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EDITORIAL

Balancing bleeding, thrombosis and myocardial injury: A call for balance and precision medicine for aspirin in neurosurgery

Subhrashis Guha Niyogi, Akash Batta, Bishav Mohan

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Abstract

Perioperative management of antiplatelet therapy involves a delicate balancing of the risk of periprocedural blood loss with the cardiovascular and thrombotic risk to the patient. Due to the unique nature of neurosurgery, perioperative bleeding may have devastating consequences and cause major morbidity and mortality. The recommendation to discontinue aspirin prior to major neurosurgical procedures rests upon conventional practice, expert consensus with priority given to avoidance of any major bleed. On the contrary recent prospective data do not support the existence of additional bleeding risk in patients continuing aspirin compared to those who stop aspirin prior to procedure. Patients with cardiovascular and metabolic comorbidities are increasingly encountered in the operation theatre these days. In these patients, prevention of myocardial injury after non-cardiac surgery (MINS) is an important focus for perioperative risk reduction. Prolonged (≥ 7 days) cessation of antiplatelets is one of the most important predictors of MINS. This complicated milieu of risks and benefits highlights the difficulty of practicing evidence-based medicine and minimizing harm in patients on aspirin needing neurosurgery.

Key Words: Neurosurgery; Aspirin; Myocardial injury after non-cardiac surgery; Thrombotic risk; Haemorrhagic complications; Platelet function assessment

Core Tip: The decision to continue or discontinue aspirin during the perioperative period is nuanced and must be tailored to each patient. The procedure-related bleeding risks of neurosurgery must be weighed against the potential patient-specific risks of thromboembolism, major adverse cardiac events as well as subclinical myocardial injury after non-cardiac surgery (MINS). MINS increases the risk of both early and late postoperative morbidity and mortality and can be triggered by prolonged (≥ 7 days) cessation of antiplatelets. Practice guidelines incorporating the latest evidence and point-of-care tests of platelet function are possible aids in this complicated scenario.

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INTRODUCTION

Aspirin is currently one of the mainstays in primary as well as secondary prevention of thromboembolic events[1]. It selectively and irreversibly acetylates cyclooxygenase-1 in platelets and megakaryocytes, rendering them unable to synthesize thromboxane A_2 (TxA_2) for their lifetime. This inhibits platelet aggregation and prolongs the bleeding time. However, since it inhibits only the TxA_2 mediated pathway of platelet aggregation, not the major adenosine diphosphate-purinergic receptor P2y ($ADP\text{-}P2Y_{12}$) pathway, even in presence of chronic aspirin ingestion, ADP, collagen, thrombin can trigger effective platelet aggregation and cause haemostasis. While specialized methods can demonstrate aspirin effect, most point-of-care coagulation assays in clinical use do not reveal the change from the use of aspirin[2,3]. Work is on-going towards developing appropriate platelet function tests to quantify this effect[4,5].

ASPIRIN AND PREPROCEDURAL CONSIDERATIONS

The "partial inhibition" of platelet aggregation by Aspirin has led to a controversy around the perioperative use of Aspirin. It is important to balance the risk of potential periprocedural blood loss against the cardiovascular and thrombotic risk to the patient while managing antiplatelet therapy perioperatively.

Perioperative blood management guidelines by the American Society of Anesthesiology in 2015 and 2005 had recommended continuation of aspirin on "a case-to-case basis" as opposed to discontinuation of non-aspirin antiplatelet drugs like clopidogrel, ticagrelor, or prasugrel if clinically feasible. This was based on two randomized controlled trials in noncardiac surgeries, demonstrating comparable bleeding in patients receiving aspirin or placebo[6,7].

The more recent European guidelines provide a class I recommendation to withhold aspirin in surgeries with high bleeding risk, namely intracerebral and spinal neurosurgery in addition to vitreoretinal surgery[8]. Kulikov *et al*[9] explore the evidence base and the controversy surrounding this recommendation in a narrative review in the April 2024 issue of the journal. They have meticulously described the retrospective and prospective evidence base and highlighted the significant number of articles describing the safe conduction of neurosurgery with the continuation of aspirin, with no haemorrhagic complications. As they describe, the recommendation to discontinue aspirin rests largely upon the perceived risk of bleeding, exemplified by anecdotal case reports of major bleed and expert opinion. Extant practice here is to err on the side of caution and first to cause no harm. Taking an evidence-based call here is difficult, as randomized prospective data is sparse.

A recent systematic review has attempted to quantitatively synthesize the incidence of bleeding and thrombotic complications after elective craniotomies, capturing 646 unique patients across 7 studies. Though haemorrhagic complications were similar in patients with and without continuation of aspirin [haemorrhagic complication rate 3%, 95% confidence interval (95%CI): 0.01-0.05 *vs* 3%, 95%CI: 0.01-0.09 respectively; $P = 0.90$], it is worth noting that only 28.6% of these patients reflect prospective data[10].

Myocardial infarction, heart failure, ventricular arrhythmias and cardiac death are the classical major adverse cardiac events observed after non-cardiac surgery. While current standards of management have made these rare, many more patients have been found to suffer peri-operative myocardial injury but not fulfil the criteria for myocardial infarction. This injury, revealed by an asymptomatic rise in cardiac troponins, leads to late postoperative morbidity and mortality. Timely secondary prophylaxis achieves significant harm reduction in these cases. Hence, prevention of myocardial injury after non-cardiac surgery (MINS) is an important focus for perioperative risk reduction.

Saka *et al*[11] have prospectively investigated this in the elective neurosurgical context. 64 (20.5%) of 312 patients undergoing major or minor neurosurgery with comorbidities like coronary and peripheral artery disease, valvular heart disease, heart failure, atrial fibrillation, pulmonary embolism, cerebrovascular disease and age ≥ 65 years had MINS in their cohort. Prolonged (≥ 7 days) cessation of anticoagulants and antiplatelets was the most important predictor of MINS with an odds ratio of 4.9 (95%CI: 2.1-9.4) With the current lifestyle, dietary, environmental, medical, and socio-economic risk factors, and improvements in medical care, more and more patients live with multisystemic comorbidities these days. A similar trend has been observed in patients coming for neurosurgery and neurocritical care[12]. Hence, if a patient coming for neurosurgery is on aspirin for primary or secondary prevention of MACE, it is conceivable that they'll have a

high comorbidity burden, and continuation of platelet inhibitors would lead to significant harm reduction in them.

Likewise, neurosurgical patients are at a high risk of perioperative venous thromboembolism due to prolonged immobility, release of brain tissue thromboplastin, osmotic diuresis and intravascular fluid shifts, and benefit from continued thromboprophylaxis[13].

Of course, the promise of long-term harm reduction must be balanced with avoidance of short-term risks. Due to the unique nature of neurosurgery, perioperative bleeding may have devastating consequences and cause major morbidity and mortality. While intraoperative bleeding may be direct and cause hemodynamic compromise, poor perfusion and end-organ damage including secondary neurological injury, post-operative bleeding in intracerebral or neuraxial enclosed spaces may cause direct compressive or ischemic neurological injury and neuro-deficit. High vigilance, serial neurological examination and neuroimaging are necessary to pick up such complications early.

Bleeding during neurosurgery is affected by many factors - some of them related to the disease, some to the patient and his/her comorbidities, and some specific to the surgical procedure. While continuation of aspirin may be feasible in the majority of patients undergoing neurosurgical procedures, certain scenarios may pose unique challenges which make the continuation of aspirin tricky. A tumour with high vascularity may lead to higher perioperative blood loss and also a poor operative field causing suboptimal resection especially in those continuing aspirin. A patient with preexisting coagulopathy, for example, due to comorbid hepatic or renal disease, sepsis, trauma, or drugs like non-steroidal anti-inflammatory drugs, carbamazepine, thiazides or selective-serotonin-reuptake inhibitors may have synergistic action with the continued aspirin with resultant excess bleeding. Control of unexpected bleeding may be difficult in minimally invasive neurosurgical procedures with restricted visualization of the surgical field, leading to a poor outcome. All these situations in particular may tilt the balance in favour of aspirin cessation to limit short-term bleeding risk.

There is also significant variability in the clinical response to aspirin which needs to be considered during perioperative anticoagulation management and platelet therapy. Development and use of point-of-care tests like the VerifyNow Aspirin Assay® or Platelet Function Analyzer® now allow us to characterize that[14]. The VerifyNow Aspirin Assay® has already been used to identify hyper-responders to aspirin therapy, who have more perioperative bleeding and transfusion during cardiac surgery with ongoing aspirin[15]. Similar investigations in neurosurgical patients can also help identify those at an increased risk of bleeding on aspirin, and the drug interrupted accordingly.

CONCLUSION

Perioperative medicine has been moving to precision medicine with individualization, calibration and targeting of therapeutic choices. Further generation of high-quality evidence in large prospective cohorts can lead to the adoption of an evidence-based precision approach to the management of aspirin in neurosurgery. While major evidence gaps exist, individualized perioperative decision-making and point-of-care testing can help avoid unnecessary anti-platelet therapy interruption. Precision medicine to balance the risks of bleeding and thrombosis will lead to optimum harm reduction and the best possible outcomes in neurosurgical patients.

FOOTNOTES

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EDITORIAL

Catheter ablation using pulsed-field energy: Do we finally have the magic wand to defeat atrial fibrillation?

Ernesto Cristiano, Hussam Ali, Eduardo Celentano, Riccardo Cappato

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Abstract

Clinical outcomes of catheter ablation remain suboptimal in patients with atrial fibrillation (AF), particularly in those with persistent AF, despite decades of research, clinical trials, and technological advancements. Recently, pulsed-field ablation (PFA), a promising non-thermal technology, has been introduced to improve procedural outcomes. Its unique feature of myocardial selectivity offers safety advantages by avoiding potential harm to vulnerable adjacent structures during AF ablation. However, despite the global enthusiasm within the electrophysiology community, recent data indicate that PFA is still far from being a "magic wand" for addressing such a complex and challenging arrhythmia as AF. More progress is needed in mapping processes rather than in ablation technology. This editorial reviews relevant available data and explores future research directions for PFA.

Key Words: Atrial fibrillation; Pulsed field ablation; Radiofrequency ablation; Electroporation; Electroanatomic mapping; Catheter ablation; Interventional cardiology; Cardiac arrhythmias

Core Tip: Pulse-field ablation is an emerging technology in the field of arrhythmia ablation based on electroporation method, particularly adopted for atrial fibrillation. While there is growing interest in the safety and efficacy of catheter ablation using electroporation, several aspects of its long-term effectiveness and procedural limitations require further investigation before pulse-field ablation can be considered a definitive solution for atrial fibrillation.

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INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia, associated with increased mortality and morbidity, and has a substantial impact on the global health system. Catheter ablation (CA), primarily based on pulmonary vein isolation (PVI), represents a valid approach to managing this arrhythmia, particularly when symptomatic and drug-refractory. However, outcomes of CA remain suboptimal in AF patients, especially in those with persistent arrhythmia[1,2].

In recent years, pulsed-field ablation (PFA), a non-thermal energy source based on irreversible electroporation, has been introduced into clinical practice with the aim of improving CA outcomes in AF patients[3]. However, electroporation has a longstanding history as a therapeutic modality in various medical fields, such as oncology. In the 1980s, direct current shock was used for CA, but significant complications, including arcing and barotrauma, coupled with the success of the emerging request for comments technology, led to the discontinuation of PFA in clinical settings[4].

Over the past decade, preclinical studies have shown that modern PFA has the potential to create tissue-selective ablation lesions through short, high-energy electrical pulses that induce cell death while minimizing the side effects associated with thermal energy sources[5]. Initial human trials of PFA have demonstrated the safety and efficacy of AF ablation procedures, with high rates of immediate PVI and durable results confirmed through invasive remapping, along with relatively low rates of arrhythmia recurrence. Consequently, various catheter platforms utilizing electroporation have been developed and tested for the catheter-based ablation of cardiac arrhythmias, primarily AF.

This editorial examines the methodology of PFA, preclinical and clinical data, and explores future directions for its development. Although several studies have reported promising results with this new technology, limited data are available on long-term outcomes, healthcare utilization, and costs compared to standard radiofrequency CA. Due to its tissue selectivity and rapid induction of cell death, PFA could represent an efficient and potentially safer option compared to conventional ablation techniques[2,3], with potential applications in other ablation procedures beyond AF. In this editorial, current evidence on the use of PFA for the treatment of AF and its potential impact on healthcare utilization and costs will be discussed, drawing on relevant clinical studies published in the literature and offering insights for future research directions. Additionally, we will address the possible limitations and drawbacks of this technology.

CURRENT KNOWLEDGE

PFA mechanism of action

The exposure of cells to high-voltage electric pulses induces an increase in membrane permeability through electroporation[6]. This cellular membrane injury can be either reversible or irreversible. The former is typically used in gene transfer and enhanced drug delivery[7], while the latter leads to cell death in the targeted area. PFA can trigger various types of cell death, including apoptosis, necrosis, necroptosis, and pyroptosis[8]. The specific type of cell death induced by electroporation depends on pulse parameters, cell and tissue type, treatment conditions, and other factors[9,10]. This approach has been successfully employed as a novel non-thermal ablation method for soft tissues, such as tumors.

The main stages of electro-permeabilization are: (1) Initiation of membrane electrical conductivity and permeability [the transmembrane voltage (TMV), must exceed a "critical" potential value]; (2) Expansion and intensification of conductivity and permeability; (3) Partial recovery of membrane conductivity and permeability, while still allowing transmembrane diffusion of ions and molecules once the TMV drops below the "critical" value; and (4) Resealing of the membrane, with gradual restoration of its physiological impermeability. In the end, cells retain a memory of the alterations in physiological processes and reactions to stressors for several hours[6].

Main characteristics

This new form of ablative energy has several important characteristics that have quickly gained acceptance within the electrophysiology community. PFA has a tissue-specific effect, meaning that myocardial cells are damaged at specific energy frequencies and durations, while sparing fibroblasts, vascular tissue, and gastrointestinal structures[9]. Consequently, in theory, PFA delivery should not harm surrounding vessels, the esophagus, or nervous structures, including the phrenic nerve. This could eliminate the risk of esophageal damage, thereby preventing ulcers and atrio-

esophageal fistula. Additionally, PFA is not associated with permanent phrenic nerve injury[11]. Moreover, because connective tissue is unaffected by this energy form, the risk of pulmonary vein stenosis is minimized[12]. Current clinical studies appear to support these hypotheses.

Clinical data

Preliminary data suggest that PFA may result in shorter ablation times compared to PVI. The ADVENT trial demonstrated that, among patients with paroxysmal AF receiving catheter-based therapy, PFA was non-inferior to conventional thermal ablation after a 3-month blanking period, in terms of antiarrhythmic drug use, cardioversion, repeat ablation, as well as efficacy and serious adverse events at 1 year[13]. Aldaas *et al*[14], in their meta-analysis, confirmed these results, showing a significantly shorter procedural time compared to thermal ablation.

Safety data

In the ADVENT and MANIFEST-PF trials, the new procedure was confirmed to be safe in terms of pulmonary vein stenosis, esophageal injury, and phrenic nerve damage[13,15]. A recent meta-analysis[14] reported no significant differences in overall procedural complications between conventional ablation and PFA strategies. However, it is worth noting that one death in the ADVENT trial was due to peri-procedural cerebral hypoxia in the PFA arm. More recently, as experience with this technology has expanded, cases of acute renal failure secondary to PFA-induced hemolysis have been reported[16,17].

Overall, other data suggest that PFA is associated with longer fluoroscopy times compared to thermal ablation energy sources (greater than 20 minutes in the PFA group *vs* over 10 minutes in the thermal ablation group, according to Aldaas *et al*[14] analysis).

FUTURE APPLICATIONS

An increasing number of studies are focusing on the ablation of persistent AF, showing promising preliminary results, as demonstrated in the PULSE-AF trial, which recruited both paroxysmal and persistent AF patients[18], as well as in the single-arm study by Reddy *et al*[19].

Although still in its early stages, the application of this energy form in the ventricles for the ablation of ventricular tachycardias seems promising. PFA has shown potential in creating more effective lesions within scarred myocardial tissue, and its inherent repetition dependency could improve therapeutic outcomes[20].

Moreover, the use of PFA for epicardial ablation and mobile myocardial structures, such as papillary muscles and moderator bands, or for bipolar applications targeting mid-myocardial structures like the interventricular septum or the left ventricular free wall, could represent new frontiers in PFA application. However, the high rate of coronary spasm may limit this use, although no conclusive evidence has yet been presented in the literature[21,22].

Recently, Nies *et al*[21] reported initial experiences confirming that these targets can be successfully ablated with PFA *in vivo*, creating deep epicardial and transmural left ventricular lesions. However, much research is still needed to determine the long-term safety and efficacy of these applications.

Furthermore, hybrid approaches to AF ablation using PFA have not yet been evaluated. However, thermal radiofrequency approaches, including both convergent and robotic methods, have shown varying degrees of success, particularly for persistent and long-standing AF, as reflected in recent AF ablation consensus statements[23-25], potentially paving the way for future PFA research.

Given PFA's promising properties, it will be interesting to see whether using this energy form with a different ablation device could overcome the current technical limitations.

Currently, the inspIRE study has evaluated the safety and efficacy of a fully integrated biphasic PFA system with a variable-loop circular catheter for treating drug-refractory paroxysmal AF, confirming the novel system's safety and effectiveness[26]. Additionally, the SmartfIRE system recently tested a dual-energy focal catheter designed to deliver both radiofrequency and unipolar/biphasic PFA, integrated with a three-dimensional mapping system, and demonstrated acute success with an acceptable safety profile in the treatment of paroxysmal AF, confirming PVI durability at 3-month remapping[27].

The development of more flexible devices that better adapt to anatomy and are less cumbersome, such as point-by-point ablation catheters, could represent an upgrade to current PFA technology, making it suitable for more challenging ventricular or even epicardial ablations. However, the effectiveness and potential advantages of this method in these regions remain to be demonstrated. Notably, while the atrium is a thin structure, the ventricle has considerable thickness, and given that the electric field strength diminishes inversely with the square of the distance, even a few extra millimeters could render PFA ineffective in thicker myocardial tissue.

The other side of the coin

All that glitters is not gold. Currently, the only commercially available system for PFA is FARAPULSE (Boston Scientific). This system was designed specifically for AF ablation, leading to some limitations, primarily its poor maneuverability, as reported by Zhang *et al*[20]. In fact, the device is not well-suited for more complex structures such as valve apparatuses or recesses, making energy application challenging, particularly in cases of complex or anomalous anatomies. This limitation could at least partially be addressed by routinely using computed tomography imaging to select appropriate cases for this type of device. Additionally, the potential risk of entrapment should not be overlooked, due to the complex flower-shaped structure of the catheter and the possible excessive manipulations required in some challenging anatomies[20,28].

Secondly, there is currently no electroanatomical mapping system available. This limitation results in increased fluoroscopy times and challenges in approaching unusual anatomies. However, this issue is expected to be resolved soon, as the NAVIGATE-PF study of the FARAVIEW software module is ongoing, which will allow for the integration of FARAPULSE with the RHYTMIA HDx mapping system.

Contact has always been an important parameter for ablative success in the main thermal technologies, already implemented in ablation indices (conventional radiofrequency and very-high short-duration techniques)[29-31]. The absence of a catheter-tissue contact parameter may present a limitation in current PFA technology. Moreover, the flower structure of the catheter does favor uniform contact, which may lead to non-uniform, incomplete, or reversible lesions.

Beyond technical challenges, there are also electrophysiological issues that need to be addressed. The AF ablation procedure with FARAPULSE seems designed to make it as accessible as possible to the "new generation" of electrophysiologists, reducing the complexity of the procedure and increasing the learning curve[32]. While this is beneficial, it may trivialize the electrophysiological approach underlying the evaluation of the substrate. Currently, the evaluation of electrical insulation of the pulmonary veins appears to be rudimentary. No solid studies have yet confirmed the long-term efficacy of PVI or its correlation with the maintenance of sinus rhythm.

Two significant complications arise with PFA that do not have direct counterparts in radiofrequency ablation. The first is coronary spasm; there is evidence that energy application, particularly in the mitral isthmus region, can potentially lead to arrhythmias or intraprocedural ST-elevation myocardial infarction in up to 40% of patients undergoing mitral isthmus ablation[33,34]. The second complication is acute kidney injury related to hemolysis; specifically, the number of applications correlates with an increased risk of acute kidney injury, as shown in two independent studies[16,17].

Furthermore, the long-term results of this method regarding AF are not yet known. The randomized ADVENT study itself was published only in 2023, with a follow-up period of just one year.

CONCLUSION

PFA represents a viable alternative to traditional thermal ablation, which has been extensively studied. However, due to this novelty, there is currently insufficient evidence regarding its long-term efficacy in treating AF, particularly in cases of persistent and long-standing persistent AF. In these instances, randomized trials comparing PFA to conventional and hybrid/convergent ablation techniques, as well as to antiarrhythmic drug therapy, will be crucial for future research. Despite the technological advancements and the innovative potential introduced by PFA in the management of AF, considerable challenges remain. It is akin to having discovered a new "magic formula" that is yet to be fully understood. Nevertheless, there is certainly ample opportunity for improvement in this "magic wand".

FOOTNOTES

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EDITORIAL

Thoughts on recent articles on cardiopulmonary resuscitation

Thirugnanasambandan Sunder

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Abstract

Comments were made on some thought-provoking articles, which included articles that dealt with cardiac arrest (CA). Two articles on CA elaborate on the role of automated compression devices to provide chest compressions during cardiopulmonary resuscitation (CPR) in "hostile" environments and on a predictive model in cases of out-of-hospital CA (OHCA). CPR after CA has been practiced for centuries, and the evolution until current modern-day practices are discussed. The delay in adopting efficient techniques of resuscitation by the medical community for decades is also touched upon. Both in-hospital and OHCA are discussed along with guidelines and strategies to improve outcomes. Areas of possible research in the future are mentioned.

Key Words: Cardiac arrest; Cardiopul-monary resuscitation; Extracorporeal cardiopulmonary resuscitation; Automatic compression devices; Automated external defibrillators

Core Tip: Volume No. 15 of the *World Journal of Cardiology* for 2023 published 12 monthly issues. This editorial comments on some of the thought-provoking articles on cardiac arrest. The evolution and current status of cardiopulmonary resuscitation are discussed. Future directions which might improve survival are mentioned.

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INTRODUCTION

Cardiac arrest (CA) is one of the most demanding medical emergencies, requiring immediate action. Timely and appropriate treatment can be lifesaving. If the victim is fortunate due to the availability of people who are well trained in cardiopulmonary resuscitation (CPR) techniques, full recovery is possible with no neurological deficit. Widespread awareness of the urgency of this condition and techniques of basic life support among the lay public is needed. As CA can happen anywhere and to anyone, out-of-hospital CA (OHCA) is particularly challenging.

While commencement of adequate chest compressions are vital in maintaining circulation, delivery of electrical energy to defibrillate the heart during CPR is vital, especially in the first few minutes in achieving return of spontaneous circulation (ROSC). Governmental policies in many countries aimed at making automated external defibrillators (AEDs) available in public places with a view to assisting in OHCA is a welcome move.

Despite an increase in our understanding of the disease process over the last few decades, there have not been significant improvements in outcomes of CPR, especially in OHCA. The most critical aspect is the time frames involved. Time to starting CPR, time to delivery of first defibrillation, and adequate ventilation are important determinants of clinical outcomes. The degree of neurological recovery is thus an important aspect, which has a significant impact on the patient's life.

This editorial commentary looks back at some of the articles published recently in the *World Journal of Cardiology*. Among these articles, which cover wide range of topics in cardiology, those on CAs are the subject of discussion in this editorial.

ARTICLES ON CA

Two articles on CA were published recently in *World Journal of Cardiology*. In one article, Latsios *et al*[1] discuss use of automatic compression device to protect rescuers in "hostile" environments, while Wang *et al*[2] discuss OHCAs.

CA refers to the complete cessation of any effective cardiac contraction with no circulation, and will lead to death if not resuscitated immediately. Attempts to revive patients have been described in the 16th century. Andreas Vesalius, at the age of 28, described resuscitation in 1543 and is regarded as father of resuscitation[3].

Different components of CPR were discovered, and strategies developed at different times over the last few centuries. Unfortunately, these notable findings were not recognized and were not put to good clinical use for decades since their discovery.

Evolution of CPR

Artificial respiration progressed with the development of positive pressure ventilation in the 18th and 19th centuries. Sternal compressions were described by John Hill in 1868, but it is unclear whether the intent was to ventilate the lungs or compress the heart[4]. Although external cardiac massage had been discovered, work by Moritz Schiff encouraged use of internal cardiac massage for resuscitation. Internal cardiac massage was first described in 1901 by Keene for CA after an abdominal operation and by 1952, a successful revival was achieved in 33% of cases[4]. The landmark publication in 1960 by Kouwenhoven *et al*[5] on closed-chest cardiac massage ushered in the era of modern CPR. They reported a series of 20 patients who were all, quite remarkably, revived and reported to be well 14 months later. This led to the abandoning of internal cardiac massage. Defibrillation of the heart was reported on experiments carried out in 1899 and was not clinically achieved in humans until 50 years later. In 1964, the airway, breathing, and circulation of CPR was published by Safar[6]. The first CPR guidelines was published by an ad hoc Committee on CPR by National Academy of Sciences in 1966[7]. The most recent guidelines is the 2023 focused update of the American Heart Association on Advanced cardiac life support and CPR[8] and provides "recommendations on the use of medications, temperature management, percutaneous coronary angiography, extracorporeal CPR, and seizure management."

Inordinate delay in adopting useful resuscitation strategies

As elaborated above, the inordinate delay by the medical community in adoption of effective resuscitation processes has to be noted so that it is not repeated. In his publication, based on the Fitzpatrick lecture that he delivered to the Royal College of Physicians, Chamberlain[3] discusses the discoveries and anguishes on the lamentable delay by the medical community in adopting useful treatments. Regarding the delay in clinical acceptance and practical adoption of these discoveries related to CPR, he quotes "So often our predecessors 'did not learn' when it seems in retrospect that they should have done, and so often they were 'never quite there' for developments that then had to wait many years. We share the same frailties and are no doubt guilty of the same sorts of errors. History will be our judge too."

Current practice of near-continuous review of evidence with timely adoption of effective strategies

The International Liaison Committee on Resuscitation (ILCOR) was founded in 1992 with a panel of international experts [9]. The committee provides an International Consensus on CPR and Emergency Cardiac Care Science with Treatment Recommendations (CoSTR). Initially, the ILCOR guidelines with CoSTR were published once every 5 years; the last 5-year update was published in 2015. To avoid delay in adopting reliable new techniques, as aspired by Chamberlain[3], the ILCOR initiated a process from 2016 looking at continuous review and update of the science of resuscitation. Subsequently, annual ILCOR CoSTR statements are being published, the most recent of which is the 2023 ILCOR Summary Statement[10].

While the ILCOR scrutinizes the evidence and aims to provide the best possible recommendation, given the clinical scenario, it is readily apparent that the clinical reports when graded for quality are most often low quality evidence, which are subject to bias and other variables leading to weak recommendations. Data from OHCAs are more challenging to use due to the heterogenous and varying levels of expertise of bystanders until trained paramedics arrive.

Pathophysiology of CA and post CA syndrome

In 2002 Weisfeldt and Becker[11], who felt that the pathophysiology of ischemia and reperfusion is a function of time, described three time-sensitive phases after CA: The electrical phase (up to 4 minutes after ventricular fibrillation arrest), the circulatory phase (up to 10 minutes after arrest) and the metabolic phase (after 10 minutes commencing after the circulatory phase). These time-sensitive phases underscore the importance of achieving, whenever possible, an early ROSC. Figure 1 summarizes the three phases of CA and survival in each of these phases using defibrillation with or without CPR as described by Vilke *et al*[12].

In a successfully revived patient, the complex pathophysiological effects of ischemia and reperfusion in all organs of the body were described by Negovsky[13], who coined the term "post resuscitation syndrome." This was then referred to as post CA syndrome (PCAS) by ILCOR[14] in their guidelines published in 2008. PCAS includes brain injury, myocardial dysfunction, and systemic effects of ischemia and reperfusion.

OHCA and prehospital ROSC

Approximately 424000 and 27500 OHCA occur annually in the United States and Europe respectively, of whom 1 in 12 (8.3%) victims survive to return home[15]. In China, the annual OHCA is approximately 550000 with 1.3% survival[2]. Among victims of OHCA, prehospital ROSC is vital and has better neurological outcomes. The global survival of OHCA at 1 year after discharge is 7.75%.

AED and public access defibrillation

AEDs allow immediate defibrillation by untrained bystanders. Recommendations suggest placement and availability in public places where there is a high likelihood of OHCA. Public access AEDs are now increasingly available. Underutilization of public AEDs is common[16]. Challenges in the use of AEDs by the public and possibilities to increase them are discussed in the review article by Ringh *et al*[17].

Automated compression devices

It has been long recognized that automated compression devices (ACDs) can be put to meaningful use during CPR. They are two types: The piston driven type and the load distribution band type. They can provide high-quality compression in terms of nonstop regular frequency, depth and prolonged periods of compression, while eliminating back injury to the rescuers during CPR[18] and eliminating rescuer fatigue. ACD frees the hands, and the rescuer can devote their attention to other vital processes.

Discussion about the recent articles on CA

In the recent issue of *World Journal of Cardiology*, Latsios *et al*[1] published an interesting article titled "Cardiac arrest and cardiopulmonary resuscitation in "hostile" environments: Using automated compression devices to minimize the rescuers' danger." The authors discussed an important and often overlooked aspect of emergency treatment, namely, the risks to the rescuer. Similar to the risks confronted by the rescue teams for natural calamities or major accidents, the risks to the healthcare worker delivering CPR can be significant. The authors describe the types of ACDs available and discuss the advantages and disadvantages of both types of ACDs. ACDs are not without risks to the patient. Trauma due to ACDs can result in rib fracture and improperly placed devices can cause trauma to liver and other organs. Therefore, the use of ACDs come with a "learning curve." This can be offset by offering structured training sessions to the emergency team. Effective cardiac compressions are the key to successful resuscitation. Physical fatigue of the rescuers, especially in locations that may be hazardous to the rescuer, can result in suboptimal chest compressions and inferior outcomes. Both in-hospital CA and OHCA are considered. The "hostile" in-hospital locations include cardiac catheterization laboratory with its inherent radiation hazards and the intensive care unit/ward setting in patients with coronavirus disease 19. CAs in the emergency room (ER) are considered to be OHCAs, since most of them are brought to ER with ongoing CPR. The main limitations of the ACDs have been delay in the time to first defibrillation and time to deployment (deployment pause). Transport of a victim of CA with ongoing CPR is perhaps most challenging. Except for the time taken to deploy, the use of any type ACD is beneficial in terms of ROSC and survival[19]. The authors have elaborately considered the available evidence on ACDs[15,20,21]. Many randomized controlled trials and individual studies have compared manual chest compressions with ACDs. The results of these studies are often mixed and conflicting. Notwithstanding the above, it is noteworthy that the use of ACDs was recommended in the 2021 guidelines of European Resuscitation Council in special circumstances such during percutaneous intervention[22,23] or coronavirus disease[23]. The authors also touched upon an important aspect, namely the use of ACDs as a bridge to organ donation, and nicely pointed out that a reduction in "warm ischemia time" is possible with ACDs in appropriate circumstances. The authors, while reiterating that there is no evidence to support or refute the "routine" use of ACDs in CA, do make a convincing argument to consider ACDs in a "hostile" environment, ensuring both superior outcomes and rescuer safety.

In the recent issue of *World Journal of Cardiology*, Wang *et al*[2] published an interesting article titled "Establishment of a prediction model for prehospital return of spontaneous circulation in out-of-hospital patients with cardiac arrest." The authors conducted this remarkable study on an important condition that has major public health implications. It has been demonstrated that patients with prehospital ROSC have better outcomes, and the authors set out to describe a predictive

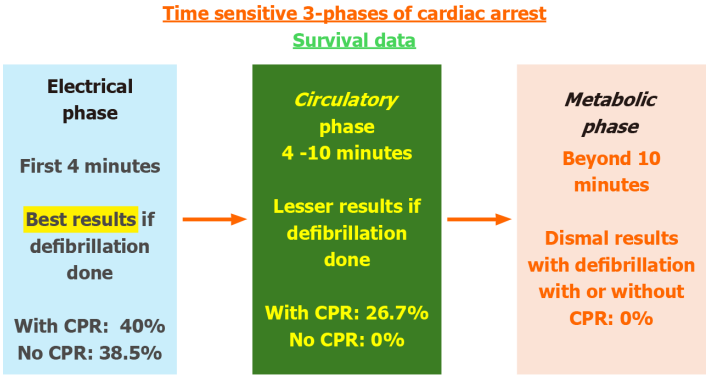

Figure 1 Time-sensitive three phases of cardiac arrest with survival rates. CPR: Cardiopulmonary resuscitation.

model for the same. This was a multicenter retrospective study involving 2685 patients across 150 hospitals from January 2012 to December 2019. The incidence of prehospital ROSC was 5.8%. The authors looked at factors prior to the arrival of an emergency team for OHCA. They identified six factors, namely, age, bystander CPR, initial rhythm, CPR duration, ventilation mode, and etiology, using least absolute shrinkage and selection operator regression and multivariate logistic regression. Each factor was assigned a numerical score, and the total of the score was predictive of the probability of ROSC (P-ROSC). A nomogram prediction model was established based on these influencing factors. The area under the receiver operating curve was 0.963. Decision curve analysis confirmed good clinical usability. The authors quite rightly conclude that this model could effective predict P-ROSC in victims of OHCA and will be a valuable tool to aid clinical decision making.

Future trends

While the science behind resuscitation has been understood to a large degree, it is the prompt delivery of the knowledge amassed to the victim of CA that poses a major problem. Steps to tackle this "bottleneck" of prompt and universal delivery of adequate CPR should be the way forward to improve the current dismal outlook, especially in cases of OHCA.

An animal-based pilot study looking at "automated CPR," which combines automatic defibrillation and chest compression at the same time, has been published and appears promising[24]. The authors have demonstrated the feasibility of combining ACD and AED and used this "automated CPR" device in five pigs. These were compared to conventional CPR in six pigs. The authors demonstrated significant reductions in time to charge, time to defibrillate, and time to resume chest compressions in the "automated CPR" group. If superior outcomes with survival advantage can be demonstrated, this "automated CPR" would be value addition in selected cases.

Decades of experience tell that the single most important factor is the time to first intervention, namely defibrillation and chest compression, which have the most significant impact on achieving full recovery. Widespread community awareness programs about basic life support can improve the results and outcomes of CPR provided by "bystanders." Usage of AEDs, despite availability, is reportedly low, and this single point reiterates the need for more aggressive awareness programs. With the availability of social media platforms, dissemination of such knowledge is entirely feasible. The emphasis of awareness programs should be on timeliness and prompt action without which a lot of the effort expended in performing CPR can become futile.

Lessons learnt

Looking back historically, it is rather sobering that the medical community took its time in adopting efficient resuscitation techniques. Nonetheless, it is indeed gratifying to note the near-continuous review of available evidence on resuscitation by ILCOR with its worldwide representation. Humanity will only be best served if all units are kept updated of the latest guidelines.

To summarize, the need for timely intervention cannot be over emphasized and is worthy of reiteration. Universal availability of AEDs and emergency teams that would provide prompt assistance, while ideal, is not possible in the real world. The healthcare infrastructure varies between countries and within states in the same country.

To improve the outcomes of this dismal condition, the CA situation can be viewed from perspectives of the victim and the health care provider. From the victim's aspect, carrying a health card is often beneficial to oneself and helps health care provider.

From the healthcare provider aspects, availability of equipment to deliver is vital. Emergency teams are often well equipped in terms of training and equipment but are not available within minutes of CA.

In cases of OHCA, it is often the bystanders who are the first to respond and it is the bystanders who need to be trained and knowledgeable. Bystanders are the people who must be "targeted" to provide basic life support for these unfortunate victims of CA. Bystander providers of CPR have increased recently, and the emphasis should be in equipping the bystanders with knowledge and training so that basic life support can be provided.

P-ROSC and timely intervention is achievable only if the bystander contribution increases. It is impractical to assume that emergency teams will always arrive within minutes.

CONCLUSION

Despite advances in healthcare, OHCA is still an important cause of death. Survival is directly related to the quality and adequacy of the initial rescue therapy offered. High quality CPR with early defibrillation plays a vital role. Increasing public awareness and education about CPR, provision of robust emergency services, ensuring appropriate use of available of AEDs in public places will improve outcomes in this group of patients.

FOOTNOTES

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REVIEW

Molecular and metabolic landscape of adenosine triphosphate-induced cell death in cardiovascular disease

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Abstract

The maintenance of intracellular and extracellular adenosine triphosphate (ATP) levels plays a pivotal role in cardiac function. In recent years, burgeoning attention has been directed towards ATP-induced cell death (AICD), revealing it as a distinct cellular demise pathway triggered by heightened extracellular ATP concentrations, distinguishing it from other forms of cell death such as apoptosis and necrosis. AICD is increasingly acknowledged as a critical mechanism mediating the pathogenesis and progression of various cardiovascular maladies, encompassing myocardial ischemia-reperfusion injury, sepsis-induced cardiomyopathy, hypertrophic cardiomyopathy, arrhythmia, and diabetic cardiomyopathy. Consequently, a comprehensive understanding of the molecular and metabolic underpinnings of AICD in cardiac tissue holds promise for the prevention and amelioration of cardiovascular diseases. This review first elucidates the vital physiological roles of ATP in the cardiovascular system, subsequently delving into the intricate molecular mechanisms and metabolic signatures governing

AICD. Furthermore, it addresses the potential therapeutic targets implicated in mitigating AICD for treating cardiovascular diseases, while also delineating the current constraints and future avenues for these innovative therapeutic targets, thereby furnishing novel insights and strategies for the prevention and management of cardiovascular disorders.

Key Words: Adenosine triphosphate induced cell death; Cardiovascular diseases; Myocardial ischemia-reperfusion injury; Molecular mechanisms; Metabolic pathways

Core Tip: Understanding the mechanisms behind adenosine triphosphate (ATP)-induced cell death (AICD) is crucial for addressing various cardiovascular diseases. AICD, triggered by elevated extracellular ATP levels, differs from other forms of cell death and has emerged as a significant contributor to conditions such as myocardial ischemia-reperfusion injury, sepsis-induced cardiomyopathy, and diabetic cardiomyopathy. This review explores the physiological roles of ATP in the cardiovascular system and delves into the molecular and metabolic mechanisms underlying AICD. Identifying therapeutic targets to mitigate AICD holds promise for treating cardiovascular diseases, although challenges remain. This review provides valuable insights and strategies for preventing and managing cardiovascular disorders.

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INTRODUCTION

Over the past decade, the Committee on Cell Death Nomenclature has diligently crafted a comprehensive delineation of cell demise, integrating various perspectives encompassing morphology, biochemistry, and functionality[1]. Studies have made novel insights into the mechanisms governing diverse cell death mechanisms. Research has elucidated the intricate interplay of apoptosis, necrotic apoptosis, pyroptosis, and apoptosis in the etiology of cardiovascular disorders[2]. Adenosine triphosphate (ATP) serves as a multifaceted signaling molecule within cells, as it assumes a pivotal role in cellular energy metabolism. There has been a recent surge in investigations delving into ATP-induced cell death (AICD). AICD represents a distinct mode of cellular demise elicited by heightened extracellular ATP (eATP) levels, distinguishing it from conventional forms of cell death like apoptosis and necrosis. Nonetheless, the specific methods and modalities behind AICD continue to be unresolved [3].

Intracellular ATP typically maintains a delicate equilibrium, serving as a pivotal currency for energy transfer, signaling cascades, and cellular metabolism. Both external stimuli or internal insults can perturb this balance, leading to disruptions in intracellular ATP homeostasis, eATP release, and ultimately cellular demise[2]. Concurrently, AICD causes the release of inflammatory mediators, inducing local or systemic inflammatory cascades and causing metabolic dysregulation. Among the myriad metabolic alterations observed in cardiovascular diseases, lipid metabolism disorders prominently stand out [4]. Additionally, lipid metabolism contributes to the deposition of heat-sensitive proteins during disease onset, underscoring the intricate interplay between lipid metabolism and thermal protein deposition. Nevertheless, excessive thermal protein deposition can induce an overwhelming inflammatory response and tissue damage, exacerbating cardiovascular disease progression and prognosis[5,6].

During AICD, alterations in phospholipid distribution across the cell membrane are observed alongside disruptions in ATP homeostasis, culminating in membrane destabilization and rupture. This phenomenon is intricately linked to cellular damage and inflammation in cardiovascular pathologies[7]. Investigations have elucidated the mechanism underlying ATP-mediated T cell demise through P2X7 receptor (P2X7R) activation[8]. Consequently, P2X7R expression emerges as a pivotal determinant of AICD, not only offering insights into the immunomodulatory mechanisms underlying cardiovascular diseases but also presenting novel avenues for therapeutic intervention[9,10].

To date, substantial evidence underscores the intricate association between AICD and cardiovascular disease pathogenesis, implicating inflammatory responses, cellular damage, and immune dysregulation as pivotal mediators. In this comprehensive review, we elucidate the intricate regulation of ATP homeostasis and delineate the underlying mechanisms of lipid metabolism. Moreover, we delve into the progression of AICD in cardiovascular pathologies and explore its potential implications in the context of arrhythmias.

MECHANISM AND REGULATION OF ATP HOMEOSTASIS AND AICD

As a multifaceted signaling molecule, ATP orchestrates pivotal biological activities within cellular microenvironments,

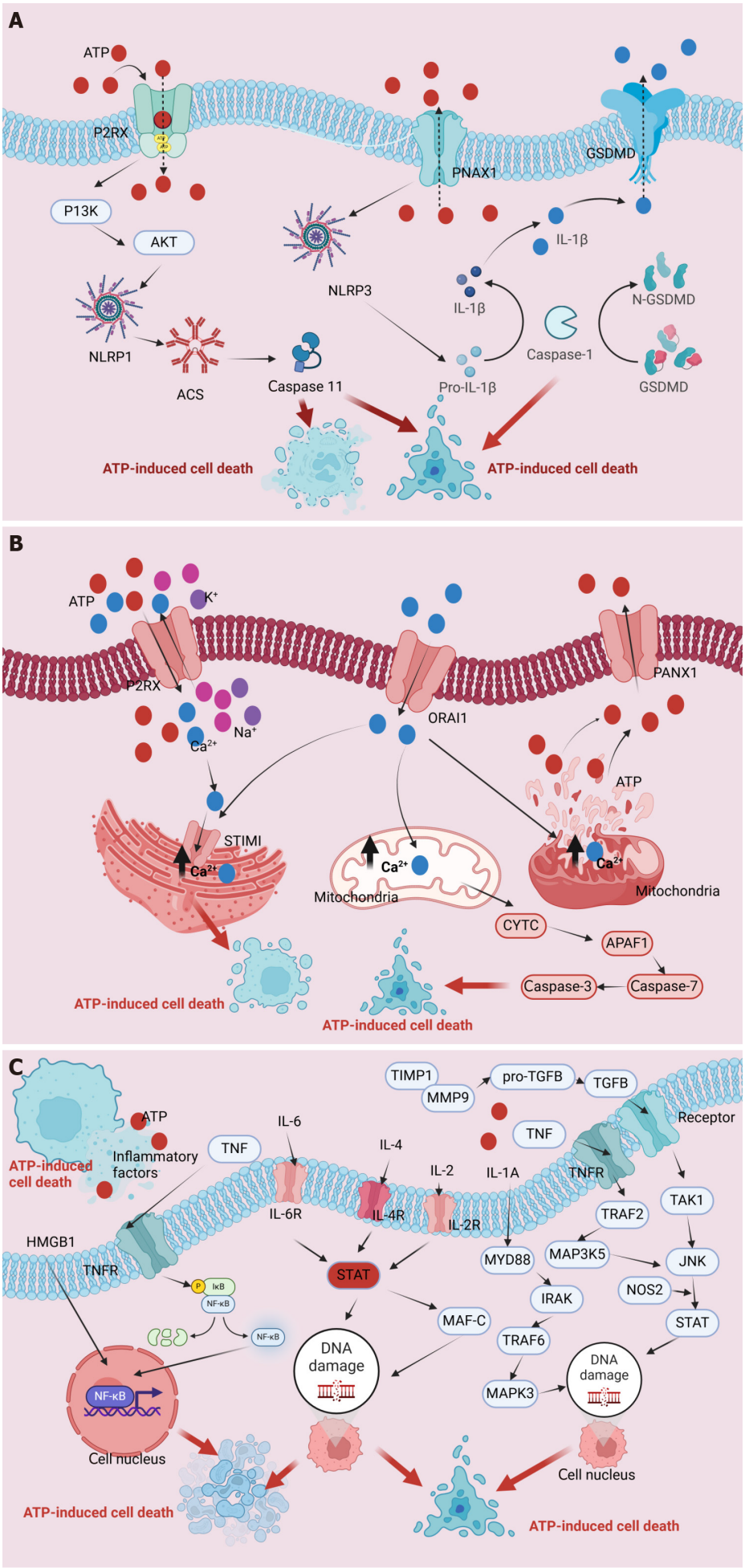
including metabolic processes, signal transduction cascades, and energy transfer. The intricate balance of intracellular ATP levels, termed ATP homeostasis, is meticulously maintained through the interplay of synthesis and utilization processes within cells. However, this equilibrium can be disrupted following internal injuries or external stimuli, leading to elevated extracellular ATP (eATP) levels and subsequent intracellular ATP release[11]. This perturbation results in AICD, mediated by several well-elucidated mechanisms and regulatory pathways. ATP primarily engages with extracellular P2R proteins, particularly the P2X7R family, triggering a cascade of events that includes the activation of associated receptors such as NOD-like receptor family pyrin domain-containing protein 1 (NLRP1) and NLRP3. This activation cascade meticulously coordinates apoptotic signals, encompassing caspases-1, -3, and -11, while also implicating necrotic effectors, such as gasdermin E and gasdermin D, ultimately leading to cellular demise[2]. Secondarily, ATP's interaction with ion channels on the cell membrane modulates ion balance, notably through P2X7R activation-induced opening of ion channels, leading to intracellular calcium ion (Ca^{2+}) accumulation within various cellular compartments, including the Golgi apparatus and mitochondria. This aberrant Ca^{2+} influx induces nuclear DNA damage, precipitating cellular demise. Additionally, ATP triggers mitochondrial dysfunction, evident in the loss of mitochondrial membrane potential, disruption of the mitochondrial respiratory chain, production of reactive oxygen species (ROS), and the disruption of mitochondrial membrane permeability. These aberrations culminate in cellular demise. Moreover, ATP induces immune-inflammatory responses and cell death pathways, leading to the release of inflammatory mediators such as interleukin (IL)-1β, IL-18, tumor necrosis factor (TNF)-α, IL-2, IL-4, IL-6, IL-10, C-C chemokine ligand 5, and CXC motif chemokine ligand 2, ultimately driving cell death (Figure 1)[12].

ATP IN THE HEART INDUCES CELL DEATH

Upon external stimuli or internal injury, elevated eATP levels and intracellular ATP release induces cell demise. ATP induces cellular demise by inducing mitochondrial membrane potential loss through membrane K^+/Na^+ imbalance, mitochondrial respiratory chain disruption, ROS production, and linear membrane permeability alterations. As a result, it coordinates immune-inflammatory reactions, initiates cell death pathways and AICD, leading to the secretion of inflammatory mediators including IL-1β, IL-18, TNF-α, IL-2, IL-4, IL-6, IL-10, C-C chemokine ligand 5, and CXC motif chemokine ligand 2, ultimately resulting in cellular demise[2]. Additionally, P2 receptor-mediated ATP exerts an anti-apoptotic effect, involving pathways such as phosphoinositide 3-kinase, extracellular signal regulated kinase 1 and 2, mitoKATP, and nitric oxide synthase pathway[13]. Moreover, the production of ROS and oxidative stress serve as central mechanisms responsible for cellular damage and dysfunction. Sirtuin 6 (SIRT6), a member of the sirtuin family of NAD^+-dependent class III deacetylases, holds a pivotal role in resisting oxidative stress. SIRT6 upregulates AMP/ATP levels and activates the adenosine 5'-monophosphate-activated protein kinase (AMPK)-forkhead box O3α (FoxO3α) axis, triggering the expression of downstream antioxidant genes, such as manganese superoxide dismutase and catalase. This process alleviates intracellular oxidative stress and confers protection against ischemic heart injury[14]. Furthermore, myocardial ischemia-reperfusion injury (IRI) involves multiple mechanisms, including ROS production, changes in cellular osmotic pressure, and inflammatory reactions. Calcium overload, oxygen level fluctuations, and mitochondrial ROS are major contributors to the irreversible opening of the mitochondrial permeability transition pore (mPTP). These processes are intricately associated with NLRP3 inflammasome activation, governing the maturation and secretion of IL-1β and IL-18[15]. Consequently, upregulation of the caspase-1 pathway and IL-18 release further exacerbates cell death. Moreover, endothelial dysfunction occurs regardless of myocardial IRI presence, resulting from oxygen level fluctuations, reduced nitric oxide production, and excessive ROS generation. This ultimately leads to the expression of adhesion molecules and leukocyte infiltration. The central role of the NLRP3 inflammasome in modulating coronary blood flow alterations *via* endothelial dysfunction underscores its significance in ischemic heart disease pathology[16].

Additionally, ATP interacts with peripheral purine type 2 receptors, specifically P2X7R, while simultaneously activating associated receptors, such as NLRP1 and NLRP3. This activation triggers apoptotic signals involving caspase-1, caspase-3, and caspase-11, and involves necrotic proteins like gasdermin E and gasdermin D[2]. Caspase-1 has emerged as a molecular target with the potential to impede cardiovascular disease progression, notably heart failure (HF), owing to its pivotal role in fostering inflammation and cardiomyocyte loss. Studies suggest that left ventricular assist device implantation modulates caspase-1 expression levels, thus altering inflammatory and apoptotic aspects of the heart. Inflammation appears pivotal in modulating caspase-1 signaling and its downstream effects, including apoptosis. However, caspase-1 deficiency exacerbates myocardial hypertrophy in renal ischemia-reperfusion mouse models[17,18]. Additionally, inflammation assumes a crucial role in HF onset, progression, and prognosis. The NLRP3 inflammatory complex serves as a pivotal hub in chronic inflammatory responses, fostering the generation of pro-inflammatory cytokines IL-1β and IL-18, thereby exacerbating inflammation. Thus, inhibition of downstream factors of the NLRP3 inflammatory complex and its signaling pathway holds promise as a novel intervention strategy for HF treatment[19].

However, pharmacological inhibition of eATP or genetic ablation of P2X7Rs disrupts the function of the myocardial NLRP3 inflammatory complex during stress overload, highlighting the pivotal role of the ATP/P2X7 axis in cardiac inflammation and hypertrophy. eATP induces hypertrophic alterations in cardiomyocytes *via* an NLRP3- and IL-1β-dependent mechanism. Research on the sympathetic nervous system indicates that sympathetic efferent nerves are the main source of eATP. The depletion of ATP released by sympathetic efferent nerves and the elimination of cardiac afferent nerves or lipophilic β receptors lead to reduced cardiac eATP levels, subsequently inhibiting the activation of the NLRP3 inflammatory complex, IL-1β production, and adaptive myocardial hypertrophy in response to pressure overload [20].


A
ATP
P2RX
PNAX1
GSDMD
P13K
AKT
IL-1β
NLRP3
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NLRP1
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Caspase 11
Caspase-1
Pro-IL-1β
GSDMD
ATP-induced cell death
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B
ATP
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ATP-induced cell death
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pro-TGFB
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IL-6
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ATP-induced cell death
Inflammatory factors
IL-4
IL-2
IL-1A
TNFR
TAK1
IL-6R
IL-4R
IL-2R
TRAF2
HMGB1
TNFR
STAT
MYD88
MAP3K5
JNK
IκB
NF-κB
IRAK
NOS2
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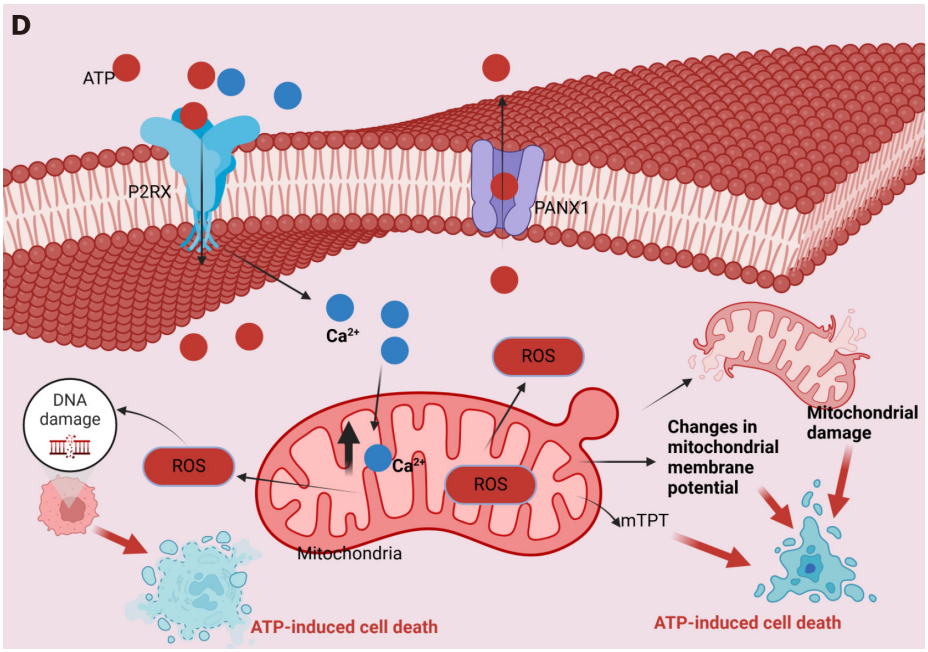

Figure 1 Regulation mechanism of adenosine triphosphate homeostasis and adenosine triphosphate-induced cell death. A: P2 receptor activation pathway; B: Ca^{2+} pathway induces cell death pathways; C: The induction of cell death by adenosine triphosphate results in the release of immune inflammatory factors and activation of immune pathways that further promote cell death; D: The concurrent depletion of mitochondrial membrane potential, disruption of mitochondrial integrity, generation of reactive oxygen species, and alterations in mitochondrial membrane permeability jointly contribute to the ultimate demise of the cell. ATP: Adenosine triphosphate; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; PNAX1: Pannexin-1; GSDMD: Gasdermin D; NLRP3: NOD-like receptor family pyrin domain-containing protein 3; IL: Interleukin; ACS: Apoptosis-associated speck-like protein containing a caspase recruitment domain; ORAI1: Calcium release activated calcium channel protein 1; STIM1: Stromal interaction molecule 1; CYTC: Cytochrome c; APAF1: Apoptotic protease-activating factor 1; HMGB: High-mobility group box; TNF: Tumor necrosis factor; TIMP1: Tissue inhibitor of matrix metalloprotease 1; MMP: Matrix metalloproteinase; TGF: Transforming growth factor; NF-κB: Nuclear factor κB; STAT: Signal transducer and activator of transcription; MYD88: Myeloid differentiation factor-88; TRAF2: Tumor necrosis factor receptor associated factor 2; TAK1: Beta-activated kinase 1; JNK: c-Jun N-terminal kinase; MAP3K5: Mitogen-activated protein kinase kinase kinase 5; IRAK: Interleukin-1 receptor-associated kinase; MAF-C: MAF BZIP transcription factor C; NOS2: Nitric oxide synthase; ROS: Reactive oxygen species; mTPT: Mitochondrial permeability transition.

Moreover, the chloride/bicarbonate ion exchangers AE1, AE2, and AE3 are integral membrane proteins involved in pH regulation across vertebrate tissues, modulated by neurohormonal regulation. Co-expression of AE1 and AE3 in cardiomyocytes facilitates purine agonist ATP-induced cation exchange. ATP stimulates the phosphorylation of tyrosine residues on AE1, leading to the activation of Fyn tyrosine kinase and the binding of Fyn and FAK to AE1. Inhibiting Src-family kinases *in vivo* using compounds like genistein, herbimycin A, or ST638 effectively blocks ATP-triggered AE1 activation. Microinjection of anti-C-terminal Src kinase 1 antibodies or recombinant C-terminal Src kinase, which inhibits Src-family kinase activation, significantly reduces ATP-induced AE1 activation. Moreover, microinjection of anti-FAK antibodies and expression of Phe397 FAK dominant negative mutants in cardiomyocytes impede purine-induced AE1 activation. As a result, tyrosine kinases have emerged as crucial regulators in the acute modulation of intracellular pH and cellular function, particularly in the excitation-contraction coupling of cardiomyocytes[21]. Mild mitochondrial uncoupling in cardiomyocytes triggered by uncoupling agents prompts signal transducer and activator of transcription 3 (STAT3) activation and ATP upregulation. However, excessive mitochondrial uncoupling results in STAT3 inhibition, ATP depletion, and subsequent cellular damage. The development of mitochondrial uncoupling agents with a precisely calibrated dose window that induces mild uncoupling represents a promising approach for enhancing cardiac protection [22].

The human heart relies on a diverse range of energy substrates to maintain its normal contractile function. Under physiological conditions, glucose and long-chain fatty acids (FAs) serve as the primary substrates involved in cardiometabolic processes. However, during stress, there is a shift in substrate preference towards glucose or FAs, which has been implicated in heart disease[23,24]. Research indicates that the pannexin-1 channel is responsible for releasing ATP, subsequently activating fibroblasts within the heart[25]. When cardiac fibroblasts are exposed to ATP or its non-hydrolyzed analog benzoyl ATP, they undergo apoptosis. Similarly, TNF-α, a cytokine linked to the advancement of chronic HF, exacerbates cell death. Similar effects were observed in a murine cardiac muscle cell line, where TNF-α counteracted the decrease in *P2X(6)* mRNA expression typically seen with prolonged exposure to agonists. This indicates that TNF-α disrupts a protective mechanism intended to prevent calcium overload and eventual calcium-dependent cell death by inhibiting ATP-induced P2X6 desensitization[26]. Moreover, stromal interaction molecule 1, a well-known calcium detector within the endoplasmic reticulum calcium reservoir, is increasingly acknowledged as a crucial factor in regulating cardiac hypertrophy and diabetic cardiomyopathy[27,28]. Consequently, a range of proteins involved in regulating cellular ATP homeostasis play crucial roles in AICD[16-20,23-26,29-58] (Table 1).

Table 1 Principal modulators of iron metabolism involved in adenosine triphosphate-induced cell death

Gene	Function	Role in AICD	Effects of genetic deletion or overexpression	Ref.
P2RX7	Inflammation and immune regulation, neurotransmission, apoptosis and autophagy	Activates inflammatory mediators and increases calcium ions	Its activation is closely related to the development of cardiac diseases such as cardiomyopathy, myocardial infarction and myocarditis	[29]
CASP3	Execution stage of apoptosis	CASP3 cleavage by CASP1/4/5/11 forms pores, releasing proinflammatory cytokines	Caspase contributes to the progressive decline in systolic function observed in heart failure by facilitating the degradation of myofibrillar protein. Therefore, the selective inhibition of CASP3's proteolytic function may offer a promising strategy for mitigating or reversing the effects of heart failure	[30]
PANX1	Widely involved in ATP and ion permeability, can effectively reduce CCI induced mechanical pain and thermal hyperalgesia	P2X7 activation opens PANX1 channels, releasing ATP and triggering cell death pathways	PANX1 channels release ATP, which then activates fibroblasts in the heart and promotes the development of cardiac fibrosis after myocardial infarction. PANX1 deficiency results in atrioventricular block, delayed ventricular depolarization, significantly prolonged QT interval and rate-corrected QT interval, and an increased incidence of atrial fibrillation following intraatrial burst stimulation	[25,31]
NLRP3	It plays an important role in inflammation and immune responses and can sense various stimuli inside and outside the cell	Upon activation by stimulatory signals, NLRP3 forms an inflammasome, triggering CASP1 activation. This in turn leads to the release of cytokines and apoptosis	Involved in the process of ischemia-reperfusion injury and endothelial dysfunction, affecting the changes of coronary blood flow; participate in chronic inflammatory response and myocardial hypertrophy, accelerate the production of pro-inflammatory cytokines, leading to the occurrence and development of heart failure	[16,19,20]
CASP1	Membrane hyperpolarization; mitochondrial depolarization and positive regulation of IL-1α production	CASP1 triggers the processing of cytokines, pyrosis, and inflammation, thereby orchestrating the inflammatory response	Involved in inflammation and loss of heart muscle cells. LVAD implantation may alter the inflammatory and apoptotic characteristics of the heart by regulating CASP1 expression levels. CASP1 deficiency resulted in more obvious myocardial hypertrophy in renal ischemia-reperfusion mice	[17,18]
P2RY1	Activates downstream signals	P2RY1 has the capacity to elevate calcium ion levels within the Golgi apparatus	*P2RY1* gene is associated with the development of heart disease and the response to anticoagulant therapy. Meanwhile, the polymorphism of *P2RY1* gene is associated with the onset age of myocardial infarction, which may have a protective effect or influence the progression of myocardial infarction	[32]
P2RY11	Immune regulation, neurotransmission, insulin secretion	It plays a role in immune inflammatory mechanisms	The *P2RY11* gene is implicated in the regulation and repair of inflammatory processes in the heart. Enhanced expression of this gene may facilitate myocardial fibrosis and play a crucial role in the restoration of cardiac function following acute myocardial infarction	[20]
ORAI1	Calcium ion coupling is involved in the activation and proliferation of immune cells	Increased intracellular calcium ions	The *ORAI1* gene plays an important role in the heart, especially in cardiac diseases such as cardiac hypertrophy and heart failure, and is involved in regulating the flow of calcium ions in cardiomyocytes, affecting the systolic and diastolic functions of the heart	[33]
STIM1	Calcium ion sensor. It is involved in immune cell activation, muscle contraction and cell cycle regulation	STIM1 responds to ATP-induced calcium influx by activating ORAI1, thereby contributing to cell death	STIM1 plays a pivotal role in regulating SOCE and Ca^{2+} storage replenishment, crucial for heart development and growth. Additionally, the *STIM1* gene modulates energy substrate preferences in the heart, with implications for metabolic disorders like cardiac hypertrophy and diabetic cardiomyopathy. Elucidating its molecular mechanisms could lead to the discovery of novel therapeutic targets for the prevention and treatment of cardiac metabolic diseases	[23,24]
CASP8	Modulating apoptosis	CASP8 causes apoptosis	It is involved in apoptosis and cytokine processing and is crucial for heart development and hematopoietic function. Lack of CASP8 leads to defects in heart muscle development and a decrease in hematopoietic progenitor cells	[34]
CASP9	Modulating apoptosis (programmed	CASP9 causes apoptosis	The *CASP9* gene is involved in mitochondria-	[35]

	cell death)		mediated apoptosis in the heart. As an inhibitor of CASP9, HAX-1 protein protects cardiomyocytes from apoptosis and maintains cardiac function	
CASP7	The executive stage of catalytic apoptosis	CASP7 causes apoptosis	Inhibition of CASP7 can reduce myocardial infarction size and apoptosis, providing a new strategy for the treatment of myocardial ischemia	[36]
P2RX3	Involved in the conduction of sensory neurons and the perception of pain	NA	It is involved in pain signal transduction caused by myocardial ischemia and is a potential therapeutic target	[37,38]
NLRP1	Regulates inflammation and immune response	Upon activation, NLRP1 triggers CASP1 activation, leading to the induction of pyroptosis and the release of IL-1β and IL-18	*NLRP1* gene is closely related to cardiovascular diseases. The NLRP1 inflammatory complex expressed by *NLRP1* gene is involved in the pathogenesis of cardiovascular diseases and may be a potential therapeutic target	[39]
P2RX4	Involved in cellular signaling	P2RX4 promotes AICD (pyroptosis) through the activation of the NLRP3 inflammasome, resulting in the production of IL-1β and IL-18	The *P2RX4* gene in the heart may influence blood pressure and kidney function by regulating vascular tension	[40]
P2RX5	Involved in neurotransmission and pain regulation	NA	*P2RX5* gene may be related to varicose veins and synaptic vesicles in the heart, and it is involved in cardiac development and functional regulation	[41]
SAPK	Involved in cellular stress response and inflammation regulation	ATP triggers cell death through SAPK pathways, modulating apoptosis, necrosis, and stress signaling mechanisms	It plays a role in regulating cardiomyocyte hypertrophy and apoptosis. MiR-350 induces cardiomyocyte hypertrophy by inhibiting the SAPK pathway, suggesting that the *SAPK* gene is a key regulator of pathologic heart hypertrophy and apoptosis	[42]
p38 MAPK	It is involved in cell signaling, cell stress response, inflammation regulation, apoptosis and other biological processes	ATP stimulates p38MAPK, ultimately leading to cell death *via* apoptosis and necrosis	It is involved in the regulation of cardiomyocyte proliferation, apoptosis and hypertrophy. Involved in the regulation of stress response and cardiomyocyte differentiation, its balance in terms of protective and deleterious effects affects cardiac function	[43]
ASK1	It regulates biological processes such as cell survival and death, inflammatory response, cell stress response, and oxidative stress	Elevated levels of ATP trigger cellular stress, activating ASK1 and subsequent downstream pathways, ultimately leading to cell death	ASK1 activation can lead to hypertrophy, fibrosis and dysfunction of the heart	[44]
NOX2	It plays a crucial role in the generation of reactive oxygen species within cells, thereby regulating physiological processes including cell signaling, immune response, and oxidative stress	ATP stimulates NOX2 activation, leading to ROS production, which induces oxidative stress and potentially triggers cell death	Increased NOX2 activity may lead to diaphragmatic dysfunction, which can trigger symptoms of heart failure	[45]
Bax	It is involved in regulating biological processes such as cell development, immune response and tumor suppression	Elevated levels of ATP trigger Bax activation, resulting in mitochondrial dysfunction and apoptotic cell death	It is involved in the process of myocardial apoptosis induced by ischemia	[46]
MLC	It plays a pivotal role in regulating muscle contraction and movement, thereby influencing biological processes including cell morphology and motility	Depletion of ATP impairs muscle contraction by compromising myosin function and cellular viability	Reduced MLC expression is associated with the pathogenesis of heart failure	[47]
ROCK I	It orchestrates biological processes encompassing cell morphology, polarity, and contraction, integral to functions like cell migration, muscle contractility, and cytoskeletal remodeling	ATP stimulates P2X7Rs, triggering apoptosis through the Rho/ROCK pathway, potentially involving ROCK I	It plays a vital role in signal transduction and regulation within cardiomyocytes; involvement in the regulation of Cav 3.2 channels and stabilization of HIF-1α may increase the risk of arrhythmia during ischemia	[48,49]
ERK1/2	It is involved in the regulation of biological processes such as cell growth, proliferation, differentiation and cell survival, and affects cell signaling and cell fate determination	ERK1/2 promotes cell survival and opposes apoptosis, yet sustained activation can ultimately trigger cell death. By activating the ERK1/2 pathway, it plays a pivotal role in determining cell fate	Signaling pathways involved in adaptive or adaptive remodeling; involved in cardiomyocyte hypertrophy and survival	[50,51]
P2X6	It is involved in the regulation of biological processes such as cell	Activation may elevate calcium levels, potentially initiating cell	*P2X6* gene is up-regulated in chronic heart failure, and its activation may be involved in the	[26]

	signaling, apoptosis and inflammatory response, and may play a role in neurotransmitter release and pain transmission	death mechanisms	pathological process of chronic heart failure	
CYTC	The electron transport molecules in the mitochondrial respiratory chain are involved in cellular respiration and energy production, as well as regulating the process of apoptosis	During cellular stress, the release of cytochrome c from mitochondria initiates the apoptotic process	Phosphorylation at Thr50 increases with aging, which can inhibit cardiomyocyte apoptosis, especially apoptosis caused by hypoxia/reoxidation, and protect cardiac function	[52]
TNF-α	It plays a crucial role in regulating biological processes encompassing inflammation, immune response, and apoptosis, thereby exerting significant influence on inflammatory conditions, immune disorders, and tumor progression	ATP triggers cell death by activating TNF-α and initiating apoptosis or necroptosis pathways. In response to ATP, immune cells produce TNF-α, thereby amplifying the cellular response	The *TNF-α* gene plays a key role in heart failure, promoting inflammation and cell damage. Increased expression of TNF-α in failing hearts correlates with disease severity and is a potential therapeutic target	[53]
P2RY5	It is involved in cell signaling, skin development, pigmentation and other biological processes, which may be related to hair follicle development and skin pigment distribution regulation	NA	In the heart, it may be associated with inflammation and Crohn's disease activity index, and its expression level may be associated with cardiac dysfunction	[54]
P2RY14	It plays a pivotal role in regulating biological processes including immune and inflammatory responses, potentially contributing to the activation of immune cells and the release of inflammatory mediators	NA	*P2RY14* gene may be involved in the inflammatory process of ischemic acute kidney injury in the heart, and its expression changes are related to the development of AKI after cardiac surgery, which may be a potential therapeutic target for preventing and alleviating ischemic AKI	[55]
P2RY13	It regulates cellular immune response, participates in the regulation of inflammatory response and immune cell activation, and plays a significant role in immune regulation and inflammatory processes	P2Y13 may play a significant role in ADP receptors, primarily implicated in maintaining ATP homeostasis	Variations in the *P2RY13* gene are associated with cardiovascular risk markers that may affect heart health	[56]
P2RY12	It plays a crucial role in platelet aggregation, thrombosis, and hemostasis, thereby contributing significantly to blood coagulation and vascular repair processes	P2Y12 may play a role in ADP receptors, mainly involved in ATP homeostasis	The receptor encoded by the *P2RY12* gene regulates platelet aggregation in the heart, preventing clots from forming. The use of P2Y12 inhibitors protects the heart and reduces the risk of myocardial infarction and reperfusion injury	[57]
P2RY6	It is integral to cell signaling and inflammation regulation, potentially contributing to the activation of immune cells and the secretion of inflammatory mediators	P2Y6 may play a role in calcium signaling processes	In hypertrophic cardiomyopathy, *P2RY6* gene-associated lncRNAs exhibit significant upregulation and may regulate cardiac growth, serving as potential biomarkers and therapeutic targets for hypertrophic cardiomyopathy	[58]

AICD: Adenosine triphosphate-induced cell death; P2RX7: Purinergic receptor P2X7; CASP3: Caspase-3; PANX1: Pannexin-1; NLRP3: NOD-like receptor family pyrin domain-containing protein 3; CASP1: Caspase-1; P2RY1: P2Y purinoceptor 1; P2RY11: P2Y purinoceptor 11; ORAI1: Calcium release activated calcium channel protein 1; STIM1: Stromal interaction molecule 1; CASP8: Caspase-8; CASP9: Caspase-9; CASP7: Caspase-7; P2RX3: Purinergic receptor P2X3; NLRP1: NOD-like receptor family pyrin domain-containing protein 1; P2RX4: P2X purinoceptor 4; P2RX5: P2X purinoceptor 5; SAPK: Stress-activated protein kinase; p38 MAPK: p38 mitogen-activated protein kinases; ASK1: Apoptosis signal regulating kinase 1; NOX2: NADPH oxidase 2; Bax: BCL2 associated X; MLC: Myosin light chain; ROCK I: Rho-associated, coiled-coil containing protein kinase 1; ERK1/2: Extracellular signal regulated kinase 1 and 2; P2X6: P2X purinoceptor 6; CYTC: Cytochrome c; TNF-α: Tumor necrosis factor alpha; P2RY5: P2R purinoceptor 5; P2RY14: P2R purinoceptor14; P2RY13: P2R purinoceptor 13; P2RY12: P2R purinoceptor 12; P2RY6: P2R purinoceptor 6; ATP: Adenosine triphosphate; CCI: Chronic constriction injury; IL: Interleukin; NA: Not available; SAPK: Stress-activated protein kinase; ROS: Reactive oxygen species; TNF: Tumor necrosis factor; LVAD: Left ventricular assist device; HAX-1: Hematopoietic lineage substrate-1-associated protein X-1; MLC: Myosin light chain; HIF-1α: Hypoxia-inducible factor-1α; AKI: Acute kidney injury; lncRNA: Long noncoding RNA.

AICD IN CARDIOVASCULAR DISEASE

The coordinated activation of various gene networks involving energy usage, mitochondrial ATP synthesis, heart muscle contraction, and ion movement is essential for preserving normal heart function. Transcriptional regulators, such as estrogen-related receptors (ERRs), play pivotal roles in coordinating these gene networks, regulating cellular metabolism, and contraction mechanisms. ERRs, particularly ERRα and ERRγ, have emerged as critical regulators of cardiac function, as their deficiency leads to cardiac dysfunction, especially under increased workload conditions. Intriguingly, in diabetic cardiomyopathy, metabolic inflexibility is linked to increased mitochondrial FA oxidation and ERRγ expression, hinting at a possible role of persistent ERRγ expression in cardiogenic outcomes[27]. Furthermore, studies have revealed the regulatory role of pannexin-1 half-channel activity by eATP-sensitive P2X7Rs. Nonetheless, the precise mechanisms

governing how eATP-sensitive P2X7Rs regulate the opening and closing of Px1 half-channels remain largely elusive. Evidence suggests that under pathological conditions like ischemia, P2X7R activation leads to the opening of Px1 half-channels, resulting in the influx of large amounts of extracellular Ca^{2+} and the subsequent release of intracellular ATP, ultimately culminating in cell death[28]. Furthermore, the seamless provision of energy is paramount for maintaining the normal contractile and relaxation functions of the heart. Therefore, metabolic disorders and impaired mitochondrial bioenergy, leading to disruptions in ATP production, are implicated in various heart diseases[59].

Myocardial IRI

IRI represents a prevalent and life-threatening clinical complication affecting various organs, including the heart, liver, kidneys, and brain[60]. Myocardial IRI is characterized by multifaceted mechanisms, including the generation of ROS, alterations in cellular osmotic balance, and inflammatory responses. Excessive calcium, variations in oxygen levels, and the generation of mitochondrial ROS collectively leads to the permanent opening of the mPTP, resulting in harmful effects. ROS generation and subsequent oxidative stress are key mechanisms responsible for cellular damage and dysfunction during cardiac IRI. These processes are intricately connected to NLRP3 inflammasome activation, which facilitates cell demise by enhancing the caspase-1 pathway and IL-18 secretion[15].

NLRP3 belongs to the nucleotide-binding domain (NOD)-like receptor family and is expressed by various immune and non-immune cells. When activated, NLRP3, together with apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and procaspase-1, come together to create the NLRP3 inflammasome complex. This assembly regulates inflammation by cleaving pro-inflammatory cytokines IL-1β and IL-18, promoting pyroptotic cell death[61]. Significantly, targeting the NLRP3 inflammasome holds promise as a therapeutic strategy for ischemic stroke, with MCC950 demonstrating potential clinical efficacy[62]. Moreover, in hypertensive target organ damage, various triggers such as oxidative stress and inflammation activate the NLRP3 inflammasome, leading to the release of pro-inflammatory cytokines that worsen tissue damage and dysfunction[63].

Research using heterozygous SIRT6 knockout [SIRT6 (+/-)] mice and cardiomyocyte models *in vitro* has elucidated SIRT6's role in modulating oxidative stress and myocardial damage during IRI. Partial loss of SIRT6 exacerbates myocardial damage, ventricular remodeling, and oxidative stress. In mice subjected to myocardial I/R, restoring SIRT6 expression *via* direct cardiomyocyte injection of adenovirus vectors to reexpress it rescues the adverse effects of SIRT6 knockout on ischemic hearts. Partial SIRT6 deletion hinders myocardial function recovery after I/R. Importantly, SIRT6 increases AMP/ATP levels, activates the AMPK-FoxO3α axis, and boosts the expression of downstream antioxidant genes, such as manganese superoxide dismutase and catalase. This sequence mitigates intracellular oxidative stress, leading to the protective effect against ischemic heart damage. Thus, SIRT6 activation of FoxO3α in an AMP/ATP-driven, AMPK-dependent manner enhances antioxidant defense mechanisms and suppresses oxidative stress, thereby shielding the heart from IRI[14].

Furthermore, investigations have demonstrated that the reversal of calcium ion entry into cardiac cells can lead to a decrease in mechanical function, disruption of cell ultrastructure, depletion of ATP levels, increase in intracellular calcium ions, and initiation of cell apoptosis. Intracellular calcium overload influences various pathways involved in the apoptotic cascade. Exposure of the heart to a brief period without calcium followed by reintroduction of calcium results in significant structural and functional changes in the myocardium, a phenomenon commonly known as the "calcium paradox". The heart experiencing the calcium paradox serves as an exemplary model for understanding the mechanisms of cellular injury caused by intracellular calcium overload at the cardiomyocyte level after reoxygenation following hypoxia or ischemia. A study aimed to determine whether cardiomyocytes undergo apoptosis after 5 minutes of calcium depletion followed by 30 minutes of calcium restoration. It is important to note that cardiomyocytes subjected to 30 minutes of ischemia followed by 60 minutes of reperfusion have exhibited apoptotic cell death[64].

Diabetic cardiomyopathy

Diabetes is a common comorbidity in cardiovascular disease, heightening the heart's susceptibility to IRI. As a result, individuals with diabetes often have a worse prognosis following acute myocardial infarction compared to those without diabetes. Importantly, diabetes exacerbates myocardial IRI by activating the NADPH oxidase pathway in an AMPK-dependent manner, ultimately resulting in different types of programmed cell death[65,66]. Additionally, diabetic cardiomyopathy, a condition marked by heart muscle dysfunction regardless of coronary artery disease and hypertension, is worsened by diabetes. Mitochondrial dysfunction emerges as a key feature of diabetic cardiomyopathy, with mitochondria exerting varied effects on cardiomyocyte function, including oxidative stress, metabolic shifts, intracellular signaling, and cell death. Normally, damaged mitochondria undergo mitophagy, a process that breaks down dysfunctional mitochondria for lysosomal degradation. However, impaired mitophagy leads to the buildup of dysfunctional mitochondria, resulting in cardiomyocyte death[60,67].

Type 2 diabetes mellitus (T2DM) is a rapidly spreading condition, with cardiovascular issues being the leading cause of death among diabetic patients. Prolonged high blood sugar levels impair vascular function by affecting the function of vascular smooth muscle cells (VSMCs) and intracellular calcium dynamics. To investigate intracellular calcium signaling in VSMCs from Zucker diabetic obese rats, Fura-2/AM calcium imaging was performed. The findings revealed that T2DM reduces calcium release from the sarcoplasmic reticulum while increasing the activity of store-operated channels. Additionally, key calcium export mechanisms (SERCA, PMCA, and NCX) show heightened activity during the initial stages of ATP-induced calcium transients. However, during later stages, calcium entry increases alongside a decrease in NCX, SERCA, and PMCA activity, resulting in a shortened decay time of ATP-induced calcium transients during the early phase and an increased amplitude during the subsequent plateau. Elevated cytoplasmic calcium levels in VSMCs may contribute to vascular dysfunction associated with T2DM[68].

Heart damage due to sepsis

Sepsis stands as a prominent global cause of mortality and morbidity. Autophagy is a cellular process that facilitates the degradation and recycling of damaged organelles and proteins, and it is posited to confer a protective effect against sepsis-induced myocardial dysfunction (SIMD). Experimental models of septicemia were established in male Sprague-Dawley rats *via* cecal ligation and puncture. Assessment of cardiac damage involved examining serum markers, echocardiographic parameters, histological analysis with hematoxylin and eosin staining, evaluating cardiac mitochondrial health using transmission electron microscopy, measuring ATP and mitochondrial DNA levels, and quantifying cardiac oxidative stress using REDOX markers in cardiac tissue samples. To assess gene and protein expression levels, real-time polymerase chain reaction and western blotting techniques were utilized. Chromatin co-immunoprecipitation and quantitative real-time polymerase chain reaction were utilized to analyze the binding of histone deacetylase (HDAC) to the phosphatase and tensin homolog (PTEN) promoter and the histone acetylation level of the PTEN promoter.

The results revealed that valproic acid (VPA) alleviated mitochondrial impairment, oxidative stress, and inflammation in septic rats, thereby reducing SIMD by enhancing myocardial autophagy levels. This effect was mediated by VPA-induced autophagy, which downregulated PTEN expression through HDAC1 and HDAC3 in septic rat myocardial tissue. Furthermore, VPA promoted myocardial autophagy by upregulating PTEN expression and inhibiting the protein kinase B/mammalian target of rapamycin pathway, thereby ameliorating SIMD[69]. Moreover, research has highlighted the protective effects of irisin against both acute and chronic myocardial injury. Treatment with irisin mitigated cardiomyocyte death and myocardial dysfunction induced by lipopolysaccharide (LPS). Mechanistically, LPS exposure induced mitochondrial oxidative damage, resulting in ATP depletion in cardiomyocytes and activating apoptosis through caspase. Conversely, irisin preserved mitochondrial function by inhibiting LPS-induced mitochondrial fission mediated by dynamin-related protein 1. Notably, irisin restored the c-Jun N-terminal kinase-large tumor suppressor kinase 2 signaling pathway associated with dynamin-related protein 1-mediated mitochondrial fission activation induced by LPS, suggesting its potential as a promising therapeutic approach for SIMD[70]. Furthermore, exogenous carbon monoxide can regulate mitochondrial energy metabolism by influencing the expression of peroxisome proliferator-activated receptor-gamma coactivator 1-alpha, nuclear respiratory factor 1, and mitochondrial transcription factor A. As a result, it improved cardiac function in sepsis[71].

Hypertrophic cardiomyopathy

M-iPSC-CMs were obtained from a patient harboring a mitochondrial 16S rRNA gene (MT-RNR2). Hypertrophic cardiomyopathy (HCM) represents a condition characterized by cardiac hypertrophy, diastolic dysfunction, and sudden cardiac death, particularly prevalent among young individuals. The involvement of mitochondrial DNA mutations in HCM pathogenesis has been recognized. Induced pluripotent stem cell-derived cardiomyocytes have diminished mitochondrial protein levels, thereby resulting in mitochondrial dysfunction and ultrastructural aberrations. Simultaneously, the mutation resulted in a decrease in the ATP/ADP ratio and mitochondrial membrane potential, ultimately leading to an increased intracellular Ca^{2+} concentration, a characteristic feature of various HCM-specific electrophysiological abnormalities[72]. Furthermore, phosphorus-31 magnetic resonance spectroscopy studies conducted in rats revealed a significant impairment in cardiac energy metabolism, characterized by a reduced phosphocreatine to ATP ratio (-31%, $P < 0.05$)[73]. The *MYBPC3* gene, which encodes myocardial myosin-binding protein C, stands as the predominant genetic factor underlying HCM. Remarkably, myocardial fibrosis (MF) emerged as a pivotal player in HCM development. Nevertheless, the precise mechanism by which mutant MYBPC3 contributes to MF remains unclear. A model featuring R495Q mutant pigs was established using cytosine base editing technology, leading to early onset MF shortly after birth. Intriguingly, the "heart-specific" MYBPC3 gene was transcribed and expressed at the protein level not only in cardiac fibroblasts across different species but also in NIH3T3 fibroblasts. CRISPR-mediated ablation of Mybpc3 in NIH3T3 fibroblasts triggered nuclear factor κB signaling pathway activation, resulting in enhanced expression of transforming growth factor-beta 1 and other proinflammatory genes. Increased levels of transforming growth factor-beta 1 led to the upregulation of hypoxia-inducible factor-1 alpha and its downstream glycolytic targets, such as GLUT1, PFK, and LDHA. This resulted in enhanced aerobic glycolysis and elevated ATP production rates, accelerating cardiac fibroblast activation and ultimately contributing to HCM progression[74].

Potential link between AICD and arrhythmia

Approximately one-third of individuals afflicted with mitochondrial disease experience some manifestation of cardiomyopathy, often characterized by symptoms such as HF and arrhythmias. The primary source of ATP production occurs *via* oxidative phosphorylation of FAs and carbohydrates within the mitochondrial respiratory chain[75]. Mitochondria serve as the principal ATP suppliers, crucial for fulfilling the heart muscle's energy requirements to sustain continuous electrical activity and contractile function. Emerging evidence suggests that mitochondrial dysfunction can deleteriously affect cardiac electrical function by reducing ATP synthesis and triggering excessive ROS production. This disrupts intracellular ion homeostasis and membrane excitability, ultimately increasing the risk of arrhythmias[76]. Furthermore, ventricular fibrillation is closely associated with myocardial ischemia. Sudden cardiac death can be the initial clinical presentation of myocardial ischemia or infarction in approximately 20%-25% of patients. Fatal arrhythmias often result from a complex sequence of pathophysiological abnormalities, arising from intricate interactions among coronary vascular events, myocardial injury, changes in autonomic tone, metabolic conditions, and cardiac ion status. The timing of ischemic onset also plays a crucial role, with a substantial surge in ventricular arrhythmias typically observed within the first few minutes, persisting for about 30 minutes[77].

In large animal hearts, regional ischemia generally induces two distinct stages of ventricular arrhythmia. The first stage (1A), occurring around 5 to 7 minutes after perfusion cessation, is characterized by membrane depolarization, slight

acidification in intracellular and extracellular spaces, and minor disturbances in membrane potential. The subsequent stage of ventricular arrhythmia (1B) emerges between 20 and 30 minutes post-perfusion cessation, during which ischemia-induced changes in K^+ and pH stabilize. The onset of arrhythmia in this stage is presumed to be associated with electrolytic coupling between cells, evident from the rapid rise in tissue impedance preceding arrhythmia. Research has demonstrated that interventions like ischemic preconditioning can attenuate the effects of subsequent ischemia by postponing the emergence of electrolytic coupling between cells, thereby delaying the occurrence of ischemia-induced arrhythmias[78]. Additionally, acute ischemia triggers the opening of K(ATP) channels, inducing cardiomyocyte acidosis and hypoxia, resulting in significant repolarization dispersion across the boundary region. Concurrently, abnormalities in intracellular Ca^{2+} handling manifest within the initial minutes of acute myocardial ischemia, potentially serving as a significant contributor to arrhythmogenesis in individuals with coronary artery disease[77].

AICD IS A PROMISING THERAPEUTIC TARGET IN THE CARDIOVASCULAR SYSTEM

Due to its crucial role in heart disease pathogenesis, AICD holds significant promise as a therapeutic target in the cardiovascular field. Here, we present an overview of diverse small molecules that impede AICD pathways and discuss their potential applications across various heart disease models[30,36,63,79-109] (Table 2). Persistent low-level inflammation is a fundamental factor in various diseases, particularly cardiovascular conditions. While efforts to address inflammation in cardiovascular disease are still in their early stages, they are an area of significant interest. P2X7R, an ATP-activated ion channel, stands out as a promising target for the development of new drugs, primarily involved in regulating inflammatory responses and cell death mechanisms[110]. Due to its pivotal function in inflammation and immune responses, P2X7R stands out as a promising target for treating inflammatory conditions. Research has shown that Rhein hinders ATP/BZATP-triggered calcium increase, pore formation, ROS production, reduced phagocytosis, IL-1β release, and cell death by blocking P2X7Rs in rat peritoneal macrophages[111]. Stimulation of P2X7 and the resulting increase in IL-1β and IL-18 levels are linked to the development of several cardiovascular conditions, such as high blood pressure, artery hardening, tissue damage from restricted blood flow followed by restoration, and heart weakening. However, medications that block P2X7 have shown effectiveness in lowering blood pressure in individuals with hypertension and slowing down artery hardening in experimental animals. Trials in clinical settings have revealed that drugs inhibiting IL-1β and IL-18 can notably lower the likelihood of major negative heart events, including heart attacks and HF[79]. Additionally, P2X7 stands out among P2X receptors because it can operate as both a typical receptor activated by a molecule and a channel that allows substances to pass through, causing cell death when exposed to ATP for extended periods[112]. Furthermore, mild disruption of mitochondrial coupling provides protective effects against various diseases. However, identifying mild disruption induced by chemical agents remains uncertain. Research has shown that typical chemical agents such as FCCP, niacinamide, and BAM15 induce two-phase changes in STAT3 activity in heart muscle cells - boosting STAT3 at low concentrations while suppressing it at high concentrations, albeit with different ranges of doses. Low doses of these agents activate STAT3 by slightly increasing mitochondrial ROS production and subsequently activating JAK/STAT3 in heart muscle cells. Conversely, high doses of these agents lead to STAT3 suppression, reduced ATP production, and heart muscle cell death. Excessive disruption triggers STAT3 inhibition through excessive mitochondrial ROS production and reduced AMPK activation induced by ATP. Low doses of mitochondrial uncoupling agents alleviate doxorubicin-induced STAT3 inhibition and heart muscle cell death, with STAT3 activation playing a crucial role in the cardiac protective effects of these agents. Mild disruption of mitochondrial coupling in heart muscle cells by these agents is characterized by STAT3 activation and increased ATP levels. Conversely, excessive disruption leads to STAT3 inhibition, decreased ATP levels, and cellular damage. Developing mitochondrial uncoupling agents with an optimal dose range to induce mild disruption represents a promising approach for protecting the heart[22].

Studies indicate that simultaneous exposure to LPS and ATP leads to pronounced ASC speck formation, caspase-1 activation, cell death, and ROS production. Inhibiting the ATP-gated purinergic receptor P2X7 significantly reduces caspase-1 activation, while sodium vanadate effectively induces caspase-1 activation. Moreover, adjunctive therapy with ethanol reverses caspase-1 activation, ASC speck formation, and ROS production triggered by LPS and ATP. In HepG2 cells, both LPS and ATP signaling are required for ASC speck formation and caspase-1 induction. Additionally, P2X7 may play a critical role in inflammasome activation, and ethanol's acute effects on the inflammasome may involve reduced ROS production, thereby enhancing tyrosine phosphatase activity[113].

Moreover, another investigation demonstrated that CORM-3 effectively impedes NLRP3 inflammasome activation by obstructing the interaction between NLRP3 and the adaptor protein ASC, thereby alleviating myocardial dysfunction in septic mice[15]. Moreover, when J774 cells are stimulated with LPS and ATP, they display characteristics akin to pyroptosis, including increased expression of *IL-1β* mRNA and protein, activation of caspase-1, assembly of the inflammasome, and cell death. Cathelicidin LL-37 (LL-37) effectively inhibits LPS/ATP-induced IL-1β expression, caspase-1 activation, inflammasome assembly, and cell death. Notably, LL-37 disrupts the binding of LPS to target cells and reduces ATP-induced/P2X7-mediated caspase-1 activation. These findings suggest that LL-37 can counteract LPS activity and suppress P2X7 response to ATP, thereby mitigating LPS/ATP-induced pyroptosis. Hence, leveraging LL-37's dual actions on LPS binding and P2X7 activation may present novel strategies for managing sepsis[114].

P2X7R assumes a pivotal function in diverse pathological states linked to tissue damage and inflammation, rendering human P2X7R an appealing therapeutic target. Through evaluation of human P2X7R-mediated Ca^{2+} responses, three compounds (C23, C40, and C60) were identified from a pool of 73 top-ranked compounds. These compounds underwent additional characterization utilizing Ca^{2+} imaging, patch clamp current recording, YO-PRO-1 uptake, and propyl iodide

Table 2 Summary of small-molecule modulators in adenosine triphosphate-induced cell death-related diseases

Drug	Mechanism	Targets	Ref.
P2X7 antagonist	Inhibit P2RX7 function	High blood pressure; atherosclerosis	[79]
IL-1β and IL-18 inhibitors	Inhibit the release of IL-1β and IL-18	Myocardial infarction and heart failure	[79]
Caspase-3 inhibitors	Inhibit the proteolysis of caspase-3	Reduces or reverses heart failure	[30]
S-propranolol	Decreased caspase-3 activity	I/R injury	[80]
Spirolactone	Inhibits alpha-adrenergic vasoconstriction in the arteries	Drug-resistant hypertension	[81]
Prosulfanilone and carbenolone	Blocking thrombin-induced calcein outflow and reducing Ca^{2+} inflow, ATP release, platelet aggregation, and thrombosis at the *in vitro* arterial shear rate	Arterial thrombus	[82]
Curcumin, resveratrol, notoginseng lactone and allicin	Inhibition of NLRP3 inflammasome	Hypertension TOD	[63]
Pubescenoside A active compound	It inhibited NLRP3 inflammatory activation and induced Nrf2 signaling pathway	I/R injury	[83]
Resveratrol (PIC)	TG storage and caspase 1 activity were inhibited	Atherosclerosis	
MRS-2179	Inhibit platelet aggregation	Thrombotic syndrome	[84,85]
MRS2500	Inhibit P2RY1	Thrombus	[86]
NF157	Inhibit inositol phosphate accumulation	I/R injury	[87]
SKF96365	The entry of orai1 Ca^{2+} was inhibited	Atherosclerosis	[88]
ML9	Inhibition of STIM1	Hypertrophy and Ca^{2+} overload due to I/R; cardiomyocyte death	[89]
TDCPP	Decreased STIM1 expression of and increased GSK3β phosphorylation	I/R injury	[90]
MMPSI	Selective inhibition of caspase 3/7	Myocardial ischemic injury	[36]
Acetyl-tyr-val-ala-asp chloro-methyl ketone	They blocked caspase activation	Myocardial injury induced by ischemia and reperfusion; myocardial infarction	[91]
Hypericin	Up-regulation of autophagy after myocardial infarction	Myocardial infarction	[92]
MRS-2339	Activated the heart P2X receptor	Heart failure	[93]
Propofol	Induced autophagy	I/R injury	[94]
Carvedilol	Novel vasodilator beta-adrenergic receptor antagonist and potent antioxidant	Myocardial I/R induced apoptosis	[95]
Midazolam	Inhibit p38 MAPK	Myocardial I/R injury	[96]
Ulinastatin	Inhibit inflammation, oxidative stress and apoptosis	Chronic heart failure	[97]
Kaempferol	Inhibition of ASK1	Cardiac hypertrophy	[98]
KN-93	Inhibition of NOX2	Cardiac remodeling and heart failure	[99]
Acacetin	Inhibit oxidative stress, inflammation and apoptosis	Diabetic cardiomyopathy	[100]
CETP inhibitor	Elevated phosphorylation levels of vascular myosin light chain and myosin phosphatase target subunit 1, a protein that promotes contractility, along with enhanced reactive ROS production	Hypertension	[101]
Fasudil	ROCKI inhibition	Coronary vasospasm, angina pectoris, hypertension, heart failure	[102,103]
Isosteviol (STV)	ERK1/2 is selectively activated in cells exposed to stress	Myocardial ischemia-reperfusion	[103]
Adriamycin (DOX)	Induced oxidative stress	Heart failure	[105]
Plasminogen activator inhibitor 1	Release the pro-inflammatory cytokine TNF-α	Thromboembolism complication	[106]
Rosuvastatin	MG53 up-regulation was induced	Myocarditis	[107]
Na^+/H^+ exchanger 1	Catalyze increased intracellular Na uptake	Hypertrophy of heart; heart failure	[108]
Prasugrel	Inhibit P2RY12	ST-segment elevation myocardial	[109]

	infarction following primary percutaneous coronary intervention

P2RX7: Purinergic receptor P2X7; IL: Interleukin; I/R: Ischemia/reperfusion; ATP: Adenosine triphosphate; NLRP3: NOD-like receptor family pyrin domain-containing protein 3; TOD: Target organ damage; Nrf2: NF-E2-related factor-2; P2RY1: P2Y purinoceptor 1; STIM1: Stromal interaction molecule 1; GSK: Glycogen synthase kinase; MAPK: Mitogen-activated protein kinases; ASK1: Apoptosis signal regulating kinase 1; NOX2: NADPH oxidase 2; ROS: Reactive oxygen species; ROCK I: Rho-associated, coiled-coil containing protein kinase 1; ERK1/2: Extracellular signal regulated kinase 1 and 2; TNF: Tumor necrosis factor.

cell death assay. The findings revealed that all three compounds effectively inhibited BZATP-induced Ca^{2+} response and demonstrated potent protective effects against AICD[115]. Moreover, the anti-inflammatory effects of P2X7R antagonists stem from their ability to inhibit P2X7R-mediated secretion of pro-inflammatory cytokines from activated macrophages. P2X7R antagonists reliably hinder ATP-triggered casein release, a phenomenon not observed in P2X7R(-/-) mouse macrophages and unrelated to cellular apoptosis. Nevertheless, our findings indicate that P2X7R activation may independently contribute to tissue injury by facilitating protease release, distinct from its pro-inflammatory actions mediated by IL-1 cytokines[116]. Furthermore, recent studies have shown that exposure of HeLa cells to interferon-gamma leads to increased expression of *P2X7* mRNA and full-length protein, altering ATP-dependent calcium flux and rendering the cells susceptible to ATP-induced apoptosis. Importantly, P2X7 antagonists hold promise in attenuating this apoptotic reaction[117].

CONCLUSION

In summary, AICD plays a prominent role in the pathogenesis of cardiovascular disease, contributing to tissue damage, inflammation, and adverse remodeling. Understanding the molecular and metabolic landscape of AICD provides valuable insights into disease mechanisms and identifies potential therapeutic targets. Future research efforts should focus on addressing the limitations, advancing our understanding of these pathways, and developing targeted interventions to improve clinical outcomes in cardiovascular patients. Continued exploration of small molecules, biologics, and gene-based therapies targeting AICD pathways may lead to the development of innovative treatments for cardiovascular diseases. Conducting well-designed clinical trials to evaluate the efficacy and safety of novel therapeutic interventions targeting AICD is essential for translating preclinical findings into clinical practice.

FOOTNOTES

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MINIREVIEWS

E-cigarettes and arterial health: A review of the link between vaping and atherosclerosis progression

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Abstract

Recent studies have suggested an evolving understanding of the association between vaping, specifically electronic cigarette (e-cigarette) use, and the progression of atherosclerosis, a significant contributor to cardiovascular disease. Despite the prevailing perception of vaping as a safer alternative to traditional tobacco smoking, accumulating evidence suggests that the aerosols emitted by e-cigarettes contain harmful constituents that may promote endothelial dysfunction, oxidative stress, inflammation, and dyslipidemia—key mechanisms implicated in atherosclerosis pathogenesis. While past research, including experimental studies and clinical investigations, has shed light on the potential cardiovascular risks associated with vaping, gaps in knowledge persist. Future research endeavors should focus on interpreting the long-term effects of vaping on atherosclerosis development and progression, exploring the impact of different e-cigarette formulations and user demographics, and identifying effective strategies for mitigating the cardiovascular consequences of vaping. By identifying and addressing these research gaps, we can enhance our understanding of the cardiovascular implications of vaping and inform evidence-based interventions and policies to safeguard public health.

Key Words: E-cigarettes; Vaping; Atherosclerosis; Cardiovascular disease; Dyslipidemia; Oxidative stress; Nicotine

Core Tip: E-cigarette use has been linked to various cardiovascular risks, including the progression of atherosclerosis. Despite the perception of vaping as a safer alternative to smoking, evidence suggests that e-cigarette aerosols contain harmful substances that contribute to endothelial dysfunction, oxidative stress, inflammation, and dyslipidemia. These mechanisms are crucial in the development and progression of atherosclerosis. This review explores multiple facets of e-cigarettes and arterial health, focusing on the connection between vaping and atherosclerosis progression. It presents up-to-date evidence on pathophysiology and significant clinical implications, the impact of various constituents, and discusses contemporary public health strategies.

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INTRODUCTION

Electronic cigarettes, also known as e-cigarettes, have rapidly emerged as a popular alternative to traditional tobacco cigarettes since their introduction in the mid-2000s[1]. The rise in popularity of e-cigarettes can be attributed to the perception that e-cigarettes are less harmful compared to conventional smoking, as well as the appealing variety of flavors and the convenience of use, not requiring combustion. Their lack of smoke and the absence of a lingering odor make them more socially acceptable. Additionally, their small, handheld design makes them easy to carry and use discreetly in various settings, without attracting the negative attention often directed at conventional smokers. E-cigarettes have been marketed both as smoking cessation tools and as recreational products, further boosting their use among different age groups and demographics. These battery-operated devices vaporize a liquid solution (e-liquid) containing nicotine, flavorings, and other additives to create an inhalable aerosol, which users then inhale in a process commonly referred to as "vaping"[2]. Advancements in technology and design have made e-cigarettes more user-friendly and efficient, contributing to their widespread adoption. These improvements include longer battery life, customizable settings, and a variety of flavors that can make e-cigarettes an appealing alternative to traditional cigarettes. The global e-cigarette market has experienced exponential growth, with an estimated 68 million users worldwide in 2020, a figure projected to reach 84.4 million by 2025[3]. This surge in popularity is particularly evident among youth and young adults, with a 78% increase in e-cigarette use among high school students in the United States from 2017 to 2018[4].

Proponents of e-cigarettes argue that these devices offer a less harmful alternative to conventional smoking and may aid in smoking cessation efforts[1]. This is because e-cigarettes can reduce exposure to many harmful chemicals found in traditional cigarettes. However, the rapid rise in e-cigarette use has raised significant public health concerns. Critics argue that while e-cigarettes may contain fewer toxic substances compared to traditional cigarettes, they are not without health risks[5]. Because the use of e-cigarettes is relatively new, the long-term health effects of e-cigarette use is largely unknown and necessitates further research. However, prevailing concerns include the potential for nicotine addiction, respiratory issues, and emerging evidence of cardiovascular harm[6,7]. Furthermore, the prevalent use among youth has sparked fears of a new generation addicted to nicotine, potentially leading to a gateway effect where users transition to conventional cigarettes. Public health officials also worry about the insufficient regulation of these e-cigarette products, which can vary widely in terms of quality and safety. Understanding the full spectrum of health implications is crucial for developing appropriate regulatory policies and public health strategies.

Understanding the cardiovascular implications of vaping is of paramount importance, given that cardiovascular disease (CVD) remains the leading cause of death globally. In 2019, an estimated 17.9 million people died from CVDs, representing 32% of all global deaths[8]. This staggering statistic underscores the critical need to identify and mitigate all potential risk factors for CVD, including emerging threats like e-cigarette use. Central to the pathogenesis of CVD is atherosclerosis, a progressive condition characterized by the accumulation of lipids, inflammatory cells, and fibrous elements in the arterial walls[9]. This buildup, known as atherosclerotic plaque, can narrow the arteries, reduce blood flow, and, if ruptured, lead to life-threatening events such as myocardial infarction and ischemic stroke[10]. Over time, the plaque can harden and further restrict blood flow, exacerbating cardiovascular issues. The development and progression of atherosclerosis are influenced by various factors, including endothelial dysfunction, oxidative stress, inflammation, and dyslipidemia[11]. Lifestyle factors such as diet and physical activity in addition to smoking, play significant roles in the onset and severity of atherosclerosis. This comprehensive review examines the link between vaping and arterial health, aiming to inform evidence-based policies, guide public health strategies and regulatory policies, and ultimately work towards reducing the global burden of CVD.

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E-CIGARETTES AND CARDIOVASCULAR HEALTH

As e-cigarette use increases, understanding its potential role in exacerbating each of these conditions is essential to inform both public health and clinical interventions. Given the current gaps in knowledge regarding the long-term cardiovascular effects of vaping, this narrative review was designed to synthesize and analyze the existing literature to fully understand and interpret the risks of this common recreational activity. A comprehensive search strategy was employed on May 13, 2024 using the terms: "e-cigarettes," "vaping," "arterial health," "atherosclerosis," and "cardiovascular effects." PubMed, Scopus, and Web of Science databases were utilized for the search. Inclusion criteria comprised of peer-reviewed articles, most published within the last ten years, and other articles centered on e-cigarette usage.

Conventional cigarette smoking is a well-established risk factor for atherosclerosis and CVD. The toxic constituents in tobacco smoke, including nicotine, carbon monoxide, and oxidative compounds, contribute to endothelial damage, platelet activation, and a prothrombotic state, accelerating atherosclerotic plaque formation and increasing the risk of acute cardiovascular events[12]. Given these established risks, the cardiovascular safety of e-cigarettes has come under scrutiny. While e-cigarettes are often marketed as a safer alternative to traditional smoking, emerging research suggests that the aerosols produced by these devices may not be as benign as initially thought. Studies have shown that e-cigarette aerosols contain harmful substances such as ultrafine particles, diacetyl (a chemical linked to "popcorn lung," a severe lung disease characterized by scarring and narrowing of the small airways), volatile organic compounds (VOCs), and heavy metals like nickel, tin, and lead[13,14]. These constituents have the potential to induce oxidative stress, inflammation, and endothelial dysfunction-all of which are key processes in the initiation and progression of atherosclerosis[15,16].

Moreover, the nicotine content in e-cigarettes, often comparable to or higher than that in traditional cigarettes, raises additional concerns. Nicotine is known to increase heart rate, blood pressure, and myocardial contractility, which can exacerbate existing cardiovascular conditions[17]. It also stimulates the release of catecholamines, which can further stress

the cardiovascular system. Nicotine has been shown to promote angiogenesis and contribute to the growth and destabilization of atherosclerotic plaques, increasing the risk of acute cardiovascular events[18]. These effects make nicotine a significant concern for individuals with or at risk for CVD. The flavoring agents and other additives in e-cigarettes also undergo chemical changes during the heating process, producing potentially harmful byproducts. For instance, the formation of formaldehyde and other aldehydes during vaping have been linked to cellular damage and inflammation [19]. The stakes are high, and as the prevalence of e-cigarette use continues to rise, particularly among younger populations who may not have otherwise used tobacco products, understanding the comprehensive impact of these products on health becomes increasingly critical. This includes not only the immediate physiological effects but also the long-term consequences of sustained use and the potential for increased susceptibility to other cardiovascular risk factors.

The belief that vaping is a safer alternative to traditional smoking is largely driven by aggressive marketing strategies that highlight e-cigarettes' reduced harmful chemicals compared to conventional cigarettes and promote them as smoking cessation tools. The initial regulatory landscape for e-cigarettes was relatively lenient, enabling rapid market penetration without extensive health impact assessments, which further fueled these misconceptions. Although e-cigarettes may lack many of the harmful components of tobacco smoke, they still contain addictive substances like nicotine and pose substantial risks to cardiovascular health. A nationally representative cross-sectional survey of young individuals (ages 11-18) in Great Britain revealed that while 63% of respondents had accurate perceptions of e-cigarettes, only 9% had accurate perceptions of nicotine. The study by East *et al*[20] found that neither smoking nor e-cigarette use was associated with accurate perceptions of nicotine harm, highlighting a significant gap in knowledge about the dangers of nicotine dependence and the overall risks associated with e-cigarettes use.

E-cigarette or vaping use-associated lung injury (EVALI) is well documented in the literature. E-cigarettes heat nicotine extracted from tobacco to create an aerosol with a multitude of other flavors and chemicals. While often regarded as less harmful than smoking, the use of e-cigarettes, or vaping, is not considered to be safe. The chemicals in e-cigarettes, such as propylene glycol, vegetable glycerin, acetaldehyde, acrolein, and formaldehyde, are attributed to irreversible lung damage and disease, and have caused tremendous harm in cases of explosions and burns[19]. In February 2020, the CDC confirmed over 2800 cases of EVALI and 68 deaths attributed to e-cigarette or vaping use[21].

CARDIOVASCULAR RISKS: E-CIGARETTES *VS* TRADITIONAL TOBACCO

Conventional tobacco products contain over 7000 chemicals, many of which are highly toxic to both the lungs and heart [22]. Among these, tar, nicotine, carbon monoxide, formaldehyde, ammonia, and benzene are particularly harmful. Cardiovascular risks associated with the use of tobacco products include immediate and long-term increases in both heart rate and blood pressure, vasoconstriction, reduced blood flow to the heart thereby impeding blood flow to the tissues, blood clots, arterial damage, and arrhythmias. These changes are directly related to coronary artery disease, heart attacks, hypertension, and strokes. Tobacco inhalation, primarily due to nicotine and carbon monoxide found in traditional tobacco products, is a main risk factor for atherosclerotic CVD. Nicotine stimulates the release of catecholamines, which increases heart rate and blood pressure, while carbon monoxide reduces oxygen delivery to the heart muscle[23].

E-cigarette use contributes to CVD in multiple ways. In addition to flavoring, nicotine, and metal particles, e-cigarettes also contain glycerol and propylene glycol, which undergo thermal decomposition. This process leads to the formation of potentially toxic compounds such as acrolein and acetaldehyde. These compounds can subsequently cause macrophage activation, DNA damage, sympathetic dominance, hyperlipidemia, and endothelial dysfunction, leading to proinflammatory phenotypes and oxidative stress, ultimately contributing to CVD[24]. Another example is the effect of nicotine on adipocytes and the cardiovascular system. As Espinoza-Derout *et al*[24] portray in their review, nicotine from e-cigarettes produces the release of free fatty acids (FFAs) and adipokines. This results in macrophage activation as well as the activation of an inflammatory phenotype which substantially diminishes cardiovascular system function. Nicotine also directly affects the vascular system by promoting angiogenesis and smooth muscle cell proliferation, which can destabilize atherosclerotic plaques and increase the risk of thrombotic events[25].

The cardiovascular effects of dual users of both e-cigarettes and combustible cigarettes are evident in medical literature. An analysis by Osei *et al*[26] identified a 36% increased risk of CVD in those who use both e-cigarettes and combustible cigarettes, compared to those who only use combustible cigarettes. These findings reinforce the harm of e-cigarettes, not only when used alone, but also in conjunction with traditional cigarettes. Dual use can result in higher overall nicotine exposure and exposure to a broader spectrum of toxic substances from both traditional and e-cigarettes, which compounds the adverse effects. Results from the Framingham Heart Study corroborate these findings and demonstrate a positive association between aortic stiffness and cardiovascular events as a result of regular e-cigarette use [24]. Aortic stiffness, as measured by pulse wave velocity, is an indicator of vascular aging and a predictor of cardiovascular events. These findings demonstrate how arterial stiffening, as a result of e-cigarette use, leads to not only increased risk of myocardial infarction, but also increased risk of heart failure and mortality[24]. The cardiovascular risks associated with both conventional tobacco and e-cigarette use are summarized in Table 1.

CONSTITUENTS OF E-CIGARETTE AEROSOLS

The perception of e-cigarettes as a safer alternative to traditional smoking largely stems from the absence of combustion in the vaping process. Unlike conventional cigarettes, which burn tobacco to produce smoke containing thousands of chemicals, e-cigarettes heat a liquid solution (e-liquid) to generate an inhalable aerosol, commonly referred to as "vaping"

Table 1 Comparison of e-cigarettes and traditional cigarettes

Category	E-cigarettes	Traditional cigarettes
Key components	Nicotine, flavorings, metal particles, glycerol, propylene glycol	Nicotine, tar, carbon monoxide, formaldehyde, ammonia, benzene
Toxic compounds	Acrolein, acetaldehyde (formed through thermal decomposition)	> 7000 chemicals, including tar and carbon monoxide, many of which are highly toxic
Immediate cardiovascular effects	Increases in heart rate and blood pressure due to nicotine; causes DNA damage, endothelial dysfunction, and oxidative stress	Immediate increases in heart rate and blood pressure; vasoconstriction, reduced blood flow to the heart, blood clots, and arrhythmias
Long-term cardiovascular effects	Aortic stiffness, proinflammatory phenotypes, hyperlipidemia, endothelial dysfunction, increased risk of myocardial infarction, heart failure, and mortality	Coronary artery disease, heart attacks, hypertension, strokes; arterial damage, reduced oxygen delivery to the heart muscle
Mechanism of cardiovascular harm	Nicotine causes macrophage activation and release of FFAs and adipokines, promoting inflammatory responses and oxidative stress	Nicotine stimulates catecholamine release, increasing heart rate and blood pressure; carbon monoxide reduces oxygen delivery to the heart muscle
Impact of dual use	Increases overall nicotine exposure and exposure to a broader spectrum of toxic substances, compounding adverse effects; 36% increased risk of CVD	Similar risks compounded by additional exposure to harmful chemicals when combined with e-cigarette use
Additional risks	Potential exposure to metal particles and other contaminants from e-cigarette devices	Exposure to tar and numerous carcinogenic substances not present in e-cigarettes

CVD: Cardiovascular disease; FFAs: Free fatty acids.

[1,6]. However, the composition of this aerosol is far from benign, containing a complex mixture of potentially harmful substances that may contribute to cardiovascular risk. It is important to note that the levels of harmful constituents can vary widely depending on the e-liquid composition, device characteristics, and user behavior (*e.g.*, device power settings, puffing patterns)[27].

Nicotine

The primary psychoactive component in most e-liquids, nicotine, is a highly addictive substance with well-documented cardiovascular effects. Nicotine stimulates the sympathetic nervous system, leading to increased heart rate, blood pressure, and myocardial contractility[17]. These hemodynamic changes can exacerbate existing cardiovascular conditions and increase the workload on the heart. Moreover, nicotine has been implicated in endothelial dysfunction, a critical initiating event in atherosclerosis. It impairs endothelium-dependent vasodilation, promotes oxidative stress, and enhances the expression of adhesion molecules, facilitating the adhesion and migration of inflammatory cells into the arterial wall[28]. Nicotine also contributes to the progression of atherosclerotic plaques. It stimulates the proliferation and migration of vascular smooth muscle cells (VSMC) and enhances the release of growth factors like basic fibroblast growth factor, which can accelerate plaque growth[18]. Furthermore, nicotine has been shown to promote angiogenesis within plaques, increasing their vulnerability to rupture and subsequent thrombotic events[25].

Ultrafine particles

E-cigarette aerosols contain high concentrations of ultrafine particles (UFPs), defined as particles less than 100 nanometers in diameter. These particles are of particular concern because their small size allows them to penetrate deep into the lungs and even enter the systemic circulation[29]. UFPs have been associated with increased oxidative stress, inflammation, and alterations in heart rate variability, all of which can contribute to atherosclerosis[30]. In the context of atherosclerosis, UFPs can directly interact with endothelial cells, causing mitochondrial damage, increased production of reactive oxygen species (ROS), and activation of pro-inflammatory pathways[31]. They can also translocate into the bloodstream and interact with circulating immune cells, promoting a systemic inflammatory response that exacerbates atherosclerotic processes[32].

Flavorings and additives

The wide array of flavors available for e-cigarettes is a major factor in their appeal, especially among youth. However, these flavoring compounds, often considered "generally recognized as safe" for ingestion, may pose risks when inhaled. For instance, diacetyl, a butter-flavored chemical, has been linked to bronchiolitis obliterans, or "popcorn lung," when inhaled in high concentrations[33]. In terms of cardiovascular effects, certain flavoring compounds have been shown to impair endothelial function. A study by Fetterman *et al*[34] found that flavoring chemicals like vanillin and cinnamaldehyde, the major flavor components of vanilla and cinnamon, respectively, induced oxidative stress and inflammatory responses in endothelial cells, impaired nitric oxide (NO) production, and reduced cell viability. NO is crucial for maintaining vascular homeostasis, and its reduction is a hallmark of endothelial dysfunction in atherosclerosis.

Free radicals and ROS

The heating process in e-cigarettes can lead to the formation of free radicals and ROS, highly reactive molecules that can cause cellular damage. Vaping has been shown to increase markers of oxidative stress in humans, such as 8-isoprostane, a product of lipid peroxidation[16]. Oxidative stress is a key driver of atherosclerosis, contributing to endothelial dysfunction, VSMC proliferation, and oxidation of low-density lipoprotein (LDL) cholesterol, which is more readily taken up by macrophages to form foam cells in atherosclerotic lesions[35]. The chronic exposure to ROS and the resulting oxidative stress can also lead to vascular remodeling, characterized by the thickening of the arterial wall and loss of elasticity, which are hallmarks of hypertension and atherosclerosis. Additionally, ROS-mediated damage to mitochondrial DNA and proteins can impair cellular energy metabolism, further exacerbating cardiovascular dysfunction[36].

Heavy metals

Analysis of e-cigarette aerosols has revealed the presence of toxic metals such as lead, nickel, tin, and copper, likely originating from the heating coils or other device components[14]. These metals can accumulate in the body and have been associated with cardiovascular toxicity. For example, lead exposure has been linked to hypertension, coronary heart disease, and peripheral arterial disease, partly due to its ability to induce oxidative stress and inflammation[37]. Several studies have confirmed the presence of these heavy metals in e-cigarette aerosols. One study by Goniewicz *et al*[38] demonstrated that the concentrations of cadmium and nickel in e-cigarette aerosols were similar to those found in traditional cigarette smoke. A later study by Olmedo *et al*[39] found significant levels of chromium, nickel, and lead in these aerosols, often at concentrations higher than those found in conventional cigarettes, raising concerns about the effects of exposure to these various toxic metals.

Carbonyls

When e-liquids are heated at high temperatures, they can produce carbonyls like formaldehyde, acetaldehyde, and acrolein. These compounds are known cardiovascular toxicants. Acrolein, in particular, has been shown to modify apolipoprotein A-I (ApoA-I), the major protein component of high-density lipoprotein (HDL), impairing its cardioprotective functions[40]. Acrolein can also induce endothelial dysfunction, platelet activation, and vascular inflammation [41]. Meanwhile, acetaldehyde forms adducts with proteins and lipids to disrupt their normal function. These acetaldehyde-protein adducts can impair the function of crucial enzymes involved in cellular metabolism and antioxidant defense, leading to inflammation[42].

PATHOPHYSIOLOGY

Atherosclerosis, the primary underlying cause of CVD, is a complex, multifaceted process involving the accumulation of lipids, inflammatory cells, and fibrous elements in the arterial walls[9]. This accumulation leads to the formation of atherosclerotic plaques, which can narrow arteries, reduce blood flow, and, if ruptured, cause life-threatening events like myocardial infarction and stroke[10]. The pathogenesis of atherosclerosis involves several interrelated mechanisms, including endothelial dysfunction, oxidative stress, inflammation, and dyslipidemia. Emerging evidence suggests that e-cigarette use may contribute to each of these mechanisms, thereby potentially accelerating atherosclerosis progression.

Endothelial dysfunction

Endothelial dysfunction refers to the impairment of the normal physiological functions of the endothelium, the single layer of cells lining blood vessels. Healthy endothelium plays a crucial role in vascular homeostasis by regulating vasodilation, inflammation, thrombosis, and smooth muscle cell proliferation[43]. Endothelial dysfunction is considered the earliest detectable change in the development of atherosclerosis, preceding the formation of visible plaques[44]. It is characterized by a reduction in the bioavailability of NO, which is produced by endothelial cells, and serves as an essential molecule for vascular health. Several studies have demonstrated that e-cigarette use can impair endothelial function. Chatterjee *et al*[16] exposed healthy, non-smoking young adults to e-cigarette aerosol and found acute impairment in flow-mediated dilation (FMD), a measure of endothelium-dependent vasodilation. The reduction in FMD was comparable to that observed with traditional cigarette smoking, suggesting that vaping can acutely impair endothelial function even in young, healthy individuals[16]. This impairment in endothelial function is a critical early step in the development of atherosclerosis. *In vitro* studies have also provided insights. Fetterman *et al*[34] exposed human endothelial cells to e-cigarette flavorings and found that certain compounds, such as vanillin and cinnamaldehyde, increased oxidative stress, reduced NO production, and impaired angiogenesis. NO is a potent vasodilator and inhibitor of platelet aggregation, inflammation, and smooth muscle cell proliferation—all protective against atherosclerosis. The nicotine in e-cigarettes may also contribute to endothelial dysfunction. Nicotine has been shown to increase endothelial cell apoptosis, decrease NO synthase activity, and upregulate the expression of adhesion molecules like vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, which facilitate the recruitment of inflammatory cells into the arterial wall[18].

Oxidative stress

Oxidative stress occurs when there is an imbalance between the production of ROS and the body's ability to neutralize them with antioxidants. ROS can damage cellular components, including DNA, proteins, and lipids. In the context of atherosclerosis, oxidative stress plays a pivotal role by promoting endothelial dysfunction, oxidizing LDL into toxic

oxLDL, stimulating VSMC proliferation, and activating inflammatory pathways[35,45]. E-cigarette aerosols contain a variety of compounds that can induce oxidative stress, significantly contributing to the pathogenesis of poor cardiovascular health. A study by Anderson *et al*[46] found that e-cigarette use increased levels of 8-isoprostane, a marker of lipid peroxidation and oxidative stress, in the urine of users. This increase was comparable to that seen in traditional cigarette smokers, indicating that e-cigarettes can generate similar oxidative burdens. The heating process in e-cigarettes can also lead to the formation of reactive carbonyl species (RCS) such as formaldehyde, acetaldehyde, and acrolein[47]. These RCS can deplete cellular glutathione, a key antioxidant, and form protein adducts that disrupt cellular function. Glutathione is essential for neutralizing ROS and maintaining redox balance within cells. When depleted, cells are more susceptible to damage. Acrolein has been shown to react with and deplete glutathione leading to further cellular injuries [48]. Moreover, e-cigarette aerosols contain the UFPs that penetrate deep into the lungs and even enter the systemic circulation[29]. UFPs have been shown to induce oxidative stress in endothelial cells by increasing mitochondrial ROS production and activating NADPH oxidase[31]. This oxidative stress can stimulate the migration of vascular smooth muscle cells to form plaques.

Inflammation

Inflammation is a key driver of atherosclerosis at all stages, from initiation to progression and complications. The inflammatory response in atherosclerosis involves the recruitment and activation of various immune cells, including monocytes, macrophages, and T-cells, within the arterial wall[9]. These cells release pro-inflammatory cytokines, chemokines, and growth factors that amplify the inflammatory milieu, promote plaque growth, and contribute to plaque instability[49]. Several studies have demonstrated that e-cigarette use can induce both local and systemic inflammation. A study by Reidel *et al*[50] found that acute e-cigarette exposure in mice led to increased pulmonary inflammation, as evidenced by elevated levels of pro-inflammatory cytokines [interleukin (IL)-6, IL-1β] and increased macrophage infiltration in the lungs. These pulmonary effects could contribute to systemic inflammation, a key factor in atherosclerosis progression. In humans, Moheimani *et al*[51] observed increased levels of soluble intercellular adhesion molecule-1 (sICAM-1) in the serum of e-cigarette users. sICAM-1 is a marker of endothelial activation and inflammation, and its elevation suggests that vaping may promote a pro-inflammatory state conducive to atherosclerosis.

The nicotine in e-cigarettes may also contribute to inflammation. Nicotine has been shown to activate nuclear factor kappa-B (NF-κB), a key transcription factor that regulates the expression of pro-inflammatory genes[52]. Activation of NF-κB leads to increased productions of cytokines such as tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-6, which further enhance the inflammatory process[18]. Additionally, nicotine can stimulate the release of pro-inflammatory cytokines from immune cells and increase leukocyte-endothelial cell adhesion, such as macrophages and T cells, facilitating the infiltration of inflammatory cells into the arterial wall, another key step in plaque development[18].

Dyslipidemia

Dyslipidemia refers to abnormal levels of lipids in the blood, typically characterized by elevated LDL cholesterol, reduced HDL cholesterol, and/or increased triglycerides. Dyslipidemia is a major risk factor for atherosclerosis because LDL particles can penetrate the arterial wall, become oxidized, and trigger an inflammatory response that promotes plaque formation[53]. Conversely, HDL plays a protective role by promoting reverse cholesterol transport and exerting anti-inflammatory and antioxidant effects[54]. While research on the lipid-altering effects of e-cigarettes is still emerging, several studies suggest that vaping may contribute to an atherogenic lipid profile. A study by Majid *et al*[55] found that e-cigarette use was associated with lower levels of HDL cholesterol and higher levels of triglycerides in a population-based study. This lipid pattern is consistent with increased cardiovascular risk. The mechanisms by which e-cigarettes may induce dyslipidemia are multifaceted. Nicotine has been shown to increase lipolysis and FFA release, leading to increased hepatic triglyceride synthesis[17]. These FFAs are taken up by the liver and converted to triglycerides, contributing to hypertriglyceridemia[17]. Additionally, oxidative stress and inflammation induced by e-cigarette constituents can impair HDL function. When acrolein modifies ApoA-I, its ability to promote cholesterol efflux from macrophages is inherently reduced[40]. Furthermore, flavorings in e-cigarettes may also contribute to dyslipidemia. Farsalinos *et al*[33] found that certain flavoring compounds contained high levels of diacetyl and acetyl propionyl. While these compounds are primarily associated with respiratory risks, they may also have systemic effects, including lipid metabolism disruption, although more research is needed to understand these mechanisms. These findings challenge the notion that vaping is a safe alternative to traditional smoking and underscore the need for further research to fully understand the long-term cardiovascular implications of e-cigarette use.

PRE-CLINICAL, CLINICAL, AND OBSERVATIONAL EVIDENCE

Several key findings have been found when examining animal models in pre-clinical experimental studies assessing the cardiovascular effects of e-cigarettes. E-cigarette aerosols show milder impacts on cardiovascular health such as less severe vascular impairment and aortic stiffness in mice when compared to traditional cigarette smoke. Additionally, atherosclerosis-prone mice did not develop atherosclerotic plaques when exposed to e-cigarette aerosols as they did when exposed to cigarette smoke. However, both human and animal studies reveal that vaping can still lead to inflammation, endothelial dysfunction, and oxidative stress albeit to a lesser extent than traditional smoking[56]. Both e-cigarette aerosols and liquids have also been found to induce oxidative stress and cytotoxicity in vascular and myocardial endothelial cells during *in vitro* studies. These effects are exacerbated by the activation of heating elements in e-cigarettes which could potentially be linked to the presence of metals such as copper nanoparticles in the aerosols[57].

More recent *in vivo* studies emphasize the potential risks of vaping on cardiovascular health by revealing increased cytokine levels, inflammation, oxidative stress, platelet activation, and thrombogenesis risk following exposure to e-cigarette aerosols[57]. Observations of decreased cardiac ejection fraction and increased oxidative stress in mice exposed to e-cigarette aerosols highlight the potential impact vaping can have on cardiac function[56]. Observational and clinical studies investigating the cardiovascular effects of vaping provide insights into the potential risks that are associated with e-cigarettes. Although the cardiovascular toxicity caused by traditional cigarettes and nicotine are well-documented, the potential long-term cardiovascular effects of vaping are unclear. Epidemiological studies suggest an increased incidence of adverse cardiovascular outcomes among e-cigarette users such as myocardial infarctions, coronary heart disease, chest pain and arrhythmias. The frequency of e-cigarette use correlates with the severity of these outcomes, with severity diminishing as usage decreases. Individuals with known polytobacco use face a higher cardiovascular risk compared to individuals who exclusively use e-cigarettes, complicating the interpretation of study findings in the presence of polytobacco use[56].

Studies have found that even short-term use of e-cigarettes can lead to increased heart rate, elevated blood pressure, and arterial stiffness, effects that can all occur independently of the presence of nicotine in e-liquids. Additionally, acute exposure to e-cigarettes has been shown to prefer sympathetic dominance which may lead to potential disruption of cardiovascular function due to e-cigarette use. While e-cigarettes may produce similar cardiovascular changes as traditional cigarettes, these studies suggest that the range and type of these effects can vary[56]. E-cigarette aerosols contain metals like lead, chromium, nickel and manganese as well as low levels of polycyclic aromatic hydrocarbons, VOCs, and phenolic compounds. Although these levels are generally lower than what is found in traditional cigarette smoke, certain parameters such as high battery voltage can increase the production of toxic substances in e-cigarette aerosols to levels comparable to cigarettes. These toxic substances have the ability to induce pathological mechanisms such as inflammation and oxidative stress which raises concerns about their potential cardiotoxic effects[17].

GAPS IN KNOWLEDGE AND FUTURE RESEARCH DIRECTIONS

Much of the current evidence comes from short-term studies, *in vitro* experiments, or animal models. Long-term epidemiological studies are needed to definitively establish the impact of chronic e-cigarette use on atherosclerosis progression and cardiovascular events in humans. Given the diversity of e-cigarette devices, e-liquid formulations, and user behaviors, future research should consider these variables to provide a more nuanced understanding of the cardiovascular risks associated with vaping. This approach would provide a more thorough understanding of the cardiovascular risks associated with vaping, considering the complexity and variability of use.

The variability of the device in power settings, puffing patterns, and e-liquid compositions can significantly influence the levels of harmful chemicals inhaled by users. While some studies have examined individual toxicants such as nicotine, heavy metals, VOCs, and carbonyl compounds, they often do not capture the combined and potentially synergistic effects of these components[5,58]. While these individual constituents have been studied, the combined and possibly synergistic effects of these components in the unique matrix of an e-cigarette aerosol remain largely unexplored. The unique matrix of an e-cigarette aerosol creates a complex interplay between these elements, which could lead to health effects that are not predictable from studying each component in isolation. This underscores the need for research that assesses the overall cardiovascular impact of e-cigarette aerosols rather than focusing on individual constituents alone.

Current research frequently relies on biomarkers of oxidative stress and systemic inflammation, such as C-reactive protein and IL-6, to infer potential cardiovascular risks associated with e-cigarette use[59]. Although these biomarkers are correlated with atherosclerosis, they provide only indirect evidence of actual disease progression. The lack of longitudinal studies specifically examining vascular changes in e-cigarette users means that the link between vaping and atherosclerosis progression remains speculative. Direct measurements of arterial health, such as carotid intima-media thickness or coronary artery calcium scans, are necessary to draw more definitive conclusions about the role of e-cigarettes in CVDs [60]. By addressing these knowledge gaps, we can inform evidence-based policies and interventions to protect public health in the face of the evolving e-cigarette landscape.

As electronic cigarette use continues to rise, there is increasing importance to explore the short-term and long-term risks, including the potential effects of electronic cigarette use associated with increased cardiovascular risk. To date, little information is known regarding the role electronic cigarettes may have in perpetuating CVDs, including progression to atherosclerosis. Current studies attempting to connect e-cigarette use to atherosclerotic progression are limited due to the majority of studies assessing short-term effects, conducting *in vitro* experiments, or using animal models, restricting application of results to human models. Additionally, the precise mechanisms by which components of e-cigarettes might exert their effects remain poorly understood, particularly given the constantly evolving composition of these products as new flavors and additives are introduced to the market.

However, proinflammatory mediators have been identified, serving as a basis for further exploration. In a cross-sectional study analyzing the risk of atherosclerosis in young people with chronic electronic cigarette use, users of electronic cigarette products for greater than one year were found to have increased levels of monocyte-derived foam cell formation (MDFCF) and monocyte transendothelial migration (MTEM) when compared to nonusers[61]. Both MDFCF and MTEM serve as key facilitators in the development of atherosclerosis. The increase in pro-atherosclerotic markers in electronic cigarette users emphasizes the need for further investigation of the association between vaping and atherosclerotic development through longitudinal studies. Efforts to bridge the current gaps in literature are necessary to mitigate current public health policy regarding electronic cigarette use and advance cardiovascular health in the general

public.

While future research should aim at better understanding the cardiovascular risks electronic cigarette use can impose, there are significant challenges in conducting such studies. Aside from nicotine, there has been very little studies that assess the potential health effects of the various chemical additives in vaping liquids[62]. Additionally, electronic cigarettes are relatively new, having been introduced to the U.S. less than 20 years ago[63]. The exploitation of long-term electronic cigarette use will take years to uncover, limiting researchers to controlled studies within human populations. Further consideration should be given to the potential effects of electronic cigarette use in populations with comorbidities compared to healthy populations, including the risks of second-hand exposure to electronic cigarette aerosols.

Impact of different e-cigarette formulations

The variation in e-cigarette formulations presents a significant challenge to public health understanding and regulatory oversight. These formulations range widely in terms of nicotine concentrations, types of solvents (such as propylene glycol and vegetable glycerin), and flavoring chemicals, each of which can have distinct toxicological profiles. Notably, research indicates that certain flavor additives can undergo thermal degradation during vaping to produce compounds with known toxicity, such as formaldehyde and acrolein, which are both implicated in CVDs[64-67]. Thus, the type and concentration of ingredients in e-cigarettes can significantly influence the risk of atherosclerosis by affecting endothelial cell function, promoting oxidative stress, and triggering inflammatory pathways.

Given the rapid pace of product innovation in the vaping industry, regulatory bodies face the challenge of keeping up with the introduction of new products. This situation calls for adaptive regulatory strategies that can swiftly respond to new evidence regarding the safety of these products. Comprehensive toxicological assessments and standardized testing methods for new and existing e-cigarette formulations are essential to ensure consumer safety and to guide consumers towards less harmful options.

User demographics

Another gap within our current knowledge is the role that user demographics play in the relationship between vaping and cardiovascular health. Emerging evidence suggests that the cardiovascular effects of vaping may vary significantly across different age groups, genders, and individuals with varying health conditions. For instance, adolescents and young adults, who are at a critical stage of cardiovascular development, might be more susceptible to the negative effects of nicotine and other e-cigarette constituents. Additionally, women may experience different effects compared to men, possibly due to differences in body fat distribution, hormonal levels, and metabolic processes, which can influence how substances like nicotine are metabolized and affect the body. Furthermore, individuals with pre-existing health conditions such as hypertension or diabetes may experience accelerated progression of atherosclerotic conditions when exposed to e-cigarette aerosols. These insights underscore the importance of demographic-specific studies that can provide tailored risk assessments and help develop targeted public health interventions. Such research is crucial for crafting effective health advisories and preventive measures that consider the diverse susceptibilities and risk factors present in the general population.

E-cigarette use and regulation across the globe

The regulation of e-cigarettes varies significantly across different countries, impacting their usage patterns and public health outcomes. In the United States, e-cigarettes are regulated by the Food and Drug Administration as tobacco products under the Family Smoking Prevention and Tobacco Control Act. Regulations focus primarily on restricting youth access by limiting the sale of flavored products and enforcing age verification. Despite these efforts, e-cigarette use has surged, particularly among adolescents and young adults[4]. In contrast, the United Kingdom has taken a more permissive approach, viewing e-cigarettes as harm-reduction tools for adult smokers seeking to quit traditional tobacco use. Public Health England even endorses e-cigarettes as being 95% less harmful than conventional cigarettes, integrating them into smoking cessation programs[68]. These divergent regulatory frameworks reflect differing public health strategies, influencing the extent and nature of e-cigarette use in each country.

Across Europe, approaches to e-cigarette regulation vary, with the European Union's Tobacco Products Directive providing a common regulatory framework that includes advertising bans, product content limitations, and warning labels. Some countries, such as France and Germany, have adopted strict regulations, while others, like Sweden, allow more liberal access[69]. These differing approaches have resulted in wide variations in usage rates across the continent, with some nations reporting high levels of adult use for smoking cessation, while others see more recreational use among younger populations. Meanwhile, in countries like Australia and Japan, e-cigarettes containing nicotine are largely banned unless prescribed by a doctor, reflecting a much more restrictive stance. This has led to an underground market in some regions, where unregulated products potentially pose even greater health risks due to a lack of quality control.

In Asia, many countries have imposed outright bans on e-cigarettes due to concerns over public health, safety, and youth uptake. Singapore, India, and Thailand are among the countries that have implemented such measures, with authorities emphasizing the potential dangers of unregulated products and nicotine addiction[70]. As of December 2021, e-cigarettes are completely banned in Singapore, Thailand, Bhutan, India, Sri Lanka, and Timor-Leste[71]. In Japan, Cambodia, and Australia, e-cigarettes containing nicotine are also prohibited. However, the effectiveness of these bans has been mixed; some reports suggest an increase in black-market sales of e-cigarettes and related products. The lack of proper labeling on most e-cigarette devices further complicates efforts by authorities to regulate them effectively. These disparities in regulatory and enforcement practices across the globe reflect differing perspectives on the risks and benefits of e-cigarettes, with significant implications for public health and atherosclerosis progression research.

Strategies to reduce cardiovascular risks of vaping

To effectively mitigate the cardiovascular risks posed by vaping, a multi-faceted approach is required. This approach should include both regulatory measures and public health interventions tailored to the unique challenges posed by e-cigarettes. Regulations might involve setting standards for maximum allowable concentrations of harmful constituents, banning particularly dangerous flavoring chemicals, and enforcing stricter controls over product labeling and marketing practices. Additional age restrictions could be implemented by raising the minimum purchase age for e-cigarette purchase to 25 years. It would be essential for businesses selling these products to strictly enforce this age restriction, potentially in collaboration with local law enforcement, to prevent younger individuals from obtaining e-cigarettes. Furthermore, marketing restrictions could require enhanced warning labels beyond the current nicotine warnings. These labels could highlight potential risks, such as the development of CVD and other cardiovascular effects. By adding these warnings, consumers may be more cautious when considering e-cigarette products, particularly if they have a family history of related health issues.

Public health interventions could include education campaigns that specifically address the risks of e-cigarettes and encourage cessation among current users, particularly focusing on high-risk demographic groups. Thorough screening of patients' usage status, along with counseling on the risks of both tobacco and e-cigarettes, should be emphasized during all medical visits, regardless of specialty or current usage status. Community-wide campaigns, particularly targeting younger and high-risk populations, can be launched to educate the public about the dangers of electronic cigarettes. Additional public health interventions could involve programs that offer social and medical support to assist current e-cigarette users in their efforts to quit. Continued innovation in developing safer e-cigarette technologies, such as alternative nicotine delivery systems that minimize harmful byproducts, is also necessary. Collaboration between scientists, manufacturers, and policymakers is crucial to align product development with public health goals, ultimately reducing the burden of CVD associated with vaping.

These implications for public health are significant, emphasizing the importance of evidence-based interventions and policies to educate youth on the dangers of e-cigarettes and advocate for further regulation of all tobacco-based products. A systematic review by Mylocopos *et al*[72], investigates non-regulatory interventions at different stages, from interactive video games tailored to children and youth at an individual level, to educational sessions in schools and campus bans. It also evaluates mass media campaigns in the community and advocates for further research on school-based peer leader programming and best practices when it comes to community public health education. The impact of these research findings underscores the importance of ensuring up-to-date public health guidelines and regulations at various levels. Currently, the United States Food and Drug Administration (FDA) authorizes the sale of 23 e-cigarette devices with a disclaimer to clarify that the products are not safe or "FDA approved"[73]. The disclaimer also notes the harm and addictive potential of nicotine products and discourages anyone from starting tobacco use, however, more public health education is needed to reach groups at higher risk of tobacco use, including youth and even younger children.

CONCLUSION

While vaping is often perceived as a safer alternative to traditional tobacco smoking, emerging literature underscores the dangers of e-cigarette aerosols. Vaping can influence atherosclerosis development through mechanisms such as endothelial dysfunction, oxidative stress, inflammation, and dyslipidemia. In summarizing findings from experimental, clinical, and observational studies to highlight a consensus on the cardiovascular risks associated with e-cigarette use, it is clear that significant gaps in knowledge remain and challenge the notion of its safety. These knowledge gaps highlight the imperative of public health education and regulation of these products in order to promote long-term cardiovascular health.

Understanding the long-term effects of e-cigarette use on atherosclerosis and overall cardiovascular health remains critical. Longitudinal studies are needed to assess these impacts fully. Additionally, the diversity of e-cigarette devices, formulations and user behaviors complicate risk assessment, underscoring the need for comprehensive research that accounts for all variables. These future studies must understand how age, gender, and pre-existing health conditions influence the cardiovascular effects of vaping to enable more precise and relevant health recommendations. Addressing these research gaps will provide a more complete picture of the risks and guide the development of effective interventions.

Informed public health strategies are essential to mitigate the cardiovascular risks associated with vaping. Evidence-based interventions and policies must be developed and evaluated to regulate e-cigarette use and reduce harm. Public health guidelines should be routinely updated to reflect novel research findings, and further emphasize the potential cardiovascular dangers of e-cigarette use. Educational campaigns can raise awareness about these risks, and should particularly target vulnerable populations such as youth and individuals with pre-existing health conditions. By prioritizing informed strategies and continuing rigorous research, public health authorities can better protect individuals from the cardiovascular risks of vaping and e-cigarette use.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Independent prognostic value of lipocalin-2 in congenital heart disease-associated pulmonary artery hypertension

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Abstract

BACKGROUND

Timely and accurate evaluation of the patient's pulmonary arterial pressure (PAP) is of great significance for the treatment of congenital heart disease. Currently, there is no non-invasive gold standard method for evaluating PAP.

AIM

To assess the prognostic value of lipocalin-2 (LCN2) in relation to PAP in patients with congenital heart disease associated with pulmonary artery hypertension.

METHODS

We conducted a retrospective analysis of 69 pediatric patients diagnosed with

ventricular septal defects. The patients' clinical and laboratory data were collected. The serum LCN2 concentrations were compared between the pulmonary arterial hypertension (PAH) group and the nonPAH group. The correlation of LCN2 concentration with PAH classification was evaluated using binary logistic regression analysis. The receiver operating characteristic (ROC) curve was used to evaluate the diagnostic potential of LCN2 for PAH.

RESULTS

Serum LCN2 concentration significantly correlated with patients' mean PAP (r = 0.544, P < 0.001), but not correlated with creatinine (P = 0.446) or blood urea nitrogen (P = 0.747). LCN2 levels were significantly correlated with PAH in both univariate [odds ratio (OR) 1.107, 95%CI: 1.033-1.185, P = 0.004)] and multivariate regression analysis (OR 1.150, 95%CI: 1.027-1.288, P = 0.015). ROC curve analysis revealed an area under the curve of 0.783 for LCN2. At the cutoff value of 19.42 ng/mL, the sensitivity and specificity of LCN2 for diagnosing PAH is 90.19% and 55.56%, respectively. LCN2 concentration also significantly correlated with the post-repair mean PAP in patients with congenital heart disease (r = 0.532, P = 0.009).

CONCLUSION

LCN2 is emerging as a candidate biomarker for assessing PAP in patients with congenital heart disease. Its high sensitivity in diagnosing PAH makes it a valuable tool in patient management.

Key Words: Congenital heart disease; Pulmonary arterial hypertension; Lipocalin-2; Endothelin-1; Biomarker

Core Tip: This retrospective study demonstrates that lipocalin-2 (LCN2) blood levels significantly correlated with the mean pulmonary arterial pressure of patients with congenital heart disease (CHD). In particular, LCN2 was significantly correlated with the post-repair mean pulmonary arterial pressure of CHD patients. LCN2 has emerged as a candidate biomarker for CHD, and its high sensitivity to pulmonary arterial hypertension diagnosis makes it highly valuable in patient management.

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is characterized by a sustained increase in pulmonary arterial pressure (PAP) and pulmonary vascular resistance[1]. Among the different forms of pediatric PAH, PAH caused by congenital heart disease (PAH-CHD) is particularly significant.

Timely intervention to block abnormal left-to-right shunting in the heart can usually normalize elevated PAP. However, partial patients continue to experience persistent or even worsening PAH, which may be attributed to delayed shunt correction[2,3]. Timely and accurate evaluation of PAP is crucial for the management of congenital heart disease (CHD) patients with left-to-right shunt. At present, evaluations of PAP through echocardiography faces notable limitations. For instance, measurements obtained *via* echocardiography often significantly differ from those obtained through right heart catheterization. Additionally, echocardiography has proven inadequate in predicting mortality in PAH patients, particularly those classified as New York Heart Association functional class III–IV with RV dilation[4,5]. There remains a need for reliable non-invasive gold standard methods to assess PAP.

Lipocalin-2 (LCN2), also known as neutrophil gelatinase-associated lipocalin, is a 25-kDa protein that belongs to the lipocalin family. LCN2 is expressed in various tissues, including the liver, kidney, lung, and adipose tissue, playing pivotal roles in diverse physiological and pathological processes[6,7]. We previously demonstrated that LCN2 is upregulated in PAH-CHD, where it promotes pulmonary artery smooth muscle cell proliferation and helps resist apoptosis [8-10]. LCN2 has also been reported play roles in Kawasaki disease-related PAH[11]. These studies suggest that LCN2 may play an important role in PAH and serve as a potential biomarker for PAH. Furthermore, LCN2 has been identified as a biomarker for acute kidney injury[12,13] and is involved in the development of chronic kidney diseases, including diabetic nephropathy and renal fibrosis[14]. Given the strong physiological and pathological connections between the heart and kidneys[15,16], it is necessary to clarify whether LCN2 upregulation in PAH-CHD patients is a consequence of renal dysfunction.

The aim of the present study was to evaluate the independent predictive value of LCN2 on PAP in a series of consecutive pediatric patients with ventricular septal defect (VSD), for whom right ventricular catheterization pressure, blood cell counts, and biochemical parameters were accessible. Additionally, we compared the predictive values of LCN2 and endothelin-1 (ET-1), a candidate biomarker for PAH[17].

MATERIALS AND METHODS

Subjects

The present study retrospectively collected data from Chinese children with CHD who received treatment at Beijing Children's Hospital over a 4-year period from January 2019 to December 2022. The clinical and laboratory data of the patients were extracted from hospital registry systems by two academic surgeons. This study was approved by the Beijing Children's Hospital Ethics Committee, and all patients or their parents or legal guardians provided written informed consent.

We collected data from pediatric patients who were primarily diagnosed with VSD following cardiac surgery. The inclusion criteria comprised: (1) Surgical repair of VSD; (2) Age less than 72 months; (3) Measurement of PAP *via* intra-operative right ventricular catheterization; and (4) Preoperative serum samples preserved in the biologic sample bank of our hospital. The exclusion criteria included: (1) Cases with abnormal cardiac structures other than VSD or VSD accompanied with atrial septal defect (n = 51); (2) Cases with heart diseases other than CHD (n = 1); (3) Cases with other systemic diseases (n = 2); and (4) Cases that received medications influencing cardiac or renal function during the last 3 months prior to surgery (n = 0). Overall, 69 patients (41 females and 28 males) were included in this study.

ELISA assays

The serum levels of LCN2 and ET-1 were measured using LCN2/NGAL Human ELISA Kit (EHLCN2; Thermo Fisher, Waltham, MA, United States) and ET-1 Human ELISA Kit (EIAET1; Thermo Fisher) following the manufacturer's instructions.

Statistical analysis

The mean PAP (mPAP) was measured through intra-operative right ventricular catheterization. PAH is defined as mPAP > 20 mmHg according to the classification established at the 6th World Symposium of Pulmonary Hypertension[18]. Patients were divided into the PAH group and nonPAH group based on their mPAP values. The diameter of the defect was measured during surgery, and for patients with multiple defects, the defect diameter was calculated based on the total area of all defects.

Continuous variables are expressed as median (Q1, Q3), while categorical variables are expressed as proportion. The Mann-Whitney U test was utilized for comparisons between two independent groups for numerical variables, and the chi-square test was employed for categorical variables, such as the sex of the patients. The Fisher exact test was applied when at least one expected count was less than 5. Pearson correlation was determined between two continuous variables, and Spearman correlation was used when categorical data were included. Odds ratio (OR) and 95%CI were calculated using binary logistic regression analysis. Variables with a P value less than 0.15 in univariate regression were included in the multivariate regression model. The receiver operating characteristic (ROC) curve was employed to evaluate the diagnostic values of the variables. A bilateral P value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 25.0 (IBM Corp., Armonk, NY, United States), Medcalc 19.0 or GraphPad Prism 8.0.

RESULTS

Patients' characteristics

The clinical and laboratory characteristics of the PAH and nonPAH patients are summarized in Table 1. A total of 69 children with CHD participated in this study, including 41 (59.4%) females and 28 (40.6%) males, with a median age of 14.6 months (range 3 months to 55 months). Significant differences were observed between the nonPAH and PAH group in creatinine, blood urea nitrogen (BUN), glucose, mPAP, LCN2 and ET-1. There were no significant differences in sex, age, systolic blood pressure, diastolic blood pressure, ejection fraction, defect diameter, or other laboratory factors between the two groups.

Significant difference in renal function between nonPAH and PAH groups

As shown in Table 1, there were significant differences in median values of creatinine (21.8 μmol/L *vs* 27.8 μmol/L, P < 0.001) and BUN (3.0 mmol/L *vs* 4.2 mmol/L, P = 0.015) between the nonPAH and PAH groups. Pearson correlation analysis demonstrated a significant correlation between mPAP and both creatinine (r = 0.389, P < 0.001) and BUN (r = 0.328, P = 0.006), as shown in Table 2. These results suggest that the PAH group exhibits poorer renal function compared to the nonPAH group among CHD children.

Serum LCN2 concentration significantly correlated with mPAP of VSD patients

According to Table 2, there was a significant correlation between LCN2 and mPAP (r = 0.544, P < 0.001) in VSD children. However, LCN2 does not significantly correlate with creatinine (r = 0.094, P = 0.446) or BUN (r = -0.040, P = 0.747). Even after excluding confounding factors in multivariate regression analysis, LCN2 remained uncorrelated with creatinine or BUN, as shown in Table 3.

To further explore the relationship between LCN2 and PAH, binary logistic regression analysis was conducted. In the univariate regression analysis (Table 4), variables with a P value less than 0.15 (include age, creatinine, white blood cell and LCN2) were included in the multivariate logistic regression model. BUN was excluded in the model due to its significant collinearity with creatinine. The diameter of the defect was also included in the multivariate model based on

Table 1 Baseline characteristics of the nonpulmonary arterial hypertension and pulmonary arterial hypertension patients

Variables	Total number	nonPAH	PAH	*P* value
Number	69	18	51	-
Sex, number of males	69	7 (38.9)	21 (41.2)	0.866
Age in months	69	8.5 (5.4, 12.0)	11.0 (7.0,19.0)	0.094
BMI	68	15.4 (13.8, 17.4)	15.1 (14.1, 16.6)	0.451
Creatinine in μmol/L	68	21.8 (18.0, 26.5)	27.8 (24.3, 33.6)	< 0.001
BUN in mmol/L	68	3.0 (2.1, 3.7)	4.2 (2.8, 5.1)	0.015
Albumin in g/L	67	42.6 (39.6, 43.7)	43.5 (41.4, 45.3)	0.243
Glucose in mmol/L	65	4.6 (4.1, 5.0)	4.1 (3.8, 4.4)	0.036
Hemoglobin in g/L	69	116 (101, 123)	118 (108, 128)	0.448
Platelets as 10^9/L	69	276 (247, 314)	267 (221, 344)	0.995
White blood cells as 10^9/L	46	8.3 (5.7, 9.7)	8.7 (7.5, 11.0)	0.140
SBP in mmHg	66	93.0 (84.5, 95.0)	95.0 (86.5, 101.5)	0.144
DBP in mmHg	66	55.0 (48.5, 60.0)	55.0 (45.0, 60.0)	0.860
EF as %	67	65.0 (62.0, 66.3)	65.0 (65.0, 69.5)	0.072
Diameter in mm	66	10.0 (7.5, 13.0)	10.0 (8.0, 14.8)	0.219
mPAP in mmHg	69	17.7 (16.7, 18.8)	29.4 (24.6, 40.1)	< 0.001
LCN2 in ng/mL	69	19.3 (16.9, 27.6)	33.4 (23.9, 46.3)	< 0.001
ET1 in μg/mL	69	0.14 (0.07, 0.31)	0.30 (0.10, 0.72)	0.049

Data are *n* (%). Sex is expressed as a proportion; continuous variables are expressed as median (Q1, Q3). Diameter means the diameter of the defect, which was measured during surgery. BMI: Body mass index; BUN: Blood urea nitrogen; DBP: Diastolic blood pressure; EF: Ejection fraction; ET-1: Endothelin-1; LCN2: Lipocalin-2; mPAP: Mean pulmonary artery pressure; PAH: Pulmonary arterial hypertension; SBP: Systolic blood pressure.

its clinical relevance. As shown in Figure 1, after adjusting for confounding variables, LCN2 was significantly correlated with PAH (OR 1.150, 95%CI: 1.027-1.288, $P = 0.015$). LCN2 remained significantly correlated with PAH (OR 1.123, 95%CI: 1.032-1.222, $P = 0.007$) after excluding the white blood cell count from the model, given the considerable missing values for this parameter and its insignificance in relation to PAH.

LCN2 exhibits a higher diagnostic potential for PAH in patients with VSD than ET-1

From Table 2, it is evident that both LCN2 and ET-1 are significantly correlated with mPAP in VSD children. However, in the binary logistic regression analysis, ET-1 did not show a significant correlation with mPAP in either the univariate (Table 4) or multivariate (Table 5) analyses. These results indicate that LCN2 exhibits a strong correlation with mPAP compared to ET-1. The diagnostic values of LCN2 and ET-1 for predicting PAH were evaluated using the ROC curve method. As illustrated in Figure 2A, LCN2 demonstrated a larger area under the curve (AUC) of 0.783 compared to 0.657 for ET-1 when predicting PAH in CHD patients. For LCN2, with a best cutoff value of 19.42 ng/mL, the sensitivity, specificity and Yonden's index for diagnosing PAH were 90.19%, 55.56% and 0.4575, respectively. Conversely, for ET-1, with a best cutoff value of 0.39 μg/mL, the sensitivity, specificity and Yonden's index in diagnosing PAH were 45.10%, 94.44% and 0.3954, respectively (Table 6).

LCN2 concentration significantly correlated with the post-repair mPAP of VSD patients

The post-repair mPAP values (intra-operative) of 23 patients were recorded. All 23 patients exhibited a decrease in post-repair mPAP compared to pre-repair levels. Among these, seven patients were classified as nonPAH and 16 as PAH based on their post-repair mPAP values. Notably, four patients transitioned from pre-repair PAH to post-repair nonPAH. Table 7 shows that correlation analysis indicates a significant relationship between pre-repair mPAP and both post-repair mPAP ($r = 0.471$, $P = 0.023$) and mPAP decrease ($r = 0.883$, $P < 0.001$) following repair surgery. LCN2 was significantly correlated with post-repair mPAP ($r = 0.532$, $P = 0.009$), but it did not show a significant correlation with mPAP decrease ($r = 0.181$, $P = 0.407$). Conversely, ET-1 was not correlated with either post-repair mPAP ($r = 0.140$, $P = 0.523$) or mPAP decrease ($r = 0.298$, $P = 0.167$). From Figure 2B, we can see that the LCN2 concentration in post-repair PAH patients was higher than that in nonPAH patients (31.6 ng/mL *vs* 25.5 ng/mL, median value), although this difference was not statistically significant ($P = 0.154$).

Table 2 Correlations of mean pulmonary artery pressure, lipocalin-2 and endothelin-1 with clinical variables

Variables	mPAP		LCN2		ET-1	
	r	*P* value	*r*	*P* value	*r*	*P* value
Sex	0.087	0.475	0.031	0.800	-0.115	0.347
Age in months	0.298	0.013	0.319	0.008	0.048	0.698
BMI	-0.089	0.483	-0.128	0.310	-0.248	0.046
Creatinine in μmol/L	0.389	0.001	0.094	0.446	-0.156	0.205
BUN in mmol/L	0.328	0.006	-0.040	0.747	-0.070	0.568
Albumin in g/L	0.066	0.594	-0.072	0.563	-0.238	0.052
Glucose in mmol/L	-0.174	0.166	0.021	0.869	-0.004	0.973
Hemoglobin in g/L	0.217	0.074	0.080	0.514	-0.173	0.156
Platelets as 10^9/L	0.007	0.958	-0.128	0.293	-0.098	0.422
White blood cells as 10^9/L	0.345	0.019	0.291	0.050	0.107	0.480
SBP in mmHg	0.135	0.280	0.074	0.554	0.033	0.795
DBP in mmHg	0.097	0.438	0.106	0.399	0.003	0.983
EF as %	-0.107	0.388	-0.176	0.155	-0.021	0.864
Diameter in mm	0.371	0.002	0.081	0.516	0.230	0.063
mPAP in mmHg	-	-	0.544	< 0.001	0.508	< 0.001
LCN2 in ng/mL	0.544	< 0.001	-	-	0.427	< 0.001
ET1 in μg/mL	0.508	< 0.001	0.427	< 0.001	-	-

BMI: Body mass index; BUN: Blood urea nitrogen; DBP: Diastolic blood pressure; EF: Ejection fraction; ET-1: Endothelin-1; LCN2: Lipocalin-2; mPAP: Mean pulmonary artery pressure; SBP: Systolic blood pressure.

Table 3 Multivariate logistic regression analysis to define the correlation between lipocalin-2 and renal function in ventricular septal defect patients

Variables	Creatinine[1]			BUN[1]		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Age in months	1.077	1.006-1.153	0.034	1.117	1.010-1.235	0.031
BMI	1.226	0.913-1.648	0.175	-	-	-
Albumin in g/L	1.089	0.901-1.315	0.378	1.016	0.837-1.232	0.875
Glucose in mmol/L	-	-	-	0.635	0.294-1.371	0.248
Hemoglobin in g/L	-	-	-	1.042	0.992-1.094	0.102
mPAP in mmHg	1.065	0.992-1.142	0.082	1.086	1.008-1.170	0.030
LCN2 in ng/mL	0.962	0.914-1.014	0.147	0.972	0.922-1.025	0.294

[1]Variable was binarized based on its median value.
BMI: Body mass index; BUN: Blood urea nitrogen; LCN2: Lipocalin-2; mPAP: Mean pulmonary artery pressure; OR: Odds ratio.

DISCUSSION

PAH associated with CHD is a subgroup of pulmonary hypertension (PH). While there are established expert guidelines for managing PH, there is a notable lack of evidence specifically addressing the management of PAH in patients with CHD. The advancements in the management of CHD have significantly improved survival rates, allowing many children to reach adulthood. However, a considerable number of these children experience various cardiac sequelae, including persistent or progressive PAH[19]. Therefore, timely and accurate assessment of PAP levels is crucial for the effective management of patients with CHD. Unfortunately, there are currently no robust biomarkers available for evaluating PAP, particularly in the context of CHD patients. This underscores the importance of identifying and assessing new

Table 4 Univariate logistic regression analysis to determine the related factors of pulmonary arterial hypertension and lipocalin-2

Variables	Correlation with PAH			Correlation with LCN2[1]		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Sex, males	1.1	0.366-3.303	0.865	1.212	0.463 ± 3.172	0.696
Age in months	1.05	0.985-1.119	0.137	1.050	1.002 ± 1.101	0.043
BMI	0.868	0.669-1.127	0.289	0.859	0.676 ± 1.091	0.213
Creatinine in μmol/L	1.204	1.066-1.359	0.003	1.021	0.952 ± 1.094	0.566
BUN in mmol/L	1.684	1.089-2.606	0.019	0.967	0.711 ± 1.316	0.832
Albumin in g/L	1.114	0.942-1.317	0.205	1.050	0.930 ± 1.186	0.432
Glucose in mmol/L	0.648	0.346-1.213	0.175	0.763	0.431 ± 1.350	0.353
Hemoglobin in g/L	1.017	0.982-1.053	0.345	1.006	0.977 ± 1.036	0.686
Platelets as 10^9/L	1	0.995-1.006	0.887	0.999	0.995 ± 1.004	0.841
White blood cells as 10^9/L	1.259	0.960-1.651	0.096	1.111	0.908 ± 1.361	0.306
SBP in mmHg	1.036	0.984-1.091	0.176	1.018	0.977 ± 1.060	0.401
DBP in mmHg	0.998	0.955-1.044	0.944	1.027	0.983 ± 1.073	0.239
EF as %	1.099	0.966-1.250	0.152	0.932	0.834 ± 1.040	0.207
Diameter in mm	1.106	0.944-1.296	0.211	1.011	0.883 ± 1.157	0.877
mPAP in mmHg	-	-	-	1.084	1.026 ± 1.145	0.004
LCN2 in ng/mL	1.107	1.033-1.185	0.004	-	-	-
ET-1 in μg/mL	10.028	0.896-112.196	0.061	2.101	0.887 ± 4.979	0.092

[1]Variable was binarized based on its median value.

BMI: Body mass index; BUN: Blood urea nitrogen; DBP: Diastolic blood pressure; EF: Ejection fraction; ET-1: Endothelin-1; LCN2: Lipocalin-2; mPAP: Mean pulmonary artery pressure; OR: Odds ratio; PAH: Pulmonary arterial hypertension; SBP: Systolic blood pressure.

Table 5 Multivariate logistic regression analysis to define the correlation between endothelin-1 concentration and risk for pulmonary arterial hypertension

Variables	OR (95%CI)	*P* value
Age in months	0.994 (0.914-1.081)	0.889
Creatinine in μmol/L	1.232 (1.056-1.436)	0.008
Diameter in mm	0.984 (0.811-1.195)	0.871
ET-1 in μg/mL	9.681 (0.650-144.192)	0.099

ET-1: Endothelin-1; OR: Odds ratio.

biomarkers that could aid in the evaluation of PAP in this population, ultimately enhancing disease management and patient outcomes.

In the present study, we evaluated the predictive value of LCN2 for PAP in VSD patients. Our findings indicate that the blood level of LCN2 significantly correlates with PAH in VSD patients, as demonstrated through both univariate and multivariate regression analyses. ROC curve analysis reveals that LCN2 has a superior diagnostic value compared to ET-1 (with AUC 0.783 *vs* 0.657). Notably, LCN2 exhibits a sensitivity for diagnosing PAH that exceeds 90% at a cutoff value of 19.42 ng/mL, making it a valuable tool for screening patients suspected of having PAH. Therefore, for CHD patients with suspected PAH, LCN2 emerges as a crucial reference for estimating PAP and guiding treatment decisions. Conversely, the diagnostic potential of ET-1 for PAH is inferior to LCN2. There is no significant correlation between blood ET-1 concentration and mPAP. In the ROC curve analysis, however, ET-1 demonstrates a high specificity for diagnosing PAH at 94.44%, indicating that it holds utility as a confirmatory marker in the diagnostic evaluation of PAH.

LCN2 is a multifunctional protein that can be up-regulated in diverse pathological processes, including immunological abnormalities, metabolic diseases, and multiple types of tumors[20-22]. In particular, LCN2 is a marker for kidney injury and renal dysfunction, and its concentration significantly increases during both acute and chronic kidney injuries[12-14].

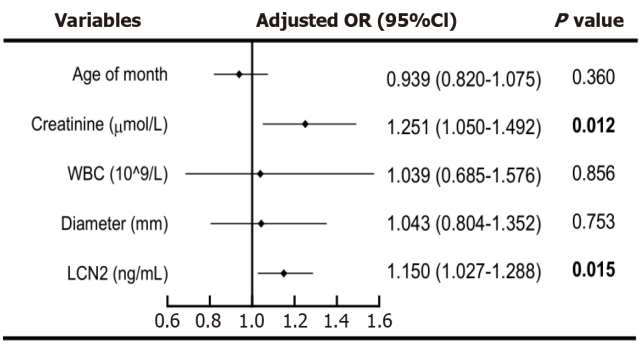

Figure 1 Multivariate logistic regression analysis the correlation between lipocalin-2 concentration and risk for pulmonary arterial hypertension. LCN2: Lipocalin-2; OR: Odds ratio; WBC: White blood cells.

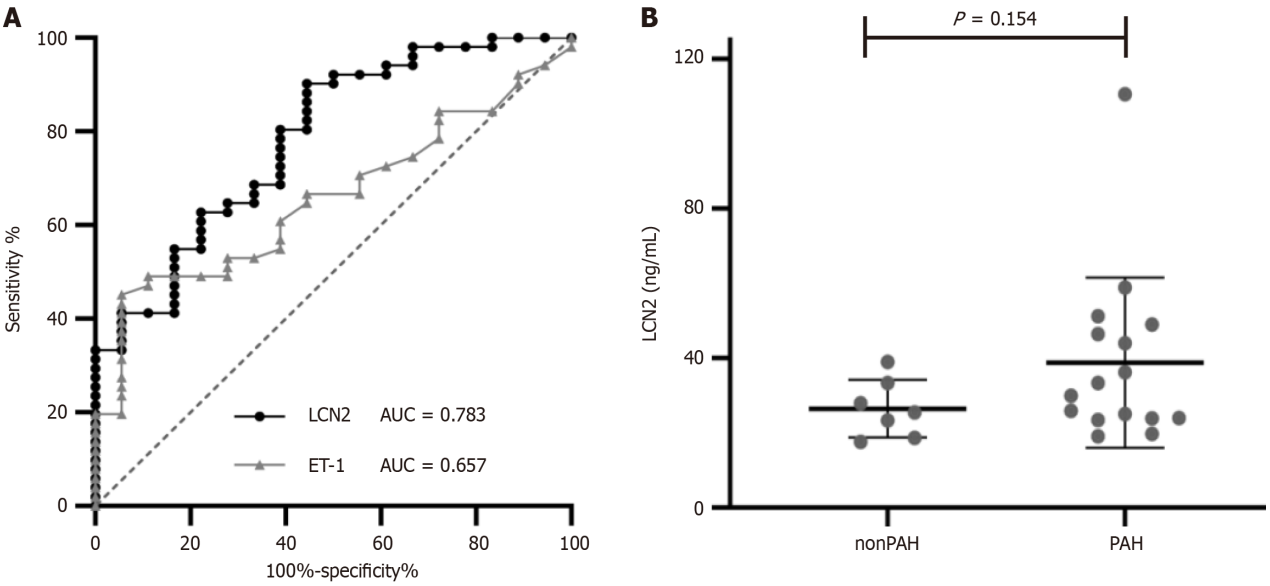

Figure 2 Receiver operating characteristic curve and comparison of lipocalin-2 concentration. A: Receiver operating characteristic curve of blood lipocalin-2 (LCN2) and endothelin-1 as predictors for pulmonary arterial hypertension (PAH); B: Comparison of LCN2 concentration between nonPAH and PAH patients after repair surgery. AUC: Area under the receiver operating characteristic curve; ET-1: Endothelin-1.

Given the close functional connection between the heart and kidneys, many CHD patients also exhibit abnormal renal function[23,24]. In the present study, we observed significant differences in renal function between the nonPAH and PAH groups. Additionally, we found that mPAP is significantly correlated with blood creatinine and BUN levels in VSD children. However, it is crucial to determine whether elevated LCN2 levels are primarily due to renal dysfunction or cardiovascular abnormalities. Despite the presence of abnormal renal function in CHD patients, we did not identify any significant correlation between LCN2 blood levels and creatinine or BUN in either univariate or multivariate regression analyses. This finding suggests that the renal abnormalities present are not sufficient to induce a significant increase in LCN2 levels. Consequently, our results imply that increased LCN2 in patients with CHD is more likely associated with PAH-related pathology rather than renal dysfunction. This underscores the potential role of LCN2 as a biomarker specifically linked to PAH in the context of CHD.

Our previous studies, along with recent reports from others, have demonstrated that LCN2 plays a significant role in promoting pulmonary artery smooth muscle cell proliferation and inhibiting apoptosis[8-11]. In our most recent study [25], we highlighted a critical role for LCN2 in glycolytic regulation, which is central to the metabolic theory in PH progression[26,27]. This association may serve as the molecular basis for the correlation between LCN2 and PAH, independent of renal dysfunction that may be present. The multifaceted roles of LCN2 in various physiological and pathological processes[28-30] render it an intriguing molecule for further research and potential therapeutic applications. Delving deeper into the mechanisms through which LCN2 exerts its effects could yield valuable insights not only for the development of new diagnostic tools for PAH but also for enhancing treatment strategies aimed at this challenging condition.

A recent report by Zhang *et al*[31] evaluated the relationship between LCN2 and PH in patients with CHD[31]. However, the types of CHD included in their study were not classified or specified, and they did not take into account the potential impact of renal function on LCN2 levels. While the authors concluded that LCN2 levels are elevated in patients with CHD, they reported a reference value of LCN2 for predicting PH at just 8.1 pg/mL. This value is substantially lower

Table 6 Predictive values of lipocalin-2 and endothelin-1 for pulmonary arterial hypertension

	AUC	Youden's index	Sensitivity, %	Specificity, %	Cutoff value
LCN2	0.783	0.4575	90.19	55.56	19.42 ng/mL
ET-1	0.657	0.3954	45.10	94.44	0.39 μg/mL

AUC: Area under the receiver operating characteristic curve; ET-1: Endothelin-1; LCN2: Lipocalin-2.

Table 7 Correlations of post-repair mean pulmonary artery pressure with clinical variables, *n* = 23

Variables	Post-operative mPAP		mPAP decrease	
	r	*P* value	*r*	*P* value
Sex, male	0.404	0.056	0.303	0.161
Age in months	0.347	0.105	0.434	0.039
BMI	-0.141	0.531	-0.050	0.826
Creatinine in μmol/L	-0.150	0.493	0.248	0.255
BUN in mmol/L	0.236	0.278	0.411	0.052
Albumin in g/L	0.313	0.156	0.029	0.897
Glucose in mmol/L	-0.045	0.849	-0.057	0.813
Hemoglobin in g/L	0.223	0.306	0.163	0.458
Platelets as 10^9/L	-0.066	0.764	0.107	0.628
White blood cells as 10^9/L	0.186	0.507	0.623	0.013
SBP in mmHg	0.094	0.677	0.043	0.848
DBP in mmHg	0.361	0.099	0.185	0.410
EF as %	-0.311	0.148	-0.037	0.867
Diameter in mm	0.398	0.060	0.552	0.006
Pre-repair mPAP in mmHg	0.471	0.023	0.883	< 0.001
LCN2 in ng/mL	0.532	0.009	0.181	0.407
ET-1 in μg/mL	0.140	0.523	0.298	0.167

BMI: Body mass index; BUN: Blood urea nitrogen; DBP: Diastolic blood pressure; EF: Ejection fraction; ET-1: Endothelin-1; mPAP: Mean pulmonary artery pressure; SBP: Systolic blood pressure; LCN2: Lipocalin-2.

than our findings, which indicated LCN2 levels of 25 ng/mL[8] in healthy children. Results from other studies reported levels ranging from 0.9 to 5.9 ng/mL or 9.8 to 25.7 ng/mL[32,33]. Compared to the study by Zhang *et al*[31], our research provides more objective and informative results regarding LCN2 Levels in the context of CHD and PH.

In CHD patients with a left-to-right shunt, elevated PAP may not always normalize after the closure of the shunt[1,34]. The reason behind why some CHD patients experience a permanent reversal of PAH following shunt closure, while others continue to exhibit persistent PAH, remain unclear. In our study, we recorded post-repair PAP values for 20 PAH patients; four experienced a reversal of elevated PAP to normal levels, while the remaining patients continued to show signs of PAH. Notably, we found that LCN2 concentration was significantly correlated with post-repair mPAP. Furthermore, patients with post-repair PAH exhibited higher levels of LCN2 compared to non-PAH patients. These findings suggest that blood LCN2 levels could serve as a potential biomarker to indicate whether PAH can be reversed after shunt closure in CHD patients. This highlights the need for future studies with larger sample sizes to further validate LCN2's prognostic value in predicting the outcomes of PAH after surgical intervention. Exploring this relationship could enhance our understanding of PAH in CHD patients and inform clinical decision-making regarding treatment strategies.

Limitations

This study has some limitations. First, it is a single center cross-sectional study with a relatively small number of research subjects. Future prospective and multicenter studies with larger patient populations will be necessary to enhance the generalizability of the findings. Second, this study focused exclusively on patients with VSD or VSD accompanied by

atrial septal defect, which represent relatively simple types of CHD. Given the diversity of CHD, particularly in children with complex conditions, such as those with segmental PH or a combination of group 1 and group 2 PH, the diagnosis and management of PH must be customized to account for the individual patient's unique anatomical and hemodynamic conditions. Therefore, caution should be exercised when interpreting the results. Third, all patients enrolled in our study underwent right ventricular catheterization. However, most CHD patients with simple lesions typically do not require cardiac catheterization. Consequently, patients who were unwilling or did not require right heart catheterization were excluded from this study, introducing a selection bias. Finally, the determination of post-repair PAH in this study relied on intra-operative ventricular catheterization results obtained after shunt closure. It is important to note that with the cessation of anesthesia and the patient's recovery, the final PAP values may change. This potential bias is challenging to avoid and may impact the interpretation of the results. Addressing these limitations in future research will be crucial for validating the findings and enhancing our understanding of LCN2's role in PAH among CHD patients.

CONCLUSION

In conclusion, this retrospective study demonstrated that LCN2 blood levels significantly correlate with mPAP in CHD patients. LCN2 has emerged as a candidate biomarker for CHD patients, and its high sensitivity in diagnosing PAH underscores its potential value in patient management.

FOOTNOTES

Author contributions: Wang GL and Liu AJ conceptualized and designed the research; Guo ZK, Bai S and Li XF screened patients and acquired clinical data; Wang GL, Guo ZK, Chen PG, Jiao H and Kong XH performed data curation, visualization, and interpretation; Wang GL, Li YX and Liu AJ wrote the manuscript; Wang GL and Liu AJ performed reviewing and final editing; All authors have read and agreed to the published version of the manuscript. Both Wang GL and Liu AJ have played important and indispensable roles in the experimental design, data interpretation and manuscript preparation as the co-corresponding authors. Wang GL conceptualized, designed, and supervised the project, including literature collection, manuscript submission and revision, with a focus on the association between lipocalin-2 concentration and risk for pulmonary arterial hypertension. Liu AJ played a crucial role in data re-analysis and re-interpretation, figure plotting, comprehensive literature searching, and preparing the final manuscript submission, focusing specifically on the diagnostic value of lipocalin-2 in PAH. The collaboration between Wang GL and Liu AJ was essential to the publication of this manuscript.

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Informed consent statement: All patients or their parents (or legal guardians) provided written informed consent.

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ORIGINAL ARTICLE

Retrospective Study

Trends in cardiovascular and cerebrovascular health scores in the Kailuan population from 2006 to 2011

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Abstract

BACKGROUND

The American Heart Association defines cardiovascular health in terms of four behaviors (smoking, diet, physical activity, and body weight) and three factors (plasma glucose, cholesterol, and blood pressure). By this definition, the prevalence of ideal cardiovascular health behaviors and factors (ICHBF) is negatively correlated with all-cause mortality and risks of cardiovascular and cerebrovascular diseases and malignancy.

AIM

To investigate the changing trends of cardiovascular and cerebrovascular health scores in the Kailuan study population from 2006 to 2011.

METHODS

The Kailuan population data from three health checkups held in 2006-2007, 2008-2009, and 2010-2011 were analyzed, and the constituent ratios of cardiovascular and cerebrovascular health behaviors and factors at ideal, intermediate, and poor levels were calculated by using Huffman and Capewell method. Simultaneously, the cardiovascular and cerebrovascular health behavior and factor scores were calculated.

RESULTS

From 2006 to 2007, the proportion of people with ideal physical exercise, low salt

diet, ideal body mass index, ideal total cholesterol level, no smoking, ideal blood sugar, and ideal blood pressure was 13.12%, 9.34%, 49.17%, 64.20%, 49.27%, 69.99%, and 20.55%, respectively, in men with a health score of 8.46, and 12.00%, 9.13%, 61.60%, 64.28%, 98.19%, 78.90% and 36.92% in women, with a score of 10.02. From 2008 to 2009, the proportion was 16.09%, 14.04%, 51.94%, 65.02%, 40.18%, 66.44%, and 17.04% in men, with a score of 8.18, and 16.860%, 17.360%, 64.010%, 67.433%, 98.220%, 76.370%, and 42.340% in women, with a score of 10.12. From 2010 to 2011, the proportion was 12.22%, 17.65%, 49.40%, 68.33%, 48.17%, 64.67%, and 14.68% in males, having a score of 8.21, while in females, the proportion was 11.83%, 18.09%, 49.40%, 67.85%, 98.82%, 74.52%, and 37.78%, with a score of 9.90.

CONCLUSION

The prevalence of ideal cardiovascular and cerebrovascular health behaviors and factors is low in the Kailuan study population due to inadequate scores of relevant health metrics.

Key Words: Cardiovascular diseases; Cerebrovascular diseases; Health behaviors and factors; Kailuan study; Retrospective study

Core Tip: The American Heart Association defines ideal cardiovascular health as the concurrent presence of ideal health parameters (blood glucose, total cholesterol, and blood pressure levels) and ideal health behaviors (weight status, diet, physical activity, and smoking). Our study design was retrospective and based on the Kailuan study. This prospective study was initiated in July 2006 to evaluate the risk factors and interventions for cardiovascular diseases and cerebrovascular diseases in the Kailuan community population, with several articles having been published on such chronic non-communicable diseases. A fixed population was constituted from these 57659 participants, and their cerebrovascular and cardiovascular health parameters and behaviors were surveyed from 2006 to 2011. Furthermore, the distributions of cardiovascular health parameters and behaviors were portrayed, and their health scores were estimated.

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INTRODUCTION

The American Heart Association (AHA) defines ideal cardiovascular health as the concurrent presence of ideal health parameters (blood glucose, total cholesterol, and blood pressure levels) and ideal health behaviors (weight status, diet, physical activity, and smoking)[1]. Cerebrovascular and cardiovascular conditions are the leading cause of death worldwide and remain one of the foremost health challenges faced by the global population. Moreover, the prevalence of ideal cardiovascular health parameters and behaviors is negatively correlated with all-cause morality along with the innate risk of cardiovascular conditions and malignancies. Several identical risk factors have now been identified for increased risks of cerebrovascular and cardiovascular conditions across varying populations, although the incidence and disease burden vary by region. However, there has been a decline in the occurrence of cerebrovascular and cardiovascular diseases (CVD) owing to major lifestyle improvements[2].

Ideal cardiovascular health metrics are also protective against cerebrovascular diseases[3,4]. Continuous improvement of ideal cardiovascular and cerebrovascular health behaviors and factors exhibits positive significance for the prevention of CVD and cerebrovascular diseases.

Our study design was retrospective and based on the Kailuan study. This prospective study was initiated in July 2006 to evaluate the risk factors and interventions for CVD and cerebrovascular diseases in the Kailuan community population, with several articles having been published on such chronic non-communicable diseases[5-7]. The Ethics Committee of Kailuan General Hospital approved this study.

Kailuan community is a functional community owned and managed by Kailuan group, which pays for the health examinations of all in-service and retired employees every two years[8]. A total of 11 medical institutions are responsible for the healthcare services of the whole community.

Three health examinations were organized successively in 2006-2007, 2008-2009, and 2010-2011 which were attended by 57659 employees, while others undertook one or two health examinations. A fixed population was constituted from these 57659 participants, and their cerebrovascular and cardiovascular health parameters and behaviors were surveyed from 2006 to 2011. Furthermore, the distributions of cardiovascular health parameters and behaviors were portrayed, and their health scores were estimated.

MATERIALS AND METHODS

Subjects

A total of 57659 people participated in all three health examinations (2006-2007, 2008-2009, and 2010-2011) and were included as subjects; their cardiovascular and cerebrovascular health behaviors and factors were evaluated from 2006 to 2011. The inclusion criteria were: (1) Age ≥ 18 years; (2) Cognitive ability sufficient to fill in the questionnaire by themselves; and (3) Signed an informed consent form. Subjects with missing data on cardiovascular and cerebrovascular health behaviors and factors were excluded.

Definition of cardiovascular and cerebrovascular health metrics behaviors and factors

The determination of cardiovascular and cerebrovascular metrics in our study was based on the seven criteria proposed by the AHA[1]. According to the definition of the AHA, smoking, leisure-time physical activity, and diet are defined as cerebrovascular health behaviors, and body weight, fasting plasma glucose, total cholesterol, and blood pressure are defined as cerebrovascular health factors. Never-smoker or quitting smoking ≥ 12 mo ago, diet score = 4/5, ≥ 150 min/wk moderate intensity or ≥ 75 min/wk vigorous intensity or ≥ 150 min/week moderate and vigorous physical activity, body mass index (BMI) < 25 kg/m^2, fasting plasma glucose < 100 mg/dL, total cholesterol < 200 mg/dL, and systolic blood pressure (SBP) < 120 mmHg or diastolic blood pressure (DBP) < 80 mmHg are defined as ideal health behaviors and factors. Intermediate health behaviors and factors are quitting smoking < 12 mo ago, diet score = 2/3, 1-149 min/wk moderate intensity or 1-74 min/wk vigorous intensity or 1-149 min/wk moderate and vigorous physical activity, BMI 25.0-29.9 kg/m^2, fasting plasma glucose 100-125 mg/dL or treated to goal, total cholesterol 200-239 or treated to goal, and SBP 120-139 mmHg or DBP 80-89 mmHg or treated to goal. Poor health behaviors and factors include current smoker, diet score = 0/1, no physical activity, BMI ≥ 30 kg/m^2, fasting plasma glucose ≥ 126 mg/dL, total cholesterol ≥ 240 mg/dL, and SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. Diet score (scale: 0-5) is calculated based on 1 point for each of the following five components: ≥ 4.5 cups per day fruits/vegetables; ≥ two 3.5 oz servings of fish per week; < 1500 mg/d sodium; ≤ 450 kcal (36 oz) per week sweets/sugar-sweetened beverages; and ≥ three servings per day whole grains (1.1 g of fiber in 10.0 g of carbohydrate; 1.0 oz equivalent servings).

There was no vegetable intake in the Kailuan study questionnaire, and the 2002 National Nutrition and Health Survey of China showed that only 18.4% of Chinese people consumed < 6 g of salt daily. Considering the impact of salt intake in the Chinese population, we used the salt preference index to replace the dietary structure index proposed by the AHA. Since the specific daily salt intake could not be accurately measured, we divided the salt preference into high, medium, and low levels, with low level replacing the ideal level of AHA metrics. The questionnaire provided an approximation of whether an individual's salt preference was "ideal", "intermediate", or "poor" as described previously[8].

Our seven cardiovascular and cerebrovascular health behaviors and factors are as follows: Never-smoker, low salt preference, very active (≥ three times/wk and ≥ 30 min each time) physical activity, BMI < 25 kg/m^2, fasting plasma glucose < 100 mg/dL, total cholesterol < 200 mg/dL, and SBP < 120 mmHg or DBP < 80 mmHg were defined as ideal health behaviors and factors. Intermediate health behaviors and factors were former smoker but not now, medium salt preference, moderately active physical activity, BMI 25.0-29.9 kg/m^2, fasting plasma glucose 100-125 mg/dL or treated to goal, Total cholesterol 200-239 or treated to goal, and SBP 120-139 mmHg or DBP 80-89 mmHg or treated to goal. Poor health behaviors and factors included current smoker, high salt preference, inactive (none), BMI ≥ 30 kg/m^2, fasting plasma glucose ≥ 126 mg/dL, total cholesterol ≥ 240 mg/dL, and SBP ≥ 140 mmHg or DBP ≥ 90 mmHg.

Definition of cardiovascular and cerebrovascular health scores

To capture individual-level changes, we used the Huffman and Capewell method[1], which provides a cardiovascular score based on an aggregate of all seven cardiovascular health metrics (poor = 0 points; intermediate = 1 point; ideal = 2 points; scale: 0-14 points for all metrics). This score was not a risk prediction tool but contributed to assessing individual-level trends amid population-level trends.

Survey questionnaire and anthropometric determination

Specific procedures can be found in prior studies[9-11].

Statistical analysis

SPSS 19.0 software (IBM, Chicago, IL, United States) was used for statistical analyses. Behavioral, sociodemographic, and clinical parameters were described that influenced gender differences. Continuous data are expressed as the mean ± SD.

RESULTS

Out of 57659 people participating in the three physical examinations held from 2006 to 2011, 12461 people had incomplete data on health and behavioral factors; hence 45198 subjects were finally included in the statistical analysis, including 34720 (77.82%) men and 10478 women, respectively. In 2006, the average age was (47.9 ± 11.6) years. Additionally, the proportion of people with ideal physical exercise, low salt diet, ideal body mass index, ideal total cholesterol level, no smoking, ideal blood sugar, and ideal blood pressure was 13.12%, 9.34%, 49.17%, 64.20%, 49.27%, 69.99%, and 20.55% for men, and 12.00%, 9.13%, 61.60%, 64.28%, 98.19%, 78.90%, and 36.92% for women from 2006 to 2007. The 2008-2009 data revealed that the proportion of men with ideal physical exercise, low salt diet, ideal body mass index, ideal total

cholesterol level, no smoking, ideal blood sugar, and ideal blood pressure was 16.09%, 14.04%, 51.94%, 65.02%, 40.18%, 66.44%, and 17.04%, and it was 16.86%, 17.36%, 64.01%, 67.433%, 98.22%, 76.37%, and 42.34% for women. From 2010-2011, the proportion of men with ideal physical exercise, low salt diet, ideal body mass index, and ideal total cholesterol level, no smoking, ideal blood sugar, and ideal blood pressure was 12.22%, 17.65%, 49.40%, 68.33%, 48.17%, 64.67%, and 14.68%, and it was 11.83%, 18.09%, 49.40%, 67.85%, 98.82%, 74.52%, and 37.78% in women. The prevalence of ideal cardiovascular and cerebrovascular health behaviors and factors of different genders from 2006 to 2011 is shown in Table 1 and Table 2. The prevalence of poor and intermediate cardiovascular and cerebrovascular health behaviors and factors of different genders from 2006 to 2011 was described in our previous research[11].

The health scores of men and women in 2006, 2008, and 2010 were 8.46 and 10.02, 8.18 and 10.12, as well as 8.21 and 9.90, respectively; the distribution of cardiovascular and cerebrovascular health behaviors and factor scores of different genders from 2006 to 2011 are shown in Table 3 and Table 4.

The mean ± SD of body mass index, blood pressure, fasting blood glucose, and total cholesterol levels of different genders from 2006 to 2011 are shown in Table 5 and Table 6.

DISCUSSION

Our results revealed that the distribution of cardiovascular and cerebrovascular health behaviors and factors in this study population was low from 2006 to 2011; since the ideal level of population composition was not high, the resultant score was low. Therefore, effective health education programs are needed to improve individual and group health behaviors. Furthermore, the definition of eating habits and physical exercise that we proposed was different from that suggested by the AHA; however, if AHA-defined outlines were implemented, the health behavior and factors and scores of this population might have been worse.

To interpret these results, it is necessary to understand the association between the characteristics of the study population as well as the cardio- and cerebrovascular health in China. China has the largest smoking population[12], with around 300 million adult smokers, which constitute nearly one-third of global smokers, and the economic burden caused by smoking is about 350 million dollars every year[13]. In our study, the number of smokers was half of the entire study population, suggesting that smoking was an important risk factor for CVD and cerebrovascular diseases[14,15]. Henceforth, quitting smoking might reduce the incidence of CVD and cerebrovascular diseases in China[16,17]. The Healthy China 2030 initiative intends to reduce the prevalence of smoking from 27.7% in 2015 to 20.0% by 2030. Hence, all tobacco control measures implemented in China to date should be reviewed, along with existing gaps and future opportunities[13].

In our study, the observation of more than 50.0% of male smokers may be related to the specific population that we surveyed. We surveyed employees of a coal enterprise in northern China, and due to factors, such as work pressure and their own education level, there may be a higher number of smokers among this population. With our health education and promotion efforts, the smoking population will be greatly improved. In 2015, Beijing adopted tobacco control laws that prohibited smoking in indoor public places nationwide and actively made provisions for smoke-free environments in hospitals, schools, and other institutions, thus causing a decline in the smoking rate of adults and adolescents in Beijing to 19.9% and 1.1%, respectively. Beijing was awarded the "World No Tobacco Day Award" twice by the World Health Organization (WHO)[18,19]. Accordingly, we should formulate and implement stricter anti-smoking regulations in this population to increase the number of people who quit smoking.

A predominant risk factor in the Chinese population for cerebrovascular and cardiovascular conditions, including representative hypertension, is a high-salt diet[20,21]. Reduction in dietary salt intake per WHO recommendations, even a modest amount, might show great benefits globally; 1.65 million cases of CVD-associated deaths can be avoided every year, along with significantly reduced expenditure for the health care systems, individuals, and their family members [22]. In our study, the proportion of high salt and low salt diets in this population was not high, and most people had a moderate intake of salt. Unlike Western countries, the majority of salt intake in Western countries comes from processed foods[23]. The salt intake of Chinese residents mainly comes from the salt added in household cooking, which determines that strengthening the popularization of salt reduction knowledge and behavior can significantly reduce the salt intake of Chinese people. In fact, as early as 2017, the Chinese government had set a goal to reduce the national salt intake by 20% by 2030[24]. Local governments such as Beijing, Shanghai, and Shandong have also organized salt reduction projects in many provinces and cities, including promoting low sodium salts and salt reduction tools. We believe that there will be a significant reduction in salt intake in the future.

As another important component of cardiovascular and cerebrovascular health behavior, active physical exercise can not only reduce blood pressure but also improve blood glucose and blood lipid levels along with other indicators[25]. In 2020, the WHO released the Guide to Physical Exercise and Sitting Behavior, which focused on avoiding sedentary behavior, increasing physical activity, and improving physical conditions. For superior health benefits, adults should do either 150-300 min of moderate-intensity or 75-150 of vigorous aerobic exercises every week and focus on strength training[26]. In our study, the population who do not participate in physical exercise on a daily basis is relatively high and shows an upward trend, which may be related to the aging of the population, as we continue to observe this group of people and their exercise behavior decreases with age. This also reminds us that with the arrival of global aging, we need to focus on the exercise status of the elderly population. It is worth mentioning that if we strictly evaluate physical exercise according to the regulations of the WHO, the proportion of people who lack exercise will be higher.

Hence, effective promotion of physical education might lead to increased physical activity in individuals, thus improving population health. Emphasis on preventing stroke is crucial since it increases the burden on public health due

Table 1 Distribution (2006-2007, 2008-2009, and 2010-2011) of ideal levels of cardiovascular and cerebrovascular health metrics for men (Kailuan study)

	2006-2007	2008-2009	2010-2011
Smoking	49.27	40.18	48.17
Salt	9.34	14.04	17.65
Physical activity	13.12	16.09	12.22
Body weight	49.17	51.94	49.40
Glucose	69.99	66.44	64.67
Total cholesterol	64.20	65.02	68.33
Blood pressure	20.55	17.04	14.68

Table 2 Distribution (2006-2007, 2008-2009, and 2010-2011) of ideal levels of cardiovascular and cerebrovascular health metrics for women (Kailuan study)

	2006-2007	2008-2009	2010-2011
Smoking	98.19	98.22	98.82
Salt	9.13	17.36	18.09
Physical activity	12.00	16.86	11.83
Body weight	61.60	64.01	62.73
Glucose	78.90	76.37	74.52
Total cholesterol	64.28	67.43	67.85
Blood pressure	36.92	42.34	37.78

to prolonged disability. The foremost objective of stroke prevention is to manage correctable risk factors like arterial hypertension, a prime contributor to stroke. Therefore, appropriate measures for controlling blood pressure are mandatory for the hypertensive population[27]. According to the WHO, raised blood pressure affects > 1 billion adults globally, with an annual mortality of 9 million individuals, and is considered the chief physiological risk factor for angiocardiopathies[28]. Early and timely interventions for hypertension and comorbidities can reduce the higher expenditures for chronic diseases (*e.g.*, angiocardiopathies and cerebrovascular conditions), as well as quality-of-life deterioration[29].

The WHO formulated the Global NCD Action Plan 2013-2020, which consisted of objectives and a draft framework for holistic monitoring for preventing and controlling noninfectious diseases worldwide. Based on this, it also initiated a joint action with other member countries, the United Nations, as well as other global partners, to lower the smoking rate and the mean sodium consumption by 30% among all individuals aged ≥ 15 years and the entire population by 2025, respectively. Additionally, the prevalence rates of diabetes and obesity as well as elevated blood pressure are reduced by 10% and 25% in the underactive population. Furthermore, the risk of premature death from chronic non-communicable diseases such as CVD is relatively reduced by 25%[30,31].

Although our study was a cross-sectional study, this is an important supplement to databases in related fields, which can provide a basic reference for future research. Our next step should be to enhance the proportion of ideal cerebrovascular and cardiovascular health parameters and behaviors among this subset of the population through intervention-strengthening techniques.

CONCLUSION

The prevalence of ideal cerebrovascular and cardiovascular health parameters and behaviors is low in the Kailuan study population due to inadequate scores of relevant health metrics.

Table 3 Distribution (2006-2007, 2008-2009, and 2010-2011) of cardiovascular and cerebrovascular health score for men (Kailuan study)

Score	Proportion (%)		
	2006-2007	2008-2009	2010-2011
0			0.01
1			0.05
2	0.03	0.23	0.28
3	0.64	0.95	0.92
4	1.84	2.60	2.59
5	4.43	5.60	5.69
6	8.52	10.38	10.46
7	13.77	15.67	15.32
8	18.61	19.61	18.85
9	20.66	18.90	18.22
10	17.43	13.82	14.90
11	9.74	8.03	8.61
12	3.59	3.47	3.39
13	0.52	0.62	0.62
14	0.08	0.05	0.08
Average score	8.46	8.18	8.21

Table 4 Distribution (2006-2007, 2008-2009, and 2010-2011) of cardiovascular and cerebrovascular health score for women (Kailuan study)

Score	Proportion (%)		
	2006-2007	2008-2009	2010-2011
0			0.01
1		0.13	0.06
2		0.06	0.04
3	0.04	0.06	0.10
4	0.24	0.29	0.35
5	0.88	0.99	1.36
6	2.16	2.90	3.22
7	4.98	5.11	6.28
8	10.18	9.27	10.08
9	16.31	14.12	15.74
10	20.95	19.83	20.24
11	23.97	22.89	23.18
12	17.40	18.23	14.96
13	2.65	5.63	3.94
14	0.26	0.66	0.54
Average score	10.02	10.12	9.90

Table 5 Body mass index, blood pressure, fasting blood glucose, and total cholesterol levels of men from 2006 to 2011

	Men (mean ± SD)		
	2006-2007	2008-2009	2010-2011
Body mass index	25.21 ± 3.43	25.02 ± 3.39	25.27 ± 3.37
Systolic blood pressure, mmHg	128.63 ± 18.13	129.16 ± 17.43	128.88 ± 16.03
Diastolic blood pressure, mmHg	83.28 ± 11.18	84.65 ± 10.93	84.56 ± 10.19
Fasting blood glucose, mg/dL	97.27 ± 25.62	99.95 ± 26.57	99.93 ± 24.59
Total cholesterol, mg/dL	187.22 ± 45.38	192.25 ± 51.24	185.51 ± 36.82

Table 6 Body mass index, blood pressure, fasting blood glucose, and total cholesterol levels of women from 2006 to 2011

	Women (mean ± SD)		
	2006-2007	2008-2009	2010-2011
Body mass index	24.34 ± 3.66	24.14 ± 3.61	24.25 ± 3.53
Systolic blood pressure, mmHg	121.97 ± 17.51	119.8 ± 17.14	120.75 ± 16.45
Diastolic blood pressure, mmHg	78.23 ± 10.1	77.86 ± 9.94	78.23 ± 9.83
Fasting blood glucose, mg/dL	94.14 ± 24.34	95.86 ± 27.35	95.84 ± 22.94
Total cholesterol, mg/dL	189.02 ± 37.91	187.28 ± 54.75	186.62 ± 46.8

FOOTNOTES

Author contributions: Yu Y, Liu ZJ, and Wu SL designed the research study; Yu Y, Zhang ZX, Liu ZJ, and Wu SL performed the research; Yin SF was responsible for statistical analysis; Yu Y was responsible for drafting of the manuscript; Wu SL and Liu ZJ contributed equally to this work as co-corresponding authors; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Role of a new inflammation predictor in predicting recurrence of atrial fibrillation after radiofrequency catheter ablation

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Abstract

BACKGROUND

Radiofrequency catheter ablation (RFCA) has become an important strategy for treating atrial fibrillation (AF), and postoperative recurrence represents a significant and actively discussed clinical concern. The recurrence after RFCA is considered closely related to inflammation. Systemic immune inflammation index (SII) is a novel inflammation predictor based on neutrophils, platelets, and lymphocytes, and is considered a biomarker that comprehensively reflects the immune inflammatory status of the body.

AIM

To explore the predictive effect of the SII on AF recurrence after RFCA and its predictive value in combination with the existing APPLE score for AF recurrence after RFCA in patients with non-valvular AF (NVAF).

METHODS

We retrospectively included 457 patients with NVAF first receiving RFCA and classified them into the recurrent or non-recurrent group. We also investigated the predictive role of SII on AF recurrence following RFCA. Finally, we explored and compared the additional predictive value of the SII after combining with the APPLE score.

RESULTS

After 12 months of follow-up, 113 (24.7%) patients experienced recurrence. High SII has been demonstrated to be an independent predictor for postoperative AF recurrence. Receiver operating characteristic and decision curve analysis (DCA), as well as net reclassification improvement (NRI) and integrated discrimination

improvement (IDI) results, showed that SII combined with the APPLE score had higher predictive efficiency than using the SII or APPLE score alone. The area under the curve of the combined model (0.662, 95% confidence interval: 0.602-0.722) significantly increased compared with that of the SII and APPLE scores alone ($P < 0.001$). The combined model resulted in an NRI of 29.6% and 34.1% and IDI of 4.9% and 3.5% in predicting AF recurrence compared with the SII and APPLE scores alone, respectively (all $P < 0.001$). The SII, APPLE score, and their combination demonstrated greater clinical utility than did the treat-all and treat-none strategies over the 20–80% risk threshold according to the DCA.

CONCLUSION

The SII was a predictor of recurrence after RFCA of AF. Moreover, the SII enhanced the predictability of the APPLE score for post-RFCA AF recurrence, providing valuable insights for physicians to optimise patient selection and develop personalised treatment plans.

Key Words: Systemic immune inflammation index; Atrial fibrillation; Radiofrequency catheter ablation; APPLE score; Recurrence

Core Tip: We explored the role of the systemic immune inflammation index (SII) in predicting recurrence of atrial fibrillation (AF) after radiofrequency catheter ablation (RFCA). We show that the SII is a predictive factor for postoperative recurrence of AF after RFCA and enhances the ability of the APPLE score to predict postoperative recurrence of AF.

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INTRODUCTION

Atrial fibrillation (AF), the most common arrhythmia observed in clinical settings, affects 46 million people worldwide [1]. This condition is closely related to increased mortality rates and thromboembolic events, particularly stroke and heart failure, including left ventricular dysfunction, hospitalisation, reduced athletic ability, and reduced quality of life[2].

Radiofrequency catheter ablation (RFCA) is an efficacious method of controlling rhythm. Numerous studies have shown that catheter ablation has marked advantages in preventing AF recurrence, reducing AF burden, and improving long-term outcomes for patients. RFCA has proven to be the first-line therapy for paroxysmal AF, and is recommended as a Class Ia procedure according to international guidelines[3]. However, the recurrence rate of AF after initial catheter ablation has been observed to be as high as 20%-50%[4]. Therefore, the clarity of risk factors for postoperative recurrence in patients with AF after RFCA, as well as establishment of predictive models to estimate the risk of postoperative recurrence, is crucial for assisting the development of individualised treatment plans in clinical practice. Moreover, this can provide new research ideas for reducing AF recurrence after RFCA.

Although numerous studies and meta-analyses have explored the risk factors for AF recurrence after RFCA, these factors alone have limited predictive value for recurrence after RFCA. Therefore, an increasing number of studies have developed scoring systems that integrate multiple risk factors. Scoring systems commonly used in clinical practice to predict AF recurrence after RFCA include the APPLE, CAAP-AF, CHA2DS2-VASc, MB-LATER, and HATCH scores. However, the predictive power of these scoring systems is limited, and their accuracy requires improvement[5]. Therefore, further research is necessary to improve existing risk prediction models.

Recurrence after RFCA is considered closely related to inflammation. Systemic immune inflammation index (SII) is a recently proposed novel inflammation predictor based on neutrophils, platelets, and lymphocytes, and is considered a biomarker that comprehensively reflects the immune inflammatory status of the body. SII was initially used to predict the prognosis of various cancers. Recently, some studies have shown that SII can determine a patient's risk of cardiovascular diseases[6,7]. Zhang *et al*[6] have demonstrated through their research that SII is an independent prognostic factor for persistent left ventricular systolic dysfunction in patients with perinatal cardiomyopathy. Therefore, SII may be a useful tool for identifying high-risk patients with perinatal cardiomyopathy. A study by Öcal *et al*[7] showed that SII could better predict the length of hospital stay and long-term prognosis of patients with ST-segment elevation myocardial infarction receiving primary percutaneous coronary intervention treatment. However, limited research exists on SII in predicting the recurrence of AF. Therefore, this study aimed to explore the correlation between the SII and AF recurrence after RFCA and estimate the additional predictive power of the SII when administered alongside the APPLE score. This study aimed to provide a basis for accurately assessing the recurrence risk after RFCA in patients with AF, as well as information for guiding the development of personalised treatment strategies.

MATERIALS AND METHODS

Study population

This unicentric retrospective study retrospectively included patients with non-valvular AF (NVAF) who were hospitalised at Weifang People's Hospital and underwent RFCA for AF for the first time between August 2019 and July 2022. The inclusion criteria were as follows: (1) Diagnosed with NVAF or paroxysmal or non-paroxysmal AF; (2) Age > 18 years; (3) Suitable for first-time radiofrequency ablation for AF; and (4) Provision of informed consent for this process. The exclusion criteria were as follows: (1) Acute and chronic inflammatory diseases, liver and kidney dysfunction, coagulation dysfunction, or severe heart failure indicating contraindication for surgery; (2) Incomplete clinical and imaging data; (3) Severe bradycardia, such as sick sinus syndrome or third-degree atrioventricular block; and (4) Left atrial appendage thrombosis as identified on echocardiography.

Data collection

All baseline demographic, clinical, laboratory, and echocardiographic data were obtained from the electronic medical information record system of Weifang People's Hospital. The following baseline data were collected: Sex, age, height, weight, smoking history, medical history (heart failure, hypertension, diabetes mellitus, vascular disease, coronary atherosclerotic heart disease, prior stroke/transient ischemic attack, and type of AF), and echocardiographic parameters (left atrial diameter, left ventricular ejection fraction, and left ventricular end-diastolic diameter). We collected the following laboratory parameters: High-density lipoprotein cholesterol; total cholesterol; triglyceride; low-density lipoprotein cholesterol; B-type natriuretic peptide; serum uric acid; serum creatinine; fasting blood glucose; and white blood cell, lymphocyte, monocyte, neutrophil, and platelet counts. Blood samples were collected from all included patients on the second day after admission and before RFCA.

The Chronic Kidney Disease Epidemiology Collaboration formula was applied in calculating the estimated glomerular filtration rate (eGFR)[8]. The SII level was computed using the following equation: Neutrophils × platelets ÷ lymphocytes [9]. Furthermore, CHA2DS2-VASc and APPLE scores for each patient were calculated based on relevant scoring criteria. The scoring criteria for CHA2DS2-VASc score are as follows: Hypertension, congestive heart failure (CHF), diabetes mellitus, vascular disease, age 65 to 74 years, and female sex (1 point each); and previous history of transient ischemic attack or stroke and age ≥ 75 years (2 points each)[10]. The scoring criteria for the APPLE score are as follows: Age ≥ 65 years, persistent AF, left atrial diameter ≥ 43 mm, impaired eGFR ≤ 60 mL/min/1.73 m^2, and EF < 50% (1 point each)[11].

Radiofrequency ablation procedure

Transthoracic echocardiography was conducted before the procedure to assess heart structure and function. Before the procedure, transesophageal echocardiography or cardiac computed tomography angiography (CTA) was performed to exclude the presence of a left atrial thrombus. Before ablation, all patients underwent cardiac CTA to assess the structures of the pulmonary vein and left atrium. All operational procedures were conducted under appropriate analgesia with fentanyl. A femoral venous puncture was performed using the Seldinger technique, and a standard ten-pole catheter was interposed into the coronary sinus through the right femoral vein. Subsequently, a single trans-septal puncture was conducted under fluoroscopic direction. After a single trans-septal puncture, a pentary catheter (Biosense Webster, Irvine, CA, United States) was first inserted for modelling. After modelling was completed, the pentary catheter was replaced by an ablation catheter for ablation. Unfractionated heparin was administered intravenously before or immediately following a transseptal puncture, and an activated clotting time of 250-300 seconds was maintained. Radiofrequency ablation was conducted under the guidance of the CARTO3 navigation system (Biosense Webster, Irvine, CA, United States). The ablation catheters used during the ablation process were all catheters with pressure sensors (THERMOCOOL SMARTTOUCH, SF, Catheter).

All patients with AF underwent circumferential pulmonary vein isolation (CPVI). In cases of non-paroxysmal AF, the operator could perform additional linear ablation based on their discretion (left atrial roof, bottom, posterior wall, mitral isthmus, and tricuspid isthmus lines). After completing the ablation, if the AF did not terminate, electrical cardioversion was conducted to restore sinus rhythm. At the end of the ablation, isolation of all pulmonary veins with a bidirectional block was confirmed[12].

Follow-up and endpoint

After RFCA, all patients were prescribed oral anticoagulants and amiodarone for 3 months. Subsequently, oral anticoagulants were continued for patients with a high risk of stroke (CHA2DS2-VASc scores ≥ 2 and ≥ 3 for male and female patients, respectively). The outpatient follow-ups at the 1st, 3th, 6th, and 12th month after ablation were conducted for 12 months. Each follow-up visit included clinical assessment, 12-lead electrocardiogram (ECG), and 24-hours Holter monitoring. If the patients had any symptoms related to AF, we performed further ECGs and Holter ECG examinations. Our endpoint included AF recurrence following catheter ablation in the 1-year follow-up period. After blanking for 3 months, any atrial arrhythmia lasting over 30 s on 12-lead ECG or 24-hours Holter monitoring was defined as AF recurrence[13]. Because all patients are regularly reviewed according to medical orders upon discharge, we can obtain this information by consulting the electronic medical information record system of Weifang People's Hospital.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, United States), R programming language (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria), and MedCalc software (version 20.0, MedCalc Software, Ostend, Belgium). Normally distributed continuous data were expressed as

mean ± SD, while abnormally distributed data were expressed as median (interquartile range). Categorical data were indicated as numbers (percentages). Categorical data among different groups were compared using Fisher's exact test or the χ^2 test. Comparison among groups was performed using a Student's *t*-test or the Mann–Whitney *U* test.

Factors independently predicting AF recurrence risk were identified using univariate and multivariate logistic regression. Variables satisfying $P < 0.05$ from univariate regression were incorporated into multivariable regression, and those associated with the SII and APPLE scores were excluded from the multivariate logistic regression analysis. Subsequently, the receiver operating characteristic (ROC) curve was plotted to calculate the best threshold of the SII to predict AF recurrence. Additionally, we utilised the area under the curve (AUC), relative integrated discrimination improvement (IDI), and net reclassification improvement (NRI) to estimate the significance of SII, APPLE score, and their combination in predicting AF recurrence following catheter ablation among patients with AF. Finally, we conducted a pairwise comparison of the ROC curves using the DeLong test, and decision curve analysis (DCA) was used to assess the clinical usefulness. Statistical significance was set at $P < 0.05$ (two-tailed).

RESULTS

Baseline patient characteristics

Baseline characteristics of the study patients are presented in Table 1. Overall, 457 patients (mean age 61.32 ± 9.97 years, 62.8% male) with NVAF who received RFCA were included in this study. The mean CHA2DS2-VASc score was 2.09 ± 1.61. The AF type was paroxysmal and persistent in 68.5% and 31.5% of the patients, respectively.

Patients were classified into the following two groups: Those with no AF recurrence (non-recurrence, $n = 344$) and those with AF recurrence (recurrence, $n = 113$), with an incidence of AF recurrence of 24.72%. The frequency of non-paroxysmal AF remarkably increased among patients with AF recurrence. APPLE scores remarkably increased in the recurrence group compared to that in the non-recurrence group. Additionally, the left atrial diameter in the recurrence group dramatically increased compared to that in the non-recurrence group. Furthermore, B-type natriuretic peptide, neutrophils, lymphocytes, and SII levels increased in the recurrence group, whereas eGFR level decreased compared to that in the non-recurrence group. However, no significant differences were detected in other parameters between these two groups.

Association between SII and recurrence of AF

As shown in Figure 1A, the recurrence group had a significantly higher SII level than the non-recurrence group (516.11 ± 260.91 *vs* 428.37 ± 221.24). Additionally, based on multivariate regression, SII [odds ratio (OR): 2.257; 95% confidence interval (95%CI): 1.219-4.179, $P = 0.001$] and APPLE score (OR: 1.723; 95%CI: 1.338-2.219, $P < 0.001$) independently predicted the recurrence risk among patients following radiofrequency ablation (Table 2). ROC curve analysis indicated that the AUC of SII was 0.597 (95%CI: 0.53500.659, $P < 0.001$; Figure 1A), with the best truncation value of 619.27 (sensitivity: 31.86% and specificity: 85.47%). According to the best truncation value, patients were classified into the low (SII < 619.27) or high (SII ≥ 619.27) SII group. The AF recurrence rate of the high SII group significantly increased compared to that of the low SII group (20.81% *vs* 41.37%, $P < 0.001$; Figure 1B), and the AUC of the APPLE score was 0.624 (95%CI: 0.563-0.684, $P < 0.001$).

SII in the refinement of risk stratification for AF recurrence

We performed an ROC curve analysis to assess the significance of SII and APPLE scores in predicting AF recurrence. The AUCs for the SII and APPLE scores were 0.597 (95%CI: 0.535–0.659, $P < 0.001$; Figure 2A) and 0.624 (95%CI: 0.563-0.684, $P < 0.001$), respectively (Figure 2B). Furthermore, we applied the best truncation value derived from the ROC curve analysis to convert the SII into a binary variable and subsequently integrated this binary SII variable into the APPLE score. The AUC of the combined model was 0.662 (95%CI: 0.602–0.722, $P < 0.001$; Figure 2C), remarkably increased compared with that of the SII and APPLE scores alone ($P < 0.001$; Figure 2D).

To further assess the additional predictive capacity of the combined model, we performed the IDI and NRI analyses. Based on the NRI and IDI analyses, the combined model significantly improved the prediction of AF recurrence after RFCA compared with the SII and APPLE scores alone. Compared with using the SII and APPLE scores alone, the use of the combined model resulted in an NRI of 29.6% and 34.1% (all $P < 0.001$) and an IDI of 4.9% and 3.5% (all $P < 0.001$), respectively, in predicting AF recurrence (Table 3).

DCA was used to evaluate clinical utility (Figure 3), demonstrating that the SII, APPLE score, and their combination were effective (compared to treat-all and treat-none strategies) over the 20%-80% risk threshold. The combined model exhibited superior clinical utility compared to the SII and APPLE scores in the DCA. Therefore, this combined model is promising for clinical use.

DISCUSSION

RFCA is an effective and reliable therapy for drug-resistant AF; however, recurrence after RFCA remains a major clinical issue. In this study, the 1-year recurrence rate in patients with AF who received radiofrequency ablation for the first time was 24.7%, which was comparable to that in previous reports[4]. Thus, this study explored the correlation between simple and easily obtainable clinical variables before ablation and AF recurrence after RFCA. The SII and APPLE were found to

Table 1 Baseline characteristics of study population

Characteristics	All patients (*n* = 457)	Patients without recurrence (*n* = 344)	Patients with recurrence (*n* = 113)	*P* value
Age (years)	61.32 ± 9.97	60.92 ± 10.15	62.56 ± 9.33	0.128
Male sex	287 (62.8)	223 (64.8)	64 (56.6)	0.145
BMI (kg/m^2)	25.68 ± 3.44	25.71 ± 3.51	25.57 ± 3.24	0.683
Hypertension	221 (48.4)	161 (46.8)	60 (53.1)	0.245
Diabetes mellitus	87 (19)	65 (18.9)	22 (19.5)	0.893
Stroke/TIA	49 (10.7)	40 (11.6)	9 (8)	0.275
Heart failure	44 (9.6)	31 (9)	13 (11.5)	0.436
Smoking	78 (17.1)	60 (17.4)	18 (15.9)	0.711
NPAF	144 (31.5)	92 (26.7)	52 (46)	< 0.001
CHA2DS2-VASc score	2.09 ± 1.61	2.04 ± 1.62	2.22 ± 1.59	0.32
APPLE	1.004 ± 0.95	0.88 ± 0.86	1.37 ± 1.08	< 0.001
LVEF (%)	62.48 ± 7.35	62.74 ± 7.18	61.69 ± 7.82	0.187
LAD (mm)	39.3 ± 5.52	38.71 ± 5.42	41.08 ± 5.45	< 0.001
LVDD (mm)	49.91 ± 4.38	49.85 ± 4.18	50.11 ± 4.94	0.58
TC (mmol/L)	4.38 ± 1.01	4.35 ± 1.00	4.45 ± 1.07	0.409
TG (mmol/L)	1.60 ± 1.11	1.60 ± 1.04	1.62 ± 1.3	0.856
LDL (mmol/L)	2.6 ± 0.91	2.56 ± 0.88	2.69 ± 0.98	0.200
HDL (mmol/L)	1.15 ± 0.31	1.15 ± 0.33	1.15 ± 0.24	0.86
Glucose (mmol/L)	5.6 ± 1.74	5.6 ± 1.8	5.61 ± 1.53	0.978
BNP (pg/mL)	98 (51, 158)	93 (46.25, 155.5)	130 (61, 186.5)	0.022
eGFR (mL/min/1.73 m^2)	94.91 ± 14.18	95.72 ± 14.02	92.44 ± 14.43	0.033
Uric acid (μmol/L)	337.98 ± 90.37	338.91 ± 87.36	335.18 ± 99.33	0.704
Creatinine (mmol/L)	68.25 ± 51.62	68.54 ± 58.73	67.37 ± 16.9	0.834
White blood cell count (× 10^9/L)	6.15 ± 1.44	6.1 ± 1.41	6.3 ± 1.5	0.184
Neutrophils (× 10^9/L)	3.68 ± 1.15	3.6 ± 1.11	3.95 ± 1.26	0.005
Lymphocytes (× 10^9/L)	1.93 ± 0.58	1.97 ± 0.57	1.81 ± 0.58	0.012
Monocytes (× 10^9/L)	0.39 ± 0.26	0.4 ± 0.3	0.39 ± 0.11	0.722
Platelet count (× 10^9/L)	215.19 ± 53.3	214.87 ± 53.28	216.15 ± 53.59	0.824
SII	450.06 ± 234.47	428.36 ± 221.24	516.11 ± 260.91	0.002

Data were expressed as mean ± SD, median with 25th and 75th percentile or *n* (%). BMI: Body mass index; NPAF: Non-paroxysmal atrial fibrillation; LVEF: Left ventricular ejection fraction; LAD: Left atrial diameter; LVDD: Left ventricular end-diastolic diameter; TC: Total cholesterol; TG: Total glyceride; LDL: Low density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol; BNP: B-type natriuretic peptide; eGFR: Estimated glomerular filtration rate; SII: Systemic immune inflammation index.

provide important information regarding the risk of AF recurrence after RFCA. Additionally, SII was demonstrated to provide additional predictive value to the APPLE regarding recurrence after RFCA, presenting increased clinical applicability. This information is crucial for formulating treatment plans and the post-treatment follow-up of patients with AF.

Inflammatory factors, which are recognised as biological markers, can predict the incidence of AF and its recurrence after RFCA[14]. This may be due to the interaction between inflammation and oxidative stress, which further exacerbates the damage, necrosis, apoptosis, and fibrosis of atrial muscle cells, leading to electrical and structural remodelling of the atrium, thereby promoting the occurrence and maintenance of AF[15]. As inflammatory cytokines, interleukin (IL)-6, IL-1β, and tumour necrosis factor (TNF) can cause the proliferation and activation of cardiac fibroblasts, leading to myocardial fibrosis[16]. However, although cardiac magnetic resonance imaging is useful for evaluating left atrial fibrosis [17], owing to its high cost, it has not been widely used in clinical practice. Additionally, detecting inflammatory indicators, such as TNF, IL-1β, and IL-6, requires specific detection methods and unconventional testing in clinical work.

Table 2 Univariate and multivariate Logistic regression analysis of atrial fibrillation recurrence

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
NPAF	2.335 (1.503-3.627)	< 0.001		
APPLE	1.689 (1.351-2.112)	< 0.001	1.723 (1.338-2.219)	< 0.001
LAD	1.084 (1.041-1.129)	< 0.001		
BNP	1.002 (1-1.003)	0.023	1 (0.998-1.002)	0.901
eGFR	0.985 (0.97-0.999)	0.035		
Neutrophils	1.297 (1.08-1.557)	0.005		
Lymphocytes	0.608 (0.412-0.899)	0.013		
High SII	2.686 (1.637-4.406)	< 0.001	2.257 (1.219-4.179)	0.01

OR: Odds ratio; 95%CI: 95% confidence interval; NPAF: Non-paroxysmal atrial fibrillation; LAD: Left atrial diameter; BNP: B-type natriuretic peptide; eGFR: Estimated glomerular filtration rate.

Table 3 Measures of predictive accuracy and improvement using systemic immune inflammation index +APPLE score in prognostication of recurrent atrial fibrillation

		NRI	*P* value	IDI	*P* value
SII	APPLE	0.127	0.2347	0.014	0.341
SII	SII + APPLE	0.296	0.00392	0.049	< 0.001
APPLE	SII + APPLE	0.341	0.00037	0.035	< 0.001

IDI: Integrated discrimination improvement; NRI: Net reclassification improvement; SII: Systemic immune inflammation index.

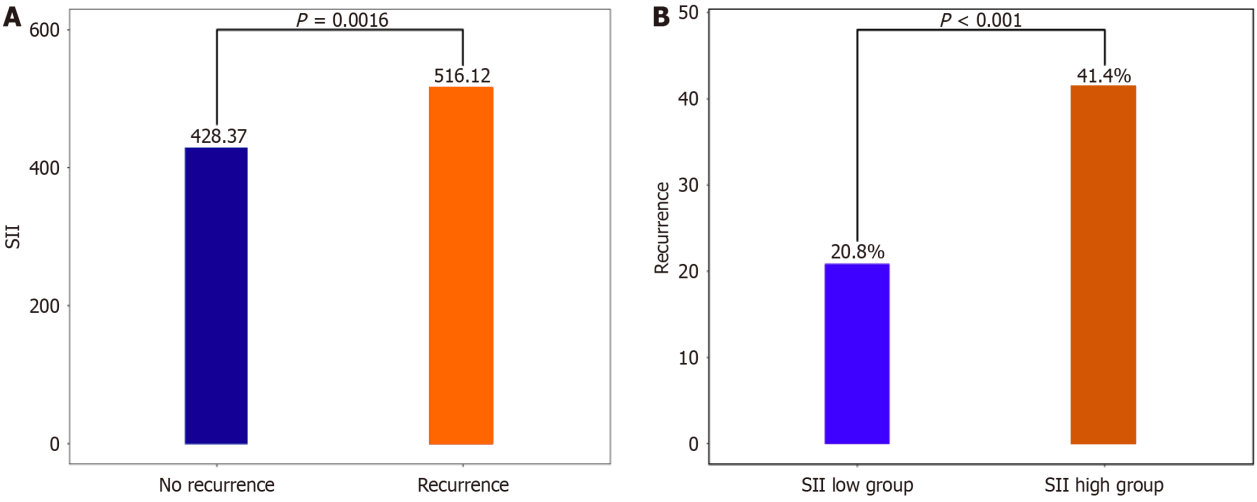

Figure 1 Comparison of variables between two groups. A: Comparison of systemic immune inflammation index level; B: The patients developing atrial fibrillation recurrence post-ablation divided into the low group and the high group by the optimal cut-off value of pre-ablation systemic immune inflammation index level.

Therefore, we need an easily accessible and cost-effective method to evaluate inflammation and the resulting myocardial fibrosis.

Recently, numerous studies have used inflammatory factors, such as C-reactive protein, to predict the prognosis of AF. However, the types of inflammatory cells involved in these inflammatory factors are relatively small, mostly one or two, and their response efficiency to the immune inflammatory state of the body is poor. The SII is a new and convenient inflammatory marker calculated based on neutrophils, lymphocytes, and platelets. It offers a more comprehensive reflection of the body's inflammatory state than assessing individual white blood cells, neutrophils, and lymphocytes

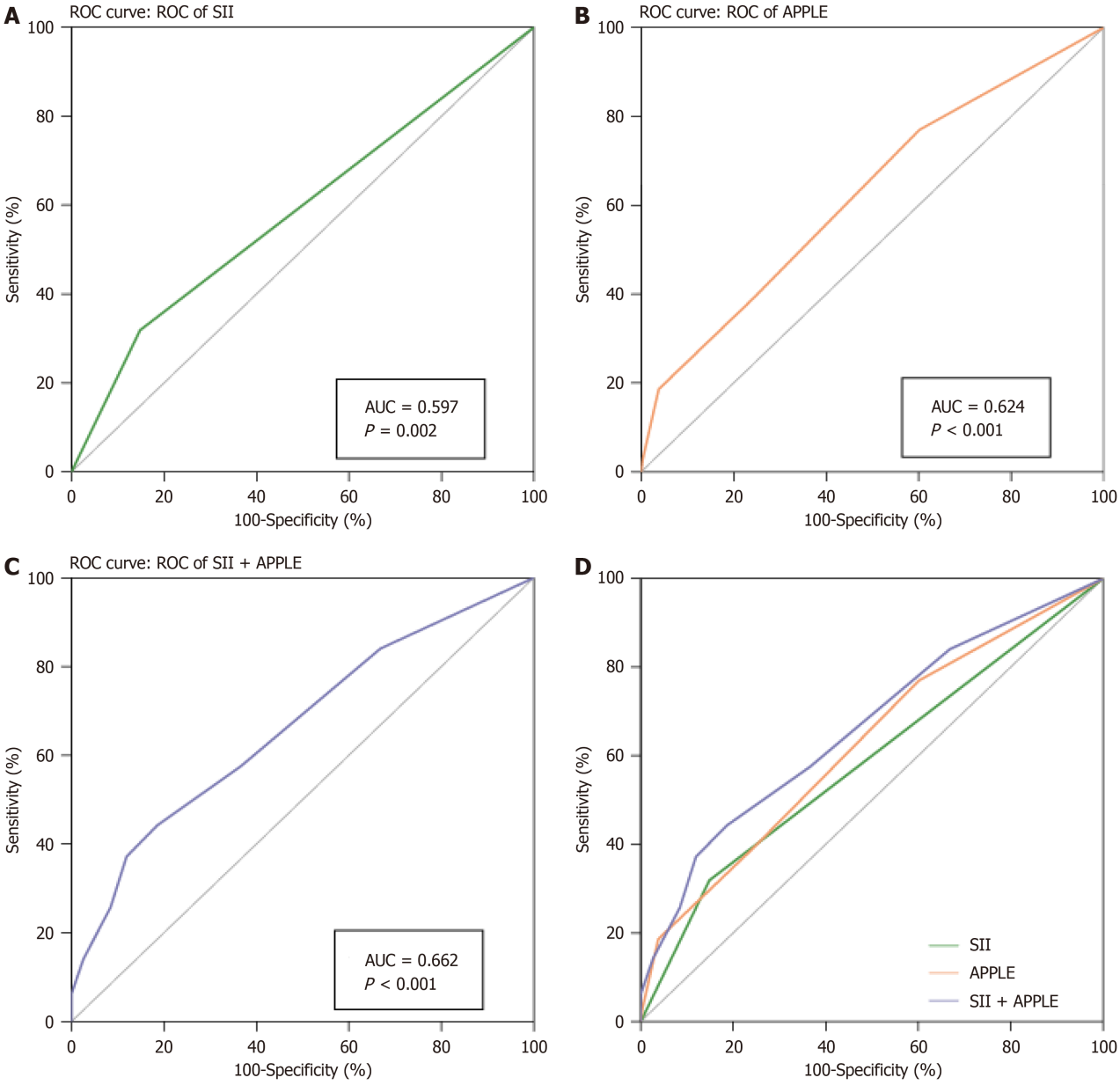

Figure 2 Receiver operating characteristic curves and comparison of various variables. A: Receiver operating characteristic (ROC) of systemic immune inflammation index (SII) for predictor of recurrence of atrial fibrillation (AF) after radiofrequency catheter ablation (RFCA); B: ROC of APPLE score for predictor of recur-rence of AF after RFCA; C: ROC of the combined model for predictor of recurrence of AF after RFCA; D: ROC of SII, APPLE score, and the combined model for predictor of recurrence of AF after RFCA. ROC: Receiver operating characteristic; SII: Systemic immune inflammation index.

[18]. Elevated neutrophil and platelet counts indicate activation of the inflammatory pathway, whereas an increase in lymphocytes indicates activation of the immune pathway[19,20]. One plausible reason for heightened SII levels is the simultaneous increase in neutrophil and platelet counts, which can secrete large amounts of vascular endothelial growth factors, thereby accelerating the release of inflammatory factors[21,22]. Alternatively, a decrease in lymphocytes associated with systemic stress may contribute to an inflammatory response[22]. Building on these insights, Lin *et al*[23] proved that the SII is a potential biomarker of AF in patients presenting with ischemic stroke. Kaplan *et al*[24] expanded on this by demonstrating that, for patients with paroxysmal AF, an increase in AF recurrence following cryo-based ablation might be associated with a higher preprocedural SII. This study contributes significantly to the body of knowledge as it identifies preoperative SII after radiofrequency ablation as an independent predictor of postoperative recurrence. Moreover, the SII enhanced the significance of the APPLE score in predicting post-RFCA AF recurrence. The SII included in this study provides highly accessible data for clinical practice, enhancing the significance of the APPLE score in predicting AF recurrence without additional examination costs, thereby making it suitable for promotion in clinical practice.

This study investigated the recurrence of AF, specifically late recurrence, within 3-12 months after the first RFCA. Previous studies have shown that the APPLE score is mainly used for late AF recurrence after RFCA[11]; therefore, this score is appropriate to use for research. The results of this study also demonstrate the application value of the APPLE score in predicting the recurrence of AF after RFCA. The APPLE score contains age > 65 years (A), persistent AF (P),

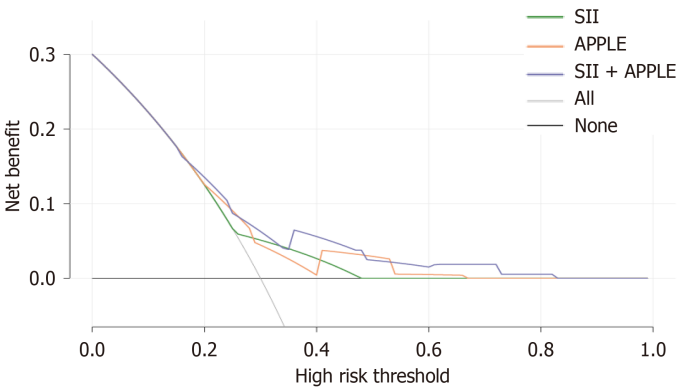

Figure 3 Decision curve analysis of the systemic immune inflammation index, APPLE score and combined model. SII: Systemic immune inflammation index.

chronic renal insufficiency (P), left atrial diameter ≥ 43 mm (L), and left ventricular ejection fraction < 50% (E) as independent predictive factors for recurrence after radiofrequency ablation. The predictive scoring system proposed by Kornej *et al*[25] assigns one point to each risk factor, resulting in a possible score range of 0-5 points. Further external investigations verify the good predicting performance of the APPLE score for AF recurrence post-RFCA and provide good differentiation among populations with low, moderate, and high risk of AF recurrence following radiofrequency ablation of AF[26,27]. As demonstrated by Kornej *et al*[28], the APPLE score was significant for predicting left atrial low-voltage areas. Additionally, studies have shown that a surgical approach targeting low-voltage areas in the left atrium for matrix modification based on CPVI is more effective than CPVI[29]. Nevertheless, whether the SII helps predict low-voltage areas in the left atrium requires further research.

The efficacy of SII in enhancing the prediction of AF recurrence after RFCA using the APPLE score may be related to the following aspects: First, studies have shown that SII is positively correlated with age, with higher levels of SII corresponding with an increase in age[30]. Age is also an independent risk factor for APPLE score. Second, a study on the adult population in the United States found a positive correlation between SII and chronic kidney disease (CKD), and SII can be considered a positive indicator for timely identification and treatment guidance of CKD[31]. Additionally, chronic renal insufficiency is an independent risk factor for the APPLE score. Furthermore, Tang *et al*[32]'s research indicates that SII is associated with CHF. The high level of SII is closely related to the poor short-term prognosis in critically ill patients with CHF, including 30-and 90-day and hospital all-cause mortalities, as well as the occurrence of major cardiovascular adverse events, and is expected to be a simple and effective prognostic evaluation indicator. Similarly, left ventricular ejection fraction < 50% is an independent risk factor for APPLE score. Finally, studies have shown that SII is significantly elevated in patients with persistent AF[33]. Moreover, persistent AF is an independent risk factor for the APPLE score. Therefore, the SII enhanced the significance of the APPLE score in predicting AF recurrence after RFCA.

A study compared the predictive abilities of known AF scoring systems (MB-LATER, CHADS2, CHA2DS2-VASc, BASE-AF2, CAAP-AF, APPLE, and HATCH) in a large Chinese cohort of patients with AF who underwent RFCA[34]. According to NRI and IDI, the MB-LATER score demonstrated superior performance in predicting post-ablation AF recurrence in this population. However, in this study, owing to the lack of statistical analysis of patients with early recurrence after RFCA, MB-LATER scores could not be obtained. In the future, we plan to conduct further research to estimate the additional predictive value of the SII for the MB-LATER score.

This study had some limitations. First, it relied exclusively on research data derived from a solitary retrospective study conducted at a single tertiary hospital. The small sample size and a lack of long-term continuous recording of heart rhythm post-ablation introduce a potential source of unavoidable bias. Therefore, further validation through multicentre prospective studies is required to address these limitations and enhance the generalisability of the findings. Second, in this study, an intracardiac monitor was not used to perform long-term continuous heart rhythm monitoring on patients after RFCA, which may lead to missed diagnosis in some asymptomatic patients with paroxysmal AF and result in a low recurrence rate. Finally, this study was conducted during the COVID-19 pandemic, which may have led to missing follow-ups of some patients and resulting in bias.

CONCLUSION

The SII, as a new inflammatory marker, contributes to predicting AF recurrence post-RFCA. Moreover, the SII enhanced the significance of the APPLE score in predicting AF recurrence after RFCA. This marker can help physicians optimise patient selection and develop personalised treatment plans.

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FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

Nocturnal sentry duty and cardiometabolic characteristics in armed forces personnel

Yen-Po Lin, Yi-Chiung Hsu, Ko-Huan Lin, Kun-Zhe Tsai, Chen-Chih Chu, Yen-Chen Lin, Gen-Min Lin

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Abstract

BACKGROUND

Sleep deprivation can lead to increased body weight and blood pressure (BP), but the latent effects of partial sleep deprivation related to required night sentry duties within a short-term period on cardiometabolic characteristic changes in military personnel are unclear.

AIM

To investigate the association between night sentry duty frequency in the past 3 months and cardiometabolic characteristics in armed forces personnel.

METHODS

A total of 867 armed forces personnel who were aged 18-39 years and did not take

any antihypertensive medications in Taiwan in 2020 were included. The frequency of night sentry duty was self-reported *via* a questionnaire (average number of night sentry shifts per month for the past 3 months). Hemodynamic status was assessed *via* the resting BP and pulse rate (PR). Cardiometabolic risk factors were defined according to the International Diabetes Federation criteria. Multivariable linear regression analyses of the associations between night sentry duties and PR, BP, and other metabolic syndrome (MetS) marker levels were performed, with adjustments for age, sex, substance use, body mass index and aerobic fitness. Multiple logistic regression analysis was carried out to determine the associations between night sentry duties and the prevalence of each MetS feature.

RESULTS

There was an association between night sentry duties and PR [standardized β (standard error) = 0.505 (0.223), P =0.02], whereas there was no association with systolic and diastolic BP. In addition, there was an inverse association between night sentry duties and high-density lipoprotein cholesterol (HDL-C) levels [standardized β = -0.490 (0.213), P = 0.02], whereas there was no association with the other metabolic marker levels. Compared with personnel without night sentry duties, those with ≥ 1 night sentry shift/month had a greater risk of impaired fasting glucose (≥ 100 mg/dL) [odds ratio: 1.415 (confidence interval: 1.016-1.969)], whereas no associations with other MetS features were found.

CONCLUSION

Among military personnel, the burden of night sentry duty was positively associated with the resting PR but inversely associated with HDL-C levels. In addition, personnel with partial sleep deprivation may have a greater risk of impaired fasting glucose than those without partial sleep deprivation.

Key Words: Armed forces personnel; Cardio-metabolic characteristics; Night sentry duty; Partial sleep deprivation

Core Tip: This study examined the associations between the mean frequency of night sentry duty in the past 3 months and cardiometabolic characteristics in armed forces personnel. We found an association between the frequency of night sentry duty and pulse rate [PR, standardized β (standard error) = 0.505 (0.223), P = 0.02] and an inverse association with high-density lipoprotein cholesterol levels [standardized β = -0.490 (0.213), P = 0.02], whereas there was no association with systolic or diastolic blood pressure or other metabolic biomarker levels. In addition, personnel with ≥ 1 night shift/month had a greater risk of impaired fasting glucose. In conclusion, the latent effects of partial sleep deprivation in military personnel may increase the resting PR and lead to metabolic abnormalities.

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INTRODUCTION

Sleep deprivation, also known as sleep insufficiency, is defined as an inadequate quality and/or duration of sleep to support decent performance, alertness and health[1]. In the U.S., sleep deprivation is estimated to affect one-third of Americans, with an increased prevalence in recent years[2]. Sleep deprivation can cause unstable moods, such as erratic behavior, anxiety, depression and irritability, and lead to poor cognitive function and psychotic episodes[3-5]. In addition, insufficient sleep has been linked to adverse somatic changes, *e.g.*, obesity, diabetes, increased blood pressure (BP) and heart rate, and cardiovascular diseases[6-10]. These psychosomatic adverse effects of sleep deprivation may be related to the sympathetic nervous system[11] and hypothalamic-pituitary-adrenal system activation[12]. However, most of these previous studies highlighted the effects of total sleep deprivation, whereas few studies have investigated the effects of partial sleep deprivation, which is characterized by short-term interruptions (2-3 hours) during sleep at night, with a frequency of less than twice a week.

Armed forces personnel experience greater mental stress and receive regular training to maintain superior physical fitness. On military bases, armed forces personnel are required to take night sentry shifts with a span of a few hours, which interrupts their sleep at night. It is estimated that the frequency of night sentry duty for armed forces personnel in Taiwan is approximately once per week. In the United States and Taiwan, the prevalence of overweight or obesity and metabolic syndrome (MetS) has increased to over 40% among all military personnel[13,14]. Since the latent effects of partial sleep deprivation on cardiometabolic abnormalities are unclear, this study aimed to clarify the associations of night sentry duties with hemodynamic and metabolic characteristics in military personnel, who have rarely been invest-

igated in Taiwan or other regions.

MATERIALS AND METHODS

Study population

This cross-sectional study included 867 military participants from the ancillary Cardiorespiratory Fitness and Health in Armed Forces sleep study conducted in Taiwan in 2020. The ancillary study has been described in detail previously[15,16]. In summary, this study aimed to examine the sleep behaviors and comorbidities of military personnel and their associations with cardiometabolic health. Those with any antihypertensive, lipid-lowering or antidiabetic medication use were excluded from this study. The study design was approved by the Ethics Committee of the Mennonite Christian Hospital (No. 16-05-008), Hualien City, Taiwan, and was performed in accordance with the Helsinki Declaration, as revised in 2013. All participants were informed of the protocol of this study and provided written informed consent.

Night sentry duty assessment

The participants responded to a questionnaire concerning their frequency of night sentry duty (days per month) in the past 3 months, which was reported as 0, 1, 2, 3, 4, or 5 days. The span of each night sentry shift was limited to 2-4 hours, which was between a quarter and a half of the total nocturnal sleep time (8 hours) according to the regulation of each military base. Participants who had to work at night and had total nocturnal sleep deprivation were excluded from this study.

Definitions of cardio-metabolic characteristics

The participants were asked to have an uninterrupted nocturnal sleep duration of 8 hours and fast without any caffeine-containing or sympathomimetic agent use for longer than 12 hours before the health examination in 2020. The participants' BPs and pulse rates (PRs) were measured once on the right upper arm by an automatic device *via* the oscillometric method (FT201 Parama-Tech Co., Ltd., Fukuoka, Japan) after a 15-minute rest period and with the participant in a seated position[17-20]. If the initial systolic BP level was ≥ 130 mmHg and/or diastolic BP was ≥ 80 mmHg, a second BP measurement was performed, and the final BP level was defined as the average of the initial and second BP measurements. In addition, if the initial PR was < 50 beats/min or ≥ 100 beats/min, the participant was asked to take a second break for 15 minutes, and the PR was rechecked directly by a physician for one minute, which was treated as the final value. Echocardiography was performed to assess the left ventricular mass (LVM), left ventricular ejection fraction (LVEF) and left atrium (LA) diameter according to the latest United States guidelines[21] in selected participants (n = 280).

According to the International Diabetes Federation's criteria for Chinese individuals[21], MetS is defined as having three or more of the following clinical features: (1) Central obesity defined by a waist circumference (WC) ≥ 80 cm for women and ≥ 90 cm for men; (2) An impaired fasting plasma glucose (FPG) level ≥ 100 mg/dL; (3) Hypertriglyceridemia defined by a plasma triglyceride level ≥ 150 mg/dL; (4) A high-density lipoprotein cholesterol (HDL-C) level < 50 mg/dL for women and < 40 mg/dL for men; and (5) Hypertension defined by a systolic BP ≥ 130 mmHg and/or a diastolic BP ≥ 85 mmHg at rest[22]. Triglyceride, FPG, and HDL-C levels were analyzed *via* an automated analyzer (Olympus AU640, Kobe, Japan)[23-25].

Covariates

The body height and body weight of each participant were measured while they were standing during the health examination in 2020. Body mass index (BMI) was defined as the body weight (kg) divided by the body height squared (m^2). Body surface area was calculated to assess the LVM index according to the Dubois formula[26]. The participants self-reported their habits for substance use, such as smoking, betel nut chewing and alcohol consumption (active *vs* former/never)[27,28]. Notably, betel nut consumption is prevalent in Southeastern Asian individuals and has been associated with several metabolic disorders[29,30]. In addition, the aerobic fitness of each participant was evaluated *via* the time to complete a 3000-m run test following the health examination in the same year.

Statistical analysis

The clinical characteristics of the participants who were classified into 3 groups by night sentry duty frequency (0, 1-2, and ≥ 3 shifts/month) were compared *via* the chi-square test for categorical variables and analysis of variance (ANOVA) for continuous variables. For the selected participants who underwent echocardiography, the LVM index, LVEF and LA diameter were compared *via* analysis of covariance (ANCOVA), with adjustments for age, sex and systolic BP. Multivariable linear regression analyses of the associations of night sentry duty (treated as a continuous variable) with the PR, BP, and other MetS biomarkers were performed separately, with adjustments for age, sex and substance use (Model 1) and additionally for BMI and cardiorespiratory fitness (Model 2). Multivariate logistic regression analysis was carried out to determine the associations of night sentry duty (treated as a categorical variable) with the prevalence of MetS and its related features separately. The covariates in the models were selected because of their potential as contributors to MetS. Statistical analyses were performed *via* SPSS software for Windows (SPSS Inc., Chicago, IL, United States). A P value of < 0.05 was considered indicative of statistical significance.

RESULTS

Table 1 reveals the clinical characteristics of participants without night sentry shifts in the past 3 months (n = 506), those with 1-2 night sentry shifts/month (n = 220) and those with ≥ 3 night sentry shifts/month (n = 141) on the basis of their responses to the questionnaire. The mean age was approximately 28 years, and there were no significant differences in sex distribution between the groups. With respect to substance use status, participants with 0 and 1-2 night sentry shifts/month had a greater prevalence of active cigarette smoking than did participants with ≥ 3 night sentry shifts/month. For hemodynamics, a faster PR was found in individuals with ≥ 3 night sentry shifts/month than in individuals in the other two groups, while there were no differences in systolic BP, diastolic BP, or pulse pressure, defined as "systolic BP-diastolic BP", between the groups. For BMI and metabolic biomarkers, no significant differences were found between the groups. For the echocardiographic characteristics of the selected participants, accounting for approximately one-third of the overall participants (32.3%), there were no differences in the LVM index, LVEF or LA diameter after adjustment for age, sex and systolic BP, although the mean values of the LVM index and LA diameter increased in those with a greater number of night sentry shifts/month.

Table 2 shows the results of multivariable linear regression analyses of the association of the frequency of night sentry duty with the PR and BP separately. Although there was an association between night sentry duty and diastolic BP in the crude model, there were no multivariable-adjusted associations for systolic or diastolic BP or pulse pressure. In contrast, there was an association between night sentry duty and the PR after adjustment for the potential covariates [standardized β (standard error) = 0.505 (0.223), P = 0.02 in Model 2).

Table 3 shows the results of multivariable linear regression analyses of the association of the frequency of night sentry duty with each MetS biomarker level except BP. There were no associations of night sentry duty with WC, serum triglyceride levels or FPG levels in the crude or multivariable models, whereas there was an inverse association between night sentry duty and HDL-C levels in the crude and multivariable models [standardized β = -0.490 (0.213), P = 0.02 in Model 2].

Table 4 shows the results of multivariable logistic regression analyses of the frequency of night sentry duty try duty for the prevalence of MetS and its related features. Compared with those without night sentry duties, participants with ≥ 1 night sentry shift/month were more likely to have impaired FPG [odds ratio (OR) and 95% confidence interval: 1.415 (1.016-1.969)] after adjustment for the potential covariates in Model 2. In contrast, the associations for prevalent MetS and other features were not significant. Moreover, there were no greater associations for hypertriglyceridemia or impaired FPG with a greater number of night sentry shifts. Compared with those without night sentry shifts, those with 1-2 night sentry shifts/month were more likely to have impaired FPG and hypertriglyceridemia [ORs: 1.481 (1.013-2.167) and 1.804 (1.131-2.879), respectively], which were greater than the association magnitudes in those with ≥ 3 night sentry shifts/month [ORs: 1.316 (0.839-2.062) and 1.053 (0.580-1.911), respectively].

DISCUSSION

The main findings of this study were that among armed forces personnel, there was a positive linear association between night sentry duty and the resting PR but an inverse linear association with HDL-C levels. In addition, participants with any night sentry shifts within a month may have a greater risk of impaired fasting glucose than those without any night sentry shifts.

Although many studies have demonstrated an association of sleep deprivation with increased BP and hypertension, most previous studies were performed to examine the acute and chronic impacts of sleep deprivation on BP levels and hypertension[6]. In some animal model studies, chronic sleep deprivation led to cardiac remodeling and dysfunction, which were confirmed by specific gene expression[31,32]. Notably, this study is the first to investigate the latent effects of partial sleep deprivation, *e.g.*, night sentry duty, on the hemodynamic characteristics of young military personnel. This study revealed that the frequency of night sentry duty was positively associated with the PR or heart beat rather than with BP levels or hypertension. Mechanisms for the increased PR in response to acute or chronic sleep deprivation have been proposed to be associated with increased psychological stress and neurohormonal system activation[5-7]. It is possible that occasional partial sleep deprivation at night may not significantly affect the daytime resting BP or related cardiac structures and function if adequate nocturnal sleep or short-term sleep recovery follows[32]. However, the latent effect on the increased resting PR remains, which has been associated with cardiovascular health and longevity[33,34].

With respect to the latent effect of partial sleep deprivation at night on metabolic health, this study revealed a novel finding of a linear inverse association between the frequency of night sentry duty try duty frequency and HDL-C levels, which has not been previously reported. To the best of our knowledge, HDL-C levels are correlated with sex, body weight, plasma triglyceride levels, aerobic fitness, and inflammation[35-37]. The mechanisms underlying the inverse association with partial sleep deprivation are not fully understood, which may be explained in part by increased low-grade inflammation related to sleep deprivation[38]. In addition, there were greater associations for low HDL-C levels in those with a greater frequency of night shifts (ORs: 1.057 and 1.198, respectively, for 1-2 and ≥ 3 night shifts/month), which was related to the linear inverse association with HDL-C levels, despite statistical nonsignificance. In contrast, this study revealed that participants with any night shifts (≥ 1)/month had a greater possibility of impaired FPG than those without night shifts. Notably, the associations for impaired FPG were not significant; the highest probability was noted in participants with 1-2 night shifts/month, followed by those with ≥ 3 night shifts/month (ORs: 1.481 and 1.316, respectively). This finding may account for the insignificant linear associations for FPG. In a randomized crossover trial, restricting sleep to 6.2 hours or less per night, as measured by actigraphy over 6 weeks, was associated with a 14.8%

Table 1 Clinical characteristics of military participants classified by night sentry duty frequency

	Night sentry duty 0/month (*n* = 506)	Night sentry duty 1-2/month (*n* = 220)	Night sentry duty ≥ 3/month (*n* = 141)	*P* value
Age (years)	28.01 ± 6.21	28.71 ± 5.90	28.89 ± 5.82	0.17
Male, *n* (%)	434 (85.8)	199 (90.5)	129 (91.5)	0.07
Substance use, *n* (%)				
Alcohol drinking	208 (41.1)	87 (39.5)	45 (31.9)	0.14
Betel nut chewing	74 (14.6)	35 (15.9)	11 (7.8)	0.07
Cigarette smoking	252 (49.8)	108 (49.1)	51 (36.2)	0.01
Time for a 3000-m run (seconds)	906.65 ± 134.39	905.29 ± 161.73	922.10 ± 101.86	0.46
Body mass index (kg/m^2)	24.69 ± 3.99	24.57 ± 3.76	24.59 ± 3.28	0.91
Systolic BP (mmHg)	117.40 ± 14.30	117.45 ± 12.34	116.97 ± 12.52	0.93
Diastolic BP (mmHg)	69.47 ± 11.00	69.73 ± 9.11	70.27 ± 9.21	0.71
Pulse pressure (mmHg)	47.93 ± 10.55	47.72 ± 9.58	46.69 ± 9.82	0.44
Pulse rate (bpm)	73.34 ± 10.87	72.22 ± 10.68	75.03 ± 9.24	0.04
Blood test				
Total cholesterol (mg/dL)	171.21 ± 31.43	174.28 ± 35.25	171.64 ± 31.12	0.49
LDL-C (mg/dL)	104.65 ± 28.65	107.03 ± 31.02	106.98 ± 29.69	0.50
HDL-C (mg/dL)	50.80 ± 10.88	50.35 ± 10.71	48.43 ± 9.96	0.07
Serum triglycerides (mg/dL)	100.39 ± 83.01	108.85 ± 72.47	106.06 ± 82.73	0.39
Fasting glucose (mg/dL)	94.28 ± 9.15	95.09 ± 10.74	95.09 ± 9.10	0.47
Echocardiographic parameters[1]				
LVMI (g/m^2)	73.76 ± 11.91	76.00 ± 14.85	77.46 ± 13.78	0.20
LVEF (%)	61.43 ± 4.85	62.30 ± 4.93	62.81 ± 4.65	0.14
LA diameter (mm)	32.60 ± 4.48	32.65 ± 4.44	33.70 ± 4.12	0.38

[1]Participant numbers for night sentry duty: 0/month, 1-2/month, and ≥ 3/month were 154, 83 and 43, respectively, and echocardiographic parameters were compared with adjustments for age, sex and systolic blood pressure.
BP: Blood pressure; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; LA: Left atrium; LVEF: Left ventricular ejection fraction; LVMI: Left ventricular mass index.

Table 2 Associations between night sentry duty frequency and levels of various hemodynamic parameters

	PR		SBP		DBP		PP	
	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
Crude model	0.558 (0.226)	0.01	0.300 (0.288)	0.29	0.482 (0.215)	0.02	-0.182 (0.221)	0.41
Model 1	0.569 (0.227)	0.01	0.054 (0.280)	0.84	0.251 (0.206)	0.22	-0.197 (0.218)	0.36
Model 2	0.505 (0.223)	0.02	0.086 (0.268)	0.74	0.266 (0.203)	0.18	-0.180 (0.214)	0.40

Data are presented as standardized β and standard error (SE) using linear regression analysis. Model 1: Age, sex, alcohol drinking, betel nut chewing, cigarette smoking adjustments. Model 2: Age, sex, alcohol drinking, betel nut chewing, cigarette smoking, body mass index and time for a run adjustment.
DBP: Diastolic blood pressure; PP: Pulse pressure; PR: Pulse rate; SBP: Systolic blood pressure.

increase in insulin resistance independent of adiposity in both pre- and postmenopausal women[8], which was consistent with the findings regarding partial sleep deprivation and the development of impaired FPG in this study. However, the effects of sleep deprivation on hypertriglyceridemia have been inconsistent in prior studies, which revealed a lower level of serum triglycerides in individuals with acute sleep deprivation[39,40], and the lipid paradox may be mediated by proinflammatory conditions[40]. Given that the latent effect of partial sleep deprivation in this study seems to have increased triglyceride levels despite borderline significance (P = 0.09 in the multivariable linear regression analysis and P

Table 3 Associations between night sentry duty frequency and levels of metabolic syndrome biomarkers

	WC		HDL-C		TG		FPG	
	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
Crude model	0.321 (0.231)	0.16	-0.598 (0.230)	0.009	3.094 (1.705)	0.07	0.365 (0.205)	0.07
Model 1	0.075 (0.209)	0.72	-0.493 (0.221)	0.02	2.610 (1.623)	0.10	0.212 (0.204)	0.29
Model 2	0.147 (0.112)	0.18	-0.490 (0.213)	0.02	2.613 (1.577)	0.09	0.218 (0.202)	0.28

Data are presented as standardized β and standard error (SE) using linear regression analysis. Model 1: Age, sex, alcohol drinking, betel nut chewing, cigarette smoking adjustments. Model 2: Age, sex, alcohol drinking, betel nut chewing, cigarette smoking, body mass index and time for a run adjustment. FPG: fasting plasma glucose; HDL-C: high-density lipoprotein cholesterol; TG: serum triglycerides; WC: waist circumference.

Table 4 Associations of night sentry duty frequency categories with metabolic syndrome and related features

	Hypertension	Central obesity	Reduced HDL-C	Increased TG	Impaired FPG	Metabolic syndrome
No night duty (reference)	1.000	1.000	1.000	1.000	1.000	1.000
Night duty ≥ 1/month	1.094 (0.758-1.579)	1.110 (0.676-1.823)	1.111 (0.741-1.665)	1.487 (0.980-2.256)	1.415 (1.016-1.969)[a]	1.464 (0.873-2.456)
No night duty (reference)	1.000	1.000	1.000	1.000	1.000	1.000
Night duty 1-2/month	1.084 (0.706-1.663)	0.991 (0.551-1.782)	1.057 (0.657-1.701)	1.804 (1.131-2.879)[a]	1.481 (1.013-2.167)[a]	1.755 (0.984-3.130)
Night duty ≥ 3/month	1.109 (0.678-1.816)	1.311 (0.672-2.555)	1.198 (0.695-2.066)	1.053 (0.580-1.911)	1.316 (0.839-2.062)	1.059 (0.509-2.202)

[a]$P < 0.05$.

Definitions: Hypertension was defined as systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg; central obesity was defined as waist circumference ≥ 90 cm in men and ≥ 80 cm in women; reduced high-density lipoprotein was defined as < 40 mg/dL in men and < 50 mg/dL in women; increased serum triglycerides was defined as ≥ 150 mg/dL; impaired fasting plasma glucose was defined as ≥ 100 mg/dL; metabolic syndrome was defined as having 3 or more of the above five features. Data are presented as odds ratio (OR) and confidence interval using multiple logistic regression analysis with adjustments for age, sex, alcohol drinking, betel nut chewing, cigarette smoking, body mass index and time for a run adjustment. FPG: Fasting plasma glucose; HDL-C: High-density lipoprotein cholesterol; TG: Serum triglycerides.

= 0.08 in the multivariable logistic regression analysis), more evidence is needed to confirm the association with dyslipidemia.

There were several limitations in this study. First, this cross-sectional study could not establish causal associations. Second, the frequency of night sentry duty for each participant was assessed by a self-reported response to a questionnaire, which may not be accurate, although recall within 3 months should be acceptable. Third, this study included armed forces personnel who were required to have a regular schedule for nocturnal sleep (full time for 8 hours) for analysis; this provided the strength to unify the total sleep time at night, estimated to be 5-6 hours in those on night sentry duty, although no objective assessment for sleep time using a device for each participant was performed. Finally, obstructive sleep apnea could cause sleep deprivation, which may confound the results and lead to bias[41,42]. In contrast, there were several advantages in this study. To our knowledge, exercise training has been shown to reduce the PR and BP and improve metabolic profiles, which may attenuate the adverse effects of night sentry duty in military personnel revealed in our previous studies[43-45]. The benefits related to exercise training were also observed in military personnel in other regions and in the general population[46-49]. In this study, cardiorespiratory fitness levels were adjusted for in the models, which could largely diminish bias.

CONCLUSION

Among military personnel, night sentry duty was positively associated with the resting PR but inversely associated with HDL-C levels. Compared with those without night duties, individuals with partial sleep deprivation due to any number of night shifts per month may have a greater risk of impaired FPG, while the risk of hypertriglyceridemia was not confirmed. The clinical implications are that uninterrupted nocturnal sleep is crucial for maintaining both good hemodynamic and metabolic health, especially insulin sensitivity, in relatively healthy young adults. Sleep recovery for a few weeks following a night sentry shift should be implemented as a practical program to prevent the development of

adverse hemodynamic, metabolic and cardiac dysfunction in military personnel.

FOOTNOTES

Author contributions: Lin YP and Hsu YC wrote the article and contributed equally; Lin KH collected the data; Tsai KZ analyzed the data; Chu CC and Yen-Chen Lin reviewed the data, edited and made critical revisions related to important intellectual content. Lin GM and Lin KH contributed to conception and design of the CHIEF Sleep study, and acquired and interpreted the data; all authors approved the final version of the article to be published.

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Informed consent statement: All participants were informed of the protocol of this study and gave written informed consent.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Data sharing statement: As the CHIEF study materials were obtained from the military in Taiwan, the data were confidential and not allowed to be opened in public. If there are any needs for clarification, the readers can contact Dr. Lin, the corresponding author, for sharing the data.

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CASE REPORT

Right ventricular diverticulum following a pulmonary valve placement for correction of tetralogy of Fallot: A case report

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Abstract

BACKGROUND

Ventricular diverticula are a rare congenital cardiac disorder presenting with an extremely low incidence. The presence of an apical diverticulum of the right ventricle has been associated with other congenital heart diseases such as tetralogy of Fallot. An important defining characteristic of ventricular diverticula that separates them from aneurysms through imaging techniques, is that they possess myocardial contraction synchronous to the adjacent walls, contributing to the ventricular stroke volume, so they do not usually require surgical treatment.

CASE SUMMARY

A 15-year-old male, currently asymptomatic, in follow up due to a pulmonary valve prosthesis placement and a history of corrected tetralogy of Fallot at 18 months old, underwent a cardiac magnetic resonance imaging in February 2024. A diverticulum was detected in the apical inferolateral wall of the right ventricle, which was not documented in the cardiac magnetic resonance imaging prior to valve prosthesis placement.

CONCLUSION
Right ventricular diverticula are a rare entity. To this date we could not find another case of a pulmonary valve placement, followed by a right ventricular diverticulum appearance.

Key Words: Right ventricular diverticulum; Tetralogy of Fallot; Pulmonary valve placement; Magnetic resonance imaging; Case report

Core Tip: Cardiac magnetic resonance imaging characterization is the gold standard for classifying anatomical abnormalities of the right ventricular wall. In asymptomatic patients, conservative management and close follow-up are recommended since no arrhythmias or thrombotic events occurred after the diverticulum was discovered; However, in some cases where there is a high risk of thrombosis (when the diverticulum is large or associated with arrhythmias or other malformations such as ventricular septal defect), anticoagulation is recommended. Surgery also is mainly reserved for cases of large and symptomatic diverticula.

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INTRODUCTION

Ventricular diverticula are a rare congenital cardiac disorder presenting with an extremely low incidence ratio of 0.013 to 0.016, both for right and left diverticula, appearing mainly in the anterolateral wall of the apex.

Ventricular diverticula are not common. Since 1940, 200 cases have been reported and only 18 to 20 cases belong to the right ventricle. Autopsy series have found an incidence of 0.4%, while computed tomography scans have reported a frequency of 2.2%[1].

The presence of an apical diverticulum of the right ventricle has been associated with other congenital heart diseases such as tetralogy of Fallot and ventricular septal defects. An important defining characteristic of ventricular diverticula that separates them from aneurysms through imaging techniques, is that they possess myocardial contraction like the adjacent walls, contributing to the ventricular stroke volume, so they are not usually treated surgically[2].

Among imaging modalities, echocardiography has been considered a good first approach to the diagnosis; However, cardiac magnetic resonance imaging (CMR) has risen as the main tool for morphological and functional characterization [3].

CASE PRESENTATION

Chief complaints

A 15-year-old male, currently asymptomatic, attends a CMR control study in February 2024, incidentally detecting a saccular lesion in the apical inferolateral wall of the right ventricle compatible with a ventricular diverticulum.

History of present illness

The patient is currently asymptomatic, in follow-up due to the placement of a pulmonary valve prosthesis and corrected tetralogy of Fallot.

History of past illness

Afterbirth diagnosis of tetralogy of Fallot, corrected at 18 months old, with placement of an infundibular patch, presenting satisfactory evolution; In the long-term follow-up, at the age of 11 years, he developed severe pulmonary insufficiency and main stenosis, as well as right ventricle and atrial enlargement, which triggered dyspnea to great exertion. A protocol for transcatheter pulmonary valve replacement surgery was successfully carried out in January 2023 (Table 1).

Physical examination

On physical examination, the patient presented with normal vital signs, rhythmic heart sounds with pulmonary hyper flow, pulmonary auscultation was normal.

Table 1 Summary timeline

Age	Event	Work up
0 months	Diagnosis of tetralogy of Fallot	Tracking
18 months	Tetralogy of Fallot correction	Infundibular patching and correction of IVC
11 years	Onset of high-exertional dyspnea	Tracking
14 years	Echocardiogram and MRI showed pulmonary insufficiency severe and main stenosis	A transcatheter pulmonary valve prosthesis replacement
15 years	Incidental findings of diverticulum in right ventricle	Post-surgical follow-up with CMR

MRI: Magnetic resonance imaging; IVC: Interventricular communication; CMR: Cardiac magnetic resonance imaging.

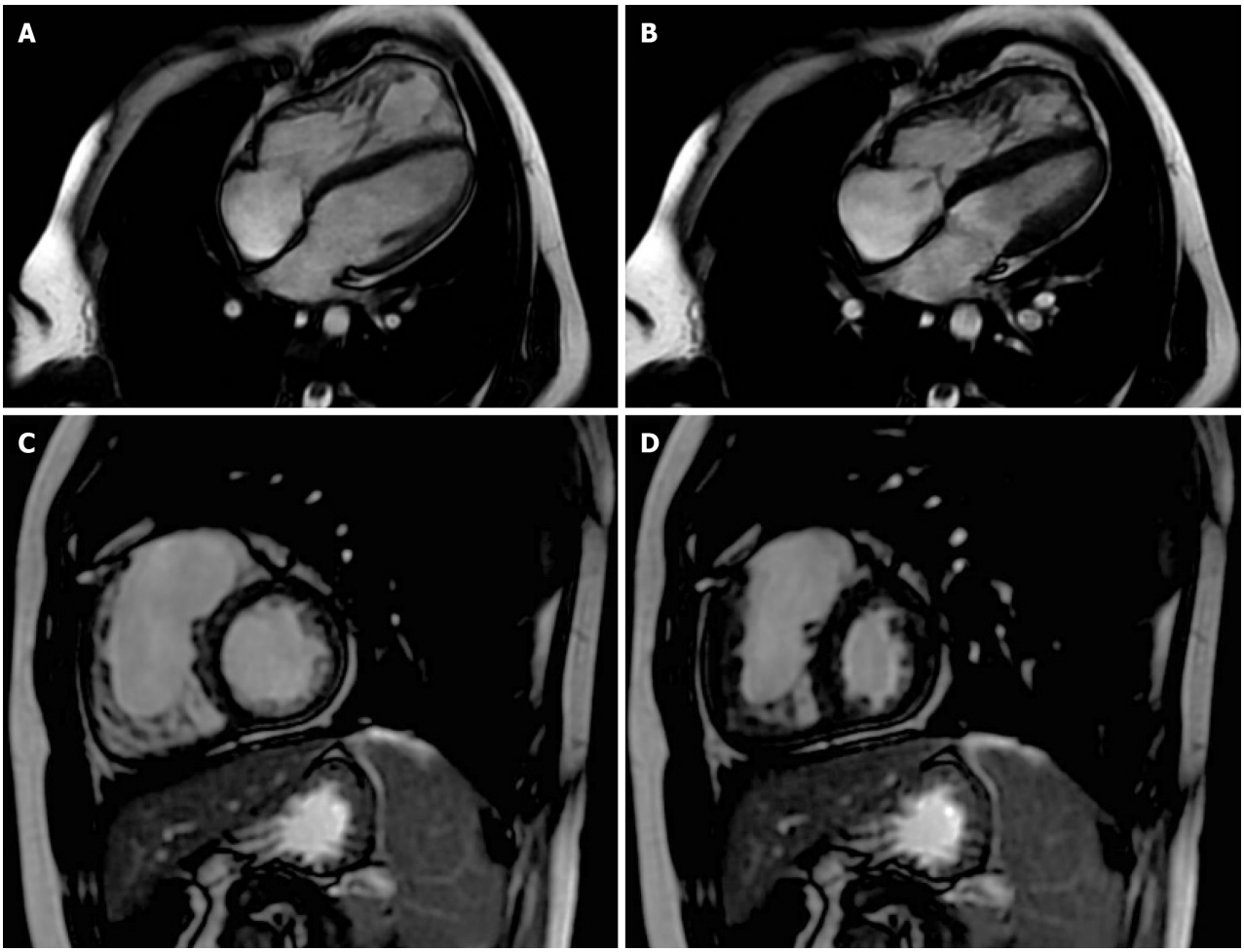

Figure 1 Cardiac magnetic resonance imaging cine sequences (June 2022). A: Four chamber view: Enlargement of the right ventricle and increased right ventricle trabeculation; B: Systolic image showing tricuspid valve regurgitation; C: Short axis in diastole; D: Short axis in systole. No saccular lesion of the right ventricle was observed in this study.

Imaging examinations

The patient was approached in the past for presenting dyspnea at great exertion, for which a transthoracic echocardiogram was performed in January 2022, reporting: Mild pulmonary stenosis, severe pulmonary failure and right ventricular dilation. Subsequently, in June 2022, contrasted magnetic resonance imaging (MRI) was performed as part of the pre-surgical protocol (Figure 1), identifying: Pulmonary valve showed severe pulmonary insufficiency and main stenosis: 2.2 meters/seconds; area: 2.5 cm^2; regurgitant volume (RV): 30.1 mL; regurgitant fraction (RF): 48%. Tricuspid valve with RV: 6.4 mL; RF: 10.3%.

The late gadolinium enhancement (LGE) sequence showed enhancement of the right atrium wall, and the patch of the right ventricular outflow tract (RVOT). The study concluded a right ventricular dilation, mild pulmonary stenosis, moderate pulmonary insufficiency, and mild tricuspid regurgitation (Figure 2A and B, Figure 3).

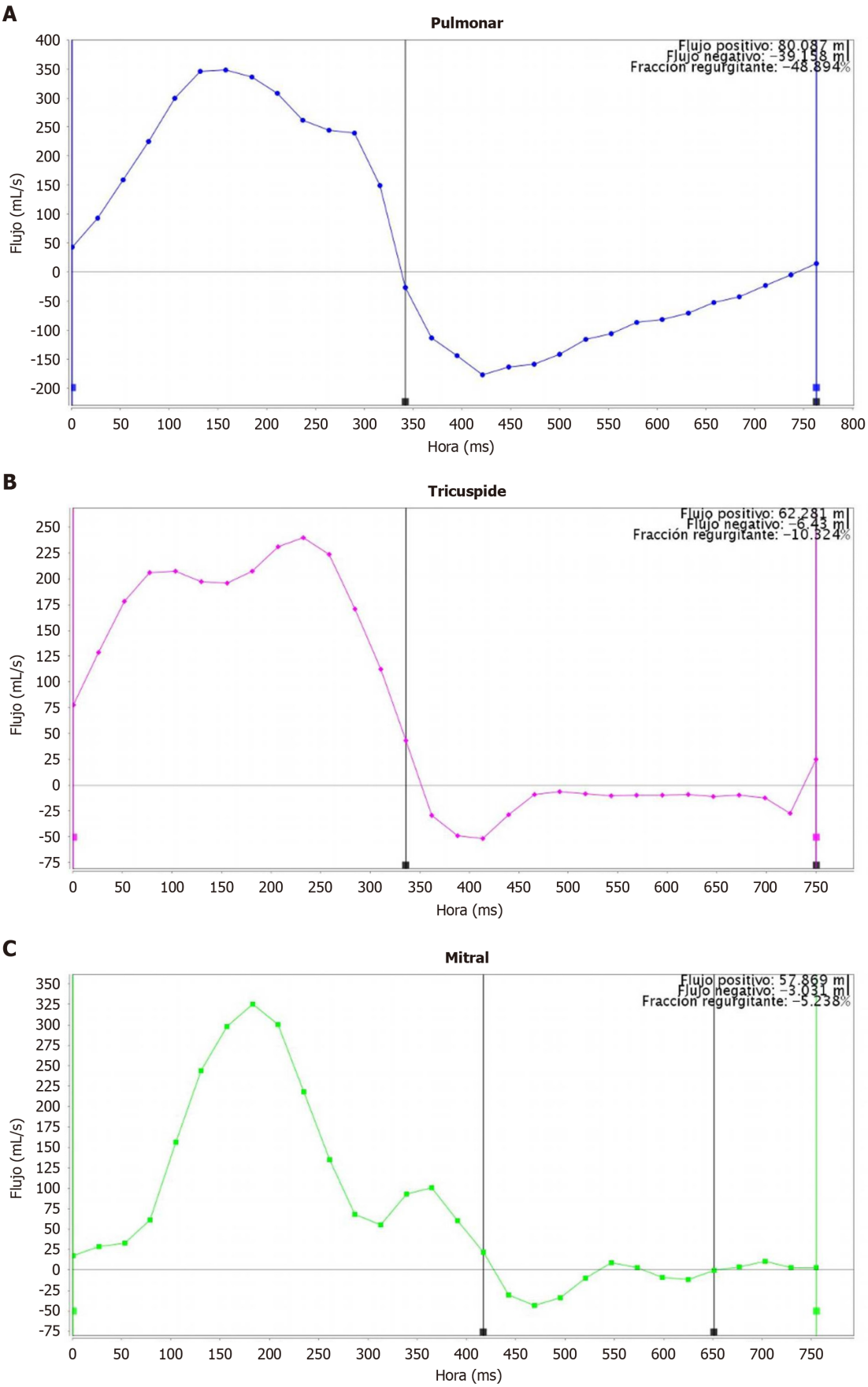

Figure 2 Cardiac magnetic resonance (June 2022). A: Flow-versus-time graph shows valvular pulmonary insufficiency a regurgitant volume of 39.1 mL *per* beat and regurgitant fraction of 48.8%; B: Valvular tricuspid insufficiency; a regurgitant volume of 6.4 mL *per* beat and regurgitant fraction of 10.3%; C: Cardiac magnetic resonance (June 2024). Flow-versus-time graph shows paravalvular leak a regurgitant volume of 4.8 mL *per* beat and regurgitant fraction 14.8%.

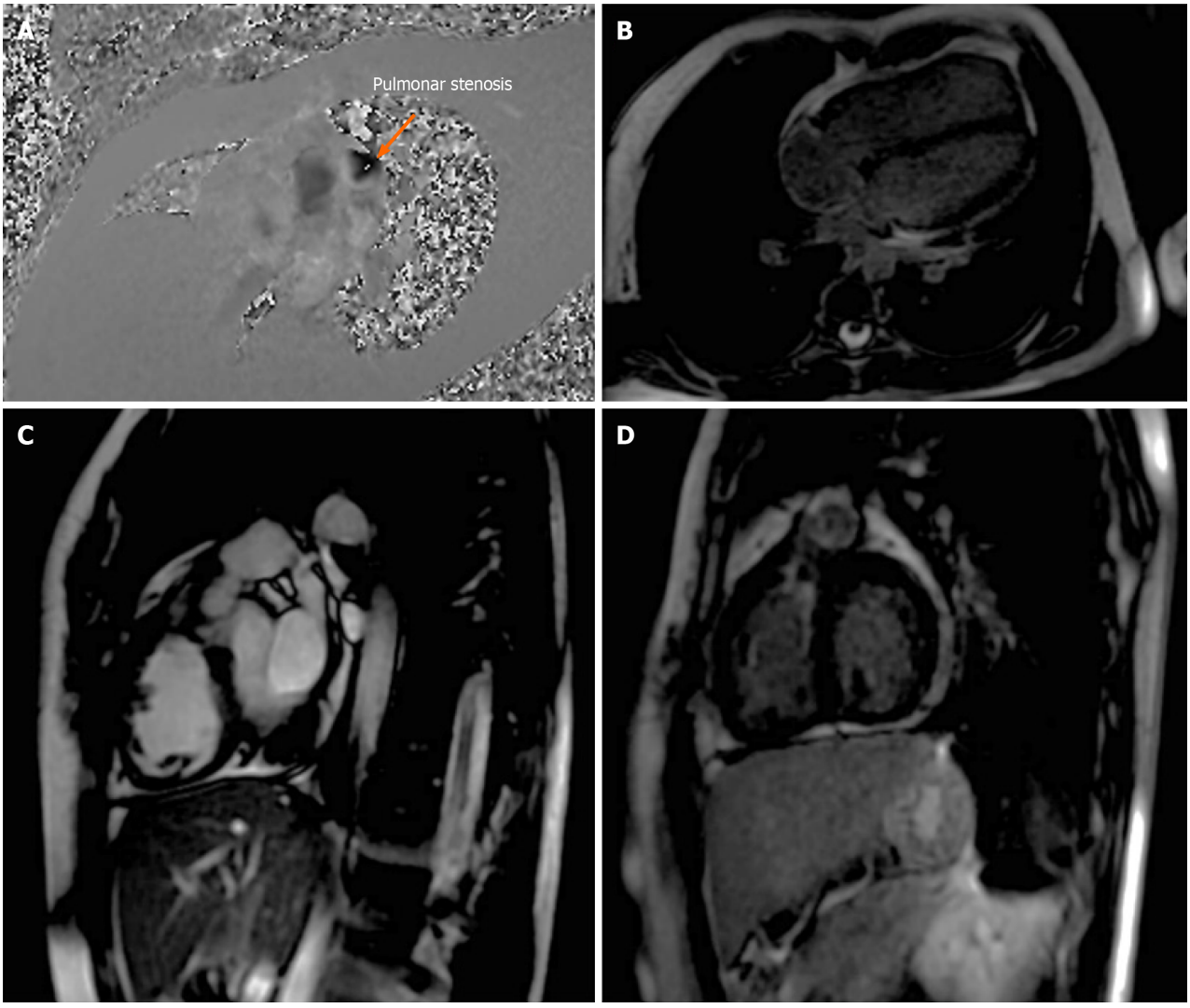

Figure 3 Cardiac magnetic resonance cine sequences (June 2022). A: Phase-contrast imaging; Right ventricular outflow tract stenosis and increased velocity; B and D: Late gadolinium enhancement sequence; Right atrial enhancement and right ventricular outflow tract; C: Cine sequence; Right ventricular outflow tract obstruction.

Subsequently, a transcatheter pulmonary valve was placed in January 2023 without any incident being reported during the surgery.

A follow-up MRI scan performed in February 2024 (Figure 4A and B) showed: Saccular image in the apical segment of the inferolateral wall of the right ventricle, which showed synchronous contraction, suggestive of diverticulum with a neck of 9 mm, longitudinal axis of 21 mm and transverse axis of 7 mm (Figure 4C).

Valve prosthesis with paravalvular leakage, regurgitant volume of 4.8 mL, and regurgitating fraction of 14.8% moderate-severe tricuspid regurgitation with regurgitant volume of 49.6% (Figure 2C and Figure 5). After surgery, the control MRI (Figure 6) showed a right ventricle of normal size.

FINAL DIAGNOSIS

It was concluded that the formation of a right ventricular diverticulum was associated with tetralogy of Fallot.

TREATMENT

The patient underwent medical treatment with 100 mg orally (PO) day, clopidogrel 75 mg PO day and captopril 12.5 mg PO q 12 hours.

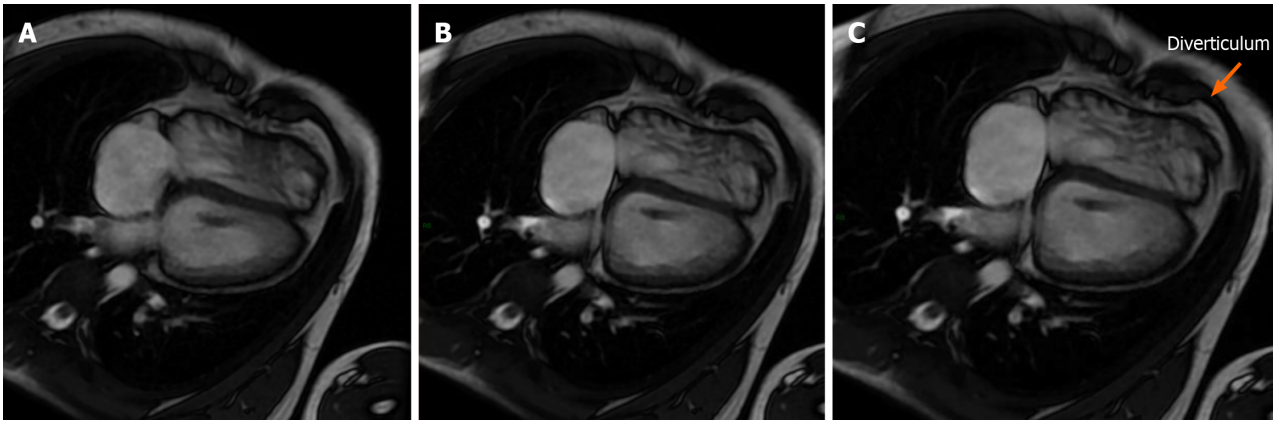

Figure 4 Cardiac magnetic resonance (February 2024) diverticulum of the inferolateral wall of the right ventricle after pulmonary valve prosthesis. A: Four chamber view: Diastole; B: Four chamber view: Systole; C: Four chamber saccular image in the inferolateral wall of the right ventricle, which showed synchronous movement and contraction like the rest of the myocardium.

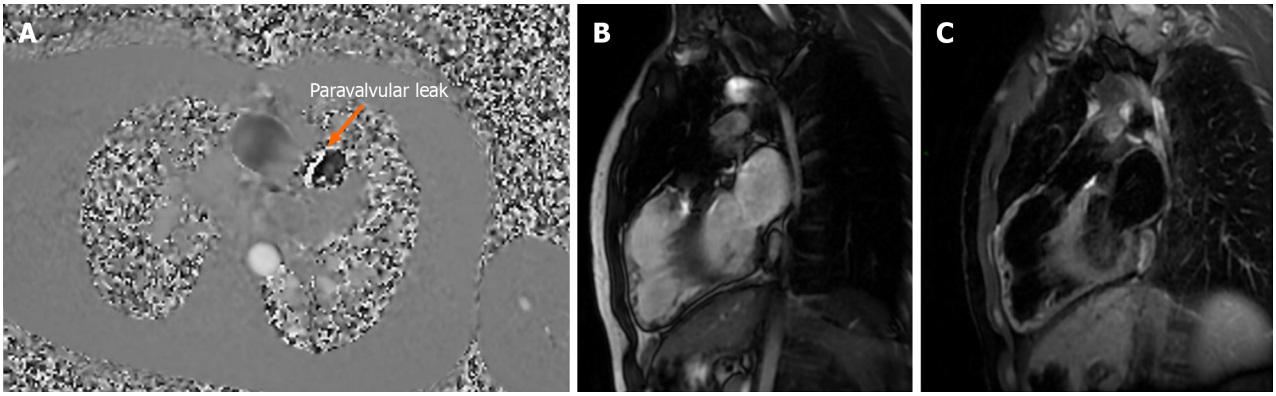

Figure 5 Cardiac magnetic resonance control right ventricular outflow tract cine sequences, T2 weight. A: Phase-contrast imaging; Paravalvular leak; B and C: After pulmonary valve placement (February 2024).

OUTCOME AND FOLLOW-UP

The patient will continue under medical follow-up and therapeutic behaviors will be regulated according to the evolution.

DISCUSSION

Within the current review in the literature, there are no similar case reports to this unusual presentation.

Right ventricular wall anomalies are rare[4]. They are divided into congenital (diverticulum) and acquired (aneurysm) secondary to trauma, iatrogenic aneurysm (due to surgical procedure) or secondary to myocarditis according to their etiology. The differential diagnosis should be made according to the history and image characteristics, especially by CMR.

In our case, the aneurysm was ruled out, with CMR being crucial since it demonstrated synchronous mobility of the lesion with respect to the wall of the right ventricle in a cine sequence, (the aneurysm would show asynchronous mobility or akinesia) in addition, the LGE images showed no evidence of reinforcement of the wall, ruling out infarction or fibrosis. In T2 weighted sequences, no wall edema or associated thrombus was found.

The echocardiogram, being operator-dependent and partially evaluating RV by position, may miss some defects, especially in patients with poor acoustic windows. The gold standard for characterization of RV wall defects by imaging is by CMR.

Due to the low incidence of this pathology, there is little information allowing the establishment of therapeutic strategies; in asymptomatic patients, as in our case, conservative management and close follow-up are recommended since no arrhythmias or thrombotic events occurred after the diverticulum was discovered; However, in some cases where there is a high risk of thrombosis (when the diverticulum is large or associated with arrhythmias or other malformations such as ventricular septal defect), anticoagulation is recommended. Surgery also is mainly reserved for cases of large and symptomatic diverticula[5].

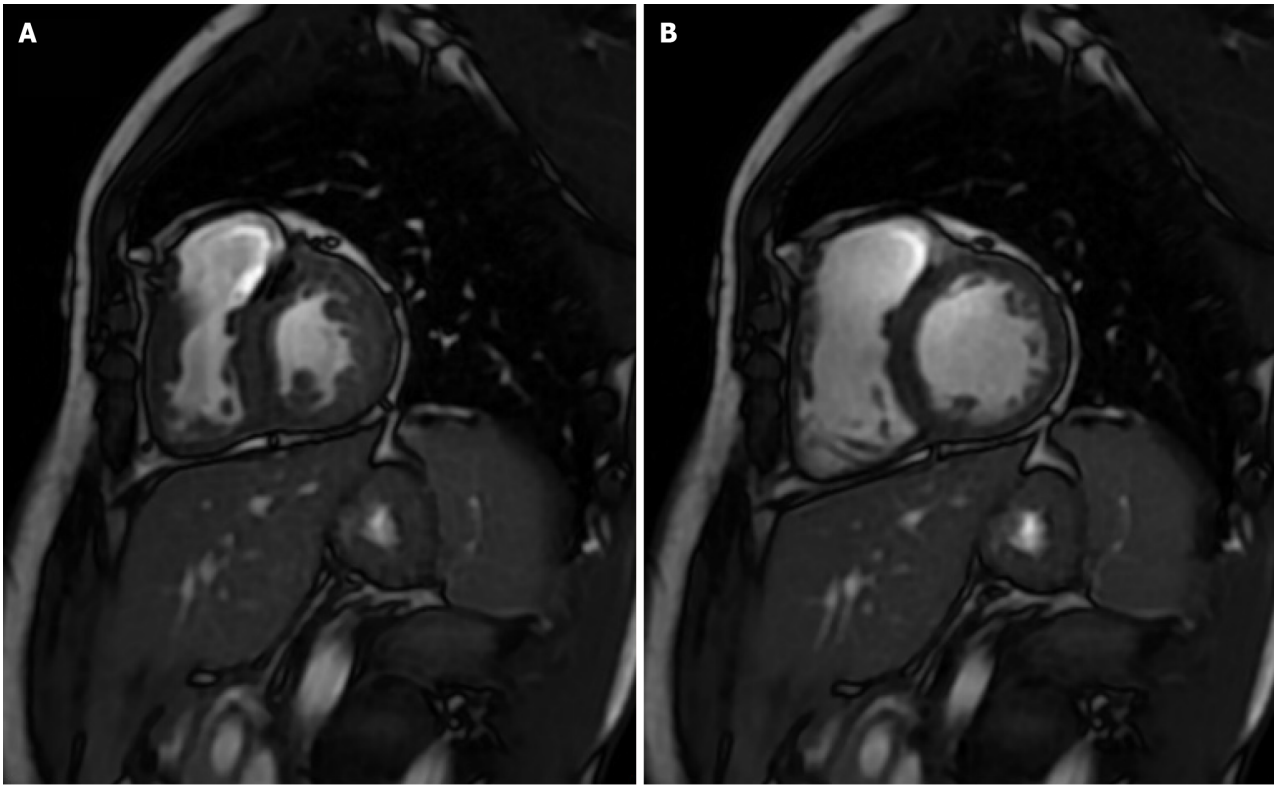

Figure 6 Cardiac magnetic resonance cine sequences short axis (February 2024) normal right ventricle. A: Systole; B: Diastole.

Patients with corrected tetralogy of Fallot should be adequately monitored as they normally require surgical re-interventions, either due to residual obstruction of the RVOT or pulmonary regurgitation. Residual obstruction of the RVOT can lead to progressive concentric hypertrophy of the RV which implies a greater risk factor for the future development of ventricular tachycardia; In addition, if there is an association with a diverticulum (as in our case), monitoring and closer evaluation is important because of the additional risk of arrhythmia.

Between 40% to 85% of patients will develop pulmonary regurgitation in the medium and long term follow-up, at 5 or 10 years. This results in RV volume overload with progressive dilation that may be accompanied by tricuspid regurgitation and RV dysfunction. In these cases, pulmonary valve replacement is recommended as it allows us to reduce RV volumes, increase left ventricular ejection fraction and improve the patient's functional status[6].

In our case report, paravalvular leakage was found through CMR after the placement of valve prosthesis (an incidence to this event is located between 2%-3%, usually due to the dehiscence of the valve with the native tissue)[7].

Although the association of diverticulum with tetralogy of Fallot has been reported, there seem to be no such cases after a placement of a pulmonary valve. In this case, the absence of it in the study prior to the prosthesis installation is probably due to masking of dilation of the right ventricle; characterization by CMR was crucial to be able to differentiate it from an aneurysm (which imply important differences in treatment).

CONCLUSION

Right ventricular diverticula are a rare entity, normally associated with tetralogy of Fallot or Cantrell's pentalogy. To this date we could not find another case of a pulmonary valve placement, followed by a right ventricular diverticula formation.

FOOTNOTES

Author contributions: Martinez Juarez D conception and design of case; Gomez Monterrosas O reviewed the manuscript; Tlecuitl Mendoza A wrote the manuscript; Zamora Rosales F analysis and interpretation of the data; Álvarez Calderón R reviewed the manuscript; Cepeda Ortiz DA wrote the manuscript; Espinosa Solis EE acquisition of the data.

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CASE REPORT

Nicorandil as a promising therapeutic option for ventricular arrhythmia: A case report and review of literature

Ling-Yu Bai, Ming Zhao, Kui-Ying Ma

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Abstract

BACKGROUND

Ventricular arrhythmia is a common type of arrhythmia observed in clinical practice. It is primarily characterized by premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation. Abnormal formation or transmission of cardiac electrical impulses in patients affects cardiac ejection function. It may present with symptoms such as palpitations, dyspnea, chest discomfort, and reduced exercise tolerance. In severe cases, ventricular arrhythmia can even lead to death. Therefore, prompt treatment is very much essential upon diagnosis. The symptoms did not improve after previous conventional drugs and electrical defibrillation treatment, but the ventricular arrhythmia was prevented after the addition of nicorandil.

CASE SUMMARY

A 75-year-old female patient was admitted to the hospital because of intermittent chest tightness, shortness of breath for 10 days, and fainting once for 7 days. Combined with laboratory tests and auxiliary examination, the patient was tentatively diagnosed with coronary heart disease or arrhythmia-atrial fibrillation. After admission, the patient had intermittent ventricular arrhythmia, which was uncontrolled with lidocaine, defibrillation, and amiodarone. However, when she was treated with nicorandil, the ventricular arrhythmia stopped. Nicorandil mitigates the action potential duration by facilitating the opening of potassium ion channels, thereby regulating the likelihood of premature and delayed depolarization in two distinct phases and subsequently averting the onset of malignant ventricular arrhythmia. Nicorandil may inhibit ventricular arrhythmia by dilating coronary arteries, improving coronary microcirculation and reducing myocardial fibrosis.

CONCLUSION

Nicorandil is a drug with dual effects. It could be used as a new therapeutic

option for inhibiting ventricular arrhythmias.

Key Words: Nicorandil; Ventricular arrhythmia; Electrical storm; Phase 2 early after-depolarization; Amiodarone; Microcirculation; Myocardial fibrosis; Lidocaine; Case report

Core Tip: The frequent occurrence of ventricular arrhythmia can be life-threatening, so the treatment of ventricular arrhythmia is particularly important. Treatment of ventricular arrhythmia includes pharmacological and nonpharmacological options. Our patient after receiving medical treatments include lidocaine, amiodarone, and electric defibrillation. Ventricular arrhythmia was not controlled. After application of nicorandil, ventricular arrhythmia was controlled and the rate of patient recovered sinus heart rate. Nicorandil provides a new idea for treating ventricular arrhythmia.

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INTRODUCTION

Electrical storm (ES), also known as sympathetic storm and ventricular electric storm, refers to a state of unstable ventricular electrical activity. It is characterized by three or more episodes of ventricular tachycardia (VT) or ventricular fibrillation (VF) within a 24-hour period. This condition is dangerous and associated with a high mortality rate. The clinical occurrence of ES is on the rise with the increasing incidence of coronary atherosclerotic heart disease, heart failure, and other related conditions. Typically, it leads to evident hemodynamic disturbances. which is difficult to manage with medication alone, necessitating the use of electroconversion or defibrillation for termination. Clinically, the mortality rate of ES is high[1,2]. The most common cause of ES is malignant, arrhythmia triggered by acute myocardial ischemia. Excessive excitation of the sympathetic nervous system is an important factor that triggers ES. Nicorandil is a unique clinical drug with dual effects[3]. The first effect of nicorandil is to open adenosine triphosphate (ATP)-sensitive potassium ion channels. Another effect of nicorandil, similar to nitrate esters, is to open to the K^+-ATP channels on the myocardial fiber cell membrane. This action leads to the dilation of coronary arteries, increased blood flow, reduced occurrence of angina, inhibition of coronary microvascular spasm, decreased endothelial cell damage, improvement in microcirculation, reduced myocardial fibrosis, and reduced ventricular arrhythmia[4]. Nicorandil can also reduce Ca^{2+} influx by opening the K^+-ATP channel of myocardial cell mitochondria, prevent Ca^{2+} overload in mitochondria, and protect or restore mitochondrial function, simulating myocardial ischemic preconditioning to protect myocardial cells[5]. Hirose *et al*[6] also found that long-term use of nicorandil in gaq transgenic mice can shorten the QT interval and reduce the occurrence of ventricular premature contractions. The patient in this case used nicorandil to reduce the occurrence of ESs.

CASE PRESENTATION

Chief complaints

A 75-year-old female patient presented with intermittent chest tightness, shortness of breath for 10 days, and fainting once for 7 days.

History of present illness

Ten days ago, the patient had no obvious causes or triggers, and intermittent chest tightness and shortness of breath, which were obviously related to activities. Oral administration of cold medicine and Huoxiang Zhengqi water did not relieve the symptoms. Seven days ago, the patient suddenly had amaurosis during activity and developed syncope. A few minutes later, she woke up on her own, without incontinence, limb twitching, occasional nausea, vomiting, and sweating. She immediately went to Tongliao District Hospital by 120 ambulances, and was admitted to the Department of Cardiology with suspected coronary atherosclerotic heart disease.

History of past illness

Paroxysmal atrial fibrillation for > 6 years without treatment, hypertension for > 10 years (highest blood pressure 180/100 mmHg), intermittent oral administration of amlodipine besylate 5 mg/day, unmonitored blood pressure, and no history of infectious diseases, vaccination, food or drug allergies, or trauma. Fifteen years after lumbar spine fracture surgery and right lower limb fracture surgery; 20 years after hysterectomy for uterine fibroids, with no history of blood transfusion.

Personal and family history
No history of smoking and alcohol consumption, as well as no family genetic history.

Physical examination
Vital signs: Temperature 36.5 °C, blood pressure 145/80 mmHg, pulse rate 124 beats/minute, respiratory rate 20 breaths/minute.

Physical examination: Double lung smell and dry, wet rale, small heart boundary, heart rate 164 beats/minute, irregular, different first heart sound, short pulse, no murmur, soft abdomen, no tenderness and rebound pain, no edema in either limb, no obvious positive signs after residual body examination.

Laboratory examinations
In June 28, 2023, complete blood count (CBC): White blood cell (WBC) count (10.7 × 10^9/L); neutrophil (NEU) percentage (88.7%); NEU count (9.54 × 10^9/L); lymphocyte (LYM) percentage (7.1%); monocyte (MON) count (0.41 × 10^9/L); MON percentage (3.9%); eosinophil percentage (EOS%) (0.2%); platelet count (297 × 10^9/L); hemoglobin (HGB) (121 g/L); C-reactive protein (6.57 mg/L); N-terminal prohormone of brain natriuretic peptide (NT-ProBNP) (2677 pg/mL); high sensitivity troponin I (47.9 pg/mL); K^+ (3.3 mmol/L); creatine kinase (CK) (7 U/L); CK-type M and B (CK-MB) (2.03 U/L); lactate dehydrogenase (LDH) (244 U/L); hydroxybutyrate dehydrogenase (HBDH) (146.2 U/L); D-dimer (DD) (1.27 mg/L); fibrinogen (FIB) (3.93 g/L). In July 5, 2023, WBC count (17.6 × 10^9/L); NEU percentage (83.9%); NEU count (14.76 × 10^9/L); LYM percentage (7.4%); MON count (1.43 × 10^9/L); MON percentage (8.2%); EOS% 0.4%; platelet count (352 × 10^9/L); HGB (137 g/L); FR-C-reactive protein (86.3 mg/L); CK (29 U/L); CK-MB-M (1.19 U/L); LDH (290 U/L); HBDH (177.2 U/L); NT-ProBNP (1940.5 pg/mL). In July 6, 2023, K^+ (4.3 mmol/L); CK (27 U/L); CK-MB-M (13.4 U/L); LDH (315 U/L); HBDH (234 U/L); CBC: WBC count (16.01 × 10^9/L); NEU percentage (83.3%); NEU count (13.33 × 10^9/L); LYM percentage (6.6%); LYM count (1.06 × 10^9/L); MON count (1.55 × 10^9/L); MON percentage (9.7%); EOS% (0.2%); platelet count (354 × 10^9/L); HGB (134 g/L); FIB (6.03 g/L); DD (3.4 mg/L); NT-ProBNP (2669 pg/mL); high sensitivity troponin I (22 pg/mL); myoglobin < 21 ng/mL; alanine transaminase (18.8 U/L); g-glutamyl transpeptidase (106 U/L); aspartate transaminase (23.4 U/L); total protein (55.8 g/L); albumin (32.4 g/L); alkaline phosphatase (146 U/L); cystatin-C (1.05 mg/L). In July 7, 2023, CK (26.3 U/L); CK-MB-M (11.1 U/L); LDH (320.2 U/L); HBDH (235.7 U/L); urine analysis no abnormality seen; blood fat no abnormality seen. In July 8, 2023, WBC (11.38 × 10^9/L); NEU percentage (76.1%); NEU count (8.65 × 10^9/L); LYM percentage (13.7%); MON count (0.97 × 10^9/L); stool for routine occult blood (+); NT-ProBNP (2767 pg/mL); HGB A1c (5.3%). In July 9, 2023, CBC: WBC count (9.48 × 10^9/L); NEU percentage (68.5%); NEU count (8.65 × 10^9/L); LYM percentage (19.4%); stool for routine: Occult blood (-); arterial blood gas: pH = 7.44; K^+ (4.43 mmol/L). In July 10, 2023, ST: Occult blood (-); arterial blood gas: pH = 7.44; K^+ (4.8 mmol/L); NT-ProBNP (609.7 pg/mL). In July 13, 2023, WBC count (9.91 × 10^9/L); NEU percentage (71.8%); NEU count (7.12 × 10^9/L); LYM percentage (17.3%); platelet count (447 × 10^9/L); HGB (131 g/L); NT-ProBNP (129.2 pg/mL). In July 14, 2023, K^+ (4.46 mmol/L); CBC: WBC count (9.14 × 10^9/L); NEU percentage (70.7%); NEU count (6.47 × 10^9/L); LYM percentage (18.2%); platelet count (420 × 10^9/L); HGB (130 g/L); FIB (4.17 g/L); DD (1.48 mg/L). In July 17, 2023, K^+ (4.46 mmol/L); CBC: WBC count (8.03 × 10^9/L); NEU percentage (63.3%); NEU count (5.08 × 10^9/L); LYM percentage (24%); platelet count (364 × 10^9/L); HGB (129 g/L); NT-ProBNP (30.8 pg/mL).

Imaging examinations
In June 28, 2023, chest computed tomography, diagnostic opinions: (1) Double pneumonia changes, except for pulmonary edema; (2) Calcification in the upper lobe of the right lung; (3) Bilateral pleural effusion; (4) Heart enlargement; and (5) Multiple liver cysts. In June 30, 2023, cardiac color ultrasound showed: Double atrial enlargement, left ventricular wall movement abnormality, decreased left heart function, aortic valve calcification, posterior mitral annular calcification and regurgitation (mild), tricuspid regurgitation (mild), ejection fraction (EF) 33%. In July 6, 2023, bedside heart color ultrasound: Mitral regurgitation (small), aortic regurgitation (small), reduced cardiac function, EF 46%. Pleural color ultrasound showed bilateral pleural effusion, with a possible investigation range of 3 cm. In July 11, 2023, thoracic color ultrasound showed bilateral pleural effusion, with the right depth of 5.8 cm and left depth of 4.4 cm. In July 13, 2023, chest color ultrasound showed bilateral pleural effusion with a depth of 7.6 cm on the right and 3.9 cm on the left.

FINAL DIAGNOSIS
Coronary artery atherosclerotic heart disease, unstable angina arrhythmia, frequent ventricular premature beat, short array VT, VF, heart function grade III.

TREATMENT
The patient was treated with oxygen inhalation, electrocardiography (ECG) monitoring, and oral drugs (aspirin, pravastatin, and metoprolol tartrate), hypodermic injection of low molecular weight heparin, drug infusion (cefoperazone sodium sulbactam sodium, ginkgo damol, tolasemide, furosemide, spironolactone diuresis and potassium supplementation). At 00:18 am the next day, under night monitoring, VF and loss of consciousness were detected. Cardiopul-

monary resuscitation was performed, and sinus rhythm was restored after asynchronous 200 joules defibrillation. The aforementioned medication continued. However, there were still intermittent episodes of VT. On June 30, 2023, at 00:01 am, intravenous injection of lidocaine and infusion did not improve the symptoms. At 00:19 am, heart rhythm developed short array VT and VF after atrial fibrillation (Figure 1A). Given a 200 joules cardioversion immediately, sinus rhythm was still not restored. Immediately after intravenous injection of amiodarone, 150 mg was added to 150 mL glucose for continuous pumping. At 00:23 am, the ECG showed that atrial fibrillation, with a heart rate of 166 beats/minute, QTc 493 ms (Figure 1B). However, the patient still had intermittent seizure VT. For further treatment, she was transferred to the intensive care unit. The electrocardiogram of sinus bradycardia was performed at 09:43 am, heart rate was 47 beats/minute, QTc 539 ms, and amiodarone was stopped (Figure 1C). At 05:41 pm on July 5, 2023, ECG monitoring showed ventricular arrhythmia, and after electrical defibrillation, the patient still had intermittent attack, and received lidocaine intravenous injection and infusion at 04:59 am on July 6. The heart rhythm was continuous VT and VF after addition of esmolol; therefore, she was transferred to our department.

When she was entered to the Department of Cardiology at our hospital, ECG monitoring showed sudden onset of short-term VT. After a few seconds, the heart rhythm spontaneously turned into sinus, which was followed by intravenous injection of 5 mg lidocaine. After sustained intravenous infusion of lidocaine, ventricular premature beats occurred intermittently. Potassium magnesium solution and nicorandil infusion were given. Ultrasonic cardiogram showed an EF of 45%, NT-ProBNP (2669 pg/mL), and chest ultrasound showed bilateral pleural effusion of approximately 3 cm. A definite diagnosis of heart failure was made, and recombinant human brain natriuretic peptide treatment was given. Emergency blood routine examination showed elevated WBCs, and symptomatic treatment with antibiotics was initiated. However, the patient still had intermittent premature ventricular beats and nicorandil was given with intravenous fluids. The heart rhythm was atrial fibrillation at 09:00 am (Figure 1D). After cedilanid intravenous injection, ECG still showed atrial fibrillation, and metoprolol tartrate tablets controlled heart rate. At 06:01 pm on July 8, 2023, heart rhythm was converted to sinus rhythm of 49 beats/minute, QTc 433 ms (Figure 1E). Metoprolol tartrate tablets were stopped but rivaroxaban, atorvastatin, sacubitril valsartan sodium tablets, torsemide and spironolactone were continued. No further ventricular premature beats occurred thereafter. On July 13, re-examination with chest ultrasound showed that the right-sided pleural effusion was 6.1 cm and the left side was 3.9 cm. The patient requested surgical treatment and underwent elective coronary angiography, which showed an irregular anterior descending branch with lesions from the opening to the proximal segment; the most severe stenosis was 70%-85%, and the anterior blood flow was thrombolysis in myocardial infarction (TIMI) grade 3. The circumflex artery was irregular, with 80%-90% stenosis in the distal segment and TIMI grade 3 forward blood flow. The right coronary artery was irregular, with diffuse long lesions in the proximal to distal segments; the most severe stenosis was 50%-60% in the proximal segment, 50%-60% in the middle segment, and 70%-80% in the distal segment. The anterior blood flow was TIMI grade 3. The patient had coronary heart disease. After consultation with her family, we decided to treat the descending branch lesion and chose a suitable time to treat the circumflex branch lesion. A Gureater 3.5 mm × 24 mm drug-eluting stent was implanted in the anterior descending artery lesion. After surgery, antiplatelet aggregation, stable plaque, crown expansion and diuresis were continued, and the patient was discharged after her condition improved. After discharge, treatment continued with oral aspirin, clopidogrel, rivaroxaban, atorvastatin, nicorandil, sacubitril valsartan sodium tablets, torsemide, and spironolactone.

OUTCOME AND FOLLOW-UP

The ventricular arrhythmia stopped and the patient's condition improved and she was discharged. After discharge, she had no further attack of ventricular arrhythmia and her condition was stable.

DISCUSSION

ES is a prevalent form of ventricular arrhythmia in clinical cardiology, characterized by three or more occurrences within a 24-hour period. It arises from disrupted ventricular heart rhythm and presents with symptoms such as palpitations, dyspnea, chest discomfort, reduced exercise tolerance, and often triggered by emotional stress. In severe cases, it can lead to heart failure, posing a significant risk to life. Therefore, it is crucial to identify and correct the mechanisms of ventricular arrhythmias[7]. The pathogenesis of ventricular arrhythmia is multifaceted. The involvement of myocardial injury, neurohumoral changes, and abnormalities in calcium channels are the main causes of ES[8-10]. The initiation and perpetuation of ES rely on overexcitation of the sympathetic nervous system. This overexcitation triggers a swift surge in the secretion of endogenous catecholamines, prompting the influx of sodium and Ca^{2+} into the myocardial cell membrane, and the efflux of potassium ions (such as myocardial infarction, major trauma, surgery, emotional excitement, *etc.*). Consequently, the action potential of myocardial cells is prolonged, ultimately leading to the development of malignant arrhythmias. Previous studies have reported that long-term myocardial ischemia and hypoxia in patients with coronary heart disease may lead to myocardial fibrosis, and myocardial fibrosis is one of the causes of arrhythmia[6]. Patients with coronary heart disease often have arrhythmia, and most of them have ventricular phase contraction. Nicorandil inhibits myocardial fibrosis and reduces ventricular arrhythmia by improving the microcirculation. Defibrillation during the treatment of patients experiencing ESs can exacerbate the excessive excitation of the sympathetic nervous system.

In the case of patients exhibiting stable hemodynamics and nonorganic heart disease, treatment may not be necessary when symptoms are mild or absent. when symptoms become apparent, lidocaine can be administered as the preferred medication[11]. Originally developed as a local anesthetic, lidocaine possesses antiarrhythmic properties. It is used in

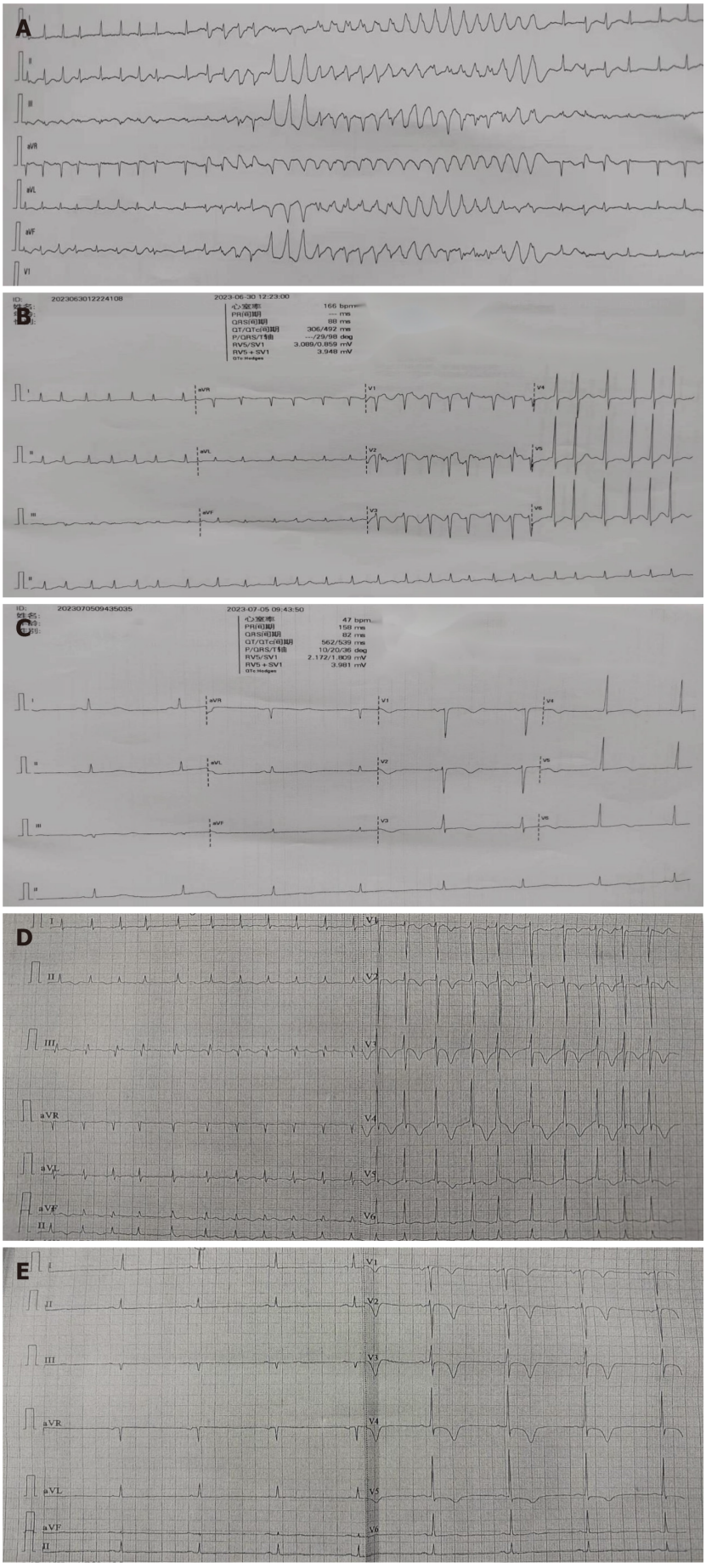

Figure 1 Patient outcomes. A: The heart rhythm of patient developed short array ventricular tachycardia and ventricular fibrillation after atrial fibrillation; B: Atrial

fibrillation, with a heart rate of 166 beats/minute, QTc 493 ms; C: Sinus rhythm, with a heart rate of 47 beats/minute, QTc 539 ms; D: Heart rhythm of patient was atrial fibrillation; E: Heart rhythm was converted to sinus rhythm with rate 49 beats/minute, QTc 433 ms.

various medical procedures such as epidural anesthesia, infiltration and surface anesthesia, as well as nerve conduction block[12]. Additionally, lidocaine can be used in cases where ventricular bradycardia or premature contractions are induced by acute myocardial infarction[13]. It is classified as a class 1B drug in the treatment of arrhythmia. These medications possess the ability to moderately impede sodium channels, thereby hindering the depolarization process during phase 4 of the action potential. Consequently, they diminish the rate of depolarization, widen the threshold, and alleviate abnormal autonomous activity. However, they do not impede the depolarization rate or conductivity during phase 0 of the action potential of myocardial cells[14]. Consequently, these drugs are suitable for treating VT in patients with stable hemodynamics. Nonetheless, they may elicit adverse reactions such as dizziness and consciousness disorders. Additionally, they may occasionally lead to sinus node suppression and atrioventricular block[15-17].

Amiodarone is a frequently used class III medication in the management of anti-arrhythmia. Its mechanisms of action include diminishing the autonomy of the sinoatrial node, impeding atrial conduction fibers, and obstructing sodium, potassium, and Ca^{2+} channels. It also prolongs the QT interval. Additionally, it influences α and beta adrenal hormones, exerting a noncompetitive inhibitory effect that prolongs the non-responsiveness of the sinoatrial node and ventricular muscles. This medication decelerates the conduction between the sinoatrial node and the atrioventricular node, thereby ameliorating arrhythmia[18-23]. In this particular case, the ECG showed ventricular arrhythmia. Despite continuous treatment involving lidocaine, amiodarone, and electrical defibrillation, VT did not show any improvement. Consequently, no ES occurred after the application of nicorandil.

Nicorandil, a potassium channel opener, is prominently characterized by shortening the action potential time course in the ventricle and Purkinje fibers. In the latest antiarrhythmic drug classification, it was designated as a class IIIb metabolism-dependent potassium channel opening agent, shortening the action potential duration and ECG QT interval in all cardiomyocytes except sinuatrial node cells[24]. Hirose *et al*[6] treated gaq transgenic mice with nicorandil over an extended period and revealed that the drug prevented the occurrence of arrhythmia by shortening the duration of action potentials and QT interval. K^+-ATP channels are expressed by various types of cells in cardiac tissue, such as cardiomyocytes, vascular smooth muscle cells, and autonomic neurons. K^+-ATP channels are also present in the sarcolemma and mitochondria of these cells. K^+-ATP channels are nearly closed under normoxic conditions[25-27]. However, under ischemic conditions, depletion of intracellular ATP concentration and accumulation of ischemia-related metabolites, such as adenosine diphosphate and lactate, open the channels. Nicorandil is a mixed compound of ATP channel openers and nitrate and is commonly used as a coronary vasodilator for treatment of angina pectoris. In patients with acute myocardial infarction, nicorandil before coronary intervention may reduce infarct size and ischemia-reperfusion-induced arrhythmia by reducing the absence of rebleeding phenomenon[28-30]. Studies have shown that K^+-ATP channel opening may have important biological actions that prevent cardiac fibrosis. Nicorandil attenuated myocardial-infarction-induced cardiac fibrosis in rats, and its beneficial actions on differentiations of fibroblast were blocked by adding glibenclamide which is a blocker of K^+-ATP channels[31]. Nicorandil thus improves the microcirculation and reduces the ventricular arrhythmia by inhibiting myocardial fibrosis. Therefore, it can be concluded that nicorandil has the potential to prevent the development of malignant arrhythmias[31,32].

How does nicorandil contribute to the prevention of arrhythmias? After the patient experienced electrical defibrillation treatment, lidocaine treatment was tried. Lidocaine, a local anesthetic that also has antiarrhythmic properties, reduces the occurrence of ventricular arrhythmia by affecting stage 4 of action potential depolarization. However, in the present case, ventricular arrhythmia was not controlled by lidocaine. Subsequently amiodarone treatment was tried, but caused prolonged QTc and repolarization, which induced ventricular arrhythmia, aggravating the situation. Therefore, lidocaine and amiodarone were both discontinued. After these treatments failed to effectively control ventricular arrhythmias, we finally treated them with nicorandil. Subsequently, the patient was treated with a combination of lidocaine and nicorandil, resulting in the absence of VT. Because the outward or inward current can prolong the action potential, this current change is likely to induce ventricular arrhythmia. It is suggested that nicorandil prevents phase 2 early after depolarization[33], enabling shortening of the QT interval, as it can prolong the plateau phase by inhibiting a large inward current in this phase, thereby reactivating the L-type calcium channel and forming early and late depolarization of myocardial cells. In theory, the duration of the action potential can be regulated by the interplay between depolarization and repolarization currents, without necessitating automatic calcium release from the sarcoplasmic reticulum or activation of sodium and calcium inward currents. Any augmentation of inward current and reduction of outward current can lead to premature and delayed depolarization. In addition, under myocardial ischemia, it opens K^+-ATP channels, and then nicorandil inhibited myocardial fibrosis, dilated coronary arteries, improved microcirculation, and reduced arrhythmia.

CONCLUSION

Nicorandil is a drug with dual effects. First, it is a metabolism-dependent K^+ channel opening agent that can open ATP-sensitive potassium channels. Secondly, nicorandil has a similar effect as nitrate ester, and opens the K^+-ATP channel on cardiac muscle fiber cell membranes, leading to coronary artery expansion, increased blood flow, reduced occurrence of angina, inhibition of coronary microvascular spasm, reduced endothelial cell damage, improved microcirculation, and

reduced myocardial fibrosis and ventricular arrhythmia. Nicorandil can also reduce the influx of Ca^{2+} by opening K^+-ATP channels in mitochondria, prevent calcium overload in mitochondria, and protect or restore mitochondrial function, mimicking myocardial ischemic preconditioning to protect cardiomyocytes. In the latest classification of antiarrhythmic drugs, nicorandil belongs to class B drugs. K^+-ATP channels open when intracellular ATP decreases, K^+ outflow increases, action potential plateau shortens, voltage-dependent Ca^{2+} channel activity decreases, Ca^{2+} influx decreases, shortening myocardial tissue action potential recovery time, refractory period and QT interval. In the present case, the patient had frequent ventricular arrhythmia due to myocardial ischemia and reperfusion, so the ventricular arrhythmia was controlled immediately by nicorandil. We conclude that nicorandil is a new treatment option for ventricular arrhythmia, especially with myocardial ischemia and hypoxia in coronary heart disease.

FOOTNOTES

Author contributions: Bai LY and Ma KY performed the study; Bai LY and Zhao M analyzed the data; Bai LY wrote the manuscript; and all authors have read and approved the final manuscript.

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LETTER TO THE EDITOR

Comparative breakthrough: Umbilical cord mesenchymal stem cells *vs* bone marrow mesenchymal stem cells in heart failure treatment

Peng Li

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Abstract

In this article, we evaluate the comparative efficacy and safety of mesenchymal stem cells (MSCs) derived from bone marrow (BM-MSCs) and umbilical cord (UC-MSCs) in the treatment of heart failure and myocardial infarction. MSCs have gained importance as living bio drug due to their regenerative potential, with BM-MSCs being the most extensively studied. However, UC-MSCs offer unique advantages, such as noninvasive collection and fewer ethical concerns. This systematic review and meta-analysis summarizes data from 13 randomized controlled trials, which included a total of 693 patients. Their study shows that UC-MSCs significantly improved left ventricular ejection fraction by 5.08% at 6 months and 2.78% at 12 months compared with controls, while BM-MSCs showed no significant effect. Neither cell type showed significant changes in 6-minute walk distance. In addition, UC-MSCs and BM-MSCs had comparable safety profiles, with no significant differences in major adverse cardiac events, except for a lower rehospitalization rate observed with BM-MSCs. These results position UC-MSCs as a promising alternative in MSC-based therapies for cardiac disease, offering potential improvements in cardiac function while maintaining a favorable safety profile. Future research should focus on optimizing administration protocols and further exploring the long-term benefits and mechanisms of UC-MSCs in cardiac repair.

Key Words: Mesenchymal stem cells; Heart failure; Umbilical cord-derived mesenchymal stem cells; Bone marrow-derived mesenchymal stem cells; Left ventricular ejection fraction; 6-minute walking distance; Cardiac regeneration therapy

Core Tip: This article provides a comparative analysis of umbilical cord-derived mesenchymal stem cells (UC-MSCs) and bone marrow-derived mesenchymal stem cells (BM-MSCs) for the treatment of heart failure. UC-MSCs significantly increase left ventricular ejection fraction and exhibit a favorable safety profile, positioning them as a promising alternative to BM-MSCs. Future research should focus on optimizing administration protocols and understanding the long-term benefits of UC-MSCs in cardiac therapy.

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TO THE EDITOR

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide despite advances in pharmacological treatment[1]. Heart failure (HF), a common endpoint of various CVDs, results from the progressive decline of cardiac function due to the formation of fibrous scars after myocardial infarction (MI)[2]. Conventional treatments primarily provide symptomatic relief without addressing the underlying problem of myocardial tissue loss [3]. In this context, regenerative medicine, particularly mesenchymal stem cells (MSCs) therapy, has emerged as a promising approach to repair and replace damaged myocardium[4].

MSCs are multipotent stromal cells capable of differentiating into various cell types, including cardiomyocytes[5]. They exhibit unique properties such as high proliferation rates, secretion of proangiogenic and anti-inflammatory factors, and evasion of immune surveillance, making them ideal candidates for cell-based therapies[6]. MSCs can be derived from various tissues, including bone marrow (BM-MSCs) and umbilical cord (UC-MSCs), with each tissue having different advantages and limitations[7]. BM-MSCs are the most extensively studied MSC type in clinical settings. In preclinical models, they have shown the potential to improve cardiac function and reduce scar tissue[8]. However, their therapeutic efficacy in clinical trials has been modest, possibly due to factors such as donor age, comorbidities, and quality of cell preparations[9]. In contrast, UC-MSCs derived from medical waste are increasingly recognized for their noninvasive collection procedure, lack of ethical concerns, and superior proliferative ability[10]. UC-MSCs are younger and possess embryonic cell-like properties, which may contribute to their increased therapeutic potential[11]. This article aims to evaluate the comparative safety and efficacy of BM-MSCs and UC-MSCs in the treatment of HF and MI.

SAFETY AND EFFICACY OF BM-MSCS AND UC-MSCS FOR CVD

By analyzing data from 13 randomized controlled trials (RCTs) involving 693 patients, the authors evaluate key clinical outcomes such as left ventricular ejection fraction (LVEF), 6-minute walk distance (6MWD), and major adverse cardiac events. Their study shows that UC-MSCs significantly improved LVEF by 5.08% (MD 5.08, 95%CI: 2.20%-7.95%; P = 0.0005) at 6 months and 2.78% (MD 2.78, 95%CI: 0.86-4.70; P = 0.004) at 12 months compared with controls, while BM-MSCs showed no significant effect[12]. UC-MSCs have demonstrated greater improvement in LVEF compared to BM-MSCs, likely due to several key factors. UC-MSCs exhibit enhanced proliferative capacity, allowing for increased cell viability and a greater number of cells participating in myocardial repair. They also have superior paracrine activity, which means they release higher levels of growth factors and cytokines that promote angiogenesis, reduce apoptosis, and modulate inflammation more effectively than BM-MSCs[10,13]. Additionally, UC-MSCs possess a higher immunomodulatory capacity, reducing local immune responses and creating a more favorable environment for myocardial regeneration[10,13]. These combined factors likely contribute to the observed superior improvements in LVEF with UC-MSC therapy.

The efficacy of MSC therapy for HF can vary depending on the underlying cause of the disease. Studies suggest that MSCs may be more effective in treating ischemic HF, such as that caused by MI, due to their ability to promote angiogenesis and reduce scar formation in the ischemic myocardium[13]. In contrast, for non-ischemic HF, such as those due to cardiomyopathy or valvular disease, MSCs may show more limited efficacy, as these conditions involve more complex pathological mechanisms, such as genetic mutations or mechanical abnormalities, that are less responsive to cellular therapy[7-10]. Therefore, the underlying etiology of HF should be considered when determining the potential benefits of MSCs therapy.

In addition, it would be prudent to consider treatment-related complications when comparing UC-MSCs and BM-MSCs in cardiac therapy. Although both cell types are generally regarded as safe, minor complications such as transient fever, local pain at the injection site, and mild immune responses have been reported in some studies[10,13]. Importantly, UC-MSCs are considered to have a lower risk of immune rejection due to their lower expression of major histocompatibility complex molecules, which could reduce complications compared to BM-MSCs[10]. However, there are also concerns regarding the long-term safety of MSC therapies, such as the potential for tumorigenesis or ectopic tissue formation, necessitating further investigation through longer-term studies.

CARDIOPROTECTION MECHANISM OF MSC

MSCs have attracted considerable attention due to their cardioprotective properties, which are mainly attributed to their multiple mechanisms of action. These mechanisms include direct differentiation, paracrine signaling, immunomodulation, and extracellular vesicle (EV) production, resillience and adaptablity, and together contribute to myocardial repair and functional recovery after cardiac injury[14] (Figure 1).

Figure 1 Cardioprotection mechanism of mesenchymal stem cells.

One of the main mechanisms by which MSCs exert cardioprotective effects is their ability to differentiate into cardiomyocytes and vascular endothelial cells. This differentiation ability enables MSCs to replace damaged myocardial tissue and contribute to the formation of new blood vessels, thereby improving cardiac repair and perfusion[15]. However, the extent of direct differentiation is limited, and the predominant mechanism of action is thought to be paracrine signaling[16]. MSCs secrete a variety of bioactive molecules, including growth factors, cytokines and chemokines, which mediate their paracrine effects. These secreted factors promote angiogenesis, reduce apoptosis, inhibit fibrosis and stimulate endogenous cardiac progenitor cells, thereby facilitating myocardial repair[17,18].

Immunomodulation is another crucial mechanism by which MSCs confer cardioprotection. MSCs interact with various immune cells, including T cells, B cells, natural killer cells and macrophages, and modulate their activity to create an anti-inflammatory environment that favors tissue repair[19]. For example, MSCs can induce the polarization of macrophages toward the M2 phenotype, which is associated with tissue repair and regeneration[20]. In addition, MSCs secrete anti-inflammatory cytokines such as interleukin-10 and transforming growth factor β, which further attenuates the inflammatory response[21].

EVs released by MSCs also play a crucial role in their cardioprotective effects. EVs, including exosomes and microvesicles, are rich in proteins, lipids, and nucleic acids that can affect target cells and tissues. MSC-derived EVs have been shown to deliver microRNAs and other regulatory molecules to cardiac cells, thereby modulating gene expression and promoting cardiac repair[22]. For example, miR-126 and miR-210, which are present in MSC-derived exosomes, have been associated with enhancing angiogenesis and reducing apoptosis in ischemic cardiac tissue[23,24]. In addition, MSCs secrete angiogenic factors such as vascular endothelial growth factor, fibroblast growth factor, and hepatocyte growth factor, which promote the formation of new blood vessels in the damaged myocardium. This improves blood supply and oxygen delivery to the heart tissue[25].

UC-MSCs and BM-MSCs have shown potential in myocardial regeneration and cardiac remodeling, with both therapies demonstrating improvements in cardiac function and reductions in scar size. UC-MSCs have been noted for their greater proliferative capacity and lower immunogenicity, which may enhance myocardial repair by promoting angiogenesis and reducing fibrosis. BM-MSCs, while effective, tend to have reduced differentiation potential with age, possibly limiting their regenerative abilities compared to UC-MSCs[26]. Further clinical trials are needed to validate these findings and establish standardized protocols for their application in HF and MI[27].

CONCLUSION

The advent of regenerative medicine, particularly the use of MSCs, offers a promising therapeutic approach to address the underlying myocardial damage and improve cardiac function. Despite no observed differences in the 6MWD between the two MSC types, UC-MSCs present a more favorable safety profile and are associated with a lower rate of rehospital-

ization. The promising results of UC-MSCs can be attributed to their unique characteristics, including noninvasive collection, fewer ethical concerns, higher proliferative capacity, and embryonic-cell-like properties. These advantages position UC-MSCs as a viable and potentially superior alternative to BM-MSCs for cardiac regeneration therapy. However, several challenges remain, including the need for standardized cell isolation, administration protocols, and long-term studies to validate these findings and optimize clinical applications[28,29]. Future research should focus on enhancing the therapeutic efficacy of MSCs through preconditioning strategies, identifying biomarkers for predicting treatment outcomes, and understanding the long-term effects and underlying mechanisms of MSCs therapy in cardiac repair. Additionally, large-scale RCTs are necessary to confirm the benefits of UC-MSCs and establish them as a standard treatment for HF and MI. In conclusion, UC-MSCs hold significant promise for advancing cardiac regeneration therapy, offering a new avenue for improving heart function and patient outcomes. By addressing the current challenges and continuing to explore innovative approaches, MSC-based therapies have the potential to revolutionize the treatment landscape for HF and MI.

FOOTNOTES

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LETTER TO THE EDITOR

Sodium-dependent glucose transporter 2 inhibitors: Transforming diabetic cardiomyopathy management

Chun-Han Cheng, Wen-Rui Hao, Tzu-Hurng Cheng

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Abstract

This article addresses the substantial findings of a study on sodium-dependent glucose transporter 2 inhibitors (SGLT2is) and their effects on myocardial function in patients with type 2 diabetes and asymptomatic heart failure. The editorial explores the broader implications of the study findings for clinical practice, thus highlighting the pivotal role of SGLT2is in improving cardiac function, reducing oxidative stress, and attenuating inflammation. It emphasizes the importance of early intervention with SGLT2is in preventing the progression of diabetic cardiomyopathy; hence, these inhibitors have the potential to transform the management of asymptomatic heart failure in patients with diabetes.

Key Words: Sodium-dependent glucose transporter 2 inhibitors; Diabetic cardiomyopathy; Asymptomatic heart failure; Cardiac function; Type 2 diabetes

Core Tip: This article emphasizes the clinical importance of sodium-dependent glucose transporter 2 inhibitors (SGLT2is) in managing myocardial function for patients with type 2 diabetes and asymptomatic heart failure. By improving cardiac function, reducing oxidative stress, and lowering inflammation, SGLT2is present a promising therapeutic strategy. Early intervention with SGLT2is can prevent the progression of diabetic cardiomyopathy, highlighting their transformative potential in the treatment of asymptomatic heart failure in patients with diabetes.

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TO THE EDITOR

Sodium-dependent glucose transporter 2 inhibitors (SGLT2is) have proven effective in managing type 2 diabetes by improving glycemic control. However, emerging research highlights their broader cardiovascular benefits. Recent studies, such as one by Grubić Rotkvić *et al*[1], demonstrate the positive impact of SGLT2is on myocardial function in patients with type 2 diabetes and asymptomatic heart failure[1]. This editorial examines these findings within the growing field of cardiovascular care advancements, emphasizing how SGLT2is's cardioprotective properties extend beyond glucose regulation. A key takeaway is that SGLT2is play a crucial role in slowing the progression of heart failure in diabetic patients, signaling a shift toward early intervention strategies. This is particularly significant for addressing diabetic cardiomyopathy, a condition characterized by structural and functional changes in the myocardium due to diabetes. The study by Grubić Rotkvić *et al*[1] reveals that SGLT2is can improve myocardial function in patients with asymptomatic heart failure[1], aligning with broader evidence from studies like those by Matthews *et al*[2], which show that SGLT2is benefit both heart and kidney health, even in non-diabetic patients[2]. Further evidence supporting the cardiovascular benefits of SGLT2is comes from a network meta-analysis by Lv *et al*[3], which highlights a reduced risk of new-onset atrial fibrillation compared to other hypoglycemic agents[3]. Understanding the mechanisms behind these effects is critical. Xie *et al*[4] discuss the clinical potential of SGLT2is to induce autophagy, a process that may slow atherosclerosis progression, a key concern in diabetic cardiomyopathy[4]. Autophagy is essential for cellular homeostasis, making this mechanism particularly relevant for long-term cardiovascular health. In addition to their heart-protective properties, SGLT2is also offer renal benefits, which are closely tied to cardiovascular health. For instance, Zhang *et al*[5] found that SGLT2is reduce renal lipid deposition and improve renal oxygenation in newly diagnosed diabetic patients [5]. These findings highlight the holistic benefits of SGLT2is, which simultaneously address cardiovascular and renal complications associated with type 2 diabetes. Overall, the study by Grubić Rotkvić *et al*[1] adds to the growing body of evidence supporting the use of SGLT2is in comprehensive cardiovascular care for diabetic patients[1]. By prioritizing early intervention and leveraging the multifaceted benefits of SGLT2is, healthcare providers can better manage diabetic cardiomyopathy and related complications. This research underscores the evolving role of SGLT2is, not only in controlling blood glucose but also in improving cardiovascular outcomes, offering new insights into the management of type 2 diabetes and its associated risks.

Mechanisms of action

SGLT2is are primarily recognized for their ability to reduce glucose reabsorption in the kidneys, thereby lowering blood sugar levels. However, their benefits extend well beyond glycemic control, particularly in the cardiovascular system. In patients with type 2 diabetes and asymptomatic heart failure, SGLT2is have been shown to enhance myocardial function through several interrelated mechanisms. One key mechanism is the reduction of oxidative stress, a major contributor to cardiac dysfunction in diabetes. SGLT2is inhibit the activity of NADPH oxidase, a key enzyme in the production of reactive oxygen species (ROS)[4]. By decreasing ROS generation, SGLT2is help preserve mitochondrial function and protect cellular integrity. This reduction in oxidative stress is crucial for maintaining the health of myocardial cells, especially in diabetic cardiomyopathy, where oxidative damage drives cardiac dysfunction. Studies have demonstrated that SGLT2is mitigate oxidative damage, improving cardiac outcomes in diabetic patients with heart failure[1]. Inflammation is another critical factor in the progression of heart failure and cardiovascular diseases. SGLT2is reduce inflammatory markers such as C-reactive protein (CRP) and interleukin-6, both of which play key roles in cardiovascular health [5]. By decreasing systemic inflammation, these inhibitors help slow the progression of heart failure. This anti-inflammatory effect improves both renal and cardiac outcomes, further supporting their cardioprotective role. In addition to these effects, SGLT2is enhance endothelial function, which is essential for maintaining vascular health. Improved endothelial function promotes better myocardial perfusion and reduces cardiac workload. Enhanced vascular function has been observed in patients treated with SGLT2is, with better myocardial outcomes, particularly in heart failure contexts[1,2]. Another important mechanism is the promotion of autophagy, a cellular process that clears damaged cells and prevents atherosclerosis progression. By inducing autophagy, SGLT2is reduce plaque formation in the vasculature and protect myocardial function[6]. This process not only prevents further oxidative damage but also improves the myocardium's ability to cope with metabolic stress, ultimately enhancing cardiac outcomes. SGLT2is also benefit myocardial energetics by promoting a metabolic shift from glucose to fatty acids and ketone bodies as energy sources.

This shift is particularly beneficial in heart failure, where the heart's energy demand often exceeds its supply. Ketone bodies, produced during periods of low glucose availability, provide a more efficient energy source for the failing heart, requiring less oxygen for ATP production compared to glucose or fatty acids. SGLT2is enhance the expression of enzymes involved in ketone body metabolism, facilitating this shift and improving cardiac efficiency[4]. By optimizing energy use, SGLT2is reduce metabolic stress on the heart, alleviating its workload and improving overall function. Finally, the renal benefits of SGLT2is indirectly contribute to cardiovascular health. These drugs reduce renal lipid deposition and improve renal oxygenation, which alleviates the burden on the heart. Improved renal function lowers blood pressure and reduces the risk of heart failure progression[5], further contributing to their cardioprotective effects. In sum, the cardioprotective mechanisms of SGLT2 inhibitors in patients with type 2 diabetes and asymptomatic heart failure are multifaceted. These drugs reduce oxidative stress and inflammation, enhance endothelial function, promote autophagy, optimize myocardial energetics, and improve renal function. Together, these mechanisms form a comprehensive cardioprotective profile[1,2].

Clinical implications

The findings have significant implications for clinical practice, particularly in the management of diabetic cardiomyopathy. SGLT2is have demonstrated promise not only in improving glycemic control but also in offering cardioprotective benefits. These drugs extend their effects beyond glucose regulation, reducing cardiovascular complications in both diabetic and non-diabetic individuals, as noted in recent research[2]. This dual action provides a critical opportunity for early intervention, especially in patients with type 2 diabetes and asymptomatic heart failure. Supporting this, evidence suggests that early use of SGLT2is can prevent the progression from asymptomatic to symptomatic heart failure, reducing the onset of conditions such as atrial fibrillation[3]. Given the high incidence of diabetic cardiomyopathy in type 2 diabetes, as highlighted in recent studies[7], early integration of SGLT2is into treatment regimens could substantially lower the long-term burden of heart failure. The cardioprotective mechanisms of these inhibitors are multifaceted, impacting several biological pathways. Research has shown that SGLT2is enhance myocardial energy metabolism, reduce myocardial fibrosis, and decrease inflammation and oxidative stress, as seen in studies on myocardial function and ventricular remodeling[6,8]. These actions collectively improve left ventricular function and mitigate adverse ventricular remodeling following acute myocardial infarction, suggesting that SGLT2is can not only halt but potentially reverse early-stage cardiac damage. Furthermore, clinical evidence demonstrates that SGLT2is improve cardiac function in diabetic patients, reducing the risk of progression to more advanced heart failure[1]. This aligns with findings showing that SGLT2is improve cardiac oxygenation and myocardial function, both crucial for preventing adverse outcomes in diabetic cardiomyopathy[5]. Also, the reduction of inflammation, as indicated in studies of inflammation and cardiovascular health, emphasizes the broad therapeutic potential of these drugs[9]. From a clinical perspective, incorporating SGLT2is into treatment protocols could significantly improve patient outcomes. By addressing both metabolic and cardiovascular factors in type 2 diabetes, this comprehensive approach leads to better long-term outcomes and reduces the incidence of heart failure. The research underscores the transformative potential of SGLT2is in managing diabetic cardiomyopathy, emphasizing the importance of early intervention in preventing disease progression.

Broader implications for cardiovascular care

The use of SGLT2is in patients with type 2 diabetes and asymptomatic heart failure offers significant public health and economic benefits, extending beyond individual patient outcomes. These medications have been shown to reduce the incidence and severity of heart failure, leading to fewer hospitalizations and decreased healthcare costs. Positive effects on myocardial function further support their inclusion in treatment guidelines for this population[1]. A key aspect of the broader cardiovascular impact of SGLT2is is their ability to prevent new-onset atrial fibrillation[3], a serious and costly complication associated with diabetes. By reducing the incidence of atrial fibrillation, SGLT2is not only improve patient outcomes but also alleviate the financial burden on healthcare systems, which must manage the high costs of arrhythmia-related complications. The pharmacoeconomic benefits of SGLT2is are especially evident in the context of heart failure. By slowing its progression, these medications reduce the frequency of acute cardiovascular events, translating into fewer hospital admissions and decreased reliance on costly interventions such as mechanical circulatory support or heart transplants. Preventing advanced heart failure and mitigating complications such as myocardial infarction lead to substantial long-term savings. Improved cardiac oxygenation and myocardial function are critical to preventing severe cardiac deterioration, as evidenced by studies showing that SGLT2is improve these key factors[5]. Mechanistically, SGLT2is offer benefits by enhancing myocardial energy metabolism, reducing fibrosis, and attenuating inflammation and oxidative stress, all of which contribute to their pharmacoeconomic advantages[6,8]. These actions not only improve left ventricular function but also promote broader cardiovascular health in diabetic patients, making SGLT2is a cost-effective addition to diabetes management. From a healthcare systems perspective, incorporating SGLT2is into treatment regimens has the potential to significantly lower costs associated with managing diabetic cardiomyopathy and related cardiovascular diseases. Research has highlighted the inflammation-reducing properties of SGLT2is, which further support their potential to reduce recurrent hospitalizations and the need for intensive medical interventions[9]. This aligns with the growing emphasis on preventive care, where early intervention can substantially reduce long-term healthcare expenditures. Largely, integrating SGLT2is into the treatment strategies for diabetic patients offers dual advantages: Improved clinical outcomes and reduced healthcare costs. Recent findings advocate for a paradigm shift in care, emphasizing the pharmacoeconomic impact of these inhibitors in managing both metabolic and cardiovascular health. By addressing not only glycemic control but also cardiovascular complications, SGLT2is provide a cost-effective and comprehensive approach to improving the quality of life for diabetic patients while alleviating financial strain on healthcare systems.

Future directions

The research on the cardiovascular benefits of SGLT2is has revealed promising findings, paving the way for further investigations into their long-term effects on heart function in patients with type 2 diabetes and asymptomatic heart failure[1]. While the short-term benefits of these inhibitors are well-established, future studies should focus on understanding their extended effects on myocardial function, particularly concerning the reduction of heart failure progression and hospitalizations. Additionally, there is a critical need to explore the role of SGLT2is in preventing adverse cardiac remodeling following acute myocardial infarction. Evidence suggests that SGLT2is may offer protective mechanisms that mitigate long-term deterioration of heart function post-infarction[8]. Understanding these effects could solidify the role of SGLT2is in post-infarction care protocols, potentially expanding their application in cardiovascular settings beyond diabetes management. Another important area for future research is optimizing the timing and dosage of SGLT2is treatment. Synthetic approaches have been proposed to enhance the clinical application of these inhibitors[4]. Investigating how these factors influence efficacy across different populations—such as those with varying stages of heart failure or comorbid conditions like hypertension—can refine clinical guidelines and ensure optimal use of SGLT2is among diverse patient groups. In addition to cardiovascular benefits, SGLT2is may offer neuroprotective effects, as shown in studies involving neurodegenerative disease models[10]. These findings suggest that SGLT2is could have clinically significant impacts on the nervous system for patients with both diabetes and neurodegenerative disorders. Expanding research to include these effects may uncover new therapeutic applications, extending the role of SGLT2is in multimodal care for diabetes and associated comorbidities. Exploring the effects of SGLT2is on other critical organ systems, particularly the kidneys, is vital. Studies indicate that SGLT2is can enhance renal function by reducing lipid deposition and cellular senescence[2,11]. This research aligns with efforts to address the complex metabolic dysfunctions associated with type 2 diabetes, where SGLT2is may play a key role in preventing kidney disease progression. Future studies should also examine how SGLT2is influence metabolic pathways, such as lipid metabolism and autophagy, with implications for conditions like atherosclerosis. Evidence suggests that SGLT2is can induce autophagy, providing a protective mechanism against atherosclerosis progression[6]. The observed benefits in metabolic health, including reductions in visceral fat and improvements in insulin sensitivity[12], further support the notion that SGLT2is are integral components of comprehensive diabetes management. Finally, advanced modeling techniques can help predict patient-specific pharmacokinetics and pharmacodynamics of SGLT2is. These models can assist in developing individualized treatment plans, ensuring that SGLT2is are administered in ways that maximize benefits for each patient. As more data becomes available, personalized treatment approaches incorporating these inhibitors can enhance patient care and reduce the risk of adverse outcomes. The growing body of clinical evidence underscores the need for SGLT2is to be integrated more broadly into clinical guidelines. These inhibitors not only provide glycemic control but also offer cardiovascular and systemic benefits, making them a cornerstone in managing diabetic cardiomyopathy and related comorbidities. By continuing to explore their diverse applications and optimizing their use, SGLT2is have the potential to revolutionize diabetes and cardiovascular care.

CONCLUSION

The study by Grubić Rotkvić *et al*[1] provides vigorous evidence supporting the efficacy of SGLT2is in enhancing myocardial function in patients with type 2 diabetes and asymptomatic heart failure[1]. The editorial tensions the multi-dimensional mechanisms through which SGLT2is exert their cardioprotective effects, including improvements in cardiac function and reductions in myocardial stress. The evidence highlights the potential of SGLT2is to not only improve glucose control but also mitigate cardiovascular complications associated with diabetes. Recent research corroborates and extends these findings (Table 1). For instance, Xu *et al*[6] demonstrated that empagliflozin, an SGLT2is, attenuates atherosclerosis progression through the induction of autophagy, suggesting that these agents may offer additional cardiovascular benefits beyond glycemic control[6]. Another study showed that SGLT2 inhibitors alleviate renal lipid deposition and improve renal oxygenation, highlighting their protective effects on kidney function, which is closely linked to cardiovascular health[5]. The metabolic advantages of SGLT2 inhibitors, including visceral fat reduction and improved metabolic dysfunction, have also been emphasized[12]. These findings align with other research showing reductions in inflammatory markers such as CRP associated with SGLT2 inhibitor use, reinforcing their role in managing systemic inflammation and metabolic disturbances in diabetes[9]. In terms of clinical implications, the early use of SGLT2is appears promising for preventing the progression of diabetic cardiomyopathy. The evidence suggests that incorporating these drugs early in treatment regimens could significantly impact cardiovascular outcomes by reducing the burden of heart failure and potentially slowing disease progression[3,8]. As research continues to evolve, SGLT2is may solidify their role as a cornerstone in managing cardiovascular risk in diabetes. Their comprehensive benefits, including cardioprotective, nephroprotective, and metabolic advantages, offer new avenues for improving patient outcomes and reducing the overall burden of cardiovascular disease in diabetic populations. Continued investigation will be essential to fully elucidate their mechanisms and optimize their use in clinical practice[13].

Table 1 Effects of sodium-dependent glucose transporter 2 inhibitors on cardiovascular outcomes in type 2 diabetes and associated conditions: A comparative analysis of clinical studies and mechanistic insights[1]

Study	Objective	Key findings	Mechanistic insights	Clinical implications
Grubić Rotkvić *et al*[1]	To assess the impact of SGLT2is on myocardial function in patients with type 2 diabetes and asymptomatic heart failure	SGLT2is improve myocardial function and reduce heart failure symptoms	Enhanced myocardial metabolism and reduced cardiac stress	Potential benefits for patients with asymptomatic heart failure, suggesting a need for broader use in heart failure management
Lv *et al*[3]	To evaluate the effect of various hypoglycemic agents on the risk of new-onset atrial fibrillation	SGLT2is are associated with a lower risk of new-onset atrial fibrillation compared to other hypoglycemic agents	Reduced atrial fibrillation risk may be linked to improved glycemic control and cardiovascular stability	SGLT2is may be preferred in diabetic patients with a high risk of atrial fibrillation
Xie and Zhao[4]	To review the synthetic approaches and clinical applications of SGLT2is	SGLT2is show significant promise in managing type 2 diabetes and associated cardiovascular conditions	Inhibition of glucose reabsorption leads to improved cardiovascular outcomes and reduced oxidative stress	Highlights the growing role of SGLT2is in comprehensive diabetes care
Zeng *et al*[11]	To investigate the effects of SGLT2is on kidney senescence in an animal model	SGLT2is down-regulate latent transforming growth factor beta binding protein 2 expression, improving kidney function and reducing senescence	Modulation of renal fibrosis pathways and oxidative stress reduction	Potential benefits for preventing kidney disease progression in diabetic patients
Xu *et al*[6]	To explore the impact of empagliflozin on atherosclerosis progression	Empagliflozin attenuates atherosclerosis by inducing autophagy	Activation of autophagic pathways that counteract atherosclerotic changes	Empagliflozin may offer cardiovascular protection beyond glycemic control
Zhang *et al*[5]	To evaluate the effects of SGLT2is on renal lipid deposition and oxygenation in newly diagnosed type 2 diabetes patients	SGLT2is reduce renal lipid deposition and improve renal oxygenation levels	Enhanced renal metabolism and oxygenation may prevent renal complications	Supports the use of SGLT2is for improving renal health in diabetes
Tsukagoshi-Yamaguchi *et al*[12]	To analyze metabolomic changes associated with ipragliflozin and metformin treatment	Ipragliflozin leads to visceral fat reduction and improved metabolic profiles	Alterations in metabolite profiles associated with fat metabolism and reduction	Highlights ipragliflozin's potential in managing metabolic syndrome components in diabetes
Matthews *et al*[2]	To review the impact of SGLT2is on cardiovascular and renal outcomes irrespective of diabetes status	SGLT2is show beneficial effects on heart and kidney health even in non-diabetic populations	Cardiovascular and renal protective effects are due to mechanisms beyond glucose control	Supports broader application of SGLT2is in heart and kidney disease management
Ünal *et al*[10]	To evaluate neuroprotective effects of empagliflozin in a Parkinson's disease model	Empagliflozin shows neuroprotective effects through ketogenesis and autophagy	Involvement of ketogenesis and autophagy in mitigating neurodegenerative processes	Suggests potential for SGLT2is in neurodegenerative diseases
Chen *et al*[8]	To assess the impact of SGLT2is-pretreated macrophage transplantation on ventricular remodeling post-myocardial infarction	SGLT2is pretreatment improves ventricular remodeling and reduces adverse outcomes	Enhanced macrophage function and reduced myocardial fibrosis	Potential use of SGLT2is in post-infarction recovery strategies

[1]This table provides a comparative analysis of recent clinical studies examining the impact of sodium-dependent glucose transporter 2 inhibitors (SGLT2is) on cardiovascular outcomes in patients with type 2 diabetes and related conditions. It includes information on study objectives, key findings, mechanistic insights, and clinical implications. The findings demonstrate the benefits of SGLT2is in improving myocardial function, reducing the risk of atrial fibrillation, attenuating atherosclerosis, and enhancing renal and metabolic health. The table captures the diverse effects of these inhibitors on cardiovascular and systemic health beyond their role in glucose management. SGLT2is: Sodium-dependent glucose transporter 2 inhibitors.

FOOTNOTES

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