Title: Right ventricular strain rate during exercise accurately diagnoses athletes with right ventricular arrhythmias

Brief title: Exercise strain rate detects arrhythmias in athletes

Authors: Mathias Claeys, MD^{a,b}; GC^{a,b,c}, PC, CD, JUV, RDB, RW, HH, ALG

Word count: 4535 (introduction to figure legends)

Affiliations:

- ^a Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium
- ^b Division of Cardiology, University Hospitals Leuven, Leuven, Belgium
- ^c Baker Heart and Diabetes Institute, Melbourne, Australia
- ^d Division of Cardiology, University of Antwerp, Edegem, Belgium

Funding: This study was funded by a grant (Project G.0465.10N) from the Fund for Scientific Research Flanders (FWO), Brussels, Belgium

Disclosures:

MC: none; ALG has received grants from the Fund for Scientific Research Flanders (FWO) and from the National Health and Medical Research Council (NHMRC) of Australia; J-UV ##; RDB: none; PC: none; HH ##; RW is supported as a postdoctoral clinical researcher by the Fund for Scientific Research Flanders (FWO); GC is supported by a postdoctoral research grant from the Frans Van De Werf Fund for Clinical Cardiovascular Research, the UZ Leuven Future Fund and from the Mathilde Horlait-Dapsens Scholarship.

Address for correspondence:

Mathias Claeys, MD
Department of Cardiovascular Medicine
University Hospitals Leuven
Herestraat 49
B-3000 Leuven, Belgium

Phone: +32 16 344 235 Fax: +32 16 344 240
E-mail: mathias.claeys@uzleuven.be
Twitter : @ClaeysMathias

Acknowledgements:

Introduction

The differentiation between physiological cardiac remodelling due to intensive endurance exercise and maladaptive remodelling in endurance athletes with a propensity for complex ventricular arrhythmias can pose a difficult clinical conundrum. Amongst endurance athletes, ventricular arrhythmias often originate from the right ventricle (RV).¹ The degree of RV dysfunction at rest in athletic cohorts with so-called exercise-induced or gene-elusive arrhythmogenic cardiomyopathy (ARVC) is often mild despite the association with life-threatening arrhythmias.² This results in diagnostic overlap as also healthy endurance athletes typically develop substantial RV remodelling characterized by chamber dilation and a low-normal ejection fraction.³

Cardiac imaging during exercise has been proposed to improve risk stratification amongst athletes at risk for complex RV arrhythmias.⁴ Using exercise cardiac magnetic resonance (exCMR), we demonstrated that exercise evaluation can unmask RV contractile dysfunction in athletes with RV arrhythmias despite there being no abnormalities at rest.⁵ However, widespread use of exCMR is constrained and exercise echocardiography may be an attractive alternative because of its availability and high cost-effectiveness. Recently, more advanced echocardiographic modalities based on deformation imaging have been proposed as a means to increase diagnostic power, but so far these have not been evaluated during exercise.⁶

Therefore, we sought to compare RV performance during bicycle exercise echocardiography in healthy non-athletic controls (NAs), healthy endurance athletes (EAs) and subjects with exercise-induced ARVC (ei-ARVCs) with the aim of identifying the most accurate non-invasive echocardiographic parameter for differentiating athletes with underlying arrhythmogenic RV pathology. We hypothesized that deformation imaging during exercise would more accurately

identify subjects with intrinsic RV myocardial disease as compared with standard resting and exercise measures.

Methods

Subjects

In the current study, ei-ARVC subjects which were included in a previous study were compared with an expanded cohort of EAs and NAs. Therefore some of the data from the current cohort has been published previously, but the current study represents completely new measures of RV function during exercise and image data was analysed independently.⁵ For the recruitment and inclusion of ei-ARVCs, the following criteria were used: 1) previous or current competitive sports participation and intensive training (> 6 hours week); 2) presence of RV arrhythmias (excluding idiopathic RVOT-VT) with monomorphic left bundle branch block morphology (either sustained, non-sustained for ≥ 3 beats at a rate ≥ 120 b.p.m., or frequent isolated premature ventricular beats ≥ 2000 /day); 3) at most mild structural and functional abnormalities consistent with ‘athlete’s heart’^{4,7}; 4) no evidence of inherited/genetic disease. Athletes with moderate or severe RV functional or structural abnormalities at rest were excluded, as this is not typical for ‘exercise-induced’ or ‘gene-elusive’ ARVC. Healthy EAs and NAs were recruited via local advertisements and were eligible if they had no history of cardiovascular disease and if there was no evidence of structural or functional cardiovascular pathology on electrocardiogram and echocardiogram. In addition, EAs had to perform regular endurance exercise (≥ 6 h/weeks), while NAs could only participate in recreational sports activity (≤ 3 h/week of mild-to-moderate non-competitive endurance exercise). The study conformed to the Declaration of Helsinki and was approved by the local Ethics Committee. All participants provided written informed consent.

Study Design

First, stepwise cardiopulmonary exercise testing (50W +25W/min protocol) was performed on an upright cycle ergometer (ER900 and Oxycon Alpha, Jaeger, Germany) until exhaustion. Through breath-by-breath analysis minute ventilation (VE), oxygen consumption (VO₂), and carbon dioxide production (VCO₂) were assessed. Additional measures included peak heart rate, peak power and the ventilatory equivalent for carbon dioxide (VE/VCO₂) slope. In those subjects with an ICD, the device was reprogrammed so that all pacing and shocks were suspended during the exercise protocol. None of the subjects was paced.

Secondly, after at least 3 hours of rest to ensure full recuperation, bicycle exercise echocardiography with lateral tilt was performed on a programmable, electronically-braked semi-supine ergometer (Easystress, Ecogito Medical sprl, Liege, Belgium) both at rest and during low and moderate intensity exercise defined as 25% and 60% of peak power. Each stage lasted approximately 5 minutes depending on patient echogenicity and respiratory interference. Beta-blockers, non-dihydropyridine calcium-channel blockers and anti-arrhythmic drugs were withheld for at least 24 hours prior to the study protocol.

Stress echocardiography

Images were acquired using a Vivid E9 ultrasound system and analysed offline using EchoPAC version 113 (both GE Vingmed Ultrasound AS, Horten, Norway). First, the LV outflow tract diameter was determined from a parasternal long axis (PLAX) view at rest. Then, at each stage, different image sets were acquired and at least 10 cardiac cycles were stored for each set during exercise. LV volumes and ejection fraction, RV areas and fractional area change (RVFAC) and tricuspid annular plane systolic excursion (TAPSE) were analysed from a single-plane (RV-focused) apical 4-chamber view. Cardiac output was calculated as heart rate multiplied with stroke

volume, determined by the Doppler velocity time integral method in the LVOT (apical 5-chamber view). Systolic pulmonary artery pressure (PASP) was estimated from the maximal trans-tricuspid regurgitant velocity on CW Doppler without the addition of right atrial pressure. Determination of PASP was enhanced with agitated colloid contrast.⁸ Mean pulmonary artery pressure was calculated using the Chemla formula.⁹ Two-dimensional speckle tracking LV and RV free-wall longitudinal strain (SL) and strain rate (SRL) were acquired and analysed from single-plane (RV focused) apical 4-chamber grey-scale images (60-90 frames/s) in accordance with contemporary guidelines.^{10,11} Myocardial dispersion index (MDI) was calculated as the standard deviation of the contraction duration (time-to-peak-strain) in a 6-segment LV and RV model. Timing parameters were corrected for differences in R-R interval using Bazett's formula.

Statistics

Sample size calculation was based on our observation that RV function is similar at rest in healthy athletes and athletes with VA and the assumption, consistent with the results of Vitarelli et al, that the increase in RV_{FW}SL of ei-ARVCs would only be 25% of that of healthy EAs (Δ SL=0.9 vs. Δ SL=3.6).^{5,12} Accordingly, a sample size of n=12 was determined with an 80% power to detect a difference between athletes with and without VA (α =5%, $1-\beta$ =80%, n=12). Data were analysed using SPSS Statistics version 24 (IBM Corporation, Amonk, USA) and Analyse-it version 5.10 (Analyse-it Software Ltd, Leeds, UK). Normality was ensured using the Shapiro-Wilk test and variables are presented as means ($\pm$ standard deviation) or as medians (with 25% and 75% percentiles) accordingly. Categorical variables were compared using a Chi² test (or Fischer Exact test) and continuous data by either a Kruskal-Wallis H test or a one-way analysis of variance with the Bonferroni post-hoc correction. The cardiac response to exercise was assessed using mixed linear models that included subject group, exercise stage and their interaction as fixed effects with

the Bonferroni post-hoc correction for multiple comparisons. To account for the repeated nature of the data, an unstructured variance-covariance matrix was included. Pressure-flow relationships (i.e. P/Q slopes) were calculated through linear regression of the individual mean pulmonary artery pressure-cardiac output points obtained during exercise. Receiver-operating characteristics (ROC) were constructed and the area-under-the-curve (AUC) was calculated to identify the best echocardiographic parameter for distinguishing ei-ARVCs. Diagnostic performance of different parameters was compared using the Delong Delong Clarke-Pearson method.¹³ Intra- and interobserver variability of echocardiographic measures were assessed at rest and during exercise in a sample of 15 subjects (5 out of each group) and evaluated through the coefficient of variation and the intra-class correlation coefficient (two-way mixed and absolute agreement quoted), analysed on different cardiac cycles within the image set. A P-value of <0.05 was considered statistically significant.

Results

Baseline characteristics and cardiopulmonary exercise test

Forty-six male subjects (12 NAs, 17 healthy EA's and 17 ei-ARVCs) were included in the study. The baseline characteristics and results of the cardiopulmonary exercise test are summarized in Table 1. The three groups were of similar age but athletes with RV arrhythmias had a larger body surface area and had competed in sports longer compared to both other groups. ei-ARVCs had discontinued intensive sports on average 6.3 ($\pm$ 5.5) years prior to the evaluation. Eight ei-ARVCs had an ICD and 15 received anti-arrhythmic drug treatment, either alone or in combination. As evident from Supplementary Table 1, 11 ei-ARVCs met the Task Force Criteria for a definitive diagnosis of ARVC whilst 6 met criteria for possible ARVC. None of the subjects had clinical evidence of inherited disease nor a mutation on desmosomal gene sequencing. Subjects who met

the major ARVC Task Force arrhythmia criteria were more likely to have an ICD compared to those who did not ($p<0.05$). Isolated minor ARVC criteria were also present in 4 healthy EAs; two EAs had minor repolarization abnormalities and two EAs had a history of frequent ($> 500/24h$) ventricular premature beats. Healthy EAs had a significantly higher exercise capacity compared to both other groups as evident from their higher peak oxygen consumption and peak power (both $p<0.001$ between groups).

Biventricular response to exercise

The results of the exercise echocardiography protocol are summarized in Table 2 and Fig. 1 and 2. At rest and consistent with exercise-induced cardiac remodelling, EAs had greater LV volumes compared to NAs. RV areas of both EAs and ei-ARVCs were higher compared to controls ($p\leq 0.001$ between groups). There were no major differences in either LV or RV functional parameters at rest. RV afterload measured by systolic pulmonary artery pressure was similar across the three groups.

During exercise, echocardiographic measures were obtained in the majority of subjects. At moderate intensity, LV ejection fraction and RVFAC could be determined in 44 subjects (96%) and LV and RV speckle tracking deformation parameters could be reliably obtained in 40 (87%; 16 EAs, 9 NAs, 15 ei-ARVCs) and 37 subjects (80%, 15 EAs, 8 NAs, 14 ei-ARVCs) respectively. Similar changes during exercise were observed using both 2D echocardiographic and deformational measurements. Left ventricular function augmented during exercise in all three groups (Fig. 1), but the increase was blunted in ei-ARVCs ($p<0.05$ for interaction for LV ejection fraction, LVSL and LVSRL). However, at peak exercise only LVSL was lower in ei-ARVCs, whereas LVEF and LVSRL were similar. In contrast, the exercise-induced augmentation in RV function was clearly impaired (Fig. 2). RV functional parameters were consistently lower in ei-

ARVCs and neither RVFAC nor RV_{FW}SL increased during exercise (Fig. 2B, $p=0.001$ and Fig. 2C, $p=0.038$ for interaction respectively). RV_{FW}SRL on the other hand increased in ei-ARVCs to a lesser extent compared to both other groups (Fig. 2D, $p<0.001$ for interaction). The change in afterload during exercise did not differ between groups (Supplementary Fig. 1). Echocardiographic measures of LV and RV function had good to excellent reproducibility both at rest and during exercise with intra-class correlation coefficients ranging from 0.91 to 0.99 for intra-observer variability and 0.71 to 0.99 for inter-observer variability (Supplementary Table 2). An example of a characteristic RV SRL curve of an EA and an ei-ARVC is provided in Fig. 3.

Timing and mechanical dispersion at rest and during exercise

When corrected for heart rate, there were no differences in the time-to-peak shortening of both ventricles at rest (Supplementary Table 3). However, ei-ARVCs had a higher LV MDI and tended to have a higher RV MDI compared to NAs and EAs. During exercise, RV free wall time-to-peak-strain was significantly longer in ei-ARVCs compared to both NAs and EAs (both $p<0.01$). As opposed to resting measures, there were no differences in either LV or RV dispersion during exercise.

Discrimination of subjects with arrhythmias

As evident from Table 3 and Fig. 4, RV measures at rest were unable to differentiate ei-ARVCs from apparently healthy subjects (EAs and NAs combined) with the exception of RV mechanical dispersion index which had moderate discriminatory power [AUC= 0.72 (0.54–0.90)]. At moderate exercise intensity, the diagnostic performance of RV functional parameters to identify ei-ARVCs increased significantly. A RV_{FW}SRL > -2.35 (i.e. more positive) had a 93% sensitivity and 82% specificity for discriminating ei-ARVCs. Exercise-to-rest differences, with the exception of Δ TAPSE, had reasonable to good accuracy (Supplementary Fig. 2) as well. Separate ROC analysis

for the comparison of ei-ARVCs with EAs and NAs revealed similar diagnostic performance and cut-offs (Supplementary table 4 and Supplementary Fig. 3).

RV functional impairment is proportional to disease severity

When we separately assessed athletes with a more severe phenotype as evidenced by the clinical decision to implant a defibrillator (ICD), several interesting observations could be made (Supplementary Fig. 4). Firstly, as might be expected, subjects with an ICD clearly had more pronounced RV dysfunction. During exercise, RVFAC only increased in ei-ARVCs without an ICD (Supplementary Fig. 4A) while $RV_{FW}SL$ did not increase in either subgroup (Supplementary Fig. 4B). $RV_{FW}SRL$ increased in both subgroups of ei-ARVCs, but to a lesser degree compared to healthy subjects (Supplementary Fig. 4C). Importantly, $RV_{FW}SRL$ during moderate exercise intensity [AUC 0.91 (0.78 – 1.00)] was the only variable that accurately differentiated ei-ARVC without an ICD from healthy subjects (Supplementary Table 5 and Supplementary Fig. 5; $p < 0.05$ for comparison of AUC versus all other variables). In contrast, neither RVFAC nor $RV_{FW}SL$ at rest or during exercise had sufficient discriminatory power.

Discussion

In this study, we examined the diagnostic performance of bicycle exercise echocardiography to differentiate male subjects with exercise-induced ARVC from apparently healthy male endurance athletes and non-athletic controls. We found that ARVC subjects had impaired RV functional reserve, which was concealed at rest but unmasked during exercise. Furthermore, exercise parameters outperformed resting measurements in identifying subjects with RV arrhythmias. $RV_{FW}SRL$ at moderate exercise intensity was the most accurate discriminator of disease and the only echocardiographic parameter able to identify those subjects with a milder phenotype. Thus,

evaluation of strain rate during exercise may be a promising non-invasive means of identifying subtle RV dysfunction that is not apparent at rest.

Deformation imaging in arrhythmogenic RV pathology

Cardiac deformation or strain imaging quantifies cardiac motion and enables evaluation of regional and global myocardial function on a spatial and temporal basis.¹⁴ As longitudinal shortening accounts for the majority of RV stroke volume generation, longitudinal deformation is a reliable estimator of RV function in healthy subjects.^{15,16} In patients with ARVC, deformation imaging unmasks subclinical disease and even identifies subjects at risk of disease progression or ventricular arrhythmias.^{17–19} Moreover, amongst asymptomatic ARVC mutation carriers nearly 50% of individuals have an abnormal deformation pattern, which is associated with an increased risk of disease progression at follow-up.^{20,21} Intriguingly, these abnormalities were most pronounced in the basal RV free wall, a region where lower strain and strain rate values have also been observed in healthy athletes.²²

Previously we have demonstrated that the ambiguity of lower RV strain values in athletes can be resolved by exercise imaging and evaluation of RV functional reserve.²³ Using a similar approach, we observed no difference in RV function between healthy athletes and non-athletic controls when measurements were performed when the greatest load is imposed on the RV, i.e. during exercise. However, in ei-ARVCs exercise, was able to unmask RV dysfunction, which was concealed at rest. These results are in line with our previous report on RV contractile dysfunction occurring during exercise in ei-ARVCs as assessed by exCMR.⁵ However, the novelty of the current study is that we were able to show the same hemodynamic differences using simpler methodology. Given the widespread availability of exercise echocardiography and the implementation of deformation

measurements in contemporary guidelines, these hemodynamic alterations can be detected in daily clinical practice.

Previous studies assessing RV functional reserve have predominantly looked at the relative change in peak strain from rest-to-exercise.^{24,25} Vitarelli et al identified ΔSL as the most accurate parameter to identify subjects with ARVC.¹² However, in these studies cardiac function was already impaired in the rested state, as opposed to our cohort in which RV function was ostensibly normal at rest. An important finding in our current study is that $RV_{FW}SRL$ during exercise was the most accurate discriminator of RV disease and outperformed all other measurements of RV function. As such, our results indicate that RV strain rate may be well suited to evaluate RV functional reserve and identify subclinical disease in athletes, and potentially in other populations. Conversely, mechanical dispersion appeared to be only discriminative at rest. We speculate this might relate the effects of exercise on electrical dispersion and the pathophysiological differences between gene-elusive and gene-positive disease.

Clinical implications

The complex interaction between genetic and environmental factors governing the development of RV arrhythmias in athletes, fuels a continued debate about the exercise-induced arrhythmia phenotype.²⁶ Regardless, accurate identification of intrinsic RV disease is relevant in athletes as complex VA frequently arise from the right side and vigorous exercise has a detrimental effect on the ARVC phenotype.^{1,27,28} However, the differentiation between athlete's heart and pathological RV remodelling is often difficult and requires a multi-modality approach.²⁹ Our current data demonstrate that exercise imaging facilitates disease discrimination and is able to depict those ei-ARVCs with a more severe phenotype, which is important for risk stratification and disease management. As strain rate more closely corresponds to intrinsic myocardial contractility, we may

hypothesize that measures of RV deformation imaging during exercise might have superior accuracy, particularly in early disease stages when only minor abnormalities are expected, but this remains to be established in future studies.³⁰

Study limitations

The modest sample size may have increased the probability of type II statistical errors while multiple comparisons increase the likelihood of type I errors. Nevertheless, this is the largest study to date to investigate ei-ARVCs with deformation imaging during exercise. Secondly, the results could have been confounded by disease heterogeneity, RV remodelling, prior athletic training and time since sports withdrawal of ei-ARVCs. However, as RV function did not differ between EAs and NAs and diagnostic performance was similar when both groups were analysed separately, a substantial influence is unlikely. Thirdly, the negative inotropic/chronotropic effect of anti-arrhythmic drugs or the RV lead could have influenced the exercise response in ei-ARVCs. The pharmacological effects were minimized by ensuring a wash-out > 24h. Moreover, the residual effect is likely minimal given the greater impairment of RV function whereas a drug effect would be biventricular. Furthermore, the absence of more than mild tricuspid regurgitation and similar apical deformation between eiARVCs with and without ICD (despite apical lead position) argue against a direct or indirect effect of the RV lead on the exercise response. Fourthly, the presence of pathology or an RV lead precludes a blinded. We tried to minimize bias by analysing image data before accessing clinical data and by evaluating subjects in a random order. Finally, speckle-tracking deformation imaging has some inherent technical limitations. Firstly, adequate image quality was not available in every subject. However high-quality images were still acquired in the vast majority and similar patterns were observed both by different echocardiographic measures and previously using gold standard exCMR.⁵ Secondly, the limited temporal resolution of 2D strain

may have led to under-sampling with an underestimation of true peak values. However, this limitation pertains to all groups and even though heart rate was higher in healthy subjects, meaningful differences were still demonstrable. Tissue Doppler Imaging has superior temporal resolution, but is challenging to perform during exercise due to its angle-dependency and increased noise and we have previously demonstrated good agreement between both techniques at rest and during exercise.²³

Conclusion

Exercise deformation imaging holds promise as a non-invasive diagnostic tool to identify intrinsic RV dysfunction which is not detectable at rest. Strain rate appears to be the most accurate parameter and should be incorporated in future, prospective studies to identify subclinical disease and assess outcome at an early stage.

Acknowledgements:

None

References

1. Heidbüchel H, Hoogsteen J, Fagard R, Vanhees L, Ector H, Willems R, et al. High prevalence of right ventricular involvement in endurance athletes with ventricular arrhythmias. Role of an electrophysiologic study in risk stratification. *Eur Heart J* 2003;**24**:1473–1480.
2. Borgquist R, Haugaa KH, Gilljam T, Bundgaard H, Hansen J, Eschen O, et al. The diagnostic performance of imaging methods in ARVC using the 2010 Task Force criteria. *Eur Heart J Cardiovasc Imaging* 2014;**15**:1219–1225.

3. Oxborough D, Sharma S, Shave R, Whyte G, Birch K, Artis N, et al. The right ventricle of the endurance athlete: the relationship between morphology and deformation. *J Am Soc Echocardiogr* 2012;**25**:263–271.
4. La Gerche A, Heidbüchel H, Burns AT, Mooney DJ, Taylor AJ, Pfluger HB, et al. Disproportionate exercise load and remodeling of the athlete's right ventricle. *Med Sci Sports Exerc* 2011;**43**:974–981.
5. La Gerche A, Claessen G, Dymarkowski S, Voigt J-U, De Buck F, Vanhees L, et al. Exercise-induced right ventricular dysfunction is associated with ventricular arrhythmias in endurance athletes. *Eur Heart J* 2015;**36**:1998–2010.
6. Haugaa KH, Basso C, Badano LP, Bucciarelli-Ducci C, Cardim N, Gaemperli O, et al. Comprehensive multi-modality imaging approach in arrhythmogenic cardiomyopathy-an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2017;**18**:237–253.
7. D'Ascenzi F, Pelliccia A, Corrado D, Cameli M, Curci V, Alvino F, et al. Right ventricular remodelling induced by exercise training in competitive athletes. *Eur Heart J Cardiovasc Imaging* 2016;**17**:301–307.
8. Claessen G, La Gerche A, Voigt J-U, Dymarkowski S, Schnell F, Petit T, et al. Accuracy of Echocardiography to Evaluate Pulmonary Vascular and RV Function During Exercise. *JACC Cardiovasc Imaging* 2016;**9**:532–543.
9. Chemla D, Castelain V, Humbert M, Hébert J-L, Simonneau G, Lecarpentier Y, et al. New formula for predicting mean pulmonary artery pressure using systolic pulmonary artery pressure. *Chest* 2004;**126**:1313–1317.
10. Voigt J-U, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the

EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:1–11.

11. Badano LP, Kolias TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging* 2018;**19**:591–600.

12. Vitarelli A, Cortes Morichetti M, Capotosto L, De Cicco V, Ricci S, Caranci F, et al. Utility of strain echocardiography at rest and after stress testing in arrhythmogenic right ventricular dysplasia. *Am J Cardiol* 2013;**111**:1344–1350.

13. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;**44**:837–845.

14. Collier P, Phelan D, Klein A. A Test in Context: Myocardial Strain Measured by Speckle-Tracking Echocardiography. *J Am Coll Cardiol* 2017;**69**:1043–1056.

15. Focardi M, Cameli M, Carbone SF, Massoni A, De Vito R, Lisi M, et al. Traditional and innovative echocardiographic parameters for the analysis of right ventricular performance in comparison with cardiac magnetic resonance. *Eur Heart J Cardiovasc Imaging* 2015;**16**:47–52.

16. Carlsson M, Ugander M, Heiberg E, Arheden H. The quantitative relationship between longitudinal and radial function in left, right, and total heart pumping in humans. *Am J Physiol Heart Circ Physiol* 2007;**293**:H636–644.

17. Teske AJ, Cox MG PJ, Te Riele ASJM, De Boeck BW, Doevendans PA, Hauer RNW, et al. Early detection of regional functional abnormalities in asymptomatic ARVD/C gene carriers. *J Am Soc Echocardiogr* 2012;**25**:997–1006.

18. Sarvari SI, Haugaa KH, Anfinssen O-G, Leren TP, Smiseth OA, Kongsgaard E, et al. Right ventricular mechanical dispersion is related to malignant arrhythmias: a study of patients with arrhythmogenic right ventricular cardiomyopathy and subclinical right ventricular dysfunction. *Eur Heart J* 2011;**32**:1089–1096.
19. Leren IS, Saberniak J, Haland TF, Edvardsen T, Haugaa KH. Combination of ECG and Echocardiography for Identification of Arrhythmic Events in Early ARVC. *JACC Cardiovasc Imaging* 2017;**10**:503–513.
20. Mast TP, Taha K, Cramer MJ, Lumens J, van der Heijden JF, Bouma BJ, et al. The Prognostic Value of Right Ventricular Deformation Imaging in Early Arrhythmogenic Right Ventricular Cardiomyopathy. *JACC Cardiovasc Imaging* 2019;**12**:446-455.
21. Mast TP, Teske AJ, Walmsley J, van der Heijden JF, van Es R, Prinzen FW, et al. Right Ventricular Imaging and Computer Simulation for Electromechanical Substrate Characterization in Arrhythmogenic Right Ventricular Cardiomyopathy. *J Am Coll Cardiol* 2016;**68**:2185–2197.
22. Teske AJ, Prakken NH, De Boeck BW, Velthuis BK, Martens EP, Doevendans PA, et al. Echocardiographic tissue deformation imaging of right ventricular systolic function in endurance athletes. *Eur Heart J* 2009;**30**:969–977.
23. La Gerche A, Burns AT, D’Hooge J, Macisaac AI, Heidbüchel H, Prior DL. Exercise strain rate imaging demonstrates normal right ventricular contractile reserve and clarifies ambiguous resting measures in endurance athletes. *J Am Soc Echocardiogr* 2012;**25**:253-262.e1.
24. Bhatt SM, Wang Y, Elci OU, Goldmuntz E, McBride M, Paridon S, et al. Right Ventricular Contractile Reserve Is Impaired in Children and Adolescents With Repaired Tetralogy of Fallot: An Exercise Strain Imaging Study. *Journal of the American Society of Echocardiography* 2018;

25. D'Andrea A, Limongelli G, Baldini L, Verrengia M, Carbone A, Di Palma E, et al. Exercise speckle-tracking strain imaging demonstrates impaired right ventricular contractile reserve in hypertrophic cardiomyopathy. *International Journal of Cardiology* 2017;**227**:209–216.
26. Guasch E, Mont L. Diagnosis, pathophysiology, and management of exercise-induced arrhythmias. *Nat Rev Cardiol* 2017;**14**:88–101.
27. James CA, Bhonsale A, Tichnell C, Murray B, Russell SD, Tandri H, et al. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *J Am Coll Cardiol* 2013;**62**:1290–1297.
28. Saberniak J, Hasselberg NE, Borgquist R, Platonov PG, Sarvari SI, Smith H-J, et al. Vigorous physical activity impairs myocardial function in patients with arrhythmogenic right ventricular cardiomyopathy and in mutation positive family members. *Eur J Heart Fail* 2014;**16**:1337–1344.
29. Chivulescu M, Haugaa K, Lie ØH, Edvardsen T, Ginghină C, Popescu BA, et al. Right ventricular remodeling in athletes and in arrhythmogenic cardiomyopathy. *Scand Cardiovasc J* 2018;**52**:13–19.
30. Ferferieva V, Van den Bergh A, Claus P, Jasaityte R, Veulemans P, Pellens M, et al. The relative value of strain and strain rate for defining intrinsic myocardial function. *Am J Physiol Heart Circ Physiol* 2012;**302**:H188-195.

Tables

Table 1. Baseline Characteristics

	EAs (n=17)	NAs (n=12)	ei-ARVCs (n=17)	P-value
Clinical				
Age (y)	34±8	37±13	39±8	0.362
Male	17	12	17	1
BSA (m ²)	1.97±0.11	2.00±0.11	2.10±0.12 †	0.006
Years of endurance sports	10 (6 – 21)	7 (0 – 13)	20 (10 – 28) *	0.017
Hours of endurance sports per week	14 (8 – 16) *	1 (0 – 3)	11 (5 – 14) *	<0.001
ICD	0	0	8	
Cardiopulmonary exercise test				
Peak VO ₂ (ml.kg ⁻¹ .min ⁻¹)	54.5±8.7 *	37.2±7.2	38.1±7.7 †	<0.001
Peak Power (Watts)	372±60 *	261±51	310±52 †	<0.001
Peak HR (b.p.m.)	179±10	174±19	165±22	0.073
Peak RER	1.19±0.09	1.21±0.06	1.20±0.08	0.811
VE/VCO ₂ slope	26±3	25±4	27±3	0.131

P-values for group comparison. *,† = p<0.05 Bonferroni post-hoc compared to NAs/EAs respectively. *BSA*, body surface area; *EAs*, endurance athletes; *ei-ARVCs*, exercise-induced ARVC; *HR*, heart rate; *ICD*, implantable cardioverter-defibrillator; *NAs*, non-athletes; *RER*, respiratory exchange ratio; *VE*, minute ventilation; *VCO₂*, CO₂ production; *VO₂*, oxygen consumption.

Table 2. Echocardiographic parameters at rest and during moderate exercise.

	EAs (n=17)	NAs (n=12)	ei-ARVCs (n=17)	P-value
Rest				
HR (b.p.m.)	58±8*	71±13	62±12	0.011
LVEDV (ml)	150±24*	109±19	121±30†	<0.001
LVESV (ml)	62±17*	44±11	48±22	0.015
LVSV (ml)	88±13*	65±10	72±14†	<0.001
LVEF (%)	58.9±6.1	60.4±4.2	61.3±7.9	0.565
LVSL	-18.0±1.9	-17.7±2.2	-18.1±3.1	0.905
LVSRL	-1.01±0.11	-1.13±0.17	-1.01±0.13	0.056
RVEDA (cm ²)	29.2±5.2*	22.2±3.6	30.6±6.0*	<0.001
RVESA (cm ²)	16.1±3.5*	12.2±2.2	18.1±5.0*	0.001
RVFAC (%)	44.9±5.7	44.8±6.7	41.1±6.9	0.180
TAPSE (mm)	27±5	25±4	26±4	0.395
RV _{FW} SL	-25.4±3.8	-25.6±2.9	-24.8±4.6	0.817
RV _{FW} SRL	-1.42±0.28	-1.53±0.28	-1.30±0.28	0.090
PASP (mmHg)	20±4	21±4	23±4	0.068
Exercise				
HR (b.p.m.)	127±12	121±12	111±18†	0.014
LVEDV (ml)	152±30*	115±21	123±24†	0.001
LVESV (ml)	47±16	37±9	41±14	0.120
LVSV (ml)	104±17*	78±13	80±17†	<0.001
LVEF (%)	69.3±5.3	68.4±3	66.4±7.5	0.348
LVSL	-21.9±1.9	-22.8±2.2	-20.0±3.3*	0.030
LVSRL	-1.44±0.18	-1.39±0.30	-1.24±0.22	0.334
RVEDA (cm ²)	27.1±4.6*	21.6±3.8	30.8±6.5*	<0.001
RVESA (cm ²)	12.7±3.3	9.4±1.9	17.9±6.3*†	<0.001
RVFAC (%)	53.7±6.2	56.3±4.3	43.0±9.6*†	<0.001
TAPSE (mm)	36±4	33±3	33±5	0.072
RV _{FW} SL	-31.8±2.87	-32.2±3.4	-26.4±5.8*†	0.003
RV _{FW} SRL	-2.54±0.38	-2.73±0.51	-1.80±0.42*†	<0.001
PASP (mmHg)	43±8	43±6	44±8	0.921

P-values for group comparison. *,† = $p < 0.05$ Bonferroni post-hoc compared to NAs/EAs respectively. *EDA*, end-diastolic area; *EDV*, end-diastolic volume; *EF*, ejection fraction; *ESA*, end-systolic area; *ESV*, end-systolic volume; *FAC*, fractional area change; *HR*, heart rate; *PASP*, systolic pulmonary artery pressure; *SL*, longitudinal strain; *SRL*, longitudinal strain rate.

Table 3. Accuracy of different parameters to identify subjects with exercise-induced ARVC compared to healthy subjects (athletes and non-athletic controls combined).

	AUC (mean $\pm$ 95% CI)	P-value	Cutoff value	Sensitivity (%)	Specificity (%)
RVFAC _{rest}	0.66 (0.49 – 0.82)	0.067	-	-	-
RV _{FWSL} _{rest}	0.53 (0.35 – 0.71)	0.794	-	-	-
RV _{FWSRL} _{rest}	0.62 (0.45 – 0.79)	0.165	-	-	-
RVMDI _{rest}	0.72 (0.54 – 0.90)	0.016	32	63	85
RVFAC _{ex}	0.84 (0.71 – 0.96)	<0.001	49.9	81	82
RV _{FWSL} _{ex}	0.82 (0.66 – 0.98)	0.002	-28.9	79	91
RV _{FWSRL} _{ex}	0.95 (0.88 – 1.00)	<0.001	-2.35	93	82
RVMDI _{ex}	0.57 (0.37 – 0.78)	0.473	-	-	-

RV fractional area change (RVFAC), RV free-wall longitudinal strain (RV_{FWSL}) / strain rate (RV_{FWSRL}) and RV myocardial dispersion index at rest and during exercise (ex).

Figure Legends

Figure 1. LV function during exercise

Evolution of (A) ejection fraction (LVEF), (B) longitudinal strain (LVSL) and (C) strain rate (LVSRL) in non-athletic controls (NAs), subjects with exercise-induced ARVC (ei-ARVCs) and endurance athletes (EAs). Data are presented as means and standard error of the mean. Coloured p-values indicate main effect of exercise. *,† p<0.05 Bonferroni post-hoc compared to NAs and EAs respectively.

Figure 2. RV function during exercise

Evolution of (A) tricuspid annular plane systolic excursion (TAPSE), (B) fractional area change (RVFAC), (C) free-wall longitudinal strain (RV_{FW}SL) and (D) strain rate (RV_{FW}SRL) in non-athletic controls (NAs), subjects with exercise-induced ARVC (ei-ARVCs) and endurance athletes (EAs). Data are presented as means and standard error of the mean. Coloured p-values indicate main effect of exercise. *,† p<0.05 Bonferroni post-hoc compared to NAs and EAs respectively.

Figure 3. RV free-wall strain rate at rest and during exercise.

Basal (red), mid (blue) and apical (pink) RV free-wall strain rate during exercise at rest (upper row) and during exercise (lower row) in a healthy endurance athletes (left column) and an exercise-induced ARVC subject (right column) with peak systolic strain rate indicated by white arrows.

Figure 4. ROC curves for echocardiographic parameters at rest and during exercise.

Diagnostic performance of RV fractional area change (RVFAC), free wall longitudinal strain (RV_{FW}SL), strain rate (RV_{FW}SRL) and myocardial dispersion index (RVMDI) at rest and during exercise to discriminate endurance athletes with ventricular arrhythmias from apparently healthy subjects (endurance athletes and non-athletic controls combined).

Supplementary Table 1. Medication, ARVC Task Force Criteria, Baseline and exercise ECG.

	EAs (n=17)	NAs (n=12)	ei-ARVC (n=17)		P-value
			ICD –	ICD +	
Medications					
Beta-blocker	-	-	6	5	N/A
Calcium-antagonist	-	-	2	0	
Flecainide	-	-	0	2	
Amiodarone	-	-	1	2	
Sotalol	-	-	0	2	
Cibenzoline	-	-	0	1	
ARVC Task Force Criteria					
Definite	0	0	3	8	<0.001
Borderline	0	0	0		
Possible	4	0	6	0	
ARVC Task Force Criteria Details					
Global or regional dysfunction and structural alterations					
Major	0	0	1	4	0.010
Minor	0	0	1	0	1
Repolarization abnormalities					
Major	0	0	3	4	0.001
Minor	2	0	2	3	0.135
Depolarization/conduction abnormalities					
Major	0	0	0		1
Minor	0	0	2	5	0.001
Ventricular Arrhythmias					
Major	0	0	3	7	<0.001
Minor	2	0	6	1	0.025
Family History					
Major	0	0	0		1
Minor	0	0	0		1

Supplementary Table 1. Medication, ARVC Task Force Criteria, Baseline and exercise ECG. (continued)

	EAs (n=17)	NAs (n=12)	ei-ARVC (n=17)		P-value
			ICD –	ICD +	
Baseline ECG					
Sinus Rhythm	17	12	17		1
Incomplete LBBB	0	0	1	1	0.327
Incomplete RBBB	6	1	3	1	0.239
RBBB	0	0	0	1	1
Unspecified BBB	0	0	0	1	1
TWI V1-V2 (minor)	2	0	1	2	0.104
TWI V1-V3 (major)	0	0	3	4	0.001
TWI V1-V4 & RBBB (minor)	0	0	0	1	1
TWI V4-V6 (minor)	0	0	1	0	1
ε-wave (major)	0	0	0		1
S-wave upstroke > 55ms (minor)	0	0	0	3	0.104
QRS _{rest} (ms)	96±11	99±8	101±6	109±17	0.097
QRS _{exercise} (ms)	90±11	90±12	93±13	105±17	0.115
Exercise ECG					
Any ectopics	6	3	8	6	0.005
Non-RVOT morphology	3	2	3	4	0.331
Multiple Morphologies	0	0	1	0	1
Frequent ectopy (>50)	0	0	4	0	0.031
Non-sustained VT	0	0	3	0	0.104

P-values for 3 groups comparison. (*ei-*)ARVC, (*exercise-induced*) arrhythmogenic right ventricular cardiomyopathy; EAs, endurance athletes; (L)(R)BBB; (*left*)(*right*) bundle branch block; NAs, non-athletic controls; VT, ventricular tachycardia.

Supplementary Table 2. Observer variability for the different echocardiographic measures

	Intra-observer			Inter-observer		
	CV (%)	ICC (95% CI)	Mean difference $\pm$ SD	CV (%)	ICC (95% CI)	Mean difference $\pm$ SD
Rest						
LVEF (%)	2.61	0.93 (0.72 – 0.98)	1.55 $\pm$ 1.15	4.26	0.83 (0.32 – 0.95)	2.51 $\pm$ 1.71
LVSL	4.07	0.91 (0.72 – 0.97)	0.75 $\pm$ 0.56	9.08	0.77 (0.32 – 0.92)	1.55 $\pm$ 1.04
LVSRL	5.06	0.92 (0.73 – 0.97)	0.05 $\pm$ 0.05	8.05	0.85 (0.56 – 0.95)	0.08 $\pm$ 0.06
TAPSE (mm)	3.10	0.98 (0.94 – 0.99)	0.82 $\pm$ 0.63	3.68	0.97 (0.92 – 0.99)	1.00 $\pm$ 0.76
RVFAC (%)	4.28	0.97 (0.91 – 0.99)	1.82 $\pm$ 1.54	5.94	0.94 (0.82 – 0.98)	2.66 $\pm$ 2.17
RVSL	4.74	0.95 (0.87 – 0.98)	1.19 $\pm$ 1.68	5.94	0.96 (0.88 – 0.99)	1.38 $\pm$ 1.15
RVSRL	8.02	0.96 (0.86 – 0.99)	0.11 $\pm$ 0.11	10.42	0.94 (0.75 – 0.98)	0.13 $\pm$ 0.11
Exercise at high intensity						
LVEF (%)	1.86	0.94 (0.80 – 0.98)	1.24 $\pm$ 1.19	5.49	0.71 (0.00 – 0.93)	3.58 $\pm$ 1.91
LVSL	4.04	0.93 (0.80 – 0.98)	0.80 $\pm$ 0.79	5.53	0.89 (0.65 – 0.96)	1.12 $\pm$ 0.84
LVSRL	6.15	0.93 (0.78 – 0.98)	0.09 $\pm$ 0.08	11.32	0.74 (0.22 – 0.91)	0.16 $\pm$ 0.13
TAPSE (mm)	2.86	0.99 (0.97 – 1.00)	0.93 $\pm$ 0.57	2.51	0.99 (0.97 – 1.00)	0.81 $\pm$ 0.64
RVFAC (%)	2.97	0.99 (0.98 – 1.00)	1.47 $\pm$ 1.14	7.01	0.97 (0.91 – 0.99)	3.18 $\pm$ 2.33
RVSL	4.10	0.99 (0.96 – 0.99)	1.12 $\pm$ 0.87	7.93	0.95 (0.85 – 0.98)	2.28 $\pm$ 1.55
RVSRL	6.13	0.98 (0.94 – 0.99)	0.14 $\pm$ 0.12	9.52	0.94 (0.81 – 0.98)	0.23 $\pm$ 0.22

Supplementary Table 3. Timing parameters, corrected for HR, at rest and during exercise at high intensity

	EAs (n=17)	NAs (n=12)	ei-ARVC (n=17)	P-value
Rest				
Peak SL _{LV} (ms)	390 ± 26	386 ± 28	391 ± 35	0.922
Peak SL _{RVFW} (ms)	379 ± 21	381 ± 32	399 ± 40	0.188
LV dispersion (ms)	39 ± 10	29 ± 8	42 ± 14 *	0.035
RV dispersion (ms)	23 ± 10	21 ± 11	35 ± 20	0.028
Exercise				
Peak SL _{LV} (ms)	400 ± 28	386 ± 16	405 ± 26	0.159
Peak SL _{RVFW} (ms)	377 ± 24	369 ± 24	416 ± 34 *†	0.001
LV dispersion (ms)	38 ± 10	35 ± 12	37 ± 13	0.764
RV dispersion (ms)	32 ± 10	32 ± 10	33 ± 10	0.923

Timing parameters were corrected for R-R interval using Bazett's formula. P values for group comparison. *,† = p<0.05 Bonferroni post-hoc compared to EAs and NAs respectively. *EA*, endurance athletes; *ei-ARVC*, exercise-induced ARVC; *NAs*, non-athletes.

Supplementary Table 4. Accuracy of different parameters to identify athletes with RV arrhythmias.

	AUC (mean $\pm$ 95% CI)	P-value	Cutoff value	Sensitivity (%)	Specificity (%)
ei-ARVC vs. EAs					
RVFAC _{rest}	0.67 (0.48 – 0.85)	0.098	-	-	-
RV _{FWSL} _{rest}	0.52 (0.32 – 0.72)	0.850	-	-	-
RV _{FW SRL} _{rest}	0.58 (0.38 – 0.78)	0.438	-	-	-
RV MDI _{rest}	0.70 (0.51 – 0.89)	0.048	32	65	82
RVFAC _{ex}	0.81 (0.67 – 0.96)	0.002	47	63	94
RV _{FWSL} _{ex}	0.82 (0.65 – 0.99)	0.004	-28.9	79	93
RV _{FW SRL} _{ex}	0.95 (0.87 – 1.00)	<0.001	-2.35	93	80
RV MDI _{ex}	0.57 (0.36 – 0.79)	0.504	-	-	-
ei-ARVC vs. NAs					
RVFAC _{rest}	0.66 (0.45 – 0.87)	0.150	-	-	-
RV _{FWSL} _{rest}	0.53 (0.32 – 0.74)	0.791	-	-	-
RV _{FW SRL} _{rest}	0.65 (0.44 – 0.86)	0.200	-	-	-
RV MDI _{rest}	0.76 (0.57 – 0.94)	0.031	32	63	90
RVFAC _{ex}	0.91 (0.81 – 1.00)	<0.001	50	81	100
RV _{FWSL} _{ex}	0.82 (0.63 – 1.00)	0.021	-29.8	79	86
RV _{FW SRL} _{ex}	0.94 (0.83 – 1.00)	0.001	-2.35	93	86
RV MDI _{ex}	0.57 (0.30 – 0.85)	0.607	-	-	-

AUC, P values for ROC curve and sensitivity and specificity for RV fractional area change (RVFAC), RV free wall longitudinal strain (RV_{FWSL}), RV free wall longitudinal strain rate (RV_{FW SRL}) and RV myocardial dispersion index at rest and during exercise (ex). *EA*, endurance athletes; *ei-ARVC*, exercise-induced ARVC; *NAs*, non-athletes.

Supplementary Table 5. Accuracy of different parameters to identify subjects with exercise-induced ARVC with and without an ICD from healthy athletes.

	AUC (mean $\pm$ 95% CI)	P-value	Cutoff value	Sensitivity (%)	Specificity (%)
ICD					
RVFAC _{rest}	0.82 (0.65 – 0.99)	0.011	44	88	59
RV _{FWSL} _{rest}	0.71 (0.49 – 0.94)	0.090	-	-	-
RV _{FW SRL} _{rest}	0.76 (0.53 – 0.99)	0.040	-1.34	75	65
RVFAC _{ex}	0.99 (0.96 – 0.99)	<0.001	47	100	94
RV _{FWSL} _{ex}	0.97 (0.90 – 1.00)	0.001	-28.9	100	93
RV _{FW SRL} _{ex}	1.00	<0.001	-2.13	100	100
No ICD					
RVFAC _{rest}	0.53 (0.28 – 0.78)	0.808	-	-	-
RV _{FWSL} _{rest}	0.65 (0.44 – 0.87)	0.205	-	-	-
RV _{FW SRL} _{rest}	0.58 (0.35 – 0.81)	0.501	-	-	-
RVFAC _{ex}	0.64 (0.41 – 0.87)	0.268	-	-	-
RV _{FWSL} _{ex}	0.71 (0.45 – 0.97)	0.107	-	-	-
RV _{FW SRL} _{ex}	0.91 (0.79 – 1.00)	0.002	-2.35	88	80

AUC, P values for ROC curve and sensitivity and specificity for RV fractional area change (RVFAC), RV free wall longitudinal strain (RV_{FWSL}) and RV free wall longitudinal strain rate (RV_{FW SRL}) at rest and during exercise (ex).

Supplementary Figure 1. Pulmonary vascular load.

Evolution of mean pulmonary artery pressure (P) with cardiac output (Q) during incremental exercise in non-athletic controls (NAs), subjects with exercise-induced ARVC (ei-ARVC) and endurance athletes (EAs). Data are presented as individual values with group mean and standard error of the mean.

Supplementary Figure 2. ROC curves for echocardiographic exercise-to-rest differences.

Diagnostic performance of exercise-to-rest differences of RV fractional area change ($\Delta RVFAC$), RV free wall longitudinal strain ($\Delta RV_{FW}SL$), RV free wall longitudinal strain rate ($\Delta RV_{FW}SRL$) and tricuspid annular plane systolic excursion ($\Delta TAPSE$) in subjects with exercise-induced ARVC compared to apparently healthy subjects (endurance athletes and non-athletic controls combined).

Supplementary Figure 3. ROC curves for rest and exercise parameters of exercise-induced ARVC patients versus endurance athletes and controls subjects separately.

Diagnostic performance of RV fractional area change (RVFAC), RV free wall longitudinal strain (RV_{FW}SL), RV free wall longitudinal strain rate (RV_{FW}SRL) and RV myocardial dispersion index at rest (left column) and during exercise (right column) to discriminate subjects with exercise-induced ARVC (ei-ARVC) from endurance athletes (EAs, upper row) and non-athletic controls (NAs, lower row).

Supplementary Figure 4. RV function during exercise in subjects with exercise induced ARVC with and without an ICD.

Evolution of (A) RV fractional area change (RVFAC) (B) RV free wall longitudinal strain (RV_{FW}LS) and (C) RV free wall longitudinal strain rate (RV_{FW}SRL) during exercise. Data are presented as means and standard error of the mean at each workload. Colored p-values indicate main effect of exercise. *,†,‡ p<0.05 Bonferroni post-hoc compared to NAs / EAs / ICD (-) respectively. EAs, endurance athletes; ICD (+), exercise-induced ARVC subjects with implantable cardioverter-defibrillator; ICD (-), exercise-induced ARVC subjects without implantable cardioverter-defibrillator; NAs, non-athletic controls.

Supplementary Figure 5. ROC curves for echocardiographic parameters at rest and during exercise to identify subjects with exercise induced ARVC with and without an ICD.

Diagnostic performance of RV fractional area change (RVFAC), RV free wall longitudinal strain (RV_{FW}SL) and RV free wall longitudinal strain rate (RV_{FW}SRL) at rest (dotted lines) and during exercise (solid line) to identify ei-ARVC subjects without ICD (left panel) and with ICD (right panel) from healthy endurance athletes. *EAs*, endurance athletes; *ICD (+)*, exercise-induced ARVC subjects with implantable cardioverter-defibrillator; *ICD (-)*, exercise-induced ARVC subjects with ventricular arrhythmias without implantable cardioverter-defibrillator.