Echocardiographic deformation imaging unmasks global and regional mechanical dysfunction in patients with idiopathic ventricular fibrillation: A multicenter case-control study

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BACKGROUND Idiopathic ventricular fibrillation (IVF) is diagnosed in patients with sudden onset of ventricular fibrillation of unidentified origin. New diagnostic tools that can detect subtle abnormalities are needed to diagnose and treat patients with an underlying substrate.

OBJECTIVE The purpose of this study was to explore echocardiographic deformation characteristics in IVF patients.

METHODS Echocardiograms were analyzed with deformation imaging by 2-dimensional speckle tracking. Global and regional measurements of the left ventricle (LV) and right ventricle (RV) were performed. Regional LV deformation patterns were evaluated for the presence of postsystolic shortening. Regional RV deformation patterns were classified as type I (normal) or type II/III (abnormal).

RESULTS In total, 47 IVF patients (mean age 45 years; left ventricular ejection fraction [LVEF] 56%) and 47 healthy controls (mean age 41 years; LVEF 60%) were included. IVF patients showed more global deformation abnormalities as indicated by lower LV global longitudinal strain (18.5% ± 2.6% vs 21.6% ± 1.8%; P < .001) and higher LV mechanical dispersion (41 ± 12 ms vs 26 ± 6 ms; P < .001). In addition, IVF patients showed more regional LV postsystolic shortening compared to healthy controls (50% vs 11%; P < .001). Abnormal RV deformation patterns were observed in 16% of IVF patients and in none of the control subjects (P < .001).

CONCLUSION We were able to show both regional and global echocardiographic deformation abnormalities in IVF patients. This study provides evidence that localized myocardial disease is present in a subset of IVF patients.

KEYWORDS Deformation imaging; Idiopathic ventricular fibrillation; Speckle tracking; Strain echocardiography; Ventricular arrhythmia

Introduction

Idiopathic ventricular fibrillation (IVF) has been diagnosed in patients with sudden onset of ventricular fibrillation (VF), the origin of which is not identified after extensive diagnostic testing. Thus, the diagnosis of IVF depends on the absence of an evident substrate for VF by exclusion of coronary artery disease, structural cardiac diseases, and primary arrhythmia syndromes.2 Importantly, IVF may be an inheritable condition that also suggests risk of VF in currently asymptomatic family members.3 With the increased sophistication of diagnostic modalities, the presence of several disease entities has been identified in patients with VF previously considered idiopathic.1

Imaging modalities such as echocardiography and cardiovascular magnetic resonance imaging (CMR) play important roles in the standard diagnostic workup of IVF patients. By definition, IVF is characterized by a lack of overt structural and functional abnormalities detected by conventional imaging and fulfill current cutoff values for cardiomyopathies. However, detailed endocardial and epicardial mapping in IVF patients revealed that localized structural alterations...
underlie the condition in a significant subset of patients. However, even in these patients, conventional imaging lacks sensitivity for detection of these subtle changes. Therefore, application of novel imaging techniques would be of added value in IVF patients.

Echocardiographic deformation imaging is an advanced and widely available imaging technique that has provided unique information on regional and global myocardial function. The technique is already being applied in the field of (inherited) arrhythmia syndromes. For example, right ventricular (RV) deformation imaging has been shown to enable detection of an early electromechanical substrate in patients with arrhythmogenic cardiomyopathy (ACM) and was proven to have prognostic value in relatives who were in a subclinical stage of disease. In primary arrhythmia syndromes such as long QT syndrome and Brugada syndrome, deformation imaging revealed abnormal myocardial contraction patterns, which previously had been linked to ventricular arrhythmias. Therefore, echocardiographic deformation imaging may play a role in the search for an arrhythmogenic substrate in IVF patients or in defining subsets of IVF patients having distinct underlying pathophysiological mechanisms.

In this study, we aimed to explore echocardiographic deformation characteristics in IVF patients. Our hypothesis was that deformation abnormalities precede signs of disease on conventional imaging in IVF patients and therefore may help classify and stratify patients and their family members who are at risk.

**Methods**

**Study population**

Patients were selected from a Dutch registry of IVF patients between 1996 and 2020. Patients were included in the registry if they had experienced a cardiac arrest with an initial shockable rhythm, and no diagnosis had been made after comprehensive clinical assessment. Patients from 2 tertiary referral centers in The Netherlands (Amsterdam University Medical Center and University Medical Center Utrecht) with an echocardiogram of sufficient image quality were included for analysis. Echocardiograms recorded within the first 2 weeks after the cardiac event were excluded from analysis due to potential cardiac stunning. The subsequent follow-up echocardiogram with the highest image quality was included. Patients with cardiac pathology at the time of echocardiography were excluded (Figure 1). In addition to subjects with idiopathic VF, a group of age- and sex-matched control subjects was included. The control group consisted of a mixed group of (1) healthy nonathlete volunteers and (2) patients who visited the outpatient clinic but were found to be free of cardiac disease (eg, noncardiac chest pain or genotype elusive family members who visited the outpatient clinic for screening). This study was approved by the local ethics committee of the participating centers and conformed to the principles of the Declaration of Helsinki.

**Clinical investigations**

Enrolled patients underwent a detailed investigation of their medical history, physical examination, and standard investigations including resting 12-lead electrocardiography and cardiac imaging with echocardiography and/or CMR. Additional investigations, such as coronary artery imaging, Holter monitoring, exercise test, sodium channel blocker provocation, endomyocardial biopsy, and genetic testing, were performed at the treating physician’s discretion. Patients with the DPP6 haplotype, a genetic variant associated with short-coupled torsades de pointes/IVF, were included in the group of IVF patients. All patients underwent cardiac follow-up at a large tertiary center having electrophysiological expertise, where the IVF diagnosis was continuously evaluated and reconsidered. Additional diagnostic tests were performed when deemed appropriate. The diagnostic and outcome data in the registry are updated yearly.

**Echocardiographic evaluation**

**Conventional echocardiography**

All echocardiograms were performed as part of routine clinical care. Only echocardiograms performed using Vivid 7, E9, and E95 machines (GE Healthcare, Horten, Norway) were included. Measurements were performed by 2 operators (KT, HB). Blinding was not possible because IVF patients typically have an implantable cardioverter-defibrillator (ICD), in contrast to control subjects. The 2 operators were unfamiliar with the clinical characteristics of the patients. Conventional echocardiographic measurements were performed in accordance with current recommendations. Measurement of left ventricular ejection fraction (LVEF) was performed by either 2-dimensional (2D) Simpson biplane method or 3-dimensional volume measurements.

**Deformation imaging methods**

Longitudinal strain analysis was performed by 2D speckle tracking using EchoPAC Version 203 (GE Healthcare). All analyses were performed in accordance with current recommendations. Postprocessing methods have previously been described.

For left ventricular (LV) deformation imaging, apical 4-, 2-, and 3-chamber views were analyzed. Images were excluded from analysis in case of low frame rate (<50 per second), foreshortening, or >1 segment required exclusion (eg, due to insufficient window). Timing of aortic valve closure was derived from 2D recordings in the apical 3-chamber view. RV deformation imaging was performed only if an RV-focused, apical 4-chamber view of sufficient quality was available. Single wall analysis was performed on the RV free wall. Timing of pulmonic valve closure was derived from spectral Doppler recordings in the RV outflow tract. LV or RV deformation imaging was not performed in subjects who had a history of catheter ablation in the LV or RV, respectively.
Global deformation imaging parameters
All global deformation imaging parameters are reported as absolute values. LV global longitudinal strain (GLS) was defined as the average global peak strain (in percent) from the 3 apical views. LV mechanical dispersion (MD) was defined as the standard deviation of time to peak longitudinal strain (in milliseconds) from the 18 LV segmental deformation curves. LV GLS, 18% and LV MD, 45 ms, as used at our center, were considered abnormal. RV free-wall strain was defined as the average systolic peak strain (in percent) from the 3 RV free-wall segments.

Regional deformation imaging parameters
The 18 regional LV deformation curves were evaluated for the presence of postsystolic shortening. Postsystolic shortening was defined as longitudinal myocardial shortening after aortic valve closure. Postsystolic shortening was considered present if postsystolic index ≥10%. The postsystolic index was calculated as follows:

\[
\text{postsystolic index} = \frac{\text{peak strain} - \text{systolic peak strain}}{\text{peak strain}} \times 100\%
\]

The 3 regional RV free-wall deformation curves (basal, mid, apical) were evaluated according to the classification of Mast et al.\(^7\) The deformation patterns were consequently classified as follows: type I = normal deformation pattern; type II = delayed onset of shortening, decreased systolic peak strain, and postsystolic shortening; and type III = systolic stretching and large postsystolic shortening.

Statistical analysis
Statistical analysis was performed using IBM SPSS Statistics Version 25.0 for Windows (IBM Corp., Armonk, NY). Continuous variables are given as mean ± SD or median [interquartile range]. Comparisons between continuous variables were performed using the independent samples Student \(t\) test or Mann-Whitney \(U\) test. Categorical variables are given as frequency and percentage and were compared using the \(\chi^2\) test or Fisher exact test, as appropriate. \(P < .05\) was considered significant.

Results
Baseline characteristics and diagnostic testing
Table 1 lists the baseline characteristics of the IVF patients. Echocardiograms with the highest image quality that were recorded after the initial cardiac arrest were included (median timeframe 56 [29; 133] months). IVF patients were aged 45 ± 12.9 years at the time of echocardiography, and 51.1% were male. Control subjects were aged 41 ± 12.1 years at the time of echocardiography, and 34.0% were male. Table 2 lists the diagnostic tests performed.
Outcome of DNA analysis
ICD implanted 47 (100)
Postanoxic encephalopathy 11 (23.4)
Witnessed event 38 (84.4)

Circumstances during occurrence of VF
Male 24 (51.1)

Diagnostic tests performed in the IVF patients
Table 2

<table>
<thead>
<tr>
<th>Test</th>
<th>IVF subjects (n = 47)</th>
<th>Control subjects (n = 47)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA analysis</td>
<td>44 (93.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac imaging</td>
<td>47 (100)</td>
<td>47 (100)</td>
<td></td>
</tr>
<tr>
<td>Echocardiography</td>
<td>47 (100)</td>
<td>47 (100)</td>
<td></td>
</tr>
<tr>
<td>Cardiac MR</td>
<td>35 (76.1)</td>
<td>42 (89.4)</td>
<td></td>
</tr>
<tr>
<td>Coronary angiography or CT angiography</td>
<td>42 (89.4)</td>
<td>42 (89.4)</td>
<td></td>
</tr>
<tr>
<td>Exercise stress test</td>
<td>26 (55.3)</td>
<td>34 (72.3)</td>
<td></td>
</tr>
<tr>
<td>Holter monitoring</td>
<td>26 (55.3)</td>
<td>34 (72.3)</td>
<td></td>
</tr>
<tr>
<td>Sodium channel blocker provocation</td>
<td>15 (31.9)</td>
<td>15 (31.9)</td>
<td></td>
</tr>
<tr>
<td>Ergonovine provocation</td>
<td>5 (10.6)</td>
<td>8 (17.0)</td>
<td></td>
</tr>
<tr>
<td>Signal-averaged ECG</td>
<td>8 (17.0)</td>
<td>8 (17.0)</td>
<td></td>
</tr>
<tr>
<td>Endomyocardial biopsy</td>
<td>44 (93.6)</td>
<td>44 (93.6)</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as median [interquartile range], mean ± SD, or n (%).

ICD = implantable cardioverter-defibrillator; IVF = idiopathic ventricular fibrillation.

**Echocardiogram**

Conventional echocardiography
Table 3 lists the echocardiographic measurements of the IVF and control cohorts. Among the conventional measurements, only LVEF differed significantly between groups, being lower in IVF patients than in control subjects (56% ± 6% vs 60% ± 5%, respectively; P < .001). Global RV function was not different between IVF patients and control subjects, nor were LV and RV dimensions.

Deformation imaging
Deformation imaging measurements are given in Table 3 and Figure 2. LV deformation imaging was performed in 44 IVF subjects (94%) and 47 control subjects (100%), whereas RV deformation imaging could be reliably performed in 31 IVF subjects (66%) and 29 control subjects (62%).

With regard to global deformation imaging, LV GLS was lower in IVF patients than in control subjects (18.5% ± 2.6% vs 21.6% ± 1.8%; P < .001). LV MD was higher in IVF patients than in control subjects (41 ± 12 ms vs 26 ± 6 ms; P < .001). According to our center-specific cutoff values, abnormal GLS and MD were significantly more prevalent in IVF patients than in controls (Table 3).

With regard to regional deformation imaging, 22 IVF subjects (50%) showed regional LV post-systolic shortening in at least 1 segment, which was more frequent than in control subjects (5 [11%]; P < .001). Ten IVF subjects (23%) had post-systolic shortening in ≥2 segments, which was seen in only 1 of the control subjects. With regard to RV deformation imaging, 6 IVF subjects (19%) had an abnormal deformation pattern, which was not seen in any of the control subjects (Table 3 and Figure 2).

Patients with MD >45 ms more frequently received ICD therapy than patients with MD <45 ms (50% vs 32%; P = .242). IVF patients with ICD therapy also had slightly lower GLS values than patients without ICD therapy (mean GLS 18 vs 19; P = .352). However, these observations were not significant.

**Discussion**

In the present explorative study, we investigated echocardiographic deformation characteristics in IVF patients. We found that deformation imaging has the ability to reveal both global and regional mechanical alterations in IVF patients compared to findings on deformation characteristics in age- and sex-matched control subjects (Figure 2). These results suggest that “idiopathic VF” may be less associated with a completely structurally normal heart than previously...
Deformation imaging was performed in 47 patients with idiopathic ventricular fibrillation (IVF) and 47 healthy controls. **Top:** Left ventricular (LV) deformation abnormalities such as postsystolic shortening (PSS), mechanical dispersion (MD) >45 ms, and global longitudinal strain (GLS) <18% were significantly more prevalent in IVF patients (top left) vs controls (top right). Abnormal right ventricular (RV) patterns according to the classification of Mast et al7 were also seen more frequently in IVF patients. **Middle, left:** LV deformation imaging of an IVF patient shows low GLS values (long white arrow), pronounced MD (colored arrows), and PSS (short white arrow). **Middle, right:** LV deformation imaging in a control patient shows normal values and patterns. **Bottom, left and right:** RV deformation imaging in an IVF patient (left) shows an abnormal type II pattern (red arrow) in the basal segment, whereas imaging in the control patient (right) shows normal patterns in all segments. 2CH = 2-chamber; 4CH = 4-chamber; APLAX = apical long axis; VF = ventricular fibrillation.
appreciated, which is compatible with the significant subset of IVF patients having localized structural alterations demonstrated by detailed endocardial and epicardial mapping.\textsuperscript{4,17}

**Global deformation abnormalities**

Conventional imaging showed that LVEF was slightly lower in patients compared to healthy controls (56% vs 60%), but these values were still within normal range. To characterize myocardial function beyond conventional echocardiographic techniques, we applied 2D speckle tracking software, which allows assessment of myocardial tissue deformation. Deformation imaging also revealed significant systolic dysfunction in IVF patients. Although this is a novel finding, it is possible that IVF patients who were resuscitated might have suffered from some degree of global cardiac ischemia during their circulatory arrest, which could have resulted in slightly lower systolic function. However, because GLS seems to be able to detect subtle changes preceding deterioration of LVEF in these subjects is the cause of VF or a consequence of the circulatory arrest remains unknown.

IVF patients also had higher LV MD compared to controls. LV MD, which represents heterogeneity in LV contractility, has been associated with malignant ventricular arrhythmias in several cardiac diseases, such as prior myocardial infarction,\textsuperscript{19} ACM,\textsuperscript{20} and long QT syndrome.\textsuperscript{21} The pronounced LV MD in our IVF cohort might reflect subtle (interstitial) fibrosis in myocardial tissue, which may be caused by either cardiac arrest or a yet undiscovered underlying disease. Given that MD is also seen in primary electrical diseases in which fibrosis is assumed to be completely absent, MD in IVF may be a sign of disturbed electrical conduction of the myocardium. A recent population-based study showed that a longer duration of repolarization on the surface electrocardiogram is associated with higher LV MD values, which supports the hypothesis that LV MD represents not only mechanical properties of the myocardium but also electrical properties.\textsuperscript{22} In our cohort, the sample size was too small to determine the value of LV MD as a prognostic factor in IVF patients; this should be further explored in a larger prospective study.

**Regional deformation abnormalities**

We observed significantly more regional deformation abnormalities in IVF patients vs controls. Although the global deformation abnormalities possibly could be explained by the cardiac ischemia caused by global hypoperfusion during circulatory arrest, this is less likely for regional deformation abnormalities as coronary artery disease was ruled out in every patient.

Previous literature showed that a significant subset of previously unexplained sudden cardiac arrest patients show localized electrical alterations during endocardial and epicardial mapping.\textsuperscript{4} Prior experimental studies have shown that small ventricular lesions are able to promote VF inducibility.\textsuperscript{23,24} Endocardial/epicardial mapping results in IVF patients revealed that the pathology in most cases involved only a part of the ventricular wall rather than being transmural and only covered a limited surface area.\textsuperscript{4} This might explain why these subtle abnormalities cannot be perceived by conventional imaging but can be revealed by deformation imaging.

The RV deformation patterns of 6 patients in our cohort share similarities with previously described RV abnormalities in patients with ACM.\textsuperscript{6,7,25} Previous literature showed that an RV electromechanical substrate as detected by deformation imaging may already be present in desmosomal mutation carriers who are in a subclinical disease stage.\textsuperscript{7} In addition, in IVF patients, high-density endocardial/epicardial mapping showed a high prevalence of structural abnormalities in the RV.\textsuperscript{4} Cases of IVF patients diagnosed with ACM during follow-up have been reported.\textsuperscript{26} Previous literature confirms that IVF does not necessarily indicate a complete absence of any disease, and that some early-stage ACM patients might not be recognized as such. In IVF and particularly DPP6-related IVF, the Purkinje system seems to play a pivotal role, particularly in the RV free wall, which also might result in changed regional deformation.\textsuperscript{27}

**Study limitations**

Due to the retrospective nature of this study, the availability of echocardiographic imaging and its quality was limited. An echocardiogram performed with Vivid 7 E9 and E95 machines and appropriate quality was available in 47 patients (29.9%) in our IVF registry, potentially leading to selection bias. Not all patients underwent systematic diagnostic assessment; however, this is common in IVF studies in a real-world setting and is partly explained by the inclusion of patients with the Dutch DPP6 risk haplotype in whom the amount of diagnostic tests performed typically is lower than in other IVF patients.\textsuperscript{28,29} Because an ICD is inserted in all IVF patients after the event for secondary prevention, observers cannot be fully blinded when performing measurements, and this is deemed an inevitable limitation. Lastly, due to the small sample size of this study, the correlation between clinical follow-up data and echocardiographic deformation abnormalities was merely exploratory.

**Future perspectives**

The exact mechanism of these global and regional echocardiographic deformation abnormalities remains to be elucidated. In future research it would be interesting to correlate these deformation abnormalities with T1 mapping in IVF patients to further explore a potential underlying substrate. A large prospective study is needed to confirm and further explore these deformation abnormalities, as well as correlate these echocardiographic findings with CMR and prognostic outcome measures. Furthermore, it would be relevant to study the subgroup of IVF patients with a clear
inheritable nature, as in these families we currently often lack the ability to define currently asymptomatic family members at risk for VF.

Conclusion

We were able to show both global and regional echocardiographic deformation abnormalities in patients with IVF. This study provides evidence that localized myocardial disease is present in a subset of IVF patients. Future prospective studies are needed to confirm and further explore the clinical value of our findings.

References