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Sessie 4 Cardiomyopathies

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Exercise in Arrhythmogenic Right Ventricular Cardiomyopathy: Safe Levels and Incremental Prognostic Value to the Risk Calculator

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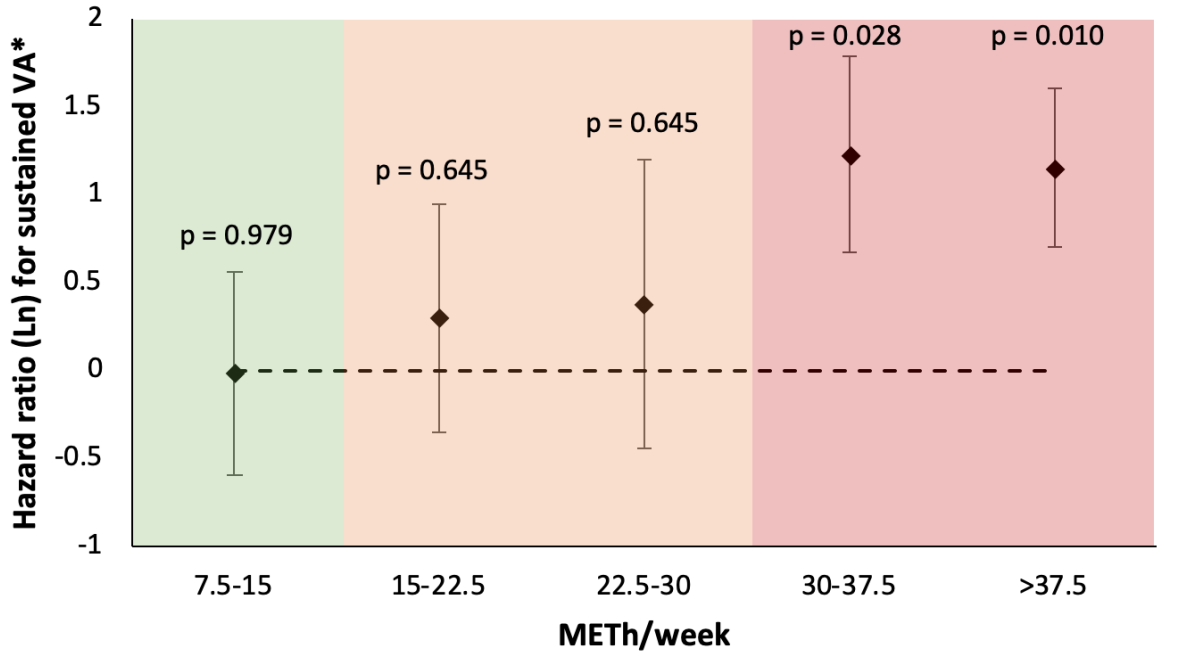
Purpose:
While exercise is associated with increased ventricular arrhythmia (VA) risk in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC), it is not included in the ARVC risk calculator for sustained VA (www.arvcrisk.com). This study evaluates the incremental value of exercise participation in risk prediction.
Methods:
We interviewed patients diagnosed with ARVC without prior sustained VA regarding their exercise participation. Using the average metabolic equivalent hours (METh) three years prior to diagnosis, we evaluated the prognostic value of exercise with Kaplan-Meier and Cox-models. Levels of exercise participation were categorized by the American Heart Association (AHA) recommended minimum of 7.5 METh/week. For comparison with prior literature, athlete status was defined using three cut-off values: >18, >24, and >36 METh/week.
Results:
We included 176 patients (43.2% male, age 38±16 years), among whom 53 (30%) experienced sustained VA during 7±5 years of follow-up. Relative to those exercising below AHA minimum, exercise up to 15 METh/week showed no effect on risk (p=0.979), whereas >15 METh/week showed a trend towards higher risk (p=0.645), and >30 METh/week showed significantly higher arrhythmic risk (p<0.028)(Figure). While all three definitions of athlete status were associated with higher risk of events (hazard ratios 2.53-2.91), their observed risk corresponded well with predicted risk from the current risk calculator. Adding athlete status showed no significant improvement to the model (AIC difference <2).
Conclusion:
Exercise does not aggravate risk of sustained VA when limited to 15 METh/week, corresponding to ~2 hours of jogging. Furthermore, exercise holds no incremental prognostic value over the current risk calculator.

Keywords:
ARVC, Exercise, Ventricular arrhythmia

Figure:



*reference group: 0-7.5 METh/week (based on American Heart Association recommended minimum)

Strain by Feature-tracking Cardiac Magnetic Resonance Predicts Sustained Ventricular Arrhythmias in Arrhythmogenic Right Ventricular Cardiomyopathy

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Purpose:
Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by ventricular dysfunction and ventricular arrhythmias (VA). Arrhythmic risk assessment is important, since timely implantation of an implantable cardioverter-defibrillator can be life-saving. This study investigates whether the novel method, feature-tracking cardiac magnetic resonance (FT-CMR), is able to predict VA in ARVC patients.

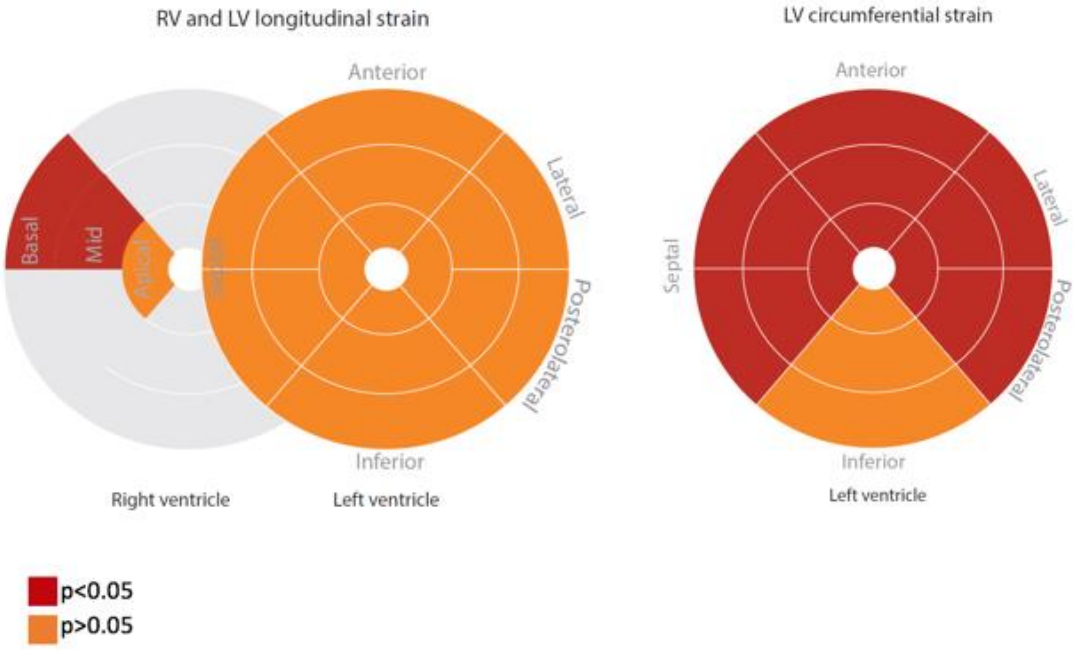
Methods:
CMR images of 123 ARVC patients (42% male, 41.2±15.9yrs) without prior VA were analyzed for global and regional right (RV) and left ventricular (LV) strain. Primary outcome was sustained VA in follow-up. To determine the predictive value of FT-CMR over traditional parameters, we performed multivariable regression analyses assessing each strain parameter in combination with 1) LGE; 2) ARVC CMR 2010 Task Force Criteria (TFC) and; 3) the ARVC risk calculator separately.

Results:
During 4.3[2.1-8.1]yrs follow-up, 20% experienced VA in follow-up. Compared to patients without VA, those with VA had significantly reduced RV and LV function ($p \leq 0.02$) and increased presence of LGE($p=0.008$). For RV longitudinal and LV circumferential strain, global and regional strain were significantly reduced in patients with vs. without VA ($p \leq 0.04$) (Figure). Multivariable analysis showed that corrected for; 1) LGE, LV global and regional and RV mid strain remained significant predictors; 2) CMR TFC, both LV and RV global and regional strain remained significant predictors; 3) ARVC risk calculator, LV global and septal strain remained significant predictors.

Conclusion:
Both RV and LV strain are reduced in patients with VA during follow-up. Strain by FT-CMR remains a significant predictor of VA when corrected for conventional CMR parameters and the ARVC risk calculator, suggesting incremental value over traditional risk prediction parameters.

Keywords:
Cardiac Magnetic resonance imaging, Feature tracking CMR

Figure:
Schematic overview of longitudinal (left) and circumferential (right) regional strain differences between patients with and without VA during follow-up (red=regional difference significant; orange=regional difference not significant).



2D-Echocardiography vs Cardiac MRI Strain using Deep learning: a Prospective Cohort Study in Patients with HER2-positive Breast Cancer undergoing Trastuzumab.

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Purpose:
We aimed to study the predictive value of early two-dimensional (2D) speckle tracking echocardiography (STE) for left ventricular ejection fraction (LVEF) changes during trastuzumab treatment for HER2-positive breast cancer.
Methods:
HER2-positive breast cancer patients receiving trastuzumab, with or without anthracycline, underwent 2DE-ST at baseline and after 3 and 6 months (m) trastuzumab. Cardiac magnetic resonance (CMR) imaging (with ST) was performed at baseline and 6m. We studied the correlation between 2DE-ST- and CMR-derived global longitudinal strain (GLS) and global radial strain (GRS) measured at the same time. Additionally, we associated baseline and 3m 2DE-ST measurements with later CMR-LVEF, and with cardiotoxicity, defined as CMR-LVEF <45% and/or absolute decline >10% during trastuzumab.
Results:
47 patients were included. Median baseline LVEF was 60.4%. GLS measurements based on 2DE-ST and CMR showed weak correlation (Pearson's r=0.33; P=0.041); GRS measurements were uncorrelated (r=0.09; P=0.979). 2DE-LVEF at baseline and 3m, and 2DE-STE-GLS at 3m were predictive of CMR-LVEF at 6m. In contrast, the change in 2DE-ST-GLS at 3m was predictive of the change in CMR-LVEF at 6m, whereas the change in 2DE-LVEF was not (Table 1). Importantly, the 11 patients (28%) who developed cardiotoxicity had larger 2DE-ST-GLS change at 3m than those who did not (median 5.2% versus 1.7%; odds ratio for 1% difference change 1.81, 95% confidence interval 1.11 – 2.93; P=0.016; explained variance 0.34).
Conclusion:
Correlations between 2DE-ST and CMR-derived measurements are weak. Nevertheless, ST-measurements appeared useful to improve the performance of 2DE in predicting LVEF changes after 6m of trastuzumab treatment.

Keywords:
Speckle tracking echocardiography, Cardiac MRI, HER2-positive breast cancer

Figure:
Table 1. Association between measures obtained by 2DE-ST before anthracycline, before trastuzumab and after 3 months trastuzumab, and CMR-LVEF at 6 monts

2DE	CMR-LVEF after 6m TZT (mean difference + 95% CI)	Change in CMR-LVEF after 6m TZT (mean difference + 95% CI)	Cardiotoxicity (OR, 95% CI)
Before TZT			
LVEF, %	0.85 (0.42, 1.27)*	0.32 (-0.16, 0.80)	0.88 (0.75, 1.02)
ST-GLS, %	-0.42 (-1.31, 0.46)	-0.28 (-1.14, 0.58)	1.13 (0.87, 1.46)
3 Months TZT			
LVEF, %	0.59 (0.30, 0.88)*	0.29 (-0.04, 0.61)	0.85 (0.74, 0.98)*
ST-GLS, %	-1.14 (-2.07, -0.19)*	-0.62 (-1.54, 0.30)	1.36 (0.94, 1.84)
Change at 3 months TZT			
LVEF, %	0.30 (-0.11, -0.71)	0.21 (-0.19, 0.61)	0.90 (0.80, 1.01)
ST-GLS, %	-1.17 (-2.14, -0.20)*	-1.10 (-2.02, -0.18)*	1.81 (1.11, 2.93)*

Utility of Genetics for Risk Stratification in Paediatric Dilated Cardiomyopathy

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Purpose:
Dilated cardiomyopathy (DCM) in children may have an underlying genetic cause in a substantial number of cases. We describe the current practice and results of genetic evaluation in children with DCM and evaluate genotype-phenotype correlations that may guide prognosis.

Methods:
We performed a multicentre prospective observational study in children diagnosed with DCM from 2010 to 2017.

Results:
One hundred forty-four patients were included. Initial diagnostic categories consisted of idiopathic DCM in 67 children (47%), familial in 18 (13%), neuromuscular in 7 (5%), inborn error of metabolism in 4 (3%), malformation syndrome in 2 (1%), myocarditis in 23 (16%) and 'other' in 23 (16%). Median follow-up time was 2.1 years [IQR 1.0-4.3]. Hundred-seven patients (74%) underwent genetic testing. A likely pathogenic (LP) or pathogenic (P) variant was found in 39 children (36%); the majority in MYH7 (n=9). Three patients had more than one LP/P variant. In at least 6/39 patients (15%) the variant occurred de novo. During the study, 39 patients (27%) reached a study endpoint (SE: all-cause death or heart transplantation). Transplant-free survival was significantly lower in patients with a LP/P variant (P=0.005). Children who carried a LP/P variant were 2.8 times more likely to reach a SE compared to children without, while clinical characteristics at diagnosis did not differ (HR 2.8; 95%CI 1.3-5.8, P=0.007).

Conclusion:
Genetic testing is useful to predict clinical outcome in children with DCM and should be incorporated into the initial work-up. Patients with a LP/P variant have a poorer prognosis than patients without LP/P variant.

Keywords:
dilated cardiomyopathy, genetic testing, paediatric cardiology

Blood Biomarkers for Hypertrophic Cardiomyopathy Development and Progression – Systematic Review & Meta-analysis

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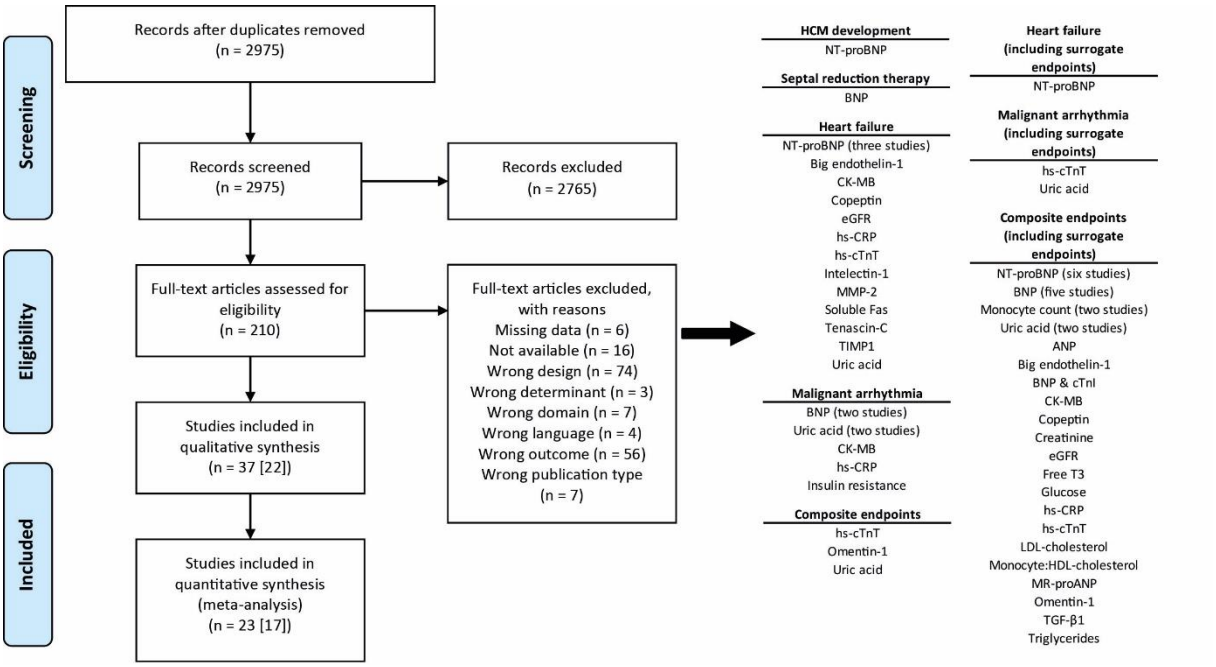
Purpose:
Hypertrophic cardiomyopathy (HCM) is the most prevalent monogenic heart disease. HCM is an important cause of sudden cardiac death and may also lead to heart failure and outflow tract obstruction. However, disease severity is highly variable and incomplete penetrance is observed among genotype-positive family members. Risk stratification remains limited. The aim of this study was to assess the prognostic utility of plasma and serum biomarkers.
Methods:
A systematic literature search was performed on Pubmed, Embase and the Cochrane library. Studies were eligible based on: 1) cohort study, 2) serum or plasma biomarker, 3) outcome involving development of HCM in carriers of pathogenic genetic variants, outflow tract obstruction, heart failure and/or malignant ventricular arrhythmia. Risk of bias was assessed using the QUIPS tool. Meta-analyses were performed using a random-effects model.
Results:
A total of 37 studies (22 without cohort overlap) were included. Median cohort size was 150 patients (interquartile range 92-428), median follow-up duration 3.5 years (interquartile range 2.3-5.9). Overall, 20 biomarkers were shown to predict any outcome or composite endpoint of multiple outcomes in at least one study. BNP, NT-proBNP, high sensitivity CRP and monocyte count predicted composite endpoints in multiple studies; BNP, NT-proBNP and uric acid predicted specific outcomes in two studies each. Pooled analyses were limited due to heterogeneity in outcomes and modelling strategies. Overall, risk of bias was moderate and quality of evidence was low-moderate.
Conclusion:
Several blood biomarkers were identified as predictors of HCM outcomes. However, multicentre prospective studies are required to validate their prognostic utility.

Keywords:
Hypertrophic cardiomyopathy, Prognosis, Biomarker

Figure:
Flow diagram of study inclusion and main results of the qualitative assessment of included studies. The numbers in square brackets in the flow diagram indicate the number of studies without potential cohort overlap. Biomarkers shown to be predictive for the outcomes of interest, including composite endpoints containing surrogate endpoints (atrial fibrillation, stroke, non-sustained ventricular tachycardia, unexplained syncope, implantable cardioverter-defibrillator implantation, periprocedural mortality and/or all-cause mortality), in at least one study. If a biomarker was shown to predict an outcome in multiple studies without potential cohort overlap, the number of (non-overlapping) studies is given. ANP, atrial natriuretic peptide; BNP, ventricular (brain or B-type) natriuretic peptide; CK-MB, creatine (phospho)kinase MB isoform; CRP, C-reactive protein; cTnI/-T, cardiac troponin I/T; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs, high sensitivity; LDL, low-density lipoprotein; MMP, matrix metallopeptidase (metalloproteinases); MVA, malignant ventricular arrhythmia; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PICP, Propeptide of procollagen type I; T3, triiodothyronine; TIMP1, TIMP (tissue inhibitor of metalloproteinases) metallopeptidase inhibitor 1; TGF, transforming growth factor.



The Effect of Exercise Exposure on Biventricular Tissue Replacement in Patients with the Phospholamban p.Arg14del Founder Mutation

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Purpose:
Exercise accelerates the onset and aggravates the phenotype in arrhythmogenic cardiomyopathy (ACM) patients carrying a mutation in desmosomal genes. Whether exercise also impacts phenotypic development of non-desmosomal mutation carriers remains unknown. This study investigates the association of exercise with tissue replacement on cardiac magnetic resonance imaging (CMR) in phospholamban (PLN) mutation carriers.
Methods:
We included 115 PLN p.Arg14del carriers (38% male, 44±15 years) who underwent exercise interview and CMR including gadolinium enhancement imaging. Exercise exposure was defined as participation in endurance sports with high dynamic demand (>70% VO2max) for >50hrs/year. Ventricular tissue characterization (stratified by fat, fibrosis or both), right ventricular (RV) and left ventricular (LV) dimensions and function were compared between participants with and without exercise exposure. Survival free from ventricular arrhythmias and heart failure were evaluated by Kaplan-Meier method.
Results:
Tissue replacement was observed in 53 (46%) subjects, with LV fibrosis being most frequent (n=49, 92%), followed by RV fibrosis (n=9, 17%) and fat in either ventricle (n=5, 9%). LV fibrosis typically affected the posterolateral wall (n=31/49 [63%] cases)(Figure 1). LV fibrosis was not associated with exercise exposure (p=0.58), but was associated with LV dilatation (p<0.01), LV dysfunction (p<0.01), and shorter survival free from ventricular arrhythmia (p<0.01) and heart failure (p<0.01). Exercise exposure did not affect biventricular function (p≥0.77) nor arrhythmic or heart failure outcomes (p≥0.62).
Conclusion:
Exercise exposure is not associated with morphological/functional CMR abnormalities or outcomes in PLN p.Arg14del carriers. LV fibrosis heralds adverse clinical course with more ventricular arrhythmias and heart failure.

Keywords:
Cardiomyopathy, Exercise exposure, Cardiac magnetic resonance

Figure:
Figure 1 Bull's eye plot (17 segment model, according to the American Heart Association) representing fibrosis in the left ventricle in all subjects and stratified by exercise exposure. Percentages represent the number of subjects with fibrosis in that segment. Differences per segment stratified by exercise exposure were not significant.