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ORIGINAL ARTICLE

Integrating Exercise Into Personalized Ventricular Arrhythmia Risk Prediction in Arrhythmogenic Right Ventricular Cardiomyopathy

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BACKGROUND: Exercise is associated with sustained ventricular arrhythmias (VA) in Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) but is not included in the ARVC risk calculator (arvcrisk.com). The objective of this study is to quantify the influence of exercise at diagnosis on incident VA risk and evaluate whether the risk calculator needs adjustment for exercise.

METHODS: We interviewed ARVC patients without sustained VA at diagnosis about their exercise history. The relationship between exercise dose 3 years preceding diagnosis (average METh/wk) and incident VA during follow-up was analyzed with time-to-event analysis. The incremental prognostic value of exercise to the risk calculator was evaluated by Cox models.

RESULTS: We included 176 patients (male, 43.2%; age, 37.6±16.1 years) from 3 ARVC centers, of whom 53 (30.1%) developed sustained VA during 5.4 (2.7–9.7) years of follow-up. Exercise at diagnosis showed a dose-dependent nonlinear relationship with VA, with no significant risk increase <15 to 30 METh/wk. Athlete status, using 3 definitions from literature (>18, >24, and >36 METh/wk), was significantly associated with VA (hazard ratios, 2.53–2.91) but was also correlated with risk factors currently in the risk calculator model. Thus, adding athlete status to the model did not change the C index of 0.77 (0.71–0.84) and showed no significant improvement (Akaike information criterion change, <2).

CONCLUSIONS: Exercise at diagnosis was dose dependently associated with risk of sustained VA in ARVC patients but only above 15 to 30 METh/wk. Exercise does not appear to have incremental prognostic value over the risk calculator. The ARVC risk calculator can be used accurately in athletic patients without modification.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: arrhythmogenic right ventricular dysplasia ■ exercise ■ prognosis

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart disease characterized by fibrofatty replacement of the myocardial wall, frequent life-threatening ventricular arrhythmias (VA), and a higher risk of sudden cardiac death.[1] In approximately two-thirds of the patients, a disease-causing mutation is identified,[2] most commonly in genes encoding desmosomal proteins, impairing both electrical and mechanical myocardial function.

Exercise promotes development of ARVC in at-risk individuals and is associated with earlier disease onset, higher risk of arrhythmias, and worse structural disease

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WHAT IS KNOWN?

- Exercise is shown to promote disease progression of arrhythmogenic right ventricular cardiomyopathy and increase risk of ventricular arrhythmias. While patients are commonly recommended to restrict exercise, there is little evidence to support a definition for the upper limit.
- Exercise history is not included in the recently published prediction model arvcrisk.com for estimating the risk of ventricular arrhythmia in individual patients. Theoretically, this might cause the model to underestimate the risk in athletic patients.

WHAT THE STUDY ADDS

- The risk of incident sustained ventricular arrhythmia appears to increase nonlinearly with exercise dose, showing no significant increase up until 15 to 30 METh/wk, supporting the European Society of Cardiology recommendation to restrict exercise to 15 METh/wk.
- While patients with an athletic history are indeed at higher risk of ventricular arrhythmias, this higher risk is accurately predicted by the current arvcrisk.com model, showing no need to add athlete status to the model.
- Athlete status significantly correlates with multiple predictors in the current prediction model, such as age at diagnosis, number of inverted T waves, and right ventricular ejection fraction. This is in line with previous studies reporting exercise to promote disease progression and explains why exercise failed to improve the model predictions in our study.

Nonstandard Abbreviations and Acronyms

AHA	American Heart Association
ARVC	arrhythmogenic right ventricular cardiomyopathy
HR	hazard ratio
MET	metabolic equivalent
VA	ventricular arrhythmia

in patients. Most clinicians now advise exercise restriction, as this was recently suggested to be effective in VA risk reduction.[3,4] However, it is well established that exercise is beneficial for physical and mental health, reducing the risk of other cardiovascular diseases, osteoporosis, type 2 diabetes, anxiety, and depression.[5] Unfortunately, it remains uncertain to what extent exercise should be restricted and if there is a level of exercise safe for ARVC patients that allows the general physical and mental health benefits of exercise to remain. Several studies have posited that low-intensity or noncompetitive activities may be safer for ARVC patients,[6,7] but these had limited statistical power or did not precisely define type or intensity of exercise.

We recently developed a risk calculator for incident sustained VA in patients newly diagnosed with ARVC without prior sustained VA (arvcrisk.com).[8] By design, this did not include the quantity of exercise exposure in generating risk estimates, as the aim was to develop a prediction model using risk factors that were consistently collected in participating centers and readily available in clinical practice. Nonetheless, not integrating exercise raises valid concerns about the accuracy of predictions in athletes.[9]

To address these important clinical queries, we designed a study combining exercise data collected by interview from 3 large ARVC registries to (1) better quantify the dose-dependent relationship of exercise at diagnosis and risk of incident sustained VA and (2) evaluate the incremental value of adding exercise to the risk calculator model and test whether it can be accurately used in athletic patients or requires modification.

METHODS

Study Design and Population

This is a retrospective, observational, longitudinal multicenter cohort study. Patients eligible for inclusion were (1) definite ARVC patients per 2010 Task Force Criteria without sustained VA before their diagnosis who (2) participated in a detailed exercise interview in 1 of the 3 participating ARVC centers: Johns Hopkins Hospital (Baltimore, MD), Oslo University Hospital (Oslo, Norway), and the University Medical Center Utrecht (Utrecht, the Netherlands). All participants provided written informed consent, and the study protocols were approved by local Institutional Review Board/ethics boards. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Collection

Demographic and clinical data were collected as previously described in detail in the manuscript describing development of the ARVC risk calculator.[8] Briefly, data were collected independently by each center following standard operating procedures. All ECG data and genetic variants were additionally reviewed by an electrophysiology team and genetic specialist team, respectively, for validity. The outcome of the first sustained VA was defined as the occurrence of either (aborted) sudden cardiac death, ventricular fibrillation, spontaneous sustained ventricular tachycardia (lasting >30 s at >100 beats per minute or with hemodynamic instability requiring cardioversion), or appropriate implantable cardioverter defibrillator intervention. Time to event was defined as the time from inclusion at the time of diagnosis by 2010 Task Force Criteria to first incident sustained VA or censoring by death, heart transplantation, or last clinical follow-up.

Exercise History

The exercise history of all included patients was obtained through a structured telephone or in-person interview according

to previously published protocols.[6,10] Exercise data included in this analysis included all exercise, recreational or competitive, done on a regular basis during the 3 years before diagnosis. For each exercise activity, we determined the intensity in metabolic equivalents (METs) based on the 2011 Compendium of Physical Activities.[11] Only activities requiring at least 3 METs were considered as exercise in this study. The exercise dose was calculated by first multiplying the MET of each individual activity by the reported duration (METh) and then combining these values and averaging per week (METh/wk).

To evaluate the association of exercise dose with the predefined outcome, first we considered exercise as a continuous value expressed as METh/wk. Second, we divided exercise dose into 5 categories based on multiples of the American Heart Association (AHA)–recommended minimum of 7.5 METh/week,[5] that is, below minimum (<1×, 0–7.5 METh/wk), ≥1× (7.5–15 METh/wk), ≥2× (15–30 METh/wk), ≥4× (30–60 METh/wk), and ≥8× the minimum (≥60 METh/wk). Furthermore, we estimated the prognostic value of athlete status using 3 definitions shown to be significantly associated with higher arrhythmia risk in prior ARVC studies: >18 METh/wk,[3,12] >24 METh/wk,[13] and >36 METh/wk.[14]

Data Analysis

Statistical analysis was performed in RStudio, version 1.1.414 (Boston, MA). Continuous variables were expressed as mean±SD or median (first quartile to third quartile) and compared using the *t* test or Mann-Whitney *U* test as appropriate. Categorical variables were compared using the χ^2 or Fisher exact test. Two-tailed *P* of <0.05 was considered statistically significant. Survival analysis was performed using the Kaplan-Meier method and the Cox-proportional hazard model. Multiple testing was corrected with the Benjamini and Hochberg method. In total, 7% of data were missing and as described previously assumed to be at random and imputed using multiple imputation by chained equations.[8] The Cox model linearity assumption of continuous variables was evaluated using martingale residuals. Possible interactions of exercise with sex, age, and genetic variants were tested. Model performance of the risk calculator with and without the addition of exercise was calculated by Harrel C statistic. Akaike information criterion as relative estimator of prediction error was used for model selection, for which difference of >2 was considered significant.

RESULTS

Population Characteristics

In total, 176 patients were included (Table 1). Almost half (76; 43.2%) were men, with an average age of 37.6±16.1 years at the time of diagnosis. The majority (134; 76.1%) of patients had a pathogenic or likely pathogenic variant (eg, mutation), most frequently in the *PKP2* gene (105; 59.7%). During 5.4 (2.7–9.7) years of follow-up, 53 (30.1%) developed the composite outcome of sustained VA.

Most patients were enrolled at the Johns Hopkins Hospital (105; 59.7%) and the Oslo University Hospital (47; 26.7%; Table S1). Most had been included (164; 93.2%) in the original risk calculator development cohort; the remainder were patients with new diagnoses at our centers.

Table 1. Population Characteristics

	Risk calculator cohort	Study cohort	*P* value
Total	528	176	
Male sex	236 (44.7)	76 (43.2)	0.793
Age at diagnosis, y	38.2±15.5	37.6±16.1	0.660
Proband	263 (49.8)	77 (43.8)	0.191
Pathogenic variant (mutation)	340 (64.4)	134 (76.1)	0.001
PKP2	258 (48.9)	105 (59.7)	0.018
DSP	23 (4.4)	11 (6.2)	
DSG2	17 (3.2)	3 (1.7)	
PLN	26 (4.9)	5 (2.8)	
Multiple	6 (1.1)	4 (2.3)	
Other	10 (1.9)	6 (3.4)	
Symptomatic	307 (58.1)	96 (54.5)	0.584
Recent cardiac syncope	48 (9.1)	15 (8.5)	0.844
24-h PVC count	1076 (300–3798)	847 (231–3008)	0.299
Nonsustained VT	231 (43.8)	66 (37.5)	0.302
Leads with TWI (II, III, aVF, and V_1–V_6)	3 (2–5)	3 (2–5)	0.880
RVEF, %	48 (38–51)	48 (38–55)	0.086
Follow-up, y	4.8 (2.4–9.3)	5.4 (2.7–9.7)	0.496
Sustained VA	146 (27.7)	53 (30.1)	0.595
Sustained VT	35 (6.6)	11 (6.2)	0.754
Appropriate ICD intervention	102 (19.3)	40 (22.7)	
VF/aborted SCD	6 (1.1)	2 (1.1)	
SCD	3 (0.6)	0 (0.0)	

ICD indicates implantable cardioverter defibrillator; PVC, premature ventricular complex; RVEF, right ventricular ejection fraction; SCD, sudden cardiac death; TWI, T-wave inversion; VA, ventricular arrhythmia; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Based on the demographics, clinical characteristics, and outcomes during follow-up, this cohort with exercise interviews was similar to the overall risk calculator cohort (Table 1). The only significant difference was a higher proportion of pathogenic/likely pathogenic variant carriers in the study cohort (76.1% versus 64.4%; *P*=0.001).

Exercise Dose and Incidence of VA

Overall, the median exercise dose at diagnosis was 2.4 (10.7–52.6) METh/wk. This was significantly higher in patients who experienced sustained VA during follow-up (16.8 [9.0–38.9] versus 7.4 [4.5–10.9]; *P*<0.001; Figure S1). The association between exercise dose as a continuous variable and the risk of sustained VA was plotted for visual analysis, revealing a nonlinear relationship that appeared to fit an S-shaped curve (Figure S2). As this violates the

linearity assumption of the Cox regression model for continuous variables, we treated exercise dose categorically using multiples of the AHA-recommended minimum of 7.5 METh/wk. Kaplan-Meier curves for incident sustained VA among patients fitting in these 5 exercise dose categories are plotted in Figure 1. Notably, the survival curves of the first 3 categories (<1×, ≥1×, and ≥2× AHA minimum) showed considerable overlap, and only the patients exercising ≥4× (P=0.003) and ≥8× (P<0.001) the recommended AHA minimum had significantly higher incidence of sustained VA compared with the lower 3 categories.

Consistent with this, relative to exercising below 7.5 METh/wk (Figure 2), there was no clear difference in sustained VA risk at exercising between 7.5 to 15 METh/wk (hazard ratio [HR], 0.99 [95% CI, 0.32–3.06]; P=0.981) or 15 to 30 METh/wk (HR, 1.37 [95% CI, 0.44–4.29]; P=0.579), with the first significant increase at >30 METh/wk (HR, 3.00 [95% CI, 1.17–7.68]; P=0.022). Similar results were found when adjusting for sex and age (Figure S3). Additionally, no significant interaction was found between any category of exercise and sex (P>0.220), age (P>0.182), carriers of a pathogenic variant (P>0.475), or carriers of a *PKP2* pathogenic variant specifically (P>0.266).

Athlete status has been shown to be a significant predictor for risk of sustained VA in ARVC in prior studies using 3 athlete definitions (ie, >18, >24, and >36 METh/wk). In this cohort, all 3 definitions of athlete status at diagnosis were significantly associated with an increased risk of incident VA in univariable analysis. As shown in Figure 3, the HR ranged from 2.53 ([95% CI, 1.40–4.55] P=0.002) for >18 METh/wk to 2.91 ([95% CI, 1.68–5.03] P<0.001) for >36 METh/wk.

Exercise History in Personalized Risk Prediction

To assess whether exercise at diagnosis could further refine personalized risk prediction, we first tested the performance of the current ARVC risk calculator model for personalized risk prediction of incident sustained VA in this cohort. Without modification, it showed a C statistic of 0.77 (95% CI, 0.71–0.84) consistent with prior results.[8]

Athlete status was added to the model using each of the 3 definitions for athlete previously used in the ARVC literature. The resulting adjusted HR was 1.31 ([95% CI, 0.69–2.49] P=0.412) for the >18 METh/wk definition, 1.43 ([95% CI, 0.76–2.70] P=0.270) for the >24 METh/wk definition, and 1.67 ([95% CI, 0.93–3.02] P=0.088) for the >36 METh/wk definition (Table 2). The C statistic remained similar to the original risk calculator model, and none of the definitions

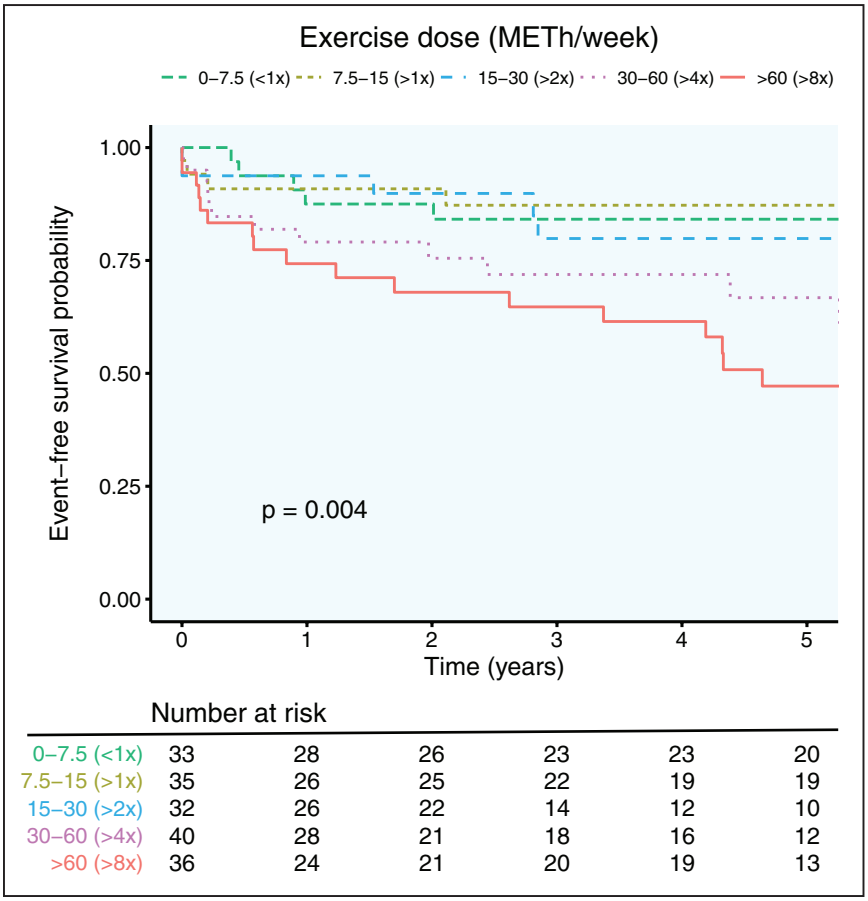

Figure 1. Exercise dose and sustained ventricular arrhythmia (VA)–free survival.
Kaplan-Meier plot showing the sustained VA-free survival of the cohort divided into 5 categories of exercise dose, based on multiples of the American Heart Association–recommended minimum of 7.5 METh/wk.

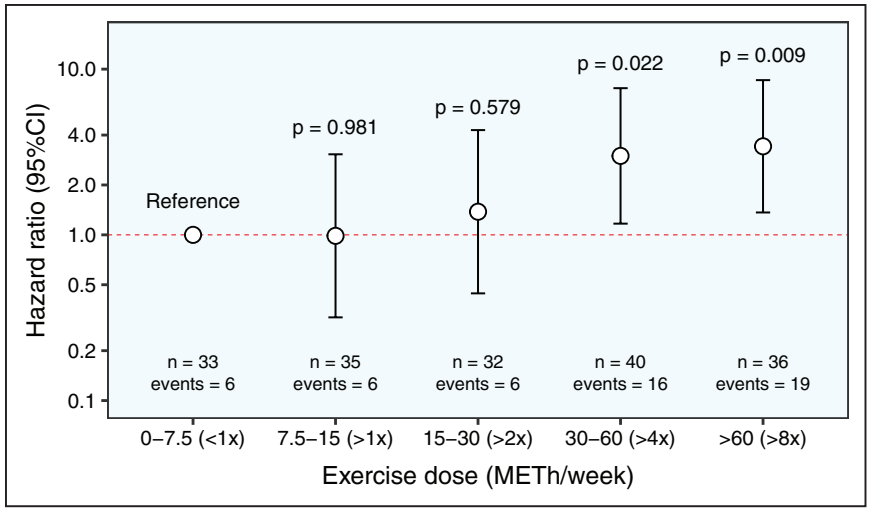

Figure 2. Dose-dependent association of exercise dose and sustained ventricular arrhythmia risk. Plot of the hazard ratios (*y* axis) per exercise dose (*x* axis) with the 0- to 7.5-METh/wk group as reference. Error bars are 95% CIs.

reduced the model Akaike information criterion by >2 indicating no significant improvement. As a visual confirmation, we plotted the risk calculator predictions stratified by athletes (triangles) and nonathletes (circles) and superimposed the actual observed risk of sustained VA (red crosses) in Figure 4, showing that the risk calculator–derived predictions are within range of the observed risks in this cohort.

In addition, all 3 definitions of athlete status showed significant or borderline significant associations with at least 5 of the predictors in the current risk model (Table S2; Figure S4). Specifically, we found athletes to have a younger age, higher 24-hour premature ventricular complex count, a higher proportion with nonsustained ventricular tachycardia, more T-wave inversions on ECG, and a lower right ventricular ejection fraction, all associated with a higher risk of sustained VA.

DISCUSSION

In this study, we aimed to refine understanding of the influence of exercise in arrhythmic risk prediction in patients with newly diagnosed ARVC. Although prior studies have established that exercise is associated with risk of sustained VA, it remains uncertain how best to integrate exercise into personalized risk prediction and provide more quantifiable estimates of the amount of exercise associated with increased VA risk. These limitations are caused by a deficit in statistical power in prior studies, lack of granularity in exercise data, or both.[6,7,10,12,13,15] Our current study includes the largest cohort to date of patients with newly diagnosed ARVC with detailed exercise history at a similar stage of disease (definite diagnosis, no history of sustained VA).

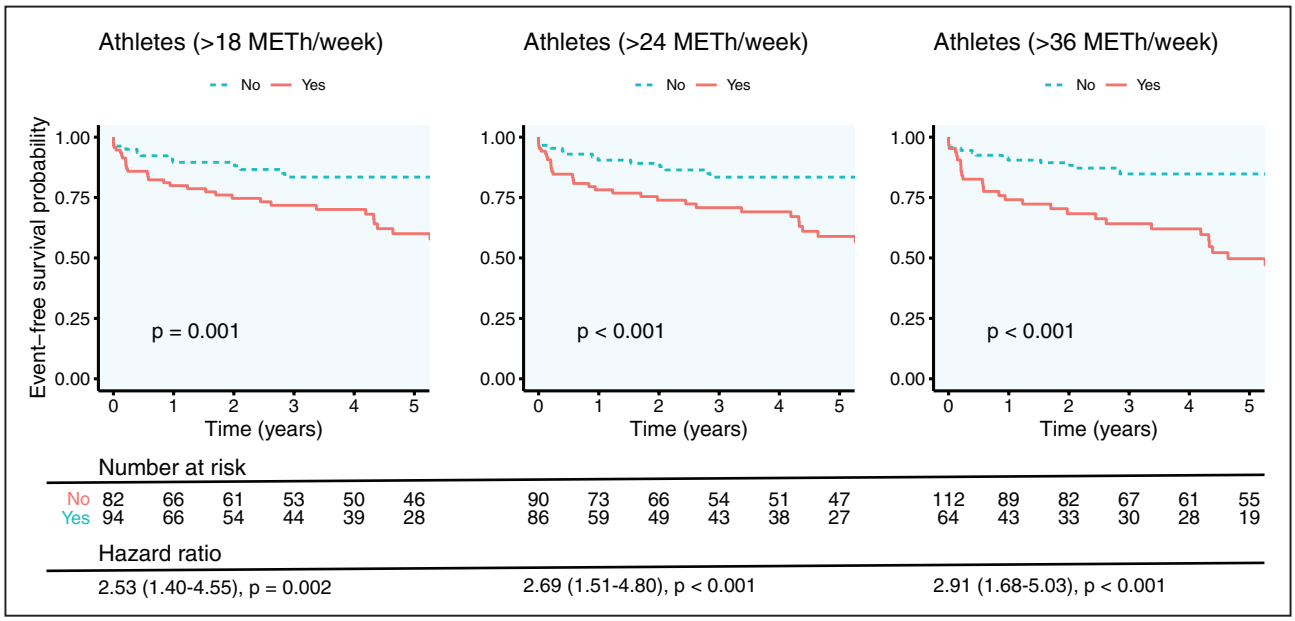

Figure 3. Athlete status as sustained ventricular arrhythmia (VA) risk predictor. For each exercise dose cutoff value defining athletes, a Kaplan-Meier plot for event-free survival is shown stratified by athletes (red lines) and nonathletes (blue dotted lines), as well as the univariable hazard ratio for incident sustained VA.

Table 2. Personalized Risk Prediction

	Adjusted HR (95% CI)	*P* value	C statistic (95% CI)	AIC
Risk calculator model	…	…	0.77 (0.71–0.84)	411.7
+Athlete defined as >18 METh/wk	1.31 (0.69–2.49)	0.412	0.77 (0.71–0.84)	+1.3
+Athlete defined as >24 METh/wk	1.43 (0.75–2.70)	0.270	0.78 (0.71–0.84)	+0.8
+Athlete defined as >36 METh/wk	1.67 (0.93–3.02)	0.088	0.78 (0.71–0.84)	−0.9

AIC indicates Akaike Information Criterion; and HR, hazard ratio.

Our study has several interesting results that will inform both current clinical care and future research. First, the association between exercise at diagnosis and risk of incident sustained VA appears to be nonlinear and dose dependent. Exercise limited to 15 to 30 METh/wk (2–4× the AHA-recommended minimum for healthy adults) appeared not to elevate VA risk beyond the natural ARVC development, hinting at a threshold model for safe exercise for future research. Second, while athletic patients had a higher risk of VA, this higher risk was accurately predicted by the risk calculator. Therefore, the current risk calculator (arvcrisk.com) can be applied in decision-making for implantable cardioverter defibrillator placement without alterations to athletes newly diagnosed with ARVC.

Quantifying the Relationship Between Exercise and Risk of Incident Sustained VA

Prior studies have provided indisputable evidence of the relationship between exercise and risk of sustained VA in ARVC patients and family members.[6,7,10,12,13,15] The effect of exercise dose on arrhythmic risk was demonstrated using predefined definitions of athlete status, competitive versus recreational exercise, or a single cutoff value based on quantiles or receiver operating characteristics analysis. Recently, a study by Wang et al[4] provided data hinting at dose dependency (in a cohort of family members with pathogenic variants), showing that the proportions of patients with VA increased with increasing exercise dose. However, no definite conclusions can be drawn as this result was derived from cross-sectional analysis with limited statistical power. In the current study, we evaluated the association of exercise dose with incident sustained VA using a longitudinal analysis. Our results provide the first detailed, quantified description suggesting a nonlinear dose-dependent relationship of exercise with VA outcomes, indicating that there may be a threshold below which exercise causes little to no increase in risk of incident sustained VA.

Toward a Safe Exercise Threshold

Exercise is important for health in the general population, and the AHA recommends at least 7.5 METh/wk.[5] However, it is uncertain to which extent patients with ARVC can enjoy the health benefits from exercising without increasing their arrhythmic risk, which is a major concern for many patients who are often young and likely active. Defining a safe exercise threshold, if any, is, therefore, a highly sought-after topic of scientific debate.[16] The European Society of Cardiology recently published a guideline in which patients with ARVC are advised to practice up to 150 minutes of low- to moderate-intensity (3–6 MET) exercise per week, equivalent to ≈15 METh/wk.[17] An example of this dose would be 2.5 hours of light running (at 4 mph). Of note, this recommendation has a weak level of evidence C (expert opinion).

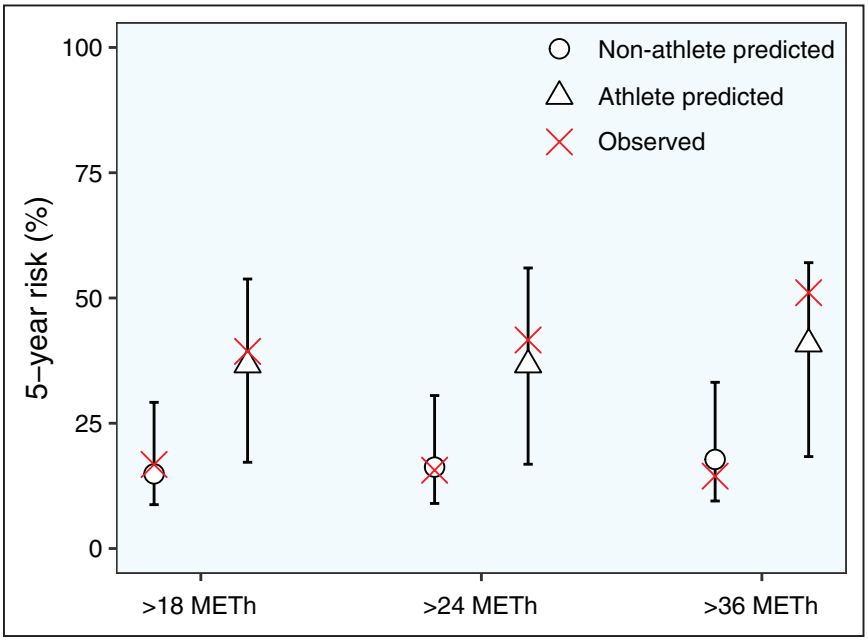

Figure 4. Observed vs predicted risk in athletes.
Plot of the observed 5-y sustained ventricular arrhythmia (VA) risk with 95% CI (black) stratified by athlete (triangles) and nonathlete (circles) status, for all 3 definitions of athlete. Superimposed is the predicted risk from the 5-y arrhythmogenic right ventricular cardiomyopathy sustained VA risk calculator (red crosses).

Prior studies have hinted at a safe level of exercise, for example, Ruwald et al[7] showed that recreational sport does not increase risk, but no threshold quantification was provided. Similarly, Lie et al[6] showed that those participating only in low-intensity (3–6 MET) exercise at presentation had the lowest proportion with VA, but the analysis was cross-sectional and not suitable to define a quantifiable threshold. Sawant et al[18] observed that *PKP2* mutation carriers restricting exercise below the upper bound of the recommended AHA minimum (<12.5 METh/wk) did not develop sustained VA. While suggestive for a potential safe threshold, this result was derived from a small cohort of 28 subjects only.

In our study, participation in up to 15 to 30 METh/wk of exercise at diagnosis was not associated with a higher risk of incident sustained VA in follow-up. While this is in line with the suggested threshold of 12.5 METh/wk by Sawant et al, as well as the European Society of Cardiology threshold of exercise up to 15 METh/wk, our findings, of course, refer to the exercise dose at diagnosis only. Whether continuing exercise at this level after diagnosis is similarly relatively safe needs prospective study. It is standard in our programs to recommend that newly diagnosed patients avoid competitive or frequent high-intensity endurance exercise consistent with professional guidelines, and most patients do their best to comply.

Exercise in Personalized Risk Prediction

Patients with ARVC with a substantial exercise participation history (ie, athletes) are at higher risk of sustained VA.[6,7,10] But the risk calculator for incident sustained VA (arvcrisk.com) does not specifically include an exercise metric.[8] This possible limitation has raised concerns about the validity of its predictions in athletes.[9] Reassuringly, Gasperetti et al[14] recently validated the risk calculator in a cohort of 25 Italian athletes (defined as those practicing >6 hours per week of >6 MET activities during the past 3 years) showing the risk calculator predictions to be accurate. However, these results were inconclusive due to the small sample size and the absence of nonathletes.

Our results confirm and extend this finding. We evaluated the incremental value of exercise dose and athlete status to the risk calculator estimate, using the 3 athlete definitions used in prior ARVC studies (>18, >24, and >36 METh/wk). Our results confirm that while indeed patients with an athletic history have a higher risk of sustained VA, this effect is rendered nonsignificant when corrected for the predicted risk generated by the risk calculator (Table 2). This is further confirmed by the reassuring agreement observed between the observed risk of sustained VA and the predictions from the risk calculator, regardless of exercise history (Figure 4). A possible explanation for this is the significant correlations we found between exercise and predictors currently in the calculator. The strongest correlation was that athletes were at younger age at diagnosis but showed higher premature ventricular complex count, more nonsustained ventricular tachycardia, more T-wave inversions, and a lower right ventricular ejection fraction as well. Therefore, the higher risk associated with athlete status appears to be already accounted for in the calculator. The nature of these correlations and whether athlete status could have incremental predictive value in alternative prediction models remains to be investigated in the future. Nonetheless, our results suggest that risk predictions generated by the ARVC risk calculator are equally accurate for both athletes and nonathletes.

Clinical Implications

This study shows that while athletes diagnosed with ARVC have a higher risk of incident sustained VA than nonathletes, the risk calculator (arvcrisk.com) provides accurate predictions for both. The risk calculator can be used by clinicians and newly diagnosed athletic or sedentary ARVC patients alike to estimate risk of developing a first sustained VA and use this information in shared decision-making regarding implantable cardioverter defibrillator implantation and other management options. As is true for the general ARVC risk calculator, risk calculator estimates for any VA are only accurate for patients who have not yet had a documented sustained VA.

The current study revealed a nonlinear dose-dependent effect of exercise history and the risk of sustained VA in patients diagnosed with ARVC without prior sustained VA, with no significant increase in risk below 15 to 30 METh/wk. This is a promising result advancing both our understanding of the relationship between exercise and VA and our search to specify a safe threshold. While our results specifically investigate only the influence of exercise at diagnosis on risk prediction, they do help establish what may be a reasonable exercise threshold for further study.

Study Limitations

Most of our study participants had pathogenic/likely pathogenic variants (76.1%), primarily of the *PKP2* gene (59.7%). Generalization to highly arrhythmogenic genetic variants (eg, males with *TMEM43* S358L) or populations in which the association of exercise with arrhythmic risk remains understudied (eg, *DSP*) should be met with caution. While our cohort of 176 patients provides sufficient statistical power to analyze incremental value of exercise to the preestablished risk calculator model, it did not allow for further exploration by fitting alternative prediction models. As exercise data were collected retrospectively through interviews, recall bias might have influenced the results. Finally,

this analysis captures exercise at the time of diagnosis. Patients in our centers are currently recommended to limit exercise when diagnosed and nearly all comply. Thus, the safety of exercise into the future for this progressive condition remains uncertain and will require longitudinal prospective studies of exercise. It is also worth noting that while this study provides insight into exercise relative to incident VA, data suggest that exercise also promotes structural progression.[6,10] This current study was not designed to assess whether the exercise necessary to accelerate structural progression is the same as for VA risk and there is as yet no risk calculator for structural progression in ARVC.

Conclusions

Exercise in patients with ARVC is associated with a significant increase in risk of sustained VA in a dose-dependent manner. However, our study revealed this relationship to be nonlinear, with no significant risk increase in ARVC patients exercising below 15 to 30 METh/wk at diagnosis. Future research is required to confirm this as a safe threshold for exercise continuation after diagnosis. Furthermore, while athletes have a 2.5 to 2.9× higher risk of sustained VA, this increase is largely already indirectly incorporated in the risk score from the ARVC risk calculator (arvcrisk.com). Adding athlete status to the prediction model showed no significant improvement, and the risk calculator provided accurate predictions for athletes with ARVC. The ARVC risk calculator can be used without modification for newly diagnosed athletes and nonathletes alike to estimate risk of incident VA.

ARTICLE INFORMATION

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