Athletic Status and Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy: From Physiological Observations to Pathological Explanation

Rahul Jain, M.B.B.S., M.D., F.A.C.P * †

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a heritable condition characterized by replacement of cardiomyocytes, primarily in the right ventricle, by fibrofatty tissue. A number of genetic studies have identified mutations in various components of cardiac desmosomes that appear to precede fibrofatty replacement. The resulting disruption of normal myocardial architecture in ARVD/C results in right ventricular (RV) dysfunction, life-threatening arrhythmias and sudden cardiac death. There is a striking incidence of athletic individuals affected by this disease. Currently there is no explanation for the association between athletic activity and development of ARVD/C.

The goal of this paper is to suggest that increased levels of nitric oxide (NO) and reactive oxygen species, secondary to endurance exercise, initiates a cascade of reactions leading to fibrofatty changes in the RV and thus ARVD/C. This involves increased expression of adipogenic and fibrogenic genes as one of the steps in pathogenesis. According to the hypothesis, arrhythmias can happen in the presence or absence of pathological changes secondary to NO effects on remodeling and ion channels, respectively. Furthermore, the different effects of prolonged exercise on the RV and left ventricle (LV) could help explain the incidence of ARVD/C as a primarily RV disease. Verification of this hypothesis would have prognostic and management implications. Drugs inhibiting NO production might benefit patients with ARVD/C. A better un-
nderstanding of exercise physiology in terms of NO production would help to redefine the management scheme in terms of exercise in patients with ARVD/C. A redirection of research towards identification of special physiological markers would be appropriate, and may reveal additional steps leading from tissue exposure to NO, to pathological changes.

**Introduction**

**ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA/CARDIOMYOPATHY (ARVD/C)** is a heritable condition characterized by replacement of cardiomyocytes, primarily in the right ventricle, by fibrofatty tissue (1). The resulting disruption of normal myocardial architecture in ARVD/C can result in severe right ventricular (RV) dysfunction, life-threatening arrhythmias and sudden cardiac death. There is substantial evidence that this fibrofatty replacement is preceded by mutation-related desmosomal changes (2-9). Mutations in ARVD/C-related genes demonstrate incomplete penetrance and variable expressivity, implicating environmental factors and other genetic modifiers in the etiology of this disease.

There is a striking incidence of athletic individuals affected by this disease (10). Evidence for this association between exercise and the phenotypic expression of ARVD/C was provided by Daubert et al., (11) who found that individuals with ARVD/C performing intensive and regular sport activities had symptoms at a younger age and that palpitations, syncope, and sudden death were more frequent in the athletic group than in patients with ARVD/C who were not athletically inclined. This clinical finding has been validated in animal models (12). Kirchhof et al. showed that at the age of 10 months, right ventricles were enlarged in plakoglobin +/- mice (heterozygous plakoglobin deficient mice). Endurance training (8 weeks of daily swimming) caused premature right ventricular dilatation and dysfunction in plakoglobin +/- mice at 5 to 6 months of age, compared to wildtype mice, where there was no difference in training intensity between the genotypes. Training intensity correlated with training-induced right ventricular enlargement in plakoglobin +/- mice only. There was no difference in left ventricular size or function between genotypes. Right heart size and function were not different between genotypes at earlier ages (12). Though there is a strong relationship between exercise and phenotypic expression of ARVD/C, there is neither a mechanistic explanation for this, nor reasonable explanation for why ARVD/C is primarily a RV disease. In an attempt to explain how exercise is related to the development of ARVD/C and its complications I hypothesize that increased nitric oxide (NO) levels secondary to endurance exercise lead to changes that could explain the early onset and rapid progression of ARVD/C.
Hypothesis
The hypothesis can be summarized as follows: Increased levels of NO and resulting reactive oxygen species secondary to endurance exercise causes early onset and rapid progression of ARVD/C.

Evaluation of the Hypothesis
Known and Published Data:
Desmosomal dysfunction in ARVD/C
Desmosomes are comprised of multiple proteins which interact to form a macromolecular complex that links the intermediate filaments (desmin in cardiac myocytes) of a cell to the intermediate filaments of adjacent cells through the transmembrane proteins. (Figure 1)
The transmembrane domain portion is formed from 2 distinct cadherin proteins, desmocollin and desmoglein which bind to the intracellular linker protein, plakoglobin. Desmoplakin, via its amino-terminal domain, binds to plakoglobin. The link to the cytoskeleton occurs with binding of the intermediate filaments to the carboxyl-terminal domain of desmoplakin, an event required for tissue stability. Another desmosomal protein, plakophilin also binds plakoglobin and is thought to be important in desmosomal stability (13). Some component proteins of the desmosome have been shown to be involved in signal transduction, with plakoglobin involved in transcription regulation via interaction with TCF/LEF transcription factors (14) and plakophilin involved in regulating cell adhesion through direct regulation of E Cadherin and p120 (13,15).

Comprehensive exonic sequence analysis of the known desmosomal ARVD/C-related genes currently identifies a salient mutation in approximately 50% of ARVD/C probands (16). Furthermore, Garcia-Gras et al., (17) showed that suppression of desmoplakin expression leads to nuclear localization of the desmosomal protein plakoglobin, and a twofold increase in canonical Wnt-beta-catenin signaling through Tcf/Lef1 transcription factors. The ensuing phenotype is increased expression of adipogenic and fibrogenic genes and accumulation of fat droplets.

Different effects of prolonged exercise on the Right and Left Ventricles
Douglas et al. studied the effects of prolonged exercise on the right and left ventricles in humans (18). Their study involved 41 ultra-endurance athletes with a mean age of 38 ± 10 years (similar to the average age of ARVD/C patients in most studies). Two dimensional echocardiography and Doppler velocimetry were performed before, immediately on finishing, and during recovery from, the Hawaiian Ironman Triathlon. Results showed that the RV increased in size at race finish at both end-diastole and end-systole. During recovery, the RV returned toward normal but remained significantly larger than at baseline. The emptying fraction, or percent change in area, did not change with exercise or recovery. In contrast to the RV, the left ventricle (LV) decreased in size at end-diastole at race finish and was larger than at baseline during recovery. The percent change in LV area, or emptying fraction, did not vary. There was a smaller decrease, if any, in total pulmonary resistance than was found in the systemic circulation. RV work was increased 3.6 to 5.2 fold, whereas during the same exercise, LV work increased from only 2.1 to 2.8 fold. Other studies have shown an increase in systolic, diastolic and mean pulmonary artery pressure with exercise. (19, 20, 21).

This study clearly elucidates different responses of RV and LV to prolonged exercise with marked increase of RV workload compared to LV workload.
Different anatomy of Right Ventricle
The RV wall is thinner than the wall of the LV. ARVD/C primarily affects certain locations of the RV: the RV outflow tract, the apex, and the subtricuspid area of the RV, the so called “triangle of dysplasia” where the thinnest parts of the RV are located (22).

Increased production of Nitric Oxide during Exercise
Maeda et al in 2004, (23) showed that moderate regular exercise increases basal production of NO in elderly women. In the study 15 women (59-69 years of age) were subjected to 3 months of aerobic exercise training. There was significant increase in plasma concentration of NO and plasma cGMP concentration after the exercise training. These results were supported by other studies demonstrating induction of production of NO post exercise (24, 25). The increase in NO bioactivity dissipates within weeks of training cessation, however studies also indicate that if exercise is maintained, the short-term functional adaptation is succeeded by NO-dependent structural changes (24).

The mechanisms by which exercise training enhances NO production are not fully understood. One of the postulated mechanisms is that exercise induces an integrated physiological response, resulting in an increase in circulating neurohumoral factors (26), which may exert an influence on NO production (27).

It has been demonstrated that regular exercise in healthy older humans significantly decreases the concentration of plasma endothelin-1 (ET-1), a potent vasoconstrictor peptide produced by vascular endothelial cells (28). It has been reported that the NO and ET-1 production pathways engage in cross-talk (29). Therefore, it is possible that the decrease in ET-1 production by exercise training contributes to the increased production of NO by regular exercise. Furthermore, it is also considered that the increased blood flow velocity induced by exercise may elicit endothelial shear stress resulting in NO production. It has been reported that mechanical deformation of the endothelium by defined shear or cyclic stretching increases endothelial nitrous oxide synthase (eNOS) gene expression, proteins, and activity in vitro (30,31). Increased hemodynamic shear stress and/or endothelial stretching induced by repeated bouts of exercise could enhance the long-term biosynthesis of endothelial NO, thus causing an increase in plasma NO concentration.

Nitric Oxide and Cardiac Remodeling
NO is a free radical gas and is readily diffusible with a very short half-life, lasting only seconds. NO is synthesized from L-arginine through catalytic reaction with different isoforms of nitric oxide synthase (NOS), including the neuronal type 1 isoform (nNOS), the inducible type 2 isoform (iNOS), and the endothelial, type 3 isoform
(eNOS). nNOS and eNOS are constitutively expressed enzymes and are regulated predominantly at the post-translational level, whereas in most cell types, iNOS is only expressed in response to appropriate stimuli (32).

High levels and sustained production of NO increases cardiac myocyte apoptosis.

In disease states associated with cytokine activation or inflammation, cardiac iNOS expression has been shown to be induced in endothelial cells, vascular smooth muscle cells, macrophages, and cardiac myocytes. (33) Guanylyl cyclase catalyzes the formation of cGMP, which serves as a second messenger for NO and acts on a number of downstream targets, including ion channels, phosphodiesterases and kinases in a cell-type specific manner. (32) Calderone et al. (34) demonstrated that the NO donor S-nitroso-N-acetyl-D,L-penicillamine (SNAP) causes a concentration-dependent decrease in alpha1-adrenoreceptor-stimulated protein synthesis in isolated neonatal cardiac myocytes, confirming that exogenous NO exerts inhibitory effects on cardiac myocyte hypertrophy. A number of recent studies collectively indicate that NO can modulate both hypertrophy and apoptosis in the heart. (35,36,37) Wollert and Drexler (32) in their review concluded that low levels and transient release of NO by eNOS exert beneficial effects on the remodeling process by reducing cardiac myocyte hypertrophy, cavity dilation and mortality. By contrast, high levels and sustained production of NO by iNOS seem to be maladaptive by reducing ventricular contractile function, and increasing cardiac myocyte apoptosis, as well as mortality (32).

Discussion
ARVD/C is a heritable cardiomyopathy with desmosomal mutations present in almost 50% of patients. The majority of ARVD/C patients are involved in endurance exercise. To explain the association of endurance exercise and ARVD/C we hypothesise that an increased level of NO is involved in the pathogenesis of ARVD/C. The explanation is based on known facts in literature and speculation based on the literature.

People involved in endurance exercise have a sustained rise in NO levels. This results in the generation of reactive oxygen species. Since the RV and LV respond differently to exercise, with more workload experienced by the RV, we speculate there may be greater production of NO in RV cardiomyocytes as compared to LV cardiomyocytes. During exercise, higher concentrations of circulatory NO being returned to RV through venous return along with a greater and sustained production of NO in RV cardiomyocytes would result in higher levels of reactive oxygen species in the RV. These reactive oxygen species, through a cascade of steps, could result in fetal gene induction including gene expression of adipogenic and fibrogenic genes.

Mutation in desmosomal genes results in unstable desmosomes. Increased RV workload with endurance exercise exaggerates this instability, and would result in greater amounts of free plakoglobin (or other desmosomal proteins) translocating into the nucleus. Plakoglobin, through competition with beta-catenin, suppresses signaling through the canonical Wnt/beta-catenin-Tcf/Lef pathway. Suppression of Wnt/beta-catenin provokes adipogenesis, fibrogenesis, and apoptosis. (14-16)
The above steps may culminate in early and more rapidly progressive ARVD/C, manifesting primarily and initially in the RV. The above hypothesis can also explain the mechanism involved in development of arrhythmias in ARVD/C. As a result of desmosomal mutations there is mechanical and electrical uncoupling. Altered tissue architecture, due to the fibrofatty infiltration together with desmosomal mutations, leads to a delay in electrical activation, providing a substrate for reentry and thereby arrhythmias. The pathogenesis of ARVD/C based on the hypothesis is illustrated in Figure 2.

It is important to emphasize that NO is produced in people who do not have ARVD/C. But it is the speculated combination of higher sustained levels of NO and desmosomal mutation which may ultimately lead to the manifestation of ARVD/C. To test this hypothesis, studies are required to elucidate the various steps leading from exercise to development of disease. One of the study designs is as follows. First, family members of ARVD/C patients who are positive for mutations in desmosomal genes but phenotypically negative can be divided into two groups, persons who continue exercising and those who stop. NO levels in ARVD/C mutation positive family members should be measured immediately after exercise and between exercise periods. The RV and LV chamber dimensions at the baseline level and after exercise can be followed serially. This data can then be correlated with phenotypic changes, if any, over time.

Consequences of the Hypothesis
Verification of this hypothesis would have prognostic and management implications. Drugs inhibiting NO production might benefit patients with ARVD/C. A better understanding of exercise physiology in terms of NO production would help to redefine the management scheme in terms of exercise.
in patients with ARVD/C. A redirection of research towards identification of special physiological markers would be appropriate, and may reveal additional steps leading from NO production to pathological changes.

This hypothesis can also explain the increased prevalence of ARVD/C in males as compared to females, since males tend to be more involved in endurance exercise. This also implies that ARVD/C might not be restricted to RV but might progress with time to LV since both RV and LV experience increased workload, though RV more so than LV. Another implication of this hypothesis is that not all patients with mutations might express this disease for long, or they might have subclinical disease in the form of prolonged RV activation time if they are not involved in endurance exercise.

Conclusion
The NO hypothesis may explain the association between exercise and ARVD/C development and progression. Further studies, testing and confirming the hypothesis may yield alternative forms of treatment and management guidelines.

References


