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Editorial board member of *World Journal of Cardiology*, Hai-Long Dai, MD, PhD, Chief Physician, Professor, Department of Cardiology, Yan'an Affiliated Hospital of Kunming Medical University, Kunming 650051, Yunnan Province, China. dhlkm@qq.com

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MINIREVIEWS

Candida endocarditis: Update on management considerations

Yasser Jamil, Akintayo Akinleye, Mojtaba Mirzaei, Matthew Lempel, Kassem Farhat, Samuel Pan

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Yasser Jamil, Akintayo Akinleye, Mojtaba Mirzaei, Kassem Farhat, Department of Internal Medicine, Yale School of Medicine, Waterbury, CT 06708, United States

Matthew Lempel, Department of Rheumatology, Yale School of Medicine, New Haven, CT 06510, United States

Samuel Pan, Department of Infectious Disease, Yale School of Medicine, Waterbury, CT 06708, United States

Corresponding author: Yasser Jamil, MD, Staff Physician, Department of Internal Medicine, Yale School of Medicine, No. 64 Robbins Street, Waterbury, CT 06708, United States. yasser.jamil@yale.edu

Abstract

The rise in incidence rates of invasive candidiasis warrants an increase in attention and efforts toward preventing and treating this virulent infection. Cardiac involvement is one of the most feared sequelae and has a poor prognosis. Despite the introduction of several novel antifungal agents over the past quarter century, complications and mortality rates due to Candida endocarditis have remained high. Although fungal endocarditis has a mechanism similar to bacterial endocarditis, no specific diagnostic criteria or algorithm exists to help guide its management. Furthermore, recent data has questioned the current guidelines recommending a combined approach of antifungal agents with surgical valve or indwelling prostheses removal. With the emergence of multidrug-resistant *Candida auris*, a focus on improved prophylactic measures and management strategies is necessary.

Key Words: Candida; Candida endocarditis; Fungal endocarditis; Invasive fungal infection

Core Tip: The incidence of Candida infective endocarditis has observed a noticeable rise. Despite the progress in medical understanding, Candida endocarditis (CE) continues to be linked with a notable increase in in-hospital mortality. This comprehensive review aims to elucidate the existing diagnostic modalities for identifying CE while emphasizing their inherent limitations. Furthermore, we clarify the prevailing standard treatment protocols, encompassing medical and surgical interventions. Additionally, we highlight the role of screening techniques in identifying high-risk patients and explore the discussion of prophylactic measures tailored to specific patient phenotypes.

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INTRODUCTION

Although our understanding of endocarditis has evolved since its first description by William Osler in the late 19th century, it remains a disease of high morbidity and mortality[1,2]. Candida endocarditis (CE) which accounts for only 1%-2% of all endocarditis cases, is associated with a mortality rate as high as 80%[3-6]. Given that CE is particularly rare, formal studies comparing various management approaches and subsequent outcomes are limited. Current guidelines recommend a treatment regimen of antifungal agents combined with surgical interventions, whether valves or indwelling prostheses removal[7,8]. However, individuals suffering from CE often have multiple comorbidities and are at high risk for reinfection, making conducting invasive interventions challenging.

Furthermore, the uptrend in fungemia incidence rates in recent years has led to an increased number of patients at risk for CE[9]. Nonetheless, CE studies have relatively small sample sizes, which make them insufficiently powered to get robust research evidence into use. Therefore, this review explores the current diagnostic techniques and treatment considerations when evaluating and managing patients with CE.

BACKGROUND AND EPIDEMIOLOGY

Per definition, community-onset candidemia occurs within 48 h of hospitalization, with most cases identified on the day of admission, whereas nosocomial candidiasis occurs after 48 h of hospitalization[10]. The incidence of invasive candidiasis in the community and nosocomial infections has increased. There has been a noticeable increase in the incidence of community-acquired cases since the 1970s due to the intravenous drug (IVD) use epidemic, the use of impure brown heroin, and poor harm reduction practices, which have been associated with *Candida albicans* (CA)[11]. With the implementation of harm reduction strategies in the 1990s, the causative organisms have shifted to non-albicans Candida (NAC) species. The increased likelihood of the latter among IVD users has led again to the recognition of IVD use as an important risk factor for candidemia[12].

Different factors were found to increase the incidence of nosocomial candidemia, including increased antibiotics use, prolonged fluconazole prophylaxis in immunocompromised patients, use of total parenteral nutrition, and use of long-term catheters and medical devices[13-16]. Additional risk factors include malignancies of the gastrointestinal tract, genitourinary tracts, and the breast associated with CA infection and hematologic malignancy associated with NAC infection. Lastly, immunosuppressive therapies, including chronic steroid therapy, have been found to increase the incidence of CE and mortality risk[17].

Different Candida species can lead to advanced clinical infections, yet the most common agent leading to CE remains CA despite distinct patient characteristics and underlying risk factors[18]. Moreover, *Candida parapsilosis* was linked to infected medical devices such as prosthetic valves and transmitted through direct contact[19-21]. *Candida dubliniensis* and *Candida glabrata* are predominantly found among human immunodeficiency virus/acquired immunodeficiency syndrome patients with oral thrush and patients who are immunosuppressed on broad-spectrum antibiotics, respectively [18,22]. Although CA is primarily sensitive to antifungals, there is an emergence of intrinsic resistance of various Candida species to antifungals. Thus, it is essential to conduct antifungal susceptibility to ensure appropriate coverage[23]. *Candida auris* has recently emerged as a pathogen of significant concern worldwide, especially among chronically hospitalized patients. It is intrinsically resistant to multiple currently available antifungal therapies with a high mortality rate, often due to delayed diagnosis and initiation of antifungal therapy[24].

Despite the availability of effective antifungal therapy in most cases, mortality rates related to candidemia remain elevated, ranging from 30%-80%[25]. The latter is likely attributed to patients predisposing factors such as immunocompromised status and malignancies, recent surgery, and prior infective endocarditis (IE). Early diagnosis and administration of appropriate antifungal therapies *via* a multidisciplinary approach may have improved mortality rates over the years[4,23,27-28].

DIAGNOSTIC EVALUATION

Healthcare providers should be vigilant of an underlying CE when managing high-risk febrile patients with predisposing factors such as IVD users, prolonged antibiotic therapy, indwelling central venous catheter, prosthetic heart valve, history of endocarditis, parenteral nutrition, neutropenia, and diabetes mellitus[29]. Although the clinical presentation of CE can sometimes be indistinguishable from those of bacterial endocarditis, the loss of visual acuity, presence of cutaneous nodules, and cerebral embolization should raise concerns for a Candida infection[30,31]. Nevertheless, it remains a challenge to establish the diagnosis and differentiate CE from bacterial endocarditis.

In 1994, Durack *et al*[32] proposed the Duke Criteria, which are used to classify each case as definite, possible, or probable, and has been validated in several subsequent studies. Additionally, further trials emphasized Duke Criteria's high diagnostic sensitivity and specificity[33-35]. Furthermore, in 2000, Li *et al*[36] introduced the modified Duke Criteria, which have become the standard of care. Nevertheless, these criteria were developed to evaluate patients with suspected left-sided native valve IE, as its sensitivity is low in patients with cardiac device infection, prosthetic valves, and right-sided IE[37]. Duke Criteria were primarily implemented in the workup of bacterial endocarditis; however, to date, there are no specific diagnostic criteria for fungal endocarditis.

Fungal culture

Isolation of the causative organism is critical in establishing the microbiologic diagnosis and selecting appropriate therapeutic agents. However, Candida traditionally does not grow well in standard bacterial blood culture media, if at all, requiring a longer time for the organism to grow. The sensitivity of detection of Candida in blood cultures is limited to 50%-75%[38,39]. In one case series from France, 14% of 620 IE cases had negative blood cultures, while another study showed that 31% had negative cultures[40]. Hence, this will delay the diagnosis and treatment, which could lead to drastic outcomes. Therefore, modifications to the original Duke Criteria have been suggested to include additional risk factors, such as CRP/ESR elevation, hematuria, central non-feeding venous lines, and peripheral lines, as part of the criteria. These, in turn, led to increased diagnostic sensitivity[42]. However, when the modified Duke Criteria was tested in blood culture-negative IE, it performed poorly, possibly due to the lack of serological criteria[43].

Immunoassay studies-1, 3-β-D-glucan

In light of earlier addressed issues related to fungal isolation and culture difficulties, which remain the gold standard of diagnostic testing, non-culture-based tests have been developed, and some have found clinical applications. 1, 3-β-D-glucan is a polysaccharide ubiquitous in the fungal cell wall. Its detection in the serum with a cutoff of 60 pg/mL has a sensitivity and specificity of 69.9% and 87.1%, respectively, in a patient with candidemia[31]. It carries several advantages, including improved sensitivity on serial testing, strong specificity, positive likelihood ratio, and most importantly, antifungal agents do not affect 1, 3 β-D-glucan serum levels[44,45]. In a patient with *Candida glabrata* IE, β-D-glucan was found to be a helpful tool in assessing treatment response, whereby after treatment, the assay became negative[46]. Hence, this could be used as a screening tool for CE and to monitor clinical response to therapy.

Mannan antigen and anti-mannan antibody

Mannan is an essential constituent of the Candida cell wall. Both mannan and anti-mannan antibodies have been found in the serum of patients with candidiasis. A meta-analysis by Mikulska *et al*[47] showed that combined testing using immunosorbent assays for detecting mannan antigen and anti-mannan antibodies have a sensitivity of 83% and specificity of 86% in patients with invasive candidiasis. However, its usefulness is limited due to rapid clearance from the bloodstream. Furthermore, immunosuppressed patients may not develop adequate antibody response against the mannan antigen, thus resulting in false negative tests[48].

Polymerase chain reaction

The development of molecular diagnostic techniques has improved the ability to identify the causative pathogen and decreased the required time for microorganism identification from days to hours. Rice *et al*[49] found polymerase chain reaction (PCR) to have a threefold increase in sensitivity in detecting causative agents in the setting of IE compared to traditional bacterial Gram-stain and culture. Multiple cases of successful diagnosis of culture-negative fungal endocarditis utilizing this technique have been reported[50,51]. Multiplex PCR systems, such as BioFire®, are now employed routinely in clinical settings and have been shown to offer a rapid and accurate diagnosis of selected Candida species in fungemic patients. Recent advancements have also led to the development of a novel immuno-based microfluidic device that can rapidly detect CA in under 2 h with a capture efficiency of 77.4% ± 4.4%[52]. Matrix-assisted laser desorption/ionization-time of flight mass spectrometry is a technique that analyzes large biomolecules, such as DNA, protein, and sugar, as unique molecular fingerprints to allow rapid and accurate identification of microorganisms to decrease wait time for establishing correct diagnosis and initiation of appropriate therapy[53,54].

Limitations

These non-culture-based tests have several disadvantages, which have limited their widespread use. The yield of these tests is time-sensitive, and results might be altered with antifungal administration, which increases the possibility of false negative results. The accuracy of the test and its ability to make an identification depend on the quality of the database from which the test references, which is ever-expanding and improving. Thus, careful interpretation of test results is essential since sometimes the test may detect multiple or unusual organisms, which implies a critical determination of their clinical relevance. The availability of the test remains limited, and the turn-around time is significant, making them

not a first-line diagnostic tool. Finally, these tests are costly, further limiting their widespread use[55,56].

IMAGING MODALITIES

The use of echocardiography in the diagnosis of endocarditis is well established. Transthoracic echocardiogram (TTE) has a sensitivity of approximately 70% in the diagnosis of native-valve endocarditis (NVE) and about 50% for prosthetic-valve endocarditis (PVE). The sensitivity for each will improve to more than 90% when a transesophageal echocardiogram (TEE) is used, suggesting the superiority of TEE. For fungal endocarditis, echocardiography has shown an overall sensitivity of 77%[6]. Indeed, for patients with candidemia, TTE was shown to detect vegetation in 2.9% of patients compared to 11.5% of patients with TEE[57]. Moreover, TTE had a sensitivity of 88.9% with NVE and 76.5% with PVE in the diagnosis of CE compared to TEE, which had an improved sensitivity of 92% with NVE but a worse sensitivity of 61.1% in the case of PVE, which could be related to the small sample of patients with PVE that underwent TEE[4,6].

Other imaging techniques have been developed that have shown promising applications in diagnosing endocarditis [38]. Positron emission tomography with 2-deoxy-2-(fluorine-18) fluoro-D-glucose integrated with computed tomography (18F-FDG-PET/CT), which identifies increased uptake of labeled glucose by cells in inflamed tissue, has improved sensitivity and specificity of the modified Duke criteria to 82% and 96%, respectively, even better if the NVE cases were excluded, up to 96% and 94% if only PVE and cardiac-device-related IE are considered. Limitations of this technique include potential myocardial and respiratory artifacts that need to be gated out, difficulty distinguishing between inflammatory from infectious lesions, and limited ability to detect small vegetations along the device leads[58]. 18F-FDG-PET/CT was reported to help diagnose CE and improve accuracy. Hence, it is promising in situations where TTE/TEE might not be diagnostic[59].

Single photon emission tomography with technetium 99m-hexamethyl propylene amine oxime (HMPAO)-labeled autologous leukocytes (^{99}mTc-HMPAO-labeled SPECT/CT), on the other hand, takes advantage of the natural homing and recruitment of leukocytes to the site of inflammation/ infection to identify potential areas of abnormality. This technique does require additional time to prepare and complete compared to ^{18}F-FDG-PET/CT. It takes time to obtain, isolate, and prepare autologous leukocytes from the host, and the images are acquired in multiple phases. Other imaging limitations include affectation by metallic artifacts, non-specific bowel activity due to hepatic HMPAO excretion, and its limited ability to detect small vegetations[60]. These techniques are technically challenging and require well-trained radiologists who are familiar with the technique. Therefore, they are not widely available and are usually implemented when other evaluation techniques, such as echocardiograms, are inconclusive. The yield of either study may be affected by antibiotic exposure; thus, finding the optimal time to utilize this imaging modality to achieve the maximal result in the course of patient evaluation remains an important question[61,62]. Nevertheless, these techniques have demonstrated very promising results in the diagnosis of PVE and cardiac device-related IE, with one study showing a sensitivity of 80%, specificity of 91%, negative predictive value of 80%, and positive predictive value of 91% using ^{18}F-FDG PET/CT and 60%, 100%, 100%, and 85% for ^{99}mTc-HMPAO-SPECT/CT, that the use of nuclear imaging study when appropriate has been included as a consideration in European IE guidelines[61-63].

MANAGEMENT

Medical management

Current Infectious Diseases Society of America (IDSA) guidelines recommend treating native or prosthetic valve CE with either a lipid formulation of amphotericin with or without flucytosine or a high dose echinocandin for initial therapy, with step-down therapy to fluconazole for patients who have susceptible isolates, that have demonstrated clinical improvement, and have cleared Candida from their bloodstream. Step-down therapy to oral voriconazole can be used for susceptible isolates that are not susceptible to fluconazole. Valve replacement is recommended if there is no contraindication, followed by continued antifungal treatment for six weeks after surgery. Finally, long-term therapy with fluconazole is recommended for patients who cannot undergo valve replacement[8]. Despite this seemingly straightforward algorithm, this infection has seen little or no improvement in patient outcomes. While this may indicate an inherent defect in our approach to treatment, one must further analyze this sophisticated pathogen and the hosts most likely to become infected.

As Candida is known to form biofilms that result in decreased cell membrane ergosterol content through reduced expression of ergosterol biosynthetic genes while upregulating the expression of genes involved in amino acid and nucleotide metabolism and efflux pumps[64,65], a combination antifungal regimen would theoretically be more effective in the treatment of fungal infection. However, using an *in vitro* model, Pai *et al*[66] compared the activities of flucytosine, micafungin, and voriconazole as either single agents or in combination against several Candida species and found no difference in the reduction of fungal burden between triple *vs* single agent antifungal therapy. Conversely, a 2011 meta-analysis of 64 cases of CE who received fluconazole alone, concurrently, or in sequence with other antifungals without surgical intervention suggested that multiple-agent therapy is preferable. In this study, Smego and Ahmad[67] reported that combination regimens, including fluconazole cured or improved 86% and 68% of patients with native and prosthetic valve infections, respectively. Furthermore, fluconazole administered alone was associated with a 42% rate of relapse or death. At the same time, the best outcomes were found in patients maintained on chronic suppressive fluconazole therapy following an initial amphotericin or echinocandin regimen for a minimum of six months. Although antifungal

agents tend to have significant side effects and drug-drug interaction profiles, prolonged fluconazole use is relatively benign. In a retrospective study of individuals receiving chronic fluconazole for suppression of artificial implant infection, Penk and Pittrow[68] found no significant adverse events. Of note, this study's maximum duration of treatment was 4.5 years, and the maximum daily dose was 750 mg.

A study compared amphotericin B and echinocandin-based therapy directly. While there was a higher percentage of older patients in the echinocandin group and the majority of infections in the amphotericin B group were community-acquired, the rates of utilization of combination antifungal therapy, suppressive antifungal therapy and adjunctive surgery were statistically equivalent. Mortality rates measured in-hospital, at 42 d and 1 year, did not differ between the two groups. Based on this study, the echinocandin group could be a better choice of initial therapy given similar clinical outcomes and a better side effect profile than amphotericin[69].

Combination antifungal therapy of amphotericin B and flucytosine was shown to have similar clinical outcomes compared to an antifungal followed by adjunctive surgical intervention[70]. Different antifungal combinations have been tried, including azoles plus echinocandins, 5-FC-combination therapies, and polyenes plus azoles[71]. Amphotericin B and flucytosine have been found to work synergistically, albeit with nephrotoxic side effects[67]. Furthermore, the combination of amphotericin B and fluconazole demonstrated antagonism[69]. IDSA guidelines recommend echinocandins with or without fluconazole as first-line therapy, which was found to be non-inferior to amphotericin B in managing endocarditis[8,69]. Additional challenges are encountered with NAC species, such as *Candida lusitaniae* and *Candida krusei*, which are intrinsically resistant to polyenes and fluconazole, respectively[72,73].

Significant differences in clinical outcomes have been observed between right and left-sided disease in bacterial and fungal infections[74-6]. In a 2018 retrospective study, Siciliano *et al*[77] found that patients with isolated right-sided CE had a 32% mortality rate *vs* 61% for left-sided disease. Furthermore, individuals with right-sided disease have lower rates of acute heart failure and perivalvular complications. While right-sided CE still portends a poor prognosis, isolated valve involvement should be a characteristic considered when discussing outcomes and treatment options.

Surgical management

Literature on the surgical approach in CE is limited to small prospective studies with conflicting evidence and weak recommendations. For instance, 15 case reports from patients with CE showed that a combination of surgical and medical, when carried out early on admission, had lower mortality than single therapy[27]. A meta-analysis of 879 cases of CE found that patients who underwent adjunctive surgery had lower mortality. However, higher mortality was seen in surgical repairs before 1980, fungal monotherapy, and left-sided endocarditis. Although, this did not meet statistical significance[70]. In contrast, an observational cohort study in 2015 failed to show mortality benefits between those undergoing surgical therapy and those receiving medical treatment alone[69]. The European Society of Clinical Microbiology and Infectious Diseases recommends earlier surgery in the setting of prosthetic valves as opposed to infection involving native valves[38]. The need for surgical intervention may differ among cases caused by different Candida species. A recent retrospective study showed that surgery was performed earlier in cases of CE caused by *Candida parapsilosis* compared to CA endocarditis[78]. Rivoisy *et al*[79] demonstrated that in patients with prosthetic valve CE, early surgery was not associated with better survival at six months compared to medical management alone with liposomal amphotericin B induction and long-term suppression with fluconazole.

A newer approach with minimally invasive surgical intervention with angioVac has been used in right-sided IE with vegetation debulking. A meta-analysis of AngioVac-assisted vegetation debulking demonstrated procedural and clinical success of 89.2% and 79.1%, respectively. Also, greater than 50% vegetation removal was achieved in 90% and bacteremia clearance of 82.5% with procedure-related complications of 10.1%. However, documentation of this approach for left-sided endocarditis is not yet available[80]. It has been proposed that debulking in CE can lead to the resolution of fungemia similar to bacteremia in bacterial endocarditis[81].

PROPHYLACTIC MEASURES

Prophylactic measures have been given to selected patients at high risk of complications from candidemia. Several studies have explored high-risk populations, and many were found to have similar underlying genetic alterations leading to candidemia. Some generic modifications include Toll-like receptor signaling influence and certain single nucleotide polymorphisms[82-84]. A meta-analysis by Shorr *et al*[85] showed that prophylactic fluconazole reduced the risk of infection but failed to show improved mortality. The latter was also demonstrated in another randomized controlled trial between 1995-2000 in 26 intensive care units (ICU), where patients with central line catheters were randomized to fluconazole 800 mg *vs* placebo. It also failed to improve primary composite outcomes, including fever resolution, absence of invasive fungal infection, and discontinuation of prophylaxis due to toxicity and the need for additional systemic antifungal medication[86]. On the other hand, prophylaxis might increase the risk of resistance to antifungal drugs, which was described in the SNETRY Antifungal surveillance program that underlined both intrinsic and acquired resistance to fluconazole based on differences in species distribution among the geographic areas, variation in antifungal usage and infection control practice. Other disadvantages include cost and side effects[87]. IDSA guidelines report that prophylaxis with fluconazole (12 mg/kg) loading dose and then 6 mg/kg daily gained weak recommendation when administered to high-risk ICU patients[8]. This points to the need for a new screening modality to identify patients at high risk for severe candidemia and its complications.

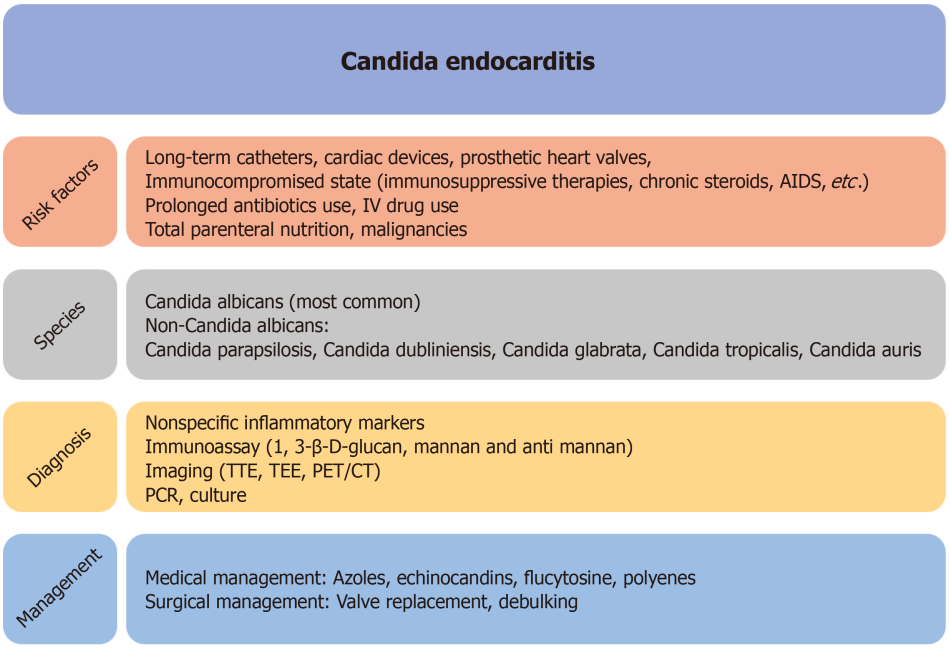

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Figure 1 Central Illustration. AIDS: Acquired immunodeficiency syndrome; TEE: Transesophageal echocardiogram; TTE: Transthoracic echocardiography; PCR: Polymerase chain reaction; PET/CT: Positron emission tomography/computed tomography.

CONCLUSION

Despite advances in cardiac surgery and antifungal therapy, overall mortality and morbidity due to CE have not improved significantly. Given the increasing incidence of candidemia and the emergence of multi-drug resistant Candida species, there is an urgent need for further development of fungal-specific diagnostic criteria, including novel diagnostic tests, and management guidelines, both therapeutic and surgical. While the modified Duke criteria have been applied to diagnose fungal endocarditis, one of the major criteria requires positive blood cultures, which can be a source of delay in diagnosing CE. As there are limited data regarding some of the newer diagnostic techniques, criteria specific for fungal endocarditis utilizing fungal antigens and PCR technology would lead to earlier diagnosis and treatment (Figure 1).

New techniques, such as minimally invasive suction thrombectomy, can remove and debulk vegetations[88,89] without the risk and complications associated with conventional surgery and may provide alternative solutions. Current and future innovations in diagnostic tests and medical and surgical management of CE will permit earlier recognition of infection, reduce rates of potential complications, and improve long-term outcomes. The most successful strategy will likely require increased attention to the prophylactic reduction of indwelling foreign devices, antibiotic stewardship, and dedicating resources to the IVD use epidemic.

FOOTNOTES

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ORCID number: Yasser Jamil 0009-0008-5853-4538.

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Mo-Wei Kong, Zhen-Ying Pei, Xiong Zhang, Qiu-Juan Du, Qiang Tang, Jun Li, Guo-Xiang He, Department of Cardiology, Guiqian International General Hospital, Guiyang 550018, Guizhou Province, China

Corresponding author: Mo-Wei Kong, MD, Doctor, Department of Cardiology, Guiqian International General Hospital, No. 1 Dongfeng Avenue, Wudang, Guiyang 550018, Guizhou Province, China. 1600181272@qq.com

Abstract

Despite the high prevalence of straight back syndrome (SBS), there is still limited research on this condition, posing challenges for effective diagnosis and treatment. The disease has been known for a long time, but there have been few related studies, which mostly consist of case reports. These studies have not been systematically summarized, making it difficult to meet the current needs of diagnosis and treatment. This article summarized the existing literature and comprehensively reviewed the diagnosis, pathogenesis, treatment, and research status of mitral valve prolapse related to SBS. We specifically emphasized the mechanisms and prognosis of SBS combined with mitral valve prolapse and discussed the latest research progress in this disease.

Key Words: Straight back syndrome; Mitral valve prolapse; Arrhythmia; Review; Diagnosis; Treatment

Core Tip: Straight back syndrome (SBS), a benign skeletal abnormality of the thorax, is typically accompanied by mitral valve prolapse. Despite its prevalence, there is limited research on this condition, making effective diagnosis and treatment challenging. Recent studies have revealed controversy on SBS and its related mechanisms. This review focused on the mechanisms and current research progress of SBS associated with mitral valve prolapse.

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INTRODUCTION

Straight back syndrome (SBS), also known as flat chest syndrome, is characterized by the disappearance of the normal kyphotic curvature of the thoracic spine, which results in a decrease in the anterior-posterior diameter of the chest and restriction of the heart (Figure 1). It was first reported by Rawlings[1] in 1960. Due to the presence of heart murmurs during cardiac examinations, patients are often referred to the cardiology department for evaluation[2]. Mitral valve prolapse (MVP) is a valvular heart disease characterized by soft texture of the mitral valve, which can billow upward and back into the left atrium during heart contraction (prolapse). Prolapse of the mitral valve can lead to mitral regurgitation. If the MVP causes significant enlargement of the atria, arrhythmias may occur. Previously, SBS-associated MVP was considered a "pseudo-heart disease," and patients may have no symptoms or only mild clinical symptoms such as chest tightness and shortness of breath. Even when severe symptoms occur, they are mostly thought to be due to mechanical and structural changes resulting from compression of the large blood vessels in the heart[3]. However, recent studies have found that SBS-associated MVP may be related to the expression of genes, which has attracted wide attention and controversy[2].

In clinical practice, some patients with MVP are often misdiagnosed as having "senile valve disease" or "congenital heart disease" due to the lack of primary disease diagnostic criteria. In the clinic, it is not uncommon for SBS to cause changes in cardiac structure and circulatory function[4]. However, the clinical manifestations can vary widely, often leading to misdiagnosis. Unfortunately, despite being discovered over 60 years ago, research on this subject remains scarce and often centers on case reports. Presently, these studies lack systematic summarization and fail to meet the current diagnostic and treatment reference needs. Therefore, this article comprehensively reviewed the literature on the diagnosis, pathogenesis, treatment, and research status of SBS-related MVP and provided clinical assistance by summarizing the latest and most significant achievements in this field.

DIAGNOSIS AND EPIDEMIOLOGY

SBS is a benign thoracic skeletal malformation that is often misdiagnosed as heart disease as it can cause heart murmurs detectable on physical examination[5]. Patients are usually asymptomatic, and the most common symptoms are chest pain and palpitations. However, there is a lack of large-scale epidemiological investigations into the incidence of SBS in the general population. A previous study by Jiang and Li[6] reported that among 114 SBS patients, the vast majority of cases (108) occurred in individuals under 40 years of age, with approximately 60% (66 cases) occurring in those aged between 20-40 years. The prevalence in females was higher than that in males. The incidence rate significantly decreased, and symptoms were milder in patients over 40 years of age, which may be due to reduced lung tissue and chest wall elasticity with increasing age, leading to natural alleviation of the condition[7]. A study in 2022 found that thoracic vertebrae may undergo degenerative changes with increasing age. In the general population, this change may cause excessive thoracic kyphosis, but in patients with SBS, it may relieve symptoms[8].

In 1956, Deleon *et al*[9] first proposed a diagnostic criterion for SBS, which was a ratio of anterior-posterior to transverse thoracic diameter less than 1/3 measured at the T8 level. In 1980, Davies *et al*[10] revised this criterion and proposed a diagnostic criterion for SBS on lateral chest radiographs, where the distance from the midpoint of the T8 vertebral body to the vertical line connecting the anterior borders of T4 and T12 was less than 1.2 cm (Figure 2). SBS typically occurs in young, lean individuals who lack normal thoracic kyphosis, leading to a decreased sagittal diameter of the thorax[11]. Auscultation may reveal splitting of the second heart sound, and a prominent murmur is generally caused by compression of the right ventricular outflow tract by the sternum, which lessens with deep inspiration. X-ray examination is the most important diagnostic method, especially left lateral images, where the spinal thoracic segments appear straight and the sagittal diameter is narrowed. Twigg *et al*[12] measured the ratio of thoracic anterior-posterior to transverse diameter in 24 patients with SBS and 100 normal individuals, revealing a mean ratio of 37.1%, which is lower than the normal value of 40.0%. Furthermore, X-ray features may include a heart-thorax ratio ≤ 0.5, protruding pulmonary artery segments, leftward shift of the cardiac silhouette, or signs of a pseudo-enlarged heart. In SBS patients, electrocardiography generally demonstrates normal values. In some patients, due to compression of the heart and positional changes, V1 leads may show a rsR' pattern, avR for the Qr pattern, R/S > 1, or R/S = 1, and some individual patients may exhibit high voltage of the left ventricle, sinus bradycardia, and incomplete right bundle branch block.

In some ultrasonography results of SBS patients, there may be a concomitant finding of MVP. Previous studies have suggested that this may be related to the compression-induced deformation of the mitral valve due to narrowing of the sagittal diameter[13]. However, a study conducted in 2020 indicated that both SBS and MVP may be inherited in an autosomal dominant manner[14]. It is believed that the vertebral malformation occurs during the 8th wk of gestation before ossification of the spine, and the penetrance is incomplete, with a higher expression frequency observed in female subjects. It has been reported in the international literature that 17%-23% of MVP patients have scoliosis, while 54%-67%

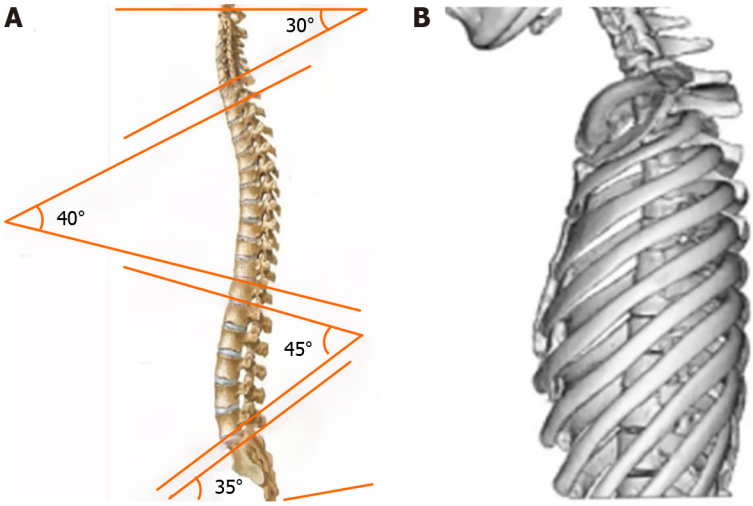

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Figure 1 Differentiating between normal individuals and individuals with straight back syndrome with physiological distortion. A: The human spine typically exhibits physiological curvature; B: In individuals diagnosed with straight back syndrome, this curvature is noticeably absent.

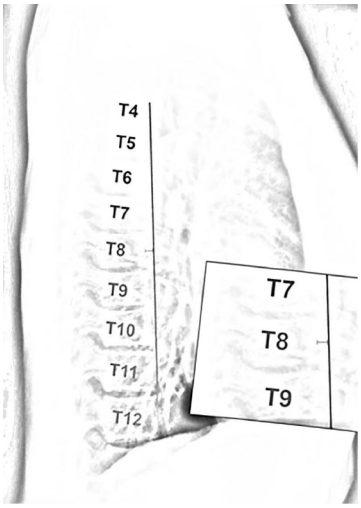

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Figure 2 Diagnostic criterion for straight back syndrome on lateral chest radiographs, where the distance from the midpoint of the T8 vertebral body to a vertical line connecting the anterior borders of T4 and T12 is less than 1.2 cm.

of scoliosis patients have concomitant MVP[15]. Based on these studies, it can be inferred that the higher incidence of MVP in SBS is not only a result of physical factors but is also related to genetic factors. National literature has not reported such a high incidence rate, which may be due to inadequate knowledge at the time.

SBS WITH COMORBIDITY MECHANISMS

SBS is often associated with several complications, and the underlying mechanisms are still not fully understood. One theory suggests that compression of the thorax could reduce lung capacity and cause hypoxia, leading to various cardiovascular and respiratory problems. Recent studies have shown that compression may also affect the functioning of the autonomic nervous system, leading to abnormal heart rate variability[16]. Additionally, the reduced sagittal diameter of the chest could lead to mechanical distortion of the heart and major vessels, causing abnormal blood flow[17]. In the study by Grillo *et al*[18], MVP was the most common associated cardiac disease, occurring in approximately 64% of SBS cases. Some studies suggest that the high incidence of MVP and scoliosis in SBS patients may be related to a common genetic background, but further research is needed to clarify this relationship.

Mechanisms underlying the co-occurrence of MVP in SBS

In several previous studies, there was consistent evidence of the co-occurrence of SBS and MVP[19], but it was not until

2017 that Movahed *et al*[20] demonstrated a statistically significant association between these two conditions. In their study, 77% of SBS patients underwent mitral valve repair or replacement due to severe mitral regurgitation caused by MVP. There are two hypotheses regarding the mechanism of SBS co-occurring with MVP. The first hypothesis, proposed by Chen *et al*[3], suggests that scoliosis and MVP are both manifestations of a more common disease, which is inherited in an autosomal dominant manner with incomplete penetrance. Family studies have found a tendency towards clustering of MVP and scoliosis, indicating that these diseases may have a genetic basis.

Additionally, a number of genome-wide association studies have identified several genetic variations associated with SBS, some of which may affect the susceptibility of MVP and scoliosis. For example, one study found that the *LRP2* gene located at 9q22.32 was associated with the susceptibility of scoliosis and MVP[21], whereas another study found a close relationship between the *EFEMP1* gene located at 5q35.3 and both scoliosis and MVP[22]. Furthermore, recent research has suggested that the MVP comorbidity in SBS may be related to the TGF-β signaling pathway, which induces cardiomyocyte apoptosis and promotes fibroblast proliferation[23].

It has also been discovered that SBS and floppy mitral valve disease are both inherited in an autosomal dominant manner with a significant family history, and three possible gene loci (16p12.1-p11.2, 11p15.4, and 13p31.3-p32.1) have been reported[24]. Floppy mitral valve causes enlargement of the mitral valve orifice area, elongation or rupture of the chordae tendineae, and enlargement of the mitral annulus, ultimately leading to MVP. It is believed that these malformations occur during the 8th wk of gestation before ossification of the spine, with incomplete penetrance and higher expression frequency in female subjects[4]. These studies suggest that genetic variations and molecular mechanisms may play important roles in the high incidence of MVP and scoliosis in SBS patients. However, the notion of a "more common disease" proposed by Chen *et al*[3] has yet to be proven.

Another hypothesis suggests that physical compression is a primary factor leading to the co-occurrence of MVP in SBS. The thoracic spine of SBS patients loses its normal posterior convex curvature, resulting in a decreased distance between the sternum and spine. This leads to compression of the heart and torsion of the major vessels, ultimately leading to distorted mitral valve morphology due to pressure[25]. The study by Chen *et al*[3] indirectly supported this view using cardiac magnetic resonance imaging to identify a correlation between the site of cardiac compression in SBS patients and the occurrence of arrhythmia. This evidence indicated that some, if not all, of the cardiac alterations seen in SBS are influenced by physical compression factors.

Mechanisms underlying the cardiac morphological changes and arrhythmia comorbidity in SBS

The causes of cardiac morphological abnormalities in SBS may include: (1) Differing degrees of cardiac pulsation restriction due to varying degrees of front-to-back narrowing of the thoracic cavity caused by flat thoracic vertebrae; (2) Left atrial compression, which increases pulmonary circulation resistance and reduces returning blood volume; and (3) Long-term frequent rapid arrhythmia causing cardiac enlargement and decreased cardiac function. In the study by Chen *et al*[3] among SBS patients with cardiac morphological abnormalities, 54.2% showed a consistent location between arrhythmia origin and the cardiac compression site, suggesting that mechanical compression of the heart may lead to enhanced aberrant electrophysiological activity in the heart through the activation of self-regulatory mechanisms.

Previous understanding of SBS was limited to chest wall deformities, which may cause mild symptoms such as palpitations, chest tightness, and chest pain, while severe cases may have morphological functional changes in the heart chambers, valves, and major vessels. However, recent studies have compared cardiac magnetic resonance imaging, electrocardiogram, and electrophysiological data of 43 SBS patients and found a relationship between the cardiac compression site and arrhythmia occurrence in addition to the morphological and functional changes caused by flat chest walls[3]. This study proposed that arrhythmias are the result of cardiac compression. However, a study conducted in 2013, found that MVP comorbid with various arrhythmias is very common, with ventricular arrhythmias being the most frequent, potentially due to increased sympathetic nervous activity and stimulation of the myocardium by prolonged chordae tendineae[26]. Given that MVP frequently co-occurs with SBS, it may be one of the reasons for the frequent occurrence of arrhythmias in SBS. This view has been partially confirmed by recent research. In the study by Xia *et al*[27], 8.3% of MVP patients were found to have preexcitation syndrome, and follow-up results showed a generally good prognosis for SBS comorbid with MVP.

SBS comorbid with cardiac murmurs

In SBS patients, cardiac murmurs may sometimes be heard on auscultation, but detailed examination often reveals no cardiac abnormalities. There have been reports of SBS being misdiagnosed as cardiac diseases with abnormal heart sounds, such as atrial septal defect, pulmonary valve stenosis, or mitral regurgitation[3]. The mechanism underlying cardiac murmurs in SBS has not been well studied, but a more credible explanation is that the loss of thoracic physiological kyphosis in SBS patients causes displacement of the heart and great vessels. This leads to the right ventricle and pulmonary artery being closer to the posterior sternum, increasing the contact area between the sternum and the posterior heart margin, resulting in a "strengthened" jet effect of blood flow, almost invariably causing grade I-III systolic murmurs in the pulmonary valve auscultation area of each patient[28]. Due to prolonged compression of the heart on the dorsal margin of the sternum, the heart is subjected to long-term overload, causing hypertrophy of cardiomyocytes characterized by increased cell volume, diameter, and length. When hypertrophy reaches the critical limit, it increases the systolic wall tension of the ventricular wall, leading to the parallel proliferation of myocardial fiber cells, followed by thickening of the myocardial fibers. As a result, the thickness of the ventricular wall increases and the cavity does not expand significantly, leading to outflow tract obstruction and the production of murmurs (Figure 3).

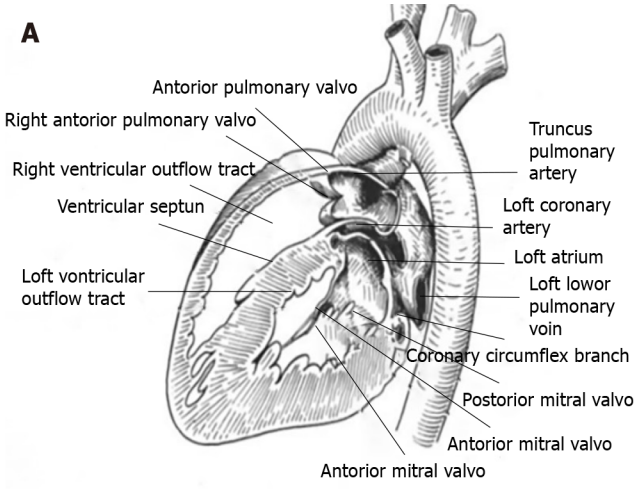

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Figure 3 Comparison of right ventricular outflow tract between normal patients and patients with straight back syndrome. A: Right ventricular outflow tract patency in a normal individual; B: Right ventricular hypertrophy and narrowing of the right ventricular outflow tract in a patient with straight back syndrome.

RESEARCH STATUS

It has been over 60 years since SBS was first reported in 1960[1]. Despite the long history, the literature on this topic remains relatively scarce, with case reports dominating the available data (Figure 4). According to recent statistics, the past 10 years have seen the greatest SBS-related research activity, and significant breakthroughs have been made.

Xu *et al*[29] conducted a retrospective analysis of 16 cases of misdiagnosed situs inversus totalis and summarized the clinical features of SBS patients. The authors emphasized the importance of chest X-ray lateral films and concluded that echocardiography is an effective diagnostic tool for SBS. Another study conducted in the same year also highlighted the importance of chest X-ray lateral films as a key diagnostic feature of SBS (Figure 5)[30].

Hou *et al*[31] investigated a method for diagnosing SBS by combining the ratio of the distance from the anterior edge of the T8 vertebral body to the posterior edge of the sternum to the anterior-posterior diameter of the thorax with the ratio of the distance from the anterior edge of the T8 vertebral body to the posterior edge of the sternum to the transverse diameter of the thorax and the curvature arc height from T3 to T12. Recently, studies have also shown that this diagnostic method was more reliable for diagnosing SBS[32-35]. In a recent study of 1569 randomly selected patients who underwent 64-row chest computed tomography (CT) scans, it was found that CT could identify signs that were not visible on X-ray films, leading to a more accurate diagnosis of SBS and a better correlation of clinical symptoms with imaging findings, as has also been reported in studies overseas. Matsumoto *et al*[33] recently used echocardiography and right ventricular angiography to uncover the mechanism underlying the change in heart murmur with respiration, which they found to be due to variation in the diameter of the right ventricular outflow tract during respiration. It was not until 2017 that Marbella *et al*[34] investigated the statistical correlation between SBS and MVP and revealed that 27% of patients with severe mitral valve regurgitation caused by MVP also had SBS.

In terms of treatment, Betz *et al*[35] reported the successful case of a 19-year-old patient with SBS who presented with spinal pain and exertional dyspnea. The patient's symptoms were relieved by a 12-wk course of treatment involving corrective exercises, traction, and posture adjustment. In another study, the use of 3D printing technology to simulate chest wall replacement tissue was reported to alleviate severe compression symptoms in an SBS patient[17]. Another complication of SBS is tracheomalacia caused by chronic compression of the trachea and main bronchi, resulting in decreased mediastinal diameter. In 2021, Schmid *et al*[36] successfully cured a 36-year-old female patient suffering from this condition by proximal aortic, brachial artery, sternoplasty, and anterior tracheal fixation surgery.

SBS is a benign thoracic skeletal abnormality that is usually associated with MVP and a heart murmur often detected during physical examination. Patients are usually asymptomatic, with chest pain and palpitations being the most common symptoms. X-ray examination is the most important diagnostic tool, showing a straightened thoracic spine and a decreased anterior-posterior diameter in the thoracic segment. Recent studies have confirmed the importance of echocardiography and CT in the diagnosis of SBS. The mechanism of SBS with MVP may be due to genetic or physical factors (compression), and the mechanism of heart murmur may also be due to physical factors or indirect causes following MVP.

Although SBS was discovered some time ago, there have been relatively few related studies. Recent studies have explored the importance of diagnostic tools in SBS and reemphasized the clinical features of SBS to avoid misdiagnosis. Some studies have also identified the mechanisms of arrhythmia in patients with SBS and the possible mechanism of heart murmur changing with respiration. Progress has been made in the treatment of SBS in some patients with severe compression symptoms through corrective exercise, traction, 3D printing technology, and surgery.

All these studies have achieved success under the development of new equipment and technologies, which may be one of the reasons for the rapid increase in related research in the past decade. Looking back on the development of medicine

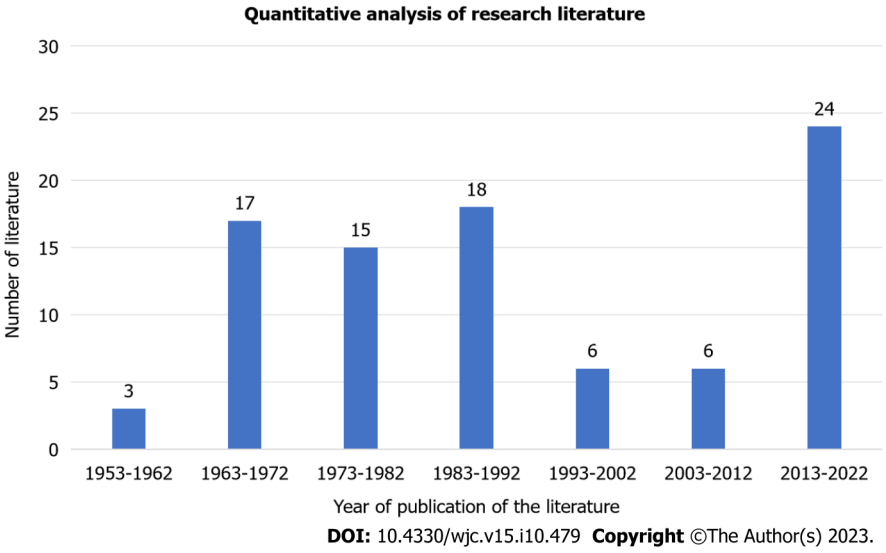

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Figure 4 Distribution of straight back syndrome publications from 1953 to 2022.

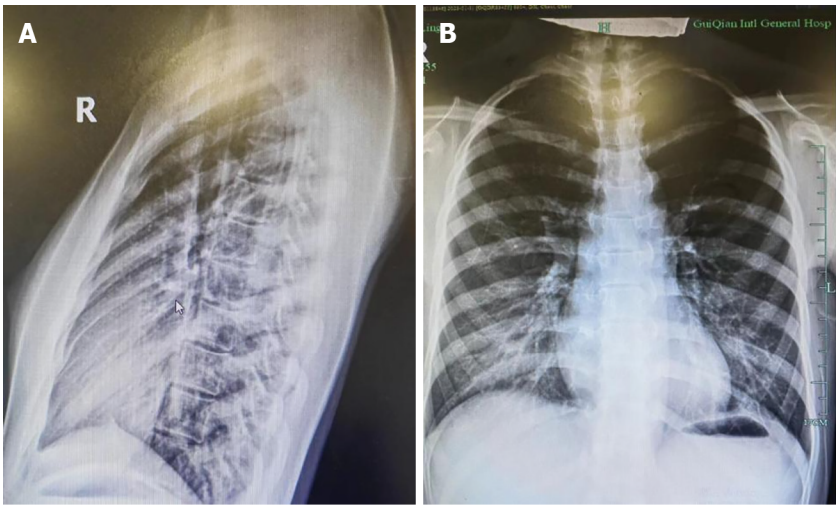

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Figure 5 Chest X-ray film of a patient with straight back syndrome. A: Lateral chest X-ray; B: Anteroposterior chest X-ray.

in recent years, adjusting or updating existing diagnostic and treatment methods to improve the quality of life of SBS patients and reduce or eliminate serious complications caused by diseases is the focus of clinical physicians and an important direction of academic research. We hope that this article will serve as a stimulus for future research and provide new ideas.

CONCLUSION

SBS is a thoracic skeletal malformation often accompanied by MVP. Diagnostic criteria include the ratio of anterior-posterior to transverse thoracic diameter and specific X-ray features. The co-occurrence of SBS and MVP may be due to genetic variation and molecular mechanisms or physical compression. Cardiac morphology and arrhythmia in SBS may be caused by restricted cardiac pulsation, left atrial compression, and sympathetic activity. Recent studies have emphasized the importance of chest X-rays, echocardiography, and CT scans for diagnosing SBS. New methods for diagnosing SBS with MVP have been proposed. Treatment options include exercise, traction, posture adjustment, 3D printing, and surgical interventions.

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FOOTNOTES

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Country/Territory of origin: China

ORCID number: Mo-Wei Kong 0000-0002-1214-164X.

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MINIREVIEWS

Value of cardiac magnetic resonance on the risk stratification of cardiomyopathies

Rafael Vidal-Perez, Mariana Brandão, Wael Zaher, Ruben Casado-Arroyo, Alberto Bouzas-Mosquera, Ricardo Fontes-Carvalho, Jose Manuel Vazquez-Rodriguez

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Rafael Vidal-Perez, Alberto Bouzas-Mosquera, Servicio de Cardiología, Unidad de Imagen y Función Cardíaca, Complexo Hospitalario Universitario A Coruña Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), A Coruña 15006, Galicia, Spain

Mariana Brandão, Ricardo Fontes-Carvalho, Department of Cardiology, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia 4434-502, Portugal

Wael Zaher, Ruben Casado-Arroyo, Department of Cardiology, Hôpital Erasme, Université Libre de Bruxelles, Brussels 1070, Brussels, Belgium

Ricardo Fontes-Carvalho, Cardiovascular R&D Centre - UnIC@RISE, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Porto 4200-319, Portugal

Jose Manuel Vazquez-Rodriguez, Servicio de Cardiología, Complexo Hospitalario Universitario A Coruña, A Coruña 15006, A Coruña, Spain

Corresponding author: Rafael Vidal-Perez, FACC, FESC, PhD, Reader (Associate Professor), Staff Physician, Servicio de Cardiología, Unidad de Imagen y Función Cardíaca, Complexo Hospitalario Universitario A Coruña Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), As Xubias de Arriba-84, A Coruña 15006, Galicia, Spain. rafavidal@hotmail.com

Abstract

Cardiomyopathies represent a diverse group of heart muscle diseases with varying etiologies, presenting a diagnostic challenge due to their heterogeneous manifestations. Regular evaluation using cardiac imaging techniques is imperative as symptoms can evolve over time. These imaging approaches are pivotal for accurate diagnosis, treatment planning, and optimizing prognostic outcomes. Among these, cardiovascular magnetic resonance (CMR) stands out for its ability to provide precise anatomical and functional assessments. This manuscript explores the significant contributions of CMR in the diagnosis and management of patients with cardiomyopathies, with special attention to risk stratification. CMR's high spatial resolution and tissue characterization capabilities enable early detection and differentiation of various cardiomyopathy subtypes. Additionally, it offers valuable insights into myocardial fibrosis, tissue viability, and left ventricular function, crucial parameters for risk stratification and predicting adverse cardiac events. By integrating CMR into clinical practice, clinicians can tailor

patient-specific treatment plans, implement timely interventions, and optimize long-term prognosis. The non-invasive nature of CMR reduces the need for invasive procedures, minimizing patient discomfort. This review highlights the vital role of CMR in monitoring disease progression, guiding treatment decisions, and identifying potential complications in patients with cardiomyopathies. The utilization of CMR has significantly advanced our understanding and management of these complex cardiac conditions, leading to improved patient outcomes and a more personalized approach to care.

Key Words: Cardiac magnetic resonance; Cardiomyopathies; Prognosis; Dilated cardiomyopathy; Hypertrophic cardiomyopathy; Restrictive cardiomyopathy

Core Tip: Cardiomyopathies encompass a diverse range of diseases affecting the heart muscle, each with varied causes. Symptoms of cardiomyopathies can manifest differently and change over time, necessitating regular evaluation through cardiac imaging techniques. These approaches play a crucial role in diagnosis, treatment guidance, and prognosis optimization. To enhance the precision of anatomical and functional evaluation and obtain valuable prognostic insights, cardiovascular magnetic resonance (CMR) is typically employed. By integrating CMR into clinical practice, clinicians can tailor patient-specific treatment plans, implement timely interventions, and optimize long-term prognosis This manuscript aims to explore how the CMR contribute to the diagnosis and management of patients with cardiomyopathies specially focus on the risk stratification.

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INTRODUCTION

Cardiomyopathies encompass a diverse range of diseases affecting the heart muscle, each with varied causes. The European Society of Cardiology (ESC) traditionally categorizes them into hypertrophic, dilated, arrhythmogenic, restrictive, or other forms[1]. Moreover, they are further classified as either familial/genetic or non-familial/non-genetic. We must highlight that this classification is highly discussed[2].

Symptoms of cardiomyopathies can manifest differently and change over time, necessitating regular evaluation through cardiac imaging techniques. These approaches play a crucial role in diagnosis, treatment guidance, and prognosis optimization.

Patient evaluation involves gathering medical history, conducting a physical examination, and performing an electrocardiogram (ECG). Transthoracic echocardiography (TTE) can raise suspicions of cardiomyopathy. To enhance the precision of anatomical and functional evaluation and obtain valuable prognostic insights, cardiovascular magnetic resonance (CMR) is typically employed. In some cases, nuclear medicine tests or cardiovascular computed tomography may also be necessary.

This manuscript aims to explore how the CMR contribute to the diagnosis and management of patients with cardiomyopathies.

CARDIOMYOPATHIES WITH DILATED PHENOTYPE

CMR plays a crucial role in the diagnosis and evaluation of dilated cardiomyopathies (DCM). We usually distinguish the DCM on the basis of the etiology between two groups, the non-ischemic DCM (NIDCM) and ischemic DCM (IDCM).

Non-ischemic dilated cardiomyopathy

CMR plays a crucial role in the diagnosis and management of NIDCM. NIDCM is characterized by left ventricular (LV) enlargement, systolic dysfunction, and myocardial fibrosis without significant coronary artery disease[3] and absence of other abnormal loading conditions like hypertension, valvular heart disease or congenital heart disease. CMR provides a noninvasive and accurate assessment of LV morphology, function, and remodeling[3]. It allows for the quantification of myocardial fibrosis, which is useful in assessing viability in ischemic cardiomyopathy[4]. CMR can also provide detailed and clinically useful information about the type and severity of cardiac damage by characterizing tissue changes in the myocardium[5].

One important application of CMR in NIDCM is the identification and characterization of fibrosis microstructure. Late gadolinium enhancement (LGE) imaging, a technique used in CMR, can detect enhancement patterns associated with fibrosis in NIDCM patients[6]. Fibrosis microstructure has been found to modulate reentry in NIDCM, and understanding these variations can improve risk stratification and guide treatment decision[6]. Computational modeling based on CMR images has been used to examine variations in fibrosis microstructure and quantify their effect on reentry inducibility and mechanism[6]. This information can help identify patients at high risk of sudden cardiac death (SCD) and guide the selection of appropriate interventions[6]. CMR is also valuable in differentiating NIDCM from other cardiomyopathies. CMR-derived myocardial parameters, such as total LV myocardial mass index and percentage of non-compacted myocardium, have been found to be discriminators between patients with LV non-compaction cardiomyopathy, other cardiomyopathies, and healthy controls[6]. This differentiation is important for accurate diagnosis and appropriate management of patients with NIDCM[7].

Furthermore, CMR can provide prognostic information in NIDCM. Global longitudinal strain (GLS) of the left ventricle measured by CMR feature tracking (FT) analysis has revealed enhanced prognostic utility when compared to conventional parameters in NIDCM[8]. Moreover, researchers have investigated the prognostic significance of right ventricular (RV) GLS through CMR-FT analysis has been evaluated in a cohort of individuals with NIDCM[8]. These investigations collectively highlight the promising ability of CMR to predict significant cardiac events and events related to heart failure in patients with NIDCM[8].

In relation with sequences like T2-STIR, T1, T2 and Extracellular volume (ECV) mapping there is controversial data some experts state that T1 and ECV have limited value that is explained by the reduced precision in NIDCM due to thinning of the myocardium[9]. Other authors have claimed some potential value of T1 and ECV, elevated ECV and T1 measurements have demonstrated prognostic significance regardless of LV ejection fraction (LVEF) and the presence of LGE[10]. Moreover, an elevated native T2 value suggests the potential existence of myocardial edema, potentially indicating the presence of inflammatory cardiomyopathy[11]. These methods present encouraging novel approaches for risk assessment; nevertheless, additional validation remains necessary.

In summary, CMR is playing a crucial role in the diagnosis, risk stratification, and prognostication of NIDCM. It provides valuable information about LV morphology, function, and remodeling, as well as the presence and characteristics of myocardial fibrosis. CMR can differentiate NIDCM from other cardiomyopathies and help guide treatment decisions. Additionally, CMR-derived parameters, such as GLS, have shown prognostic value in NIDCM. Overall, CMR is a valuable tool in the comprehensive evaluation and management of NIDCM patients.

Ischemic dilated cardiomyopathy

CMR plays a crucial role in the diagnosis and evaluation of IDCM. IDCM is a type of DCM that is caused by ischemic heart disease (IHD)[12]. Approximately 70% of heart failure cases have been attributed to IHD[13]. From the SOLVD study, IHD tended to have a greater impact than NIDCM, with double the risk of hospitalization and quadruple the risk of death[14].

CMR as we shown before this technique can aid in the differentiation of ischemic from non-ischemic cardiomyopathy subtypes. Currently, CMR-derived cardiac imaging is effective for both definition of IHD and for ischemia detection, with important diagnostic and prognostic implications[15].

The "function-perfusion-tissue characterization" triad should be studied in IHD for an adequate evaluation of cardiac viability and ischemic burden. As mentioned, the subendocardial distribution of LGE identifies an ischemic injury as opposed to fibrosis with meso- or subepicardial distribution, typical of non-ischemic alterations[16] CMR is also effective in defining myocardial viability through discrimination of LGE extension and segmental kinesis[4,17].

From the SPINS registry, extensive ischemic burden was related to a higher risk of major cardiac event, including hospitalization for congestive heart failure (HF), and revascularization was associated with a protective effect only in the extensive ischemia subset[18-21].

CARDIOMYOPATHIES WITH HYPERTROPHIC PHENOTYPE

LV hypertrophy (LVH) is most frequently caused by pressure overload. However, in cardiomyopathies, LVH occurs in the absence of abnormal loading conditions – hypertrophic cardiomyopathy (HCM) accounts for the majority of these cases.

CMR imaging has consolidated its role among the multimodality evaluation of myocardial disease, mostly due to high spatial resolution and unique ability for tissue characterization[22,23]. Non-invasive tissue characterization is crucial for differential diagnosis of LVH, identification of HCM phenocopies and risk stratification. This distinctive feature of CMR has led to a decrease in the use of endomyocardial biopsy (EMB) in cardiomyopathies with LVH, that is now restricted to few indications[24,25]. A recent position statement limited EMB use to patients with LVH in whom non-invasive evaluation produces inconclusive or discordant results, and there is clinical suspicion of phenocopies, particularly infiltrative or storage disease for which target treatment is available[25].

An Integrative CMR approach, Incorporating morphofunctional assessment with tissue characterization, including identification of the presence, location, and pattern of LGE, and combined with parametric mapping findings (particularly, native T1 and ECV), can be of value for differential diagnosis of hypertrophic phenotypes of cardiomyopathy (Table 1).

Table 1 Cardiac magnetic resonance findings in hypertrophic cardiomyopathy and phenocopies

	Morphologic features	Tissue characterization		
		LGE	Mapping	ECV
Athlete's heart	Balanced increase in wall thickness and cavity size	Absent or in RV insertion points	Normal or decreased T1	Normal or decreased
Hypertrophic cardiomyopathy (sarcomeric)	Typically asymmetric LVH, with septal predominance	Mid-mural, patchy, affecting most hypertrophied segments; transmural in advanced stages	Increased native T1, regardless of LGE presence, reflecting interstitial fibrosis	Increased ECV attributed to fibrosis
Amyloidosis	Symmetric or asymmetric LVH	Subendocardial, global, diffuse; transmural in advanced stages. LGE reflects infiltration, not fibrosis; abnormal gadolinium kinetics	Marked increase in native T1 value (AL > ATTR) due to protein accumulation	Markedly increased ECV reflecting protein accumulation
Fabry disease	Concentric LVH, prominent papillary muscles, RV hypertrophy	Mid-mural, basal inferolateral segment	Decreased native T1 values (lipid storage); pseudonormalization in advance stages due to fibrosis. Elevated T2 levels due to inflammation	Normal ECV

ECV: Extracellular volume; LGE: Late gadolinium enhancement; LVH: Left ventricular hypertrophy; RV: Right ventricle.

Athlete's heart

CMR is also useful for distinguishing pathological LVH from physiological adaption to exercise. The "athlete's heart" is characterized by biventricular, symmetrical remodelling, and is associated to a concomitant and proportional increase in cavity size[26,27]. Specific reference values of ventricular size and function for athletes have been reported by D'Ascenzi *et al*[27] In athletes, the degree of hypertrophy is usually mild, and LV wall thickness rarely exceeds 12 mm[28]. Moreover, reversal of adaptative LVH can be achieved with detraining[29]. When present, in athletes, LGE is usually confined to the RV insertion points (mostly the inferior), and its presence has been correlated with training load and intensity[30]. This pattern of fibrosis does not affect prognosis nor requires further evaluation in otherwise healthy athletes[30]. Mapping data may further differentiate "athlete's heart" from HCM: While the latter is usually associated with increased native T1 and ECV (reflecting interstitial fibrosis)[28,30], these parameters are normal, or even decreased, in athletes. Although echocardiography remains the major imaging tool for athlete pre-participation screening, CMR can be paramount in situations where suspicious of myocardial disease persists based on symptoms, family history, electrocardiographic or echocardiographic data.

HCM

HCM is defined by unexplained LVH in a non-dilated LV with wall thickness ≥ 15 mm or, alternatively, ≥ 13 mm, in the presence of positive family history or a disease-causing gene variant[22]. HCM, the most common genetic cardiovascular disease, with a prevalence of 1:200-1:500, is caused by sarcomeric gene mutations, that are inherited as an autosomal dominant trait[31]. There is marked phenotypic heterogeneity among HCM probands, even among individuals from the same family, that occasionally poses a challenge in terms of diagnosis and risk stratification.

Morphofunctional evaluation: The "classical" HCM phenotype consists of asymmetrical, septal-predominant hypertrophy, that may be associated to dynamic LV tract obstruction (LVOTO)[31]. In hypertrophied hearts, CMR enables precise measurement of maximal wall thickness and an accurate portrayal of LVH pattern, extent and distribution[28]. This is of particular importance in the presence of midventricular or apical variants of HCM, in which echocardiographic evaluation encounters limitations[23].

The presence of apical aneurysms is associated to higher rates of ventricular arrhythmias (VA), SCD, thromboembolic events, and heart failure in patients with HCM[32,33]. CMR has enabled more frequent identification of this high-risk subset of patients, by detecting small aneurysms that may remain unnoticed during non-contrast echocardiographic evaluation[23] but are still relevant for risk stratification. Accordingly, the presence of an apical aneurysm, regardless of size, has been considered a major risk factor by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, assigning it a class IIa (level of evidence B) recommendation for implantable cardioverter-defibrillator (ICD) implantation for primary prevention of SCD[34]. The ESC guidelines on SCD prevention have recently included LV apical aneurysm as an additional factor for consideration of an ICD (class IIb recommendation, level of evidence B)[35], even in patients with a low estimated risk according to the HCM Risk-SCD score[36].

Detection of thrombi within the scared LV apex also carries meaningful management considerations. In a recent study, Lee *et al*[37] found a linear relationship between aneurysm size and the risk of adverse events, including apical thrombus formation and thromboembolic stroke. Moreover, patients with an aneurysm size ≥ 2 cm showed a significant increase in 5-year SCD risk (9.7% *vs* 2.9%, $P = 0.037$)[37].

Other morphologic abnormalities related to HCM can be further demonstrated by CMR, including mitral subvalvular apparatus abnormalities or myocardial crypts. Maron *et al* reported the presence of myocardial crypts – narrow, deep blood-filled invaginations within LV myocardium – in 61% of genotype positive/phenotype negative (G+P-) patients without overt LV hypertrophy, suggesting this morphologic feature to be part of the phenotypic expression of HCM[38].

Contrastingly, in a large Danish cohort assessed by computed tomography, LV crypts were frequent among the general population, and were not associated with a composite endpoint of death, myocardial infarction, heart failure, or stroke [39]. However, among family members of patients with HCM, the presence of crypts may prompt careful follow-up to monitor progression to an overt phenotype.

Another subclinical marker of HCM observed by CMR has been proposed by the same group – LV apical-basal muscle bundles. LV muscle bundles were suggested as a latent marker in G+/P- individuals, and were related to HCM phenotypic expression, irrespective of LV wall thickness[40].

CMR is useful for depicting papillary muscle (PM) architecture and functional abnormalities. PM hypertrophy (minor axis diameter > 11 mm or combined mass > 7 g/m^2) is present in more than half of HCM cases, and my contribute to mid-ventricular obstruction[41,42]. Additional abnormalities that contribute to LVOTO, such as accessory, bifid or displaced PM, can be adequately demonstrated by CMR[41].

Tissue characterization: The presence of LGE in HCM reflects replacement fibrosis, and its prognostic value is well-established[43]. LGE is found in more than half of HCM patients, usually presenting an mid-mural pattern within the most hypertrophied segments[43,44]. In advanced stages of the disease, LGE with transmural extension can be observed and carries a worse prognosis[44].

LGE has been consistently associated increased SCD incidence, and its presence and extent was included as a major risk factor in the ACC/AHA risk stratification algorithm[34] and, more recently, in the 2022 ESC Guidelines for prevention of SCD[35]. In a landmark multicenter study, LGE exceeding 15% of the LV mass was associated with a > 2-fold risk of SCD in patients who were deemed low risk by conventional tools, compared with patients in whom LGE was absent[43]. Therefore, presence of "extensive LGE" (≥ 15% of total LV mass) is regarded as a high-risk parameter, and in HCM patients without a defibrillator, CMR should be repeated every 3-5 years to monitor LGE progression and reconsider SCD prevention strategies[23,34].

T1 mapping and ECV (derived from native and post-contrast T1) allow for identification of diffuse, interstitial fibrosis [23]. Native T1 and ECV may be elevated in segments without LGE, and even in variant carriers without overt LVH[28]. Mapping techniques allow differentiation of HCM from phenocopies (Table 1).

Edema with abnormal T2 findings (T2-Stir) could be observed in HCM patients often indicative of an acute myocardial injury (*i.e.*, ischemic extravascular damage) and associated with electrical instability[45].

Perfusion: Microvascular dysfunction is part of the pathophysiology of HCM and can be evaluated by means of CMR perfusion imaging. In HCM, reduced myocardial blood flow correlates with increased LV wall thickness and mass, presence of LGE, and increased ECV[23,28]. Aguiar Rosa *et al*[46] showed that increased ischemia severity, assessed by CMR, was associated with higher values of native T1 and greater LGE extension. Patients with severe ischemia demonstrated higher incidence of atrial arrhythmias and performed poorer in cardiopulmonary stress testing[46].

HCM phenocopies

CMR has an increasing role in the evaluation of rare forms of myocardial disease that also manifest with LVH, otherwise known as phenocopies of HCM. In such cases, family history, electrocardiographic patterns and extracardiac manifestations may raise diagnostic suspicion, that may be corroborated by imaging findings.

Amyloidosis: Cardiac amyloidosis (CA) produces LV "pseudo-hypertrophy", resulting from interstitial expansion due to amyloid fibrils deposition, rather than from myocyte proliferation[47]. Transthyretin (ATTR), both hereditary and wild-type, and immunoglobulin-derived light chain amyloidosis are responsible for most cases of amyloid-related myocardial disease[48]. Extracellular expansion in CA is depicted in CMR parametric mapping findings by a marked increase in native T1 Levels and ECV[28]. Patients with CA show global, diffuse subendocardial LGE, that may become transmural in more advanced stages of the disease. This pattern of LGE, in the adequate setting, is very specific for CA[49]. LGE not rarely extends to the RV and the atria, particularly in ATTR[28]. Another characteristic CMR feature in CA is the abnormal gadolinium kinetics, with myocardial nulling preceding with the blood pool, or an equalization of these points [48,49]. More detailed information will be provided in the section entitled cardiomyopathies with restrictive phenotype.

Fabry disease: Fabry disease (FD), an X-linked lysosomal storage disorder, usually leads to concentric LVH, due to both glycosphingolipid accumulation and myocyte hypertrophy[50]. Prominent PM s are a typical feature of FD, as is concomitant RV hypertrophy[28,44].

Parametric mapping is of particular utility for the differential diagnosis of FD. Native T1 decreases with lipid deposition[22]; accordingly, in early stages of FD, native T1 values are low, when compared to normal reference values and other forms of LVH[28,50]. However, as disease progresses and replacement fibrosis becomes evident, pseudo-normalization of native T1 relaxation times occurs[28,50]. ECV remains within normal range in LGE-free areas[50], since FD leads to intracellular storage of glycosphingolipids. T2 values can be elevated due inflammatory response triggered by lipid accumulation.

LGE is present in > 50% of FD patients, and is usually located in the LV basal inferolateral segment, with a mid-mural or subepicardial pattern[22,44,49]. Presence of LGE has been reported in female mutation carriers without LVH[49]. Similar to HCM, presence of LGE in FD is associated to adverse outcomes and poor response to replacement therapy[50].

CARDIOMYOPATHIES WITH RESTRICTIVE PHENOTYPE

Less than 5% of all cardiomyopathy cases are attributed to restrictive cardiomyopathies (RCM), which have a diverse range of causes[51].

RCM is characterized by a significant alteration in myocardial compliance, presenting severe diastolic dysfunction while maintaining preserved systolic function, especially in the early stages. The initial diagnosis typically involves a TTE that reveals normal or increased LV wall thickness, often with a concentric or symmetric distribution, along with a restrictive pattern observed through Doppler analysis. It also shows the absence of LV dilation, preserved LVEF, and significant biatrial enlargement[52]. However, while TTE plays a crucial role in the initial assessment and raising diagnostic suspicions, its utility becomes limited when establishing a differential diagnosis. In such cases, CMR imaging becomes highly relevant.

Two of the most common entities where CMR is essential are the endomyocardial fibrosis (EMF) and CA.

EMF

EMF represents a rare subtype of RCM. It is characterized by an unusual thickening of the endocardium, resulting from the deposition of fibrous tissue[53]. This condition is typically secondary to various factors, including infections (often found in tropical regions), inflammation, exposure to toxic agents, among others. Echocardiographic observations in EMF include apical obliteration due to thickening of the endocardium, a reduction in ventricular cavity size, and a pronounced restrictive diastolic pattern. EMF can primarily affect the left ventricle, both the left and right ventricles (in approximately 50% of cases), or predominantly the right ventricle[54]. The presence of apical thrombus is also a frequently encountered feature.

CMR is the gold standard for EMF evaluation and specifically for localization, characterization, and quantification of fibrous tissue by LGE sequences. LGE strongly correlates with histopathological findings and its extension is associated with increased mortality risk[55]. CMR may also identify apical thrombus or calcifications.

CA

In patients with CA, cine sequences or functional assessment methods provide a means to observe the structural characteristics of the infiltrated myocardium. These characteristics encompass biventricular hypertrophy, thickening of cardiac valves, interatrial septum, pericardial effusion, and biatrial dilation. Additionally, these techniques enable the precise evaluation of both systolic and diastolic function[56]. It is essential to not only focus on the assessment of the LV but also on the other cardiac chambers. Notably, the involvement of RV has been identified as a predictor of mortality in CMR, consistent with findings from TTE[57]. As the disease advances into later stages, there is a notable increase in atrial volume and dysfunction. This phenomenon is attributed to the direct infiltration of amyloid fibrils into the atria and indirectly to elevated filling pressures due to diastolic dysfunction.

The Table 2 summarizes the main cardiac magnetic resonance (CMR) findings in CA with an explanation of the prognostic and diagnostic implications.

To sum up, CMR represents a complementary diagnostic step in the evaluation of patients suspected of having CA. This imaging method is not widely accessible in numerous medical facilities, and its lengthy duration per study restricts the total number of examinations feasible in a day.

ARRHYTHMOGENIC CARDIOMYOPATHY

Arrhythmogenic cardiomyopathy (ACM) is an inherited cardiomyopathy characterized by replacement of myocardium by fatty and fibrous tissue. Historically named Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) because of the RV involvement, the late recognition of left and biventricular forms led to the new term ACM, encompassing both phenotypes. VA through macro-reentry mechanism related to the fibrofatty involvement is one of the main clinical presentations, manifesting in the worst case by SCD. In the advanced stages, the disease is characterized by heart failure [58,59].

Diagnosis criteria established by the International Task Force (ITF) included morphological (dysfunction and structural alteration) and anatomopathological characterization, ECG abnormalities, history of arrhythmias and family history[60]. CMR role was limited to evaluation of regional RV motion wall, RV ejection fraction (RVEF) and RV end-diastolic volume. Critics have been raised about the absence of LV involvement and the limited role of CMR. In 2020, the Padua Criteria was proposed, revisiting the ITF criteria by including tissue characterization provided by CMR. Functional or structural abnormality is enough for the diagnosis[61]. Pathogenic mutations, ECG abnormalities, or VA are no longer sufficient. This highlights the role of CMR, which has become one of the preferred non-invasive imaging techniques, allowing an increase of diagnostic sensitivity for ACM. CMR offers an advanced evaluation of the heart, including ventricular morphology, volume, thickness, ejection fraction, regional motion, myocardial fibrous, adipose content, edema, flow, LGE, as well as new emerging and promising feature as global longitudinal and circumferential strain (assessed by using feature-tracking CMR). Despite its complete evaluation, CMR has some limitations: fatty infiltration is nonspecific and does not preclude the diagnosis.

Prognosis in ACM is mostly related to VA. ICD being the only intervention improving survival[62], risk stratification is vital to identify the high-risk patients benefiting the most from primary prevention ICD implantation. RV dysfunction and syncope history are strong predictor for arrhythmia event and have been both included in the guidelines. CMR is not included in the risk stratification recommendations, neither in the 2019 Heart Rhythm Society guidelines[63], nor the 2022

Table 2 Cardiac magnetic resonance findings in cardiac amyloidosis. Prognostic and diagnostic implications

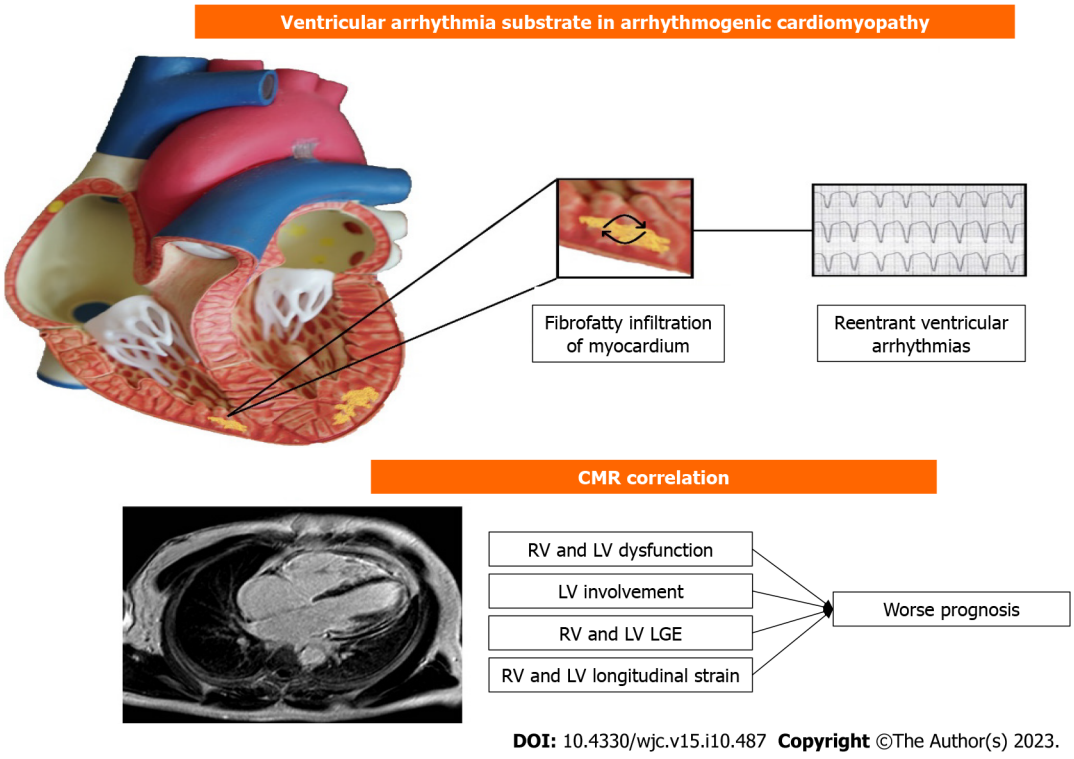
Parameter	Implications	Ref.
Reduction of the total left atrial emptying fraction in AL-CA patients	+ Related to more advanced stages of the disease and with a worse functional class; + Increase in 2 years-mortality if its value < 16%	Mohty *et al*[79]
MCF and LAS in AL-CA patients	+ If LAS > -7% and MCF < 52.6% greatest risk of death and heart transplantation	Arenja *et al*[80]
Anterior aortic plane systolic excursion in AL-CA patients	+ Best predictive value for transplant-free survival	Ochs *et al*[81]
Strain	+ Correlates well with the level of LGE uptake an alternative to LGE where contrast should not be used; + GLS impaired robust predictor of all-cause mortality in AL-CA patients	Wan *et al*[82]
Look-Locker sequence (T1 sequence with different inversion times)	+ Increased risk of death if it is impossible to obtain a normal myocardial signal on LGE using this sequence with inversion time over than 300 ms	Mekinian *et al*[83]
LGE	+ Typical pattern is a diffuse subendocardial uptake and also it was described a transmural pattern enhancement and less frequently a focal patchy one; + Controversy exists regarding the prognostic implication	Maceira *et al*[84], Fontana *et al*[85], Raina *et al*[86]
The difference in the intramyocardial T1 value post-gadolinium between subepicardium and subendocardium	+ Worse survival when that difference was lower than 23 ms	Maceira *et al*[84]
Diffuse subendocardial uptake detected using a modified LGE-CMR protocol with visual T1 assessment	+ High diagnostic precision (PPV 93%, NPV 90%); + Significantly associated with 2 yr mortality	Austin *et al*[87], White *et al*[88]
RV gadolinium uptake in AL-CA patients	+ Independent predictor of survival during a period of 6 mo follow up	Wan *et al*[89]
QALE	+ Score > 9 predicted worse survival, especially useful in patients with a subendocardial LGE pattern	Wan *et al*[90]
Noncontrast T1-mapping	+ A cut-off value of 1020 ms had high sensitivity and specificity (around 90%) for identifying amyloid patients with possible or definite cardiac involvement	Karamitsos *et al*[91]
T1 mapping with native T1 and extracellular volume	+ Patients with AL-CA and suspected cardiac involvement had increased values; + Only ECV had a significant prognostic implication with greater mortality if its value was > 44%; + Basal ECV had the best prognostic value amongst myocardial T1 mapping parameters	Karamitsos *et al*[91], Lin *et al*[92], Wan *et al*[93]
T2-weighted imaging	+ No gadolinium administration is needed; + A decreased myocardial signal intensity compared with skeletal muscle was associated with shortened survival; + T2 ratio value < 1.36 had a weak sensitivity and specificity (63% and 73% respectively) to predict cardiac involvement	Wassmuth *et al*[94], Legou *et al*[95]

AL-CA: Light chain cardiac amyloidosis; CMR: Cardiovascular magnetic resonance; ECV: Extracellular volume; GLS: Global longitudinal strain; LAS: Long axis strain; LGE: Late gadolinium enhancement; MCF: Myocardial contraction fraction; NPV: Negative predictive value; PPV: Positive predictive value; QALE: Query amyloid late enhancement score; RV: Right ventricle.

ESC guidelines for the management of patients with VA and the prevention of SCD[35]. In this context, CMR role is only limited to diagnosis. A 2019 consensus expert developed the ARVC 5-year Risk-VAs calculator: A prediction model for VA risk to guide decision regarding primary prevention ICD (www.arvcrisk.com)[64]. CMR is included only to assess RVEF. CMR parameters of tissue characterization and regional wall motion of both ventricles were not included. The role of CMR in risk stratification remains to be determined. Lack of consistent studies explains the absence of CMR from the risk stratification recommendation, even though some emerging data shows the potential prognosis information provided by CMR.

Different CMR phenotype of ACM are associated with different prognoses. Normal CMR has an excellent negative predictive value for major clinical events[65-67]. Tandri *et al*[68] showed that delayed gadolinium enhancement of RV correlates with inducible VT during electrophysiology testing. Lie *et al*[69] confirm that CMR findings, as low RVEF, RV wall-contraction abnormalities, or RV aneurysms are predictors of life-threatening ventricular arrhythmia. Evaluation of longitudinal strain by feature-tracking CMR could also bring risk stratification information, as reduced strain seems to be associated with sustained VA[70].

Regarding the LV involvement, its association with adverse outcomes is inconsistent[71]. Presence of LV dysfunction is associated with arrhythmic adverse outcomes as reported by a small European registry[72]. Some studies have suggested that CMR imaging features of LV phenotypes, as fat infiltration and LGE, in ACM may be associated with adverse outcomes. Aquaro *et al*[66] highlight that the different CMR presentations of ACM are associated with different prognoses, LV involvement (LV dominant and biventricular) being the worst prognosis. Zhang *et al*[73] confirm the bad prognosis of LV LGE, being associated with an increased risk of ICD therapy and cardiac death, independently of LVEF. LV myocardial assessment by CMR could also predict the HF-related event risk as reported by Chun *et al*[74]. On the contrary LV dysfunction was not a predictor of arrhythmic risk in two meta-analysis[75,76]. Zghaib *et al*[77] showed that LV fibrofatty infiltration in CMR was not associated with arrhythmic outcomes. The role of identification of LV



DOI: 10.4330/wjc.v15.i10.487

Figure 1 Correlation between cardiac magnetic resonance and ventricular arrythmia in arrhythmogenic cardiomyopathy. CMR: Cardiac magnetic resonance; RV: Right ventricle; LV: Left ventricle; LGE: Late gadolinium enhancement.

involvement by CMR and its prognosis significance remains to be established.

There is some potential speculation on some cases of ACM that could be explained by an inflammatory activity or hot phase, if the diagnosis it is in a very early-stage sequences like T2-STIR for oedema detection could help[78], this hot phase could be related with arrhythmias during the disease.

To finalise, CMR role in diagnosis is well established (Figure 1). Regarding the risk stratification, only RV function is validated in international guidelines and risk calculator. Lack of consistent data about correlation between CMR characterization and adverse outcomes could explain the absence of CMR role from guidelines, but a few emerging studies show new evidence about CMR imaging, Indicating that the presence of structural abnormalities in the RV as observed through CMR plays a crucial role in evaluating the risk of arrhythmias. : RV dilatation, dysfunction and LGE are among the strongest predictors. Regarding the LV involvement, the few data are contradictory, but may trend towards an association with high-risk event. CMR may have a promising role in association with classical clinical feature, but further studies are needed to better define CMR place in risk stratification.

CONCLUSION

Cardiovascular imaging methods play a vital role in investigating cardiomyopathies, furnishing valuable diagnostic and prognostic insights. The inclusion of CMR in the evaluation of all patients is highly recommended, owing to its ability to offer comprehensive anatomical, functional, and tissue-specific data, which holds significant prognostic value. While other imaging techniques might be employed selectively, the integration of multiple modalities of cardiac imaging assumes a crucial role in clinical decision-making, leading to enhanced patient management and care outcomes.

FOOTNOTES

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Country/Territory of origin: Spain

ORCID number: Rafael Vidal-Perez 0000-0001-9944-8363; Mariana Brandão 0000-0001-9913-0435; Wael Zaher 0000-0002-0537-9262; Ruben Casado-Arroyo 0000-0002-3876-6074; Alberto Bouzas-Mosquera 0000-0002-2741-732X; Ricardo Fontes-Carvalho 0000-0003-2306-8393; Jose Manuel Vazquez-Rodriguez 0000-0003-0888-6937.

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ORIGINAL ARTICLE

Retrospective Study

Integrated analysis of comorbidity, pregnant outcomes, and amniotic fluid cytogenetics of fetuses with persistent left superior vena cava

Xin Yang, Xin-Hui Su, Zhen Zeng, Yao Fan, Yuan Wu, Li-Li Guo, Xiao-Yan Xu

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Xin Yang, Xin-Hui Su, Zhen Zeng, Yao Fan, Yuan Wu, Li-Li Guo, Xiao-Yan Xu, Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China

Corresponding author: Xiao-Yan Xu, PhD, Doctor, Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1095 Jiefang Avenue, Wuhan 430030, Hubei Province, China. xuxiaoyan@tjh.tjmu.edu.cn

Abstract

BACKGROUND

Persistent left superior vena cava (PLSVC) is the most common venous system variant. The clinical characteristics and amniotic fluid cytogenetics of fetuses with PLSVC remain to be further explored.

AIM

To develop reliable prenatal diagnostic recommendations through integrated analysis of the clinical characteristics of fetuses with PLSVC.

METHODS

Cases of PLSVC diagnosed using prenatal ultrasonography between September 2019 and November 2022 were retrospectively studied. The clinical characteristics of the pregnant women, ultrasonic imaging information, gestational age at diagnosis, pregnancy outcomes, and amniocentesis results were summarized and analyzed using categorical statistics and the chi-square test or Fisher's exact test.

RESULTS

Of the 97 cases diagnosed by prenatal ultrasound, 49 (50.5%) had isolated PLSVC and 48 (49.5%) had other structural abnormalities. The differences in pregnancy outcomes and amniocentesis conditions between the two groups were statistically significant ($P < 0.05$). No significant differences were identified between the two groups in terms of advanced maternal age and gestational age ($P > 0.05$). According to the results of the classification statistics, the most common intracardiac abnormality was a ventricular septal defect and the most common extracardiac abnormality was a single umbilical artery. In the subgroup analysis, the concurrent combination of intra- and extracardiac structural abnormalities was a risk factor for adverse pregnancy outcomes (odds ratio > 1, $P < 0.05$). Additionally, all abnormal cytogenetic findings on amniocentesis were observed in the comorbidity group. One case was diagnosed with 21-trisomy and six cases was

diagnosed with chromosome segment duplication.

CONCLUSION
Examination for other structural abnormalities is strongly recommended when PLSVC is diagnosed. Poorer pregnancy outcomes and increased amniocentesis were observed in PLSVC cases with other structural abnormalities. Amniotic fluid cytogenetics of fetuses is recommended for PLSVC with other structural abnormalities.

Key Words: Persistent left superior vena cava; Prenatal diagnosis; Amniotic fluid cytogenetics; Pregnancy outcome; Integrated analysis; Comorbidity

Core Tip: Our study was performed for providing reliable prenatal diagnostic advice through integrated analysis of the clinical characteristics of fetuses with persistent left superior vena cava (PLSVC). We retrospectively studied 97 cases of PLSVC diagnosed using prenatal ultrasonography. Of the 97 cases diagnosed by prenatal ultrasound, 49 (50.5%) had isolated PLSVC and 48 (49.5%) had other structural abnormalities. We found that PLSVC is associated with a certain percentage of other combined structural abnormalities. Examination for other structural abnormalities is strongly recommended when PLSVC is diagnosed. Poorer pregnancy outcomes and increased amniocentesis were observed in PLSVC cases with other structural abnormalities.

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INTRODUCTION

Persistent left superior vena cava (PLSVC) is the most common venous system variant. The incidence rate of PLSVC in congenital heart disease is approximately 5%-6%, whereas it is only 0.3%-0.5% in the normal population[1,2]. Previous research has shown that the probability of adverse pregnancy outcomes in isolated PLSVC is lower, and the risk of adverse pregnancy outcomes is significantly increased when combined with other malformations[3]. With improvements in genetic examination technology, some studies have reported that the proportion of fetal chromosomal abnormalities among PLSVC fetuses has significantly increased, which is different from the classic opinion of this disease[4,5].

Since fetal ultrasound examinations are unaffected by pulmonary gases, the prenatal period is the best time to perform vascular examinations[6,7]. Previous studies on PLSVC have focused on a few aspects, some only on the types of comorbidities and others only on pregnancy outcomes. There is a lack of comprehensive studies that provide reliable conclusions for patients and clinicians.

Our study retrospectively collected the clinical data, including the age of the pregnant women, ultrasonic imaging information, pregnancy outcomes, and amniocentesis results, from 97 cases of fetal PLSVC. We integrated clinical information, imaging features, and molecular-level results to provide reliable advice to patients and clinicians in multiple dimensions. Fetal PLSVC cannot be viewed as a purely vascular anatomical variant, and this disease is associated with a certain percentage of other combined structural abnormalities. Therefore, examination for other structural abnormalities should be performed when PLSVC is diagnosed.

MATERIALS AND METHODS

Study population

Ninety-seven patients with PLSVC diagnosed using prenatal ultrasonography at Tongji Hospital between September 2019 and November 2022 were retrospectively studied. Clinical characteristics included maternal age, gestational weeks, prenatal ultrasound images, specific types of combined intra- and extracardiac abnormalities, pregnancy outcomes, amniocentesis conditions, and results. The range of maternal age was 22 to 39 years, with a mean age of 30.36 ± 3.94 years. The weeks of gestation at which PLSVC was diagnosed in our hospital was 18 to 34 wk, and the average weeks of gestation was 24.72 ± 3.99 wk. There were 87 single pregnancies (89.7%) and 10 twin pregnancies (10.3%), including two double chorionic villi and double amniotic sac twin fetuses (20.0%) and eight cases of single chorionic villi and double amniotic sac twin fetuses (80%). This study was approved by the Ethics Committee of Tongji Hospital.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Pregnancy at 12 to 34 wk of gestation; (2) complete clinical data; and (3) standard and clear cardiac ultrasound images.

The exclusion criteria were as follows: (1) Pregnancy with three or more fetuses; (2) frequent fetal movement leading to poor-quality echocardiography; and (3) incomplete clinical data.

Ultrasound instruments and examinations

Using the color Doppler ultrasound instruments GE VOLUSON E8 and VOLUSON E10 (GE, Milwaukee, WI, United States) with a probe frequency of 2 to 5 MHz, after determining the fetal orientation and the relationship between the viscera and heart position, the fetal heart examination conditions were selected. The fetal heart segmental analysis method was used to determine the heart, blood vessel structure, and connection relationship. The focus was on four-chamber heart, three-vessel, and three-vessel trachea sections, combined with color Doppler observation of the blood flow direction and vascular morphology[8,9]. According to prenatal screening guidelines, a comprehensive ultrasound examination was performed on fetuses diagnosed with PLSVC to determine whether there are any concomitant intracardiac or extracardiac abnormalities[10,11].

Statistical analysis

Statistical software (SPSS 26.0, IBM Corp., Armonk, NY, United States) was used for the data analysis. The measurement data conforming to a normal distribution are expressed as the mean ± SD. The independent samples *t*-test was used for comparison between groups, and the paired sample *t*-test was used for comparison within groups. Count data are expressed as cases (%), and the χ^2 test or Fisher's exact probability method was used for comparison between groups. Statistical significance was set at $P < 0.05$.

RESULTS

Comparison of clinical characteristics between the group with isolated PLSVC and the group with additional malformations

Ninety-seven cases diagnosed using prenatal ultrasound were included in our study, including 49 cases (50.5%) with isolated PLSVC and 48 (49.5%) with other structural abnormalities. The mean age in the isolated PLSVC group was 30.39 ± 4.04 years, and the mean age of those having PLSVC with other malformations was 30.46 ± 3.89 years. There was no statistically significant difference in gestational age between the two groups. The clinical characteristics of the patients are shown in Table 1. We summarized the maternal age, number of fetuses, gestational weeks at first diagnosis, pregnancy outcomes, and amniocentesis conditions. After statistical analysis, we found significant differences in pregnancy outcomes and amniocentesis conditions between the two groups ($P < 0.05$). No statistical differences were found between the two groups in terms of maternal age, number of fetuses, and gestational weeks at first diagnosis. These observations demonstrate that PLSVC with other structural abnormalities may be associated with more adverse pregnancy outcomes. Pregnant women were more likely to be recommended for amniocentesis diagnosis.

Types of intracardiac structural abnormalities in PLSVC fetuses

After summarizing the clinical features, we found that a considerable proportion of PLSVC cases had other structural abnormalities. We summarized the specific types of abnormalities observed with PLSVC to provide a reference for improving the accuracy of ultrasound screening.

Among the included cases, 22 presented with cardiovascular system abnormalities, including 11 with both intracardiac and extracardiac abnormalities. The specific types and number of cases are listed in Table 2. Among these, interventricular septum defects were the most common, followed by aortic coarctation. These results indicate that when a PLSVC is found, scanning of the interventricular septum and aortic arch should be performed.

Types of extracardiac structural abnormalities in PLSVC fetuses

In addition to the cardiovascular system, the types of combined abnormalities of other systems in PLSVC were relatively complex, with 37 cases of abnormalities in extracardiac structures, including 11 combined with both intracardiac and extracardiac abnormalities. The specific types and numbers of cases are listed in Table 3. Among them, a single umbilical artery was observed in the largest number of cases, followed by persistent right umbilical vein and urinary system abnormalities. These results indicate that when PLSVC is found, scanning of the umbilical vascular structure and urinary system should be performed.

Subgroup analysis of combined intra- and extracardiac abnormalities

Based on the above observations, we found that the number of patients with PLSVC combined with intra- and extracardiac abnormalities was not consistent. Therefore, we further investigated how intra- and extracardiac structural abnormalities affect pregnancy outcomes through subgroup analysis. In our case series, 13 (13.4%) patients with PLSVC terminated their pregnancy, and 84 (86.6%) continued their pregnancy. Among the 13 terminated pregnancy cases, 12 (92.3%) had other structural abnormalities and seven (53.8%) had both intracardiac and extracardiac structural abnormalities. We found that patients with PLSVC with extracardiac abnormalities had the highest sustained pregnancy

Table 1 Clinical characteristics in the isolated persistent left superior vena cava group and the persistent left superior vena cava with other malformations group, *n* (%)

	Isolated PLSVC (*n* = 49)	PLSVC with other malformations (*n* = 48)	χ^2	*P* value
Age				
< 35 years old	42 (85.7)	39 (81.3)	0.35	0.55
≥ 35 years old	7 (14.3)	9 (18.7)		
Number of fetuses				
Singleton	43 (87.8)	44 (91.7)	0.40	0.53
Twins	6 (12.2)	4 (8.3)		
Gestational age at initial diagnosis				
Before 28 wk	46 (93.9)	45 (93.8)	0.001	0.97
After 28 wk	3 (6.1)	3 (6.2)		
Pregnancy outcome				
Persistent pregnancy	48 (98.0)	36 (75.0)	11.01	0.001
Terminated pregnancy	1 (2.0)	12 (25.0)		
Amniocentesis status				
No apparent abnormalities	5 (10.2)	14 (29.2)	15.33	< 0.001
Abnormal results	0 (0.0)	7 (14.6)		
No amniocentesis performed	44 (89.8)	27 (56.2)		

PLSVC: Persistent left superior vena cava.

Table 2 Specific types of intracardiac structural abnormalities in 97 cases of persistent left superior vena cava, *n* (%)

Type of intracardiac structural abnormalities	*n* (%)
Ventricular septal defect	7 (31.8)
Aortic coarctation	5 (22.7)
Tetralogy of Fallot	3 (13.6)
Right-sided aortic arch	3 (13.6)
Left pulmonary artery originating from the right pulmonary artery	1 (4.5)
Single atrium with complete endocardial cushion defect	1 (4.5)
Midline heart with ventricular wall hypertrophy	1 (4.5)
Absence of right superior vena cava	1 (4.5)
Total	22 (100)

rates. Using statistical methods, we compared the other subgroups with this group to identify risk factors. In terms of sustained pregnancy rate, the presence of simultaneous abnormal cardiac and extracardiac structures was a risk factor affecting sustained pregnancy rate (odds ratio > 1, $P < 0.05$). Specific data are presented in Table 4.

Amniotic fluid cytogenetics of fetuses with PLSVC

Amniotic fluid cytogenetics enables further investigation of cases with imaging abnormalities and plays an irreplaceable role in clarifying the etiology. In our case series, 26 pregnant women chose amniocentesis, including five isolated PLSVC cases and 21 PLSVC cases with other abnormalities. No obvious abnormalities were observed in the amniocentesis results of the isolated PLSVC group. However, amniocentesis results in the group with combined intracardiac and extracardiac abnormalities displayed a certain proportion of anomalies, including one case with 21-trisomy and six cases with abnormal copy number variations (CNVs). Despite the limited research data on CNVs in PLSVC cases, specific types of analysis can still provide effective information for clinical practice. Six cases of abnormal CNVs were identified as repetitions of chromosomal regions, including two cases classified as potentially benign, three cases classified as variants of uncertain significance, and one as potentially pathogenic. The results are presented in Table 5. These observations

Table 3 Specific types of extracardiac structural abnormalities in 97 cases of persistent left superior vena cava, *n* (%)

Type of extracardiac structural abnormalities	*n* (%)
Single umbilical artery	9 (24.3)
Persistent right umbilical vein	6 (16.2)
urinary system abnormalities	6 (16.2)
Neurological system abnormalities	3 (8.1)
Pleural effusion	2 (5.4)
Pulmonary cystadenoma	2 (5.4)
Absence of nasal bone	2 (5.4)
Gallbladder abnormalities	2 (5.4)
Situs inversus	1 (2.7)
Scoliosis	1 (2.7)
Multiple malformations	3 (8.1)
Total	37 (100)

Table 4 Analysis of pregnancy outcomes in persistent left superior vena cava with intracardiac and extracardiac abnormalities

Type	Persistent pregnancy, *n* (%)	OR	95%CI	*P* value
PLSVC only with extracardiac abnormalities	24 (92.3)			
PLSVC only with intracardiac abnormalities	8 (72.7)	4.5	0.63-31.95	0.12
PLSVC with intracardiac and extracardiac abnormalities	4 (36.3)	21.0	3.16-139.67	0.001

PLSVC: Persistent left superior vena cava.

Table 5 Six cases with abnormal copy number variation sequencing results in persistent left superior vena cava

	Chromosomal location	Variation type	Fragment size	Clinical significance
1	Chromosome 15	Repetition	0.4 Mb	Potentially benign
2	Chromosome 2	Repetition	0.5 Mb	Potentially benign
3	Chromosome 11	Repetition	3.9 Mb	VUS
4	Chromosome 19	Repetition	187.4 Kb	VUS
5	Chromosome 1	Repetition	2.3 Mb	VUS
6	Chromosome 1	Repetition	> 10 Mb	Potential pathogenicity

VUS: Variants of uncertain significance.

imply that CNVs may be associated with PLSVC combined with other abnormalities. When PLSVC cases with other abnormalities are detected, amniocentesis may contribute to the prenatal diagnosis and clinical decision-making.

DISCUSSION

PLSVC is the most common venous system variant. However, the risk of adverse pregnancy outcomes is significantly increased when PLSVC is combined with other malformations. Our study was performed to provide reliable prenatal diagnostic recommendations through integrated analysis of the clinical characteristics of fetuses with PLSVC.

Fetal ultrasound examination is not affected by pulmonary gases; therefore, ultrasound can comprehensively observe the superior vena cava, and prenatal screening is the best time for PLSVC[7]. Several case reports have demonstrated difficulties in the diagnosis of PLSVC in adults, and certain patients require special examination methods[12,13]. PLSVC has typical sonographic features, with a cross-sectional view of the PLSVC visible on the left side of the pulmonary artery

in a three-vessel tracheal section[14]. In cases of PLSVC, approximately 90% enter the right atrium through the coronary sinus and approximately 10% directly enter the left atrium. In patients presenting with the left superior vena cava entering the right atrium through the coronary sinus, a dilated coronary sinus is observed on a four-chamber view[15,16]. Some cases in this study were not detected in the mid-trimester systematic screening, and most missed cases were twins. The limitations associated with scanning due to mutual fetal occlusion may be the main reason for missed diagnoses. This study integrates clinical factors, imaging information, and amniotic fluid cytogenetic information. As such, it is innovative compared to previous studies, showing that PLSVC is not just a simple anatomical variant, but is also associated with a higher rate of other structural abnormalities. In cases of PLSVC combined with other structural abnormalities, there are differences in pregnancy outcomes and amniocentesis.

This study classified and summarized the types and proportions of intra- and extracardiac abnormalities associated with PLSVC. These types of intracardiac and extracardiac abnormalities are consistent with previous research findings, both domestic and international[17-20]. A previous case report indicated that PLSVC can occur with anorectal malformation, an abnormality that we did not observe[21]. However, in this study, the proportion of patients with concurrent intracardiac and extracardiac abnormalities (n = 11) was slightly higher than that in similar studies from China[22]. Our results indicate that when a PLSVC is detected, scanning of the interventricular septum, aortic arch, umbilical vascular structure, and urinary system should be performed. These findings may help clinicians reduce the incidence of missed diagnoses.

Pregnancy is a dynamic process, and the composition of fetal peripheral blood also varies with gestational age[23,24]. Amniotic fluid cytogenetics maintains a relatively stable state and greatly improves the accuracy of prenatal diagnoses, especially in cases with imaging abnormalities. Chromosome karyotype analysis is the gold standard for diagnosing chromosomal-related diseases; however, traditional chromosome karyotype analysis cannot detect chromosomal microdeletions or microduplications below 5-10 Mb.

Genomic copy number variant sequencing (CNV-seq) is a second-generation sequencing-based test that can be used to identify CNVs as an aid to prenatal diagnosis when a pregnant woman has an indication for interventional prenatal diagnosis and provides informed consent. Studies have found that the proportion of PLSVC fetuses with chromosomal-related abnormalities is 12.5%, and in isolated PLSVC cases, the proportion of chromosomal-related abnormalities can reach 7%[4]. Du *et al*[5] also demonstrated that in PLSVC cases, especially in cases of combined intracardiac and extracardiac abnormalities, the proportion of chromosomal abnormalities significantly increases. Most previous studies in China focused on chromosomal abnormalities, such as permanent left superior vena cava combined with trisomy 21 and trisomy 18, lacked a summary of the classification of abnormal results of PLSVC combined with CNVs[22,25].

In this study, a total of 26 pregnant women chose amniocentesis for diagnosis, including one case with 21-trisomy and six cases with abnormal CNVs results, all of which showed duplication of chromosomal regions, of which five cases were microduplications of less than 10 Mb.

This study had some limitations. Because the PLSVC incidence rate is only 0.3%-0.5% in the normal population[26], the number of included cases was small, which means that the credibility of the study needs to be further improved. In addition, no significant pathogenic abnormalities were found in the isolated PLSVC group, and in seven cases, abnormalities were found in the amniocentesis results of the group with other abnormalities. The risks of abnormal karyotypes and CNVs may increase in the presence of comorbidities. However, because amniocentesis is an invasive test with some risks[27], the comorbidity group chose to undergo amniocentesis more often, leading to confounding factors in the analysis. However, this study innovatively integrated and analyzed data at clinical, imaging, and genetic molecular levels, which can provide reliable prenatal diagnostic recommendations.

CONCLUSION

In conclusion, examination for other structural abnormalities should be performed when PLSVC is diagnosed. Poor pregnancy outcomes and increased amniocentesis were observed in PLSVC cases with other structural abnormalities. Amniotic fluid cytogenetics of fetuses is recommended for PLSVC with other structural abnormalities.

ARTICLE HIGHLIGHTS

Research background

Persistent left superior vena cava (PLSVC) is the most common venous system variant. Previous research has shown that the probability of adverse pregnancy outcomes in isolated PLSVC is lower, and the risk of adverse pregnancy outcomes is significantly increased when combined with other malformations. In recent years, some studies have reported that the proportion of fetal chromosomal abnormalities among PLSVC fetuses has significantly increased, which is different from the classic opinion on this disease. There is a lack of comprehensive studies that provide reliable conclusions for patients and clinicians.

Research motivation

In recent years, the advancement of prenatal diagnostic technology has overturned traditional concepts of some diseases.

Research objectives
We integrated clinical information, imaging features, and molecular-level results to provide reliable advice to patients and clinicians in multiple dimensions.

Research methods
We retrospectively collected cases of PLSVC diagnosed using prenatal ultrasonography between September 2019 and November 2022. The clinical characteristics of the pregnant women, ultrasonic imaging information, gestational age at diagnosis, pregnancy outcomes, and amniocentesis results were summarized and analyzed.

Research results
The differences in pregnancy outcomes and amniocentesis conditions between the two groups were statistically significant ($P < 0.05$). According to the results of the classification statistics, the most common intracardiac abnormality was a ventricular septal defect and the most common extracardiac abnormality was a single umbilical artery. Additionally, all abnormal cytogenetic findings on amniocentesis were observed in the comorbidity group.

Research conclusions
PLSVC is associated with a certain percentage of other combined structural abnormalities. Examination for other structural abnormalities is strongly recommended when PLSVC is diagnosed. Poorer pregnancy outcomes and increased amniocentesis were observed in PLSVC cases with other structural abnormalities. Integrated analysis of multiple levels could provide more information.

Research perspectives
In future studies, researchers should collect more amniotic fluid cytological data and follow-up prognosis of related fetuses.

FOOTNOTES

Author contributions: Yang X and Su XH performed the conception and design; Zeng Z and Guo LL performed the development of methodology; Fan Y and Wu Y contributed to the analysis and interpretation of data; Yang X and Su XH contributed to the writing and review of the manuscript; Xu XY performed the study supervision; Yang X and Su XH contributed equally to this work; all authors had final approval of the submitted versions.

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ORCID number: Xin Yang 0000-0001-9753-4241; Xin-Hui Su 0009-0002-0317-288X; Zhen Zeng 0000-0002-2816-2939; Yao Fan 0000-0002-5214-6146; Yuan Wu 0009-0002-4727-2903; Li-Li Guo 0009-0008-3454-1581; Xiao-Yan Xu 0000-0002-0996-6819.

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ORIGINAL ARTICLE

Retrospective Study

Establishment of a prediction model for prehospital return of spontaneous circulation in out-of-hospital patients with cardiac arrest

Jing-Jing Wang, Qiang Zhou, Zhen-Hua Huang, Yong Han, Chong-Zhen Qin, Zhong-Qing Chen, Xiao-Yong Xiao, Zhe Deng

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Jing-Jing Wang, Qiang Zhou, Zhen-Hua Huang, Yong Han, Chong-Zhen Qin, Zhong-Qing Chen, Xiao-Yong Xiao, Zhe Deng, Department of Emergency Medicine, Shenzhen Second People's Hospital/The First Affiliated Hospital of Shenzhen University Health Science Center , shenzhen 518035, Guangdong Province, China

Corresponding author: Zhe Deng, Doctor, MD, PhD, Chief Doctor, Chief Physician, Doctor, Occupational Physician, Professor, Teacher, Department of Emergency Medicine, Shenzhen Second People's Hospital/The First Affiliated Hospital of Shenzhen University Health Science Center, Sungang Road, Futian District, Shenzhen 518035, China. dengzhe202209@163.com

Abstract

BACKGROUND

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death worldwide.

AIM

To explore factors influencing prehospital return of spontaneous circulation (P-ROSC) in patients with OHCA and develop a nomogram prediction model.

METHODS

Clinical data of patients with OHCA in Shenzhen, China, from January 2012 to December 2019 were retrospectively analyzed. Least absolute shrinkage and selection operator (LASSO) regression and multivariate logistic regression were applied to select the optimal factors predicting P-ROSC in patients with OHCA. A nomogram prediction model was established based on these influencing factors. Discrimination and calibration were assessed using receiver operating characteristic (ROC) and calibration curves. Decision curve analysis (DCA) was used to evaluate the model's clinical utility.

RESULTS

Among the included 2685 patients with OHCA, the P-ROSC incidence was 5.8%. LASSO and multivariate logistic regression analyses showed that age, bystander cardiopulmonary resuscitation (CPR), initial rhythm, CPR duration, ventilation mode, and pathogenesis were independent factors influencing P-ROSC in these patients. The area under the ROC was 0.963. The calibration plot demonstrated

that the predicted P-ROSC model was concordant with the actual P-ROSC. The good clinical usability of the prediction model was confirmed using DCA.

CONCLUSION

The nomogram prediction model could effectively predict the probability of P-ROSC in patients with OHCA.

Key Words: Cardiac arrest; Cardiopulmonary resuscitation; Recovery spontaneous circulation; Logistic regression analysis; Predictive model

Core Tip: A large gap in the rate of prehospital return of spontaneous circulation remains between China and other countries and that the relative contributions of aid measures of the factors to prehospital return of spontaneous circulation vary across countries. There is still not such model, including pre-emergency medical service intervention factors and Prehospital emergency measures, developing for prehospital return of spontaneous circulation in China. Compared to similar models from other countries, the model proposed in the present study is interpretable, convenient to implement, easy to comprehend in busy prehospital processing, and comprehensive, including prehospital drug administration. Therefore, it could serve as a potentially assistive tool for clinical aid decision-making.

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INTRODUCTION

Out-of-hospital cardiac arrest (OHCA), a leading cause of death worldwide, has an average incidence of (30.0-97.1) cases per 100000 person-years[1], with a survival rate of only 8.8% at hospital discharge[2]. In China, 550000 people develop OHCA annually[2] with a survival rate of only 1.3% after discharge, making OHCA a major public health issue. The survival rate from hospital discharge of patients with OHCA who have achieved a return of spontaneous circulation (ROSC) to hospital handover is still approximately 10%[3]. Moreover, patients with prehospital ROSC (P-ROSC) have better neurological outcomes compared with those who do not. Some areas regions have reported high ROSC rates during hospital handovers, such as 25% in England[4] and 29.1% in Tasmania, Australia[5]. In China, however, the P-ROSC rate was only 6.26% in a recent survey in Beijing[6], demonstrating that a large gap still exists between countries.

Investigations have reported a range of pre-emergency medical service (EMS) intervention factors for patients with OHCA that are associated with P-ROSC, including age, prehospital drug administration, witnessed status, first rhythm, and response time[7]. The relative contribution of each of these factors to P-ROSC varies across countries. However, no model including pre-EMS intervention factors and prehospital emergency measures has been developed for ROSC during hospital handovers in China. Therefore, the development of an effective prediction model is required for ROSC during hospital handovers based on pre-EMS intervention factors and prehospital emergency measures.

This study aimed to identify independent factors associated with P-ROSC and develop and evaluate a nomogram model in China to predict whether ROSC can be achieved during the prehospital period in OHCA.

MATERIALS AND METHODS

Study design and setting

A multicenter retrospective study was conducted at the Shenzhen Center for Prehospital Care, which covered all hospitals in Shenzhen; that is, approximately 150 hospitals, from January 2012 to December 2019. All first-aid measures were performed according to the American Heart Association (AHA) Guidelines for cardiopulmonary resuscitation (CPR).

Participants

We retrospectively collected data from emergency medical technicians (EMTs). The inclusion criteria were patients with OHCA aged ≥ 18 years, The exclusion criteria were incomplete cases, dead patients (*i.e.*, rigor mortis, lividity, decomposition, or decapitation) without CPR by the EMTs, and patients whose family members forwent all treatments.

Data collection

Data were gathered from two sources: The Registration System of Pre-hospital First Aid Information and Statistics and the Patient Care Report Form. The extracted data included clinical features such as sex, age, time of arrest (*i.e.*, 0-8, 8-16, or 16-24 min), season of arrest, bystander CPR, initial rhythm, CPR duration, ventilation mode, defibrillation, epinephrine dose, use of other drugs (atropine, lidocaine, and amiodarone), and outcomes (P-ROSC).

According to the 2015 AHA guidelines, ROSC was defined as the clinical indication of the presence of vital signs, including palpable pulses or blood pressure.

Statistical analysis

IBM SPSS Statistics for Windows, version 26.0, and R 3.1.2 were used to perform all analyses. The *t*-test and Mann–Whitney U test were used for numerical variables, while the chi-square test was applied to categorical variables. A model was established using least absolute shrinkage and selection operator (LASSO) regression and multivariable backward regression. For the LASSO regression, lambda.min (a minimum mean squared error) and lambda.1se (lambda.min with one standard error) were identified as the goodness penalty lambda based on the lambda-choosing path[8]. To screen for potential predictive factors, LASSO regression models with a lambda.1 se penalty were constructed. The variables selected *via* LASSO were included in a multivariate backward regression analysis to identify the independent influencing features of patients with OHCA. A nomogram prediction model was then constructed based on the variables with statistical significance. The discrimination and calibration of the model were assessed using receiver operating characteristic (ROC) and calibration curves, as well as the Hosmer–Lemeshow test. Internal verification was performed by strengthening the bootstrap method for 1000 repetitions, as shown in the calibration curves. The clinical practicability of the model was evaluated using decision curve analysis (DCA) according to the net benefit with different threshold probabilities.

RESULTS

A total of 2685 cases of patients with OHCA satisfied the inclusion and exclusion criteria. Table 1 presents the characteristics of all OHCA incidents in which first-aid treatment was implemented.

Feature selection and model development

We applied LASSO regression to identify potential predictors and then employed multivariate backward logistic regression to establish the model. As shown in Figure 1, the LASSO regression identified seven features through the lambda.1se penalty: Age, bystander CPR, initial rhythm, CPR duration, ventilation mode, use of amiodarone and lidocaine, and etiology. A model was then formed based on the factors evaluated using multivariate logistic regression (Table 2, Figure 3), during which amiodarone was eliminated.

Validation of the predictive model

The area under the receiver operating characteristic curve (AUC) of the P-ROSC prediction model was 0.9627 (95%: 0.9485-0.9769), which demonstrated the good discrimination ability of the model (Figure 3). A strengthened bootstrap self-sampling method was used to verify the model internally. Furthermore, the calibration plots fitted well with the ideal curves (Figure 4), indicating that the predicted probability was consistent with the actual probability, as suggested by the results of the Hosmer–Lemeshow test (χ^2 = 8.421, df = 8, P = 0.3935). DCA to evaluate the clinical utility showed a net benefit for the "treat-all" or "treat-none" strategy (Figure 5), which suggested that the model was clinically useful.

DISCUSSION

The survival to hospital discharge in patients with OHCA worldwide is only 4.5%[9]. P-ROSC is a short-term survival event. However, recent studies have shown that patients who achieve P-ROSC have better neurological outcomes than those who do not[10,11]. Therefore, pre-EMS intervention factors and prehospital emergency measures have been analyzed to evaluate whether EMS intervention measures, including drug treatments, are necessary to inform EMT decisions to terminate the rescue following an appropriate determination to terminate resuscitation.

Age is an influencing factor in OHCA outcomes[12], age is considered as an influencing factor of OHCA outcomes. Consistent with the results of previous studies[13], age was significantly associated with ROSC in the adjusted model (OR: 0.98, P < 0.001) in the present study. In terms of etiology, cardiovascular system diseases accounted for the largest proportion of patients with OHCA (53.3%) in this study, while OHCA caused by central nervous system diseases had the highest rate of P-ROSC failure, followed by patients with traumas.

In some regions, the number of CPR bystanders has reached 50%, particularly in advanced countries[14]. However, although it is increasing annually, the bystander CPR rate remained poor in the current study. Rajan *et al*[15] suggested that sustained bystander CPR could increase by more than two-fold. In our study, CPR by bystanders increased the chances of ROSC by 2.6-fold (P = 0.004) compared with no bystander CPR.

The initial rhythm is another critical factor because timely defibrillation can increase the ROSC rate when a shockable rhythm occurs[16]. In the present study, the initial rhythm was also an essential variable of P-ROSC after adjusting for other variables (P < 0.001). Moreover, patients with agonal electrocardiography (Ag ECG) characteristics, such as slow

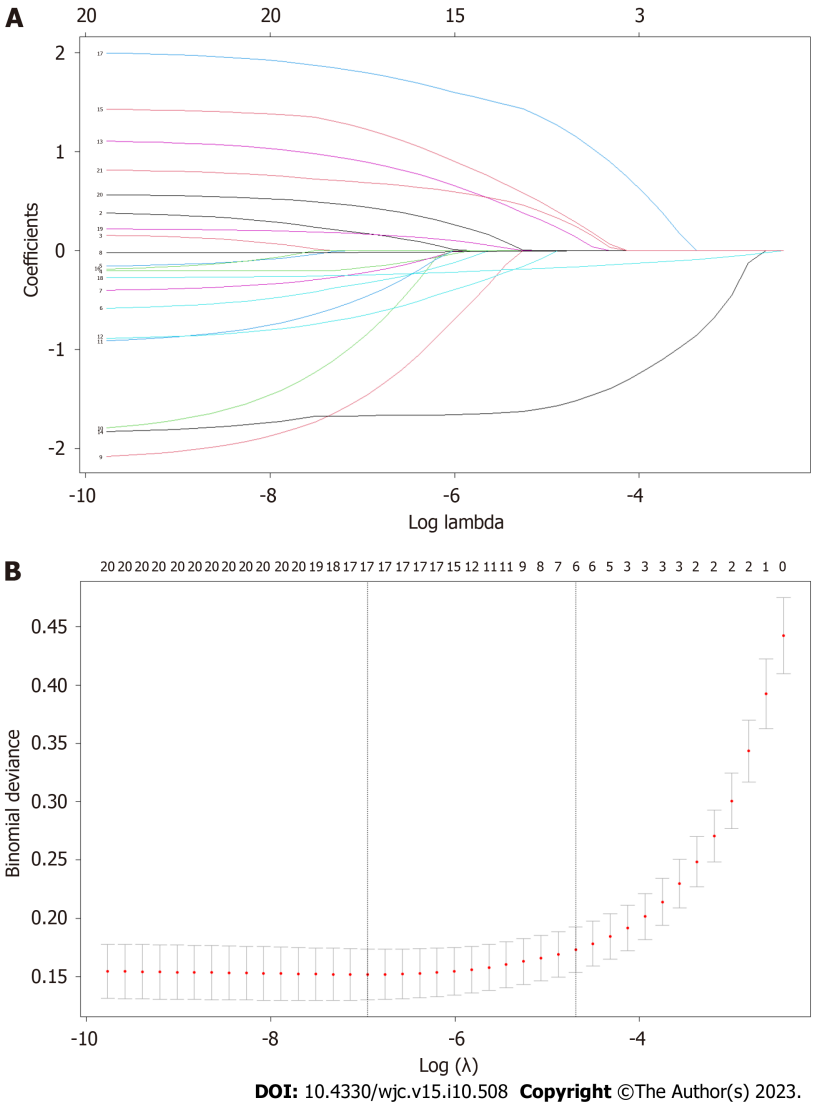

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Figure 1 Factor selection of prehospital return of spontaneous circulation *via* least absolute shrinkage and selection operator regression.
A: Least absolute shrinkage and selection operator coefficient profiles of the 17 features. A coefficient profile plot was conducted against the log (lambda, λ) sequence; B: Through 10-fold cross-validation, and the optimal parameter (lambda, λ) selection *via* the minimum criteria. A partial likelihood deviance (binomial deviance) curve was plotted versus log λ. The dotted vertical line on the right was drawn at lambda.1se and four features were selected.

ventricular escape and bradycardia, who progressed to OHCA during treatment, had a higher P-ROSC rate, implying that a shorter time of no reflow time could improve prognosis.

Furthermore, CPR duration is a vital factor in predicting OHCA outcomes. Despite advances in CPR, no comprehensive agreement has been reached regarding the duration of CPR and the time for its termination in patients with OHCA. Funada *et al*[17] reported that CPR sustained in patients with OHCA > 26 min commonly caused ROSC failure. In the present study, the optimal cut-off time was 27.5 min and each additional minute of CPR was related to a 22% decrease in the probability of P-ROSC (OR: 0.78, $P < 0.001$) after adjustment for variable. Moreover, some studies suggested no possibility of ROSC in CPR lasting > 30 min, usually accompanied by irreversible damage to the brain[18]. Hence, uncertainties in the proper termination rules for CPR in basic and advanced life support care could increase pressure on ambulance transport, competition for medical resources, and risk of exposure to public accidents owing to high-speed transport[19]. However, the appropriate resuscitation termination for patients with OHCA remains controversial. Based on the model performance, we found that patients with OHCA and organ function as well as family abandonment of rescue do not require resuscitation times > 30 min. Conversely, in terms of OHCA of young adults (such as sudden cardiac deaths and sudden deaths of unknown causes), ECG manifestations of ventricular fibrillation or bradycardia, or a slow ventricular escape, the intensity of continuous resuscitation should be strengthened until the family approves that resuscitation can be terminated, even beyond 30 min of sustained CPR.

Finally, regarding prehospital advanced airway management (AAM) in patients with OHCA[20,21], some studies have shown that endotracheal intubation (ETI) can improve the probability of sustained ROSC, survival to hospital discharge, and neurologic outcomes[22]. In the present study, ETI was significantly associated with P-ROSC (OR: 8.28, $P < 0.001$). Moreover, Benoit *et al*[23] suggested that a delay in ETI was related to worse ROSC outcomes. In addition, Izawa *et al*[24] confirmed that AAM resulted in better survival in patients with non-shockable rhythms than in those with shockable

Table 1 Characteristics of the patients with out-of-hospital cardiac arrest

Features	Patients			*P* value
	Total (*n* = 2685)	ROSC failure (*n* = 2529)	ROSC (*n* = 156)	
Gender				0.730
Female	668 (24.9)	631 (25.0)	37 (23.7)	
Male	2017 (75.1)	1898 (75.0)	119 (76.3)	
Age	56.18 ± 17.98	56.63 ± 17.96	49.01 ± 16.82	< 0.001
Season				0.570
Spring	636 (23.7)	599 (23.7)	37 (23.7)	
Summer	625 (23.3)	582 (23.0)	43 (27.6)	
Autumn	666 (24.8)	632 (25.0)	34 (21.8)	
Winter	758 (28.2)	716 (28.3)	42 (26.9)	
Time (min)				0.029
08-16	953 (35.5)	888 (35.1)	65 (41.7)	
16-24	1049 (39.1)	984 (38.9)	65 (41.7)	
00-08	683 (25.4)	657 (26.0)	26 (16.7)	
Bystander CPR				< 0.001
No	2246 (83.6)	2135 (84.4)	111 (71.2)	
Yes	439 (16.4)	394 (15.6)	45 (28.8)	
Initial rhythm				< 0.001
VF/VT	293 (10.9)	232 (9.2)	61 (39.1)	
Asystole/PEA	2358 (87.8)	2278 (90.1)	80 (51.3)	
Ag ECG (slow ventricular escape, bradycardia)	34 (1.3)	19 (0.8)	15 (9.6)	
Duration of CPR	35 (15.0)	38 (18.0)	10 (16.0)	< 0.001
ETI				< 0.001
No	2194 (81.7)	2104 (83.2)	90 (57.7)	
Yes	491 (18.3)	425 (16.8)	66 (42.3)	
DF				< 0.001
No	2000 (74.5)	1914 (75.7)	86 (55.1)	
Yes	685 (25.5)	615 (24.3)	70 (44.9)	
Epinephrine dose	3 (3.0)	3 (3.0)	3 (2.0)	< 0.001
Atropine				0.243
No	2081 (77.5)	1966 (77.7)	130 (83.3)	
Yes	604 (22.5)	563 (22.3)	26 (16.7)	
Lidocaine or amiodarone				< 0.001
No	2556 (95.2)	2426 (95.9)	135 (86.5)	
Yes	129 (4.8)	103 (4.1)	21 (13.5)	
Etiology				0.019
Cardiac	1430 (53.3)	1327 (52.5)	103 (66.0)	
Trauma	122 (4.5)	116 (4.6)	6 (3.8)	
Toxicosis or asphyxia	45 (1.7)	44 (1.7)	1 (0.6)	
Brain and nervous	64 (2.4)	60 (2.4)	4 (2.6)	

Unknow and other	1024 (38.1)	982 (38.8)	42 (26.9)

VF: Ventricular fibrillation; VT: Ventricular tachycardia; PEA: Pulseless electrical activity; Ag ECG: Agonal electrocardiogram; CPR: Cardiopulmonary resuscitation; ETI: Endotracheal intubation; DF: Defibrillation.

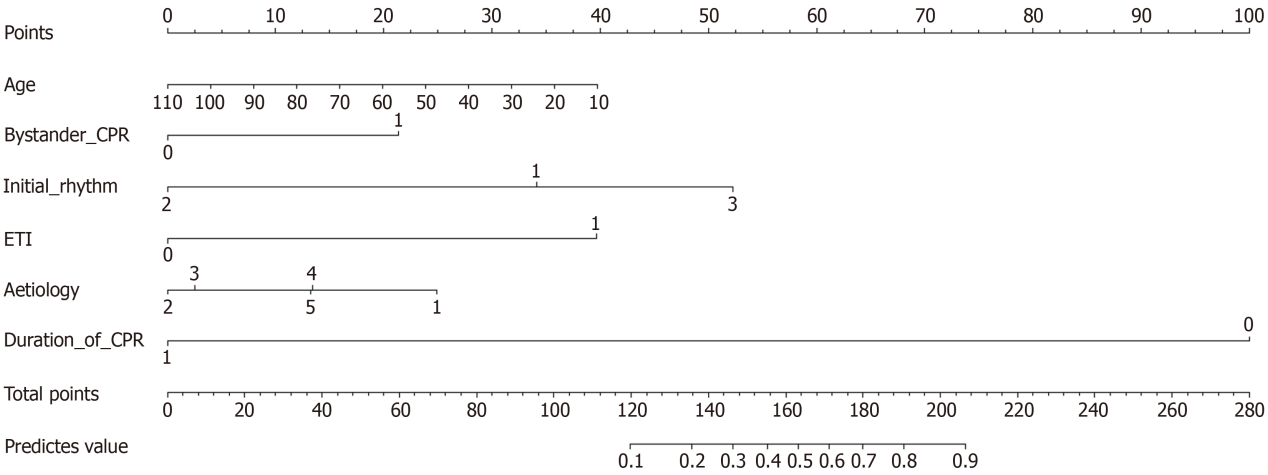

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Figure 2 Nomogram prediction model of prehospital return of spontaneous circulation. Six predictors were included: Age, bystander cardiopulmonary resuscitation (CPR), initial rhythm, CPR duration, ventilation mode, and etiology. Each variable was assigned a score on a point-scale axis. The total score was easily calculated by adding each single score. The probability of prehospital return of spontaneous circulation is estimated by projecting the total score to the lower total-point scale.

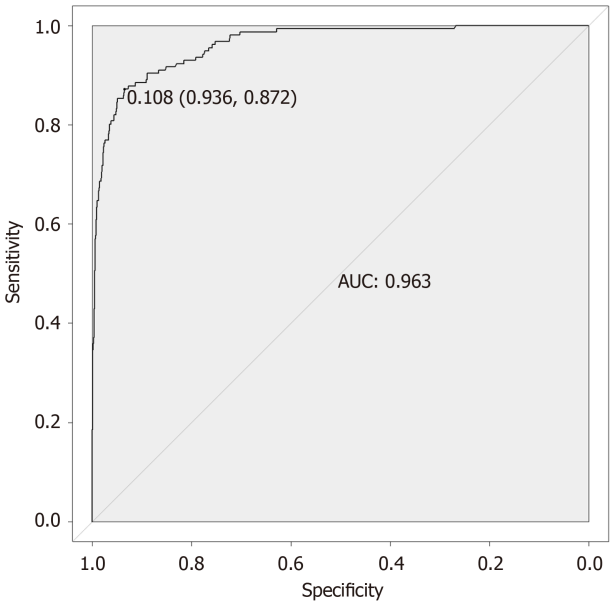

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Figure 3 Receiver operating characteristic curves of prehospital return of spontaneous circulation model. The area under the receiver operating characteristic curve of the prehospital return of spontaneous circulation prediction model was 0.9627 (95%: 0.9485-0.9769).

rhythms, which might indicate the impact of shockable rhythms on the role of ETI in OHCA. Therefore, the effects of ETI in such situations warrant further investigation.

Ji *et al*[4], Morgan *et al*[5], and Navab *et al*[13] and others have established models in the United Kingdom, Australia, and Iran, respectively, to describe the influencing factors of clinical features and prehospital emergency measures on the ROSC rate as well as the survival rate of patients with OHCA. However, these researchers did not collect data on prehospital drug administration, including the use and dosage of epinephrine or other drugs. We developed a simple model applied to OHCA of all etiologies that covered pre-EMS intervention factors and prehospital emergency measures, including drugs and their dosage, although prehospital drug administration was not included in the model. Liu *et al*[7]

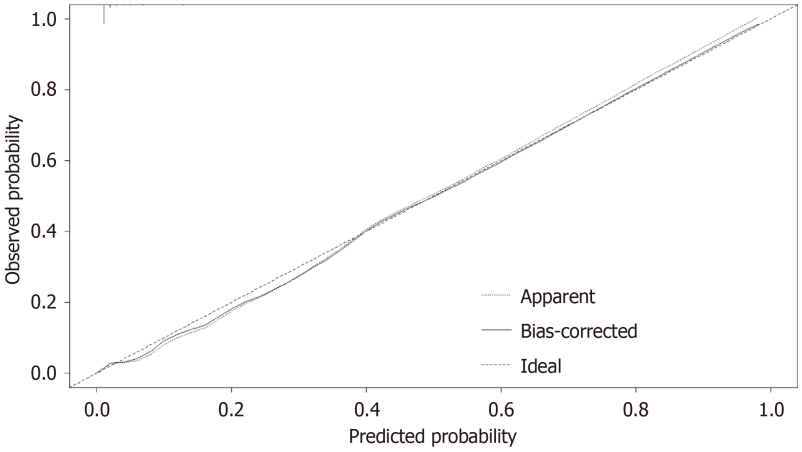

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Figure 4 Calibration curves of the prehospital return of spontaneous circulation model. The dotted line represents the apparent model, while the solid line is bias-corrected by strengthening bootstrapping.

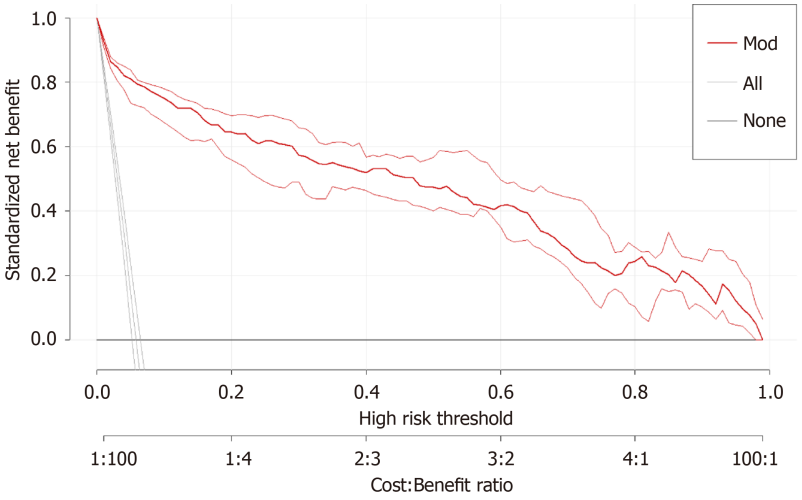

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Figure 5 Decision curve analysis of the prehospital return of spontaneous circulation model. The X- and Y-axes show the threshold probabilities and net benefits, respectively. The solid red line indicates the prehospital return of spontaneous circulation model. The "All" and "None" lines represent interventions for all or none of the patients, respectively.

developed a P-ROSC score for patients with OHCA that also collected prehospital drug administration data. However, the model was not appropriate for trauma-induced OHCA, which limited its wide application. Another prospective study that included individuals between 1998 and 2008 generated the RACA score, which is a widely applicable score for ROSC in OHCA. However, it is not a contemporary cohort[25].

Limitations

Due to the retrospective design, the accuracy of data collection and potential confounders could not be assessed, and the identification of specific causalities was limited. Furthermore, incomplete data restricted the research. In addition, we did not collect no-reflow time data because the number of patients with OHCA witnessed by bystanders at the scene was too small.

CONCLUSION

We developed a simple and accessible model to predict the probability of achieving P-ROSC in China. The P-ROSC, with just six factors, is interpretable, convenient to implement, and comprehensive in busy prehospital processing; thus, it could serve as a possible assistive tool for clinical-aid decision-making.

Table 2 Multivariable logistic regression analysis of prehospital return of spontaneous circulation

Features	Multivariable analysis			Selected factors for model		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Age	0.98	0.964-0.997	0.018	0.98	0.964-0.996	0.017
Bystander CPR			0.004			0.001
No	1			1		
Yes	2.621	1.36-5.051		2.854	1.504-5.414	
Initial rhythm			< 0.001			< 0.001
VF/VT	1			1		
Asystole/PEA	0.174	0.087-0.349	< 0.001	0.16	0.081-0.318	< 0.001
Ag ECG (slow ventricular escape, bradycardia)	4.539	0.89-23.15	0.069	4.103	0.806-20.895	0.089
CPR duration	0.778	0.75-0.807	< 0.001	0.776	0.749-0.805	< 0.001
ETI			< 0.001			< 0.001
No	1			1		
Yes	8.227	4.384-15.439		8.288	4.441-15.465	
Lidocaine or amiodarone			0.113			
No	1					
Yes	2.271	0.823-6.271				
Etiology			0.008			0.007
Cardiac	1			1		
Trauma	0.156	0.037-0.65	0.011	0.145	0.035-0.601	0.008
Toxicosis or asphyxia	0.171	0.007-4.026	0.275	0.163	0.007-3.907	0.263
Brain and nervous	0.393	0.079-1.95	0.253	0.371	0.075-1.844	0.226
Unknow and other	0.384	0.205-0.721	0.003	0.389	0.208-0.728	0.003

OR: Odds ratio; CI: Confidence interval; VF: Ventricular fibrillation; VT: Ventricular tachycardia; ETI: Endotracheal intubation; PEA: Pulseless electrical activity; Ag ECG: Agonal electrocardiography; CPR: Cardiopulmonary resuscitation.

ARTICLE HIGHLIGHTS

Research background

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death worldwide. In China, 550000 people develop OHCA annually with a survival rate of only 1.3% after discharge, making OHCA a major public health issue.

Research motivation

A large gap of prehospital return of spontaneous circulation (P-ROSC) rate remains between China and other countries and that the relative contributions of aid measures for each of these factors to P-ROSC vary across countries. There are still not such model, including pre-EMS intervention factors and Prehospital emergency measures, have currently been developed for P-ROSC in China.

Research objectives

To develop a nomogram prediction model which is interpretable, convenient to implement, easy to comprehend in busy prehospital processing, and comprehensive, including prehospital drug administration. Therefore, it could serve as a potentially assistive tool for clinical aid decision-making.

Research methods

Clinical data of patients with OHCA were retrospectively analyzed A nomogram prediction model for P-ROSC in patients with OHCA was developed and validate.

Research results

Among the included 2685 patients with OHCA, the P-ROSC incidence was 5.8%. LASSO and multivariate logistic regression analyses showed that age, bystander cardiopulmonary resuscitation (CPR), initial rhythm, CPR duration, ventilation mode, and pathogenesis were independent factors influencing P-ROSC in these patients. The area under the ROC was 0.963. The calibration plot demonstrated that the predicted P-ROSC model was concordant with the actual P-ROSC. The good clinical usability of the prediction model was confirmed using decision curve analysis.

Research conclusions

We developed a simple and accessible model to predict the probability of achieving P-ROSC in China. The P-ROSC, with just six factors, is interpretable, convenient to implement, and comprehensive in busy prehospital processing; thus, it could serve as a possible assistive tool for clinical-aid decision-making.

Research perspectives

If we go one step further, we start to conduct prospective studies to identify the specific causalities and to improve the accuracy of data collection.

FOOTNOTES

Co-first authors: Jing-Jing Wang and Qiang Zhou.

Author contributions: Wang JJ, Zhou Q contributed equally to this work and share first authorship; Deng Z, Wang JJ, and Zhou Q designed the research study; Wang JJ and Zhou Q analyzed the data and wrote the manuscript; Deng Z were responsible for revising the manuscript for important intellectual content; Wang JJ, Zhou Q, Huang ZH, Han Y, Qin CZ, Qin CZ, and Xiao XY performed the primary literature and data extraction; All authors read and approved the final version.

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Institutional review board statement: The study was reviewed and approved by the Shenzhen Center for Prehospital Care Institutional Review Board [(No. 2023-071-02PJ)].

Informed consent statement: This study meets the conditions for applying for exemption from informed consent in China, and the exemption from informed consent has been approved.

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

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Country/Territory of origin: China

ORCID number: Zhe Deng 0000-0002-9776-7261.

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SYSTEMATIC REVIEWS

Cardiovascular complications following medical termination of pregnancy: An updated review

Tejveer Singh, Ajay K Mishra, Nikhil Vojjala, Kevin John John, Anu A George, Anil Jha, Michelle Hadley

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Tejveer Singh, Anu A George, Department of Internal Medicine, Saint Vincent Hospital, Worcester, MA 01608, United States

Ajay K Mishra, Anil Jha, Michelle Hadley, Division of Cardiology, Saint Vincent Hospital, Worcester, MA 01608, United States

Nikhil Vojjala, Department of Internal Medicine, Post-Graduation Institute of Medical Education and Research, Chandigarh 00000, India

Kevin John John, Department of Internal Medicine, Tufts Medical Center, Boston, MA 01212, United States

Corresponding author: Ajay K Mishra, FACP, MBBS, MD, Academic Fellow, Division of Cardiology, Saint Vincent Hospital, 123 Summer Street, Worcester, MA 01608, United States. ajay.mishra@stvincenthospital.com

Abstract

BACKGROUND

Around 1 million cases of medical termination of pregnancy (MTP) take place yearly in the United States of America with around 2 percent of this population developing complications. The cardiovascular (CVD) complications occurring post MTP or after stillbirth is not very well described.

AIM

To help the reader better understand, prepare, and manage these complications by reviewing various cardiac comorbidities seen after MTP.

METHODS

We performed a literature search in PubMed, Medline, *RCA*, and google scholar, using the search terms "abortions" or "medical/legal termination of pregnancy" and "cardiac complications" or "cardiovascular complications".

RESULTS

The most common complications described in the literature following MTP were infective endocarditis (IE) (n = 16), takotsubo cardiomyopathy (TTC) (n = 7), arrhythmias (n = 5), and sudden coronary artery dissection (SCAD) (n = 4). The most common valve involved in IE was the tricuspid valve in 69% (n = 10). The most observed causative organism was group B Streptococcus in 81% (n = 12). The most common type of TTC was apical type in 57% (n = 4). Out of five patients de-

veloping arrhythmia, bradycardia was the most common and was seen in 60% (3/5) of the patients. All four cases of SCAD-P type presented as acute coronary syndrome 10-14 d post termination of pregnancy with predominant involvement of the right coronary artery. Mortality was only reported following IE in 6.25%. Clinical recovery was reported consistently after optimal medical management following all these complications.

CONCLUSION
In conclusion, the occurrence of CVD complications following pregnancy termination is infrequently documented in the existing literature. In this review, the most common CVD complication following MTP was noted to be IE and TTC.

Key Words: Cardiovascular complications; Termination of pregnancy; Infective Endocarditis; Stress cardiomyopathy; Outcome

Core Tip: The most common cardiovascular complications following the medical termination of pregnancy (MTP) are infective endocarditis (IE) and takotsubo cardiomyopathy (TTC). The most common organism identified in IE is group B Streptococcus and the tricuspid valve is the most common valve involved. TTC occurs most commonly in the first trimester after MTP. Spontaneous coronary artery dissection mostly presents with chest pain and the right coronary artery is the most common vessel to be involved. Bradyarrhythmia is the most common arrhythmia noted. These patients improve with appropriate medical management and mortality tends to be low.

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INTRODUCTION

The legality of abortion and the various restrictions imposed on the procedure vary significantly among various states of the United States and are ever-changing. The initial law, Roe *vs* Wade, which was made in 1973, streamlined the decision-making process. Over the last 50 years, there has been a paradigm change in the perspective of patients regarding the termination of pregnancy in the United States. Centers for Disease Control (CDC) reports an abortion rate of 11.4 for the year 2020 with around 1 million abortions taking place annually in the United States. Around 2% of this population have been reported to develop complications[1].

Due to the recent identification of female-specific factors associated with a greater cardiovascular (CVD) risk, it provides the potential to implement effective and targeted preventative measures to decrease disease burden at an individual and population level[2]. Therefore, having an understanding of the female specific risk stratification and prevention is important. Recent CVD risk guidelines have included miscarriage and stillbirth as risk factors for women[3]. Because of the changing times and laws, we must highlight various CVD complications which are associated with the termination of pregnancy[4]. In this article, we review the various cardiac comorbidities reported after the medical termination of pregnancy (MTP). We also describe their clinical profile, management, and outcomes observed in these patients. Various systemic reviews discuss the complications associated with the termination of pregnancy. However, none describes cardiac complications following the same. Therefore, this article can contribute towards a better under-standing, and facilitate preparedness and management of the cardiac complications following termination of pregnancy.

MATERIALS AND METHODS

In this review, we aimed to describe the demographic details, clinical presentation, diagnosis, and management of the various CVD complications following MTP. We used the meta-analysis guidelines for the material and methodology of our study.

Search strategy

We performed a systemic search in various bibliographic databases including PubMed, Medline, *RCA*, and google scholar databases, using the search terms "abortions" or "medical/legal termination of pregnancy" and "cardiac complications" or "cardiovascular complications". The reference citation analysis tool was also used to find more articles. We screened references of the initial articles for identifying other relevant articles. Search strategies were tailored to each database for identifying relevant articles. All search outputs were exported to Microsoft Excel version 2022. For those articles where the main text was missing, we reached out to the authors. We acknowledge their support in sharing their work with us.

Study selection

All articles reported in English including adult patients (age > 18 years) published before August 2022, were eligible to be included in this review. Articles lacking clinical details, including comments, opinions, and letters, were excluded. The inclusion and exclusion criteria for the patients were established in advance before the initiation of the study. To be included in this review, articles had to provide clinical details of the pregnancy and the reported cardiac complication. For those articles where the main text was missing, we directly contacted the authors. We acknowledge their support in sharing their work with us. We added complete information on the studies included in this study. Two reviewers independently screened the abstracts. Cardiac complications had to fulfill the diagnostic definitions as described below.

Definitions

Infective endocarditis: Cases of infectious endocarditis (IE) had to fulfill the Modified Duke's criteria, which include the presence of either a blood culture of the organism consistent with IE or an echocardiogram showing positive evidence of IE, abscess, new partial dehiscence of a prosthetic valve, or new regurgitation (major criteria). Minor criteria include a previous heart condition or history of intravenous drug use, fever, presence of microorganisms not typically seen with IE, immunological phenomena such as glomerulonephritis, Roth spots, or vascular phenomena such as major arterial emboli or Janeway lesions. The presence of two major criteria, one major and three minors, or five minor criteria is diagnostic for definitive IE[5].

Takotsubo cardiomyopathy: Cases of takotsubo cardiomyopathy (TTC) had to fulfill the Mayo Clinic diagnostic criteria, which include: (1) Transient left ventricular systolic dysfunction with regional wall motion abnormalities extending beyond a single epicardial coronary distribution; (2) Absence of obstructive coronary disease or any angiographic evidence of acute plaque rupture; (3) Presence of new electrocardiogram (EKG) changes as either sinus tachycardia (ST)-segment elevation and/or T wave inversion or elevation in cardiac troponin levels; and (4) Documentation of absence of pheochromocytoma or myocarditis[1].

Spontaneous coronary artery dissection: Cases of spontaneous coronary artery dissection (SCAD) had to provide details of coronary angiography, which used an iodinated contrast agent to fill the lumen of coronary arteries and X-rays to image the lumen. Alternatively, if an alternate imaging modality such as optical coherence tomography or intravascular ultrasound was used to delineate the cause of narrowing and showed a tear or blood accumulation in the arterial wall, it would also be eligible for inclusion[6].

Cardiac arrhythmia: To be included in this review, reported arrhythmias had to have details of an investigation showing the pattern of the arrhythmia[7].

Risk and bias assessment: Two reviewers (Singh T and Vojjala N) independently screened for risk of error and bias in the articles. Disagreements were resolved through final verification and consensus of the third reviewer (Mishra AK)[8].

Data extraction: Extracted data include information on the publication year, authors, study type, and methodology. We also extracted data on study participants, including recent age, gender, clinical presentation, CVD, imaging, and laboratory parameters and management. Finally, we studied the outcomes, including CVD complications and mortality[9,10].

Data synthesis and analysis: Continuous variables are expressed as the mean or percentages. Given the small sample size under each subgroup, we were not able to identify any odds or associations.

RESULTS

The initial screening identified 300 cases that were published between 1990 and 2022, of which 34 fulfilled the inclusion criteria, as shown in the PRISMA diagram (Figure 1). These included 16 cases of IE, seven cases of TTC, six cases of arrhythmia, and five cases of SCAD. The clinical profile, management, and outcomes of these events are described in Tables 1-4[11-41].

Of the 16 cases of IE following abortion, 15 occurred following elective surgical abortion and one was a case of clandestine induced abortion. Only two patients had an underlying risk factor for IE, including a history of aortic valve replacement (AVR)/mitral valve replacement (MVR) for IE and rheumatic heart disease. The median age of these patients was 24 years[15-37]. Following termination of pregnancy, the initial clinical presentation occurred as early as one week after the abortion to as late as several weeks, with the most delayed presentation seen 60 d after the abortion. Data on prior antibiotic prophylaxis was available for 11 patients, four of whom received prophylaxis, including doxycycline in two cases, ampicillin and gentamicin in one, and a combination of ciprofloxacin and doxycycline in one. The tricuspid valve was the most commonly involved, as seen in 11 patients (69%), with multivalvular involvement in two patients and rare pulmonary valve involvement in one patient (6%). Group B Streptococcus (GBS) was the most common organism detected in these patients (n = 13, 81%), with culture being negative in one patient. *Escherichia coli* and methicillin sensitive *Staphylococcus aureus* were positive in one patient each. Most patients had IE related complications at the time of presentation, with the most common complication being septic emboli as seen in 69% (n = 11) followed by heart failure in 19% (n = 3). All patients were treated with intravenous antibiotics and 56% (n = 9) required surgical intervention, including MVR in two patients, tricuspid valve replacement in four, AVR in two, and pulmonary valve replacement in one. An embolectomy was performed on one patient, along with medical management. The prognosis for this subset of patients was good, with a mortality rate of 6% (n = 1) in Table 1[10-25].

Table 1 Patients with infective endocarditis following medical termination of pregnancy

No.	Age/details	Time interval	Antibiotic prophylaxis	Microbiological diagnosis	Valves involved	Other complications	Management	Final outcome	Ref.
1	17 yr/clandestine abortion	28 d	No	Neg	TV	None	Mx	Survived	[10]
2	30 yr/post ciprofloxacin and doxycycline	10 d	No	GBS	MV	S Ar, R Ar	Mx, MVR	Survived	[11]
3	31 yr/post-surgical abortion	48 d	No	GBS	TV	STE	Mx, TVR	Survived	[12]
4	37 yr/post-surgical abortion, past history of AVR/MVR for IE	60 d	Yes (ampicillin and gentamycin)	GBS	AV	SE	Mx	Survived	[13]
5	18 yr/elective abortion	Several weeks	No	GBS	TV	SE	Mx	Survived	[14]
6	30 yr/elective abortion	28 d	No	GBS	TV	SE, 1st HB	Mx, TVR	Survived	[15]
7	33 yr/elective abortion	28 d	No	GBS	TV	SE, VRA	Mx, TVR	Survived	[16]
8	24 yr/elective abortion	28 d	No	GBS	TV	SE, RHF	Mx	Survived	[17]
9	15 yr/elective abortion	7 d	Doxycycline	GBS	PV	SE, PAA	Mx, PVR	Survived	[18]
10	15 yr/elective abortion	11 d	Ciprofloxacin + doxycycline	GBS	AV	HF, AR	Mx, AVR	Survived	[19]
11	18 yr/elective abortion	14 d	Doxycycline	GBS	TV	SE	Mx, Emb	Survived	[20]
12	22 yr/elective abortion	7 d	-	GBS	TV	SE, PAA, TR	Mx	Lost to follow-up	[21]
13	Young female	-	-	-	Mu	-	Mx, AVR, TVR	Death	[22]
14	37 yr	11 d	-	GBS	TV	SE, SI	Mx	Survived	[23]
15	25 yr/rheumatic heart disease	14 d	-	MSSA	Mu	SE	Mx	Survived	[24]
16	21 yr	21 d	-	E coli	MV	HF	Mx, MVR	Survived	[25]

GBS: Group B streptococcus; MSSA: Methicillin sensitive staphylococcus aureus; MV: Mitral valve; TV: Tricuspid valve; AV: Aortic valve; PV: Pulmonary valve; Mu: Multiple valves involved; S Ar: Septic arthritis; R Ar: Reactive arthritis; STE: Septic thromboembolism; SE: Septic embolism; 1st HB: First degree heart block; VRA: Valve ring abscess; RHF: Right heart failure; PAA: Pulmonary artery aneurysm; HF: Heart failure; TR: Tricuspid regurgitation; AR: Aortic regurgitation; SI: Sacroilitis; Mx: Medical management; MVR: Mitral valve replacement; PVR: Pulmonary valve replacement; AVR: Aortic valve replacement; Emb: Embolectomy; TVR: Tricuspid valve replacement.

TTC was reported in seven cases in the literature as a post-abortion CVD complication. The mean age at presentation was 34.4 years, with a range of 22 to 43 years. Of the four patients (57%) for whom gestational age was available, all had undergone an abortion or miscarriage in the first trimester (within less than 12 wk). Three (43%) patients had experienced miscarriages, two (29%) had undergone surgical termination of pregnancy, and one had undergone an elective abortion. One patient had a history of myoma removal surgery during the 14th wk of pregnancy, which resulted in fetal death four weeks later and led to five recurrent episodes of TTC that improved with follow-up care. The most common presentation in the emergency department was chest pain, which was reported by three (43%) patients, with one patient experiencing right-sided pain radiating to the neck and the other two experiencing severe left-sided, non-radiating acute pain. Other common presentations included hypotension (n = 1), abdominal pain, and vaginal bleeding (n = 1). Abnormal EKG finding was reported in three (43%) patients only. EKG findings in most patients were normal sinus rhythm (n = 2) or T wave inversion (n = 2) in the inferior and anteroseptal walls. Other EKG findings included up-sloping ST depression (n = 1) and sinus tachycardia (n = 1). Troponin levels were available and elevated in six (86%) patients. Coronary angiography was performed on six (86%) patients who did not show any evidence of obstructive coronary artery disease. Echocardiograms in all seven (100%) patients reported a reduced ejection fraction (EF) of less than 40%, with the most common wall involvement being the apex in 57% (n = 4) and basal wall in 29% (n = 2). Only 43% were started on guideline-directed medical therapy (n = 3). Treatment for these patients commonly included beta-blockers (BB) and angiotensin-converting-enzyme inhibitors (ACEi) in 43% (n = 3), and diuretics in 29% (n = 2). Other pharmacological agents used for treatments

Table 2 Patients with takotsubo cardiomyopathy following medical termination of pregnancy

No.	Age, gestation	Clinical feature	TTC criteria: EKG and Trop; echo; coronary angiography negative; pheochromocytoma	Possible pathophysiology	Treatment given	Outcome: Mortality and EF repeat	Ref.
1	36 yr, 12 wk gestation	Misc; hypovolemia	ECG: ST and Trop T elevated; eCHO: TTE (35%) EF, hypok LV apex; coronary angiography: Negative	Catecholamine surge: (1) Direct toxicity; (2) Coronary vasoconstriction; and (3) Microvascular spasm	IV furosemide	5th d repeat echo: LV to EF: 60%. F/u: 11 mo, no relapse	[26]
2	22 yr, gestation: NA	Post Sx TOP with evacuation of retained POC; hypovolemia	EKG: Normal and Trop T elevated; 2D echo: DCM; coronary angiography: Negative	Catecholamine release post procedure	Diuretics. Bisoprolol and lisinopril	Echo: Repeat day 2 had EF 56%. Follow-up, full recovery	[27]
3	37 yr, Misc	Chest pain, radiating to the neck	EKG: ST depression, Trop T elevated; 2D echo: EF < 40%; coronary angiography: Negative	NA	NA	F/u echo EF normal. F/u Trop T normal	[28]
4	43 yr, gestation: NA	Chest pain	EKG: Normal and Trop T elevated; echo: LV hypokinesia, apical, diaphragmal, posterio-basal segments; coronary angiography: Negative	Stress factors: (1) H/o fetal death at 18 wk gestation; and (2) Domestic stress	Beta-blockers, ACE inhibitors, aspirin	5 d later, 2D echo EF 72%, normal wall movements. F/u: Developed 4 episodes of TTC, 6 mo, 9 mo, 10 mo, and 19 mo later. With eventual normalization of EF	[29]
5	43 yr, 9 wk gestation	Post Sx TOP. Shock, hypoxia, cardiac arrest requiring CPR	EKG: T wave inv, Trop T elevated; echo: LV EF 33%, LV apex hypo/akinesia; angiography: NA	h/o autoimmune diseases; post-op stress; cervical infiltration of epinephrine	Infusion of levosimendan	Echo: 3 mo later showed return of the LV function to normal	[30]
6	28 yr, 12 wk gestation	Chest pain	EKG: T wave inv, Trop T elevated; echo: EF (30%-35%); hypokinesia mid ventricular and hyperKinesia apical and basal wall; coronary angiography: Negative	Post abortion depression; suicidal ideation	Carvedilol. Lisinopril spironolactone	F/u echo: NA. Hemodynamically stable on follow-up	[31]
7	32 yr, 10 + 1 wk gestation; Misc	Abdominal pain, vaginal bleeding. Later underwent POC evacuation	EKG: Intermittent VT and QRS broadening. Trop T: NA; TTE: EF: 32%, global LV hypokinesia and akinesia of inferior and inferio-septal wall; coronary angiogra gestation phy: Negative	Septic miscarriage with blood C/S: Group C Streptococcus; amphetamine usage	IV antibiotics	Full recovery in 6 wk. 2D echo: Normal on repeat	[32]

Misc: Miscarriage; POC: Product of conception; Sx TOP: Surgical termination of pregnancy; CPR: Cardiopulmonary resuscitation; ST: Sinus tachycardia; DCM: Dilated cardiomyopathy; VT: Ventricular tachycardia; Post-op: Post-operation; EF: Ejection fraction; LV: Left ventricle; TTC: Takotsubo cardiomyopathy; TTE: Transthoracic echocardiography; NA: Not available; EKG: Electrocardiogram; C/S: Culture and susceptibility; F/u: Follow-up.

included aspirin, antibiotics, spironolactone, and levosimendan (n = 1 each). Six (87%) patients with available follow-up information had echocardiograms showing restoration of EF. Following the initial episode, one patient had five distinct episodes of TTC recurrence following an altercation with her partner. No recurrences were reported for the remaining patients, and there were no reported mortalities[26-32].

In four reported cases of SCAD following abortion or stillbirth, individual patient data was available for three patients. The median age of these patients was 36 years, with a range of 33 to 41 years. All three patients presented within 14 d of undergoing abortion or stillbirth. The most common clinical presentation was chest pain, which was reported by two patients (50%). EKG changes in these patients included ST elevation, with the most common leads involved being the inferior leads (50% of patients), mimicking acute myocardial infarction. Cardiac biomarkers were normal in all cases. Echocardiography was performed on two patients, with one showing normal findings and the other showing decreased left ventricle contractility with an EF of 30%. Coronary angiography showed dissection in the right coronary artery in two patients (one with proximal involvement and one with distal involvement) and the left anterior descending artery in one. Management included percutaneous coronary intervention besides medical management for two of the three patients. All three patients survived the event. One patient had no similar episode after eight months of follow-up, while the other patient had a remnant anoxic brain injury[33-36].

Out of five patients developing arrhythmia, the most common type reported was bradycardia which was seen in 60% (n = 3) of patients. Other two patients developed an arrhythmia post administration of prostaglandin F2 alpha drugs. The two patients who developed bradycardia did so after the passage of the product of conception (POC) and the application of pressure to their cervix. The mechanism which was speculated to cause this was the triggering of the vagus nerve during this process, resulting in the development of bradycardia. In all these patients, bradycardia improved after forceps assisted removal of the POC. There was also a patient who developed supraventricular tachycardia (SVT) after the administration of the misoprostol injection[37-41].

Table 3 Patients with spontaneous coronary artery dissection following medical termination of pregnancy

No.	Age	C/F and EKG	Labs and imaging	Angiography	Management and prognosis	Ref.
1	36 yr	Chest pain 2 wk post abortion. ECG: STE in V2-V4, STD in inferior leads	Cardiac biomarkers: Normal. Echo: Normal	Angiography: Type C dissection in LAD	Management: PCI with stenting to LAD. Survived, no similar episodes at follow-up after 8 mo	[33]
2	41 yr	2 wk post still birth, became unresponsive, cardiac arrest post CPR, ROSC. ECG: STE in leads 2, 3, avF	Cardiac biomarkers: Normal. Echo: Decreased LV contractility, EF: 30%	Angiography: Type 2 SCAD involving distal RCA	Management: Medical management. Survived post cardiac arrest, anoxic brain injury	[34]
3	33 yr	Chest pain 10 d post abortion. EKG: STE in inferior leads	Cardiac biomarkers: Increased	Angiography: Dissection involving RCA	Management: PCI. Survived	[35]
4	N/A	2 cases had SCAD a/w stillbirth and miscarriage	N/A	N/A	N/A	[36]

C/F: Clinical features; EKG: Electrocardiogram; N/A: Not applicable; STE: Sinus tachycardia elevation; STD: Sinus tachycardia depression; CPR: Cardiopulmonary resuscitation; ROSC: Return of spontaneous circulation; SCAD: Spontaneous coronary artery dissection; LV: Left ventricle; EF: Ejection fraction; LAD: Left anterior descending artery; RCA: Right coronary artery; PCI: Percutaneous coronary intervention.

Table 4 Patients with arrhythmia following medical termination of pregnancy

No.	Age	Clinical details	Arrythmia observed	Possible mechanism for arrythmia	Treatment given	Outcome	Ref.
1	NA, 2nd trimester	Induced by PGF2a	Bradycardia	Drug induced hypokalemia	NA	NA	[37]
2	32 yr, 20th wk gestation	Induced by PGF2a	Bradycardia and hypotension	PG acting on ventricular receptor	IV RL, 0.5 mg atropine no response	F/u 1 mo EKG and echo normal	[38]
3	37 yr, 10 wk gestation	In miscarriage	Bradyarrythmia	POC through cervix trigger vagal stimulation	POC removed	EKG normal on F/u	[39]
4	42 yr, 12 wk gestation	Miscarriage, with lower abdominal pain	Bradyarrythmia with hypotension. USG TVS: POC in UC	POC through cervix, triggering vagus	POC removed	BP and HR improved	[40]
5	Age: NA, 2nd trimester	Induced by PGF2α and IV oxytocin	Bradycardia, hypothermia and hypotension	Rupture of the cervix	NA	NA	[41]

PGF2a: Prostaglandin F2 alpha; NA: Not available; USG: Ultrasound; TVS: Transvaginal ultrasound; POC: Product of conception; UC: Uterine cavity; RL: Ringer lactate; F/u: Follow-up; EKG: Electrocardiogram; BP: Blood pressure; HR: Heart rate.

DISCUSSION

In the year 2020, the CDC reported rate of abortion was 11.2 abortions per 1000 women of age 15-44 years in the United States[1]. The type of abortion can also be classified as either being safe (performed in a safe, clean environment with experienced providers and no legal restrictions) or unsafe (performed with hazardous materials and techniques, by a person without the needed skills, or in an environment where minimal medical standards are not met)[42]. Abortion related complications and deaths occur predominantly in unsafe abortions and in settings where it is illegal[43]. Complications following an abortion can be diverse. The maternal mortality rate following safe, legal induced abortion for 2013-2019 was reported to be 0.43 deaths per 100000 reported legal abortions[1]. Pregnancy is a state of altered neuro-humoral balance and continuous inflammation with significant effects on the physiology of the CVD system[44-47]. It is probable that even abortion or stillbirth can also result in altered neuro-humoral balance and chronic inflammatory changes affecting the functioning of the CVD system[4,42]. In this descriptive review, we highlight the various CVD complications following MTP reported in the medical literature. We identified four distinct CVD complications following MTP, which have been defined as above (Figure 2).

IE

In this review, IE was the most common CVD complication observed following MTP. While multiple organisms are reported to cause IE, in these patients the most common organism causing IE was GBS, which is a common colonizer of the genital tract and lower gastrointestinal tract[48,49]. The reported risk factors that predispose to GBS IE are diabetes mellitus, malignant disease, advanced liver disease, human immunodeficiency virus, alcohol use disorders, and injection drug use[50]. Surgical abortion has been reported to be an independent risk factor for IE in patients with GBS, irrespective

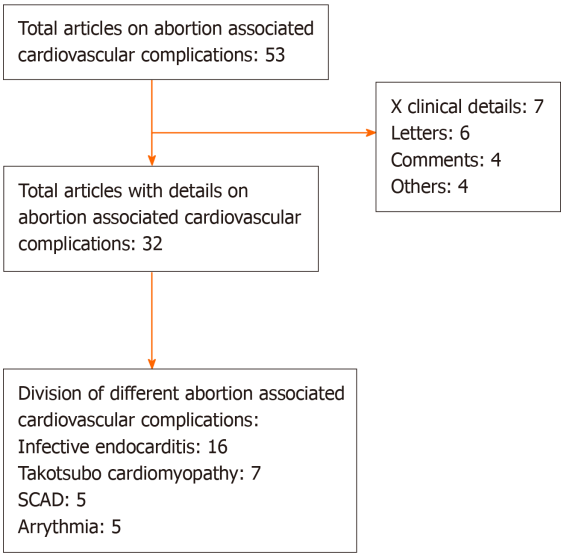

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Figure 1 Flow diagram of study participant inclusion. SCAD: Sudden coronary artery dissection.

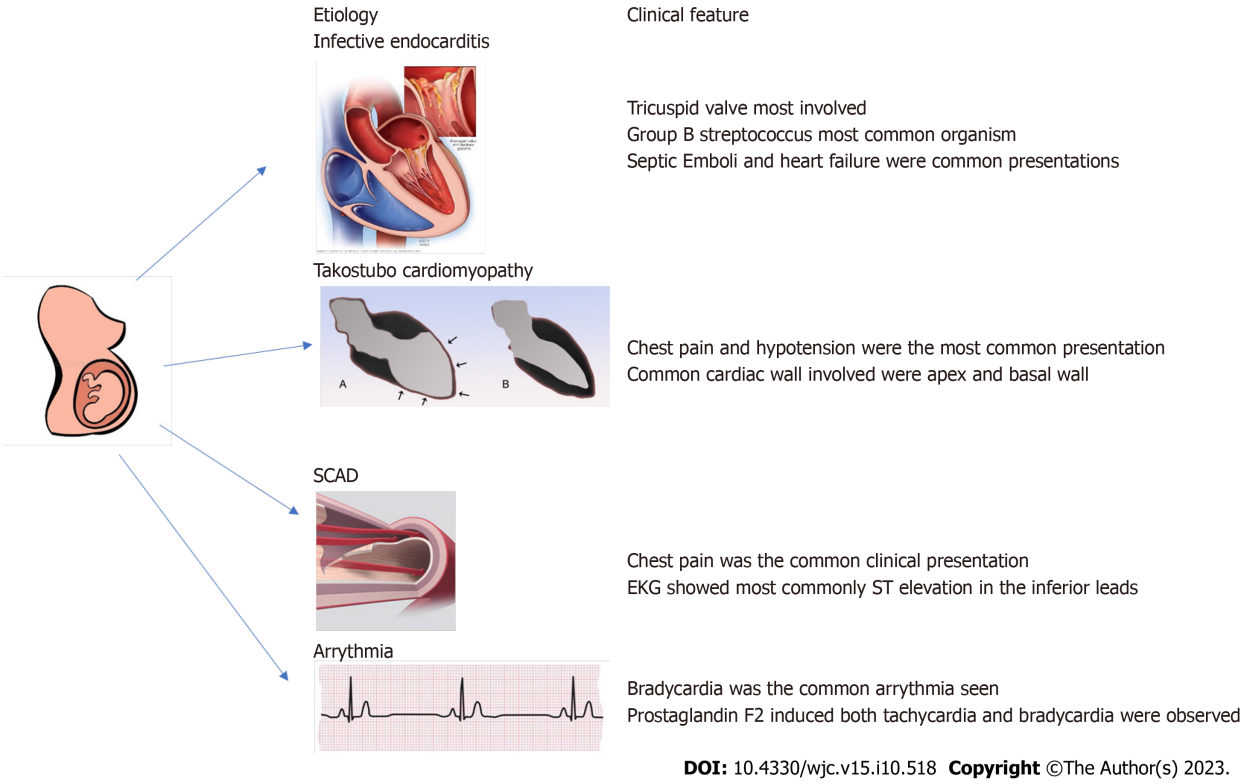

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Figure 2 Cardiovascular complications following medical terminations of pregnancy. SCAD: Sudden coronary artery dissection; EKG: Electrocardiographic.

of the presence or absence of underlying structural heart disease or antibiotic prophylaxis before the procedure[12,13]. The Society of Obstetricians and Gynaecologists of Canada recommends antimicrobial prophylaxis for patients who are undergoing surgical abortion to reduce the incidence of post-abortion infections[51]. This recommendation is based on a meta-analysis of 12 randomized controlled trials conducted in pregnant women at less than 16 wk gestation. Patients who received antibiotics during the abortion procedure had a 0.58 (0.47-0.71) relative risk of developing upper genital tract infection, compared to those who did not receive the antibiotics[52]. A single appropriate antibiotic regimen was not recommended in the study. Though antibiotic therapy has been shown to prevent genitourinary infections, antibiotics were not uniformly administered in the above subsets of patients. Clinicians providing MTP should be aware of this rare complication in patients with risk factors as mentioned above. So far there are no studies to guide antibiotic prophylaxis in patients undergoing MTP, however, patients with risk factors for developing GBS IE might benefit from pre-procedure

prophylaxis. In a study done in Sweden on women undergoing an induced abortion, the administration of antibiotics reduced the post-abortion complications in patients with positive bacterial screening to the level with those having negative bacterial screening[53]. Despite the above study, given the rarity of this complication, prolonged prophylactic anti-biotic courses are not feasible or evidence-based.

The most common valve involved was the tricuspid valve, but multivalvular involvement was also seen[15,17,21,54]. Pelvic infections occurring after a septic abortion can provide a portal of entry for bacteria through pelvic veins into the venous system. This can subsequently spread to the right-sided circulation, eventually causing tricuspid endocarditis. Most of these patients presented with constitutional symptoms like chills, anorexia, and weight loss. Complications including septic pulmonary emboli are common among patients with right-sided IE, occurring in up to 75% of patients with tricuspid involvement. Clinical manifestations of such emboli include cough, pleuritic chest pain, hemoptysis, and dyspnoea[42,55,56]. In our study, the common complications seen were septic emboli and heart failure. All patients were treated with appropriate antibiotics based on culture and sensitivity results[57-61]. Patients with septic emboli, para-valvular abscess, conduction blocks, and the presence of large vegetations required surgical management as shown in Table 1. Overall, the prognosis was good with a mortality of 6.25%.

TTC

TTC, also called transient apical ballooning syndrome, was initially described in Japan in 1990[62,63]. Improved access to coronary angiography has led to increased recognition of TTC in patients presenting with symptoms of acute coronary syndrome, with studies reporting a 20-fold increase in incidence from 2006 to 2012[64-66]. Mayo Clinic Criteria and International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria) are two of the most commonly used tools to establish the diagnosis[64,67]. In our study, Mayo Clinic Criteria was used. TTC has been reported to be precipitated in 70% of patients by several acute triggers including emotional, natural disaster, illness, envenomation, infection, *etc.*[68-70]. In this paper we discuss TTC precipitated following MTP. Patients who developed TTC post MTP presented with symptoms and signs of ACS including chest pain, ST-T wave changes in EKG, and elevated troponin as seen in patients with other precipitators of TTC[71]. In this review apical wall involvement was the most common echocardiographic abnormality, as reported by Templin *et al*[64] in 81.7% of their patient population (n = 1750)[72]. Multiple mechanisms have been proposed to precipitate TTC[72]. The various mechanisms postulated to precipitate TTC in this review were catecholamine surge following physical and emotional distress (depression, posttraumatic stress disorder, and suicidal ideation) and exogenous epinephrine[26,31,32]. It has been hypothesized that direct myocardial damage from catecholamines may cause TTC and the regional wall motion abnormalities occur due to the regional distribution of adrenergic receptors. At presentation all these patients had low left ventricular EF, however, less than half of the patients were treated with guideline directed medical therapy with ACEi and BB. Interestingly, no mortality was reported and at follow-up all these patients were found to have normal left ventricular ejection fraction.

SCAD

SCAD is a rare condition, with an estimated prevalence of 0.2% to 1.1%[49,73]. The prevalence of SCAD post pregnancy, stillbirth, and abortion remains unknown. There are several proposed mechanisms for the development of SCAD in these situations, including structural changes to the vascular system due to excess progesterone during pregnancy leading to the loss of normal corrugation of elastic fibers, increasing the fragmentation of reticular fibres, and decreasing the amounts of mucopolysaccharides reducing the strength of vessel wall, increased mechanical stress on the coronary artery during labor, prolonged coronary artery spasm, and the use of uterotonic drugs[36,74-77]. Maternal risk factors, such as multiple pregnancies, advanced age, and anxiety, may also increase the risk of SCAD due to repeated exposure to high levels of progesterone and altered neuro-hormonal balance[74,75,77]. In this review, SCAD was reported within 2 wk of MTP presenting as an ACS. Although the risk of SCAD post pregnancy and stillbirth may differ, early intervention with high clinical suspicion can result in good outcomes, as reported in various studies[44,73,78].

Arrhythmia

Bradycardia was the most common arrhythmia observed in our review[35-37,47]. The common cause of bradycardia is vagal stimulation during the passage of the fetus or POC through the cervix, a phenomenon known as cervical vasovagal shock[39,40]. This is typically observed with retained POC, and management often involves dilatation and curettage to remove the POC. In a study conducted in Cambridge, Kyejo *et al*[40] suggest that for patients with symptomatic bradycardia secondary to cervical shock, it is important to stop cervical manipulation and remove all instruments, keep the patient in the supine position with legs elevated to improve venous return, and, if necessary, administer 500-600 microgram of IV atropine followed by a saline flush. In this review, removal of the POC with forceps improved shock and bradycardia. Other causes of arrhythmia observed in our patients include prostaglandin F2 and E (misoprostol), which have been linked to tachycardia and SVT. A study in mice suggests that these medications may cause tachyarrhythmias due to their direct effect of inflammatory mediators on the heart[79]. Stopping the medications resulted in the improvement of arrhythmias in these patients.

This review has several limitations. It included all the patients with MTP and reported CVD complications from various case reports over the years, which had varied uniformity in reporting. These patients were young and lacked baseline echocardiography or electrocardiography. All the reports of SCAD and TTC consistently did not report cardiac catheterization results[80]. Reports did not mention functional status at discharge, recurrence, and long-term follow-up details[81-84]. However, the strengths of this study are: (1) Having a strict inclusion criterion for each clinical entity; and (2) Evidence-based detailing on the clinical profile and the outcome of each described complication. As per the authors' knowledge, there are previous studies done including Kyriacou *et al*[3] who have reported that women with previous

pregnancy loss, following a miscarriage, stillbirth, and induced abortion, are at higher risk of coronary heart disease and stroke. However, this is the first review detailing the clinical profile, imaging details, complications, and outcomes of the various CVD complications following MTP.

CONCLUSION

In conclusion, CVD complications are uncommon following MTP. The most frequently reported complications are IE and TTC. IE can occur in these subgroups of patients without risk factors for IE. Periprocedural antibiotics prophylaxis was not uniformly administered. IE can occur within 1 wk of MTP, and the most common organism identified is GBS. The most commonly involved valve reported is the tricuspid valve, and the most common complication reported is septic emboli. More than half of the IE patients required surgical intervention owing to worsening heart failure, valvular regurgitation, para valvular abscess, conduction block, and embolic phenomenon. TTC most commonly occurred after MTP in the first trimester. Most patients presented with acute chest pain, troponin elevation, and nonspecific ST-T changes. The most common pattern of TTC as identified by echocardiography was apical. All these patients had low EF at presentation and at follow-up most had normal EF even though only half of them were treated with ACEi and BB. SCAD occurred within 2 wk of MTP. Most patients presented with chest pain and EKG abnormalities. The most common vessel involved in dissection was the right coronary artery. Bradycardia was the most common pattern of arrhythmia noted and occurred during the time of MTP and was self-limiting. All patients with the above complications improved with appropriate medical management. Overall, mortality was low in this population.

ARTICLE HIGHLIGHTS

Research background

Millions of medical terminations of pregnancy (MTP) take place yearly in the United States of America with a smaller percentage of this population developing complications. There is a lack of structured reporting of the cardiovascular (CVD) complications in this subset of patients.

Research motivation

The CVD complications occurring post MTP or after stillbirth are not very well described. The literature on the various CVD comorbidity following MTP is scanty.

Research objectives

In this review we aimed to study the various cardiac comorbidities seen after MTP, which will help the reader better understand, prepare, and manage these complications.

Research methods

A literature search in multiple databases including PubMed, Medline, *RCA* and google scholar, using the search terms "abortions" or "medical/Legal termination of pregnancy" and "cardiac complications" or "cardiovascular complications" were conducted. All research studies, clinical studies, case series, and case reports with relevant clinical details were included.

Research results

The most common complications described in the literature following MTP were infective endocarditis (IE), takotsubo cardiomyopathy (TTC), arrhythmia, and sudden coronary artery dissection (SCAD). The most common valve involved in IE was the tricuspid valve. The most observed causative organism of endocarditis was group B Streptococcus. The most common type of TTC was apical. Bradycardia was the most common arrhythmia. All four cases of SCAD-P type presented as acute coronary syndrome with predominant involvement of the right coronary artery. Mortality was only reported following IE in 6.25%. Clinical recovery occurred after optimal medical management following all these complications.

Research conclusions

The most common CVD complications following the MTP are IE, TTC, bradycardia, and SCAD. Most of these complications are adequately treated with appropriate medical management.

Research perspectives

As per the authors' knowledge, this is the first review detailing on the clinical profile, imaging details, complications, and outcomes of the various CVD complications following MTP.

FOOTNOTES

Author contributions: Mishra AK and Hadley M planned and formulated the study; Singh T and Vojjala N collected and analysed the data; Singh T, Mishra AK, John KJ, George AA, and Jha A completed the manuscript; Singh T and Mishra AK revised the manuscript; Mishra AK and Hadley M reviewed the manuscript; and Hadley M approved the manuscript.

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Country/Territory of origin: United States

ORCID number: Tejveer Singh 0000-0002-2342-4223; Ajay K Mishra 0000-0003-4862-5053; Nikhil Vojjala 0000-0001-7238-1058; Kevin John John 0000-0003-3382-0294; Anu A George 0000-0002-6769-732X.

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META-ANALYSIS

Do cardiopulmonary resuscitation real-time audiovisual feedback devices improve patient outcomes? A systematic review and meta-analysis

Nitish Sood, Anish Sangari, Arnav Goyal, Christina Sun, Madison Horinek, Joseph Andy Hauger, Lane Perry

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Nitish Sood, Anish Sangari, Arnav Goyal, Madison Horinek, Lane Perry, Medical College of Georgia, Augusta University, Augusta, GA 30912, United States

Christina Sun, Dental College of Georgia, Augusta University, Augusta, GA 30912, United States

Joseph Andy Hauger, Department of Chemistry and Physics, Augusta University, Augusta, GA 30912, United States

Corresponding author: Nitish Sood, BSc, Medical College of Georgia, Augusta University, No. 1120 15th Street, Augusta, GA 30912, United States. nsood@augusta.edu

Abstract

BACKGROUND

Cardiac arrest is a leading cause of mortality in America and has increased in the incidence of cases over the last several years. Cardiopulmonary resuscitation (CPR) increases survival outcomes in cases of cardiac arrest; however, healthcare workers often do not perform CPR within recommended guidelines. Real-time audiovisual feedback (RTAVF) devices improve the quality of CPR performed. This systematic review and meta-analysis aims to compare the effect of RTAVF-assisted CPR with conventional CPR and to evaluate whether the use of these devices improved outcomes in both in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA) patients.

AIM

To identify the effect of RTAVF-assisted CPR on patient outcomes and CPR quality with in- and OHCA.

METHODS

We searched PubMed, SCOPUS, the Cochrane Library, and EMBASE from inception to July 27, 2020, for studies comparing patient outcomes and/or CPR quality metrics between RTAVF-assisted CPR and conventional CPR in cases of IHCA or OHCA. The primary outcomes of interest were return of spontaneous circulation (ROSC) and survival to hospital discharge (SHD), with secondary outcomes of chest compression rate and chest compression depth. The methodological quality of the included studies was assessed using the Newcastle-Ottawa scale and Cochrane Collaboration's "risk of bias" tool. Data was analyzed using R

statistical software 4.2.0. results were statistically significant if $P < 0.05$.

RESULTS

Thirteen studies ($n = 17600$) were included. Patients were on average 69 ± 17.5 years old, with 7022 (39.8%) female patients. Overall pooled ROSC in patients in this study was 37% (95% confidence interval = 23%-54%). RTAVF-assisted CPR significantly improved ROSC, both overall [risk ratio (RR) 1.17 (1.001-1.362); $P = 0.048$] and in cases of IHCA [RR 1.36 (1.06-1.80); $P = 0.002$]. There was no significant improvement in ROSC for OHCA (RR 1.04; 0.91-1.19; $P = 0.47$). No significant effect was seen in SHD [RR 1.04 (0.91-1.19); $P = 0.47$] or chest compression rate [standardized mean difference (SMD) -2.1; (-4.6-0.5)]; $P = 0.09$]. A significant improvement was seen in chest compression depth [SMD 1.6; (0.02-3.1); $P = 0.047$].

CONCLUSION

RTAVF-assisted CPR increases ROSC in cases of IHCA and chest compression depth but has no significant effect on ROSC in cases of OHCA, SHD, or chest compression rate.

Key Words: Real-time audiovisual feedback; Cardiopulmonary resuscitation; Cardiac arrest; Return of spontaneous circulation; Survival to hospital discharge; Cardiopulmonary resuscitation quality

Core Tip: Real-time audiovisual feedback (RTAVF) devices have been shown to significantly improve cardiopulmonary resuscitation (CPR) quality in manikin/simulation studies. Despite this improvement, previous reviews have not seen a translation into improvement in patient outcomes. This systematic review and meta-analysis is the largest one to-date conducted on this topic, including 13 studies and 17600 patients. We found that the use of RTAVF devices significantly improves CPR quality metrics of chest compression rate and depth. Contrary to prior literature, we found that usage significantly increases return of spontaneous circulation in cases of in-hospital cardiac arrest but does not improve survival to hospital discharge.

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INTRODUCTION

Nearly 356000 out-of-hospital cardiac arrest (OHCA) cases and 292200 in-hospital cardiac arrest (IHCA) cases occur annually in the United States, making cardiac arrest one of the leading causes of natural death in America[1-3]. In addition, the incidence of cardiac arrest cases has increased over the last twenty years, but little progress has been made in improving survival to hospital discharge (SHD) and functional status including neurological and cardiovascular outcomes[2,4]. Consequently, cardiac arrest places a significant burden on public health and society and remains important to research and manage effectively[5,6].

High quality cardiopulmonary resuscitation (CPR) increases survival outcomes in cases of cardiac arrest[7-14]. The International Liaison Committee on Resuscitation guidelines specifically emphasize the quality of manual chest compression, including proper hand position, hands off time, compression rate, and compression depth[15]. However, the quality of CPR performed by healthcare workers (HCWs) often does not meet recommended guidelines, with the average rate of chest compressions and compression depth being lower than recommended[16-25].

Real-time audiovisual feedback (RTAVF) devices have enabled improvement in consistency and quality of CPR both inside and outside the hospital[26,27]. The American Heart Association (AHA) and the International Liaison Committee on Resuscitation have recommended the use of RTAVF devices for CPR training[28-30]. Previous systematic reviews and meta-analyses examining the effect of RTAVF devices during cardiac arrest cases concluded that RTAVF-assisted CPR resulted in closer adherence to CPR guidelines but not improved patient outcomes[31,32]. However, these studies focused on simulation manikin studies, including only three human trials. This systematic review and meta-analysis aims to compare the effect of RTAVF-assisted CPR with conventional CPR and to evaluate whether the use of these devices improved outcomes in both in-hospital and OHCA patients.

MATERIALS AND METHODS

Search Strategy

Database searches were performed by two independent authors in PubMed, SCOPUS, the Cochrane Library, and EMBASE with individualized search strategies developed for each database (Supplementary Table 1). The search included all studies from the establishment of the database to July 27, 2020 without language, methodology, or document filters. References cited in relevant reviews and included studies were also examined. The current systematic review and meta-analysis was constructed in accordance with the PRISMA 2009 guidelines.

Study Eligibility

Studies were included if HCWs were performing CPR using RTAVF devices, where HCWs were defined as anyone with medical training including physicians, nurses, paramedics, emergency medical services, physician assistants, and medical residents. Studies must compare RTAVF-assisted CPR with CPR performed without any device or disabled audiovisual feedback features on cardiac arrest patients, and complete data must be available with a minimum of two metrics reported with measures of central tendency and variability. Language was restricted to English. Simulation studies, animal studies, case reports, conference abstracts, reviews, trial protocols, and studies with incomplete or missing data were excluded.

Review Process and Data Collection

Abstracts of studies were reviewed for relevance by two independent authors. Abstracts with common agreement between reviewers were identified for further review of the full manuscript. Disagreements regarding the inclusion or exclusion of any studies were independently resolved by a third author. Data was extracted from articles selected for inclusion in the present study. Primary outcomes of interest were patient outcomes: return of spontaneous circulation (ROSC) and SHD. Secondary outcomes of interest were CPR quality metrics: chest compression rate and chest compression depth. Mean values and standard deviations were extracted from studies. Methodological quality was reviewed utilizing the Newcastle-Ottawa Quality Assessment scale for cohort studies and using the Cochrane Collaboration's "risk of bias" tool for randomized controlled trials (RCT)[33,34]. Methodological quality was assessed by two independent authors with disagreements resolved by a third author.

Statistical Analysis

Data was analyzed using R statistical software 4.2.0. Random-effects models were used[35,36]. When values were presented as interquartile range or range or median, they were converted into mean and standard deviation for analysis using the methodology presented in Wan *et al*[37] 2014. Pooled risk ratio (RR) or standardized mean difference (SMD) was calculated for binary and continuous metrics respectively[38-40]. Heterogeneity was assessed using I^2[41,42]. Publication bias was assessed using funnel plots and Egger's tests. Results were statistically significant if $P < 0.05$.

RESULTS

Study Selection

A PRISMA flow diagram is shown in Figure 1. The systematic search of articles identified 9422 results. 102 full-text articles were identified as potentially relevant after title and abstract screening. Thirteen studies were included after full-text review (Figure 1)[8,26,27,43-52]. Thirteen studies reported data on ROSC and ten reported data on SHD. Important characteristics for each study are summarized in Table 1.

Study Characteristics

A total number of 17600 participants from 13 studies were included for analysis. Patients were on average 69 ± 17.5 years old, with 7022 (39.8%) female patients. All studies were published between the years 2006 and 2020. Six studied the influence of RTAVF devices in OHCA, while six studied their influence in IHCA. One examined both OHCA and IHCA (Table 1)[44]. All studies examined adult populations, with Park *et al*[49] 2018 examining patients greater than 15 years old.

Risk of Bias

Risk of bias was assessed in all 13 studies. Of the studies included, four were RCTs[45,46,51,52]. Using Cochrane's Risk of Bias tool, the risk of bias was assessed to be low risk in three RCTs and medium risk in one RCT (Supplementary Table 2). Using the Newcastle-Ottawa Scale, the risk of bias was assessed to be low in eight studies and medium in one study (Supplementary Table 3). Egger's test found no evidence of publication bias in any outcomes of interest (Supplementary Figure 1).

Outcomes

Pooled ROSC was 37% (95% confidence interval (CI) = 23%-54%) (Supplementary Figure 2A). Park *et al*[49] 2018 was identified as a potential outlier using leave-one-out sensitivity analysis with the lowest survival rate of 9%. Visual inspection of the associated funnel plot found no clear asymmetry (Supplementary Figure 2B).

Table 1 Characteristics of included studies

Ref.	Region	Enrollment year	*n*	Female	ROSC	Setting	Study type
Abella *et al*[26], 2007	United States	2002-2005	156	71	43%	IHCA, adult patients	Prospective cohort
Goharani *et al*[45], 2019	Iran	2015	900	546	55%	IHCA, adult patients	RCT
Hostler *et al*[46], 2011	United States, Canada	2007-2009	1587	1000	45%	OHCA, adult (> 20 yr)	RCT
Kramer-Johansen J *et al* [27], 2006	London, Norway, Sweden	2002-2003	284	106	19%	OHCA, adult	Non-randomized controlled trial
Lakomek *et al*[47], 2020	Germany	2016	196	112	54%	OHCA, adult	Non-randomized controlled trial
Vahedian-Azimi *et al*[52], 2020	Iran	2013-2014	22	10	27%	IHCA, adult	RCT
Vahedian-Azimi *et al*[51], 2016	Iran	2014	80	49	54%	IHCA, adult (≥ 18 yr)	RCT
Couper *et al*[43], 2015	England	2009-2013	400	182	40%	IHCA, adult (≥ 18 yr)	Prospective cohort
BoBrow *et al*[8], 2013	Arizona	2008-2011	484	162	23%	OHCA, adult (≥ 18 years)	Prospective cohort
Crowe *et al*[44], 2015	Arizona	2010-2013	101	27	42%	OHCA/IHCA, adult	Prospective before-after
Sutton *et al*[50], 2014	Pennsylvania	2011-2013	8	2	50%	IHCA, children (1-8 yr)	Prospective cohort
Lukas *et al*[48], 2012	Germany	2007-2011	638	184	50%	OHCA, adults (> 18 yr)	Retrospective Matched-pair analysis
Park *et al*[49], 2018	South Korea	2013-2016	12670	4571	9%	OHCA, > 15 yr	Before-after

ROSC: Return of spontaneous circulation; IHCA: In-hospital cardiac arrest; RCT: Randomized controlled trials; OHCA: Out-of-hospital cardiac arrest.

ROSC

Thirteen trials reported ROSC as an outcome of interest (n = 17600). ROSC occurred in 1693 patients (21.0%) in the RTAVF-assisted CPR group and 1602 patients (16.8%) in the conventional CPR group. All studies included data on ROSC in both the RTAVF-assisted CPR group and the conventional CPR group. Using a random-effects model, patients in the RTAVF group were significantly more likely to achieve ROSC than the conventional CPR group (RR 1.17; 95%CI = 1.001-1.362; P = 0.048) (Figure 2).

Subgroup analysis revealed that the location of cardiac arrest was significantly correlated with patient outcomes (P value for interaction = 0.02) (Supplementary Figure 3). ROSC in the setting of IHCA was significantly improved in the RTAVF group (RR 1.36; 1.06-1.80; P = 0.002). However, ROSC in the setting of OHCA was not significantly different between the two groups (RR 1.04; 0.91-1.19; P = 0.47).

Potential causes of heterogeneity in ROSC were explored, with subgroup analysis on study type comparing RCTs with non-RCTs, and region comparing studies within Europe, Middle East/Asia, and North America (Supplementary Figure 4). Heterogeneity remained significant within at least one subgroup in both analyses.

SHD

Ten trials reported SHD as an outcome of interest (n = 16684). SHD was reported in 994 patients (13.1%) in the RTAVF-assisted CPR group and in 1028 patients (11.2%) in the conventional CPR group. No significant difference was found in SHD between the two groups (RR 1.23; 0.94-1.60; P = 0.12) (Figure 3). Subgroup analysis found no significant correlation between SHD and the location of cardiac arrest (P value for interaction = 0.26) (Supplementary Figure 5).

Secondary Outcomes

Eight studies reported compression rate as an outcome of interest (n = 2804). The average compression rate was 107.3 ± 9.4 in the RTAVF-assisted CPR group and 117.5 ± 13.8 in the conventional CPR group, with a nationally recommended rate of 100-120 compressions per minute[53]. A non-significant difference was seen between the two, with patients in the intervention group receiving a lower compression rate [SMD -2.1; (-4.6-0.5); P = 0.09] (Supplementary Figure 6). While both groups had an average compression rate within the nationally recommended guidelines, the proportion of compressions that fell between 100-120 compressions per minute was likely higher in the intervention group than in the control group (Supplementary Figure 6). Eight studies reported compression depth as an outcome of interest (n = 2625). The average compression depth was 4.59 cm ± 0.91 cm in the intervention group and 4.24 cm ± 1.29 cm in the control group, with a nationally recommended compression depth of 5-6 cm in the average adult[53]. Neither group had an average compression depth that met AHA guidelines. However, a significant difference was seen between the two

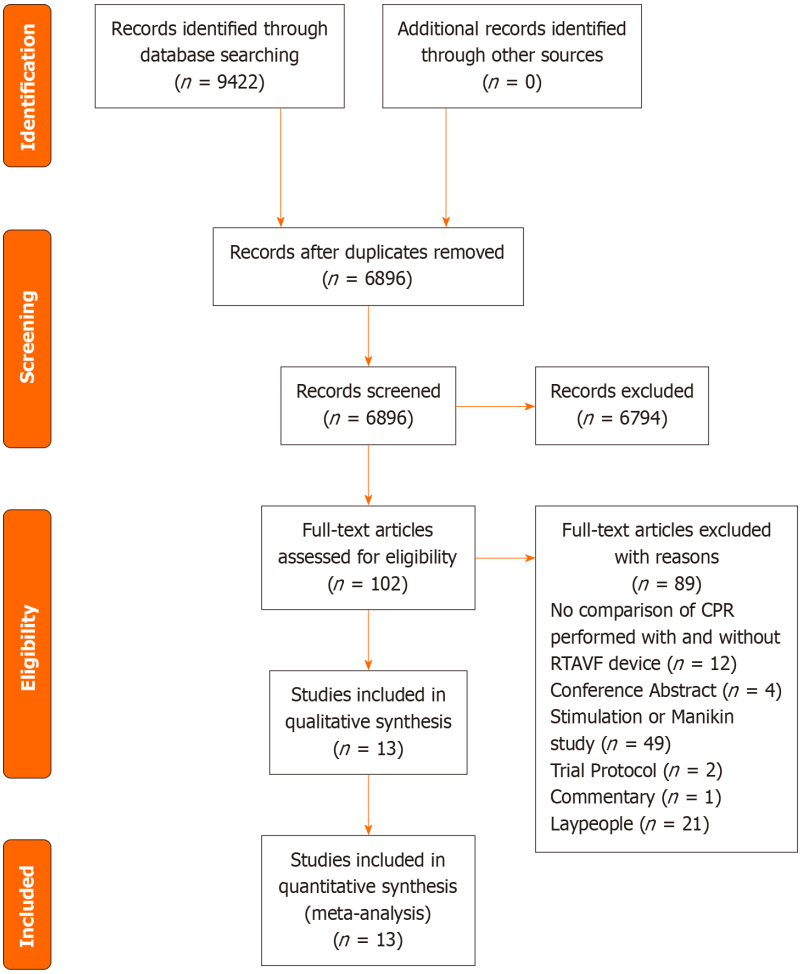

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Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram of included and excluded articles.

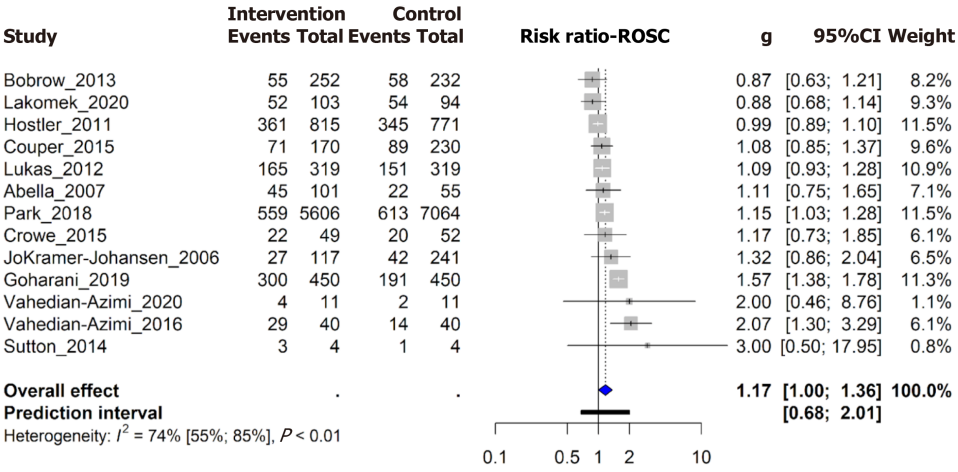

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Figure 2 Forest plot of return to spontaneous circulation. ROSC: Return of spontaneous circulation.

groups, with patients in the intervention group receiving a higher compression depth, closer to AHA guidelines [SMD 1.6 (0.02-3.1); P = 0.047] (Supplementary Figure 7).

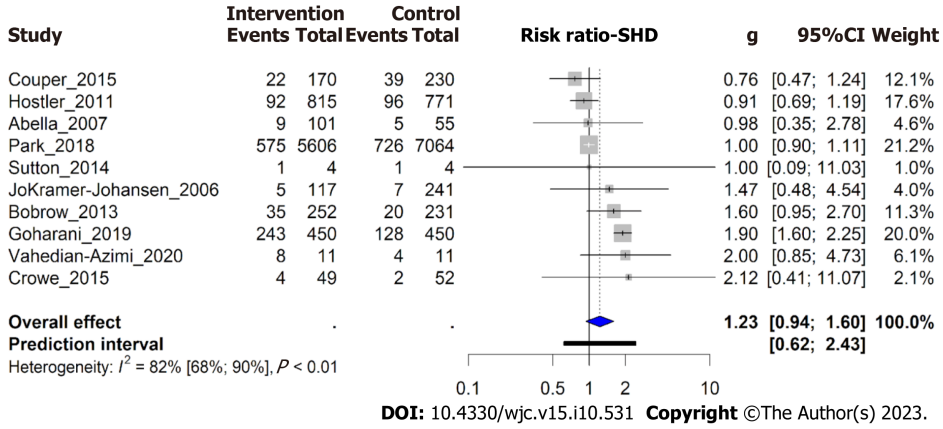

Figure 3 Forest plot of survival to hospital discharge. SHD: Survival to hospital discharge.

DISCUSSION

This manuscript analyzed the most recent evidence with regards to the efficacy of real-time audiovisual feedback devices in improving CPR quality and patient outcomes. A total of 13 studies (n = 17600) were included, making it the largest study of this topic to date.

Currently, patient outcomes after cardiac arrest remain poor. This meta-analysis found an average ROSC of 37%, which is consistent with previous literature findings ranging between 13% and 72%[54-59].

The AHA mandated that beginning January 2019, all AHA courses that teach adult CPR will be required to use a real-time audiovisual feedback device. These devices typically measure one or more of the following CPR metrics: Chest compression rate, depth, hand position, recoil, ventilation volume, ventilation rate, and hands-off time. Multiple types of feedback devices exist, including manikins with integrated sensors, devices that can be added to existing manikins, and hand-held devices that can be easily transferred from patient to patient[60]. As this meta-analysis examined the effect of using RTAVF devices during CPR on patient outcomes, the only type of RTAVF devices that were analyzed were hand-held devices that can be used during CPR on patients, rather than manikin-based RTAVF devices.

Thirteen studies with a total of 17600 patients were analyzed. These studies were a mixture of 4 RCT, 2 non-RCT, 4 cohort studies, 2 before-after studies, and 1 matched pair registry study. Studies took place across the globe with only 5 in the United States. These studies were both clinically and statistically heterogenous, with varying protocols and outcomes. Despite this heterogeneity, all studies did examine the primary outcome of ROSC with ten of thirteen also examining SHD.

Contrary to prior literature reviews, this analysis found that the use of real-time audiovisual feedback devices did significantly improve ROSC in cases of IHCA. This may be because prior meta-analyses included only three human intervention studies, while this meta-analysis had a larger number of studies and patients[31,32]. In addition, Kirkbright *et al*[32] 2013, Gugelmin-Almeida *et al*[31] 2021, and Lv *et al*[61] 2022 included only 1, 2, and 5 studies focusing on IHCA, respectively. This meta-analysis found that the location of cardiac arrest played a significant role in whether RTAVF devices influenced ROSC, with a significant increase in ROSC seen in cases of IHCA and no such increase seen in cases of OHCA. This could be another reason why prior reviews found no significant impact of RTAVF devices on ROSC. In particular, Lv *et al*[61] 2022 found that RTAVF-assisted CPR did not improve ROSC across all studies, but did not differentiate between ROSC outcomes in IHCA and OHCA settings. These findings suggest that hospitals should prioritize the rollout and adoption of RTAVF devices in areas most likely to see IHCA, such as intensive care units, telemetry units, and EDs, rather than with paramedics or ambulances[62,63]. This difference in survival may be due to the inherent rushed nature of CPR for patients suffering OHCA. Unlike cases of IHCA where a dedicated HCW can focus exclusively on performing high quality CPR, in cases of OHCA, paramedics may be obligated to multi-task, performing CPR while also keeping track of the other required tasks to bring the patient into the hospital safely. As such, the quality of CPR may be reduced in cases of OHCA *vs* IHCA. Another explanation could be tied to the fact that the time-to-CPR from arrest is lower in cases of IHCA *vs* OHCA, and as such CPR quality may play a more important role in IHCA than in OHCA[64,65].

Despite the increase in ROSC when using RTAVF devices, no similar increase was seen in SHD. This insignificance may relate to how CPR quality plays little role in the improvement of survival after ROSC. It could also be due to the presence of comorbidities including heart failure, sepsis, and myocardial infarction and that effective CPR is one factor among many steps required for improved survival. Without additional improvements in other steps required in the care of post-cardiac arrest patients, the increase in CPR quality may be insufficient to translate into improved SHD.

Repeated studies in the literature have shown that CPR quality when performed on manikins improves when using a RTAVF device[31,32]. Consistent with existing literature, this meta-analysis also found that CPR quality was increased in RTAVF-assisted CPR. The average compression rate in both groups fell within AHA guidelines, while the average compression depth in both groups fell outside of AHA guidelines[53]. However, for both compression rate and depth, the RTAVF group was more likely to have a higher proportion of compressions falling within guidelines compared to the conventional CPR group, showing that RTAVF-assisted CPR was superior to conventional CPR. Prior studies have shown

the importance of proper compression depth in patient outcomes[10,16,66]. In CPR training courses being taught with RTAVF devices, a larger focus should be put on achieving adequate compression depth.

Overall, the evidence suggests that RTAVF-assisted CPR is of superior quality than conventional CPR. In addition, RTAVF-assisted CPR has a small benefit in patient outcomes, specifically improving ROSC in cases of IHCA. However, this meta-analysis has multiple limitations. First, the studies examined were both statistically and clinically heterogeneous, with varying study parameters, outcomes, and designs, limiting the internal validity of the meta-analysis. This was partially accounted for using a random-effects model and by subgroup analysis, but not all heterogeneity could be accounted for. This may partially be due to the limitations of I^2 as a metric for heterogeneity. This study contained relatively larger studies than most examining this topic, and prior literature has documented that as sampling error decreases, I^2 tends to increase, which can erroneously lead to assumptions that clinical heterogeneity has also increased. In addition, as this meta-analysis examined the class of all RTAVF devices used in CPR, some degree of clinical heterogeneity is expected, as the expected effects of individual devices can vary. Second, nine of these thirteen studies were not RCT, which can introduce sources of both confounding and selection bias. However, ROSC outcomes of cardiac arrest patients are dependent upon many non-controllable factors that cannot undergo randomization including time from arrest to CPR initiation and presence of shockable rhythm which may limit the advantage an RCT would have over other nonrandomized studies designs. Third, this meta-analysis only examined RTAVF devices that could be used during CPR on patients rather than RTAVF devices that are built into manikins. As such, these results cannot be extrapolated to that class of RTAVF devices. Fourth, this meta-analysis only reviewed publications in the literature until 2020, precluding studies published thereafter from inclusion in this analysis. Fifth, this meta-analysis was limited by the evidence that could be extracted from prior reports in the literature, and evidence on long-term patient outcomes and neurological function from RTAVF-assisted CPR is lacking. Future research should examine such cohorts and associated long-term outcomes. In addition, further research into why the improvements seen in ROSC with RTAVF-assisted CPR were not translated into improvements in SHD is warranted, along with research examining which RTAVF device provides the highest improvement in patient outcomes and CPR quality.

CONCLUSION

This meta-analysis examined 13 studies (n = 17600) and found that RTAVF-assisted CPR resulted in a significantly increased rate of ROSC, specifically in cases of IHCA but did not improve SHD. This is a novel finding, with prior meta-analyses finding that the use of RTAVF devices did not significantly improve patient outcomes. Consistent with what has been found previously, the use of RTAVF devices resulted in improved CPR quality, as measured by compression rate and depth.

ARTICLE HIGHLIGHTS

Research background

Cardiac arrest is a leading cause of mortality in America and continues to grow in prevalence. Cardiopulmonary resuscitation (CPR) increases survival outcomes in cases of cardiac arrest; however, healthcare workers often do not perform CPR within recommended guidelines. Real-time audiovisual feedback (RTAVF) devices provide live feedback on CPR performance and subsequently improves the quality of CPR performed.

Research motivation

Effective CPR in cardiac arrest is critical to emergent management and stabilization. RTAVF-assisted CPR devices may improve performance, compliance with recommended guidelines, and survival, therefore, this systematic review and meta-analysis seeks to compare the effect of RTAVF-assisted CPR devices with conventional CPR on patient outcomes in the setting of in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA).

Research objectives

To investigate the impact of RTAVF-assisted CPR on patient outcomes and CPR quality with respect to in- and OHCA.

Research methods

The literature search was conducted on PubMed, SCOPUS, the Cochrane Library, and EMBASE from inception to July 27, 2020, for studies reporting patient outcomes and/or CPR quality metrics between an RTAVF-assisted CPR and conventional CPR in the setting of IHCA or OHCA. The primary outcomes of interest extracted and analyzed were return of spontaneous circulation (ROSC) and survival to hospital discharge (SHD). Data was analyzed using R statistical software 4.2.0. Results were statistically significant if $P < 0.05$.

Research results

Thirteen studies (n = 17600) were included after deduplication, screening, and full-text analysis. Patients were on average 69 ± 17.5 years old, with 7022 (39.8%) female patients. Overall pooled ROSC was 37% among all studies. RTAVF-assisted CPR significantly improved ROSC in the case of IHCAs and improved chest compression depth. No significant

improvements were seen in ROSC in cases of OHCA, SHD, or compression rate.

Research conclusions

This meta-analysis found that RTAVF-assisted CPR increases ROSC in the setting of IHCA but has no significant effect on ROSC in the setting of OHCA or SHD. Consistent with previous manikin simulation studies, the meta-analysis found that RTAVF-assisted CPR results in improvements in both chest compression rate and depth.

Research perspectives

Cardiac arrest remains a leading cause of mortality with increasing prevalence. The findings of this study suggest that RTAVF-assisted CPR may improve ROSC in the setting of IHCAs but not in the setting of OHCA. Hospitals should prioritize implementing RTAVF devices in areas with the highest rates of IHCA rather than to paramedics or ambulances.

FOOTNOTES

Author contributions: Sood N, Sangari A, and Goyal A contributed equally to this work; Sood N and Sangari A designed the research study; Sood N, Sangari A, and Goyal A performed the research; Sood N performed the statistical analysis; Sood N, Sangari A, Goyal A, Sun C, Horinek M, Hauger JA, and Perry L analyzed the data and wrote the manuscript; Sood N, Sangari A, Goyal A, Sun C, Horinek M, Hauger JA, and Perry L reviewed the manuscript before submission; All authors have read and approved the final manuscript.

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Country/Territory of origin: United States

ORCID number: Nitish Sood 0000-0003-1516-0691; Anish Sangari 0000-0002-4388-7620; Arnav Goyal 0000-0002-6346-7690; Christina Sun 0009-0001-4701-4683; Madison Horinek 0009-0008-1748-2831.

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CASE REPORT

Systemic right ventricle complications in levo-transposition of the great arteries: A case report and review of literature

Mohamed Ramzi Almajed, Abdulla Almajed, Naoshin Khan, Mark S Obri, Karthikeyan Ananthasubramaniam

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Mohamed Ramzi Almajed, Naoshin Khan, Mark S Obri, Department of Internal Medicine, Henry Ford Hospital, Detroit, MI 48202, United States

Abdulla Almajed, College of Medicine and Medical Sciences, Arabian Gulf University, Manama 00000, Bahrain

Karthikeyan Ananthasubramaniam, Heart and Vascular Institute, Henry Ford West Bloomfield Hospital, West Bloomfield, MI 48322, United States

Corresponding author: Karthikeyan Ananthasubramaniam, FACC, MD, Staff Physician, Heart and Vascular Institute, Henry Ford West Bloomfield Hospital, 6777 W Maple, West Bloomfield, MI 48322, United States. kananth1@hfhs.org

Abstract

BACKGROUND

Congenitally corrected levo-transposition of the great arteries (L-TGA) is a congenital heart disease in which the ventricles and great arteries are transposed from their typical anatomy. In L-TGA, the double discordance, atrioventricular and ventriculoarterial, create an acyanotic milieu which allows patients to survive their early decades, however, progressive systemic right ventricle (sRV) dysfunction creates complications later in life. sRV dysfunction and remodeling predisposes patients to intracardiac thrombus (ICT) formation.

CASE SUMMARY

A 40-year-old male with L-TGA presented with symptoms of acute decompensated heart failure. In childhood, he had surgical repair of a ventricular septal defect. In adulthood, he developed sRV dysfunction, systemic tricuspid valve (sTV) regurgitation, and left-bundle branch block for which he underwent cardiac resynchronization therapy. Transthoracic echocardiogram showed a sRV ejection fraction of 40%, severe sTV regurgitation, and a newly identified sRV ICT. ICT was confirmed by ultrasound-enhancing agents and transesophageal echocardiography. Our patient was optimized with guideline-directed medical therapy and diuresis. Anticoagulation was achieved with a vitamin K antagonist (VKA) and he was later referred for evaluation by advanced heart failure and heart transplant services.

CONCLUSION

Anticoagulation with VKA is the mainstay of treatment in the absence of conclusive data supporting direct oral anticoagulant use in ICT in patients with

congenital heart disease. This case illustrates the natural history of L-TGA and highlights the importance of surveillance and monitoring with dedicated cardiac imaging to identify complications.

Key Words: Levo-transposition of the great arteries; Systemic right ventricle; Congenital heart disease; Intracardiac thrombus; Anticoagulation; Direct oral anticoagulant; Case report

Core Tip: Patients with congenital heart disease such as levo-transposition of the great arteries experience progressive cardiac dysfunction and remodeling which manifests as heart failure. This predisposes patients to the formation of intracardiac thrombus (ICT). We present a case of progressive systemic right ventricle (sRV) dysfunction resulting in an apical thrombus. Review of literature identified no cases of sRV thrombus making this one of the first reports. Guidelines do not exist for anticoagulation in patients with congenital heart disease and ICT. Therefore, clinical decisions are extrapolated from anticoagulation principles in patients without congenital heart disease. Considerations for direct oral anticoagulants in this population should be individualized and involve shared decision making.

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INTRODUCTION

Congenitally corrected transposition, or levo-transposition of the great arteries (L-TGA) is a rare congenital heart disease with an estimated prevalence of 0.4%-1.0% among patients with congenital heart disease[1,2]. The double discordance, atrioventricular and ventriculoarterial, creates an acyanotic milieu in which both pulmonary and systemic circulations exist and freely communicate[3]. This phenomenon, which is alluded to as "congenitally corrected", allows patients to survive their early decades with minimal cardiac complications. A large prospective survival study found that 95.5% of patients survive the first month of life; 72.7% survive to the age of 3 and this percentage of patients continues to live to the age of 15[1]. Survival data among adults is variable due to the presence of different associated cardiac lesions and the heterogenous surgical interventions these patients undergo[4]. Among all patients with L-TGA, a minority survive beyond the fifth decade of life due to cardiac complications[5]. In those who undergo surgical correction as children, the 10-year survival rate ranges from 60%-70%[6,7].

The natural history of L-TGA involves a wide spectrum of cardiac complications that manifest during early adulthood. The atypical anatomy and pathophysiologic circulation with the systemic right ventricle (sRV) in L-TGA predisposes patients to progressive sRV dysfunction, systemic tricuspid valve (sTV) regurgitation, and conduction defects including heart block[8]. Patients commonly present with clinical manifestations of heart failure as the lifetime prevalence is 34% in L-TGA as opposed to 1%-2% across the general population[9,10].

A large multicenter study found that by the age of 45, heart failure develops in 67% of patients with L-TGA and associated cardiac lesions whereas it develops in 25% of patients with L-TGA and no associated cardiac lesions[9]. Anatomical surgical repair, which aims to correct the double discordance by making the morphologic left ventricle the systemic ventricle and the morphologic right ventricle the pulmonary ventricle, is associated with higher survival rates and lower morbidity[11-13]. Physiologic surgical repair, which targets associated cardiac lesions without correcting the double discordance, is associated with higher rates of sRV dysfunction and mortality in adulthood[14].

We report a case of sRV thrombus in a patient with L-TGA who presented with acute decompensated heart failure (ADHF) and discuss the state of current literature regarding anticoagulation management.

CASE PRESENTATION

Chief complaints

A 40-year-old male with L-TGA presented to the hospital with ADHF. Upon review of systems, he had no chest pain, palpitations, lightheadedness, or syncope; he also denied cough, sputum production, or fever. He was not recently ill and had no sick contacts.

History of present illness

Symptoms started three-weeks prior to presentation with progressive shortness of breath on exertion, orthopnea, paroxysmal nocturnal dyspnea, and bilateral lower limb swelling. His symptoms were severe enough to make conversation difficult and limited his activities of daily living.

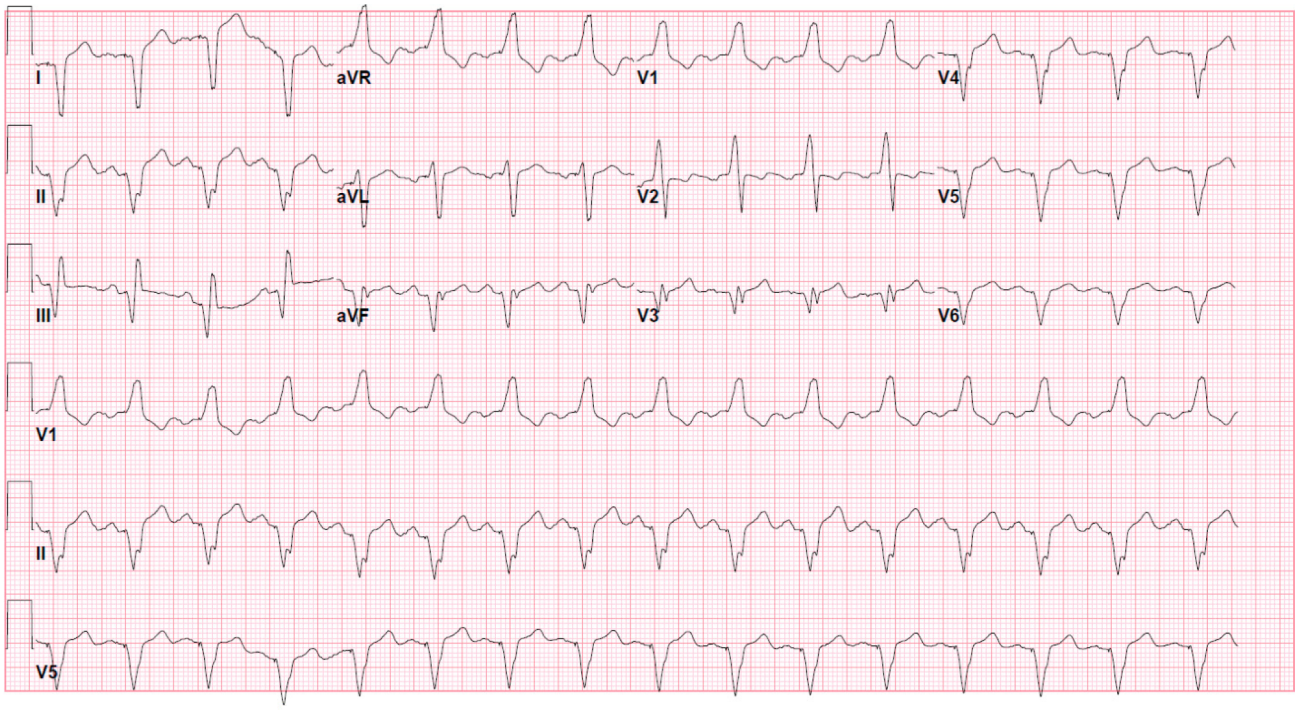

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Figure 1 Electrocardiogram showing an atrial-sensed ventricularly-paced rhythm without acute abnormalities.

History of past illness

His medical history was remarkable for L-TGA with an associated ventricular septal defect, he underwent physiologic surgical closure of the septal defect at three years of age. He was monitored by a pediatric cardiologist in childhood and early adulthood during; he remained free of cardiac symptoms during this time and was eventually lost to follow-up. At the age of thirty-five, he was hospitalized for ADHF and was found to have sRV dysfunction with severely reduced global systolic function and severe sTV regurgitation. He was also noted to have a progressive conduction disease as his previously known first degree atrioventricular block was replaced by a newly identified left-bundle branch block. He was medically managed for heart failure and underwent cardiac resynchronization therapy with biventricular pacemaker implantation. He followed with the advanced heart failure and transplant service but was then lost to follow-up for several years until this latest presentation to the hospital.

Personal and family history

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

Physical examination

During this presentation, the patient was tachycardic (108 beats per minute) and tachypneic (25-40 breaths per minute); blood pressure was 104/68 mmHg and he was not hypoxic on room air. Height was 168 cm and weight was 92 kg. Physical exam was positive for decreased bilateral breath sounds with mild crepitation. Jugular venous distension was present and pitting edema was noted in the bilateral lower limbs.

Laboratory examinations

Laboratory tests were notable for a brain natriuretic peptide of 472 pg/mL, high-sensitivity troponin of 16 ng/L, venous lactate of 1.2 mmol/L, and creatinine of 0.80 mg/dL (Table 1). Electrocardiogram showed an atrial-sensed ventricularly-paced rhythm without acute abnormalities (Figure 1).

Imaging examinations

Chest X-ray was remarkable for cardiomegaly with small bilateral pleural effusions (Figure 2). Chest pulmonary angiography was negative for pulmonary embolism, pericardial effusion, or pneumothorax (Figure 3). His cardiac anatomy of L-TGA is visualized on chest computed tomography (Figure 4).

FURTHER DIAGNOSTIC WORK-UP

Our patient was managed for ADHF with guideline-directed medical therapy including diuresis with intravenous

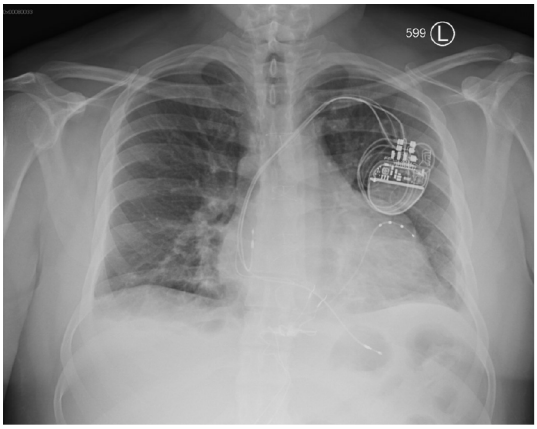

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Figure 2 Chest X-ray showing cardiomegaly with small bilateral pleural effusions with unremarkable pulmonary vasculature. Biventricular pacemaker is present at the right chest.

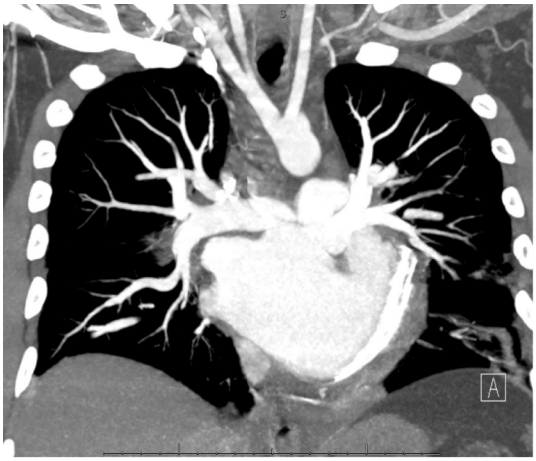

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Figure 3 Chest pulmonary angiography demonstrating a levo-transposition of the great arteries cardiac anatomy. Examination was negative for pulmonary embolism, pericardial effusion, or pneumothorax.

furosemide 40 mg once daily, oral metoprolol succinate 50 mg once daily, oral losartan 50 mg once daily, and oral dapagliflozin 10 mg daily. He had rapid clinical improvement with resolution of his symptoms and was transitioned to oral diuretic as needed.

Transthoracic echocardiogram obtained prior to discharge showed a mildly reduced global sRV ejection fraction of 40%, severe sAV regurgitation, and a newly identified apical thrombus in the sRV (Figures 5-8). Transesophageal echocardiogram confirmed this finding with visualization of a 2.07 cm by 1.43 cm well-circumscribed mass.

FINAL DIAGNOSIS

The final diagnosis was ADHF complicated by a systemic right ventricular thrombus in the setting of L-TGA.

TREATMENT

The presence of a sRV thrombus posed a dilemma given the limited literature on this topic. Our patient was anticoagulated with a vitamin K antagonist (VKA) and later referred for evaluation by advanced heart failure and heart transplant services.

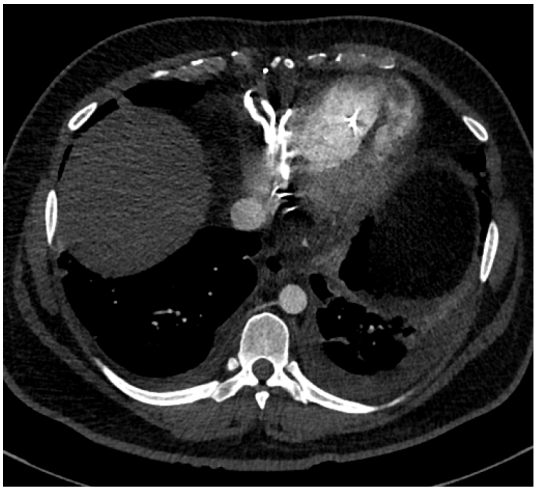

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Figure 4 Computed tomography of the chest detailing the patient's cardiac anatomy of levo-transposition of the great arteries. Venous circulation consists of the right atrium, left ventricle, and pulmonary artery. Systemic circulation consists of the pulmonary vein, left atrium, right ventricle, and aorta. Patient has a left-sided aortic arch with typical configuration.

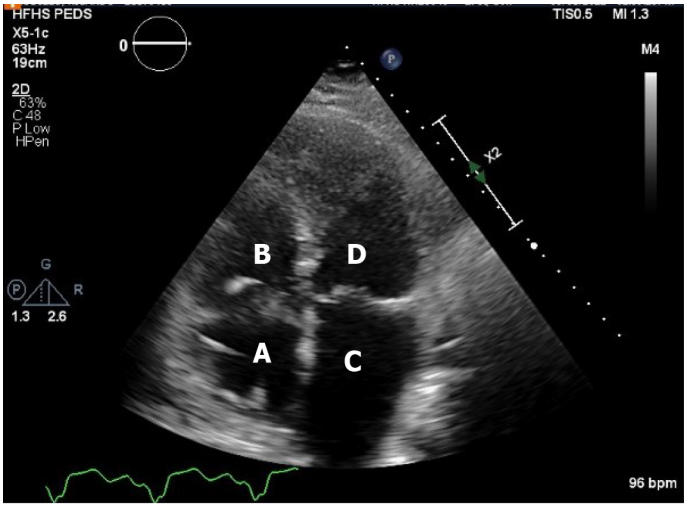

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Figure 5 Transthoracic echocardiography demonstrating the patient's classic levo-transposition of the great arteries anatomy. A: Right atrium; B: Venous left ventricle; C: Left atrium; D: Systemic right ventricle. Visualized is an apically displaced systemic tricuspid valve opening into systemic right ventricle.

OUTCOME AND FOLLOW-UP

On subsequent follow-up visits, our patient's symptoms of heart failure continued to improve with medical optimization and cardiac rehabilitation. Transthoracic echocardiogram was performed 5 mo after the index echocardiogram that identified the sRV thrombus; it demonstrated interim resolution of the sRV thrombus with improvement in sAV regurgitation and estimated pulmonary artery systolic pressure (Table 2). Cardiopulmonary exercise testing (CPX) provides objective measures of cardiovascular fitness and allows them to be tracked over time; our patient's peak oxygen uptake (peak VO_2), a strong prognostic indicator in heart failure, showed improvement (Table 3). Tables 2 and 3 allow readers to understand the natural history and progression of L-TGA in adults by demonstrating findings from CPX and echocardiography from the patient's initial visit in 2016 to the last known follow-up in 2022.

DISCUSSION

Intracardiac thrombus (ICT) involves the formation of a blood clot within the heart chambers. It typically occurs in the setting of acute myocardial infarction, left ventricular aneurysm, and cardiomyopathy with dilated chambers[15]. Pathophysiology of thrombus formation involves an interplay of prothrombotic state, tissue endothelial injury, and blood

Table 1 Pertinent laboratory investigations

Investigation	Patient result	Reference range
Sodium (mmol/L)	138	135-145
Potassium (mmol/L)	4.1	3.5-5.0
Chloride (mmol/L)	104	98-111
Carbon dioxide (mmol/L)	22	21-35
Blood urea nitrogen (mg/dL)	19	10-25
Creatinine (mg/dL)	0.80	< 1.28
Venous lactate (mmol/L)	1.2	< 2.1
High-sensitivity troponin (ng/L)	16	< 18
Brain natriuretic peptide (pg/mL)	472	< 50

Table 2 Cardiopulmonary exercise testing trend over time

Date of CPX	Peak HR (bpm)	Duration (min)	Peak VO_2 (ml/kig/min)	VO_2 at anerobic threshold (ml/kig/min)	Peak VO_2 (% of age predicted)	Peak RER	Actual METS achieved	VE-VO_2 slope	Peak double product	O_2 pulse rest	O_2 pulse peak
June 16, 2016	85 (46% predicted max)	12.0	18.2	13.5	47	1.28	5.2	28.0	11900	4	16
February 16, 2017	145 (78% predicted max)	13.5	22.4	16.4	59	1.23	6.4	25.6	22040	4	12
September 6, 2018	173 (94% predicted max)	10.5	20.1	-	58	1.20	5.7	28.8	25258	3	11
June 13, 2022	173 (96% predicted max)	9.5	19.5	-	56	1.17	5.6	22.8	21106	3	11

CPX: Cardiopulmonary exercise testing; HR: Heart rate; METS: Metabolic equivalent of task; RER: Respiratory exchange ratio; VE: Ventilatory efficiency.

stasis as described by Virchow's triad[16-18]. Systemic embolization of left-sided ICT results in clinical manifestations of stroke and transient ischemic attack, mesenteric ischemia and infarction, renal infarction, and acute limb ischemia. Pulmonary embolization of right-sided ICT results in pulmonary embolism. Diagnostic gold standard is identification of a thrombus on cardiac magnetic resonance imaging, although echocardiography with the use of echocardiographic contrast agents is a widely used initial modality[19].

ICT of the sRV is sparsely covered in the literature with limited data and guidelines available regarding the approach to management. Clinicians resort to extrapolating from practice standards for systemic left ventricular (sLV) thrombus. A review of literature identified no published case reports of sRV thrombus.

Current American and European guidelines for ICT in patients with structurally typical hearts are covered by class IIa, LOE C recommendations. Standard of care consists of anticoagulation with a VKA for 3-6 mo with an international normalized ratio (INR) target range of 2.0-3.0 followed by repeat imaging to assess for thrombus resolution[20,21]. Anticoagulation in this population has been shown to decrease major cardiovascular events including cerebral and systemic sequala of thrombus embolization[22]. Patients who have interval resolution of ICT on repeat imaging typically have anticoagulation discontinued, although some experts continue anticoagulation as a preventative measure in select patients with persistent and significant sLV wall hypokinesis due to the higher risk of recurrence[23]. In the absence of data on this population, patients with sRV dysfunction who develop right ventricular thrombus, such as our patient, can be similarly managed with anticoagulation using a VKA followed by repeat imaging.

Oral anticoagulant (OAC) agent of choice for the treatment of ICT has classically been a VKA as opposed to a direct OAC (DOAC), as early available literature demonstrated clinically significant difference in outcomes between the two agents. The largest study to date, a multicenter cohort study compared 514 patients with sLV thrombus and demonstrated a higher risk for stroke and systemic embolism with DOAC therapy compared to VKA which suggests against efficacy equivalence[24]. However, more recent data derived from small-scale randomized controlled trials, cohort studies, and case series report similar outcomes and support the use of DOAC for sLV thrombus which has led experts to adopt it as an off-label alternative[23,25-31]. A recent scientific statement by the American Heart Association carried out a comprehensive meta-analysis of all published studies that compared VKA and DOAC use in sLV thrombus, it

Table 3 Echocardiography trend over time

Date of study	Type of study	sRV parameters	sAV valve parameters	vLV parameters	vAV valve parameters	LA parameters	RA parameters	PA pressure (mmHg)	Other details
April 13, 2016	Transthoracic	Severely reduced global RV SF. Moderately enlarged RV	Severe Reg (sAV Reg Vmax 4.17 m/s)	Mildly reduced LV SF (41%). Restrictive pattern of diastolic filling (G3)	Moderate-Severe Reg (vAV Reg Vmax 346.72 cm/s)	Mildly dilated	Normal	51	Side by side great arteries, anterior aorta consistent with L Trasnpostion of the Great Arteries (congenitally corrected). S/P VSD repair with intact patch in basal septum
November 10, 2016	Transthoracic	Normal size and global systolic function (RV % FAC, A4C: 54.5%)	Moderate-Severe Reg (sAV Reg Vmax 5.28 m/s)	Mildly reduced LV SF (41%). Moderate hypokinesis of entire septal wall. Normal pattern of LV diastolic filling	Moderate Reg (vAV Reg Vmax 246.26 cm/s). Mildly thickened	Mildly dilated	Dilated	N/A	S/P BiV PPM
February 16, 2017	Transthoracic	Mildly reduced global RV SF (RV % FAC, A4C: 44.7%). RV wall thickness is moderately increased	Severe Reg (sAV Reg Vmax 5.00 m/s)	Mildly reduced LV SF (48%). Normal size	Mild-moderate Reg (vAV Reg Vmax 332.84 cm/s)	Moderately dilated	Normal	52	Interim mild improvement in systemic RV function but persistent systemic AV valve severe regurgitation with moderate pulmonary hypertension
February 27, 2017	Transthoracic	EF 54% (biplane)		EF 51% (A4C)					Limited study to quantify ventricular function
September 25, 2018	Transthoracic	Mild dysfunction. RV wall thickness is moderately increased	Moderate-Severe Reg (sAV Reg Vmax 4.74 m/s)	Mildly reduced LV SF (47%). Normal size	Mild Reg (vAV Reg Vmax 243.67 cm/s)	Mildly dilated	Normal	32	Overall no major changes noted compared to prior studies eccept for mild fluctuations in systemic RV function.
May 1, 2022	Transthoracic	Mildly reduced global RV SF (40%)	Moderate-Severe Reg (sAV Reg Vmax 4.71 m/s)	EF 45%	Moderate Reg (vAV Reg Vmax 328.85 cm/s)	Moderately dilated	Normal	46	There is a 1.3 cm × 1.3 cm, well circumscribed mass with echolucent center, seen apically, and likely represents a thrombus. Saline contrast bubble study -ve
May 4, 2022	Transesophageal	N/A	Moderate-Severe Reg (sAV Reg Vmax 2.46 m/s)	Moderately reduced LV SF (35%). Normal thickness	Moderate-Severe Reg (vAV Reg Vmax 383.31 cm/s)	N/A	N/A	N/A	Well-circumscribed mass measuring 2.07 cm × 1.43 cm in the morphologic RV/Systemic ventricle with central echolucency. Saline contrast bubble study was negative
September 30, 2022	Transthoracic	Mildly reduced global RV SF (40-45%). Mildly enlarged sRV	Mild-Mod Reg	Low-normal LV SF function	Moderate-Severe Reg (vAV Reg Vmax 228.43 cm/s)	Upper normal	Normal	24	Interim resolution of small systemic RV apical thrombus. Extensive trabeculation related to systemic RV hypertrophy noted

A4C: Apical 4 chamber; EF: Ejection fraction; FAC: Fractional area change; LA: Left atrium; LV: Left ventricle; PA: Pulmonary artery; PPM: Permanent pacemaker; RA: Right atrium; RV: Right ventricle; SAV: Systemic atrioventricular valve; SF: Systolic function; S/P: Status post; SRV: Systemic right ventricle; vAV: Venous atrioventricular valve; vLV: Venous left ventricle; VSD: Ventricular septal defect; N/A: Not applicable.

demonstrated no differences in therapeutic efficacy and safety; the statement concluded that the use of DOAC for sLV thrombus is a reasonable alternative to VKA[32]. This practice-changing statement is a yet to be reflected in society guidelines and adopted by other organizations.

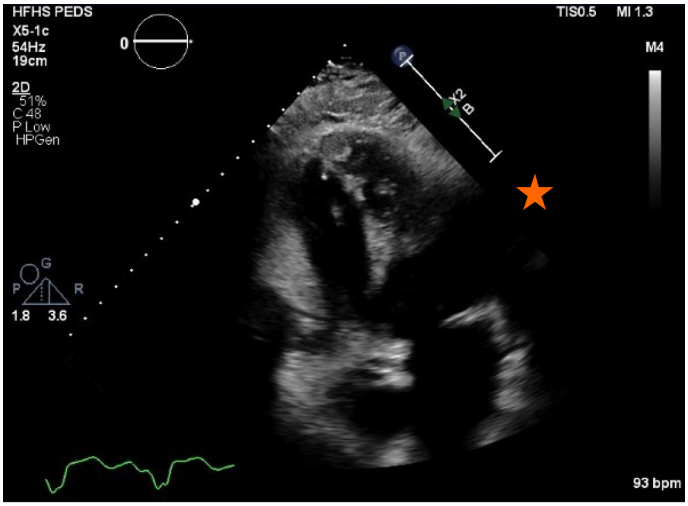

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Figure 6 Transthoracic echocardiography in apical four chamber view showing an systemic right ventricle apical thrombus. This view highlights the importance of visualizing the true apex of the systemic right ventricle as the thrombus is not seen in Figure 5 where the apex is foreshortened.

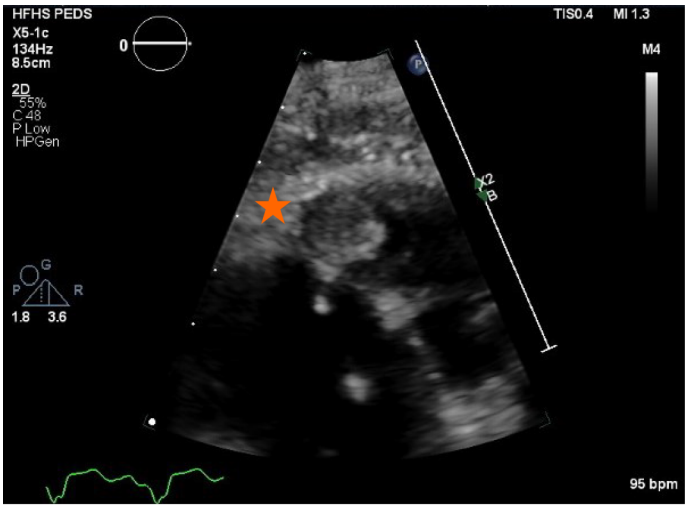

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Figure 7 Transthoracic echocardiography highlighting the systemic right ventricle apical thrombus. A 1.3 cm × 1.3 cm well circumscribed mass with an echolucent center.

Clinical consensus for the management of sRV thrombus in patients with congenital heart disease has been derived from the management principles of sLV thrombus in patients without congenital heart disease; it consists of OAC, interval repeat imaging, and case-by-case evaluation of anticoagulation duration. The advent of DOAC therapy has seen it become the OAC agent of choice for most anticoagulation indications which has raised questions regarding its applicability in the treatment of sRV thrombus in the setting of the limited data. The international NOTE registry evaluated 530 adults with congenital heart disease treated with OAC for various indications and concluded non-inferior efficacy and safety of DOAC use compared to VKA; subgroup analysis of 76 patients with sRV found high efficacy and safety rates[33, 34]. Another similar study of 215 patients with different congenital heart diseases quoted high efficacy rates but non-negligible bleeding risks[35]. However, a retrospective cohort review of a German nationwide registry of 6504 adults with congenital heart disease on OAC determined that DOAC use was associated with higher rates of thromboembolism, bleeding, major adverse cardiac events, and all-cause mortality compared to VKA[36]. The discrepancy of results between the former and latter studies raises concerns can be explained by the significant heterogeneity including differences in age and complexity of lesions in the latter's study population. In the absence of conclusive data supporting DOAC use in sRV thrombus in patients with congenital heart disease, VKA remains the OAC of choice.

Patients with sRV thrombus are typically younger than those with sLV thrombus given the earlier development of heart failure in the setting of congenital heart disease. The structural cardiac anomalies and abnormal hemodynamics are likely contributors to abnormal flow and blood stasis, this predisposes patients to thrombus formation. Younger patients are more likely to have educational and workplace commitments that cause time constraints. VKA therapy is particularly challenging in this population as dietary restrictions and frequent laboratory testing results in difficulty achieving and

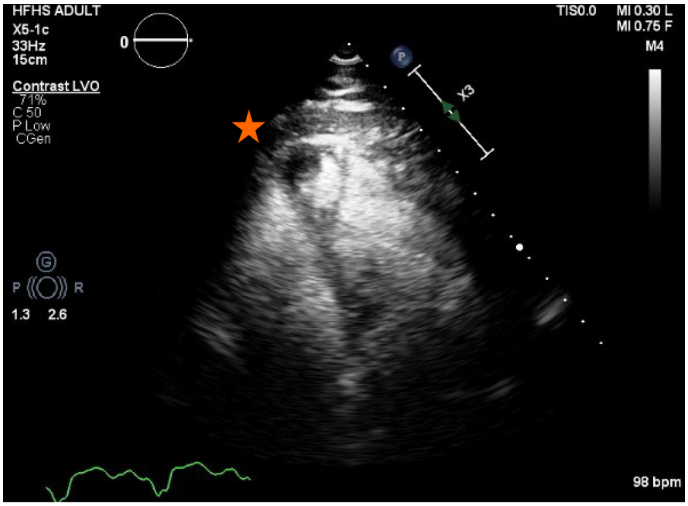

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Figure 8 Transthoracic echocardiography with intravenous contrast demarcating the apical thrombus in the systemic right ventricle.

maintaining therapeutic INR levels; lower time in therapeutic range is associated with higher risk of stroke in patients with sLV[37]. Further studies evaluating the safety and efficacy of DOAC agents in sRV thrombus are necessary.

CONCLUSION

Systemic right ventricular thrombus is a rare complication of congenital heart disease. We describe the first reported case of sRV thrombus in a patient with L-TGA who presented with ADHF. Management of this condition is driven by expert opinion and extrapolation of treatment principles from ICT in patients with structurally normal hearts.

In the absence of conclusive data supporting DOAC use in sRV thrombus in patients with congenital heart disease, VKA bridged with intravenous heparin or subcutaneous low-molecular weight heparin and remains the time-honored approach particularly in patients with recent large thrombi and in the setting of dysfunctional ventricles or slow flow states. Transitioning to a DOAC in these cases should be individualized to a patient characteristics and imaging features; it should involve shared decision making regarding limited and conflicting literature. This case illustrates the natural history of L-TGA and highlights the importance of surveillance and monitoring in this patient population to prevent and treat complications.

FOOTNOTES

Author contributions: Almajed MR, Almajed A, Khan N, Obri M, Ananthasubramaniam K contributed equally to this work; All authors evaluated the case, reviewed the literature, and wrote the manuscript; All authors have read and approve of the final manuscript.

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ORCID number: Mohamed Ramzi Almajed 0000-0001-6161-8494; Karthikeyan Ananthasubramaniam 0000-0001-5837-496X.

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