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Modern treatment of ventricular arrhythmias

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Modern treatment of ventricular arrhythmias

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Editorial: Modern treatment of ventricular arrhythmias

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Editorial on the Research Topic
Modern treatment of ventricular arrhythmias

Ventricular arrhythmias (VA) encompass a wide spectrum of clinical conditions, ranging from benign conditions, such as isolated ectopic beats in patients without structural heart disease, to life-threatening emergencies, such as electrical storms in patients with very advanced structural heart disease. Owing to the great variety of clinical conditions, pathophysiological mechanisms, and therapeutic approaches, VA have been the focus of a thriving body of literature.

A bibliometric analysis by Wang S. et al., presented in this special issue, shows that in the last 20 years, ~7,000 papers have been published about VA, with "catheter ablation" being one of the main topics. A large amount of research contributed to the latest update of European guidelines on VA and sudden death (1), where catheter ablation earned quite a high number of class I and IIa indications, thanks to technological advances driving important results of clinical trials.

Catheter ablation may also be curative in clinical situations that are challenging for both clinical and anatomical issues. Jiang et al. provide us with data from a pediatric cohort of 6 patients aged 8.4 years, ±2.6 years, presenting with VA originating from the moderator band of the right ventricle. This paper enriches this special issue, representing a good example of how catheter ablation could also be effective in this insidious condition typical of young patients with VA originating in a difficult to access anatomical area. Access to catheter ablation is often limited by patients' hemodynamic instability, either due to the high number of arrhythmias or to the extent of left ventricular dysfunction. In this regard, the use of the PAINESD score has been proposed to identify patients more likely to be at risk of hemodynamic collapse during the procedure (2). According to this score, which is measured from 0 to 36 points, patients scoring more than 17 points showed a 24% risk of acute hemodynamic decompensation. Additionally, acute hemodynamic decompensation during the procedure was associated with a worse prognosis in the short-term. For these patients a mechanical circulatory support may be useful to maintain a good perfusion during catheter ablation and also to help with procedure-related complications.

This is the rationale behind two papers in this special issue. The first is a review by Tavazzi et al. that explains the physiology, workflow, and indications for the clinical use of mechanical left ventricular assist devices to support electrophysiological procedures. The second paper, by Delmas et al. describes a new type of percutaneous, and rather inexpensive, left ventricle assist device (IVAC2L by PulseCath®; Amsterdam; The Netherlands) that can be connected to any standard and widely available intra-aortic balloon pump drive-console. This new device can provide a pulsatile flow by aspirating from the left ventricle during systole and injecting into the aorta during diastole. Available data on this new technology comes mainly from animal studies on cardiogenic shock and its use to support electrophysiological procedures, although potentially very promising, still needs to be evaluated.

Despite newer technology, an increase in operators' experience and the potential use of circulatory support, ablation's success rate is still suboptimal and/or ablation may not be available in every center 24 h a day. Therefore, there is a need for alternative treatments to address VA, such as during an electrical storm. In the European guidelines already mentioned (1), for the first time neuromodulation is considered an additional weapon to halt electrical storms. This is an emerging field and represents the biggest breakthrough in modern emergency treatment of VA. Wu et al. explore the mechanisms underlying neuromodulation by demonstrating that by reducing the activity of sympathetic nerves that connect to the heart, the optical activation of the dorsal horn of the thoracic cord can prevent VA in an animal ischemia/reperfusion model. These results encourage a larger use of neuromodulation and, among the different ways to block sympathetic activation, percutaneous stellate ganglion block (3) is by far the easiest and the fastest for patients with electrical storm whose indications and clinical use should be encouraged (4).

After the acute phase, the goal is to prevent recurrences. With this in mind, the central role of sympathetic activation has been well-recognized in arrhythmias of genetic origin, such as in long QT syndrome, where sympathetic cardiac denervation has been proven to be highly effective in preventing clinical recurrences (5). The use of cardiac sympathetic denervation has been recently extended to the treatment of VA in patients with structural heart disease with very good results (6, 7). Additionally, stereotactic radiotherapy of VA is an emerging technique for the treatment of VA recurrences that has shown promising results (8, 9).

In this special issue, we are proud to present the work by Huang et al. describing the first case of recurrent VA effectively treated with a single 12-Gy dose. The future of this technique might be characterized by the use of less energy with a high safety profile and by the probable use of other energy sources as particle therapies (10). Little has been discovered in recent years about new antiarrhythmic drugs. One of the papers in this collection is a review by Wang X. et al. on the pharmacological effects of Xin Su Ning, a multicomponent medicine derived from traditional Chinese medicine. Cellular electrophysiological studies have shown how this medicine is both a sodium and potassium channel regulator similar to amiodarone. It plays a myocardial protective role during the ischemia/reperfusion phase, and has been shown to reduce the number of ectopic beats in patients with viral myocarditis. In a three-arm randomized clinical trial involving more than 800 patients, it performed like mexiletine by reducing the number of premature ectopic beats.

Many patients with a history of VA and/or a structural heart disease are implanted with a cardioverter defibrillator. In these patients, supraventricular arrhythmias may be a potential cause of inappropriate shocks, so their treatment is essential. Zhang et al. report on their 10-year experience of 34 supraventricular arrhythmias ablations in 101 patients with hypertrophic cardiomyopathy. They found no recurrences after the ablation of arrhythmias other than atrial fibrillation (AF) and observed a AF-free survival rate of 87.5 and 49.5% at 1 and 7 years, respectively, after AF ablation. To reduce recurrences, it is essential to validate the effectiveness of ablation. Wei et al. demonstrate how adenosine administration could help to confirm the ablation success of an accessory pathway.

In summary, treating patients with VA is one of the greatest challenges of modern cardiology. In recent times, more sophisticated tools are becoming available for cardiologists and electrophysiologists to use against VA. Deciding how and when to use these resources, such as pharmacological therapy, implantable cardioverter defibrillator, catheter ablation, left ventricular assist devices, neuromodulation, and potentially, radiotherapy, is a difficult task. We believe that this Research Topic, which we had the privilege of editing, will provide enlightening and original insights into this fascinating topic.

Author contributions

SS and RR are responsible for conceptualizing, writing, and revising this paper. Both authors approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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Xin Su Ning—A Review of Basic and Clinical Pharmacology Integrated With Traditional Chinese Medicine Antiarrhythmic Theory

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Xin Su Ning (XSN) is a patented multicomponent medicine, which was certified in 2005 by the China State Food and Drug Administration to be produced pharmaceutically and to be used clinically. The XSN capsule was developed from an effective formula composed by Prof. Shuwen Ding of Shandong University of Traditional Chinese Medicine. Through more than 30 years of clinical observation, Prof. Ding concluded that XSN has a significant effect on arrhythmia with phlegm-heat heart-disturbed syndrome according to the traditional Chinese medicine (TCM) diagnosis. XSN, derived from a classical TCM formula Huanglian Wen Dan Decoction, is formulated with 11 Chinese herbal medicines to treat cardiac ventricular arrhythmia. Clinical evidence suggests that it is particularly efficacious for the arrhythmias induced by cardiac ischemia and viral myocarditis without obvious adverse reactions being reported. Cellular electrophysiological studies in ventricular myocytes revealed that XSN prolongs the duration and suppresses the amplitude of the action potential (AP), which is supported by the blockage of sodium and potassium channels indicating the characteristics of class I and III antiarrhythmic drugs. A recently reported double-blind, placebo-controlled, multicenter clinical trial of XSN enrolled 861 patients (ChiCTR-TRC-14004180) and showed that XSN significantly inhibited premature ventricular contraction (PVC). The cellular electrophysiological discoveries provided the mechanistic evidence for the clinical efficacy on inhibition of PVC by XSN as demonstrated in the clinical trial. These studies, for the first time, provided exclusive evidence that multicomponent TCM antiarrhythmic medicine can be evaluated using conventional research methods that have been used for antiarrhythmic drug discoveries for decades. We aimed to give a comprehensive review on XSN including its origin with the support of TCM theory, its pre-licensing clinical use and development, and its

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Abbreviations: AAD, anti-arrhythmic drugs; AECG, abdominal electrocardiograph; ALT, alanine aminotransferase; AP, action potential; APD, action potential duration; AST, aspartate aminotransferase; CI, confidence interval; ECG, electrocardiogram; ER, effective response; FAS, full analysis set; HPLC, high-performance liquid chromatography; HR, heart rate; I/R, ischemia-reperfusion; ISL, isoliquirigenin; LVDP, left ventricular diastolic pressure; MW, molecular weight; ODS chromatography, octadecyl silane column chromatography; PHHD, phlegm-heat heart-disturbed syndrome; PVC, premature ventricular contraction; RP-HPLC, reversed-phase high performance liquid chromatography; RPP, rate-pressure product; Scr, serum creatinine; SER, significantly effective response; TCM, traditional Chinese medicine; TER, total effective response; XSN, Xin Su Ning.

pharmacological and clinical study discoveries. The review will be summarized with the discoveries reported in a novel network pharmacological study that introduced a weight coefficient, which made it possible to evaluate the pharmacological properties of the TCM formula with regard to its formation based on TCM theory. Limitations regarding XSN's basic and clinical research and possible future studies are listed. We hope that the advances in how XSN was studied may offer useful guidance on how other TCM could be studied with respect to the integrity of the TCM formulas.

Keywords: antiarrhythmia, TCM theory, cellular electrophysiology, randomized clinical trial, pharmacology, Xin Su Ning, multicomponent medicine

1 INTRODUCTION

Chinese medicine has been practiced and developed for thousands of years along with the Chinese civilization. It is one of the well-developed traditional medicines in the world with comprehensive theories to guide the everyday practices; traditional Chinese medicine (TCM) accumulated rich medical knowledge in treating patients with sufficient efficacies. A distinguished feature of TCM is its multi-herbal, hence multicomponent nature, which is designed to act systematically to restore the tilted balance of the body evidenced with various diseases. The wide range of theories guiding TCM including holistic considerations, syndrome differentiation and treatment, and yin–yang theories are fundamental in deriving the most effective treatments.

Cardiac arrhythmia (arrhythmia) refers to the abnormal frequency, rhythm, origin, and conduction velocity or excitation order of the heart impulses. Arrhythmia is a common cardiovascular disease, which has serious health consequences. Arrhythmia can be caused by many cardiovascular diseases such as coronary heart disease, rheumatic heart disease, hypertensive heart disease, and viral myocarditis, and it can also be caused by the side effects of drugs. Treating arrhythmia with currently prescribed drugs or radiofrequency ablation all have limitations, particularly in elderly patients, who have increased risks of hypertension, diabetes mellitus, and coronary heart diseases. In addition, many antiarrhythmic drugs may inhibit certain cardiac functions and actually cause further arrhythmia, or the proarrhythmic effect, as side effects, which limits the clinical use of existing drug treatments due to poor tolerance and compliance (Huang and Wang, 2004; Li, 2011).

Amiodarone and other class I and III antiarrhythmic drugs are commonly prescribed to treat arrhythmia. Amiodarone, whilst widely considered effective in treating supraventricular and ventricular tachyarrhythmia, presents significant side effects. Chronic use of amiodarone causes serious adverse effects to several organs and tissue types, including the heart. Cardiac adverse reactions may include impairment to sinus beat formation and conduction and inducing significant bradycardia, with disproportionate impact on patients with pre-existing conditions, leading to dangerous polymorphic ventricular arrhythmia or torsade de pointes (Colunga Biancatelli et al., 2019). Amongst other side effects, ocular alterations are the most frequent with up to 98% of patients experiencing corneal microdeposits. The adverse reactions of other class I and III antiarrhythmic drugs are also well studied and documented due to decades of use (Caron and Libersa, 1997; Ji et al., 2017). These illustrate a clear demand for effective drugs with better safety profiles for chronic use.

Treating arrhythmia using TCM may have potential advantages. The XSN capsule is derived from an effective formula composed and used by Prof. Shuwen Ding of Shandong University of Traditional Chinese Medicine, which was built on decades of accumulation of knowledge and practical experience in treating arrhythmia. Prior to approval by a regulatory authority, XSN was used as a physician-prescribed decoction by Prof. Ding for over 3 decades, and it was certified in 2005 by the China State Food and Drug Administration to be produced pharmaceutically and to be used clinically. XSN is the first TCM approved for the treatment of arrhythmia with specific characteristics according to Chinese medicine theories, which were termed phlegm-heat heart-disturbed (PHHD) syndrome. XSN received National New Medicine Certification (Z20050131) and has been included in the Chinese Pharmacopoeia (2015 Edition). Based on the pathogenesis of PHHD syndrome arrhythmia (tachyarrhythmia), XSN was developed from Huanglian Wen Dan Decoction recorded in "Liu Yin Tiao Bian" written by Tingzhen Lu in the Qing dynasty, with the addition of Qinghao and Changshan, which are known for their anti-malarial and anti-arrhythmia properties (Ding et al., 2018).

The formula of XSN is composed of the herbs in proportion as follows: 300–360g Coptidis Rhizoma (Huanglian, *Coptis chinensis* Franch.), 225–265 g Pinelliae Rhizoma (Banxia, *Pinellia ternata* [Thunb.] Makino), 225–265 g Poria (Fuling, *Poria cocos* [Schw.] Wolf), 150–180 g Aurantii Fructus Immaturus (Zhishi, *Citrus aurantium* L.), 225–265 g Dichroae Radix (Changshan, *Dichroa febrifuga* Lour.), 438-50 g Nelumbinis Plumula (Lianzixin, *Nelumbo nucifera* Gaertn.), 225–265 g Sophorae flavescentis Radix (Kushen, *Sophora flavescens* Ait.), 225–265 g Artemisiae annuae Herba (Qinghao, *Artemisia annua* L.), 150–180 g Ginseng Radix et Rhizoma (Renshen, *Panax ginseng* C. A. Mey.), 225–265 g Ophiopogonis Radix (Maidong, *Ophiopogon japonicus* (L.f) Ker Gawl.), and 150–180 g Nardostachyos Radix et Rhizoma (Gancao, *Glycyrrhiza uralensis* Fisch.) (Wang, 2005).

1.1 Aim of the Review

We aim to present a comprehensive review of XSN that would answer the following questions:

1) The development history of XSN as an antiarrhythmic TCM
2) What are the pharmacological properties of XSN as a multicomponent antiarrhythmic medicine?
3) Why does XSN have to be multi-herbal and formulated with the 11 particular herbs?
4) What are the TCM theories that guide the formation of the XSN formula?
5) What are the pharmacological properties of the individual herbs that formulated XSN?
6) What are the pharmacological properties of some of the compounds isolated from these herbs?
7) Why does XSN not display proarrhythmic reactions while effectively treating cardiac arrythmias?
8) The limitation of the available basic and clinical studies of XSN and possible further studies

2 PHARMACOLOGICAL AND TOXICOLOGICAL STUDIES OF XIN SU NING

2.1 Pre-Licensing Pharmacodynamic Studies

These data were filed by the China State Food and Drug Administration for approval of production and clinical use of XSN in China (Wang, 2005).

The pre-licensing pharmacological studies showed that XSN significantly suppressed cardiac arrhythmia induced by the chemical reagents matrin, calcium chloride, chloroform, and isoproterenol. In cardiac ischemia–induced arrhythmia, XSN can delay the onset of ventricular arrhythmia and shorten the time of arrhythmia. XSN could also lower the total cholesterol level of normal rats and reduce blood viscosity, hematocrit value, and fibrinogen.

1) Improve hemorheology

The high (2.56 g/kg/d), medium (1.03 g/kg/d), and low (0.51 g/kg/d) dose of XSN can significantly reduce the blood lipid of rats and can improve the hemorheology index of rats ($p < 0.01$).

2) Anti-ischemia–induced arrhythmia

The high, medium, and low dose groups of XSN can significantly reduce the incidence of Q wave, VP, and VT induced by coronary artery ligation ($p < 0.05$).

In addition, XSN can also prolong the incubation period of arrhythmia ($p < 0.05$) and shorten the duration of arrhythmia ($p < 0.05$), suggesting that it has an obvious inhibition effect on arrhythmia induced by coronary artery ligation in rats.

3) Protect the heart from I/R-induced damage

High, medium, and low dose groups of XSN significantly prolonged the incubation period of arrhythmia induced by myocardial ischemia-reperfusion (I/R) ($p < 0.05$), shortened the duration of arrhythmia ($p < 0.05$), reduced the incidence and mortality of VT and VF, and reduced the degree of ST elevation ($p < 0.05$).

2.2 Pre-Registration Toxicological Studies

1) Acute toxicity test

The maximum dosage of XSN was 43.74 g/kg/d in mice, which was about 500 times the daily dosage of clinical adults (Wang, 2005). Histopathological examination showed no pathological changes related to administration in the heart, liver, spleen, lung, kidney, and adrenal gland. No abnormal changes in weight, hematology, and blood biochemical indexes were found in the recovery period.

2) Long-term toxicity test

The long-term toxicity test was carried out in rats for 90 days, followed by recovery for 20 days. The dose administrated was 5.25 g/kg/d, which was about 60 times the daily dosage for clinical adults. Histopathological examination in the heart, liver, spleen, lung, kidney, and adrenal gland showed no pathological changes related to the long-term administration of XSN. No abnormal changes in weight, hematology, and blood biochemical indexes were found in the recovery period.

2.3 The Cellular Electrophysiological Properties of Xin Su Ning

Studies using patch clamp electrophysiological methods to study the effects of XSN on action potential (AP) and ionic channels of isolated cardiac myocytes have discovered, as illustrated in **Figure 1**, that XSN is not only a potassium channel regulator but also a sodium channel blocker (Ma et al., 2017; Wang et al., 2018). It could prolong the duration and suppress the amplitude of AP, indicating the inhibition of sodium and potassium channels, hence inhibiting the reentrant arrhythmia by increasing the effective refractory period. The effect of XSN is similar to that of amiodarone and other class I and III antiarrhythmic drugs (Ma et al., 2020).

The blockade effects of XSN on sodium and potassium channels of the isolated rat cardiac ventricular myocytes were further observed in expressed human hNav1.5 and hERG channels (Wang et al., 2019c).

2.4 The Effect of XSN on the Myocardium Conduction Properties of Human iPSC-Derived 2D Myocardial Tissue Studied in a Multi-Electrode Array System

It was recently reported that XSN significantly reduced the velocity of the myocardial conduction at concentrations higher than 0.4 g/L and significantly suppressed the amplitude of the initial phase of field action potential (FAP) conducted by Na^+. At 1.6 g/L, XSN prolonged the duration of Na^+ conduction, and at concentrations higher than 0.1 g/L, inhibited the maximum

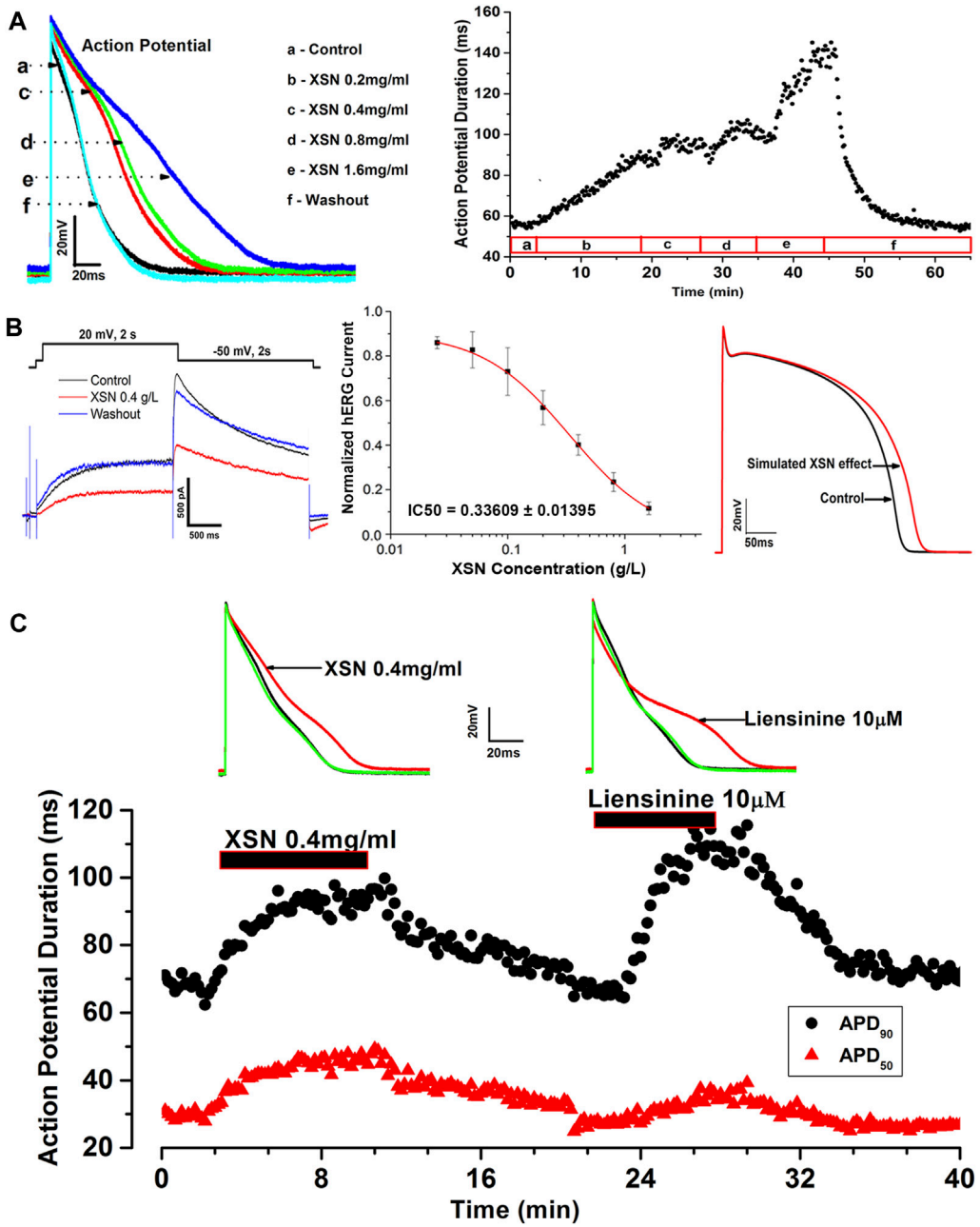

FIGURE 1 | Effect of XSN and liensinine on APD of cardiac myocytes and computational simulation of human AP. **(A)** Data plot shows the concentration-dependent and reversible effect of XSN on APD, from which the superimposed AP traces were extracted to show the effect of XSN at various concentrations indicated by the keys. **(B)** XSN reversibly blocks the hERG channel in a dose-dependent manner with an IC_{50} of 0.34 mg/ml as the keys indicated, which was used to simulate the effect of XSN on human AP. **(C)** Shows the comparative effect of XSN and liensinine on APD (Ma et al., 2020).

velocity of Na^+ conduction. The myocardial beating interval was significantly prolonged, and the rate of the beating also decreased under all the concentrations of XSN applied. Furthermore, XSN also prolonged FAP duration even at the lowest concentration applied (0.025 g/L) and decreased the FAP amplitude significantly at the highest concentration studied (Wang et al., 2021).

2.5 Xin Su Ning Protects the Heart From I/R-Induced Injury

The cardio-protective effect of XSN in I/R-induced injury in the isolated heart was evaluated. As demonstrated in **Figure 2**, XSN produced significant recovery of left ventricular diastolic pressure (LVDP) in comparation with the control. XSN's role in improving cardiac systolic function on the I/R injured rat

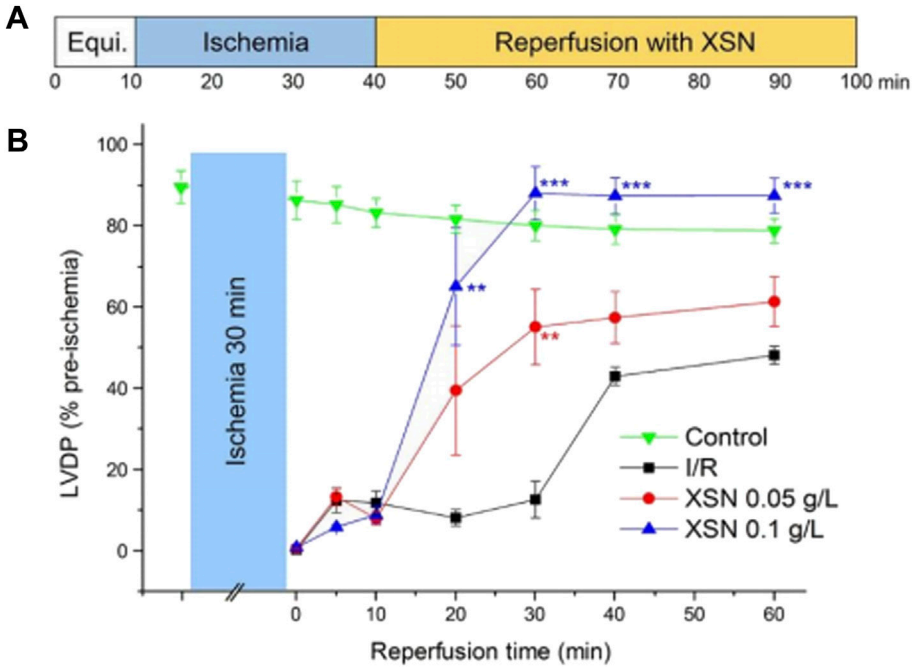

FIGURE 2 | Protective effect of XSN on ischemia/reperfusion-induced injury of the heart. **(A)** Protocol of contractile function of an I/R perfused rat heart; **(B)** % rate of LVDP of rat hearts after XSN treatment versus control (Wang et al., 2018).

heart was achieved by increasing LVDP, rate-pressure product (RPP), max dP/dt, and min dP/dt. These protective effects may contribute to the antiarrhythmic effect of XSN (Wang et al., 2018).

2.6 The Effect of the Active Components of Xin Su Ning on hERG and hNav1.5 Channels

Several isolated components of XSN were studied to identify the likely contributions that they may make to the antiarrhythmic action of XSN. Among the components tested, liensinine, from Lianzixin (*Plumula nelumbinis*), one of the 11 herbs in XSN, was speculated to be an important component that affects the electrophysiological properties of cardiac myocytes. However, liensinine showed APD prolongation action with a different repolarization profile than XSN; liensinine had effects on APD_{90} only, whereas XSN impacted both APD_{90} and APD_{50} significantly (**Figure 1B**), which illustrated well the complexity of XSN as a multicomponent medicine in exerting its clinical efficacy (Ma et al., 2020).

The effect of liquiritigenin and isoliquirigenin, compounds in GanCao (one of the 11 herbs formulating XSN), were reported to be active antiarrhythmic components: isoliquirigenin blocks both hERG and Nav1.5 channels, while liquiritigenin blocks Nav1.5 channels, which indicates that both compounds would contribute to the class I and III antiarrhythmic action of XSN (Wang et al., 2019a; Sweeney et al., 2019; Mujahid et al., 2020).

3 CLINICAL STUDIES OF XIN SU NING

3.1 Pre-Registration Clinical Studies

Based on clinical study authorization number (1999) ZL-12 issued by the China State Drug Administration, XSN capsule was used to treat 300 cases of premature ventricular contraction with PHHD syndrome from August 2000 to January 2003 by the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine, Shandong Provincial Hospital, Qilu Hospital of Shandong University, and Shaanxi Provincial Hospital of Traditional Chinese Medicine. The comparator medicine used in the study was Xin Lv Ning tablets.

The total effective rate on premature ventricular contraction (PVC) with the XSN group was 53.7% compared with the control group's rate of 42.9% ($p = 0.044$). The total effective rate in symptomatic relief with the XSN group was 66.0% compared with the control group's rate of 54.3% ($p = 0.024$). The XSN group also significantly relieved the symptoms of palpitation ($p < 0.05$). The onset time of treatment of chest tightness, insomnia, and dreaminess in the XSN group was shorter than that in the control group ($p < 0.05$). The results of safety studies showed that the XSN capsule had no adverse effects on blood, urine, stool routine, and heart, liver, and kidney functions, which indicated that XSN is an effective and safe medicine for treating PVC arrhythmia in humans.

3.2 Other Clinical Case Studies

In 2011, a study reported a total effective rate of 88.5% in 26 cases of frequent PVCs treated with XSN (Lin et al., 2011). In another

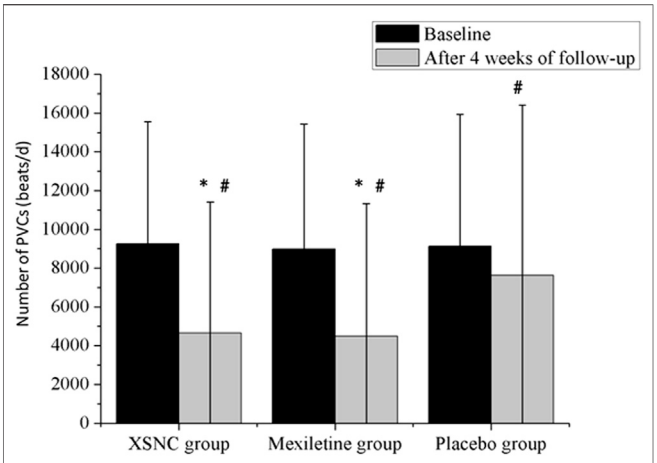

FIGURE 3 | Total number of PVCs from baseline to 4 weeks after treatment in the trial groups. PVCs, premature ventricular contractions. #p < 0.001 vs. baseline, *p < 0.001 vs. the placebo group. Continuous data were presented as the mean ± standard deviation (SD). A smaller number of PVCs were observed after a 4-week treatment than at baseline, in the XSN group (4645.89 ± 6,772.17 vs. 9,250.56 ± 6,297.37 beats/d, p < 0.0001), the mexiletine group (4480.37 ± 6,851.37 vs. 8,983.23 ± 6,439.02 beats/d, p < 0.0001), and the placebo group (7,617.16 ± 8,794.66 vs. 9,129.63 ± 6,796.15 beats/d, p < 0.0001). In addition, compared to the placebo group, the XSN group and the mexiletine group had a statistically significant change in the total PVC frequency after the 4-week treatment period (p < 0.0001) (Ma et al., 2020).

study in 2008, the efficacy evaluation of XSN in the treatment of 30 viral myocarditis cases was reported; the results showed that the total effective rate was 83%, which was significantly more than that of the control group (p < 0.05) (Wang and Lu, 2008). In addition, the study published in 2000 by the Affiliated Hospital of Shandong University of Traditional Chinese Medicine evaluated XSN in a 90-patient trial (Yuan and Zhou, 2000). The clinical curative effects of XSN were observed and compared with those of propafenone and atenoloum (PRO.&ATL.). The study demonstrated an overall efficacy of 85% with XSN in treating arrhythmia, similar to that demonstrated in the PRO.&ATL groups. Besides, the XSN group had a better effect on improving the overall conditions in patients with PVCs complicated with coronary heart disease, but PRO.&ATL groups did not show the same therapeutic benefit. XSN displayed clinical effects on atrial and ventricular premature beats, atrial fibrillation, paroxysmal supraventricular tachycardia, and sinus tachycardia, and the curative effect on mild and moderate arrhythmias was better than that on severe arrhythmias. At the same time, it can also reduce the blood lipid level of some patients with hyperlipidemia, improve their hemorheological indexes, and change the state of coronary insufficiency and cardiac function in some patients (Yuan and Zhou, 2000).

3.3 Randomized Controlled Trial

The results of a three-armed, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial of XSN were reported recently (Ma et al., 2020). This trial was registered in the Chinese Clinical Trial Register Center (ChiCTR-TRC-14004180) and ran between April 2014 and January 2016 across 39 hospitals in mainland China. The study enrolled 861 eligible patients randomly assigned in a ratio of 2:2:1 to receive XSN (XSN four capsules, 0.48 g per capsule plus simulated mexiletine two pills, n = 343), mexiletine (mexiletine two pills, 50 mg per pill plus simulated XSN four capsules, n = 345), or the placebo (simulated XSN four capsules plus simulated mexiletine two pills, n = 173). Each participant took the treatments three times per day for 4 weeks. At the end, a total of 779 (90.48%) patients (307 in the XSN group, 320 in the mexiletine group, and 173 in the placebo group) completed the 4-week follow-up and were included in the final efficacy analyses (Zhai et al., 2017).

The PVC numbers at baseline were not significantly different between the XSN group, the mexiletine group, and the placebo group (p = 0.5886). In comparison to the placebo group, the XSN group and the mexiletine group both had a statistically significant change in the total PVC frequency (p < 0.0001, **Figure 3**).

In the study, it was found that XSN improved the overall counts of PVCs and PVC-related symptoms in a pre- and posttreatment analysis, and its efficacy was noninferior to that of mexiletine, a class Ib conventional anti-arrhythmic drug (AAD), and was significantly superior to that of the placebo. In the safety set analysis, adverse events were reported in 50 patients, including 18 in the XSN group, 21 in the mexiletine group, and 11 in the placebo group (p = 0.8430). Neither death nor serious adverse events related to XSN were reported during the study. Compared with the placebo group, the administration of XSN had no significant impact on the liver, kidney functions, and the ECG parameters (**Table 1**). The result from this randomized controlled trial aligns with more than 30 years of clinical use of XSN in China (Ma et al., 2020).

4 THE MEASURABLE CHEMICAL COMPOUNDS IN XIN SU NING

The main chemical compositions contained in the XSN capsule were studied by silica gel column chromatography, octadecyl silane (ODS) column chromatography, Sephadex LH-20 column chromatography, reversed-phase high performance liquid chromatography (RP-HPLC), and other chromatographic separation methods (Zhang, 2017a). Overall, 22 monomer compositions were separated, and their structures were identified. These compounds are berberine, daucosterol, sophora flavescens chalcone, coptisine, dihydroberberine, dihydrocoptisine, dihydrocoptisine, hesperidin, jateorhizine, isoliquiritigenin, Kushenol O, sophocarpidine, sophocarpine, coumarin, N-trans-feruloyltyramine, liquiritigenin, nobiletin, hesperetin, 8-oxyberberrubine, 4-(2-hydroxy-vinyl)-benzene-1,2-diol, 5-demethenyl nobiletin, scopoletin, and β-sito-sterol. Among them, five chemical compositions are from Huanglian, four from Zhishi, four from Kushen, two from Gancao, and the remaining seven from other medicinal materials.

As shown in **Figure 4**, there were 29 common peaks in different batches of the XSN capsule, and 12 peaks were identified (Zhang et al., 2017). The identified peaks were peak

TABLE 1 | Laboratory evaluations and ECG parameter changes between the two groups, medium (range) (Ma et al., 2020).

Variables	XSN group		Mexiletine group		Placebo group	
	0 weeks	4 weeks	0 weeks	4 weeks	0 weeks	4 weeks
Laboratory tests						
ALT, IU/L	33 (4–41)	21 (5–40)	38 (9–50)	32 (7–48)	21 (8–42)	22 (8–43)
AST, IU/L	27 (4–40)	18 (21–72)	21 (5–40)	18 (17–59)	20 (6–45)	23 (7–53)
Scr, mmol/L	71 (62–106)	69 (60–106)	60 (53–97)	61 (44–105)	51 (44–104)	56 (44–106)
ECG parameters						
QT interval, ms	402 (280–464)	399.5 (297–442)	405 (297–493)	406 (318–483)	397 (326–492)	402 (337–487)
Mean HR, bpm	73 (67–103)	73 (67–96)	74 (67–89)	73 (68–89)	72 (67–99)	72 (64–93)
Maximum HR, bpm	114 (102–127)	115 (101–127)	114 (103–128)	114 (102–126)	112 (100–124)	114 (102–126)
Minimum HR, bpm	51 (47–75)	51 (46–86)	51 (47–75)	52 (47–71)	52 (36–78)	51 (36–75)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine; ECG, electrocardiogram; HR, heart rate; XSN, Xin Su Ning.

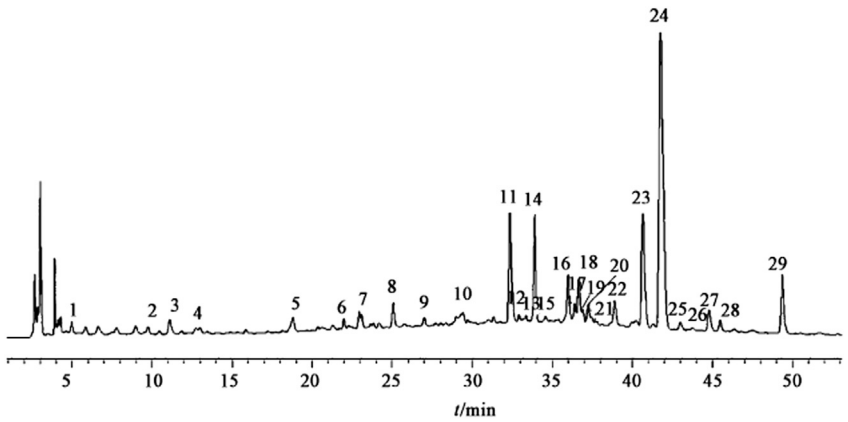

FIGURE 4 | HPLC fingerprint and identification of peaks of XSN capsules. (Zhang et al., 2017).

No. 2 (sophoridine), peak No. 14 (scopoletin), peak No. 11 (scopoletin), peak No. 1 (hesperidin), peak No. 14 (neohesperidin), peak No. 16 (epiberberine), peak No. 17 (Dihydroberberine), peak No. 18 (jatrorrhizine), peak No. 19 (berberine), peak No. 21 (Dihydroberberine), peak No. 23 (palmatine), peak No. 24 (berberine), and peak No. 29 (glycyrrhizic acid). Among them, peaks 5, 8, 16, 17, 19, 21, 22, 23, 24, 25, and 27 belong to Huanglian, peaks 10, 11, and 14 belong to Zhishi, peaks 20, 28, and 29 belong to Gancao, peak 1 belongs to Banxia, peak 3 belongs to ginseng, peak 9 belongs to Qinghao, peak 26 belongs to Changshan, peak 2 belongs to Kushen, peak 4 may come from Banxia, Qinghao, Ginseng, and Gancao, peak 5 may come from Huanglian, Changshan, and Qinghao, peak 6 can be from Changshan or Lianzixin, peak 7 can be from Huanglian or Zhishi, and peak 12 can be from Kushen or Maidong. The analytical method of HPLC fingerprint is stable and reliable with fine repeatability, which provides a reference for study on a material basis and quality control of the XSN capsule.

In another study, ultrahigh-pressure liquid chromatography coupled with linear ion trap-Orbitrap tandem mass spectrometry (UHPLC-LTQ-Orbitrap) was used on XSN. 41 compounds were identified that may contribute to the therapeutic effects of XSN. These data showed that berberine, palmatine, scopoletin, liquiritigenin, naringenin, formononetin, nobiletin, tangeretin, 5-demethylnobiletin, kushenol E, and kurarinone might function as candidate markers for qualitative evaluation of XSN (Guo et al., 2018).

5 PHARMACOLOGY NETWORK STUDY OF XIN SU NING

TCM is one of the well-known traditional medicines used and developed through a thousand years of human history with the distinguished feature of a multi-herbal/multicomponent nature, which has been a major obstacle to evaluating its clinical efficacy using conventional pharmacological methods. Along with the development of computational simulation of biological activities, computational network pharmacology opens up possibilities for predicting the pharmacological actions of multicomponent TCM. However, the network pharmacology approach has been taking all the components in a formula in equal weighting, ignoring the relative proportion of each component in the analysis. Since the relative proportion of each herb is critical in terms of clinical outcome guided by the herbal formulation theory of Chinese

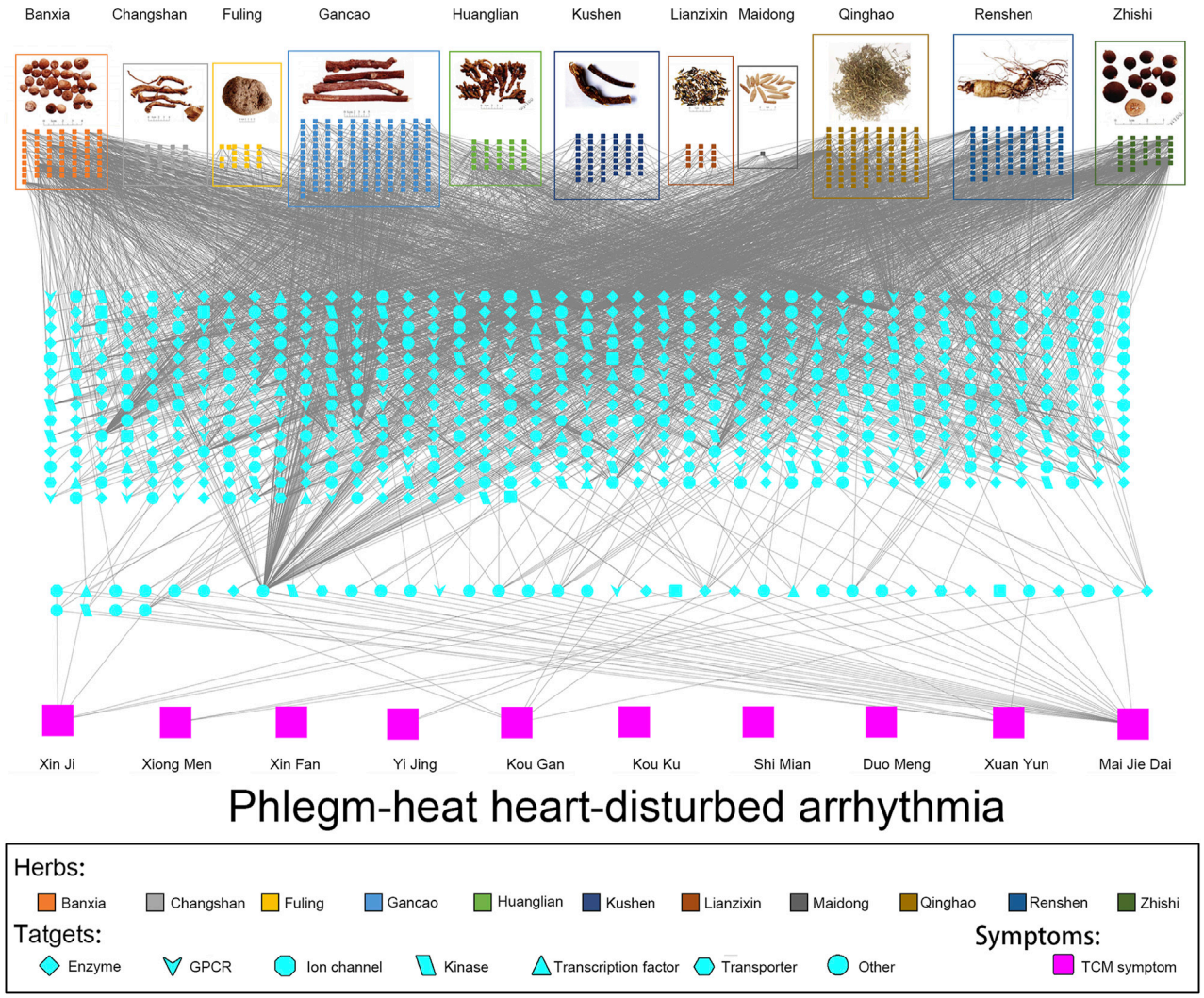

FIGURE 5 | Panoramagram of the pharmacological mechanism of XSN for treating PHHD arrhythmia. **(A)** 11 herbs that formulated XSN are shown in the box with different colors, and the components of each herb are shown in small squares with the same color as their source herb. **(B)** Target spectrum of XSN. All the targets were corresponding to the component in panel A; the 41 targets showed in the dash line box in the bottom are the overlapping target set between the XSN target spectrum and the PHHD-arrhythmia target spectrum. Targets were shown in different shapes according to the classifications as indicated in the keys. **(C)** Arrhythmia with Zheng and relative TCM symptoms. Ten TCM symptoms of PHHD arrhythmia were represented by large pink squares in the bottom panel (Wang et al., 2019b).

medicine, a novel approach which takes into account the relative proportion of different herbs has been introduced to evaluate the potential pathways of the antiarrhythmic TCM XSN. This was done by introducing a novel parameter, a weight coefficient, to calculate the concentrations of all the measurable compounds in XSN. This allowed for the creation of a more realistic concentration-related pharmacological panorama linked with the syndromes of PHHD arrhythmia (Wang et al., 2019b).

In this study, a total of 963 monomer components from the 11 herbs of XSN were collected from Chemical Components of Source Plants in Traditional Chinese Medicine and the TCMSP database. Statistics relating to the chemical properties found in the 11 herbs and XSN's target spectrum were summarized. The contents of 47 of the 963 components were quantified, with the rest set to the lowest value in analysis.

The pharmaconetwork analysis also reviewed the relationship between Zheng (TCM syndrome), which is represented by the series of characteristics with clinical manifestations and symptoms and all target genes. There are 10 TCM symptoms of arrhythmia relating to PHHD: Xin Ji (palpitations), Xiong Men (respiratory distress), Xin Fan (boredom), Yi Jing (panic attack), Kou Gan (xerostomia), Kou Ku (bitter taste in the mouth, not bad breath in the mouth), Shi Mian (insomnia), Duo Meng (dreaminess), Xuan Yun (vertigo), and Mai Jie Dai (includes

two types of pulses; Jie Mai is knotted or bound pulse, which is slow and relaxed and stops at irregular intervals. Dai Mai means the pulse displays regularly intermittent abnormality). Hence, the panoramic view of the integrative pharmacological mechanism of XSN is interpreted in **Figure 5**. This panoramagram elaborates the relationships between the XSN formula, herbs, components, targets, symptoms, and PHHD arrhythmia; the pharmacological network consisted of 963 components, 618 targets, and 10 symptoms.

The evidence obtained so far demonstrated that XSN exerts an impact on PHHD syndrome arrhythmia through both fast-acting and long-acting mechanisms. On the fast-acting mechanism, XSN regulates multiple ion channels. On the long-acting mechanism, XSN protects the heart from ischemia reperfusion injury, inhibits the apoptosis of cardiomyocytes, and improves glucose and lipid metabolism.

6 THEORIES OF TCM AND PRINCIPLES OF XIN SU NING FORMULATION

6.1 Discussion of TCM Theories on Tachyarrhythmia

Even though the term arrhythmia was not coined in ancient TCM books, symptoms of arrhythmia were widely recorded. The earliest descriptions of arrhythmia symptoms could be traced to "Su Wen: Zhi Zheng Yao Da Lun" and "Ling Shu: Ben Shen" and included the words "Palpitation with emptiness," "Fear and anxious," and "The heart meridian does not flow smoothly, causing a feeling of anxiousness and abnormal heartbeat." "Su Wen: Ping Ren Qi Xiang Lun" said "Pulse beats irregularly will cause death," which was the earliest explanation of arrhythmia-induced sudden death. Although the exact date is unknown, it is widely believed that the book of Su Wen and Ling Shu was written more than 2000 years ago in the Western Han Dynasty (Hebei Medical College, 2009; Wang, 2016).

Simple analogies using Western medicine is not adequate in explaining the full meaning behind the heart, phlegm, and heat. The heart relates to mental behavior and the neurological state of mind. Therefore, when the heart "spirit" is disturbed, patients have symptoms such as insomnia, anxiety, and palpitation. The concept Heart in Chinese medicine mainly refers to the circulatory system and the nervous system, and they are easily blocked or obstructed to cause malfunction (Jiao et al., 2015). This is why PHHD is classified as an "excess" syndrome; the heat and the phlegm must be cleared to treat the symptoms in the circulatory system and the neuronal system successfully.

Heat is a state of the body, where if an individual is in the heated state, the body manifests inflamed ulcers, a red-colored tongue, swollen body parts, dry stools, sore throats, and a series of other symptoms particularly associated with inflammation.

Jin-ye fluids are bodily liquids other than blood. This may include urine, sweat, saliva, and gastric juices. Disturbance to Jin-ye would lead to a range of physiological responses that produce phlegm, similar to mucus generation. Phlegm can be considered an imbalance to homeostasis. Based on TCM theories, if phlegm-heat is stuck at the throat, then the patient would suffer from a sore throat. If the phlegm is stuck at the chest, then the patient would suffer from chest pain, chest tightness, and nausea. If phlegm-heat obstructs the mind, it would also obstruct the heart Qi, causing irregular pulse rhythm and incongruity. Therefore, phlegm-heat culminates in disturbing the heart, and the resulting symptoms are palpitation, panic, restlessness at night, mental disorder, a yellow greasy tongue, and other manifestations. Hence, phlegm-heat is responsible for various kinds of diseases, affecting many internal organs. There are many records about the pathogenesis of arrhythmia in ancient literature. For example, "Qian Jin Yi Fang" says: "Irregular heart beat is caused by phlegm-heat" (Sun, 2014).

Therefore, treatments for different symptoms need to be matched to their respective original disturbances. Every Chinese herb has its own unique traits, which have different impacts on these disturbances. For example, Huanglian is cold in nature, and one of the actions of Huanglian is to regulate heart function. Clinically, patients' symptoms are likely to be complex in nature, with roots of the illnesses implicating multiple organs. As a result, the herbs in a formula are composed in an orderly manner according to the Emperor–Minister–Adjuvant–Courier configuration. Each herb exerts its impact through its unique attributes, and the synergistic effects produce higher efficacy (than a single herb or compound does) and lower side effects.

6.2 History and Components of Xin Su Ning

In the 1980s, most of the treatments of arrhythmia with TCM were based on treating a lack of Qi, Qi deficiency. General signs of deficiency are fatigue, frail and weak movement, paleness, and incomplete engagement with life. Qi is a broad term in Chinese culture. In the context of clinical medicine, it means the dynamics of producing energy. However, nowadays, there are great changes in our living environment including natural and social environment, living conditions, dietary habits, etc. (Ding et al., 2018). The high-fat and high-sugar diet, coupled with reduced physical activity, would affect the normal operation of Jin-ye and cause the accumulation of pathological phlegm and dampness in the body. The high-intensity nature of the modern work environment makes the spirit prone to nervousness, which would affect the mind and make it more likely to generate the PHHD syndrome. Arrhythmia with typical clinical manifestation of this kind of syndrome takes a large proportion of the clinical treatment, and as far as we know, XSN is the only medicine for treating PHHD arrhythmia (Yuan and Zhou, 2000).

XSN is adapted from Huanglian Wen Dan Decoction recorded in Tingzhen Lu's "Liu Yin Tiao Bian" in the Qing Dynasty (Lu, 1982), which has the effect of removing phlegm and heat. Huanglian, Banxia, Fuling, Gancao, and Zhishi are from Huanglian Wen Dan Decoction; Changshan, Lianzixin, Qinghao, and Kushen were added to strengthen the antiarrhythmic effect of XSN. PHHD is classified as heat persisting in the body for a long time without dissipating, which leads to fluids concentrating as phlegm (Jiao et al., 2015). Common PHHD symptoms are palpitation, distress, insomnia and dreamful sleep, dry stool, red tongue (the tongue body is red, especially at the tip, which is often swollen and painful) with a yellow and greasy coating (Bi, 2015; Zhang

TABLE 2 | Antiarrhythmic properties of the herbal medicines that formulated XSN.

Herbs	Direct and indirect antiarrhythmic properties	References
Coptidis Rhizoma (Huanglian, *Coptis chinensis* Franch.)	Prolonging APD and the effective refractory period, eliminating the reentry impulse, and displaying significant antiarrhythmic effects. Promoting extracellular calcium influx, increasing intracellular calcium, improving sinus node function, and changing cardiac conduction from the unidirectional block to the bidirectional block. Inhibiting the activity of cholinesterase, enhancing the effect of acetylcholine, and increasing the membrane potassium conductance and the intracellular potassium outflow	Wang and Lu (2008); Xu and Gu (2017); Siqin et al. (2014); Dai and Luo (2001); Qiu (2018); Yang (2008)
Pinelliae Rhizoma (Banxia, *Pinellia ternata* [Thunb.] Makino)	Quinidine-like anti-arrhythmia effect. Banxia extract has significant inhibition effect on PVC in dogs caused by barium chloride. Increasing coronary flow and amplitude of the cardiac contraction curve of the isolated rabbit heart	Ding et al. (2018); Teng et al. (1983); Teng et al. (1985); Liu and Li (1997)
Poria (Fuling, *Poria cocos* [Schw.] Wolf)	Improving urinary retention and cardiac function in chronic heart failure rat models, inhibiting the occurrence of cardiac hypertrophy, improving hemodynamics, enhancing myocardial contractility, and improving myocardial diastolic function and cardiac output	Li et al. (2015a); Yang (2012)
Aurantii Fructus Immaturus (Zhishi, *Citrus aurantium* L.)	Zhishi can enhance myocardial contractility and increase cardiac output and coronary flow	Yang (2007); Zhang et al. (2009); Han et al. (2010); Xu et al. (2009); Huang et al. (2012)
Dichroae Radix (Changshan, *Dichroa febrifuga* Lour.)	Intravenous injection of Changshan alkali into anesthetized dogs can reduce the amplitude of cardiac contraction. Changrolin has quinidine-like anti-arrhythmia effect. The combination of Qinghao and Changshan has protective effect on arrhythmia and shortens the duration and frequency of arrhythmia	Zhang and Huang (1956); Yu et al. (1997); Chen et al. (2010); Fan et al. (2020); Jiao (2006); Liu (2007)
Nelumbinis Plumula (Lianzixin, *Nelumbo nucifera* Gaertn.)	The alkaloids in Lianzixin can shorten the recovery time of the sinus rhythm and reduce the incidence of ventricular fibrillation in mice induced by chloroform and delay the occurrence time of ventricular fibrillation in mice. Liensinine and neferine can inhibit the transmembrane transport of Na+, Ca2+, and K+ and produce synergistic antiarrhythmic effect. Isoliensinine may antagonize stretch-induced arrhythmia by blocking stretch-activated ion channels	Zeng et al. (2007); Wang et al. (1992); Dong et al. (2012); Chen et al. (2006)
Sophorae flavescentis Radix (Kushen, *Sophora flavescens* Ait.)	Kushen alkaloid compounds have anti-atherosclerosis effect. It has been reported to have dilating effects on the coronary artery and peripheral blood vessels, increase myocardial oxygen supply, and reduce myocardial oxygen consumption. Matrine has an effect on arrhythmia induced by low calcium and low magnesium. Matrine is effective on arrhythmia after myocardial infarction. Oxymatrine can effectively prolong the QT interval and the effective refractory period, increase the excitability threshold of the myocardial diastolic phase, promote the decrease in myocardial cell autonomy and triggered activity	Chen et al. (2018); Chen et al. (2016); Li et al. (2012); Sui et al. (2008); Zhang et al. (2008); Li et al. (2015b); Wang and Liu (2011); Chen et al. (2018)
Artemisiae annuae Herba (Qinghao, *Artemisia annua* L.)	Qinghao can significantly inhibit arrhythmia in rats induced by coronary ligation, electrical stimulation, or aconitine. It can also protect the heart from myocardial ischemia induced by pituitrin in rats and accelerate the heart rate. Artemisinin could inhibit the release of intracellular Ca2+ by interfering with the outward rectifying K+ current in ventricular myocytes, and it can significantly prolong the atrial effective refractory period and shorten the duration of atrial fibrillation in rats	Shi (2015); Qiao et al. (2007); Wang and Pei (2020); Li et al. (2020); Reid et al. (2016)
Ginseng Radix et Rhizoma (Renshen, *Panax ginseng* C. A. Mey.)	Ginsenosides can inhibit arrhythmia by affecting potassium and calcium channels and protecting myocardial cells from injury caused by ischemia reperfusion or chemical reagents. Ginsenoside Rb1 significantly inhibited the L-type calcium current and the transient outward potassium current in ventricular myocytes. Ginsenoside Re can inhibit the voltage-dependent sodium channel current and the transient outward potassium channel current in ventricular myocytes. Ginsenoside Rg3 can slow down the apoptosis of rat cardiomyocytes and protect the myocardium	Chen et al. (2015); Pei et al. (2011); Yong et al. (2013); Zhang et al. (2013); Wang et al. (2015b); You and Tian (2021)

(Continued on following page)

TABLE 2 | (*Continued*) Antiarrhythmic properties of the herbal medicines that formulated XSN.

Herbs	Direct and indirect antiarrhythmic properties	References
Ophiopogonis Radix (Maidong, *Ophiopogon japonicus* (L.f) Ker Gawl.)	Maidong may have antiarrhythmic effects by improving myocardial blood supply. Maidong saponins can reduce the excitability and automaticity of the right atrium muscles and prolong the refractory period of the left atrium. Maidong polysaccharide can enhance the tolerance of myocardial ischemia and hypoxia, increase coronary flow, protect ischemic myocardial cells, promote the proliferation and differentiation of endothelial progenitor cells in rats with myocardial ischemia-reperfusion, repair the ischemic myocardium, and restore cardiac function	Yu et al. (2014); Yu et al. (2014); Xin et al. (2011)
Nardostachyos Radix et Rhizoma (Gancao, *Glycyrrhiza uralensis* Fisch.)	Liquorice can inhibit arrhythmias caused by aconitine and ouabain. It can also shorten the time of arrhythmias induced by BaCl2 in rats and significantly slow down heart rates. It can protect the myocardium and has obvious anti–myocardial ischemia activities. Gancao can reduce ectopic pacing and improve ECG conduction	Pan (2004); Zhang et al. (2015); Xu and Zhang (1997)

et al., 2020), and knotted or regularly intermittent pulse. Depending on the severity of phlegm heat interfering with the nervous system, some mental symptoms may also occur, such as boredom or even irritability (Ren et al., 2012; Xing et al., 2015). Prevalence of PHHD has risen in recent years due to changing lifestyles, and XSN is designed specifically to treat this type of arrhythmia.

The prescription aims to clear away heat and phlegm and soothe the heart and palpitations. Therefore, XSN, developed from Huanglian Wen Dan Decoction, has demonstrated significant clinical benefit, particularly relating to the PHHD type of arrhythmia.

The antiarrhythmic pharmacological properties obtained through modern research of each herb is summarized in **Table 2**. Each herb of XSN will be further discussed below. However, XSN is not simply composed of herbs with antiarrhythmic properties. A good Chinese medicine formula conducts "Emperor–Minister–Adjuvant–Courier" principles so as to produce the best clinical efficacy and minimal side effects. Therefore, every herb in XSN is essential in producing the clinical efficacy.

It should be noted that a large number of ancient books of TCM are cited as references in this study. The year of references is the year when modern scholars reorganized the manuscripts and published them, which does not represent the years that ancient books were written in. Take this sentence as an example: "Ben Cao Gang Mu" recorded that "Huanglian could cure palpitation (Tang, 2009)." "Ben Cao Gang Mu" was written by Shizhen Li of the Ming Dynasty in 1578 AD. The book contains 52 chapters, including 1892 herbal medicines (including a small number of other types of medicine) and more than 10,000 prescriptions. It is a collection of achievements of pharmacy before the 16th century in China.

6.2.1 Coptidis Rhizoma (Huanglian, *Coptis chinensis* Franch.)

Huanglian is the rhizome of *Coptis chinensis* Franch., *C. deltoidea* C. Y. Cheng et Hsiao, or *C. teeta* Wall (Ranunculaceae) (Liu et al., 2017). Huanglian is bitter in taste and cold in nature. One of the actions of Huanglian is to regulate heart function. It could clear heat and dry dampness. "Ben Cao Gang Mu" recorded that "Huanglian could cure palpitation (Tang, 2009)." Therefore, the ancients used Huanglian to treat jaundice, high fever, and dental ulcers and soothe palpitation, chest pain, and anxiousness and insomnia, such as Huanglian An Shen Decoction in "Zhizhi Fang" (Wang, 2014).

Huanglian mainly contains berberine, jatrorrhizine, palmatine, epiberberine, and coptisine. The content of total alkaloids is as high as 70–80%. In addition, there are lignans, phenolic acids, flavonoids, volatile oils, and polysaccharides and some trace elements necessary for the human body (Wei et al., 2014; Wang L. et al., 2015).

Modern pharmacological studies have shown that Huanglian not only has broad-spectrum antimicrobial and antiviral effects but also has the effects of reducing myocardial autonomy, prolonging APD and the effective refractory period, eliminating reentry impulse and displaying significant antiarrhythmic effects, improving outcomes of heart failure and anti-myocardial ischemia, and improving myocardial microcirculation in the treatment of cardiovascular and cerebrovascular diseases (Wang and Lu, 2008; Xu and Gu, 2017). Berberine is the main component of Huanglian (Wang et al., 2014). Previous studies and clinical reports have shown that berberine has significant antiarrhythmic effects on arrhythmias with different etiologies (Siqin et al., 2014). Importantly, berberine was demonstrated to increase intracellular calcium through extracellular calcium influx, improving sinus node function (Dai and Luo, 2001). Berberine can selectively antagonize ouabain-induced ventricular arrhythmia in animals, and its antiarrhythmic effect may be related to the inhibition of Na^+ influx in the myocardium (Qiu, 2018). Berberine has been demonstrated to prevent or treat experimental ventricular arrhythmias caused by $CaCl_2$, adrenaline, ouabain, aconitine, electrical stimulation, and coronary artery ligation. Its antiarrhythmic mechanism may be related to the reduction of

myocardial automaticity, prolongation of APD and the effective refractory period, and elimination of the reentry impulse. Berberine can significantly inhibit atrial, ventricular premature beat, supraventricular tachycardia, and other arrhythmias (Yang, 2008). Besides, palmatine is another major component of Huanglian. The content of total alkaloids is second only to that of berberine, accounting for 1.28–2.12% (Zhou and Shen, 2004), and palmatine hydrochloride can inhibit arrhythmia induced by chloroform, adrenaline, and ouabain in rats. In addition, palmatine was also reported to have an antagonistic effect on chloroform-induced atrial fibrillation in mice (Chen and Fang, 1992).

6.2.2 Pinelliae Rhizoma (Banxia, *Pinellia ternata* [Thunb.] Makino)

Banxia is the root of *Pinellia ternate* (Thumb). Breit., which belongs to the Pinellia genus of Araceae (Wang and Wang, 2020). Banxia is spicy in taste, warm in nature, and promotes the health of the digestive system and lungs. Its functions include eliminating dampness and dissipating phlegm, eliminating swelling and dispersing stagnation, and treating phlegm-rich cough, chest stuffiness, dizziness, palpitation, etc. "Ben Cao Gang Mu" recorded that "In addition to treating abdominal distension, it is also used for dizzy and eye blurry (Tang, 2009)." "Ben Jing:" "The main use of Banxia is to treat chills and fever, sore throat, dizziness, chest swelling and cough (Mo, 2015)." The main active components of Banxia are alkaloids: ephedrine, choline, etc. In addition, Banxia aqueous solution contains a variety of nucleosides: guanosine, thymidine, adenosine, cytidine, uridine, etc. Banxia also contains aromatic components such as vanillic acid, caffeic acid, ferulic acid, *p*-hydroxycinnamic acid, and urine black acid. In addition, there are volatile oils, long chain fatty amino acids, and polysaccharides (Kurata et al., 1998).

Pharmacological studies have revealed that Banxia has anti-inflammatory and anticancer properties. The Ningxin alkaloid component of Banxia has quinidine-like antiarrhythmic effect (Ding et al., 2018). Some studies have shown that intravenous injection of Banxia extract (equivalent of 0.2–0.3 g crude drug/kg) has significant effect on PVCs in dogs caused by barium chloride; in 39 out of 40 studies, after administration of Banxia extract, the PVCs were rapidly inhibited without recurrence, showing an effective rate of 98% (Teng et al., 1983; Teng et al., 1985). In another study, the average duration of PVCs induced by barium chloride was shortened from 81 to 39 min by intragastric administration of Banxia water extract in rats. In addition, studies have shown that Banxia can increase coronary flow and amplitude of the cardiac contraction curve of an isolated rabbit heart (Liu and Li, 1997).

6.2.3 Poria (Fuling, *Poria cocos* [Schw.] Wolf)

Fuling is the dried sclerotia of the fungus *Poria cocos* (Schw.) Wolf. It was first recorded in "Shen Nong Ben Cao Jing" in the Han Dynasty. Its taste is light and sweet, and it is mild in nature. It promotes the health of the heart, lungs, digestive function, and kidneys. It is mainly used for the treatment of phlegm, palpitation, diarrhea, restlessness, and insomnia (Wu, 2016).

Fuling is made of predominantly beta-pachyman, which accounts for about 93% of the dried products. It also contains fatty acids, such as lauric acid, palmitic acid, and dodecanoic acid, as well as ergosterol, lecithin, and other inorganic components. Fuling is widely used in dysuria and edema (Wu et al., 2014). Studies showed that Fuling could downregulate the expression of aquaporin 2 (AQP2) mRNA and protein, reduce the excretion of AQP2 in urine, and downregulate the expression of arginine vasopressin in plasma and expression of mRNA of vasopressin receptor 2, thereby improving urinary retention and cardiac function in rats with chronic heart failure. Fuling polysaccharide can inhibit the occurrence of myocardial hypertrophy, improve hemodynamics, enhance myocardial systolic function, improve myocardial diastolic function, and increase cardiac output in rats with myocardial hypertrophy (Li G. et al., 2015). Pharmacological studies have shown that Fuling has a diuretic effect. It has been reported that it may be due to the Fuling-induced activation of the Na^+ K^+ ATPase on the cell membrane (Yang, 2012).

6.2.4 Aurantii Fructus Immaturus (Zhishi, *Citrus aurantium* L.)

Zhishi is the dried young fruit of *Citrus aurantium* L. and its cultivated variety or sweet orange (*Citrus sinensis* Osbeck). It tastes bitter, spicy, and sour. It is slightly cold in nature, and it can dissolve Qi, dissipate over-accumulation, dissolve phlegm, and remove nodules. Zhishi is mainly used to treat accumulation-related internal stagnation, swelling pain, phlegm-induced stagnation, chest obstruction, chest knot, and so on. Zhishi is a common prescription as a mild soothing agent of the chest and is frequently prescribed for the treatment of coronary heart diseases in the clinic (Lv, 2017).

Studies have shown that the main active components of Zhishi are flavonoids, volatile oil, and a number of alkaloids. Flavonoids are the most abundant components in Zhishi, including dihydroflavones and polymethoxyflavones. Alkaloids are the main components of Zhishi to strengthen the heart and improve blood pressure, mainly including synephrine, n-methyltyramine, quinoline, and narcotine and norepinephrine (Yang, 2007; Zhang et al., 2009; Han et al., 2010). Several flavonoids in Zhishi can improve gastric emptying and small intestinal propulsion in rats with functional dyspepsia, and the effect of hesperidin on gastric emptying and small intestinal propulsion may be related to the increase in motilin secretion (Huang et al., 2012). Flavonoids in Zhishi can improve the symptoms of gastric ulcer induced by indomethacin in rats, mainly through the expression of gastric cyclooxygenase-2 (COX-2) (Hamdan et al., 2014). Research also showed that flavonoids from Zhishi inhibited adipogenesis through the Akt signaling pathway in 3T3-L1 cells (Ji et al., 2003; Jiao et al., 2007; Kim et al., 2012). It is reported that Zhishi can enhance myocardial contractility, increase cardiac output, improve heart pumping function, increase coronary flow, which would reduce myocardial oxygen consumption, and improve myocardial metabolism (Xu et al., 2009).

6.2.5 Dichroae Radix (Changshan, *Dichroa febrifuga* Lour.)

Changshan was first recorded in the "Shen Nong Ben Cao Jing." It is the dried roots of *Dichroa febrifuga* Lour. Changshan is bitter and spicy in taste, and it has toxicity when used inappropriately. It promotes the health of the lungs, the liver, and the heart. It is often used in the treatment of malaria.

The main active components in Changshan are quinazolone alkaloids. Its total alkaloid content is about 0.1%. The main alkaloids are changshanine, anomaline, neochangshanine, and berberine. Pharmacological studies have shown that Changshan has antimalarial, antipyretic, and antineoplastic effects. Intravenous injection of Changshan alkali into anesthetized dogs can reduce the amplitude of cardiac contraction and increase the volume of the spleen and the kidney (Zhang and Huang, 1956). Changrolin is an antiarrhythmic drug that is a chemical derivative of Changshan B. Changrolin has a negative inotropic effect, which can reduce the automaticity of the papillary muscle, prolong the functional refractory period, and reduce the excitability and the APA. Changrolin's effects have been observed to be similar to those of quinidine (Yu et al., 1997). Changrolin inhibited delayed rectified K^+ currents (I_K), and it also induced a concentration-dependent inhibition of sodium currents (I_{Na}) (Chen et al., 2010).

Prof. Ding used Qinghao and Changshan together to treat arrhythmia. The combination of the two herbs has a significant effect of clearing away heat and resolving phlegm, generating superior therapeutic effects. The cardiovascular cases treated by Prof. Ding in the last 10 years were further analyzed. A total of 2,850 cases of tachyarrhythmia such as premature cardiac contraction were treated. 90% of the patients were accompanied with PHHD symptoms, and they were treated with Qinghao, Changshan, and other herbs (Fan et al., 2020). Studies have shown that Qinghao and Changshan can significantly reduce the incidence of arrhythmia induced by pituitrin and coronary artery ligation and shorten the duration and frequency of arrhythmia. The combination of Qinghao and Changshan has protective effect on arrhythmia induced by aconitine, barium chloride, and chloroform and has a protective and therapeutic effect on arrhythmia caused by acute myocardial ischemia induced by coronary artery ligation in dogs (Jiao, 2006; Liu, 2007).

6.2.6 Nelumbinis Plumula (Lianzixin, *Nelumbo nucifera* Gaertn.)

Nelumbinis Plumula is the dried spire and radicle of the mature seeds of *Nelumbo nucifera* Gaertn., a plant of the Nymphaeaceae family (Zhao, 2018). Lianzixin tastes bitter, and it is cold in nature. It could regulate the heart, lungs, and kidney function. Lianzixin has been used to treat insomnia, anxiety, spermatorrhea, thirst, swelling, and pain of the eyes (Song et al., 1995).

Research into the chemical compositions of Lianzixin revealed that the main components are alkaloids and flavonoids, which have shown pharmacological effects including antitumor, cardiovascular protection, antioxidation, inhibiting liver fibrosis, lowering blood sugar, bacteriostasis, and anti-inflammation (Dong et al., 2012; He and Yu, 2012; Liao and Lin, 2012). Animal experiments have shown that phenolic alkaloids in Lianzixin can shorten the recovery time of the sinus rhythm and reduce the mortality rate and can reduce the incidence of ventricular fibrillation in mice induced by chloroform and delay the occurrence time of ventricular fibrillation in mice (Zeng et al., 2007). Studies have shown that liensinine and neferine, which are extracts of Lianzixin, can inhibit the transmembrane transport of Na^+, Ca^{2+}, and K^+ and produce synergistic antiarrhythmic effect (Wang et al., 1992; Dong et al., 2012). Besides, isoliensinine may antagonize stretch-induced arrhythmia by blocking stretch-activated ion channels (Chen et al., 2006).

In addition, silica gel column chromatography, ODS column chromatography, and RP- HPLC were used to study the chemical constituents of the ethyl acetate fraction of the 80% ethanol extract of Lianzixin. Four compounds were isolated, and their structures were identified by physicochemical properties and modern spectroscopy: (1*R*,1′*R*) Neferine *N*-Oxide, (1*R*,1′*R*) Neferine, liensinine, and isoliensinine. Among them, (1R, 1′r) neferine N-oxide is a new compound with no pharmacological properties being reported in the literature (Zhang, 2017a).

6.2.7 Sophorae Flavescentis Radix (Kushen, *Sophora flavescens* Ait.)

Kushen is the dry root of *Sophora flavescens* Ait., a plant of the Leguminous family (Zhao et al., 2015). Kushen has a bitter taste, and its thermal properties belong to the cold category. Kushen has effects on the heart, liver, stomach, large intestine, and bladder meridians and could dry dampness, promote urination, kill parasites, and stop itching. It could treat diseases including phlegm-heat diseases, jaundice, and itching skin. Furthermore, "Ben Cao Xin Bian" recorded that "Kushen is used to eliminate sudden heartache" (Chen, 2018). The main bioactive components of Kushen are alkaloids and flavonoids.

A large number of literatures have shown that Kushen alkaloid (matrine) compounds have antitumor, anti-atherosclerosis, antivirus, immunosuppressive, hepatoprotective and cholagogic, anti-parasitic, and other pharmacological effects (Chen et al., 2016). Matrine reduces the amplitude of the action potential under arrhythmic conditions, implying the sodium channel blockade effect (Li et al., 2012), and weakens the effect of the I_{KM3} current (Sui et al., 2008) and has a significant effect on arrhythmia induced by low calcium and low magnesium (Zhang et al., 2008). The blocking of I_{kr} by matrine may be one of the mechanisms of prolonging the effective refractory period, reducing the incidence of the ectopic rhythm and treating arrhythmia (Huang and Liu, 2008). Besides, oxymatrine has some effects on arrhythmia caused by abnormal electrophysiology of the slow-response autonomic cells in the left ventricular outflow tract induced by ischemia and hypoxia (Li X. et al., 2015). Animal experiments have confirmed that oxymatrine can effectively prolong the QT interval and the effective refractory period, increase the excitability threshold of the myocardial diastolic phase, promote the decrease in

myocardial cell autonomy, and trigger activity (Wang and Liu, 2011; Chen et al., 2018).

6.2.8 Artemisiae Annuae Herba (Qinghao, *Artemisia annua* L.)

Qinghao is the dried aerial part of *Artemisia annua* L. It has a bitter and spicy taste and is cold in nature. It promotes the health of the liver and the gall bladder. Qinghao has effects on the liver and gall bladder meridians and could treat diseases including indigestion, malaria, constipation, gastrointestinal disorders, distention, and jaundice.

The main chemical constituents of Qinghao are sesquiterpenoids, dahlias, coumarins, phenylpropionic acid, and volatile oils (Huizhen et al., 1998). Studies have shown that Qinghao can significantly inhibit arrhythmia in rats induced by coronary ligation, electrical stimulation, or aconitine. It was found that artemisinin could inhibit the release of intracellular Ca^{2+} by interfering with outward rectifying K^+ current in ventricular myocytes (Qiao et al., 2007). Artemisinin can significantly prolong the atrial effective refractory period and shorten the duration of atrial fibrillation in rats. It is speculated that artemisinin can upregulate the expression level of the Cav1.2 calcium channel and downregulate the expression levels of CaMK II, resulting in the inhibition of the p-Ry R2 level, which has a therapeutic effect on atrial fibrillation in rats (Wang and Pei, 2020). The effects of artemisinin and amiodarone on the QT interval and the QRS interval in rats were observed by using the rat arrhythmia model induced by barium chloride. The results showed that the effect of artemisinin (20.0 mg/kg) on the shortening QT interval was better than that of amiodarone and with fewer side effects (Li et al., 2020). Artemisinin can significantly improve the cardiac systolic function of diabetic cardiomyopathy by improving myocardial fibrosis and improve cardiac diastolic function to some extent (Li et al., 2016), and artemisinin can inhibit left ventricular hypertrophy and improve the cardiac function of adult rats after coarctation of the aorta (Reid et al., 2016). Qinghao can also protect the heart from myocardial ischemia induced by pituitrin in rats and accelerate the heart rate. In addition, Qinghao has anti-malaria, anti-schistosomiasis, anti-asthmatic, anti-systemic lupus erythematosus, and antitumor effects (Shi, 2015).

6.2.9 Ginseng Radix et Rhizoma (Ginseng, *Panax ginseng* C. A. Mey)

Ginseng is a perennial herb, a plant of the Araliaceae family (Li Q. et al., 2019). Ginseng has a sweet, slightly bitter taste and is mildly warm in nature. It promotes the health of the digestive system, lungs, and heart. It can be used to treat fatigue, shortness of breath, and chronic cough due to the deficiency of lungs and calm the mind (Wu, 2016).

Ginsenoside and Ginseng polysaccharides are the main chemical constituents in Ginseng. 3–5% of Ginseng roots and rhizomes is ginsenoside (Yang, 2016). Modern studies have shown that ginsenosides can inhibit arrhythmia by affecting potassium and calcium channels and protecting myocardial cells from injury caused by ischemia reperfusion or chemical reagents (Chen et al., 2015).

It was found that ginsenoside Rb1 significantly inhibited the L-type calcium current and the transient outward potassium current in ventricular myocytes (Pei et al., 2011). Ginsenoside Re can inhibit the voltage-dependent sodium current and the transient outward potassium current in ventricular myocytes (Yong et al., 2013). Ginsenoside Rg1 can promote the formation of coronary collateral vessels in the ischemic myocardium of rats, which may be related to the promotion of vascular endothelial growth factor expression and the recovery of ischemic heart function (Zhang et al., 2013). Ginsenoside Rg3 can slow down the apoptosis of rat cardiomyocytes and protect the myocardium (Wang Y. et al., 2015). In addition, Ginsenoside Rb can inhibit ventricular remodeling, improve myocardial ischemia, and protect the myocardium (You and Tian, 2021). Upon combined use of ginsenoside Re (20 μmol/L) and ginsenoside Rg1 (80 μmol/L), the inhibitory effect of the L-type calcium channel was stronger than those of ginsenoside Re and Rg1 alone (Han et al., 2019). Therefore, it is speculated that the antiarrhythmic effect of ginseng may be a combination of several effective components.

6.2.10 Ophiopogonis Radix (Maidong, *Ophiopogon japonicus* (L. f) Ker Gawl.)

Maidong is the dried tuberous root of the perennial evergreen herb *Ophiopogon japonicus*. Maidong is sweet and bitter in taste and cold in nature. It has effects on the heart, lungs, and stomach, generates fluids, and moistens lungs and relieves cough. It can be used for hemoptysis, thirst, dry mouth, irritability, and constipation. "Shen Nong Ben Cao Jing" listed Maidong as the top grade of nourishing moistening lungs and stated that taking Maidong over the long term would lead to retaining youthful vitality (Wu, 2016; Zhang, 2017b).

The main active components of Maidong are steroidal saponins and hyper-isobrass (Bai, 2014). Pharmacological studies have shown that Maidong has anti-cardiovascular and cerebrovascular diseases, anti-aging, anticancer, and anti-inflammatory properties as well as regulating the functions of the immune system. Maidong may have antiarrhythmic effects by improving myocardial blood supply. Maidong saponins can reduce the excitability and automaticity of the right atrium muscles and prolong the refractory period of the left atrium (Yu et al., 2014). Maidong polysaccharide MDG-1 can enhance the tolerance of myocardial ischemia and hypoxia, increase coronary blood flow, protect ischemic myocardial cells, and promote the proliferation and differentiation of endothelial progenitor cells in rats with myocardial ischemia-reperfusion. It can also reduce the content of ischemia-modified albumin in blood, repair the ischemic myocardium to the greatest extent, and restore cardiac function (Xin et al., 2011).

6.2.11 Nardostachyos Radix et Rhizoma (Gancao, *Glycyrrhiza uralensis* Fisch)

Gancao is the dried root and rhizome of the leguminous plant *Glycyrrhiza uralensis*, *Glycyrrhiza inflata*, or *Glycyrrhiza glabra*.

Gancao is sweet in taste and mild in nature. It has effects on the heart, lungs, and digestive system and could benefit Qi. It moistens lungs and stops coughing, moderates spasms, stops pain, and clears heat. It also harmonizes the harsh characteristics of other herbs and eliminates various toxic actions. It could be used to treat fatigue, loose stools, irregular or intermittent pulse, shortness of breath, painful spasms of the abdomen or legs, carbuncles, sores, and soreness of the throat. "Shang Han Lun" recorded a famous prescription for the treatment of palpitation and irregular heartbeats, and the prescription takes Gancao as the principal herb (Li and Liu, 1985).

The main components of Gancao are glycyrrhizic acid and glycyrrhizin (Chen et al., 2000). Modern studies have shown that Gancao can inhibit arrhythmias caused by aconitine and ouabain. It can also shorten the time of arrhythmias induced by $BaCl_2$ in rats and significantly slow down heart rates, and its effects are dose dependent. It can protect the myocardium and has obvious anti–myocardial ischemia activities (Pan, 2004; Zhang et al., 2015). Gancao can also reduce ectopic pacing and improve ECG conduction (Xu and Zhang, 1997).

In addition, since ancient times, Gancao has had the reputation of "detoxifying hundreds of herbs." Chinese doctors often added Gancao to decoctions to reduce or eliminate its toxicity. Modern clinical application of Gancao can antagonize the toxicity of some chemical drugs and can also treat heavy metal poisoning, such as arsenic (Li P. et al., 2019). Pharmacological studies show that the material basis of reducing toxicity of Gancao is glycyrrhizin and glycyrrhetinic acid (Fujisawa et al., 2000; Jung et al., 2017; Wang and Han, 2018). This is one of the reasons why the combination of multiple herbs can not only enhance the curative effect but also reduce the side effects.

6.3 The Forming Principles of Xin Su Ning

The XSN capsule is tailored toward the pathogenesis of the "heated phlegm with heart disturbance causing blockade of the heart meridian" type of arrhythmia. Modified based on the ancient Huanglian Wen Dan Decoction, XSN is formulated with the aforementioned herbs: Huanglian, Banxia, Fuling, Zhishi, Changshan, Lianzixin, Kushen, Qinghao, Ginseng, Maidong, and Gancao. Its effects include clearing the heat and dissolving phlegm, replenishing Qi, and relieving palpitation.

The principle of "Emperor–Minister–Adjuvant–Courier" elaborates the status of each herb in the formulation (Kaptchuk, 2014). Emperors are the herbs in the formula used to treat the main symptoms of the disease. They reflect the principal direction of the formula, and they are indispensable. Huanglian and Banxia are the emperors of XSN, whose principal effects are resolving phlegm and clearing the heat of the heart, respectively. Besides, the cold nature of Huanglian is neutralized by the warm nature of Banxia.

Ministers are herbs which enhance the actions of the "Emperor" to treat the main syndrome or disease. Lianzixin, Qinghao, and Changshan are ministers of XSN. They help Huanglian and Banxia to resolve phlegm and clear the heat of the heart (Yuan, 2000). They both enter the heart meridian and could clear away the heart disturbances and calm the mind. When used together, they will remove phlegm and clear heat and relieve irritation.

Adjuvants are the herbs that are used to treat subordinated and accompanying symptoms and reduce potential side effects of Emperors or Ministers. Fuling, Zhishi, and Kushen are the adjuvants to regulate Qi and dissipate phlegm (Li, 2005). Fuling is mild in nature. It promotes the health of the heart. Zhishi is slightly cold in nature and promotes the health of the digestion. It could help digestion, dissolve phlegm, and remove abnormal nodules. Kushen has the effect of dissolving phlegm and relieving uneasiness of the mind and tranquilizing the body at the same time. It could strengthen the digestion, help to resolve phlegm, and clear heat.

Couriers are herbs that help to coordinate the drug actions in the formulation and make them work better together and also reduce side effects. Ginseng, Maidong, and Gancao are couriers in the decoction. Gancao can tonify Qi, harmonize the herbs, and reduce the side effect as well. Ginseng is mild and slightly warm in nature and could strengthen the organs, tonify Qi, and calm the mind. Maidong is slightly cold in nature. It affects the heart, lungs, and digestive system. The combination of Ginseng and Maidong is used like Sheng Mai Decoction to relieve palpitation and shortness of breath and calm the mind.

Overall, the whole prescription nourishes the body and balances the Qi and the blood. It aims to harmonize yin and yang, dissolve the phlegm-heat, relieve mental stress, resist fear, and stop palpitation.

7 THE LIMITATIONS OF THE AVAILABLE BASIC AND CLINICAL STUDIES OF XSN AND POSSIBLE FURTHER STUDIES

The fundamental difference between new drug discovery studies and the pharmacological studies of TCM is the former being initiated in scientific research laboratories and the latter being based on long-time clinical use in patients. Therefore, how to rigorously evaluate the clinical efficacy of TCM has been the most important question in this field of study. The cellular electrophysiological study is the conventional method used in antiarrhythmic drug discovery studies, and the data generated form the base for antiarrhythmic drug classifications. Hence, the available data on cellular electrophysiological property of XSN were reviewed in this article. However, in order to fully understand the action mechanisms of the multicomponent XSN and its clinical efficacy in comparison with other antiarrhythmic drugs, there are more basic and clinical studies that need to be carried out:

1. The effect of XSN in cardiac arrhythmic models, including various diseases' model-induced arrhythmias.
2. Clinical studies with longer periods and more patients to compare the differences between XSN and other antiarrhythmics in therapeutic and toxicological profiles.
3. The pharmacological studies of all the active components of XSN.

4. Bioinformatic studies of XSN's clinical efficacy.
5. The quality standard and control studies of XSN.

8 CONCLUSION

XSN as a clinically effective antiarrhythmic TCM displays the characteristics of class I and III antiarrhythmics, which was confirmed using conventional cellular electrophysiological research methods that have been used for discovering antiarrhythmic drugs for the last few decades. The unique property that XSN possesses is its safety profile in comparison with other antiarrhythmic drugs.

The multicomponent nature of XSN has made it multitargeting, which allows XSN to exert its cardioprotective actions while regulating the ion channels to suppress cardiac arrhythmias.

XSN is the first TCM approved in China for the treatment of PHHD arrhythmia according to Chinese medicine theories. The 11 herbs that formulated XSN display various pharmacological properties; following TCM theory, they were mixed with particular proportions of each herb that formulated XSN. The safety profile of XSN gives it the potential of further research and development.

We hope that the advances in how XSN was studied may offer useful guidance on how other TCM could be studied with respect to the integrity of the TCM formulas.

Comment

All the classical books of traditional Chinese medicine cited in this article were written in ancient times and then compiled by modern scholars. The year in the reference is the time when the book was published by modern scholars.

AUTHOR CONTRIBUTIONS

Y-LM conceived the review; XW and Y-LM designed and wrote the manuscript and contributed to the conception of the review. SD provides guidance for XSN's TCM theories. TW and Y-LM edited the manuscript, assisted in the literature search, and critically revised the article for important intellectual content. All the authors have read and approved the final manuscript.

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Characteristics and Long-Term Ablation Outcomes of Supraventricular Arrhythmias in Hypertrophic Cardiomyopathy: A 10-Year, Single-Center Experience

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Background: A variety of supraventricular arrhythmias (SVAs) may occur in patients with hypertrophic cardiomyopathy (HCM). The characteristics and long-term ablation outcomes of different types of SVAs in HCM have not been comprehensively investigated.

Methods: We retrospectively enrolled 101 consecutive patients with HCM who were referred to the electrophysiology and arrhythmia service from May 2010 to October 2020. The clinical features and ablation outcomes were analyzed.

Results: Seventy-eight patients had SVAs, which comprised 50 (64.1%) cases of atrial fibrillation (AF), 16 (20.5%) of atrial flutter (AFL), 15 (19.2%) of atrioventricular reentrant tachycardia (AVRT), 11 (14.1%) of atrial arrhythmia (AT), and 3 (3.8%) of atrioventricular nodal reentrant tachycardia (AVNRT). Thirty-four patients underwent catheter ablation and were followed up for a median (interquartile range) of 58.5 (82.9) months. There was no recurrence in patients with non-AF SVAs. In patients with AF, the 1- and 7-year AF-free survival rates were 87.5 and 49.5%, respectively. A receiver operator characteristic analysis showed that a greater left ventricular end-diastolic dimension (LVEDD) was associated with a higher recurrence of AF, with an optimum cutoff value of 47 mm (c-statistic = 0.91, $p = 0.011$, sensitivity = 1.00, specificity = 0.82). In Kaplan–Meier analysis, patients with a LVEDD $\geq$ 47 mm had worse AF-free survival than those with a LVEDD $<$ 47 mm (log-rank $p = 0.014$).

Conclusions: In this unique population of HCM, AF was the most common SVA, followed in order by AFL, AVRT, AT, and AVNRT. The long-term catheter ablation outcome for non-AF SVAs in HCM is satisfactory. A greater LVEDD predicts AF recurrence after catheter ablation in patients with HCM.

Keywords: hypertrophic cardiomyopathy, supraventricular arrhythmia, atrial fibrillation, catheter ablation, outcomes

INTRODUCTION

Tachyarrhythmias often cause palpitations and can precipitate syncope in patients with hypertrophic cardiomyopathy (HCM) (1, 2). Several studies have shown that a variety of ventricular and supraventricular arrhythmias (SVAs) may occur in these patients (1–10). Ventricular tachycardia (VT) is the most commonly recorded fatal arrhythmic event for sudden cardiac death (1, 2). Among all types of SVAs in HCM, atrial fibrillation (AF) has been the most extensively investigated because it affects a large proportion of these patients, involves a high risk of stroke, and is often poorly tolerated (1, 2, 11–23). For rhythm control in patients with HCM and AF, catheter ablation can be beneficial in some patients who have drug refractory symptoms or who are unable to take anti-arrhythmic drugs. However, the success rate of catheter ablation varies among different studies (1, 2).

The prevalence and characteristics of other types of SVAs have not been as well-studied as those for AF. Different types of SVAs, including atrial flutter (AFL), atrial tachycardia (AT), atrioventricular nodal reentrant tachycardia (AVNRT), and atrioventricular reentrant tachycardia (AVRT), were first identified in patients with HCM in several electrophysiological studies in the 1980s (8, 24–26). Interestingly, relatively few studies have evaluated catheter ablation of these SVAs (27–29). The current guidelines recommend that SVAs other than AF in patients with HCM should be ablated if there is an ablatable substrate (2). However, to date, the long-term ablation outcomes of non-AF SVAs have not been reported.

The understanding of HCM has improved in the modern era, but arrhythmias in patients with HCM have not been well-studied in China. Therefore, this study aimed to comprehensively investigate the characteristics and long-term ablation outcomes of AF and non-AF SVAs in a Chinese population with HCM.

MATERIALS AND METHODS

Study Population

Between May 2010 and October 2020, 101 consecutive symptomatic patients with HCM were referred to the Arrhythmia Center, Fuwai Hospital, Beijing, for electrophysiology and arrhythmia service. The referral reasons included symptoms of palpitations, syncope or presyncope, and with or without abnormal electrocardiographic (ECG) or 24-h Holter monitoring. This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board and Ethics Committee. Informed consent was obtained from all participants.

Diagnosis of HCM

HCM was defined by a wall thickness ≥ 15 mm in one or more left ventricular myocardial segments measured by echocardiography and/or cardiovascular magnetic resonance imaging, which was not explained solely by loading conditions (1, 2). In this study, all patients were evaluated by echocardiography and 44 (43.6%) were also evaluated by cardiovascular magnetic resonance. Greatest thickness measured at any site in the left ventricular wall was considered as the maximal thickness. In patients with intensive physical training, hypertension, valve diseases, or lesser degrees of wall thickening (13-14 mm), the diagnosis was made by at least two experts from the Cardiomyopathy Center (1, 2). In this study, seven patients had a maximal wall thickness of 13-14 mm. Left ventricular outflow tract obstruction was defined as an instantaneous peak Doppler left ventricular outflow tract pressure gradient of ≥30 mmHg (1, 2). A gradient ≥50 mmHg was considered to be hemodynamically significant (1, 2). HCM was divided into three types according to the site of the hypertrophic segment: interventricular septum only, apex only, and multi-segment (≥2 segments of the left ventricular wall).

Diagnosis of SVAs

SVAs included in this study were AF, AFL, AT, AVRT, and AVNRT. Sinus tachycardia was not included. An initial diagnosis of arrhythmia was made by ECG and Holter monitoring in all patients. The minimum duration to establish the diagnosis of clinical and symptomatic SVA was at least 30 s, or entire 12-lead ECG. In those who underwent an electrophysiological study (EPS), a more precise diagnosis was established. The EPS-diagnosed population included 16 (32%) of the 50 AF, 7 (44%) of the 16 AFL, 3 (27%) of the 11 AT, 10 (67%) of the 15 AVRT, and 3 (100%) of the 3 AVNRT. Other patients were diagnosed on the basis of ECG and Holter after discussion between at least two electrophysiologists.

Ventricular tachyarrhythmias and bradyarrhythmias were also recorded. Ventricular tachyarrhythmias included VT and frequent premature ventricular contraction (defined as ≥ 700 per 24 h). Bradyarrhythmias included sinus node dysfunction and atrioventricular block. Atrioventricular block included first-degree, second-degree, and third-degree atrioventricular block.

EPS and Catheter Ablation

Anti-arrhythmic drugs were discontinued five half-lives or more before EPS and catheter ablation. AF catheter ablation was performed in patients with multiple symptomatic episodes of AF in whom anti-arrhythmic drugs failed to control the frequency of AF or in whom anti-arrhythmic drugs were not tolerated. AF catheter ablation mainly consisted of antral pulmonary vein isolation by radiofrequency ablation or cryoablation. An EPS was performed in patients who were suspected of having other types of SVAs. Radiofrequency ablation was performed after initiating SVAs by routine programed stimulation.

Follow-Up

Patients who underwent ablation were followed up by out-patient visits or telephone calls in 3 months, 6 months, 12 months, and every 1 year thereafter. All-cause death, cardiac death, stroke, and recurrence of tachycardia were recorded. The final census date for this study was January 15, 2021.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)] as appropriate, and categorical parameters are showed as ratio or percentage. For continuous data, either student *t*-test or Mann-Whiney *U*-test was conducted between two independent samples

as appropriate. For comparisons of continuous data among multiple groups, analysis of variance or non-parametric analyses were used when the assumption of normality is in doubt. Chi-square test was used for categorical data. Receiver operative characteristic curves were used to determine the best cutoff values of predictors. Kaplan-Meier curve was carried out and log rank *p*-value was calculated in survival analysis. A *p*-value of <0.05 was considered statistically significant. Data analyses were performed using R version 4.0.2.

RESULTS

The Spectrum of Arrhythmias in the Overall Population

Of all 101 patients, 4 had no evidence of arrhythmia. In the overall cohort with arrhythmia, 63 (65%) patients were male, and the median (IQR) age at admission was 58 (23.5) years old (**Supplementary Table 1**). **Figure 1** displays the spectrum of all arrhythmias. Of the 97 patients diagnosed with arrhythmia, 86 (88.7%) had tachyarrhythmias and 35 (36.1%) had bradyarrhythmias. Specifically, 62 (63.9%) patients only had tachyarrhythmias, 11 (11.3%) only had bradyarrhythmias, and 24 (24.7%) had both. Of the 35 patients with bradyarrhythmias, 15 (42.9%) only had sinus node dysfunction, 18 (51.4%) only had atrioventricular block, and two (5.7%) had both. Of the 86 patients with tachyarrhythmias, 15 (17.4%) had VT or frequent premature ventricular contraction and 78 (90.7%) had SVAs. The clinical features of all patients with arrhythmias are shown in **Supplementary Table 1**.

Baseline Characteristics of Patients With SVAs

In the SVA population ($n = 78$), 50 (64.1%) patients had AF, 16 (20.5%) had AFL, 15 (19.2%) had AVRT, 11 (14.1%) had AT, and three (3.8%) had AVNRT (**Figure 1**). **Table 1** presents the characteristics of the SVA population. No comparisons were performed because of the relatively small size in each subgroup. There was a male preponderance in the overall SVA population and all of the subgroups, except for the AT group. The median (IQR) age at onset of arrhythmia-related symptoms and age at admission in the overall SVA population were 55 (27) and 59 (23) years, respectively. Patients with AVRT, AVNRT, or AFL appeared to be younger, and patients with AF or AT were older at the onset of arrhythmia-related symptoms and at admission. A history of syncope was reported in 15% (19.2%) of all patients. More than half of the patients with AT had syncope. A positive family history of HCM was recorded in eight (6.4%) patients.

Comorbid disorders were recorded in 36 (46.2%) patients. Hypertension was the most frequent (39.7%) comorbid disease, followed by coronary artery disease (17.9%) and diabetes mellitus (16.7%). Pulmonary hypertension was observed by echocardiography in eight (10.3%) patients. The rate of hypertension was more frequent in patients with AT than those in other patients. The New York Heart Association functional class was evaluated in all of the patients at admission. Most patients were in functional class I/II (91%). The AT group appeared to have more patients in functional class III/IV than other subgroups.

Table 2 shows the baseline echocardiography parameters. The multi-segment (50%) and interventricular septum (42.3%) comprised the majority of hypertrophic types, and only six (7.7%) involved the apex. The median (IQR) maximum left ventricular wall thickness was 19 (6) mm in all patients and tended to be smaller in the AVRT group than in the other subgroups. More patients in the AT subgroup had left ventricular outflow tract obstruction than those in the other subgroups. Most patients appeared to have a normal systolic function with a median (IQR) left ventricular ejection fraction of 63% (10.3), a normal left ventricular end-diastolic dimension (LVEDD) of 45 (8.3) mm, and a greater left atrial dimension of 41 (11) mm. The left ventricular ejection fraction and LVEDD appeared to be similar among the subgroups. Patients with AFL had the greatest left atrial dimension, while the AVNRT group had the smallest.

Medical treatment information was obtained in all patients (**Supplementary Table 2**). Beta-blockers and non-dihydropyridine-calcium channel blockers were used in 63 (81%) patients to improve symptoms of HCM. Other patients were not treated with these drugs because of the presence of bradyarrhythmia. The most frequently used anti-arrhythmic drugs were amiodarone (24.4%) and sotalol (10.3%).

Comparisons between persistent AF and paroxysmal AF are shown in **Supplementary Table 3**. Patients with persistent AF were heavier ($p = 0.017$) and had a greater body surface area ($p = 0.022$) than patients with PAF. The echocardiographic parameters and functional class were similar in the two groups. Significantly more patients with persistent AF used warfarin ($p = 0.036$) for anticoagulation than those with paroxysmal AF. More patients with paroxysmal AF used amiodarone for rhythm control than those with persistent AF ($p = 0.043$).

Catheter Ablation for SVAs

Among the patients with SVAs, 43 were scheduled for catheter ablation. Eventually, ablation was not performed in eight patients and failed in one patient. Two patients scheduled for AF ablation were not ablated. One of these patients was not ablated because of acute heart failure pre-procedure and one because of failure of placing a coronary sinus electrode and atrial transseptal puncture. Tachycardia was not initiated in three patients who were suspected of having AVNRT or AVRT, and in three patients who were suspected of having AT. Ablation was terminated in one patient with AF because of acute injury to the phrenic nerve.

Finally, 34 patients underwent catheter ablation successfully, and 16 of them had AF (**Figure 2**). Of the remaining 18 patients, 9 had AVRT, 6 had AFL, and 3 had AVNRT. One patient was ablated for both AF and AVRT, and one was ablated for both AF and AFL. Of the 16 patients who had AF ablation, 4 had persistent AF and 12 had paroxysmal AF. Three of these patients were ablated with the cryoablation method and 13 with the radiofrequency ablation method. The other 18 patients with non-AF SVAs were ablated with the radiofrequency ablation method. The characteristics of patients who underwent catheter ablation are shown in **Supplementary Table 4**.

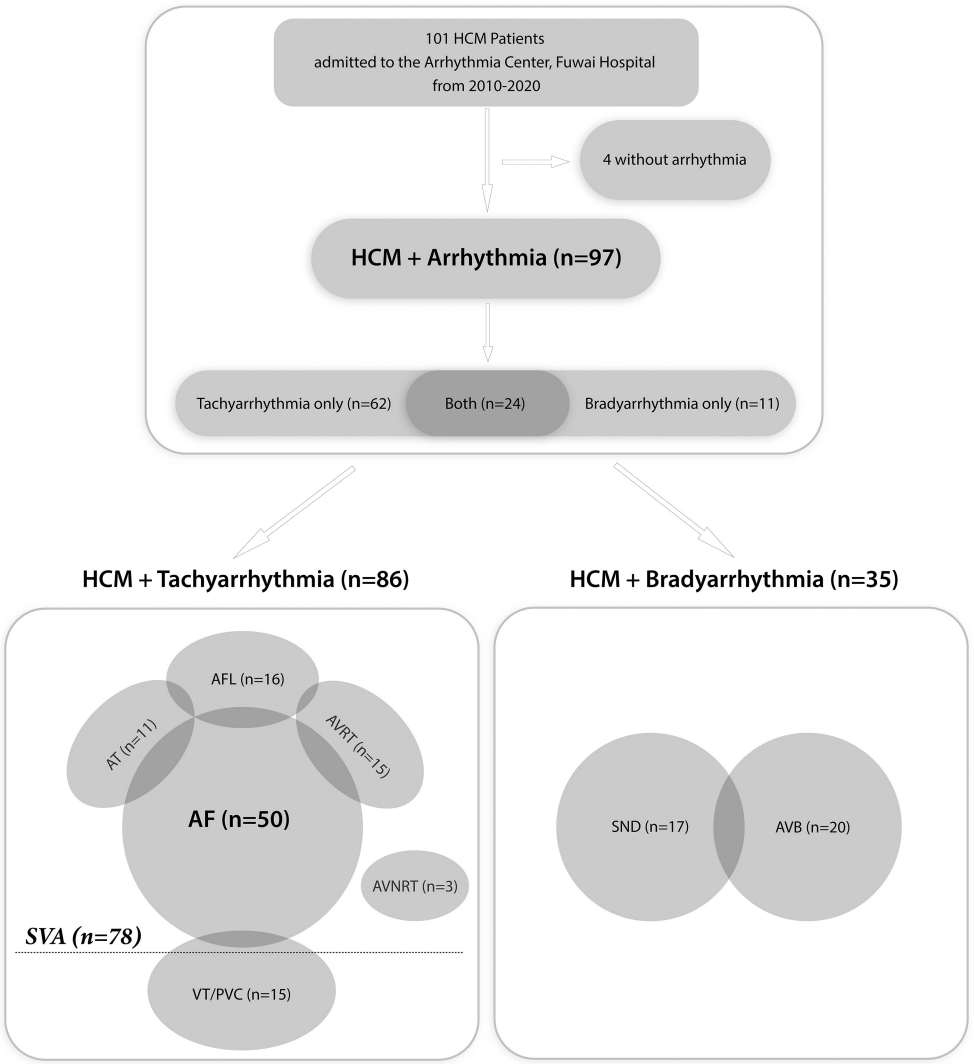

FIGURE 1 | Flow chart of all patients with arrhythmias. HCM, hypertrophic cardiomyopathy; SVA, supraventricular tachyarrhythmia; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; AVRT, atrioventricular reentrant tachycardia; AVNRT, atrioventricular nodal reentrant tachycardia; VT, ventricular tachycardia; PVC, premature ventricular contraction; SND, sinus node dysfunction; AVB, atrioventricular block.

Outcomes and Survival Analysis

Patients who underwent ablation were followed up for a median (IQR) of 58.5 (82.9) months, and no death or stroke event occurred. There was no recurrence in the 18 patients who were ablated for other types of SVAs. Five patients who were ablated for AF experienced recurrence. A survival analysis using the Kaplan–Meier curve method in patients who were ablated for AF is shown in **Figure 3**. The 1- and 7-year AF-free survival rates were 87.5 and 49.2%, respectively (**Figure 3A**). The AF-free survival was similar in patients with paroxysmal and persistent AF (data not shown).

All of the echocardiographic and clinical factors were compared between patients who experienced recurrences and patients who did not (**Supplementary Table 5**). Among all of the parameters, LVEDD was the only parameter that was significantly different between the two groups ($p = 0.009$, **Supplementary Table 5**). A receiver operator characteristic analysis showed that a greater LVEDD was associated with a higher recurrence of AF, with an optimum cutoff value of 47 mm (c-statistic = 0.91, $p = 0.011$, sensitivity = 1.00, specificity = 0.82) (**Figure 4**). In Kaplan–Meier analysis, patients with a LVEDD $\geq$ 47 mm had a worse AF-free survival than those with a LVEDD $<$ 47 mm (log-rank $p = 0.014$) (**Figure 3B**).

DISCUSSION

HCM has a prevalence of 1 case per 200-500 persons in the general population and affects ∼20 million people globally (30). HCM has been underrecognized in third-world countries including China for many years, but an awareness of this disease

TABLE 1 | Demographic and clinical characteristics.

Parameters	All SVA (*n* = 78)	AF (*n* = 50)	AFL (*n* = 16)	AT (*n* = 11)	AVRT (*n* = 15)	AVNRT (*n* = 3)
Male gender, *n* (%)	50 (64.1)	26 (52)	12 (75)	4 (36.4)	11 (73.3)	3 (100)
Weight, kg	70 ± 14.9	71 ± 14.3	68 ± 15.7	67 ± 18.6	64 ± 14.5	82 ± 7.9
Height, cm	169 ± 8.3	168 ± 9.2	169 ± 7.1	164 ± 9.5	169 ± 6.5	174 ± 6.0
BSA, m^2	1.79 ± 0.21	1.79 ± 0.22	1.76 ± 0.21	1.71 ± 0.26	1.73 ± 0.19	1.96 ± 0.10
BMI, kg/m^2	24.6 ± 4.19	25.1 ± 3.86	23.5 ± 4.53	24.7 ± 4.72	22.5 ± 4.31	27.3 ± 3.51
Age at admission, y	59 (23)	63 (21)	43 (25)	66 (14)	48 (30)	43 (NA)
Age at arrhythmia symptom onset, y	55 (27)	59 (23)	38 (29)	63 (23)	36 (38)	43 (NA)
Arrhythmia symptoms coincided with SVA events on Holter, *n* (%)	69 (88)	43 (86)	16 (100)	9 (82)	15 (100)	3 (100)
Age at HCM symptom onset, y	51 (29)	58 (23)	35 (31)	62 (25)	32 (28)	43 (NA)
History of syncope, *n* (%)	15 (19.2)	7 (14)	4 (25)	6 (54.5)	2 (13.3)	0 (0)
Family history of HCM, *n* (%)	5 (6.4)	4 (8)	1 (6.3)	0 (0)	0 (0)	0 (0)
SCD risk score, %	2.24 ± 1.54	2.13 ± 1.63	3.09 ± 1.49	2.39 ± 1.74	1.85 ± 0.96	1.56 ± 0.19
ICD implantation, *n* (%)	2 (2.6)	2 (4.0)	0 (0)	1 (9.1)	0 (0)	0 (0)
Comorbidities, *n* (%)	36 (46.2)	24 (48)	8 (50)	5 (45.5)	3 (20)	2 (66.7)
HTN, *n* (%)	31 (39.7)	20 (40)	4 (25)	7 (63.6)	7 (46.7)	1 (33.3)
CAD, *n* (%)	14 (17.9)	9 (18)	2 (12.5)	3 (27.3)	1 (6.7)	1 (33.3)
DM, *n* (%)	13 (16.7)	10 (20)	1 (6.3)	2 (18.2)	2 (13.3)	1 (33.3)
CHD, *n* (%)	3 (3.8)	3 (6)	1 (6.3)	0 (0)	0 (0)	0 (0)
VHD, *n* (%)	2 (2.6)	2 (4)	1 (6.3)	0 (0)	0 (0)	0 (0)
PH, *n* (%)	8 (10.3)	7 (14)	2 (12.5)	0 (0)	0 (0)	0 (0)
History of stroke, *n* (%)	8 (10.3)	4 (8)	4 (25)	2 (18.2)	1 (6.7)	0 (0)
NYHA-FC, *n* (%)						
I/II	71 (91.0)	46 (92)	15 (92.7)	11 (63.6)	15 (100)	15 (100)
III/IV	7 (9.0)	4 (8)	1 (6.3)	4 (36.4)	0 (0)	0 (0)

SVA, supraventricular tachyarrhythmia; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; AVRT, atrioventricular reentrant tachycardia; AVNRT, atrioventricular nodal reentrant tachycardia; BSA, body surface area; BMI, body mass index; HCM, hypertrophic cardiomyopathy; HTN, hypertension; CAD, coronary artery disease; DM, diabetes mellitus; CHD, congenital heart disease; VHD, valvular heart disease; PH, pulmonary hypertension; NYHA-FC, New York Heart Association functional class.

TABLE 2 | Echocardiography parameters.

Parameters	All SVA (*n* = 78)	AF (*n* = 50)	AFL (*n* = 16)	AT (*n* = 11)	AVRT (*n* = 15)	AVNRT (*n* = 3)
HCM types						
IVS hypertrophy	33 (42.3)	21 (42)	6 (37.5)	4 (36.4)	6 (40)	1 (33.3)
Apex hypertrophy	6 (7.7)	5 (10)	0 (0)	0 (0)	1 (6.7)	0 (0)
Multi-segment hypertrophy	39 (50)	24 (48)	10 (62.5)	7 (63.6)	8 (53.3)	2 (66.7)
LVOT obstruction, *n* (%)	19 (24.4)	13 (26)	2 (12.5)	5 (45.5)	3 (20)	0 (0)
Ejection fraction, %	63 (10.3)	63 (11.5)	61 (6.5)	65 (10.0)	65 (11.0)	60 (NA)
LA dimension (AP), mm	41 (11.0)	43 (8.5)	45 (13.8)	39 (15.0)	38 (10.0)	25 (NA)
LVEDD, mm	45 (8.3)	45 (8.0)	44 (13.8)	45 (9.0)	43 (9.0)	46 (NA)
Max LV thickness, mm	19 (6)	19 (5.3)	23 (6.50)	19 (4.0)	16 (4.0)	25 (NA)
Mitral regurgitation ≥ moderate, *n* (%)	9 (11.6)	6 (12)	2 (12.5)	1 (9.1)	1 (6.7)	0 (0)

SVA, supraventricular tachyarrhythmia; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; AVRT, atrioventricular reentrant tachycardia; AVNRT, atrioventricular nodal reentrant tachycardia; HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; LVOT, left ventricular outflow tract; ECHO, echocardiography; LA, left atrial; AP, anteroposterior; LVEDD, left ventricular end-diastolic dimension; LV, left ventricle.

is now penetrating the health care system in China (30). This study aimed to provide a comprehensive clinical profile of different types of SVAs and report the long-term outcomes of catheter ablation in a tertiary-based HCM population in China. Unlike other studies of arrhythmia in a general HCM population, the particular population in the present study were patients with HCM who were referred to the Arrhythmia Center who already had arrhythmia-related symptoms

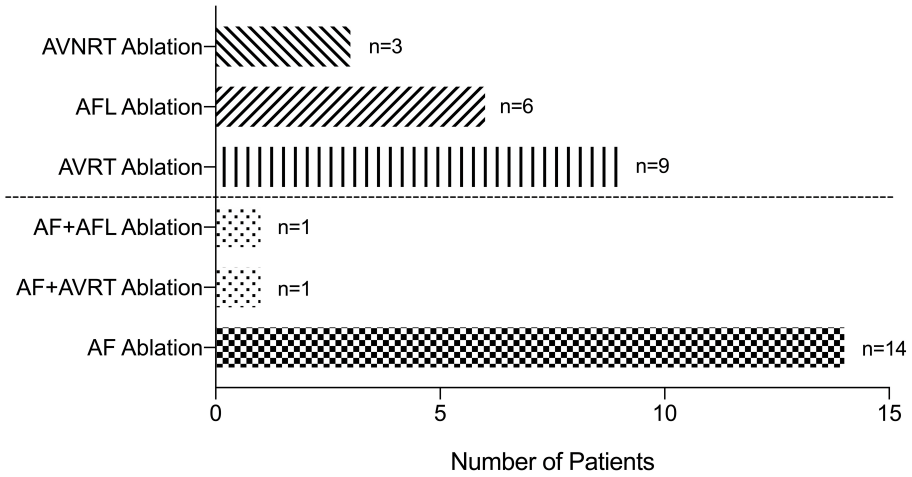

FIGURE 2 | Patients underwent successful ablation. AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; AVRT, atrioventricular reentrant tachycardia; AVNRT, atrioventricular nodal reentrant tachycardia.

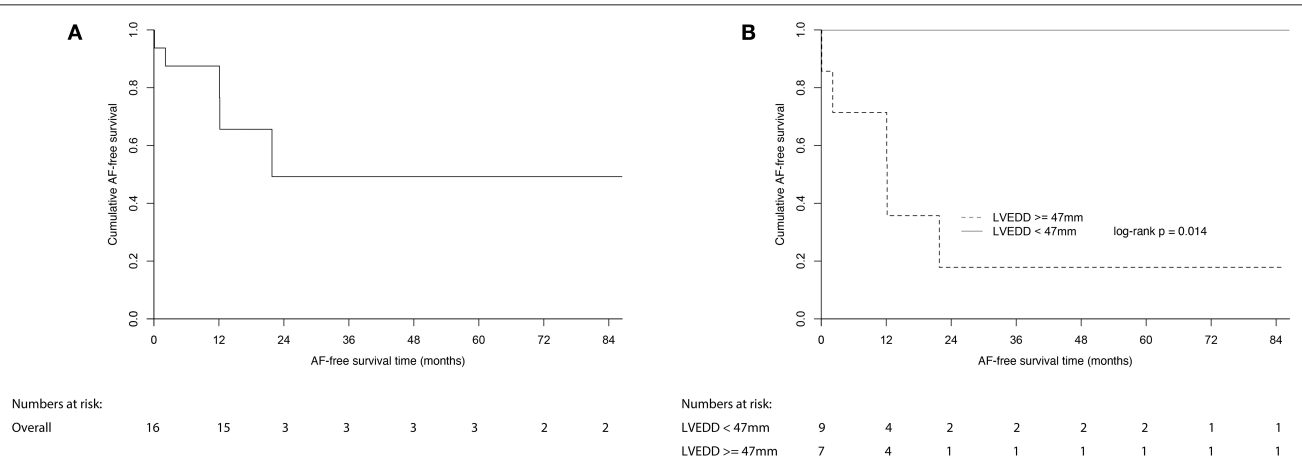

FIGURE 3 | Estimated AF-free survival of **(A)** all patients with AF underwent ablation; **(B)** patients with AF underwent ablation divided by LVEDD of 47 mm. AF, atrial fibrillation; LVEDD, left ventricular end-diastolic dimension.

with or without an abnormal ECG indicating arrhythmia at enrollment.

In this study, among the 86 patients with tachyarrhythmia, 78 (90%) had SVAs, in whom AF was the most common, followed by AFL, AVTR, focal AT, and AVNRT. AF was the most common arrhythmia in the present population, and it accounted for 64% of SVAs, 58% of tachyarrhythmias, and 52% of arrhythmias. This prevalence is consistent with previous studies (2, 15). Of the 50 patients with AF, 7 (14%) also had AFL. This percentage is similar to that reported in a study conducted by Rowin and colleagues (15). Surprisingly, 15 (15.5%) patients had AVRT, including 5 with Wolff-Parkinson-White syndrome. Fananapazir et al. showed that accessory atrioventricular pathways were only present in seven (5%) patients and only one had a record of AVRT (8). In their study, dual atrioventricular nodal pathways were present in three patients and neither of them had records of spontaneous AVNRT. However, in our study, three (3.1%) patients had AVNRT. Additionally, 11 (11.3%) patients were diagnosed with focal AT by ECG and Holter monitoring. Except for AFL, no reentrant AT was diagnosed in this study.

The first choice of rhythm control strategy in HCM patients with AF is antiarrhythmic drugs (1, 2). Catheter ablation is also an important option, while it is less effective than in the general population (1, 2). In this study, successful catheter ablation was performed in 16 patients in whom 3 with cryoablation and the other 13 with radiofrequency ablation. The ablation strategy was pulmonary vein isolation in 13 patients with persistent AF and in two patients with persistent AF. In the other two patients with persistent AF, ablation for adjunctive lines was performed. A meta-analysis of 15 studies conducted by Zhao et al. reported a pooled single-procedure success rate of 45.5% at 18 months (14). Another meta-analysis by Providencia et al. included five studies and showed that the single-procedure success rate was 38.7% in patients with HCM (31). The success rate of AF ablation

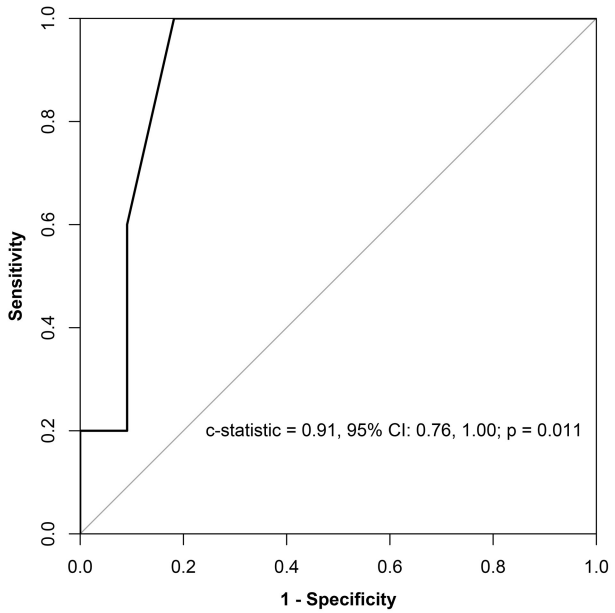

FIGURE 4 | Prognostic sensitivity and specificity of LVEDD for AF recurrence. LVEDD, left ventricular end-diastolic dimension; CI, confidential interval; AF, atrial fibrillation.

in our study was relatively high, and this finding could have occurred for the following reasons: (1) the sample size was relatively small; (2) patients who underwent catheter ablation were carefully evaluated and selected; (3) most (75%) of the patients had paroxysmal AF; and (4) some patients might have had recurrence without symptoms. Further randomized studies on AF ablation in patients with HCM are required.

There have only been a few studies on ablation in patients with HCM in other types of SVAs, including AFL, AVRT, and AVNRT. On the basis of the European Society of Cardiology guideline recommendations that EPS should be performed in patients with palpitations and the ablatable substrate for SVAs should be treated, we performed catheter ablation in 20 patients with other types of SVAs. Of the 20 patients, 1 had AVRT ablated simultaneously with AF and 1 had AFL ablated simultaneously with AF. Of the 10 patients with AVRT, 6 were left-sided and 4 were right-sided accessory pathways. All of the three AVNRTs were the slow-fast type. Of the seven AFLs ablated, five were typical cavotricuspid isthmus-dependent and two were non-cavotricuspid isthmus-dependent from the left atria. During follow-up, there was no recurrence of AFL, AVRT, or AVNRT. The success rate of catheter ablation was similar to that in the general population. The present study provides further evidence for EPS and ablation of non-AF SVAs in HCM.

In this study, we could not obtain genotype information which is important for classifying the etiology of HCM. Some etiologies might be associated with arrhythmia. Monda et al. and Limongelli et al. concluded that pre-excitation, atrioventricular block, and concentric left ventricular hypertrophy might be diagnostic clues for non-sarcomeric etiologies (32, 33).

LIMITATIONS

Firstly, this was a retrospective analysis from a single tertiary arrhythmia center. Therefore, there was likely to have been patient selection bias. Second, genotype information was not available in this study. Future studies on the relationship between genotype and SVAs in HCM are required. Third, some patients in this study were diagnosed by ECG and Holter monitoring rather than EPS, which might not have been precise, especially in patients with AT and AVRT. However, these cases were discussed thoroughly between at least two electrophysiologists in our center. Lastly, although this was a 10-year analysis, the sample size was small. One reason for this small sample size is that HCM is not a common disease and it is underrecognized in many places in China. Another reason for this small sample size is that the general population of HCM is referred to the Cardiomyopathy Center in our hospital while the population in this study only included patients with HCM who were referred to the electrophysiology and arrhythmia service. Surprisingly, this is a unique population that has not been previously reported. Further multicenter studies of SVAs in the general HCM population are required.

CONCLUSIONS

In this unique population of HCM, AF was the most common SVA, followed in order by AFL, AVRT, AT, and AVNRT. The long-term catheter ablation outcome for non-AF SVAs in HCM is satisfactory. A greater LVEDD predicts AF recurrence after catheter ablation in patients with HCM.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because research data is confidential. Data sharing requests are required to meet the policies of the hospital and the funder. Requests to access the datasets should be directed to doctortangmin@yeah.net.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Fuwai Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

H-DZ, J-TZ, P-HF, SZ, and MT: study conception and design. H-DZ and MT: analysis and interpretation of data, drafting of the article, and obtaining of funding. H-DZ, LD, S-XW, BZ, X-TD, L-XH, Y-JQ, F-YY, T-JF, J-TZ, WH, P-HF, SZ, and MT: critical revision of the article for intellectual content and final approval of the article. J-TZ, P-HF, WH, SZ, and MT: provision of study materials or patients. H-DZ, P-HF, SZ, and MT: statistical expertise. H-DZ, J-TZ, P-HF, WH, SZ, and MT: administrative,

technical, or logistic support. H-DZ, LD, and S-XW: collection of data. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.766571/full#supplementary-material

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GENERAL COMMENTARY
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Commentary: Characteristics and Long-Term Ablation Outcomes of Supraventricular Arrhythmias in Hypertrophic Cardiomyopathy: A 10-Year, Single-Center Experience

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Keywords: atrial fibrillation, hypertrophic cardiomyopathy, random error, survival analysis, Kaplan-Meier

A Commentary on

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INTRODUCTION

This paper is a commentary on the article "Characteristics and Long-Term Ablation Outcomes of Supraventricular Arrhythmias in Hypertrophic Cardiomyopathy: A 10-Year, Single-Center Experience (1)." The authors aimed to identify a cut-off value of left ventricular end-diastolic dimension (LVEDD) to predict atrial fibrillation (AF) recurrence after catheter ablation in patients with hypertrophic cardiomyopathy (HCM). However, there are inconsistencies between Figures 3A,B in numbers at risk, as well as, between the Kaplan-Meier curve and corresponding numbers at risk in the Figure 3B in the original manuscript. Furthermore, the receiver operative characteristic curves (ROC) analysis to find an optimal cut-off is not a reliable or accurate approach with such a small sample size ($n = 16$). Therefore, the conclusion of Zhang et al. that a greater LVEDD predicts AF recurrence after catheter ablation in patients with HCM may be unreliable.

MAIN TEXT

In the original manuscript, the inconsistency in numbers at risk between Figures 3A,B, as well as the inconsistency between the Kaplan-Meier curve and corresponding numbers at risk in Figure 3B, ought to get our attention. Firstly, in Figure 3A there are 15 patients at 12 months of follow-up in the Kaplan-Meier curve, while in Figure 3B, there are only 8 patients. Among them are 4 patients in the subgroup with LVEDD < 47 mm and 4 patients with LVEDD ≥ 4.7 mm. Hence, there are 7 patients missing in Figure 3B at the 12-month time point.

As a matter of fact, there are further inconsistencies: in Figure 3A, a proportion of 1/3 among the 15 patients remaining at the 24-month time point has had a relapse, i.e., 5 patients, and according to the text, the subgroup with LVEDD < 47 mm does not appear to have experienced any events during the follow-up period, so all of those had LVEDD ≥ 47 mm. However, in Figure 3B, there

were only 7 patients fulfilling the criterion of LVEDD $\geq$ 47 mm, and of those, 4 are remaining in the curve at the 12-month time point suggesting only 3 patients with LVEDD $\geq$ 47 mm had relapsed into AF at that point.

Secondly, as described in the original manuscript, Figure 3B shows that "In Kaplan-Meier analysis, patients with a LVEDD $\geq$ 47 mm had a worse AF-free survival than those with a LVEDD $<$ 47 mm (log-rank $p = 0.014$) (1)". As the Figure 3B shows that of the 16 patients who had AF ablation, although, the cumulative AF-free survival in the subgroup with LVEDD $<$ 47 mm is a straight line, which means that the subgroup does not appear to have experienced any events during the follow-up period, the corresponding Number at risk, at the bottom of the Figure 3B, in LVEDD $<$ 47 mm subgroup does not match to the straight line. Moreover, it is difficult to believe that log-rank testing would be significant with such small numbers in the Kaplan-Meier curve.

Only 19% of their ablation patients have two or more years of follow-up. Hence, the title is misleading as there is not really a meaningful 10-year follow-up to show.

Furthermore, to determine an optimal cut-off value of LVEDD by receiver operating characteristic (ROC) analysis to predict AF recurrence after catheter ablation in patients with HCM in a sample size of 16 persons may be a kind of irrationality, which causes the occurrence of random error. In consequence, the conclusion of Zhang et al. that a greater LVEDD predicts AF recurrence after catheter ablation in patients with HCM may be unreliable. Our task group hopes the authors can give a reasonable explanation.

DISCUSSION

Keeping the data consistent with the figure helps the reader not to be confused and is more conducive to the exchange of the author's clinical experience. When ROC was used to determine the optimal cut-off values of predictors, a larger sample size may make the conclusion more reliable.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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ORIGINAL RESEARCH
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Administration of Adenosine Triphosphate Provides Additional Value Over Programmed Electrophysiologic Study in Confirmation of Successful Ablation of Atrioventricular Accessory Pathways

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Objectives: To study the benefit of adenosine triphosphate (ATP) in evaluating ablation endpoints of accessory pathways (AP) and subsequent long-term prognosis.

Methods: We reviewed consecutive patients with supraventricular tachycardias due to APs that underwent radiofrequency catheter ablation (RFCA) from January 2016 to September 2018 in our center. The patients were divided into two groups: the ATP group (who had passed both the ATP test and PES after ablation as the endpoint) and the non-ATP group (who had passed PES only after ablation as the endpoint). We reviewed the patients' intra-cardiac electrograms and analyzed their long-term outcomes.

Results: In total, 1,343 patients underwent successful RFCA. There were 215 patients in the ATP group with one lost to follow-up. There were 1,128 patients in the non-ATP group with 39 lost to follow-up. Twenty-three patients in the ATP group demonstrated additional electrophysiological entities due to ATP administration, including reappearance of the ablated APs in 16 patients, discovery of PES-undetected APs in 5, induction of atrial fibrillation in 5, premature atrial contractions in 1, and premature ventricular contractions in another. During the 7 to 39 months (average 24.4 ± 9.5 months) follow-up, the recurrence rate was 8.41% (18/214) in the ATP group and 6.80% (74/1,084) in the non-ATP group. In subjects with recurrence, 14 patients (14/18 = 77.8%) in the ATP group and 50 patients (50/74 = 67.6%) in the non-ATP group accepted redo ablations. Among the ATP-group, all the 14 redo APs were the old ones as before. Among the non-ATP-group, redo ablations confirmed that 39 APs were the old ones, while 20 APs were newly detected ones which had been missed previously. The difference in recurrent

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AP locations confirmed by redo procedures between the two groups was significant ($p = 0.008$). In the non-ATP group, 20 (40%) of redo cases were proven to have multiple APs, while 33 (3.3%) cases who did not suffer from recurrence had multiple APs. Existences of multiple APs in recurred cases were significantly higher than that in non-recurred ones in the non-ATP group ($p < 0.001$), while there was no such difference in the ATP group ($p = 0.114$).

Conclusions: The existence of multiple APs was more common in recurrent cases if ATP was not used for confirmation of ablation endpoints. ATP probably has additional value over PES alone by detecting weak AP conductions. ATP can evoke atrial and ventricular arrhythmias.

Keywords: adenosine triphosphate, programmed electrophysiologic study, catheter ablation, accessory pathways, long-term outcomes

INTRODUCTION

There are usually two methods to determine successful ablation endpoints for accessory pathways (AP). One is programmed electrophysiological study (PES), the other is medication confirmation, including injection of isoproterenol which can activate sympathetic nerves and adenosine/adenosine triphosphate (ATP) which can block the atrioventricular (AV) node to feature the existence of APs if still there (1, 2). Catecholamine sensitivity is an uncommon feature of APs (3). Although isoproterenol can change reentrant coupling between APs and the AV node, it seldom affects APs directly, except for a few isoproterenol-sensitive APs (4). Adenosine and ATP have been used for determination of AP ablation endpoints for years, but previous studies were mostly cross-sectional and seldom provided follow-up data (5, 6). Many electrophysiologists now prefer to do PES alone to test the endpoint since PES is considered adequate to determine the presence of most APs especially when they could be easily detected before ablation. We evaluated that the administration of ATP in combination with PES could be superior to PES alone in confirmation of ablation endpoints of APs, based on long-term follow-up data.

METHODS

Patient Population and Pre-procedural Preparation

We reviewed consecutive cases with supraventricular tachycardias due to APs demonstrated by intracardiac PES that underwent radiofrequency ablation from January 2016 to September 2018 in our hospital. All patients were older than 14 years of age and all of them or their guardians had signed informed consents for invasive PES and ablation before the procedure. We divided the patients into two groups: those who had passed both PES and ATP testing for the absence of an AP as the endpoint of catheter ablation (ATP group) and those without administration of ATP (non-ATP group) that underwent PES alone. Contraindications to ATP such as asthma, bronchitis, chronic obstructive pulmonary diseases, heart failure, uncontrolled hypertension, or significant ischemia were excluded before the ATP test. The following patients were excluded from the analysis: 1. Those who had experienced previous AP ablations before January 1, 2016, 2. patients with acute unsuccessful outcomes of AP ablations in our hospital, 3. patients who did not consent to AP ablation following PES.

Electrophysiological Study

Two quadripolar mapping catheters including a His bundle catheter, and right ventricular apex (RVA) catheter were placed via the right femoral vein under fluoroscopic guidance. A decapolar (2-8-2 mm inter-electrode space) coronary sinus (CS) vein catheter was placed either via the left/right femoral vein or via the left sub-clavicular vein. Intracardiac electrocardiograms during sinus rhythm and arrhythmia were analyzed. Electrophysiological study techniques including burst pacing, programmed stimulation, entrainment, and His bundle refractory premature ventricular stimulus (RS2) were used for diagnosis of the arrhythmia mechanism.

We divided the A-V annulus into 12 parts: I. Left posterior septum, II. left posterior free wall, III. left lateral free wall, IV. left anterior free wall, V. coronary sinus orifice, VI. right posterior septum, VII. right inferior free wall, VIII. right superior free wall, IX. epicardial posterior septum within the coronary sinus, X. His region, XI. aorto-mitral continuity, and XII. nodo-ventricular fibers. Divided AP locations are shown in **Supplementary Figure 1**.

Ablation and Procedure Endpoints

Three-dimensional electro-anatomical mapping systems (Carto 3, Biosense Webster, Diamond Bar, CA and Ensite NAVX, Abbott, Minneapolis, MN) were used for most procedures, while some procedures were guided only by fluoroscopy. Temperature-controlled ablation catheters were applied to most patients (55–60°C, 40–70 W), while irrigated catheters were used in some challenging cases (43°C, 20–40 W, saline flow 17–30 mL/min). The ablation targets were located on the atrio-ventricular annulus with the earliest local atrial potential during ventricular pacing or tachycardia for concealed APs, and the earliest local ventricular potential for manifest APs, with AP potentials if available. For

nodo-ventricular fibers, ablation was done at the slow AV nodal pathway area, the lower region of the Triangle of Koch.

For the non-ATP group, after successful ablation of the AP, PES was conducted including S1S1, S1S2, and S1S2S3 stimulation in the atrium and ventricle on the ipsilateral side and the contralateral site of the AP in turn by the ablation catheter or the RVA catheter. If no antegrade A-V conduction (pre-excitation) or retrograde V-A conduction via APs (V-A dissociation during ventricular pacing) was observed, the procedure was considered successful and concluded after at least a 30-min waiting time in total post-ablation.

For the ATP group, if the patients had passed the above PES after initial ablation without evidence of AP, subjects underwent administration of the ATP test. Ventricular pacing was used temporarily with either the RVA catheter or the ablation catheter to ensure the right/left ventricle could be captured as a protection against slow ventricular rhythm during the ATP test. An ATP bolus was rapidly injected via the peripheral vein to block the AV node. If the patient's body weight was <50 kg, a lower bolus of 20 mg of ATP was injected. If the patient's body weight was more than 75 kg, a higher bolus of 40 mg of ATP was injected. Otherwise, a bolus of 30 mg of ATP was injected. When block of AV node was observed without antegrade A to V conduction or reappearance of pre-excitation, ventricular pacing from the ipsilateral side of the AP was performed to detect retrograde V to A conduction as a sign of concealed AP conduction. The procedure was concluded if there was no evidence of an AP, confirmed by ATP testing plus PES.

Follow-Up

All the patients were tele-connected to our follow-up staff by mobile application software which assisted in keeping in long-term touch with the medical aid of our center. Patients were advised to contact our follow-up staff if they had any recurrent symptoms and/or abnormal ECG findings. All the patients were routinely followed up over 1 month with a 12-lead surface ECG and inquiry of the existence of palpitations or other arrhythmia-related symptoms by EP faculty in the out-patient clinic. Afterwards, the follow-up staff would be consistently available to the patients *via* a mobile app. For any recurrent symptoms reported, patients would arrange visits to doctors in the out-patient clinic. Patients were also advised to go to the emergency room immediately whenever they suffered from recurrent symptoms to record real-time ECGs. Some patients accepted 24-h Holter monitoring. If confirmation of SVT was still obscure, they would endure trans-esophageal atrial pacing. Once recurrence was confirmed, the patient would be advised to have a redo ablation. Moreover, all the patients received telephone follow-ups between March 2019 and April 2019 for inquiry of long-term outcomes. Patients were considered free from recurrences if they fulfilled any one of the following criteria: 1. Negative ECG findings of delta waves without palpitations or dyspnea; 2. real-time ECG with symptoms but no evidence of supraventricular tachycardia and delta waves; and 3. negative findings of trans-esophageal pacing.

Statistical Analysis

Measurement variables are presented as mean ± standard deviation. Categorical variables are presented as percentages. Redo procedures performed on the same patients were assumed to be independent. A Chi-squared test (Pearson's Chi-squared test or Fisher's exact test) was done for comparison of categorical variables between the ATP group and the non-ATP group and for comparison of factors related to recurrences within each group.

RESULTS

General Data

There were a total of 1,362 patients with APs that underwent electrophysiology study during this period. Nineteen patients were excluded from further analysis, including 11 failed cases, 3 fasciculo-ventricular bundles that did not need ablation, 2 intermittent manifest APs without retrograde conduction that did not need ablation, and 3 para-Hisian APs where ablation was not performed. In the remaining 1,343 patients, 215 patients comprised the ATP group (1 lost to follow-up, 214 were enrolled in further statistics, mean age 36.8 ± 14.3 years) and 1,128 patients were within the non-ATP group (39 lost to follow-up, 1,089 enrolled in further statistics, mean age 41.4 ± 15.0 years). Three-dimensional electro-anatomical mapping systems (Carto 3 and Ensite NAVX) were used for 952 patients, while procedures for the other 391 patients were guided only by fluoroscopy. Temperature-controlled ablation catheters were applied in 1,304 cases (55–60°C, 40–70 W), while irrigated catheters were applied in 39 cases (43°C, 20–40 W, irrigation flow 17–30 mL/min). The enrollment flow chart is shown in **Figure 1**. Baseline data are shown in **Table 1**.

Distributions of All the Detected APs in Both Groups During the First Procedure

The distributions of all the detected APs in both groups during the first procedure are shown in **Figures 2A,B**. AP distributions of the ATP group were: I-18 (7.7%), II-10 (4.3%), III-23 (9.9%), IV-62 (26.6%), V-18 (7.7%), VI-10 (4.3%), VII-40 (17.2%), VIII-30 (12.9%), IX-5 (2.1%), X-14 (6%), AMC-2 (0.9%), and NV-1 (0.4%), totaling 233 APs (100%). AP distributions of the non-ATP group were: I-91 (7.9%), II-60 (5.2%), III-95 (8.2%), IV-614 (53.3%), V-68 (5.9%), VI-22 (1.9%), VII-83 (7.2%), VIII-82 (7.1%), IX-14 (1.2%), X-22 (1.9%), and AMC-2 (0.2%), totaling 1,153 APs (100%) (**Supplementary Table 1**). The distributions of all the AP locations were significantly different between the two groups (Pearson Chi-square value = 81.785, $p < 0.001$).

Phenomena Observed After ATP Administration

Among the ATP group, 23 patients showed additional arrhythmia substrates after administration of ATP during their first procedures. Among them, 16 patients' ablated APs which had passed PES re-appeared after initial ablation. These APs were further ablated until passing both ablation endpoints. Five patients showed evidence of APs other than the ablated ones that had not been detected by PES (**Figure 3**). All these missing APs were further ablated and tested again. Five patients had

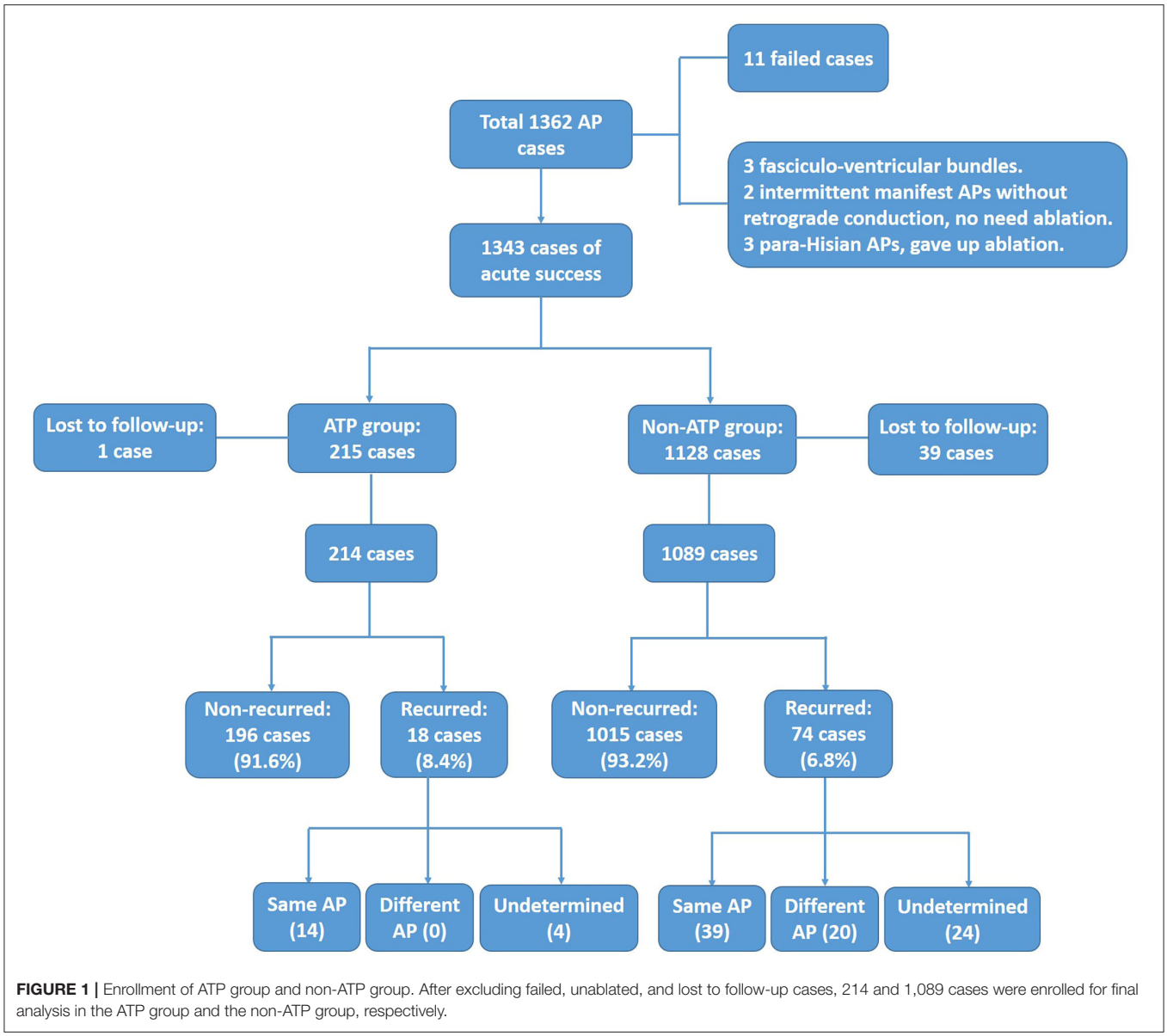

FIGURE 1 | Enrollment of ATP group and non-ATP group. After excluding failed, unablated, and lost to follow-up cases, 214 and 1,089 cases were enrolled for final analysis in the ATP group and the non-ATP group, respectively.

paroxysmal atrial fibrillation (PAF, **Figure 4**) lasting from 15 s to 5 min. One patient had frequent premature atrial contractions (PAC) and PAC did not disappear when ATP faded away. PAC ablation was done at the same time after additional informed consent of the patient and her family was obtained since we considered it would likely happen repeatedly in the patient's daily life. One patient had frequent premature ventricular contractions (PVC) that subsequently abated within 5 min of ATP bolus. Details are shown in **Supplementary Table 2**. On retrospective review, there were two patients with AP re-appearance during ATP testing that failed to be identified before conclusion of the procedures and suffered from recurrence during follow-up. They accepted redo ablations after their previous intra-cardiac electrograms had been reviewed.

Almost all patients who underwent ATP testing experienced related symptoms, including chest pressure, dyspnea, or flushing. At the same time, transient sinus bradycardia and complete AV node block were observed. Symptoms usually faded away within 1 min as normal sinus rhythm and AV node conduction restored. With the use of ventricular pacing backup and low flow oxygen supply, all the patients endured the above symptoms safely. There were no occurrences of bronchoconstriction, oxygen saturation decrease, severe hypotension, and/or malignant arrhythmias.

Severe Complications of Ablation

One subject in the ATP group with two concealed APs (one at the left anterior free wall, the other at the left posterior septum) suffered from second degree A-V block with 2:1 A-V conduction at the end of ablation, likely due to edema caused by prolonged ablation in the posterior septal area which extended to the atrioventricular node. After 2 days of monitoring and

TABLE 1 | General demographic data and clinical status of both groups.

Factors	ATP group ($n = 214$)	Non-ATP group ($n = 1,089$)	*P*-value
Age, years	36.8 ± 14.3	41.4 ± 15.0	<0.001
Gender, %	M: 127 (58) W**:** 87 (42)	M: 649 (60) W: 440 (40)	0.946[a]
Body weight (kg)	60.6 ± 11.1	53.8 ± 11.5	<0.001
Body mass index (kg/m^2)	22.2 ± 3.9	22.9 ± 5.0	0.182
Hypertension	17 (7.9)	91 (8.4)	0.841[b]
Diabetes	5 (2.3)	34 (3.1)	0.823[c]
Renal insufficiency	1 (0.5)	3 (0.3)	0.513[f]
Hyperglycemia or gout	7 (3.3)	29 (2.7)	0.620[d]
Baseline structural heart diseases	7	57	0.224[e]
Type of heart diseases	Coronary artery disease 1 Myocardial non-compaction 1 Mitral valve prolapse 1 Atrial septal defect 1 Ebstein's anomaly 1 Tricuspid insufficiency 1 Unclassified cardiomyopathy 1	Coronary artery disease 14 Mitral valve prolapse 9 Ebstein's anomaly 7 Hypertrophic cardiomyopathy 4 Rheumatic heart disease 4 Fallot tetralogy 1 Ventricular septal defect 1 Atrial septal defect 1 Aortic bicuspid valve 5 Left ventricle non-compaction 1 Tricuspid insufficiency 3 Aortic valve replacement 1 Restrictive cardiomyopathy 1 Myocarditis 2 Dilated cardiomyopathy 1 Unclassified cardiomyopathy 2	

M, man; W, woman.
[a]*Pearson Chi-Square value 0.005.*
[b]*Pearson Chi-Square value 0.04.*
[c]*Pearson Chi-Square value 0.265.*
[d]*Pearson Chi-Square value 0.246.*
[e]*Pearson Chi-Square value 1.476.*
[f]*Analyzed by Fisher's exact test.*

intravenous dexamethasone infusion of 10 mg per day, he made a complete recovery from an A-V block.

One subject in the non-ATP group experienced pericardial tamponade during ablation of an AP at the right free wall of the tricuspid annulus after a steam pop. Pericardial drainage was performed, and the AP was ablated successfully. One subject in the non-ATP group was diagnosed with a hemothorax after ablation with 330 ml of bloody fluid drawn out. Another subject in the non-ATP group was also diagnosed with a hemothorax and recovered with conservative care. Their hemothorax was caused by a sub-clavicular vein puncture for the insertion of a coronary sinus electrode which injured the pleura.

Other patients survived their procedures safely.

Follow-Up Outcomes

Among the ATP group, 18 patients (18/214 = 8.4%) had recurrence. There was no significant difference in the recurrence rate between the two groups ($p = 0.399$). Fourteen recurrent patients (14/18 = 77.8%) accepted redo procedures and all were confirmed to have the same APs as their first procedures. Two (2/14 = 14.3%) of them were discovered to have multiple APs, while redo procedures demonstrated that all of them had only 1 recurred AP, 14 in total. The locations and percentages of recurrent APs are listed in **Figure 2A** and are depicted in **Figure 5A**. The remaining four recurred cases did not accept redo procedures; however, their surface ECGs showed the same morphology of delta waves as previously seen which suggested that the recurrent APs were likely the same as before. Since the AP locations of these four patients were not confirmed by redo procedures, they were not included in further statistical analysis. On the other hand, 7 out of the 196 patients who did not suffer from recurrence had multiple APs (3.6%).

Among the non-ATP group, 74 patients (74/1,089 = 6.8%) had recurrence. Fifty recurrent patients (50/74 = 67.6%) accepted redo ablations. These patients were discovered to have had a total of 59 APs by redo procedures, including 39 "old" ones and 20 newly detected ones. Twenty (20/50 = 40%) of them were proved to have multiple APs, summed up by their first and redo procedures. Their redo procedures demonstrated one to three recurrent APs for everyone. The locations and percentages of the 59 recurrent APs are listed in **Figure 2B** and depicted in **Figure 5B**. The remaining 24 recurrent patients did not accept redo procedures to prove their accurate AP locations; however, the above 9 patients' surface ECGs during follow-up showed the

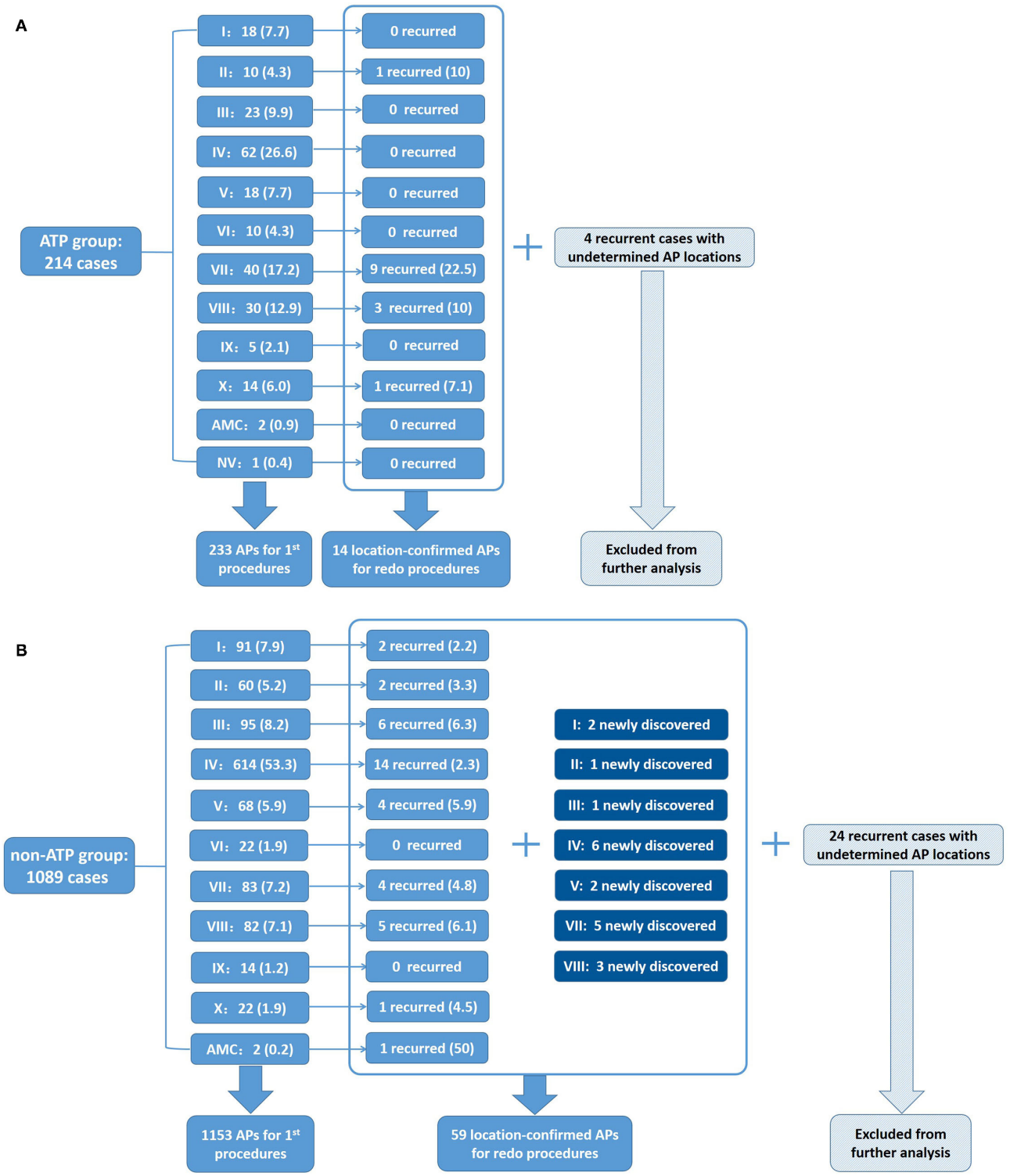

FIGURE 2 | Distributions of APs detected in the ATP group and the non-ATP group. **(A)** Distribution percentages of APs in the ATP group in first procedures and recurrence percentages redo procedures of the ATP group. Four recurrent cases with undetermined AP locations were excluded from further analysis. **(B)** Distribution percentages of APs in the first procedures and recurrence percentages in redo procedures of the non-ATP group. Twenty-four recurrent cases with undetermined AP locations were excluded from further analysis.

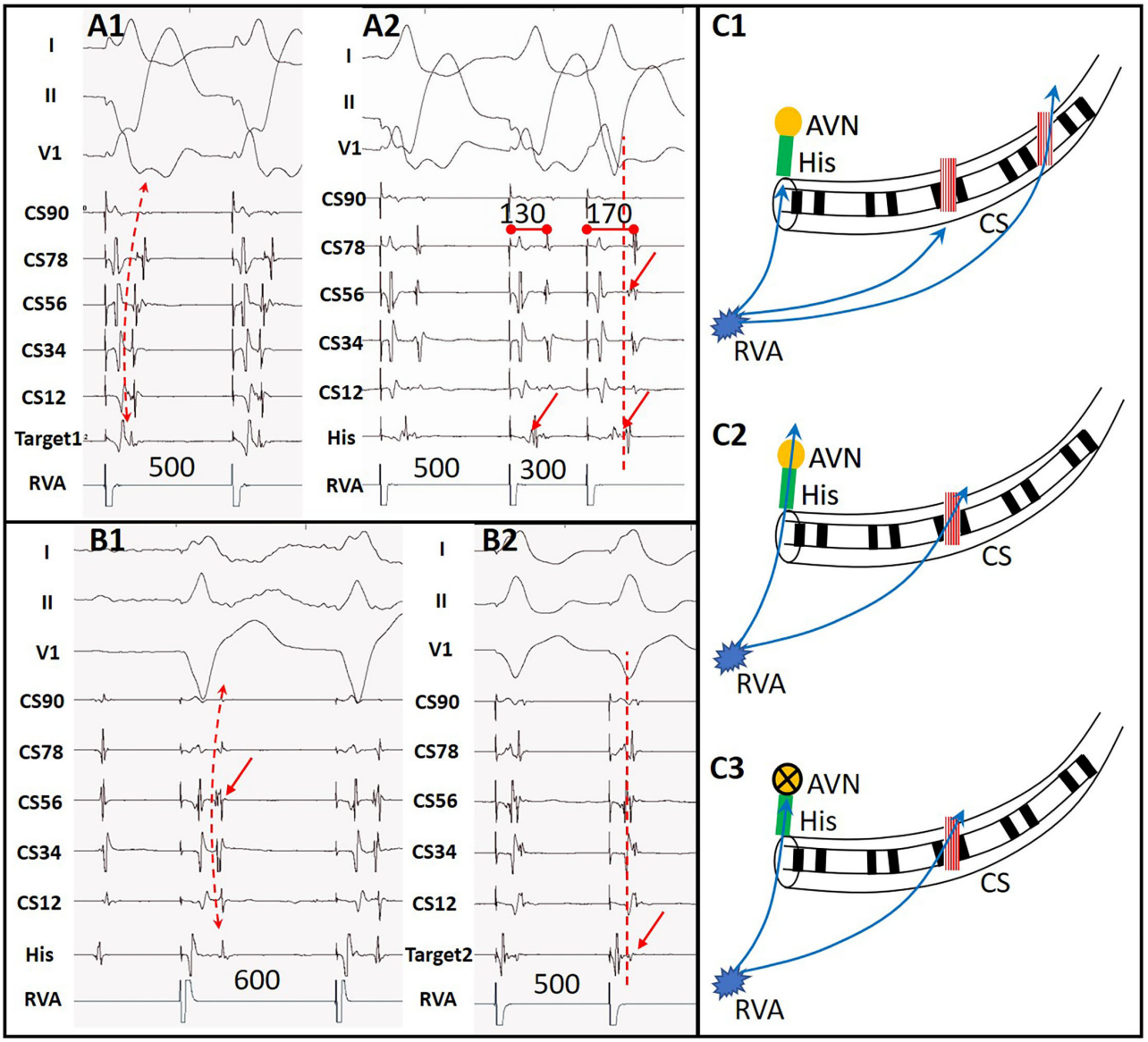

FIGURE 3 | A case with another AP detected by ATP. **(A1)** Ventricular stimulation showed acentric retrograde V-A conduction indicating a left lateral wall AP. **(A2)** Decremental V-A conduction after ablation of the first AP with the earliest retrograde A at CS56. **(B1)** Retrograde V-A conduction during ATP functioning with the earliest retrograde A at CS56, indicating a second AP *in situ*. **(B2)** Target of the second AP near CS56. **(C1)** Sketch map of predominant retrograde conduction via the first AP at the left lateral wall during RVA pacing as **(A1)**. **(C2)** Simultaneous retrograde conduction via AVN and the second AP during RVA pacing after elimination of the first AP as **(A2)**. **(C3)** Retrograde conduction *via* the second AP at CS56 during ATP functioning as **(B1)**. RVA, right ventricular apex; AVN, atrio-ventricular node; CS, coronary sinus; His, His bundle.

same morphology of delta waves as before, which suggested that the recurrent APs were likely the old ones. These unconfirmed APs were also excluded from further statistical analysis. On the other hand, 33 out of the 1,015 patients who did not suffer from recurrence had multiple APs (3.3%).

New AP locations of recurrent cases confirmed by redo procedures between the two groups were significantly different ($p = 0.008$, by Fisher's exact test, **Supplementary Table 3**). Existences of multiple APs in the two groups were not significantly different ($p = 0.415$; **Supplementary Table 4**). Existences of multiple APs in recurred cases were significantly higher than that in non-recurred ones in the non-ATP group ($p < 0.001$; **Table 2**).

We listed some factors that were potentially related to long-term AP recurrences in both groups including age, gender, body weight, body mass index, hypertension, diabetes, renal insufficiency, hyperurecemia/gout, and baseline structural heart diseases. We analyzed their relations to AP recurrence in both groups, respectively, only to find that male gender and larger body weight were significantly related to higher AP recurrence in

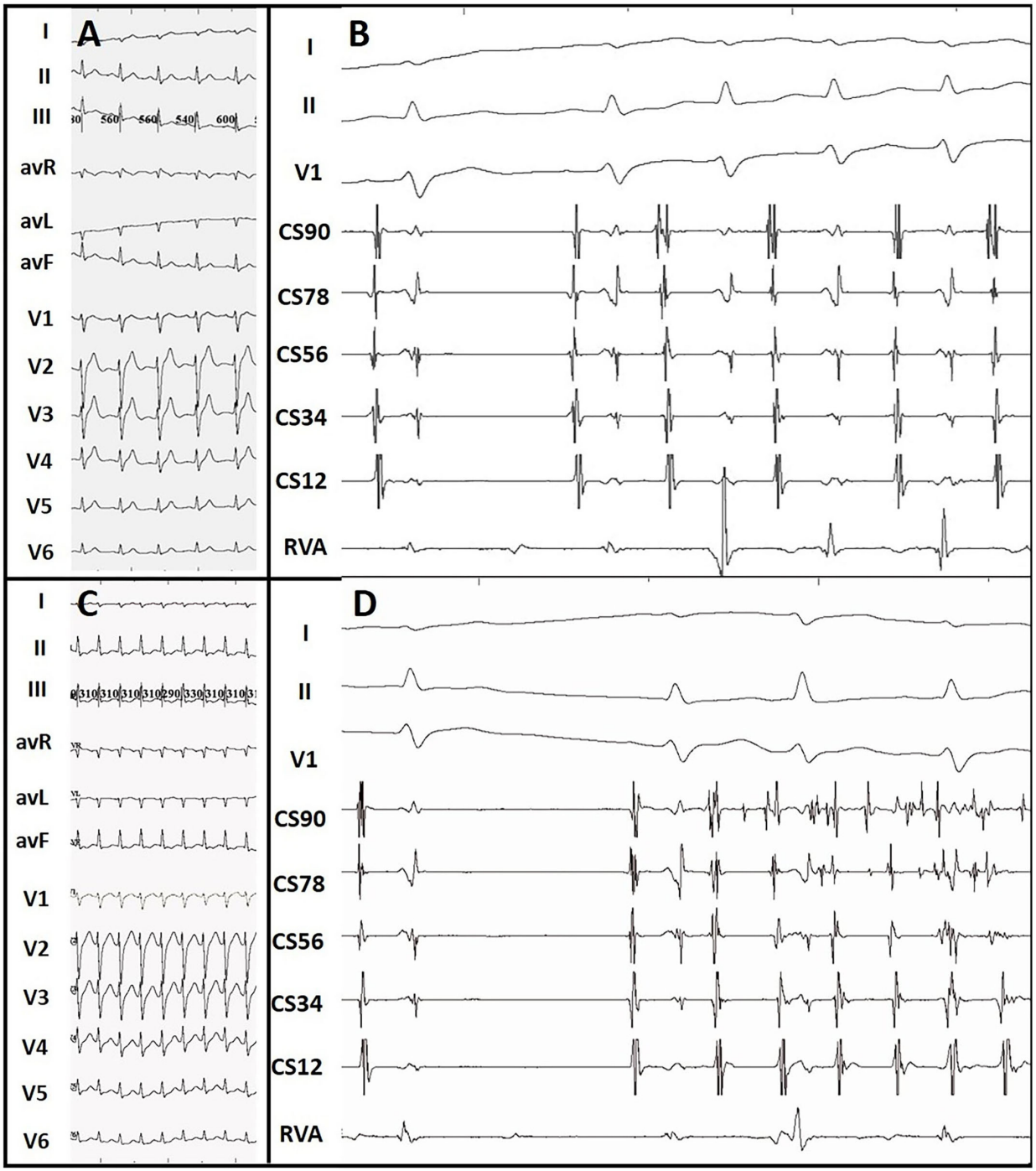

FIGURE 4 | ATP-induced paroxysmal atrial tachycardia and atrial fibrillation. **(A)** Sinus surface ECG. **(B)** ATP-induced paroxysmal atrial tachycardia. **(C)** Surface ECG during supraventricular tachycardia. **(D)** ATP-induced paroxysmal atrial fibrillation. Atrial tachycardia and atrial fibrillation terminated within 10 s and 5 min, respectively.

the non-ATP group, while none of the above factors were related to recurrence in the ATP group. The results are shown in **Table 3**.

DISCUSSION

The major findings of the present study are as follows:

1. The existence of multiple APs increases recurrent risk if ATP was not used for confirmation of ablation endpoints.
2. Sufficient ATP not only unmasks dormant AP conduction after initial ablation, but also reveals weak APs that are less conductive than the AV node under PES.
3. ATP can evoke atrial and ventricular arrhythmias.

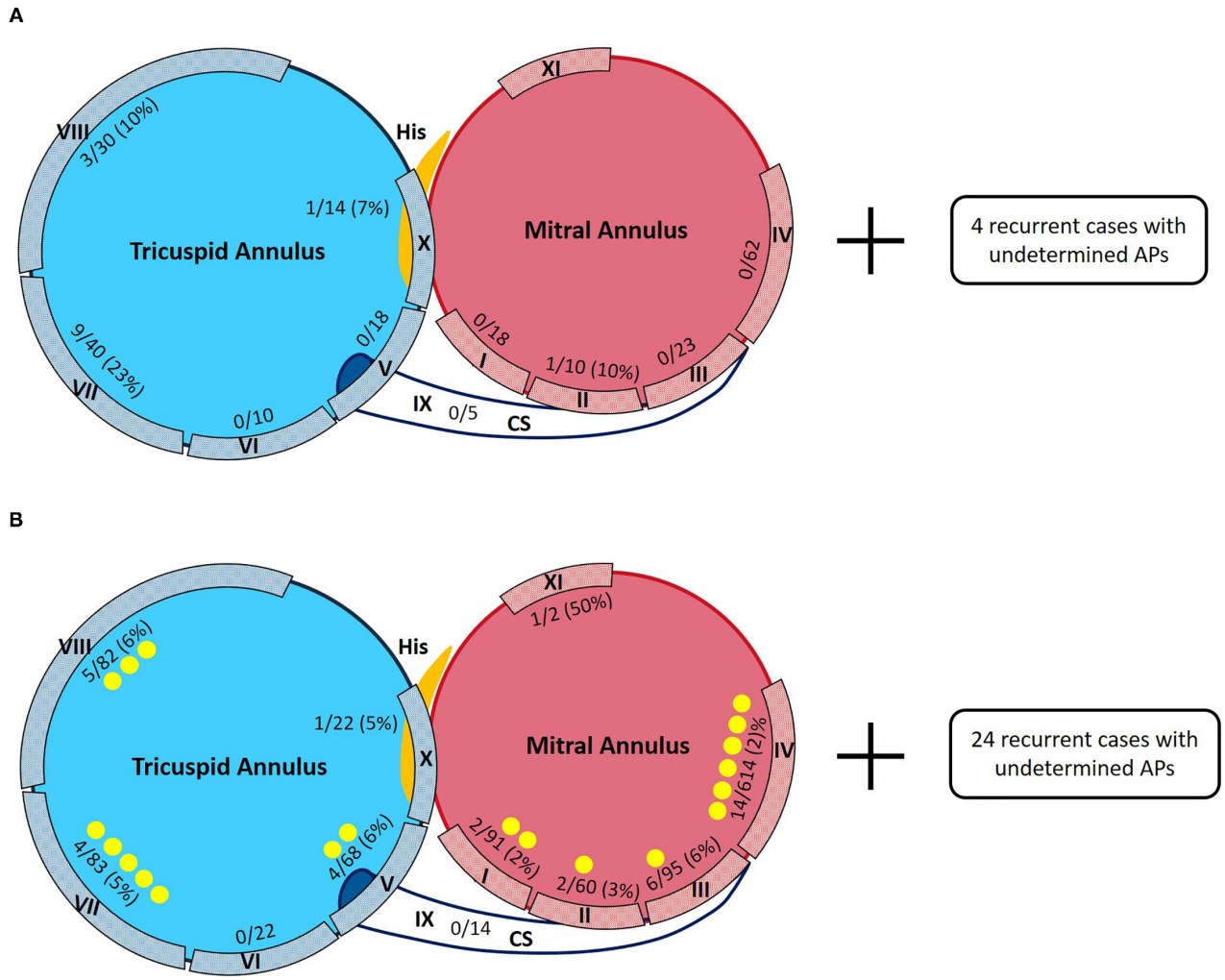

FIGURE 5 | Sketch maps of APs detected in the ATP group and the non-ATP group. Denominators are numbers of APs detected during the first procedures. Numerators are numbers of recurred APs confirmed by redo procedures. Yellow points are for the newly discovered APs during redo procedures. **(A)** Distributions of APs in the ATP group in first and redo procedures. Four recurrent cases with undetermined AP locations were excluded from further analysis. **(B)** Distributions of APs in the non-ATP group in first and redo procedures. Twenty-four recurrent cases with undetermined AP locations were excluded from further analysis.

4. ATP bolus injection is safe with ventricular back-up pacing.

It has long been proven that existence of multiple APs is a risk factor for recurrence after ablation (7). This study also attained similar results. While our main discovery was that sufficient ATP administration for endpoint confirmation of AP ablation probably improved long-term outcomes.

ATP can be rapidly degraded into adenosine diphosphate (ADP), with ADP degraded into adenosine monophosphate (AMP) and AMP dephosphorylated into adenosine, it is conceivable that some of the ATP effects on the AV node are mediated by adenosine. ATP has a similar function to adenosine which can block AV nodal conduction transiently and reversibly but seldom blocks AP conduction (except for those rare AV node-dependent APs, such as nodo-ventricular and nodo-fascicular APs). The half-life of ATP is about 30 s. The effect of both adenosine and ATP on the AV node resembles the action of slow channel blocking agents, such as verapamil and manganese chloride (8). It was suggested that the AV block caused by adenosine is associated with suppression of isoproterenol-enhanced I_f and I_{ca} (9). The rapid onset and transient duration of the adenosine- and ATP-induced AV block are also similar to the effects of acetylcholine on the AV node (10). Adenosine and ATP have long been utilized in emergency rooms to terminate narrow-QRS tachycardias (11, 12). Since ATP solely blocks AV nodal conduction, it can be useful for the detection of extra-nodal pathways. It is additionally useful in EP labs for the differential diagnosis between supraventricular tachycardia and ventricular tachycardia and for testing of ablation endpoints of APs.

TABLE 2 | Differences in existence of multiple APs between recurred and non-recurred cases in both groups.

Grouping	Status	Multiple APs (%)	Single APs (*p*%)	Patients	*P*-value
ATP group	Non-recurred	7 (3.6)	189 (96.4)	196	0.114[a]
	Recurred + redo	2 (14.3)	12 (85.7)	14	
	Recurred + non-redo	–	–	4	
Non-ATP group	Non-recurred	33 (3.3)	982 (96.7)	1,015	<0.001[b]
	Recurred + redo	20 (40)	30 (60)	50	
	Recurred + non-redo	–	–	24	

[a]*Pearson Chi-square value 3.657.*
[b]*Pearson Chi-square value 136.*

TABLE 3 | Factors potentially related to long-term outcomes of both groups.

Factors	ATP group (*N* = 214)			Non-ATP group (*N* = 1,089)		
	Recurred (*n* = 18)	Non-recurred (*n* = 196)	*P*-value	Recurred (*n* = 74)	Non-recurred (*n* = 1,015)	*P*-value
Age, years	33.8 ± 15.2	37.2 ± 14.2	0.338	41.1 ± 15.4	41.5 ± 15.0	0.825
Gender, %	M: 11 (61) W: 7 (39)	M: 119 (61) W: 77 (39)	0.963[a]	M: 37 (50) W: 37 (50)	M: 612 (60) W: 403 (40)	0.014[b]
Body weight (kg)	56.6 ± 12.3	61.1 ± 11.1	0.118	57.7 ± 9.8	62.5 ± 11.6	0.009
Body mass index (kg/m^2)	20.9 ± 2.7	22.5 ± 3.4	0.227	22.2 ± 3.3	23.0 ± 5.1	0.284
Hypertension	0	17 (8.7)	0.371[d]	7 (9.5)	84 (8.3)	0.749[c]
Diabetes	0	5 (2.6)	1[d]	3 (4.1)	31 (3.1)	0.499[d]
Renal insufficiency	0	1 (0.5)	1[d]	1 (1.4)	2 (0.2)	0.19[d]
Hyperglycemia or gout	1 (5.6)	6 (3)	0.464[d]	4 (5.4)	25 (2.5)	0.101[d]
Baseline structural heart diseases	2 (11.1)	5 (2.6)	0.109[d]	1 (1.4)	57 (5.6)	0.175[d]

[a]*Pearson Chi-square value 0.002.*
[b]*Pearson Chi-Square value 6.072.*
[c]*Pearson Chi-Square value 0.102.*
[d]*Analyzed by Fisher's Exact Test.*
Renal dysfunction was defined as eGFR < 60 ml/min. Since the enrollment of both groups was not decided randomly, no comparison was made between groups.

Besides its blocking function, ATP has also been reported to provoke dormant electrical conduction. It can provoke reconnection between the left atrium and the pulmonary veins after initially successful pulmonary vein isolation (13). The mechanism of this phenomenon is thought to be secondary to membrane hyperpolarization of partially depolarized cardiac tissue caused by ablation impairment (14). It can also induce atrial tachycardias (15) and premature ventricular ectopies (16, 17) by its potential to activate muscular sleeve fibers. The above phenomena were also observed in our series of patients. We observed episodes of AF after ATP injection in several patients. The detailed mechanism of ATP inducing arrhythmias is not clear, but some believe that it mainly depends on the ATP-sensitive K^+ channels. Li and colleagues reported that adenosine-induced AF is driven by localized reentry in RA areas with highest expression of adenosine A1 receptors and its downstream G protein-coupled inwardly rectifying potassium (GIRK) channels ($I_{K,Ado}$) (18). Such research has suggested that there exists some molecular basis for ATP and adenosine to induce arrhythmias. In our opinion, ATP is helpful in the induction of certain arrhythmias which are due to activation of localized muscular sleeves. There were also reports on adenosine unmasking recurrent dormant AP conduction right after catheter ablation (5, 6). Dormant AP conduction was reported to be associated with higher rates of recurrent AP conduction requiring repeat ablation and possibly via AP membrane potential hyperpolarization. Alvarez prospectively applied 108 ATP tests on Wolff-Parkinson-White patients undergoing ablation procedures. After successful ablation confirmed by PES, ATP was injected. The diagnostic accuracy of the ATP test was 95%, sensitivity 69%, specificity 100%, and positive and negative predictive values 100 and 95%, respectively. They suggested that ATP administration has a high predictive value for AP early recurrence (19). However, none of these studies had control groups and reported the results of long-term follow-up.

Our study also observed the same phenomena as above. Most APs detected during redo procedures in both groups were initial ones. There were 7.4% of cases in the ATP group that demonstrated having dormant APs right after injection of ATP. However, we still observed something new. All the APs of the recurrent cases in the ATP group were initial ones, while only 66% of the APs of recurrent cases in the non-ATP group were initial ones. In addition, ATP also discovered new APs in five cases after initial ablations.

All these patients continued with ablation until they passed both tests as a reinforced endpoint. This phenomenon suggested that injured APs were likely to "hide" themselves during routine PES, especially when there was more predominant conduction through the AV node. Some inactive APs may also remain undiscovered during PES if AV nodal conduction was superior until the AV node was blocked by ATP. This phenomenon may be due to three factors. One is that the prolonged refractory period of injured APs prevents detection by PES. Another is the activating effect of ATP on AP bundles. The third is the prolonged waiting time due to PES plus ATP testing. All of the above suggested that passing PES plus ATP testing as a combined endpoint of AP ablation was helpful to successfully eliminate APs. Although a full-dosage ATP bolus aiming to result in complete AV block can cause obvious transient side effects, it is nevertheless safe under the protection of ventricular pacing and by avoiding the contraindications to this agent, including asthma, glaucoma, severe urinary obstruction, etc.

Recurrence rates of AP conduction after successful ablation were 5–8% according to past studies (20–22). In our study, the recurrence rate was 8.4% in the ATP group and 6.8% in the non-ATP group, like others. The fact was that the recurrence rate was higher in the ATP group than in the non-ATP group in our study, although not statistically significant, suggesting that the combined procedural endpoint did not seemingly benefit long-term prognosis. We consider this finding to be mainly caused by selection bias of the operating physicians who were prone to use ATP in more challenging cases subjectively, such as those APs on the free wall of the tricuspid annulus, APs within CS, APs on AMC, etc. Since ATP testing helps us to observe many extra electrophysiologic phenomena during ATP testing, especially evidence of new APs which had not been discovered by routine PES and reappearance of ablated APs, we can still conclude that ATP provides additional value over PES alone in confirmation of an ablation endpoint for APs. Moreover, the recurrent APs within the ATP group during long-term follow-up were the same ones, while the recurrent APs within the non-ATP group during follow-up were prone to be newly detected ones. This difference between the two groups was statistically significant. This also suggested that ATP testing may help discover all APs present at an initial ablation procedure, potentially resulting in better long-term outcomes.

A past study administered a small bolus of ATP to patients with APs. They found that failure of an intravenous bolus injection of 8 mg of ATP to produce V-A conduction block identified the presence of an AP with a sensitivity of 84%, specificity of 71%, and predictive value of 72%. The effects of ATP on the AV node were concordant with the effects of a combination of verapamil and propranolol in 91% of patients, suggesting that this dose of ATP was an equipotent AV nodal blocker with a short duration of action (23). We considered an 8-mg ATP bolus via peripheral veins inadequate to block the AV node completely. It is more likely to terminate supraventricular tachycardia by alternating AV nodal refractory periods than causing complete AV nodal block which is required for AP detection in the EP lab. Under the protection of ventricular pacing, a larger bolus of ATP between 30 and 40 mg is safe even when complete AV block occurs with a resultant slow ventricular escape rhythm. ATP's very short half-life also safeguards its utilization.

We also tried to find out the traditional factors that were potentially related to AP recurrence. We only found that male gender and larger body weight were significantly related to higher AP recurrence in the non-ATP group, while none of the above factors were related to recurrence in the ATP group. But we do not consider this result as meaningful.

LIMITATIONS

The main limitation of this study is its retrospective design and personal selection bias based on selective ATP application by different operators. Based on the positive findings during ATP testing in addition to PES, this study is still representative in a way. Further prospective studies are necessary to obtain a more conclusive determination of the benefits of such testing.

CONCLUSIONS

The existence of multiple APs was more common in recurrent cases if ATP was not used for confirmation of ablation endpoints. ATP probably adds additional value over PES alone by detecting weak AP conductions. ATP can evoke atrial and ventricular arrhythmias. With the use of temporary ventricular back-up pacing, higher dosage ATP testing is safe in patients without contraindications to this agent.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committee, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

WW and XF collected the data and wrote the manuscript. MS and XW polished the language. XZ, HL, HD, and ZL did the procedures. YL did statistics. YX and SW funded the research. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.716400/full#supplementary-material

Supplementary Figure 1 | Preset location distributions of accessory pathways. I: left posterior septum, II: left posterior free wall, III: left lateral free wall, IV: left anterior free wall, V: right posterior septum (coronary sinus orifice), VI: 6 o'clock in tricuspid annulus, VII: 6–9 o'clock in tricuspid annulus, VIII: 9–12 o'clock in tricuspid annulus, IX: proximal coronary sinus including middle cardiac vein (epicardial), X: para-Hisian accessory pathways (target with H potential), AMC: aortomitral continuity.

Supplementary Table 1 | Distributions of all detected APs in both groups during the index procedure.

Supplementary Table 2 | Results of ATP testing at the first procedures.

Supplementary Table 3 | Difference in recurrent AP locations confirmed by redo procedures between the two groups.

Supplementary Table 4 | Differences in existence of multiple AP cases in both groups.

Supplementary Table 5 | Differences in existence of multiple APs between recurred and non-recurred cases in both groups.

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Optical Activation of the Dorsal Horn of the Thoracic Spinal Cord Prevents Ventricular Arrhythmias in Acute Myocardial Ischemia-Reperfusion Rats

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Background and Objectives: Spinal cord stimulation can prevent myocardial ischemia and reperfusion arrhythmias, but the relevant neurons and mechanisms remain unknown. Thus, this study applied optogenetic techniques to selectively activate glutamatergic neurons at the thoracic spinal cord (T1 segment) for examining the anti-arrhythmia effects during acute myocardial ischemic-reperfusion.

Methods: Adeno-associated viruses (AAVs) carrying channelrhodopsin-2 (ChR2, a blue-light sensitive ion channel) CaMKIIα-hChR2(H134R) or empty vector were injected into the dorsal horn of the T1 spinal cord. Four weeks later, optogenetic stimulation with a 473-nm blue laser was applied for 30 min. Then, the myocardial ischemia-reperfusion model was created by occlusion of the anterior descending coronary artery for ischemia (15 min) and reperfusion (30 min). Cardiac electrical activity and sympathetic nerve activity were assessed continuously.

Results: CaMKIIα-hChR2 viral transfection is primarily expressed in glutamatergic neurons in the spinal cord. Selective optical stimulation of the T1 dorsal horn in the ChR2 rat reduced the ventricular arrhythmia and arrhythmia score during myocardial ischemia-reperfusion, preventing the over-activation of cardiac sympathetic nerve activity. Additionally, optical stimulation also reduced the action potential duration at the 90% level (APD90) and APD dispersion.

Conclusion: Selective optical stimulation T1 glutamatergic neurons of dorsal horn prevent ischemia-reperfusion arrhythmias. The mechanism may be associated with inhibiting sympathetic nervous system overexcitation and increasing APD dispersion during myocardial ischemia-reperfusion.

Keywords: ischemia-reperfusion, ventricular arrhythmia, optogenetic, spinal cord, sympathetic nerve activity

INTRODUCTION

Acute myocardial ischemia causes cardiac injury, arrhythmias and excessive sympathetic excitation through complex spinal cord circuits (1). Sympathetic hyperactivity is associated with arrhythmia (2) and neural remodeling (3). Previous studies have reported that epidural anesthesia or spinal cord stimulation (SCS) reduces sympathetic excitation and malignant ventricular arrhythmias (4). SCS modulates afferent nervous signals (5), sympathetic neurotransmitter release (6, 7), and autonomic dysregulation (4). Multiple interactions among neurons in the thoracic spinal cord may be involved in cardiac sympathetic overactivation (8).

However, the low specificity and permissive effects on the spinal cord hinder the illustration of the detailed mechanism of SCS. The optogenetic selective modulation of the spinal cord neurons allows for determining the role of neuronal circuits (9, 10). The selective expression of the photosensitive protein (channel rhodopsin-2, ChR2) in neurons makes light-induced neural electrical activity possible (11, 12). Importantly, a micro-wireless optogenetic device was designed for optogenetic stimulation spinal cord in freely moving rodents (13, 14). A study showed that the optogenetic stimulation of sympathetic preganglionic neurons in the spinal cord regulated cardiorespiratory activity (15).

Previous studies have shown that experimental coronary occlusion causes abnormal sympathetic reflex, myocardial non-uniform recovery of excitability, and dispersion of refractoriness in the myocardium (16–18). The dorsal root section reduces ischemia arrhythmias through the interruption of the sympathetic reflex (19). Our recent studies have also found that abolishing afferent nerve activities at the dorsal horn prevents arrhythmia and cardiac remodeling (2, 20). In this study, we try to determine whether optical activation of the glutamatergic neurons in the dorsal horn affects sympathetic reflex activity during acute myocardial ischemia-reperfusion.

METHODS

Animals and Groups

Adult male rats (Sprague Dawley, weight 180–210 g) were randomized into the ChR2 group ($n = 10$) and control group ($n = 10$) who received adeno-associated virus (AAV) or empty control. All experimental procedures were approved by the Animal Care and Use Ethics Committee of Yijishan Hospital and performed in accordance with the Guideline for the Care and Use of Laboratory Animals of the National Institutes of Health's guiding principles.

Virus Injection

All rats were placed in a spinal stereotaxic frame with forceps clamped to spinal processes C2 and T2 after anesthetizing with 10% chloral hydrate (0.3 g/kg body weight, i.p.). Spinal surgery was performed as previously described (21). AAV9-containing Ca(2+)/calmodulin-activated protein kinase II-α (CaMKIIα) prompter with or without -hChR2(H134R) (PackGene Biotech, 10^{13} vg/ml) was drawn up into a 10 μl Hamilton syringe with a glass pipette and pulled to a 20 μm tip (Hamilton, Shanghai, Ch). Then AAVs (3 μl) were injected into the dorsal horn (0.5 mm depth) under control by a stereotaxic micromanipulator through previously reported methods (11). The injection and needle retention were kept for 10 min to let the virus penetrate evenly into the dorsal horn (**Figure 1A**).

Electromyography and Optical Stimulation

Needle electrodes were inserted into the left upper limb 4 weeks after virus injection to record electromyography (EMG) (100–30,000 Hz filters) offline (RM6240, Chengdu, China). After EMG implantation, the muscles were carefully dissected from C2 to T2. The animals were then clamped to the dorsal C2 and T1 processes of the spinal cord in the spinal stereotactic frame to prevent spinal cord movement during the whole process of optical stimulation (11) (Details were shown in **Supplementary Materials**). Optical stimulation was performed by a laser stimulator with blue light (473 nm, Newton Co., Ltd., Hangzhou, China) through a 200 μm diameter optical fiber. Before ischemia and reperfusion, the rats received optogenetic activation for 30 min (1 min laser on and 4 min laser off, repeated 6 times). Different stimulation parameters (0, 2, 5, 10, 20, 50, and 50 mW, 10 ms pulse at frequency of 1 Hz) were applied to each side of the dorsal horn. As shown in **Figures 1D,E**, EMG gradually increased with enhanced stimulation intensity. Stimulation parameters with a pulse width of 10 ms and intensity of 20 mW/m^2 were selected as the final study. According to previous reports, SCS with 90% of the motor threshold can protect the ischemic heart (22). In this study, we selected proper optical stimulation parameters which induce EMG but no limb movement (11).

Ischemia-Reperfusion Model

According to our previous report, we created a rat model of myocardial ischemia-reperfusion (23). In brief, rats were subjected to occlusion of the coronary artery to induce myocardial ischemia for 15 min and then released for 30 min for reperfusion. Successful myocardial ischemia was judged by the ST-segment elevation on ECG and pallor changes in the heart immediately after ligation. Blue light stimulation was administered 30 min prior to ischemia.

Cardiac Monophasic Action Potential Measurement and Analysis

Monophasic action potentials (MAPs) were recorded and analyzed using a Biosignal analysis software according to our previously developed method (RM6240, Chengdu, China) (24). In brief, a pair of electrodes were placed on the base and free wall of the heart, and the control electrode was connected to the skin. The MAP data were recorded and stored in a computer for further analysis (24, 25) (**Figure 3A**). APD90 was defined as the duration of 90% repolarization (APD90). APD dispersion (APDd) was calculated by subtracting the minimum APD from the maximum APD.

Arrhythmia Analysis

Electrocardiography (ECG) recording and arrhythmia identification complied with Lambeth Convention criteria

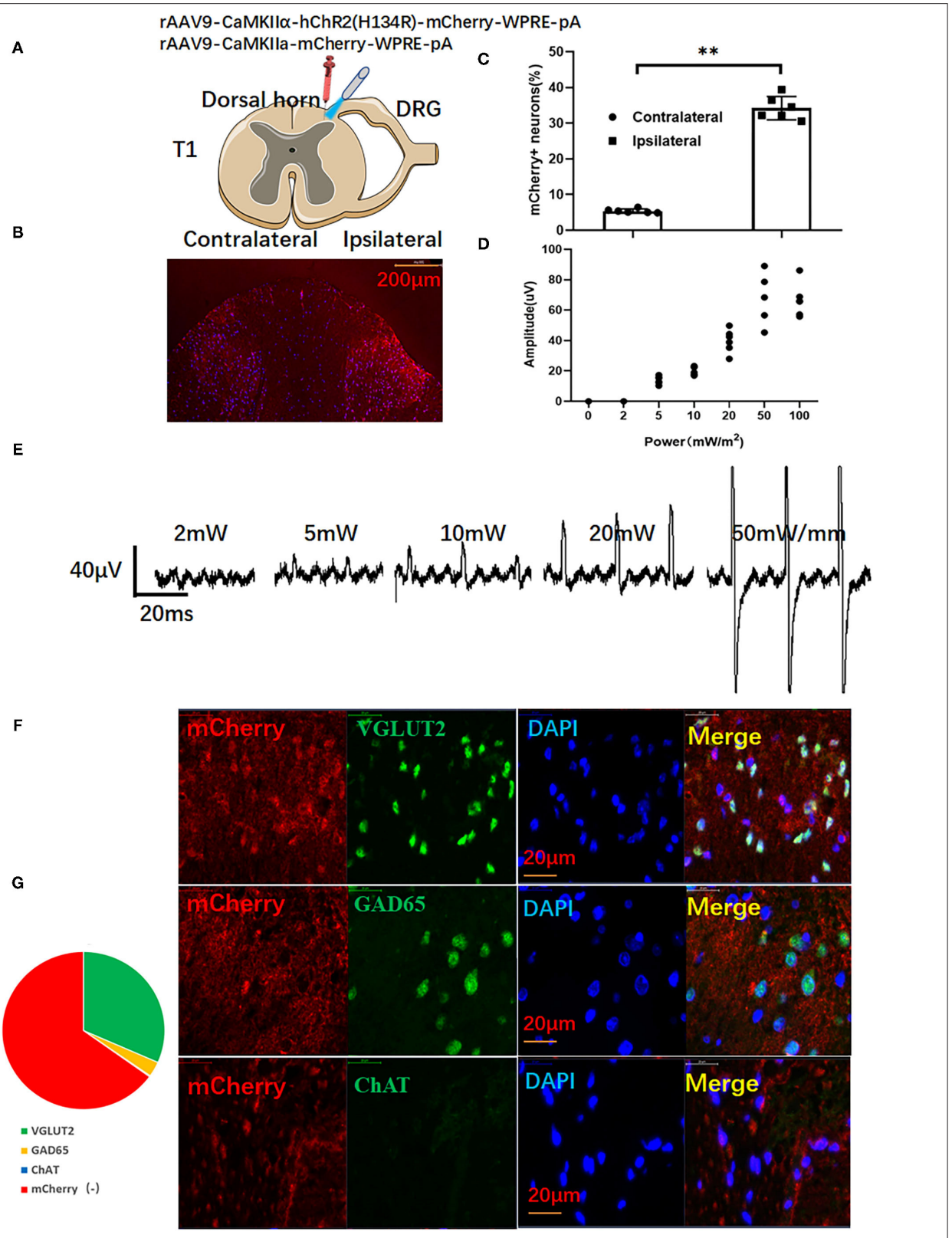

FIGURE 1 | The activation of ChR2-expressing glutamatergic neurons in the dorsal horn induces myoelectric potentials of the left upper limb. **(A)** Adeno-associated virus (AAV)-carrying ChR2 or empty vector-transfected left dorsal horn (red syringe) for optical stimulation by a blue laser (473 nm). **(B)** Representative images of mCherry in the dorsal horn. **(C)** Viral transfection efficiency. **(D)** The optical stimulation of dorsal horn neurons induces electromyography (EMG) of the left upper limb

(Continued)

FIGURE 1 | and representative traces of EMG **(E)**. **(F)** mCherry-positive cells expressed major glutamatergic neuron marker VGLUT2, minor GABAergic neuron marker GAD65, but not cholinergic neuron marker ChAT. **(G)** The relative ratio of mCherry-positive neurons. A paired *t*-test was used to compare mCherry positive cells between ipsilateral and contralateral dorsal horns. ($n = 10$ for each group; $^{**}P < 0.01$).

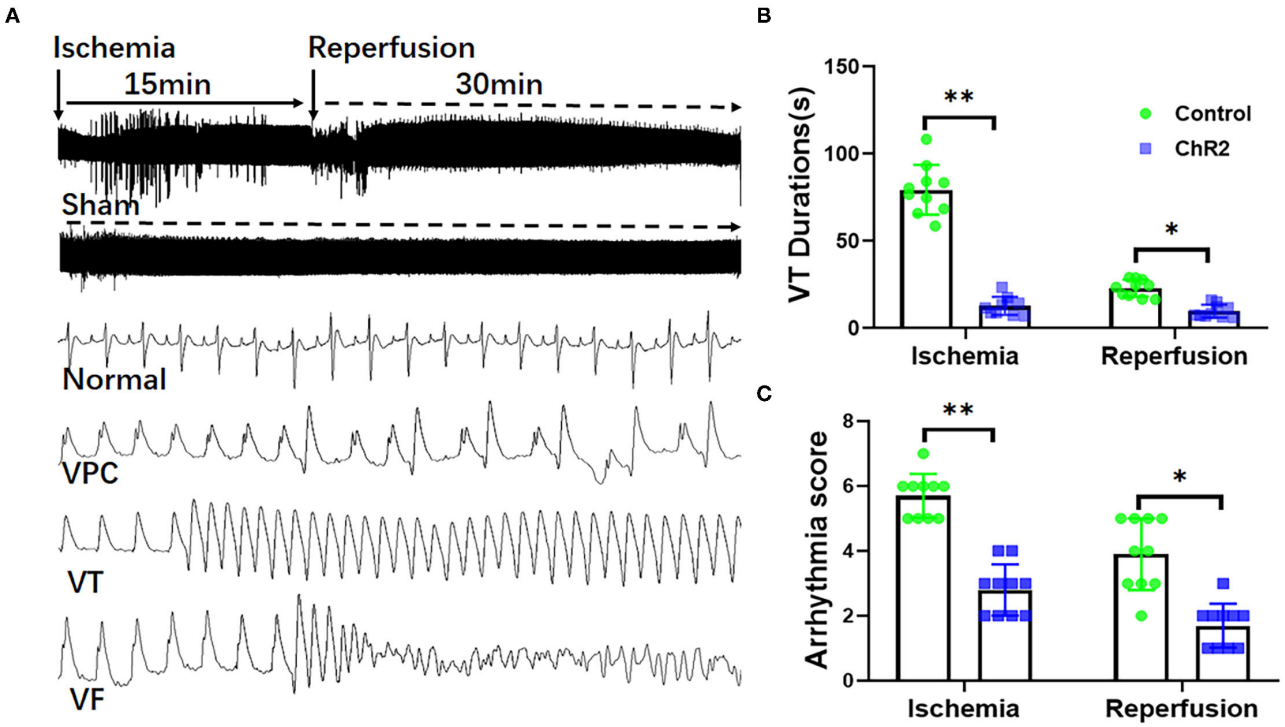

FIGURE 2 | Selective optical stimulation of the dorsal horn prevents arrhythmias during myocardial ischemia-reperfusion. Representative traces of ECG and arrhythmias including ventricular premature contraction (VPCs), ventricular tachycardias (VTs), and ventricular fibrillation (VF) during 15 min of ischemia and 30 min of reperfusion **(A)**. Analysis of VT and VF showed that optical stimulation of the dorsal horn significantly inhibited VT duration **(B)** and arrhythmia score **(C)**. Data are expressed as mean ± SD. A paired *t*-test was used to compare parameters before and after light stimulation and a *t*-test was used to compare differences between the ChR2 and control groups ($n = 10$ for each group; $^{*}P < 0.05$, $^{**}P < 0.01$).

(26). Ischemia-reperfusion induced arrhythmia analysis was used to calculate the duration of ventricular arrhythmia (VA), ventricular fibrillation (VF), and ventricular arrhythmia score, shown as follows: 0: < 10 ventricular premature contractions (VPCs); 1: ≥ 10 VPCs; 2: 1–5 episodes of ventricular tachycardia (VT); 3: > 5 VTs or 1 ventricular fibrillation (VF), 4: 2–5 episodes of VF; 5: > 5 episodes of VF; 6: VT, VF, or both for a duration ≤ 300 s; 7: VT, VF, or both for a duration > 300 s.

Measurement of Cardiac Sympathetic Nervous Activity

Cervical sympathetic nerve activity (CSNA) was recorded as previously described (2, 20). In brief, CSNA was recorded by a biological data acquisition system (RM6240, Chengdu, China) using two pairs of hook electrodes (2 mm interval) for offline further analysis. The CSNA amplitude was continuously recorded during baseline, light stimulation, myocardial ischemia, and reperfusion phases.

Immunohistochemistry

The fluorescent protein mCherry, the glutamatergic neuron marker VGLUT2, the GABAergic neuron marker GAD65, and the cholinergic neuron marker ChAT (VGLUT2, 1:200; GAD65, 1:300; ChAT, 1:100; Abcam) were used for colocalization analysis of the ratio of different neurons. Myocardial tissue sections were processed for immunofluorescence as before (24).

Statistical Analysis

All data were expressed as means ± SD. Student *t*-test was used to evaluate the difference between the ChR2 and Control groups. A paired *t*-test was used to compare variables with or without optical stimulation. Significant differences among baseline, ischemia, and reperfusion were evaluated using one-way ANOVA, followed by a *post-hoc* Newman–Keuls multiple comparison test. Statistical analyses were performed using SPSS 16.0 (IBM, New York, USA), and $P < 0.05$ was considered significant.

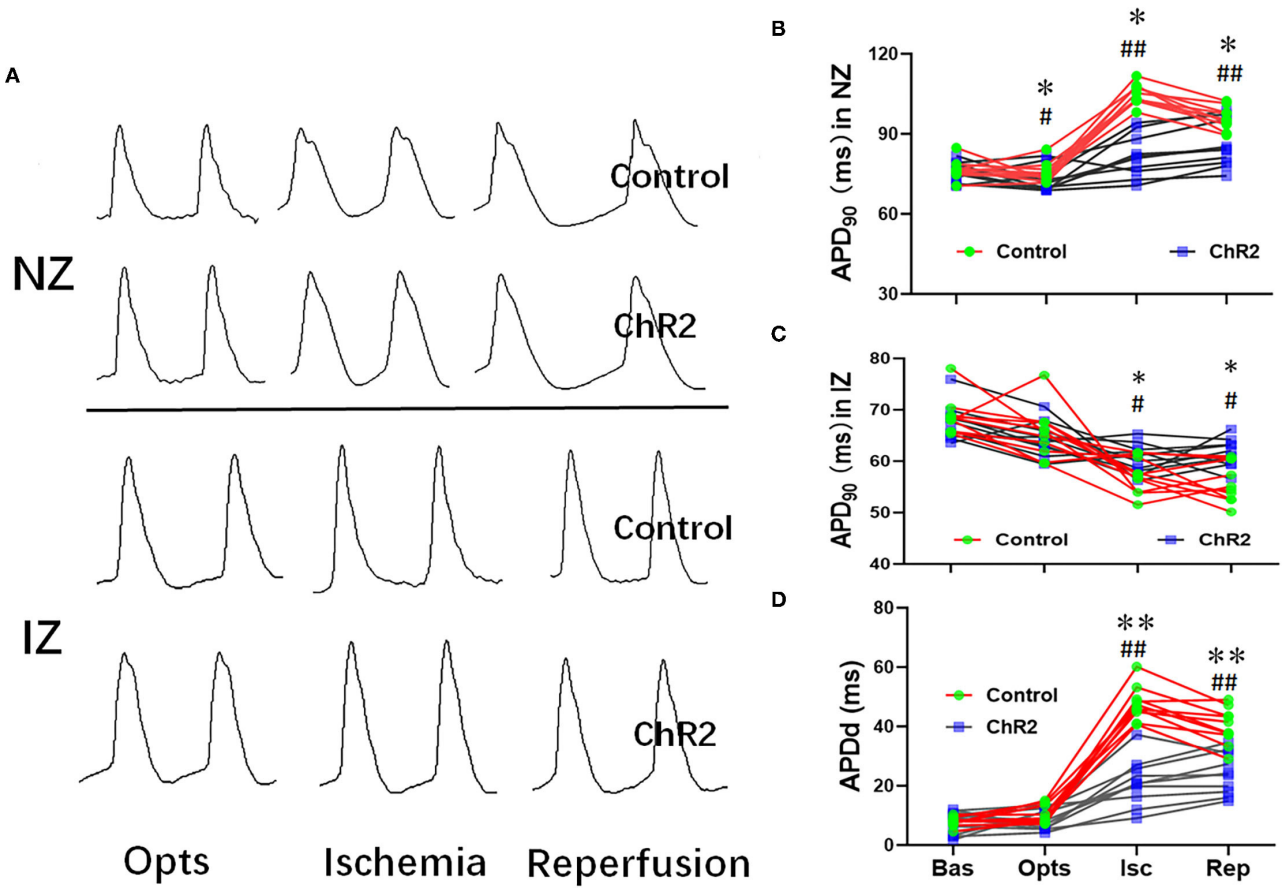

FIGURE 3 | Selective optical stimulation of the dorsal horn prevents cardiac APD abnormalities during myocardial ischemia-reperfusion. Representative traces of monophasic action potentials (MAPs) both none-infarcted zone (NZ) and infarcted zone (IZ) during 15 min of ischemia and 30 min of reperfusion **(A)**. Quantitative analysis of APD_{90} at baseline (Bas), optical stimulation (Opts), ischemia (Isc), and reperfusion (Rep) from NZ **(B)** and IZ **(C)**. **(D)** Optical stimulation of ChR2 can significantly decrease APD dispersion during myocardial ischemia-reperfusion. Data are expressed as mean ± SD. A paired *t*-test was used to compare parameters before and after light stimulation and a *t*-test was used to compare differences between the ChR2 and control groups ($n = 10$ per group; $^{*}P < 0.05$, $^{**}P < 0.01$ vs. Control; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. Baseline).

RESULTS

Activation of ChR2-Expressing Dorsal Horn Neurons Induces Left Upper Limb Muscle Activity and Myoelectric Potentials in Anesthetized Rats

As shown in **Figure 1B**, red signals of mCherry can be seen at the ipsilateral dorsal horn. However, there were only a few mCherry positive signals in the contralateral dorsal horn (**Figures 1B,C**). As shown in **Figures 1D,E**, an increased EMG was recorded at the left upper limb of rats. When the stimulation intensity was above 50 mW/mm, forelimb contraction could be observed in rats. Thus, stimulation parameters (20.3 ± 2.8 mW/mm, pulse width: 10 ms) were selected as subsequent spinal cord stimulation. As shown in **Figures 1D,F**, immunofluorescence double staining showed that most merged neurons were co-stained with the glutamatergic neuron marker VGLUT2 and mCherry(+). Only a few neurons were co-stained with GABAergic neuron marker GAD65. Almost no neurons co-expressed the cholinergic neuron marker ChAT with mCherry (**Figure 1G**).

Selective Activation of Glutamatergic Neuron in Dorsal Horn Prevents Ischemia-Reperfusion Arrhythmia

As shown in **Figure 2A**, both myocardial ischemia and reperfusion-induced ventricular arrhythmias like VPCs, VT, and VF. Optical stimulation significantly reduced the VT durations during ischemia (12.6 ± 5.2 s vs. 79.2 ± 14.3 s, $P < 0.05$) and reperfusion (9.6 ± 3.6 s vs. 22.8 ± 4.9 s, $P < 0.05$; **Figure 2B**). Optical stimulation significantly reduces the arrhythmia score of VA during the ischemia (2.8 ± 0.8 vs. 5.7 ± 0.7, $P < 0.01$) and reperfusion (1.7 ± 0.7 vs. 3.9 ± 1.1, $P < 0.05$; **Figure 2C**).

Selective Activation of Glutamatergic Neuron in Dorsal Horn Prevents Prolongation of APD in Ischemia-Reperfusion Heart

During the myocardial ischemia and reperfusion, APD was significantly prolonged in the non-infarct zone (NZ) but shortened in the infarct zone (NZ) (**Figures 3A–C**). As a result,

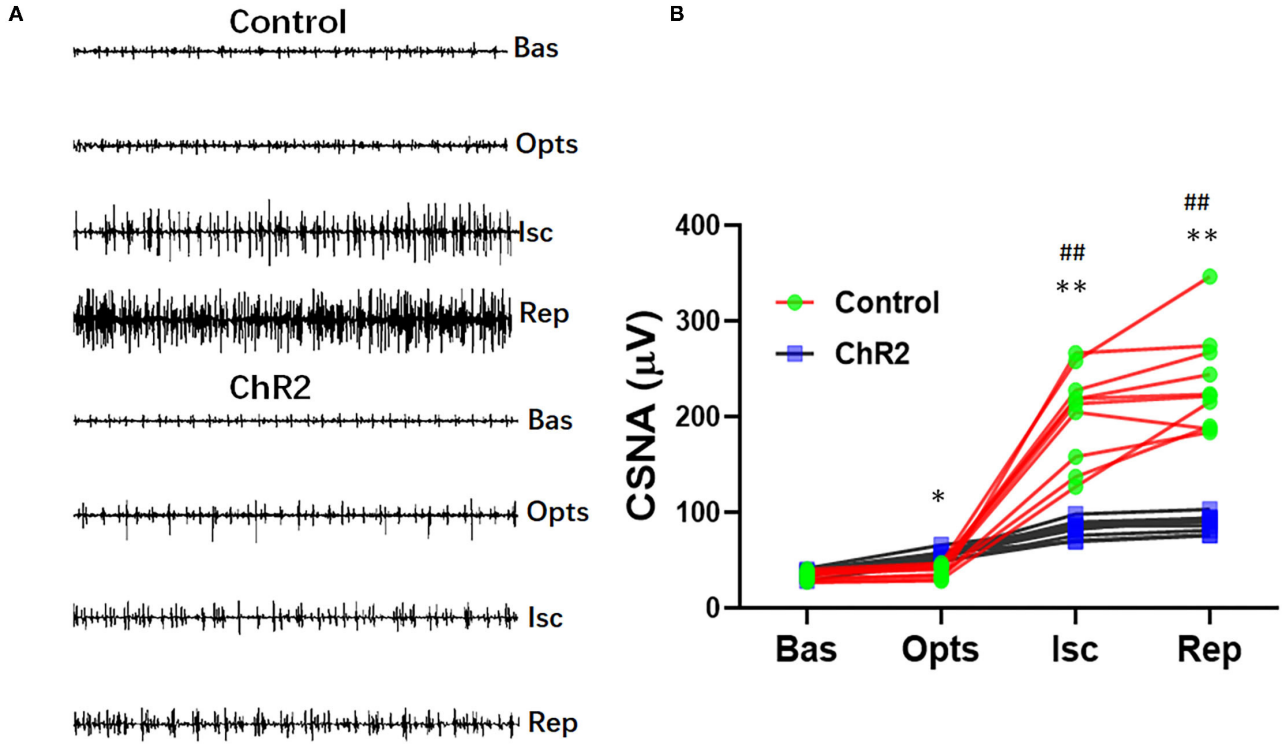

FIGURE 4 | Selective optical stimulation of the dorsal horn prevents cardiac sympathetic hyperactivity during myocardial ischemia-reperfusion. **(A)** Representative traces of cardiac sympathetic nerve activity (CSNA) during 15 min of ischemia and 30 min of reperfusion from control and ChR2 rats. **(B)** Quantitative analysis of CSNA at baseline (Bas), optical stimulation (Opts), ischemia (Isc), and reperfusion (Rep). Data are expressed as mean ± SD. A paired *t*-test was used to compare parameters before and after optical stimulation and a *t*-test was used to compare differences between the ChR2 and control groups ($n = 10$ per group; $^{*}P < 0.05$, $^{**}P < 0.01$ vs. Control; $^{\#\#}P < 0.01$ vs. Baseline).

APD dispersion in the control group increased significantly during myocardial ischemia (47.7 ± 5.7 ms vs. 7.8 ± 1.5 ms, $P < 0.01$) and reperfusion (39.9 ± 6.2 ms vs. 7.8 ± 1.5 ms, $P < 0.01$). Compared with the control group, optical stimulation significantly reduced APD dispersion both in ischemia (21.2 ± 7.9 ms vs. 47.7 ± 5.7 ms, $P < 0.01$) and reperfusion phrase (24.2 ± 7.0 vs. 39.9 ± 6.2 ms, $P < 0.01$; **Figure 3D**).

Selective Activation of the Dorsal Horn Prevents Ischemia-Reperfusion Cardiac Sympathetic Hyperactivity

Optical stimulation of the dorsal horn neurons significantly increased CSNA compared with the control group (55.3 ± 4.9 vs. 38.9 ± 6.6 μV, $P < 0.05$). CSNA significantly increased during myocardial ischemia and reperfusion in the control group (202.9 ± 47.7 vs. 33.6 ± 4.7 μV, $P < 0.01$; **Figures 4A,B**). However, optical stimulation of dorsal horn glutamatergic neurons significantly prevented CSNA during ischemia (82.6 ± 8.7 vs. 202.9 ± 47.7 μV, $P < 0.01$) and reperfusion (88.7 ± 8.7 vs. 235.3 ± 50.2 μV, $P < 0.01$; **Figure 4B**).

DISCUSSION

Optogenetic methods have been used to activate or inhibit specific neurons by stimulating selectively the ChR2 or Arc in target cells (10). It is reported that different promoters can selectively express a photosensitive protein to optically stimulate specific neurons in the spinal cord (11). Micro-wireless LED-optic devices can also optogenetic stimulate the spinal cord in freely moving rodents (13, 14). Previous studies have shown that optical stimulation dorsal horn causes muscle movement in animals (11, 12). As a preliminary study, we demonstrated that selectively activating glutamatergic neurons of the dorsal horn in T1 can prevent ventricular arrhythmias during myocardial ischemia and reperfusion and reduce sympathetic discharges and APD dispersion.

Previous studies have shown that SCS significantly ameliorates myocardial ischemia and ventricular arrhythmias during ischemia and reperfusion (4, 22). SCS significantly inhibits the abnormal activity of neurons in the dorsal horn at the T1–4 level (5). In this study, we confirmed that the pre-activation of glutamatergic neurons in the T1 dorsal horn inhibited ventricular arrhythmias during ischemia-reperfusion, suggesting that glutamatergic neurons played an important role in the protective mechanisms of SCS. However, further studies are still needed to clarify the interplay among spinal neurons.

Abnormal cardiac APD or dispersion of refractoriness is an important mechanism of ischemia-reperfusion arrhythmias (16, 18, 27). SCS alleviates the shortness of repolarization and dispersion of repolarization in ischemic heart SCS (4, 28). In this study, during ischemia and reperfusion, the activation of

glutamatergic neurons in the dorsal horn can shorten the APD in the none ischemic area and prolong the APD in the ischemic area, so as to improve the APD dispersion of the heart.

This study indicates that glutamatergic neurons in the dorsal horn may be involved in the protective mechanism of SCS. A study showed that myocardial ischemia led to partial spinal cord neuron activity, including dorsal horn neurons and interneurons (8). SCS decreases myocardial injury by producing protective substances such as dynorphin in the local spinal cord (6, 29). Previous studies have confirmed the possibility of optical stimulation of specific neurons of the spinal cord to illustrate spinal functional circuits (11, 15, 30–32). This study found that activation of glutamatergic neurons prevented cardiac sympathetic nerve discharge during ischemia-reperfusion. These results suggest that the pre-activation of glutamatergic neurons in the dorsal horn inhibits followed overexcitation of cardiac sympathetic during myocardial ischemia-reperfusion.

As a preliminary study, this work has some limitations. First, ChR2 was also expressed in some GABAergic neurons. We are not sure whether GABAergic neurons participate in the anti-arrhythmic effect in this study. Second, further study is required to determine the long-term effect of the optical stimulation of glutamatergic neurons in the dorsal horn. Third, this study did not determine whether optical stimulation of the dorsal horn terminates arrhythmias during myocardial ischemia and reperfusion.

CONCLUSION

The present study showed that specific stimulation of glutamatergic neurons in the dorsal horn of the T1 spinal cord can significantly inhibit arrhythmias and improve APD abnormalities during ischemia-reperfusion. The protective mechanism may be associated with the regulation of the cardiac-spinal reflex circuit and the inhibition of overexcitation of the cardiac sympathetic nerve during the ischemia-reperfusion.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The animal study was reviewed and approved by Yijishan Hospital Institutional Animal Care and Use Committee.

AUTHOR CONTRIBUTIONS

DW and KL: participated in research design. YW, ZL, YL, and ZH: conducted experiments. DW and YW: performed data analysis. DW: wrote or contributed to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.753959/full#supplementary-material

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Effectiveness and Safety of a Prolonged Hemodynamic Support by the IVAC2L System in Healthy and Cardiogenic Shock Pigs

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Background: Mechanical circulatory supports are used in case of cardiogenic shock (CS) refractory to conventional therapy. Several devices can be employed, but are limited by their availability, benefit risk-ratio, and/or cost.

Aims: To investigate the feasibility, safety, and effectiveness of a long-term support by a new available device (IVAC2L) in pigs.

Methods: Experiments were carried out in male pigs, divided into healthy ($n = 6$) or ischemic CS ($n = 4$) groups for a median support time of 34 and 12 h, respectively. IVAC2L was implanted under fluoroscopic and TTE guidance under general anesthesia. CS was induced by surgical ligation of the left anterior descending artery. An ipsilateral lower limb reperfusion was created with the Solopath® system. Reperfusion was started after 1 h of support in healthy pigs and upon IVAC2L insertion in CS pigs. Hemodynamic and biological parameters were monitored before and during the whole period of support in each group.

Results: Occurrence of an ipsilateral lower limb ischemia was systematic in healthy and CS pigs in a few minutes after IVAC2L implantation, and could be reversed by the arterial reperfusion, as demonstrated by distal transcutaneous pressure in oxygen ($TcPO_2$) and lactate normalization. IVAC2L support decreased pulmonary capillary wedge pressure (PCWP) (15.3 ± 0.3 vs. 7.5 ± 0.9 mmHg, $p < 0.001$), increased systolic blood pressure (SBP) (70 ± 4.5 vs. 101.3 ± 3.1 mmHg, $p < 0.01$), and cardiac output (CO) (4.0 ± 0.3 vs. 5.2 ± 0.6 l/min, $p < 0.05$) in CS pigs; at CS onset and after 12 h of support, without effects on heart rate or pulmonary artery pressure (PAP). Non-sustained ventricular arrhythmias were frequent at implantation (50%). A non-significant hemolysis was observed under support in CS pigs. Bleedings were frequent at the insertion and/or operating sites (30%).

Conclusion: Long-term support by IVAC2L is feasible and associated with a significant hemodynamic improvement in a porcine model. These preclinical data open the door for a study of IVAC2L in human ischemic CS, keeping in mind the need for systematic reperfusion of the lower limb and the associated risk of bleeding.

Keywords: mechanical circulatory support, IVAC2L, porcine model, safety, efficiency, cardiogenic shock

INTRODUCTION

Cardiogenic shock (CS) is defined as an organ hypoperfusion secondary to the impaired cardiac output (CO). It comes in different forms, ranging from a mild hypoperfusion or low CO, to an array of deep shock with secondary multiorgan failure. Criteria for defining cardiogenic shock (CS) in humans associate with systolic blood pressure (SBP) <90 mmHg or need for vasopressors; pulmonary congestion or increased left ventricular pressures; and organ malperfusion signs (1). Myocardial infarction (MI) and its complications are the main causes of CS in ∼40–60% of cases (1–3). It is a common medical situation affecting 60,000–70,000 patients per year in Europe (4) and 5–15% of acute coronary syndromes (2).

Despite therapeutic advances involving medication, early revascularization, and initial close supervision in specialized intensive care units (ICUs) of patients with MI, prognosis remains poor with immediate mortality of 40–50% of cases (2). Optimal management combines coronary reperfusion with classic intensive care management to restore tissue oxygenation through volume management, mechanical ventilation, vasopressors, and/or inotropes (1, 5, 6).

In 15–20% of the cases designated as refractory CS, classical drugs are ineffective. In these cases, mechanical circulatory supports (MCS) have been developed for a dual role: first, to ensure CO to prevent or treat organ failure secondary to hypoperfusion and second, to allow the unloading of the ventricles and to promote myocardial recovery (5, 7).

Regarding circulatory support, data are conflicting and large-scale randomized studies are lacking. After the IABP-SHOCK 2 study (8), the interest of intra-aortic balloon pump (IABP) has been severely questioned and its position in the management of CS was clearly downgraded in class IIIB for routine use (9).

Given the heterogeneity of clinical presentations, the diversity of therapeutic approaches in the absence of large-scale randomized studies with unequivocal results, the United States and European recommendations remain poorly directive and precise concerning the type and the timing of MCS (level of recommendation IIBC for European Society of Cardiology; and IIAb for American, Indian, and Canadian Heart Failure and Interventional Cardiology societies) (7, 9–12).

In this context, new support devices are emerging, and the difficulty for the clinician is to find assistance tailored to the patient whatever in terms of effectiveness (left ventricular unloading and output delivery) and safety (bleeding, vascular complications, hemolysis, infection, and reliability). Furthermore, in the current economic climate, their benefit-risk ratio must necessarily be weighted by the costs generated. Consequently, preclinical research is essential for the implementation of the necessary knowledge on the topic.

The IVAC2L (PulseCath®; Amsterdam; The Netherlands) is a new MCS which has obtained the European conformity (CE) marking in the indication of high-risk percutaneous coronary intervention (PCI) in 2015 (13). Device is inserted into the left ventricle through retrograde crossing of the aortic valve from a percutaneous femoral approach and is connected to an extra-corporeal membrane pump. Using EKG triggering, blood is aspirated from the left ventricle through the inlet tip into the membrane pump during systole and ejected from the pump through the catheter valve into the ascending aorta during diastole, resulting in a pulsatile support, with additional output, systolic unloading of the left ventricle, and diastolic counter-pulsation.

At present, use of IVAC2L is limited to case reports and case series (14–16) for few minutes during high-risk PCI. It seems to generate a rate of up to 1.4 l/min and to decrease the pulmonary capillary wedge pressure (PCWP). Its price, lower than the other available devices, and its compatibility with any standard and widely available IABP drive-console which is widely available, potentially makes this device more accessible. However, until now, it was never studied for extended support periods beyond 2 h, nor in the CS indication. An initial personal *ex-vivo* evaluation of the IVAC2L circulatory support system and its insertion kit (Solopath®) was performed and highlighted a high risk of limb ischemia secondary to the 19 Fr arterial cannulation justifying associating an arterial reperfusion.

The present study was developed to investigate the feasibility, safety, and efficiency of a long-term support by this new available device IVAC2L (PulseCath®) in a porcine model of CS.

MATERIALS AND METHODS

All experiments were reviewed and approved by the national INSERM French Ethics Committee for animal experimentation (CE201609131807621V8). The procedure for the care and sacrifice of study animals was in accordance with the European Community Standards on the Care and Use of Laboratory Animals. Details on materials and methods are described in **Supplementary Material**.

Abbreviations: CS, cardiogenic shock; DBP, diastolic blood pressure; CO, cardiac output; FA, femoral artery; IABP, intra-aortic balloon pump; MBP, mean blood pressure; MCS, mechanical circulatory support; MI, myocardial infarction; PAP, pulmonary artery pressure; PCI, percutaneous coronary intervention; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure; SVO_2, mixed venous oxygen saturation; $TcPO_2$, transcutaneous oxygen pressure.

Circulatory Support

The iVAC 2L (PulseCath®; Amsterdam; The Netherlands) has 3 essential components: (1) the extra-corporeal membrane pump containing a blood chamber and an air chamber separated by a thin flexible membrane, (2) a bi-directional flow catheter, and (3) a patented rotating two-way valve. The blood chamber is connected to the bi-directional flow catheter and the air chamber to a mainstream intra-aortic balloon pump (IABP) console. The total chamber volume is 40 ml and the pump can eject a maximum volume of blood of 21 mL. The bi-directional flow catheter has a total length of 105 cm and a 17 Fr (5.9 mm) outer diameter. At 6 cm from the inlet tip, the catheter has an integrated two-way valve that pivots around two axes.

Animals

All animals investigated (6 healthy and 6 CS pigs) were adult male pigs (*Sus scrofa domestica*) of 6–8 months old (mean weight 80–100 kg).

After initial intramuscular pre-medication (ketamine and midazolam), anesthesia was induced and maintained by continuous intravenous association of midazolam—propofol—sufentanyl—cisatracurium besilate. During experiments, pigs were under invasive mechanical ventilation under assisted volume-controlled mode (tidal volume 8 ml/kg, positive end-expiratory pressure (PEEP) 5 cm H_2O, initial FiO_2 100%, and then, adjusted to a saturation of 94–96%). Vascular filling and vasopressors were used as needed to maintain mean blood pressure (MBP) between 65 and 80 mmHg.

Antiarrhythmic preparation was made by amiodarone to prevent the expected risk of ventricular arrhythmias.

IVAC2L Insertion and Management

The right common femoral artery (FA) was exposed through an oblique incision in the groin crease. Then, an anterograde puncture of the FA allowed the insertion of a 7 Fr Super Arrow-Flex™ sheath (Teleflex, Wayne, PA, USA). Next, a retrograde puncture was performed above the previous site to insert the 19 Fr SoloPath™ balloon expandable transfemoral system (Terumo Corp., Tokyo, Japan). Finally, Super Arrow-Flex™ sheath was connected to the Solopath sheath to perfuse the right inferior limb.

The IVAC2L system implantation was performed as previously described through the aortic valve in the left ventricle under fluoroscopic and TTE guidance (13, 17). The extra-corporeal membrane pump was connected to the IABP console (Arrow ACAT 2 Wave) which was then activated and synchronized to the animal thanks to the EKG and invasive blood pressure monitoring.

In the case of ventricular arrhythmia, additional intravenous injections of antiarrhythmic were made (amiodarone +/− lidocaine bolus).

An initial intravenous bolus of unfractionated heparin (UFH) (30 UI/kg) was made at reperfusion insertion time and anticoagulation target (activated clotting time between 200 and 250 s) was then maintained by continuous intravenous infusion (2,500–6,000 UI/h).

Cardiogenic Shock Induction

After median sternotomy and pericardiotomy, the left anterior descending (LAD) was isolated and a ligation site was located at the level of the second diagonal branch. Before ligation, the animals received a new bolus of amiodarone to prevent possible arrhythmias. Then, MI was induced by the ligation of the LAD (4-0 Prolene wire). After ligation, segment ST-elevation on electrocardiography and a color change in the ventricular myocardium occurred in all animals. Two pericardial drains were placed and incision was closed in anatomic layers. Cardiogenic shock was defined according to usual definition (1). If CS was not obtained in few minutes, an additional and proximal ligation of the LAD was made.

Monitoring

A non-invasive monitoring of heart rate, blood oxygen saturation, and EKG was continuously performed. Invasive SBP, diastolic blood pressure (DBP), and MBP were monitored by using an arterial catheter. A Swan-Ganz catheter monitored pulmonary artery pressure (systolic pulmonary artery pressure [sPAP]), mean pulmonary artery pressure [mPAP], diastolic pulmonary artery pressure [dPAP], PCWP, and CO using the thermodilution approach (Vigilance II, Edwards®).

Lower limb perfusion was clinically assessed (heat, cutaneous coloration time) and a continuously transcutaneous pressure in oxygen ($TcPO_2$) monitoring was also used (TCM 400-2, Radiometer SAS®, France) during experiments.

Respiratory (arterial and venous blood gases) and renal (creatinine, kaliemia, natremia, and chloremia) functions, systemic and distal limb perfusion (lactate), and hemostase (TQ, aPTT) were repeatedly monitored by a relocated biology monitor (EPOC, CoagPoc, EDGE®). Other biological samples were frozen to realized specific *post-hoc* analysis (LDH and troponin).

Statistical Analyses

Statistical evaluation and figures were performed with Graph Pad Prism version 6.0 for Windows (Graph Pad Software, La Jolla, CA, USA). Normal distributed continuous variables are expressed as the means ± SEM. Categorical variables are expressed as absolute numbers and percentages.

In healthy pigs, comparisons between values obtained at different time points with On and Off support were made by a 2-way ANOVA (**Figures 1**–**3**). Moreover, hemodynamic parameters obtained during support On vs. Off, were averaged and compared with each other by an unpaired *t*-test (**Supplementary Table 1**).

In CS pigs, comparison between pigs at different time points was made by a paired 1-way ANOVA (**Table 1**, **Figures 4**–**6**). Moreover, main clinical, biological, and hemodynamic parameters were averaged at baseline, CS, and on support (H4 and H12). They were compared by using a 1-way ANOVA followed by Dunett's test for multiple comparisons. Comparisons of baseline vs. CS, H4 vs. CS, and H12 vs. CS were reported (**Table 1**).

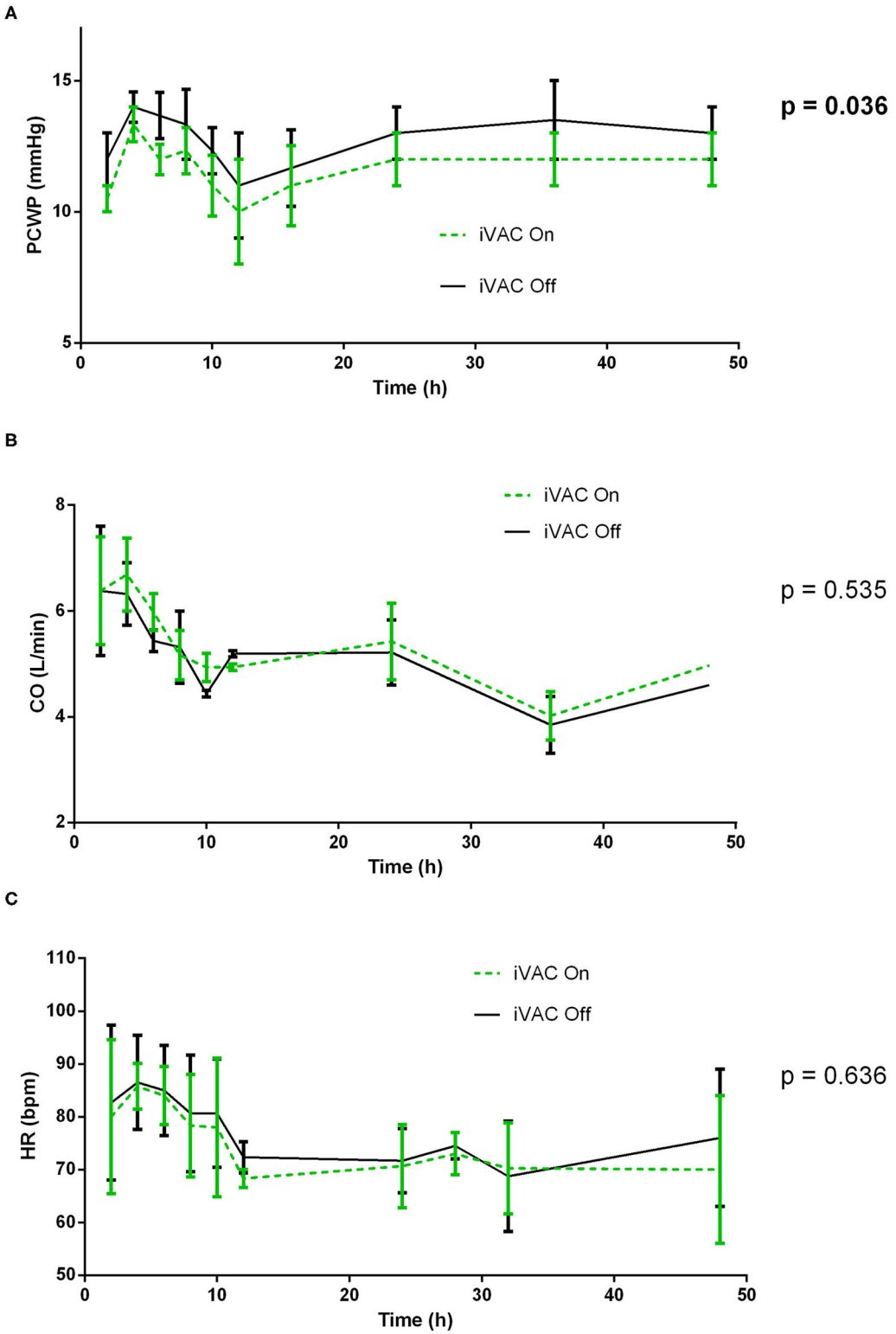

FIGURE 1 | Comparative analysis of pulmonary wedge pressure **(A)**, cardiac output (CO) **(B)**, and heart rate **(C)** with and without IVAC2L support in healthy pigs. At different times (H0, H2, H4, H6, H8, H10, H12, H16, H24, H36, and H48), the IVAC2L support was deactivated by turning Off the extra-corporal pump during 5 min and then, reactivated until next time point. Invasive and non-invasive hemodynamic parameters were recorded throughout the procedure and until 48 h. Parameters are presented at each time points by mean ± SEM ($n = 6$). The values of p were obtained by comparing On and Off values for each parameter. CO, cardiac output; HR, heart rate; PCWP, pulmonary capillary wedge pressure; SEM, standard error of mean.

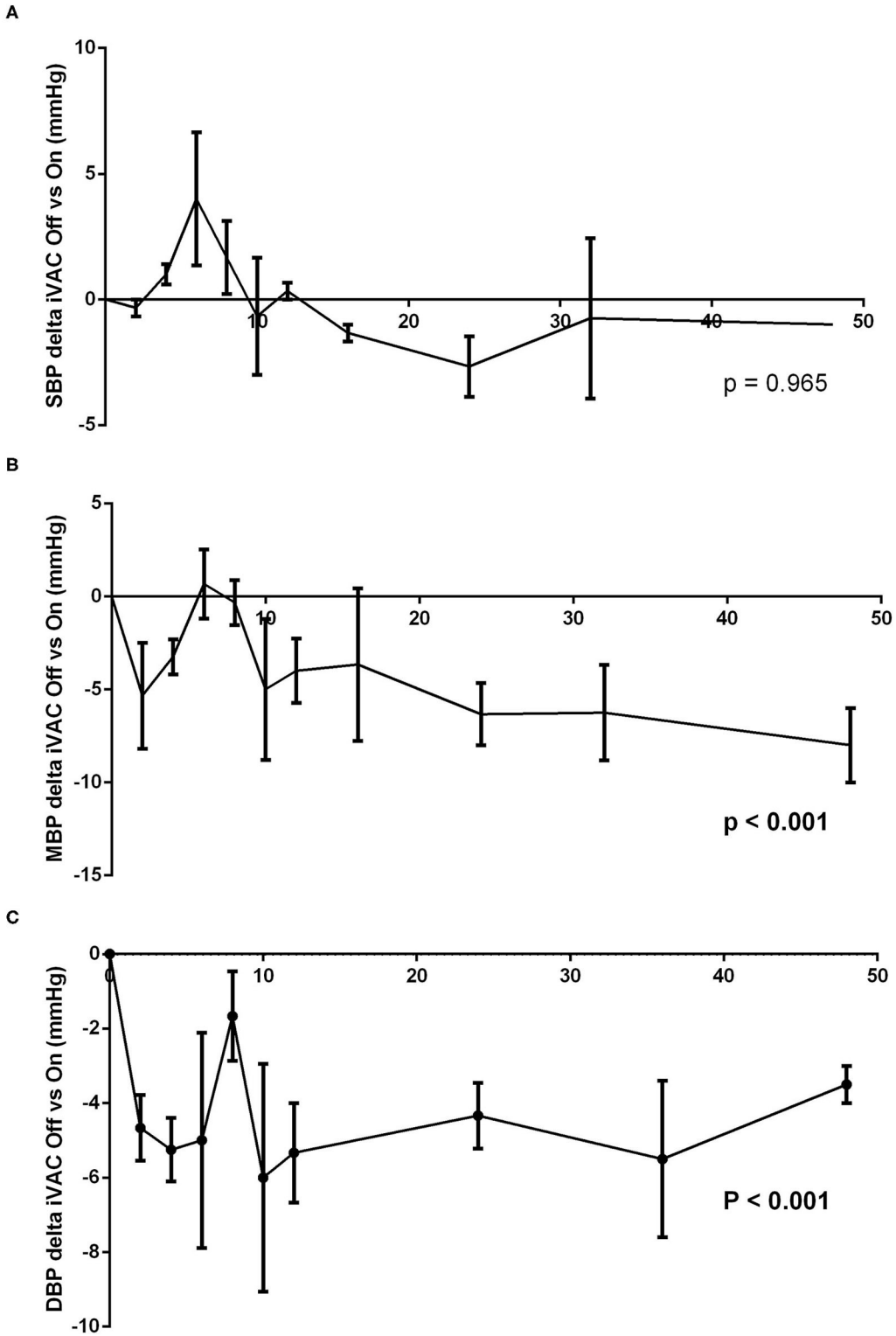

FIGURE 2 | Analysis of difference between systolic blood pressure (SBP) **(A)**, mean blood pressure (MBP) **(B)**, and diastolic blood pressure (DBP) **(C)** with and without IVAC2L support in healthy pigs. At different times (H0, H2, H4, H6, H8, H10, H12, H16, H24, H36, and H48), the IVAC2L support was deactivated by turning Off the extra-corporal pump during 5 min and then, reactivated until next time point. Invasive and non-invasive hemodynamic parameters were recorded throughout the procedure and until 48 h. Data are presented at each time points by the delta pressure mean between IVAC2L On and Off ± SEM ($n = 6$). The values of p were obtained by comparing the delta pressure On and Off for each parameter. DBP, diastolic blood pressure; MBP, mean blood pressure; SBP, systolic blood pressure; SEM, standard error of mean.

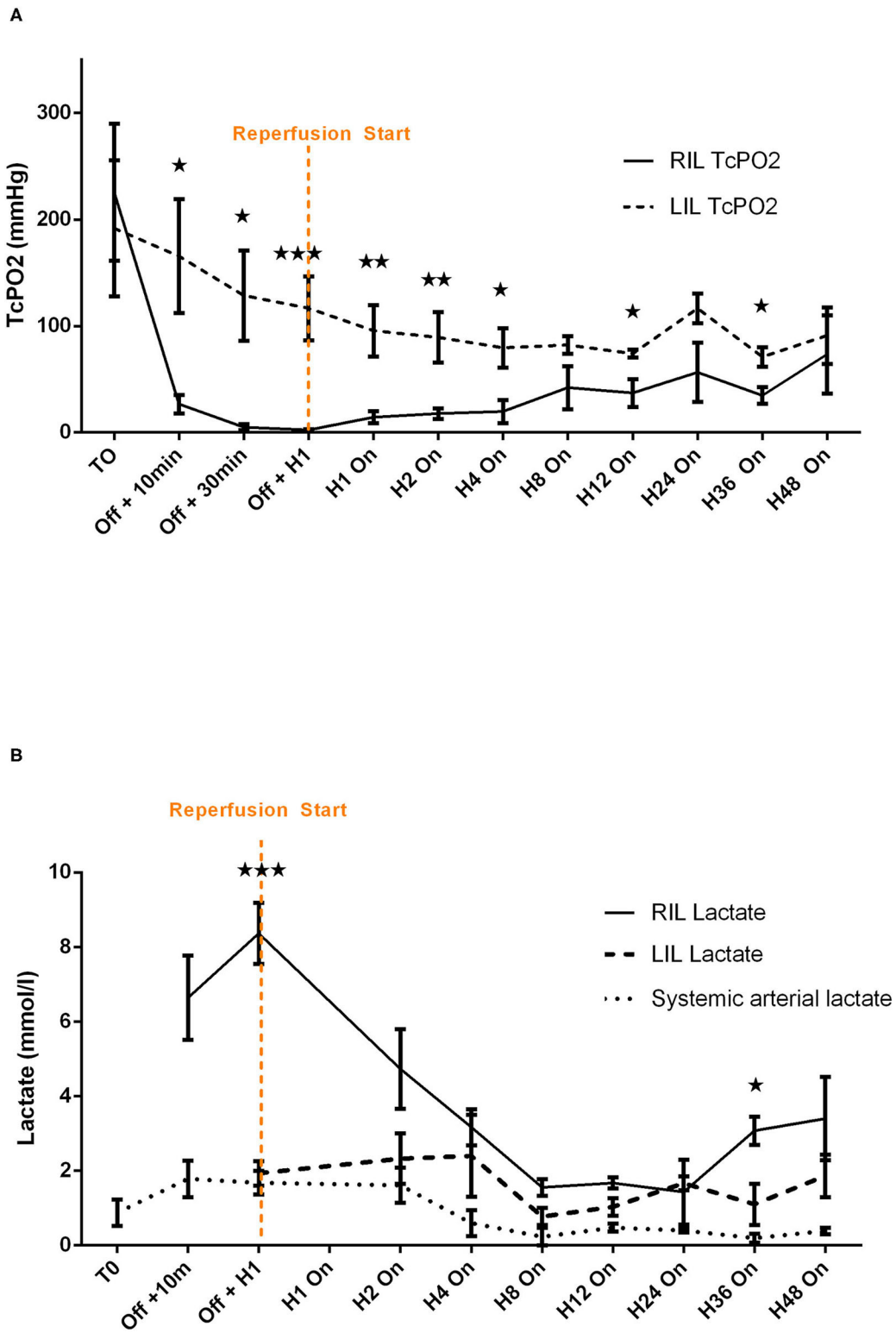

FIGURE 3 | Comparative analysis of transcutaneous pressure in oxygen **(A)** and lactate **(B)** evolution before and after reperfusion start in healthy pigs. Transcutaneous pressure in oxygen ($TcPO_2$) are presented at each time points by mean ± SEM ($n = 6$). The values of p were obtained by comparing RIL (IVAC2L) and LIL. *$p < 0.05$; **$p < 0.01$, and ***$p < 0.001$. T0, basal measure after sedation; H1, 1 h post reperfusion On; H4, 4 h after reperfusion On; H8, 8 h after reperfusion On; H12, 12 h after reperfusion On; H24, 24 h after reperfusion On; H36, 36 h after reperfusion On; H48, 48 h after reperfusion On; LIL, left inferior leg; *n*, number of pigs; Off, Solopath inserted but reperfusion Off; RIL, right inferior leg; SEM, standard error of mean; $TcPO_2$, transcutaneous pressure in oxygen.

TABLE 1 | Comparative analysis of pigs' characteristics before and during cardiogenic shock (CS) under IVAC2L support.

	Basal H0		Cardiogenic Shock		Under support H4		Under support H12		*p*-value Basal vs CS	*p*-value H4 vs CS	*p*-value H12 vs CS
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM			
HEMODYNAMIC DATA											
SBP (mmHg)	105.8	5.3	70.0	4.5	95.8	2.1	101.3	3.1	**0.001**	**0.01**	**0.003**
DBP (mmHg)	60.0	4.5	38.3	2.5	55.0	4.2	49.3	5.5	**0.017**	**0.042**	0.101
MBP (mmHg)	76.8	4.3	55.3	5.2	72.8	3.6	67.0	6.2	**0.01**	**0.026**	0.108
HR (bpm)	86.5	9.6	83.8	6.0	75.3	5.5	91.8	9.7	0.99	0.82	0.84
EtCO2 (mmHg)	39.5	4.9	31.0	2.9	32.5	3.6	30.5	2.4	**0.03**	0.9	0.99
BIOLOGICAL DATA											
Art pO2 (mmHg)	553.0	54.0	355.8	82.5	321.5	79.4	364.1	77.5	**0.02**	0.88	0.99
Art hemoglobin (dg/L)	8.2	0.6	7.6	0.6	7.3	0.8	5.7	0.6	0.756	0.937	0.066
Bicarbonates (mmol/L)	32.8	0.9	27.1	1.0	29.7	1.2	25.9	2.2	0.05	0.467	0.895
Sodium (mmol/L)	146.5	3.0	145.8	2.5	143.8	1.9	144.8	2.1	0.843	0.240	0.710
Potassium (mmol/L)	3.7	0.2	3.8	0.1	4.1	0.1	4.4	0.4	0.899	0.689	0.689
Arterial lactate (mmol/L)	1.6	0.3	3.9	0.5	2.0	0.4	0.8	0.8	**0.030**	**0.036**	**0.010**
Creatinine (μmol/L)	141.2	26.2	162.2	20.9	158.8	26.3	181.9	18.0	0.275	0.985	0.321
SWAN-GANZ DATA											
sPAP (mmHg)	24.8	0.5	27.3	1.5	24.8	2.8	23.8	1.5	0.561	0.561	0.321
dPAP (mmHg)	15.8	1.3	14.3	1.3	12.8	1.9	11.3	1.1	0.781	0.350	0.142
mPAP (mmHg)	19.0	1.4	19.3	1.8	17.8	2.0	16.8	0.9	0.999	0.823	0.533
CO (L/min)	8.7	0.6	4.0	0.3	5.1	0.1	5.2	0.6	**0.002**	**0.033**	0.173
PCWP (mmHg)	6.3	0.6	15.3	0.3	7.3	0.5	7.5	0.9	**<0.0001**	**<0.0001**	**<0.0001**

One-way ANOVA followed by Dunnett's multiple comparison tests were used to compare each point to CS onset. Art, arterial; CO, cardiac output; DBP, diastolic blood pressure; dPAP, diastolic pulmonary artery pressure; EtCO2, expired carbon dioxide; HR, heart rate; MBP, mean blood pressure; mPAP, mean pulmonary artery pressure; SBP, systolic blood pressure; SEM, standard error of mean; PCWP, pulmonary capillary wedge pressure; sPAP, systolic pulmonary artery pressure. Values in bold represent significant values ($p < 0.05$).

The value of $p < 0.05$ was considered significant. Following signs are used to symbolize the value of p: $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$.

RESULTS

Long-Term Support by IVAC2L in Healthy Pigs

Kinking of iliac artery and device length limited the correct placement of the device in 1 pig, which was excluded from the analysis. The entire procedure was performed in 6 pigs with a median support time of 34 h (3 pigs were under support during 48 h).

IVAC2L Associated Hemodynamic Effect in Healthy Pigs

At different times, the IVAC2L support was deactivated by turning Off the extra-corporal pump during 5 min and then reactivated until next time point. Invasive and non-invasive hemodynamic parameters were recorded throughout the procedure and until 48 h. Activation of the IVAC2L support was associated with a non-significant increase in DBP and MBP (**Supplementary Figure 1**) and a significant decrease in PCWP (**Figure 1**, **Supplementary Table 1**). Analysis of delta pressure between IVAC2L On vs. Off showed significant increase in MDB and DBP (**Figures 2B,C**) without significant changes in SBP (**Figure 2A**), CO, heart rate, or PAP (**Supplementary Table 1**, **Figure 1**, and **Supplementary Figure 2**).

IVAC2L Associated Limb Ischemia and Effectiveness of Distal Reperfusion in Healthy Pigs

Limb ischemia appeared systematically in a few minutes with clinical evidence (loss of distal pulse, paleness, coldness, and mottling of the limb) and was confirmed by a rapid and significant fall of ipsilateral TcPO2 (**Figure 3A**) and a marked rise of ipsilateral distal lactate (**Figure 3B**).

The implementation of retrograde reperfusion of the ipsilateral limb by a 7 Fr catheter connected to the Solopath® system was possible in all animals. Few minutes of reperfusion was clinically effective for all animals with a disappearance of previous signs. A trend to $TcPO_2$ normalization vs. contralateral limb (left lower limb) appeared in a few hours and remained stable after H4 until 48 h of support (**Figure 3A**), even if significant difference between right and left limb persisted (**Supplementary Table 2**). Lactate normalized rapidly with levels comparable with the contralateral limb after 1 h and remained stable until 48 h of support except at H36 (**Figure 3B** and **Supplementary Table 3**).

IVAC2L Associated Complications in Healthy Pigs

The IVAC2L implantation was associated with non-sustained ventricular arrhythmias in 3 (50%) cases which were resolved after anti-arrhythmic drugs. A significant increase in LDH

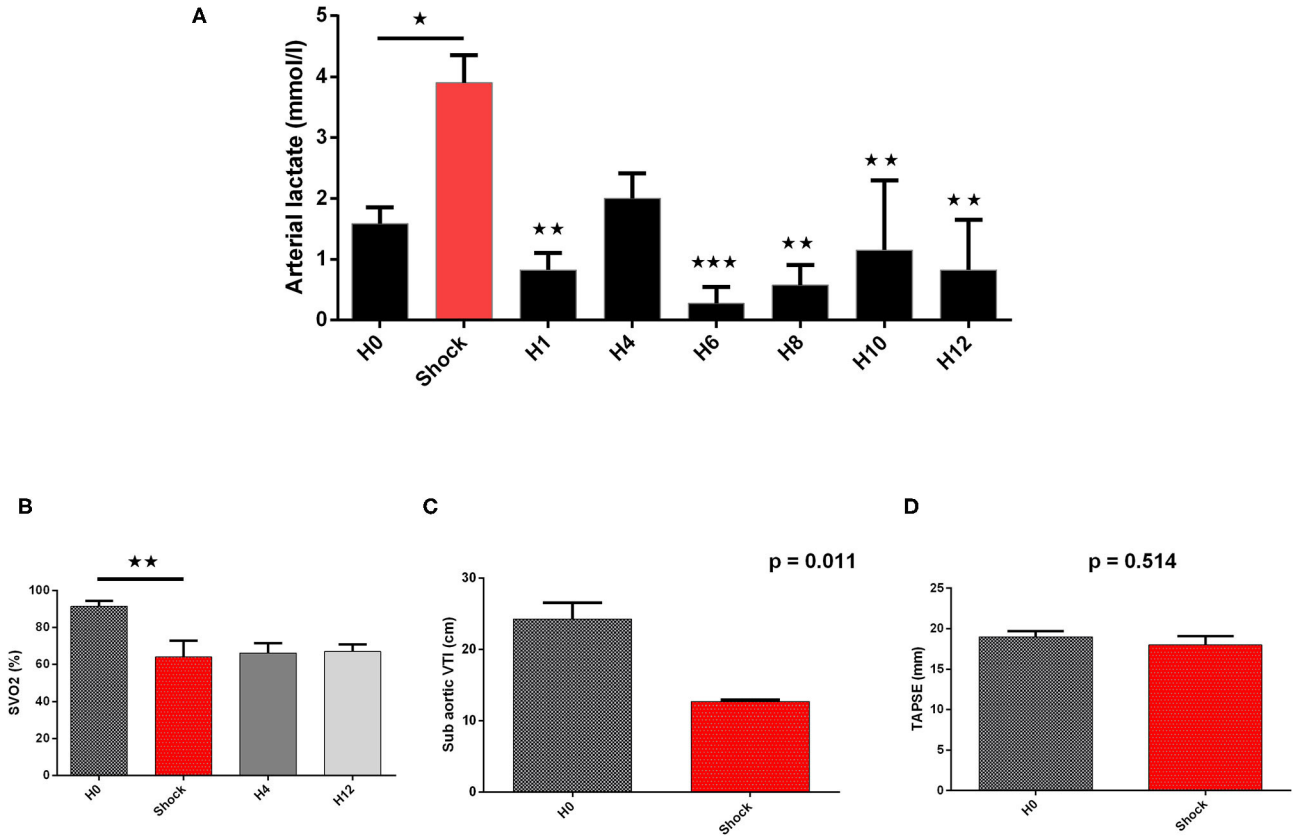

FIGURE 4 | Biological and echographical markers of cardiogenic shock (CS) evolution. Lactate and SVO_2 are presented at baseline (H0), at CS onset, and after IVAC2L implantation as mean ± SEM ($n = 4$). The values of p were obtained by comparing each point to CS point for arterial lactate and SVO_2. Echographical parameters (TAPSE and sub-aortic VTI) were recorded at baseline and at CS onset before IVAC2L implantation and are reported as mean ± SEM. The values of p were obtained by comparing sub-aorticVTI and TAPSE. *$p < 0.05$; **$p < 0.01$, and ***$p < 0.001$ vs. shock. H0, baseline; H1, 1 h post CS; H4, 4 h after CS; H12, 12 h after CS; SEM, standard error of mean; SVO_2, venous oxygen saturation; TAPSE, tricuspid annular systolic excursion; VTI, velocity time integral.

appeared after IVAC2L placement and remained until 48 h (**Supplementary Figure 3**). One episode of clinical hemolysis was noted and resolved after IVAC2L repositioning and vascular filling. Two transient cavitation phenomena were observed due to malposition of the inflow cannula resolving after replacement under TTE guidance.

Mid-term Support by IVAC2L in CS Pigs

Severe MI was induced in 6 pigs as demonstrated by significant EKG modification and troponin release (**Supplementary Figure 4**), but 2 pigs presenting with refractory electrical storm were excluded. Finally, CS was obtained for 4 pigs which were included in the study with a total support time of 12 h.

Cardiogenic shock was confirmed by a significant decrease in blood pressure (SBP and MBP) associated with a fall of CO assessed by the non-invasive (sub-aortic velocity time integral) and invasive (CO by Swan-Ganz) measures (**Table 1**, **Figures 4**–**6**). Significant mixed venous oxygen saturation (SVO_2) decrease and lactate increase defined tissue malperfusion to complete the classic definition of CS which was obtained for all pigs (**Table 1** and **Figure 4**). Right ventricle function parameters (tricuspid annular systolic excursion [TAPSE] and S' tricuspid (baseline: 8.5 ± 2.9 vs. shock: 7.5 ± 2.9 cm/s, $p = 0.09$) were preserved (**Table 1** and **Figure 4**) and left ventricular failure was confirmed by an increase in PCWP (**Figure 6**), signing a classic left mono-ventricular CS associated with MI.

IVAC2L Associated Hemodynamic Effect in CS Pigs

The IVAC2L start was associated with a significant increase in DBP, MBP, and SBP compared with CS (**Table 1** and **Figure 5**). A significant and persistent decrease in PCWP associated with an increase in CO was observed without significant change in PAP or heart rate (**Table 1** and **Figure 6**). During IVAC2L support, we observed a significant decrease and normalization of arterial lactate which was maintained at H12 indicating a correction of tissue malperfusion even if SVO_2 did not normalize completely (**Table 1** and **Figure 4**).

Effectiveness of Distal Reperfusion in CS Pigs

The implementation of retrograde reperfusion of the IVAC2L ipsilateral limb was possible in all pigs and was clinically effective for all animals. No difference in distal right inferior limb lactate

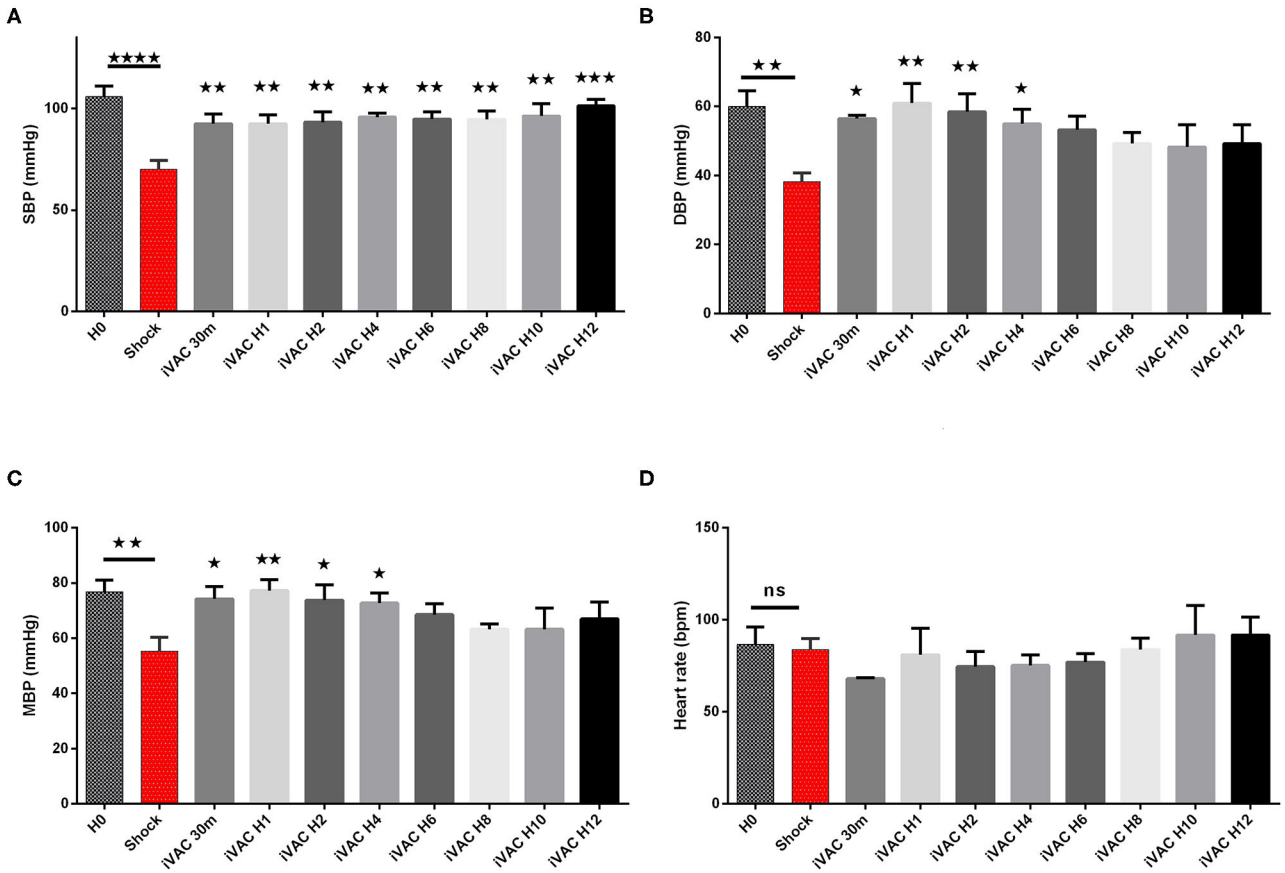

FIGURE 5 | Hemodynamic parameters of IVAC2L support efficiency in CS pigs. Systolic blood pressure **(A)**, diastolic blood pressure **(B)**, mean blood pressure **(C)** and heart rate **(D)** are presented here. Parameters are presented as mean ± SEM ($n = 4$). The values of p were obtained by comparing the first baseline data to CS data, and second by comparing CS to others time points under IVAC2L support to CS onset (H4, H12). *$p < 0.05$; **$p < 0.01$, ***$p < 0.001$ vs. shock, and ****$p < 0.0001$. H0, baseline; H1, 1 h post CS; H4, 4 h after cardiogenic shock; H12, 12 h after CS. DBP, diastolic blood pressure; H0, baseline; HR, heart rate; MBP, mean blood pressure; SBP, systolic blood pressure; SEM, standard error of mean.

between H0 and during support, neither between the right and left limb was found (**Supplementary Figure 5**).

IVAC2L Associated Complications in CS Pigs

At implantation, premature ventricular beats or non-sustained arrhythmias appeared in 2 (50%) cases which resolved after IVAC2L replacement and anti-arrhythmic drugs. Initial non-significant LDH elevation was observed at H1 and rapidly resolved (**Supplementary Figure 6**). Bleedings were frequent at the IVAC2L implantation femoral site ($n = 2$, 50%) and/or intra-thoracic due to pleural or pericardial effusion needing surgical revision ($n = 3$, 75%) explaining hemoglobin drop during support (**Table 1** and **Supplementary Figure 7**).

One episode of IVAC2L external ventricle and reperfusion thrombosis has been observed during the prolonged heparin withdrawal at H10 due to severe intra-thoracic bleedings at the operative site. This episode was associated with hemodynamic instability and lower limb ischemia justifying a replacement of the circulatory support and surgical revision.

DISCUSSION

Using a double approach with a healthy and a CS pig model, we demonstrate the feasibility and effectiveness of a long-term support by IVAC2L. Major points were demonstrated: (a) the occurrence of an ipsilateral lower limb ischemia was systematic and could be prevented or reversed by an arterial reperfusion created from the Solopath® system; (b) the IVAC2L increased blood pressure (MBP and DBP) and decreased PCWP in healthy pigs; (c) the IVAC2L increased blood pressure (SBP, MBP, and DBP), decreased PCWP and increased CO in CS pigs; and (d) IVAC2L support was associated with the hemolysis and bleeding which will require special attention when using prolonged support in humans.

To date, no animal or human data support the long-term use of IVAC2L circulatory support. Although the device has obtained a CE approval for short-term support during high-risk PCI in 2015, published experience with IVAC2L application in humans is scarce and concern <50 patients in few expert centers for high-risk PCI (14, 15). Only one case report addresses its place in

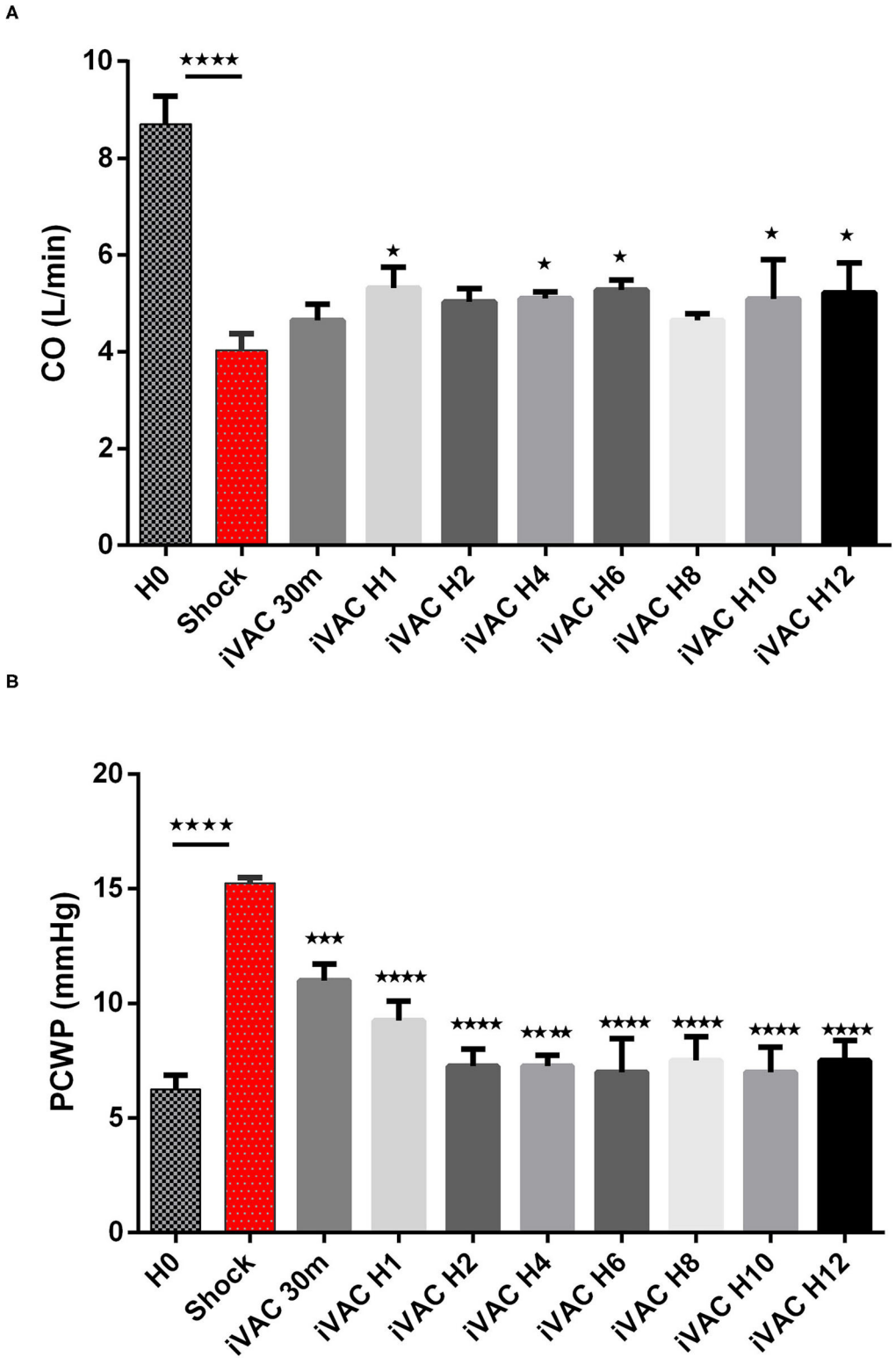

FIGURE 6 | Evolution of cardiac output **(A)** and PCWP **(B)** in CS pigs before and after IVAC2L support. Parameters are presented as mean ± SEM ($n = 4$). The values of p were obtained by comparing the first baseline data to CS data, and second by comparing CS to others time points under IVAC2L support to CS onset (H4, H12). *$p < 0.05$, ***$p < 0.001$ vs. shock, and ****$p < 0.0001$. CO, cardiac output; H0, baseline; H1, 1 post CS; H4, 4 h after CS; H12, 12 h after CS; PCWP, pulmonary capillary wedge pressure; SEM, standard error.

the left ventricle unloading under veno-arterial extracorporeal membrane oxygenation support (18) and no published data describe its use in CS case. Therefore, there is a need for preclinical data before long-term use in humans, especially in case of CS situation.

To our knowledge, we conducted the first study on long-term support with IVAC2L circulatory device and confirmed the feasibility of IVAC2L implantation under fluoroscopic and transthoracic echocardiography guidance. As expected, and previously described, IVAC2L insertion was associated with premature ventricular beats and non-sustained ventricular arrhythmias in 1 on 2 cases justifying the premedication with anti-arrhythmic drugs (amiodarone and/or lidocaine) even in humans. In 1 case, the implantation was not effective due to device length limitation, as previously described in the first published human cases. A total length of 105 cm could be limiting in a case of vascular tortuosities or in tall subject and may be anticipated by the preprocedural multi-slice CT as suggested by some authors (14).

As expected, we confirmed the occurrence of an early ipsilateral lower limb ischemia secondary to the implantation of the IVAC2L through a Solopath® system in all pigs. Surprisingly, this predictable complication was not previously described in the rare published data (13–15). Although arteries of pigs and humans share the same wall structure, they differ by their size and this could explain that ischemia appeared early within few minutes in all our pigs whatever their hemodynamic situations (healthy or CS pigs). In addition, our longer median support time (34 and 12 h in healthy and CS pigs, respectively) differed with previous shorter support in high-risk PCI (between 67 and 122 min) (14, 15). This early and severe lower limb ischemia justified a lower limb reperfusion creation. After hemodynamic *ex-vivo* tests (data not shown), we chose to create it through the Solopath® system and demonstrated here its feasibility and also its safety. Short- and long-term clinical but also biological monitoring proved its efficiency until 48 h in healthy pigs (lactate normalization and $TcPO_2$ progressive increase) and 12 h in CS pigs (right inferior leg lactate stability under support) indicating its possible use for long-term support in humans.

As shown previously, the hemodynamic effects in the absence of hemodynamic instability (healthy pigs) were less pronounced than in CS situation, although IVAC2L improved the PCWP, DBP, and MBP significantly (14, 15). We could assume that left ventricular unloading and CO generated by the counterpulsation created by IVAC2L, may be more pronounced in case of increased left ventricular pressure and low CO as demonstrated by higher significant effect in CS pigs (SBP, MBP, DBP, and CO). Moreover, the drop in PCWP in healthy pigs without associated change in CO, seems to show that IVAC2L takes over from the heart to provide part of the total flow. Some authors found a delay between IVAC2L start and hemodynamic effect that we do not observe here, but they reported invasive measures during the first minutes of support while our first evaluation was at 30 min. We found a trend toward a decrease effect on hemodynamics (DBP, MDP, and SBP) with time in healthy and CS pigs without changes on CO or PCWP. This may be secondary to vasoplegia and/or hypovolemia associated with the systemic inflammatory response syndrome and/or bleedings secondary to the IVAC2L itself but also to our pig model especially in CS situation (large sternotomy with intrathoracic inflammation and bleedings). Interestingly the beneficial hemodynamic effects that we observed translated into biological effects (systemic lactate normalization and trend to SVO_2 correction), reflecting a correction of the organ failure induced by the initial shock. Finally, we did not demonstrate any change in the PAP, confirming the place of IVAC2L for left mono-ventricular failure and its support.

Bleedings were frequent secondary to the large vascular access needed, but above all to our CS model necessitating a large surgical approach (sternotomy, pericardiectomy, and ligation of the coronary vessels). Some severe intra-thoracic bleedings needing surgical revision and vascular filling explain the drop in hemoglobin in the CS group. So, anticoagulation explained, at least partly, the hemorrhagic complications but as demonstrated by thrombotic complication (thrombosis of the external ventricle and/or tube of the IVAC2L), curative anticoagulation is mandatory during support. There was no damage to cardiac structures (aortic or mitral valve, left ventricle, and pericardium) as assessed by the macroscopic analysis of the heart after explantation at the end of the procedure. As anticipated, LDH increased under support, especially early after implantation and in healthy pigs. This difference between healthy and CS pigs, may be explained by a time correlation with possible progressive increase under support (partial micro-thrombosis of the system, inflammation, and cumulative effects) but also by a probable higher turbulence and flow conflicts between the pump and the native heart in healthy pigs.

Study Limitations

A first limitation is the apparent small sample size of our study, but in the present study, each pig serves as its own witness in the healthy group, and significant differences were observed in terms of limb ischemia—reperfusion, but also in terms of hemodynamic. Our low number of CS pigs does not allow a definitive conclusion but generates hypotheses justifying the pursuit of research on the IVAC2L support. Second, the initial period of 48 h of support was not achieved for all healthy pigs, but it is the first description of prolonged general anesthesia in pigs (maximum 54 h in our study) and the first IVACL2L support >2 h to our knowledge (median support of 34 and 12 h in healthy and CS pigs, respectively). Third, contrary to the previous publication of MCS in CS situation, we did not use the pressure volume loop to define CS and approach hemodynamic effects of our MCS (19, 20), but we use TTE and Swan Ganz catheter monitoring as it is used in clinical practice. Fourth, we used surgical ligation of the LAD artery to create our ischemic CS model. Our invasive open chest model was associated with bleeding and a systemic inflammatory response syndrome that may explain the relative instability of our hemodynamic results over time. Recently, a model of total percutaneous ischemic CS has been described based on an intracoronary ethanol injection titration under the fluoroscopic guidance (20, 21). It is possible that this model initially made it possible to visualize a more stable hemodynamic effect over time, by limiting the hypovolemia and vasoplegia secondary to bleeding. Finally, we did not compare

IVAC2L with others available device as IABP, Impella pump (Abiomed, MA, USA) or veno-arterial extracorporeal membrane oxygenation (22, 23) but only studied long-term support with IVAC2L in two clinical situations (stable and unstable hemodynamic). Future research addressing these comparisons will be needed.

CONCLUSION

Long-term support by IVAC2L system is feasible and associated with significant blood pressure and CO increase, more pronounced in the case of hemodynamic instability in a large animal model. These large animal data open the door to the study of IVAC2L in ischemic CS in humans, keeping in mind the need for systematic reperfusion of the lower limb and the associated risk of bleeding.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by National INSERM French Ethics Committee for animal experimentation (CE201609131807621V8).

AUTHOR CONTRIBUTIONS

CD, OL, FL, BM, and JM-P contributed to the conception and design of the study. CD, OL, and JM-P contributed to the interpretation of the results. CD, JP, GJ, RA, SB, HC, GB, BM, OL, and PV carried out the animal experiments. CD, GJ, HC, GB, PV, and JM-P contributed to sample preparation. CD, GJ, RA, SB, HC, GB, and PV collected the data. CD and RA organized the database. CD performed the statistical analysis and wrote the first draft of the manuscript. All authors provided critical feedback and helped shape the research, analysis, and manuscript. All authors read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.809143/full#supplementary-material

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ORIGINAL RESEARCH
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Electrocardiographic Characteristics and Catheter Ablation of Ventricular Arrhythmias Originating From the Moderator Band in Children

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Aims: To investigate the electrocardiographic (ECG) characteristics and catheter ablation of ventricular arrhythmias (VAs) originating from the moderator band (MB) in children.

Methods: A total of six children who had VAs originating from the MB—as confirmed by electrophysiological study—and who underwent catheter ablation between January 2016 and December 2020 were retrospectively reviewed. During the procedure, a three-dimensional electroanatomic mapping system was used to facilitate three-dimensional anatomical reconstruction, mapping and ablation. Patients' clinical characteristics, ECG features and procedural data were collected and analyzed.

Results: The mean age was 8.4 ± 2.6 years (range: 5.3–11 years) and mean weight was 27.7 ± 11.4 kg (range: 17–47 kg). Four patients presented with frequent premature ventricular contraction (PVC), one patient presented with frequent PVC and non-sustained ventricular tachycardia, and one patient presented with sustained monomorphic ventricular tachycardia. The QRS duration averaged 126.3 ± 4.6 ms. In all patients, the VAs had left bundle branch block QRS with left superior frontal plane axes, rapid downstrokes of the QRS in the precordial leads, and late precordial transitions (>V_4). During the same period, 10 cases of VAs originated from the posterior-lateral wall of the tricuspid annulus, with a mean QRS duration of 152.8 ± 6.4 ms. Compared to that, VAs of MB origin have narrower QRS widths, downstroke slopes in the inferior lead, sharper downstroke slopes in the precordial lead, and smaller R-wave amplitudes in the V_6 lead. All patients experienced immediate ablation success with activations earlier than QRS by 26.0 ± 3.5 ms, and no procedural complications occurring. Only one case had recurrent PVC during a follow-up period ranging from 6 to 36 months.

Conclusion: MB VAs in children have distinctive ECG morphology and electrophysiological characteristics. Catheter ablation using a three-dimensional electroanatomic mapping system is safe and effective in these patients.

Keywords: ventricular arrhythmias, moderator band, catheter ablation, electrocardiographic morphology, electrophysiological characteristics

INTRODUCTION

The moderator band (MB) of the right ventricle (RV) is a muscular structure containing Purkinje fibers that extend from the septum to the free wall of the RV (1). Ventricular arrhythmias (VAs) originating from the MB are rare in children, and relevant clinical experience and research on them are limited. VAs that originate in the MB are characterized by their specialized anatomical structures and distinct electrophysiological and electrocardiographic features. Additionally, the mapping and catheter ablation of MB VAs remains challenging. In this study, we described the electrocardiographic characteristics, mapping and ablation in children with VAs originating from the MB.

MATERIALS AND METHODS

Patient Population

A total of six children with premature ventricular contraction (PVC) or ventricular tachycardia (VT) that originated from the MB and underwent ablation between January 2016 and December 2020 were enrolled in the study. All patients underwent routine pre-procedural evaluations, including notation of myocardial injury markers, electrocardiograms (ECGs), chest X-rays, 24 h Holter monitoring and transthoracic echocardiography (TTE). Structural heart disease was excluded as an underlying factor in all patients. The study was approved by the Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University. All procedures complied with the Declaration of Helsinki, and parents provided informed consent.

Electrocardiographic Analysis

Twelve-lead surface sinus rhythm ECGs, and VAs, were recorded before the procedure. The morphology, duration, amplitude and precordial vector transition of VA QRS were analyzed.

Electrophysiologic Study and Radiofrequency Ablation

All patients discontinued antiarrhythmic drugs at least five half-lives before the procedures. VAs were preliminarily determined to have originated from the RV using 12-lead ECG. The procedure was performed under general anesthesia in all six cases. An 8.5 F Swartz sheath was placed in the right atrium to assist in catheter manipulation and increase its stability. A CARTO electroanatomic mapping system (Biosense Webster, Diamond Bar, CA, USA) was used to guide the electroanatomic mapping, and three-dimensional anatomic reconstruction of the RV was performed (**Figure 1**). A 3.5-mm irrigated-tip catheter (ThermoCool SmartTouch, Biosense Webster, Diamond Bar, CA) was used for mapping and ablation. Activation mapping was performed during the onset of VA (**Figure 2**) and further detailed activation mapping was performed to determine the earliest activity. The site of origin was also verified using pace mapping (**Figure 2**), and the ablation target was selected in the site where the QRS activation morphologies and pace mapping were consistent with those of clinical VAs. If no VAs were noted, isoproterenol infusion and/or burst pacing from the RV were performed to provoke VAs.

Radiofrequency energy was applied at a power of 30–35 W and a maximal temperature of 45°C. If PVC/VT termination occurred within the first 10 s, the site was regarded to be an effective ablation target, and radiofrequency delivery continued for 60–120 s, followed by local ablation near the target. If not, the ablation was terminated and the target was retargeted. Immediate ablation success was defined as the absence of spontaneous or inducible PVC/VT with repeated isoproterenol infusion and/or RV pacing for at least 30 min after final elimination of the VA. If PVC/VT was observed again during a minimum 30-min observation period, re-ablation at the original target with increased radiofrequency energy or re-mapping to a new target was performed.

Follow-Up

After the procedure, continuous ECG telemetry monitoring was performed for 24 h. All patients had ECG, TTE and 24 h Holter monitoring for 1 day after the procedure, and were then scheduled for follow-ups at 1, 3, 6, 12, 24, and 36 months after the procedure. During the follow-up, the absence of VT/PVC, or a reduction of more than 75% in the total number of PVCs with the same morphology compared to pre-procedural results on 24 h Holter monitoring, was considered an indication of long-term success.

Statistical Analysis

Statistical analysis was performed using SPSS software version 23.0 (SPSS Inc., Chicago, IL). Categorical data were expressed as counts and/or percentages, and continuous variables were presented as means ± standard deviation (SD). Comparisons were performed using χ^2 tests and Student's *t*-tests. *P*-values < 0.05 were considered statistically significant.

RESULTS

General Characteristics

From January 2016 to December 2020, 161 consecutive children with VAs at our center underwent radiofrequency ablation with a three-dimensional electroanatomic mapping system. Ninety-six cases originated from the RV. The immediate success rate was 96.9% (156/161), and the recurrence rate was 6.8% (11/161). Six patients from this cohort presented with VAs originating from the MB. Of these cases, three were males. The mean age was 8.4 ± 2.6 years (range: 5.3–11 years) and mean weight was 27.7 ± 11.4 kg (range: 17–47 kg). Four patients presented with frequent PVC, one patient presented with frequent PVC and non-sustained VT, and one patient presented with sustained monomorphic VT. Pre-procedural hypersensitive troponin T and N-terminal brain natriuretic peptide precursors were normal in all patients, as were cardiac sizes and left ventricular ejection fraction on TTE. Further, no evidence of organic heart disease was found. All patients had taken at least one antiarrhythmic medication, and were undergoing radiofrequency ablation for the first time. Patient characteristics are shown in **Table 1**.

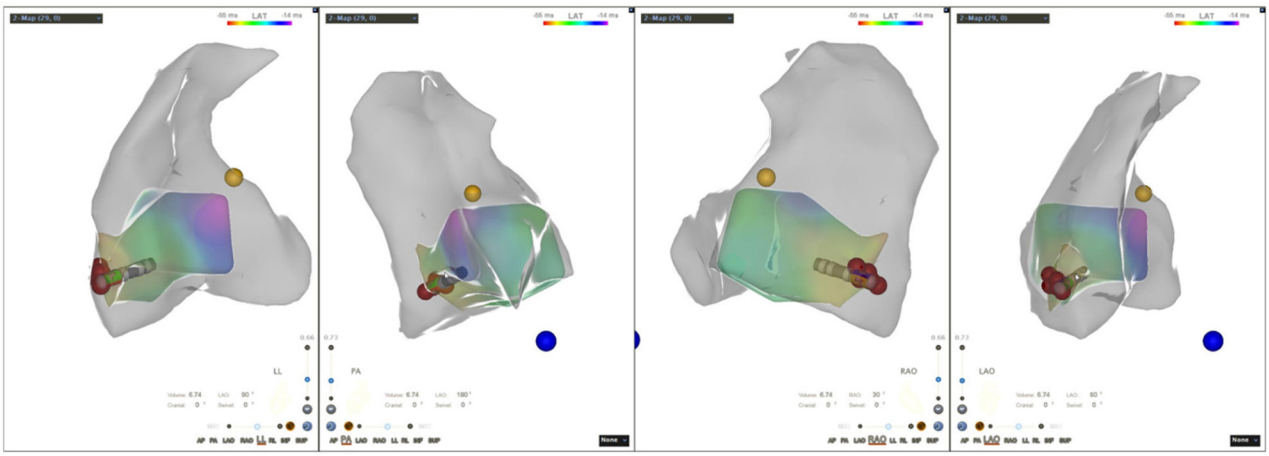

FIGURE 1 | Three-dimensional electroanatomic model of the right ventricle (RV-LL-PA-RAO-LAO). RV, right ventricle; LL, left lateral; PA, posteroanterior; RAO, right anterior oblique; LAO, left anterior oblique.

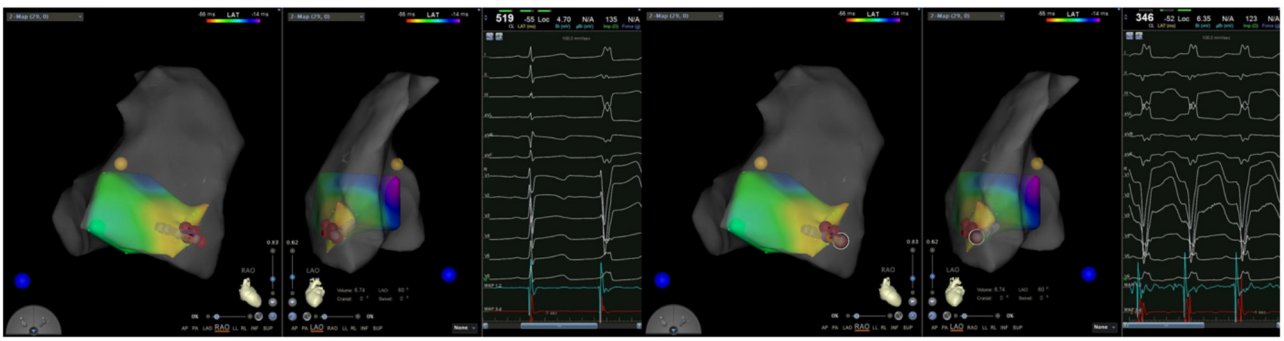

FIGURE 2 | (Left) Activation mapping; (Right) Pace mapping is used to verify that the morphology of premature ventricular contraction is consistent with surface electrocardiogram.

TABLE 1 | General characteristics.

Case	Age (years)	Sex	Weight (kg)	LVEF (%)	Clinical arrhythmia	PVC burden (%)	Antiarrhythmic medication
1	11	Male	33	64	PVC/NSVT	14.1	Propafenone
2	11	Male	47	63	PVC	21.1	Propafenone
3	5.3	Female	17	65	PVC	25.2	Propafenone, Sotalol
4	5.8	Female	19	64	PVC	11.0	Propafenone
5	10	Female	30	64	PVC	12.1	Propafenone
6	7	Male	20	64	SMVT	–	Propafenone, Amiodarone

LVEF, left ventricular ejection fraction; PVC, premature ventricular contraction; NSVT, non-sustained ventricular tachycardia; SMVT, sustained monomorphic ventricular tachycardia.

Electrocardiographic Characteristics

All patients presented with normal sinus rhythms, and the QRS morphologies of clinical VAs were recorded using an ECG before all procedures (**Figure 3**). Electrocardiographic characteristics are listed in **Table 2**. The mean QRS duration during VA was 126.3 ± 4.6 ms (range: 120–132 ms), suggesting a pattern of left bundle branch blocks. The VAs had fast downstroke slopes at the QRS in the precordial lead, with precordial transition later than lead V_4. Precordial transitions were later for the VAs than for sinus rhythms, and the QRS amplitudes of lead

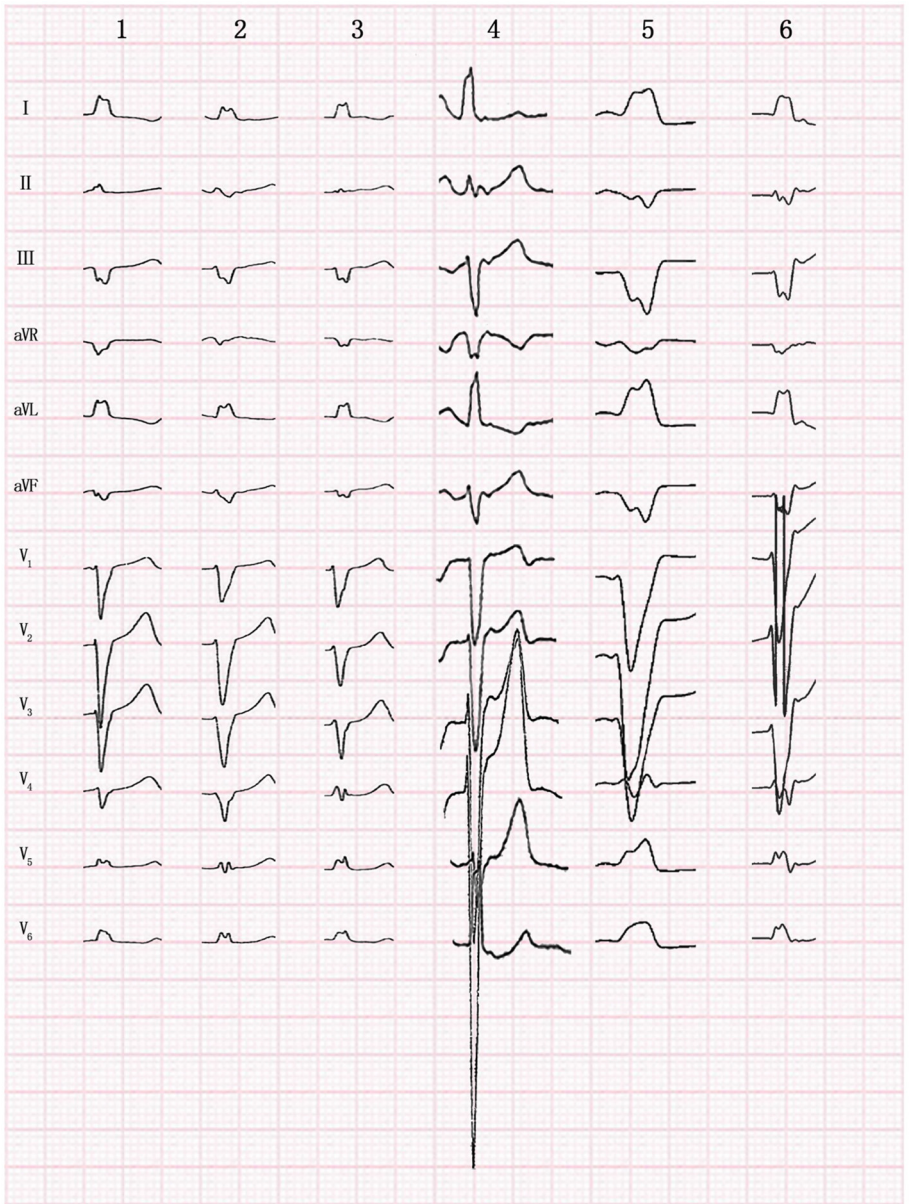

FIGURE 3 | Twelve-lead morphology of premature ventricular contraction originating from the moderator band in 6 patients.

V_6 were lower than those of sinus rhythms. VA morphologies included left superior axes, with positive QRS complexes in leads I and aVL, and negative QRS complexes in leads III and aVF. Downstroke slopes at the inferior lead QRS had notches, and the aVR leads QRS complexes were negative, with low amplitude and stumbles. During the same period, 10 cases of VAs originated from the posterior-lateral wall of the tricuspid annulus, with a mean QRS duration of 152.8 ± 6.4 ms (range: 142–162 ms). Compared with the VAs originating from the posterior-lateral wall of the tricuspid annulus, QRS duration in VAs that originated from the MB was significantly narrower ($P = 0.001$) (**Figure 4**).

Mapping and Ablation

During the procedure, all six patients had spontaneous PVC/VT. Activation mapping was used to confirm ablation targets. The mean local activation at the sites of successful ablation was 26.0 ± 3.5 ms (range: 22–32 ms) before the onset of the PVC/VT at the QRS complex on the surface ECG. A Purkinje potential at the effective ablation site which preceded the ventricular activation during PVC was found in three patients. This potential was also noted in sinus rhythm (**Figure 5**). The mean ablation time was 165 ± 52.8 s (range: 90–240 s) and mean procedure time was 81.7 ± 31.3 min (range: 60–140 min). Among the 6 cases, 4 cases did not receive radiation at all, and the fluoroscopic time of

TABLE 2 | Electrocardiographic characteristics.

Case	Baseline ECG	Axis	Morphology	QRS duration during arrhythmia (ms)	Transition during arrhythmia	Transition in sinus rhythm
1	Normal	Left superior	LBBB	126	V_5	V_3
2	Normal	Left superior	LBBB	130	V_5	V_2
3	Normal	Left superior	LBBB	122	V_5	V_3
4	Normal	Left superior	LBBB	120	V_6	V_2
5	Normal	Left superior	LBBB	128	V_5	V_4
6	IRBBB	Left superior	LBBB	132	V_5	V_3

ECG, electrocardiogram; LBBB, left bundle branch block; IRBBB, incomplete right bundle branch block.

the other 2 cases was no more than 1 min, with radiation dose of 1 mGy, respectively. Immediate ablation success without any complications was achieved in all cases (**Table 3**).

Follow-Up

The patients were followed for 6–36 months after their procedures. A 5-year-old girl with PVC burden of 25.2% had recurrent PVC 1 month after the procedure. The procedure was acutely successful. The patient responded poorly to two antiarrhythmic drugs (propafenone and sotalol) before the procedure, but responded well to a single antiarrhythmic drug (propafenone) after the procedure. The case didn't undergo a second procedure for arrhythmia recurrence. There was no recurrence of PVC/VT in the other five patients.

DISCUSSION

VAs are common arrhythmias in children. Of these arrhythmias, PVC/VT that originate from the RV are the most frequent (2). The majority of VAs originating from the RV originate from the right ventricular outflow tract and tricuspid annulus (3, 4). MB origin, however, is rare– accounting for just 6.3% of the RV origins in the present study. As such, there are few reports on VAs that originate from MB. To our knowledge, this is the first study on MB-originating VAs in children.

The MB is part of the septomarginal trabeculation, which extend across the RV. It is a muscular structure that connects the septum to the free wall of the RV. The MB emanates from the septomarginal trabeculation on the septal side. It attaches to the septal papillary muscle and to the anterior superior papillary muscle on the free wall side. The MB contains the RV conduction system (a Purkinje fiber bundle) which cross the endocardium from the interventricular septum and spreads to the RV free wall, supplying the subendocardial ventricular plexus (1). The physiological function of the MB is mainly to direct blood to the pulmonary artery during systole and to prevent RV hyperdilation during diastole. The morphology of the MB varies, showing significant diversity in size, length, and insertion origin. Origin and insertion origins differences may be the main drivers of morphological variety on ECGs (5). The MB is also supplied by nerve fascicles containing cholinesterase. These characteristic morphological and structural features of the MB may be associated with the occurrence of arrhythmias.

Our findings are similar to those noted in a former study on 10 adults with idiopathic VAs originating from the MB (6). All patients with MB arrhythmias had left bundle branch block morphologies with left superior axes. MB VAs have a relatively narrow QRS duration, and a large downstroke QRS slope in the precordial lead, with transitions that are later than both lead V_4 and sinus QRS. VAs morphologies generally have positive QRS complexes in the inferior lead, with downstroke QRS slopes. The QRS complex of the I and aVL leads is positive, and the aVR lead is negative, with low amplitude and stumbles. The electrocardiographic characteristics of MB VAs were similar to those of VAs originating from the posterior-lateral wall of the tricuspid annulus. Thus, MB VAs are easily misdiagnosed as originating from the tricuspid annulus. However, careful identification reveals some distinction in the ECG signatures of the two origins. VAs of MB origin have narrower QRS widths, downstroke slopes in the inferior lead, sharper downstroke slopes in the precordial lead, and smaller R-wave amplitudes in the V_6 lead. VAs originating from the posterior-lateral wall of the tricuspid annulus, however, have negative QRS complexes in lead II and later precordial transitions. These electrocardiographic differences may be closely related to the unique anatomical location and electrophysiological features of the MB. Electrical activation of MB VAs can simultaneously spread to the septal free walls of the RV, with less time required for RV activation and better synchronization of RV depolarization compared to VAs of tricuspid annular origin.

It has been found that it is easy to induce ventricular fibrillation in PVCs of MB origin in patients with normal heart structures (7). The role of the Purkinje conduction system in triggering idiopathic ventricular fibrillation has also been previously demonstrated. Possible explanations for this phenomenon include that Purkinje cells are more prone to occur earlier post-depolarization than other regions of the ventricular myocardium, and that Purkinje fibers may lose intrinsic protective mechanisms due to tissue refractoriness abnormalities (8, 9). Thus, it may be beneficial for patients with idiopathic ventricular fibrillation to record PVCs that may have MB origins, in order to use it as a potential ablation target. In some patients with idiopathic ventricular fibrillation, empiric

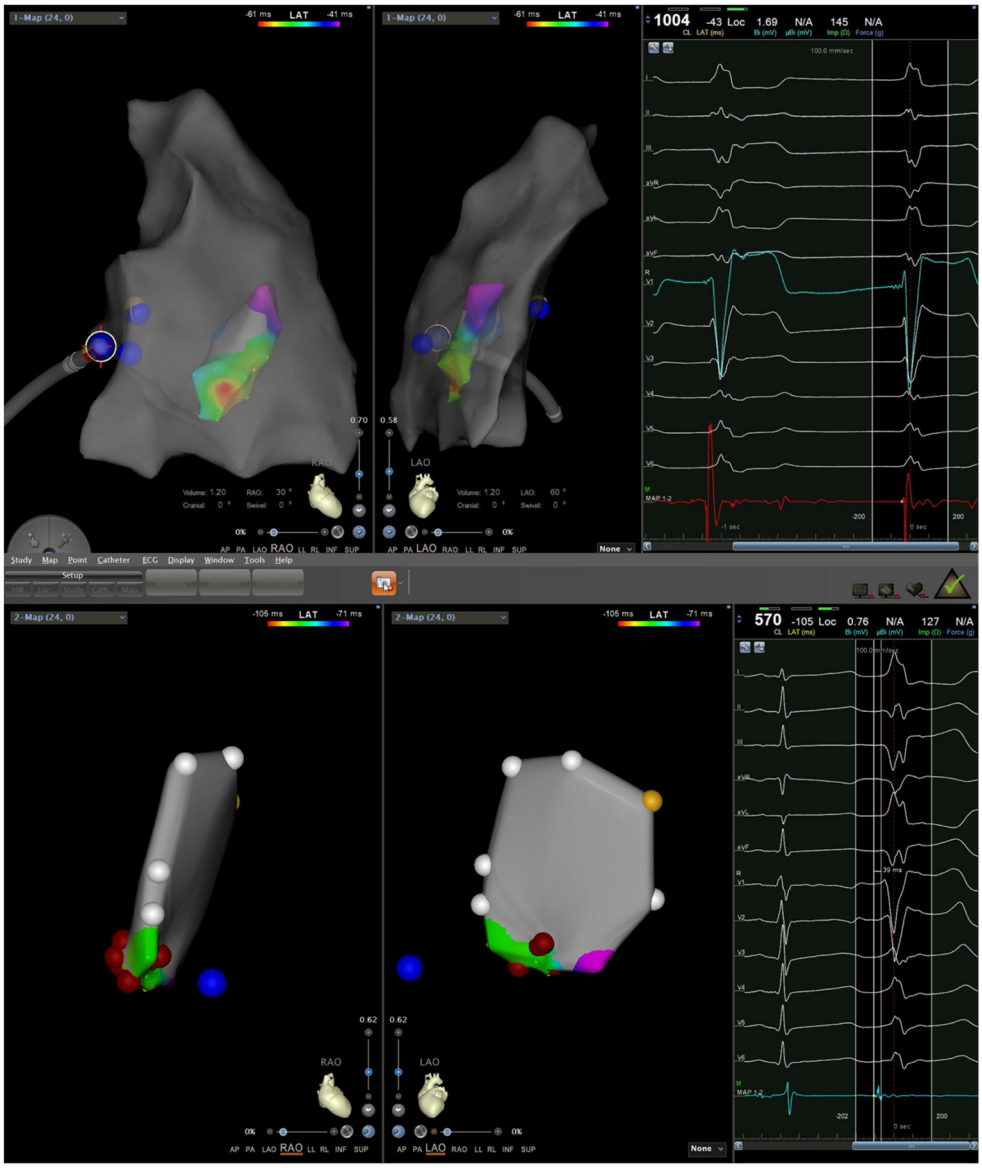

FIGURE 4 | Electrocardiogram (ECG) comparison between premature ventricular contraction (PVC) originating from the moderator band (MB) and the posterior-lateral wall of tricuspid annulus. In the figure above, the left ECG was MB origin, while the right was origin of the posterior lateral wall of the tricuspid annulus by pacing. In the figure below, the ECG was spontaneous PVC originating from the posterior-lateral wall of tricuspid annulus. PVC of MB origin has a sharper slope of downstroke in the precordial lead.

MB ablation can eliminate arrhythmias (6). Among the six patients in our study, one had inducible sustained VT, and one had inducible non-sustained VT. No PVC-induced ventricular fibrillation occurred.

In our study, ablations were based on the earliest PVC activities as determined by activation mapping, and ablation targets were further confirmed by pace mapping in sinus rhythm. In general, ablation of VAs can be performed based on pace-mapping in sinus rhythm to identify the origin if there is no inducible PVC/VT during the procedure. However, due to the similar QRS morphology of each segment of the MB, simple pace-mapping has limited value in determining the origin of MB VAs. Therefore, the mapping and ablation of this site should be performed using activation mapping when possible, and the accuracy of the ablation target can be further verified using a combination of activation mapping and pace mapping. A Purkinje potential can often be recorded at the earliest activation site during PVC or during sinus rhythm, and right bundle branch blocks are common after ablation. This is consistent with distribution of the right bundle branch, and also aligns with a study on the mechanisms of VT caused by the right bundle branch and Purkinje fibers at the MB

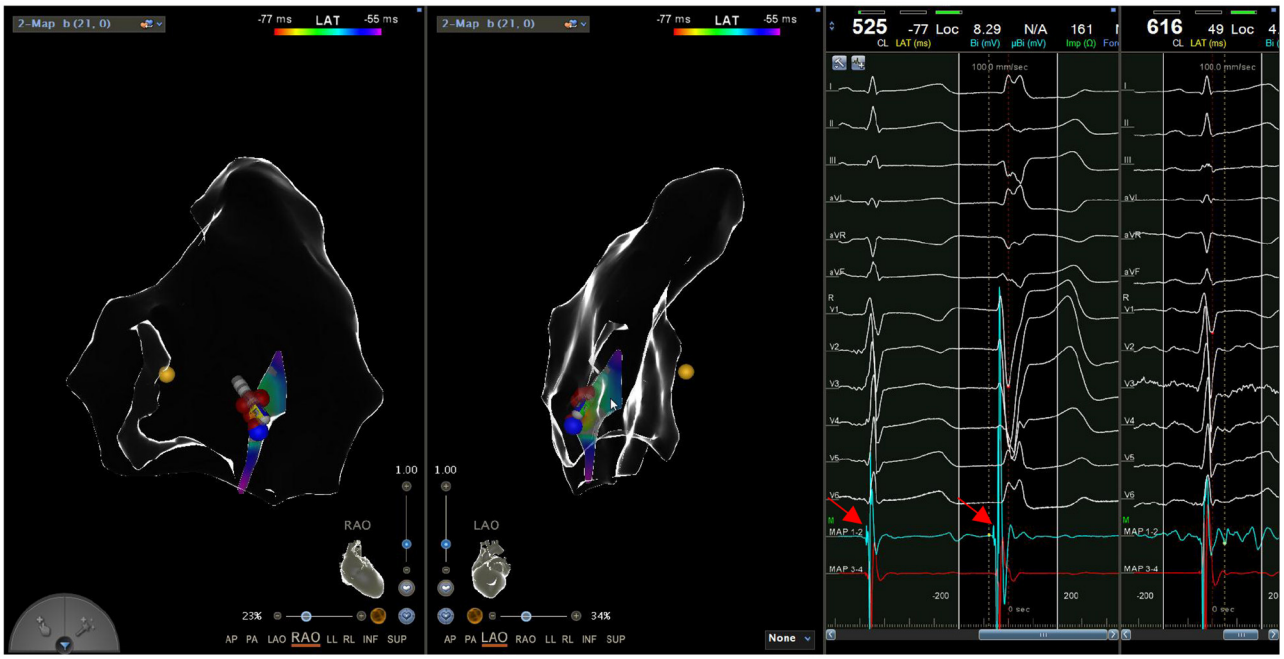

FIGURE 5 | A Purkinje potential (arrow) is recorded in both sinus rhythm and PVC in a continuous way.

TABLE 3 | Ablation and follow-up.

Case	Purkinje potential	Pre-PVC (ms)	Ablation time (s)	Procedure time (min)	Fluoroscopic time (min)	Radiation dose (mGy)	Immediate success	ECG post-procedure	Follow-up duration (months)	Recurrence
1	Yes	25	180	60	0.2	1	Yes	Normal	6	No
2	No	25	90	60	0	0	Yes	Normal	12	No
3	No	22	120	60	0	0	Yes	Normal	12	Yes
4	Yes	24	240	90	0	0	Yes	CRBBB	24	No
5	Yes	28	180	80	0	0	Yes	Normal	24	No
6	No	32	180	140	1	1	Yes	CRBBB	36	No

PVC, premature ventricular contraction; ECG, electrocardiogram; CRBBB, complete right bundle branch block.

site (6). Sadek et al. reported that PVC termination could be achieved by ablating the right bundle branch in one patient, but it was not observed in the remaining nine patients (6). We occasionally noted changes in QRS morphology during ablation, probably indicating a change in the exit site and eventual PVC elimination after extensive ablation. The site of successful ablation location along the MB was variable, including the septal insertion, the body of the MB, and the free wall insertion (6). Unfortunately, since we did not use intracardiac echocardiography (ICE), we could not further identify the exact site of successful ablation location along the MB.

As a part of the RV papillary muscle system, the MB is a beating structure in the cardiac cavity. The ablation success rate of MB VAs using three-dimensional electroanatomic mapping system alone is not high, but can be improved with ICE (10). However, ICE requires a minimum 11 F of vascular sheath, and so can rarely be used in children. In this study, a three-dimensional anatomic reconstruction of RV was performed, and a satisfactory target was mapped using the CARTO electroanatomic mapping system. All ablations were immediately successful, with Swartz sheaths supporting the ablation catheter. One of six patients had PVC recurrence, but this was still a significant improvement compared with pre-procedure rates. Low success and high recurrence are likely related to issues related to catheter-target contact or catheter stability. Despite adequate visualization with ICE, part of patients required a second procedure despite an acutely successful initial procedure (6). The potential mechanism for recurrence is challenging catheter contact and stability resulting in lower power delivery to the thick intracavitary structure.

None of these cases underwent cardic magnetic resonance imaging (MRI) prior and post the procedure. In our opinion, prior imaging (for example cardiac MRI) and RV segmentation

or fibrosis segmentation may shorten procedure time, but seem to have little effect on reducing radiation exposure time due to the use of a three-dimensional electroanatomic mapping system. A post-procedure MRI may be helpful in determining the exact anatomic location of ablation. In the future, we plan to perform cardiac MRI prior and post the procedure for some patients with VAs of special site origin, especially to spot the anatomic location of ablation sites through post-procedure MRI.

VAs of MB origin are uncommon, and related reports are also rare. Although the sample size of this study was small, we described the ablation of VAs originating from the MB in children for the first time. The electrocardiographic and electrophysiological characteristics were consistent, and certain features were summarized for reference. Our results should be confirmed in a larger sample size. In this study, target localization mainly relied on the three-dimensional electroanatomic mapping system: no ICE was used to accurately map the ablation site on the MB. Thus, there were some limitations related to the anatomical localization of the target.

CONCLUSION

VAs originating from the MB are rare, particularly in children, and have unique ECG and electrophysiological characteristics. Catheter ablation of such VAs is challenging. However, the clinical effects of mapping and ablation using a three-dimensional electroanatomic mapping system are satisfactory.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DJ and BH designed the study and performed the research. JL, XY, LZ, and YY performed the research and analyzed the data. DJ wrote the manuscript. DL and CS supervised the study. All authors contributed to manuscript revision, read, and approved the submitted version.

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Mechanical circulatory support in ventricular arrhythmias

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In atrial and ventricular tachyarrhythmias, reduced time for ventricular filling and loss of atrial contribution lead to a significant reduction in cardiac output, resulting in cardiogenic shock. This may also occur during catheter ablation in 11% of overall procedures and is associated with increased mortality. Managing cardiogenic shock and (supra) ventricular arrhythmias is particularly challenging. Inotropic support may exacerbate tachyarrhythmias or accelerate heart rate; antiarrhythmic drugs often come with negative inotropic effects, and electrical reconversions may risk worsening circulatory failure or even cardiac arrest. The drop in native cardiac output during an arrhythmic storm can be partly covered by the insertion of percutaneous mechanical circulatory support (MCS) devices guaranteeing end-organ perfusion. This provides physicians a time window of stability to investigate the underlying cause of arrhythmia and allow proper therapeutic interventions (e.g., percutaneous coronary intervention and catheter ablation). Temporary MCS can be used in the case of overt hemodynamic decompensation or as a "preemptive strategy" to avoid circulatory instability during interventional cardiology procedures in high-risk patients. Despite the increasing use of MCS in cardiogenic shock and during catheter ablation procedures, the recommendation level is still low, considering the lack of large observational studies and randomized clinical trials. Therefore, the evidence on the timing and the kinds of MCS devices has also scarcely been investigated. In the current review, we discuss the available evidence in the literature and gaps in knowledge on the use of MCS devices in the setting of ventricular arrhythmias and arrhythmic storms, including a specific focus on pathophysiology and related therapies.

KEYWORDS

mechanical circulatory support (MCS), arrhythmias, extracorporeal membrane oxygenation (ECMO), hemodynamic, review

Introduction

Ventricular arrhythmias are responsible for a significant number of sudden cardiac deaths (SCD) (1). Implantable cardioverter defibrillators (ICD) have been extensively proven to be superior to antiarrhythmic drugs in preventing ventricular arrhythmias in high-risk patients (2–4). Nonetheless, ICDs do not prevent the recurrence of ventricular arrhythmias; even when necessary and lifesaving, shocks have a severe impact on quality of life (5).

Heart failure with reduced ejection fraction is burdened with a higher risk of SCD and poor prognosis. Left ventricular ejection fraction (LVEF) has been recognized as the strongest predictor of ventricular arrhythmias and mortality in patients with cardiomyopathies (6), and it represents the main criterion in the decision-making process when considering the implantation of an ICD as primary prevention (7). Reduced LVEF was also found to be an independent predictor of ventricular arrhythmia recurrence in patients with ischaemic heart disease and ICD as secondary prevention (8). Nonetheless, the prediction of SCD still represents a clinical challenge for cardiologists. In the future, the selection of candidates may not only rely on echocardiography-derived LVEF but on multiparametric imaging, including cardiac magnetic resonance and strain echocardiography (9).

Catheter ablation (CA) of ventricular tachycardia (VT) represents a percutaneous technique that can permanently treat VT and prevent its recurrence. Current expert consensus recommends using CA for recurrent VT refractory to antiarrhythmic therapy or in those who tolerate antiarrhythmic drugs poorly (10). Preprocedural planning, mainly based on 12-lead ECG findings, is a fundamental step given the choice of mapping and ablation strategies. To achieve a successful ablation, four different strategies have been developed to map VT: activation mapping, entrainment mapping, pace mapping, and substrate mapping. Each of these techniques has its own advantages and applications in a specific context based on the arrhythmogenic mechanism and the hemodynamic tolerance of ventricular arrhythmia (11).

Patients requiring CA for ventricular arrhythmias may present with structural heart disease, commonly ischemic heart disease. In such a clinical scenario, acute hemodynamic decompensation during the CA procedure is not uncommon, affecting 11% of patients and is associated with an increased mortality rate (12). In addition, the coexistence of structural heart disease reduces the hemodynamic tolerance to the onset of VT episodes, making activation and entrainment mapping unfeasible and unsafe in patients without cardiovascular support. The use of general anesthesia, particularly if prolonged, for CA procedures further increases the risk of cardiovascular decompensation. Other clinical factors associated with acute hemodynamic decompensation during CA are advanced age, the presence of comorbidities (diabetes mellitus and chronic obstructive pulmonary disease), and presentation with VT storm (12).

Mechanical circulatory support (MCS) devices, such as Impella and venoarterial extracorporeal membrane oxygenation (VA ECMO), may represent an appealing tool to support blood pressure and guarantee adequate end-organ perfusion during the CA of VT. However, MCS implantation carries its own costs and intrinsic risk of complications, mainly related to bleeding and vascular complications (13, 14). For these reasons, the selection of ideal candidates for MCS insertion during CA is fundamental, especially if a preemptive insertion of these devices is considered to increase the safety of the CA procedure (15, 16).

Despite the increasing use of MCS during CA of ventricular arrhythmias, both as rescue therapy for the onset of acute hemodynamic decompensation and as a prophylactic strategy to avoid cardiovascular instability, robust evidence deriving from large randomized clinical trials is missing, and most of the current knowledge is based on the experience of specialized centers. A recently published systematic review by Mariani *et al.* analyzed the available evidence regarding the use of temporary MCS in life-threatening arrhythmias with interesting conclusions about the application of the PAINESD risk score, as further discussed, and the prophylactic use of VA ECMO for an electrical storms (17). Nonetheless, a significant lack of knowledge still exists regarding patient and device selection and ideal timing for implantation during CA for VT and electrical storms.

This review aims to provide an overview of the existing literature on MCS in patients with ventricular arrhythmias and arrhythmic storms, highlighting the benefits and gaps in knowledge for each therapeutic strategy.

Percutaneous MCS support during arrhythmia-related cardiogenic shock

Cardiac output (CO) is determined by the heart rate (HR) and by the stroke volume (SV) of the left ventricle (LV). The latter is the difference between end-diastolic (EDV) and end-systolic volume (ESV).

- $CO = HR * SV$
- $SV = EDV - ESV$

From the first equation, it is easy to understand that (extreme) bradycardia will lead to decreased cardiac output and eventual low-output cardiogenic shock (CS) (18). In parallel, atrial, and ventricular tachyarrhythmias can result in diminished time for ventricular filling in diastole (EDV) as well as the loss of the atrial contribution to ventricular diastolic filling (EDV). This ultimately results in lower SV and, thus, CO. These sustained tachyarrhythmias (those that do not result in

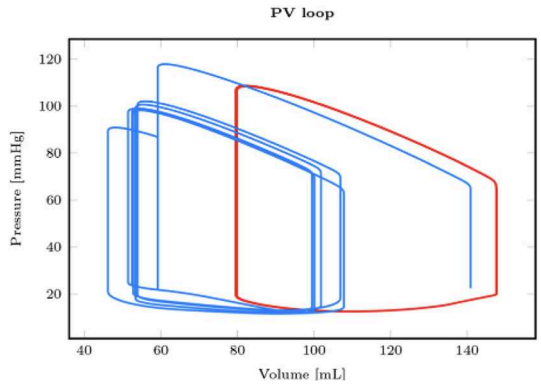

FIGURE 1
Comparison between a reference healthy pressure-volume loop in sinus rhythm (red) and the one obtained in hemodynamically tolerated ventricular tachycardia [reproduced with permission from (19)].

ventricular fibrillation and SCD) are generally only the cause of cardiogenic shock in the already compromised ventricle. Figure 1 illustrates the effect of a (hemodynamically tolerated) VT on the pressure-volume loop with a reduction of the preload, resulting in a decreased SV and CO (19).

Main causes of cardiogenic shock related to arrhythmias

Table 1 provides a (non-extensive) overview of the most frequent causes of brady- and tachyarrhythmias associated with CS. Any arrhythmia can be secondary to pre-existing underlying cardiomyopathy (e.g., ischemic or dilated cardiomyopathy) and thus a direct cause of the CS state or the other way around. Indeed, frequent arrhythmias [mainly atrial fibrillation (AF)] can ultimately lead to arrhythmia-induced cardiomyopathy and refractory CS (20). Reports on arrhythmia-induced CS are scarce and probably underrecognized, but Hékimian et al. reported that CS was the first disease manifestation in 60% of their non-ischemic VA ECMO population with recent onset of supraventricular arrhythmia (21).

Acute sustained bradycardia is most frequently related to hypoxia (22), conduction abnormalities, drug intoxications (23), or underlying (ischemic) cardiomyopathy. Sustained tachyarrhythmias can be divided into (more benign) supraventricular tachycardia and (malignant) ventricular tachycardia. AF is the most common sustained supraventricular arrhythmia, and its most important risk factor comes with age (4% of the population over 60 has a sustained episode of AF) (24). In general, supraventricular tachycardias are well-tolerated unless they rise on top of the already compromised ventricle. Arrhythmia-induced cardiomyopathy should be suspected in patients with tachyarrhythmia and dilated cardiomyopathy of no clear etiology (25).

TABLE 1 Etiologies of bradycardia- and tachycardia-induced cardiogenic shock.

Bradycardia induced cardiogenic shock (sinus-, idioventricular-, escape rhythm, . . .)	
(Acute) cardiac disease	Ischemia, myocarditis, cardiomyopathies, . . .
Hypoxia	Pulmonary embolism, acute respiratory distress syndrome, . . .
Drug induced	Beta blocker intoxication, calcium channel blockers, digoxin, amiodarone, . . .
Hypothermia	
Device failure	Pacemaker dysfunction, lead fracture, . . .
Ion disturbances	Hyperkalemia, hypermagnesemia
(Acute) conduction abnormalities	Sinus or atrioventricular disturbances, atrial fibrillation or flutter
Congenital heart or conduction abnormalities	
Tachycardia induced cardiogenic shock (VF, VT, torsades de pointes, AF, atrial flutter, . . .)	
(Acute) cardiac disease	Ischemia, myocarditis, cardiomyopathies, . . .
Drug induced	Cocaine, methamphetamine
Ion disturbances	Hypokalemia, hypomagnesemia
Valvular heart disease	
Congenital heart or conduction abnormalities	Brugada syndrome, long-QT syndrome

The most frequent malignant tachyarrhythmia is ischemia-induced sustained VT, which can result in ventricular fibrillation (VF), SCD, or CS. VT can be related to a new onset acute myocardial infarction or rising from scar tissue from a previous insult (26). Lethal ventricular arrhythmias have been reported to occur in more than 10% of all acute myocardial infarction cases, and survival in these patients is poor.

Ventriculo-arterial coupling and uncoupling during an arrhythmic storm

In a normal cardiac cycle, the LV overcomes the diastolic blood pressure during the isovolumetric contraction phase until the aortic valve opens and the intraventricular blood gets ejected (Figure 2, the left part of the trace; ventriculoarterial coupling). However, during a low output state (e.g., an arrhythmogenic VT storm), the drop in preload and diastolic filling time will

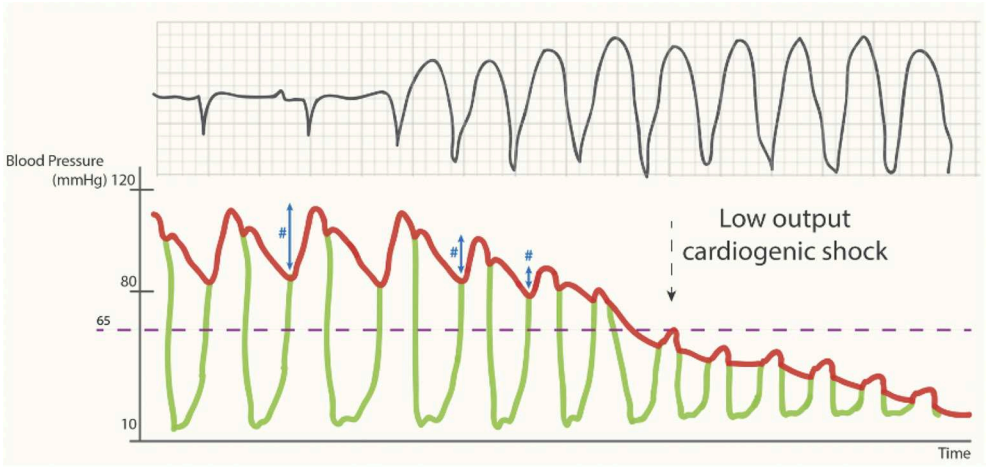

FIGURE 2
Cardiac output during (unsupported) sustained ventricular tachycardia. Loss of pulse pressure (#) and cardiac output during the arrhythmogenic storm phase [reproduced with permission from (27)].

eventually result in a drop in pulse pressure and perfusion pressure, ultimately leading to a cardiac arrest phase (Figure 2, the right side of the trace) (27).

This drop in the native cardiac output during an arrhythmic storm can be partly covered by the insertion of a percutaneous mechanical circulatory support device (e.g., an Impella-device), which offers a continuous forward flow of blood from the LV into the aorta. This flow is both afterload sensitive, with end-organ perfusion increasing with lower systemic vascular resistance, and preload dependent, requiring sufficient volume from the right ventricle to operate effectively. If the failing LV can no longer overcome afterload in the new equilibrium of increased mean arterial pressure and reduced preload created by the continuous flow of the percutaneous MCS device, the arterial trace will flatten. This process is called ventriculoarterial uncoupling (Figure 3) (28).

MCS during arrhythmia-induced cardiogenic shock

Bradycardia-induced CS can often be reversed by positive chronotropic agents or urgent temporary (ventricular) pacing, which leaves physicians a time window for diagnosing and resolving the underlying cause.

Management of patients with CS shock and (supra) ventricular arrhythmias is particularly difficult. Inotropic treatment, such as dobutamine, is recommended for CS but may exacerbate supraventricular tachycardia or accelerate the heart rate in these patients. Antiarrhythmic drugs (e.g., amiodarone) often have negative inotropic effects and may exacerbate the CS state. Electrical reconversions often risk worsening circulatory failure or cardiac arrest in these critically ill CS patients. Therefore, urgent implementation of MCS devices can be an effective way of stabilizing CS patients and allowing physicians a time window of stability to investigate the underlying cause of the arrhythmia and allow therapeutic interventions (e.g., revascularization and semi-urgent ablation) (21). The field of MCS in arrhythmia-related CS is highly unexplored and needs further investigation.

Left ventricular assist devices and ventricular hemodynamics

Left ventricular assist devices (LVADs) are used to support a failing heart as a temporary means (bridge to recovery and bridge to transplant) or as destination therapy. The interaction between reduced native cardiac function and continuous flow generated by LVAD creates a complex interplay, which may impact the restoration of LV performance.

An elegant *in vitro* study by Viola et al. confirmed how LVAD flow affects intraventricular hemodynamics and pressure. Indeed, the unloading of LV generated by LVAD causes a reduction in ventricular peak systolic pressure, which is related to LVAD output (29). Considering that an increment in intraventricular pressure leads to adverse remodeling of LV myocardium, LVAD, with its unloading effect, may help recover native cardiac function. Recovery of physiological hemodynamic conditions in patients treated with long-term LVAD is still a complex matter of debate with an emerging working hypothesis (30).

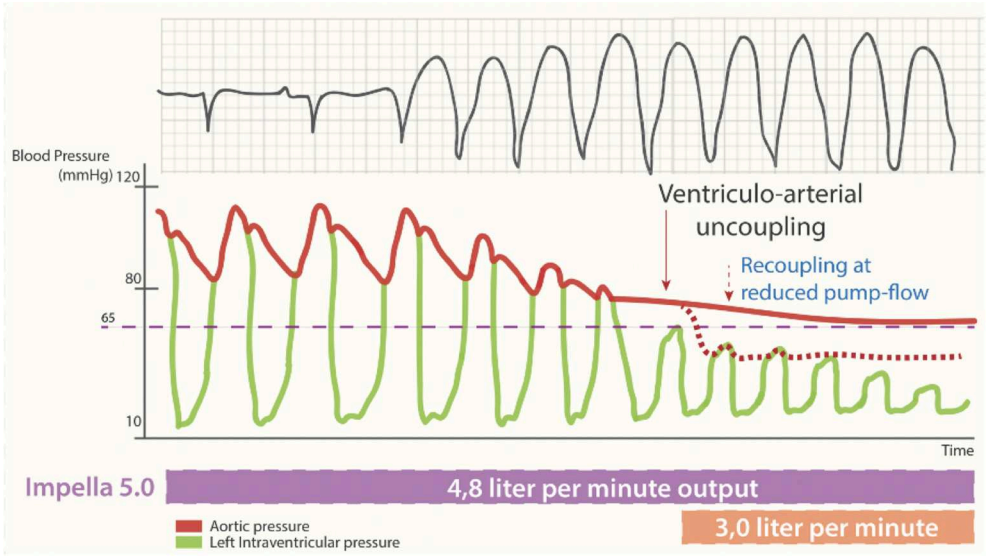

FIGURE 3
Cardiac output during percutaneous MCS supported sustained ventricular tachycardia. Loss of pulse pressure and cardiac output during the arrhythmogenic storm phase. Ventriculo-arterial uncoupling with sustained output, generated by non-pulsatile output (4.8 L/min) by the Impella-5.0 support and resulting in a systemic blood pressure of 65 mmHg [reproduced with permission from (27)].

Percutaneous MCS during catheter ablation for ventricular arrhythmias

Rescue MCS and preemptive MCS during CA for ventricular arrhythmias

Hemodynamic instability, CS, and cardiac arrest are all potential severe complications of CA ablation during electrophysiological studies with a consequent detrimental impact on outcomes and an increased 30-day, 6-month, and 1-year mortality rates (12). A case series of intraprocedural implantation of VA ECMO as rescue therapy for acute hemodynamic deterioration during CA for an electrical storm showed a poor prognosis with high short-term mortality of almost 90%, despite a high rate of CA success (83%) (31).

The dismal prognosis of patients experiencing cardiovascular instability during CA, even after the emergent implantation of MCS, has redirected focus from the stabilization of periprocedural acute hemodynamic decompensation to the identification of preemptive strategies to support high-risk patients. Promising results derived from a single-center study showed lower 30-day mortality (4 vs. 58%) in patients who received pre-emptive insertion of percutaneous LVAD (Impella) compared to patients undergoing rescue insertion of MCS (15).

Although the evidence is still scant, the clinical rationale for preemptive implantation of temporary MCS during high-risk CA of VT is strong. The adequate timing of temporary MCS implantation for high-risk patients (i.e., with structural heart disease, comorbidities, and multiple ICD shocks) undergoing CA of VT is still under debate. However, it is evident that this aspect is of pivotal importance given the high mortality rate of patients requiring emergent implantation of MCS during CA procedures. For this reason, it is crucial to identify, before the procedure, those patients who may experience acute hemodynamic deterioration during the CA of VT.

PAINESD score and the risk of hemodynamic decompensation

In 2015, Santangeli et al. studied the prevalence and predictors of periprocedural acute hemodynamic decompensation in patients undergoing radiofrequency CA for scar-related VT. In this study, almost one out of 10 patients experienced hemodynamic instability, impacting mortality. The authors identified eight clinical factors predicting periprocedural acute hemodynamic decompensation (PAINESD risk score): advanced age, chronic obstructive pulmonary disease, use of general anesthesia, ischemic cardiomyopathy, heart failure (NYHA classes III and IV), lower LV ejection fraction, presentation with VT storm, and diabetes mellitus (12).

The same study group demonstrated that the percutaneous LVAD implantation prophylactic strategy effectively decreased the incidence of periprocedural acute hemodynamic decompensation. This finding was in synchrony with a reduction in mortality and/or requirement for heart transplantation comparing patients with prophylactic percutaneous LVAD and patients requiring rescue MCS. However, when further

analyzing the different categories in the PAINESD score, a considerable benefit in mortality was found in those patients considered at high risk [PAINESD score $\geq$ 15: hazard ratio (HR) 0.43; 95% confidence interval (CI) 0.21–0.87; p-value = 0.02]. Conversely, patients with a predicted low risk of acute hemodynamic decompensation did not experience any benefit (PAINESD score $\leq$ 8: HR 0.63; 95% CI 0.24–1.66; p-value = 0.35) (16).

In their systematic review, Mariani et al. calculated the PAINESD score in the studies published after 2016, showing higher values of the PAINESD score in patients requiring temporary rescue MCS during CA. They confirmed how preemptive implantation of temporary MCS positively influenced the survival rate compared to rescue MCS strategies, particularly in the case of electrical storm. The authors stressed how the PAINESD risk score could be considered a "*robust tool to identify high-risk patients who might benefit from temporary prophylactic MCS during electrophysiological studies*." They suggested a PAINESD cut-off score of 15 for considering preemptive implantation of temporary MCS, particularly if prolonged VT mapping is required or long phases of unstable VT are expected (17).

Influence of MCS on the success rate of ablation

Temporary MCS may not only provide cardiovascular support in the case of acute hemodynamic decompensation during CA but may also represent a tool for facilitating the treatment of VT. Some studies have addressed the question of whether temporary MCS influences the success of VT ablation.

Effective ablation of unstable VT with activation and entrainment mapping may be hampered by poor hemodynamic tolerance of induced arrhythmia. In these scenarios, pace and substrate mappings are classically used to find an ablation target while the patient is in sinus rhythm. However, successful ablation is obtained at the expense of scar mapping and ablation (32, 33). In addition, an alternative strategy may be required for those who experience persistent VT after unsuccessful substrate-guided CA, VT related to non-ischemic dilated cardiomyopathies, and VT originating from extensive scars (34).

The feasibility and the advantages of this approach in patients with scar-related ventricular arrhythmias started being assessed in small groups of patients almost 10 years ago. One of the first studies was published by Miller et al. in 2011. They showed how temporary MCS with Impella 2.5 guaranteed end-organ perfusion during prolonged periods of unstable VT, leading to procedural advantages compared to support with an intra-aortic balloon pump (IABP) or no mechanical support (35).

One year later, Bunch et al. analyzed a cohort of high-risk patients with hemodynamically unstable VT undergoing CA guided by activation and entrainment mapping and assisted by Tandem Heart. Despite longer procedure times, the outcomes of acute complications (including death and stroke) and freedom from ICD or therapies for sustained VT were comparable to a matched cohort undergoing substrate mapping without temporary MCS (36).

In a retrospective study, Aryana et al. demonstrated a shorter total radiofrequency ablation time for patients receiving percutaneous LVAD for CA of unstable VT compared to procedures without MCS. That was accompanied by a reduced length of hospital stay (37). The substrate mapping technique is less effective for CA in individuals with ventricular arrhythmias related to non-ischemic cardiomyopathies; in this subset of patients, a combined approach with temporary MCS and activation/entrainment mapping may be particularly beneficial (38).

Despite the differences found in diverse case series, the long-term follow-up did not reveal any statistically significant difference in rates of VT recurrence between patients undergoing CA with and without temporary MCS (39, 40). These findings may be related to heterogenous patient selection and etiologies of arrhythmias in currently available studies (17). Only one study showed how percutaneous LVAD support was associated with a lower composite endpoint of 30-day rehospitalization, redo-VT ablation, recurrent ICD, and 3-month mortality (37).

In the context of hemodynamically tolerated ventricular arrhythmias, the substrate-based CA strategy has proven to have similar acute procedural efficacy and VT recurrence compared with activation and entrainment mapping, with a comparable rate of complications and mortality (41). For those patients who underwent substrate-based CA of unstable VT with arrhythmia recurrence, despite the successful modification of the substrate, ablation guided by activation or entrainment mapping and supported by temporary MCS may represent a reasonable treatment strategy (34).

Comparison of temporary MCS devices

Different devices, from IABP to VA ECMO, have been proposed as hemodynamic support during CA procedures, thus further increasing the variability between the studies. Each MCS device can guarantee a different level of cardiovascular assistance. Unfortunately, only a few studies have addressed the specific issue of direct comparison between MCS devices.

IABP was proven less effective in providing hemodynamic support than percutaneous LVAD (Impella 2.5) during CA for VT. In a multicentre study, Reddy et al. found that

implantation of Impella or Tandem Heart facilitated activation and entrainment mapping of several unstable VTs with fewer rescue shocks compared to patients supported with IABP (40). A retrospective analysis comparing percutaneous LVAD (Impella, Tandem Heart, and VA ECMO) with IABP proved better short-term outcomes in terms of mortality, length of hospital stay, the incidence of acute kidney injury, and 30-day rehospitalization in patients supported by percutaneous LVAD (37). Despite better performance in periprocedural support during CA for unstable VT, no significant differences were found when analyzing intermediate and long-term outcomes, such as VT recurrence and mortality (37).

Impella and Tandem Heart have specific contraindications to their implantation: LV thrombosis, mechanical aortic valve replacement, and ventricular septal defect. These contraindications must be considered when choosing a temporary MCS device. Furthermore, these two devices are burdened with technical limitations related to the requirement of transeptal puncture for Tandem Heart and electromagnetic interference during mapping for Impella (34).

VA ECMO can provide both biventricular and respiratory support, thus allowing its use in extreme conditions of hemodynamic instability, such as cardiac arrest, and as a bridge to recovery or heart transplantation (42, 43). Complete cardiovascular and respiratory support benefits are counterbalanced, especially in the case of femoral percutaneous cannulation, with a retrograde infusion of blood. The consequent LV afterload increase can trigger a vicious cycle leading to increased wall stress and myocardial oxygen consumption (42).

Given its unparalleled capacity to provide end-organ perfusion, VA ECMO represents a useful solution for hemodynamic support in adult patients presenting with electrical storm, VT refractory to antiarrhythmic therapy, and recurrent VF. The combination of hypotension due to refractory VT/VF, cardiac stunning related to repeated shocks, and the frequent requirement for sedation/anesthesia during CA for VT/VF arrhythmic storms may precipitate acute hemodynamic decompensation (34). In the presence of CS related to electrical storm refractory to antiarrhythmic therapy, emergent implantation of VA ECMO may represent a rescue strategy capable of achieving a survival rate after the implantation of 50% (44). However, a smaller case series enrolling 21 patients showed a higher mortality rate (88%) in patients receiving VA ECMO for acute hemodynamic decompensation during CA of VT, despite a high procedural success rate (31).

VA ECMO is the most commonly used temporary MCS device as a rescue strategy for cardiovascular support in children requiring radiofrequency ablation for tachycardia-induced cardiomyopathy (45, 46), for management of hemodynamically unstable primary arrhythmias in newborns and infants (47), and hemodynamic support during acute fulminant myocarditis complicated by arrhythmias (48).

Impact of permanent ventricular assist devices on arrhythmias

Permanent ventricular assist devices (VADs) represent a therapeutic option for end-stage heart failure as a bridge to heart transplantation or even as "destination therapy" (49). The reported incidence of ventricular arrhythmias after the implantation of LVAD ranges from 20 to 60% (50). If the short-term effects may be negligible, the impact of long-term and recurrent ventricular arrhythmias in patients with long-term LVAD must not be overlooked. In fact, the persistence of ventricular arrhythmia in these patients may cause right heart dysfunction, ultimately leading to hemodynamic compromise (51). From a mortality point of view, the presence of ventricular arrhythmias after LVAD implantation did not affect short-term mortality but significantly increased long-term one (52). Proposed mechanisms for developing ventricular arrhythmias in these patients are multiple and encompass (51, 53): preload alteration with chamber collapse and "suction-related" VT, changes in myocardial electrolyte balance, primary cardiomyopathy, device-related mechanical stimulation, and hypersympathetic state. Predictors of post-operative ventricular arrhythmias after the implantation of LVAD are the history of pre-LVAD ventricular arrhythmias and duration of heart failure (54–56), and the role of underlying cardiomyopathy type is still debated. The findings regarding the onset of ventricular arrhythmias after the implantation of LVAD have been recently summarized in a review (52).

Lin et al. have addressed the role of ventricular arrhythmias in patients with biventricular assist devices (BIVAD) in a retrospective cohort study (57). The prevalence of ventricular arrhythmias in patients treated with BIVAD was high and similar to a propensity-matched LVAD population (46 and 38%, respectively). They also found that patients with sustained ventricular arrhythmias after BIVAD implantation had worse composite outcomes.

Venoarterial ECMO in arrhythmic storms

Patients with CS refractory to inotropic agents and vasopressors have a poor prognosis, and the VA ECMO offers the ability to restore hemodynamics and prevent end-organ damage. Time to decision and time to initiate VA ECMO is crucial. A narrow "window of opportunity" for rescue VA ECMO intervention exists, beyond which a patient may develop hypoperfusion brain damage, multiorgan failure, reperfusion sepsis, and is too ill to benefit from a temporary MCS (58).

The applications of the VA ECMO in life-threatening arrhythmias encompass arrhythmogenic storm triggered by cardiac ischemia, fulminant myocarditis with ventricular arrhythmias, periprocedural in the cath-lab, accidental

hypothermia, and some poisonings (particularly with a concoction of the yew tree needles or the recreational drugs like cocaine or amphetamine) (59). Right ventricular failure may also trigger intractable arrhythmias, like in Ebstein anomaly or other congenital heart diseases, potentiated by positive end-expiratory pressure-induced acute *cor pulmonale*.

In a patient younger than 70 years with cardiac arrest, an ideal therapeutic window for a VA ECMO start (i.e., the time from a collapse to running extracorporeal life support) is within 40 min from the witnessed collapse. The maximum associated delay with acceptable rates of cerebral performance score (CPS) 1–2 is up to 60 min. Crucial is decision-making at 10–15 min of refractory cardiac arrest. That also relates to the expected transfer to the facility or the ECMO to the scene and percutaneous cannulation times of ∼14–20 min (60).

The time from collapse to the provision of advanced life support should not be more than 5 minutes and the initial rhythm on the scene associated with a favorable outcome is a shockable VF/VT (60, 61). Other parameters linked to favorable outcomes are time to defibrillation and time to percutaneous coronary intervention in a coronary ischemic event. The contraindications to extracorporeal life support (ECLS) are age above 70 years, unwitnessed cardiac arrest, prolonged time of cardiopulmonary resuscitation (CPR) assuming prolonged time to run ECMO, pre-existing irreversible neurologic, oncologic, or other systemic disease limiting the potential for recovery, a contraindication to systemic anticoagulation, aortic dissection, cardiac tamponade, and severe aortic insufficiency (61).

ECMO has demonstrated its impact on outcomes of cardiac arrest and CS (62). The survival benefits of ECMO in refractory cardiac arrest were demonstrated in the *CHEER (mechanical CPR, hypothermia, ECMO, and early reperfusion) trial*. The investigators reported rates of survival to hospital discharge up to 60% among recipients of ECMO after in-hospital cardiac arrest (IHCA), especially when related to cardiac etiology (63). Acute myocardial infarction or ischemia is the most common cause, accounting for nearly 35–50% of cardiac arrests. Pulseless VT/VF is the initial rhythm in 13–39% of IHCA patients, where temporary MCS and ECMO are used increasingly. The 3-fold increase in the utilization of ECMO in the IHCA over the last decade significantly increased the overall hospital survival from 35.4 to 43.5% ($p < 0.0001$) (64). ECMO yielded more favorable results in patients who suffered IHCA than in out-of-hospital cardiac arrest (OHCA) (60). Recent advances in the care of the OHCA (60) have shown a favorable neurological outcome at 180 days in both study (31.5%) and control (22%) groups related to an established bundle of early intra-arrest transport, invasive assessment, and treatment in both the ECMO and conservative arms of the trial.

The use of VA ECMO during periprocedural arrhythmia is increasing. A substantial mortality benefit was observed among high-risk patients identified with a PAINESD risk score or suffering from electrical storm and treated with preemptive temporary MCS (17). The patients supported predominantly by urgent VA ECMO for periprocedural life-threatening arrhythmias were characterized by older age, more ischemic cardiomyopathies, worse LV ejection fraction, and more comorbidities than the control group. Regardless of unfavorable profiles and the rates of pump failures in the VA ECMO cohort, the rescue ablation successfully prevented recurrences of ventricular arrhythmias and resulted in a comparable 1-year outcome between arrhythmic storms with and without VA ECMO support (65).

Severe accidental hypothermia is associated with ventricular arrhythmias (66–69), and the patient should be referred to the nearest hospital with an ECLS availability. VA ECMO implementation is recommended in severe hypothermia patients (i.e., body temperature <28°C, Swiss hypothermia scale III-IV) and hemodynamic instability defined as ventricular arrhythmias or cardiac arrest (66, 68–70). The call to activate the ECLS pathway or to take a hypothermia patient with a maintained airway and palpable bradyarrhythmia (sinus, junctional rhythm, or atrial fibrillation with slow ventricular response) to the nearest hospital might be challenging. The presence of hypothermia under 30°C significantly limits the chance for cardioversion, either electric or pharmacologically potentiated (66, 69).

A study demonstrated a promising hospital survival of 89% with an outstanding CPS in a case series of patients with severe hypothermia retrieved in a European urban area and treated in an established ECLS and extracorporeal-CPR center. The rewarming requires a short duration of the VA ECMO (median 48 h) with decreasing blood flow and lower sweep gas flow. These are related to an early afterload effect on the heart recovering from hypothermia and hypothermia-related low CO_2 production (71).

The cannulation should not interfere with the CA techniques if inserted as periprocedural support with a femoro-femoral approach, representing the desirable configuration for periprocedural support or during ECLS.

In all the settings, the return arterial cannula may frequently block the distal leg perfusion, which is, in most centers, solved by routine cannulation of the prograde 6–7F vascular sheath into the superficial femoral artery. The insertion should be as close to the ECMO return cannula as possible because the no-flow segment between them soon becomes a site of thrombus formation.

A minimum cardiac output of 1–2 l/min should be maintained even in circulatory failure supported by the VA ECMO, which would secure LV unloading and prevent intracardiac thrombus formation. If this is not possible, the available methods of unloading are Impella, a surgical vent of the LV either through the mitral valve and left atrial auricle or transseptal approach, or to a certain degree, also with the IABP (72, 73).

Details regarding VA ECMO configuration, hemodynamics, and complications are beyond the scope of the current review and are detailed elsewhere.

Stellate ganglion blockade during MCS

As detailed above, MCS is an effective strategy to rest the heart and support the circulation when it is compromised by ineffective cardiac contraction during an arrhythmic storm. Although sinus rhythm may be restored after the initiation of VA ECMO in the ECLS setting, intractable ventricular arrhythmias may persist despite full circulatory support. In a recent publication of patients treated with MCS during arrhythmic storm, no differences between survivors and non-survivors were noted according to the use of antiarrhythmic drugs (amiodarone, lidocaine, and/or electrolyte adjustment) (74).

The percutaneous blockade of the stellate ganglion has been described in different populations, including in patients with electrical storm on MCS. It is a minimally invasive (either blind or ultrasound-guided) technique that has been demonstrated to relieve ventricular arrhythmic burden in a remarkable rate of patients when all other pharmacological therapies failed without serious complications (75–77).

Arrhythmias in COVID-19

Large studies have reported an overall prevalence of arrhythmias after SARS-CoV-2 infection that ranges from 10 to 20%, although the incidence is greatly increased in individuals with severe disease. Arrhythmias are supraventricular in most of the critically ill patients with COVID-19. However, 40% of the overall arrhythmias are ventricular tachyarrhythmias, bradyarrhythmias, and conduction defects, which are associated with remarkably high mortality (78).

Inflammatory cytokines, particularly TNF, IL-1, and IL-6, may exert significant arrhythmogenic effects *via* several mechanisms, including complex modulatory activities on the expression and function of specific ion channels and gap junction-forming connexins, cytochrome system inhibition, and structural remodeling by activating the myofibroblast-driven synthesis of extracellular matrix responsible for cardiac fibrosis (79). Additionally, oxygen mismatch and sympathetic activation may also work as triggers for arrhythmias. In a large cohort of patients hospitalized with COVID-19, an independent association between infection status and QTc prolongation and a direct correlation between IL-6 levels and QTc interval were shown (80).

During the COVID-19 pandemic, a provision of ECMO services has been offered, underscoring the need to select cases that may benefit from ECMO placement. The use of MCS for CS was rather low during the pandemic, although the number of cardiac arrests was higher, at least during the "first wave" (81). Cardiac abnormalities also prolong the long-COVID syndrome with arrhythmias, which are part of the symptoms of post-acute sequelae (82). The burden of heart failure with all the relevant clinical consequences, including cardiac dysautonomia, is expected in patients who experienced severe COVID-19 infection and have recovered.

Final considerations

MCS is an effective strategy to support hemodynamics in patients with an arrhythmic storm. The choice of the device should be driven by the team experience, clinical setting, and amount of cardiocirculatory support required. Collateral therapies, such as titrated drugs, metabolic adjustment, and percutaneous stellate ganglion blockade, are essential to stabilize the arrhythmic burden and need further investigation.

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Mapping the research trends and hot topics of ventricular arrhythmia: A bibliometric analysis from 2001 to 2020

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Background: Studies of ventricular arrhythmia (VA) have drawn much scholarly attention over the past two decades. Our study aimed to assess the current situation and detect the changing research trends of VA quantitatively and qualitatively.

Materials and methods: All the information used in our statistical and bibliometric analysis were collected and summarized from papers retrieved from the Web of Science Core Collection (WoSCC) database on December 22, 2021 using certain criteria. Visual analytics were realized using CiteSpace, VOSviewer, the bibliometrix R package, and the bibliometric online analysis platform.

Results: A total of 6,897 papers (6,711 original articles, 182 proceedings papers, three book chapters, and one data paper) were published in 796 journals that concentrated on the research areas of cardiovascular and critical care medicine. The most productive country and influential institution was the USA and the Mayo Clinic, respectively. *Heart Rhythm* (551 articles and 8,342 local citations) published the most manuscripts. The keyword co-occurrence and co-citation network of references analyses revealed that the most popular terms were ventricular tachycardia, ventricular fibrillation, catheter ablation, implantable cardioverter defibrillator (ICD), and sudden cardiac death (SCD). Further, the burst detection analysis demonstrated that topics strongly associated with clinical prognosis, such as meta-analysis, long-term outcomes, and impact, were new concerns.

Conclusion: Our study offers a comprehensive picture of VA research and provides profound insights into the current research status. Moreover, we show that new topics within the VA research field have focused more on prognosis and evidence-based clinical guidelines.

KEYWORDS

ventricular arrhythmia, bibliometric analysis, R package bibliometrix, CiteSpace, VOSviewer

Introduction

The heart, the most vital organ of the human body, is a rhythmic pump that maintains the blood circulation system. Although its most fundamental anatomical structure and physiological functions were fully interpreted for the first time by William Harvey as early as 1628, our understanding of cardiac dysfunction and the prevention and palliation of related pathogenesis remains limited (1). Cardiovascular disease (CVD) is the leading cause of sudden cardiac death (SCD) worldwide, and in many cases, SCD is preceded by life-threatening cardiac arrhythmias, especially sustained ventricular arrhythmia (VA), which is frequently promoted by different types of CVD (e.g., acute coronary/non-coronary occlusion, left ventricular dysfunction, various types of cardiomyopathies, and primary electrophysiological abnormalities) (2–6). Even worse, the complexity of pathogenesis and heterogeneity of cardiac structural abnormalities have imposed tremendous challenges and additional difficulties for both the basic research domain of cardiac biology and clinical management and practice.

Fortunately, scientific and technological advances over recent decades have been rapid and we are no longer limited to anti-arrhythmic drug (AAD) therapy. The multiple new technologies and constantly updating clinical guidelines have helped obtain accurate diagnoses as well as prevent sudden death and recurrences of VA, thereby improving poor prognoses to some extent. Specifically, available and effective techniques for disease detection and treatment, such as 24-h ambulatory electrocardiogram (ECG) monitoring, pacemakers, implantable cardioverter defibrillators (ICDs), automated external defibrillators for cardiac arrest, and radiofrequency catheter ablation procedures, are all based on a better understanding of cardiac imaging in electrophysiology, myocardial biomechanics, and cardiac hemodynamics (1–3, 7). At the same time, many robust VA-related clinical guidelines, particularly those drafted and updated by the American Heart Association (AHA) and the Canadian Cardiovascular Society, have re-emphasized the great therapeutic value of ICDs and considered the cost-effectiveness of treatment decisions; they have also reiterated the importance of AAD medications as a crucial therapy for symptomatic treatment and the acute/long-term management of sustained VA in patients with structural heart disease (2, 8). Even so, extant research on VA and the relevant clinical guidelines for management still fall short, remain controversial, and require further detailed discussions. For instance, as stated by the AHA, there is a lack of evidence from highly reliable randomized controlled trials (RCTs) that AADs for VA improve survival when provided for the primary or secondary prevention of SCD, except for beta-blockers. Moreover, the overall incidence of specific AAD-induced arrhythmias, underlying mechanisms, and optimal methods to prevent other clinical side-effects and reduce risk remain unknown (2, 9).

Bibliometric analysis is frequently used to explore trends and hot topics in medical research fields, which enables the quantitative and visual measurement of research articles relating to countries/regions, institutions, journals, authors, and keyword networks (10). However, bibliometric studies of VA are scarce, with few comprehensive quantitative assessments of the status and trends of basic and clinical research. In this original research, by reviewing 6,897 papers published in 796 journals that concentrated on the research areas of cardiovascular and critical care medicine, we examined the existing circumstances and potential foci of the pertinent literature on VA published globally over the past 20 years. We hope that this original research will provide valuable insights and inspiration for future studies of VA.

Materials and methods

Data source and retrieval strategies

The Web of Science Core Collection (WoSCC), which is one of the largest bibliometric databases, was selected to collect the raw data to conduct our bibliometric analysis. To improve both precision and recall, the following search string was used within the document TITLE field: "TI = (Ventricular parasystole OR Ventricular *rhythmia* OR Ventricular tachycardia OR Ventricular fibrillation* OR Ventricular flutter OR Ventricular premature complex*)" with a time span from 2001 to 2020. The initial search returned 14,565 records. With the retrieval strategies refined by document type (article) and language (English), 6,953 records were finally obtained. All these article records were downloaded on the same day (December 22, 2021) to avoid the bias caused by frequent database updates.

Data collection and extraction

Before being used for the descriptive analysis and bibliometric visualization, all the main information in our raw data (including article titles, authors and affiliations, countries, and journals) was converted into different txt formats according to the requirements of the software and then separately imported into CiteSpace (Drexel University, Philadelphia, United States; version 5.8.R3c SE), VOSviewer (Leiden University, Leiden, the Netherlands; version 1.6.17), a bibliometric online analysis platform,[1] and RStudio (version 4.1.2) (11) using the bibliometrix R package.[2] To ensure accuracy, the data collection and extraction processes were independently performed by two authors.

1 http://bibliometric.com/
2 http://www.bibliometrix.org

TABLE 1 Summary of the bibliometric characteristics for articles in ventricular arrhythmia research.

Description for bibliometric characteristics	Results
Articles	6,897
Timespan	2001: 2020
Sources (Journals, Books, etc.)	796
References	75,600
Average citations per articles	24.12
Keywords Plus	6,645
Author' s keywords	7,021
Authors	24,358
Author appearances	53,114
Authors of SA-articles	115
Authors of MA-articles	24,243
SA-articles	127
Articles per author	0.283
Co-Authors per article	7.7
Collaboration Index	3.58
Article types	
Article	6,711
Proceedings paper	182
Book chapter	3
Data paper	1

SA, single-authored; MA, multi-authored.

Bibliometric analysis and science mapping

In the next step, we performed our bibliometric analysis in two stages. We first conducted descriptive statistics for the main document characteristics (annual number of publications, countries, affiliations, authors, and journals) and sorted them by the corresponding counts. To systematically and comprehensively analyze the overall trend of the research topic and of publications or citations, we relied on several frequently used evaluation metrics including Freeman's betweenness centrality and the total/average number of article citations. In addition, to further evaluate the scientific impact of the most productive authors and journals, other indicators universally accepted by scholars, such as the h-index, m-index, quartile in category (Journal Citation Reports, JCR), and cited half-life (CHL), were introduced into the bibliometric evaluation system.

Additionally, to provide more comprehensive insights into highly cited documents in the field, we used the PlumX metrics (citations, usage, captures, mentions, and social media), derived from the Scopus database, to assess the impact of the research on social media. Citations reflect traditional measures of research impact; usage encompasses the counts of views, article downloads, library holdings, clicks, collaborators, and video plays; captures track the number of times an article is bookmarked, favorited, exported, and subscribed; mentions represent the number of citations in reviews, websites, topics, comments, and blogs; and social media show the frequency of likes, tweets, and shares across various platforms (12, 13).

Next, we performed bibliometric visualization and science mapping using a combination of the bibliometric online analysis platform and the other three types of software mentioned above to capture hidden patterns (conceptual, social, and intellectual network structures) and the dynamic evolution over time in the study area (14). Finally, we constructed collaboration network maps of countries, affiliations, and authors as well as carried out author keywords co-occurrence analysis, cited documents co-citation and cluster analysis, and burst detection analysis on the basis of the corresponding bibliographic records. For more details, parameter settings for CiteSpace are showed as follows: the number of years per slice was set to "1"; the selection criterion was set to "g-index"; and the scale factor k was set to "25"; furthermore, the options "pathfinder" and "non-pruning" were selected in order to retain the most salient structure of the network. Moreover, VOSviewer was used to create the term maps by the following options: "Creating a map based on bibliographic data," "reading raw data from bibliographic database files," "type of analysis: co-occurrence," "unit of analysis: all authors keywords," "counting method: full counting," and "minimum number of the occurrence of a keyword: 20." Definitions of some major statistical terms, metrics, and indices were summarized and provided in the **Supplementary Table 1**. Please see the **Supplementary material** for more details.

Results

Overview of the ventricular arrhythmia publications

Altogether, 6,897 documents comprising 6,711 articles, 182 proceedings papers, three book chapters, and one data paper were used for the bibliometric analysis based on our retrieval strategy and inclusion/exclusion criteria (time span from January 1, 2001 to December 31, 2020). Because different software programs use different counting and ranking algorithms, our ranking patterns showed subtle differences. Therefore, all the ranking metrics were identified using the combined results of the software and platform mentioned above. **Table 1** summarizes the bibliometric statistics for the main data. The 6,897 documents related to VA research derived from 796 sources, covering 75,600 references and 24,358 authors. Additionally, 7,021 article keywords were reclassified and reclustered as "keywords plus" (6,645) based on the additional features of the WoSCC database. Moreover, the average number of citations per article was 24.12, which indicated that VA has been attracting significant research attention in the field of CVD. Furthermore, only 115 (0.47%) studies of VA were single-authored, while the remaining were multi-authored (24,243; 99.53%); the proportion of co-authors per article

and collaboration index were 7.7 and 3.85%, respectively, suggesting that VA-related articles often require broad scientific collaboration.

Figures 1A,B show the growth in annual publications and annual average citations for papers related to VA research from 2001 to 2020, respectively. Overall, a steadily increasing trend with only minor fluctuations was clearly apparent for annual publications. There were two turning points in the number of publications in 2008 and 2018 and a peak in 2020. Similarly, the average number of citations per year fluctuated from 2.172 (2008) to -3.693 (2015), peaking in 2003, 2006, 2011, 2015, and 2018; this might be due to the emergence of a large number of published and updated clinical guidelines.

Distribution and collaboration of countries and affiliations

The sampled articles on VA stemmed from 72 countries and 4,786 affiliations. As shown in **Table 2**, the top 10 most productive countries and affiliations were identified by the total publications sorted by the corresponding author's country and affiliation. Among the 72 countries, the United States contributed the greatest number of publications (7098), followed by China (2091), Japan (1887), Germany (1216), and Italy (1207). In addition, with regard to the betweenness centrality in this social network, we found that the United States (centrality = 0.90) again had the highest value, demonstrating that it was the most influential country, far exceeding the United Kingdom (0.08) and Canada (0.07).

The visual network analysis showed the collaborations among countries, identifying that the most frequent cooperation appeared between the United States and China, followed by the United States and Japan (**Figure 2A**), which validated the significance of the centrality metric. Among the 4,786 affiliations, the Mayo Clinic topped the list (295), while Brigham and Women's Hospital had a relatively high influence (centrality = 0.12), followed by the University of California Los Angeles (0.11) and Harvard University (0.07). Similarly, **Figure 2B**, drawn by CiteSpace, presents the collaboration network of affiliations involved in all 6,897 publications on VA research, showing a low distribution density (0.0161) and a centrality of the top 10 affiliations below 0.15 (**Table 2**). These results indicate that the distribution is relatively dispersed and that further academic collaborations are needed.

Authors' contributions to ventricular arrhythmia research

Table 3 shows the top 10 most productive of the 24,358 authors in the past 20 years, ranked by the number of publications. In addition to productivity (represented by the number of articles published by an author), the academic impact (represented by the average number of local citations) cannot be underestimated and should be considered when evaluating an author's contributions to and relevance in a field. Taking all these conditions together, the top three best-performing authors, Francis E. Machlinski (123 articles; 1,997 citations), William G. Stevenson (111 articles; 2,029 citations), and David J. Callans (103 articles; 1,438 citations), were the most productive authors with a high average number of local citations and high contribution rate of authors to publications. Moreover, William G. Stevenson can be seen as an influential scholar on this topic, as reflected by an uninterrupted series of publications over the past two decades (**Figure 3A**). Interestingly, Fred Morady was the only author to publish VA-related studies as neither the first author nor the corresponding author, but still exhibited relatively high productivity and influence.

As described in "Materials and methods" section, to better assess the scientific impact and relevance of the community and avoid bias, other well-established indicators were introduced into our bibliometric analysis. **Table 3** also lists the h-index and m-index of the top 10 most productive authors. The overwhelming majority of these authors had an excellent combination of productivity and influence, apart from Yoshifusa Aizawa, who had published 68 articles but only received 251 local citations with an average number of local citations of 3.69, a local h-index of 18, and an m-index of 0.86. The m-index, calculated from the h-index weighted for an author's career duration in years, is considered to be a highly representative measure of an individual's scientific achievement (15). More interestingly, except for the top three best-performing authors mentioned above, Pasquale Santangeli is extremely competitive and highly influential on this topic despite not having published papers in this field until 2010 (**Figure 3A** and **Table 3**). Similar to above, **Figure 3B** shows the authors' collaboration networks in VA research, again highlighting that better networking is necessary to facilitate domestic and international collaborations and co-authorships across academia.

Journal distribution

As mentioned above, 796 journals published 6,897 articles in this field over the sampled 20 years. **Figure 4** shows that the distribution of the most important journals in terms of contributions was in accordance with Bradford's literature dispersion law (16). To characterize these high-impact journals more representatively, **Table 4** lists the top 10, which published 2,823 articles (accounting for 40.93% of all the publications in our bibliometric study). As expected, most VA-related studies were published in the most prestigious and highest-ranking journals in the field of CVD, while only one journal (*Resuscitation* tied with *Journal of the American College of*

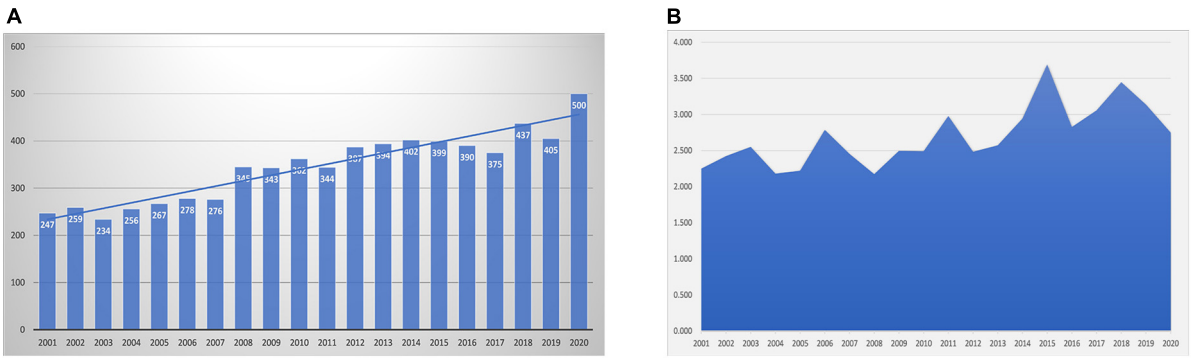

FIGURE 1
An overall view of publications in ventricular arrhythmia research field. Annual scientific publications of publications **(A)** and changing trends of annual average article citations **(B)** in the Web of Science Core Collection database, 2001-2020.

TABLE 2 The top 10 most active countries and affiliations contributing to scientific production in ventricular arrhythmia (ordered by articles count).

Rank	Countries	Articles	Centrality	TC	AC	Affiliations	Articles	Centrality	TC	AC
1	USA	7,098	0.90	72,862	31.61	Mayo Clin	295	0.07	1,560	5.29
2	China	2,091	0.03	5,975	8.50	Univ Calif Los Angeles	207	0.11	1,792	8.66
3	Japan	1,887	0.01	11,816	16.90	Harvard Univ	194	0.08	1,760	9.07
4	Germany	1,216	0.05	7,893	21.68	Johns Hopkins Univ	146	0.04	899	6.16
5	Italy	1,207	0.05	11,386	36.85	Leiden Univ	145	0.07	1,432	9.88
6	France	1,021	0.06	6,583	32.11	Univ Michigan	137	0.04	1,390	10.15
7	Canada	808	0.07	7,248	33.56	Brigham and Womens Hosp	135	0.12	1,887	13.98
8	Netherlands	808	0.04	8,150	32.09	Natl Yang Ming Univ	133	0.02	312	2.35
9	England	730	0.08	5,697	23.44	Univ Alabama Birmingham	129	0.02	1,061	8.22
10	Spain	674	0.04	3,308	19.69	Univ Penn	128	0.04	1,038	8.11

TC, total number of article citations; AC, average number of article citations.

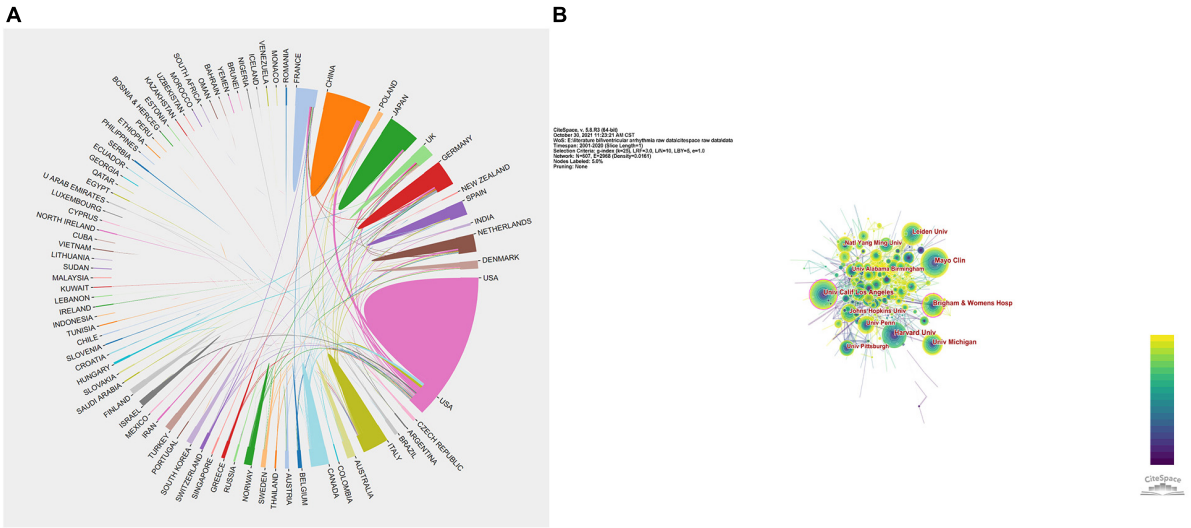

FIGURE 2
Cooperative relationship and intensity among authors' countries and affiliations. Cooperation network map of collaborating countries **(A)** and affiliations **(B)** for ventricular arrhythmia research.

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TABLE 3 The top 10 most relevant authors that published articles on ventricular arrhythmia research (ordered by articles count).

Rank	Author	Articles	AFF	Centrality	TLC	ALC	First author counts	First author citations	Average first author citations	Corresponding author counts	h-index	m-index
1	Marchlinski, FE	123	15.20	0.01	1,997	16.24	2	86	43.00	44	42	2.21
2	Stevenson, WG	111	14.93	0.03	2,029	18.28	5	281	56.20	29	41	1.95
3	Callans, DJ	103	10.92	0.00	1,438	13.96	1	5	5.00	6	38	2.00
4	Morady, F	80	9.59	0.01	1,242	15.53	0	0	0.00	0	32	1.52
5	Santangeli, P	79	6.10	0.00	552	6.99	12	166	13.83	14	24	2.00
6	Aizawa, Y	68	8.25	0.00	251	3.69	9	47	5.22	17	18	0.86
7	Zeppenfeld, K	68	8.43	0.05	737	10.84	3	69	23.00	34	27	1.50
8	Bogun, F	67	7.69	0.01	1,080	16.12	15	363	24.20	62	29	1.45
9	Della Bella, P	67	6.59	0.01	756	11.28	9	192	21.33	24	27	1.35
10	Dixit, S	67	6.49	0.00	1,132	16.90	3	91	30.33	10	31	1.63

TLC, total number of local citations; ALC, average number of local citations; AFF, articles fractionalized frequency.

Cardiology in eighth place) belonged to the emergency and critical care medicine area. Further, the top three journals published more than half of the papers listed in this table. However, in terms of local citations received, the advantage of the top three journals diminished compared with *Circulation* and the *Journal of the American College of Cardiology*, validating the need for other evaluation metrics. Therefore, after comprehensive consideration, both productivity and influence coupled well in *Circulation*, the *Journal of the American College of Cardiology*, and *Heart Rhythm*, which was reflected not only by the higher impact factors, but also by the appreciable h- and m-indices (see **Table 4** for more details). Furthermore, the m-index of *Circulation: Arrhythmia and Electrophysiology* (one of the *Circulation* series) was far ahead of its counterparts in this area, which presents great output potential for scientific research on VA. Additionally, combined with the data provided by the Journal Citation Reports assessment system and bibliometric online analysis platform, our research results imply that the top 10 journals are mainly concentrated in Q1 and Q2, which indicates that most are highly influential in the relevant domains.

The CHL of these journals refers to the time (in years) required for the articles to reach nearly half of the current citations received. Usually, a higher CHL value for a journal suggests a higher citation frequency of papers previously published in this journal than those published recently. The vast majority of the top 10 most productive journals scored relatively high CHL values (above 5); among these, the CHL values of *Pacing and Clinical Electrophysiology*, the *American Journal of Cardiology*, and *Circulation* exceeded 10. These results indicate that additional and recent high-quality studies are constantly needed for future scientific activities and clinical research.

Highly cited articles

Table 5 lists the characteristics of the top 10 most globally cited articles, including their titles, first authors, journals, publication years, number of global/local citations, number of citations per year, and detailed PlumX metrics (obtained from the Scopus database). The predominant study types of these documents were clinical trials and related guidelines published in journals, especially *Circulation*, while animal experiments occupied a certain proportion. **Table 5** also shows that Silvia G. Priori, who published fewer relevant articles on this topic than those authors listed in **Table 4**, paid more attention to high-quality clinical trials and the potential for clinical translation; further, when he or she was the first author, the total number of global citations was at its peak. However, in addition to the two clinical guidelines drafted and released in 2015, the publication dates of all the remaining highly cited articles in *Circulation* were earlier than 2010, again verifying the efficiency of the CHL for evaluating the rate at which a journal ages.

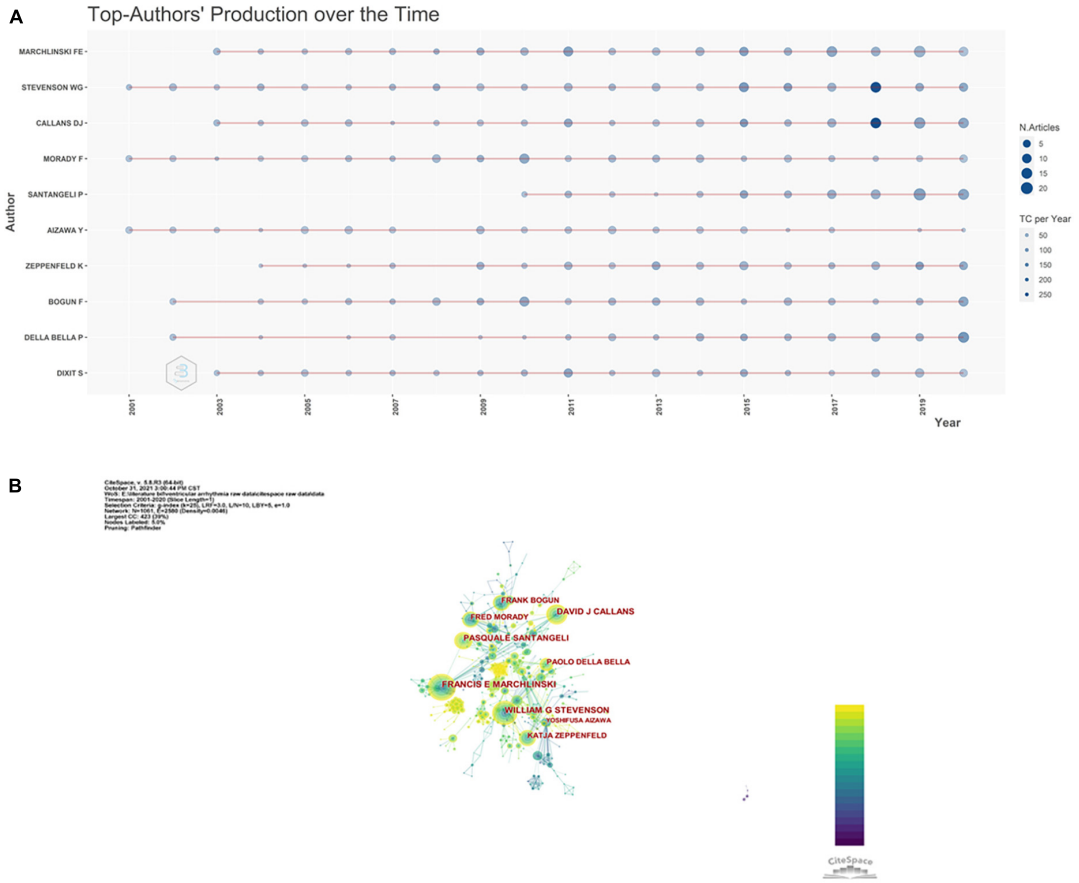

FIGURE 3
Distribution of author contributions to ventricular arrhythmia research. Top 10 authors' production over time **(A)** and cooperation network map of collaborating authors **(B)**.

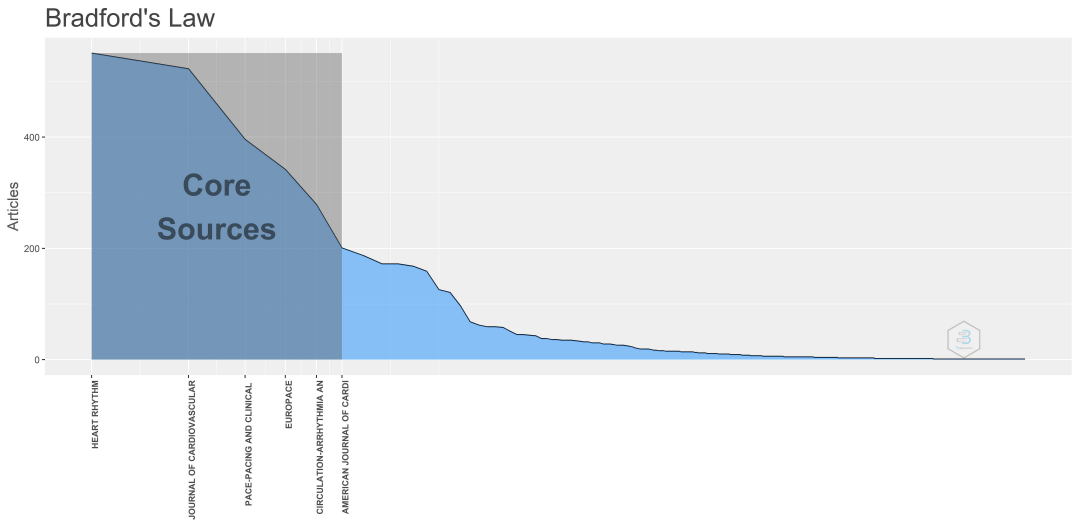

FIGURE 4
Journal distribution of publications in ventricular arrhythmia research according to Bradford's law.

Next, we used the PlumX metrics to offer a novel perspective in our bibliometric study. Although some differences were found in the results for the citations owing to the different counting types and algorithms in the different databases, the trends of the citations were still similar between the outcomes. However, most yielded low scores for usage and captures, particularly the former. Aside from the multicenter study by Jim Christenson et al., clinical trial by Michael O. Sweeney, and clinical guideline by Silvia G. Priori et al., in terms of mentions and social media, the number of citations received by the rest was very low, which was an unexpected finding.

Keyword co-occurrence and analysis

VOSviewer was used to create a distinct and intuitive network map using a co-occurrence analysis based on the article keywords in publications on VA research. Each sphere gizmo represented a keyword or key phrase whose size and color separately indicated the frequency of its appearance (recurrence in the same article counted as one) and average number of citations. In addition, the distance and degree of thickness of the lines between two sphere gizmos implied a more complex co-occurrence relation and vastly diverse link strength, respectively. As illustrated in **Figure 5A**, of the 7,021 samples, 165 keywords were finally screened out based on a threshold of at least 20 occurrences and then classified into seven clusters. Additionally, **Figure 5B** shows the change in these keywords over time, where the scale bar at the bottom right shows the color gradient indicating the different years. To make the analysis results more intuitive and visual, the hierarchical "word cloud" constructed using the specific R package was then introduced (**Figure 5C**).

Reference co-citation and cluster network analysis

To further explore hot topics in VA-related research, a co-citation network map of the top co-cited references (except duplicates) and its other manifestation (the same network in a hierarchical order based on time) were created using CiteSpace (**Figures 6A,B**). The different clusters in **Figure 6A** are represented by different background colors and the size of each cluster is formed by different node types, indicating the number and centrality of the co-cited articles. Similarly, in **Figure 6B**, each node position indicates the time of co-citation and the size is proportional to the number of co-citations of the relevant reference. Finally, all the co-cited references were clustered into 15 major labels, including ventricular tachycardia (VT), catheter ablation, fibrillation, biventricular pacing, and left ventricular assist device. **Figure 6B** also shows a much more distinct co-citation network of references in a timeline view,

TABLE 4 The top 10 most productive journals that published articles on ventricular arrhythmia research (ordered by articles count).

Rank	Journal title	Countries	Articles	TLC	ALC	IF (2020)	h-index	m-index	Quartile in category (2020 JCR)	Cited Half-life
1	Heart Rhythm	USA	551	8,342	15.14	6.343	65	3.61	Q1	5.8
2	Journal of Cardiovascular Electrophysiology	USA	523	8,222	15.72	2.871	50	3.25	Q2	8.2
3	Pace-pacing and Clinical Electrophysiology	USA	396	4,584	11.58	1.976	29	1.38	Q3	10.4
4	Europace	England	342	3,066	8.96	5.214	33	1.57	Q1	5.0
5	Circulation-arrhythmia and Electrophysiology	USA	279	4,444	15.93	6.572	56	4.00	Q1	6.0
6	American Journal of Cardiology	USA	201	6,787	33.77	2.778	37	1.76	Q2	11.9
7	Circulation	USA	187	26,707	142.82	29.690	85	4.05	Q1	11.1
8	Journal of the American College of Cardiology	USA	172	16,000	93.02	24.093	80	3.81	Q1	7.6
9	Resuscitation	Ireland	172	2,677	15.56	5.262	37	1.76	Q1	6.1
10	Journal of Interventional Cardiac Electrophysiology	Netherlands	168	945	5.63	1.900	17	0.90	Q3	5.0

TLC, total number of local citations; ALC, average number of local citations; IF, impact factors.

TABLE 5 The top 10 most global popular articles and their bibliometric parameters (ordered by the number of global citations).

Rank	Article titles	Authors	Journal	Publication years	GC	LC	TC/Y	PlumX metrics				
								Citations	Usage	Captures	Mentions	Social Media
1	"2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC)"	Priori, SG	European Heart Journal	2015	1,220	91	174.29	1,985	67	1,346	10	15
2	"Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction"	Sweeney, MO	Circulation	2003	999	30	52.58	1,204	9	279	1	51
3	"Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia"	Priori, SG	Circulation	2001	902	154	42.95	597	7	135	1	0
4	"ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death A Report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death) Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society"	Zipes, DP	Circulation	2006	811	106	50.69	936	188	358	4	2
5	"2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death"	Priori, SG	Europace	2015	796	74	113.71	459	39	239	6	0
6	"Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia"	Priori, SG	Circulation	2002	717	170	35.85	912	1	352	0	0
7	"Infarct tissue heterogeneity by magnetic resonance imaging identifies enhanced cardiac arrhythmia susceptibility in patients with left ventricular dysfunction"	Schmidt, A	Circulation	2007	551	84	36.73	609	91	336	0	0
8	"Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure"	Li, DS	Circulation	2001	534	14	25.43	597	10	133	0	0
9	"Chest Compression Fraction Determines Survival in Patients with Out-of-Hospital Ventricular Fibrillation"	Christenson, J	Circulation	2009	518	6	39.85	551	3	314	4	166
10	"Adverse hemodynamic effects of interrupting chest compressions for rescue breathing during cardiopulmonary resuscitation for ventricular fibrillation cardiac arrest"	Berg, RA	Circulation	2001	500	22	23.81	569	498	295	0	0

LC, the number of local citations; GC, the number of global citations; TC/Y, the number of total citations per year.

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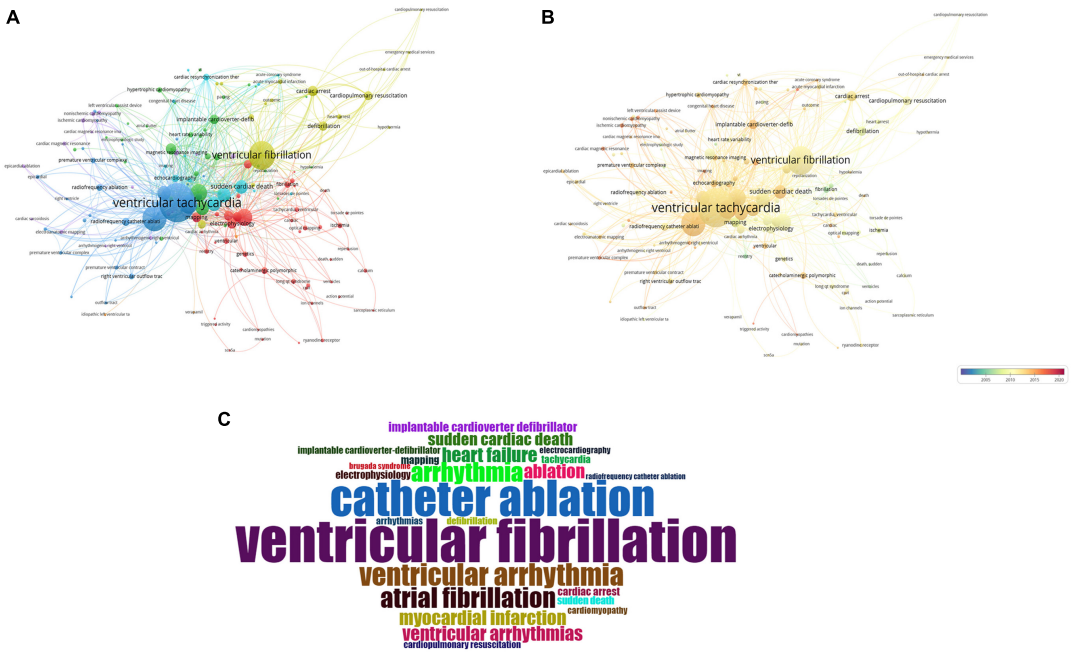

FIGURE 5
Co-occurrence and cluster analysis of author keywords. Network view map of author keywords co-occurrence **(A)**, the form of time distribution **(B)**, and word cloud chat **(C)**.

clearly illustrating the higher degrees of citation bursts in cluster labels at different time points (e.g., #0, #1, #3, and #6).

Burst detection analysis

Burst detection analysis, a computational technique for detecting sudden changes in events and other types of information, can be used to identify emerging concepts and themes that have attracted considerable attention in a field (17). The sky-blue line represents the time interval during 2001 to 2020, while the durations of each burst are plotted by the red line. **Figure 7** shows the 25 keywords with the strongest citation bursts based on the consideration of research or clinical significance, indicating the evolution of VA research over the past two decades. Outcomes ranked first with the highest burst strength (26.44), followed by coronary artery disease (25.18), association (17.12), bundle branch block (15.67), and acute myocardial infarction (14.93). Moreover, there was a significant turning point in VA-associated research around 2012, when a sudden shift from pathogenesis to clinical practice occurred (see the "Discussion" section for more details).

Discussion

In this original research, we conducted a bibliometric analysis of 6,897 publications on VA research from 2001 to 2020 using the visualization and statistical functions of the WoSCC database, a bibliometric online analysis platform, the bibliometrix R package, CiteSpace, and VOSviewer to identify the present situation and recent trends in research in this field. We found that the number of VA-related publications has steadily increased over the past two decades and peaked in the most recent year. The overwhelming contributions to these manuscripts were made by authors' countries with highly economic and medical developments: By country, the United States ranked first, followed by China and Japan. Europe and the United States dominated the list of the top 10 most productive countries for VA publications, with only two from Asia. Similarly, the distribution of affiliations was concentrated in Europe and North America except for the National Yang Ming University from the Taiwan Province of China; imbalances in the development and distribution of medical resources account for this difference. Furthermore, the origin and consistent development of modern arrhythmia-related research and technology use, including the proposal of the early terminology and doctrine, "era of Einthoven and Thomas Lewis" maturation of electrocardiography, and establishment of cardiomyocyte electrophysiology, have mainly been attributed to collaborations among the authors, countries, and institutions in the Western world (1, 5, 18, 19).

In addition, combining the outcomes of the journal distribution analysis and the analysis of highly cited articles in the field clearly showed that *Circulation's* status as the leading

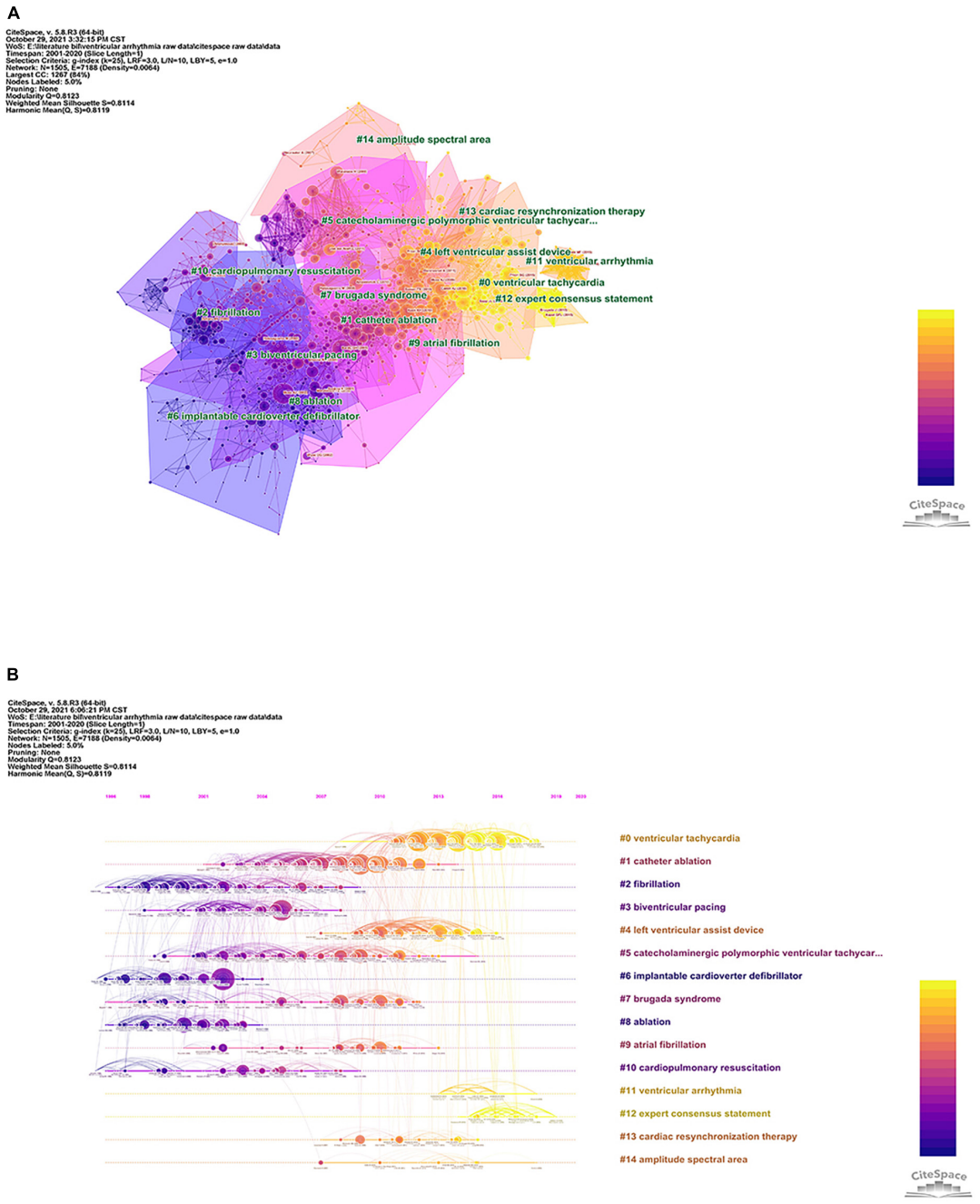

FIGURE 6
References' co-citation and cluster analysis. Network map of co-cited references on ventricular arrhythmia research **(A)** and the timeline view with corresponding cluster labels on the right side **(B)**.

journal in the field is well deserved based on its number of publications on VA as well as their substantial influence. However, as shown by the CHL values and publication years, the vast majority of the most-cited papers in these journals was used as fundamental and background knowledge for the citing articles. Furthermore, despite animal experiments and clinical investigations representing a considerable proportion of the top 10 most-cited articles, all related academic outcomes were published before 2010. This illustrates that the study of VA has evolved to a relatively mature stage and that more creative and innovative ideas and study designs are essential for the future evolution of this active field of scientific research.

Another important factor influencing the scholarly impact of these studies is the authoritative guidelines in this field,

Keywords	Year	Strength	Begin	End	2001 - 2020
coronary artery disease	2001	**25.18**	2001	2006	
bundle branch block	2001	**15.67**	2001	2008	
acute myocardial infarction	2001	**14.93**	2001	2005	
torsade de pionte	2001	**11.87**	2001	2006	
dynamics	2001	**10.79**	2001	2009	
muscle	2001	**9.99**	2001	2004	
sudden death	2001	**12.18**	2002	2007	
vulnerability	2001	**8.80**	2002	2004	
reentry	2001	**12.00**	2003	2009	
cellular basis	2001	**9.04**	2004	2012	
defibrillation	2001	**9.97**	2006	2009	
arrhythmogenesis	2001	**8.43**	2007	2013	
ventricular tachycardia	2001	**10.23**	2008	2012	
scar	2001	**14.52**	2013	2020	
multicenter	2001	**10.68**	2013	2018	
guideline	2001	**13.71**	2014	2020	
american heart association	2001	**9.10**	2014	2020	
safety	2001	**8.42**	2015	2020	
association	2001	**17.12**	2016	2020	
task force	2001	**8.77**	2016	2020	
esc guideline	2001	**10.03**	2017	2020	
meta-analysis	2001	**9.74**	2017	2020	
long term outcomes	2001	**9.16**	2017	2020	
outcomes	2001	**26.44**	2018	2020	
impact	2001	**11.86**	2018	2020	

FIGURE 7
Burst detection with keywords in publications on ventricular arrhythmia research (only the top 25 keywords with the strongest citation bursts were shown).

including the origin and development of techniques for advancing VA treatment mentioned above as well as the updates and summaries of extraordinary authoritative clinical guidelines drafted and revised since the mid-1980s by the AHA, the American College of Cardiology, and the European Society of Cardiology, which account for the imbalanced distribution of high-impact medical journals and publications (2). Our findings were unexpected but reasonable in terms of the PlumX metrics. We did not expect to find the extraordinarily low number of social media use and records in the Scopus database for highly cited publications (specifically the mentions and social media metrics in **Table 5**). In the conventional sense, clinical guidelines are more likely to be shared on social media platforms and users than basic medicine experiments. Obviously, this is not the case. A major reason for this is the time to publication. Despite continuous and rapid advances in online social media over the past 20 years, it is difficult to keep pace with the medical literature due to the specific characteristics of academic papers such as their timeliness and fast update cycles. Moreover, academic researchers' information management capability and familiarity with modern network techniques vary from person to person. The recent study by Ortega showed that journals with their own Twitter accounts often receive more tweets and higher citation frequencies than those without. This study made an interesting attempt to explore how the dissemination of content in an online social network influences the citation of research paper in their corresponding journals (20). Therefore, it is tempting to speculate that the PlumX metrics indeed provide a clear competitive advantage to those scientists active on social platforms by increasing the impact and dissemination of their

research to the public (13, 20–22). Moreover, this inference was also proven by Christenson and his scientific research team, whose study ranked ninth in **Table 5** with 166 citations on social media. In summary, to enhance their scientific influence and academic performance for different audiences, scholars need to broaden their horizons and make progress over time.

Next, our analysis of research hot topics and prediction of future trends using keyword co-occurrence analysis, co-citation network analysis, and burst detection analysis showed the central topics of the investigation of VA over time. These topics included pathogenesis/mechanisms (e.g., ventricular/atrial premature contraction/tachycardia/fibrillation, reentry, bundle branch block, and hypokalemia), the diagnosis of primary diseases/etiologies (e.g., coronary artery disease, Brugada syndrome, acute myocardial infarction, and cardiomyopathy), common arrhythmia-associated complications (e.g., sudden cardiac arrest, heart failure, and SCD), therapeutic technological innovations [e.g., radiofrequency catheter ablation (RFCA), left ventricular assist device, and implant cardiac resynchronization therapy defibrillator (CRT-D)], authoritative evidence-based guidelines and expert consensus statements (e.g., the AHA, the European Society of Cardiology, multicenter and meta-analysis), and prognostic assessment and prediction [short/long term outcomes, amplitude spectral area (AMSA), and impact]. Because of the diversity of etiologies and complexity and continuity of pathophysiological processes in VA, the above keyword results should be summarized and generalized. Moreover, VA is affected by a variety of factors, and it eventually develops a more severe form and a poor prognosis if timely interventions are not performed (i.e., malignant arrhythmias such as VT, ventricular fibrillation [VF], and even SCD) (3, 4, 6). Furthermore, as reported in our recent bibliometric study for cardiopulmonary resuscitation (CPR), although a great amount of research and constantly updated guidelines and therapeutic measures have focused on SCD secondary to VF and the continuous exploration of effective means to improve prognosis, overall survival from SCD remains low (23). Nevertheless, we cannot ignore the achievements already been made. For instance, based on the results above, AMSA, one of the cluster labels (shown in **Figures 6A,B**, #14), was also extracted from the co-cited references. Briefly, AMSA, whose algorithm was suggested, quantitated, determined, and gradually refined by Charles G. Brown et al. over the past 25 years, is considered as a potential and practical prognosticator for measuring the probability of successful defibrillation and guiding the optimal timing of defibrillation, which has been studied in clinical trials and large animal experiments. In addition, a large number of researchers are convinced that AMSA is suitable for clinical transformation, although many questions and challenges remain (24–27).

The response of any treatment intervention is likely to be limited in the advanced disease stage. By contrast, the early detection and intervention of arrhythmogenesis and aggressive prevention of SCD have become research foci and hot topics in the field. As ECG technology matures, various types of VAs can be quickly identified and precisely diagnosed at an earlier time. Consequently, our results revealed that scholars have, over the past two decades, become more likely to pay attention to therapeutics that have great advantages of potential clinical application. Among them, cardiac resynchronization therapy pacing (CRT-P), ICD, and RFCA play pivotal roles. Numerous landmark clinical trials, guidelines, and preclinical studies have confirmed the survival benefit of subcutaneous and transvenous ICD therapy for the primary and secondary prevention of SCD among candidates for various cardiovascular comorbidities and complications (2, 3, 7, 28, 29). Similarly, CRT-P has also long been included in international clinical guidelines as a fundamental and proven efficacious treatment mainly owing to its modification of the natural history of pathologic changes in patients with heart failure and electrical dyssynchrony and incremental improvement of patient symptoms and survival (28, 30, 31). However, the combined device of CRT-P and ICD, called a CRT-D, remains extremely controversial in terms of a number of factors including the appropriate population, success rates of implantation, risk of major complications, cost and cost-effectiveness, and indications for therapeutic use. Larger, multicenter, and high-quality RCTs should be conducted to address this issue (32–35). Unlike the former two, RFCA targets clinical arrhythmias to prevent recurrence and has a broader spectrum of indications, including different sites of origin of arrhythmogenesis. Furthermore, percutaneous catheter ablation has been considered to be a consistently effective treatment for recurrent VT and is performed with increasing frequency. Nevertheless, many unanswered questions remain, and challenges in the current era should be investigated and addressed by high-quality and large-scale clinical trials, such as the optimal timing for VT ablation, ablation in hemodynamically unstable and non-ischemic VT, and lack of emerging technologies (2, 3, 7, 8, 36, 37).

Compared with the keywords co-occurrence and analysis, the timeline views of the co-citation cluster and burst detection analyses more closely exemplify the changing trends of scientific hot topics in this field. As outlined previously, there has been a sudden shift from pathogenesis to clinical aspects in relevant VA studies since 2013, especially the attention given to clinical guidelines and evidence-based medicine. Indeed, constantly summarized expert consensus statements and updated clinical guidelines by authoritative scientific societies are crucial to help inform and guide clinical decision making for patients with VA. Theoretically, high-quality evidence-informed clinical guidelines are widely cited and drawn on. Therefore, the citation pattern and bibliometric distribution were naturally greatly impacted, which was also confirmed by the analysis results. However, a large amount of high-quality evidence for curative options is still lacking, although the use of these treatments

has been repeatedly and highly recommended in many versions of VA guidelines.

Taken together with our results from the analysis of hot topics, one intervention strategy that attracted our attention is AAD. Although it did not appear in any of our results—either as a keyword in the co-occurrence and burst detection analyses or as a cluster label in the co-citation network analysis—it is still recommended because of its capability to control arrhythmias and improve symptoms. Moreover, as previously mentioned, evidence for AAD as an effective medication for VA-induced SCD and safe use remains limited and largely controversial (2, 3, 8, 9, 38). Even so, AAD medications have failed to become the primary concern to researchers compared with the widespread availability and effectiveness of the star therapy techniques mentioned in the previous paragraph. Importantly, it is essential for researchers and scholars to understand the mechanisms of action of antiarrhythmic drugs, and arrhythmogenesis is only a preliminary step in the appropriate selection of an AAD medication. Consequently, as well as higher-quality RCTs and meta-analyses focusing on mortality benefit and careful risk/benefit analysis with the chronic use of AAD (except beta-blockers) being needed, future studies should pay attention to its narrow therapeutic window, side effects, and proarrhythmic effects to overcome current clinical challenges and develop more rational applications.

Overall, the field has reached relative maturity and major scientific and academic breakthroughs are difficult to achieve in the near term unless landmark technological innovations are available. Nevertheless, this does not mean that the existing research results and evidence are adequate, and there is no room for further improvement. More creative experimental approaches and research ideas are required. An excellent paradigm for this is the recent work by Salvatore R. Aiello et al., whose experimental design and protocol were ingenious and clinically meaningful. This comparative study combined a large animal experiment with a clinical guideline-driven resuscitation protocol, and positive results were obtained, although the research topic was focused but not novel (i.e., AMSA) (39). More importantly, the starting point of this experimental design offers a significant benefit and valuable reference to researchers in this field.

Conclusion

Our analysis of 6897 papers on VA-related research using the graphs and charts formed by bibliometric methods (i.e., CiteSpace, VOSviewer, the bibliometrix R package, and a bibliometric online analysis platform) demonstrated that the understanding of pathophysiological progression, effective intervention, and improvement in disease prognosis has advanced markedly over the past two decades, with relevant research deepening and being more fruitful and comprehensive. The findings of this study can assist researchers, scientists, and medical staff with more directional topic selection and experimental design schemes by offering a comprehensive picture of VA research and providing collective and constructive information.

To the best of our knowledge, this is the first bibliometric study of VA-related research activities. However, this study has the following major limitations. First, the data were only collected from the WoSCC database, which may have resulted in some selection bias. Second, some of the articles' keywords and phrases as well as the cluster labels in the results appeared more than once because of the number of synonyms and different expressions. Finally, owing to space limitations, only a small proportion of the extracted cluster labels and keywords were discussed and only the first author in the clinical guidelines was shown in the tables presented in this paper. Nevertheless, the results obtained in this study were reliable and valid.

As research on VA is increasing significantly, the results of this study will change over time. Thus, this research requires constant updating in the coming years. Our team has provided an in-depth analysis and insights into the current research status. Although VA is relatively established and has made significant achievements, more reliable evidence (especially high-quality prospective studies) is needed to bridge the gap in evidence-based medicine; Moreover, wider adoption of social media and more novel ideas are necessary to develop and prompt popularization for the field further.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for this study in accordance with the local legislation and institutional requirements. Written informed consent was not required for this study in accordance with the local legislation and institutional requirements.

Author contributions

XL, QY, and CZ contributed to the conception of the study, supervised the manuscript, and finalized the manuscript. TJ and SW performed the experiment, analyzed most of the data, and wrote the initial draft of the manuscript. GL contributed by refining the ideas and carrying out additional

analyses. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.856695/full#supplementary-material

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Case report: Stereotactic body radiation therapy with 12 Gy for silencing refractory ventricular tachycardia

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Background: Encouraging results have been reported for the treatment of ventricular tachycardia (VT) with stereotactic body radiation therapy (SBRT) with 25 Gy. SBRT with 12 Gy for refractory VT was designed to reduce long-term cardiac toxicity.

Methods: Stereotactic body radiation therapy-VT simulation, planning, and treatment were performed using standard techniques. A patient was treated with a marginal dose of 12 Gy in a single fraction to the planning target volume (PTV). The goal was for at least $\geq$ 95% of the PTV to be covered by at least 95% of 12 Gy radiation.

Results: From April 2021 through June 2022, a patient with refractory VT underwent treatment. The volume for PTV was 65.8 cm^3. The mean radiation dose administered to the heart (the heart volume excluding the PTV) was 2.2 Gy. No acute or late toxicity was observed after SBRT. Six months after SBRT, the patient experienced new monomorphic right ventricular outflow tract (RVOT) VT. Interestingly, the substrate of the left ventricular basal to middle posteroseptal wall before SBRT was turned into scar zones with a local voltage $<$ 0.5 mV. Catheter ablation to treat RVOT VT was performed, and the situation remains stable to date.

Conclusion: This study reports the first patient with refractory VT successfully treated with 12.0 Gy SBRT, suggesting that 12 Gy is a potential dose to treat refractory VT. Further investigations and enrollment of more patients are warranted to assess the long-term efficacy and side effects of this treatment.

KEYWORDS

refractory, ablative, radiosurgery, stereotactic body radiation therapy, ventricular tachycardia, volumetric-modulated arc therapy

Introduction

Ventricular tachycardia (VT) is a life-threatening disease that is caused by electric reentry within and around patches of myocardial scarring (1), especially in patients with postmyocardial infarction (post-MI) heart failure. The implantation of a cardioverter-defibrillator (ICD) prevents sudden cardiac death, but ICD shocks are also associated with mortality (2, 3). Recently, cardiac imaging and electroanatomic mapping (EAM) have improved in guiding the ablation procedure to identify the VT substrate and to ablate these regions, with encouraging results (4, 5). However, following such procedures, the recurrence rate after a first VT ablation is 12.0–62.0% (6, 7), so patients must undergo repeated catheter ablation procedures (8).

Stereotactic body radiation therapy (SBRT) is an advanced external beam radiotherapy technique that precisely delivers a high radiation dose with an image-guided technique to targets in a few fractions (9, 10). Recently, encouraging results were reported for patients with VT who were treated with SBRT (11, 12). Cuculich et al. (11) documented that all awake patients treated with SBRT in a single fraction of 25 Gy exhibited a 99.9% decrease in the VT burden compared to the baseline. In a subsequent phase I/II trial, the frequency of VT episodes or premature ventricular contraction (PVC) burden was reduced by 75.0% in 89.0% of patients, as reported by Robinson et al. (12).

However, 10.5% of patients in that study experienced grade 3 treatment-related adverse effects, 11.1% developed grade 2 radiation pneumonitis, and 28% exhibited pericardial effusions (12). Calculation of the late radiation response of the heart by equivalent dose in 2-Gy fractions (EQD2, corrected for fractionation with alpha/beta ratio = 2.5) showed that the administration of 25 Gy in one fraction might actually elicit the same response as 152 Gy (13). Interestingly, radiosurgery with 12 Gy provides a high rate of control of acoustic neuroma (14), which provides insight into abnormal nerve behavior that may be reversed by radiosurgery with marginal doses of 12 Gy.

A stereotactic ablative radiosurgery (SARS) for refractory VT (SARS-VT) trial was established at our institution after obtaining approval from the Human Experimentation Committee of Far Eastern Memorial Hospital (FEMH108074-F) to reduce long-term cardiac toxicity, improve quality of life, and search for the optimal radiation ablation dose. Here, we report the first patient in the world with refractory VT who was treated with SBRT using 12 Gy radiation and was followed for more than 1 year. This patient had a favorable outcome with a satisfactory quality of life.

Case report

Patient history

A 63-year-old man had a past history of type 2 diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease and congenital bicuspid aortic valve stenosis with coronary artery disease. Coronary artery angioplasty and stenting to the right coronary artery and left circumflex artery had been performed more than 10 years prior. The patient had developed congestive heart failure (New York Heart Association, functional class II to III) with a reduced ejection fraction and a left ventricular ejection fraction (LVEF) of less than 35% in the past 3 years. Two years before this presentation, he received xenograft aortic valve replacement due to rapidly progressive aortic valve stenosis and coronary artery bypass graft with saphenous vein graft (SVG) anastomosis to the left anterior descending artery. A dual-chamber implanted cardioverter-defibrillator (ICD) was also implanted for subsequent sustained monomorphic VT.

One year ago, the patient had a recurrent VT storm with ICD shock. The twelve-lead electrocardiogram revealed two different morphologies of clinical VT (**Figures 1A,B**). Both VT morphologies indicated right bundle branch block morphology; one involved the superior axis, and the other involved the inferior axis, which suggested an origin of VT from the left ventricular septal wall. During the electrophysiology study, bipolar voltage mapping with a three-dimensional (3D) CARTO mapping system (Biosense, Diamond Bar, CA) suggested the presence of a large, uneven, mixed scar and viable zone in the area of the left ventricular basal to middle posteroseptal wall (**Figures 2A,C,E**). We defined the border zone as where

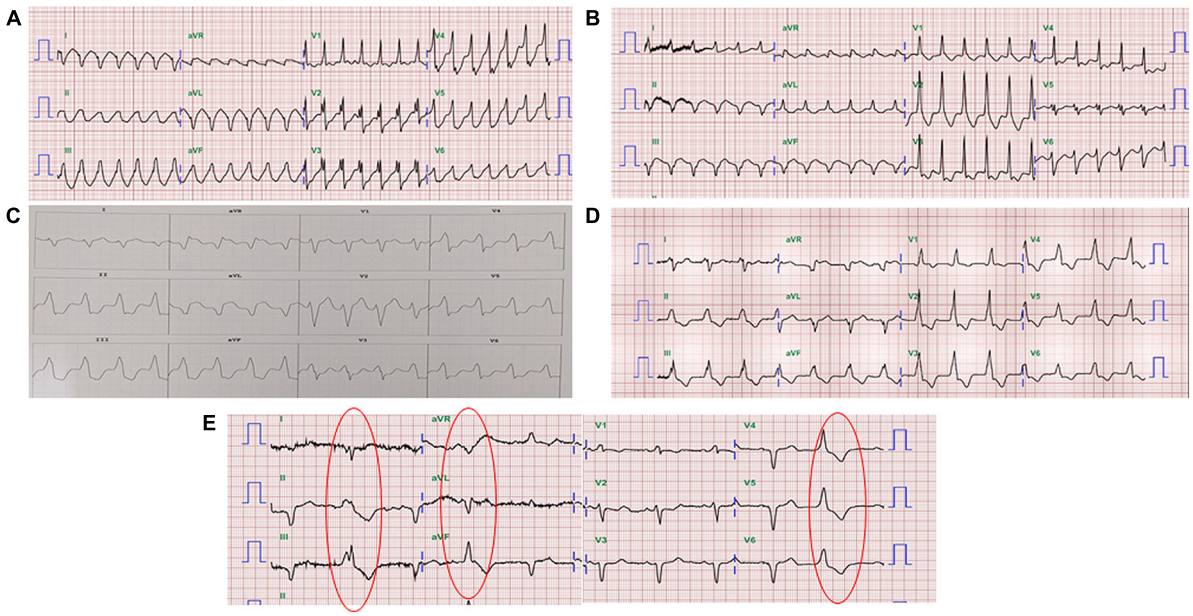

FIGURE 1
Twelve-lead electrocardiography of the patient. **(A)** VT with right bundle branch block morphology and an inferior axis. **(B)** VT with right bundle branch block morphology and a superior axis. **(C)** VT with the origin in the RVOT. **(D)** Slow VT with all positive concordance in the precordial leads and an inferior axis suggested at a different location from the initial therapy zone. **(E)** The morphology of ventricular premature beats was the same as the morphology of the slow VT.

the voltage was <1.5 mV. Local abnormal ventricular activity (LAVA) was identified as a substrate using a PENTARAY® NAV ECO high-density mapping catheter near the scar margin. Endocardial ablation with LAVA elimination was performed with an acute end point of non-inducibility under ventricular extrastimuli. However, recurrent VT storms still occurred 5 months after catheter ablation, with a total of 21 episodes of ICD therapy (15 events of antitachycardia pacing and 6 events of shock). The patient received a detailed explanation of the treatment that would be given in the SARS-VT trial from both the treating electrophysiologist (the first author) and the radiation oncologist (the last author). After discussion, he agreed to receive ablated cardiac radiotherapy at a dose of 12 Gy. The patient provided written informed consent to receive treatment. All the authors participated in data collection and analysis.

Stereotactic body radiation therapy planning and delivery

The procedural workflow is shown in **Figure 3**. Multimodal imaging combining scar imaging, including the 3D CARTO mapping system (Biosense, Diamond Bar, CA), respiratory phase-correlated 4-dimensional computed tomography (4D-CT) simulation with a 2.5 mm slice thickness (Discovery CT590 RT, GE Healthcare, Chicago, IL, USA), cardiac magnetic resonance imaging (MRI) and ^{99m}Tc-sestamibi myocardial perfusion imaging was done offline to delineate a target for ablation. The substrate was targeted at the clinical target volume (CTV) and was segmented through corroboration of all previously acquired imaging and electrocardiographic imaging data by the radiation oncologist and electrophysiologist. An internal target volume (ITV) was created from the phased-binned 4D-CT to account for the maximum range of motion that was assessed by reviewing the playback of all the phases of the 4D-CT overlaid with the reference CT scan. The amplitude for the target was approximately 5 mm. This result was similar to previous reports (12, 15, 16). The data reported that cardiac motion was variable depending on the specific substructure of the heart but was within 5 mm (15, 16). The planning target volume (PTV) was generated as a 3-mm volumetric expansion from the ITV. A plan was developed in the Pinnacle3 planning system (version 9.8.1, Philips Medical Systems, Madison, WI, USA).

A dose of 12 Gy in a single fraction was prescribed to the PTV with the goal of achieving maximal dose coverage while avoiding a dose in excess of the calculated dose constraints for surrounding organs, including the heart and coronary arteries. The goal was for at least ≥ 95% of the PTV to be covered by at least 95% of the prescribed dose (12 Gy). Beam geometry was optimized to avoid the ICD geometrically. Optimization was used to place prescription hotspots (areas receiving > 100% of the prescription dose)

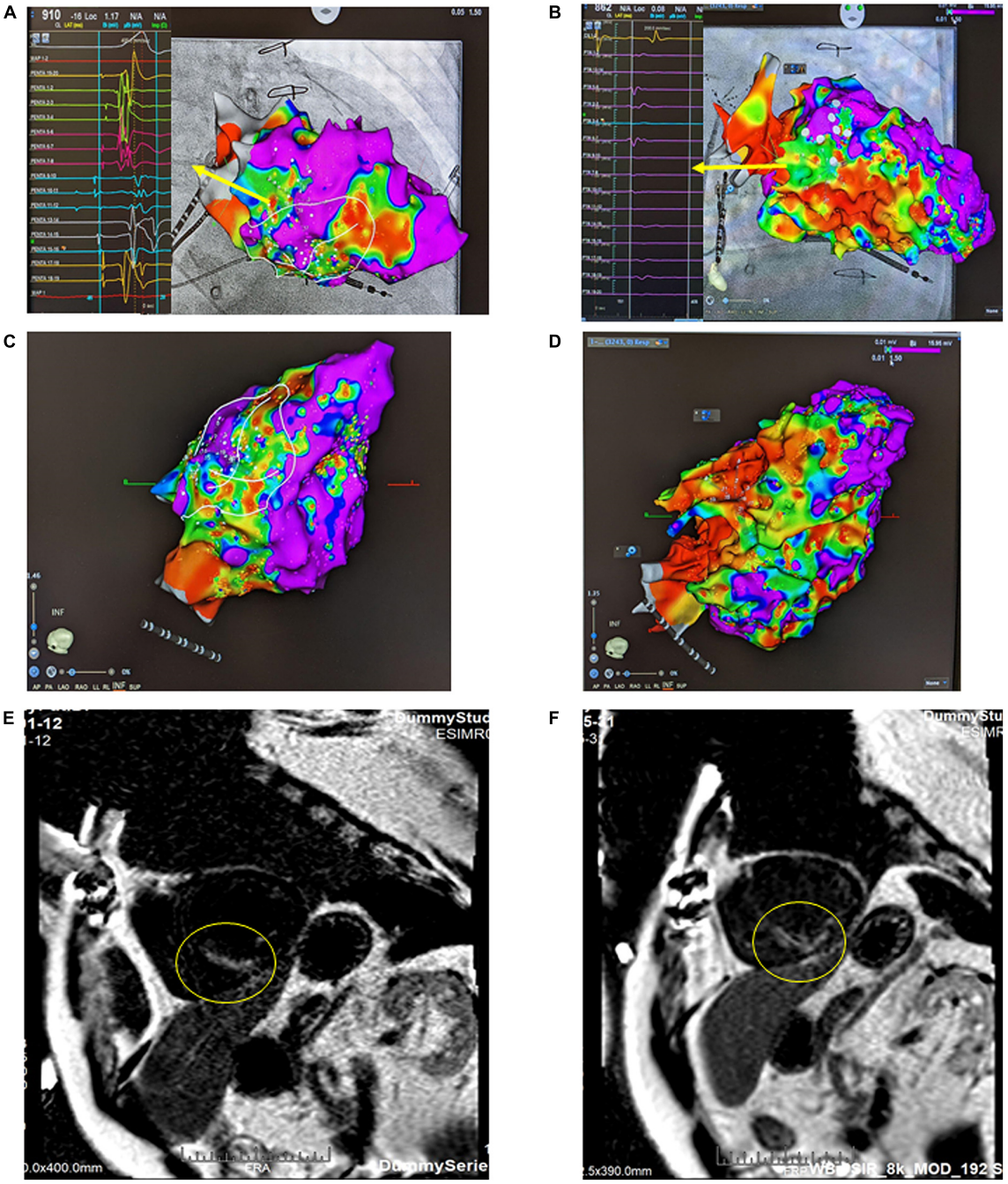

FIGURE 2
Bipolar voltage mapping with a 3D CARTO mapping system (Biosense, Diamond Bar, CA). **(A)** The presence of a large, uneven, mixed scar and viable zone in the area of the left ventricular basal to the middle posteroseptal wall from the right anterior oblique (RAO) view. The arrow indicates LAVA, the substrate, as the target ablation zone. **(B)** After SBRT, the therapy zone became a scar zone. The arrow indicates local voltage < 0.5 mV. **(C)** Inferior view of the left ventricle (LV) before SARS. **(D)** Inferior view of the left ventricle (LV) after SBRT. **(E)** Cardiac MRI using a wide-band sequence before SBRT. A delay in the enhancement of the mid-basal septal wall and mid-inferior wall was noted, which indicated scar formation in this area. **(F)** Cardiac MRI after SBRT. The previously shown delay in enhancement of the mid-basal septal wall and mid inferior wall was still present; however, the affected area was slightly larger than that on the previous MRI.

within the ITV and CTV, enabling the ITV and CTV to be covered by up to 125 and 150% of the prescribed dose, respectively (**Figure 4**).

The criteria for the arteries, esophagus, stomach, lungs, and spinal cord were based on those used in a previous report (16). The plan was subjected to and passed standard internal physics

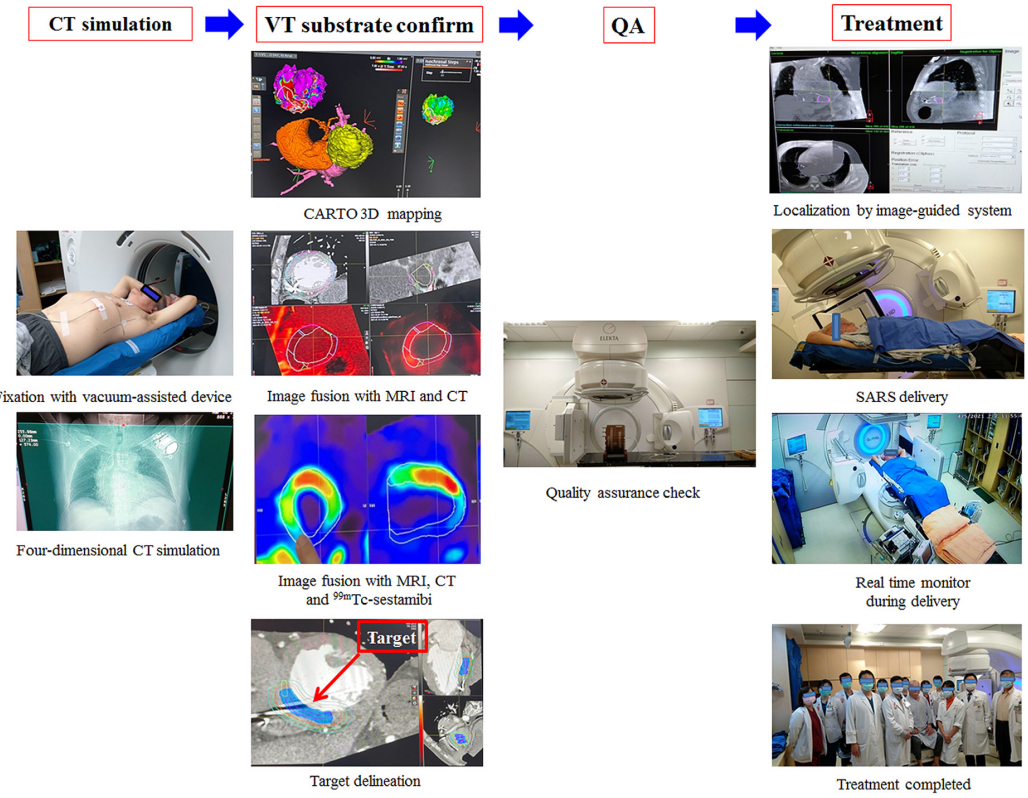

FIGURE 3
Multimodal imaging combined with scar imaging, including the CARTO mapping system (Biosense, Diamond Bar, CA), CT, MRI and ^{99m}Tc-sestamibi MPI, was used offline to delineate a target for ablation. A plan was developed in the Pinnacle3 planning system (version 9.8.1, Philips Medical Systems, Madison, WI, USA). One day before treatment, quality assurance was performed. On the day of treatment, the patient was immobilized on the vacuum device, and cone-beam computed tomography (CBCT) was used for patient setup and target localization. The treatment unit was aligned with the patient, and a dose of 12 Gy was delivered precisely by volumetric-modulated arc therapy (VMAT) through a linear accelerator machine (Versa HDTM, Elekta, Crawley, West Sussex, UK) with 6 MV photons.

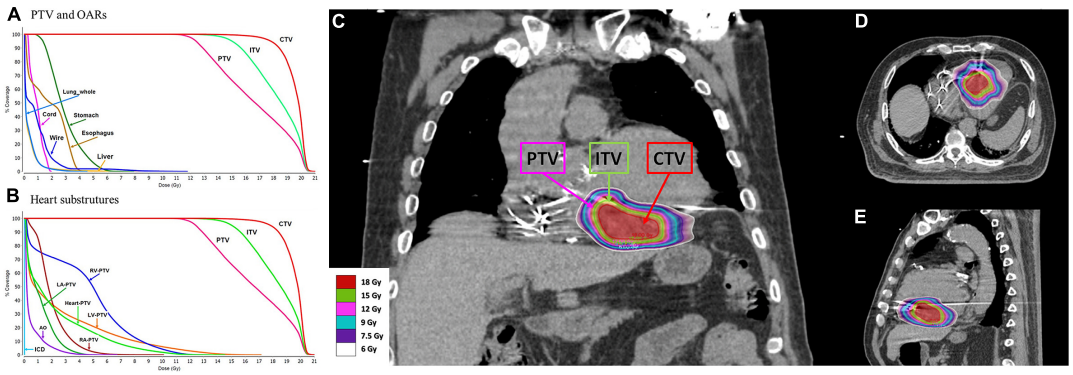

FIGURE 4
The substrate was targeted at the clinical target volume (CTV). An internal target volume (ITV) was created from the phased-binned 4D CT images to account for the maximum range of motion that was assessed by reviewing the playback of all the phases of the 4D-CT overlaid with the reference CT scan. The planning target volume (PTV) was generated as a 3-mm volumetric expansion from the ITV. The goal was for at least $\geq$ 95% of the PTV to be covered by at least 95% of the prescribed dose (12 Gy). Optimization was performed to place prescription hotspots (areas receiving $>$ 100% of the prescribed dose) within the ITV and CTV, enabling the ITV and CTV to be covered by up to 125% and 150% of the prescribed dose, respectively. **(A)** Dose volume histogram (DVH) for the PTV and organs at risk. **(B)** DVH for the PTV and heart substructures. RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium; AO, aorta; ICD, cardioverter-defibrillator. **(C)** Coronal view of the plan with color wash. **(D)** Transverse view of the plan with color wash. **(E)** Sagittal view of the plan with color wash.

quality assurance on a calibrated phantom 1 day before delivery. On the day of treatment, the patient was immobilized on the vacuum device (Klarity, R7515NL-44NL). We used cone-beam computed tomography (CBCT) for patient setup and target localization. The treatment unit was aligned with the patient, and SBRT of 12 Gy was delivered precisely without sedation or anesthesia by an image-guided radiotherapy-equipped linear accelerator (volumetric-modulated arc therapy, VMAT, Versa HDTM, Elekta, Crawley, West Sussex, UK).

Results

Patient and treatment

The CTV, ITV, and PTV were recorded. The target volumes for the CTV, ITV, and PTV were 23.23, 42.45, and 65.75 cm^3, respectively. The conformal index was 1.03. The treatment dose rate was 1,400 MU/min for a total marginal dose of 12 Gy with 6 MV flattening-filter-free beams, and the duration of the treatment session was 24 min. The mean radiation dose administered to the heart (the heart volume excluding the PTV) was 2.2 Gy. The maximal doses (<0.03 cc) administered to the left and right coronary arteries were 4.2 and 6.9 Gy, respectively. The maximal dose administered to the mitral valve was 6.5 Gy. The medium doses to the left and right ventricles were 0.8 and 5.0 Gy, respectively. The maximal dose administered to the spinal cord and maximal esophageal dose were 2.0 and 4.4 Gy, respectively. The dosimetry details are shown in **Table 1**.

Safety

No acute toxicity was observed during or immediately after SBRT. No adverse effects were observed from ICD during or after SBRT. No adverse events were related to SBRT during the whole 1-year observation period.

Efficacy

Before SBRT, the patient received two types of antiarrhythmic agents (amiodarone and mexiletine), a maximal tolerated dose of bisoprolol, sacubitril/valsartan and empagliflozin (25 mg daily), which have been suggested to reduce the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure. After SBRT and the second electrophysiology study, antiarrhythmic agents and optimal medical treatments for heart failure remained unchanged. Six months after SBRT, 16 episodes of antitachycardia pacing (ATP) plus ICD shock occurred in 24 h. Based on the protocol, a second SBRT needed to be delivered. The patient underwent a second electrophysiology study to confirm the original therapy zone. Interestingly, the substrate of the left ventricular basal to middle posteroseptal wall before SBRT had turned into scar zones with a local voltage < 0.5 mV (**Figures 2B,D,F**). One monomorphic right ventricular outflow tract (RVOT) VT was easily inducible (**Figure 1C**). No low-voltage zone or LAVA was observed in this zone through high-density voltage mapping. Catheter ablation to the RVOT VT was performed with an acute end point of non-inducibility under ventricular extrastimuli. During follow-up, another morphology of sustained slow VT with a rate of 92 bpm was noted, without hemodynamic compromise. The morphology of slow VT was all positively concordant in the precordial leads and inferior axis, which indicated a different origin of VT (**Figure 1D**). Due to the wider QRS and electric replacement interval of the ICD, we upgraded the ICD to a cardiac resynchronization therapy defibrillator (CRT-D). The upgrade to CRT-D may also significantly reduce the frequency of VT. The burden of ventricular arrhythmia has been markedly reduced since then. The morphology of the ventricular premature complex was the same as that of slow VT (**Figure 1E**). **Figure 5** describes the New York Heart Association (NYHA) functional classification, blood pressure, left ventricular ejection fraction (LVEF) and laboratory data with a timeline for the patient before, during and after treatment.

Discussion

This report is the first to describe SBRT with a PTV dose of 12 Gy performed in a patient with recurrent VT. The target volume for SBRT was delineated using the CARTO mapping system, with subsequent matching by MRI, ^{99m}Tc-sestamibi myocardial perfusion imaging and 4D-CT imaging. SBRT with 12 Gy silenced the abnormal electrical activity of the substrate and successfully reduced the VT burden during the follow-up period.

Cardiac SBRT with 25 Gy in one fraction is a new and innovative treatment for patients with refractory VT (**Table 2**). To date, eight case reports (17–24) and 11 case series (11, 12, 25–32) have been published. Ninety-one patients were treated with a radiation dose of 25 Gy, and one patient was treated with 24 Gy. The rate of reduction in the VT burden by SBRT was approximately 69–90% (11, 12, 26, 27, 31). However, the rate of recurrent VT after SBRT was 20–100%. Treatment with 25 Gy in one fraction, when corrected for the late radiation effect for fractionation with alpha/beta ratio = 2.5, was equivalent to 152 Gy (13). During the ENCORE VT study (12), two patients experienced grade 3 heart failure exacerbation and pericarditis. Additionally, five patients presented with grade 2 pericardial effusions, and two patients experienced grade 2 radiation pneumonitis. Similarly, Neuwirth et al. (26) reported that one patient exhibited grade 3 late radiation-related

TABLE 1 The calculated doses to organs at risk and heart substructures for patients treated with stereotactic body radiation therapy (SBRT) 12 Gy.

Prescription to PTV	SBRT (Gy)	EQD2 (Gy, α/β = 10)	EQD2 (Gy, α/β = 2.5)	SBRT (Gy, FEMH)	EQD2 (Gy, α/β = 10)	EQD2 (Gy, α/β = 2.5)	Decrease (%) when compared to 25.0 Gy (α/β = 10)	Decrease (%) when compared to 25.0 Gy (α/β = 2.5)
	25.0	72.9	152.8	12.0	22.0	38.7		
Organs at risk							48.7–93.0%	55.0–96.3%
Spinal cord	Dmax ≤ 14 (16, 20, 29, 33)	28.0	51.3	Dmax: 2.0	1.9	1.9	93.0%	96.3%
Esophagus	Dmax ≤ 14.5–19.0 (16, 20, 29, 33, 49)	29.6–45.9	54.8–90.8	Dmax: 4.4	5.3	6.8	82.1–88.5%	87.6–92.5%
Stomach	Dmax < 12.4–22.0 (20, 29)	23.2–58.7	41.1–119.8	Dmax: 8.0	11.9	18.5	48.7–79.7%	55.0–84.6%
Total lung	V7 Gy remaining volume > 1500 c.c. (16, 20, 29, 33)	V9.9	V14.8	V7 Gy remaining volume:2319.8 c.c.	V9.9	V14.8		
Liver	V11.0 remaining volume > 700 c.c. (16)	V19.3	V33.0	V11.0 remaining volume:1579.09 c.c.	V19.3	V33.0		
Heart substructures							51.2–91.8%	58.3–98.3%
Mean Heart	6.0 (20)	8.0	11.3	2.2	2.3	2.3	71.3%	79.6%
Aorta	Dmax: 20.0–25.0 (49)	50.0–72.9	100–152.8	Dmax: 7.2	10.4	15.6	79.2–85.7%	84.4–89.8%
Left atrium	Median dose ≤ 4.4 (49)	5.3	6.8	Median dose: 0.9	0.8	0.6	85.5%	91.2%
Right atrium	Median dose ≤ 4.4 (49)	5.3	6.8	Median dose: 1.8	1.7	1.7	67.9%	75.0%
Left anterior descending artery	Dmax: 14.0–22.0 (20, 29, 49)	28.0–58.7	51.3–119.8	Dmax: 4.2	4.8	6.3	82.9–91.8%	87.8–94.7%
Right coronary artery	Dmax: 12.0–22.0 (20, 29, 49)	28.0–58.7	38.7–119.8	Dmax: 6.9	9.8	14.5	65.0–83.3%	62.5–87.9%
Left ventricle	Medium: 11.3 (16)	20.1	34.7	Medium: 0.8	0.7	0.6	96.5%	98.3%
Right ventricle	Medium: 8.3 (16)	12.7	19.9	Medium: 5.0	6.2	8.3	51.2%	58.3%
Aortic valve	Median dose: 3.5 (16)	3.9	4.7	Median dose: 1.1	1.1	0.9	73.7%	80.9%
Mitral valve	Dmax: < 20.0 (29)	50.0	100.0	Dmax: 6.5	8.9	12.9	82.2%	87.1%
ICD (major electronics)	Dmax ≤ 2.0 (49)	2.0	2.0	Dmax: 0.03	0.03	0.02	98.5%	98.5%

The data were compared to the constraints or dose limitations for patients who were treated with SBRT 25 Gy.

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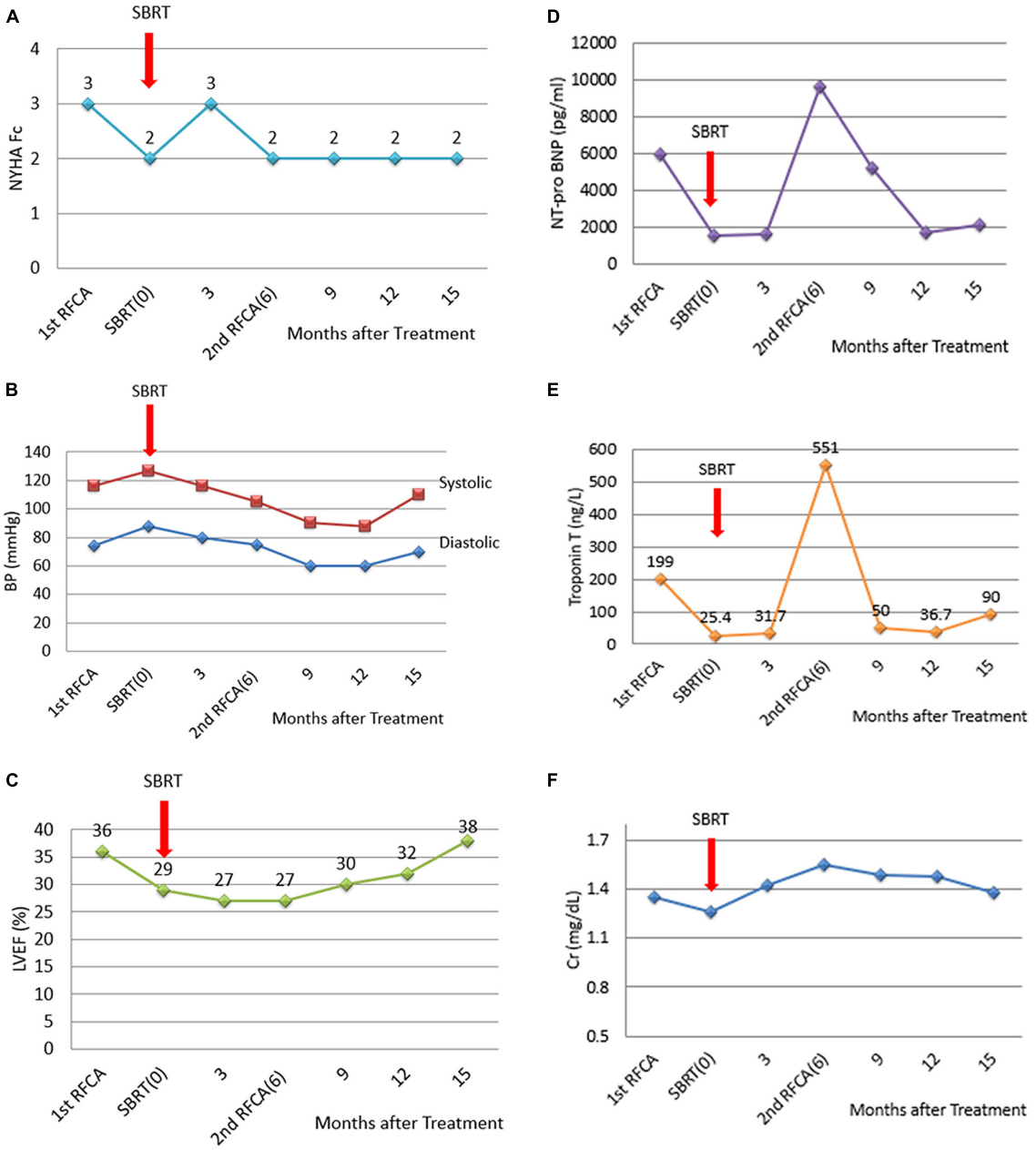

FIGURE 5
Diagrams of the NYHA functional classification, blood pressure, LVEF and laboratory data with a timeline for the patient before, during and after the treatment. **(A)** NYHA functional classification, explaining the severity of heart failure. **(B)** Blood pressure. **(C)** LVEF improved slightly after catheter ablation to the RVOT VT. The second electrophysiological study documented successful local treatment with SBRT using 12 Gy at the left ventricular basal to middle posterior septal wall. However, **(D)** NT-pro-BNP and **(E)** Troponin T levels increased 6 months after SBRT because of recurrent electric storms derived from the RVOT VT. After catheter ablation of the RVOT VT, serum NT-proBNP and troponin T levels decreased. **(F)** Serum creatinine levels remained unchanged.

progression of mitral regurgitation and changes in valvular morphology 17 months after radiosurgery. Qian et al. (33) reported that 3 of six patients experienced adverse effects after SBRT with 25 Gy: one suffered from pneumonia 1 month later; another had severe left ventricular dysfunction, mitral regurgitation and tricuspid regurgitation and developed heart failure decompensation 104 days later; and the other presented with moderate pericardial effusion 396 days later. Therefore, the potential risks for late radiotherapy-related effects of cardiac toxicity should still be considered with caution.

SBRT (20 Gy or higher) is associated with reduced capillary density, myocardial degeneration and fibrosis (34, 35).

TABLE 2 Comparison of a patient with refractory VT treated with SBRT using a dose of 12 Gy at the Far Eastern Memorial Hospital (FEMH) with a selected published series of patients treated with SBRT.

References	Modality	PTV volume (c.c.)	Number of patients	Dose (Gy)	Treatment time	Episodes before RT	Episodes after RT	VT recurrence	Follow-up (mo: month; wk: week; d: day)
Loo et al. (17)	CyberKnife	NR	1	25	90 min	VT: 562/2 mo	VT: 52/mo	3 mo post-SBRT 100% (1/1)	9 mo
Cvek et al. (18)	CyberKnife	NR	1	25	114 min	PVCs: 9–10%	PVCs: 1–3%	NR	120 d
Wang et al. (25)	CyberKnife, TrueBeam Linear Accelerator	NR	4	25	Mean: 64.2 min	NR	NR	NR	NR
Cuculich et al. (11)	TrueBeam Linear Accelerator	49	5	25	14 min	Mean VT: 1315	Mean VT: 4	4 wk after SBRT, 20% (1/5, Patient 4) of patients had recurrent VT	12 mo
Haskova et al. (19)	CyberKnife	NR	1	25	NR	Incessant VT	Disappeared	NR	8 mo
Jumeau et al. (20)	CyberKnife	21	1	25	45 min	LVEF: 15%	LVEF: 30%	NR	4 mo
Robinson et al. (12)	TrueBeam or Edge Linear Accelerator	Median: 98.9	19	25	Median: 15.3 min (5.4–32.3)	119	3	69% (11/16) of patients had recurrent VT between the end of the 6-wk blank period and the 6-mo follow-up.	13 mo
Neuwirth et al. (26)	CyberKnife	22.15	10	25	Mean: 68 min	212	26	In total, 80% (8/10) of patients had recurrent VT. (1) Patients 4 and 1 experienced recurrences of VT up to 3 and 6 months after radiosurgery, respectively. (2) Patients 6 and 8 presented with a higher number of VT episodes after SBRT. (3) Three of the 10 patients experienced an electric storm.	Median: 28 mo
Krug et al. (21)	TrueBeam Linear Accelerator	42.2	1	25	55 min	VT: 5.1	VT: 1.6	One more week 100% (1/1)	57 d
Zeng et al. (22)	CyberKnife	NR	1	24	NR	VT: 189	VT: 0	NR	4 mo
Lloyd et al. (27)	TrueBeam linear accelerators	81.4	10	25	30 min	VT: 1065	VT: 332	Recurrent but with a 94% reduction in VT seconds	176 d
Gianni et al. (28)	CyberKnife	143	5	25	82 min	Total VT: 296	Total VT: 306	All patients (100%)	Mean: 12 mo
Martí-Almor et al. (23)	TrueBeam Linear Accelerator	–	1	25	–	Right ventricular ejection fraction: 30%	Right ventricular ejection fraction: 33%	NR	4 mo

(Continued)

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TABLE 2 (Continued)

References	Modality	PTV volume (c.c.)	Number of patients	Dose (Gy)	Treatment time	Episodes before RT	Episodes after RT	VT recurrence	Follow-up (mo: month; wk: week; d: day)
Mayinger et al. (24)	MR-Linac with 6 MV flattening-filter-free photons	269	1	25	2 h and 28 min	–	VT aggravation 24 h after SBRT	NR	3 mo
Ho et al. (29)	TrueBeam Linear Accelerator	Mean: 54.5	7	25	Median beam-on time: 12.7 min	88	23	Excluding 1 patient who died, 50% (3/6: Patients 1, 2, and 5) of patients had recurrent VT.	Median: 14.5 mo
Yugo et al. (30)	TrueBeam Linear Accelerator	83.2	3	25	Mean: 71 min	140	54	All patients (100%)	NR
Lee et al. (31)	Linear Accelerator (Varian Medical Systems/Elekta)	94.5	7	25	Mean: 38.7 min	NR	The overall reduction in the VT burden was 85%	Recurrent VT but no clear state	6 mo
Chin et al. (32)	Novalis Tx Medical Linear Accelerator	121.4	8	Median: 25	average: 18.2 min	Median VT: 35	Median VT: 10.5	Excluding 4 patients who died, 100% (4/4) of the patients had recurrent VT after SBRT. (1) Patient 2: at 1 year (2) Patient 3: at 8 mo (3) Patient 6: at 3 mo (4) Patient 7: at 1 mo	7.8 mo
Qian et al. (33)	TrueBeam Linear Accelerator	319.5	6	25	Beam-on time: 13.8 min	Median VT: 42	Median VT: 29	In total, 83% (5/6) of the patients had recurrent device-treated VT at 97 d.	231 d
FEMH	VMAT Linear Accelerator (Versa HD)	65.75	1	12	24 min			No recurrence	16 mo

D, days; min, minutes; mo, months; NR, not reported; wk, weeks; VMAT, volumetric-modulated arc therapy.

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Endothelial vacuolization and disruption of gap junctions on electron microscopy specimens is noted after SBRT as relatively acute effects that occur well before cellular DNA damage–related apoptosis and fibrosis begin (27). Additionally, severe architectural disruption, inflammatory cell infiltration, fibrin deposition and necrosis in myocardial tissue caused by high-dose irradiation in swine have been reported (22, 30, 31). Notably, irradiation with 16 Gy to the mouse heart induced mitochondrial damage and metabolic alterations of the cardiac tissue and led to structural remodeling, functional injury and fibrotic alterations (36). Interestingly, the severity and extent of myocardial injury, such that it reduced resting myocardial perfusion in rats, became more evident at the end of 6 months after 20 Gy heart irradiation in a single fraction (37). Similarly, when ^{13}N-ammonia PET/CT myocardial perfusion imaging (MPI) was used to detect changes in myocardial perfusion induced by the administration of 20 Gy in one fraction to beagle dogs, the data showed a 10% reduction in LVEF at 6 and 12 months after irradiation (38). Similar findings have also been recently documented in human myocardium after SBRT, consistent with the preclinical models (19). Considering all these published observations, high-dose irradiation of the heart potentially results in cardiac damage.

More importantly, the published data show that the potential rate of recurrent VT after SBRT is 20–100% (**Table 1**). In contrast to those who received 25 Gy, three patients who received lower SBRT doses (median dose of 20 Gy) achieved clinically positive outcomes, as reported by Qian et al. (33). Ho et al. (29) delivered 20 Gy to the PTV with effective results that were lower than those of other reports. Lehmann et al. (39) suggested that ablated RT doses to create a complete atrioventricular conduction block and point doses to the coronary arteries should be < 10 Gy to remain safe. Radiosurgery with 12 Gy provides a high control rate for acoustic neuromas (14). Additionally, for patients with benign tumors adjacent to the anterior visual pathway who were treated by single-fraction stereotactic radiosurgery with less than 12 Gy vs. 12 Gy, the probability of radiation-induced optic neuropathy was 0% vs. 10% (40). Sharma et al. (41) demonstrated that 12 Gy caused mitochondrial degeneration. Mitochondria play an important role in cellular stress signals activated for acute, chronic nerve cell injury and nerve cell death (42) and maintain homeostasis and cellular integrity (43). Dysfunctional mitochondria affect neuronal trafficking across neurons. As mentioned above, mitochondrial damage in cardiac tissue could lead to structural remodeling, functional injury and fibrotic alterations (36). Moreover, 12 Gy irradiation has upregulated matrix metalloproteinase (MMP)-2 and MMP-9 activity. MMP-2 and MMP-9 degrade collagen IV of basement membranes, weakening the structural integrity (44). Notably, in the study of the late radiation response of canines, the median effective dose (ED_{50}) for pericardial fibrosis in 2 Gy fractions was 46.1 Gy (13). However, for 12 Gy in one fraction corrected for fractionation with alpha/beta ratio = 2.5, the EQD2 was 38.7 Gy. Therefore, abnormal nerve reentry may be silenced by degenerating or dysfunctional mitochondria related to SBRT of 12 Gy, which could affect the neuronal trafficking process, structural remodeling and cellular integrity but also decrease the risk of pericardial fibrosis.

The Radiation Therapy Oncology Group (RTOG) 90-05 suggested that 15, 18, and 24 Gy could eradicate brain tumors of 31–40, 21–30, and less than 20 mm, respectively (45). Cardiac SBRT 25 Gy exhibited robust clinical efficacy in humans and shortened the QRS interval to electrophysiologic reprogramming (46). However, conduction velocity reprogramming could be achieved by treatment with as little as 15 Gy of radiation as well as 25 Gy does, suggesting that 15 Gy of RT may be a good dose to achieve electrical conduction reprogramming without transmural fibrosis (46). Interestingly, the RT dose that caused the formation of connective tissue in the myocardium of the left ventricle and septum significantly in the canine study by 2 Gy fractions was 68.0 Gy, and myocytolysis was 70.4 Gy given in 2 Gy fractions (13). Corrected for fractionation with alpha/beta ratio = 2.5, the EQD2 values of 15 and 18 Gy in one fraction were 58.3 and 82.0 Gy, respectively. In other words, conduction velocity reprogramming may be induced by 15 Gy, and 15 Gy does not cause myocardium fibrosis because its EQD2 is less than 68.0 Gy. The EQD2 of 18 Gy equal to 82.0 Gy (i.e., over 68 Gy) means it has a greater chance of causing transmural fibrosis. These lines of evidence support the potential strategy of giving 12 Gy of SBRT to the PTV, and the dose grading in the ITV and CTV to substate was 15 and 18 Gy, respectively. The results for the patient reported here were efficient, as confirmed by high-density mapping, MRI and EKG (**Figures 2B,D,F**).

Darby et al. (47) reported that rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray. Hohmann et al. (48) noted that 3 months after VT was treated by SBRT, the left ventricular ejection fraction (LVEF) decline was correlated with mean dose and V20Gy. Considering the respective EQD2 with alpha/beta ratios = 10 and 2.5 for acute and late effect calculations, the mean heart dose was decreased by 6 Gy (71%) and 9 Gy (80%), respectively. On the other hand, the respective risk of acute and late toxicity of coronary events or heart toxicity could be reduced by 42 and 67%, respectively. Similarly, the acute and late effect doses to the heart substructures were decreased by 40–93 and 58–98%, respectively, when compared with treatment with 25 Gy. All together, the evidence supports the hypothesis that the administration of a lower radiosurgery dose to stop VT recycling and prevent damage to cardiac tissue in the long term may be a feasible idea, but more cases and longer follow-up times are needed to ensure efficacy. Additionally, the patient experienced recurrent VT, and a repeat bipolar voltage mapping study with the 3D CARTO mapping system confirmed a new lesion located at the RVOT, which was explained using the CARTO mapping

system to check the electric reentry activity before retreatment. Because a lower radiosurgery dose provides a second chance to re-irradiate patients safely when they experience recurrent VT, relocalization of recurrent VT becomes more important for secondary irradiation.

To the best of our knowledge, this case report is the first in the world of a patient with refractory VT treated with SBRT using 12 Gy, and successful local treatment was confirmed by the 3D CARTO system, cardiac MRI and serial clinical EKG, suggesting that 12 Gy is a good dose for refractory VT. However, this study only describes the results from the first patient who was successfully treated with SBRT at this dose. Further study of more patients is warranted to assess the long-term efficacy and side effects of this treatment, as well as its mechanism of action and cost-effectiveness.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Human Experimentation Committee of Far Eastern Memorial Hospital (FEMH108074-F). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant/s for the publication of this case report.

Author contributions

C-HH, S-HH, Y-WW, and P-WS contributed to conception and design of the study. S-YW, M-CT, H-JT, and H-PY performed the image-fusion localization. Y-HL, W-PC, and H-HL take care of patient. C-HH and S-HH wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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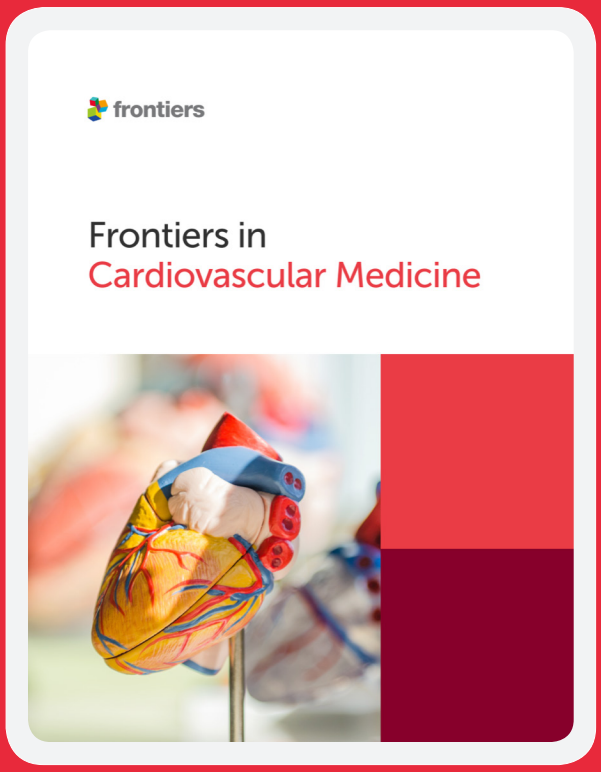

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