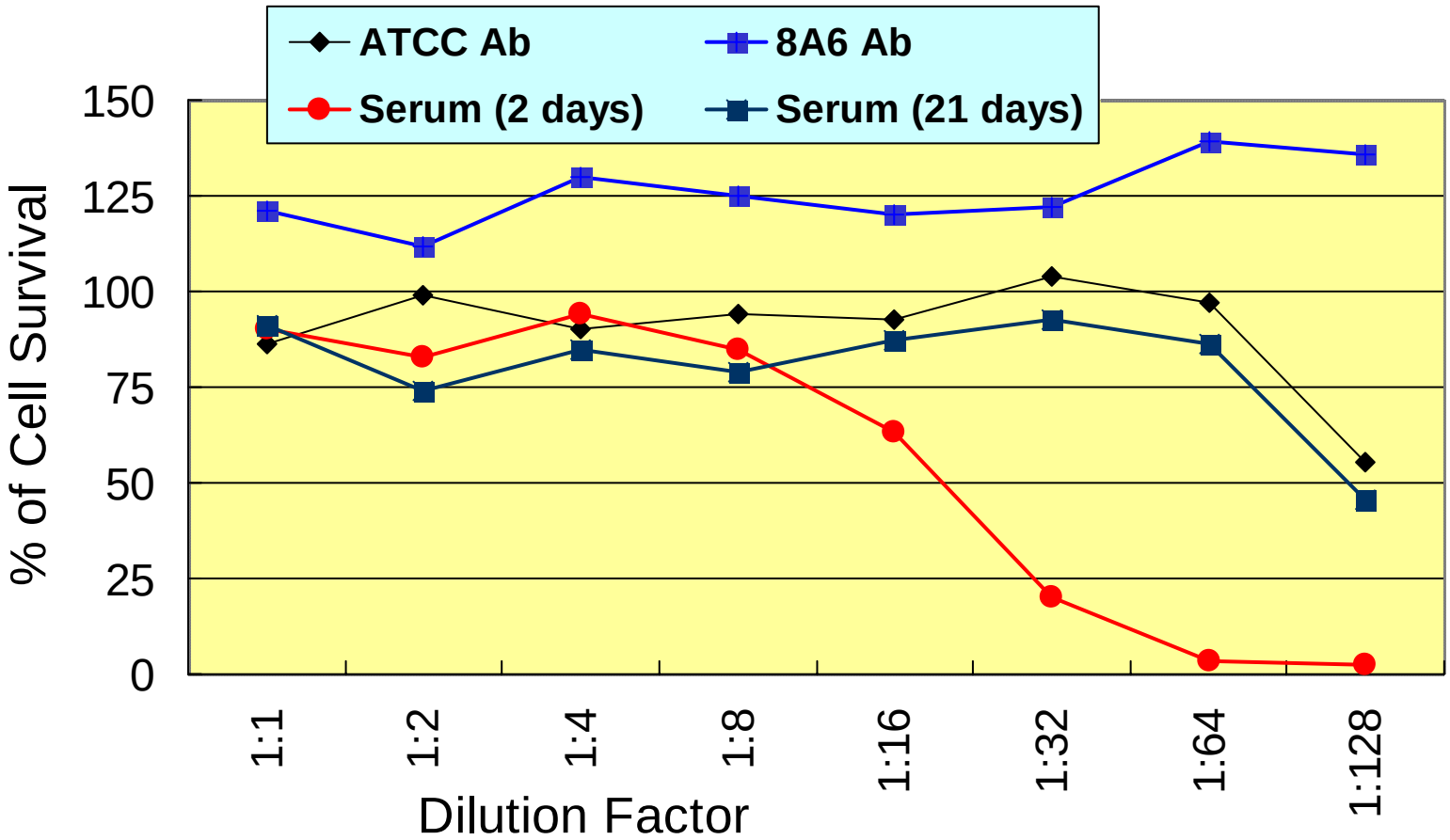
Interferon-alpha2

Hypersensitivity

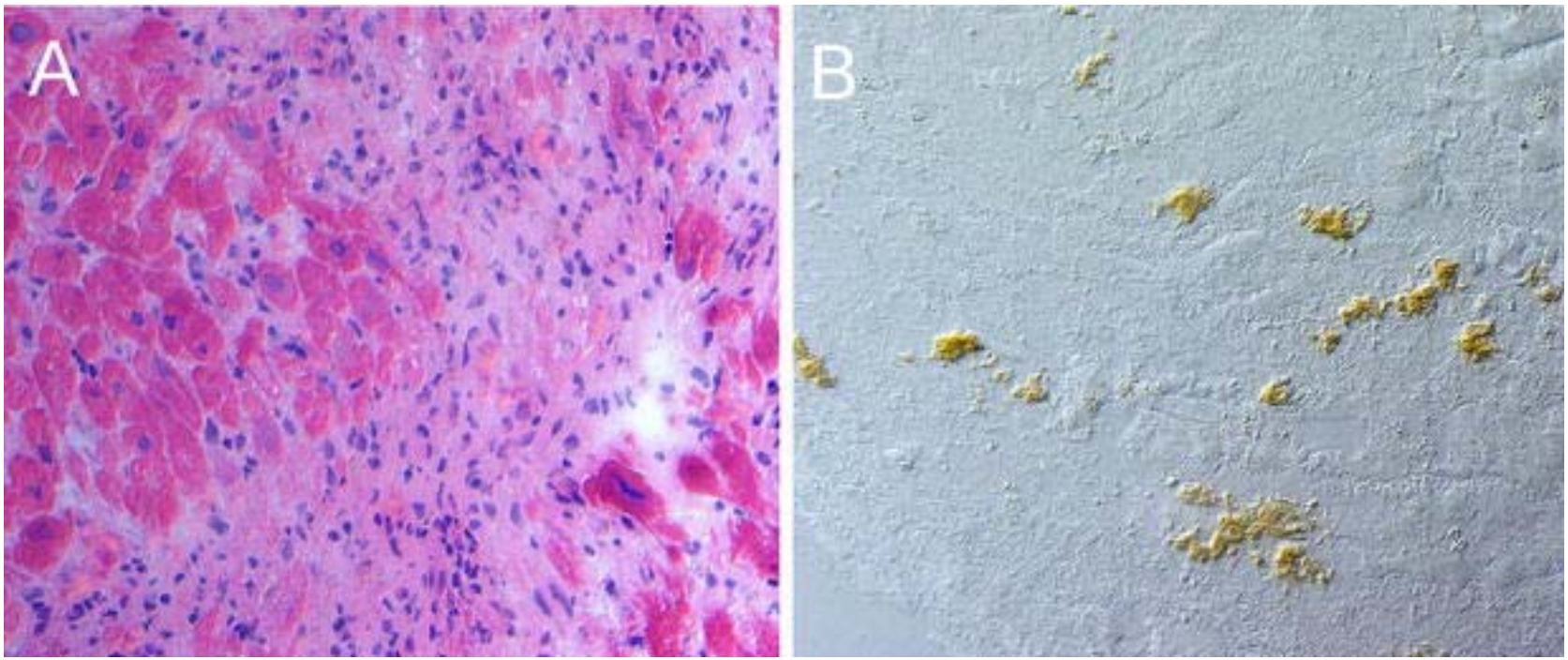
Diagnosis of Viral Myocarditis

- Serology
  - 4-fold increase of Neutralization Ab titer
- Virus culture in tissue
- Viral genomes in tissue
  - by PCR, Hybridization
- Viral proteins in heart

Neutralization Ab Test (MTT Assay)

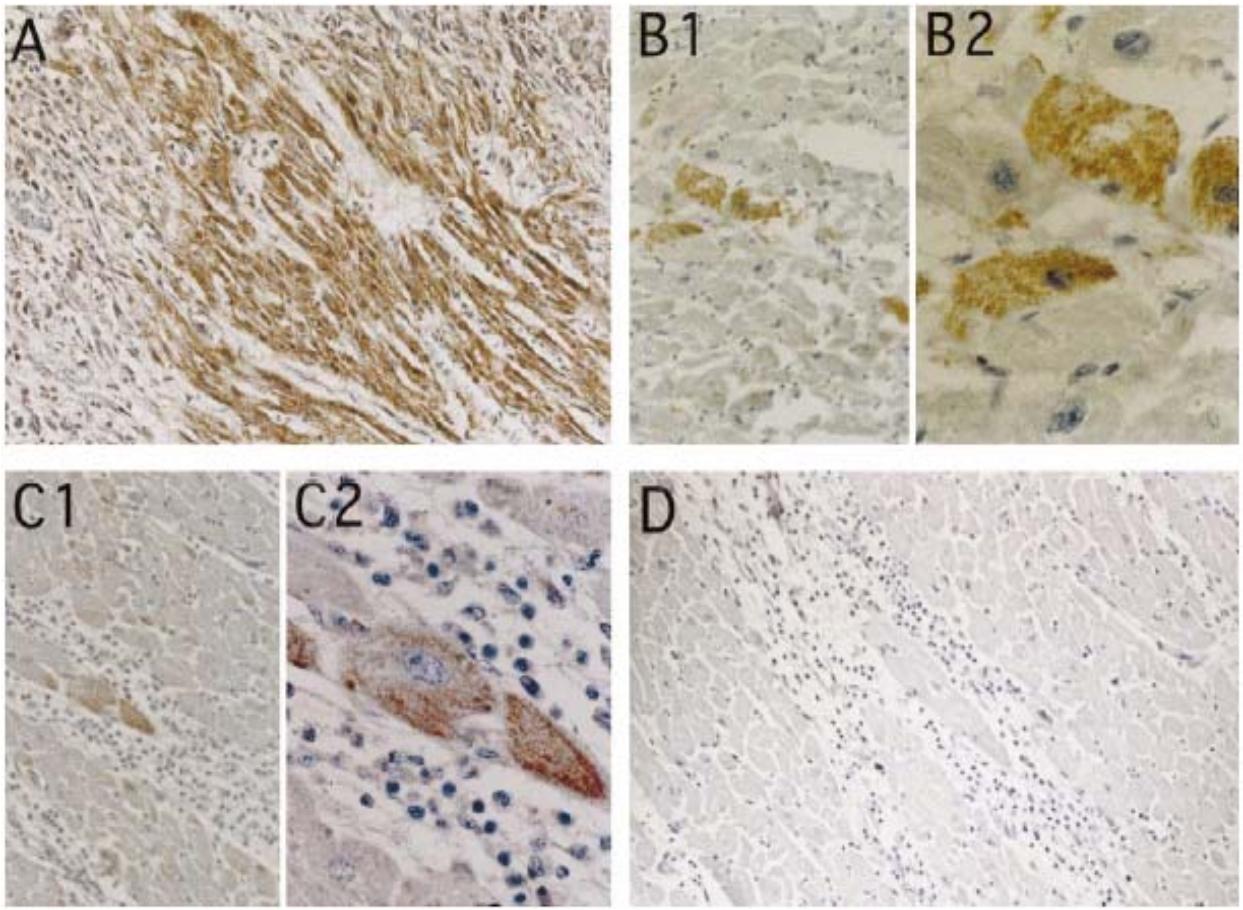


Detection of enteroviral Genome by *in situ Hybridization* in CVB2 myocarditis



Badorff C. Med Microbiol Immunol (Berl). 2003 Aug 12

Detection of enteroviral capsid protein VP1 by immunohistochemistry



A : fatal myocarditis

B : D-CMP

C: Chronic myocarditis

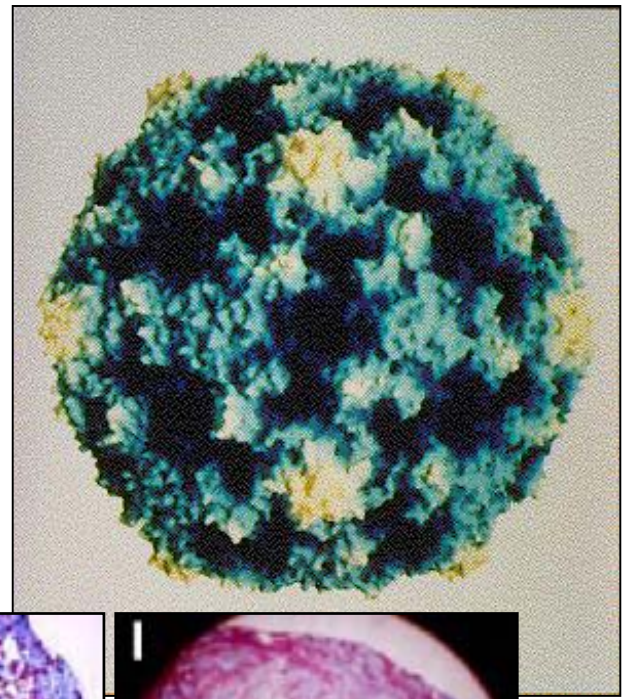
D : Negative control with IgG2a

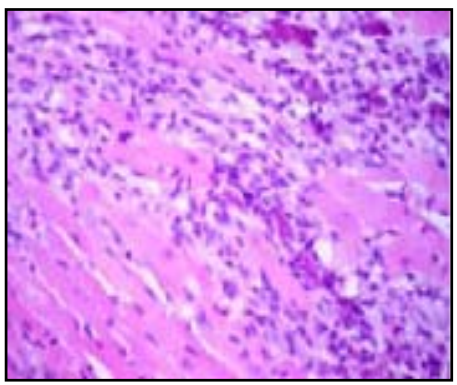
x200 : A, B1, C1, D

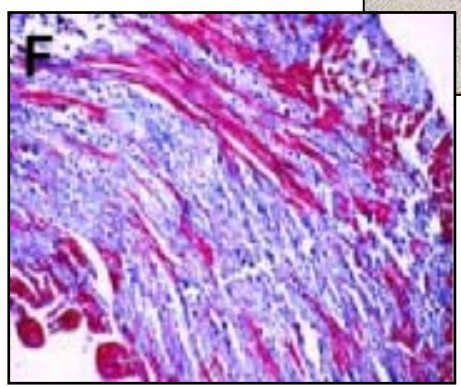
x600 : B2, C2

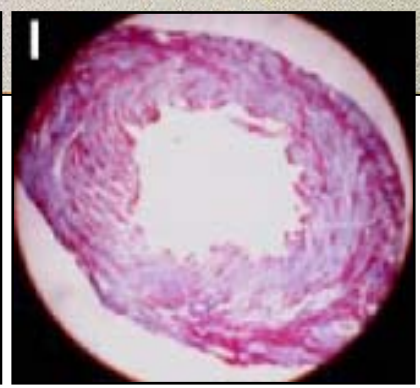
Coxsackievirus Type B3 (CVB3)

- 7.4 Kb ssRNA picornavirus
  - like as polio-, echo-, rhinovirus
- highly cardiotropic
- induces myocarditis
- progress to cardiomyopathy







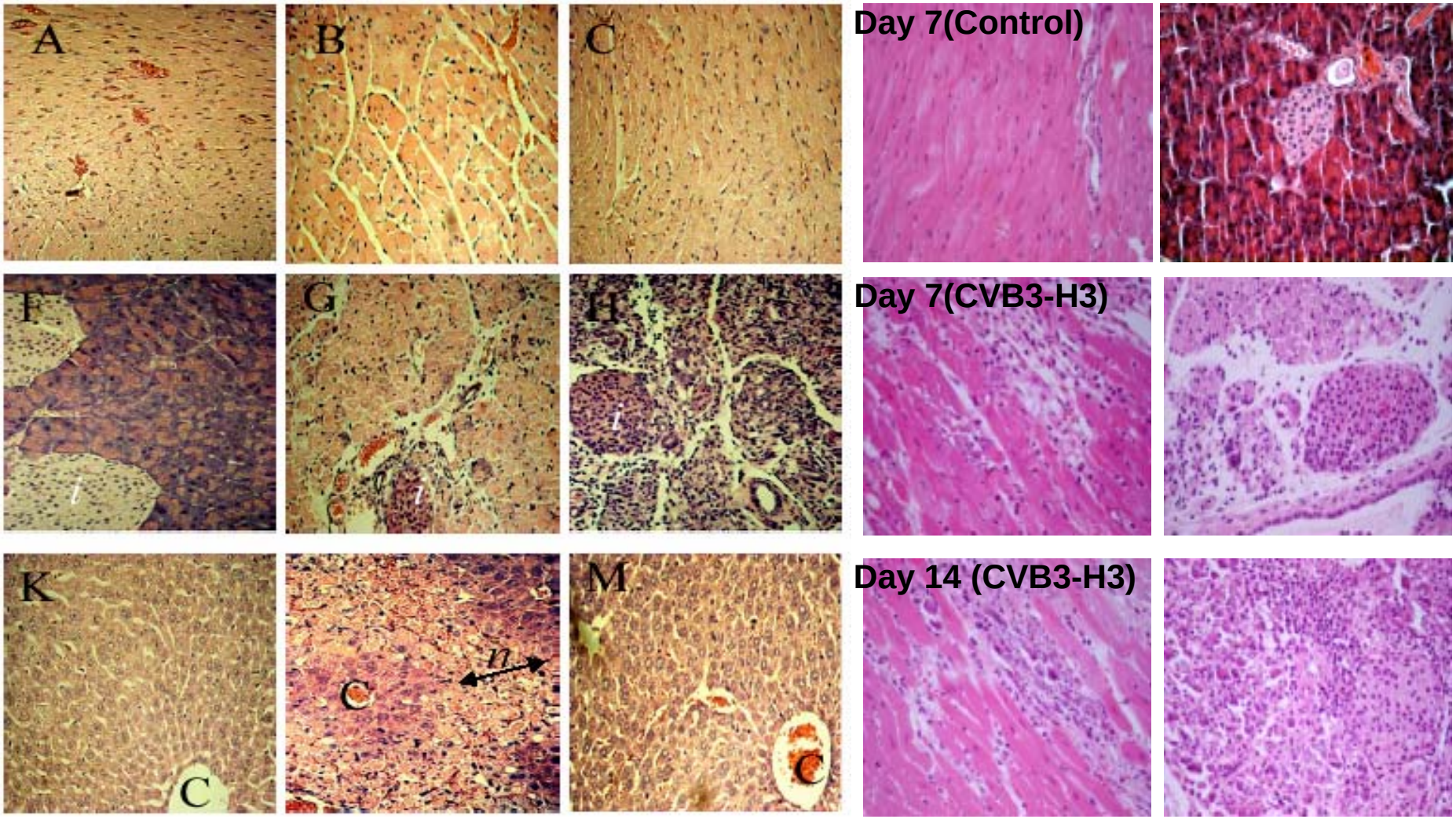


Diseases Associated with Coxsackievirus

Table 1. Diseases associated with coxsackievirus infections

	Mild diseases	*Severe diseases*
Acute diseases	Rash	Aseptic meningitis
	Upper respiratory	Encephalitis, paralysis
	Myalgia	Hepatitis
	Pyrexia of unknown origin	Pancreatitis
		Pleurodynia
		Pericarditis
		Myocarditis
		Keshan disease
Chronic diseases		Insulin-dependent diabetes mellitus
		Myocarditis
		Dilated cardiomyopathy
		Meningitis/encephalitis

Diseases Associated with Coxsackievirus



Time Course of Viral Myocarditis

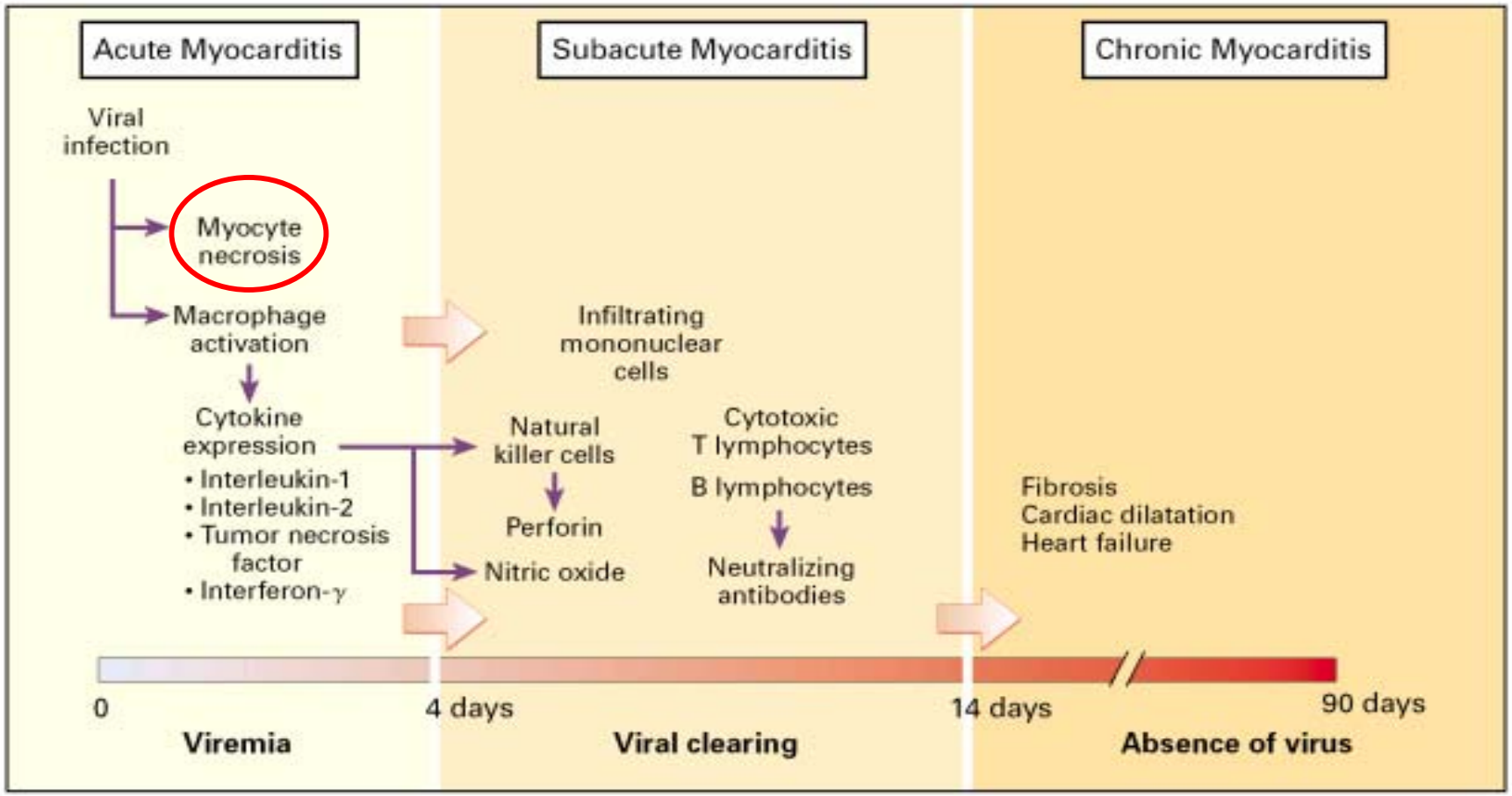


Figure 2. Time Course of Experimental Viral Myocarditis in Mice.
Adapted from Kawai[11] with the permission of the publisher. The timeline is not drawn to scale.

Clinical Presentation & Evolution

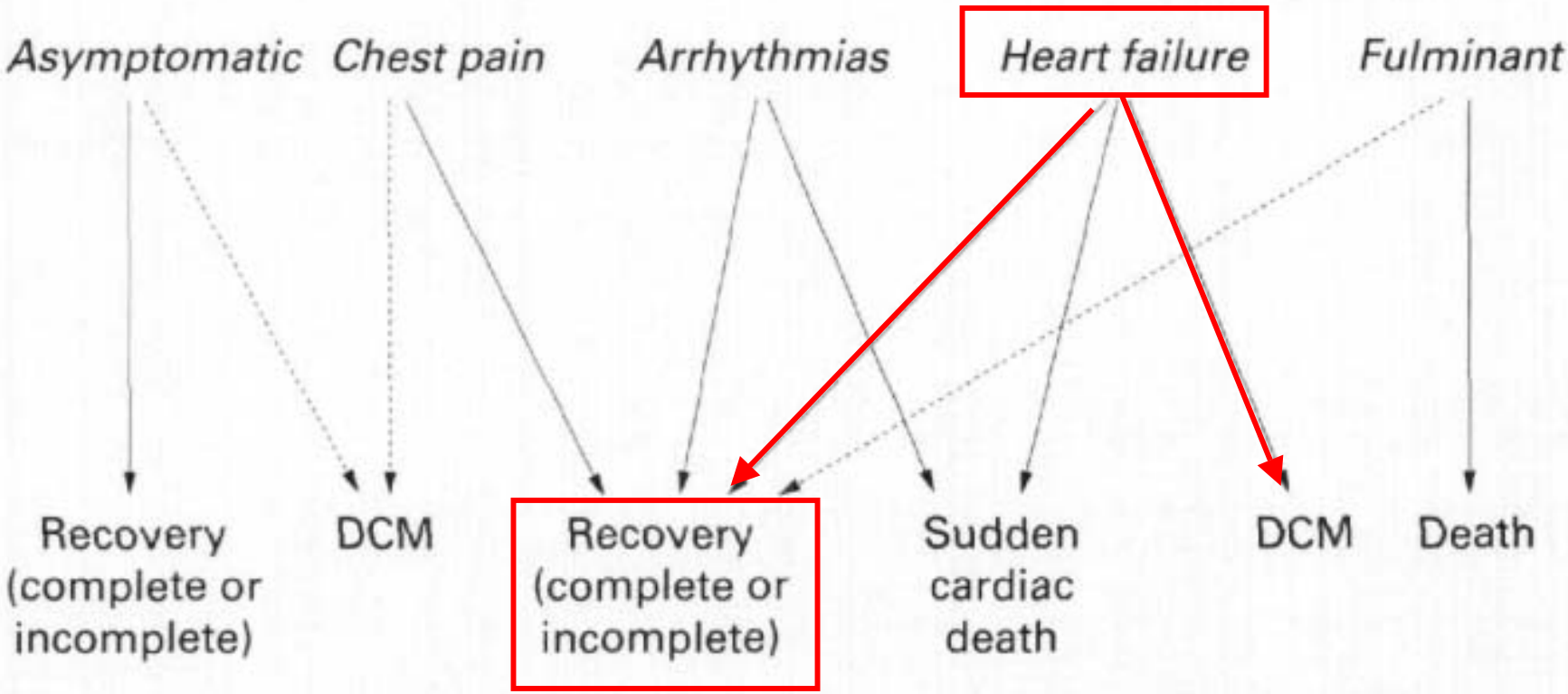
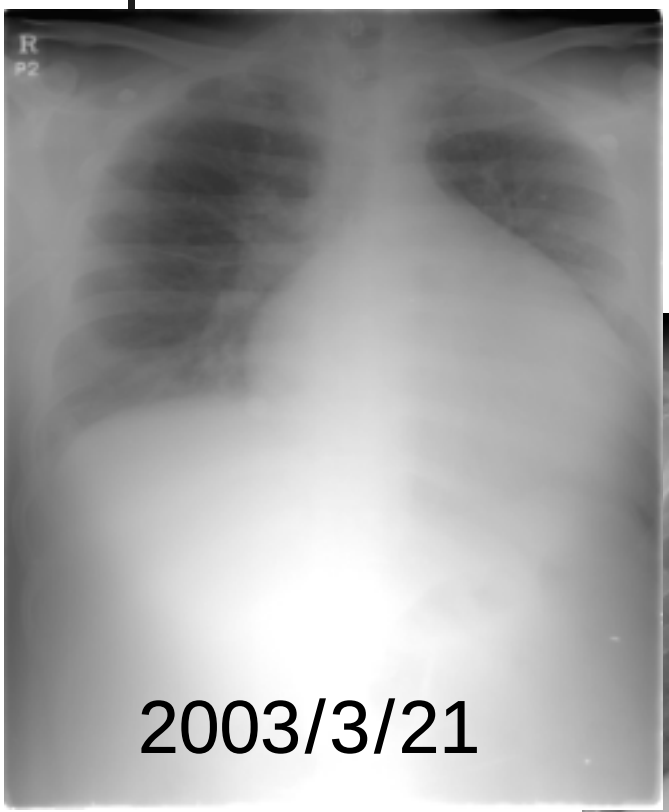


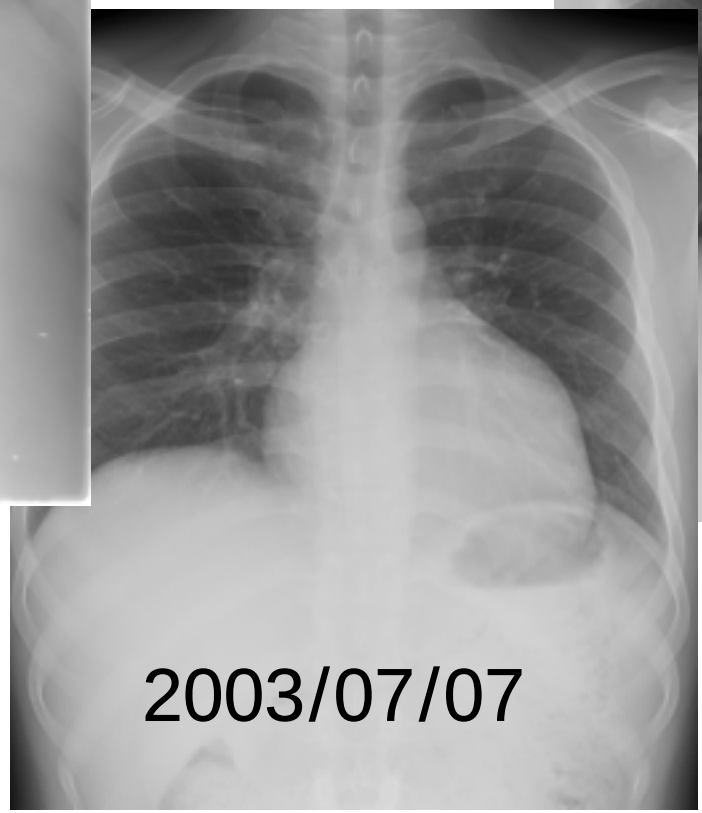
Figure 3 Clinical presentation and evolution of acute viral myocarditis (dotted lines indicate potential evolution). DCM, dilated cardiomyopathy.

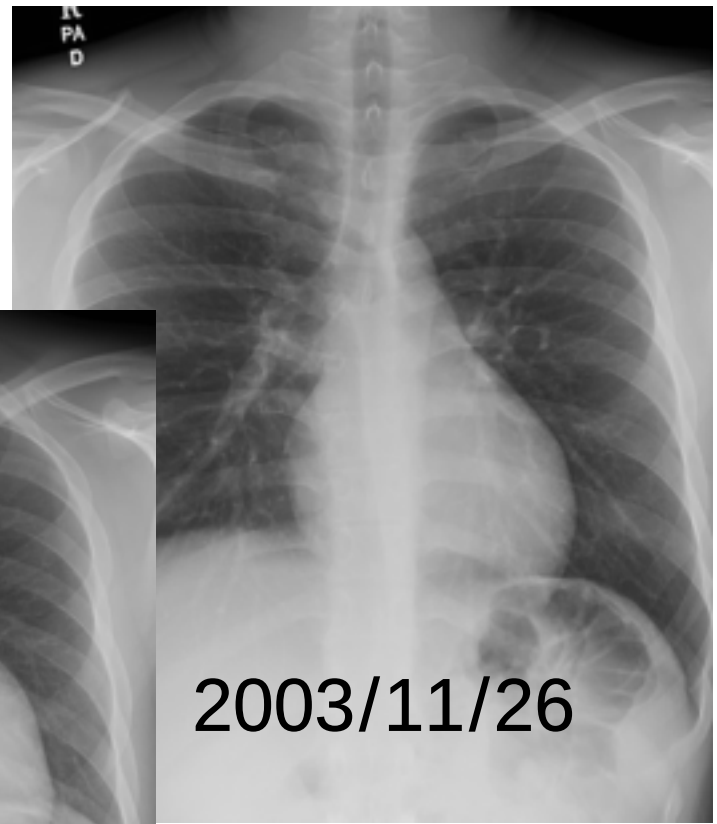
Enteroviral Infection Manifested by Dilated Cardiomyopathy

Male / 20

Chest PA

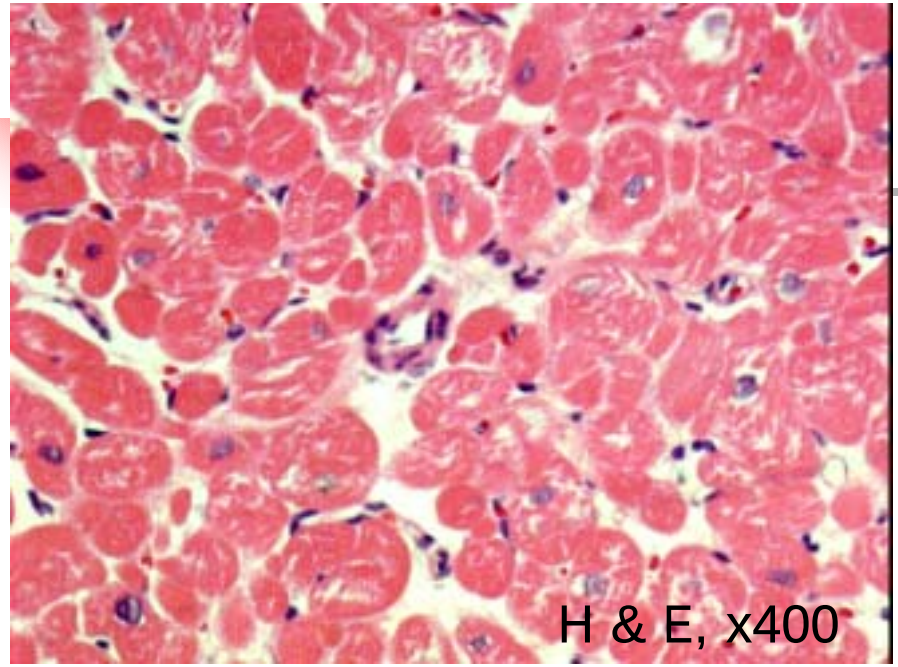


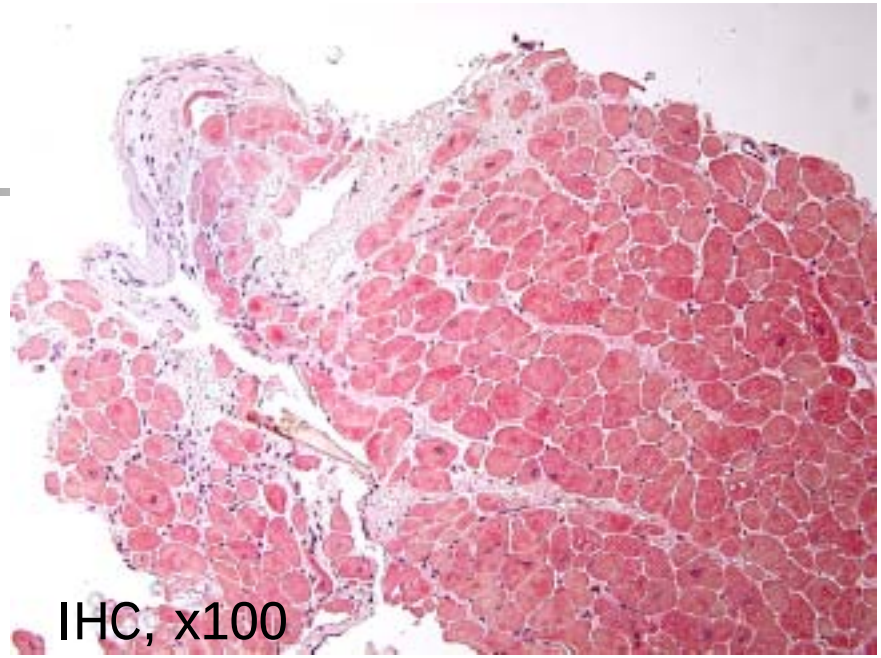


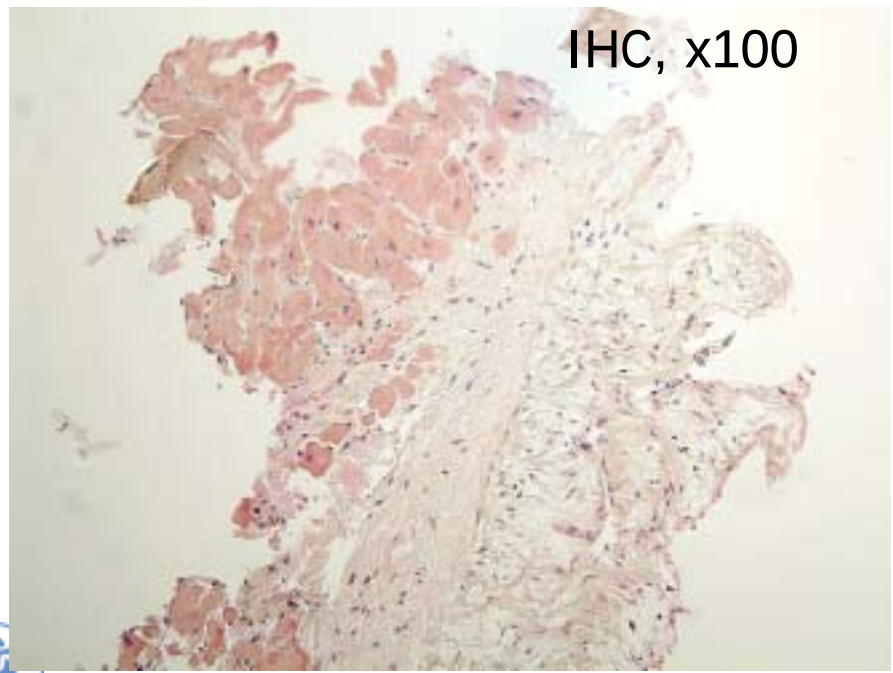


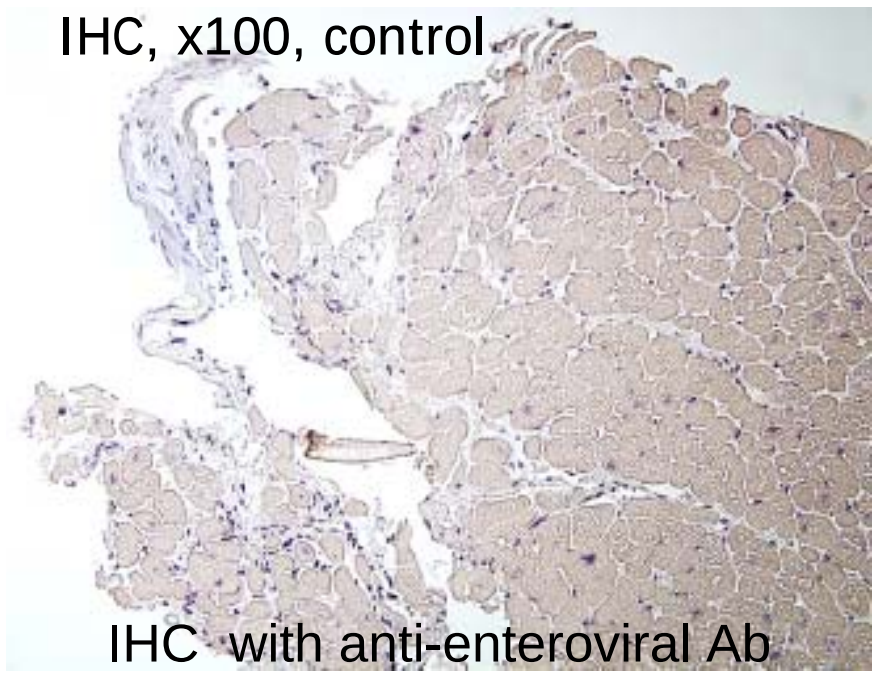
Echocardiography and NT-proBNP

	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


H & E, x400


IHC, x100


IHC, x100


IHC, x100, control
IHC with anti-enteroviral Ab

Clinical Presentation & Evolution

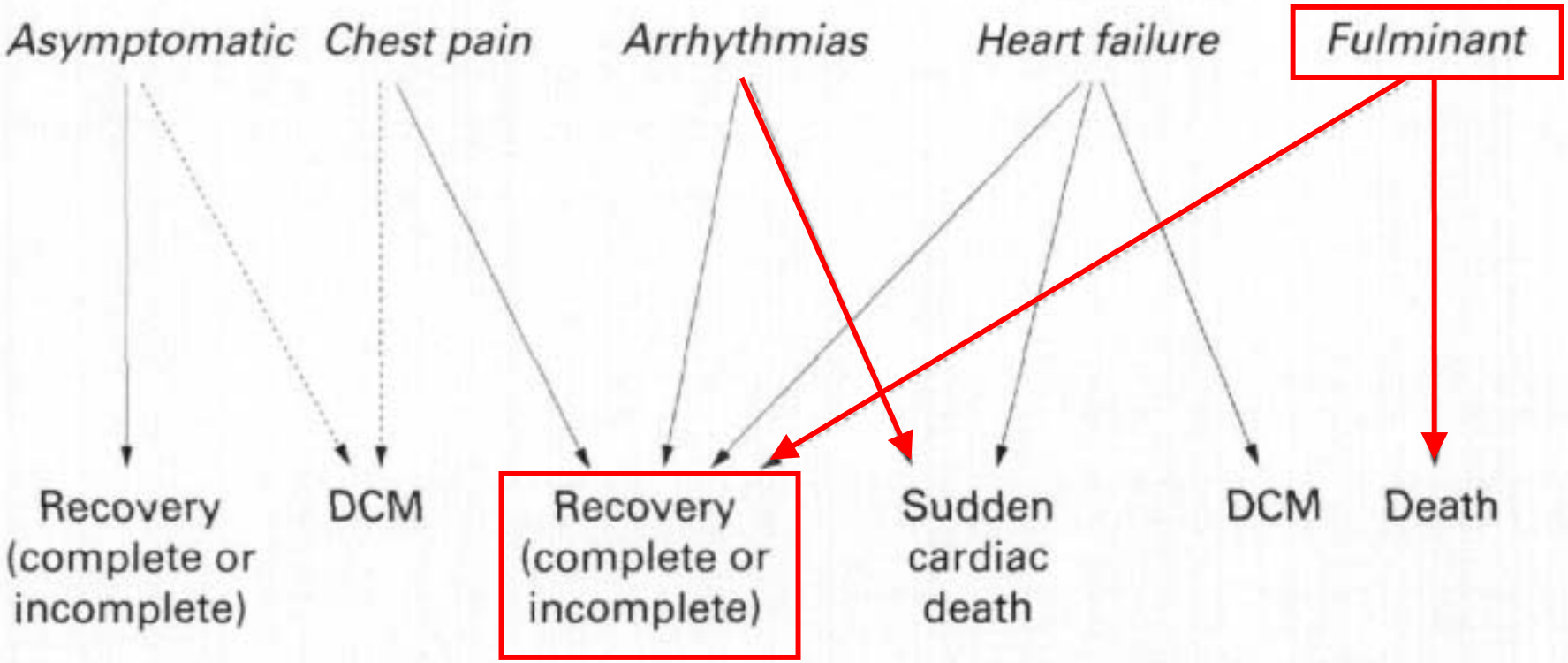
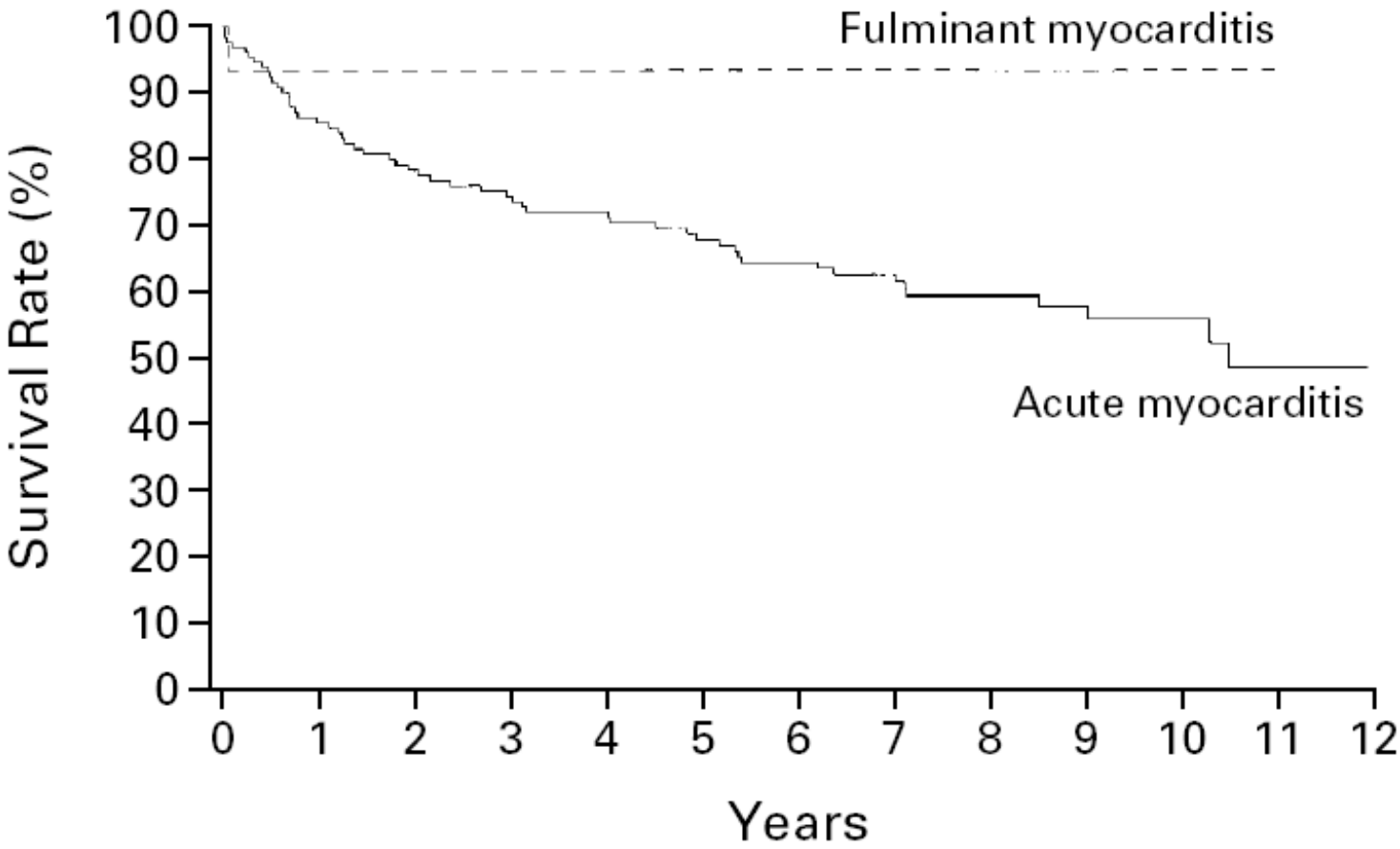


Figure 3 Clinical presentation and evolution of acute viral myocarditis (dotted lines indicate potential evolution). DCM, dilated cardiomyopathy.

Unadjusted Transplantation-free Survival According to Clinicopathological Classification



N Engl J Med 2000;342:690-5

Fulminant Myocarditis with Pancreatitis

Male / 15

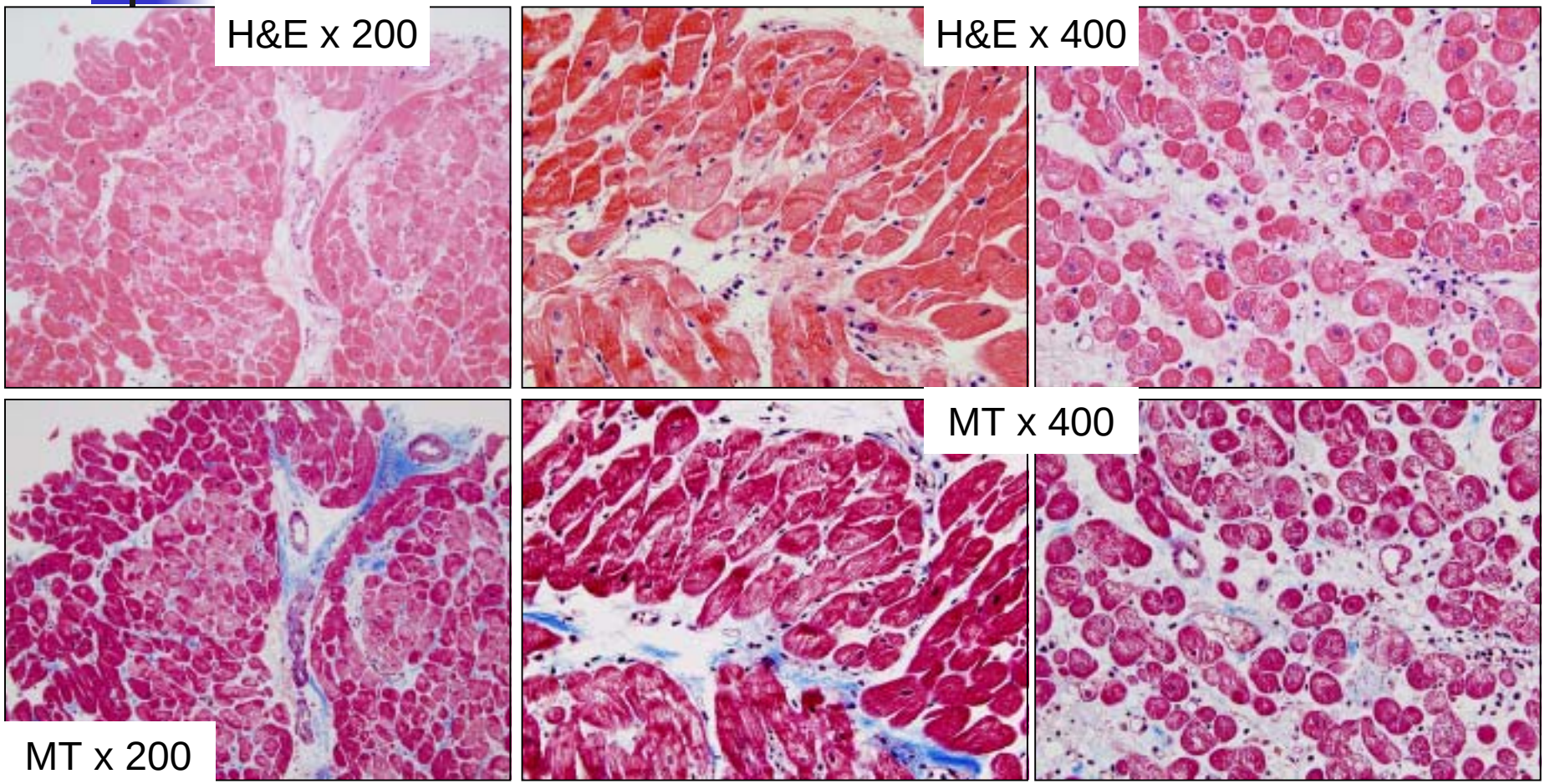
Case Summary – initial presentation

- A 15-year-old boy was admitted with anterior chest discomfort for three days at a university Hospital.
- One week earlier, he had had flu-like symptoms.
- On hospital day 2, ventricular tachycardia and complete RBBB developed. Shock and urine output decreased.
- CPR was done for 2 times and started hemodialysis.
- Echocardiography showed low EF (15-20%), moderate TR, MR and moderate pulmonary HT.
- He was transferred to SMA at hospital day 14.

Laboratory Findings - pancreatitis

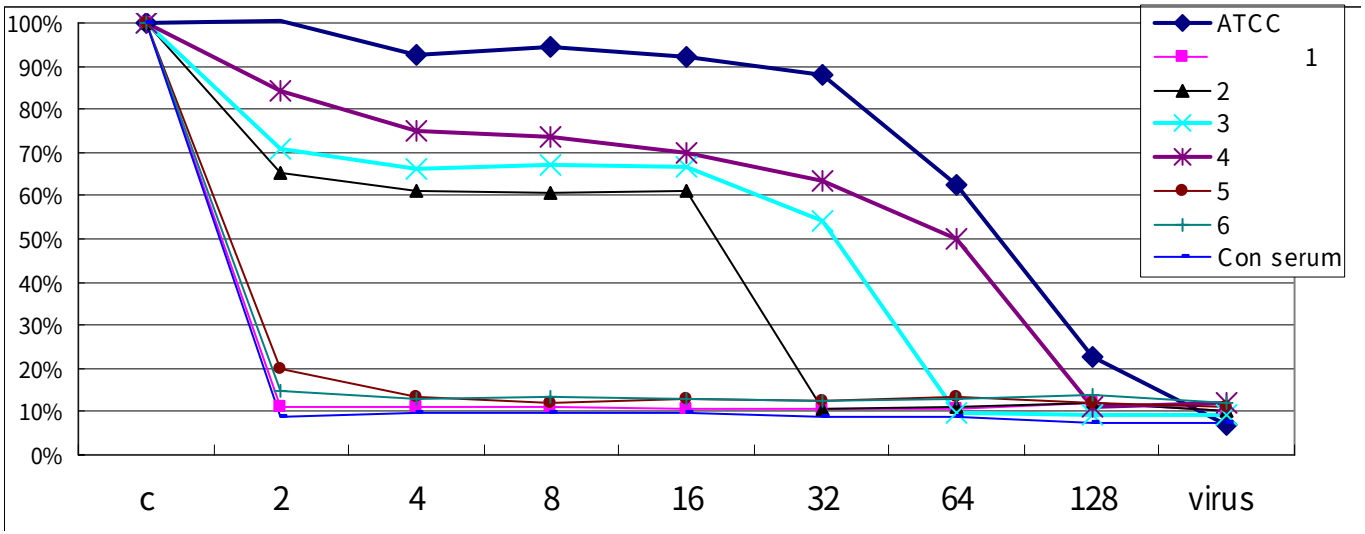
	01/30	02/8	2/16	03/16
	Day 1	Day 9	Day 17	OPD
LVID s/d	50/59	39/55		40/55
EF	22	45		55
Amylase / Lipase	159 / 938	164 / 739	131 /454	83 / 131
AST / ALT	16 / 102	24 /12	23 / 25	12 / 17
CK-MB	6.41	4.90		
NT-proBNP	35000	5805	1991	287.4

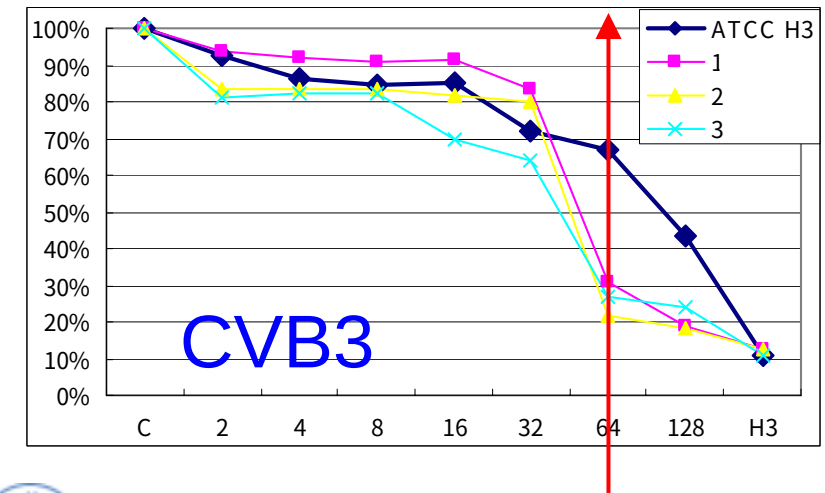
Endomyocardial biopsy findings done at hospital day 12 (+ 2 weeks)

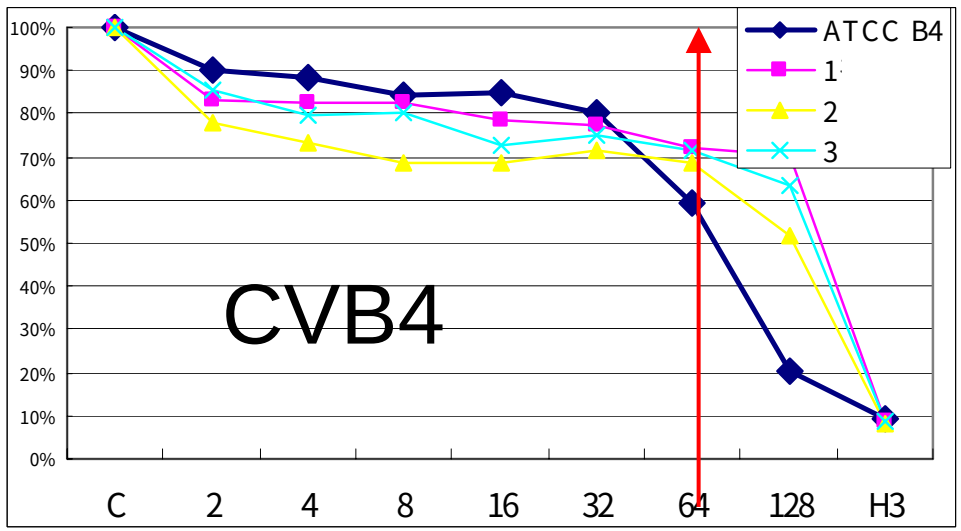


Focal mild hypertrophy of muscle cells and enlarged nuclei with focal microcalcifications. Few inflammatory cell infiltration. Minimal interstitial fibrosis. No evidence of viral inclusion

Neutralization test with serial sera

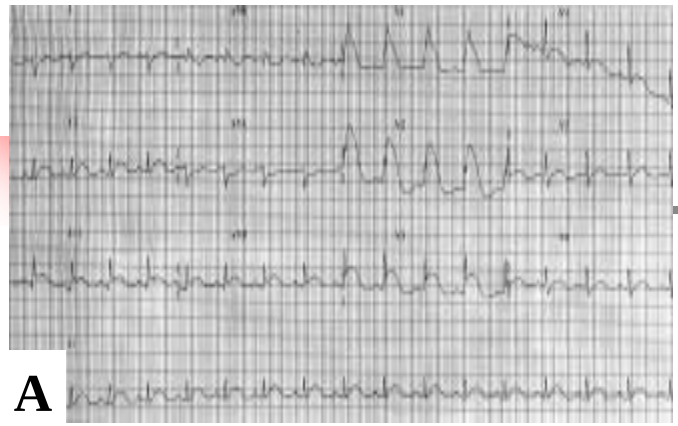


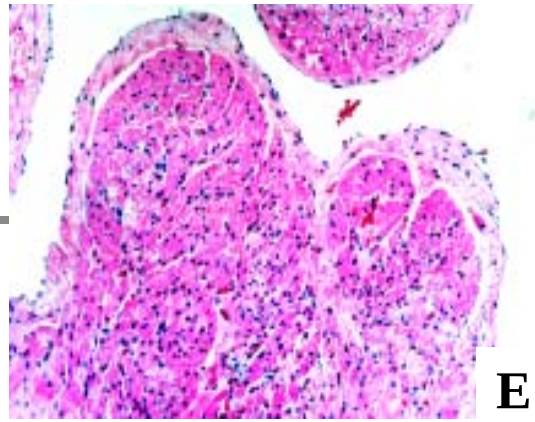


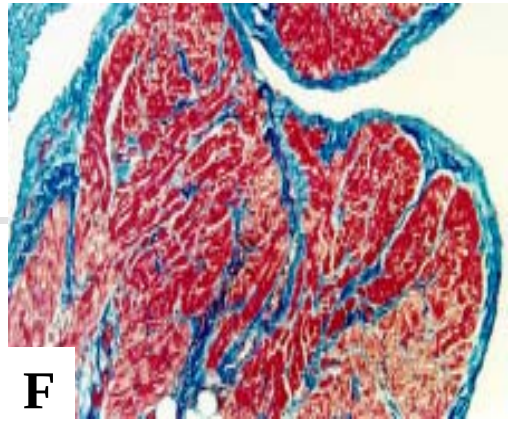


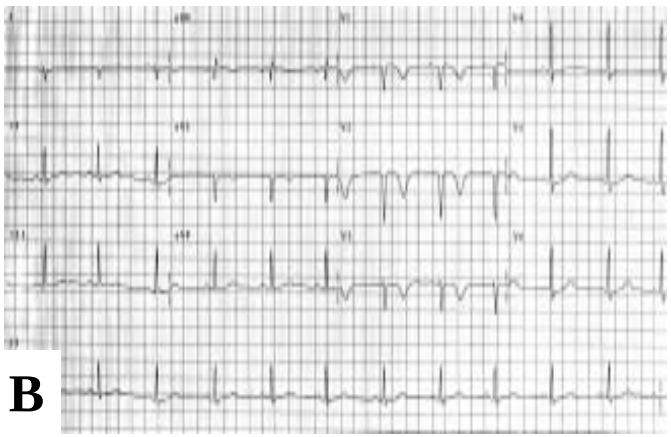
Fulminant Coxsackieviral B3 Myocarditis

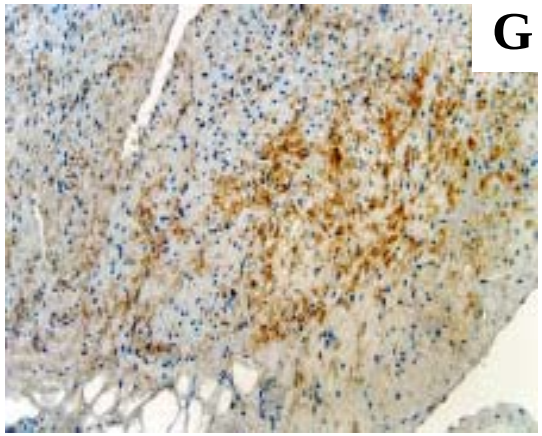
First Case Report; Identified CVB3 VP1 proteins
in the tissue biopsy from human Fulminant myocarditis
Female / 18

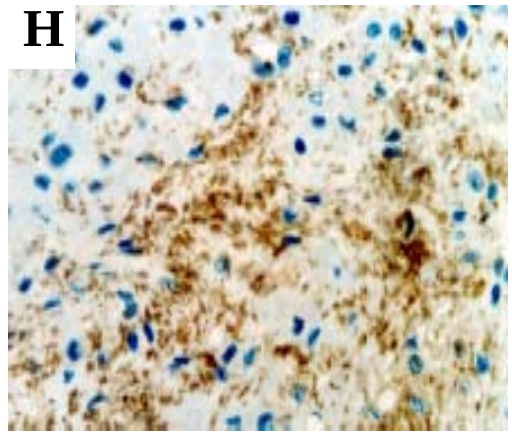


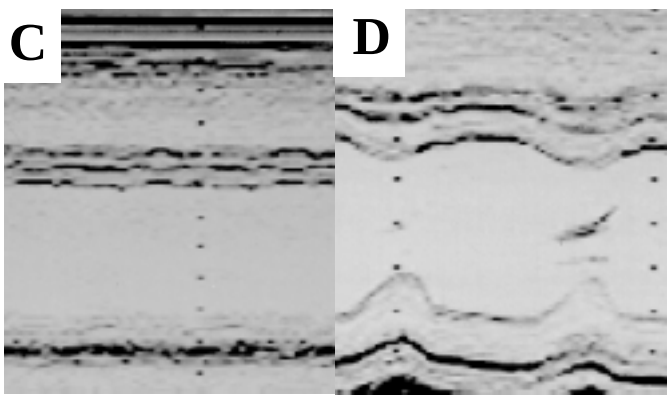












Case of fulminant Coxsackieviral myocarditis

A, C) EKG and Echo at ER

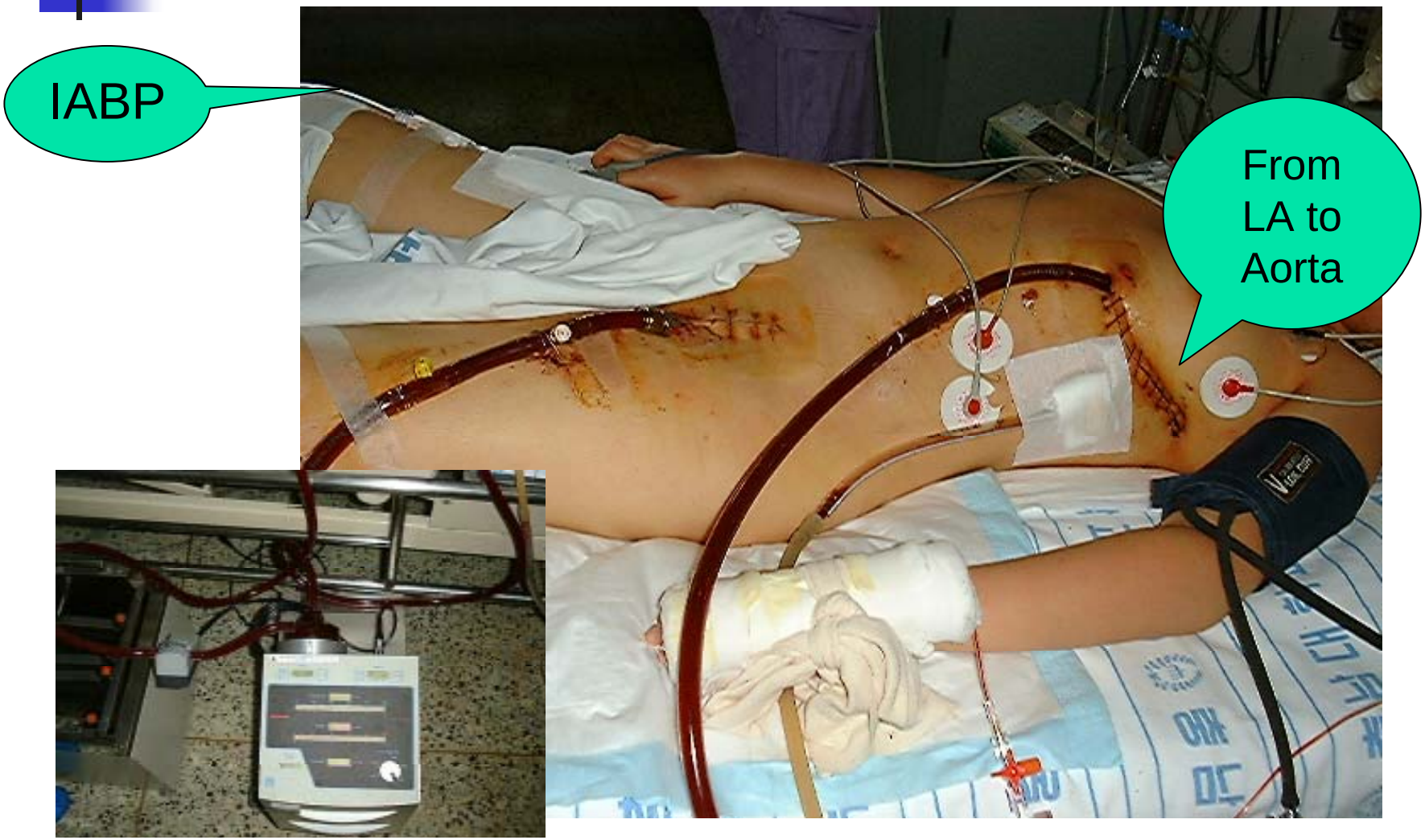
B, D) EKG and Echo at day 10

E) Left auricle (H& E stain, x200)

F) Left Auricle (Masson's Trichrome stain, x200)

G,H) Immunohistochemistry probed by anti-enteroviral VP1 Ab.(G; x100,H; x400)

Ventricular Assistant Device



Fulminant Myocarditis Treated with EBS

Myocarditis with Hepatitis

Male / 14

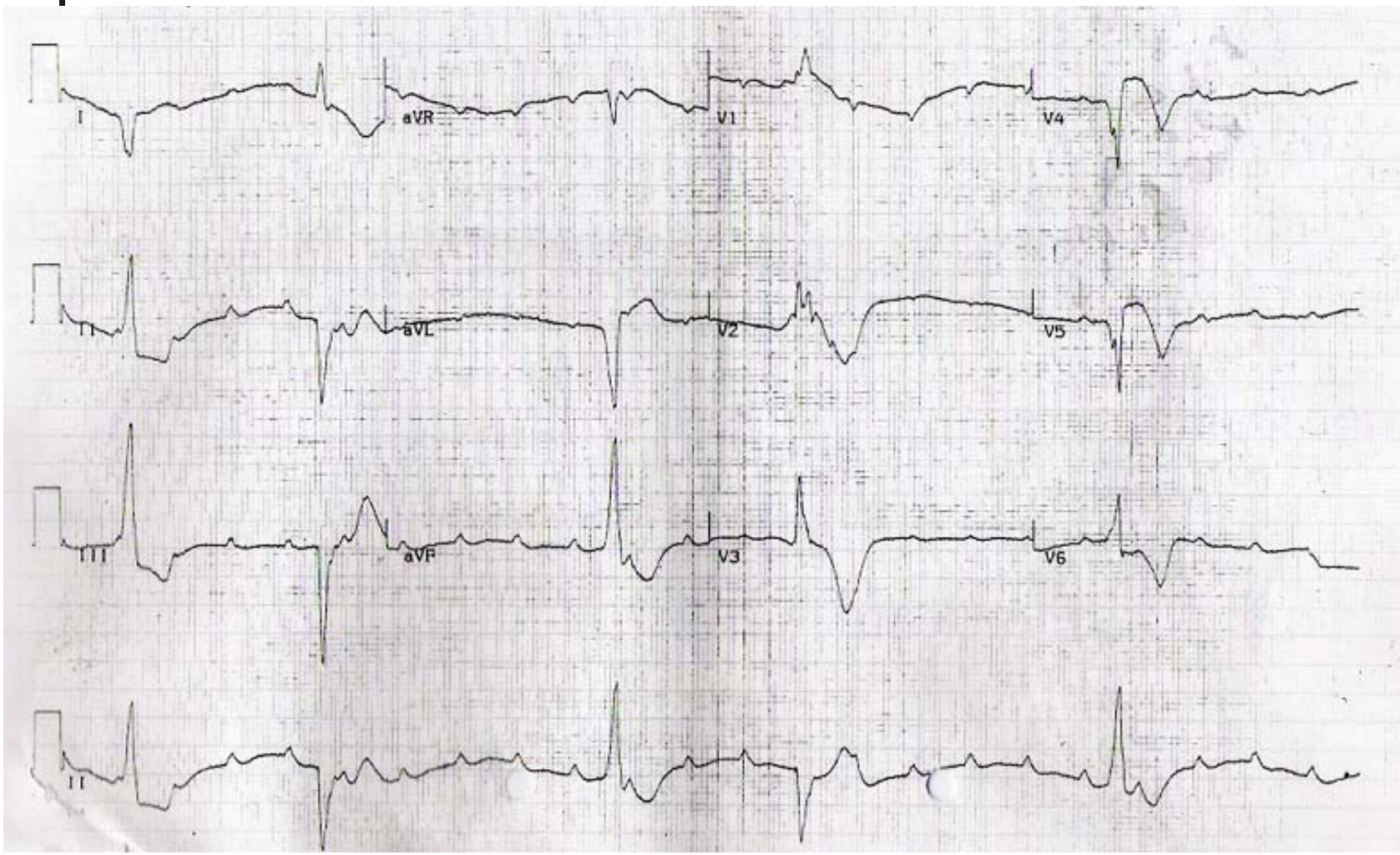
Case Summary – initial presentation

- 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).

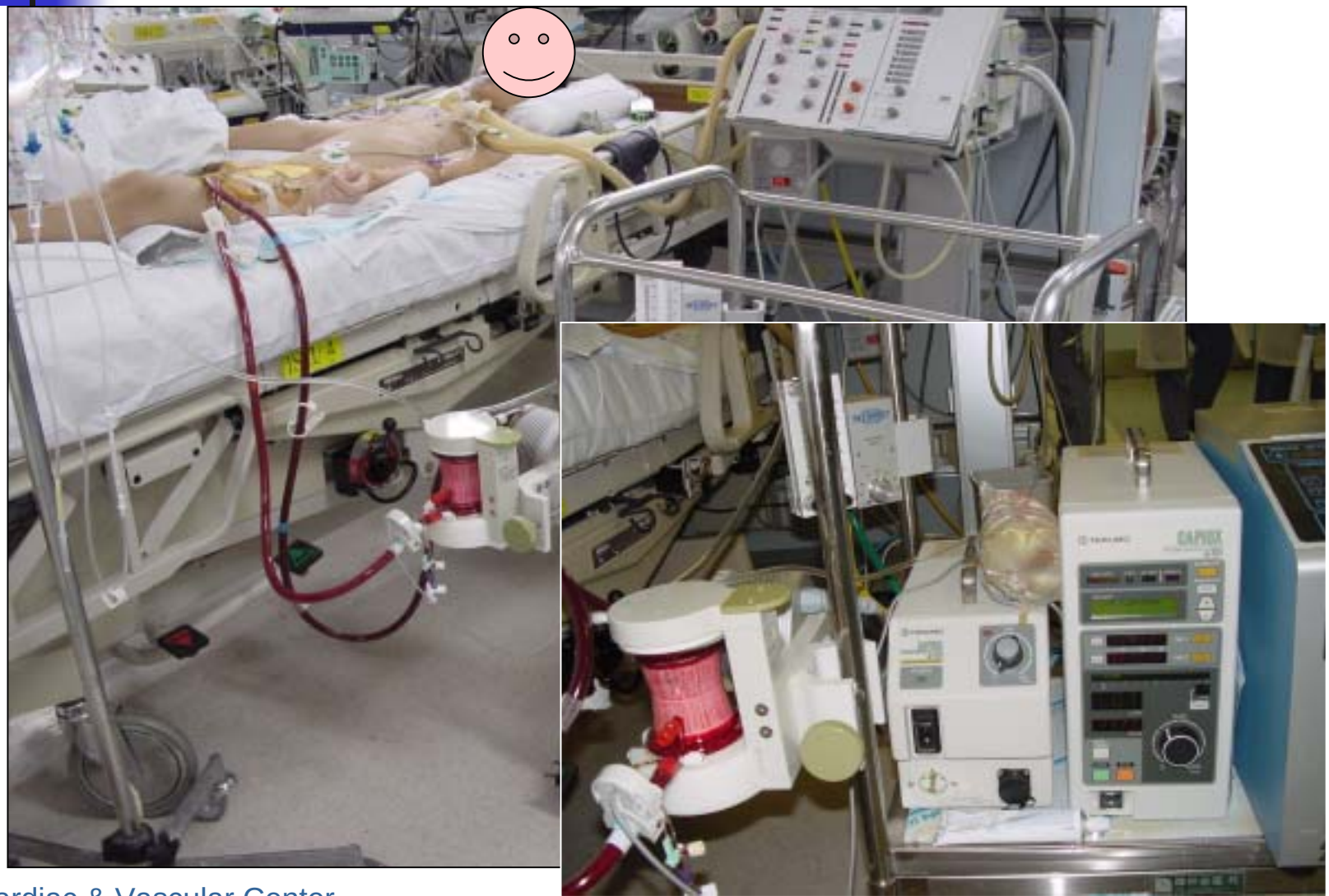
Case Summary – EKG



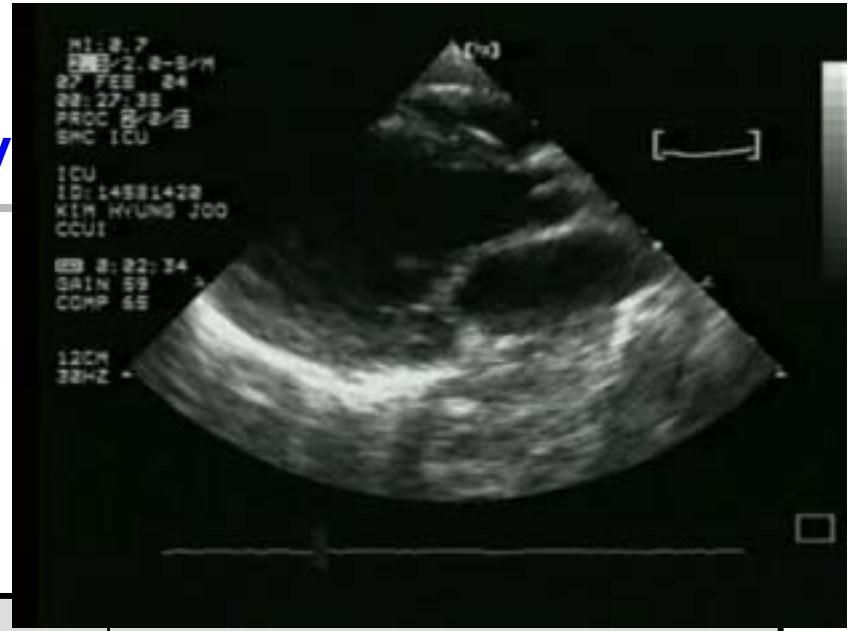
Case Summary – Hospital course

- 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.
- 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.

EBS continuous flow



Echocardiography

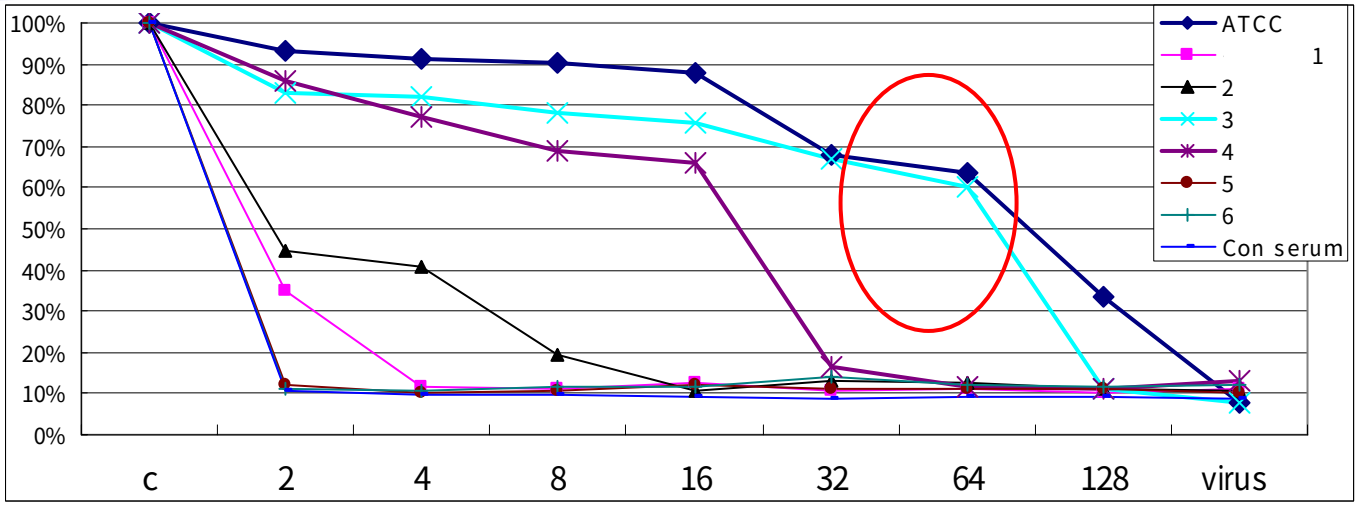


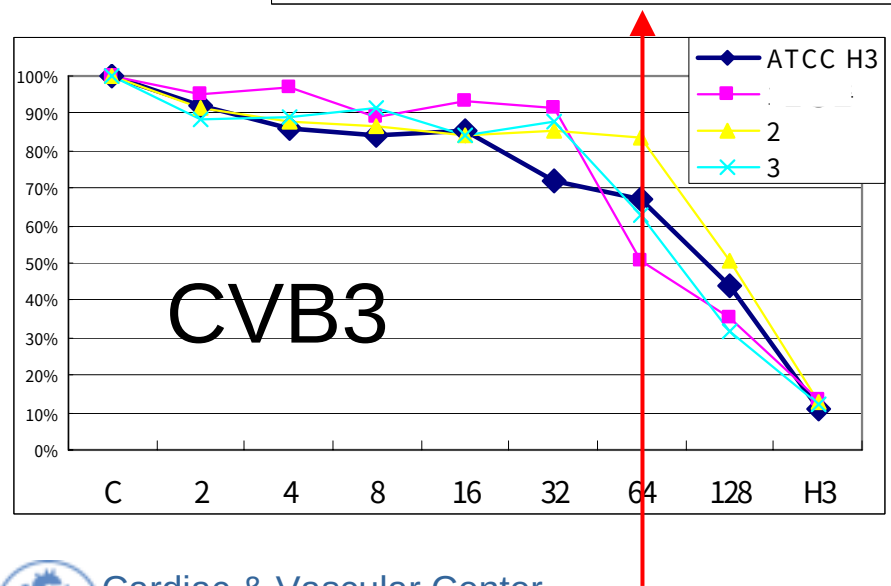
Date	Hosp day	LVID s/d (mm)	EF(%)	Other findings
Feb. 06 1 pm	0	Size were normal range	60	Mild MR on color Doppler Global hypokinesia (especially anterior & IVS)
Feb. 07 6 pm	1		30	
Feb. 07 10 pm	1		20	
Feb. 13	7	29/42	53	Hypokinesia (IVS & aneriorior wall) - pericardial effusion
Feb. 23	16	32/48	55.5	Normal Wall motion

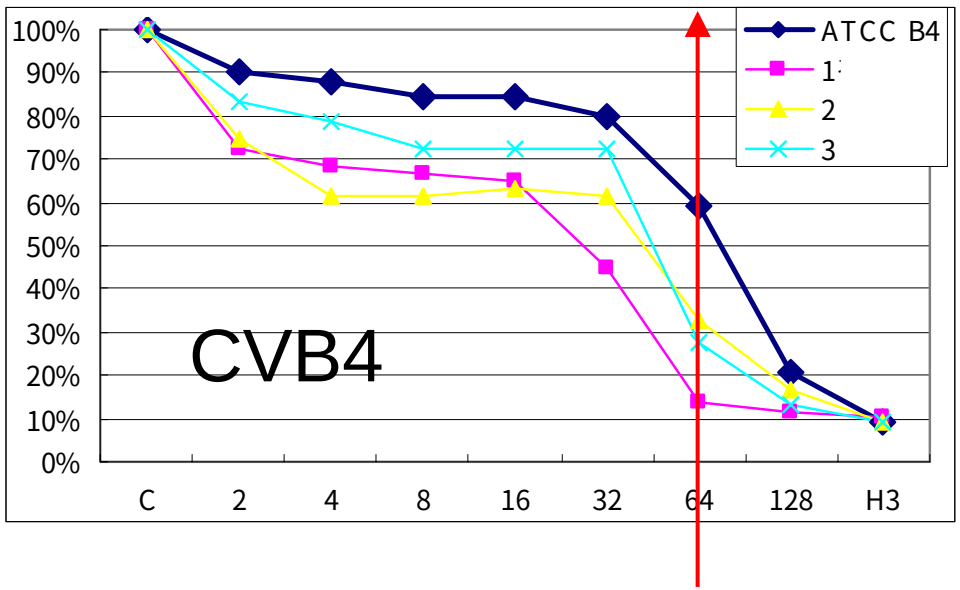
Laboratory Findings - hepatitis

	02/07	02/14	02/23	03/08
	Day 1	Day 7	Day 16	OPD
LVID s/d	-	29/42	32/48	-
EF	60→20	53	55.5	-
AST/ ALT	5730 / 3500	110 / 742	29 / 86	16 / 14
CK-MB	22.43	3.56		0.36
NT-proBNP	-	2093	1109	272.6

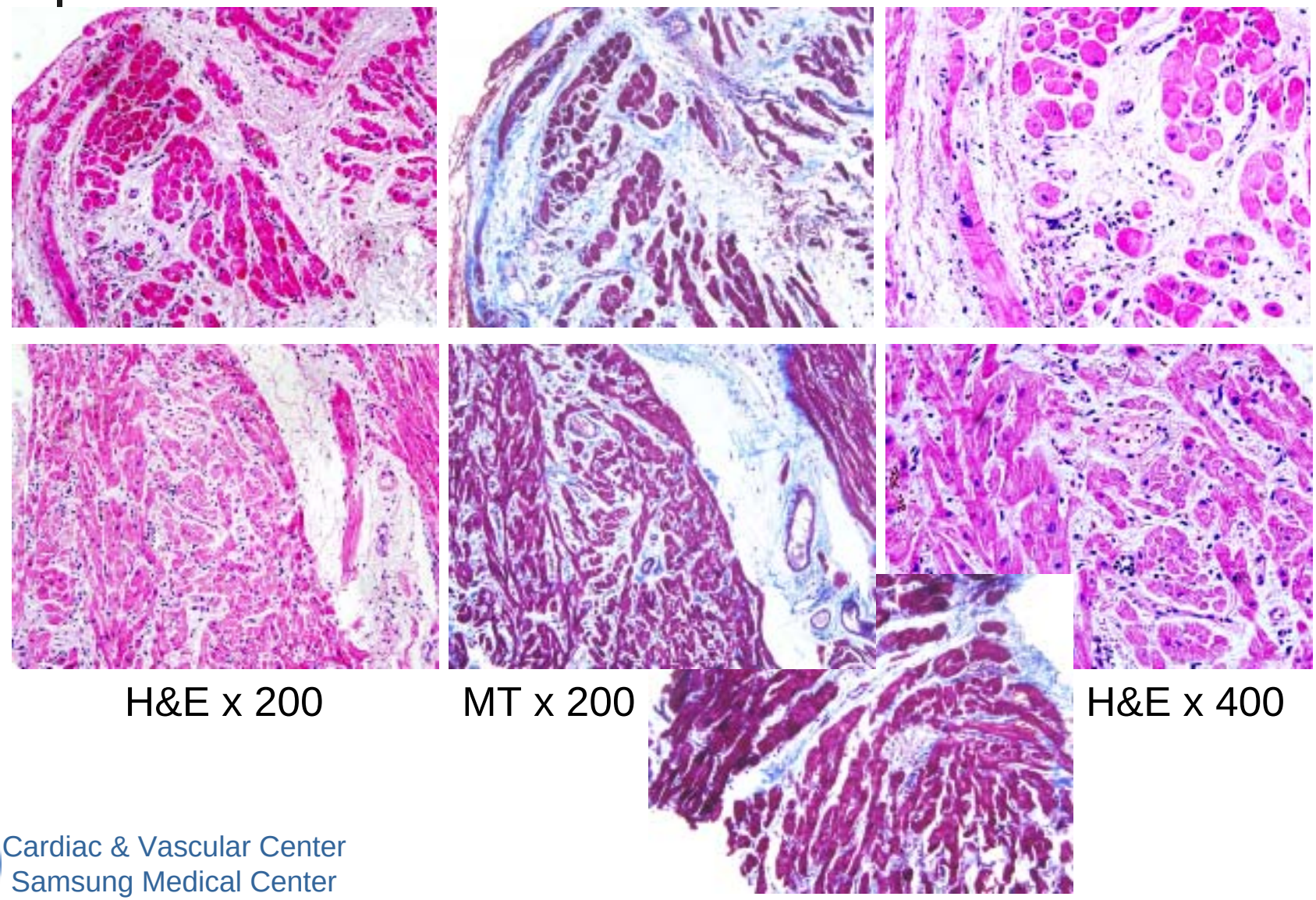
Neutralization test with serial sera







Endomyocardial biopsy findings done at hospital day 10 (H&E, MT staining)



H&E x 200 MT x 200 H&E x 400

Fulminant Coxsackieviral B4 Infection

Dystrophin cleaved in infected myocytes in human tissue

VAD applied Female / 57

Case Summary – initial presentation

- A 57-year-old woman was admitted with anterior chest pain for a day.
- Three days earlier, she had had flu-like symptoms.
- The patient had a positive troponin I (49.97 ng/ml) result and an elevated level of creatinine phosphokinase-MB (98.27 ng/ml)
- A coronary angiogram showed no thrombus and no clinically significant stenosis.

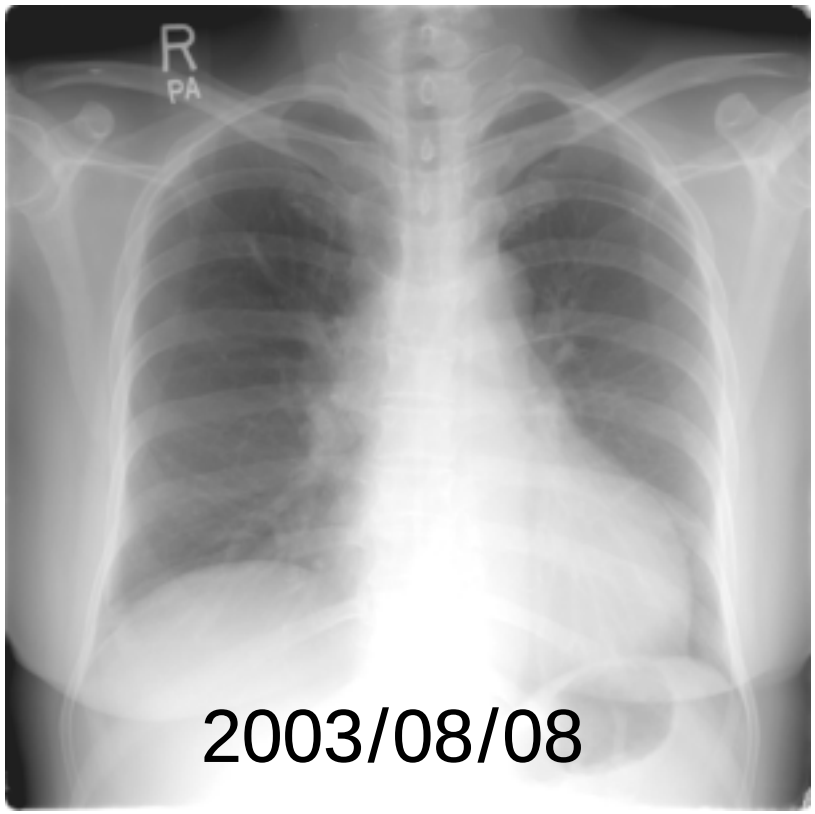
Case Summary – Hospital course

- Eight hours after admission, shock and pulmonary edema developed.
- Her ejection fraction became less than 15 percent from over 60% at admission.
- Despite the use of an intra-aortic balloon pump for four hours, her shock and pulmonary edema progressed, and recurrent ventricular tachycardia occurred.
- Mechanical circulatory support was started with a left ventricular assist device. (550 BIO-Console, Medtronics, Bio-Medicus, ECMO).

Case Summary – Hospital course

- After 96 hours of support with the left ventricular assist device (ECMO), left-ventricular-wall motion was restored and her ejection fraction was 56 percent on echocardiography.
- ECMO was removed after 5 days. She was discharged after 35 days without any symptoms of heart failure.

Chest PA



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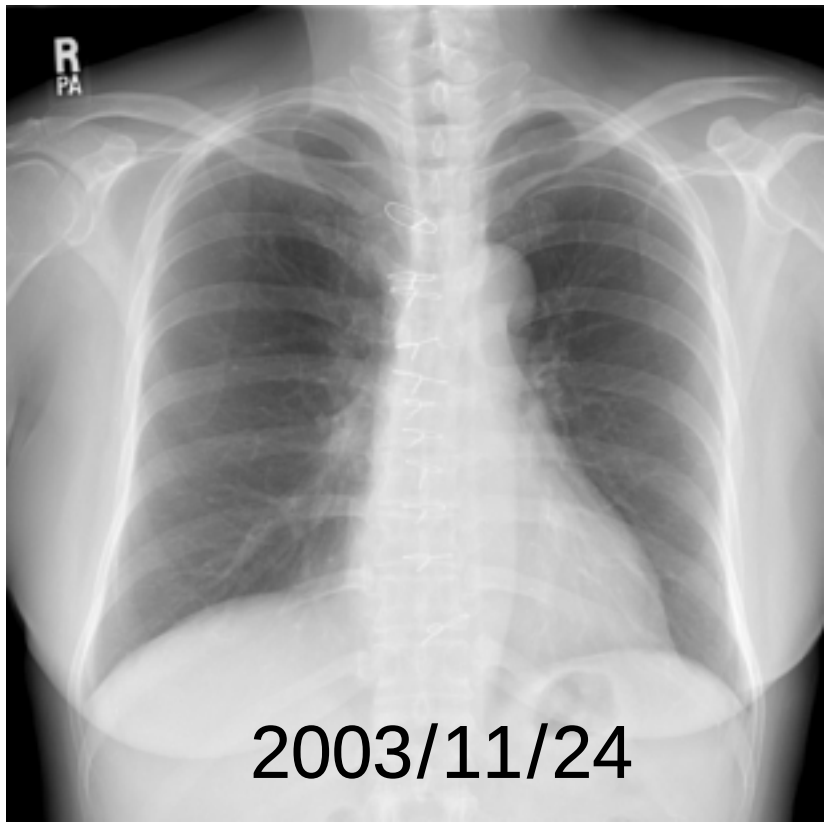
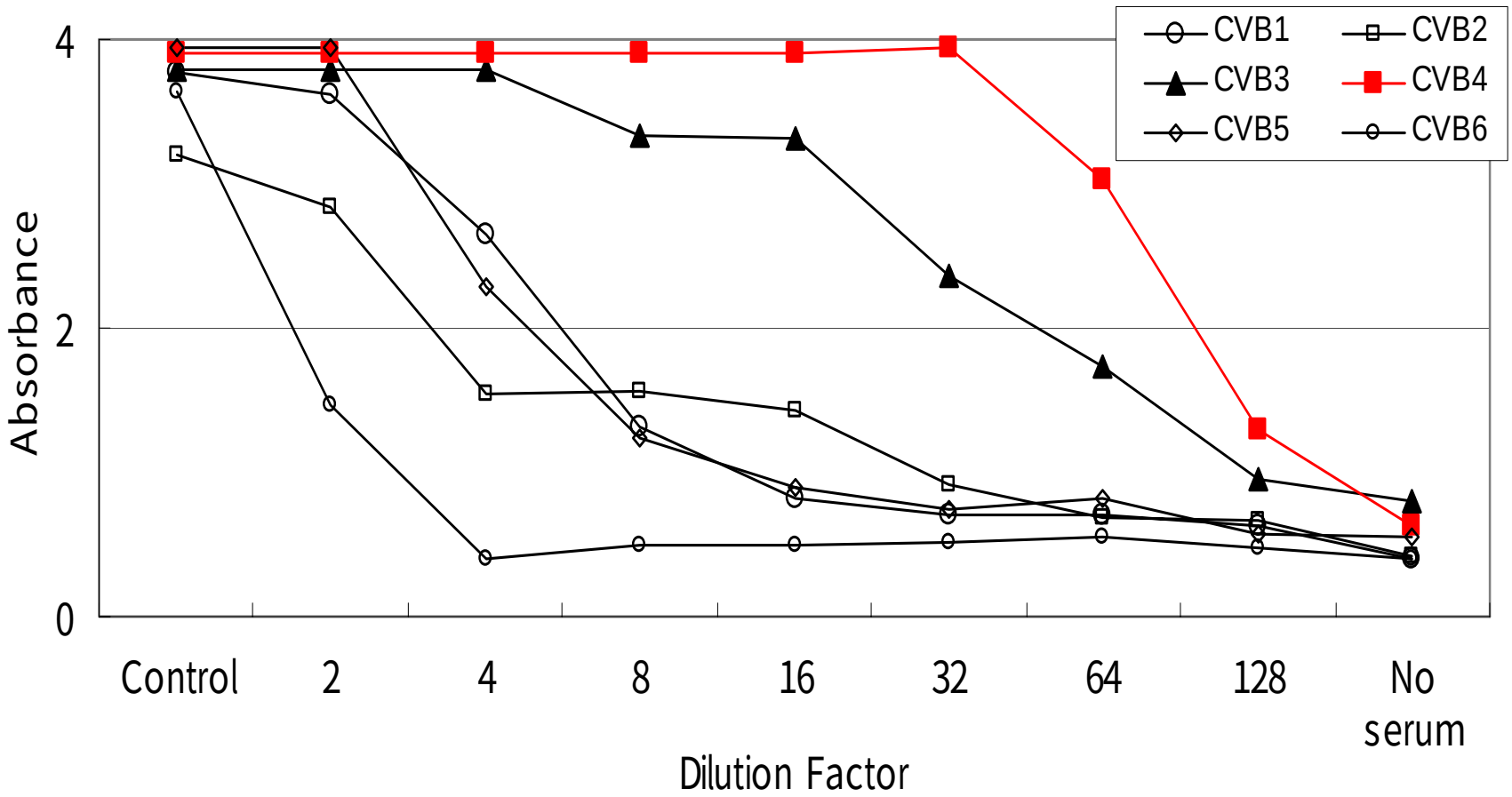
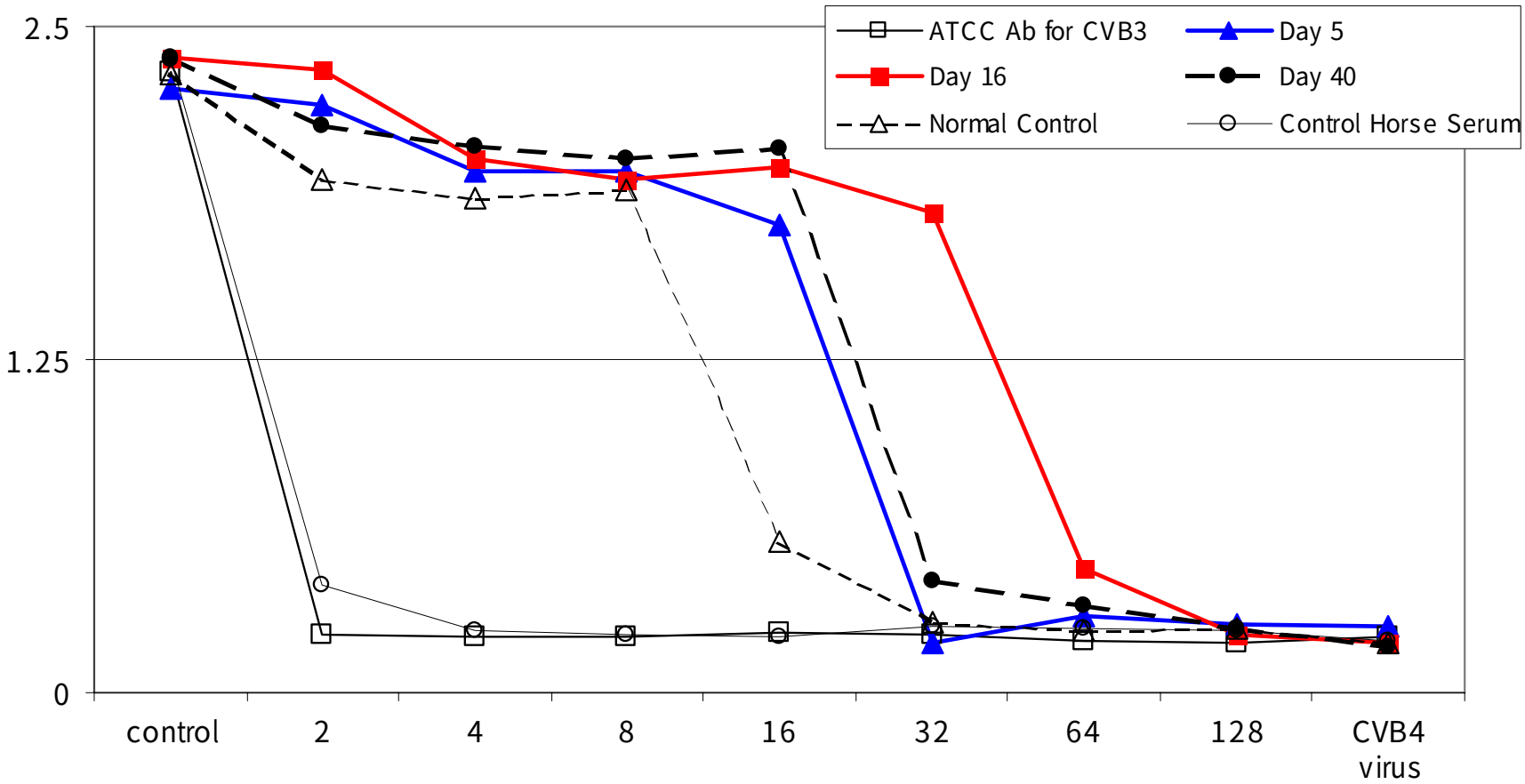


2003/11/24

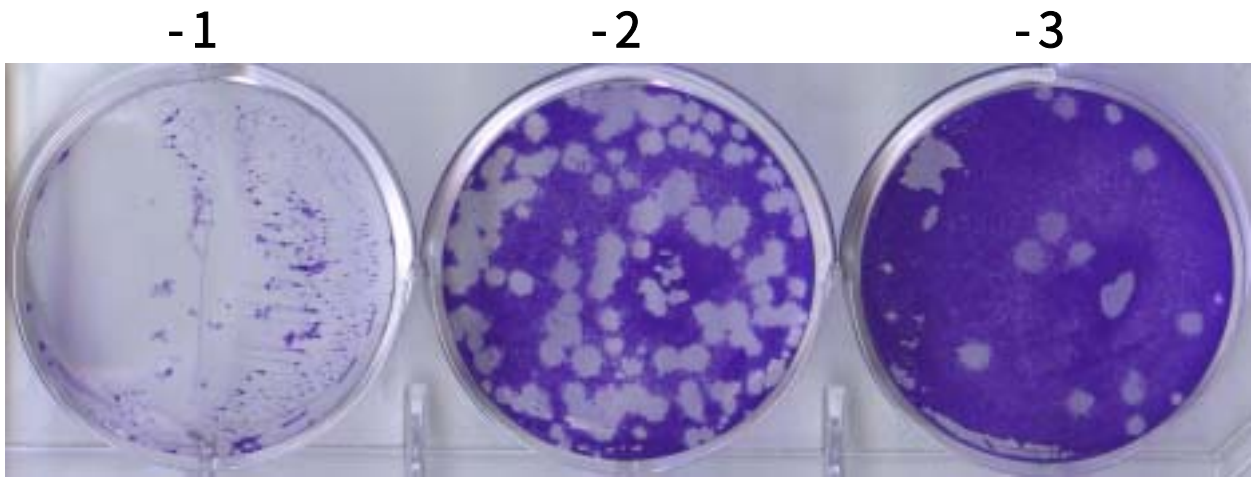
Neutralization Test for all CVB Serotypes with day 15 serum



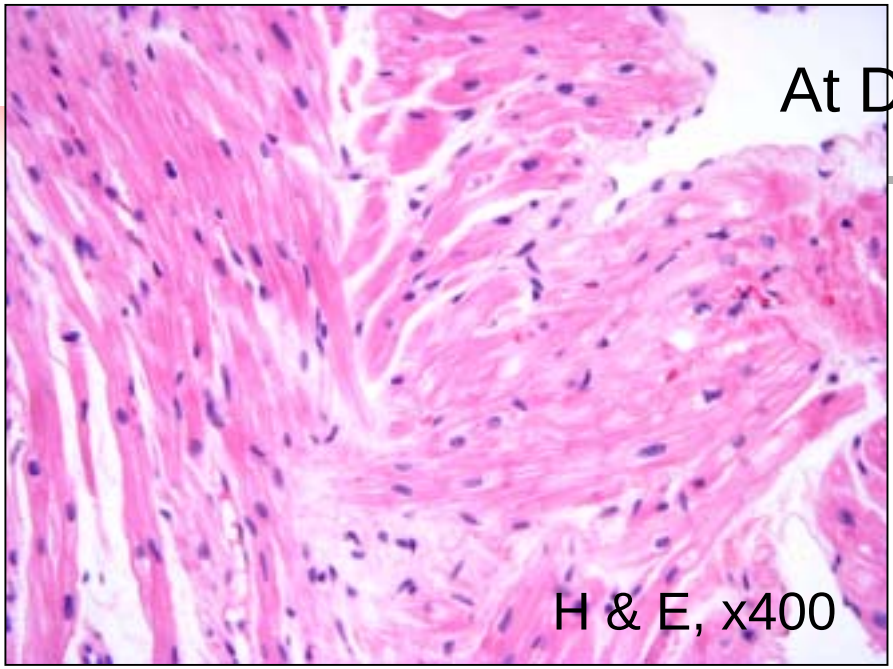
Neutralization Test for CVB4

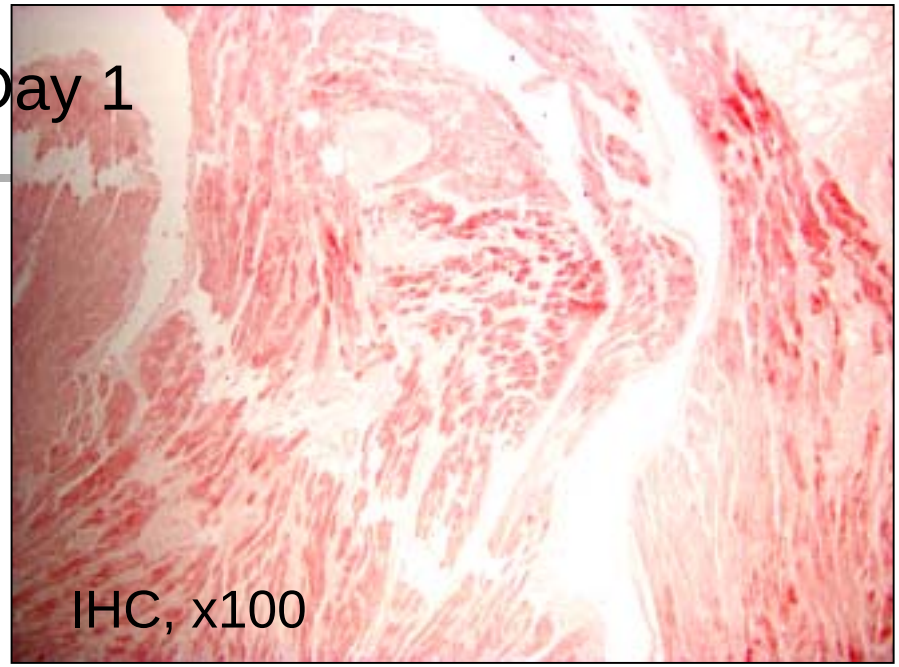


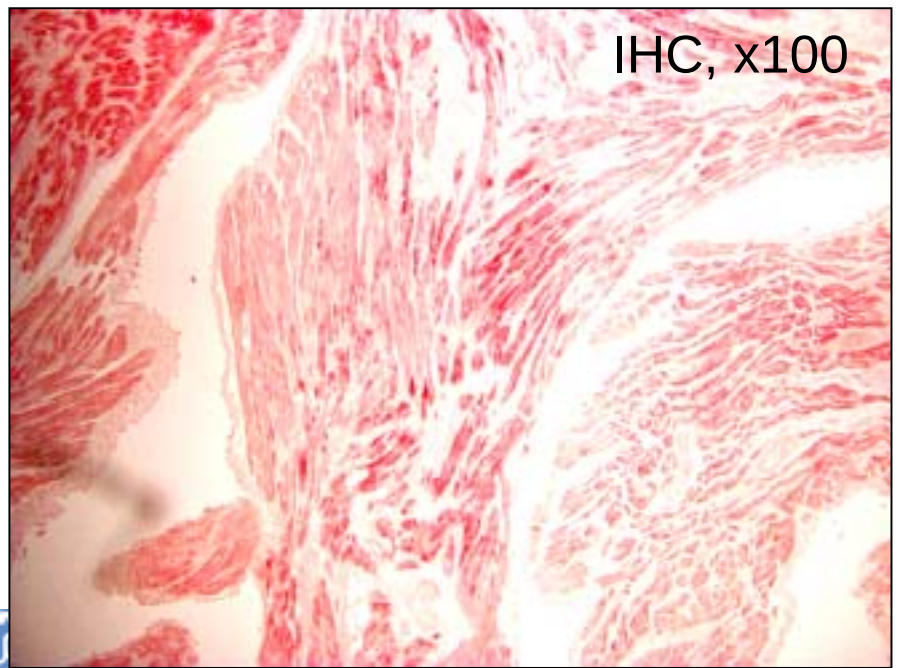
PFU assay from tissue on HeLa

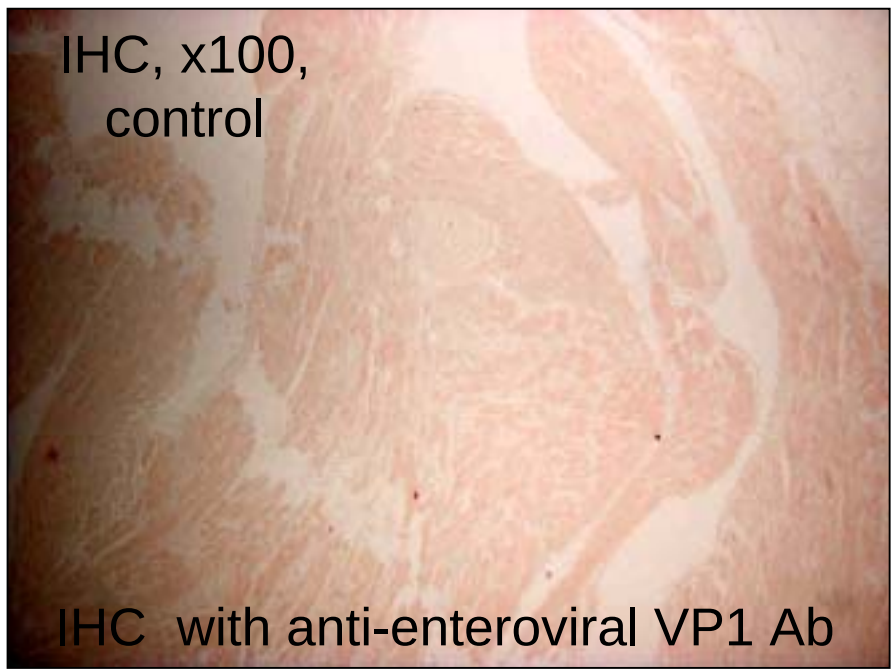


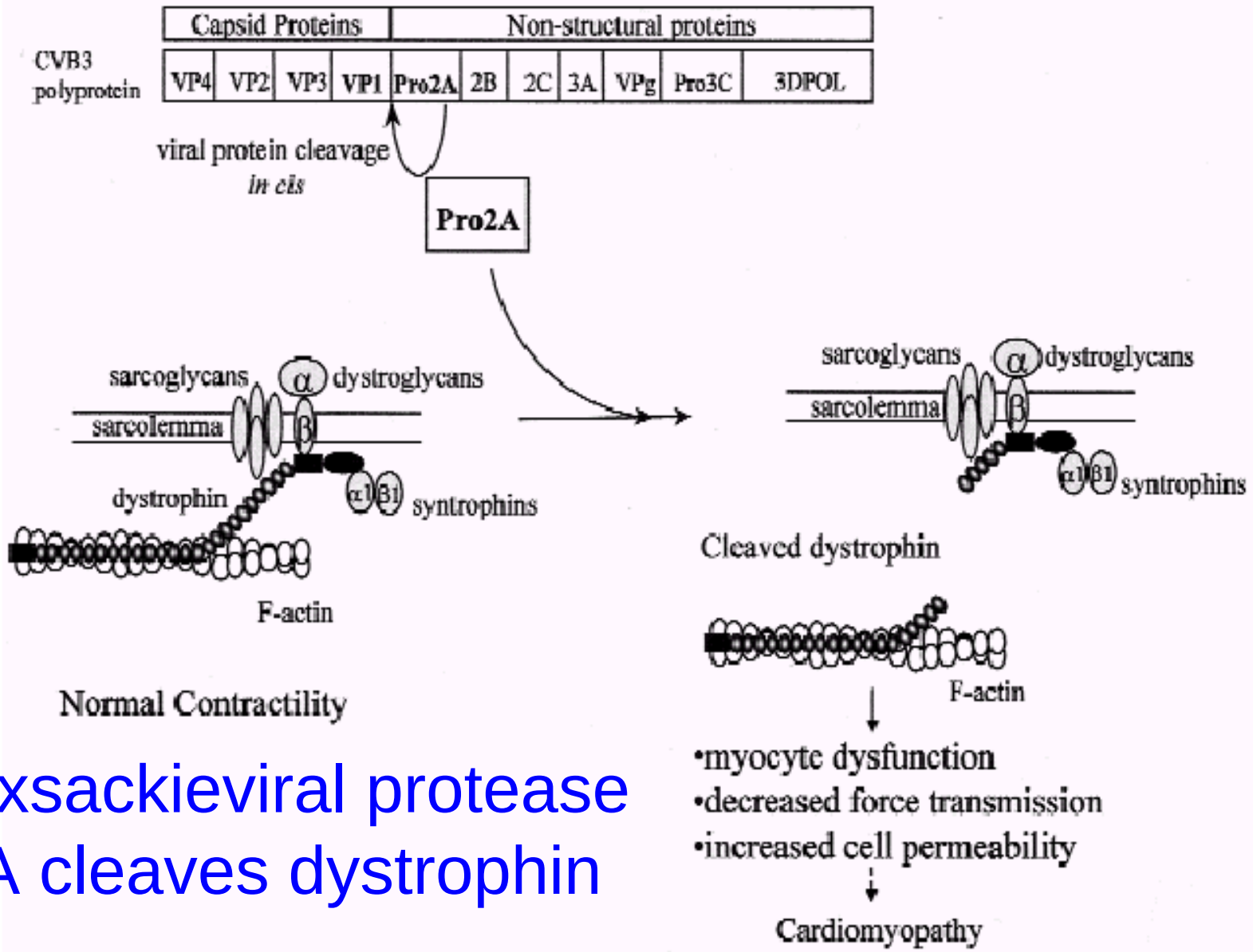
Viable virus was isolated from frozen left atrial tissue at day 1.
The final concentration of virus was 1.5 x 10^4 PFU/ml


At Day 1
H & E, x400


IHC, x100


IHC, x100

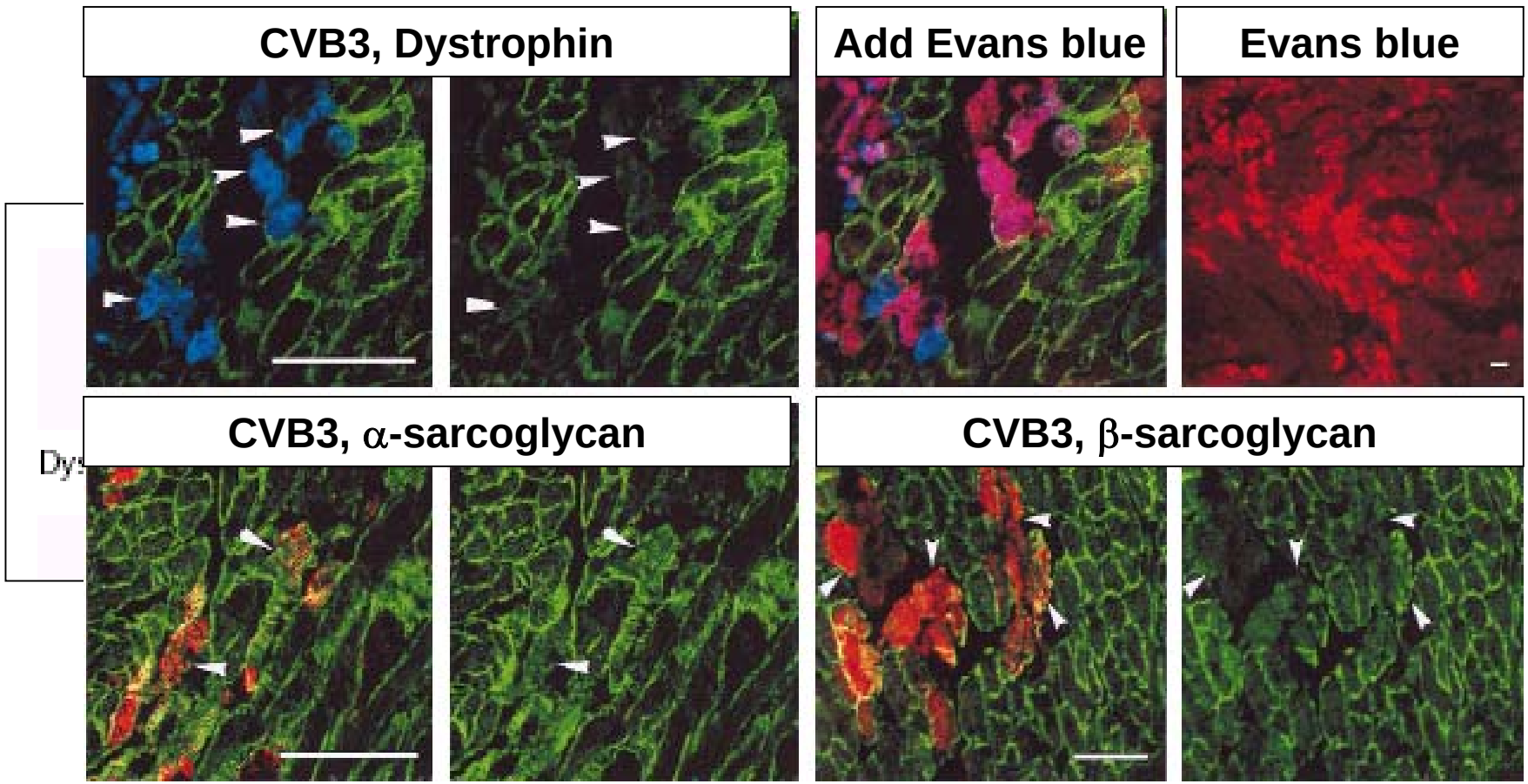

IHC, x100,
control
IHC with anti-enteroviral VP1 Ab



Coxsackieviral protease 2A cleaves dystrophin

Badorff, Nat Med 5:320, 1999

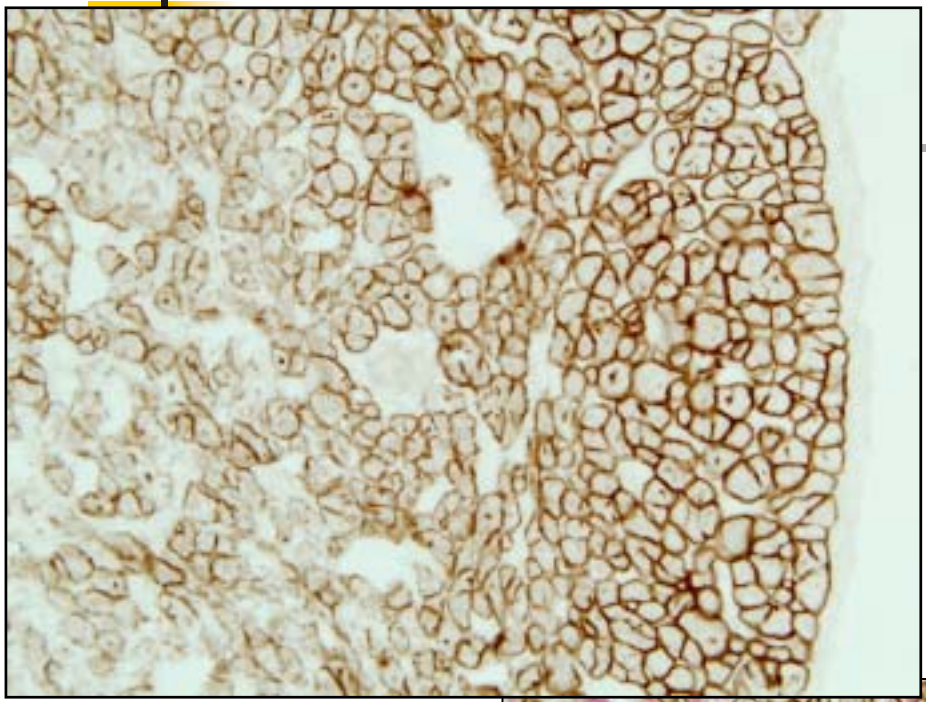
CVB3 protease 2A cleaves dystrophin-Sarcoglycan Complexes

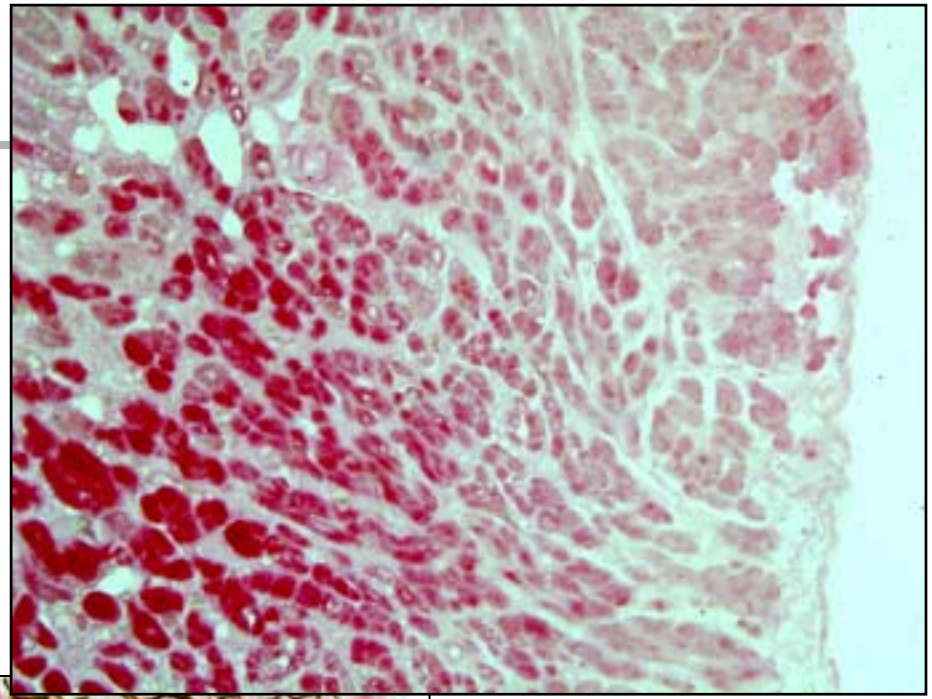


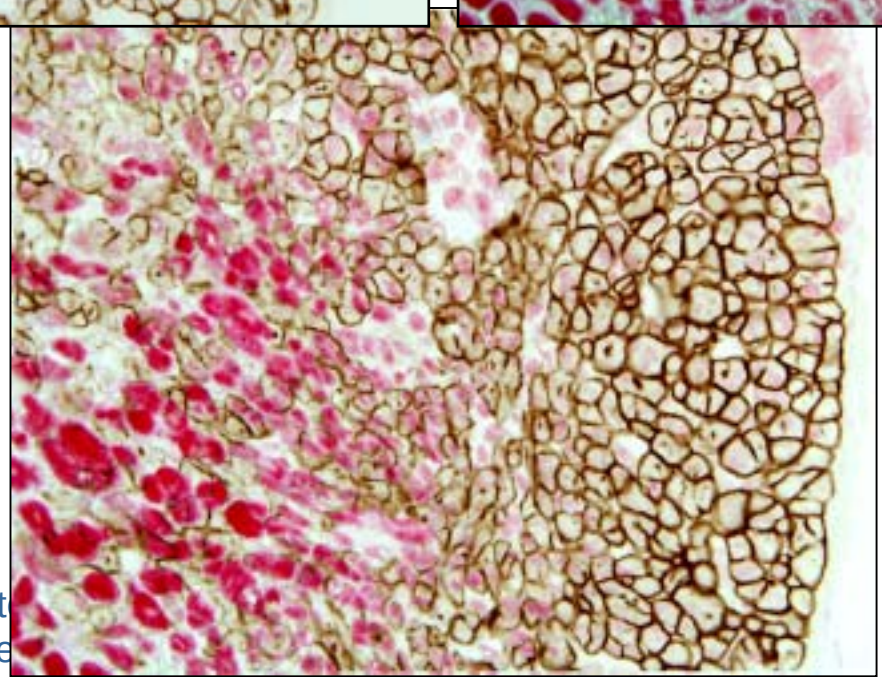
Badorff, Nat Med 5:320, 1999

Anti-dystrophin-DAB at day1

Anti-enteroviral VP1-alkaline P' at day 1







x 200

Merged

Therapeutic Guideline of Fulminant Myocarditis

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) ——

52 patients for 3 years

(Apr. 1997 – Mar. 2000)

Age (years)	*47.9±16.0*
M/F	*26/26*
Etiology	
Idiopathic	*34 (65.4%)*
Viral	*14 (26.9%)*
Eosinophilic	*2 (3.8%)*
Giant cell	*2 (3.8%)*
Definitive diagnosis	
Endomyocardial biopsy	*43*
Autopsy	*10*

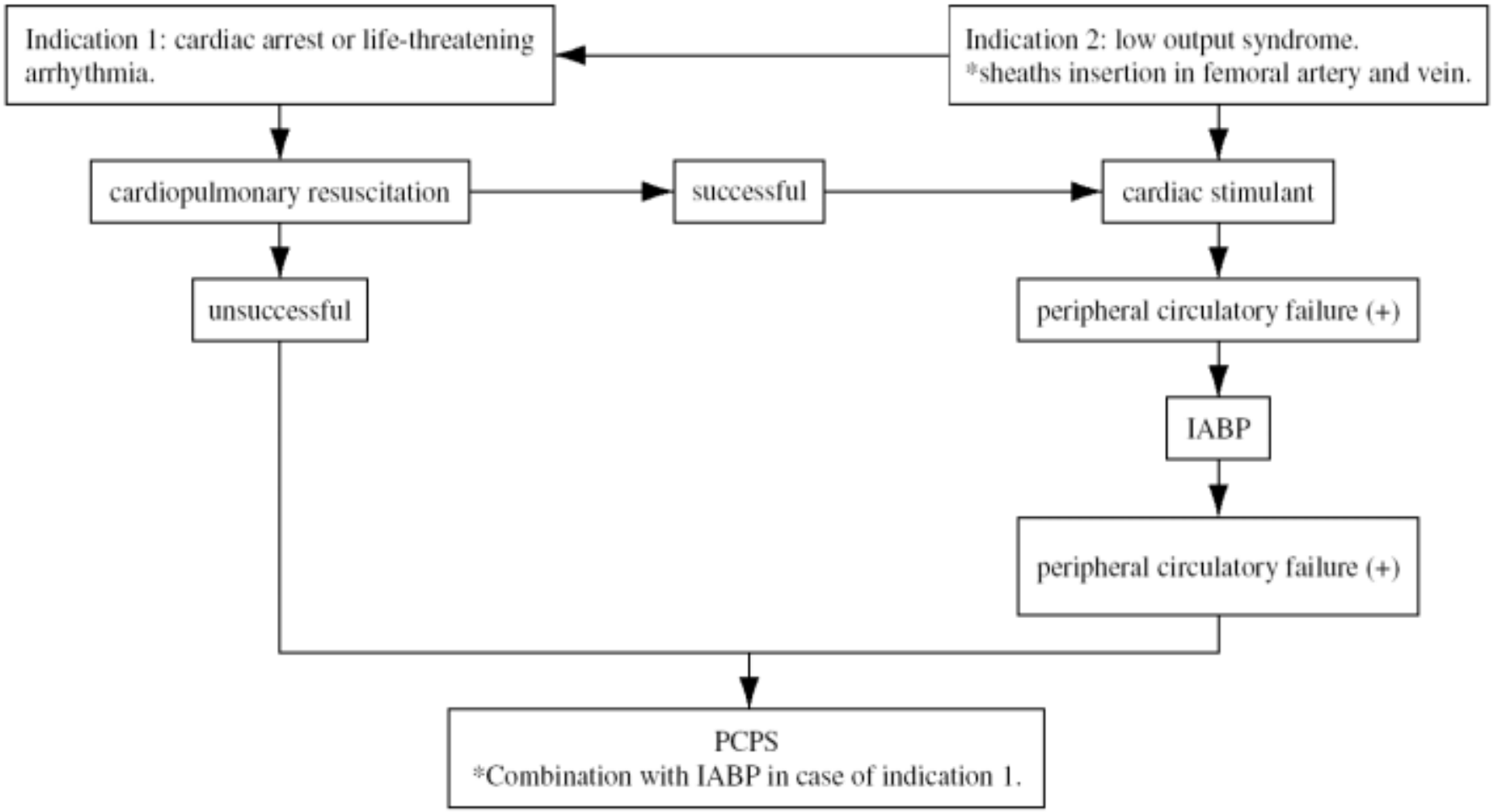
Circ J 2002;66:133

Initial and Cardiac Symptoms

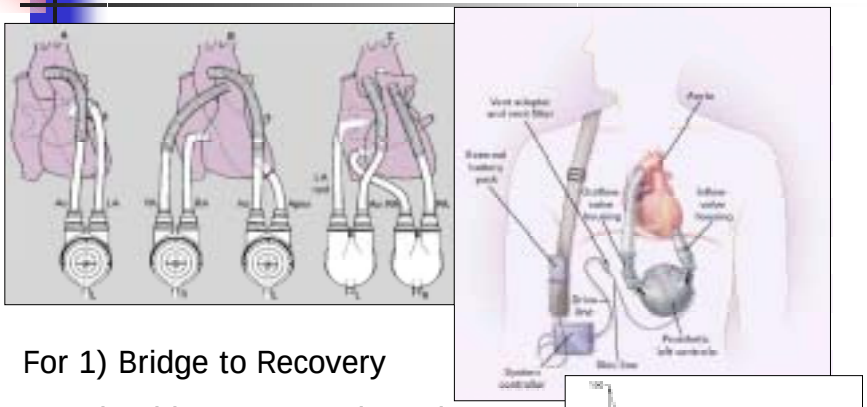
Initial symptoms	(n=52)
Increased fever	32 (61.5%)
General fatigue	12 (23.1%)
Cough	11 (21.2%)
Nausea/vomiting	8 (15.4%)
Arthralgia/myalgia	6 (11.5%)
Headache	6 (11.5%)
Chest pain	3 (5.8%)
Syncope/cramp	3 (5.8%)
Diarrhea	3 (5.8%)
Appetite loss	3 (5.8%)
Pharyngalgia	2 (3.8%)
Palpitation	2 (3.8%)
Abdominal pain	1 (1.9%)
Epigastralgia	1 (1.9%)
Back pain	1 (1.9%)
Dyspnea	1 (1.9%)
Chest discomfort	1 (1.9%)
Common cold	1 (1.9%)

Cardinal symptoms	(n=51)
Dyspnea	20 (39.2%)
Shock	15 (29.4%)
Nausea/vomiting	11 (21.6%)
Increased fever	11 (21.6%)
Syncope/cramp	10 (19.6%)
Chest pain	9 (17.6%)
General fatigue	6 (11.8%)
Abdominal pain	3 (5.9%)
Diarrhea	2 (3.9%)
Palpitation	2 (3.9%)
Coughing	1 (2.0%)
Cyanosis	1 (2.0%)
Headache	1 (2.0%)
Cardiopulmonary arrest	1 (2.0%)
Epigastralgia	1 (2.0%)
Back pain	1 (2.0%)

Guidelines of PCPS for acute fulminate myocarditis (1)



Ventricular Assistant Device

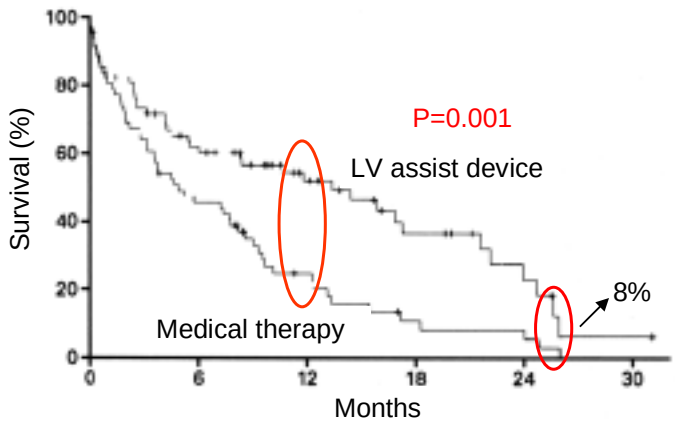


For 1) Bridge to Recovery

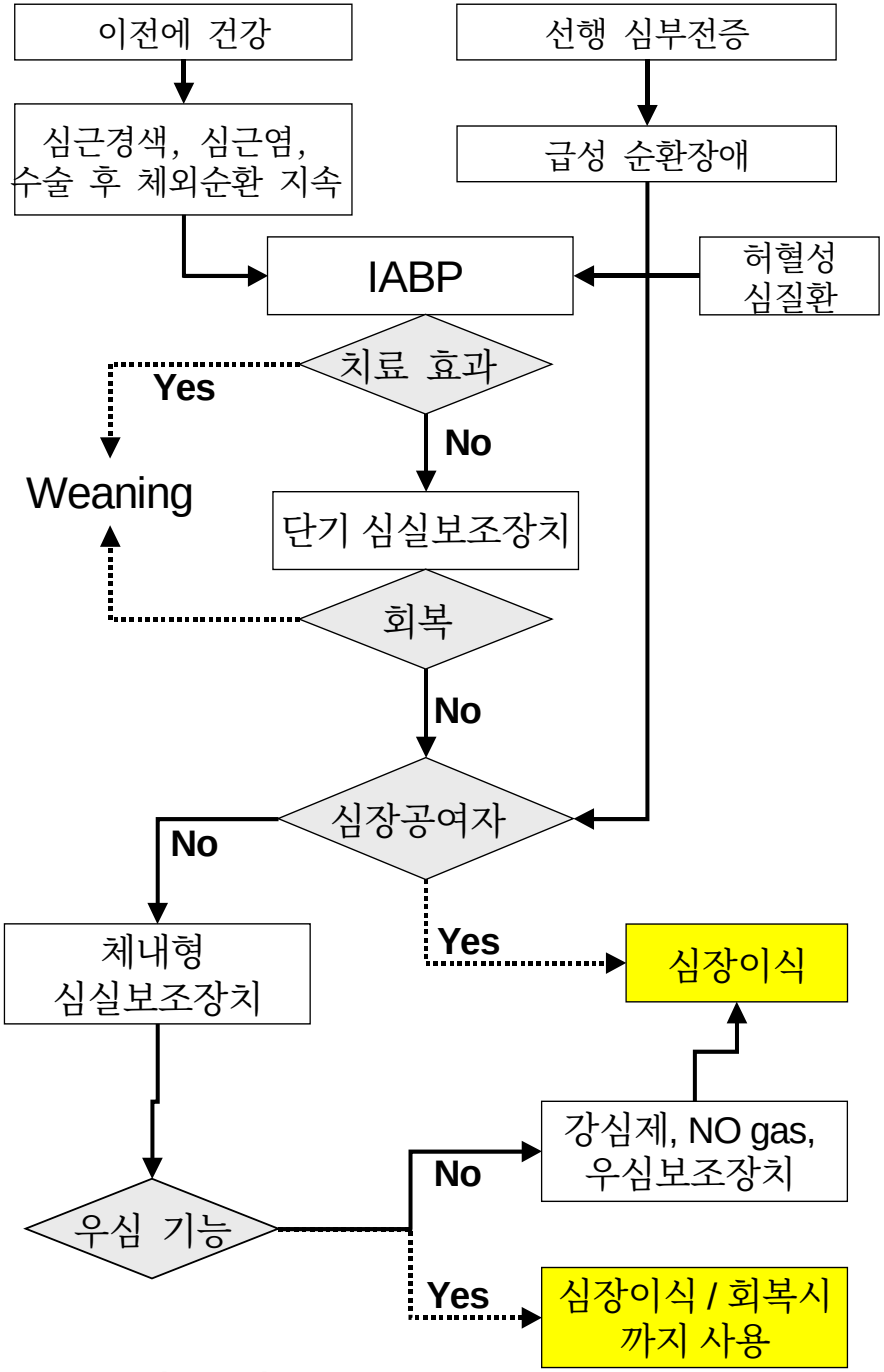
2) Bridge to Transplantation

REMATCH, NEJM 2001;345:1435

REMATCH study

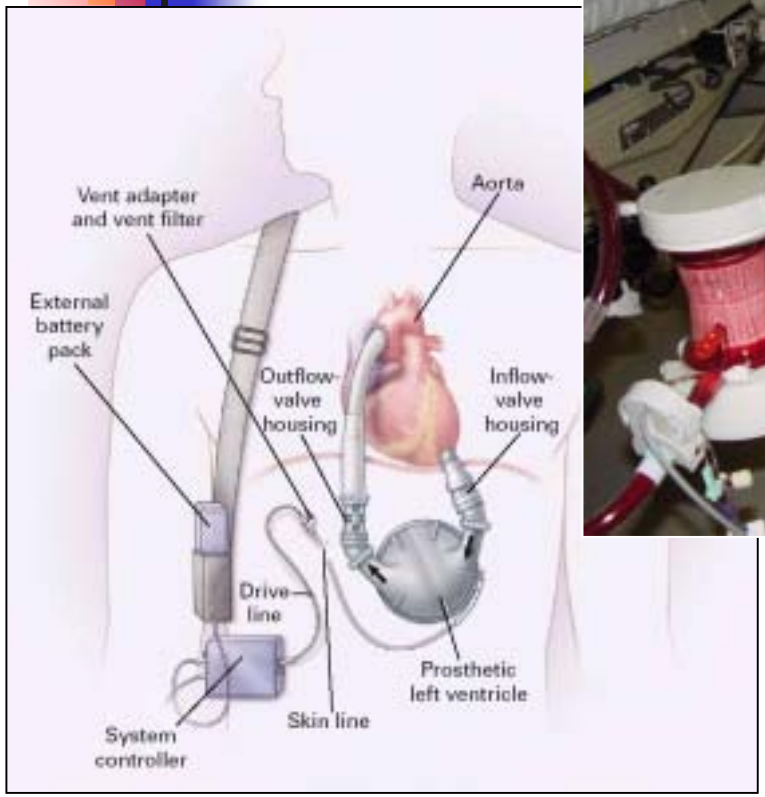


No. at Risk						
LV assist device	68	38	22	11	5	1
Medical therapy	61	27	11	4	3	0

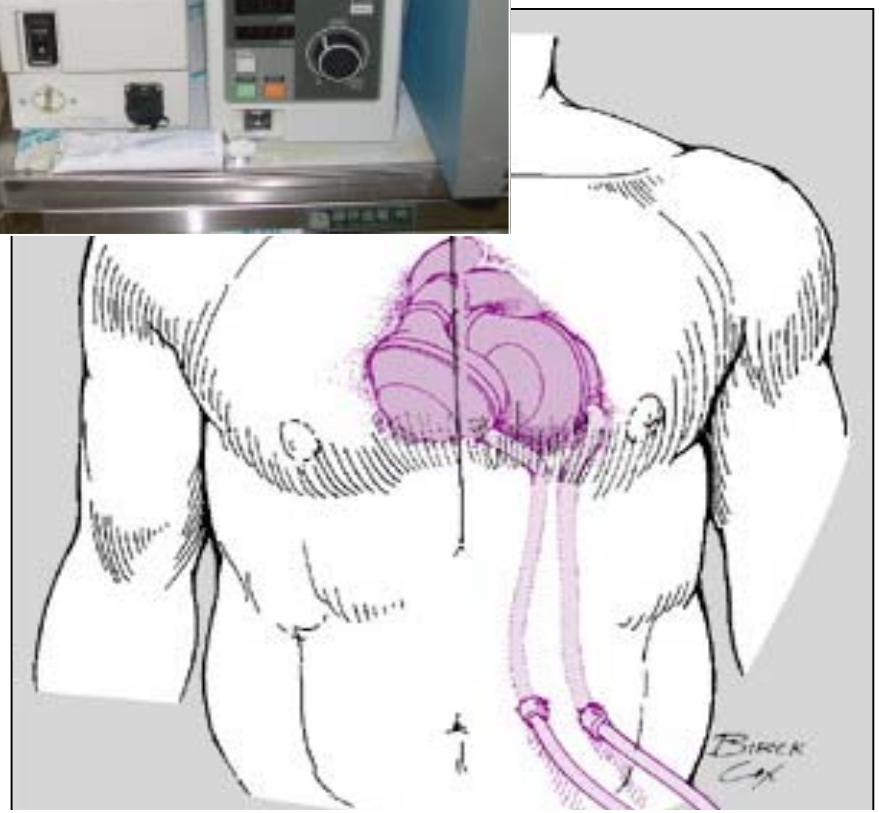


N Engl J Med 2001;345:1435

VAD



EBS



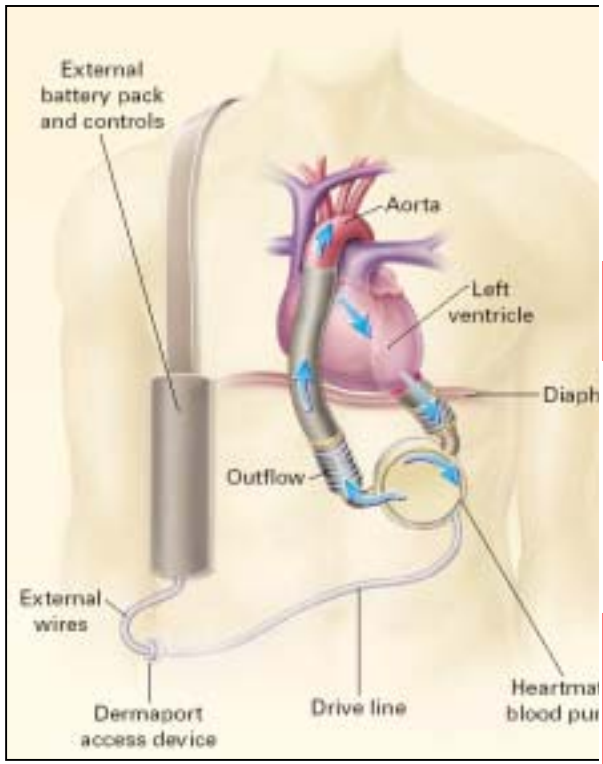
Artificial Heart

Mechanical pumps for Cardiac Support

Pump Type*	Advantages	Disadvantages	Indications
Extracorporeal nonpulsatile†	Simple cannulation, inexpensive, univentricular or biventricular, readily available, extensive clinical experience	Short-term support, requires continuous availability of trained bedside personnel, systemic anticoagulant therapy needed, bleeding and thromboembolism possible, patient necessarily bedridden, no potential for rehabilitation	Postcardiotomy ventricular dysfunction, neonatal respiratory failure (extracorporeal membrane oxygenation)
Extracorporeal pulsatile‡	Univentricular or biventricular	Short-term support, systemic anticoagulant therapy needed, patient usually bedridden, bleeding and thromboembolism possible, limited potential for rehabilitation	Postcardiotomy ventricular dysfunction, right-sided heart failure after left ventricular assist device implantation, bridge to transplantation
Implantable pulsatile§	Potential for outpatient and long-term support, excellent potential for rehabilitation	Expensive, univentricular support, abdominal placement required, infection possible, mechanical failure possible, bleeding and thromboembolism possible	Bridge to transplantation, bridge to recovery, potential long-term use
Total artificial heart¶	Biventricular support, orthotopic placement	Not FDA-approved, bleeding and thromboembolism possible, bulky external console, systemic anticoagulant therapy needed, infection possible, mechanical failure possible, expensive	Biventricular failure, bridge to transplantation

Thermo-Cardiosystems device

Development of VAD



Year	Event
1954	Development of the cardiopulmonary-bypass machine
1964	Chartering of the Artificial Heart Program by the National Heart, Lung, and Blood Institute
1966	First use of a pneumatic device as a bridge to recovery
1967	First human heart transplantation
1969	First successful use of a pneumatic total artificial heart as a bridge to transplantation
1970s	Development of a variety of extracorporeal and implantable pneumatic ventricular assist devices
1974	Redirection of the efforts of the Artificial Heart Program toward the development of implantable devices
1984	First implantation of a total artificial heart as a permanent device
1985	Multicenter evaluation of left ventricular assist devices as a bridge to transplantation
1991	Moratorium on the use of the total artificial heart
1993	FDA approval of a New Investigational Device exemption for a total artificial heart
1994	FDA approval of a left ventricular assist device as a bridge to transplantation
1994	First use of a wearable left ventricular assist device
1996–present	Recruitment of patients for a randomized trial comparing wearable left ventricular assist device with medical therapy

N Engl J Med 2001;345:1435

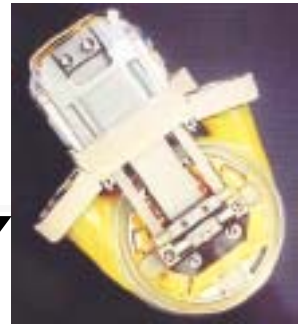
Indications for Device support

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 vasculapathy
6. Fulminant myocarditis

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)

Current Status of Mechanical Cardiac Support Devices in USA



Types of Devices	ECMO	Centrifugal	Abiomed	Thoratec	Novacor	HeartMate	Cardiowest
FDA approved indications	N/A	N/A	Post-cardiotomy recovery	Post-cardiotomy recovery and bridge	Bridge	Bridge	Bridge*
Position	External	External	External	External	Internal	Internal	Internal
Ventricular support	Cardiopulmonary	Left, right or both	Left, right or both	Left, right or both	Left only	Left only	Left and right
Patient size	Small-large	Small-large	Small-large	Medium-large	Large	Large	Large
Average duration	Short	Short	Intermediate	Intermediate to long	Long	Long	Long
Power source	Electric	Electric	Pneumatic	Pneumatic	Electric	Electric or pneumatic	Pneumatic
Cannulation site	Arterial and venous	Arterial, atrial or ventricular	Arterial, atrial or ventricular	Arterial, atrial or ventricular	Ventricular	Ventricular	N/A
Native ventricle	Remains	Remains	Remains	Remains	Remains	Remains	Removed
Anti-coagulation	Yes	Yes	Yes	Yes	Yes	No	Yes
Patient ambulation	No	No	Yes, restricted	Yes	Yes	Yes	Yes
Wearable	No	No	No	No	Yes	Yes	No
Patient discharge	No	No	No	No	Yes	Yes-electric, yes-pneumatic*	No
Device cost	$	$	$$	$$ to $$$$	$$$$	$$$$	N/A

*Investigational device exemption (IDE). ECMO = extracorporeal membrane oxygenation; FDA = Food and Drug Administration.

Anticipated Survival According to Severity of Advanced Heart Failure

Disease entity	Severity of Heart Failure	Expected more than 50% Mortality
Cardiogenic shock	Chronic HF with exacerbation into critical low output state	In-hospital
	Acute myocardial infarction	
	Post-cardiotomy shock	
Chronic heart failure	dependent on intravenous inotropic therapy	3-6 months
	class IV symptoms on oral therapy	12-24 months
	Refractory symptoms at rest or minimal exertion	less than 12 months
	Risk factors such as decreasing sodium, increasing creatinine and/or BUN	less than 12 months
	Stabilization as class III	more than 24 months
Heart failure	refractory ventricular arrhythmias	Variable, not estimated
Chronic severe post-transplant graft dysfunction with allograft vasculopathy		less than 12 months

Consensus Conference Report,
JACC 2001;37:340

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	Indicators of cardiac function
(1) pH, BE	(1) Wall motion
(2) SVO_2	(2) EF, %FS
(3) LA	(3) Ejection time
(4) TB (or AKBR)	(4) $ETCO_2$
(5) Blood biochemistry	(5) CI
(6) Urinary amount	

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.

The end points for critical populations

Primary end point: All-cause mortality
Secondary end points:
- A. Quality of life
- B. Functional capacity, for example:
  - Exercise capacity (if applicable)
  - Hemodynamics
  - Ability to leave hospital
- C. Cost
  - Device cost—system and replacement parts
  - In-hospital costs
  - Out-of-hospital costs (to include medical, caregiver-related and, possibly, travel-related costs)
  - Cost-effectiveness*
- D. Components of morbidity (75), including:
  - Thromboembolism
  - Neurologic events
  - Infection
  - Bleeding
  - End-organ dysfunction
  - Right heart failure
  - Psychiatric episode
  - Rehospitalization (if discharged)
    - Cardiac causes:
      - Worsening heart failure
      - MI
      - Arrhythmia
    - Non-cardiac reasons
- E. Device malfunction (to be specified in detail)
- F. Device failure (to be specified in detail)

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 150–200 s by prescribing nafamostat mesilate, hemostasis, blood transfusion (maintain above Hb 10 g/dl and plt 5.0×10^{4}/μl).
(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 1.0 L/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 $L \cdot min^{-1} \cdot m^{-2}$

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.

Predictors of Clinical Manifestations and Courses In Patients with Acute Fulminant Coxsackievirus Myocarditis

	Age/Sex	Initial Manifestation	EF normalized	MCS/ Inotropics	CVB type
NFM (n=5)	F/25	Dyspnea	> 2 year	No	CVB3
	M/31	Fever	9 days	No	CVB3
	M/46	Chest pain	8 days	No	CVB3
	M/22	Dyspnea	12 months	No/yes	CVB3
	M/31	Dyspnea	0	No	CVB3/4
FM (n=5)	F/57	Dizziness	6 days	VAD	CVB4
	M/15	Chest pain	48 days	No/yes	CVB3/4
	M/14	Dyspnea	8 days	EBS	CVB3
	F/59	Chest pain	0	IABP	Adeno
	F/9	Chest pain	5 days	No/IABP	Adeno

Laboratory Markers between FM and NFM

	NFM	FM	P value
Age	29.2±10.1	30.8±22.3	ns
Initial NT pro-BNP	7500±3305	18420±12320	ns
Peak TnI	24.8±33.5	889.2±610.8	P<0.05
Peak CK-MB	14.7±21.7	60.1±67.7	P<0.05
WBC	6695±639	8595±5600	P<0.05
Initial ESR	14±0	31.5±17.6	ns
Initial CRP	3.29±3.67	6.21±3.05	ns

Cytokines between FM and NFM

	NFM	FM	P value
RVSP by Doppler	44.4±3.2	31.5±2.1	P<0.05
IL-1β	below detectable range		ns
IL-6	below detectable range		ns
hIL-6 (pg/ml)	28.6±9.3	239.7±124.1	P<0.05
TNFRII(pg/ml)	4.2±1.7	26.85±11.9	P<0.05
TNF-α	below detectable range		ns

Predictors of Clinical Manifestations and Courses In Patients with Acute Fulminant Coxsackievirus Myocarditis

- The clinical courses of acute FM and NFM CVB myocarditis are too different .
- Among the initial laboratory findings, leukocytosis, initial cardiac enzymes, CK-MB, TnI, and cytokines, hIL-6 and TNFRII, may be helpful to predict the course of acute CVB myocarditis
- Since the patients with FM recover without residual LV dysfunction within one month and had more excellent long-term prognosis, the aggressive hemodynamic support is warranted.

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  - Neil Berkely
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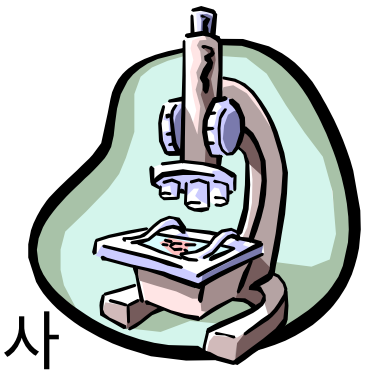
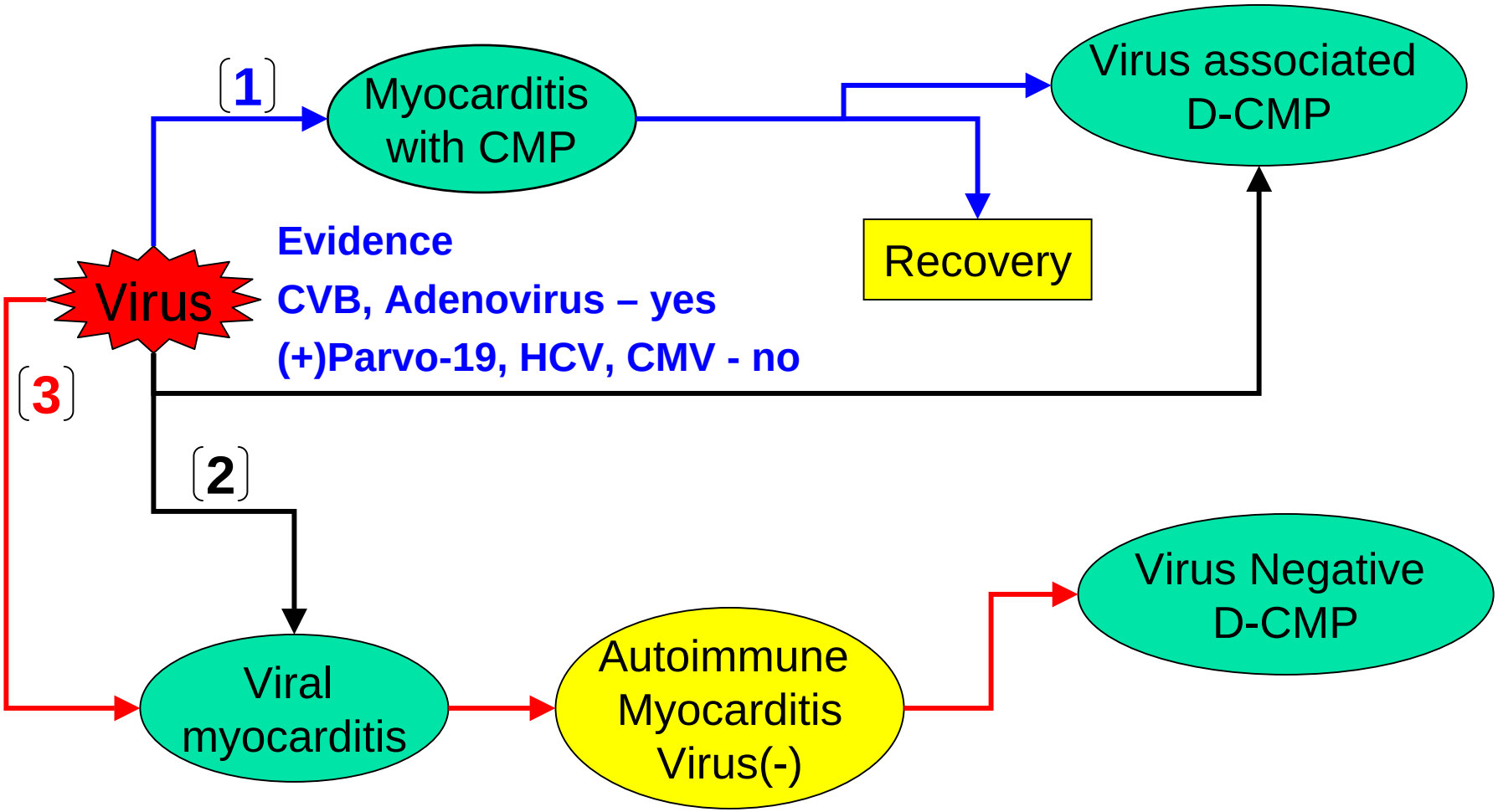
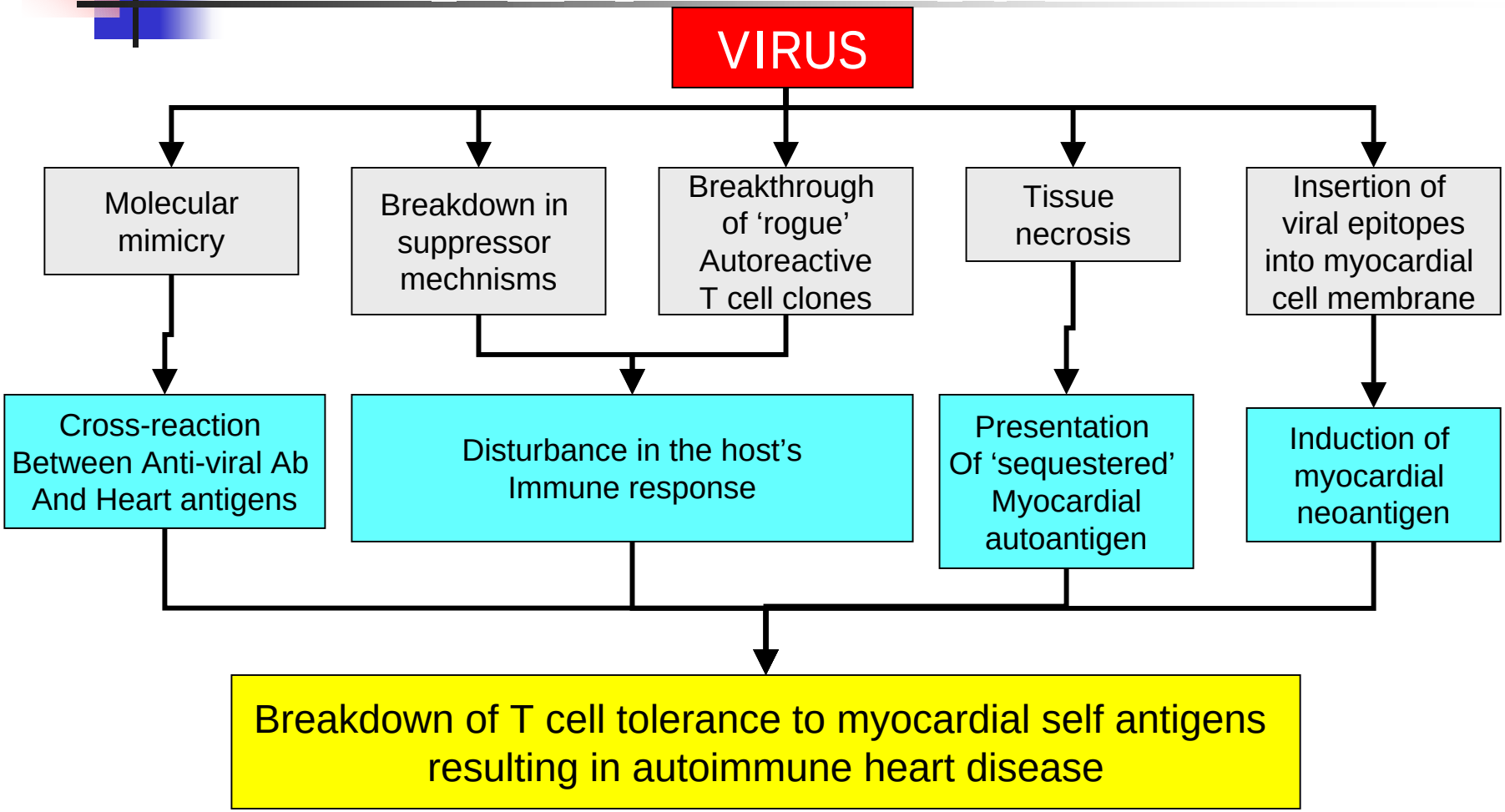
- Andrea Henke, PhD, University of Jena, Germany
- 삼성서울병원 분자치료연구실
  - 김덕경 교수
  - 연구원 : 임병관, 신재옥, 김경리
- 충남대학교병원 : 박은신
- 서울대학교 유전공학연구소 : 김선영 박사
- 바이로메드 ㈜ : 김종묵박사, 호성현연구원



Transformation of Myocarditis/Inflammatory cadiomyopathy to idiopathic D-CMP

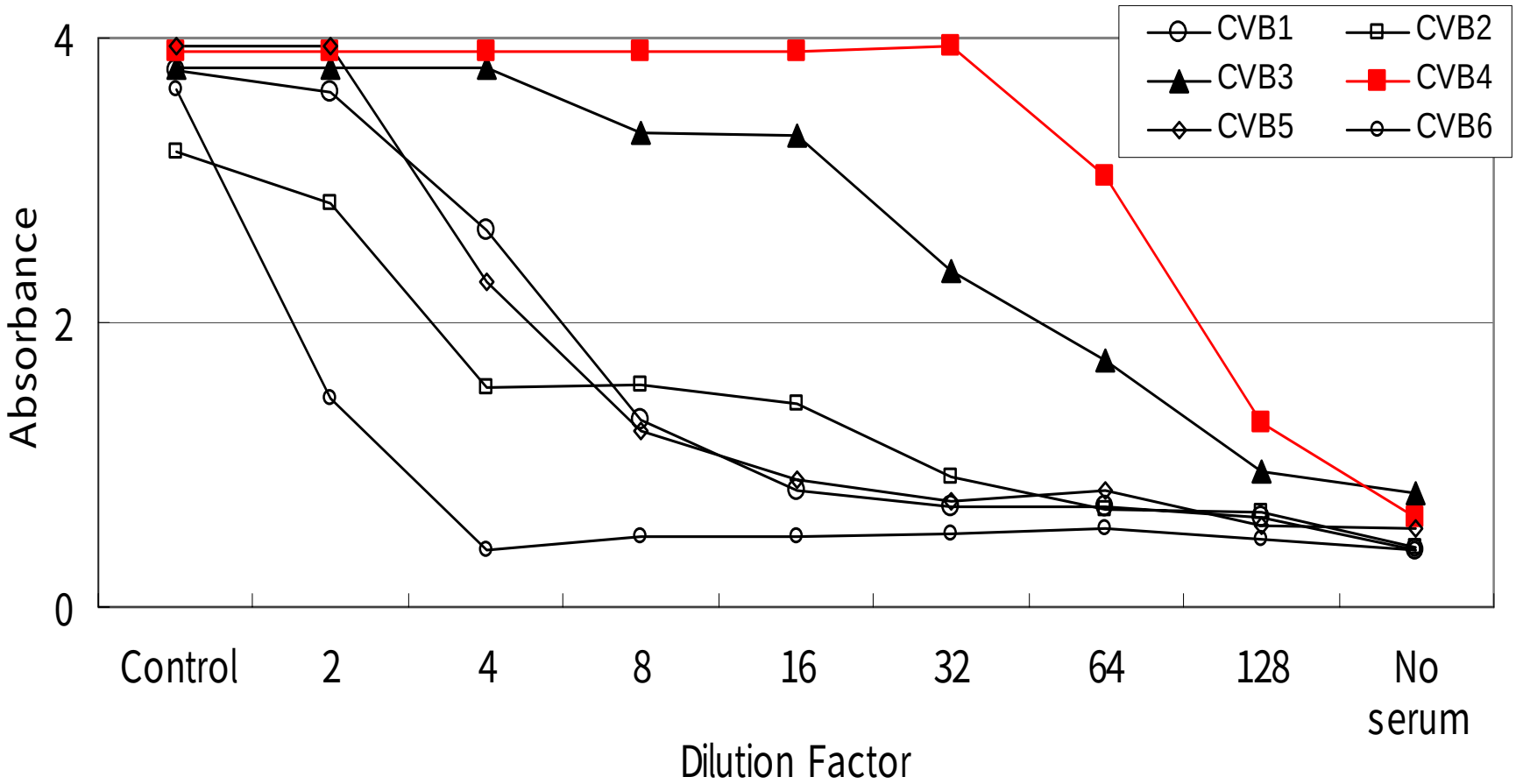


Mechanisms of Virus-induced autoimmune heart disease

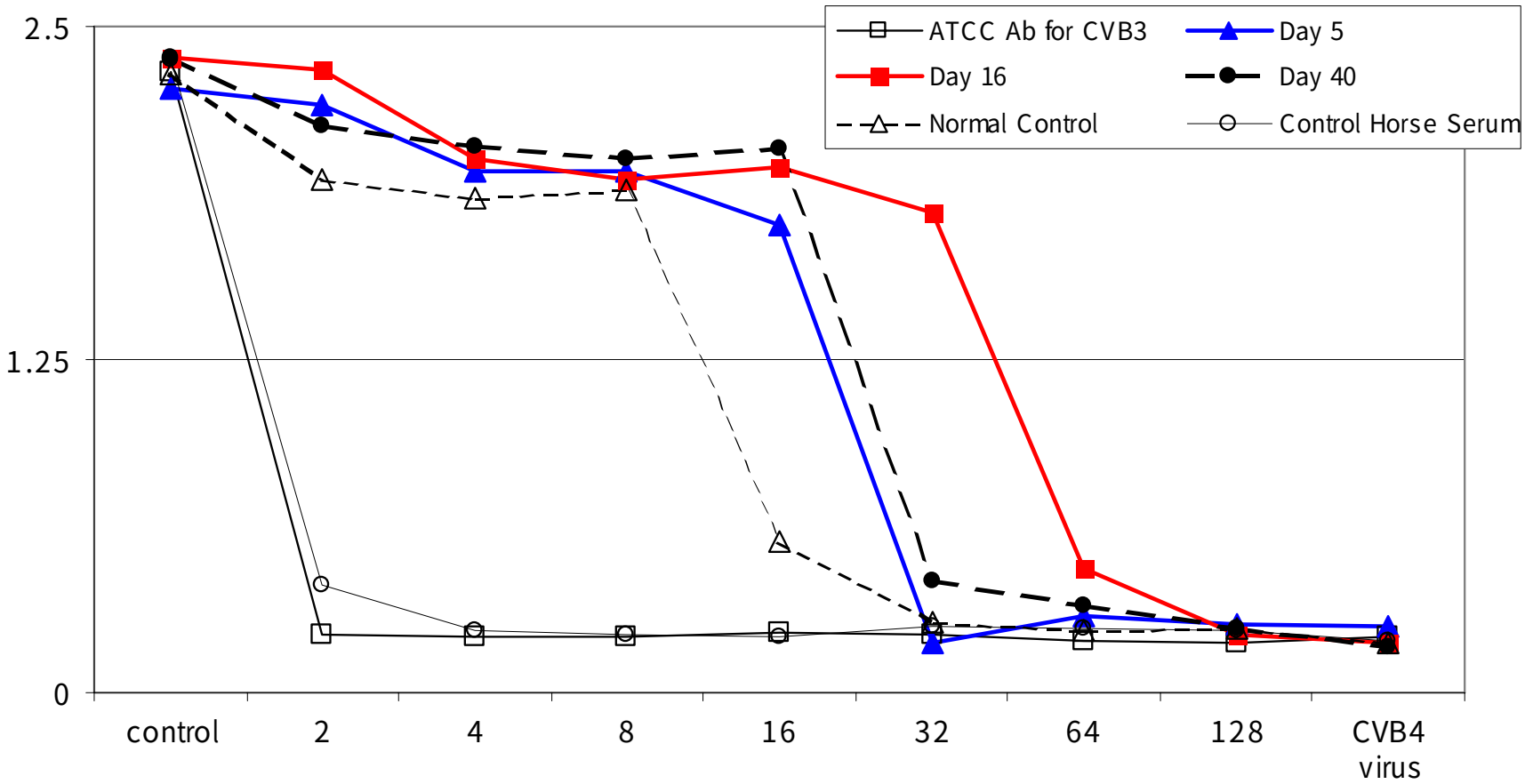


Hypothetical mechanism of virus-induced or precipitated autoimmune Heart disease.
None of these has been proven in patients with other autoimmune conditions.

Neutralization Test for all CVB Serotypes



Neutralization Test for CVB4



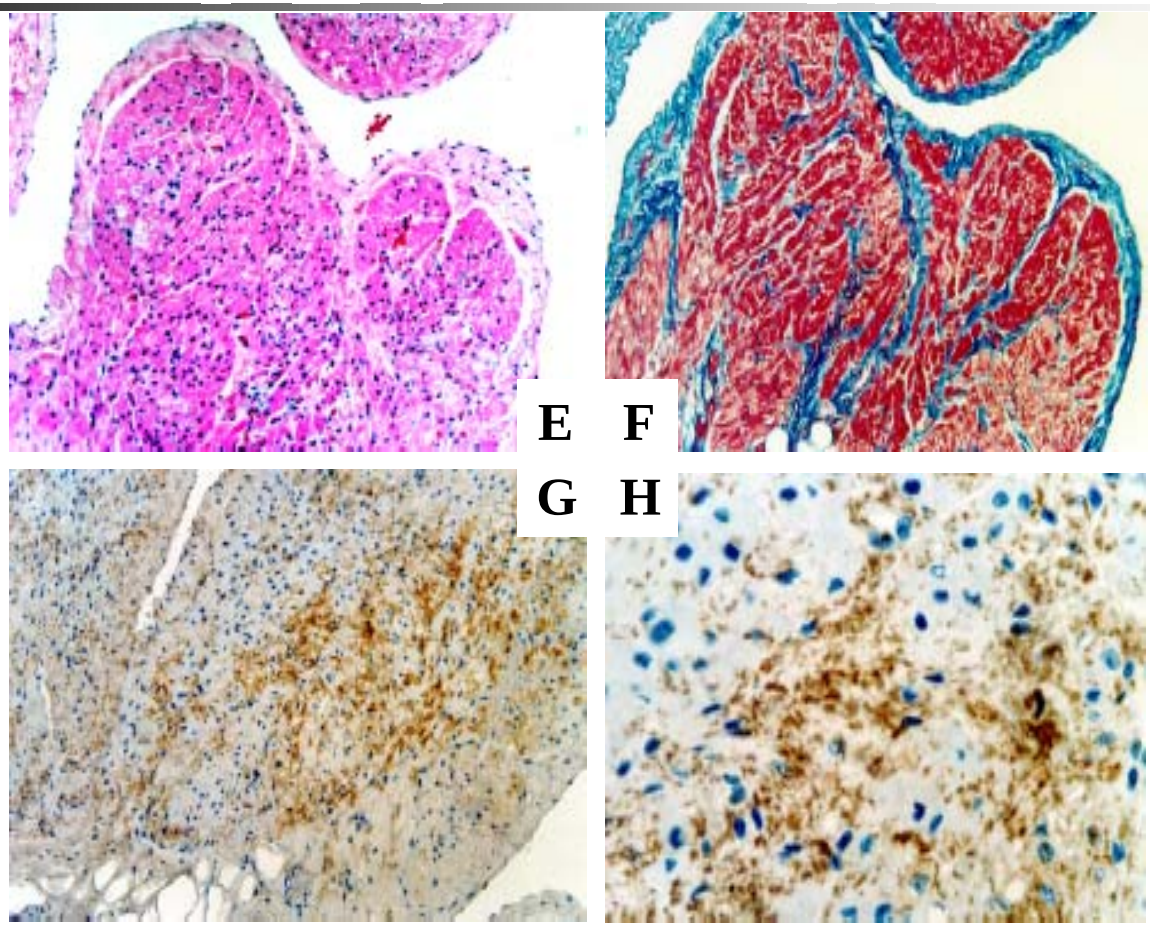
Incidence of Viral Genomes in Myocardium

MYOCARDITS			
Bowles/1986	Enterovirus	northern	50(%)
Kandolf/1991	Enterovirus	*In situ*	20-25
Maisch/1989	CMV	*In situ*	20
Schonian/1991	CMV	PCR/*In situ*	10
Martin/1994	Enterovirus	PCR	23
	Adenovirus		44
DILATED CARDIOMYOPATHY			
Kandolf/1991	Enterovirus	*In situ*	20
Schonian/1991	CMV	*In situ*	15
Schonian/1993	CMV	PCR	<5
Matsumori/1995	HCV	PCR	17(%)

Prevalence of Myocarditis by Biopsy

Reference	Years	Positive Biopsy Results	Patient Group
		% (no./total no.)	
Dec et al.[106]	1975–1983	67 (18/27)	Patients with recent-onset cardiomyopathy (<6 mo of symptoms)
Parrillo et al.[109]	1982–1988	37 (38/102)	Patients referred to the National Institutes of Health for randomized trial of prednisone in idiopathic dilated cardiomyopathy
Mason et al.[6]	1986–1989	10 (214/2233)	Patients screened for the Myocarditis Treatment Trial
McCarthy et al.[110]	1984–1997	14 (252/1757)	Large single-center series from Johns Hopkins University
McNamara et al.[111]	1996–1998	16 (10/62)	All patients with recent-onset dilated cardiomyopathy enrolled in the Intervention in Myocarditis and Acute Cardiomyopathy trial
Drucker et al.[112]	1985–1991	51 (20/39)	Children referred with the clinical syndrome of suspected myocarditis
Midei et al.[113]	1983–1988	78 (14/18)	Women with peripartum cardiomyopathy from a single center (Johns Hopkins)
Bozkurt et al.[114]	1990–1998	9 (1/11)	Women with peripartum cardiomyopathy from a single center (University of Pittsburgh)

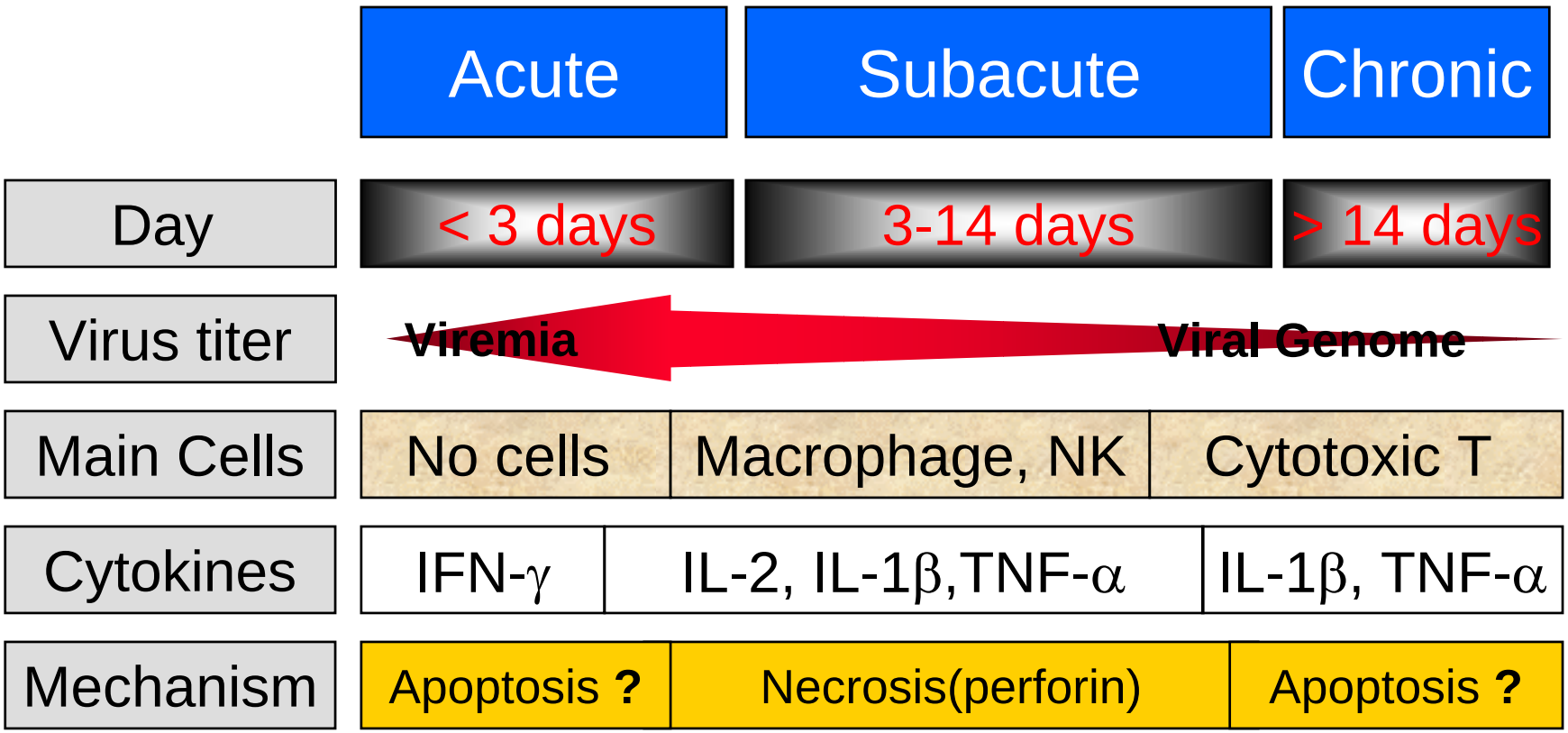
Detection of enteroviral capsid protein VP1 by immunohistochemistry



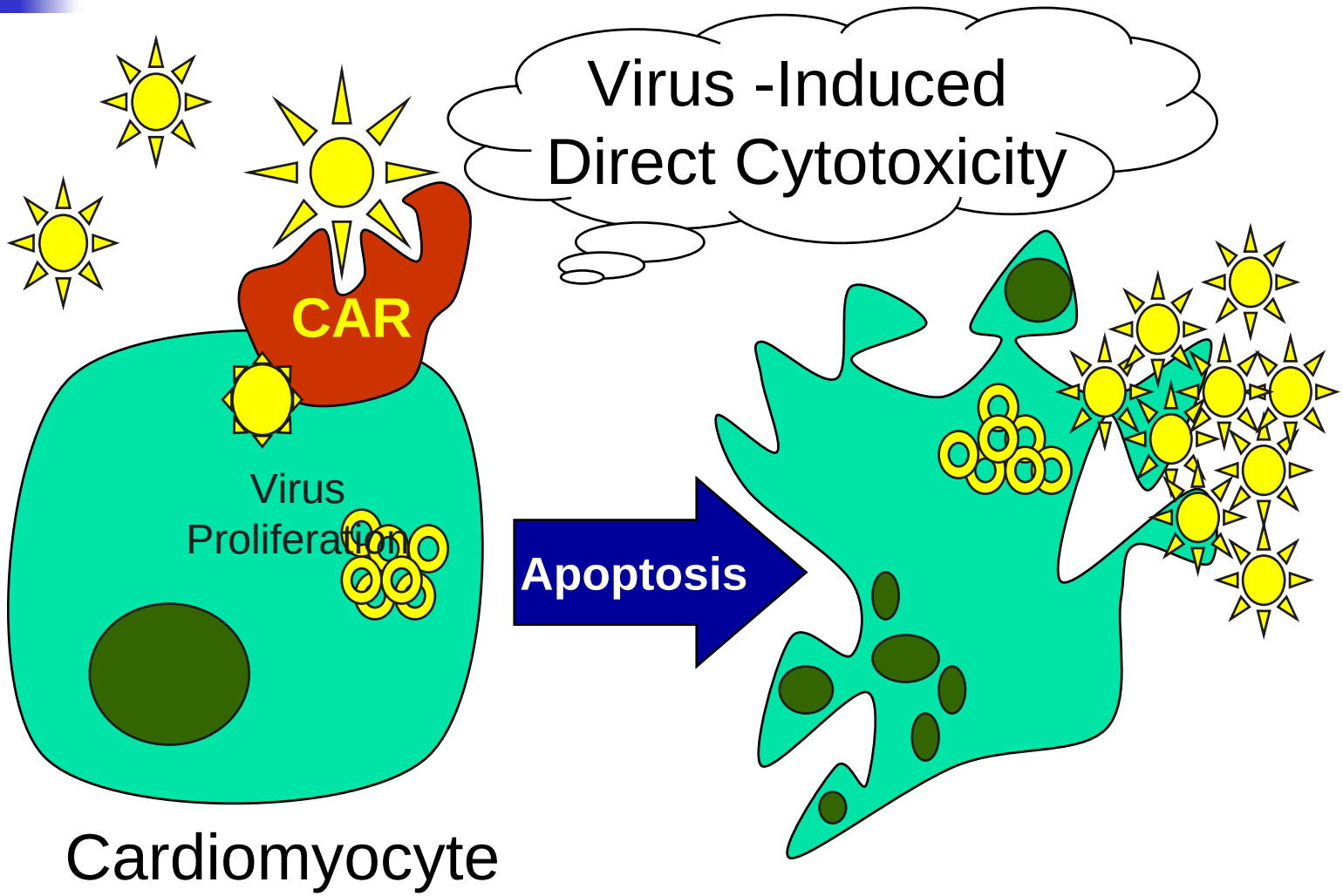
E) Left auricle, H& E stain, x200 F) Masson's Trichrome stain, x200)

G,H) Immunohistochemistry probed by anti-enteroviral VP1 Ab.(G; x100,H; x400)

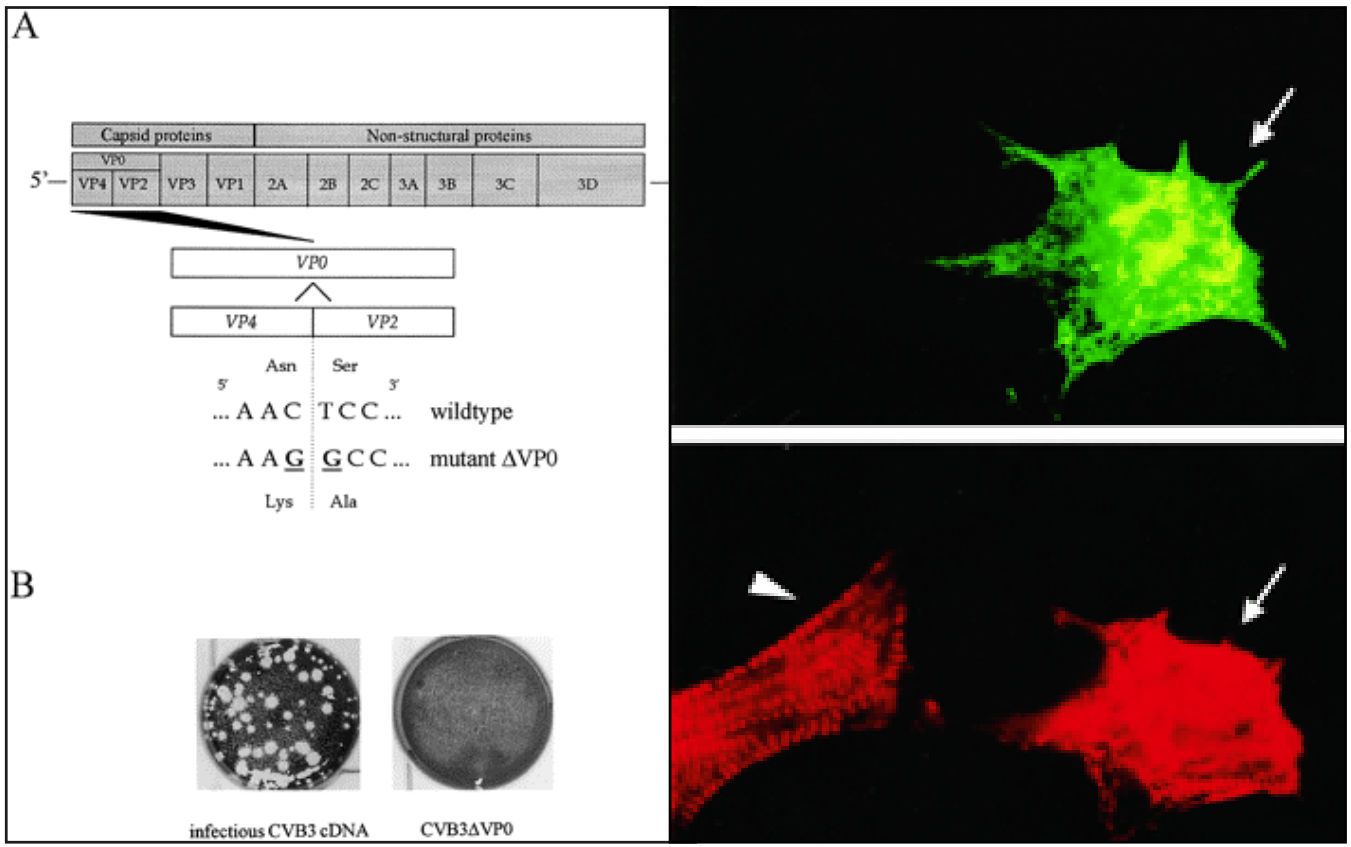
Host Responses after Viral Infection



Myocyte Injury in Acute Phase

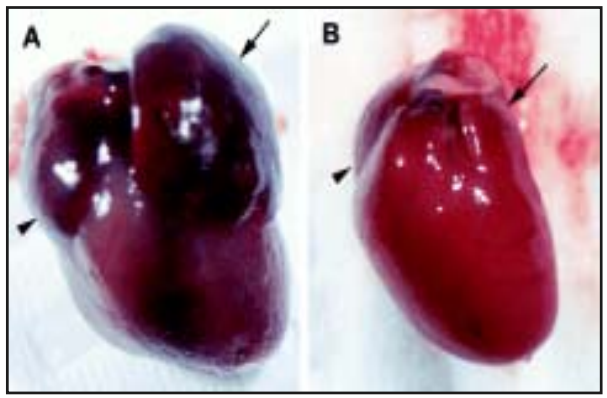


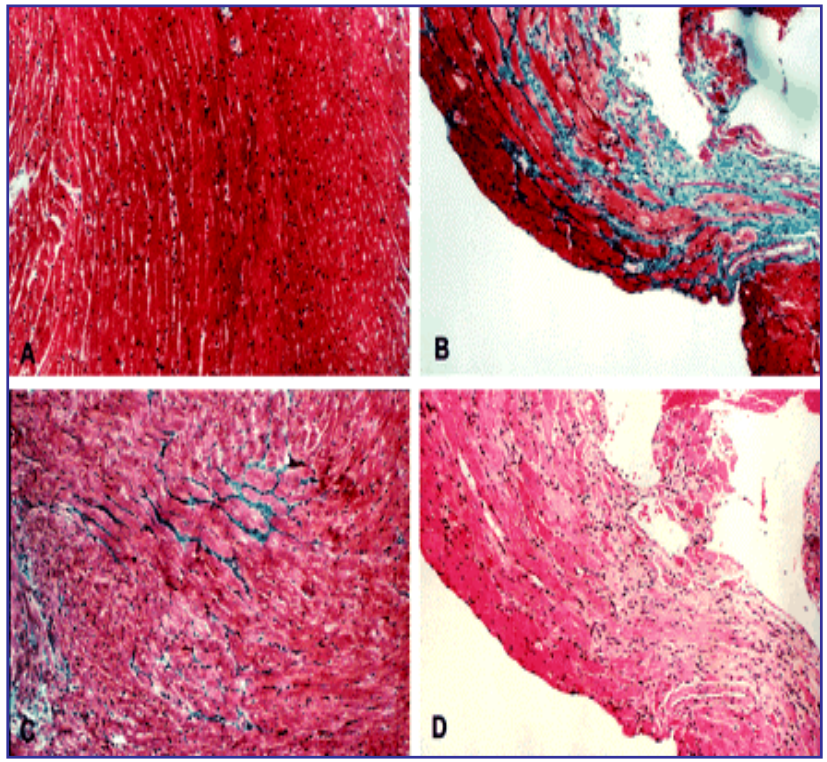
Replication-defective CVB3 infection



Replication defective Vaccinia-CVB3-dVP0 virus infection can induce myofibril disruption

CVB3-dVP0 Transgenic Animal





CVB3-dVP0 transgenic animal shows d-CMP phenotype, increased ANF expression and myocardial fibrosis

Case Summary – HIS and Nt test

- Serial histological and immunohistochemical analysis of the right atrial appendage, that underwent biopsy at the time of insertion and removal of LVAD, showed the enteroviral capsid protein VP1 (primary antibody, Novocastra Laboratories) over the entire right atrial wall with scanty inflammation infiltrates.
- Her serum neutralized coxsackievirus B4 (CVB4) in a neutralization test performed with CVB4 (American Type Culture Collection, J.V.B. Benschoten) as a control virus.
- The titer of neutralizing antibody in her serum at 16 days was more than four times the titer at 5 days and 40 days.

Devices for circulatory support currently used in

1. acute circulatory support < 1 month
   - cardiac failure after cardiac operations, myocardial infarction shock or acute cardiomyopathy due to myocarditis or other causes, with a potential likelihood of recovery.
2. more prolonged support from 30 days to <1 year in
   - Waiting for transplantation but deteriorate before a heart becomes available and require mechanical support prior to transplantation.
   - chronic HF regain ventricular function and are able to have the devices removed without requiring transplantation.
3. permanent support as an alternative to transplantation
   - irreversible cardiac failure that might require circulatory support, but they are not good candidates for cardiac transplantation.

Therefore, if devices are inserted, they must be considered permanent or “destination therapy” and are currently investigational.