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Symposium 7

How to Differentiate Patients with LV Hypertrophic Disorders

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Introduction

1. To make an accurate diagnosis in patients with clinically unexplained left ventricular hypertrophy (LVH) is often difficult.
2. Most of the patients have been diagnosed as having hypertrophic cardiomyopathy.
3. Correct diagnosis becomes important, because specific treatment is now available for some of the disorders.
4. Fabry disease is one of the disorders for which a specific treatment has been developed.

Fabry Disease

1. In cardiology, Fabry disease including cardiac variant have been classified as one of the specific cardiomyopathies.
2. It has been reported that the disease may be more common than previously believed.
3. Enzyme replacement therapy (ERT), a specific and effective therapy, is now available for the disease.
4. It becomes very important for cardiologists to differentiate Fabry disease at early stage.

Fabry Disease

1. Deficiency of the lysosomal hydrolase α-galactosidase A (α-gal A)
2. Defect leads to the systemic accumulation of glycolipids, especially ceramidetrihexoside.
3. X-linked, panethnic disorder: frequency of ~1/40,000 males in the USA
4. Manifestations due to accumulation of glycolipids mainly in vascular endothelial cells
   Angiokeratoma, Acroparesthesias, Hypohidrosis,
   Corneal opacities.
   Dysfunction of the kidney, brain, and heart

Atypical Variant of Fabry Disease (Cardiac Fabry Disease)

1. First reported in 1989
2. Manifestations limited to the heart
3. Patients have LVH due to deposition of glycolipids in the cardiomyocytes.

Overview

1. Incidence
2. Clinical Features
3. ERT and the heart

1603 male patients referred to the cardiology section of Kagoshima University Hospital

↓

Echocardiogram (≥13 mm)

↓

230 patients identified with LVH

↓

Measurement of plasma α-gal A activity

↓

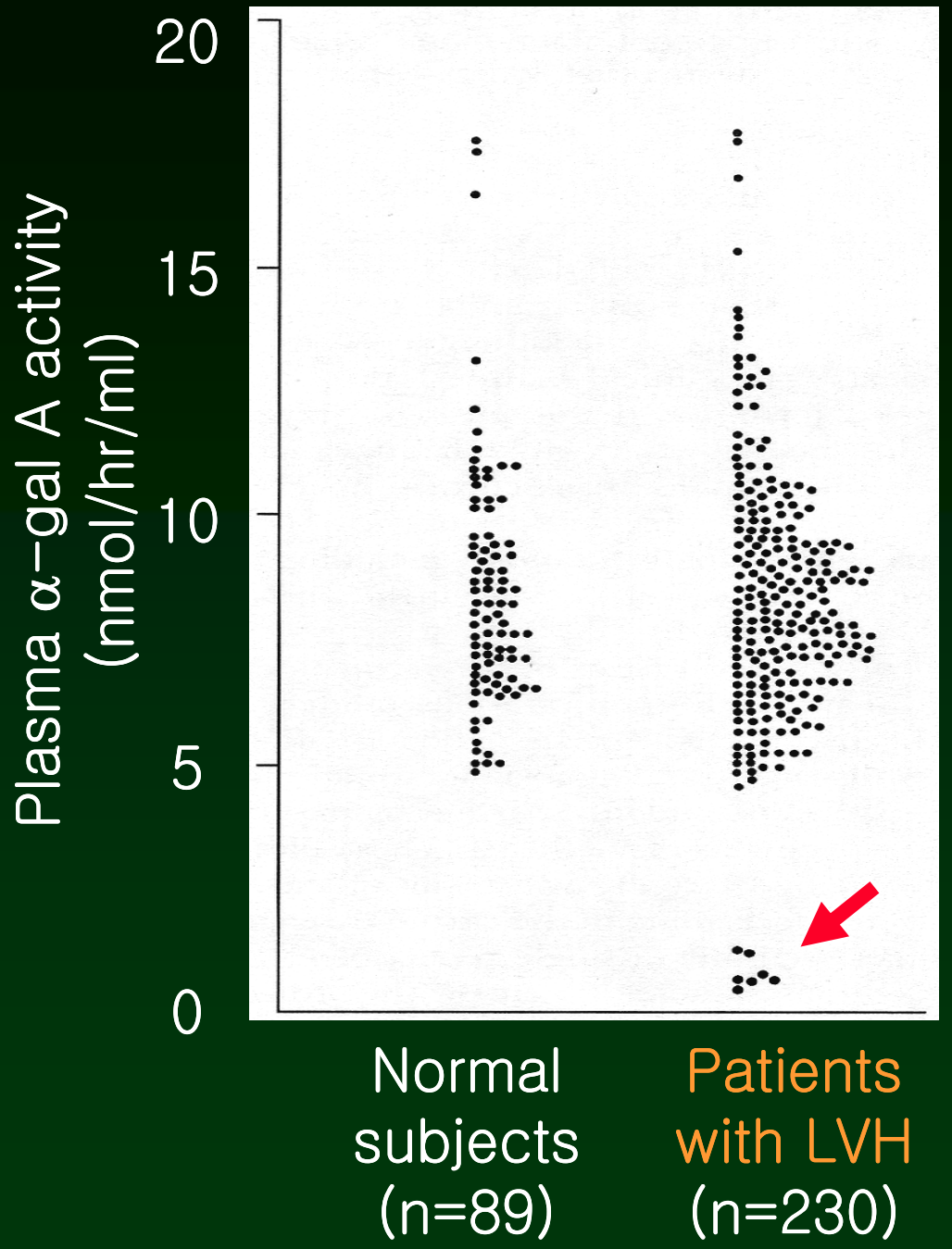
7 patients diagnosed with Fabry disease

↓

Assessment of clinical manifestations
Evaluation of endomyocardial-biopsy findings
Gene analysis of the α-gal A gene

N Engl J Med 1995; 333: 288-293.

Plasma α-Gal A Activity in Male Patients With LVH



N Engl J Med 1995; 333: 288-293.

Characteristics of 7 Patients Diagnosed With Fabry Disease

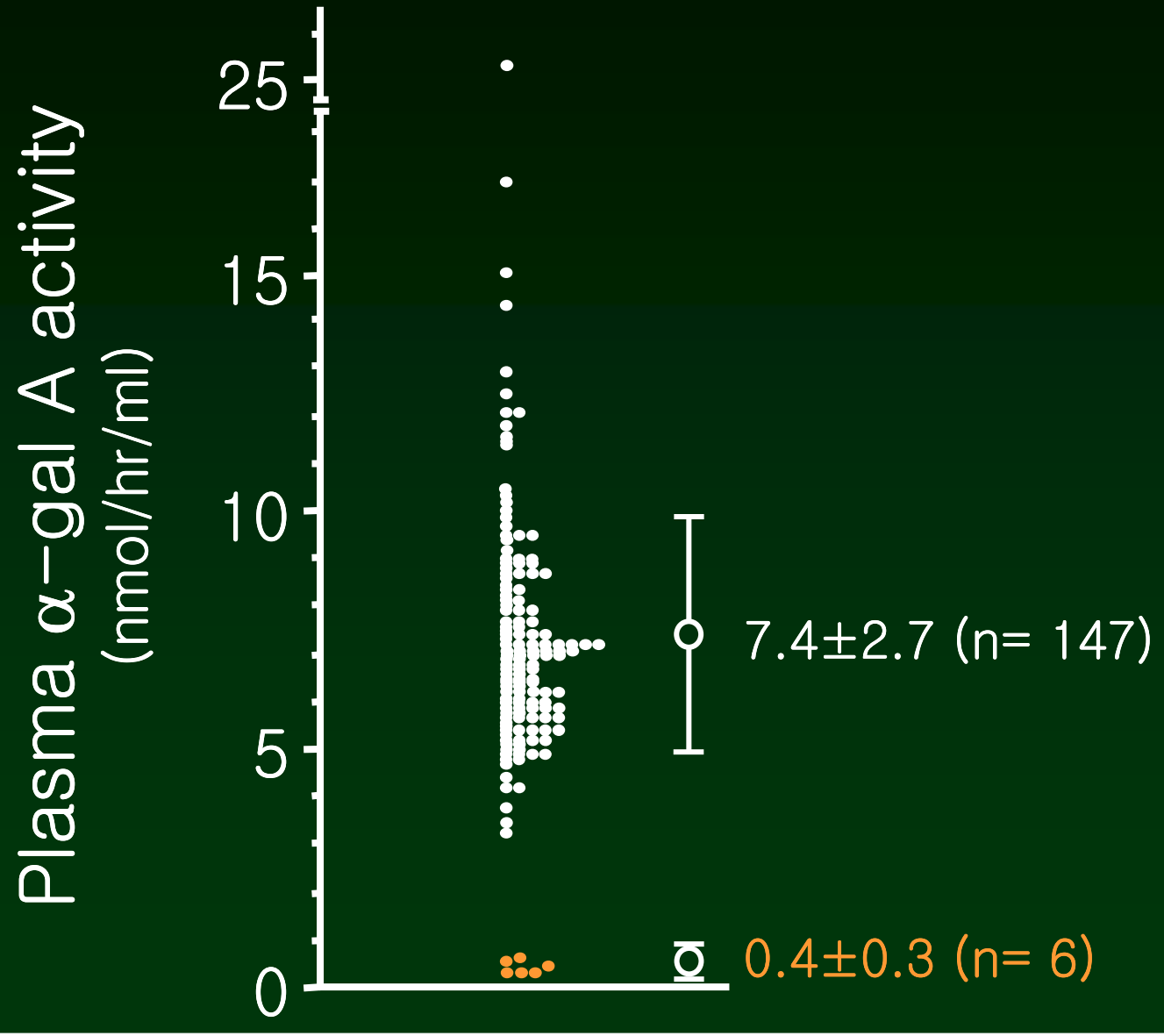
Patient No.		1	2	3	4	5	6
Age (yr)	66	69	62	62	55	70	72
Plasma α-gal A (nmol/hr/ml)	1.2	0.6	1.2	0.6	0.4	0.7	0.6
LV wall thickness							
IVSth (mm)	20	20	13	13	16	15	15
LVPWth (mm)	20	17	13	12	16	15	14
Hypertension	−	−	−	+	−	−	−
Albuminuria	−	−	−	+	−	−	−
Cerebrovascular damage	−	−	−	+	−	+	−
Angiokeratoma	−	−	−	−	−	−	−
Acroparesthesias	−	−	−	−	−	−	−
Hypohidrosis	−	−	−	−	−	−	−
Corneal opacities	−	−	−	−	−	−	−

1. Seven unrelated patients with atypical variant of Fabry disease, whose manifestations were limited to the heart, were found among 230 men with LVH (3% incidence rate).
2. We designated these cardiac variants as “cardiac Fabry disease.”
3. Fabry disease should be considered as a cause of unexplained LVH.

153 consecutive male patients
who had been given a diagnosis of
HCM
at St. George's Hospital in UK
Measurement of plasma α-gal A activity
↓
Patients given a diagnosis of Fabry disease
↓
Assessment of clinical manifestations
and
echocardiographic findings

Circulation 2002; 105: 1407-1411.

Plasma α-gal A Activity in 153 Male Patients With HCM in UK



Prevalence of Fabry Disease in Kagoshima and in UK

	Kagoshima		UK
Subjects	LVH	HCM	HCM
No. of patients	230	93	153
Fabry disease	7	6	6

Prevalence of Fabry Disease in Patients With HCM in Germany

Subjects; 250 consecutive patients with HCM in Germany

Methods; Right ventricular endomyocardial-biopsy

Pathological examination

	No. of patients	Fabry disease	Prevalence
Male	154	17	11.0%
Female	96	4	4.2%
Total	250	21	8.4%

Beer et al., Eur Heart J 2000; 21 suppl: 424

Prevalence of Fabry Disease in Patients With HCM in Italy

Subjects; 96 consecutive patients with HCM in Italy

Methods; Endomyocardial-biopsy
Pathological examination

	No. of patients	Fabry disease	Prevalence
Male	62	2	3.3%
Female	34	4	12.0%
Total	96	6	6.3%

Chimenti et al., Circulation 2004; 110: 1047-1053.

1. Fabry disease may present with a several percent incidence rate in patients with unexplained LVH among different ethnic population.
2. A multicenter study for screening of cardiac Fabry disease among patients with LVH in Korea is now underway.
3. Plasma α-gal A activities should be evaluated for patients with unexplained LVH

Overview

1. Incidence
2. Clinical Features
3. ERT and the heart

Subjects:

11 male patients with cardiac Fabry disease

Age at diagnosis; 46 – 73 (yr)

Mean; 56 (yr)

Methods:

1) Echocardiogram
2) Cardiac catheterization
3) ECG, Holter ECG

Cardiac Findings at Diagnosis

	No. of patients	
Echocardiogram		
LVH (≧13 mm)	11 / 11	(100%)
LV dilatation (≧58 mm)	2 / 11	(19%)
LV asynergy	8 / 11	(73%)
Deteriorated FS (27% ≧)	6 / 11	(55%)
Cardiac catheterization		
Elevated LV EDP (≧13 mmHg)	9 / 10	(90%)

ECG Findings at Diagnosis

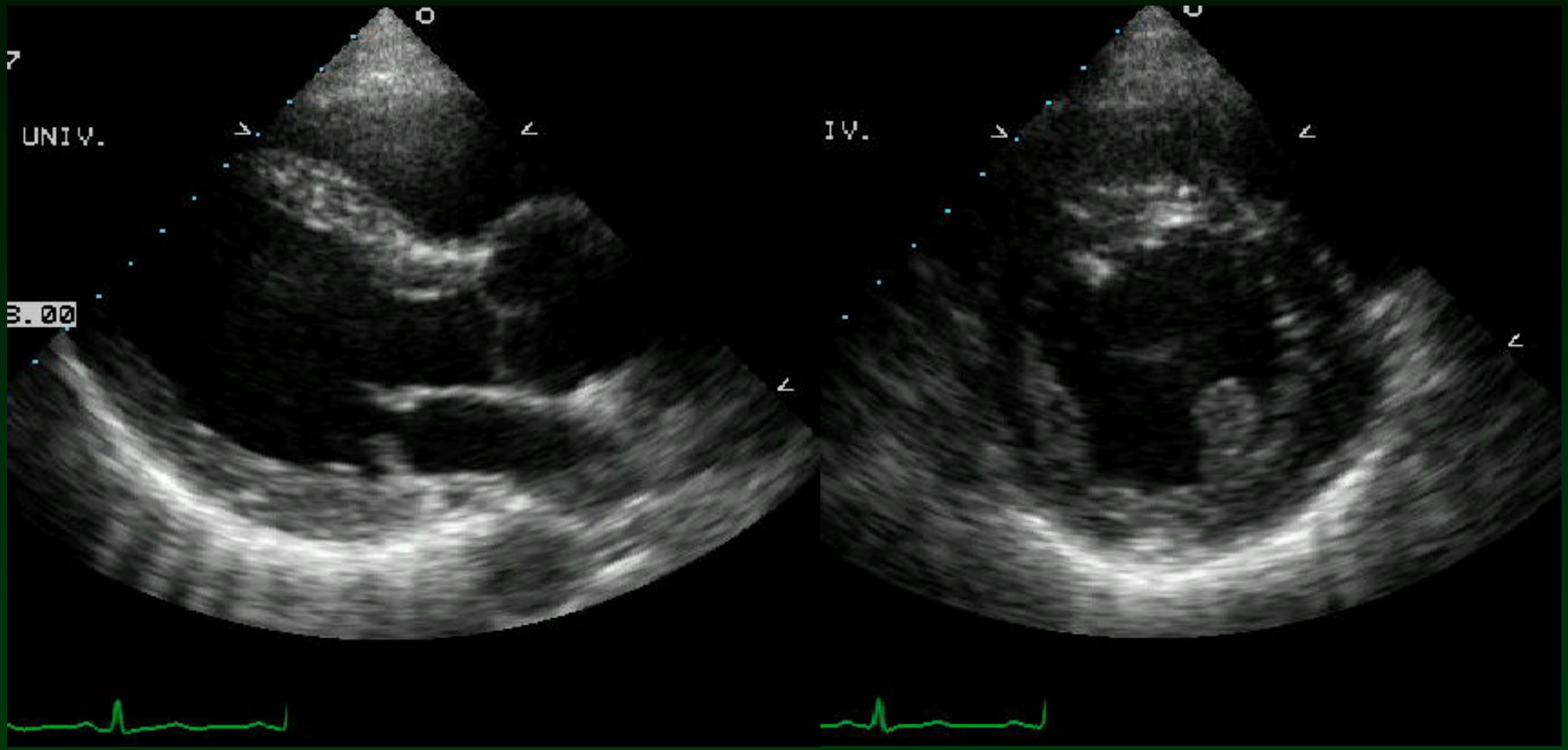
	No. of patients	
Permanent pace maker	2 / 11	(18%)
Atrioventricular block	4 / 11	(36%)
Intraventricular conduction delay (78%)	7 / 9	
LV high voltage (44%)	4 / 9	
Abnormal Q wave (44%)	4 / 9	

Time Course of the Disease

1. Attenuation of LVH
   Thinning of basal posterior wall
2. Worsening of LV dysfunction
   Severe diastolic and systolic dysfunction
3. Worsening of conduction delay and/or VPC
   Attenuation of LV high voltage

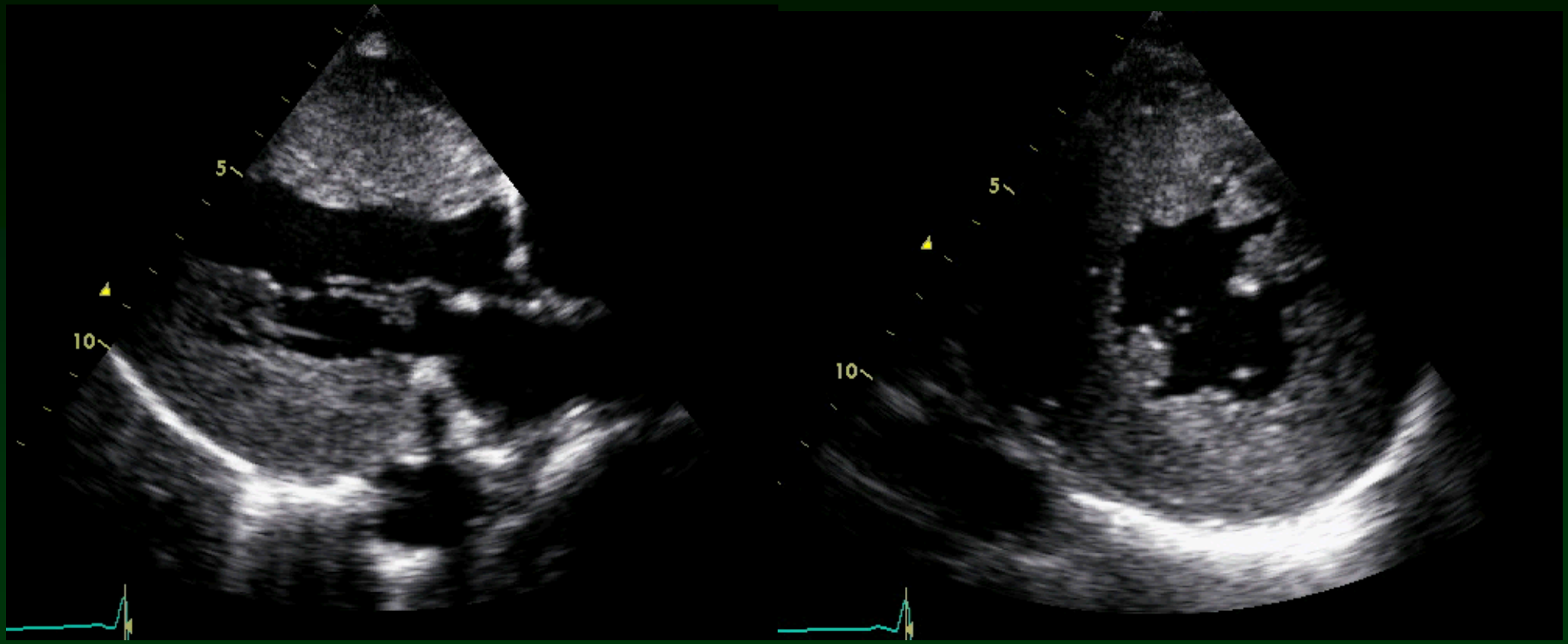
Onset of heart failure and/or fatal arrhythmia

29 yr, Male



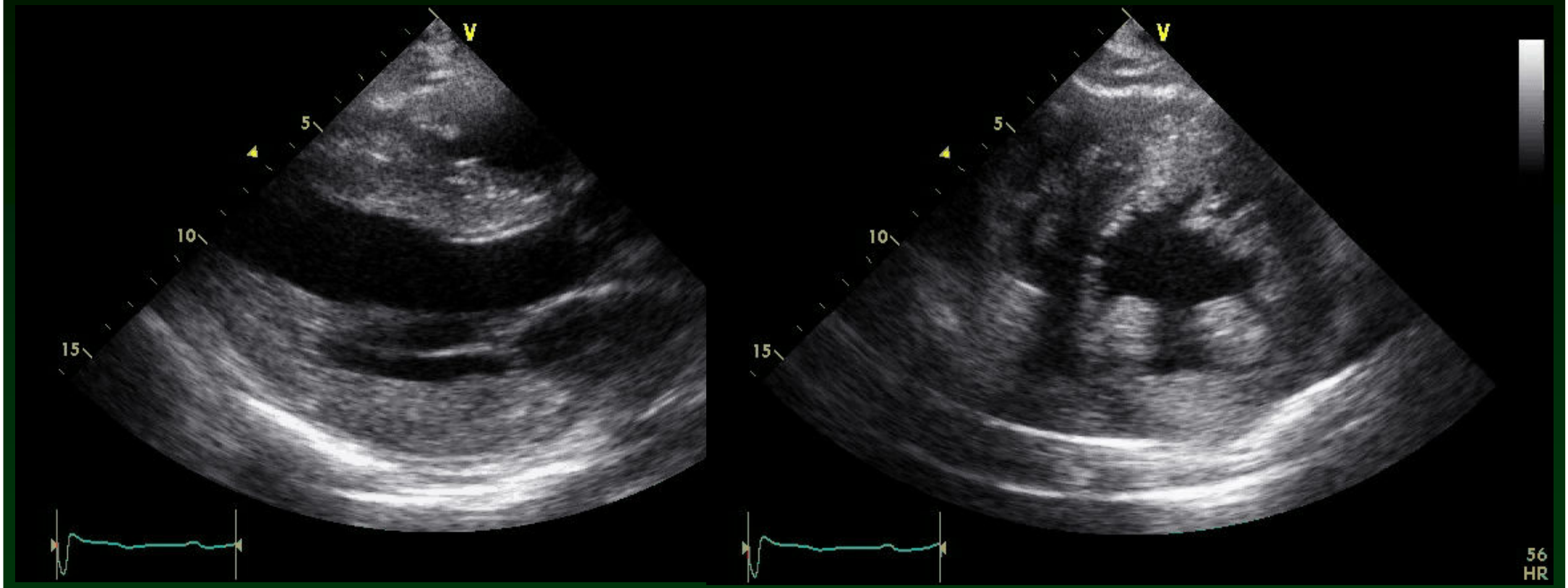
Mild LVH

43 yr, Male



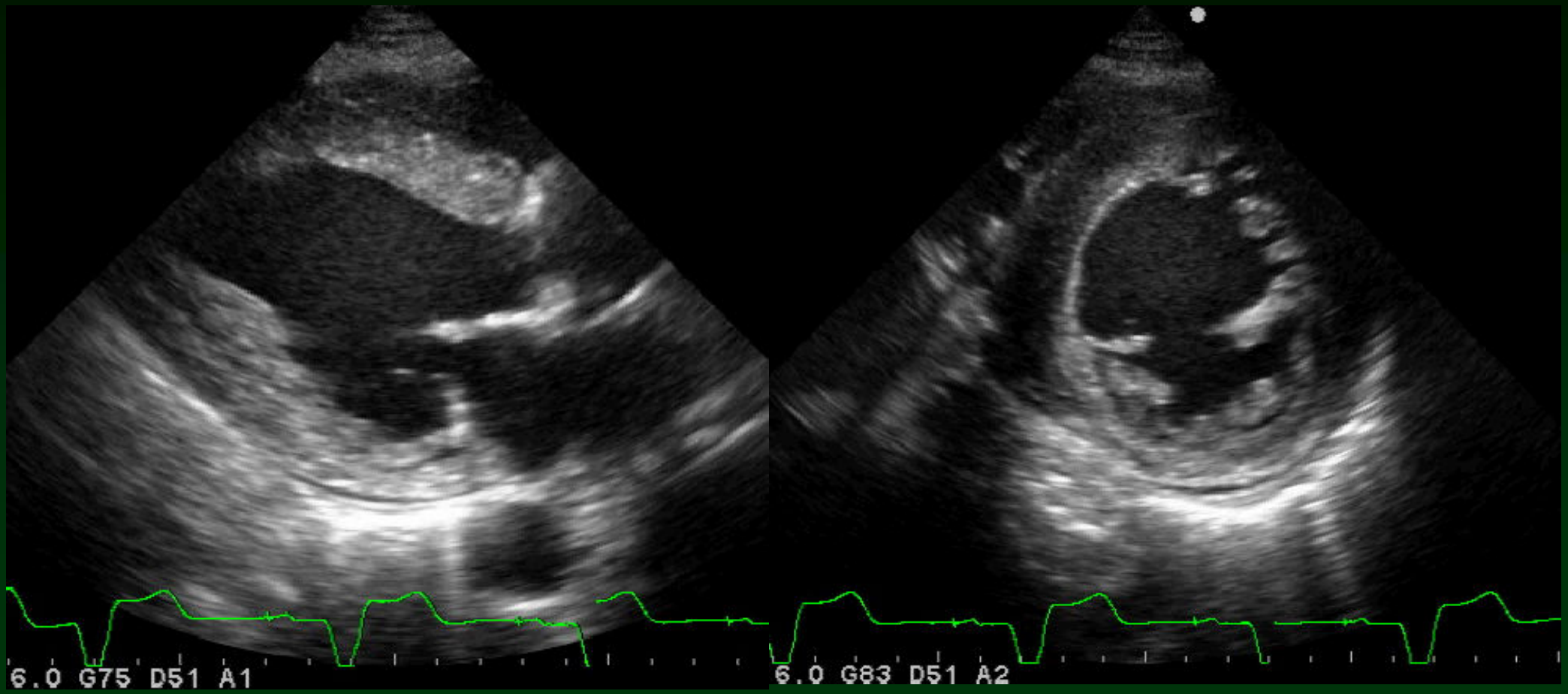
Mimicking HCM

52 yr, Male



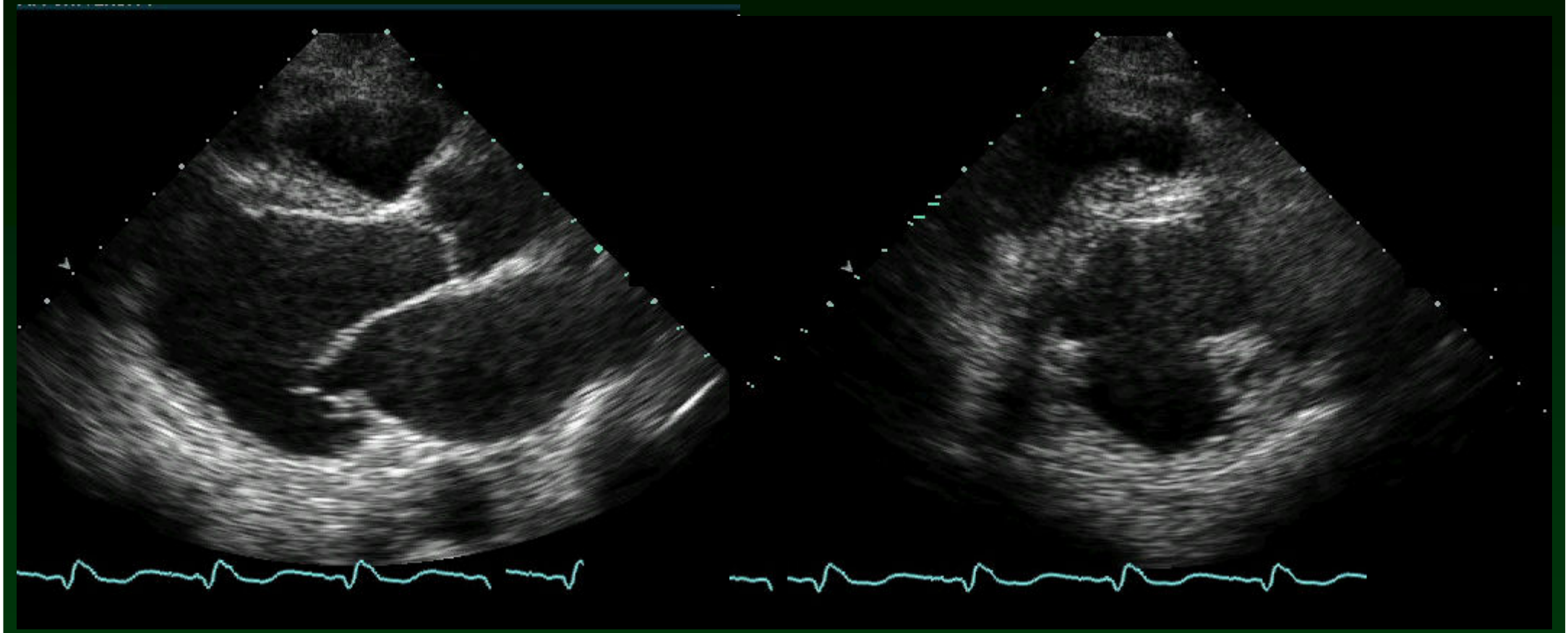
Mimicking HCM

51 yr, Male



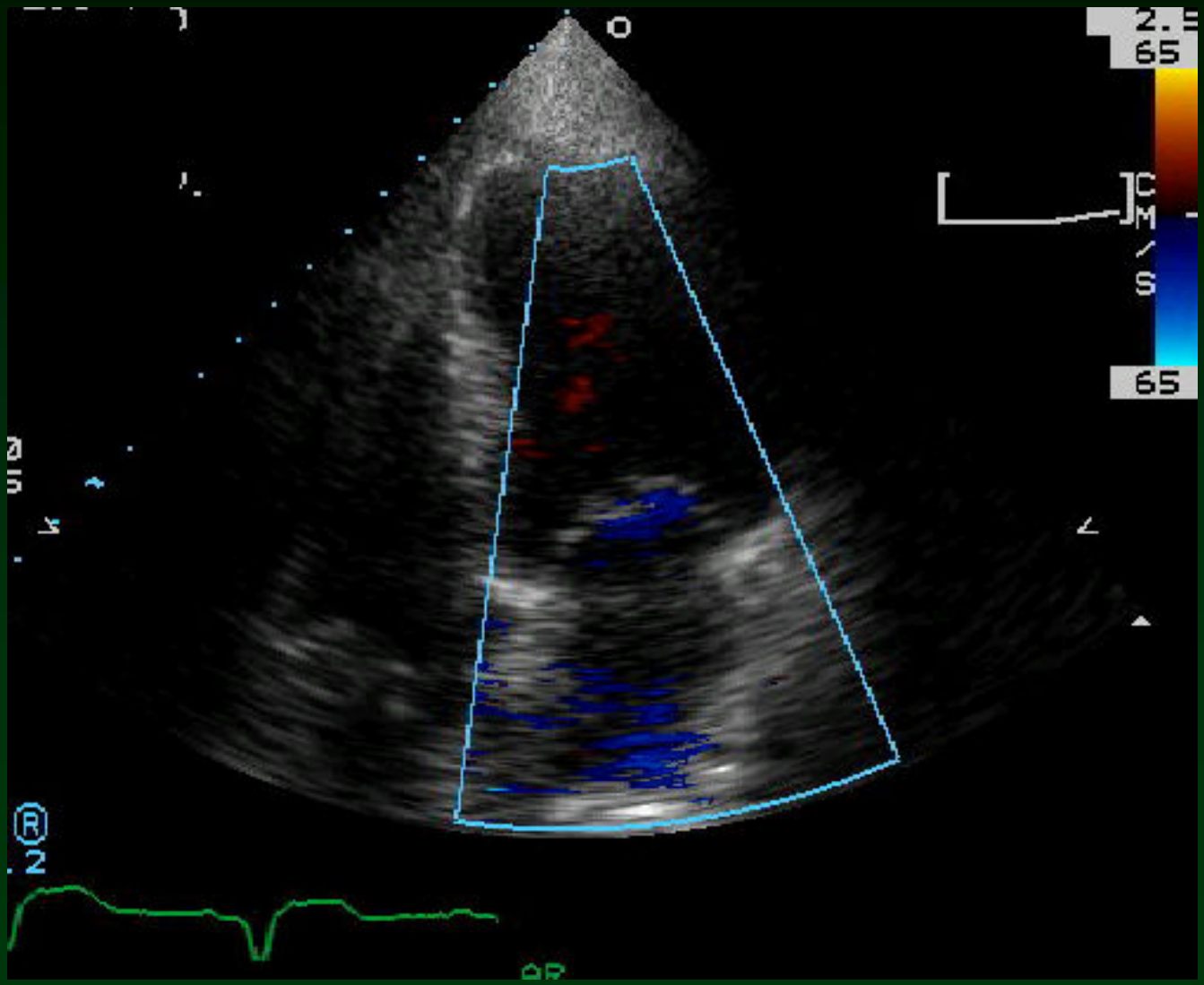
Mimicking dilated phase of HCM

77 yr, Male



Mimicking dilated phase of HCM

77 yr, Male

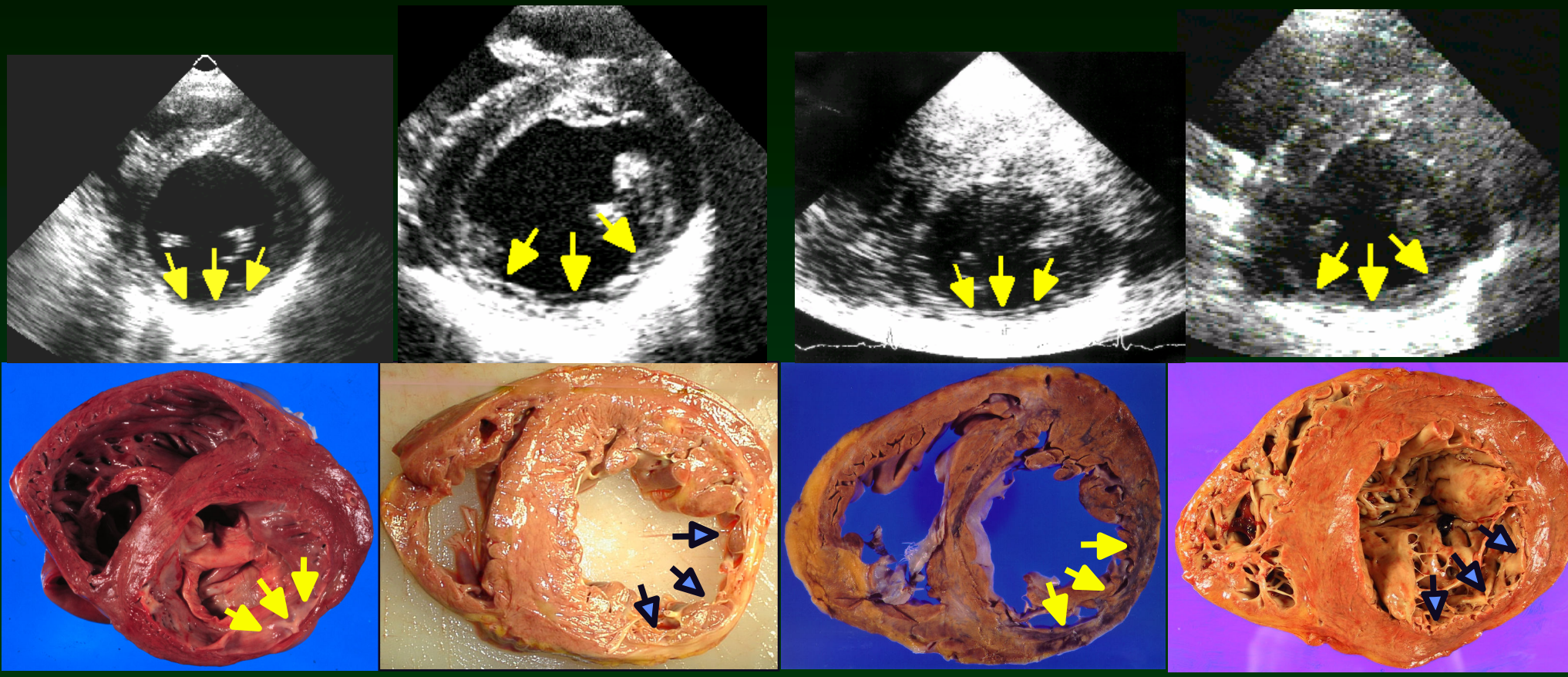


Clinical Characteristics of Autopsied Patients

Patient No.	1	2	3	4
Age of death (yr)	66	68	63	66
Cause of death	Ventricular fibrillation	Heart failure	Heart failure	Heart failure	Heart failure
Plasma α-gal A (nmol/hr/ml)	1.2	1.2	1.3	1.0	0.4
IVSth (mm)	20	17	16	17	16
LVPWth (mm)	20	14	16	16	16
Coronary angiogram	Normal	Normal	Normal	Normal	Normal
Albuminuria	–	–	–	–
Serum creatinine (mg/dl)	1.2	0.9	0.9	1.1
Angiokeratoma	–	–	–	–
Acroparesthesia	–	–	–	–
Hypohidrosis	–	–	–	–
Corneal opacity	–	–	–	–

Echo vs Histology

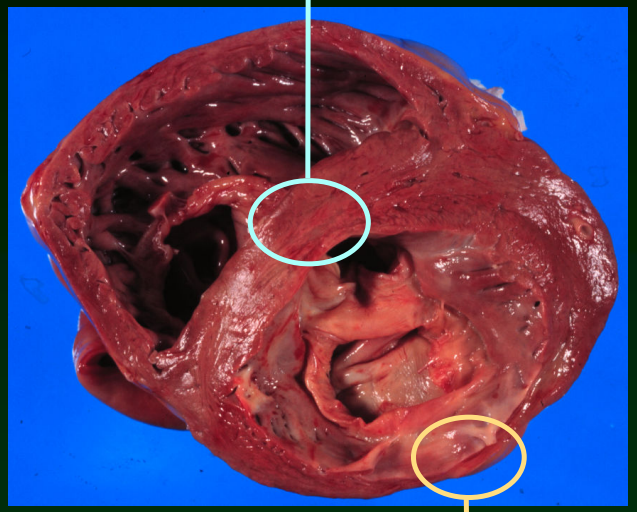
Case 2 Case 3 Case 4 Case 5



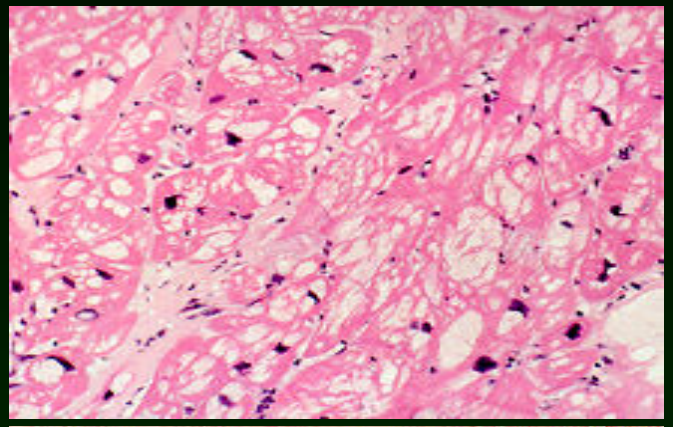
Thinning of basal posterior wall

Pathological Findings of the Heart

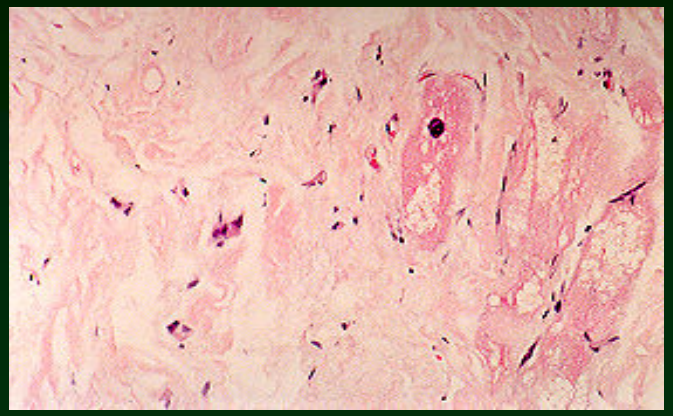
Case 2



H.E. staining

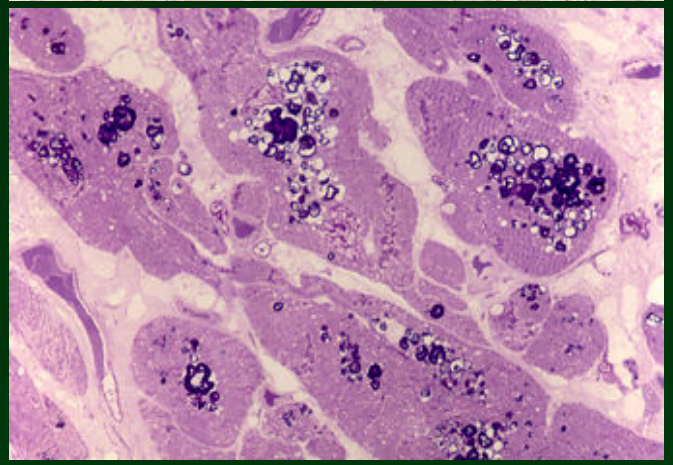


H.E. staining

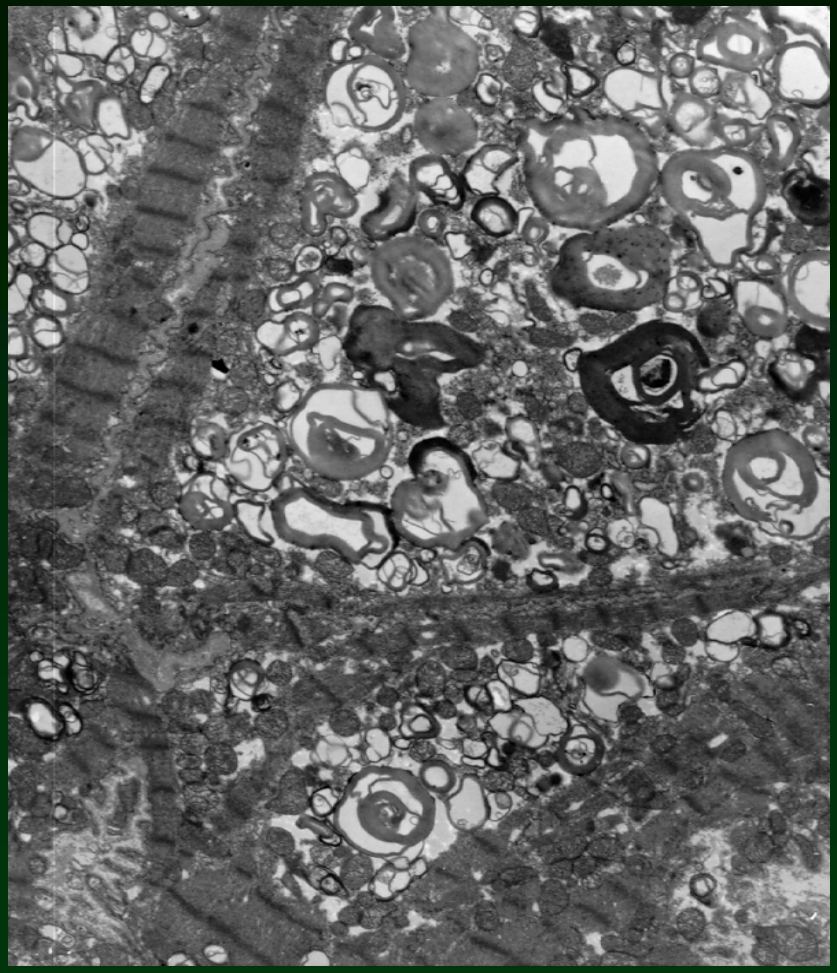


Case 3

T.B. staining



Electron Microscopy



Low magnification

High magnification

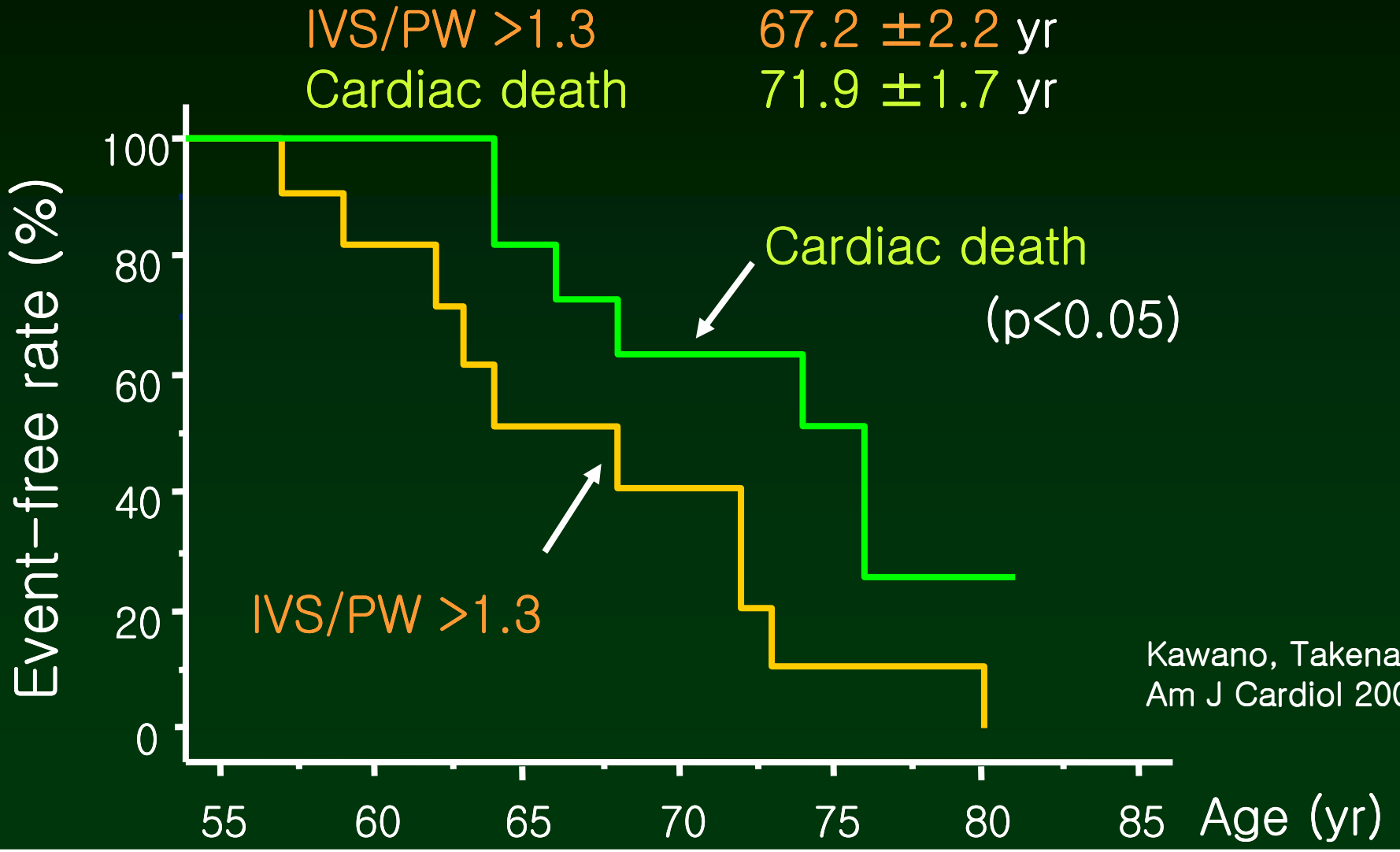
Significance of Asymmetric Basal Posterior Wall Thinning in Patients with Cardiac Fabry's Disease.

Kawano, Takenaka et al., Am J Cardiol 2007; 99.

To evaluate whether disappearance of basal posterior hypertrophy and elevation of Tei index can be predictors of cardiac death.

Event-free Rate:

Disappearance of Basal Posterior Hypertrophy and Cardiac Death

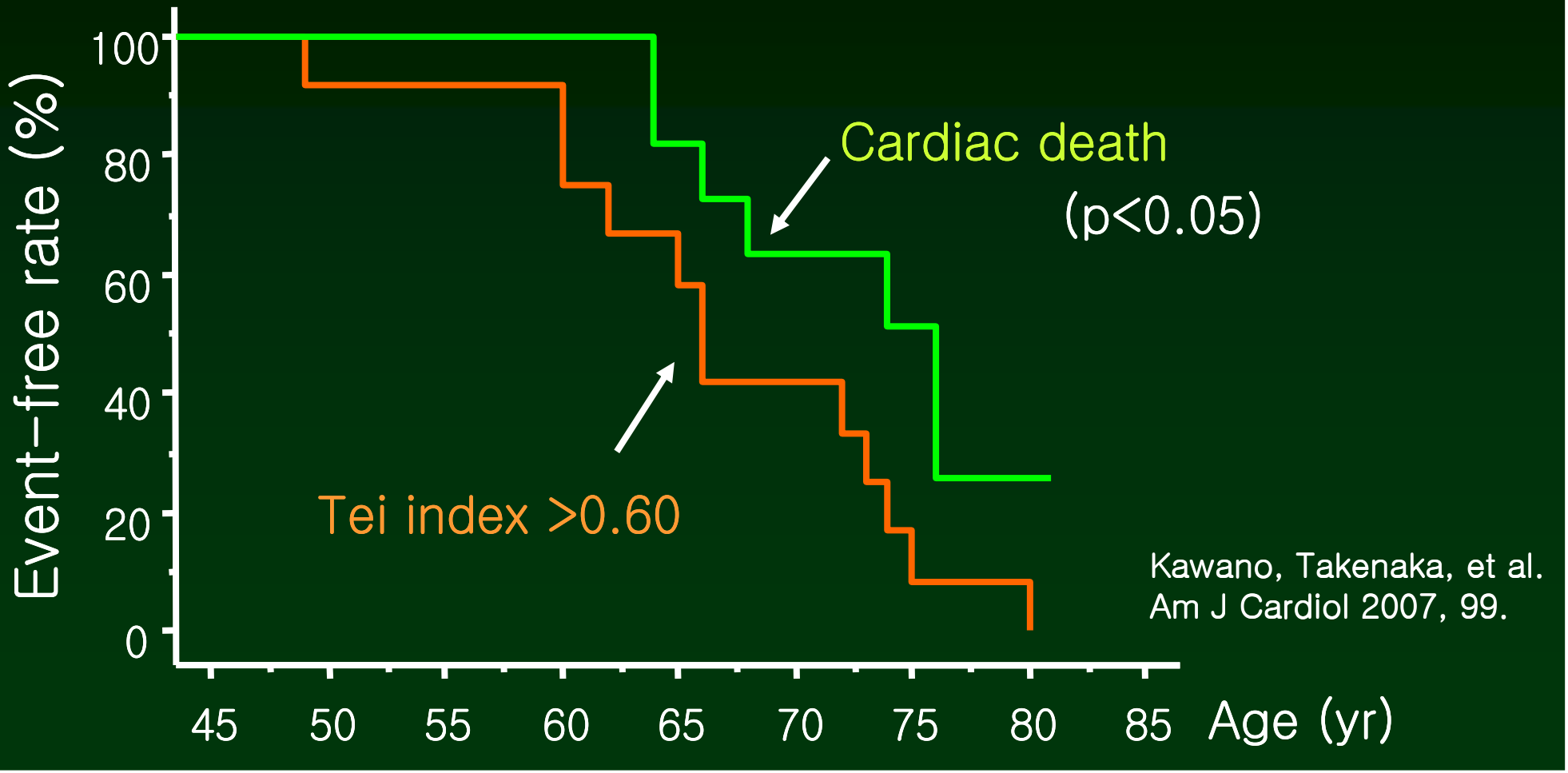


Kawano, Takenaka, et al.
Am J Cardiol 2007, 99.

Event-free Rate:

Tei index >0.60 and Cardiac Death

Tei index >0.60 66.8 ±2.5 yr
Cardiac death 71.9 ±1.7 yr



Kawano, Takenaka, et al.
Am J Cardiol 2007, 99.

Disappearance of basal posterior hypertrophy and elevated Tei index is a characteristic echocardiographic finding which precedes cardiac death in patients with cardiac Fabry disease.

Female carriers (Heterozygote) – 1

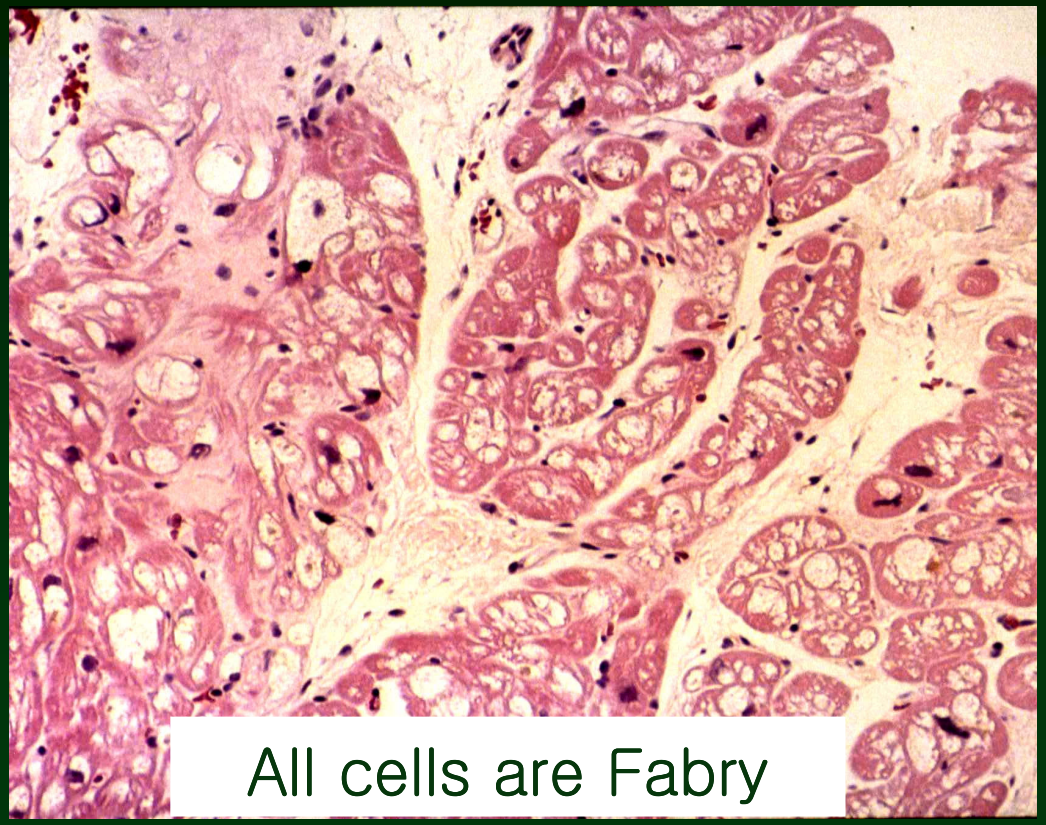
1. Fabry disease is an X-linked disorder.
2. Female carriers have 2 X chromosomes, one is normal and the other is mutated.
3. At the cellular level, female carriers have two populations of cells, one with normal and the other with mutant enzymatic activity resulting from the random inactivation of one X chromosome in each cell early in embryogenesis.

Female carriers (Heterozygote) – 2

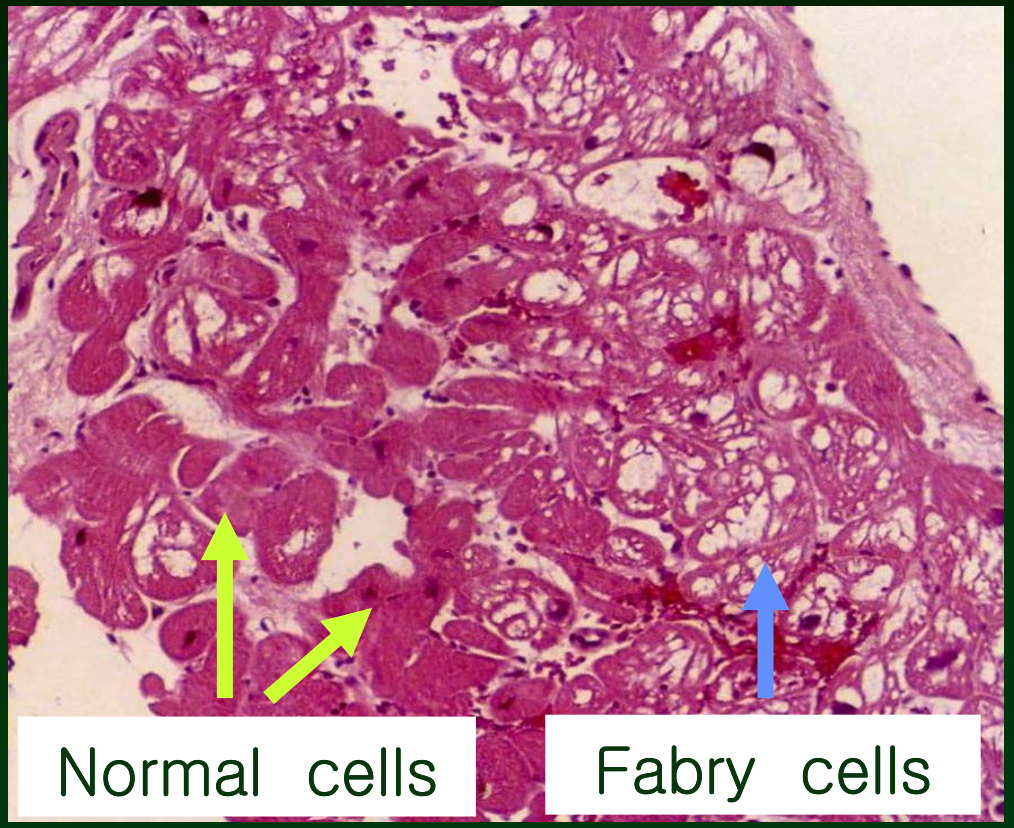
1. Theoretically, 50% of the cells are normal and the remaining 50% are diseased in female carriers.
2. Female carriers may have attenuated form of the disease. They usually are asymptomatic, although rarely can be as severely affected as males.

Endomyocardial-Biopsy Specimen

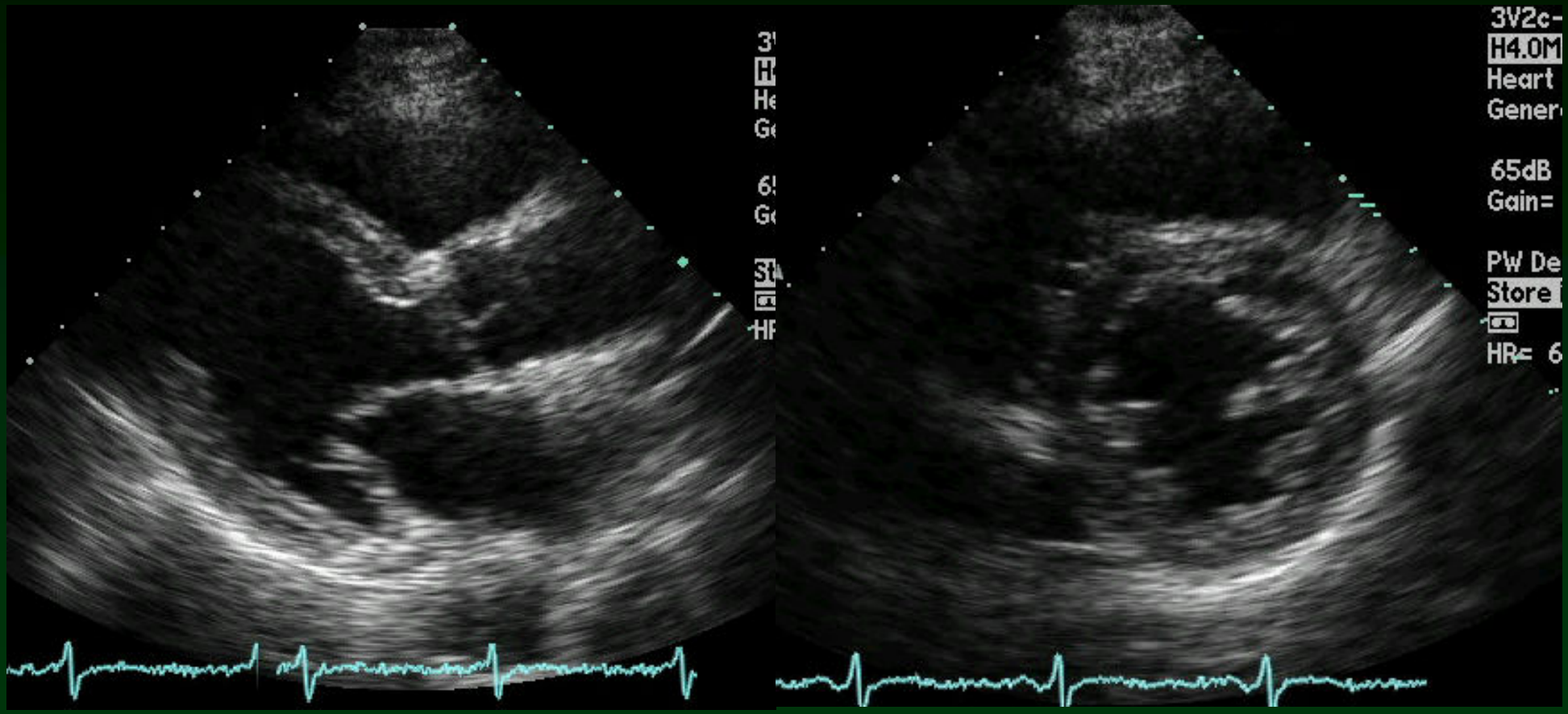
Male
(hemizygote, X'Y)



Female
(heterozygote, X'X)

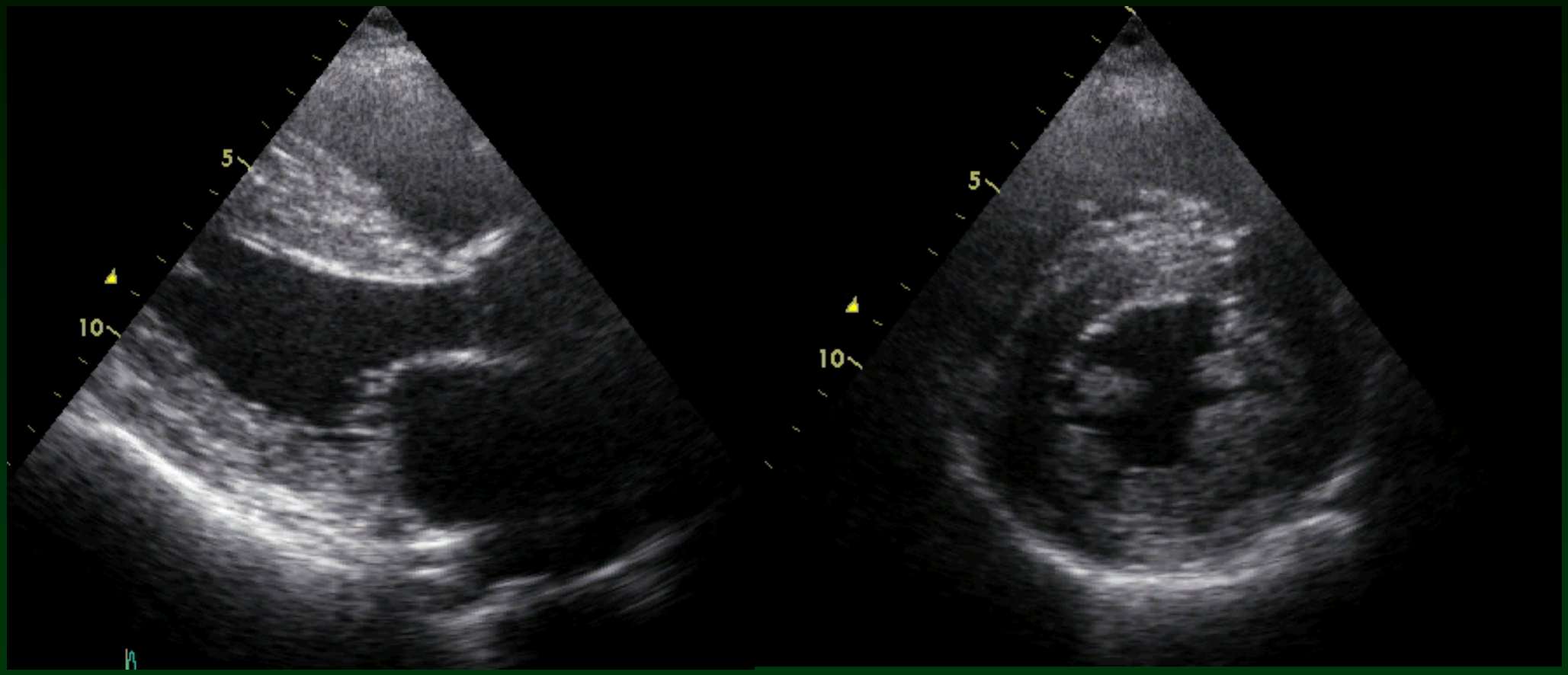


56 yr, Female



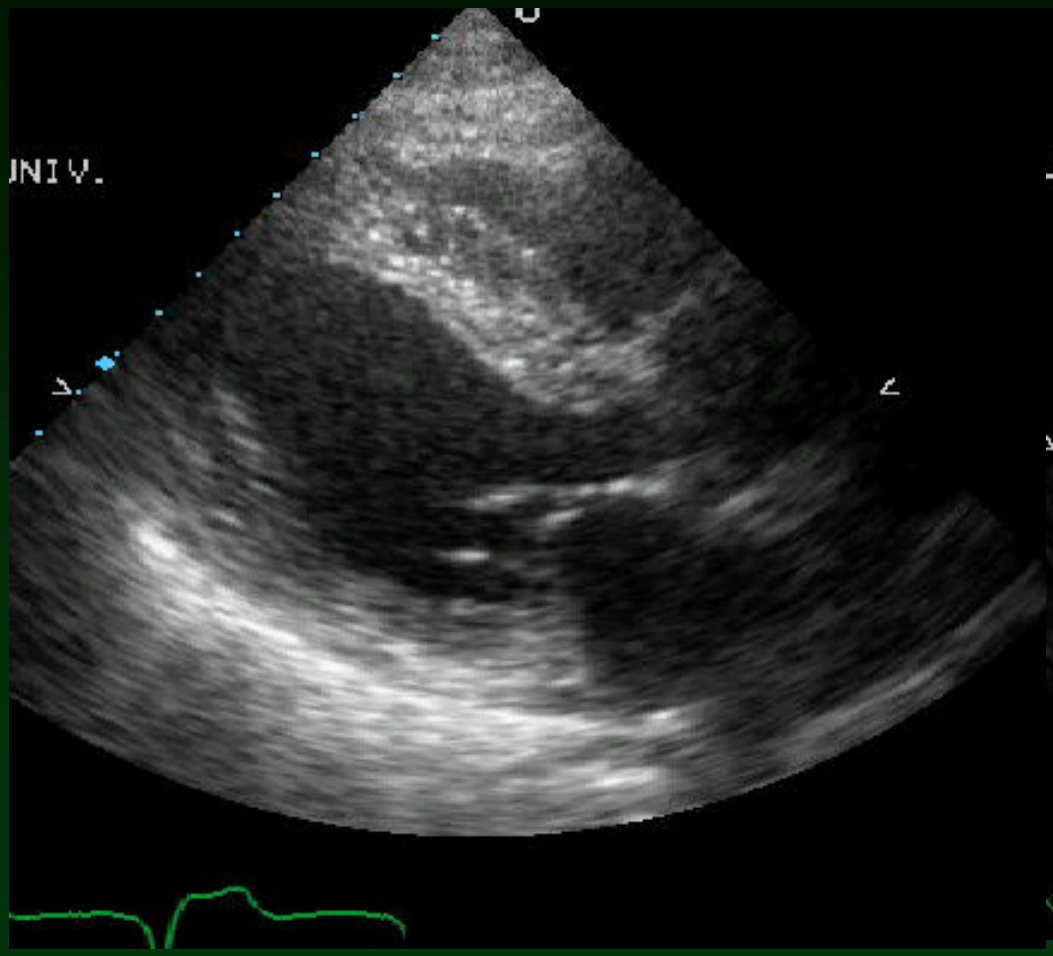
Looks like normal

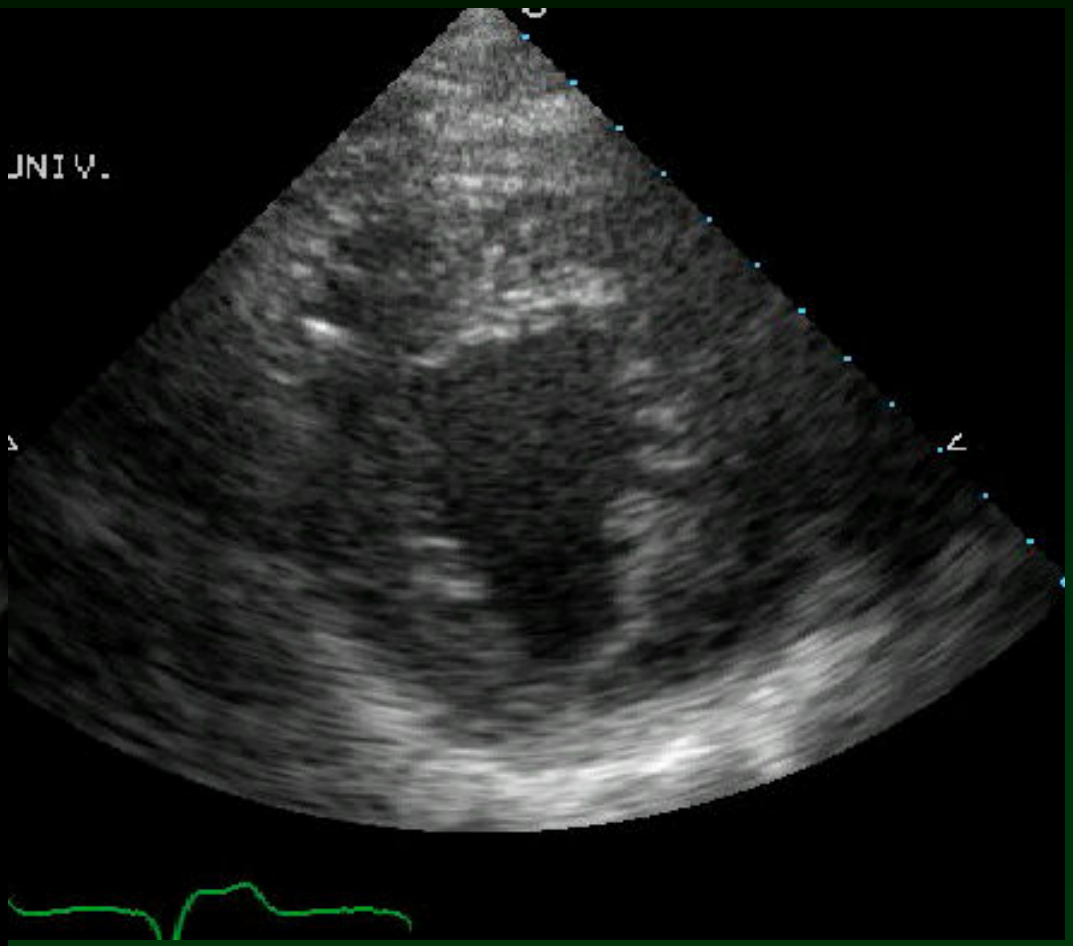
61 yr, Female



Mimicking HCM

78 yr, Female





Mimicking dilated phase of HCM

Overview

1. Incidence
2. Clinical Features
3. ERT and the heart

Treatment for Fabry Disease

1. Enzyme Replacement Therapy (ERT)

Approved in Europe (2001)
Approved in USA (2003)
Approved in Japan (2004)
Approved in Korea (2004)

2. Gene Therapy

Experimental studies using
retroviral, adeno-associated viral,
or

Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease: A prospective strain rate imaging study

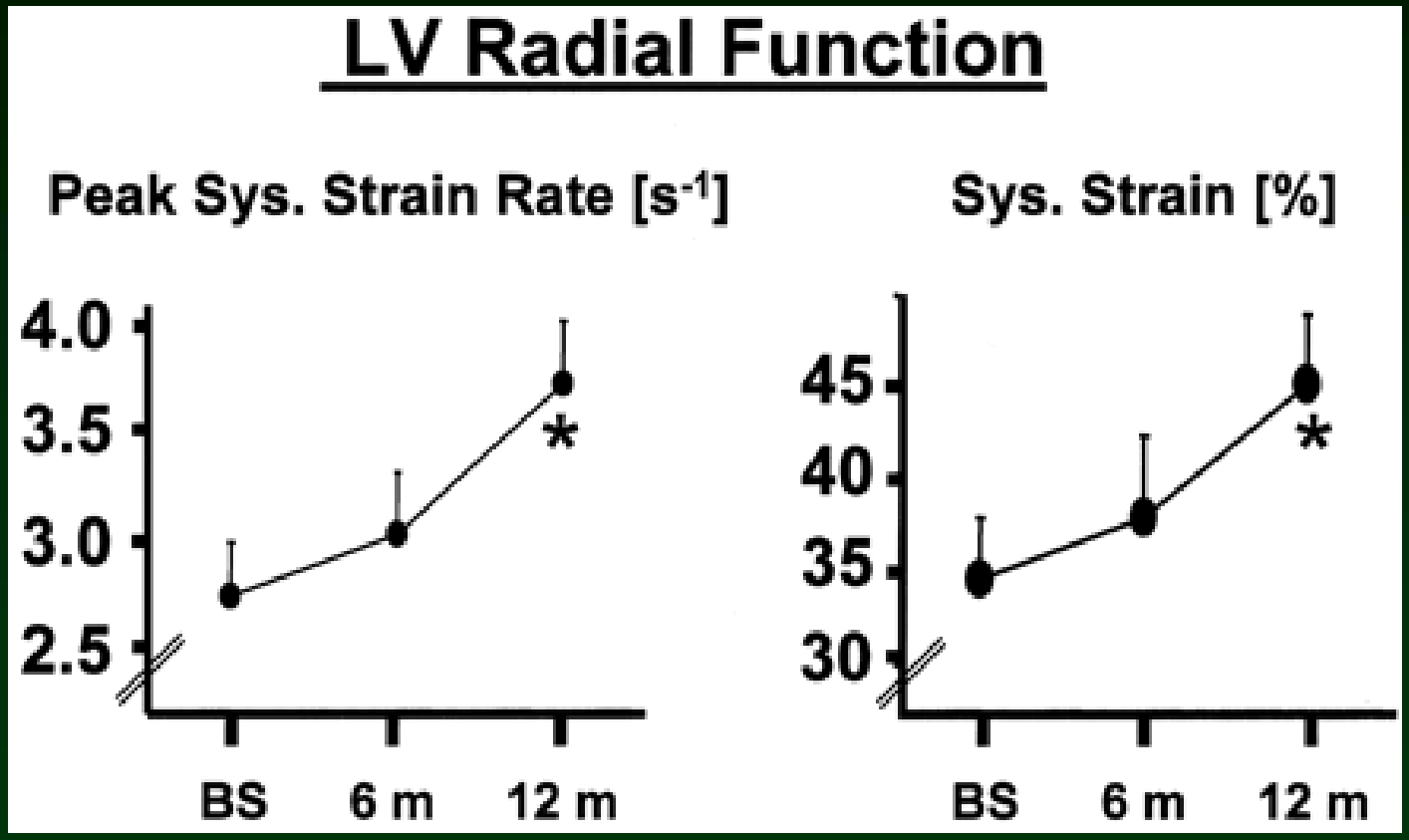
Weidemann et al., Circulation 2003; 108.

Echocardiographic and MRI Findings
Before and After ERT

16 patients (Age 42±3 yr)

	Before ERT	After ERT (12 months)	
DcT	242±11	258±12	n.s.
E/A	1.3±0.2	1.4±0.1	n.s.
EF (%)	62±1	64±1	n.s.
LVPWth (mm)	13.8±0.6	11.8±0.6	p<0.05
LV mass (g)	201±18	180±21	p<0.05

LV Radial Function
Before and After 6 and 12 Months of ERT



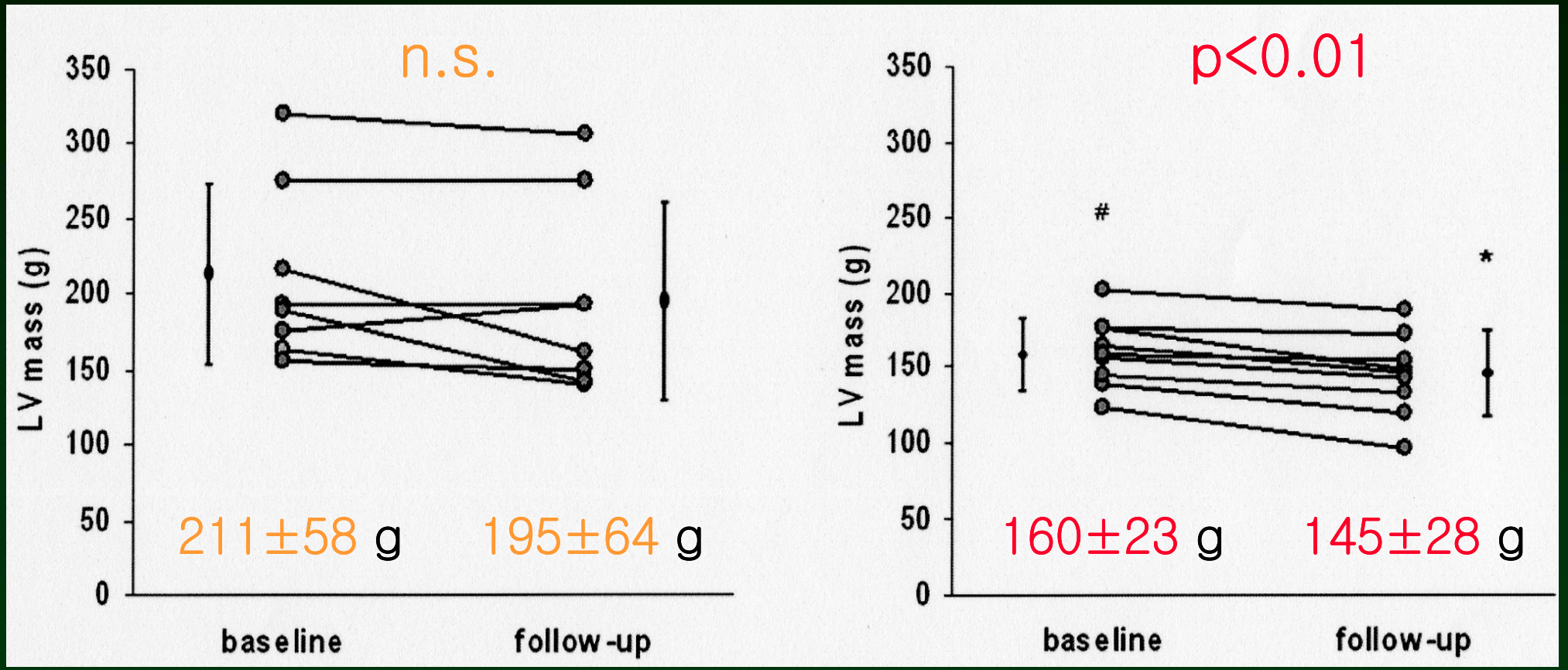
Weidemann et al., Circulation 200

Impact of enzyme replacement therapy on cardiac morphology and function and late enhancement in Fabry's cardiomyopathy

Beer et al., Am J Cardiol 2006; 97.

Efficacy of ERT: Changes of LV mass

Fibrosis (+)



Fibrosis (–)

Beer et al. Am J Cardiol 2006, 97.

First studies have done for patients with preserved global LV function and have shown efficacy of ERT to reduce LVH and improve regional LV function.

Enzyme Replacement Therapy

Questions need to be clarified

1. Who should be treated?

   All hemizygotes and heterozygotes?

2. When should ERT be started?

   Is ERT effective for patients with deteriorated LV function?

3. How long should ERT be continued?

   For life-long?

Specific and effective therapy is now available for patients with Fabry disease, so it is very important to diagnose patients with the disease at early stage.

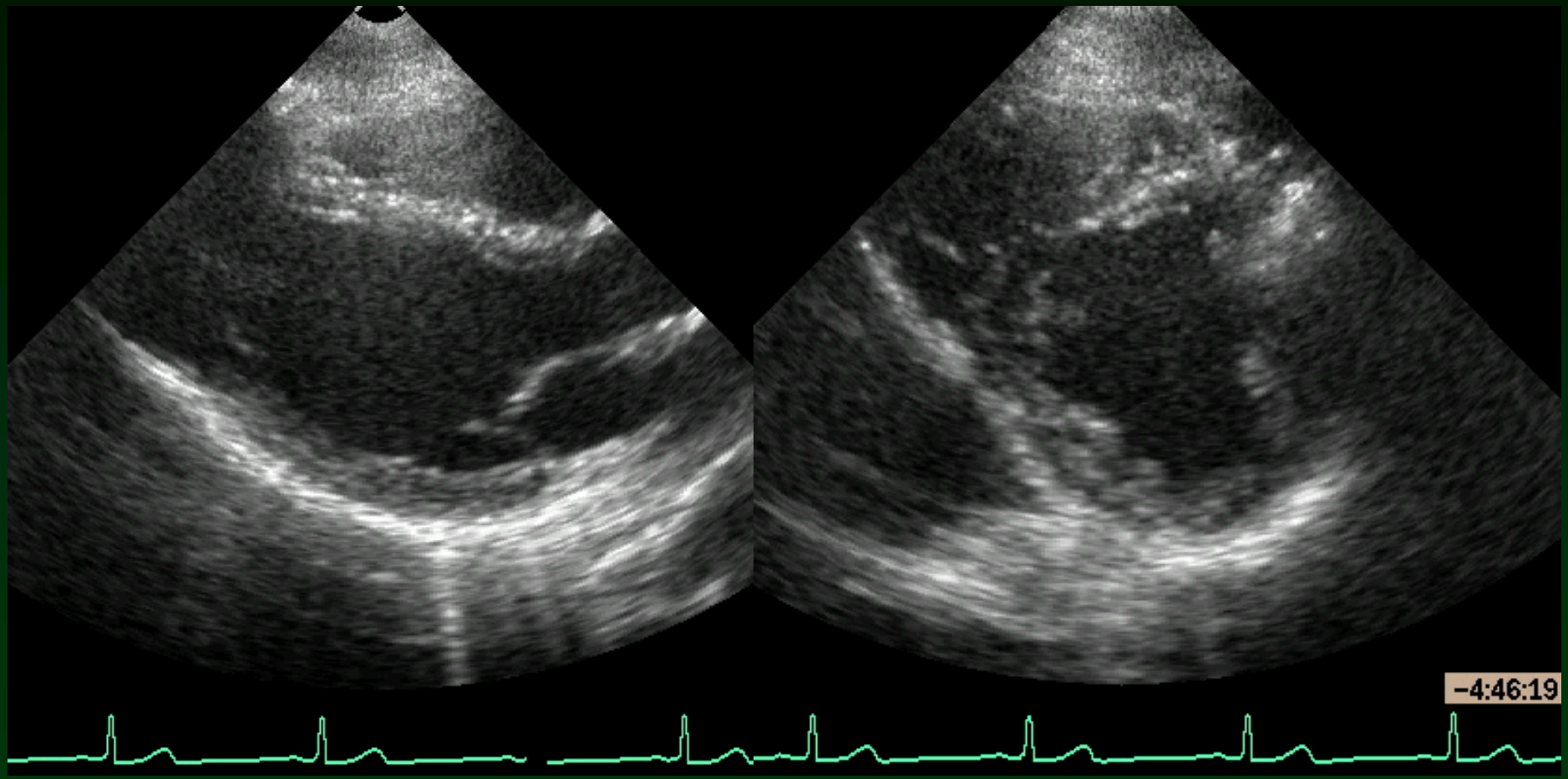
Can cardiologists suspect Fabry disease, especially cardiac variant of the disease, by routine non-invasive cardiac examinations?

1. It is not easy to differentiate Fabry disease from the other unexplained LVH by routine non-invasive examinations such as ECG, echocardiogram and MRI.
2. At present, plasma α-galactosidase A activities should be evaluated for patients with unexplained LVH.
3. We wish to find out some specific findings which can lead to suspect Fabry disease by routine examinations.

Cardiac Findings at Diagnosis

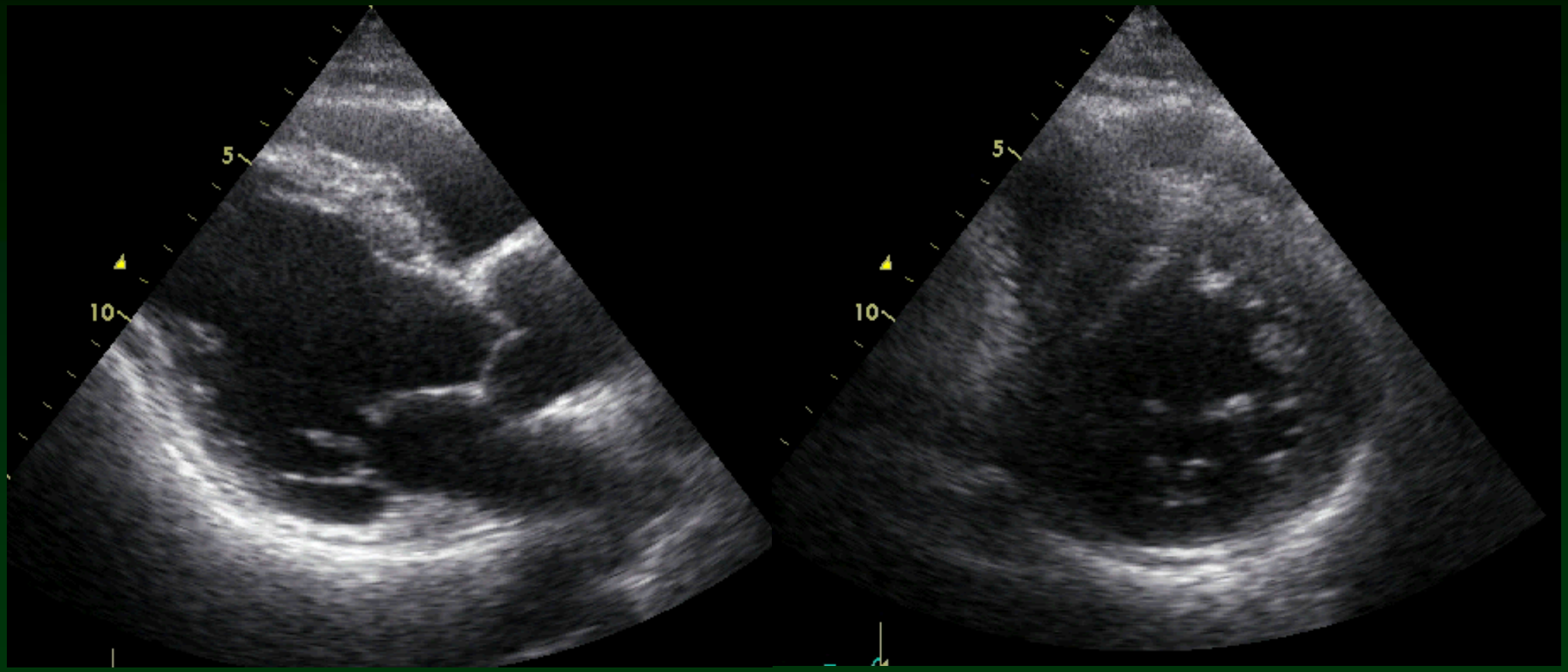
1. Left ventricular hypertrophy
2. LV dysfunction
   diastolic and/or systolic dysfunction
3. ECG abnormalities
   atrioventricular block,
   intraventricular conduction delay,
   LV high voltage,
   abnormal Q wave,
   VPC

28 yr, Male



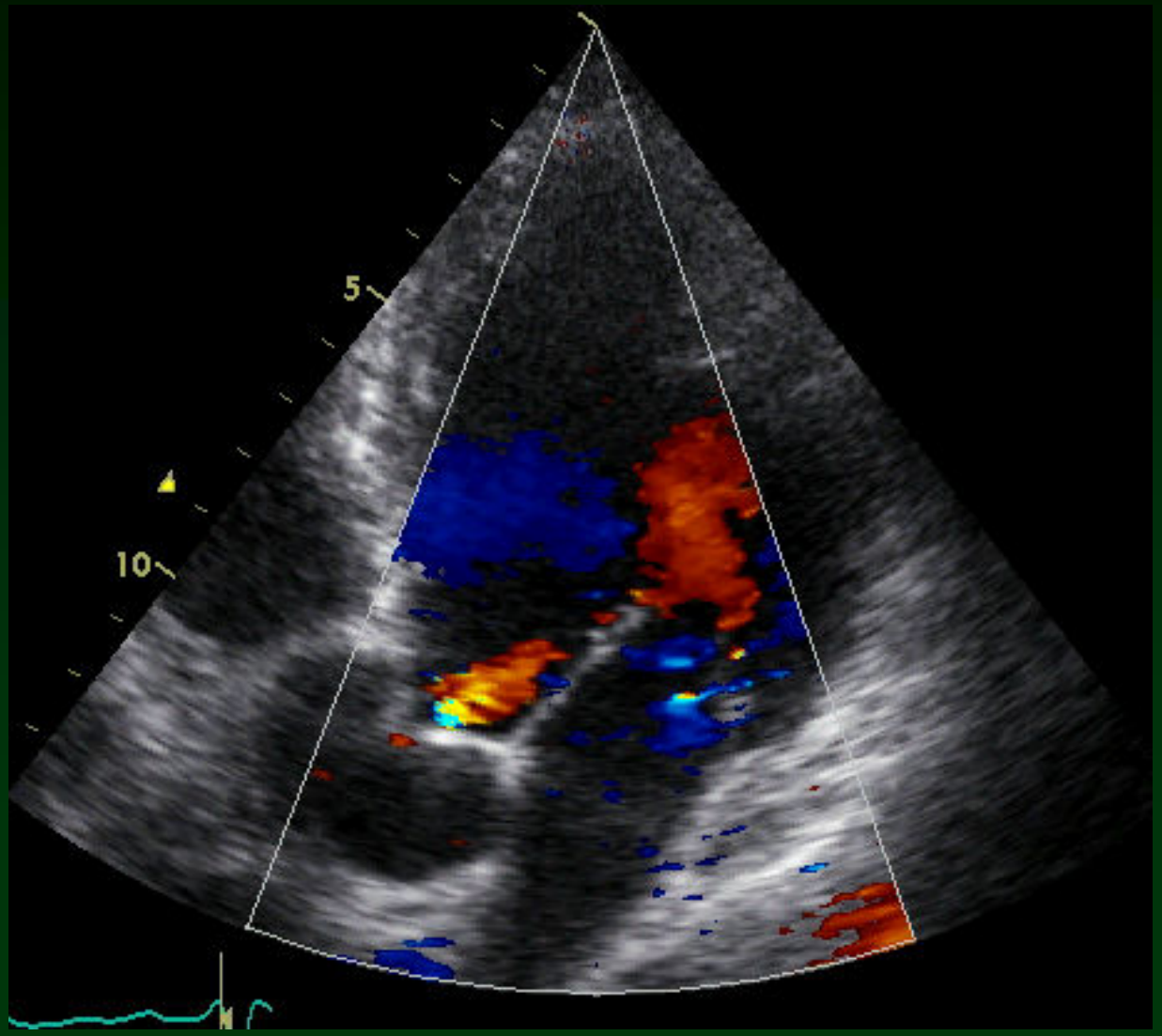
Looks like normal

81 yr, Male

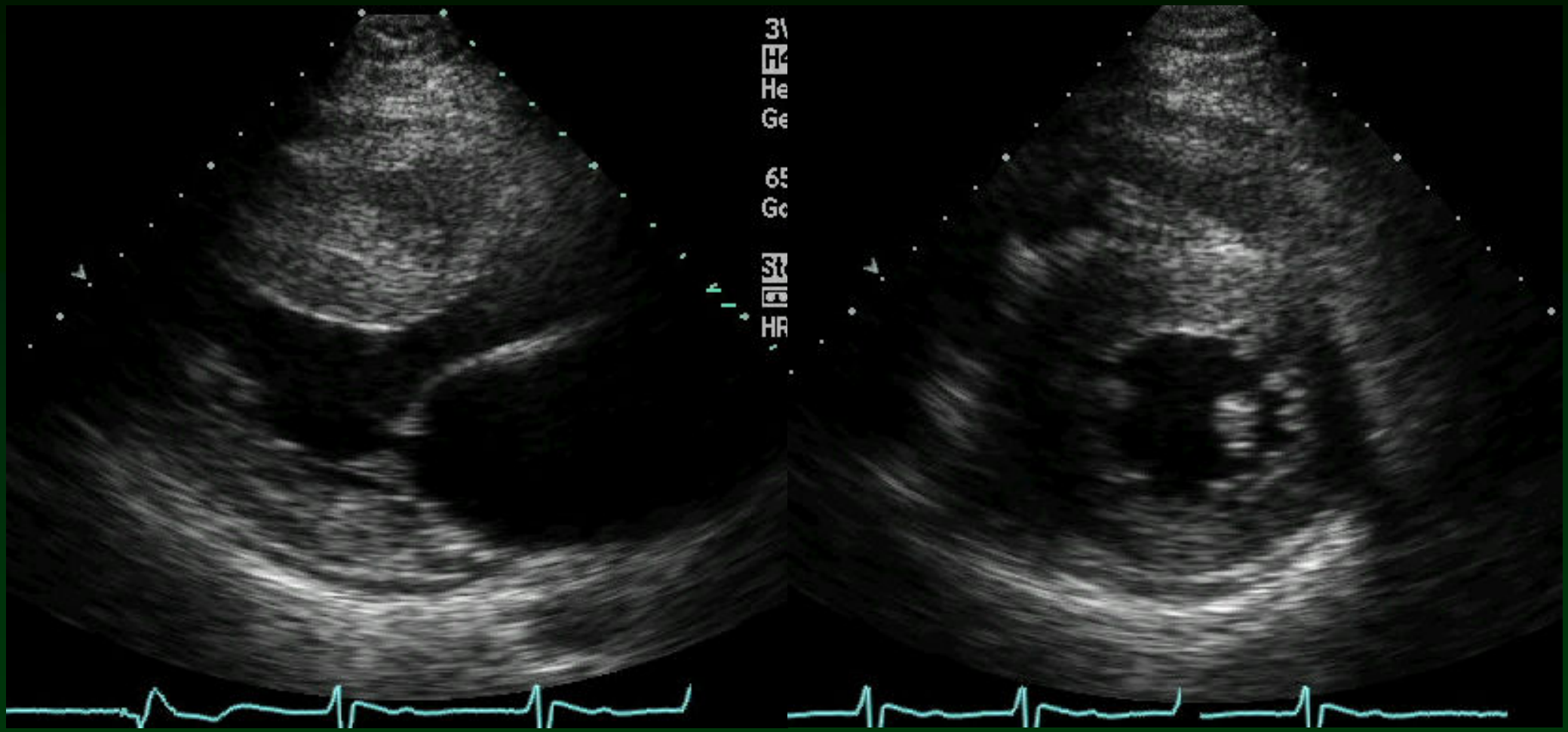


Mimicking dilated phase of HCM

81 yr, Male



57 yr, Female



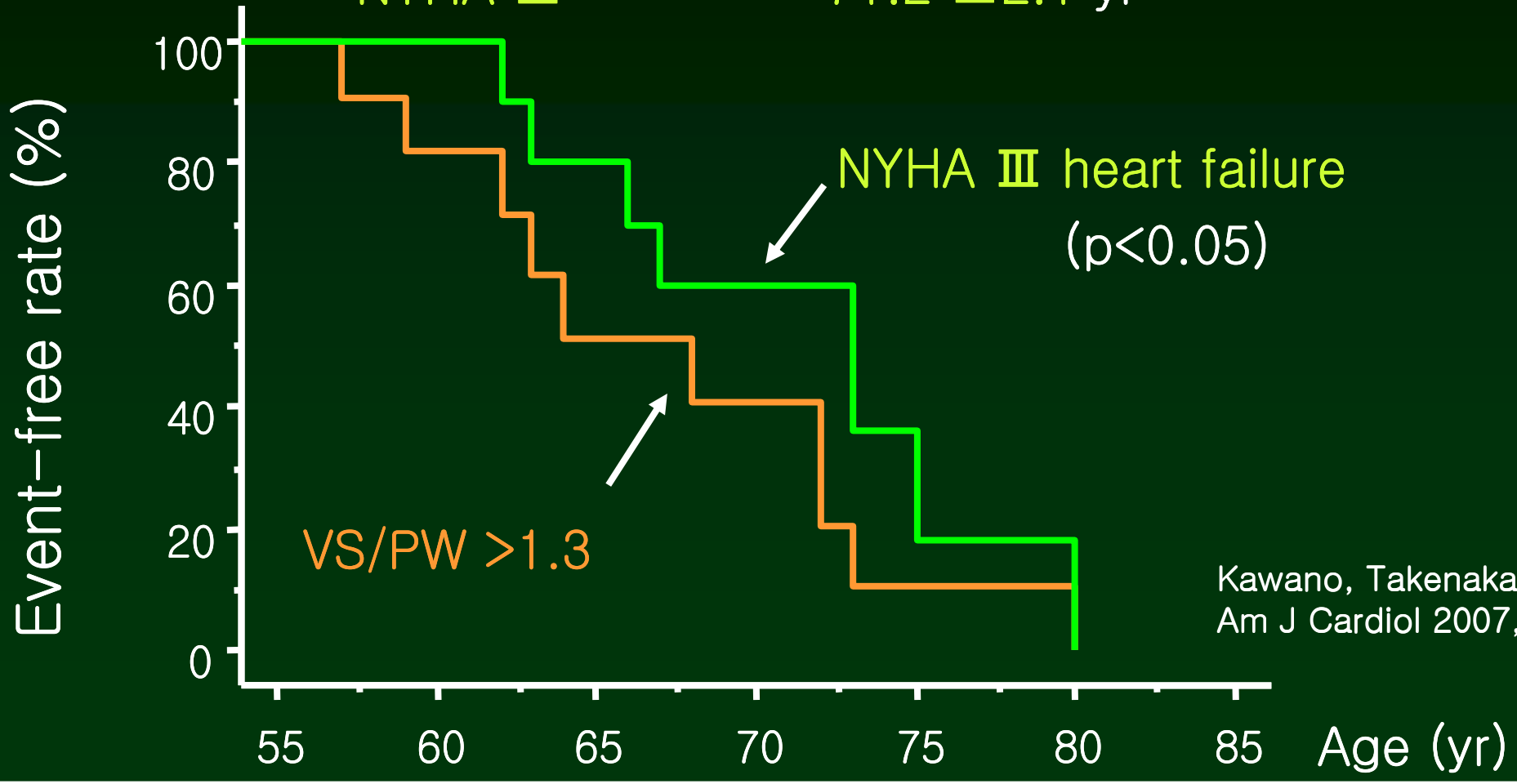
Mimicking HCM

Event-free Rate:

Disappearance of Basal Posterior Hypertrophy and NYHA III Heart Failure

VS/PW >1.3 67.2 ±2.2 yr

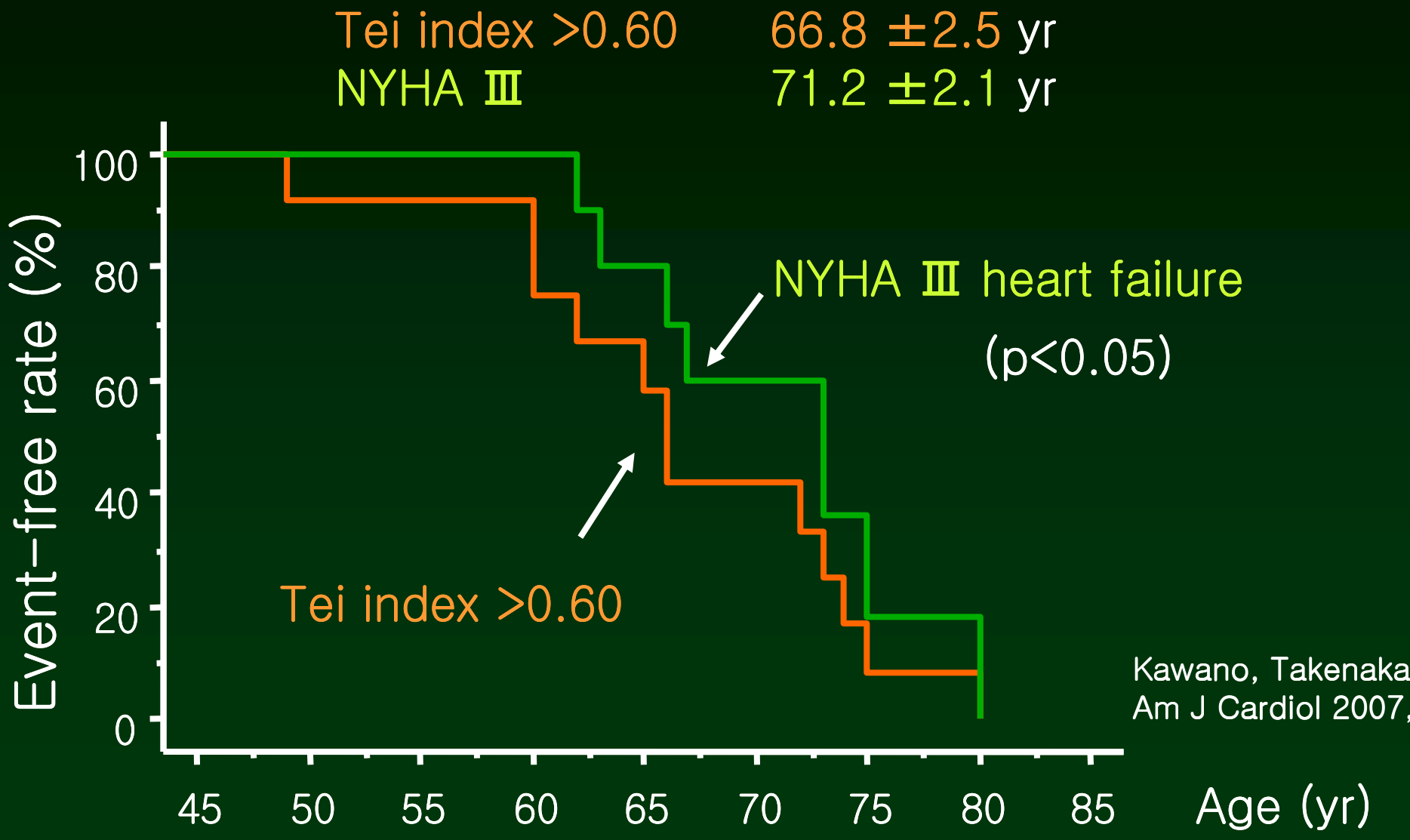
NYHA Ⅲ 71.2 ±2.1 yr



Kawano, Takenaka, et al.
Am J Cardiol 2007, 99.

Event-free Rate:

Tei index >0.60 and NYHA III Heart Failure



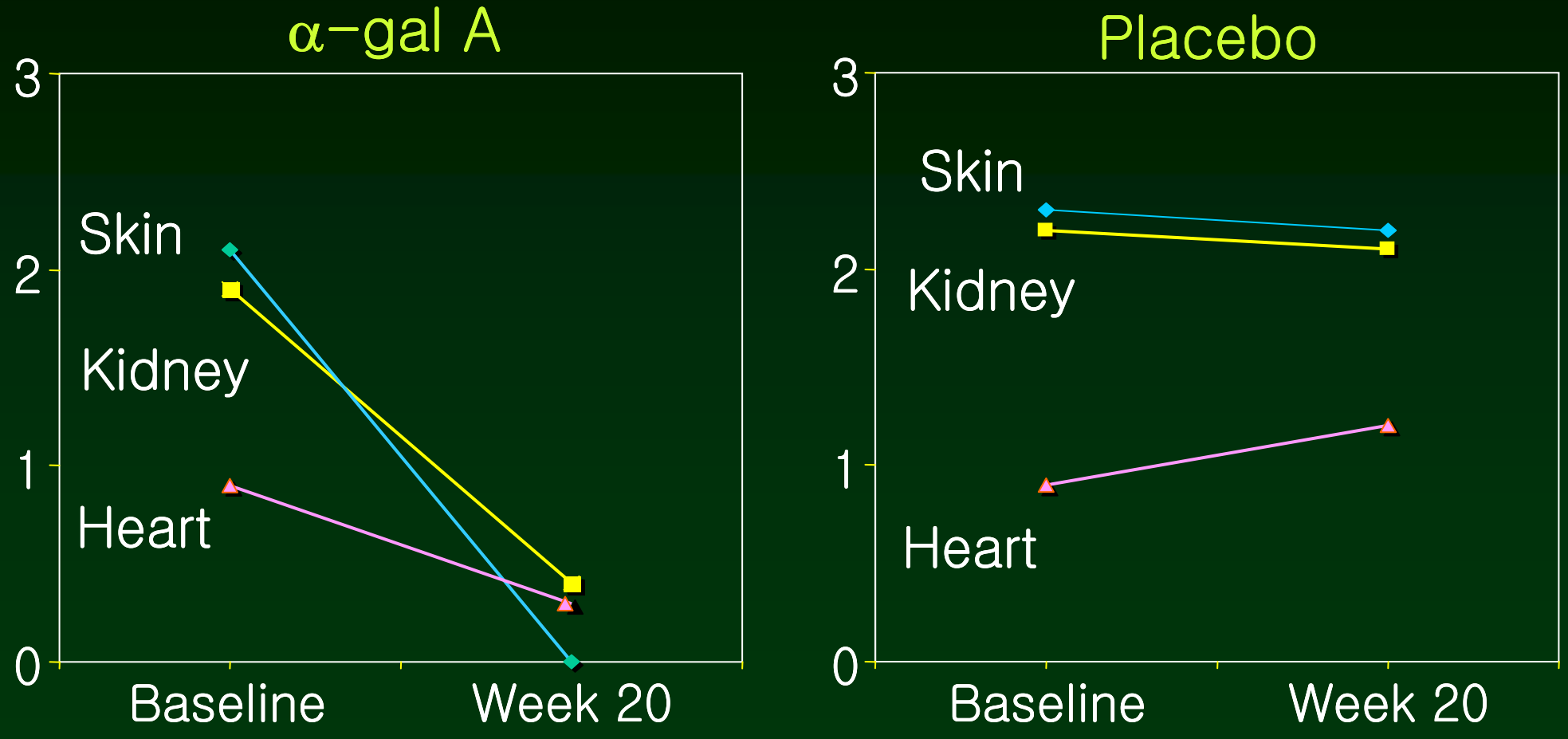
Kawano, Takenaka, et al.
Am J Cardiol 2007, 99.

Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry's Disease.

Eng, Desnick et al., N Engl J Med 2001; 345.

Efficacy of ERT

Mean Capillary Endothelium Scores

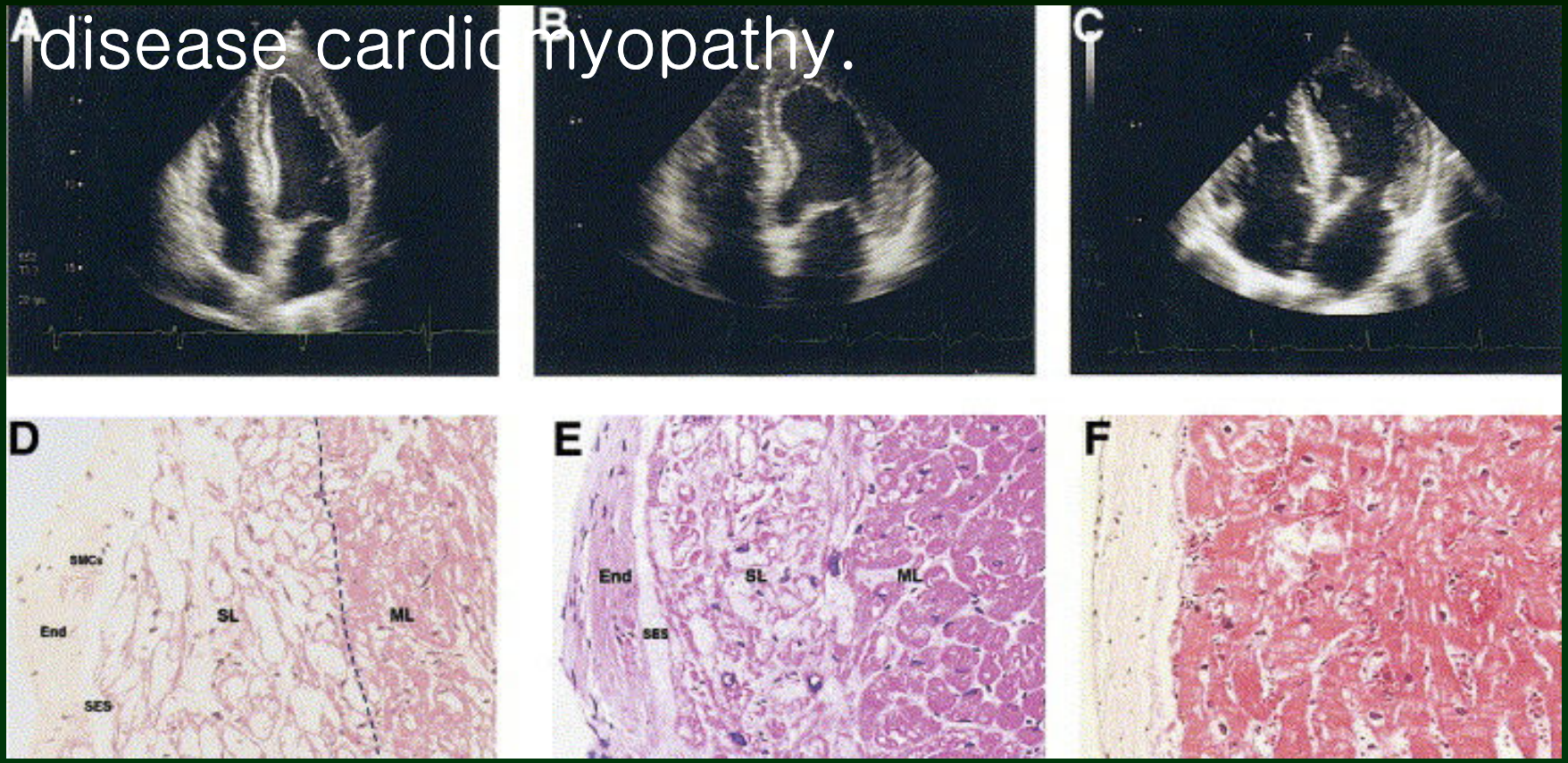


N Engl J Med 2001; 345.

Fabry's disease cardiomyopathy:
Echocardiographic detection of endomyocardial glycosphingolipid compartmentalization

Pieroni et al., J Am Coll Cardiol 2006; 47.

Echocardiographic binary appearance of LV endocardial border, reflecting endomyocardial glycosphingolipids compartmentalization, represents a sensitive and specific diagnostic hallmark of Fabry's disease cardiomyopathy.



Pieroni et al., J Am Coll Cardiol 2006; 47.