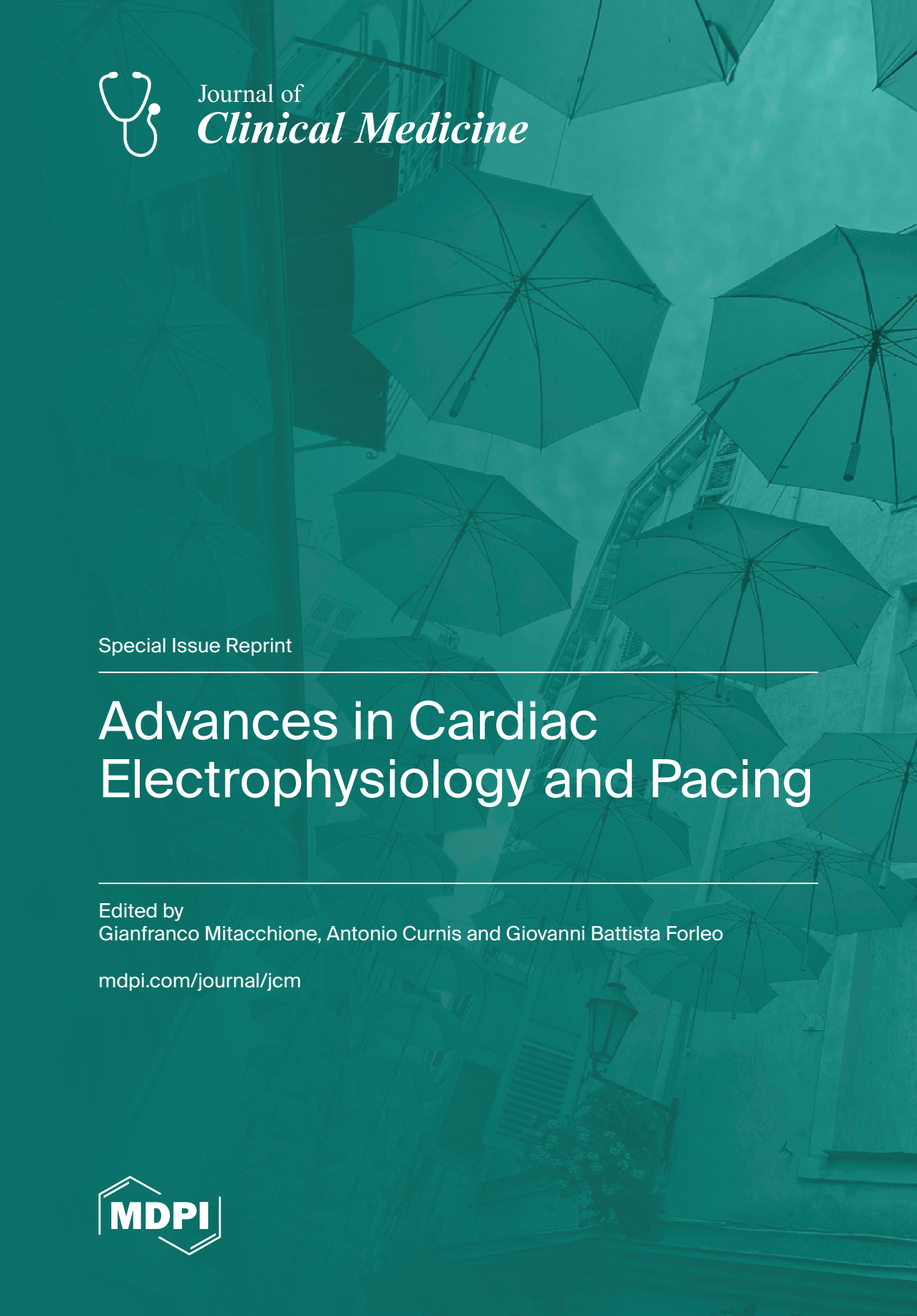

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Advances in Cardiac Electrophysiology and Pacing

Edited by
Gianfranco Mitacchione, Antonio Curnis and Giovanni Battista Forleo

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Editors

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Cover image courtesy of Gianfranco Mitacchione

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About the Editors

Gianfranco Mitacchione

Gianfranco Mitacchione graduated from medical school at the University of Bari (Italy). He completed his cardiology residency at the University of Insubria (Varese, Italy) and subsequently obtained a PhD in Experimental and Translational Medicine at the same university. He attended a two-year fellowship in cardiovascular physiology at New York Medical School (Valhalla, NY-USA) and Lewis Kats School of Medicine at Temple University (Philadelphia, PA-USA).

Gianfranco Mitacchione started his medical career as a Cardiac Electrophysiologist at "Spedali Civili" University Hospital of Brescia. From 2018, he has been serving as a Senior Consultant Cardiac Electrophysiologist in the Electrophysiology and Cardiac Pacing Unit at "Luigi Sacco" University Hospital of Milan (Italy). Gianfranco Mitacchione is one of the most acclaimed Italian opinion leaders in leadless pacing. He is a Fellow of the Italian Heart Rhythm Society (AIAC) and is part of the expertise group on "lead extraction" of the same Scientific Society. From 2022, he has also been part of the regional council of Lombardy of the Italian Heart Rhythm Society (AIAC). Gianfranco Mitacchione contributed to several international research projects publishing more than 50 articles (H-index 15). In 2023, he achieved a National Scientific qualification as Associate Professor in the Italian higher education system.

Antonio Curnis

Antonio Curnis received his medical degree from University of Brescia (Italy) and subsequently completed his cardiology residency at the same university. From 1996 to 1997, he enhanced his professional skills at the Electrophysiology and Cardiac Pacing Unit of "Freie und Hansestadt" Hospital in Hamburg directed by Prof. K.H. Kuck, and, in 1999, worked at the Interventional Laboratory of Santa Cruz Hospital in Lisbon directed by Prof. J. Melo.

In 2015, he was appointed Associate Professor at Cardiology School of Medicine at the University of Brescia. He is currently Head of the Cardiac Electrophysiology and Pacing Unit at "Spedali Civili" University Hospital of Brescia, one of the main international referrals in the field of transvenous lead extraction and advanced cardiac pacing. From 2006 to 2008, he was Vice President of the National Council of the Italian Heart Rhythm Society (AIAC). He is a tutor of the University Master in Electrophysiology and Cardiac Pacing at University of Insubria and Brescia.

He participated as an investigator in several international study projects, publishing more than 200 articles (H-index: 35).

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Giovanni Battista Forleo received his medical degree from the University of Florence and completed his cardiology residency at the Catholic University of Sacred Heart in Rome. After the clinical fellowship, in 2006, he obtained a PhD at the Tor Vergata University of Rome. In 2009, he was appointed Adjunctive Professor at the University of Rome "Tor Vergata" and is currently an Adjunctive Professor at the University of Milan. Giovanni B. Forleo served as Staff Cardiologist at the University Hospital of Tor Vergata of Rome, where he was Head of Cardiac Electrophysiology from 2007 to 2016. Currently, he is Section Head of Electrophysiology and Cardiac Pacing at the University Hospital "Luigi Sacco" in Milan.

He serves on the editorial boards of some medical journals and is a reviewer for several international journals. He is the author of 100 peer-reviewed articles (H-index: 23). His major area of research is related to cardiac pacing and electrophysiology.

Giovanni B. Forleo participated as an Investigator, Member of the Steering Committee and Chairman/Co-chairman in several national and international studies. He has been part of the national council of the Italian Heart Rhythm Society (AIAC).

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Editorial

Cardiac Implantable Electronic Devices Breakthrough: Are We Ready to Face the Future?

Gianfranco Mitacchione

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Since its inception cardiac electrical therapy has evolved, with transvenous pacemakers (PMs) and implantable cardiac defibrillators (ICDs) providing significant benefits in terms of improved quality of life and reducing mortality in patients with cardiac conduction disturbances and/or requiring protection against ventricular arrhythmias. Nonetheless, cardiac implantable electronic devices (CIEDs) remain associated with a significant rate of combined short- and long-term system adverse events, such as lead malfunctions, pulse generator pocket complications, and local/systemic infections—with these latter events characterized by high morbidity, protracted antimicrobial therapy, and long-term hospitalization resulting in a substantial financial burden for the healthcare system.

Overwhelmingly, transvenous lead extraction (TLE) has proven to be the most effective solution for CIED-related infective complications and malfunctions, with a high overall efficacy and safety record. There are several tools tailored specifically to remove transvenous devices.

In order to minimize CIEDs-related adverse events, pacing and high-voltage device manufacturers have recently undergone an impressive technological development, introducing on the market new "*unconventional*" devices, which are characterized by new implant sites and different interactions with intracardiac sites. These new devices are confirming a significant outcome, but in the cases of adverse events the removal can still be challenging. Indeed, it seems that TLE technologies do not keep up with the times in respect to new CIEDs.

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1. The Advent of Leadless Pacing

Leadless pacemakers (LPMs) have been a major breakthrough in the management of bradyarrhythmia and as an alternative to the standard transvenous PMs. LPM implantation has been steadily increasing over time. To date, the Micra transcatheter pacing system (Micra VR-MC1VR01, Medtronic, Inc., Minneapolis, MN, USA) is the only leadless device available on the market. It was approved by the CE in 2015 and subsequently the FDA approved it in 2016. Recently, the introduction of second generation LPMs (Micra AV-MC1AVR1) has expanded the pacing modes to obtain atrioventricular (AV) synchronous pacing, thus providing an interesting alternative in the scenario of leadless pacing [1].

LPM showed a high safety and efficacy profile when compared to transvenous PMs, with a reduction of 51% in major complications in the early post-procedural period. This is due to the characteristics of the devices' designs, which avoid complications associated with transvenous leads and surgical pockets [2]. Despite this safety profile, a small percentage of patients still require system revision for device-related adverse events (i.e., premature battery depletion), with the need to optimize electrical features [3].

Recently, serious concerns related to LPMs have been experienced with the Nanostim Leadless Cardiac Pacemaker (St. Jude Medical, St Paul, MN, USA). This device was permanently withdrawn from the market in 2017 for several safety advisories such as battery premature depletion and disfunction of the retrieval catheter.

The main concern regarding LPMs is that these devices are not designed to be removed; moreover, actual technologies and tools for lead extraction are of limited use for these devices, with scarce experiences reported in the literature [4].

On 7 February 2022, Abbott announced the world's first patient implants of a dual-chamber leadless pacemaker system as part of its AVEIR DR i2i™ pivotal clinical study. The Aveir™ dual-chamber leadless pacemaker (Abbott Cardiovascular Systems Inc., Chicago, IL, USA) is a leadless pacemaker comprising two separate parts, separately screwed in the right atrium and right ventricle that are able to communicate with each other to guarantee AV synchrony. This is a clinical milestone, but there are several concerns about the ability to remove them if required.

2. High Voltage Electrical Therapy

Subcutaneous ICD is currently a reasonable solution for patients requiring implantation of a cardioverter defibrillator with no indications of cardiac resynchronization, bradycardia support, or antitachycardia pacing. This device is characterized by the absence of leads in the central venous circulation and inside the cardiac chambers, thus avoiding the risk of vascular obstruction, thrombosis, infection, and cardiac perforation. Therefore, S-ICD is a first line indication in several cases such as pediatric patients, patients with lack of vascular access, or patients at very high risk of infection. Despite the notable safety and efficacy profile, cases of device-related complications (unappropriated shocks and/or local infections) have been reported [5]. First experiences on S-ICD lead extraction require specific tools, specifically when fibrotic adhesions have developed around the parasternal coil [6].

To date, the only S-ICD available on the market is the Emblem™ MRI S-ICD system (Boston Scientific, Marlborough, MA, USA). The system was approved by the FDA in 2012, although some series were recalled in 2021 due to premature battery depletion. The lead, with an 8 cm shock coil, is vertically positioned in the subcutaneous tissue of the chest, parallel to and 1–2 cm from the left sternal midline followed by a horizontal segment until it reaches the left anterior axillary line. First experiences on S-ICD lead extraction are encouraging [5]; however, they require specific tools, especially when fibrotic adhesions develop around the parasternal coil.

A new S-ICD system has been developed (EV ICD™ System. Medtronic, Inc., Minneapolis, MN, USA). The new system is characterized by a single lead implanted under the sternum that can pace patients out of ventricular tachycardia (but not bradycardia). This specifical feature could also play a negative role in case of device removal, particularly after a consistent time.

Finally, leadless cardiac pacing and subcutaneous defibrillator technologies are about to be merged. In fact, Boston Scientific recently presented (American Heart Association Scientific Sessions 2021) preclinical data on the EMPOWER MPS device, a leadless pacemaker that is able to communicate with the Emblem™ S-ICD. This promises not only to deliver antitachycardia pacing therapy, but also to pace in VVIR mode.

3. Conclusions

Several technological progresses have been made in order to minimize CIEDs-related adverse events. These translate into the development of miniaturized CIED, avoiding as much as possible any interaction with intracardiac tissues. Unfortunately, adverse events from these devices still remain. In this field, further efforts are needed to improve the safety of the devices and develop new techniques that could overcome these unresolved issues, particularly in the field of "new" CIEDs extraction.

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Article

Vacuum-Implemented Removal of Lead Vegetations in Cardiac Device-Related Infective Endocarditis

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Abstract: When approaching infected lead removal in cardiac device-related infective endocarditis (CDRIE), a surgical consideration for large (>20 mm) vegetations is recommended. We report our experience with the removal of large CDRIE vegetations using the AngioVac system, as an alternative to conventional surgery. We retrospectively reviewed all infected lead extractions performed with a prior debulking using the AngioVac system, between October 2016 and April 2022 at our institution. A total of 13 patients presented a mean of 2(1) infected leads after a mean of 5.7(5.7) years from implantation (seven implantable cardioverter-defibrillators, four cardiac resynchronization therapy-defibrillators, and two pacemakers). The AngioVac system was used as a venous–venous bypass in six cases (46.2%), venous–venous ECMO-like circuit (with an oxygenator) in five (38.5%), and venous–arterial ECMO-like circuit in two cases (15.4%). Successful (>70%) aspiration of the vegetations was achieved in 12 patients (92.3%) and an intraoperative complication (cardiac perforation) only occurred in 1 case (7.7%). Subsequent lead extraction was successful in all cases, either manually (38.5%) or using mechanical tools (61.5%). The AngioVac system is a promising effective and safe option for large vegetation debulking in CDRIE. Planning the extracorporeal circuit design may represent the optimal strategy to enhance the tolerability of the procedure and minimize adverse events.

Keywords: AngioVac; lead; pacemaker; CDRIE

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1. Introduction

Trends in cardiac device implantation in recent decades have reflected the global population aging phenomena [1,2]. With growing large-scale adoption of transcatheter aortic valve replacement and the related risk of atrio-ventricular block, the implementation of guidelines for primary and secondary prevention of cardiac adverse events in heart failure, as well as the intrinsic senescence of conduction tissues in older individuals, the use of pacemakers (PM) and implantable cardioverter-defibrillators (ICD) has become a routine practice.

Late septuagenarians and octogenarians represent the most frequently treated age group [1,2], where multi-organ comorbidities are extremely common. In this scenario, the annual incidence of cardiac device-related infective endocarditis (CDRIE) ranges from 1.5% to 2.5%, generating a significant social and mortality burden [1,3,4]. According to the most recent European Heart Rhythm Association (EHRA) guidelines [5], infected lead extraction is always recommended and a percutaneous approach is the first choice (TLE: transvenous lead extraction). Although the high rates of successful percutaneous removal, in-hospital mortality can reach 2.3%, especially when a systemic infection is suspected [6]. In these

settings, as well as in large (>20 mm) vegetations, a vacuum-assisted aspiration of the mass or a conventional surgical approach is suggested [5].

The AngioVac system (AngioDynamics, Latham, NY, USA) is a novel percutaneous technology that includes an aspiration cannula combined with a filter, a centrifugal pump, and a venous or arterial reinfusion cannula, intended for the intravascular aspiration of right-sided masses. This device has found an application for CDRIE vegetations debulking before lead extraction [7–14]. A systematic review of literature by Rusia et al. in 2019 collected a total of 88 patients in whom this device has been successfully adopted to treat CDRIE in 97.7% of cases [15]. However, the level of evidence is still low [5] and the feasibility and efficacy profiles of the AngioVac system are still under active investigation [16]. Moreover, the extracorporeal circuit's configurations that can be adopted with this device have not been investigated systematically.

We report our single-center experience with the percutaneous vacuum-assisted removal of large CDRIE vegetations using the AngioVac system before transvenous lead extraction. In particular, we provide a structured decisional algorithm for the planning of the extracorporeal circuit's configurations to provide the most adequate respiratory and/or hemodynamic support during the procedure.

2. Materials and Methods

2.1. Study Population

We conducted a retrospective review of all consecutive infected lead extractions, performed with a prior debulking of vegetations using the AngioVac system, between October 2016 and April 2022 at our institution. All patients signed the informed consent to the operation and use of data for scientific purposes. The study was approved by the local ethics committee (protocol 39677, June 2022).

Baseline clinical and demographic characteristics of patients, intraoperative variables, and in-hospital events were collected by hospital charts and imaging data review. Successful mass removal was defined by the aspiration of >70% of the mass as displayed on intraoperative transesophageal echocardiography, and device safety by the rate of procedural complications, as previously described [13,16].

2.2. Procedure Planning

According to the guidelines [5], all patients with large (>20 mm) CDRIE vegetations or systemic infection underwent a multidisciplinary evaluation to plan a surgical extraction of the infected device [17] (Figure 1). When feasible, percutaneous vacuum-assisted aspiration of the mass with the AngioVac system was the preferred approach, followed by a transvenous lead removal.

The respiratory and hemodynamic status of the patient guided the subsequent decisional steps. Three different configurations of the extracorporeal circuit were adopted at our institution (Figure 2). If the patient was hemodynamically stable and the cardiac function was preserved, a standard venous–venous bypass circuit where the AngioVac cannula suctions venous blood which is reinfused through another venous vessel was used. This circuit was upgraded with an oxygenator, realizing a venous–venous ECMO-like configuration, if the patient had compromised ventilatory function that required respiratory support during the procedure. Finally, in the case of septic shock, impaired ventricular function, or larger masses with a consistent risk of hemodynamically impacting pulmonary embolization, a venous–arterial ECMO-like configuration was chosen. In this circuit design, the AngioVac aspiration cannula filters venous blood was returned to the patient through an arterial cannula (after being oxygenated), ensuring adequate circulatory support.

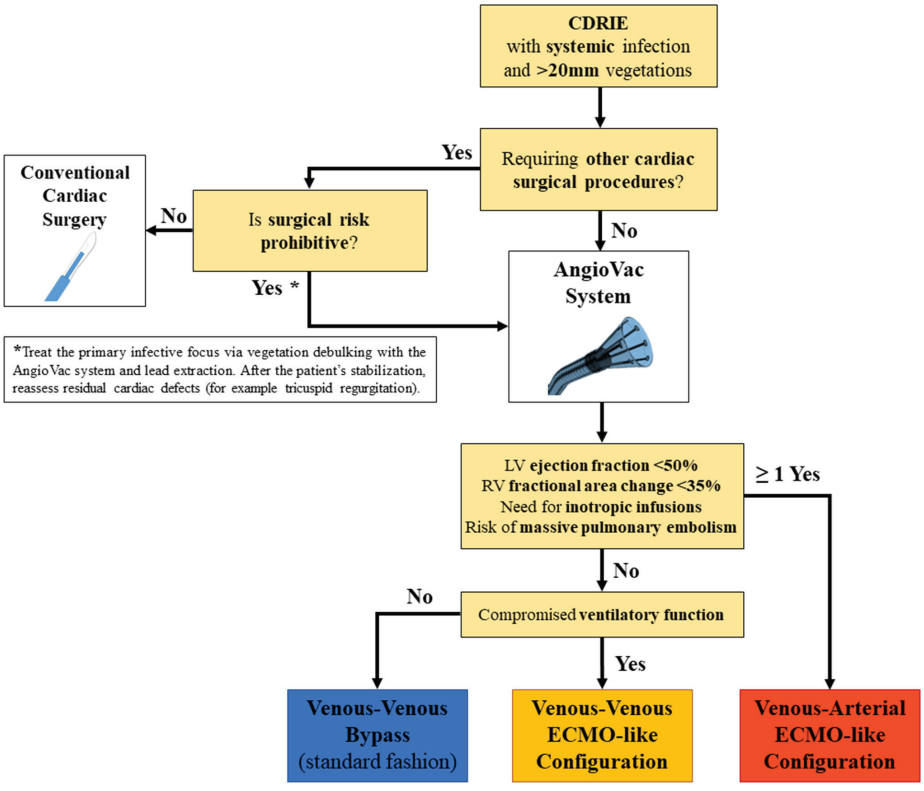

Figure 1. Decisional algorithm for management of CDRIE with large vegetations or systemic infection.

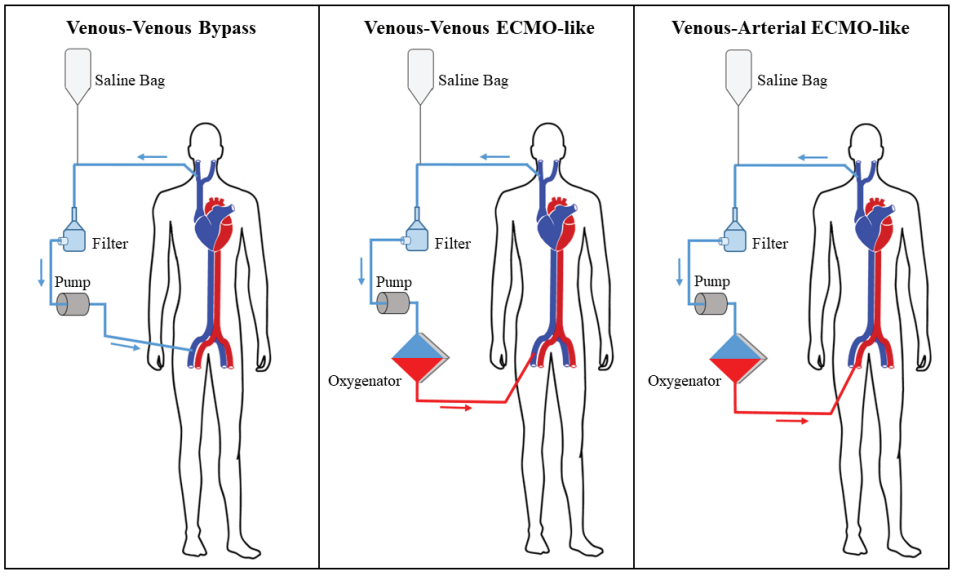

Figure 2. Different configurations of the AngioVac system circuit.

2.3. Operative Technique

The procedure was performed under general anesthesia and the operating room was equipped with three-dimensional transesophageal echocardiography and fluoroscopy. For pacemaker-dependent patients, a temporary transvenous pacing device was placed. Angiography of the left subclavian vein was performed and a stiff guidewire was placed from the LFV or RFV into the RIJV to potentially place an occlusion balloon in case of vessel perforation. The cardiac device pocket was incised and leads were prepared with a locking stylet (Liberator, Cook Vascular Inc., Bloomington, IN, USA) and a compression coil (One-Tie, Cook Vascular Inc.).

A 5000 IU bolus of unfractionated heparin was administered to achieve partial heparinization with a target activated clotting time >180 s. The 22F AngioVac aspiration cannula was placed in the right internal jugular vein (RIJV), the right or left femoral vein (RFV, LFV), or a combination of these accesses. To facilitate the insertion of the suction cannula, a 26 Fr Gore DrySeal venous sheath (W.L. Gore & Associates, Newark, DE, USA) was used. All the three generations of the AngioVac cannula were used: first generation with a straight tip and a balloon-activated funnel; second generation with a 20° angled tip and a balloon-activated funnel; and third generation with a 20° or 180° angled tip and a self-expanding nitinol funnel.

Subsequently, the reinfusion cannula was placed in another venous or arterial vessel, depending on the intended strategy. If a venous–venous configuration was planned, all vessels were cannulated percutaneously preferentially. In the case of a venous–arterial ECMO-like configuration, a surgical exposition of the femoral vessels was performed. Vessels' cannulation and the extracorporeal circuit set-up was carried out by the cardiac surgeon, who was assisted by the electrophysiologist for lead, guide, and cannula visualization using fluoroscopy.

The AngioVac cannula was driven under transesophageal echocardiographic guidance into the right of the heart and used for the debulking of lead vegetations by the cardiac surgeon. Even if a successful (>70%) removal of the mass was achieved, it was common that small residual vegetations could persist onto the leads, due to strong adherences. To prevent the embolization of these residual masses, the AngioVac cannula was left in place in the right atrium close to the lead and the aspiration was continued while the extraction was accomplished. This allowed the suction of small vegetation debrides that were mobilized during the catheters' extraction. TLE was performed by the electrophysiologist either manually or mechanically using Evolution RL Lead Extraction tools (Cook Vascular Inc.), depending on the encountered tissue resistance, as we previously described [17]. The AngioVac cannula was extracted and transesophageal echocardiography was used to rule out valvular injury and pericardial effusion. The DrySeal sheath and the reinfusion cannula were removed and hemostasis of access sites was completed. Finally, samples from the device pocket and leads were sent for microbiological analysis.

2.4. Statistical Analysis

Quantitative variables were summarized as mean (standard deviation (SD)) and median (interquartile range (IQR)) and categorical variables as counts and percentages. Analyses were performed using SPSS 23.0 (IBM Corporation, Armonk, NY, USA).

3. Results

During the study period, we performed 13 AngioVac-assisted infected lead removals (13 males; mean age 63.6 [12.2] years). Patients presented a mean of 2 (1) infected leads after a mean of 5.7 (5.7) years from implantation. In seven cases (53.8%), the infected device was an ICD, in four (30.8%) a cardiac resynchronization therapy-defibrillator (CRT-D), and in the other two (15.4%) a PM. Complete preoperative characteristics are summarized in Table 1. Of note, two patients (15.4%) had a previous cardiac surgery operation (coronary artery bypass graft surgery; correction of double-outlet right ventricle with ventricular septal defect closure and right ventricle to pulmonary artery homograft), five (38.5%) had

moderate- or severe-associated tricuspid valve regurgitation due to the mass interference with leaflet coaptation, and eight (61.5%) presented positive blood cultures (see Table 2 for isolated germs).

Table 1. Preoperative characteristics of patients (n = 13).

	Overall (n = 13)	
	Mean (SD)	**Median (IQR)**
Age (years)	63.6 (12.2)	67.1 (55.8–73.6)
Weight (kg)	73.9 (10.2)	76 (66.5–81)
Height (m)	1.73 (0.06)	1.72 (1.70–1.76)
Body surface area (m^2)	1.87 (0.13)	1.88 (1.77–1.97)
Body mass index (kg/m^2)	24.6 (3.4)	25.1 (21.1–26.3)
Serum creatinine (mg/dL)	1.12 (0.88)	0.87 (0.83–1)
Hemoglobin (g/L)	11.1 (1.9)	10.2 (9.7–12.7)
Left ventricular ejection fraction	0.43 (0.13)	0.36 (0.35–0.54)
Right ventricular fractional area change	0.42 (0.11)	0.41 (0.33–0.52)
Time from device implantation (years)	5.7 (5.7)	5 (0.9–9.4)
Number of infected leads	2 (1)	2 (1–3)
Mass dimension (mm)	37.2 (18.6)	39 (26–40.5)
MELD score	11 (5)	9 (8–12)
Karnofsky scale	71 (20)	70 (60–90)
Zubrod scale	2 (1)	2 (1–3)
	N	**%**
Male	13	100
Comorbidities		
Dyslipidemia	8	61.5
Arterial hypertension	6	46.2
Previous cardiac arrest	5	38.5
Smoke	4	30.8
Diabetes mellitus	4	30.8
Congestive heart failure	2	15.4
Renal replacement therapy	1	7.7
Previous cerebrovascular accident	1	7.7
Coronary artery disease	1	7.7
Previous cardiac surgery	2	15.4
Previous percutaneous coronary intervention	4	30.8
Preoperative anticoagulation	6	46.2
Preoperative antiplatelet therapy	5	38.5
Positive blood culture	8	61.5
Preoperative inotropic support	1	7.7
Preoperative tricuspid valve regurgitation		
Absent	3	23.1
Mild	5	38.5
Moderate	3	23.1
Severe	2	15.4
Type of implanted device		
Implantable cardioverter-defibrillator	7	53.8
CRT-D	4	30.8
Pacemaker	2	15.2

Table 1. *Cont.*

	Overall (n = 13)	
	Mean (SD)	**Median (IQR)**
Indication to implantation		
Secondary prevention of cardiac arrest	6	46.2
Primary prevention of cardiac arrest	5	38.5
Symptomatic atrio-ventricular block	2	15.2
Number of masses		
One mass	9	69.2
Two masses	3	23.1
Three masses	1	7.7

CRT-D: Cardiac resynchronization therapy-defibrillator.

Table 2. Isolated germs from preoperative blood cultures (n = 8) and from intraoperative samples (n = 3).

Isolated Germs from Preoperative Blood Cultures	**Patients with Positive Blood Cultures (n = 8)**	
	N	**%**
Staphylococcus epidermidis	2	25
Enterobacter cloacae	2	25
Enterobacter faecalis	1	12.5
Acinetobacter baumanii	1	12.5
Staphylococcus aureus	1	12.5
Staphylococcus lugdunensis	1	12.5
Isolated Germs from Intraoperative Samples	**Patients with Positive Intraoperative Samples (n = 3)**	
	N	**%**
Staphylococcus epidermidis	1	33.3
Staphylococcus warneri	1	33.3
Rhizobium radiobacter	1	33.3

In most of the cases (nine patients, 69.2%), the mass was single and its mean diameter was 37.2 (18.6) mm (Figure 3). Two patients (15.4%) had a mass < 25 mm, two (15.4%) between 25 and 30 mm, three (23.1%) between 30 and 40 mm, and six (46.2%) $\geq$ 40 mm. Mass debulking was conducted using the AngioVac system in three different configurations: venous–venous bypass circuit in six cases (46.2%), venous–venous ECMO-like circuit in five (38.5%) to provide respiratory support, and venous–arterial ECMO-like circuit in two (15.4%) to ensure full hemodynamic stabilization during the procedure. The cannulation sites for blood aspiration and reinfusion are described in Table 3. Subsequent extraction of infected leads was achieved manually in five cases (38.5%) and using dedicated mechanical tools (Evolution RL Lead Extraction, Cook Vascular Inc.) in 8 (61.5%).

Table 3. Intraoperative details and circuit configurations (n = 13).

	Overall (n = 13)	
	Mean (SD)	**Median (IQR)**
Total operative time (min)	237 (91)	230 (173–328)
Fluoroscopy time (min)	7.8 (5.8)	7.1 (2.7–13.7)
AngioVac time: cannulation, aspiration, decannulation (min)	95 (25)	90 (65–120)
	N	**%**
Cannula generation		
First generation	3	23.1

Table 3. *Cont.*

	Overall (n = 13)	
	Mean (SD)	**Median (IQR)**
Second generation	5	38.5
Third generation	5	38.5
Venous–venous bypass configuration	6	46.2
Aspiration cannula site		
RFV	3	50
RIJV	2	33.3
RFV + RIJV	1	16.7
Reinfusion cannula site		
LFV	4	66.7
RFV	2	33.3
Venous–venous ECMO-like configuration	5	38.5
Aspiration cannula site		
RFV	2	40
RIJV	1	20
LFV	1	20
Right atrium	1	20
Reinfusion cannula site		
LFV	4	80
RFV	1	20
Venous–arterial ECMO-like configuration	2	15.4
Aspiration cannula site		
RFV	2	100
Reinfusion cannula site		
RFA	2	100
Type of lead removal		
Mechanical removal	8	61.5
Manual removal	5	38.5
Histopathological analysis		
Thrombus	13	100
Successful aspiration	12	92.3

LFV: left femoral vein. RIJV: right internal jugular vein. RFA: right femoral artery. RFV: Right femoral vein.

Successful aspiration (>70%) of the mass was achieved in 12 patients (92.3%, Video S1). In particular, a complete (100%) aspiration of the mass was accomplished in all successful cases. In the other case, a correct alignment of the aspiration cannula (first generation with a straight tip) with the tricuspid valve was not possible. A partial (50%) aspiration of the vegetation was accomplished (residual mass <20 mm) and the infected lead was subsequently extracted without complications. In all cases, all the infected leads were successfully extracted.

We reported one intraoperative complication (7.7%): during the insertion of the DrySeal guide, cardiac perforation occurred at the right ventricular free wall, requiring conversion to sternotomy to control the bleeding. However, the mass was successfully removed using the AngioVac cannula placed directly into the right atrium, through the atrial appendage. Of note, mass fragmentation and/or its embolization during the procedure never occurred.

In the postoperative period, the most common morbidities were: acute kidney injury requiring renal replacement therapy in four (30.8%), new-onset atrial fibrillation in two (15.4%), access site injury in one (7.7%), severe tricuspid regurgitation requiring tricuspid valve replacement (although severe regurgitation was present preoperatively) in one (7.7%), and the need for temporary venous–arterial ECMO support in one (7.7%). Complete postoperative outcomes are presented in Table 4. The grade of tricuspid valve regurgitation at discharge improved or remained stable in all cases. Noticeably, thirty-day mortality was 0%.

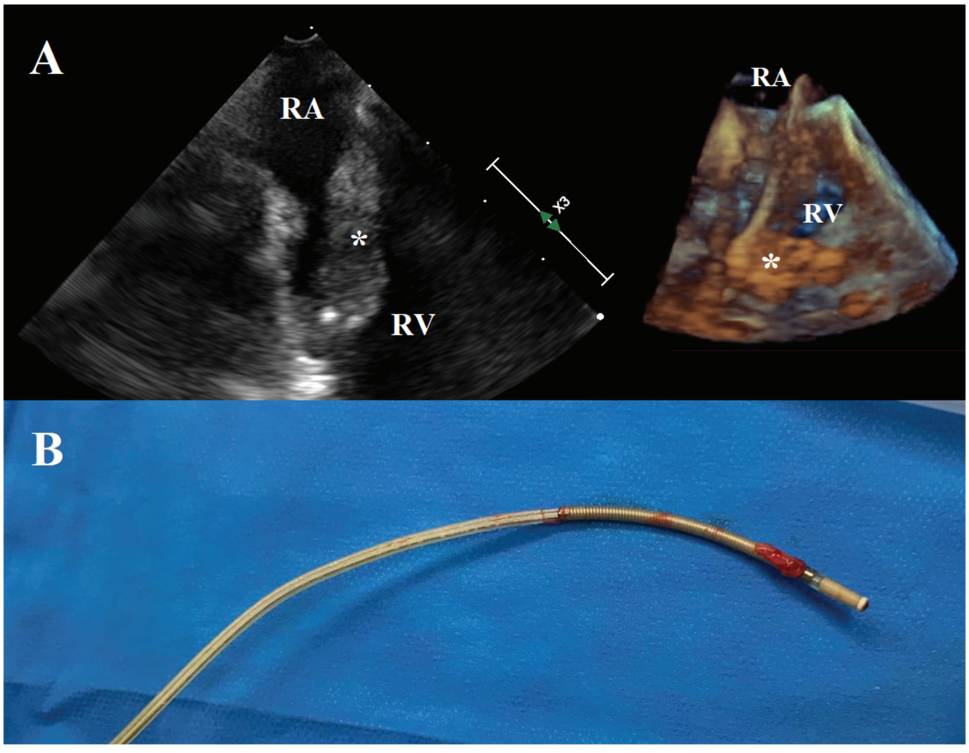

Figure 3. Intraoperative echocardiographic view of large lead vegetations (30 mm × 90 mm, Panel) (**A**). Extracted PM lead (Panel) (**B**). RA: right atrium. RV: right ventricle. *: vegetation.

Table 4. Postoperative outcomes (n = 13).

	Procedure Survivors (n = 13)	
	Mean (SD)	**Median (IQR)**
Creatinine peak (mg/dL)	1.23 (0.56)	1.02 (0.83–1.62)
Hemoglobin nadir (g/L)	10.8 (1.3)	11.1 (9.5–11.6)
Left ventricular ejection fraction	0.44 (0.11)	0.40 (0.36–0.55)
Right ventricular fractional area change	0.38 (0.07)	0.40 (0.34–0.44)
Intensive care unit stay (days)	5 (8)	3 (1–4)
Total hospital stay (days)	26 (21)	21 (16–30)
Karnofsky scale at discharge	75 (31)	90 (70–95)
Zubrod scale at discharge	2 (1)	1 (1–3)
	N	**%**
Acute kidney injury	4	30.8
Renal replacement therapy	4	30.8
New-onset atrial fibrillation	2	15.4
Access site injury	1	7.7
Tricuspid valve replacement	1	7.7
Postoperative ECMO support	1	7.7
Tricuspid valve regurgitation at discharge		
Absent	4	30.8
Mild	5	38.5
Moderate	3	23.1
Severe	1	7.7
30-day mortality	0	0

4. Discussion

In the current era, the landscape of infective endocarditis has dramatically changed. Implanted cardiovascular devices have increased exponentially, as well as the clinical complexity of patients [1,18]. The presence of an intravascular foreign material is the most important predisposing factor for early or late microorganism colonization, an issue that can be only partially controlled by improved implantation techniques and device technologies. In fact, early CDRIE can affect more than 10% of patients, especially in the older age groups [19], and the risk of late CDRIE cumulates every year from implantation [1]. Prompting the removal of the infected device can impact the patient's outcome positively [20], particularly when a systemic infection is present. However, large vegetations and septic status require further surgical consideration.

At our institution, the strict and valuable collaboration between electrophysiologists and cardiac surgeons has been translated into a multidisciplinary approach to complex CDRIE [17]. Given the promising efficacy and safety of the AngioVac system for the treatment of life-threatening intracardiac masses [16,21–23], we incorporated this device in our decisional algorithm of CDRIE (Figure 1), as a valid alternative to conventional surgery. In our experience, we performed a total of 13 percutaneous vacuum-assisted removals of large CDRIE vegetations using the AngioVac system, with encouraging results.

Our treated population was mainly composed of individuals who were implanted with ICD or CRT-D for primary or secondary prevention of cardiac adverse events. This aspect underlines the intrinsic fragility of our cohort of patients, in whom a previous cardiac arrest or chronic congestive heart failure affected more than half of the individuals (Table 1). In this setting, infected lead extraction and related risk of embolization can be poorly tolerated and may precipitate dramatically. Many authors attempted to quantify the risk of pulmonary embolization during these procedures but reported rates are sparse, ranging from 0 to 55% [24–27]. Different imaging techniques and thresholds for the definition of significant pulmonary embolization can partially account for this inhomogeneity of data. Moreover, a linear correlation between the risk of embolization and lead vegetation size has not been demonstrated [28,29]. Recently, Caiati et al. concluded that CDRIE vegetation size is not a determinant of postoperative outcomes of percutaneous lead extraction [29]. However, the maximal dimension of vegetations was below 10 mm in most of the patients in their analysis. Thus, these results can hardly be translated into our cohort, where vegetations measured up to 40 mm on average (Table 1). We speculate that the paradigm of vegetation size as a prognostic predictor in valvular infective endocarditis [30] can be applied to our treated population, in whom a surgical consideration before extraction was mandatory to guarantee a safe lead extraction.

Although a clear benefit of vacuum-assisted debulking of lead vegetations over a conventional percutaneous extraction has not yet been proven [9], the preliminary results of the AngioVac system for the aspiration of intracardiac masses are promising [16]. Successful removal rates vary depending on the specific origin and location of the mass, ranging between 60 and 80% in larger registries and series [16,31]. However, when considering CDRIE vegetations debulking, procedural success is >90% in most of published reports [7,11–13,32]. In a recent multi-center cohort including 101 patients, Starck et al. proved a percutaneous vacuum-assisted aspiration to be completely successful in 94% of CDRIE [13], similarly to conventional TLE procedures [33]. Our work aligns with these outstanding results, with 12/13 successful procedures (92.3%). The only patient in whom a partial debulking (50%) was performed due to an unsatisfactory alignment of the first-generation aspiration cannula (with a straight tip) with the tricuspid valve could now benefit from the most recent cannula's designs. In fact, the third-generation AngioVac cannulas can mount 20° and 180° angled tips, which further enhance the mobility and adaptability of the system (Video S1). Moreover, we suggest that a dual approach using two different aspiration accesses (RFV + RIJV) might allow a complete suction of the vegetation, particularly when the femoral approach does not consent a satisfactory targeting of the

mass. In our experience, this strategy permitted a successful mass debulking in one patient, when the third-generation cannulas were not available.

Intraoperative complications commonly related to the AngioVac procedure entail cardiac perforation, valve damage, arrhythmias, access sites injury, and mass fragmentation with subsequent embolization [16,31]. As previously stated, these events could rapidly lead to circulatory collapse in fragile patients. Moreover, CDRIE could be associated with septic status, a condition in which a venous–venous bypass could be poorly tolerated [13]. The Indigo Thrombectomy system (Penumbra Inc, Alameda, CA, USA) is an alternative percutaneous cannula that has been adopted to suction lead vegetations in hemodynamically unstable patients because it does not require an extracorporeal venous–venous bypass [34]. However, the inability to return blood to the patient generates considerable blood loss during the procedure [34].

To overcome all these issues, we opted for the AngioVac system and we tailored the extracorporeal circuit configuration to the patient's preoperative hemodynamic status, cardiac performance, and the characteristics of the vegetations (Figure 1). Thanks to the exceptional versatility of the AngioVac system, the extracorporeal circuit can be adapted to the patient's needs simply by moving the reinfusion cannula from a venous to an arterial vessel and interposing an oxygenator. In relatively low-risk patients, with preserved respiratory and cardiac function and affected by smaller vegetations, we routinely adopted the standard venous–venous bypass (six cases, 46.2%). In case of respiratory compromise of any kind, we included an oxygenator in the circuit (five cases, 38.5%), realizing a venous–venous ECMO-like configuration. This design guarantees that oxygenated blood is returned to the patient, supporting his/her ventilatory function that could be further impaired by fluid administration and hemodilution during the procedure. Finally, when cardiac performance is affected, in the case of septic status, or if extremely mobile and large vegetations are at high risk of massive pulmonary embolization, we chose a venous–arterial ECMO-like configuration (two patients, 15.4%) that can provide full hemodynamic support. Although an arterial reinfusion has rarely been adopted in larger cohorts treated with the AngioVac system (3.8% of cases in the RAPID registry [16]), we consider this approach a valid option to treat patients with prohibitive surgical risk safely, bypassing the well-known limitations of the standard venous–venous circuit. In the multi-center experience reported by Starck et al. (in which a venous–venous configuration was used in all cases), two of the three major complications that occurred during the CDRIE vegetation debulking were hemodynamic collapses of patients [13]. We speculate that planning a venous–arterial ECMO-like configuration in high-risk patients has the potential to further minimize this complication, guaranteeing adequate circulatory support during the aspiration maneuvers.

With this strategy, we reported a very low intraoperative complication rate (7.7%), which is consistent with the previous series [11–13,15,32]. Similarly, 30-day mortality was absent and postoperative complications directly device-related affected only a small percentage of patients (Table 4). Particular consideration during lead extraction should be given to preserving the tricuspid valve competence, to avoid the need for a subsequent reparative open surgery. George et al. observed a considerable rate (43.5%) of worsening regarding the severity of regurgitation after the procedure [32], which can be related to both the initial vacuum-assisted vegetation debulking and the lead extraction per se. In our experience, tricuspid regurgitation remained stable or slightly improved in all cases, underlying the presence of both a mechanism of mass interference with leaflet coaptation and an intrinsic valve disease (mainly due to annular dilatation and leaflet damage by leads and CDRIE). In only one case, tricuspid regurgitation remained severe after infected lead extraction, requiring surgical replacement. We herein support the safety of the AngioVac device in also avoiding tricuspid valve damage during mass debulking in CDRIE.

5. Limitations

The main limitations of our work are the small number of treated patients, its retrospective design, and the lack of a control population, although larger single-center

experiences with the AngioVac system in CDRIE are rare. A specific sub-analysis of the ongoing prospective RAPID registry [16] is hoped to give better insight into the role of vacuum-assisted debulking of vegetations before lead extraction. Finally, further data are needed to prove the efficacy and safety of the venous–arterial ECMO-like configuration of the AngioVac system on a larger scale.

6. Conclusions

The AngioVac system represents a promising effective option for large vegetation debulking before infected lead extraction in CDRIE. The extracorporeal circuit design can be tailored to the patient's hemodynamic status, cardiac performance, and vegetations characteristics. With this strategy, we reported an excellent successful removal rate, with a concomitant acceptable intraoperative complication rate. A percutaneous vacuum-assisted infected lead extraction emblematizes the valuable collaboration between electrophysiologists and cardiac surgeons in managing high-risk CDRIE.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11154600/s1, Video S1. A case of CDRIE treated with the AngioVac system.

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Data Availability Statement: Data available on request to the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

CDRIE	cardiac device-related infective endocarditis
CRT-D	cardiac resynchronization therapy-defibrillator
ECMO	extracorporeal membrane oxygenation
ICD	implantable cardioverter-defibrillator
IQR	interquartile range
LFV	left femoral vein
PM	pacemaker
RFV	right femoral vein
RIJV	right internal jugular vein
SD	standard deviation

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Clinical Management of New-Onset Atrial Fibrillation in COVID-19 Patients Referred to a Tertiary Cardiac Arrhythmia Center after Hospital Discharge

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Abstract: Background: Available reports on the post-discharge management of atrial fibrillation (AF) in COVID-19 patients are scarce. The aim of this case series was to describe the clinical outcomes of new-onset AF in COVID-19 patients referred to a tertiary cardiac arrhythmia center after hospital discharge. Methods: All consecutive patients referred to our center for an ambulatory evaluation from 18 May 2020 to 15 March 2022 were retrospectively screened. Patients were included in the current analysis if new-onset AF was diagnosed during hospitalization for COVID-19 and then referred to our clinic. Results: Among 946 patients, 23 (2.4%) were evaluated for new-onset AF during COVID-19. The mean age of the study cohort was 71.5 ± 8.1 years; 87.0% were male. Median time from COVID-19 discharge and the first ambulatory evaluation was 53 (41.5–127) days; median follow-up time was 175 (83–336) days. At the in-office evaluation, 14 (60.9%) patients were in sinus rhythm, and nine patients were in AF. In 13.0% of cases, oral anticoagulation was stopped according to CHADS-VASc. Eight patients in AF were scheduled for electrical cardioversion; one patient was rate-controlled. Four patients were treated with catheter ablation (CA) during follow-up. Two post-cardioversion AF recurrences were detected during follow-up, while no recurrences were diagnosed among patients who underwent CA. Conclusion: Our data suggest that AF may not be considered as a simple bystander of the in-hospital COVID-19 course. Management of new-onset AF in post-COVID-19 patients referred to our clinic did not significantly differ from our usual practice, both in terms of long-term oral anticoagulation and in terms of rhythm control strategy.

Keywords: atrial fibrillation; COVID-19; cardiac arrhythmias; rhythm monitoring; catheter ablation

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1. Introduction

In addition to an established respiratory involvement [1,2], a significant myocardial injury in Coronavirus disease (COVID-19) has been ascertained, often triggered by macro- and microthrombosis, as well as by direct cardiac damage [3–10]. Indeed, as a consequence, cardiac arrhythmias and acute coronary syndromes (ACS) have been widely reported as potential issues, especially in hospitalized patients, often worsening COVID-19 patients' prognosis [11–18]. In particular, in up to 44% of COVID-19 patients admitted to the intensive care unit (ICU), brady- and tachyarrhythmias were detected, and thus, up to 17.6% of admitted patients experienced atrial fibrillation (AF) [4,19]. Of the total 9564 patients included in this study from Mountantonakis et al., 1687 (17.6%; 95% CI 16.9–18.4%) experienced AF during hospitalization; among these, 1109 patients (65.7%; 95% CI 63.4–68.0%)

had new-onset AF [19]. Moreover, it has been progressively highlighted that AF, and particularly new-onset AF, is an independent predictor of in-hospital mortality, when compared to patients with a history of AF [19]. Interestingly, it has emerged that the presence of structural heart disease was not associated with a higher risk of in-hospital mortality in patients developing AF, suggesting that new-onset AF is independent from any previous cardiac disorder, either structural or arrhythmogenic [19]. Nevertheless, if it has been reported that many people with mild–moderate disease recover within 2 weeks, a certain amount of patients do not return to baseline even after 14–21 days, and possibly develop the so-called "post-COVID-19 syndrome", with a non-negligible involvement of the cardiovascular system [20]. Several longitudinal studies on the Post-Acute COVID-19 Syndrome have been summarized in a review from Dixit et al. [21], who have reported that the rate of COVID-19 cardiovascular patients' rehospitalizations may significantly vary, being up to 15.1% [22]. Indeed, the rise in post-COVID 19 cardiac manifestations is expected to have detrimental consequences for the prevalence and economic projections of the cardiac patient, with atrial tachyarrhythmias and AF representing a significant part of the entire spectrum. To date, available reports on new-onset AF in COVID-19 are mainly focused on the arrhythmic in-hospital management; therefore, the aim of this case series was to describe the clinical outcomes of new-onset atrial fibrillation in COVID-19 patients referred to a tertiary cardiac arrhythmia center after hospital discharge.

2. Methods

2.1. Study Population

All consecutive patients referred to our tertiary cardiac arrhythmia center (Luigi Sacco University Hospital, Milan, Italy) for an ambulatory evaluation from 18 May 2020 (date of the first lockdown ending in Italy) to 15 March 2022 were retrospectively screened. Patients were included in the current analysis if new-onset AF was diagnosed during hospitalization for COVID-19 and then referred for a subsequent clinical evaluation in our arrhythmia center clinic after discharge. Patients with a previous history of AF were excluded from the current analysis. Patients' follow-up and further clinical evaluations or intervention were left to physicians' and patients' choice.

2.2. Data Collection and Study Outcomes

Baseline demographic and clinical characteristics, as well as patient treatment and clinical outcome data, were obtained from in-hospital electronic medical records. All data were retrospectively analyzed. First-diagnosed or new-onset AF was defined according 2020 European Guidelines [23]. A confirmed case of COVID-19 was defined by a positive result on a reverse-transcriptase polymerase chain reaction (RT-PCR) assay performed on a nasopharyngeal swab, according to the World Health Organization (WHO) guidelines. This study was conducted in accordance with the Declaration of Helsinki. Outcomes of the current analysis were:

- Clinical management of new-onset AF in the study cohort;
- AF recurrence after physician intervention in the follow-up period.

2.3. Data Collection and Study Outcomes

Categorical variables were reported as counts (percentage). Normality of distribution was tested for all continuous variables using a Shapiro–Wilk test. Continuous variables are reported as mean standard deviation (s.d.) or as median (IQR, interquartile range) if normally or nonnormally distributed, respectively. All statistical analyses were performed using STATA version 14.0 (Stata Corp, College Station, TX, USA).

3. Results

3.1. Baseline Characteristics

Among 946 patients referred to our tertiary cardiac arrhythmia center for an ambulatory visit from 18 May 2020 to 15 March 2022, 23 patients (2.4%) were evaluated after

hospital discharge for new-onset AF detected during COVID-19 hospitalization. Characteristics of the study cohort are reported in Table 1. Overall, the mean age of the entire study cohort was 71.5 ± 8.1 years; 20 patients (87.0%) were male. As for cardiovascular risk factors, 14 (60.9%) and 2 (8.7%) patients suffered from hypertension and diabetes, respectively, while, as for history of previous cardiac disease, two patients (8.7%) had a previous history of cardiomyopathy, with an ischemic etiology in both cases, resulting in heart failure (HF) with reduced ejection fraction in one case. When considering significant comorbidities, three patients (13.0%) showed vascular diseases, with a history of stroke/TIA in one case; two patients (8.7%) suffered from CKD. The median CHA2DS2-VASc score was 2 (1–3), while the median HAS-BLED score was 2 (1–2), with one patient having a previous history of significant bleeding (gastrointestinal).

Table 1. Characteristics of the study cohort.

	Cohort (*n* = 23)
Age (years), mean ± s.d.	71.5 ± 8.1
Male, *n* (%)	20 (87.0)
Diabetes, *n* (%)	2 (8.7)
Hypertension, *n* (%)	14 (60.9)
Underlying cardiac disease, *n* (%)	2 (8.7)
Ischemic cardiomyopathy, *n* (%)	2 (8.7)
HFrEF, *n* (%)	1 (4.3)
Vascular disease, *n* (%)	3 (13.0)
LA volume index (ml/m^2), median (IQR)	22 (18–24)
Moderate to severe MR, *n* (%)	1 (4.3)
History of stroke/TIA, *n* (%)	1 (4.3)
CKD, *n* (%)	2 (8.7)
CHA_2DS_2-VASc, median (IQR)	2 (1–3)
CHA_2DS_2-VASc < 2 (female) or < 1 (male), number of patients (%)	3 (13)
HAS-BLED, median (IQR)	2 (1–2)
Previous history of major bleeding, *n* (%)	1 (4.3)
Need for ICU hospitalization, *n* (%)	0 (0)
Need for CPAP during COVID-19 admission, *n* (%)	4 (21.7)
Anticoagulation at discharge, *n* (%)	21 (91.3)
DOACs, *n* (%)	19 (82.6)
LMWH, *n* (%)	2 (8.7)
Antiarrhythmic drugs at discharge, *n* (%)	11 (47.8)
Amiodarone, *n* (%)	8 (34.8)
Flecainide, *n* (%)	3 (13.0)
Cardioversion during admission, *n* (%)	16 (69.6)
VAs during COVID-19 admission, *n* (%)	1 (4.3)
Time from discharge to first ambulatory evaluation (days), median (IQR)	53 (41.5–127)
Follow-up time (days), median (IQR)	175 (83–336)
Patients monitored with an ILR, *n* (%)	15 (65.2)
ILR implanted during admission, *n* (%)	10 (43.5)
ILR implanted during post-discharge follow-up, *n* (%)	5 (21.7)

Abbreviations: CKD = chronic kidney disease; DOACs = direct anticoagulants; HFrEF = heart failure with reduced ejection fraction; ICU = intensive care unit; ILR = implantable loop recorder; IQR = interquartile range; LA = left atrial; LMWH = low-molecular-weight heparin; s.d. = standard deviation; MR = mitral regurgitation; TIA = transient ischemic attack.

3.2. Patient Management and Clinical Outcomes

All patients were admitted due to COVID-19 in our institution, with no patient needing intensive care unit (ICU) admission. During admission, in 16 (69.6%) cases, the arrhythmia terminated during admission for a spontaneous, pharmacological, or electrical cardioversion. Twenty-one (91.3%) patients were discharged on oral anticoagulation treatment (19 patients on direct anticoagulants (DOAC) and 2 patients on low-molecular-weight heparin), while in two cases, no long-term anticoagulation treatment was started. In 11 (47.8%)

cases, an antiarrhythmic drug treatment was set up, mostly with amiodarone. Fifteen (65.2%) patients were implanted with an implantable loop recorder (ILR) to evaluate the arrhythmic burden; among those, 10 patients underwent ILR implantation during the in-hospital admission, while five patients were scheduled to implant an ILR after the post-discharge in-office evaluation.

The median time from COVID-19 discharge to the first ambulatory evaluation was 53 (41.5–127) days. At the time of the in-office evaluation, 14 (60.9%) patients were in sinus rhythm, while nine patients were in AF. As per current guidelines for the management of AF [23], in three (13.0%) cases (all in sinus rhythm), oral anticoagulation was stopped (in all cases, at least 4 weeks after AF onset), with two patients showing CHADS-VASc score = 0 and one patient showing CHADS-VASc score = 1 (female sex). In 1 out of 2 patients who were not on anticoagulant therapy at discharge, a DOAC therapy was started in-office, due to CHADS-VASc score = 3; all patients on low-molecular-weight heparin were shifted to DOACs. Regarding rhythm control management, 8 out of 9 patients in AF were scheduled for an electrical cardioversion, while in one patient, a rate control strategy was chosen. Four patients were treated with catheter ablation (CA) during follow-up: one with a laser-balloon technique with pulmonary vein isolation (PVI) and three with radiofrequency CA (two patients underwent PVI, while one patient underwent PVI + posterior wall isolation due to persistent AF). During the follow-up time (median 175 (83–336) days), among the 14 patients who were in sinus rhythm at the first clinic evaluation, five patients experienced at least one AF recurrence. Moreover, two post-cardioversion AF recurrences were detected during follow-up, while no recurrences were detected among patients who were treated with CA. The clinical management of the study cohort is summarized in Figure 1. A three-dimensional bipolar voltage map of the left atrium after radiofrequency CA of persistent AF is shown in Figure 2.

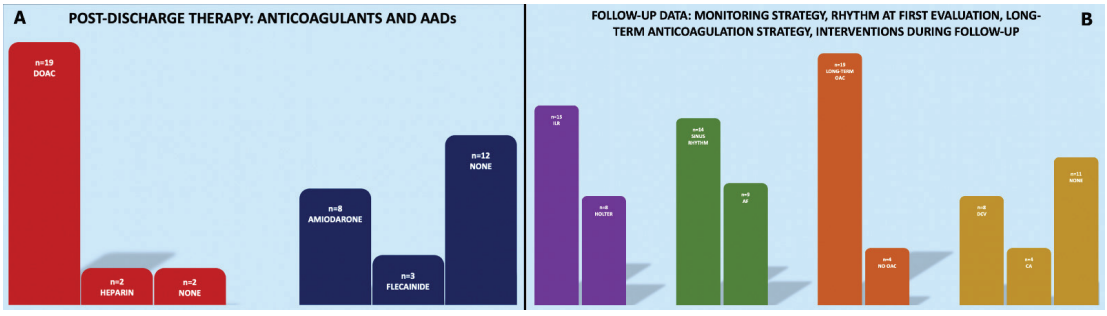

Figure 1. Clinical management of the study cohort: post-discharge therapy (**A**) and follow-up data (**B**). (**A**) Red bars summarize anticoagulant therapy at discharge: 19 patients were discharged on direct oral anticoagulants (OAC), 2 patients were discharged on heparin, and 2 patients were discharged without anticoagulation. Blue bars summarize antiarrhythmic drug (AAD) therapy at discharge: 8 patients were discharged on amiodarone, 3 patients were discharged on flecainide, and 12 patients were discharged without AADs. (**B**) Purple bar summarizes the rhythm monitoring strategy that was chosen at discharge: 15 patients were followed up with an implantable loop recorder (ILR), either implanted during admission or implanted during follow-up, while 8 patients were followed up with periodic Holter-ECG evaluations. Green bars summarize patients' cardiac rhythms at the first in-clinic evaluation: 14 patients were in sinus rhythm, while 4 patients were in AF. Orange bars summarize clinical choices regarding OAC: in 19 patients, a long-term OAC strategy was started, while in 4 cases, OAC was terminated. Yellow bars summarize any intervention during follow-up: 8 direct cardioversions (DCV) and 4 catheter ablations (CA) were performed.

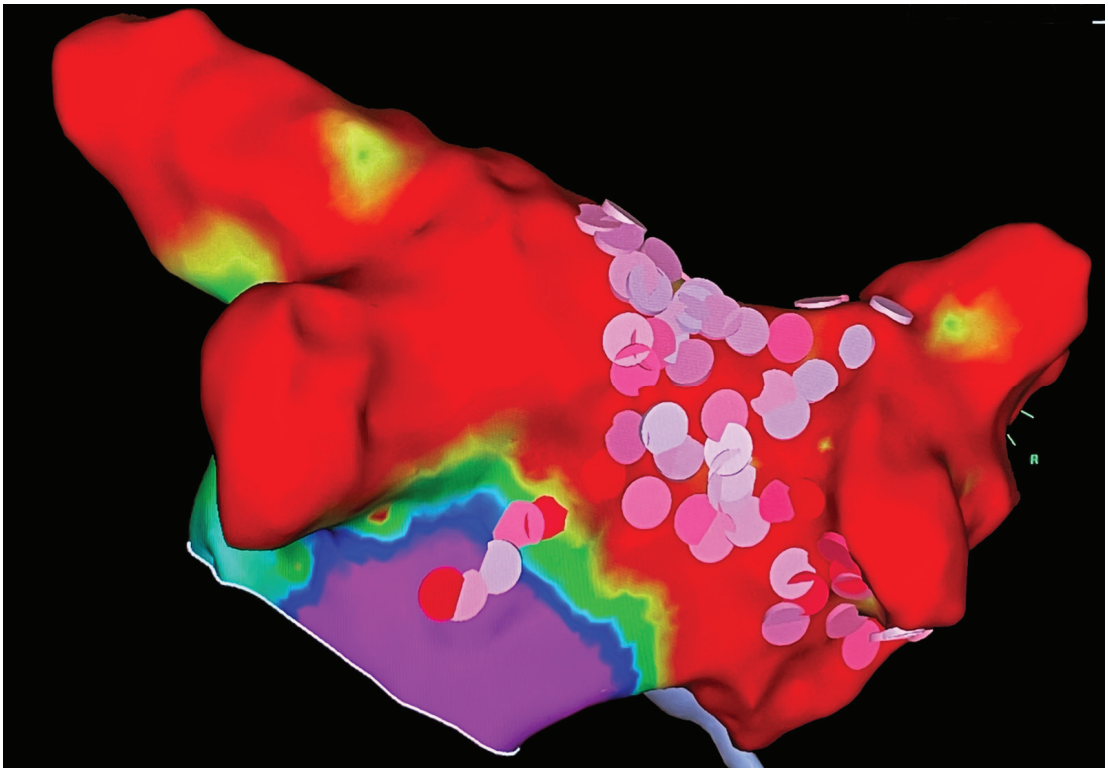

Figure 2. Three-dimensional bipolar voltage map of the left atrium after radiofrequency catheter ablation of persistent AF; pink dots indicate radiofrequency pulses on the posterior wall.

4. Discussion

In this case series of patients referred to our tertiary cardiac arrhythmia for first-diagnosed AF in COVID-19, AF management was neither limited nor strictly related to the course of the disease itself. Indeed, 60.1% of the entire cohort were either in AF at the first post-discharge in-office evaluation or experienced at least one AF recurrence during follow-up. Moreover, 52.2% of the entire cohort was either cardioverted or underwent CA during follow-up, and in 87% of cases, an indication of long-term anticoagulation was given by the cardiac electrophysiologist. Therefore, new-onset AF had a significant impact on patients' clinical status, and clinical management did not significantly differ from our usual practice, both in terms of long-term oral anticoagulation and in terms of the rhythm control strategy proposed to these patients.

4.1. Arrhythmogenesis in COVID-19 after the Acute Phase

Several reports have clarified how COVID-19 infection is related to an increased risk of cardiac arrhythmias by several pathophysiological mechanisms, such as myocardial injury (mainly due to hypoxia, ischemia, or direct viral damage) and extracardiac processes (cytokine storm or electrolyte imbalance), that may induce or precipitate cardiac arrhythmias, especially in patients with a pre-existing propensity [24,25]. The predominant COVID-19 manifestation is respiratory involvement, potentially increasing intracellular calcium and potassium levels, which, along with a hyperadrenergic tone, contribute to the development of early and late afterdepolarizations, as well as enhanced cellular excitability and electrical conduction velocity [26]. All these mechanisms that contribute to the arrhythmogenic mechanisms triggering AF are closely related to the acute phase of COVID-19, but

it is not completely understood how they could be responsible for further recurrences or for AF maintenance. However, despite an insufficient understanding of the underlying anatomic and functional basis for AF, it is known that the vulnerable electrophysiological and/or anatomical substrate needed for AF maintenance did not completely match with the triggers needed to initiate AF. Notwithstanding, both parasympathetic and sympathetic stimulation play a role both in triggering and maintaining AF [27] and, in this regard, the emerging concept of COVID-19-induced dysautonomia, which has been linked with the post-COVID syndrome, significantly impairing cardiovascular homeostasis, as witnessed by a significantly lower heart rate variability (HRV) compared to healthy controls, may show a pivotal role also in AF maintenance and recurrences [28,29].

- Apart from hypoxia, SARS-CoV-2's direct penetration into myocardial cells through the receptors of the angiotensin-converting enzyme-2 (ACE-2), as well as activation of virus-triggered CD8+ T lymphocytes, might result in myocardial injury, remodeling, and adverse cardiac outcomes, seen as subclinical or overt myocarditis [30]. Cellular damage, ionic imbalance, and gap junction dysfunction may result in early afterdepolarizations and delayed afterdepolarizations, along with reduced or increased conduction velocity and decreased refractoriness, increasing the likelihood of circus-type reentry [31]. These mechanisms are also of the utmost importance in triggering AF out of the acute phase since inflammation is known to be associated with recurrent AF through the involvement of cellular degeneration, apoptosis, and subsequent atrial fibrosis, which is extremely difficult to determine clinically [27].
- Myocardial ischemia, mostly due to a hyperinflammatory response, microvascular dysfunction, proatherogenic effects, and vasculitis, might induce significant myocardial sequelae, leading also to a non-transient endothelial dysfunction [32,33]. Indeed, a recent growing body of evidence links AF to atrial and systemic endothelial dysfunction. A postulated *liaison* between AF and endothelial dysfunction includes inflammatory or oxidative stress as well as common pathway biomarkers, which might feed a vicious cycle resulting in worse endothelial dysfunction and persistent AF [34].

Finally, when evaluating echocardiographic characteristics, only one patient showed significant (at least moderate) mitral regurgitation, while the LA volume index was overall within normal range. If it is true that this was a globally old cohort, the prevalence of a known cardiovascular disease was low, and this might be the best explanation for these findings. Nevertheless, also a subclinical "atrial cardiomyopathy" may have led these patients to be more susceptible to the development of new-onset AF than others. All these mechanisms, as well as individual susceptibility, might underpin AF onset and lead to recurrences, thus corroborating arrhythmogenesis also outside of the acute COVID-19 phase, as witnessed in our case series.

4.2. Long-Term Management of New-Onset AF Detected during COVID-19

As previously described, several risk factors have been regarded as triggers for the development of new-onset AF in COVID-19, not accounting for only the inflammatory state, as in septic patients. Indeed, several reports have determined how new-onset AF may occur in up to 20% of patients suffering from sepsis and 46% from septic shock, while it might aggravate the course of up to 30–50% of patients who underwent cardiothoracic surgery [35]. When considering indications for post-discharge oral anticoagulation in this setting, it has been described how most patients who developed new-onset AF were not anticoagulated at the time of discharge [35]. Indeed, although specific indications and guidelines have not been provided so far, most recent guidelines for AF highlight that in patients at risk of stroke, anticoagulation is recommended to be continued long-term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the characterization of AF as a first-diagnosed episode [23]. However, although clinical outcomes of new-onset AF are less favorable than paroxysmal AF [36], prescription rates are the lowest in patients with first-diagnosed AF [37]. To date, no specific data regarding long-

term anticoagulation in patients with new-onset AF and COVID-19 have been published. Thus, in our case series, the choice of long-term anticoagulation was always based on the CHA2DS2-VASc score and bleeding risk, as per the latest guidelines, and AF was never considered a mere infection-related epiphenomenon. DOACs were the preferred strategy in all cases, due to their favorable pharmacological profile, and physicians also based their clinical choice on the available data in this setting (although scarce), considering DOACs as the safest approach in managing non-valvular AF during the COVID-19 pandemic [38,39]. No significantly ischemic or hemorrhagic events were detected in the study cohort during follow-up.

- Regarding the antiarrhythmic strategy, a rate versus a rhythm control strategy was chosen depending on the managing physician's choice and patient preferences as well. When considering patients who were still in AF during the post-discharge evaluation, the vast majority of patients were referred to a rhythm control strategy due to the well-known lower risk of adverse cardiovascular outcomes among patients with early AF treated with a rhythm control strategy, especially in cases of associated cardiovascular conditions [40]. The only case that was treated with a rate control strategy was an elderly patient who refused to be scheduled for an electrical cardioversion. Criteria for CA were based on a shared decision-making process, always summarizing baseline clinical characteristics and patients' wishes. Age, comorbidities as well as AF burden (whenever possible in patients who were implanted with a loop recorder), and patients' symptoms were always evaluated prior to CA. CA was offered whenever the managing physician thought CA would be the best treatment option, even in light of recent trials (EAST-AF-4 net, EARLY-AF, and STOP-AF) that have demonstrated the superiority of early rhythm control over rate control [40–42]. Of course, patients' wishes were always taken into account, and only patients who had chosen CA as the best treatment option according to the benefit/risk ratio were treated with CA. Most patients who were treated with direct cardioversion were offered CA too, but they preferred to try to achieve rhythm control with a non-invasive strategy. Regarding the four cases who were referred for CA, physician choice was based on the presence of an underlying cardiac disease and/or on at least one cardiovascular risk factor, in order to improve clinical outcomes. Moreover, 3 out of 4 patients experienced at least one post-discharge AF recurrence (preferably detected with an ILR strategy, allowing a better recognition of arrhythmic episodes [43]), while one case was a persistent AF patient who experienced an early recurrence after an in-hospital electrical cardioversion. If it is indeed true that our small sample size does not allow us to make proper comparisons, no AF recurrences were detected in the post-CA group, while two recurrences were detected in the post-cardioversion group, corroborating recent evidence pointing towards the superiority of CA when compared to a drug-related rhythm control strategy in achieving freedom from AF, even in an early-AF setting [40–42,44]. Of note, as per current good clinical practice, all CA procedures were performed out from the infective state, at least 3 months after discharge.

4.3. Limitations

This case series presents several limitations. First, this was a purely retrospective analysis, significantly hampered by the small sample size. Second, several patients who might have developed AF during in-hospital admission might have not been referred to our arrhythmology clinic for a specific follow-up and therefore their clinical management strategy may have differed significantly when compared to our approach. Third, our small cohort did not include ICU patients, who are known to experience infection-related arrhythmia more frequently than non-severe patients due to several risk factors. Fourth, we did not include patients with new-onset AF during COVID-19 at home, which is very difficult to diagnose and examine. Fifth, despite including only patients that were not already been diagnosed with AF, we acknowledge that there may be a bias related to the inclusion of patients that may have already suffered from previous asymptomatic

and unknown AF episodes at the time of the first evaluation. Sixth, we are not able to provide complete details of the vaccination status of all patients. Nevertheless, due to the wide enrollment timeframe, we expected that the vaccination status was very variegated, ranging from non-vaccinated patients hospitalized during the first phase, to fully vaccinated patients that were included later. Moreover, even if we acknowledge that the latest reported data are pointing towards a possible correlation between the COVID-19 vaccine and AF [45], these data come from an extremely large registry and thus such correlations would be impossible on our limited sample size. On the other hand, it should be underlined that we included only patients with new-onset AF detected during COVID-19 hospitalization, so that a link between new-onset AF and vaccination may be reasonably excluded.

5. Conclusions

Our data suggest that COVID-19 may trigger or reveal AF in vulnerable patients, who may frequently experience AF recurrences during follow-up. Therefore, AF should not be considered as a simple bystander of the in-hospital COVID-19 course. Management of new-onset AF post-COVID-19 patients referred to our specialistic electrophysiology clinic resembles our usual clinical practice, both in terms of long-term oral anticoagulation indications and in terms of rhythm control strategy.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

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Long-Term Follow-Up of Catheter Ablation for Premature Ventricular Complexes in the Modern Era: The Importance of Localization and Substrate

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Abstract: Background: Large-scale studies evaluating long-term recurrence rates in both idiopathic and non-idiopathic PVC catheter ablation (CA) patients have not been reported. **Objective:** To evaluate the efficacy and safety of idiopathic and non-idiopathic PVC CA, investigating the predictors of acute and long-term efficacy. **Methods:** This retrospective multicentric study included 439 patients who underwent PVC CA at three institutions from April-2015 to December-2021. Clinical success at 6 months' follow-up, defined as a reduction of at least 80% of the pre-procedural PVC burden, was deemed the primary outcome. The secondary aims of the study were: clinical success at the last available follow-up, predictors of arrhythmic recurrences at long-term follow-up, and safety outcomes. **Results:** The median age was 51 years, with 24.9% patients being affected suffering from structural heart disease. The median pre-procedural PVC burden was 20.1%. PVCs originating from the RVOT were the most common index PVC observed (29.1%), followed by coronary cusp (CC) and non-outflow tract (OT) LV PVCs (23.1% and 19.0%). The primary outcome at 6 months was reached in 85.1% cases, with a significant reduction in the 24 h% PVC burden (−91.4% [−83.4; −96.7], $p < 0.001$); long-term efficacy was observed in 82.1% of cases at almost 3-year follow-up. The presence of underlying structural heart disease and non-OT LV region origin (aHR 1.77 [1.07–2.93], $p = 0.027$ and aHR = 1.96 [1.22–3.14], $p = 0.005$) was independently associated with recurrences. **Conclusion:** CA of both idiopathic and non-idiopathic PVCs showed a very good acute and long-term procedural success rate, with an overall low complication. Predictors of arrhythmic recurrence at follow-up were underlying structural heart disease and non-OT LV origin.

Keywords: catheter ablation; premature ventricular complexes; arrhythmic recurrences; clinical outcomes; complications

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1. Introduction

In common clinical practice, premature ventricular complexes (PVCs) are one of the most frequently encountered cardiac arrhythmia. Besides being related to potentially debilitating symptoms, PVCs are common in patients with LV dysfunction and are often organized as runs of non-sustained ventricular tachycardia (NSVT). PVCs may represent the consequence or the cause of LV dysfunction or dilation, with a burden of >24% that has been shown to be independently associated with PVC-induced cardiomyopathy [1]. Single-center studies have demonstrated that catheter ablation (CA) is superior to pharmacological

therapy in decreasing PVC burden and improving cardiac function [2,3], but these findings are mostly based on small-sample-size studies, as summarized in a meta-analysis from Zang et al. [4] on this topic. This report has outlined how CA of frequent PVCs improves cardiac function, especially in patients with LV dysfunction. The safety and efficacy of CA has then been confirmed in one large-scale trial from Latchamsetty et al., retrospectively enrolling 1185 idiopathic PVC patients [5]. Nevertheless, Holter ECG monitoring at follow-up was not available in all patients in this study; thus, complete data to assess procedural efficacy were reported in 490 patients. It is known that the highest success rate, along with the lowest peri-procedural complication rate, is observed in patients with PVCs originating from the RVOT, followed by PVC arising from the LVOT. However, few data on the relationship between specific PVC sites of origin and CA clinical outcomes are currently available, with no specific report addressing CA of PVCs arising from the coronary cusps (CC). Besides CC, data on the clinical outcomes of PVC CA arising from other non-OT locations are scarce as well, the main reason being that those are typically challenging locations, such as the LV summit and papillary muscles, due to their anatomy. The LV summit is the highest portion of the LV epicardium, being located near the left main coronary artery, and may account for up to 14.5% of LV ventricular arrhythmias (VAs), according to some reports [6]. Moreover, the papillary muscles are also a well-known source of VAs in both structurally normal and abnormal hearts, with PVCs arising from this location potentially playing a role in triggering even ventricular fibrillation [7]. Therefore, the purpose of this real-world study was to evaluate efficacy, clinical outcomes, and procedural complications of both idiopathic and non-idiopathic PVC CA, stratified for sites of origin, and to determine the predictors of acute and long-term efficacy.

2. Materials and Methods

2.1. Patient Population

All consecutive patients undergoing catheter-based PVC ablation at three tertiary centers for cardiac electrophysiology (EP) (IRCCS Ospedale San Raffaele, Milan, Italy; Luigi Sacco University Hospital, Milan, Italy; University Hospital "Lancisi-Salesi", Ancona, Italy) from April 2015 to December 2021 were retrospectively enrolled in this observational multicenter study. The study was approved by the Local Institutional Review Board and complies with the Declaration of Helsinki.

2.2. Procedural Details

All antiarrhythmic drugs were withdrawn at least 3 days prior to the procedure. Three-dimensional electroanatomical mapping and pace mapping with Carto System (Biosense Webster Inc., Irvine, CA, USA) or EnSite NavX Endocardial Solutions System (St. Jude Medical, Inc., St. Paul, MN, USA) were used to detect the earliest ectopic ventricular activation. Activation mapping was used if PVCs occurred frequently enough, otherwise the CA procedure relied mostly on pace mapping. If few PVCs were observed at baseline, and there was a consistent documentation of significant pre-procedural PVC burden, intravenous administration of isoproterenol and/or programmed ventricular stimulation was performed to try to induce ventricular arrhythmias and then compared to the baseline PVC. When endocardial mapping was not satisfactory, a mapping catheter was advanced via the CS to obtain an epicardial map from the great cardiac vein (GCV) or anterior interventricular vein (AIV). An irrigated-tip ablation catheter was used to perform radiofrequency (RF) lesions. Catheter choice and the use of robotic magnetic navigation system was left to the operator's discretion, as well as the use of ablation index to guide CA. The need to perform coronary angiography during CA for PVC arising from the LV summit was also left to the electrophysiologist's discretion. Whenever ablation from the GCV was needed, RF was delivered for a maximum of 20 W per 30 s, and RF was stopped earlier in case of sudden drops of impedance and/or PVC sudden interruption. For left-sided procedures, either via a transeptal access or via a retroaortic approach, heparin boluses were administered to maintain an activated clotting time $\geq$300 s during the whole procedure.

After ablation, the "watching time" was set at 30 min to ensure procedural success, which was defined as the disappearance or the non-inducibility of the targeted PVC.

2.3. Data Collection and Follow-Up Strategies

All data were collected into a centralized, anonymized spreadsheet. Demographics and cardiovascular comorbidities were assessed for all patients enrolled in the study. Additionally, a 12-lead ECG capturing the index PVC both in precordial and peripheral leads and a 24-ECG Holter retrieved in all patients prior to the index ablation procedure were analyzed. For PVC characterization, the following data were collected: 24 h% burden; number of couplets/24 h; number of triplets; PVC QRS duration (in ms); and PVC coupling cycle (in ms). In accordance with PVC morphology, axis, and final ablation site, PVC origin was determined. PVCs were then grouped into 5 classifier groups, as follows: (a) CC PVC; (b) left ventricular outflow tract (LVOT) PVC; (c) non-outflow tract LV (non-OT LV) PVC; (d) right ventricular outflow tract (RVOT) PVC; (e) non-outflow tract RV (non-OT RV) PVC. Those 5 classifiers were used to group study patients in the study sub-cohorts. After discharge from the index procedure, follow-up strategies were at the discretion of a single physician, with most patients being first evaluated at 6 months' follow-up (first follow-up visit). The first evaluation always included a full cardiovascular examination, a 12-lead ECG and a 24 h Holter ECG; otherwise, patients were excluded from the current analysis. Subsequently, all patients were usually evaluated every 12 months thereafter, including a 24 h Holter ECG. Patients who were followed-up for less than 6 months were excluded from this study as well.

2.4. Variable Definitions and Study Outcomes

A patient was deemed to have a structural heart disease in the presence of a diagnosed structural cardiomyopathy (such as ischemic heart disease, myocarditis, non-ischemic cardiomyopathy, and moderate to severe valvular heart disease). Chronic kidney disease (CKD) was defined as a glomerular filtration rate (GFR) < 60 mL/min. The primary outcome of the study was the clinical success of CA at 6 months of follow-up from the index procedure. Consistently with previous studies on this topic [5], the clinical success of CA was defined as a reduction of at least 80% in the pre-procedural 24 h PVC burden at follow-up Holter ECGs. The secondary aims of the study were: (a) to report the rate of clinical success of CA at the last available follow-up assessment; (b) to report the predictors of arrhythmic recurrences at long-term follow-up; (c) safety outcomes deemed as major post-procedural complications, including: vascular access issues (vascular hematoma, pseudoaneurysms, and atrioventricular fistula), pericardial effusion, pericardial tamponade requiring or not requiring pericardiocentesis and/or cardiac surgery, and transient or permanent conduction system damage (i.e., resulting in atrioventricular block).

2.5. Statistical Analysis

All analyses were performed using STATA v.13 (StataCorp LLC, 4905 Lakeway Drive, College Station, TX, USA). Normality of distribution of continuous variables was tested using a Shapiro–Wilk test. Normally and non-normally distributed variables were reported as mean standard deviation (s.d.) and as median (interquartile range (IQR)), as appropriate. Categorical variables were reported as count (percentage). Comparisons of continuous variables among different groups were performed through one-way analysis of variance (ANOVA) or through a Kruskal–Wallis test, according to distribution. Pairwise comparisons between non-normally distributed variables were performed using a pairwise Wilcoxon test. Comparisons of categorical variables were performed using a chi-squared or a Fisher exact test, as appropriate. Survival from arrhythmic recurrence was reported graphically using Kaplan–Meier (KM) curves. Differences between KM curves were assessed through a log-rank test. Pre-specified predictors of arrhythmic recurrence were tested using a univariate Cox regression model and their association to outcomes reported with hazard ratios (HRs). A multivariate Cox regression was then fitted, including all predictors which

were significantly associated with the outcome at univariate analysis. Adjusted hazard ratios were reported (aHRs). A two-tailed $\alpha < 0.05$ was considered statistically significant through the study.

3. Results

3.1. Patient Population

A total of 439 patients were enrolled in the study. The median age at index procedure was 51 [36–62] years and 65.5% of patients were male. The arrhythmic burden at the time of procedure was elevated, with the median% PVC burden being 20.1% [11.6–34.5] and patients presenting a median of 377 [128–668] PVC couplets and 57 PVC triplets at the pre-procedural 24 h Holter ECG assessment. The origin of index PVC was distributed as follows: CC *n* = 101 (23.1); LVOT *n* = 70 (16.0); non-OT LV *n* = 83 (19.0); RVOT *n* = 127 (29.1); and non-OT RV *n* = 56 (12.8). The median PVC QRS duration was 148 [136–157] ms and the PVC coupling cycle was 478 [427–538] ms. A structural heart disease was present in a quarter of the study cohort (*n* = 109, 24.9%), with ischemic cardiomyopathy being the most common etiology (*n* = 44, 10.0%). The complete characteristics of the study population are reported in Table 1.

Table 1. Baseline Characteristics of the Study Cohort.

Study Population (*n* = 437)	
Age (years), median [IQR]	51 [36–62]
Male, *n* (%)	286 (65.5)
Diabetes, *n* (%)	42 (26.9)
HF, *n* (%)	26 (6.0)
Hypertension, *n* (%)	87 (19.9)
CKD, *n* (%)	10 (2.9)
AF, *n* (%)	23 (5.3)
Sport practice, *n* (%)	57 (13.0)
LVEF (%), mean ± s.d.	54.1 ± 9.9
Structural heart disease, *n* (%)	109 (24.9)
PVC localization	
CC, *n* (%)	101 (23.1)
LVOT, *n* (%)	70 (16.0)
Non-OT LV, *n* (%)	83 (19.0)
RVOT, *n* (%)	127 (29.1)
Non-OT RV, *n* (%)	56 (12.8)
PVC QRS length, median [IQR]	148 [136–157]
PVC coupling, median [IQR]	478 [427–538]
Arrhythmic burden	
24 h PVC burden %, median [IQR]	20.1 [11.6–34.5]
N of Couplets, median [IQR]	377 [128–668]
N of Triplets, median [IQR]	57 [24–92]
Palpitations, *n* (%)	274 (62.7)
Pharmacological therapy	
Beta-blockers, *n* (%)	216 (49.4)
Class Ic, *n* (%)	140 (32.0)
Class III, *n* (%)	110 (25.2)

Abbreviations: AF: atrial fibrillation, CC: coronary cusp, CKD: chronic kidney disease, HF: heart failure, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, PVC: premature ventricular complex, RVOT: right ventricular outflow tract.

3.2. Procedural Data

Among the 439 patients enrolled, 354 patients underwent PVC ablation using contact-force Biosense Webster Inc. (Irvine, CA, USA) catheters (mostly Thermocool SmartTouch® catheters), 74 using St. Jude Medical (St. Paul, MN, USA) catheters (mostly the FlexAbility ablation catheter), and 11 using the Stereotaxis Niobe® Robotic Magnetic Navigation System (St. Louis, MO, USA) with catheters based on their contact force systems. Ablation-index-guided procedures were based on Thermocool SmartTouch® catheters. The overall procedural time and fluoroscopy time were 118.9 ± 45.5 min and 30 [20–35] min, respectively, with an average of 317 [180–570] s of RF time. Peri-procedural success was high (97.5%) and complications uncommon (10/439, 2.2%; $n = 1$ pericardial tamponade; $n = 4$ pericardial effusion; and $n = 5$ vascular access complications). Table 2 reports the overall cohort and by their PVC localization peri-procedural characteristics.

Table 2. Procedural Characteristics.

	Overall (n = 437)	CC (n = 101)	LVOT (n = 70)	Non-OT LV (n = 83)	RVOT (n = 127)	Non-OT RV (n = 56)	p Value
Procedure time (min), mean ± s.d.	118.9 ± 45.5	107.5 ± 42.0	124.7 ± 55.0	129.1 ± 44.3	117.6 ± 41.9	120.0 ± 48.1	**0.043**
Fluoroscopic time (min), median [IQR]	30 [20–35]	25 [20–30]	28 [15–40]	30 [25–45]	30 [20–35]	20 [15–35]	**0.002**
Radiofrequency time (s), median [IQR]	317 [180–570]	279 [180–600]	345 [179–575]	378 [200–721]	300 [188–515]	280 [176–580]	0.573
Power (W), mean ± s.d.	42.1 ± 10.6	46.9 ± 9.9	49.2 ± 8.0	43.8 ± 9.9	35.2 ± 8.4	37.3 ± 9.4	**<0.001**
Ablation-index-guided, n (%)	206 (47.1)	51 (50.5)	21 (30.0)	37 (44.6)	77 (60.6)	20 (35.7)	**<0.001**

Abbreviations: CC: coronary cusps; F.U.: follow-up, LVOT: left ventricular outflow tract, OT: outflow tract, RVOT: right ventricular outflow tract. Statistically significant values have been indicated in bold.

3.3. Study Outcomes and Outcome Predictors

The median follow-up of the study was 34 [24–40] months. All patients completed their first follow-up visit. At first follow-up post index procedure, a significant reduction in the PVC burden was observed (median 24 h% burden: 1.5 [0.3–3.0]; median % reduction from baseline: −91.4% [−83.4; −96.7], $p < 0.001$), with 372 (85.1%) patients being free from arrhythmia recurrences. A significant decrease in 24 h% PVC burden was observed independently from PVC localization, but the rate of freedom from recurrences was significantly lower in patients with PVC originating from the non-OT LV area (70.0%), compared to the other localization (CC: 85.1%; LVOT: 88.1%; RVOT: 91.3%; non-OT RV: 92.9; $p < 0.001$). The 24 h% PVC burden and the rates of freedom from recurrences remained stable between the 6-month and last follow-up assessment in the entire cohort (85.1% vs. 82.1%; $p = 0.230$) and in the by-localization groups as well (CC: 88.1% vs. 83.2%, $p = 0.321$; LVOT: 81.4% vs. 80.0%, $p = 0.834$; 70.0% vs. 68.7%, $p = 0.856$; 92.9% vs. 88.2%, $p = 0.415$; 92.9% vs. 89.3%, $p = 0.504$). When evaluating anti-arrhythmic drug (AAD) therapy, the rate of patients on anti-arrhythmic drug (AAD) therapy was as follows: (1) 6-month follow-up: class IC AAD: 13.5%, sotalol 6.6%, amiodarone 5%, and without AAD 74.9%; (2) Last follow-up: class IC AAD 5.7%, sotalol 2.5%, amiodarone 1.8%, and without AAD 90%. The complete outcome data are reported in Table 3. The changes in 24 h% burden over time stratified by PVC localization are reported in Figure 1. By arising zones, freedom from arrhythmias is graphically displayed through the KM curves reported in Figure 2. Table 4 reports the clinical predictors of arrhythmic recurrences at long-term follow-up: the presence of structural heart disease, as well as the area of origin of PVC being the non-OT LV area, were associated with a lower freedom from arrhythmia at the last available follow-up. A higher PVC burden at the time of diagnosis was instead associated with a higher freedom from recurrences at follow-up. These three predictors remained significantly associated with arrhythmic recurrences even at multivariate analysis (aHR 1.96 [1.22–3.14], $p = 0.005$, aHR 1.77 [1.07–2.93], $p = 0.027$, and 0.96 [0.95–0.98], $p < 0.001$, respectively). On the other

hand, the use of AAD during follow-up was not associated with the primary outcome at univariate analysis, as follows: HR 1.12 [0.67–1.87], $p = 0.656$.

Table 3. Study Outcome.

	Baseline	6-mo F.U.			Last F.U.		
	Burden % Median [IQR]	Burden % Median [IQR]	*p*	Procedure Success (%)	Burden % Median [IQR]	*p*	Procedure Success (%)
Overall Cohort ($n = 437$)	20.1 [11.6–34.5]	1.5 [0.3–3.0]	**<0.001**	372 (85.1)	1.1 [0.1–3.1]	0.402	359 (82.1)
CC ($n = 101$)	23.3 [18.0 –34.7]	1.8 [0.4–4.0]	**<0.001**	89 (88.1)	1.8 [0.3–4.0]	0.167	84 (83.2)
LVOT ($n = 70$)	22.1 [12.8–34.9]	1.5 [0.3–2.8]	**<0.001**	57 (81.4)	1.4 [0.2–2.6]	0.330	56 (80.0)
Non-OT LV ($n = 83$)	15.1 [5.8–26.9]	1.5 [0.3–4.0]	**<0.001**	58 (70.0)	1.6 [0.3–3.8]	0.403	57 (68.7)
RVOT ($n = 127$)	20.9 [11.6–34.9]	1.2 [0.2–2.6]	**<0.001**	116 (91.3)	1.2 [0.3–2.6]	0.108	112 (88.2)
Non-OT RV ($n = 56$)	18.2 [11.2–34.2]	2.0 [0.4–2.9]	**<0.001**	52 (92.9)	2.1 [0.4–2.9]	0.345	50 (89.3)

Abbreviations: CC: coronary cusps; F.U.: follow-up, LVOT: left ventricular outflow tract, OT: outflow tract, RVOT: right ventricular outflow tract. Statistically significant values have been indicated in bold.

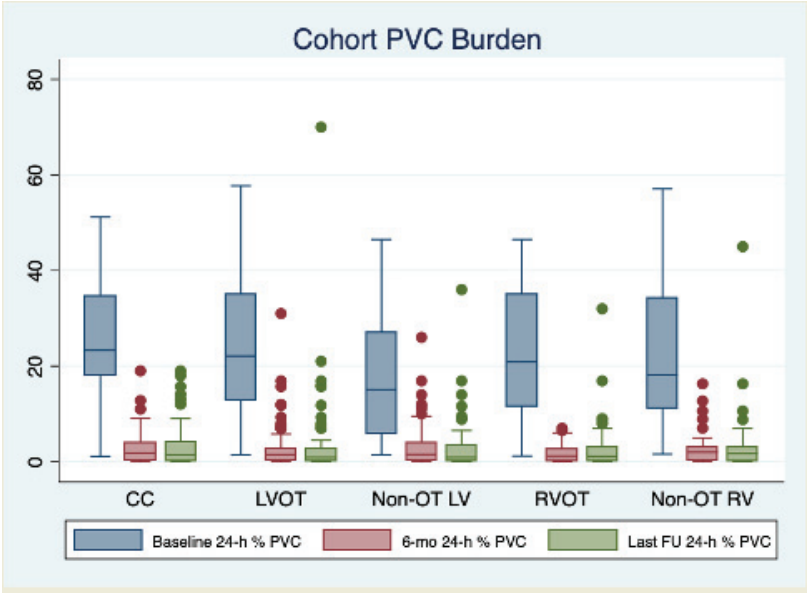

Figure 1. Changes in 24 h% burden over time stratified by PVC localization. Abbreviations: CC: coronary cusps, LV: left ventricle, LVOT: left ventricular outflow tract, OT: outflow tract, RV: right ventricle, RVOT: right ventricular outflow tract.

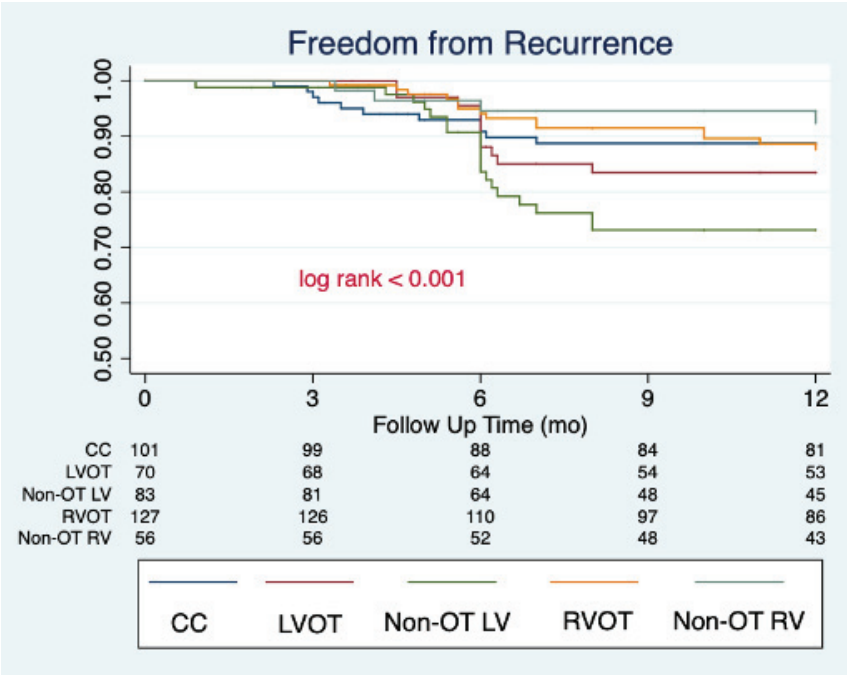

Figure 2. Clinical success of PVC catheter ablation stratified by arising zones, graphically displayed by Kaplan–Meier curves.

Table 4. Primary outcome predictors.

	HR [IQR]	*p*	aHR [IQR]	*p*
Sex	0.79 [0.50–1.25]	0.319		
Age (/year)	1.01 [0.98–1.02]	0.628		
Sport	0.63 [0.29–1.37]	0.244		
HF	0.95 [0.70–1.29]	0.739		
LVEF (/%)	1.01 [0.97–1.03]	0.872		
Structural heart disease	2.15 [1.37–3.38]	**<0.001**	1.96 [1.22–3.14]	**0.005**
AAD use during follow-up	1.12 [0.67–1.87]	0.656		
PVC burden	0.96 [0.94–0.97]	**<0.001**	0.96 [0.95–0.98]	**<0.001**
PVC QRS length (/ms)	0.98 [0.97–1.01]	0.118		
PVC coupling (/ms)	0.99 [0.99–1.01]	0.283		
CC origin	0.85 [0.50–1.46]	0.557		
LVOT origin	1.06 [0.60–1.90]	0.830		
Non-OT LV origin	2.60 [1.62–4.17]	**<0.001**	1.77 [1.07–2.93]	**0.027**
Non-OT RV origin	0.61 [0.35–1.07]	0.084		
RVOT origin	0.51 [0.22–1.17]	0.112		

Abbreviations: AAD: antiarrhythmic drugs, CC: coronary cusp, HF: heart failure, HR: hazard ratio, IQR: interquartile range, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, PVC: premature ventricular complex, RVOT: right ventricular outflow tract. Statistically significant values have been indicated in bold.

4. Discussion

This study represents one of the largest experiences addressing the long-term outcomes of idiopathic and non-idiopathic PVC patients undergoing a catheter ablation procedure with modern technologies. The main results of the study may be summarized as follows:

PVC ablation is a common procedure, routinely performed in third-level electrophysiology centers. PVCs originating from the RVOT were the most common index PVC observed (29.1%), closely followed by CC and non-OT LV PVCs (23.1% and 19.0%).

The PVC ablation procedure had a very good acute procedural success rate (97.4%). A significant reduction in the 24 h% PVC burden was observed after PVC ablation (−91.4% [−83.4; −96.7], $p < 0.001$), with high rates of clinical success observed at 6 months and after an average of almost 3 years of follow-up (85.1% vs. 82.1%; respectively).

While a significant reduction in PVC burden was observed consistently across patients with PVC with different localizations, clinical success was significantly lower in patients with PVC originating from the non-OT LV regions (70.0% at 6 mo; 68.7% at last follow-up).

PVC origin from the non-OTF LV region (aHR 1.96 [1.22–3.14], $p = 0.005$) and the presence of an underlying structural heart disease (aHR 1.77 [1.07–2.93], $p = 0.027$) were independently associated with higher rates of arrhythmic recurrences during follow-up.

CA of CC PVCs showed favorable outcomes at long-term follow-up (83.2%), ranging between RVOT and LVOT success rate (88.2% and 80.0%, respectively).

Complications were quite uncommon, being present in 2.2% of the entire cohort; these were mostly related to vascular access complications, with only one pericardial tamponade.

4.1. PVC Ablation and Clinical Outcomes

The long-term success rate of PVC ablation significantly varies, depending on the characteristics of the examined cohort. Indeed, in a meta-analysis from Zang et al. [4] the overall success rate ranges from 66% to 90%. The highest success rate was reached by Takemoto et al. [8], enrolling patients with frequent RVOT-PVC without evidence of structural heart disease, while Penela et al. [9] had the lowest procedural success, enrolling patients with LVEF < 50% of any etiology, with no particular exclusion criteria. These median success rates, along with differences mostly depending on the PVC arising zones and the underlying cardiac diseases, were subsequently confirmed in more recent trials, with Latchamsetty et al. [5] showing a 71–85% of long-term procedural success for idiopathic PVCs and Han et al. [10] having a 72.7% long-term success rate of PVC originating from periprosthetic aortic valve region ablations. Our findings are in line with these studies, with an overall success rate in our cohort (defined as a reduction of at least 80% of the pre-procedural 24 h PVC burden, according to these previous reports) of 85.1% at 6 months and of 82.1% at almost 3 years of follow-up, including patients with both idiopathic and non-idiopathic PVCs, our cohort being adequately heterogeneous with respect to other works. When analyzing the predictors of success of CA, the non-OT LV origin (LV summit, papillary muscles, and mitral valve left anterior/posterior fascicle) was the major determinant of PVC recurrence during follow-up (aHR 1.96 [1.22–3.14], $p = 0.005$), along with the presence of structural heart disease (aHR 1.77 [1.07–2.93], $p = 0.027$). On the other hand, the highest success rate was observed in patients with PVCs arising from the RV, either from the RVOT or from non-RVOT structures.

These results are surely not unexpected, but robust comparisons between groups are still lacking in the literature. Indeed, when analyzing predictors of adverse outcome in patients with frequent PVCs, in this large cohort study from Voskoboinik et al. [11], patients with structural heart disease were excluded from both validation cohorts. Moreover, Im et al. [12] showed that right ventricular PVC was among the unadjusted predictors of late PVC recurrence; however, the multivariate analysis failed to show that PVC site of origin was among the independent predictors for long-term success. Furthermore, patients with a history of structural heart disease were excluded. Several hypotheses may underpin our findings. First, papillary muscle PVCs are known to have a high recurrence rate, thus requiring longer RF delivery time and overall procedural times, although intracardiac echocardiography (ICE)-guided CA has been reported to be highly efficacious [13,14]. The non-systematic use of intracardiac echocardiography in all patients may partially explain the lower success rate of CA of non-OT LV PVCs in our cohort. Indeed, as described by Enriquez et al., ICE is crucial to guarantee adequate catheter–tissue contact and the correct orientation of the catheter tip during mapping and ablation. Moreover, ICE is essential to recognize increased echogenicity in the papillary muscles, identifying focal areas of scar that might highlight the site of arrhythmia origin, potentially corresponding to areas of low

voltage and late potentials in sinus rhythm [15]. Second, LV summit and interventricular septum PVCs represent a major challenge as well, often requiring extensive mapping and subsequent ablation from the septal RVOT, coronary sinus, great cardiac vein, sub-aortic region, and sinuses of Valsalva, significantly prolonging the procedure and reducing the success rate even in the hands of experienced operators [16,17]. In our cohort, the need to perform coronary angiography during PVC ablation was left to the electrophysiologist's discretion, and was mostly used during LV summit catheter ablations, before delivering RF from challenging locations, such as the GCV or whenever there was the strong suspicion of delivering RF near the coronary arteries, based on ICE imaging. Due the significant challenge that this location poses, if the earliest activation strategy failed in eliminating the target PVC, a "sandwich" ablation strategy, targeting the area from the opposite side, was attempted as a first-line choice. Whenever this protocol was also not effective in reaching the procedural success, and the managing clinician, in accordance with the patient, chose to perform a "redo" procedure, a subsequent alcohol ablation was attempted. Third, the "*liason*" between non-OT LV PVC and structural cardiac disease, which is, however, an independent predictor of PVC recurrence after CA, may also contribute to explaining our findings. Patients with underlying ischemic and non-ischemic cardiopathies are indeed known to be at the lowest rate of procedural success, as reported by Kazdri et al. [18] showing an acute procedural success of 60% in non-ischemic cardiomyopathies.

Another important result of our study that should be mentioned in terms of procedural success is that patients with the highest pre-procedural burden are less keen to develop recurrences during follow-up. If this finding may initially appear counterintuitive, we believe that in these patients, mapping and precisely locating the target PVC is easier, therefore guaranteeing more efficient CA. Furthermore, it is evident that the rate of patients without AAD has significantly increased during follow-up, with most clinicians deciding to stop the AAD during follow-up. In our cohort, the use of AAD did not show an impact on the clinical success of PVC ablation, being not associated with the primary outcome of our study at univariate analysis.

Our results on CC PVC ablation should be briefly discussed as well. The overall procedural success rate of these PVC was found to be halfway between OT and non-OT RV and LV PVC, being achieved in 88.1% of patients at 6-month follow-up and 83.2% at long-term follow-up. Our success rate was overall slightly higher to that reported by other groups in the literature [5,10,19]. Indeed, differently from Latchamsetty et al. [5], showing that PVCs originating in the aortic cusps were at the highest risk of recurrence soon after papillary muscle PVCs, in our study, CC PVCs showed a higher success rate than LVOT PVC. Although lower power settings are often used in the aortic cusps to minimize the risk of complications and coronary artery injury [20], the consolidation of the RF lesion from both sides of the aortic cusps has allowed us to reach favorable clinical outcomes in those cases, without paying the price of a high number of complications.

Our findings may have significant implications in clinical practice, especially when counseling patients about treatment options, always bearing in mind that the site of origin of PVC needs to be accurately evaluated with prediction algorithms [21], considering this significant influence on ablation outcomes. Moreover, an overall very favorable PVC burden reduction should encourage the managing clinician to offer CA as a robust treatment option in this scenario.

4.2. Ablation Index Use in PVC Ablation

One of the most significant novelties of our study is represented by operators reporting the use of the ablation index (AI) module in 47.1% of the procedures. In recent days, the use of AI guidance for PVC ablation has been extensively investigated and a prospective study by Gasperetti et al. showed that AI guidance was superior to standard procedures in the management of idiopathic RVOT PVCs [22,23]. Validated procedural cut-offs, however, are currently limited to the RVOT area and no specific assessment in patients with an underlying structural heart disease has been performed. In this study, no specific cut-offs

were given to operators, nor was a pre-determined AI protocol set in place. Both the use and the extent of reliance on AI was left completely to the choice of the individual operator. The use of an AI module in almost half of the procedures, however, shows how this multiparameter index has consistently taken part in the routine clinical practice of tertiary EP centers. Apart from a potential increase in procedural safety, one of the main advantages of AI guidance is the reduction in the inter- and intra-operator variability [24]. The standardization of cardiac EP procedures is appealing to the cardiac electrophysiology community as it helps increasing the reproducibility of results and the adherence to good clinical practices, and it reduces complications. AI is an already accepted tool, often used during PVC ablation. Its further investigation in the setting of specific structural heart substrates is, however, needed, as well as the definition of localization-specific AI thresholds.

4.3. Safety Endpoints

Major complications were quite uncommon in our cohort, with 2.2% suffering either from vascular access complications (50%) or from RF energy-related issues, with 1 (10%) pericardial tamponade, which was solved after pericardiocentesis. Despite our cohort being a priori at high risk of developing procedural complications, being—at least partially—represented by patients who also underwent non-OT LV ablation procedure, the overall number of life-threatening complications was overall low when compared to other clinical experiences. Indeed, it is generally believed that RF delivery near or on valvular structures in the heart can be performed safely [19], even though some cases have shown that ablation on or near the aortic valve can lead to valve dysfunction or coronary artery injury [25,26]. We believe that the high number of EP procedures performed in all the institutions involved in this study may be the main explanation of this finding.

4.4. Study Limitations

First, all the institutions participating in this study are tertiary referral EP centers, with all procedures being performed by experienced electrophysiologists; therefore, our clinical outcomes may not reflect outcomes achieved by less experiences by less-experienced operators. Second, despite reporting baseline ECG data and long-term Holter ECG, echocardiographic data were not available at follow-up, so eventual resolution of PVC-induced cardiomyopathy after CA could be not systematically assessed. Third, the decision on antiarrhythmic drug therapy interruption/continuation was left to every managing clinician during follow-up, without a pre-specified per-protocol recommendation. Fourth, the periodic patients' evaluation with 24 h Holter ECG, that was performed yearly after the first follow-up visit (unless otherwise indicated), may have led to a partial underestimation of PVC recurrences, especially in asymptomatic patients. Last, the quantitative evaluation of symptom improvement after CA was not systematically performed according to a pre-specified clinical scale.

5. Conclusions

In our cohort from third-level EP centers, CA of both idiopathic and non-idiopathic PVCs showed a very good acute and long-term procedural success rate, with an overall low complication. Predictors of arrhythmic recurrence at follow-up were underlying structural heart disease and non-OT LV origin. CA of coronary cusp PVCs showed favorable long-term follow-up outcomes, ranging between RVOT and LVOT success rate.

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Brief Report

Biventricular Arrhythmogenic Cardiomyopathy Associated with a Novel Heterozygous *Plakophilin-2* Early Truncating Variant

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Abstract: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a hereditary condition that can cause sudden cardiac death in young, frequently athletic individuals under the age of 35 due to malignant arrhythmias. Competitive and endurance exercise may hasten the onset and progression of ARVC, leading to right ventricular dysfunction and potentially fatal ventricular arrhythmias earlier in life. In this article, we present a novel, pathogenic, early truncating heterozygous variant in the *PKP2* gene that causes biventricular arrhythmogenic cardiomyopathy and affects a family, of which the only member with the positive phenotype is a competitive endurance athlete.

Keywords: arrhythmogenic cardiomyopathy; plakophilin-2; exercise

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1. Introduction

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) (OMIM: 609040) is a hereditary condition that causes malignant arrhythmias in young, often athletic subjects below the age of 35 years and can lead to sudden cardiac death (SCD) [1]. Human cardiac tissue and animal models lacking *plakophilin-2* (*PKP2*) were found to have defective cell–cell coupling, decreased conduction velocity and a pathological activation of the Hippo pathway leading to enhanced adipogenesis [2]. Sports activity plays a key role in the penetrance of the disease, formation of arrhythmic events and progression to heart failure [3]. Competitive sports activity is not recommended in both the index patient and phenotypically unaffected family members carrying the same pathogenic variant [4]. However, exercise testing can be performed safely in this group of patients and can provide important information in patients who appear phenotypically unaffected [5,6]. In this report we describe a family who harbors a novel, pathogenic, heterozygous early truncating variant in the *PKP2* gene in which the only phenotype-positive member is a competitive endurance athlete.

2. Materials and Methods

A thorough medical and family history covering three generations was obtained from the index patient. We also performed a 12-lead electrocardiogram (ECG), exercise stress testing, transthoracic echocardiography (TTE), flourine-18 fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT), 48 h Holter ECG, and cardiac magnetic resonance imaging (MRI). His first-degree relatives are asymptomatic and their cardiologic workup including exercise test, TTE and genetic cascade screening was carried out.

The Prepito (Perkin Elmer, Waltham, MA, USA) DNA Blood250 kit was used to extract DNA from an ethylenediaminetetraacetic acid (EDTA) blood sample. For molecular genetic analyses, the SwissDNAlysis Cardiopanel (Agilent, SureSelectQXTTarget Enrichment, Santa Clara, CA, USA) was used, and high-throughput sequencing (Illumina MiSeq) was performed, with 92.3% of bases sequenced with a Q-score $\geq$ Q30. 98.8% of the analyzed gene segments had a coverage of $\geq$20×. The average sequencing depth of the analyzed gene segments was 270.7×. The patient was examined for 173 genes related with inherited heart disease, of which 16 are associated with ARVC (*CTNNA3*, *DES*, *DSC2*, *DSG2*, *DSP*, *JUP*, *LDB3*, *LMNA*, *PKP2*, *PLN*, *RYR2*, *SCN5A*, *TGFB3*, *TMEM43*, *TP63*, and *TTN*) according to the evidence-based evaluation of gene validity for ARVC by the most recent 2022 European Society of Cardiology guidelines [7].

The sequences were aligned and realigned locally against the human reference genome (GRCh37hg19) using lllumina alignment software version 2.5.42.7 (Burrows–Wheeler algorithm and Genome Analysis Toolkit for variant calling). Variants with an allele frequency <5% in the coding regions including the flanking intronic regions (±8 bp) were scored. Data interpretation was performed using Variant Studio 3.0, Varsome Clinical, dbSNP153, the gnomAD database, PubMed, and ClinVar. Using standard Sanger sequencing, all variations in this study were confirmed. Multiplex Ligation dependent Probe Amplification (MLPA) was used for relative copy number analysis to detect deletions and duplications (copy number variation analysis) in the *RYR2* (Exon 3 und 97), *DSP* (Exon 1, 5, 7, 21 und 24), *PKP2* (Intr. 1, up, Exon 1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14), *TGFB3* (Exon 1, 6, 7), *JUP* (Exon 2,9,12), *DSC2* (Exon 1, 7 und 17) und *DSG2* (Exon 1, 6 und 15) genes (MRC Holland; SALSA P168 (D1-0520)). Data analysis was performed with Coffalyser.Net (v.140721.1958, MRC-Holland, Amsterdam, The Netherlands).

For the genetic testing of the family members, genetic analysis of exon 3 of the *PKP2*-gene (NM_004572.3; LRG 398t1; rs752060568) was performed using a plasma polymerase chain reaction (PCR) followed by direct Sanger sequencing. The primers were as follows: Forward, 5′-CATACCACAGACAGTACCAGCA-3′ and reverse, 5′-CCAGAAGTGCCAGCTCAT GC-3′.

3. Results

The index patient was a 31-year-old male and suffered from paroxysmal palpitations in the last 3 years, which occurred particularly during and shortly after physical activity. The patient was very athletic since early adulthood and took part in marathons on a regular basis. His family history of three generations was unremarkable. A first cardiologic investigation was carried out in a peripheral hospital. The 12-lead surface ECG showed T wave inversions in V1-V3 (Figure 1A). During bicycle ergometry several monomorphic premature ventricular complexes (PVC) and non-sustained ventricular tachycardia (VT) episodes (left-bundle branch block morphology, inferior axis, maximum 6 beats, around 200 beats/min) evolved, which persisted in the recovery phase (Figure 1B, black arrow). Of note, under maximal physical stress, a second PVC with a right-bundle branch block morphology occurred (Figure 1B, red arrow) suggesting left ventricular (LV) involvement. At the end of the recovery period, the PVC frequency decreased again. Based on these findings, the referring cardiologist suspected for ARVC and transferred the patient to our referral center for further investigations. Our echocardiographic evaluation showed a dilated right ventricle (RV) (parasternal long axis RV outflow tract = 36 mm (17.5 mm/m^2) parasternal short axis RV outflow tract = 38 mm (18.5 mm/m^2) with reduced area of shortening (fac = 27%) and normal longitudinal function (TAM = 18 mm; S′ = 10 cm/s). On the RV inflow view, a subtricuspid aneurysm and multiple sacculations of the RV free wall were noticeable (Figure 1C,D, white markers). Circumscribed akinesia of the LV lateral apical wall was also detected. According to the revised task force criteria [8], the major criteria for ARVC were fulfilled on cardiac MRI (right ventricular end-diastolic volume index: 111 mL/m^2 and RV ejection fraction = 45%). A subtricuspid RV aneurysm, as well as microaneurysms of the remaining RV free wall, was present (Figure 1E, red arrows and Supplemental Video S1). In addition to RV involvement, late gadolinium

enhancement and fatty deposits were visible in the LV lateral wall (apical to midventricular) (Figure 1F,G, yellow arrows and blue Asterix) and the apical part of the lateral wall was akinetic (LV ejection fraction = 54%). This finding confirmed biventricular involvement and biventricular arrhythmogenic cardiomyopathy according to the recent 2020 Padua Criteria [9]. Myocardial inflammation and active cardiac sarcoidosis were excluded with 18F-FDG PET/CT and apart from frequent PVCs (2.6%/24 h) no VT episodes were depicted on Holter ECG.

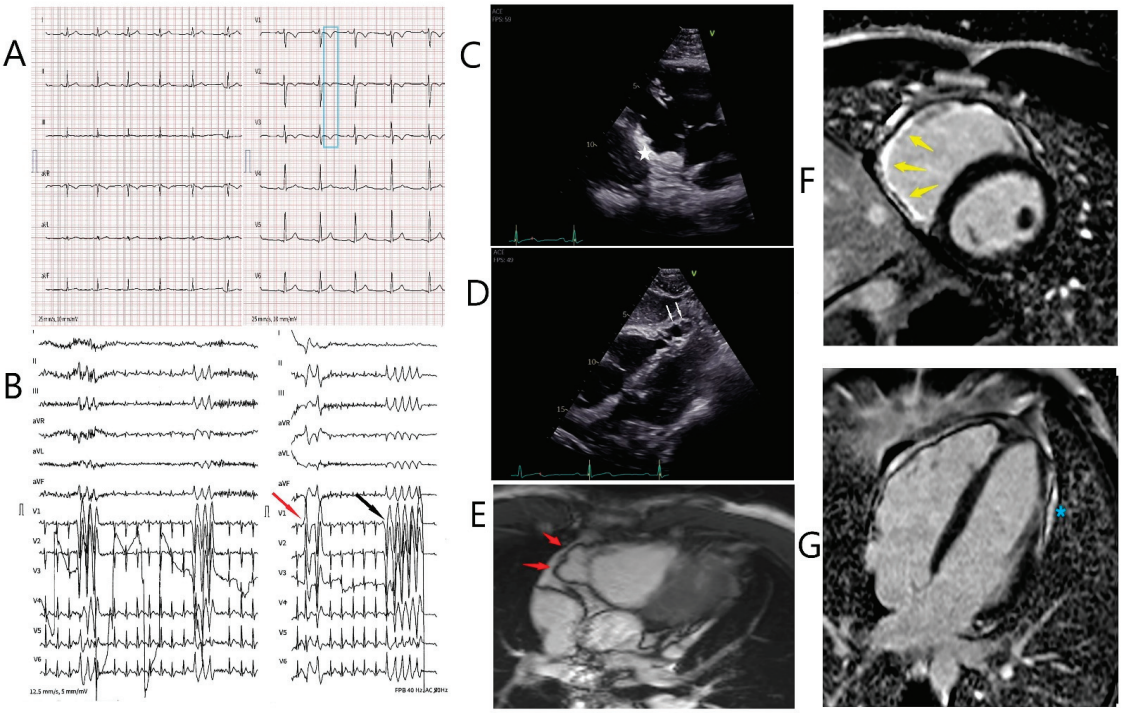

Figure 1. Diagnostic work-up in the index patient. (**A**). 12-lead electrocardiogram showing sinus rhythm with T wave inversions in V1–V3 (blue box). (**B**). Recovery phase of bicycle ergometry. Right (red arrow) and left bundle branch block (LBBB) morphology premature ventricular complexes and non-sustained ventricular tachycardia with a LBBB morphology (black arrow) and an inferior axis are shown. (**C**,**D**). Transthoracic echocardiogram showing the subtricuspid aneurysm (white asterisk) on the RV inflow view and multiple sacculations of the right ventricular free wall (white arrows). (**E**). Multislice 4 chamber MRI view showing a subtricuspid aneurysm of the right ventricular free wall (red arrows). (**F**). Late gadolinium enhancement of the subtricuspid right ventricular wall (yellow arrows, Phase-sensitive inversion recovery (PSIR) short axis view). (**G**). Late gadolinium enhancement of the lateral wall of the left ventricle (blue asterisk, PSIR 4 chamber view).

Genetic testing revealed a novel heterozygous nonsense variant in the *PKP2* gene (808C > T p. (Gln270Ter) in exon 3) that causes an early truncation of the protein, which was confirmed by Sanger sequencing. It was classified as pathogenic (class V) according to the 2015 American College of Medical Genetics Criteria [10]. Cascade screening of the asymptomatic patient's mother (64 years old), father (70 years old) and sister (33 years old) showed that the patient's father and sister harbored the same heterozygous 808C > T p. (Gln270Ter) *PKP-2* variant. Both did not report a history of participating in competitive sports, and thorough cardiac evaluation of these two genotype positive family members showed normal findings.

4. Discussion

The most frequent gene linked to ARVC is *PKP2* [11]. The *PKP2* cardiomyopathy is inherited autosomally dominantly and is thought to affect primarily the RV, making it specifically associated with ARVC. Competitive and endurance exercise may accelerate the onset and progression of ARVC, resulting in potentially life-threatening ventricular arrhythmias and RV dysfunction at a younger age. Although it has been shown in previous studies that early truncation of the *PKP2* C-terminus likely causes ARVC irrespective of transcript position [12], desmosomal and non-desmosomal variants can create a certain genetic potential for the development of ARVC, but exercise has an important role in determining the development, severity, and pattern of phenotypic expression. Competitive and endurance exercise can cause structural heart changes even in healthy amateur athletes [13] and it is suggested that exercise-induced ARVC may develop without underlying major genetic drivers [14]. In this family, exercise restrictions for all three genotype-positive family members were recommended because the exercise intensity is the only known difference among them. A primary prophylactic subcutaneous implantable cardioverter defibrillator (S-ICD) was only implanted in the index patient. Patients with ARVC have a relatively significant chance of receiving inappropriate ICD shocks with S-ICD, even when the SMART Pass algorithm (SP; Boston Scientific Corporation, Natick, MA, USA) is activated [15]. Based on his substantial long-term risk of lead failure and vascular consequences, our young, athletic patient preferred a primary prevention S-ICD during the shared decision-making process.

As a marathon runner, the index patient was the only one to develop ARVC in his family, indicating that while the novel *PKP2* variant provides a genetic risk, it is insufficient to cause an ARVC phenotype on its own. It is important to consider that other genetic and environmental factors can modify the individual threshold for disease penetration. The altered proteins in the intercalated discs interfere with normal cell adhesion, mechanical stability, cell-to-cell communication, and electrical connection. It has been hypothesized that mechanical stress, such as that caused by exercise, leads to instability, inflammation and fibro-fatty infiltration. [16]. Exercise has been shown to cause a greater increase in wall stress on the RV than the LV [17] but biventricular disease is possible in *PKP-2* cardiomyopathies [18]. Thanks to cascade genetic testing, a large number of individuals and their families can be screened at early phenotypic phases, allowing for the implementation of suitable preventive measures.

5. Conclusions

Taken together, we describe a novel, pathogenic, heterozygous early truncating variant in the *PKP2* gene causing biventricular arrhythmogenic cardiomyopathy and affecting a family, in which the only phenotype-positive member is a competitive endurance athlete. This highlights the importance of environmental factors such as endurance exercise for disease penetrance and progression in patients with classical right-dominant ARVC associated with (likely) pathogenic variants in *PKP-2*.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11247513/s1, Video S1: Cardiac magnetic resonance imaging of the index patient.

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Data Availability Statement: Upon urgent request and associated need, our data are available, while our upmost intention is to protect our patients' privacy.

Conflicts of Interest: AS received educational grants through his institution from Abbott, Bayer Healthcare, Biosense Webster, Biotronik, Boston Scientific, BMS/Pfizer, and Medtronic; and speaker/advisory board /consulting fees from Medtronic and Novartis.

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Article

Isolated Atrial Fibrillation, Inflammation and Efficacy of Radiofrequency Ablation: Preliminary Insights Based on a Single-Center Endomyocardial Biopsy Study

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Abstract: The aim of the study was to evaluate the inflammatory changes in the myocardium, based on endomyocardial biopsy (EMB) data in patients undergoing radiofrequency ablation (RFA) for idiopathic atrial fibrillation (AF). A total of 67 patients with idiopathic AF were enrolled in the study. Patients underwent the intracardiac examination, RFA of AF, and EMB with histological and immunohistochemical studies. The catheter-treatment effectiveness, and occurrence of early and late recurrences of atrial tachyarrhythmias, were assessed depending on the identified histological changes. Nine patients (13.4%) did not have any histological changes in the myocardium according to EMB. Fibrotic changes were detected in 26 cases (38.8%). Inflammatory changes according to the Dallas criteria were observed in 32 patients (47.8%). The follow-up period for patients averaged 19.3 ± 3.7 months. The effectiveness rates of primary RFA were 88.9% in patients with the intact myocardium, 46.2% in patients with fibrotic changes of varying severity, and 34.4% in patients with the presence of criteria for myocarditis. No early recurrence of arrhythmias was observed in patients with unchanged myocardia. The presence of inflammatory and fibrotic changes in the myocardium increased the rates of early and late arrhythmia recurrences and accordingly halved the effectiveness RFA of AF.

Keywords: atrial fibrillation; inflammation; histological myocarditis; endomyocardial biopsy; radiofrequency ablation

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1. Introduction

The introduction should briefly place the study in a broad context and highlight atrial fibrillation (AF) as the most common arrhythmia with heterogeneous clinical manifestations often observed in clinical practice. AF is the cause of one-third of hospitalizations for cardiac arrhythmias. Current clinical guidelines recommend avoiding the term "lone" or isolated AF. However, in clinical practice, there are patients without any clinical and echocardiographic signs of cardiovascular and pulmonary disease, and conditions such as acute infections, recent cardiac surgery, thoracic or abdominal operations, and systemic inflammatory diseases [1].

It Is known that an essential element of AF pathophysiology is atrial remodeling, which has three main components: structural, electrical, and mechanical [2]. Inflammation is an important factor in structural remodeling. Indeed, Lau et al. showed that the inflammatory infiltration in the atrial myocardium was detected in patients with isolated AF. Further evidence for the association between AF and inflammation is increased concentrations of serum inflammatory markers, such as C-reactive protein (CRP), TNF-α, interleukins, and cytokines [3]. Besides, the level of serum inflammatory markers increases in patients

with both isolated AF and AF associated with the underlying disease [4]. However, it is challenging to explain the occurrence of cellular infiltration and an increase in inflammatory markers only by the fact of AF without the presence of an infectious agent.

The diagnosis of idiopathic AF often suggests the presence of unrecognized myocardial lesion with a certain etiology. One of the most common causes for idiopathic AF is chronic myocarditis occurring without vivid clinical manifestation [5]. Endomyocardial biopsy (EMB)-based confirmation of active myocarditis, which can initially be suspected in patients with a combination of minimal clinical and laboratory-instrumental signs, provides the basis for successful administration of anti-inflammatory and immunosuppressive therapy.

Myocarditis can be difficult to diagnose, primarily due to the heterogeneity of its clinical manifestations. Data on the prevalence of myocarditis are limited, and there are no studies on the subclinical course of this disease. Available studies of myocardial biopsies in young people who suddenly died suggest the presence of myocarditis in 2 to 42% of cases [6,7]. The absence of a specific clinical picture, clear association with the previous infection, changes in exercise tolerance, and changes in ECG and echocardiography data often do not allow suspicion of the presence of myocarditis; spontaneous recovery completely excludes further diagnostic searches in this direction. However, the evolution of viruses, their rapid spread, tendency to chronicity, and the onset of an autoimmune component increase the number of patients with progressive cardiac dilatation and a poor prognosis. Currently, myocarditis is commonly defined as an inflammatory heart disease where diagnosis is established according to the histological (Dallas criteria), immunological, and immunohistochemical criteria (14 or more lymphocytes per square mm, including up to four monocytes and seven or more $CD3^+$ T-lymphocytes). The cause of myocarditis often remains unknown. It is believed that the cause of myocardial damage in most cases is a viral infection. Therefore, polymerase chain reaction of the myocardial tissue sample allows detection of enterovirus, adenovirus, parvovirus B19, herpes simplex virus types 1, 2, and 6, cytomegalovirus, and Epstein-Barr virus during histological and immunological studies [8]. Delayed acute viral disease and occurrence as a result of latent subacute myocarditis is probably not uncommon in the modern world, but the occurrence spontaneously resolves without consequences in most patients. In some cases, myocarditis persists and leads to the development of fibrosis, onset of tachyarrhythmias and/or heart failure. AF represents one of these manifestations. Current treatment for AF mainly involves the use of interventional techniques such as radiofrequency isolation of the pulmonary veins, application of multiple damage lines, etc. At the same time, intracardiac intervention allows an EMB to be performed to confirm inflammatory or degenerative myocardial disease. Therefore, we set a goal to evaluate the contribution of inflammation to the clinical outcomes of the radiofrequency ablation (RFA) of AF.

2. Materials and Methods

2.1. Study Population and Design

We examined 274 patients (182 men, 66.4%) aged 30 to 55 years (mean age of 42.2 ± 18.6 years) admitted to the clinic with a diagnosis of AF. The inclusion criterion was diagnosis of idiopathic AF. The exclusion criterion was the presence of associated diseases: arterial hypertension, obesity, diabetes mellitus, dyslipidemia, cardiovascular, autoimmune, pulmonary diseases, thyroid pathology, or other diseases that could potentially cause AF. While staying in the hospital, all patients underwent the following examinations: 12-lead ECG, Holter ECG monitoring, bicycle ergometry, six-minute walking test, clinical and biochemical blood tests, 24-h blood pressure monitoring, transthoracic echocardiography, stress test to exclude coronary heart disease (myocardial perfusion scintigraphy or stress ECHO), and in case of a positive stress test, multispiral computer or invasive coronary angiography to exclude atherosclerotic changes in the coronary arteries and, accordingly, ischemic genesis of arrhythmia. If pathological changes were detected during the examination, the patient was excluded from the study. The study included 67 patients (22.9%), in whom the cause of AF was not found by any methods available to us. Of these patients,

43 individuals (64.2%) were men aged 34 to 50 years (mean age of 41.1 ± 7.6 years). Upon admission to the clinic, all these 67 patients complained of palpitations. Persistent AF was in 29 patients (43.3%), and long-term persistent (for more than one year) in 38 cases (56.7%). The duration of arrhythmic history was 5.7 ± 1.4 years. The specific pharmacotherapy before admission to the hospital was not carried out, since it was initially believed that all patients had isolated AF. All patients with the persistent AF took antiarrhythmic drugs for AF prevention at the outpatient stage (before the hospitalization): amiodarone in 73.2% of cases, sotalol in 11.3% of patients, and propafenone in the rest of patients (15.6%). For the arrhythmia-paroxysms termination, amiodarone was used as a first line and propafenoneas a second line. All patients with long-term persistent AF before hospitalization were receiving β-blockers as drugs for heart-rate control. However, it should be noted that, according to the past medical history, patients previously took all available antiarrhythmic drugs, and the average number of medications taken was 2.8. At hospital discharge, after the interventional AF treatment, all patients were prescribed with the antiarrhythmic therapy for three months at least. Amiodarone was prescribed to patients who had long-term persistent AF before AF ablation and propafenonein to the remaining patients. The anticoagulation therapy was not prescribed before AF ablation, as all patients had no more than 1 CHA2DS2-VASc score. After the ablation, all patients were with the oral anticoagulation for three months.

The study was approved by the Local Ethics Committee and conformed to the Declaration of Helsinki on Human Research. Written informed consent was obtained from every patient after explanation of the protocol, its aims, and potential risks.

All patients underwent the interventional AF treatment. Computer angiotomography with reconstruction of the left atrium, transesophageal echocardiography, and anticoagulant therapy were used as preparation for the procedure. Also cardiac magnetic resonance (MRI) with contrast and late gadolinium enhancement was performed in all patients before AF ablation with the Vantage Titan 1.5T scanner (Toshiba, Tokyo, Japan). In all cases, before ablation, electroanatomic mapping of the left atrium was performed with the reconstruction of bipolar maps and the identification of areas with reduced amplitude, as well as with an electrical "scar". The radiofrequency antral isolation of the pulmonary veins, the posterior wall of the left atrium, and the mitral isthmus of the heart were performed using the CARTO system (Biosense Webster, Irvine, CA, USA) in all cases. Vein isolation was monitored with the Lasso circular mapping catheter (Biosense Webster, Irvine, CA, USA). The sinus rhythm, if necessary, was restored by electrical cardioversion. After the sinus rhythm restoration, EMB was performed. Biopsies were taken under X-ray control from the apex, interventricular septum (IVS), and right ventricular outflow tract. Of 67 patients who underwent EMB, 47 also underwent interatrial septum (IAS) biopsy under the transesophageal ultrasound control without any complications. The obtained samples were labeled accordingly and fixed in 10% buffered neutral formalin.

2.2. Histological and Immunohistochemical Studies

Paraffin sections were stained with hematoxylin and eosin, picrofuxin, and tolluidine blue; cardiac amyloidosis was excluded in patients over 45 years old by staining with Congo red. An immunohistochemical study was carried out to determine the immunophenotype of infiltrating cells (CD3, CD45, CD68) in each fragment of the endomyocardium and to detect the expression of cardiotropic virus antigens. The following antibodies were used: rabbit polyclonal antibodies to CD3 (Spring BioScience, Pleasanton, CA, USA), mouse monoclonal antibodies to CD45R0 (MONOSAN, Uden, The Netherlands), mouse monoclonal antibodies to CD68 (DCS), rabbit polyclonal antibodies to VP-2 protein of parvovirus B19 (Dako Cytomation), mouse monoclonal antibodies to VP-1 protein of enteroviruses (MONOSAN, Uden, The Netherlands), rabbit polyclonal antibodies to herpes virus type 2 (Dako Cytomation, Glostrup, Denmark), mouse monoclonal antibodies to herpes simplex virus type 1 (Leica Microsistems, Wetzlar, Germany), mouse monoclonal antibodies to adenovirus (Leica Microsistems, Wetzlar, Germany), mouse monoclonal antibodies to

early cytomegalovirus nuclear protein (Dako Cytomation, Glostrup, Denmark), and mouse monoclonal antibodies to Epstein-Barr virus LMP antigen (Dako Cytomation, Glostrup, Denmark). High-temperature antigen unmasking was performed when performing studies with antibodies to CD3, CD68, parvovirus B19, adenovirus, cytomegalovirus, herpes simplex virus type 1, 2, and LMP antigen of Epstein-Barr virus. A multivalent horseradish peroxidase diaminobenzidine (HRP-DAB) detection system (Spring BioScience, USA) was used to visualize the studied antigens.

The study of histological preparations was carried out at the light-optical level using an AxioLab A1 Zeiss microscope (Carl Zeiss AG, Jena, Germany). The 1997 Marburg agreement was used for morphological verification of myocarditis [9]. The infiltrating cells were counted, taking into account their immunophenotype (CD3, CD45, and CD68) [10,11].

2.3. Clinical Follow-Up

All patients had sinus rhythm on discharge from the clinic. After the procedure, all patients were prescribed antiarrhythmic and anticoagulant drugs for three months. The first three months of follow-up was considered a blind period, and the effect of the procedure was not evaluated; however, the occurrence of AF episodes was considered early relapses. All episodes of AF more than 30 s recorded on ECG or 24-h ECG monitoring, as well as symptomatic paroxysms, were considered an early relapse. Follow-up included an evaluation of complaints, ECG registration biquarterly, and Holter ECG monitoring twice every six months. The results of EMB and immunohistochemical studies were immediately provided to patients, with appropriate recommendations to follow.

2.4. Statistical Analysis

Statistical analysis was performed using the Statistica 10.0 software package and MedCalc 13. Continuous variables were expressed as mean ± standard deviation. The Shapiro-Wilk test was used to assess the normality of variable distribution. To assess the differences between the variables, the non-parametric Mann-Whitney test for independent samples was used. The Spearman test was used to estimate the correlation coefficient between quantitative variables. Efficacy analysis was performed using logistic regression analysis. To evaluate the independent predictors of CRT response, forward-stepwise logistic regression analysis was used with an entry criterion of $p < 0.05$ and a removal criterion of $p > 0.1$. Receiver-operating characteristic (ROC) analysis was used to determine the diagnostic efficiency of the methods. Intra- and inter-observer reproducibility was assessed with intraclass correlation coefficients (ICC): p-value < 0.05 was considered significant.

3. Results

According to EMB results, no histological changes in the myocardium of the right ventricle (RV) were found in nine patients (13.4%). Fibrotic changes in the myocardium were detected in 26 cases (38.8%) including in predominantly perivascular fibrosis in 11 patients (42.3%), small focal fibrosis in eight patients (30.8%), and perimuscular fibrosis in seven patients (26.9%) (Figures 1–3).

Inflammatory changes in the myocardium were detected in 32 patients (47.8%), including nine patients (28.1%) with lymphocytic infiltration of less than 14 lymphocytes per mm^2 (Figures 4 and 5). The data obtained with EMB from RV and IAS were comparable. Inflammatory changes in RV correspond to a similar finding in IAS, while fibrotic changes in RV correspond to the same evidence in IAS. According to the results of immunohistochemical analysis, the virus expression was detected in one of these patients (3.1%). A combination of human herpes simplex virus type 2 and Epstein-Barr was found. No virus expression was detected in the remaining patients.

According to the Dallas criteria, the presence of histological myocarditis was revealed in 23 patients (34.3%) (Figure 6). Moreover, the virus expression was detected in 18 of these patients (78.3%), according to the results of immunohistochemical analysis. One patient (5.6%) was found to express three viruses: enterovirus, human herpes simplex virus

type 1, and Epstein-Barr virus; six patients (33.3%) had the presence of two viruses: one patient had a combination of parvovirus and herpes simplex virus type 2; three patients had a combination of enterovirus and herpes simplex virus type 1; and two patients had a combination of Epstein-Barr virus and human herpes simplex virus type 2. The presence of one viral antigen was detected in 11 cases (61.1%), including five patients (27.8%) with Epstein-Barr virus, three patients (16.7%) with enterovirus (Figure 7), two patients (11.1%) with human herpes simplex virus, and one patient (5.6%) with parvovirus. Another five patients (21.7%) did not have viral infection.

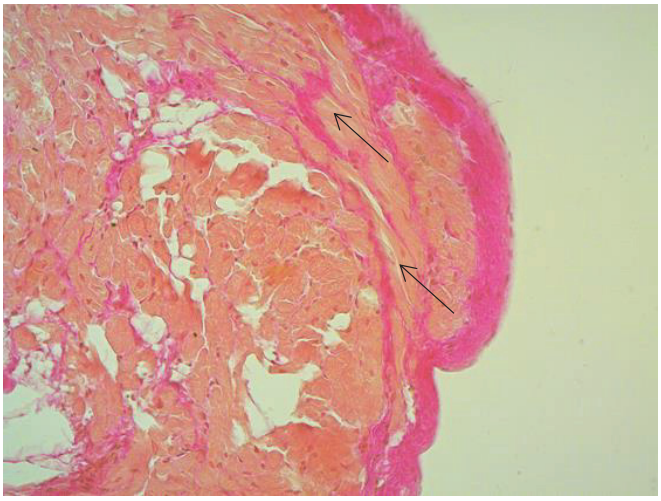

Figure 1. Perimuscular fibrosis in IVS, ×100, staining according to Van Gieson. The arrows indicate the connective tissue proliferation.

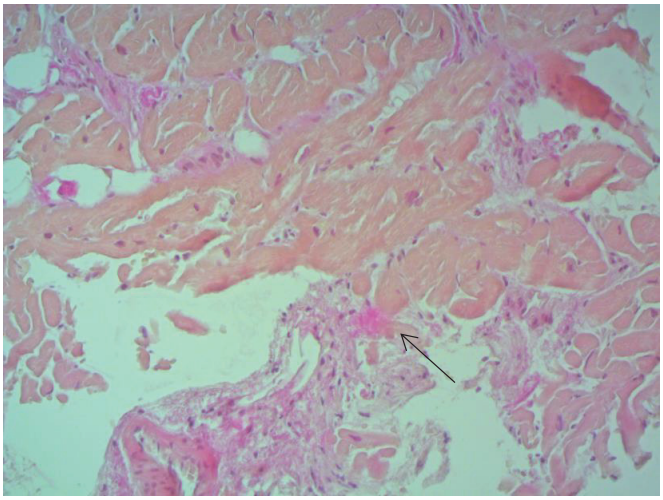

Figure 2. Small focal fibrosis in IVS ×200, staining according to Van Gieson. The arrow indicates the focus of connective tissue proliferation.

When comparing the results of EMB from IAS and electroanatomic mapping, the results of both studies largely coincided. If there was an intact myocardium according to the EMB data, then no areas with reduced amplitude, and no electrical "scar", were

detected according to the bipolar voltage map. If fibrosis was diagnosed by EMB, then according to the bipolar voltage map, areas with reduced amplitude as well as an electrical "scar" were detected (Figure 8).

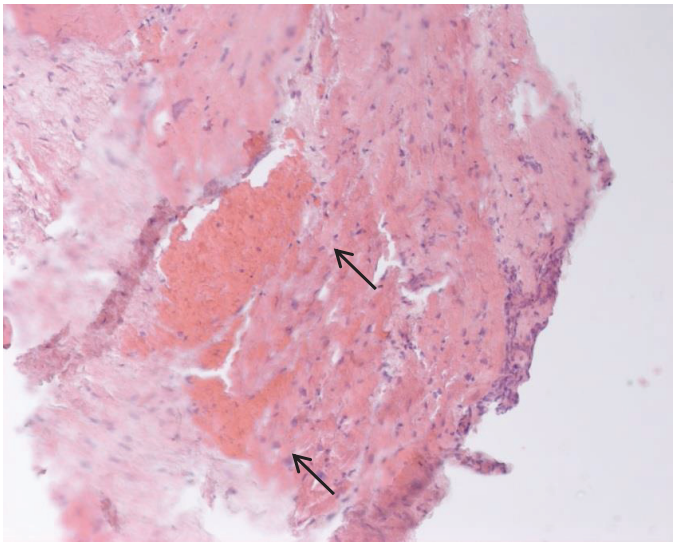

Figure 3. Fibrosis in IAS ×200, staining according to Van Gieson. The arrows indicate the foci of connective tissue proliferation.

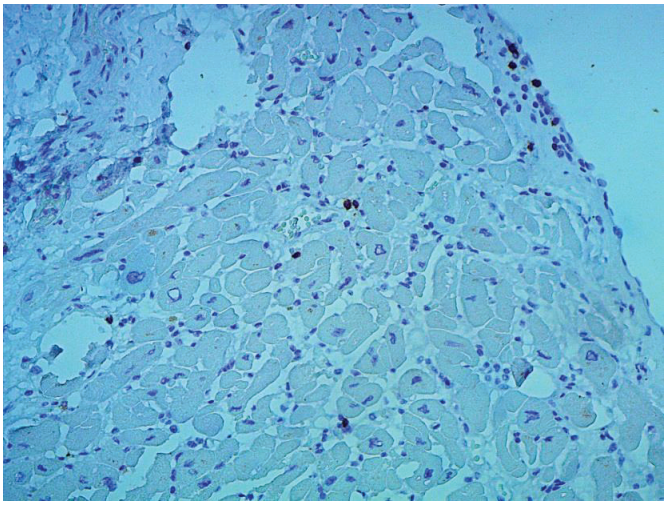

Figure 4. Endomyocardial infiltration with CD3+ lymphocytes. Immunohistochemical study, antibodies to the Epstein-Barr virus, ×200.

According to the 16–28-month follow-up results (on average 19.3 ± 3.7 months), the patients were divided into two groups. Group 1 comprised individuals who had no AF recurrence during follow-up according to the objective and subjective examinations. Group 2 comprised patients with reported relapses of AF or other atrial tachyarrhythmias. Data are presented in Table 1.

Considering that 35 patients did not have arrhythmia paroxysms (group 1), the overall efficiency of a single procedure was 52.2%. Early relapses were reported in 26 (41.3%) cases: in 14 patients (22.2%) with fibrotic changes and in 12 patients (19.1%) with inflammatory signs. During further follow-up, the paroxysms of arrhythmias were recorded in 27 patients (42.9%), of whom one patient (1.6%) had an intact myocardium, nine patients (14.3%) had fibrotic changes, and 17 patients (26.9%) had inflammatory signs.

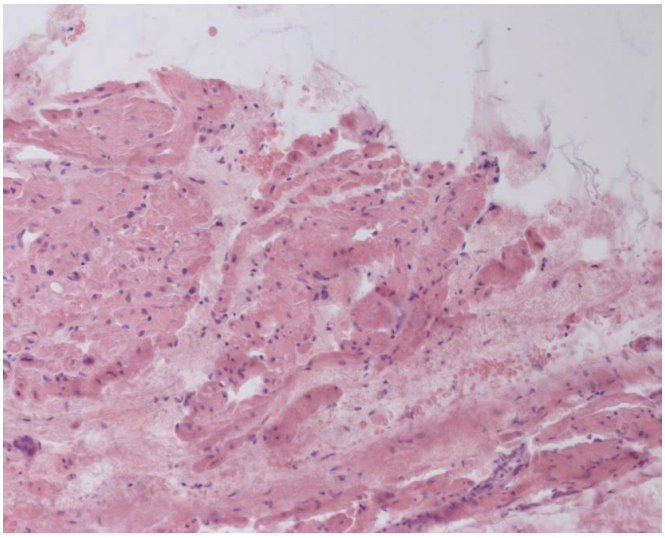

Figure 5. Endomyocardial infiltration of IAS with lymphocytes, ×200. Hematoxylin-Eosin Staining.

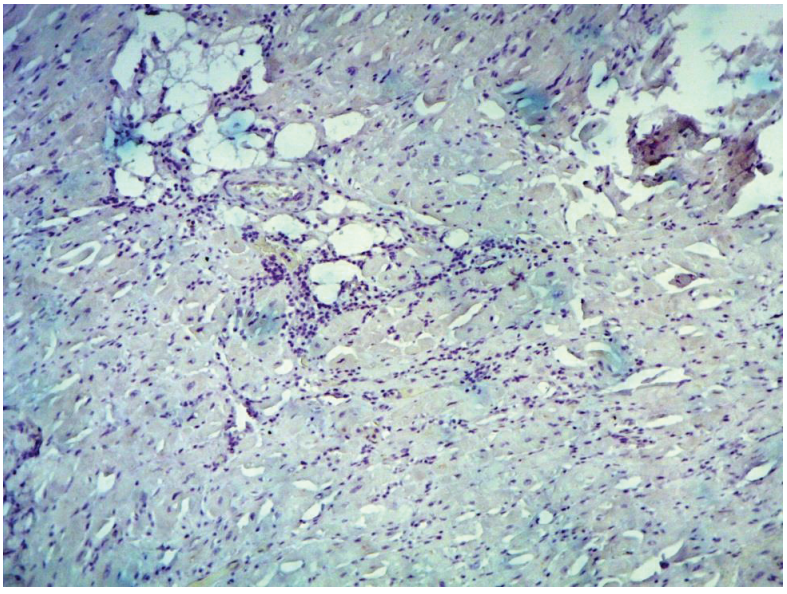

Figure 6. Active lymphocytic histological myocarditis, ×100. Hematoxylin-Eosin staining.

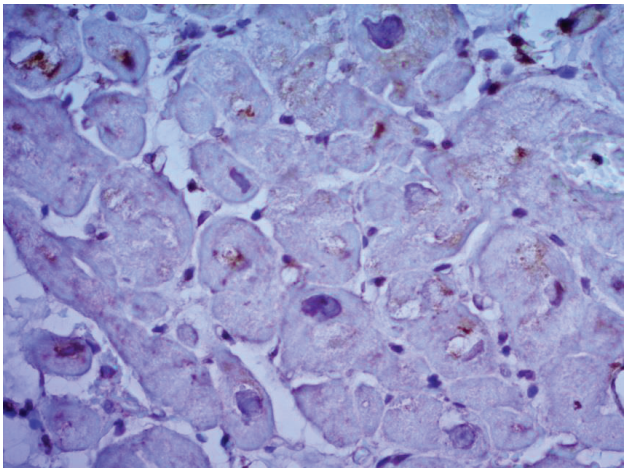

Figure 7. Expression of the enterovirus antigen VP1 in the myocardium. Immunohistochemical study, monoclonal mouse antibodies, ×400.

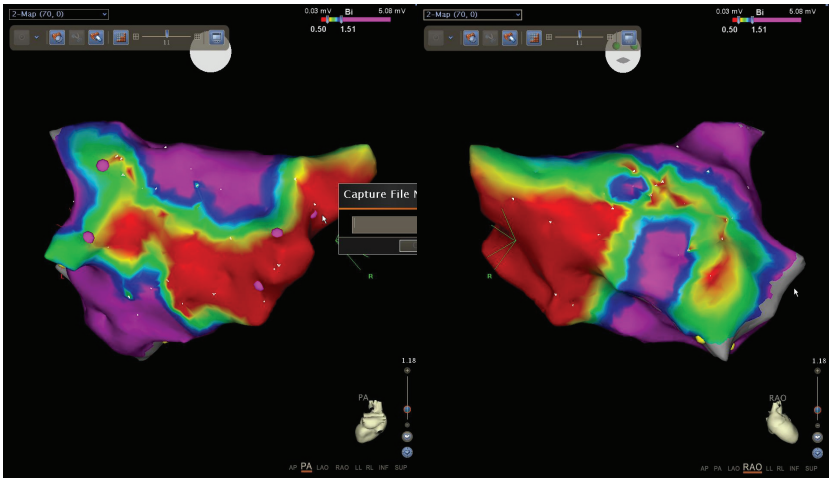

Figure 8. Bipolar voltage map of a patient with the ineffective RFA of AF and fibrosis identified by IAS biopsy. Posterior and right oblique projections. Notes: red-color areas of the atrial signal amplitude less than 0.5 V; magenta areas of the atrial signal amplitude more than 1.5 V; gradient color signals - a transition zone. Purple dots indicate the PV ostiums.

Table 1. Effectiveness of RFA AF in various histological changes in the myocardium.

Parameters	Group 1 (n = 35), n (%)	Group 2 (n = 32)	
		Early Recurrence, n (%)	Late Recurrence, n (%)
No changes in EMB (n = 9)	8 (88.9)	-	1 (11.1)
Fibrotic changes (n = 26)	12 (46.2)	14 (53.8)	9 (34.6)
• perivascular fibrosis (n = 11)	3 (11.5)	8 (30.8)	7 (26.9)
• small focal fibrosis (n = 8)	3 (11.5)	5 (19.2)	2 (7.7)

Table 1. *Cont.*

Parameters	Group 1 (*n* = 35), *n* (%)	Group 2 (*n* = 32)	
		Early Recurrence, *n* (%)	Late Recurrence, *n* (%)
• perimuscular fibrosis (*n* = 7)	6 (23.1)	1 (3.8)	-
Inflammatory changes (*n* = 32)	15 (46.9)	12 (37.5)	17 (53.1)
• lymphoid infiltration (*n* = 9)	4 (12.5)	3 (9.5)	5 (15.6)
• histological myocarditis (*n* = 23)	11 (34.4)	8 (25.0)	12 (37.5)

4. Discussion

On one hand, the introduction of the RFA AF method into clinical practice, as described by M. Haissaguerre in 1998, opened up the possibility of eliminating arrhythmia. On the other hand, the diagnostic search in many cases was limited by routine ECG registration of tachycardia [12]. The use of endocardial interventions for AF has become globally widespread. However, the overall effectiveness of procedures, according to different authors, rarely exceeds 80% [13]. Changing techniques, and creating additional lines and areas of damage, can increase the efficiency, but to a rather moderate degree. Most likely, the limitations are not caused by a low efficiency of procedure itself, but rather they are due to the fact that a purely mechanistic-anatomical approach is used, as a rule, during the interventional treatment when the veins are electrically isolated and lines are applied without paying attention to the causes of AF. However, the etiology and pathophysiology of AF are multifaceted, and subclinical inflammation, and its consequences including the development of fibrotic changes, may play an essential role in AF development.

In our study, using standard examination methods only in 67 (24.5%) out of 274 patients admitted to the clinic with a diagnosis of idiopathic AF we were unable to detect cardiovascular or other diseases that could potentially explain the onset of arrhythmias. Among these 67 patients with idiopathic AF with no clinical and anamnestic data for the presence of inflammation, almost half (47.8%) of them had the inflammatory changes in the myocardium with the cellular infiltration or criteria for histological myocarditis. Immunohistochemical study allowed detection of the virus expression in the myocardium of most of these patients (59.4%). It should be noted, however, that the lack of data for the presence of a viral infection in negative patients does not exclude the potential presence of other viruses, which could not be detected by the virus-specific diagnostic kits used in our study.

The role of inflammation in the pathogenesis of isolated AF remains equivocal and limited. It is well known that the information regarding the presence of myocarditis and fibrosis could be obtained non-invasively using MRI. In our study, MRI performed in all patients did not disclose any finding consistent with biopsy results. The controversial nature of our data may be explained by the fact that this type of examination is highly dependent on the type of scanner and the doctor who conducts the study. Another important method in the non-invasive diagnostics of inflammation is the assessment of systemic concentrations of inflammatory biomarkers. In several studies, the association of inflammation markers and AF occurrence has been demonstrated. In 2018, we published an article in which we showed that in patients with isolated AF, the plasma levels of TNF-a, IL-1ß, IL-6, IL-8, neopterin, and high-sensitivity C-reactive protein exceeded that in comparison with healthy volunteers, while the concentration of IL-10 did not differ. Markers of renin-angiotensin-aldosterone system, particularly plasma renin activity and aldosterone concentration, were within the range of reference values. In this study, a specific serum marker of the latent myocarditis in patients with AF was IL-6 at a concentration of more than 1.6 pg/mL, and the marker of latent viral myocardial infection was neopterin at concentrations >13.2 nmol/L [14]. The increased levels of these markers can serve as a sign of latent viral myocarditis in AF of unclear etiology.

While assessing the effectiveness of the intervention based on the results of histological examination, we found that the effectiveness of primary RFA in patients with the intact myocardium was 88.9%. However, the effectiveness of primary RFA dropped to 46.2% in patients with fibrotic changes of varying severity and was only 34.4% in the presence of criteria for histological myocarditis. Early recurrences of arrhythmias were absent in patients with unchanged myocardium. Patients with the presence of fibrotic changes more often (53.8%) had early relapses and less often late relapses (34.6%), which, to some extent, can be considered associated with a favorable prognosis, despite the presence of fibrotic changes in the myocardium. We observed the inverse relationship in patients with the presence of inflammatory changes: late relapses were detected more often (53.1%) whereas early relapses were found less often (37.5%). This observation most likely indicates the presence of a persisting and ongoing inflammatory process underlying the onset of recurrent arrhythmias. This portion of patients requires more thorough diagnostics, monitoring, and specific treatment.

Unfortunately, the amount of data on available approaches to diagnose atrial myocardial inflammation in vivo is limited to date. Atrial EMB may be dangerous due to the risk of potential complications, but other diagnostic modalities are not always justified in otherwise absolutely-healthy patients, primarily because it is hard to suspect myocarditis if AF is the only symptom of disease. On the one hand, inflammatory changes occurring in the atria are less dangerous and cannot be the primary cause of sudden cardiac death or heart failure. On the other hand, the capabilities of detecting atrial inflammation are limited. Meanwhile, the atria in comparison with the ventricles are more vulnerable to fibrosis and connective-tissue proliferation due to the lower myocardial mass, which ultimately results in the anisotropic propagation of excitation and the occurrence of atrial tachyarrhythmias.

However, according to the published data, Yamaguchi et al. performed the intracardiac ECHO-guided endocardial biopsy in patients with AF. The authors have shown that biopsy from the right atrium (RA) septum seems to be a feasible and safe technique, although the significance of the RA biopsy in clinical practice is still unclear. Also Yamaguchi et al. detected an inverse relationship between bipolar voltage and fibrosis. However, there was variation in fibrosis, especially in patients whose voltage was in the middle range. At the end of the article, the authors concluded that factors other than fibrosis could affect voltage, e.g., myocyte cell size, myocyte disarray, intercellular-spacing, myofibrillar loss, infiltration with adipocytes. However, the impacts of these factors on voltage have not been analyzed, and future studies are warranted [15]. In our study, we conducted endocardial biopsies from IAS with the transesophageal ECHO control. We agree that this procedure seems to be a feasible and safe technique, however, when comparing the results of EMB from IAS and electroanatomic mapping, in our case the results of both studies have largely coincided. Thus, the significance of the RA biopsy in clinical practice requires additional justification. Moreover, it is well known that Mitrofanova et al. in the article "Histological evidence of inflammatory reaction associated with fibrosis in the atrial and ventricular walls in a case-control study of patients with history of atrial fibrillation" have shown that histological signs of chronic inflammation affecting ventricular myocardium are strongly associated with AF and demonstrate significant correlation with fibrosis extent that cannot be explained by cardiovascular comorbidities otherwise [16].

The inflammatory changes in the atrial myocardium identified in our study raise more questions than answers. First of all, this work using an EMB-based approach represents an investigative study and should not be extended to widespread clinical practice. However, the identified inflammatory changes in the atrial myocardium in AF patients require further comprehensive investigation and, above all, the search for the ways of non-invasive or minimally invasive diagnostics. On the other hand, the implementation of such methods in clinical practice would require baseline data, which prompt a clinician to suspect the presence of myocarditis.

The second question is whether the presence of subclinical inflammation and viral infection in the cardiomyocytes of otherwise healthy patients requires therapy. If so, what

should be the treatment goal: the elimination of arrhythmia as the leading symptom or the virus elimination? If the arrhythmia is eliminated, will this mean that the myocardium is healthy and there is no viral infection and subacute myocarditis, which could lead to sudden cardiac death or the development of inflammatory cardiomyopathy and heart failure after an indefinite time? If the treatment goal is to eliminate the virus, then comprehensive etiotropic therapy, which, as a rule, takes longer than one month, would be a priority without a doubt. However, it may be challenging to convince otherwise-healthy patients of treatment necessity. The most important question is how to monitor the effectiveness of the therapy: via the second biopsy or other diagnostic modalities? Will these methods allow study of the processes occurring in the myocardium? The infection consequences, i.e. the amount and extent of fibrous tissue in the atria and ventricles, remains an essential problem as they are known to lead to the onset and progression of atrial and ventricular remodeling.

Only nine (13.4%) of a rather small group of patients included in the study had no histological changes. These cases perhaps may be considered a variant of true electrical heart disease manifested in the form of AF. However, this statement is limited by the capabilities of diagnostic methods used in the study.

4.1. Study Limitations

The present study had some limitations. Our study was single-center and included a small group of patients with isolated AF. Because of this, this study is underpowered and its findings are only hypothesis-generating. Therefore, future research requires larger scale multicenter studies. In our work, we did not assess the adverse cardiac events such as thromboembolic events or heart failure during follow-up. Moreover, we used RFA as a treatment for AF, but we did not treat underlying histological myocarditis. We did not perform the high-density mapping using a multi-pole diagnostic catheter for bipolar voltage maps of the left atrium, but performed mapping with an ablation catheter.

4.2. New Knowledge Gained

The significance of EMB is supported by its ability to reveal the etiology of histological myocarditis and AF, specifically, in MRI negative patients. EMB results confirm the presence of histological myocarditis and, accordingly, may help in choosing etiotropic treatment.

5. Conclusions

The diagnostic term "idiopathic AF" is used unreasonably often in clinical practice. According to our data obtained during a standard examination, only 24.5% of patients had no diseases, which could potentially lead to the development of arrhythmia. The histological findings showed that only about 10% of AF patients had a true idiopathic form of arrhythmia, while half of AF patients had latent inflammatory changes in the myocardium and the remaining patients had fibrotic changes as a result of inflammation. Our findings indicate that the presence of inflammatory and fibrotic changes in the myocardium may increase the rates of early- and late-arrhythmia recurrences in patients undergoing RFA for AF. However, further studies are warranted to investigate in-depth this possible relationship.

Author Contributions: R.E.B.: study concept, study design, enrollment of patients, performing intracardiac examination, ARF of AF, and EMB, patient follow up, data analysis and interpretation, writing the original manuscript, manuscript revision, and approval for publication; M.S.K.: performing intracardiac examination, ARF of AF, and EMB, patient follow up manuscript revision, and approval for publication; Y.V.R.: performing histological and immunohistochemical studies, data analysis and interpretation, manuscript revision, and approval for publication; S.I.S.: patient examination, manuscript revision, and approval for publication; R.B.T.: patient examination, manuscript revision, and approval for publication; N.D.A.: manuscript revision, preparation, and approval for publication; S.V.P.: overall supervision of research, study concept, study design, manuscript revision, and approval for publication. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Science (protocol code 163 and 08/11/2017).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish paper in an anonymous form.

Data Availability Statement: According to the internal regulations of the Institute, all data are the property of the Institute and can only be provided anonymously after an official request.

Conflicts of Interest: The authors declare no conflict of interest.

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Review

Catheter Ablation for Atrial Fibrillation in Structural Heart Disease: A Review

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Abstract: Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. Patients with structural heart disease (SHD) are at an increased risk of developing this arrhythmia and are particularly susceptible to the deleterious hemodynamic effects it carries. In the last two decades, catheter ablation (CA) has emerged as a valuable strategy for rhythm control and is currently part of the standard care for symptomatic relief in patients with AF. Growing evidence suggests that CA of AF may have potential benefits that extend beyond symptoms. In this review, we summarize the current knowledge of this intervention on SHD patients.

Keywords: atrial fibrillation; catheter ablation; structural heart disease

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1. Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia in clinical practice [1] and it is even more frequent in patients with structural heart disease (SHD) [2].

SHD encompasses a heterogeneous group of patients that share some important features, whatever the underlying disease. First, they are characterized by reduced hemodynamic tolerance to elevated heart rates and/or to the loss of atrial contribution to LV filling, which are associated with AF; second, in this population, the choice of anti-arrhythmic drugs (AADs) is limited, owing to possible side-effects; and third, the probability of rhythm control success on AADs is lower than in non-SHD patients [3]. Additionally, SHD patients are less represented in large clinical trials on AF catheter ablation (CA); therefore, except for a suggested higher recurrence rate [4], little evidence is available concerning interventional management of these patients.

The purpose of this article is to briefly review the clinical knowledge on interventional treatment of AF in this population.

Structural Heart Disease Definition

"Structural heart disease" (SHD) is an over-reaching term first introduced by Martin Leon at the 1999 Transcatheter Cardiovascular Therapeutics Meeting to encompass all cardiac disease processes [5].

The European Society of Cardiology (ESC) guidelines identify AF as secondary to SHD when a left ventricle (LV) systolic or diastolic dysfunction is demonstrated or LV hypertrophy, valvular disease, and/or other SHDs are documented [6]. Subsequent literature evolved the nomenclature so that, currently, SHD includes: (a) heart failure with reduced ejection fraction (HFrEF, previously severe or moderate LV systolic dysfunction); (b) heart failure with preserved ejection fraction (HFpEF, previously LV diastolic dysfunction); (c) valvular heart disease (VHD), ranging from prosthetic valves to rheumatic ones; and (d) specific cardiomyopathies, such as hypertrophic cardiomyopathy (HCM) [7].

According to the ESC Guidelines definition, criteria to identify SHD patients are based on non-specific parameters [7]. Thus, the SHD impact on AF prevalence and patient's

prognosis could be different according to the underlying pathology and the severity of the disease.

In studies dealing with AF, specific biomarkers to assess hemodynamic status (e.g., natriuretic peptides) are rarely available and seldom reported and the degree of atrial remodeling is not uniformly defined because of the use of different parameters and imaging techniques (e.g., echocardiography or magnetic resonance).

2. Impact of SHD on AF

Independently of the underlying disease, a common final pathway is supposed to lead to AF: elevated left atrial pressure, causing "atrial myopathy" [8]. Indeed, atrial hypertension is associated with chamber dilation, extracellular matrix remodeling, autonomic imbalance, and calcium handling defects, which have a well demonstrated proarrhythmic effect and are involved in the induction and maintenance of AF [9,10].

The actual incidence and prevalence of AF in the overall SHD population have not been assessed, but data are available for specific subgroups.

2.1. HFrEF

In 2003, Maisel estimated that the AF prevalence ranges from <10% in New York Heart Association (NYHA) functional class I patients to nearly 50% in NYHA IV patients. Overall, HF patients have a sixfold increased risk of AF in the long term [11].

Both AF and HF have a higher prevalence in the elderly, and this might partially explain the correlation between the degree of functional impairment and the occurrence of AF. Nevertheless, there are several pathophysiological reasons for why they are supposed to favor each other, leading to the concept that "AF begets HF and vice versa" [12].

In particular, myocardial inflammation and fibrosis, leading to atrial interstitial fibrosis, are present in both AF and HF. Thus, during exertion, AF itself could be less tolerated in HF patients and, thereby, may trigger clinical recognition of this condition.

In a sample from the Framingham cohort including data between 1980 and 2012, it was found that a greater proportion of individuals have AF without HF, and AF more commonly precedes HF than in cohorts studied in previous years [12]. However, different strategies to detect AF have been implemented over time, making these results hardly comparable. Regarding the temporal relationship between AF and HF onset, it has been noted that patients who develop HF first and AF later have a worse clinical progression compared with the opposite [13].

2.2. HFpEF

HFpEF often coexists with other cardiac diseases; thus, it might be difficult to isolate its specific effect. Diastolic dysfunction should be graded according to American Society of Echocardiography recommendations and the evaluation should be based on parameters that are not affected by the presence of AF [14].

In a population study by Chen et al., one-third of patients with isolated diastolic dysfunction and HF-related symptoms show AF in the ECG presentation [15].

In a longitudinal study by Tsang and colleagues, abnormal LV diastolic function is associated with new onset of AF in almost 10% of cases within 4 years. In particular, the presence of grade 2 or 3 diastolic dysfunction was associated with a 2.5-fold increase in AF recurrence risk when compared with grade 1 dysfunction or normal diastolic function [16].

2.3. Valvular Heart Disease (VHD)

The presence of rheumatic mitral stenosis, repaired mitral valve or prosthetic valve are three different conditions. The presence of just one of the three is sufficient to distinguish valvular and non-valvular AF [17].

In 1990, data from surgical series were published by Wipf et al., who reported an AF prevalence close to 75% in rheumatic heart disease (RHD) at the time of surgical treatment [18]. In addition, in early studies on patients treated with AAD, AF frequently

complicated RHD, with more than 30% of patients with AF episodes over long-term follow-up [19].

Even if a decline in RHD prevalence was recorded in Western countries, the presence of a valvular heart disease is still associated with a 1.8–3.4-fold increased risk for AF [20], and mitral stenosis and mechanical prosthetic valves are associated with a further increase in thromboembolic risk [21].

2.4. Cardiomyopathies

Hypertrophic cardiomyopathy (HCM) is the most common hereditary cardiomyopathy [22], and thus the best investigated. The estimated prevalence of AF in HCM is 22.5% and the annual incidence is 3.1% [23].

The maintenance of sinus rhythm could be of a particular importance in HCM patients, as this is associated with a significant improvement in the New York Heart Association functional (NYHA) class and quality-of-life score [24]. These benefits seem to depend on heart rate control and atrial active contraction, which increase the LV filling, reducing outflow obstruction.

Furthermore, dyspnea and other heart failure symptoms are frequently associated with AF, which is a major cause of hemodynamic deterioration and an ominous prognostic indicator [24].

3. Catheter Ablation

Most structural heart diseases are associated with some degree of atrial hypertension, remodeling, and fibrosis. Marrouche and colleagues have reported that extensive atrial fibrosis is associated with a significant decrease in AF ablation effectiveness [25]. Thus, patients with SHD are expected to have a high rate of AF recurrence and to be less responsive to CA compared with non-SHD patients [26].

The evaluation and comparison among studies on CA in SHD is made difficult by the differences in the ablation strategy, energy sources, and endpoints.

To date, pulmonary veins' isolation (PVI) is recommended for the index procedure in both paroxysmal AF (PAF) and persistent AF (PerAF) patients [27]. More extensive ablation strategies are not supported by consistent data [28]. In particular, no evidence supports a different approach in SHD patients, even if, in this population, there is a widespread tendency to extend ablation beyond PVI, adding lines or complex fragmented atrial electrogram (CFAE) and extra-pulmonary foci ablation.

Radiofrequency is the most represented energy source in the literature on SHDs, whereas cryoballoon results have been reported only in registries [29].

Finally, studies are hardly comparable because of the differences in the assessment of AF recurrence. In many cases, AF detection is based on symptoms or on electrocardiography and/or prolonged cardiac monitoring triggered by symptoms. In some instances, loop recorders are implanted, providing continuous monitoring throughout the follow-up. In the specific setting of SHD, AF is more often symptomatic, thus symptom-based detection might be somehow more reliable than in the general population.

3.1. CA in HFrEF

AF ablation in HFrEF patients has been studied in several randomized clinical trials (RCTs). CA was compared either to other rhythm control strategies (AADs) or to rate control (drugs and/or ablate and pace). In most studies, extrapulmonary lesions, such as left atrial lines or CFAE, were added to PVI; single or multiple procedures were possible. The endpoints ranged from symptom recurrence, documented AF recurrence, and functional improvement (NYHA class, 6 min walk distance, QoL scores, peak oxygen consumption, LVEF, and BNP) to hard ones such as mortality and hospitalization.

Table 1 shows the results of the main studies, with some of them deserving specific considerations.

The CAMERA MRI trial included only idiopathic systolic dysfunction and used cardiac magnetic resonance to assess LVEF [30]. A significant improvement in LVEF (18 ± 13%) in the group of patients treated with catheter ablation and a reduction in LV end-systolic volume (-24 ± 24 mL/m^2 vs. -8 ± 20 mL/m^2, $p < 0.0001$) were observed; furthermore, extensive late gadolinium enhancement (LGE) was a negative predictor of LV functional improvement. Of note, MacDonald et al. published a similar study that failed to show an improvement in LVEF and other functional endpoints, probably owing to a larger proportion of advanced HF patients (90% NYHA III or more) [31].

More recently, RCTs comparing CA to AADs for rhythm control strategy focused on hospitalization or mortality. The AATAC trial compared CA to amiodarone in patients with PerAF [32]. An implanted device was used to detect AF. CA was more effective in preventing recurrences (30% vs. 66%; $p < 0.001$), preventing unplanned HF hospitalization (31% vs. 57%; $p < 0.001$), and reducing all-cause mortality (8% vs. 18%; $p = 0.037$).

CASTLE-AF enrolled 363 HFrEF patients, randomized to PVI ablation or medical (both rate and rhythm control) therapy [33]. Patients had PAF or PerAF, LVEF < 35%, NYHA functional class equal to II or greater, an ICD or CRTD device, and should have failed a prior treatment with AAD. At 38-month follow-up, CA reduced the risk of death or HF hospitalization (28.5% vs. 44.6%, $p = 0.006$). Both all-cause mortality (13.4% vs. 25%, $p = 0.01$) and cardiovascular death (HR 0.49, $p = 0.009$) were significantly reduced in the ablation arm. Arrhythmia-free survival at 5 years was 63% in the ablation group and 22% in the medical therapy arm. Nevertheless, only 10% of screened patients were included in the study, so these results could be applied only in really selected patients.

Interestingly, in a sub-analysis of CASTLE-AF [34], Brachman and colleagues found that a reduction in AF burden below 50% after 6 months of catheter ablation was associated with a significant reduction in all-cause mortality and hospitalizations for HF. The same relationship could not be found if patients were stratified according to AF recurrence after ablation, defined by the HRS consensus statement of at least one AF episode longer than 30 s following the procedure [4]. The authors speculate that this might be explained by a survival benefit proportionate to the time spent in sinus rhythm and by the reduction in AF burden, being an epiphenomenon of reverse atrial and ventricular remodeling following ablation. Overall, these considerations may prompt a paradigm shift in how procedural efficacy is defined.

In 2019, the AMICA trial was stopped owing to futility because a similar improvement in LVEF was obtained in both the CA group and the medical therapy group [35]. Of note, LVEF improved more than expected from the literature in the control group.

Lastly, the RAFT-AF trial compared all-cause mortality and HF events in both HFrEF and HFpEF patients with AF randomized to ablation-based rhythm control or to pharmacologic rate control [36]. Despite showing a non-significant trend for improved outcomes with ablation-based rhythm control (29% relative risk reduction, $p = 0.066$), the trial was stopped early for apparent futility. It must be noted that the decision to terminate the trial was taken following the 2017 ad-interim analysis, when the available results found a trend for a worse outcome with CA, which was eventually overturned in the final results. Notwithstanding this, ablation-based therapy was associated with significantly greater gains in quality of life, 6 min walk distance, and LVEF. In addition, there was a significantly greater fall in NT-proBNP levels in the ablation group.

The results of these trials have been included in a 2020 meta-analysis that, in a population of 1112 HF patients, has demonstrated a consistent benefit of CA compared with AADs in terms of all-cause mortality (49% relative risk reduction (RRR), $p = 0.0003$), re-hospitalizations (56% RRR, $p = 0.003$), LVEF improvement (mean improvement of 6.8%, $p = 0.0004$), AF/AT recurrence (96% RRR, $p < 0.00001$), and quality of life ($p = 0.007$), without significant differences concerning safety [37]. Overall, these results highlight the physiologic and clinical advantage of maintaining sinus rhythm in HF patients, as well as the effectiveness of CA in pursuing this objective. Interestingly, in the same meta-analysis, a second subset of studies comparing pharmacologic rhythm control to rate control failed

to demonstrate clinically significant benefits. This may be explained by a lower efficacy of AADs in maintaining sinus rhythm and by the neutralization of the benefits of sinus rhythm by the adverse effects of these medications.

Furthermore, any rhythm control strategy is at high risk of failure when used in too advanced stages of the disease [38].

3.2. CA in HFpEF

Few data are available on CA in patients with HFpEF because of the recent definition of this nosologic entity.

In the study by Cha et al., the 1-year arrhythmia-free survival after CA was 84% in patients with normal LV function and significantly lower when diastolic or systolic dysfunction was found at echocardiography (75% and 62%, respectively) [39]. Of note, in the diastolic dysfunction group, patients were older and more frequently had hypertension. Nevertheless, both systolic and diastolic dysfunction were significant predictors of increased AF recurrence risk, even after correction for these potential confounders.

Hu et al. showed an association between diastolic abnormality, low voltages at LA electro-anatomical map, and recurrence rates [40]. Even if limited by the low number of patients enrolled, this study suggests a pathophysiological link between extensive fibrosis and CA failure in HFpEF.

A meta-analysis on six observational studies comparing CA in HFpEF and HFrEF found no differences in terms of procedural efficacy, periprocedural adverse events, or re-hospitalizations between the groups, but highlighted a significantly lower mortality at follow-up in the HFpEF group (mean difference of 0.41; 95% CI 0.18–0.94) [41].

Using retrospective data from a national administrative database, Krishnamurthy and colleagues found that CA in patients with HFpEF, compared with patients without HF, is associated with more procedural complications, all-cause readmissions, cardiac readmissions, noncardiac readmissions, and early mortality. Nevertheless, when adjusting for age, sex, and comorbidities, only all-cause readmissions maintain a statistically significant increased risk (OR 1.52; $p = 0.002$) [42]. These results suggest that increased procedural complications, readmission, and early mortality following CA in HFpEF patients are mainly driven by concomitant risk factors, such as age and comorbidities, rather than by HFpEF itself.

Finally, a significant group of HF patients was included in the CABANA trial and randomized to catheter ablation versus drug therapy [43]. In the related sub-group analysis of 778 patients with HF [44], 91% of these had LVEF > 40% and 79% had LVEF > 50%. This sub-group analysis can thus be considered the first randomized prospective collection of data on AF ablation in HFpEF. A significant reduction in the composite outcome of death, disabling stroke, serious bleeding, and cardiac arrest (HR: 0.64, 95% CI 0.41–0.99), as well as in all-cause mortality alone (HR: 0.57, 95% CI: 0.33−0.96), was found; notably, these beneficial results were not evident in the main trial including both HF and non-HF patients. In addition, patients undergoing CA experienced a considerable improvement in quality of life indicators and, not surprisingly, a lower incidence of AF recurrence and burden in each of the 12-month follow-up assessments to the end of the 5-year observation period. Interestingly, compared with other studies, patients were randomized to treatment within a relatively short period of time from their diagnosis of AF (median 1.1 years); as it is known that rhythm control pursued early in the course of AF is associated with better outcomes and that CA is more effective than AADs in maintaining sinus rhythm [45], part of the beneficial effects seen in the CABANA subgroup may be explained by early intervention. Overall, these data reinforce the role of CA in HFpEF, especially when administered in the early stages of the disease.

3.3. Valvular Heart Disease (VHD)

Few studies on CA in patients with uncorrected VHD are available, owing to the strong indication of valvular defect correction before trying the invasive treatment of AF [46]. The results are not consistent; a study found no difference in arrhythmias recurrence between

VHD patients and non-VHD patients, but, notably, the recurrence rate was higher in patients with larger left atria in both groups [47]. Nevertheless, in moderate VHD patients, AF recurrence is more frequent than in non-VHD patients after discontinuation of AADs in the long-term follow-up [48].

Surgical ablation during valve surgery is a valid option [49] and its results are superior to a subsequent single CA procedure [50], but this analysis extends beyond the aim of this paper.

Catheter ablation in patients with prosthetic valves remains challenging; lower effectiveness, higher complication rates, greater radiation exposure, and higher incidence of post-ablation atrial tachycardia were reported [50,51]. Furthermore, a possible role of non-PV foci was suggested by the evidence that a strategy including extended PVI and non-PV trigger elimination is associated with a higher 12-month and long-term arrhythmia-free survival [52].

According to a meta-analysis by Santangeli et al., CA of valvular AF is associated with an increased risk of recurrences in patients with MVR, but it is feasible and safe, despite the presence of prosthetic valves or annuloplasty rings, in experienced centers [53].

3.4. Hypertrophic Cardiomyopathy (HCM)

To date, the role of AF ablation in this setting needs to be inferred from non-randomized observational studies, because no RCT is available. The success rate of AF ablation is lower than in patients without HCM [54]. The procedural results were evaluated in a meta-analysis by Zhao et al. [55]; a single ablation procedure is frequently followed by arrhythmia relapses and antiarrhythmic drugs and/or multiple procedures could be required. In particular, the probability of 3 months' freedom from arrhythmias after a single procedure is estimated to be 79%, while at 18 months, most patients experienced AF recurrences.

The association between AF recurrence and wall thickness or left ventricle (LV) outflow tract obstruction is not predictive, while left atrial (LA) structure, diameter, and electrical features, as well as the presence of LV apical aneurysm, seem to predict post procedural outcome [55–57].

Besides the possible presence of gaps in the isolation lesions set, two interesting hypotheses are proposed to explain the higher recurrence rate seen in HCM patients: the response of hypertrophic tissue to RF is different from that of normal myocardial tissue and non-PV foci are more frequent in HCM patients. The former might be the cause of PV stenosis, which occurs more often in these patients [58]. The latter is supported by the high frequency of post-ablation non-AF atrial tachycardias (38.4%) that have either macro-reentry or localized reentry as an underlying mechanism [59]. This may be explained by the extensive structural alterations seen in HCM atria and may be a reason to pursue a non-PVI-only ablation strategy [60].

3.5. CA Technique in SHD

Following the description of pulmonary veins' isolation (PVI) as the first effective CA strategy for AF [61], different techniques have been described in terms of both energy source (e.g., radiofrequency, cryo-energy, and electroporation) and ablation targets beyond PVI (e.g., posterior wall isolation and rotor ablation). Despite a flourishing body of literature on the role of these different techniques in AF, all of the aforementioned trials have been carried out using radiofrequency as ablation energy and few studies have specifically addressed the topic of CA strategies in SHD.

Recently, a retrospective analysis of the ONE-Stop Italian registry on Cryoballoon (CB) PVI was published [29]. The procedure time, fluoroscopic time, and complication rate were not different in a subgroup of 282 SHD patients as compared with the non-SHD cohort. The recurrence rate was similar in both groups at 13-month follow-up (22.0% vs. 21.6%; $p = 0.895$) and was not related to either left atrial size or LVEF. Of interest, the percentage of SHD patients on AAD treatment decreased from 70.7% to 28.7% after CB-PVI ($p = 0.001$). Because of its retrospective nature, the study suffers from possible selection bias

and included SHD patients with minimal or no reduction in LVEF. Similar results have been found in an international cohort including 318 patients with HF; that is, procedure-related safety and long-term efficacy following PVI through cryoablation were comparable in patients with and without HF [62]. Altogether, these results suggest that CB-PVI is feasible and safe in the SHD setting and that additional benefits might be obtained through the reduction in AAD usage.

More extensive atrial remodeling is present in persistent AF (as opposed to paroxysmal) and when AF is associated with HF. Therefore, mechanisms other than PVs' firing have been hypothesized for AF initiation and maintenance in these settings. Although meta-analyses suggest a potential incremental benefit in terms of procedural efficacy for extra-PVI lesions in patients with persistent AF [63,64], no conclusive evidence has been provided to date. Furthermore, in 2014, a meta-regression analysis reported no differences in sinus rhythm maintenance between the PVI-only approach and extended left atrial ablation in patients with AF and HFrEF [65]. Interestingly, however, in a small single-center study on paroxysmal AF, non-PV triggers were found to be more frequent in patients with LVEF < 35% compared with those with LVEF > 50% (69.1% vs. 26.6%; $p < 0.001$); ablation of these triggers, in addition to PVI, resulted in improved long-term procedural success (75.0% vs. 32.2%; $p < 0.001$) [66]. Thus, further investigation is needed to definitively assess the role of additional lesions in addition to PVI in these contexts.

Table 1. Main trials comparing CA for AF in HF. Bold character is for study primary outcome. Asterisks (*) denote statistical significance. AAD: anti-arrhythmic drugs; AFEQT: atrial fibrillation effect on quality of life; AVN: atrio-ventricular node; CRT: cardiac resynchronization therapy; EF: ejection fraction; ICD: implantable cardioverter-defibrillator; MLHFQ: Minnesota living with heart failure questionnaire; NYHA: New York Heart Association; PAF: paroxysmal atrial fibrillation; PerAF: persistent atrial fibrillation.

	PABA-CHF [67] (2008)	**ARC-HF [68] (2013)**	**CAMTAF [69] (2014)**	**CAMERA-MRI [30] (2017)**	**AATAC [32] (2016)**	**CASTLE-AF [33] (2018)**	**CABANA Subgroup [44]** (2021)	**RAFT-AF [36] (2022)**
Sample size	81	52	50	68	203	363	778	411
Population	EF < 40% NYHA II-III PAF/PerAF	EF < 35% NYHA II-IV PerAF	EF < 50% NYHA II-IV PerAF	EF < 45% (MR) NYHA II–IV PerAF No CAD	EF < 40% NYHA II-III PerAF ICD/CRT-D	EF < 35% NYHA II-IV PAF/PerAF ICD/CRT-D	NYHA II-IV PAF/PerAF >65 years or <65 years + 1 risk factor for stroke	NYHA II/III PAF/PerAF High NT-proBNP
Control group	AVN ablation + CRT	Rate control	Rate control	Rate control	Amiodarone	Pharmacologic rate or rhythm control	Pharmacologic rate or rhythm control	Pharmacologic rate control
Follow-up (months)	6	12	12	6	24	60	60	24
AF-free survival	71% AAD off	68% AAD off	38% AAD off	56% AAD off	**70% AAD off vs. 34% with AAD ***	63.1% AAD off vs. 21.7% with AAD *	73% AAD off vs. 42% with AAD *	85.6% AAD off vs. 12.9% with AAD *
LVEF	**35% vs. 28% ***	+5.6% *	**40% vs. 31% ***	**Δ 18% vs. 4.4% ***	Δ 8.1% vs. 6.2% *	Δ 8.0% vs. 0.2% *		10.1% vs. 3.8% *
Peak O_2		**Δ +3.07 mL/kg/min ***	22 vs. 18 mL/kg/′ *					
BNP		Δ −124 vs. −18 pg/mL *	126 vs. 327 pg/mL *	98 vs. 247 pg/mL *				−77.1% vs. −39.2% *
6′ walk (m)	**340 vs. 297 ***	+21 vs. −10 (n.s.)			Δ 22 vs. 10 *	Δ 0 vs. −30		Δ 44.9 vs. 27.5 *
QoL	**MLHFQ 60 vs. 81 ***	MLHFQ median −15.5 vs. −5 *	MLHFQ 24 ± 22 vs. 47 ± 22 *	SF 36 physical score 48.5 vs. 44.6 *	MLHFQ Δ 11 vs. 6 *		AFEQT 2.5 vs. 7.4 *	MLHFQ −5.4 *
Clinical outcome					Death: 8% vs. 18% *	**Death/hospitalization: 28.5% vs. 44.6% ***	**Death/stroke/bleeding: 9.0% vs. 12.3% ***	**Death/HF event: 23.4% vs. 32.5%**

4. Conclusions

Catheter ablation in SHD patients could be technically challenging, but it is feasible and safe. The best ablation strategy is not well defined; although non-PV additional lesions are a common practice, a PVI-only approach might have a role even in SHD patients. Whatever the initial ablation method, multiple procedures are often needed. Evidence of the improvement in LV function and quality-of-life is available in particular for HFrEF patients, while data on hospitalization and mortality are encouraging but limited to very specific subsets. Overall, despite that, in SHD patients, CA shows a higher AF recurrence rate, the clinical benefit could be more significant in the setting of SHD.

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The Value of Left Ventricular Mechanical Dyssynchrony and Scar Burden in the Combined Assessment of Factors Associated with Cardiac Resynchronization Therapy Response in Patients with CRT-D

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Abstract: Background: Cardiac resynchronization therapy (CRT) improves the outcome in patients with heart failure (HF). However, approximately 30% of patients are nonresponsive to CRT. The aim of this study was to determine the role of the left ventricular (LV) mechanical dyssynchrony (MD) and scar burden as predictors of CRT response. Methods: In this study, we included 56 patients with HF and the left bundle-branch block with QRS duration ≥ 150 ms who underwent CRT-D implantation. In addition to a full examination, myocardial perfusion imaging and gated blood-pool single-photon emission computed tomography were performed. Patients were grouped based on the response to CRT assessed via echocardiography (decrease in LV end-systolic volume ≥15% or/and improvement in the LV ejection fraction ≥5%). Results: In total, 45 patients (80.3%) were responders and 11 (19.7%) were nonresponders to CRT. In multivariate logistic regression, LV anterior-wall standard deviation (adjusted odds ratio (OR) 1.5275; 95% confidence interval (CI) 1.1472–2.0340; $p = 0.0037$), summed rest score (OR 0.7299; 95% CI 0.5627–0.9469; $p = 0.0178$), and HF nonischemic etiology (OR 20.1425; 95% CI 1.2719–318.9961; $p = 0.0331$) were the independent predictors of CRT response. Conclusion: Scar burden and MD assessed using cardiac scintigraphy are associated with response to CRT.

Keywords: heart failure; left bundle-branch block; mechanical dyssynchrony; response to cardiac resynchronization therapy; gated SPECT myocardial perfusion imaging

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1. Introduction

Heart failure (HF) is a rapidly growing public health issue, with an estimated prevalence of more than 37.7 million individuals globally [1]. In the developed world, this disease affects approximately 2.0% of the adult population [2]. In the United States, the total percentage of the population with HF is projected to rise from 2.4% in 2012 to 3.0% in 2030 [3,4]. In Russian Federation, the prevalence of chronic HF (CHF) is 10.2% [5]. The main cause of CHF is coronary heart disease, which accounts for about 70.0%, and the remaining 30.0% are nonischemic heart diseases [6]. More than two decades of research has established the role of cardiac resynchronization therapy (CRT) in medically refractory, mild to severe systolic HF with abnormal QRS duration and morphology [7]. The prolongation of QRS (120 ms or more) occurs in 14.0% to 47.0% of HF patients and the ventricular conduction disturbance, most commonly the left bundle-branch block (LBBB), is present in approximately one-third of HF, leading to the mechanical dyssynchrony (MD) of ventricles [6,8]. Prospective randomized studies of patients with both ischemic HF (IHF) and nonischemic HF (NIHF) have shown that CRT translates into long-term clinical benefits, such as improved quality of life, increased functional capacity, reduction in hospitalization for HF, and overall mortality [9–11]. These patients qualified as responders to

CRT [12,13]. However, CRT is effective in 70.0% of patients, and the remaining 30.0% do not respond to the device therapy [7,14]. This finding suggests that the existing criteria for patient selection to CRT are not always effective. In this regard, it is necessary to search for additional selection criteria or prognostic markers for CRT response in patients with CHF.

Some studies have shown that the ventricular MD assessment using transthoracic echocardiography (TTE), magnetic resonance imaging (MRI), computed tomography (CT), and single-photon emission computed tomography (SPECT) can play a key role in the prediction of CRT response [15–19]. However, according to other studies, TTE indicators are not reliable CRT response predictors [20]. The application of MRI, despite its high accuracy and information content, is limited by its high cost and complexity of cardiac protocols, and it is an operator-dependent method [21]. By contrast, gated myocardial perfusion imaging (MPI) and gated blood-pool SPECT (gBPS) are simpler, have higher reproducibility, and allow for the detection of the area of ventricular MD and impaired myocardial flow and scarring [22]. The predictive value of MD and scar burden assessed via MPI remains disputable. In some studies, MD is correlated with the positive response to CRT in patients with HF of ischemic and nonischemic etiologies [23,24]. However, another work shows the absence of MD prognostic significance in patients with IHF [25,26]. The good prognostic value of scar burden assessed via cardiac scintigraphy has been demonstrated in several studies [27]. However, papers devoted to the combined assessment of the factors associated with reverse remodeling, which can be used for the improved selection of patients for CRT, are rare [28].

The aim of this study was to identify the significance of MD and scar burden assessment using MPI and gBPS as a combined predictor of CRT response in patients with HF of ischemic and nonischemic etiologies.

2. Materials and Methods

2.1. Patient Population and Study Design

Patients with indications for CRT according to the ESC guidelines were included in this clinical, nonrandomized, open, prospective study [29]. The inclusion and exclusion criteria were determined in accordance with the research project "Single-Photon Emission Computed Tomography for Prediction and Evaluation of Cardiac Resynchronization Therapy Efficacy in Chronic Heart Failure Patients" (ClinicalTrials.gov, NCT03667989). Patients who were included in the study met the following criteria: the presence of HF (ischemic or nonischemic etiology), sinus rhythm, permanent LBBB with QRS duration $\geq$150 ms, New York Heart Association (NYHA) functional class (FC) of HF II-III, left ventricular ejection fraction (LVEF) $\leq$35%, and optimal medical therapy for at least 3 months. Individuals with NYHA FC of HF 0, I, IV, decompensated HF, recent myocardial infarction (less than 3 months), recent revascularization (within last 3 months), other cardiac intervention, acute HF decompensation, right bundle-branch block, previously implanted pacemaker or cardioverter–defibrillator, severe comorbidity, cognitive impairment, or with indications of revascularization and heart transplantation, as well as patients under 18 years of age, were excluded. HF etiology was considered ischemic in the presence of significant coronary artery disease ($\geq$50% stenosis in one or more of the major coronary arteries) and/or a history of myocardial infarction or prior revascularization.

All patients underwent full physical examination (6 min walk distance test (6MWDT), electrocardiography (ECG), transthoracic echocardiography (TTE), Holter ECG monitoring, coronary angiography, and blood analyses), MPI with 99mTc–methoxy isobutyl isonitrile (99mTc–MIBI) and gBPS before device implantation. In all cases, CRT devices with the defibrillation function (CRT-D) were implanted, according to the ESC guidelines [29]. All patients received the basic therapy in accordance with the present guidelines. The follow-up was performed 6 months after CRT-D implantation.

2.2. Consent

The study was carried out in accordance with the principles of the Helsinki Declaration and with the standards of good clinical practice. The study protocol was approved by the local ethics committee. All the participants received written informed consent prior to the study inclusion. Ethical approval by the hospital review committee and patient consent according to the institutional guidelines were obtained.

2.3. Minute Walk Distance Test

The assessment of HF FC was performed in accordance with the NYHA criteria, using 6MWDT before and 6 months after CRT-D implantation. For the analysis, the walking distance in meters and NYHA FC were used, and the following ranking was used:

- More than 551 m—the patient has no signs of HF;
- A distance of 426–550 m—I FC of HF;
- A distance of 301–425 m—II FC of HF;
- A distance of 151–300 m—III FC of HF;
- Less than 150 m—IV FC of HF.

2.4. TTE Acquisition and Analysis

TTE with the intracardiac hemodynamic parameter assessment was performed using Philips HD15 PureWave (the Netherlands) ultrasound machine before and after 6 months of CRT-D implantation. The examination was carried out from standard positions with the determination of the left atrium (LA) and right ventricle (RV) sizes, interventricular septum (IVS) and LV posterior-wall (LVPW) thickness, LV end-systolic dimension (LVESD), LV end-diastolic dimension (LVEDD), LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), the index of myocardial mass (IMM), LVEF, right ventricular systolic pressure (RVSP), stroke volume (SV), LV end-systolic index (LVESI), LV end-diastolic index (LVEDI), the left atrial index (LAI), and the right atrial index (RAI). The mitral, tricuspid, and aortic valve functions, as well as the right and left ventricular contractility, were assessed.

2.5. Scintigraphic Data Acquisition

The scintigraphy examination was performed using CZT SPECT/CT (GE Discovery 570C, GE Healthcare, Haifa, Israel) with low-energy multi-pinhole collimators and 19 stationary detectors [30]. Each detector contained 32 × 32 pixelated (2.46 × 2.46 mm) CZT elements. The energy window was symmetrically centered to ± 20% of the 140 keV Tc-99m photopeak. The images were reconstructed on the dedicated workstation (Xeleris 4.0; GE Healthcare, Haifa, Israel).

The time interval between MPI and gBPS examinations ranged from 1 to 2 days. MPI was performed first in all patients.

2.6. MPI Acquisition and Analysis

MPI was performed according to the standard ECG-gated (16 frames/cardiac cycle) rest protocol [30] approximately 60 min after the administration of 138–357 MBq of 99mTc–MIBI. All patients were imaged in a supine position with arms placed over their heads for an acquisition time of 7 min. A low-dose CT scan (120 kV, 20 mA) was performed for the attenuation correction. All images were reconstructed using the iterative reconstruction (60 iterations; Green OSL α 0.7; Green OSL β 0.3) and Butterworth post-processing filter (frequency 0.37; order 7) in a 70 × 70-pixel matrix with 50 slices. MPI data were processed using Corridor 4DM (University of Michigan, Ann Arbor, MI, USA) software. The reconstructed MPI included the standard cardiac short and vertical and horizontal long axes and the 17-segment bull's eye map. Each of the 17 segments was scored based on a semiquantitative 5-point scoring system (from 0—normal uptake to 4—no radiotracer uptake) [31]. The summed rest score (SRS) of all segments was quantified. Scar burden was defined as all segments with abnormal radiotracer uptake at rest.

2.7. gBPS Acquisition and Analysis

gBPS was performed following in vivo labeling patient's red blood cells with a 99mTc–pertechnetate dose of 555–720 MBq [32]. The data were acquired with ECG gating (16 frames/cardiac cycle). The patients were imaged in a supine position with arms placed over their heads for an acquisition time of 10 min. No attenuation correction was used. Images were reconstructed using iterative reconstruction (60 iterations; Green OSL α 0.7; Green OSL β 0.3) and a Butterworth post-processing filter (frequency 0.52; order 5) in a 70 $\times$ 70-pixel matrix with 57 slices. The image quantification and phase analysis were obtained with the Quantitative Blood-Pool SPECT 2009.0 (Cedars-Sinai Medical Center, Los Angeles, CA, USA) software, which allowed for an evaluation of the functional variables of LV and RV. Ventricular contours were adjusted manually when required. The following parameters for both ventricles were determined: the peak emptying rate (PER, expressed as EDV/s), the peak filling rate (PFR, EDV/s), and the second peak filling rate (PFR2, EDV/s).

The severity of intra- and interventricular dyssynchrony was evaluated using the Fourier transform method. Global MD indices were evaluated for ventricles' phase standard deviation (SD), histogram bandwidth (HBW), and phase entropy (PE). Interventricular dyssynchrony (IVD) was calculated according to the histogram peak of LV and RV. Moreover, the following regional MD indices were assessed: SD and E. The regional analysis of LV MD was based on the assessment of the free wall (FW), anterior wall (AW), lateral wall (LW), inferior wall (IW), and septal wall (SW) of LV. The mean effective radiation dose for the entire study protocol was 7.48 $\pm$1 mSv (range 5.1–10.3 mSv) per patient.

2.8. CRT-D Implantation and Programming

The active-fixation atrial (AL) and defibrillation leads (DLs), as well as the passive-fixation LV lead, were positioned under fluoroscopic guidance using a transvenous approach. DL was implanted into the right ventricular apex or interventricular septum. Lead positions were confirmed via fluoroscopy in the posteroanterior (PA) and left anterior oblique (LAO) view and the intraoperative threshold testing. The capture threshold, sensing amplitude, and impedance measurements of the leads were performed using the pacing system analyzer (Medtronic, Minneapolis, MN, USA) with sterile crocodile clip cables.

The implantation of the LV pacing lead was performed by cannulating one of the tributaries of the coronary sinus using the delivery system. The venogram was performed in AP and LAO projections. Access to the target branch within the coronary sinus and subsequent advancement of the LV lead was performed using an "over-the-wire" technique. In case of troubles with the target vein branch cannulation, we used the "interventional" technique with inner catheters (subselector). The intraoperative threshold testing was performed for checking the optimal pacing threshold and phrenic nerve stimulation after LV lead was positioned to the target vein.

CRT-D programming was carried out in accordance with international standards [33]. In every CRT-D device, the monitoring zone was programmed with a heart rate of 140–170 beats per minute (bpm) for more than 50 consecutive cycles without antitachycardia pacing (ATP) and shock therapy. The ventricular tachycardia (VT) zone was programmed for 170–200 bpm with 30 cycles and with ATP ($\geq$1 burst pacing and $\geq$1 ramp pacing) and shock therapy (first shock with the submaximal shock discharge). The ventricular fibrillation (VF) zone was programmed for $\geq$201 bpm with 12 cycles and with ATP during CRT-D charging and the maximum shock discharge. The atrioventricular (AV) delay interval was programmed 20–40 ms less than the native AV delay. Biventricular pacing was switched on in all patients, and the V–V interval (left ventricle $\rightarrow$ right ventricle) was optimized using the surface ECG to obtain the narrowest QRS complex.

2.9. Clinical Follow-Up, CRT-D Data Acquisition, and Analysis

The follow-up information was acquired for 56 of the 64 patients who were included in the prospective analysis. The information about arrhythmic events was determined from CRT-D interrogation reports. The arrhythmic events (VT, VF, atrial fibrillation, and

the appropriate and inappropriate ICD therapy) and CRT-D lead system parameters were evaluated at follow-up. The flowchart of the study is shown in Figure 1. The primary endpoint was a decrease in LVESV ≥15% or/and an improvement in LVEF ≥5% [26,34].

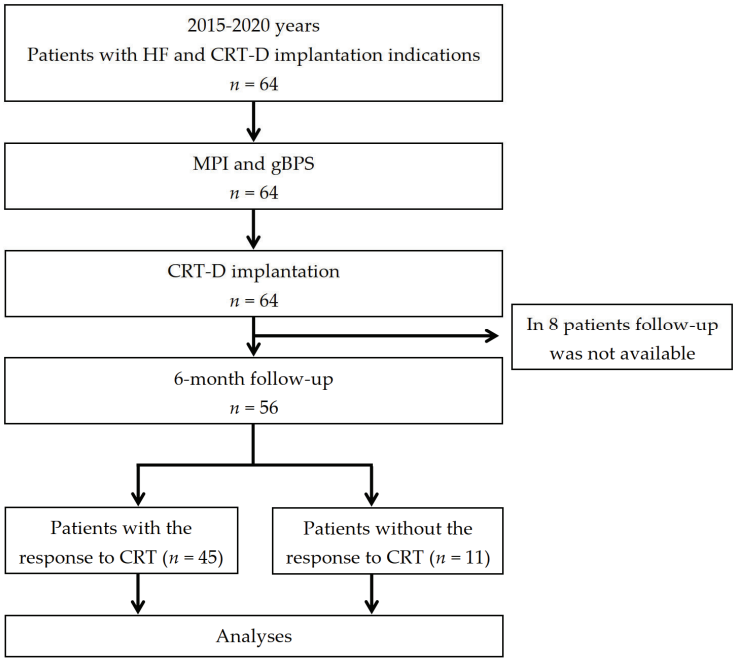

Figure 1. Study flowchart: HF—heart failure; MPI—myocardial perfusion imaging; gBPS—gated blood-pool SPECT; CRT—cardiac resynchronization therapy; CRT-D—CRT devices with the defibrillation function.

2.10. Statistical Analysis

Statistical analysis was performed using the software package Statistica 10.0, StatSoft (USA). The Shapiro–Wilk test was used to assess the normality of the distribution of the trait. For variables with the normal distribution, the mean value (M) and standard deviation (SD) were calculated, while for others, the median (Me) with an interquartile range [Q_1, Q_3] were calculated. The nonparametric Mann–Whitney test for independent samples and the Wilcoxon test for dependent samples were used. The nonparametric Spearman analysis was used to assess the correlations between the pairs of quantitative features. Efficacy analysis was performed using logistic regression analysis. The forward-stepwise logistic regression analysis was used to evaluate the independent predictors of CRT response. Receiver operating characteristic (ROC) analysis was used to determine the diagnostic efficiency of the method using MedCalc statistical software package. We considered significant p values <0.05.

3. Results

3.1. Patients' Baseline Clinical and Follow-Up Characteristics

A total of 56 (100.0%) patients who underwent MPI, gBPS, CRT-D implantation, and 6-month follow-up were included in this study. The first group consisted of 45 (80.3%) individuals with a response to CRT (RESP), and the second group comprised 11 (19.7%) patients without response (non-RESP). The baseline demographics and clinical characteristics of the included patients are shown in Table 1. Considering all patients, the mean age was 57.0 ± 11.5 years, and 35 (62.5%) patients were males. The baseline 6MWDT, HF class NYHA, QRS duration, TTE parameters, arrhythmias before CRT-D implantation, LV

lead position, HF etiology, comorbid pathologies, and medical therapy records between the groups are also shown in Table 1. There were no significant differences between the groups in baseline demographics and clinical characteristics.

Table 1. Baseline demographics and clinical characteristics of enrolled patients.

Demographic and Clinical Characteristics	Total (n = 56)	RESP (n = 45)	Non-RESP (n = 11)	$P_{2–3}$
	1	2	3	
Age, year, mean ± SD	57.0 ± 11.5	56.7 ± 11.8	58.4 ± 10.8	0.680
Male gender, *n* (%)	35 (62.5)	28 (62.2)	7 (63.6)	0.950
Ischemic heart failure, *n* (%)	22 (39.3)	15 (33.4)	7 (63.6)	0.124
Nonischemic heart failure, *n* (%)	34 (60.7)	30 (66.6)	4 (36.4)	0.124
6 min walk distance test, m, mean ± SD	284.5 ± 66.3	288.3 ± 64.8	269.0 ± 73.1	0.312
Heart failure:				
II functional class NYHA, *n* (%)	23 (41.1)	20 (44.4)	3 (27.3)	0.386
III functional class NYHA, *n* (%)	33 (58.9)	25 (55.6)	8 (72.7)	0.386
QRS duration, ms, Me [Q1; Q3]	165.0 [160.0; 180.0]	165.0 [160.0; 180.0]	165.0 [155.0; 185.0]	0.657
LVEF, % [Q1; Q3]	28.0 [22.0; 31.0]	28.0 [21.0; 31.0]	28.0 [25.0; 32.0]	0.502
LVESV, ml [Q1; Q3]	171.0 [131.5; 217.5]	169.0 [133.0; 210.0]	208.0 [121.0; 232.0]	0.598
History of sustained VT, *n* (%)	5 (8.9)	3 (6.7)	2 (18.2)	0.563
History of ventricular fibrillation, *n* (%)	1 (1.8)	1 (2.2)	0 (0.0)	0.917
Comorbidities:				
Hypertension, *n* (%)	22 (39.3)	15 (33.4)	7 (63.6)	0.124
Left ventricular hypertrophy, *n* (%)	45 (80.3)	35 (77.8)	10 (90.9)	0.509
Diabetes mellitus, *n* (%)	8 (14.3)	6 (13.3)	2 (18.2)	0.812
Body mass index, kg/m^2, mean ± SD	28.9 ± 5.0	28.7 ± 5.3	29.7 ± 3.8	0.509
Dyslipidemia, *n* (%)	23 (41.0)	18 (40.0)	5 (45.4)	0.788
GFR, ml/min, mean ± SD	72.2 ± 21.2	72.3 ± 22.7	71.8 ± 13.7	0.804
Therapy:				
Beta-blockers, *n* (%)	53 (94.6)	43 (95.5)	10 (90.9)	0.820
Loop diuretics, *n* (%)	44 (78.6)	33 (73.3)	11 (100.0)	0.176
Potassium-sparing diuretics, *n* (%)	43 (76.8)	36 (80.0)	7 (63.6)	0.409
ACEI, *n* (%)	33 (58.9)	26 (57.8)	7 (63.6)	0.772
Antiplatelet agents, *n* (%)	33 (58.9)	24 (53.3)	9 (81.8)	0.148
Statins, *n* (%)	31 (55.3)	25 (55.6)	6 (54.5)	0.967
Amiodarone, *n* (%)	20 (35.7)	16 (35.5)	4 (36.4)	0.975
Angiotensin II receptor blocker, *n* (%)	19 (33.9)	15 (33.4)	4 (36.4)	0.914
LV lead position:				
Lateral vein, *n* (%)	18 (32.1)	16 (35.5)	2 (18.2)	0.380

Table 1. *Cont.*

Demographic and Clinical Characteristics	Total (n = 56)	RESP (n = 45)	Non-RESP (n = 11)	$P_{2–3}$
Posterolateral vein, *n* (%)	20 (35.7)	16 (35.5)	4 (36.4)	0.975
Anterolateral vein, *n* (%)	10 (17.8)	8 (17.7)	2 (18.2)	0.991
Posterior vein, *n* (%)	8 (14.2)	5 (11.1)	3 (27.3)	0.415
Pacing QRS duration, ms, Me [Q1; Q3]	140.0 [130.0; 140.0]	140.0 [130.0; 140.0]	140.0 [130.0; 140.0]	0.243
Quadripolar LV lead, *n* (%)	28 (50.0)	24 (53.3)	4 (36.3)	0.392
Bipolar LV lead, *n* (%)	28 (50.0)	21 (46.7)	7 (63.7)	0.392
Paced AV delay, ms, Me [Q1; Q3]	150.0 [140.0; 150.0]	150.0 [140.0; 150.0]	150.0 [150.0; 150.0]	0.464
Sensed AV delay, ms, Me [Q1; Q3]	120.0 [100.0; 120.0]	120.0 [100.0; 120.0]	120.0 [100.0; 125.0]	0.215
Interventricular delay, ms, Me [Q1; Q3]	22.5 [12.5; 40.0]	25.0 [15.0; 40.0]	20.0 [10.0; 40.0]	0.885

Values are mean ± SD and Me [Q1; Q3] for continuous variables and *n* (%) for categorical variables. ACEI—angiotensin-converting enzyme inhibitors, GFR—glomerular filtration rate, non-RESP—patients without response to cardiac resynchronization therapy, RESP—patients with response to cardiac resynchronization therapy, VT—ventricular tachycardia, NYHA—New York Heart Association, LV—left ventricular, LVEF—left ventricular ejection fraction, LVESV—left ventricular end-systolic volume, AV—atrioventricular.

Both groups were comparable in terms of pre-CRT-D implantation scintigraphic parameters, except SRS, RV PFR, and MD indicators, assessed via MPI and gBPS. In RESP patients, the right ventricular peak filling rate (RV PFR) (p = 0.005), the left ventricular anterior-wall entropy (LV AW_E) (p = 0.001), the left ventricular anterior-wall standard deviation (LV AW_SD) (p = 0.0001), the right ventricular free-wall standard deviation (RV FW_SD) (p = 0.011), the left ventricular entropy (LV_E) (p = 0.033), and IVD (p = 0.022) were significantly higher, and SRS (p = 0.018) and RV PFR2 (p = 0.028) were significantly lower than in non-RESP subjects. A detailed comparison of pre-CRT-D implantation scintigraphic parameters is presented in Table 2.

Both groups were comparable in terms of TTE parameters before CRT-D implantation. In RESP patients 6 months after CRT-D implantation, LVESD (p = 0.015), LVEDD (p = 0.04), LVESV (p = 0.005), LVESI (p = 0.019), and LVSI (p = 0.02) were significantly lower, and LVEF (p < 0.001) was significantly higher than in non-RESP patients. The QRS duration 6 months after CRT-D implantation did not differ significantly between the groups. In RESP patients, QRS duration was 140.0 ms [130.0; 140.0], and non-RESP was 140.0 ms [130.0; 140.0] (p = 0.243).

Both groups were comparable in terms of the number of I (p = 0.215) and II (p = 0.332) HF class NYHA patients after 6 months of CRT-D implantation. The quantity of III HF class NYHA patients in the non-RESP (n = 7 (63.6%)) group was significantly higher than in the RESP (n = 9 (20.0%)) group (p = 0.026). Additionally, 6MWDT in the RESP (382.4 ± 88.1 m) group was significantly higher than in the non-RESP (288.1 ± 73.1 m) group (p = 0.003) after 6 months of CRT-D implantation.

Table 2. Scintigraphic characteristics before CRT-D implantation.

Scintigraphic Parameters	Total (n = 56)	RESP (n = 45)	Non-RESP (n = 11)	$P_{2–3}$
	1	2	3	
Gated Blood-Pool SPECT:				
IVD, ms	67.1 [38.1; 102.4]	71.8 [42.0; 112.7]	39.2 [9.0; 76.7]	0.022
LV HBW, °	203.0 [192.0; 222.0]	203.0 [186.0; 222.0]	216.0 [192.0; 234.0]	0.190
LV PE, %	72.0 [62.0; 73.0]	72.0 [62.0; 73.0]	64.0 [59.0; 66.0]	0.033
RV HBW, °	120.0 [99.0; 198.0]	120.0 [96.0; 186.0]	198.0 [198.0; 204.0]	0.053
RV PE, %	62.0 [59.5; 67.0]	62.0 [60.0; 67.0]	63.0 [59.0; 67.0]	0.375
RV FW_SD, °	28.0 [16.0; 36.5]	28.0 [20.0; 44.0]	16.0 [13.0; 26.0]	0.011
LV S_SD, °	35.0 [23.0; 40.5]	35.0 [25.0; 42.0]	23.0 [19.0; 32.0]	0.105
LV S_E, %	65.0 [56.0; 72.5]	65.0 [59.0; 73.0]	56.0 [50.0; 58.0]	0.061
LV AW_SD, °	25.0 [11.5; 28.0]	25.0 [17.0; 29.0]	10.0 [10.0; 12.0]	<0.001
LV AW_E, %	50.0 [36.0; 57.5]	50.0 [45.0; 61.0]	36.0 [33.0; 37.0]	0.001
LV LW_SD, °	12.0 [9.0; 16.0]	12.0 [9.0; 15.0]	16.0 [9.0; 20.0]	0.109
LV LW_E, %	36.0 [32.0; 47.0]	36.0 [31.0; 47.0]	37.0 [33.0; 52.0]	0.327
LV IW_SD, °	28.0 [26.0; 37.0]	28.0 [26.0; 37.0]	27.0 [25.0; 37.0]	0.312
LV IW_E, %	59.0 [55.5; 61.50]	59.0 [56.0; 61.0]	60.0 [54.0; 62.0]	0.470
LV PER	−0.81 [−1.18; −0.53]	−0.78 [−1.13; −0.44]	−1.01 [−1.38; −0.57]	0.364
LV PFR	0.745 [0.53; 1.045]	0.7 [0.53; 1.00]	0.94 [0.6; 1.27]	0.154
LV PFR2	0.63 [0.535; 0.64]	0.63 [0.48; 0.63]	0.64 [0.58; 0.66]	0.092
RV PER	−1.66 [−2.39; −0.81]	−1.55 [−2.41; −0.6]	−1.72 [−2.17; −1.22]	0.672
RV PFR	1.38 [1.01; 1.71]	1.51 [1.08; 1.77]	1.01 [0.92; 1.08]	0.005
RV PFR2	1.31 [1.23; 1.63]	1.31 [1.22; 1.57]	1.63 [1.39; 1.63]	0.028
Myocardial perfusion imaging:				
SRS, %	7.5 [4.0; 14.0]	6.0 [3.0; 12.0]	13.0 [9.0; 16.0]	0.018

Values are expressed as Me [Q1; Q3]. IVD—interventricular dyssynchrony, LV HBW—left ventricular histogram bandwidth, LV PE—left ventricular phase entropy, RV HBW—right ventricular histogram bandwidth, RV PE—right ventricular phase entropy, RV FW_SD—right ventricular free-wall standard deviation, LV S_SD—left ventricular septal-wall standard deviation, LV S_E—left ventricular septal-wall entropy, LV AW_SD—left ventricular anterior-wall standard deviation, LV AW_E—left ventricular anterior-wall entropy, LV LW_SD—left ventricular lateral-wall standard deviation, LV LW_E—left ventricular lateral-wall entropy, LV IW_SD—left ventricular inferior-wall standard deviation, LV IW_E—left ventricular inferior-wall entropy, LV PER—left ventricular peak emptying rate, LV PFR—left ventricular peak filling rate, LV PFR2—left ventricular peak filling rate on the second peak, RV PER—right ventricular peak emptying rate, RV PFR—right ventricular peak filling rate.

3.2. Events According to the CRT-D Interrogation Data

During 6 months of follow-up, VT events were registered in seven (12.5%) patients from both groups. In the first group (RESP patients), VT was registered in four (7.1%) patients: three unsustained VT with spontaneous termination and one sustained VT, terminated using ATP therapy. In the second group (non-RESP patients), VT was registered in three (5.4%) cases (p = 0.353). There were only three unsustained VT with spontaneous termination (p = 0.297). There were no lead dysfunction, dislocation, and inappropriate ICD therapy in either group. In RESP patients 6 months after device implantation, according to the CRT-D interrogation data, the paced atrioventricular delay was 148.7 ± 14.5 ms, the sensed atrioventricular delay was 110.0 ± 16.1 ms, the interventricular delay (first LV) was 25.0 ms [15.0; 40.0], and the time of biventricular pacing was 98.1 ± 1.9%. In non-RESP individuals 6 months after CRT-D implantation, the paced atrioventricular delay was

153.6 ± 18.0 ms (p = 0.464), the sensed atrioventricular delay was 116.8 ± 18.2 ms (p = 0.215), the interventricular delay (first LV) was 20.0 ms [10.0; 40.0] (p = 0.885), and the time of biventricular pacing was 98.7 ± 0.4% (p = 0.433).

3.3. CRT Response Predictors

According to the ROC analysis, the SRS and MD indicators (RV PFR, LV AW_E, LV AW_SD, RV FW_SD, LV_E, IVD, and RV PFR 2) were statistically significant predictors of CRT response (Table 3).

Table 3. The ROC analysis results.

Parameters	95% CI	Cut-off	AUC	Sensitivity	Specificity	p
SRS	0.596–0.841	≤7.0%	0.731	60.00	90.91	0.001
RV PFR	0.639–0.872	>1.15	0.771	66.67	90.91	<0.001
LV AW_E	0.689–0.906	>39.0%	0.815	80.00	90.91	<0.001
LV AW_SD	0.757–0.947	>13.0°	0.873	84.44	90.91	<0.001
RV FW_SD	0.616–0.856	>27.0°	0.749	64.44	90.91	0.004
LV_E	0.572–0.823	>68.0%	0.709	68.89	90.91	0.006
IVD	0.590–0.836	>91.8	0.725	40.00	100.00	0.005
RV PFR 2	0.580–0.829	≤1.38	0.716	73.33	81.82	0.013

Notes: 95% CI—95% confidence interval, AUC—area under the curve, IVD—interventricular dyssynchrony, LV AW_E—left ventricular anterior-wall entropy, LV AW_SD—left ventricular anterior-wall standard deviation, LV_E—left ventricular entropy, RV FW_SD—right ventricular free-wall standard deviation, RV PFR—right ventricular peak filling rate, RV PFR 2—right ventricular peak filling rate on the second peak, SRS—summed rest score.

The multivariate logistic regression analysis included the following indicators: QRS duration, gender, HF etiology, LV lead position, 6 min walk distance test, LVESV, LVEF, SRS, and MD. This analysis showed that only myocardial perfusion defects and MD indicators assessed via MPI and gBPS such as LV AW_SD (OR 1.5275; 95% CI 1.1472–2.0340; p = 0.0037) and SRS (OR 0.7299; 95% CI 0.5627–0.9469; p = 0.0178) and also HF with a nonischemic etiology (OR 20.1425; 95% CI 1.2719–318.9961; p = 0.0331) were the independent predictors of CRT response.

The CRT response prediction model was performed considering the combination of LV AW_SD, SRS, and the presence of nonischemic HF etiology. When ROC analysis was performed with the prediction model, the AUC was 0.949, Sen = 95.56, Spe = 81.82, and p < 0.001 (Figure 2).

The pairwise comparison of CRT response probability indicators revealed that the ROC curve with SRS (p = 0.001), HF nonischemic etiology (p < 0.001), the mechanical dyssynchrony indicators assessed via MPS and gBPS (IVD (p = 0.01), LVE (p < 0.001), RV PFR 2 (p = 0.003), RV PFR (p = 0.005), LV AW_E (p = 0.037), and RV FW_SD (p = 0.014)) ROC curves showed significant differences, with the exception of LV AW_SD (p = 0.089) (Table 4).

Table 4. The ROC curves' pairwise comparison.

	AD	MSE	95% CI	p
CRT RPI~NIHF	0.298	0.0811	0.139–0.457	<0.001
CRT RPI~SRS	0.218	0.0670	0.0869–0.349	0.001
CRT RPI~LV AW_SD	0.0768	0.0453	−0.0119–0.165	0.089

Table 4. *Cont.*

	AD	MSE	95% CI	*p*
CRT RPI~IVD	0.224	0.0881	0.0516–0.397	0.010
CRT RPI~LVE	0.240	0.0623	0.118–0.362	<0.001
CRT RPI~RV PFR 2	0.233	0.0804	0.0757–0.391	0.003
CRT RPI~RV PFR	0.179	0.0638	0.0538–0.304	0.005
CRT RPI~LV AW_E	0.134	0.0646	0.00765–0.261	0.037
CRT RPI~RV FW_SD	0.200	0.0817	0.0398–0.360	0.014

Notes: 95% CI—95% confidence interval, AD—area difference, CRT RPI—cardiac resynchronization therapy response probability indicator, IVD—interventricular dyssynchrony, LV AW_E—left ventricular anterior-wall entropy, LV AW_SD—left ventricular anterior-wall standard deviation, LV_E—left ventricular entropy, RV FW_SD—right ventricular free-wall standard deviation, RV PFR—right ventricular peak filling rate, RV PFR 2—right ventricular peak filling rate on the second peak, NIHF—nonischemic heart failure, SRS—summed rest score, MSE—mean squared error.

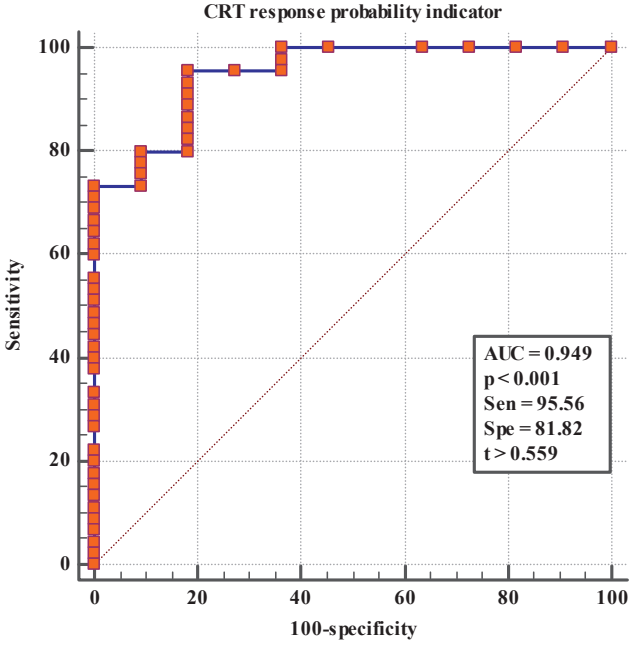

Figure 2. CRT response probability indicator, calculated according to the predictive model. AUC—area under the curve, Sen—sensitivity, Spe—specificity, t—threshold value.

4. Discussion

In the present study, it was shown that mechanical dyssynchrony (left ventricular anterior-wall standard deviation) and the scar burden assessed via cardiac scintigraphy in patients with HF of different etiologies may have prognostic value. Thus, HF with a nonischemic etiology, a low value of SRS, and a high value of LV AW_SD are favorable predictive indicators of CRT response. This may be due to the smaller size of the scar and the involvement of the anterior LV wall in mechanical dyssynchrony.

The nonischemic origin of HF was previously reported to predict reverse remodeling in patients with more advanced HF symptoms. According to Ypenburg et al., CRT responders and patients with super responses more frequently had a nonischemic etiology of HF [35]. In a study by Verhaert et al., it was shown that the female gender and the nonischemic etiology of HF were associated with a much greater initial response to CRT [36]. Another study

by Said et al. found that women showed a greater echocardiographic response to CRT at 6 months of follow-up [37]. However, after the adjustment for body surface area and ischemic etiology, no differences were found in LV function measures or survival, suggesting that having a nonischemic etiology is responsible for greater response rates in women treated with CRT [37]. In our study, the number of patients with ischemic HF and nonischemic HF did not significantly differ in the groups of responders and nonresponders ($p = 0.124$). However, multivariate logistic regression showed that the nonischemic etiology of HF is an independent predictor of CRT response (95% CI 1.2719–318.9961; $p = 0.0331$). Furthermore, the subanalyses of multiple prospective randomized studies, including the Multicenter InSync Randomized Clinical Evaluation (MIRACLE), Cardiac Resynchronization—Heart Failure (CARE-HF), and Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy (MADIT-CRT), have confirmed the finding of greater reverse remodeling in HF with a nonischemic etiology [28,38].

The clinical significance of the scar burden assessed with MPI was demonstrated in several studies. Thus, in a study by Adelstein E. et al., it was found that among ischemic cardiomyopathy patients, lesser scar burden evaluated via SPECT MPI (SRS < 27) was associated with more favorable survival and reverse remodeling following CRT, with outcomes similar to nonischemic cardiomyopathy patients [27]. High scar burden (SRS $\geq$ 27) was associated with the lack of LV functional improvement, the absence of reverse remodeling, and worse survival [27]. In our study, patients with HF of different etiologies were included, and a comparison of the groups with ischemic and nonischemic etiologies was not performed. In patients with HF, myocardial perfusion impairment can vary widely and may be associated with the presence of myocardial fibrosis due to myocardial infarction in ischemic HF patients, or the presence of interstitial fibrosis, which may play a crucial role in the process of myocardial remodeling [39]. Recent studies revealed that myocardial fibrosis is an independent predictor of mortality and morbidity in patients with dilated cardiomyopathy undergoing CRT [40]. Additionally, in our study, which included mixed samples of patients with ischemic and nonischemic etiologies, the SRS assessed using MPI $\leq$ 7.0 was an independent significant predictor for CRT patient selection (95% CI 0.5627–0.9469; $p = 0.0178$).

The predictive value of LV mechanical dyssynchrony for CRT patient selection measured via MPI and gBPS was widely studied. In a study with 142 CRT patients, LV mechanical dyssynchrony parameters such as the systolic histogram bandwidth (95% CI 0.98–1.00, $p = 0.041$), the diastolic-phase standard deviation (95% CI 0.94–1.00, $p = 0.041$), and the diastolic histogram bandwidth (95% CI 0.98–1.00, $p = 0.028$) were significant independent predictors of CRT response only for nonischemic HF patients [25]. For ischemic HF individuals, none of the LV mechanical dyssynchrony parameters were statistically significant [25]. In a study by Henneman M. et al. with 42 CRT patients, the ROC analysis showed that the optimal cut-off values for the phase standard deviation and histogram bandwidth were 43° (sensitivity and specificity of 74%) and 135° (sensitivity and specificity of 70%), respectively [41]. In a study with 324 consecutive individuals with nonischemic HF CRT patients, it was shown that the systolic-phase standard deviation, adjusted to age, hypertension, diabetes, aspirin, beta-blockers, diuretics, QRS, and LVEF, was an independent predictor of all-cause mortality (HR 1.97, 95% CI 1.06–3.66, $p = 0.033$) [42]. In our study, the responders and nonresponders did not differ in terms of such indicators of global LV mechanical dyssynchrony as the phase standard deviation and histogram bandwidth, and these indicators had no prognostic value, but the LV phase entropy was higher in the responders' sample. However, the novelty of our study was the use of gBPS for assessing the regional mechanical dyssynchrony indicators separately for the septum, anterior, posterior, and lateral walls of LV. These indicators (LV AW_E, LV AW_SD, and RV FW_SD) with IVD and contractile function indicators (RV PFR and RV PFR 2) were statistically significant predictors of CRT response. The multivariate logistic regression showed that LV AW_SD (OR 1.5275; 95% CI 1.1472–2.0340; $p = 0.0037$) was the independent predictor of CRT response. This may indicate that the assessment of regional myocardial dyssynchrony may provide additional information for successful resynchronization therapy.

However, disagreements with previous studies underline the importance of these findings and the need for future large-scale studies.

There are few publications about the combined assessment of the factors associated with reverse remodeling, which can be used for the improved selection of patients for CRT. The significance of the CRT response score was shown in a major randomized trial MADIT-CRT (n = 1761) [28]. This score included seven factors associated with the echocardiographic response to CRT-D and made up the response score (female sex, nonischemic HF, LBBB, QRS duration $\geq$150 ms, prior hospitalization for HF, left ventricular end-diastolic volume $\geq$125 mL/m^2 and left atrial volume <40 mL/m^2). The multivariate analysis showed a 13% ($p < 0.001$) increase in the clinical benefit of CRT-D per one-point increment in the response score (range, 0–14) and a significant direct correlation between the risk reduction associated with CRT-D and the response score quartiles: Patients in the first quartile did not reveal a significant reduction in the risk of HF or death with CRT-D (hazard ratio = 0.87; $p = 0.52$); patients in the second and third quartiles had 33% ($p = 0.04$) and 36% ($p = 0.03$) risk reductions, respectively; and patients in the upper quartile experienced a 69% ($p < 0.001$) risk reduction ($p = 0.005$). In our study, the multivariate logistic regression with inclusion factors such as QRS duration, gender, HF etiology, LV lead position, 6 min walk distance test, LVESV, LVEF, SRS, and mechanical dyssynchrony indicators assessed via gBPS showed that LV AW_SD, SRS, and HF with a nonischemic etiology were the independent predictors of CRT response (95% CI 0.856–0.990; AUC = 0.949; Sen = 95.56; Spe = 81.82; $p < 0.001$).

According to a study by Forleo et al., quadripolar leads allowed for nonapical pacing with acceptable electrical parameters in the majority of CRT recipients, although differences were found among the currently available devices [43]. In our study, quadripolar and bipolar LV leads from various manufacturers were implanted. A detailed analysis of lead characteristics between different companies was not performed. However, a comparison between the groups of responders and nonresponders to CRT in terms of the number of implanted quadripolar and bipolar LV leads was made. The comparative analysis between the groups did not reveal significant differences ($p = 0.392$).

Thus, the predictive model with the combination of LV AW_SD, SRS, and the presence of nonischemic HF etiology has a high prognostic value and can be used as an additional CRT response predictor in patients with HF of different etiologies.

Study Limitations

The limitations of this study included its relatively small sample size and short follow-up period; the left ventricular mechanical dyssynchrony indicators were not determined in terms of their dynamics, and this was a nonrandomized, single-center study.

5. Conclusions

In patients with HF of ischemic and nonischemic etiologies, the left ventricular mechanical dyssynchrony assessed via gBPS may be useful in identifying responders to CRT. In these patients, a combined assessment of the factors associated with reverse remodeling (HF with a nonischemic etiology, LV AW_SD, and SRS) can be used for the improved selection of patients for CRT.

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Data Availability Statement: According to the internal regulations of the Institute, all data are the property of the Institute and can only be provided anonymously after an official request.

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Systematic Review

Systematic Review on S-ICD Lead Extraction

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Abstract: Background and purpose: Subcutaneous implantable cardioverter defibrillators (S-ICDs) have emerged in recent years as a valid alternative to traditional transvenous ICDs (TV-ICDs). Therefore, the number of S-ICD implantations is rising, leading to a consequent increase in S-ICD-related complications sometimes requiring complete device removal. Thus, the aim of this systematic review is to gather all the available literature on S-ICD lead extraction (SLE), with particular reference to the type of indication, techniques, complications and success rate. Methods: Studies were identified by searching electronic databases (Medline via PubMed, Scopus and Web of Science) from inception to 21 November 2022. The search strategy adopted was developed using the following key words: subcutaneous, S-ICD, defibrillator, ICD, extraction, explantation. Studies were included if they met both of the following criteria: (1) inclusion of patients with S-ICD; (2) inclusion of patients who underwent SLE. Results: Our literature search identified 238 references. Based on the abstract evaluation, 38 of these citations were considered potentially eligible for inclusion, and their full texts were analyzed. We excluded 8 of these studies because no SLE was performed. Eventually, 30 studies were included, with 207 patients who underwent SLE. Overall, the majority of SLEs were performed for non-infective causes (59.90%). Infection of the device (affecting either the lead or the pocket) was the cause of SLE in 38.65% of cases. Indication data were not available in 3/207 cases. The mean dwelling time was 14 months. SLEs were performed using manual traction or with the aid of a tool designed for transvenous lead extraction (TLE), including either a rotational or non-powered mechanical dilator sheath. Conclusions: SLE is performed mainly for non-infective causes. Techniques vary greatly across different studies. Dedicated tools for SLE might be developed in the future and standard approaches should be defined. In the meantime, authors are encouraged to share their experience and data to further refine the existing variegated approaches.

Keywords: subcutaneous implantable cardioverter defibrillator; S-ICD; ICD; extraction; explantation; infection

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1. Introduction

Since their development, Implantable Cardioverter Defibrillators (ICDs) have been a fundamental part of the primary and secondary prevention of sudden cardiac death (SCD) [1]. Although transvenous ICDs (TV-ICDs) are still the standard of care, their long-term use is associated with a variety of device-related complications, such as infections or lead displacement and rupture, in some cases requiring surgical revision or even the extraction of the entire device [2,3]. Subcutaneous ICDs (S-ICDs) thus became a valid alternative to reduce the occurrence of adverse events related to the presence of intravenous leads, especially in young patients with a long life expectancy, normal heart, and no need for

pacing or cardiac resynchronization therapy, at increased risk of infections and with limited vascular access [4,5]. Since S-ICDs have consistently been proved to be effective in terminating malignant arrhythmias, the implantation of such devices is rising. In parallel with the growing number of S-ICDs implanted, there is an absolute increase in S-ICD-related complications (e.g., infection) that may require complete system removal [6–8]. Although transvenous lead explantation (TLE) is a relatively common procedure, with several approaches, dedicated tools and specific guidelines [9], S-ICD lead extraction (SLE) still relies on poor clinical data regarding its technical execution (with simple manual traction as the only established method), efficacy and safety [10,11]. This could be particularly relevant not only for the increasing necessity of extraction procedures, but also for the growing dwelling time of the S-ICDs implanted, typically associated with the development of fibrotic adherences and calcifications around the lead that could interfere with extraction [10]. Thus, the aim of this systematic review is to gather all the available literature on SLE, with particular reference to type of indication and the method used to perform the extraction.

2. Materials and Methods

2.1. Design

This systematic review was conducted and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [12]. The systematic review was not registered.

2.2. Study Selection

Studies were identified by searching electronic databases (Medline via PubMed, Scopus and Web of Science) from inception to 21 November 2022. The literature search used text and relevant indexing to capture data on S-ICD lead extraction. The search strategy adopted was developed using the following key words: subcutaneous, S-ICD, defibrillator, ICD, extraction, explantation. The string adopted for PubMed was ("subcutaneous" OR "S-ICD") AND ("defibrillator" OR "ICD") AND ("extraction" OR "explantation"). Only studies in English were included in the review. Studies were included if they met both of the following criteria: (1) inclusion of patients with S-ICD; (2) inclusion of patients who underwent SLE.

2.3. Data Extraction

Information was extracted from each included study regarding the (1) baseline characteristics of patients and country where the study was performed; (2) indications for SLE; (3) dwelling time; (4) technique used for SLE; (5) complications; (6) success; and (7) management after SLE. Two authors (R.V. and E.F.) independently extracted data from studies and entered them into the data extraction form. Disagreements were resolved by discussion; if no accord was reached, it was planned that a third author (P.C.) would decide.

2.4. Quality Assessment

The JBI tool was used to perform the quality assessment of the included studies [13]. Supplementary Materials S1 reports how studies were rated.

3. Results

3.1. Study Selection

Our literature search identified 238 references (Figure 1). Based on the abstract evaluation, 38 of these citations were considered potentially eligible for inclusion, and their full texts were analyzed in more detail [10,11,14–49]. We excluded 8 of these studies because no SLE was performed [10,18,19,21,27,29,46,47]. Eventually, 30 studies were included [10,11,14–17,20,22–26,28,30–41,43–45,48,49].

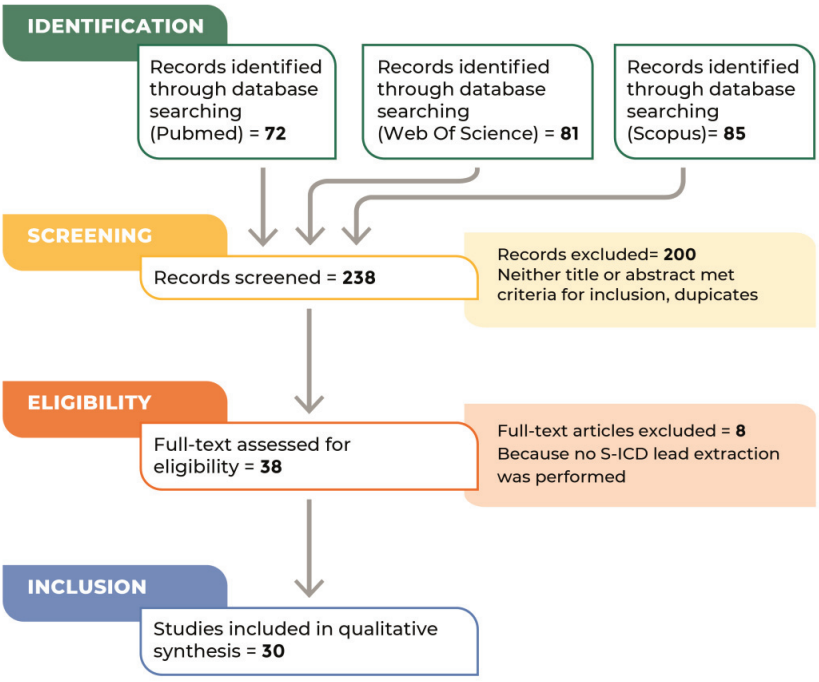

Figure 1. Flow chart of the literature search.

3.2. Characteristics of the Studies

Overall, 207 patients were included in this analysis. One patient underwent SLE twice [43]. Of the 30 included studies, the majority (16/30) were retrospective cohort studies [15–17,22,23,26,30,33,36–38,41,43,44,48,49]. Five were prospective studies [14,31,32,34,35], and the remaining nine were case reports [10,11,20,24,25,28,39,40,45]. The number of patients included in the studies ranged from 1 to 1637. The full study characteristics are summarized in Table 1.

Table 1. Characteristics of the included studies.

Author, Year of Publication	Design	Study Population, Country	No. of Pts Who Underwent S-ICD Lead Extraction
Gold 2022 [14]	Prospective cohort study	1637 S-ICD pts (Post Approval Study), U.S.	5
Giacomin 2022 [15]	Retrospective cohort study	36 consecutive S-ICD pts after TLE, Italy	4
Russo 2022 [16]	Retrospective cohort study	317 consecutive S-ICD pts (besides 290 TV-ICD), Italy	1
Pothineni 2022 [17]	Retrospective cohort study	64 S-ICD explanted pts, U.S.	64
Migliore 2021 [10]	Case report	1 S-ICD pt after TLE, Italy	1
Allison 2021 [20]	Case report	1 S-ICD pt, U.S.	1
Chung 2021 [22]	Retrospective cohort study	144 S-ICD pts, Germany	11
Van der Stuijt 2021 [23]	Retrospective cohort study	72 S-ICD pts who underwent elective PGR, Netherlands	1
Gutleben 2020 [24]	Case report	1 S-ICD pt with BrS, Germany	1
Mitacchione 2020 [25]	Case report	1 S-ICD pt with DCM, Italy	1
Behar 2020 [26]	Retrospective cohort study	32 S-ICD explanted pts, France	32
Patel 2020 [28]	Case report	1 S-ICD pt with DCM, US	1
Noel 2020 [30]	Retrospective cohort study	108 S-ICD pts, France	6

Table 1. *Cont.*

Author, Year of Publication	Design	Study Population, Country	No. of Pts Who Underwent S-ICD Lead Extraction
Schaller 2019 [31]	Prospective cohort study	13 pts (3 PM, 9 TV-ICD, 1 S-ICD) presenting for CIED extraction due to infection, U.S.	1
Migliore 2019 [32]	Prospective cohort study	101 S-ICD pts, Italy	2
Ip 2019 [11]	Case report	1 S-ICD pt with ICM, U.S.	1
Migliore 2019 [33]	Retrospective cohort study	44 S-ICD pts with AC, Italy	1
Orgeron 2018 [34]	Prospective cohort study	29 S-ICD pts with AC, U.S./Italy	3
Viani 2019 [35]	Prospective cohort study	229 pts who underwent TV-ICD extraction and subsequent S-ICD or TV-ICD implantation, Italy	3
Nakhla 2018 [36]	Retrospective cohort study	21 pts who underwent Medtronic SQC extraction, U.S.	21
Quast 2018 [37]	Retrospective cohort study	118 S-ICD pts, Netherlands	10
Sponder 2018 [38]	Retrospective cohort study	236 S-ICD pts, Austria	4
Clacaianu 2017 [39]	Case report	1 S-ICD pt, France	1
Morani 2017 [40]	Case report	1 S-ICD pt with BrS, Italy	1
Frommeyer 2016 [41]	Retrospective cohort study	24 S-ICD pts with electrical heart disease or idiopathic VF, Germany	1
Brouwer 2016 [43]	Retrospective cohort study	123 S-ICD pts, Netherlands	7 *
Boersma 2016 [44]	Retrospective cohort study	866 S-ICD pts, International	1
Frommeyer 2015 [45]	Case series	93 S-ICD pts, Germany	6
Theuns 2015 [49]	Retrospective registry	55 S-ICD pts, Europe/New Zealand	5
Jarman 2013 [48]	Retrospective registry	111 S-ICD pts, U.K.	10

S-ICD, subcutaneous implantable cardioverter defibrillator; TLE, transvenous lead extraction; TV-ICD, transvenous implantable cardioverter defibrillator; PGR, pulse generator replacement; Brs, Brugada Syndrome; DCM, dilated cardiomyopathy; PM, pacemaker; CIED, cardiovascular implantable electronic device; ICM, ischemic cardiomyopathy; AC, arrhythmogenic cardiomyopathy; SQC, subcutaneous shocking coils; pt, patient; pts, patients. * 1 pt underwent extraction twice.

3.3. Indications for S-ICD Extraction

Overall, the majority of SLEs were performed for non-infective causes (59.90%). Among these, the occurrence of inappropriate shocks was responsible for 16.91% of total SLEs, necessity for cardiac resynchronization therapy (CRT) was responsible for 8.70%, progression of disease to heart transplantation or left ventricular assist device (LVAD) implantation was responsible for 7.25% and sensing issues were responsible for 4.35%. Infection of the device (affecting either the lead or the pocket) was the cause of SLE in 38.65% of cases. Indication data were not available in 3/207 cases [17,22]. The full list of all the indications is reported in Table 2.

3.4. Dwelling Time

The mean time from implantation to extraction (i.e., dwelling time) of S-ICDs was 14 months, ranging from 30 days [37] to over 8 years [36]. The dwelling time was not available in 10 studies [14–16,20,22,23,32,35,38,44]. The majority of studies in which this information was reported showed a mean time of one year or less [24,26,33,36,39,43,45,48]. The dwelling time was particularly short in studies where infections were the indication for more than 50% of SLEs performed [31,36,37,43].

Table 2. Indications for SLE.

Indication for SLE	Total Population, *n* = 207
Non-infective, *n* (%)	124 (59.90%)
-Inappropriate shocks, *n* (%)	35 (16.91%)
-Necessity for CRT, *n* (%)	18 (8.70%)
-Heart transplantation/LVAD, *n* (%)	15 (7.25%)
-Sensing issues, *n* (%)	9 (4.35%)
-Lead/pocket erosion, *n* (%)	8 (3.86%)
-Ineffective therapy, *n* (%)	8 (3.86%)
-Necessity for pacing, *n* (%)	7 (3.38%)
-Lead rupture, *n* (%)	5 (2.42%)
-Defibrillation threshold testing failure, *n* (%)	5 (2.42%)
-Patient discomfort, *n* (%)	5 (2.42%)
-Lead malposition, *n* (%)	4 (1.93%)
-Technical issues, *n* (%)	2 (0.97%)
-Reel syndrome, *n* (%)	1 (0.48%)
-Necessity for MRI, *n* (%)	1 (0.48%)
-Premature battery depletion, *n* (%)	1 (0.48%)
Infective (pocket or lead), *n* (%)	80 (38.65%)
Not specified, *n* (%)	3 (1.46%)

CRT, cardiac resynchronization therapy; LVAD, left ventricular assist device; MRI, magnetic resonance imaging.

3.5. Method Used for SLE

In the studies analyzed, SLE required a two- or three-incision technique, depending on the way the lead was originally inserted and on eventual complications. The first incision was performed generally along the midaxillary line, in order to open the pocket and remove the pulse generator, freeing also the proximal part of the lead. The second incision was then executed on the region of xiphoid apophysis, fundamental to release the suture anchoring the lead and usually exploited as the access to extract the proximal and distal ends of the lead. An additional incision could be performed at the level of the manubriosternal junction in order to reach the distal coil of the lead, cutting eventual sutures that anchored it to the periosteal fascia or releasing it from fibrous tissue. Manual traction was then applied to unthread the lead, generally from subxiphoid access. In some cases, typically characterized by a long dwelling time, fibrosis of the tissues around the lead offered resistance to its removal, requiring the use of a mechanical sheath to relieve it [9,10,18,24,26]. This tool, originally designed for TLE, is manufactured to be slipped around the lead and then, with traction and counter-traction and simultaneous rotation, progressively advanced over the catheter. This technique allows the operator to dilatate and to break off fibrotic tissue along the lead, favoring its removal. Additional treatment could then be executed according to the S-ICD extraction's indication (e.g., local antimicrobial treatment in case of pocket infection). The extraction technique was described in 11 studies [10,11,17,20,24–26,28,36,40,41], a minority of those included in this analysis. Among these studies, 7/11 were case reports [10,11,20,24,25,28,40]. Table 3 reports the methods used for SLE in our study population.

Table 3. Methods used for SLE.

Method Used for SLE	Total Population, *n* = 207
Manual traction, *n* (%)	99 (47.83%)
Additional incisions, *n* (%)	11 (5.31%)
Tools (sheaths), *n* (%)	14 (6.76%)
Not reported, *n* (%)	83 (40.10%)

SLE, S-ICD lead extraction.

3.6. Complications and Success Rate

There were no periprocedural complications reported during SLE. This point was specifically addressed by the two included studies reporting the greatest numbers of SLEs [17,26]. Pothineni et al. reported that in their cohort of 64 patients who underwent SLE, no complications occurred [17]. The secondary endpoint of the study by Behar et al. [26] included procedural complications, and again, no procedure-related complications were reported.

Only 1 case of procedural failure occurred among the 207 reported because the lead could definitely not be extracted [26].

3.7. Management after SLE

Table 4 reports which management options were chosen after SLE, including the percentages of S-ICD or TV-ICD reimplantation.

Table 4. Management after SLE.

Management after SLE	Total Population, *n* = 207
ICD reimplantation, *n* (%)	102 (49.28%)
-S-ICD reimplantation, *n* (%)	25 (12.08%) *
-TV-ICD reimplantation, *n* (%)	75 (36.23%)
-Unspecified ICD reimplantation, *n* (%)	1 (0.48%)
-Scheduled for S-ICD, *n* (%)	1 (0.48%)
Heart transplantation, *n* (%)	7 (3.38%)
Medically managed, *n* (%)	1 (0.48%)
Declined reimplantation, *n* (%)	13 (6.28%)
Not known, *n* (%)	84 (40.58%)
-Lost to follow-up, *n* (%)	5 (2.42%)
-Not reported, *n* (%)	79 (38.16%)

ICD, subcutaneous implantable cardioverter defibrillator; TV-ICD, transvenous implantable cardioverter defibrillator. * 1 pt was reimplanted twice.

Of note, in the study by Brouwer et al., one patient underwent a second S-ICD extraction after SLE during subsequent follow-up for recurrent infection [43].

4. Discussion

To the best of our knowledge, our study is the first systematic review on SLE.

According to our systematic review, the majority of SLEs are performed for non-infective causes (59.90%). These data differ from those for TLEs, which are performed mainly for infective causes (52.8%) [50]. Among the non-infective indications for SLE, inappropriate shocks accounted for the most part (16.91%). Moreover, sensing issues accounted for 4.35% of cases. Despite rare cases of undersensing of ventricular fibrillation [17], sensing issues usually include refractory oversensing due to myopotential, P- or T-wave oversensing or R-wave double counting [30]. Eventually, oversensing may lead to inappropriate shocks. Inappropriate shocks are a well-known drawback of S-ICDs, significantly affecting patients' quality of life [51]. However, recent data showed a consistent reduction in inappropriate shocks by S-ICDs (3.1% in 1 year) with the use of high-rate cutoffs, as well as current generation electrogram filtering and discrimination algorithms [52]. Additionally, exercise tests before S-ICD implantation, especially in patients with Brugada syndrome, may further reduce the incidence of future inappropriate shocks [53]. Given all the abovementioned improvements, we can expect a decrease for such indications in future studies on SLE.

A necessity for resynchronization therapy or pacing is among other prominent causes for SLE. Even though it usually cannot be predicted at implantation, accurate selection of candidates for S-ICD implantation must be performed to minimize this possible scenario.

The dwelling time was very different in our systematic review on SLE compared to that reported for TLE. In fact, our study showed a mean time from implant to extraction

of 14 months, compared to a mean dwelling time of 6.4 years in the ELECTRA study on TLE [50]. This discrepancy can be explained by several factors. First, in the studies included in our systematic review, many authors included patients in which the device was removed within a year and with simple manual traction; these procedures are better referred to as "explantation", according to the terminology used for transvenous PM/ICDs. Other authors did not mention at all the dwelling time or the approach used for extraction, but we decided to include all studies in order to gather all the available literature in the field. Secondly, S-ICDs have been available since the early 2010s, whereas transvenous PM/ICDs were released on the market several years prior, and long-term follow-up data are available. Lastly, infections on transvenous PM/ICDs may occur as part of a systemic infection/bacteremia with the source of infection coming from a different site. In the case of S-ICDs, infections are primarily local and related to the implantation procedure; therefore, they tend to occur earlier. In fact, we found that the dwelling time was particularly short in studies where infections were the indication for more than 50% of SLEs [31,36,37,43].

Regarding techniques for SLE, simple manual traction is the easier way, and it was sufficient to remove S-ICD leads in many of the cases reported (99/207) (Table 3). However, this approach cannot always be pursued due to fibrosis surrounding the parasternal coil. According to our systematic review, in 14/207 cases, tools were used to complete a successful SLE. Patel et al. were the first authors to report the successful use of a rotating mechanical dilator sheath (TightRail, Spectranetics) for SLE [28]. Later on, Allison et al. replicated an SLE using the rotating mechanical dilator sheath (TightRail, Spectranetics), but also with the aid of a bulldog lead extender (Cook Medical) [20]. Migliore et al. reported the use of a non-powered mechanical dilator sheath (LR-TSS-11.0, Cook Medical) to disrupt fibrotic adhesions around the coil and the distal tip of the S-ICD lead [10]. The lead was then retracted into the sheath and successfully extracted in the absence of any complications. These studies highlight the absence of a common strategy and of dedicated tools for SLE, which might be developed in the future.

After SLE, a large number of patients (75/207) underwent TV-ICD reimplantation (Table 4). A minor part of the cohort underwent S-ICD reimplantation (25/207). Of note, one patient was extracted and reimplanted twice with an S-ICD because of recurrent local infection [43]. This event highlights the importance of a waiting period before reimplantation to allow complete healing from infection. In this scenario, wearable ICDs may act as a bridge therapy. In the study by Van der Stuijt et al. [23], the authors provided a patient with a wearable ICD after SLE for 3 months, allowing the resolution of infection with antibiotics before S-ICD reimplantation.

Limitation

Our study has several limitations. The results are based primarily on retrospective studies and case reports, and we acknowledge the risk of overlapping cohorts among different studies. Furthermore, as discussed above, no clear distinction was made between explantation and extraction, and all cases of S-ICD lead removal were collectively considered as SLE. Finally, we could not exclude possible bias due to overlapping cohorts between some of the included studies.

5. Conclusions

According to our systematic review, the causes for SLE are primarily non-infective, and the dwelling time seems to be lower compared to that in the literature data on TLE. Techniques vary greatly across different studies, including manual traction and the use of either rotational or non-powered mechanical sheaths. Dedicated tools for SLE might be developed in the future, and standard approaches should be defined. In the meantime, authors are encouraged to share their experience and data to further refine the existing variegated approaches.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12113710/s1. Supplementary Material: Quality Assessment.

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Long-Term Outcomes of Transvenous Lead Extraction: A Comparison in Patients with or without Infection from the Italian Region with the Oldest Population

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Abstract: Background: The gold standard for the treatment of cardiac implantable electronic devices (CIEDs)-related infection and lead malfunction is transvenous lead extraction (TLE). To date, the risk of mortality directly related to TLE procedures is relatively low, but data on post-procedural and long-term mortality are limited, even more in the aging population. Methods: Consecutive patients with CIEDs who underwent TLE were retrospectively studied. The primary outcome was the endpoint of death, considering independent predictors of long-term clinical outcomes in the TLE aging population comparing patients with and without infection. Results: One hundred nineteen patients (male 77%; median age 76 years) were included in the analysis. Eighty-two patients (69%) documented infection, and thirty-seven (31%) were extracted for a different reason. Infected patients were older (80 vs. 68 years, p-value > 0.001) with more implanted catheters (p-value < 0.001). At the last follow-up (FU) available (median FU 4.1 years), mortality reached 37% of the patient population, showing a statistically significant difference between infected versus non-infected groups. At univariable analysis, age at TLE, atrial fibrillation, and anemia remained significant correlates of mortality; at multivariable analysis, only patients with anemia and atrial fibrillation have a 2.3-fold (HR 2.34; CI 1.16–4.75) and a 2.5-fold (HR 2.46; CI 1.33–4.54) increased rate of death, respectively. Conclusion: Our long-term data showed that aging patients who underwent TLE for CIED-related infection exhibit a high mortality risk during a long-term follow-up, potentially leading to a rapid and effective procedural approach in this patient population.

Keywords: lead extraction; device infection; lead malfunction; aging population

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1. Introduction

The implant rate of cardiac implantable electronic devices (CIEDs) has increased progressively due to increasing life expectancy [1–8], and, more commonly today, CIEDs are implanted in older patients with many comorbidities [7–9]. Advanced age is related to multiple comorbidities and frailty, potentially increasing the probability of complications during invasive procedures [9,10]. Although infrequent, CIED-related infections, as well as lead malfunction, represent a serious complication after cardiac device implantation [5], with several data showing device complications associated with significant mortality and morbidity [7–9]. Transvenous lead extraction (TLE) represents the gold standard for

the treatment of CIED-related infection and lead malfunction [8]. To date, the mortality risk directly related to TLE procedures is relatively low [6–8], while data regarding post-procedural and long-term mortality are limited [8,9,11]. Considering the aging population, TLE will play an increasing role in the future management of these subjects. Therefore, in our study, we analyze independent predictors of long-term clinical outcomes of patients undergoing TLE, assessing the prognostic role of an infective indication on long-term survival in the aging population.

2. Methods

We identified a cohort of 119 consecutive patients undergoing TLE at our institution in the Liguria region. Liguria is an Italian region located in the northwest part of Italy, and it is currently the oldest Italian Region [12]. We retrospectively analyzed patient characteristics, procedural indications, and clinical outcomes. For the purpose of the study, the patient population was categorized as infected and non-infected, following the Heart Rhythm Society (HRS) consensus document on TLE [10] and European Heart Rhythm Association (EHRA) expert consensus statement on lead extraction [13]. An infective indication included a systemic (bacteremia and/or endocarditis) or local (pocket infection or erosion) infection, while a non-infective indication included lead malfunction and venous thrombosis. The primary endpoint of the study was a comparison of long-term mortality between patients with or without infection after hospital discharge. Secondary endpoints included complete procedural success, procedural failure, and the occurrence of complications defined by the HRS and EHRA consensus [10,13]. For the aim of the study, we considered complications as only the adverse events occurring before hospital discharge. In particular: death, cardiac tamponade, cardiac/vascular avulsion or tear, respiratory arrest, pulmonary embolism, and stroke were regarded as major complications, whereas complications that did not meet the major criteria were considered minor complications.

2.1. Extraction Techniques

After obtaining written informed consent, invasive hemodynamic monitoring through an arterial line was placed. Procedures were performed under general anesthesia and cardiac surgical backup. Device removal and disconnection of the lead(s) were performed through an infraclavicular incision. The lead(s) were extracted through a subclavian approach. Lead removal with simple traction was attempted as the first step. If lead removal proved unsuccessful, the lead was cut; a locking stylet (Liberator Cook Medical) was introduced, and traction was reattempted. If this still proved unsuccessful at the "first step", a mechanical sheath was used, eventually considering a powered sheath (Evolution Cook Medical) when necessary. Laser-assisted lead extraction was never performed in our center. Complete procedural success was achieved if all targeted leads/lead material were removed from the vascular space, while clinical success was achieved if all targeted leads/lead material were removed with retention of a small lead portion (<5 cm), with no impact on the outcome goals. In cases of infection, complete removal of both foreign material and infected tissue was mandatorily performed. Failure was considered if neither complete procedural success nor clinical procedural success was achieved.

2.2. Antibiotic Therapy

In patients with device infection, an empiric antibiotic therapy such as daptomycin (i.v. 8–10 mg/kg every 24 h) or vancomycin (i.v. 30–60 mg/kg/day) until a potential microbiological identification was performed according to the clinical scenarios. Cefepime (i.v. 2 g every 8 h) or ceftriaxone (i.v. 2 g every 24 h) or gentamycin (i.v. 5–7 mg/kg every 24 h) were only considered in case of systemic symptoms [14]. In patients with systemic infection, once the pathogen was identified (usually within 3 days), the antibiotic treatment was tailored to the antimicrobial susceptibility pattern. In this scenario, the collaboration between cardiologists and infectious disease specialists with expertise in the field of CIED-related infection was of primary importance. The duration of therapy could depend on the

presence or lack thereof of concomitant systemic infection and could vary from 2 weeks in case of isolated pocket infection to typically 4–6 weeks in case of positive blood cultures and or vegetations. In particular, all patients with systemic infection underwent appropriate antibiotic treatment after removal according to antibiograms of positive bacteria cultures and current guidelines [14].

2.3. Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range) and compared with the Student T test or Mann–Whitney test, as appropriate. Categorical variables were expressed as frequencies and percentages and compared with the Chi-square or Fisher exact test, as appropriate. Time-to-event curves were built, and survival was compared between infected and non-infected patients using the log-rank test. Univariable and multivariable Cox analyses were carried out to explore the predictors of survival, deriving hazard ratios (HR), and associated 95% confidence intervals. Candidate variables were entered in the multivariate analysis when proven to be significant univariate predictors. All tests were 2-tailed, and $p < 0.05$ was considered significant. Statistical analysis was performed using "R" software (the R foundation for statistical computing version 3.6.2. using the "meta" package).

3. Results

Between January 2014 and April 2020, 119 patients (224 leads) underwent TLE, out of which 82 patients (69%) had an infection diagnosis (181 leads). Males represented 77% of patients, and the median age at the TLE procedure was 76 (67–82) years. Table 1 shows the baseline characteristics of the patient population. Infected patients were older (80 vs. 68 years, p-value > 0.001), with more implanted catheters (p-value < 0.001) despite a lower incidence of heart failure (43.4% versus 65.7%, p-value = 0.03), whereas other comorbidities were balanced compared to non-infected patients. The median time from first device implantation to TLE was longer in the infected population (109 months versus 66 months, $p = 0.03$) compared to non-infected patients. Table 2 shows a comparison between infected and non-infected patients. In the infection-related group (82 patients), pathogenic organisms were identified in 18% of cases: positive microbiologic culture results showed Gram-positive in 15% of cases, and *Staphylococcus aureus* was the most commonly detected bacterium, as shown in Figure 1. Moreover, we compared the characteristics of patients with local infection versus systemic infection, documenting no significant difference among baseline characteristics (See Table S1 from Supplementary Materials). Among TLE procedures, a total of 224 leads were extracted, with a mean of 1.9 ± 0.9 lead per procedure. The mean procedural time was 129 ± 50.2 min; the oldest lead was in place for 396 months. Complete procedural success was achieved in 84.9% of patients, with a 91.6% clinical success rate. In total, 194 leads (81.1%) were removed completely, 16 leads (6.7%) were removed with retention of a small portion of lead without negatively affecting outcome goals and therefore leading to clinical success, one lead (0.42%) was submitted to surgical lead extraction, and one lead (0.42%) was considered as failure. Procedural characteristics are reported in Table 3.

Table 1. Overall study population characteristics.

Variable	n = 119 (%)
Male sex	92 (77.3%)
Coronary artery disease	40 (36.4%)
Heart failure	56 (50.5%)
Atrial fibrillation	40 (36.4%)
Systemic arterial hypertension	74 (67.3%)
Diabetes	24 (21.8%)
Hemoglobin, g/dL	12.3 ± 2.0.
Anemia Men (<13.5 g/dL under 70; <12 g/dL over 70) Women (<11.5 g/dL)	24 (22%)
White blood cells, 10^9/L <4500 (leukopenia) 4500–9800 (normal range) >9800 (leukocytosis)	 37 (34.3%) 60 (55.6%) 11 (10.2%)
C-reactive protein ≥3 mg/dL	71 (72.5%)
Creatinine, mg/dL	1.1 (0.5)
Chronic kidney disease (men: ≥1.4 mg/dL, women: ≥1.2 mg/dL)	31 (28.7%)
Positive blood cultures *Methicillin-Resistant-Staphylococcus aureus* *Methicillin-Susceptible-Staphylococcus aureus* *K. pneumoniae* *S. epidermidis* *E. faecalis, E. faecium* *P. mirabilis* * out of 82 pts diagnosed with infection	15 (18.3%) * 8 3 1 1 1 1
Left ventricular ejection fraction <30% 30–50% >50%	 16 (18.4%) 39 (44.8%) 32 (36.8%)
Age at extraction, years	76.4 (15.4)
Infection local systemic * out of 82 pts diagnosed with infection	 67 (82%) * 15 (18.3%) *
Number of implants 1 2 3 4	 46 (60.5%) 19 (25%) 9 (11.8%) 2 (2.6%)
Time from to catheters, months	84.5 (85)
Type of device Single pacemaker (PM) Single Implantable cardioverter-defibrillator (ICD) Dual PM Dual ICD Cardiac resynchronization therapy pacemaker (CRT-P) Cardiac resynchronization therapy defibrillator (CRT-D)	 4 (3.5%) 22 (19.1%) 42 (36.5%) 15 (13%) 12 (10.4%) 20 (17.4%)

Table 1. *Cont.*

Variable	n = 119 (%)
Coil	
Single	33 (61.1%) *
Dual	21 (38.9%) *
* out of 58 pts implanted with single ICD, dual ICD, CRT-D	
Number of catheters	
1	31 (26.7%)
2	55 (47.4%)
3	22 (19%)
4	8 (6.9%)
Number of extracted catheters	
0	3 (2.6%)
1	36 (31%)
2	51 (44%)
3	18 (15.5%)
4	8 (6.9%)
Previously abandoned catheter ≥1	14 (12.1%)
Technique of extraction	
Traction	9 (7.56%)
Mechanical dilator sheath	93 (78.15%)
Powered sheath	13 (10.9%)
Procedure duration, minutes	129 ± 50.2
Procedural success	
complete	101 (84.9%)
clinical	8 (6.7%)
surgical extraction	2 (1.7%)
procedural failure	1 (0.8%)
complications	7 (5.9%)
Follow up, months	49 (48)

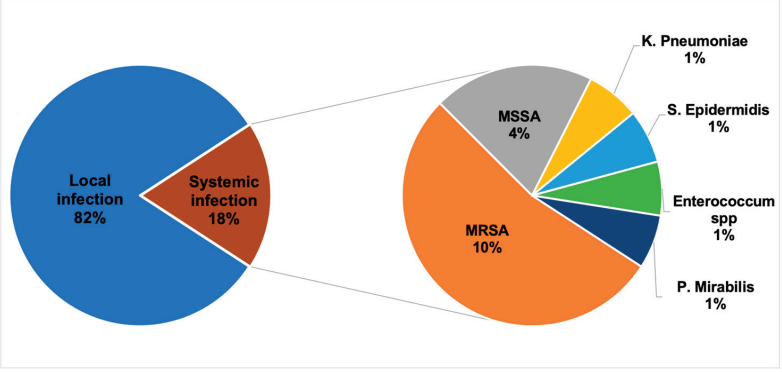

Figure 1. Microbiology of transvenous lead extraction from 82 patients with infection. MSSA = Meticillin-Sensitive *Staphylococcus aureus*, MRSA = Methicillin-resistant *Staphylococcus aureus*.

Table 2. Study population stratified by diagnosis of infection.

Variable	Infected (n = 82)	Non Infected (n = 37)	*p*-Value
Male sex	65 (79.3%)	27 (73%)	0.45
Coronary artery disease	24 (30%)	14 (38%)	0.60
Heart failure	33 (43.4%)	23 (65.7%)	0.03
Atrial fibrillation	27 (36%)	13 (37%)	0.91
Systemic arterial hypertension	54 (71%)	20 (59%)	0.21
Diabetes	18 (23.7%)	6 (17.6%)	0.48
Anemia	17 (22.4%)	7 (20.6%)	0.89
White blood cells <4500 (leukopenia) 4500–9800(normal range) >9800 (leukocytosis)	 26 (35%) 40 (53%) 9 (12%)	 11 (33%) 20 (61%) 2 (6%)	0.68
C-reactive protein ≥3 mg/dL	57 (81%)	14(50%)	0.002
Creatinine, mg/dL	1.1 (0.65)	1.1 (0.4)	0.25
Chronic kidney disease	23 (30.6%)	8 (24.2%)	0.49
Left ventricular ejection fraction <30% 30–50% >50%	 11 (18%) 25 (41%) 25 (41%)	 5 (19.2%) 14 (53.8%) 7 (27%)	0.43
Age at extraction, years	79.7 (12)	68.3 (20.8)	<0.001
Number of implants 1 2 3 4	 32 (58.2%) 15 (27.3%) 6 (10.9%) 2 (3.6%)	 14 (66.6%) 4 (19%) 3 (14.2%) 0 (0%)	0.84
Older leads, months	109 (82)	66 (65.6)	0.03
Type of device Single PM Single ICD Dual PM Dual ICD CRT-P CRT-D	 3 (3.8%) 9 (11.2%) 36 (45%) 6 (7.5%) 10 (12.5%) 16 (20%)	 1 (2.9%) 13 (37.1%) 6 (17.1%) 9 (25.7%) 2 (5.8%) 4 (11.4%)	<0.001
Coil (yes/no)	31 (38.75%)	26 (74.2%)	<0.001
Coil Single Dual * out of 58 pts implanted with single ICD, dual ICD, CRT-D	 15 (51.7%) * 14 (48.2%) *	 18 (72%) * 7 (28%) *	0.13
Number of catheters 1 2 3 4	 13 44 16 8	 18 11 6 0	<0.001
Previously abandoned catheter ≥1	13 (16%)	1 (2.9%)	0.06

Table 3. Procedural Characteristics stratified by diagnosis of infection.

Variable	Infected (n = 82)	Non Infected (n = 37)	*p*-Value
Procedure duration, minutes	125 ± 47.4	137 ± 55.6	0.22
Number of extracted catheters			
0	-	3 (8.6%)	<0.001
1	14 (17.3%)	22 (62.9%)	
2	42 (51.9%)	9 (25.7%)	
3	17 (21%)	1 (2.8%)	
4	8 (9.8%)	-	
Previously abandoned catheter ≥1	13 (16%)	1 (2.9%)	0.06
Technique of extraction			
Traction	6 (7.4%)	3 (8.6%)	0.90
Mechanical dilator sheath	64 (79%)	29 (82.8%)	
Powered sheath	10 (13.6%)	3 (8.6%)	
Procedural success			
complete	72 (87.8%)	29 (78.4%)	0.30
clinical	4 (4.9%)	4 (10.8%)	
surgical extraction	1 (1.2%)	1 (2.7%)	
procedural failure	0 (0%)	1 (2.7%)	
complications	5 (6.1%)	2 (5.4%)	

3.1. Procedural Complications

A single case (0.84%) of death was documented in the subject with an indication of lead malfunction due to cardiac avulsion during the procedure. Surgical extraction was required in three cases after cardiac tamponade. In a fourth case, initially performed for lead malfunction, the procedure failed because of a lead fracture at the level of the left subclavian. A total of seven intraprocedural complications occurred, including two strokes.

3.2. Short-Term Outcome

Ten patients (8.4%) died at the hospital (25-days average after TLE), six of whom individuals had infectious indications for TLE (three local and three systemic). The three patients with systemic infection died of multiorgan failure secondary to sepsis due to methicillin-resistant *Staphylococcus aureus*, *P. aeruginosa* or *K. pneumoniae*. Four patients with no infection died at short-term follow-up: two patients died in the hospital due to progressive heart failure 15 days after TLE, one patient died of a complication of a renal biopsy performed during hospitalization (exsanguinating retroperitoneal hemorrhage), last patient at 85 years old died due to spontaneous cerebral hemorrhage 1 week after TLE.

3.3. Long-Term Outcome

At the last follow-up available (median observation time 49 months, range: 1–93 months), mortality reached 37% of the patient population, including only patients after hospital discharge. The mortality analysis ended on January 2023: reasons for death during long-term outcomes were not available for most patients. Kaplan Meier curves describing mortality after hospital discharge of the TLE population showed a statistically significant difference between infected versus non-infected groups (Figure 2).

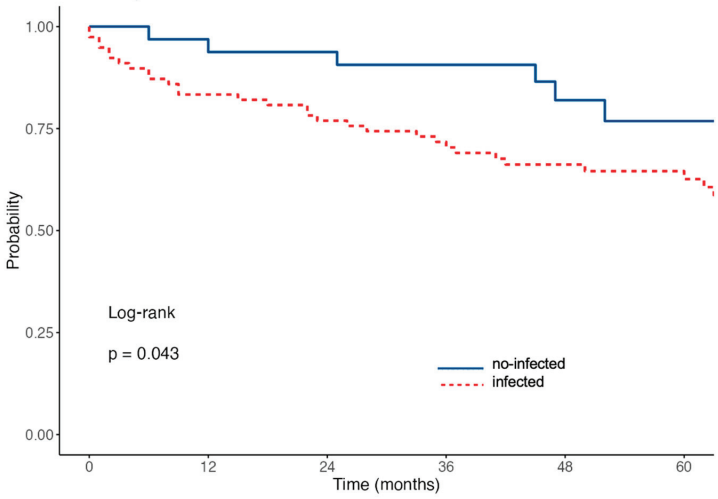

Figure 2. Kaplan Meier analysis of all-cause death after hospital discharge.

3.4. Predictors of Mortality

Univariable and multivariable analyses by Cox regression identified several correlates of mortality (Table 4). At univariable analysis, age at TLE, atrial fibrillation, and anemia remained significant correlates of mortality. In particular, the instantaneous mortality rate increases by 3% per year of patient age (HR 1.03; CI 1.01–1.06). At multivariable analysis, patients with anemia and atrial fibrillation have a 2.3-fold (HR 2.34; CI 1.16–4.75) and a 2.5-fold (HR 2.46; CI 1.33–4.54) increased rate of death, respectively.

Table 4. Univariate and multivariate Cox regression for all-cause death.

	Univariable		Multivariable	
Variable	**HR (95% CI)**	***p*-Value**	**HR (95% CI)**	***p*-Value**
Infective indication	1.46 (0.76–2.78)	0.25		
Age at extraction	1.03 (1.01–1.06)	0.009	1.03 (1.00–1.06)	0.05
Coronary artery disease	1.71 (0.94–3.10)	0.08		
Atrial fibrillation	2.81 (1.56–5.07)	0.001	2.54 (1.37–4.72)	0.003
Systemic arterial hypertension	0.84 (0.47–1.53)	0.58		
Diabetes	1.66 (0.87–3.17)	0.12		
Anemia	2.02 (1.1–3.73)	0.05	1.9 (0.99–3.64)	0.009
Chronic kidney disease	1.63 (0.90–2.96)	0.11	1.78 (1.10–2.86)	0.02
Left ventricular ejection fraction	0.99 (0.96–1.02)	0.58		
Heart failure	0.88 (0.49–1.58)	0.65		
Presence of coil	0.70 (0.40–1.23)	0.22		
Multiple leads (n $\geq$ 2)	1.42 (0.73–2.76)	0.30		
Older leads	1.00 (1.00–1.01)	0.41		

4. Discussion

This study analyzes long-term mortality in TLE procedures from a medium-volume single center in the oldest Italian Region: not by chance, the patients are older compared to other large studies such as LExlCon [15], ELECTRa [16], and PROMET [17] (mean age 76 versus 63–65 years, respectively), while the proportion of males is comparable to the

aforementioned studies (79.3%) [15–17]. In the results, long-term mortality is significantly higher in the older median-age CIED-infected population when compared to the non-infected population; actually, infection-related indications were different when compared to larger studies (68.9% in our study versus 46–57%) [15–17]. This finding may be because of the lower threshold for performing TLE in non-infected CIEDs, due to a potentially higher procedural risk in the older population since octogenarians are deemed as high-risk candidates for TLE; despite in previous little populations, the old age could not influence TLE effectiveness, being successfully performed [18,19].

The procedural success rate was achieved in 91.6%, a slightly lower percentage than the studies mentioned above (94.3–98.7%) [15–17] without any significant difference when comparing CIED-infected and non-infected populations. Intraprocedural mortality was low (0.84%) and comparable to large series: the ELECTRa registry [16] showed a procedural mortality of 0.5%, while Wazni O et al. [15] showed a procedural mortality of 0.28%. On the other hand, in-hospital mortality was 8.4%: older age and overlapping comorbidities could increase the risk in patients requiring TLE. According to a prospective multicenter study [16], age over 68 years is a predictor of increased all-cause mortality during hospitalization. Finally, the results show that long-term mortality is significantly higher in the older median-age CIED population, documenting an all-cause mortality rate of 37% during the entire follow-up period. Long-term mortality after TLE is significantly higher in patients with infection; notably, the survival curves of patients undergoing TLE for infection diverge from those of patients undergoing TLE for lead malfunction or other indications from the first few months after hospital discharge. These findings are consistent with a recent report from Arabia et al. [20], documenting that patients who perform TLE for CIED-related infection may exhibit a 30% mortality rate during a 6.5 median follow-up. Migliore et al. [18] recently described long-term mortality in elderly patients undergoing TLE: the main indication for TLE was an infection in 84.3% of cases with an overall mortality rate of 29% during a mean follow-up of ≈2 years. Finally, Henrikson et al. [21] described midterm mortality in a small population undergoing TLE for infectious indications, documenting a 30% mortality rate during the follow-up.

In our results, anemia and atrial fibrillation were the strongest correlates of mortality in multivariable analysis, and age at the extraction reached statistical significance. Therefore, in an older population undergoing TLE, more effort should be dedicated to the preoperative e postoperative treatment of comorbidities such as severe anemia and poorly managed atrial fibrillation. Moreover, considering that survival continues to be burdened by the progression of multiple chronic diseases beyond the clinical resolution of the infection, old patients who undergo successful TLE (especially for an infectious cause) remain at high risk of death at a median follow-up of 49 months. Also, infection prevention may have a significant impact on long-term mortality reduction. In particular, a preoperative antibiotic strategy combined with an early procedural approach is extremely important in order to have the best clinical condition at baseline and potentially a more favorable prognosis, also in older populations. Not by chance, today's recommendations suggest complete device and lead removal for all patients with CIED infection [10].

5. Limitations

In terms of limitations, this study is a retrospective analysis and thus is subject to bias. The main limitation is the small number of patients (n: 119), which limits data analysis. The cohort was limited to a single, medium-volume academic center, and the experience may differ at other types of institutions. In addition, the details regarding the mode of death are not available.

6. Conclusions

This study evaluates the long-term outcomes of TLE in elderly patients with or without infection from a single-center experience. Our data show that patients undergoing TLE

for CIED-related infection have a high risk of mortality during a long-term follow-up, potentially leading to a rapid and effective procedural approach in this patient population.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12134543/s1, Table S1 Study population characteristics stratified by diagnosis of local versus systemic infection.

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Electroanatomical Conduction Characteristics of Pig Myocardial Tissue Derived from High-Density Mapping

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Abstract: Background: Ultra-high-density mapping systems allow more precise measurement of the heart chambers at corresponding conduction velocities (CVs) and voltage amplitudes (VAs). Our aim for this study was to define and compare a basic value set for unipolar CV and VA in all four heart chambers and their separate walls in healthy, juvenile porcine hearts using ultra-high-density mapping. Methods: We used the Rhythmia Mapping System to create electroanatomical maps of four pig hearts in sinus rhythm. CVs and VAs were calculated for chambers and wall segments with overlapping circular areas (radius of 5 mm). Results: We analysed 21 maps with a resolution of 1.4 points/mm^2. CVs were highest in the left atrium (LA), followed by the left ventricle (LV), right ventricle (RV), and right atrium (RA). As for VA, LV was highest, followed by RV, LA, and RA. The left chambers had a higher overall CV and VA than the right. Within the chambers, CV varied more in the right than in the left chambers, and VA varied in the ventricles but not in the atria. There was a slightly positive correlation between CVs and VAs at velocity values of <1.5 m/s. Conclusions: In healthy porcine hearts, the left chambers showed higher VAs and CVs than the right. CV differs mainly within the right chambers and VA differs only within the ventricles. A slightly positive linear correlation was found between slow CVs and low VAs.

Keywords: conduction velocity; voltage; ultra-high-density mapping; heart; pig

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1. Introduction

Cardiac arrhythmias are a disruption of the normal cardiac rhythm and can range from simple changes in heart rate to complex fibrillation events. They may result in various clinical symptoms, from reduced physical resilience to sudden cardiac arrests [1]. Atrial fibrillation is the most common sustained arrhythmia, affecting 0.51% of the world's population. Its worldwide prevalence has increased by 33% over the past 20 years and is expected to rise by >60% in the coming 30 years [2].

Re-entry mechanisms cause many cardiac arrhythmias. The zones of slow conduction play a key role in developing and maintaining reentrant tachycardias [1,3–5]. Therefore, treatment by catheter ablation involves the ablation of slow conduction or low voltage zones [6] that can be identified with ultra-high-density mapping systems [7].

Until recently, there have been few, mostly incomplete data on conduction velocities in healthy hearts.

Hansson et al. collected data from the right atrial wall with an epicardial electrode array [8]. Martin et al. measured conduction velocities and electrogram amplitudes in different sections of re-entry circuits, mainly among patients with ischemic cardiomyopathy [5]. Kléber et al. observed the time course of left ventricular conduction velocity changes during induced ischemia in isolated porcine hearts [9].

None of these studies provided an overall approach with reference values or comparisons between physiological conduction velocity and voltage amplitude in all four heart chambers. Characterizing normal heart electrical physiology is crucial to distinguish between physiological and diseased patterns.

In this study, we aimed to define and compare a basic value set for unipolar conduction velocities and voltage amplitudes in all four heart chambers and their separate walls in healthy, in vivo porcine hearts using ultra-high-density mapping. In addition, we analysed whether conduction velocity and voltage amplitude are correlated in healthy hearts. Our velocity calculations for the three-dimensional myocardial surface were based on overlapping circular areas.

2. Materials and Methods

Experimental data were collected from four juvenile healthy swine (German Landrace x Pietrain; 31–41 kg (mean 36 kg), 3–4 months old), two of which were female (pigs 3 and 4). The study was approved by the government of Bavaria (ROB-55.2-2532.Vet_02-1 7-174).

2.1. Electroanatomical Mapping

Electrophysiological studies were performed in vivo under general anaesthesia and mechanical ventilation during intrinsic sinus rhythm. Sedation was administered intramuscularly with ketamine (10–15 mg/kg), azaperone (2 mg/kg), and atropine (1 mg). Anaesthesia was introduced with 1% and maintenance with 2% propofol i.v. We administered acetylsalicylic acid (250 mg i.v.) and heparin (150 IE/kg i.v. as a bolus and 200 IU/mL i.v. as continuous drip infusion depending on activated clotting time) for intraoperative anticoagulation after the sheath was placed. Intraoperative analgesia was provided by fentanyl boluses (0.015 mg/kg i.v.) every 20–30 min, and metamizole (40–50 mg/kg i.v.) was administered before the first incision. Transvenous catheters were inserted under fluoroscopic guidance. Access to the left heart was gained via a transseptal approach. Electroanatomical mapping was performed during sinus rhythm using Rhythmia, an ultra-high-density mapping system (Boston Scientific Corp., Marlborough, MA, USA), and its proprietary, 64-lead, multi-electrode basket mapping catheter Intellamap Orion (Boston Scientific Corp., USA). The sedation dosage was constant throughout the whole period of mapping to ensure comparable conditions between the different maps. The catheter is bidirectionally steerable and consists of eight splines, each containing eight electrodes spaced 2.5 mm apart [10].

2.2. Post-Processing in Rhythmia

After completing the electrophysiological studies, the annotated beats were manually checked for plausibility and, if necessary, reannotated in Rhythmia to specifically ensure that no His–Purkinje-system signals were falsely annotated. Transitions to other cardiac chambers, arteries, and veins were identified based on the morphology and amplitude of electrograms and marked as cutouts (blue in Figure 1). The mean heart rate was calculated for each mapping procedure.

2.3. Calculation of Local Conduction Velocity and Voltage Amplitude

To compute local conduction velocities and voltage amplitudes from the measured activation times while considering the variability of wavefront directions, we defined circular areas with an approximately 5 mm radius on the map surfaces and left out the cutouts. We used spherical filters from ParaView (v.5.8.0 and 5.10.0, Kitware Inc., New York, NY, USA) to create circular areas on the curved heart surface [11,12], as shown in

Figure 1. Additional simulations were created for each heart chamber, where the circles only cover the septal, lateral, posterior, or anterior region in the case of ventricles plus the superior of the atria, respectively.

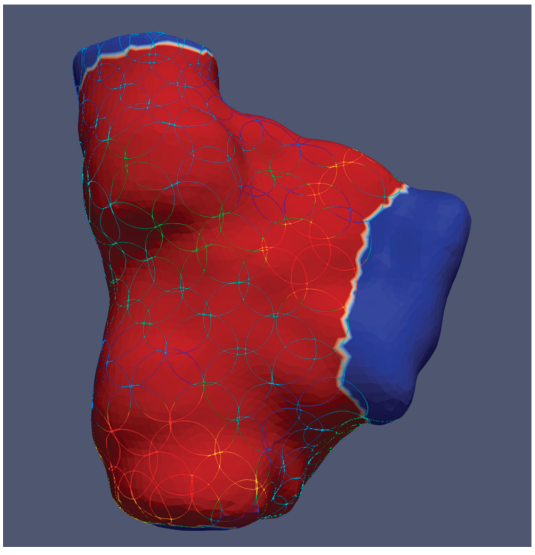

Figure 1. Example of a right atrium showing circular areas for calculating local conduction velocities and voltage amplitudes in ParaView. The blue colour indicates transitions to the venae cavae and right ventricle, where no circles are placed.

The mean voltage amplitude and conduction velocity of the covered map surface were calculated for each sphere. We divided the theoretical circle diameter, determined from the actual circular surface area, by the time difference between the first and last activations in each area to calculate conduction velocity, as seen in (1).

$$conduction\ velocity = \frac{2 \times \sqrt{\frac{area}{\pi}}}{\Delta\ activation} \quad (1)$$

All values and metadata were calculated and exported from ParaView using a custom-written Python script.

2.4. Statistical Analysis

Statistical analysis was performed using the statistical programming language R, v4.1.2 [13].

The relationship between conduction velocity and voltage amplitude, respectively, with the two factors mapping location and heart rate, was investigated by means of linear mixed effects analysis using lme4 [14,15] since repeated measurements, and a varying number of observations were obtained from four individuals. Mapping location and heart rate were used as fixed effects (with no interaction term). As a random effect, we used random intercepts for the pigs to account for inter-individual variation. The velocity was log-transformed in the linear model to obtain a normal distribution.

We used the lmerTest [16,17] and emmeans [18] packages for post hoc tests and comparisons, i.e., to compare the estimated mean values of the response variables for all levels of the explanatory variable under consideration. Tukey's HSD was used for all pairwise comparisons and Sidak for targeted comparisons to adjust for multiple comparisons.

Post hoc test results are reported on the original scale. All estimated values are provided for a heart rate of 90 bpm. Estimates are reported in the format (estimate ± standard error,

p-value). Correlations were tested via Pearson's correlation coefficient, reported in the format (r (degrees of freedom) = r-statistic, p = p-value). Velocity values of >6 m/s were defined as outliers and ignored in the calculations. The p-values of <0.05 were considered significant. Measured amplitude values are reported as unipolar signals.

3. Results

A total of 21 maps were analysed, each consisting of 5632 ± 295 measurement points. The map surfaces had 131 ± 8 spheres, each covering an area of 77.8 mm^2 ± 0.05, including 105 ± 0.19 measurement points. Therefore, the mapping resolution was 1.4 points/mm^2. The volumes in Table 1 correspond to three-dimensional electroanatomic maps. Since these measurements also include transitions to the other chambers and adjacent parts of the vessels (excluded in the further calculations), the calculated volumes overestimate the actual size of the chambers, especially for the right atria.

Table 1. Overview of the recorded maps, the mean heart rate during the procedure, the number of recorded measurement points, map volume, and the number of circles in whole maps and regions of each map.

Pig	Map-Nr.	Mapping Location	Heart Rate	Nr. of Points	Volume (mL)	Nr. of Circles Whole Map	Lateral Circles	Septal Circles	Posterior Circles	Anterior Circles	Superior Circles
1	1	RA	115	6839	77.65	184	30	23	26	-	9
1	4	RA	115	6907	77.65	184	30	23	26	-	9
1	5	LV	122	4806	53.16	122	10	14	20	21	-
1	9	LV	130	4726	53.16	122	10	14	20	21	-
2	10	RA	120	7475	69.66	167	21	17	16	-	11
2	12	RA	134	7475	69.66	167	21	17	16	-	11
2	14	LV	120	5060	50.10	129	11	13	26	24	-
2	16	LV	86	5060	50.10	129	11	13	26	24	-
2	18	LA	86	4835	39.95	100	11	10	16	12	15
2	20	LA	90	4964	40.68	100	11	10	16	12	15
2	21	RV	104	6440	68.88	138	12	16	17	21	-
2	23	RV	95	6445	68.64	138	12	16	17	21	-
3	25	RA	130	7815	81.00	193	30	35	33	-	10
3	26	RV	135	3547	33.95	74	9	13	9	14	-
3	32	RV	150	4698	35.82	66	10	9	6	6	-
5	36	RA	95	6848	64.54	176	41	21	21	-	13
5	37	RV	110	3158	25.93	84	12	15	16	9	-
5	39	RA	145	6799	69.00	186	45	32	26	-	24
5	42	RV	132	3420	28.04	84	12	15	16	9	-
5	44	LA	145	5481	40.70	105	4	9	10	9	11
5	45	LA	171	5481	40.70	105	4	9	10	9	11

3.1. No Influence of Sex on Conduction Velocity and Voltage Amplitude

Since the study was performed on two male and two female pigs, we performed a linear mixed-effects analysis to test whether sex affected conduction velocity and voltage amplitude. In our study, sex had no influence on conduction velocity (p = 0.50) or voltage amplitude (p = 0.30).

3.2. Mean Velocity and Voltage of Heart Chambers during Sinus Rhythm

The overall unipolar conduction velocity at a heart rate of 90 bpm is highest in the left atrium (LA) (0.79 ± 0.05 m/s), followed by the left ventricle (LV) (0.59 ± 0.04 m/s), the right ventricle (RV) (0.54 ± 0.03 m/s), and the right atrium (RA) (0.50 ± 0.03 m/s).

The overall unipolar voltage amplitude at a heart rate of 90 bpm is highest in the LV (10.98 ± 0.34 mV), followed by the RV (7.83 ± 0.32 mV), LA (4.81 ± 0.35 mV), and RA (3.35 ± 0.31 mV) (Figure 2).

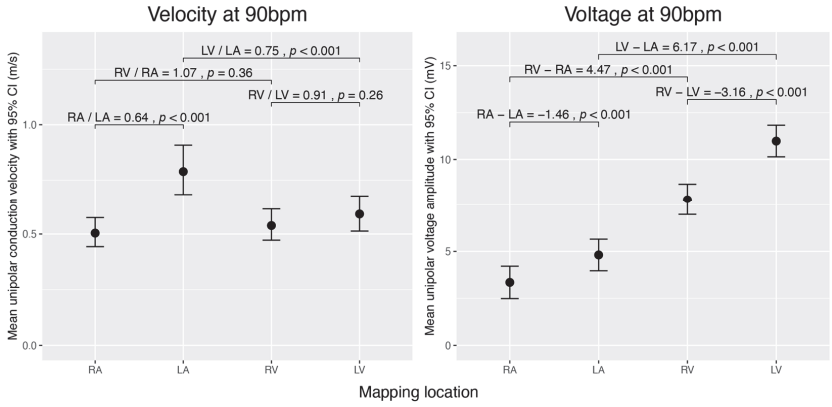

Figure 2. Comparison of estimated unipolar conduction velocities and voltage amplitudes during sinus rhythm across the cardiac chambers (RA, LA, RV, and LV) normalized to 90 bpm. The left graph displays mean conduction velocities (m/s), and the right graph shows mean voltage amplitudes (mV) with 95% confidence intervals. Brackets denote selected pairwise comparisons between chambers, with *p*-values testing if the ratio of mean velocities equals 1 or the difference in mean voltages equals 0 mV. The data were obtained using linear mixed-effects models and analysed using estimated marginal means. For velocity, we analysed the data on the log scale and then back-transformed the results for interpretation.

3.3. Velocity and Voltage Differences between Chambers

3.3.1. Inter-Atrial and Inter-Ventricular Comparison

We compared conduction velocities and voltage amplitudes between the atria and between the ventricles. The RA conducts significantly slower ($\times 0.64 \pm 0.03$, $p < 0.001$) and has a lower voltage amplitude (-1.46 mV $\pm$ 0.19, $p < 0.001$) than the LA. By contrast, the voltage amplitude is higher in the LV than in the RV (-3.16 mV $\pm$ 0.21, $p < 0.001$), and no significant difference in conduction velocity was observed between the ventricles (Figure 2).

3.3.2. Comparison between Atria and Ventricles of the Left and Right Heart

We then compared the conduction velocity and voltage amplitude between the atrium and ventricle of the same half of the heart. In the left chamber of the heart, the conduction velocity was higher in the atrium than in the ventricle ($\times 0.748 \pm 0.041$, $p < 0.001$). We found no significant difference in conduction velocity between RA and RV. Voltage amplitudes were generally lower in the atria than in the ventricles ($p < 0.001$) (Figure 2).

3.4. Regional Velocity and Voltage Characteristics within Each Chamber

Each heart chamber was divided into subregions representing different walls. The following conduction velocity and voltage amplitude estimates are normalized to a heart rate of 90 bpm.

3.4.1. Conduction Velocity

In the RA, the conduction velocity was highest in the posterior wall (0.61 ± 0.04 m/s), compared to the superior (0.42 ± 0.04 m/s, $p < 0.044$), lateral (0.44 ± 0.03 m/s, $p < 0.001$), and septal walls (0.48 ± 0.03 m/s, $p = 0.009$). In the RV, the anterior wall (0.44 ± 0.04 m/s) showed the lowest conduction velocity and was significantly different from the posterior (0.83 ± 0.08 m/s, $p < 0.001$), lateral (0.69 ± 0.07 m/s, $p < 0.001$), and septal walls (0.63 ± 0.06 m/s, $p = 0.008$). All other walls within these right heart chambers did not differ significantly.

Within the LA, the superior wall had the highest conduction velocity (1.09 ± 0.12 m/s) and was significantly faster than the anterior wall, which had the slowest conduction velocity (0.72 ± 0.09, $p = 0.043$). We did not find any significant difference in conduction velocity between any other regions of the LA and LV (Figure 3).

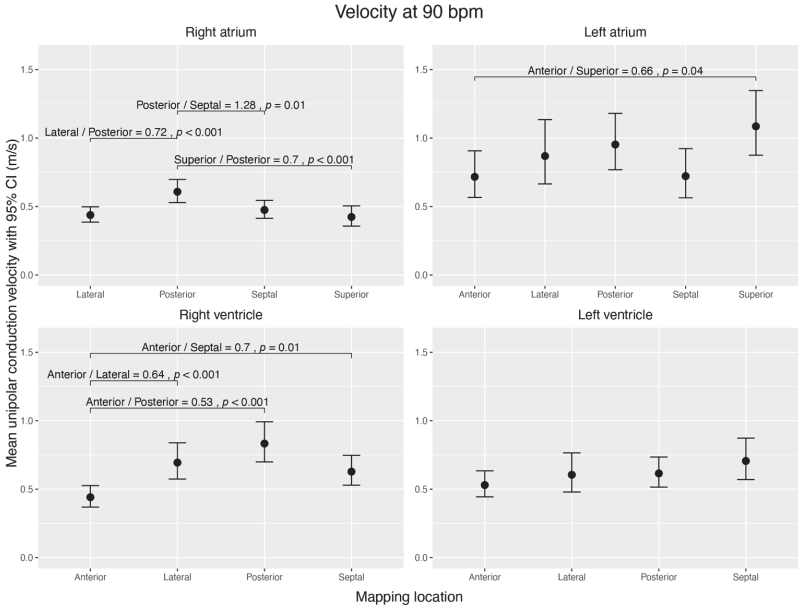

Figure 3. Visualization of estimated mean unipolar conduction velocities (m/s) during sinus rhythm, normalized to 90 bpm, across distinct regions of each cardiac chamber and their pairwise comparisons. The figure shows four subplots, each representing a cardiac chamber (right atrium, left atrium, right ventricle, and left ventricle), with potential mapping regions (anterior, posterior, lateral, septal, and superior). The 95% confidence interval is given for each mean velocity. Brackets highlight significant contrast ratios ($p < 0.05$) between the regions within the corresponding chamber, indicating divergence from a ratio of 1. The data were obtained using linear mixed-effects models and estimated marginal means. We conducted tests on the log scale and subsequently back-transformed the results for interpretation.

3.4.2. Voltage Amplitude

The atria showed no voltage differences between different walls.

The RV had high voltage amplitudes at the posterior (9.59 ± 0.52 mV) and septal walls (10.64 ± 0.52 mV), which were significantly higher than at the anterior (5.95 ± 0.52 mV) and lateral (6.73 ± 0.54 mV) walls ($p < 0.001$).

Within the LV, the posterior wall (8.89 ± 0.52 mV) had the lowest voltage amplitude and was significantly different from any other ($p < 0.001$). The lateral wall (13.48 ± 0.61 mV) had the highest voltage amplitude (anterior vs. lateral $p = 0.041$; posterior vs. lateral $p < 0.001$; septal vs. lateral $p < 0.001$) (Figure 4).

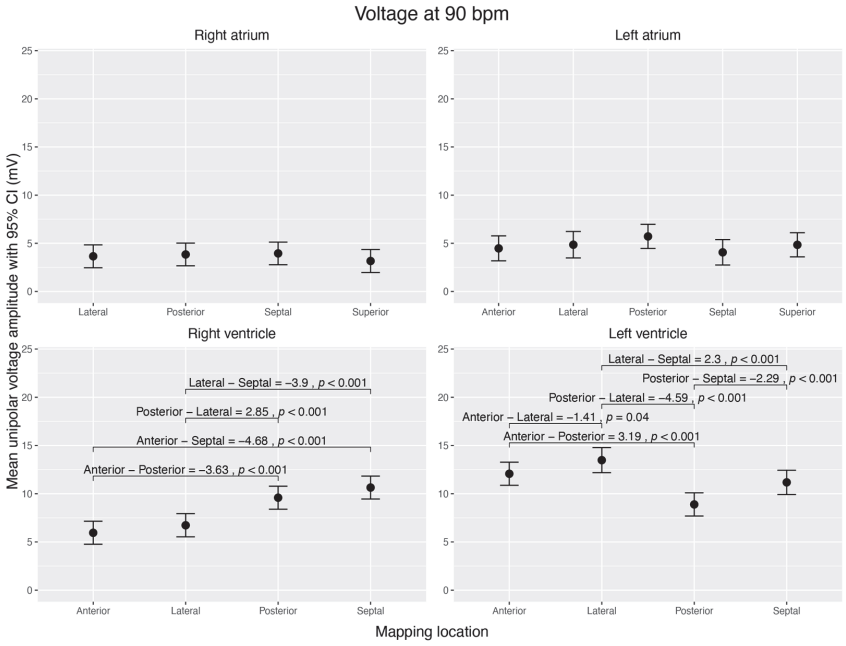

Figure 4. Visualization of estimated mean unipolar voltage amplitudes (mV) during sinus rhythm, normalized to 90 bpm, across distinct regions of each cardiac chamber and their pairwise comparisons. The figure shows four subplots, each representing a cardiac chamber (right atrium, left atrium, right ventricle, and left ventricle), with potential mapping regions (anterior, posterior, lateral, septal, and superior). The 95% confidence interval is given for each mean voltage. Brackets highlight significant voltage mean differences ($\Delta > 0$ mV; $p < 0.05$) between the regions within the corresponding chamber. Data were derived from linear mixed-effects models with estimated marginal means.

3.5. Correlation of Velocity and Voltage

No general linear correlation between voltage amplitude and conduction velocity (r(2736) = 0.05, $p = 0.008$) was observed ($|r| < 0.2$).

Separated by mapping location, we found a low positive linear correlation between voltage amplitude and conduction velocity (r(408) = 0.30, $p < 0.001$) for the LA. In the other heart chambers, no linear correlation was observed (RA r(1252) = 0.11, $p < 0.001$; LV r(496) = 0.09, $p = 0.053$; RV r(574) = −0.07, $p = 0.114$) (Figure 5).

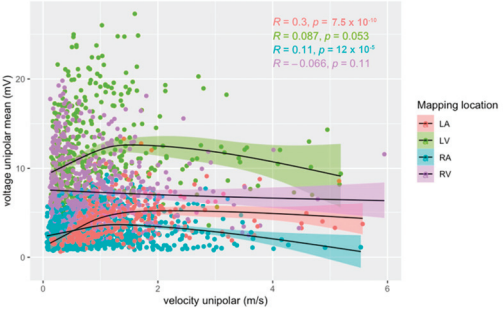

Figure 5. Relationship between unipolar voltage amplitude and unipolar conduction velocity for right (blue) and left (red) atria, and right (purple) and left (green) ventricles during sinus rhythm. Pearson's correlation coefficients and their *p*-values for each heart chamber are provided.

At velocities of <1.5 m/s, a low positive linear correlation between voltage amplitude and conduction velocity was observed in the LA ($r(310) = 0.47$, $p < 0.001$), LV ($r(424) = 0.23$, $p < 0.001$), and RA ($r(1105) = 0.25$, $p < 0.001$). No correlation was found in the RV ($r(496) = -0.09$, $p = 0.05$).

4. Discussion

To our knowledge, the current study is the first to use an ultra-high-density mapping system to systematically analyse intrinsic conduction velocities and voltage amplitudes in healthy pig hearts.

Our first key finding was that the highest conduction velocity of the heart chambers was found in the LA, whereas the highest amplitudes were measured in the LV. The left heart chambers showed higher voltage amplitudes and conduction velocities than their right counterparts. One explanation might be that a high conduction velocity in the left heart chambers is crucial to ensuring a synchronized electrical excitation of the chambers because of their larger size and greater myocardial mass [19]. As gap junctions seem to be the main determinant of conduction velocity in healthy myocardium [1], our observation may lead to the hypothesis that gap junction coupling might be higher in left-sided myocardium than right-sided myocardium.

Our second key finding was that within one heart chamber, conduction velocity varied more in the right heart chamber than in the left. In the RA, the posterior wall showed higher conduction velocities than the septal, lateral, and superior wall segments. In the RV, the anterior wall showed lower conduction velocities than the lateral, posterior, and septal wall segments. Within the LA, only the superior and anterior walls differed significantly, with the superior wall conducting the fastest. We interpret this finding as a measurement of the fast-conducting Bachmann bundle, which confirms the validity of our data [20,21]. The LV did not show any significant differences in conduction velocities between different segments.

Our third key finding was that there was no significant difference in voltage amplitude within the atria, except for one within the ventricles. In the RV, the posterior and septal walls showed higher voltage amplitudes than the anterior and lateral walls. In the LV, the lateral wall showed the highest voltage amplitude, whereas the posterior wall showed the lowest. The amplitudes in all segments of the ventricles were in the high range of >5 mV. In other words, no relevant low-voltage areas could be identified in absolute numbers. Further investigations should reveal whether differences in this high-amplitude range correspond to physiological structures.

Our fourth key finding was that in healthy, juvenile pig hearts, there was a slightly positive correlation between conduction velocity and voltage amplitude at velocities <1.5 m/s in all chambers except the RV. This finding might be due to the correlation between slow conduction zones and low-voltage areas in partially scarred myocardium [22,23].

The mapping resolution was very high compared to the published data. On average, the maps in our analysis showed a mapping resolution of 1.4 points/mm^2 compared to the resolutions of 0.2 points/mm^2 in another work characterizing left atrial slow conduction zones among patients with atrial fibrillation [24]. The number of mapping points is crucial to identifying critical ablation targets [7].

Our data are comparable to published human data on conduction velocities derived from electrodes with small surfaces and small inter-electrode distances. Martin et al. measured the conduction velocities among patients with ischemic cardiomyopathy [5]. Kléber et al. observed that myocardial tissue showed an ischemia-induced slowing of conduction velocity [9]. In contrast, Sanders et al. compared a prolonged conduction velocity in the right lateral atrium of patients with sinus node diseases to a matching group of patients with normal sinus node function. They conducted a second comparative analysis among patients with congestive heart failure and another matching group. The conduction velocities were 10 times higher than the pigs' velocities in our study. The reason for this may

lie in the mapping technique used by Sanders at the time, which was a non-high-density 3D mapping system [25,26] with a very rough analysis of conduction velocity.

In our analysis, we used unipolar signals, not bipolar signals, to calculate ultra-high-density 3D voltage maps. Moreover, unipolar mapping has been useful for identifying alterations in voltage amplitude, reflecting histologically proven viable myocardium in the scar areas of ischemic origin [27], as well as low-voltage areas in the LA.

Limitations

Our data are derived from healthy porcine hearts, and their validity might be limited when transferred to human hearts. Healthy human heart measurements and outside interventions for all four heart chambers remain scarce for ethical reasons. Studies describing models to estimate local atrial conduction velocities [28] may develop and verify their models with the help of porcine heart data. Since pigs' cardiovascular system, heart size, and body weight are similar to those of humans, we used a pig model as a valuable preclinical model [29]. The volumes in our study are smaller than in adult human hearts (RA 100 mL [30], LA 129 $\pm$ 44 mL [31], RV 44–101 mL [32], LV 58–120 mL [33]), possibly due to the juvenile age of the pigs (31–41 kg, 3–4 months old).

The porcine hearts were healthy and juvenile. Correlations between conduction velocities and voltage amplitudes that are presumed and observed in diseased hearts may be absent in healthy hearts. Therefore, conclusions regarding diseased and aged hearts can be misleading.

The sample size was limited to four pigs due to animal welfare. Despite using the random effect 'heart', we cannot rule out the possibility that strong inter-individual differences interfered with our statistical model.

The signals were recorded with one ultra-high-density mapping system and one distinct mapping catheter. There are several mapping systems on the market with different mapping catheter designs. As there are no head-to-head comparisons between different ultra-high-density mapping systems, limitations or advantages are unknown with regard to signal quality.

Since the velocity was calculated using time differences between the first and last excitations in the circle, colliding wavefronts might be misinterpreted. The probability of colliding wavefronts in healthy hearts should be low. The small radius of the circles prevents disturbances in analysing velocities due to colliding wavefronts.

The heart chambers and different segments of each heart chamber were mapped consecutively. Therefore, an overtime effect on velocities or voltages cannot be fully excluded. We tried to keep the influence of time low by adhering to strict timelines for mapping. Furthermore, we did not administer any anti-arrhythmic drugs that could influence cardiac electrophysiology.

Heart rate was estimated over a recording period of approximately 5 min, which may cause inaccuracies in the heart rate analysis. To allow a better interpretation of results, we assumed a linear relation in our mixed-effects model, which provided a good approximation of higher-dimensional interactions.

Anaesthesia has been shown to influence cardiac electrophysiology [34–37]. The pigs were mapped under stable sedation to ensure comparability with the electrophysiological baseline circumstances. Specifically, we cannot rule out systematic bias in the absolute values of conduction velocity.

5. Conclusions

In healthy porcine hearts, conduction velocities and voltage amplitudes differ between the left and right heart chambers. Within each heart chamber, voltage amplitude differs only in the ventricles and conduction velocity differs more in the right than in the left chambers.

There is a slightly positive correlation between conduction velocity and voltage amplitude at velocities of <1.5 m/s in the atria and LV of healthy porcine hearts.

A comprehensive characterization of the conduction velocities and voltage amplitudes of all heart chambers could facilitate future computations for human heart models.

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Antiplatelet and Anti-Coagulation Therapy for Left-Sided Catheter Ablations: What Is beyond Atrial Fibrillation?

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Abstract: Aim: International guidelines on the use of anti-thrombotic therapies in left-sided ablations other than atrial fibrillation (AF) are lacking. The data regarding antiplatelet or anticoagulation strategies after catheter ablation (CA) procedures mainly derive from AF, whereas for the other arrhythmic substrates, the anti-thrombotic approach remains unclear. This survey aims to explore the current practices regarding antithrombotic management before, during, and after left-sided endocardial ablation, not including atrial fibrillation (AF), in patients without other indications for anti-thrombotic therapy. **Material and Methods:** Electrophysiologists were asked to answer a questionnaire containing questions on antiplatelet (APT) and anticoagulation therapy for the following left-sided procedures: accessory pathway (AP), atrial (AT), and ventricular tachycardia (VT) with and without structural heart disease (SHD). **Results:** We obtained 41 answers from 41 centers in 15 countries. For AP, before ablation, only four respondents (9.7%) used antiplatelets and two (4.9%) used anticoagulants. At discharge, APT therapy was prescribed by 22 respondents (53.7%), and oral anticoagulant therapy (OAC) only by one (2.4%). In patients with atrial tachycardia (AT), before ablation, APT prophylaxis was prescribed by only four respondents (9.7%) and OAC by eleven (26.8%). At discharge, APT was recommended by 12 respondents (29.3%) and OAC by 24 (58.5%). For VT without SHD, before CA, only six respondents (14.6%) suggested APT and three (7.3%) suggested OAC prophylaxis. At discharge, APT was recommended by fifteen respondents (36.6%) and OAC by five (12.2%). Regarding VT in SHD, before the procedure, eight respondents (19.5%) prescribed APT and five (12.2%) prescribed OAC prophylaxis. At discharge, the administration of anti-thrombotic therapy depended on the LV ejection fraction for eleven respondents (26.8%), on the procedure time for ten (24.4%), and on the radiofrequency time for four (9.8%), with a cut-off value from 1 to 30 min. **Conclusions:** Our survey indicates that the management of anti-thrombotic therapy surrounding left-sided endocardial ablation of patients without other indications for anti-thrombotic therapy is highly variable. Further studies are necessary to evaluate the safest approach to these procedures.

Keywords: left-sided ablations; anticoagulation therapy; ventricular tachycardia; atrial tachycardia

1. Introduction

Catheter ablation (CA) procedures are associated with a potential threat of thromboembolic complications in patients without other indications for anti-thrombotic therapy. Catheter instrumentation activates the clotting cascade and, consequently, increases the risk of thrombus formation [1,2], particularly in the case of procedures performed on the left side of the heart. Most of the available data are focused on periprocedural anticoagulation regimens and describe CA procedures for atrial fibrillation (AF) [3–5]. However, the anticoagulation protocols during other left-sided ablation procedures are not well assessed, particularly in complex ablations with extensive radiofrequency applications. The purpose of our survey was to address the contemporary clinical practices of electrophysiologists in antiplatelet (APT) and anticoagulation therapy (OAC) for left-sided endocardial CA, other than AF, in patients without other indications for antithrombotic therapy.

2. Methods

An online questionnaire consisting of multiple-choice questions was prepared and sent via SurveyMonkey to centers among electrophysiologists' scientific network that performed left-sided ablation. The responses were collected from 1 February 2019 to 15 March 2019. This study complied with the European General Data Protection Regulation law. All centers that took the survey agreed to participate in the study.

2.1. Data Collected

The questionnaire collected information on antithrombotic management before, during, and after left-sided endocardial CA procedures, except for AF, in patients without other indications for anti-thrombotic therapy. Left-sided ablation for atypical atrial flutter was also excluded. The left-sided endocardial CA procedures that were evaluated included CA of an accessory pathway (AP), atrial tachycardia (AT), ventricular tachycardia (VT) without known structural heart disease (SHD), and VT in SHD. Antithrombotic therapy included all pharmacological agents used to treat or avoid thromboembolism, including vitamin K antagonists (VKA), novel oral anticoagulants (NOAC) as well as APTs such as aspirin and P2Y12 inhibitors.

The questionnaire also collected information about the type of center (academic vs. public vs. private), the country of location, the number of procedures/year, the number of left-sided ablation procedures/year, and the number of electrophysiologists working in the EP lab.

The complete questionnaire is provided in Appendix A.

2.2. Statistical Analysis

Categorical data were reported as numbers and percentages. The mean (standard deviation [SD]) and the median (interquartile range [IQR]) have been used for the description of normally and non-normally distributed data, respectively. All data were analyzed using SPSS v 20.0 (SPSS Inc., Chicago, IL, USA). The authors had full access to the data and take full responsibility for its integrity. All authors have read and agreed to the manuscript as written.

3. Results

The centers were contacted to participate to the survey through EHRA database. Forty-one centers from 15 countries responded (63.4% university hospitals, 24.4% public hospitals, and 12.2% private hospitals) (Table 1).

Table 1. Countries of responders.

Italy	12 (29.3%)
Russia	7 (17.1%)
France	3 (7.3%)
Turkey	3 (7.3%)
Austria	2 (4.9%)
Belgium	2 (4.9%)
Croatia	2 (4.9%)
Greece	2 (4.9%)
Romania	2 (4.9%)
United Kingdom	2 (4.9%)
Germany	1 (2.4%)
Poland	1 (2.4%)
Spain	1 (2.4%)
Saudi Arabia	1 (2.4%)

The median number of EP procedures per center was in the range of 503 to 441 per year. The number of left-sided procedures per year was in the range of 37 to 21 (not including AF CA).

3.1. Accessory Pathway

Before CA, the majority of respondents (35, or 85%) did not use antithrombotic therapy. Only four respondents (9.7%) administered APT and two (4.9%) administered OAC (Figure 1). During CA, heparin was used by 85.4% (Figure 2) to maintain the ACT target of 300–350 s in 36.6% of cases (Figure 3). Heparin was used to irrigate the sheaths by 22 respondents (53.7%). After CA, APT was prescribed by twenty-two respondents (53.7%) and OAC only by one (2.4%) (Figure 4).

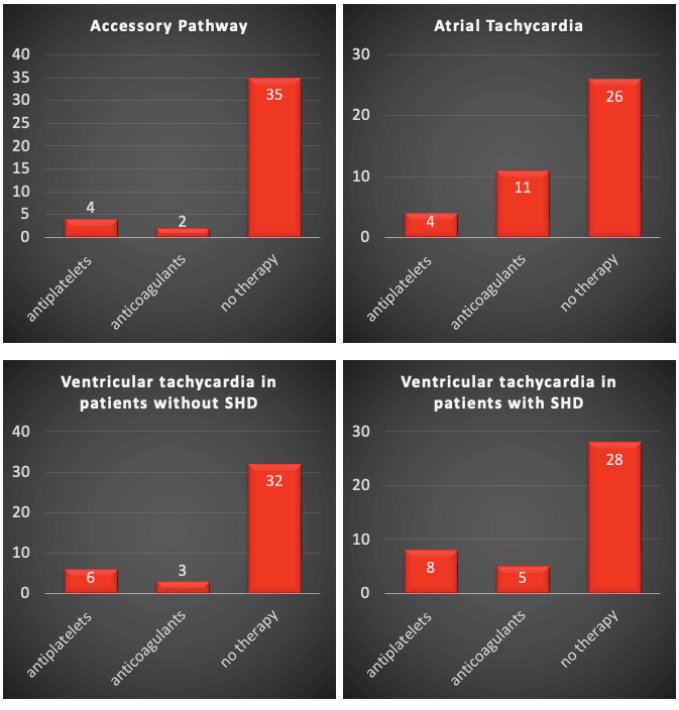

Figure 1. Anti-thrombotic management before ablation. SHD: structural heart disease.

Figure 2. Use of heparin during ablation. AP: accessory pathway, AT: focal atrial tachycardia, VT: ventricular tachycardia, SHD: structural heart disease.

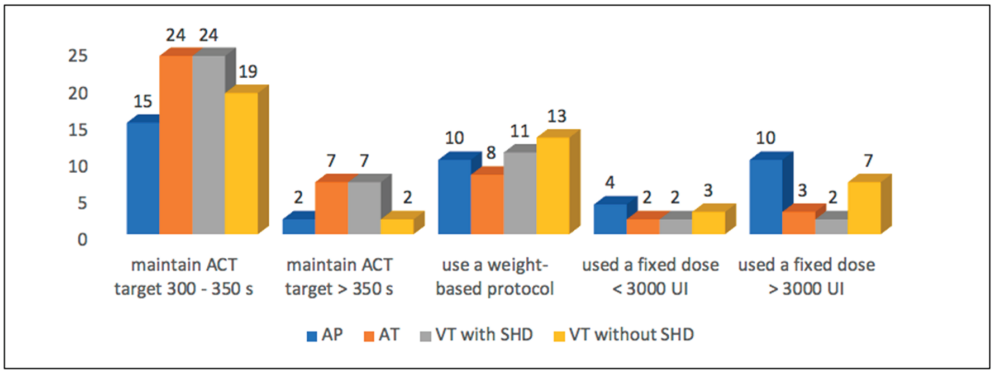

Figure 3. Heparin dosage during ablation. AP: accessory pathway, AT: atrial tachycardia, VT: ventricular tachycardia, SHD: structural heart disease, ACT: activated clotting time.

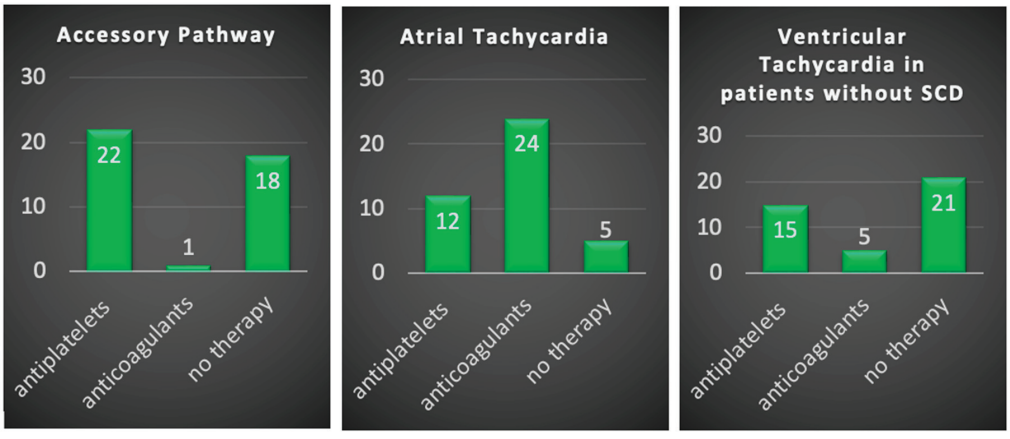

Figure 4. Anti-thrombotic management at discharge. SHD: structural heart disease.

3.2. Atrial Tachycardia

Before CA, APT prophylaxis was recommended by only four respondents (9.7%) and OAC by eleven (26.8%) (Figure 1). During the procedure, almost all respondents (40, or 97.6%) used heparin (Figure 2), and an ACT target of 300–350 s was adopted in 58.5% of cases (Figure 3). The sheaths were routinely irrigated with continuous intravenous heparin by 25 respondents (61%). After CA, APT was recommended by 12 respondents (29.3%) and OAC by 24 (58.5%) (Figure 4).

3.3. Ventricular Tachycardia in Patients without Structural Heart Disease

Before CA, only six respondents (14.6%) suggested antiplatelets and three (7.3%) suggested anticoagulation prophylaxis (Figure 1). During ablation, almost all respondents (40, or 97.6%) used heparin (Figure 2), maintaining an ACT target of 300–350 s in 46.3% of cases (Figure 3). Continuous intravenous heparin was used by 22 respondents (53.7%) to irrigate the sheaths. After CA, APT was recommended by fifteen (36.6%) and OAC by five respondents (12.2%) (Figure 4).

3.4. Ventricular Tachycardia in Patients with Structural Heart Disease

APT and OAC prophylaxis before CA were prescribed by eight (19.5%) and five (12.2%) respondents, respectively (Figure 1). Conversely, the intraprocedural use of heparin was adopted by all respondents (Figure 2), maintaining an ACT target of 300–350 s in 58% of cases (Figure 3). The sheaths were routinely irrigated with continuous intravenous heparin by 26 respondents (63.4%). After CA, the choice of administering APT was based on the left ventricular ejection fraction (LVEF), the procedure time, and the radiofrequency time, with a cut-off value ranging from 1 to 30 min for eleven (26.8%), ten (24.4%), and four (9.8%) respondents, respectively. (Figure 1). During CA, all respondents used heparin (Figure 2), maintaining an ACT target of 300–350 s in 58% of cases (Figure 3). The sheaths were routinely irrigated with continuous intravenous heparin by 26 respondents (63.4%). After CA, the administration of APT depended on the left ventricular ejection fraction (LVEF) for eleven respondents (26.8%), on the procedure time for ten (24.4%), and on the radiofrequency time for four (9.8%), with a cut-off value ranging from 1 to 30 min.

4. Discussion

Nowadays, CA is considered the strategy of choice for a wide range of arrhythmias in light of its high percentage of success and its low rate of complications [6]. With regard to thromboembolic complications, it is worth mentioning that manipulating catheters and simultaneously performing lesions during procedures may increase thrombotic risk, particularly in left heart procedures [7–10].

An incidence of cerebral embolism (CE) and peripheral arterial embolism of 0.46–0.06% in left-sided CS has been reported by Hindricks [8].

In the MERFS registry [8], which analyzed 1715 subjects who underwent right-sided ablation (AV node re-entrant tachycardia or AV junction ablation), the rates of CE, pulmonary embolism (PE), and venous thrombosis (VTE) were 0.06%, 0.23%, and 1.04%, respectively. On the other hand, the percentages of pericardial tamponade (PT), pericardial effusion (PEff), and major bleeding (MB)/hematoma have been reported as 0.17%, 0.41%, and 0.11%, respectively.

In the NASPE registry [11], among 2142 adults who underwent right-sided ablation, the rates of thrombo-embolism, PT, and MB/hematoma have been shown to be 0.14%, 0.09%, and 0.28%, respectively. In contrast, no embolic events have been reported after the CA of left free-wall accessory pathways in 418 adults.

In Atakr Multicenter's registry [12], it has been observed that thromboembolic events occurred in 0.7% and 1.1% of patients who underwent right-sided and left-sided CA, respectively, in the absence of other risk factors for systemic embolization.

In comparison, rates of PT, PEff, and MB/hematoma of 0.6%, 1.9%, and 3.5%, respectively, were described [12].

Furthermore, embolic complications after CA procedures in patients with VT seem to be lower in the absence of SHD compared to patients with structural abnormalities.

However, an anticoagulation strategy is usually used during CA procedures, consisting of administering a venous bolus of heparin (50–100 U/kg) followed by a heparin infusion with the aim of maintaining an ACT above 300 s [13–15].

Nevertheless, the intraprocedural risk of a systemic thromboembolic event is significantly lowered by the intravenous administration of heparin or bivalirudin [16]. Despite this, the post-procedural risk remains considerable, and it should be accurately evaluated [16]. Indeed, it has been shown that cerebral events, including subclinical ones, cause long-term neurocognitive impairment [17].

However, data regarding either the APT or the OAC approach after CA are limited.

Our survey sheds light on the fact that considerable variation exists in the management of OAC and APT surrounding left-sided non-AF endocardial CA in patients without other indications for anti-thrombotic therapy.

However, it should be highlighted that for some indications, the respondents largely agreed not to use antithrombotic medication, whereas the indications varied considerably for other procedures. During left-sided electrophysiological procedures, due to an increase in the thrombophilic state, a three-fold increase in the incidence of thromboembolic complications (1.8–2%) was observed, compared with an overall rate of only 0.6% when all CA procedures are considered [18]. Despite this important data that differs from AF indications [4], no guidelines indicate the correct choices in this setting. The only indication was given by the consensus document published in 2015 [18] and by a recent consensus on ventricular arrhythmias [19].

A previous survey about the prevention of VTE after EP procedures was conducted; however, it described only right-sided ablation [20]. To our knowledge, this is the first survey about left-sided ablations.

4.1. Accessory Pathway

Patients undergoing accessory pathway (AP) CA are more likely to be young, without risk factors for thromboembolic events, or those who are at low risk. Only a single catheter in the left atrium (LA) or left ventricle (LV) is commonly used; moreover, the ablation (CA) is usually focal, resulting in much shorter total CA times and less time spent in the left atrium. For this reason, Sticherling et al. [18] recommend neither anti-thrombotic prophylaxis before AP ablation, nor the post-interventional use of OAC or APT.

Moreover, previous studies reported an incidence of 0.46–2% [8,16] of thromboembolic events related to AP ablation and, recently, Głowniak et al. documented the presence of silent cerebral infarcts after AP ablation [21]. Thakur et al. [22] reported that 2% of embolic events were late incidences in left-sided accessory pathways CA, in spite of the intraprocedural administration of heparin followed by APT for 3 months after CA.

For this reason, continuous flushing of the sheaths and antithrombotic therapy (with 5000–15,000 U or 90–200 U/kg of intravenous sodium heparin followed by 1000 U/h) are advised during the procedure to avoid thrombus formation [18].

Our survey showed a different scenario: 15% of surveyed participants used antithrombotic prophylaxis before CA of the accessory pathway and 50% used it after CA. On the other hand, the heparin dose was mainly driven by the activated clotting time (ACT) value, and only half of the participants irrigated the sheaths during procedures.

4.2. Atrial Tachycardia

In contrast to patients with atrial flutter, who are thought to have the same risk of thromboembolism as patients with AF [23], there is no clear data regarding thromboembolic risk in patients with FAT. In our survey, only about a quarter of respondents used OAC in patients with FAT prior to the procedure, and about one-fifth recommended APT. During CA procedures, almost all the participants were heparinized. The respondents administered heparin to their patients based on ACT control, and over half of them also used heparin

in side flushes. Heparinization with ACT > 300 s is a standard of care in left-sided CA procedures according to the most recent European guidelines for AF management [24]; however, it was not specified whether the continuous irrigation of the sheaths further reduced the risk of thromboembolic complications.

After the CA procedure, slightly more than half of the participants recommended OAC, and a quarter preferred to give antiplatelet agents. The rationale for using OAC after AF ablation included the risk of arrhythmia in the blanking period and the phenomenon of atrial stunning following sinus rhythm restoration [25]. Again, there is no data on the prevalence of LA appendage thrombus after left-sided FAT CA. More data is needed to understand if the risk of thromboembolic events in FAT is similar to that in AF, and hence if respective antithrombotic therapy should be warranted.

4.3. Ventricular Tachycardia in Patients without Structural Heart Disease

VT can also occur in a structurally normal heart [26]. Idiopathic VTs (the most common type) are typically monomorphic because they originate from a single focus, and can be ablated by the limited delivery of radiofrequency energy to the site of origin of the arrhythmia [15]. Probably due to the limited area of CA, the risk of thromboembolism in patients without SHD undergoing VT ablation is lower than in patients with SHD [27], but data about the correct management of antithrombotic therapy in these procedures are not available, and there is a large variability among participants.

In a survey regarding intraprocedural anticoagulation among the writing committee members of the EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias [28], for idiopathic VA, 48% of the respondents used ACT levels longer than 250 s, 39% longer than 300 s, and 13% longer than 350 s. However, a clear distinction was not made between VT with and without SHD regarding antithrombotic therapy after CA. Our data confirmed the use of heparin during ablation. However, a difference in terms of ACT targets has been reported. Indeed, the data from our survey indicated that the achieved ACT values were higher, ranging from 300 to 350 s (Figure 2).

4.4. Ventricular Tachycardia in Patients with Structural Heart Disease (SHD)

Our results showed that anti-thrombotic therapy was variable in patients undergoing LV substrate ablation.

According to the 2019 HRS/EHRA/APHRS/LAHRS Consensus [19], antithrombotic therapy should not be adopted before CA; however, this point is not generally agreed upon.

Regarding anticoagulation during the CA procedure, previous authors have suggested different protocols: a bolus of at least 5000 U after the insertion of sheaths followed by a 1000 U/h heparin infusion without intra-procedural ACT monitoring [29], or strict ACT monitoring with the target values of 200–250 s [30]. In contrast, according to the consensus document, after sheath insertion, the administration of a bolus of intravenous heparin (bolus dose empirically 5000–10,000 U or 50–100 U/kg) should be followed by a continuous infusion of 1000–1500 U/h in order to maintain an ACT level of 300 s. Our data are not consistent with these indications. Indeed, the ACT target is higher (300–350).

Regarding post-procedural anticoagulation management, in our survey, APT was prescribed after CA by 53.6% of respondents and OAC by 31.7%.

However, there are no conclusive data in this sense [31,32], and the choice of APT after CA depends on the physician [7] (Table 2).

Another important part of the data to consider is the role of OAC with warfarin or NOACs for patients who received extensive areas of CA, or those who are at increased risk of thromboembolism. In a paper by Reddy et al. [33], and in the Multicenter Thermocool Ventricular Tachycardia Ablation Trial [34], the choice between VKA or aspirin after a VT ablation depended on the extension of the CA area (Table 2). In the SMASH VT study [33], OAC was continued for 4 to 6 weeks (providing that they had more than five CA lesions). In the Multicenter Thermocool Ventricular Tachycardia Ablation Trial [34] patients received OAC for 3 months in cases in which CA was performed on over 3 cm of the lesion area.

Table 2. Antithrombotic management after ablation of ventricular tachycardia in structural heart disease.

Study	Antithrombotic Strategies Post Ablation	Duration of Antithrombotic Therapy
Chen et al. (1996) [28]	None	
Calkins et al. (2000) [31]	No indication	
Reddy et al. (2007) [33]	- VKA	4–6 weeks
	- Aspirin if <5 ablation lesions	
Stevenson et al. (2008) [34]	- VKA for ablation area >3 cm	3 months
	- aspirin 325 mg for ablation area <3 cm	
Aliot et al. (2009) [35]	- VKA for large ablation area	6–12 weeks
Kuck et al. (2010) [32]	No indication	
Cronin et al. (2019) [19]	- VKA for extensive ablation	No indication
	- antiplatelet agent for less extensive ablation	
Shivkumar et al. (2019) [15]	- OAC for at least 4 weeks	Based on preexisting indications

VKA: vitamin K antagonist; OAC: oral anticoagulant therapy.

The EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias [35], published in 2009, recommended 6–12 weeks of warfarin after CA over large endocardial areas. However, the latest version [19] suggested that anticoagulation is reasonable after less extensive endocardial VT ablation, or with OAC after extensive endocardial VT ablation (classes of recommendation IIa and IIb, and level of evidence C, respectively) even without a specific indication regarding the timing.

More recently, according to Shivkumar et al., it should be advisable to continue OAC after VT CA for at least 4 weeks in these patients and this indication should be extended to all cases of extensive ablation. With regard to long-term OAC, the choice should be based on whether preexisting indications exist or not [15]. Despite this evidence, in our survey, only four respondents followed this indication. More respondents decided to prescribe OAC or APT therapy according to the LV ejection fraction (26.8%).

5. Limitations

This study has several limitations. These data represent the most current practices among some electrophysiologists, which may not represent the standards of practitioners in other countries, or those in other settings. Moreover, voluntary participation can represent a selection bias. It should be noted that this may be exacerbated by the fact that the centers and not the individual doctors received the survey. The use of anti-thrombotic therapy depends on the radiofrequency time and the LV ejection fraction, but no data are available on the drugs used. Moreover, the choice of treatment in clinical practice is likely to be influenced by diverse clinical factors.

6. Conclusions

Our survey showed that there is considerable variation in the management of antithrombotic therapy surrounding left-sided non-AF endocardial CA in patients without other indications for anti-thrombotic therapy. Further studies are necessary to evaluate the optimal approach to these procedures.

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Informed Consent Statement: Patient consent was waived because it was a survey.

Data Availability Statement: Not applicable.

Conflicts of Interest: Evgeny N. Mikhaylov is a consultant for Biosense Webster and Boehringer Ingelheim and received speaker honoraria from Biosense Webster, Boehringer Ingelheim, Pfizer, Medtronic, and Boston Scientific. The other authors have nothing to declare.

Appendix A

Questionnaire:

1. Center characteristic
    a. Type of institution (University Hospital, Public Hospital, Private Hospital)
    b. Country
    c. Number of procedures/year
    d. Number of left-sided ablation procedures/year (accessory pathway, atrial tachycardia, ventricular tachycardia)
2. Before left-sided ablation—In the absence of other indications for anti-thrombotic therapy...
    a. Do you use antiplatelet prophylaxis in:
        - the accessory pathway? yes/no
        - atrial tachycardia? yes/no
        - ventricular tachycardia with structural heart disease? yes/no
        - ventricular tachycardia without structural heart disease? yes/no
    b. Do you use anticoagulation prophylaxis in:
        - the accessory pathway? yes/no
        - atrial tachycardia? yes/no
        - ventricular tachycardia with structural heart disease? yes/no
        - ventricular tachycardia without structural heart disease? yes/no
3. During left-sided ablation—In the absence of other indications for anti-thrombotic therapy
    a. Do you use heparin in:
        - the accessory pathway? yes/no
        - atrial tachycardia? yes/no
        - ventricular tachycardia with structural heart disease? yes/no
        - ventricular tachycardia without structural heart disease? yes/no
    b. Do you use heparin to irrigate the sheath introducers? yes/no
    c. For the heparin dose do you
        i. maintain ACT target 300–350 s
        ii. maintain ACT target >350 s
        iii. use a weight-based protocol
        iv. use a fixed dose < 3000 Units
        v. use a fixed dose > 3000 Units
4. After ablation—In the absence of other indications for anti-thrombotic therapy...
    a. Do you prescribe antiplatelet therapy after the ablation of
        - the accessory pathway? yes/no
        - atrial tachycardia? yes/no
        - ventricular tachycardia with structural heart disease? yes/no
        - ventricular tachycardia without structural heart disease? yes/no

b. After the ablation of a ventricular tachycardia with structural heart disease, does the use of anti-thrombotic therapy depend on the procedure time? yes/no
c. After ablation of ventricular tachycardia with structural heart disease, does the use of anti-thrombotic therapy depend on the radio frequency time? yes/no
d. If yes, which is the cut-off (minute of radiofrequency)?
e. After ablation of ventricular tachycardia with structural heart disease, does the use of anti-thrombotic therapy depend on the LV ejection fraction? yes/no

5. Is the anti-thrombotic protocol the same among physicians at the same center? yes/no

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