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ABOUT COVER

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The primary aim of *World Journal of Cardiology* (*WJC*, *World J Cardiol*) is to provide scholars and readers from various fields of cardiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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EDITORIAL

Cardiovascular diseases in European ethnic minorities: Beyond the traditional cardiovascular risk factors

Mohamed Bamoshmoosh

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Abstract

This editorial is intended to be a reflection on cardiovascular disease (CVD) burden in European ethnic minorities. In some European countries, ethnic minority realities, due to their recent appearance, are still to be studied in depth. The experience of several European countries, where the migration processes started earlier, even more than a century ago, can help by being an example. Many studies have shown that major differences in CVD burden exist not only between countries, but also within the same country when considering different social strata and ethnic groups. The CV risk factors underlying heart disease have been well established. Important epidemiological studies have helped us understand that the underlying causes of heart disease as well as the behaviors that can help prevent them are the same. We are now well aware that CVD should be treated by considering a holistic approach. This is why the social determinants (SDs) of health that may worsen the disease burden or that, vice versa, may improve the treatment, and even more significantly, the prognosis of a patient's illness should be taken into consideration. For ethnic minority patients, this holistic, hermeneutic approach is of importance. Several SDs of health that influence CVDs have been identified but their relevance for the health of ethnic minorities has not yet been clearly defined. In some European countries, most ethnic minorities are largely also religious minorities. Only a few studies have evaluated the role of religion, which is an important SD that affects the probability of having CV risk factors and diseases. Adolescents, particularly those belonging to the second generation, seem to be the weak link. If we believe that these young people are really citizens of their country of birth, then a way of recognizing their belonging to the community starts from a will to better understand their condition, in order to assist them while they grow physically and mentally. Thinking about safeguarding the health of this population should be more than a health task, rather a goal of social justice.

Key Words: Cardiovascular diseases; Cardiovascular risk factors; European ethnic minorities; Social determinants of health

Core Tip: A wealth of data highlight the existence of important differences in cardiovascular (CV) disease burden within the same country, when considering different social strata and ethnic groups. Both CV diseases and risk factors have been shown to be related to several social determinants of health. Thus, in ethnic minority individuals, a holistic, hermeneutic approach should be considered.

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INTRODUCTION

With the end of the Cartesian dualism that the mind and body exist as distinct entities, the biomedical paradigm, according to which the cardiovascular (CV) system is merely a set of hydraulic pipes and an array of valves and pumps, has lost some of its predominance. In addition, the reduced prevalence and incidence of the most common intermediate risk factors (*e.g.* hypertension, diabetes, dyslipidemia, smoking, sedentary behavior), as a result of increasingly effective drugs and lifestyle changes and the improved surgical and interventional procedures for the correction of diseased pipes, valves and pumps, proved not to be enough to reduce CV morbidity and mortality[1]. Both longitudinal and cross-sectional epidemiological studies have identified several important international, national and regional CV health gradients that cannot be explained with the sole use of the previous biomedical paradigm criteria.

In the field of cardiology, research on conventional risk factors has been successful in significantly reducing the CV disease (CVD) burden in ethnic minority individuals. With this approach, however, the feeling is to arrive probably when the game is almost over. Moreover, only a few studies have evaluated traditional CV risk factors and CVDs in European ethnic immigrants, and the landscape shows green patches with large barren areas[2]. However, over the last two decades, growing attention has been devoted to ethnic minorities in the scientific literature, although no definitive conclusion can be drawn on the effect of traditional CV risk factors in this population due to the limited number of studies, different outcome measures and sometimes inconclusive results. This disappointing situation has led clinicians and epidemiologists to search for novel risk factors to account for the lower CV morbidity and mortality observed in high-income countries[3] and to develop a new approach to better define the burden of CV risk factors and diseases.

According to this new paradigm, body organs, and particularly the CV system, are to be put in a model where the main essence of the human being should be considered, that is, its sociality. It is only by considering social factors such as socioeconomic, cultural, gender and ethnic issues that some of these inconsistencies could be adequately addressed. Therefore, both CV diseases and risk factors have been linked to several social factors that affect their occurrence positively or negatively. These social factors, largely occurring outside the formal medical and healthcare setting, include the social determinants (SDs) of CVDs[4], which are also defined as the causes of the causes of traditional CV risk factors [5]. As outlined in the scientific statement from the American Heart Association, "at present, the most significant opportunities for reducing death and disability from CV disease in the United States lie with addressing the SD of CV outcomes"[4]. This holds true for industrialized countries, but also for developing countries.

Nowadays, we are well aware that CVDs should be treated with a holistic approach. For ethnic minority patients, this holistic, hermeneutic approach is even more important. Nevertheless, most health research funding is primarily allocated to tackle biomedical challenges, rarely addressing specifically the role of the SDs of health. The concept of SDs of health related to CVDs was first introduced in 1980, highlighting the increasing social inequalities[6] associated with increased CVD mortality in high-income countries[7]. One of the first reports to address this issue was the Black Report (named after chairman Sir Douglas Black, President of the Royal College of Physicians) published in the United Kingdom in 1980 [8]. The report showed that, among the British population, morbidity and mortality were unequally distributed, and that since the establishment of the National Health Service (NHS) in 1948, these inequalities have been increasing rather than diminishing. The conclusion of the report was that these inequalities were not related to shortcomings in the NHS, but rather to the fact that health is influenced by many other social inequalities, including income, education, housing, diet, and conditions at work. Thus, the report recommended to combat inequalities in health through a wide strategy of social policy measures. Since the formalization of the Commission of Social Determinants on Health by the World Health Organization (WHO) in 2005 chaired by Sir Michael Marmot, research on the SDs of health has increased significantly[9].

It is not easy to give a simple definition of the SDs of health. Sociology, and more in-depth medical sociology, deal extensively with this topic. The WHO Regional Office for Europe, which reflects much of the work developed at the International Centre for Health and Society at University College London, gives a comprehensive description of SD: "SD of health are the conditions in which people are born, grow up, live, work and age. These conditions influence a person's opportunity to be healthy, his/her risk of illness and life expectancy. Social inequities in health–the unfair and avoidable

differences in health status across groups in society–are those that result from the uneven distribution of SD"[10]. Thus, according to the WHO definition, health and illness and the resources to prevent illness and its effects are not distributed randomly throughout human society[11]. Tackling these inequities should be a high priority at all levels of governance because from the social point of view it achieves health equity and avoids unfair, unjust, avoidable, and unnecessary suffering. Tackling these inequities is advantageous also economically because on the long run it reduces the costs of health services and increases government revenue by improving productivity[12]. Finally, addressing these issues is not only a moral and a human rights imperative, but it helps promoting human well-being, prosperity, and sustainable development[13].

Several SDs of health that influence CV risk factors and diseases have been identified but their relevance for the health of ethnic minorities has not yet been clearly defined. As outlined in a recent report of the WHO Regional Office for Europe, although Europe is regarded as one of the healthiest and most prosperous regions in the world, substantial health inequalities exist both between and within countries, with trends showing that these gaps did not change or widened over the last decades. The WHO stigmatizes health inequalities within and between countries by simply considering they should never happen[14].

Many reports have shown that health inequalities are particularly pronounced in European ethnic minorities[15]. Moreover, the recent coronavirus disease 2019 (COVID-19) pandemic disproportionately affected ethnic minority groups, and this trend was also observed among healthcare personnel. The higher incidence of COVID-19 in ethnic minorities is also related to their SDs of health[16]. However, it is worth noting that there is a difference between minority health and health disparities. Although some ethnic minority individuals or groups have higher socioeconomic position (SEP), are highly educated, and have adequate access to care and thus may have even better health outcomes than the general population, health disparities may persist suggesting that additional factors, such as biology, cultural and environmental interactions, and structural discrimination may contribute to health disparities[17].

Ethnic minorities have been present for more than a century in many northern European countries. Historically, in southern Europe, there have been religious minorities, but ethnic minorities began to settle after World War II, especially in the last three decades of the 20th century. Europe still needs migrant labor in many sectors to fill low-skilled jobs because of the falling of birth rates and the aging populations[2]. Nevertheless, while the first waves of immigrants were well accepted and managed to organize ethnic minority realities, more recent immigrants have found it difficult to be integrated and feel that they are not accepted. This is also related to the fact that after the recent economic downturns, in several European countries, anti-immigrant parties have made electoral gains with anti-ethnic and anti-Islamic rhetoric. This negative perception is now seriously affecting also the already settled ethnic minorities, especially Muslims.

The offspring of ethnic minorities, born and raised in Europe, should not be involved in such debates. Ethnic minority youth should be considered an integral part of the society to which they actually belong and should be protected through legal and policy measures. This goal could be achieved also by taking care of the health of ethnic minority individuals, as health is an essential element of well-being. However, data on ethnic minority health in Europe are heterogeneous, with little research dealing with the health of first-generation[18] and beyond first-generation migrants[19], limiting the possibility of monitoring and improving their health. Unfortunately, Europe does not have an institute such as the United States National Institute on Minority Health and Health Disparities or a law equivalent to the 1993 United States National Institutes of Health (NIH) Revitalization Act, which demand researchers to include in their studies ethnic minority populations, unless there is a scientific reason not to do so. In the United States, it is not legally, ethically, or scientifically acceptable to exclude ethnic minorities from scientific research[20].

In an era of budgetary constraints, the high costs of fieldwork implementation, alongside insufficient researchers' experience to access ethnic minorities, and probably also lack of interest, are among the reasons for the scarcity of ethnic minority health research[21]. Conducting research that includes people from ethnic minority groups will allow European research to become equitable, ethical, and not institutionally racist. Advancing the understanding, for instance, of the relationships between CV risk factors and diseases[22] will improve the healthcare not only of ethnic minorities, but also of the general population. In this regard, research on international and national interethnic differences and similarities provides a unique view of the role of environmental and genetic factors in CVD development[23]. The health of the whole population improves when all segments of the population benefit from the health system. It is unfair if ethnic minorities are subject to direct or indirect social and health discrimination, increasing inequalities. In order to narrow the inequalities of ethnic minorities who have higher CV risk factor prevalence than the general population, their CV risk factors should be treated faster than those of the more advantaged ethnicities. Otherwise, the inequalities between different ethnicities will widen or, at best, remain unchanged[15]. Although this is not an easy goal to achieve, it represents a formidable challenge for public health research and practice.

As recently emphasized by the United States NIH, after "rigorous scientific approaches to minority health and health disparities, building on decades of studies addressing social inequality and health, behavioral epidemiology, and access to quality health care", "it is not enough to identify factors that contribute to health disparities: Intervention science must be applied in full force to seek solutions"[24]. Ethnic minority health inequalities can be reduced by removing physical, behavioral and cultural barriers to healthcare, closing disparities in quality of care, designing public health strategies, and implementing interventions to reduce health risks at the community level. Practically, in the field of CVD, for instance, it means to screen African or South Asian ethnic individuals at a younger age, to use new approaches to estimate their risk, to start treatment at lower thresholds, to lower blood pressure therapeutic goals, to lower obesity cutoffs, and to intensively monitor them to reduce their high premature mortality[25,26].

Most European ethnic research usually focused on both first-generation immigrants and ethnic minorities despite the often-divergent needs of the two groups. Thus, the utility of dedicated research on ethnic minority adolescents[25]. Another issue is related to irregular or undocumented migrants who are not officially registered and to refugees, whose numbers are increasing. Although all EU member states have formally recognized the right for every person to the

highest attainable standard of physical and mental health, many of these individuals are not engaged in or able to afford health care[27]. On the other side, refugees are at increased CVD risk due to interruption of medical care along the migratory route, psychological stressors, post-traumatic stress syndrome, and racism. For these individuals, the organizational and administrative issues including language, cultural and communication barriers, alongside their economic situation, limits the possibility of controlling their CVD risk burden. Thus, refugees seem to have a different CV risk factor pattern than migrants from the same country[28].

Undoubtedly, primordial prevention, when correctly done, leads to good results. However, individual prevention and treatments are expensive, especially for those who are in the lower social strata, and do not always completely solve the problems. Today, not much can be done regarding the genetic or epigenetic causes of CVDs in ethnic minorities. In my opinion, however, the main task is to move medical prevention from a purely biomedical approach that analyses conventional risk factors to give particular importance to the SDs of CVDs.

The end of the biomedical dominance has opened new horizons on the role of ethnicity and society and their dynamics in the determinism of diseases. Except for variations by country and age, no other epidemiological variable is as potent as ethnicity in exploring population-level differences in major CV risk factors and diseases[29]. The role of SDs of health is of special relevance if analyzed within ethnic minorities. This is because the society exerts a sui generis role in ethnic minorities. The existence of ethnic minorities is affected by the society in which they live. Thus, the role of SDs of health in individuals belonging to an ethnic minority is crucial. Particular attention should be given to the role of three SDs, which should not be considered singularly; rather their interaction should be sought.

Firstly, the role of the SEP as it is probably the most important SD factor, whose effects on the health of the whole society have been extensively studied[4]. In particular, the SEP of ethnic minority adolescents is conditioned by external factors linked to the type of the society in which they live, and also by internal factors related to the ethnic minority and the specific individual characteristics[30]. For ethnic minority adolescents as well as for autochthonous adolescents, the most commonly used SEP indicators are income, education level, employment, life course context, psychological stress, and neighborhood characteristics. It is not yet known to what extent the SEP of southern European ethnic minority adolescents is converging to that of autochthonous adolescents, similarly to what is happening in other European societies.

The acculturation process is the second SD. The Berry framework, which considers both the will to acquire the way of life of the host country and that to preserve the values of one's own country of origin, is the one most studied[31]. Data from the literature show that ethnic minorities have different acculturation processes, and often these differences are present also within families of the same ethnic group or even between the same family members. Some communities, such as the Chinese, usually maintain traditional attitudes for generations, while communities from eastern European countries have greater assimilation attitudes, whereas other communities, such as those from the Middle East or North Africa, prefer integrational models. It is important to note that, despite having an impact, the acculturation process alone cannot account for the CV risk factor and disease burden of the various ethnic minorities due to its intrinsic difficulty in being understood and measured[32].

The third SD is religion; an important SD that affects the probability of having CV risk factors and diseases. In some European countries, most ethnic minorities are largely also religious minorities. Religion, despite being an important identity factor, is not usually taken into consideration in medicine[33], especially when it comes to young people. Nevertheless, religion was found to influence CV risk factors and diseases in adult populations[34]. For those who believe, religion may condition many elements of their life, beginning from simple nutrition to the acculturation process itself.

Adolescents, particularly those of beyond second generation and of mixed ethnic background couples, seem to be the weak link. If we really believe that these young people are citizens of their country of birth, then a way of recognizing their belonging to the community starts from a will to better understand their condition, in order to assist them while they grow physically and mentally. Thinking about safeguarding the health of this population should be more than a health task, rather a goal of social justice.

CONCLUSION

A wealth of data highlight the existence of important differences in CVD burden within the same country, when considering different social strata and ethnic groups. Both CV diseases and risk factors have also been shown to be related to several SDs of health. Thus, in ethnic minority individuals, a holistic, hermeneutic approach should be considered.

FOOTNOTES

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EDITORIAL

Predictors of permanent pacemaker implantation following transcatheter aortic valve replacement-the search is still on!

Sudesh Prajapathi, Akshyaya Pradhan

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Abstract

Several anatomical, demographic, clinical, electrocardiographic, procedural, and valve-related variables can be used to predict the probability of developing conduction abnormalities after transcatheter aortic valve replacement (TAVR) that necessitate permanent pacemaker (PPM) implantation. These variables include calcifications around the device landing zone and in the mitral annulus; pre-existing electrocardiographic abnormalities such as left and right bundle branch blocks (BBB), first- and second-degree atrioventricular blocks, as well as bifascicular and trifascicular blocks; male sex; diabetes mellitus (DM); hypertension; history of atrial fibrillation; renal failure; dementia; and use of self-expanding valves. The current study supports existing literature by demonstrating that type 2 DM and baseline right BBB are significant predictors of PPM implantation post-TAVR. Regardless of the side of the BBB, this study demonstrated, for the first time, a linear association between the incidence of PPM implantation post-TAVR and every 20 ms increase in baseline QRS duration (above 100 ms). After a 1-year follow-up, patients who received PPM post-TAVR had a higher rate of hospitalization for heart failure and nonfatal myocardial infarction.

Key Words: Bundle branch block; Self expanding aortic valve; Atrioventricular node; Diabetes mellitus; QRS duration

Core Tip: Several anatomical, demographic, clinical, electrocardiographic, procedural, and valve-related variables predict the probability of developing conduction abnormalities after transcatheter aortic valve replacement (TAVR) that necessitate permanent pacemaker placement. The current study reinforces the existing literature by demonstrating that type 2 diabetes mellitus and baseline right bundle branch block are significant predictors of pacemaker implantation post-TAVR. The study investigators also revealed a novel linear relationship between the post-TAVR incidence of pacemaker implantation with every 20 ms increase in baseline QRS duration. Interestingly, pacemaker implantation following TAVR was predictive of future cardiovascular events at 1 year.

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INTRODUCTION

High-grade atrioventricular (AV) block and new-onset left bundle branch block (BBB) are the most common conduction abnormalities that occur after transcatheter aortic valve replacement (TAVR). However, almost 50% of these may improve with the resolution of perivalvular edema and inflammation post-TAVR. Previous studies have demonstrated that approximately 60%–96% and 2%–7% of patients develop high-degree AV block within 24 and 48 h, respectively[1]. At present, a trend toward early discharge from the hospital post-TAVR (median day 2) has led to an increase in the incidence of permanent pacemaker (PPM) implantation post-TAVR. However, the overall rates of PPM implantation within 30 d of TAVR have remained constant (11%) since 2012[2]. Various anatomical, demographic, clinical, electrocardiographic, procedural, and valve-related factors contribute to post-TAVR conduction blocks and have been previously reported. The anatomical proximity of the bundle of His and AV nodes to the aortic valve (Figure 1) and the direct mechanical injury to this conduction system during valve deployment, along with individual variation in the anteroposterior positioning of the AV node and His bundle close to the AV valve, increase the risk of developing post-TAVR heart block[3]. Mitral annular calcifications and calcifications near the device landing zone further increase this risk[4]. In addition, pre-existing electrocardiographic abnormalities, such as right and left BBB, first- and second-degree AV blocks, as well as bifascicular and trifascicular blocks, increase the necessity for PPM implantation during or after the procedure. Anatomically, the left bundle is anterior and closer to the aortic annulus and is prone to injury during valve deployment; this makes pre-existing right BBB among the most significant risk factors[4], aside from the patients' clinical and demographic traits. A study that analyzed 62083 patients who underwent TAVR from 2012 to 2017 reported that male sex, diabetes mellitus (DM), hypertension, history of atrial fibrillation (AF), renal dysfunction, and dementia were significant predictors of PPM implantation within 30 d post-TAVR[2,5]. Both a history of AF and new-onset AF were found to be independently associated with an increased risk of PPM implantation post-TAVR. A meta-analysis revealed that new-onset AF is associated with mortality, stroke, major bleeding, PPM implantation, and longer in-hospital stay[6]. The use of self-expandable valves (SEV) was also found to pose a higher risk of conduction abnormalities post-TAVR than the use of balloon-expandable valves (BEV). In previous studies, the incidence rate of new-onset left BBB was found to be higher in patients who received a self-expandable CoreValve (Medtronic Inc., Minneapolis, MN, United States) (27%, range 9%–65%) than those who received the balloon-expandable Sapien valve (Edwards Lifesciences Inc., Irvine, CA, United States) (11%, range 4%–18%)[4]. However, there is a scarcity of data to compare new-generation SEVs with BEVs. A recent trial that compared the two valves demonstrated equivalence for primary valve-related efficacy endpoints of all-cause mortality, stroke, moderate or severe prosthetic valve regurgitation, and PPM implantation within 30 d post-TAVR[7].

Various procedural factors such as transapical access, balloon pre- and post-dilation, prosthesis oversizing (more than 15%–20%), and lower implantation depth also add to the risk (Figure 2)[4].

In a retrospective cohort study published in the journal by Nwaedozie *et al*[8], patients undergoing TAVR between 2012 and 2019, were followed for 1 year. The effect of baseline DM, supraventricular arrhythmia, and pre-existing nonspecific interventricular conduction delay (QRS duration > 120 ms without any right BBB or left BBB morphology) on the incidence of PPM implantation post-TAVR was analyzed[8]. The study included 357 patients with a mean age of 80 years. Of these patients, 57 (16%) required PPM implantation post-TAVR whereas the remainder did not. With the exception of type 2 DM, which predominated in the pacemaker group, baseline variables such as cardiac risk factors and valve type were similar across the two groups. In this study, the frequency of pacemaker implantation was significantly greater in individuals with pre-existing DM, pre-existing right BBB, QRS duration > 120 ms, and prolonged QTc interval. Furthermore, the incidence of pacemaker implantation continuously increased for every 20-ms increase in duration of baseline QRS segment (above 100 ms). A marginally significant finding was the association between preoperative supraventricular arrhythmia (AF, atrial flutter, junctional rhythm) and a higher incidence of PPM implantation. The association between DM and the risk of PPM implantation post-TAVR was also previously reported, although not extensively studied. The present study reported baseline DM as a significant predictor of pacemaker implantation post-TAVR [adjusted odds ratio (OR) = 2.16]. Furthermore, a previous study has reported that pre-existing right BBB and QRS duration > 120 ms predict the need for PPM implantation post-TAVR[4]. However, this study vehemently indicated the

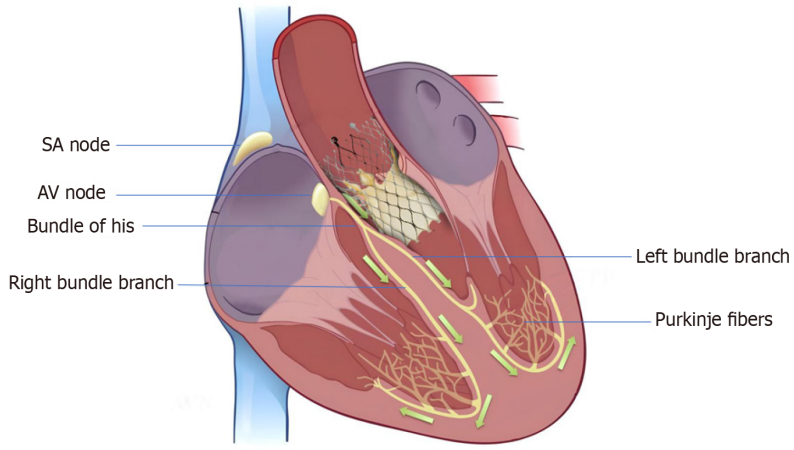

Figure 1 Anatomical proximity of the transcatheter aortic valve replacement valve to the cardiac conduction system. SA: Sino-atrial; AV: Atrio-ventricular.

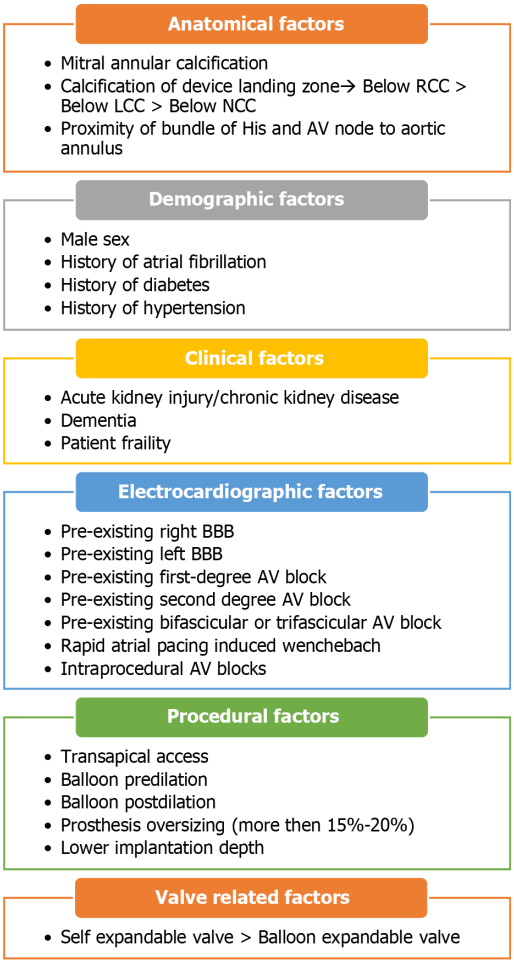

Figure 2 Predictors of permanent pacemaker implantation after transcatheter aortic valve replacement[1-5]. RCC: Right coronary cusp; LCC: Left coronary cusp; NCC: Non-coronary cusp; AV: Atrioventricular; BBB: Bundle branch block.

increasing OR for the incidence of pacemaker implantation for every 20-ms increase in duration of QRS segment greater than 100 ms. No previous study has demonstrated such a collinear association between QRS duration and an increased risk of PPM implantation post-TAVR. Moreover, only a few studies in the literature have demonstrated the association of pre-existing nonspecific interventricular conduction delay, defined as QRS duration > 120 ms without any right BBB or left BBB morphology, with the risk of PPM implantation post-TAVR. Patients with a longer QTC interval had an OR of 2.94 for PPM placement compared with those with a normal QTc interval due to the collinearity between the QRS and QTc intervals. The authors reported that QTc intervals and PPM implantation did not significantly correlate after strati-

fication by abnormal QRS intervals. In previous studies, a history of AF was found to be consistently associated with the incidence of PPM implantation post-TAVR. However, the present study reported that a history of supraventricular arrhythmia (composite of AF, atrial flutter, and junctional rhythm) is marginally associated with the risk of PPM implantation post-TAVR (P = 0.54), which appears to be a novel finding in the existing literature. This finding in the present study seems to have been driven by a higher number of patients with AF than those with atrial flutter and junctional rhythm in the supraventricular arrhythmia group. Contrary to the existing literature, this study did not show a statistically significant increase in the risk of PPM implantation with SEVs compared with BEVs. The authors owe this to the long experience of operators with SEV in their institution. Additionally, manufacturer-assisted changes in SEV implantation techniques such as usage of cusp overlap technique and shallower implantation of TAVR valve in the left ventricular outflow tract possibly avoid the anatomical proximity with the conduction system during TAVR. The investigators reported a higher incidence of hospitalization for heart failure and nonfatal myocardial infarction (MI) at 1-year follow-up in the PPM cohort, with no difference in mortality. As this study is a retrospective review conducted in a single center, it might not accurately represent the situation in other geographical areas. Furthermore, the valves were not randomly assigned to the patients according to any predetermined criteria; rather, the assignment was decided by the multidisciplinary TAVR team. Although an equal distribution of valves in both groups was observed, the author claimed that this factor might not have affected the study results. This study supports the existing literature by demonstrating that type 2 DM and baseline right BBB are significant predictors of PPM implantation post-TAVR. For the first time, this study demonstrated a linear association between the incidence of PPM implantation post-TAVR and every 20-ms increase in duration of baseline QRS segment (above 100 ms). Thus, regardless of the side of BBB morphology, patients with a QRS duration above 100 ms are more likely to require permanent PPM implantation post-TAVR. The post-TAVR PPM cohort was also reported to have a higher rate of hospitalization for heart failure and nonfatal MI at 1-year follow-up, although no significant difference in mortality was observed. However, future studies are warranted to validate these findings, and the pathophysiological basis needs to be elucidated.

CONCLUSION

In summary, this study adds several unique predictors to the existing ones, such as a history of supraventricular arrhythmia and increased QRS duration above 100 ms. Interestingly, the use of SEV in this study did not result in a higher risk of PPM implantation compared with BEV, as previously reported. This could be due to manufacture-assisted changes in SEV implantation techniques, allowing shallow implantation depth. The present study supports the existing literature by demonstrating that type 2 DM and baseline right BBB are significant predictors of PPM implantation post-TAVR.

FOOTNOTES

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EDITORIAL

Mechanistic insights into fasting-induced autophagy in the aging heart

Hannaneh Parvaresh, Katarzyna Paczek, Md Abdul Alim Al-Bari, Nabil Eid

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Abstract

Autophagy is a prosurvival mechanism for the clearance of accumulated abnormal proteins, damaged organelles, and excessive lipids within mammalian cells. A growing body of data indicates that autophagy is reduced in aging cells. This reduction leads to various diseases, such as myocardial hypertrophy, infarction, and atherosclerosis. Recent studies in animal models of an aging heart showed that fasting-induced autophagy improved cardiac function and longevity. This improvement is related to autophagic clearance of damaged cellular components *via* either bulk or selective autophagy (such as mitophagy). In this editorial, we summarize the mechanisms of autophagy in normal and aging hearts. In addition, the protective effect of fasting-induced autophagy in cardiac aging has been highlighted.

Key Words: Aging; Autophagy; Heart; Fasting; Mitophagy

Core Tip: Autophagy is an essential mechanism for the clearance of harmful cellular components, which accumulate with age. However, autophagic machinery decreases with age, resulting in various diseases, such as cardiac hypertrophy. Recently, fasting-induced autophagy has been reported to improve cardiac function in animal models of aging *via* normalization of defective autophagic machinery. Therefore, autophagy is an important target for the prevention of cardiac pathologies in the geriatric population.

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INTRODUCTION

Cardiac aging

Improvements in treatment procedures have contributed to increased life expectancy and growth in the aged population, especially in industrialized countries[1]. Aging is associated with a structural and functional decline in multiple organs, such as the heart. A sedentary lifestyle can also accelerate the incidence of aging-related diseases, including cardiovascular disease (CVD)[2-5].

Cardiovascular aging affects both the heart and the blood circulation system through slow and progressive alterations that can result in the development of left ventricular hypertrophy, diastolic dysfunction, coronary artery disease, stroke, hypertension, atherosclerosis, atrial fibrillation, and heart failure[6-9]. Aortic valve sclerosis is a valvulopathy associated with aging and is characterized by myxomatous degeneration, collagen deposition, and progression to aortic stenosis (AS)[10]. AS is an indicator of increased CVD risk and is mainly defined as increased leaflet calcification and decreased leaflet mobility[11]. Moreover, approximately 13%-16% of elderly people suffer from aortic regurgitation[12], which results in left ventricular dilation and dysfunction over time. Another valvular change related to aging is mitral annular calcification, which usually accompanies aortic valve sclerosis[13].

The free radical theory of aging and the mitochondrial theory have been suggested to explain the cellular deterioration observed in aging and suggest that the age-related decline in mitochondrial function and structure is a major driver of cardiomyocyte senescence, which causes endothelial dysfunction, alteration in the vasculature, and/or vascular injury [14].

Cellular senescence is activated following multiple stressors, including the elevation of reactive oxygen species (ROSs); proinflammatory cytokines; and metabolic, mechanical, and chemical toxicity. Cellular senescence impairs the repair and regeneration of damaged cells in cardiovascular tissues[15-17]. Cellular senescence is characterized by genome instability, telomere attrition, and mitochondrial dysfunction[18].

Dysfunctional mitochondria produce less ATP while also generating increased amounts of ROS[19], exposing aged cardiomyocytes to high levels of oxidative stress. Autophagic and proteasomal degradation are the main mechanisms for the removal of damaged mitochondria and abnormal proteins in aged postmitotic cardiomyocytes. However, these mechanisms decline with age[20]. Eventually, when these mechanisms are unable to compensate for the accumulated cellular damage, stem-cell exhaustion and altered intercellular communication occur, further contributing to aging[18].

Autophagy in cardiac aging: Reduced autophagy accelerates cardiac aging

Autophagy activity is usually reduced with age[21]. A decrease in autophagy in the hearts of aged flies[22] and aged C57BL/6 mice (20-26 months old) has been reported[23,24].

Autophagy is a protective housekeeping mechanism critical for cellular homeostasis and survival. Long-lived, damaged, and dysfunctional organelles; misfolded proteins; and invading pathogens are eliminated through this degradation process, providing building components for cellular renovation to effectively adapt cells to stressful conditions, such as nutrient deprivation, hypoxia, or oxidative stress[25,26].

Autophagy can be selective or nonselective. Under starvation conditions, the protein and any cytoplasmic content can be non-selectively targeted for catabolic recycling to maintain cellular energy production. However, there are also selective forms of autophagy that specifically target damaged organelles. For instance, mitophagy is a type of autophagy that selectively removes damaged mitochondria[27]. Mitochondria play a substantial role in cellular functions as well as cellular death. Thus, mitochondrial dysfunction is a crucial determinant of lifespan across species[28,29].

Three types of autophagy have been recognized: Macroautophagy, microautophagy, and chaperone-mediated autophagy, all of which lead to the turnover of intracellular components *via* various mechanisms. "Autophagy" is a term that generally refers to macroautophagy, which is the most prevalent form of autophagy[30,31].

Molecular machinery of autophagy

Autophagy is initiated when several autophagy-related gene products (Atg1-Atg12) and other proteins are organized to form a phagophore. These proteins consist of at least five molecular components that mediate fusion between autophagosome (AP) and lysosomes: (1) The Atg1/unc-51-like kinase complex; (2) the Beclin 1/class III phosphatidylinositol 3-kinase (PI3K) complex; (3) Atg9 and vacuole membrane protein 1; (4) two ubiquitin-like proteins (Atg12 and Atg8/LC3)

conjugation systems; and (5) proteins that mediate fusion between APs and lysosomes[25,32].

The initial step of AP formation starts with Beclin1 (Atg6) and class III PI3K, which play crucial roles in vesicle isolation. Other Atg proteins are involved in Beclin-1-mediated formation of the Class III PI3K complex. In the next step, the AP undergoes elongation *via* two conjugation systems. First, Atg12 is conjugated to Atg5 with the help of Atg7 and Atg10[33,34], followed by the conjugation of phosphatidylethanolamine to microtubule-associated protein 1 LC3 *via* Atg4, Atg7 and Atg3. Consequently, the cytoplasmic LC3 (LC3-I) is converted to membranous (LC3-II) form, which is responsible for formation and maturation of the AP[35]. In the end, fusion of APs and lysosomes occurs with the formation of autolysosome (AL) for degradation and recycling[36].

The protein kinases mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) are implicated in the regulatory mechanisms of autophagy. Autophagy is inhibited by the mTOR. Phosphorylation of Unc-51 Like autophagy activating kinase-1 (ULK1) by AMPK is involved in autophagy promotion, although mTOR represses this process[37]. Figure 1 demonstrates the various mechanisms of autophagy in mammalian cells.

Autophagy in the heart

Accumulating evidence reveals that autophagy plays essential homeostatic roles in the heart under normal physiological conditions and during the aging process; additionally, it has an essential role in improving the immune response and reducing inflammation[38]. Consequently, any perturbations to this process in the cardiovascular system can elicit harmful effects on health.

Autophagy attenuates with age and has serious implications for heart structure and function. A decrease in autophagy causes the development of heart failure, hypertension, atherosclerosis, and ischemic heart disease[39].

Mitophagy is the selective autophagic clearance of damaged mitochondria and is crucial for the bioenergetics of the cardiovascular system; thus, mitophagy dysfunction is generally accompanied by cardiac disorders[27,40,41]. In addition, studies have suggested that autophagic degradation of damaged mitochondria decelerates cardiovascular senescence and has a positive effect on the healthy lifespan of animals[42-44].

Age-induced impairment of autophagy

Cardiomyocytes undergo age-related changes in proteostasis pathways, resulting in calcium homeostasis impairment, ROSs induction, hypertrophy and fibrosis, and eventual structural damage and diminished cardiac function. Moreover, with age, the MTOR-1 complex is significantly upregulated, and the AMPK pathway is downregulated. In addition, transcription factors involved in autophagy and lysosomal proteins such as TFEB and Forkhead transcription factor (FOXO) 3 are deactivated with advanced aging, resulting in reduced expression of autophagy genes[28-31].

Any defect in the autophagy process accelerates aging; likewise, aging is suppressed when autophagy is stimulated. Deletion of atg5, a cardiac-specific autophagy-related gene, in adult mice leads to an accelerated aging phenotype, including the development of cardiac hypertrophy, left ventricular dilatation, and contractile dysfunction[20,45].

Mutations in the atg4c gene increase the risk of heart disease in elderly patients and eventually death[46]. Cardiomyocyte-specific deletion of glycogen synthase kinase-3 in mice reduced basal autophagy levels and accelerated cardiac aging[47]. Dysfunction of autophagy with age slows the turnover of damaged proteasomes and contributes to age-associated CVD and cardiomyocyte senescence[48]. Mitophagy is impaired in aged mice, and mitophagy induction improves mitochondrial function and reduces arterial wall stiffness[49].

Acyl-coenzyme A binding protein (ACBP), which is encoded by a diazepambinding inhibitor (DBI), acts as an extracellular feedback inhibitor of autophagy[50]. It appears that high ACBP/DBI values correlate with future cardiovascular events (such as heart surgery, myocardial infarction, and stroke), suggesting that ACBP/DBI is indeed a biomarker of biological aging[39].

Mechanisms underlying age-related cardiac remodeling: involvement of autophagy

Although there are many potential causes underlying the decline in cardiovascular function with age, a major determinant of the aging process is likely the progressive loss of quality control due to reduced autophagy.

Hyperactivation of mTOR and reduced AMPK activity[51] in old age can directly inhibit autophagy by inactivating the pro-autophagic ULK1 complex[52], contributing to the downregulation of autophagy activity.

It is conceivable that exposure to excessive ROS during aging promotes the accumulation of oxidized proteins, mitochondrial DNA mutations, and protein misfolding[53]. Additionally, several cytosolic and mitochondrion-localized proteins involved in autophagy regulation become dysfunctional, thus contributing to abnormal mitochondrial turnover and the removal of damaged mitochondria[54]. This chain of events results in impaired autophagy due to exhaustion of the aged autophagic machinery.

In addition, it has been proposed that a hallmark of aging in postmitotic cells, such as cardiomyocytes, is the aggregation of nondegradable structures inside lysosomes, termed lipofuscin, which impedes lysosomal function and therefore can likely inhibit autophagy[55].

It has been shown that intracellular calcium has a key regulatory effect on cardiomyocyte autophagy. Inositol 1,4,5-trisphosphate (IP3) receptors mediate calcium release and transfer to mitochondria. This process inhibits autophagy by suppressing AMPK activation[56]. Since evidence has shown that IP3 receptors are upregulated in the aged, hypertrophied, and failing myocardium of rodents[57] and humans[58], increased IP3 receptor-mediated calcium signaling likely exacerbates autophagy in the aging heart[59].

FOXO and sirtuin proteins are also major metabolic regulators that mediate age-related vascular changes, particularly endothelial dysfunction[9].

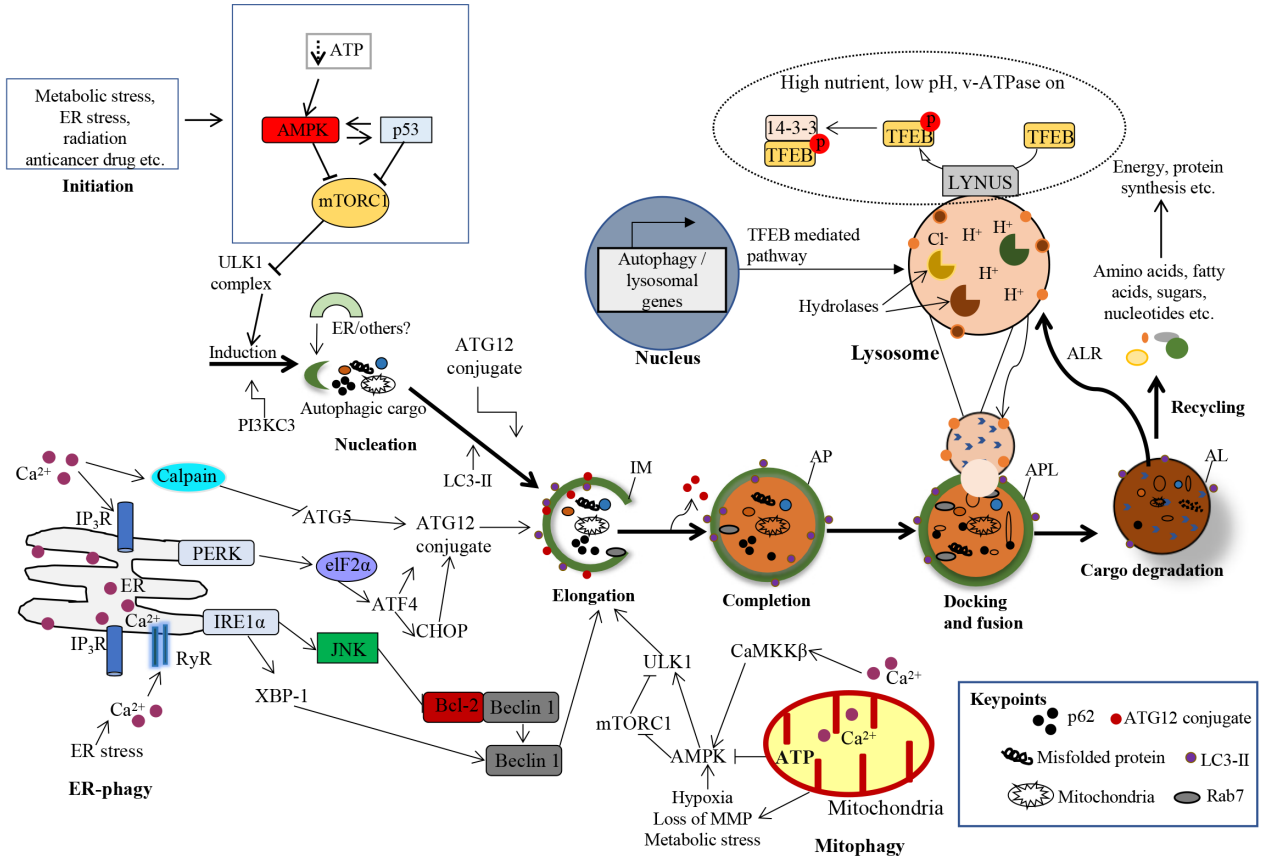

Figure 1 Molecular mechanisms of various stages of autophagy. Autophagy is activated in response to various cellular stresses and is triggered by a decrease in rapamycin complex 1 (mTORC1) activity due to the activation of AMP-activated protein kinase (AMPK) or p53 signaling. mTORC1 suppresses the activity of Unc-51-like autophagy activating kinase 1 (ULK1) complex. Therefore, inhibition of mTORC1 causes the initialization of the ULK1-mediated formation of the isolation (autophagosomal) membrane (IM) in association with the class III phosphatidylinositide 3-kinase complex. The IM expands into an autophagosome (AP) with a double-layer membrane, which can engulf any cellular component, including proteins, damaged organelles, and lipid droplets. The AP merges with the lysosome (*via* LAMP-1, 2), forming autophagolysosome or autolysosome (AL), and resulting in the degradation of the cargo by cathepsins and the autophagic lysosome reformation. The nucleation, elongation and maturation of the IM are dependent on two ubiquitin-like conjugation systems (ATG12 and ATG8), which involve multiple autophagy proteins, including Beclin1, ATG5, ATG16 and MT-associated protein 1 LC3. The AL provides an acidic milieu for hydrolytic enzymes to digest the engulfed components. Nuclear localization of transcription factor EB is critical to the formation of lysosomes and to the enhanced expression of autophagy proteins. Importantly, autophagy could be selective of mitochondria (mitophagy) or ER (ER-phagy). However, the detailed mechanisms of this selected autophagy are beyond the scope of this study[28]. AMPK: AMP-activated protein kinase; PI3KC3: Phosphatidylinositide 3-kinase complex; APL: Autophagolysosome; AL: Autolysosome; ALR: Autophagic lysosome reformation; IM: Isolation (autophagosomal) membrane; TFEB: Transcription factor EB; mTORC1: Rapamycin complex 1. Citation: Al-Bari MAA, Ito Y, Ahmed S, Radwan N, Ahmed HS, Eid N. Targeting Autophagy with Natural Products as a Potential Therapeutic Approach for Cancer. *Int J Mol Sci* 2021; 22: 9807. Copyright ©The Author(s) 2021. Published by MDPI.

Dietary activation of autophagy in the heart via caloric restriction or fasting

Dietary interventions involving caloric restriction (CR) and fasting are among several stress stimuli that can induce autophagy in response to food deprivation[60-62]. CR was defined as a reduction in caloric intake using a diet containing adequate amounts of protein, vitamins, and minerals[63]. CR is a potent inducer of autophagy in the heart[64], and its positive impacts on health and lifespan in various model organisms, primates and humans have been studied[65-67]. CR is the most potent physiological stimulus of autophagy and ameliorates cardiac dysfunction (systolic and diastolic) and attenuates myocardial hypertrophy and fibrosis at the cardiomyocyte level. CR reduces mitochondrial damage, lipid accumulation, oxidative stress, apoptosis, telomere shortening, senescence marker levels, and circulating proinflammatory cytokine levels[68].

Autophagy plays an important role in CR-mediated longevity[69] *via* clearance of damaged mitochondria, reduction of oxidative stress, improvement of insulin sensitivity and suppression of inflammatory responses[61,62].

Short-term CR for 10 wk in mice rejuvenated symptoms of the aging heart, such as significant improvement in diastolic function and regression of age-dependent cardiac hypertrophy[70]. Moreover, CR reversed age-dependent cardiac proteome remodeling and mitigated oxidative damage and ubiquitination in these mice.

In aged animals, hypertrophy, and fibrosis, as well as systolic and diastolic dysfunctions, improved after CR[68,71]. The beneficial effects of CR observed in cardiomyocytes include enhanced mitochondrial fitness and reduced oxidative stress, apoptotic cell death, inflammation, and importantly, senescence[68]. In vasculature, CR helps improve endothelial cell function and attenuates collagen deposition, elastin remodeling, and oxidative stress; as a result, CR reduces arterial stiffness[72]. Another study revealed improvements in numerous markers of cardiovascular health in humans after short-

term periodic fasting, which is also a pro-autophagic dietary regimen[73].

Intermittent fasting (IF) has attracted the attention of researchers as a dietary intervention associated with better compliance and long-term adherence than CR in recent years[74]. IF consists of regular cycles of times with no or minimal caloric intake interrupted by periods of normal food consumption. Alternate day fasting delays cardiac aging in rats, as determined by reduced hypertrophy and fibrosis[75,76] and extended lifespan[77]. The advantageous effects of life-long alternate-day fasting were attributed to reduced phosphoinositide 3-kinase signaling, which was associated with reduced myocardial collagen deposition, oxidative stress, inflammatory markers, and B-type natriuretic peptide levels[75,78].

A fasting-mimicking diet (FMD) is considered another form of dietary intervention in which individuals consume low amounts of calories, sugars, and proteins but high amounts of unsaturated fats. Studies of FMD effects in mice have shown improved cognitive function and a rejuvenated immune system, in addition to promoting lifespan and health factors by reducing cancer incidence, obesity, and inflammation[79]. FMD was investigated in humans, and the findings showed reduced age-related CVD risk factors, including reduced blood pressure, body mass index, fasting glucose, and inflammation, as well as an improved lipid profile[80].

The efficacy of fasting on autophagy in the heart was assessed in male FBN rats by randomly dividing them into different groups of equal amounts of protein, vitamin, and mineral intake, while the CR groups received 20% less food from a 125% fortified diet for six weeks. Additionally, in addition to one simple CR group, two other CR groups were given 5 or 50 mg/kg/day resveratrol. Compared with AL group, a marked reduction of expression of p62 (autophagy substrate) in the left ventricle was observed in the CR and Resv-50 rats, indicating enhanced cardiac autophagy in the CR group. Similarly, a significant overexpression of Beclin-1 was found in the Resv-50 and CR animals. The CR + Resv-50 group of rats showed dramatically attenuated doxorubicin-induced damage, which can be due to enhanced autophagy [81]. Another study investigated the autophagic response of CR on diabetic rat hearts. Diabetic and nondiabetic rats were exposed to a CR diet (30% energy reduction) for 32 wk. Compared with those of diabetic AL rats, diabetic CR rats exhibited an increase in the hepatic and cardiac LC3-II/LC3-I ratio (indicating enhanced autophagy)[82].

A high-fat diet (HFD) (fat 60% kcal/100 kcal fat) was given to the FVBN male mice for 4-20 wk, after which they were subjected to overnight fasting to study the mechanisms of fasting-induced autophagy in the fatty mice heart. After 24 h of fasting, there was a significant conversion of LC3-I conversion to LC3-II in lean mice heart but was not associated with a change in diet-induced obesity (DIO) mice. Furthermore, fasting suppressed mTOR in both lean and DIO mice, as indicated by increased AMPK phosphorylation and enhanced dephosphorylation of S6. Interestingly, mTOR inhibition was greater in obese mice. Taken together, these findings indicate that fasting activates autophagy in the hearts of lean mice[83].

Godar *et al*[84] investigated the impacts of IF on the autophagy-lysosome machinery in the myocardium. The authors studied the effects of fasting after 24 h, followed by 24 h of refeeding or 24 and 48 h of fasting for six weeks. The AP abundance increased dramatically after 48 h of fasting. Treatment with chloroquine (an autophagy inhibitor) was associated with a significant increase in LC3-II and SQSTM1/p62 after 24 h of fasting but not in fed mice. Thus, fasting induces autophagy in cardiomyocytes; however, autophagy returns to basal levels on gestational days.

The effects of IF on right ventricular (RV) function in a rat model of pulmonary arterial hypertension (characterized by RV mitochondrial dysfunction and resultant lipotoxicity and microbiome dysbiosis) were explored. IF improved RV systolic and diastolic function and decreased RV cardiomyocyte hypertrophy and fibrosis, which was likely mediated by autophagy activation[85]. These protective effects could be related to autophagy activation.

Recent findings from studies also show that cardiometabolic parameters (*e.g.*, adiposity, insulin sensitivity, and cardiac function) can be influenced by the time of day at which food is consumed[86]. To test the hypothesis that fasting during the sleep period elicits beneficial adaptation effects on cardiac function, wild-type mice were fasted for 24 h or for either the 12-h light/sleep phase or the 12-h dark/awake phase. Repression of myocardial p-mTOR and protein synthesis occurred during the dark phase; both parameters remained elevated in the hearts of fasted mice during the light phase. In contrast, markers of autophagy (*e.g.*, LC3-II) exhibited peak responses to fasting during the light phase. Collectively, these data show that the responsiveness of the heart to fasting is temporally partitioned[86].

IF alleviated HFD-induced obesity cardiomyopathy in male C57BL/6J mice by improving cardiac functional and structural impairment and serum lipid metabolic disorders induced by HFD through decreasing lipid deposition, apoptosis and m6A methylation in the heart[87].

Researchers compared the effects of alternate day fasting on elderly (aged 24 months) and young (aged 6 months) male rats. The results of this study indicated that alternate day fasting protected against inflammation and fibrosis in the heart during aging by inhibiting oxidative damage and NF-κB activation[76]. Other studies have shown that fasting preconditioning activates AMPK, induces autophagy, decreases ROS levels, and inhibits NF-κB signaling in the cardiac tissues of rats[88]. In addition, compared with fasting controls, IF in human subjects resulted in autophagy upregulation and reduced levels of proinflammatory cytokines, indicating the protective effects of fasting on the vascular system. This effect is most likely mediated by the anti-inflammatory effects of autophagy[89]. We investigated fasting-induced autophagy among large groups of population in the UAE during Ramadan (the holy Islamic fasting month). The results of this study will be published shortly in specific journals. Furthermore, these results were presented in part at the Sharjah First International Conference on Fasting, February 28-29, 2024, at Sharjah University, United Arab Emirates[90].

CONCLUSION

In conclusion, fasting-induced autophagy is beneficial for ensuring cardiac function, preventing disease, and improving longevity. However, additional studies *in vivo* in animal models of cardiac aging are needed to determine the specific

molecular mechanisms involved in normalizing autophagy by fasting. In addition, large-scale studies on humans are needed. Ramadan fasting, a type of IF (a common religious practice) in Islamic countries, could be investigated in large groups of geriatric people with or without cardiac diseases. Importantly, further *in vitro* research should be directed toward human cardiac tissues to better understand the molecular mechanisms of fasting-induced autophagy and its beneficial effects on longevity pathways and prevention of CVDs.

FOOTNOTES

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EDITORIAL

Interest of thoracic ultrasound after cardiac surgery or interventional cardiology

Martin Boussuges, Philippe Blanc, Fabienne Bregeon, Alain Boussuges

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Abstract

Thoracic ultrasound has attracted much interest in detecting pleural effusion or pulmonary consolidation after cardiac surgery. In 2016, Trovato reported, in the *World Journal of Cardiology*, the interest of using, in addition to echocardiography, thoracic ultrasound. In this editorial, we highlight the value of assessing diaphragm function after cardiac surgery and interventional cardiology procedures. Various factors are able to impair diaphragm function after such interventions. Diaphragm motion may be decreased by chest pain secondary to sternotomy, pleural effusion or impaired muscle function. Hemidiaphragmatic paralysis may be secondary to phrenic nerve damage complicating cardiac surgery or atrial fibrillation ablation. Diagnosis may be delayed. Indeed, respiratory troubles induced by diaphragm dysfunction are frequently attributed to pre-existing heart disease or pulmonary complications secondary to surgery. In addition, elevated hemidiaphragm secondary to diaphragm dysfunction is sometimes not observed on chest X-ray performed in supine position in the intensive care unit. Analysis of diaphragm function by ultrasound during the recovery period appears essential. Both hemidiaphragms can be studied by two complementary ultrasound methods. The mobility of each hemidiaphragms is

measured by M-mode ultrasonography. In addition, recording the percentage of inspiratory thickening provides important information about the quality of muscle function. These two approaches make it possible to detect hemidiaphragm paralysis or dysfunction. Such a diagnosis is important because persistent diaphragm dysfunction after cardiac surgery has been shown to be associated with adverse respiratory outcome. Early respiratory physiotherapy is able to improve respiratory function through strengthening of the inspiratory muscles *i.e.* diaphragm and accessory inspiratory muscles.

Key Words: Ultrasonography; Diaphragm; Phrenic nerve; Hemidiaphragm; Thickening fraction; Physiotherapy

Core Tip: Diaphragm dysfunction can be secondary to cardiac surgery or atrial fibrillation ablation *via* phrenic nerve injury. In patients with comorbidities such as obesity and cardiac or respiratory diseases, unilateral diaphragm paralysis may be poorly tolerated. Diaphragm ultrasound is the most appropriate tool for early diagnosis.

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INTRODUCTION

The diaphragm is the main inspiratory muscle and contributes to 60%-70% of the total ventilation at rest. It is a musculotendinous structure (2-4 mm) with a central tendinous portion and a peripheral muscular portion. It includes two hemidiaphragms: The right with a dome positioned higher than the left. Motor innervation of the diaphragm comes from two phrenic nerves formed from the C3-C5 nerve roots. The left and right phrenic nerves cross the neck and thorax between the mediastinal surface of the parietal pleura and the fibrous pericardium to reach the corresponding hemidiaphragm. The left phrenic nerve is close to the subclavian artery and passes in front of the pericardial sac of the left ventricle. The right phrenic nerve runs superficial to the anterior scalene muscle and right subclavian artery and passes over the right atrium and right ventricle. Arterial blood flow to the diaphragm comes from collaterals of the internal mammary artery, collaterals of the abdominal aorta, and vessels originating from intercostal arteries. During contraction, the diaphragm shortens and moves caudally, leading to an expansion of the thoracic cavity. This phenomenon increases abdominal pressure and decreases alveolar pressure below atmospheric pressure resulting in airflow into the lungs[1]. Various procedures used in patients with heart diseases can impair diaphragmatic function. Diaphragm dysfunction was exceptionally reported after central vein cannulation and pacemaker battery change[2,3]. In contrast, this was regularly observed after cardiac surgery and atrial fibrillation ablation[4,5]. We underline in this editorial the interest of assessing diaphragm function after such procedures.

DIAPHRAGM DYSFUNCTION AFTER CARDIAC SURGERY

Impaired diaphragmatic function was reported in a significant percentage of patients after cardiac surgery. Depending on the detection method and the delay from the surgery, diaphragm dysfunction has been variously estimated: 21% for Dimopoulou *et al*[6], 38% for Bruni *et al*[7], 46% for DeVita *et al*[8], and 75% for Moury *et al*[9]. In a recent observational study[10], symptomatic diaphragm dysfunction was found in 272 out of 3577 patients (7.6%). In our experience (unpublished study), the percentage of diaphragm dysfunction in patients admitted in a cardiac rehabilitation center after cardiac surgery was 15% (39 out of 264 patients). Diaphragm ultrasound detected weakness in 10% of cases and hemidiaphragm paralysis in 5%. Various mechanisms may explain diaphragm dysfunction in these patients. Diaphragmatic motion may be reduced by chest pain secondary to sternotomy, pleural effusion or impaired muscle function[11]. Furthermore, phrenic nerve damage is a well-known, complication of cardiac surgery. It has been shown that the phrenic nerve can be injured through thermal lesions secondary to topical cardiac cooling with ice-cold solution in the pericardium. To reduce the risk of injury, the use of insulation pads placed between the heart and the left pericardium has been proposed to protect the phrenic nerve from hypothermic surgery[12,13]. The use of warm-blood cardioplegia has also demonstrated its interest in reducing the risk of diaphragm paralysis[14]. However, other mechanisms may explain phrenic nerve damage during cardiac surgery. During coronary artery bypass grafting, phrenic nerve injury may be secondary to direct surgical trauma during dissection of the internal mammary artery (IMA) or indirect injury due to stretching by the sternal retractor[15]. In addition, IMA harvesting may result in decreased blood flow to the phrenic nerve through ligation of some branches such as the pericardiacophrenic artery. These mechanisms could explain the increased risk of phrenic nerve dysfunction in patiens who underwent IMA harvesting compared to the group that did

not undergo IMA harvesting[16]. Inflammation secondary to cardiopulmonary bypass surgery may also be involved in the development of diaphragm dysfunction *via* significant production of reactive oxygen species and proinflammatory and pro-apoptotic signaling pathways activation[17].

DIAPHRAGM DYSFUNCTION INDUCED BY ATRIAL FIBRILLATION ABLATION

Minimally invasive treatment of atrial fibrillation appeared in the late 1990s and is now widely used as a safe alternative to antiarrhythmic drugs. Procedures have improved while the number of patients eligible for such treatments has increased.

The most commonly used fibrillation ablation techniques are thermal energy sources with cold (cryoablation around -55°C) or heat (radiofrequency heating around +55°C). Due to the short distance between the ablation site and the phrenic nerve, thermal injury is not uncommon (mainly on the right side) resulting in diaphragmatic dysfunction. Electromyography-guided phrenic nerve monitoring has been proposed to prevent serious phrenic nerve injury during superior vena cava isolation. Detection of reduced contraction of the diaphragm during the procedure leads to the change in the ablation trajectory[18,19]. Despite the development of prevention strategies, new sophisticated devices and experienced operators, phrenic nerve injuries remain a possible outcome of up to 15% for early transient paralysis of the diaphragm, which usually disappears at the end of the procedure. Persistent symptomatic diaphragmatic paralysis is rare (reported in less than 1% of cases). A large population study from the "Netherlands Heart Registration" focused on persistent diaphragm dysfunction (> 24 h) among 7433 procedures performed between 2016 and 2017[20]. The incidence of persistent diaphragm paralysis was 0.7%, the risk being increased in womens. In a recent prospective, multicenter study conducted in 375 subjects comparing cryoballoon to radiofrequency, data showed that cryoablation has the highest level of phrenic nerve injury with 7.20% transient paralysis compared to 3.20% for radiofrequency[21]. Today, a new non-thermal energy modality, called pulse field ablation (PFA) therapy has emerged. PFA therapy involves the application of high voltage levels to tissues in order to induce hyperpermeabilization of cell membranes and cell death through the mechanism of irreversible electroporation. This procedure is believed to be more selective than thermal procedures and may be less damaging to the phrenic nerve[22].

DETECTION OF DIAPHRAGM DYSFUNCTION BY ULTRASOUND

Chest ultrasound has gained much interest in detecting pleural effusion and pulmonary consolidation or edema after cardiac surgery. In 2016, Trovato[23] reported, in the *World Journal of Cardiology*, the interest of using, in addition to echocardiography, thoracic ultrasound for cardiologists. Since the frequency of diaphragm dysfunction is significant after cardiac surgery and atrial fibrillation ablation, the ultrasound analysis of diaphragm function is important.

Ultrasound methods

The two hemidiaphragms can be studied by two complementary ultrasound methods. Diaphragm mobility can be recorded by a sub-costal approach using a cardiac probe[24-26]. Excursions of both hemidiaphragms are measured by M-mode ultrasonography during various volitional maneuvers such as quiet breathing (Figure 1) voluntary sniffing and deep inspiration. In addition, it is useful to measure the thickness changes at the zone of apposition during breathing (Figure 2, Video) by a superficial probe using B-mode[27]. The percentage of thickening during inspiration provides important information about the quality of the muscle function of the diaphragm[28]. These two approaches make it possible to detect paralysis or weakness of hemidiaphragm.

Diagnosis of hemidiaphragm paralysis

In patients with unilateral diaphragmatic paralysis, hemidiaphragm movement is absent or paradoxical when breathing at rest[29,30]. During voluntary sniffing, a paradoxical movement (*i.e.* cranial) of the hemidiaphragm (Figure 3) is reported using M-mode ultrasonography[29,30]. During deep inspiration, a biphasic movement can be recorded with a first paradoxical movement followed by a cranio-caudal excursion[30]. The study of inspiratory thickening is important to support the results of the diaphragm excursion analysis. The failure of the paralyzed diaphragm to thicken results in a decrease in the thickening fraction (TF) calculated as the difference between the diaphragm thickness measured at the end of maximal inspiration and the diaphragm thickness at the end of expiration divided by the diaphragm thickness at the end of expiration×100. No significant thickening (TF less than 20%) or thinning of paralyzed hemidiaphragm is observed [31].

Diagnosis of diaphragm weakness

In some patients, diaphragm dysfunction occurred without complete paralysis i.e. diaphragm weakness. Diaphragm weakness can be detected using normal values of excursions and thickening previously determined from the study of healthy controls[32,33]. First, no criteria for complete paralysis should be recorded by ultrasound: No paradoxical movement should be observed during the various maneuvers and the TF should be greater than 20%. Secondly, excursions during deep inspiration should be below the lower limit of normal (LLN) depending on the side and gender according to the reference values[32].

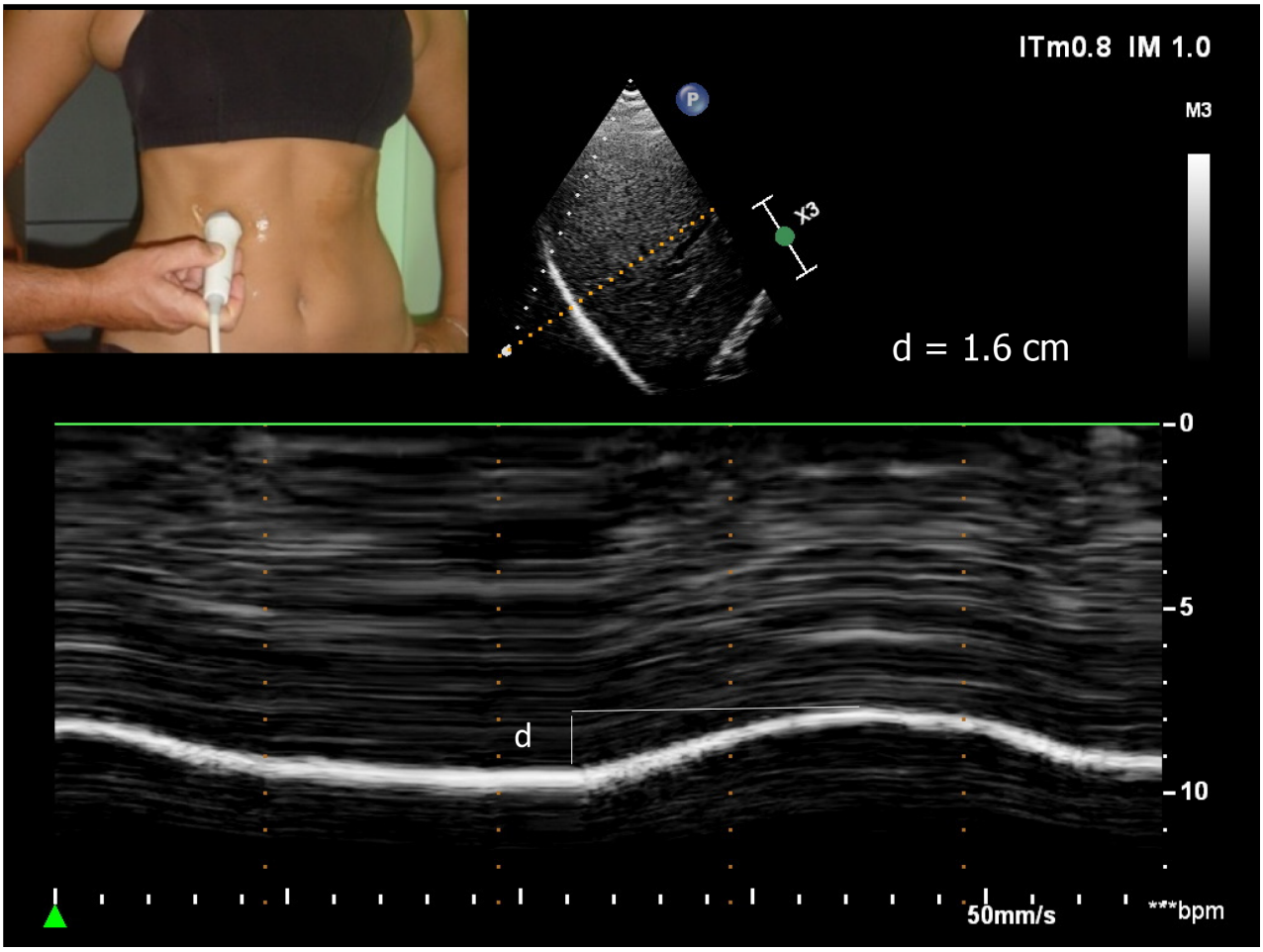

Figure 1 Diaphragmatic motion recorded by M-mode ultrasonography during quiet breathing d: Measurement of diaphragm excursion = 1.6 cm.

Severity of the weakness may be based on the decrease of the excursion from the lower limit of the normal and the measurement of the thickening fraction[34].

Patients can be classified as follows: (1) Mild hemidiaphragm dysfunction when the excursion is slightly below the lower limit of normal during deep inspiration (excursion > LLN – 1 cm) and a normal or slightly decreased thickening fraction (> 40%); (2) Severe hemidiaphragm dysfunction in patients with a marked decrease in hemidiaphragm excursion (< LLN – 1 cm) associated with a marked decrease in thickening fraction (< 40%).

CLINICAL CONSEQUENCES OF DIAPHRAGM DYSFUNCTION

The complete loss of function of one hemidiaphragm leads to a restrictive syndrome with a decrease in vital capacity of about 25%. After unilateral diaphragm paralysis, a compensatory increase in neural drive to the functioning hemidiaphragm was demonstrated[35], leading to large excursions to the healthy side[36]. The activity of accessory inspiratory muscles is also increased[37].

Disorders induced by diaphragm paralysis can take a wide variety of clinical pictures[38]. Bilateral diaphragm paralysis leads to respiratory failure most often requiring ventilatory support. In case of unilateral hemidiaphragm dysfunction, the compensatory mechanism is effective in patients without severe comorbidities and clinical disorders remain weak. Most often, dyspnea is mild and appears during exercise or in supine position. In contrast, in patients with obesity or with severe pre-existing cardiac or respiratory disease, the impairment in respiratory function leads to clinical disorders that can reach respiratory failure. After cardiac surgery, diaphragm dysfunction is associated with a risk of postoperative pneumonia, mechanical ventilation (non-invasive and invasive ventilation) and increased length of stay in the intensive care unit[39].

Diagnosis may be delayed, indeed, respiratory disorders induced by diaphragm dysfunction are frequently attributed to pre-existing heart disease or pulmonary complications secondary to the procedure. Furthermore, elevated hemidiaphragm secondary to diaphragm dysfunction is sometimes not seen on chest X-ray perfomed in supine position in the intensive care unit. Diagnosis is sometimes made later, for exemple when admitted to a cardiac rehabilitation center[40]. It remains important because persistent diaphragm dysfunction is associated with late respiratory complications[39].

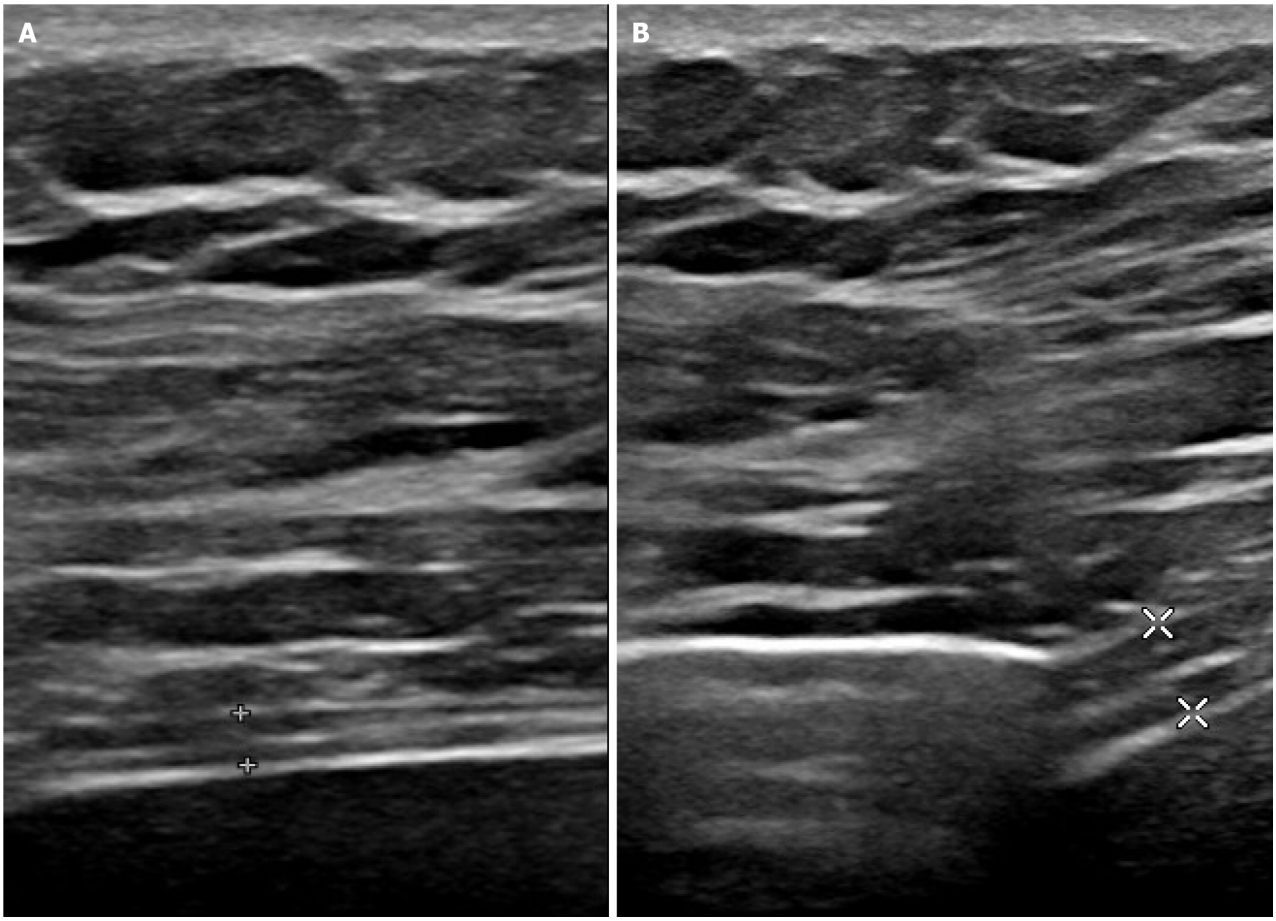

Figure 2 Measurement of thickening fraction using B mode ultrasonography. A: End of expiration (1.7 mm); B: End of maximal inspiration (3.8 mm). Measurement of diaphragm thickness at expiration (1.7 mm), and at deep inspiration (3.8 mm) – here thickening fraction = (3.8–1.7)/ 1.7 = 123%.

In addition, high frequency of obstructive sleep apnea (OSA) has been reported in patients with diaphragm dysfunction[41]. It is therefore important to seek sleep apnea in these patients because it is recognized that OSA is a risk factor for cardiovascular disease[42].

Less frequently, right-to-left shunt was associated with right hemidiaphragm paralysis[43,44]. The mechanism was a redirection of blood flow from the inferior vena cava directly through the patent foramen ovale secondary to a distortion of cardiac anatomy induced by hemidiaphragmatic paralysis. In patients with hypoxemia, closure of the patent foramen ovale may be necessary[45].

TREATMENT

Treatment of diaphragm dysfunction is mainly based on respiratory physiotherapy. In unilateral diaphragm paralysis, inspiratory muscle training improves clinical condition through strengthening of healthy hemidiaphragm and accessory inspiratory muscles[46,47]. The long-term prognosis of hemidiaphragm paralysis is usually favorable with a decrease in respiratory disorders due either to the adaptation of healthy inspiratory muscles, or to the spontaneous improvement of diaphragmatic function.

In a population of patients with diaphragm paralysis of various etiologies, Gayan-Ramirez *et al*[48] reported functional recovery in the first year after diagnosis in 43% of cases and in two years in 52% of cases. After pediatric cardiac surgery complicated by phrenic nerve injury, recovery was documented in about 55% of children over a median follow-up period of 353 d[49]. In patients with hemidiaphragm paralysis secondary to atrial fibrillation ablation, after a mean follow-up of 3 years, 66% of the study population had complete recovery, 17% had partial recovery, and 17% had no recovery[5]. The average recovery time was 4 months after injury. In cases of poor tolerance of diaphragm paralysis, mechanical ventilatory support such as non-invasive ventilation may be required[50]. In patients with hemidiaphragm paralysis having no recovery and suffering from disabling respiratory disorders, diaphragm plication can be proposed. Surgery is performed through open thoracotomy or video-assisted thoracoscopy[51]. Plication of hemidiaphragm reduces dyspnea, and increases both lung function test and exercise capacity[52,53]. The improvement in quality of life persists for a long time. It is therefore recommended to consider diaphragm plication in patients with unilateral diaphragm paralysis who have an impairment of quality of life secondary to chronic dyspnea.

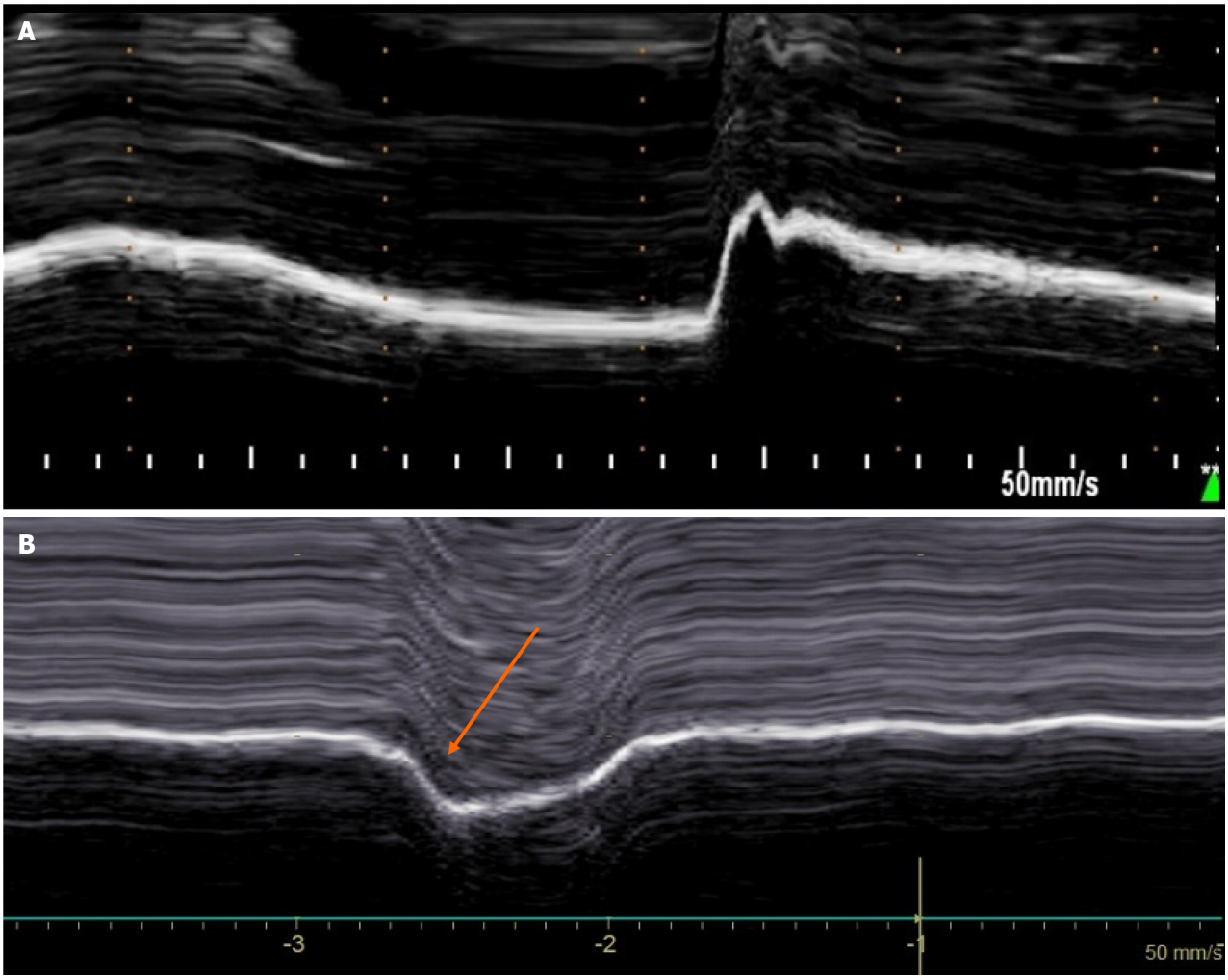

Figure 3 Diaphragmatic motion recorded by M-mode ultrasonography during voluntary sniffing. A: Normal motion; B: Paradoxical movement (arrow) in patient with hemidiaphragm paralysis.

CONCLUSION

Cardiac surgery and atrial fibrillation ablation can damage the phrenic nerve causing diaphragm dysfunction. Clinical disorders can be wrongly attributed to pre-existing heart or respiratory diseases, so systematic evaluation of diaphragm function by ultrasound after a procedure at risk of phrenic nerve injury is particularly useful. In such patients, respiratory physiotherapy is able to improve respiratory function through the strengthening of inspiratory muscles. Repeated ultrasound examinations should be performed to monitor potential recovery of diaphragm function. In case of lack of recovery and persistent disabling respiratory disorders, diaphragm plication can be proposed.

FOOTNOTES

Author contributions: The article project was designed by Boussuges A; Boussuges M, Blanc P, Bregeon F, and Boussuges A contributed equally to the article by conducting a literature review, drafting the article, making critical revisions and approving the final version.

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MINIREVIEWS

Cardiac arrest, stony heart, and cardiopulmonary resuscitation: An updated revisit

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Abstract

The post-resuscitation period is recognized as the main predictor of cardiopulmonary resuscitation (CPR) outcomes. The first description of post-resuscitation syndrome and stony heart was published over 50 years ago. Major manifestations may include but are not limited to, persistent precipitating pathology, systemic ischemia/reperfusion response, post-cardiac arrest brain injury, and finally, post-cardiac arrest myocardial dysfunction (PAMD) after successful resuscitation. Why do some patients initially survive successful resuscitation, and others do not? Also, why does the myocardium response vary after resuscitation? These questions have kept scientists busy for several decades since the first successful resuscitation was described. By modifying the conventional modalities of resuscitation together with new promising agents, rescuers will be able to salvage the jeopardized post-resuscitation myocardium and prevent its progression to a dismal, stony heart. Community awareness and staff education are crucial for shortening the resuscitation time and improving short- and long-term outcomes. Awareness of these components before and early after the restoration of circulation will enhance the resuscitation outcomes. This review extensively addresses the underlying pathophysiology, management, and outcomes of post-resuscitation syndrome. The pattern, management, and outcome of PAMD and post-cardiac arrest shock are different based on many factors, including in-hospital cardiac arrest *vs* out-of-hospital cardiac arrest (OHCA), witnessed *vs* unwitnessed cardiac arrest, the underlying cause of arrest, the duration, and protocol used for CPR. Although restoring spontaneous circulation is a vital sign, it should not be the end of the game or lone primary outcome; it calls for better understanding and aggressive multi-disciplinary interventions and care. The

development of stony heart post-CPR and OHCA remain the main challenges in emergency and critical care medicine.

Key Words: Cardiac arrest; Out-of-hospital cardiac arrest; In-hospital cardiac arrest; Post-resuscitation; Myocardial dysfunction; Cardiopulmonary resuscitation; Stony heart

Core Tip: Despite the advances in emergency and critical care management, the outcomes post-cardiac arrest (in-hospital or out-of-hospital) remain challenging. Post-cardiac arrest myocardial dysfunction and circulatory failure are the main predictors of cardiopulmonary resuscitation outcomes. The pattern, management, and outcome of these predictors differ between subjects based on many factors. A better understanding of the pathophysiology of these two predictors is of utmost importance to achieve better post-cardiac arrest outcomes. Although restoring spontaneous circulation is a vital sign, it should not be the end of the game or lone primary outcome; it calls for aggressive multi-disciplinary interventions and care.

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INTRODUCTION

Cardiac arrest and cardiopulmonary resuscitation: An estimated 17.7 million people died due to cardiovascular disease (CVD), and this number represents about 31% of the global deaths[1]. Sudden cardiac arrest (SCD) occurs in more than 800000 patients per year[2]. More than 100000 SCD have been noticed among the American female population, indicating this is a significant issue in health care[3]. It has been shown that outcomes after cardiac arrest improve significantly when cardiopulmonary resuscitation (CPR) is performed promptly at a high-quality level[4]. Interestingly, remarkable regional and interindividual differences exist in the survival rates of cardiac arrest incidence and outcomes[5,6]. However, the incidence of SCD depends on its definition[7]. The quality of CPR has changed over time, and accordingly, the likelihood of restoration of spontaneous circulation (ROSC) and survival after cardiac arrest is expected to be improved[8]. Despite advances in CPR, poor survival rates remain challenging, even with the ROSC. Almost one-tenth and one-quarter of the out-of-hospital (OHCA) and in-hospital (IHCA) cardiac arrests survive hospital discharge[9]. The survival rate after IHCA is approximately twice that of OHCA, as the earlier ROSC is achieved in almost 50% of the IHCA [10,11]. The post-resuscitation period is the main predictor of CPR outcomes, as during this period, a multi-systemic insult phenomenon called post-cardiac arrest syndrome (PCAS) occurs, including four elements of variable degrees and intensity[12,13]. This phenomenon may happen in five phases post-ROSC in terms of immediate (20 min), early (within 12 h), intermediate (within 72 h), recovery (after three days), and rehabilitation phase[14,15]. These elements include hypoxic brain injury, systemic ischemia–reperfusion injury (IRI), myocardial dysfunction, and the persistent underlying cause of cardiac arrest[12,13]. This phenomenon results from initial systemic ischemia and no-flow local circulations followed by reperfusion injury during resuscitation and the ROSC. During cardiac arrest, the brain and cardiac injuries occur and play a critical role in the patient's survival and quality of life. Secondary brain injury could lead to late death in approximately two-thirds and one-quarter of patients who sustained OHCA and IHCA, respectively. Whereas early death, which may occur within the first three days, is mainly related to post-cardiac arrest myocardial dysfunction (PAMD)[16]. PAMD is a commonly reversible sort of myocardial stunning that often responds to small doses of inotropes. Therefore, if detected and treated early, PAMD could reach its base level eight hours following ROSC, potentially improving on the first day and normalizing by the third day. Otherwise, in addition to the systemic IRI and vasodilation, multiorgan failure takes place and leads to death. Such IRI results in oxidative stress that causes cardiac injury and ventricular dysfunction, which peaks at 8-24 h after cardiac arrest. The systematic inflammatory response of IRI leads to several detrimental sequences such as vasoplegia, microcirculatory dysfunction, hypercoagulability, relative adrenal and Vasopressin insufficiency, immunosuppression, hyperglycemia, transient bacteremia, and eventually multiorgan failure[13]. The persistence of tissue hypoxia during cardiac arrest leads to the activation of immune, complement, and coagulation pathways. It ends up with systemic inflammatory response syndrome (SIRS) within three hours post-resuscitation[9]. Furthermore, the body organs' metabolism switches to anaerobic status due to the minimal cellular reserve and insufficient tissue oxygen delivery. The latter condition, in addition to the ongoing myocardial stunning (or PAMD), activated dysfunctional vascular endothelium, and microcirculatory failure, exaggerates the hemodynamic instability and organ failure[9].

PAMD DIAGNOSIS

The diagnosis of PAMD requires the presence of low cardiac index (CI), decreased left ventricular systolic and diastolic function, and right ventricular dysfunction after cardiac arrest and ROSC. Studies in patients with post-cardiac arrest provided evidence of reduced left ventricular ejection fraction (LVEF) within the first day after ROSC in two-thirds or more of cases[17-19]. Vasopressor dependence or the presence of shock is not an indicator of PAMD after cardiac arrest, as each or both may arise from vascular dysfunction in the absence of myocardial involvement[20]. On the other hand, the presence of myocardial dysfunction after cardiac arrest is not a forecast for the necessity of vasopressors or worse outcomes, at least when adjusted for the severity of cardiac arrest, shock, and vasopressor use. Nevertheless, experts still assume that the likelihood of PAMD is a significant cause of death after successful CPR[21]. Why do some patients initially survive successful resuscitation, and others do not? Also, why does the myocardium response vary after resuscitation? These questions have kept scientists busy for several decades. By modifying the conventional modalities of resuscitation together with new promising agents, rescuers will be able to salvage the jeopardized post-resuscitation myocardium and prevent its progression to a dismal, stony heart, which is the extreme form of PAMD[22]. The actual incidence of PAMD is still unclear in the literature because of the use of different definitions, small studies population, and diversity of cardiac function assessment[17]. Community awareness and staff education are crucial for improving and shortening the resuscitation time and attaining optimal short- and long-term outcomes. Awareness of PCAS components before and early after the restoration of circulation will improve the outcomes of CPR[23]. Restoration of adequate circulation and favorable long-term outcomes should be the main aim of resuscitation[24]. Several factors are associated with the development and impact of PAMD. These factors help healthcare providers anticipate which person would need early diagnostic evaluation, such as serial electrocardiogram, echocardiography, and specific treatments. Yao *et al*[25] have shown that almost 50% of OHCA is followed by myocardial dysfunction and that early myocardial dysfunction is not always associated with neurologically intact survival. The reversibility of PAMD reflects an aggressive on-time treatment strategy, and such dysfunction and the hemodynamic status should not affect the decision to discontinue treatment as both are usually reversible. After the initial phases of the ROSC, the neurologic status determines the patient's resuscitation outcome[26].

Furthermore, post-resuscitation shock, which is a complex pathophysiological condition occurring in 50%-70% of patients who experienced a cardiac arrest, is an early and transient complication of the post-resuscitation phase[27]. The optimal mean arterial pressure target during post-resuscitation shock needs further elaboration, and mechanical circulatory support could be required in selected cases whenever the neurological prognosis is expected to be favorable [27]. PAMD plays a role in early re-arrest after post-ROSC; it was reported in six percent of transported post-ROSC survivors[17,28]. Patients who develop re-arrest or another critical event (23%) are less likely to survive[28]. Of note, as a part of PAMD, the diastolic dysfunction measured by the isovolumetric relaxation time on echocardiography was found to be an independent predictor of mortality regardless of the patient's age, initial rhythm, duration of CPR, and doses of epinephrine[29].

ELECTRICAL SHOCK AND PAMD

Although defibrillation of a shockable rhythm as early as possible is the most critical factor in this sensitive period, the times before and after defibrillation and thoracic compressions (peri-shock) should be as short as possible[30,31]. A study showed that electrical shock of prolonged VF had an unfavorable outcome if a non-perfusing rhythm followed it compared to a primary asystole; this difference was attributed to the myocardial electrical injury[32]. Myocardial stunning and PAMD could also arise due to the use of defibrillators during resuscitation depending on the shock timing, frequency, amount of delivered energy, and waveform[33,34]. The electrical shock causes a decrease in the CI and contractility in addition to an increase in the ventricular end-diastolic pressure[17,34]. A prior study showed that the survival rate to hospital discharge was higher in patients presenting with pulseless electrical activity (PEA)/asystole without subsequent VT/VF than in patients with PEA/asystole with subsequent VT/VF[35]. Therefore, early defibrillation with concurrent high-quality CPR is critical for VF/pulseless VT, whereas epinephrine use with high-quality CPR is essential for better outcomes for non-shockable rhythms[36]. A meta-analysis showed that shockable rhythm conversion from asystole was associated with pre-hospital ROSC and survival to hospital discharge compared to PEA [37]. Also, earlier shockable rhythm conversion was associated with higher favorable neurological outcomes in OHCA patients within one month compared to late conversion.

HEMODYNAMIC STATUS AND PAMD

More than a decade ago, Laurent *et al*[20] evaluated 165 survivors of OHCA and found that the higher the dosages of epinephrine and the number of defibrillations during CPR, the higher the likelihood of cardio-circulatory instability and the need for more vasopressor support, which was necessary for more than half of the patients. The mean LVEF is lower in patients with hemodynamic instability. Patients who presented with a low CI on the first day after a cardiac arrest are more likely to die in the hospital due to multiorgan failure. In patients who survived cardiac arrest, efforts and multidisciplinary care could regain normal hemodynamic parameters within the first three days. Of note, the hemodynamic status did not influence the neurologic outcomes in some cases[20]. However, the autoregulation of the cerebral circulation is disrupted after ROSC, and therefore, up to three-thirds of cases require inotropic support cases due to

microvascular impairment and PAMD-induced hypotension[17,38].

An interesting study on more than 600 patients in whom echocardiogram findings were recorded within three months before the occurrence of IHCA[21]. The authors found a 25% reduction of the LVEF from its baseline values within 72 h post-IHCA in 14% of the cohort. The likelihood of survival was lower in patients whose LVEF before their cardiac arrest was less than 45%.

In the targeted temperature management (TTM) study, the LVEF on the first-day post-OHCA was severely reduced in 28% of patients and moderately reduced in 48% of patients[19]. The LVEF patterns did not distinguish patients with higher and lower vasopressor requirements or those with different target temperatures (36 °C *vs* 33 °C), which precluded the association between PAMD and systemic hemodynamics.

Post-cardiac arrest shock

Hypotension and shock in terms of SBP less than 90-100 mmHg or mean arterial pressure of less than 60-65 mmHg and the need for vasopressor use were reported in more than half of patients with ROSC in different studies. However, these factors were associated with adverse neurological outcomes and recurrence of cardiac arrest[17,39]. Furthermore, the mean arterial pressure and survival rate were inversely correlated after ROSC.

The pathophysiological processes after ROSC were described as initial low CI followed by vasodilation and subnormal systemic vascular resistance. The preliminary end stage is a capillary leak from the SIRS, which is responsible for drawing parallels to the septic shock-like states[20,40]. This period, with extreme vasoplegia, necessitates a continuous and rising need for vasopressors and peaks after one day, including an initial 6-hour period of apparent stabilization[20,40]. Following ROSC, endocrine dysfunctions occur in terms of pituitary-adrenal axis activation and functional adrenal abnormality with low cortisol secretion, which was more evident in non-survivor patients in some studies[41,42]. Also, relatively low vasopressin levels after cardiac arrest could contribute to the vasoplegia condition[43]. This was supported by an experimental study demonstrating that Vasopressin may prevent, to some extent, the cellular toxicity that could happen from excessive beta-adrenergic stimulation[17]. An RCT on IHCA showed that administration of vasopressin and epinephrine, methylprednisolone (during CPR), and a stress dose of hydrocortisone (during a shock stage of ROSC requiring vasopressors) is associated with better outcomes in terms of survival to discharge and favorable neurological status than epinephrine without Vasopressin[44]. A more recent study showed improvement occurred only in the ROSC in the vasopressin-methylprednisolone group rather than in the placebo group[45]. However, animal studies indicated that any vasopressin and/or epinephrine during resuscitation of OHCA is associated with reduced microcirculatory cerebral blood flow (CBF)[46,47]. During cardiac arrest, CBF is already losing 60% during chest compression only, and it needs at least 3 min of ROSC to be normalized[48]. The current Western guidelines do not recommend using Vasopressin and glucocorticoids in IHCA and OHCA[45,49]. However, few studies attributed the improvement of PAMD and peri-arrest cerebral ischemia to the impact of Vasopressin on the early improved post-arrest mean arterial pressure and central venous oxygen saturation, the use of less dosages of epinephrine, the shorter duration of CPR, and the use of methylprednisolone during resuscitation[36,44,50].

THE MULTIFACTORIAL POST-CARDIAC ARREST SYNDROME

The main pathways that could explain the development of PAMD include the IRI, catecholamine-induced myocardial injury, cytokine-mediated cardiac dysfunction, microvascular dysfunction, adrenal insufficiency, mitochondrial dysfunction, cardiac stunning related to the harmful effect of direct-current countershock, and iatrogenic interventions like therapeutic hypothermia (TH), propofol, remifentanil, and vasopressors in some instances[17,51,52]. The cardiovascular IRI represents the primary chain between cardiac arrest and the development of PAMD, shock, and multiorgan failure; it initiates the release of pro-inflammatory cytokines, SIRS, and sepsis-like status[19,53,54]. The intensity of this inflammatory response is a determinant of the mortality post-ROSC. The intense cytokine activity directly depresses the myocardium and induces mitochondrial dysfunction with further lactic acidosis[55]. Excess catecholamines during CPR may lead to myocardial dysfunction by several mechanisms, including calcium overload, beta-receptor downregulation and desensitization, and overproduction of toxic reactive oxygen species (ROS); the latter may end up with ischemic myocardial contracture and stony heart[17,22,56]. Figure 1 shows the mechanism and pathophysiology of post-cardiac arrest myocardial dysfunction and stony heart.

Coagulofibrinolytic changes in the post-cardiac arrest syndrome

IRI-induced coagulofibrinolytic changes mimic sepsis-like constellations but are less distinctive and accused of worse outcomes post-cardiac arrest as the coagulation and fibrinolysis are not adequately balanced during resuscitation[54,57]. The imbalance occurs during the early phase of cardiac resuscitation, as the resultant hyperfibrinolysis (t-PA release) is tracked by less endogenous fibrinolysis and fibrinolytic shutdown[57]. Augmented coagulation, followed by disseminated intravascular coagulation, leads to disturbances at the microcirculatory level, like the "no-reflow" phenomenon in the brain, and, finally, a multiorgan dysfunction[54].

The extension of the no-reflow phenomenon is multifactorial and mainly depends on the ischemic/hypoxia time and the coagulation system response[57,58].

As a result of the systemic IRI, the damage-associated molecular patterns (DAMPs) are substantially produced from the stressed cells and enhance the pro-inflammatory cytokines released from the immune and endothelial cells[59]. These DAMPs exaggerate the tissue factor-dependent coagulation and factor XII- and factor XI-dependent activation, and they inhibit the fibrinolysis process through the effects of the cell-free DNA, which is a form of the DAMP. Fibrinolytic

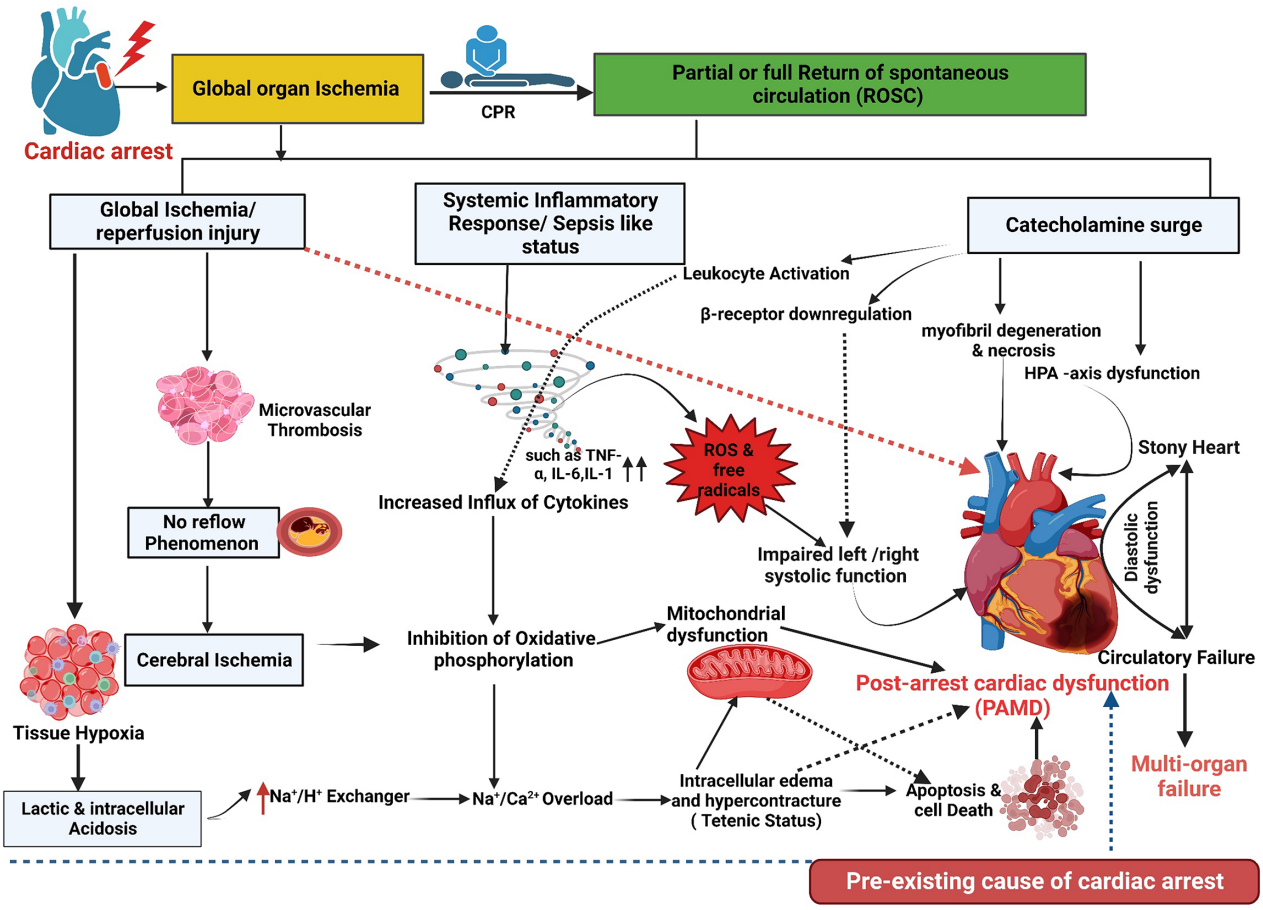

Figure 1 Mechanism, pathophysiology, and outcome of post-cardiac arrest myocardial dysfunction and stony heart (illustration created using Biorender.com). CPR: Cardiopulmonary resuscitation.

shutdown occurs post-cardiac arrest secondary to the marked increases in PAI-1 after the first 24 h and DAMPs release. Studies showed that, during the post-arrest period, patients had higher plasma levels of DAMPs, including cell-free DNA, which were associated with higher hospital mortality as well[60].

It is not surprising that the severity of hyperfibrinolysis differs according to the underlying cause of arrest[61]. Previous studies indicated that the time from the onset of cardiac arrest to the first CPR and the duration of CPR are primary causes of hyperfibrinolysis[62].

MULTI-DISCIPLINARY APPROACH FOR PAMD AND CIRCULATORY FAILURE

The role of cytokine removal

Studies have shown that IL-6 Levels could predict the need for vasopressors, multiorgan failure, and mortality post-cardiac arrest[63,64]. A significant mediator of cytokine-induced cardiac dysfunction is the TNF-α; it directly affects myocardial inotropy, responsiveness to beta-adrenergic stimulation, and mitochondria function[65,66]. Therefore, trials aim to remove inevitably appearing cytokines after cardiac arrest that could impact the outcome after ROSC. For instance, Infliximab administered during the peri-arrest period showed some improvement in animal studies, whereas etanercept failed[67]. Unfortunately, there are limited animal and human studies, predominantly on cyclosporine and corticosteroids after cardiac arrest[67,68].

Restoration of blood flow

There is also a shadow when there is light. ROSC usually goes hand in hand with a flood of toxic ROS, leading to a second wave of injury. Energy depletion caused by cardiac arrest leads to muscle contraction like tetanic stimulation, consecutively to the thickening of the wall and a reduction in the cavity volume. Depending on its extent, this phenomenon can result in irreversible stony heart[56]. An initially promising NHE inhibitor (*e.g.*, Cariporide) has shown, in animal studies, a reduction in PAMD, dysrhythmias, and mortality through its potential preventing effect on the cellular injury during the IRI[69,70].

TH and TTM

The effects of TH and TTM on the neurological outcomes post-cardiac arrest have been demonstrated in various studies [71]. Mild TH affects hemodynamics by improving the inotropic property of the myocardium, preserving diastolic relaxation, reducing heart rate, and increasing the systemic vascular resistance (SVR), induction of 'cold diuresis,' stabilization of MAP, and reducing the vasopressor dosages[72-74]. A prior study showed that TH displayed in the first 12 h a lower CI, lower heart rate, and higher SVR with no effect on the MAP and stroke volume[75]. However, Annborn *et al*[76] demonstrated no benefit on the survival or shock status after OHCA in patients treated with TTM at 33 °C compared to 36 °C. Nevertheless, after rewarming, a more extended period of vasopressor support is still needed in patients with OHCA[77]. The 2022 International Consensus on Cardiopulmonary Resuscitation recommended not to routinely use prehospital cooling with a rapid infusion of large volumes of cold intravenous fluid immediately after ROSC and suggested active fever prevention for at least 72 h for patients who remain comatose after ROSC[49]. Also, patients who remained in a coma and had mild hypothermia after ROSC should not be actively rewarmed to attain normal body temperature[49].

Preload, arterial pressure, and organ perfusion optimization

Low cardiac output requires volume replacement, possibly due to systemic capillary leakage from systemic IRI and cytokine release after ROSC. Therefore, administering at least 1 Liter of isotonic fluid should be standard in patients with low blood pressure after successful CPR to keep central venous pressure between 8 and 12 mmHg[17,78]. For close monitoring, invasive blood pressure monitoring is of utmost importance in hypotensive patients requiring vasopressors and or inotropes. Among various vasopressors that can be used to restore SBP ≥ 90 mmHg and MAP ≥ 70 mmHg in the first 72 h, norepinephrine is commonly used with a lower risk of arrhythmia. In contrast, vasopressors like dopamine increases the risk of arrhythmia and may increase mortality[78-80]. Epinephrine and Vasopressin with or without low-dose hydrocortisone are other choices to overcome refractory vasoplegia[17,44,81].

Inotropic support (*i.e.*, dobutamine) benefits patients with pending end-organ perfusion impairment in terms of low urine output after fluid resuscitation, low cardiac output, low central venous oxygen saturation, refractory acidosis, and warranting PAC insertion[72,82]. There were two sides of the inotropic support after cardiac arrest. On the one hand, protocols that utilize goal-directed therapy suggest inotropic agents improve cardiac output and tissue oxygen delivery. On the other hand, it is known that inotropes cause dysrhythmias, and the optimal cardiac output may vary from patient to patient. The efficacy and use of vasopressors and inotropic agents are based on the relative receptor potency. There is diversity in their potency, reflecting the variation in the circulatory effects and the potential side effects. Thus, there is not enough evidence to point out which vasopressor or inotrope is superior to another in terms of survival and neurological outcome[82-86]. Therefore, the decision to use it should be taken carefully, and it is better to be used only for patients with a combination of low cardiac output plus evidence of inadequate tissue perfusion.

The PPOO is crucial after ROSC, particularly in IHCA patients, as most of the deaths in this group are related to refractory shock, recurrent arrest, and multiorgan failure, in contrast to neurological injury in addition to shock in OHCA patients[87,88]. However, the optimal MAP and mixed venous oxygen saturation values ensure acceptable cerebral perfusion without burdening other tissues like the myocardium, which remains unchanged. In this regard, Ameloot *et al* [89] proposed a range of 80 mmHg and 70% of these two parameters, respectively, to keep cerebral perfusion at 65%. To attain better organ perfusion, the global body ischemia post-cardiac arrest reflecting the mitochondrial dysfunction and oxidative phosphorylation impairment[90] needs further elaboration in both IHCA and OHCA in large sample-sized research.

Mechanical support

In selected patients, mechanical circulatory support can restore hemodynamic stability and end-organ perfusion; it acts as a bridge to definitive therapy in patients with refractory shock to maximal medical treatment. This can be achieved using an intra-aortic balloon pump, Impella, left ventricular assist device, and venoarterial extracorporeal membrane oxygenator[91-93].

Coronary intervention

The decision to do and timing of coronary intervention after cardiac arrest due to myocardial infarction is an ongoing discussion. A recent meta-analysis showed that early intervention (within the first 24 h) was associated with significantly better survival and neurologic outcomes. However, it was graded as low-quality[94]. Moreover, this beneficial outcome was observed in patients without ST-segment elevation myocardial infarction, in contrast to non-statistically significant results in patients with ST-segment elevation myocardial infarction.

OUTCOMES OF IHCA AND OHCA

In a multicenter study including 2075 admissions with IHCA and OHCA, the IHCA patients had significantly higher comorbidities, lower lactate, greater utilization of invasive hemodynamics and mechanical circulatory support, lesser TTM and lesser in-hospital mortality (36.1% *vs* 44.1%) than IHCA patients[95]. Another study on 779 post-cardiac arrest patients[96] revealed that IHCA patients were older, less frequently male, and less frequently without comorbidity. The initial cardiac rhythm was more often non-shockable, all delay-times such as ROSC and no-flow, and time to advanced life support were shorter in IHCA. Cardiac cause of the arrest was less common, long-term neurological outcome was better, and the mortality at 30 d was lower in the IHCA than OHCA patients.

CONCLUSION

The pattern, management, and outcome of PAMD and post-cardiac arrest shock are different based on many factors, including IHCA *vs* OHCA, witnessed *vs* unwitnessed cardiac arrest, the underlying cause of arrest, and the duration of and protocol used for CPR. Although ROSC is a vital sign, it should not be the end of the game or lone primary outcome; it calls for aggressive multi-disciplinary interventions and care. The development of stony heart post-CPR and OHCA remain the main challenges in emergency and critical care medicine. A better understanding of the pathophysiology of PAMD and circulatory failure after ROSC is of utmost importance to achieve better post-cardiac arrest outcomes.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Sex and racial disparities in non-alcoholic fatty liver disease-related cardiovascular events: National inpatient sample analysis (2019)

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Abstract

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) increases cardiovascular disease (CVD) risk irrespective of other risk factors. However, large-scale cardiovascular sex and race differences are poorly understood.

AIM

To investigate the relationship between NAFLD and major cardiovascular and cerebrovascular events (MACCE) in subgroups using a nationally representative United States inpatient sample.

METHODS
We examined National Inpatient Sample (2019) to identify adult hospitalizations with NAFLD by age, sex, and race using ICD-10-CM codes. Clinical and demographic characteristics, comorbidities, and MACCE-related mortality, acute myocardial infarction (AMI), cardiac arrest, and stroke were compared in NAFLD cohorts by sex and race. Multivariable regression analyses were adjusted for sociodemographic characteristics, hospitalization features, and comorbidities.

RESULTS
We examined 409130 hospitalizations [median 55 (IQR 43-66) years] with NFALD. NAFLD was more common in females (1.2%), Hispanics (2%), and Native Americans (1.9%) than whites. Females often reported non-elective admissions, Medicare enrolment, the median age of 55 (IQR 42-67), and poor income. Females had higher obesity and uncomplicated diabetes but lower hypertension, hyperlipidemia, and complicated diabetes than males. Hispanics had a median age of 48 (IQR 37-60), were Medicaid enrollees, and had non-elective admissions. Hispanics had greater diabetes and obesity rates than whites but lower hypertension and hyperlipidemia. MACCE, all-cause mortality, AMI, cardiac arrest, and stroke were all greater in elderly individuals ($P < 0.001$). MACCE, AMI, and cardiac arrest were more common in men ($P < 0.001$). Native Americans (aOR 1.64) and Asian Pacific Islanders (aOR 1.18) had higher all-cause death risks than whites.

CONCLUSION
Increasing age and male sex link NAFLD with adverse MACCE outcomes; Native Americans and Asian Pacific Islanders face higher mortality, highlighting a need for tailored interventions and care.

Key Words: Non-alcoholic fatty liver disease; Cardiovascular disease; Major cardiovascular and cerebrovascular events; Sex/gender disparities; Mortality

Core Tip: Non-alcoholic fatty liver disease is associated with adverse major cardiovascular and cerebrovascular events, especially with increasing age and male sex. Native Americans and Asian Pacific Islanders had higher all-cause mortality.

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INTRODUCTION

With the global rise in obesity and metabolic diseases, non-alcoholic fatty liver disease (NAFLD) has become a prevalent condition. It is now widely recognized that NAFLD has numerous extrahepatic consequences[1] including an increased risk of cardiovascular disease (CVD) independent of traditional cardiovascular risk factors[2,3]. Understanding NAFLD and its impact on patient outcomes is of utmost importance, given its intricate underlying mechanisms. This is particularly significant because various modifiable behavioral factors play a role in the development and progression of the condition. Therefore, gaining insight into NAFLD and exploring the potential effects of lifestyle interventions can significantly enhance patient outcomes[4]. Risk factors for NAFLD are well-established and can be categorized as modifiable, such as smoking, sedentary lifestyle, poor nutrition habits, and physical inactivity, or non-modifiable, including genetic background, fat metabolism, and age[5]. The exploration of sex and racial disparities in cardiovascular outcomes related to NAFLD is an area that has received limited attention and remains largely unexplored on a broader scale. The current body of evidence in this regard is lacking, highlighting the need for further research to address these gaps in knowledge[6]. Therefore, this study was conducted to investigate the association between NAFLD and major cardiovascular and cerebrovascular events (MACCE) using a nationally representative sample in the United States.

MATERIALS AND METHODS

Source of data

The 2019 National Inpatient Sample (NIS) database of the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality was examined. The NIS is the largest all-payer inpatient healthcare dataset accessible to the public in the United States. With an annual average of 7 million unweighted discharges (and

about 35 million weighted nationwide discharges), the dataset comprises around 20% of United States hospitalizations across 50 states. For each inpatient admission, the NIS includes one primary diagnosis and up to 24 sary discharge diagnoses. Due to the de-identified nature of NIS data, permission from the IRB is not mandatory. The HCUP website provides additional information regarding the database[7].

Study population

We identified all hospitalizations with NAFLD in the 2019 NIS database using the K76.0 ICD-10-CM code. We included hospitalizations of adults (18 years and older) with a primary or secondary diagnosis of NAFLD. The latter code has been demonstrated to have a positive predictive value of over 91% for identifying NAFLD and has been previously recommended for use by an expert panel consensus statement for identifying NAFLD in administrative health databases or electronic health records, allowing researchers to ensure accurate identification and classification of NAFLD cases[8,9].

Study outcomes

The primary outcome of interest was to identify gender and racial disparities in NAFLD- related MACCE, including all-cause mortality, acute myocardial infarction (AMI), cardiac arrest, and stroke. Secondary outcomes included clinical, demographic, and hospital-level characteristics, and comorbidities associated with NAFLD hospitalizations by ethnicity and gender. Last, we evaluated and compared across subgroups of gender and race the median duration of hospital stay (in days) and total hospital charges (in USD) due to NAFLD-related MACCE in NAFLD hospitalizations.

Statistical analyses

The prevalence of NAFLD was calculated per sex and race categories. Using Pearson's Chi-square test for categorical variables and the Mann Whitney *U* test for continuous variables, we compared the clinical, demographic and hospital-level characteristics of NAFLD hospitalizations between subgroups of interest: sex and race. Discharge records with missing data for sex or race (< 5% of data) were excluded from analysis. The continuous and categorical variables were expressed as medians and percentages, respectively. To determine statistical significance, a two-tailed alpha level of less than 0.05 was used. The NIS database discharge weight (DISCWT) was utilized to derive national estimates and complex survey modules were used to perform analyses. Multivariate logistic regression analyses were performed to evaluate the independent associations of sex and race with NAFLD-related MACCE, while adjusting for social-demographic and hospitalization characteristics and comorbidities: age, sex, race, household income quartile, payer status, type of admission, hospital bed size, location/teaching status, region, comorbidities including hypertension, diabetes mellitus, hyperlipidemia, obesity, smoking, peripheral vascular disease, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass graft (CABG), drug abuse, prior stroke or transient ischemic attack, and prior venous thromboembolism (VTE). The results of logistic regressions were reported using adjusted odds ratios (aOR), 95%CI, and *P* values. The SPSS statistics 25.0 software package (IBM Corp, Armonk, New York, United States) was used for all statistical analyses.

RESULTS

Participant characteristics

Our study included 409130 NAFLD hospitalizations [median age = 55 years (IQR = 43-66)]. Social-demographic and clinical characteristics, comorbidities and outcomes were stratified based on sex and race independently.

Prevalence of NAFLD

The prevalence of NAFLD was higher in males compared to females (1.5% *vs* 1.2%). Among races, the prevalence of NAFLD was highest in Hispanic (2.0%) and Native American (1.9%) patients, compared to White (1.3%), Black (1.0%), Asian-Pacific Islander (1.2) and Other (1.5%). Blacks had the lowest prevalence of NAFLD (all $P < 0.001$, Table 1).

Sex disparities in social-demographic and clinical characteristics, comorbidities and outcomes

The females had a median age of 55 years (IQR 42-67). Despite a similar length of stay between genders, females were charged higher costs associated with the admission (41695 USD *vs* 40952 USD). Female patients were more often from lowest income quartile, Medicare enrollees, and had non-elective admissions. Compared to males, females demonstrated lower rates of hypertension, hyperlipidemia, complicated diabetes but higher rates of obesity and uncomplicated diabetes (Table 2).

Racial disparities in social-demographic and clinical characteristics, comorbidities and outcomes

Despite a similar length of stay across all races, the Hispanics [median age: 48 years (IQR 37-60)] and the Asian-Pacific Islanders (median age: 56 years) were charged the highest median costs (48351 USD and 51003 USD). The majority of the Hispanic patients came from the lowest income quartile (37.3%), were Medicaid enrollees (33.5%), and underwent non-elective admissions (85.7%). The Hispanics exhibited lower prevalence rates of hypertension, hyperlipidemia, but higher rates of diabetes and obesity compared to Whites (Table 3).

Odds of MACCE, all-cause mortality, AMI, cardiac arrest, and stroke

Males had a greater risk of MACCE (aOR 1.22) ($P < 0.001$), AMI (aOR 1.35) ($P < 0.001$) and Cardiac arrest (aOR 1.54) ($P <$

Table 1 Prevalence of non-alcoholic fatty liver disease based on gender and race from the national inpatient sample analysis (2019)

Prevalence of NAFLD	Count	%	Total hospitalizations
Sex	NAFLD diagnoses		
Male	195475	1.5%	12978685
Female	213655	1.2%	17236228
Race	NAFLD-related diagnoses		
White	264475	1.3%	19851043
Black	43875	1.0%	4519150
Hispanic	66265	2.0%	3262700
Asian-Pacific Islander	9995	1.2%	826270
Native American	3745	1.9%	201155
Others	13250	1.5%	858436

NAFLD: Non-alcoholic fatty liver disease.

0.001). Native Americans (aOR 1.64) ($P < 0.001$) followed by Asian Pacific Islanders (aOR 1.18) ($P < 0.001$) had significantly higher odds of all-cause mortality compared to whites (aOR 1.00) ($P < 0.001$) (Table 4). Older patients had significantly higher odds of MACCE (aOR 3.01) ($P < 0.001$), all-cause mortality (aOR 4.13) ($P < 0.001$), AMI (aOR 2.81) ($P < 0.001$), cardiac arrest (aOR 2.24) ($P < 0.001$) and stroke (aOR 2.58) ($P < 0.001$) (Table 4).

DISCUSSION

NAFLD is associated with obesity and insulin resistance as comorbidities. In obese individuals, the expansion of adipose tissue results in adipocyte dysfunction and increased insulin resistance, thereby leading to lipolysis. This results in elevated levels of circulating free fatty acids and leptin, with decreasing adiponectin levels, ultimately leading to intrahepatic fat accumulation. The situation is exacerbated by a diet high in carbohydrates and fat, which further contributes to fat accumulation in the liver[10]. Additionally, the expansion of adipose tissue promotes infiltration of immune cells into both adipocytes and the liver, leading to chronic inflammation. Prolonged inflammation triggers hepatic stellate cells to mediate fibrosis, ultimately resulting in cirrhosis. Obesity is an independent risk factor for cardiovascular events, as it can also contribute to the development of diabetes mellitus, hyperlipidemia, hypertension, and sleep disorders, thereby indirectly exacerbating cardiovascular risks[11].

Strong evidence indicates that NAFLD causes chronic inflammation through the release of pro-inflammatory cytokines (IL-6, TNF-a, CRP), hepatokines (FGF-21, fetuin-A), adhesion molecules, and procoagulant factors from the liver, resulting in endothelial dysfunction with systemic atherosclerosis, which makes the NAFLD an independent risk factor for cardiovascular disease[12-14]. Additionally, NAFLD is associated with a higher risk of left ventricular hypertrophy [15], left ventricular diastolic dysfunction[16], and atrial fibrillation[17], all of which contribute to adverse cardiovascular outcomes. It has also been reported that the presence of NAFLD is associated with poor clinical outcomes in STEMI patients and that greater severity of NAFLD is associated with higher mortality rates in such patients[18]. We intended to examine the differences in cardiac and cerebrovascular outcomes (MACCE) between different sex and racial groups of NAFLD patients. This was a large-scale retrospective cross-sectional study comparing NAFLD outcomes by ethnicity and gender.

The social-demographic and clinical characteristics and comorbidities of the patients were compared over groups of sex and race. The comorbidities studied in these groups included hypertension, DM, hyperlipidemia, obesity, PVD, prior MI, prior stroke, prior VTE, chronic pulmonary disease, tobacco use, and drug use. An analysis conducted in 2015 as part of the Framingham Heart Study revealed a strong independent association between hepatic steatosis and subclinical cardiovascular disease outcomes, regardless of other metabolic risk factors[19]. Furthermore, In a study using data from NHANES, patients with NAFLD demonstrated to develop increased odds of developing cardiovascular disease[20]. Their study lacked to control for conditions like hyperlipidemia or systemic hypertension. However, this limitation was addressed in our study through adjustments for a comprehensive range of comorbid conditions, including hyperlipidemia and hypertension, thereby enhancing the robustness of our findings. Patients with NAFLD often have one or more components of the metabolic syndrome, which is a known risk factor for cardiovascular disease[21]. This makes NAFLD independently associated with cardiovascular disease. Moreover, our study revealed that the prevalence of hypertension, diabetes with and without chronic complications, hyperlipidemia, and obesity were significantly higher in all racial groups among NAFLD patients. While the relationship between NAFLD and diabetic complications remains unclear, it is worth noting that individuals with steatosis and type 1 diabetes may be at a heightened risk of developing cardiovascular disease and subsequent cardiovascular complications[22]. Therefore, it is of utmost importance to screen high-risk groups for NAFLD-related fibrosis, and the American Association of clinical endocrinology clinical practice guideline for the

Table 2 Baseline characteristics, comorbidities and outcomes in non-alcoholic fatty liver disease hospitalizations by sex, 2019, *n* (%)

		Male	Female	*P* value
Age (yr) at admission, median [IQR]		55 [43-65]	55 [42-67]	
Race	White	67.0	64.8	< 0.001
	Black	10.1	11.7	< 0.001
	Hispanic	15.9	17.0	< 0.001
	Asian-Pacific Islander	2.7	2.3	< 0.001
	Native American	0.9	1.0	< 0.001
	Others	3.4	3.2	< 0.001
Median household income national quartile for patient ZIP code	0-25	28.3	30.3	< 0.001
	25-50	25.4	26.1	< 0.001
	50-75	25.6	24.8	< 0.001
	75-100	20.7	18.7	< 0.001
Primary expected payer	Medicare	32.6	36.2	< 0.001
	Medicaid	20.2	22.2	< 0.001
	Private including HMO	34.0	33.0	< 0.001
	Self-pay	8.6	5.9	< 0.001
	No charges	0.9	0.5	< 0.001
	Others	3.8	2.2	< 0.001
Elective versus non-elective admission	Non-elective	88.2	80.4	< 0.001
	Elective	11.8	19.6	< 0.001
Region of hospital	Northeast	17.3	16.5	< 0.001
	Midwest	21.4	20.6	< 0.001
	South	38.1	39.3	< 0.001
	West	23.2	23.6	< 0.001
Location/teaching status of hospital	Rural	6.0	6.2	< 0.001
	Urban non-teaching	18.0	18.9	< 0.001
	Urban teaching	76.0	74.8	< 0.001
Comorbidities				
Hypertension, complicated		18.5	16.3	< 0.001
Hypertension, uncomplicated		45.1	42.5	< 0.001
Diabetes with chronic complications		21.7	21.0	< 0.001
Diabetes without chronic complications		13.5	15.8	< 0.001
Hyperlipidaemia		41.5	38.6	< 0.001
Obesity		32.3	43.6	< 0.001
Peripheral vascular disease		6.8	4.9	< 0.001
Prior MI		5.8	3.4	< 0.001
Drug abuse		6.5	4.4	< 0.001
Tobacco use disorder		25.3	17.5	< 0.001
Chronic pulmonary disease		18.7	25.0	< 0.001
Prior TIA/stroke without neurologic deficit		4.2	4.6	< 0.001
Prior VTE		4.7	5.2	< 0.001
In-hospital outcomes				

MACCE (ACM/AMI/CA/stroke)		6.2	4.6	< 0.001
All-cause mortality		1.4	1.3	0.001
AMI - all diagnoses T1/T2MI combined		3.4	2.2	< 0.001
Acute VTE		2.8	2.2	< 0.001
Dysrhythmia		15.1	10.7	< 0.001
Cardiac arrest		0.7	0.5	< 0.001
Stroke		1.5	1.3	< 0.001
Disposition of patient	Routine discharge	73.3	73.2	< 0.001
	Transfers to short term facilities	2.4	1.8	< 0.001
	Other: Includes SNF, ICF, another type of facility	9.4	10.1	< 0.001
	HHC	10.7	12.0	< 0.001
	AMA	2.8	1.5	< 0.001
Length of stay (d), median [IQR]		3 [2-6]	3 [2-5]	< 0.001
Total charges (USD), median [IQR]		40952 [23123-75209]	41695 [24443-72705]	< 0.001

P < 0.05 indicates statistical significance. NAFLD: Non-alcoholic fatty liver disease; HMO: Health Maintenance Organization; MACCE: Major adverse cardiovascular and cerebrovascular events; ACM: All-cause mortality; MI: Myocardial infarction; AMI: Acute myocardial infarction; CA: Cardiac arrest; T2MI: Type 2 myocardial infarction; TIA: Transient ischemic attack; VTE: Venous thromboembolism; SNF: Skilled Nursing Facility; ICF: Intermediate Care Facility; HHC: Home Health Care; AMA: Against medical advice.

diagnosis and management of NAFLD strongly recommend screening patients with type 2 diabetes using the Fibrosis (FIB)-4 index[23]. Other metrics such as the NAFLD activity score, a validated grading system for disease activity[24] and noninvasive assessments of hepatic fibrosis, like the NAFLD fibrosis score, are specific to NAFLD. The NAFLD fibrosis score considers factors such as age, body mass index, hyperglycemia, aminotransferase levels, platelet count, and albumin [25]. Elevated NAFLD fibrosis scores may correlate with heightened cardiovascular disease mortality[26]. These assessment tools are essential for stratifying the NAFLD population into distinct grading categories, enabling targeted screening for adverse cardiovascular outcomes. Establishing a causal relationship between NAFLD and cardiovascular disease will be challenging due to the complex interplay of overlapping metabolic disturbances in these individuals, such as obesity, diabetes, hypertension, atherogenic dyslipidemia, and visceral adiposity. Further research is necessary to clarify this mechanistic link. Nevertheless, regardless of causality, it is crucial for endocrinology and primary care clinicians to recognize individuals with NAFLD as being at a heightened risk of cardiovascular complications.

Our findings showed that males had greater risk of MACCE, AMI, and cardiac arrest compared to females. Native Americans, followed by Asian Pacific Islanders, were found to have significantly higher odds of all-cause mortality compared to other racial groups. The literature offers multiple studies demonstrating higher prevalence of NAFLD among males compared to females[27,28], which could be attributable to greater consumption of high-calorie drinks and alcohol, and higher frequency of insulin resistance[29]. To improve this poor trend among male population, public health measures should be implemented targeting optimal control of comorbidities among males in the community. The higher prevalence of NAFLD among Hispanics is also consistent with prior studies[30]. This could be attributed to a higher prevalence of chronic diseases such diabetes or metabolic syndrome, genetic and lifestyle differences, or access to healthcare among this racial group[30]. Regarding genetic factors, one of the most researched genes is the Patatin-like phospholipase domain-containing protein 3 (PNPLA3), which is responsible for encoding a membrane-bound phospholipase protein that regulates the use and storage of energy resources. Hispanics more often have an allele of PNPLA3 (rs738409[G]) that causes an increased hepatic accumulation of fat compared to Blacks, who have a different allele of PNPLA3 (rs6006460[T]) that in turn results in lower hepatic fat accumulation[31]. In a striking revelation, a study focusing on Native American patients with Medicare in the United States uncovered that nearly half of the patients grappled with severe cardiovascular conditions, while also bearing a heightened load of cardiovascular risk factors such as hypertension, diabetes, and hyperlipidemia[32]. These alarming findings parallel our own study, which demonstrated that Native Americans faced elevated odds of in-hospital mortality. This stark correlation underscores the profound and widespread racial disparities in cardiovascular health across the United States[33]. Consequently, there is a pressing need for the implementation of comprehensive multilevel interventions in healthcare, encompassing individual- and community-level factors for Native Americans and Asian/Pacific Islanders diagnosed with NAFLD, to enhance cardiovascular health. This approach must be complemented by strategic investments in communities to tackle the socioeconomic determinants of health, ultimately leading to improved cardiovascular outcomes within these populations.

Clinical implications

It is crucial to understand the implications of NAFLD, the increasing worldwide incidence of hepatic disease caused by

Table 3 Baseline characteristics, comorbidities and outcomes in non-alcoholic fatty liver disease hospitalizations by race, 2019

Variables		White	Black	Hispanic	Pacific Islander	Native American	Others	Total	*P* value
Age at admission		57	53	48	56	48	52	55	
Sex	Male	48.6	44.2	46	51	44.3	49.8	47.8	< 0.001
	Female	51.4	55.8	54	49	55.7	50.2	52.2	< 0.001
Median household income national quartile for patient ZIP code	0-25	24.6	48.7	37.3	12.6	47.4	29.1	29.4	< 0.001
	25-50	26.6	22.5	25.5	16.9	26.6	23.6	25.7	< 0.001
	50-75	26.8	17.8	23.6	28.1	19.2	24.5	25.2	< 0.001
	75-100	21.9	11.1	13.6	42.4	6.7	22.8	19.8	< 0.001
Primary expected payer	Medicare	38.8	32.1	21.8	31	23.8	25	34.5	< 0.001
	Medicaid	16.4	28.5	33.5	19.3	45.8	26.8	21.2	< 0.001
	Private including HMO	35.4	27.8	28.7	41.5	18.8	33.4	33.4	< 0.001
	Self-pay	5.9	8	11.9	5	5.4	10.6	7.2	< 0.001
	No charges	0.5	0.7	1.5	0.6	0.1	0.7	0.7	< 0.001
	Others	3	2.8	2.6	2.6	6	3.5	2.9	< 0.001
Elective versus non-elective admission	Non-elective	83.4	86	85.7	86.5	88	83.7	84.2	< 0.001
	Elective	16.6	14	14.3	13.5	12	16.3	15.8	< 0.001
Region of hospital	Northeast	17.6	16.1	13.9	15.8	2.9	28.9	17	< 0.001
	Midwest	24.8	21	7.2	9.6	17.9	10.3	20.6	< 0.001
	South	39.1	51.2	35.1	17.6	19	36.7	39	< 0.001
	West	18.5	11.7	43.7	57.1	60.2	24.2	23.4	< 0.001
Location/teaching status of hospital	Rural	7.8	3.5	1.7	1	15.2	2.5	6.1	< 0.001
	Urban non-teaching	19.1	14.4	19.4	18.2	16.3	16.9	18.5	< 0.001
	Urban teaching	73.1	82.1	78.9	80.8	68.5	80.6	75.5	< 0.001
Comorbidities									
Hypertension, complicated		17.9	23.5	12	18.6	15.5	12.6	17.4	< 0.001
Hypertension, uncomplicated		45.3	45.7	37.6	40.9	36	40.8	43.7	< 0.001
Diabetes with chronic complications		20.6	24.3	22.2	26	22.2	18.5	21.4	< 0.001
Diabetes without chronic complications		14	14.3	16.7	18.4	16.3	15.9	14.6	< 0.001
Hyperlipidaemia		42.3	35	34.4	49.9	25	36.4	40	< 0.001
Obesity		38	39.7	40.5	23.1	35.4	36.2	38.2	< 0.001
Peripheral vascular disease		6.6	4.9	3.8	8.4	2.1	3.9	5.8	< 0.001
Prior MI		5.2	4.3	2.6	3.9	3.7	2.8	4.6	< 0.001
Drug abuse		5.4	7.3	4.3	3	9.3	4.3	5.4	< 0.001
Tobacco use disorder		22.9	26	13.1	12.2	25.9	16.7	21.2	< 0.001
Chronic pulmonary disease		24.3	23.7	14.4	14.2	20.7	16.7	22.1	< 0.001
Prior TIA/stroke		4.6	5.7	3.3	4	2.9	3.1	4.4	< 0.001
Prior VTE		5.5	6.3	2.8	2	1.7	3.5	5	< 0.001
In-hospital outcomes									

MACCE (ACM/AMI/CA/stroke)		5.6	5.5	4.2	6.6	4.9	5.3	5.3	< 0.001
All-cause mortality		1.4	1.4	0.9	1.7	2.1	1.2	1.3	< 0.001
AMI		2.9	2.6	2.2	3.4	1.9	3.1	2.7	< 0.001
Acute VTE		2.6	2.8	1.9	1.8	0.9	2	2.5	< 0.001
Dysrhythmia		15	10.7	6.6	11.5	6.9	9.3	12.8	< 0.001
Cardiac arrest		0.6	0.7	0.4	0.5	0.4	0.6	0.6	< 0.001
Stroke		1.3	1.7	1.3	1.8	0.9	1.2	1.4	< 0.001
Disposition of patient	Routine discharge	70.9	73.1	81.2	74.6	78.1	78	73.2	< 0.001
	Transfers to short term facilities	2.2	1.7	1.7	2.2	2.8	2.1	2.1	< 0.001
	Other[1]	11.2	9.8	5.2	8.5	7.2	6.3	9.8	< 0.001
	HHC	12.3	11	9.1	11.7	5.9	9.7	11.4	< 0.001
	AMA	2	3	1.9	1.3	3.9	2.7	2.1	< 0.001
Length of stay (d), median		3	4	3	3	3	3	3	< 0.001
Total charges (USD), median		39745	39028	48351	51003	35127	45309	41448	< 0.001

[1]Includes Skilled Nursing Facility, Intermediate Care Facility, Another Type of Facility.

P < 0.05 indicates statistical significance. NAFLD: Non-alcoholic fatty liver disease; HMO: Health Maintenance Organization; MACCE: Major adverse cardiovascular and cerebrovascular events; ACM: All-cause mortality; MI: Myocardial infarction; AMI: Acute myocardial infarction; CA: Cardiac arrest; TIA: Transient ischemic attack; VTE: Venous thromboembolism; AMA: Against medical advice.

Table 4 Adjusted odds of major cardiovascular and cerebrovascular events, all-cause mortality, acute myocardial infarction, cardiac arrest, stroke by age, gender and race

Groups	MACCE		All-cause mortality		AMI		Cardiac arrest		Stroke	
	aOR (95%CI)	*P* value	aOR (95%CI)	*P* value	aOR (95%CI)	*P* value	aOR (95%CI)	*P* value	aOR (95%CI)	*P* value
18-44	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
45-64	2.31 (2.06-2.59)		3.00 (2.42-3.72)		2.23 (1.87-2.66)		2.08 (1.55-2.80)		1.90 (1.52-2.38)	
≥ 65	3.01 (2.61-3.47)		4.13 (3.11-5.48)		2.81 (2.29-3.45)		2.24 (1.52-3.31)		2.58 (1.96-3.39)	
Male *vs* female	1.22 (1.14-1.30)		1.04 (0.92-1.18)	0.539	1.35 (1.24-1.48)	< 0.001	1.54 (1.26-1.88)	< 0.001	1.04 (0.01-1.19)	0.579
White	Reference	0.125	Reference	0.001	Reference	0.121	Reference	0.272	Reference	0.377
Black	1.00 (0.90-1.11)		0.89 (0.72-1.10)		0.95 (0.81-1.11)		1.16 (0.86-1.57)		1.25 (1.03-1.53)	
Hispanic	0.88 (0.79-0.98)		0.69 (0.56-0.85)		0.93 (0.81-1.08)		0.75 (0.55-1.02)		1.07 (0.87-1.31)	
Asian/Pacific Islander	1.06 (0.86-1.30)		1.18 (0.82-1.69)		1.06 (0.81-1.38)		0.77 (0.42-1.43)		0.99 (0.69-1.42)	
NA	1.14 (0.81-1.61)		1.64 (1.04-2.60)		0.91 (0.53-1.56)		0.74 (0.25-2.15)		0.86 (0.41-1.81)	
Others	1.11 (0.92-1.34)		0.91 (0.62-1.33)		1.33 (1.06-1.67)		1.05 (0.62-1.78)		0.99 (0.68-1.45)	

Multivariable logistic regression was adjusted for baseline patient and hospital level characteristics, and relevant pre-existing cardiovascular and extra-cardiac comorbidities. AMI: Acute myocardial infarction; aOR: Adjusted odds ratio; MACCE: Major adverse cardiac and cerebrovascular events.

NAFLD, aggressive public health measures are needed to target optimal control of comorbidities among the general population. This can be achieved through education on lifestyle modification, exercise, and dietary changes, including low calorie and high glycemic index foods, increased consumption of omega 3 and monounsaturated fatty acids. If lifestyle and dietary changes are unsuccessful, bariatric surgery may be considered[34]. Early diagnosis and proper management of NAFLD and related risk factors are essential to prevent atherosclerosis and other cardiovascular outcomes, particularly in high risk and underserved racial and ethnic groups. Furthermore, comprehensive multilevel interventions in healthcare, addressing individual and community level factors, are urgently needed for Native Americans and Asian/Pacific Islanders diagnosed with NAFLD to enhance cardiovascular health and reduce disparities. These efforts must be complemented by strategic investments in communities to address the socioeconomic determinants of health, ultimately leading to improved cardiovascular outcomes within these populations and promoting health equity.

Limitations

This retrospective cross-sectional study has limitations tied to its reliance on ICD-10 codes for identifying NAFLD hospitalizations, potentially influenced by coding accuracy and completeness. Because it focused solely on hospitalized patients, the findings may not fully capture NAFLD characteristics in the general population. The study's use of a 2019 sample might not be entirely representative of the broader NAFLD patient population over time. The study design doesn't provide insights into causality, and unmeasured confounding variables may impact observed associations. Generalizability is confined to the United States population and may not extend to regions with different demographics or healthcare systems. Notably, the study did not consider the severity of NAFLD, including crucial factors such as NAS score, NAFLD fibrosis score, FIB-4 index, and ultrasonography findings. The absence of this information in the NIS database hinders a comprehensive understanding of the disease's nuances. Furthermore, the lack of established screening guidelines for NAFLD exacerbates the issue, as its asymptomatic nature and the absence of a correlation with elevated liver function enzymes make it easily overlooked in clinical settings. Hence, our results are only representative of a small group of patients already diagnosed with NAFLD and may not reflect the actual disease burden[13,18,35]. This could be crucial when considering that certain racial groups may not have access to ideal healthcare services and meticulous laboratory evaluation and may not be aware of the severity of their NAFLD, thereby being underrepresented in the included data. Additional potential limitations may include limited availability of thorough clinical data, potential misclassification or underreporting of comorbid conditions, lack of long-term follow-up data, conceivable changes in coding practices over time, and inability to account for lifestyle and behavioral factors that could influence NAFLD and cardiovascular outcomes.

CONCLUSION

The findings from this study indicated that NAFLD is linked to a greater risk of major cardiovascular events, especially among older males, and that Native Americans and Asian Pacific Islanders with NAFLD have higher all-cause mortality. These results emphasize the need for early detection and comprehensive management of cardiovascular risk factors in NAFLD patients, as well as the significance of addressing racial and gender disparities in outcomes. Future research directions may include investigating the mechanisms involved in contributing to the increased cardiovascular risk in individuals with NAFLD, exploring sex- and race-specific risk factors, and assessing the effectiveness of targeted interventions in improving cardiovascular outcomes. Strategies enhancing access to healthcare and addressing the disparities in NAFLD-related outcomes across sexes and racial/ethnic groups may also be a subject of future research.

ARTICLE HIGHLIGHTS

Research background

This study delves into the impact of non-alcoholic fatty liver disease (NAFLD) on cardiovascular disease risk, focusing on the underexplored variances in cardiovascular outcomes across different sexes and races within a large, nationally representative United States inpatient sample.

Research motivation

The motivation for this research was to elucidate the relationship between NAFLD and major cardiovascular and cerebrovascular events (MACCE), particularly investigating the sex and racial disparities, to inform future healthcare strategies and interventions.

Research objectives

The objective was to examine the association of NAFLD with MACCE across various subgroups by age, sex, and race, aiming to highlight specific population needs and guiding tailored healthcare approaches.

Research methods

The study utilized a thorough analysis of the National Inpatient Sample, with multivariable regression models adjusted

for sociodemographic and clinical factors, to compare MACCE-related outcomes in patients with NAFLD.

Research results

It found that NAFLD prevalence varies by sex and race, with adverse MACCE outcomes more common in older age groups and males, and higher all-cause mortality observed in Native Americans and Asian Pacific Islanders.

Research conclusions

The study revealed critical links between NAFLD, MACCE, age, and sex, as well as significant racial disparities in mortality rates, underscoring the necessity for customized care to improve health outcomes.

Research perspectives

This research paves the way for future studies focused on individualized patient care and highlights the importance of considering demographic variables in medical research and healthcare provision.

FOOTNOTES

Co-first authors: Rupak Desai and Ali Tariq Alvi.

Author contributions: Desai R designed the methodology and performed analysis; Desai R, Alvi AT, Vasavada A, Pulkurthi YS, Patel BA, Mohammed AS, Doshi S and Ogbu I were involved with data curation, visualization, and interpretation; Alvi AT, Pulkurthi YS, Patel BA, Vasavada A, and Mohammed AS were involved with writing of manuscript; Desai R, Alvi AT, Doshi S and Ogbu I performed reviewing and final editing; all authors have read and agreed to the published version of the manuscript; Desai R and Alvi AT are designated co-first authors, with Desai R contributing substantially to conceptualization, methodology, and editorial work, and Alvi AT to data curation, visualization, interpretation, and writing.

Institutional review board statement: Since the data included in this review were deidentified and already available in the publicly accessible databases, the IRB review was not mandatory. This review was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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ORIGINAL ARTICLE

Clinical Trials Study

Epicardial adipose tissue in obesity with heart failure with preserved ejection fraction: Cardiovascular magnetic resonance biomarker study

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Abstract

BACKGROUND

Obesity has become a serious public health issue, significantly elevating the risk of various complications. It is a well-established contributor to Heart failure with preserved ejection fraction (HFpEF). Evaluating HFpEF in obesity is crucial. Epicardial adipose tissue (EAT) has emerged as a valuable tool for validating prognostic biomarkers and guiding treatment targets. Hence, assessing EAT is of paramount importance. Cardiovascular magnetic resonance (CMR) imaging is acknowledged as the gold standard for analyzing cardiac function and morphology. We hope to use CMR to assess EAT as a bioimaging marker to evaluate HFpEF in obese patients.

AIM

To assess the diagnostic utility of CMR for evaluating heart failure with preserved ejection fraction [HFpEF; left ventricular (LV) ejection fraction ≥ 50%] by measuring the epicardial adipose tissue (EAT) volumes and EAT mass in obese patients.

METHODS
Sixty-two obese patients were divided into two groups for a case-control study based on whether or not they had heart failure with HFpEF. The two groups were defined as HFpEF+ and HFpEF-. LV geometry, global systolic function, EAT volumes and EAT mass of all subjects were obtained using cine magnetic resonance sequences.

RESULTS
Forty-five patients of HFpEF- group and seventeen patients of HFpEF+ group were included. LV mass index (g/m^2) of HFpEF+ group was higher than HFpEF- group ($P < 0.05$). In HFpEF+ group, EAT volumes, EAT volume index, EAT mass, EAT mass index and the ratio of EAT/[left atrial (LA) left-right (LR) diameter] were higher compared to HFpEF- group ($P < 0.05$). In multivariate analysis, Higher EAT/LA LR diameter ratio was associated with higher odds ratio of HFpEF.

CONCLUSION
EAT/LA LR diameter ratio is highly associated with HFpEF in obese patients. It is plausible that there may be utility in CMR for assessing obese patients for HFpEF using EAT/LA LR diameter ratio as a diagnostic biomarker. Further prospective studies, are needed to validate these proof-of-concept findings.

Key Words: Heart failure with preserved ejection fraction; Epicardial adipose tissue; Obesity; Cardiac magnetic resonance

Core Tip: The purpose of this research is to assess the diagnostic utility of cardiovascular magnetic resonance for evaluating heart failure with preserved ejection fraction (HFpEF) by measuring the epicardial adipose tissue (EAT) volumes in obesity. There is a strong correlation between increased EAT volumes and HFpEF in obesity. Moreover, EAT/Left atrial left-right (LA LR) diameter ratio is highly associated with HFpEF in obesity. Given the significant findings, there may be some diagnostic utility in cardiac magnetic resonance for assessing obesity for HFpEF.

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INTRODUCTION

Obesity has become a serious public health issue, significantly elevating the risk of various complications, including heart disease, type 2 diabetes, and hypertension[1]. It is a well-established contributor to heart failure (HF)[2]. Heart failure with preserved ejection fraction (HFpEF) is a prevalent and deadly clinical syndrome characterized by HF with a left ventricular ejection fraction (LVEF) ≥ 50%. Within the broader HFpEF population, the obesity-HFpEF phenotype has been identified as a distinct subset, potentially necessitating specific treatments[3]. Recently, there is growing recognition of the importance of anti-atherogenic and anti-inflammatory effects, known as 'meta-inflammatory' mechanisms, in the treatment of "obese HFpEF"[4]. Therefore, evaluating HFpEF in obesity is crucial.

Epicardial adipose tissue (EAT) refers to the fat surrounding the heart in the epicardium, also known as visceral fat[5]. Studies have linked EAT with HF, revealing higher EAT volume in HF patients with HFpEF[6,7]. Consequently, EAT has emerged as a valuable tool for validating prognostic biomarkers and guiding treatment targets[8,9]. Hence, assessing EAT is of paramount importance.

Accurate detection and quantification of EAT can be accomplished through 2-dimensional (2D) echocardiography, contrast-free computed tomography (CT), and magnetic resonance imaging (MRI)[10]. Echocardiography, a widely used cardiac imaging method for EAT measurement, does not expose patients to ionizing radiation[11,12]. However, it predominantly provides 2D cardiac images, measuring only the thickness, not the volume or mass of EAT[13]. Additionally, echocardiography-derived measurements may be more prone to inter-observer errors compared to cross-sectional modalities. Consequently, echocardiography is only accurate for measuring the maximum EAT thickness[14]. Nevertheless, the definitive EAT thickness threshold for use as a prognostic biomarker is yet to be determined[15]. Moreover, the applicability of EAT thickness is often constrained by suboptimal acoustic windows in obese patients.

More recently, the heightened EAT in patients exhibiting the HFpEF phenotype can be assessed through CT, potentially indicating adverse cardiac function[16]. Evaluation of cardiac function is feasible. However, CT is constrained by radiation exposure. Cardiovascular magnetic resonance (CMR) imaging is acknowledged as the gold standard for analyzing cardiac function and morphology[17]. Utilizing three-dimensional cine images, CMR enables accurate and reproducible quantification of EAT thickness, volume, and mass. Some recent CMR studies have compared EAT quantities in HFpEF groups with controls, emphasizing the need to focus on EAT beyond an individual's overall body fat concerning HFpEF[18,19]. However, it is conceivable that obesity could confound such findings due to the general

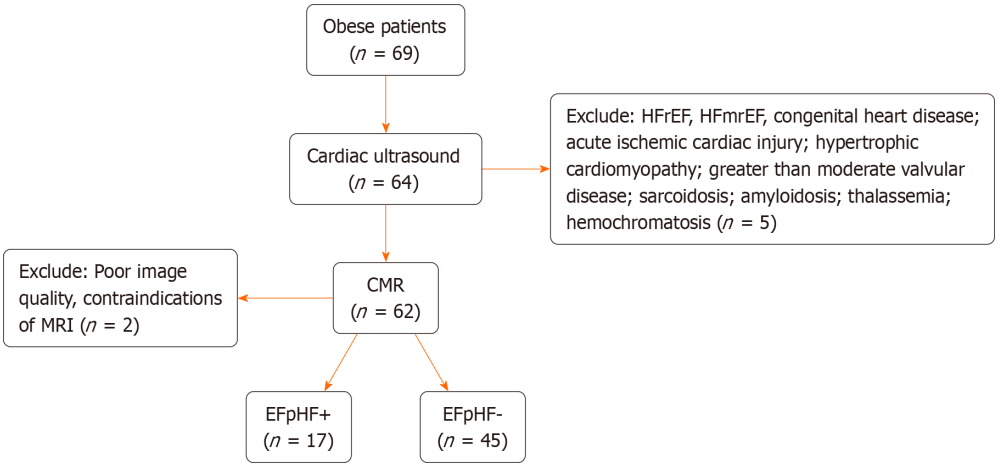

Figure 1 The study flow diagram. HFrEF: Heart failure with reduced ejection fraction; HFmrEF: Heart failure with mid-range ejection fraction; MRI: Magnetic resonance imaging.

increase in adipose tissue throughout the body. To our knowledge, no studies have investigated EAT metrics (including volume or mass) in obese patients using CMR to determine the association with HFpEF and whether EAT metrics could serve as a biomarker for predicting HFpEF in the obese population. Therefore, this study aims to employ CMR to examine EAT in the obese population with and without HFpEF, considering the association with co-morbidities, biomarkers, contractility parameters, and myocardial function assessed by CMR.

MATERIALS AND METHODS

Study participants

The study followed a case-control, prospective clinical design, enrolling 69 obese individuals from October 2019 to August 2020 at Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital. HFpEF patients meeting specific criteria were included: (1) Left ventricular (LV) ejection fraction ≥ 50%, assessed by echocardiography; (2) New York Heart Association class ≥ II, with either E/e' > 13 and mean e'septal and lateral wall < 9 cm/s on echocardiography; (3) plasma brain natriuretic peptide (BNP) > 35 pg/mL[20]. Exclusion criteria were: (1) general contraindication to CMR; (2) poor imaging quality; (3) heart failure with mid-range ejection fraction (HFmrEF) and heart failure with reduced ejection fraction (HFrEF); (4) congenital heart disease; (5) acute ischemic cardiac injury; (6) hypertrophic cardiomyopathy; (7) greater than moderate valvular disease; (8) sarcoidosis; (9) amyloidosis; (10) thalassemia; and (11) hemochromatosis. The study complied with the 1964 Declaration of Helsinki and subsequent amendments.

Five patients were excluded due to exclusion criteria, and 2 were excluded for poor image quality and MRI contraindications. Seventeen obese patients with HFpEF and 45 obese patients without HFpEF, meeting inclusion criteria with matched gender and age, were recruited. Obesity was defined as a body mass index (BMI) ≥ 30.0 kg/m^2, following Asian-Pacific cutoff points[21]. All participants provided written, informed consent. BMI (kg/m^2) was calculated, and measurements included blood pressure, serum cholesterol, serum triglycerides, serum high-density lipoprotein cholesterol, and serum low-density lipoprotein cholesterol. Fasting glucose and hemoglobin A1c levels were also assessed. The study flow diagram is depicted in Figure 1.

Magnetic resonance protocol

All examination data were obtained using a 3.0 Tesla magnetic resonance scanner (Prisma, Siemens, Erlangen, Germany) equipped with a 32-channel cardiac coil. Cine imaging was acquired through retrospective ECG gating with balanced steady-state free-precession during horizontal and vertical long-axis views, and in 16 short-axis slices covering the entire left ventricle to evaluate left ventricular function and cardiac mechanics. Data in the short-axis plane were collected at the mid-ventricular level. Imaging parameters comprised a repetition time of 326.6 ms, echo time of 1.09 ms, flip angle of 35°, field of view of 385 × 385 mm^2, matrix of 156 × 192, slice thickness of 8 mm, slice gap of 4 mm, receiver bandwidth of 1085 Hz/px, GRAPPA acceleration factor 2, linear phase-encoding ordering, and 25 cardiac phases.

Data analysis

EAT was defined as the fat between the myocardium and the visceral pericardium. The borders of the EAT image were manually delineated on contiguous end-diastolic short-axis slices from the base to the apex using commercially available software (cvi42, Circle Cardiovascular Imaging Inc., Calgary, Canada) (Figure 2). Additionally, LV endocardial and epicardial borders were manually outlined slice by slice based on the initial contour set at end-diastole. EAT mass was estimated by multiplying the EAT volume by 0.92[22]. CMR image analyses were independently conducted by two experienced radiologists who were blinded to the study. LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV mass were measured and normalized to body surface area. LV stroke volume (LVSV) was calculated by

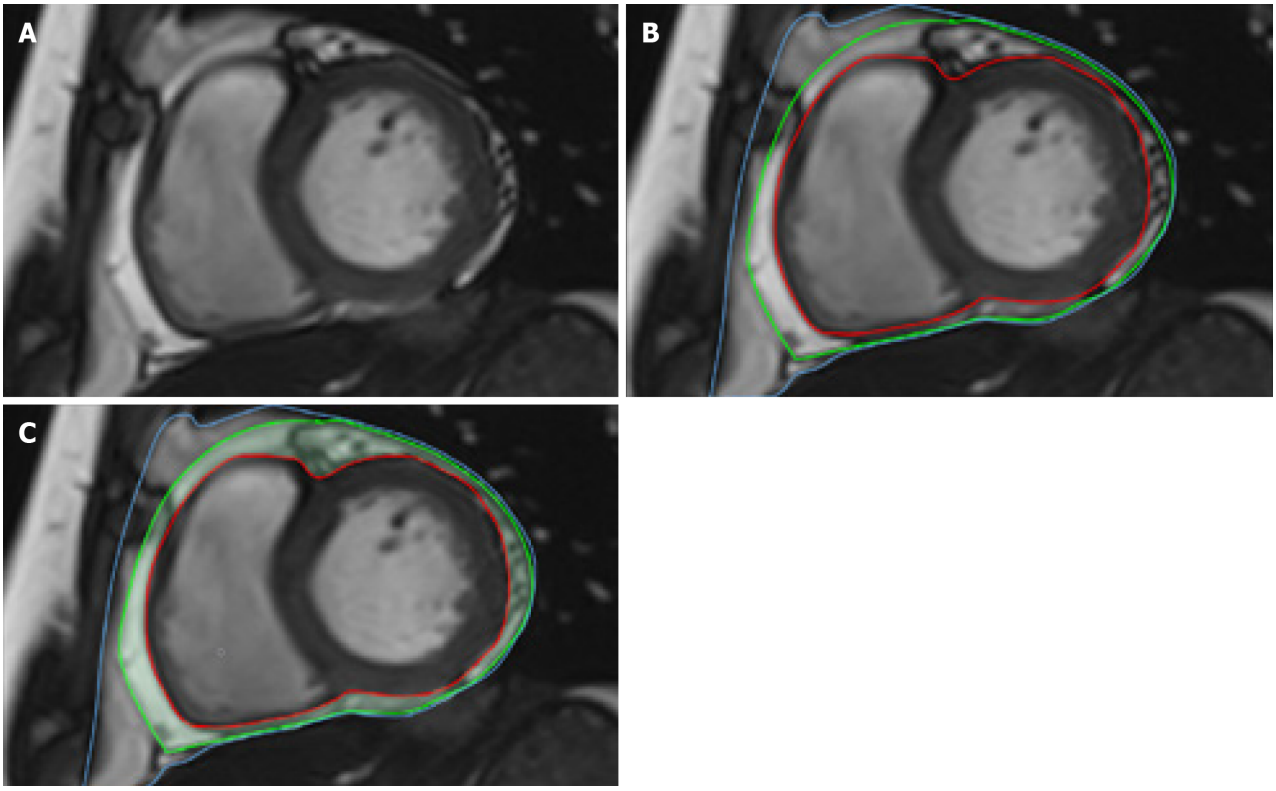

Figure 2 Epicardial adipose tissue image. A: Volume measurement of epicardial adipose tissue outlining the contours of the myocardium in short-axis images of end-diastole; B: The visceral pericardium (green line), myocardium (red line) and the parietal (blue line) in the same short-axis image; C: EAT: Epicardial adipose tissue (laurel-green area).

subtracting LVESV from LVEDV. LVEF was computed as LVSV/LVEDV × 100%. The measurement of left atrial anterior-posterior (LA AP) diameter and left atrial left-right (LA LR) diameter followed a previously reported method[23].

Statistical analysis

The normality of continuous samples was assessed using the Kolmogorov-Smirnov test for normal distribution. Group comparisons were conducted using Student's t-test for continuous variables or Fisher's exact test for categorical variables. Initial univariate analyses and stepwise multivariate linear regression analyses were executed to identify predictors of the odds of HFpEF in the obese population. Covariates with a univariate P value < 0.10 were included in the multivariate logistic regression analysis[24,25]. Pearson's correlation coefficient was employed for correlation analyses. A P value < 0.05 was considered significant. Intra- and inter-observer repeatability of parameters derived from CMR were assessed using the intra-class correlation coefficient (ICC) in 30 randomly selected patients from the same cohort[26]. An ICC > 0.75 was considered indicative of good agreement[27]. Descriptive and comparative statistical analyses were carried out using SPSS version 23.0 (IBM Corp., Armonk, United States) and GraphPad Prism v. 8.0 (GraphPad Software, Inc., CA, United States).

RESULTS

Baseline characteristics

Table 1 summarizes the baseline characteristics. The mean ages of the obese populations with HFpEF (HFpEF+) and without HFpEF (HFpEF-) were 42.94 ± 3.37 years and 36.60 ± 1.80 years, respectively (P > 0.05). In the HFpEF+ group, 17.6% were older than 60 years, compared to 0.02% in the HFpEF- group. Among HFpEF+ patients, 64.7% were males, while 55.6% of HFpEF- patients were males. No significant differences were observed in body surface area (BSA), BMI, BNP, and resting diastolic blood pressure, but there were significant differences between the two groups (P < 0.05). The prevalence of fatty liver was higher in the HFpEF- group (58.8%) compared to the HFpEF+ group (28.9%) (P = 0.0253), with no significant differences in other complications. Resting systolic blood pressure (SBP), regardless of medication control, was significantly higher in HFpEF+ patients than in the HFpEF- group (P = 0.0370).

CMR parameters of left ventricular morphology and function epicardial adipose tissue of the obesity in populations with and without HFpEF

The measurements' results are detailed in Table 2. In terms of morphological characteristics, the HFpEF+ group displayed

Table 1 Baseline characteristics and laboratory findings of the obesity in populations with and without heart failure with preserved ejection fraction, *n* (%)

Parameter	HFpEF+ (*n* = 17)	HFpEF- (*n* = 45)	*P* value
Age (yr)	42.94 ± 3.37	36.60 ± 1.80	0.0819
> 60A	3 (17.6)	1 (0.02)	0.0275[a]
Male gender	11 (64.7)	25 (55.6)	0.5227
BSA (m^2)	2.17 ± 0.07	2.13 ± 0.04	0.639
Weight (kg)	102.60 ± 5.49	103.00 ± 4.37	0.9667
BMI (kg/m^2)	35.78 ± 1.28	33.5 ± 0.99	0.2093
Systolic blood pressure (mmHg)	139.80 ± 4.73	130.90 ± 1.84	0.0370[a]
Diastolic blood pressure (mmHg)	86.59 ± 3.21	82.51 ± 1.61	0.2174
Complications			
Diabetes	9 (20.0)	4 (23.5)	0.7653
Hypertension	6 (35.3)	6 (13.3)	0.052
Hyperlipidemia	8 (47.1)	13 (28.9)	0.1652
Hyperuricemia	4 (23.5)	12 (26.7)	0.8051
Fatty liver	10 (58.8)	13 (28.9)	0.0253[a]
Biomarkers			
BNP (pg/mL)	22.67 ± 5.21	21.63 ± 2.95	0.86
Laboratory investigations			
Serum cholesterol (mmol/L)	5.01 ± 0.26	5.06 ± 0.16	0.8666
Serum triglycerides (mmol/L)	2.13 ± 0.21	1.85 ± 0.17	0.3609
Serum HDL (mmol/L)	1.06 ± 0.06	1.17 ± 0.03	0.0766
Serum LDL (mmol/L)	3.05 ± 0.20	3.12 ± 0.13	0.7818

[a]$P < 0.05$.

Data were given as means ± standard deviations. HFpEF: Heart failure with preserved ejection fraction; BSA: Body surface area; BMI: Body mass index; BNP: Brain natriuretic peptide; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

significant remodeling with a greater LV mass index compared to the HFpEF- group. No significant differences were observed in other morphological and functional parameters between the two groups. Regarding epicardial adipose tissue, both EAT volume and EAT mass were significantly larger in HFpEF+ individuals, and these differences persisted after adjustment for BSA ($P = 0.04$ for EAT volume/BSA and $P = 0.04$ for EAT mass/BSA). A significant difference in the EAT/LA LR diameter ratio was observed between the two groups ($P = 0.02$) (Figure 3).

Associations of epicardial adipose tissue and morphological and functional parameters in HFpEF+ group

The correlation analysis results of all four epicardial adipose tissue parameters (EAT volume, EATi, EAT mass, EAT mass index) with eight CMR-measured LV morphological and functional parameters are presented in Table 3. No significant correlations were observed.

Logistic regression analysis

In univariate logistic regression analysis, EAT mass index [odds ratio (OR) = 1.05, $P = 0.04$, 95%CI: 1.00-1.10], EATi (OR = 1.05, $P = 0.04$, 95%CI: 1.00-1.09), and EAT/LA LR diameter ratio (OR = 3.99, $P = 0.03$, 95%CI: 1.17-13.58) showed significant associations with HFpEF. EAT volume (OR = 1.02, $P = 0.051$, 95%CI: 1.00-1.04) trended toward an association with HFpEF. In multivariate analysis, the variable associated with HFpEF in the obese population was the EAT/LA LR diameter ratio (OR = 4.60, $P = 0.02$, 95%CI: 1.22-17.35) (Table 4).

Intraobserver and interobserver variability

Table 5 summarizes the ICC values for both intraobserver and interobserver reproducibility. The eight CMR-measured parameters demonstrated high reproducibility, ranging from 0.71 to 0.93 for intra-observer and 0.88 to 0.98 for inter-observer, respectively.

Table 2 Cardiac magnetic resonance parameters of chamber size, function, epicardial adipose tissue volume of the obesity in populations with and without heart failure with preserved ejection fraction

CMR parameters	HFpEF+ (*n* = 17)	HFpEF- (*n* = 45)	*P* value
Conventional parameters			
LVEF (%)	0.60 ± 0.03	0.64 ± 0.01	0.0797
LV mass index (g/m^2)	61.38 ± 4.55	52.68 ± 1.40	0.0181[a]
LVEDD (mm)	52.74 ± 1.80	50.20 ± 0.57	0.0833
LVMWT (mm)	10.32 ± 0.40	9.66 ± 0.25	0.1765
LVEDVi (mL/m^2)	74.00 ± 5.52	69.16 ± 1.72	0.2716
LVESVi (mL/m^2)	32.12 ± 5.87	24.84 ± 0.78	0.0592
LA AP diameter (mm)	41.37 ± 1.53	42.15 ± 0.87	0.6518
LA LR diameter (mm)	67.85 ± 2.55	70.63 ± 1.18	0.2686
Epicardial adipose tissue			
EAT volume (mL)	160.00 ± 7.13	139.80 ± 5.39	0.0449[a]
EATi (mL/m^2)	74.20 ± 3.16	65.37 ± 2.23	0.0360[a]
EAT mass (g)	147.20 ± 6.56	128.60 ± 4.98	0.0451[a]
EAT mass index (g/m^2)	68.26 ± 2.91	60.10 ± 2.06	0.0359[a]
EAT/LA AP diameter ratio	3.56 ± 0.18	3.11 ± 0.14	0.0843
EAT/LA LR diameter ratio	2.19 ± 0.11	1.84 ± 0.08	0.0203[a]
EAT/LV mass ratio	1.21 ± 0.09	1.17 ± 0.06	0.7737
EAT/LV volume ratio	0.99 ± 0.08	0.92 ± 0.04	0.4158

[a]$P < 0.05$.

Data were given as means ± standard deviations. AP: Anterior-posterior diameter; CMR: Cardiovascular magnetic resonance; LA: Left atrial; LR: left-right diameter; LVEDVi: Left ventricular end-diastolic volume index; LVEF: Left ventricular ejection fraction; LVESVi: Left ventricular end-systolic volume index; LVMWT: LV maximal wall thickness; LVEDD: Left ventricular end-diastolic diameter; EAT: Epicardial adipose tissue; EATi: Epicardial adipose tissue index.

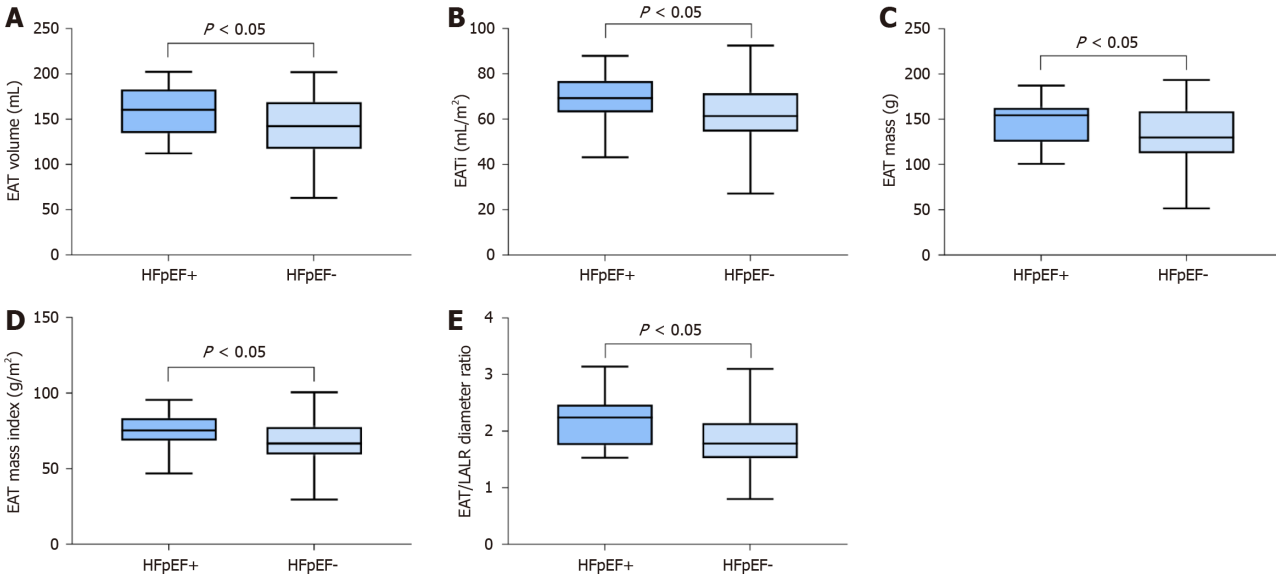

Figure 3 Comparison of different epicardial adipose tissue parameters in obese population with and without heart failure with preserved ejection fraction. A: Epicardial adipose tissue volume group; B: Epicardial adipose tissue index group; C: Epicardial adipose tissue mass group; D: Epicardial adipose tissue mass index group; E: Epicardial adipose tissue/left atrial left-right diameter ratio group. EAT: Epicardial adipose tissue; LA: Left atrial; LR: Left-right diameter; HFpEF: Heart failure with preserved ejection fraction.

Table 3 Relationships between epicardial adipose tissue and morphological and functional parameters in heart failure with preserved ejection fraction positive group

Pearson's correlation (*r*, *P*)	EAT volume (mL)	EATi (mL/m²)	EAT mass (g)	EAT mass index (g/m²)
LVEF (%)	-0.101, 0.698	0.245, 0.343	-0.101, 0.698	0.245, 0.343
LV mass index (g/m^2)	0.286, 0.265	-0.039, 0.881	0.286, 0.265	-0.039, 0.882
LVEDD (mm)	0.083, 0.751	-0.102, 0.696	0.083, 0.751	-0.102, 0.697
LVMWT (mm)	0.022, 0.932	-0.314, 0.219	0.022, 0.932	-0.314, 0.219
LVEDVi (mL/m^2)	-0.018, 0.946	-0.213, 0.412	-0.018, 0.946	-0.213, 0.412
LVESVi (mL/m^2)	0.028, 0.916	-0.213, 0.411	0.028, 0.916	-0.213, 0.411
LA AP diameter (mm)	0.354, 0.179	0.158, 0.558	0.354, 0.179	0.158, 0.558
LA LR diameter (mm)	0.231, 0.389	0.193, 0.474	0.231, 0.389	0.193, 0.474

All $P > 0.05$. AP: Anterior-posterior diameter; CMR: Cardiovascular magnetic resonance; LA: Left atrial; LR, Left-right diameter; LVEDVi: Left ventricular end-diastolic volume index; LVEF: Left ventricular ejection fraction; LVESVi: Left ventricular end-systolic volume index; LVMWT: LV maximal wall thickness; LVEDD: Left ventricular end-diastolic diameter; EAT: Epicardial adipose tissue; EATi: Epicardial adipose tissue index.

Table 4 Variables associated with the heart failure with preserved ejection fraction in obesity population

Variables	Lower/upper	
	Univariate analysis (OR, 95%CI, *P* value)	Multivariate analysis (OR, 95%CI, *P* value)
Age (yr)	1.040 (0.994, 1.088) 0.087	1.046 (0.979, 1.117) 0.183
BMI (kg/m^2)	1.057 (0.969, 1.154) 0.213	
BMI > 35 kg/m^2	2.812 (0.558, 14.179) 0.210	
Diabetes	1.231 (0.323, 4.689) 0.761	
Hypertension	3.545 (0.952, 13.201) 0.059	4.580 (1.008, 20.803) 0.049[a]
LVEF (%)	0.002 (0.000, 7.482) 0.136	
LVEDVi (mL/m^2)	1.020 (0.984, 1.058) 0.288	
LVESVi (mL/m^2)	1.063 (0.958, 1.178) 0.249	
LA AP diameter (mm)	0.977 (0.884, 1.080) 0.646	
LA LR diameter (mm)	0.963 (0.900, 1.030) 0.267	
EAT mass index (g/m^2)	1.049 (1.002, 1.098) 0.042[a]	0.963 (1.054, 0.880) 0.416
EAT mass (g)	1.020 (1.000, 1.041) 0.051	
EATi (mL/m^2)	1.045 (1.002, 1.090) 0.042[a]	
EAT volume (mL)	1.019 (1.000, 1.038) 0.051	
EAT/LA AP diameter ratio	1.794 (0.915, 3.519) 0.089	
EAT/LA LR diameter ratio	3.989 (1.171, 13.584) 0.027[a]	9.226 (1.070, 79.512) 0.043[a]
EAT/LV mass ratio	1.236 (0.300, 5.098) 0.770	
EAT/LV volume ratio	2.299 (0.317, 16.658) 0.410	

[a]$P < 0.05$.

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; EAT: Epicardial adipose tissue; EATi: Epicardial adipose tissue index; CI: Confidence interval; OR: Odds ratio.

DISCUSSION

In this study, we conducted a comprehensive comparison of EAT volume, mass, and functional characteristics, as determined by CMR, among individuals with obesity in the absence of HFpEF (HFpEF-) and HFpEF+ groups. The main findings of our study are as follows: (1) EAT volume and EAT mass were significantly increased in the obese HFpEF+

Table 5 Intra-observer and inter-observer reproducibility for epicardial adipose tissue parameters

	Intra-observer			Inter-observer		
	CV (%)	ICC	95%CI	CV (%)	ICC	95%CI
EAT volume (mL)	24.6	0.929	(0.885, 0.939)	18.4	0.900	(0.746, 0.963)
EATi (mL/m^2)	23.0	0.913	(0.846, 0.951)	17.6	0.903	(0.753, 0.964)
EAT mass (g)	26.3	0.931	(0.878, 0.962)	17.9	0.900	(0.746, 0.963)
EAT mass index (g/m^2)	23.7	0.913	(0.846, 0.951)	31.0	0.978	(0.941, 0.992)
EAT/LA AP diameter ratio	35.9	0.734	(0.561, 0.846)	18.5	0.882	(0.696, 0.957)
EAT/LA LR diameter ratio	28.4	0.710	(0.526, 0.831)	19.9	0.928	(0.807, 0.974)
EAT/LV mass ratio	34.7	0.870	(0.774, 0.927)	31.3	0.978	(0.941, 0.992)
EAT/LV volume ratio	29.4	0.929	(0.874, 0.961)	31.6	0.973	(0.928, 0.963)

EAT: Epicardial adipose tissue; EATi: Epicardial adipose tissue index; LA: Left atrial; AP: Anterior-posterior; LR: Left-right; LV: Left ventricular; ICC: Intra-class correlation coefficient.

group compared to the obese HFpEF- group, and these differences persisted after adjustment for BSA; (2) in the obese population, the EAT/LA LR diameter ratio can serve as an alternative method to differentiate between HFpEF+ and HFpEF- groups; and (3) a higher EAT/LA LR diameter ratio was associated with a higher risk of HFpEF after adjusting for potential confounders.

The utilization of CMR for EAT measurement in our study provides a comprehensive assessment of cardiac structure and function in individuals with HFpEF[28]. Additionally, our study contributes to the existing literature by implementing and evaluating the quantification of EAT using MRI during diastole[29]. In a prior study, we demonstrated CMR's sensitivity and accuracy in detecting conventional atrial geometry in dialysis patients with HFpEF[30]. The present study, employing CMR to measure EAT, holds significant strengths over prior investigations examining the association between EAT and HFpEF in an obese population.

Our findings revealed that EAT volume and EAT mass, determined by CMR, were significantly higher in the HFpEF+ group compared to the HFpEF- group, with significant differences in EATi and EAT mass index as well. EAT, recognized as a risk factor for heart failure, particularly in the obese population[30,31], is implicated as an independent risk factor for HFpEF[32,33]. EAT's invasion into and around coronary arteries contributes to microvascular dysfunction, ventricular dilatation, and heart failure[12]. Adipocytes within EAT possess endocrine functions, synthesizing aldosterone and angiotensinogen[34]. Moreover, EAT serves as a marker for inflammatory factors[35]. Consistent with previous echocardiographic studies associating EAT thickness with HFpEF[36], our results further support this relationship.

In our study, there was a significant increase in LV mass index in the HFpEF+ group compared to the HFpEF- group. The space between the myocardial surface and the visceral pericardium may be filled with EAT, potentially covering the entire epicardium[37]. In the obese population, the excess EAT could impose an increased burden on both ventricles, ultimately leading to left ventricular hypertrophy[38]. These findings are consistent with prior investigations into obesity. A previous study utilizing CMR demonstrated that individuals with uncomplicated obesity and HFpEF exhibited extensive LV geometric remodeling, impaired ventricular function, and increased myocardial thickness[39].

Our research revealed that the EAT/LA LR diameter ratio was higher in the HFpEF+ group compared to the HFpEF- group, and this ratio was significantly associated with HFpEF. While no prior study has specifically investigated changes in the EAT/LA LR diameter ratio, it has been demonstrated to be impaired before left atrial enlargement in obese patients with HFpEF experiencing diastolic heart failure[40]. A recent study utilizing transthoracic echocardiography indicated that increased EAT thickness was linked to poorer left atrial function in HFpEF[41]. Additionally, another echocardiography-related study suggested that the presence of increased EAT is associated with a greater increase in cardiac filling pressures in patients with the obese phenotype of HFpEF[11]. Thus, the utilization of EAT/LA LR, assessed through CMR, could play a crucial role in the differentiation and diagnosis of obese HFpEF in clinical practice in the future. The EAT/LA LR diameter ratio may serve as a novel imaging biomarker.

Our study demonstrated no correlation between the four epicardial adipose tissue parameters (EAT volume, EATi, EAT mass, EAT mass index) and CMR-measured LV morphological and functional parameters. This finding aligns with some of the current studies[39]. It is plausible that our sample size is relatively small, and more conclusive results may emerge in the future with a larger sample size.

According to prior studies, age significantly contributes to EAT accumulation and may exert a substantial influence on its buildup[42]. In our study, there was no significant difference in age between the two groups, indicating that the effect of age on EAT was excluded. Despite the lack of statistical significance, there appears to be a trend towards older age in patients with HFpEF, supported by a higher proportion of subjects aged over 60 years in the HFpEF+ cohort. Additionally, resting SBP was significantly higher in HFpEF+ patients than in the HFpEF- group. Patients with HFpEF exhibit reduced aortic distensibility and increased systolic blood pressure[43]. Previous findings suggest that obesity has a detrimental impact on prehypertension and hypertension, irrespective of general obesity or abdominal obesity presence [44].

CONCLUSION

EAT/LA LR diameter ratio is highly associated with HFpEF in obese patients. It is plausible that there may be utility in CMR for assessing obese patients for HFpEF using EAT/LA LR diameter ratio as a diagnostic biomarker. Further prospective studies, are needed to validate these proof-of-concept findings.

ARTICLE HIGHLIGHTS

Research background

Obesity has become a serious public health issue, significantly elevating the risk of various complications. It is a well-established contributor to Heart failure with preserved ejection fraction (HFpEF). Evaluating HFpEF in obesity is crucial. Epicardial adipose tissue (EAT) has emerged as a valuable tool for validating prognostic biomarkers and guiding treatment targets. Hence, assessing EAT is of paramount importance. Cardiovascular magnetic resonance (CMR) imaging is acknowledged as the gold standard for analyzing cardiac function and morphology. We hope to use CMR to assess EAT as a bioimaging marker to evaluate HFpEF in obese patients.

Research motivation

The aim of this study was to clarify the utility of using CMR-measured EAT as a diagnostic biomarker for assessing HFpEF in obese patients.

Research objectives

This study aims to employ CMR to examine EAT in the obese population with and without HFpEF, considering the association with co-morbidities, biomarkers, contractility parameters, and myocardial function assessed by CMR.

Research methods

The study was designed as a case-control, prospective clinical study. Obese patients were divided into two groups for a case-control study based on whether or not they had heart failure with HFpEF. The two groups were defined as HFpEF+ and HFpEF-. LV geometry, global systolic function, EAT volumes and EAT mass of all subjects were obtained using cine magnetic resonance sequences. The novelty of this study is to investigate EAT metrics (including volume or mass) in obese patients using CMR to determine whether or not EAT metrics are associated with HFpEF and whether EAT metrics appear to be a biomarker for predicting HFpEF in the obese population.

Research results

Forty-five patients of HFpEF- group and seventeen patients of HFpEF+ group were included. LV mass index (g/m^2) of HFpEF+ group was higher than HFpEF- group ($P < 0.05$). In HFpEF+ group, EAT volumes, EAT volume index, EAT mass, EAT mass index and EAT/ left atrial (LA) left-right (LR) diameter ratio were higher compared to HFpEF- group. In multivariate analysis, higher EAT/LA LR diameter ratio was independently associated with higher odds ratio (OR = 4.597) of HFpEF.

Research conclusions

There was a strong correlation between increased EAT volumes and HFpEF in the obese. EAT/LA LR diameter ratio is highly associated with HFpEF in the obese.

Research perspectives

Given the significant findings, there may be some diagnostic utility in CMR for assessing the obese for HFpEF.

FOOTNOTES

Co-first authors: Ju-Wei Shao and Bing-Hua Chen.

Co-corresponding authors: Jing Ma and Lian-Ming Wu.

Author contributions: Shao JW and Wu LM were scientific study designers; Ma J, Chen BH, and Wu LM were involved in data collection; Shao JW and Chen BH contributed to data analysis; and Shao JW, Abu-Shaban K, Baiyasi A, and Wu LM were involved in manuscript writing and revision; All authors read and approved the final manuscript; Special thanks to Booth TC for revising the manuscript. Ma J and Wu LM as co-corresponding authors are threefold. First, the research was conducted through a joint effort, with co-corresponding authorship rightly mirroring the shared workload and commitment needed for both the study's execution and the ensuing publication. This approach also facilitates efficient handling of post-submission processes, thereby bolstering the paper's integrity and excellence. Second, the research group comprised individuals with varied specialties and backgrounds, making the appointment of co-corresponding authors a representation of this multidisciplinary nature. This arrangement allows for a thorough and nuanced exploration of the subject matter, thereby deepening the reader's comprehension through diverse expert insights. At last, Ma Jing and Wu LM made equally significant contributions throughout the research journey. Selecting them as co-corresponding authors honors their joint efforts, underscoring the importance of teamwork and cooperative spirit inherent in this project.

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Clinical trial registration statement: We didn't register this trial on the Clinical Trial Registration platform prior to this trial.

Informed consent statement: This is a retrospective study. All the data are from our database. All patients were anonymised and the data collection was a health check. We have signed Informed Consent Form for this study.

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CASE REPORT

Severe hypoxemia after radiofrequency ablation for atrial fibrillation in palliatively repaired tetralogy of Fallot: A case report

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Abstract

BACKGROUND

Patients with tetralogy of Fallot (TOF) often have arrhythmias, commonly being atrial fibrillation (AF). Radiofrequency ablation is an effective treatment for AF and does not usually cause severe postoperative hypoxemia, but the risk of complications may increase in patients with conditions such as TOF.

CASE SUMMARY

We report a young male patient with a history of TOF repair who developed severe hypoxemia after radiofrequency ablation for AF and was ultimately confirmed to have a new right-to-left shunt. The patient subsequently underwent atrial septal occlusion and eventually recovered.

CONCLUSION

Radiofrequency ablation may cause iatrogenic atrial septal injury; thus possible complications should be predicted in order to ensure successful treatment and patient safety.

Key Words: Atrial fibrillation; Radiofrequency ablation; Tetralogy of Fallot; Right-to-left shunt; Hypoxemia; Medical decision; Case report

Core Tip: More attention should be paid to patient hemodynamics before and after radiofrequency ablation in those with a potential risk of right-to-left shunt such as tetralogy of Fallot patients. These patients may need to be further evaluated before or during surgery to make safer treatment decisions. This case may provide an important reference for the proper preparation and perioperative management of atrial fibrillation under special circumstances.

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INTRODUCTION

Tetralogy of Fallot (TOF) has been reported to be the most common cyanotic congenital heart disease with an incidence of 0.34 per 1000 Live births[1,2]. With the development of medical technology, the survival rate of patients with TOF has significantly increased; however, long-term complications can occur. Atrial arrhythmia is one of the most common late complications after the repair of TOF (and is generally related to myopathy caused by atrial surgical scarring, right atrial dilatation, and valve reflux[3,4]). However, rhythm control and heart rate control are not effective in preventing atrial fibrillation (AF) in patients with TOF[4], and radiofrequency ablation has become an important method of treating these patients[5]. Multiple studies have confirmed the safety and feasibility of this treatment[6,7], but few reports have focused on the risk of transatrial septal puncture in patients with TOF. Here, we report a case of severe hypoxemia in a patient with TOF who developed a right-to-left shunt after radiofrequency ablation for AF. This case provides an important reference for the surgical risk assessment and final decision in the treatment of similar patients, and may effectively prevent the occurrence of serious complications.

CASE PRESENTATION

Chief complaints

A 32-year-old man visited our center due to "heart palpitations for 2 mo".

History of present illness

In the past 2 mo, the patient had persistent palpitations without obvious inducement, but there was no discomfort such as chest pain and dyspnea.

History of past illness

The patient had sustained palpitations recently and had a history of similar attacks in the past. He completed a 12-lead electrocardiogram (ECG) in the outpatient clinic and was diagnosed with AF. The patient still had palpitations and discomfort after taking metoprolol sustained-release tablets for heart rate control, and was admitted to the hospital for catheter ablation of AF. He had a history of TOF, and underwent palliative correction surgery 20 years ago, involving correction of complex congenital heart disease and pulmonary artery artificial vascular implantation.

Personal and family history

The patient denied any family history of congenital heart disease and AF.

Physical examination

Surgical scars were seen on the chest, arrhythmia was present, a systolic murmur was heard in the auscultation area of the pulmonary valve, and the cardiac boundary was enlarged.

Laboratory examinations

No obvious abnormalities were found during preoperative examinations such as routine blood and liver and kidney function tests.

Imaging examinations

The 12-lead ECG showed AF (Figure 1). Transthoracic echocardiography confirmed the changes after TOF correction and pulmonary artery implantation, with the formation of collateral circulation between the descending aorta and the left pulmonary artery, no shunt at the ventricular septum level, enlargement of the right heart, and moderate to severe tricuspid regurgitation (Figure 2). Transesophageal echocardiography did not show the atrial septal shunt, which ruled out the possibility of "pentalogy of Fallot" in this patient. In addition, pulmonary venous computed tomography angiography (CTA) was performed preoperatively to evaluate pulmonary venous structure and function, showing that

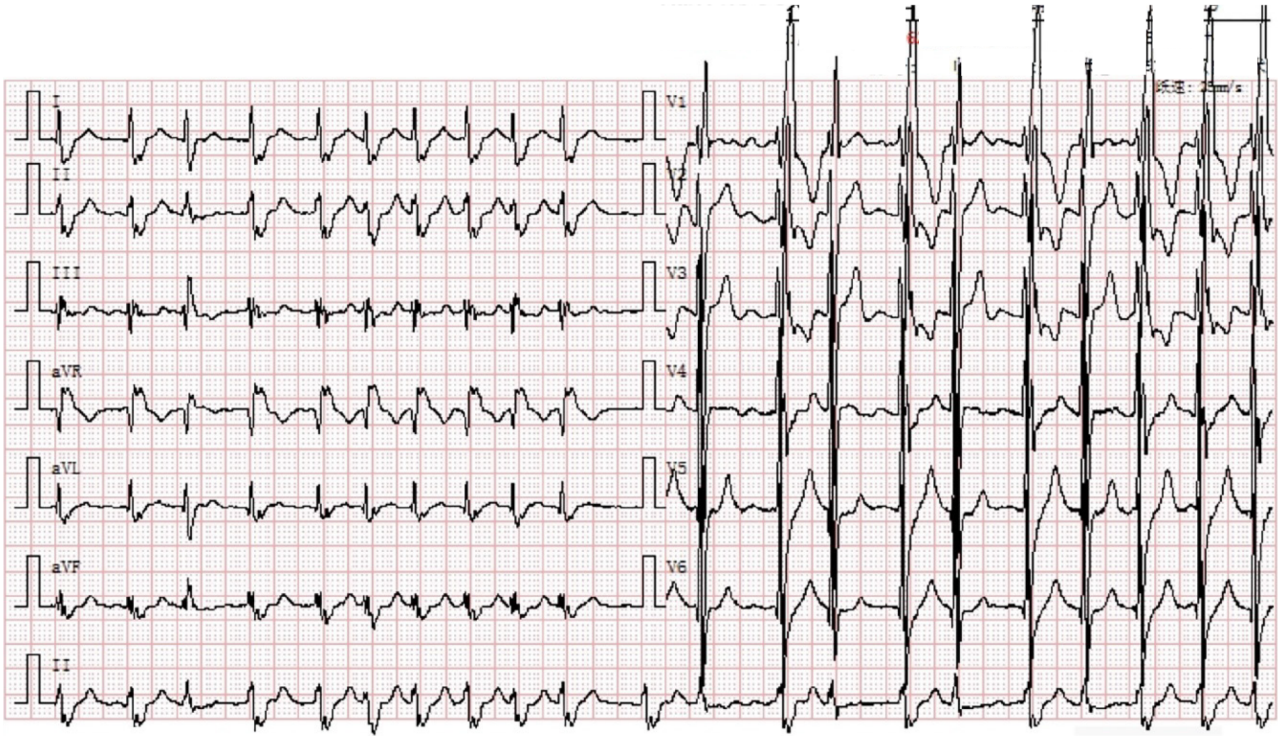

Figure 1 The patient's admission electrocardiogram indicating atrial fibrillation.

the right heart was significantly enlarged, and no obvious filling defect was found in the lumen. An artificial blood vessel shadow was seen between the right pulmonary artery and the right ventricle. The left side of the descending aorta was connected to the left pulmonary artery by another artificial blood vessel (Figure 3). These two artificial vessels may have reduced the symptoms of right ventricular outflow tract obstruction.

FINAL DIAGNOSIS

Based on the clinical manifestations and imaging findings, the patient was initially diagnosed with AF, and post-repair for TOF.

TREATMENT

After completing the evaluation, pulmonary vein isolation and BOX isolation were performed under the guidance of the CARTO® system, and an ablation catheter was delivered to the bilateral pulmonary veins by an atrial septal puncture method under the guidance of ultrasound to complete electrical isolation during the operation. Intraoperative oxygen saturation was maintained at 90%-93%. No obvious complications were observed following catheter withdrawal. After ablation, the ECG showed sinus rhythm and dual-source atrial premature contractions. The outcome of the operation was satisfactory and met our expectations.

On the second day after ablation, the patient complained of chest tightness and shortness of breath without obvious inducement, and blood oxygen saturation decreased gradually, reaching a minimum of 50%. Oxygen saturation was only maintained at 70%-75% by oxygen inhalation. Physical examination revealed poor mental status, distention of the jugular vein, cyanosis of the mouth and lips, and decreased temperature in the extremities. Arterial blood gas analysis showed that the partial pressure of carbon dioxide was 25 mmHg, the partial pressure of oxygen was 42 mmHg, and the blood pH and bicarbonate concentration were within the normal range. Blood tests showed a brain natriuretic peptide level of 2716 ng/mL. In light of the patient's history of congenital heart disease, acute heart failure was considered, an echocardiogram was performed, and a new right-to-left shunt approximately 9 mm wide was identified (Figure 4). After multidisciplinary consultation, hypoxemia due to circulatory hypoxia caused by an arteriovenous shunt, and atrial septal defect repair surgery were considered. However, blood oxygen saturation should be maintained before surgery to prevent damage to important organs, while endotracheal intubation was of little help to correct hypoxemia in this patient and may even have aggravated hypoxia. Therefore, the patient was transferred to the intensive care unit and a veno-venous extracorporeal membrane oxygenation intubation was performed. Postoperative oxygen saturation was maintained above 90%. Arterial blood gas analysis showed 29 mmHg of carbon dioxide and 85 mmHg of oxygen.

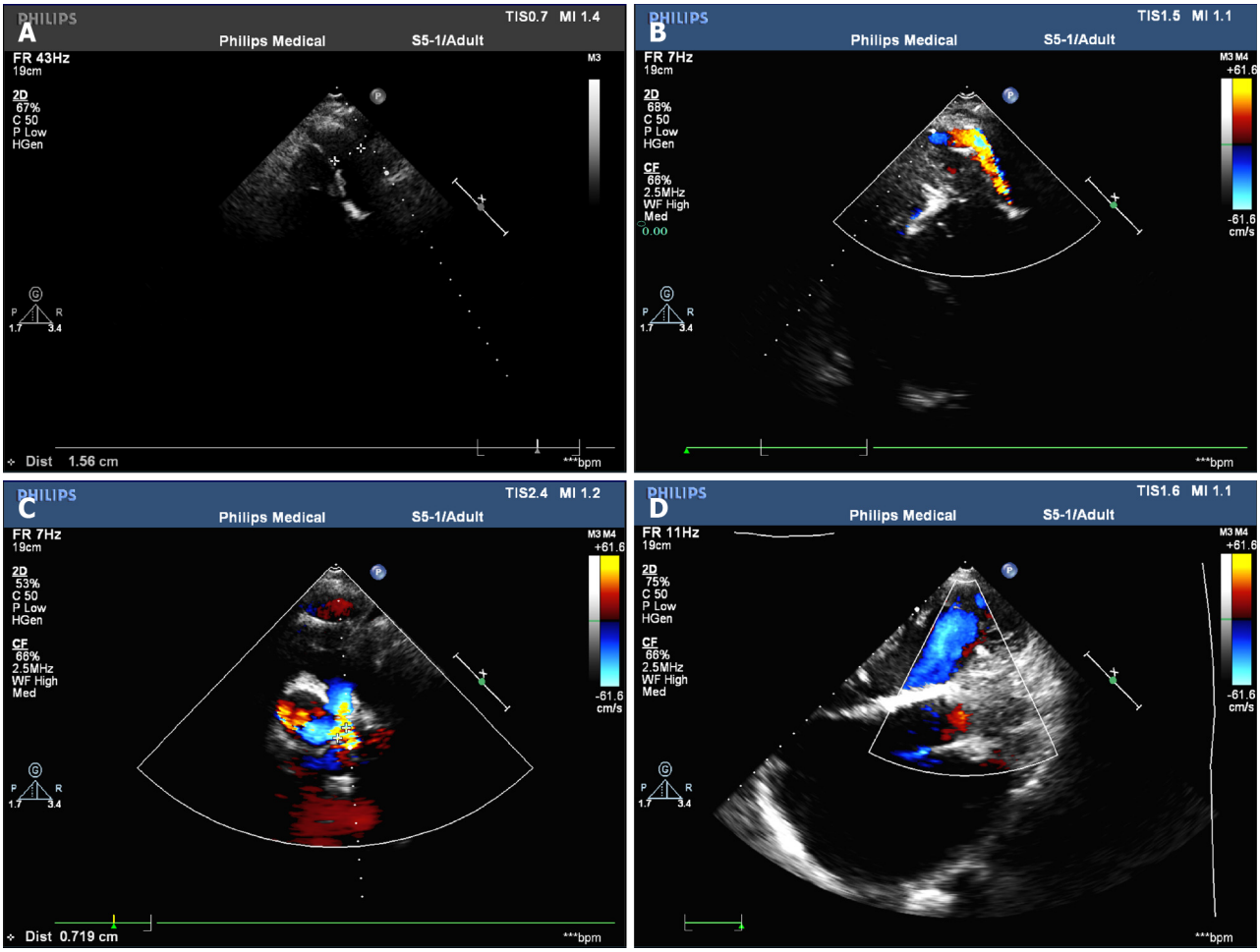

Figure 2 Preoperative echocardiography. A and B: Artificial blood vessel shadow and blood flow signal can be seen between the descending aorta and the left pulmonary artery; C: Moderate to severe tricuspid regurgitation can be seen during cardiac systole; D: No significant residual shunt was observed at the interventricular septal level.

When the patient's vital signs became stable, we communicated with his family and an atrial defect closure was subsequently performed with insertion of a 14 mm occluder (Figure 5). Oxygen saturation was maintained above 90% in the shutdown state of extracorporeal membrane oxygenation after occlusion. Following administration of anti-infection and anticoagulation therapy, the patient's condition improved and he was discharged.

OUTCOME AND FOLLOW-UP

The patient's oxygen saturation was normal and there were no episodes of AF after the operation.

DISCUSSION

AF has been reported with a higher probability in patients with TOF and occurs at a younger age than in the general population[8]. Ablative therapy has been proved to be an effective curative treatment modality for AF[5]. A previous study proved that AF progresses more rapidly in patients with TOF and conventional antiarrhythmic drugs are not effective[4]. With the development of electrophysiological techniques, the success rate of ablation at the lesion site in the presence of complex arrhythmogenic scarring and substrate in patients with TOF has improved. Current reports focus on the recurrence of postoperative arrhythmias and the quality of life of patients, and have confirmed the efficacy of radiofrequency ablation in the treatment of AF after repair of TOF[7,9]. However, there have been few reports on the risks of radiofrequency ablation in patients with TOF. Due to congenital abnormalities, patients with TOF may not be able to tolerate atrial septal puncture during radiofrequency ablation in terms of cardiac infrastructure and hemodynamics.

Typically, transseptal puncture for radiofrequency ablation of AF does not cause serious complications and does not require special treatment[9]. However, in this report, atrial septal puncture resulted in severe hypoxemia. It is known that patients with TOF usually develop right ventricular outflow tract obstruction, and this hemodynamic abnormality may still be present even after surgical treatment. In this case, the patient underwent TOF palliative surgery, in which the

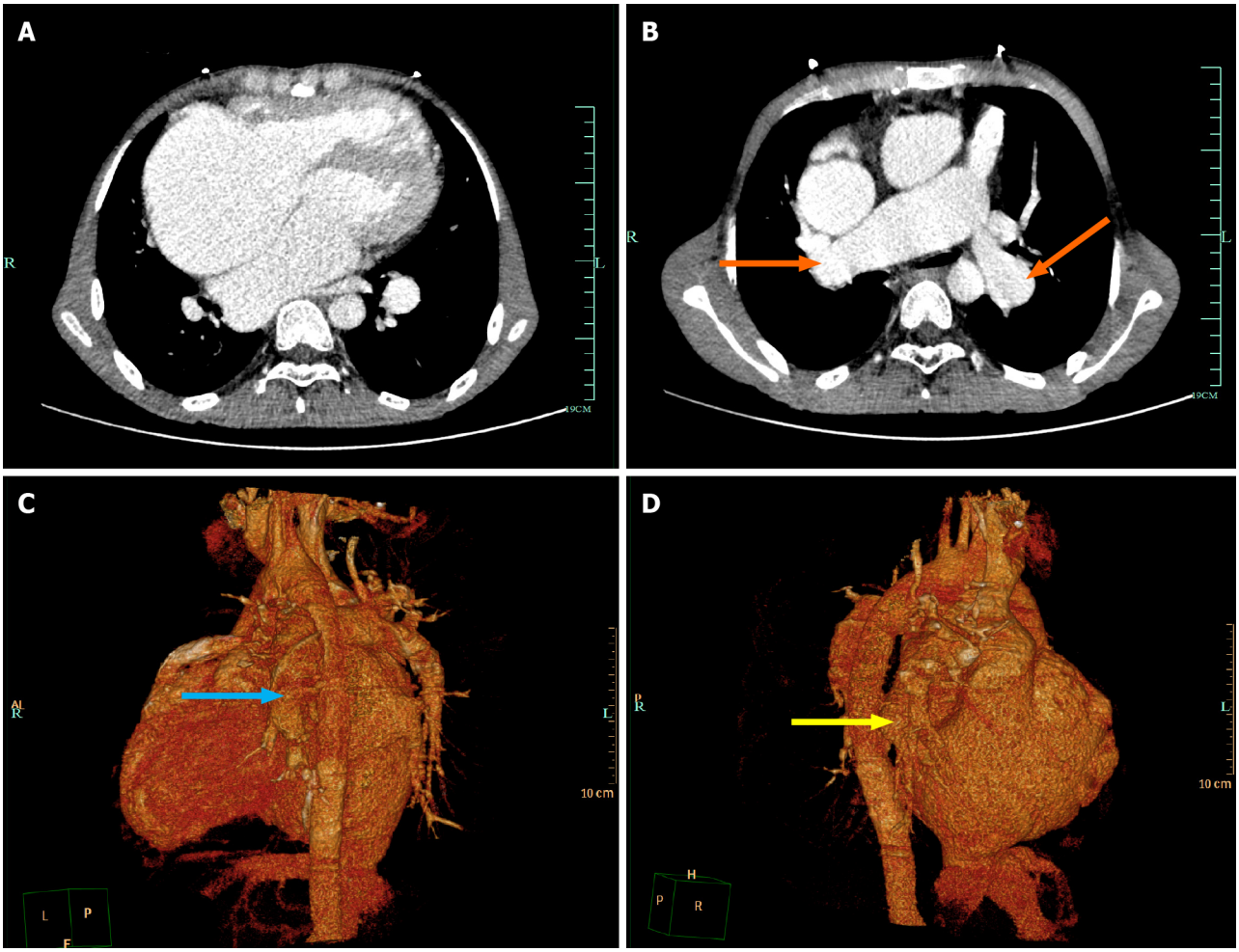

Figure 3 Preoperative pulmonary venous computed tomography angiography imaging. A: The right heart was significantly enlarged; B: Artificial blood vessel shadow can be seen on computed tomography angiography (orange arrow); C: The left side of the descending aorta is connected to the left pulmonary artery by an artificial vessel (blue arrow); D: The artificial blood vessel is visible between the right pulmonary artery and the right ventricle (yellow arrow).

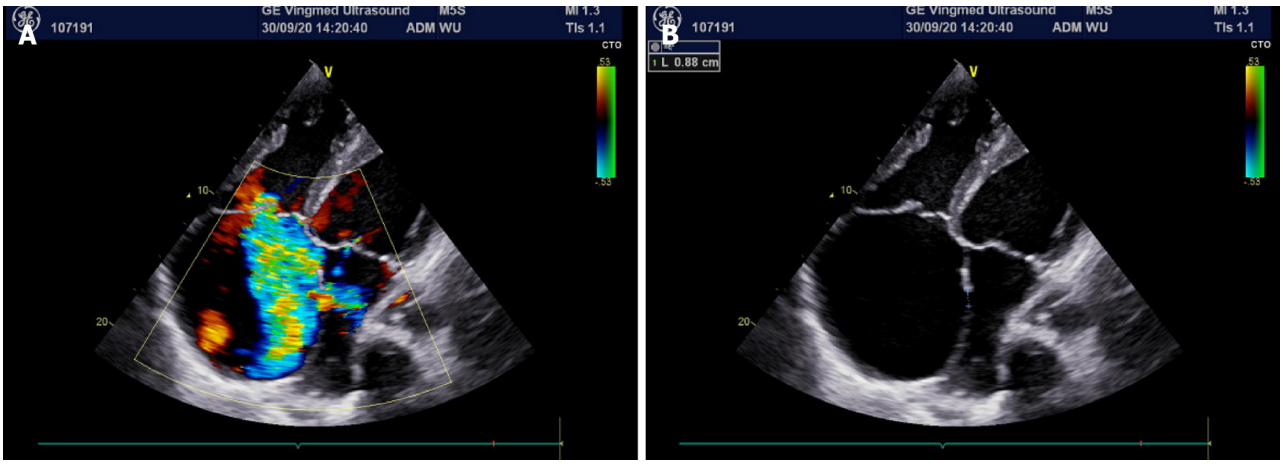

Figure 4 Postoperative cardiac ultrasound. A: Doppler ultrasound showed multicolored blood flow between the left and right atria, indicating the presence of atrial septal defect; B: The diameter of the atrial septal defect was about 0.88 cm.

implantation of artificial blood vessels relieved some, but not all, of the pulmonary hypertension. In addition, during the preoperative ECG examination, the right heart was enlarged and the tricuspid valve showed medium-severe regurgitation, which suggested that during the systolic period, a large amount of blood flow regurgitated into the right atrium, resulting in high pressure in the right atrium. If an atrial septal defect is present at the same time, a right-to-left shunt is likely to form, resulting in hypoxemia. Transatrial septal puncture during radiofrequency ablation resulted in this condition followed by the subsequent development of hypoxemia. Unfortunately, we failed to accurately assess the

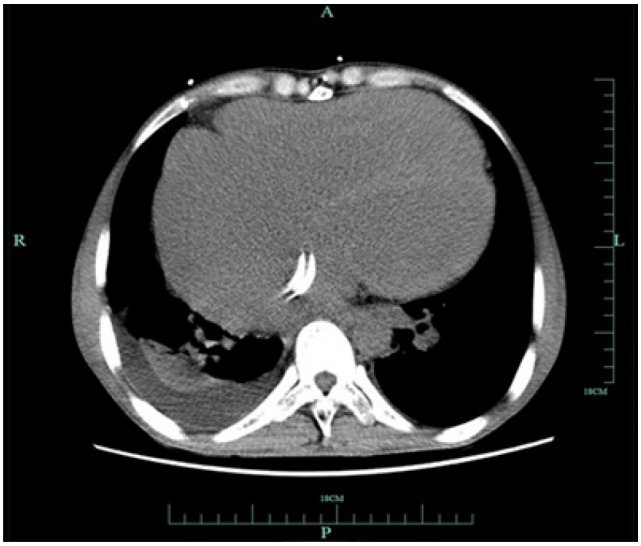

Figure 5 Postoperative pulmonary imaging showed implantation of the atrial septal occluder.

right atrial pressure and predict the risk of atrial septal puncture leading to subsequent disease.

Usually, no serious pulmonary hypertension occurs after correction of TOF[10], but there are still a small number of patients with significantly increased pressure in the right ventricular outflow tract[11,12]. This long-term complication not only affects the quality of life of patients, but also increases the potential risk of atrial septal puncture therapy. Preoperative elevated pulmonary artery pressure has been shown to promote the risk of right-to-left shunt in iatrogenic atrial septal defects[13]. In addition, the persistence of an iatrogenic atrial septal defect leading to refractory hypoxemia has been reported in several cases[14,15], and studies have shown that patients with iatrogenic atrial septal defects are more likely to have hemodynamic abnormalities, heart failure, and other conditions[16,17]. These results suggest that patients with right ventricular outflow tract abnormalities and iatrogenic atrial septal defects are more likely to develop hypoxemia. Following the diagnosis and treatment of this critically ill patient, we believe that it may be possible to effectively reduce the occurrence of postoperative hypoxemia by accurately detecting the right heart pressure through the right cardiac catheter in advance for patients with right-to-left shunt risk. This method is not only suitable for TOF, but can also be used for preoperative evaluation of patients with pulmonary malformation, pulmonary embolism, chronic obstructive pulmonary disease, and other diseases to reduce the risk of surgery.

CONCLUSION

More attention should be paid to patient hemodynamics before and after radiofrequency ablation in those with a potential risk of right-to-left shunt such as TOF patients. These patients may need to be further evaluated before or during surgery to make safer treatment decisions. This case provides an important reference for appropriate treatment decisions and perioperative management of AF under special circumstances.

FOOTNOTES

Co-first authors: Zhi-Hang Li and Lian Lou.

Co-corresponding authors: Jian Yang and Xuan Zhang.

Author contributions: Li ZH, Lou L, and Chen YX participated in the data collection, and writing and literature analysis of the article. All authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Li ZH was responsible for article writing and case information collection, and Lou L was responsible for article revision and literature review. Li ZH and Lou L made equal major contributions to this article, so they are listed as the co-first authors. Yang J and Zhang X contributed equally to this work as co-corresponding authors. They all provided constructive suggestions on case selection, diagnosis and treatment process, prognosis analysis, writing guidance, and so on. To sum up, the author ranking above reflects our recognition and respect for the efforts of the authors, as well as the recognition of the teamwork spirit of this research.

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