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Too young to compete?

Relevance to genes and other considerations

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Overview

- Genotyping children/adolescents in the context of pre-participation screening
  1. medical considerations
  2. ethical considerations

- Exercise and the developing heart
  3. long-term concerns

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Screening in practice
ESC/IOC Recommendation

- Basic screening
  - Personal and familial history
  - Physical examination
  - Resting 12-lead ECG

  - Genetic evaluation
    - in those with suspected phenotype or familial presence

    - in all… ?
      - high throughput sequencers > whole genome scanning
      - at a reasonable cost
      - direct-to-customer testing…

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European Sports Cardiology Recommendations

Lippincott Williams & Wilkins
a Wolters Kluwer business

Position Paper

Recommendations for participation in leisure-time physical activity and competitive sports in patients with arrhythmias and potentially arrhythmogenic conditions
Part I: Supraventricular arrhythmias and pacemakers

Hein Heidbüchel[a], Nicole Panhuyzen-Goedkoop[b,c], Domenico Corrado[d], Ellen Hoffmann[e], Allessandro Biffi[f], Pietro Delise[g], Carina Blomstrom-Lundqvist[h], Luc Vanhees[i], Per IvarHoff[j], Uwe Dorwarth[e] and Antonio Pelliccia[f] on behalf of the Study Group on Sports Cardiology of the European Association for Cardiovascular Prevention and Rehabilitation

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Sports Cardiology of the European Society of Cardiology
athletes by also incorporating guidelines
arrhythmias and arrhytr
stressing

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Position Paper

Recommendations for participation in leisure-time physical activity and competitive sports of patients with arrhythmias and potentially arrhythmogenic conditions
Part II: Ventricular arrhythmias, channelopathies and implantable defibrillators

Hein Heidbüchel[a], Domenico Corrado[b], Allessandro Biffi[c], Ellen Hoffmann[d], Nicole Panhuyzen-Goedkoop[e], Jan Hoogsteen[f], Pietro Delise[g], Per Ivar Hoff[h] and Antonio Pelliccia[c] on behalf of the Study Group on Sports Cardiology of the European Association for Cardiovascular Prevention and Rehabilitation

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This consensus paper on behalf of the Study Group on Sports Cardiology of the European Society of Cardiology for
previous one on guidelines for sports participation in competitive and recreational athletes with
arrhythmias and pacemakers. The question of imminent life-threatening arrhythmias is especially
of ventricular rhythm disorder is documented, or when the patient is diagnosed to
disorder. Frequent ventricular premature beats or nonsustained ventricul
pathology and increased risk. Their finding should prompt a thore
and electrophysiological techniques. This should allow
that carries a more ominous prognosis. Rec
and asymptomatic gene carriers
Brugada syndrome, cate
pathy and othe
subt

Channelopathies and familial cardiomyopathy:

List of recommendations, mostly restrictions.

"Similar for asymptomatic mutation carriers"

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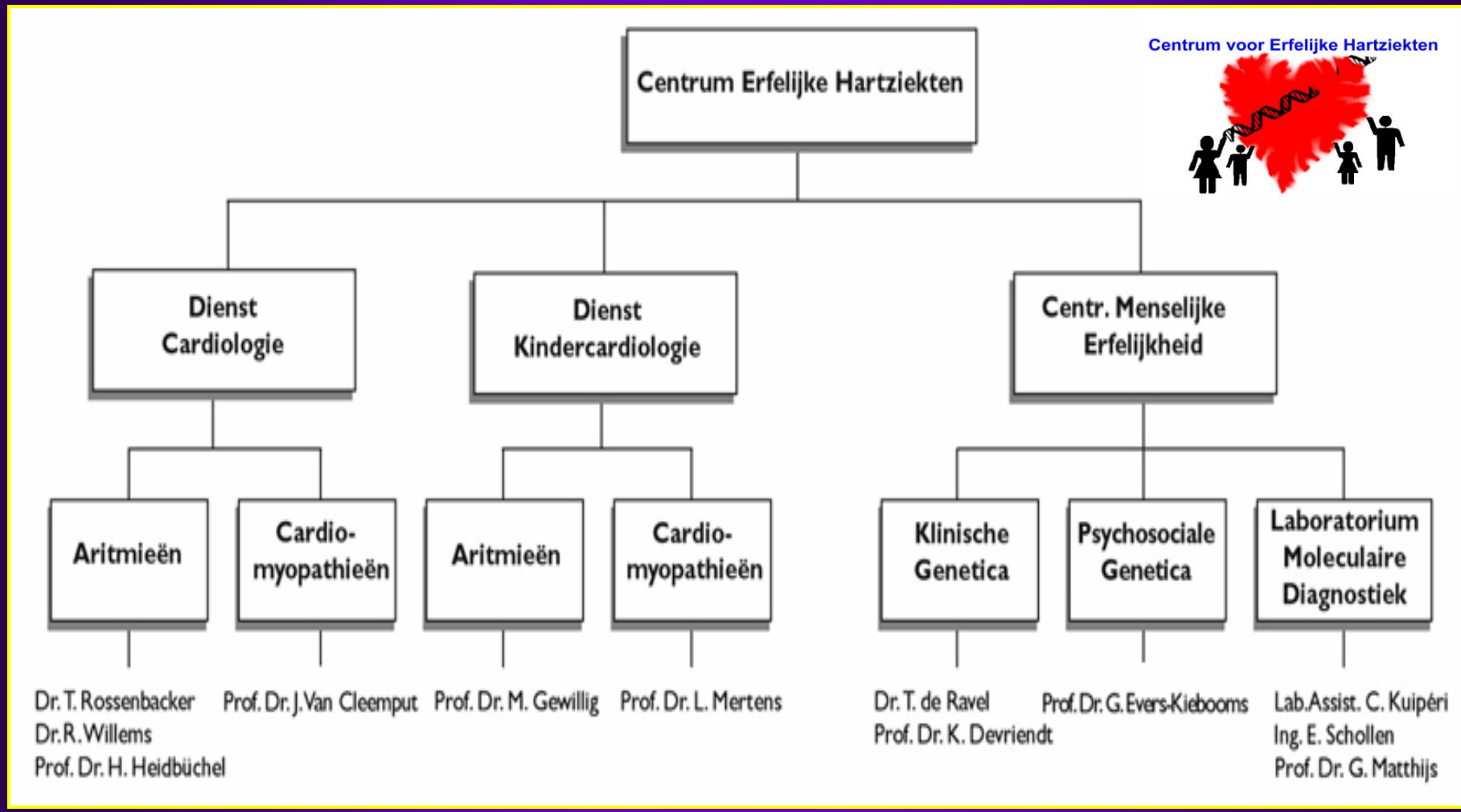
Center for Hereditary Heart Diseases, Leuven



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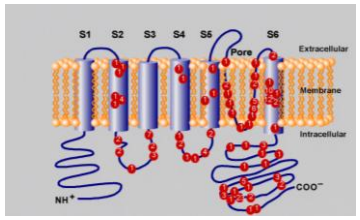
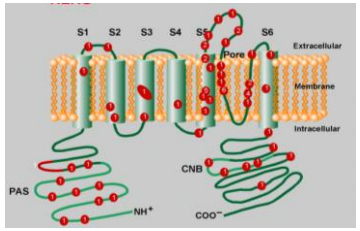
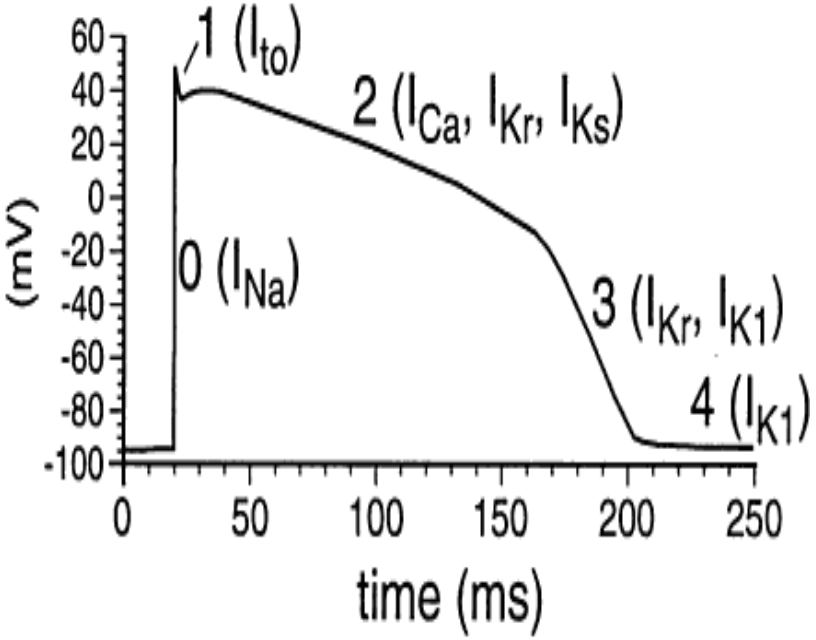
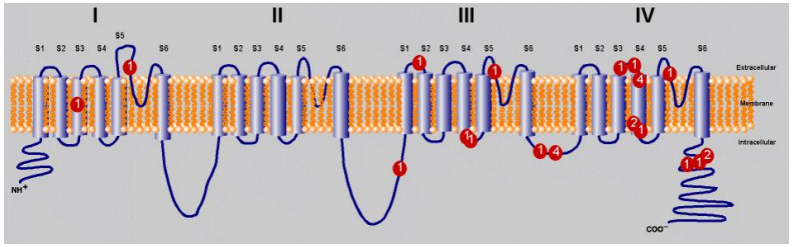
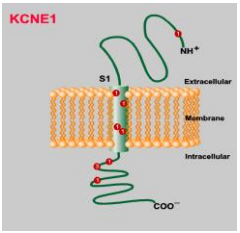
Genetic evaluation:
multiple candidate genes - multiple mutations

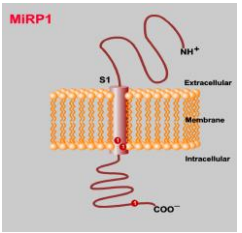












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Medical considerations

1. Is the genetic variant really a mutation?
   - not a problem for truncated proteins
   - uncertain for many missense mutations
     - population prevalence
     - comparison with other species
     - protein modeling
     - family co-segregation studies
     - in vitro functional evaluation
       - channelopathies: OK
       - cardiomyopathies: much more difficult
   - SNP: increasing vulnerability…

1. Skinner & Love, Heart Rhythm 2010

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Medical considerations

2. Genotyping as a diagnostic test

- genetic evaluation cannot exclude diagnosis
  - unknown genes
  - interactions with other genes and environmental modifiers
- even if positive genotype: no certitude about phenotype
  - non-penetrance
  - variable expression
- i.e.: no substitute for phenotyping
  - but is difficult to interpret in adolescents

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Medical considerations

3. Genotyping as a prognostic test
   - i.e.: risk-stratification dependent on genotype
     - "genotype-phenotype correlations"

   e.g. risk-stratification LQTS based on QTc/gender/type[1]
   - not waterproof
   - restrict sport to LQT1 and -2 carriers, but not to LQT3?[2]
   - advice concerning type of sport: swimming, diving, … vs other?[2]

1. Priori et al, N Eng J Med 2003;
2. Heidbuchel et al, for the Section on Sports Cardiology, EJCPR 2006

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Medical considerations

4. Genotyping as a predictive test

- Meaningfulness depends on:

  1. Degree of certainty in predicting disease + outcome
     - Non-penetrance and variable expression…

  2. Availability of preventive measures that affect outcome
     - How much will sports restriction affect outcome?
     - And does this apply in the same way to children as to adults?

- Clinical arena is a wide spectrum…

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Ethical considerations

1. Informed consent
   - how much information?
   - formally: if <18y: parents give consent
     - but child has its rights to have partaking in decision ! [1]
     - therefore:
       - no testing for diseases starting in adulthood, or
       - testing few years before disease may become manifest
   - "free consent"
     - pressure of family / parents
     - official screening programs

1. Eur Soc on Human Genetics: Borry et al, Eur J Hum Genet. 2009

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Ethical considerations

2. Privacy

- consensus not to pass genetic information to others
  - team physician ≠ treating physician
  - team manager, authorities, …
  - but restricting sports = passing information
- rule: patient informs those that he wants to inform

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Ethical considerations

3. The patient has the right NOT to know
   - even after information has been gathered
   - but can get in conflict with right of others to know…
     - child wants to know vs. parent does not want:
       - who has priority… ?
       - no clear ethical consensus; depends on individual circumstances.

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Ethical considerations

4. Non-directivity
   - advice may not steer towards particular decision.
   - could a fortioriy be applied to all screening findings…
   - balance between
     right of patient to decide freely
     and
     perceived freedom of patient to decide
     (e.g. competitive athletes)

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Ethical considerations

5. High-throughput sequencing

- how to deal with unclassified variants?
- how to deal with incidental findings?
- genome made available for study
  - but tells who you are: not anonymous!
  - and tells 50% of what your family members are
  - no minors in biobanks unless personal medical benefit is likely.

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"Sports injuries in young athletes are a public health issue" [1]

- Related to increased intensity and volume:
  1. acute injuries
  2. overuse injuries
     - some specically associated with children and adolescents
     - particularly vulnerable because processes of growth
  3. long-term medical impact (e.g. osteoarthritis)
     - under-investigated so far…, fruitful area for future research.

1. Frisch et al, Brit Med Bulletin 2009

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After a marathon, triathlon or other endurance event

- Increases in CK-MB, cTnT, cTnI in 40-57% [6-12]
- LV: rarely dysfunction [2-4,6,7]
- RV: dilatation and hypokinesia in ±30% [1,5,6,7] to 100% [13]

1. Douglas, JACC 1990; 2. Niemelä, Circ 1984; 3. Douglas, Circ 1987; 4. Rifai, Am J Cardiol 1999;
5. Davila-Roman, JACC 1997; 6. Neilan, Circ 2006; 7. La Gerche, Heart 2008; 8. Neumayr, Am J Cardiol 2002;
9. Ohba, Am Heart J 2001; 10. Bonetti, Int J Sports Med 1996; 11. Shave, Med Sci Sports Exerc 2004;
12. Scharhag, Am Heart J 2005; 13. Mousavi et al, Am J Cardiol 2009

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RV morphological changes
Acute > Chronic ?

- Hypothesis:
  - Repeated RV insults may result in long-term RV dysfunction
  - There may be a limit to what is healthy for the RV…
- Facilitating factors?
  1. Performance enhancing drugs?
  2. Genetic predisposition?
  3. Other … ?

1.Heidbuchel et al, Eur Heart J 2003; 2. Ector & Heidbuchel, Eur Heart J 2007;
3. La Gerche et al, Heart 2008; 4. La Gerche, Heidbuchel & Priori, ESC 2009

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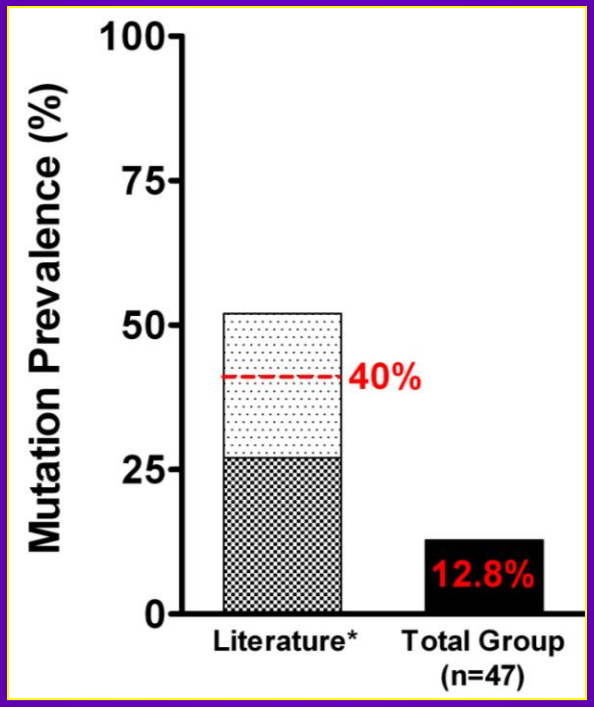
Desmathlete trial
Mutation findings in 47 athletes with "ARVC"

- 9 different heterozygous desmosomal sequence variants in 10 patients
  - 7 novel - 2 previously known
  - 5 (in 6 patients, 12.8%) manifestly pathogenic



LaGerche & Heidbuchel, Heart 2010 (in press)

*: 1. Sen-Chowdhry et al, Circ 2007; 2. Dalal et al, Circ 2006; 3. Gerull et al, Nature Genetics 2004; 4. Pilichou et al, Circ 2006; 5. van Tintelen et al, Circ 2006; 6. den Haan et al, Circ Cardiovasc Genetics 2009; 7. Sen-Chowdhry et al, JACC 2007

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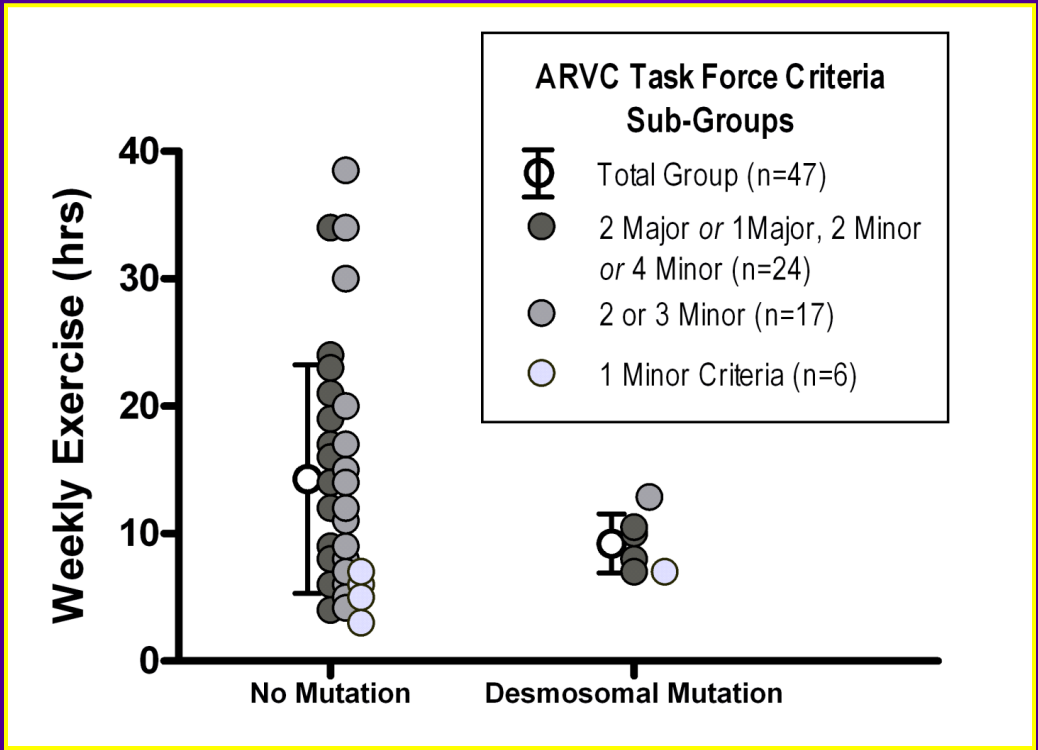
Desmathlete trial
genotype vs. phenotype vs. exercise level

- Athletes without a desmosomal mutation performed more exercise
  - 14.3±8.9 vs. 9.2±2.3, p=0.005
- No athlete performing above average exercise had a mutation.



1. LaGerche & Heidbuchel, Heart 2010 (in press)

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"Sports injuries in young athletes are a public health issue" [1]

- Needed:
  - awareness (of athletes, trainers, therapists, scientists)
  - prevention programmes (and their evaluation)
    - including passive prevention:
      - protective equipment,
      - rules, …

1. Frisch et al, Brit Med Bulletin 2009

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Youth Olympic Games

Promotion of sports because it's healthy?

Too young to compete?

even if we thoroughly screen them

phenoypically,

psychologically,

or genotypically…