ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2024 September 26; 16(9): 496-549

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 16 Number 9 September 26, 2024

EDITORIAL

ORIGINAL ARTICLE

Retrospective Study

CASE REPORT

LETTER TO THE EDITOR

ABOUT COVER

Editorial Board Member of *World Journal of Cardiology*, Alexander E Berezin, MD, MSc, PhD, Professor, Department of Internal Medicine, Zaporozhye State Medical University, Zaporozhye 69035, Ukraine. aeberezin@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 2024 Edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJC* as 1.9; JIF without journal self cites: 1.9; 5-year JIF: 2.3; JIF Rank: 123/220 in cardiac and cardiovascular systems; JIF Quartile: Q3; and 5-year JIF Quartile: Q2. The *WJC*'s CiteScore for 2023 is 3.3 and Scopus CiteScore rank 2023: Cardiology and cardiovascular medicine is 189/387.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; **Production Department Director:** *Xiang Li*; **Cover Editor:** *Yun-Xiaojiao Wu*.

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
September 26, 2024

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 2024 September 26; 16(9): 496-501

DOI: 10.4330/wjc.v16.i9.496

ISSN 1949-8462 (online)

EDITORIAL

Hypertrophic cardiomyopathy and left ventricular non-compaction: Distinct diseases or variant phenotypes of a single condition?

Natalia Przytuła, Ewa Dziewięcka, Mateusz Winiarczyk, Katarzyna Graczyk, Agnieszka Stępień, Paweł Rubiś

Specialty type: Cardiac and cardiovascular systems

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

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade C

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Hu HS

Received: May 27, 2024

Revised: August 2, 2024

Accepted: August 21, 2024

Published online: September 26, 2024

Processing time: 114 Days and 14.3 Hours

Natalia Przytuła, Ewa Dziewięcka, Mateusz Winiarczyk, Katarzyna Graczyk, Agnieszka Stępień, Paweł Rubiś, Department of Cardiac and Vascular Diseases, Saint John Paul II Hospital, Krakow 31-202, MA, Poland

Ewa Dziewięcka, Mateusz Winiarczyk, Katarzyna Graczyk, Agnieszka Stępień, Paweł Rubiś, Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University Collegium Medicum, Saint John Paul II Hospital, Krakow 31-202, MA, Poland

Corresponding author: Ewa Dziewięcka, MD, PhD, Doctor, Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University Collegium Medicum, Saint John Paul II Hospital, 80 Prądnicka Street, Krakow 31-202, MA, Poland. ewa@dziewiecka.pl

Abstract

Hypertrophic cardiomyopathy (HCM) is a genetically determined myocardial disease characterized by an increased thickness of the left ventricle (LV) wall that cannot be solely attributed to abnormal loading conditions. HCM may present with an intraventricular or LV outflow tract obstruction, diastolic dysfunction, myocardial fibrosis and/or ventricular arrhythmias. Differentiating HCM from other diseases associated with LV hypertrophy, such as hypertension, aortic stenosis, or LV non-compaction (LVNC), can at times be challenging. LVNC is defined by excessive LV trabeculation and deep recesses between trabeculae, often accompanied by increased LV myocardial mass. Previous studies indicate that the LVNC phenotype may be observed in up to 5% of the general population; however, in most cases, it is a benign finding with no impact on clinical outcomes. Nevertheless, LVNC can occasionally lead to LV systolic dysfunction, manifesting as a phenotype of dilated or non-dilated left ventricular cardiomyopathy, with an increased risk of thrombus formation and arterial embolism. In extreme cases, where LVNC is associated with a very thickened LV wall, it can even mimic HCM. There is growing evidence of an overlap between HCM and LVNC, including similar genetic mutations and clinical presentations. This raises the question of whether HCM and LVNC represent different phenotypes of the same disease or are, in fact, two distinct entities.

Key Words: Left ventricle hypertrabeculation; Hypertrophic cardiomyopathy; Left ventricle non-compaction; Left ventricle hypertrophy; Left ventricle obstruction

Core Tip: Hypertrophic cardiomyopathy (HCM) is a genetic myocardial disease marked by increased left ventricle (LV) wall thickness in the absence of abnormal loading conditions. Differentiating HCM from other conditions with LV hypertrophy, such as hypertension, aortic stenosis, or LV non-compaction (LVNC), can be challenging. LVNC is characterized by excessive LV trabeculation and deep recesses, affecting up to 5% of the general population. While typically benign, LVNC can occasionally lead to systolic dysfunction and arterial embolism. The overlap between HCM and LVNC, including genetic mutations and clinical features, raises the question of whether they are distinct diseases or variations of the same condition.

Citation: Przytuła N, Dziewięcka E, Winiarczyk M, Graczyk K, Stępień A, Rubiś P. Hypertrophic cardiomyopathy and left ventricular non-compaction: Distinct diseases or variant phenotypes of a single condition? *World J Cardiol* 2024; 16(9): 496-501
URL: https://www.wjgnet.com/1949-8462/full/v16/i9/496.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i9.496

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common form of primary, genetically determined cardiomyopathy (CMP)[1]. Caused by mutations in genes encoding sarcomere proteins, it results in structural changes in myocardial tissue, manifesting as pathological left ventricular hypertrophy (LVH) in terms of either an increase in left ventricular (LV) mass, LV wall thickness, or both (Figure 1A). The HCM phenotype can be diagnosed using transthoracic echocardiography (TTE) or cardiac magnetic resonance imaging (CMR) [2]. The diagnostic criterion for HCM is the presence of LVH in any myocardial segment measuring at least 15 mm, not attributable to excessive LV load[1]. Although HCM is estimated to have a prevalence of 0.2%, most patients remain undiagnosed due to the oligo-symptomatic nature of the disease[1]. However, in instances of more pronounced LVH, alongside diastolic dysfunction, arrythmias, or even systolic dysfunction, patients may present with shortness of breath, chest pain, palpitations, and signs indicative of heart failure [3,4].

HCM is primarily associated with LV muscle thickening; however, morphological changes also commonly involve the entire mitral valve apparatus. These changes can include hypertrophy and/or an increased number of papillary muscle heads, atypical papillary location, and/or elongation of the mitral leaflets (Figure 1B)[5]. Additionally, LVH can present with varying degrees and morphological traits, even among members of the same family or individuals with the same mutation[6]. Typically, LVH is classified into concentric or eccentric forms, with further differentiation based on the location of LV thickening, such as asymmetric septal hypertrophy, symmetric hypertrophy, or apical hypertrophy (Figure 1C and D). The apical form of HCM, predominantly found in individuals of Asian descent, occurs in approximately 2% of Caucasians[7]. Due to its frequently asymptomatic course, apical HCM is often detected incidentally during the evaluation of heart failure symptoms or through cascade screening of relatives.

PATHOLOGY OF LV NON-COMPACTION *VS* HYPERTRABECULATION

Approximately 15 days after fertilization, the heart tube is formed, primarily composed of cardiomyocytes. Around three weeks later, it develops into the four-chambered heart[8]. Initially, the heart muscle consists of trabeculae, which elongate and thicken during subsequent stages, ultimately merging into a uniform, compact muscle. Disruptions in gene expression due to a congenital or spontaneous mutation can impede this process, resulting in increased LV trabeculation or a 'spongy' myocardial structure. While numerous genes involved in LV development have been identified in mice, most have yet to be confirmed in humans[8].

LV non-compaction (LVNC) was first described in the 1990s, and its definition has evolved over the years[9]. Current definitions include specific and distinct diagnostic criteria for CMR imaging, with a noncompacted/compacted layer ratio ≥ 2.3, and for TTE, with a noncompacted/compacted layer ratio > 2[10,11]. The American Heart Association continues to classify LVNC as a distinct genetically determined CMP. However, the latest guidelines from the European Society of Cardiology (ESC) in 2023 introduced significant changes. The ESC replaced the term 'LVNC' with 'hypertrabeculation', while retaining the previous diagnostic criteria[1,12]. The authors of the ESC guidelines argue that the high prevalence of 'hypertrabeculation' (or 'LVNC') in the general population, including healthy individuals[13], supports the notion that 'hypertrabeculation' should be considered an anatomical variant of LV morphology rather than a structure which is pathological in nature.

There are also many other general medical conditions that can cause cardiac muscle hypertrophy, including arterial hypertension, aortic stenosis, myocarditis, or hyperthyroidism, complicating the diagnosis of primary or secondary hypertrophy. In all patients, the most common causes of secondary hypertrophy should be ruled out first. Additionally, the closest family should be included in the extended cardiological diagnostics. Genetic tests also appear to be helpful, but they are not widely available[14,15].

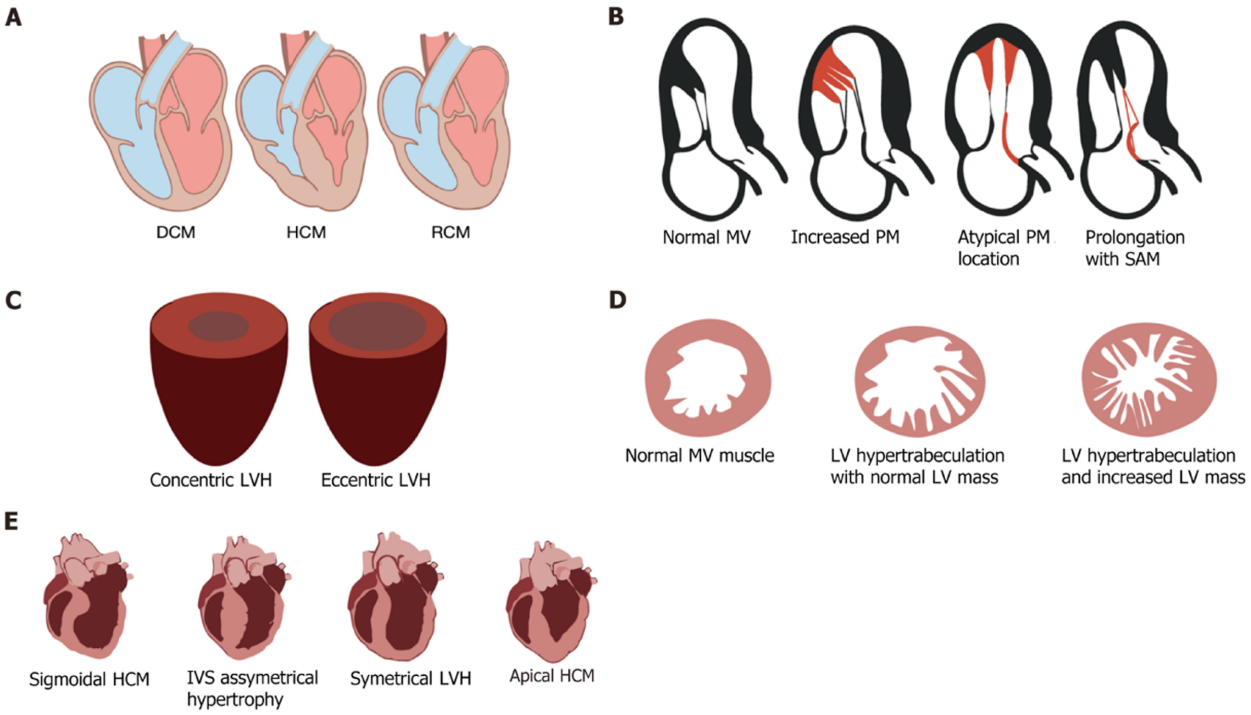


Figure 1 Different morphological changes in hypertrophic cardiomyopathy. A: Different cardiomyopathy (CMP) phenotypes. Dilated cardiomyopathy: Dilated CMP with left ventricle (LV) enlargement and hypokinesia. Hypertrophic cardiomyopathy (HCM): With increased LV mass or thickness. Restrictive cardiomyopathy: Restrictive CMP with enlarged atria; B: Morphological changes in mitral apparatus in HCM. Increased number and mass of papillary muscle heads, their atypical location, and elongation of the mitral leaflets; C and E: Different types and localization of LV hypertrophy; D: Phenotypic continuum between normal LV mass and structure, LV hypertrabeculation with normal LV mass [fulfilled diagnostic criteria for LV non-compaction (LVNC)], and hypertrabeculation with increased LV mass (fulfilled diagnostic criteria for LVNC and HCM). DCM: Dilated cardiomyopathy; HCM: Hypertrophic cardiomyopathy; IVS: Intraventricular septum; LV: Left ventricle; LVH: Left ventricular hypertrophy; MV: Mitral valve; PM: Papillary muscle; RCM: Restrictive cardiomyopathy; SAM: Systolic anterior motion.

LV HYPERTROPHY AND HYPERTRABECULATION

Despite the clear definition of HCM, complexities arise in patients exhibiting an atypical "spongy" myocardial structure. Over the years, discussions have centered on the continuum of 'hypertrabeculation' observed in healthy individuals with normal LV mass, or in those with coexisting increased LV mass in HCM, despite the presence of normal levels of thickness in the compacted LV muscle (Figure 1E). According to the definition, patients with increased LV mass, regardless of the LV muscle structure (compacted *vs* non-compacted), can also meet the criteria for an HCM diagnosis. Therefore, it is crucial to distinctly evaluate both the compacted and non-compacted LV layers, including the mass of trabeculae and papillary muscles, when assessing LV muscle thickness or LV mass in CMR and TTE (Figure 1F). Experts have long debated whether 'hypertrabeculation' in HCM (or other CMP phenotypes, including dilated CMP-DCM) significantly affects disease progression. A limited number of reports suggest that hypertrabeculation is associated with an increased arrhythmia frequency, LV systolic dysfunction, or an increased risk of thromboembolic complications[16].

Here, we report the case of a 58-year-old woman admitted to a tertiary cardiology clinic due to exercise-induced dyspnea over the preceding couple of months. Her previous medical history included arterial hypertension and smoking, and, at admission, she was on ramipril 5 mg and amlodipine 5 mg. TTE revealed HCM with intraventricular obstruction, a maximal wall thickness of 20 mm, LV mass of 86 mg/cm^2, and a resting LV intracavitary gradient of 76 mmHg (Figure 2A and D). CMR showed increased LV trabeculation, meeting LVNC criteria (C/NC layer ratio 6 mm:13 mm) (Figure 2C and D), and identified a thrombus in the LV apex extending to the papillary muscles (dimensions 32 mm × 12 mm × 16 mm) (Figure 2E), causing LV cavity obliteration.

Echocardiographic assessment of normal LV muscle thickness in these patients can be challenging. The 'spongy' myocardial structure can hamper accurate thickness measurement, raising the question of whether to measure the thickness of both the compacted and non-compacted layers, or merely the former, in the HCM diagnosis. In this case, the intracavity thrombus, mimicking the LV muscle, may also lead to an overestimation of LVH (Figure 2B). The thrombus formation was likely promoted by the spongy structure of the LV muscle and intracavitary narrowing, causing 'blood stasis' in the apex (Figures 2D and E)[17,18]. Due to the increased risk of systemic embolism with thrombus detection, oral anticoagulant therapy (warfarin or direct oral anticoagulants) should be considered for 3-6 months, guided by repeat imaging examinations[19]. In light of this, the patient was prescribed dabigatran 150 mg b.i.d.

In HCM, regardless of the presence of thrombus or LV hypertrabeculation, recommended therapy for intraventricular or LV outflow tract obstruction typically includes beta-blockers or non-dihydropyridine calcium channel blockers. If these are ineffective, novel therapy with mavacamten (if available) should be considered[1]. In this case, 5 mg of bisoprolol was initiated. Follow-up TTE showed a decrease in intraventricular obstruction at the apex with a resting gradient of 24 mmHg and 32 mmHg after the Valsalva maneuver and a reduction in LV thrombus. Consequently, the

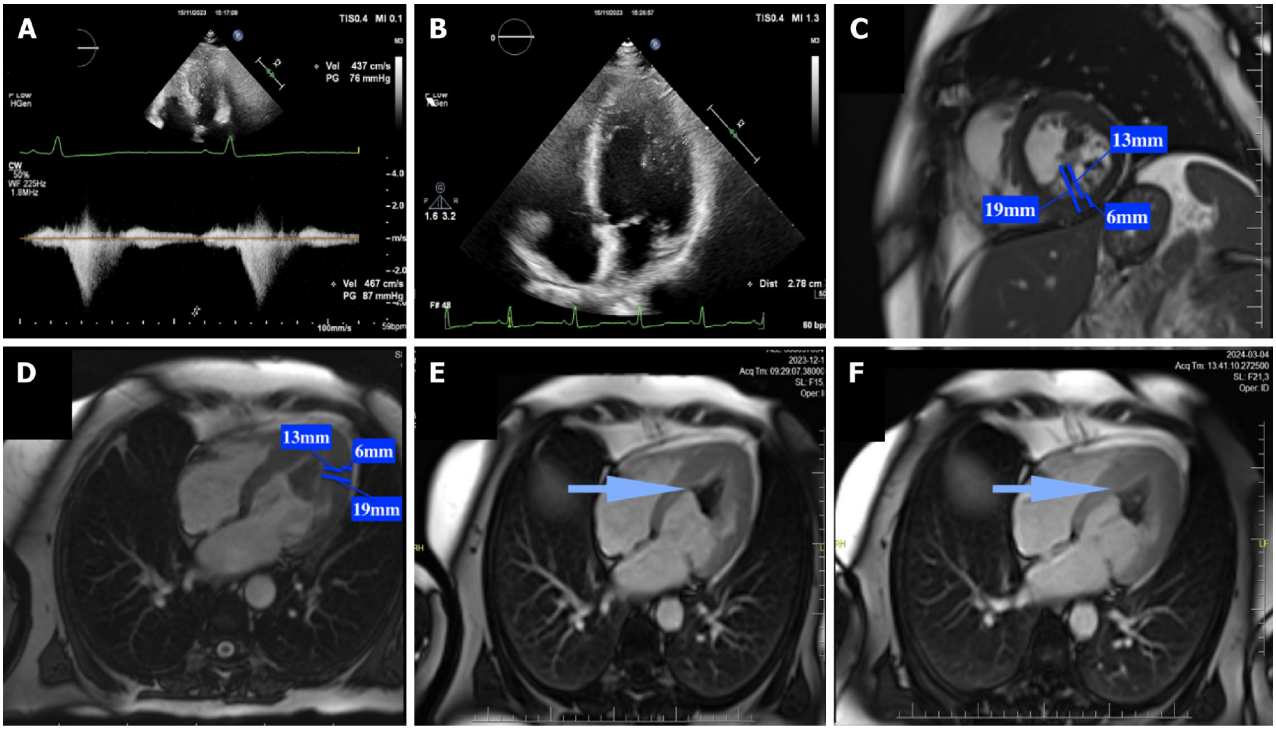


Figure 2 Images from transthoracic echocardiography and cardiac magnetic resonance imaging of a 58-year-old woman with coexistence of left ventricle hypertrophy and hypertrabeculation leading to intracavitary obstruction with heart failure symptoms, and left ventricle thrombus formation with subsequent transient ischemic attack. A: Pulse-wave Doppler from apical 4-chamber transthoracic echocardiography (TTE) view showing intracavitary obstruction at the level of the papillary muscles (maximal resting gradient of 76 mmHg); B: Left ventricle (LV) apical hypertrophy in apical 4-chamber view in TTE; C and D: LV hypertrabeculation in cardiac magnetic resonance short axis view and 4-chamber view (ratio of thickness of non-compacted to compacted layers 2.1: 13 mm and 6 mm); E and F: LV thrombus entering between the LV trabeculae and recesses in short axis view and 4-chamber view (blue arrow).

gradient reduction improved LV blood flow, including outflow from the apex, which likely decreased the risk of thrombus formation and propagation, while thrombus dissolution led to reduced LV obstruction.

CONCLUSION

Historically, LVNC was identified as a distinct form of CMP with a somewhat unpredictable course. However, advancements in imaging quality and the increased availability of CMR have revealed that 'hypertrabeculation' is prevalent even among healthy individuals, occurring independently of symptomatic cardiomyopathies. Emerging data highlight genetic mutations associated with 'LVNC', particularly in patients with coexisting CMP, such as HCM or DCM. In these patients, 'hypertrabeculation' can significantly worsen disease progression, increasing the risk of LV thrombus formation, LV systolic and diastolic dysfunction, and exacerbating mid-cavitary obstruction. Moreover, hypertrabeculation significantly complicates the accurate assessment of actual LV muscle mass and volume, thereby challenging the establishment of a reliable diagnosis of HCM and DCM.

FOOTNOTES

Author contributions: Dziewięcka E and Rubiś P were responsible for conceptualization, methodology, and funding acquisition; Rubiś P was responsible for validation and supervision; Dziewięcka E was responsible for formal analysis, writing review, editing, and project administration; Przytuła N, Dziewięcka E, Winiarczyk M, Graczyk K, and Stępień A were responsible for investigation and data curation; Przytuła N was responsible for writing original draft preparation; all authors have read and agreed to the published version of the manuscript.

Supported by The Department of Scientific Research and Structural Funds of Medical College, Jagiellonian University, No. N41/DBS/000594.

Conflict-of-interest statement: The Authors declare no conflict of interest.

Country of origin: Poland

ORCID number: Natalia Przytuła 0009-0006-4948-8045; Ewa Dziewięcka 0000-0002-7921-5447; Mateusz Winiarczyk 0000-0002-0176-7882; Katarzyna Graczyk 0000-0002-8586-5657; Agnieszka Stępień 0000-0002-7996-5379; Pawel Rubiś 0000-0002-6979-3411.

S-Editor: Luo ML
L-Editor: Webster JR
P-Editor: Zhang YL

REFERENCES

1 **Arbelo E**, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, Bezzina CR, Biagini E, Blom NA, de Boer RA, De Winter T, Elliott PM, Flather M, Garcia-Pavia P, Haugaa KH, Ingles J, Jurcut RO, Klaassen S, Limongelli G, Loeys B, Mogensen J, Olivotto I, Pantazis A, Sharma S, Van Tintelen JP, Ware JS, Kaski JP; ESC Scientific Document Group. 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J* 2023; **44**: 3503-3626 [PMID: 37622657 DOI: 10.1093/eurheartj/ehad194]

2 **Gassenmaier T**, Petritsch B, Kunz AS, Gkaniatsas S, Gaudron PD, Weidemann F, Nordbeck P, Beer M. Long term evolution of magnetic resonance imaging characteristics in a case of atypical left lateral wall hypertrophic cardiomyopathy. *World J Cardiol* 2015; **7**: 357-360 [PMID: 26131341 DOI: 10.4330/wjc.v7.i6.357]

3 **Saccheri MC**, Cianciulli TF, Morita LA, Méndez RJ, Beck MA, Guerra JE, Cozzarin A, Puente LJ, Balletti LR, Lax JA. Speckle tracking echocardiography to assess regional ventricular function in patients with apical hypertrophic cardiomyopathy. *World J Cardiol* 2017; **9**: 363-370 [PMID: 28515855 DOI: 10.4330/wjc.v9.i4.363]

4 **Arsenos P**, Gatzoulis KA, Tsiachris D, Dilaveris P, Sideris S, Sotiropoulos I, Archontakis S, Antoniou CK, Kordalis A, Skiadas I, Toutouzas K, Vlachopoulos C, Tousoulis D, Tsioufis K. Arrhythmic risk stratification in ischemic, non-ischemic and hypertrophic cardiomyopathy: A two-step multifactorial, electrophysiology study inclusive approach. *World J Cardiol* 2022; **14**: 139-151 [PMID: 35432775 DOI: 10.4330/wjc.v14.i3.139]

5 **Maron MS**, Maron BJ. Clinical Impact of Contemporary Cardiovascular Magnetic Resonance Imaging in Hypertrophic Cardiomyopathy. *Circulation* 2015; **132**: 292-298 [PMID: 26216086 DOI: 10.1161/CIRCULATIONAHA.114.014283]

6 **Kubo T**, Kitaoka H, Okawa M, Hirota T, Hoshikawa E, Hayato K, Yamasaki N, Matsumura Y, Yabe T, Nishinaga M, Takata J, Doi YL. Clinical profiles of hypertrophic cardiomyopathy with apical phenotype--comparison of pure-apical form and distal-dominant form. *Circ J* 2009; **73**: 2330-2336 [PMID: 19838003 DOI: 10.1253/circj.cj-09-0438]

7 **Oko-sarnowska Z**, Pyda M, Trojnarska O, Klisiewicz A, Kukulski T, Dziuk M, Płońska-gościniak E. Imaging in hypertrophic cardiomyopathy. Expert consensus statement of the Polish Clinical Forum for Cardiovascular Imaging. *Kardiol Pol* 2015; **73**: 39-59 [DOI: 10.5603/kp.2015.0205]

8 **Buijtendijk MFJ**, Barnett P, van den Hoff MJB. Development of the human heart. *Am J Med Genet C Semin Med Genet* 2020; **184**: 7-22 [PMID: 32048790 DOI: 10.1002/ajmg.c.31778]

9 **Chin TK**, Perloff JK, Williams RG, Jue K, Mohrmann R. Isolated noncompaction of left ventricular myocardium. A study of eight cases. *Circulation* 1990; **82**: 507-513 [PMID: 2372897 DOI: 10.1161/01.cir.82.2.507]

10 **Petersen SE**, Selvanayagam JB, Wiesmann F, Robson MD, Francis JM, Anderson RH, Watkins H, Neubauer S. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. *J Am Coll Cardiol* 2005; **46**: 101-105 [PMID: 15992642 DOI: 10.1016/j.jacc.2005.03.045]

11 **Jenni R**, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. *Heart* 2001; **86**: 666-671 [PMID: 11711464 DOI: 10.1136/heart.86.6.666]

12 **Maron BJ**, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB; American Heart Association; Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; Council on Epidemiology and Prevention. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* 2006; **113**: 1807-1816 [PMID: 16567565 DOI: 10.1161/CIRCULATIONAHA.106.174287]

13 **de la Chica JA**, Gómez-Talavera S, García-Ruiz JM, García-Lunar I, Oliva B, Fernández-Alvira JM, López-Melgar B, Sánchez-González J, de la Pompa JL, Mendiguren JM, Martínez de Vega V, Fernández-Ortiz A, Sanz J, Fernández-Friera L, Ibáñez B, Fuster V. Association Between Left Ventricular Noncompaction and Vigorous Physical Activity. *J Am Coll Cardiol* 2020; **76**: 1723-1733 [PMID: 33032733 DOI: 10.1016/j.jacc.2020.08.030]

14 **Barreto-Chaves ML**, Senger N, Fevereiro M, Parletta AC, Takano A. Impact of hyperthyroidism on cardiac hypertrophy. *Endocr Connect* 2020; **9**: R59-R69 [PMID: 32101527 DOI: 10.1530/EC-19-0543]

15 **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]

16 **Ljungman C**, Bollano E, Rawshani A, Nordberg Backelin C, Dahlberg P, Valeljung I, Björkenstam M, Hjalmarsson C, Fu M, Mellberg T, Bartfay SE, Polte CL, Andersson B, Bergh N. Differences in phenotypes, symptoms, and survival in patients with cardiomyopathy-a prospective observational study from the Sahlgrenska CardioMyoPathy Centre. *Front Cardiovasc Med* 2023; **10**: 1160089 [PMID: 37139129 DOI: 10.3389/fcvm.2023.1160089]

17 **Hamada M**. Left Ventricular Thrombus in Hypertrophic Cardiomyopathy. *Intern Med* 2019; **58**: 465-467 [PMID: 30333417 DOI:

10.2169/internalmedicine.1646-18]

18 **Sherrid MV**, Bernard S, Tripathi N, Patel Y, Modi V, Axel L, Talebi S, Ghoshhajra BB, Sanborn DY, Saric M, Adlestein E, Alvarez IC, Xia Y, Swistel DG, Massera D, Fifer MA, Kim B. Apical Aneurysms and Mid-Left Ventricular Obstruction in Hypertrophic Cardiomyopathy. *JACC Cardiovasc Imaging* 2023; **16**: 591-605 [PMID: 36681586 DOI: 10.1016/j.jcmg.2022.11.013]

19 **Byrne RA**, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan GA, Dweck MR, Galbraith M, Gilard M, Hinterbuchner L, Jankowska EA, Jüni P, Kimura T, Kunadian V, Leosdottir M, Lorusso R, Pedretti RFE, Rigopoulos AG, Rubini Gimenez M, Thiele H, Vranckx P, Wassmann S, Wenger NK, Ibanez B; ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023; **44**: 3720-3826 [PMID: 37622654 DOI: 10.1093/eurheartj/ehad191]

World Journal of Cardiology

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

World J Cardiol 2024 September 26; 16(9): 502-507

DOI: 10.4330/wjc.v16.i9.502

ISSN 1949-8462 (online)

EDITORIAL

Addressing the alarming link between nonalcoholic fatty liver disease and cardiovascular mortality in men

Wen-Rui Hao, Chun-Han Cheng, Tzu-Hurng Cheng

Specialty type: Cardiac and cardiovascular systems

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

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade B
Novelty: Grade C
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Shen M

Received: July 5, 2024
Revised: August 21, 2024
Accepted: September 5, 2024
Published online: September 26, 2024
Processing time: 75 Days and 15.2 Hours

Wen-Rui Hao, Division of Cardiology, Department of Internal Medicine, Shuang Ho Hospital, Ministry of Health and Welfare, Taipei Medical University, New Taipei 23561, Taiwan

Wen-Rui Hao, Division of Cardiology, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei 11002, Taiwan

Chun-Han Cheng, Department of Medical Education, Linkou Chang Gung Memorial Hospital, Taoyuan 33305, Taiwan

Tzu-Hurng Cheng, Department of Biochemistry, School of Medicine, College of Medicine, China Medical University, Taichung 404328, Taiwan

Corresponding author: Tzu-Hurng Cheng, PhD, Professor, Department of Biochemistry, School of Medicine, College of Medicine, China Medical University, No. 91 Xueshi Road, North District, Taichung 404328, Taiwan. thcheng@mail.cmu.edu.tw

Abstract

This editorial discusses the key findings presented in Batta and Hatwal's recent paper titled "Excess cardiovascular mortality in men with non-alcoholic fatty liver disease: A cause for concern!", which was published in the *World Journal of Cardiology*. Their original article highlights a notable correlation between non-alcoholic fatty liver disease (NAFLD) and increased cardiovascular mortality risk in men. The present commentary explores the implications of their findings, discussing potential mechanisms, risk factors, and the urgent need for integrated clinical approaches to mitigate the dual burden of these diseases. Emphasis should be placed on the importance of early detection, lifestyle modifications, and interdisciplinary collaboration for improving patient outcomes. This editorial aims to highlight the broad implications of NAFLD for cardiovascular health and to advocate for increased awareness and proactive management strategies within the medical community.

Key Words: Non-alcoholic fatty liver disease; Cardiovascular mortality; Men's health; Integrated clinical approaches; Risk factors

Core Tip: Men with nonalcoholic fatty liver disease (NAFLD) have a significantly increased risk of cardiovascular mortality, which is a major health concern. Early detection and comprehensive management strategies targeting both NAFLD and cardiovascular risk factors are essential to mitigate excess mortality.

Citation: Hao WR, Cheng CH, Cheng TH. Addressing the alarming link between nonalcoholic fatty liver disease and cardiovascular mortality in men. *World J Cardiol* 2024; 16(9): 502-507
URL: https://www.wjgnet.com/1949-8462/full/v16/i9/502.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i9.502

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has emerged as a major global health concern, affecting a substantial portion of the population worldwide. This editorial focuses on a key aspect of NAFLD, namely its association with excess cardiovascular mortality in men. Recent epidemiological studies and clinical observations have underscored that men with NAFLD have notably higher risks of cardiovascular events and mortality compared with their counterparts without this condition[1]. The increasing prevalence of NAFLD parallels the worldwide increase in obesity and metabolic syndrome, highlighting the intricate relationship between liver health and cardiovascular outcomes[2]. Despite advancements in understanding the pathogenesis and systemic implications of NAFLD, effective strategies for managing cardiovascular risks in patients with NAFLD remain limited and under-researched[3]. This editorial synthesizes the available evidence, discusses the underlying mechanisms linking NAFLD to cardiovascular mortality in men, and proposes potential methods for enhancing clinical management and patient outcomes[1]. By addressing these topics comprehensively, we intend to stimulate further research and inform clinical guidelines, thereby helping to reduce the dual burden of NAFLD and cardiovascular disease.

EPIDEMIOLOGICAL EVIDENCE

Recent epidemiological studies have consistently highlighted a concerning association between NAFLD and increased cardiovascular mortality risk, particularly in men. This association has been identified in diverse populations and through various methodologies, reinforcing the robustness of the correlation despite variations in demographic profiles and risk factor distributions[1-5]. The prevalence of NAFLD has increased in tandem with obesity rates, underscoring the urgent need to address the cardiovascular implications of NAFLD. The synergy between NAFLD and cardiometabolic conditions such as type 2 diabetes mellitus complicates this landscape and worsens both cardiovascular and liver-related outcomes[4]. Studies have demonstrated that NAFLD is a significant predictor of cardiovascular mortality, with men exhibiting a higher risk than women; sex-specific factors should this be considered in clinical management[1,6]. In addition to cardiovascular mortality, disparities in the prevalence and effects of metabolic-dysfunction-associated steatotic liver disease (MASLD) are notable across socioeconomic strata. For instance, a study reported that MASLD was disproportionately prevalent in low-income and lower-middle-income countries, reflecting a global health burden that is compounded by inconsistent access to health-care resources and preventive measures[3]. Research has identified specific dietary patterns and metabolic dysfunctions that predispose individuals to MASLD. The findings emphasize the role of lifestyle factors, such as diet, in the progression of NAFLD and MASLD. For example, healthy eating patterns have been linked to a reduced risk of MASLD, suggesting that dietary modification is a viable preventive strategy[5]. Conversely, inadequate dietary interventions have been demonstrated to be ineffective in mitigating disease progression, a finding that underscores the importance of tailored nutritional strategies. The identification of novel therapeutic targets is crucial for managing NAFLD and its cardiovascular implications. Recent studies have highlighted various potential treatments, such as epigallocatechin gallate, which alleviates NAFLD by inhibiting dipeptidyl peptidase 4 (DPP-4) activity, and the Yanxiao Di'naer formula, which has achieved promising outcomes according to metabolomic and RNA sequencing results[7,8]. These interventions represent ongoing efforts to address the progression of NAFLD and its sequelae. Understanding the intricate pathophysiological mechanisms underlying NAFLD and MASLD is essential for designing targeted preventive strategies and treatment modalities. This comprehensive approach aims to reduce cardiovascular mortality and address the broader spectrum of metabolic and hepatic complications associated with NAFLD and MASLD, which are becoming more prevalent[9,10]. Overall, although the epidemiological evidence linking NAFLD to increased cardiovascular mortality in men is robust, further research is required to elucidate the full spectrum of implications and optimize the relevant management strategies.

UNDERLYING MECHANISMS

The pathophysiological mechanisms linking NAFLD to increased cardiovascular mortality are multifaceted and involve several interconnected pathways. Insulin resistance, a hallmark of NAFLD, not only promotes hepatic lipid accumulation

but also contributes significantly to systemic inflammation and dyslipidemia[1,4]. These metabolic disturbances foster a proatherogenic environment by impairing endothelial function and promoting plaque formation[2]. Chronic inflammation, another critical feature of NAFLD, exacerbates this process by perpetuating atherosclerosis through the secretion of proinflammatory cytokines[3]. Additionally, oxidative stress, which is intensified by the presence of hepatic steatosis, further amplifies cardiovascular risk by damaging endothelial cells and promoting vascular dysfunction[5]. An oxidative milieu not only accelerates atherogenesis but also exacerbates systemic inflammation, creating a vicious cycle that contributes to adverse cardiovascular outcomes[7]. In addition to these mechanisms, genetic factors play a crucial role in the pathophysiology of NAFLD and its cardiovascular implications. Variants in genes such as *PNPLA3*, *TM6SF2*, and *MBOAT7* have been linked to increased risks of hepatic steatosis and cardiovascular diseases[11]. These genetic predispositions can influence lipid metabolism, inflammatory responses, and overall disease progression. Additionally, dysregulation in lipid metabolism, a central feature of NAFLD, contributes significantly to cardiovascular risk. Elevated levels of triglycerides and altered lipoprotein profiles promote the formation of atherogenic lipoprotein particles, which contribute to atherosclerosis[12]. Furthermore, the interplay between NAFLD and the gut microbiota has emerged as a key area of research. Dysbiosis, which refers to an imbalance in gut microbial communities, can influence NAFLD progression by modulating systemic inflammation, insulin resistance, and lipid metabolism[13]. The cumulative effect of these interconnected pathways results in an interplay between NAFLD and cardiovascular morbidity, which necessitates comprehensive management strategies that address both liver and cardiovascular health[8]. Overall, understanding the underlying mechanisms is crucial for developing targeted therapies that mitigate the cardiovascular risk associated with NAFLD. Future research should continue to explore these pathways to identify novel therapeutic targets and interventions aimed at reducing the burden of cardiovascular mortality in individuals with NAFLD[9,10]. By addressing the metabolic dysregulation, genetic factors, inflammatory processes, and gut microbiota associated with both NAFLD and cardiovascular disease, clinicians can optimize patient outcomes and improve overall cardiovascular health in this high-risk population.

CLINICAL IMPLICATIONS AND CHALLENGES

Managing cardiovascular risk in patients with NAFLD or MASLD is challenging because of the unique metabolic and inflammatory profiles associated with liver fat accumulation, which traditional cardiovascular risk assessment tools often underestimate[1]. Comprehensive management strategies must integrate both liver health and cardiovascular risk factors, addressing the complex interaction between metabolic dysfunction and cardiovascular disease[2,4]. Type 2 diabetes significantly exacerbates outcomes related to cardiovascular health, liver disease, and cancer; personalized management strategies tailored to the multifaceted nature of MASLD are thus required[3,4]. Emerging treatment strategies for NAFLD and MASLD include both lifestyle interventions and pharmacological therapies. Lifestyle modifications, such as dietary changes and increased physical activity, are fundamental in managing these conditions. Specific dietary patterns, such as the Mediterranean diet, have shown promise in improving liver health and reducing cardiovascular risk[5]. Pharmacological interventions are evolving, with several novel agents under investigation. These include glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors, which have been demonstrated to have beneficial effects in terms of liver fat reduction and cardiovascular outcomes[9]. Recent advancements have also been made in targeting the specific molecular pathways involved in NAFLD and MASLD. For example, studies have indicated that drugs targeting the NLRP3 inflammasome and TLR4 pathways can reduce liver inflammation and fibrosis[14,15]. Additionally, agents such as epigallocatechin gallate have been effective in inhibiting DPP-4 activity and thereby ameliorating NAFLD[7]. Noninvasive biomarkers and imaging techniques are increasingly being used to assess disease progression and therapeutic response and enable the creation of precise and personalized treatment plans[16,17]. Recent research efforts have aimed to develop and validate specific treatment methods and interventions for improving cardiovascular health in patients with NAFLD. For example, observational and genetic studies have established an association between NAFLD and calcific aortic valve disease, suggesting that cardiovascular complications are a major concern for these patients[11]. Additionally, diagnostic biomarkers such as CXCL9, IL2RB, and SPP1 have been identified as potential indicators of comorbid atherosclerosis and nonalcoholic steatohepatitis, and these findings provide new avenues for early detection and targeted therapy[18]. Global health initiatives must be launched to provide equitable access to care and tailored interventions to mitigate the disparities in the prevalence and effects of MASLD in low-income and lower-middle-income countries[3,7]. Implementing comprehensive guidelines that integrate metabolic and liver-specific approaches is crucial for improving patient outcomes globally[19]. Overall, managing cardiovascular risk in patients with NAFLD or MASLD requires a paradigm shift toward integrated, personalized care strategies. These strategies should incorporate comprehensive risk assessment tools, novel therapeutic approaches, and global health initiatives to optimize patient outcomes and reduce the burden of cardiovascular disease in this vulnerable population. The transition from NAFLD to MASLD highlights the importance of adopting new terminologies and comprehensive management guidelines to effectively address the interplay between metabolic and liver diseases.

ONGOING RESEARCH AND POTENTIAL FUTURE STUDIES

Recent studies have begun to explore the complex relationship between NAFLD and cardiovascular diseases. Batta and Hatwal noted excessively high cardiovascular mortality in men with NAFLD and reported an urgent need to obtain primary data to validate their findings and examine the underlying mechanisms[1]. Similarly, Riley *et al*[4] discussed the

synergistic effect of type 2 diabetes and MASLD on various health outcomes, including those related to cardiovascular and liver diseases. Their findings highlight the importance of conducting longitudinal studies to elucidate various causal relationships and potential interventions. The shift from the term NAFLD to MASLD, as discussed by Malnick and Zamir [2], reflects a broader understanding of the disease's metabolic origins and the key implications for future research. This new terminology encourages a more comprehensive approach to studying the disease in which the metabolic dysfunctions involved are considered. Future studies should focus on examining the genetic and environmental factors contributing to MASLD and identifying potential therapeutic targets. Beygi *et al*[20] reviewed various strategies for managing MASLD, including medication therapy and nutritional interventions. They emphasized the need for clinical trials to test the efficacy of these treatments in diverse populations. Observational and genetic studies, such as those conducted by Hao *et al*[11], have revealed associations between NAFLD and other conditions such as calcific aortic valve disease, suggesting new avenues for research into shared pathophysiological pathways. Wu *et al*[18] identified potential diagnostic biomarkers of comorbid atherosclerosis and nonalcoholic steatohepatitis, and their results pave the way for the development of more precise diagnostic tools. Huang *et al*[5] identified a strong association between beneficial lifestyle modifications and reduced mortality risk in patients with NAFLD, underlining the relevance of lifestyle interventions in managing the disease. These findings should be validated in randomized controlled trials to establish causality and facilitate the development of optimal intervention strategies. The role of triglyceride–glucose indices in predicting mortality in patients with NAFLD, as highlighted by Chen *et al*[12], suggests that metabolic markers are crucial in risk stratification and management. Future research should validate these indices in larger cohorts and diverse populations. Studies on sex and race-ethnic disparities in MASLD, such as that conducted by Fu *et al*[6], are crucial in understanding the disease's epidemiology and developing targeted interventions. Given the aforementioned disparities, more inclusive research that considers genetic, social, and environmental factors affecting disease prevalence and progression is needed. Research on noninvasive biomarkers and their prognostic value, as reviewed by Amoroso *et al*[16], has demonstrated that these biomarkers have promise in predicting disease outcomes and tailoring treatment plans. These biomarkers should be validated in large, multicenter studies to verify their reliability and applicability in clinical practice. The exploration of novel therapeutic agents, such as those discussed by Yang *et al*[7] and Zheng *et al*[8], provides hope for new treatment options for NAFLD and MASLD. These studies underscore the relevance of ongoing research into the molecular mechanisms of the disease and the development of targeted therapies. Overall, this review of the literature has revealed key gaps and opportunities in NAFLD and MASLD research. Specifically, ongoing and future studies should focus on longitudinal data collection, genetic and environmental factors, the efficacy of various treatments, and the development of noninvasive diagnostic tools. Addressing these areas will yield new primary data, advance the understanding of the disease, and improve patient outcomes.

FUTURE DIRECTIONS AND RESEARCH NEEDS:

Future research should prioritize elucidating the precise mechanisms through which NAFLD predisposes individuals to increased cardiovascular mortality risk, focusing on sex-specific disparities and tailored management strategies. The synergistic effect of type 2 diabetes and MASLD on cardiovascular outcomes underscores the need for comprehensive studies examining the interplay of these diseases and their shared pathophysiological pathways[2,4]. Longitudinal investigations are crucial for validating risk stratification models and therapeutic interventions aimed at mitigating cardiovascular morbidity and mortality in patients with NAFLD or MASLD[3]. Collaborative efforts among hepatologists, cardiologists, and primary care providers are essential for optimizing patient care and mitigating the increasing burden of NAFLD-related cardiovascular complications[1,10]. Furthermore, disparities in MASLD and associated cardiometabolic conditions in the diverse global context must be addressed through systematic analyses and tailored public health interventions[3,19]. Innovative approaches integrating metabolomics with RNA sequencing can provide deeper insights into the efficacy and underlying mechanisms of potential therapeutic agents for treating NAFLD and its cardiovascular consequences[8,15]. Efforts to characterize dietary patterns and their effects on MASLD underscore the potential of dietary interventions as a primary prevention strategy[5]. Additionally, increased understanding of the role of gut–liver axis interactions and mast cell involvement in liver disease progression has led to the identification of various novel therapeutic targets[13]. Insights from genetic studies underscore the relevance of identifying genetic determinants influencing susceptibility to NAFLD and cardiovascular risk in patients with coronary heart disease[21]. Overall, future research should focus on integrating multidisciplinary approaches to elucidate the mechanisms linking NAFLD to cardiovascular mortality, validate risk assessment tools, and develop effective therapeutic strategies tailored to individual patients' needs.

CONCLUSION

In conclusion, the strong correlation between NAFLD and increased cardiovascular mortality risk in men highlights a crucial intersection between liver health and cardiovascular outcomes. Epidemiological findings consistently indicate an increased cardiovascular risk in individuals with NAFLD due to shared metabolic dysregulation and inflammatory pathways[1,4]. To effectively address these connected health challenges, concerted efforts are required to enhance early detection, refine risk assessment tools, and implement integrated management strategies targeting both liver-specific pathology and cardiovascular risk factors. Future research endeavors should prioritize elucidation of the mechanistic underpinnings of NAFLD-associated cardiovascular mortality, focusing on sex-specific disparities and personalized

therapeutic approaches[3,8]. Collaborations across medical disciplines are essential for optimizing clinical pathways and improving outcomes for high-risk patients. Through bridging of the gaps in understanding and clinical practice, the dual burden of NAFLD and cardiovascular disease can be mitigated and the health trajectory of affected individuals enhanced [2,19].

FOOTNOTES

Author contributions: Hao WR and Cheng CH primarily responsible for writing; Cheng TH overseeing revisions; all authors have read and approved the final manuscript.

Conflict-of-interest statement: All authors declare having no conflicts of interest.

Country of origin: Taiwan

ORCID number: Tzu-Hurng Cheng 0000-0002-9155-4169.

S-Editor: Lin C
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **Batta A**, Hatwal J. Excess cardiovascular mortality in men with non-alcoholic fatty liver disease: A cause for concern! *World J Cardiol* 2024; **16**: 380-384 [PMID: 39086893 DOI: 10.4330/wjc.v16.i7.380]
2 **Malnick SDH**, Zamir D. From non-alcoholic fatty liver disease to metabolic-associated steatotic liver disease: Rationale and implications for the new terminology. *World J Hepatol* 2024; **16**: 863-866 [PMID: 38948440 DOI: 10.4254/wjh.v16.i6.863]
3 **Danpanichkul P**, Suparan K, Dutta P, Kaeosri C, Sukphutanan B, Pang Y, Kulthamrongsri N, Jaisa-Aad M, Ng CH, Teng M, Nakano M, Morishita A, Alkhouri N, Yang JD, Chen VL, Kim D, Fallon MB, Diaz LA, Arab JP, Mantzoros CS, Noureddin M, Lazarus JV, Wijarnpreecha K. Disparities in metabolic dysfunction-associated steatotic liver disease and cardiometabolic conditions in low and lower middle-income countries: a systematic analysis from the global burden of disease study 2019. *Metabolism* 2024; **158**: 155958 [PMID: 38942169 DOI: 10.1016/j.metabol.2024.155958]
4 **Riley DR**, Hydes T, Hernadez G, Zhao SS, Alam U, Cuthbertson DJ. The synergistic impact of type 2 diabetes and MASLD on cardiovascular, liver, diabetes-related and cancer outcomes. *Liver Int* 2024 [PMID: 38949295 DOI: 10.1111/liv.16016]
5 **Huang X**, Gan D, Fan Y, Fu Q, He C, Liu W, Li F, Ma L, Wang M, Zhang W. The Associations between Healthy Eating Patterns and Risk of Metabolic Dysfunction-Associated Steatotic Liver Disease: A Case-Control Study. *Nutrients* 2024; **16** [PMID: 38931312 DOI: 10.3390/nu16121956]
6 **Fu CE**, Teng M, Tung D, Ramadoss V, Ong C, Koh B, Lim WH, Tan DJH, Koh JH, Nah B, Syn N, Tamaki N, Siddiqui MS, Wijarnpreecha K, Ioannou GN, Nakajima A, Noureddin M, Sanyal AJ, Ng CH, Muthiah M. Sex and Race-Ethnic Disparities in Metabolic Dysfunction-Associated Steatotic Liver Disease: An Analysis of 40,166 Individuals. *Dig Dis Sci* 2024 [PMID: 38940975 DOI: 10.1007/s10620-024-08540-4]
7 **Yang M**, Yan R, Sha R, Wang X, Zhou S, Li B, Zheng Q, Cao Y. Epigallocatechin gallate alleviates non-alcoholic fatty liver disease through the inhibition of the expression and activity of Dipeptide kinase 4. *Clin Nutr* 2024; **43**: 1769-1780 [PMID: 38936303 DOI: 10.1016/j.clnu.2024.06.018]
8 **Zheng DX**, Hou Q, Xue TT, Gao X, Geng RY, Wen LM, Wang Z, Yin Q, Yin HL, Hu JP, Yang JH. Efficacy and mechanism of action of Yanxiao Di'naer formula for non-alcoholic steatohepatitis treatment based on metabolomics and RNA sequencing. *J Ethnopharmacol* 2024; **333**: 118487 [PMID: 38925322 DOI: 10.1016/j.jep.2024.118487]
9 **Lawitz EJ**, Fraessdorf M, Neff GW, Schattenberg JM, Noureddin M, Alkhouri N, Schmid B, Andrews CP, Takács I, Hussain SA, Fenske WK, Gane EJ, Hosseini-Tabatabaei A, Sanyal AJ, Mazo DF, Younes R; NCT05296733 Investigators. Efficacy, tolerability and pharmacokinetics of survodutide, a glucagon/glucagon-like peptide-1 receptor dual agonist, in cirrhosis. *J Hepatol* 2024 [PMID: 38857788 DOI: 10.1016/j.jhep.2024.06.003]
10 **Vacca M**, Kamzolas I, Harder LM, Oakley F, Trautwein C, Hatting M, Ross T, Bernardo B, Oldenburger A, Hjuler ST, Ksiazek I, Lindén D, Schuppan D, Rodriguez-Cuenca S, Tonini MM, Castañeda TR, Kannt A, Rodrigues CMP, Cockell S, Govaere O, Daly AK, Allison M, Honnens de Lichtenberg K, Kim YO, Lindblom A, Oldham S, Andréasson AC, Schlerman F, Marioneaux J, Sanyal A, Afonso MB, Younes R, Amano Y, Friedman SL, Wang S, Bhattacharya D, Simon E, Paradis V, Burt A, Grypari IM, Davies S, Driessen A, Yashiro H, Pors S, Worm Andersen M, Feigh M, Yunis C, Bedossa P, Stewart M, Cater HL, Wells S, Schattenberg JM, Anstee QM; LITMUS Investigators, Tiniakos D, Perfield JW, Petsalaki E, Davidsen P, Vidal-Puig A. An unbiased ranking of murine dietary models based on their proximity to human metabolic dysfunction-associated steatotic liver disease (MASLD). *Nat Metab* 2024; **6**: 1178-1196 [PMID: 38867022 DOI: 10.1038/s42255-024-01043-6]
11 **Hao QY**, Zeng YH, Lin Y, Guo JB, Li SC, Yang PZ, Gao JW, Li ZH. Observational and genetic association of non-alcoholic fatty liver disease and calcific aortic valve disease. *Front Endocrinol (Lausanne)* 2024; **15**: 1421642 [PMID: 39045267 DOI: 10.3389/fendo.2024.1421642]

12 **Chen Q**, Hu P, Hou X, Sun Y, Jiao M, Peng L, Dai Z, Yin X, Liu R, Li Y, Zhu C. Association between triglyceride-glucose related indices and mortality among individuals with non-alcoholic fatty liver disease or metabolic dysfunction-associated steatotic liver disease. *Cardiovasc Diabetol* 2024; **23**: 232 [PMID: 38965572 DOI: 10.1186/s12933-024-02343-7]

13 **Nair B**, Kamath AJ, Tergaonkar V, Sethi G, Nath LR. Mast cells and the gut-liver Axis: Implications for liver disease progression and therapy. *Life Sci* 2024; **351**: 122818 [PMID: 38866220 DOI: 10.1016/j.lfs.2024.122818]

14 **Xia J**, Chen H, Wang X, Chen W, Lin J, Xu F, Nie Q, Ye C, Zhong B, Zhao M, Yun C, Zeng G, Mao Y, Wen Y, Zhang X, Yan S, Wang X, Sun L, Liu F, Zhong C, Xia P, Jiang C, Rao H, Pang Y. Sphingosine d18:1 promotes nonalcoholic steatohepatitis by inhibiting macrophage HIF-2α. *Nat Commun* 2024; **15**: 4755 [PMID: 38834568 DOI: 10.1038/s41467-024-48954-2]

15 **Yong Q**, Huang C, Chen B, An J, Zheng Y, Zhao L, Peng C, Liu F. Gentiopicroside improves NASH and liver fibrosis by suppressing TLR4 and NLRP3 signaling pathways. *Biomed Pharmacother* 2024; **177**: 116952 [PMID: 38917754 DOI: 10.1016/j.biopha.2024.116952]

16 **Amoroso M**, Augustin S, Moosmang S, Gashaw I. Non-invasive biomarkers prognostic of decompensation events in NASH cirrhosis: a systematic literature review. *J Mol Med (Berl)* 2024; **102**: 841-858 [PMID: 38753041 DOI: 10.1007/s00109-024-02448-2]

17 **Younossi ZM**, Mangla KK, Berentzen TL, Grau K, Kjær MS, Ladelund S, Nitze LM, Coolbaugh C, Hsu CY, Hagström H. Liver histology is associated with long-term clinical outcomes in patients with metabolic dysfunction-associated steatohepatitis. *Hepatol Commun* 2024; **8** [PMID: 38727678 DOI: 10.1097/HC9.0000000000000423]

18 **Wu X**, Yuan C, Pan J, Zhou Y, Pan X, Kang J, Ren L, Gong L, Li Y. CXCL9, IL2RB, and SPP1, potential diagnostic biomarkers in the co-morbidity pattern of atherosclerosis and non-alcoholic steatohepatitis. *Sci Rep* 2024; **14**: 16364 [PMID: 39013959 DOI: 10.1038/s41598-024-66287-4]

19 **European Association for the Study of the Liver (EASL)**; European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol* 2024; **81**: 492-542 [PMID: 38851997 DOI: 10.1016/j.jhep.2024.04.031]

20 **Beygi M**, Ahi S, Zolghadri S, Stanek A. Management of Metabolic-Associated Fatty Liver Disease/Metabolic Dysfunction-Associated Steatotic Liver Disease: From Medication Therapy to Nutritional Interventions. *Nutrients* 2024; **16** [PMID: 39064665 DOI: 10.3390/nu16142220]

21 **Heerkens L**, Geleijnse JM, van Duijnhoven FJB. Dietary and genetic determinants of non-alcoholic fatty liver disease in coronary heart disease patients. *Eur J Nutr* 2024; **63**: 1847-1856 [PMID: 38864867 DOI: 10.1007/s00394-024-03431-w]

World Journal of Cardiology

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

World J Cardiol 2024 September 26; 16(9): 508-511

DOI: 10.4330/wjc.v16.i9.508

ISSN 1949-8462 (online)

EDITORIAL

Recognizing and preventing complications regarding bioresorbable scaffolds during coronary interventions

George Latsios, Leonidas Koliastasis, Konstantinos Toutouzas, Kostas Tsioufis

Specialty type: Cardiac and cardiovascular systems

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

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade C
Novelty: Grade C
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Hasibuzzaman MA

Received: August 2, 2024
Revised: August 30, 2024
Accepted: September 6, 2024
Published online: September 26, 2024
Processing time: 47 Days and 21.5 Hours

George Latsios, Leonidas Koliastasis, Konstantinos Toutouzas, Kostas Tsioufis, Department of Cardiology, Hippokration General Hospital, Athens Medical School, National and Kapodistrian University of Athens, Athens 11527, Greece

Corresponding author: George Latsios, MD, PhD, Academic Fellow, Attending Doctor, Lecturer, Department of Cardiology, Hippokration General Hospital, Athens Medical School, National and Kapodistrian University of Athens, Alexandroupoleos 9, Athens 11527, Greece. glatsios@gmail.com

Abstract

The evolution of coronary intervention techniques and equipment has led to more sophisticated procedures for the treatment of highly complex lesions. However, as a result, the risk of complications has increased, which are mostly iatrogenic and often include equipment failure. Stent dislodgement warrants vigilance for the early diagnosis and a stepwise management approach is required to either expand or retrieve the lost stent. In the era of bioresorbable scaffolds that are not radiopaque, increased caution is required. Intravascular imaging may assist in detecting the lost scaffold in cases of no visibility fluoroscopically. Adequate lesion preparation is the key to minimizing the possibility of equipment loss; however, in the case that it occurs, commercially available and improvised devices and techniques may be applied.

Key Words: Bioresorbable scaffolds; Stent dislodgement; Complication prevention; Coronary complications; Equipment failure

Core Tip: Adequate lesion preparation is key to minimizing the possibility of equipment loss with bioresorbable scaffolds; however, in the case that it occurs, commercially available and improvised devices and techniques may be applied.

Citation: Latsios G, Koliastasis L, Toutouzas K, Tsioufis K. Recognizing and preventing complications regarding bioresorbable scaffolds during coronary interventions. *World J Cardiol* 2024; 16(9): 508-511
URL: https://www.wjgnet.com/1949-8462/full/v16/i9/508.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i9.508

INTRODUCTION

The evolution of coronary intervention techniques and equipment has revolutionized the quality of percutaneous coronary angioplasty; however, the increase in complexity comes along with more complications, most of which are iatrogenic and preventable. Calcified lesions are the most difficult to manage and require vigilance to prevent complications, such as equipment loss. In the case report by Sun *et al*[1], we read, with interest, the successful management of such a complication with a stepwise approach using intravascular imaging and common coronary balloons. In the process of treating a calcified lesion, a bioresorbable scaffold (BRS) was dislodged from its balloon in the proximal left anterior descending artery, which was confirmed by intravascular ultrasound (IVUS). The authors managed to oppose the dislodged scaffold by crossing and inflating balloons of incremental diameter through the lost scaffold, resulting in the resolution of the index complication and treatment of the lesion.

LESION PREPARATION AND TREATMENT

The treatment of calcified or tortuous lesions requires a stepwise approach targeting plaque modification and 1 : 1 balloon pre-dilatation[2,3]. The goal is stent delivery, appropriate expansion, and apposition. However, inadequate preparation may lead to balloon/stent entrapment, failure in deflating the balloon, or stent dislodgement. In particular, stent unloading into the coronary circulation may compromise the blood flow and embolize in distal segments from which retrieval is impossible. Algorithms incorporating all available tactics have been developed and published, which are targeted at preventing harmful sequelae[4]. Furthermore, the role of intravascular imaging has been repeatedly highlighted in large clinical trials, with optical coherence tomography (OCT) and IVUS showing better clinical and procedural results in stable and acute settings[5-7]. Recently, the INVICTUS trial demonstrated the non-inferiority of OCT compared to IVUS[8].

EQUIPMENT FAILURE

Most stent dislodgements happen during an aggressive effort to cross a resistant lesion followed by pullback of the wedged stent in the lesion. Partial dislodgement, if recognized on time, can be managed by sequential inflation of the proximal part of the stent, followed by the rest of it, firstly with its balloon and then the addition of smaller balloons until full expansion. In the case of the stent being already placed in the correct target, the procedure can be completed; otherwise, more manipulations (additional stents, bifurcation techniques) may be required. However, if full unloading occurs, the primary consideration should be to not lose the wire position that runs through the lost stent. Then, if not embolized, incremental diameter balloons, starting with small balloons (0.75 mm), may be placed into the unexpanded stent to expand it to full apposition. If this is not possible, a second wire may be placed next to it, and with the help of a second and more distally partially inflated balloon, the stent may be retrieved and pulled back into the catheter. Of value are the catheter extensions that may be placed proximally to the lost stent, thus facilitating the retrieval. The easiest technique, nevertheless, is the position of two more guide wires and entrapment of the lost stent by twisting the wires, resulting in retrieval of the whole catheter–wire system "*en-bloc*"[9]. The caveat of this move is that repeat cannulation and wire crossing through a "prepared" and potentially dissected lesion is necessary. The snare approach is sometimes the only way of retrieval in cases with difficult anatomy, distal embolization, or loss/protrusion in the aorta. Commercially available snares may be used with or without the help of guide extensions[10]. The improvised use of equipment to function as snares (using long wires), alligator forceps, and other commercially available retrieval devices can be used based on the availability of each catheter lab[11-14]. Crushing the stent on the intima by expanding a second stent is the last transcatheter resort; however, it is not an option for proximal vessel parts, bifurcations, and the left main artery. Surgical retrieval may be required if all the above fail.

The situation is more complicated when a BRS is dislodged. The interest in the BRS has returned with the development of next-generation metallic scaffolds, with the magnesium alloy ones being the main representatives in large clinical trials [15,16]. The problem is the limited visibility of the scaffold, which is often imaged by intravascular imaging or by identifying the proximal and distal radiopaque markers. The markers of newer scaffold generations are more visible by fluoroscopy, facilitating the detection and placement[17]. All the above-mentioned techniques may be used for BRS, except for the crush technique. Crushing and entrapping a BRS has not been published before and there is no previous experience. The most important consideration is the potential interference with scaffold resorption and if resorbed completely, the void that will be created between the stent and the vessel wall. From our perspective, to understand the behavior of the extent of manipulation of BRS, trials investigating the treatment of bifurcation lesions are necessary.

CONCLUSION

As new scaffolds are being developed and enter into everyday practice, we should not only be vigilant to manage complications but adapt our techniques to the scaffold design. Intravascular imaging has a crucial role in identifying the complications and in controlling the outcomes.

FOOTNOTES

Author contributions: Latsios G was responsible for conception, writing, design, drafting, revision, and final approval; Koliastasis L was responsible for writing, drafting, revision, and final approval; Toutouzas K and Tsioufis K were responsible for writing, overall supervision, and final approval; all of the authors read and approved the final version of the manuscript to be published.

Conflict-of-interest statement: The authors declare that they have no competing interests.

Country of origin: Greece

ORCID number: George Latsios 0000-0002-9133-9258; Leonidas Koliastasis 0000-0002-7966-9174; Kostas Tsioufis 0000-0002-7636-6725.

S-Editor: Luo ML
L-Editor: A
P-Editor: Wang WB

REFERENCES

1 **Sun T**, Zhang MX, Zeng Y, Ruan LH, Zhang Y, Yang CL, Qin Z, Wang J, Zhu HM, Long Y. Unloading and successful treatment with bioresorbable stents during percutaneous coronary intervention: A case report. *World J Cardiol* 2024; **16**: 484-490 [PMID: 39221188 DOI: 10.4330/wjc.v16.i8.484]

2 **Barbato E**, Shlofmitz E, Milkas A, Shlofmitz R, Azzalini L, Colombo A. State of the art: evolving concepts in the treatment of heavily calcified and undilatable coronary stenoses - from debulking to plaque modification, a 40-year-long journey. *EuroIntervention* 2017; **13**: 696-705 [PMID: 28844031 DOI: 10.4244/EIJ-D-17-00473]

3 **Guagliumi G**, Pellegrini D, Maehara A, Mintz GS. All calcified nodules are made equal and require the same approach: pros and cons. *EuroIntervention* 2023; **19**: e110-e112 [PMID: 37283129 DOI: 10.4244/EIJ-E-23-00002]

4 **Giannini F**, Candilio L, Mitomo S, Ruparelia N, Chieffo A, Baldetti L, Ponticelli F, Latib A, Colombo A. A Practical Approach to the Management of Complications During Percutaneous Coronary Intervention. *JACC Cardiovasc Interv* 2018; **11**: 1797-1810 [PMID: 30236352 DOI: 10.1016/j.jcin.2018.05.052]

5 **Li X**, Ge Z, Kan J, Anjum M, Xie P, Chen X, Khan HS, Guo X, Saghir T, Chen J, Gill BUA, Guo N, Sheiban I, Raza A, Wei Y, Chen F, Mintz GS, Zhang JJ, Stone GW, Chen SL; IVUS-ACS Investigators. Intravascular ultrasound-guided versus angiography-guided percutaneous coronary intervention in acute coronary syndromes (IVUS-ACS): a two-stage, multicentre, randomised trial. *Lancet* 2024; **403**: 1855-1865 [PMID: 38604212 DOI: 10.1016/S0140-6736(24)00282-4]

6 **Holm NR**, Andreasen LN, Neghabat O, Laanmets P, Kumsars I, Bennett J, Olsen NT, Odenstedt J, Hoffmann P, Dens J, Chowdhary S, O'Kane P, Bülow Rasmussen SH, Heigert M, Havndrup O, Van Kuijk JP, Biscaglia S, Mogensen LJH, Henareh L, Burzotta F, H Eek C, Mylotte D, Llinas MS, Koltowski L, Knaapen P, Calic S, Witt N, Santos-Pardo I, Watkins S, Lønborg J, Kristensen AT, Jensen LO, Calais F, Cockburn J, McNeice A, Kajander OA, Heestermans T, Kische S, Eftekhari A, Spratt JC, Christiansen EH; OCTOBER Trial Group. OCT or Angiography Guidance for PCI in Complex Bifurcation Lesions. *N Engl J Med* 2023; **389**: 1477-1487 [PMID: 37634149 DOI: 10.1056/NEJMoa2307770]

7 **Lee JM**, Choi KH, Song YB, Lee JY, Lee SJ, Lee SY, Kim SM, Yun KH, Cho JY, Kim CJ, Ahn HS, Nam CW, Yoon HJ, Park YH, Lee WS, Jeong JO, Song PS, Doh JH, Jo SH, Yoon CH, Kang MG, Koh JS, Lee KY, Lim YH, Cho YH, Cho JM, Jang WJ, Chun KJ, Hong D, Park TK, Yang JH, Choi SH, Gwon HC, Hahn JY; RENOVATE-COMPLEX-PCI Investigators. Intravascular Imaging-Guided or Angiography-Guided Complex PCI. *N Engl J Med* 2023; **388**: 1668-1679 [PMID: 36876735 DOI: 10.1056/NEJMoa2216607]

8 **Kang DY**, Ahn JM, Yun SC, Hur SH, Cho YK, Lee CH, Hong SJ, Lim S, Kim SW, Won H, Oh JH, Choe JC, Hong YJ, Yoon YH, Kim H, Choi Y, Lee J, Yoon YW, Kim SJ, Bae JH, Park DW, Park SJ; OCTIVUS Investigators. Optical Coherence Tomography-Guided or Intravascular Ultrasound-Guided Percutaneous Coronary Intervention: The OCTIVUS Randomized Clinical Trial. *Circulation* 2023; **148**: 1195-1206 [PMID: 37634092 DOI: 10.1161/CIRCULATIONAHA.123.066429]

9 **Colón-Arias F**, Moronta-Franco M, Gutiérrez-Martínez A. Coronary stent embolization during percutaneous coronary intervention: Successful retrieval using twisting guide wire technique by radial approach. *J Cardiol Cases* 2021; **23**: 271-273 [PMID: 34093906 DOI: 10.1016/j.jccase.2021.01.008]

10 **Kohli SK**, Lim YP, Lai SH, Tan JW, Taggart D, Kharbanda R, Carrié D, Boudou N. How should I treat stent dislodgement in a STEMI patient resulting in dissection of left main and left circumflex arteries? *EuroIntervention* 2013; **9**: 527-531 [PMID: 23965359 DOI: 10.4244/EIJV9I4A85]

11 **Han Z**, Zhu Y, Lu W, Qiu C. A Novel Retrieval Equipment for Coronary Stent Dislodgement. *JACC Cardiovasc Interv* 2023; **16**: 357-358 [PMID: 36792260 DOI: 10.1016/j.jcin.2022.11.026]

12 **Eeckhout E**, Stauffer JC, Goy JJ. Retrieval of a migrated coronary stent by means of an alligator forceps catheter. *Cathet Cardiovasc Diagn* 1993; **30**: 166-168 [PMID: 8221873 DOI: 10.1002/ccd.1810300218]

13 **Deftereos S**, Raisakis K, Giannopoulos G, Kossyvakis C, Pappas L, Kaoukis A. Successful retrieval of a coronary stent dislodged in the brachial artery by means of improvised snare and guiding catheter. *Int J Angiol* 2011; **20**: 55-58 [PMID: 22532772 DOI: 10.1055/s-0031-1272547]

14 **Kutkut I**, Khan B, Hunley SO, Lawson BD, Gertz ZM. Dislodged Coronary Stents: The Presnaring Technique. *J Invasive Cardiol* 2023; **35**: E156-E157 [PMID: 36884363 DOI: 10.25270/jic/22.00216]

15 **Gao RL**, Xu B, Sun Z, Guan C, Song L, Gao L, Li C, Cui J, Zhang Y, Dou K, Chen J, Mu C, Liu H, Li A, Li Z, Xie L, Yang Y, Qiao S, Wu Y, Stone GW. First-in-human evaluation of a novel ultrathin sirolimus-eluting iron bioresorbable scaffold: 3-year outcomes of the IBS-FIM trial. *EuroIntervention* 2023; **19**: 222-231 [PMID: 37038724 DOI: 10.4244/EIJ-D-22-00919]

16 **Haude M**, Wlodarczak A, van der Schaaf RJ, Torzewski J, Ferdinande B, Escaned J, Iglesias JF, Bennett J, Toth GG, Joner M, Toelg R, Wiemer M, Olivecrano G, Vermeersch P, Garcia-Garcia HM, Waksman R. A new resorbable magnesium scaffold for de novo coronary lesions (DREAMS 3): one-year results of the BIOMAG-I first-in-human study. *EuroIntervention* 2023; **19**: e414-e422 [PMID: 37334655 DOI: 10.4244/EIJ-D-23-00326]

17 **Haude M**, Wlodarczak A, van der Schaaf RJ, Torzewski J, Ferdinande B, Escaned J, Iglesias JF, Bennett J, Toth G, Joner M, Toelg R, Wiemer M, Olivecrona G, Vermeersch P, Garcia-Garcia HM, Waksman R. Safety and performance of the third-generation drug-eluting resorbable coronary magnesium scaffold system in the treatment of subjects with de novo coronary artery lesions: 6-month results of the prospective, multicenter BIOMAG-I first-in-human study. *EClinicalMedicine* 2023; **59**: 101940 [PMID: 37113674 DOI: 10.1016/j.eclinm.2023.101940]

World Journal of Cardiology

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

World J Cardiol 2024 September 26; 16(9): 512-521

DOI: 10.4330/wjc.v16.i9.512

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Retrospective Study

Contemporary nationwide trends in major adverse cardiovascular events in young cannabis users without concomitant tobacco, alcohol, cocaine use

Rupak Desai, Priyatham Gurram, Adil S Mohammed, Rishabh B Salian, Shanmukh Sai Pavan Lingamsetty, Sandeep Guntuku, Ravi Venkata Sai Krishna Medarametla, Rawnak Jahan, Zainab Muslehuddin, Paritharsh Ghantasala

Specialty type: Cardiac and cardiovascular systems

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

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Rajeswari S

Received: May 14, 2024
Revised: July 26, 2024
Accepted: August 7, 2024
Published online: September 26, 2024
Processing time: 128 Days and 5.7 Hours

Rupak Desai, Department of Outcomes Research, Independent Researcher, Atlanta, GA 30033, United States

Priyatham Gurram, Adil S Mohammed, Paritharsh Ghantasala, Department of Internal Medicine, Central Michigan University College of Medicine, Saginaw, MI 48602, United States

Rishabh B Salian, Department of Medicine, Kasturba Medical College, Mangalore 575001, India

Shanmukh Sai Pavan Lingamsetty, Sandeep Guntuku, Ravi Venkata Sai Krishna Medarametla, Department of Medicine, Mamata Medical College, Khammam 507002, India

Rawnak Jahan, Department of Medicine, Bangladesh Medical College, Dhaka 110015, Bangladesh

Zainab Muslehuddin, Department of Internal Medicine, Wayne State University, Sinai Grace Hospital, Detroit Medical Center, Detroit, MI 48201, United States

Co-first authors: Rupak Desai and Priyatham Gurram.

Corresponding author: Paritharsh Ghantasala, FACP, MD, Assistant Professor, Department of Internal Medicine, Central Michigan University College of Medicine, 1000 Houghton Avenue, Saginaw, MI 48602, United States. paritharshghantasala@gmail.com

Abstract

BACKGROUND

Cannabis use has increased among young individuals in recent years. Although dependent cannabis use disorder (CUD) has been associated with various cardiac events, its effects on young adults without concurrent substance use remain understudied.

AIM

To examine trends in hospitalizations for major adverse cardiac and cerebrovascular events (MACCE) in this cohort.

METHODS
We used the National Inpatient Sample (2016-2019) to identify hospitalized young individuals (18-44 years), excluding those with concurrent substance usage (tobacco, alcohol, and cocaine). They were divided into CUD+ and CUD-. Using International Classification of Diseases-10 codes, we examined the trends in MACCE hospitalizations, including all-cause mortality (ACM), acute myocardial infarction (AMI), cardiac arrest (CA), and acute ischemic stroke (AIS).

RESULTS
Of 27.4 million hospitalizations among young adults without concurrent substance abuse, 4.2% (1.1 million) had co-existent CUD. In CUD+ group, hospitalization rates for MACCE (1.71% *vs* 1.35%), AMI (0.86% *vs* 0.54%), CA (0.27% *vs* 0.24%), and AIS (0.49% *vs* 0.35%) were higher than in CUD- group ($P < 0.001$). However, rate of ACM hospitalizations was lower in CUD+ group (0.30% *vs* 0.44%). From 2016 to 2019, CUD+ group experienced a relative rise of 5% in MACCE and 20% in AMI hospitalizations, compared to 22% and 36% increases in CUD- group ($P < 0.05$). The CUD+ group had a 13% relative decrease in ACM hospitalizations, compared to a 10% relative rise in CUD- group ($P < 0.05$). However, when adjusted for confounders, MACCE odds among CUD+ cohort remain comparable between 2016 and 2019.

CONCLUSION
The CUD+ group had higher rates of MACCE, but the rising trends were more apparent in the CUD- group over time. Interestingly, the CUD+ group had lower ACM rates than the CUD- group.

Key Words: Cannabis; Major adverse cardiac and cerebrovascular events; Myocardial infarction; Cardiac arrest; Stroke; All-cause mortality; Young adults; Trends

Core Tip: Higher rates of major adverse cardiac and cerebrovascular events were observed in young adults with cannabis use disorder (CUD), while noting a relative decrease in all-cause mortality hospitalizations compared to those without CUD.

Citation: Desai R, Gurram P, Mohammed AS, Salian RB, Lingamsetty SSP, Guntuku S, Medarametla RVSK, Jahan R, Muslehuddin Z, Ghantasala P. Contemporary nationwide trends in major adverse cardiovascular events in young cannabis users without concomitant tobacco, alcohol, cocaine use. *World J Cardiol* 2024; 16(9): 512-521
URL: https://www.wjgnet.com/1949-8462/full/v16/i9/512.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i9.512

INTRODUCTION

Cannabis is the most widely used recreational substance, both in the United States and globally[1]. In 2022, 61.9 million people aged 12 years or older used marijuana in the past year regardless of the mode. It was highest among young adults aged 18 years to 25 years (38.2%), followed by adults aged 26 years or older (20.6%), and adolescents aged 12 years to 17 years (11.5%)[2]. As of November 2023, 40 states, along with the District of Columbia, have legalized marijuana for medical purposes, and 24 states, along with the District of Columbia, have legalized its recreational use[3]. Delta 9 tetrahydrocannabinol (THC) and cannabidiol are the two principal psychoactive components of cannabis. THC interacts with the body's endocannabinoid system *via* the cannabinoid receptors, which have a broad distribution throughout the body[4]. The possible clinical cardiovascular consequences of cannabis usage have drawn attention. Emerging research suggests that while cannabis use is often associated with relaxation and stress relief, its impact on cardiovascular health is complex and multifaceted. For instance, studies have indicated that acute cannabis consumption can lead to an increase in heart rate and blood pressure, potentially elevating the risk of cardiovascular events, especially in individuals with preexisting conditions such as hypertension or coronary artery disease[5]. There is evidence that the hemodynamic effects of cannabis may raise myocardial oxygen demand while reducing its supply, similar to smoking cigarettes[6]. Although the data is presently conflicting, there have been reports that cannabis usage is linked to adverse cardiovascular outcomes, including an increased risk of myocardial infarction and stroke, particularly in young people[7]. However, much of this evidence is confounded by other substance use, complicating our understanding of the direct impact of cannabis on cardiovascular health. In our study, we aimed to address this gap by examining contemporary trends in major adverse cardiac and cerebrovascular events (MACCE) in young hospitalized adults with dependent cannabis use or cannabis use disorder (CUD), while excluding concomitant tobacco, alcohol, or cocaine use disorders. By reducing the confounding effects of these concurrent substance abuse, we sought to better understand the impact of CUD using a modern-day nationwide cohort.

MATERIALS AND METHODS

The National Inpatient Sample is a large United States all-payer inpatient healthcare dataset containing discharge data from 20% of United States hospitals in 48 states. It includes more than 7 million discharges every year, which equals about 35 million weighted nationwide discharges from 2016-2019, with one primary and up to 39 secondary discharge diagnoses. Weighing is determined by the total number of discharges from all acute care hospitals in the United States divided by the number of discharges included in the 20% sample, which makes it nationally representative. This national data is deidentified; therefore, the institutional review board approval was not mandatory.

We identified hospitalized young adults aged 18 years to 44 years with no substance abuse disorders like tobacco, alcohol, or cocaine using the International Classification of Diseases (ICD)-10 codes F17.210, F10.2 and F14.2. We then divided this population into two groups. *i.e.*, those who have dependent CUD and those who don't have CUD using ICD-10 codes F12.20 and F12.10. CUD is defined as a problematic pattern of cannabis use that results in clinically significant impairment or distress that manifests by at least two of the DSM-5 criteria occurring within a 12-month period. The criteria include using more than intended, unsuccessful attempts to cut down, cravings, neglect of major responsibilities, physical impairment, and withdrawal symptoms, among others. The dependent CUD contains three critical elements, which are preoccupation with the acquisition of cannabis, compulsive use, and relapse to or recurrent use of cannabis.

The outcomes of the study were to determine the rates of hospitalizations for MACCE, which included events such as all-cause mortality (ACM), acute myocardial infarction (AMI), cardiac arrest (CA), and acute ischemic stroke (AIS) in this population using ICD-10 codes (I21.9, I46.9, I63). In addition to this, we aimed to analyze the trends in hospitalizations for MACCE, ACM, AMI, CA and AIS between 2016-2019 in these two cohorts. Categorical and continuous data between cohorts were assessed using Pearson's χ^2 test and Kruskal Wallis test, respectively. Whereas trends for hospitalizations between 2016 and 2019 were assessed by a linear-by-linear association test using discharge weights in SPSS v25 (IBM Corp., Armonk, NY, United States). We also performed a multivariable regression analysis for the association between CUD and MACCE along with ACM, AMI, CA, AIS. The factors adjusted for regression analysis are age, payer type, race, median household income, acquired immune deficiency syndrome, depression, chronic pulmonary disease, obesity, diabetes, hypertension, hyperlipidemia, peripheral vascular disease, cancer, prior stroke, and prior myocardial infarction. We considered a two-tailed *P* value of less than 0.05 as statistical significance.

RESULTS

From 2016 to 2019, we identified a total of 27.47 million United States nationwide hospitalizations among young patients (18-44 years) after excluding cases with a concurrent history of alcohol, tobacco, and cocaine use. Of which, 4.2% (1.1 million) patients had CUD (Figure 1). The median age at admission was consistently 28 years across the four years in CUD+ cohort, with interquartile ranges of 23 years to 44 years ($P < 0.001$) (Table 1). There was a statistically significant shift in the sex distribution among hospitalized individuals in CUD+ cohort, with male patients decreasing from 58.3% in 2016 to 55.5% in 2019 and female patients increasing correspondingly from 41.7% to 44.5%, resulting in an overall percentage of 56.8% for males and 43.2% for females ($P < 0.001$) (Table 1). Racially, White patients made up a slight majority each year, averaging 54.0% over the period, followed by Black patients and Hispanic patients, with the proportions of each group remaining relatively stable ($P <0.001$).

Socioeconomic data indicated significant disparities based on the median household income quartile for the patient's ZIP code, with the largest group falling within the 0-25th percentile each year ($P < 0.001$). In terms of healthcare coverage, a majority were covered by Medicaid, with little change year over year, averaging 51.2% (Table 1). Hospital location and teaching status also showed significant changes over time; the proportion of patients in urban teaching hospitals increased from 67.9% in 2016 to 75.9% in 2019 ($P < 0.001$), while rural and urban non-teaching hospitals saw a decrease from 24% to 16.3% (Table 1). Geographically, the South and Midwest regions were the most common hospital locations for these patients, with the South increasing from 34.3% in 2016 to 36.0% in 2019 in CUD+ cohort. Regarding comorbidities, there were statistically significant increases in hypertension (15.7% to 16.3%), diabetes (7.4% to 8.2%), hyperlipidemia (4.5% to 5.1%), and obesity (9% to 10.6%) over the four-year period ($P < 0.001$ for all) (Table 1). However, no significant change was observed in the incidence of prior myocardial infarction ($P = 0.187$) or cancer ($P = 0.147$). Notably, there was a significant but slight increase in the prevalence of prior stroke or transient ischemic attack (TIA) from 0.9% in 2016 to 1.0% in 2018 ($P = 0.004$) (Table 1).

The comparison of baseline characteristics and comorbidities between the CUD+ and CUD- cohorts is presented in Supplementary Table 1. Individuals in the CUD+ cohort were younger compared to those in the CUD- cohort, with a median age at admission of 28 years *vs* 31 years, respectively. Moreover, the CUD+ cohort had a higher proportion of males compared to the CUD- cohort (56.8% *vs* 21.6%), along with a higher representation of Black individuals (30.9% *vs* 19.5%) and individuals belonging to the lower income quartile (40% *vs* 30.6%) (Supplementary Table 1). In terms of comorbidities, the CUD+ cohort exhibited lower rates of diabetes (7.9% *vs* 9.5%), obesity (9.8% *vs* 14.3%), and hypothyroidism (2.4% *vs* 4.5%) compared to the CUD- cohort. Conversely, the rates of hypertension (16% *vs* 12.6%), hyperlipidemia (4.8% *vs* 4.3%), prior myocardial infarction (0.8% *vs* 0.5%), and depression (13.6% *vs* 7.1%) were higher in the CUD+ cohort compared to the CUD- cohort (Supplementary Table 1).

The frequency of admissions for MACCE (1.71% *vs* 1.35%), AMI (0.86% *vs* 0.54%), CA (0.27% *vs* 0.24%), and AIS (0.49% *vs* 0.35%) was higher in CUD+ group as compared to CUD- group ($P < 0.001$) (Figure 2). Interestingly, the frequency of ACM hospitalizations (0.30% *vs* 0.44%) was lower in CUD+ group compared to the CUD- group (Figure 2). From 2016 to 2019, the trends in hospitalizations for MACCE showed a greater relative increase among CUD- group (1.23% to 1.5%;

Table 1 Baseline characteristics of young adults hospitalized with cannabis use disorder in absence of concomitant tobacco/cocaine/alcohol use disorder (2016-2019)

		2016	2017	2018	2019	Overall	*P* value
Age at admission, median (interquartile range)		28 (23, 44)	28 (23, 44)	28 (23, 44)	28 (23, 44)	28 (23, 44)	< 0.001
Sex	Male	58.3	57.2	56.2	55.5	56.8	< 0.001
	Female	41.7	42.8	43.8	44.5	43.2	
Race	White	55.1	53.8	53.6	53.6	54.0	< 0.001
	Black	30.8	31.1	30.9	30.8	30.9	
	Hispanic	11.8	12.7	13.1	13.2	12.7	
	Asian/PI	1.1	1.3	1.3	1.3	1.3	
	Native American	1.2	1.0	1.1	1.1	1.1	
Median household income national quartile for patient ZIP code	0-25th	40.3	39.8	39.6	40.2	40.0	< 0.001
	26th-50th	25.1	26.5	27.1	25.6	26.1	
	51th-75th	20.9	20.2	20.1	20.9	20.5	
	76th-100th	13.7	13.5	13.2	13.3	13.4	
Payer type	Medicare	9.4	9.0	8.9	8.4	8.9	< 0.001
	Medicaid	50.6	51.9	51.6	50.6	51.2	
	Private	26.0	25.5	25.2	25.8	25.6	
	Self-pay	13.0	12.7	13.4	14.1	13.3	
	No charge	1.0	1.0	0.9	1.0	1.0	
Hospital location and teaching status	Rural	8.1	8.0	7.8	7.7	7.9	< 0.001
	Urban nonteaching	24.0	20.6	18.7	16.3	19.8	
	Urban teaching	67.9	71.5	73.5	75.9	72.3	
Hospital region	Northeast	18.6	18.7	18.6	17.6	18.4	< 0.001
	Midwest	25.1	25.4	24.6	24.6	24.9	
	South	34.3	33.4	34.3	36.0	34.5	
	West	22.1	22.5	22.5	21.8	22.2	
Comorbidities							
Hypertension		15.7	15.9	16.2	16.3	16.0	< 0.001
Diabetes		7.4	8.0	7.9	8.2	7.9	< 0.001
Hyperlipidemia		4.5	4.7	4.8	5.1	4.8	< 0.001
Obesity		9.0	9.7	10.0	10.6	9.8	< 0.001
Peripheral vascular disease		0.7	0.7	0.7	0.8	0.7	< 0.001
Prior MI		0.8	0.8	0.8	0.8	0.8	0.187
Prio stroke/transient ischemic attack		0.9	0.9	1.0	0.9	0.9	0.004
Chronic pulmonary disease		12.7	13.1	12.8	12.9	12.9	< 0.001
Hypothyroidism		2.4	2.3	2.3	2.5	2.4	0.001
Other thyroid disorders		0.6	0.7	0.7	0.8	0.7	< 0.001
Valvular heart disease		0.3	0.3	0.3	0.3	0.3	0.054
Cancer		1.0	1.0	1.0	1.0	1.0	0.147

$P < 0.05$ indicate statistical significance. MI: Myocardial infarction.

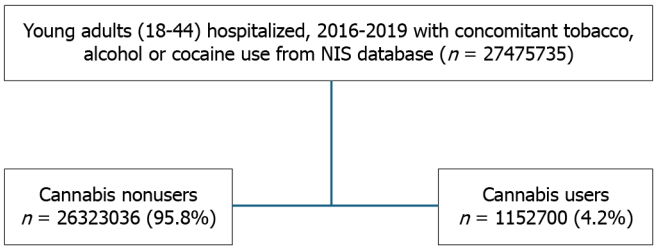


Figure 1 Flowchart showing the inclusion data for the analysis.

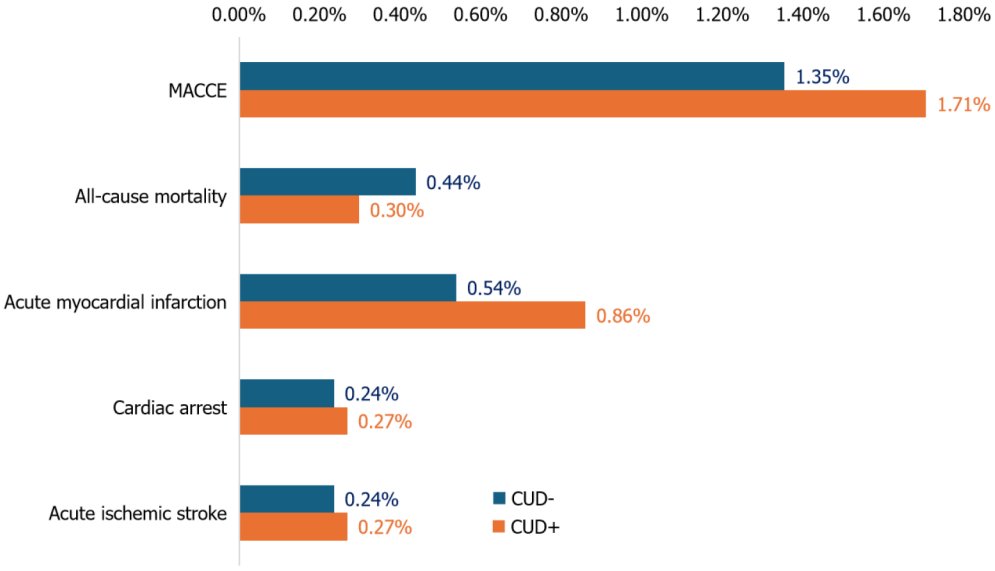


Figure 2 Frequency of major adverse cardiac and cerebrovascular events in young (18-44 years) cannabis users (1152700) *vs* non-users (26323036). Pearson's χ^2 test and Kruskal Wallis test are used to analyze the categorical and continuous variables. CUD: Cannabis use disorder; MACCE: Major adverse cardiac and cerebrovascular events.

22% relative increase, $P < 0.001$) as compared to CUD+ group (1.67% to 1.75%; 4.7% relative increase, $P = 0.018$) (Figure 3). The trends in AMI hospitalizations showed a significant relative increase among the CUD- group (0.47% to 0.64%; 36% relative increase, $P < 0.001$) as compared to CUD+ group (0.79% to 0.95%; 20% relative increase, $P < 0.001$). Surprisingly, trends in ACM showed a relative increase among the CUD- group (0.42% to 0.46%; 10% relative increase, $P < 0.001$), while the CUD+ group showed a relative decrease in ACM hospitalizations (0.32% to 0.28%; 13% relative decrease, $P = 0.043$) (Figure 3). However, trends in CA and AIS hospitalizations did not show a significant change in CUD+ group from 2016 to 2019, while the CUD- group exhibited a 11% (0.22% to 0.25%, $P < 0.001$) and 13% (0.3% to 0.4%, $P < 0.001$) relative increase in CA and AIS respectively. An age-specific analysis was conducted by stratifying the population into narrower age groups (18-24, 25-29, 30-34, 35-44), revealing a progressive increase in rates of MACCE, ACM, AMI, CA, and AIS with advancing age (Supplementary Figure 1). However, the trends in MACCE across the four-year period from 2016 to 2019 did not display significant variations across all age groups (Supplementary Figure 2).

A multivariable regression analysis did not show a significant association between cannabis use and MACCE in this population [odds ratio (OR): 1.00, 95%CI: 0.96-1.03, $P = 0.818$] (Table 2). Similarly, there was no significant association observed for ACM (OR: 0.98, 95%CI: 0.91-1.06, $P = 0.623$), AMI (OR: 1.04, 95%CI: 1.00-1.09, $P = 0.077$), CA (OR: 0.96, 95%CI: 0.88-1.03, $P = 0.252$), and AIS (OR: 0.97, 95%CI: 0.92-1.03, $P = 0.332$) (Table 2).

DISCUSSION

In recent years, recreational cannabis use among young adults has significantly increased with changing legal policies and its widespread availability. As we see this rise in cannabis consumption, there is a need to pay attention to its impact on health, particularly cardiovascular health. In this study, we examined the rates and trends of MACCE in young hospitalized adults with CUD in the absence of concomitant tobacco, alcohol, or cocaine use from 2016 to 2019. We observed that rates of MACCE (1.71% *vs* 1.35%) were higher in cannabis users than non-users. The trends in MACCE hospitalizations among cannabis users had a 5% relative increase from 2016-2019, which is consistent with a previous study that reported increasing trends in MACCE among CUD+ during 2010-2014[8]. It is imperative to consider the neurobiological underpinnings that may predispose this population to both increased health risks and the sustenance of CUD. The

Table 2 Multivariable analysis of major adverse cardiac and cerebrovascular events-related admissions in young adults with dependent cannabis use in the absence of concomitant tobacco, alcohol, or cocaine use disorder with calendar year 2016-2019

In hospital outcomes	Odds ratio	Lower 95%CI	Upper 95%CI	*P* value
Major adverse cardiac and cerebrovascular events	1	0.96	1.03	0.818
All-cause mortality	0.98	0.91	1.06	0.623
Acute myocardial infarction	1.04	1	1.09	0.077
Cerebral vascular	0.96	0.88	1.03	0.252
Acute ischemic stroke	0.97	0.92	1.03	0.332

Multivariable analysis was adjusted for factors like age, payer type, race, median household income, acquired immune deficiency syndrome, depression, chronic pulmonary disease, obesity, diabetes mellitus, hypertension, hepatolenticular degeneration, peripheral vascular disease, cancer, prior stroke/transient ischemic attack, prior myocardial infarction. $P < 0.05$ considered significant.

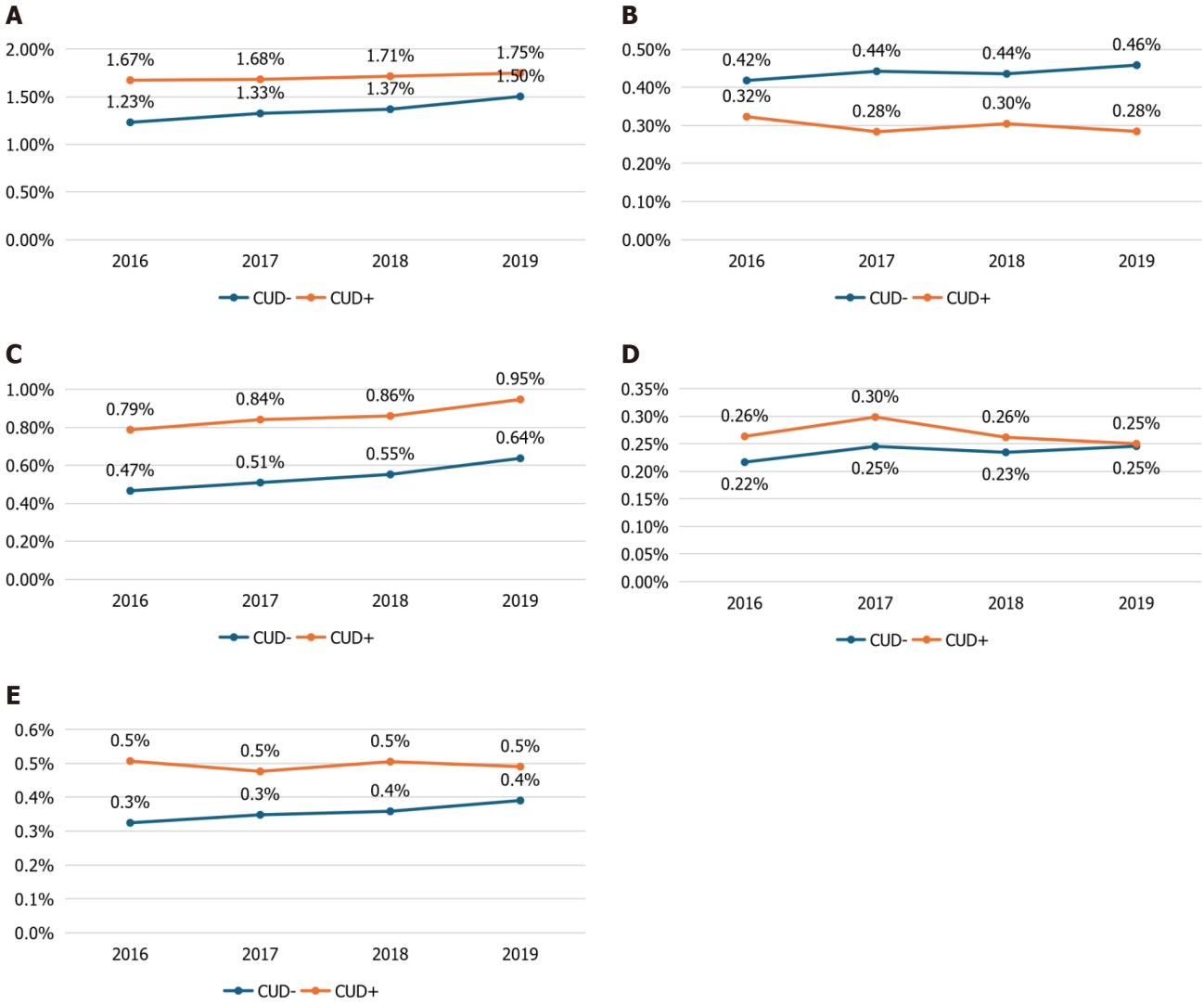


Figure 3 Trends in hospitalizations for major cardiovascular and cerebrovascular events among cannabis users vs. non-users of age 18-44 years, excluding cases with concomitant substance abuse (Alcohol, tobacco, and cocaine) from 2016-2019. A: Trends in hospitalizations for major adverse cardiac and cerebrovascular events; B: Trends in hospitalizations for all-cause mortality; C: Trends in hospitalizations for acute myocardial infarction; D: Trends in hospitalizations for cardiac arrest; E: Trends in hospitalizations for stroke. CUD: Cannabis use disorder.

process of myelination in the brain, wherein a protective layer forms around axons to expedite nerve impulse transmission, is critical for neural efficiency and functionality. Notably, young brains, particularly those under 25 years of age, have not yet achieved complete myelination, rendering them more susceptible to the influences of external substances. This developmental stage is crucial because neurons that are simultaneously active tend to forge stronger connections, adhering to the principle that "cells that fire together wire together"[9]. This mechanism is thought to underlie the formation of addiction pathways; hence, repeated cannabis use during this formative period can result in myelination patterns that inadvertently promote and sustain cannabis addiction. This neurobiological perspective provides a plausible explanation for the observed phenomenon that individuals initiating cannabis use before the age of 18 years are significantly more likely to develop a CUD compared to those who start in adulthood. Understanding these mechanisms is essential for interpreting the trends observed in our research.

Cannabinoid-1 receptors are mainly located in the cardiovascular system, the central nervous system, and peripheral vasculature, play a critical role in mediating the cardiovascular effects of THC[10]. Acute exposure to THC leads to a dose-dependent rise in blood pressure and heart rate, a reaction to which cannabis users may quickly develop tolerance, often resulting in the consumption of higher doses more frequently. Such increased usage has been linked to a higher incidence of cardiac arrhythmias and myocardial infarction[10]. Additionally, long-term THC use is associated with a more frequent occurrence of angina, potentially due to lowered angina thresholds and compromised autonomic nervous system functioning. This includes reduced efficiency in sympathetic and parasympathetic nervous system signaling, increased levels of serum aldosterone, and both central and peripheral vasoconstriction, culminating in hypertension[10]. Low to moderate doses lead to increased heart rate and blood pressure due to increased sympathetic activity. In contrast, high doses or chronic use cause decreased heart rate and blood pressure by increasing parasympathetic activity[11]. In our study, the prevalence of AMI was higher (0.86% *vs* 0.54%) among cannabis users as compared to non-users, and the trends in AMI hospitalizations among cannabis users had increased by 22% from 2016 to 2019. These findings align with previous studies that indicate cannabis use is associated with an increased prevalence of AMI, particularly among younger age groups[12]. Furthermore, AMI-related hospitalizations have seen a rise in cannabis users, even after accounting for confounding factors such as tobacco, alcohol, and other stimulant drug abuse[13]. It leads to dose-dependent changes in heart rate and blood pressure in most individuals. Moreover, CUD leads to higher levels of carboxyhemoglobin, which reduces the blood's ability to carry oxygen[14]. It also promotes platelet aggregation and activates factor VII, which can potentially contribute to blood clot formation. These changes may trigger an AMI by increasing the myocardial oxygen demand while decreasing its supply[14].

Another finding is that the prevalence of AIS was higher in cannabis users than non-users. Many recent studies also reported that cannabis use is associated with a higher prevalence of stroke even after adjusting for confounding factors like tobacco smoking[15]. Heavy cannabis users in the general community also have a higher rate of AIS, particularly among the young, with nearly three times the odds compared to non-users[16]. A prospective study by Wolff *et al*[17] revealed that cannabis use was associated with multifocal intracranial angiopathy leading to ischemic stroke in young individuals. Possible mechanisms for cannabis-induced stroke were abnormal blood flow regulation through sympathetic activity inhibition, symptomatic cerebral vasospasm, and embolism from cardiac arrhythmias[18]. In the central nervous system, THC has been observed to enhance cerebral vasculature tone and elevate central blood pressure, subsequently leading to a reduction in cerebrovascular blood flow. This diminished flow is linked to a heightened risk of cerebral vascular accidents (CVA) and TIAs, indicating a relationship between TIAs and a reversible impact of cannabis on cerebrovascular health, potentially due to temporary vasospasm and/or increased central blood pressure reducing cerebral circulation[10]. Additionally, it has been proposed that cannabis usage could elevate CVA risk in individuals predisposed to cardiovascular disease, regardless of secondary prevention with the use of anti-platelet drugs[10].

We also found that the rates of cerebral vascular (CA)-related admissions were marginally higher among cannabis users than non-users. There were reported cases of CA after cannabis use[19,20] and a few reported cases associated with synthetic cannabinoid use[21,22]. Cannabis might cause an increase in parasympathetic tone and activity, causing a sudden asystolic arrest, which may lead to sudden cardiac death[23]. The other plausible mechanistic links could be due to several interconnected mechanisms. Cannabis use may induce a sympathetic predominance, contributing to arrhythmias and blood pressure variability, thereby exerting additional strain on the cardiovascular system, especially in individuals with pre-existing cardiac conditions. Additionally, it may also trigger myocardial infarction by causing either significant coronary vasospasm or endothelial dysfunction. These factors, alone or in combination, can result in a higher risk of CA among CUD patients.

An interesting finding of this study is that cannabis users had lower rates of ACM (0.30% *vs* 0.44%) compared to non-users. Additionally, there was a decreasing trend in admissions for ACM among cannabis users from 2016 to 2019. Mixed results were reported on this association in the previous studies. Some have reported that cannabis use was associated with lower rates of ACM[24,25], while a few have reported that ACM was higher among young cannabis users hospitalized for AMI[8]. This can be partly attributed to the fact that cannabis users are often younger, male, and African American, with a reduced incidence of cardiovascular risk factors[26]. They have lower total cholesterol, reduced lipid accumulation, weight loss, and improved glycemic control[27]. The physiological effects of cannabinoids have been associated with metabolic processes, as evidenced by a lower prevalence of obesity and diabetes mellitus among marijuana users. Specifically, there is a correlation between cannabis use and lower waist circumference, and body mass index[28,29]. These findings imply that cannabis' anti-inflammatory properties might help reduce the risk factors linked to cardiovascular diseases. Additionally, medical cannabis has shown promise in reducing opioid usage for chronic pain management, resulting in improved quality of life and potentially contributing to lower mortality rates associated with opioid overdose[30]. These factors appear to influence cannabis beneficial association with ACM.

Although our study observed higher rates of MACCE, AMI, CA, and AIS among young adults with CUD, the multivariable analysis revealed no significant association between CUD and these outcomes. This indicates that the observed differences in rates between CUD+ cohorts and CUD- cohorts may be attributed to confounding factors such as age, socioeconomic status, or comorbidities. After adjusting for these confounders, cannabis by itself did not emerge as a significant risk factor for MACCE-related admissions.

Treatment for CUD primarily focuses on psychosocial interventions, with cognitive-behavioral therapy (CBT) and motivational enhancement therapy (MET) standing out for their evidence-based efficacy[31]. CBT, recommended as the first-line treatment, targets the identification and management of thoughts, behaviors, and triggers related to substance use, and has been shown to significantly reduce cannabis use among patients. Similarly, MET emphasizes building motivation for treatment and abstinence, showing comparable effectiveness to CBT. Brief interventions may be beneficial, particularly for adolescents and young adults identified outside healthcare settings, involving one to two short sessions of motivational enhancement techniques, though their long-term efficacy remains uncertain[31]. For those seeking treatment, psychosocial approaches are preferred over medication due to stronger evidence of success, with treatments doubling the likelihood of abstinence at follow-up compared to no treatment, although long-term abstinence rates are generally low. Monitoring treatment progress is critical, with weekly checks initially recommended, adjusting based on patient stability and progress. If initial responses to CBT or MET are insufficient, combining these therapies or incorporating contingency management, which uses incentives to promote abstinence, may enhance outcomes[31].

This study has a few limitations. First, the study design is observational, which means causality cannot be established. Despite efforts to exclude concomitant substance abuse and adjusting cardiovascular risk factors in multivariable regression analysis, it is challenging to determine if the higher rates of MACCE in the CUD+ group could still be influenced by other residual confounding factors as with any retrospective study. Second, the study lacks detailed information on the extent and frequency of cannabis use among the participants. This limits the ability to explore potential dose-response relationships and fully understand the impact of different patterns of cannabis consumption on MACCE. Third, the study analyzes trends over a limited timeframe (2016-2019). Long-term data and follow-up would provide a more comprehensive understanding of the relationship between cannabis use and MACCE. Literature reporting CA after cannabis use was limited to case reports/series and warrant more prospective studies to compare the independent association of CUD with CA in absence of other concomitant substance abuse. Lastly, we could not take into account the impact of medication history, other laboratory parameters, and follow-up data while performing this study, and this limitation warrants more longitudinal prospective studies. Despite these limitations, it is essential to underscore the significance of this study as it examines the trends of MACCE among hospitalized young adults within the CUD group compared to their non-CUD counterparts, distinctly in the absence of other simultaneous substance abuse. The focus on young adults is particularly pertinent, given their susceptibility to developing addictive behaviors, which could adversely impact cardiovascular and metabolic health over the long term. This foundational work not only fills a critical gap in the literature but also sets the stage for future research, guiding healthcare strategies aimed at mitigating the cardiovascular risks associated with cannabis use among young adults.

Future directions

Moving forward, the findings from this study emphasize the need for informed policy-making, especially given the increasing recreational use of cannabis among young adults. There's a pressing demand to integrate these insights into legislative discussions, ensuring safer recreational practices. Healthcare systems should allocate resources towards targeted interventions, like early screening for high-risk young adults with polysubstance abuse histories. Public awareness campaigns can further enlighten both professionals and the public about the cardiovascular risks tied to cannabis use, especially when combined with other substances. Tailored preventative care like comprehensive risk assessments and lifestyle counseling for identified high-risk groups, coupled with longitudinal studies, can provide deeper insights into the long-term effects of cannabis on cardiovascular health.

CONCLUSION

Our study revealed higher rates and growing trends in hospitalizations for MACCE, including AMI, CA, and stroke, from 2016-2019 among young adults with CUD in the absence of concurrent substance abuse. Interestingly, hospitalized cannabis users had lower rates and showed a decreasing trend for ACM during this study period. However, our multivariable analysis did not find a significant association between cannabis use and these outcomes after adjusting for confounding factors. This suggests that the observed differences in rates between CUD+ cohorts and CUD- cohorts may be influenced by factors such as age, socioeconomic status, or comorbidities rather than cannabis use alone. However, it is crucial to recognize that cannabis may still pose cardiovascular health risks through other pathways, such as its potential to increase sympathetic activity and alter hemodynamic parameters. Therefore, comprehensive risk assessment and tailored interventions are warranted for individuals with CUD to mitigate potential cardiovascular risks effectively. These findings call for long-term and comprehensive studies to explore dose-response relationships, the impact of different cannabis products, and their interaction with other risk factors. Furthermore, our findings highlight the importance of continued research to unravel the complex interplay between cannabis use and cardiovascular health outcomes in this population. By understanding these dynamics, healthcare professionals can better address the evolving landscape of cannabis use and its implications for public health and clinical practice.

FOOTNOTES

Author contributions: Desai R was responsible for conceptualization, methodology, software, formal analysis, resources, data curation, and project administration; Gurram P, Mohammad AS, Salian RB, Lingamsetty SSP, Guntuku S, Medarametla RVSK, Muslehuddin Z, Ghantasala P, and Jahan P were responsible for writing, original draft; Desai R, Gurram P, Mohammad AS, and Ghantasala P were responsible for writing, original draft, writing, review, editing, and visualization; all authors contributed to the article and approved the submitted version.

Institutional review board statement: This manuscript is exempt from Institutional Review Board Approval Form or Document since National Inpatient Sample database was used to draw specific patient samples. The National (Nationwide) Inpatient Sample (NIS) is part of a family of databases and software tools developed for the Healthcare Cost and Utilization Project (HCUP). The NIS is the largest publicly available all-payer inpatient healthcare database designed to produce U.S. regional and national estimates of inpatient utilization, access, cost, quality, and outcomes. Unweighted, it contains data from around 7 million hospital stays each year. Weighted, it estimates around 35 million hospitalizations nationally. Developed through a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality (AHRQ), HCUP data inform decision making at the national, State, and community levels.

Informed consent statement: Consent from patient was not needed as the data used has unidentified information.

Conflict-of-interest statement: All the authors declare that they have no conflicts of interest regarding the publication of this manuscript.

Data sharing statement: The data utilized in this study were derived from the National Inpatient Sample (NIS) database, which is publicly available and can be accessed through the Healthcare Cost and Utilization Project (HCUP) website (https://www.hcup-us.ahrq.gov/). Due to the nature of the NIS database, which includes de-identified patient information, there are no restrictions on data access.

Country of origin: United States

ORCID number: Rupak Desai 0000-0002-5315-6426; Priyatham Gurram 0000-0002-8640-3788; Adil S Mohammed 0000-0002-4298-6459; Rishabh B Salian 0009-0005-5324-584X; Shanmukh Sai Pavan Lingamsetty 0000-0001-9560-8390; Sandeep Guntuku 0009-0000-3012-6091; Ravi Venkata Sai Krishna Medarametla 0009-0007-6302-9774; Rawnak Jahan 0009-0006-8469-9331; Zainab Muslehuddin 0009-0006-1913-4529; Paritharsh Ghantasala 0000-0002-5963-090X.

S-Editor: Luo ML
L-Editor: A
P-Editor: Yuan YY

REFERENCES

1 **Degenhardt L**, Whiteford HA, Ferrari AJ, Baxter AJ, Charlson FJ, Hall WD, Freedman G, Burstein R, Johns N, Engell RE, Flaxman A, Murray CJ, Vos T. Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; **382**: 1564-1574 [PMID: 23993281 DOI: 10.1016/S0140-6736(13)61530-5]

2 Key substance use and mental health indicators in the United States: Results from the 2022 National Survey on Drug Use and Health (HHS Publication No. PEP23-07-01-006, NSDUH Series H-58). Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. 2023. Available from: https://www.samhsa.gov/data/report/2022-nsduh-annual-national-report

3 Marijuana Legality by State. DISA 2023. Available from: https://disa.com/marijuana-legality-by-state

4 **Gelfand EV**, Cannon CP. Rimonabant: a cannabinoid receptor type 1 blocker for management of multiple cardiometabolic risk factors. *J Am Coll Cardiol* 2006; **47**: 1919-1926 [PMID: 16697306 DOI: 10.1016/j.jacc.2005.12.067]

5 **Ravi D**, Ghasemiesfe M, Korenstein D, Cascino T, Keyhani S. Associations Between Marijuana Use and Cardiovascular Risk Factors and Outcomes: A Systematic Review. *Ann Intern Med* 2018; **168**: 187-194 [PMID: 29357394 DOI: 10.7326/M17-1548]

6 **Ghosh M**, Naderi S. Cannabis and Cardiovascular Disease. *Curr Atheroscler Rep* 2019; **21**: 21 [PMID: 30980200 DOI: 10.1007/s11883-019-0783-9]

7 **Thomas G**, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. *Am J Cardiol* 2014; **113**: 187-190 [PMID: 24176069 DOI: 10.1016/j.amjcard.2013.09.042]

8 **Desai R**, Shamim S, Patel K, Sadolikar A, Kaur VP, Bhivandkar S, Patel S, Savani S, Mansuri Z, Mahuwala Z. Primary Causes of Hospitalizations and Procedures, Predictors of In-hospital Mortality, and Trends in Cardiovascular and Cerebrovascular Events Among Recreational Marijuana Users: A Five-year Nationwide Inpatient Assessment in the United States. *Cureus* 2018; **10**: e3195 [PMID: 30402363 DOI: 10.7759/cureus.3195]

9 **Keysers C**, Gazzola V. Hebbian learning and predictive mirror neurons for actions, sensations and emotions. *Philos Trans R Soc Lond B Biol Sci* 2014; **369**: 20130175 [PMID: 24778372 DOI: 10.1098/rstb.2013.0175]

10 **Subramaniam VN**, Menezes AR, DeSchutter A, Lavie CJ. The Cardiovascular Effects of Marijuana: Are the Potential Adverse Effects Worth the High? *Mo Med* 2019; **116**: 146-153

11 **Aryana A**, Williams MA. Marijuana as a trigger of cardiovascular events: speculation or scientific certainty? *Int J Cardiol* 2007; **118**: 141-144 [PMID: 17005273 DOI: 10.1016/j.ijcard.2006.08.001]

12 **Desai R**, Patel U, Sharma S, Amin P, Bhuva R, Patel MS, Sharma N, Shah M, Patel S, Savani S, Batra N, Kumar G. Recreational Marijuana Use and Acute Myocardial Infarction: Insights from Nationwide Inpatient Sample in the United States. *Cureus* 2017; **9**: e1816 [PMID: 29312837 DOI: 10.7759/cureus.1816]

13 **Desai R**, Fong HK, Shah K, Kaur VP, Savani S, Gangani K, Damarlapally N, Goyal H. Rising Trends in Hospitalizations for Cardiovascular Events among Young Cannabis Users (18-39 Years) without Other Substance Abuse. *Medicina (Kaunas)* 2019; **55**: 438 [PMID: 31387198 DOI: 10.3390/medicina55080438]

14 **Mittleman MA**, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. *Circulation* 2001; **103**: 2805-2809 [PMID: 11401936 DOI: 10.1161/01.cir.103.23.2805]

15 **Winhusen T**, Theobald J, Kaelber DC, Lewis D. The association between regular cannabis use, with and without tobacco co-use, and adverse cardiovascular outcomes: cannabis may have a greater impact in non-tobacco smokers. *Am J Drug Alcohol Abuse* 2020; **46**: 454-461 [PMID: 31743053 DOI: 10.1080/00952990.2019.1676433]

16 **Hemachandra D**, McKetin R, Cherbuin N, Anstey KJ. Heavy cannabis users at elevated risk of stroke: evidence from a general population survey. *Aust N Z J Public Health* 2016; **40**: 226-230 [PMID: 26558539 DOI: 10.1111/1753-6405.12477]

17 **Wolff V**, Lauer V, Rouyer O, Sellal F, Meyer N, Raul JS, Sabourdy C, Boujan F, Jahn C, Beaujeux R, Marescaux C. Cannabis use, ischemic stroke, and multifocal intracranial vasoconstriction: a prospective study in 48 consecutive young patients. *Stroke* 2011; **42**: 1778-1780 [PMID: 21512186 DOI: 10.1161/STROKEAHA.110.610915]

18 **Rumalla K**, Reddy AY, Mittal MK. Recreational marijuana use and acute ischemic stroke: a population-based analysis of hospitalized patients in the United States. *J Neurol Sci* 2016; **364**: 191-196

19 **Wiliński J**, Skwarek A, Chrzan I, Zeliaś A, Borek R, Dykla DE, Bober-Fotopoulos M, Dudek D. Paroxysmal Sustained Ventricular Tachycardia with Cardiac Arrest and Myocardial Infarction in 29-Year-Old Man Addicted to Medical Marijuana-It Never Rains but It Pours. *Healthcare (Basel)* 2022; **10**: 2024 [PMID: 36292471 DOI: 10.3390/healthcare10102024]

20 **Menahem S**. Cardiac asystole following cannabis (marijuana) usage--additional mechanism for sudden death? *Forensic Sci Int* 2013; **233**: e3-e5 [PMID: 24200372 DOI: 10.1016/j.forsciint.2013.10.007]

21 **Ahmed T**, Khan A, See VY, Robinson S. Cardiac arrest associated with synthetic cannabinoid use and acquired prolonged QTc interval: A case report and review of literature. *HeartRhythm Case Rep* 2020; **6**: 283-286 [PMID: 32461896 DOI: 10.1016/j.hrcr.2020.02.002]

22 **Wan EE**, Frank D, Bang E. Synthetic cannabinoid (k2) related cardiac arrest and death in young drug abuser, D42 critical care case reports: cardiovascular disease and hemodynamics II 2018. *Am J Respir Crit Care Med* 2016; **193**: A6983

23 **Fisher BA**, Ghuran A, Vadamalai V, Antonios TF. Cardiovascular complications induced by cannabis smoking: a case report and review of the literature. *Emerg Med J* 2005; **22**: 679-680 [PMID: 16113206 DOI: 10.1136/emj.2004.014969]

24 **Simons-Linares CR**, Barkin JA, Jang S, Bhatt A, Lopez R, Stevens T, Vargo J, Barkin JS, Chahal P. The Impact of Cannabis Consumption on Mortality, Morbidity, and Cost in Acute Pancreatitis Patients in the United States: A 10-Year Analysis of the National Inpatient Sample. *Pancreas* 2019; **48**: 850-855 [PMID: 31210668 DOI: 10.1097/MPA.0000000000001343]

25 **Koola MM**, McMahon RP, Wehring HJ, Liu F, Mackowick KM, Warren KR, Feldman S, Shim JC, Love RC, Kelly DL. Alcohol and cannabis use and mortality in people with schizophrenia and related psychotic disorders. *J Psychiatr Res* 2012; **46**: 987-993 [PMID: 22595870 DOI: 10.1016/j.jpsychires.2012.04.019]

26 **Johnson-Sasso CP**, Tompkins C, Kao DP, Walker LA. Marijuana use and short-term outcomes in patients hospitalized for acute myocardial infarction. *PLoS One* 2018; **13**: e0199705 [PMID: 29995914 DOI: 10.1371/journal.pone.0199705]

27 **Dibba P**, Li A, Cholankeril G, Iqbal U, Gadiparthi C, Khan MA, Kim D, Ahmed A. Mechanistic Potential and Therapeutic Implications of Cannabinoids in Nonalcoholic Fatty Liver Disease. *Medicines (Basel)* 2018; **5**: 47 [PMID: 29843404 DOI: 10.3390/medicines5020047]

28 **Rajavashisth TB**, Shaheen M, Norris KC, Pan D, Sinha SK, Ortega J, Friedman TC. Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III. *BMJ Open* 2012; **2**: e000494 [PMID: 22368296 DOI: 10.1136/bmjopen-2011-000494]

29 **Ngueta G**, Bélanger RE, Laouan-Sidi EA, Lucas M. Cannabis use in relation to obesity and insulin resistance in the Inuit population. *Obesity (Silver Spring)* 2015; **23**: 290-295 [PMID: 25557382 DOI: 10.1002/oby.20973]

30 **Boehnke KF**, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. *J Pain* 2016; **17**: 739-744 [PMID: 27001005 DOI: 10.1016/j.jpain.2016.03.002]

31 **Connor JP**, Stjepanović D, Le Foll B, Hoch E, Budney AJ, Hall WD. Cannabis use and cannabis use disorder. *Nat Rev Dis Primers* 2021; **7**: 16 [PMID: 33627670 DOI: 10.1038/s41572-021-00247-4]

World Journal of Cardiology

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

World J Cardiol 2024 September 26; 16(9): 522-530

DOI: 10.4330/wjc.v16.i9.522

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Retrospective Study

Medical appraisal of Chinese military aircrew with abnormal results of coronary computed tomographic angiography

Jia Zeng, Yao Zhao, Di Gao, Xiang Lu, Jing-Jing Dong, Yan-Bing Liu, Bin Shen

Specialty type: Cardiac and cardiovascular systems

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

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade C

Novelty: Grade A, Grade B

Creativity or Innovation: Grade B, Grade B

Scientific Significance: Grade A, Grade B

P-Reviewer: Sawada N; Yu T

Received: July 15, 2024

Revised: August 18, 2024

Accepted: August 28, 2024

Published online: September 26, 2024

Processing time: 66 Days and 0.3 Hours

Jia Zeng, Yao Zhao, Xiang Lu, Jing-Jing Dong, Yan-Bing Liu, Bin Shen, Naval Medical Center, Naval Medical University of Chinese PLA, Shanghai 200052, China

Di Gao, No. 92329 Station Health Team, Chinese PLA, Huludao 125000, Liaoning Province, China

Co-first authors: Jia Zeng and Yao Zhao.

Corresponding author: Bin Shen, MD, Associate Chief Physician, Naval Medical Center, Naval Medical University of Chinese PLA, No. 338 Huaihaixi Road, Shanghai 200052, China. yijiacheng455@163.com

Abstract

BACKGROUND

Coronary artery diseases can cause myocardial ischemia and hypoxia, angina pectoris, myocardial infarction, arrhythmia, and even sudden death led to inflight incapacitation of aircrew. As the main cause of grounding due to illness, they severe threats to the health and fighting strength of military aircrew. Early warning in an early and accurate manner and early intervention of diseases possibly resulting in inflight incapacitation are key emphases of aeromedical support in clinic.

AIM

To figure out the flight factors and clinical characteristics of military aircrew with abnormal results of coronary artery computed tomographic angiography (CTA), thereby rendering theoretical references for clinical aeromedical support of military flying personnel.

METHODS

The clinical data of 15 flying personnel who received physical examinations in a military medical center from December 2020 to June 2023 and were diagnosed with coronary artery diseases by coronary artery CTA were collected and retrospectively analyzed, and a descriptive statistical analysis was conducted on their onset age, aircraft type and clinical data.

RESULTS

The 15 military flying personnel diagnosed with coronary artery diseases by coronary artery CTA were composed of 9 pilots, 1 navigator and 5 air combat

service workers. Multi-vessel disease was detected in 9 flying personnel, among which 8 (88.9%) were pilots. Flying personnel with multi-vessel disease had higher content of cholesterol, low-density lipoprotein cholesterol and apolipoprotein B than those with single-vessel disease.

CONCLUSION
Coronary artery diseases are the major heart disease for the grounding of flying personnel due to illness, which can lead to inflight incapacitation. Coronary artery CTA is conducive to early detection and early intervention treatment of such diseases in clinic.

Key Words: Military; Flying personnel; Coronary artery disease; Medical appraisal

Core Tip: Early warning and intervention of diseases leading to inflight incapacitation is not only the most crucial task in clinical aeromedical work, but also the key link to reduce the grounding rate, ensure the fighting strength of troops and extend the life cycle of pilots. Construction of early warning model, accurate early warning and early intervention of key parameters in the results of routine physical examination are of great military significance for ensuring the health improvement of flying personnel.

Citation: Zeng J, Zhao Y, Gao D, Lu X, Dong JJ, Liu YB, Shen B. Medical appraisal of Chinese military aircrew with abnormal results of coronary computed tomographic angiography. *World J Cardiol* 2024; 16(9): 522-530
URL: https://www.wjgnet.com/1949-8462/full/v16/i9/522.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i9.522

INTRODUCTION

Coronary artery diseases can not only cause severe complications such as myocardial ischemia and hypoxia, angina pectoris, myocardial infarction, arrhythmia, and even sudden death, but also lead to inflight incapacitation of flying personnel, which also serve as the main cause of grounding due to illness[1-3]. As a result, they act as severe threats to the health and fighting strength of military aircrew. Early warning in an early and accurate manner and early intervention of diseases possibly resulting in inflight incapacitation are key emphases of aeromedical support in clinic. A recent study in a military medical center reported that 15 military flying personnel hospitalized for physical examination had abnormal results of coronary artery computed tomographic angiography (CTA), ranking second in the disease spectra of temporary disqualification from flying. In this study, the clinical data of such personnel were retrospectively analyzed to understand the characteristics of coronary artery diseases in them and their relationships with flight factors, avoiding severe adverse events in flying (Table 1). It is now reported as follows.

MATERIALS AND METHODS

Methods

The enrolled flying personnel were assigned into a single-vessel disease group and a multi-vessel disease group based on the results of coronary artery CTA. Peripheral venous blood was harvested from the subjects in the two groups for all-item blood lipid test, and carotid artery ultrasound examination, coronary artery CTA and angiography were implemented. Then, high-risk factors for coronary atherosclerosis found in the above test and examinations were used as observation indicators. Besides, comparisons and analyses were conducted on these indicators between the two groups. In addition, a retrospective analysis was carried out on flying appraisal conclusions.

Blood lipid test

Peripheral venous blood (5 mL) was collected from all fasting subjects, followed by centrifugation. Next, the serum was harvested to determine the content of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol [Roche Diagnostics (Suzhou) Co., Ltd. China] using an automatic biochemical analyzer (cobas-c702, Roche, Germany) according to the instructions. And the apolipoprotein (Apo)B and ApoAI. ApoB and ApoAI content was measured by turbidimetric immunoassay (Daiichi Pure Chemicals Co., Ltd., Japan) using an automatic biochemical analyzer (7600, HITACHI, Japan) according to the instructions.

Electrocardiogram examination

Electrocardiogram (ECG)signals were collected with a 12-lead electrocardiograph (SE-1201, EDAN, Shenzhen, China), and the data were read by the machine and interpreted by two experienced physicians alone.

Table 1 Aircraft type, battle station and age distribution of 15 flying personnel with abnormal results of coronary artery computed tomographic angiography

Aircraft type (aviation duty)		*n*	Proportion (%)	Age (year)	Median age (year)	Flying time (hour)
Pilot	Fighter	1	6.7	40	40.0	1800
	Fighter plane (Bomber)	1	6.7	47	47.0	3000
	Bomber	1	6.7	49	49.0	3200
	Transport plane	2	13.3	48-55	51.5 ± 4.9	5000-5600
	Primary trainer	1	6.7	49	49.0	3000
	Helicopter	3	20.0	48-51	50.0 ± 1.7	2600-3100
Navigator		1	6.7	50	50.0	4000
Air combat service worker		5	33.3	42-56	52.0 ± 5.8	2100-5000

Detection of carotid plaque

The intima-media thickness (IMT) of the common carotid artery was detected at 10 mm near the bifurcation of the common carotid artery by an ultrasonic diagnostic instrument (E9, GE, United States) at the probe center frequency of 7-12 MHz The IMT was the distance from the intimal interface of the lumen far from the skin to the media adventitia interface, that is, the distance between two parallel bright lines separated by relatively hypoecho on longitudinal ultrasound images of the posterior wall of the artery. The left and right common carotid arteries were measured three times, and the average was taken. IMT ≥ 1.4 mm or presence of local bulge suggested carotid plaque formation. The IMT values of bilateral common carotid arteries plus internal and external carotid arteries were measured and their sum was recorded.

Coronary artery CTA

Coronary artery CTA was carried out in accordance with the method of intravenous injection of Ultravist 370. The severity of coronary artery stenosis was analyzed and assessed at two mutually perpendicular projection positions. For coronary vessels with diameter stenosis, an analysis was conducted on the quantity of diseased vessels and the severity of stenosis. In addition, single-vessel and multi-vessel (double vessels and above) disease groups were set up based on the quantity of diseased vessels. The maximum stenosis in single-vessel disease was recorded, and the sum of stenosis of diseased vessels was calculated.

Blood pressure test

The systolic blood pressure and diastolic blood pressure were recorded respectively.

Coronary angiography

An imaging system (Siemens DFC or Philips FD20/10) was employed for projection of left and right coronary arteries at conventional position by virtue of Judkins method through radial artery or femoral artery, and the results were evaluated by professional physicians of cardiac catheterization for coronary heart diseases. Lesions involving 1, 2 and 3 branches of the anterior descending branch, circumflex branch and right coronary artery (RCA) were regarded as single, double and triple vessel diseases, respectively. If the left main coronary artery (LM) was involved, it was recorded as involving both the anterior descending branch and circumflex branch.

Statistical analysis

Data analysis was accomplished with SPSS 24.0 software. Measurement data were expressed by (mean ± SD). The *F*-test was adopted for intergroup comparison of the measurement data with skewed distribution, while for measurement data with normal distribution and homogeneity of variance, *t*-test was utilized for their comparisons between groups, and t' test was implemented for those with heterogeneity of variance. In terms of numeration data, sample rate pairwise comparison was completed by χ^2 test or Fisher exact test. Pearson correlation analysis was carried out to clarify the correlations of systolic blood pressure, diastolic blood pressure, LDL-C, TG, TC, and serum ApoB with the sum of carotid artery IMT values, the maximum coronary artery stenosis in single vessel disease and the sum of stenosis.

RESULTS

General data

It was found that the onset age and flying time showed no statistical differences between the two groups, but the flying post was obviously different between the two groups, and the incidence rate of multi-vessel disease was obviously higher than that of single vessel disease in pilots (Table 2).

Table 2 Comparison of age, flying time and flying duties between the two groups of aircrew

Group	*n*	Pilot, *n* (%)	Age (year)	Flying time (hour)
Single vessel disease group	6	1 (16.7)	49.0 ± 4.9	3850 ± 1282.7
Multi-vessel disease group	9	8 (88.9)	48.5 ± 4.7	3750 ± 1125.1
Statistical value			0.199	0.160
P value		0.011	0.845	0.876

Table 3 Results of laboratory tests between two groups

Group	*n*	Systolic blood pressure (mmHg)	Diastolic pressure (mmHg)	TC (mmol/L)	TG (mmol/L)	LDL-C (mmol/L)	ApoB (g/L)	Sum of IMT (mm)	Number of carotid plaques (%)
Single vessel disease group	6	134.5 ± 14.6	84.1± 9.4	4.3 ± 1.4	1.3 ± 0.6	3.0 ± 1.3	0.9 ± 0.4	4.3± 0.2	2 (33.3)
Multi-vessel disease group	9	122.5 ± 10.0	78.2± 9.5	5.9 ± 3.5	1.6± 0.3	4.2 ± 3.4	1.3± 0.7	4.0± 0.6	2 (22.2)

TC: Total cholesterol; TG: Triglyceride; LDL-C: Low-density lipoprotein cholesterol; Apo: Apolipoprotein; IMT: Intima-media thickness.

Results of blood pressure test, blood lipid test, carotid artery ultrasound examination and coronary artery CTA

The multi-vessel disease group had higher levels of TC, TG, LDL-C and ApoB than single vessel disease group. However, the differences were of no statistical significance due to the small sample size (Table 3).

Specific treatment and appraisal conclusion

According to the results of relevant laboratory tests, oral administration of lipid-lowering and crown-expanding agents plus drug balloon dilatation was adopted for flying personnel needing treatment. The details are stated in Table 4.

One trainer pilot diagnosed with multi-vessel disease was grounded because he had reached the maximum flying years.

One air combat service worker was diagnosed with multi-vessel disease, and coronary angiography showed that the total coronary artery stenosis was < 120%, and single vessel stenosis > 50% was not found. He was recommended to take statins orally to stabilize plaques, strictly control blood lipid and blood pressure, and was qualified for flying.

One helicopter pilot was diagnosed with multi-vessel disease and had reached the maximum flying years. CTA indicated single vessel stenosis < 50% and total coronary artery stenosis < 120%. Coronary angiography showed single vessel stenosis of 66% and total coronary artery stenosis of 126%. Hence, grounding was suggested.

One helicopter pilot was diagnosed with multi-vessel disease. The ECG showed left ventricular hypertrophy with strain. Chest computed tomography (CT) suggested multiple plaques, so coronary artery CTA was performed. The results showed that single vessel stenosis was 25%-50%, and the total coronary artery stenosis was 100%. Coronary angiography demonstrated that single vessel stenosis was 50%, and no stenosis was found in other vessels. The pilot also had grade 2 hypertension and took Betaloc and amlodipine orally for blood pressure control, but the control outcome was unsatisfactory (148/100 mmHg). He was unqualified for specially permitted flying of overage pilots, and thus grounded.

One fighter pilot was found to have abnormal Q wave on the side wall, but he denied chest pain and other discomfort, and myocardial necrosis markers such as myocardial enzymes were normal. The results of dynamic radionuclide myocardial perfusion imaging-single-photon emission CT showed that (1) No obvious sign of myocardial ischemia was found in the left ventricle; (2) The left ventricular EF values in load state and rest state were 59% and 57%, respectively, within the normal range; and (3) The fractional flow reserve index in left anterior descending coronary artery, left circumflex coronary artery and RCA dominated areas was normal. However, an abnormal increase was detected in the blood lipid, and coronary artery CTA suggested multi-vessel disease. Flying appraisal conclusion: He was temporarily unqualified for flying. Coronary angiography was performed in time, and it was revealed that the single vessel stenosis exceeded 70%, and the total coronary artery stenosis exceeded 120%. Drug balloon dilatation was performed during the operation. Strict control of blood lipid and blood pressure was implemented after operation, after which observation on the ground was conducted for 6 months. The reexaminations showed that the coronary artery stenosis was relieved. Hence, he was qualified for specially permitted flying of two-seat planes. At present, he has flown for more than 3 years, during which the blood lipid and blood pressure were examined every three months, with LDL-C < 0.8. Besides, the physiological parameters dynamically monitored during each flight were normal. In addition, the annual coronary artery CTA and dynamic radionuclide myocardial perfusion imaging suggested normal cardiopulmonary exercise.

One transport plane pilot was diagnosed with multi-vessel disease, and had reached the maximum flying years. The physical examination showed that the ECG was normal. chest CT suggested coronary artery plaques, and coronary artery CTA showed multi-vessel disease. He received drug balloon dilatation and was unqualified for flying (Figure 1, Figure 2

Table 4 Electrocardiogram, coronary artery computed tomographic angiography and flying appraisal conclusion of 15 aircrew with coronary artery diseases

Case	ECG	Coronary artery CTA	Coronary angiography	Flying appraisal conclusion
1	Biphase or low-flat T-wave in leads V4-V6	Small calcified plaques in the middle segment of both RCA and the posterior branch of left ventricle, without stenosis of the lumen, calcified plaques in the proximal segment of RCA, with slight stenosis of the corresponding lumen, and calcified plaques in the middle segment of LAD, with mild stenosis of the corresponding lumen		Qualified
2	Normal	Calcified plaques in the proximal segment of RCA, with slight stenosis of the corresponding lumen, and calcified plaques in the middle segment of LAD, with slight stenosis of the corresponding lumen		Qualified
3	Low-flat T-wave in leads V5 and V6	Soft plaques in the proximal segment of RCA, with local mild stenosis of the lumen, mixed plaques in the proximal segment of LAD, with local mild stenosis of the lumen, and calcified plaques in the proximal segment of LCX, with local mild stenosis of the lumen	Suggested to undergo coronary angiography	Unqualified for specially permitted flying of overage pilots
4	Normal	Calcified plaques in the middle segment of LAD, with mild stenosis of the lumen, superficial myocardial bridge formation in its distal segment, and calcified plaques in the proximal and middle segments of D1 and D2, with mild stenosis of the lumen	LAD: Myocardial bridge in the middle segment, with stenosis of 40%-50% in systole, TIMI3. LCX: Stenosis of 40% of the junction between the proximal and distal segments, TIMI3. RCA: Slight stenosis of the middle segment, with rough wall, indicating the changes of arteriosclerosis, TIMI3	Qualified
5	Normal	Soft plaques in the proximal segment of RCA, with mild stenosis of the corresponding lumen, soft plaques in the proximal segments of LAD, with mild stenosis of the corresponding lumen, and calcified plaques in the middle segment of LAD, with moderate stenosis of the corresponding lumen, and soft plaques in the proximal segments of LCX, with mild stenosis of the corresponding lumen	Suggested to undergo coronary angiography	Qualified
6	Abnormal q wave in side wall	(1) Calcified plaques in the proximal and middle segments of LAD, with local moderate stenosis (50%-70%) and distal myocardial bridge; (2) Severe stenosis of intermediate branch and mild stenosis in the proximal segment of circumflex branch (30%); (3) Mild stenosis of RCA (< 50%)	LM: No abnormalities. LAD: Continuous calcification in the proximal and middle segments, with the most severe stenosis above 85%, TIMI3, a FFR value of 0.59 (normal FFR > 0.75). LCX: Thick high OM, with CTO after originating from the proximal segment, and the distal segment supplied with blood through the collateral branch. RCA: Stenosis of about 50% of the proximal lumen after opening, TIMI3	Temporarily unqualified for flying
7	T wave changes in leads II, III, avF and V3-6	Mixed plaques in the first diagonal branch of the anterior descending branch, with slight stenosis of the lumen		Qualified
8	Sinus bradycardia	Soft plaques in the proximal segment of RCA, with mild stenosis of the lumen		Qualified
9	Low-flat T wave in leads V5 and V6	Calcified plaques in the proximal segment of LAD, with slight stenosis of the corresponding lumen (< 25%)		Qualified
10	Low-flat T wave in leads V4-6	Superficial myocardial bridge formed in the middle segment of LAD, with slight stenosis of the lumen (20%)		Qualified
11	Low-flat T wave in leads V4-6	Local mild and moderate stenosis of the proximal segment of LAD, with possibility of soft plaque formation		Qualified
12	Low-flat or inverted T wave in leads II, III and avF	High-density calcified plaques in the proximal segment of LAD, with mild stenosis of the lumen		Qualified
13	Grade I atrioventricular block and left	Chest CT showed calcified plaques in coronary artery. Coronary artery CTA suggested calcified plaques in the middle segment of LAD, with slight	LAD: Stenosis of 50%, TIMI3, FFR 0.91. LM(-), LCX(-) and RCA: Abnormally thick lumen, TIMI3	Unqualified for specially permitted

	ventricular hypertrophy accompanied with mild strain	stenosis of the lumen. Small calcified plaques in D2 segment, with slight stenosis of the lumen, and small calcified plaques in middle and distal segments of LCX, with slight stenosis of the lumen		flying of overage pilots
14	Normal	Chest CT showed multiple calcified plaques in coronary artery. Coronary artery CTA indicated mixed plaques in the proximal segment, calcified plaques in the middle and soft plaques in the distal segment of RCA, with mild to moderate stenosis of the lumen. Mixed plaques in LM, with mild stenosis of the lumen. Mixed plaques in the proximal and middle segments of LAD, with mild to moderate stenosis of the lumen. Mixed plaques in the proximal segment of LCX, with mild stenosis of the lumen. Mixed plaques in the proximal and middle segments of OM, with mild to moderate stenosis of the lumen	LM(-): Presence of IB, with stenosis of 60% in IB opening. LAD: Calcification shadow in the proximal segment, stenosis of 30%-40% in the proximal and middle segments, myocardial bridge in the middle segment, with stenosis in systole, TIMI3. LCX(-) and OM: Thick. OM2: Beaded stenosis of 50%-80% in the proximal and middle segments, TIMI3, FFR 0.78. RCA: Stenosis of about 50% in the proximal and middle segments, focal stenosis of 50% in the middle segment, stenosis of 40%-50% in the middle and distal segments, eccentric stenosis of 80% in the distal segment, presence of PDA and PL, TIMI3, FFR 0.77	Unqualified for specially permitted flying of overage pilots
15	Sinus bradycardia with low-flat T wave (V5V6)	Coronary artery calcification score: 229 points. Coronary artery CTA showed calcified plaques in the proximal and middle segments of RCA, with mild stenosis of the lumen, soft plaques in the proximal segment of LAD, with mild stenosis of the lumen, superficial myocardial bridge in the middle and distal segments, without stenosis of the lumen, calcification at the proximal end of D1, without stenosis of the lumen	LM(-) and LAD: Stenosis of 50% in the proximal segment, myocardial bridge in the middle and distal segments, stenosis of about 20% in systole, stenosis of about 30% of D1 opening, TIMI3. LCX: Presence of high OM originating the proximal segment, tiny PL in the distal segment, TIMI3. RCA: Thick lumen, and two focal plaques in the middle and distal segments, with stenosis of 30%, thick PDA and PL, with TIMI3	Unqualified for specially permitted flying of overage pilots

CTA: Computed tomographic angiography; TIMI: Thrombolysis in myocardial infarction; FFR: Fractional flow reserve; LAD: Left anterior descending coronary artery; LCX: Left circumflex coronary artery; OM: Obtuse marginal branch; CTO: Chronic total occlusion; IB: Irregular branch; PDA: Posterior descending artery; PL: Posterior branch of left ventricle; ECG: Electrocardiogram; RCA: Right coronary artery; CT: Computed tomography; LM: Left main coronary artery.

and Figure 3).

The other cases were treated with statins to stabilize plaques. One year later, they underwent reexaminations, and the results denoted that the low-density lipoprotein and cholesterol were strictly controlled. Besides, the coronary artery CTA indicated no aggravation. They were recommended to receive reexaminations and follow-up every year.

DISCUSSION

Early warning and intervention of diseases leading to inflight incapacitation is not only the most crucial task in clinical aeromedical work, but also the key link to reduce the grounding rate, ensure the fighting strength of troops and extend the life cycle of pilots. Construction of early warning model, accurate early warning and early intervention of key parameters in the results of routine physical examination are of great military significance for ensuring the health improvement of military aircrew[4,5]. In Europe and the United States, the risks of major adverse cardiovascular events (MACEs) including death, myocardial infarction and revascularization (or repeated revascularization) have been used as markers of sudden incapacitation[6,7]. Through long-term follow-up of military pilots with coronary artery diseases, it is found that the annual incidence rate of MACEs is 0.6% for pilots with total coronary artery stenosis < 50%, and 1.1% for those with total coronary artery stenosis of 50%-120%. Therefore, a low risk is identified in the case of total coronary artery stenosis < 120% without single vessel stenosis > 70%, two vessel stenoses > 50%, and LM stenosis > 50%. specially permitted flying can be considered for two-seat or multi-seat plane pilots. However, the average annual risk of MACEs is 3% for pilots with total coronary artery stenosis > 120%, and it is over 3% for pilots with single vessel stenosis > 70% or two vessel stenoses > 50%, and/or LM stenosis > 50%, and the aviation risk is relatively high.

Coronary artery CTA is minimally invasive and convenient, so it can be given in priority. However, coronary artery CTA is not the gold standard for the diagnosis of coronary diseases[8]. The gold standard is coronary angiography, which is an invasive examination, and requires observation on the ground for 1-3 months after operation even if the examination results are normal. As a result, coronary angiography is not routinely used in clinic. Treadmill exercise test and coronary artery CTA can serve as effective means to screen and eliminate coronary heart diseases in military aircrew, and coronary angiography is the final method to diagnose and eliminate coronary heart diseases at present[9]. However, if a patient has abnormally high blood lipid, abnormal ECG results, and severe multi-vessel disease according to coronary artery CTA, the patient is suggested to receive coronary angiography as early as possible.

Currently, it is clearly pointed out in the special permission guidelines in China and foreign countries that after interventional therapy for coronary artery diseases and strict control of various high-risk factors, flying personnel with single-vessel disease < 50% and total coronary artery stenosis < 120% in reexaminations are qualified for piloting transport planes, helicopters and multi-seat planes and unqualified for piloting fighters[10]. The appraisal conclusion of specially permitted flying of fighter pilots needs to continue to accumulate practical experience and be strictly controlled. One fighter pilot in this study had piloted two-seat planes for over 3 years after coronary intervention. At present, the flying time is controlled to be less than 50 hours per year, the physiological indexes are closely monitored in each flight,

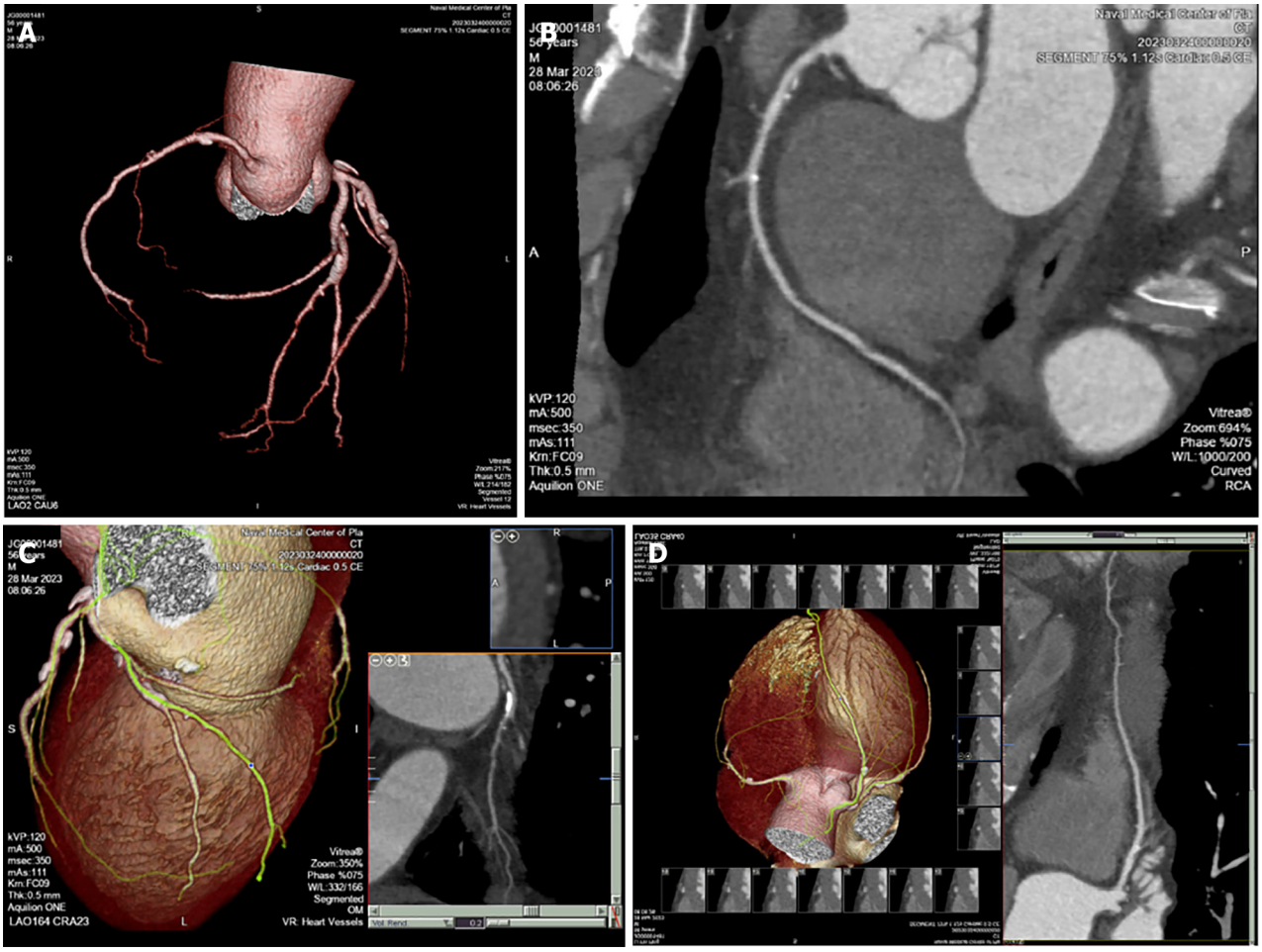


Figure 1 Transport pilot coronary computed tomographic angiography examination reveals coronary artery stenosis. A: All coronary artery images show mixed plaques with four vessel lesions and mild to moderate stenosis of the lumen; B: Right coronary artery, mixed plaques in the proximal segment, calcified plaques in the middle segment, soft plaques in the distal segment, and mild to moderate narrowing of the lumen; C: Obtuse marginal branch mixed plaques in the proximal and middle segments, with mild to moderate narrowing of the lumen; D: Left anterior descending of coronary artery, mixed plaques in the proximal and middle segments, with mild to moderate narrowing of the lumen.

and all blood lipid and blood pressure indexes are closely controlled and followed up.

Among the 15 flying personnel with coronary artery diseases in this study, there were 5 air combat service workers and 1 navigator (accounting for 40% in total), and these 6 had a relatively high incidence rate, which may be related to the fact that the selection criteria of air combat service workers are less strict than those of pilots, and the maximum service length of air combat service workers is higher than that of pilots of various aircraft. For high-risk groups aged over 45 years old, it is necessary to focus on various early warning indicators. In the multi-vessel disease group, 8 pilots (1 pilot each of helicopters, fighters and bombers) had normal ECG, but had transient chest tightness and discomfort in the past. Considering the flight safety of pilots, it was suggested to undergo additional dynamic ECG and coronary artery CTA, and the results showed abnormalities in the coronary artery[11]. In the annual physical examination, 4 pilots had normal ECG, but coronary plaques were found by thin-slice chest CT. They were suggested to receive coronary artery CTA, and abnormalities were detected. At the same time, it was uncovered that the proportion of pilots in the multi-vessel disease group was high, signifying that the disease is already in the advanced stage at the time of discovery and the symptoms are atypical at ordinary times. Therefore, it is suggested that aviation military doctors should pay attention to communication with pilots at ordinary times, ask about medical history in detail, carefully perform physical examination, and avoid dependence only on routine examination results. In particular, the tolerance of pilots is higher than that of ordinary people, so they are likely to ignore ordinary discomforts.

In this study, the TC, LDL-C and ApoB were higher in the multi-vessel disease group than those in the single vessel disease group. In the health management of air combat service workers, great importance has been attached to the concept of the full life cycle: From the pilot physical examination to grounding, close attention should be paid to these early warning indicators in each physical examination, early intervention should be implemented, and strict control of blood lipid and blood pressure should be emphasized to prevent the initial coronary events[12]. Moreover, long-term follow-up and dynamic monitoring are suggested. Furthermore, reasonable arrangement of meals and control of the total calories should be implemented, a low-fat and low-cholesterol diet should be provided, and the intake of sucrose and sugary foods should be limited. In addition, it is suggested to have appropriate physical training, ensure adequate sleeping, quit smoking and limit alcohol.

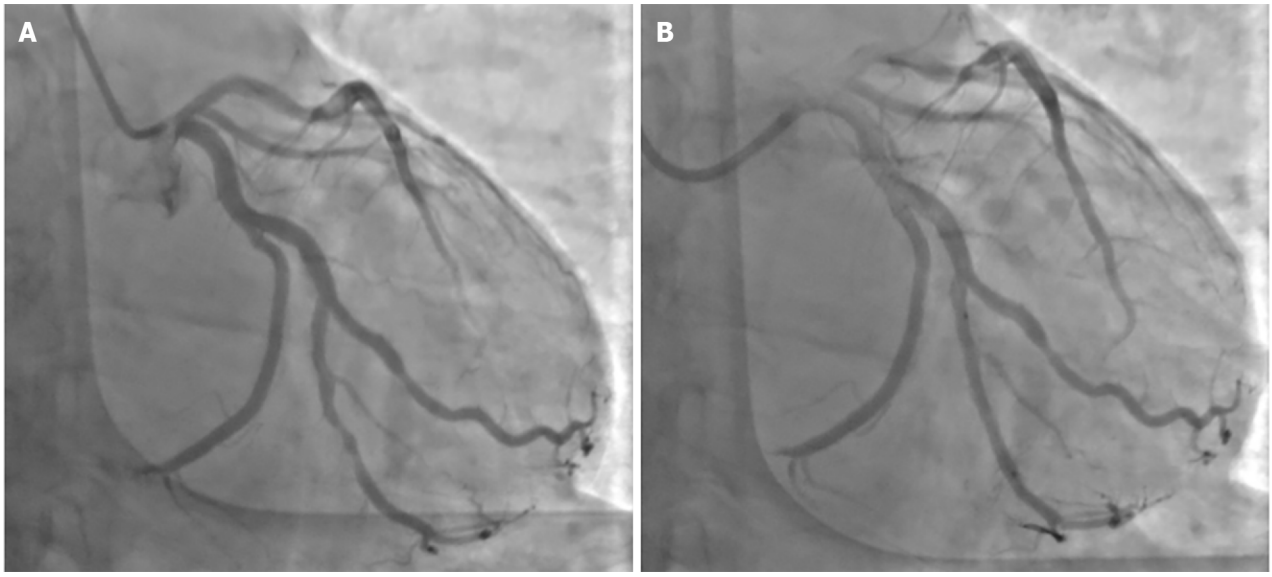


Figure 2 Coronary angiography, obtuse marginal branch 2. A: Preoperative bead like stenosis of 50%-60% in the proximal and middle segments; B: After drug balloon dilation percutaneous transluminal coronary angioplasty treatment, the narrowing of the lumen was significantly improved after dilation, showing A-type dissection and thrombolysis in myocardial infarction III blood flow.

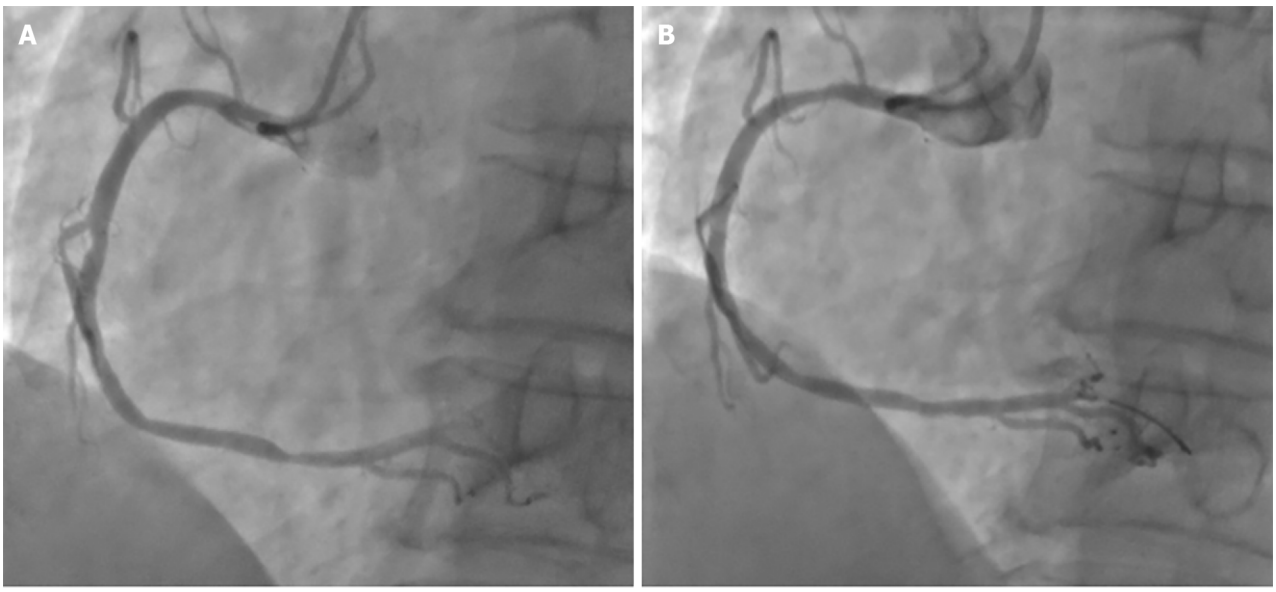


Figure 3 Coronary angiography, right coronary artery. A: Before surgery, the stenosis in the proximal and middle segments was about 50%, the stenosis in the middle segment was limited by 50%, and the stenosis in the middle and middle segments was 40%-50%. Localized eccentric stenosis in the distal segment is about 80%. Visible posterior descending artery and posterior branch of left ventricle emissions; B: After drug balloon dilation percutaneous transluminal coronary angioplasty treatment, the lumen showed significant improvement after dilation, with visible A-type dissection and thrombolysis in myocardial infarction III blood flow.

CONCLUSION

Coronary artery diseases are the main cause of flying personnel's inflight incapacitation and grounding due to illness, so it is necessary to pay close attention to relevant early warning indicators and intervene and treat them as early as possible. Coronary artery CTA is simple and noninvasive, conducive to early detection and early warning of coronary diseases in flying personnel.

FOOTNOTES

Author contributions: Zeng J and Zhao Y contributed equally to this work as co-first authors; Zeng J and Shen B designed the research; Zeng J and Zhao Y conceived of the study (equal), developed the methodology (equal), collected data (equal), analyzed and interpreted data (equal), written manuscript (equal); Zhao Y, Gao D, Lu X, Dong JJ, Liu YB and Zhang Y collected and analyzed the clinical data;

Zeng J, Zhao Y and Gao D wrote the manuscript; Shen B revised the manuscript.

Supported by Enhancement Foundation Program of Naval Medical Center of Naval Medical University.

Institutional review board statement: The study was reviewed and approved by the Naval Medical Center Institutional Review Board.

Informed consent statement: Informed written consent was obtained from the patients for the publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Data sharing statement: No additional data are available.

Country of origin: China

ORCID number: Bin Shen 0009-0004-9023-0471.

S-Editor: Lin C
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **Zerrik M**, Moumen A, El Ghazi M, Smiress FB, Iloughmane Z, El M'hadi C, Chemsi M. Screening for Coronary Artery Disease in Asymptomatic Pilots with Diabetes Mellitus. *Aerosp Med Hum Perform* 2024; **95**: 200-205 [PMID: 38486325 DOI: 10.3357/AMHP.6336.2024]
2 **Davenport ED**, Gray G, Rienks R, Bron D, Syburra T, d'Arcy JL, Guettler NJ, Manen O, Nicol ED. Management of established coronary artery disease in aircrew without myocardial infarction or revascularisation. *Heart* 2019; **105**: s25-s30 [PMID: 30425083 DOI: 10.1136/heartjnl-2018-313054]
3 **Guettler N**, Sammito S. Coronary Artery Disease Management in Military Aircrew. *Aerosp Med Hum Perform* 2023; **94**: 917-922 [PMID: 38176041 DOI: 10.3357/AMHP.6333.2023]
4 **Gunduz SH**, Metin S. Medical reasons for permanent and temporary disqualification of Turkish civil aviation pilots. *Arch Environ Occup Health* 2024; 1-8 [PMID: 38807514 DOI: 10.1080/19338244.2024.2359416]
5 **Simons R**, Maire R, Van Drongelen A, Valk P. Grounding of Pilots: Medical Reasons and Recommendations for Prevention. *Aerosp Med Hum Perform* 2021; **92**: 950-955 [PMID: 34986933 DOI: 10.3357/AMHP.5985.2021]
6 **Long Cheong RW**, See B, Chuan Tan BB, Koh CH. Coronary Artery Disease Screening Using CT Coronary Angiography. *Aerosp Med Hum Perform* 2020; **91**: 812-817 [PMID: 33187568 DOI: 10.3357/AMHP.5522.2020]
7 **Elsaid N**, Saied A, Kandil H, Soliman A, Taher F, Hadi M, Giridharan G, Jennings R, Casanova M, Keynton R, El-Baz A. Impact of stress and hypertension on the cerebrovasculature. *Front Biosci (Landmark Ed)* 2021; **26**: 1643-1652 [PMID: 34994178 DOI: 10.52586/5057]
8 **Li K**, Hu P, Luo X, Li F, Chen L, Zhao J, Wang Z, Luo W, Jin J, Qin Z. Anomalous origin of the coronary artery: prevalence and coronary artery disease in adults undergoing coronary tomographic angiography. *BMC Cardiovasc Disord* 2024; **24**: 271 [PMID: 38783173 DOI: 10.1186/s12872-024-03942-8]
9 **Holland J**, Eveson L, Holdsworth D, Nicol E. Coronary artery calcium scoring vs. coronary CT angiography for the assessment of occupationally significant coronary artery disease. *J Cardiovasc Comput Tomogr* 2022; **16**: 454-459 [PMID: 35219609 DOI: 10.1016/j.jcct.2022.02.005]
10 **Hou KC**. Challenges in Utilizing CT Coronary Angiography and CT Calcium Scoring to Determine Aeromedical Fitness for Aicrew: A Tale of 3 CTs. *Curr Probl Cardiol* 2022; **47**: 100906 [PMID: 34167842 DOI: 10.1016/j.cpcardiol.2021.100906]
11 **Guettler N**, Nicol ED, Sammito S. Exercise ECG for Screening in Military Aircrew. *Aerosp Med Hum Perform* 2022; **93**: 666-672 [PMID: 36224729 DOI: 10.3357/AMHP.6051.2022]
12 **Khazale NS**, Haddad F. Prevalence and characteristics of metabolic syndrome in 111 Royal Jordanian Air Force pilots. *Aviat Space Environ Med* 2007; **78**: 968-972 [PMID: 17955946 DOI: 10.3357/asem.2097.2007]

World Journal of Cardiology

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

World J Cardiol 2024 September 26; 16(9): 531-541

DOI: 10.4330/wjc.v16.i9.531

ISSN 1949-8462 (online)

CASE REPORT

Intracoronary thrombolysis combined with drug balloon angioplasty in a young ST-segment elevation myocardial infarction patient: A case report

Li-Qiong She, De-Kui Gao, Le Hong, Yin Tian, Hui-Zhen Wang, Sheng Huang

Specialty type: Cardiac and cardiovascular systems

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

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C, Grade D

Novelty: Grade B, Grade C

Creativity or Innovation: Grade C, Grade C

Scientific Significance: Grade C, Grade C

P-Reviewer: Adam CA; Seto AH

Received: March 27, 2024

Revised: August 28, 2024

Accepted: September 10, 2024

Published online: September 26, 2024

Processing time: 176 Days and 1.4 Hours

Li-Qiong She, Department of Critical Care Medicine, Jiangyou Second People's Hospital, Jiangyou 621701, Sichuan Province, China

De-Kui Gao, Le Hong, Sheng Huang, Department of Cardiology, Jiangyou Second People's Hospital, Jiangyou 621701, Sichuan Province, China

Yin Tian, Hui-Zhen Wang, Department of Interventional Medicine, Jiangyou Second People's Hospital, Jiangyou 621701, Sichuan Province, China

Co-first authors: Li-Qiong She and Le Hong.

Corresponding author: De-Kui Gao, Chief Doctor, Department of Cardiology, Jiangyou Second People's Hospital, No. 31 Juhui Road, Jiangyou 621701, Sichuan Province, China. 635651229@qq.com

Abstract

BACKGROUND

The combination of acute ST-segment elevation myocardial infarction (STEMI) and gastric ulcers poses a challenge to primary percutaneous coronary intervention (PPCI), particularly for young patients. The role of drug-coated balloons (DCBs) in the treatment of de novo coronary artery lesions in large vessels remains unclear, especially for patients with STEMI. Our strategy is to implement drug balloon angioplasty following the intracoronary administration of low-dose prourokinase and adequate pre-expansion.

CASE SUMMARY

A 54-year-old male patient presented to the emergency department due to chest pain on June 24, 2019. Within the first 3 minutes of the initial assessment in the emergency room, the electrocardiogram (ECG) showed significant changes. There was atrial fibrillation with ST-segment elevation. Subsequently, atrial fibrillation terminated spontaneously and reverted to sinus rhythm. Soon after, the patient experienced syncope. The ECG revealed torsades de pointes ventricular tachycardia. A few seconds later, it returned to sinus rhythm. High-sensitivity tropon in I was normal. The diagnosis was acute STEMI. Emergency coronary angiography revealed subtotal occlusion with thrombus formation in the proximal segment of the left anterior descending artery. Considering the patient's age and history of peptic ulcer disease, after the intracoronary injection of prourokinase, percu-

taneous transluminal coronary angioplasty and cutting balloon angioplasty were conducted for thorough preconditioning, and paclitaxel drug-eluting balloon angioplasty was performed without any stents, achieving favorable outcomes.

CONCLUSION
A PPCI without stents may be a viable treatment strategy for select patients with STEMI, and further research is warranted.

Key Words: STsegment elevation myocardial infarction; Recombinant human prourokinase; De novo coronary lesion; Large vessels; Drug-eluting balloon angioplasty; Case report

Core Tip: The focus of this report is the emergency management of a young patient with ST-segment elevation myocardial infarction and a history of gastric ulcers. Coronary angiography revealed near-total occlusion of the proximal left anterior descending artery. Primary percutaneous coronary intervention are likely difficult. After discussion with the patient, our strategy was to inject a novel thrombolytic agent (recombinant human prourokinase) *via* the intracoronary route to dissolve or clear the local thrombus in the coronary artery. Then, a conventional balloon combined with a cutting balloon is used for adequate pre-expansion. Finally, paclitaxel drug-eluting balloon angioplasty was performed, achieving satisfactory short-term and long-term results.

Citation: She LQ, Gao DK, Hong L, Tian Y, Wang HZ, Huang S. Intracoronary thrombolysis combined with drug balloon angioplasty in a young ST-segment elevation myocardial infarction patient: A case report. *World J Cardiol* 2024; 16(9): 531-541
URL: https://www.wjgnet.com/1949-8462/full/v16/i9/531.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i9.531

INTRODUCTION

The use of drug-coated balloons (DCBs) in treating de novo coronary lesions is controversial, especially in larger vessels [1]. There are limited data on primary percutaneous coronary intervention (PPCI) with DCBs in patients with ST-segment elevation myocardial infarction (STEMI). A novel, emergency stentless intervention strategy involving intracoronary thrombolysis and a combination of conventional and paclitaxel-coated drug balloon angioplasties achieved good short- and long-term results in a young STEMI patient with proximal left anterior descending artery subtotal occlusion and a history of gastric ulcers.

CASE PRESENTATION

Chief complaints

A 54-year-old male patient presented to the emergency department on June 24, 2019, due to recurrent chest pain for 3 days and continuous chest pain for 1 hour.

History of present illness

In the emergency room, the ECG showed significant changes. Atrial fibrillation with coupled premature ventricular contractions was observed, along with ST-segment depression in leads II, III, and AVF and ST-segment elevation in leads V1-V4. Additionally, there were suspicious ST-segment elevations and electrical alternans in leads aVR and aVL. Atrial fibrillation self-terminated very quickly and sinus rhythm was restored accompanied by second-degree type 1 atrioventricular block. Soon after, the patient experienced syncope. The ECG revealed torsades de pointes and ventricular tachycardia. There was spontaneous conversion to a stable sinus rhythm with a heart rate of 82 beats per minute, with ST-segment elevation observed in leads I, AVL, and V1-V5. High-sensitivity troponin I was 22.7 pg/mL.

History of past illness

On January 29, 2018, multiple ulcers were observed in the gastric antrum *via* fibrogastroscopy. The results of the HP test were positive. The patient was treated with pantoprazole combined with hydrotalcite, *etc*. There was no history of gastrointestinal bleeding. The patient did not review gastroscopy as directed by the doctor's orders. The patient denied a history of hypertension, diabetes, atrial fibrillation or syncope.

Personal and family history

Divorced, with one child. The patient smoked 40 cigarettes per day, on average, for 20 years. A history of alcohol consumption, drug addiction, and a family history of premature coronary heart disease were not recorded.

Physical examination

The patient's temperature was 36.3 °C, pulse velocity was 82 beats/minute, respiration rate was 20 breaths/minute, and blood pressure was 16/8.66 kPa (120/65 mmHg). His weight was 77 kg, and his height was 172 centimeters. Acute painful facial expressions. There was no jugular vein distention. No dry or moist rales were audible in either lung. The cardiac border was normal. No murmurs were detected in any of the valve auscultation areas. No edema was found in either lower extremity. No other special conditions exist.

Laboratory examinations

On the day of admission, the following test results were recorded: Plasma D-dimer level, 0.004 μg/mL; NT-proBNP level, 523.2 pg/mL; total cholesterol level, 4.59 mmol/L; triglyceride level, 3.48 mmol/L; high-density lipoprotein cholesterol level, 0.98 mmol/L; low-density lipoprotein cholesterol level, 2.37 mmol/L; potassium level, 3.04 mmol/L; sodium level, 143.7 mmol/L; chloride level, 106.1 mmol/L; total calcium level, 2.24 mmol/L; inorganic phosphorus level, 0.86 mmol/L; magnesium level, 0.92 mmol/L; random blood glucose level, 9.8 mmol/L; white blood cell count, 14.97 × 10^9/L; red blood cell count, 5.10 × 10^{12}/L; hemoglobin level, 173.0 g/L; platelet level, 174 × 10^9/L; C-reactive protein level, 0.98 mg/L; urea level, 5.54 mmol/L; creatinine level, 74.6 μmol/L; uric acid level, 290.30 μmol/L; and estimated glomerular filtration rate, 89.64 mL/min/1.73 m^2. Liver function and thyroid function were normal. The next day, the electrolyte re-examination was normal, urine glucose was positive (+), and fecal occult blood was weakly positive (±). The peak value of troponin (105204 pg/mL at 7.62 hours after onset) increased (Figure 1).

Imaging examinations

The patient's baseline ECG on January 29, 2018 shows sinus rhythm with a pulse rate of 86 beats per minute. The T waves are flattened in leads I, AVL, and V2 to V6 (Figure 2A). Within the first 3 minutes of the initial assessment in the emergency room, the ECG showed significant changes. Atrial fibrillation with coupled premature ventricular contractions was observed, along with ST-segment depression in leads II, III, and AVF and ST-segment elevation in leads V1-V4. Additionally, there were suspicious ST-segment elevations and electrical alternans in leads aVR and aVL (Figure 2B). The atrial fibrillation self-terminated, and sinus rhythm returned, with second-degree type 1 atrioventricular block (Figure 2C) and torsades de pointes ventricular tachycardia (Figure 2D). There was spontaneous conversion to a stable sinus rhythm with a heart rate of 82 beats per minute, and ST-segment elevation was observed in leads I, AVL, and V1-V5 (Figure 2E).

Further diagnostic work-up

Coronary angiography revealed subtotal occlusion of the proximal segment of the anterior descending artery (Figure 3A). After conventional balloon angioplasty (Figure 3B), the target lesion exhibited elastic retraction with approximately 70% residual stenosis (Figure 3C). Cutting balloon angioplasty (CBA) was performed (Figure 3D), and the postoperative residual stenosis was approximately 20% (Figure 3E). Eventually, drug balloon dilation was administered (Figure 3F), and the postoperative residual stenosis rate was approximately 40% (Figure 3G, Figure 4A).

The chest X-ray on June 27 showed enhanced lung markings in both lungs and a tortuous aorta, and the echocardiogram revealed a slightly enlarged left ventricle (LVDd 53 mm) and decreased left ventricular diastolic function, normal left ventricular systolic function (EF 58.57%).

FINAL DIAGNOSIS

Based on the patient's medical history, the alterations noted on the ECG, the variations in the troponin level and the results of coronary angiography, a diagnosis of acute anterolateral STEMI was confirmed.

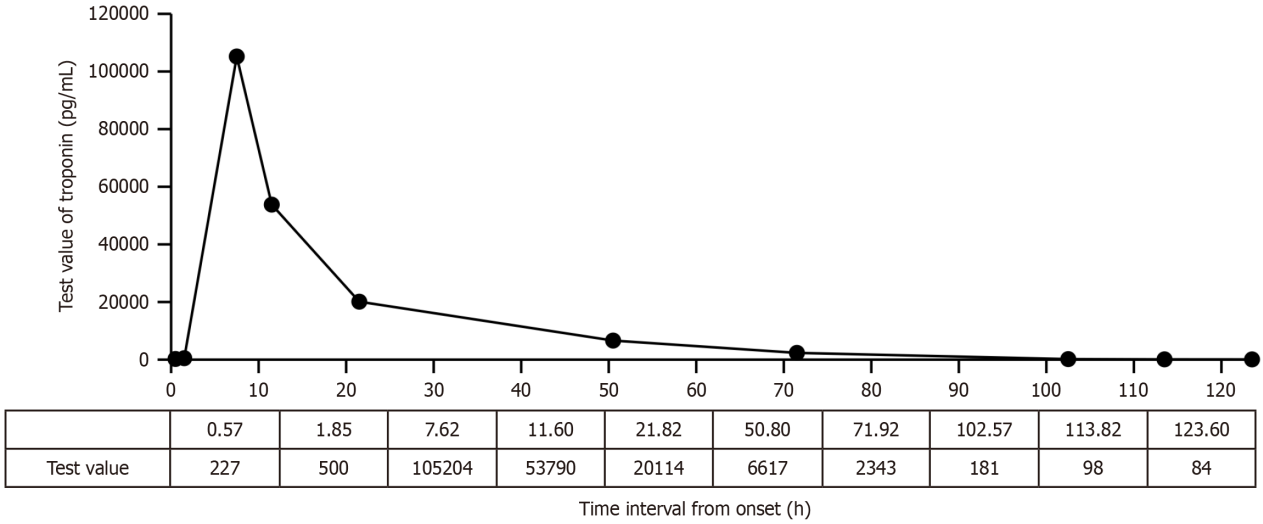
TREATMENT

In the emergency department

The patient was administered the following medications: 300 mg of enteric-coated aspirin, 180 mg of ticagrelor, 40 mg of atorvastatin calcium, and 4000 units of intravenous unfractionated heparin.

During the PPCI procedure

Systemic heparinization (5000 IU of unfractionated heparin) was performed, and the patient received 20 milligrams of recombinant human prourokinase (rhPro-UK), a thrombolytic agent, *via* a 5-Fr Tiger (TIG) diagnostic catheter and then underwent predilation with a TREK 2.5 mm × 15 mm balloon for the lesion in the proximal segment of the anterior descending artery. The balloon was inflated to pressures of 12-18 atm for 55-100 seconds to ensure full dilation. However, subsequent imaging revealed significant recoiling at the stenotic site and approximately 70% residual stenosis, indicating



	0.57	1.85	7.62	11.60	21.82	50.80	71.92	102.57	113.82	123.60
Test value	227	500	105204	53790	20114	6617	2343	181	98	84

Figure 1 Dynamic trend of the troponin level. The peak value appears at 7.62 hours after onset.

the requirement for a cutting balloon (Boston Scientific Flextome™ Cutting Balloon, 3.0 mm × 6 mm) at pressures of 6-8 atm for 55-100 seconds to reduce the residual stenosis to approximately 20%. Finally, a paclitaxel drug-eluting balloon (PDEB) (QINGZHOU Bingo DEB3020) was inflated to a pressure of 16 atm for 98 seconds. In the end, the residual stenosis was approximately 40%. The immediate net gain was 2.8 mm after pretreatment and 2.3 mm after the procedure, increasing the minimum diameter of the lumen. After each balloon dilation, 200 micrograms of sodium nitroprusside were promptly administered to prevent no-reflow, and the total dose was 1600 micrograms. At the end of the PPCI, there was no significant target vessel dissection, and the TIMI flow was grade 3 (Figure 3G, Figure 4A).

Treatment after the PPCI

Starting two hours after the PPCI, 0.6 mL of enoxaparin was injected subcutaneously, and then twice a day thereafter. Subsequently, enteric-coated aspirin at 100 mg/d, clopidogrel bisulfate at 75 mg/d, benazepril hydrochloride at 2.5 mg/d, metoprolol tartrate extended release at 12.5 mg/d, and rosuvastatin calcium at 10 mg/d were administered.

Treatment after discharge

Metoprolol tartrate sustained-release tablets at 25 mg/d, and atorvastatin calcium at 10 mg/d were administered. The remaining oral medications were approximately the same as those used during hospitalization.

OUTCOME AND FOLLOW-UP

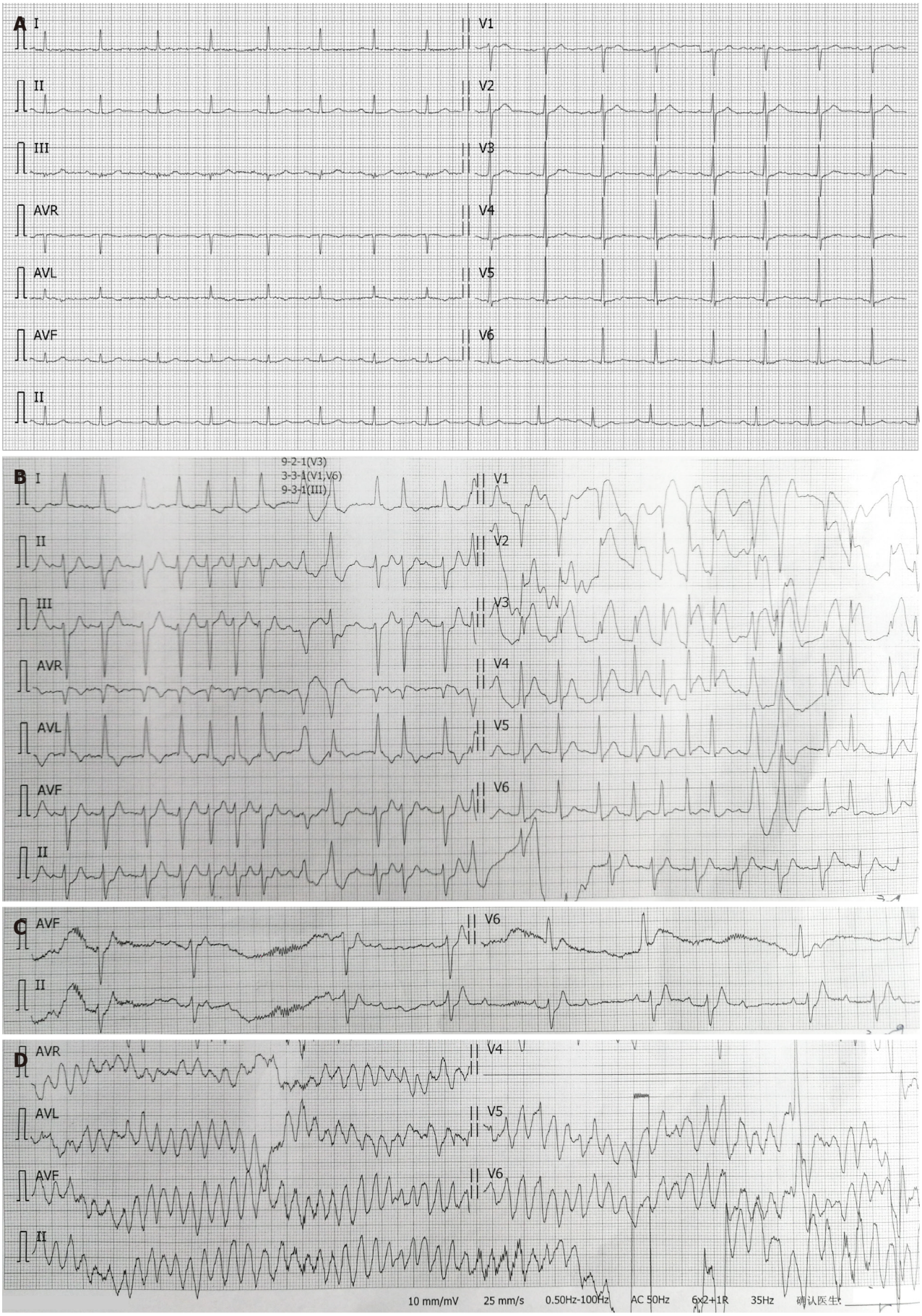
The patient's chest pain was significantly relieved after the completion of conventional balloon predilation. The ECG showed a normal rhythm after the operation. No complications, such as arrhythmia, heart failure, or bleeding, were observed. The troponin level peaked earlier. The patient was discharged on the 10th day after the operation.

After discharge, the patient took the medicine as prescribed. The patient quit smoking after coronary intervention but resumed smoking 4 months later. Occasionally, there was discomfort in the precordial region. The patient stopped taking the drugs prescribed for coronary heart disease in February 2023. On June 16, 2023, reexamination disclosed a low-density lipoprotein cholesterol level of 1.63 mmol/L. On June 19, the echocardiogram indicated an enlarged left ventricle (LVDd 55 mm) and decreased left ventricular diastolic function, normal left ventricular systolic function (EF 57.73%). At the 4-year follow-up, the residual stenosis of the target lesion was approximately 25%, with a long-term net luminal gain of 3.00 mm, and no adverse events occurred, indicating excellent long-term outcomes (Figure 4B).

DISCUSSION

Our patient was a 54-year-old individual who necessitated a PPCI. The parameters needed to evaluate the patient's risk of bleeding due to dual antiplatelet therapy could not be assessed before the operation; however, the patient reported a history of gastric ulcers. For patients with gastric ulcers, the risk of bleeding due to dual antiplatelet therapy increases significantly. We predicted that this patient had a high risk of bleeding. Therefore, after discussion with the patient, we decided to use a stentless technique (Leave Nothing Behind).

In cases of STEMI, the thrombi burden differs. The presence of thrombi limits the contact between the drug coating (paclitaxel) on the surface of the balloon and the vascular endothelium, thus decreasing the efficacy of the DCB, increasing the risk of no-reflow, and ultimately influencing the long-term efficacy of treatment. Therefore, the application


A
I
II
III
AVR
AVL
AVF
II
V1
V2
V3
V4
V5
V6
B
9-2-1(V3)
3-3-1(V1,V6)
9-3-1(III)
C
D
10 mm/mV
25 mm/s
0.50Hz-100Hz
AC 50Hz
6x2+1R
35Hz

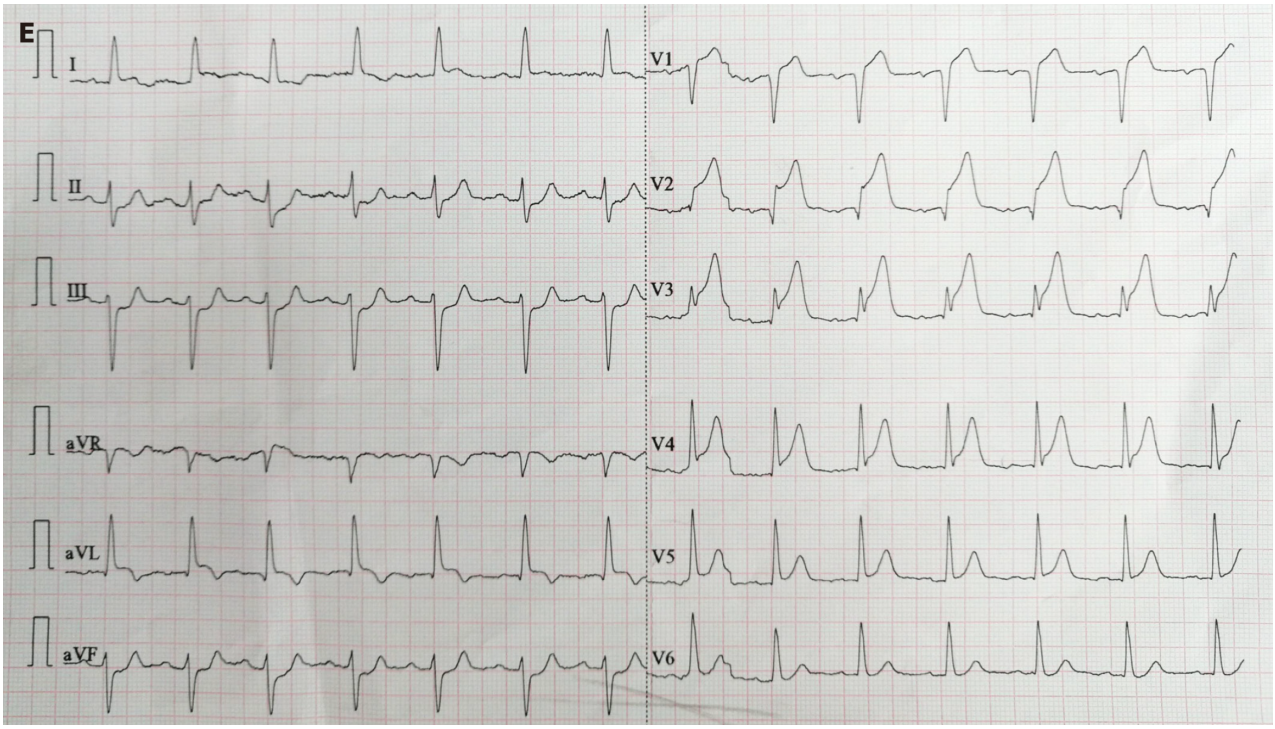


Figure 2 Transient evolution of electrocardiogram in hyperacute myocardial infarction. A: Baseline electrocardiogram (ECG) on January 29, 2018; B and C: Initial emergency ECG at 11:38 on June 24, 2019, showing atrial fibrillation with ST-segment elevation or depression in some leads, ventricular premature beats, and spontaneous conversion of atrial fibrillation to sinus rhythm with second-degree type I atrioventricular block within one minute; D and E: ECG during syncope at 11:40 on June 24, 2019, showing torsades de pointes ventricular tachycardia (TdP), with TdP lasting approximately ten seconds before spontaneous conversion to sinus rhythm with ST-segment elevation or depression in some leads.

of DCBs in the treatment of STEMI patients is limited, and data on the use of DCBs[2-5] in PPCIs are limited. Researchers use DCBs after thrombus aspiration. However, thrombus aspiration cannot improve clinical outcomes[6,7] and may increase the risk of stroke[8]. Therefore, on the basis of conventional dual antiplatelet and anticoagulant therapy, we injected a small dose of a new thrombolytic agent (rhPro-UK) into the target side vessel through a TIG catheter before the percutaneous coronary intervention (PCI) to diminish the thrombus burden.

rhPro-UK is a specific plasminogen activator. In China, it has been approved for the treatment of acute myocardial infarction. rhPro-UK is the precursor of urokinase. rhPro-urokinase is inert in plasma and does not form covalent complexes with protease inhibitors in plasma. It is a non-tissue-type plasminogen activator. Its structure is a single peptide chain with a relatively long half-life, and it can continuously exert thrombolytic effects. At present, there is no guideline or consensus on the optimal method of intracoronary thrombolysis. Judging from limited data (Table 1), the intracoronary administration of a low dose of rhPro-UK is safe and effective and does not increase the risk of bleeding in patients with STEMI undergoing PPCIs. In the literature[9-16], predilated balloons with punctured membranes, microcatheters, mother-child catheters, and aspiration catheters are used to deliver rhPro-UK (10-20 mg) to the distal and proximal segments of the target lesion as well as the target point. These tools are used mostly during the operation (after the guide wire passes through and before stent implantation) (Table 1). This approach seems to be more accurate and efficient. However, the half-life of rhPro-UK is approximately 1.9 hours. In addition to taking effect immediately when the thrombus is in direct contact with the drug, a large part of the drug will inevitably participate in countless systemic circulations. Therefore, there may be no need for "targeted" drug administration. Administering the drug before the PCI instead of after the guidewire has passed through and the balloon has been dilated, is the most time-saving approach. For patients with STEMI, we exclude any contraindications for thrombolysis before the PCI, prepare for intracoronary thrombolysis, and once a high thrombus burden is confirmed during coronary angiography, we start the intracoronary thrombolysis procedure on the target side of the coronary artery and deliver the drug through the TIG catheter. Due to the presence of side holes, some rhPro-UK enters the bloodstream immediately after being injected through the TIG catheter. The TIG catheter allows quick drug delivery, so the onset of action is shortened. Moreover, it may also reduce the risks of thrombus displacement and distal embolization caused by the delivery of guide wires and catheters. When a TIG catheter is used, no additional consumables are needed for drug delivery, and the reperfusion time is shortened. In accordance with our previous application experience, 20 mg of rhPro-UK can be used to reopen acutely occluded blood vessels within 3 minutes at the shortest. Therefore, during the period of preparation for the PCI after coronary angiography is completed, the blood flow in the target vessels of some patients is restored. When the rhPro-UK is utilized in coronary arteries, thrombus aspiration is rarely needed and tirofiban is almost never required. We believe that compared with the other methods in Table 1, the theoretical advantages are obvious, but the short-term and long-term efficacies need to be further clarified by relevant randomized controlled studies.

Table 1 Comparison of studies on the intracoronary administration of recombinant human prourokinase in ST-segment elevation myocardial infarction patients

Ref.	Infusion route of rhPro-UK	Timing of infusion of rhPro-UK	rhPro-UK dosage (mg)	rhPro-UK input target lesion location	rhPro-UK Input possible additional consumables
Wu *et al* [9]	Thrombus aspiration *via* a catheter	After thrombus aspiration	10	D	Thrombus aspiration
Jiang *et al*[10]	Puncture the balloon catheter membrane with a needle	After balloon catheter dilation	10	D	No
Geng *et al*[11]	Puncture the balloon catheter membrane with a needle	After balloon catheter dilation	10	D	No
Huang *et al*[12]	Intracoronary catheter	After thrombus aspiration and predilation and before stent implantation	20	P	Thrombus aspiration *et al*
Wang *et al*[13]	Thrombus aspiration *via* a catheter	After thrombus aspiration	20	P	Thrombus aspiration
Cao *et al* [14]	Thrombus aspiration *via* a catheter	After thrombus aspiration	10	T	Thrombus aspiration
Ma *et al* [15]	Microcatheter *via* a catheter	After thrombus aspiration and before stent implantation	20	P	Microcatheter
Fu *et al* [16]	Microcatheter/child-in-mother catheter and/or pierced balloon *via* a catheter	After the guide wire passes	10-20+[1]	T	Microcatheter/child-in-mother catheter and/or pierced balloon

[1]Each injection dose of anisodamine was 4 mg.

D: Occlusion of the distal segment of the target vessel; P: Proximal to the infarct-related lesion; T: Target lesion location; rhPro-UK: Recombinant human prourokinase.

In the early stages, a significant drawback of percutaneous transluminal coronary angioplasty (PTCA) was acute occlusion and constrictive remodeling of the target vessel after PCI. Drug-coated balloon angioplasty (DBA) is linked to the same pain points, so comprehensive improvements in drugs, consumables, and techniques are needed. Moreover, researchers have limited experience in using DBA for de novo coronary lesions and large vessel lesions and particularly limited experience in using DBA for treating STEMI, as most cases represent the tentative use of DBA in a small number of patients with a high risk of bleeding. We believe that modern PTCA is significantly different from traditional PTCA. Specifically, alterations in dual antiplatelet drugs and standardized anticoagulation measures have reduced the risk of occlusion caused by thrombosis. However, there remains a risk of acute and chronic occlusion caused by elastic recoil and constrictive remodeling. There are limited measures to decrease this risk. The use of nitrates and calcium channel antagonists may have a preventive effect. Other factors that may induce coronary artery spasm need to be evaded.

CBA can effectively reduce elastic recoil after balloon inflation[17], reduce high-risk dissection and residual stenosis, and lower the target vessel revascularization rate[18], thereby overcoming acute elastic recoil after traditional balloon angioplasty (TBA). Especially in cases of complex lesions such as calcification and fibrosis, CBA may increase the lumen diameter and more effectively restore blood flow. CBA can neatly cut the vascular endothelium and subendothelial tissue, thereby reducing or controlling the progression of dissection and increasing the likelihood that the DCB will pass and therefore make direct contact with the drug on the surface of DCBs and the subendothelial tissue of blood vessels, playing a synergistic role in exerting the effect of DCBs and reducing the long-term risk of restenosis. On the basis of our clinical practice, the results of different PTCA and stentless techniques for different target lesions in the same patient significantly differ. TBA + CBA + DBA is superior to TBA + DBA, which is superior to TBA only.

The application of DCBs in the treatment of de novo coronary artery lesions remains controversial[1], with most studies focusing on the application of such balloons in the treatment of lesions in coronary vessels with diameters less than 2.75 mm. Clinical trials[19] have demonstrated that DCBs are noninferior to drug-eluting stents (DESs) in terms of the incidence of major cardiovascular events within the first 12 months after treatment. However, the safety and efficacy of DCBs in the treatment of new coronary lesions with diameters greater than 3 mm remain unclear[20]. Nakamura *et al* [21] compared the feasibility of DESs and paclitaxel-coated balloons (PCBs) angioplasty in treating large coronary vessels with de novo coronary lesions [reference vessel diameter (RVD) ≥ 2.75 mm pre- or post-procedure] and reported a late lumen gain of 44.1% in the PCBs group over a 4-year follow-up period.

Herein, we have reported the case of a young patient with STEMI and a history of gastric ulcers. The initial ECG indicated notable instability. For patients with new coronary artery lesions, a high risk of bleeding, and a RVD > 3 mm, a PPCI is regarded as challenging. In particular, whether patients can tolerate long-term dual antiplatelet therapy after surgery is a question that must be considered. After discussion with the patient, we administered a low dose of a third-generation thrombolytic agent (rhPro-UK) to clear the coronary artery thrombus[9,22]. By using a cutting balloon to reduce elastic recoil after conventional predilation of the target vessel combined with PDEB angioplasty, satisfactory

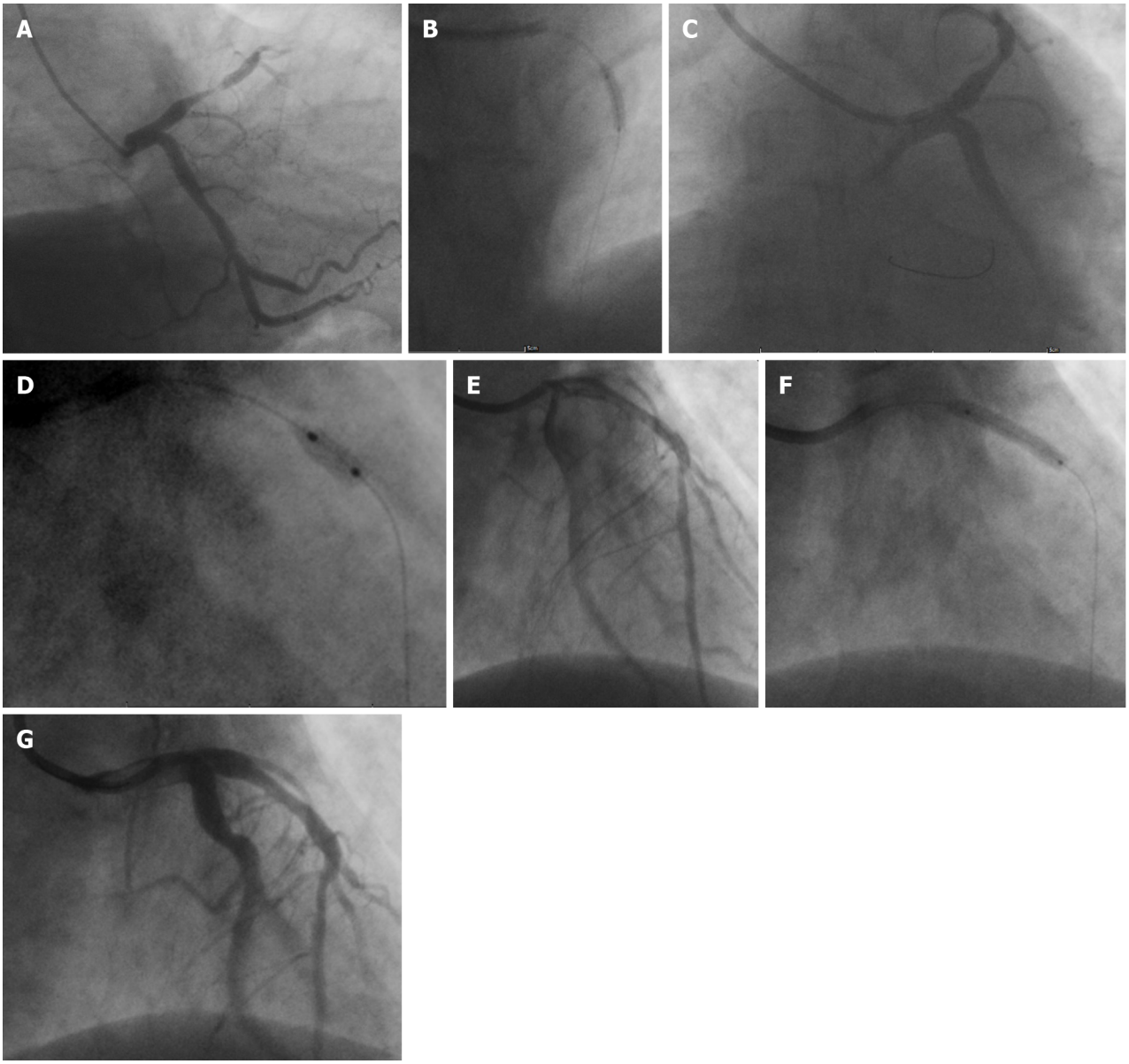


Figure 3 Procedure of target vessel operation. A: Subtotal occlusion with thrombus formation in the proximal segment of the left anterior descending artery; B: Predilation using a TREK 2.5 mm × 15 mm balloon; C: Significant recoil at the stenotic site; D: Predilation using a Boston Scientific Flextome™ Cutting Balloon 3.0 mm × 6 mm; E: Approximately 20% residual stenosis after predilation; F: Dilation using a paclitaxel drug-eluting balloon (QINGZHOU Bingo DEB3020); G: Approximately 40% residual stenosis.

short-term and long-term effects were achieved. The minimum diameter of the lumen increased by 2.8 mm before treatment and 2.3 mm after the operation. No complications emerged during or after the operation. Although the incidence of immediate residual stenosis was approximately 40%, the 4-year follow-up revealed good long-term effects, and no late lumen loss occurred[23].

Positive remodeling at the proximal and distal ends of the target lesion, along with negative remodeling of the target lesion itself, resulted in an unnatural and incongruous appearance of the proximal segment of the anterior descending artery after the procedure. Nevertheless, at the 4-year follow-up, significant positive remodeling of the target lesion was observed[24], and mild positive remodeling at both ends made the target lesion and its surrounding areas appear smooth. The vascular lumens at the proximal end of the target lesion, the target point, and the distal end of the target lesion were compared, and the net gains after 4 years were 0.26 mm, 3.00 mm, and 0.17 mm, respectively. The morphology of the target vessel was almost normal (Figure 4). This may be an important reason why the patient stopped taking medicine and smoked again in the later stage without adverse events. Since the patient did not undergo stent implantation and the morphology and function of the target vessel returned to normal, relevant drug treatment can be reduced, thereby reducing the risk of dual antiplatelet therapy required for stents and drug withdrawal in the later stage[25]. Notably, DCBs should not be used in target lesions with significant thrombi in myocardial infarction patients, as doing so may inhibit drug delivery to the vessel wall[26]. We employed rhPro-UK to clear the thrombus in the target lesion as a preparatory step for further treatment. Previously, DCBs were only recommended for the treatment of small vessel lesions, in-stent restenosis, patients at high risk of bleeding, and other special populations. However, more indications

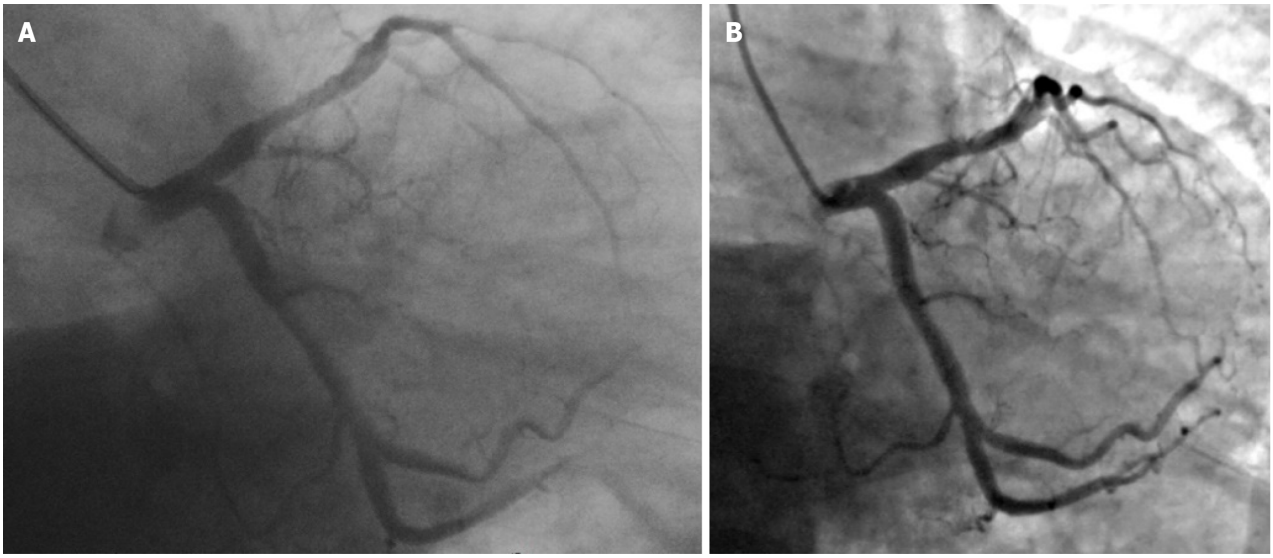


Figure 4 Comparison of the left coronary angiography images obtained in the same position. A: On June 24, 2019, the residual stenosis in the proximal segment of the left anterior descending artery (LAD) after the primary percutaneous coronary intervention was approximately 40%, and the net lumen gain at the site of the most substantial stenosis was approximately 2.3 mm (RAO 30.0°, CAU 30.0°); B: On June 19, 2023, approximately 25% residual stenosis was observed in the proximal LAD, and the net lumen gain at the site of the most substantial stenosis was approximately 3.0 mm (RAO 30.4°, CAU 29.9°).

have been added[26] despite limited knowledge on the use of DCBs for de novo coronary lesions in large vessels. In cases of elastic recoil or severe dissection, stent implantation was performed[27]. In this case, with the occurrence of elastic recoil after predilation, the residual stenosis was < 30% after a cutting balloon was used. Although elastic recoil recurred after PDEB, the post-procedure residual stenosis was > 30%[26,28], thus alternative interventional treatment should be contemplated. However, in this case, no further intervention was considered. At the 4-year follow-up, stenosis of the target lesion was approximately 25%, indicating a favorable late net increase in the lumen diameter. While the clinical outcomes at 2 years after nonstent DCB angioplasty are excellent for patients with residual stenosis < 50%[3], we believe that patients with 30–50% residual stenosis should undergo functional assessment. Unfortunately, neither FFR nor iFR was measured to further confirm whether residual stenosis was significant[29]. Evidence obtained from our clinical practice shows that standardized DCB treatment is beneficial for bifurcation lesions, large coronary artery PCI, and complex coronary interventions. We expect that precise and functional assessments of the coronary artery can be used to guide DCB treatment, especially for large vessel lesions.

CONCLUSION

The utilization of a new-generation intracoronary thrombolytic agent for thrombus clearance in target lesions, followed by thorough predilation (including CBA) and PDEB angioplasty, is a feasible PPCI strategy for young STEMI patients at high risk of bleeding (including patients with large vessel lesions). This combination has a synergistic effect and is worthy of further study.

ACKNOWLEDGEMENTS

We thank Gang Luo from the Department of Science and Education and the Medical Record Management Department of our hospital for supporting this study in terms of material preparation and other work and Liu Jian from the Department of Medical Laboratory for supporting the revision of the article.

FOOTNOTES

Author contributions: She LQ, Gao DK and Hong L contributed to manuscript writing; Gao DK and Hong L contributed to manuscript editing and data analysis; Gao DK, She LQ and Wang HZ contributed to data visualization; Tian Y, Wang HZ and Huang S contributed to data collection; She LQ contributed to conceptualization; all authors have read and agreed to the final version for submission. She LQ and Hong L contributed equally to this work as co-first authors.

Supported by Mianyang Health Commission 2019 Scientific Research Encouragement Project, No. 201948.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any

accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country of origin: China

ORCID number: Li-Qiong She 0009-0004-6399-0627; De-Kui Gao 0000-0002-0324-9712; Le Hong 0009-0006-8327-5342; Yin Tian 0009-0008-3146-1914; Hui-Zhen Wang 0009-0006-8188-0979; Sheng Huang 0009-0000-6307-9797.

S-Editor: Qu XL
L-Editor: A
P-Editor: Zheng XM

REFERENCES

1 **Zilio F**, Verdoia M, De Angelis MC, Zucchelli F, Borghesi M, Rognoni A, Bonmassari R. Drug Coated Balloon in the Treatment of De Novo Coronary Artery Disease: A Narrative Review. *J Clin Med* 2023; **12** [PMID: 37297857 DOI: 10.3390/jcm12113662]

2 **Nishihira K**, Asano Y, Shibata Y. Efficacy of paclitaxel-coated balloon angioplasty combined with intensive lipid-lowering therapy for ST-segment elevation myocardial infarction: insights from near-infrared spectroscopy. *Eur Heart J* 2024; **45**: 1576 [PMID: 38366009 DOI: 10.1093/eurheartj/ehae073]

3 **Niehe SR**, Vos NS, Van Der Schaaf RJ, Amoroso G, Herrman JR, Patterson MS, Slagboom T, Vink MA. Two-Year Clinical Outcomes of the REVELATION Study: Sustained Safety and Feasibility of Paclitaxel-Coated Balloon Angioplasty Versus Drug-Eluting Stent in Acute Myocardial Infarction. *J Invasive Cardiol* 2022; **34**: E39-E42 [PMID: 34792482 DOI: 10.25270/jic/20.00741]

4 **Vos NS**, Fagel ND, Amoroso G, Herrman JR, Patterson MS, Piers LH, van der Schaaf RJ, Slagboom T, Vink MA. Paclitaxel-Coated Balloon Angioplasty Versus Drug-Eluting Stent in Acute Myocardial Infarction: The REVELATION Randomized Trial. *JACC Cardiovasc Interv* 2019; **12**: 1691-1699 [PMID: 31126887 DOI: 10.1016/j.jcin.2019.04.016]

5 **Vos NS**, van der Schaaf RJ, Amoroso G, Herrman JP, Patterson MS, Slagboom T, Vink MA. REVascularization with paclitaxEL-coated balloon angioplasty versus drug-eluting stenting in acute myocardial infarcTION-A randomized controlled trial: Rationale and design of the REVELATION trial. *Catheter Cardiovasc Interv* 2016; **87**: 1213-1221 [PMID: 26370515 DOI: 10.1002/ccd.26241]

6 **Jolly SS**, James S, Džavík V, Cairns JA, Mahmoud KD, Zijlstra F, Yusuf S, Olivecrona GK, Renlund H, Gao P, Lagerqvist B, Alazzoni A, Kedev S, Stankovic G, Meeks B, Frøbert O. Thrombus Aspiration in ST-Segment-Elevation Myocardial Infarction: An Individual Patient Meta-Analysis: Thrombectomy Trialists Collaboration. *Circulation* 2017; **135**: 143-152 [PMID: 27941066 DOI: 10.1161/CIRCULATIONAHA.116.025371]

7 **Lagerqvist B**, Fröbert O, Olivecrona GK, Gudnason T, Maeng M, Alström P, Andersson J, Calais F, Carlsson J, Collste O, Götberg M, Hårdhammar P, Ioanes D, Kallryd A, Linder R, Lundin A, Odenstedt J, Omerovic E, Puskar V, Tödt T, Zelleroth E, Östlund O, James SK. Outcomes 1 year after thrombus aspiration for myocardial infarction. *N Engl J Med* 2014; **371**: 1111-1120 [PMID: 25176395 DOI: 10.1056/NEJMoa1405707]

8 **Jolly SS**, Cairns JA, Yusuf S, Rokoss MJ, Gao P, Meeks B, Kedev S, Stankovic G, Moreno R, Gershlick A, Chowdhary S, Lavi S, Niemela K, Bernat I, Cantor WJ, Cheema AN, Steg PG, Welsh RC, Sheth T, Bertrand OF, Avezum A, Bhindi R, Natarajan MK, Horak D, Leung RC, Kassam S, Rao SV, El-Omar M, Mehta SR, Velianou JL, Pancholy S, Džavík V; TOTAL Investigators. Outcomes after thrombus aspiration for ST elevation myocardial infarction: 1-year follow-up of the prospective randomised TOTAL trial. *Lancet* 2016; **387**: 127-135 [PMID: 26474811 DOI: 10.1016/S0140-6736(15)00448-1]

9 **Wu Y**, Fu X, Feng Q, Gu X, Hao G, Fan W, Jiang Y. Efficacy and safety of intracoronary prourokinase during percutaneous coronary intervention in treating ST-segment elevation myocardial infarction patients: a randomized, controlled study. *BMC Cardiovasc Disord* 2020; **20**: 308 [PMID: 32590944 DOI: 10.1186/s12872-020-01584-0]

10 **Jiang W**, Xiong X, Du X, Ma H, Li W, Cheng F. Safety and efficacy study of prourokinase injection during primary percutaneous coronary intervention in acute ST-segment elevation myocardial infarction. *Coron Artery Dis* 2021; **32**: 25-30 [PMID: 32310850 DOI: 10.1097/MCA.0000000000000898]

11 **Geng W**, Zhang Q, Liu J, Tian X, Zhen L, Song D, Yang Y, Meng H, Wang Y, Chen J. A randomized study of prourokinase during primary percutaneous coronary intervention in acute ST-segment elevation myocardial infarction. *J Interv Cardiol* 2018; **31**: 136-143 [PMID: 29171086 DOI: 10.1111/joic.12461]

12 **Huang D**, Qian J, Liu Z, Xu Y, Zhao X, Qiao Z, Fang W, Jiang L, Hu W, Shen C, Liang C, Zhang Q, Ge J. Effects of Intracoronary Prourokinase or Tirofiban on Coronary Flow During Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction: A Multi-Center, Placebo-Controlled, Single-Blind, Randomized Clinical Trial. *Front Cardiovasc Med* 2021; **8**: 710994 [PMID: 34409082 DOI: 10.3389/fcvm.2021.710994]

13 **Wang X**, Liu H, Wu H, Xiao Y, Bai S, Li X, Li X, Zhang L, Chen T, Li H, Liu J, Du R. Safety and efficacy of intracoronary prourokinase administration in patients with high thrombus burden. *Coron Artery Dis* 2020; **31**: 493-499 [PMID: 32073417 DOI: 10.1097/MCA.0000000000000853]

14 **Cao M**, Wang Z, Meng X, Xu Z, Gao J, Zhu W, Yu S, Zhang H. Effects of intracoronary low-dose prourokinase administration on ST-segment elevation in patients with myocardial infarction and a high thrombus burden: a randomized controlled trial. *J Int Med Res* 2022; **50**: 3000605221139723 [PMID: 36514961 DOI: 10.1177/03000605221139723]

15 **Ma FH**, Qiao ZY. [Effect of thrombus aspiration combined with microcatheter targeted application of recombinant human prourokinase on myocardial blood perfusion in patients with ST elevated acute myocardial infarction]. *Linchuang Xinxueguanbing Zazhi* 2020; **36**: 1088-1092 [DOI: 10.13201/j.issn.1001-1439.2020.12.005]

16 **Fu Y**, Gu XS, Hao GZ, Jiang YF, Fan WZ, Fan YM, Wei QM, Fu XH, Li YJ. Comparison of myocardial microcirculatory perfusion after catheter-administered intracoronary thrombolysis with anisodamine versus standard thrombus aspiration in patients with ST-elevation myocardial infarction. *Catheter Cardiovasc Interv* 2019; **93**: 839-845 [PMID: 30773796 DOI: 10.1002/ccd.28112]

17 **Li B**, Ding Y, Tian F, Chen W, Han T, Chen Y. Assessment of a Drug-Eluting Balloon for the Treatment of de novo Coronary Lesions Guided by Optical Coherence Tomography: Study Protocol for a Randomized Controlled Trial. *Cardiology* 2017; **136**: 252-257 [PMID: 27846629 DOI: 10.1159/000452125]

18 **Izumi M**, Tsuchikane E, Funamoto M, Kobayashi T, Sumitsuji S, Otsuji S, Sakurai M, Kobayashi T, Awata N. Final results of the CAPAS trial. *Am Heart J* 2001; **142**: 782-789 [PMID: 11685163 DOI: 10.1067/mhj.2001.119129]

19 **Jeger RV**, Farah A, Ohlow MA, Mangner N, Möbius-Winkler S, Leibundgut G, Weilenmann D, Wöhrle J, Richter S, Schreiber M, Mahfoud F, Linke A, Stephan FP, Mueller C, Rickenbacher P, Coslovsky M, Gilgen N, Osswald S, Kaiser C, Scheller B; BASKET-SMALL 2 Investigators. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. *Lancet* 2018; **392**: 849-856 [PMID: 30170854 DOI: 10.1016/S0140-6736(18)31719-7]

20 **Rosenberg M**, Waliszewski M, Krackhardt F, Chin K, Wan Ahmad WA, Caramanno G, Milazzo D, Nuruddin AA, Liew HB, Maskon O, Bento A, Macia JC, Frey N. Drug Coated Balloon-Only Strategy in De Novo Lesions of Large Coronary Vessels. *J Interv Cardiol* 2019; **2019**: 6548696 [PMID: 31772539 DOI: 10.1155/2019/6548696]

21 **Nakamura H**, Ishikawa T, Mizutani Y, Yamada K, Ukaji T, Kondo Y, Shimura M, Aoki H, Hisauchi I, Itabashi Y, Nakahara S, Kobayashi S, Taguchi I. Clinical and Angiographic Outcomes of Elective Paclitaxel-Coated Balloon Angioplasty in Comparison with Drug-Eluting Stents for De Novo Coronary Lesions in Large Vessels. *Int Heart J* 2023; **64**: 145-153 [PMID: 37005310 DOI: 10.1536/ihj.22-498]

22 **Fan G**, Wu XG, Jiao WP, Zhang HK, Guo DL. Safety and efficacy of intracoronary recombinant human prourokinase administration in patients with acute myocardial infarction and STsegment elevation: A metaanalysis of randomized controlled trials. *Exp Ther Med* 2023; **25**: 40 [PMID: 36569445 DOI: 10.3892/etm.2022.11739]

23 **Wang Z**, Yin Y, Li J, Qi W, Yu B, Xu Z, Zhu W, Yang F, Cao M, Zhang H. New Ultrasound-Controlled Paclitaxel Releasing Balloon vs. Asymmetric Drug-Eluting Stent in Primary ST-Segment Elevation Myocardial Infarction - A Prospective Randomized Trial. *Circ J* 2022; **86**: 642-650 [PMID: 34759131 DOI: 10.1253/circj.CJ-21-0315]

24 **Her AY**, Ann SH, Singh GB, Kim YH, Okamura T, Garg S, Koo BK, Shin ES. Serial Morphological Changes of Side-Branch Ostium after Paclitaxel-Coated Balloon Treatment of De Novo Coronary Lesions of Main Vessels. *Yonsei Med J* 2016; **57**: 606-613 [PMID: 26996558 DOI: 10.3349/ymj.2016.57.3.606]

25 **Elgendy IY**, Gad MM, Elgendy AY, Mahmoud A, Mahmoud AN, Cuesta J, Rivero F, Alfonso F. Clinical and Angiographic Outcomes With Drug-Coated Balloons for De Novo Coronary Lesions: A Meta-Analysis of Randomized Clinical Trials. *J Am Heart Assoc* 2020; **9**: e016224 [PMID: 32410493 DOI: 10.1161/JAHA.120.016224]

26 **Jeger RV**, Eccleshall S, Wan Ahmad WA, Ge J, Poerner TC, Shin ES, Alfonso F, Latib A, Ong PJ, Rissanen TT, Saucedo J, Scheller B, Kleber FX; International DCB Consensus Group. Drug-Coated Balloons for Coronary Artery Disease: Third Report of the International DCB Consensus Group. *JACC Cardiovasc Interv* 2020; **13**: 1391-1402 [PMID: 32473887 DOI: 10.1016/j.jcin.2020.02.043]

27 **Kleber FX**, Rittger H, Bonaventura K, Zeymer U, Wöhrle J, Jeger R, Levenson B, Möbius-Winkler S, Bruch L, Fischer D, Hengstenberg C, Pörner T, Mathey D, Scheller B. Drug-coated balloons for treatment of coronary artery disease: updated recommendations from a consensus group. *Clin Res Cardiol* 2013; **102**: 785-797 [PMID: 23982467 DOI: 10.1007/s00392-013-0609-7]

28 **Cox DA**, Stone GW, Grines CL, Stuckey T, Cohen DJ, Tcheng JE, Garcia E, Guagliumi G, Iwaoka RS, Fahy M, Turco M, Lansky AJ, Griffin JJ, Mehran R; CADILLAC Investigators. Outcomes of optimal or "stent-like"balloon angioplasty in acutemyocardial infarction: the CADILLAC trial. *J Am Coll Cardiol* 2003; **42**: 971-977 [PMID: 13678914 DOI: 10.1016/s0735-1097(03)00911-2]

29 **Chung JH**, Shin ES, Her AY, Lee JM, Doh JH, Nam CW, Koo BK. Instantaneous wave-free ratio-guided paclitaxel-coated balloon treatment for de novo coronary lesions. *Int J Cardiovasc Imaging* 2020; **36**: 179-185 [PMID: 31598811 DOI: 10.1007/s10554-019-01707-5]

World Journal of Cardiology

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

World J Cardiol 2024 September 26; 16(9): 542-545

DOI: 10.4330/wjc.v16.i9.542

ISSN 1949-8462 (online)

LETTER TO THE EDITOR

Left bundle branch area pacing: A new era of cardiac resynchronization therapy?

Carlo Alberto Caruzzo, Elia Rigamonti, Francesca Romana Scopigni

Specialty type: Cardiac and cardiovascular systems

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

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade D, Grade D

Novelty: Grade C, Grade C

Creativity or Innovation: Grade C, Grade C

Scientific Significance: Grade C, Grade C

P-Reviewer: Batta A

Received: June 16, 2024

Revised: July 30, 2024

Accepted: August 26, 2024

Published online: September 26, 2024

Processing time: 94 Days and 15.5 Hours

Carlo Alberto Caruzzo, Elia Rigamonti, Francesca Romana Scopigni, Department of Cardiology, Istituto Cardiocentro del Ticino, Lugano 6900, TI, Switzerland

Co-corresponding authors: Carlo Alberto Caruzzo and Elia Rigamonti.

Corresponding author: Carlo Alberto Caruzzo, MD, Doctor, Department of Cardiologia, Istituto Cardiocentro del Ticino, Via Tesserete, Lugano 6900, TI, Switzerland. carloalberto.caruzzo@gmail.com

Abstract

The recent systematic review and meta-analysis provided a comprehensive focus on the current state of cardiac resynchronization therapy (CRT). The authors determined the feasibility of physiological left bundle branch area pacing (LBBAP) in patients indicated for CRT through a careful analysis of trials. They found that LBBAP was associated with significant reductions in QRS duration, New York Heart Association functional class, B-type natriuretic peptide levels, and pacing thresholds as well as improvements in echocardiographic parameters compared to biventricular pacing.

Key Words: Left bundle branch pacing; Biventricular pacing; QRS duration; Left ventricular ejection fraction; Heart failure

Core Tip: In heart failure, conduction defects, such as left bundle branch block, are common and result in regionally delayed electrical activation. Traditional pacing modalities, such as biventricular pacing, are non-physiological and directly stimulate the common myocardium, which may limit the clinical response. Left bundle branch area pacing bypasses the pathological region of the cardiac conduction system and leads to near-physiological or true conduction system pacing for patients needing ventricular pacing for bradycardia or heart failure. There is increasing interest in physiological pacing techniques that can directly activate the specialized conduction system.

Citation: Caruzzo CA, Rigamonti E, Scopigni FR. Left bundle branch area pacing: A new era of cardiac resynchronization therapy? *World J Cardiol* 2024; 16(9): 542-545
URL: https://www.wjgnet.com/1949-8462/full/v16/i9/542.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i9.542

TO THE EDITOR

Current state and challenges of cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) with biventricular pacing (BiVP) is an established therapy for patients with left ventricular ejection fraction ≤ 35%, heart failure symptoms, and left bundle branch block with a QRS duration ≥ 150 ms or expected frequent ventricular pacing of > 20%-40%[1-4]. Over the last 25 years several randomized controlled trials have shown that CRT with BiVP reduces heart failure hospitalization (HFH) and all-cause mortality[4-7].

Left bundle branch area pacing (LBBAP) is a newer procedure for CRT that has shown promising results. A retrospective study demonstrated a statistically significant reduction in the composite outcome of death and hospitalization in patients receiving LBBAP[8]. Moreover, stimulation of the left bundle branch is a more physiological approach. It leads to a significant reduction in QRS duration[8], resulting in improved echocardiographic parameters such as ejection fraction and left ventricular end-systolic volume. This in turn translates to clinical improvements such as New York Heart Association (NYHA) functional class and quality of life[9].

LBBAP is the most recent technique established for conduction system pacing. It overcame several limitations of its predecessor, His-bundle pacing (HBP). The stimulation of the left bundle branch often shows lower thresholds, resulting in longer battery life compared to HBP[10]. Despite the initial success of the first conduction system pacing through HBP, widespread use of CRT was hindered by issues such as lead instability, dislodgements, a steep learning curve, and rapid battery depletion.

The aim of this editorial was to expound on the recent meta-analysis regarding LBBAP by Yasmin *et al*[11] in the *World Journal of Cardiology*. LBBAP is a safe and effective means for achieving physiological conduction system pacing. It involves the placement of the pacing lead tip into the left side of the interventricular septum, 15-20 mm beyond the tricuspid annulus on fluoroscopic imaging[12]. Appropriate lead placement is confirmed through various criteria, including left ventricle activation time < 80 ms and V6-V1 interpeak interval > 44 ms[13]. Left ventricle activation time is illustrated in Figure 1.

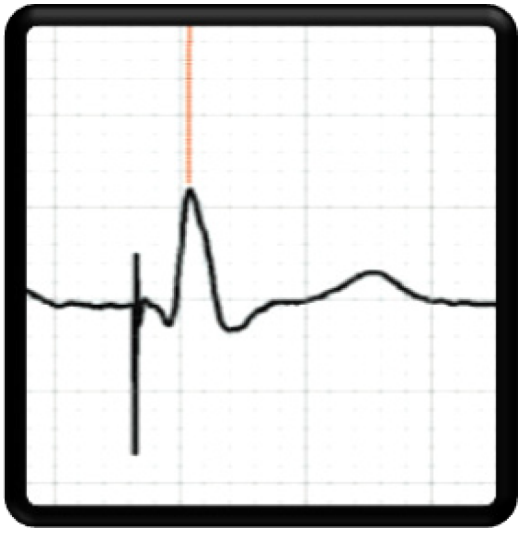


Figure 1 Left ventricle activation time is the time from the pacing artifact to the peak R wave in V6. The difference between V6 and V1 R-wave peak times is the interpeak interval. It helps clinicians distinguish between selective and non-selective left bundle branch area pacing and septal pacing. The larger the interval, the less selective the catheter will be with respect to the conduction system.

The current literature suggests that conduction system pacing is a valid alternative in terms of safety[14]. LBBAP results in a lower risk of all-cause mortality or HFH compared to BiVP and left ventricular septal pacing (LVSP), while LVSP and BiVP have a similar risk. LVSP had a higher risk of all-cause mortality compared to both LBBAP and BiVP. The echocardiographic response and super response were highest for patients treated with LBBP[15].

Choosing the ideal site for CRT is often difficult using conduction system pacing, especially in patients without left bundle branch block due to the risk of conduction block progression distal to the pacing site. Therefore, HBP and epicardial left ventricular (LV) pacing or LBBAP and epicardial LV pacing may be better options to optimize results in patients without left bundle branch block[16].

KEY ASPECTS OF LBBAP

Yasmin *et al*[11] reported in the meta-analysis that the baseline characteristics of the population were well-balanced according to sex (49.7% female). Subzposh *et al*[17] reported that females are better responders to resynchronization therapy. The meta-analysis included 389 patients with heart failure and left bundle branch block from six studies. Only one of the studies was randomized, and the median follow-up was 9 months. QRS duration was the primary outcome and was significantly reduced by LBBAP. This result is fundamentally important in corroborating the effectiveness of direct stimulation of the conduction system.

The propagation speed through the myocardium is 0.15-1.00 m/s, which is 25% of the physiological speed of the conduction pathways of the heart (3.00-4.00 m/s)[18], highlighting the inherent superiority of physiological pacing through the native conduction system. QRS duration reduction leads to reverse remodeling and avoids interventricular mechanical delay. Patients with greater QRS shortening (> 14 ms) after CRT have lower mortality and hospitalizations compared to those with smaller QRS reductions[19]. Implementing a general strategy of CRT device optimization for shorter QRS duration should lead to better clinical outcomes.

Secondary outcomes included pacing threshold, NYHA functional class, B-type natriuretic peptide level, and echocardiographic parameters such as left ventricular ejection fraction, left ventricular end-diastolic diameter, and left ventricular end-systolic diameter. Five of the included studies reported a significantly reduced pacing threshold in LBBAP compared to BiVP, which also remained considerably lower at the 6-month and 12-month follow-up.

CONCLUSION

We are in full support of the conclusions of Yasmin *et al*[11] about LBBAP as a promising modality, and we await with fervid anticipation the results of ongoing randomized controlled trials. The advantages of LBBAP over BiVP have emerged in recent years and include better ventricular electrical and mechanical resynchronization and improvements in cardiac function, NYHA function class, and clinical outcomes.

Despite these encouraging results, widespread adoption of LBBAP depends on the improvement of tools and further validation of its efficacy in large randomized clinical trials. Furthermore, randomized clinical trials with long-term follow-up are necessary to confirm the clinical benefits of conduction system pacing CRT compared with BiVP in CRT candidates. One of the biggest challenges will be to demonstrate whether this benefit translates into a sustained reduction in HFH or mortality.

FOOTNOTES

Author contributions: Caruzzo CA wrote the original draft; Rigamonti E contributed to conceptualization, writing, reviewing, editing, and received the original invitation to write the editorial; Scopigni FR participated in drafting the manuscript and critically revised its content; Caruzzo CA and Rigamonti E collaborated equally on the paper and their joint efforts in pre-publication administrative, intellectual and supervisory activities were crucial in generation and publication of the final letter; all authors have read and approved the final version of the manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Country of origin: Switzerland

ORCID number: Carlo Alberto Caruzzo 0009-0000-1328-9876.

S-Editor: Luo ML
L-Editor: A
P-Editor: Yuan YY

REFERENCES

1 **Cheng A**, Helm RH, Abraham TP. Pathophysiological mechanisms underlying ventricular dyssynchrony. *Europace* 2009; **11** Suppl 5: v10-v14 [PMID: 19861385 DOI: 10.1093/europace/eup272]

2 **Zhang S**, Zhou X, Gold MR. Left Bundle Branch Pacing: JACC Review Topic of the Week. *J Am Coll Cardiol* 2019; **74**: 3039-3049 [PMID: 31865972 DOI: 10.1016/j.jacc.2019.10.039]

3 **Cleland JG**, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005; **352**: 1539-

1549 [PMID: 15753115 DOI: 10.1056/NEJMoa050496]

4 **Bristow MR**, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; **350**: 2140-2150 [PMID: 15152059 DOI: 10.1056/NEJMoa032423]

5 **Jones S**, Lumens J, Sohaib SMA, Finegold JA, Kanagaratnam P, Tanner M, Duncan E, Moore P, Leyva F, Frenneaux M, Mason M, Hughes AD, Francis DP, Whinnett ZI; BRAVO Investigators. Cardiac resynchronization therapy: mechanisms of action and scope for further improvement in cardiac function. *Europace* 2017; **19**: 1178-1186 [PMID: 27411361 DOI: 10.1093/europace/euw136]

6 **Sapp JL**, Sivakumaran S, Redpath CJ, Khan H, Parkash R, Exner DV, Healey JS, Thibault B, Sterns LD, Lam NHN, Manlucu J, Mokhtar A, Sumner G, McKinlay S, Kimber S, Mondesert B, Talajic M, Rouleau J, McCarron CE, Wells G, Tang ASL; RAFT Long-Term Study Team. Long-Term Outcomes of Resynchronization-Defibrillation for Heart Failure. *N Engl J Med* 2024; **390**: 212-220 [PMID: 38231622 DOI: 10.1056/NEJMoa2304542]

7 **Authors/Task Force Members**, McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022; **24**: 4-131 [PMID: 35083827 DOI: 10.1002/ejhf.2333]

8 **Vijayaraman P**, Sharma PS, Cano Ó, Ponnusamy SS, Herweg B, Zanon F, Jastrzebski M, Zou J, Chelu MG, Vernooy K, Whinnett ZI, Nair GM, Molina-Lerma M, Curila K, Zalavadia D, Haseeb A, Dye C, Vipparthy SC, Brunetti R, Moskal P, Ross A, van Stipdonk A, George J, Qadeer YK, Mumtaz M, Kolominsky J, Zahra SA, Golian M, Marcantoni L, Subzposh FA, Ellenbogen KA. Comparison of Left Bundle Branch Area Pacing and Biventricular Pacing in Candidates for Resynchronization Therapy. *J Am Coll Cardiol* 2023; **82**: 228-241 [PMID: 37220862 DOI: 10.1016/j.jacc.2023.05.006]

9 **Fu Y**, Liu P, Jin L, Li Y, Zhang Y, Qin X, Zheng Q. Left bundle branch area pacing: A promising modality for cardiac resynchronization therapy. *Front Cardiovasc Med* 2022; **9**: 901046 [PMID: 36465440 DOI: 10.3389/fcvm.2022.901046]

10 **Padala SK**, Master VM, Terricabras M, Chiocchini A, Garg A, Kron J, Shepard R, Kalahasty G, Azizi Z, Tsang B, Khaykin Y, Pantano A, Koneru JN, Ellenbogen KA, Verma A. Initial Experience, Safety, and Feasibility of Left Bundle Branch Area Pacing: A Multicenter Prospective Study. *JACC Clin Electrophysiol* 2020; **6**: 1773-1782 [PMID: 33357573 DOI: 10.1016/j.jacep.2020.07.004]

11 **Yasmin F**, Moeed A, Ochani RK, Raheel H, Awan MAE, Liaquat A, Saleem A, Aamir M, Hawwa N, Surani S. Left bundle branch pacing vs biventricular pacing in heart failure patients with left bundle branch block: A systematic review and meta-analysis. *World J Cardiol* 2024; **16**: 40-48 [PMID: 38313392 DOI: 10.4330/wjc.v16.i1.40]

12 **Lewis NDH**, Cheung CC. Left Bundle Branch Area Pacing Leading the Way: Emerging Trends in Cardiac Pacing. *Can J Cardiol* 2024; S0828-282X(24)00204 [PMID: 38490448 DOI: 10.1016/j.cjca.2024.02.031]

13 **Ponnusamy SS**, Arora V, Namboodiri N, Kumar V, Kapoor A, Vijayaraman P. Left bundle branch pacing: A comprehensive review. *J Cardiovasc Electrophysiol* 2020; **31**: 2462-2473 [PMID: 32681681 DOI: 10.1111/jce.14681]

14 **Vijayaraman P**, Pokharel P, Subzposh FA, Oren JW, Storm RH, Batul SA, Beer DA, Hughes G, Leri G, Manganiello M, Jastremsky JL, Mroczka K, Johns AM, Mascarenhas V. His-Purkinje Conduction System Pacing Optimized Trial of Cardiac Resynchronization Therapy vs Biventricular Pacing: HOT-CRT Clinical Trial. *JACC Clin Electrophysiol* 2023; **9**: 2628-2638 [PMID: 37715742 DOI: 10.1016/j.jacep.2023.08.003]

15 **Zhu H**, Qin C, Du A, Wang Q, He C, Zou F, Li X, Tao J, Wang C, Liu Z, Xue S, Zeng J, Qian Z, Wang Y, Hou X, Ellenbogen KA, Gold MR, Yao Y, Zou J, Fan X. Comparisons of long-term clinical outcomes with left bundle branch pacing, left ventricular septal pacing, and biventricular pacing for cardiac resynchronization therapy. *Heart Rhythm* 2024; **21**: 1342-1353 [PMID: 38461922 DOI: 10.1016/j.hrthm.2024.03.007]

16 **Batta A**, Hatwal J. Left bundle branch pacing set to outshine biventricular pacing for cardiac resynchronization therapy? *World J Cardiol* 2024; **16**: 186-190 [PMID: 38690215 DOI: 10.4330/wjc.v16.i4.186]

17 **Subzposh FA**, Sharma PS, Cano Ó, Ponnusamy SS, Herweg B, Zanon F, Jastrzebski M, Zou J, Chelu MG, Vernooy K, Whinnett ZI, Nair GM, Molina-Lerma M, Curila K, Ellenbogen KA, Vijayaraman P. Sex-Specific Outcomes of LBBAP Versus Biventricular Pacing: Results From I-CLAS. *JACC Clin Electrophysiol* 2024; **10**: 96-105 [PMID: 37737782 DOI: 10.1016/j.jacep.2023.08.026]

18 **Prinzen FW**, Hunter WC, Wyman BT, McVeigh ER. Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. *J Am Coll Cardiol* 1999; **33**: 1735-1742 [PMID: 10334450 DOI: 10.1016/s0735-1097(99)00068-6]

19 **Borgquist R**, Marinko S, Platonov PG, Wang L, Chaudhry U, Brandt J, Mörtsell D. Maximizing QRS duration reduction in contemporary cardiac resynchronization therapy is feasible and shorter QRS duration is associated with better clinical outcome. *J Interv Card Electrophysiol* 2023; **66**: 1799-1806 [PMID: 36629961 DOI: 10.1007/s10840-022-01463-y]

World Journal of Cardiology

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

World J Cardiol 2024 September 26; 16(9): 546-549

DOI: 10.4330/wjc.v16.i9.546

ISSN 1949-8462 (online)

LETTER TO THE EDITOR

Medical dilemma: Programmed death 1 blockade (sintilimab) therapy in patients suffering from tumours combined with psoriasis

Di Jin, Yu-Wei Wang, Zhi-Min Lin, Chen Li, Ming Li

Specialty type: Dermatology

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

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade D

Novelty: Grade B, Grade B

Creativity or Innovation: Grade B, Grade C

Scientific Significance: Grade A, Grade B

P-Reviewer: Yerolatsite M

Received: June 15, 2024

Revised: August 16, 2024

Accepted: September 10, 2024

Published online: September 26, 2024

Processing time: 96 Days and 7 Hours

Di Jin, Ming Li, Department of Rheumatology, Weifang People's Hospital, Weifang 261000, Shandong Province, China

Yu-Wei Wang, Department of Cardiology, Yidu Central Hospital of Weifang, Weifang 261000, Shandong Province, China

Zhi-Min Lin, Third Affiliated Hospital, Beijing University of Chinese Medicine, Beijing 100020, China

Chen Li, Department of Rheumatology, Fangshan Hospital, Beijing University of Chinese Medicine, Beijing 102400, China

Co-first authors: Di Jin and Yu-Wei Wang.

Co-corresponding authors: Ming Li and Chen Li.

Corresponding author: Ming Li, MD, Chief Doctor, Staff Physician, Department of Rheumatology, Weifang People's Hospital, No. 151 Guangwen Street, Kuiwen District, Weifang 261000, Shandong Province, China. lalwlm@aliyun.com

Abstract

Tumour immunotherapy represented by immune checkpoint inhibitors (ICIs) has greatly improved the overall prognosis of patients with malignant tumours, and is regarded as an important breakthrough in the field of medicine in recent years. ICIs have gradually become the core of tumour therapy and are increasingly used in the clinic. In order to achieve early clinical prediction and management of immune-related adverse events (irAEs), it is still necessary to perform further research on the mechanisms, risk factors, and predictors of irAE occurrence in the future. Zhou *et al* describe the consultation of a patient with advanced gastric cancer combined with chronic plaque psoriasis. This case provides an important reference for the use of programmed cell death protein-1 (PD-1) inhibitors in patients of tumours combined with chronic plaque psoriasis. This case also highlights that screening of high-risk groups for irAEs is critical before applying PD-1 inhibitors to patients with chronic psoriasis combined with tumours. PD-1 inhibitors are new and potent antineoplastic agents that can cause serious immune-related adverse events such as toxic epidermal necrolysis release and psoriasis. Glucocorticosteroids are the first-line agents for irAEs. The incidence of rheumatic irAEs may be higher in reality, which will inevitably become a new challenge for rheumatologists and dermatologists.

Key Words: Immune checkpoint inhibitors; Tumor immunotherapy; Immune-related adverse events; Cytokine release syndrome; Psoriasis

Core Tip: The major strategies for dealing with immune-related adverse events should include scientific awareness, early diagnosis and graded management. The important direction of tumour immunotherapy research is how to reduce the adverse effects of immunotherapy and can improve the quality of patient survival. The correlation between programmed cell death protein-1 inhibitors and chronic psoriasis is gradually receiving more and more attention, and how to screen high-risk populations in the future, as well as to give the necessary and effective preventive therapeutic measures still need to be further explored.

Citation: Jin D, Wang YW, Lin ZM, Li C, Li M. Medical dilemma: Programmed death 1 blockade (sintilimab) therapy in patients suffering from tumours combined with psoriasis. *World J Cardiol* 2024; 16(9): 546-549
URL: https://www.wjgnet.com/1949-8462/full/v16/i9/546.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i9.546

TO THE EDITOR

Tumor immunotherapy, using immune checkpoint inhibitors (ICIs), has greatly improved the prognosis of patients with malignant tumors. ICIs are regarded as essential breakthroughs in recent years[1]. With the outstanding therapeutic effects of immunotherapy in clinical practice and the gradual expansion of its applications, a series of immune-related adverse events (irAEs) have become increasingly common[2]. Currently, ICIs mainly target cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed cell death ligand-1 (PD-L1). The latest data from the United States show that almost half of the patients with malignant tumors meet the indications for ICIs therapy[3]. Therefore, ICIs have gradually become the core of tumor therapy and are increasingly used in clinical settings. To achieve early clinical prediction and management of irAEs, further research on their mechanisms, risk factors, and predictors is necessary.

PD-1 INHIBITORS IN TUMOR-PSORIASIS

Zhou *et al*[4] described the consultation of a patient with advanced gastric cancer and chronic plaque psoriasis. The patient developed a severe rash with cytokine release syndrome (CRS) after sintilimab treatment. In the present case, the patient presented with a recurrent rash as the first manifestation, followed by acute hyperthermia, hypoxia, and progressive exacerbation of skin lesions, which were life-threatening and resulted in CRS. The patient was treated effectively with glucocorticoids, tolizumab, and acitretin. The glucocorticoid dose was gradually reduced, and the rash did not recur. This case provides an essential reference for using PD-1 inhibitors in patients with tumors and chronic plaque psoriasis. This case also highlights the importance of screening high-risk groups for irAEs among patients with chronic psoriasis.

IrAEs are similar to the pathogenesis of rheumatic immune diseases and can mimic most rheumatic immune diseases, such as arthritis, rheumatic polymyalgia, myositis, and psoriasis. Previous clinical trials have shown that 54%–76% of patients have different degrees of irAEs. Therefore, ICI-related irAEs have gradually become a topical and challenging issue in tumor immunotherapy[3]. The risk factors for irAEs include gender, body mass index, tumor type, drug type, and history of autoimmune disease. Predictive factors include immune cells, cytokines, chemokines, autoantibodies, the genome, and intestinal flora. For example, sex hormones lead to sex differences in immune responses, and women are more likely to develop autoimmune diseases. Bui *et al*[5] conducted a retrospective analysis of 235 patients with melanoma and found that women were more prone to skin irAEs. Cortellini *et al*[6] found a significant correlation between a high BMI and the occurrence of irAEs. Patients who are overweight (25 kg/m^2 ≤ BMI ≤ 29.9 kg/m^2) are more likely to develop irAE related to the skin, endocrine system, gastrointestinal tract, and liver. A meta-analysis of 5560 patients in clinical trials showed that 18.4% of patients treated with ICIs developed rheumatic irAEs[7]. Almost all clinical trials excluded patients with comorbid rheumatological diseases (*e.g.*, rheumatoid arthritis, spondyloarthritis, and vasculitis). Therefore, the incidence of rheumatic irAEs may be high, which will inevitably become a new challenge for rheumatologists and dermatologists.

PD-1 inhibitors can cause serious irAEs, such as toxic epidermal necrolysis and psoriasis[8]. The pathogenesis of psoriasis induced by PD-1 inhibitors has not yet been clearly defined. The presence of a genetic susceptibility gene for psoriasis may also be a contributing factor. Morelli *et al*[9] investigated the immunological and genetic profiles of two patients with metastatic melanoma and one patient with lung cancer who developed severe psoriasis after receiving PD-1 inhibitor therapy. NGS analysis revealed that all patients carried several allelic variants in psoriasis susceptibility genes,

such as HLA-C, ERAP1, and other genes of the significant psoriasis susceptibility PSORS1 locus. Previously, there were relatively few case reports on PD-1 inhibitors inducing psoriasis activity. Sui *et al*[10] reported a case of a 56-year-old man with a 25-year history of psoriasis who was first injected with sintilimab (200 mg) for lung adenocarcinoma. Two weeks later, the patient's skin showed generalized red and swollen plaques accompanied with severe itching without obvious cause. A dermatological examination revealed many plaques, scales, scratches, crusts, and pigmentation on the scalp, trunk, and limbs. The patient presented with an acute exacerbation of the typical cutaneous features of plaque psoriasis. The mechanism of PD-1 inhibitors in psoriasis exacerbation may be related to the down-regulation of PD-1 on the surface of the T-cells, which indirectly activates the downstream cytokines, such as interleukin (IL)-1, IL-17, and IL-22[11]. However, for patients who develop severe manifestations of psoriasis, the continuation of PD-1 inhibitors remains a controversial issue, and the future treatment of these patients is highly challenging. The Sui *et al*[10] recommends that the patient should discontinue sintilimab.

The main therapeutic approaches in the treatment of gastric cancer are based on surgery and chemotherapy. Thus, ICIs provide new therapeutic options for patients with gastric cancer[12]. Immune-related skin reactions are the most common side effects of ICI treatment, with an incidence rate of > 50%. Skin lesions are usually mild and do not affect the continuation of immunotherapy. The clinical manifestations vary greatly, and nonspecific macular papules are common[13]. Early diagnosis and timely intervention for irAEs are essential to improve the quality of life of patients with malignant tumors. Glucocorticosteroids are the first-line agents for irAEs, with the dose set according to the criteria for evaluating common adverse event grades and clinical severity. Individualized tapering is performed according to the patient's therapeutic response to glucocorticoids, and some patients may require tumor necrosis factor inhibitors and other monoclonal antibodies to prevent opportunistic infections and reduce the side effects of glucocorticoids.

CONCLUSION

In conclusion, the major strategies for managing irAEs should include scientific awareness, early diagnosis, and graded management. An important direction in tumor immunotherapy research is to reduce the adverse effects of immunotherapy and improve the quality of patient survival. The correlation between PD-1 inhibitors and chronic psoriasis is receiving increasing attention, and further research is required to identify high-risk populations.

FOOTNOTES

Author contributions: Jin D and Wang YW prepared the manuscript and contributed equally to this article, ensuring a cohesive presentation of the research findings; Jin D and Lin ZM were responsible for the meticulous analysis and interpretation of the case, providing essential insights that underpinned the study's conclusions; Li C and Li M were at the helm of conceptualizing and designing the research ideas, setting the stage for the study with their innovative and well-defined framework; All authors have read and approved the final manuscript, with Jin D and Wang YW recognized as co-first authors for their significant contributions to the manuscript preparation, and the collaborative efforts of the team were instrumental in bringing the research to fruition.

Supported by Weifang Health Commission's Scientific Research Program, No. WFWSJK-2023-222 and No. WFWSJK-2023-240; and the Weifang Young Medical Talent Support Project.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Country of origin: China

ORCID number: Chen Li 0000-0002-8527-1680.

S-Editor: Liu JH
L-Editor: A
P-Editor: Wang WB

REFERENCES

1 **Robert C**. A decade of immune-checkpoint inhibitors in cancer therapy. *Nat Commun* 2020; **11**: 3801 [PMID: 32732879 DOI: 10.1038/s41467-020-17670-y]
2 **Fan Y**, Geng Y, Shen L, Zhang Z. Advances on immune-related adverse events associated with immune checkpoint inhibitors. *Front Med* 2021; **15**: 33-42 [PMID: 32779094 DOI: 10.1007/s11684-019-0735-3]
3 **Johnson DB**, Nebhan CA, Moslehi JJ, Balko JM. Immune-checkpoint inhibitors: long-term implications of toxicity. *Nat Rev Clin Oncol* 2022;

19: 254-267 [PMID: 35082367 DOI: 10.1038/s41571-022-00600-w]

4 **Zhou MH**, Ye MF, Zhang ZX, Tao F, Zhang Y. Cytokine release syndrome triggered by programmed death 1 blockade (sintilimab) therapy in a psoriasis patient: A case report. *World J Clin Cases* 2024; **12**: 3555-3560 [PMID: 38983424 DOI: 10.12998/wjcc.v12.i18.3555]

5 **Bui AN**, Bougrine A, Buchbinder EI, Giobbie-Hurder A, LeBoeuf NR. Female sex is associated with higher rates of dermatologic adverse events among patients with melanoma receiving immune checkpoint inhibitor therapy: A retrospective cohort study. *J Am Acad Dermatol* 2022; **87**: 403-406 [PMID: 34252467 DOI: 10.1016/j.jaad.2021.06.885]

6 **Cortellini A**, Bersanelli M, Buti S, Cannita K, Santini D, Perrone F, Giusti R, Tiseo M, Michiara M, Di Marino P, Tinari N, De Tursi M, Zoratto F, Veltri E, Marconcini R, Malorgio F, Russano M, Anesi C, Zeppola T, Filetti M, Marchetti P, Botticelli A, Antonini Cappellini GC, De Galitiis F, Vitale MG, Rastelli F, Pergolesi F, Berardi R, Rinaldi S, Tudini M, Silva RR, Pireddu A, Atzori F, Chiari R, Ricciuti B, De Giglio A, Iacono D, Gelibter A, Occhipinti MA, Parisi A, Porzio G, Fargnoli MC, Ascierto PA, Ficorella C, Natoli C. A multicenter study of body mass index in cancer patients treated with anti-PD-1/PD-L1 immune checkpoint inhibitors: when overweight becomes favorable. *J Immunother Cancer* 2019; **7**: 57 [PMID: 30813970 DOI: 10.1186/s40425-019-0527-y]

7 **Zhang S**, Zhou Z, Wang L, Li M, Zhang F, Zeng X. Rheumatic immune-related adverse events associated with immune checkpoint inhibitors compared with placebo in oncologic patients: a systemic review and meta-analysis. *Ther Adv Chronic Dis* 2021; **12**: 2040622320976996 [PMID: 33633822 DOI: 10.1177/2040622320976996]

8 **Di Altobrando A**, Bruni F, Alessandrini A, Starace M, Misciali C, Piraccini BM. Severe de-novo palmoplantar and nail psoriasis complicating Nivolumab treatment for metastatic melanoma. *Dermatol Ther* 2020; **33**: e13363 [PMID: 32239596 DOI: 10.1111/dth.13363]

9 **Morelli M**, Carbone ML, Scaglione GL, Scarponi C, Di Francesco V, Pallotta S, De Galitiis F, Rahimi S, Madonna S, Failla CM, Albanesi C. Identification of immunological patterns characterizing immune-related psoriasis reactions in oncological patients in therapy with anti-PD-1 checkpoint inhibitors. *Front Immunol* 2024; **15**: 1346687 [PMID: 38495872 DOI: 10.3389/fimmu.2024.1346687]

10 **Sui CL**, Lin XF, He L, Zhu W. Dermoscopic features of acutely exacerbated plaque psoriasis induced by anti-programmed death-1 for lung cancer. *Chin Med J (Engl)* 2020; **133**: 2123-2125 [PMID: 32769492 DOI: 10.1097/CM9.0000000000000958]

11 **Bartosińska J**, Zakrzewska E, Purkot J, Michalak-Stoma A, Kowal M, Krasowska D, Chodorowska G, Giannopoulos K. Decreased blood CD4+PD-1+ and CD8+PD-1+ T cells in psoriatic patients with and without arthritis. *Postepy Dermatol Alergol* 2018; **35**: 344-350 [PMID: 30206445 DOI: 10.5114/ada.2018.75609]

12 **Sun J**, Zheng Y, Mamun M, Li X, Chen X, Gao Y. Research progress of PD-1/PD-L1 immunotherapy in gastrointestinal tumors. *Biomed Pharmacother* 2020; **129**: 110504 [PMID: 32768978 DOI: 10.1016/j.biopha.2020.110504]

13 **Haanen J**, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, Lyon AR, Wick W, Kostine M, Peters S, Jordan K, Larkin J; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2022; **33**: 1217-1238 [PMID: 36270461 DOI: 10.1016/j.annonc.2022.10.001]

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