Sudden Cardiac Death in the Young in Ohio

Genetics and Pathology

The Postmortem Anatomic Examination of the Heart

E Rene Rodriguez, M.D.

and

Carmela D. Tan, M.D.

Cardiovascular Pathology Subspecialty Service

Department of Pathology

Cleveland Clinic

The Postmortem Anatomic Examination of the Heart

Learning Objectives

1. You will understand the detailed anatomical targets to approach sudden cardiac death cases.

2. You will understand the planning required to maximize yield of information in the case.

3. You will understand some of the limitations of the pathologic examination fo the heart in sudden cardiac death.

The postmortem anatomic examination of the heart (I)

- Clinical history review
- Discussion of the case with attending staff
- Review of available cardiac imaging studies
- Planning of the approach to the case (dissection, special procedures)
- Time out with team of pathology staff, pathologist assitants, resident(s)
- Dissection of the heart is variable according to the needs of the individual case (Roberts'principle 3)

The Postmortem Anatomic Examination of the Heart

Learning Objectives

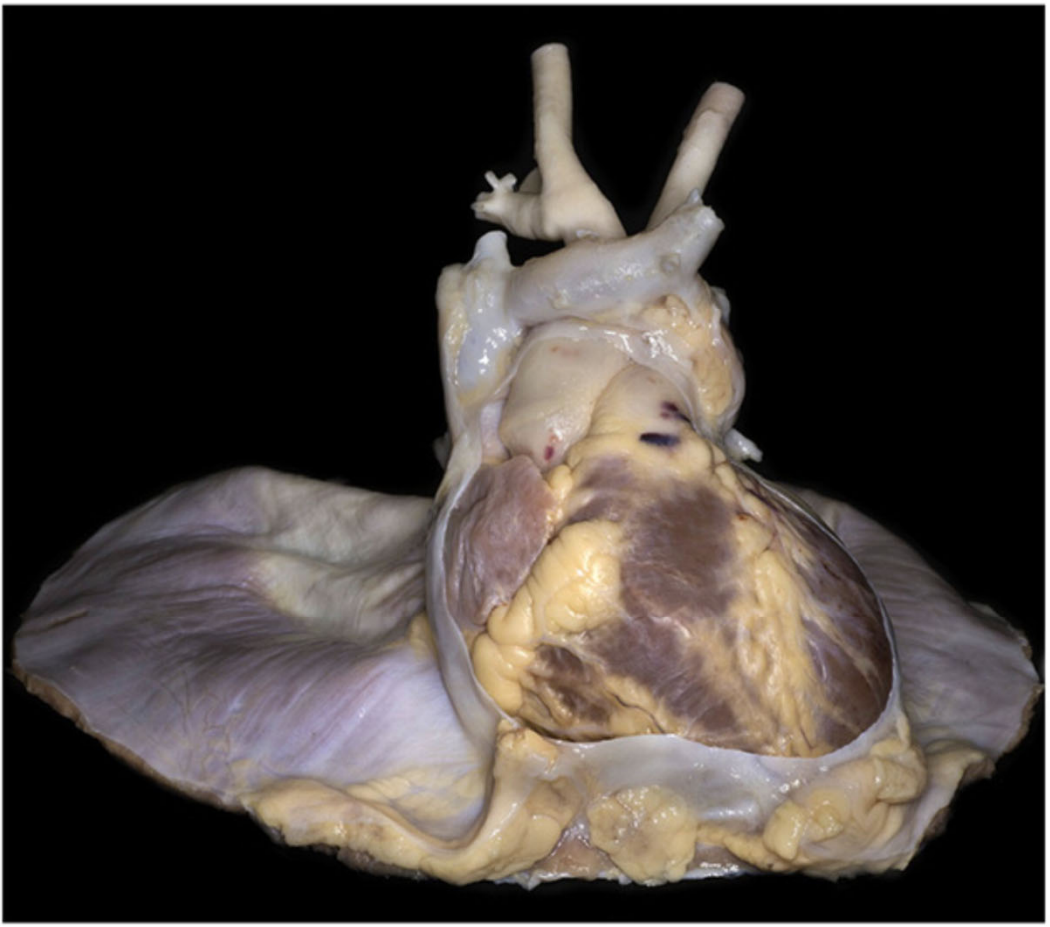
1. You will understand the detailed anatomical targets to approach sudden cardiac death cases.

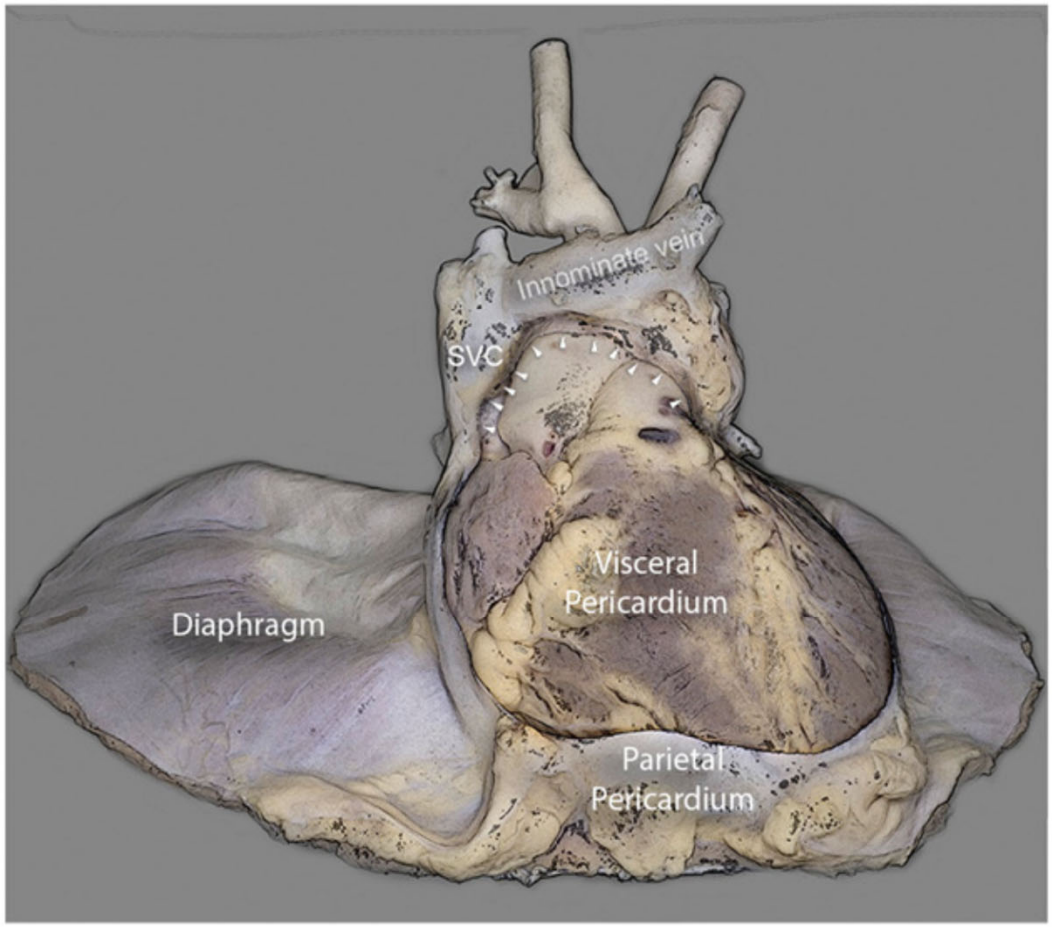
2. You will understand the planning required to maximize yield of information in the case.

3. You will understand some of the limitations of the pathologic examination fo the heart in sudden cardiac death.

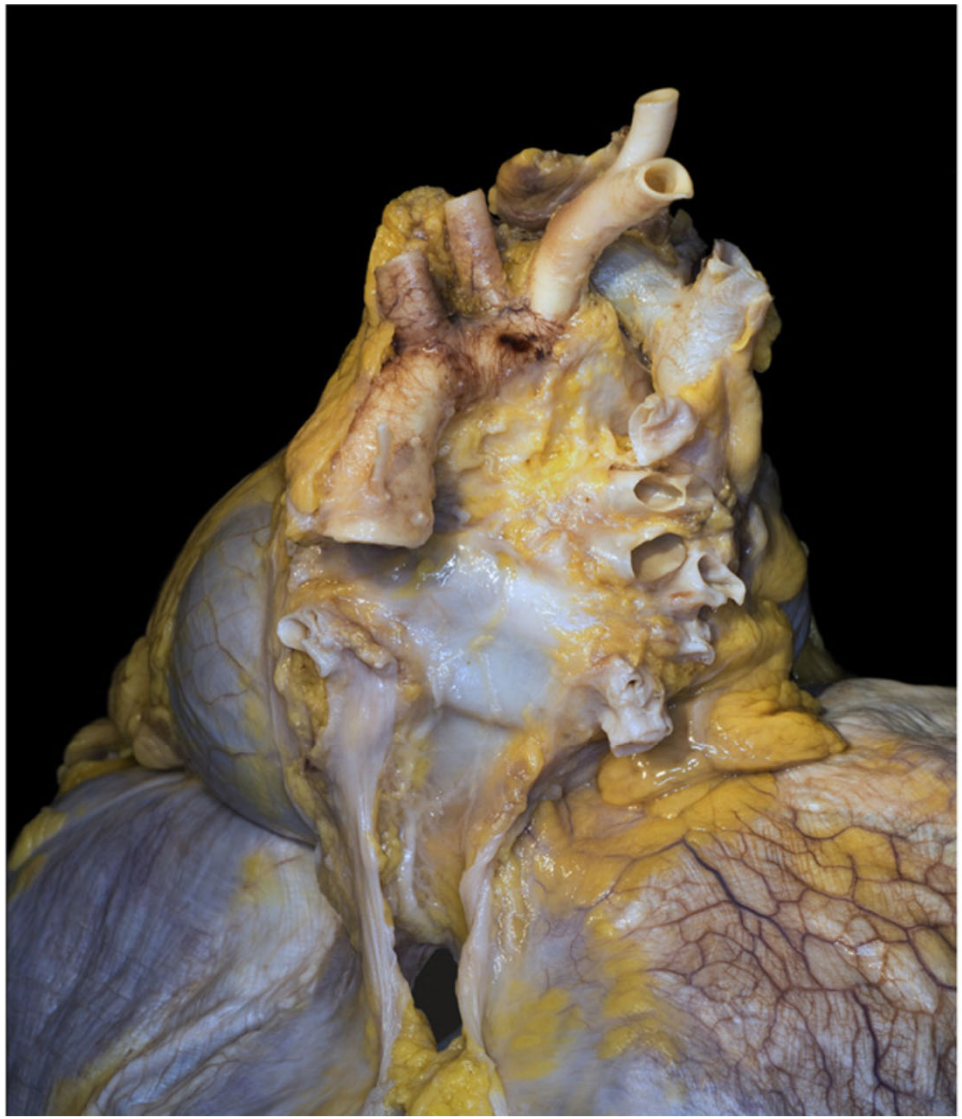
The postmortem anatomic examination of the heart (II)

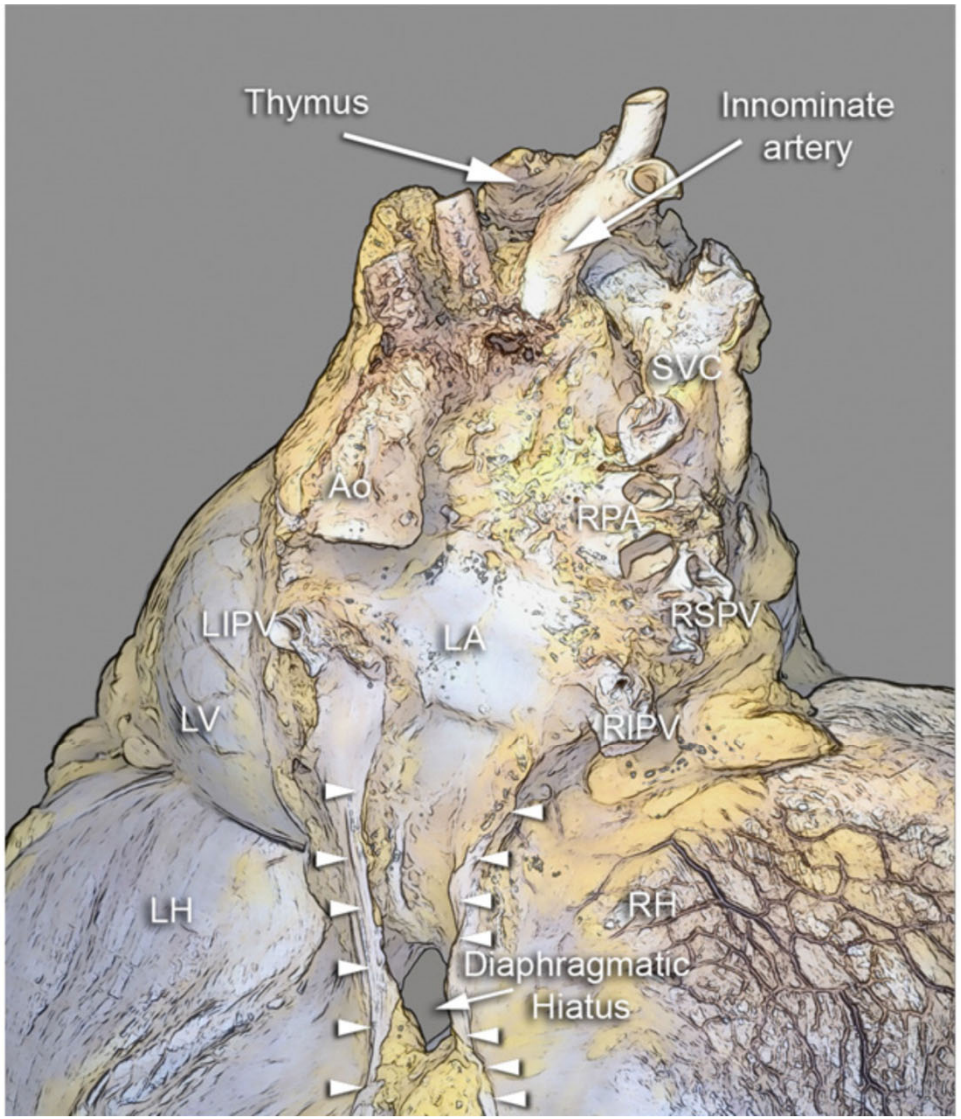
- The dissection of the heart and great vessels
- Procurement of fresh tissue as needed
- Preparation of the examination
  - Fixation
  - Planning the dissection
  - Imaging if needed



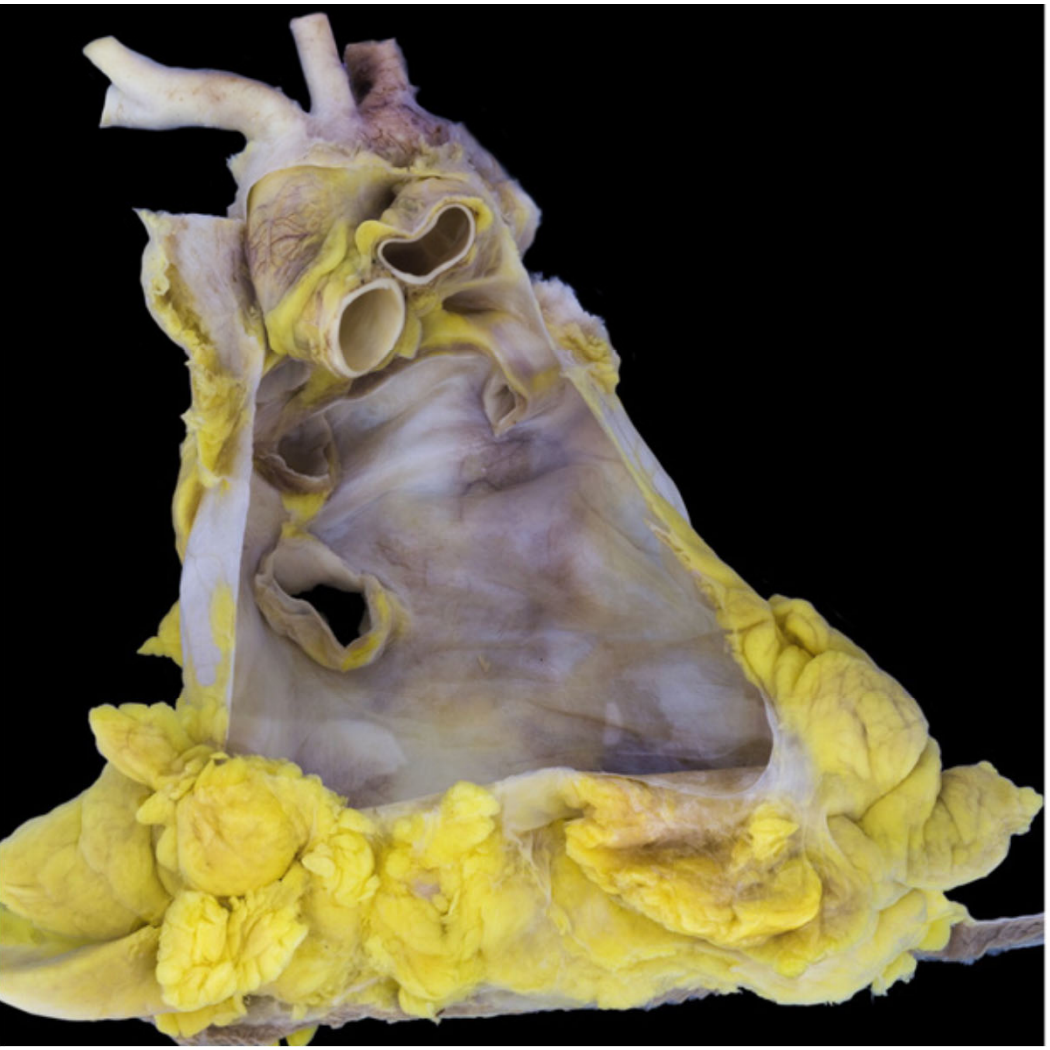


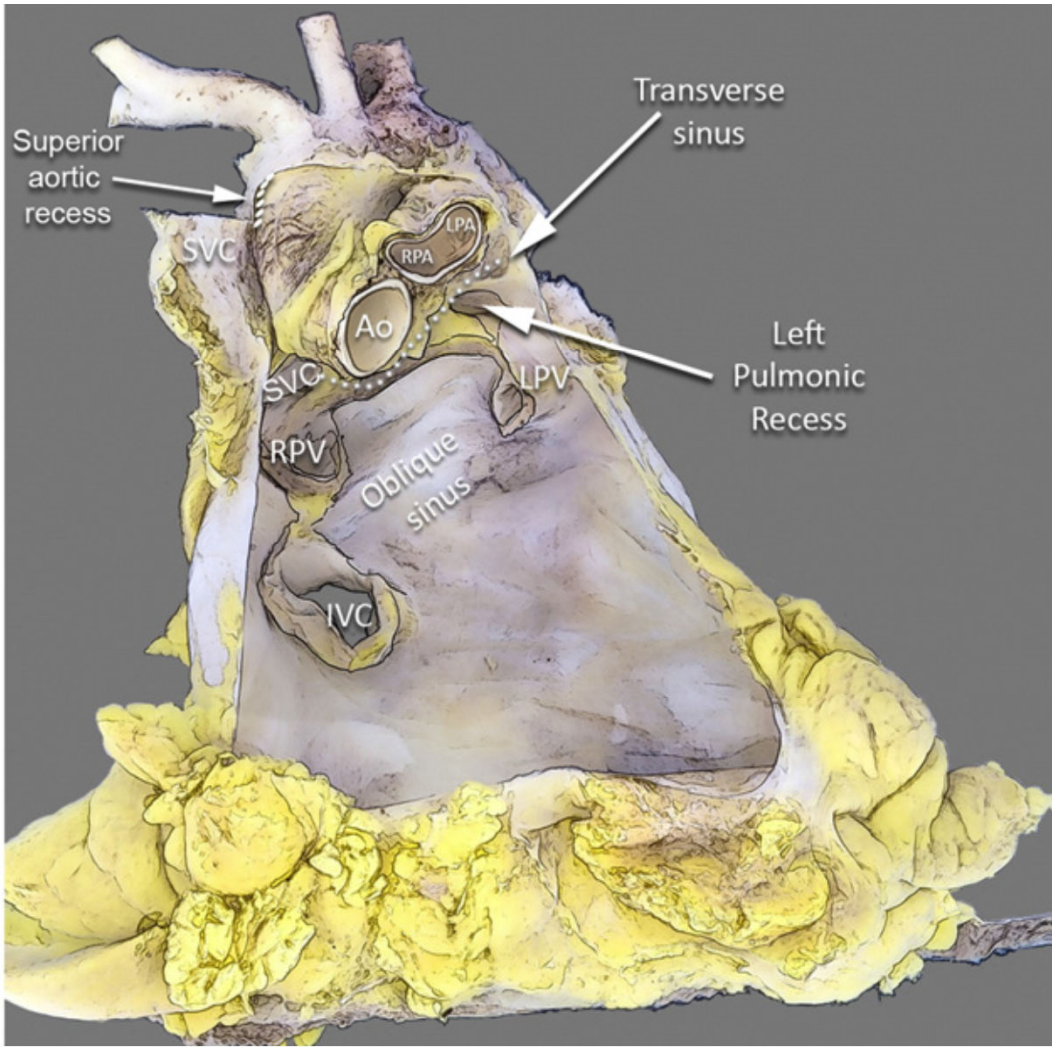
Rodriguez ER and Tan CD, Progress Cardiovasc Dis (2017): 59; 327-349





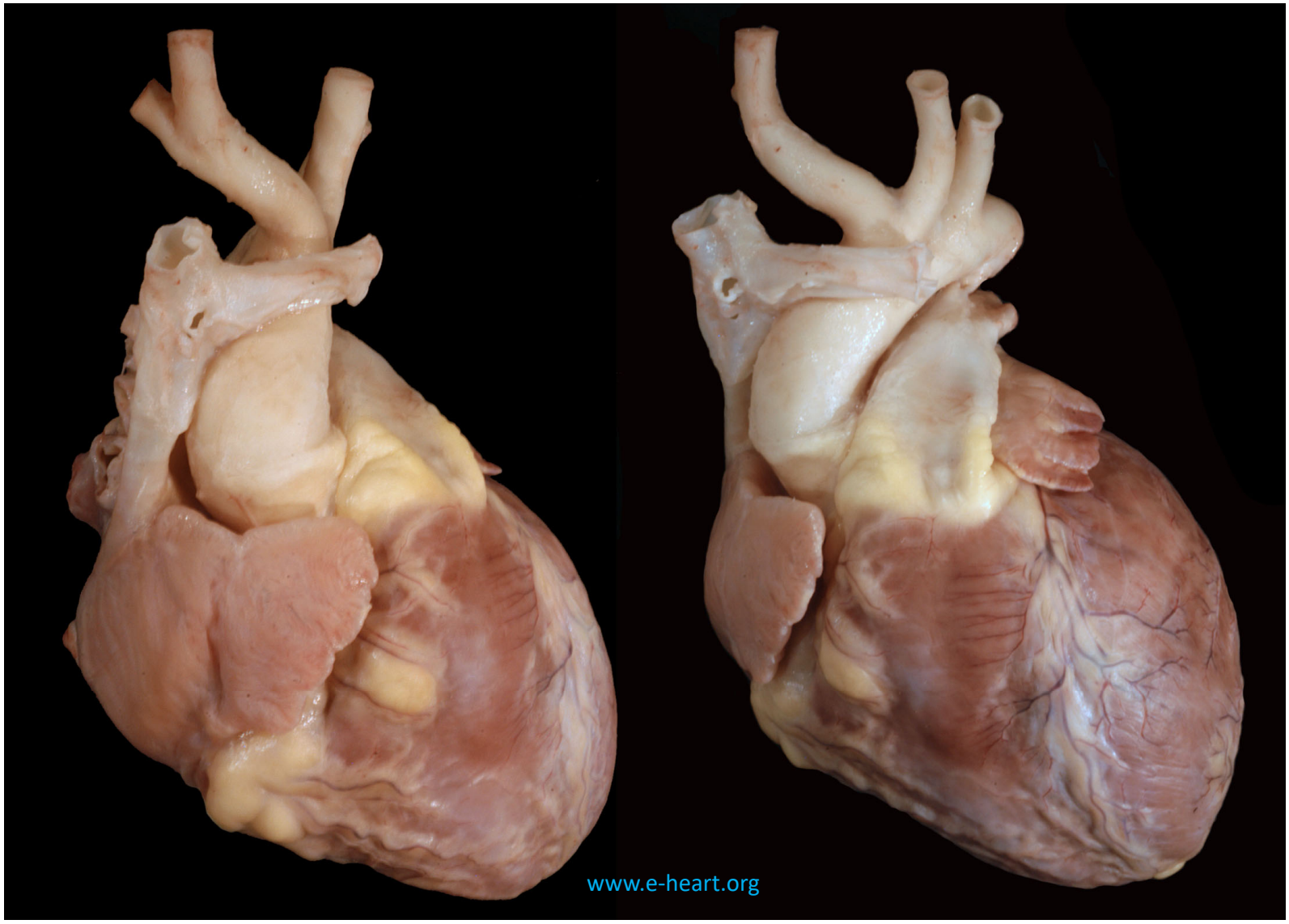
Rodriguez ER and Tan CD, Progress Cardiovasc Dis (2017): 59; 327-349



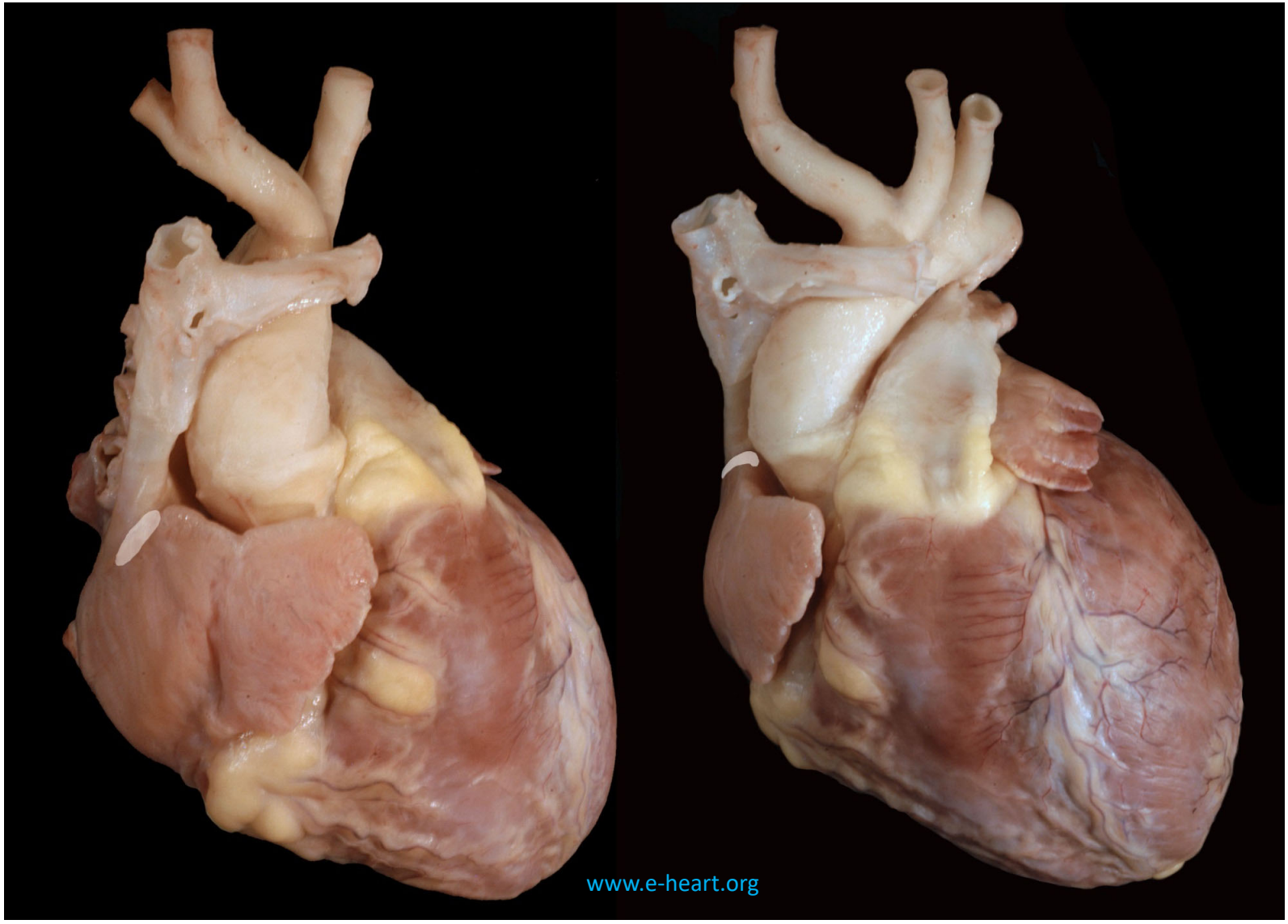


Rodriguez ER and Tan CD, Progress Cardiovasc Dis (2017): 59; 327-349

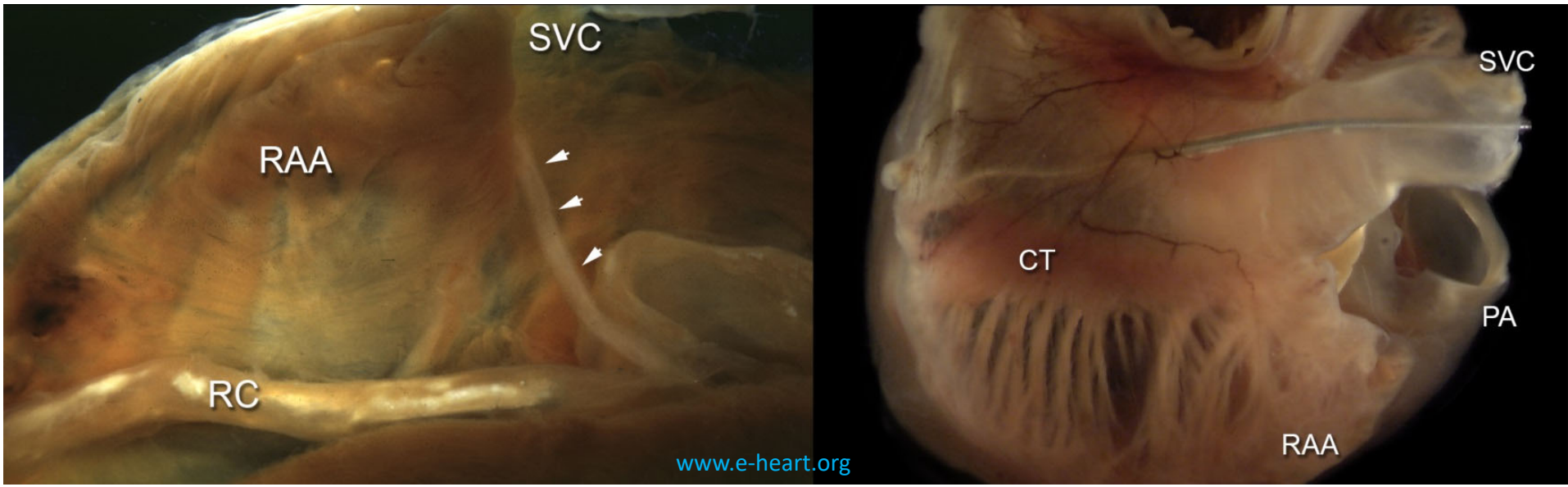
The SA node



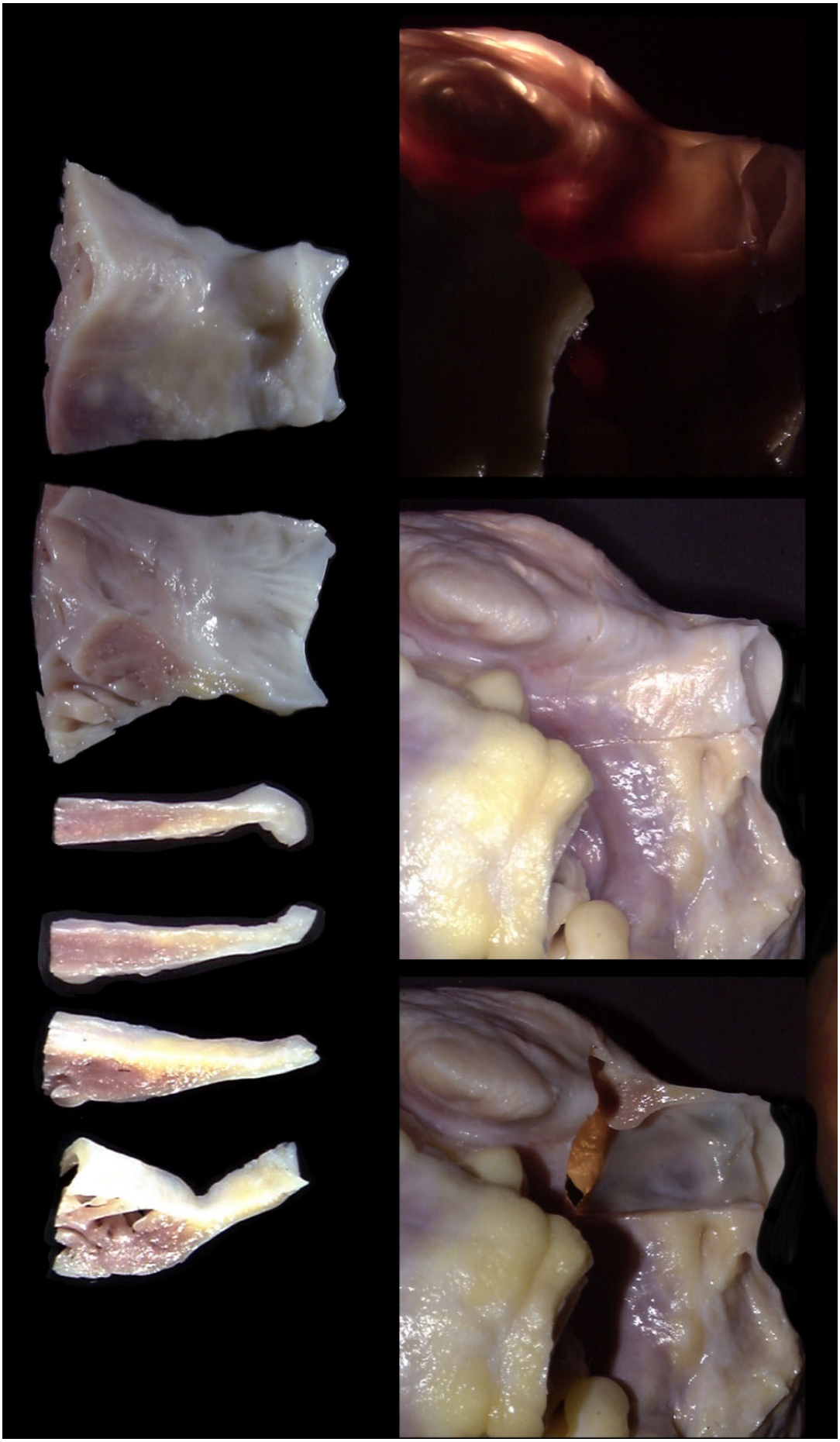
The SA node



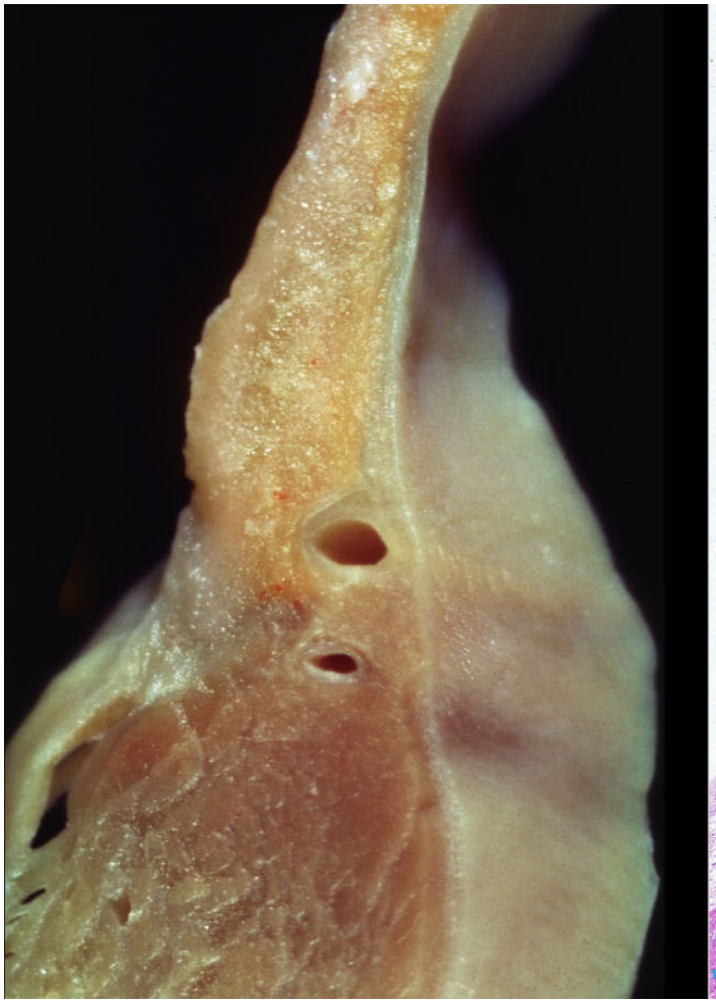
The SA node

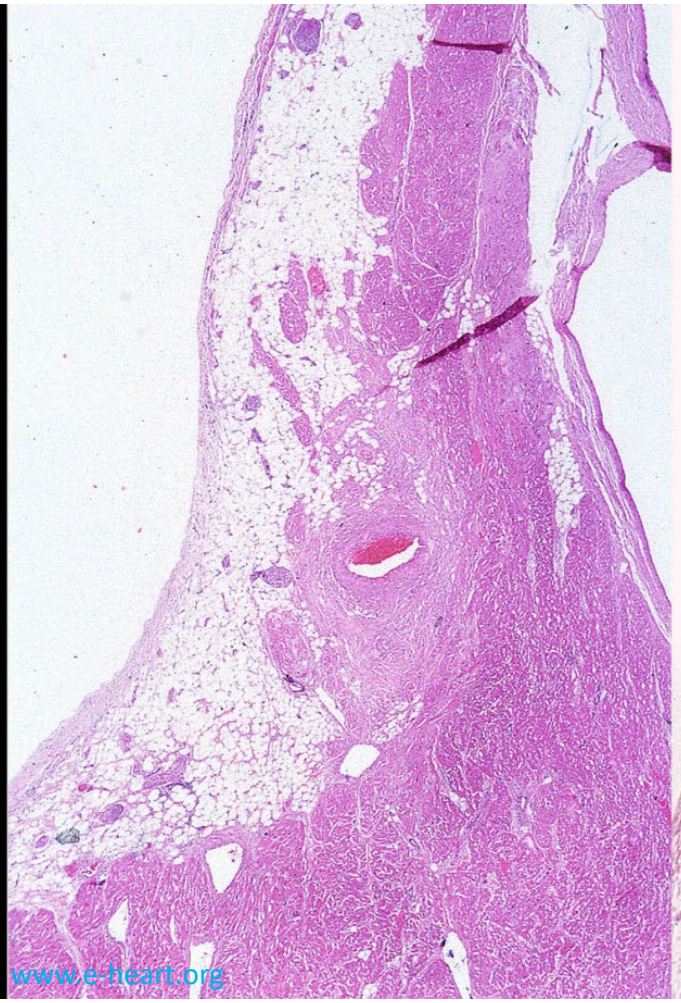


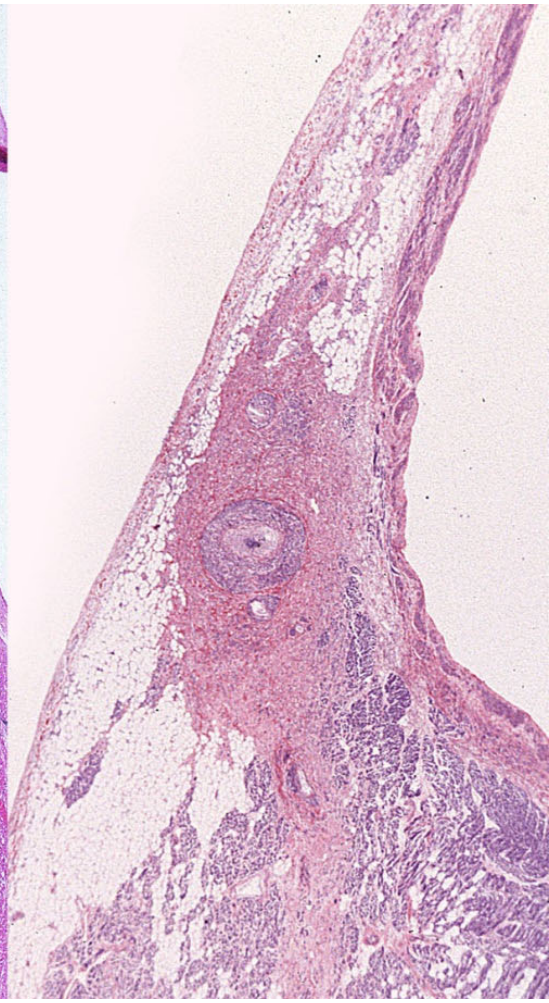
The SA node



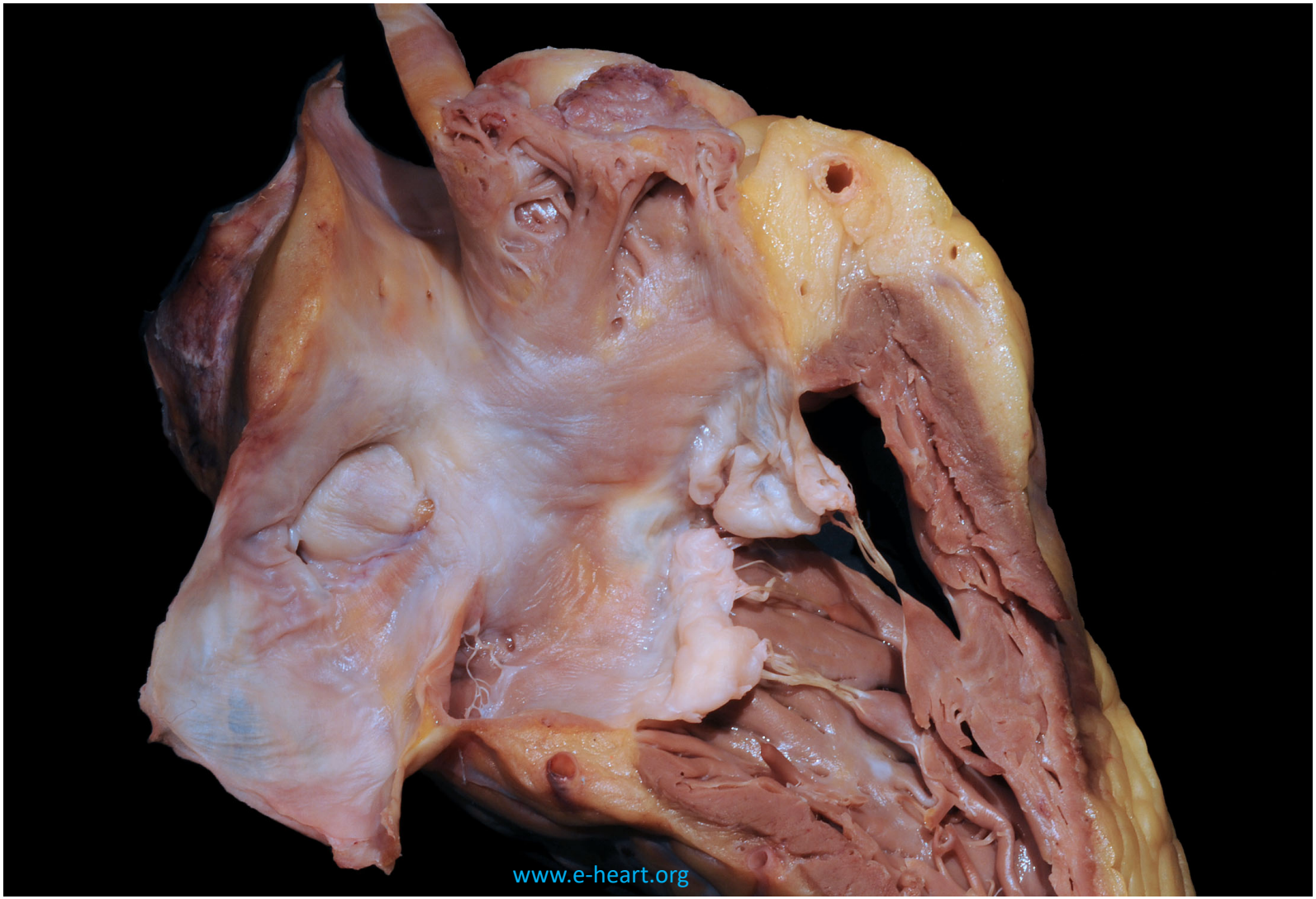
The SA node



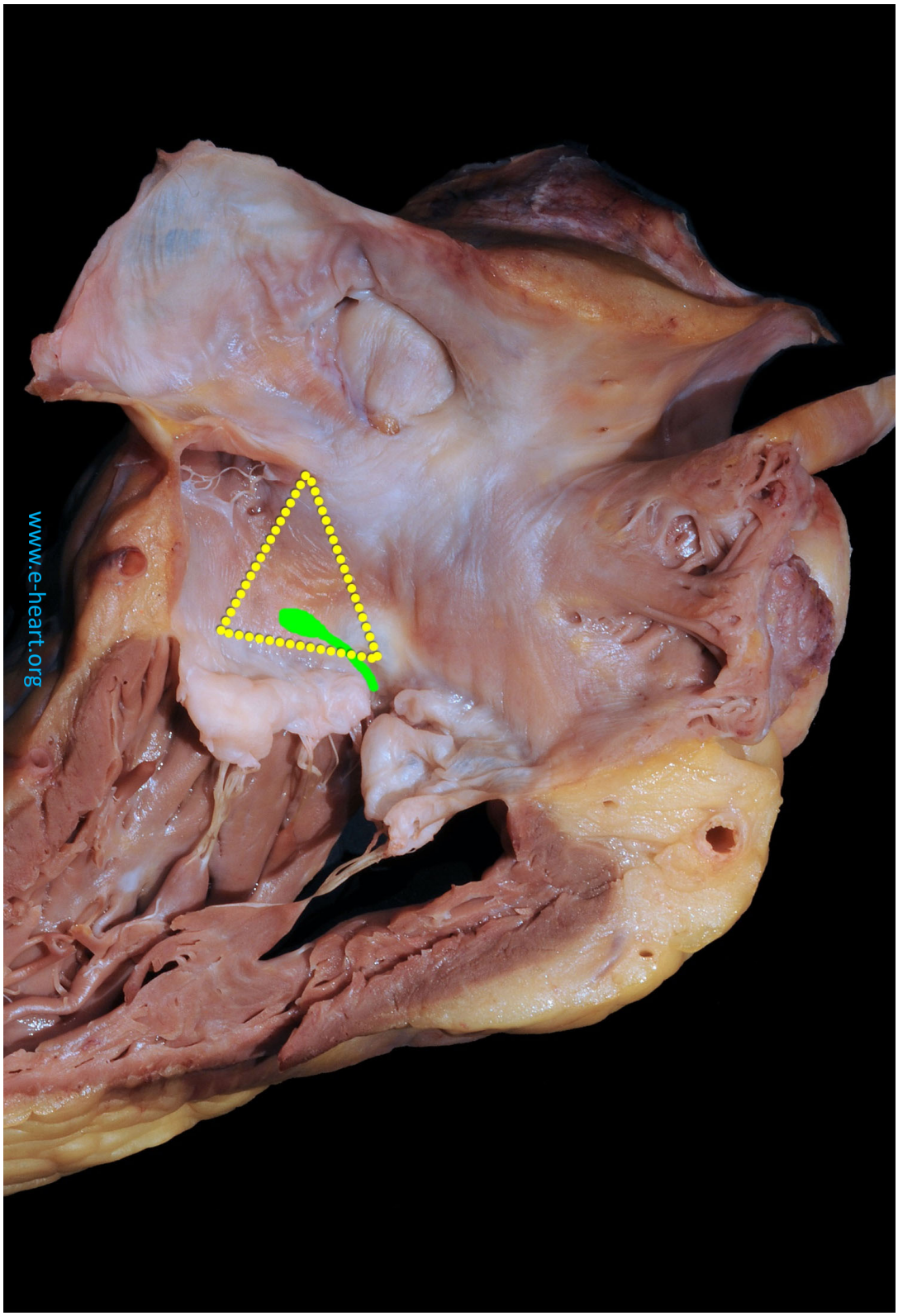




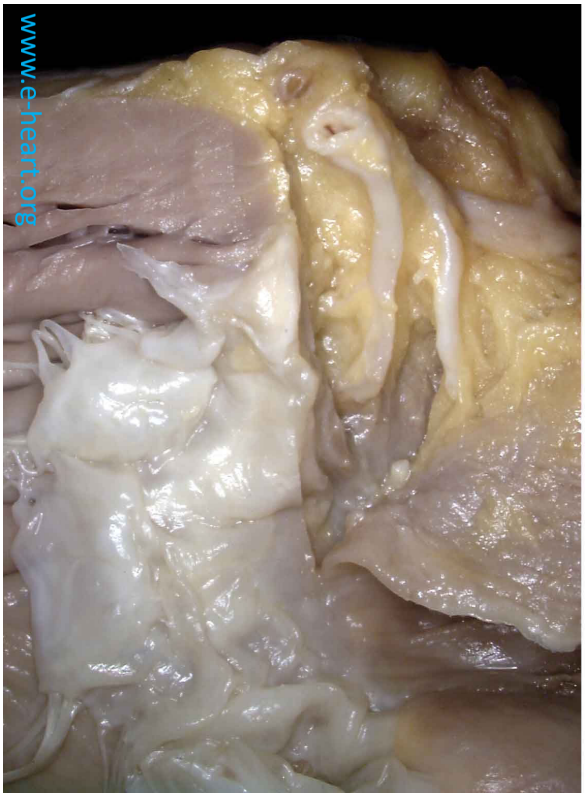
The AV node

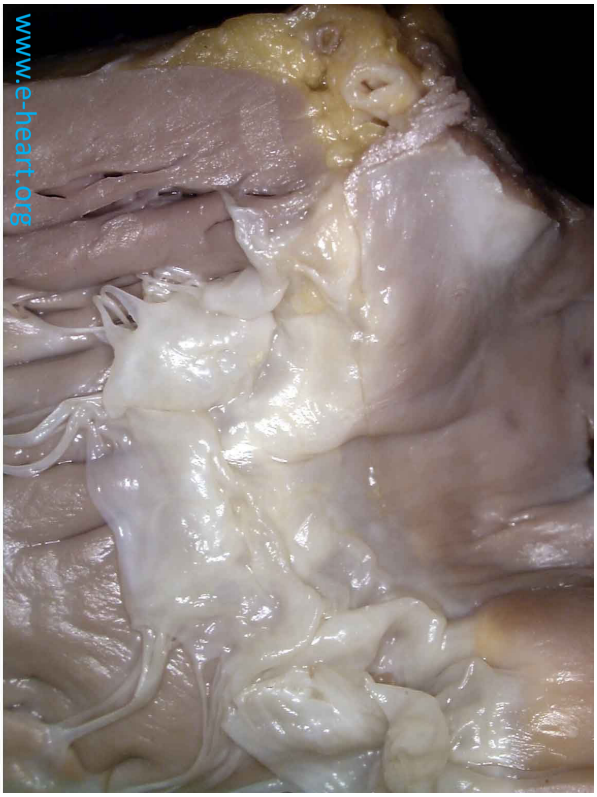


The AV node

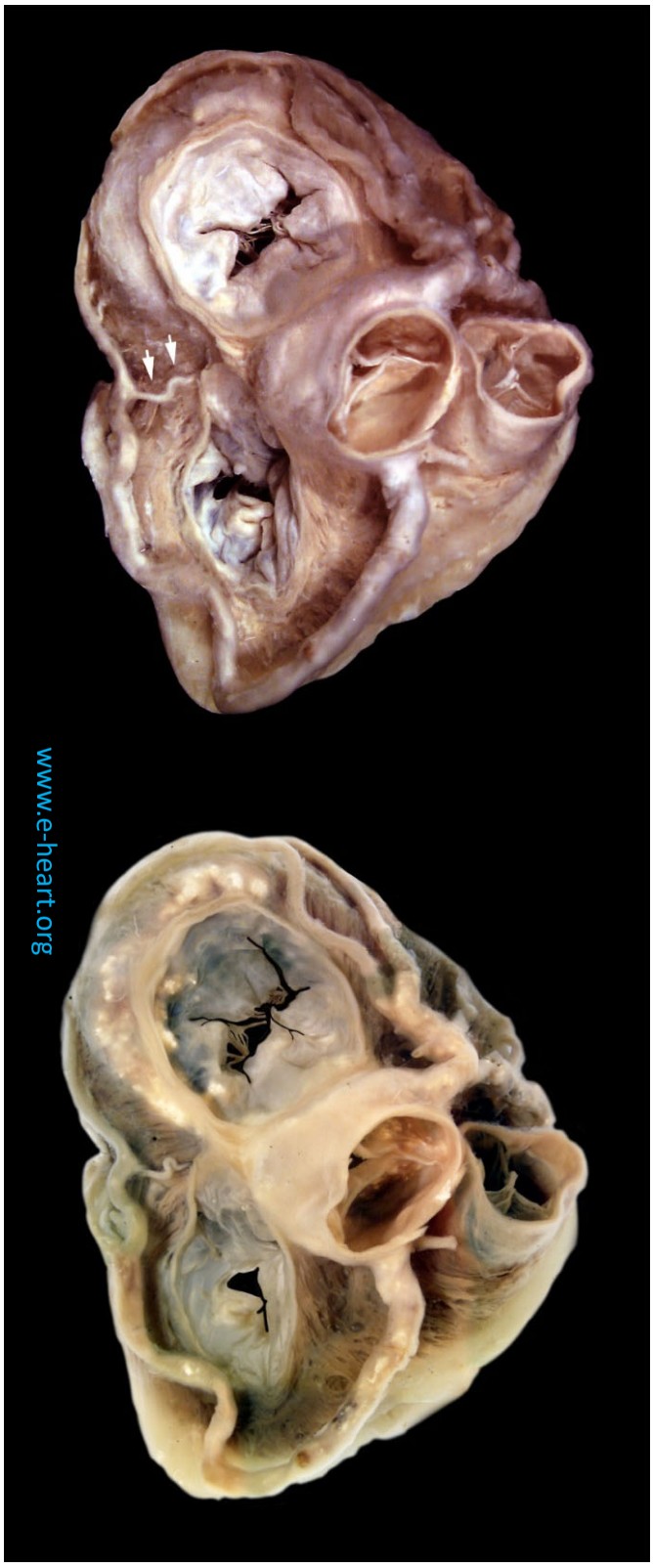


The AV node

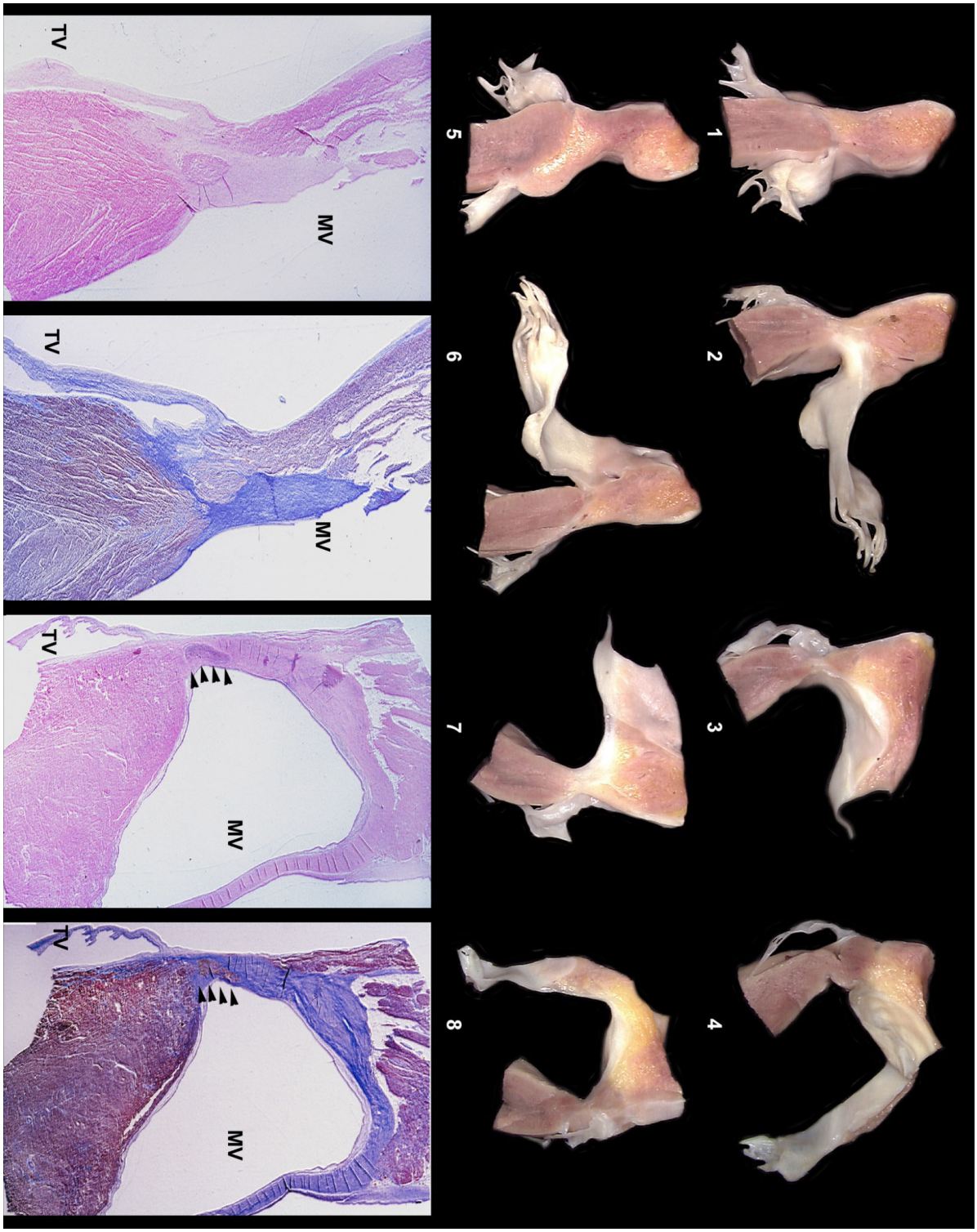




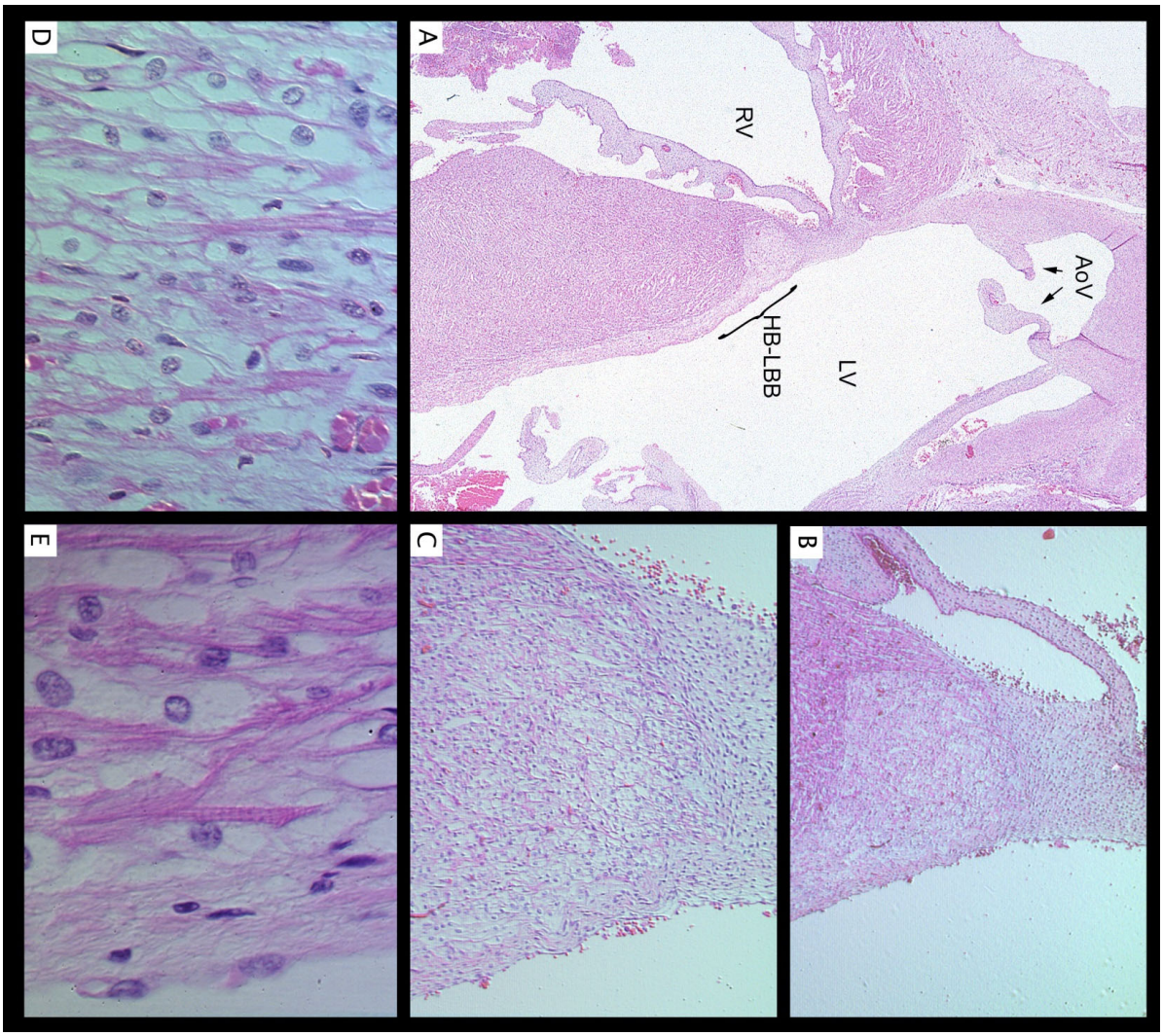
The AV node artery



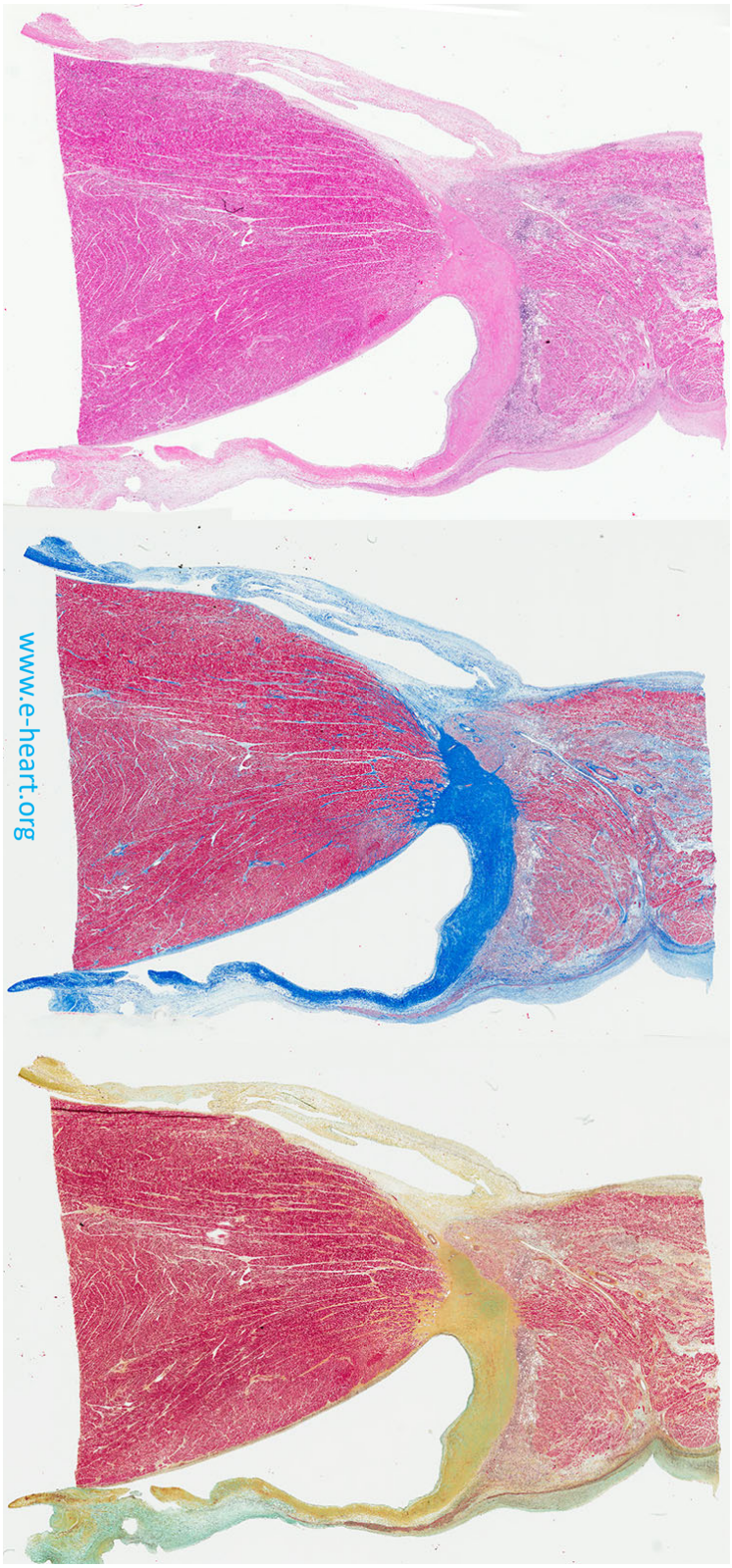
The AV node



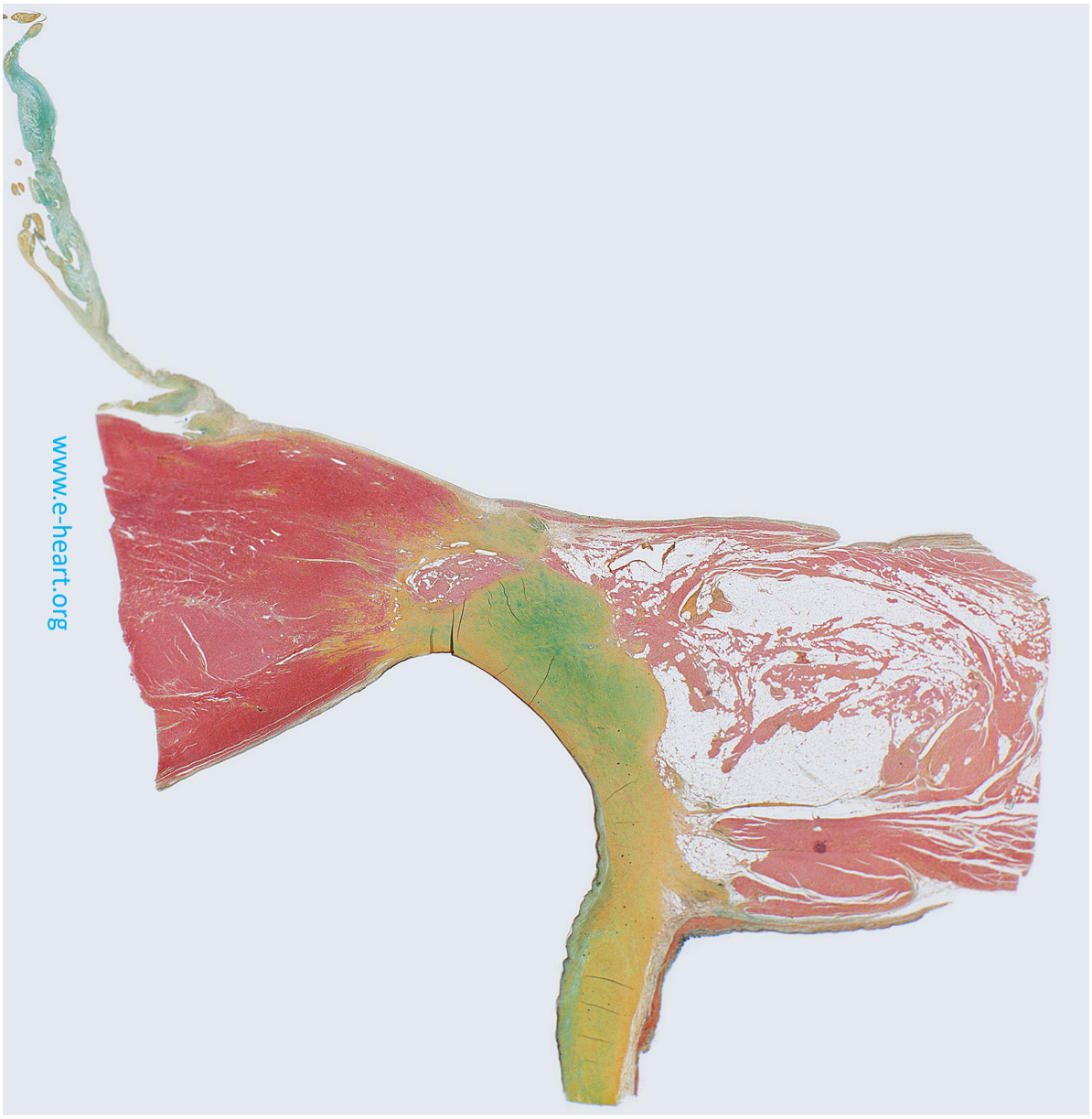
The AV node

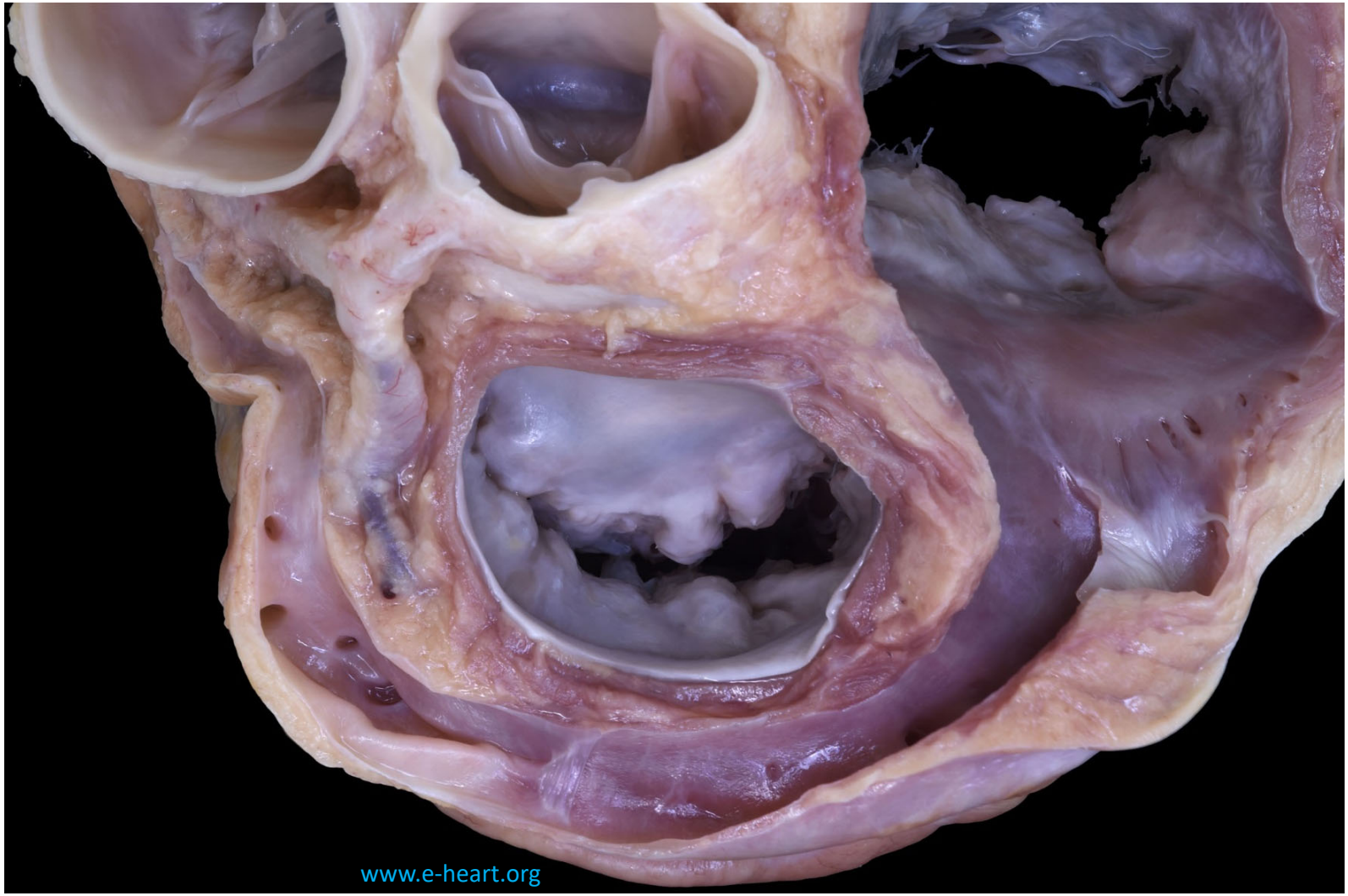


The AV node



The His bundle




www.e-heart.org

Sudden death vs. Unexpected Death

Definition of Sudden Cardiac Death

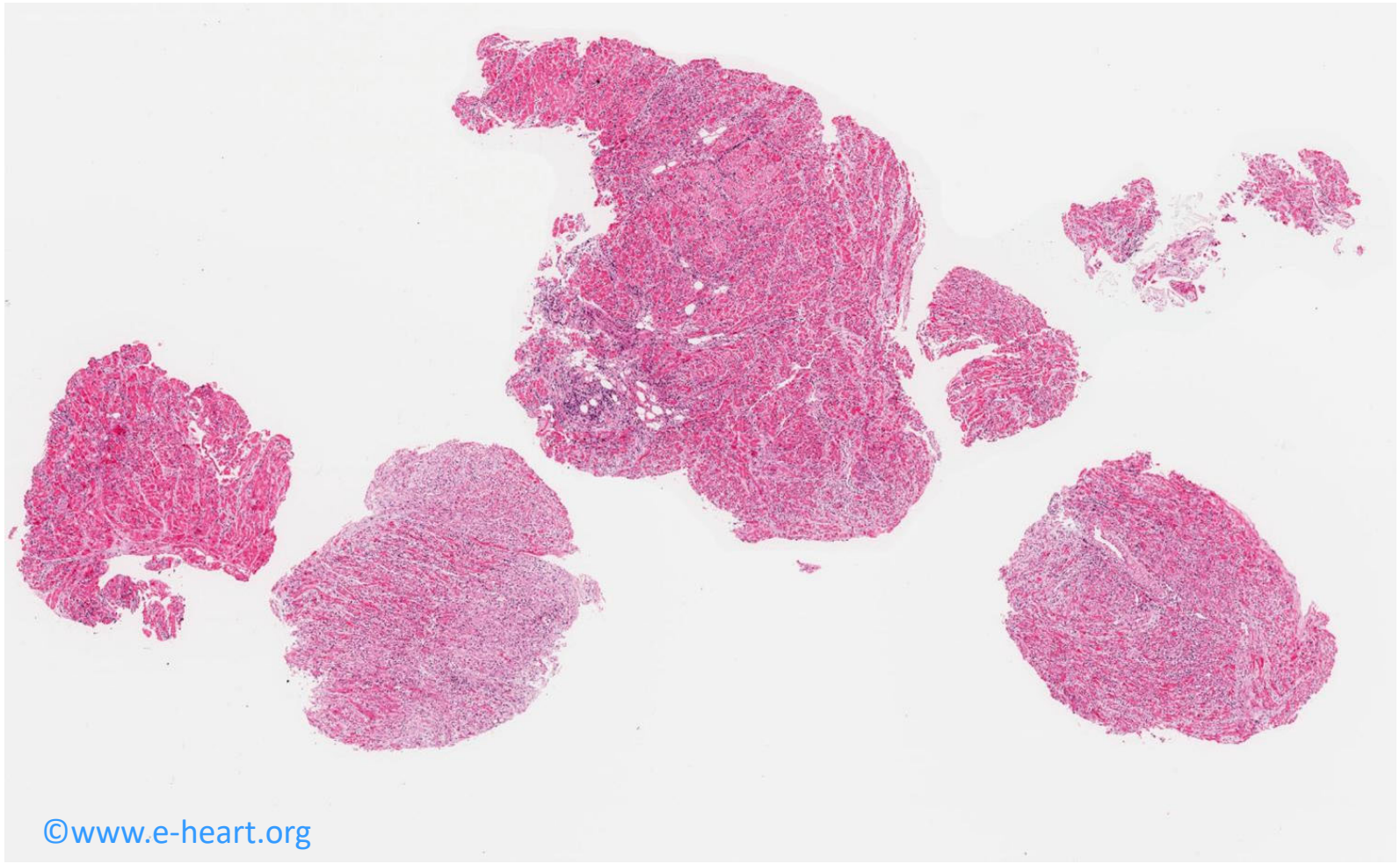
- natural, nonviolent, unexpected and occurring within 1 hour of the onset of acute symptoms
- WHO criteria: up to 24 hours
- most deaths are not witnessed

Definition of Unexpected Hospital Death

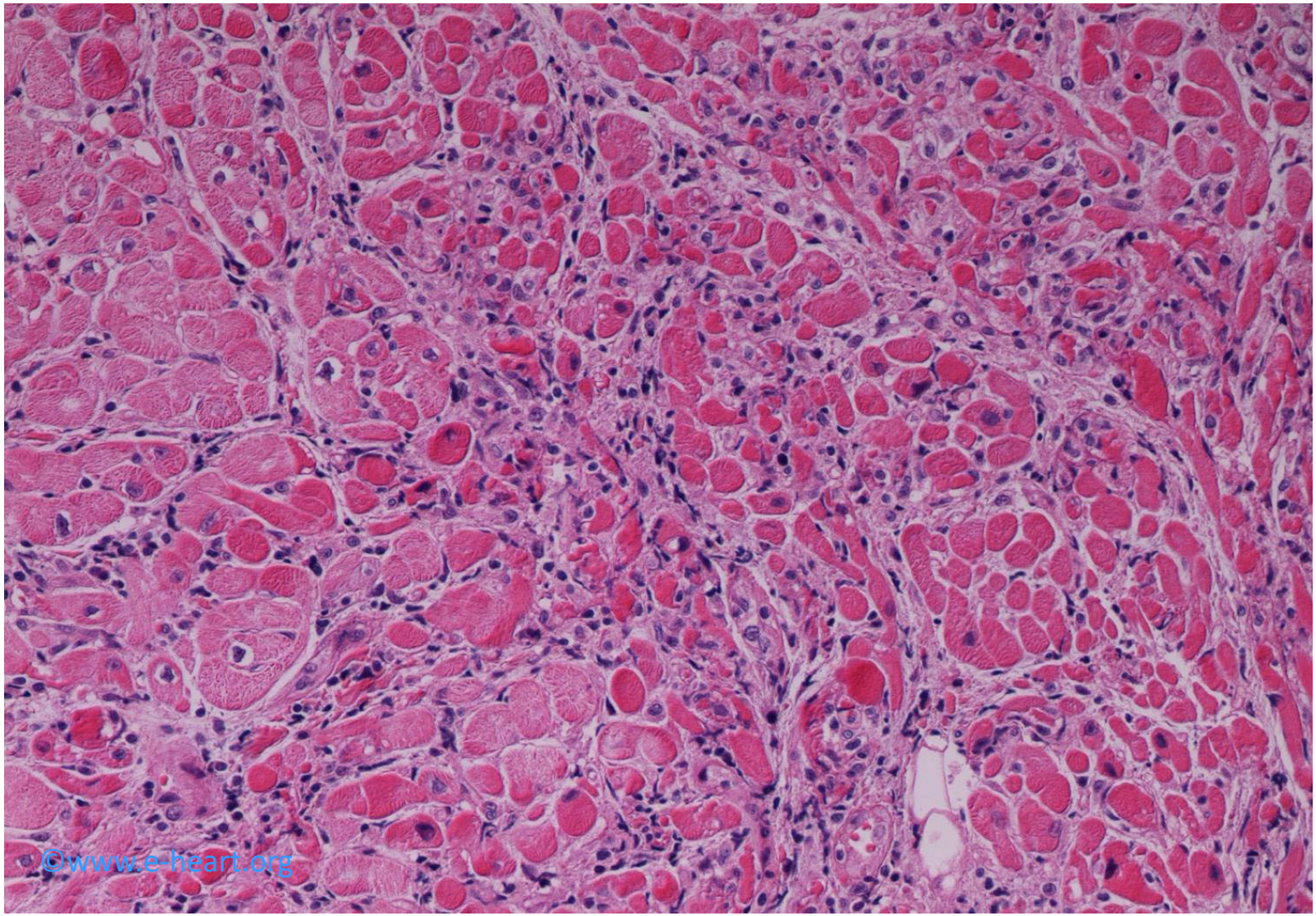
- any in-hospital death occurring on an individual who is not in critical condition

Case 1

- 11 year old male
- Low grade fever, chest pain, nausea and vomiting
- Syncopal episode
- EKG – complete heart block
- CK 1962; CKMB 10%
- Troponin I - 54



1st biopsy


©www.e-heart.org

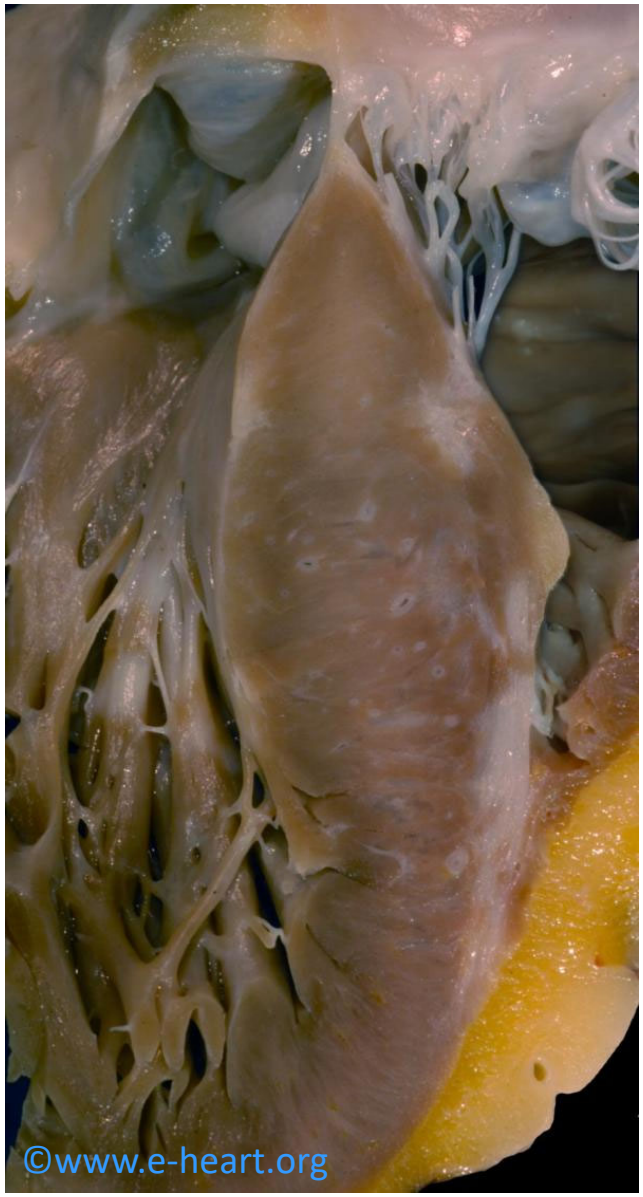
Myocarditis

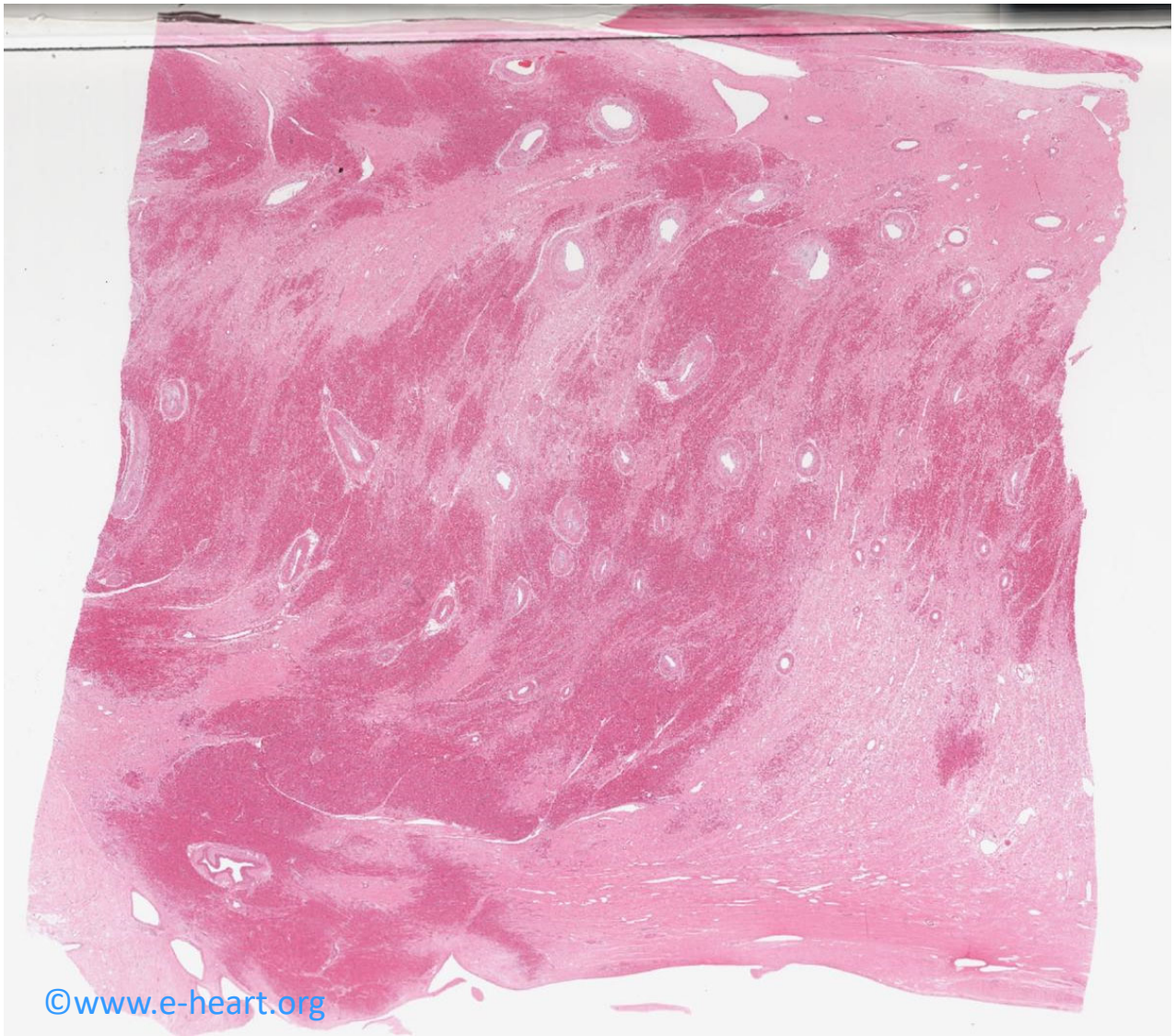
- Dallas criteria
- Myocarditis – “inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease”

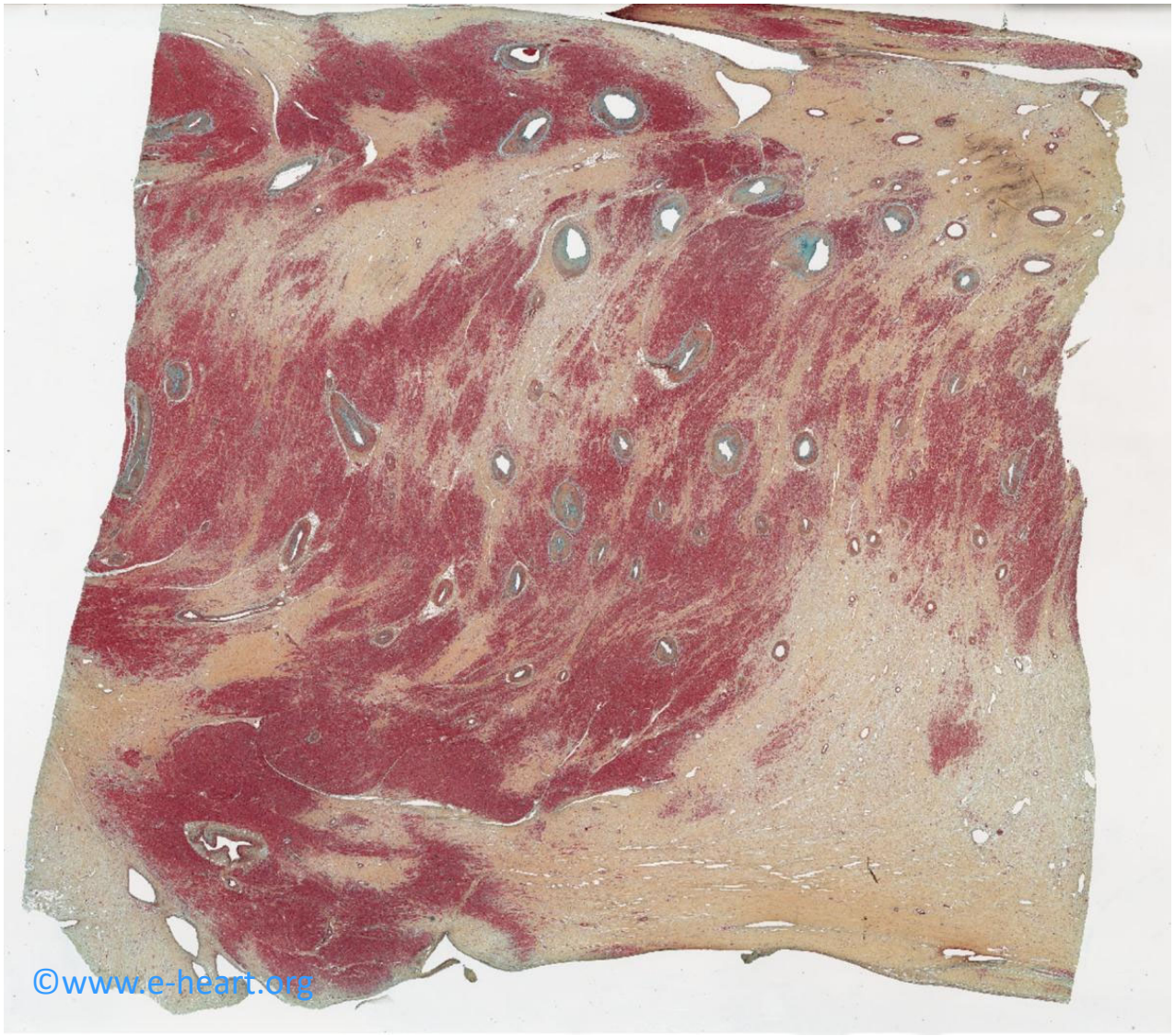
- First biopsy
  - Myocarditis with/without fibrosis
  - Borderline myocarditis
  - No myocarditis

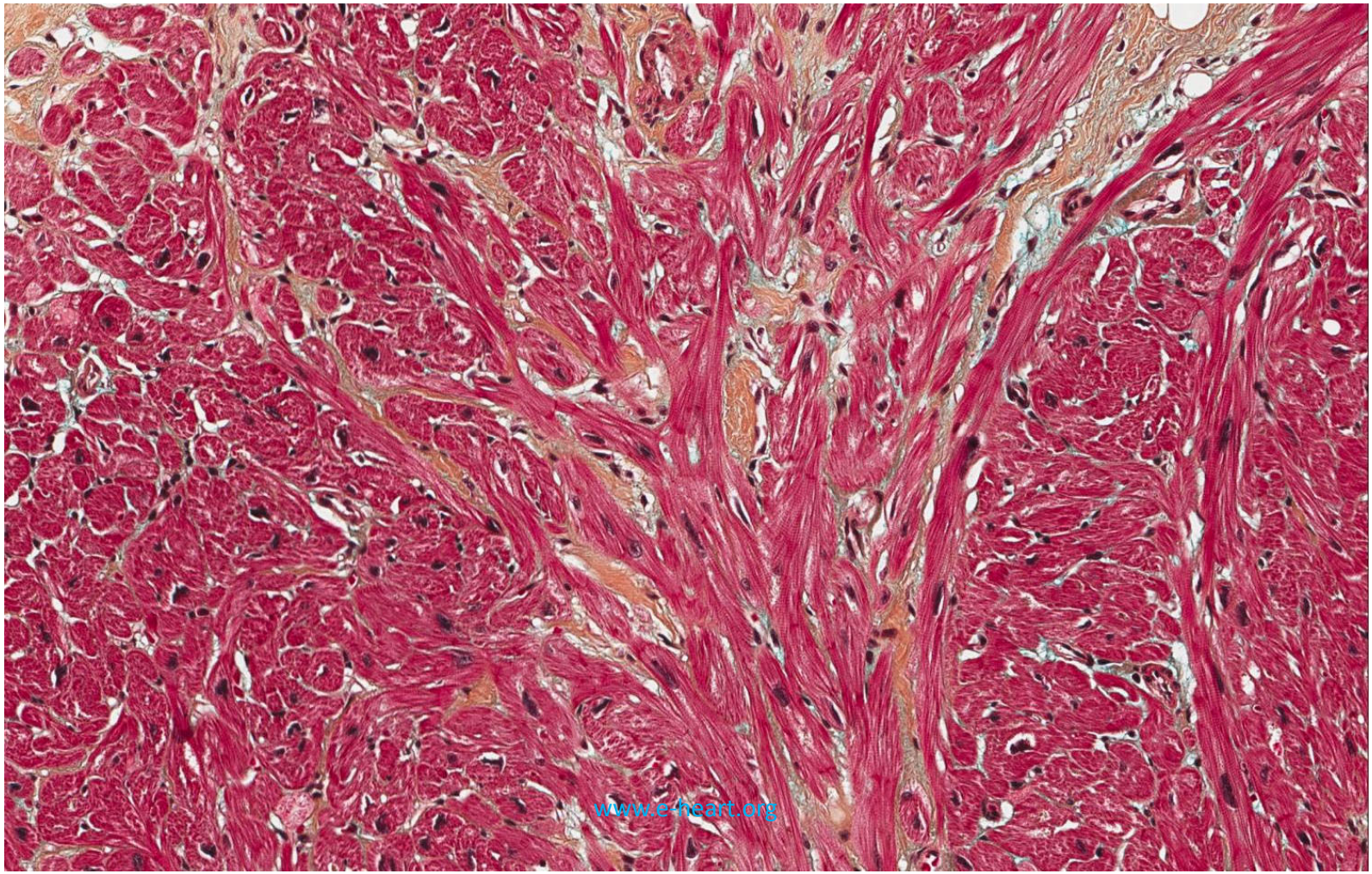
Case 2

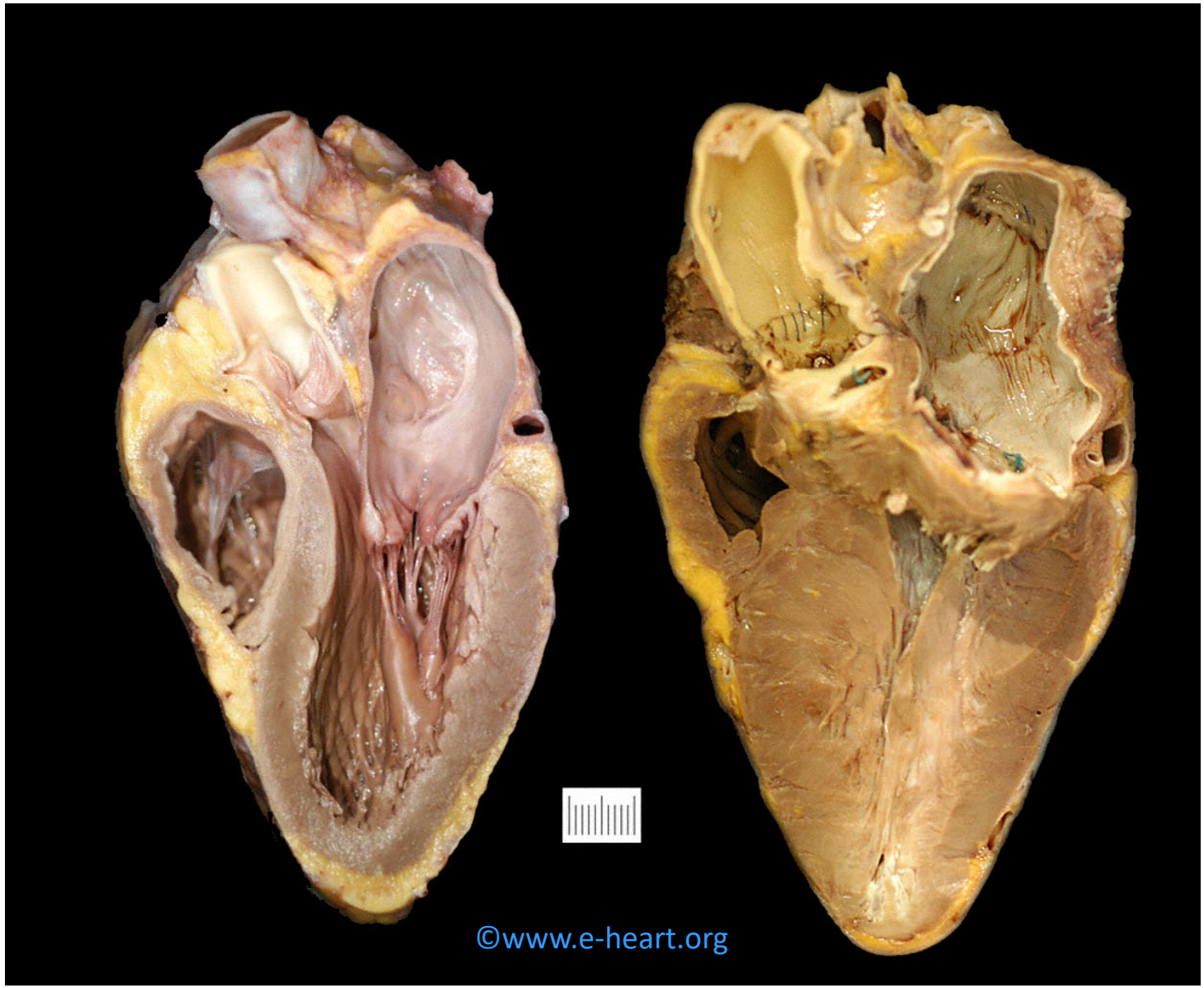
- 39 year old man
- History of sudden cardiac death at age 15 → ICD
- Had increasing shocks from device 8 years later
- Progressive diastolic heart failure


©www.e-heart.org


©www.e-heart.org


©www.e-heart.org

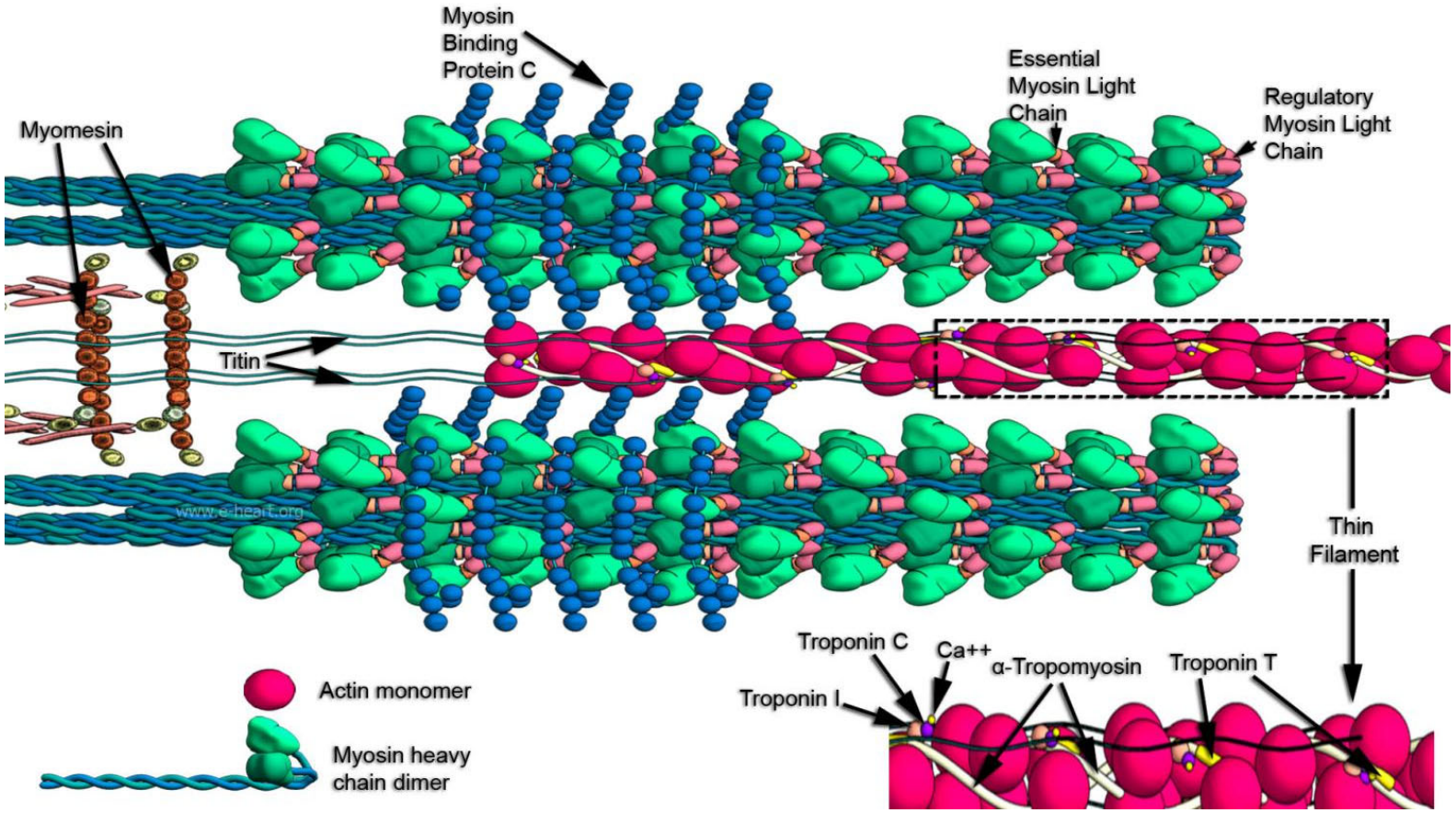

www.e-heart.org


©www.e-heart.org


©www.e-heart.org

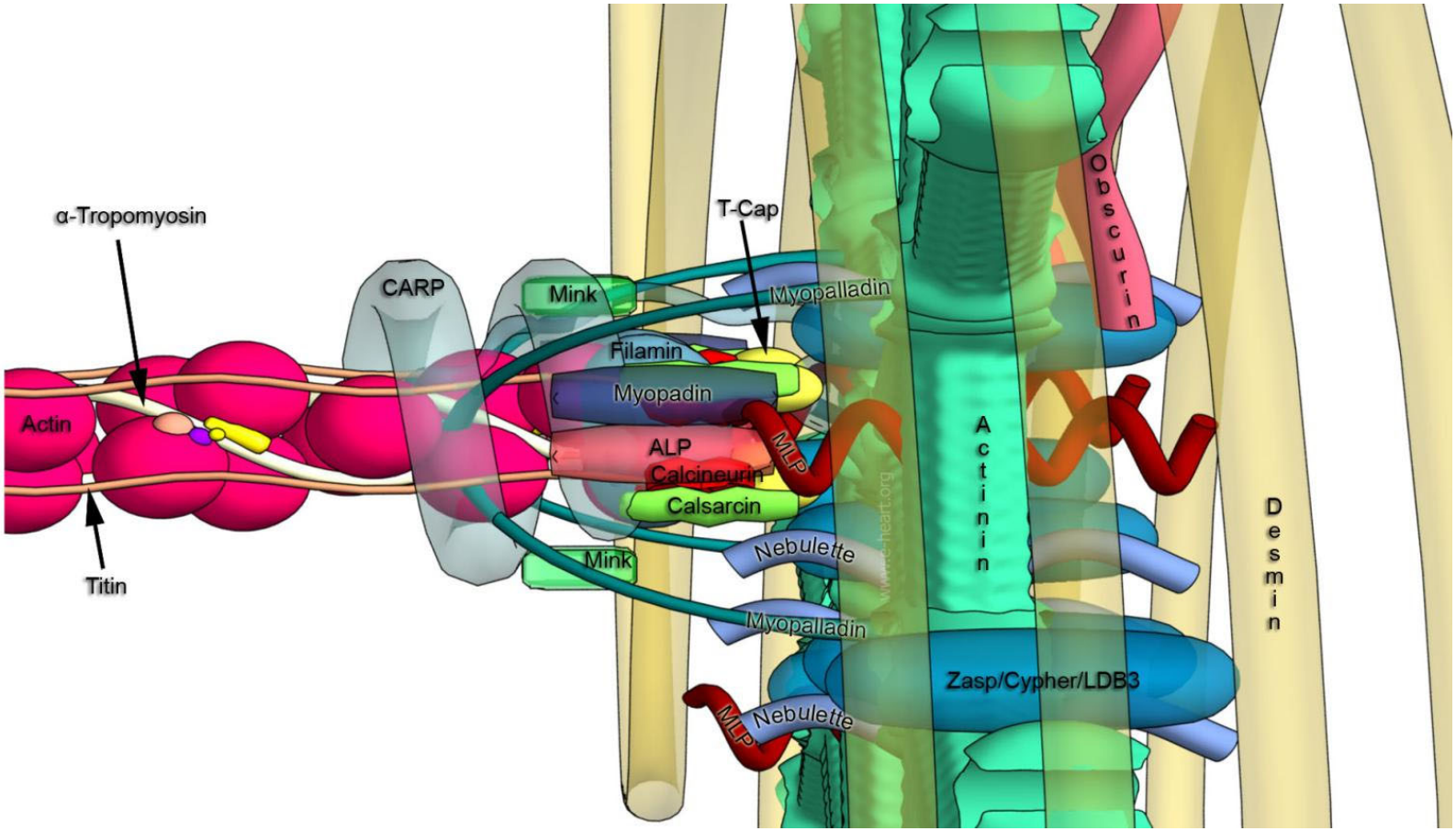
Hypertrophic cardiomyopathy

- Genetic disease of myocardium characterized by LVH in the absence of systemic or valvular disorders sufficient to cause hypertrophy
- Clinical course variable and compatible with normal life expectancy
- Most common mode of inheritance is autosomal dominant with incomplete penetrance



©www.e-heart.org

Tan CD, Rodriguez ER: Chapter 20. Molecular pathology of the cardiovascular system. Foundations in Diagnostic Pathology : Cell and Tissue Based Molecular Diagnostics. Goldblum JR, Tubbs RR, Stoler MH, Churchill Livingstone, 2008 pp 214-240

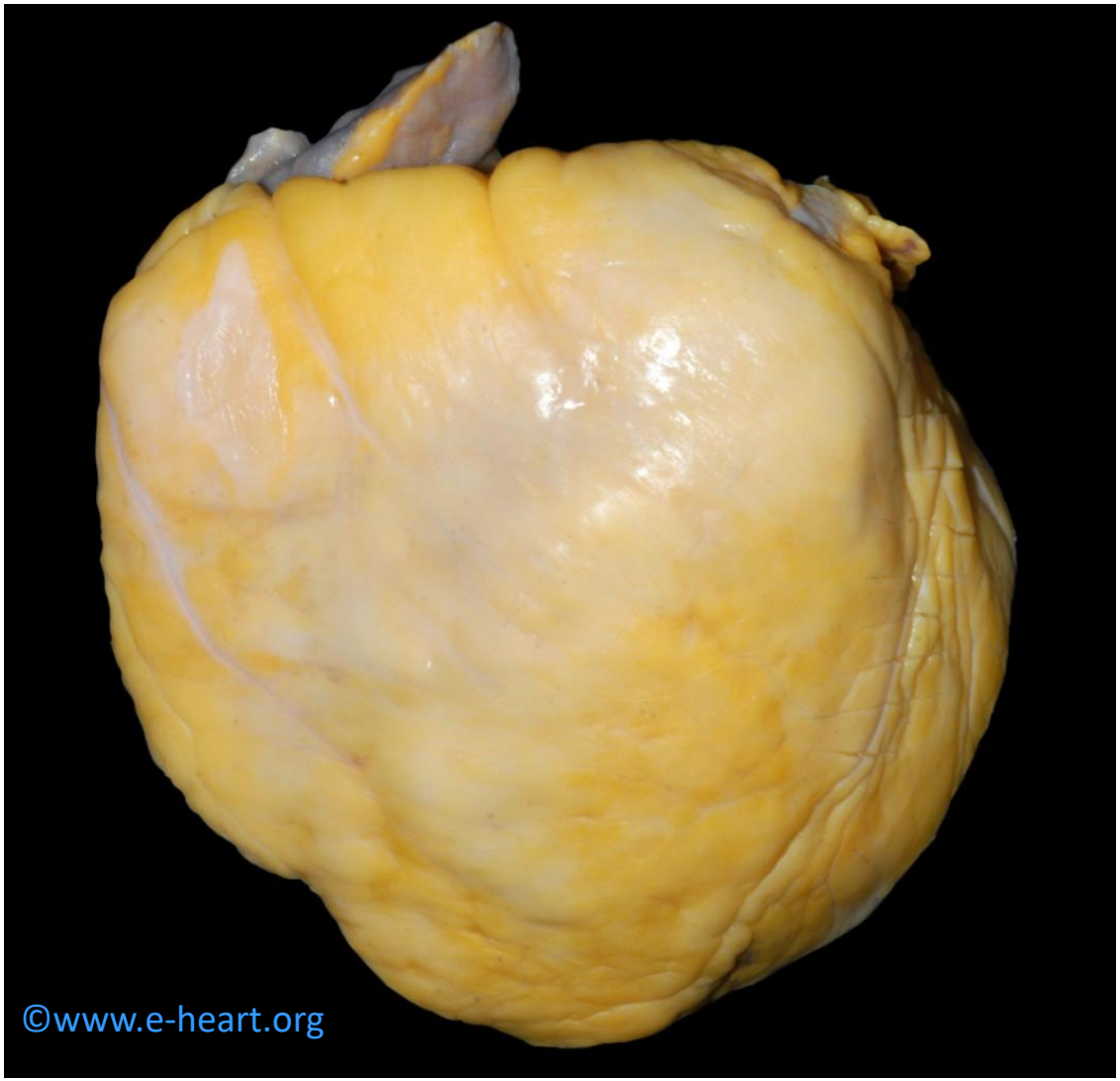


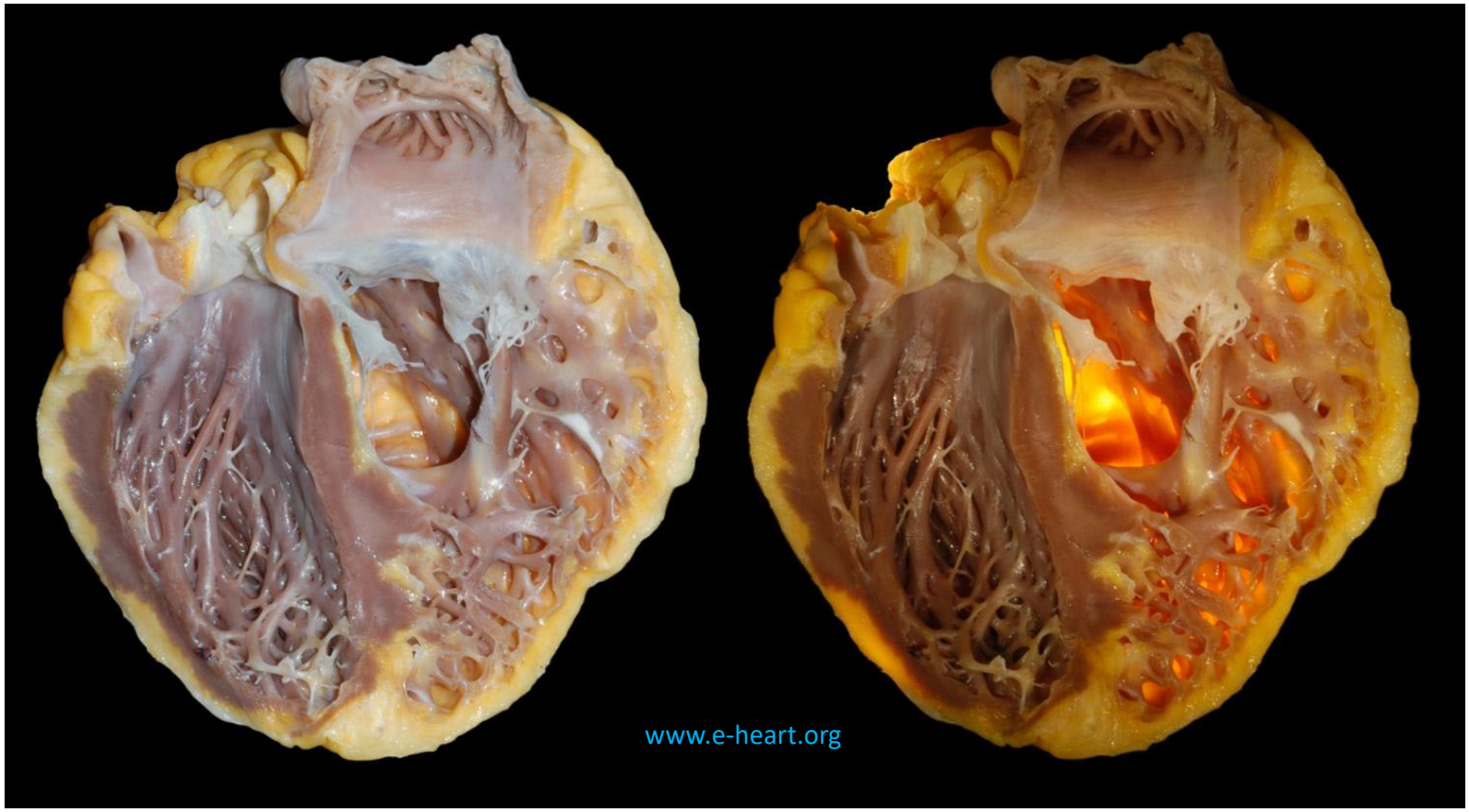
©www.e-heart.org

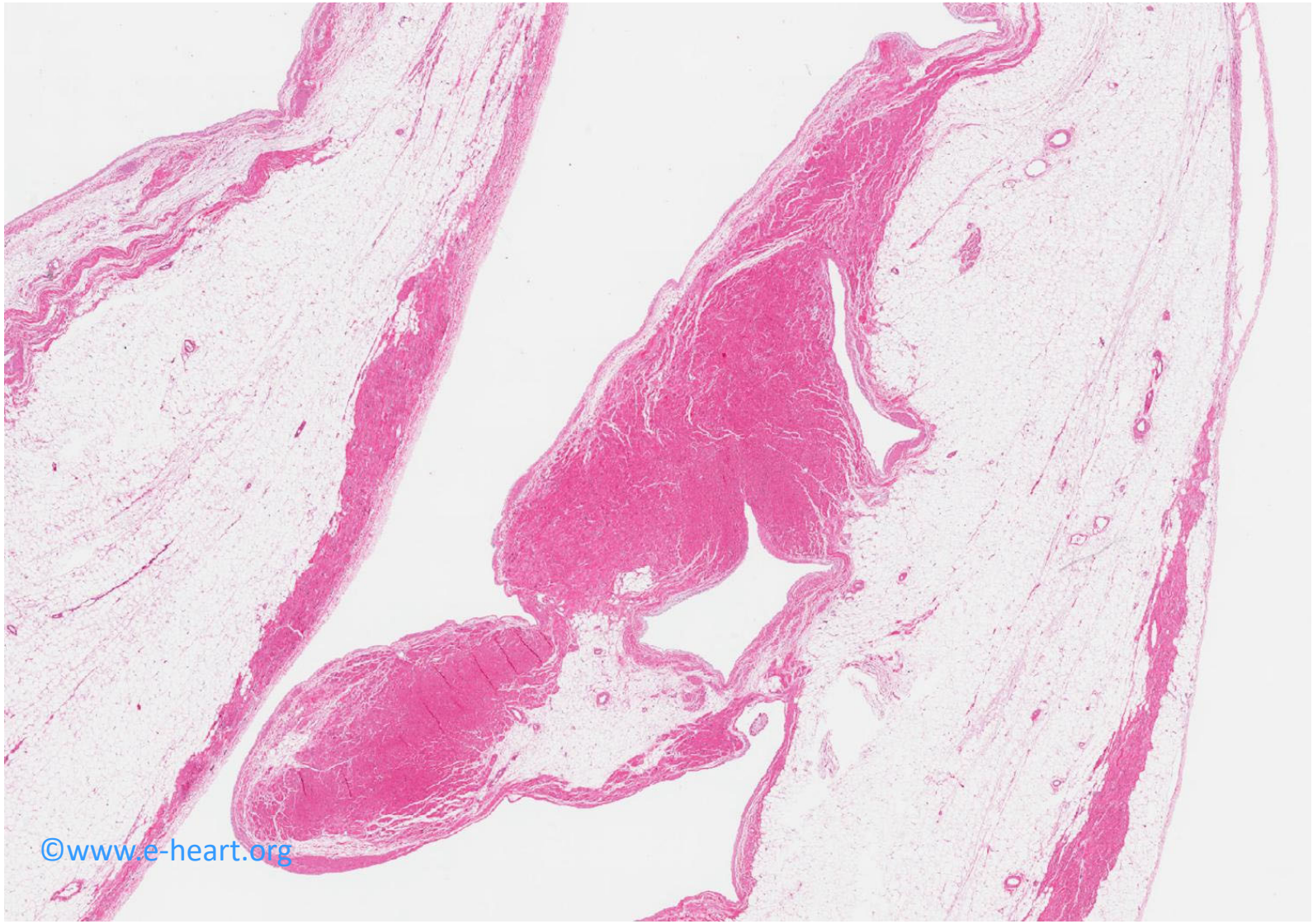
Tan CD, Rodriguez ER: Chapter 20. Molecular pathology of the cardiovascular system. Foundations in Diagnostic Pathology : Cell and Tissue Based Molecular Diagnostics. Goldblum JR, Tubbs RR, Stoler MH, Churchill Livingstone, 2008 pp 214-240

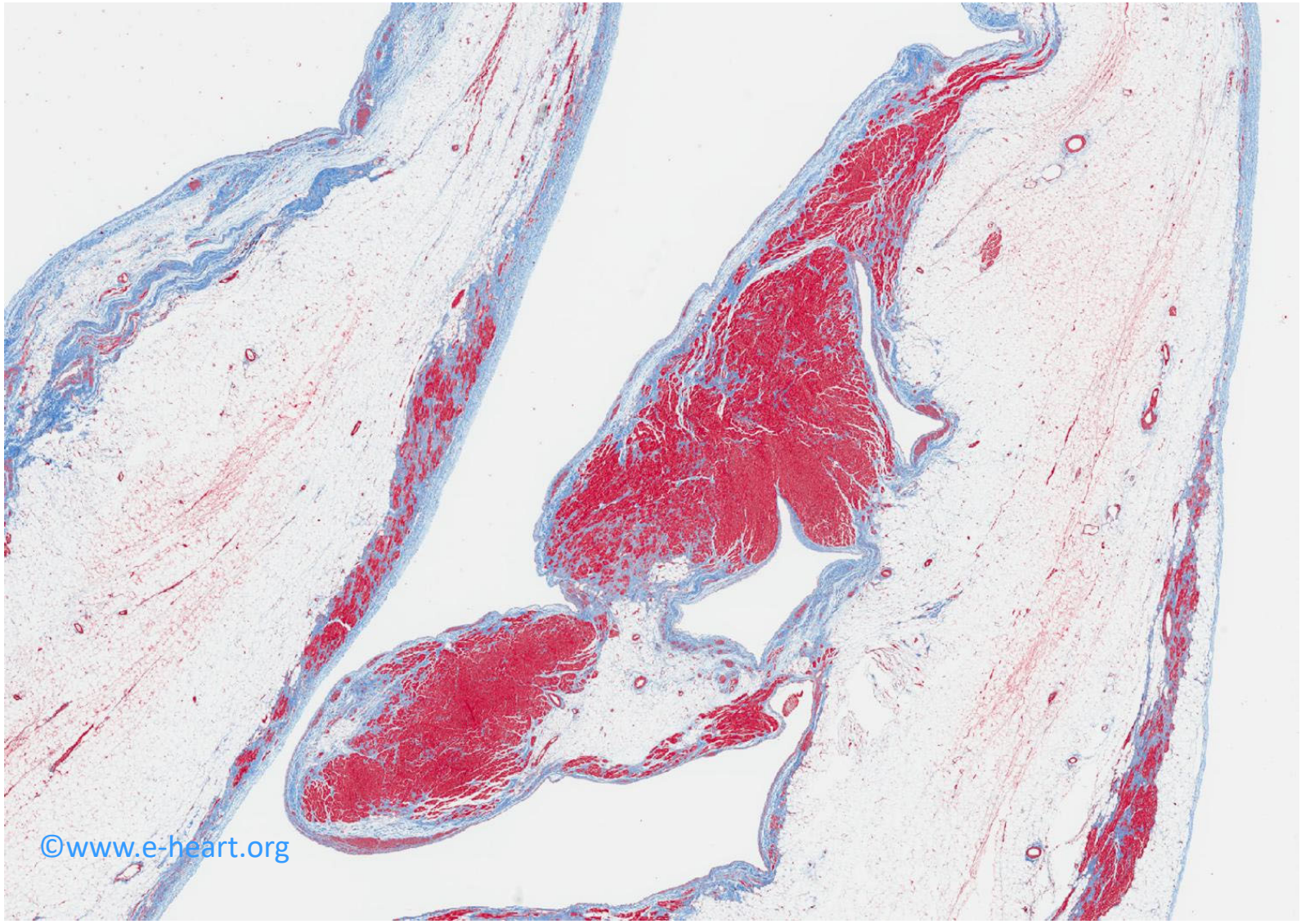
Case 3

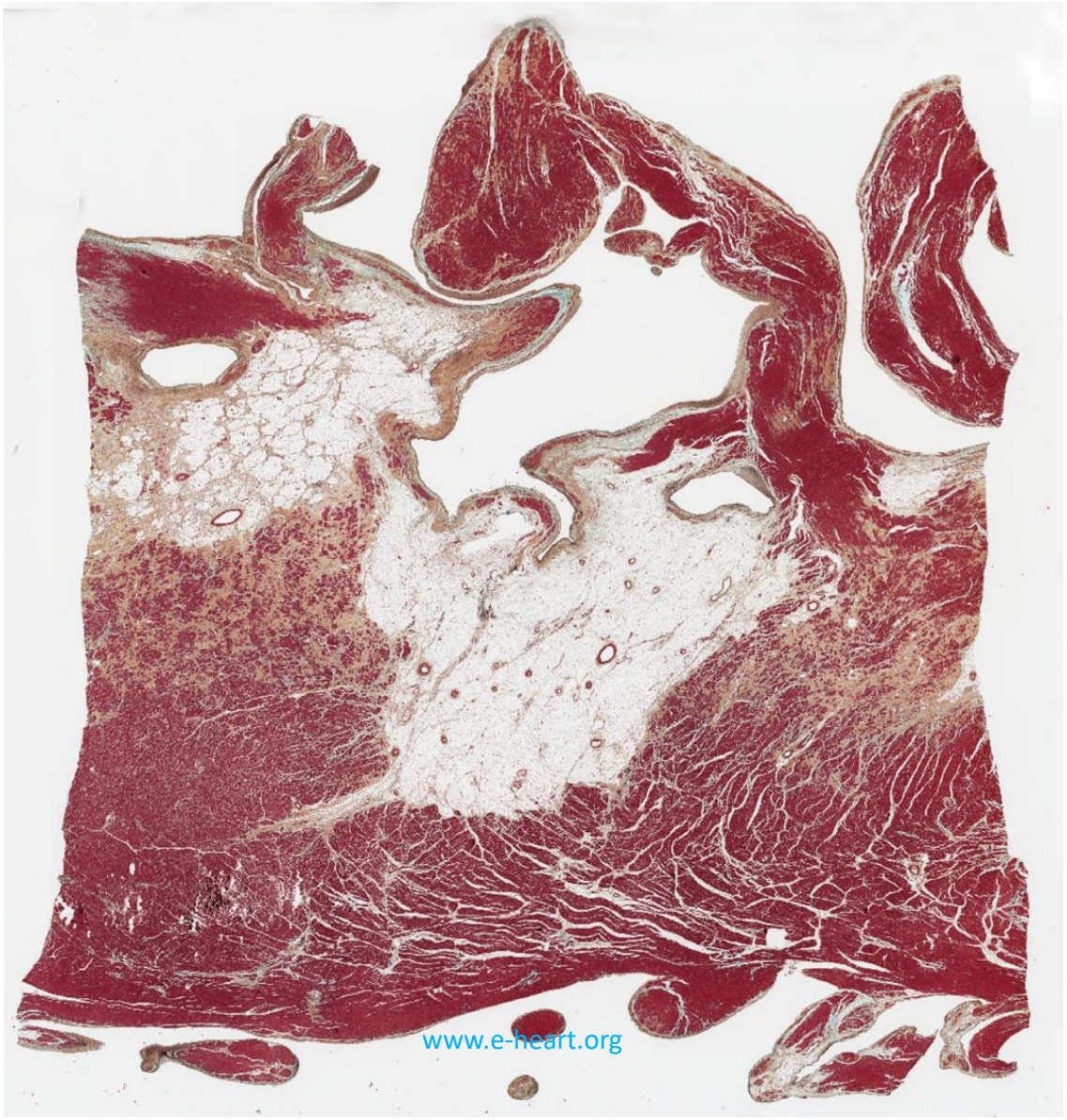
- 30 year old woman
- TIA with total resolution of symptoms
- On work-up was found to have RV dysfunction and normal LV
- ICD placed
- 3 years later, episodes of VF with ICD firing
- Recurrent ventricular arrhythmias after d/c

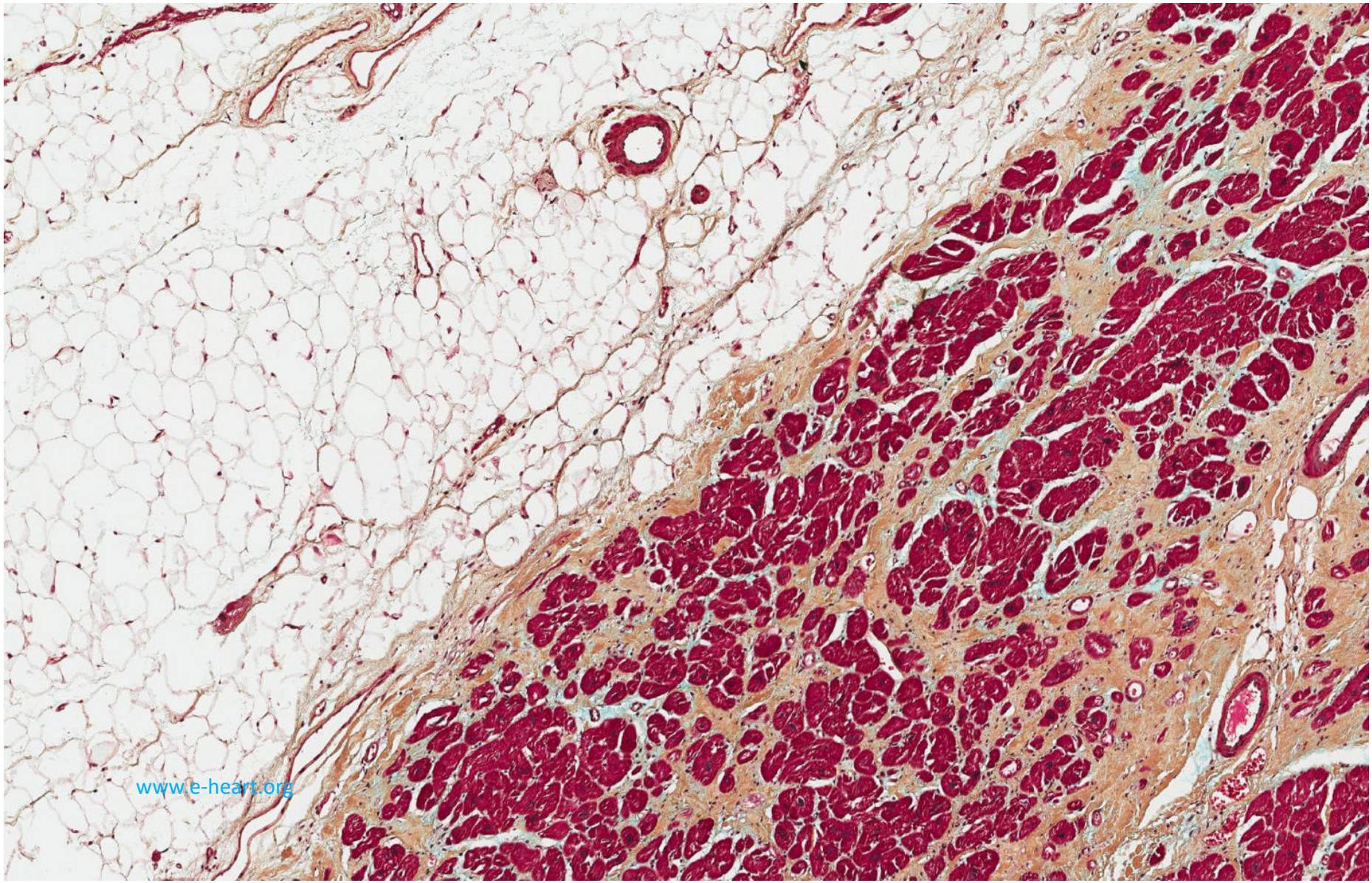

©www.e-heart.org


www.e-heart.org

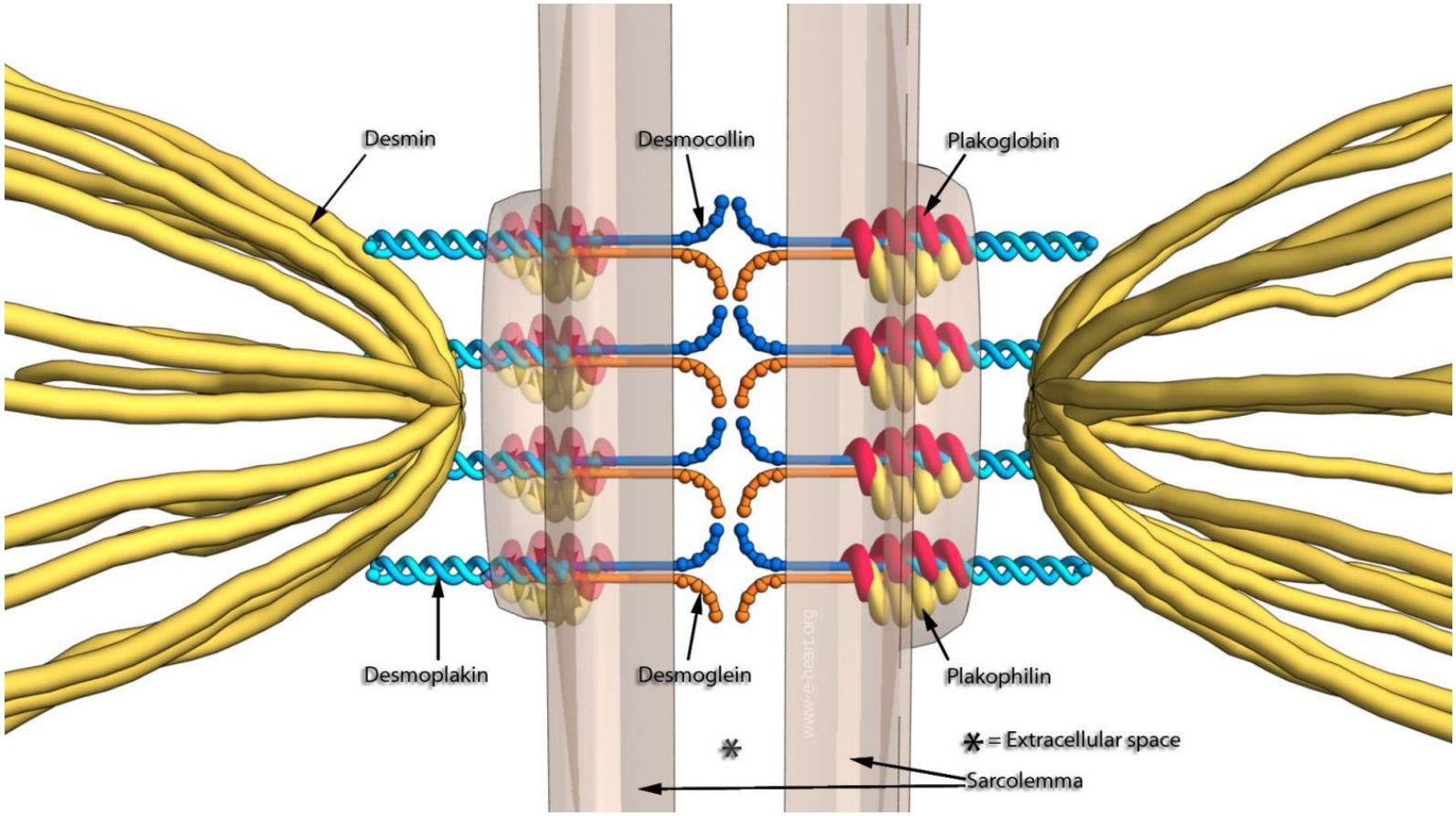

©www.e-heart.org


©www.e-heart.org


www.e-heart.org


www.e-heart.org

Desmosomal protein mutations are common in ARVD/C



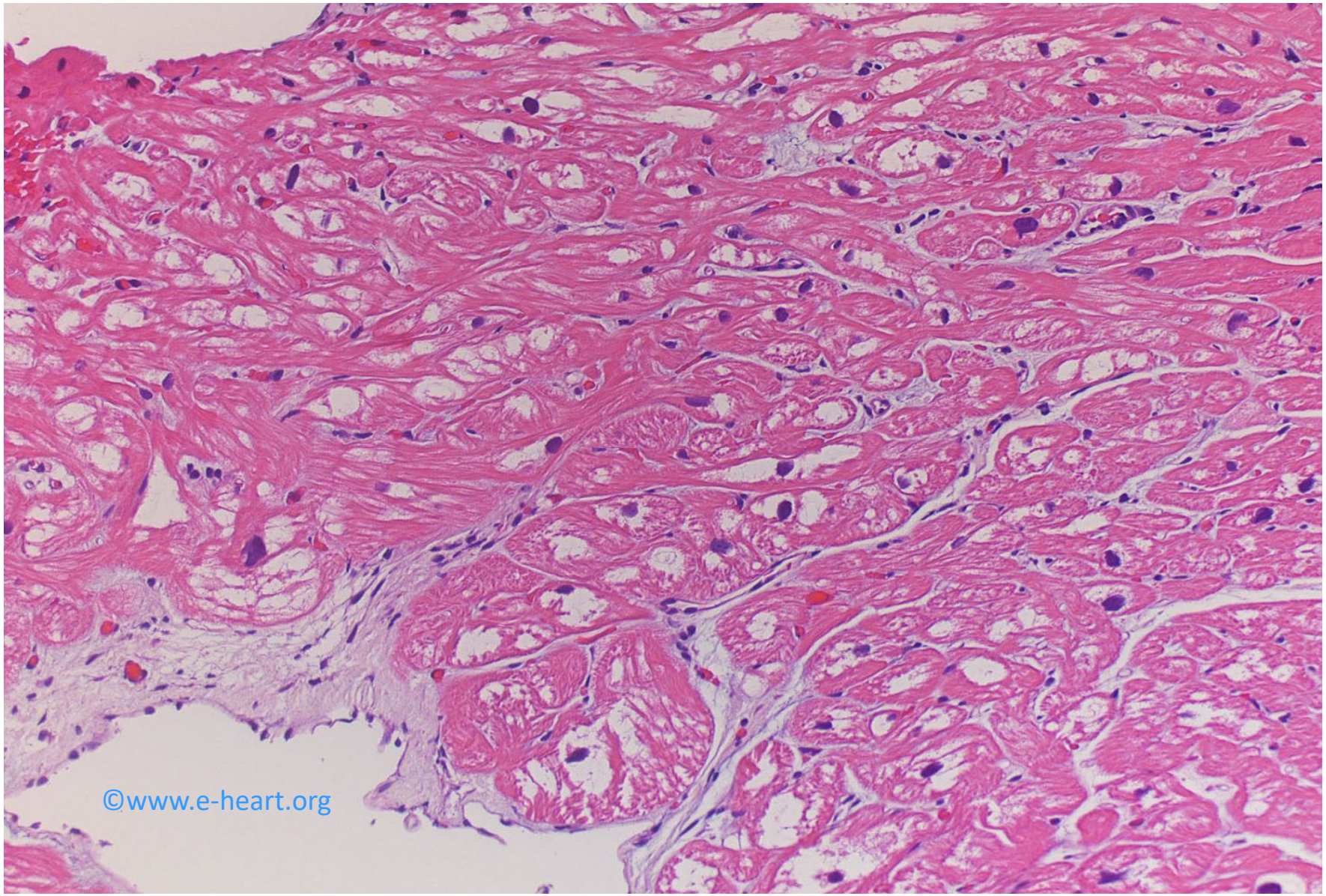
Tan CD, Rodriguez ER: Chapter 20. Molecular pathology of the cardiovascular system. Foundations in Diagnostic Pathology : Cell and Tissue Based Molecular Diagnostics. Goldblum JR, Tubbs RR, Stoler MH, Churchill Livingstone, 2008 pp 214-240

Arrhythmogenic right ventricular cardiomyopathy

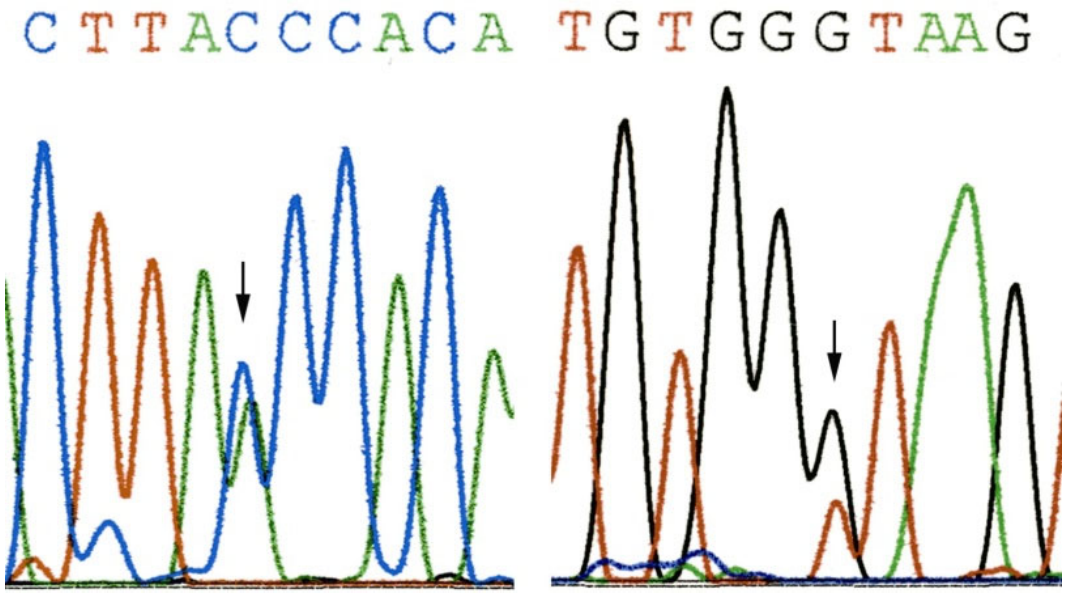
- Associated with ventricular tachycardia, syncope and sudden death
- Criteria for dx include morphological, imaging, electrocardiographic features, family history
- Familial in approximately 50% of cases with predominantly autosomal dominant pattern of inheritance

Case 4

- 48 year old woman
- Diagnosed with HCM with WPW syndrome for 10 years
- Later became dilated phenotype
- EMBx performed

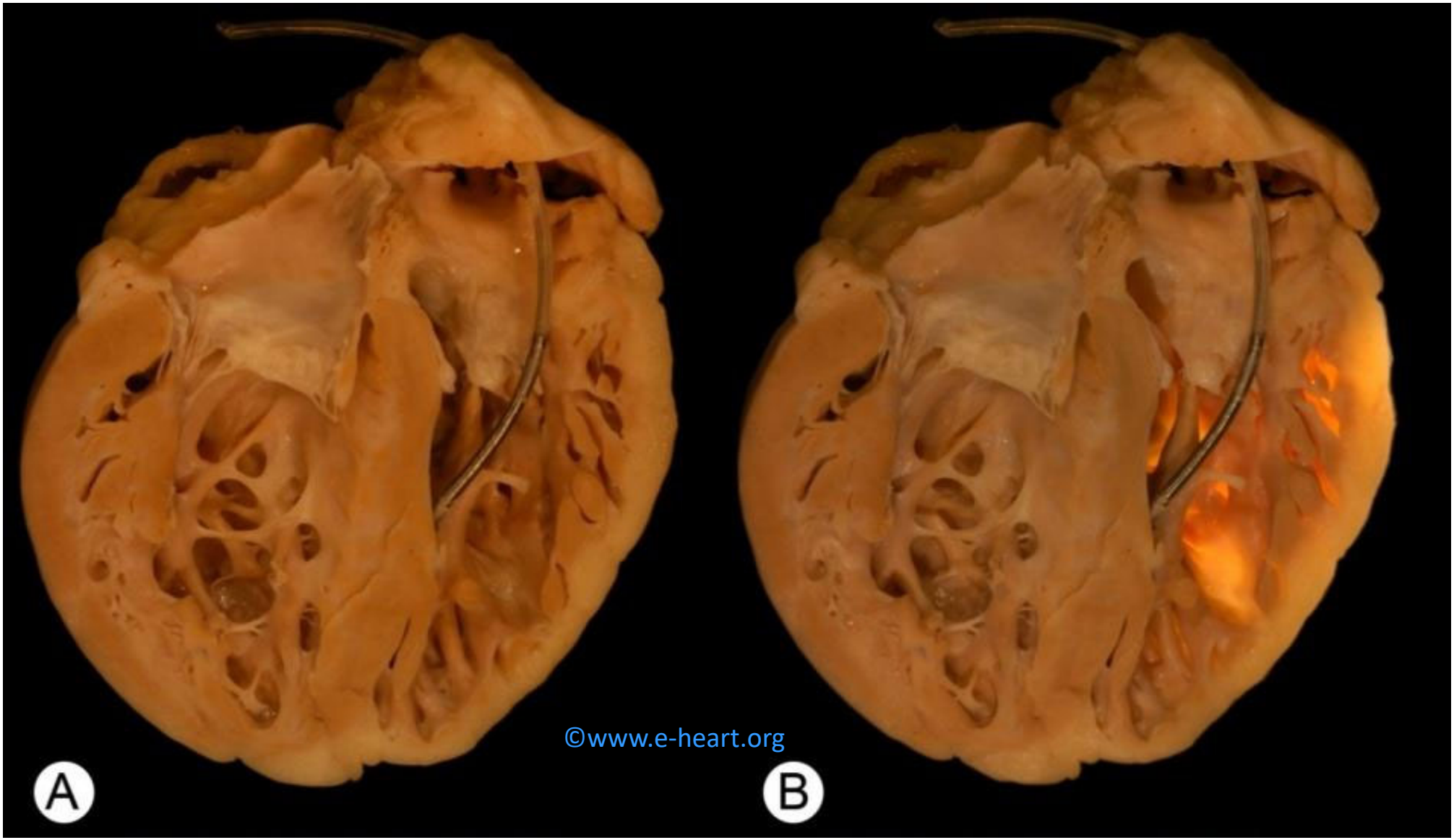

©www.e-heart.org

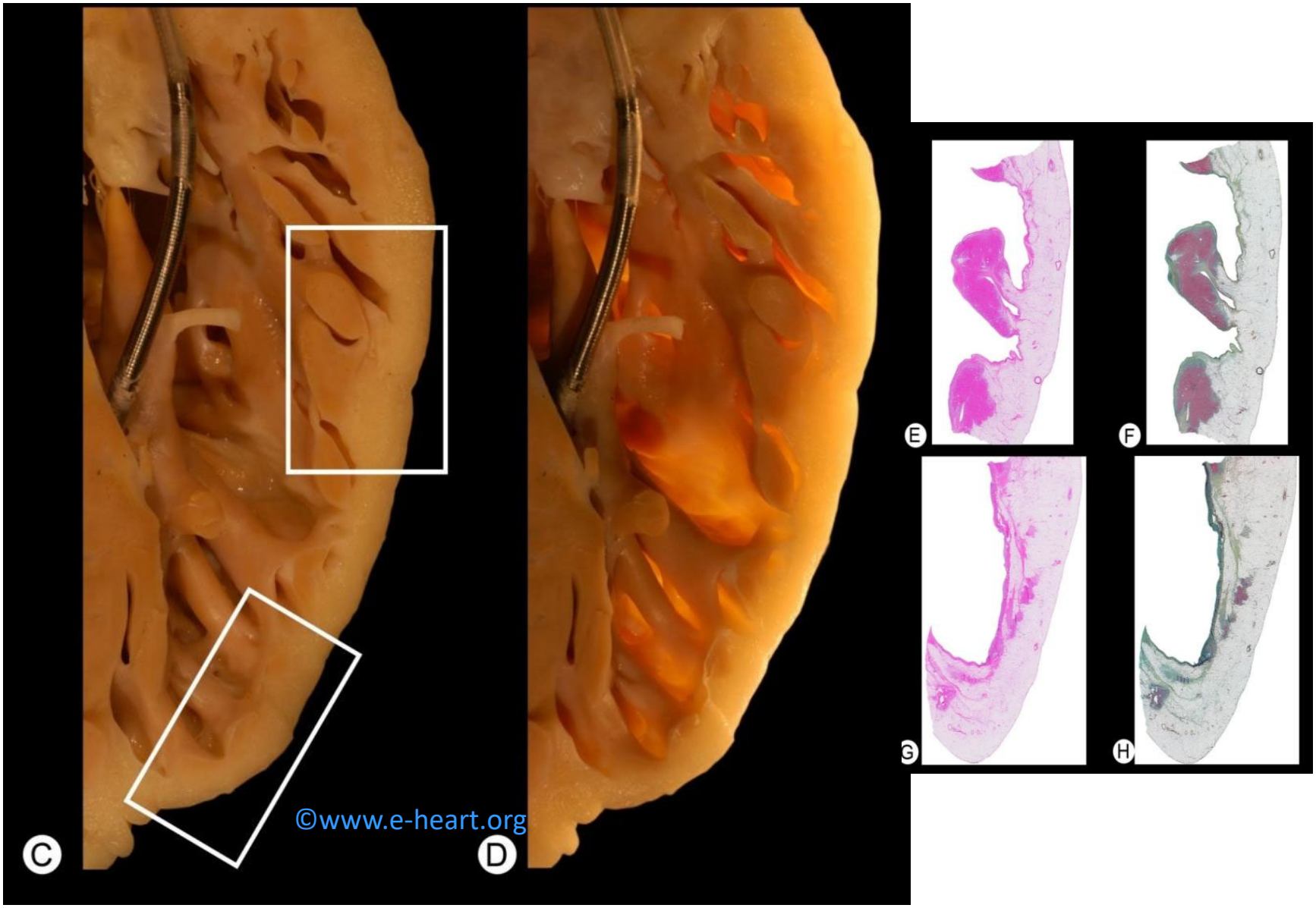
Guess diagnosis?



DNA sequencing showed a c. 1199 C>A mutation predicting a T400N amino acid change in the PRKAG2 gene

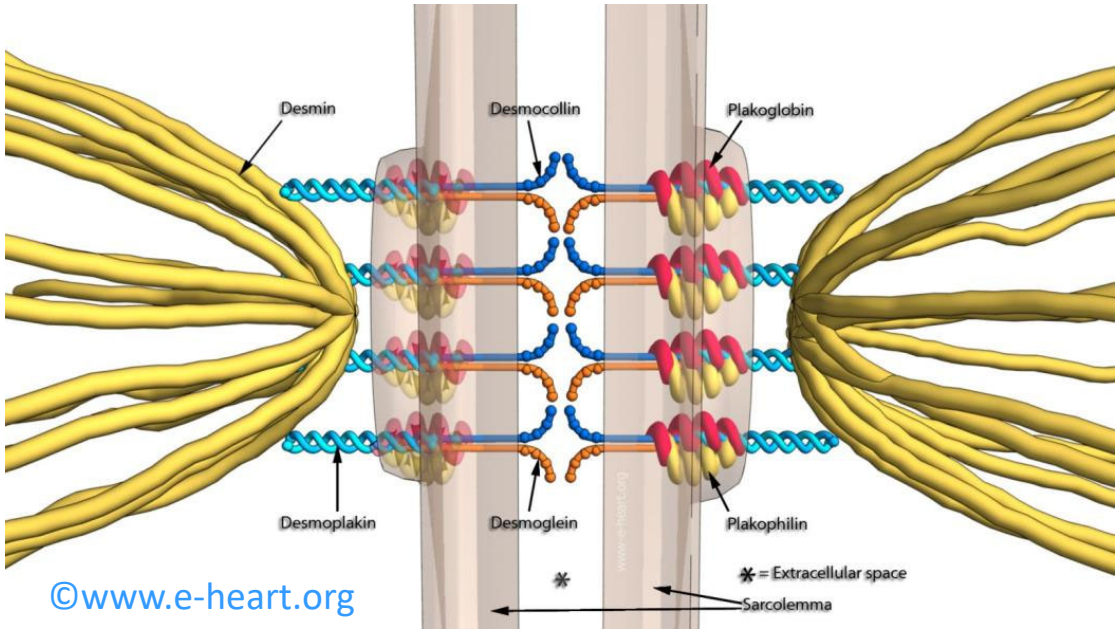
A form of glycogen storage disease which mimics HCM


©www.e-heart.org
A
B


C
D
E
F
G
H
©www.e-heart.org

In addition to the PRKAG2 mutation found which explains the GSD features this patient also had a PKP2 (Plakophilin 2) T526M mutation (considered pathogenic by some and a polymorphism by others)

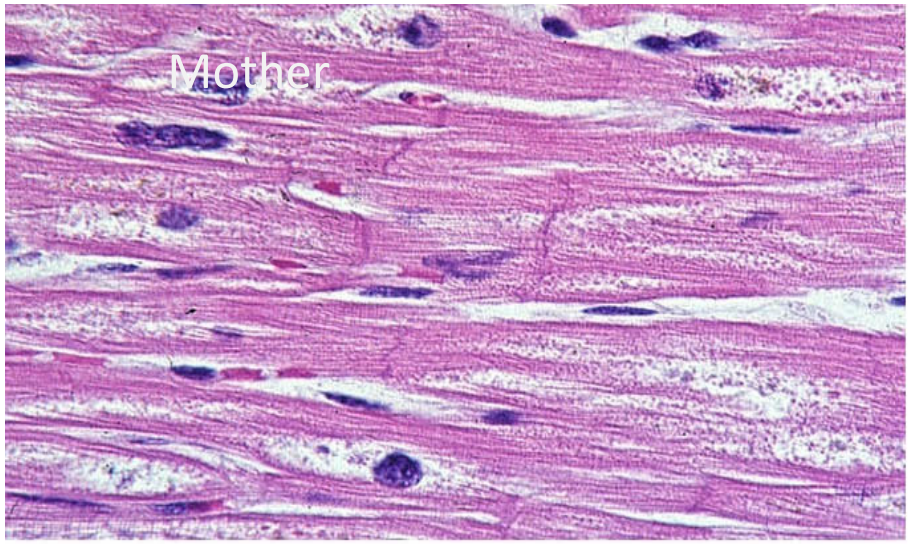
But for this patient this represent a compound heterozygote state with two mutations which explain the two pathologic phenotypes found in her heart (HCM and ARVD).
Both entities causing arrhythmias

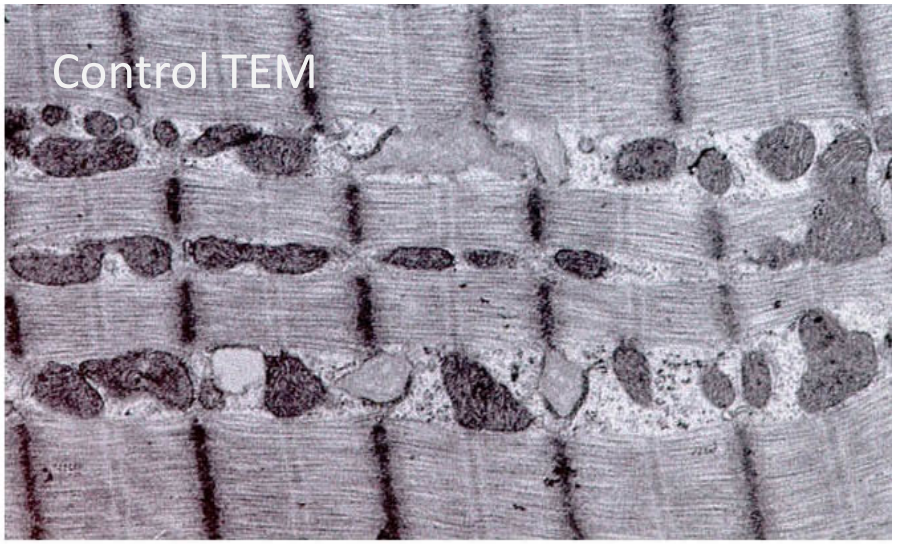


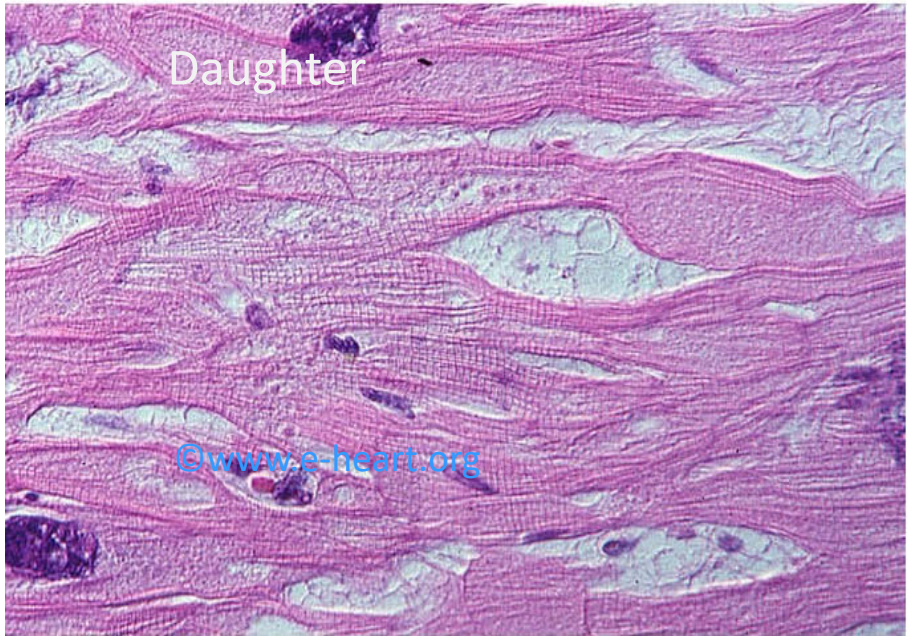
Cases 5 and 6

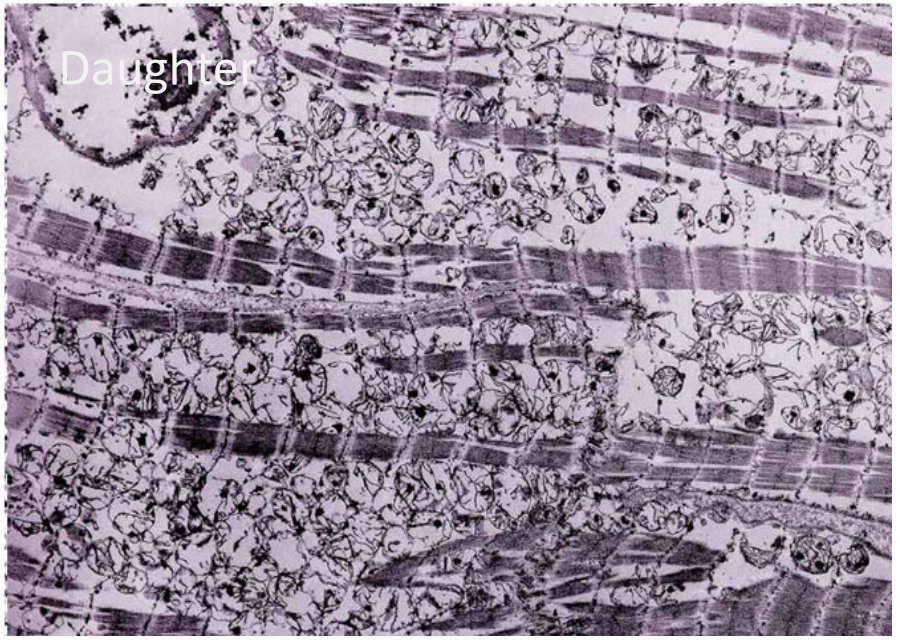
42 yo a.a. woman evaluated for recent heart failure
4 pregnancies
EMB …

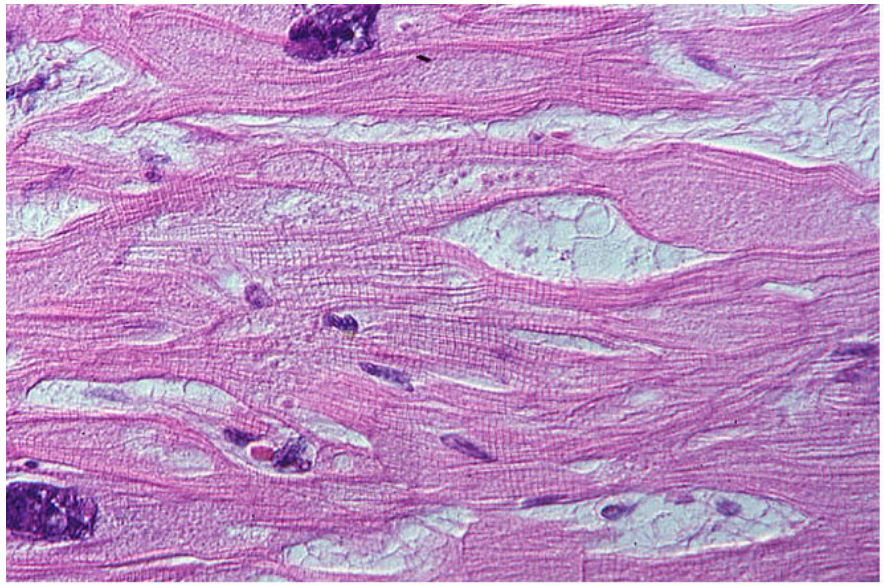
2 weeks later… her 16 year of daughter is admitted to and emergency room in frank, fulminant heart failure
EMB done…

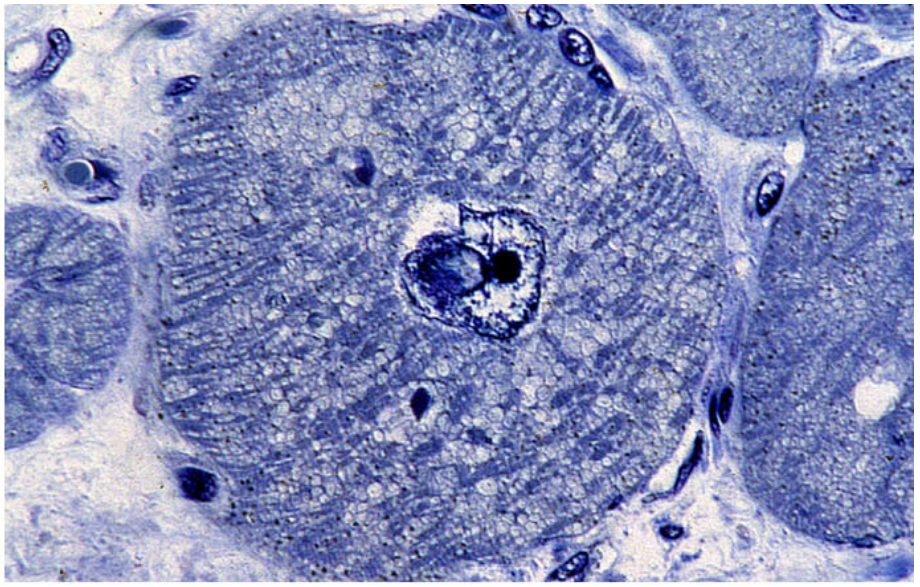

Mother

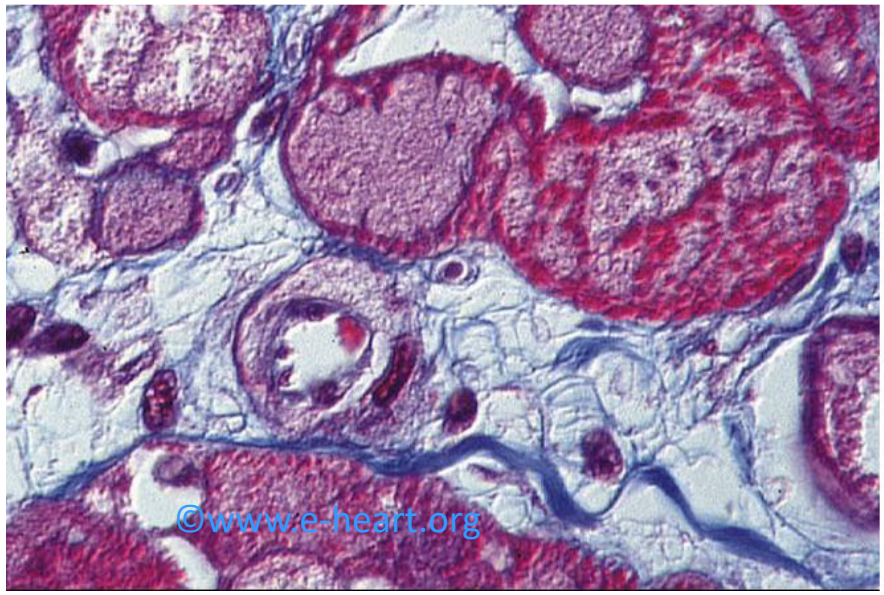

Control TEM

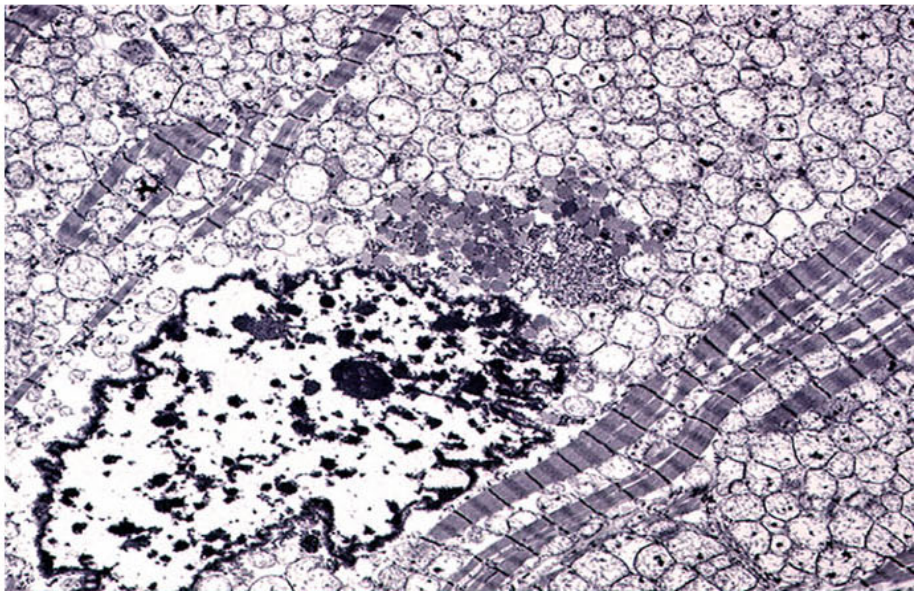

Daughter
©www.e-heart.org


Daughter

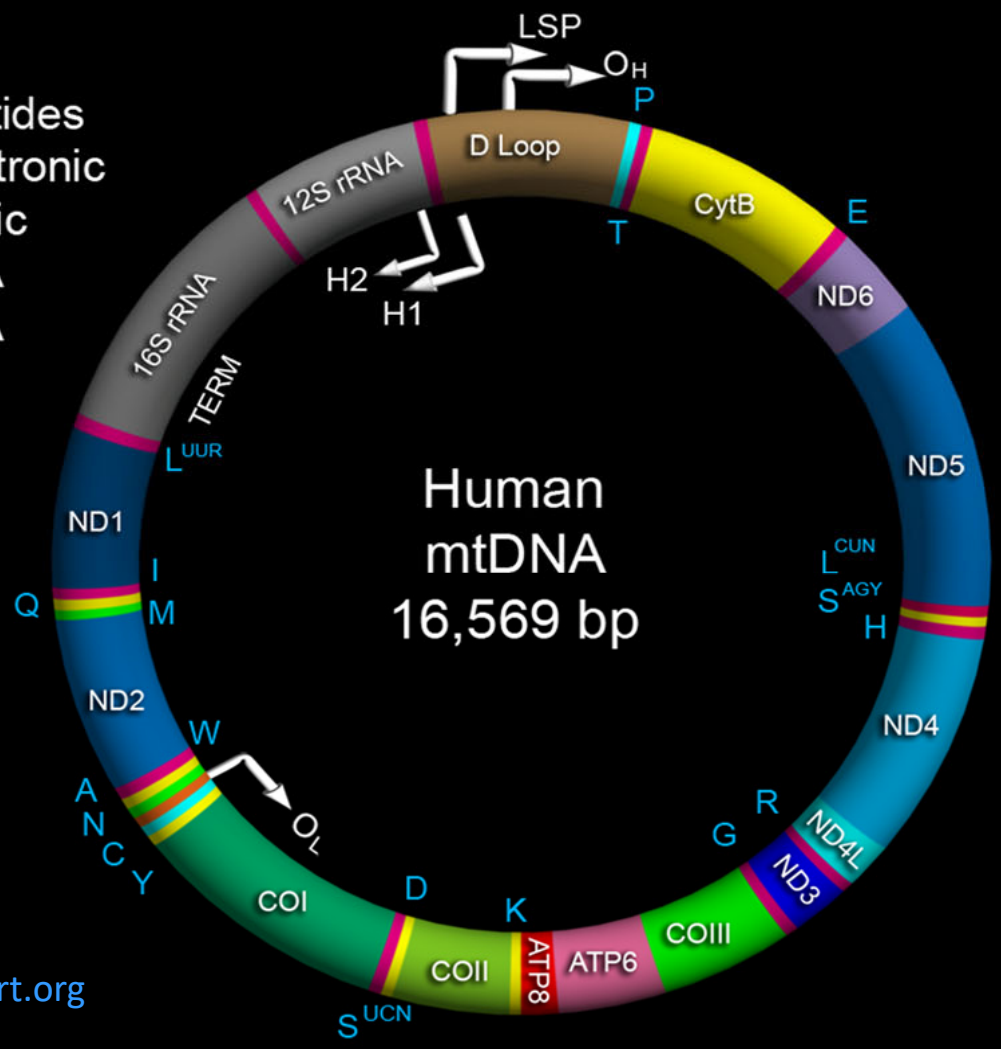





©www.e-heart.org



37 Genes
13 Polypeptides
9 monocistronic
2 bicistronic
1 12S rRNA
1 16S rRNA
22 tRNAs



LSP = Light Strand Promoter

H1 & H2 = Heavy Strand Promoters

O_H = Origin of Replication Heavy Strand

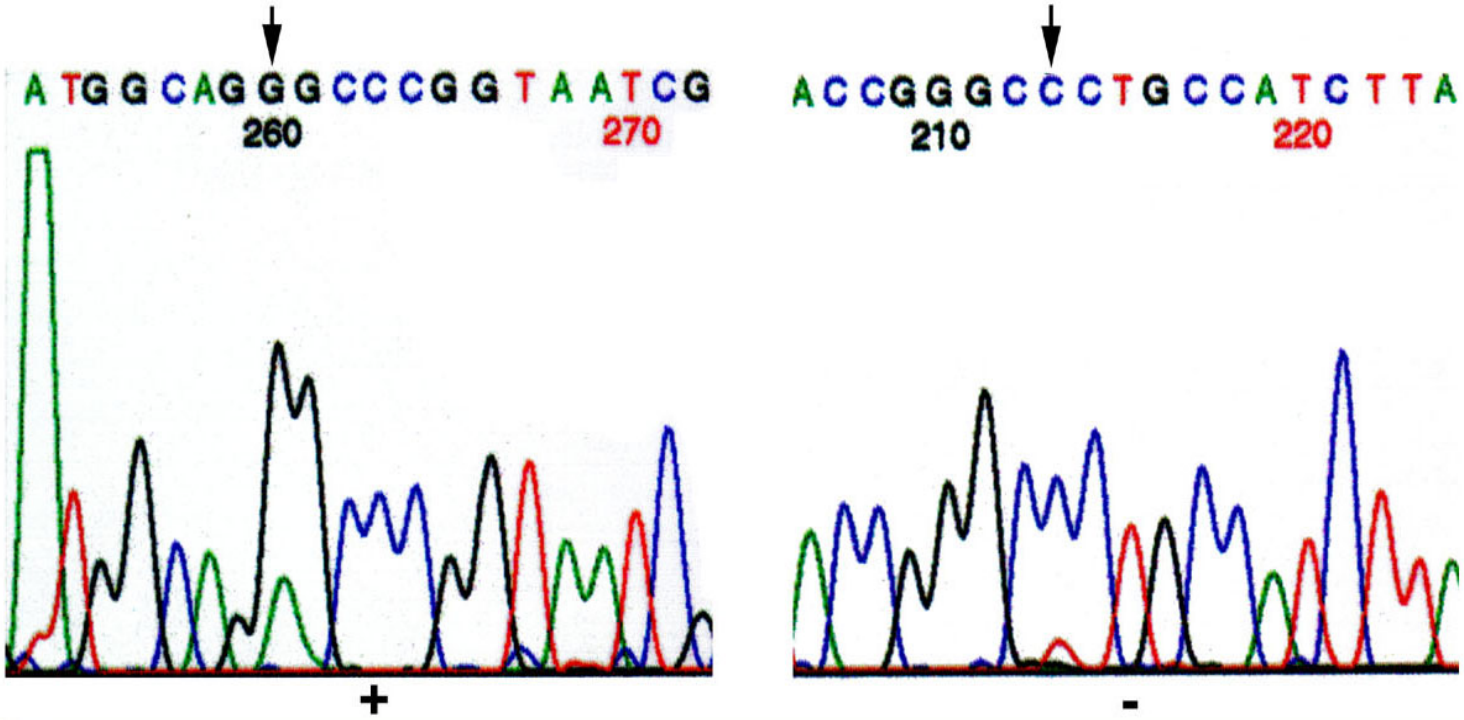
O_L = Origin of Replication Light Strand

Paternal mtDNA
< 1 in 10^4

Somatic cells
2-10 copies mtDNA
per mitochondrion

©www.e-heart.org

A3243G tRNA Leu 1 (UUR)



Mitochondrial Cardiomyopathy
2o. to A3243G mutation in
Leu1(UUR) mt tRNA

MELAS Syndrome
Myoclonic **E**pilepsy, **L**actic **A**cidosis
and **S**troke like episodes

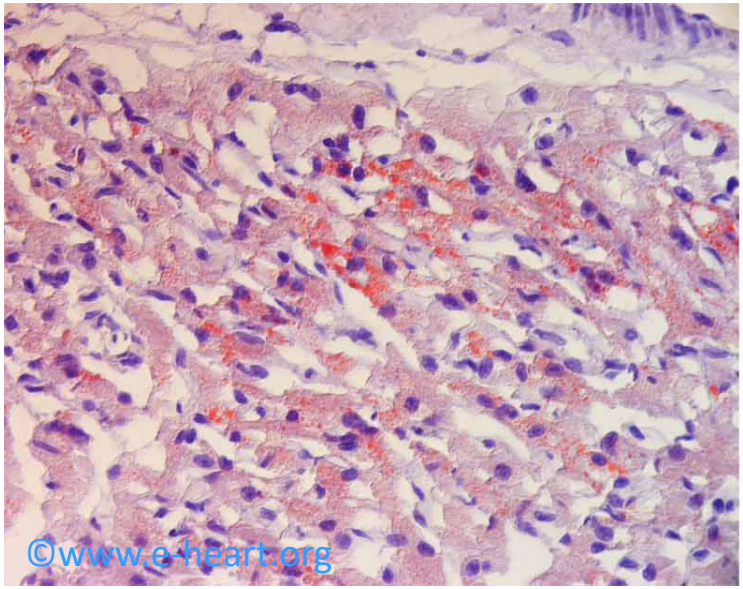
Mitochondrial cardiomyopathy

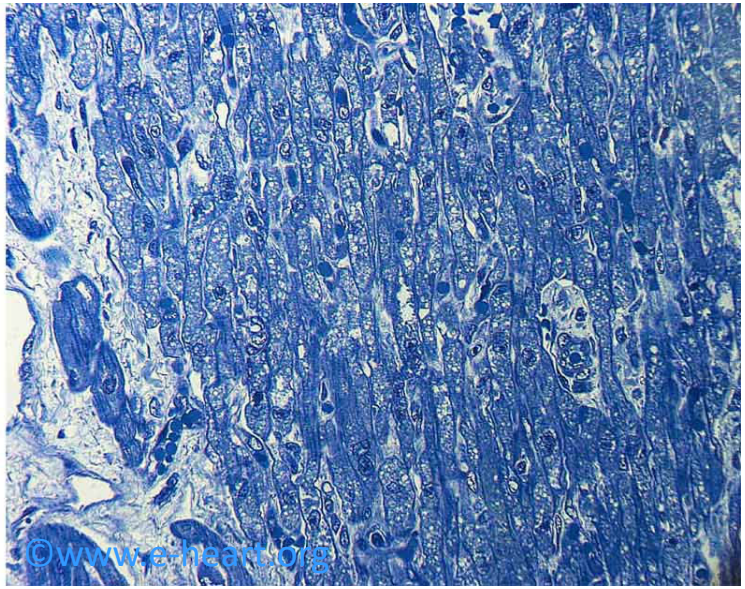
- MELAS syndrome (**M**itochondrial **E**ncephalopathy **L**actic **A**cidosis and **S**troke-like episodes)
- Produces neurologic, cardiovascular and gastrointestinal disease in different family members

What about younger patients?

- Carnitine
- Fatty acid metabolism deficiencies?

Microvesicular steatosis





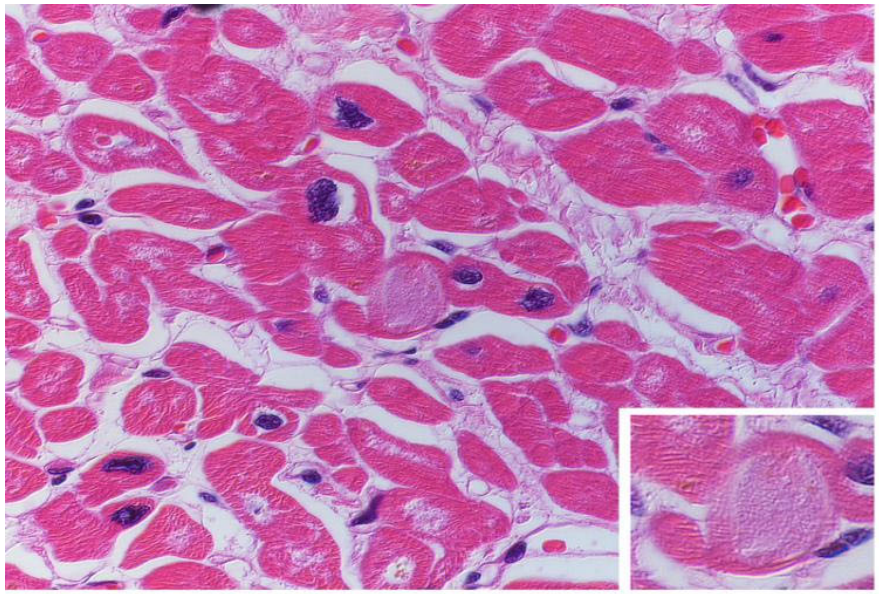
1 month old female

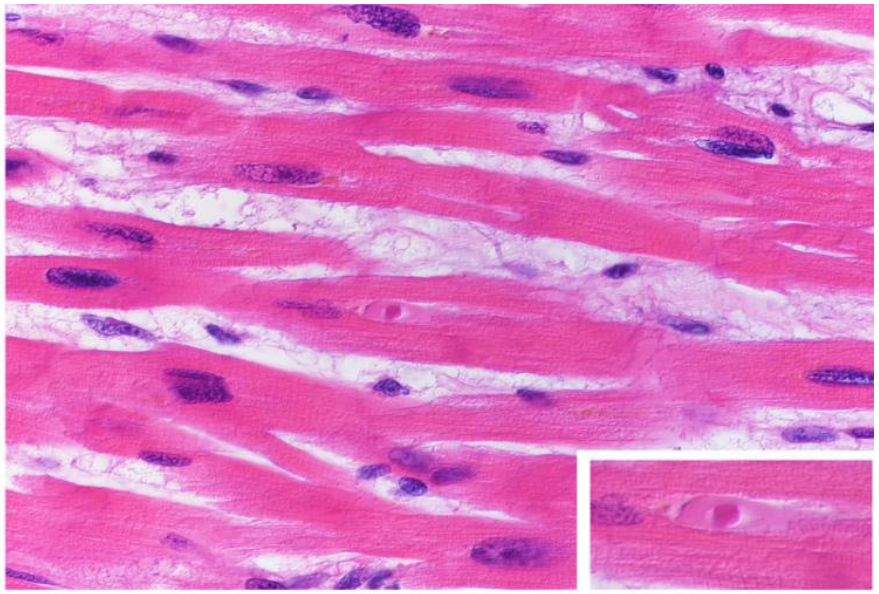
Case 7

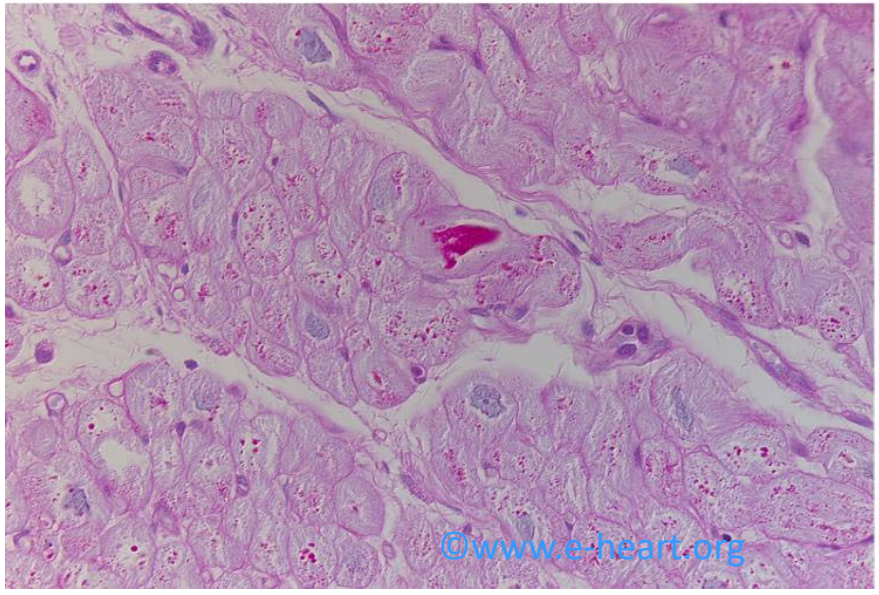
-14 yo african-american boy

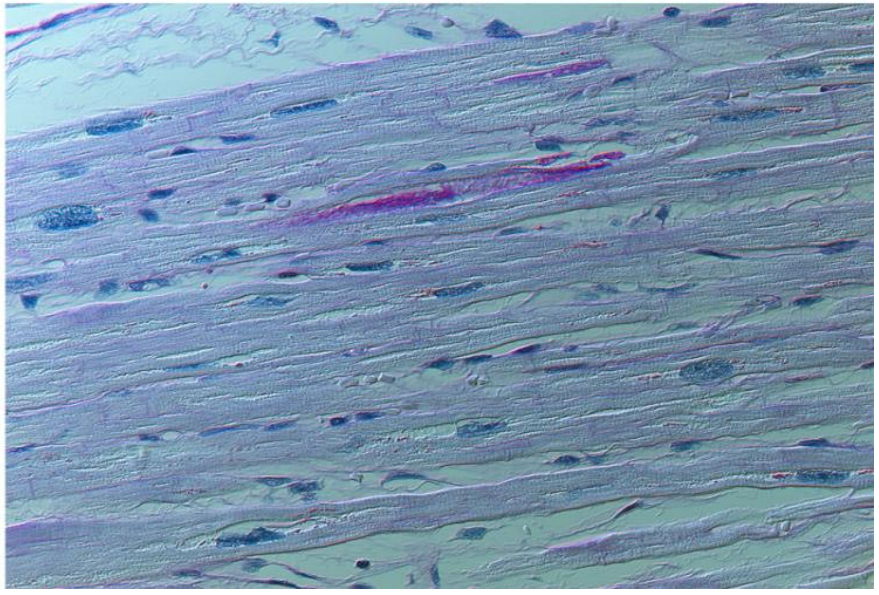
-Recent onset heart failure

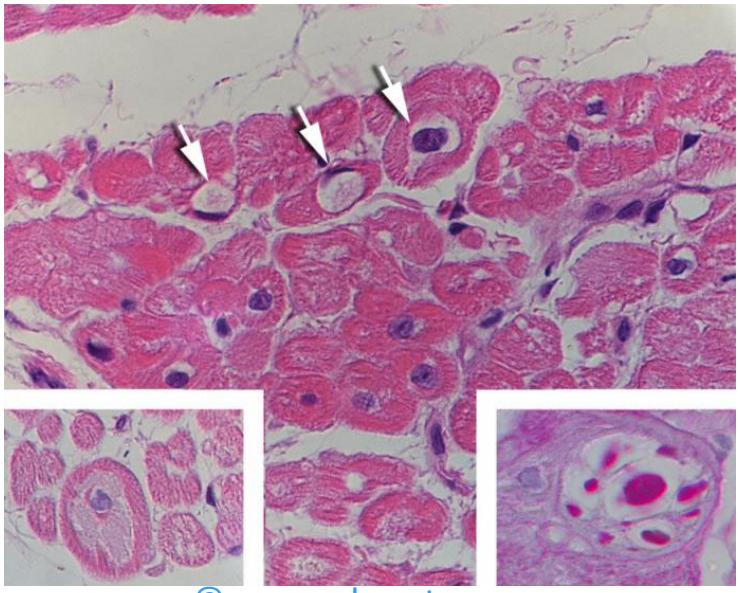
-Mother has heart failure and neurologic symptoms



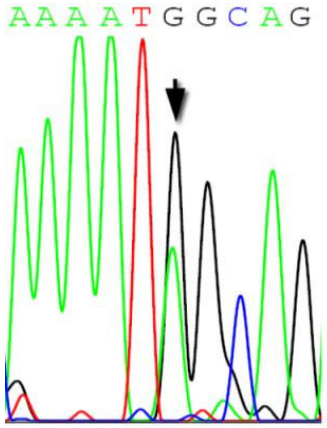


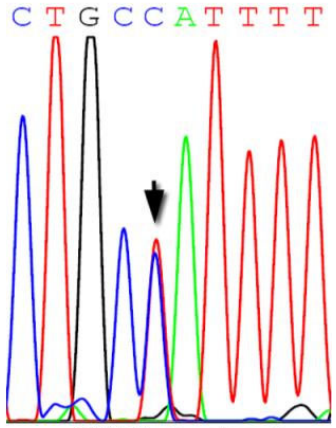

©www.e-heart.org





©www.e-heart.org

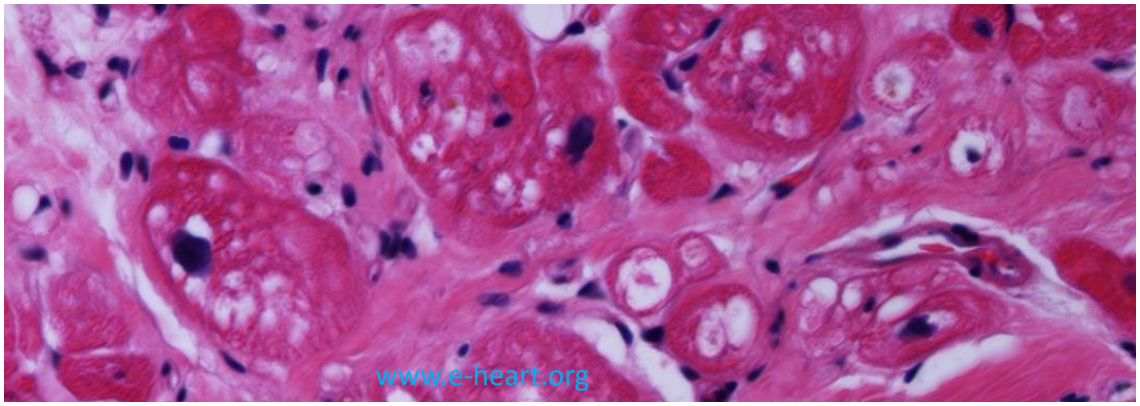




LAMP2 c. 274 G>A (Trp46X)

Final Diagnosis:
Lysosomal Associated Membrane Protein 2
LAMP2
Glycogen storage – with neurologic and cardiac involvement (Danon's Disease)

Mother diagnosed because of neurologic findings

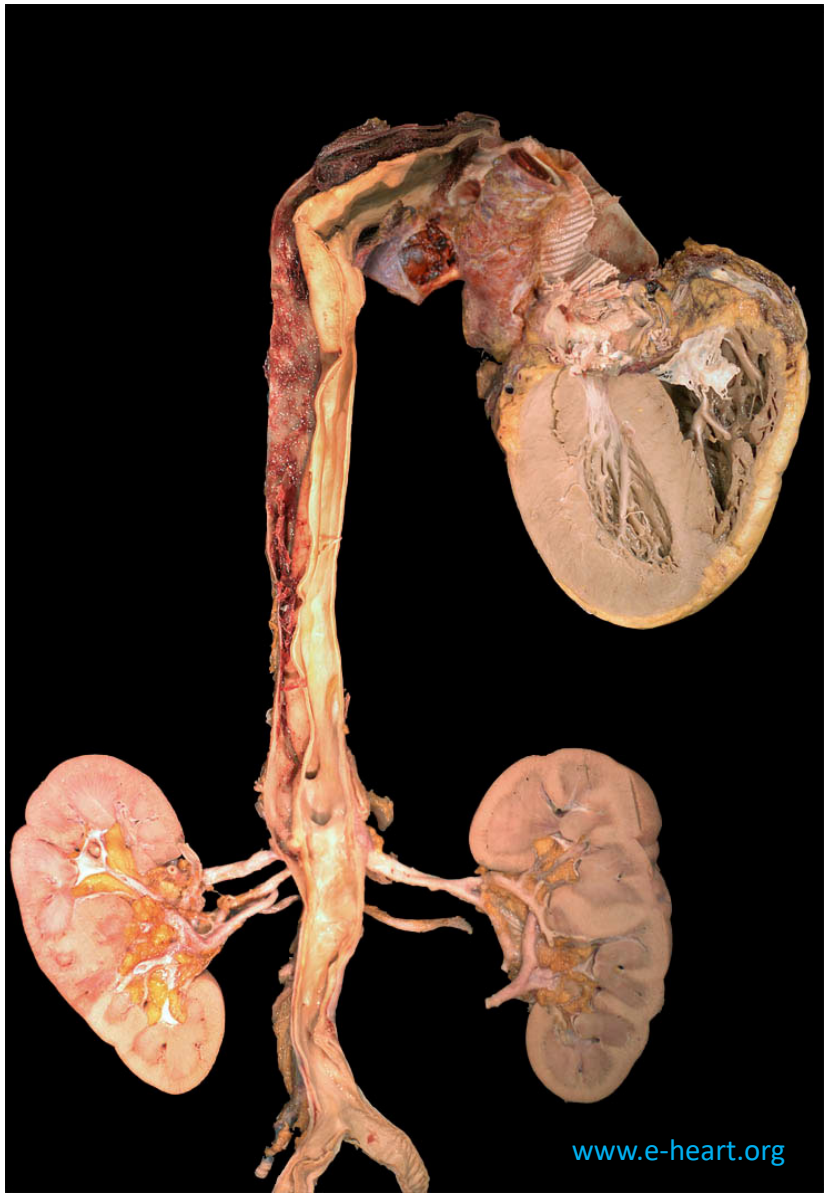


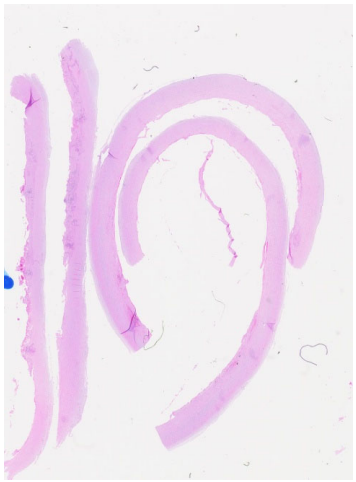
Examination of heart vessels and great vessels

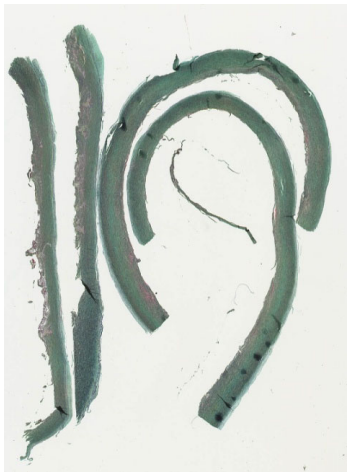
- Routine examination for developmental anomalies or acquired conditions is performed
- Great vessels are thoroughly examined for developmental and acquired conditions
- Surgical interventions may dictate different approaches to dissecting the heart

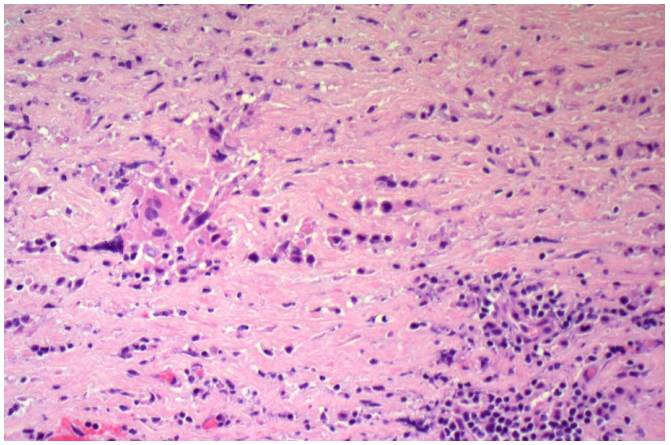
Case 8

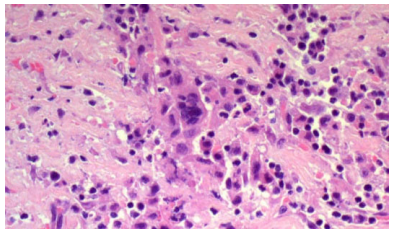
- Patient with history of giant cell aortitis
- Elective repair of large dilated aortic root and ascending aortic aneurysm
- Died suddenly 3 days after surgery

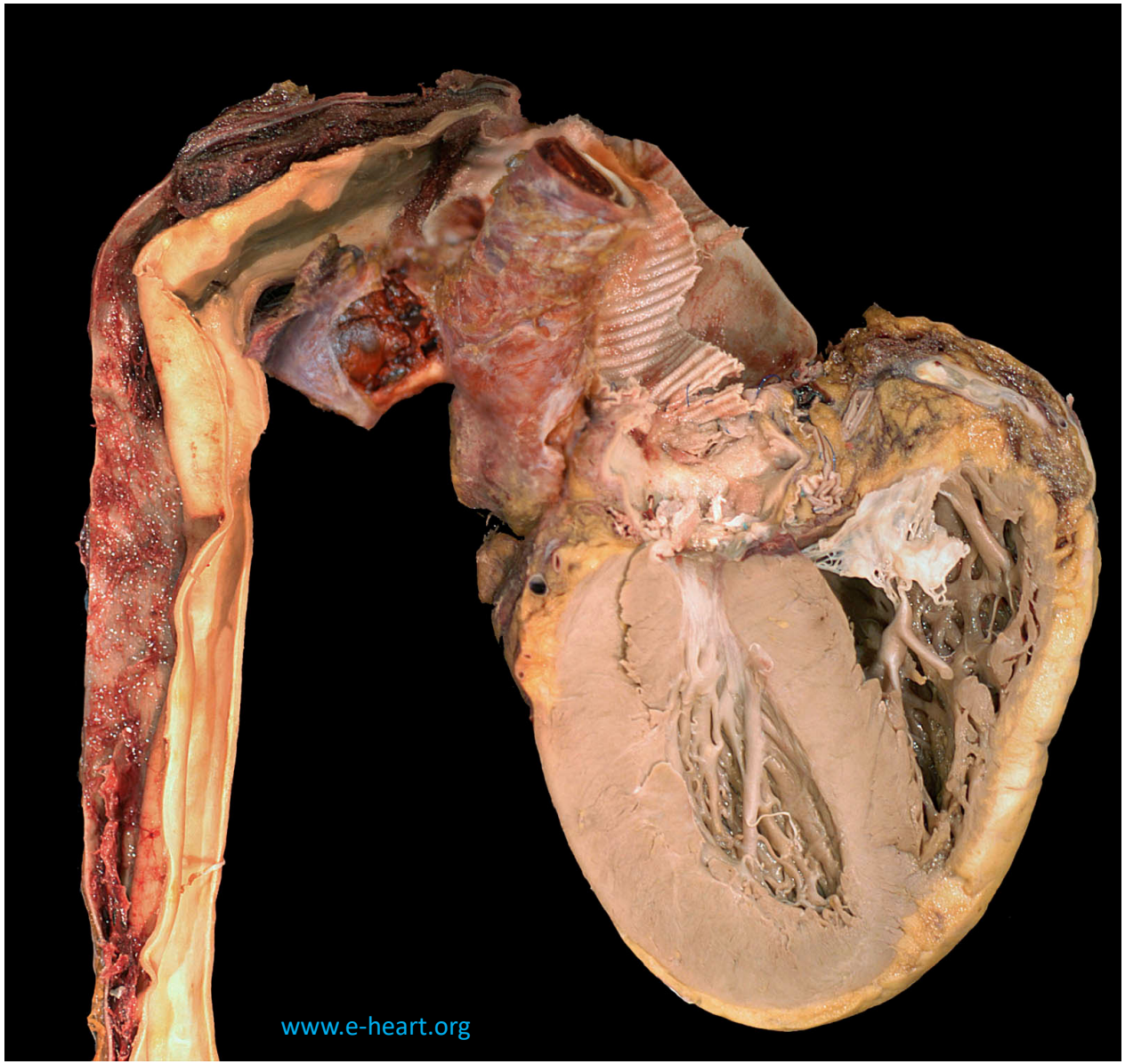

www.e-heart.org

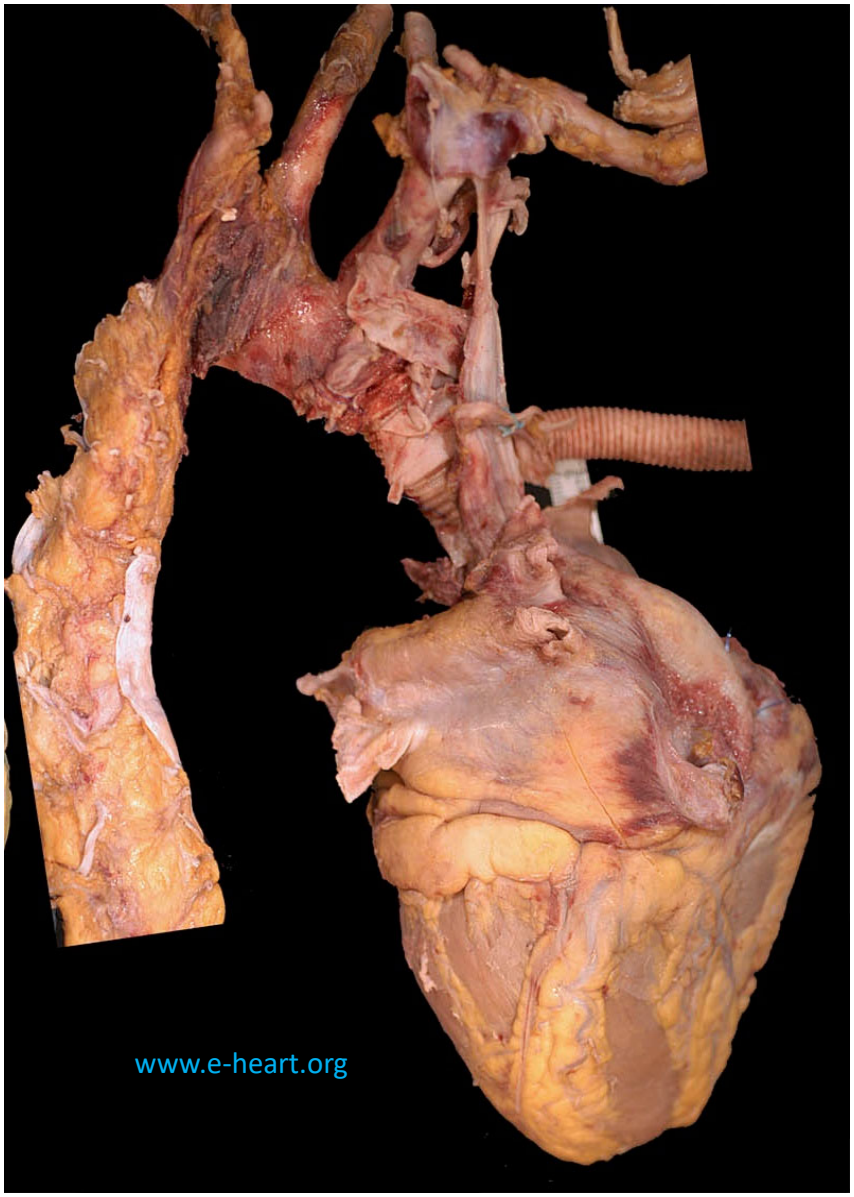


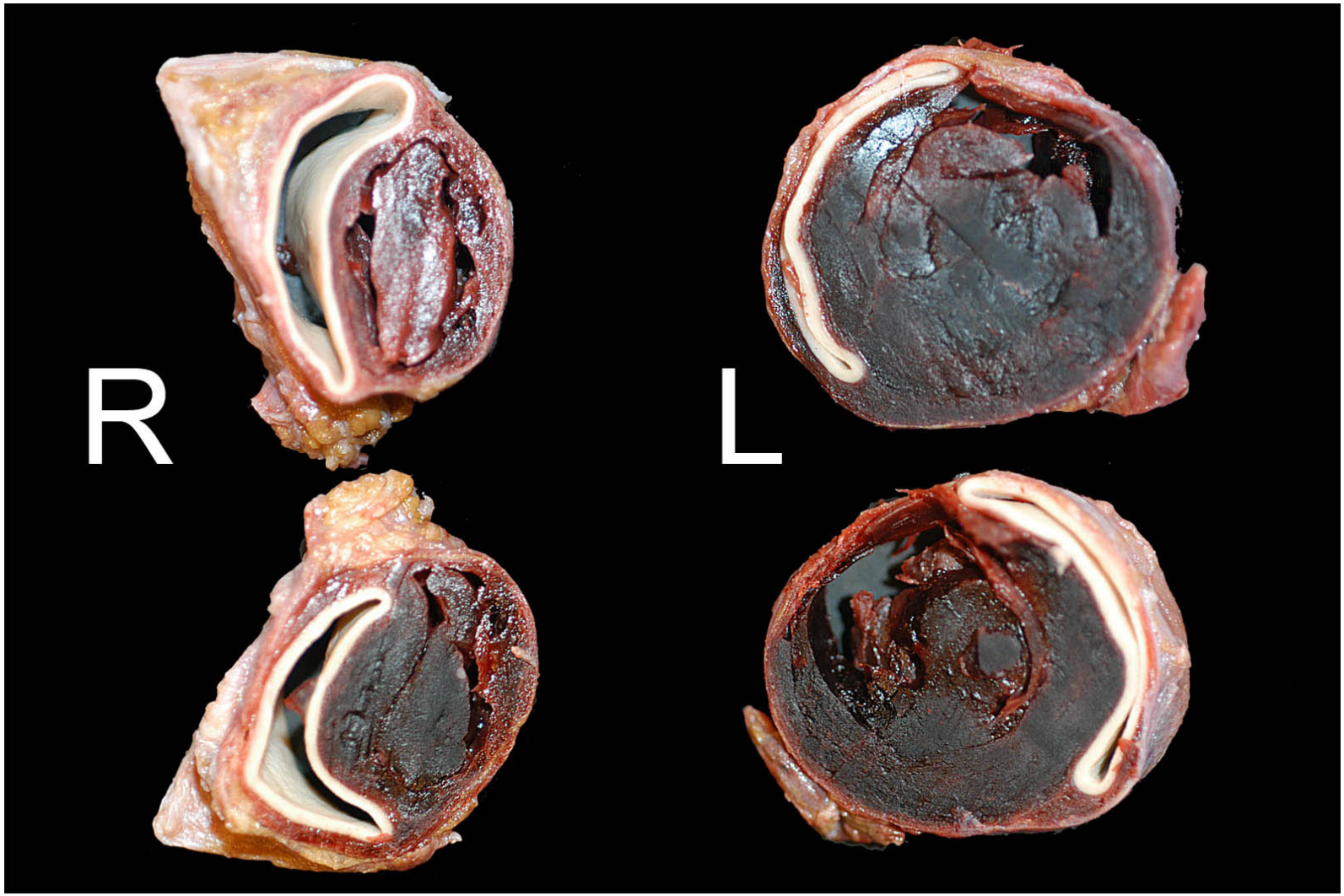


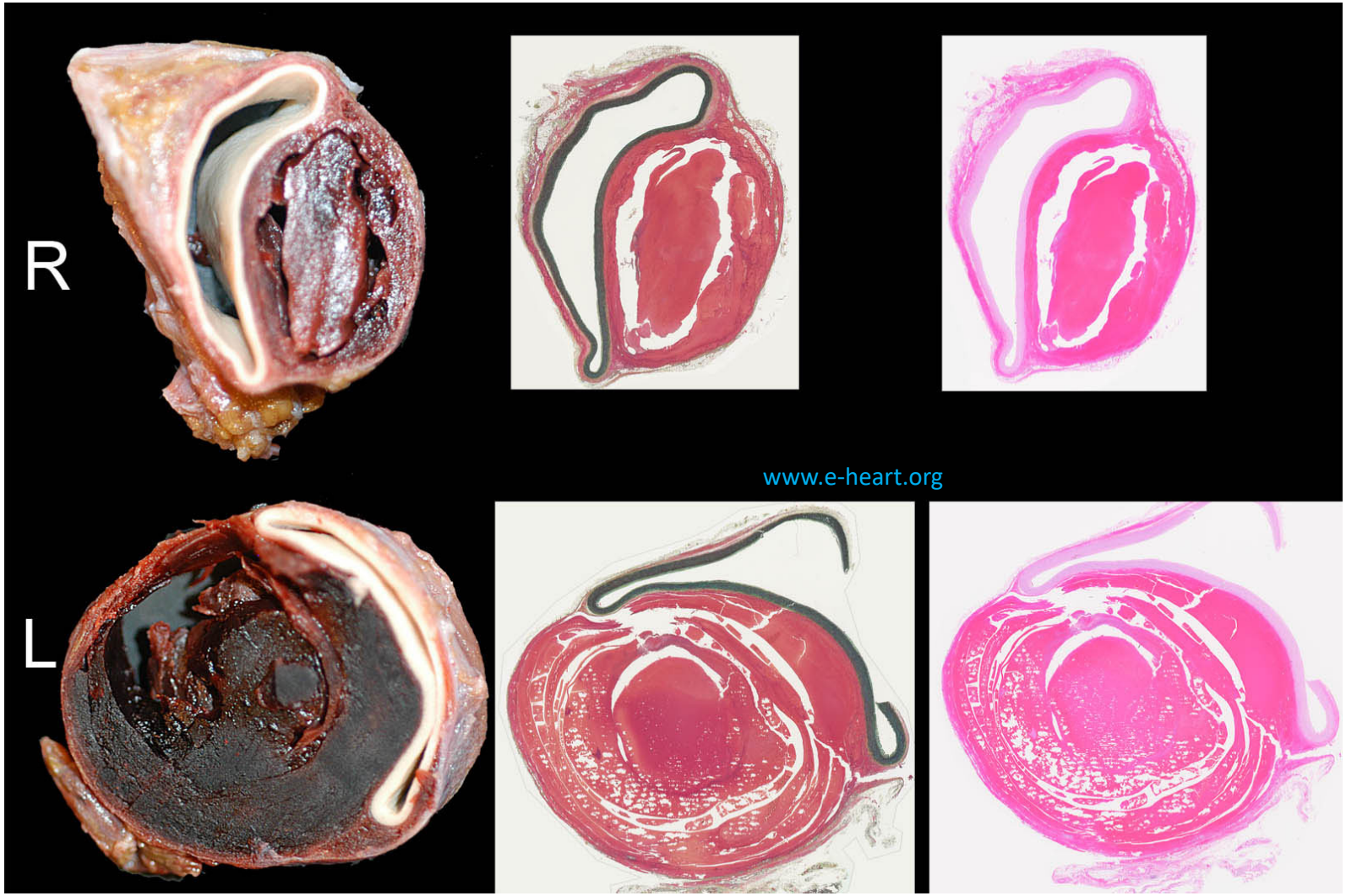





www.e-heart.org

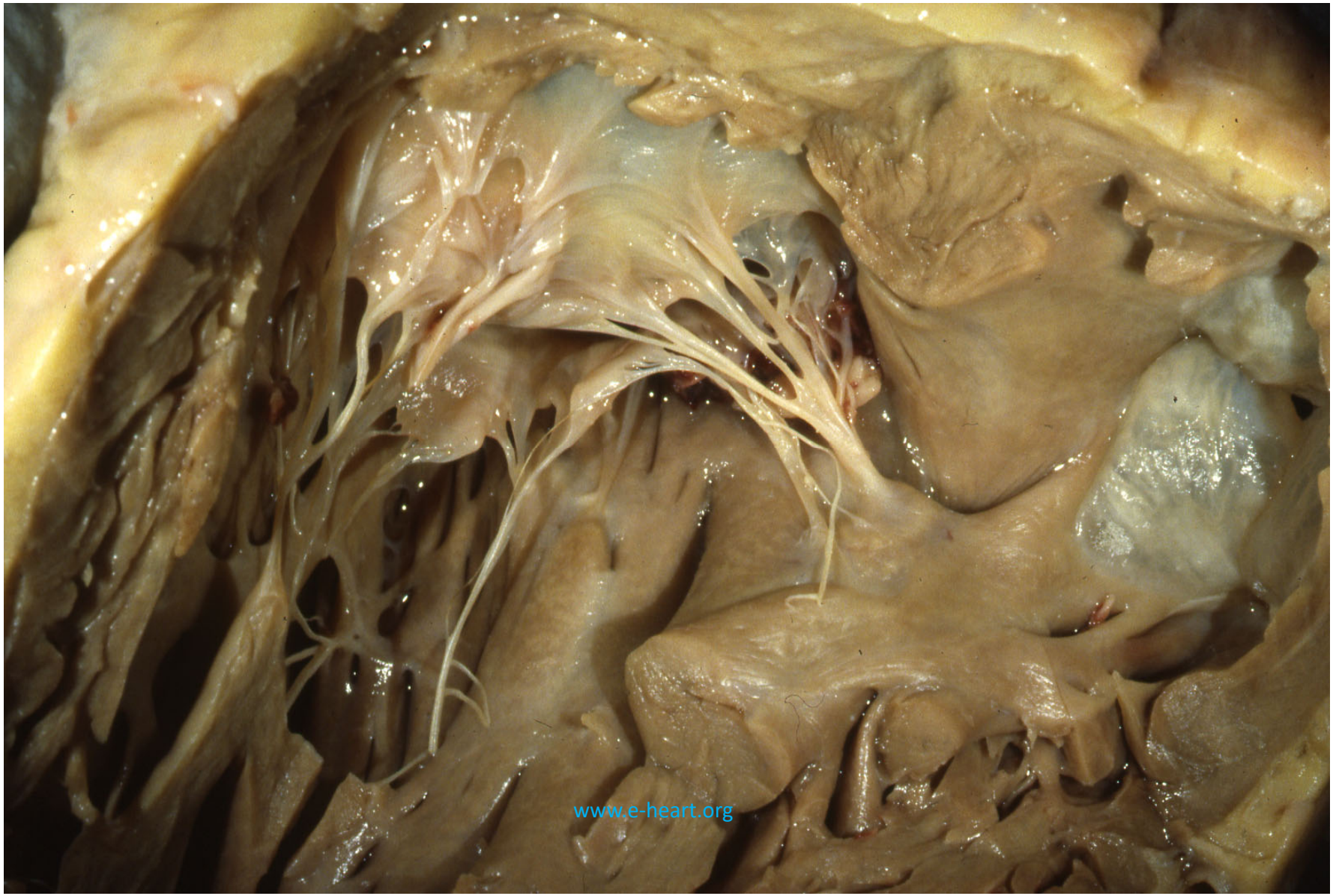

www.e-heart.org

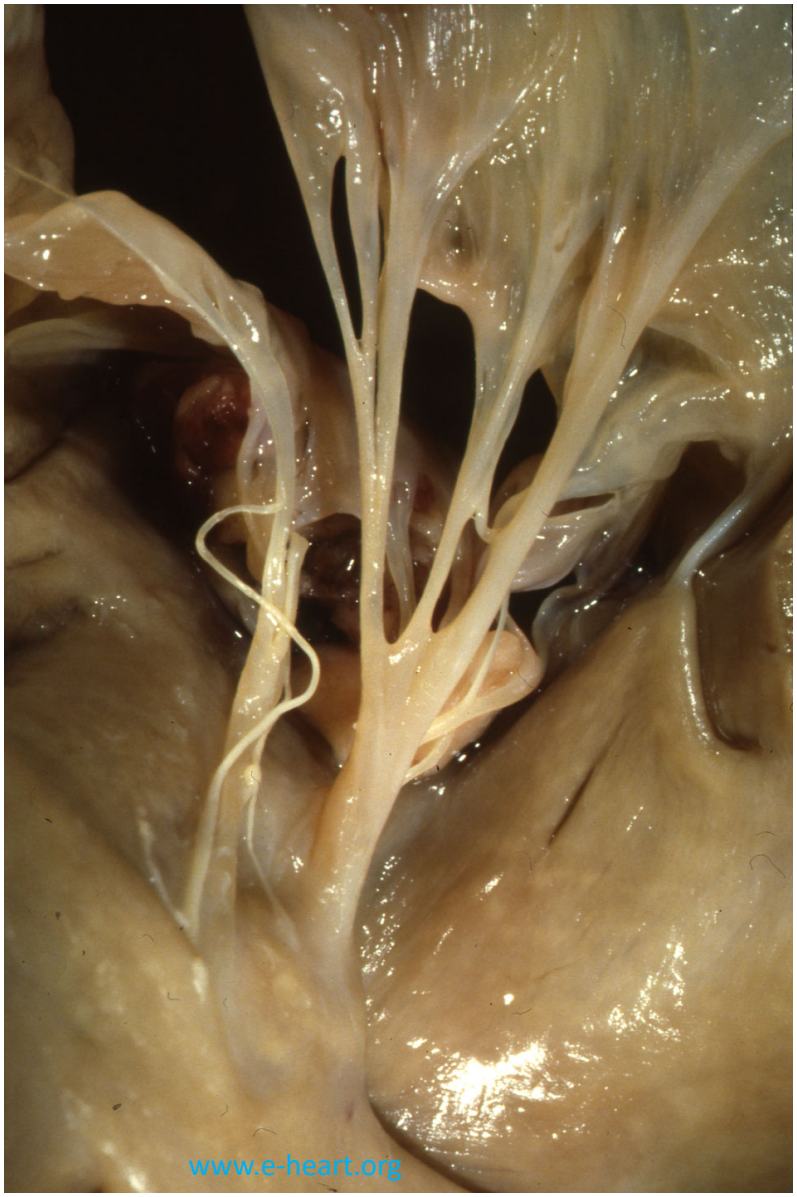

R
L

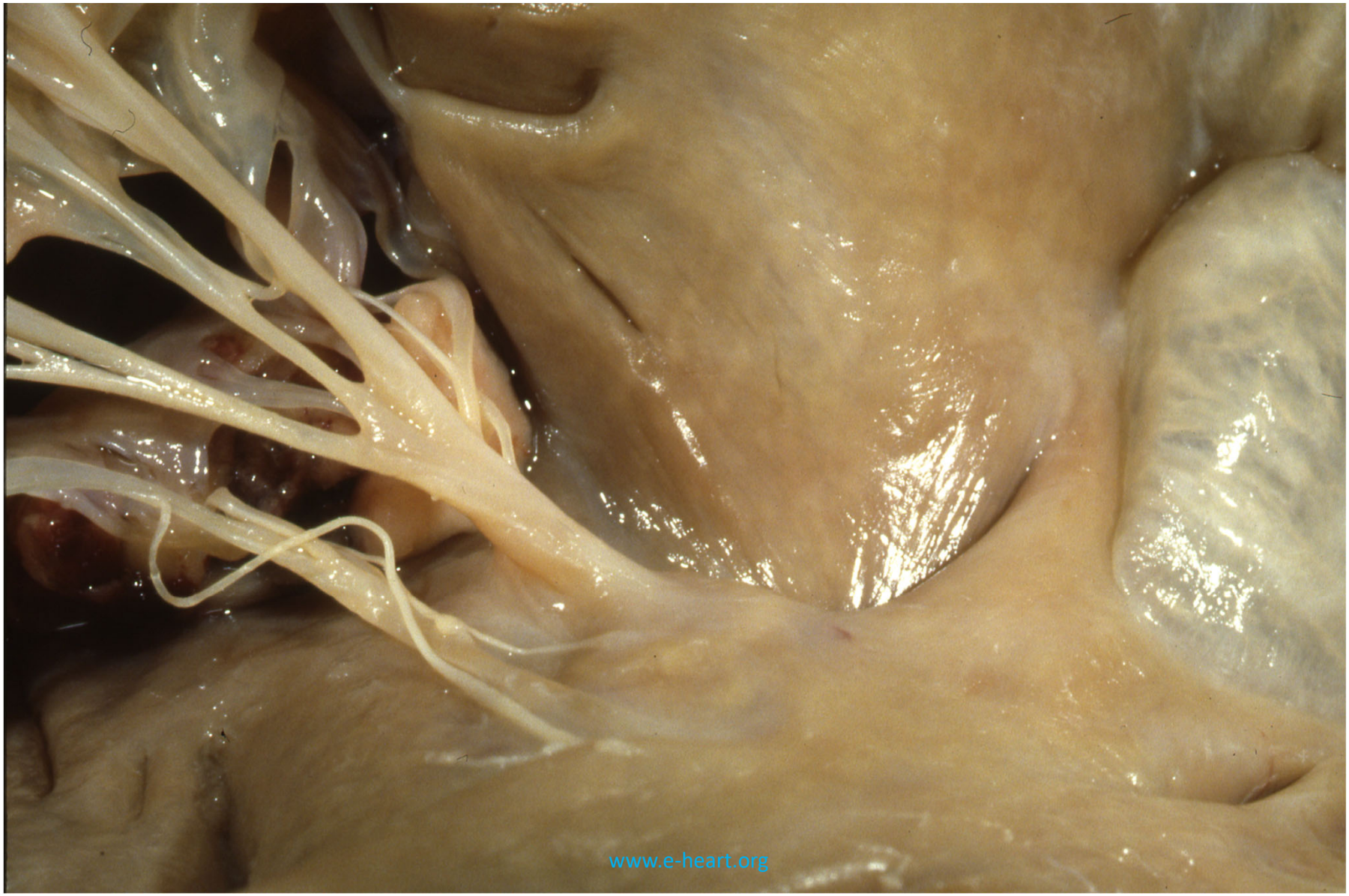

R
L
www.e-heart.org

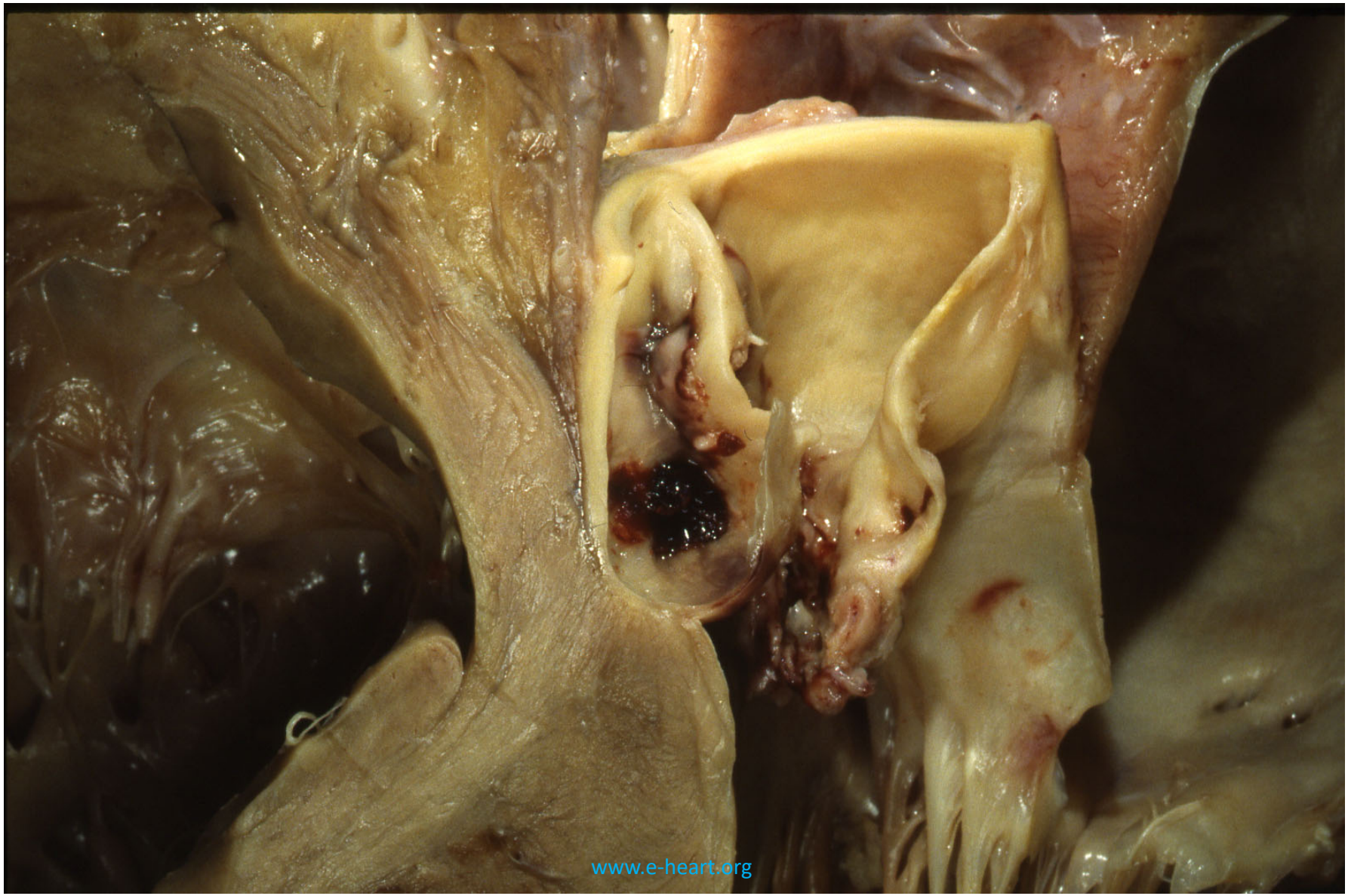
Case 9

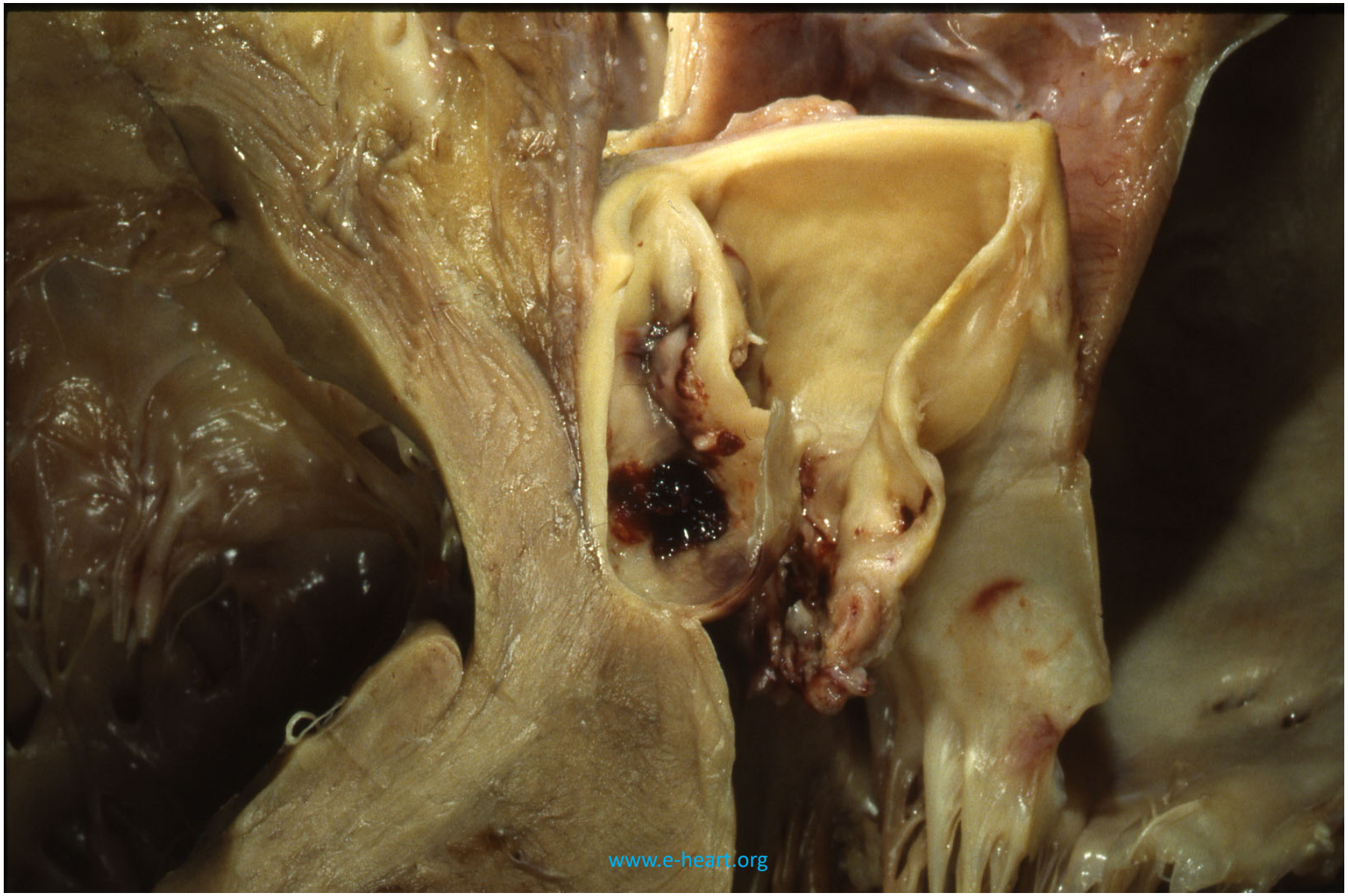
- Patient with recent diagnosis of endocarditis
- Elective valve suregery scheduled while in hospital
- Died suddenly (unexpected death)

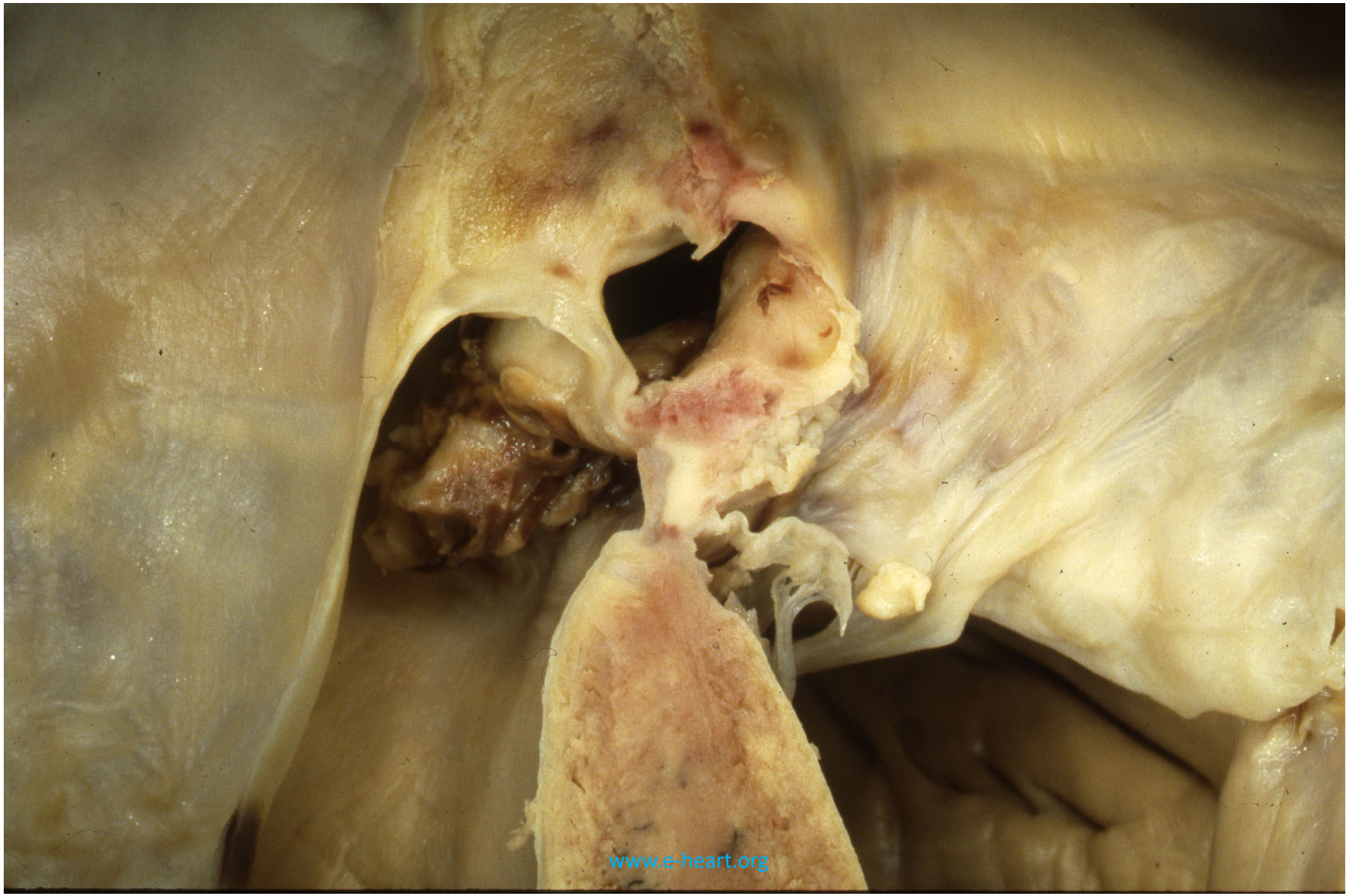

www.e-heart.org


www.e-heart.org

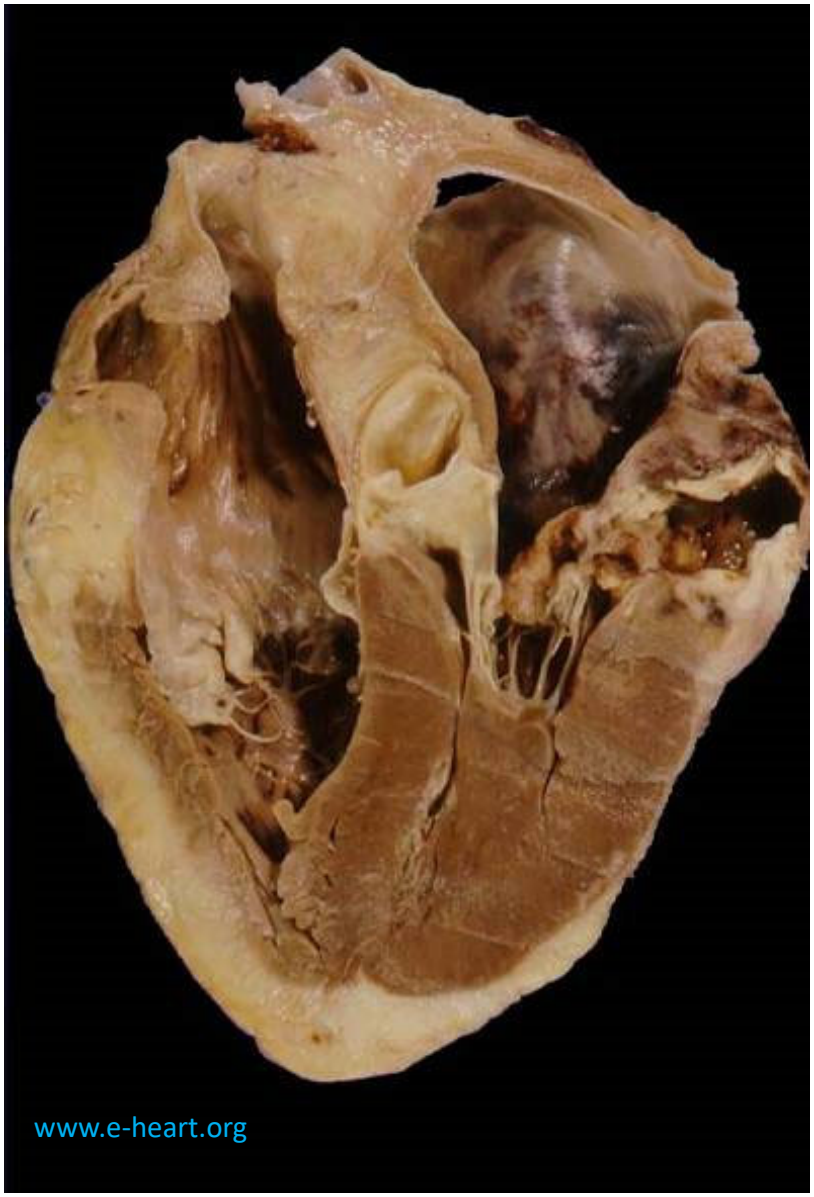

www.e-heart.org


www.e-heart.org


www.e-heart.org


www.e-heart.org

Mitral Valve endocarditis
and Ring Abscess



The Postmortem Anatomic Examination of the Heart

Learning Objectives

1. You will understand the detailed anatomical targets to approach sudden cardiac death cases.

2. You will understand the planning required to maximize yield of information in the case.

3. You will understand some of the limitations of the pathologic examination fo the heart in sudden cardiac death.

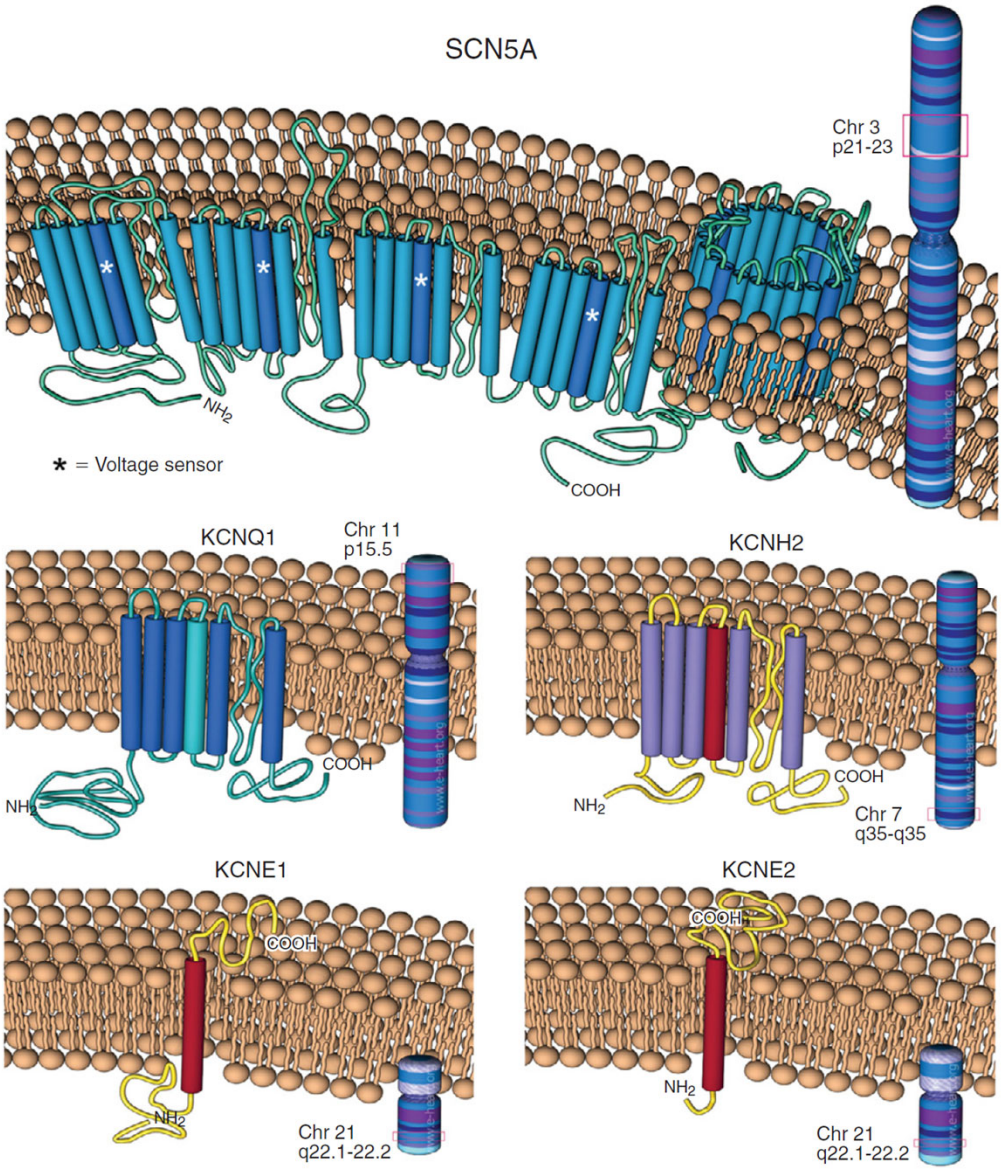
Hospital practice limitations

- Genetic or other expensive testing after death is usually not covered by third party payors or CMS
- Procurement of tissue to be frozen and used for nucleic acid extraction is an inconsistent practice
- Testing of relatives possible

Autoantibodies for cardiac channels and sudden cardiac death

Chart: Studies that Show Sudden Cardiac Death is Potentially Associated with Presence of Autoantibody Against A Cardiac Channel or Receptor		
Autoantibody	**Relationship to SCD**	**Comment**
Beta1-adrenergic receptor autoantibodies	A case-control study with 2062 patients and 824 controls found that, in patients with Ischemic Cardiomyopathy (ICM), beta 1 adrenergic receptor autoantibody was significantly higher in those who had Sudden Cardiac Death (SCD) compared to those who had Non-Sudden Cardiac Death (NSCD).	This study was done among patients with Chronic Heart Failure (CHF) and statistical significance was only shown in ICM patients, not in patients with Dilated Cardiomyopathy (DCM) [27]
	A study of 104 patients showed that presence of auto-antibodies against the second extracellular loop of the beta1 adrenergic receptor was an independent predictor of SCD.	This study was done among patients with idiopathic dilated cardiomyopathy [26]
Antibody against sarcolemmal Na-K-ATPase	A study of 100 patients and age-matched controls showed that the presence of antibody against sarcolemmal Na-K-ATPase was an independent predictor of SCD in DCM.	This study was done in patients with dilated cardiomyopathy [30]
Calcium channel autoantibody	A large-scale prospective study done with 2096 patients and 834 controls showed that the presence of calcium channel autoantibody in CHF patients (due to DCM or ICM) was an independent predictor of SCD.	The study was done in patients with CHF due to DCM or ICM [29]
	Study of 80 patients with DCM showed that calcium channel autoantibodies were the strongest independent predictor of sudden death.	The study was done in patients with DCM [28]
hERG-potassium channel	A high prevalence of hERG-binding and IKr blocking anti-Ro/SSA-52kDa antibodies were found in a prospective cohort of unselected TdP patients in 25 consecutive patients with TdP arrhythmia were prospectively collected independently of ongoing therapies and concomitant diseases.	The study was done in patients with TdP arrhythmia [35]

Cheera H et al Autoantibodie for cardiac channels and sudden cardiac death.. Curr Cardiol Review (2019: 15; 49-54



Tan CD, Rodriguez ER: Chapter 20. Molecular pathology of the cardiovascular system. Foundations in Diagnostic Pathology : Cell and Tissue Based Molecular Diagnostics. Goldblum JR, Tubbs RR, Stoler MH, Churchill Livingstone, 2008 pp 214-240

Thank you

rodrigr2@ccf.org

and

tanc@ccf.org