A Novel Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Biomarker—Anti-DSG2—Is Absent in Athletes With Right Ventricular Enlargement

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ABSTRACT

Background: Right ventricular (RV) enlargement is common in endurance athletes. It is usually considered to be physiological, but it is possible that this remodelling is adverse, manifesting as a variant of arrhythmogenic right ventricular cardiomyopathy (ARVC), termed “exercise-induced ARVC.” A novel biomarker (anti-desmoglein-2 [anti-DSG2] antibody) has been shown to indicate ARVC with high sensitivity and specificity and may be an immune response to breakdown of RV desmosomes. It is not known if this antibody is present in endurance athletes with RV enlargement but without clinical ARVC.

Methods: Middle-aged, healthy endurance athletes with RV enlargement on cardiac magnetic resonance imaging had serum tested for the presence of the anti-DSG2 antibody. All athletes also underwent electrocardiogram, family history, genetic testing, endomyocardial biopsy, and a score based on cardiac imaging using echocardiography and magnetic resonance, Holter monitoring, signal-averaged electrocardiogram (SAECG), family history, genetic testing, and endomyocardial biopsy. Some of these criteria overlap with what is observed with physiological adaptations typical of sustained endurance exercise training, including increased left and right ventricular end-diastolic remodelling seen on the spectrum of a disease known as arrhythmogenic RV cardiomyopathy (ARVC). ARVC is a rare, heritable, and progressive cardiomyopathy characterized by fibrofatty infiltration of the myocardium leading to electrical and structural dysfunction. The current gold standard for diagnosis of ARVC is a scoring system, known as the 2010 ARVC Task Force Criteria, which assigns a score based on cardiac imaging using echocardiography and magnetic resonance, Holter monitoring, signal-averaged electrocardiogram (SAECG), family history, genetic testing, and endomyocardial biopsy. Some of these criteria overlap with what is observed with physiological adaptations typical of sustained endurance exercise training, including increased left and right ventricular end-diastolic

Received for publication April 21, 2021. Accepted July 2, 2021.

Ethics Statement: This research was approved by local research ethics board, and research ethics guidelines were adhered to.

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See page 1417 for disclosure information.

https://doi.org/10.1016/j.cjco.2021.07.002
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Athletes demonstrated other characteristics of endurance training, including depolarization abnormalities (abnormal signal-averaged electrocardiogram, 19 of 30) and incomplete right bundle branch block (8 of 30). No athlete met criteria for definite or probable ARVC. None of the athletes tested positive for anti-DSG2 antibody.

Conclusions: Among middle-aged endurance athletes with RV enlargement, the anti-DSG2 antibody, a suggested ARVC biomarker, is absent in all and is highly specific in this cohort (95% confidence interval, 88%-100%). Despite significant RV remodelling, these athletes did not express a previously characterized pathologic biomarker known to be sensitive for ARVC. Physiological exercise remodelling and pathologic ARVC remodelling are likely separate processes.

Results: A total of 30 athletes (20 men, 10 women, average age 53 ± 6 years) were enrolled in this study with median RV end-diastolic volume indexes of 117.1 mL/m² (men) and 103.5 mL/m² (women). Athletes demonstrated other characteristics of endurance training, including depolarization abnormalities (abnormal signal-averaged electrocardiogram, 19 of 30) and incomplete right bundle branch block (8 of 30). No athlete met criteria for definite or probable ARVC. None of the athletes tested positive for anti-DSG2 antibody.

Conclusions: Among middle-aged endurance athletes with RV enlargement, the anti-DSG2 antibody, a suggested ARVC biomarker, is absent in all and is highly specific in this cohort (95% confidence interval, 88%-100%). Despite significant RV remodelling, these athletes did not express a previously characterized pathologic biomarker known to be sensitive for ARVC. Physiological exercise remodelling and pathologic ARVC remodelling are likely separate processes.

Methods

Study design

We studied a cohort of endurance athletes aged 45-65 years who were required to be long-term participants (10 years) of prolonged, intensive endurance running (> 40 km per week) or cycling (> 150 km per week) with exercise training maintained year-round. Athletes who engaged in > 2 hours per week of resistance training were excluded. Athletes were excluded if they had any prior diagnosis of atrial fibrillation or flutter, coronary artery disease or cardiomyopathy, significant valvular disease, heart failure, diabetes, history of thyroid disorder, sleep apnea or any reported sleep-disordered breathing, current/recent viral or chronic illness, or chronic inflammatory disease. Any prior use of antibody-mediated medication including biologic anti-inflammatory medications, intravenous immunoglobulin, or any prior plasma exchange, and use of anycardioactive drugs other than antihypertensive medications were also exclusion criteria.

Athletes underwent cardiac magnetic resonance (CMR) imaging, 24-hour Holter monitoring, and SAECG as part of a larger study (n = 92).14 The subset with RV enlargement, as defined by the ARVC Task Force major size criteria,6 were eligible for the study; inclusion criteria were an RVEDVi > 110 mL/m² for men, and > 100 mL/m² for women, on CMR imaging. Eligible participants provided consent to participate in this additional study, which included the collection of a blood sample to determine the presence of the anti-DSG2 antibody.
Holter monitoring

All athletes underwent 24 hours of continuous ECG monitoring using a standard commercially available Holter monitor (SEER-1000; Marquette MUSE, General Electric, Boston, MA). Participants were instructed to refrain from exercise during the 24-hour period but otherwise go about their usual activities. Compliance was ensured by measurement of total time worn. Data were assessed by a trained cardiologist and analyzed for the presence of arrhythmia and frequency of premature ventricular contractions.

SAECG

A trained technician performed a resting 12-lead ECG and SAECG while participants lay in the supine position. ECG and SAECG were recorded using a commercially-available system (General Electric Marquette Medical Systems Inc, Milwaukee, WI). The mean filtered QRS duration and standard QRS duration from the 12-lead ECG were measured as the system software-generated QRS duration. The SAECG was performed to collect several variables, including the filtered QRS duration (minimum averaged beats = 200), the high-frequency low-amplitude signal duration, and the root mean square voltage.

DSG-2 antibody

The presence or absence of the anti-DSG2 antibody was tested using Western blot analysis, with the same methodology as used by Chatterjee et al. in their original characterization of it as a potential ARVC biomarker. Serum of athletes was collected and analyzed using recombinant human DSG2 proteins per their protocol. Researchers were blinded to any clinical data pertaining to the samples during analysis, and to the nature of the population being studied. Samples were analyzed using positive and negative controls. The presence or absence of antibody using Western blot analysis was determined using visual quantification. Western blot testing has been previously validated against enzyme-linked immunosorbent assay (ELISA), and it was found that the threshold value at a 1 in 100 dilution was an optical density of 0.12. The antibodies were not visible or detectable in the normal individuals tested. All analyses were done at The Hospital for Sick Children in Toronto, Ontario.

CMR imaging

A standardized CMR examination was performed using a 3.0 T magnetic resonance imaging (MRI) scanner (MAGNETOM Skyra 3.0T with TIM and DOT technology, Siemens, Oakville, ON, Canada) with a phased-array cardiac coil and retrospective electrocardiographic gating, with images obtained on end-expiration breath-holds. A short-axis stack and long-axis views (2- and 4-chamber) were acquired to analyze left ventricular (LV) and RV mass, dimensions, and function. All scans were performed on the same Siemens 3T Skyra. All CMR volumetric endpoints were measured by a single reader blinded to other clinical data, using commercially available software with particular care to exclude papillary muscles and artifact (CVi42 Version 5.1; Circle Imaging, Calgary, AB). Ventricular mass and function were determined via a manual tracing of the endocardial and epicardial borders.

Results

Study population and anti-DSG2

Of 42 eligible athletes with enlarged RVs who met our inclusion criteria, 30 participants (20 male, 10 female) agreed to be tested for the anti-DSG2 antibody. Participant characteristics are reported in Table 1. Two athletes did not complete the questionnaire, and one additional athlete did report intensity of exercise. (These participants were still considered to be endurance athletes eligible for the study on the basis of their frequent participation in endurance competition, which requires extensive training.) Only 6 of 28 recorded any resistance activity. Athletes were either predominantly cyclists (1 of 10 women, 7 of 19 men), runners (3 of 10 women, 5 of 19 men), or multi-sport athletes (6 of 10 women, 7 of 19 men). One male athlete did not designate his predominant sport type. All athletes were asymptomatic and had no family history of ARVC or sudden death.

None of the athletes tested had measurable anti-DSG2 antibody by Western blot analysis.

Holter and SAECG data

All subjects underwent 24 hours of Holter monitoring. Two athletes met a minor ARVC criterion under the category of “arrhythmia” (Table 1). One male athlete had one run of 6 beats non-sustained ventricular tachycardia (NSVT) with a left bundle branch block (LBBB) morphology with an unknown axis, not captured on a 12-lead ECG (therefore meeting minor criteria). One female athlete met extrasystole criteria with 2358 premature ventricular contractions in a 24-hour period.

Minor depolarization abnormalities were common, occurring in 15 of 20 (75%) male, and 4 of 10 (40%) female athletes. A prolonged filtered QRS duration (≥114 ms) was the most common abnormality, occurring in 65% of men and 30% of women, meeting a minor task force criterion. The mean QRS duration was 115 ± 4.8 ms in men, 105.8 ± 8.5 ms in women, and 112.3 ± 7.7 ms overall. Prolonged duration of terminal QRS (<40 μV low-amplitude signal duration ≥38 ms), and root-mean-square voltage of terminal 40 ms <20 μV were also common, occurring in 30% and 17% of athletes, respectively. One athlete met 2 minor criteria, earning the label of “possible ARVC.” No athletes met task force criteria for 12-lead ECG repolarization abnormalities. One athlete had T-wave flattening in V2 and V3 but did not meet criteria for T-wave inversion. Although not part of the task force criteria, incomplete bundle branch block was also seen, occurring in 7 of 20 men and one woman.

CMR data

All athletes underwent cardiac MRI (results reported in Table 2). Athletes had a median RVEDVi of 117.1 mL/m² (interquartile range: 104.7-134.0). No athletes were found to have regional akinesia or dyskinesia, and as a result, there were no athletes who met major or minor criteria for ARVC on the basis of CMR. Median RVEF was 51.6 (49.3-55.8). Athletes demonstrated balanced biventricular dilation and function with a median LV/RV EDVi ratio of 0.90 (0.87-0.98), and LVEF/RVEF of 1.10 (1.05-1.13), although 2 male athletes had a LVEDV/RVEDV ratio <0.8.
Table 1. Demographic, ARVC task force data and anti-DSG2 antibody absence

|                        | Men (n = 20) | Women (n = 10) | Combined (N = 30) |
|------------------------|-------------|----------------|------------------|
| Age, y (mean ± SD)     | 53 ± 6      | 50 ± 5         | 52 ± 5           |
| Exercise history (median, IQR) |             |                |                  |
| Total lifetime vigorous activity, h | 4496 (3162–9159) | 5452 (446–8570) | 4589 (2314–9077) |
| Total lifetime endurance, h | 9179 (5933–10,651) | 9806 (7500–13,480) | 9621 (6239–12924) |
| VO2 max, mL/kg/min (mean ± SD) |             |                |                  |
| ARVC task force criteria categories, n (%) major / minor |             |                |                  |
| Family history of ARVC or SCD | 0 / 0       | 0 / 0          | 0 / 0            |
| Depolarization/conduction abnormalities | 0 / 15 (75) | 0 / 4 (40) | 0 / 19 (63) |
| Repolarization abnormalities | 0 / 0       | 0 / 0          | 0 / 0            |
| Arrhythmias | 0 / 1 (5) | 0 / 1 (10) | 0 / 2 (7) |
| Global or regional RV dysfunction | 0 / 0      | 0 / 0          | 0 / 0            |
| ARVC diagnosis |             |                |                  |
| Definite ARVC | 0           | 0              | 0                |
| Borderline ARVC | 0           | 0              | 0                |
| Possible ARVC | 1 (5%)      | 0              | 1 (3%)           |
| Presence of anti-DSG2 antibody | 0           | 0              | 0                |

anti-DSG2, anti-desmoglein-2; ARVC, arrhythmogenic right ventricular cardiomyopathy; IQR, interquartile range; SCD, sudden cardiac death; RV, right ventricular; SD, standard deviation; VO2 max, maximum rate of oxygen consumption; VT, ventricular tachycardia.

* Presence of an epsilon wave (major criterion), late potentials on signal-averaged electrocardiogram (minor criterion), prolonged QRS duration (minor criterion), root-mean-square voltage of terminal 40 ms (minor criterion). See text for details.

1 Inverted T waves in right precordial leads (V1, V2, and V3) in the absence of right bundle branch block (RBBB; major criterion), inverted T waves in leads V1-V4 in the presence of RBBB (minor criterion).

2 Sustained or non-sustained VT of left bundle branch block morphology with superior axis (major criterion), sustained or non-sustained VT of RV outflow configuration (minor criterion), > 500 premature ventricular beats in 24-hour period (minor criterion).

3 Diagnostic terminology for 2010 criteria: definite—2 major, or 1 major and 2 minor criteria, or 4 minor from different categories; borderline—1 major and 1 minor, or 3 minor criteria from different categories; possible—1 major or 2 minor criteria from different categories.

Discussion

In this study of middle-aged athletes with RV enlargement, none had detectable anti-DSG2 antibody in their serum. Presence of this antibody is a biomarker that has been suggested as a test for the diagnosis of ARVC, a disease that can be difficult to distinguish from normal physiological remodelling in response to exercise training. We tested a cohort of male and female endurance athletes with an average age of 52 years, who were well trained, with an average of over 9500 hours of endurance training. This suggests that RV structural and electrical remodelling in keeping with “athlete’s heart” is not associated with the same desmosomal abnormalities associated with ARVC, with which all patients have, in prior studies, detectable anti-DSG2 antibodies. As a potential test for ARVC, our cohort demonstrated no false positives (specificity 100%; 95% confidence interval 88%-100%), strengthening previous observations that anti-DSG2 antibody is specific to the disease process of ARVC.

Most athletes had characteristic electrical remodelling in response to endurance exercise, including a prolonged QRS duration and incomplete right bundle branch block (RBBB). The findings seen on SAECG that overlap with the task force criteria highlight the low specificity of SAECG for ARVC diagnosis. These changes have been previously characterized in athletes and may be secondary to the structural changes that accompany exercise training, including increased LV mass and increased RV volume. Indeed, our athlete cohort demonstrated such structural changes, including increased LV mass, slight decreases in LVEF and RVEF, and significant RV enlargement, with a median RVEDV of 117.1 mL/m² (124.8 mL/m² in men and 103.5 mL/m² in women), far exceeding what is considered normal in a typical healthy population (91 ± 15 mL/m² in men and 80 ± 16 mL/m² in women). This measurement would place the average male athlete in our study above the 99th percentile, and women above the 90th percentile, respectively (using mean values), referenced to the average population. Our findings were in keeping with results of previous cardiac MRI studies of athletes. In a larger sample of endurance athletes, from which those in our study was drawn, RV end diastolic volume index in elite endurance

Table 2. Cardiac magnetic resonance (CMR) data

| CMR measurements, median (IQR) | Men (n = 20) | Women (n = 10) | Combined (N = 30) |
|--------------------------------|-------------|----------------|------------------|
| RV EDVi, mL/m²^2              | 124.8 (115.3–138.1) | 103.5 (102.8–110.0) | 117.1 (104.7 – 134.0) |
| LV EF, %                      | 50.2 (47.1–53.7) | 54.9 (52.3–57.4) | 51.6 (49.3–55.8) |
| LV EF, %                      | 56.5 (54.4–58.0) | 59.3 (56.4–60.1) | 57.2 (55.3–59.9) |
| LV EDVi, mL/m²                | 113.3 (103.5–123.5) | 103.2 (93.5–108.0) | 109.0 (101.2–118.4) |
| LV mass index, g/m²           | 70.5 (62.5–78.4) | 58.2 (47.7–64.7) | 66.6 (57.0–75.3) |
| LV/RV EF ratio               | 1.11 (1.07–1.17) | 1.06 (1.05–1.11) | 1.10 (1.05–1.13) |
| LV/RV EDVi ratio             | 0.88 (0.85–0.95) | 0.95 (0.89–1.00) | 0.90 (0.87–0.98) |

EDVi, end-diastolic volume indexed to body surface area; EF, ejection fraction; IQR, interquartile range; LV mass index, left ventricular mass indexed to body surface area; RV, right ventricular.
athletes was larger than it was in less-trained physically active adults (112 ± 18 mL/m² vs 92 ± 14 mL/m²; P = 0.001), and RV mass index was proportionally increased (19.0 ± 3.5 g/m² vs 15.7 ± 3.4 g/m²), implying little change in relative wall thickness. This implies that RV dilation in the endurance athletes, in our population, is not accompanied by significant RV hypertrophy or wall thinning.14

The majority of athletes experienced biventricular LV and RV remodelling, with slightly larger RV volumes (median LV/RV EDVi 0.90), in keeping with previous observations. This LV/RV balance has been proposed previously as a way to distinguish the athlete’s heart from abnormal RV remodelling in disease states such as ARVC where RV-predominant remodelling is observed.16 Of note, two athletes in our cohort had a LV/RV EDVi ratio < 0.8 representing an exaggerated RV remodelling response; despite this, their anti-DSG2 antibody was negative.

There are ongoing challenges in distinguishing physiological remodelling from pathologic remodelling in athletes, which has important clinical implications regarding counseling and treatment. In one case series of ARVC misdiagnosis, a healthy athlete underwent an inappropriate implantation of an implantable cardioverter-defibrillator, and subsequent removal.17 In previous cohorts of ARVC patients, roughly 50% of cases can be directly attributed to a known underlying genetic mutation that interferes with the formation of desmosomes. These are dominantly inherited autosomal mutations; however, penetrance is incomplete, as low as 30% for mutations in PKP2 (Plakophilin-2), the most common gene associated with ARVC. It has been previously observed that athletes with ARVC are more often negative for disease-causing variants than non-athletes, leading to the hypothesis that there may exist a type of acquired “exercise-induced ARVC.”15,14 In this study, we did not perform genetic testing on any of the athletes, as clinical suspicion for ARVC was very low. No athletes met task force criteria for a “possible” or “definite” diagnosis of ARVC.

In the original study by Chatterjee et al.15 describing the sensitivity and specificity of the anti-DSG2 antibody as a diagnostic tool for ARVC, 8 of 19 patients in the original cohort, and 6 of 25 patients in the validation cohort were negative for disease-causing genetic variants (and all tested positive for the antibody). In athletes who have negative genetic testing but display clinical characteristics in keeping with a diagnosis of ARVC, we would anticipate a positive anti-DSG2 antibody test, indicating that they have ARVC with the same pathophysiology as a non-athlete. It is possible that exercise may unmask ARVC in those without identified genetic variants, by increasing the penetrance of a previously undescribed gene, as opposed to the development of ARVC de novo in an individual who would otherwise not develop “gene-elusive” ARVC. On the other hand, if such athletes were antibody negative, this would suggest that they have a condition distinct from the pathophysiology of ARVC, despite presenting with a similar phenotype. Further study into the absence or presence of the anti-DSG2 antibody in such athletes would be very useful in the refinement of diagnoses and patient management.

In this study, we examined middle-aged athletes with a long-standing history of endurance exercise, sufficient to impose cumulative RV stress that led to significant alterations in cardiovascular structure, with RV volumes well above average. Despite the significant remodelling, there was presumably no (or insufficient) cellular disruption capable of eliciting an antibody response akin to the one seen in ARVC. This finding demonstrates that extensive physiological exercise remodelling is a separate process from the pathologic remodelling in ARVC. If these data are verified in a larger and more diverse sample, it is possible that the presence or absence of the anti-DSG2 antibody in athletes with RV enlargement may help to distinguish between physiological and pathologic states.

Limitations
The most notable limitation to this study is our small and homogenous sample population. We tested only middle-aged athletes, and it is not yet known how the titre of this antibody may change with time. This is a cross-sectional study, so it is possible that these athletes may have had Anti-DSG2 present at younger age, and we do not have any long-term follow up data. Moreover, this test is likely to be most useful in those at younger ages, when ARVC typically presents (second and third decades of life). Our athletes were also limited to endurance sports. Furthermore, detailed demographic data were not collected, and characteristics such as ethnic origin may influence remodelling and ARVC risk. In order to be generalizable, this study needs to be repeated in a larger and more diverse group of athletes with different sports, ages, and demographics.

Conclusion
In a group of middle-aged endurance athletes with RV enlargement, the absence of the anti-DSG2 antibody, a biomarker for ARVC, demonstrates that it is highly specific in this cohort (95% confidence interval, 88%-100%). Despite significant RV remodelling, these athletes did not express a previously characterized marker of pathology known to be sensitive to ARVC.

Funding Sources
Funding for this study was provided in part by a grant from the Canadian Institutes for Health Research (J.G.) and the University of Toronto Innovations Fund (R.H.).

Disclosures
R.M.H. is the inventor for a patent on anti-DSG2 antibodies for the detection of arrhythmogenic cardiomyopathy, which is owned by The Hospital for Sick Children. R.M.H. owns a 7% founder stock in ARVADA Therapeutics, Inc. All the other authors have no conflicts of interest to disclose.

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