**Prevalence and Clinical Correlates of Exercise-Induced Ventricular Arrhythmias in Arrhythmogenic Right Ventricular Cardiomyopathy**

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**ABSTRACT**

**Background:** Exercise has a deleterious effect on the phenotypic expression of arrhythmogenic right ventricular cardiomyopathy (ARVC) and increases the risk of sudden death in patients with this condition. The aim of the study was to determine the prevalence and correlates of exercise-induced arrhythmias during exercise tolerance test (ETT) in patients with ARVC.

**Methods:** Between 2010 and 2019, 30 (47% males, mean age 42 ± 12 years) consecutive patients with a definite diagnosis of ARVC based on revised Task Force criteria underwent a full in-house genotypic and phenotypic characterization, including ETT at our center. Exercise-induced arrhythmic response (EIAR) was defined by the development of complex ventricular arrhythmias (bi/trigeminy, couplets, triplets and/or ventricular tachycardia) after stage 2 of exercise.

**Results:** A heart rate ≥85% of predicted was achieved by 23 (77%) patients. The average work achieved was 11.6 ± 3.5 metabolic equivalents. In 16 (53%) cases, a desmosomal pathogenic variant was found [most commonly PKP2 (n=7) and DSP (n=3)]. Most patients (n=28; 90%) exhibited at least 1 ventricular premature beat during the test. In 12 (40%) cases, an EIAR was observed. In 2 (6%) patients, ETT was interrupted due to the onset of ventricular tachycardia (sustained with a LBBB/inferior axis pattern in one case, and non-sustained LBBB/superior axis pattern in the other). Mean body surface area (BSA)-indexed left ventricular (LV) end-diastolic volumes were higher in the EIAR group (92 ± 12 ml/m2 vs 80 ± 7 ml/m2, p = 0.002), as well as right ventricular (RV) end-diastolic volumes/BSA (110 ± 18 ml/m2 vs 91 ± 27 ml/m2, p = 0.04). Subepicardial and/or mid-wall left ventricular (LV) late gadolinium enhancement (LGE) was more common in the EIAR group (67% vs 22%, p = 0.01).

**Conclusions:** Patients with ARVC commonly exhibit exercise-induced ventricular arrhythmias. Patients with more significant RV remodeling and LV involvement (based on the presence of LV dilatation and LGE) appear more susceptible to exercise-induced arrhythmias.

**Keywords:** ARVC; exercise tolerance test; late gadolinium enhancement.

**INTRODUCTION**

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart muscle disease characterized by loss of myocytes and fibrofatty replacement of right ventricular (RV) myocardium, which may act as a substrate for recurrent ventricular arrhythmias and right ventricular dysfunction1. ARVC is a common cause of cardiac arrest and sudden cardiac death (SCD) in young individuals and athletes2. The diagnosis of ARVC is often complex and based on the revised Task Force Criteria (TFC) across a series of clinical, electrocardiographic and structural traits3. Although the TFC are mainly focused on right ventricular abnormalities, recent studies have shown that ARVC is often a biventricular disease, with left ventricular (LV) involvement in up to 80% of decedents of sudden death diagnosed with this condition at post-mortem examination4.

Exercise has a deleterious effect on the phenotypic expression of the disease and increases the risk of SCD in patients with this condition5. Exercise tolerance test (ETT) is part of the diagnostic work-up and general assessment of patients with ARVC. However, the clinical significance and phenotypic correlates of exercise-induced arrhythmias detected at ETT are not clearly defined in these patients.

The aim of the study was to investigate the prevalence and correlates of ventricular arrhythmic response to exercise tolerance testing in patients with ARVC.

**METHODS**

**Study population**

Between 2010 and 2019, 91 consecutive patients with a definite diagnosis of ARVC, according to the revised Task Force criteria, were assessed at the Inherited Cardiac Conditions (ICC) clinic at King’s College Hospital and Guy’s and St Thomas’ Hospital which work jointly as a tertiary ICC referral center in London (United Kingdom). All patients underwent comprehensive evaluation including personal and family history, clinical examination, 12-lead ECG, transthoracic echocardiogram, genetic testing and 24-hour Holter monitoring. Clinical data were retrospectively evaluated. For the purpose of this study only patients that were investigated with a full in-house genotypic and phenotypic assessment including ETT done in proximity of the CMR (within 1 year), were considered. The final study population was constituted by 30 patients (9 assessed at King’s College Hospital and 21 at Guy’s and St Thomas’ Hospital); 61 patients were excluded mainly because the ETT was not performed at our institutions or because the ETT was performed at >1-year from CMR. Data was collected as part of our Institution's approved Clinical Audit. The study conforms with the principles outlined in the Declaration of Helsinki6.

**Resting 12-lead ECG**

Standard 12- lead ECGs were analysed. Care was taken in measuring T wave inversion (TWI) across the precordial leads and the maximum J-point elevation in the anterior leads (V1– V4) exhibiting TWI. Biphasic T-wave inversion was considered abnormal if the negative deflection of the T-wave was ≥ 0.1 mV. TWI ≥ 0.1 mV in ≥2 contiguous leads was considered abnormal. Deep T-wave inversion was defined as a T-wave deflection ≥ 0.2 mV7. The amplitude of the J point was measured at the end of the QRS complex (the onset of the ST-segment) with reference to the onset of the QRS complex. The J point was considered elevated if ≥ 0.1 mV. The S wave duration in leads V1-V3 was considered prolonged if > 55 msec8,9. ST-segment depression was considered significant if ≥ 0.1 mV in ≥ 2 contiguous leads. An abnormal Q wave was defined as a Q wave with duration ≥ 40 msec or a Q/R ratio > 0.25. The normal frontal cardiac axis was considered to be >−30° but <120°. Left atrial (LA) enlargement was defined by a P wave duration ≥ 0.12s in the frontal plane associated with a terminal P negativity in lead V1 of duration ≥ 0.04 s and depth ≥ 0.1 mV7. Low ECG voltages were defined as QRS amplitude ≤1.0 mV in all of the precordial leads and/orQRS amplitude ≤0.5 mV in all of the limb leads10.

**Exercise tolerance test**

Patients performed a standard Bruce Protocol treadmill test according to clinical guidelines11. Because a high-quality standard 12-lead ECG with electrodes placed on the limbs cannot be obtained during exercise, electrodes were placed on the torso (with the limb electrodes on the trunk of the body to minimize motion and muscle artefacts during exercise). A resting supine standard 12-lead ECG was obtained before exercise*.* Maximum heart rate (HR), blood pressure (BP), metabolic equivalents (METS), time of exercise (min), repolarization changes and arrhythmias during exercise were analysed. The exercise test was terminated according to patient request to stop due to symptoms (such as fatigue, dyspnea or chest pain) or if it was deemed medically necessary due to any of the following clinical findings: ST-segment elevation (>1.0 mm) in leads without preexisting Q waves because of prior myocardial infarction; persistent ≥10 mmHg decline in systolic blood pressure (SBP); a hypertensive (SBP > 280 mm Hg, diastolic blood pressure > 120 mm Hg) blood pressure response; or the development of significant arrhythmias.

Exercise-induced arrhythmic response (EIAR) was defined by the development of complex ventricular arrhythmias, after stage 2 of exercise: bi/trigeminy, ≥ 1 couplet, ≥ triplet, ≥ 1 episode of non-sustained ventricular tachycardia (NSVT) (defined as duration >3 beats but persisting less than 30 seconds and terminating spontaneously) or sustained VT (duration >30 seconds or requiring termination due to hemodynamic compromise in <30 s). Some patients had multiple exercise tolerance tests during follow-up. In these cases, the test closest to the first CMR was considered.

**Cardiovascular magnetic resonance**

Cardiovascular magnetic resonance studies were performed using 1.5T or 3T scanners (Achieva or Ingenia, Philips Healthcare; Aera, Siemens), using steady-state free precession (SSFP) breath-hold cines in long-axis planes and sequential 7mm short-axis slices from the atrioventricular ring to the apex12. Ventricular volumes and function and LV mass were measured using standard techniques13. Ventricular volumes and LV mass were indexed to body surface area (BSA)14. Right ventricular regional wall motion abnormalities (RWMA) were classified as akinesia, dyskinesia and aneurysms 15. Late gadolinium enhancement images were acquired 10 mins after an intravenous bolus injection 0.15 mmol/Kg of Gadovist to identify scar. Inversion times were adjusted to null normal myocardium and late gadolinium enhancement (LGE) images were phase swapped to exclude artefact when required. Phase-sensitive inversion recovery (PSIR) sequences were used to assess possible myocardial fibrosis in cases of arrhythmias or difficulty breath-holding. We considered the CMR right ventricular volumes and ejection fraction threshold values proposed by the revised TFC as diagnostic for ARVC3 (in combination with RV RWMAs where relevant).

**Statistical analysis**

Results are expressed as mean ± SD for continuous variables or as absolute count and relative percentage for categorical variables. Comparison between groups was performed using Student’s T-test for independent samples or the non-parametric Kruskal-Wallis test for continuous outcomes and the chi-squared test or Fisher’s exact test for categorical variables. All statistical tests were two-tailed. We set statistical significance at p<0.05.

**RESULTS**

The demographic, clinical and genetic characteristics of our cohort are reported in Table 1. The mean age at the time of the exercise stress test was 42 ± 12 years and 47% were males. Two patients were endurance athletes (engaged in > 5 hours per week in sports with high dynamic component) prior to the diagnosis of ARVC and 1 had a previous percutaneous coronary intervention (PCI) followed by coronary artery by-pass operation. Nineteen (63%) patients had a positive family history (first-degree relative with diagnosis of ARVC in 43%, with ARVC confirmed at autopsy in 10%, with SCD <35 years in 10% and with SCD < 50 years in 3%). Twenty (67%) patients had NSVT detected on 24-hour Holter monitoring and 2 of them previously suffered a resuscitated out of hospital cardiac arrest; 6 patients had an implantable cardioverter defibrillator (ICD) implanted at the time of exercise stress test and 17 (57%) were on cardiac medications (16 on β-blockers, 1 on Ace-inhibitors).

Out of the 16 patents (53%) who had a positive genetic testing, 12 patients carried a pathogenic or likely pathogenic variant in PKP2 (n=7, 23%), DSP (n=3, 10%) and in DSG (n=2, 3%) genes.

Twelve-lead ECG was abnormal in 20 (67%) patients. The most common abnormalities were anterior TWI in V1-V3 in 13 (43%) patients, low QRS voltages in 12 (41%) and lateral TWI in 4 (13%) patients. The mean HR at rest was 64 ± 13 bpm. Three patients had at least 1 premature ventricular beat (PVB) at resting ECG (2 with LBBB and inferior axis pattern and 1 with RBBB pattern) and 1 patient was in atrial fibrillation.

**CMR features**

The RV was affected in isolation in 9 (30%) patients, the left ventricle (LV) was affected in isolation in 3 (11%) cases and 15 (50%) patients exhibited biventricular disease; in 3 patients the CMR failed to show any structural or functional abnormality (Table 2). The most common RV abnormality was the presence of RWMAs, which was observed in 12 (40%) patients (predominantly affecting the free wall, the basal sub-tricuspid region and the right ventricular outflow tract).Right ventricular dilatation fulfilling a major or minor volume TFC was found in 14 (47%) patients and impaired RV systolic function (ejection fraction ≤45%) in 7 (23%) patients, with an average RV end-diastolic volume index (RVEDVi) of 99 ± 25 ml/m2. The main LV abnormality detected by CMR was myocardial LGE (n=12; 40%), mostly (n=8/12) in the inferior or the lateral walls with a predominant sub-epicardial pattern. A small proportion of patients exhibited impaired LV systolic function (LV ejection fraction (LVEF) <50%: n=3; 10%) and an average LVEF of 58 ± 8 %. The average LV end-diastolic volume index (LVEDVi) was 85 ± 16 ml/m2. Late gadolinium enhancement was detected in 17 (65%) patients as follows: 5 (19%) cases with RV LGE only, 9 (35%) cases with isolated LV LGE and 3 (11%) patients with biventricular LGE.

**Exercise tolerance test**

A heart rate ≥ 85% of predicted was achieved during exercise by 23 (77%) patients. The average work reached was 11.6 ± 3.5 metabolic equivalents and the average time of exercise was 10 ± 2 minutes (Table 3). Blood pressure response to exercise was normal in all patients. The development of new T wave inversion beyond V2 at peak exercise was observed in 4 (13%) patients and normalisation of TWI during exercise was observed in 5 (17%) patients. Some degree of ST depression (< 2 mm) at peak exercise was found in 4 (13%) cases. Most patients (n=27; 90%) exhibited at least 1 PVB during the test and 23 (77%) had an increased burden of PVBs during exercise, with a LBBB pattern with superior or inferior axis in 9 (39%).

Twelve (40%) patients exhibited EIAR. Three (10%) patients developed VT during exercise. In two patients the onset of VT occurred at peak exercise and led to cessation of the exercise test: in one case the VT was sustained with a LBBB/inferior axis pattern (lasted 56 seconds with spontaneous cardioversion during recovery), while in the other case the VT was non-sustained and with a LBBB/superior axis pattern. The third patient had a short run of NSVT (5 beats) during recovery (LBBB, late transition > V4 and superior axis). The remaining nine patients had ventricular bigeminy or trigeminy, ventricular couplets or triplets or a combination of those arrhythmias triggered by exercise. Seven of these patients showed more than 1 PVB with RBBB pattern morphology.

**Exercise Induced Ventricular Arrhythmias**

The correlation between EIAR and clinical and imaging features is summarised in table 4.

Patients exhibiting EIAR showed higher biventricular volumes at CMR as compared to those without EIAR (mean LVEDV/BSA: 92 ± 12 ml/m2 vs 80 ± 7 ml/m2, p=0.002; RVEDV/BSA: 110 ± 18 ml/m2 vs 91 ± 27 ml/m2, p=0.04). A trend toward lower LV and RV ejection fraction and more frequent RV regional wall motion abnormalities was observed in the EIAR group. Left ventricular subepicardial and/or mid-wall LV LGE was more common in patients with than without EIAR (67% vs 22%, p = 0.01). When looking at PVBs pattern during the exercise test, a RBBB pattern was more common in the EIAR group (58% vs 11%, p=0.007). No differences in the prevalence of pathogenic variants were observed between patients with and without EIAR.

**DISCUSSION**

The dangerous link between ARVC and exercise has been widely demonstrated and this condition is a common cause of SCD in apparently healthy athletes2,4. Although ETT is often part of the assessment of patients with suspected ARVC, the prevalence and the phenotypic correlates of exercise-induced arrhythmias are not well defined.

We found that ventricular arrhythmias induced by exercise are relatively common in ARVC (40% of the cases). Patients with arrhythmias during exercise had a more advanced disease often with biventricular involvement and higher prevalence of LV LGE at CMR (a sign of LV involvement). Interestingly, patients with exercise-induced arrhythmias exhibited PVBs characterized by a RBBB pattern, which suggests a LV origin.

**Exercise tolerance test in ARVC**

There is growing evidence about the deleterious effects of exercise in ARVC5. Exercise affects negatively the phenotypic expression and the arrhythmic risk in patients with ARVC2. Conversely, there is a limited body of research describing ETT features and their diagnostic and prognostic utility in these patients. Perrin et al.16 found that ETT may expose a latent electrical substrate in asymptomatic ARVC gene carriers, which is shared by patients with ARVC and a history of ventricular arrhythmias. The most common exercise-induced abnormalities in 25 ARVC symptomatic patients were found to be: new epsilon waves in 17%, superior axis premature ventricular beats in 84% and new terminal activation duration ≥55 ms in 67%. Sequeira et al.17 assessed a small cohort of young 16 patients (age <18 years) with ARVC who were investigated with ETT. The pattern and inducibility of PVBs activity were found to be highly variable. Consequently, the investigators discouraged the use of ETT for diagnostic purpose in young patients with suspected ARVC.

Our study is the first to systematically correlate exercise-induced ventricular arrhythmias at ETT with CMR features and genetic findings in patients with a definite diagnosis of ARVC according to the revised TFC. Exercise-induced ventricular arrhythmias are common in patients with ARVC and their presence was associated with specific CMR features, specifically larger biventricular volumes and subepicardial and/or mid-wall LGE. These results suggest that patients with a more advanced disease expressed by more severe remodelling tend to have a higher propensity to exercise-induced ventricular arrhythmias.

There is growing evidence that ARVC is a biventricular disease4. In this context, CMR is proved to be a valuable tool to visualize signs of possible LV involvement through LGE imaging18,19. Interestingly, the higher prevalence of LV LGE in patients with EIAR suggests that mid-wall or subepicardial scarring should be looked with particular caution, in terms of arrhythmic vulnerability during exercise. A recent autopsy study showed that 80% of athletes who died suddenly with a macroscopic and histological diagnosis of ARVC had a biventricular involvement with LV fibrosis or fibro-fatty infiltration, suggesting a possible link between LV abnormalities and SCD during exercise4.

The main clinical implication of our study is that propensity to exercise-induced ventricular arrhythmias may vary in patients with ARVC, a concept that leads to speculations on a possible variable effect and risk of sport and exercise in these patients. A better understanding of the mechanisms underlying exercise-induced ventricular arrhythmias may be the key to improve prognostic stratification and should be pursued through further studies.

**Limitations**

Although our cohort is comprehensively characterized, the sample size is small and therefore the results have to be interpreted cautiously, waiting for replications on larger studies. The main limitations of this study stem from retrospective design, reliance on registry data, and small sample size. Patients were generally encouraged to exercise principally to reach 85% of the maximally predicted HR, but submaximal tests were included (some patients were already on beta-blockers at the time of ETT). This may have limited our ability to drive meaningful conclusions on exercise capacity, which was not the main aim of the study.

**CONCLUSIONS**

Exercise-induced ventricular arrhythmias are commonly observed in ARVC. Patients with more significant biventricular remodeling and left ventricular involvement identified through subepicardial and/or mid-wall late gadolinium enhancement at CMR appear more susceptible to complex exercise-induced arrhythmias.

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**Figure legends:**

**Figure 1.** Correlates of EIAR in the study population. **Abbreviations:** BSA: body surface area; CMR: Cardiac magnetic resonance; LGE: late gadolinium enhancement, LV: left ventricle; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; RV: right ventricle; RVEDV: right ventricular end-diastolic volume, RVEF: right ventricular ejection fraction, RVESV: right ventricular end-systolic volume; RWMA: regional wall motion abnormalities.

**Figure 2.** Exercise-induced arrhythmias and mid-wall/subepicardial LGE (infero-septum and lateral wall - white arrows) in a 21 year old patient with ARVC and family history of sudden death (brother).

**Table 1**. Characteristics of patients with ARVC.

|  |
| --- |
| **Demographics**  |
| Male, n (%) | 14 (47%) |
| Age (years) | 42 ± 12 |
| **Family History** |
| 1st degree relative with ARVC | 13 (43%) |
| 1st degree ARVC confirmed at autopsy | 3 (10%) |
| 1st degree relative SCD <35 years | 3 (10%) |
| **Genetics** |
| Gene positive, n (%) | 16 (53%) |
| PKP2, n (%) | 7 (23%) |
| DSP, n (%) | 3 (10%) |
| DSG, n (%)  | 2 (6%) |
| **ECG**  |  |
| SR, n (%) | 27 (90%) |
| HR, (bpm) | 64 ± 13 |
| QRS duration, (ms) | 92 ± 12 |
| RBBB, n (%) |  / |
| LBBB, n (%) |  / |
| Low voltages precordial/limb leads, n (%)  | 12 (40%) |
| Q waves, n (%) | 4 (13%)  |
| TWI V1–V3, n (%) | 13 (43%) |
| Lateral TWI, n (%) | 4 (13%) |
| PVBs ≥1, n (%) | 3 (10%) |
| Epsilon wave, n (%) |  / |
| **Holter ECG 24h** |
| NSVT  | 20 (67%) |
| >500 PVBs | 10 (33%) |
| **Therapy** |
| ICDICD primary preventionICD secondary prevention | 6 (20%)0 6  |
| Beta-blockers | 16 (53%) |

**Abbreviations**: HR, heart rate; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; PVBs, premature ventricular beats; RBBB, right bundle branch block; RVOT, right ventricular outflow tract; SD, standard deviation; SR, sinus rhythm; TWI, T waves inversion; VT, ventricular tachycardia.

**Table 2.** CMR features in patients with ARVC.

|  |  |
| --- | --- |
| LVEDV/BSA, (ml/m2) | 85 ± 16.5 |
| LVEF, (%) | 58 ± 8 |
| LV RWMA, n (%) | 5 (19%) |
| RVEDV, (ml) | 187 ± 53 |
| RVEDV/BSA, (ml/m2) | 99 ± 25  |
| RVEF, (%) | 51 ± 8 |
| RV RWMA, n (%) | 12 (40%) |
| LGE tot, n (%)RV LGE, n (%)Biventricular LGE, n (%) | 17 (57%)8 (31%)3 (11%) |
| LV LGE, n (%) | 12 (40%) |
| CMR major volume criteria, n (%) | 10 (33%) |
| CMR minor volume criteria, n (%) | 14 (47%) |
| CMR major function criteria, n (%) | 3 (10%) |
| CMR minor function criteria, n (%) | 4 (13%) |

**Abbreviations:** BSA: body surface area; CMR: Cardiac magnetic resonance; LGE: late gadolinium enhancement, LV: left ventricle; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; RV: right ventricle; RVEDV: right ventricular end-diastolic volume, RVEF: right ventricular ejection fraction, RVESV: right ventricular end-systolic volume; RWMA: regional wall motion abnormalities.

**Table 3.** Exercise tolerance test characteristics in patients with ARVC.

|  |  |
| --- | --- |
| HR ≥85% of predicted | 23 (77%) |
| HR % of predicted  | 91 ± 13.5 |
| METs | 11.6 ± 3.5 |
| Time of exercise, (min) | 10 ± 2 |
| Systolic blood pressure (mmHg)Diastolic blood pressure (mmHg) | 158 ± 2277 ± 12 |
| PVBs any | 27 (90%) |
| PVBs > exercise | 23 (77%) |
| EIAR | 12 (40%) |
| Test stopped due to VT  | 2 (6%) |
| New T wave inversion beyond V2 | 4 (13%) |
| TWI V1-V2 normalization at peak exercise | 5 (17%) |
| ST depression with exercise | 4 (13%) |

**Abbreviations**: EIAR, exercise-induced arrhythmic response; HR, heart rate; METs, metabolic equivalents; PVBs, premature ventricular beats; SD, standard deviation; TWI, T waves inversion; VT, ventricular tachycardia.

**Table 4.** Correlates of exercise induced arrhythmic response.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Tot (30)** | **EIAR (n=12)** | **No EIAR (n=18)** | **P** |
| **Demographics** |  |  |  |  |
| Male, n (%) | 14 (47%) |  5 (28%) |  9 (75%) |  0.65 |
| Age, years | 42 ± 12 |  41 ± 13 |  45 ± 10  |  0.35 |
| **Genetics** |  |  |  |  |
| Gene positive, n (%) | 16 (53) | 5 (42%) | 11 (61%) |  0.31 |
| PKP2, n (%) | 7 (23%) | 3 (25%) | 4 (22%) |  0.85 |
| DSP, n (%) | 3 (10%) | 2 (17%) | 1 (5%) |  0.29 |
| DSG, n (%)  | 2 (3%) | 0 | 2 (11%) |  0.24 |
| **ECG** |  |
| HR [bpm] | 64 ± 13 | 57± 10 | 68 ± 13 | 0.02 |
| Low voltages, n (%) | 12 (41%) | 5 (42%) | 7 (39%) | 0.87 |
| TWI (V1–V3), n (%) | 13 (43%) | 4 (33%) | 9 (50%) | 0.36 |
| Lateral TWI, n (%) | 4 (13%) | 2 (17%) | 2 (11%) | 0.64 |
| **ETT** |
| > 1 PVB with RBBB pattern pattern morphology  | 9 (30%) | 7 (58%) | 2 (11%) | 0.007 |
| **CMR features**  |
| LVEDV/BSA, [ml/m2] | 85 ± 16.5 | 92 ± 12 | 80 ± 7 | 0.002 |
| LVEF [%] | 58 ± 8 | 55 ± 9 | 59 ± 5 | 0.06 |
| LVEF <57%, n (%) | 8 (27%) | 5 (42%) | 3 (17%) | 0.14 |
| LV LGE, n (%) | 12 (40%) | 8 (67%) | 4 (22%) | 0.01 |
| RVEDV/BSA, [ml/m2] | 99 ± 25  | 110 ± 18 |  91 ± 27 |  0.04 |
| RVEF [%] | 51 ± 8 | 49 ± 7 |  53 ± 9 |  0.2 |
| RV RWMA, n (%) | 12 (40%) | 7 (58%) | 5 (28%) |  0.1 |

**Abbreviations:** BSA: body surface area; CMR: cardiovascular magnetic resonance; DSP: desmoplakin; DSG: desmoglein; EIAR: exercise induced arrhythmic response; HR: heart rate; LGE: late gadolinium enhancement, LV: left ventricle; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; PKP2: plakophilin 2; PVBs: premature ventricular beat; RBBB: right bundle branch block; RV: right ventricle; RVEDV: right ventricular end-diastolic volume, RVEF: right ventricular ejection fraction; RWMA: regional wall motion abnormalities; TWI: T wave inversion.

**Figure 1.**



**Figure 2.**

