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Prediction of Ventricular Arrhythmias in Patients at Risk of Sudden Cardiac Death

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1. Introduction

Sudden cardiac deaths remain the major cause of mortality in the western world. Ventricular arrhythmia due to ischemic heart disease is the most frequent cause of sudden cardiac death. In patients >35 years of age, ischemic heart disease is the most frequent cause of ventricular arrhythmias. In patients <35 years of age, inherited cardiac diseases play a significant role in sudden cardiac death. Prediction of who will experience a life-threatening ventricular arrhythmia is a major challenge in current cardiology.

An implantable cardioverter defibrillator (ICD) provides efficient preventive treatment for ventricular arrhythmias and sudden death and is implanted in patients at risk. However, risk stratification of ventricular arrhythmias is insufficient and the majority of patients dying suddenly have not been evaluated for ICD therapy.

Patients after myocardial infarction are at high risk for cardiac arrhythmic events and sudden cardiac death (Zipes, 2006). Currently, LV ejection fraction (EF) is the primary parameter used to select patients for ICD therapy after a myocardial infarction. Impaired EF is shown to be a marker of increased cardiovascular mortality and sudden cardiac death. However, EF has relatively low sensitivity to detect arrhythmic risk (Buxton, 2007). A number of other diagnostic tests have been proposed to improve the accuracy for selection of patients for ICD therapy. Currently available data, however, are not adequate to routinely recommend additional risk-stratification methods for selection of patients for ICD therapy (Passman, 2007).

The presence of myocardial scar forms the substrate for malignant arrhythmias (Zipes, 1998). Heterogeneity in scar tissue may create areas of slow conduction that generate the substrate for ventricular arrhythmia post-myocardial infarction (Verma, 2005). Electrical dispersion, including both activation time and refractoriness, in infarcted tissue is a known arrhythmogenic factor, (Endresen, 1987; Han, 1964; Janse, 1989; Vassallo, 1988). Electrical abnormalities may lead to distorted myocardial function (Nagueh, 2008). Therefore, regional differences in electrical properties may cause heterogeneity of myocardial contraction which can be recognized as myocardial dyssynchrony (Yu, 2003).

In this report, a novel echocardiographic method will be presented in order to evaluate the cardiac contractility pattern in patients at increased risk of life-threatening arrhythmias.

2. Modern echocardiographic modalities

Better echocardiographic tools for more accurate assessment of ventricular function have been developed during the last 2 decades. Minor degrees of myocardial contraction

heterogeneity and contraction dyssynchrony can be demonstrated by these modern echocardiographic techniques (Reisner, 2004; Yu, 2007). One way to discover subtle wall motion abnormalities caused by electrical heterogeneity would be to use strain echocardiography (Edvardsen, 2002b). The introduction of strain echocardiography has made it possible to accurately perform quantitative and objective measures of regional ventricular function by measuring regional contraction by strain. Strain can accurately quantify timing and deformation of regional myocardial function (Edvardsen, 2002a; Reisner, 2004; Voigt, 2003).

Currently, visual assessment of regional myocardial function from 2-D image is the standard echocardiographic method to assess ventricular function in daily clinical practice. Visual assessment has had that position since the introduction of 2-D echocardiography. This method has also been established as a clinically important tool in detecting regional ventricular function, but has limited ability to detect more subtle changes in function and changes in timing of myocardial motion throughout systole and diastole. Strain echocardiographic technique may be used to accurately assess timing and function of myocardial contraction in patients with increased risk of ventricular arrhythmias. The hypotheses that echocardiography can contribute to arrhythmic risk assessment is based on the assumption that arrhythmogenic electrical abnormalities will lead to mechanical alterations which can be assessed by strain echocardiography.

2.1 Use of strain echocardiography for prediction of ventricular arrhythmias

We have recently reported that strain echocardiography can be used as a novel risk predictor of ventricular arrhythmias in patients with the long QT syndrome (Haugaa, 2009; Haugaa, 2010a). The long QT syndrome has traditionally been regarded as a purely electrical disease. Sporadic reports have indicated, however, that the electrical alterations may lead to mechanical consequences (De Ferrari, 2009; Nador, 1991). In our publications, we could show by modern echocardiographic techniques that subtle contraction heterogeneity was present in patients with the long QT syndrome, possibly due to electrical abnormalities. Therefore, these echocardiographic techniques were able to detect subtle changes in myocardial function. Furthermore, we could associate mechanical dispersion to ventricular arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy (Sarvari, 2011). Contraction heterogeneity defined as mechanical dispersion was a marker of arrhythmias in these patients and could help risk stratification of arrhythmias in so far asymptomatic mutation carriers. In a recent paper, we investigated if contraction heterogeneity due to fibrosis in infarcted myocardial tissue leads to mechanical dispersion in patients after myocardial infarction (Haugaa, 2010b). These results are briefly presented below. We presumed that the mechanical dispersion reflected electrical heterogeneity. We investigated if mechanical dispersion can predict ventricular arrhythmias in patients with risk of ventricular arrhythmias. Furthermore, we investigated if global strain by echocardiography is a better marker of arrhythmias than EF in patients after myocardial infarction.

3. Study of 85 post MI patients with an ICD

We prospectively investigated 85 post-MI patients fulfilling indications for ICD therapy. All patients had prior myocardial infarction and indication for ICD therapy according to primary or secondary prevention criteria. Arrhythmic events, defined as ventricular

arrhythmias that required appropriate anti tachycardia pacing or shock from the ICD, were recorded. During 2.3 years of follow up, 45% of the ICD patients experienced one or more episodes with sustained ventricular tachycardia or ventricular fibrillation requiring appropriate ICD therapy (anti tachycardia pacing or shock) while 55% had no sustained arrhythmia during follow up.

Speckle tracking technique by strain echocardiography was used to assess the contraction duration in each of the 16 left ventricular segments (Figure 1). Mechanical dispersion was calculated as the standard deviation from contraction durations the 16 left ventricular segments. Global left ventricular strain was obtained by averaging all segmental values for maximum shortening in a 16 segment model.

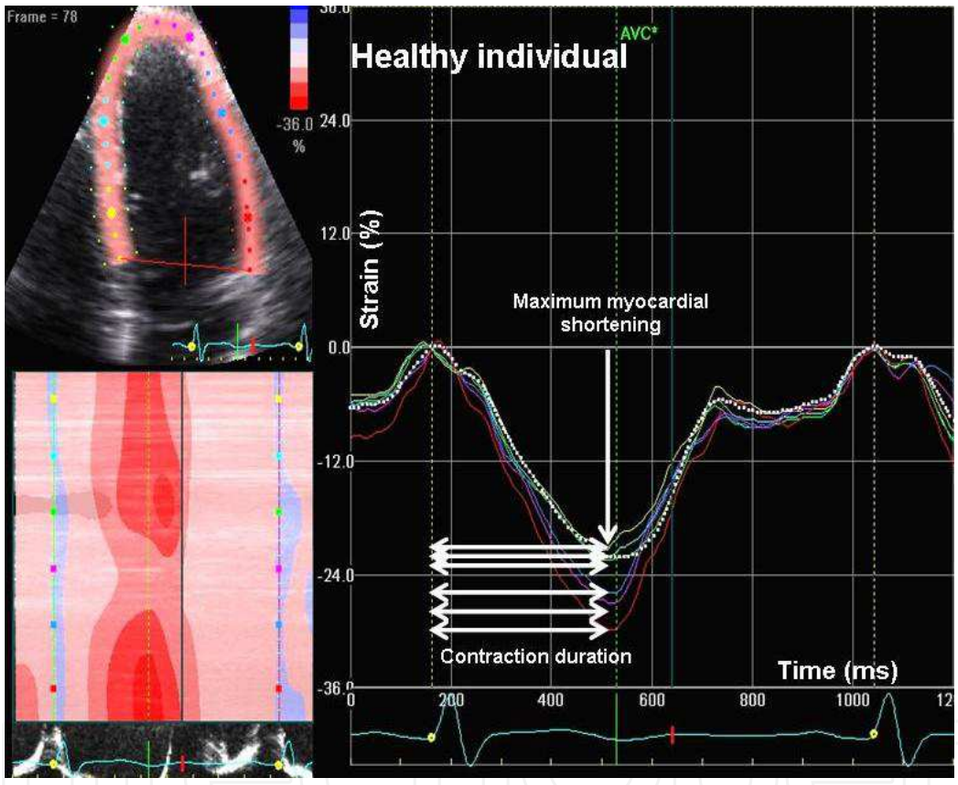

Fig. 1. Speckle tracking longitudinal strain curves from 6 segments in apical 4 chamber view from a healthy individual with synchronous ECG recording below. Segment contraction (shortening) starts during QRS and reaches a maximum myocardial shortening (white vertical arrow) at the end of the ECG T-wave. (Modified from *JACC Cardiovasc Imaging* 2010 March;**3**(3):247-56).

The study showed that mechanical dispersion was significantly more pronounced in those with arrhythmias compared to those without (Fig 2). Furthermore, mechanical dispersion was a strong and independent predictor of arrhythmias requiring ICD therapy.

Survival analyses showed that ICD patients with mechanical dispersion > 70ms showed more frequent arrhythmic events than ICD patients with dispersion < 70ms (Fig 3).

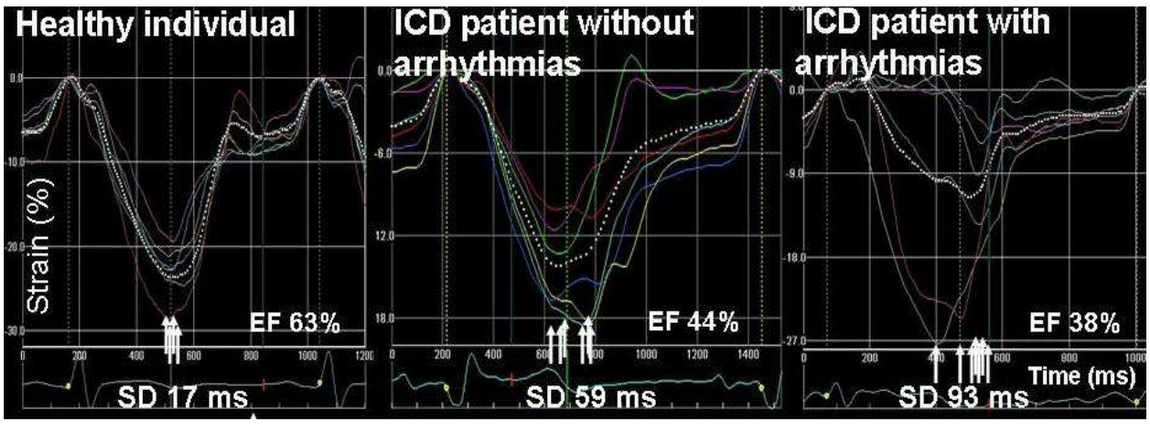

Fig. 2. Strain curves from a healthy individual (left panel), a post MI patient with arrhythmias (mid panel) and a post MI patient with recurrent arrhythmias (right panel). White arrows indicate timing of maximum myocardial shortening. The post MI patient with recurrent arrhythmias (right panel) has the most dispersed timing in myocardial contraction and thereby most pronounced mechanical dispersion. (Modified from *JACC Cardiovasc Imaging* 2010 March;**3**(3):247-56).

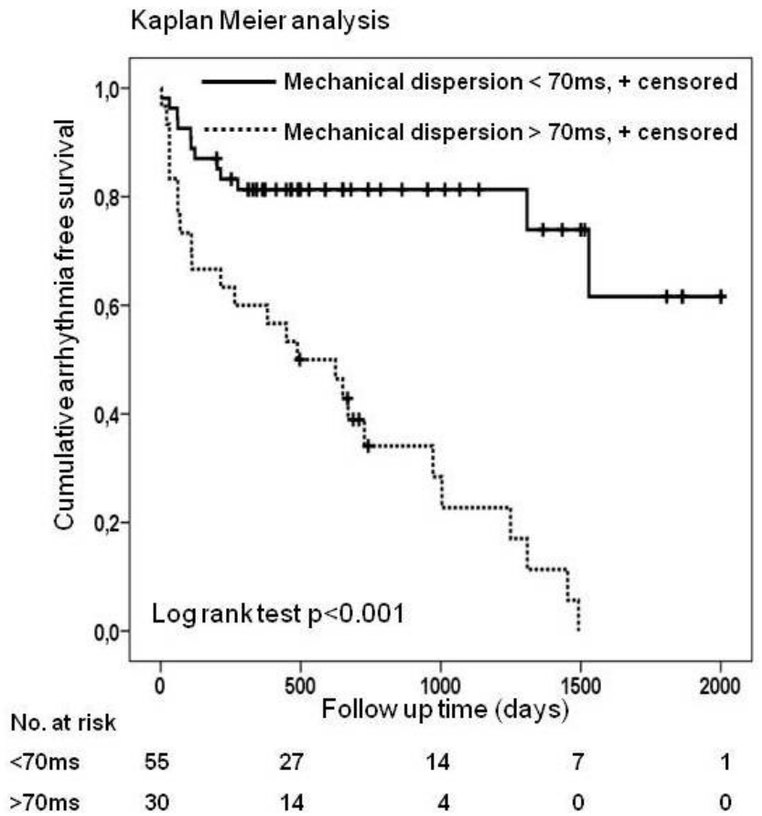

Fig. 3. Kaplan Meier analyses of 85 patients after myocardial infarction with ICD. Patients with mechanical dispersion > 70 ms have higher rate of arrhythmic events during follow up compared to patients with mechanical dispersion < 70 ms. (Modified from *JACC Cardiovasc Imaging* 2010 March;**3**(3):247-56).

In ICD patients with EF > 35%, mechanical dispersion was more pronounced in those who experienced arrhythmia compared to those without. Global strain showed better left ventricular function in those without recorded arrhythmias, while EF did not differ.
The results of the study showed that increased heterogeneity of myocardial contraction measured by strain echocardiography predicted cardiac arrhythmias better than current risk stratification tools. This novel method may improve risk stratification of cardiac arrhythmias and help the clinician to select patients for ICD therapy.

4. Electromechanical interactions

There is ample evidence from different cardiac disease models, including heart failure (Tomaselli, 2004), ischemia (Han, 1964) and infarction (Spragg, 2005; Vassallo, 1988) that increases in dispersion of conduction velocity result in susceptibility to arrhythmias (Spragg, 2005; Tomaselli, 2004). These electrical abnormalities will presumptively lead to changes in myocardial function. Assessing the extent of electrical dispersion in the individual patient has so far been difficult (Tomaselli, 2004). These findings support the idea that tissue heterogeneity in and around scarred myocardium lead to a dispersed myocardial contraction and is associated with risk of arrhythmic events.
Earlier echocardiographic studies have observed that an EF of ≤40% serves as the threshold for identifying high-risk individuals (Bigger, Jr., 1984; Greenberg, 1984). However, EF has reduced sensitivity in predicting sudden death (Buxton, 2007; Stecker, 2006). Speckle based strain has shown to be a robust technique for assessment of LV function and a recent study has demonstrated that speckle tracking strain is superior to EF for assessment of myocardial function post-myocardial infarction (Gjesdal, 2008). Global strain discriminated between those with and without arrhythmic events in post-MI patients with EF > 35%. This finding suggests that global strain might become a useful tool for risk stratification in post-myocardial infarction patients with relatively preserved LV function. Future trials should investigate if mechanical dispersion and global strain can be used to select additional patients for ICD therapy among the majority of patients after myocardial infarction with relatively preserved EF in whom current ICD indications fail.

5. Risk assessment of ventricular arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy is an inheritable, chronic and progressive cardiomyopathy and is one of the leading causes of sudden unexpected cardiac death in previously healthy young individuals (Sen-Chowdhry, 2010a; Thiene, 1988). Prevalence has been estimated to be at least 1 in 1000 (Sen-Chowdhry, 2010a).
Recent molecular genetic reports have revealed arrhythmogenic right ventricular cardiomyopathy as mainly a desmosomal disease (Xu, 2010). Mutations in one of the 5 desmosomal or 3 extra desmosomal genes so far identified, lead to progressive loss of myocytes, followed by fibro-fatty replacement. Penetrance is age and gender dependent and the progressive clinical picture is highly variable (Dalal, 2006).
Four clinical stages have been documented: An early concealed phase, overt electrical disorder, isolated right heart failure (Fig 4a), and biventricular pump failure (Fig 4b) (Basso, 1996; Sen-Chowdhry, 2007; Sen-Chowdhry, 2010a). Importantly, life-threatening arrhythmias can occur with only discrete or even absent myocardial structural changes (Sen-

Chowdhry, 2010b). Risk stratification of ventricular arrhythmias and sudden cardiac death is therefore challenging.

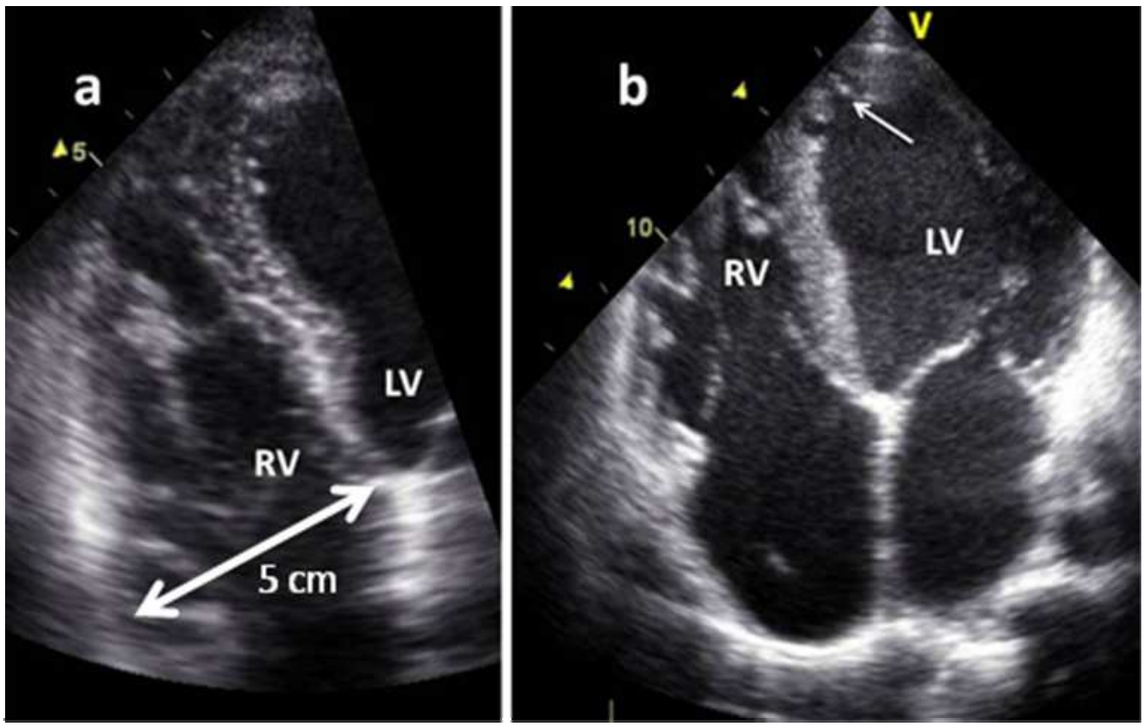

Fig. 4. Echocardiographic pictures of 2 patients with arrhythmogenic right ventricular cardiomyopathy.
A) left panel: classical right sided affection with dilatation (5 cm diameter, white arrow) and wall thinning of the right ventricle. The ICD lead is visible in the right ventricle.
B) right panel: Affection of both right and left ventricle in a patient with arrhythmogenic right ventricular cardiomyopathy. The right ventricle is dilated and with visible ICD lead. Furthermore, the left ventricle is dilated and shows apical affection of the myocardial wall (arrow).

Mechanisms of arrhythmias in early stages of arrhythmogenic right ventricular cardiomyopathy are probably due to dysfunction of desmosomal proteins and disturbed cell to cell coupling (Saffitz, 2009). In later stages of arrhythmogenic right ventricular cardiomyopathy when structural abnormalities in the myocardium have developed, reentrant ventricular arrhythmias can occur in tissue with fibro fatty replacement. Therefore, electrical conduction delay with consequent electrical dispersion has been suggested as an important mechanism of ventricular arrhythmias (Amlie, 1997; Turrini, 2001).
In a recent study we investigated if arrhythmogenic right ventricular cardiomyopathy patients had cardiac contraction heterogeneity assessed as mechanical dispersion and if contraction heterogeneity was associated with susceptibility to ventricular arrhythmias

(Sarvari, 2011). Furthermore, we investigated if mechanical dispersion was present in arrhythmogenic right ventricular cardiomyopathy mutation carriers in early stages of the disease where no structural alterations were visible.

Mechanical dispersion and strain in right and left ventricle were assessed in 36 arrhythmogenic right ventricular cardiomyopathy patients, in 23 asymptomatic arrhythmogenic right ventricular cardiomyopathy mutation carriers and in 30 healthy individuals. All 36 arrhythmogenic right ventricular cardiomyopathy patients had experienced ventricular arrhythmias either as aborted cardiac arrest or as documented sustained ventricular tachycardia and fulfilled 2010 International Task Force criteria (Marcus, 2010). They were treated with ICD in addition to medical anti arrhythmic therapy. The 23 asymptomatic mutation carriers were family members of the arrhythmogenic right ventricular cardiomyopathy patients and were diagnosed by cascade genetic screening.

Peak systolic myocardial strain by 2D speckle tracking echocardiography was assessed in 16 left ventricular segments and averaged to left ventricular global longitudinal strain in arrhythmogenic right ventricular cardiomyopathy patients. Additionally, peak systolic strain from 3 right ventricular free wall segments was averaged as a measure of right ventricular function (RV strain) (Fig 5). Contraction duration was measured as time from onset R on ECG to maximum LV and right ventricular shortening by strain. Standard deviation of contraction duration was calculated as mechanical dispersion, in a 16 left ventricular segments and a 6 right ventricular segments model.

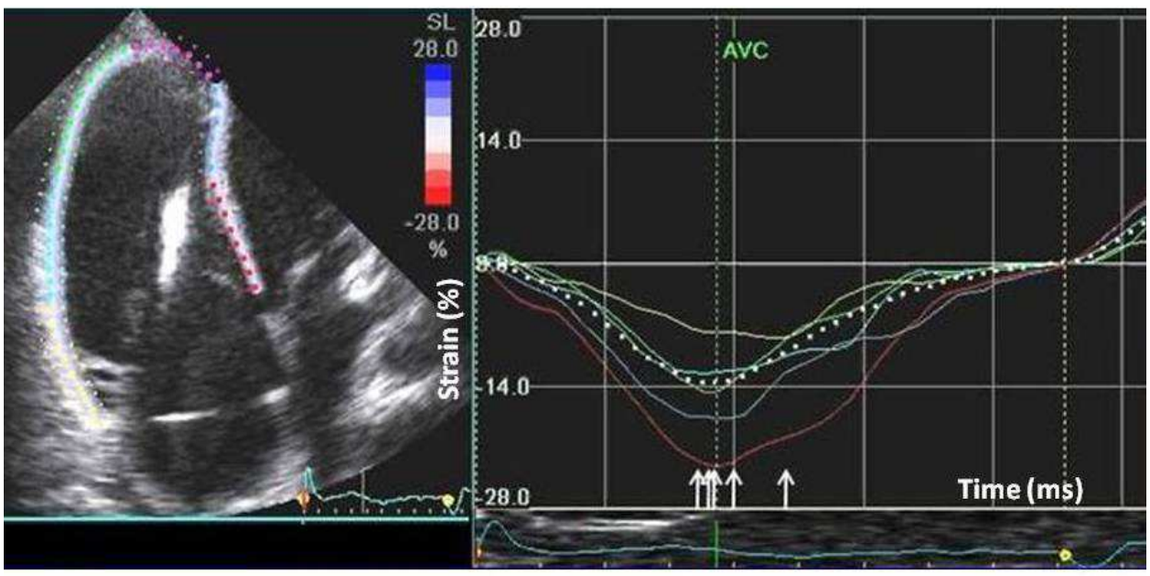

Fig. 5. Strain curves in an patient with arrhythmogenic right ventricular cardiomyopathy. Strain curves from a dilated right ventricle from apical 4 chamber view. Vertical arrows indicate the timing of maximum myocardial shortening in each right ventricular segment and are consistent with pronounced right ventricular mechanical dispersion.

Mechanical dispersion was more pronounced in arrhythmogenic right ventricular cardiomyopathy patients with arrhythmias in right and left ventricle compared to asymptomatic mutation carriers and healthy individuals (Table 1). Importantly, mechanical dispersion was more pronounced in asymptomatic mutation carriers compared to healthy individuals in both right and left ventricle, indicating sub clinical ventricular involvement. Right and left ventricular strains were reduced in arrhythmogenic right ventricular cardiomyopathy patients compared to asymptomatic mutation carriers and healthy individuals (Table 1). Reduced right and left ventricular strains were significantly correlated in arrhythmogenic right ventricular cardiomyopathy patients, indicating biventricular disease. Right and left ventricular function in asymptomatic mutation carriers were within normal range, but significantly reduced compared to healthy individuals.

	Healthy individuals (n=30)	Asymptomatic mutation carriers (n=23)	ARVC patients with arrhythmias (n=36)	P
EF (%)	64±5	63±4	57±14*	<0.01
LV strain (%)	-23±2	-20±2*	-16±5* ,**	<0.001
RV strain (%)	-28±5	-24±5*	-19±7* ,**	<0.001
LV Dispersion (ms)	22±8	42±13*	64±25* ,**	<0.001
RV Dispersion (ms)	15±8	33±20*	53±25* ,**	<0.001

Table 1. Echocardiographic results in 36 ARVC patients, 23 asymptomatic ARVC mutation carriers and 30 healthy individuals.
Mean±SD. Right column shows P-values for ANOVA test. Flags for significance are obtained from the post hoc pair-wise comparison using the Bonferroni correction. *p<0.05 compared with healthy individuals. **p<0.01 compared with asymptomatic mutation carriers. ANOVA, analysis of variance; EF, ejection fraction; RV, right ventricular; LV, left ventricular.

Risk stratification of ventricular arrhythmias in so far asymptomatic arrhythmogenic right ventricular cardiomyopathy mutation carriers is difficult. This report demonstrated that mechanical dispersion was closely related to ventricular arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy. Increased mechanical dispersion in both ventricles was present in asymptomatic mutation carriers, indicating sub clinical myocardial alterations. Importantly, pronounced mechanical dispersion was also present in individuals who had experienced arrhythmias in the early stages of arrhythmogenic right ventricular cardiomyopathy and in whom no structural alterations assessed by conventional echocardiography and magnetic resonance imaging could be assessed. These findings suggest that mechanical dispersion may be a marker of arrhythmic events and help risk stratification in so far asymptomatic arrhythmogenic right ventricular

cardiomyopathy mutation carriers. Mechanical dispersion and myocardial strains demonstrated subclinical myocardial involvement in these individuals. Longitudinal follow up studies are required to assess if these methods can provide added value in arrhythmia risk stratification in asymptomatic arrhythmogenic right ventricular cardiomyopathy mutation carriers.

Furthermore, this paper demonstrated frequent and early left ventricular involvement in arrhythmogenic right ventricular cardiomyopathy which supported recent reports of arrhythmogenic right ventricular cardiomyopathy as a biventricular disease (Kjaergaard, 2007). Biventricular impairment is probably a result of biventricular arrhythmogenic right ventricular cardiomyopathy affection, but mutual dependency of right and left ventricular hemodynamics may be considered. In patients with overt arrhythmogenic right ventricular cardiomyopathy, strain echocardiography may be a useful tool for quantification of right and left sided myocardial dysfunction.

6. Comparisons of mechanical dispersion in patients after myocardial infarction and in patients with arrhythmogenic right ventricular cardiomyopathy

Mechanical dispersion has been demonstrated in arrhythmogenic right ventricular cardiomyopathy patients and in post-myocardial infarction patients and has been shown to be a marker of recurrent ventricular arrhythmias in both conditions. The mechanisms for arrhythmias in arrhythmogenic right ventricular cardiomyopathy and in infarcted myocardial tissue are different, but have similarities regarding electrical dispersion. In arrhythmogenic right ventricular cardiomyopathy patients, mechanisms of arrhythmias are probably stage dependent, but electrical dispersion has been considered to be of importance in early and later stages of the disease (Amlie, 1997; Turrini, 2001). In post-MI patients delayed start of ventricular activation in scarred myocardium leads to a dispersed recovery of excitability (Vassallo, 1988), finally resulting in dispersed electrical repolarization. One might therefore speculate that electrical dispersion may be regarded as the final common pathway of arrhythmia mechanism in both conditions.

The extent of mechanical dispersion appeared most pronounced in post-myocardial infarction patients. This difference was probably a result of the concomitant contractile impairment in infarcted tissue which was more pronounced compared to presence of fibrosis in arrhythmogenic right ventricular cardiomyopathy. Myocardial function was significantly impaired in post-myocardial infarction patients compared to arrhythmogenic right ventricular cardiomyopathy patients. Contractile impairment will pronounce mechanical dispersion. The ranges and values of mechanical dispersion which are related to increased arrhythmic risk will therefore not necessarily be interchangeable between different myocardial diseases.

7. Future risk assessment of ventricular arrhythmias and additional patient entities

The most important patient group for further risk assessment of ventricular arrhythmias are patients after myocardial infarction representing the largest cohort of individuals at risk. Future trials should investigate if mechanical dispersion and global strain can be used to select additional patients for ICD therapy among the majority of post-myocardial infarction

patients with relatively preserved EF in whom current ICD indications fail. Furthermore, there are several large groups of patients who are at risk of ventricular arrhythmias on a non-ischemic basis, i.e. patients with idiopathic dilated cardiomyopathies, other cardiomyopathies and patients with congenital heart disease. It is of great concern that EF is currently the only parameter to select patients with idiopathic dilated cardiomyopathy for ICD therapy. There is emerging awareness of the insufficiency of EF to predict ventricular arrhythmias in these patients and further risk stratification tools are urgently needed. Mechanical dispersion may reflect the electrical dispersion and represent a fundamental arrhythmogenic factor. Furthermore, mechanical dispersion has been shown to predict arrhythmias independently of EF. Mechanical dispersion may therefore have the potential to be introduced as an additional tool in arrhythmic risk stratification in other groups of patients.

8. Conclusion

In summary, mechanical dispersion has been shown to predict ventricular arrhythmias in post-myocardial infarction patients and in patients with arrhythmogenic right ventricular cardiomyopathy and the long QT syndrome. This principle may therefore be a valuable supplement in evaluating patients at risk independently of EF. Mechanical dispersion and global strain may be useful for including more patients for ICD therapy after myocardial infarction.

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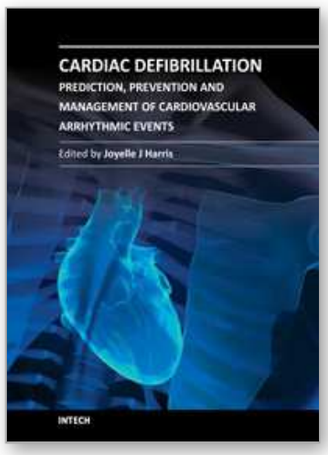

Cardiac Defibrillation - Prediction, Prevention and Management of Cardiovascular Arrhythmic Events

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Millions of people throughout the world currently depend on appropriate, timely shocks from implantable cardioverter defibrillators (ICDs) to avoid sudden death due to cardiovascular malfunctions. Therefore, information regarding the use, applications, and clinical relevance of ICDs is imperative for expanding the body of knowledge used to prevent and manage fatal cardiovascular behavior. As such, the apt and timely research contained in this book will prove both relevant to current ICD usage and valuable in helping advance ICD technology. This book is divided into three comprehensive sections in order to cover several areas of ICD research. The first section introduces defibrillator technology, discusses determinants for successful defibrillation, and explores assessments of patients who receive defibrillation. The next section talks about predicting, preventing, and managing near catastrophic cardiovascular events, and research presented in the final section examine special cases in ICD patients and explore information that can be learned through clinical trial examinations of patients with defibrillators. Each chapter of this book will help answer critical questions about ICDs.

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