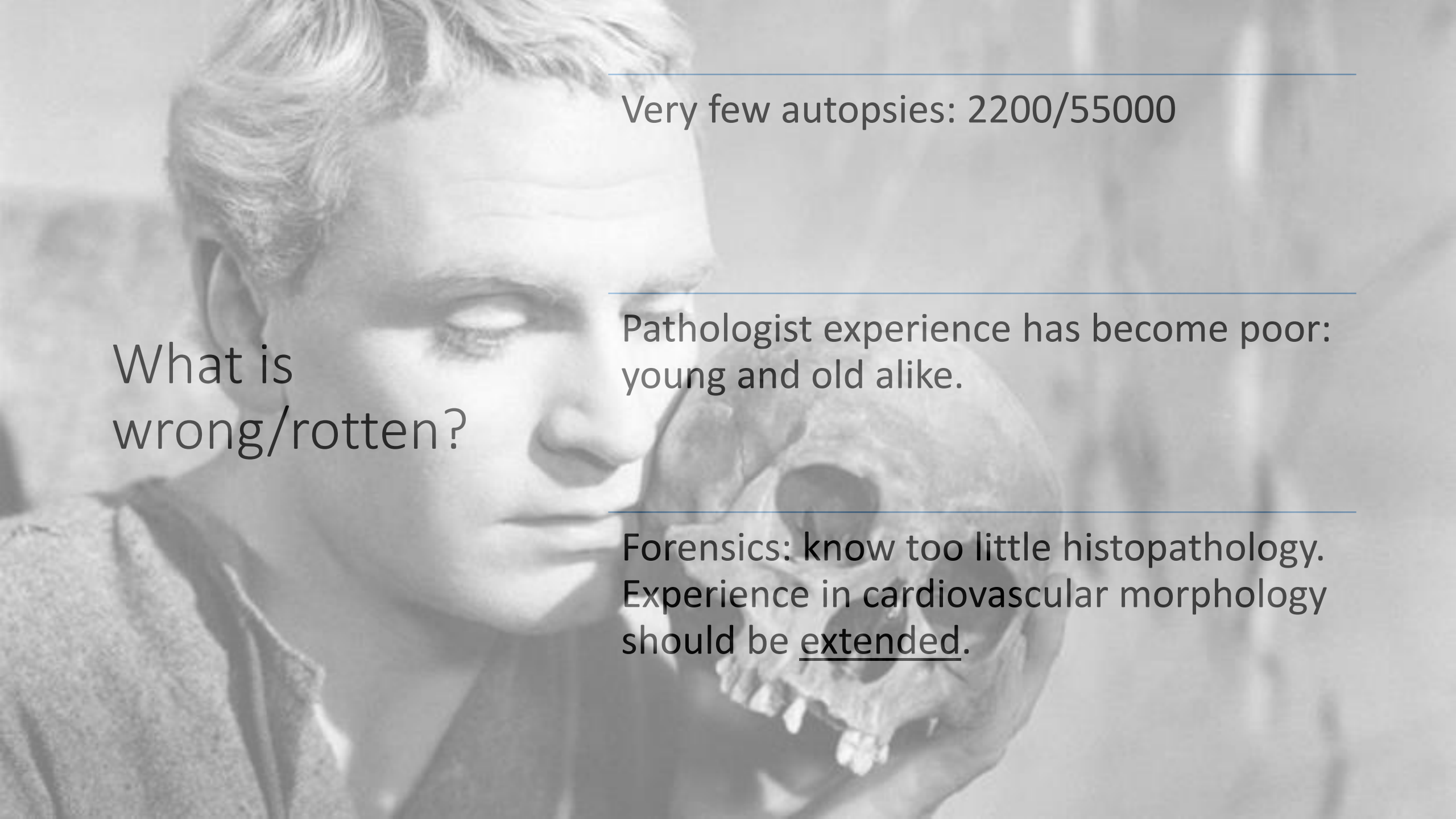


What is wrong/rotten?

Very few autopsies: 2200/55000

Pathologist experience has become poor: young and old alike.

Forensics: know too little histopathology. Experience in cardiovascular morphology should be extended.

DCM

Principles and Practice of Clinical Cardiovascular Genetics. Editors Kumar and Elliot. 2010.

Table 13–2 Classification and Etiology of Dilated Cardiomyopathy

Familial	Nonfamilial
Familial, unknown gene	Myocarditis (infective/toxic/immune)
Sarcomeric protein mutations (see HCM)	Kawasaki disease
Z band:	Eosinophilic (Churg Strauss syndrome)
ZASP	Viral persistence
Muscle LIM protein	Drugs
TCAP	Pregnancy
Cytoskeletal genes:	Endocrine
Dystrophin	Nutritional—thiamine, carnitine, selenium, hypophosphatemia, hypocalcemia.
Desmin	
Metavinculin	
Sarcoglycan complex	Alcohol
CRYAB	Tachycardiomyopathy
Epicardin	
Nuclear membrane	
Lamin A/C	
Emerin	
Intercalated disc protein mutations (see ARVC)	
Mitochondrial cytopathy	

Data from Elliott et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology working group on myocardial and pericardial diseases. *Eur Heart J.* 2008;29:270–276.

HCM

Principles and Practice of Clinical Cardiovascular Genetics. Editors Kumar and Elliot. 2010.

Table 13–1 Classification and Etiology of Hypertrophic Cardiomyopathy

Familial	Nonfamilial
Familial, unknown gene	Obesity
Sarcomeric protein disease	Infants of diabetic mothers
β-myosin heavy chain	Athletic training
Cardiac myosin-binding protein C	Amyloid (AL/prealbumin)
Cardiac troponin I	
Troponin-T	
Alpha Tropomyosin	
Essential myosin light chain	
Regulatory myosin light chain	
Cardiac actin	
alpha myosin heavy chain	
Titin	
Troponin C	
Muscle LIM protein	
Glycogen storage disease [e.g., GSD II (Pompe's disease); GSD III (Forbes' disease), AMP kinase (WPW, HCM, conduction disease)]	
Danon disease	
Lysosomal storage diseases (e.g., Anderson-Fabry disease, Hurler's syndrome)	
Disorders of fatty acid metabolism	
Carnitine deficiency	
Phosphorylase B kinase deficiency	
Mitochondrial cytopathies (e.g., MELAS, MERFF, LHON)	
Syndromic HCM	
Noonan's syndrome	
LEOPARD syndrome	
Friedreich's ataxia	
Beckwith-Wiedermann syndrome	
Swyer's syndrome (pure gonadal dysgenesis)	
Costello syndrome	
Other:	
Phospholamban promoter	
Familial amyloid	

Data from Elliott et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology working group on myocardial and pericardial diseases. *Eur Heart J.* 2008;29:270–276.

RCM

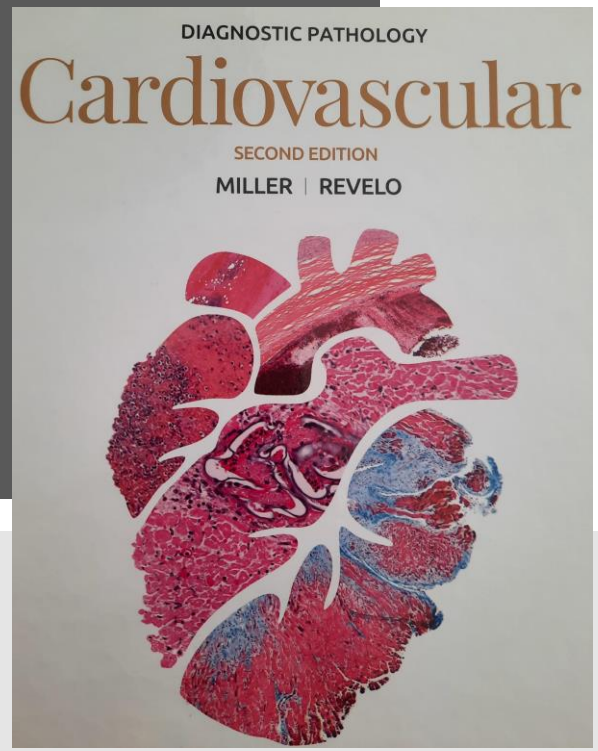
Table 13–3 Classification and Etiology of Restrictive Cardiomyopathy

Familial	Nonfamilial
Familial, unknown gene	Idiopathic
Sarcomeric protein mutations:	Amyloid (AL/prealbumin)
Troponin I (RCM+/–HCM)	Sclerodermia
Essential light chain of myosin	Endomyocardial fibrosis
Familial Amyloidosis	Hypereosinophilic syndrome
Transthyretin (RCM+neuropathy)	Drugs: serotonin, methysergide,
Apolipoprotein (RCM+nephropathy)	ergotamine, mercurial agents, busulfan
Desminopathy	Carcinoid heart disease
Pseuxanthoma elasticum	Metastatic cancers
Hemochromatosis	Radiation
Anderson-Fabry disease	Drugs: anthracyclines
Glycogen storage disease	

Data from Elliott et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology working group on myocardial and pericardial diseases. *Eur Heart J.* 2008;29:270–276.

Principles and Practice of Clinical Cardiovascular Genetics. Editors Kumar and Elliot. 2010.

ARVC



ETIOLOGY/PATHOGENESIS

Etiology

- Genetic factors
  - Multiple mutations affect 9 different genes encoding desmosomal proteins, including
    - Plakoglobin
    - Plakophilin-2
    - Desmoplakin
    - Desmoglein-2
    - Desmocollin-2
  - Extradesmosomal mutations
    - Transmembrane protein 43
    - Transforming growth factor β 3
    - Titin
    - Lamin A/C
    - Desmin
  - ARVD is hereditary disease in ≥ 50% of cases, and > 30% of patients report positive family history
  - Inheritance: Mainly autosomal dominant with incomplete penetrance
  - Less commonly, inheritance is autosomal recessive
    - Naxos disease: Characterized by palmar and plantar keratoses and thick, woolly hair
    - Carvajal syndrome: Predominately LV involvement
- Environmental factors
  - Combination of genetic & environmental factors appears to play role in pathogenesis of disease

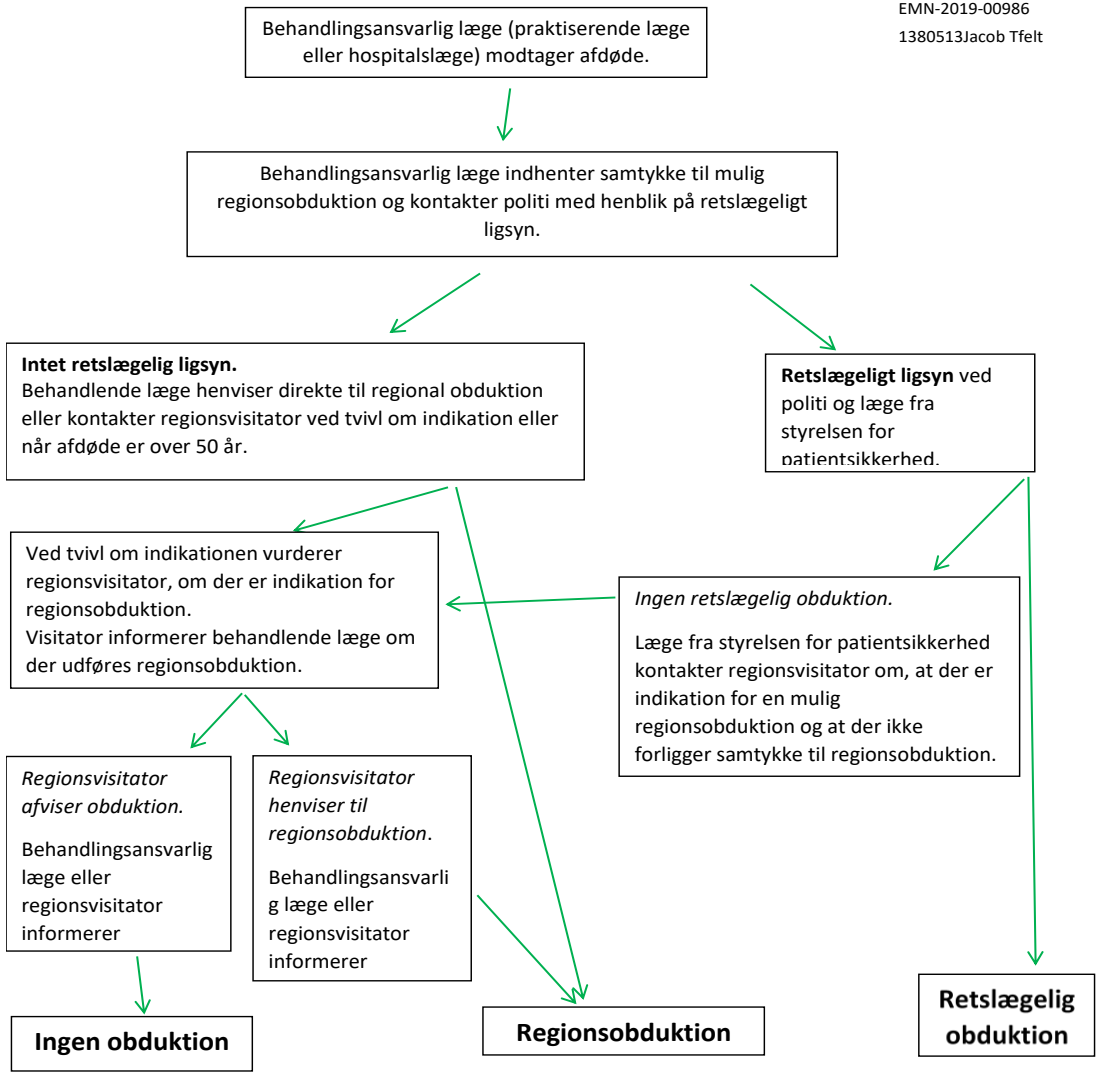
Table 12–1 Familial Thoracic Aortic Aneurysms

Designation Synonyms/Symbol	OMIM#	Inheritance	Locus	Gene	Allelic Variants
Familial thoracic aortic annuloaortic ectasia	607086	AD	11q23.3-q24?		
Aneurysm type 1; familial aortic dissection					
Erdhein cystic medial necrosis AAT1; FAA1					
Familial thoracic aortic AAT2; FAA2	607087	AD	5q13-q14 ?		
Aneurysm type 2 TAAD1					
Familial thoracic aortic AAT4; FAA4; TAAD2	132900	AD	16p13.13-p13.12	MYH11	IVS32 + 1G;
Aneurysm type 4; aortic aneurysm/dissection	160745				ARG1758GLN; with patent ductus arteriosus del72exon28
Familial thoracic aortic AAT6; familial thoracic	611788	AD	10q22-q24	ACTA2	ARG149CYS;
Aneurysm type 6; aortic aneurysm with livido					ARG258HIS; reticularis and iris flocculi; ARG258CYS thoracic aortic aneurysm with aortic dissections (TAAD3)
Familial arterial tortuosity LDS1A	609192	AD	9q33-q34	TGFBR1	MET318ARG; ascending aortic dissections ASP400GLY
Loeys-Dietz syndrome					THR200ILE; ARG487PRO; SER241LEU
LDS2A	608967	AD	9q33-q34	TGFBR1	ARG487GLN; ARG487TRP; GLY174VAL
LDS1B	610168	AD	3p22	TGFBR2	YR336ASN; ALA355PRO; GLY357TRP; ARG528HIS; ARG528CYS; IVS1, A-G, -2
LDS2B	610380	AD	3p22	TGFBR2	GLN508GLN; LEU308PRO; SER449PHE; ARG537CYS; ARG460CYS; ARG460HIS

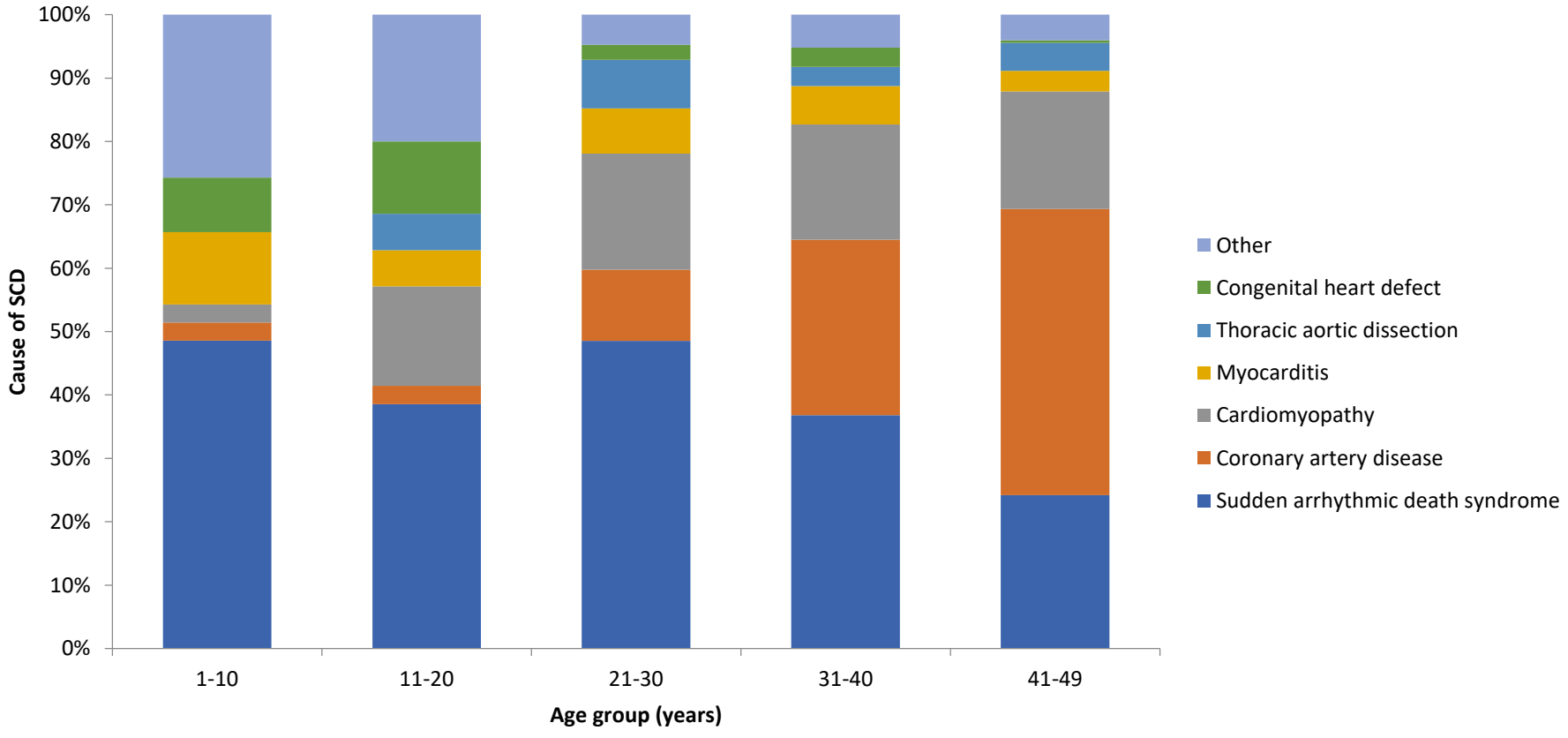
BILAG 1 FLOWCHART

Henvisning til regionsobduktion ved pludselig uventet død

19-10-2020
EMN-2019-00986
1380513Jacob Tfelt



Causes of SCD among autopsied according to age



Stiles HR 2021

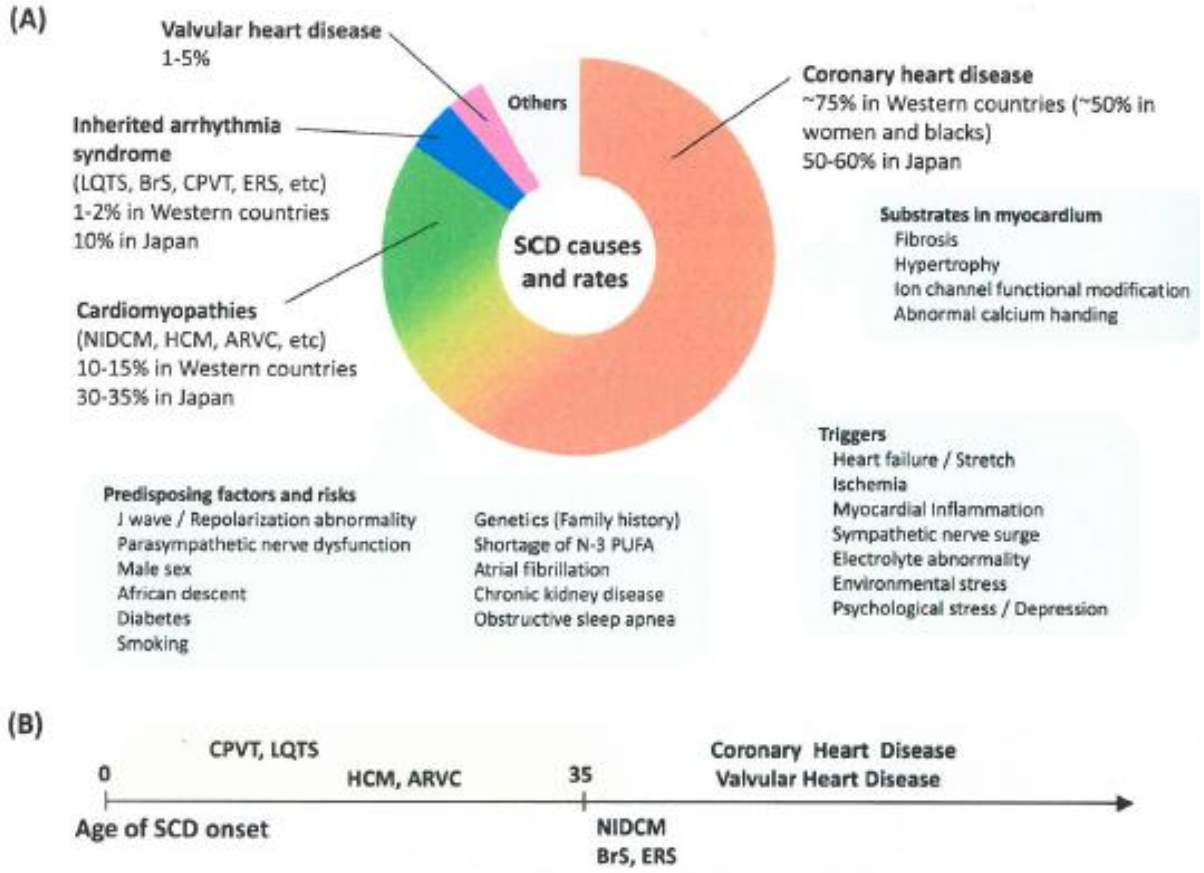


Figure 2. Causes of SCD and rates (A), and age of SCD onset in each disease (B)

A. Coronary heart disease is the leading cause of SCD, but the rates of baseline heart disease differ between Western countries and Japan.

B. SCDs occur in elderly populations in coronary heart disease and valvular heart disease, whereas most SCDs in CPVT and LQTS develop at age less than 35 years.

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; ERS, early repolarization syndrome; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; NIDCM, non-ischemic dilated cardiomyopathy; PUFA, polyunsaturated fatty acids; SCD, sudden cardiac death.

Hayashi M, Shimizu W, Albert CM. **The spectrum of epidemiology underlying sudden cardiac death.** Circ Res. 2015 Jun 5;116(12):1887-906. doi: 10.1161/CIRCRESAHA.116.304521. PMID: 26044246; PMCID: PMC4929621.

Clinical impact of autopsy findings

Certainty of diagnosis in SCD autopsies

- Certain

Massive pulmonary embolism

Haemopericardium due to aortic or cardiac rupture

Mitral valve papillary muscle or chordae tendineae rupture with acute mitral valve incompetence and pulmonary edema

Acute coronary occlusion due to thrombosis, dissection or embolism

Anomalous origin of the coronary artery from the pulmonary trunk

Neoplasm/thrombus obstructing the valve orifice

Thrombotic block of the valve prosthesis

Laceration/dehiscence/poppet escape of the valve prosthesis with acute valve incompetence

Massive acute myocarditis

C Basso et al., Virchows Arch 2008; 452: 11-18

Clinical impact of autopsy findings

Certainty of diagnosis in SCD autopsies

- Highly Probable

Stable atherosclerotic plaque with luminal stenosis >75% with or without healed myocardial infarction

Anomalous origin of the LCA from the right sinus and inter-arterial course

Cardiomyopathies (hypertrophic, arrhythmogenic right ventricular, dilated, others)

Myxoid degeneration of the mitral valve with prolapse, with atrial dilatation or left ventricular hypertrophy and intact chordae

Aortic stenosis with left ventricular hypertrophy

ECG documented ventricular pre-excitation (Wolff–Parkinson–White syndrome, Lown Ganong Levine syndrome)

ECG documented sinoatrial or AV block

C Basso et al., Virchows Arch 2008; 452: 11-18

Clinical impact of autopsy findings

Certainty of diagnosis in SCD autopsies

- Uncertain

Minor anomalies of the coronary arteries from the aorta (RCA from the left sinus, LCA from the right without inter-arterial course, high take-off from the tubular portion, LCx originating from the right sinus or RCA, coronary ostia plication, fibromuscular dysplasia, intramural small vessel disease)

Intra-myocardial course of a coronary artery (myocardial bridge)

Focal myocarditis, hypertensive heart disease, idiopathic left ventricular hypertrophy

Myxoid degeneration of the mitral valve with prolapse, without atrial dilatation or left ventricular hypertrophy and intact chordae

Dystrophic calcification of the membranous septum (±mitral annulus/aortic valve)

Atrial septum lipoma

AV node cystic tumor without ECG evidence of AV block, conducting system disease without ECG documentation

Congenital heart diseases, un-operated with or without Eisenmenger syndrome

C Basso et al., Virchows Arch 2008; 452: 11-18

- *The autopsy – Medical Practice and Public Policy. Hill and Anderson. 1988*

Table 3.1 Partial List of Diseases Discovered or Critically Clarified Through Autopsy Since 1950[a]

Cardiovascular lesions
- Tricuspid valve disease due to metastasizing carcinoid tumor
- Understanding of congenital heart lesions leading to modern surgical treatment
- Atheromatous embolism
- Asymmetric cardiac hypertrophy
- Dissecting aneurysm and variations thereon
- Primary cardiomyopathy
- Subaortic muscular stenosis
- Rheumatoid disease of aorta and aortic valve
- Complications of cardiac surgery
- Diseases of conducting system
- Idiopathic hypertrophic subaortic stenosis
- Cardiomyopathies
- Mitral valve prolapse

Bronchopulmonary lesions
- Alveolitis (diffuse alveolar damage, shock lung, respiratory distress syndrome)
- Oxygen toxicity
- *Pneumocystis* pneumonia
- Infantile respiratory distress syndrome (hyaline membrane disease)
- Legionnaire's disease
- Pulmonary alveolar proteinosis, desquamative pneumonia
- Diseases due to inhalation of industrial dusts: asbestosis, berylliosis, bagassosis, silo-filler's disease
- Lipid pneumonia
- Diffuse interstitial fibrosis

Hepatobiliary lesions
- Viral hepatitis
- Alpha-1-antitrypsin disease and cirrhosis
- Jamaican bush-tea disease (veno-occlusive disease of liver)
- Infantile kernicterus
- Neonatal giant cell hepatitis and biliary atresia
- Vinyl chloride and angiosarcoma of liver
- Tumors and hyperplasias due to oral contraceptives
- Aflatoxin-induced liver disease and tumors

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