

Arrhythmogenic Right Ventricular Cardiomyopathy

An integrated approach to inheritance, myocardial pathology and arrhythmic disease

Desmosomal susceptibility → myocardial remodeling → arrhythmia

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Learning objectives

- Explain how defective cell–cell junctions relate to a myocardial arrhythmogenic substrate.
- Recognize right-ventricular wall attenuation and fibrofatty myocyte replacement.
- Integrate morphology, family history, ECG, imaging, and molecular testing without overcalling isolated findings.
- Distinguish classic ARVC from dilated cardiomyopathy and important phenocopies.

Molecular substrate

**Morphologic
hallmark**

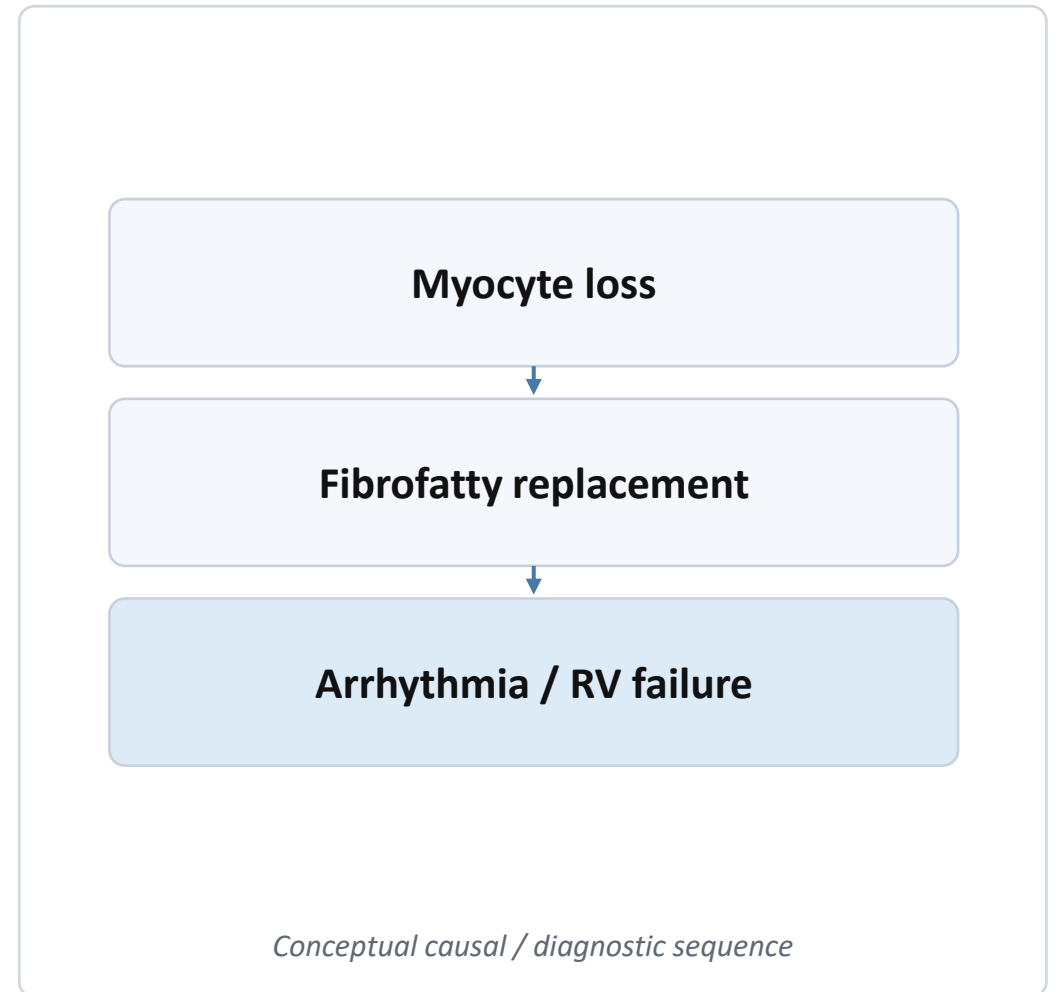
Arrhythmia / failure

**Diagnostic
integration**

Organizing framework — interpret each domain clinically

ARVC: Defining clinicopathologic lesion

- A primary myocardial disorder with predominantly right-ventricular involvement in its classic form.
- Loss of cardiomyocytes with fibrous and adipose replacement is the cardinal structural feature.
- Electrical instability may cause ventricular tachyarrhythmia and sudden cardiac death.
- Right-sided heart failure can emerge as disease advances.



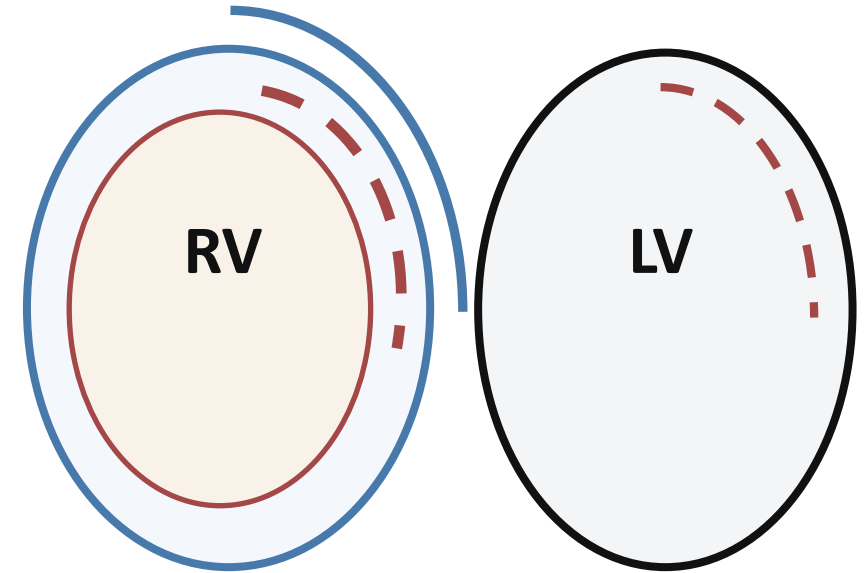
Position among cardiomyopathy phenotypes

Pattern	Dominant structural change	Typical functional issue
Dilated cardiomyopathy	Chamber dilation; variable fibrosis	Reduced systolic function
Hypertrophic cardiomyopathy	Myocardial hypertrophy / disarray	Impaired filling $\pm$ obstruction
Classic ARVC	RV myocyte loss + fibrofatty scar	Arrhythmia $\pm$ RV failure

Phenotypes overlap; These are distinctions, not exclusive categories.

ARVC is not exclusively a right-ventricular disease

- The classic phenotype is right-ventricle predominant.
- Left-ventricular involvement and left-sided failure can occur.
- Biventricular and left-dominant arrhythmogenic phenotypes broaden the clinical spectrum.
- Chamber-based names describe phenotype, not a rigid anatomic boundary.



Possible biventricular involvement

Simplified chamber schematic — not a gross specimen

Electrical disease may precede pump failure

- Ventricular arrhythmia can be the presenting manifestation before overt structural disease.
- A preserved global ejection fraction does not eliminate arrhythmic risk.
- The diagnostic assessment must evaluate electrical and structural abnormalities together.

Early electrical abnormalities



Detectable scar / regional dysfunction

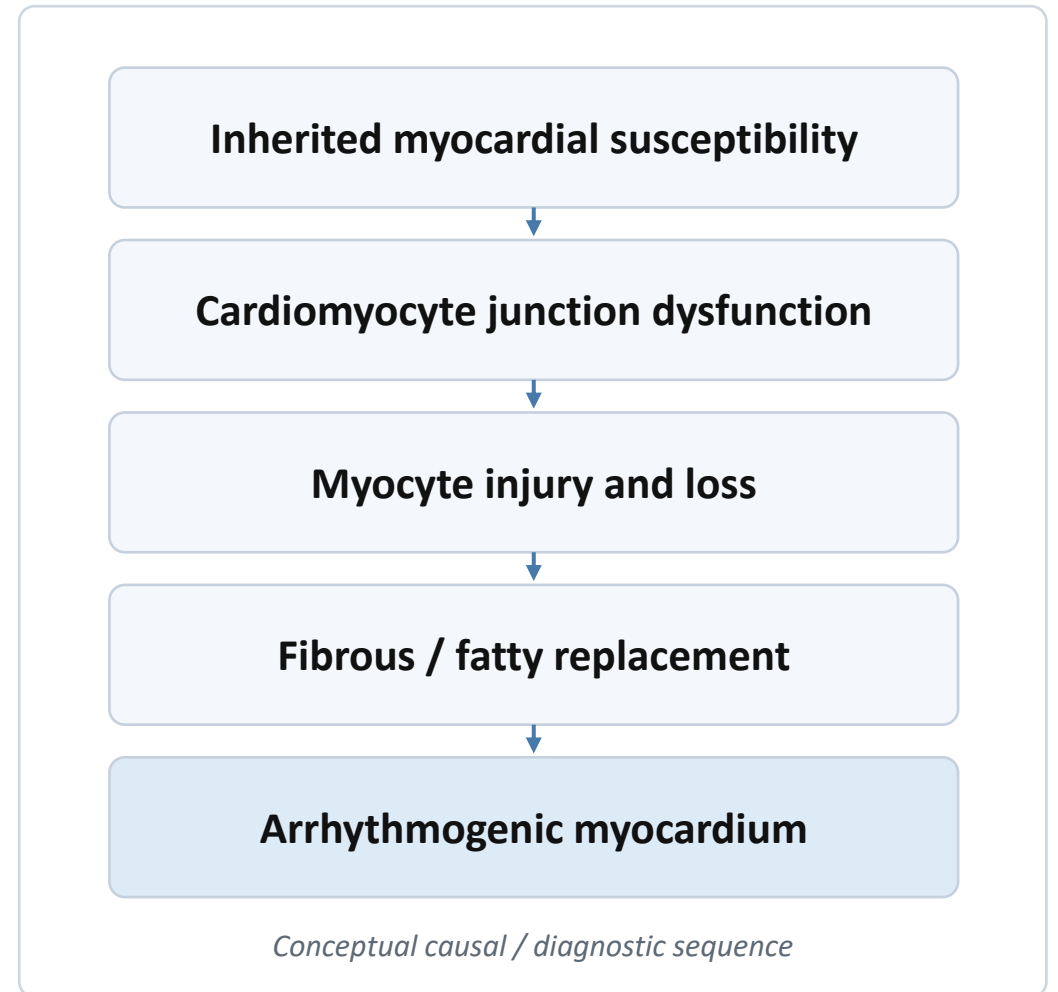


Advanced pump impairment

Conceptual causal / diagnostic sequence

The core disease sequence

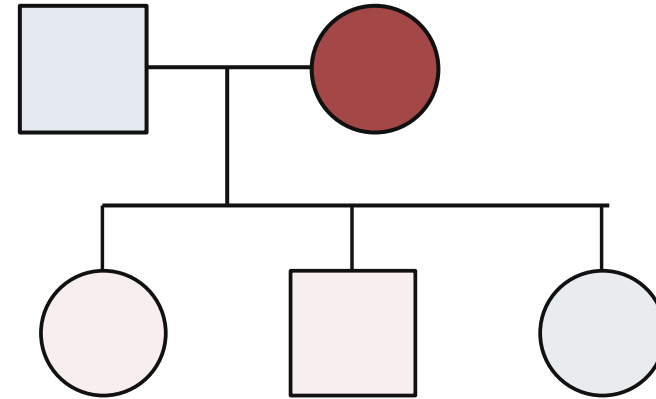
- This is a conceptual framework, not a proven one-directional mechanism for every genotype.



Different variants and environmental modifiers alter the phenotype.

Autosomal-dominant inheritance predominates

- ARVC as usually autosomal dominant.
- Variable penetrance means a genotype-positive relative may have little or no clinical phenotype.
- An apparently unaffected parent does not exclude inherited susceptibility.
- Recessive syndromic forms are important exceptions.

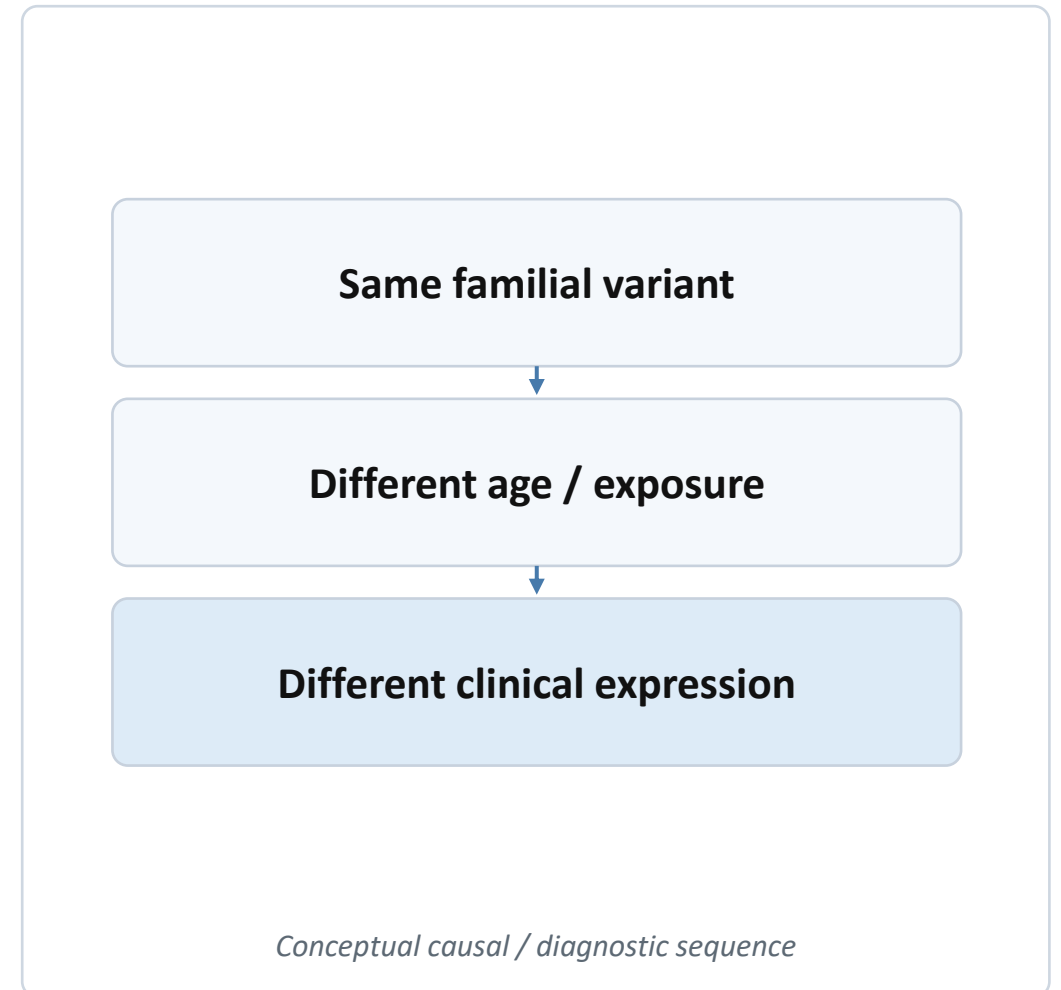


Inheritance can be shared; Disease expression differs

Illustrative pedigree, not real-family evidence

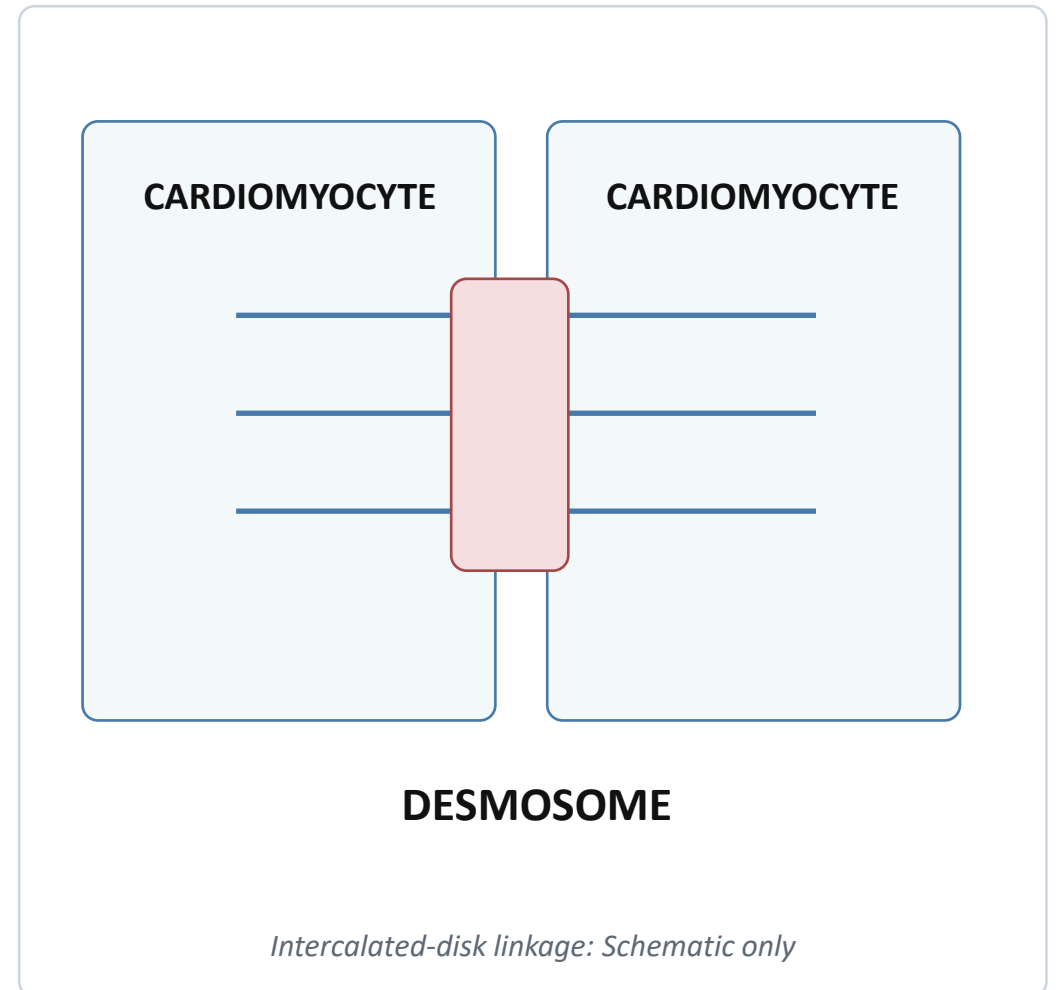
Variable penetrance versus variable expressivity

- Penetrance: Whether the disease phenotype becomes clinically evident.
- Expressivity: How severe and which manifestations occur among affected carriers.
- Age, exercise exposure, genotype, and other modifiers help explain differing family presentations.
- Do not equate lack of symptoms with absence of risk.



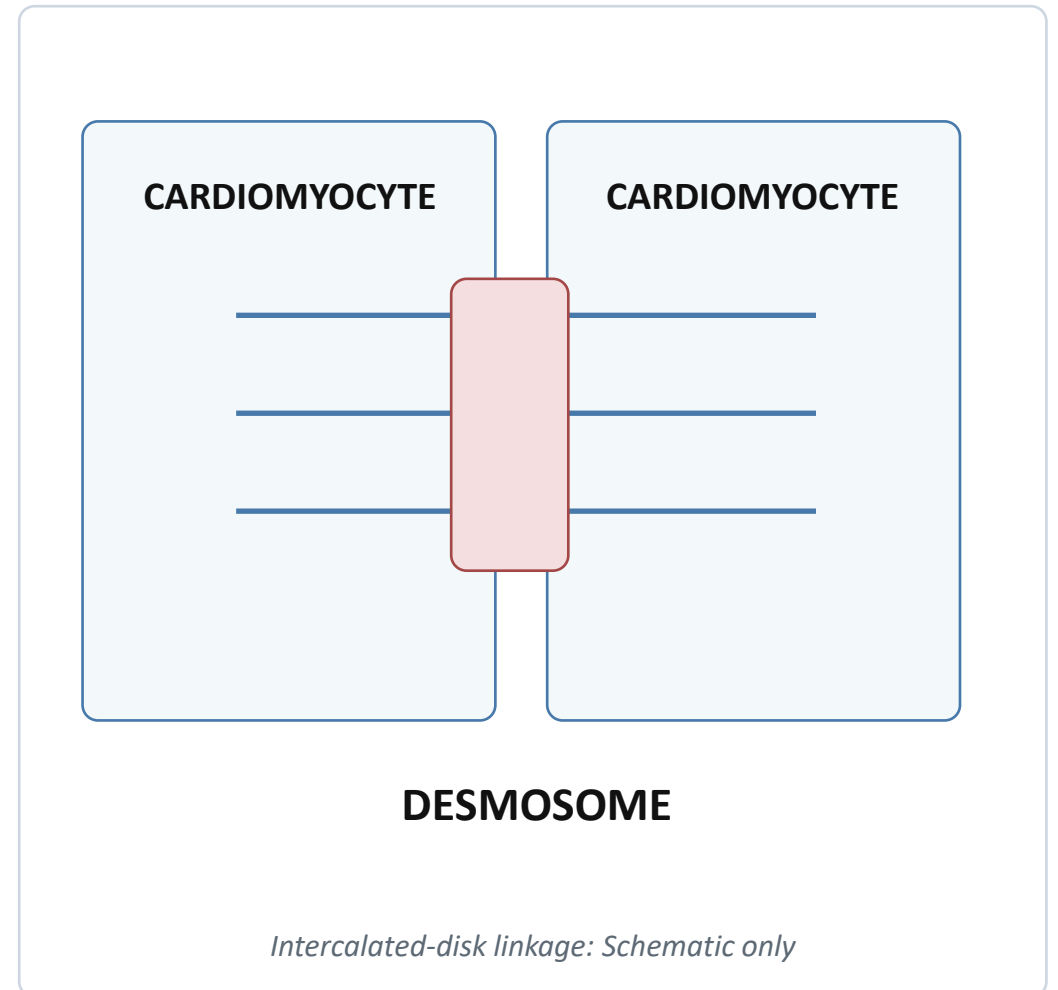
The intercalated disk: A structural-electrical interface

- Intercalated disks connect adjacent cardiomyocytes.
- Desmosomes provide mechanical adhesion under repetitive contraction.
- Disruption of junctional integrity can promote myocardial injury and electrical heterogeneity.
- A schematic illustrates the concept; It is not an ultrastructural image.



What a desmosome accomplishes

- Transmembrane cadherins link adjacent myocardial cells.
- Plaque proteins couple the membrane complex to intracellular filaments.
- The junction supports tissue integrity during repetitive mechanical strain.



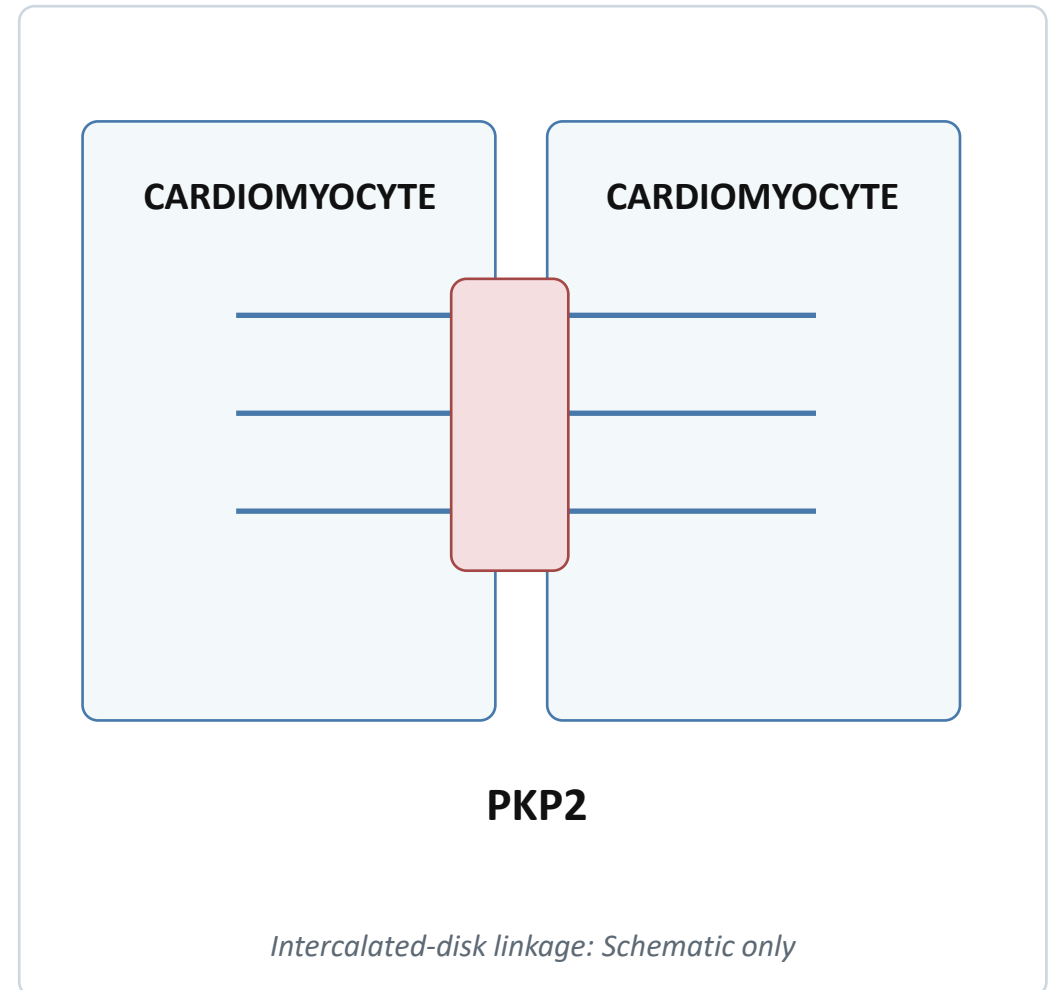
Selected desmosomal genes in ARVC

Gene	Protein	Functional compartment
PKP2	Plakophilin-2	Desmosomal plaque
DSP	Desmoplakin	Plaque-to-filament link
DSG2	Desmoglein-2	Transmembrane cadherin
DSC2	Desmocollin-2	Transmembrane cadherin
JUP	Plakoglobin	Desmosomal plaque

Gene associations reflect established clinical evidence; Variant interpretation remains gene- and allele-specific.

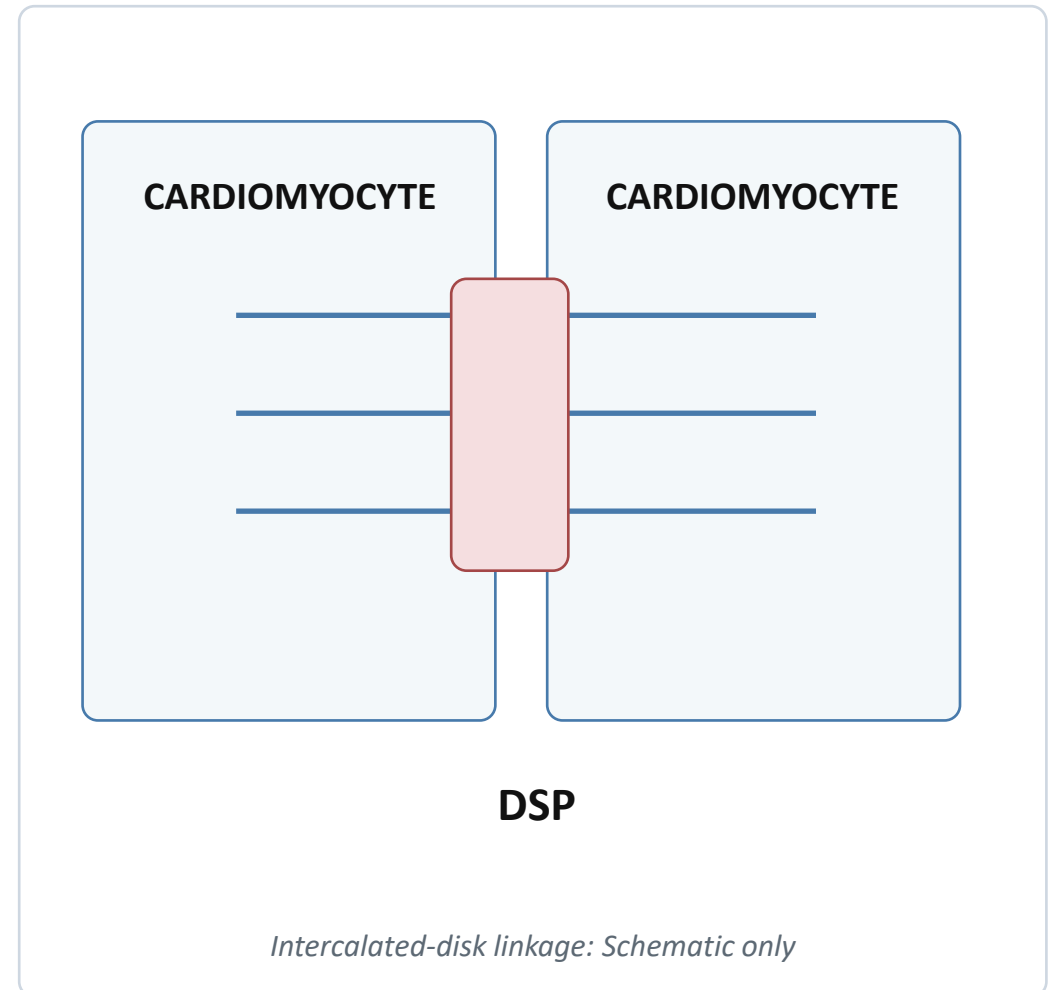
Plakophilin-2: Junctional plaque protein

- PKP2 encodes plakophilin-2, a key desmosomal plaque component.
- Pathogenic PKP2 variants are a major cause of classic ARVC.
- The gene–disease association does not mean every PKP2 variant is pathogenic.



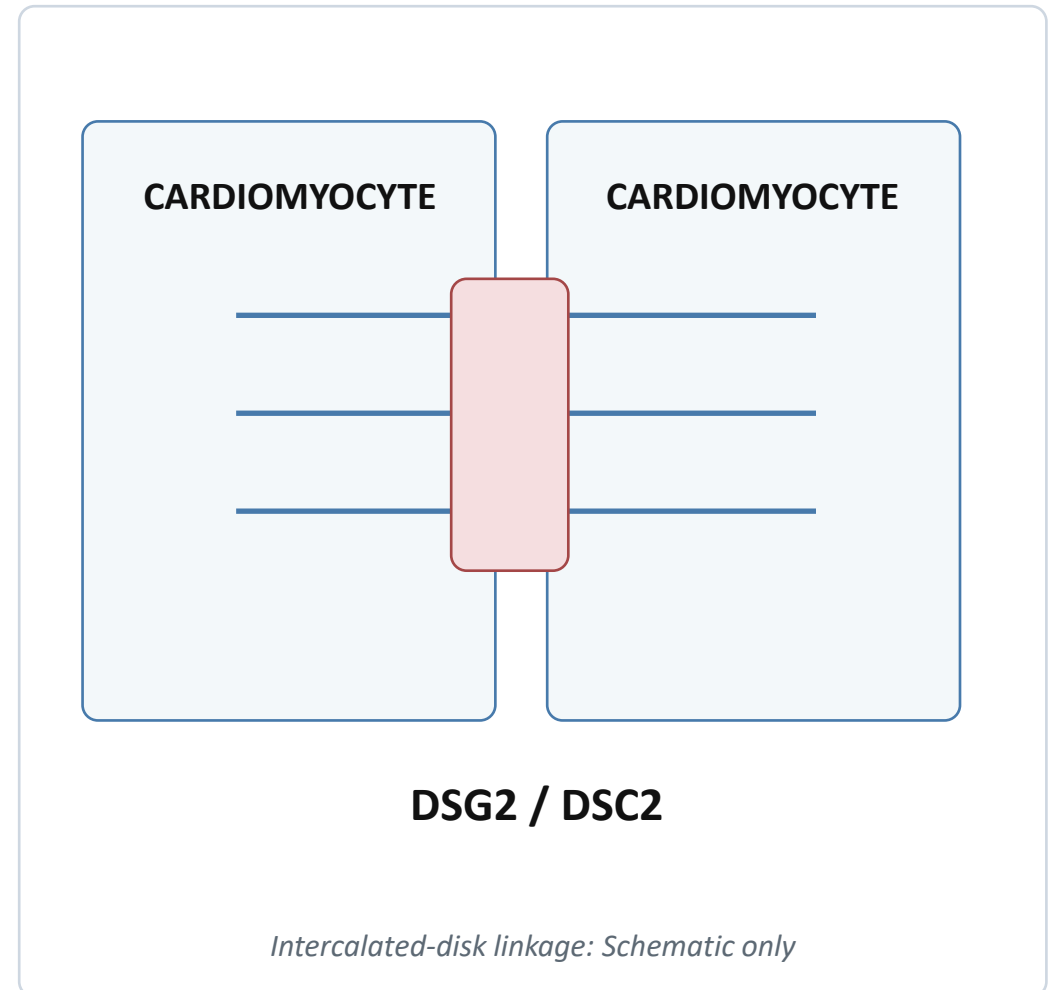
Desmoplakin links junctions to filaments

- DSP encodes desmoplakin, connecting desmosomal plaque structures with intermediate filaments.
- DSP-associated disease frequently includes substantial LV involvement.
- Inflammation-like episodes may complicate differentiation from myocarditis.



Desmoglein and desmocollin: Membrane adhesion

- DSG2 and DSC2 encode desmosomal cadherins.
- They mediate cell–cell junctional adhesion.
- Most associated ARVC is autosomal dominant; Rare biallelic disease occurs.



Plakoglobin and the Naxos association

- JUP encodes plakoglobin, a desmosomal component.
- Biallelic pathogenic JUP variants underlie the recessive Naxos syndrome.
- Naxos syndrome couples cardiomyopathy with palmoplantar keratoderma and characteristic woolly hair.
- This syndromic exception helps link skin and cardiac desmosome biology.

JUP (biallelic)

**Arrhythmogenic
cardiomyopathy**

**Palmoplantar
keratoderma**

Woolly hair

Organizing framework — interpret each domain clinically

Non-desmosomal contributors

- DES encodes desmin, an intermediate-filament protein interacting with the junctional apparatus.
- TMEM43 and PLN are among other established or moderately supported ARVC-associated genes.
- Gene–phenotype interpretation depends on evidence for the specific gene and variant.
- Not all clinically suspected cases receive a molecular diagnosis.

Gene validity

Pathogenic variant

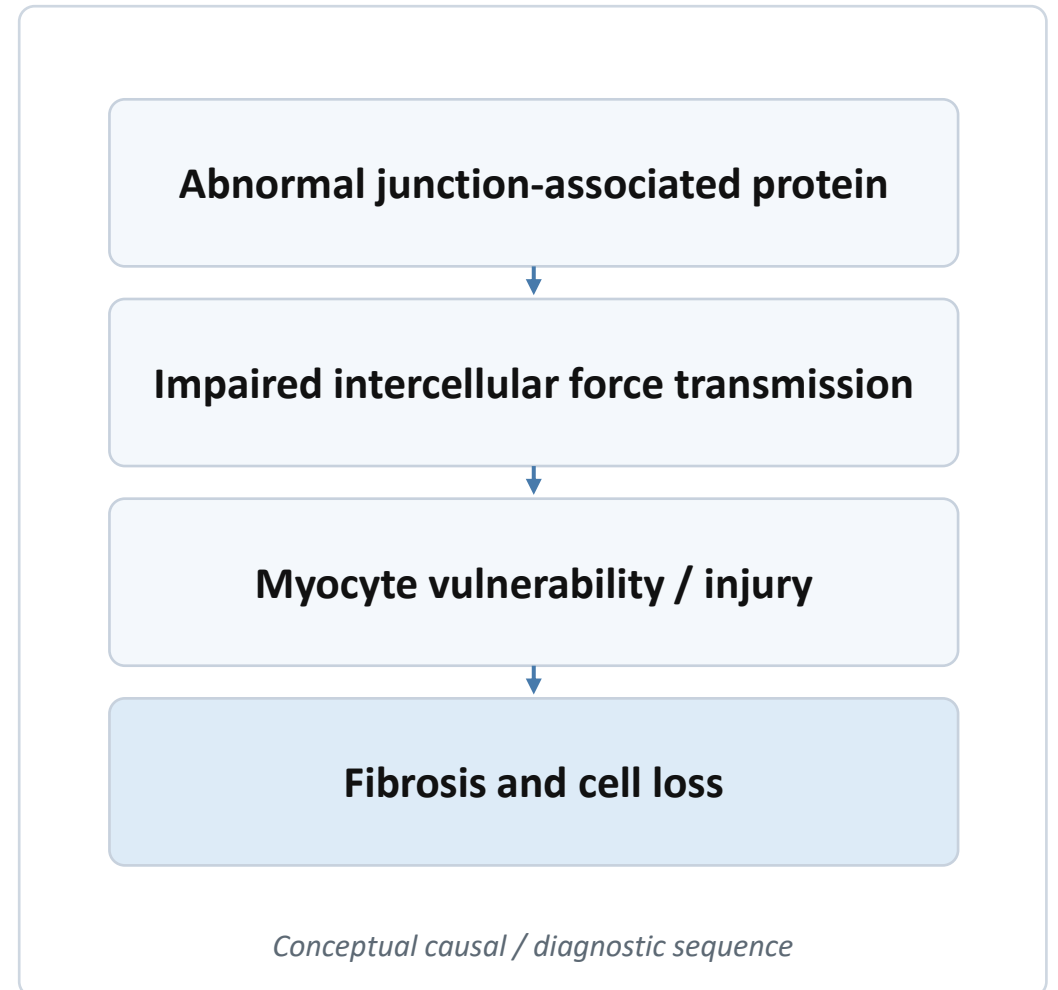
Clinical phenotype

Family segregation

Organizing framework — interpret each domain clinically

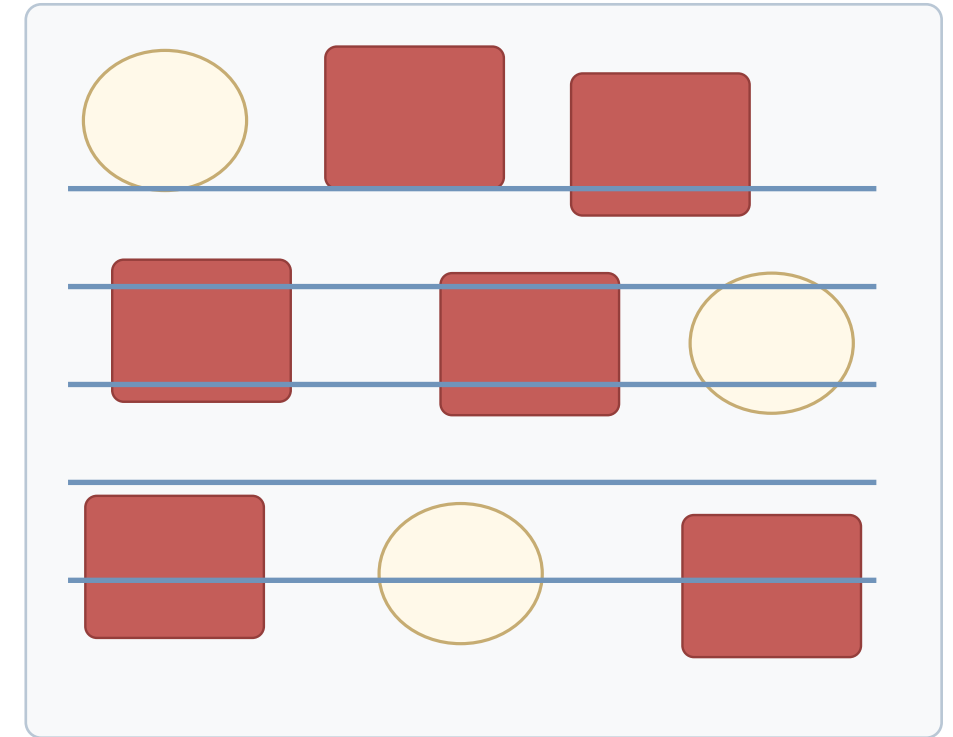
Mechanical coupling to tissue injury

- The detailed molecular sequence varies across genotypes.
- Avoid inferring a specific signaling pathway solely from the histologic phenotype.



Why myocyte loss matters

- Contracting myocardium is progressively replaced by noncontractile tissue.
- Patchy surviving cardiomyocyte bundles become separated by fibrosis.
- Both ventricular mechanics and electrical conduction can be affected.
- Fat and scar are not interchangeable biological components.



Myocytes

Collagen scar

Adipocytes

Conceptual tissue schematic — not histology or a patient specimen

How structural remodeling favors arrhythmia

- Replacement fibrosis provides an arrhythmogenic substrate.
- Anatomic scar burden and electrical risk are related but not identical.

Discontinuous surviving myocyte bundles



Spatially heterogeneous conduction

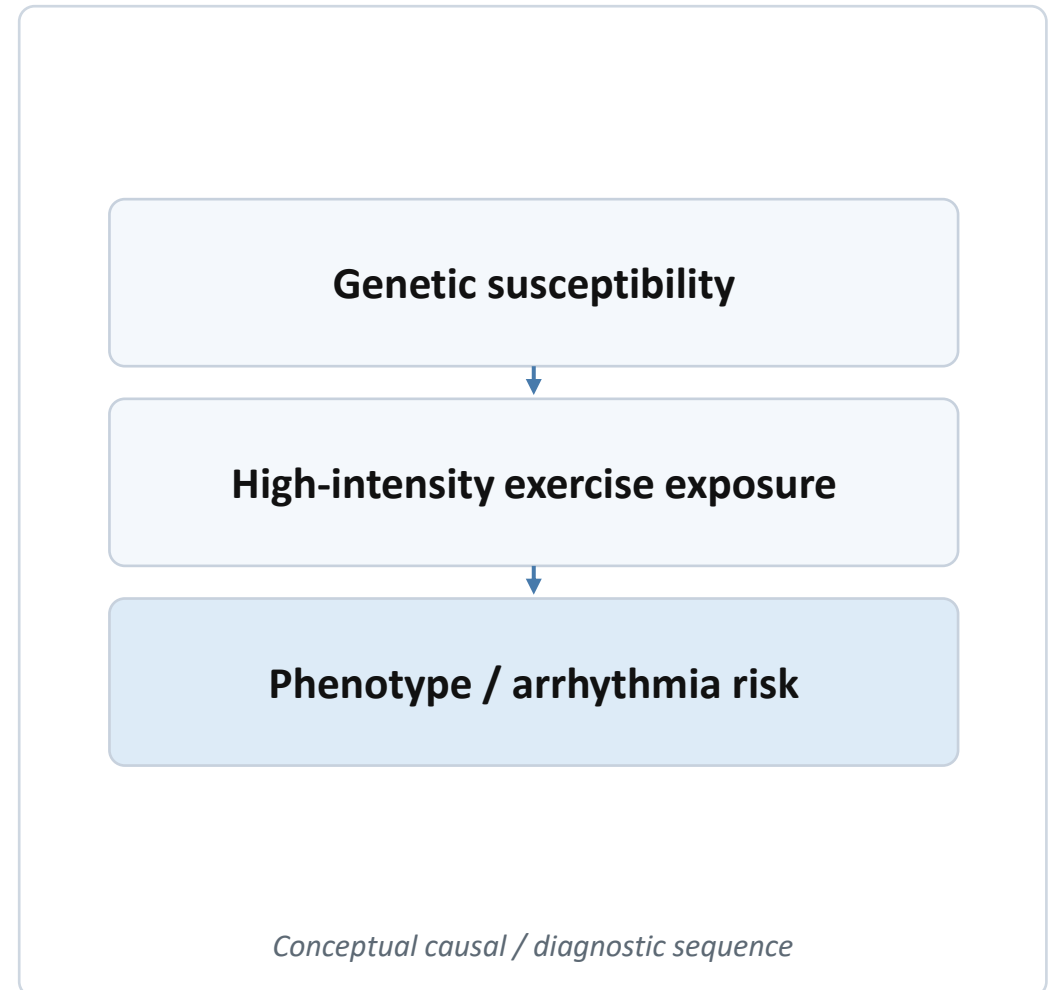


Potential re-entry / ventricular tachycardia

Conceptual causal / diagnostic sequence

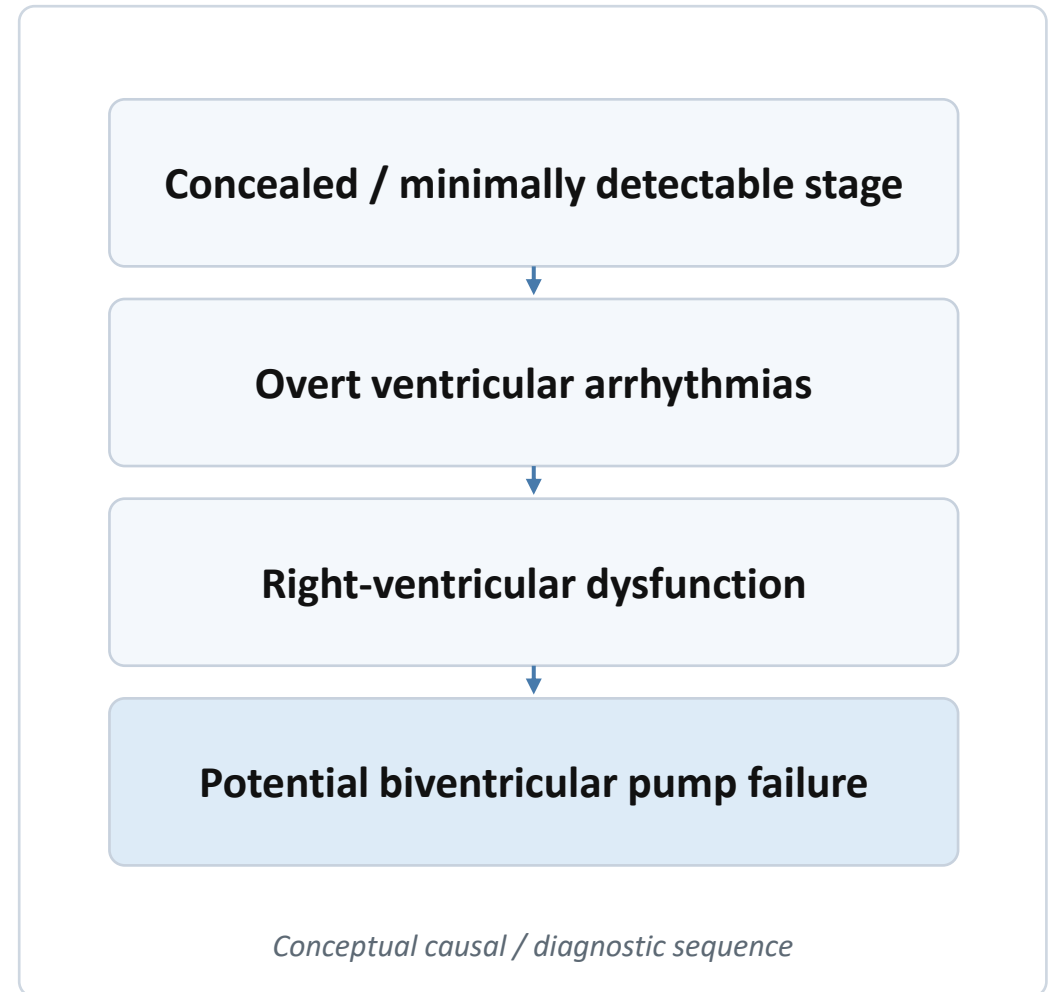
Exercise is a clinically relevant modifier

- High-intensity endurance exercise is associated with greater phenotype expression and ventricular arrhythmia risk in ARVC.
- The 2019 HRS consensus addresses exercise restriction in affected individuals.
- Activity counseling is individualized; Risk is not captured by genetics alone.



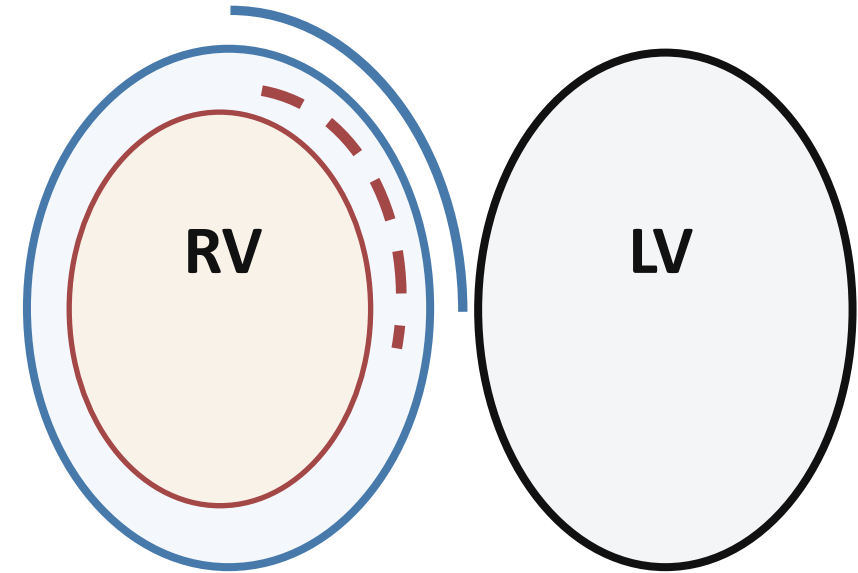
Described clinical progression

- These are conceptual phases; Patients do not necessarily traverse every phase in order.



Gross hallmark: Right-ventricular wall attenuation

- Loss of contractile myocardium can leave the RV free wall markedly thin.
- The right ventricle may be dilated, sometimes greatly.
- Near-transmural fibrofatty replacement is illustrated Fig. 12.31.
- Severe dilation can resemble dilated cardiomyopathy.



Classic RV-predominant remodeling

Simplified chamber schematic — not a gross specimen

Gross distribution is often regionally uneven

- Classic sites include the RV inflow/free wall, outflow tract, and apex.
- Regional thinning, dilation, and aneurysmal change may coexist.
- A grossly unremarkable zone does not rule out adjacent disease.

RV inflow / free wall

RV outflow tract

RV apex

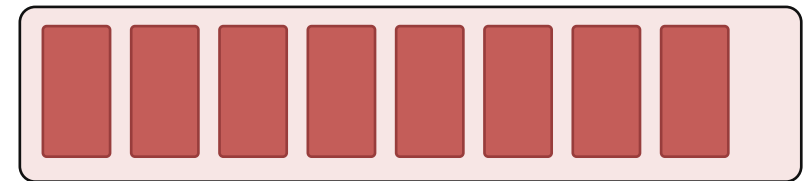
LV can also be involved

Organizing framework — interpret each domain clinically

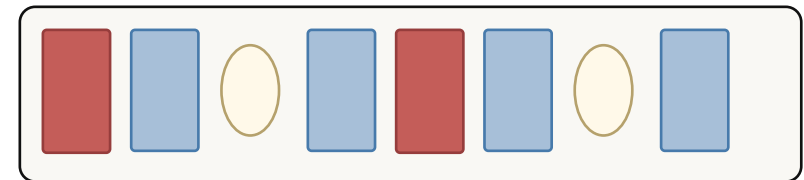
Native gross schematic: Progressive remodeling

- The conceptual diagram contrasts an intact RV wall with fibrofatty thinning.
- It illustrates distribution, not a measured wall thickness or patient specimen.
- Robbins' authentic Fig. 12.31 is the source description for near-transmural replacement.

Preserved RV wall

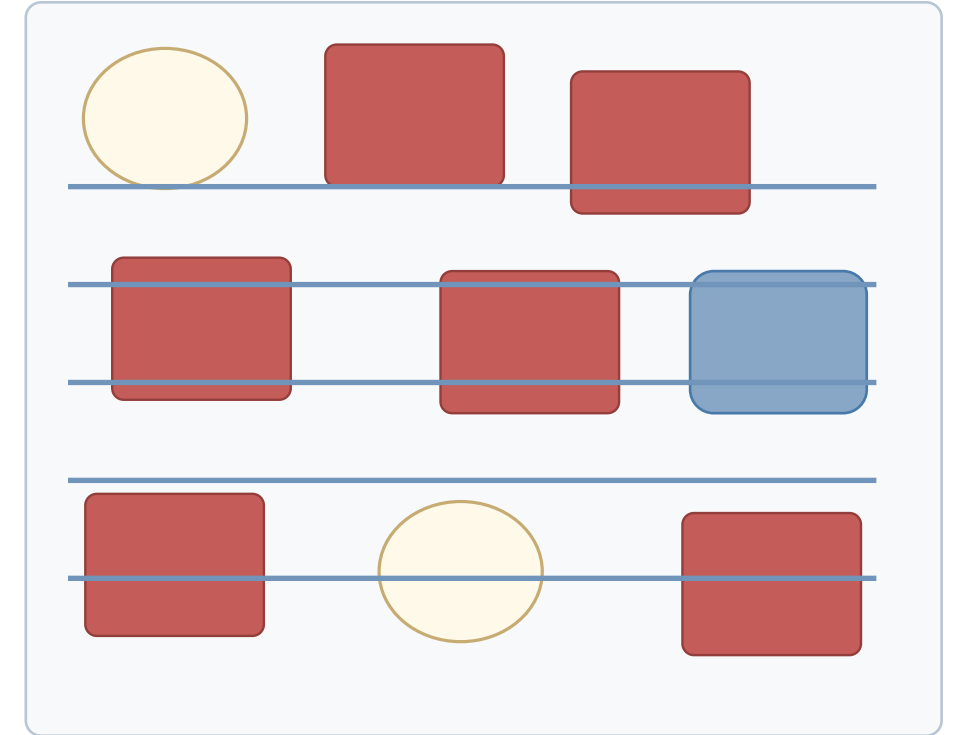


ARVC: Attenuated wall



Histology: Myocyte dropout

- Residual myocardium may be fragmented into discontinuous islands.
- Myocyte loss is the primary alteration; Adipose tissue alone is not diagnostic.
- Use the degree and distribution of myocardial replacement, not a fat-only impression.



Myocytes

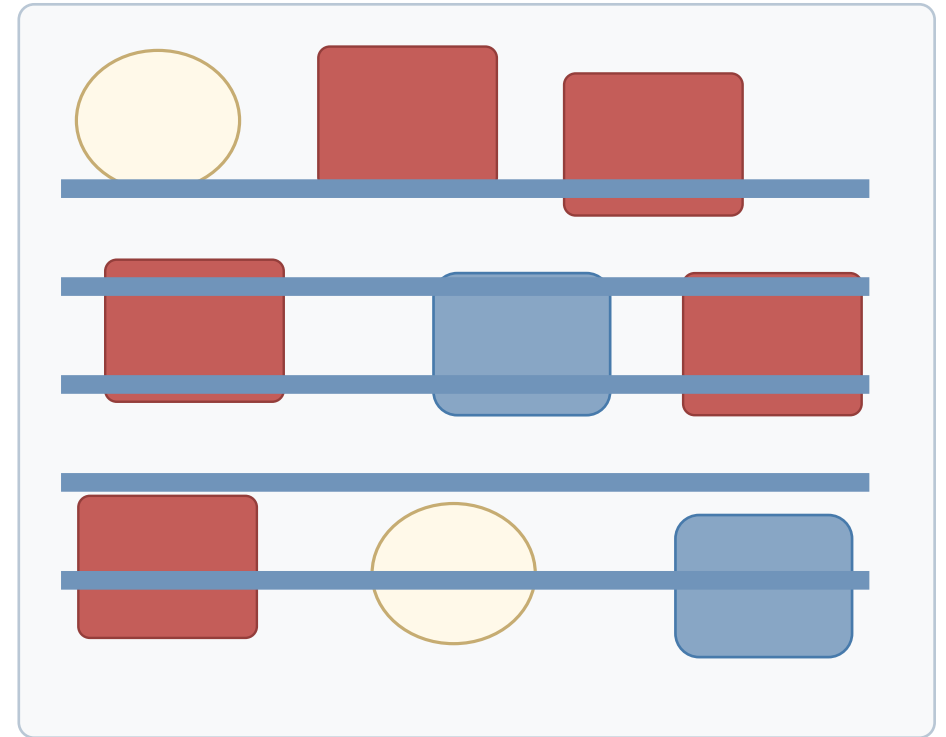
Collagen scar

Adipocytes

Conceptual tissue schematic — not histology or a patient specimen

Histology: Replacement fibrosis

- Collagen-rich scar replaces lost myocardium.
- Fibrosis may surround residual bundles of viable cardiomyocytes.
- This architectural discontinuity supplies a substrate for abnormal electrical propagation.



Myocytes

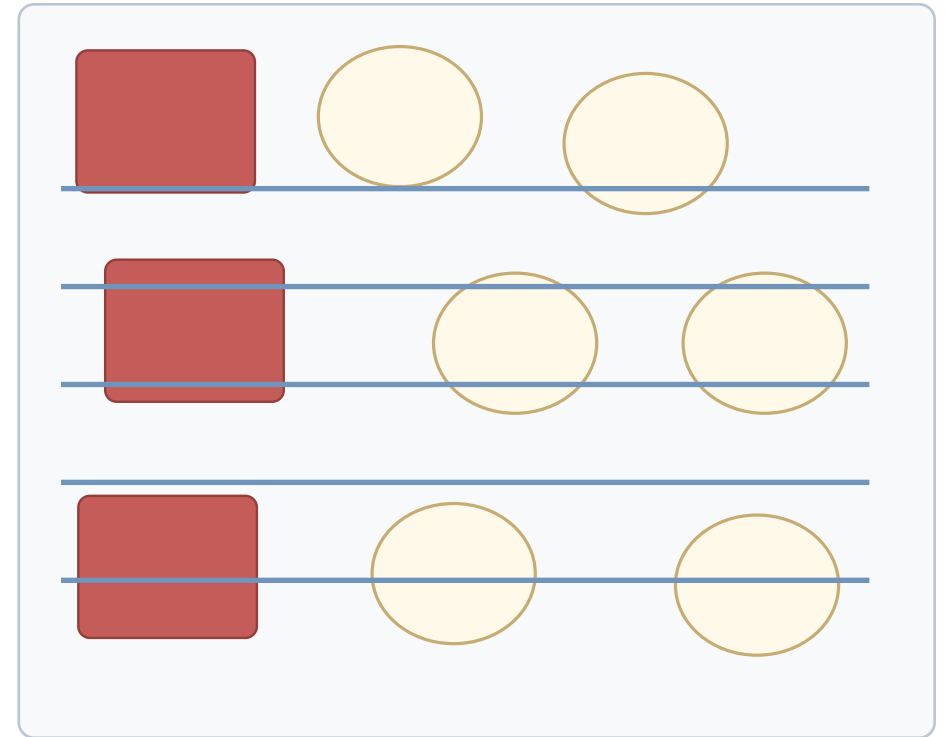
Collagen scar

Adipocytes

Conceptual tissue schematic — not histology or a patient specimen

Histology: Fatty replacement

- Adipocytes accompany the fibrotic replacement process in classic ARVC.
- Fat-containing replacement can involve much of the RV wall.
- The relevant lesion is fibrofatty myocardial replacement in the proper clinical context.



Myocytes

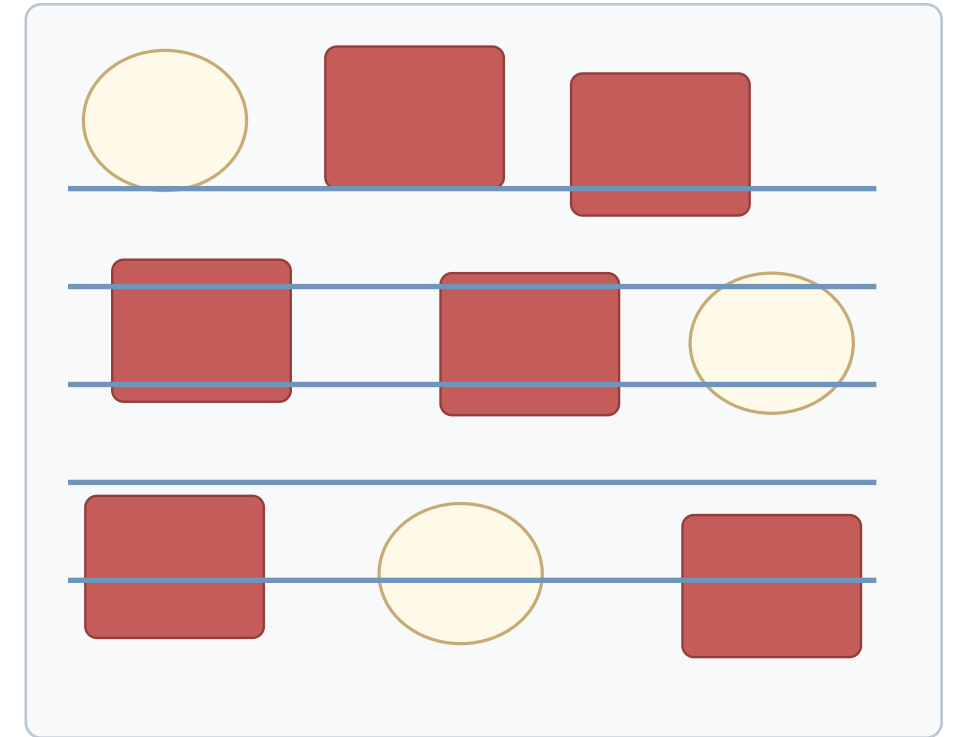
Collagen scar

Adipocytes

Conceptual tissue schematic — not histology or a patient specimen

What Masson trichrome can demonstrate

- In the Robbins figure description, myocytes stain red while collagen is blue.
- Adipose tissue appears as clear spaces after routine tissue processing.
- The stain can help separate fibrosis from retained viable myocardium.
- The schematic shown is not an authentic stained section.



Myocytes

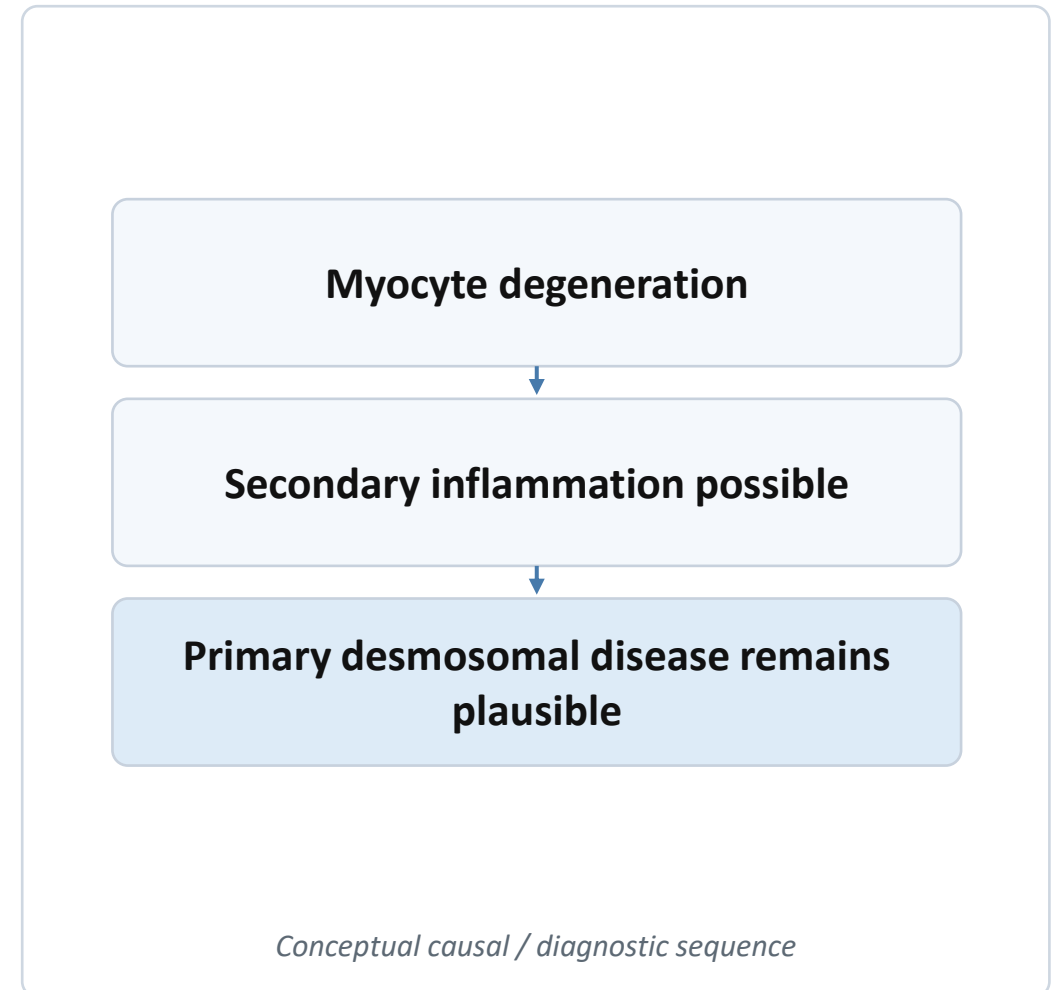
Collagen scar

Adipocytes

Conceptual tissue schematic — not histology or a patient specimen

Microscopic inflammation is not the defining cause

- Mononuclear inflammatory cells can surround degenerating cardiomyocytes.
- Robbins explicitly does not classify ARVC as primarily inflammatory.
- An inflammatory infiltrate alone does not establish myocarditis as the primary disease.



Interpretation pitfall: RV fat is nonspecific

- Physiologic or age-related RV adipose tissue may be encountered.
- Fat without fibrosis and demonstrable myocyte loss is not sufficient for ARVC.
- Sampling, topography, and clinical context prevent overdiagnosis.

Finding alone

Specificity limitation

**Corroborating
evidence**

Differential diagnosis

Organizing framework — interpret each domain clinically

Histologic sampling is inherently limited

- ARVC may be patchy, so a biopsy can miss disease.
- Biopsy of the thin RV free wall also carries procedural limitations.
- A negative specimen does not independently exclude a multisystem-criterion diagnosis.

Patchy RV lesions

Limited biopsy area

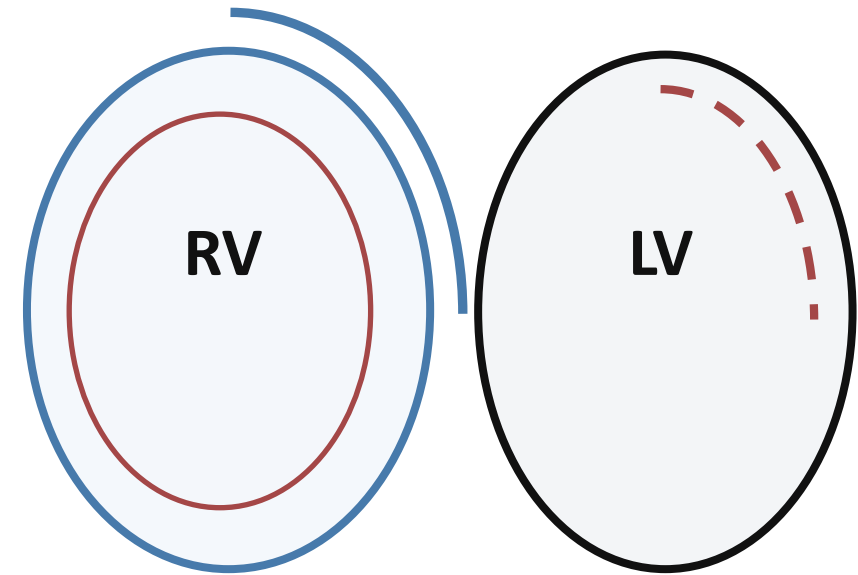
False negative risk

**Multimodal
diagnosis**

Organizing framework — interpret each domain clinically

Left-ventricular involvement changes the phenotype

- Fibrofatty myocardial changes need not remain confined to the right ventricle.
- LV-dominant disease is recognized within the broader arrhythmogenic cardiomyopathy spectrum.
- Some genotypes, particularly DSP, show increased LV involvement.



LV-predominant variant

Simplified chamber schematic — not a gross specimen

Morphologic comparison: ARVC versus DCM

Finding	Classic ARVC	Typical DCM
Main distribution	RV-predominant; LV possible	Often diffuse chamber involvement
Histology	Fibrofatty replacement + myocyte loss	Nonspecific myocyte change + fibrosis
Functional emphasis	Arrhythmia may precede failure	Global systolic dysfunction prominent
Overlap	Advanced chamber dilation	Can mimic arrhythmogenic phenotype

Classification should integrate genetics, morphology, imaging and rhythm data.

Differential diagnoses and useful discriminators

Mimic	Overlap	Important discriminator
Idiopathic DCM	Ventricular dilation, arrhythmia	Fibrofatty distribution and genotype
Myocarditis	Inflammation, scar, VT	Clinical course, tissue pattern, inflammation
Cardiac sarcoidosis	Scar, conduction disease, VT	Granulomas or extracardiac evidence
Athlete-related RV adaptation	Enlarged RV	Physiology plus absence of corroborating criteria

Why focal myocarditis is a genuine phenocopy

- Both myocarditis and arrhythmogenic cardiomyopathy can manifest with ventricular arrhythmia.
- Fibrosis and inflammation are not exclusive to either disorder.
- Certain DSP genotypes can produce inflammatory presentations.
- Diagnosis requires an integrated phenotype rather than one tissue feature.

Shared inflammation

Scar pattern

Genotype

Extracardiac findings

Organizing framework — interpret each domain clinically

Clinical presentation: Palpitations and syncope

- Palpitations may reflect premature ventricular beats or ventricular tachycardia.
- Syncope, especially unexplained or exertional, warrants serious evaluation.
- The earliest symptoms may be electrical rather than congestive.
- Family history can supply the initial clue.

Palpitations

**Presyncope /
syncope**

VT/VF

Heart failure

Organizing framework — interpret each domain clinically

Ventricular tachycardia: Chamber-of-origin clue

- Ventricular rhythms arising in the RV commonly produce a left bundle branch block (LBBB)-like QRS morphology.
- QRS configuration helps localize origin but is not diagnostic in isolation.
- Documented morphology and axis contribute to formal diagnostic criteria.

RV ventricular origin

LBBB-like QRS

Assess axis

Clinical context

Organizing framework — interpret each domain clinically

Sudden cardiac death is a major clinical concern

- Malignant ventricular tachyarrhythmias can lead to sudden cardiac death.
- Serious events may occur before severe heart failure.
- Syncope, sustained arrhythmia, ventricular dysfunction, and family factors enter risk assessment.

VT / VF

Syncope

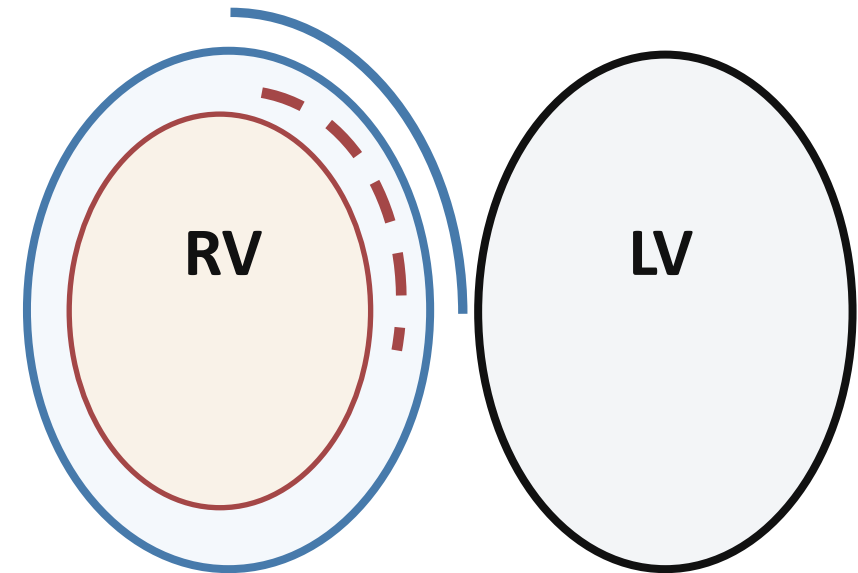
Potential SCD

Individualized risk

Organizing framework — interpret each domain clinically

Right-sided failure: A structural consequence

- Extensive RV myocyte loss impairs contractile function.
- RV dilation can accompany reduced pump performance.
- Progression may produce systemic venous congestion and reduced forward flow.
- Some patients develop concomitant LV dysfunction.



Classic RV-predominant remodeling

Simplified chamber schematic — not a gross specimen

When should ARVC be considered?

- Unexplained ventricular tachycardia with RV-origin morphology.
- Young or middle-aged person with syncope and family history of sudden death.
- Disproportionate RV abnormalities on echo/CMR.
- Relatives of a person with confirmed ARVC or a familial pathogenic variant.

Syncope / VT

Family history

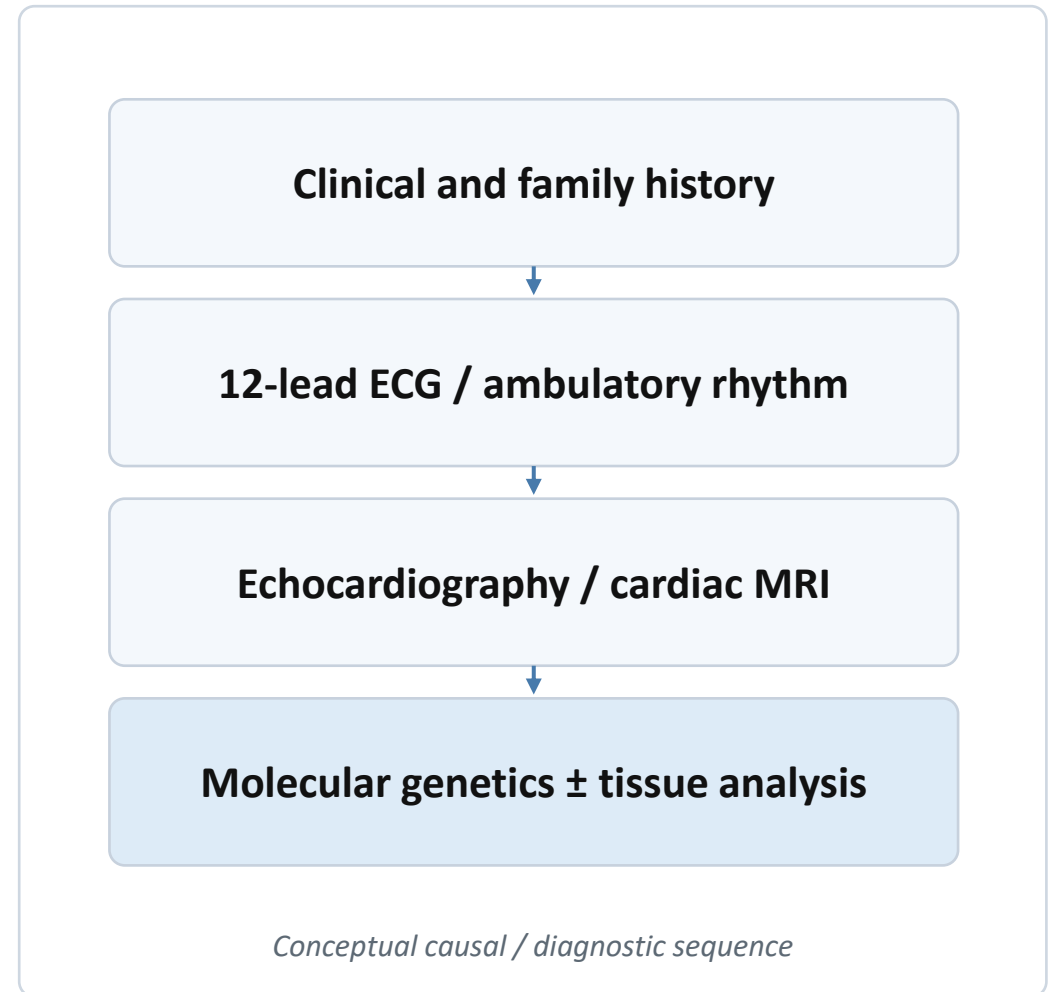
RV imaging

Genetic context

Organizing framework — interpret each domain clinically

Diagnosis uses converging evidence

- No single routine test definitively establishes or excludes the disorder.



ECG: Repolarization abnormalities

- T-wave inversion in right precordial leads is one diagnostic category.
- The lead distribution, age, and presence of complete right bundle branch block affect interpretation.
- An isolated abnormal T wave is not synonymous with ARVC.

Lead distribution

Pubertal stage / age

Bundle branch status

**Corroborating
domains**

Organizing framework — interpret each domain clinically

ECG: Depolarization abnormalities

- Epsilon waves are low-amplitude terminal signals after the QRS complex.
- They are a recognized criterion but should not be interpreted outside an experienced ECG assessment.
- Electrical criteria are integrated with imaging and clinical history.

QRS terminus

Low-amplitude signal

**Right precordial
leads**

Not standalone proof

Organizing framework — interpret each domain clinically

Ambulatory rhythm monitoring

- Holter or longer monitoring may document premature ventricular complexes and nonsustained VT.
- Arrhythmia morphology, burden, and symptoms provide complementary information.
- A normal short recording does not eliminate intermittent ventricular arrhythmias.

PVC burden

Nonsustained VT

Sustained VT

**Symptom–rhythm
relation**

Organizing framework — interpret each domain clinically

Echocardiography evaluates RV function

- Look for RV enlargement and regional wall-motion abnormalities.
- Regional akinesia, dyskinesia, or aneurysm may support a diagnostic pattern.
- The thin, complex RV geometry can make subtle abnormalities difficult to measure.

RV dimensions

Regional motion

Regional aneurysm

**Measurement
context**

Organizing framework — interpret each domain clinically

Cardiac MRI: Morphology and tissue

- CMR evaluates RV and LV chamber size, contraction, and regional motion.
- Late gadolinium enhancement (LGE) detects a scar-compatible myocardial tissue pattern.
- Interpret imaging abnormalities alongside ECG, genetics, and clinical data.

RV + LV size

Regional motion

Scar (LGE)

**Integrated
interpretation**

Organizing framework — interpret each domain clinically

MRI fat signal alone is not a diagnostic shortcut

- The Padua approach emphasizes regional structural/functional change and myocardial scar.
- Isolated fat signal lacks sufficient specificity to diagnose ARVC.
- Scar distribution, image quality, and alternative diagnoses matter.

Finding alone

Specificity limitation

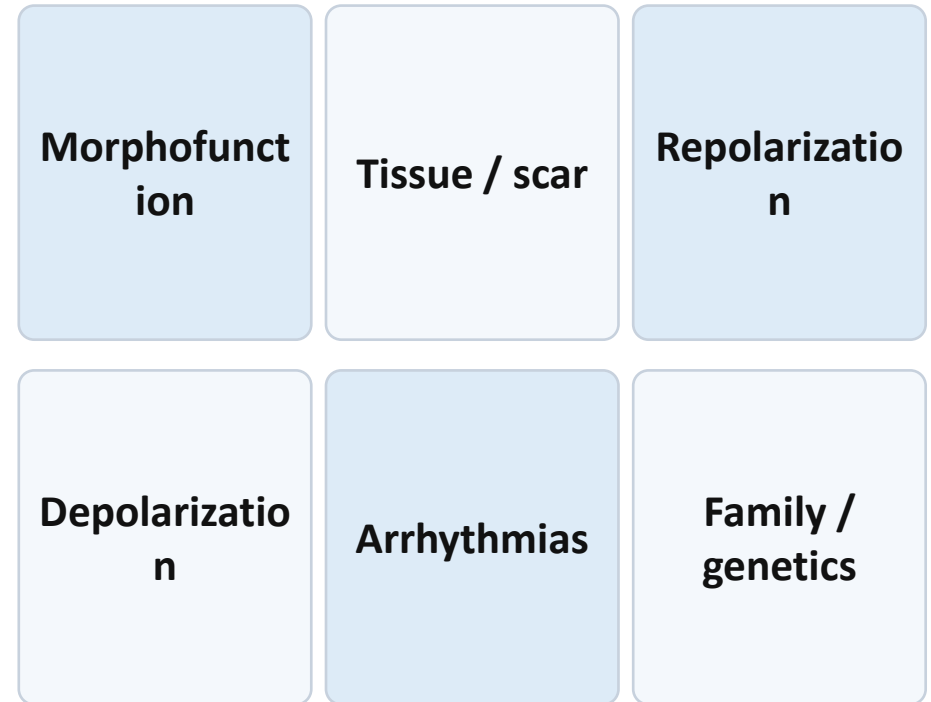
**Corroborating
evidence**

Differential diagnosis

Organizing framework — interpret each domain clinically

The Padua criteria: Six evidence domains

- Morphofunctional ventricular abnormalities.
- Myocardial structural/tissue characterization.
- Repolarization and depolarization ECG changes.
- Ventricular arrhythmias and family/genetic findings.



Organizing framework — interpret each domain clinically

Padua interpretation needs structural corroboration

- Padua criteria recognize both RV and LV phenotypes.
- At least one morphofunctional or structural criterion is required to diagnose arrhythmogenic cardiomyopathy.
- Major and minor findings are combined across diagnostic categories.
- Do not use a purely electrical finding to assign a structural disease phenotype.

RV features

LV features

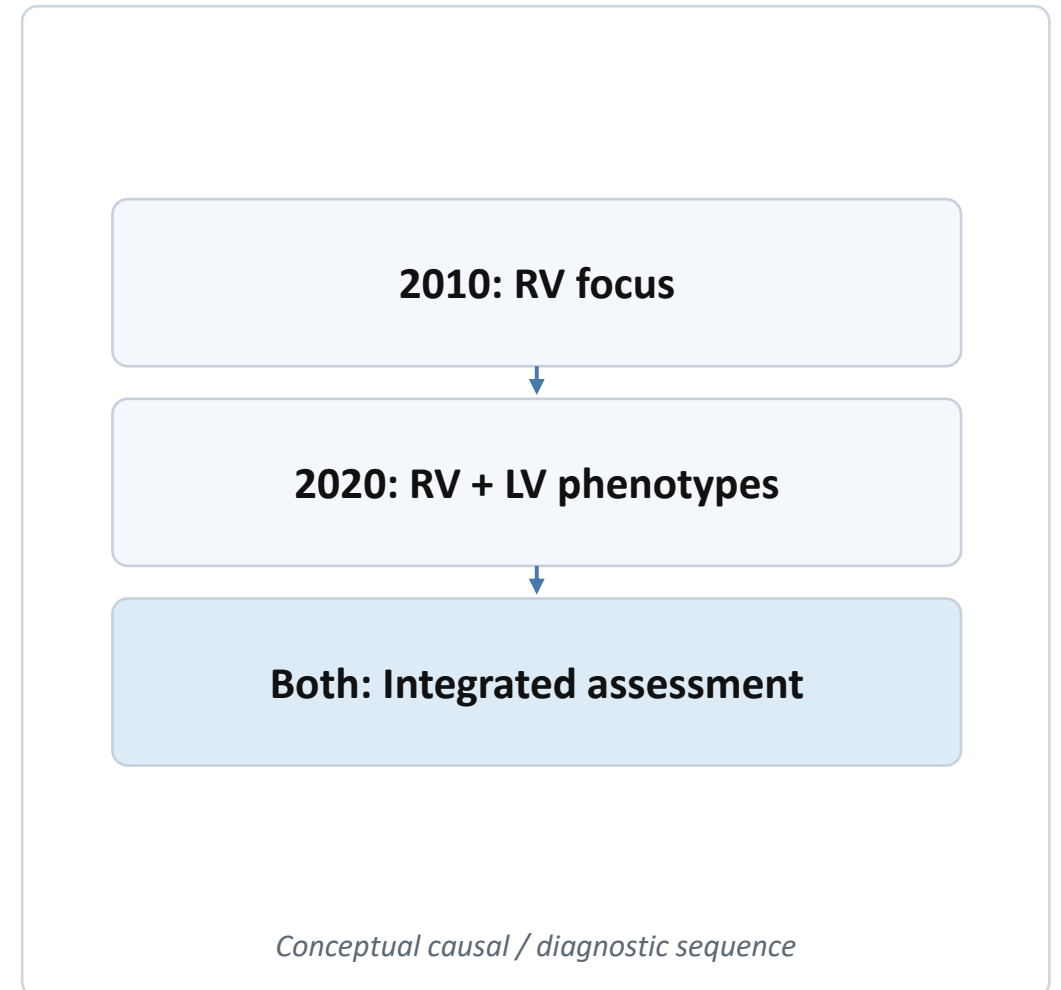
Structural criterion

**Major / minor
combination**

Organizing framework — interpret each domain clinically

2010 Task Force and 2020 Padua: Not identical

- The 2010 Task Force criteria focused on the classic RV phenotype.
- The 2020 Padua framework explicitly incorporates LV tissue characterization.
- Use one named framework consistently when describing diagnostic certainty.
- Criteria are not interchangeable by copying isolated cutoffs.



Genetic testing: The right interpretation

- A pathogenic or likely pathogenic variant in a validated gene can support diagnosis.
- A variant of uncertain significance does not confirm or exclude disease.
- A negative gene panel does not rule out a clinically compelling phenotype.
- Test the affected proband first when possible.

Gene validity

Pathogenic variant

Clinical phenotype

Family segregation

Organizing framework — interpret each domain clinically

Variant interpretation is not gene-name matching

- The gene–disease association must be established.
- Variant pathogenicity requires classification using clinical and molecular evidence.
- Penetrance and phenotype influence interpretation.
- A genetic result must be reconciled with ECG, imaging and family history.

**Gene–disease
validity**

Variant classification

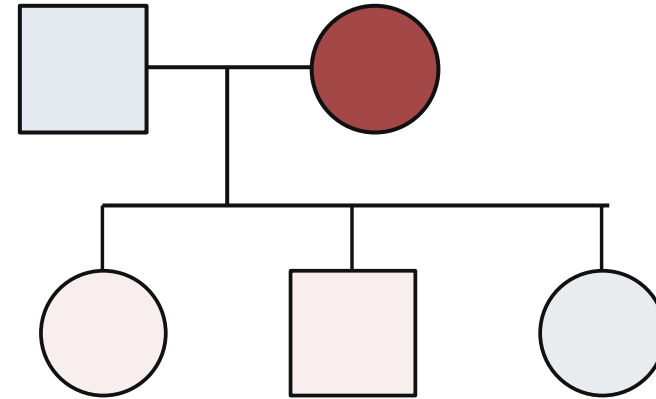
Phenotypic match

Family segregation

Organizing framework — interpret each domain clinically

Family screening is a longitudinal process

- First-degree relatives are offered ECG and cardiac imaging assessment.
- When a familial pathogenic variant exists, cascade genetic testing may be used.
- Genotype-positive relatives require periodic clinical surveillance.
- An isolated negative examination early in life may be insufficient.



Inheritance can be shared; Disease expression differs

Illustrative pedigree, not real-family evidence

Risk assessment is not a single biomarker

- Prior sustained VT/VF and arrhythmic syncope are key clinical concerns.
- Ventricular function, arrhythmia burden, genotype, and family context influence assessment.
- Decisions about an implantable cardioverter–defibrillator require specialist evaluation.
- Avoid extrapolating group-risk statistics to an individual without validated assessment.

Prior events

Arrhythmia burden

Ventricular function

**Expert shared
decisions**

Organizing framework — interpret each domain clinically

Core management principles

- Individualized reduction of strenuous exercise exposure where advised.
- Arrhythmia management and consideration of an ICD in appropriately selected patients.
- Treatment of ventricular dysfunction and heart failure when present.
- Coordinated cardiology, electrophysiology and genetics follow-up.

Exercise advice

Arrhythmia / ICD

HF care

Genetic / family care

Organizing framework — interpret each domain clinically

Pathology report: What is worth documenting?

- Distribution of RV versus LV involvement and chamber dimensions.
- Extent and location of viable cardiomyocyte loss, fibrosis, and adipose replacement.
- Presence and characterization of inflammation and other competing lesions.
- Correlate pathologic suspicion with familial, genetic and clinical findings.

Distribution

Myocyte loss

Fibrosis + fat

Differential lesions

Organizing framework — interpret each domain clinically

Clinical application: An arrhythmia-first presentation

- A 29-year-old has recurrent exertional palpitations and unexplained syncope.
- A sibling died suddenly in early adulthood; The cause was never established.
- Echocardiography raises suspicion for regional RV dysfunction.
- Question: Which test domains should be assembled before assigning a diagnosis?

Case interpretation: Assemble independent domains

- Obtain a detailed family pedigree and review available prior records.
- Document 12-lead ECG findings and ventricular arrhythmias with ambulatory monitoring.
- Characterize RV and LV morphology, function and scar with expert imaging.
- Offer genetic counseling and suitable panel testing; Adjudicate against a named framework.

Histology application: What does the lesion mean?

- Specimen description: Thin RV wall; Surviving red-staining myocytes amid blue collagen and adipocytes.
- This combination supports fibrofatty myocardial replacement in the appropriate setting.
- Question: Would abundant adipocytes alone establish ARVC?
- Answer: No—evaluate myocyte loss, fibrosis, distribution, and other findings.

Integrated synthesis: Genotype to clinical phenotype

- Desmosomal and related protein variants can weaken cardiomyocyte junctional integrity.
- Myocyte injury and replacement produce a heterogeneous arrhythmogenic substrate.
- Electrical instability may become evident before advanced pump failure.
- Diagnosis is strongest when morphology, electrical data, imaging and genetics converge.

Junctional susceptibility



Myocyte loss / scar



Electrical + mechanical phenotype

Conceptual causal / diagnostic sequence

High-yield diagnostic cautions

- Fat in the right ventricle by itself is not ARVC.
- Normal global RV function does not exclude an early arrhythmogenic phenotype.
- A variant of uncertain significance is not equivalent to a pathogenic variant.
- Inflammation does not automatically make the primary diagnosis myocarditis.

Fat ≠ diagnosis

Normal EF ≠ safe

VUS ≠ positive

**Inflammation ≠
primary cause**

Organizing framework — interpret each domain clinically

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