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Risk stratification for sudden cardiac death in patients with heart failure

Emerging role of imaging parameters

Heart failure with reduced ejection fraction is a common condition associated with a poor prognosis and risk of sudden cardiac death (SCD; □ Fig. 1). Approximately 50% of deaths, especially in mild-to-moderate cases, are sudden.

Ischemic heart disease and idiopathic dilated cardiomyopathy (DCM) are two frequent structural heart diseases associated with heart failure and SCD. Ischemic heart disease is the anatomical substrate in 80% of SCD events. Idiopathic DCM, on the other hand, accounts for 10% of SCD cases in the adult population [1], and up to 30% of deaths in patients with DCM are sudden and likely mediated by arrhythmia [2].

In these patients, multiple randomized controlled trials (with >6000 patients) demonstrated the superiority of implantable cardioverter-defibrillators (ICD) over antiarrhythmic agents for primary prevention of SCD [3].

The only indicator shown to have an association with increased risk of SCD in the setting of ischemic or nonischemic left ventricular (LV) dysfunction is LV ejection fraction (LVEF); [4–7]. Therefore, this parameter has been used as the major criterion for ICD implantation for primary prevention of SCD, often in combination with New York Heart Association (NYHA) class, and is still listed in recent guidelines [8].

However, only 35% of patients randomized to the ICD arm in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) received appropriate therapy during 3 years of follow-up [9].

It was reported that LVEF had limited accuracy in identifying patients at high risk for SCD.

Recent studies have evaluated novel echocardiographic parameters of myocardial deformation and cardiac magnetic resonance (CMR) with late-gadolinium enhancement (LGE) for risk stratification of patients with ischemic and idiopathic cardiomyopathy. This non-invasive imaging facilitates the characterization of arrhythmogenic substrate explaining the mechanism of ventricular arrhythmia. Moreover, it helps in the assessment of the anatomical substrate (viable myocardium and scar tissue) and transient factors such as myocardial ischemia.

In the present review, we describe the emerging role of these novel imaging parameters in identifying high-risk patients.

Left ventricular ejection fraction as a predictor of increased risk

Although LVEF has some limitations related to reproducibility, geometric assumptions, and experience, current guidelines for SCD risk stratification emphasize the use of this parameter.

The calculation of LVEF can be improved by using contrast echocardiography or a three-dimensional (3D) approach, but the gold standard for 3D quantification of left ventricular volumes and ejection fraction is CMR [10, 11].

The Marburg Cardiomyopathy Study (MACAS), including 343 patients with

nonischemic heart failure, revealed that the relative risk for major arrhythmic events was 2.28 for every 10% decrease in EF, in patients with sinus rhythm.

International guidelines consider an $EF \leq 35\%$ as a criterion for ICD implantation in primary prevention for patients with nonischemic heart failure [12]. However, most patients who suffer SCD have a preserved LVEF, and many patients with poor LVEF do not benefit from ICD prophylaxis.

Data from the Maastricht study confirm these findings and indicate that, among patients for whom EF was measured before an episode of SCD, 52% had an $EF > 30\%$ and 32% had an $EF > 40\%$ [13].

The use of the criterion of $LVEF < 35\%$ alone has limited power in predicting SCD in patients with nonischemic heart failure. In the DEFINITE trial, the use of low LVEF alone as an indicator for ICD placement was associated with both a low event rate of SCD in the control and treatment groups and a significant number of inappropriate ICD shocks (49 inappropriate versus 91 appropriate ICD shocks) in the treatment group [14].

Recently, results from the DANISH Study [15] suggest that for many patients with DCM, ICDs do not increase longevity.

It is clear from these data that there is a need for a better assessment of arrhythmic risk using other parameters for improved characterization and selection of patients for ICD implantation [16].

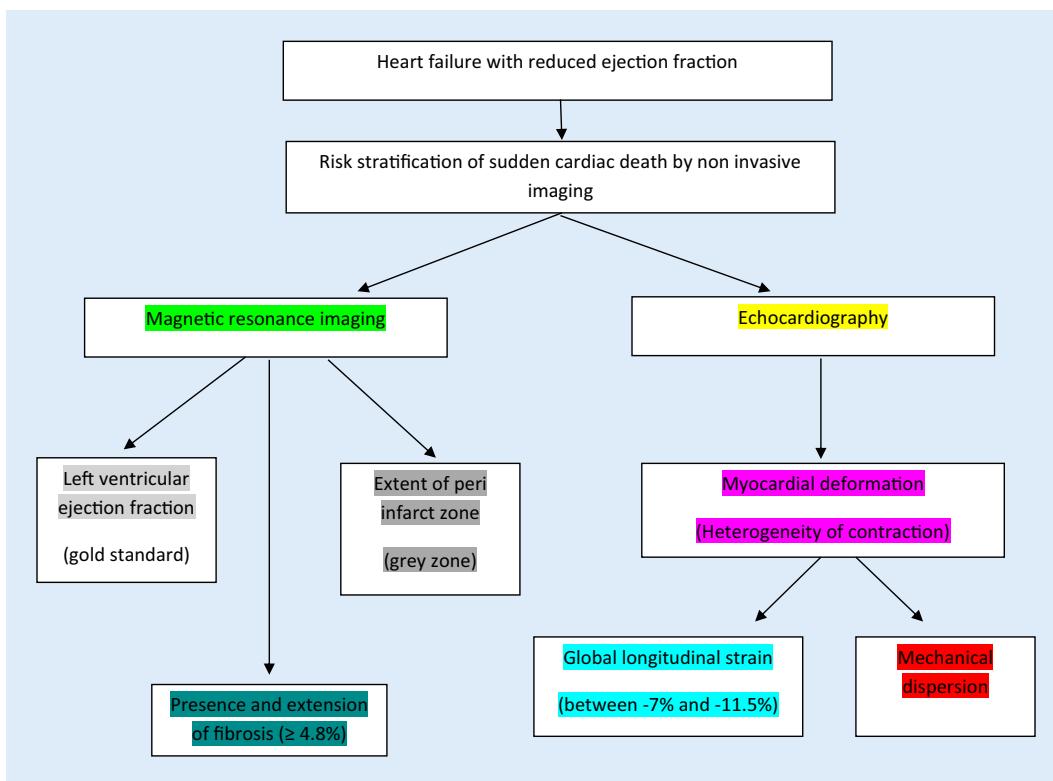


Fig. 1 ▲ Risk stratification for sudden cardiac death in cases of heart failure with reduced ejection fraction

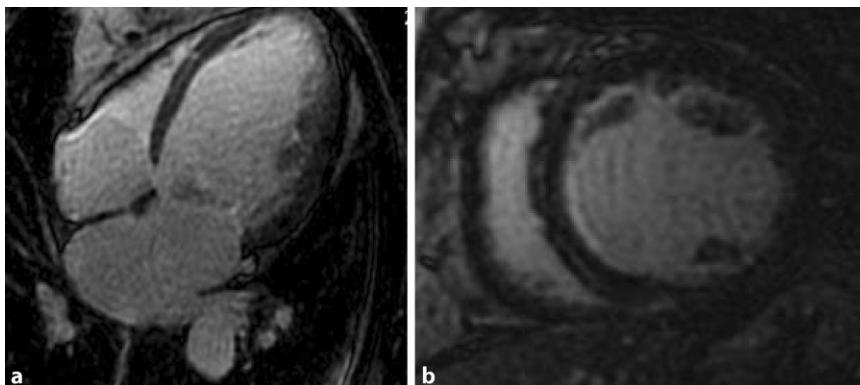


Fig. 2 ▲ Magnetic resonance imaging: four-chamber (a) and short-axis (b) views in a patient with dilated cardiomyopathy and a midwall area of fibrosis in the interventricular septum

Mechanisms of ventricular arrhythmia

The pathophysiology of ventricular arrhythmias is complex and involves the anatomical and functional substrate as well as transient factors altering the electrophysiology of the substrate.

In patients with structural heart disease such as ischemic cardiomyopathy (ICM) or DCM, re-entry is the most frequent mechanism of severe ventricular arrhythmia.

A central area of conduction block (functional or fixed), a unidirectional conduction block, and a zone of slow conduction are substrates for re-entry. In infarcted areas, scar tissue is the most common cause of fixed conduction block. Furthermore, the interposition of bundles of fibrous tissue within layers of viable myocytes is a model of spatial heterogeneity and creates electrical dispersion and areas of unidirectional conduction block and slow conduction.

Myocardial scar is less common in DCM, bundle branch re-entrant ventric-

ular tachycardia and focal automaticity ventricular tachycardia have been proposed as other arrhythmogenic mechanisms in DCM.

Noninvasive imaging and risk stratification

Role of magnetic resonance imaging

Cardiac magnetic resonance imaging has developed into a powerful tool that allows for a comprehensive cardiac assessment of left ventricular structure, function, perfusion, and tissue characteristics, including the presence or absence of fibrosis [17].

Contrast-enhanced MRI is the preferred imaging modality for evaluating the extent of scar after myocardial infarction, which is known to be an independent predictor of ventricular arrhythmias [18]. Contrast-enhanced MRI can detect scar areas as small as 0.16 g. The contrast agent is trapped in the extracellular matrix, which is increased in the infarct areas, and the scar appears as hyperenhanced, white areas. The extent and characteristics of the scar area on con-

Abstract · Zusammenfassung

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Risk stratification for sudden cardiac death in patients with heart failure. Emerging role of imaging parameters

Abstract

Background. Heart failure with reduced ejection fraction is a common condition that has a poor prognosis. Accurate selection of patients with ischemic heart disease and idiopathic dilated cardiomyopathy, who are at risk of sudden cardiac death (SCD), remains a challenge. In these cases, current indications for implantable cardioverter-defibrillators (ICD) rely almost entirely on left ventricular ejection fraction. However, this parameter is insufficient. Recently, noninvasive imaging has provided insight into the mechanism underlying SCD using myocardial deformation on echocardiography and magnetic resonance

imaging. The aim of this review article was to underline the emerging role of these novel parameters in identifying high-risk patients.

Methods. A literature search was carried out for reports published with the following terms: "sudden cardiac death," "heart failure," "noninvasive imaging," "echocardiography," "deformation," "magnetic resonance imaging," and "ventricular arrhythmia." The search was restricted to reports published in English.

Results. The findings of this analysis suggest that cardiac magnetic resonance imaging and strain assessment by echocardiography, particularly longitudinal strain, can be

promising techniques for cardiovascular risk stratification in patients with heart failure.

Conclusion. In future, risk stratification of arrhythmia and patient selection for ICD placement may rely on a multiparametric approach using combinations of imaging modalities in addition to left ventricular ejection fraction.

Keywords

Cardiac failure · Sudden cardiac arrest · Echocardiography · Myocardial deformation · Magnetic resonance imaging

Risikostratifizierung für den plötzlichen Herztod bei Patienten mit Herzinsuffizienz. Zunehmende Bedeutung von Bildgebungsparametern

Zusammenfassung

Hintergrund. Die Herzinsuffizienz mit reduzierter Ejektionsfraktion ist eine häufige Erkrankung mit schlechter Prognose. Die genaue Auswahl von Patienten mit koronarer Herzkrankheit und idiopathischer dilatativer Kardiomyopathie, bei denen das Risiko des plötzlichen Herzstodes besteht, bleibt eine Herausforderung. In diesen Fällen basieren die aktuellen Indikationen für implantierbare kardiale Defibrillatoren (ICD) fast vollständig auf der linksventrikulären Ejektionsfraktion. Allerdings ist dieser Parameter unzureichend. In letzter Zeit hat die nichtinvasive Bildgebung anhand der myokardialen Deformation in der Echokardiographie und in der Magnetresonanztomographie (MRT) Einblicke in den Mechanismus eröffnet, der dem plötzlichen

Herztod zugrunde liegt. Ziel der vorliegenden Übersichtsarbeit war es, die aufkommende Bedeutung dieser neuen Parameter für die Erkennung von Hochrisikopatienten hervorzuheben.

Methoden. Dazu wurde eine Literatursuche in Bezug auf Publikationen mit den folgenden Begriffen durchgeführt: „sudden cardiac death“, „heart failure“, „noninvasive imaging“, „echocardiography“, „deformation“, „magnetic resonance imaging“ und „ventricular arrhythmia“. Die Suche war begrenzt auf englischsprachig veröffentlichte Arbeiten.

Ergebnisse. Die Ergebnisse dieser Auswertung weisen darauf hin, dass die kardiale MRT und die Beurteilung des Strains mittels Echokardiographie, insbesondere des longitudinalen

Strains, vielversprechende Ansätze für die kardiovaskuläre Risikostratifizierung bei Patienten mit Herzinsuffizienz sein können.

Schlussfolgerung. In Zukunft könnten die Risikostratifizierung für Arrhythmien und die Patientenauswahl für eine ICD-Implantation auf einem multiparametrischen Ansatz basieren, bei dem Kombinationen von Bildgebungsmodalitäten zusätzlich zur linksventrikulären Ejektionsfraktion verwendet werden.

Schlüsselwörter

Herzversagen · Plötzlicher Herzstillstand · Echokardiographie · Myokardiale Deformation · Magnetresonanzbildgebung

trast-enhanced MRI have been related to increased risk of ventricular arrhythmias and cardiac death [19]. Moreover, the myocardial scar burden on contrast-enhanced MRI was superior to LVEF for prediction of ventricular arrhythmias [20].

In the study by Klem et al., including 137 patients considered for ICD placement, myocardial scar detected by cardiac MRI was an independent predictor of death or appropriate ICD discharge for sustained ventricular tachyarrhythmia. This study included a wider range

of LVEF and showed that in patients with $LVEF > 30\%$, significant scarring ($\geq 5\% LV$) identifies a high-risk group similar in risk to those with $LVEF \leq 30\%$; by contrast, those with $EF \leq 30\%$ and minimal scar ($< 5\%$) had similar risk to those with $EF > 30\%$ [19].

Contrast-enhanced MRI, using different signal intensity thresholds, can differentiate and quantify the core infarct zone and the peri-infarct or border zone (bundles of viable myocardium intermingling with fibrous tissue; [22]).

The infarcted myocardium can be divided into the following zones: core infarct zone; gray or peri-infarct zone; and total infarct = core + peri-infarct zones. The core and peri-infarct areas have been defined as areas with LGE signal intensity (SI) $\geq 3 SD$, and $2 SD \leq SI < 3 SD$, respectively [23, 24].

In the Roes et al. study, the extent of the peri-infarct zone was the only independent predictor of appropriate ICD therapy or cardiac mortality [19].

A recent meta-analysis [25] was performed to identify the predictive accu-

Table 1 Studies of association between myocardial fibrosis assessed via CMR and risk of arrhythmic and nonarrhythmic events in IDC and NIDCM					
Ref	Clinical setting	Number of patients	CMR parameters	End points	Results
Assomull et al. 2006 [26]	NIDCM	101	Midwall fibrosis (LGE)	All-cause death and hospitalization	Independent association with death and hospitalization
Wu et al. 2008 [30]	NIDCM and LVEF ≤ 35%	65	Presence and extent of LGE	Hospitalization for HF, appropriate ICD, cardiac death	Presence of LGE was associated with a greater risk of primary outcome
Iles et al. 2011 [38]	IDCM/NIDCM before ICD implantation	103	Regional fibrosis with LGE	Arrhythmic events and appropriate ICD therapy	LGE was associated with arrhythmic events and appropriate ICD therapy
Lehrke et al. 2011 [39]	NIDCM	184	Presence of LGE	Hospitalization for HF, cardiac death, ICD discharge	Presence of LGE was associated with composite endpoint
Gao et al. 2012 [24]	IDCM/NIDCM	124	Presence and quantification of LGE	Occurrence of appropriate ICD therapy, SCA, SCD	Myocardial scar quantification by LGE-CMR predicts arrhythmic events in patients eligible for ICD
Neilan et al. 2013 [32]	NIDCM	162	Presence and quantification of LGE	Cardiovascular death and appropriate ICD therapy	Presence of LGE was a strong predictor of major cardiac events
Li et al. 2013 [40]	NIDCM	293	Presence and extent of LGE	All-cause mortality	Presence of LGE is an independent predictor of increased all-cause mortality
Gulati et al. 2013 [34]	NIDCM	472	Presence and extent of midwall fibrosis	All-cause mortality	Midwall fibrosis provided independent prognostic information and improved risk stratification beyond LVEF for all-cause mortality and SCD
Müller et al. 2013 [41]	NICM	185	Presence, pattern and extent of LGE	All-cause mortality, heart transplantation, aborted sudden death, sustained VT or hospitalization due to decompensated heart failure	LGE-positive patients had worse prognosis. But, presence of LGE wasn't an independent risk predictor
Disertori et al. 2016 [35]	NICM/ICM	2850	Presence of LGE	SCD, aborted SCD, ventricular tachycardia/fibrillation and ICD therapy	LGE correlated with arrhythmic events (OR = 5.62)
Di Marco et al. 2017 [36]	DCM	2948	Presence of LGE	Sustained ventricular arrhythmia, appropriate ICD therapy, or SCD	LGE associated with the arrhythmic endpoint (OR: 4.3)

CMR cardiac magnetic resonance imaging, DCM dilated cardiomyopathy, HF heart failure, ICD implantable cardioverter-defibrillators, ICM ischemic cardiomyopathy, LGE late-gadolinium enhancement, LVEF left ventricular ejection fraction, NICM nonischemic cardiomyopathy, OR odds ratio, SCA sudden cardiac arrest, SCD sudden cardiac death, VT ventricular tachycardia

racy of LGE-CMR for SCD risk stratification. The extent of LGE on CMR was strongly associated with the occurrence of ventricular arrhythmias in patients with reduced LVEF (relative risk estimated at 4.33 for all, 4.63 for ICM and 3.79 for nonischemic cardiomyopathy). Core scar and the gray zone are predictors of ventricular arrhythmia events with a relative risk of 3.82 (2.19–6.66) and 5.94 (2.82–12.52), respectively.

In DCM, contrast-enhanced MRI has provided important information on the relationship between myocardial scar burden, scar location, and the risk of ventricular arrhythmias [26–28]. Scar tissue usually involves the midwall ( Fig. 2) or shows a patchy distribution.

Nazarian et al. [29] demonstrated that the distribution of myocardial scar assessed with contrast-enhanced MRI

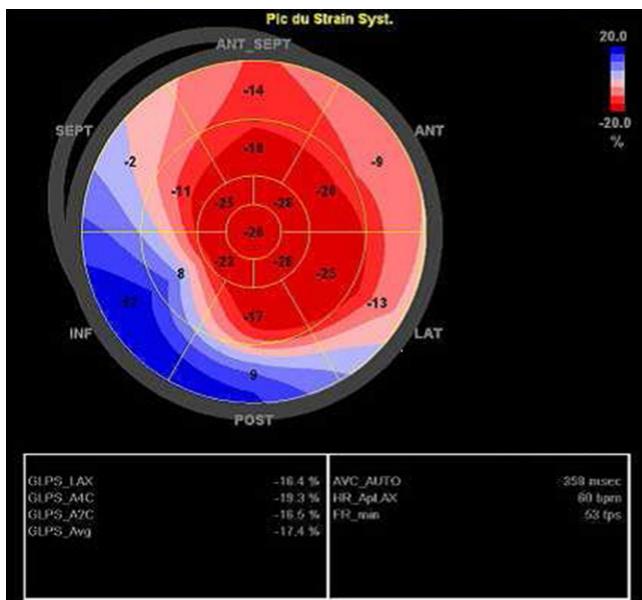
was predictive of inducible sustained monomorphic ventricular tachycardia in 26 patients with DCM. In this study and after adjustment for LVEF, the presence of fibrosis covering 26–75% of the wall thickness was associated with a ninefold increase in the risk of ventricular arrhythmia according to an electrophysiological study.

In the study by Wu et al. [30], SCD or appropriate ICD discharge were detected in 22% of patients with CMR evidence of myocardial scar versus only 8% of patients without evidence of gadolinium enhancement ($p=0.03$). In these patients, fibrosis of the midwall detected by LGE-CMR was associated with adverse cardiac events (hospitalization for heart failure, appropriate ICD firing, and cardiac death; [30, 31]).

Neilan et al. [32] determined the prognostic value of LGE in 162 patients with nonischemic cardiomyopathy, and found that cardiovascular death and appropriate ICD therapy were substantially higher in patients with LGE (24%) than in those without LGE (2%).

The presence and the extent of LGE have the strongest associations with cardiovascular death and appropriate ICD therapy: LGE presence, hazard ratio (HR): 14.5; $p<0.001$; LGE extent, HR: 1.15 per 1% increase in volume of LGE; $p<0.0001$.

However, in multivariate analyses, LGE extent was the strongest predictor of cardiovascular death and appropriate ICD therapy (a sevenfold hazard per 10% LGE extent after adjusting for patient age, sex, and LVEF; adjusted HR: 7.61; $p<0.0001$).



Role of myocardial deformation on echocardiography

Speckle-tracking imaging is a relatively new approach for assessing myocardial deformation by detecting features on grayscale 2D images.

The assessment of LV global longitudinal strain with 2D speckle-tracking echocardiography has been shown to be an accurate marker of LV function. This technique is feasible and reproducible without geometric assumptions, and is independent of LV geometry.

Since global longitudinal strain measures pure longitudinal function, and it may provide other information than EF, which is strongly influenced by the radial motion of the myocardium [44]. Global longitudinal strain has been reported to provide superior prognostic information in the setting of ischemic heart disease [44, 45].

The Bertini et al. study was a larger one including a homogeneous population with chronic ischemic heart disease (1060 patients). In this study, global longitudinal strain was independently related to all-cause mortality (HR per 5% increase, 1.69; 95% CI, 1.33–2.15; $p < 0.001$) and combined end point (all-cause mortality and heart failure hospitalization; 1.64; 95% CI, 1.32–2.04; $p < 0.001$) and patients with an LV global longitudinal strain value of $\leq -11.5\%$ had better outcome than those with LV global longitudinal strain $> -11.5\%$ [46].

Iacoviello et al. [47] studied a group of heart failure patients affected by ischemic or nonischemic DCM without a history of sustained ventricular arrhythmias. During a follow-up of 26 ± 13 months, 31 of 230 patients experienced ventricular tachycardia/fibrillation or SCD.

At multivariate analysis, global longitudinal strain remained significantly associated with ventricular arrhythmic events. The best global longitudinal strain cut-off value for the 1-year occurrence of major ventricular arrhythmias was -10.0% (73% sensitivity and 61% specificity).

Longitudinal strain also adds incremental prognostic value to EF alone for the prediction of adverse outcomes in both ischemic and nonischemic car-

diomyopathy [48]. This finding was also noted in a multicenter study that included 147 patients with heart failure with an LVEF $\leq 45\%$ (ischemic in 42.8%).

Among prognostic factors obtained by echocardiography, global longitudinal strain was the best predictor of cardiac events, and a cut-off value of -7% predicted cardiac events at 12 months with high sensitivity and specificity [49].

In the study of Motoki et al. [50], which included 194 patients with chronic systolic heart failure, global longitudinal strain was an independent prognostic factor for cardiac events in heart failure regardless of age, LVEF, ischemic etiology and E/e', and it had greater prognostic power than LVEF.

In ischemic cardiomyopathy, the functional properties of the peri-infarct zone have been evaluated with 2D speckle-tracking echocardiography (Fig. 3).

Usually, the infarct zone had the most impaired longitudinal strain, whereas the peri-infarct zones had more preserved longitudinal strain.

In 424 patients with ischemic cardiomyopathy considered for ICD implantation, the presence of impaired segmental longitudinal strain in the peri-infarct zone was independently associated with an increased risk of appropriate ICD therapy for ventricular tachycardia and fibrillation [51].

The relationship between the longitudinal peak systolic strain of the peri-infarct zone detected with speckle-tracking echocardiography and monomorphic ventricular tachycardia inducibility in patients with chronic ischemic cardiomyopathy was explored. Only longitudinal peak systolic strain of the peri-infarct zone was independently related to monomorphic ventricular tachycardia inducibility [52].

Mechanical dispersion, another strain parameter that reflects contraction heterogeneity, was recently used in a prospective, multicenter study of patients after myocardial infarction. This parameter predicted arrhythmic events independently of LVEF. A combination of mechanical dispersion and global longitudinal strain may improve the selection of patients after myocardial

infarction for ICD therapy, particularly when LVEF is $> 35\%$ [53].

Conclusion

- This review detailed the emerging role of the novel imaging parameters in identifying high risk patients with ischemic or nonischemic dilated cardiomyopathy.
- Cardiac magnetic resonance imaging can be a useful technique for the risk stratification of these patients but there is a need for a homogeneous definition for both the presence and extent of late-gadolinium enhancement to improve reproducibility and to standardize the technique.
- Strain assessment by echocardiography, particularly longitudinal strain, can also be used for cardiovascular risk stratification in patients with heart failure with greater accuracy than left ventricular ejection fraction (LVEF), but the cut-off values must be better defined.
- Future risk stratification for arrhythmia and patient selection for implantable cardioverter-defibrillator placement may rely on a multiparametric approach using combinations of imaging modalities that may complement primary reliance on LVEF.

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Declarations

Conflict of interest. I. Kammoun, E. Bennour, L. Laroussi, M. Miled, A. Sghaier, K. Rahma, B. Amine, S. Marrakchi and S. Kachboua declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

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Plötzlicher Herzstillstand bei Sportler*innen

In Deutschland erleiden Jahr für Jahr etwa 65.000 Personen einen plötzlichen Herzstillstand. Für etwa 60.000 Menschen verläuft dieses schwerwiegende kardiale Ereignis tödlich. Ein plötzlicher Herzstillstand bei jungen populären Profisportler*innen mitten auf dem Spielfeld sorgt für große Bestürzung in der Öffentlichkeit und eine hohe mediale Aufmerksamkeit. Tatsächlich sind diese Fälle aber eher eine Ausnahmeerscheinung. Denn es sind fast ausschließlich ambitionierte Hobbysportler*innen, die von einem plötzlichen Herzstillstand beim Sport betroffen sind, so die Zahlen des „Sudden Cardiac Death Registers“ (www.scd-deutschland.de). Ein erhöhtes Risiko konnte vor allem beim Fußballspielen und Laufen beobachtet werden.

Rasches Handeln rettet Leben

Ein plötzlicher Herzstillstand ist meist die Folge eines anhaltenden Kammerflimmerns, ein Zustand, bei dem sich die Herzkammern aufgrund ungeordneter elektrischer Erregungen immer wieder sehr schnell und unkoordiniert zusammenziehen und wieder lösen. Dadurch wird kein Blut mehr durch den Kreislauf gepumpt und die Betroffenen verlieren plötzlich das Bewusstsein. Bei fehlendem Puls ist eine schnelle Reanimation lebenswichtig. Denn jede Minute, in der ein Patient nach einem plötzlichen Herzstillstand nicht mittels Herzdruckmassage behandelt wird, sinkt die Überlebenswahrscheinlichkeit um 10 %.

So betont Professor Philipp Sommer, Sprecher der DGK-Arbeitsgruppe Elektrophysiologie und Rhythmologie: „Entscheidend für die Prognose des Patienten ist die sofortige Einleitung der Reanimationsmaßnahmen durch Kompression des Brustkorbs. Diese kann und soll auch unbedingt von anwesenden Laien durchgeführt werden. Nur diese Maßnahme entscheidet häufig darüber, ob und wie der Patient ein derartiges Ereignis überlebt. Alles ist besser als nichts zu tun. Als medizinischer Laie können Sie auch nie für eine suboptimale Durchführung belangt werden – also Hand auf's Herz!“

Herzerkrankungen bei jungen Menschen oft unerkannt

Die im SCD-Register dokumentierten Fälle zeigen deutlich, dass auch junge, vermeintlich gesunde Menschen oft unentdeckt unter kardiovaskulären Erkrankungen leiden, die dann zu schwerwiegenden kardialen Ereignissen führen können. Die zugrunde liegenden Erkrankungen sind dabei unterschiedlich. So verzeichnet das Register eine vorzeitige Verkalkung von Herzkranzgefäßen,

Herzmuskelentzündungen und angeborene Fehlverläufe von Herzkranzarterien als häufige Ursachen des plötzlichen Herztones bei Sportlern unter 35 Jahren. Auch virale oder bakterielle Infekte können eine Herzmuskelentzündung verursachen, sodass nicht zu früh nach einer vermeintlich überstandenen Infektion wieder mit dem Sport begonnen werden sollte.

Zur Prävention empfehlen Kardiolog*innen regelmäßige sportkardiologische Untersuchungen für Sportler*innen. So auch DGK-Presse sprecher Professor Michael Böhm: „Die kardiovaskuläre Gefährdung hängt stark vom individuellen Risikoprofil ab. Insbesondere Sportlerinnen und Sportler mit unentdeckten Herzerkrankungen haben ein besonders hohes Risiko, beim Sport einen plötzlichen Herzstillstand zu erleiden. Dieses Risiko kann durch regelmäßige Screenings stark verringert werden.“

Auf Sport verzichten müssen aber auch Sportler*innen mit kardiovaskulären Erkrankungen nicht, so Böhm weiter: „Körperliche Aktivität und auch sportliche Betätigung verringern kardiovaskuläre Ereignisse wie Herzinfarkte und Schlaganfälle über eine Verbesserung des Gesamtrisikos auch bei erkrankten Patienten“. Besonders wichtig für Patient*innen sind dabei regelmäßige kardiologische Untersuchungen und sofortige Vorstellung beim Kardiologen oder in der Notaufnahme, falls Beschwerden auftreten.

Quelle: Deutsche Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e.V., www.dgk.org