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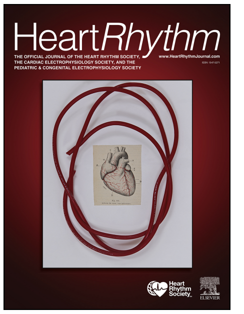

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Cardiac magnetic resonance feature tracking reveals abnormalities in patients with idiopathic ventricular fibrillation

Lisa M. Verheul, MD[1], Marco Guglielmo, MD[1], Alexander Hirsch, MD, PhD[2,3*], Stefano Figliozzi, MD[4], Pim van der Harst, MD, PhD[1], Mimount Bourfiss, MD, PhD[1], Niek H.J. Prakken, MD, PhD[5], Birgitta K. Velthuis, MD, PhD[6], Sing C. Yap, MD, PhD[2*], Rutger J. Hassink, MD, PhD[1*]

1. Department of Cardiology, UMC Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands
2. Department of Cardiology, Thorax center, Cardiovascular Institute, Erasmus MC, Dr. Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands
3. Department of Radiology and Nuclear Medicine, Erasmus MC, Dr. Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands
4. IRCCS Humanitas Research Hospital, Via Alessandro Manzoni 56, Rozzano, Milan, Italy
5. Department of Radiology, UMC Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands
6. Department of Radiology, UMC Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands

* Member of the European Reference Network of rare, low prevalence, and complex diseases of the heart; ERN GUARD-Heart (http//guardheart.ern-net.eu)

Running title: Feature tracking analysis and idiopathic VF

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Corresponding Author:

L.M. Verheul

l.m.verheul-5@umcutrecht.nl

Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands

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Research letter

The cause of sudden cardiac arrest remains undefined in approximately 5% of patients, the latter receiving the diagnosis of 'idiopathic ventricular fibrillation' (IVF). Unraveling the mechanisms underlying the arrest is a clinical need for these often young patients who may be negatively impacted by uncertainties about their prognosis, including the risk for recurrences.[1] By definition, IVF patients lack specific structural abnormalities. However, advanced imaging techniques, such as deformation imaging, can reveal early preclinical abnormalities preceding the alterations of conventional parameters like left ventricular ejection fraction (LVEF).[2] Therefore, abnormal deformation imaging may serve as an indicator of a subclinical cardiomyopathy in IVF patients. Groeneveld et al demonstrated that strain values determined with echocardiography differed between IVF patients and controls.[3] This study further investigated the use of deformation imaging through cardiac magnetic resonance (CMR) feature tracking (FT) analysis. FT can be performed by using standard balanced steady-state free-precession sequences, which are part of routine CMR protocols included in the diagnostic work-up after an arrest.

We retrospectively evaluated IVF patients from two Dutch academic centers (UMC Utrecht and Erasmus MC) and one Italian center (IRCCS Humanitas Research Hospital) who had a CMR of sufficient quality for FT (e.g., no left bundle branch block, regular cardiac rhythm without premature ventricular complexes) and LVEF≥50%. Patients were compared with an age- and sex-matched control group. CMR images were acquired on various 1.5T or 3T scanners according to local protocols at each CMR performing center. Standard short-axis and long-axis (2-, 3-, and 4-chamber views) cine images were acquired using breath-hold balanced steady-state free-precession sequences. FT analysis was performed with Circle Cardiovascular Imaging (CVI[42®] 6.1.1, Calgary, Canada). Endocardial and epicardial borders were contoured for the LV in short-axis and at least two long-axis images, depending on availability. Global peak circumferential strain (GCS), global peak longitudinal strain (GLS) and global peak radial strain (GRS) were derived. Chi-square was performed to compare categorical variables. Student's *t*-test or Mann-Whitney U test was used to compare continuous variables, as appropriate. Univariate and multivariate linear regression analyses were performed to further explore the influence of LVEF and IVF status on GLS. The study was conducted in accordance with the 2013 Declaration of Helsinki.

We included 52 IVF patients (33 (64%) males, median age 35 [25-47] years) who were compared with 52 matched controls (median age 38 [25-47], p=0.637). IVF patients underwent CMR at a median of 9 [5-13] days after the arrest. LVEF, LV end-diastolic and end-systolic volumes were comparable between IVF patients and controls (57 [53-61]% vs. 58 [55-63]%, p=0.123, Figure 1A). GLS was slightly reduced for IVF patients compared with controls (-17.1%±2.1 vs. -18.9%±1.8, p<0.001, Figure 1B). No statistical differences were found for GCS (-18.2%±2.0 vs. -18.7%±1.7, p=0.118, Figure 1C) and GRS (30.4%±5.4 vs. 31.4%±4.8, p=0.330, Figure 1D). After multivariate linear regression analysis, both LVEF and IVF status influenced GLS values. In the follow-up echocardiography conducted after a median duration of 5 [4-10] years, the mean LVEF remained at 56±4% among the 28 (54%) patients assessed. When stratifying by initial GLS values, no significant LVEF progression differences were noted between different baseline GLS values.

To our knowledge, this is the first study to explore the value of FT deformation imaging in IVF patients. Our results indicate that GLS was the only deformation imaging variable significantly impaired in this study group. GLS mainly reflects the function of the endocardial layer of the heart[4], and compared to LVEF, GLS appears superior for the detection of early cardiomyopathies, but also as a predictor for cardiovascular events.[2] Thus, our findings may suggest a presence of an underlying cardiomyopathy in a subgroup of IVF patients. A reduced GLS value at baseline might warrant a more thorough follow-up to detect early structural abnormalities in IVF patients. As a clear recommendation for IVF patients regarding imaging follow-up is currently lacking, this finding might provide more guidance. However, it cannot entirely be excluded that differences between IVF patients and controls might be related to transitory ischemia during the arrest itself which resulted in a temporarily reduced GLS. On the contrary, Purkinje fibers, one of the known origin sites of short-coupled premature ventricular complexes inducing VF in IVF are located in the endocardium.[5] It can be hypothesized that minor (undetected) structural abnormalities inducing these premature ventricular complexes influence GLS values.

The definitive clinical value remains to be determined, as these are preliminary exploratory results. Especially in combination with a comparable GCS and GRS between IVF patients and controls and a normal LVEF at follow-up, the clinical value remains unclear. However, because FT analysis does not require additional CMR sequences, it may be clinically beneficial to investigate strain with FT at baseline. Future studies should investigate larger cohorts, including IVF subtypes with structural abnormalities like inferolateral mitral annular disjunction, and incorporating right ventricle and regional strain assessment.

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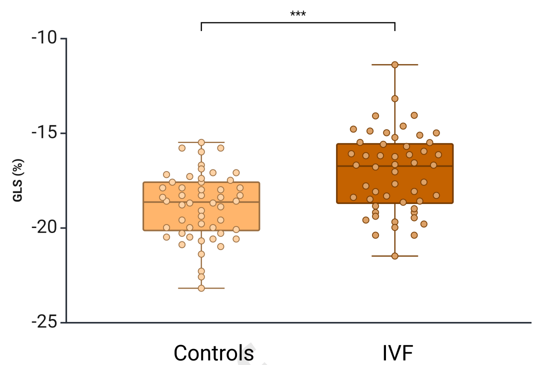
Figure legend

Figure 1. Table of conventional CMR measurements (**A**). Boxplot of GLS (**B**), GCS (**C**) and GRS (**D)** values stratified by IVF patients and controls. GLS significantly differed between IVF patients and controls, other global strain variables were comparable. Abbreviations: GCS; global circumferential strain, GLS; global longitudinal strain, GRS; global radial strain; LVEF; left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume IVF; idiopathic ventricular fibrillation.

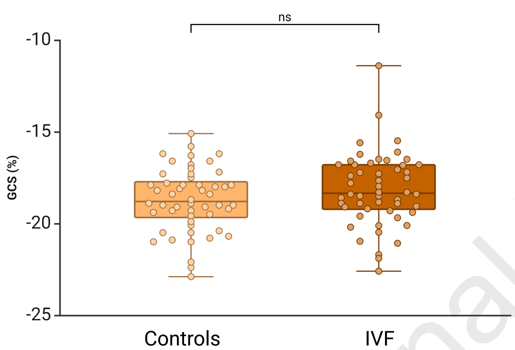
A Conventional measurements

	IVF (n=52)	Controls (n=52)	P-value
LVEF (%)	57 [53 - 61]	58 [55 - 63]	0.123
LVEDV (ml)	175±40	185±34	0.196
LVESV (ml)	79±18	76±21	0.561

B Global longitudinal strain (%)



C Global circumferential strain (%)



D Global radial strain (%)