Emerging Role of Multimodality Imaging to Evaluate Patients at Risk for Sudden Cardiac Death

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Accurate identification of patients at high risk for sudden cardiac death (SCD) has been one of the objectives of research in the last years. With an annual incidence between 184 000 and 462 000, SCD is a major public-health problem. The most common cause of SCD is a malignant ventricular arrhythmia and, in the majority of patients with SCD, the underlying anatomic substrate can be identified. Ischemic heart disease, idiopathic dilated cardiomyopathy (DCM), and hypertrophic cardiomyopathy are the most frequent structural heart diseases associated with SCD. Regardless of the underlying structural heart disease, the use of implantable cardioverter defibrillators (ICD) for secondary prevention of SCD is supported by extensive evidence demonstrating the superiority of ICD over antiarrhythmic drug therapy in reducing SCD and all-cause mortality of patients resuscitated from cardiac arrest. Furthermore, in patients with ischemic and nonischemic heart failure, the superior efficacy of ICD over antiarrhythmic therapy for primary prevention of SCD has been demonstrated in multiple randomized controlled trials with >6000 patients included. However, recommendations for ICD implantation for primary prevention in patients with other structural heart diseases such as hypertrophic cardiomyopathy or right ventricular arrhythmogenic dysplasia rely on prospective registries or retrospectively analyzed series and predictive markers of SCD have not been definitively established.

Based on inclusion criteria of multicenter ICD trials for primary prevention, left ventricular ejection fraction (LVEF) ≤35% is one of the major criteria for ICD implantation. However, patients with reduced LVEF constitute a small proportion of the individuals who die suddenly and most of the SCD events occur in patients who do not have symptoms or signs of cardiac disease yet. In addition, in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II), only 35% of patients randomized to the ICD arm received appropriate therapy during 3 years’ follow-up. These observations underscore the limited accuracy of LVEF to identify patients at high risk for SCD. Accordingly, understanding of the underlying mechanisms of SCD is needed to better identify patients with increased risk of life-threatening arrhythmias who may benefit from ICD implantation in clinical practice. Noninvasive multimodality imaging is a valuable tool that provides the most comprehensive information on different pathophysiological mechanisms related to SCD such as myocardial ischemia, myocardial scar, and viability and sympathetic neuronal dysfunction.

Mechanisms of Ventricular Arrhythmia

The pathophysiology of ventricular arrhythmias is complex and involves the anatomic and functional substrate, transient factors altering the electrophysiological stability of the substrate and proximate mechanisms of arrhythmia. In patients with structural heart disease (ischemic heart disease, dilated, and hypertrophic cardiomyopathy), reentry is the most frequent mechanism of ventricular tachycardia/fibrillation (VT/VF). A central area of conduction block (functional or fixed), an unidirectional conduction block and a zone of slow conduction, allowing the impulse to re-excite the tissue proximal to the line of unidirectional block, are prerequisites for reentry to occur and all require certain spatial heterogeneity of the tissue. In infarcted areas (and their border zones) inexcitable scar tissue is the most common cause of fixed conduction block. Furthermore, the interposition of bundles of scar/fibrous tissue within layers of viable myocytes enhances the degree of nonuniform anisotropy, favors electric uncoupling, and creates areas of unidirectional conduction block and slow conduction. In addition, cellular hypertrophy and changes in the density and distribution of gap junction channels impact strongly on cellular coupling contributing to abnormal conduction and favoring reentrant and focal arrhythmias. Current noninvasive imaging modalities, such as MRI and nuclear imaging provide important information on extent and location of myocardial fibrosis. However, the role of noninvasive imaging modalities to evaluate the relative contribution of other molecular and cellular determinants of abnormal conduction remains unexplored.

In addition, transient factors that influence the arrhythmogenic substrate may increase the electric heterogeneity. Myocardial ischemia may enhance regional electric heterogeneity of the myocardium by prolongation of the action potential duration, alteration of calcium handling and myocyte membrane properties, reduced cellular coupling, and redistribution of connexines. Furthermore, the association between altered sympathetic innervation and arrhythmia susceptibility is well established. In pathological conditions such as heart failure...
or long QT syndrome, sympathetic stimulation enhances dispersion of repolarization or induces after-depolarizations contributing to arrhythmogenesis. Also, in ischemic cardiomyopathy, the extent of denervated ventricular myocardium is strongly related to increased arrhythmogenicity.

In the last years, noninvasive imaging has provided important insight into the identification of patients at risk of SCD by characterizing the arrhythmogenic substrate and its interaction with different transient factors that modulate mechanisms of arrhythmia.

**Risk of SCD in the Various Cardiomyopathies: Role of Multimodality Imaging**

**Coronary Artery Disease and Ischemic Heart Failure**

Ischemic heart disease is the anatomic substrate in 80% of SCD events. The presence of scar tissue interspersed with bundles of viable myocardium forms the anatomic substrate for reentrant VT, the most frequent arrhythmogenic mechanism in patients with chronic heart disease. The reentrant wavefront originates from areas of viable myocardium surrounded by fibrous tissue and circulates around scar tissue that forms functional or anatomically fixed conduction block areas. These reentrant circuits have been characterized with 3-dimensional catheter-based voltage mapping techniques (Figure 1). However, these invasive imaging modalities do not take into account other transient factors such as ischemia or activation of the sympathetic nervous system that may influence the anatomic substrate and increase the susceptibility for VT/VF. Noninvasive imaging permits accurate risk stratification of patients with ischemic heart disease, providing a comprehensive assessment of the anatomic substrate (scar tissue and viable myocardium) and transient factors (myocardial ischemia and sympathetic dysfunction).

**Myocardial Scar**

The extent of myocardial scar is an independent predictor of ventricular arrhythmias. Radionuclide techniques (single photon emission computed tomography [SPECT] and positron emission tomography [PET]), and contrast-enhanced MRI are the preferred imaging modalities to assess the extent of scar formation.

With thallium-201 ($^{201}$Tl) or technetium-99m ($^{99m}$Tc) sestamibi/tetrofosmin SPECT imaging, myocardial scar is visualized as fixed perfusion defects (Figure 2). One of the first studies evaluating the association between myocardial scar and cardiovascular mortality included 1926 patients who underwent $^{201}$TI SPECT imaging and demonstrated that fixed defects were associated with a 21% relative risk of cardiovascular mortality at long-term follow-up. Likewise, in 153 survivors of SCD, the presence of scar tissue on SPECT was independently predictive of arrhythmic death and VT recurrence (hazard ratios of 4.2, 95% CI 1.3–14; P=0.02). Similarly, myocardial scar tissue is visualized as fixed perfusion defects on PET using oxygen-15 [$^{15}$O] labeled water, ammonia labeled with nitrogen-13 [$^{13}$N] and rubidium-82 [$^{82}$Rb]. Recent work involving 1432 patients undergoing $^{82}$Rb PET, revealed that the amount of myocardial scar was strongly associated with incidence of cardiac death.

Delayed contrast-enhanced MRI has the highest spatial resolution for assessment of scar tissue and has further increased the understanding of the pathophysiology of SCD in patients with ischemic heart disease. T1-weighted MRI sequences acquired 10 minutes after intravenous contrast administration permit detection of scar areas as small as 0.16 g. Compared with normal myocardium, the infarct areas have an increased extracellular matrix where the contrast agent is trapped. Using “inversion time scout” or “look locker” sequences, the time inversion is selected to null myocardial signal permitting differentiation between normal myocardial tissue and scar, which appears as hyperenhanced, white areas (Figure 2). The extent and characteristics of scar tissue on contrast-enhanced MRI have been related to increased risk of cardiac death and ventricular arrhythmias. Initial reports demonstrated the superiority of myocardial scar burden on contrast-enhanced MRI over LVEF.
for prediction of ventricular arrhythmias. Furthermore, defining different signal intensity thresholds on contrast-enhanced MRI data permits differentiation and quantification of the core infarct zone and the peri-infarct or border zone (bundles of viable myocardium intermingling with fibrous tissue). The extent of the peri-infarct zone emerged as a powerful predictor of cardiac death and ventricular arrhythmias. In 144 patients with prior myocardial infarction, the hazard ratios for all-cause and cardiovascular mortality were 1.42 (95% CI, 1.11–1.81; \(P=0.005\)) and 1.49 (95% CI, 1.09–2.03; \(P=0.014\)), respectively per each 10% increment in extent of the peri-infarct zone. Subsequently, Roes et al demonstrated that the extent of the peri-infarct zone was the only independent predictor of appropriate ICD therapies or cardiac mortality. These observations underscore the need for detailed characterization of the anatomic substrate to predict ventricular arrhythmias. Particularly, diffusion spectrum MRI tractography is a promising technique that displays the 3-dimensional myocardial fiber architecture and detects the presence of a mesh-like network of orthogonally-oriented residual myofibers within the infarct area that may increase the risk of reentrant VT (Figure 3). Other noninvasive imaging modalities have further enabled tissue and functional characterization of the peri-infarct zone and infarct core. Recent studies have demonstrated the feasibility of contrast-enhanced multidetector row computed tomography (MDCT) for tissue characterization. In addition, the functional properties of the peri-infarct zone have been evaluated with tagged-MRI and 2-dimensional speckle tracking echocardiography. In 424 patients with ischemic cardiomyopathy referred for ICD implantation to prevent SCD, the presence of impaired segmental longitudinal strain in the peri-infarct zone was independently associated with an increased risk of appropriate ICD therapy for VT/VF (hazard ratio, 1.22; 95% CI, 1.09–1.36, \(P<0.001\)).

**Figure 2.** Assessment of myocardial tissue heterogeneity in ischemic heart failure patients at risk for SCD. Multimodality imaging for evaluation of a 63-year old man with prior anterior myocardial infarction and LVEF 33% who was referred for ICD implantation for primary prevention. Coronary angiography did not demonstrate significant new coronary stenosis compared with prior angiography. With 2-dimensional speckle tracking echocardiography, regional longitudinal strain could identify the transmural infarct area in the anterior apical region (with a value of longitudinal strain >−5%), the peri-infarct zone (regions surrounding the transmural area) and the remote zone. In addition, myocardial perfusion imaging with \(^{99m}\)Tc-tetrofosmin SPECT showed in the corresponding short-axis (top), vertical long-axis (middle) and horizontal long-axis (bottom) a fixed defect in the apical segments and mid anterior wall indicating scar formation. There were no reversible perfusion defects excluding myocardial ischemia. Finally, late gadolinium enhanced MRI (LGE-MRI) confirmed a transmural infarction in the anteroseptal region with nontransmural scar in the interventricular septum.

**Figure 3.** Novel MRI techniques for tissue characterization. Diffusion spectrum MRI tractography displays the 3-dimensional myocardial fiber architecture and permits visualization of the microstructural changes that take place after myocardial infarction. Panel A shows an example of structurally normal heart. In contrast, panel B shows the formation of a mesh-like network of orthogonally-oriented residual myofibers within the infarct area. Adapted with permission from Sosnovik et al.
Myocardial Ischemia and Viability

Various studies have shown that myocardial ischemia is an important trigger of VT/VF whereas coronary revascularization reduced SCD risk.[22-37,38] Furthermore, hibernating myocardium has been associated with increased risk of SCD.[39,40] SPECT and PET imaging, stress echocardiography and myocardial perfusion MRI provide further risk stratification of patients with ischemic heart disease by assessing these transient factors (ischemia and viability) that may influence the arrhythmogenic substrate.[21,22,41-43]

SPECT myocardial perfusion imaging using $^{201}$Tl and $^{99m}$Tc as radionuclide tracers provides the largest evidence relating the presence of abnormal myocardial perfusion at peak stress and the increased risk of VT/VF and SCD.[21,22,44,45] Rachamovitch et al demonstrated in 5183 patients who underwent stress/rest dual isotope myocardial perfusion SPECT that the risk of cardiac death was associated with the severity of myocardial perfusion abnormalities at peak stress.[46] These results were recently confirmed by Piccini and coworkers, in a cohort of 6383 patients with known coronary artery disease who underwent SPECT imaging.[21] Increasing summed stress scores were independently associated with increased risk of SCD (hazard ratio, 1.16 per 3-U increase; 95% CI, 1.08–1.25, P<0.0001). Furthermore, SPECT myocardial perfusion imaging has shown to be an effective method of risk stratification in patients with known coronary artery disease but relatively preserved LVEF (>55%).[47] In this group of patients, the extent of stress myocardial perfusion defects was also associated with an increased risk of SCD (hazard ratio, 1.13 per each 3-U increase in the summed stress score; 95% CI, 1.04–1.23). These findings highlight the relevance of evaluation of the arrhythmogenic substrate and transient factors that influence this substrate, both in patients with low and preserved LVEF.

The association between myocardial viability assessed with PET and risk of ventricular arrhythmias has also been explored.[21,41] Hibernating myocardium is commonly assessed in clinical practice with 18-fluorine ($^{18}$F) fluorodeoxyglucose PET imaging combined with perfusion imaging. The so-called flow-metabolism mismatch pattern (myocardial hypoperfusion with enhanced glucose myocardial metabolism) identifies dysfunctional but viable myocardium. In contrast, hypoperfusion combined with reduced glucose metabolism indicates myocardial scar. In a series of 107 ischemic heart failure patients undergoing resting myocardial perfusion and metabolic PET imaging with $^{13}$N-ammonia and $^{18}$F-fluorodeoxyglucose, respectively, the flow-metabolism mismatch pattern was related to an increased risk of cardiac death.[41] Patients with an extent of flow-metabolism mismatch >5% of the left ventricle (LV) showed an estimated annual survival of 50%, significantly lower compared with the group of patients without flow-metabolism mismatch (92%; P=0.007).[41] More important, the study demonstrated that revascularization of patients with flow-metabolism mismatch conveyed a superior long-term outcome compared with patients who were medically treated (annualized survival rate of 88% versus 50%, P=0.003).[41]

Other noninvasive imaging modalities such as stress myocardial perfusion MRI and stress echocardiography have also provided important prognostic information.[33,42] Particularly, integrated myocardial ischemia and scar assessment with vasodilator stress MRI perfusion and contrast-enhanced MRI has demonstrated to be a powerful risk stratification tool. In 254 patients with suspected or known coronary artery disease, the presence of reversible perfusion defect (ischemia) and contrast-enhanced areas (scar) showed >3-fold independent association with cardiac death or acute myocardial infarction.[43] Similarly, the assessment of ischemia and viable myocardium with dobutamine stress echocardiography has shown to accurately predict the occurrence of VT.[21] In 90 patients with known coronary artery disease who received an ICD for primary or secondary prevention, induction of ischemia during stress echocardiography was an independent determinant of death or ICD therapy at follow-up (hazard ratio, 2.1, 95% CI, 1.2–3.5, P<0.001).[42]

Sympathetic Innervation

Cardiac sympathetic innervation imaging has emerged as an important risk stratification tool for patients with ischemic heart failure. Using radiolabeled norepinephrine analogs, the anatomic integrity and function of the sympathetic nerve terminals of the heart can be evaluated with SPECT and PET imaging.[47]

Carbon-11 ($^{11}$C) hydroxyephedrine (HED) is the most widely used PET tracer to quantify the density of sympathetic nerve terminals and its cardiac uptake correlates with norepinephrine tissue concentration.[48] Reduced retention of $^{11}$C-HED on PET images indicates the presence of regional sympathetic denervation (Figure 4). The prognostic value of $^{11}$C-HED PET cardiac innervation imaging was described by Pietilä and coworkers.[49] A total of 46 heart failure patients, including 33 patients with prior myocardial infarction, underwent $^{11}$C-HED PET imaging. During a mean follow-up period of 55 months, 11 cardiac deaths (9 SCD) and 2 heart transplants were recorded. Reduced retention of
\[ ^{11} \text{C-HED} \] was independently associated with cardiac mortality and heart transplant (hazard ratio, 19.3, 95% CI, 2.6–142; \( P=0.014 \)). \(^{25}\) In addition, the presence of denervated myocardial areas with preserved perfusion (perfusion-innervation mismatch) has been associated with an increased susceptibility for ventricular arrhythmias. \(^{50}\) Combining PET myocardial perfusion imaging with \(^{13} \text{N}-\text{ammonia} \) and cardiac innervation PET imaging with \(^{11} \text{C-HED} \) PET in an animal model of myocardial infarction, Sasano et al demonstrated that the extent of perfusion-innervation mismatch was significantly larger in the animals with induced monomorphic VT as compared with the animals without inducible VT (10±4% versus 4±2, \( P=0.02 \)).

PET imaging has a higher temporal and spatial resolution compared with SPECT imaging. However, because of the limited local availability of this imaging tool, cardiac innervation is more frequently assessed with SPECT imaging. The SPECT tracer 123-iodine (\(^{123} \text{I})\)-metaiodobenzylguanidine (MIBG) mimics the uptake, storage and release of norepinephrine in the sympathetic nerve endings. However, \(^{123} \text{I-MIBG} \) is not metabolized and does not interact with postsynaptic receptors allowing visualization of the sympathetic postganglionic presynaptic fibers using both planar and SPECT imaging. From the planar images, global myocardial MIBG uptake can be assessed using the heart-to-mediastinum (H/M) uptake ratio and the washout rate. The AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) trial, including 961 heart failure patients (68% ischemic cardiomyopathy), demonstrated the independent prognostic value of \(^{123} \text{I-MIBG} \) imaging. \(^{51}\) The occurrence of life-threatening arrhythmic events was prospectively related to cardiac sympathetic neuronal integrity quantified as the late H/M uptake ratio on planar MIBG images. The risk of arrhythmic events at follow-up was significantly higher in patients with more impaired cardiac sympathetic innervation, defined by a late H/M ratio <1.6, compared with patients with a late H/M ratio ≥1.6 (10.4% versus 3.5%, \( P<0.001 \)). In addition, using SPECT images, quantification of regional abnormalities on \(^{123} \text{I-MIBG} \) tracer uptake has also been independently related to ventricular arrhythmic events (Figure 5). \(^{52}\) In 116 heart failure patients (74% ischemic heart failure) who received an ICD device for primary or secondary prevention, a late \(^{123} \text{I-MIBG} \) SPECT summed defect score >26 discriminated between patients with and without increased susceptibility for arrhythmic events. The cumulative event rates at 3 years follow-up was significantly higher in patients with a late \(^{123} \text{I-MIBG} \) SPECT summed defect score >26 (52% versus 5%, \( P<0.01 \)) (Figure 5). At multivariate analysis, late \(^{123} \text{I-MIBG} \) SPECT defect score was an independent predictor of arrhythmic events (hazard ratio, 1.13; 95% CI, 1.05–1.21; \( P<0.01 \)) after adjusting for ICD indication (primary/secondary), heart failure etiology and other myocardial perfusion imaging-derived parameters. \(^{52}\)

These experiences demonstrate that noninvasive imaging may play an important role in the risk stratification of patients with chronic ischemic heart disease. An integrated approach evaluating the anatomic substrate and transient factors that may precipitate ventricular arrhythmias (myocardial scar, ischemia and viability and sympathetic innervation) in addition to LVEF may refine risk stratification.

**Idiopathic Dilated Cardiomyopathy**

Idiopathic dilated cardiomyopathy accounts for 10% of SCD in the adult population. \(^{3}\) In addition, up to 30% of deaths in patients with DCM are sudden. \(^{53}\) Pooled analysis from primary and secondary prevention trials including 2110 patients with DCM showed a statistically significant 31% survival benefit for ICD over medical therapy (relative risk 0.69; 95% CI, 0.56–0.86; \( P=0.002 \)). \(^{54}\) Scar-related reentrant VT, bundle branch reentrant VT and focal automaticity VT have been proposed as arrhythmogenic mechanisms in DCM. \(^{55}\) In addition, activation of the sympathetic nervous system and release of catecholamines may increase ventricular arrhythmias directly or by enhancing extracellular hypokalemia. \(^{10,56}\) In the last years, evaluation of arrhythmogenic substrate in DCM has been directed at the detection and characterization of myocardial scar and sympathetic innervation. \(^{25,57–60}\)

Contrast-enhanced MRI has provided important information on the relation between myocardial scar burden, scar location and the risk of ventricular arrhythmias. \(^{57,59,61,62}\) In DCM, scar tissue usually involves the midwall or shows a patchy distribution. In 26 patients with DCM who were referred for an electrophysiological study or ICD implantation, Nazarian et al demonstrated that distribution of myocardial scar assessed with contrast-enhanced MRI was predictive of (inducible) sustained monomorphic VT. \(^{59}\) After adjustment for LVEF, scar
Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is the most frequent cause of SCD in populations younger than 40 years. The risk of SCD is almost 1% annually in patients with hypertrophic cardiomyopathy. Compelling evidence has demonstrated that ICD is an effective life-saving treatment in patients with hypertrophic cardiomyopathy, and ≥1 risk factors. However, the heterogeneity in disease presentation and expression with its relative low prevalence, challenge the identification of hypertrophic cardiomyopathy patients at high risk for SCD. Reentry is the most common mechanism of VT and may be favored by the presence of myocardial disarray, increased fibrosis, and abnormal microvasculature. Furthermore, transient factors such as ischemia or exaggerated response to catecholamines may enhance the electrophysiological instability of the anatomic substrate, increasing the arrhythmogenic susceptibility.

One of the major risk factors for SCD is an LV thickness ≥30 mm as assessed with echocardiography (Figure 6). Ongoing research has been focused on detection of myocardial fibrosis with contrast-enhanced MRI and evaluation of its predictive value for the occurrence of life-threatening arrhythmias. Variable patterns of contrast-enhancement can be observed: transmural and nontransmural contrast-enhancement in focal, multifocal or confluent patterns. The independent association between myocardial fibrosis assessed with contrast-enhanced MRI and the risk of ventricular arrhythmias was demonstrated by Adabag and coworkers in 177 patients with hypertrophic cardiomyopathy. Patients with myocardial fibrosis had 7-fold higher risk of nonsustained VT as compared with patients without myocardial fibrosis (relative risk 7.3; 95% CI, 2.6–20.4; P<0.0001). In multivariate analysis, after adjustment for age and LV thickness, presence of myocardial fibrosis assessed with contrast-enhanced MRI was the only independent predictor of ventricular arrhythmias. In 217 hypertrophic cardiomyopathy patients, O’Halon et al showed a higher 3-year cumulative event rate in patients with myocardial fibrosis versus patients without fibrosis (25% versus 7.4%; hazard ratio, 3.4, P=0.006). The incidence of ventricular arrhythmias was higher in the group of patients with myocardial fibrosis (5.9% versus 1.2%; hazard ratio 4.97, P=0.131). However, this difference was not statistically significant and, therefore, additional evidence may be warranted to establish myocardial fibrosis as a risk marker for SCD in hypertrophic cardiomyopathy.

Myocardial ischemia is another transient factor that may favor ventricular arrhythmias in patients with hypertrophic cardiomyopathy, and has been reported in up to 62% of patients with hypertrophic cardiomyopathy during stress myocardial perfusion imaging using SPECT. In 158 patients with hypertrophic cardiomyopathy, the presence of myocardial ischemia was associated with lower 5- and 10-year cardiovascular survival rates compared with patients without ischemia (88% and 64% versus 99% and 90%, respectively; P=0.02). The presence of myocardial ischemia was an
independent predictor of cardiovascular death (hazard ratio, 1.77; 95% CI, 1.04–3.02; \( P = 0.04 \)).

Finally, an increased myocardial catecholamine concentration may lead to a downregulation of the postsynaptic myocardial \( \beta_2 \)-adrenoreceptor with subsequent development of heart failure and ventricular arrhythmias. Using PET imaging with \( ^{11} \text{C}-\text{CGP}12177 \), Choudhury et al demonstrated a reduced density of myocardial \( \beta_2 \)-adrenoreceptor in patients with hypertrophic cardiomyopathy and preserved LVEF, but the prognostic implications of these findings require additional studies.

**Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy**

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a genetically determined cardiomyopathy characterized by fibrofatty tissue replacement of the right ventricular myocardium. The genetically-determined disruption of desmosomal integrity may lead to detachment of myocytes at the intercalated discs with progressive myocyte degeneration and death and subsequent repair with fibrofatty replacement. During this progressive myocyte degeneration, 4 phases can be identified as 1) a subclinical phase with concealed structural abnormalities and no symptoms; 2) overt right ventricular electric disorder; 3) over right ventricular failure; and 4) biventricular failure. Sustained monomorphic VT with left bundle branch morphology is the most common ventricular arrhythmia. Whereas VF can occur at any phase of the disease, scar-related macro-reentrant VT is more commonly observed at later stages of the disease. The available evidence based on observational studies indicates that ICD is a reasonable therapy for secondary prevention of SCD. Identification of patients with ARVD/C and high risk for life-threatening arrhythmias to warrant ICD for primary prevention is still challenging. Recently, the criteria for diagnosing this cardiomyopathy have been revised and incorporated new evidence to improve the diagnostic sensitivity while maintaining specificity. Two-dimensional and contrast echocardiography remain the imaging techniques of choice. However, contrast-enhanced MRI has emerged as a valuable tool to characterize the right ventricular myocardium. Regional akinesia or dyskinesia or dysynchronous right ventricular contraction along with right ventricular dilatation or impaired systolic function assessed with MRI are major diagnostic criteria. Furthermore, the presence of fibrous replacement of right ventricular myocardium (with or without fatty replacement) on endomyocardial biopsy is another major diagnostic criterion of ARVD/C. Contrast-enhanced MRI has demonstrated to be a valid alternative to endomyocardial biopsy. This fibrous or fibrofatty replacement of the right ventricular myocardium appears as bright,
hyperenhanced areas on contrast-enhanced MRI (Figure 7). Moreover, the relationship between the presence of myocardial fibrosis on contrast-enhanced MRI and the occurrence of ventricular arrhythmias was demonstrated by Tandri et al in 12 patients with ARVD/C. Inducible VT on electrophysiological testing was demonstrated in 6 of 10 patients; all of them showed myocardial fibrosis of the right ventricle on contrast-enhanced MRI. In contrast, only 1 of 4 patients without inducible VT showed hyperenhancement of the right ventricle (P=0.001). Additional studies with larger series are needed to confirm these results.

In addition, the potential role of sympathetic innervation on the genesis of ventricular arrhythmias in this group of patients has been described. Loss of sympathetic neurons, increased synaptic norepinephrine confined in the heart and enhanced myocardial sensitivity to catecholamines have been proposed as underlying mechanisms of ventricular arrhythmias. With the use of 123I-MIBG SPECT, the presence of regionally reduced tracer uptake in the left ventricle was reported in patients with ARVD/C. These areas with reduced 123I-MIBG uptake, which may correspond to denervated areas, were located in the basal postero-septal segments of the left ventricle and correlated with right ventricular outflow tract origin of VT.

Fibrofatty replacement processes that progress from the epicardium toward the subendocardium may affect the sympathetic nerves at an early stage of the disease leading to heterogeneous sympathetic innervation. Furthermore, reduced presynaptic neuronal catecholamine reuptake and reduced postsynaptic β2-adrenoceptor density were demonstrated in 8 patients with ARVD/C using PET imaging and 11C-HED and 11C-CGP12177 as tracers, respectively. This reduced presynaptic reuptake of norepinephrine results in increased local levels of this catecholamine with subsequent downregulation of the postsynaptic β2-adrenoceptor. These findings are relevant given that pharmacological interventions that normalize cardiac sympathetic innervation may reduce the risk of VT and SCD.

Primary Electric Disorders
Noninvasive cardiac imaging has also provided new insights in risk stratification of this heterogeneous group of patients with normal LVEF but electrophysiological myocardial derangement that predisposes to life-threatening arrhythmias. Congenital or acquired long-QT syndrome, Wolff-Parkinson-white syndrome, Brugada’s syndrome are included in this group. Particularly, congenital long-QT syndrome is caused by
inherited channelopathies that lead to prolongation of action potential duration and repolarization, increasing the risk of early afterdepolarizations and polymorphic VT. Transmural differences in the action potential duration may increase the arrhythmogenic susceptibility. These subtle electric derangements may cause mechanical dysfunction. Particularly, 2-dimensional speckle tracking echocardiography has unraveled inhomogeneous myocardial contraction within the left ventricle in patients with long-QT syndrome. This novel echocardiographic technique permits angle-independent assessment of myocardial deformation in 3 orthogonal directions (longitudinal, radial, and circumferential). In 101 genotyped long-QT mutation carriers, including 48 symptomatic patients with documented ventricular arrhythmias, longitudinal and circumferential LV myocardial strain was measured with 2-dimensional speckle tracking echocardiography. Longitudinal strain represents the mechanical function of the subendocardial myofibers whereas circumferential strain represents the function of the midmyocardium. Indices of mechanical dispersion, calculated as differences in time to regional peak strain, were measured in the subendocardium and midmyocardium (Figure 8). Symptomatic long-QT syndrome mutation carriers showed longer QTc (495±50 ms versus 460±30 ms, P<0.001) and more pronounced QTc dispersion (56±23 ms versus 48±17 ms, P=0.04) as compared with asymptomatic carriers. Interestingly, subendocardial (longitudinal) and midmyocardial (circumferential) mechanical dispersions were significantly larger in symptomatic carriers as compared with asymptomatic carriers (45±13 ms versus 27±12 ms and 46±22 ms versus 26±21 ms, respectively; P<0.001 for both). Therefore, in primary electrical disorders, assessment of LV mechanics with novel echocardiographic techniques may be important tools to risk stratify these patients.

Conclusions
The limited value of LVEF to identify patients with high risk for SCD who may benefit from ICD implantation has promoted research to characterize and visualize the arrhythmogenic substrate and its interaction with transient factors that modulate basic arrhythmia mechanisms. Noninvasive measurements of temporal and spatial heterogeneity of dispersion of ventricular repolarization with microvolt T-wave alternans have shown high negative predictive value (97%) but low positive predictive value (19%) for arrhythmic events. Signal-averaged ECG used to detect late potentials has been also associated with the occurrence of ventricular arrhythmias in postmyocardial infarction and DCM patients. However, several limitations such as a relatively high percentage of inconclusive tests (20%–40%) and low positive predictive value hamper the integration of these techniques in clinical practice.

Noninvasive imaging has permitted to directly visualize the arrhythmogenic substrate and evaluate the transient factors that may increase the arrhythmic susceptibility. Accurate visualization of myocardial scar or fibrosis with contrast-enhanced MRI, identification of ischemic and viable myocardium with echocardiography, MRI or radionuclide imaging and evaluation of cardiac sympathetic innervation with PET and SPECT imaging may provide a comprehensive assessment of the arrhythmogenic substrate and the factors that enhance the risk of life-threatening arrhythmias. A potential strategy to optimize identification of patients who may benefit from ICD implantation could be integration of advanced ECG testing and noninvasive imaging. In a small series of 63 patients with unexplained cardiac arrest and no evidence of cardiac disease, serial testing (MRI, signal-averaged ECG, exercise testing, drug challenge, and selective electrophysiological testing) could identify the underlying cause of cardiac arrest in >50%.

In summary, noninvasive imaging has improved the insight in the mechanisms underlying SCD and integration with LVEF and advanced ECG testing would help to further improve identification of patients who may benefit from ICD implantation. The challenge for the future will be to develop accurate models for risk stratification.

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