

COR	LOE	Recommendations	References
III: Harm	B-NR	Individuals with ARVC should not participate in competitive or frequent high-intensity endurance exercise as this is associated with increased risk of ventricular arrhythmias and promoting progression of structural disease.	80,171,183,253–255,258

Competitive or frequent high-intensity endurance exercise is related to the extent of RV and LV dysfunction in patients with ARVC. Additionally, such exercise is associated with poorer outcomes for ventricular arrhythmias, whereas reducing exercise has a more favorable arrhythmic prognosis. Aiding patients and at-risk family members in making choices about participation in various types of exercise involves ongoing discussion and shared decision making.

Competitive exercise includes participation in “an organized team or individual sport that requires regular competition against others as a central component, places a high premium on excellence and achievement, and requires some form of systematic (and usually intense) training” as defined by the AHA/ACC Scientific Statement for Eligibility and Disqualification Recommendations for Competitive Athletes with Cardiovascular Abnormalities.²⁴⁹

Endurance exercise includes class C and B sports in these guidelines.²⁴⁸ Data on the effect of static exercise (Class A) on outcomes are largely absent from the literature. **Intensity** is typically measured in METs.²⁵²

For the basic science details of the mechanisms responsible for the forms of ACM, please see Section 4 Disease Mechanisms.

Section 4 Disease mechanisms

An overview of some of the disease mechanisms for ACM is shown in Figure 18.

4.1. Desmosomal defects

The cardiac ID is a highly organized structure that connects adjacent cardiomyocytes and is classically comprised of three main structures: (1) gap junctions (GJs), which metabolically and electrically connect the cytoplasm of adjacent cardiomyocytes; (2) adherens junctions (AJs), which connect the actin cytoskeleton of adjacent cells; and (3) desmosomes, which function as cell anchors and connect intermediate filaments (IFs). In addition, ion channels reside in the ID. Pathologic genetic variants in ID proteins have been associated with cardiac arrhythmias, such as BrS, ARVC, and other genetically determined ACMs.^{263,264} However, rather than being independent, all ID components work closely together by partnering with multifunctional proteins such as ZO-1, ankyrin G, and β -catenin, allowing the ID to integrate mechanical and electrical functions. GJs form a plaque surrounded by the perinexus in which free connexons reside; the connexome integrates sodium (Na_v) channels, the desmosome, and GJs; and the area composita hosts AJs and desmosomes, also integrated as adhering junctions. Furthermore, the transitional junction connects sarcomeres to the plasma membrane. The ID ensures rapid propagation of the electrical signal that initiates contraction throughout the heart and allows the cardiomyocytes to withstand the strong mechanical forces imposed by the beating of

the heart. AJs, desmosomes, GJs, and ion channels form a functional unit as the area composita. Furthermore, GJs and ion channels likely create and propagate action potentials (APs) together. Some structural components of cell–cell junctions can also interact with other ID proteins or function in signaling pathways, such as Cx43 and β -catenin. Protein deficiencies can ultimately lead not only to mechanical dysfunction (eg, AJ dysfunction) but also to arrhythmias, often via GJ remodeling, thereby illustrating the interdependency of ID components and the coupling of mechanical and electrical elements.

The lateral membrane (LM) of cardiomyocytes has a different makeup compared to the ID, hosting, among others, costameres and focal adhesions and linking sarcomeres to the extracellular matrix. The ID and LM have several proteins in common, such as vinculin and α -actinin, and ion channels.

The AJ is the primary anchor for myofibrils and connects actin filaments from adjacent cells, which allows the cell to retain its shape under mechanical stress. Furthermore, the AJ transduces signals concerning the actin cytoskeleton and senses mechanical forces on the cell. The transmembrane protein N-cadherin is the main constituent of AJs and homodimerizes with N-cadherins from adjacent cells in the extracellular space, acting as an intercellular zipper. This action provides tissue specificity during development, allowing cells to interact only with cells expressing the same cadherin. Calcium ions ensure the rod shape of N-cadherin, the intracellular domain which primarily binds β -catenin. N-cadherin also possesses regulatory functions including a role in mechanosensing. β -catenin directly interacts with the C-terminal cytoplasmic domain of N-cadherin. By associating with α -catenin and vinculin, β -catenin connects AJs to the actin cytoskeleton.

β -catenin also plays a central role in cadherin-mediated signaling and can activate the canonical Wnt signaling pathway. β -catenin translocates to the nucleus when Wnt binds its Frizzled receptor, to initiate transcription of transcription factors of the T-cell factor/lymphoid enhancer-binding factor family. The canonical Wnt pathway is crucial in cardiac development but has also been proposed as the key mechanism in certain cardiomyopathies (ie, activation induces cardiac hypertrophy). Therefore, N-cadherin has been thought to sequester β -catenin to prevent Wnt activation. Activation of the Wnt pathway increases expression of the GJ protein Cx43, and the C-terminus of Cx43 can interact with β -catenin. When Wnt is not present, cytoplasmic β -catenin is targeted for degradation by the proteasome.