Echocardiographic Markers for Arrhythmias and Cardiac Magnetic Resonance

Subjects: Cardiac & Cardiovascular Systems

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Cardiovascular diseases remain among the leading causes of death worldwide and sudden cardiac death (SCD) accounts for ~25% of these deaths. Despite its epidemiologic relevance, there are very few diagnostic strategies available useful to prevent SCD mainly focused on patients already affected by specific cardiovascular diseases. Unfortunately, most of these parameters exhibit poor positive predictive accuracy. Moreover, there is also a need to identify parameters to stratify the risk of SCD among otherwise healthy subjects.

Keywords: sudden cardiac death ; disease ; cardiac magnetic resonance ; echocardiography

1. Introduction

Echocardiography is the first and the most commonly used cardiac imaging technique. Compared to cardiac magnetic resonance and cardiac computed tomography, echocardiography is an inexpensive, rapid, and readily available imaging modality. Echocardiographic imaging of patients with ventricular arrhythmias facilitates the identification (or exclusion) of structural heart disease. Furthermore, echocardiography performed in patients who are exercising or responding to pharmacological stress can be applied to a selected group of patients with VAs triggered by ischemia [1][2].

2. Echocardiography

2.1 Left Ventricular Hypertrophy (LVH)

Increased left ventricular (LV) mass is associated with an increased risk of SCD in the general population [3][4]. LVH is associated with abnormal interstitial remodeling which can impair electrical conduction and promote Vas [5]. In the Framingham Heart Study, increased LV mass and hypertrophy as assessed by echocardiogram, were independently associated with SCD after accounting for other known risk factors [6]. LVH, defined as LV mass (adjusted for height) >143 g/m^2 in men and >102 g/m^2 in women, was associated with a 116% increase in the risk of SCD. Estimates revealed that each 50 g/m^2 incremental increase in LV mass was associated with an additional 45% increase in the risk of SCD during a mean follow-up of 10.3 years. The increased risk of SCD associated with LVH is also observed among patients diagnosed with ischemic cardiomyopathy [7].

2.2. Global and Segmental Longitudinal Strain

Several new echocardiographic parameters reflecting myocardial function have been developed in recent years. Among these are speckle tracking echocardiography (STE) which provides information on myocardial deformation by linking electrical activity to specific anatomical structures. Active myocardial deformation (strain) is assessed by tracking ultrasound markers (speckles). The analysis focuses on LV longitudinal strain and presents a value for global longitudinal strain (GLS). GLS has been independently associated with SCD, appropriate ICD therapy, and VA in patients diagnosed with ischemic cardiomyopathy, cardiac systemic sclerosis, and in patients who have undergone repair of tetralogy of Fallot. Detection of impaired segmental longitudinal strain in the peri-infarct zone is also independently associated with an increased risk of the need for ICD therapy to treat either VF or VT [8].

The transitional zone between necrotic and healthy tissue may play an important role in the pathophysiology of VAs and SCD. Mixed scar and viable tissue in peri-infarct areas represent a potential substrate for electrical re-entry and lower values of longitudinal strain on STE. Thus, detection of lower levels of longitudinal strain specifically in peri-infarct zones will help to identify subjects at increased risk for VF and VT [8][9]. Overall, reductions in parameters that reflect regional longitudinal myocardial deformation may provide incremental prognostic information beyond that provided by clinical and

conventional echocardiographic risk factors regardless of whether the origins of the cardiomyopathy were ischemic or non-ischemic [10][11].

2.3. Mechanical Dispersion

STE can also be used to measure the time to peak of longitudinal strain and a calculation of LV mechanical dispersion (LVMD). Mechanical dispersion reflects the heterogeneity of myocardial contraction as a product of electrical alterations and tissue abnormalities. High levels of LV mechanical dispersion suggest the presence of slow and heterogeneous electrical conduction of the LV myocardium (e.g., secondary to scar tissue). After a myocardial infarction, the combination of LV GLS and LVMD may suggest the need for an ICD, even in patients with an LVEF >35% [12]. Moreover, an LVMD ≥ 75 ms may be an independent predictor of SCD and malignant VAs regardless of an ischemic etiology, even in patients with LVEF > 35% [13]. Measurements of LVMD and LV GLS of hypertrophic segments may prove to be a useful tool to also stratify the risk of SCD among patients diagnosed with hypertrophic cardiomyopathy [14][15] and mitral valve prolapse [16]. Finally, STE can also be used to identify abnormalities of right ventricular (RV) function. Both RV GLS and RVMD are associated with malignant Vas [17][18].

3. Cardiac Magnetic Resonance (CMR)

CMR provides the most complete evaluation of a patient's cardiac status with good temporal and spatial resolution that facilitates the quantitative assessment of chamber size, myocardial wall thicknesses, ventricular function and mass, and segmental function, as well as the identification of anomalous coronary arteries. CMR can be used to diagnose myocarditis, amyloidosis, sarcoidosis, Chagas disease, Fabry disease, LV non-compaction cardiomyopathy (LVNC), hemochromatosis, and arrhythmogenic cardiomyopathy.

Numerous studies have considered the relevance of CMR for the study of arrhythmogenic factors that might predict SCD (Table 1, Figure 1). In particular, techniques including late gadolinium enhancement (LGE), T1 mapping, and T2 mapping, as well as those that evaluate extracellular volume can be used to identify structural changes, storage, infiltration, inflammation, fibrosis, and scarring.

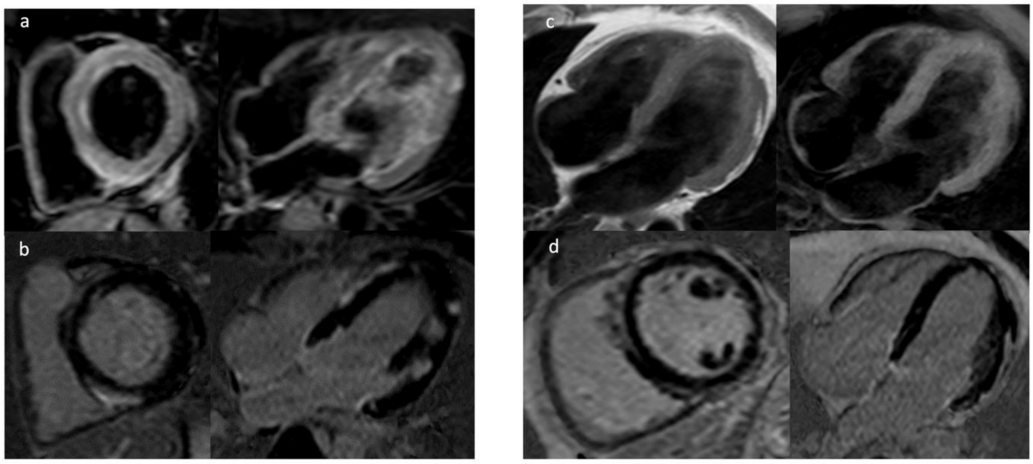

Figure 1. In the left panel T2-STIR (**a**) and PSIR-TFE (**b**) sequences showing increased signal predominantly subepicardial patchy of the left ventricular wall due to necrosis of acute myocarditis. In the right panel sequence T1-TSE and T1-Fat Sat (**c**) showing multiple areas of adipose infiltration with mesocardial and subepicardial distribution of the left ventricle walls, (**d**) extended subepicardial signal hyperintensity in PSIR sequences for the study of "Late Gadolinium Enhancement" indicative of fibrosis for Left Dominant Arrhythmogenic Dysplasia.

Table 1. Imaging parameters associated with an increased risk of malignant arrhythmias.

CMR	Pathophysiologic Background	Clinical Setting	Information
LGE	Fibrosis	ICM, NICM HCM, Myocarditis ARVC, LVNC Mitral valve prolapse	Independent predictor for VA and SCD
T1 and ECV	Tissue edema and diffuse fibrosis	ICM, NICM HCM, Myocarditis	Higher native T1 values associated with VA
T2	Myocardial edema	Myocarditis	Abnormal T2 mapping is involved in predicting major adverse events including cardiac death
LVEF	Left ventricular systolic function	ICM, NICM Myocarditis, ARVC LVNC	LV systolic dysfunction is associated with an increased risk of SCD
RVEF	Right ventricular systolic function	ARVDC	Overall increase in VA in RV dysfunction
Strain Imaging and MD	Myocardial deformation and function	ICM, NICM	Impaired strain associated with SCD

CMR: cardiac magnetic resonance; LGE: late Gadolinium enhancement; ICM: ischemic cardiomyopathy; NICM: non-ischemic cardiomyopathy; HCM: hypertrophic cardiomyopathy; ARVC: arrhythmogenic right ventricular cardiomyopathy; LVNC: left ventricular noncompaction; RVEF: right ventricular ejection fraction.

3.1. Late Gadolinium Enhancement

LGE detected 15 min after collection of contrast-enhanced CMR sequences can be used to identify patients with both ischemic and non-ischemic dilated cardiomyopathy who are at increased risk of developing malignant Vas [19][20][21][22]. The association between LGE and an arrhythmic endpoint was presented in studies in patients with LVEFs < 35% but may also be applicable in patients with a mean LVEF >35% [23]. LGE detected in patients diagnosed with myocarditis suggests an increased risk of SCD regardless of LVEF [24][25][26].

Various LGE features are relevant for arrhythmic risk stratification (e.g., findings documenting its extension, localization, and size of the border zone). While risk is increased under conditions in which LGE exceeds to include more than 5% of LV mass, detection of LGE may be relevant even at lower percentages [27][28]. There are only a few studies that have examined the association of total LGE with arrhythmic risk in patients diagnosed with chronic myocarditis. In these studies, the size of the scar was directly associated with the probability of manifesting VAs [29]. Anterior and septal as well as mid-wall LGE locations have been associated with arrhythmic events in patients with non-ischemic cardiomyopathy [30][31]. The area surrounding the region of LGE, known as the “border zone”, consists of viable and nonviable myocytes separated by scar/fibrotic tissue involved in the development of arrhythmias [32][33]. The characteristics of the border zone can predict the inducibility of VT on electrophysiological studies (EPSs), the need for appropriate ICD therapy, and the likelihood of SCD, all independently of the LVEF [34][35][36][37][38]. LGE could also be useful in patients diagnosed with hypertrophic cardiomyopathy (HCM); replacement fibrosis that is commonly detected in these patients has been associated with an adverse prognosis [39][40].

CMR plays an important role in the differential diagnosis of HCM versus athlete's heart. This modality can be used to measure LV wall thickness and detect LV hypertrophy that was not detected on echocardiography. A diagnosis of athlete's heart can be made in patients who decondition over time in association with regression in cardiac wall thickness >2 mm. By contrast, a diagnosis of HCM is suggested in cases in which the hypertrophy remains unchanged. Likewise, LGE and a focal area of LV hypertrophy that remains unchanged following deconditioning also support a diagnosis of HCM. LV remodeling associated with a diagnosis of athlete's heart typically does not result in focal areas of myocardial scarring, especially in younger individuals. However, although the detection of LGE on contrast-enhanced CMR favors the diagnosis of HCM, the absence of LGE cannot be used to exclude HCM, as this finding has been reported in only half of patients with this clinical diagnosis.

LGE assessments are limited by their semi-quantitative nature and the fact that they can provide only an estimate of irreversible myocardial damage. The methods used to detect and report LGE have not been standardized. Furthermore, LGE may be a dynamic parameter. For example, the expansion of the extracellular volume at early timepoints after cardiac injury leads to an increased volume of gadolinium distribution; as such, this finding reflects not only the fibrosis at this stage but also the interstitium. Finally, CMR is not widely available and impaired renal function is a relative contraindication for the administration of gadolinium-based contrast agents.

3.2. Mapping Techniques and Extracellular Volume

T1 and T2 mapping methods provide a quantitative approach to the assessment of cardiac tissue and reflect the magnetic properties of cardiac muscle based on its composition. T1 values are increased by tissue edema and fibrosis and are reduced by lipid (e.g., Anderson-Fabry disease) and iron overload. T1 mapping also detects diffuse fibrosis associated with both ischemic cardiomyopathy and NICM and has been explored as an independent predictor of sustained VT and the need for appropriate ICD therapy [41]. Unlike LGE, native T1 values are frequently abnormal in diffuse diseases of the myocardium and thus can provide insights into the etiology and pathogenesis of NICM. A T1 map may highlight focal areas of edema such as those accompanying acute myocarditis, acute myocardial infarction, or Takotsubo cardiomyopathy. LGE can be used to evaluate ECV, even if the role of this value in determining the risk of SCD risk remains to be evaluated. Postcontrast T1 mapping techniques combined with measurements of native T1 and hematocrit provide an estimation of the ECV [42]. Myocardial fibrosis identified by ECV measurements may be associated with hospitalization and death secondary to heart failure (HF) [43]. The ECV is also elevated in regions of chronic infarction. The main advantage of T1 mapping over LGE for the stratification of the risk of arrhythmias is the possibility of using this modality to identify diffuse myocardial fibrosis in the setting of NICM [44]. The evaluation of pre-contrast (native) and post-contrast T1 mapping images can identify diffuse myocardial fibrosis that remains undetectable by LGE [45][46].

T2-weighted sequences identify and provide a quantitative assessment of myocardial edema. There are several technical limitations to this method, including its non-standardized assessment. However, initial data suggest that an abnormal T2 mapping can be used to predict major adverse events including SCD and the need for cardiac transplantation and/or implantation of a ventricular assist device.

3.3. Feature Tracking (FT)

FT is a recently developed postprocessing tool that can be applied to CMR to acquire information on strain parameters regardless of contrast agent. One recent study revealed that measurements of LV GLS and RV-global radial strain can be used to predict outcomes in patients diagnosed with ischemic cardiomyopathy with an LVEF > 35%. This information might assist with decision making regarding ICD use in patients with ischemic cardiomyopathy with a mild or moderately reduced EF [47].

3.4. CMR in Mitral Valve Prolapse

Mitral valve prolapse (MVP) is rarely associated with SCD. In addition to the aforementioned echocardiographic parameters, CMR may also elucidate features that reflect an increased risk of malignant arrhythmias. Myocardial fibrosis associated with arrhythmias as detected by LGE [48] is mainly found at the LV posteromedial papillary muscle or the level of the inferobasal wall [49][50]. Subclinical diffuse ventricular fibrosis (which may be a precursor of focal fibrosis in MVP or a different disease in which fibrotic markers undergo up-regulation) may be a marker for early identification of patients at risk of SCD [51]. Disjunction of the mitral annulus (i.e., detachment of the root of the annulus from the ventricular myocardium located at the base of the posterior leaflet) is a pro-arrhythmogenic event [52]. Finally, LGE findings may be used to predict future adverse cardiac events associated with this finding in other clinical settings such as sarcoidosis [53][54][55][56][57].

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