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ABOUT COVER

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EDITORIAL

Inherited arrhythmias and gene therapy: Are there any ethical considerations to take into account?

Michael Spartalis, Eleftherios Spartalis, Gerasimos Siasos

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Abstract

Interventional electrophysiology represents a relatively recent subspecialty within the field of cardiology. In the past half-century, there has been significant advancement in the development and implementation of innovative ablation treatments and approaches. However, the treatment of arrhythmias continues to be inadequate. Several arrhythmias, such as ventricular tachycardia and atrial fibrillation, pose significant challenges in terms of therapeutic efficacy, whether through interventional procedures or the administration of antiarrhythmic drugs. Cardiologists are engaged in ongoing research to explore innovative methodologies, such as genome editing, with the purpose of effectively managing arrhythmias and meeting the growing needs of patients afflicted with rhythm disturbances. The field of genome editing has significant promise and has the potential to serve as a highly effective personalized therapy for rhythm disorders in patients. However, several ethical issues must be considered.

Key Words: Arrhythmia; Sudden cardiac death; Genome editing; Long QT; Channelopathies; Mutation

Core Tip: The use of genome editing to treat rhythm disturbances at the substrate level could provide a revolutionary treatment for disorders that the current standard of care is inadequate. Our knowledge of the disease is the only limit in identifying a perfect genome editing tool for several rhythm disturbances. As our understanding of gene vectors and transfer techniques progress, a novel therapy approach will be upon us, where cardiac muscles are altered to be impervious to rhythm disturbances, enhancing patients' quality of living and relieving the burden on healthcare organizations. Ethical issues will eventually arise, as the treatments will be expensive.

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INTRODUCTION

Inherited cardiac arrhythmias syndromes are a cluster of diverse disorders that predispose to life-threatening rhythm disturbances and abrupt cardiac death[1]. Due to inadequate penetrance and genetic variability, their detection is not invariably straightforward[2]. Additionally, current therapies are typically invasive and only preventative[1,2]. While often effective in relieving or preventing symptoms, current pharmacological or interventional treatments do not specifically address the underlying genetic defect or the key intermediary pathways implicated in the development of these disorders[3]. Clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 techniques, in particular, have the ability to modify the genetic electrophysiologic substrate, hence enabling treatment for many lethal disorders[4]. So far, gene therapy has enabled the *in vitro* replication of rhythm disturbances, offering a consistent framework for variable pathogenesis, pathophysiological, and drug-testing research[1-4]. Nevertheless, *in vivo* procedures still require further investigation into the techniques' reliability, precision, and efficacy.

GENOME EDITING FOR INHERITED ARRHYTHMIAS

Inherited cardiac arrhythmia syndromes are disorders characterized by one or more genetic abnormalities that enhance the incidence of rhythm disturbance and culminate in a life-long risk of unexpected death[1]. Inherited arrhythmias can be categorized as electrophysiologic equilibrium abnormalities (long QT syndrome, catecholaminergic polymorphic ventricular tachycardia), organic disorders linked to rhythm disturbances (hypertrophic cardiomyopathy), or a combination involving both a proclivity for rhythm disturbances and organic heart disease (arrhythmogenic cardiomyopathy)[5]. Certain compounds that modify agonists (beta-blockers) or ion channels (sodium channel blockers) have shown effectiveness in specific forms of familial rhythm disturbances, although individuals are often only partially shielded[5,6]. Several types of familial rhythm disturbances have a gradual course, and thus no presently known treatment effectively slows disease advancement[7]. Current research has suggested that genetic treatment for people with familial rhythm disturbances might be developed to prevent harmful rhythm disturbances as well as hinder disorder development by addressing core disorder processes[6-9]. These upcoming treatments have the ability to decrease adverse reactions significantly while also improving clinical results[10].

Because gene variability is widespread in channelopathies, additional genetic variants are being found and included in the prospective catalog of variations amenable to genetic analysis[1,11]. Even though both patient-dependent and patient-independent *in vitro* techniques could corroborate a variant's pathogenic potential, more compelling data and statistical validation of disorder etiology are required before they could be included in commonly utilized medical testing[1-4]. Furthermore, despite significant advances in comprehending the pathophysiology of familial rhythm disturbances, guidelines for treatment approaches, such as beta-blockers, left cardiac sympathetic denervation, or implantable cardioverter-defibrillator, have not altered in the previous 40 years[1-4]. The ability to incorporate unique disease-causing variants while maintaining the same genetic origin allows for an impartial assessment of different mutations[1-4]. This comparison research revealed that various variants in the same gene could be the result of unique genetic pathways, strengthening the viewpoint that the therapy of familial rhythm disturbances must shift toward targeted therapy and patient-specific treatments[2,12].

Precision Medicine emerged as a novel approach to disease treatment and prevention, which considers the unique interplay between an individual's genetic profile, environmental factors, and lifestyle factors[13]. The primary objective of this technique is to predict appropriate interventions and preventive measures that may yield greater efficacy for individual patients or, more feasibly, for cohorts of patients sharing common attributes[13]. The present method stands in opposition to the prevailing one-size-fits-all paradigm, wherein illness treatment and prevention strategies are formulated solely on the basis of randomized trials without taking into account individual variations[13].

While missense mutations are generally straightforward to edit using CRISPR/Cas9, addressing complex variants, including double heterozygosity, could present further barriers that must be overcome[1,2]. Furthermore, CRISPR/Cas9 has various disadvantages that have slowed the use of *in vivo* gene therapy in the management of rhythm disturbances[1,2]. The homologous recombination *cellular* mechanism, downregulated in terminally differentiated cell types such as

cardiac myocytes, reduces the odds of success[1,2]. Moreover, correcting a minor amount of molecules may result in pro-arrhythmic episodes, worsening the individuals' medical conditions[1,2].

Pro-arrhythmia is a potential concern of treatments that modify heart rhythm[2,4]. This issue is particularly significant in the context of adeno-associated viruses (AAV) genome editing, which could lead to myocardial heterogeneities due to cardiac myocytes that have and have not been transfected by AAV[2,4]. A rigorous assessment of pro-arrhythmic potential necessitates screening in bigger animals with pulse rate, anatomy, and heart physiology similar to humans[2,4].

Another field of ongoing research is the immunological reaction to genome editing[1,2]. In big animals given massive AAV loads, the intrinsic immunity mechanism was activated, culminating in a possibly deadly inflammatory process[4]. The formation of neutralizing antibodies following one AAV treatment presently precludes subsequent vector dosage, which might promote high-level transmission or increase genetic engineering longevity[4]. Even though AAV transduction of cardiac myocytes causes minor inflammation, the possibility of adverse immunity reactions must be addressed when the therapy carrier expresses a foreign protein[4].

Overall, current investigations of inherited arrhythmia disorders and gene therapy have revealed that these disorders may be effectively replicated in the laboratory, revealing deficient ion currents and enabling a suitable framework for molecular, analytical, and drug-testing research[2]. Even though immensely attractive, this technique remains in its infancy, and transitioning from the lab to the patient may require more study to increase the procedures' reliability, effectiveness, and accuracy. Future *in vivo* CRISPR/Cas9 investigation in heart channelopathies could eventually enable us to realize its promise to treat these disorders and make personalized medicine a reality[6-8].

Over the past decade, there have been significant developments in genome editing and its applicability to familial rhythm disturbances. Genome editing with AAV vectors has shown outstanding outcomes for non-cardiac disorders[1]. The obstacles for viral vector-based heart genome editing entail demonstrating effectiveness at transduction efficiencies feasible in individuals, as well as demonstrating safety at these dosages. Off-target complications, the formation of pro-arrhythmia, the durability of treatment, and the limitation of reversibility following therapy continue to pose major challenges for translation[6-8]. Creating techniques to counteract innate immunity and allow for recurrent doses will significantly increase the therapeutic value of viral vectors, increase safety, and resolve issues about treatment durability [1,2]. To render viral genome editing cost effective, the tremendous cost of medical-grade AAV development must be reduced. The discovery of technologies for effective and specific myocardial distribution for oligonucleotides and altered mRNAs would be a game changer.

CONCLUSION

The notion of a pathogenic genetic mutation within a gene that encodes a cardiac ion channel, resulting in a substrate extremely prone to arrhythmias, has emerged as the fundamental framework for understanding the pathophysiology of all these syndromes[14]. According to current guidelines, it is recommended that individuals diagnosed with hereditary cardiomyopathies and arrhythmia syndromes have genetic testing as a standard component of their medical management[15]. The use of genome editing to treat rhythm disturbances at the substrate level could provide a revolutionary treatment for disorders that the current standard of care is inadequate. Our knowledge of the disease is the only limit in identifying a perfect genome editing tool for several rhythm disturbances. As our understanding of gene vectors and transfer techniques progress, a novel therapy approach will be upon us, where cardiac muscles are altered to be impervious to rhythm disturbances, enhancing patients' quality of living and relieving the burden on healthcare organizations. Ethical issues will eventually arise, as the treatments will be expensive. Who will cover the cost? Will there be an accurate risk stratification and patient selection tool, or will existing disparities in access to healthcare interventions increase?

FOOTNOTES

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EDITORIAL

Quo vadis cardiac rehabilitation; the role of comprehensive cardiac rehabilitation in modern cardiology

Nenad Lakušić, Ivana Sopek Merkaš

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Abstract

In accordance with the guidelines established by prominent European and global cardiology associations, comprehensive cardiac rehabilitation (CR) stands as an officially endorsed and highly recommended therapeutic approach (class I recommendations; level of evidence A) for a diverse spectrum of cardiac patients. Nevertheless, it is a cause for concern to observe that fewer than 50% of eligible patients are being effectively referred for CR, whether in an outpatient or in-patient setting. Concurrently, studies reveal that a substantial proportion of individuals with atherosclerotic cardiovascular disease maintain unhealthy lifestyles and exhibit suboptimal management of modifiable cardiovascular risk factors, including hypertension, lipid levels, and diabetes. Beyond the conventional patient profile encompassing those recovering from acute coronary syndrome with or without percutaneous coronary intervention, as well as patients who have undergone coronary or valvular surgery, contemporary CR now emphasizes specialized subgroups of patients. These include frail elderly patients, the female population with its unique considerations, individuals burdened by multiple cardiovascular comorbidities, those who have developed psychological consequences due to a cardiac illness and particularly those grappling with chronic heart failure. This editorial seeks to offer a state-of-the-art assessment of the significance and role of comprehensive CR within modern cardiology.

Key Words: Cardiac rehabilitation; Chronic heart failure; Treatment of heart failure; Cardiovascular disease; Psychological disorders; Posttraumatic stress disorder

Core Tip: Comprehensive cardiac rehabilitation (CR) is an established and endorsed therapeutic approach for a broad spectrum of cardiac patients. Nevertheless, it is concerning that fewer than 50% of eligible patients are being effectively referred for CR, whether in an outpatient or inpatient setting. This editorial aims to offer a contemporary perspective on the significance and role of comprehensive CR in modern cardiology.

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INTRODUCTION

Cardiac rehabilitation (CR) programs involve a comprehensive medical evaluation and optimization of the health status of diverse patient groups, including those recovering from acute coronary syndrome (ACS) with or without percutaneous coronary intervention (PCI), surgical myocardial revascularization coronary artery bypass grafting (CABG), valvular surgery, various endovascular procedures transcatheter aortic valve implantation, endovascular aneurysm repair (EVAR), thoracic EVAR, *etc*., surgical management of congenital heart defects, peripheral arterial disease, and heart transplantation, among others[1].

CONTENT AND POSITIVE EFFECTS OF CR

CR programs stand as the most cost-effective intervention to ensure favorable outcomes across a broad spectrum of cardiovascular conditions[2]. These programs encompass physical training and counseling on future physical activity, the identification, assessment, and mitigation of various cardiovascular risk factors, optimization of medication regimens, psychosocial support, education on nutrition, weight management, the sustained benefits of regular exercise, its purpose, potential side effects, and the promotion of medication adherence. The overarching, long-term objectives of the CR program are to promote consistent unsupervised exercise, the adoption of a "healthy lifestyle", the reintegration of employed individuals into the workforce, and the enduring reduction of major adverse cardiac events (MACEs) as well as the deceleration of the cardiovascular continuum. Some of the well-documented short-term effects of CR encompass enhancements in lipid profiles, reductions in blood pressure, the management of type 2 diabetes, decreases in inflammation high-sensitivity C-reactive protein (hsCRP), heart rate normalization, improvements in ejection fraction, mitigation of adverse left ventricular remodeling, and the alleviation of emotional stress and depression, among others[2-4].

SAFETY OF THE CR

The safety of the CR program has remained unquestionably solid. For instance, data from the French registry of complications during CR reveal an exceptionally low incidence of expected adverse events or complications, such as 1 MACE occurring in more than 8000 stress tests, 1 MACE in every 50000 h of patient exercise, and 1.3 cardiac arrests per million hours of exercise[5].

INCONSISTENCY OF RECOMMENDATIONS *VS* CLINICAL PRACTICE RELATED TO CR

Considering all the information presented, the European Society of Cardiology and other prominent global cardiology associations have officially acknowledged CR as a highly effective and essential component in the comprehensive treatment of all categories of cardiology patients. They have included CR in their guidelines, assigning it class I recommendations and a level of evidence A[2-4,6,7]. Despite this, it remains a matter of concern that less than half of eligible patients are actually referred for CR, whether in an outpatient or inpatient setting [2,3,7,8].

On the other hand, findings from extensive studies like Euroaspire indicate that a substantial portion of patients with established atherosclerotic cardiovascular disease (CVD) continue to maintain unhealthy lifestyles and struggle with inadequate control of modifiable cardiovascular risk factors, including elevated blood pressure, unfavorable lipid profiles, and diabetes. For instance, 55% of these patients were persistent smokers, 38% were categorized as obese (with a body mass index of ≥ 30 kg/m^2), 66% engaged in physical activity for less than 30 min five times a week, 42% had blood pressure equal to or exceeding 140/90 mmHg, and 71% exhibited low-density lipoprotein cholesterol levels of 1.8 mmol/L or higher. The authors rightly emphasize that "cardiovascular prevention requires modern preventive cardiology programs delivered by interdisciplinary teams of healthcare professionals addressing all aspects of lifestyle and risk factor management, in order to reduce the risk of recurrent cardiovascular events"[9].

CENTER-BASED *VS* HOME-BASED CR

According to the new systematic review[10], home-based CR (HBCR) could offer a secure and practical alternative to traditional center-based CR (CBCR). Research suggests that the HBCR model may serve as an equitable intervention approach for stable patients with CVD across all risk levels for exercise-related cardiovascular complications, particularly for those who are unable to access CBCR services. Moreover, the integration of artificial intelligence, with its robust data mining and interpretation capabilities, holds substantial future promise for HBCR. Tailored HBCR programs can be implemented by harnessing artificial intelligence through wearable monitoring and personalized coaching[10].

HYBRID CR

In the current medical setting, the duration of hospital stays for patients with conditions like ACS or acute HF has notably shortened, often leaving insufficient time for comprehensive patient education regarding their medical condition. Hence, CR programs, whether in outpatient, inpatient, or hybrid formats, have become essential and ideal for ensuring the complete and long-term effectiveness of interventional, surgical, or medical treatments[11]. Particularly during the challenging period of the coronavirus disease 2019 pandemic[12], hybrid CR has gained prominence, proving to be a safe and efficient alternative to traditional rehabilitation care, offering numerous benefits for CVD patients[13,14]. Research have demonstrated the safety and effectiveness of hybrid CR exercise programs, which not only reduce the cost of delivery but also enhance patient participation[15,16]. In the latest review[16], it was revealed that hybrid CR provided similar short-term outcomes to traditional CR for patients with coronary artery disease. A recent systematic review[17] demonstrated that telerehabilitation, centered on exercise, is equally cost-effective when compared to traditional CBCR interventions. European Association of Preventive Cardiology strongly encourages the development and seamless integration of alternative digital modalities, like telerehabilitation, to offer comprehensive CR in a more refined and effective manner[12].

PATIENTS OUTCOMES AFTER CR

In a meta-analysis comprising 85 randomized controlled trials involving 23430 individuals with coronary heart disease, exercise-based CR demonstrated improved outcomes across short-term (6 to 12 mo), medium-term (> 12 to 36 mo), and long-term (> 3 years) follow-up periods. Short-term effects included reductions in myocardial infarction rates and all-cause hospitalizations, while medium and long-term effects were associated with decreased cardiovascular mortality[18]. Additionally, a recent study by Bauer *et al*[19] has affirmed that CR leads to a reduction in 2-year mortality following CABG.

SPECIALIZED PATIENT SUBGROUPS

In addition to the conventional patient profile (comprising individuals post-ACS with or without PCI, coronary or valvular surgery), contemporary CR now places emphasis on specialized patient subgroups. These include frail elderly patients[20], the female population, with consideration for its unique characteristics (as women are less frequently referred to CR!)[21], individuals with multiple cardiovascular comorbidities, those who have undergone transcatheter implantation or valve repair, and particularly patients with chronic heart failure (HF) (CHF)[7,22,23].

Results from global survey on barriers to CR based on gender indicate that barriers to CR differ significantly between men and women across various regions, underscoring the need for region-specific, customized approaches to overcome these challenges[24]. For women, the primary barriers to enrollment encompass a lack of awareness, cost considerations, and concerns about experiencing fatigue or pain during exercise. When it comes to program adherence, women's main difficulties involve distance, transportation, and family responsibilities. Notably, non-working women experience more pronounced CR challenges. While personalized strategies aimed at addressing these challenges were highly beneficial to patients, there is a need for the implementation of automatic referral and the provision of a choice of reimbursed CR models with elements tailored to women to effectively address the primary barriers identified[24].

PATIENTS WITH CHF AND CR

Patients with CHF exhibit a significant degree of heterogeneity, forming an increasingly diverse population with a wide array of characteristics, including comorbidities, symptoms, clinical stability or instability, with preserved or varying degrees of reduced ejection fraction of the left ventricle. In patients with compensated HF with reduced ejection fraction, regular exercise has been shown to reduce both total hospitalizations and those related to HF, enhance exercise tolerance, and improve overall quality of life, including a reduction in depressive symptoms[7,22]. Taylor *et al*[7] aptly underscores in their recent publication that CR should be regarded as an essential, the fifth pillar in the treatment of HF patients, alongside pharmacological interventions such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin

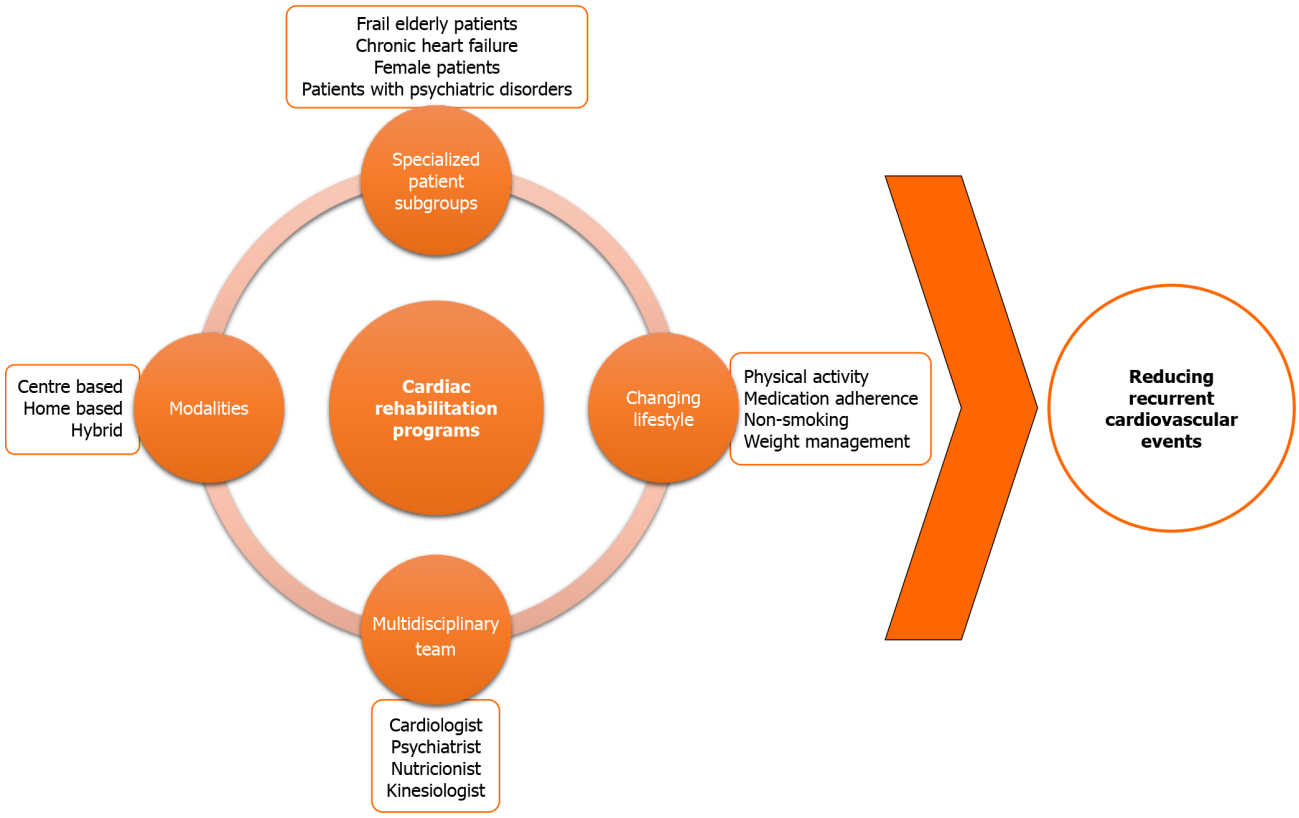

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Figure 1 Comprehensive cardiac rehabilitation in modern cardiology.

receptor-neprilysin inhibitors, sodium-glucose co-transporter 2 inhibitors, and medical devices.

ADDITIONAL ADVANTAGES OF THE CR PROGRAMS

An emerging concern in recent years has been the early recognition and intervention in a wide spectrum of psychological disorders following ACS or cardiac surgery, potentially leading to post-traumatic stress disorder. These patients often go unnoticed and are known to experience a lower quality of life, an increased incidence of MACEs, and an overall poorer prognosis compared to those without such disorders[11]. Comprehensive CR, with individualized patient assessments, provides an opportune moment for recognizing and treating these psychological disorders. A multidisciplinary team approach, which actively involves psychologists and psychiatrists, is essential for comprehensive management[11,25].

CONCLUSION

Taking all the above into account, it is evident that CR programs are effective, safe, cost-effective for society, and an indispensable component of the treatment for a broad spectrum of cardiac patients. Instead of providing a traditional conclusion, we would like to conclude this editorial with a message we consistently impart to our patients: "CR cannot change a patient's past, but it unquestionably holds the potential to enhance the future of the patient's heart, with a high-quality life without MACEs" (Figure 1).

FOOTNOTES

Author contributions: Lakušić N and Sopek Merkaš I were responsible for the conception and design of the manuscript, literature review, data collection and processing, and they wrote the first original draft; both authors issued approval for the final version to be submitted.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy and prognostic impact of Pericarpium Trichosanthis injection combined with nicorandil for intractable angina pectoris in elderly patients: A retrospective study

Jun Li, Mo-Wei Kong, Yu-Yu Xie, Ze-Bi Wang, Li Xu, Guo-Xiang He

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Abstract

BACKGROUND

Coronary artery disease (CAD) is a leading cause of global cardiovascular mortality. Refractory angina pectoris, a manifestation of CAD, requires effective drug treatments. Pericarpium Trichosanthis injection, a traditional Chinese medicine, improves cardiovascular symptoms, while nicorandil alleviates spasms and angina. Both have potential in treating CAD.

AIM

To investigate the therapeutic effects of combining Pericarpium Trichosanthis injection and nicorandil in elderly patients suffering from refractory angina caused by coronary heart disease.

METHODS

A retrospective analysis was conducted on the data of 130 patients diagnosed with refractory coronary heart disease. Based on the different treatment regimens administered during hospitalization, the patients were divided into a control group (58 cases) and a study group (72 cases). The control group received conventional treatment, which included aspirin, statins, and nitrate vasodilators. In addition to the conventional medication, the study group received a combination treatment of Pericarpium Trichosanthis injection and nicorandil.

RESULTS

After treatment, the study group showed significantly higher left ventricular ejection fraction and cardiac output, and lower brain natriuretic peptide and C-reactive protein levels compared to the control group. The study group also

exhibited improvements in angina, quality of life, exercise endurance, and lipid profiles. Multivariate logistic regression analysis revealed a relationship of lipid levels and heart function with the combined treatment. Some patients in the study group experienced headaches during treatment, but no significant adverse reactions were observed. Follow-up showed that the treatment was well-tolerated, with no drug-related adverse reactions detected.

CONCLUSION
Combination of Pericarpium Trichosanthis injection and nicorandil is more effective than conventional treatment in improving symptoms and heart function in elderly patients with refractory angina pectoris.

Key Words: Pericarpium Trichosanthis injection; Coronary heart disease; Intractable angina pectoris; Nicorandil

Core Tip: Combining Pericarpium Trichosanthis injection and nicorandil shows promise in improving symptoms and heart function in elderly patients with refractory angina caused by coronary disease, as demonstrated by a retrospective study. This combination resulted in significant improvements in left ventricular function, cardiac output, angina frequency, quality of life, exercise tolerance, and lipid profiles. The therapy was well-tolerated with minimal adverse reactions. These findings highlight the potential of this combined treatment as an effective therapeutic option for refractory angina in elderly patients.

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INTRODUCTION

Coronary artery disease (CAD) has become the leading cause of death from cardiovascular diseases worldwide, with its mortality rate only second to cancer[1]. The high prevalence of CAD is closely related to factors such as inflammation, metabolic disorders, arteriosclerosis, and thrombosis. Refractory angina pectoris is a manifestation of CAD, and refers to angina symptoms caused by coronary artery lesions that do not significantly improve or become controllable under conventional treatments (such as medication and percutaneous coronary intervention)[2]. The elderly population is a high-risk group for refractory angina, and the treatment outcomes are generally poor[2]. For refractory angina pectoris, excellent drug treatment options are crucial. Currently, drug therapy is one of the preferred methods for the treatment and prevention of cardiovascular diseases. However, many treatment options face problems such as poor efficacy and severe side effects.

Pericarpium Trichosanthis injection, a traditional Chinese medicine, is widely used in the treatment of cardio-cerebrovascular diseases[3]. Pericarpium Trichosanthis injection can improve the symptoms of cardiovascular diseases such as arteriosclerosis through its antioxidant and anti-inflammatory effects. Some studies have also found that Pericarpium Trichosanthis injection can improve blood lipids, which is beneficial for the prognosis of coronary heart disease[4]. Nicorandil relaxes coronary vascular smooth muscle by stimulating guanylyl cyclase and increasing cyclic GMP levels as well as by a second mechanism resulting in activation of K+ channels and hyperpolarizationm, that can alleviate symptoms such as coronary spasms and angina. Some studies have shown that nicorandil also has some effect in treating hypertension and heart failure[5].

In the past few decades, the combined use of Pericarpium Trichosanthis injection and nicorandil for the treatment of cardiovascular diseases has received widespread attention. However, there is currently a lack of evaluation studies for elderly patients, and it is unclear what impact this combined treatment option has on the efficacy and safety for older patients. The aim of this study was to explore the efficacy and prognostic impact of Pericarpium Trichosanthis injection combined with nicorandil in the treatment of refractory angina pectoris in elderly patients, and to provide clinical decision support for the future treatment of coronary heart disease in elderly patients.

MATERIALS AND METHODS

General information

Case data: This was a multicenter study. After screening using the inclusion and exclusion criteria, 148 patients' medical records (age 72-89 years) with coronary heart disease and refractory angina pectoris admitted to Guiqian International General Hospital and Chengdu Fifth People's Hospital between March 2021 and January 2023 were selected. After

screening and excluding cases that did not meet the criteria, a total of 130 patients were finally included in the statistical analysis, with 72 in the study group and 58 in the control group. All studies used the same method for data collection, and the screening process is shown in Figure 1. There were no significant differences in general data between the two groups ($P > 0.05$) (Table 1).

Diagnostic criteria: The diagnosis of coronary heart disease was based on the diagnostic criteria established by the Chinese Medical Association for Coronary Heart Disease: (1) Confirmation of at least one major coronary artery with luminal stenosis ≥ 50% through coronary angiography; (2) Auxiliary examinations such as electrocardiography, cardiac troponin, and exercise testing indicating myocardial ischemia, coronary heart disease, or acute coronary syndrome; and (3) Presence of typical angina symptoms such as chest tightness and chest pain. The diagnosis of coronary heart disease was made if was met and at the same time or was also met. The diagnostic criteria for refractory angina pectoris mainly included: (1) Pain: Persistent angina symptoms for > 3 mo, with no obvious cause or significant improvement despite ongoing treatment; and (2) Congestive heart failure.

Inclusion criteria: (1) Applicants who met the above diagnostic criteria; (2) Inclusion criteria; and (3) The medical records were complete.

Exclusion criteria: (1) Cardiac insufficiency secondary to other diseases; (2) Acute onset of severe myocardial infarction; (3) In severe liver disease, alanine aminotransferase and aspartate aminotransferase were twice the upper limit of the reference range; (4) Malignant tumors; and (5) Surgery within 2 wk.

Methods

Treatment approach: The control group was treated according to the conventional Western Medicine Guidelines for Coronary Heart Disease (2nd edition)[6] and the recommendations of the China Coronary Heart Disease Prevention Strategy 2015[7]. This systematic and individualized medication included nitrate drugs to dilate coronary arteries and increase myocardial blood flow, statins and antiplatelet drugs, as well as calcium channel blockers and β-receptor blockers to reduce myocardial contractility and heart rate, thereby reducing myocardial oxygen consumption. For patients with underlying diseases such as hypertension and diabetes, hypoglycemic and antihypertensive treatments were given. The treatment course was 1-2 wk, and after discharge, patients were advised to take long-term secondary prevention drugs for coronary heart disease and to attend follow-up visits at 2 mo, 6 mo, and 1 year.

The treatment group, in addition to the conventional treatment of the control group, was given a combination treatment of nicorandil and Pericarpium Trichosanthis injection. Pericarpium Trichosanthis injection (Shanghai Shybio Pharmaceutical Co. Ltd.) was administered at 12 mL/dose, once daily. Nicorandil (Sihuan Kebao Pharmaceutical) was administered at 5 mg/dose, three times daily. The treatment continued for 1-2 wk. After discharge, patients were advised to take long-term secondary preventive drugs for coronary heart disease, and nicorandil, and to attend follow-up visits at 2 mo, 6 mo, and 1 year. The clinical efficacy of the two groups of patients after treatment was compared.

Efficacy evaluation: The efficacy of treatment of refractory angina pectoris in coronary heart disease was evaluated using multiple indicators, including improvement in cardiac function, frequency and duration of angina, exercise tolerance, quality of life, and cardiovascular events[8]. Specific evaluation indicators included the following: (1) Cardiac function evaluation was performed using cardiac ultrasound, including left ventricular ejection fraction (LVEF), cardiac output (CO), stroke volume, and heart rate. Data on B-type natriuretic peptide (BNP) and C-reactive protein (CRP) were collected during the treatment process; (2) Changes in the frequency and duration of angina: The Canadian Cardiovascular Society (CCS) angina scale was used to evaluate the treatment effect based on improvement in subjective symptoms and signs; (3) Changes in exercise tolerance: Maximum exercise tolerance and angina attacks before and after treatment were evaluated through a treadmill test combined with a 6-min walking test (6MWT); (4) Changes in quality of life: Changes in quality of life were evaluated using the self-acceptance questionnaire (SAQ); and (5) Occurrence of cardiovascular events: Through 2 years of follow-up, the occurrence of cardiovascular endpoints was observed, including sudden cardiac death, myocardial infarction, heart failure, and fatal arrhythmia. Sudden cardiac death was defined as sudden and unexpected death, within 1 h after the onset of cardiac-related symptoms, or no evidence other than cardiac disease was found within 24 h after the onset of symptoms. This definition was jointly established by the American Heart Association and European Society of Cardiology[9,10]. Myocardial infarction was defined based on clinical manifestations, electrocardiography, myocardial enzyme studies, and imaging examinations[11]. Heart failure was defined by clinical manifestations such as dyspnea, fatigue, and generalized edema; signs including cardiac murmurs, enlarged cardiac borders, and increased heart rate; cardiac function assessment including elevated BNP or NT-proBNP in the blood, and echocardiography and/or magnetic resonance imaging showing decreased ventricular contractile function [12]. Fatal arrhythmia was defined by clinical manifestations of syncope or sudden death, and electrocardiography showed types of arrhythmia including ventricular tachycardia, ventricular fibrillation, and long QT syndrome[13].

Assessment and measurement of blood lipids: We determined the changes in lipid levels before and after treatment in patients through medical records. The diagnostic criteria for hyperlipidemia were: (1) Serum high-density lipoprotein (HDL) < 9.0 mmol/L; (2) Total cholesterol (TC) ≥ 2.1 mmol/L; and (3) Serum triglyceride (TG) ≥ 1.70 mmol/L.

Statistical analysis

We used SPSS version 20.0 statistical software for statistical analyses. Quantitative data that conformed to a normal distribution are expressed as the mean ± SD, and single-factor analysis of variance was used for comparisons among multiple groups; least significant difference *t* test was used for pairwise comparisons; and independent sample *t* test was used for

Table 1 General data for patients (mean ± SD), *n* (%)

	Overall (*n* = 130)	Study group (*n* = 72)	Control group (*n* = 58)	*P* value
Age (yr)	73 ± 10	72 ± 11	74 ± 6	0.42
Males	78 (60)	40 (56)	38 (66)	0.09
Heart rate (bpm)	72 ± 16	71 ± 16	72 ± 17	0.01[a]
Systolic pressure (mmHg)	114 ± 21	114 ± 20	119 ± 22	0.27
Diastolic pressure (mmHg)	73 ± 16	71 ± 9	76 ± 7	0.14
LVEF (%)	77 ± 15	77 ± 10	75 ± 11	0.47
Creatinine (mmol/L)	100 ± 52	92 ± 44	99 ± 40	0.21
Arterial high pressure	10 (8)	6 (8)	4 (7)	0.62
Diabetes mellitus	22 (17)	13 (18)	9 (16)	0.76
Dyslipidemia	44 (34)	25 (35)	19(33)	0.22
Current smoking	50 (38)	24 (33)	26(45)	0.62
Antithrombotics				
Aspirin	84(65)	50(69)	34 (59)	0.11
Clopidogrel	46 (35)	26 (36)	20 (34)	0.50
Direct oral anticoagulant	6 (5)	4(6)	2(3)	0.42

[a]$P < 0.05$, statistically significant.
LVEF: Left ventricular ejection fraction.

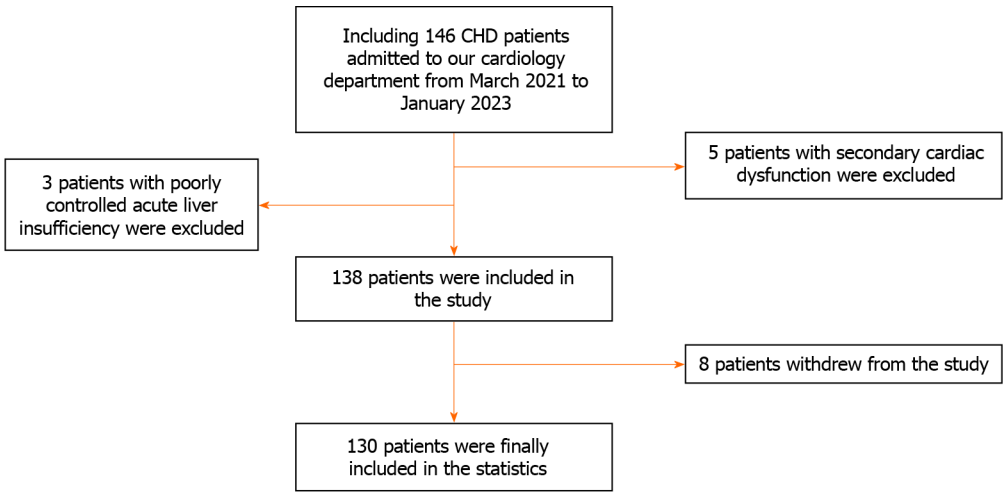

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Figure 1 Screening of study subjects. CHD: Coronary heart disease.

comparisons between two groups. Categorical data are expressed as percentages, and the χ^2 test was used for comparisons. Logistic regression analysis was performed on indicators with significant differences in single-factor analysis, and $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of cardiac function before and after treatment

Before treatment, there was no significant difference in LVEF, CO, BNP, CRP, or other indicators between the two groups ($P > 0.05$). After treatment, compared with the control group, the study group had higher LVEF and CO, and lower BNP and CRP, with significant differences ($P < 0.05$) (Table 2).

Table 2 Comparison of cardiac function before and after treatment in both groups (mean ± SD)

Group	LVEF, %		CO, L/min		BNP, ng/L		CRP, mg/L	
	Control group	Study group	Control group	Study group	Control group	Study group	Control group	Study group
Pretherapy	43.3 ± 2.2	47.3 ± 2.2	4.8 ± 0.0	5.2 ± 0.3	724.5 ± 42.5	405.7 ± 57.4	17.4 ± 3.4	11.2 ± 1.2
Post-treatment	44.7 ± 4.1	54.5 ± 4.6	4.9 ± 0.2	5.6 ± 0.4	711.5 ± 33.4	282.6 ± 44.3	17.6 ± 3.2	8.4 ± 1.2
t	0.6	14.2	0.2	0.8	31.7	296.5	4.7	5.1
P value	0.25	0.01[a]	0.38	0.04[a]	0.03[a]	0.00[a]	0.60	0.03[a]

[a]$P < 0.05$, statistically significant.

LVEF: Left ventricular ejection fraction; CO: Cardiac output; BNP: Brain natriuretic peptide; CRP: C-reactive protein.

Evaluation of angina symptoms, quality of life, and exercise tolerance before and after treatment

Before treatment, there was no significant difference in CCS angina classification, SQA scores, or 6MWT between the groups ($P > 0.05$). After treatment, compared with the control group, the study group showed improvement in chest pain symptoms, with a significant decrease in CCS angina classification ($P < 0.05$) and a significant improvement in 6MWT ($P < 0.05$). However, the improvement in SQA scores was not significant (Table 3).

Comparison of Low-density lipoprotein, High-density lipoprotein, Total cholesterol, and Triglyceride levels before and after treatment

There was no significant difference in serum low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), or triglyceride (TG) between the two groups before treatment ($P > 0.05$). After 2 mo of treatment, the study group showed a significant decrease in TC and TG compared with the control group, while LDL and HDL did not show significant changes ($P > 0.01$) (Table 4).

Multivariate logistic regression analysis of therapeutic effects of Pericarpium Trichosanthis injection combined with nicorandil

LDL, HDL, TC, and TG (lipid indexes) as well as LVEF, CO, BNP, and CRP (cardiac function indexes) were used as independent variables, and whether to use Pericarpium Trichosanthis injection combined with nicorandil was used as the dependent variable in the multiple logistic regression. LDL, TC, TG, LVEF, CO, and BNP were significantly related to the use of the combination therapy ($P < 0.05$), and the combined treatment had an inhibitory effect on LDL, TC, TG, and BNP, and a promotive effect on LVEF and CO (Table 5).

Adverse reactions and follow-up

During the treatment period, 12 (16.7%) patients in the study group experienced headaches, with an average duration of 4 d and self-resolution. Throughout the entire treatment process, there was no impact on blood pressure, heart rate, or oxygen saturation in any of the patients. All 130 patients successfully completed the treatment, and 92 (71%) completed follow-up, with a median duration of 8.5 (3-12) mo. During follow-up, two patients in the study group and three in the control group died of respiratory failure caused by coronavirus disease 2019 at the 6-12-mo follow-up. No other related adverse reactions occurred in the patients during follow-up, and there were no deaths due to other causes.

DISCUSSION

Pericarpium Trichosanthis injection is a traditional Chinese medicine formulation that has been widely used in the treatment of cardiovascular and cerebrovascular diseases in recent years. Multiple studies have shown that Pericarpium Trichosanthis injection has significant clinical efficacy and minimal adverse reactions. A clinical study demonstrated that Pericarpium Trichosanthis injection significantly reduced the severity of angina and myocardial ischemic time, while also lowering the levels of myocardial enzymes, indicating its cardioprotective effects[14]. Another randomized controlled trial demonstrated that Pericarpium Trichosanthis injection has a significant effect in relieving symptoms and improving hemodynamic parameters in patients with angina[15]. Nicorandil has been widely used in the treatment of cardiovascular diseases such as arrhythmia and hypertension. In recent years, researchers have conducted in-depth studies on the pharmacology and clinical applications of nicorandil. A meta-analysis of nicorandil extended-release tablets found that it can significantly reduce blood pressure and heart rate, with a more pronounced effect on patients with cardiovascular diseases[16]. Another prospective study on critically ill cardiovascular disease patients using a cardiac support system demonstrated that nicorandil significantly reduced mortality and the risk of cardiovascular events. Nicorandil is also widely used in protection against myocardial ischemia. A study showed that nicorandil reduced myocardial infarct size and improved myocardial contractility through various mechanisms, such as inhibiting calcium ion influx and protecting mitochondrial membrane potential[17]. However, there is currently no relevant research on the combined use of these two drugs to improve cardiac function, and there is also a lack of research into the treatment of

Table 3 Comparison of cardiac function before and after treatment between both groups (mean ± SD)

Group	CCS angina grade (score)		SAQ grade (score)		6WMT (m)	
	Control group	Study group	Control group	Study group	Control group	Study group
Pretherapy	1.6 ± 0.5	1.0 ± 0.5	66.4 ± 12.5	60.9 ± 16.0	352.4 ± 100.2	414.2 ± 84.1
Post-treatment	1.3 ± 0.7	1.8 ± 0.5	68.3 ± 10.7	63.3 ± 16.3	385.0 ± 110.1	371.2 ± 85.2
t	2.8	13.2	28.5	33.6	28.7	225.1
P value	0.76	0.02[a]	0.36	0.53	0.85	0.01[a]

[a]$P < 0.05$, statistically significant.
CCS: Canadian Cardiovascular Society; SAQ: Self-acceptance questionnaire; 6MWT: 6-min walking test.

Table 4 Comparison of blood lipid levels before and after treatment (mean ± SD)

Group	LDL (mmol/L)		HDL (mmol/L)		TC (mmol/L)		TG (mmol/L)	
	Control group	Study group	Control group	Study group	Control group	Study group	Control group	Study group
Pretherapy	3.6 ± 1.4	1.6 ± 3.1	1.3 ± 0.0	1.2 ± 0.3	9.0 ± 3.8	7.3 ± 1.4	6.2 ± 1.6	4.6 ± 0.6
Post-treatment	3.0 ± 2.1	1.4 ± 3.7	1.2 ± 0.2	1.3 ± 0.4	8.7 ± 2.2	5.2 ± 0.9	6.5 ± 1.4	3.2 ± 0.9
t	0.6	4.2	0.2	1.1	1.7	3.5	4.7	3.1
P value	0.26	0.54	0.18	0.11	0.32	0.01[a]	0.60	0.03[a]

[a]$P < 0.05$, statistically significant.
LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TC: Total cholesterol; TG: Triglyceride.

Table 5 Logistic regression analysis of therapeutic effects of Pericarpium Trichosanthis injection combined with nicorandil

Variable	SE	Wald χ^2	*P* value	OR (95%CI)
LDL	1.12	1.26	0.03	0.30 (0.08-0.49)
HDL	0.58	0.90	0.47	1.21 (1.02-1.87)
TG	1.87	3.60	0.05	0.57 (0.24-0.75)
TC	1.79	0.33	0.04	0.65 (0.43-0.69)
LVEF	0.05	0.70	0.01	1.16 (1.00-1.27)
CO	0.08	0.65	0.01	1.83 (1.02-2-36)
BNP	2.75	5.60	0.03	0.44 (0.10-0.64)
CRP	0.85	3.15	0.54	0.76 (0.23-0.95)

LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TC: Total cholesterol; TG: Triglyceride; LVEF: Left ventricular ejection fraction; CO: Cardiac output; BNP: Brain natriuretic peptide; CRP: C-reactive protein; OR: Odds ratio; CI: Confidence interval.

refractory angina. To fill this gap in the field, we conducted a retrospective study on 130 patients diagnosed with refractory angina admitted to our hospital.

In our study, the study group showed higher levels of LVEF and CO compared with the control group, while BNP and CRP levels were lower, with significant differences. This indicates that the combination therapy has significant advantages in improving heart function and reducing inflammatory responses. In the evaluation of angina improvement, quality of life, and exercise endurance, the study group demonstrated better CCS angina classification and 6MWT scores compared with the control group. This implies that the combination therapy not only improves cardiac function but also alleviates symptoms, improves quality of life, and enhances exercise endurance. These results are consistent with previous studies. Research has shown that Pericarpium Trichosanthis has the therapeutic effects of clearing heat, promoting diuresis, activating blood circulation, and dissolving stasis. It can improve microcirculation in the cardiovascular system, and promote the normal transportation and metabolism of calcium ions in myocardial cells, thereby improving heart function and alleviating angina[18]. Nicorandil, as a calcium channel blocker, can inhibit the influx of calcium ions into the vascular smooth muscle beneath the endocardium, reducing the tension and resistance of

coronary arteries, and improving cardiac hemodynamics[19]. However, there was no significant difference in SAQ scores between the two groups. This may be due to the wide individual variations among patients, as SAQ is a self-reported assessment. Additionally, the small sample size in this study may have limited the ability to detect significant differences.

The combined therapy showed a significant decrease in TC and TG levels compared with the control group, while LDL and HDL levels did not show significant changes. This suggests that the combination therapy of Pericarpium Trichosanthis injection and nicorandil can improve lipid metabolism, but has little effect on LDL and HDL levels[8]. Previous studies have found that Pericarpium Trichosanthis injection may affect lipid metabolism through various mechanisms, including reducing cholesterol synthesis, promoting cholesterol metabolism and excretion, and regulating fatty acid synthesis[20]. Current research indicates that the main active ingredients of Pericarpium Trichosanthis injection are cucurbitacin and cucurbitic acid, which have various pharmacological effects such as heat-clearing, detoxification, dampness-eliminating, phlegm-removing, lipid-lowering, antioxidant, and anti-inflammatory effects. Among them, cucurbitacin is believed to inhibit the activity of HMG-CoA reductase, thereby reducing cholesterol synthesis, while cucurbitic acid can promote cholesterol metabolism and excretion, and regulate fatty acid synthesis. This may be one of the mechanisms by which Pericarpium Trichosanthis injection reduces the incidence and mortality of chronic diseases such as cardiovascular and cerebrovascular diseases.

During the treatment period, 12 (16.7%) patients in the study group experienced headaches, which could potentially be related to nicorandil. Nicorandil is a calcium channel blocker that primarily acts on the heart and vascular smooth muscle, and is capable of dilating coronary arteries, peripheral vessels, and pulmonary arteries[21]. This results in a reduction in cardiac oxygen demand and blood ejection resistance, and a decrease in coronary artery contraction and spasm. However, during nicorandil treatment, adverse reactions such as headaches may occur, especially when first starting the medication. These headaches are usually mild and can resolve spontaneously, but they can sometimes affect the patient's comfort and quality of life. This might also be the reason why the study group did not outperform the control group in terms of SAQ scores in this study. After discharge, a total of 92 (71%) patients completed the follow-up, with a median duration of 8.5 (3-12) mo. During follow-up, some patients in both groups died from coronavirus disease 2019, and no drug-related adverse reactions were found. This suggests that the combined use of Pericarpium Trichosanthis injection and nicorandil is safe and does not increase the incidence of adverse reactions.

While this study achieved significant clinical results, it still had some limitations. The protocol did not exclude the use of other drugs, which could potentially have influenced the results. In addition, the study sample was small, and larger studies are needed to verify the safety and effectiveness of this combination therapy. Looking back at the development of healthcare in recent years, the concept of combining traditional Chinese and Western medicine and the deepening of related research, along with the development and practical use of new drugs, have all effectively improved the incidence of coronary heart disease and its complications. In the field of medical practice, appropriately adjusting or updating existing prevention methods, improving the homeostasis of the patient's internal environment as much as possible, and reducing or eliminating the adverse effects caused by the disease, are the focus of clinical physicians.

CONCLUSION

The combination of Pericarpium Trichosanthis injection and nicorandil is more effective than conventional treatment in improving symptoms and heart function in elderly patients with refractory angina pectoris.

ARTICLE HIGHLIGHTS

Research background

Coronary artery disease (CAD) is a global health concern that often leads to severe cardiovascular mortality. Refractory angina pectoris, a consequential manifestation of CAD, necessitates competent drug treatments. Two potential treatments include a traditional Chinese medicine known as Pericarpium Trichosanthis and a medication named nicorandil.

Research motivation

This research was driven by the need to investigate effective therapeutic procedures for elderly patients suffering from refractory angina pectoris due to CAD.

Research objectives

The primary objective for this research was to scrutinize the therapeutic impacts of a combined treatment, namely, Pericarpium Trichosanthis injection and nicorandil, on elderly patients with refractory angina pectoris caused by CAD.

Research methods

The study was performed as a retrospective study involving 130 patients diagnosed with refractory CAD; they were divided into control and intervention groups using digital randomization. While the control group received a routine treatment, the intervention group was subjected to the combined treatment of Pericarpium Trichosanthis injection and nicorandil.

Research results

The patients in the study group demonstrated significant enhancements in heart performance and lifestyle quality. Few patients experienced headaches, but no severe side-effects were observed. No drug-related adverse reactions were noted upon follow-up.

Research conclusions

The combined treatment of Pericarpium Trichosanthis injection and nicorandil substantially surpasses conventional treatment methods in managing symptoms and heart functionality among elderly patients suffering from refractory angina pectoris.

Research perspectives

The beneficial findings of the present study pave the way towards further exploring this combined treatment's potential varying application for CAD and its consequent complications, ultimately improving patient wellness and prolonging life spans. Promisingly, it may add a significant contribution to personalized treatment approaches for CAD patients.

FOOTNOTES

Author contributions: Kong MW and Xie YY confirmed the authenticity of all the raw data; Kong MW wrote the manuscript; Li J, Wang ZB, and Xu L reviewed and revised the manuscript; and all authors read and approved the final manuscript.

Institutional review board statement: The GIGH Research Ethics Committee (Guiyang, China) confirmed that the study complied with ethical requirements.

Informed consent statement: This study was conducted in compliance with the requirements of the Ethics Committee and informed consent was obtained from all participating patients. The privacy and confidentiality of the patients were strictly protected, and any identifying information was removed during the process of manuscript preparation to ensure patient anonymity. In the case of specific diagnostic images or other identifiable patient-related information, previous written consent was obtained and the current consent status has been maintained.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The data used in this study was collected from the databases of Guiqian International General Hospital and Chengdu Fifth People's Hospital, both of which are publicly available. The dataset includes information on demographics, medical history, and disease outcomes. The data can be accessed from the official website of Chengdu Fifth People's Hospital (www.cd5120.com). It is important to note that the dataset contains personal and private information of patients, therefore, any use or redistribution of the data beyond the scope of this study is strictly prohibited due to privacy concerns.

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CASE REPORT

Pulmonary and tricuspid regurgitation after Tetralogy of Fallot repair: A case report

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Abstract

BACKGROUND

Tetralogy of Fallot (TOF) is one of the most common congenital heart defects, and surgery is the primary treatment. There are no precise guidelines on the treatment protocol for tricuspid regurgitation (TR) as a common complication of TOF repair. The timing for treatment in patients presenting with valve regurgitation after TOF repair is often difficult to determine. Here, we report the first case of sequential treatment of pulmonary and TR using interventional therapy.

CASE SUMMARY

We present the case of a 52-year-old female patient, who had a history of TOF repair at a young age. A few years later, the patient presented with pulmonary and tricuspid regurgitation. The symptoms persisted and TR worsened following percutaneous pulmonary valve implantation. Preoperative testing revealed that the patient's disease had advanced to an intermediate to advanced stage and that her general health was precarious. Because open-heart surgery was not an option for the patient, transcatheter tricuspid valve replacement was suggested. This procedure was successful, and the patient recovered fully without any adverse effects. This case report may serve as a useful resource for planning future treatments.

CONCLUSION

Treatment of both valves should be considered in patients with tricuspid and pulmonary regurgitations following TOF repair. The interventional strategy could be an alternative for patients with poor general health.

Key Words: Tetralogy of Fallot repair; Pulmonary regurgitation; Tricuspid regurgitation; Interventional treatment; Sequential treatment; Case report

Core Tip: Tetralogy of Fallot (TOF) is a common congenital heart disease. Complications following TOF repair, including pulmonary regurgitation, tricuspid regurgitation (TR), and cardiac arrhythmia, can have a negative impact on the prognosis. In this case, the patient had been treated with percutaneous pulmonary valve implantation after TOF repair, but developed TR progression and was treated with transcatheter tricuspid valve replacement. No standardized treatment guidelines for similar patients exist, and the timing and modalities of treatment remain controversial. Therefore, whether patients who develop both types of valve regurgitation after TOF repair should be treated simultaneously or sequentially is important. A treatment plan should be developed based on the patient's overall condition, with interventional techniques being the optimal option for patients with poor baseline conditions.

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INTRODUCTION

Tetralogy of Fallot (TOF) is one of the most common cyanotic congenital heart diseases accounting for 7%-10% of all congenital heart diseases[1]. Four distinct anatomical features characterized it: Ventricular septal defect, pulmonary outflow tract obstruction, overriding aortic root, and right ventricular hypertrophy. Surgery is the primary treatment with a 30-year survival rate of patients after surgery of approximately 90%[2-4]. However, the outcomes after TOF are strongly affected by postoperative complications, including pulmonary regurgitation (PR), tricuspid regurgitation (TR), heart failure, and arrhythmias, which are closely linked to death[5,6]. These patients often undergo multiple surgeries, and percutaneous intervention is an attractive option because the procedure can be complicated by multiple sternotomies [7,8]. Challa *et al*[9] described a case of successful percutaneous insertion of a transcatheter 29 mm Edwards Sapien XT valve into the tricuspid valve in a patient who underwent TOF repair[9]. Seckeler *et al*[10] reported the case of a high-risk patient with complex adult congenital heart disease who underwent successful percutaneous tricuspid valve-in-ring placement with a SAPIEN 3 valve. Roberts *et al*[11] described 15 patients with congenital heart disease who had successful percutaneous tricuspid valve replacement with Melody valves, one of whom had TOF. Although numerous publications have described the percutaneous insertion of bioprosthetic tricuspid valves in patients with congenital heart disease, this is the first case described involving a LuX-Valve used in a patient after TOF repair and percutaneous pulmonary valve implantation (PPVI).

CASE PRESENTATION

Chief complaints

A 52-year-old female patient was admitted because of poor cardiac function and massive pleural and abdominal effusions.

History of present illness

Two years prior, she underwent PPVI with a Venus *P* valve device[12] at another hospital because of severe PR and TR. The patient improved immediately after treatment but soon developed recurrent right heart failure with severe TR, pulmonary hypertension, and extensive pleural effusion and ascites. In the previous year, she had been hospitalized multiple times for recurrent ascites with early cirrhotic changes on liver ultrasonography. The symptoms keep getting worse, presenting with progressive shortness of breath on exertion, orthopnea, paroxysmal nocturnal dyspnea, and bilateral lower limb swelling. The symptoms were severe enough to make conversation difficult and limited her activities of daily life.

History of past illness

She was admitted with a 20-year TOF repair history and a 2-year history of PPVI. The patient was diagnosed with TOF at an early age and did not undergo corrective surgery until she was an adult because of her poor financial status. Postoperative complications, such as PR, TR, and right heart failure, had progressively worsened in recent years. Cardiac ultrasonography showed ventricular septum repair, despite the patient's inability to recall details of the procedure.

Personal and family history

The patient did not have a family history of congenital heart disease, heart failure, or respiratory illness.

Physical examination

A physical examination revealed reduced bilateral breathing sounds with slight tremor. Dilatation of the jugular vein and pitted edema of the lower extremities. From a cardiac perspective, the New York Heart Association functional class was IV. Comprehensive preoperative evaluation included the 6-minute walking distance of 221 meters; a Kansas City Cardiomyopathy Questionnaire result of 58 for quality of life assessment; and an The Society of Thoracic Surgeons score of 15.57% for surgical risk evaluation.

Laboratory examinations

Laboratory examinations revealed varying degrees of reduction in peripheral blood cytopenia, liver and kidney function impairment, and a significant increase in B-type natriuretic peptide (517.2 pg/mL) and N-terminal pro B-type natriuretic peptide (1490 pg/mL).

Imaging examinations

Transthoracic echocardiography (Figure 1A) indicated torrential TR (121 mL), a dilated right heart, and a preserved left ventricular ejection fraction (LVEF) of 56%. The tricuspid annular plane systolic excursion (TAPSE) was 11 mm, and the fractional area change (FAC) was 49%. Preoperative computed tomography (CT) (Figure 2A and B) showed an enlarged right heart and a widened inferior vena cava.

FINAL DIAGNOSIS

The final diagnosis was severe TR.

TREATMENT

Owing to massive pleural and abdominal effusions, the patient was admitted to the hospital and underwent closed drainage of the thorax and abdomen. Torasemide (10 mg twice daily) and sacubitril valsartan (25 mg twice daily) were administered. After one month of medication adjustment, the patient underwent transcatheter tricuspid valve intervention and replacement.

After evaluation by a multidisciplinary team, the patient was deemed unsuitable for a second surgery because of her poor physical condition and inability to withstand the trauma of traditional surgery. Based on the patient's anatomy and condition, we decided to use the LuX-Valve developed by the team for transcatheter tricuspid valve replacement (TTVR), and a size of 30-55 was chosen (Figure 2C and D). The Institutional Review Board of Changhai Hospital approved the study protocol and data publication (No. CHEC2018-136).

The procedure was performed in the digital subtraction angiography operating room under transesophageal echocardiography and X-ray fluoroscopy guidance. We chose a minimally invasive right-fifth intercostal thoracotomy to create the delivery channel. Following angiography to determine the TR volume, the delivery system was sent to the right heart until it reached the tricuspid valve. The valve delivery system was gently retracted, and the prosthesis was released to capture the anterior leaflet. The delivery system was adjusted to ensure the graspers were in good contact with the valve leaflet and released into the right atrial disc. Finally, the anchor was secured to the ventricular septum until the valve was adjusted to minimize perivalvular leakage. The delivery system was removed, and angiography showed satisfactory valve function with no regurgitation or paravalvular leakage (Figure 2E and F). The pressure in the right atrium immediately decreased from 41 mmHg to 34 mmHg (Videos 1 and 2).

OUTCOME AND FOLLOW-UP

Transthoracic echocardiography 1 mo after the operation showed that the valve was in position with no obvious regurgitation or paravalvular leakage, with an LVEF of 57% (Figure 1B), and the enlargement of the right atrium was significantly improved (from 327 mL to 253 mL). The TAPSE and FAC became 13mm and 38%, respectively. The mean abdominal circumference reduced from 916.51 mm to 810 mm.

DISCUSSION

PR, a common complication of TOF repair, is a major cause of distant cardiac insufficiency and death[7]. Up to 36% of patients who undergo early TOF repair require pulmonary valve replacement within 30 years of surgery[13]. Compensatory cardiac mechanisms can maintain early homeostasis after TOF repair. However, with disease progression, prolonged exposure to PR and chronic right heart volume overload can lead to right heart dysfunction, progressive right ventricular dilatation, an enlarged tricuspid annulus, and worsening TR[14,15]. The incidence of moderate-to-severe TR after TOF repair is 32%[16]. Owing to delayed treatment for PR, although patients with combined TR improve immediately after pulmonary valve replacement, TR worsens and even leads to arrhythmias and sudden death in more

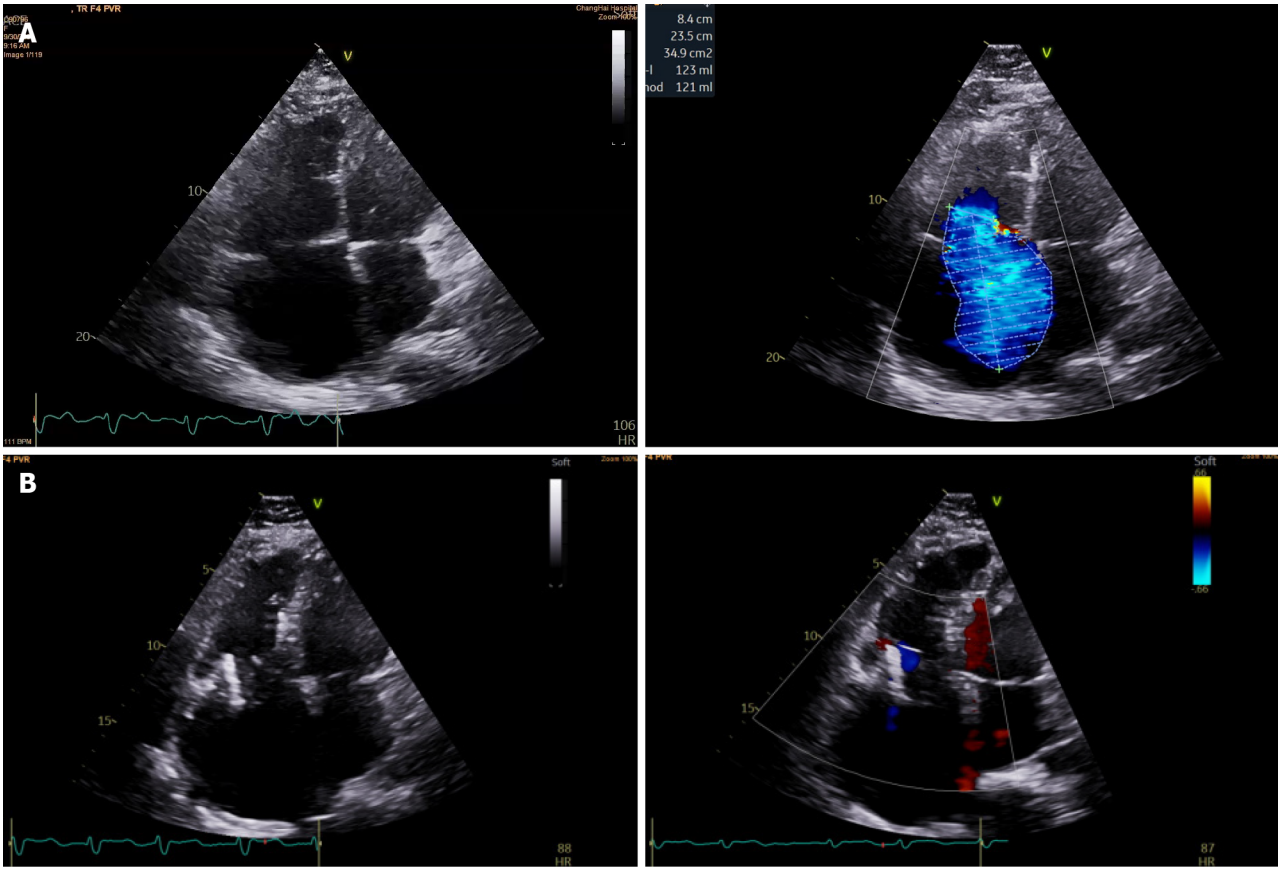

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Figure 1 Transthoracic echocardiography images. A: Preoperative transthoracic echocardiography showed an enlarged right heart and massive tricuspid regurgitation; B: Postoperative transthoracic echocardiography 1 mo showed the valve in place with no obvious regurgitation or paravalvular leakage.

than 15% of patients during long-term follow-up[17]. Numerous studies have discussed the type of treatment that is more beneficial for patients who have undergone TOF repair and subsequently develop pulmonary and tricuspid valve lesions. Most authors believe that tricuspid valve repair should be performed concurrently with pulmonary valve replacement in patients with combined moderate-to-severe TR. In the first multicenter study, the Surgical Correction of Tricuspid Insufficiency in Adult Congenital Patients requiring Pulmonary Valve Replacement (SCOTIA-PVR) and concurrent tricuspid valve intervention was shown to be safe and to improve early tricuspid valve function more than pulmonary valve replacement alone in patients with significant TR after TOF[18]. However, some studies concluded that the long-term results of pulmonary valve replacement with simultaneous tricuspid valve repair are controversial. Studies have shown no statistical difference at 6 mo between patients who underwent concurrent tricuspid valve repair and those who underwent pulmonary valve replacement alone[19]. Our patient underwent PPVI after TOF repair when she developed PR and TR. However, the patient's symptoms did not improve significantly, and right heart failure continued to progress after treatment. The reasons are as follows: (1) Although we could not obtain information about her past treatment, we speculated that the repair resulted in adhesion between the tricuspid valve and the ventricular patch. Therefore, treatment with PR does not make any sense for TR; (2) As described previously, pulmonary valve replacement alone may not improve TR, and treatment is still required. This finding indicates that both PR and TR should be considered after TOF repair; and (3) Infective endocarditis. Several studies have reported endocarditis after valve placement. Patel *et al*[20] described 4 cases of endocarditis after transcatheter pulmonary valve replacement. This may have been caused by the eccentric turbulence and thrombogenesis. Butera *et al*[21] also reported 2 cases of endocarditis following valve placement. Valve implantation is a risk factor for the development of infective endocarditis, making early monitoring and anti-infective therapy after the interventions indispensable[22].

Lesions after TOF repair are often amenable to transcatheter intervention. In selected cases, PR can be treated with transcatheter valve insertion[23]. Regarding sequential or concurrent therapy that should be used in managing PR and TR, ongoing monitoring of RV function is an important part of clinical assessment. Meanwhile, multicenter large-scale clinical studies or randomized controlled studies may help clarify whether concurrent tricuspid valve repair can improve patient prognosis.

The LuX-Valve is a novel radial-force-independent TTVR device that we previously designed. Its skirt-shaped, self-expandable, nitinol-valved stent can adapt well to an enlarged annulus and effectively prevent perivalvular leakage. The radial force-independent anchoring concept can minimize damage to the conduction bundle and reduce the occurrence of an atrioventricular block. Pre-clinical and early clinical trials[24-26] have shown that the LuX-Valve is a relatively safe and effective treatment for patients with severe TR *via* right atrial access. Patients who reach an advanced stage of the

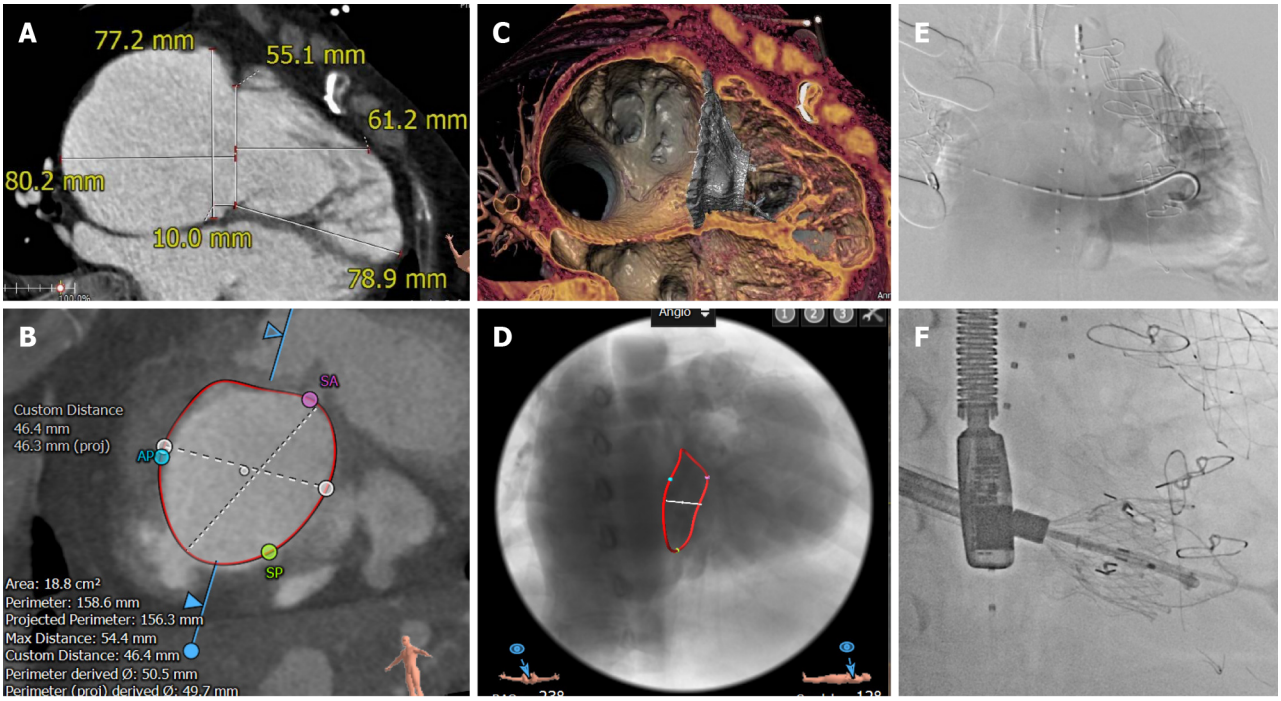

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Figure 2 Preoperative computed tomography and intraoperative digital subtraction angiography images. A and B: Computed tomography of the right ventricle revealed an enlarged right heart and tricuspid annulus; C and D: Simulating the morphology of the prosthetic tricuspid valve after placement; E: The guide wire passed through the tricuspid valve into the right ventricle and angiography indicated massive tricuspid regurgitation; F: Release of the artificial tricuspid valve.

disease are in poor general condition and cannot tolerate conventional open heart surgery. Based on our experience, interventional treatment may be a preferable option and should be considered when managing patients with TOF with advanced disease and a challenging clinical status.

CONCLUSION

Attention should be paid to the treatment of patients with postoperative complications of TOF. Multiple clinical studies are meaningful, and the formulation of relevant guidelines is helpful for the diagnosis and treatment of the disease.

FOOTNOTES

Co-first authors: Jing-Yi Cao and Xiao-Ping Ning.

Author contributions: Cao JY and Ning XP contributed to manuscript writing and editing, and data collection; Zhou GW contributed to image analysis; Li BL contributed to postoperative care and management; Qiao F, Han L, and Lu FL contributed to finishing the surgery; Xu ZY and Lu FL contributed to conceptualization and supervision; and all authors have read and approved the final manuscript.

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CASE REPORT

R-I subtype single right coronary artery with congenital absence of left coronary system: A case report

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Abstract

BACKGROUND

Isolated single coronary artery is a rare congenital anomaly. R-I subtype single coronary artery is even rarer. In this subtype, a very large right coronary artery extends in the coronary sulcus to the anterior base of the heart where it produces the left anterior descending coronary artery. Currently, only a few case reports are available in the literature for this anomaly.

CASE SUMMARY

Here, we report the case of a 62-year-old woman who presented to the cardiology clinic with decreased exercise tolerance and poor blood pressure control. The patient underwent coronary angiography (CAG) and emission computed tomography (ECT). CAG images revealed a single gigantic right coronary artery (R-I type) arising from the right coronary sinus with branches supplying the left coronary territory. The ECT results confirmed myocardial ischemia at the location of the absent left coronary artery. The ECT findings confirmed that ischemia was consistent with the vascular loss location in CAG images. In such anomalies, there is a compensatory widening of the coronary artery lumen. Medical treatment was administered, and the patient was discharged.

CONCLUSION

Isolated single coronary arteries are associated with ischemia and potentially fatal acute coronary events. Hence, controlling risk factors is critical.

Key Words: Single coronary artery; R-I type; Congenital anomaly; Emission computed

tomography; Coronary angiography; Case report

Core Tip: We present the rare case of an elderly woman with an isolated single right coronary artery (R-I subtype) detected by coronary angiography and myocardial ischemia confirmed by emission computed tomography. Since such an anomaly may be fatal in these patients, providing appropriate medical treatment promptly has a positive effect on their prognosis.

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INTRODUCTION

An isolated single coronary artery is a rare congenital anomaly in which only one coronary artery arises from the aortic trunk and supplies the entire heart *via* a single coronary ostium[1]. Such an anomaly occurs in approximately 0.024%-0.044% of the population[2]. The R-I subtype single coronary artery is even rarer, with a reported incidence of 0.0008%[3]. In the R-I variant, a single large right coronary artery (RCA) extends to the anterior base of the heart and produces the left anterior descending coronary artery, which supplies blood flow to the left side of the heart.

According to our literature review, a single RCA is exceedingly rare, and only a few cases have been reported. Saglam *et al*[4] described a 72- year- old woman with a single coronary artery anomaly who was admitted with atypical chest pain and may be a new subtype of the Lipton R-I subtype. Siddiqui *et al*[5] presented a single RCA arising from the right sinus of Valsalva in the absence of an equivalent left coronary artery system branches and associated mitral valve prolapse. Yoldaş *et al*[6] reported an extremely rare case of a 14-mo-old girl who was diagnosed with a single RCA, a coronary artery fistula communicating with the right ventricle, and congenital absence of a left coronary artery. In these reports, coronary angiography (CAG) and multidetector computed tomography CAG findings were shared. However, we did not find any case reports that further verified the presence of myocardial ischemia. Herein, we presented the case of a 62-year-old woman with an R-I subtype single coronary artery and verified that myocardial ischemia was consistent with the area of vascular loss observed in emission computed tomography (ECT) images.

CASE PRESENTATION

Chief complaints

A 62-year-old female with many cardiovascular risk factors such as diabetes, hyperlipidemia, and hypertension presented to our cardiology clinic with decreased exercise tolerance and poor blood pressure (BP) control.

History of present illness

The patient reported that the symptoms began 2 wk before presentation.

History of past illness

In addition to the cardiovascular risk factors mentioned above, the patient's history of past illnesses was not significantly different.

Personal and family history

The patient denied having a history of decreased tolerance to exercise. However, within her family, her father has a history of hypertension.

Physical examination

On physical examination, the vital signs were as follows: body temperature of 37.3 °C; heart rate of 92 beats per min; BP of 151/86 mmHg; and body mass index of 23.4 kg/m^2. Dyspnea, heart murmurs, and other signs of heart failure were not observed.

Laboratory examinations

Cardiac troponin I levels were negative. The lipid profile revealed low-density lipoprotein, high-density lipoprotein, and total cholesterol levels of 3.16, 1.19, and 4.96 mmol/L, respectively. Fasting blood glucose was 9.49 mmol/L, and 2 h after a meal the blood glucose level rose to 22.54 mmol/L. Glycosylated hemoglobin A1c was 7.51%. Electrocardiography

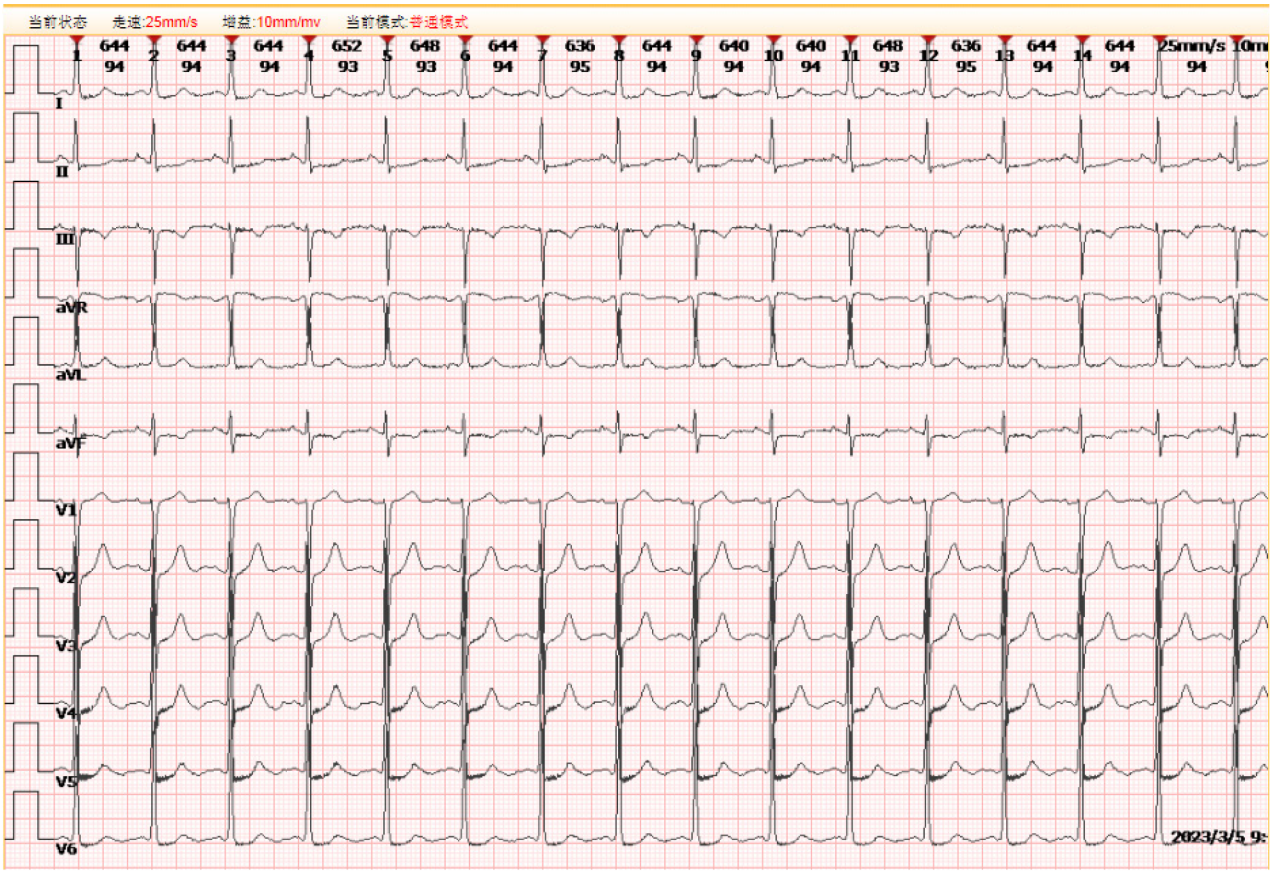

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Figure 1 Electrocardiogram of the patient. A normal sinus rhythm with ST-T wave changes in leads I, II, III, aVF, and V4-V6.

showed a normal sinus rhythm with ST-T wave slight depressions in leads I, II, III, aVF, and V4-V6 (Figure 1). The echocardiography of the heart revealed no regional wall motion abnormalities and good left ventricular systolic function.

Imaging examinations

During CAG, selective cannulation of the left coronary artery (LCA) was not possible, and nonselective injection revealed the absence of a coronary artery arising from the left coronary sinus. Aortography showed the absence of the LCA, with no other vessels arising from the left or non-coronary cusps. We could not locate the left anterior descending artery or left circumflex artery (Figure 2, Videos 1, 2, 3 and 4). After selective injection into the right coronary sinus, a single ostium was visualized (Figure 2B). The RCA is a large vessel without significant atheromatous occlusive stenosis. The RCA passed within the right coronary sulcus before continuing through the crux of the heart to the left part of the coronary sulcus and terminating anteriorly in a small vessel supplying the territory of the left anterior descending coronary artery (Figure 2C). The ECT results showed that the inferior wall basal segment, inferior lateral wall basal segment, inferior septal wall middle segment, and basal segment of the left ventricle had a small-to-medium range of moderate myocardial blood flow perfusion reduction, considering the presence of myocardial ischemia (Figure 3A). Overall, left ventricular systolic function was normal without abnormal wall motion. However, the resting left ventricular ejection fraction value of the left ventricle was normal, and the load left ventricular ejection fraction value did not increase, indicating a decrease in the left ventricular systolic reserve function (Figure 3B).

FINAL DIAGNOSIS

Combined with the patient's previous medical history and the CAG and ECT imaging findings, the final diagnosis was a single RCA of the R-I type without significant coronary atherosclerosis. Myocardial ischemia was consistent with the area of vascular loss.

TREATMENT

The patient was managed with a β blocker, angiotensin receptor enkephalin enzyme inhibitor, nitrate for hypertension, statin for hyperlipidemia, biguanides, α-glucosidase inhibitor, and sulfonylurea for diabetes. Since the patient had high

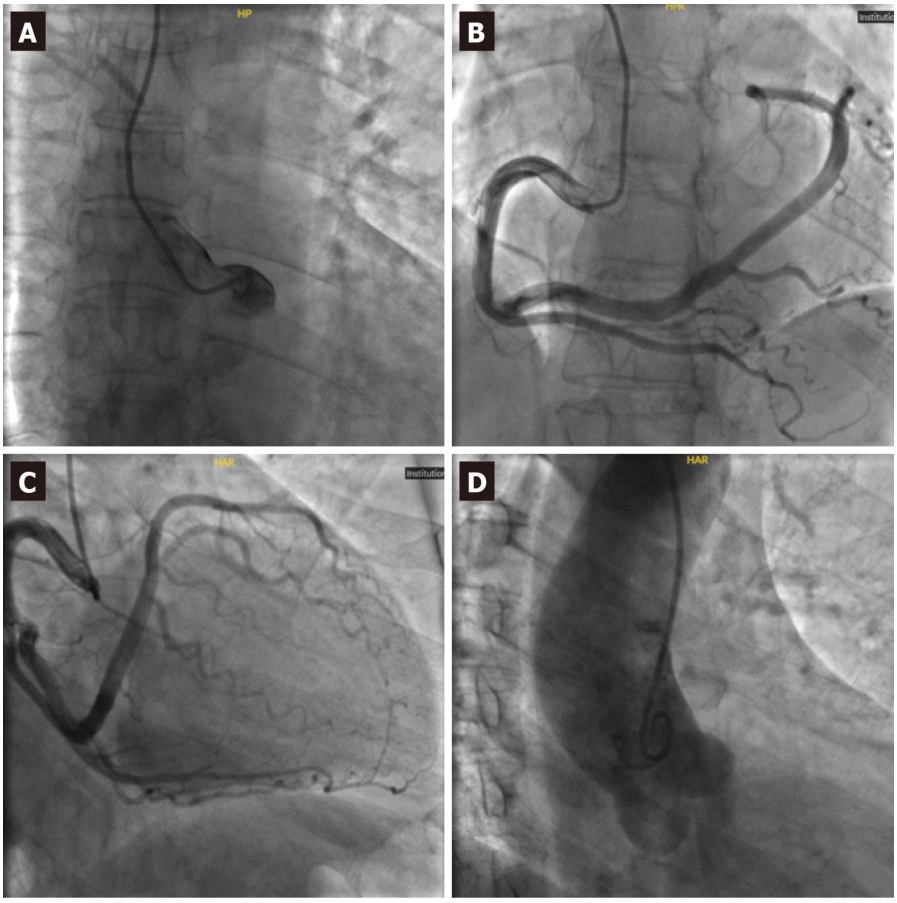

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Figure 2 Results of coronary angiography. A: Coronary angiography in multiple projections showed no coronary artery arising from the left coronary sinus; B: A single and large right coronary artery originated from the right sinus continues in the coronary sulcus; C: Right coronary artery extended to the anterior base of the heart, where it gave rise to the left anterior descending coronary artery; D: No left coronary artery was found on nonselective injection of the aortic root.

risk factors such as hypertension, diabetes, and hyperlipidemia with a single RCA, we administered aspirin (100 mg once daily) for the primary prevention of coronary heart disease and trimetazidine (35 mg twice daily) to improve myocardial hypoxia. The patient was discharged on postoperative day 3, with blood glucose and blood pressure controlled smoothly, and the symptoms disappeared.

OUTCOME AND FOLLOW-UP

At the last follow-up (6 mo postoperatively), the patient felt better with no recurrence of symptoms.

DISCUSSION

The presence of a right single coronary artery with congenital absence of the LCA (type R-I, the anomaly in the present case) is the least common type of single coronary artery, with a reported incidence of 0.0008%[3]. R-I subtype single RCA with congenital absence of left coronary system has been reported only a few times. The first reported case of a single RCA was described in 1867[7]. In a 31-year angiographic study by Villa *et al*[8], which examined the incidence of congenital coronary artery abnormalities in adults, only one R-I subtype single coronary artery was found in 13500 coronary angiography cases. Even though Desmet *et al*[9] examined 50000 coronary angiographies and Lipton *et al*[10] examined 4382 coronary angiographies, neither of them reported any cases of R-I type single coronary artery.

R-I subtype single coronary artery typically presents with a benign clinical course of disease, and the diagnosis is usually an incidental finding on noninvasive imaging. Invasive CAG can be used to diagnose symptomatic patients. Upadhyaya *et al*[11] presented the case of a young male patient with non-ST-elevated myocardial infarction. The patient was found to have a single coronary artery by employing invasive CAG. The few cases of R-I subtype detected by arteriography and autopsy have a co-compensatory mechanism of an enlarged aortic opening of regional citrate anticoagulation and an enormous dilation of the blood vessel itself with a sharp increase in lumen diameter, which can allow for perfusion of the entire heart through a single blood vessel[12,13].

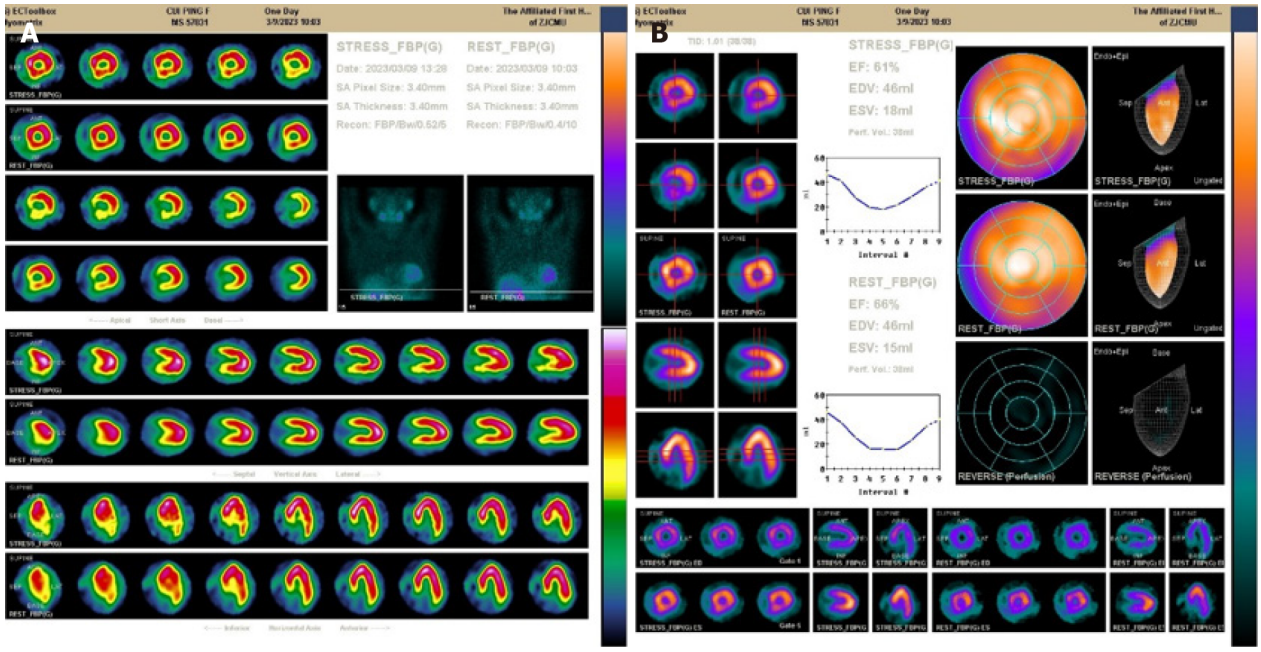

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Figure 3 Results of emission computed tomography. A: The inferior wall basal segment, inferior lateral wall basal segment, inferior septal wall middle segment, and basal segment of the left ventricle had a small-to-medium range of moderate myocardial blood flow perfusion reduction; B: Normal left ventricular systolic function without abnormal wall motion with a left ventricular ejection fraction of 66%. The load left ventricular ejection fraction was 61%.

In our case, because the patient had decreased exercise tolerance and many risk factors, she underwent CAG directly, which confirmed a single, gigantic, and hyperdominant RCA arising from the right coronary sinus with branches supplying the left coronary territory. However, this discovery was accidental. With the development of minimally invasive cardiac surgery, the number of clinically significant incidental findings detected using computed tomography has increased to 18.7%[14]. The patient was discharged on postoperative day 3 without having to undergo diagnostic computed tomography angiography. This is a limitation of the present study.

The main purpose of ECT is to observe myocardial blood perfusion and metabolism, and it is usually employed to diagnose patients with myocardial ischemia and coronary heart disease. To further confirm the presence of myocardial ischemia and the relationship between ischemia and the coronary artery-deficient area of the heart, the patient underwent ECT. The results of ECT showed that the RCA was insufficient for perfusion of the entire heart, whether at rest or after an increased cardiac load. We observed ischemia in the myocardium, where blood vessels were absent. In patients with a single coronary artery, the effect of coronary artery stenosis or occlusion may be catastrophic. Therefore, active preventive treatment is important for improving patient prognosis.

CONCLUSION

CAG revealed a congenital vascular anomaly. The presence of myocardial ischemia was confirmed by ECT. Through a literature search, we found that this is the first case report of a patient with a single RCA R-I subtype who underwent ECT to verify myocardial ischemia. Although we discovered this abnormality serendipitously in our clinical practice, acute coronary events can be fatal in these patients. Therefore, once this variant is identified, active treatment and control of risk factors are necessary to improve patient prognosis.

FOOTNOTES

Co-first authors: Ya-Ping Zhou and Lin-Li Wang.

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