

DGK Frühjahrstagung, 04.-07. April 2018
Kongresshallen Rosengarten, Mannheim

Niels-Stensen-Kliniken
Marienhospital Osnabrück

**Symposium: Rare Diseases:
Underdiagnosed and undertreated?**



**ARVC: Arrhythmogenic Right
Ventricular Cardiomyopathy**

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**Herzzentrum Osnabrück -
Bad Rothenfelde**

**Niels-Stensen-Kliniken
Marienhospital Osnabrück
Germany**



Conflict of Interest - Disclosure

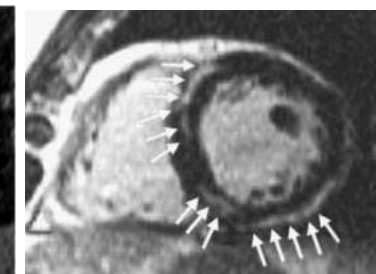
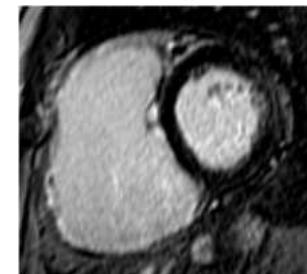
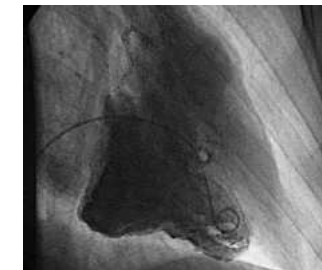
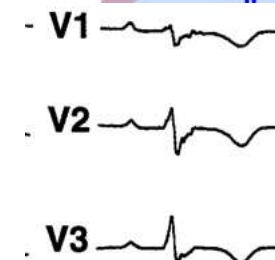
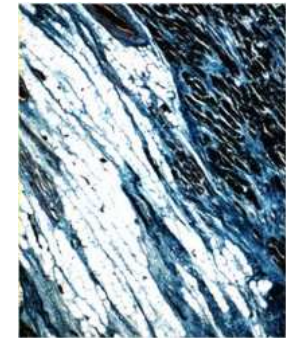
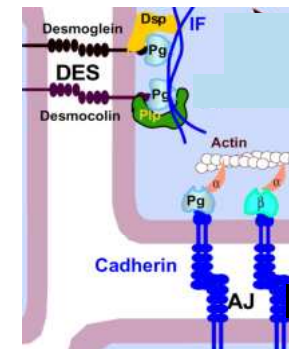
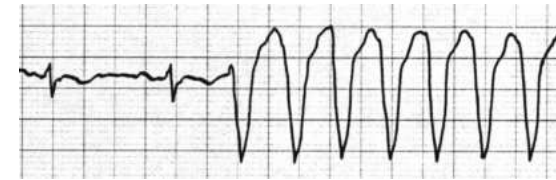
I, Thomas Wichter, DO NOT have a financial interest / arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Rare Diseases: ARVC

What is ARVC ?

Be aware of clinical features

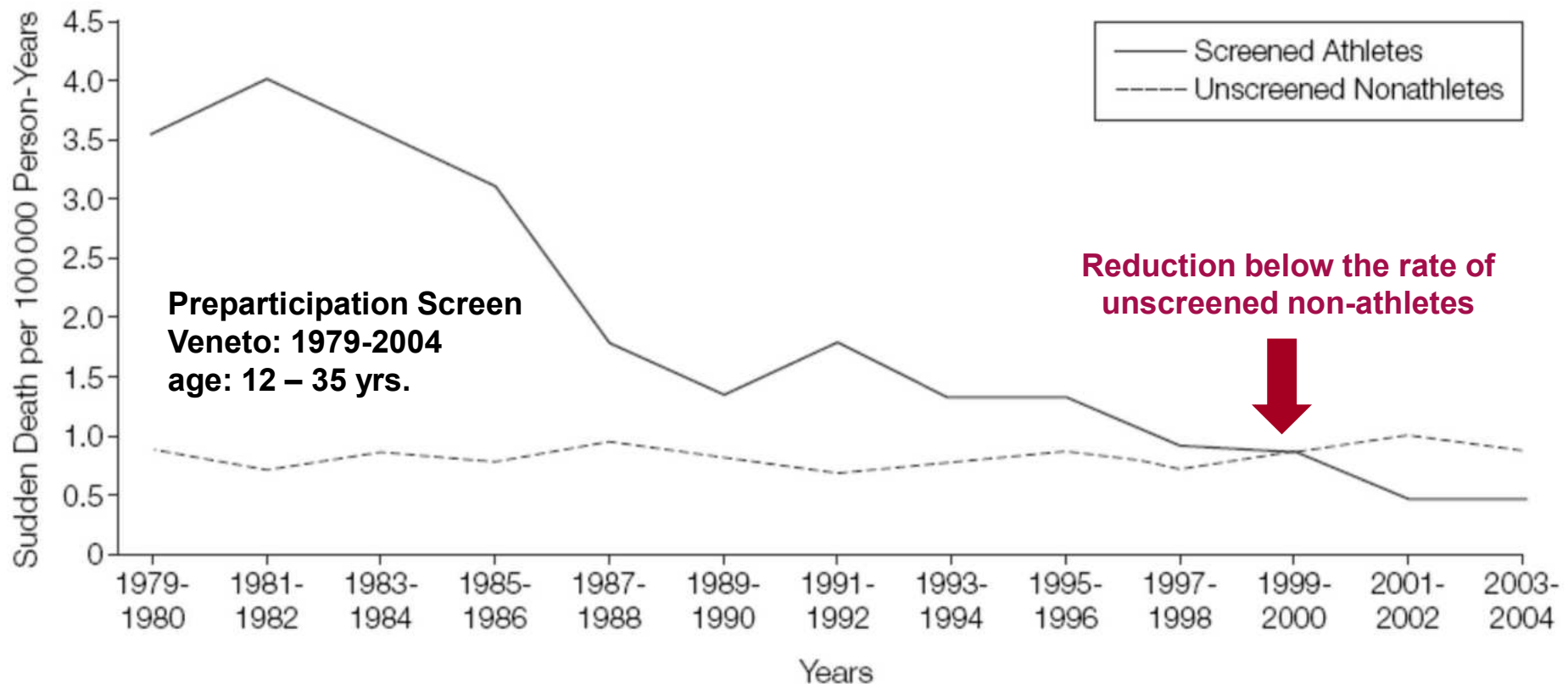
- Young, apparently healthy pts
- Ventricular arrhythmias (LBBB pattern)
- Exercise provokable arrhythmias
- High prevalence in athletes
- Family history (ARVC, unexplained SCD)
 - Genetic background (desmosomal proteins)
- Right precordial ECG abnormalities
 - T-wave inversion, QRS prolongation, ϵ -waves
- RV-enlargement / RV-dysfunction
- LV involvement possible (even dominant)



What awareness can do ...

Preparticipation Screening of Athletes

4-fold Reduction of Sudden Death in Athletes in Italy
by Disqualification of diagnosed HCM and ARVC pts



Epidemiology of ARVC

- **First descriptions date back to 18th century**
- **Rare disease (1:2000 to 1: 5000, underestimated?)**
- **Regional clustering (genetic reasons; i.e. Veneto)**
- **Difficult, multifactorial diagnosis (integrative approach)**
- **Mild or incomplete disease manifestation (expressivity)**
- **Silent or subclinical mutation carriers (penetrance)**
- **Selection bias results in different ARVC populations**
(primary vs. tertiary or arrhythmia vs. heart failure vs. genetic centres)
with respect to prevalence, expression and prognosis

Rare Diseases: ARVC

Underdiagnosed

- ... **False Negatives** (Specificity high, Sensitivity low)
- ... **Increased risk of sudden death due to undertreatment**

Overdiagnosed

- ... **False Positives** (Specificity low, Sensitivity high)
- ... **Disease „labeling“** (incl. family members)
potential consequences for social life, sports activity, insurances, etc.
- ... **Unjustified ICD indications** (incl. complications, inappr. shocks)

Misdiagnosed

- ... **other diseases mimicking ARVC remain unrecognized**
(myocarditis, sarcoidosis, cardiomyopathies, etc.)
- ... **specific treatment options not applied**

Limitations of Evidence

- **Rare disease, no diagnostic gold standard**
- **Integrated multi-modality diagnostic approach**
- **Diagnostic Criteria** (Internat. Task Force 2010),
modified to increase accuracy by gain in sensitivity without loss of specificity
 - **Wall motion and structure** (RV / LV: global + regional)
 - **Tissue characterization of walls** (histopathology)
 - **ECG depolarization** (QRS prolongation, epsilon-potential)
 - **ECG repolarization** (T-wave inversion)
 - **Arrhythmias** (LBBB-VT, exercise-induced)
 - **Genetics / family history** (mutations in desmosomal genes)
- **Treatment based on personal experience, consensus and individual decisions rather than evidenced data**

Diagnostic Criteria of ARVC

International ARVC Task Force (2010)



Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia

Proposed Modification of the Task Force Criteria

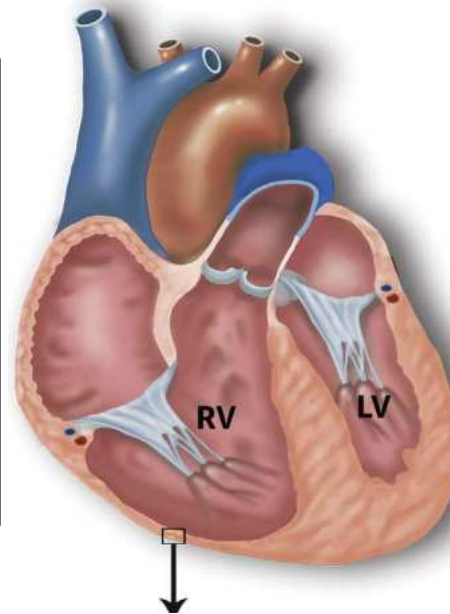
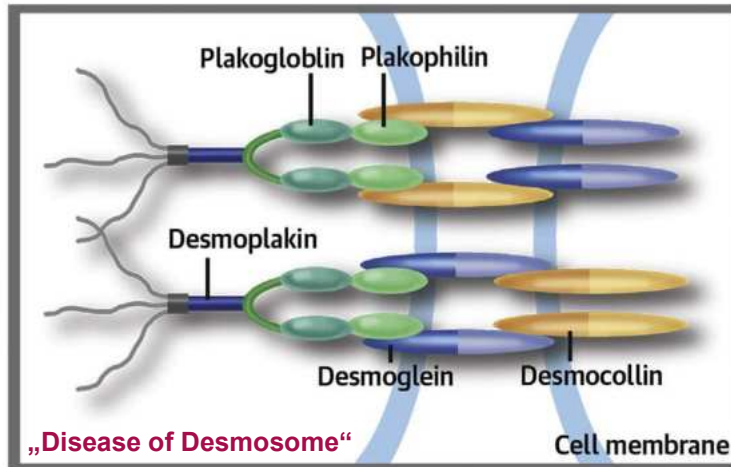
**Frank I. Marcus^{1*} Chair, William J. McKenna² Co-Chair, Duane Sherrill¹,
Cristina Basso³, Barbara Bauce³, David A. Bluemke⁴, Hugh Calkins⁵,
Domenico Corrado³, Moniek G.P.J. Cox⁶, James P. Daubert⁷, Guy Fontaine¹⁰,
Kathleen Gear¹, Richard Hauer⁶, Andrea Nava³, Michael H. Picard¹¹,
Nikos Protonotarios¹³, Jeffrey E. Saffitz¹², Danita M. Yoerger Sanborn¹¹,
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Adalena Tsatsopoulou¹³, Thomas Wichter¹⁵, and Wojciech Zareba⁸**

Diagnostic Criteria of ARVC

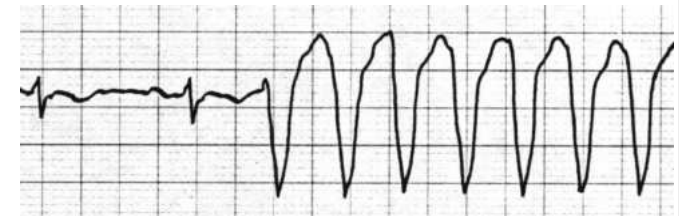
International ARVC Task Force (2010)



Genetics and Family History



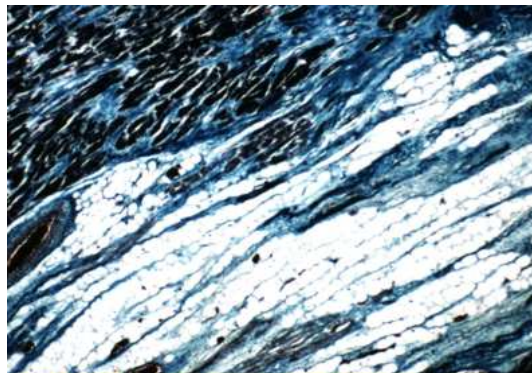
Ventricular Arrhythmias (LBBB-VT)



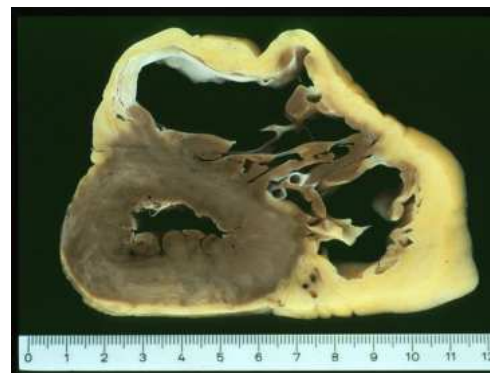
ECG: Depolarization + Repolarization



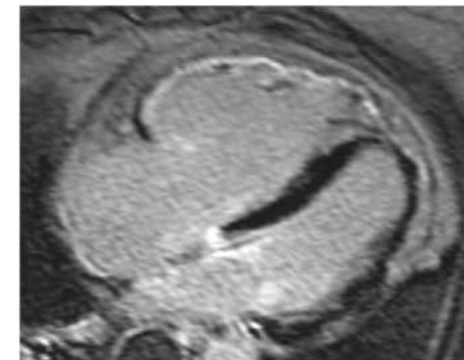
Tissue Characterization



Pathology

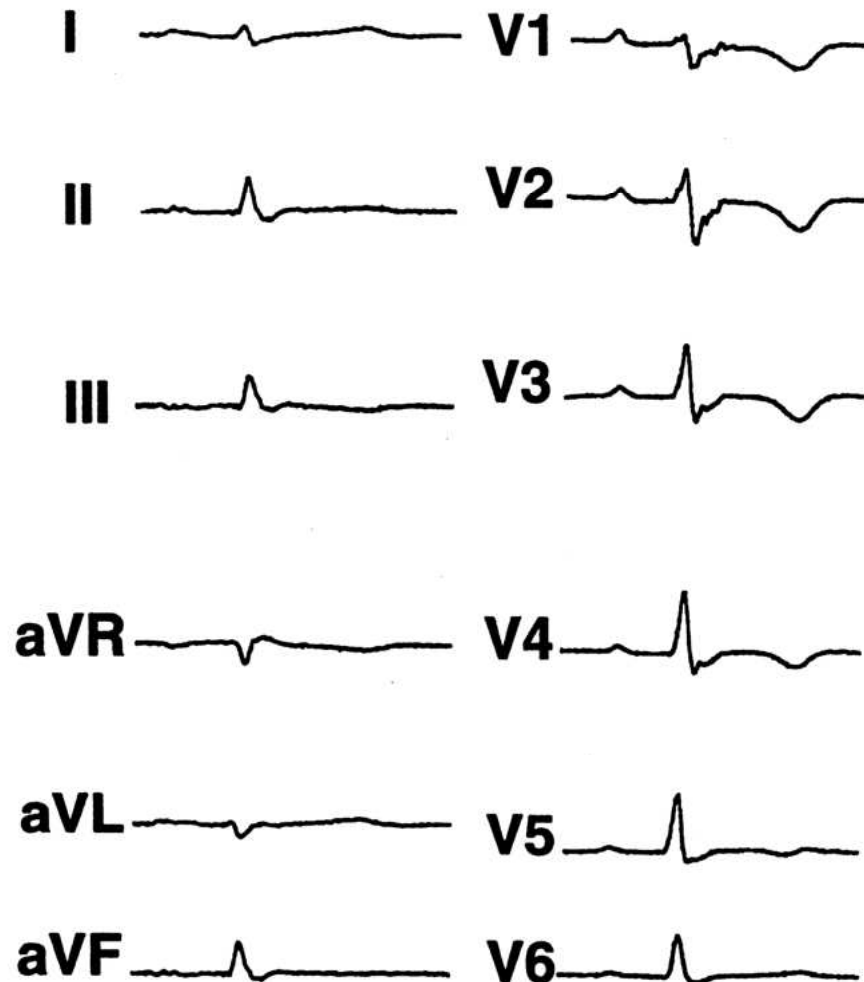


RV-/LV- Wall Motion + Structure

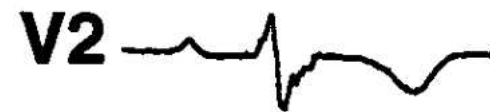


Rare Diseases: ARVC

Case-1: Cardiac Arrest



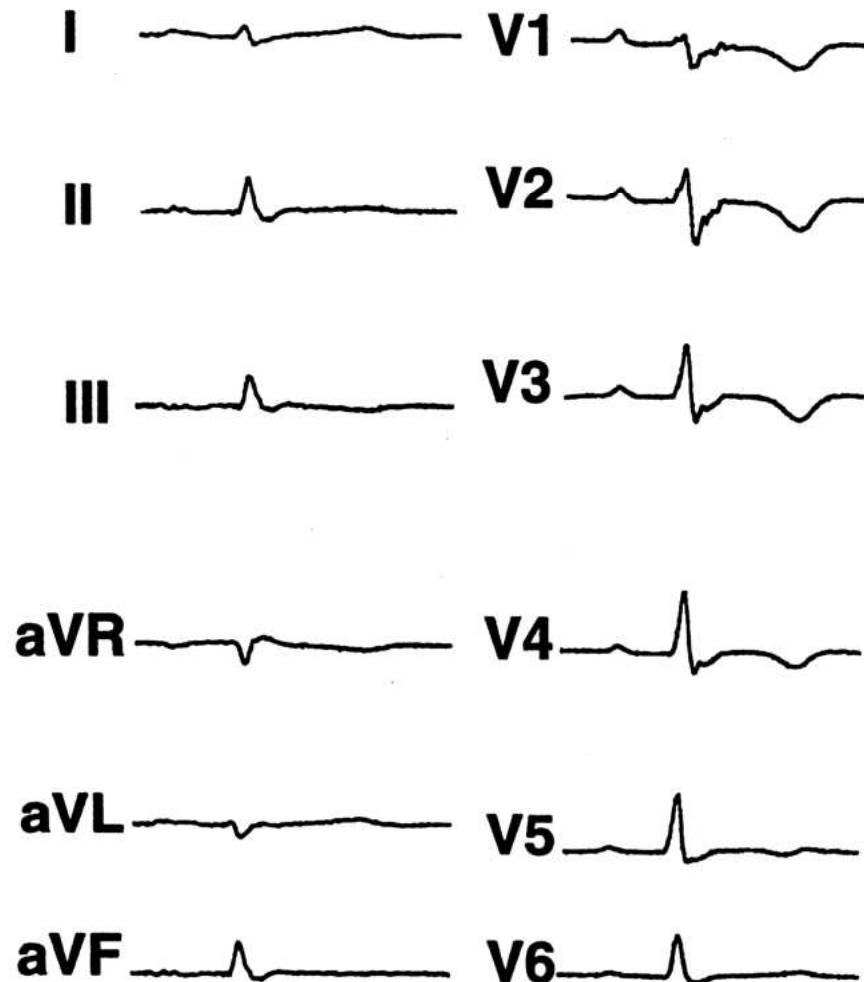
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- Cardiac arrest during soccer
- SR after 1° defibrillation
- ROSC and stable rhythm
- Family history of SCD



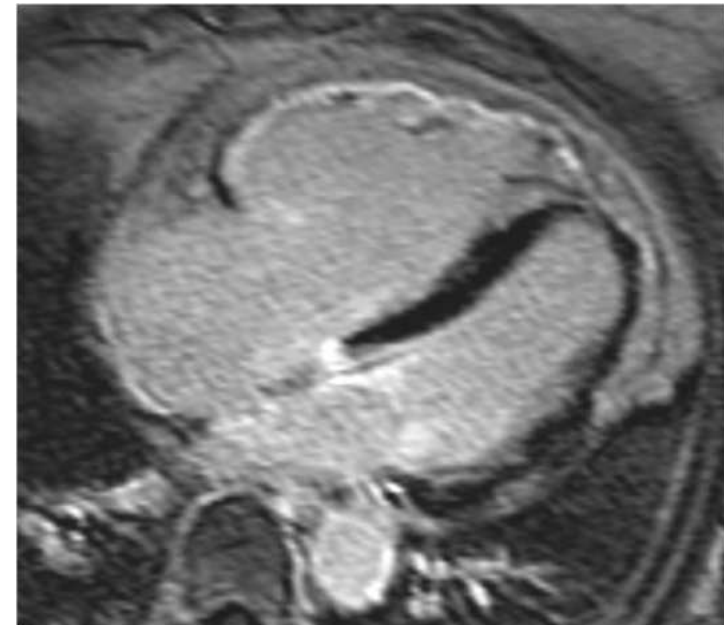
Diagnosis: ARVC

Rare Diseases: ARVC

Case-1: Cardiac Arrest



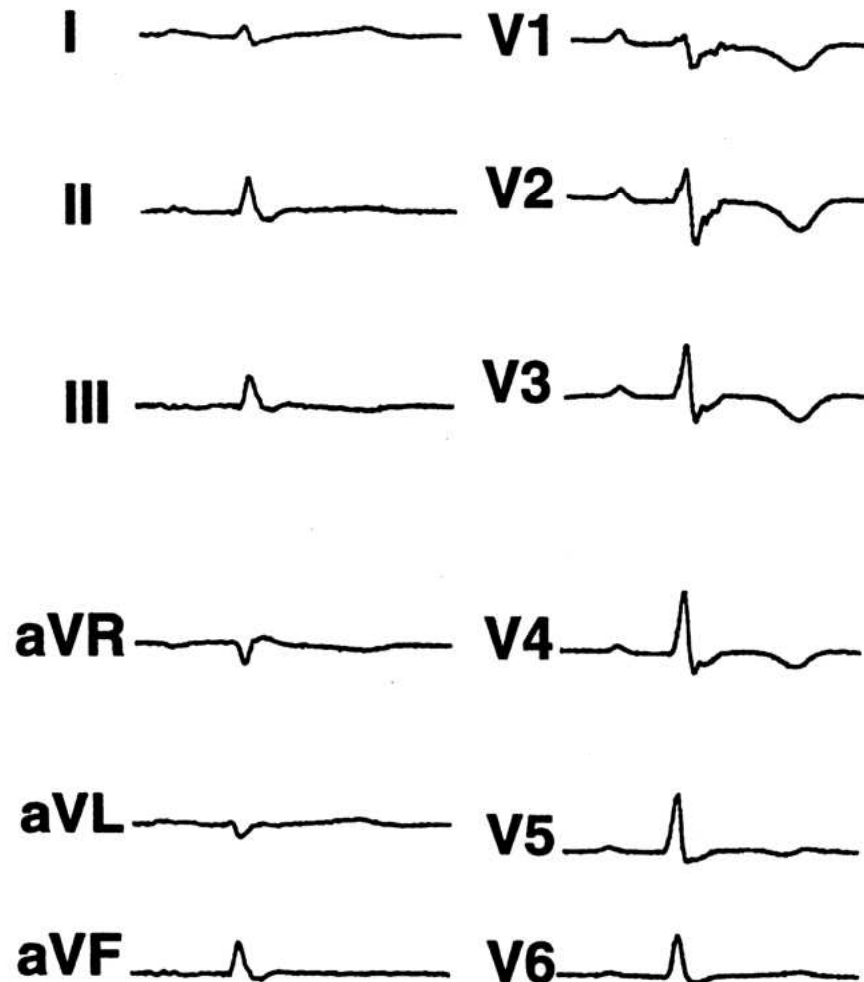
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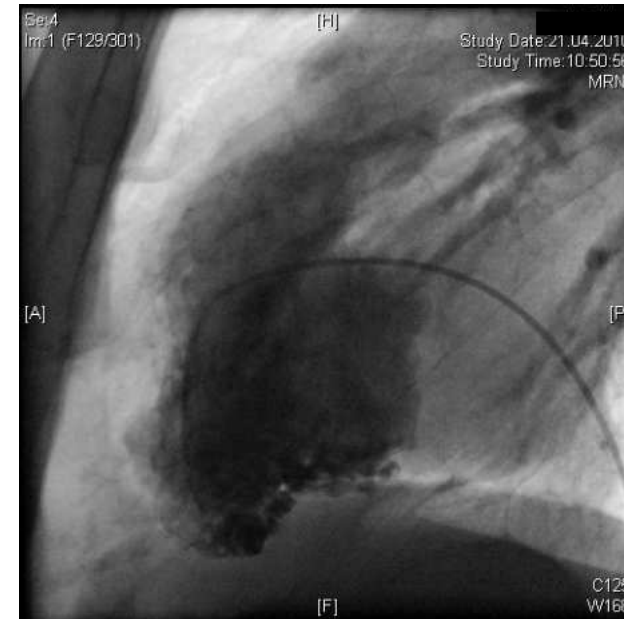
Diagnosis: ARVC

Rare Diseases: ARVC

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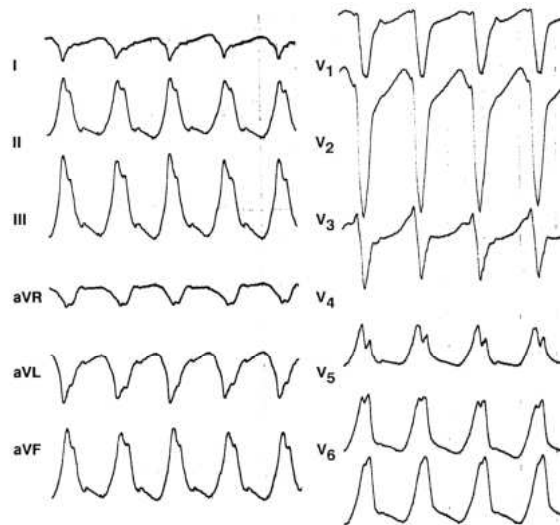
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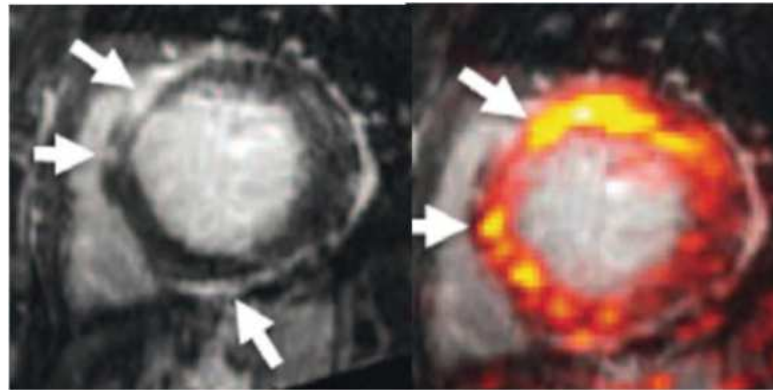
Diagnosis: ARVC

Rare Diseases: ARVC

Reassess: Is it really ARVC? Or is it rather ... ?



Idiopathic RVO-VT

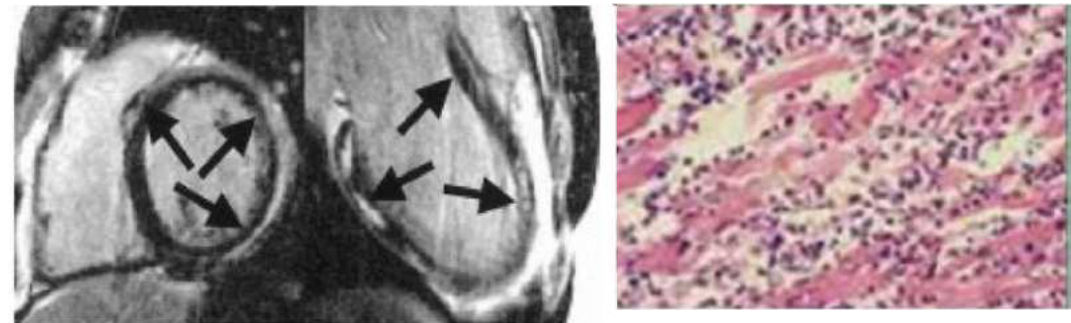


Cardiac Sarcoidosis



Restrictive CM

**Make the
correct diagnosis
for specific therapy !**



Myocarditis (acute / chronic)

Making the Correct Diagnosis

- **Detailed diagnostic evaluation** (multi-modality approach)
- **Appropriate test protocols for ARVC diagnosis**
ECG speed and filters, Angio projections, Echo views on RV,
MRI protocol and sequences, target-directed biopsy, 3D EP-Mapping
- **Avoid bias when indicating tests** (question triggers answer)
- **Expert reading and interpretation of findings**
- **Genetic testing for identification of affected relatives**
Confirmatory testing controversial (diagnosis and risk stratification)
Proband: Negative psychological + social impact may outweigh clinical value
Family: Cascade screening helps to identify subjects at risk
- **Balanced and experienced clinical evaluation**
Counselling and recommendations for management of ARVC (incl. families)

Arrhythmias in ARVC: Unique VT substrate

- **Familial, genetic basis** (desmosomal proteins)
- **Broad spectrum of clinical VA** (PVC, syncope, VT, VF)
- **Phasic clinical stages** (natural history)
- **Exercise modification** (penetrance, expression, aggravation)
- **Progressive** (exercise, competitive sports, inflammation, etc.)
- **Multifocal** (RV, LV)
- **Predilection areas** (RVOT, apex, RV-inflow)
- **Pleomorphic** (multiple VT morphologies, mostly LBBB)
- **Epicardial location** (mapping + ablation)

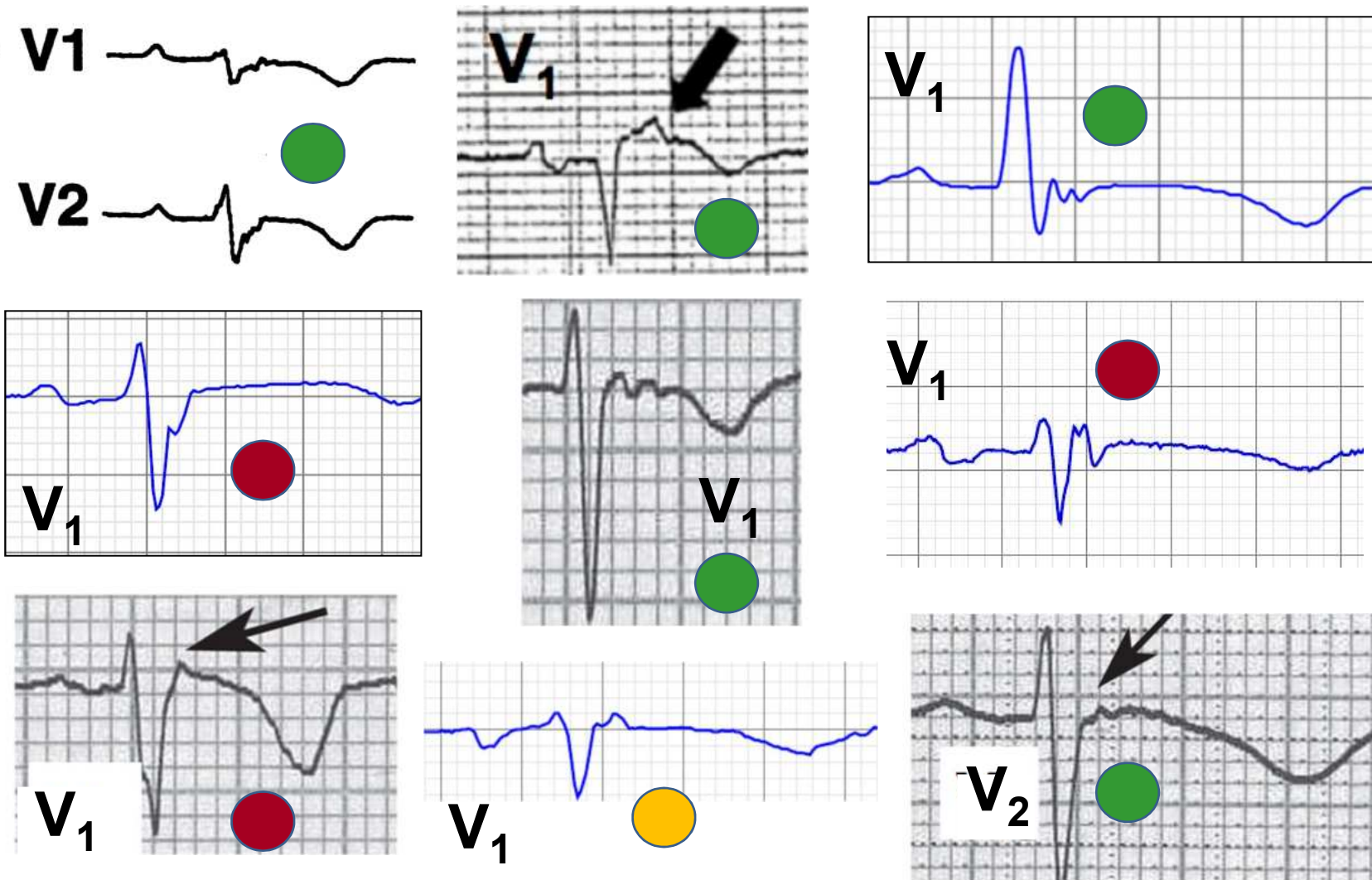
ECG Diagnostics

Most important screening tool in ARVC !

- **Inverted T-waves** in right precordial leads (V_1 - V_3)
 - Normal in children <14 yrs., only 1% in normal older individuals
 - 60-95% prevalence in ARVC (major diagnostic criterion)
 - Near 100% sensitivity when combined with LBBB-VT
 - Extent relates to degree of RV involvement in ARVC
- **QRS prolongation** in right precordial leads (V_1 - V_3)
 - Conduction delay over RV (arrhythmogenic substrate)
 - QRS >110 ms, S-wave >55 ms are sensitive markers of ARVC
- **Epsilon wave (potential)** in right precordial leads (V_1 - V_3)
 - Low amplitude signal after the end of QRS
 - Mainly present in severe manifestations of ARVC
 - High interobserver variability (no added value without other ARVC criteria)

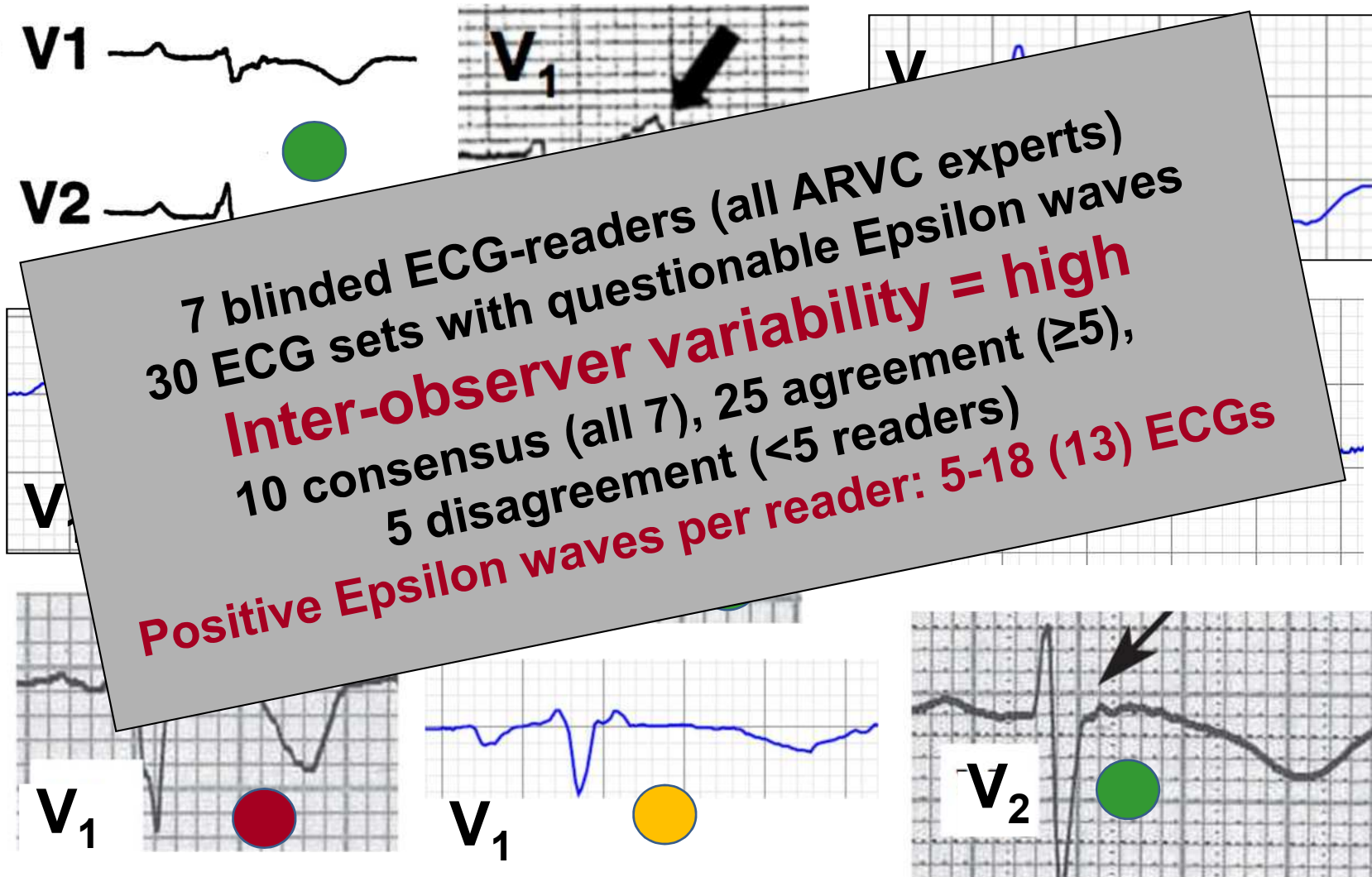
ECG: Epsilon-Potential

Epsilon wave after the end of QRS in V_{1-3} ,
separated from QRS by isoelectrical interval



ECG: Epsilon-Potential

Main message: diagnostic impact was low (no added value).
Caution in assessment when pts do not otherwise fulfill criteria



Cardiac Imaging

- **RV evaluation by imaging remains difficult**
 - Despite enormous improvement in imaging technology
 - Complex RV structure, shape and wall motion (non-symmetrical)
- **MRI depicts wall structure, motion + tissue**
 - Fatty infiltration alone is not a sufficient criterion
 - Fibrofatty replacement + abnormal regional wall motion = diagnostic
- **Appropriate imaging protocols and expert reading**
 - Multimodal diagnostic approach
 - Standardized imaging protocols and quantitative analysis
 - Interpretation by experts in imaging and ARVC
- **High degree of inter-observer variability**
 - Incorrect MRI interpretation is a frequent cause of overdiagnosing !

Ask Questions, get Answers

- **Dx: Idiopathic RV Outflow-Tract Tachycardia (RVO-VT)**
- **Q: „Clinical suspect of ARVC. Fibrofatty replacement of myocardium? Wall motion abnormalities?“**
- **A: „Findings well compatible with ARVC, but nonspecific: prominent trabeculation, epicardial fat and fibrosis, mainly over RV free wall“**

- **Dx: ARVC with LV involvement**
- **Q: „Unexplained syncope and palpitations. Structural abnormalities of the heart?“**
- **A: „Nonspecific diffuse myocardial damage, DD: mild dilative CMP (DCM), chronic myocarditis“**

Genetic Background + Testing

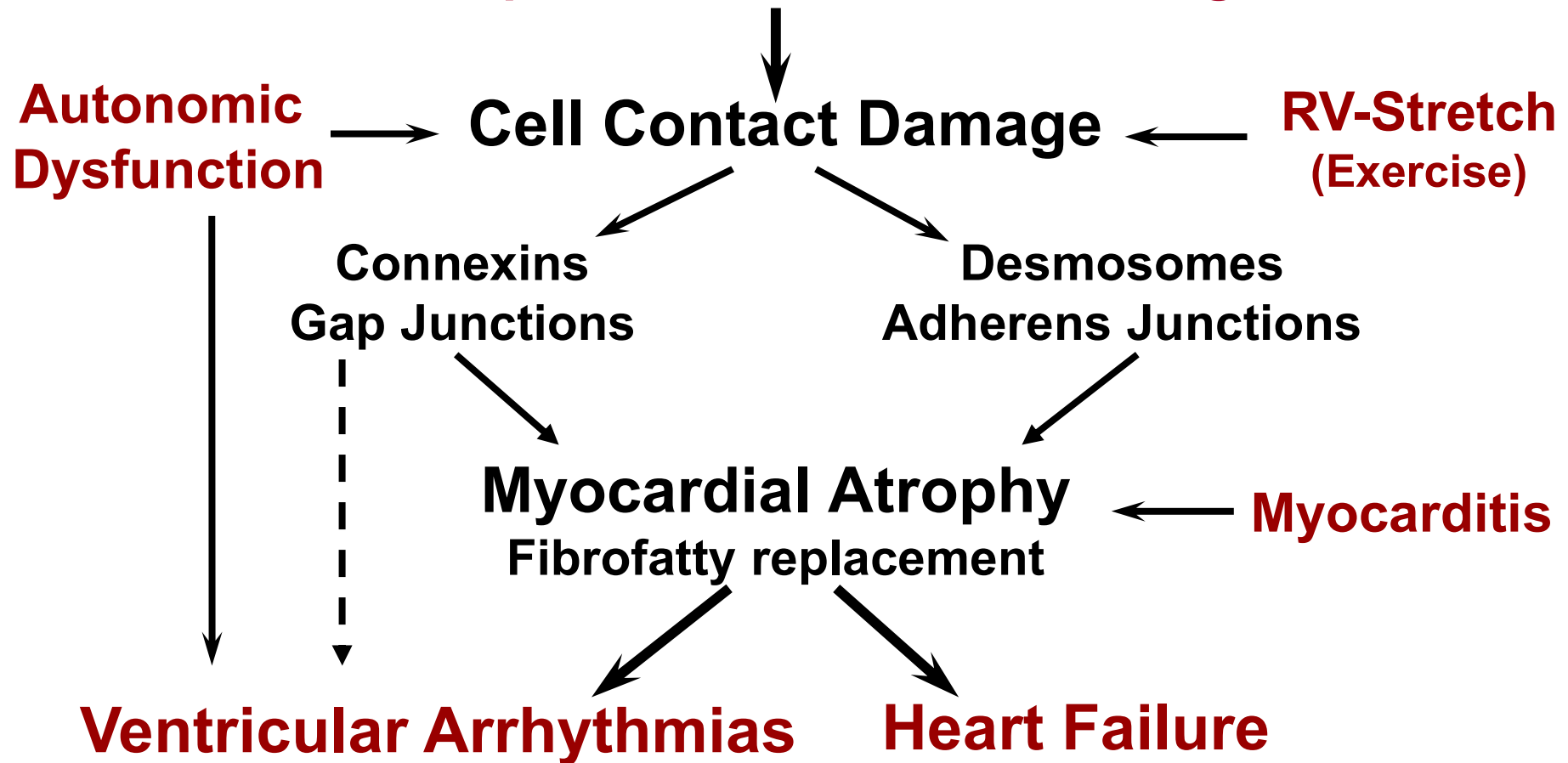
- **Gene mutations in 60-70% of ARVC**
- **Desmosomal genes affected**
 - Cell contact, adhesion and signal transduction
- **Autosomal-dominant genetic trait**
 - Reduced penetrance (silent gene carriers)
 - Variable expressivity (disease manifestation and severity)
 - Modifier genes and exogenic factors
 - Digenic or compound mutations (5-20%) may impact severity
 - Genetic polymorphism (non-specific): up to 20% of normal controls
- **Genetic counseling mandatory**
- **Genetic testing controversial**
 - Confirmatory testing rarely impacting diagnosis + risk assessment
 - Proband: usually no consequence or added benefit, but allows ...
 - ... Cascade screening: to identify / exclude gene-affected relatives



ARVC

Genetic Disposition

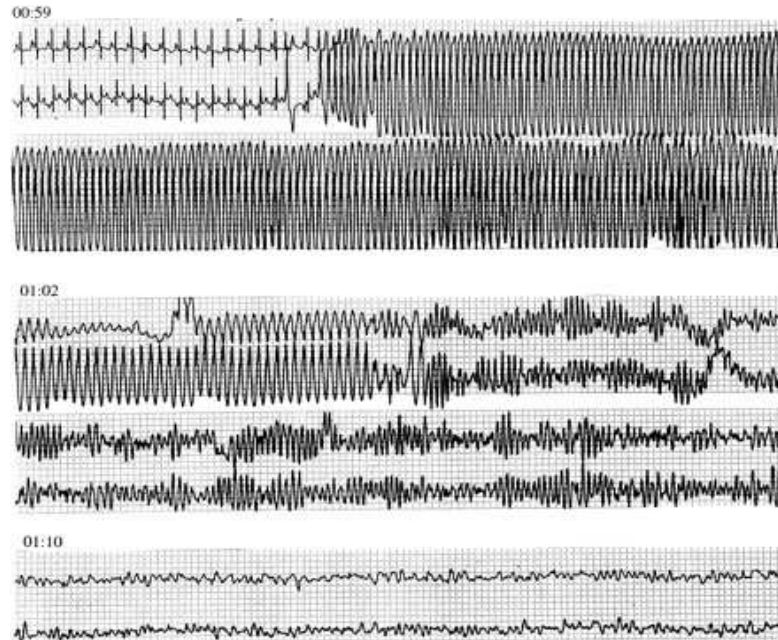
Double/compound mutations, modifier genes



Rare Diseases: ARVC

Natural Course of ARVC

- Risk of VF or fast VT: **early (concealed) phase**
(arrhythmias may precede morphological abnormalities)
- Recurrent monomorphic VT: **overt phase**
- Chronic biventricular heart failure: **end-stage**



Aziz et al., Circulation. 2000;101;825-827



Wichter T et al., 2005

Rare Diseases: ARVC

Case-2: Asymptomatic nsVT male, age 14

- **Symptom:** presyncope (vasovagal?)
- **Sports:** competitive (football)
- **Family history:** 1 questionable case
- **Genetic test:** nonspecific, Desmoplakin polymorphism
- **ECG:** normal 12-lead and SAECG
negative T in V1-V2
- **Exercise Test:** 1x nsVT (5 sec, 165 bpm)
- **Echo:** mild LV dilatation, normal RV
- **MRI:** normal RV + LV, no fat, no LGE
- **EP-Study:** normal,
no WPW, no SVT or VT/VF inducible



Rare Diseases: ARVC

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What risk ?

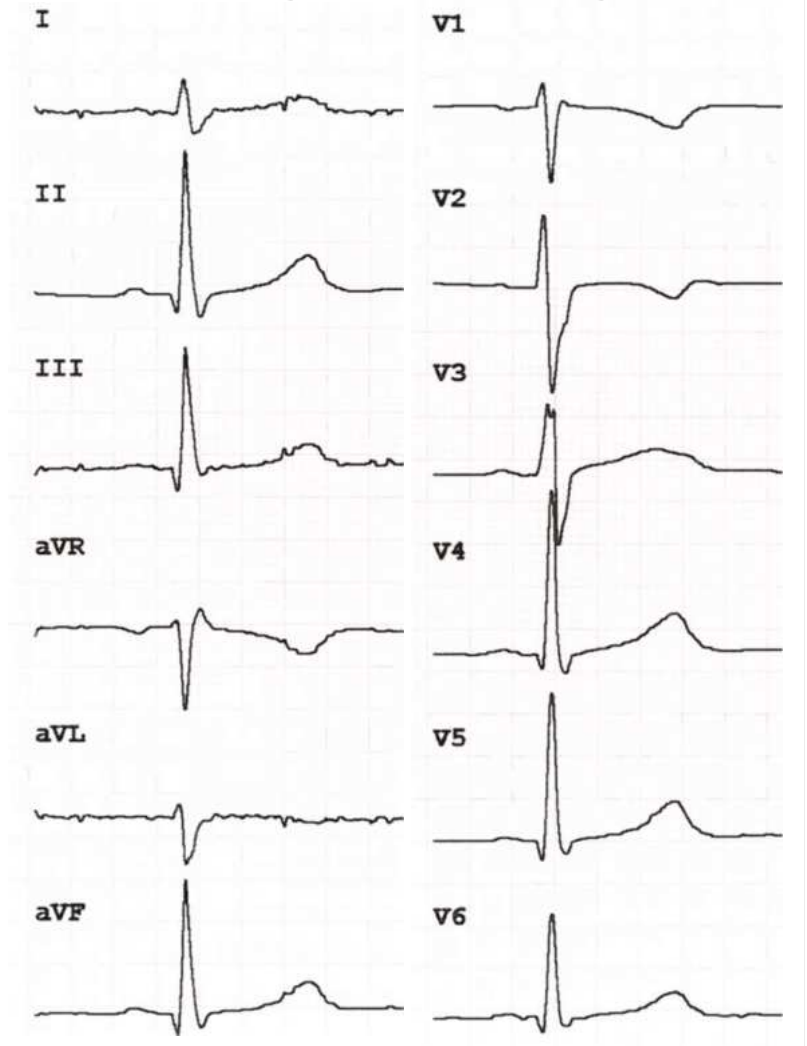
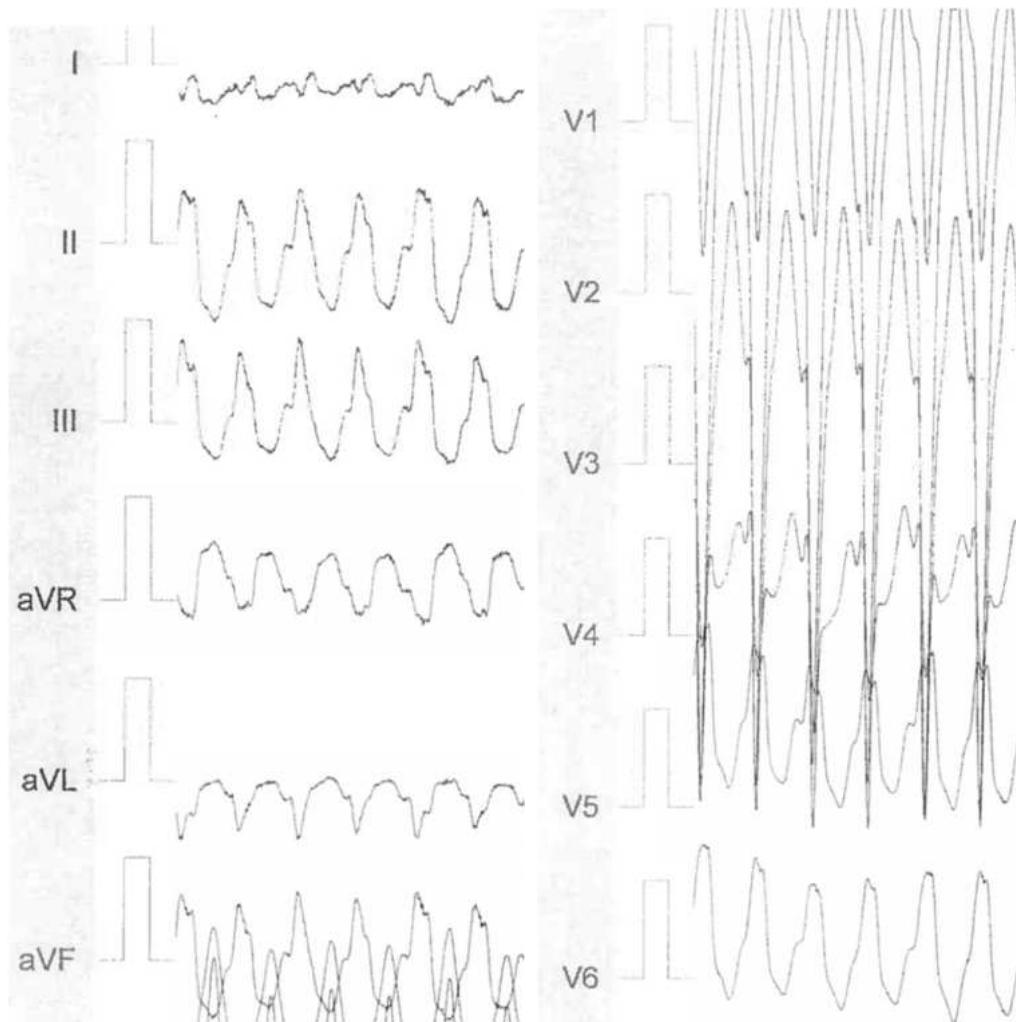


Rare Diseases: ARVC

Case-2: Asymptomatic nsVT

nsVT 5 sec (165 bpm, LBBB, inferior axis)
asymptomatic during treadmill stress test

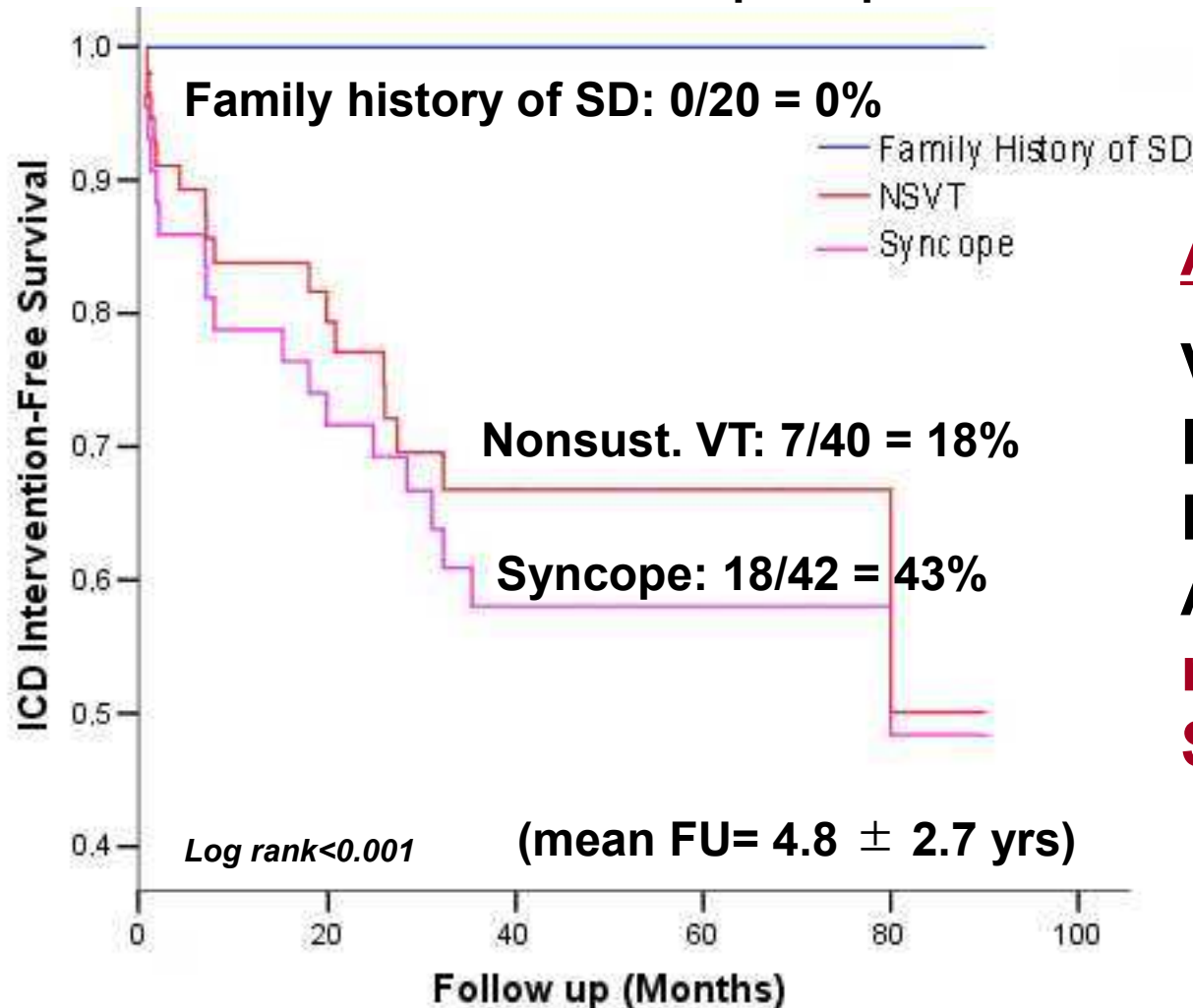
Resting ECG during SR



Risk Stratification in ARVC

Role of Syncope, nsVT, Family History

ICD intervention-free survival in prim. prevention ICD cohort



Appropriate ICD-Tx:

VT at PVS: $p = 0.98$

RV ↓ (diffuse): $p = 0.84$

Family Hx: $p = 0.14$

Age < 35: $p = 0.07$

nsVT: $p = 0.03$

Syncope: $p = 0.008$

Rare Diseases: ARVC

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Rare Diseases: ARVC

Case-2: Asymptomatic nsVT male, athlete, age 14

- Symptom: presyncope
- Sports: ...
- ECG: ...
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Defibrillator ?



Case-2: Asymptomatic nsVT

Clinically relevant questions:

- **Is this ARVC** (no structural disease detected) ?
- **Was genetic testing useful ?**
- **Should this 14 yr-old boy be labelled with a disease ?**
 - Issues of psychology, quality of life, insurances, etc.
- **What is the prognosis ?**

My personal (!) decision:

Low-dose beta-blockers
Recreational sports o.k. (non-competitive!)
Watchful waiting and reevaluation
Final diagnosis left open



Risk Stratification in ARVC

Management of ARVC

Niels-Stensen-Kliniken 
Marienhospital Osnabrück

European Heart Journal Advance Access published July 27, 2015



EUROPEAN
SOCIETY OF
CARDIOLOGY®

European Heart Journal
doi:10.1093/eurheartj/ehv162

CURRENT OPINION

Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement

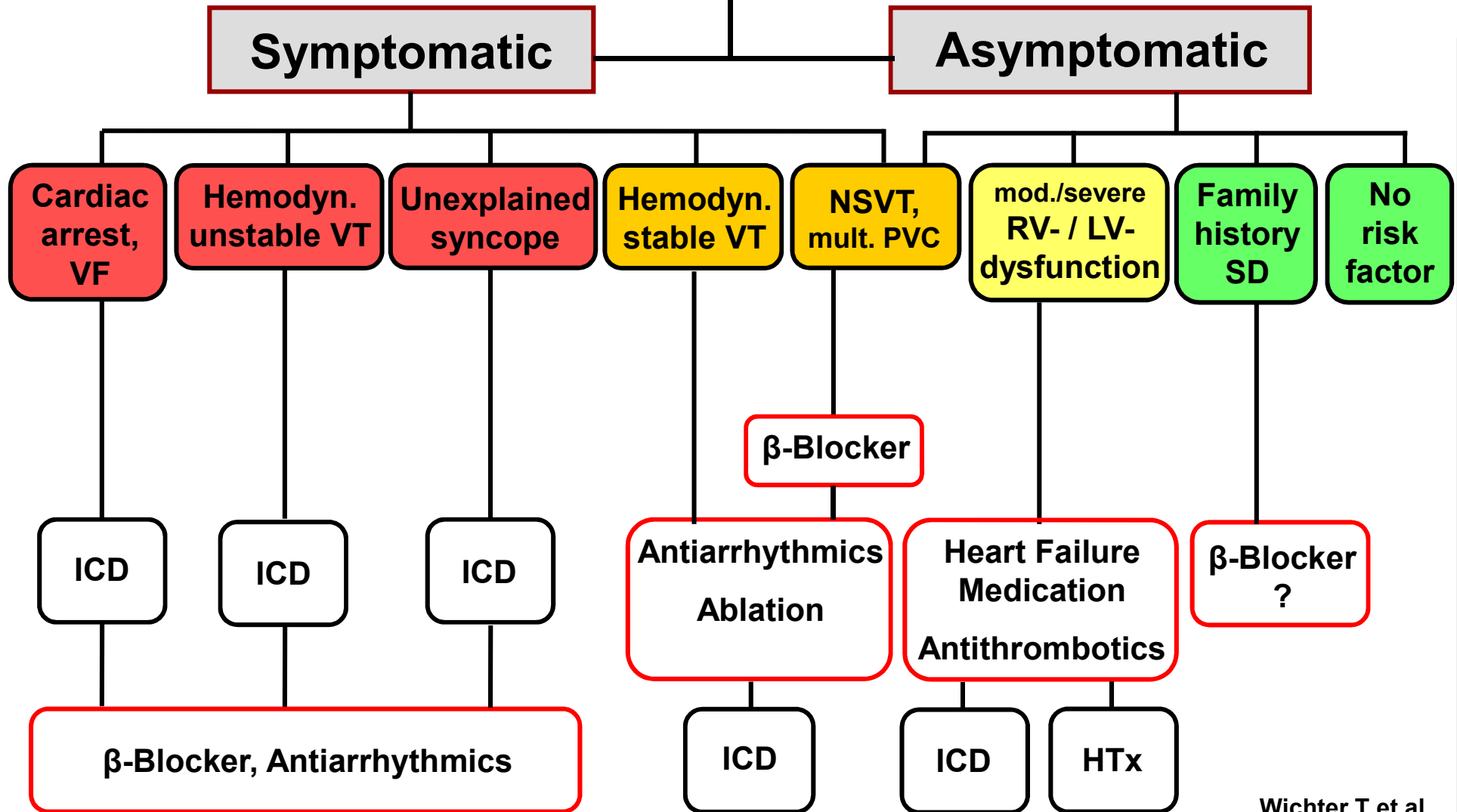
Domenico Corrado^{1*}, Thomas Wichter², Mark S. Link³, Richard Hauer⁴, Frank Marchlinski⁵, Aris Anastasakis⁶, Barbara Bauce¹, Cristina Basso¹, Corinna Brunckhorst⁷, Adalena Tsatsopoulou⁸, Harikrishna Tandri⁹, Matthias Paul¹⁰, Christian Schmied⁷, Antonio Pelliccia¹¹, Firat Duru⁷, Nikos Protonotarios⁸, NA Mark Estes III³, William J. McKenna¹², Gaetano Thiene¹, Frank I. Marcus¹³, and Hugh Calkins⁹

Eur Heart J. 2015;36: online July 27

Rare Diseases: ARVC

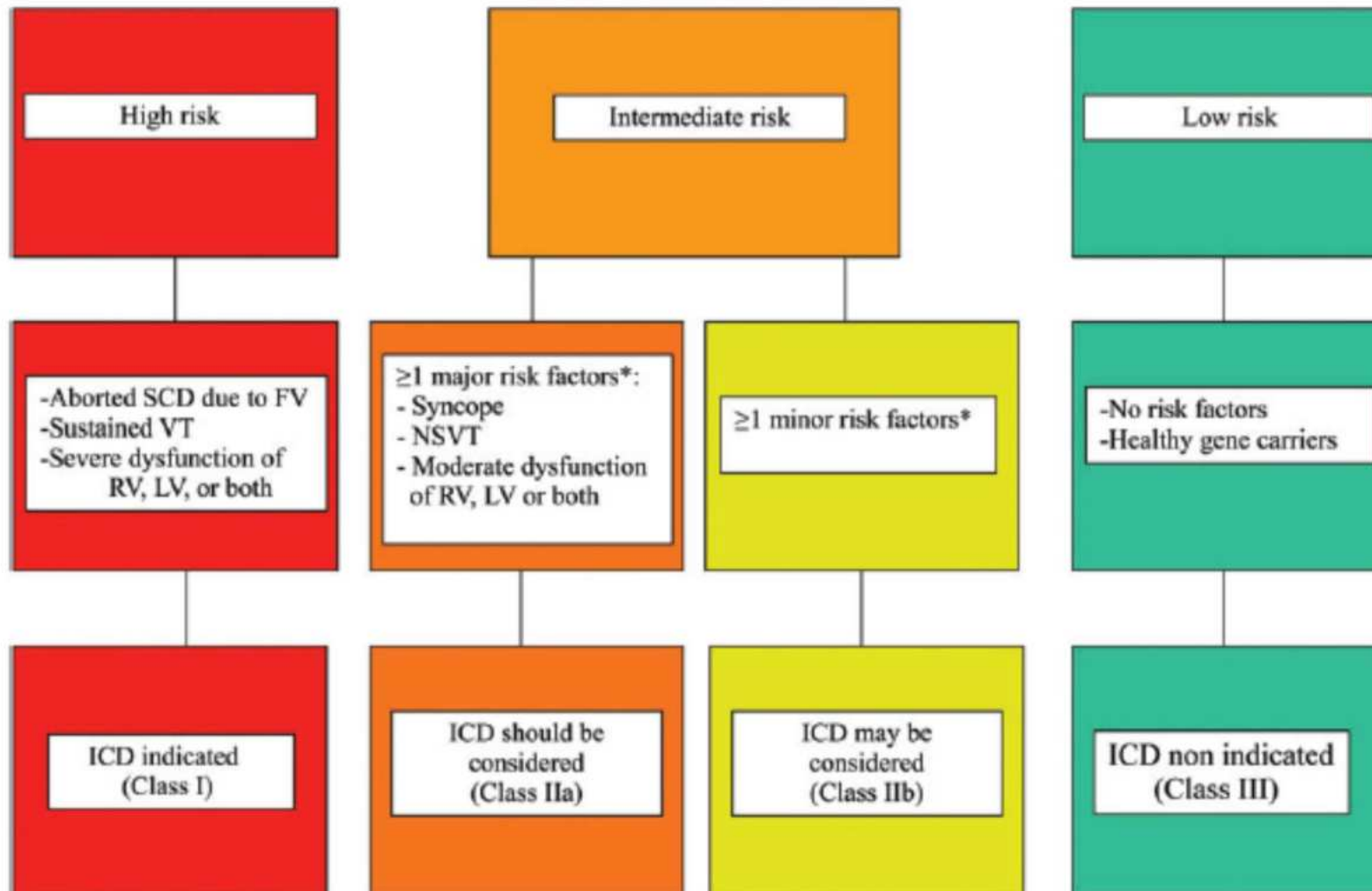


Lifestyle Changes, Discourage of Sports, Follow-up



Risk Stratification in ARVC

ICD Indication in ARVC





Provocative Statement

- **We should be the patient's „medical lawyer“**
 - Correct diagnosis, best counseling, appropriate therapy
 - Personalized medicine according to data and experience
 - Prevention of sudden death
 - Improvement in quality of life
 - Avoid overdiagnosing with psychological + social impact

- **We should not become our own „defence lawyer“**
 - Decisions and counseling not driven by medicolegal aspects
 - Doctor's peace of conscience
 - Fear of malpractice lawsuits
 - „Treat the patient, not ourselves“ (by pseudo-safety decisions)

Take-Home Messages

- **Be aware of ARVC signs + symptoms** („could it be ARVC?“)
- **Avoid underdiagnosing and undertreatment** (SCD risk)
- **Perform detailed diagnostic examination**
- **Assure expert reading + interpretation of tests**
- **Make the correct diagnosis** (Task Force Criteria 2010)
- **Think twice before you recommend genetic testing**
 - Clear consequences, integration into clinical management
- **Reassure ARVC, check for DD** („is it really ARVC?“)
- **Avoid overdiagnosing** („false labeling“ and ICD „overtreatment“)
- **Individual, personalized treatment decisions**

DGK Frühjahrstagung, 04.-07. April 2018
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Symposium: **Rare Diseases:** **Underdiagnosed and undertreated?**



ARVC: Arrhythmogenic Right Ventricular Cardiomyopathy

Thomas Wichter, MD, FESC
Professor of Medicine (Cardiology)

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