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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

Living biodrugs and how tissue source influences mesenchymal stem cell therapeutics for heart failure

Siddharth Shah, Huzaifa Sabir Nawaz, Muhammad Saeed Qazi, Hritvik Jain, Brandon Lucke-Wold

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Abstract

In this editorial we comment on the article by Safwan M *et al*. We especially focused on the cardiac function restoration by the use of mesenchymal stem cells (MSCs) therapy for heart failure (HF), which has emerged as a new treatment approach as "Living Biodrugs". HF remains a significant clinical challenge due to the heart's inability to pump blood effectively, despite advancements in medical and device-based therapies. MSCs have emerged as a promising therapeutic approach, offering benefits beyond traditional treatments through their ability to modulate inflammation, reduce fibrosis, and promote endogenous tissue regeneration. MSCs can be derived from various tissues, including bone marrow and umbilical cord. Umbilical cord-derived MSCs exhibit superior expansion capabilities, making them an attractive option for HF therapy. Conversely, bone marrow-derived MSCs have been extensively studied for their potential to improve cardiac function but face challenges related to cell retention and delivery. Future research is focusing on optimizing MSC sources, enhancing differentiation and immune modulation, and improving delivery methods to overcome current limitations.

Key Words: Mesenchymal stem cells; Heart failure; Umbilical cord-derived mesenchymal stem cells; Bone marrow-derived mesenchymal stem cells; Therapeutics for heart failure;

Biodrugs; Tissue source

Core Tip: Mesenchymal stem cells (MSCs) offer a novel regenerative approach to treating heart failure (HF), especially ischemic HF, by modulating inflammation, reducing fibrosis, and promoting tissue repair. Sources like bone marrow and umbilical cord each provide distinct benefits. Umbilical cord-derived MSCs are particularly promising due to their superior growth capacity and reduced senescence. However, challenges in cell retention and delivery persist. Current research focuses on refining MSC sources, enhancing differentiation, and improving delivery methods, paving the way for MSCs to become a pivotal therapy in HF management.

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INTRODUCTION

Heart failure (HF) is a clinical syndrome characterized by the heart's inability to pump blood effectively, leading to insufficient blood flow to meet the body's needs. Ischemic heart disease, particularly ischemic cardiomyopathy, is a leading cause of HF[1]. This form of HF, referred to as ischemic HF, arises from chronic ischemic injury to the myocardium, such as that caused by coronary artery disease or a prior myocardial infarction[2]. The prognosis of ischemic HF remains poor despite advancements in medical therapies, cardiac rehabilitation, and device-based interventions like left ventricular assist devices (LVADs). These devices have shown survival and quality of life benefits in patients with advanced HF, serving as a bridge to heart transplantation or as long-term therapy for those not eligible for transplantation[3,4]. However, while LVADs can induce partial reverse remodeling of the left ventricle[5], this improvement is rarely sufficient to allow device removal, highlighting the need for adjunctive therapies[6]. Cell therapy has emerged as a promising approach to treating ischemic HF in the last 2 decades[7]. The potential of cell therapy lies in its ability to improve cardiac function through mechanisms beyond simple regeneration of cardiomyocytes. Mesenchymal stem cells (MSCs), in particular, have garnered significant attention due to their low immunogenic potential and ability to be isolated from various adult tissues, including bone marrow, adipose tissue, and umbilical cord tissue[8]. MSCs are multipotent cells capable of self-renewal and multilineage differentiation[9]. Their therapeutic potential in HF is attributed not only to their capacity to differentiate into various cell types but also to their paracrine effects, which include antifibrotic, anti-apoptotic, anti-inflammatory, and pro-angiogenic actions[10]. Unlike whole organ transplantation or many other allogeneic cell transplants, MSC transplants do not cause rejection and may even induce tolerance to the donor, making them an attractive candidate for cell-based therapies in HF[11].

Clinical trials have shown that MSCs can improve cardiac performance in patients with chronic ischemic HF. For instance, studies involving the transendocardial injection of bone marrow-derived MSCs (BM-MSCs) have demonstrated improvements in left ventricular function and reductions in scar size[12]. However, while these findings are promising, the clinical efficacy of MSC therapy in HF remains a topic of debate, with some studies showing significant benefits and others reporting more modest outcomes.

The niche of origin of MSCs plays a crucial role in determining their therapeutic efficacy. The properties of MSCs can be highly influenced by the microenvironment from which they are harvested, making the tissue source an essential factor in evaluating the potential of these cells as living biodrugs. Figure 1 depicts different sources for MSC. The purpose of writing an editorial article on "Living Biodrugs and How Tissue Source Influences MSC Therapeutics for HF" is to shed light on the evolving field of (MSC therapies and highlight how the tissue origin of MSCs significantly impacts their therapeutic potential in HF. The article aims to explore how MSCs derived from different sources (such as bone marrow, adipose tissue, or umbilical cord) exhibit varying bioactive properties and paracrine effects, influencing outcomes in cardiac repair.

DIVERSE MSC MODALITIES

MSCs have emerged as a promising therapeutic modality for HF, particularly in the context of ischemic heart disease. MSCs, characterized by their multipotent differentiation capacity and unique immunomodulatory properties, have been extensively studied for their potential to mitigate the pathophysiological consequences of HF[13]. Originally isolated from bone marrow by Friedenstein *et al*[14], MSCs have since been identified in a variety of tissues including adipose tissue, umbilical cord, and peripheral blood, offering a diverse range of sources for therapeutic application[15].

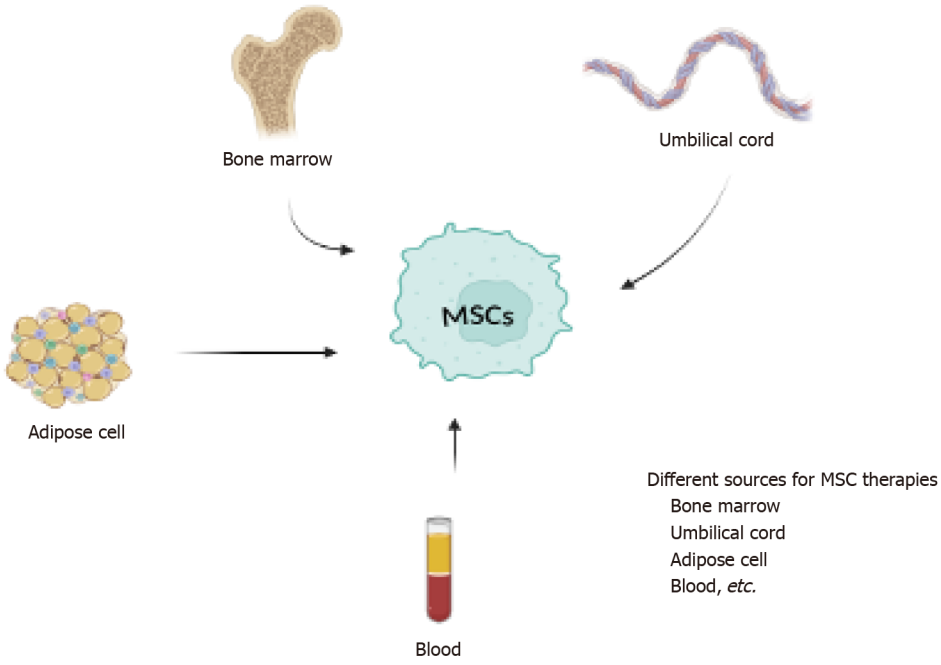

Figure 1 Different sources for mesenchymal stem cell. MSCs: Mesenchymal stem cells.

The therapeutic efficacy of MSCs in HF is attributed to their ability to modulate inflammatory responses, reduce fibrosis, and promote endogenous tissue regeneration. In particular, MSCs have been shown to exert paracrine effects that may contribute to cardiac repair and functional improvement, even in the face of limited direct engraftment and cell survival within the myocardial tissue[16]. Recent advancements in MSC therapy include the development of clinical-grade allogeneic MSC products, such as those derived from adipose tissue, which offer several advantages over autologous sources[17].

UMBILICAL CORD-DERIVED MSCS

Umbilical cord-derived MSCs (UC-MSCs), particularly those sourced from Wharton's jelly, offer notable advantages for HF therapy due to their accessibility, reduced cellular senescence, and absence of ethical concerns[18,19]. UC-MSCs can be readily isolated and expanded in vitro, demonstrating superior expansion capacity and faster growth rates compared to BM-MSCs[20]. These cells have been shown to express cardiac-specific markers such as troponin I and connexin-43 and possess the ability to differentiate into cardiomyocyte-like and endothelial cells under controlled conditions. Additionally, UC-MSCs exert significant paracrine effects that enhance vascular regeneration and provide cardiomyocyte protection, mechanisms implicated in the observed improvements in cardiac function in preclinical models of chronic ischemic cardiomyopathy and dilated cardiomyopathy[21]. The process of isolating UC-MSCs involves aseptic collection of umbilical cords from full-term placentas *via* caesarean section, followed by washing and culturing of Wharton's jelly fragments in a defined medium supplemented with fetal bovine serum and antibiotics. Cells are subsequently characterized based on International Society for Cellular Therapy guidelines and cryopreserved for clinical applications[22]. UC-MSCs, in our opinion, have significant promise for HF treatment due to their distinct advantages over other MSC sources. These cells are highly proliferative, immunoprivileged, and easily accessible, without the ethical problems associated with other stem cell sources. UC-MSCs have strong anti-inflammatory, anti-apoptotic, and pro-angiogenic capabilities, making them ideal for mending injured heart tissue in ischemia circumstances. Furthermore, their non-invasive collecting method makes them a more accessible and scalable choice for clinical applications. Given these characteristics, UC-MSCs might play a critical role in developing cell-based therapeutics for HF, providing an effective and ethical approach to cardiac regeneration.

BM-MSCS

BM-MSCs have been extensively investigated for the treatment of HF, demonstrating their potential to improve cardiac function and reduce adverse remodeling. BM-MSCs, although only representing approximately 0.01% of nucleated cells in bone marrow, exhibit robust *in vitro* expansion capabilities, maintaining their stem cell properties and multipotency [23]. Preclinical and clinical studies have shown that BM-MSCs can differentiate into cardiomyocyte-like cells, secrete a range of growth factors, cytokines, and microRNAs, and exert paracrine effects that support cardiomyocyte regeneration and reduce inflammation and fibrosis[24]. For instance, BM-MSCs have been utilized in clinical trials such as the phase III

study by Celyad SA, which tested autologous BM-MSCs with a "cardiopoietic" phenotype for chronic advanced ischemic HF[25]. This trial sought to capitalize on the benefits of autologous cells, mitigating immune incompatibility, and involved administering 600 million MSCs in multiple endoventricular injections. Despite initial promising results from earlier studies, the phase III trial did not show significant improvement in primary endpoints between MSC and placebo groups, suggesting that factors such as cell dosing and delivery methods may influence outcomes[26]. Specifically, the challenge of delivering multiple injections across a heterogeneous myocardial landscape could lead to variability in treatment efficacy and potential myocardial damage.

BM-MSCs have long been regarded as a useful alternative for HF treatment due to their well-established regeneration potential. These cells have been widely investigated and are renowned for their strong ability to control immune responses, decrease inflammation, and promote tissue repair *via* paracrine communication. However, one disadvantage of BM-MSCs is the invasive approach of extracting them, which may restrict their scalability when compared to alternative sources such as UC-MSCs. Furthermore, their therapeutic potency may reduce as donors age, impacting treatment consistency. Despite these issues, BM-MSCs remain a promising possibility for cardiac repair, particularly when derived from younger donors or improved using modern procedures.

FUTURE DIRECTIONS IN MSC THERAPY FOR HF

The future of MSC therapy for HF holds great promise as researchers explore alternative MSC sources, refine differentiation pathways, and enhance immune modulation. Novel sources such as adipose tissue, umbilical cord blood, and menstrual blood offer accessible and ethically sound alternatives to BM-MSCs, with the potential for superior therapeutic outcomes. Advances in understanding the factors that influence MSC differentiation and immune response are critical to improving their clinical efficacy. Moreover, the challenge of low MSC retention in target tissues is being addressed through innovations in delivery methods, including genetic modification, biomaterials, and pre-conditioning techniques [27]. These approaches aim to improve MSC survival, promote tissue regeneration, and ultimately enhance the therapeutic impact of MSCs in HF. As research progresses, MSC-based therapies are poised to become a key treatment option for patients with HF, offering new avenues for effective, long-term care.

CLINICAL IMPLICATION

The clinical implications of MSC therapy in HF are profound, given the cells' accessibility from various sources such as peripheral blood, adipose tissue, and bone marrow, facilitating autologous transplantation. This is particularly crucial in circumventing the immunogenic challenges often associated with allogeneic cardiac cell transfer. Additionally, emerging evidence underscores the paracrine mechanisms of MSCs, particularly through the secretion of exosomes. These 50 to 100 nm vesicles have been shown to exert cardioprotective effects, as demonstrated by Lai *et al*[28], who reported a significant reduction in myocardial infarction in an *ex vivo* murine model of ischemia-reperfusion injury.

MSC-derived extracellular vesicles (EVs) have substantial therapeutic promise in ischemic HF, due to their natural capacity to develop into diverse cell types as well as their strong paracrine actions[9]. These EVs carry a variety of bioactive chemicals that exert antifibrotic, anti-apoptotic, anti-inflammatory, and pro-angiogenic effects, all of which are necessary for heart tissue healing. They aid in retaining cardiac shape and prevent heart tissue stiffening by lowering fibrosis, while their anti-apoptotic actions protect cardiac cells from ischemia-induced death. Their anti-inflammatory characteristics reduce damaging immune responses, preventing further injury to cardiac tissue[29]. MSC-derived EVs also promote angiogenesis, which encourages the development of new blood vessels, boosting oxygen flow to ischemic areas and overall heart function. Collectively, these features make MSC-EVs a potential cell-free treatment for treating ischemic HF[30]. Adipose-derived stem cells (ADSCs) and induced pluripotent stem cells (iPSCs) are two alternative sources of MSCs with promising therapeutic applications in ischemic HF. ADSCs derived from adipose tissue are plentiful and have significant anti-inflammatory, pro-angiogenic, and antifibrotic properties, supporting heart repair by increasing blood flow and decreasing tissue damage. iPSCs, which are created by reprogramming adult cells to a pluripotent state, may develop into a variety of cell types, including cardiac cells, providing a personalized approach to rebuilding damaged heart tissue. ADSCs and iPSCs increase myocardial recovery through paracrine signaling, encouraging healing, minimizing scar tissue development, and enhancing heart function, making them valuable options for HF therapies[31].

Clinical research on MSC treatment for ischemic HF are now yielding encouraging but conflicting outcomes. Many studies have shown that MSCs derived from bone marrow, adipose tissue, and the umbilical cord can improve heart function, minimize scar tissue, and improve patient outcomes by exhibiting anti-inflammatory, anti-apoptotic, and pro-angiogenic properties. However, the variety in research designs, cell sources, administration techniques, and patient demographics has resulted in conflicting results in certain circumstances. While MSC therapy is typically safe and well tolerated, larger, standardized clinical studies are required to refine treatment procedures and thoroughly establish its efficacy. The current research is improving MSC-based treatments, bringing them closer to routine clinical use for ischemic HF. Table 1 summarizes the advantages and disadvantages of MSC Therapy.

Table 1 Advantages and disadvantages of mesenchymal stem cell therapy

MSC therapies	Comparison
Advantages	MSCs can be sourced from various tissues, including bone marrow, adipose tissue, and umbilical cord, providing multiple options for therapy
	MSCs have immunomodulatory properties, which can reduce inflammation and fibrosis, promoting tissue regeneration
	UC-MSCs are easily accessible, have reduced cellular senescence, and do not raise ethical concerns
	MSCs exhibit paracrine effects that contribute to cardiac repair and functional improvement, even without direct differentiation into cardiomyocytes
Disadvantages	The therapeutic efficacy may be limited by low cell engraftment and survival within myocardial tissue
	Clinical trials, such as those using BM-MSCs, have shown variable outcomes, with some failing to achieve significant improvements in heart failure patients
	Delivery methods, such as multiple intraventricular injections, can pose challenges and may lead to inconsistent results or myocardial damage
	Factors like cell dosing, delivery techniques, and heterogeneous myocardial environments can affect the overall success of the therapy

MSC: Mesenchymal stem cell.

CONCLUSION

In conclusion, MSCs represent a viable and potent option for HF therapy, offering advantages in terms of accessibility, proliferative capacity, and regenerative potential. Continued research and clinical trials will be essential in determining their role in the evolving landscape of HF treatment. By addressing the current limitations and refining the therapeutic strategies, MSCs have the potential to become a cornerstone of regenerative medicine for HF.

FOOTNOTES

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EDITORIAL

Dual-chamber pacing confers better myocardial performance and improves clinical outcomes compared to single-chamber pacing

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Abstract

The deleterious effects of long term right ventricular pacing are increasingly being recognized today. Current clinical practice favors the implantation of dual-chamber permanent pacemaker which maintains atrioventricular synchrony and is associated with better quality of life. However, despite the popular belief and common sense surrounding the superiority of dual-chamber pacing over single chamber pacing, the same has never been conclusively verified in clinical trials. Some observational evidence however, does exists which supports the improved cardiac hemodynamics, lower the rate of atrial fibrillation, heart failure and stroke in dual-chamber pacing compared to single-chamber pacing. In the index study by Haque *et al*, right ventricular pacing, particularly in ventricular paced, ventricular sensed, inhibited response and rate responsive pacemaker adversely impacted the left ventricular functions over 9-months compared to dual pacing, dual sensing, dual responsive and rate responsive pacemaker. Although there are key limitations of this study, these findings does support a growing body of evidence reinstating the superiority of dual chamber pacing compared to single chamber pacing.

Key Words: Permanent pacemaker insertion; Pacing induced cardiomyopathy; Dual-chamber pacemaker, Left ventricular ejection fraction; Atrial fibrillation; Heart failure; Global longitudinal strain; Stroke; Cardiovascular outcomes; Conduction system pacing

Core Tip: The detrimental effects of long-term apical right ventricular pacing (RVP) on left ventricular (LV) functions have necessitated the search for strategies to mitigate pacing-induced cardiomyopathy. Amongst them, allowing for a more physiological pacing and reducing the RVP burden by appropriate programming are the most clinically relevant interventions. The index study by the authors supports a net beneficial effect of dual responsive and rate responsive (DDDR) compared to ventricular paced, ventricular sensed, inhibited response and rate responsive (VVIR) mode in terms of better LV function and performance in the short-term by maintaining the atrio-ventricular synchrony. Further, as in prior studies, new-onset AF was more frequent with VVIR compared to DDDR.

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INTRODUCTION

Consistent pool of evidence supports the detrimental effect of long-term right ventricular pacing (RVP) on left ventricular (LV) systolic and diastolic functions. In particular, it is the apical pacing of the right ventricle that results in abnormal electrical and mechanical activation contributing to the worsening LV performance over the years[1,2]. Many have further explored the pathophysiology behind the same and highlighted the role of abnormal regional perfusion, adverse cardiac remodeling and mechanical dyssynchrony. This worsening LV mechanics eventually results in progressive heart failure which is associated with significant cardiovascular morbidity and mortality. Naturally, there has been an increasing focus on the strategies to mitigate the adverse impact of RVP in the short and the long-run[3-5].

PACING-INDUCED CARDIOMYOPATHY: RISK FACTORS AND PREDICTORS

The term pacing-induced cardiomyopathy (PiCM) is increasingly used to describe the development of new-onset LV dysfunction, that is a > 10% decline in LV ejection fraction (LVEF) irrespective of baseline after permanent pacemaker insertion (PPI), after excluding all other causes[6,7]. It is solely attributable to the left bundle branch block (LBBB) type activation patterns after PPI and the resultant asynchronous and delayed electrical activation which contributes to the abnormal myocardial contraction, depressed myocardial work, reduced systolic and diastolic functions and a shift in the LV pressure-volume curve to lower pressure and higher volumes[3].

While these manifestations are more pronounced and occur earlier in those with pre-existent LV systolic dysfunction, many patients with a preserved LV functions also have deterioration in both systolic and diastolic functions after PPI. As much as 6%-26% of patients with preserved LV functions prior to PPI, develop PiCM over a time period ranging from 3 months to well beyond 10 years[8-10]. Indeed, this worsening of LV functions is directly proportional to the pacing burden with highest likelihood of developing PiCM in those with RV pacing > 20%-40%. Other predictors of PiCM include a wider baseline or post PPI QRS, preexistent LV dysfunction or LBBB, advanced age, prior coronary artery disease and advanced infra hisian block[11-14]. However, our current understanding of these risk factors is largely based on a few heterogenous studies with variable patient populations and diverse individual and physician related factors. This makes a more comprehensive and robust assessment of these risk factors and the mitigation strategies a key unmet need.

Further, RVP has been also linked to the development of new-onset atrial fibrillation (AF). The development of AF is largely multifactorial amongst which the key players are the diastolic dysfunction, mechanical dyssynchrony with resultant mitral regurgitation and reduced systolic function both of which leads to atrial stretch and atrial electrical instability, in addition the progressive tricuspid regurgitation due to pacemaker leads also leads to atrial enlargement and eventually fibroses; all of which contribute to the development of AF[15]. The advent of AF is strongly related to worse cardiovascular outcomes with significant complications in the form of stroke, heart failure, myocardial infarction and death[16-19].

IMPACT OF PACEMAKER TYPE AND MODE ON PICM

Amongst the earlier studies, the randomized study by Andersen *et al*[20] was the first one which indicated excess cardiovascular mortality, greater decline in LVEF and New York Heart Association class, increased risk of developing AF and stroke in the ventricular paced, ventricular sensed, inhibited response (VVI) pacemaker compared to atrial pacing, atrial sensing, inhibited response (AAI) pacemaker amongst patients with sinus node disease. Later on studies by Nielsen *et al*[21] and the famous UKPACE indicated similar clinical outcomes in terms of mortality, development of heart failure and AF amongst patients with atrio-ventricular (AV) block receiving either a VVI rate responsive (VVIR) pacemaker or a dual pacing, dual sensing, dual responsive and rate responsive (DDDR) pacemaker. However, rates of stroke was higher

in the group who received a single chamber VVIR pacemaker; especially the ones functioning at a fixed rate: VVI pacemaker[22]. Another key observation amongst those receiving DDDR was that the group assigned to a short AV delay compared to those with a longer AV delay. However, the results were not replicable in the large DANPACE study wherein there was no significant across any of the clinical outcomes amongst those assigned to DDDR or VVIR stressing on the need for more robust real-world data to conclusively determine the true impact of pacemaker type on clinical outcomes[23].

Nonetheless, it is very safe to conclude that reducing RV pacing burden is one of the most important targets to mitigate PiCM and improve short and long term outcomes. The same can be achieved by choosing AAI or the DDDR mode in preference to VVIR mode, programming a longer AV delay to facilitate the native AV conduction, carefully modifying the rate responsiveness in certain groups like those with a normal sinus node function to limit unusual and higher heart rates (RV pacing) at rest or during exertion[1,24]. Another important consideration is the site of RV pacing. Pacing sites other than the apex, including at the RV outflow and septum allow for achievement of better electrical activation as reflected by a narrower QRS duration compared to apical pacing[25]. Although the PROTECT-PACE study did not demonstrate a significant difference in terms of mortality, LVEF and AF at 2 years amongst those receiving non-apical *vs* apical RV pacing, there are others which do point towards a net benefit from the non-apical compared to apical pacing [26]. Amongst these, the meta-analysis by Hussain *et al*[27] and another one by Shimony *et al*[28] indicate that those with a lower baseline LVEF and a greater baseline QRS duration are likely to benefit from non-apical pacing especially when followed over for longer durations beyond 1 year. In addition, a recent report by Samuel *et al*[29] also indicate that RV apical pacing is independently associated with development of AF post PPI which confers worse long term outcomes compared to non-apical pacing.

To this extent, biventricular pacing (BiVP) was developed as a rescue solution for those with worsening LVEF and heart failure after prior PPI. On many occasions, it could resynchronize the electrical and mechanical contraction and ultimate improve the LVEF and clinical outcomes[30]. However, there is a huge non-response rate after BiVP in this group with about 1/3rd having no change in LVEF post BiVP[6]. The most recent tool in our armamentarium is the eft bundle branch-area pacing which offers a potential solution for de-novo PiCM and those with prior response to BiVP as a means of cardiac resynchronization therapy[31-34].

IMPLICATIONS AND CLINICAL RELEVANCE OF THE INDEX STUDY BY HAQUE ET AL

The development of PiCM is in fact a continuum starting from a subtle and gradual decline in LVEF which over time adds up and qualifies as PiCM when the EF drops below the defined cut-offs. As such any decline of LVEF is clinically relevant especially early in the course after PPI. In the index study by Haque *et al*[35] the authors prospectively looked into the impact of pacing mode (DDDR *vs* VVIR) on LV functions and clinical outcomes over a period of 9 months in patients undergoing dual-chamber PPI at their tertiary-care center. They used a cross-over study design with the pacing mode being set to DDDR during the first three months followed by VVIR for the next 3 months and again DDDR for the remainder of the three months towards the end of the study.

In their cohort of 56 patients, the authors demonstrated significant impairment of both systolic and diastolic functions after PPI. The worsening diastolic functions were represented by the increase in isovolumic relaxation time (IVRT) from 85.27 ± 9.54 ms to 93.07 ± 10.38 ms at the end of study period (9 months). This increase in IVRT was most pronounced in the 3 to 6 months window when the pacemaker was kept in the VVIR mode. In regards to systolic functions, the gradual impairment was reflected in the form of decline in LVEF and increase in mean LV end-diastolic diameter. The worsening of LV systolic functions were seen with both DDDR and VVIR modes. In addition they also demonstrated reduction in stroke volume and global longitudinal strain (GLS) over the 9 months in both the arms. In addition, occurrence of new-onset AF was more common in the VVIR group compared to DDDR group. However, despite the various adverse effects of either pacing mode on myocardial functions, the overall quality of life improved throughout in either of the arms.

The study findings are crucial and in line with a growing body of evidence surrounding the superiority of dual-chamber over single chamber pacemakers. Generally, a dual-chamber pacemaker is believed to enable more physiological pacing largely attributable to the maintenance of AV synchrony[1]. Theoretically this translates into a maintained preload and stroke volume. However, the evidence from real world setting remains conflicting with no clear benefit in terms of mortality and quality of life with dual chamber pacemaker compared to single chamber. The only net benefit obtained from meta-analysis is in terms of a lower AF rate and lesser pacemaker syndrome in certain subsets receiving DDDR compared to VVIR[36].

The differences in outcomes between the 2 pacemakers is even less conspicuous in the elderly patients beyond 70 years [22]. Nonetheless, there is evidence from multiple other studies which do support the superiority of DDDR compared to VVIR in terms of perseverance of LV function and reduced heart failure related morbidity and mortality. In the dedicated prospective study by Dawood *et al*[37], DDDR was shown to be associated with a better cardiac output, a higher GLS and LVEF with 3D echocardiography and strain imaging compared to VVIR. There results were conquered by an independent recent analysis by Laksono *et al*[38], wherein DDDR was able to better maintain LV functions in patients with AV block compared to VVIR mode. Adoubi *et al*[39] also highlighted a higher heart failure related mortality in their Sub-Saharan African cohort with VVIR compared to DDDR. In another large registry by Ebert *et al*[40], though decline in LVEF was infrequent in those with normal bassline LV function, it was more prevalent in the cohort receiving VVIR compared to DDDR. More recent evidence in support of a favorable impact of DDDR compared to VVIR comes from the large meta-analysis by Shah Syed *et al*[41] comprising of 8953 patients. Although the rate of LV dysfunction on follow-up was similar in the two groups, DDDR was associated with a significantly lower incidence of AF compared to those in

VVIR mode. In the recent prospective study by Blessberger *et al*[42], DDDR was associated with improved hemodynamics and stroke volume compared to VVIR mode.

The above arguments and the findings from the index study by Haque *et al*[35], do support a net beneficial effect of DDDR compared VVIR mode in terms of better LV function and performance. However, it is crucial to understand and acknowledge the key limitations and the pitfalls of the index study before accepting the results on the face value. Firstly, the study was conducted in a tertiary care center with a small number of patients and may the cohort may not be representative of the general population. Secondly, the decline is LVEF is more prominent and discernible after 3-5 years of PPI and hence a follow-up period of 9 months may not be ideal to draw such conclusions. Thirdly, the results may not apply to those with sinus node dysfunction as none of the patient in the cohort had it. The lack of assessment of ventricular pacing burden, a key player of PiCM, is yet another major limitation. The authors have implanted all ventricular leads at the RV apex which is not ideal and not the standard practice at most center for obvious reasons as highlighted above. The authors could have further used pharmacological or exercise based echocardiography assessment to more conclusively support their findings. Hence, given the key limitations, the results of the index study should be taken with due caution and dedicated future studies are needed to validate the findings of the index study.

CONCLUSION

The detrimental effects of long-term apical RVP on LV functions have necessitated search for strategies to mitigate PiCM. Amongst them, allowing for a more physiological pacing and reduction in RV pacing burden by appropriate programming are the most relevant clinically. The index study by the authors supports a net beneficial effect of DDDR compared to VVIR mode in terms of better LV function and performance in the short-term. Further, as in prior studies, new-onset AF was more common in the VVIR group.

FOOTNOTES

Author contributions: Mohan B and Batta A designed the editorial, supervised the study and provided key feedback and suggestions; Batta A performed the literature review and data collection, analyzed the data and wrote the manuscript and subsequently revised it. All authors have read and approved the final manuscript.

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REVIEW

Cardiovascular and nonalcoholic fatty liver disease: Sharing common ground through SIRT1 pathways

Kenneth Maiese

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Abstract

As a non-communicable disease, cardiovascular disorders have become the leading cause of death for men and women. Of additional concern is that cardiovascular disease is linked to chronic comorbidity disorders that include nonalcoholic fatty liver disease (NAFLD). NAFLD, also termed metabolic-dysfunction-associated steatotic liver disease, is the greatest cause of liver disease throughout the world, increasing in prevalence concurrently with diabetes mellitus (DM), and can progress to nonalcoholic steatohepatitis that leads to cirrhosis and liver fibrosis. Individuals with metabolic disorders, such as DM, are more than two times likely to experience cardiac disease, stroke, and liver disease that includes NAFLD when compared individuals without metabolic disorders. Interestingly, cardiovascular disorders and NAFLD share a common underlying cellular mechanism for disease pathology, namely the silent mating type information regulation 2 homolog 1 (SIRT1; *Saccharomyces cerevisiae*). SIRT1, a histone deacetylase, is linked to metabolic pathways through nicotinamide adenine dinucleotide and can offer cellular protection though multiple avenues, including trophic factors such as erythropoietin, stem cells, and AMP-activated protein kinase. Translating SIRT1 pathways into clinical care for cardiovascular and hepatic disease can offer significant hope for patients, but further insights into the complexity of SIRT1 pathways are necessary for effective treatment regimens.

Key Words: AMP-activated protein kinase; Cardiovascular disease; Diabetes mellitus; Erythropoietin; Metabolic-dysfunction-associated steatotic liver disease; Nicotinamide; Nicotinamide adenine dinucleotide; Nonalcoholic fatty liver disease; Silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*); Stem cells

Core Tip: Cardiovascular disease is the principal cause of non-communicable diseases with individuals succumbing to heart disease every thirty-three seconds and has a significant comorbidity with nonalcoholic fatty liver disease (NAFLD). These two disorders impact millions of individuals across the globe, yield significant disability and death to individuals, and have a common underlying cellular pathway with silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) that may offer innovative prospects for the treatment of both cardiovascular disorders and NAFLD.

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INTRODUCTION

Non-communicable diseases (NCDs) lead to disability and death in a significant spectrum of individuals worldwide and encompass disorders that include cardiac disease, cancer, trauma, respiratory disease, stroke, Alzheimer's disease, diabetes mellitus (DM), influenza and pneumonia, kidney disease, and suicide[1-3]. Cardiac and cardiovascular disorders are the most prominent of NCDs as the leading cause of death for both women and men and greater than one million individuals suffer a heart attack every year[4-7]. Several therapeutic pathways can lessen the severity of cardiovascular disease by addressing tobacco exposure, inadequate nutrition, hypertension, serum cholesterol values, obesity, infection, and the existence of DM[8-11].

In fact, DM not only is a risk factor for cardiovascular disease, but also for liver disease and the development of nonalcoholic fatty liver disease (NAFLD), a significant comorbidity of cardiovascular disorders[12-14]. NAFLD, also known as metabolic-dysfunction-associated steatotic liver disease, is increasing in presence throughout the world and this has occurred with concurrent the rise in DM globally[15-19]. NAFLD is a chronic disorder of the liver with excessive fat accumulation and is associated with at least one metabolic risk factor, such as obesity, DM, hypertension, elevated serum triglycerides, low serum high-density lipoprotein (HDL) cholesterol, and advanced age[13,20-23]. A recent paper by the authors Batta and Hatwal[24] brings to light the clinical link between cardiovascular disease and NAFLD and that in combination these disorders can lead to an increased risk of major impairment in cardiovascular function as well as cerebral function, such as stroke.

THE METABOLIC AND PROTECTIVE PATHWAYS FOR SILENT MATING TYPE INFORMATION REGULATION 2 HOMOLOG 1 (*SACCHAROMYCES CEREVISIAE*)

Given that metabolic disorders, such as DM, are common risk factors for the development of cardiovascular disease and NAFLD, it is significant to note that a common underlying cellular pathway that can oversee both of these disorders involves the silent mating type information regulation 2 homolog 1 (SIRT1; *Saccharomyces cerevisiae*)[25-27]. SIRT1 is present in the heart, skeletal muscle, pancreas, liver, brain, spleen, and adipose tissue[13,25,28-30]. SIRT1 is a member of the sirtuin family (sirtuin 1) and is a histone deacetylase that promotes transcription of DNA through the transfer of acetyl groups from e-N-acetyl lysine amino acids to DNA histones[31-33]. Nicotinamide adenine dinucleotide (NAD^+), a coenzyme, functions as a SIRT1 substrate[22,28,34,35]. SIRT1 can control metabolic homeostasis[36,37] and functions closely with NAD^+ and the vitamin nicotinamide[22,23,34,35]. As the amide form of the vitamin B3 (niacin), nicotinamide is the precursor for NAD^+[31,38-40]. SIRT1 oversees nicotinamide phosphoribosyl-transferase that is required for NAD^+ production and is tied to circadian clock gene rhythms[41]. It is important to note that sufficient levels of NAD^+ are required to prevent vascular disease, dementia, and mitochondrial function[21,42,43]. Pools of cellular NAD^+ are susceptible to fluctuation with aging and circadian clock gene function[9,44-46]. SIRT1 activation that leads to increased levels of NAD^+ have been reported to lessen cardiac injury, maintain metabolic homeostasis, and reduce cellular inflammation[47-49].

In addition to maintaining metabolic homeostasis, SIRT1 also controls growth factor function through the activity of NAD^+[50-53]. Erythropoietin (EPO) employs SIRT1 to preserve synaptic connections for memory function[54,55], enhance survival of cardiovascular cells[56,57], and protect against toxic events with liver cells[52,58]. At the cellular level, EPO oversees SIRT1 activity to prevent mitochondrial membrane depolarization, activation of BCL2 associated agonist of cell death (Bad), and caspase pathway activity[59-61].

A COMMON CELLULAR PATHWAY INVOLVING SIRT1 FOR CARDIOVASCULAR DISEASE AND NAFLD

SIRT1 offers a clinical target for both cardiovascular disease and hepatic disease that can lead to NAFLD (Figure 1). In regard to cardiovascular disease, SIRT1 can foster the function of stem cells[62-64] and enhance cardiac function and repair[65,66]. SIRT1 can improve the function of endothelial cells[42,67,68], reduce coronary artery disease[69,70], inhibit

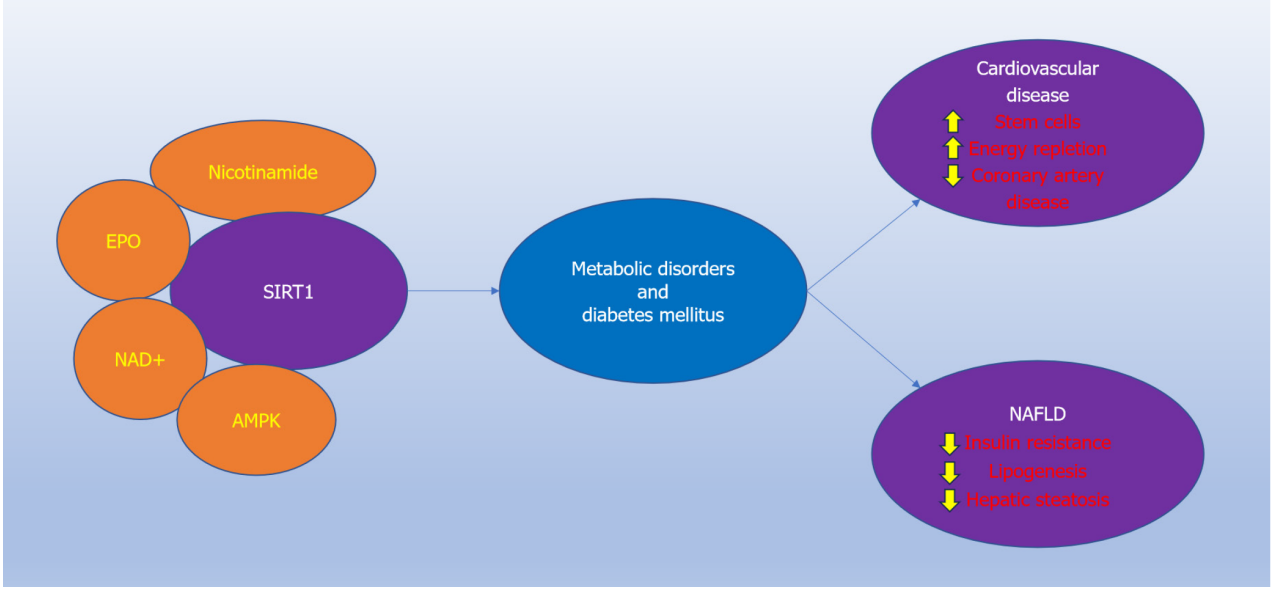

Figure 1 Silent mating type information regulation 2 homolog 1 is an integral pathway for metabolic disorders such as diabetes mellitus and the clinical outcomes for cardiovascular disease and nonalcoholic fatty liver disease. The silent mating type information regulation 2 homolog 1 (SIRT1; *Saccharomyces cerevisiae*) and the complementary pathways of SIRT1 that include nicotinamide, erythropoietin, nicotinamide adenine dinucleotide, and AMP-activated protein kinase function to maintain glucose homeostasis during metabolic disorders such as diabetes mellitus, Ultimately, the pathways of SIRT1 impact cardiovascular disease by promoting stem cell function, enhancing cellular energy repletion, and preventing coronary artery disease and influence nonalcoholic fatty liver disease by inhibiting insulin resistance, lipogenesis, and hepatic steatosis. SIRT1: Silent mating type information regulation 2 homolog 1; NAD^+: Nicotinamide adenine dinucleotide; EPO: Erythropoietin; AMPK: AMP-activated protein kinase; NAFLD: Nonalcoholic fatty liver disease.

cardiac injury during DM and metabolic disorders[37,71-73], and assist with cellular energy repletion[74,75]. Through the prevention of cellular senescence[76] to allow progenitor cell differentiation with SIRT1, cardiovascular cells are afforded the ability for heightened resistance to injury[43,67,77,78]. In the broader cardiovascular systems, SIRT1 can oversee programmed cell death with apoptosis and autophagy, control cardiac remodeling through increased mitochondrial biogenesis, limit myocardial injury, reduce insulin resistance, and prevent cardiac hypertrophy[4,30,79-83].

Liver function is dependent upon both cellular metabolism and SIRT1 pathways[13,45,84,85]. Insulin sensitivity and the maintenance of mitochondrial function require SIRT1 activation[86-89]. Activation of SIRT1 can control hepatocyte processing of lipids and glucose level maintenance to lessen the risk of the onset of metabolic syndrome dysfunction[30,31,90]. If SIRT1 activity is limited in the pancreas and liver, insulin resistance can ensue especially during high fat consumption[13,91-93]. SIRT1 also can control de novo lipogenesis and resolve hepatic steatosis that may lead to NAFLD and require activation of related pathways of AMP-activated protein kinase (AMPK)[92,94-96]. The AMPK pathway is closely linked to SIRT1 and nicotinamide in overseeing cellular metabolic homeostasis[9,72,97-99]. In recent clinical studies, treatment with oleoylethanolamide, an endogenous peroxisome proliferator-activated receptor alpha agonist, in patients with NAFLD led to increased mRNA expression levels of SIRT1 with increases in HDL cholesterol and decreases in triglyceride levels, suggesting that SIRT1 is a therapeutic target for NAFLD[100]. In addition, increased exercise in patients with NAFLD may affect lipophagy, lipolytic pathways, and reduction in oxidative stress through SIRT1 activity [101]. Through SIRT1 pathways, exercise also affects cardiac fatty acid oxidation, tissue regeneration, improved metabolic status, dietary interventions for weight management, and reduction in age-related decline of cellular metabolic pathways [45,71,75].

CONCLUSION

Cardiovascular disorders and NAFLD impact a significant number of individuals throughout the globe and share common aspects of underlying disease pathology related to cellular metabolic dysfunction and the intricate pathways of SIRT1 involving NAD^+, nicotinamide, trophic factors such as EPO, and AMPK. SIRT1 is an exciting clinical target for both cardiovascular disease and hepatic disorders, since SIRT1 activity can maintain cellular metabolic homeostasis, enhance stem cell function and differentiation, foster the survival of vascular endothelial cells, limit cardiac injury, control hepatocyte lipid production and insulin resistance, and limit hepatic steatosis that can result in NAFLD. Yet, the pathways of SIRT1 are complex and require intact cellular feedback pathways with nicotinamide, NAD^+, growth factors, and AMPK since lack of close biological control can lead to unwanted clinical outcomes such as tumorigenesis[4,26,87,102,103]. In addition, multiple pathways intersect with SIRT1 that involve cellular metabolic disease[21,35,97,104-109], apoptosis and autophagy[26,110,111], oxidative stress, inflammation, and mitochondrial impairment[25,76,111-121], and clock genes with Wnt proteins impairment[105,111,117,118,122-124]. SIRT1 offers exciting possibilities for the advancement of clinical care, but further elucidation of the protective pathways of SIRT1 for complex disorders such as cardio-

vascular disease, liver disorders, and metabolic dysfunction is necessary for the development of effective and safe clinical treatment strategies.

FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

Impact of single chamber and dual chamber permanent pacemaker implantation on left ventricular function: An observational study

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Abstract

BACKGROUND

Permanent pacemaker implantation has the potential to impact left ventricular (LV) function and hence quality of life (QoL) in the long term.

AIM

To assess the effect of single- and dual-chamber pacing on LV function and QoL.

METHODS

This study included 56 patients who underwent permanent pacing: Dual pacing, dual sensing, dual responsive and rate responsive (DDDR) for the initial 3 months and ventricular pacing, ventricular sensing, inhibited response and rate responsive (VVIR) for the next 3 months, and DDDR mode for the last 3 months. Throughout the study period, various echocardiographic parameters, functional status, and QoL were measured to assess the impact of pacing on LV function compared with baseline and at every 3 months interval.

RESULTS

A significant change appeared in cardiac function after VVIR pacing which included diastolic properties of LV as shown by increase in isovolumic relaxation time from (85.28 ± 9.54 ms) to (89.53 ± 9.65 ms). At the 3-, 6-, and 9-month follow-up, reduction in LV ejection fraction was observed to be 62.71 ± 4.66%, 61.07 ± 4.41%, and 58.48 ± 3.89%, respectively. An increase in the QoL scores was noted at every follow-up visit.

CONCLUSION
An apparent depressant effect on LV function due to right ventricular pacing, with a higher incidence of adverse outcomes in the VVIR mode. In addition, an upsurge in QoL scores for the study population was noted, which indicates improvement in the QoL of patients post-pacing, irrespective of the mode. Generally, the DDDR mode is a highly preferable pacing mode.

Key Words: Artificial pacemaker; Echocardiography; Left ventricular function; Quality of life

Core Tip: Pacemaker implantation is a common treatment for cardiac conduction disorders, but the impact of right ventricular pacing (RVP) on left ventricular (LV) function remains a concern. Limited information is available on the acute and early effects of RVP on LV function, particularly when comparing dual pacing, dual sensing, dual responsive and rate responsive (DDDR) with ventricular pacing, ventricular sensing, inhibited response and rate responsive (VVIR) pacemakers. This study found that RVP adversely affects LV function, with more significant impairment observed in VVIR mode compared to DDDR mode. However, both modes led to improvements in quality of life (QoL). The findings support the use of DDDR mode over VVIR mode for better clinical outcomes and preservation of LV function, while also improving QoL.

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INTRODUCTION

Defects in cardiac impulse generation and conduction occur at various levels in the cardiac conduction system, starting from the sinus node to the Purkinje fibres which depolarize the ventricles. When this intrinsic cardiac automaticity or conduction integrity fails, an external stimulus is required to drive the myocytes to the threshold through excitation-contraction coupling, and pacemakers provide that external stimulus[1]. Implantation of pacemakers is an effective treatment option, especially for patients with sick sinus syndrome (SSS) and atrioventricular (AV) conduction disorders [2]. The types of implants include single-chamber [single-atrial chamber pacemakers atrial pacing, atrial sensing and inhibited response (AAI), and single-ventricular chamber pacemakers ventricular pacing, ventricular sensing, inhibited response and rate responsive (VVIR) and double-chamber chamber pacemakers dual pacing, dual sensing, dual responsive and dual pacing, dual sensing, dual responsive and rate responsive (DDDR)[3].

AAI are indicated in selected patients in whom only sinus node dysfunction is present and AV node conduction is preserved, whereas VVI, VVIR, and double-chamber pacemakers are indicated in patients with AV block and complete heart blocks[3]. During the implantation of permanent pacemaker devices, the endocardial right ventricular pacing (RVP) lead is often positioned at the right ventricular (RV) apex[2]. It is well known that RVP alters normal signal conduction and may result in a reduction in the left ventricular ejection fraction (LVEF). Therefore, it is paramount to measure left ventricular (LV) function, especially during RVP[4]. Deterioration of LV function can be measured using 2D echocardiography and strain imaging techniques after dual- and single-chamber pacemaker implantation[5,6]. Quality of life (QoL) is a scientific outcome measurement strategy that evaluates treatment effectiveness and is widely assessed using the SF-36 score[6]. In addition, previous studies have shown that permanent pacemaker implantation leads to improvement in symptoms and QoL[7].

The long-term effects of right ventricular apical pacing have been previously studied; however, little information is available on the acute and early effects of RVP on LV function. Hence, this study aimed to evaluate the impact of RVP on LV function by comparing LV function impairment in dual- and single-chamber pacemakers, along with its impact on QoL.

MATERIALS AND METHODS

Study population

The study population included patients admitted for pacemaker implantation at a tertiary healthcare centre in India. Participating patients were those of all ages and of both sexes who were willing to provide consent and were undergoing permanent pacemaker implantation. Patients with preexisting LV systolic dysfunction were excluded.

Study design and methodology

This single-centre, hospital-based, prospective, observational study was conducted over a period of 9 months, during which a total of 56 patients were enrolled. Detailed demographic characteristics and baseline LV function parameters were recorded upon admission. The study population was initially kept in the DDDR mode for 3 months, post which the mode was changed to VVIR for the next 3 months, followed again by the DDDR mode. Thus, we had a cross-over study design. The pacemaker programming was conducted by the same person. After pacemaker implantation, echocardiographic parameters such as the LV size, LVEF, LV diastolic function, and LV strain were measured using Vivid E-95 4D cardiac ultrasound system (GE Health Care Technologies Inc, Chicago Illinois, United States). Echocardiography was performed by the same person on follow-up-for-changes in LV function. Echocardiographic imaging was repeated every 3 months to measure the impact of the pacemaker on LV function. In addition, the functional status of all patients was measured using the treadmill test, and they were categorised into the New York Heart Association (NYHA) functional class based on the observed symptoms, which were repeated at intervals of 3 months.

The QoL of the enrolled participants was assessed using the SF-36 questionnaire, which covers eight health domains: Physical functioning (10 items), bodily pain (2 items), role limitations due to physical health problems (4 items), role limitations due to personal or emotional problems (4 items), emotional well-being (5 items), social functioning (2 items), energy/fatigue (4 items), and general health perceptions (5 items). The scores for each domain ranged from 0 to 100, with higher scores indicating a more favourable health state. The patients received medications for comorbidities, such as hypertension, diabetes, or dyslipidaemia, as per the standard guidelines. Patients with LV dysfunction were prescribed heart failure therapy according to the guidelines.

Statistical analysis

All data were analysed using SPSS software (Version 16). Categorical variables are presented as frequencies and percentages, whereas continuous variables are presented as means and standard deviations. McNemar's test was used to establish a significant association between the study groups and various parameters. A P value of < 0.05 was considered statically significant.

RESULTS

This study comprised 56 patients, among whom 73.2% were male. The mean age observed for the study population was 57.11 ± 11.87 years, and the majority of patients (42.9%) belonged to the age group above 60 years (Figure 1). The indication for pacemaker implantation in all patients was complete heart block. None of the patients had sinus node dysfunction. The atrial lead was a tined lead placed in the right atrial appendage, and the RV endocardial lead was placed at the apex. The post-ventricular atrial refractory period (PVARP) was programmed in the automatic mode (autonomous PVARP, approximately 250 ms) to enhance protection against pacemaker-induced tachycardia.

Various echocardiographic parameters, physical tests, and QoL domains were assessed at baseline and at 3, 6, and 9 months. Measurements of several systolic and diastolic parameters revealed significant differences at various follow-ups ($P < 0.05$). The LVEF, measured using the Simpson method, showed that the mean baseline LVEF was 64.03 ± 5.36%, which decreased to 62.71 ± 4.66% after 3 months, indicating a mean change of 2.06%. At the 6-month follow-up, the mean LVEF was 61.07 ± 4.41%, and at the 9-month follow-up, a further decrease of 2.33% was observed. The mean LV end-diastolic diameter (LVEDD), a key parameter for assessing ventricular performance, increased at each follow-up. Specifically, LVEDD increased by 2.60% at 3 months, by 5.19% at 6 months, and by 3.10% at 9 months. A reduction in stroke volume was noted, with a 5.15% decrease at 6 months and a more pronounced 7.59% decrease at 9 months. Global longitudinal strain, an echocardiographic parameter used to detect LV systolic dysfunction, declined by 6.71%, 16.21%, and 8.37% at the 3-, 6-, and 9-month follow-ups, respectively. The mean value of LV end-systolic dimension (LVESD) was 23.96 ± 1.46 mm at 3 months, which increased to 25.98 ± 1.30 mm at 6 months. Isovolumic relaxation time (IVRT), which measures diastolic function, increased at every follow-up. At 3 months, the mean IVRT was 85.27 ± 9.54 ms, rising to 93.07 ± 10.38 ms at 9 months. The QoL scores improved at every follow-up, with a mean score of 74.41 ± 12.83 at 3 months, 82.05 ± 7.46 at 6 months, and 90.44 ± 5.89 at 9 months. The mean values of other measured parameters and their statistical values are summarised in Table 1. According to the NYHA classification, a large proportion of patients (92.85%) had class 1 heart failure at baseline, whereas at the 9-month follow-up, a greater number of patients (58.9%) had progressed to class 2 heart failure. These findings were statistically significant ($P < 0.05$). Further details are provided in Table 2. Outcomes such as atrial fibrillation (AF) and stroke were lower in the dual-chamber mode than in the single-chamber mode. None of the patients had AF or flutter at baseline. However, at 6 months, two patients developed transient AF, which reverted to sinus rhythm in one patient at 9 months. Further details are presented in Table 3.

DISCUSSION

Several studies have demonstrated the long-term effects of right ventricular apical pacing; however, information regarding its acute and early effects on LV function is limited. In the present study, the first significant change in LV function was observed in LVEF. Ejection fraction, which links preload, afterload, and contractility, is one of the most useful indices of LV function. Our study detected a subtle change in hemodynamic performance through a significant decrease in LVEF, consistent with previous studies where LVEF was observed to be 59.8 ± 12 in the DDDR mode of

Table 1 Various parameters at baseline and at 3 months follow-up intervals

Variable	Parameter	Baseline	3 months	3 months	6 months	6 months	9 months	*P* value
LVEF (M Mode) (%)	mean ± SD	63.69 ± 5.19	62.51 ± 4.76	62.51 ± 4.76	61.14 ± 4.71	61.14 ± 4.71	58.58 ± 4.24	< 0.001
	% Mean change	1.85		2.20		1.80		
LVEF (Simpson) (%)	mean ± SD	64.03 ± 5.36	62.71 ± 4.66	62.71 ± 4.66	61.07 ± 4.41	61.07 ± 4.41	58.48 ± 3.89	
	% Mean change	2.06		2.62		2.33		
LVEDD (MM)	mean ± SD	40.57 ± 4.07	41.01 ± 3.55	41.01 ± 3.55	43.78 ± 3.04	43.78 ± 3.04	45.14 ± 3.07	
	% Mean change	-2.60		-5.19		-3.10		
LVESD (MM)	mean ± SD	22.76 ± 2.40	23.96 ± 1.46	23.96 ± 1.46	25.98 ± 1.30	25.98 ± 1.30	27.71 ± 1.56	
	% Mean change	-5.25		-8.42		-6.67		
SV (ML)	mean ± SD	84.96 ± 20.38	80.41 ± 17.89	80.41 ± 17.89	76.26 ± 16.44	76.26 ± 16.44	70.48 ± 11.30	
	% Mean change	5.36		5.15		7.59		
E/A	mean ± SD	1.08 ± 0.191	1.18 ± 0.15	1.18 ± 0.15	1.36 ± 0.18	1.36 ± 0.18	1.50 ± 0.166	
	% Mean change	-8.86		-14.93		-10.63		
E/E′	mean ± SD	9.05 ± 2.41	9.82 ± 2.52	9.82 ± 2.52	10.79 ± 3.03	10.79 ± 3.03	11.59 ± 3.60	
	% Mean change	-8.48		-9.83		-7.48		
IVRT (MS)	mean ± SD	81.39 ± 9.45	85.25 ± 9.54	85.25 ± 9.54	89.53 ± 9.54	89.53 ± 9.54	93.07 ± 10.38	
	% Mean change	-4.78		-4.98		-3.95		
DT (SEC)	mean ± SD	187.79 ± 32.58	194.84 ± 31.20	194.84 ± 31.20	204.79 ± 31.04	204.79 ± 31.04	214.46 ± 31.01	
	% Mean change	-3.75		-5.11		-4.72		
TR (M/S)	mean ± SD	1.50 ± 0.53	1.73 ± 0.43	1.73 ± 0.43	1.99 ± 0.43	1.99 ± 0.43	2.26 ± 0.46	
	% Mean change	-15.03		-15.02		-13.60		
PASP (MM/HG)	mean ± SD	17.47 ± 5.89	20.59 ± 6.90	20.59 ± 6.90	23.35 ± 7.83	23.35 ± 7.83	26.66 ± 9.96	
	% Mean change	-17.87		-13.41		-14.16		
GLS (%)	mean ± SD	-17.95 ± 2.95	-16.74 ± 2.86	-16.74 ± 2.86	-14.03 ± 2.34	-14.03 ± 2.34	-12.85 ± 1.95	
	% Mean change	6.71		16.21		8.37		
TMT (METS)	mean ± SD	13.37 ± 3.23	11.83 ± 3.08	11.83 ± 3.08	9.75 ± 2.69	9.75 ± 2.69	8.58 ± 2.30	
	% Mean change	11.48		17.65		11.90		
QoL	mean ± SD	69.83 ± 12.29	74.41 ± 12.83	74.41 ± 12.83	82.05 ± 7.46	82.05 ± 7.46	90.44 ± 5.89	
	% Mean change	-6.55		-10.27		-10.23		

DT: Deceleration time; GLS: Global longitudinal strain; IVRT: Isovolumic relaxation time; LVEDD: Left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction; LVESD: Left ventricular end-systolic dimension; PASP: Pulmonary arterial systolic pressure; QoL: Quality of life; SV: Stroke volume; TMT: Treadmill test; TR: Tricuspid regurgitation.

Table 2 New York Heart Association classification at baseline and at 3 months follow-up intervals, *n* (%)

NYHA	Baseline	3 months	6 months	9 months
Class 1	52 (92.85)	45 (80.40)	14 (25.00)	10 (17.90)
Class 2	4 (7.15)	11 (19.60)	38 (67.90)	33 (58.90)
Class 3	0 (0.00)	0 (0.00)	4 (7.10)	13 (23.20)

NYHA: New York Heart Association.

Table 3 Outcomes at baseline and at 3 months follow-up intervals, *n* (%)

Outcomes	Baseline	3 months	6 months	9 months
Atrial fibrillation	0 (0.00)	0 (0.00)	2 (3.60)	1 (1.80)
Stroke	0 (0.00)	0 (0.00)	1 (1.80)	0 (0.00)

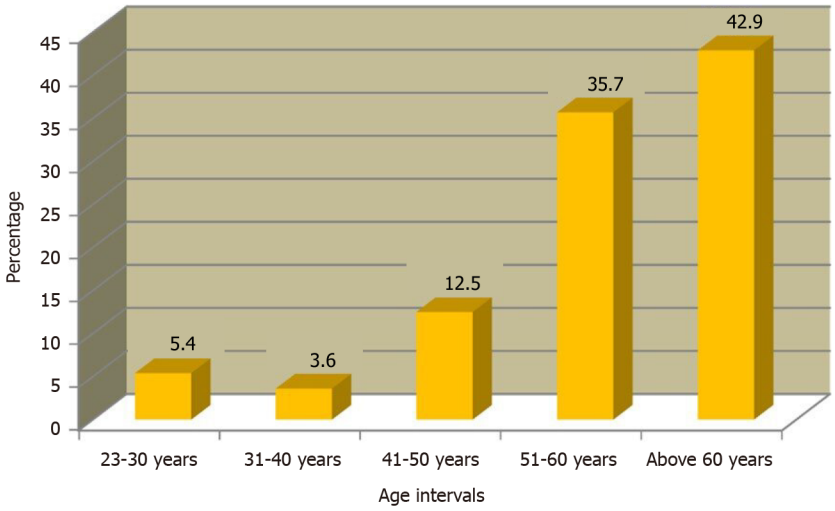

Figure 1 Age distribution among study participants.

pacing. However, a significant decrease in LVEF was observed for both pacing modes in our study, suggesting that RVP impacts LV function, particularly by altering LVEF.

In this study, over 73.2% of the study population was male, similar to previous studies in which the majority of participants were male[8,9]. Moreover, in a study conducted by Kim *et al*[10], the mean age was 58 years, comparable to that in this study (57.11 ± 11.87 years); however, in the previous study, the mean age was higher, at 73 ± 10 years[8].

IVRT is the time interval between the end of aortic ejection and the beginning of ventricular filling. In our study, a slight increase in IVRT values (89.53 ± 9.54 ms) was found in patients in the VVIR, similar to the findings of Dwivedi *et al* [9], who reported a significantly higher value in the VVIR pacing mode (135.24 ± 28.54 ms). In our study, no significant differences in IVRT values were observed in the DDDR. The mean LVEDD and LVESD in the VVIR in our study were 43.78 ± 3.04 mm and 25.98 ± 1.30 mm, respectively, whereas in the study by Dwivedi *et al*[9], the respective values were 51.6 ± 1.01 mm and 39.6 ± 1.00 mm (VVIR mode).

A study conducted by Gupta *et al*[11] in 2021 estimated the E/A and E/E´ ratios and observed a progressive increase in their values over a 6-month period, suggesting a deterioration in LV diastolic function. Our results indicate that the ratios remained within normal limits for both pacing modes throughout the study period, consistent with a previous study that measured the E/A ratio during dual-chamber pacing, where it was noted to be 0.95 ± 0.2[12].

In this study, the complications of pacemaker implantation were not significantly different between the single- and DDDR modes. The overall incidence of AF at the 6-month follow-up (VVIR mode) was 3.6%, whereas it was lower at the 9-month follow-up (DDDR mode), *i.e.*, 1.8%. However, in a study conducted by Mueller *et al*[13], a higher incidence of tachycardia was observed in patients with dual-chamber implantation. A study by Fisher *et al*[14] in 1988 indicated that the risk of stroke in patients with cardiac pacing is uncertain, although stroke has been reported in 4.5%-23% of paced patients with SSS during long-term follow-up. In our recent study, among 56 of our study population, 1.8% (1 patient) developed stroke during the VVIR mode (Figure 2).

Previous studies have suggested that a superior QoL is observed in patients with dual-chamber pacing. In a study by Lamas *et al*[15] in 1998, QoL was evaluated using the SF-36 scoring method, which showed no significant differences between the ventricular pacing and dual-chamber pacing groups at the 3- and 18-month follow-up. Our results demonstrate a significant improvement in the QoL scores for the study population in both dual- and single-pacing modes. Figure 2 depicts the centre all illustration of these study.

Limitations

This was a single-centre, prospective study conducted at a tertiary healthcare facility with a small sample size. After switching the pacemaker mode to the dual-chamber mode, the patients were followed for a short period. Additionally, the effect of different pacing sites on LV function was not evaluated, as only the RV apex lead position was available for this study. Although the patients received the medications for associated comorbidities as per the guidelines but treatment data was not assessed.

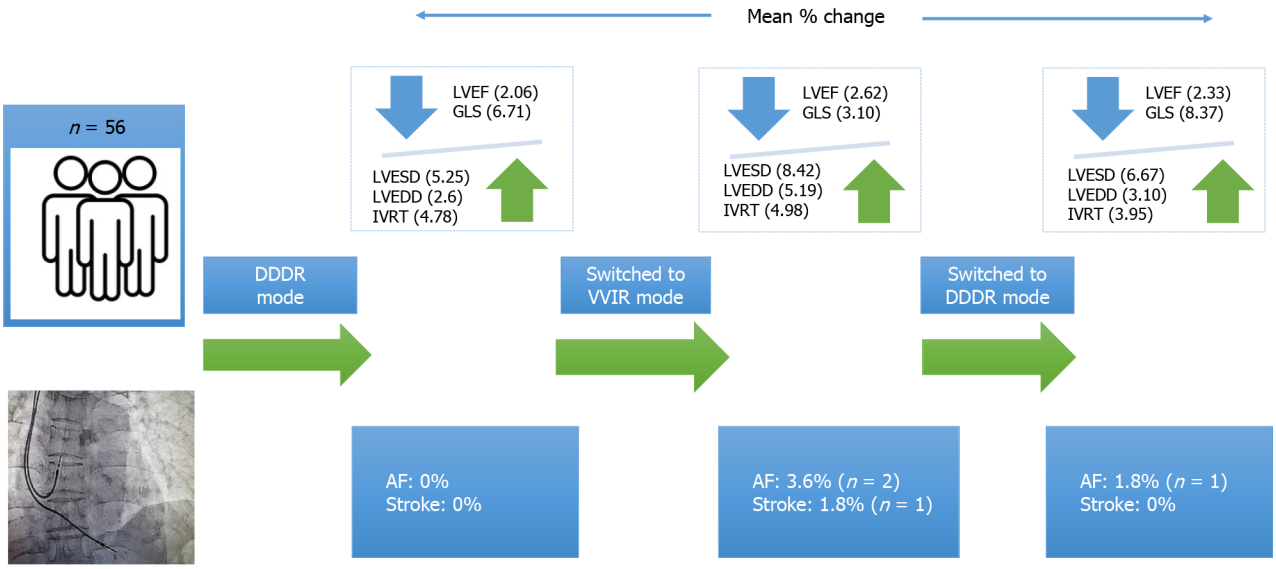

Figure 2 Central illustration of the study depicting the cross over design and benefits of dual chamber pacing.

CONCLUSION

This study suggests that RVP has a depressant effect on LV function, particularly in the VVIR mode. The DDDR mode appeared to achieve better clinical outcomes, with lower incidences of AF, stroke, and heart failure compared with the VVIR mode. Furthermore, health-related QoL significantly improved after pacemaker implantation. Overall, these findings indicate that the DDDR pacing mode is preferable to the VVIR mode.

FOOTNOTES

Author contributions: Haque M performed a literature search, data acquisition, and experimental studies and prepared manuscript; Bhandari M conducted clinical studies, data analysis, and manuscript preparation; Pradhan A conducted the study and prepared the manuscript; Vishwakarma P contributed to study design, data acquisition, and manuscript preparation; Singh A led the concept, clinical studies, data analysis, and manuscript preparation; Shukla A conducted a literature search, performed analysis, and prepared the manuscript; Chaudhary G was involved in designing the concept, performing statistical analysis and review manuscript; Sethi R contributed to study design, data acquisition, and manuscript preparation; Chandra S conducted clinical studies, data analysis, and manuscript preparation; Jaiswal A led the concept, clinical studies, data analysis, and manuscript preparation; Dwivedi SK performed the study and did statistical analysis of the data. All authors approved the final draft and are accountable for the manuscript's content.

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CASE REPORT

Cardiac hypertrophy in polycythemia vera: A case report and review of literature

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Abstract

BACKGROUND

The combination of polycythemia vera (PV) with pathological cardiac hypertrophy is uncommon. In this study, we describe a case of PV accompanied by pathological cardiac hypertrophy. It is hypothesized that the pronounced cardiac hypertrophy in this patient has a strong connection with PV.

CASE SUMMARY

In 2021, a 34-year-old Chinese man experienced chest constriction, shortness of breath, and palpitations during vigorous activity. Each episode lasted several minutes and resolved spontaneously following cessation of vigorous activity. He occasionally experienced syncope and vertigo without a headache. He underwent cardiac magnetic resonance imaging and was diagnosed with "hypertrophic cardiomyopathy (HCM)". He was discharged after receiving symptomatic treatment, which resulted in an improvement. He presented to our department with chest constriction, shortness of breath, and respiratory distress for one month while climbing to the second floor in 2023. His blood pressure was 180/100 mmHg at the time of admittance, and he was receiving antihypertensive treatment. He had a history of PV for 2 years without treatment. Symptomatic treatment was implemented concurrently with the administration of hydroxyurea upon admission. Good blood pressure control was observed during the long-term follow-up, and echocardiography did not reveal any progression of myocardial hypertrophy.

CONCLUSION
Clinicians managing PV patients should remain highly vigilant regarding the risks of thrombosis and cardiovascular complications, particularly in those with refractory hypertension.

Key Words: Polycythemia vera; Cardiomyopathy hypertrophic; Hypertension; Thrombosis; Case report

Core Tip: Clinicians should be highly vigilant regarding the risk of thrombosis and cardiovascular complications when managing patients with polycythemia vera (PV). In young patients with hypertension, who have excluded common secondary causes and have difficult-to-control blood pressure, there should be an alert for PV. The coexistence of PV and myocardial hypertrophy is rarely reported. The myocardial hypertrophy observed in this case, which is difficult to explain for other reasons, proposes a new hypothesis that PV may be a potential trigger. Cytoreductive therapy may be an important factor in improving the patient's myocardial hypertrophy.

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INTRODUCTION

Polycythemia vera (PV) is a rare hematologic disorder that is classified as chronic myeloproliferative neoplasms (MPNs). The disease is distinguished by the acquired clonal proliferation of red blood cells, which leads to a significantly elevated peripheral blood hematocrit (HCT) and increased blood viscosity. It is also characterized by splenomegaly, elevated white blood cell and platelet counts, and other potential symptoms. Furthermore, complications such as thrombosis and hemorrhage may develop during the disease[1,2]. The relationship between the risk of cardiovascular disease and the underlying mechanisms of MPNs has been explained by a plethora of clinical and mechanistic studies in recent years[3]. Although numerous case reports have investigated the relationship between PV and thrombotic diseases, there are relatively few reports that have examined the association between PV and myocardial hypertrophy.

This study presents a case of PV complicated with cardiac hypertrophy. It offers a comprehensive description of the patient's experience with antihypertensive medication and gives a thorough overview of their long-term follow-up. An in-depth literature review was also conducted to investigate the possible link between PV and the risk of cardiovascular disease, focusing on clinical case studies. The objective is to provide new perspectives and insights for assessing cardiovascular risk and analyzing prognosis in patients with MPNs. These results not only enhance our comprehension of the correlation between PV and cardiovascular disease but also have significant implications for future clinical management guidelines.

CASE PRESENTATION

Chief complaints

A 34-year-old man presented with a two-year history of chest tightness and dyspnea, which worsened over the past month leading to hospital admission.

History of present illness

Two years ago, during vigorous activity, he experienced episodes of chest tightness, dyspnea, and palpitations lasting several minutes each time, resolving spontaneously upon cessation of activity. He occasionally felt dizzy but denied headaches, blurred vision, or syncope. He underwent echocardiography and cardiac magnetic resonance imaging (MRI) at our hospital and was diagnosed with HCM, for which symptomatic treatment was initiated. One month ago, he developed severe chest tightness and dyspnea with exertion, such as climbing to the second floor, accompanied by respiratory distress but without precordial pain.

History of past illness

The patient had a 10-year history of hypertension, with peak blood pressure reaching 200/150 mmHg. Current treatment includes sustained-release calcium channel blocker (nifedipine 30 mg QD) and beta-blocker (metoprolol 47.5 mg QD), maintaining blood pressure at 170-180/120-130 mmHg. Secondary hypertension screening conducted three years ago showed minimal suspicion of secondary hypertension. The patient had a stroke three years ago and has had erythrocytosis for the past three years. A bone marrow examination suggested PV, but no further investigation or treatment was

pursued. He had no history of smoking, alcohol abuse, or type 2 diabetes mellitus.

Personal and family history

His father and uncle died from a brain hemorrhage. His brother's routine blood examination showed erythrocytosis, and echocardiography indicated interventricular septum and left ventricular posterior wall thickness of 14-15 mm, suggesting myocardial hypertrophy. A bone marrow aspiration has not yet been performed.

Physical examination

The patient was alert and oriented, with no other abnormal findings observed.

Laboratory examinations

Table 1 shows the blood test results, including hemoglobin and erythrocyte count, *etc*. The results of blood tests at the time of successive hospitalizations are also shown.

Imaging examinations

Table 2 shows the findings of cardiac color Doppler ultrasound for all previous hospitalizations.

FINAL DIAGNOSIS

Based on his symptoms, medical history, blood tests, and imaging examination, the patient was diagnosed with HCM, PV, stage 3 hypertension (extremely high risk), and lacunar cerebral infarction.

TREATMENT

Upon admission, diltiazem hydrochloride tablets (30 mg BID) and sacubitril-valsartan (100 mg QD) were added to the original antihypertensive drugs nifedipine controlled-release tablets (30 mg QD) and metoprolol succinate (47.5 mg QD). During hospitalization, following a consultation with the hematology department, hydroxyurea (0.5 g BID) was added to reduce erythrocyte levels, and aspirin (100 mg QD) was prescribed for thromboprophylaxis. The patient was discharged when his symptoms of chest tightness and shortness of breath improved after pharmacological treatment. He continued the same medication regimen, and no modifications were made to the treatment plan during the follow-up period.

OUTCOME AND FOLLOW-UP

One month after discharge, the patient adhered to the prescribed treatment regimen. The patient's hemoglobin levels returned to normal, blood pressure was controlled at 140/90 mmHg, and no further progression of myocardial hypertrophy was observed.

DISCUSSION

PV is a MPN that is characterized by abnormal proliferation of the red cell lineage in the bone marrow, resulting in an abnormal expansion of red blood cells in the bloodstream. The blood is thickened as a result of this abnormal increase in red blood cells, which slows blood flow and increases the risk of thrombosis. In PV patients, thrombosis is one of the most prevalent complications and causes of mortality[1]. PV may also result in complications such as leukemia, bone marrow fibrosis, and hemorrhage events. Currently, it is believed that the cardiovascular mortality risk in PV patients can be significantly reduced by maintaining HCT levels below 45% through intensified therapy[4]. This further confirms the correlation between PV and increased cardiovascular disease risk. Table 3 is a compilation of case reports from PubMed documenting instances of PV occurring with concomitant cardiovascular diseases. According to the literature, cardiac complications—including myocardial infarction, heart failure, and structural changes in the heart—are particularly important in this comprehensive analysis of PV cases combined with cardiovascular diseases. Coronary artery thrombosis is frequently observed in individuals with PV and is characterized by the formation of thrombi with a honeycomb appearance[5,6]. This may be due to the process of thrombus recanalization following blockage. It is also possible for some PV patients to have recanalization without the need for coronary artery intervention. This can occur by conservative therapy after the occurrence of coronary artery thrombosis. This suggests that symptoms may not be severe in certain PV patients after experiencing coronary thrombosis. Hence, it is essential to be vigilant of potential cardiac problems in PV patients who experience nonspecific symptoms such as chest tightness, dyspnea, or fatigue. In such cases, it may be important to consider experimental dual antiplatelet or anticoagulant therapy[7]. In addition to cardiovascular embolism, individuals with PV are also at risk of cerebrovascular embolism, which can potentially result in a stroke[8]. In this instance, the patient initially manifested symptoms of stroke upon admission.

Table 1 Blood test results of the patient at successive hospitalizations

Parameters	March 2021	January 2022	August 2022	October 2023	December 2023	Reference range
Hemoglobin	200 g/L	200 g/L	178 g/L	181 g/L	155 g/L	120-160 g/L
Hematocrit	0.595 L/L	0.569 L/L	0.516 L/L	0.524 L/L	0.449 L/L	0.4-0.5 L/L
Erythrocyte count	6.79×10^{12}/L	6.63×10^{12}/L	6.01×10^{12}/L	5.99×10^{12}/L	4.63×10^{12}/L	4×10^{12}-5.5×10^{12}/L
White blood cells	9.22×10^{9}/L	7.49×10^{9}/L	8.14×10^{9}/L	9.16×10^{9}/L	8.7×10^{9}/L	4×10^{9}-10×10^{9}/L
Platelet count	197×10^{9}/L	227×10^{9}/L	209×10^{9}/L	223×10^{9}/L	257×10^{9}/L	100×10^{9}-300×10^{9}/L

Table 2 Results of cardiac color Doppler ultrasound

Parameters	March 2021	January 2022	August 2022	October 2023
IVS (mm)	22	20.6	20.2	22
LVPW (mm)	21.9	28.9	18	16.4
EF%	75.4	75.8	67.2	68.4

IVS: Interventricular; LVPW: Left ventricular posterior wall; EF: Ejection fraction.

The underlying causes of thrombosis in individuals with PV are not fully understood; however, they may be related to higher HCT levels, increased blood viscosity, excessive platelet activation, and leukocytosis[9]. These factors collectively contribute to a hypercoagulable state in patients. Hence, considering the study findings described above, it is crucial to prioritize the prevention of thrombosis in the treatment guidelines for PV. This is particularly important for individuals with risk factors such as a history of thrombosis, age > 60 years, hypertension, hyperlipidemia, and leukocytosis. Regular phlebotomy and aspirin therapy (81 mg/day) are advised regardless of risk stratification[1]. Consideration may be given to twice-daily aspirin dosing for patients who are resistant to once-daily aspirin or at a higher risk of arterial thrombosis [2]. The potential of cytoreductive therapy to reduce thrombotic risk remains controversial. Pegylated interferon is an efficacious treatment for PV patients who are resistant to or intolerant of hydroxyurea, while hydroxyurea is the first-line cytoreductive therapy[10]. Nevertheless, there is currently no controlled trial that has confirmed the superiority of peg-IFN over hydroxyurea. A multicenter randomized controlled study has shown that cytoreductive therapy significantly decreases the risk of thrombotic recurrence. Antiplatelet agents and oral anticoagulants have also shown some efficacy in recurrence prevention[11]. Conversely, a large prospective multicenter study indicated a significant association between antiplatelet therapy and reduced risk of cardiovascular events, whereas cytoreductive therapy did not show such an association[12]. Despite the current lack of definitive conclusions regarding cytoreductive therapy and thrombotic risk, it may be considered an adjunctive therapy to antiplatelet treatment in high-risk thrombotic populations[13]. In patients with venous thrombosis, the addition of warfarin can further reduce recurrence rates[14]. However, maintaining a balance between thrombotic and bleeding risks is crucial during antithrombotic therapy. While the overall incidence rate of major hemorrhage in PV patients is 0.9%, it increases to 2.8% patient-years with combined antiplatelet and vitamin K antagonist therapy. Therefore, continuous monitoring of bleeding and thrombotic events in patients remains paramount.

The present case involves a patient with a history of previous cerebrovascular embolism who was admitted with symptoms of chest tightness and dyspnea, along with a positive Brain Natriuretic Peptide, indicating potential microcirculatory disorders alongside concerns about thrombotic recurrence. Therefore, the primary focus of treatment for this patient is aimed at preventing further thrombotic events. Conversely, the current therapy of aspirin and hydroxyurea has shown beneficial therapeutic effects in managing this patient's condition.

Moreover, there is scarce literature on the association of PV with cardiac structural changes. Hence, this case report on PV combined with myocardial hypertrophy holds particular clinical significance, offering a new perspective on the diversity and complexity of cardiac complications in PV.

Table 4 outlines the diagnostic criteria that distinguish common causes of myocardial hypertrophy, including hypertension and HCM. Hypertension-induced myocardial hypertrophy typically presents with symmetric characteristics, evidenced by echocardiography showing uniformly hypoechoic thickened myocardium[15], often with a wall thickness ≤ 15 mm. In contrast, HCM is characterized by ventricular wall thickening, particularly asymmetric hy-pertrophy of the interventricular septum. This condition often results in a reduced left ventricular cavity, and basal septal hypertrophy can lead to left ventricular outflow tract obstruction[16]. Fabry disease frequently manifests with concentric hypertrophy[17], and its diagnosis mostly depends on genetic testing. Amyloidosis leads to symmetrical myocardial hypertrophy[18], usually without evidence of ventricular high voltage on electrocardiography. It is identified with radionuclide imaging or cardiac biopsies. Athletes often experience physiological hypertrophy, which is marked by an increase in the thickness of the left ventricular wall.

In the present case, cardiac MRI of the patient revealed symmetric hypertrophy of the cardiac walls: Septum 17.3 mm, anterior wall 17.9 mm, lateral wall 21.0 mm, and inferior wall 17.7 mm. Cardiac ultrasound indicated extreme symmetric hypertrophy of the ventricular walls, which does not completely align with the etiological characteristics outlined in

Table 3 Case reports of polycythemia vera complicated with cardiac disease

Ref.	Biographical information	Diagnosis	Therapy	Prognosis	Pivot
Bahbahani *et al*[9]	Egyptian woman aged 37 years	Acute myocardial infarction, PV	Thrombolysis, hydroxyurea 15 mg/kg, aspirin 81 mg	After 4 weeks, myocardial perfusion imaging of the patient revealed no evidence of myocardial ischemia. Coronary CT angiography showed normal findings	Young individuals without atherosclerosis and its associated risk factors may experience cardiovascular thrombotic events due to PV
Zaman *et al*[7]	61-year-old female	Heart failure, microcirculatory disorder, PV	Normally treated with bloodletting, aspirin, and clopidogrel after diagnosis	During follow-up, the patient did not experience any new episodes of chest pain	PV can lead to microembolism in the cardiac microcirculation, resulting in impaired cardiac function
Duran Luciano and Sabella-Jiménez[31]	52-year-old Hispanic male	Acute myocardial infarction, *JAK2* negative PV	Antiplatelet, anticoagulation, and PCI therapy	Follow-up revealed improvement in cardiac function compared to previous assessments	*JAK2*-negative PV can also lead to cardiovascular thrombotic events
Inami *et al*[32]	64-year-old male	Acute myocardial infarction, recurrence of myocardial infarction after PCI, PV	PCI treatment, phlebotomy, and hydroxyurea for PV	No complications occurred	Patients with PV have a high risk of intrastent thrombosis following PCI
D'Onofrio *et al*[33]	86-year-old female	Severe stenotic aortic valve, pulmonary edema, post aortic valve replacement, respiratory circulatory failure	Aortic valve replacement, ECMO, CPR	The patient died	PV accompanied by severe thrombocytosis precluded antiplatelet and anticoagulant therapy, resulting in death from cerebral hemorrhage. Autopsy revealed extensive white thrombi formation in both the aortic valve and ventricles
Butt and Latif[34]	49-year-old male	Dilated cardiomyopathy, New York Classification III	Aspirin 100 mg, ramipril and bisoprolol in an increasing dose titration regimen. Furosemide 40 mg	During follow-up, the ejection fraction improved from 18% to 42%	Microvascular myocyte necrosis is considered the sole plausible pathophysiology of the cardiomyopathy
Haroun *et al*[35]	71-year-old Ethiopian man	PV, pericardial effusion, post-PV myelofibrosis	Discontinuation of hydroxyurea, pericardiocentesis	At 8 weeks following the initial consultation, during outpatient follow-up, complete blood cell counts revealed a leukocyte count of 13.6 × 10^9 cells/L, hemoglobin level of 9.9 g/dL, and platelet count of 556000/L	PV progressed to bone marrow fibrosis, resulting in extramedullary hematopoiesis and the formation of pericardial effusion

CT: Computed tomography; PV: Polycythemia vera; PCI: Percutaneous coronary intervention; *JAK2*: Janus kinase 2; ECMO: Extracorporeal membrane oxygenation; CPR: Cardiopulmonary resuscitation.

Table 4 Characteristics of different cardiac hypertrophy diseases

Name of disease	Typical features	Means of identification
HCM	Asymmetric septal hypertrophy, often accompanied by left ventricular outflow tract obstruction	Genetic testing and cardiac MRI
Hypertensive heart disease	Symmetrical myocardial hypertrophy, generally, ventricular wall thickness is ≤ 15 mm	History of hypertension for many years
Fabry disease	Concentric hypertrophy	α-Galactosidase A activity assay, *GLA* gene test
Myocardial amyloidosis	Symmetrical myocardial hypertrophy, characterized on electrocardiography by low voltage or normal voltage	Radionuclide imaging, cardiac biopsy line histology and amyloid staining
Physiological hypertrophy	In athletes, the unique condition of mild, uniform left ventricular wall thickening may be accompanied by an increase in left ventricular cavity diameter	Cardiopulmonary exercise test

HCM: Hypertrophic cardiomyopathy; MRI: Magnetic resonance imaging.

Table 4. Clinical studies have identified various cardiac issues in PV patients, including chamber enlargement, interventricular septal hypertrophy, pulmonary hypertension, left ventricular systolic and diastolic dysfunction, and impaired relaxation of the valve fibrous ring[4]. Therefore, it is speculated that PV may play a role in the process of myocardial hypertrophy. The precise mechanisms leading to such profound myocardial hypertrophy in patients with PV remain unclear and necessitate further research to elucidate potential pathways[19,20]. In this case, the duration of hypertension in the patient was longer than the time at which myocardial hypertrophy was detected, and the patient's sibling also exhibited signs of myocardial hypertrophy. Consequently, it is challenging to attribute the myocardial hypertrophy solely to factors such as hypertension, genetic predisposition, HCM, or PV. However, we believe that PV plays a significant role within the context of these multifactorial influences. Cardiac color Doppler imaging is necessary in patients with PV, as cardiac complications are extremely severe. The prognosis of patients is significantly improved by the timely intervention that is made possible by the early detection of indications of left ventricular systolic dysfunction through cardiac color Doppler. The utilization of tissue Doppler imaging (TDI) technology provides a new approach for the earlier diagnosis of myocardial dysfunction in patients with PV. Research suggests that the longitudinal strain of the left ventricular myocardium and the decreased TDI parameters of the fibrous ring around the atrioventricular valve can be used as early diagnostic criteria for myocardial dysfunction in PV patients[21].

Several mechanisms for myocardial hypertrophy in patients with PV are currently proposed. Firstly, the increased red blood cell mass in PV patients increases blood viscosity, which in turn increases vascular resistance[22], particularly in the microcirculation and arterioles, increasing left ventricular afterload. This viscosity increase can occasionally lead to microvascular flow obstruction[23], which can impact the delivery of oxygen and nutrients, as well as the removal of waste metabolites, resulting in relative myocardial hypoxia. To accommodate the increased afterload and oxygen demand, myocardial cells undergo hypertrophy to improve contractility and preserve the equilibrium between oxygen supply and demand. Secondly, erythropoietin (EPO) may possess cardioprotective properties[24]. Thus, cardiac complications may result from decreased EPO levels in PV patients. Thirdly, Janus kinase 2 (*JAK2*) gene mutations, as one of the primary pathogenic mechanisms of PV, have been associated with myocardial hypertrophy in animal models[25]. The *JAK2 V617F* mutation can lead to cardiac disease through inflammatory mechanisms, and can cause myocardial hypertrophy[26]. Mechanistically, the mutation increases JAK-STAT pathway expression, which subsequently enhances the expression and activation of the Absent in melanoma 2 (AIM2) inflammasome. The activated AIM2 inflammasome then stimulates the production of the inflammatory cytokine interleukin-1β, promoting apoptosis and contributing to the pathophysiological processes of cardiovascular diseases[27].

After conducting investigations for secondary hypertension in our patient and ruling out other potential causes, refractory hypertension in this young patient appears closely linked to PV. The patient had a long-standing history of hypertension, with inadequate blood pressure control on nifedipine and metoprolol. Consequently, upon admission, diltiazem and sacubitril/valsartan were added to the treatment regimen. Following the addition of hydroxyurea and aspirin to the treatment plan, blood pressure control significantly improved. During follow-up, there was no observed progression of myocardial hypertrophy or further issues with blood pressure control. The initial antihypertensive regimen was insufficient, but after adjusting the medication and incorporating hydroxyurea, blood pressure improved, suggesting that the combination of these medications may have enhanced the patient's prognosis. Additionally, there was a decrease in the patient's erythrocyte levels. Although hydroxyurea appears to play a crucial role, we cannot disregard the potential contributions of sacubitril/valsartan and diltiazem in suppressing erythrocyte production. This challenging case of resistant hypertension underscores the difficulties in managing hypertension in patients with PV, indicating that antihypertensive strategies in this population can be particularly complex. For cardiologists, it is essential to monitor hemoglobin levels in young patients with hypertension. Adhering to the World Health Organization (WHO) criteria for the diagnosis of PV[28], early intervention is recommended for patients meeting diagnostic criteria to prevent adverse outcomes. The WHO diagnostic criteria for PV are summarized in Table 5. Comprehensive diagnostic evaluations are advised to confirm the diagnosis and ensure appropriate management of patients. With regard to hematologists, it is crucial that they assess cardiovascular risk in PV patients during treatment and to implement appropriate interventions to prevent adverse events.

In PV patients with concurrent hypertension, antihypertensive medications that are currently available are effective in reducing blood pressure. Among them, ACE inhibitors may be the best option since they reduce blood pressure while also limiting abnormal red blood cell production, thereby minimizing the requirement for cytoreductive treatment[29].

Management of PV extends beyond the responsibility of hematologists and requires a multidisciplinary approach. PV is associated with a high risk of cardiovascular events, necessitating the involvement of cardiologists. The primary risk in PV is thrombosis; thus, vascular surgeons are crucial in managing patients with deep vein thrombosis. Additionally, given the potential for PV to progress to acute leukemia, oncologists must provide ongoing monitoring. A multidisciplinary management strategy that integrates the expertise of hematologists, cardiologists, vascular surgeons, oncologists, and other specialists can facilitate the development of a comprehensive treatment plan, addressing all aspects of the disease to improve patient outcomes and quality of life.

Following analysis of the patient's historical data on left ventricular posterior wall thickness and hemoglobin levels (Figure 1), a correlation between these variables was identified. Decreasing hemoglobin levels corresponded to a reduction in the degree of myocardial hypertrophy. Furthermore, effective hypertension control correlated with decreased myocardial hypertrophy[30]. The reversibility of myocardial hypertrophy in this patient further supports the diagnosis of secondary myocardial hypertrophy.

Future research should focus on further experimental studies and data analysis to elucidate the intrinsic mechanisms linking cardiovascular disease risk with PV. Investigating the role of tumor-associated genes in ventricular remodeling could provide a theoretical foundation for cardiovascular risk assessment and prognosis in PV patients, as well as uncover new mechanisms underlying cardiovascular disease.

Table 5 World Health Organization criteria for polycythemia vera

Major criteria	Minor criterion
Hemoglobin 16.5 g/dL in men Hemoglobin 16.0 g/dL in women, or Hematocrit 49% in men Hematocrit 48% in women, or increased RCM[1]	Subnormal serum erythropoietin level
BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)	
Presence of *JAK2 V617F* or *JAK2* exon 12 mutation	

[1]Diagnosis of polycythemia vera requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion.
RCM: Red cell mass; *JAK2*: Janus kinase 2.

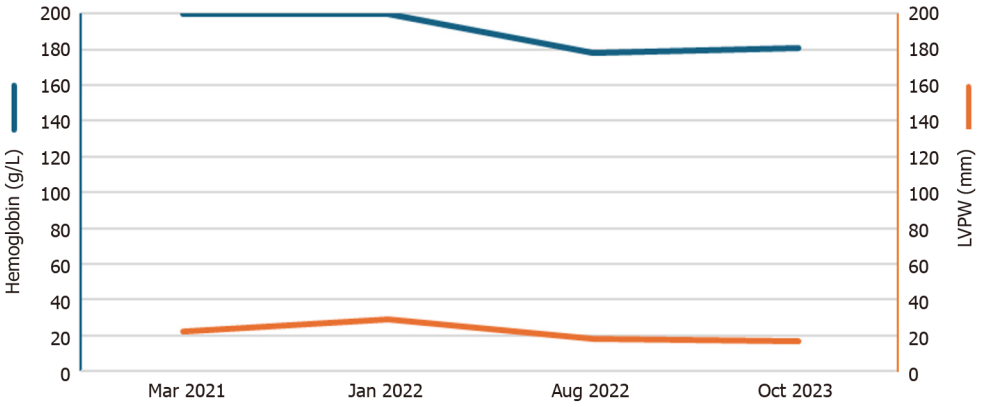

Figure 1 Line graphs of the posterior wall of the left ventricle and hemoglobin data for all previous hospitalizations of this patient. At higher levels of hemoglobin, the thickness of the posterior wall of the left ventricle increases. Subsequently, the thickness of the posterior wall of the left ventricle decreases as the hemoglobin level decreases. LVPW: Left ventricular posterior wall.

Future studies could be conducted in the following specific areas to validate the hypotheses proposed in this paper and to explore the relationship between PV and cardiac complications: (1) Prospective cohort studies: Regularly measure blood viscosity in PV patients and correlate these measurements with cardiac imaging results (*e.g.*, echocardiography, MRI); (2) Experimental research: Utilize tissue oxygenation monitoring techniques (*e.g.*, near-infrared spectroscopy) to assess myocardial oxygen supply in PV patients. Combine these assessments with measurements of cardiac biomarkers (*e.g.*, lactate dehydrogenase, natriuretic peptides) to analyze the specific effects of erythrocytosis on myocardial metabolism and hypertrophy; (3) Comparative prospective studies: Evaluate cardiac function and myocardial hypertrophy in PV patients with varying levels of EPO. Consider interventional studies to assess whether EPO replacement therapy offers protective effects against cardiac complications; and (4) Clinical observational studies: Given that animal models have demonstrated myocardial hypertrophy in *JAK2*-mutant mice, perform clinical observational studies to analyze the relationship between *JAK2* mutations and cardiac inflammatory markers, and assess their impact on cardiac structure and function. Exploring these research directions in depth will enhance our understanding of the mechanisms underlying myocardial hypertrophy in PV patients and provide more effective prevention and treatment strategies.

CONCLUSION

This report details a case of PV combined with myocardial hypertrophy. The observed myocardial hypertrophy and symptoms of hypertension may be associated with PV. Clinicians managing PV patients should remain highly vigilant regarding the risks of thrombosis and cardiovascular complications, particularly in those displaying refractory hypertension. Compared to historical cases, the occurrence of myocardial hypertrophy in this case, which is difficult to attribute to other causes, proposes a new hypothesis that PV could be a potential underlying trigger. Therefore, early diagnosis and management of cardiovascular diseases in PV patients are crucial for improving long-term prognosis. It is hoped that this case, along with others in the future, can present similar observational results, thereby contributing to a better understanding of the pathophysiology and management of myocardial hypertrophy in patients with PV.

FOOTNOTES

Author contributions: Ma BS wrote the first draft and corrected the manuscript; Ma BS and Zhai SH collected the data; Chen WW and

Zhao QN revised and contributed equally to the manuscript and figures as co-corresponding authors; all authors have read and approved the final manuscript.

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LETTER TO THE EDITOR

Kill two birds with one stone: Hapatologist's approach to metabolic dysfunction-associated steatotic liver disease and heart failure

Yusuke Hirao, Clarke Morihara, Tomoki Sempokuya

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Abstract

Heart failure (HF) is a major global public health concern, and one of the less commonly known risk factors for HF development is metabolic dysfunction-associated steatotic liver disease (MASLD), as they share a similar pathophysiological background. In this article, we evaluated a recently published review article by Arriola-Montenegro *et al*. This article briefly summarizes the common pathophysiology of HF and MASLD development and evaluates the available therapeutic options to treat both conditions. Clinical practice guidelines highlight the importance of initiating and titrating guideline-directed medication therapy (GDMT) for patients with HF with reduced ejection fraction. GDMT is comprised of the four pillars currently proposed in most clinical practice guidelines, namely angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose co-transporter 2 inhibitors (SGLT-2i). Given the similarity of pathophysiology and risk factors, recent studies for GDMT regarding ACEIs, ARBs, mineralocorticoid receptor antagonists, and SGLT-2i have shown beneficial effects on MASLD. Nonetheless, other medications for both conditions and novel therapies require more robust data and well-designed clinical studies to demonstrate their efficacies in both conditions.

Key Words: Metabolic dysfunction-associated steatotic liver disease; Heart failure; Heart failure with reduced ejection fraction; Non-pharmacological; Pharmacological; Surgical intervention

Core Tip: Due to common risk factors and underlying pathophysiologic mechanisms, there is a significant association between heart failure with reduced ejection fraction and metabolic dysfunction-associated steatotic liver disease. This article will explore the current pharmacological and non-pharmacological interventions.

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TO THE EDITOR

Worldwide, heart failure (HF) represents a significant clinical, economic, and public health concern. Globally, 64.3 million people suffered from HF in 2017, and it is estimated to cost $69.8 billion in the United States in 2030[1]. HF is also considered to be most prevalent amongst adults aged greater than 60 years old[2]. Ischemia, tachyarrhythmias, infiltrative conditions, cardiac toxin exposure, substance use, and structural conditions such as valvular heart disease are common risk factors for HF development[3,4]. Treatment of HF remains multimodal with management of the underlying etiology in addition to utilization of Guideline Directed Medical Therapy (GDMT). At the core of GDMT remains four pillars consisting of different medication classes which include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose co-transporter 2 inhibitors (SGLT-2i)[5]. Interestingly, metabolic dysfunction-associated steatotic liver disease (MASLD), formally known as non-alcoholic fatty liver disease (NAFLD), is an emerging risk factor for HF as it may share a similar pathophysiological mechanisms[3,6]. MASLD is a fatty infiltration of the liver without hepatocellular inflammation due to metabolic risk factors. Whereas metabolic dysfunction-associated steatohepatitis (MASH) is defined as the presence of adipose tissue leading to lipotoxicity and inflammatory damage to hepatocytes[7]. A recently published review article by Arriola-Montenegro *et al*[3], evaluated therapies to target both HF with reduced ejection fraction (HFrEF) and MASLD[3]. HFrEF and MASLD represent two prevalent comorbidities sharing similar pathophysiological mechanisms. Moreover, emerging epidemiological investigations substantiate a robust and independent correlation between MASLD and HF, with an approximate prevalence of HF among MASLD patients being 6.4%[8]. The pathophysiological relationship between MASLD and HFrEF involves substances that contribute towards further dysregulation such as adipokines and proinflammatory cytokines including leptin. Leptin has been associated with profibrotic activity while working at the level of the liver. Meanwhile, leptin may also be associated with endothelial dysfunction as well as cardiac hypertrophy. Other notable mediators include tumor necrosis factor-α and interleukin (IL)-6, both which confer to hepatocyte damage. Additionally, another mediator IL-33 has been noted to be released in the setting of hepatocyte injury and shown to potentiate further fibrosis. Meanwhile, the release of IL-33 by the heart has been associated as a reaction towards myocardial fiber stretching[9].

MASLD and cardiovascular disease (CVD) both possess similar risk factors (*i.e.*, sedentary lifestyle, smoking, physiological stress, and sleep deprivation). Furthermore, the presence and accumulation of visceral and ectopic fat acts as a further stimulus towards inflammatory pathway activation and release of toxic metabolites further contributing to each pathologies. CVD is known to be prevalent in patients with MASH, particularly in those with severe liver disease, remaining a leading cause of mortality. Respectfully, CVD risk factors should be proactively managed in this population [10].

THERAPIES

Non-pharmacological therapies

Primary therapeutic interventions for MASLD consist of lifestyle modifications, which include dietary alterations, increased physical activity, and weight management. Typical recommendations for patients in the hepatology clinic include trialing the Mediterranean diet, 150 minutes of moderate to high-intensity aerobic exercise with strength training, and goal weight reduction of 7%-10% of body weight[11]. These lifestyle modifications alter adipose tissue distribution and improve the risks of developing cardiovascular comorbidities[12]. When optimal results are not achieved with lifestyle modifications, bariatric surgery should be considered in obese patients with associated comorbidities. Bariatric surgery has been shown to have the potential for long-term improvement or even resolution of MASLD, both clinically and histologically. This also mitigates CVD risk among obese patients by improving glucose tolerance and lipid profiles [13]. Moreover, recent meta-analyses have revealed a decreased incidence of HF and myocardial infarction following bariatric surgery[14].

Pharmacological therapies

Several evidence-based pharmacologic interventions for HFrEF have shown a beneficial effect on MASLD therapies. As the backbones of GDMT for HFrEF, ACEIs and ARBs have potential beneficial effects on MASLD treatment[15]. ACEIs

and ARBs are both known to have mortality benefits in hospitalized patients with HFrEF, advanced kidney disease, and for MASLD treatment. ACEIs, and ARBs also inhibit Angiotensin II, a key contributor to abnormal lipid metabolism[16]. This in turn, decreases lipid accumulation in the liver and diminishes the risk of fibrosis. SGLT-2i, which are also used for type 2 diabetes treatment, may inhibit the development of MASLD and improve histological features of hepatic steatosis or steatohepatitis[17]. The possible mechanism of SGLT-2i in MALSD management is weight loss and reduction of visceral fat by inhibition of de novo hepatic lipogenesis[18]. A recent meta-analysis demonstrated SGLT-2i induced a significant decrease in liver enzymes involving serum alanine, aspartate aminotransferases, gamma glutamyl transferases, in addition to decreasing liver steatosis[19]. Another meta-analysis also evaluated the efficacy of SGLT-2i to significantly decrease serum alanine aminotransferase, gamma-glutamyl transferase levels and liver fat content on imaging techniques compared to placebo/reference therapy[20]. Additionally, the risk of cardiovascular death or hospitalization amongst patients with HFrEF regardless of type 2 diabetes mellitus (T2DM) status has been shown to be reduced with SGLT-2is. SGLT-2i seems to be a promising pharmacological option for both MASLD and HFrEF. Patients with NAFLD and HFrEF also have potential for favorable outcomes with the use of mineralocorticoid receptor antagonists (MRAs) such as spironolactone and eplerenone. In a mouse model, eplerenone effectively improved insulin resistance and MALSD-associated histological change by acting on Kupper cells and macrophages[21]. Another mouse model study demonstrated spironolactone not only improved accumulation of triglycerides within the liver but also suppressed the expression of proinflammatory, gluconeogenic, and lipogenic enzymes[20]. Additionally, spironolactone and vitamin E combination therapy may convey improvement with insulin resistance within an *in vivo* study[21]. These results indicate that MRAs may be pivotal treatments for both MASLD and HFrEF. For novel medications, resmetirom is an oral, liver-directed, thyroid hormone receptor beta-selective agonist and is currently the most recent and only United States Food and Drug Administration (FDA) approved treatment of MASH with liver fibrosis (F2 and F3). MAESTRO-NASH trial, a phase 3 trial, involving adults with biopsy-confirmed NASH and a fibrosis stage of F1B, F2, or F3 [stages range from F0 (no fibrosis) to F4 (cirrhosis)] demonstrated that both the 80-mg and the 100 mg dose of resmetirom were superior to placebo with respect to NASH resolution and improvement in liver fibrosis by at least one stage[22]. As this is a recent FDA-approved medication in as of March 2024, long-term data is currently lacking, in addition to an unknown effect on HF risk modification. Glucagon-like peptide 1 (GLP-1) receptor agonists promote weight loss by improving hyperglycemia and delaying gastric emptying[23]. These provide an appealing therapeutic choice amongst patients with MASLD, particularly those with obesity and diabetes mellitus. Although observations regarding utilization of GLP-1 receptor agonists in those with MASLD suggest benefit, while randomized trials infer an absence of benefit in HF related outcomes in addition to uncertainty involving safety amongst those with HFpEF[24]. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide, and a GLP-1 receptor, is a novel medication for the treatment of T2DM and has provided encouraging results amongst ongoing clinical trials, for T2DM in addition to improving body weight and steatosis[25]. Currently, there is no available data to support the evidence of tirzepatide in patients with HFrEF, but a clinical trial assessing the efficacy and safety of tirzepatide in patients with HF with preserved ejection fraction and obesity is being undertaken (ClinicalTrials.gov ID: NCT04847557). Although many practitioners are leery of using statins in patients with liver disease, statins have been reported as safe for patients with MASLD, including those with advanced liver disease, and are also associated with a clear reduction in cardiovascular morbidity and mortality. For the management of dyslipidemia in MASLD, moderate- to high-intensity statins should be the preferred agents based on lipid associated risk level and atherosclerosis atherosclerotic cardiovascular disease risk score[11]. Regrettably, there is currently a lack of data elucidating favorable effects of sacubitril/valsartan, beta-blockers, hydralazine, isosorbide nitrates, ivabradine, or digoxin, on MASLD.

CONCLUSIONS

Numerous recent studies have revealed a strong correlation between HF, particularly the HFrEF subtype, and MASLD. Various pathophysiological mechanisms have been proposed, most of which revolve around common factors contributing to systemic inflammation. To the present time, a variety of pharmacologic and non-pharmacologic treatments have been explored in patients simultaneously managing HFrEF and MASLD. Specific pharmacologic therapies such as diet, ACEIs, ARBs, MRAs, SGLT-2i inhibitors, and bariatric surgery have been implicated to be effective. Yet, there continues to be an absence of solid data and well-designed clinical trials regarding several other pharmacologic therapies and innovative treatments which may be potentially beneficial for patients with these conditions.

FOOTNOTES

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Effects of sodium-dependent glucose transporter 2 inhibitors in patients with type 2 diabetes mellitus and asymptomatic heart failure

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Abstract

Sodium-dependent glucose transporter 2 inhibitors (SGLT2i) have been increasingly used with proven efficacy in patients with heart failure (HF), regardless of diabetes status. Grubić Rotkvić *et al* recently published an observational study on SGLT2i therapy in patients with type 2 diabetes mellitus and asymptomatic HF. They found that the use of SGLT2i led to reduced cardiac load and improved cardiovascular performance, reinforcing the evolving paradigm that SGLT2i are not merely glucose-lowering agents but are integral to the broader management of cardiovascular risk in patients with type 2 diabetes mellitus. The study by Grubić Rotkvić *et al* contributes to the growing body of literature supporting the early use of SGLT2i in patients with diabetic cardiomyopathy, offering a potential strategy to mitigate the progression of HF. Future larger studies should be conducted to confirm these findings, and explore the long-term cardiovascular benefits of SGLT2i, particularly in asymptomatic patients at risk of developing HF.

Key Words: Heart failure; Cardiovascular risk; Diabetes mellitus; Mortality; Sodium-dependent glucose transporter 2 inhibitors

Core Tip: Grubić Rotkvić *et al* published an observational study on the use of sodium-dependent glucose transporter 2 inhibitors (SGLT2i) in patients with type 2 diabetes mellitus and asymptomatic heart failure. Their findings included reduced cardiac load and improved cardiovascular performance related to the use of SGLT2i. This suggests that SGLT2i are not merely glucose-lowering drugs; they are integral to the broader cardiovascular management in patients with type 2 diabetes mellitus.

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TO THE EDITOR

The expanding interest in sodium-dependent glucose transporter 2 inhibitors (SGLT2i) as a cornerstone therapy in the management of heart failure (HF) has significantly impacted contemporary cardiology. A recent observational study by Grubić Rotkvić *et al*[1] provides crucial insights into the utility of SGLT2i in patients with type 2 diabetes mellitus (T2DM) who exhibit asymptomatic HF. Their study builds on previous data by focusing on the mechanisms underlying the cardioprotective effects of SGLT2i in this specific patient population.

IMPACT OF SGLT2I ON MYOCARDIAL FUNCTION

This prospective observational study evaluated a cohort of patients with T2DM receiving dual antidiabetic therapy, including metformin and either SGLT2i or dipeptidyl peptidase-4 inhibitors. The study divided treatment arms into two subgroups based on baseline parameters such as high-sensitivity C-reactive protein, myeloperoxidase, global longitudinal strain (GLS), N-terminal pro-brain natriuretic peptide, and systolic and diastolic blood pressures.

The results indicated that SGLT2i therapy led to a significant reduction in oxidative stress and inflammatory markers, particularly myeloperoxidase and high-sensitivity C-reactive protein, especially in patients with elevated baseline levels of these biomarkers. This aligns with evidence highlighting the anti-oxidative and anti-inflammatory properties of SGLT2i, contributing to their cardiovascular benefits[2,3]. Notably, there was a greater reduction in the studied variables in the patients with high baseline values, irrespective of the treatment group, after follow-up.

EXPANDING THE LITERATURE ON SGLT2I'S CARDIOPROTECTIVE MECHANISMS

Recent meta-analyses have underscored the multifaceted benefits of SGLT2i beyond glycemic control. SGLT2i have consistently demonstrated a significant reduction in HF hospitalisation and cardiovascular mortality across various populations, including patients with and without T2DM. These outcomes were particularly pronounced in patients with HF and reduced ejection fraction[4,5]. SGLT2i received a class IA recommendation for treatment of patients with HF and reduced ejection fraction, regardless of diabetes mellitus status, according to the American College of Cardiology and American Heart Association and guidelines[6,7]. The EMPULES trial is a multicentre international double-blind, clinical trial that randomised 530 patients with acute HF to receive empagliflozin or a placebo. The trial reported decreased mortality and HF-related hospitalisations during the 90-day follow-up, regardless of left ventricular ejection fraction and diabetes status[8]. The recent European Society of Cardiology recommended the use of SGLT2i as a class IA treatment for patients with HF and left ventricular ejection fraction (> 40%) to reduce HF-related hospitalisation and cardiovascular mortality[9]. Further, SGLT2i also demonstrated efficacy in patients with HF with preserved ejection fraction. The EMPEROR-Preserved trial and subsequent meta-analyses revealed a reduction in HF-related hospitalisations or cardiovascular death in these patients, thereby establishing SGLT2i as a versatile tool for managing HF across the ejection fraction spectrum[10,11].

MECHANISTIC INSIGHTS AND CLINICAL IMPLICATIONS

The protective cardiovascular effects of SGLT2i are attributed to several mechanisms, including osmotic diuresis, which leads to volume reduction, decreased blood pressure, and improved ventricular loading conditions. Additionally, SGLT2i reduce myocardial fibrosis, oxidative stress, and sympathetic nervous system activation, all of which are critical in HF pathophysiology[2]. Moreover, SGLT2i provide substantial renoprotective effects, particularly in patients with T2DM. They reduce the risk of adverse renal outcomes, likely by modulating intraglomerular pressure and reducing hyperfiltration[12]. This dual benefit for both the cardiovascular and renal systems makes SGLT2i appealing for managing

patients at high cardiovascular risk, regardless of established HF[13]. The European Society of Cardiology guidelines recommend SGLT2i as a class IA treatment for patients with HF and chronic kidney disease to decrease HF-related hospitalisations and cardiovascular mortality[9]. Despite the proven beneficial effects of SGLT2i in patients with HF and T2DM, caution is warranted for patients at risk of diabetic ketoacidosis, especially those with changes in insulin doses or dietary intake. A meta-analysis involving 60580 patients reported a doubled risk of diabetic ketoacidosis in patients with T2DM receiving SGLT2i, especially in those aged ≥ 60 years and those on SGLT2i for more than 52 weeks[14].

SIGNIFICANCE OF THE FINDINGS AND FUTURE DIRECTIONS

The study by Grubić Rotkvić *et al*[1] provides a nuanced understanding of the cardiometabolic benefits of SGLT2i, particularly in the early stages of HF. The observation that SGLT2i improve GLS and attenuates sympathetic nervous system activation without significantly lowering N-terminal pro-brain natriuretic peptide levels suggests that SGLT2i may exert their cardioprotective effects through mechanisms independent of natriuretic peptide modulation. The improvement in myocardial function, as evidenced by enhanced GLS and reduced oxidative stress, underscores the potential of SGLT2i in preventing the progression from asymptomatic to symptomatic HF in patients with diabetes[15,16].

However, the study also has limitations including the small sample size and short follow-up period, which may preclude definitive conclusions regarding the long-term benefits of SGLT2i use in this patient group. Moreover, the variability in effects among the different agents belonging to the SGLT2i and dipeptidyl peptidase-4 inhibitors classes warrants further large-scale studies to elucidate the differential effects of these drugs on cardiovascular outcomes.

CONCLUSIONS

The findings of the study by Grubić Rotkvić *et al*[1] reinforce the evolving paradigm that SGLT2i are not merely glucose-lowering agents but are integral to the broader management of cardiovascular risk in patients with T2DM. The study contributes to the growing literature supporting the early use of SGLT2i in diabetic cardiomyopathy, offering a potential strategy to mitigate the progression of HF. Future large studies should be conducted to confirm these findings and explore the long-term cardiovascular benefits of SGLT2i, particularly in asymptomatic patients at a risk of developing HF.

FOOTNOTES

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LETTER TO THE EDITOR

SGLT2 inhibitors in the prevention of diabetic cardiomyopathy: Targeting the silent threat

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Abstract

Heart failure (HF) is a major global health challenge, particularly among individuals with type 2 diabetes mellitus (T2DM), who are at significantly higher risk of developing HF. Diabetic cardiomyopathy, a unique form of heart disease, often progresses silently until advanced stages. Recent research has focused on sodium-dependent glucose transporter 2 inhibitors (SGLT2i), originally developed for hyperglycemia, which have shown potential in reducing cardiovascular risks, including HF hospitalizations, irrespective of diabetic status. In this editorial we comment on the article by Grubić Rotkvić *et al* published in the recent issue of the *World Journal of Cardiology*. The investigators examined the effects of SGLT2i on myocardial function in T2DM patients with asymptomatic HF, finding significant improvements in stroke volume index and reductions in systemic vascular resistance, suggesting enhanced cardiac output. Additionally, SGLT2i demonstrated anti-inflammatory and antioxidant effects, as well as blood pressure reduction, though the study's limitations—such as small sample size and observational design—necessitate larger randomized trials to confirm these findings. The study underscores the potential of early intervention with SGLT2i in preventing HF progression in T2DM patients.

Key Words: Sodium-dependent glucose transporter 2 inhibitor; Diabetes mellitus; Heart failure; Pathophysiology; Inflammation; Oxidative stress

Core Tip: Sodium-dependent glucose transporter 2 inhibitors show promise in improving cardiac function and reducing cardiovascular risks in patients with type 2 diabetes mellitus and asymptomatic heart failure (HF). Early intervention with these drugs could be key in preventing the progression of diabetic cardiomyopathy, making them an important consideration in managing high-risk diabetic patients before symptoms of HF emerge.

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TO THE EDITOR

Heart failure (HF) continues to be one of the most formidable challenges in modern medicine and is a leading cause of morbidity and mortality worldwide, with a 5-year mortality rate comparable to that of malignancies[1]. The burden is particularly heavy among individuals with type 2 diabetes mellitus (T2DM), who face a significantly elevated risk—two to five times higher—of developing HF compared to those without diabetes[2]. In the intersection of these two chronic conditions lies diabetic cardiomyopathy, a unique form of heart disease that develops independently of other diabetic complications, and often remains asymptomatic until it progresses to a more severe stage[3].

The growing recognition of this silent threat has spurred research into potential therapeutic interventions, with Sodium-dependent glucose transporter 2 inhibitors (SGLT2i) emerging as a promising class of drugs. Originally developed for diabetes treatment, SGLT2i have shown unexpected efficacy in reducing cardiovascular risks, including the burden of HF, regardless of the type or stage of HF and the diabetic status of the patient, as shown by groundbreaking trials such as EMPAREG-OUTCOME, DAPA-HF, EMPEROR-Reduced, EMPULSE and EMPEROR-Preserved[4,5].

A recent observational study by Grubić Rotkvić *et al*[6] delves into the effects of SGLT2 inhibitors on myocardial function in patients with T2DM and asymptomatic HF[6]. The study focuses on HF stages A and B, where early intervention could potentially alter the trajectory of the disease before symptoms manifest. Patients in this study were treated with either SGLT2i or dipeptidyl peptidase-4 inhibitors (DPP-4i), with a comprehensive follow-up over six months to assess various biomarkers and echocardiographic parameters. The findings of this study, although nuanced, shed light on the potential benefits of SGLT2i in a subset of diabetic patients who are often under the radar.

Slow left ventricle relaxation, especially at elevated heart rates, is a prominent feature of HF with preserved ejection fraction and, together with myocardial stiffening and impaired ventricular-arterial coupling, contributes to reduced stroke volume and abnormal systolic function during stress, even when systolic function appears normal at rest[7]. In contrast with the findings from a recent meta-analysis, which did not demonstrate a significant mean change in stroke volume with SGLTi therapy, the study by Grubić Rotkvić *et al*[6] showed that SGLT2i therapy was associated with a significant increase in stroke volume index, suggesting an improvement in cardiac output—an effect that may be linked to a reduction in systemic vascular resistance[8].

The mechanisms underlying the cardioprotective action of SGLT2i remain debated and are still under investigation, given that SGLT2i is not expressed in the human myocardium[9]. Among the putative mechanisms are anti-inflammatory and antioxidant pathways. Specifically, we have previously shown that, according to a meta-analysis of 30 studies on rodents, administration of SGLT2i is associated with a reduction in inflammatory markers (interleukin-6, tumor necrosis factor-alpha, C-reactive protein, monocyte chemoattractant protein-1)[10]. Such findings have been reported also in human studies, as evidenced in a meta-analysis by Buttice *et al*[1] A potential mechanism involves the restoration of autophagy, where SGLT2i activate the sirtuin 1/adenosine monophosphate-activated protein kinase pathway while inhibiting the autophagy-inhibiting Akt/mammalian target of rapamycin complex 1 pathway, reducing inflammation and oxidative stress[1,1]. The authors did not report significant differences based on treatment allocation, possibly owing to DPP4i-related anti-inflammatory effects[1]. The investigators further found that treatment of such patients with antidiabetic agents produced an improvement in circulating myeloperoxidase, suggesting their antioxidant effect. Indeed, SGLT2i are known to possess antioxidant properties, as highlighted in numerous preclinical and clinical studies[1].

An important observation of this study is the changes in blood pressure (BP). According to the results, there were significant reductions with both drug classes in patients with systolic and diastolic BP above the cutoffs. While SGLT2i are not predominantly known for the BP-lowering effects, accumulated evidence suggests a secondary effect in BP regulation, possibly through inhibition of the sympathetic nervous system and the renin-angiotensin-aldosterone system [1]. As shown by Iqbal *et al*[17] in a meta-analysis of 10 randomized controlled trials, SGLT2i reduced 24-hour ambulatory systolic BP and diastolic BP by approximately 5 mmHg and 3 mmHg, respectively[1]. The BP-lowering effects of DPP4i are perhaps lesser known. However, it should be stated that according to a systematic review and meta-analysis of 15 trials conducted by Zhang *et al*[18], DPP4i produced greater systolic and diastolic BP reductions compared to placebo (3 mmHg and 1 mmHg, respectively)[1]. However, when compared to SGLT2i, their effects on BP were of lesser magnitude [1], a difference that was not seen in the study of Grubić Rotkvić *et al*[6] A possible explanation for such discrepancy is the limited sample size which might not have allowed for a reliable head-to-head comparison[6].

The study by Grubić Rotkvić *et al*[6] provides valuable insights but is limited by several factors that affect the generalizability and robustness of the findings. The small sample size reduces the statistical power of the study, making it difficult

to draw definitive conclusions, while the short follow-up period may not allow for the observation of long-term effects. Furthermore, its observational design is prone to bias and confounding, as it does not control for potential differences between patient groups that could influence outcomes. The reliance on surrogate markers, such as stroke volume index and high sensitivity C-reactive protein, though informative, may not fully capture the broader clinical impact of SGLT2i, particularly in relation to hard endpoints like hospitalization or mortality. Additionally, the absence of randomization increases the risk of selection bias, which further limits the ability to establish causality. To confirm these findings and better understand the cardioprotective effects of SGLT2i, larger, randomized controlled trials with longer follow-up are essential, particularly in patients with asymptomatic HF. These trials should aim to clarify the underlying mechanisms and assess clinically meaningful outcomes.

In conclusion, the study by Grubić Rotkvić *et al*[6] contributes to the growing body of evidence supporting the use of SGLT2i in diabetic patients with early-stage, asymptomatic HF. These findings highlight the potential for SGLT2 inhibitors to alter the trajectory of diabetic cardiomyopathy by offering both metabolic and cardioprotective benefits. This high-risk group of patients must be kept on our "radar", as early intervention with SGLT2i could prevent or delay HF progression, reduce hospitalization rates, and improve long-term cardiovascular outcomes. As our understanding of their mechanisms evolves, SGLT2i are poised to play a pivotal role in the prevention and management of HF in T2DM patients, making them a critical consideration in clinical decision-making. Larger trials and long-term follow-up studies will further inform optimal patient selection and timing of intervention.

FOOTNOTES

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