ABSTRACT
Heart failure with preserved ejection fraction (HFpEF) is an increasingly recognized disorder. Many clinical trials have failed to demonstrate benefit in patients with HFpEF but have recognized alarming rates of sudden cardiac death (SCD). Genetic testing has become standard in the workup of patients with otherwise unexplained cardiac arrest, but the genetic architecture of HFpEF, and the overlap of a genetic predisposition to HFpEF and arrhythmias, is poorly understood. An understanding of the genetics of HFpEF and related SCD has the potential to redefine and generate novel diagnostic, prognostic, and therapeutic tools. In this review, we examine recent pathophysiological and clinical advancements in our understanding of HFpEF, which reinforce the heterogeneity of the condition. We also discuss data describing SCD events in patients with HFpEF and review the current literature on genetic underpinnings of HFpEF. Mechanisms of arrhythmogenesis which may lead to SCD in this population are also explored. Lastly, we outline several areas of promise for experimentation and clinical trials that have the potential to further advance our understanding of and contribute to improved clinical care of this patient population.

RÉSUMÉ
L’insuffisance cardiaque à fraction d’ejection préservée (ICFEP) est une anomalie de plus en plus reconnue. De nombreux essais cliniques n’ont pas permis de démontrer les avantages chez les patients atteints d’ICFEP, mais ont permis de reconnaître les taux alarmants de mort subite d’origine cardiaque (MSC). Le dépistage génétique est désormais un examen qui fait partie du bilan de santé des patients qui subissent un arrêt cardiaque inexpliqué autrement, mais l’architecture génétique de l’ICFEP et le chevauchement entre la predisposition génétique à l’ICFEP et la predisposition aux arythmies demeurent mal compris. La compréhension de la génétique de l’ICFEP et de la MSC associée a le potentiel de redefinir et de générer de nouveaux outils de diagnostic, de pronostic et de traitement. Dans la présente revue, nous nous sommes penchés sur les récentes avancées physiopathologiques et cliniques dans notre compréhension de l’ICFEP, qui renforcent l’hétérogénéité de cette maladie. Nous nous sommes aussi intéressés aux données qui décrivent les événements de MSC chez les patients atteints d’ICFEP et passons en revue la littérature actuelle sur les fondements génétiques de l’ICFEP. Les mécanismes de l’arythmogénèse qui peuvent mener à la MSC au sein de cette population sont aussi abordés. Enfin, nous présentons plusieurs domaines d’expérimentation prometteurs et les essais cliniques qui ont le potentiel de faire progresser notre compréhension et de contribuer à l’amélioration des soins cliniques au sein de cette population de patients.

Heart failure (HF) is a syndrome characterized by degrees of poor perfusion and congestion of systemic and/or pulmonic venous systems. HF typically manifests clinically with signs and symptoms of fluid retention. An important diagnostic tool in the management of HF is echocardiography. Among the various roles of this tool is that it allows for measurement of the left ventricular (LV) ejection fraction (EF). Measurement of EF in patients with HF carries significant implications for clinical
management because it groups patients based on whether they have HF with reduced EF (HFrEF), HF with mildly reduced EF, or HF with preserved EF (HFpEF). This review focuses on HFpEF, commonly defined as HF with an EF $\geq$ 50%. Recent reviews of HFrEF and HF with mildly reduced EF can be found elsewhere.5,6

HFpEF is characterized by signs and symptoms of HF with evidence of preserved EF and impaired cardiac filling.7 Historically, rates of sudden cardiac death (SCD) and other cardiovascular (CV)-related deaths have been grossly similar between patients with HFpEF and those with HFrEF (Table 1). However, SCD rates have been increasing in the HFpEF population due to a growing understanding of the condition and advances in its care over time.9,10 This decrease stands in stark contrast to rates of SCD in patients with HFrEF. Despite its growing prevalence, the condition continues to be poorly understood, especially the mechanisms of SCD in such cases.10,11

In this review, we summarize and provide an update on the potential pathophysiological mechanisms of HFpEF and explore how these can translate into improvements in clinical care. Moreover, we review detailed epidemiologic data on SCD in patients with HFpEF to define the scope of this problem. We also discuss the emerging role of genetics in both furthering our understanding of SCD in HFpEF and predicting risk. Lastly, we propose areas of future research that have the potential to improve the prediction of and prevention of SCD in patients with HFpEF.

**HFpEF: Pathophysiology, Diagnosis, and Outcomes**

The pathophysiological understanding of HFpEF has evolved significantly since the pivotal reports of patients with congestive HF but normal EF in the 1980s.12-14 Accounts of patients with HFpEF published since these original papers describe a prevailing mechanistic hypothesis of HFpEF as a disorder of diastolic dysfunction, as opposed to the systolic dysfunction seen in HFrEF.15,16 This mechanism was validated through rigorous studies of HFpEF patients, which demonstrated impaired active relaxation and increased chamber stiffness leading to diastolic dysfunction and HF.17 These data established that a key, hallmark feature of HFpEF is a diastolic pressure-volume relationship that is shifted up and to the left, indicating elevated LV pressures and reduced filling during diastole.

Subsequent to these reports, large-scale analyses of patients with HF revealed that it is a heterogenous condition with unique patient characteristics, including older age, higher female preponderance, and a significantly higher rate of comorbidities.18 These findings suggested that HFpEF may be more accurately described as the complex interplay of multiple systemic processes that constrain cardiac function.19,20 With this model, diastolic dysfunction would be one of many pathologic manifestations. These developments led to a hallmark paper involving echocardiography, peripheral arterial tonometry, and gas exchange studies of patients with HFpEF designed to assess cardiac and peripheral vascular function and response to exertional stress.21 This trial provided evidence that despite a finding of diastolic dysfunction, these patients had abnormalities affecting multiple cardiovascular (CV) domains. The overarching pathophysiology is abnormal cardiac and systemic reserve that at early stages is present only with exertion but progresses over time to signs and symptoms even at rest. The abundance of mechanistic studies since this publication have further contributed to a view of HFpEF as being heterogeneous and based on individual patient characteristics (Fig. 1). Unique combinations of distinct mechanisms converge to arrive at deficits in global reserve, with diastolic dysfunction as a key finding.22-25 Not included in this definition of HFpEF are other HF syndromes in which EF is preserved but an underlying mechanism is clear, such as an infiltrative cardiomyopathy or valvular heart disease. An important future research direction is to group patients with HFpEF into subpopulations based on comorbidities such as atrial fibrillation or obesity and investigate differences in outcomes or underlying mechanisms based on subdiagnoses.

Clinical application of the underlying pathophysiology may allow for both improved identification of patients at risk

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**Table 1. Comparison of rates of sudden cardiac death (SCD) among the general population and patients with heart failure with preserved vs reduced ejection fraction (HFpEF and HFrEF, respectively)**

| Registry                    | Rate (SCD) | Sources | Registry                    | Rate (SCD) | Sources | Registry                    | Rate (SCD) | Sources | Registry                      | Rate (SCD) | Sources |
|-----------------------------|------------|---------|-----------------------------|------------|---------|-----------------------------|------------|---------|--------------------------------|------------|---------|
| Minnesota Heart Survey      | 26.0       | 53      | Minnesota Heart Survey      | 10.7       | 53      | Global registry             | 20.0       | 50      |                               |            |         |
| JCARE-CARD Registry         | 23.0       | 53      | JCARE-CARD Registry         | 10.7       | 53      |                               |            |         |                               |            |         |
| Kyoto Congestive Heart Failure Registry | 14.8   | 53      | Kyoto Congestive Heart Failure Registry | 10.2   | 53      |                               |            |         |                               |            |         |

Proportions are relative to all-cause death and represent percentage of total mortality.
and more-accurate diagnosis. Large-scale analyses have identified risk factors and comorbidities common to both HFrEF and HFpEF, such as past myocardial infarction, diabetes, and atrial fibrillation. However, risk factors specific to HFpEF include hypertension, body mass index (BMI), older age, and female sex. A raised index of suspicion from identifying these risk factors requires further diagnostic workup. Assessment of key signs and symptoms of HF should precede key diagnostic investigations, such as echocardiography, measurement of natriuretic peptide levels, and invasive hemodynamic exercise testing. Newly developed clinical decision-making tools can aid with the diagnosis of HFpEF; these include the HFA Pre-test Assessment, Echocardiography & Natriuretic Peptide, Functional Testing, Final Aetiology (HFA-PEFF) and Heavy, Hypertensive, Atrial Fibrillation, Pulmonary Hypertension, Elder, Filling Pressure (H2FPEF) scores. Research to refine and develop new diagnostic tools is rapidly ongoing, and promising areas include new biomarkers with increased testing accuracy and application of machine-learning tools to echocardiographic data sets to increase data quality and yield.

Upon diagnosis, the natural progression of HFpEF involves foreground episodes of exacerbation and improvement, with background deterioration of pump function over time. In sharp contrast to developments in treatments for many other CV diseases, a sparsity of positive findings from trials in HFpEF patients have led to its treatment being mostly symptomatic, with diuretics given to relieve congestion during exacerbations. Subgroup analyses of major trials, such as Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction (PARAGON-HF), which investigated sacubitril-valsartan, and Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT), which investigated spironolactone, have led to these medications being considered for use in patients with specific EF ranges.
The recent Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved) trial, investigating empagliflozin, a sodium-glucose cotransporter 2 inhibitor, showed reductions in the composite primary outcome of CV death or HF hospitalization in patients with HFrEF.40 This finding was consistent whether diabetes was present or absent. The benefit of sodium-glucose cotransporter 2 inhibitor drugs in HFrEF was very recently replicated with dapagliflozin, but whether this class of drugs will become the standard first line of therapy for HFrEF remains to be seen.41 Nevertheless, the lack of currently available treatment options has contributed to morbidity outcomes for patients with HFrEF.42,43 A large systematic review of 8 randomized controlled trials (RCTs) and 24 epidemiologic studies with mode-of-death data showed that roughly 60% of deaths are CV-related.44 This finding is consistent with results of cohort analyses from the TOPCAT and PARAGON-HF trials, which also showed a nearly 60% rate of CV-related death in patients with HFrEF, irrespective of their treatment allocation.45,46

SCD in HFrEF

Epidemiologic studies directly comparing modes of death in patients with HF show that SCD is more common in patients with HFrEF than in those with HFrEF (Table 1).47 However, outcome data of patients with HFrEF show that roughly 60% of deaths are CV-related, and that one of the most common CV-related modes of death is sudden death, comprising 30%-40% of CV-related deaths.44-46 This value differs noticeably among studies, particularly for RCT outcome data of carefully selected patient populations as compared to epidemiologic data based on observational studies.47 RCT outcome data show sudden death comprising ~40% of CV-related deaths, whereas epidemiologic data show averages near 30%. One explanation for this difference is an inconsistency among trial definitions of “sudden death,” which is a broad term that captures several different acute endpoint processes. These include both processes that are non-arrhythmic in nature, such as pulmonary embolism, aortic dissection, and stroke, and processes that are arrhythmic in nature, such as ventricular fibrillation and pulseless ventricular tachycardia. Most recently, sudden death has been categorized as SCD if it meets certain criteria—an effort to standardize definitions and identify patients who may benefit from SCD prevention efforts. A widely accepted definition of SCD is unexpected death within 1 hour of symptom onset or 24 hours from the last symptom-free observation of the deceased, in the absence of a noncardiac cause. The former is classified as a witnessed SCD, the latter as an unwitnessed SCD.48,49

Despite an abundance of detailed data on outcomes in patients with HFrEF, accurate prevalence estimates of SCD, as defined by consensus criteria, in patients with HFrEF are scarce. One major reason for this lack of estimates is that many trials have not provided sufficient detail relating to patients’ modes of death to be able to differentiate SCD from sudden death.44,50 Many studies assume a diagnosis of SCD when details surrounding a sudden death episode are lacking. Doing so, however, may lead to overestimation of the rates of true SCD. This assumption may also capture nonshockable rhythms, such as pulseless electrical activity, that are not amenable to SCD prevention efforts, such as insertion of an implantable cardioverter defibrillator (ICD). Nevertheless, until more trials are completed with detailed data on modes of death, SCDs are believed to comprise a significant portion of the deaths on which sudden death prevalence estimates are based.51,52

Given the high prevalence of SCD, a rapidly growing body of research is aimed at predicting which patients among those with HFrEF are at highest risk of SCD.53-55 A competing risks analysis from the TOPCAT trial revealed that male sex and presence of insulin-dependent diabetes mellitus are independent risk factors for SCD in patients with HFrEF.56 Moreover, a recently developed SCD risk prediction model was found to have a Harrell’s C index of 0.74, indicating fairly high predictive accuracy. This model was based on the 6 variables of age, sex, history of myocardial infarction, history of diabetes mellitus, presence of bundle branch block on the electrocardiogram, and N-terminal pro-brain natriuretic peptide level.57 Another such study used different clinical variables found on history, electrocardiography, and lab studies for SCD risk prediction in HFrEF, and the analysis yielded a Harrell’s C index of 0.71.56 One study evaluated associations between multiple echocardiographic markers and SCD outcomes.57-59 Among the several echocardiographic parameters interrogated, LV global longitudinal strain (GLS) was found to be the most predictive of SCD in patients with HFrEF after multivariate adjustment. Despite these advances, the evidence base for SCD events in patients with HFrEF is still expanding, and trials to test ICD placement in these patients have not yet occurred. SCD has now become a therapeutic target in HFrEF, and progress to uncover actionable mechanisms has become a key goal. Study of the genetics of HFrEF and SCD is a promising path forward.

Genetics of HFrEF and SCD

The genetic architecture of disease is a fundamental concept that has informed investigations into the genetic underpinnings of human disease.58,59 Broadly, diseases can be described as being monogenic or polygenic. A monogenic disease is one in which a single genetic locus has a large effect on disease development. Polygenic diseases are those in which many genetic loci have compounding effect sizes of varying degrees on disease development. Diseases are unlikely to fall strictly into these 2 categories and rather are likely to exist on a spectrum between the 2. Studies to date suggest that although monogenic conditions leading to HF may exist, the syndrome is more consistent with a polygenic basis of disease, especially HFrEF, which has a more heterogeneous pathophysiology than HFrEF.

For these reasons, research into the genetics of HF has focused mostly on the development of polygenic risk scores (PRSs) based on large genome-wide association studies (GWASs). A PRS is a weighted effect size sum of numerous genetic risk variants found to be associated with a disease.60 The score allows for estimation of risk of disease onset or severity. Risk variants are typically identified through large GWASs involving patients and controls and most commonly occur as single-nucleotide polymorphisms (SNPs). SNPs are single-nucleotide changes of genomic DNA, with variable
downstream effects. Potential downstream consequences depend on factors that include location of the SNP and the specific nucleotide change involved.61

Most GWASs of HF so far have approached the disease broadly, without defining patient subgroups with HFrEF and HFrEF based on echocardiographic data (Fig. 2).62-66 This approach was used in a landmark recent GWAS meta-analysis with 47,309 HF cases and 930,014 controls.65 This study found that 12 independent genetic risk variants at 11 genomic loci are associated with HF. All variants shared associations with coronary artery disease, atrial fibrillation, or reduced LV function, suggestive of an overlapping genetic etiology. This analysis was the first published from the Heart Failure Molecular Epidemiology for Therapeutic Targets (HERMES) consortium and was designed to address undifferentiated HF syndrome to maximal statistical power and discover genetic contributions to common pathophysiological mechanisms.67

One limitation with this trial, however, is that all participants are of European ancestry, limiting the generalizability to other populations and clinical practice.

The Global Biobank Meta-analysis Initiative (GBMI) is a recently developed network of 19 biobanks from 4 continents with the goal of conducting high-powered and ancestrally diverse GWAS analyses.68 This resource represents more than 2.1 million individuals, who have provided consent, across 6 different ancestry groups, with genetic data linked to electronic health records. This HF GWAS is the largest diverse such study to date. A preprint of the first analysis by this group identifies 14 putatively novel loci for HF, but these have not been classified as being related to HFrEF vs HFrEF. Moreover, the study shows that 2 of these newly identified loci reached genome-wide significance only when non-European ancestry samples were included in the meta-analysis. This finding underscores the importance of genetic diversity in GWASs, especially when considering generalizability of findings to heterogenous populations. PRS scores developed using both the GBMI cohort and the HERMES cohort were validated and tested on a patient subgroup with HFrEF. The highest-performing PRS score achieved an adjusted odds ratio of 1.487 for HFrEF, with a P value of 8e-13. These findings suggest that large-scale GWASs and calculation of the PRS have the potential to inform stratification of genetic risk for HFrEF development. Similar trials, with patients grouped based on EF, may demonstrate phenotype-specific genetic variants, offering greater insight into the pathophysiology and candidate pathways for therapies.

One such GWAS trial focusing on phenotype-specific forms of HF has very recently been completed. A preprint of this trial of 19,495 HFrEF patients and 19,589 HFrEF patients shows a unique genetic architecture for each phenotype.69 Although 13 genetic loci were found to be associated with HFrEF at genome-wide significance, only 1 locus was found in association with HFrEF. This locus was near the fat mass- and obesity-associated (FTO) gene. FTO has been found to be strongly associated with BMI, and mutations in this gene have been shown to predispose patients to childhood and adult obesity.70 Moreover, these findings are consistent with data from clinical trials of patients with HFrEF showing unique disease phenotypes in patients with higher BMIs.26,71,72 In a study of 266 patients, HFrEF patients with elevated BMIs did not perform as well on invasive

Figure 2. Common genetic variants found in genome-wide association studies of heart failure. Most studies to date have failed to differentiate patients by ejection fraction and so phenotype-specific data on heart failure with preserved ejection fraction and heart failure with reduced ejection fraction are scarce. Reproduced from Lumbers et al.67 under Creative Commons Attribution 4.0 International (CC BY 4.0) license.
hemodynamic exercise testing, compared to controls and patients with HFrEF with normal BMIs. In a more recent trial, computed tomography scans were used to obtain a visceral adipose tissue (VAT) area, which was correlated with invasive hemodynamic exercise testing results. The VAT area was found to be higher in women with HFrEF, with no similar finding in men with or without HFrEF. Increases in VAT area were also correlated with worsening hemodynamic parameters during exercise testing, but only in women with HFrEF. Collectively, the clinical trial data partially validate the findings of these GWASs and suggest a role for obesity in the pathophysiology of HFrEF. Although the downstream mechanisms remain to be fully explicated, these results suggest that GWASs can identify HFrEF-specific disease pathways, which can then be further investigated in clinical trials for development of novel therapeutic or diagnostic approaches.

Results from a recent large-scale meta-analysis of HF GWASs were recently shared in a preprint publication. Analysis of over 90,000 HF and >1,000,000 control cases revealed several genes associated with HF, but unfortunately, with no distinction based on EF subtype. A candidate gene significantly associated with an increased HF risk at an odds ratio of 1.19 was the gene encoding for apolipoprotein C3 (APOC3). Strong evidence shows associations between loss-of-function mutations in APOC3 with altered lipid metabolism and downstream ischemic vascular disease. However, the gene’s role in HF pathophysiology has not been studied extensively. Because of the gene’s involvement in cholesterol metabolism and downstream atherosclerotic disease risk, mutations in APOC3 possibly contribute to HF pathogenesis, through an ischemic mechanism or through changes in adiposity similar to those seen with mutations in FTO. Also, whether APOC3 variants play a similar role in HF pathophysiology across EF gradients is currently unknown. These questions are important for follow-up studies to address.

Similar-scaled investigations into the genetic predisposition of HF patients to SCD are lacking, especially studies focusing on those with HFrEF. Currently, no large-scale GWASs have been published. The most relevant findings come from genetic sequencing studies of patients with SCD who were retrospectively found to have HF on medical chart review. The largest study to date assessed the prevalence of rare genetic variants in 600 SCD cases vs 600 controls in an effort to identify likely pathogenic/pathogenic (LP/P) variants. This study found 14 LP/P variants in 15 patients, 4 of whom (27.7%) had a former diagnosis of HF on medical chart review. Two patients carried likely pathogenic titin (TTN) mutations associated with dilated cardiomyopathy; 1 patient carried a pathogenic low-density lipoprotein receptor (LDLR) mutation associated with familial hypercholesterolemia; and 1 patient carried a likely pathogenic potassium voltage-gated channel subfamily H member 2 (KCNH2) mutation associated with long-QT syndrome (LQTS). No information was provided on the EF of these patients, and so whether they were best characterized as having HFrEF or not is unclear. The authors validated their findings by means of a prospective cohort study. Whole-exome sequencing of 4525 patients found LP/P variants in 41 patients. Over a median follow-up of 14.3 years, CV death occurred in 9.8% of patients (4 of 14) with an LP/P variant, and in 3.6% of patients (161 of 4483) without such a variant. This finding was statistically significant and highlights potential genetic susceptibilities for SCD in those with HF. However, a key shortcoming of these data is the lack of clinical detail on patients with HF, such as EF values and downstream analyses involving HFrEF and HFrEF subgroups. Larger trials with more detailed clinical data on patient characteristics will further identify genetic variants that are most relevant to patients with HFrEF.

Proposed Mechanisms for SCD in HFrEF

Several processes can lead to SCD, such as acute pump failure, ventricular arrhythmias, bradyarrhythmias, asystole, or electrical-mechanical dissociation. Consensus has not yet been reached on the dominant process underlying SCD in HFrEF, or the proportion of patients suffering from any given cause. Although some studies reveal similar rates of ventricular arrhythmias leading to cardiac arrest in patients with HFrEF, vs in those with HFrEF, this finding has not been consistent. More trials in this area will help elucidate the common underlying drivers of SCD in HFrEF. This review is focused specifically on the mechanisms of ventricular arrhythmias, using both basic and clinical literature to date.

Although most cases of HFpEF are the result of myocardial ischemia, the heterogeneous nature of HFpEF suggests involvement of several arrhythmogenic mechanisms that can predispose patients to ventricular arrhythmias and SCD. Broadly, these mechanisms can be categorized as being related to triggered activity and substrate formation. Each mechanism includes genetic and acquired contributors. Although they are posited to be unique entities, most probably the 2 mechanisms have unique interplays, based on patient-specific characteristics.

Evidence of increased triggered activity in HF patients was first documented in cardiomyocytes, mostly from patients with advanced HFrEF. Cells displayed prolonged action potentials that were driven mainly by reduced transient outward (Ito) K⁺ current density and a milder reduction of delayed rectifier (Ikr) current density. Later studies found that reduction of Ito current densities in patients with HF is correlated with mRNA levels of the Kv4.3, which is the major subunit responsible for Ito in humans. This finding suggests that reduction of K⁺ currents in HF is a transcriptionally regulated process and indicative of an initially adaptive response. The prevailing model was that prolonging the action potential was initially adaptive because increased depolarization led to prolonged excitation-contraction coupling and compensated for decreased cardiac output. However, this short-term adaptation becomes pathologic in later HF stages as the prolonged action potential duration allows for early afterdepolarizations, which can serve as triggers for re-entrant circuits and drive ventricular arrhythmias. Although this process was initially studied mainly in HFrEF, this process was subsequently also found in models of HFrEF. Mouse models of HFrEF have replicated these results by showing that delayed repolarization and QTc prolongation due to reduced potassium currents predispose mice to ventricular arrhythmias and SCD. Data have also emerged that are suggestive of altered calcium handling as a mechanism of increased triggered activity in HF. This possibility was based on findings of expression-level changes of the
sodium-calcium exchanger (NaCaX) in HFrEF. However, more recent analyses of isolated myocardium from HFrEF patients have reported conflicting results surrounding this mechanism, and so it is not yet fully established. Establishing a role for the NaCaX in HFrEF pathophysiology is an important goal for follow-up experiments. Lastly, data do suggest bradycardia and asystole as potential mechanisms of SCD in HFrEF patients, especially those with end-stage renal disease requiring dialysis. The specific pathways through which these events occur have yet to be fully determined. However, one hypothesis is that electrolyte imbalances occurring with end-stage renal disease and prolonged repetitive diastasis cycles may reduce the automaticity of the sinus node and predispose patients to bradycardia, asystole, and SCD.

Mechanisms of tissue substrate formation also play a key role in arrhythmogenesis and can contribute to SCD as an outcome in HF. Owing to the significant role of myocardial ischemia and infarction in HFrEF, post-ischemic fibrosis and scarring play a major role in substrate formation. However, arrhythmogenic substrate formation is found to be more multifaceted in HFrEF. First, increased epicardial adipose tissue, related to either lifestyle choices or genetic variants in FTO, is a key pathophysiological process in HFrEF, with associations with poor patient outcomes. One proposal was that, similar to the disease process of arrhythmogenic right ventricular cardiomyopathy, the epicardial adipose tissue can act as a tissue substrate for re-entrant circuit formation to increase the propensity for ventricular arrhythmias that may lead to SCD. Modelling studies show that adipose tissue can be pro-arrhythmogenic through reductions in conduction velocity and distortion of wavefront propagation. Electrophysiological mapping studies of sheep hearts followed by histologic analyses for markers of adipose tissue confirm these findings and show an increase in adiposity at sites of ventricular tachycardia activation. These findings suggest that the increased adiposity seen in HFrEF can serve as tissue substrate for re-entrant circuit formation and ventricular arrhythmogenesis, and predispose patients to SCD.

A better understood mechanism of arrhythmogenic substrate formation in HFrEF is fibrosis. Endomyocardial or intraoperative biopsies from patients with HFrEF have shown increased collagen 1 and 3 levels in association with decreased major collagenases such as matrix metalloproteinase-1. The largest myocardial tissue analysis of patients with HFrEF, studying endomyocardial biopsies from 108 patients, found increased myocardial fibrosis through histologic staining with Masson’s trichome in 93% of patients. Different degrees of fibrosis were found in these patients, and most cases were classified as mild. These fibrotic changes are believed to be inflammatory-mediated, based on concurrent findings of significantly increased staining for CD68+ monocytes, CD3+ T-cells, and CD11+ and CD45+ panleukocytes. These findings correlated with increased staining for pro-fibrotic mediators, such as transforming growth factor-β, tumor necrosis factor-α, tissue inhibitor of metalloproteinase (TIMP) metalloproteinase inhibitor 1, and soluble ST2. Preclinical research shows that improvements in diastolic dysfunction and overall survival can be achieved in rat models of HFrEF through use of cardiosphere-derived cells to decrease fibrosis and inflammation. These findings were more recently validated in prospective clinical trials of patients with HFrEF. By means of cardiac magnetic resonance (CMR) T1 mapping and late gadolinium enhancement (LGE), numerous studies have demonstrated increased extracellular volume in patients with HFrEF, compared to that in controls. LV biopsies allowed for direct correlation of extracellular matrix on histology with CMR T1 contrast times. These studies show a direct association between cardiac fibrosis measured through extracellular volume and clinical outcomes of HF hospitalization and all-cause mortality in patients with HFrEF. A recent systematic review and meta-analysis found value for multi-parametric CMR in prognosticating for patients with HFrEF. Specifically, patients with scar on LGE or T1-mapped fibrosis were estimated to have a worse prognosis. These findings provide support for use of LGE-based quantification of fibrosis in prognosticating for HFrEF patients and identifying patients who would benefit from ICD intervention.

The electrophysiological effects of increased fibrotic tissue have been well characterized. Through distortion of wavefront morphology and conduction velocity, areas of fibrosis are well known tissue substrates for re-entrant circuit formation and arrhythmias. When coupled with increased triggered activity, this situation is ideal for arrhythmia onset and propagation, with potential for progression to SCD. These findings can provide further mechanistic explanation for the reportedly high rates of nonsustained ventricular tachycardia (NSVT) in patients with HFrEF.

Lastly, an analysis of rare genetic variants in patients with SCD found a few patients with a past history of HF carrying LP variants in TTN previously associated with dilated cardiomyopathy. The arrhythmogenic nature of TTN variants is now well known, and although it is mostly associated with early-onset atrial fibrillation, data have shown increased fibrosis in patients with TTN cardiomyopathies associated with increased rates of lethal ventricular arrhythmias. A TTN cardiomyopathy may be one mechanism of HFrEF development, but it may also carry implications for the SCD risk of this specific HFrEF phenotype. Large-scale genetic analyses of HFrEF patients to investigate this hypothesis have not yet been done.

**Future Directions**

Although understanding of SCD as an outcome of HFrEF has improved, definite areas require further study. These areas revolve largely around improving understanding of the genetics of HFrEF and those at highest risk of disease onset and SCD as an outcome, which requires clinical trials in patients with HFrEF to assess SCD prevention efforts, and more basic mechanistic experimentation with HFrEF models with a goal of providing biomarkers or novel candidate drug targets. Most GWASs done to date have focused on all patients with HF and have lacked ancestral diversity. A key future direction should be the performance of GWASs with detailed clinical data to better characterize patients and their disease phenotypes. With the recent GBMI collaboration as an example, an emphasis should be placed on ancestral diversity to accurately reflect the heterogeneity of patient populations and increase the generalizability of findings. Availability of detailed information on HF phenotypes and patient outcomes would allow for development of PRPs for prediction of which patients are at risk of HFrEF onset, progression, and specific outcomes such as SCD.
Recent reports of high NSVT rates in patients with HFpEF present this as a clinical target for SCD risk stratification. These studies include data from interrogations of loop recorders or permanent pacemakers in HFpEF patients. Detailed characterization of these NSVT episodes is lacking, but they have been reported to occur at heart rate ranges of 160-200 beats per minute and at a median longest duration of roughly 4 seconds. Follow-up prospective trials with Holter or longer-term ambulatory monitoring can allow for correlation of NSVT burden with outcomes such as SCD. Moreover, CMR imaging and correlation with NSVT burden and SCD can further strengthen its prognostic yield.

Lastly, in sharp contrast to availability of agents to address many other diseases, only a paucity of disease-modifying agents is available for patients with HFpEF. One reason for this may be an insufficient understanding of HFpEF pathophysiology. To address this, we need patient-specific HFpEF models that can accurately capture the heterogeneous and multifactorial mechanisms involved. Induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) may be one option. Through development of in vitro cardiomyocyte models directly from individual patients, iPSC-CM technology allows for the mechanistic investigation of disease processes unique to an individual’s genetic background. This process may identify new candidate targets for drug therapies. Recently developed iPSC-CM workflows enabling high-throughput studies of drug repurposing and screening can expedite therapeutic development.

**Conclusion**

In summary, the pathophysiology of HFpEF is heterogeneous, but the overarching mechanism is abnormal cardiac and systemic reserve. Outcome studies of patients with HFpEF are showing an increasing rate of SCD as a mode of death, and this is becoming the single most common outcome for patients with HFpEF. GWASs have shed some light on the genetic contributors to HFpEF risk, onset, and progression, but they have not yet described a genetic susceptibility to SCD. With ongoing improvements in clinical characterization and phenotyping, including standardized outcome definitions, comprehensive imaging with echocardiography or magnetic resonance imaging, long-term electrocardiographic monitoring, and determination of ancestry, the potential is greater to define genetic drivers of morbidity and mortality in HFpEF.

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