GENEReviews

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Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy, Autosomal Dominant

[*[ARVC, ARVD, Arrhythmogenic Right Ventricular Cardiomyopathy, Arrhythmogenic Right Ventricular Dysplasia]*]

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Summary

Disease characteristics. Autosomal dominant arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is characterized by progressive fibrofatty replacement of the myocardium that predisposes to ventricular tachycardia and sudden death in young individuals and athletes. It primarily affects the right ventricle; with time, it may also involve the left ventricle. The presentation of disease is highly variable even within families, and affected individuals may not meet established clinical criteria. The mean age at diagnosis is 31 years (±13; range: 4-64 years).

Diagnosis/testing. The diagnosis of autosomal dominant ARVD/C is made using a combination of noninvasive and invasive tests to detect abnormalities in cardiac structure and rhythm. The six genes known to be associated with autosomal dominant ARVD/C are: *TGFB3* (locus name: ARVD1; protein: transforming growth factor beta-3), *RYR2* (locus name ARVD2; protein: ryanodine receptor 2), *TMEM43* (locus name ARVD5; protein: transmembrane protein 43), *DSP* (locus name ARVD8; protein: desmoplakin), *PKP2* (locus name ARVD9; protein: plakophilin-2), *DSG2* (locus name: ARVD10; protein: desmoglein-2), and *DSC2* (locus name: AVD11; protein: desmocollin-2). Four additional genes associated with autosomal dominant ARVD/C have been mapped but not identified (locus names ARVD3, ARVD4, ARVD6, and ARVD7). Additional loci remain undetermined. Molecular genetic testing is available on a clinical basis for *RYR2*, *TMEM43*, *DSP*, *PKP2*, *DSG2*, and *DSC2*.

Management. *Treatment of manifestations:* Management is individualized and focused on prevention of syncope, cardiac arrest, and sudden death through use of antiarrhythmic medication, implantable cardioverter-defibrillators, and rarely, heart transplantation. Individuals who present with clinical signs of right heart failure and/or left ventricular dysfunction and have a history of ventricular tachycardia should be treated aggressively. *Testing of relatives at risk:* screening by noninvasive tests annually during puberty and every two to three years after puberty.

Genetic counseling. Autosomal dominant ARVD/C is inherited in an autosomal dominant manner. A proband with autosomal dominant ARVD/C may have the disorder as a result of a new gene mutation. The proportion of cases caused by *de novo* mutations is unknown. Each child of an individual with autosomal dominant ARVD/C has a 50% chance of inheriting the mutation. Prenatal testing for families in which a *PKP2* disease-causing mutation has been identified is available. Prenatal testing for mutations in the other genes known to cause ARVD/C may be available through laboratories offering custom prenatal testing.

Diagnosis

Clinical Diagnosis

The diagnosis of autosomal dominant arrythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is made using a combination of noninvasive and invasive diagnostic tests to detect abnormalities in cardiac structure and rhythm.

Noninvasive Testing—Noninvasive testing includes 12-lead ECG, signal-averaged ECG (SAECG), echocardiography, cardiac MRI, Holter monitoring, and exercise stress testing.

ECG findings:

- Inverted T waves in the right precordial leads (V2 and V3) in individuals older than age 12 years in the absence of a right bundle branch block
- Incomplete right bundle branch block. Epsilon wave (electical potentials at the end of the QRS complex)

Newer data suggest that the following could be more specific for ARVD [Nasir et al 2004, Peters et al 2007]:

- Right precordial QRS prolongation
  - QRS in (V1+V2+V3)/(V4+V5+V6) of 1.2 or higher
  - QRS in V1-3 of 110 ms or higher
- Prolonged right precordial S-wave upstroke
- T-wave inversion in V1-V3

Echocardiogram findings:

- Dilation of the right ventricle with reduction of right ventricular function with no (or only mild) left ventricular impairment
- Localized right ventricular aneurysms
- Regional right ventricular hypokinesia

3D echocardiography, a new experimental imaging modality, may be useful. Currently, interpretation is variable based on the center's expertise in reading 3D echocardiograms and features specific for ARVD; guidelines have not been established.

Note: Because cardiac MRI is contraindicated in persons with defibrillators, 3D ECG can be considered in these cases [Prakasa et al 2006].

Cardiac MRI findings:

- Fibrofatty infiltration of the right ventricle
- Dilation and thinning of the right ventricle

- Regional right ventricular hypokinesia
- Reduced right ventricle function
- Trabecular disarray
- Right ventricular aneurysm

Cardiac MRI criteria for ARVD have not been established. Cardiac MRI can distinguish fat from muscle but can be subject to a high degree of intra-observer variability in identifying right ventricular free wall thinning and fatty infiltration in persons with a mild phenotype. In experienced centers, it may be capable of detecting ARVD [Sen-Chowdhry et al 2006].

Cardiac MRI in children has not demonstrated an increased ability to detect early changes of ARVD; however, this could be the result of the disease not manifesting at earlier ages [Fogel et al 2006]. Further studies are needed.

24-hour Holter monitoring

- Ventricular tachycardia (sustained and nonsustained)
- Frequent ventricular extrasystoles (>1000/24 hours)

Invasive Testing—Invasive testing includes electrophysiologic testing, right ventricular angiography, and right ventricular endomyocardial biopsy.

Invasive testing should be considered based on the results of the noninvasive testing and performed when clinically indicated to confirm ARVD/C. Nearly all tests are highly variable in their findings in ARVD/C and additional criteria are being evaluated [Nasir et al 2004]:

- **Right ventricular angiography (RVA).** Enlarged right ventricle with segmental abnormalities

  Note: The gold standard for imaging the right ventricle remains RVA, although MRI has good sensitivity and specificity for ARVD/C [Tandri et al 2003, Stevenson & Kalman 2004, White et al 2004]. MRI has the advantage of being noninvasive.

- **Right ventricular endomyocardial biopsy.** Fibrofatty replacement of the myocardium (predominantly in the apex, right ventricular outflow tract, and right ventricular inflow tract) and/or atrophy of the right ventricular myocardium

  Note: The biopsy must sample an affected region to be diagnostic.

- **Electrophysiologic (EP) study.** Ventricular tachycardia easily induced with ventricular pacing and extrastimulation
- **3D electroanatomic voltage mapping** maps low voltage areas of the right ventricle that correlate with fibrofatty replacement [Corrado et al 2005]. This method is still experimental.

Family History—Family history of a known diagnosis of ARVD/C, early or sudden death, and an inheritance pattern consistent with autosomal dominant inheritance support the diagnosis. A simplex case of ARVD/C (i.e., a single occurrence in a family) may result from reduced penetrance and/or represent a rare form of autosomal recessive ARVD/C. Family history of syncope and/or enlarged heart should be further investigated. If available, medical records of relatives should be reviewed for verification.

Diagnostic Criteria—Diagnostic criteria have been established [McKenna et al 1994]. The ARVD/C phenotype is widely variable and some affected individuals may not meet the strict

criteria outlined in this section [Nava et al 2000, Hamid et al 2002, Gerull et al 2004]; however, such individuals may still be at risk for cardiovascular events including arrhythmias. According to the Task Force of the Working Group Myocardial and Pericardial Disease, the European Society of Cardiology, and the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology, the diagnosis of ARVD/C is established in individuals who meet the following:

- Two major criteria **or**
- One major **and** two minor criteria **or**
- Four minor criteria

Global and/or regional dysfunction and structural alterations

- **Major**
  - Severe right ventricular dilation and reduction of right ventricular function with no (or only mild) left ventricular impairment
  - Localized right ventricular aneurysms (akinetic or dyskinetic areas with diastolic bulging)
  - Severe segmental dilation of the right ventricle
- **Minor**
  - Mild global right ventricular dilation and/or ejection fraction reduction with normal left ventricle
  - Mild segmental dilation of right ventricle
  - Regional right ventricular hypokinesis

Tissue characterization of walls

- **Major.** Fibrofatty replacement of myocardium observed on endomyocardial biopsy

Repolarization abnormalities

- **Minor.** Inverted T waves in right precordial leads (V2 and V3) (age >12 years, in absence of right bundle branch block)

Depolarization/conduction abnormalities

- **Major.** Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V1-V3)
- **Minor.** Late potential (signal-averaged ECG)

Arrhythmias

- **Minor**
  - Left bundle branch block-type ventricular tachycardia (sustained and nonsustained) on ECG, Holter, or exercise testing
  - Frequent ventricular extrasystoles (>1,000/24 hours on Holter monitoring)

Family history

- **Major.** Familial disease confirmed at necropsy or surgery
- **Minor**

- Familial history of premature sudden death (<35 years) suspected to be caused by right ventricular dysplasia
- Familial history (clinical diagnosis based on present criteria)

Since publication of the ARVD Task Force Diagnostic Criteria in 1994, studies have been performed to reevaluate the sensitivity of the criteria for early ARVD changes. The ARVD Task Force Diagnostic Criteria have not been formally revised. Some of the proposed changes to criteria:

- Inclusion of left ventricular involvement in ARVD, as some studies have shown more left ventricular manifestations than originally described [Sen-Chowdhry et al 2007]
- Quantification of fibrofatty involvement of the myocardium by endomyocardial biopsy to subclassify into major and minor criteria [Peters 2006]
- Specific ECG changes [Peters et al 2007]

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. Seven genes are known to be associated with autosomal dominant ARVD/C:

- ***TGFB3*** (locus name ARVD1), transforming growth factor beta-3 gene [Rampazzo et al 2003, Beffagna et al 2005]
- ***RYR2*** (locus name ARVD2), which encodes the protein ryanodine receptor 2 [Tiso et al 2001]
- ***DSP*** (locus name ARVD8), which encodes the protein desmoplakin [Rampazzo et al 2002]
- ***PKP2*** (locus name ARVD9), which encodes the essential armadillo-repeat protein of the cardiac desmosome, plakophilin-2 [Gerull et al 2004]
- ***DSG2*** (locus name ARVD 10), which encodes the protein desmoglein-2 [Awad et al 2006, Pilichou et al 2006]
- ***DSC2*** (locus name ARVD 11), which encodes the protein desmocollin-2 [Heuser et al 2006, Syrris et al 2006]
- ***TMEM43*** (locus name ARVD5), which encodes the protein transmembrane protein 43 [Merner et al 2008]

Other loci

- ARVD3, 14q12-q22 [Severini et al 1996]
- ARVD4, 2q32.1-q32.3 [Rampazzo et al 1997]
- ARVD6, 10p14-p12 [Li et al 2000, Matolweni et al 2006]
- ARVD7, 10q22 [Melberg et al 1999]
- Additional undetermined loci

Clinical testing

- **Sequence analysis.** The percentage of ARVD/C associated with *DSP*, *PKP2*, *DSG2*, *DSC2*, *TGFB3* or *TMEM43* gene mutations may be as high as 42.5% [Pilichou et al 2006], although the limited sample size makes accurate estimates impossible.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Arrhythmogenic Right Ventricular Dysplasia / Cardiomyopathy, Autosomal Dominant

Test Method	Mutations Detected	Proportion of AD [1] ARVD/C Attributed to Mutations in This Gene	Mutation Detection Frequency [2]	Test Availability
Mutation scanning/ sequence analysis	*RYR2* sequence variants	Rare	50%-70% [3]	Clinical Testing
	DSP sequence variants	6%-16%	Unknown [4]	Clinical Testing
	TMEM43 sequence variants	Unknown		Clinical Testing
	PKP2 sequence variants	11%-43%		Clinical Testing
Deletion testing	*PKP2* exonic and whole gene deletions		Unknown [5]	
Mutation scanning/ sequence analysis	*DSG2* sequence variants	12%-40%	Unknown [4]	Clinical Testing
	DSC2 sequence variants	Rare		Clinical Testing
	TGFB3 sequence variants			Research only

1. AD = autosomal dominant

2. Proportion of affected individuals with a mutation(s) as classified by gene/locus and test method

3. In ideal testing candidates with clinical diagnosis, although study population is those individuals with diagnosis of malignant hyperthermia susceptibility or central core disease only

4. Percentage of mutations detected by the test method is currently unknown, as a limited number of mutations have been identified and thus it is not known whether other types of mutations (e.g., exonic or whole gene deletions) not detected by the test method are present in this gene.

5. Mutation frequency is known only based on mutations detected by sequence analysis.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

A diagnosis of ARVD is made based on clinical diagnosis and the Task Force diagnostic criteria.

To date, gene mutation status has not been incorporated into the diagnostic criteria:

- Genetic testing should be considered in individuals who have a clinical diagnosis of ARVD based on the diagnostic criteria.
- A case can be made to offer genetic testing to all with a clinical diagnosis of ARVD with a negative family history based on the high rate of reduced penetrance identified with the ARVD genes identified thus far.

Establishing the subtype of ARVC/D in a proband. Once a clinical diagnosis of ARVD is made, genetic testing can establish the subtype of ARVD. Because all subtypes of ARVD are diagnosed using the same diagnostic criteria and because no significant genotype/phenotype correlations have been identified in the ARVD disease-causing genes, classification of the

subtype is done through gene testing. If genetic testing is performed and a mutation is not identified, the clinical diagnosis of ARVD is still applicable.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the disease-causing mutations in the family.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

RYR2

- **Catecholaminergic polymorphic ventricular tachycardia(CPVT).** Mutations in *RYR2* have been identified in individuals with CPVT [Priori et al 2000, Laitinen et al 2001]. CPVT [OMIM 604772] is an autosomal dominant disorder characterized by stress-related, bi-directional ventricular tachycardia in the absence of both structural heart disease and a prolonged QT interval [Coumel et al 1978, Leenhardt et al 1995]. It may present with syncopal events in childhood and adolescence. It has been suggested that CPVT and ARVD/C represent a phenotypic spectrum. However, families in which both CPVT and ARVD are present have not been described, and unique *RYR2* mutations have been associated with each disorder.
- **"Atypical" or "borderline" long QT syndrome (LQTS).** *RYR2* mutations have been identified in persons with "atypical" or "borderline" LQTS who did not have mutations identified in the five genes associated with LQTS [Tester et al 2005].

***DSP*.** Palmoplantar keratoderma with left ventricular cardiomyopathy and woolly hair/Carvajal syndrome [OMIM 605676] is an autosomal recessive disease characterized by ventricular dilated cardiomyopathy associated with keratoderma and woolly hair [Carvajal-Huerta 1998, Norgett et al 2000]. A homozygous nonsense mutation in *DSP* was reported to cause Carvajal syndrome in an Ecuadorian family with documented consanguinity. In addition, an individual with autosomal recessive ARVD, woolly hair, and a pemphigous-like skin disorder was also described as having a mutation in *DSP* [Alcalai et al 2003].

***PKP2, SG2, DSC2, TGFB, and TMEM43*.** No other phenotypes have been associated with mutations in these genes.

Clinical Description

Natural History

Autosomal dominant arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a myocardial disorder that predominantly affects the right ventricle. ARVD/C is a progressive disorder characterized by fibrofatty replacement of the myocardium, predisposing to ventricular tachycardia and sudden death in young individuals and athletes [Marcus et al 1982, Thiene et al 1988, Corrado et al 1998, Fontaine et al 1998]. Pathology in ARVD/C may also extend to involve the left ventricle [Horimoto et al 2000, Hamid et al 2002].

The most common presenting symptoms are heart palpitations, syncope, and death. The four described phases of ARVD are: (1) concealed phase (no clinical manifestations of ARVD, but potential risk of sudden cardiac death); (2) an overt electrical disorder (characterized by symptomatic arrhythmias); (3) right ventricular failure; and (4) a biventricular pump failure (resembles dilated cardiomyopathy) [Dalal et al 2005]. Left ventricle involvement can occur at any of the above stages [Sen-Chowdhry et al 2007].

In a long-term study of 37 families that included 132 living affected individuals, none of the affected individuals were diagnosed in infancy. Two children were diagnosed at ages four and six years [Nava et al 2000]. The mean age at diagnosis was 31 years (±13; range: 4-64 years) (see Figure 1).

The principal characteristic of arrhythmogenic cardiomyopathies is the tendency for ventricular arrhythmia and sudden death in the absence of overt ventricular dysfunction. The increased risk of sudden death in ARVD/C is thought to relate to sudden ventricular arrhythmias.

The percentage of sudden death that arises from ARVD/C is controversial [Firoozi et al 2003, Tabib et al 2003]. In a study of 160 probands fulfilling clinical criteria for ARVD/C, 24 died during follow-up, resulting in an overall mortality rate of 18.5% and an annual mortality rate of 2.3% [Hulot et al 2004]. Mean age at death (±SD) was 54 years (±19). Of the 24 deaths, 21 were cardiovascular deaths, among which seven were sudden cardiac deaths and 14 were a result of progressive heart failure (seven ventricular tachycardia or fibrillation occurring during an acute episode of severe cardiac failure, five terminal heart failure, and two rapid deaths after a cardiac transplantation) [Hulot et al 2004] (see Figure 2).

More studies have investigated the propensity to arrhythmia in ARVD. Lemola et al [2005] reported that of the 24 persons who received an implantable cardioverter-defibrillator (ICD), ten received appropriate shocks, four had inappropriate shocks, three had a heart transplant, one died of heart failure, and one died suddenly despite delivery of several device charges. However, it is important to note that not every ICD discharge may be associated with an arrhythmia leading to sudden death; some arrhythmias occur in normal cardiac function and therefore the denotation of "appropriate shocks" may be misleading. In a separate study of 100 persons with ARVD (diagnosed clinically or via autopsy), 31 experienced sudden cardiac death [Dalal et al 2005]. Of those diagnosed with ARVD while living, the death-free survival time was 94% in persons older than age 60 years (mainly as a result of receiving ICDs to prevent sudden cardiac death).

In a long-term study of 11 families with ARVD5, 50% of males considered at high risk for ARVD/C died by age 39 years and 50% of females considered high risk died by age 71 years. Mortality in these families was reduced by 28% in males who received an ICD [Hodgkinson et al 2005]. A study involving fifteen families with ARVD5 linked to the *TMEM43* locus on chromosome 3p25 and including clinical data from 137 subjects identified a median age of disease onset of 32 years in males and 44 years in females. Penetrance was 100% by age 63 years in males and age 76 years in females [Merner et al 2008]. In this study, the relative risk of dying was 6.8 times greater in affected males than in affected females.

A similar gender bias was identified with those with mutations in *PKP2* (ARVD9). Among individuals with a mutation, 67% of males (compared to 35% of females) met Task Force Criteria; however, gender differences in age of diagnosis or survival were not significant [Dalal et al 2006]. Note that these findings may not be applicable to other genetic forms of ARVD/C.

Genotype-Phenotype Correlations

Currently, insufficient genotypic data limit genotype-phenotype correlations. Furthermore, marked variation in phenotype can be observed in individuals from the same family who have the same pathogenic mutation [Gerull et al 2004, Dalal et al 2006].

An increasing number of individuals with ARVD who are compound heterozygotes within the same gene are being reported [Tiso et al 2001, Awad et al 2006]. This finding could account for the greater disease severity in families in which two mutations have been identified.

Penetrance

In the single family with a mutation in *DSP* reported by Rampazzo et al [2002], penetrance was estimated at 50%. Other estimates of penetrance in kindreds with autosomal dominant ARVD are as low as 20%-30% [Sen-Chowdhry et al 2005].

Evaluation of first-degree relatives of an individual with a *PKP2* mutation identified two individuals with the mutation who met clinical criteria for ARVD/C and four individuals with the mutation who had either a normal phenotype or mild disease manifestations [Gerull et al 2004].

A second family with a *PKP2* mutation had a family history of two sudden deaths at young ages and five living relatives with the mutation, only one of whom met clinical criteria [Gerull et al 2004].

Further studies are needed to establish the penetrance of the other genetic forms of ARVD.

Anticipation

Anticipation has not been observed.

Nomenclature

Arrythmogenic right ventricular cardiomyopathy (ARVC) has had numerous names including Uhl anomaly and right ventricular dysplasia.

Until 1996, ARVC was called arrythmogenic right ventricular dysplasia (ARVD) [Richardson et al 1996]. Currently the terms ARVC and ARVD are used interchangeably.

A disease called Venetian cardiomyopathy and/or right ventricular cardiomyopathy that is very similar to ARVD/C occurs in the Veneto region of Italy.

Prevalence

The exact prevalence of autosomal dominant ARVD/C is unknown but may be estimated at 1:1000 to 1:1250 in the general population [Peters 2006].

The prevalence of ARVD is greater in certain regions, such as Italy and Greece (Island of Naxos), where it can be as high as 0.4%-0.8% [Thiene & Basso 2001].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Naxos disease. An autosomal recessive form of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) has been observed on the island of Naxos, Greece. Naxos disease also includes palmoplantar keratoderma and peculiar woolly hair [OMIM 601214]. Naxos disease is caused by a homozygous 2-nucleotide deletion in *JUP*, the gene encoding plakoglobin (also known as γ-catenin), a key component of desmosomes and adherens junctions [McKoy et al 2000]. Penetrance is complete by adolescence [Protonotarios et al 2001].

ARVD/C and anterior polar cataract (APC). A single family with ARVD/C and subscapular cataract, a rare hereditary form of lens opacity, has been described [Frances et al 1997]. The proband and his sister both had ARVD/C and APC. The gene responsible for APC previously was linked to 14q24qter. Parents of the sibs were second cousins.

Cardiomyopathy. Many forms of cardiomyopathy may mimic aspects of ARVD/C. Cardiomyopathies may arise from genetic, toxic, or immunologic insults. Clinical testing may be useful to distinguish cardiomyopathy from ARVD/C. See Dilated Cardiomyopathy Overview.

Active myocarditis. Inflammation of the myocardium defines acute myocarditis. Myocarditis may arise from viral or other pathogen exposure as well as toxic or immunologic insult. Clinical testing may be useful to distinguish myocarditis from ARVD/C.

Coronary artery disease and myocardial infarction. Coronary artery disease, or atherosclerotic narrowing of the coronary arteries, may lead to acute or chronic ischemic conditions that may mimic aspects of ARVD/C. Clinical testing may be useful to distinguish these from ARVD/C.

Right ventricular outflow tract tachycardia (RVOT) is a clinical arrhythmia condition that is not typically associated with structural heart disease as is seen in ARVD/C. ECG and cardiac imaging may be useful to distinguish these disorders.

Brugada syndrome is characterized by ST segment abnormalities in leads V_1-V_3 on the ECG and a high risk of ventricular arrhythmias and sudden death. Considerable clinical overlap may be present. One discriminating factor is the right ventricular dilation and fibrofatty infiltration that is characteristic of ARVD/C but rarely seen in Brugada syndrome.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC/D), the following evaluations are recommended:

- ECG
- Echocardiogram and/or MRI, depending on the expertise of the imaging center
- Electrophysiology study to assess the risk of ventricular arrhythmias and potentially perform an ablation to decrease the arrhythmias or assess the appropriateness of device insertion (such as an implantable cardioverter defibrillator)

Treatment of Manifestations

Most affected individuals live a normal lifestyle. Education regarding sudden death risk to affected adults and parents of affected children is an important aspect of management. Management of individuals with ARVD/C is complicated by incomplete information on the natural history of the disease as well as variable expressivity of the disease. Management of patients with ARVC should be individualized and based on the specific results of detailed investigation.

Management is focused on prevention of syncope, cardiac arrest, and sudden death (see Prevention of Primary Manifestations). Recent studies suggest that individuals who present with clinical signs of right heart failure and/or left ventricular dysfunction and have a history

of ventricular tachycardia are at high risk and should be treated aggressively [Hulot et al 2004].

Prevention of Primary Manifestations

Antiarrhythmic medications

- Beta-blockers
- Amiodarone
- Sotalol

Implantable cardioverter-defibrillators (ICDs). ICD placement should be considered in anyone with a clinical diagnosis of ARVD. No guidelines have been published on the most appropriate time to place an ICD.

Persons who seem to be at the highest risk are those who have been resuscitated or who are unresponsive to or intolerant of antiarrhythmic therapy and those with a history of sudden cardiac arrest in first-degree relatives.

The appropriate time to place an ICD in an individual at moderate risk is not known because ICD efficacy in ARVD may be affected by progressive fibrofatty involvement of the right ventricle, which may obscure appropriate sensing of the ICD.

In one study, 66% (n=44/67) of persons with ARVD with ICDs received appropriate* shocks from their ICD for treatment of a sustained ventricular arrhythmia and 24% (n=16/67) received inappropriate shocks for sinus tachycardia, supraventricular tachycardia/atrial fibrillation, or oversensing. However, it should be noted that it is difficult to determine whether the ventriculartachycardia was sustained or whether it would have self-corrected without the shock. This study found that the incidence of appropriate ICD therapies was greatest for persons with definite ARVD compared to those with probable ARVD. However, even in those with probable ARVD, nearly one third received appropriate intervention from the ICD.

*Note: 'Appropriate' refers to proper sensing and delivery of defibrillation based on device function.

Therefore, ICD placement should be considered even in those who do not meet ARVD diagnostic criteria according to the international Task Force definitions but have probable ARVD (meeting fewer criteria) and positive findings on electrophysiologic study [Piccini et al 2005].

Surveillance

Screening for cardiac involvement in persons with ARVD is essential to ascertain severity and disease progression over time. Screening recommendations:

- ECG, annually or more frequently depending on symptoms
- Echocardiogram,annually or more frequently depending on symptoms
- Cardiac MRI, annually or more frequently depending on symptoms

Agents/Circumstances to Avoid

Individuals with RVD may be discouraged from vigorous athletic activity including competitive athletics because of the strain caused on the right heart; however, conflicting views exist on restriction of vigorous athletic activity in persons with ARVD or those at risk for ARVD.

Testing of Relatives at Risk

It is appropriate to offer molecular genetic testing to at-risk sibs if the disease-causing mutations are identified in an affected family member so that morbidity and mortality can be reduced by early diagnosis and treatment.

Evidence of autosomal dominant ARVD/C is found in 30% to 50% of family members screened by noninvasive tests [Nava et al 1988, Hermida et al 1997]:

- During puberty, at-risk relatives should be assessed at least once a year.
- After puberty, at-risk relatives should be assessed every two to three years or as determined by the managing cardiologist.

Molecular genetic testing of asymptomatic at-risk family members may be available if the disease-causing mutation has been identified in an affected family member.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Heart transplantation is considered when ARVD has progressed to right or left ventricular heart failure. Severe diffuse biventricular involvement simulating dilated cardiomyopathy and requiring heart transplantation seems to be rare.

Cardiac catheter ablation of tissue causing abnormal rhythms is usually not effective because of the multiple sites of primary ventricular tachycardias.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Autosomal dominant arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with autosomal dominant ARVD/C have an affected parent.
- A proband with autosomal dominant ARVD/C may have the disorder as the result of a new gene mutation. The proportion of cases caused by *de novo* mutations is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include cardiac MRI or echocardiogram, ECG and molecular genetic testing if the mutation has been identified in the proband.

Note: Although some individuals diagnosed with autosomal dominant ARVD/C have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset or reduced penetrance of the disease in the affected parent.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected and/or has a disease-causing mutation, the risk to the sibs of inheriting the mutation is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband is lower. Variable expressivity and reduced penetrance are common.
- Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of an individual with autosomal dominant ARVD/C has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents. If a parent is found to be affected or to have a disease-causing mutation, his or her family members are at risk.

Related Genetic Counseling Issues

See Management, Testing of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk for ARVD/C caused by a *PKP2* mutation (locus name ARVD9) is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

No laboratories offering molecular genetic testing for prenatal diagnosis for mutations in the other genes known to cause ARVD/C are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified. For laboratories offering custom prenatal testing, see Testing.

Requests for prenatal testing for conditions such as ARVD/C that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Arrhythmogenic Right Ventricular Dysplasia / Cardiomyopathy, Autosomal Dominant

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
ARVD1	*TGFB3*	14q24	Transforming growth factor beta-3
ARVD10	*DSG2*	18q12.1-q12.2	Desmoglein-2
ARVD11	*DSC2*	18q12.1	Desmocollin-2
ARVD2	*RYR2*	1q42.1-q43	Ryanodine receptor 2
ARVD3	Unknown	14q12-q22	Unknown
ARVD4	Unknown	2q32.1-q32.3	Unknown
ARVD5	*TMEM43*	3p25	Transmembrane protein 43
ARVD6	Unknown	10p14-p12	Unknown
ARVD7	Unknown	10q22.3	Unknown
ARVD8	*DSP*	6p24	Desmoplakin
ARVD9	*PKP2*	12p11	Plakophilin-2

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Arrhythmogenic Right Ventricular Dysplasia / Cardiomyopathy, Autosomal Dominant

107970	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 1; ARVD1
125645	DESMOCOLLIN 2; DSC2
125647	DESMOPLAKIN; DSP
125671	DESMOGLEIN 2; DSG2
180902	RYANODINE RECEPTOR 2; RYR2
190230	TRANSFORMING GROWTH FACTOR, BETA-3; TGFB3
600996	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 2; ARVD2
602086	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 3; ARVD3
602087	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 4; ARVD4
602861	PLAKOPHILIN 2; PKP2
604400	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 5; ARVD5
604401	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 6
607450	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 8; ARVD8
609040	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 9; ARVD9
609160	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 7
610193	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 10; ARVD10
610476	ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA, FAMILIAL, 11; ARVD11
612048	TRANSMEMBRANE PROTEIN 43; TMEM43

Table C. Genomic Databases for Arrhythmogenic Right Ventricular Dysplasia / Cardiomyopathy, Autosomal Dominant

Locus Name	Gene Symbol	Locus Specific	Entrez Gene	HGMD
ARVD1	*TGFB3*	TGFB3	7043 (MIM No. 190230)	TGFB3
ARVD10	*DSG2*		1829 (MIM No. 125671)	DSG2
ARVD11	*DSC2*	DSC2	1824 (MIM No. 125645)	
ARVD2	*RYR2*	RYR2	6262 (MIM No. 180902)	RYR2
ARVD3	Unknown	Gene Connection for the Heart	424 (MIM No. 602086)	
ARVD4	Unknown	Gene Connection for the Heart	425 (MIM No. 602087)	
ARVD5	*TMEM43*	TMEM43	79188 (MIM No. 612048)	
ARVD6	Unknown	Gene Connection for the Heart	27038 (MIM No. 604401)	
ARVD7	Unknown		497658 (MIM No. 609160)	
ARVD8	*DSP*	DSP	1832 (MIM No. 125647)	DSP
ARVD9	*PKP2*	PKP2	5318 (MIM No. 602861)	PKP2

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Defects in intercellular connections are one pathogenic mode that leads to arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C). This is suggested by mutations in the genes encoding two desmosomal proteins, desmoplakin *(DSP)* and plakoglobin *(JUP*), associated with ARVD8/Carvajal syndrome and Naxos disease respectively.

Altered calcium homeostasis may provide another pathogenic pathway in ARVD/C as suggested by mutations in the *RYR2* gene in ARVD2. *RYR2* has an important role in calcium release from the sarcoplasmic reticulum and the regulation of excitation-contraction coupling. An impaired intracellular calcium concentration and altered excitation-contraction coupling may predispose to arrhythmias. In addition, impaired intracellular calcium may lead to cellular necrosis, promoting fibrosis and adipose replacement [Tiso et al 2001].

RYR2

Normal allelic variants: The gene consists of 105 exons, coding a 565-kd monomer, making it one of the largest human genes.

Pathologic allelic variants: In a study by Tiso et al [2001], four missense mutations were identified in four Italian families in highly conserved regions of *RYR2*. These mutations differ from those found in the *RYR2* gene in CPVT. Mutations in *RYR2* have also been identified in 'atypical' long QT syndrome [Tester et al 2005].

Normal gene product: The ryanodine receptor 2 regulates calcium flux in the intracellular space and mediates cardiac muscle excitation-contraction coupling [Tiso et al 2001].

Abnormal gene product: *RYR2* mutations are thought to result in an uncontrolled calcium leak in the cardiac myocyte, leading to arrhythmia.

DSP

Normal allelic variants: The gene consists of 24 exons, coding 2,871 amino acids.

Pathologic allelic variants: In a study by Rampazzo et al [2002], one missense mutation was identified in exon 7 of the proband in an Italian family. At least eight other mutations (nonsense and missense) have been identified in eight different families [Bauce et al 2005, Yang et al 2006].

Normal gene product: Desmoplakin, together with plakoglobin, anchors to desmosomal cadherins, forming an ordered array of nontransmembrane proteins, which then bind to keratin intermediate filaments (IFs) [Kowalczyk et al 1997, Smith & Fuchs 1998, Leung et al 2002]. Desmosomes are major cell-cell junctions, particularly abundant in epidermal cells and in cardiomyocytes [Gallicano et al 1998, Smith & Fuchs 1998]. In addition, desmosomes have been shown to maintain cell integrity as well as participate in cell death and lipid metabolism [Yang et al 2006].

Abnormal gene product: Abnormalities in desmoplakin are speculated to lead to desmosomal instability and defective desmosomes cannot sustain the constant mechanical stress in contracting cardiomyocytes leading to cardiac dysfunction and cell death [Yang et al 2006]. Data from a desmoplakin-deficient mouse model suggest that abnormal desmosomes lead to abnormal β-catenin signaling through Tcf-Lef1 transcription factors resulting in dedifferentiation of myocytes into adipocytes [Garcia-Gras et al 2006].

PKP2

Normal allelic variants: The gene consists of 14 exons.

Pathologic allelic variants: In a study by Gerull et al [2004], 25 heterozygous mutations were identified in 32 of 120 unrelated probands. Of the 25 *PKP2* mutations, 12 were insertion-deletion mutations, six were nonsense mutations, four were missense mutations, and three were splice-site mutations. Dalal et al [2006] identified another nine families with *PKP2* mutations.

Normal gene product: Similar to desmoplakin, plakophilin-2 is a protein of the desmosome and provides structural and functional integrity to adjacent cells.

Abnormal gene product: Abnormalities in plakophilin are thought to perturb intercellular connections and lead to arrhythmia.

DSG2

Normal allelic variants: The gene consists of 15 exons spanning 48.6 kb. No polymorphisms have been identified.

Pathologic allelic variants: At least 12 mutations have been described. One individual was identified as a compound heterozygote [Awad et al 2006].

Normal gene product: Desmoglein-2 (DSG2) is a member of the desmoglein family and is an essential component of the desmosome. DSG2 is expressed in myocardium.

Abnormal gene product: The effect of an abnormal gene product is unknown at this point; loss of DSG2 results in early embryonic lethality in knockout mice.

DSC2

Normal allelic variants: The gene consists of 17 exons spanning 32 kb. No polymorphisms have been identified.

Pathologic allelic variants: Three mutations have been described.

Normal gene product: Desmocollin-2 (DSC2) is ubiquitously expressed in desmosomal tissues and is the only one of three desmocollin isoforms present in cardiac tissue. DSC2 is found in two forms, a and b, produced by alternate splicing of exon 16. Desmocollins bind to desmogleins through their extracellular domains in a Ca2+-dependent manner and their cytoplasmic domains have binding sites for plakoglobin.

Abnormal gene product: Desmocollin mutations resulting in an isoform lacking the last 37 amino acid residues of the carboxyl-terminal domain of DSC2a are unable to bind plakoglobin. It is unknown how the mutations affect desmosome formation, but it is speculated that it would result in impaired desmosomes.

TGFB3

Normal allelic variants: The gene consists of seven exons. No polymorphisms have been identified.

Pathologic allelic variants: Two mutations have been described, one in the 5' untranslated region of the gene and the second in the 3' untranslated region of the gene [Beffagna et al 2005].

Normal gene product: *TGFB3* encodes for transforming growth factor beta-3, which encodes for a cytokine-stimulating fibrosis and modulates cell adhesion.

Abnormal gene product: It is currently unknown how mutations in *TGFB3* cause ARVD.

TMEM43

Normal allelic variants: The *TMEM43* gene consists of 12 exons coding for 400 amino acids.

Pathologic allelic variants: In a study by Merner et al [2008], one putative pathologic variant, the missense change Ser358Leu was identified in 15 families, all of Newfoundland ancestry. Whether this variant is the causative mutation requires further testing, as it may rather be a neutral variant that is in linkage disequilibrium with the causal mutation. Whether *TMEM43* is implicated in individuals with ARVD outside this region of Newfoundland is unknown.

Normal gene product: The *TMEM43* gene codes for a novel transmembrane protein. By bioinformatics analysis, the primary sequence suggests that this protein may be a target of PPARγ. Bioinformatics predicts the protein to be a membrane protein with several post-translational modification sites [Merner et al 2008]. Functional studies are needed.

Abnormal gene product: The pathologic mechanism of the abnormal gene product is unknown.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select*  *for the most up-to-date Resources information.*—ED.

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia
ARVD.net

American Heart Association
National Center
7272 Greenville Avenue
Dallas TX 75231
Phone: 800-AHA-USA-1 (800-242-8721)
www.americanheart.org

Sudden Arrhythmia Death Syndromes (SADS) Foundation
508 East South Temple Suite 20
Salt Lake City UT 84102
Phone: 800-786-7723; 801-531-0937
Fax: 801-531-0945
Email: sads@sads.org
www.sads.org

ARVD Patient Registry
ARVD Registry

European ARVC/D Clinical Registry Database
Email: cardpath@unipd.it
European ARVC/D Registry

North American ARVD Registry
Phone: 800-483-2662
Email: kgear@email.arizona.edu
www.arvd.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

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Revision History

- 10 July 2008 (cd) Revision: sequence analysis available clinically for *TMEM43* mutations (ARVD5)
- 12 December 2007 (me) Comprehensive update posted to live Web site
- 5 April 2006 (cd) Revision: Clinical testing for *DSP* and *PKP2* available; prenatal diagnosis for *PKP2* available
- 18 April 2005 (me) Review posted to live Web site
- 6 July 2004 (em) Original submission

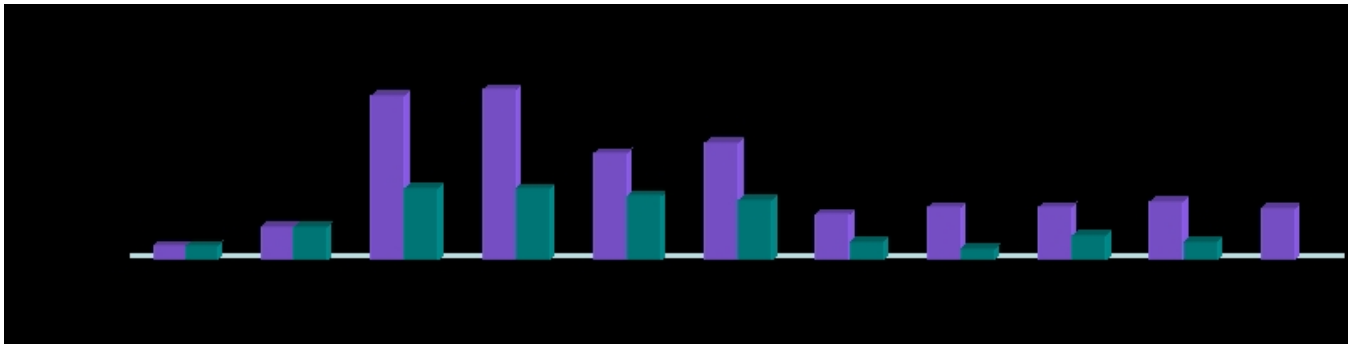

Figure 1. Age of affected individuals at time of diagnosis (purple bars) and at time of onset of arrhythmias (teal bars). On the x-axis, the age of subjects; on the y-axis, the number of subjects [Nava et al 2000, with permission].

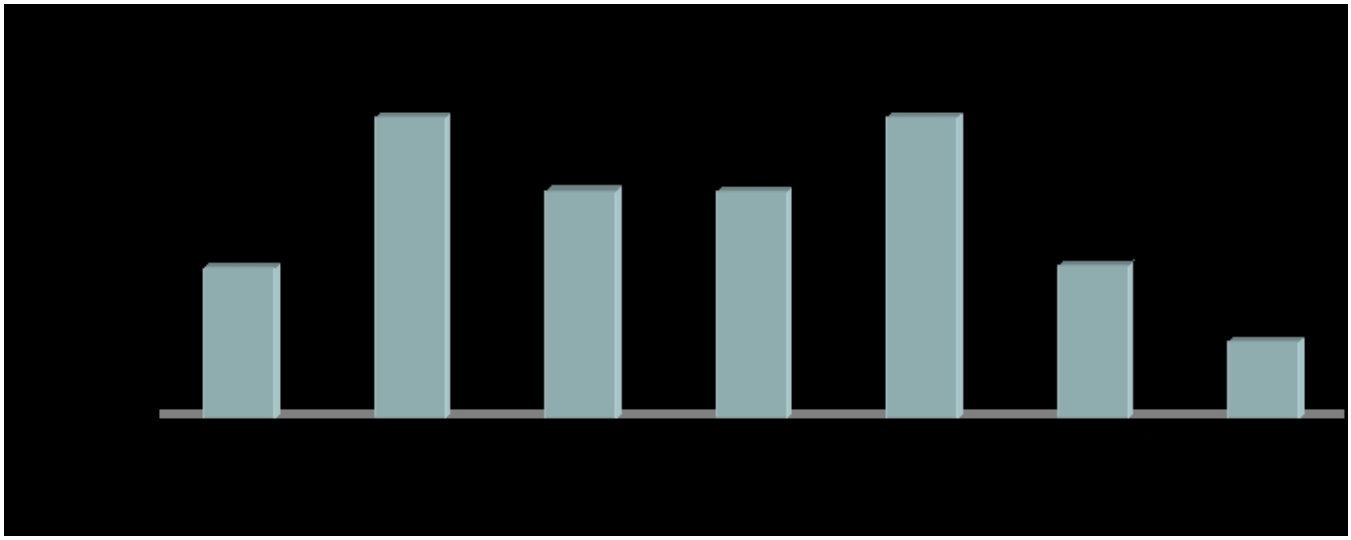

Figure 2. Age of affected individuals at time of sudden death. On the x-axis, the age of subjects at the time of death; on the y-axis, the number of subjects [Nava et al 2000, with permission].