ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2023 December 26; 15(12): 623-654

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 15 Number 12 December 26, 2023

EDITORIAL

ORIGINAL ARTICLE

Retrospective Study

CASE REPORT

World Journal of Cardiology

Monthly Volume 15 Number 12 December 26, 2023

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Cardiology*, Salim R Surani, MD, MPH, MSHM, FACP, FAASM, FCCP, FCCM, Adj. Clinical Professor, Department of Pharmacy & Medicine, Texas A&M University, Corpus Christi, TX 78405, United States. srsurani@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Cardiology* (*WJC*, *World J Cardiol*) is to provide scholars and readers from various fields of cardiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJC mainly publishes articles reporting research results and findings obtained in the field of cardiology and covering a wide range of topics including acute coronary syndromes, aneurysm, angina, arrhythmias, atherosclerosis, atrial fibrillation, cardiomyopathy, congenital heart disease, coronary artery disease, heart failure, hypertension, imaging, infection, myocardial infarction, pathology, peripheral vessels, public health, Raynaud's syndrome, stroke, thrombosis, and valvular disease.

INDEXING/ABSTRACTING

The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJC* as 1.9; IF without journal self cites: 1.8; 5-year IF: 2.3; Journal Citation Indicator: 0.33. The *WJC*'s CiteScore for 2022 is 1.9 and Scopus CiteScore rank 2022: Cardiology and cardiovascular medicine is 226/354.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Ramdas G Pai, Dimitrios Tousoulis, Marco Matteo Ciccone, Pal Pacher

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

PUBLICATION DATE
December 26, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2023 December 26; 15(12): 623-626

DOI: 10.4330/wjc.v15.i12.623

ISSN 1949-8462 (online)

EDITORIAL

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

Michael Spartalis, Eleftherios Spartalis, Gerasimos Siasos

Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Yang YQ, China

Received: September 25, 2023
Peer-review started: September 25, 2023
First decision: November 9, 2023
Revised: November 12, 2023
Accepted: November 28, 2023
Article in press: November 28, 2023
Published online: December 26, 2023

Michael Spartalis, Gerasimos Siasos, 3rd Department of Cardiology, National and Kapodistrian University of Athens, Athens 11527, Greece

Eleftherios Spartalis, Laboratory of Experimental Surgery and Surgical Research, Medical School, National and Kapodistrian University of Athens, Athens 11527, Greece

Corresponding author: Michael Spartalis, Doctor, FACC, FESC, MS, MSc, PhD, 3rd Department of Cardiology, National and Kapodistrian University of Athens, 152 Mesogeion Ave, Athens 11527, Greece. msparta@med.uoa.gr

Abstract

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

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

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

Citation: Spartalis M, Spartalis E, Siasos G. Inherited arrhythmias and gene therapy: Are there any ethical considerations to take into account? *World J Cardiol* 2023; 15(12): 623-626
URL: https://www.wjgnet.com/1949-8462/full/v15/i12/623.htm
DOI: https://dx.doi.org/10.4330/wjc.v15.i12.623

INTRODUCTION

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

GENOME EDITING FOR INHERITED ARRHYTHMIAS

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

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

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

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

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

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

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

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

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

CONCLUSION

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

FOOTNOTES

Author contributions: All authors contributed equally to this paper in conception and design of the letter, literature review and analysis, drafting, critical revision, editing, and providing final approval of the manuscript.

Conflict-of-interest statement: Michael Spartalis, Eleftherios Spartalis and Gerasimos Siasos have nothing to disclose.

Country/Territory of origin: Greece

ORCID number: Michael Spartalis 0000-0002-7442-838X; Eleftherios Spartalis 0000-0003-4451-8074.

S-Editor: Liu JH
L-Editor: A
P-Editor: Yuan YY

REFERENCES

1 **Bezzerides VJ**, Prondzynski M, Carrier L, Pu WT. Gene therapy for inherited arrhythmias. *Cardiovasc Res* 2020; **116**: 1635-1650 [PMID: 32321160 DOI: 10.1093/cvr/cvaa107]

2 **Lalaguna L**, Ramos-Hernández L, Priori SG, Lara-Pezzi E. Genome Editing and Inherited Cardiac Arrhythmias. *Adv Exp Med Biol* 2023; **1396**: 115-127 [PMID: 36454463 DOI: 10.1007/978-981-19-5642-3_8]

3 **Marian AJ**, Braunwald E. Hypertrophic Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. *Circ Res* 2017; **121**: 749-770 [PMID: 28912181 DOI: 10.1161/CIRCRESAHA.117.311059]

4 **Spartalis M**. Genome Editing and Atrial Fibrillation. *Adv Exp Med Biol* 2023; **1396**: 129-137 [PMID: 36454464 DOI: 10.1007/978-981-19-5642-3_9]

5 **Wolf CM**, Berul CI. Molecular mechanisms of inherited arrhythmias. *Curr Genomics* 2008; **9**: 160-168 [PMID: 19440513 DOI: 10.2174/138920208784340768]

6 **Bagnall RD**, Weintraub RG, Ingles J, Duflou J, Yeates L, Lam L, Davis AM, Thompson T, Connell V, Wallace J, Naylor C, Crawford J, Love DR, Hallam L, White J, Lawrence C, Lynch M, Morgan N, James P, du Sart D, Puranik R, Langlois N, Vohra J, Winship I, Atherton J, McGaughran J, Skinner JR, Semsarian C. A Prospective Study of Sudden Cardiac Death among Children and Young Adults. *N Engl J Med* 2016; **374**: 2441-2452 [PMID: 27332903 DOI: 10.1056/NEJMoa1510687]

7 **Hocini M**, Pison L, Proclemer A, Larsen TB, Madrid A, Blomström-Lundqvist C; Scientific Initiative Committee, European Heart Rhythm Association. Diagnosis and management of patients with inherited arrhythmia syndromes in Europe: results of the European Heart Rhythm Association Survey. *Europace* 2014; **16**: 600-603 [PMID: 24711616 DOI: 10.1093/europace/euu074]

8 **Priori SG**, Napolitano C, Memmi M, Colombi B, Drago F, Gasparini M, DeSimone L, Coltorti F, Bloise R, Keegan R, Cruz Filho FE, Vignati G, Benatar A, DeLogu A. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2002; **106**: 69-74 [PMID: 12093772 DOI: 10.1161/01.cir.0000020013.73106.d8]

9 **Goff ZD**, Calkins H. Sudden death related cardiomyopathies - Arrhythmogenic right ventricular cardiomyopathy, arrhythmogenic cardiomyopathy, and exercise-induced cardiomyopathy. *Prog Cardiovasc Dis* 2019; **62**: 217-226 [PMID: 31004608 DOI: 10.1016/j.pcad.2019.04.002]

10 **Al-Khatib SM**, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Granger CB, Hammill SC, Hlatky MA, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RL. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm* 2018; **15**: e73-e189 [PMID: 29097319 DOI: 10.1016/j.hrthm.2017.10.036]

11 **Hylind RJ**, Ladouceur VB, Fynn-Thompson F, Hourigan SE, Bezzerides VJ, Abrams DJ. Genotype-phenotype-guided medical and surgical intervention in long QT syndrome. *HeartRhythm Case Rep* 2018; **4**: 14-17 [PMID: 29379719 DOI: 10.1016/j.hrcr.2017.09.001]

12 **Calkins H**, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Cosedis Nielsen J, Curtis AB, Davies DW, Day JD, d'Avila A, Natasja de Groot NMS, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T; Document Reviewers:. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace* 2018; **20**: e1-e160 [PMID: 29016840 DOI: 10.1093/europace/eux274]

13 **Gnecchi M**, Sala L, Schwartz PJ. Precision Medicine and cardiac channelopathies: when dreams meet reality. *Eur Heart J* 2021; **42**: 1661-1675 [PMID: 33686390 DOI: 10.1093/eurheartj/ehab007]

14 **Adler A**, Novelli V, Amin AS, Abiusi E, Care M, Nannenberg EA, Feilotter H, Amenta S, Mazza D, Bikker H, Sturm AC, Garcia J, Ackerman MJ, Hershberger RE, Perez MV, Zareba W, Ware JS, Wilde AAM, Gollob MH. An International, Multicentered, Evidence-Based Reappraisal of Genes Reported to Cause Congenital Long QT Syndrome. *Circulation* 2020; **141**: 418-428 [PMID: 31983240 DOI: 10.1161/CIRCULATIONAHA.119.043132]

15 **Zeppenfeld K**, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, Charron P, Corrado D, Dagres N, de Chillou C, Eckardt L, Friede T, Haugaa KH, Hocini M, Lambiase PD, Marijon E, Merino JL, Peichl P, Priori SG, Reichlin T, Schulz-Menger J, Sticherling C, Tzeis S, Verstrael A, Volterrani M; ESC Scientific Document Group. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022; **43**: 3997-4126 [PMID: 36017572 DOI: 10.1093/eurheartj/ehac262]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com