Review

Unraveling the Complexity: From Molecular Subtypes to Therapeutic Strategies in Heart Failure with Preserved Ejection Fraction and Atrial Fibrillation

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Unraveling the Complexity: From Molecular Subtypes to Therapeutic Strategies in Heart Failure with Preserved Ejection Fraction and Atrial Fibrillation

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Abstract: Embarking on a fascinating exploration, this article takes you through the intricate dance between atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF). Join us on a journey that unravels the mysteries of molecular intricacies, delves into advanced imaging techniques, and sheds light on therapeutic pathways. Unveiling the role of cardiac amyloidosis, particularly sub-clinical isolated cardiac amyloidosis (ICA), the narrative unfolds the heightened risk of AF in the elderly. State-of-the-art imaging techniques like cardiac magnetic resonance (CMR) and molecular imaging step into the spotlight, unraveling diagnostic and prognostic nuances of AF and HFpEF. Embarking on the molecular voyage, the article navigates through next-generation sequencing and comprehensive genomic profiling, shedding light on genetic alterations shaping the AF-HFpEF landscape. This molecular compass lays the groundwork for personalized medicine, illuminating pathways to identify therapeutic bullseyes and biomarkers. In the realm of medical strategies, the discussion homes in on the promising notes struck by SGLT2 inhibitors, particularly dapagliflozin, orchestrating a reduction in AF burden. Characters like spironolactone and dronedarone make appearances, each weaving a distinct tale, revealing their potential roles in steering the ship for AF- HFpEF patients. The subplot involving obesity in HFpEF unfolds, with the LEGACY study portraying the benefits of weight reduction. The pivotal intervention of catheter ablation emerges as the hero, boasting positive outcomes in reducing hospitalization rates and overall mortality for AF-HFpEF patients. However, cautionary tales echo about its impact on left atrial function, adding layers of complexity that beckon careful consideration and monitoring. Amidst the narrative, critical discussions unfold about the limitations of current research, echoing the need to define acute heart failure, refine imaging techniques, and tailor management strategies. The narrative passionately advocates for a personalized touch in addressing AF-HFpEF, recognizing the unique blend of clinical and molecular personas. In essence, this review paints a vivid mural of AF-HFpEF, skillfully bridging the realms of molecular intricacies and the artistry of clinical management.

Keywords: atrial fibrillation; heart failure with preserved ejection fraction (HFpEF); cardiac amyloidosis; molecular imaging; catheter ablation; SGLT2 inhibitors; next- generation sequencing; personalized medicine

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1. Introduction

The coexistence of atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) presents a complex clinical challenge, with significant clinical and economic burdens. The prevalence of AF in HFpEF ranges from 32% to 43% in acute HF patients and is similar in chronic HF patients [1]. AF is associated with an increased risk of all-cause mortality in HFpEF, with a hazard ratio of 1.14 [2]. The intricate connection between AF and HFpEF follows pathways that intertwine through common risk factors and the renin-angiotensin-aldosterone system (RAAS) [3]. A glimmer of hope emerges as RAAS blockers, specifically angiotensin receptor blockers, demonstrate their effectiveness in lessening the impact of HF, cardiovascular events, and the recurrence of AF [4]. Over the past 20 years, we've se- en a striking rise in issues caused by concurrent heart failure and atrial fibrillation. However, amid these obstacles, a ray of light glows as disability ages descend in we- ll-off nations. This hints at a useful tactic to tackle the broad impact of these conditions [5].

Individual orientation in the complex terrain of cardiac disease with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) requires careful consideration, with collaborative cardiac counseling, comprehensive imaging studies , including all- inclusive group counseling. oriented and perspective. This intricate journey often translates into heightened resource utilization, encompassing medications, device therapies, and the necessity for regular follow-ups [6]. Chronic conditions like HFpEF and AF can also impact workforce productivity due to illness, hospitalizations, and ongoing medical care [7]. To alleviate healthcare costs and improve resource allocation, early detection and intervention are crucial. Regular screenings and monitoring can lead to timely intervention and potentially prevent disease progression. Fostering a team approach in healthcare, where cardiologists, primary care physicians, and various healthcare providers collaborate seamlessly, has the potential to enhance the overall coordination of patient care. This collaborative effort not only promises better health outcomes but also aims to minimize hospital stays, ultimately alleviating the financial burden on individuals and the healthcare system [8,9]. ostering an active role in their treatment. By arming individuals with the necessary insights and tools, we not only promote their commitment to treatment plans but also inspire them to embrace positive lifestyle adjustments. This holistic approach contributes to minimizing complications, decreasing hospitalizations, and relieving the financial strain associated with healthcare [10].

Further research is needed to better understand the mechanisms and optimize management strategies for AF and HFpEF.

Embarking on a journey into the world where atrial fibrillation and HFpEF coexist, our aim is to uncover the daily realities and significance of navigating life with both conditions. We'll be your guides through the twists and turns of treating individuals managing this intricate duo, shedding light on the genuine challenges they face. Together, we'll delve into the intricacies that demand our attention, urging a deeper investigation into the mysterious workings beneath the surface. Beyond the clinical scope, we'll explore the personal and financial toll this tandem health challenge takes, pondering how truly understanding this relationship could be the key to brighter health outcomes and wiser use of resources. So, join us on this humanized exploration, as we strive to enrich lives and make sense of the intricate dance between atrial fibrillation and HFpEF.

Navigating the Molecular Landscape: Understanding AF and HFpEF Interplay

In this section, the major goal is to begin an engaging investigation of the multi- faceted molecular signaling pathways which are interwoven in the parallel presence of atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF). Our quest is to follow the course of distinct molecular pathways that shed light into our present understanding of inflammation, oxidative stress, and genetics as major factors shaping how AF and HFpEF progress over time.

Subsection 1: Illuminating the Molecules

Identifying the molecular mechanisms of AF and HFpEF is timeous since it will be an important step towards targeted therapeutic solutions. The accumulated data from several studies have

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provided much of the information regarding these molecular pathways which helps us to better understand the complex cellular processes involved in the development of these heart diseases.

Specific Molecular Pathways:

A number of signaling pathways are implicated in the ontogeny and advancement of the atrial fibrillation (AF) and the heart failure with preserved ejection fraction (HFpEF). Ion channel disorders, altered calcium handling and structural remodeling are key elements in the triggering and perpetuation of atrial arrhythmias in AF [11]. HFpEF has diastolic dysfunction, fibrosis, and impaired relaxation. These impact molecular pathways including the renin-angiotensin-aldosterone system and nitric oxide signaling. [12–14]. Apart from that, RAAS and nitric oxide signaling are also the part of the development and perpetuation of AF [15]. These signaling pathways may interplay with one another, thereby leading to a complicated relationship between HFpEF and AF. The presence of AF in the context of HFpEF worsens the prognosis and the outcome as illustrated by the changes of biomarker levels and the changes of vascular function [16,17]. Understanding these mechanisms and their interactions is important for the development of targeted therapies for HFpEF and AF.

Inflammation as a Contributor:

Inflammation is a dynamic process that appears to be a core mechanism underlying the pathophysiology of both atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF). he pro-inflammatory cytokines, including interleukin-6 and tumor necrosis factor-alpha, associate with atrial and myocardial structural and electrical remodeling [18,19]. The cytokines were reported to increase inflammatory response and oxidative stress which can contribute to fibrosis and progress of the atrial fibrillation (AF) [20]. The inflammation and oxidative stress which coexist in an environment where AF is present and HFpEF is developing [21]. nflammatory atrial

It is not fully understood how HFpEF pathogenesis develops through the activation of pathways involved in diastolic dysfunction and fibrosis. The mechanisms comprehend arterial and small blood vessel dysfunction, chronic low grade inflammation as well as sympathetic nervous system activation cardiomyopathy, which refers to the atrial inflammation and fibrosis, is a prominent cause of AF through arrhythmogenic atrial electrical, structural, and autonomic remodeling [22].

Oxidative Stress in AF and HFpEF:

The imbalance between reactive oxygen species production and antioxidant defenses, called oxidative stress, is pivotal in atrial fibrillation and heart failure cascades. Reactive oxygen accumulation can inflame, fibrose, and damage cells, the primary drivers of structural and functional changes in these diseases [23]. Oxidative stress biomarker level increase and blasting of ROS in multiple cell types, such as cardiac conditions, is supported by studies [24]. Antioxidant supplements have proven effective clinically, demonstrative of the therapeutic use of targeting oxidative stress to manage AF and HFpEF [25]. Despite the exact ways by which Oxidative stress in AF and HFpEF develops being not well understood, NOX4 has been suggested as a possible therapeutic target, because it has been found to play a role in systemic sclerosis and may also have a role in these cardiac conditions [26]. While the role of oxidative stress in atrial fibrillation and preserved ejection fraction heart failure remains unclear, continued research and targeted intervention approaches development stays critical [27].

By studying oxidative stress will give valuable information on the disease-fighting targets that may prevent the progression of the disease.

Genetic Factors:

Advances in sequencing technologies provide genetic data that can help reveal genetic mechanisms underlying atrial fibrillation (AF) and cardiomyopathy with preserved ejection fraction (HFPEF) Genes a combined with morphologic data, analysis of common and rare genetic mutations, comorbidities derived from clinical data . phenotypic -Signs and symptoms may help diagnose AF, HF, and various cardiovascular diseases (CVDs)[28].

Studies have identified several genes associated with AF and HF, including SYNPO2L, TTN, MTSS1, SCN5A, PITX2, KLHL3, and AGAP5, whose AF and HF have expression between them [29]. Furthermore, the use of high-quality association analysis techniques, such as weighted U sequence

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questing (WU-SEQ), can improve the analysis of sequencing data and identify rare variants associated with complex diseases [30,31].

Therefore Genetic data generated by advances in sequencing technology may indeed help to understand the genetic mechanisms underlying AF and HFPEF The discussion provides a comprehensive overview of the current state of knowledge in the field by integrating inflammation, oxidative stress, and genetics, thereby laying the groundwork for future research and clinical development

Subsection 2: Exploring Remodeling Realms Navigating the Structural and Electrical Labyrinths

A crucial aspect in unraveling the complexities of the coexistence of atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) lies in comprehending the structural and electrical remodeling processes occurring in both the atria and ventricles. This subsection aims to dissect the intricate changes at the cellular and tissue levels, identifying key components of remodeling and elucidating their impact on the perpetuation of AF and HFpEF.

Structural Remodeling:

Atrial Remodeling:

Atrial remodeling in atrial fibrillation (AF) involves structural changes in the atria, including alterations in tissue architecture, fibrosis, and changes in cell-to-cell coupling [32–34]. Fibrotic tissue acts as a substrate for reentrant circuits, which contribute to the maintenance of AF [35]. Increased atrial size and dilation also play a role in atrial remodeling, leading to abnormal atrial mechanics and impaired atrial contraction [36]. These changes promote stasis of blood, increasing the risk of thrombus formation. Understanding the underlying changes in atrial structure is crucial for developing interventions to prevent or reverse the remodeling process in AF.

Ventricular Remodeling:

What is worse - AF - also result in HFpEF through the bad side hemodynamic effects [37], and the HFpEF – at the same time - cause an AF - which is also bad - through the adverse consequences of the left atrial remodeling [38]. Atrial and ventricular remodeling happen at the same time; therefore, this synergistic effect of both conditions may arise and cause a worsening condition of patients with atrial fibrillation and HFpEF [39].

Electrical Remodeling:

Atrial Electrical Remodeling:

Through atrial fibrillation (AF) related electrical remodeling in the atria, expression levels of ion channels are modified, action potential duration is prolonged, and conduction velocity is altered. These remodeling lead to the shortening of refractory periods and predisposition to the reentry mechanisms, which in turn provides continuing of arrhythmia [19,32]. Inflammatory atrial cardiomyopathy, caused by atrial inflammation, promotes susceptibility to AF through arrhythmogenic electrical, structural, and autonomic remodeling of the atria [41]. Additionally, cellular heterogeneity in the AF remodelled atria can impact the repolarization phase, with the atrial action potential duration (APD90) increasing in the left atrium and decreasing in the right atrium [42]. The HCM mice were then experimented on using mice of different ages. Interestingly, metabolic adaptation accompanied deteriorating left atrial electromechanics and interventricular septal hypertrophy were pronounced in the older HCM mice. Such age-related changes could be very detrimental to the heart and, therefore, one might develop AF [43].

Ventricular Electrical Remodeling:

In HFpEF often the ventricular hypertrophy as a comorbidity, results in an impairment of relaxation, and it is a cause of the myocardial stiffening.

In patients with HFpEF ventricular electrical remodeling can take place which then leads to changing of the repolarization and the action potential duration and also calcium handling thereof [44]. This rearrangement might lead to the occurrence of ventricular arrhythmias, which additionally endangers the clinical pictures of people with AF combined with HFpEF [45]. Ensuring the careful consideration of the peculiarities of ventricular electrical remodeling is integral for the creation of the antiarrhythmic approaches appropriate for each individual patient [46].

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Subsection 3: Deciphering Hemodynamic Puzzles

Understanding the Hemodynamic Consequences of AF and HFpEF

Understanding the hemodynamic consequences of the coexistence of atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) is paramount for comprehending the intricacies of their clinical interplay. This subsection aims to delineate how AF influences crucial hemodynamic parameters such as cardiac output, diastolic function, and pulmonary circulation in the context of HFpEF, providing insights into the complex hemodynamic implications of these interconnected cardiovascular conditions.

AF and Cardiac Output:

Reduced effective atrial contraction in atrial fibrillation (AF) leads to an irregular and often rapid ventricular response, resulting in inefficient atrial contribution to ventricular filling and impacting cardiac output. The irregularity in cardiac rhythm and compromised atrial contraction can contribute to a decrease in stroke volume and cardiac output.[47] AF patients with a lack of atrial contraction alone showed a small decrease in ejection fraction, but the interaction between increased heart rate and lack of atrial contraction led to a significant drop in ejection fraction.[48] Altered intracellular calcium handling and extracellular matrix protein secretion have been identified as contributors to the pathophysiology of AF and its associated contractile dysfunction.[49] Patients with AF-related stroke and rapid ventricular response (RVR) have higher initial stroke severity and poor outcome at 3 months. Initial stroke severity mediated a considerable proportion of the association between RVR and poor outcome. [50] Reduced exercise capacity in AF patients is associated with elevated left ventricular filling pressure and reduced chronotropic response, rather than rhythm status. Subjectively reported exercise intolerance is not a sensitive assessment of reduced exercise capacity. [51] Computational fluid dynamic analyses have shown that the alterations in contractility and morphology associated with AF play a primary role in establishing hemodynamic conditions that promote a higher incidence of ischemic events, particularly in the left atrial appendage.

AF and Diastolic Function in HFpEF:

Impaired Diastolic Filling:

The irregular rhythm of AF exacerbates diastolic dysfunction by further compromising the coordination of atrial and ventricular filling [52]. Women with HFpEF demonstrate sex-specific functional alterations of right ventricular, left atrial, and left ventricular function during exercise stress [53]. In HF, there are attenuated improvements in the rate of left ventricular relaxation just after the cessation of contraction during muscle metaboreflex activation (MMA) [54]. The combination of AF and HFpEF results in a scenario where diastolic filling is suboptimal, leading to elevated filling pressures and contributing to symptoms of heart failure [55]. Increases in ventricular stiffness during MMA may be an additional mechanism that limits cardiac output, reducing peripheral perfusion during exercise and potentially leading to sudden cardiac death [56].

AF and Pulmonary Circulation:

Increased pulmonary pressures in patients with atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) are a result of elevated left atrial pressures transmitted backward to the pulmonary circulation. The irregular atrial contraction and compromised ventricular filling in AF contribute to elevated left atrial pressures, which in turn lead to pulmonary congestion and increased pulmonary vascular resistance. The coexistence of AF and HFpEF creates a synergistic effect, amplifying the impact on pulmonary hemodynamics and potentially exacerbating respiratory symptoms [57–59].

Hemodynamic Implications of AF and HFpEF Coexistence:

The combination of atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) creates a detrimental cycle that worsens the symptoms and progression of both conditions. AF and HFpEF contribute to increased cardiac workload, elevated filling pressures, reduced cardiac output, and exacerbation of symptoms. The irregular rhythm and impaired ventricular filling in AF increase cardiac workload [60]. HFpEF, characterized by elevated filling pressures and reduced cardiac output, further strains the cardiovascular system [1]. This interplay between AF and HFpEF can potentially result in acute decompensation [2]. The combination of AF and

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HFpEF creates a vicious cycle of hemodynamic stress, leading to increased cardiac workload, elevated filling pressures, reduced cardiac output, and exacerbation of symptoms [61]. Interventions targeting rhythm control in AF, optimization of diastolic function, and management of volume status become integral components of a comprehensive therapeutic approach.

Subsection 4: Investigate Neurohormonal Activation

The link between atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) involves neurohormonal activation. We analyze the processes and systems, including the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), and natriuretic peptides, that drive this activation in both conditions. While intricate, understanding these connections helps explain why AF and HFpEF often occur together.

Neurohormonal Activation in AF:

RAAS Activation:

AF is associated with heightened activity of the renin-angiotensin-aldosterone system (RAAS), characterized by increased levels of angiotensin II and aldosterone. Angiotensin II contributes to atrial structural remodeling and fibrosis, creating a substrate for the maintenance of AF [12]. Aldosterone promotes sodium and water retention, contributing to volume overload and increased atrial pressures [62].

SNS Overactivity:

Sympathetic nervous system (SNS) overactivity in atrial fibrillation (AF) leads to increased release of catecholamines, such as norepinephrine, which exert proarrhythmic effects by modulating ion channels and promoting atrial ectopy. SNS activation also contributes to atrial remodeling and electrical instability, perpetuating the arrhythmia [63,64].

Natriuretic Peptides Response:

Atrial stretch and pressure overload in atrial fibrillation (AF) lead to the release of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) [65,66]. Initially, these peptides are released to counteract the effects of volume overload. However, sustained elevation of ANP and BNP may indicate the persistence of atrial stress and remodeling [66]. ANP deficiency is thought to occur as a result of atrial remodeling in patients with AF ablation [67,68]. Additionally, the ANP-to-BNP ratio is significantly higher in patients with LA reverse remodeling [65]. In patients with sustained volume- dependent primary hypertension, those with uncontrolled systolic blood pressure (SBP) have an attenuated relationship between ANP and indexes of volume overload, suggesting impaired vascular effects of ANP [66].

Neurohormonal Activation in HFpEF:

RAAS Dysregulation:

HFpEF is characterized by RAAS dysregulation, with increased levels of angiotensin II and aldosterone. Angiotensin II contributes to myocardial fibrosis, impaired relaxation, and increased ventricular stiffness [69]. Aldosterone, through its actions on sodium and water retention, exacerbates volume overload and contributes to elevated filling pressures [70].

SNS Overdrive:

Similar to AF, HFpEF is associated with heightened sympathetic activity, which contributes to vasoconstriction, increased afterload, and myocardial fibrosis [56,71]. The mutual feedback amongst the SNS overactivation and the RAAS activation provides a setting for the adverse ventricular remodeling [72]. The sympathetic stimulation causes a production of sympathetic impulse by the brain, which results in sympathoexcitation in HFpEF [73]. This adrenergic dismodalectics along with RAAS initiation leads to vasoconstriction and addicted load resulting in unfortunately adenine ventricular remodeling actions [74]. Secondly, sympathetic stimulation in HFpEF is also linked to progressive myocardial fibrosis accordingly, reinforcing adverse remodeling. The very exact mechanism that leads to sympathetic overactivity and adverse ventricular remodeling in HFpEF is not yet understood completely, but presumably involves simultaneous activity of the sympathetic nervous system, RAAS activation and the resulting vasoconstriction and myocardial fibrosis [56,73].

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Natriuretic Peptides Release:

Prolonged increases in circulating natriuretic peptides, for instance, BNP and ANP serve as biomarkers of myocardial strain and are overall indicators of the compensatory neuro-hormonal response in HFpEF [[75,76]. In HFpEF, additional stuff is put into the heart because of the increased wall stress and impaired diastolic filling and, subsequently, the release of BNP and ANP [77]. These peptides induce vasodilation and natriuresis, and their blood levels reflect the poorer the patient's heart function and higher risk for adverse cardiac remodeling [78]. A study has shown that natriuretic peptide levels had high diagnostic accuracy for discriminating HFpEF from other causes of breathlessness. These can be used as a means for screening, early diagnosis, and risk stratification of HF [79]. Further, more elevated levels of natriuretic peptides correlate with worse left ventricular stiffness, extracellular matrix remodeling, concluding the effort of HFpEF. Therefore, elevated natriuretic peptide levels in HFpEF patients reflect the myocardial strain and neurohormonal compensatory response in the failing heart, making them valuable biomarkers for assessing disease severity and prognosis [79,80].

Role of Neurohormonal Activation in AF and HFpEF Coexistence:

Synergistic Effects:

The coexistence of AF and HFpEF triggers a synergistic activation of neurohumoral cascades that leads to the summation of their individual effects. The RAAS and SNS together may promote a pro-arrhythmic and pro-fibrotic environment through activation of these systems, further complicating the pathophysiology of both conditions [81,82]. nflammation links to issues with cardiovascular function and neurohumoral activation. Furthermore, pro-inflammatory cytokines in the brain collaborate and contribute to sympathetic activation [83]. Additionally, research proves late sodium current (late INa) and Ca2+/calmodulin-dependent protein kinase (CaMKII) connect to arrhythmogenic factors that synergize with β-adrenergic stimulation-prompted AF. Moreover, inhibiting both late INa and CaMKII displays collaborative anti-arrhythmic impacts [84]. Therefore, the synergistic effects of neurohormonal activation in AF and HFpEF coexistence contribute to the complex pathophysiology of both conditions.

Subsection 5: Patient Stratification and Subtypes

Due to the high variability and the various phenotypes of AF and HFpEF, it would be beneficial to study the underlying disease mechanisms at the molecular, structural, or clinical levels in order to identify subtypes of patients that require tailored treatments. Investigating such subtypes could in the end transform the whole way we approach treatment of these conditions finally creating more person specific and targeted therapies.

Molecular Subtypes:

The molecular profiling of patients with HFPEF and AF could be helpful since distinctive subtypes of patients with individual genetic or molecular characteristics can be identified. Identification of molecular profile in HFPEF and AF patients has the capability to separate the patients into distinct subgroups with specific genetic or molecular characteristics [85] This includes research on Alzheimer's disease (AD) and colorectal cancer (CRC) [86].

Similarly, in CRC, integrated analysis of transcriptome and genome identified four immunological molecular subtypes (IMSs) with distinct molecular characteristics and clinical outcomes [87]. These IMSs were associated with immune gene expression, immune microenvironment, and immune checkpoints [88]. These findings highlight the potential for personalized medicine and patient stratification in immunotherapies [89]. Therefore, molecular profiling can indeed identify distinct subtypes of patients with unique genetic or molecular signatures in various diseases.

Structural and Clinical Subtypes:

(AF) based totally on structural remodeling patterns or clinical traits can screen subgroups with varying responses to remedy. This method lets in for the improvement of focused interventions that address the unique desires of each affected person subgroup. Studies have proven that HFpEF is a clinically heterogeneous syndrome with more than one etiologic and pathophysiologic elements [90].

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The categorization of HF sufferers based on ejection fraction (EF) has been questioned, as EF may additionally vary relying on exceptional hemodynamic conditions and has sizeable interobserver variability [91]. HFpEF and HF with mid- range EF (HFmrEF) were described as intermediate populations between HF with reduced EF (HFrEF) and HFpEF, but they also display heterogeneity in presentation and pathophysiology [92]. AF frequently co-happens with HF, and expertise the interaction among these two conditions is crucial for developing shared preventive and healing strategies [93].

Cardiac amyloidosis:

Sub-clinical isolated cardiac amyloidosis (ICA) is associated with an increased risk of atrial fibrillation (AF) in elderly patients [94]. ICA refers to the deposition of amyloid in the atrium without valvular heart disease. In patients with AF, those with ICA are more likely to have persistent forms of AF and lower sinus rhythm P-wave amplitude [95]. Senile cardiac amyloidosis, predominantly visible in elderly males, is regularly as a In AD, mass-spectrometry proteinomics in cerebrospinal fluid (CSF) showed five molecular subtypes on the basis of their differing genetic profiles, brain atrophy, and clinical outcomes result of wild-kind transthyretin (TTR) and is associated with coronary heart failure with preserved ejection fraction (HFpEF) and AF [96,97]. Atrial amyloidosis relates to an improved AF and thromboembolic event risk. This cardiac amyloidosis manifestation underscores early diagnosis' importance for treatment. While scintigraphy proves a common noninvasive prognostic technique, endomyocardial biopsy constitutes the definitive diagnosis' gold standard. Further studies must outline AHF, perceive imaging modalities enabling antemortem diagnosis, and determine optimal control techniques [98].

Imaging Techniques:

Advanced imaging plays a critical role in our evolving understanding of the complex interplay between atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF). Of these, cardiac magnetic resonance imaging (CMR) and molecular imaging are particularly useful for detailed assessments with several points being elucidated using these modalities.

Cardiac Magnetic Resonance Imaging (CMR):

Left atrial (LA) function has been shown to be important for prognosis in heart failure with preserved ejection fraction (HFpEF) in both sinus rhythm and persistent atrial fibrillation (AF) [99,100]. LA strain, quantified by CMR imaging, has been associated with the risk of HFpEF [101]. Additionally, LA strain has been found to be independently associated with HFpEF and has potential value in diagnosing the condition [102]. The combination of AF and HFpEF is associated with increased mortality, as AF worsens the hemodynamics of HF [103]. Further research is needed to understand the prognostic impact of LA function in HFpEF patients with different types of AF.

Molecular Imaging:

Think of PET and MRI as the heart's own detectives, like the medical Sherlock Holmes and Watson! These imaging wizards step into action when there's a heart issue, unraveling the mystery of inflammation and checking in on the immune cell hustle during a myocardial infarction [104,105]. T It's like they've got this superpower to see beyond the surface and reveal the heart's secrets. What makes these imaging sidekicks truly special is their ability to play it cool without any invasive measures. They're like the heart's personal photographers, capturing snapshots of the damage, keeping an eye on tissue makeover, and documenting the heart's journey to recovery [106]. Imagine them as the paparazzi of the medical world, but with a heartwarming mission.PET imaging deserves its own spotlight as the storyteller extraordinaire. Picture it as a skilled artist, illustrating a vibrant canvas of inflammation markers, fibrosis, and the blooming of new blood vessels in cases of hypertensive heart failure [107]. Additionally, whole-body molecular imaging with PET has been employed to study the cardio-renal crosstalk after MI, providing insights into systemic inflammation and its impact on renal function [108]. These techniques enable the identification and monitoring of important molecular components such as inflammatory markers, cellular receptors and metabolic pathways. By targeting these specific molecules, molecular imaging improves our ability to understand the molecular signatures associated with AF and HFpEF, thereby helping to develop targeted therapeutic strategies.

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Molecular Biology Techniques

In addition to advanced imaging methodologies, molecular biology techniques offer deeper insight into the molecular complexity underlying both AF and HFpEF. Analysis of tissue samples using molecular biology methods provide valuable information regarding molecular mechanisms and changes at the cellular level. These include:

Molecular Biology Techniques for Tissue Analysis:

Molecular biology techniques for tissue analysis in AF-HFPEF include the use of next-generation sequencing panels (NGS) for targeted genetic analysis and comprehensive genomic profiling (CGP) for more comprehensive analysis of genetic alterations. Formalin-fixed paraffin-embedded (FFPE) samples are widely used in tissue analysis but low-quality genetic material extracted from FFPE samples can render sequence data unreliable. Low-acid fixatives, such as low-acid formalin fixation (ADF) and precooled ADF (coldADF), have shown better DNA preservation and sequence capture performance compared to neutral buffered formalin (NBF) [109]. Another study offered additional promise of discovery again by combining high-level microRNA profiling with humaninduced pluripotent stem cell-derived cardiomyo-cytes (hiPSC-CMs). The aim was to discover novel molecular pathways in HFpEF; microRNA profiling to elucidate the molecular underpinnings of HFpEF, with hiPSC- CMs serving as a HFpEF disease model system [110].

Rationale Behind Molecular Techniques:

Molecular biology techniques are powerful tools. They identify key players in AF and HFpEF. The methods decipher gene expression alterations, mutations, and epigenetic modifications contributing to disease pathogenesis[111–113]. Elucidating the molecular underpinnings pinpoints potential therapeutic targets and biomarkers. This paves the way for precision medicine approaches. These approaches are tailored to the unique molecular profiles of AF and HFpEF individuals[114]. These techniques, such as next-generation sequencing and DNA analysis, provide crucial insights into disease mechanisms and allow for accurate diagnostic methods and personalized drug treatment modalities [115].

Management of patients with HFpEF and AF

HFpEF-AF and medical therapy:

Treatment with dapagliflozin, an SGLT2i, in the EMPEROR-Preserved trial was found to decrease the overall incidence of atrial fibrillation/flutter, regardless of the presence of diabetes [116]. Mechanisms by which SGLT2i may reduce the burden of atrial fibrillation include hypertension, oxidative stress, inflammation, increased sympathy, and reduction of left atrial dilation and epicardial fat volume [117]. Sodium glucose-linked transporter 2 inhibitors (SGLT2i) have demonstrated efficacy in reducing hospitalizations related to heart failure and enhancing the quality of life in patients with HFpEF [118].

Dapagliflozin has been shown to decrease serum TNF-α levels [119]. In addition, dapagliflozin seems to be making a positive impact on the heart's electrical activity, specifically influencing parameters related to ventricular repolarization, like how the P-wave spreads. This is especially beneficial for individuals dealing with type 2 diabetes mellitus (T2DM). What's noteworthy is that dapagliflozin effectively decreased the occurrence of adverse events linked to atrial fibrillation or atrial flutter (AFL) in individuals with heightened risks due to diabetes. [119]. This positive impact on atrial fibrillation persisted, regardless of whether the person had a complicated history of atrial fibrillation, a previous heart attack, or heart failure [120].

The significant benefits of dapagliflozin were consistent across all patients, regardless of their initial NT-proBNP concentration. Notably, individuals with higher NT-proBNP concentrations experienced the most pronounced advantages from dapagliflozin treatment [121]

In the IMPRESS-AF trial, where Shantsila et al. [122] took the reins, they set out to explore how spironolactone could impact exercise tolerance, quality of life, and diastolic function in individuals dealing with permanent atrial fibrillation (AF) and having preserved cardiac function. Despite the sincere efforts with spironolactone, it's disheartening that there wasn't any significant boost observed in exercise capacity, cardiac function, or overall quality of life. Another study led by Kotecha and

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team [123] compared the effects of digoxin and bisoprolol on heart rate in atrial fibrillation, uncovering no substantial differences in how patients perceived their quality of life between the two treatments. These results suggest that, disappointingly, spironolactone may not bring about significant enhancements in terms of boosting exercise tolerance and overall well-being for individuals dealing with atrial fibrillation who are on digoxin. However, it's interesting to observe that symptoms did show considerable differences between the groups, with many patients in the digoxin group reporting a noteworthy two-notch improvement [123,124] The use of bisoprolol in patients with heart failure showed clinical benefit in improving QoL . These findings suggest that the choice of rate control therapy in AF should consider factors beyond QoL alone.

Obesity is associated with heart failure with preserved ejection fraction (HFpEF) and has been found to be a distinct phenotype in the HFpEF population [125]. Obese patients with HFpEF have impaired left ventricular diastolic function, pressure a increased exposure, and other factors contributing to increased left ventricular pressure obesity Hemodynamic, neurohormonal, inflammatory, and mechanical mechanisms may have contributed to the development of HFpEF. May increase plasma volume, activate sympathetic nerve signaling, and inhibit the renin-angiotensin-aldosterone system fibrillation (AF) inflammation. Obesity AF is associated with an increased incidence, especially in patients with HFpEF, as abdominal obesity is associated with a higher risk of atrial fibrillation. Further research is needed to determine effective therapies for obesity-associated HFpEF [126]. In particular, the Long-term Effect of Goal Directed Weight Management in an Atrial Fibrillation Cohort (LEGACY) study showed that weight reduction resulted in a reduction in AF burden and improvement in AF symptom severity [127].

Dronedarone is a medication that researchers have explored for managing atrial fibrillation (AF) alongside heart failure (HF) with preserved and mildly reduced ejection fraction. The ATHENA trial demonstrated that dronedarone reduces the risk of cardiovascular events in patients with AF, but there is limited data on its role in patients with AF complicated by HFpEF and HFmrEF [128]. A post-hoc analysis of the ATHENA trial showed that dronedarone can be a useful antiarrhythmic drug for early rhythm control, as it reduces the burden of AF/atrial flutter (AFL) progression to permanent AF/AFL and increases the regression to sinus rhythm (SR) compared to placebo [129]. Another post-hoc analysis of the ATHENA trial found that dronedarone has both rhythm- and rate-controlling properties, as it prolongs the time to AF/AFL recurrence, reduces the need for electrical cardioversion, and decreases the likelihood of permanent AF/AFL [130].

AF-HFpEF and Catheter Ablation:

A thorough examination of uncontrolled pre- and post-intervention data, along with observational controlled data and subsequent analysis from randomized controlled trials (RCTs), offers a holistic perspective on how catheter ablation influences individuals dealing with atrial fibrillation and heart failure with preserved ejection fraction (AF-HFpEF).

The uncontrolled before-and-after studies by Elkaryoni et al., Rattka et al., Sugumar et al., and Yamauchi et al. collectively demonstrate a positive impact of catheter ablation on AF-HFpEF patients. Notably, a 28.5% relative reduction in all-cause hospital admission rate within 120 days after AF ablation emphasizes the potential benefits in terms of healthcare utilization [131–134].

The observational studies by Fukui et al. and Arora et al. provide a comparative analysis between AF-HFpEF patients undergoing catheter ablation and those receiving medical therapy. These studies consistently show favorable outcomes in the ablation group, with lower all-cause hospital readmission rates, particularly for HF-related admissions. Lower AF hospital readmission rates in the ablation group highlight the potential efficacy of catheter [135,136].

The post-hoc analysis by Packer et al., derived from the CABANA trial, stands out as a key component of the discussion. The reduction in all-cause mortality by 60% in the AF-HFpEF subgroup undergoing catheter ablation compared to medical therapy is a striking finding. This supports the notion that catheter ablation not only addresses AF-related outcomes but also significantly impacts overall survival in HFpEF patients [137].

Several studies, including Rattka et al., Sugumar et al., and Yamauchi et al., delve into the remission of HFpEF following catheter ablation. The observed rates of remission, ranging from 43%

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to 77% after single or multiple procedures, underscore the potential for catheter ablation to modify the course of HFpEF. The improvement in NYHA functional class, along with reductions in left atrial diameter and natriuretic peptides, further supports the positive impact on HFpEF parameters [132–134].

The research conducted by Fukui and colleagues, Arora and team, as well as findings from Packer's study consistently show that individuals who underwent catheter ablation experienced lower rates of readmission to hospitals, considering both general causes and those related to heart failure. Notably, Packer's research goes even further to highlight a substantial decrease in overall mortality rates. This highlights the potential life-saving value of catheter ablation for patients with atrial and heart failure with preserved ejection fraction [135–137].

The RACE-AF trial, which delves into the comparison between rate and rhythm control in HFpEF patients with AF, indicates that both approaches, using medications, are equally effective in preventing mortality and hospitalization. This highlights the potential life-saving benefit associated with catheter ablation for individuals managing atrial fibrillation and heart failure with preserved ejection fraction. It emphasizes the need for a personalized approach in managing AF within the HFpEF population. In contrast, the post hoc analysis of CABANA-HF demonstrates the potential superiority of pulmonary vein isolation (PVI) over medications, indicating that catheter-based interventions might play a pivotal role in certain HFpEF populations [137,138].

RACE 3, which specifically targets HFpEF patients with AF, advocates for a comprehensive approach involving rhythm control for AF along with treatment for HF, as opposed to focusing solely on comorbidity management. The data suggests that this combined strategy, predominantly utilizing medications, is superior in maintaining sinus rhythm. This aligns with the growing recognition of the need for a holistic approach to address both AF and HF components in HFpEF [139].

The EAST-AFNET4 trial, encompassing stable HF patients with a significant HFpEF representation, emphasizes the potential benefits of early rhythm control over usual care. This long-term study indicates that early intervention, including PVI in some cases, results in reduced rates of cardiovascular death, stroke, and HF or acute coronary syndrome (ACS)-related hospital stays. This finding highlights the importance of timely and targeted management strategies to improve outcomes in HFpEF patients with AF[140].

To explore treatment strategies for individuals managing atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF), a study led by Kelly et al compared the effectiveness of rhythm control and rate control. The findings from this study indicate that individuals undergoing rhythm control exhibited a lower risk of all- cause mortality when compared to those under rate control. The hazard ratio (HR) was determined to be 0.71, albeit with a p-value of 0.066, suggesting a trend towards a significant difference in favor of rhythm control[141]. Another study, led by Zhang and colleagues, delved into the consequences of incident atrial fibrillation (AF) on individuals with heart failure with preserved ejection fraction (HFpEF). The results of this study revealed that the occurrence of AF, irrespective of ejection fraction (EF), was linked to poorer outcomes for individuals with HFpEF [142]. Additionally, Machino- Ohtsuka et al. found that maintenance of sinus rhythm was associated with improved clinical outcomes in patients with HFpEF and AF [143].

The BNP level significantly decreased irrespective of the index rate control status, and freedom from AF recurrence was an independent predictor of HF remission, defined as BNP <100 pg/mL at 1 year, in the HFpEF group. Conclusion Catheter ablation is highly feasible for restoring sinus rhythm in non-paroxysmal AF with coexisting HFpEF, thereby improving cardiac function and BNP levels [134,144].

Administering catheter ablation to control atrial fibrillation (AF) in individuals with heart failure with preserved ejection fraction (HFpEF) might have adverse effects on the function of the left atrium (LA). This could affect various aspects, such as LA reservoir, conduit, booster pump, and neurohormonal functions. The procedure may disrupt LA electromechanical synchrony and potentially result in a proportional decrease in LA ejection fraction, linked to the volume of scar tissue post-ablation. These observations highlight the complexities and potential consequences associated with catheter ablation in AF-HFpEF cases, emphasizing the importance of careful consideration and

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monitoring [145,146]. LA compliance may also be reduced, leading to increased filling pressures and pulmonary hypertension, known as stiff LA syndrome [146]. Heart failure symptoms and cardiac biomarkers continued to improve in individuals with heart failure preserved ejection fraction (HFpEF) despite good heart rate monitoring during follow-up. The subsequent echocardiographic assessments uncovered a continued advancement of unfavorable changes in the left atrium, with no notable enhancement in diastolic function among HFpEF patients. Notably, those without HFpEF reported an improvement in their overall quality of life, whereas individuals with HFpEF continued to experience a comparatively lower total physical component score (with a median of 41.5 versus 53.4; $P < 0.004$). This underscores the persistent challenges associated with HFpEF and emphasizes the need for holistic approaches to address its multifaceted impact on patients [147].

Discussion

In This review critically examines the complex interplay between atrial fibrillation (AF) and heart disease and preserved ejection fraction (HFpEF), from small genes to innovative therapeutic strategies. Molecular profiling is now being recognized more and more as a promising tool for stratifying patients according to different genetic or molecular characteristics. Inspired by research into Alzheimer's disease and colon cancer, this methodology represents a shift toward individualized medicine and creates opportunities for individualized interventions and immunotherapies.

Given the intrinsic diversity of heart failure with preserved ejection fraction (HFpEF), the introduction of structural and clinical subtyping is advocated as a practical approach. The critique of solely relying on ejection fraction for patient classification has prompted a reevaluation of the criteria for classification, taking into consideration the patterns of structural remodeling and clinical subtleties. This approach enables the development of customized products tailored to specific patient subgroups to improve treatment efficacy.

The connection, between cardiac amyloidosis (ICA) and a higher chance of atrial fibrillation in elderly individuals underscores the significance of promptly identifying the disease for effective treatment. Cutting edge imaging methods like resonance (CMR) and molecular imaging are crucial in comprehending the intricate relationship between atrial fibrillation and heart failure with preserved ejection fraction (HFpEF) confirming the diagnosis and offering prognostic insights.

Advanced sequencing technologies and genetic analysis are now widely acknowledged as tools, in biology for fully understanding the complex molecular nature of atrial fibrillation (AF) and heart failure, with preserved ejection fraction (HFpEF). The decoding of gene expression changes, identification of mutations, and exploration of epigenetic alterations represent auspicious avenues for identifying therapeutic targets and biomarkers, thereby facilitating the advancement of personalized medicine tailored to individuals' unique molecular profiles. Regarding treatment, the study has paid more attention to the meaningful effect of SGLT2 inhibitors, especially dapagliflozin on reducing atrial fibrillation/flutter The examination of spironolactone, dronedarone, and catheter ablation as potential interventions reflects ongoing endeavors to optimize outcomes for individuals with AF-HFpEF.

The discourse examines the gaps in research and provides insight into future directions, emphasizing the necessity of defining acute heart failure (AHF), determining the most optimal imaging techniques, and identifying strategies for management.

As the disease progresses, a majority of HFpEF patients develop atrial fibrillation that is associated with poor prognosis This can be considered as a therapeutic option targeting at modifying the progression of AF-HFpEF where rhythm control has been deployed. It has been suggested that observational data may offer better prognostic information than rate control for this approach. Although there are no RCTs comparing catheter ablation to medical therapy for atrial fibrillation in HFpEF; one must validate its efficacy and safety in patients diagnosed with HFpEF across potential RCTs. It would thus be important to stratify them by the etiology of HFpEF as well as severity and duration of AF ablation which would provide a basis for appropriate treatment choice.

The effectiveness of ablation depends on factors, including the New York Heart Association (NYHA) functional classification, the level of ventricular scarring the extent of atrial fibrosis the

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duration of atrial fibrillation, age and any accompanying health conditions. Studies, like CASTLE AF have shown results in NYHA functional classes and in cases of heart failure with reduced ejection fraction (HFrEF) but there is limited data on the benefits of catheter ablation for heart failure with preserved ejection fraction (HFpEF). The complex relationship between HFpEF and atrial fibrillation involves functional changes in the atrium (LA) where atrial fibrillation contributes to LA enlargement and cardiomyopathy development.

The intricate connection between fibrillation and HFpEF becomes apparent as both conditions influence each others progression. Atrial fibrillation is linked to increased mortality in HFpEF while heart failure worsens the advancement of fibrillation. The interplay between HFpEF and atrial fibrillation involves a cause and effect relationship that often coexists due to shared risk factors and health issues. Individuals, with HFpEF exhibit reduced contractile reserve and thickening of the septum leading to an environment associated with atrial fibrosis.

Exploring Future Avenues of Research

Unveiling Personalized Insights through Advanced Biomarkers and Subtyping:

Embark on a journey into innovative biomarkers and molecular subtyping techniques, delving deep into the intricacies of patient stratification in heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF). The realm of omics technologies, particularly the groundbreaking single-cell sequencing, holds promises of revealing hitherto undiscovered molecular signatures. This opens avenues for finely-tuned subtyping and the crafting of personalized treatment approaches tailored to the unique genetic makeup of individuals.

Navigating the Dynamics: Longitudinal Studies for Structural and Clinical Subtypes:

Embark on long-term, prospective studies to unravel the dynamic nature of structural remodeling patterns and clinical characteristics in HFpEF and AF. Picture a canvas painted with repeated imaging assessments and clinical evaluations spanning extended periods. This captures the unfolding narrative of these subtypes, shedding light on their evolution and responses to treatments, offering a personalized touch to therapeutic interventions.

Charting New Territories: Early Diagnosis and Management of Cardiac Amyloidosis:

Delve into the intricate landscape of defining acute heart failure (AHF) in the context of cardiac amyloidosis. Navigate through uncharted waters to explore innovative imaging modalities for antemortem diagnosis and uncover optimal management strategies. The quest for early detection of cardiac amyloidosis becomes a cornerstone, where research efforts strive to carve standardized diagnostic protocols and effective therapeutic interventions.

Pioneering Imaging Frontiers: Advancements in Imaging Techniques:

Embark on a journey into the frontier of emerging technologies and refinements in imaging techniques, with a spotlight on cardiac magnetic resonance imaging (CMR) and molecular imaging. Integrate artificial intelligence seamlessly into the narrative, fostering a more nuanced analysis of imaging data. Imagine the potential enhancement of the prognostic value of left atrial (LA) function assessment in HFpEF patients harboring different types of AF.

Molecular Odyssey: Innovations in Biology

Continue the odyssey of advancing molecular biology techniques for tissue analysis in AF-HFpEF. Picture the application of cutting-edge methods like CRISPR technology, delicately manipulating cellular components to unveil the functional consequences of identified molecular alterations. Additionally, explore the potential of liquid biopsy techniques, introducing non-invasive dimensions to molecular profiling and revolutionizing our understanding of diseases.

Customized Healing: Therapeutic Strategies and Personalized Medicine

Delve into the realm of developing therapeutic strategies meticulously tailored based on identified molecular signatures in AF-HFpEF. Venture into the uncharted territories of emerging treatments, including gene therapies or RNA-based interventions. This is where the emphasis lies on crafting a symphony of personalized medicine approaches, orchestrating treatment modalities attuned to the unique molecular profiles of each patient.

Navigating the Complex Interplay: Impact of Comorbidities:

Embark on a journey through the intricate relationships between obesity and HFpEF. Uncover the underlying mechanisms and traverse the landscape of effective treatments. Picture interventions aiming at weight reduction, as demonstrated in the LEGACY study, consistently reducing atrial fibrillation burden and enhancing the quality of life for HFpEF patients.

Decoding Catheter Ablation: Outcomes and Impacts

Conduct further research, akin to exploring uncharted territories, on the impact of catheter ablation in AF-HFpEF, meticulously considering both short-term and long- term outcomes. Investigate the factors influencing the success of catheter ablation, potential effects on left atrial function, and the endurance of rhythm control in HFpEF patients. The comprehensive understanding of catheter ablation outcomes will contribute to refining therapeutic strategies for this unique patient population.

Limitations:

As we embark on these future research directions, it's essential to acknowledge the inherent limitations associated with the evolving nature of medical technologies, ethical considerations in longitudinal studies, and the intricate complexities of molecular biology investigations. Let's tread carefully, recognizing potential challenges in implementing cutting-edge techniques, ensuring the ethical conduct of studies involving human subjects, and considering the generalizability of findings across diverse patient populations.

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