ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2024 April 26; 16(4): 168-216

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 16 Number 4 April 26, 2024

EDITORIAL

MINIREVIEWS

SCIENTOMETRICS

CORRECTION

World Journal of Cardiology

Monthly Volume 16 Number 4 April 26, 2024

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Cardiology*, Ramachandra Barik, DNB, MD, Full Professor, Department of Cardiology, All India Institute of Medical Sciences, Bhubaneswar 751019, Odisha, India.
cardioramachandra@gmail.com

AIMS AND SCOPE

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

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

INDEXING/ABSTRACTING

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

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Si Zhao*; **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
April 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 April 26; 16(4): 168-172

DOI: 10.4330/wjc.v16.i4.168

ISSN 1949-8462 (online)

EDITORIAL

Pacemaker post transcatheter aortic valve replacement: A multifactorial risk?

Stephane Noble, Karim Bendjelid

Specialty type: Cardiac and cardiovascular systems

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Jha AK, United States

Received: November 21, 2023
Peer-review started: November 21, 2023
First decision: January 24, 2024
Revised: February 1, 2024
Accepted: March 18, 2024
Article in press: March 18, 2024
Published online: April 26, 2024

Stephane Noble, Department of Medicine, Structural Heart Unit, University Hospital of Geneva, Geneva 1211, Switzerland

Karim Bendjelid, Department of Acute Medicine, Geneva University Hospitals, Geneva 1211, Switzerland

Corresponding author: Stephane Noble, MD, Assistant Professor, Department of Medicine, Structural Heart Unit, University Hospital of Geneva, 4 rue Gabrielle Perret Gentil, Geneva 1211, Switzerland. stephane.noble@hcuge.ch

Abstract

Pacemaker post-transcatheter aortic valve replacement is related to multifactorial risk. Nwaedozie *et al* brought to the body of evidence electrocardiogram and clinical findings. However, procedural characteristics have at least as much impact on the final need for a permanent pacemaker and potentially on the pacing rate. In this regard, long-term follow-up and understanding of the impact of long-term stimulation is of utmost importance.

Key Words: Transcatheter aortic valve replacement; Permanent pacemaker implantation; Conduction abnormalities; Right bundle branch block; Left bundle branch block

Core Tip: Since the first transcatheter aortic valve replacement (TAVR) in 2002, TAVR has become a recognized alternative therapy to symptomatic severe aortic stenosis independently of the surgical risk score. The multiple iterations of the delivery systems and transcatheter heart valves (THV) over time associated with better patient assessment and the growing experience and expertise of the operators improved the procedural and follow-up results. However, despite the possibility of repositioning and partially recapturing some of the self-expanding THV and generally higher implantation targets, the need for a permanent pacemaker remains the most frequent complication post-procedure.

Citation: Noble S, Bendjelid K. Pacemaker post transcatheter aortic valve replacement: A multifactorial risk? *World J Cardiol* 2024; 16(4): 168-172
URL: https://www.wjgnet.com/1949-8462/full/v16/i4/168.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i4.168

INTRODUCTION

Since the first transcatheter aortic valve replacement (TAVR) in 2002, TAVR has become a recognized alternative therapy to symptomatic severe aortic stenosis independently of the surgical risk score. The multiple iterations of the delivery systems and transcatheter heart valves (THV) over time associated with better patient assessment and the growing experience and expertise of the operators improved the procedural and follow-up results[1-3]. However, despite the possibility of repositioning and partially recapturing some of the self-expanding THV and generally higher implantation targets, the need for a permanent pacemaker remains the most frequent complication post-procedure. Importantly, the left bundle branch travels commonly 2 to 3 mm below the base of the interleaflet triangle between the noncoronary and right coronary leaflets and is therefore at risk for interaction with the THV[4].

Conductance disturbances and the need for permanent pacemaker implantation post-TAVR are multifactorial and have an important clinical and economic impact (price of the pacemaker implantation, higher length of stay)[5]. In a multicenter European trial using balloon-expandable valves, conductance abnormalities were the second most common reason for prolonged hospitalization after logistic causes[6]. Delayed atrioventricular block can be seen up to 8 d post-TAVR in 7% of the cases, but patients without conduction abnormalities immediately post-TAVR did not present any delayed high-degree conduction disorder in a multicentric report including 1064 patients[7]. The European Society of Cardiology (ESC) guidelines on cardiac pacing gave a class I indication for permanent pacemaker implantation in the context of a complete atrioventricular block or new alternating bundle branch block and a class IIa for right bundle branch block and new conductance disturbance (PR prolongation or axis changes)[8]. Interestingly, a class IIa for ambulatory ECG monitoring or electrophysiology study was given in the setting of persistent new left bundle branch block > 150 ms or PR > 240 ms with no further prolongation during 48 h and a class IIb in the context of pre-existing conduction abnormalities with prolongation of > 20 ms of the QRS and PR interval.

In the present issue of the Journal, Nwaedozie *et al*[9] assessed the effects of baseline nonspecific interventricular conduction delay and supraventricular arrhythmia on post-TAVR permanent pacemaker need and also reported the impact of permanent pacemaker implantation on clinical outcomes at one year. In this regard, they retrospectively analyzed the single-center cohort of a tertiary hospital in central Wisconsin, United States involving 357 patients who underwent a TAVR (95.2% of transfemoral approach) between January 2012 and December 2019 using balloon-expandable and self-expanding THV in 53.8% and 46.2%, respectively.

One of the strengths of the study is that they analyzed the rate of pacemaker dependency at follow-up, which was as high as 78.9% one month post-pacemaker implantation. In addition, board-certified cardiologists reviewed the ECG. They found a permanent pacemaker rate of 16% at one year with no significant differences between self-expanding (17.6%) and balloon-expandable (14.6%) THV. Their pacemaker rates are similar to the Medtronic self-expanding THV in the Evolut Low-Risk trial (17.4% at 30 d and 19.4% at one year) and slightly above what we could expect with the Edwards SAPIEN 3 balloon-expandable valve (PARTNER 3 trial: 6.6% at 30 d and 7.5% at one year)[10,11]. The median time of implantation in the study by Nwaedozie *et al*[9] was 2 d, and half of the patients underwent pacemaker implantation within 48 h post-TAVR. Complete atrioventricular block was the predominant indication (66.7%) and the other indications were as follows: left ventricle dysfunction (10.5%), symptomatic bradycardia (8.8%), and symptomatic second atrioventricular block (1.8%).

The main findings of this trial are that pre-TAVR type II Diabetes Mellitus and QRS duration > 120 ms, regardless of the presence of bundle branch blocks were predictors of permanent pacemaker need post-TAVR. They also demonstrated a linear association between post-TAVR permanent pacemaker rate for every 20 ms prolongation of the QRS duration above 100 ms. Finally, at one year, there were more heart failure hospitalizations (28% *vs* 14%, $P = 0.022$) and myocardial infarction (9% *vs* 2%, $P = 0.031$) in the group requiring a permanent pacemaker.

The limitations of this report are related to the design of the study which is a retrospective analysis of a single center experience with a relatively small number of patients ($n = 357$) treated over 8 years. During this long period, there were multiple THV iterations, implantation technique refinements, and a regular expansion of the indication creating a heterogenous population. The results have to be brought into perspective. Indeed, not only does the baseline ECG influence the post-procedural risk of permanent pacemaker need (particularly the presence of a right bundle branch block[5]), but also the left ventricular outflow tract (LVOT) anatomy and the calcium burden and repartition as well as the valve type used (*i.e.*, balloon-expandable *vs* self-expanding THV), and finally patient and procedural characteristics (*i.e.*, the height of implantation, percentage of oversizing, the technique of implantation, pre- and post-dilatation, resheathing and recapture).

Recently, the best clinical practices concerning the view of valve deployment have progressively switched from a three-cusp view to a combination of cusp overlap and three-cusp views, particularly for the self-expanding valves[12]. When using the cusp-overlap view, we focus on the non-coronary cusp which is on the left side of the screen, whereas the right and left cusps are superimposed on the right side of the screen. This view allows the elongation of the LVOT and subsequently a more precise height of implantation. It also contributes to eliminating the parallax of the delivery catheter, deploying the valve in a true coplanar view, and better aligning the THV commissures[12]. The cusp overlap technique

has been associated with a lower pacemaker implantation rate at 30 d than the conventional technique in a meta-analysis including 1227 Medtronic Evolut valves (cusp overlap technique: 641 *vs* co-planar view: 586).

In the cusp overlap technique, the implantation height was 1.03 mm higher and the incidence of pacemaker rate was 9.8% compared to 20.6% in the conventional technique[13]. However, the incidence of a left bundle branch block did not defer. In a propensity-matched analysis on a small Spanish cohort (92 patients in each group with no baseline characteristic differences), there was a significant reduction of new onset of left bundle branch block and reduced P wave and QRS widening at one year in the cusp overlap technique group compared to the conventional technique group[14]. There was also a significant reduction in a combined primary endpoint including pacemaker implantation, hospitalization and cardiovascular death at one year[14]. Recently, the interim analysis of the Optimize PRO TAVR study showed again the benefit of the cusp overlap technique in 400 patients[15]. This study reports the absence of moderate or severe paravalvular leak and the lowest pacemaker rate (9.8% at 30 d) in a multicenter prospective study with the Evolut platform using the cusp overlap technique and an "optimized TAVR care pathway". The pacemaker rate was as low as 5.7% when the 4-step cusp overlap technique was precisely followed.

Importantly, Nwaedozie *et al*[9] did not report data on the procedural depth of THV implantation which is a major predictor of the need for a permanent pacemaker post-TAVR. To emphasize the role of the implantation technique and volume-outcome relationship, in a sub-analysis of the Evolut low-risk trial, there was a substantial variation in the rate of permanent pacemaker implantation from site to site in this study including 699 patients from 84 centers, with a lower rate of pacemaker need in high volume centers[3,16]. The sites with a low pacemaker rate had higher implantation at the non-coronary and left coronary sinus levels and fewer patients with an implantation depth of more than 5 mm[16].

Finally, the long-term data post-pacemaker implantation after TAVR are conflicting. Right ventricular pacing is associated with electromechanical dyssynchrony, left ventricular remodeling, increased risk of atrial fibrillation, and tricuspid regurgitation. In a series of 377 post-TAVR patients at one year, a stimulation rate > 40% of the time was associated in a propensity-matched analysis with a higher risk of cardiovascular mortality and hospitalization for heart failure[17]. More physiological pacing such as cardiac resynchronization in cases of reduced left ventricular ejection fraction is recommended to decrease the adverse outcome. His bundle or conduction system stimulation is also a more physiological pacing, which should be promoted. Of note, in the later series, 6 patients had His stimulation with no event or hospitalization during follow-up. In 2020, a meta-analysis including 30 studies showed a higher risk at one year of all-cause death and heart failure hospitalization after new onset of left bundle branch block or peri-procedural pacemaker implantation[18]. In addition, post TAVR new onset of left bundle branch block was associated with an increased risk of cardiac death and need for pacemaker implantation at one year[18]. In a recent meta-analysis of 31 studies with a mean follow-up of 22 months, new permanent pacemaker implantation after TAVR was associated with a higher risk of all-cause death and heart failure hospitalization[19]. Conversely, data from the nationwide, population cohort study with 3420 TAVR performed between 2008 and 2018 in Sweden, 481 (14.1%) required permanent pacemaker implantation within 30 d post procedure[20]. With a median follow-up of 2.7 years, there was no difference in long-term survival between patients who were or were not implanted with a permanent pacemaker (survival at 5 and 10 years: 52.7% and 10.9% in the pacemaker group and 53.8% and 15.3% in the group without a pacemaker, respectively).

CONCLUSION

In conclusion, pacemaker post-TAVR is related to multifactorial risk. Nwaedozie *et al*[9] brought to the body of evidence ECG and clinical findings, but procedural characteristics have at least as much impact on the final need for a permanent pacemaker and potentially on the pacing rate. Long-term follow-up and understanding of the impact of long-term stimulation is of utmost importance.

FOOTNOTES

Co-corresponding authors: Stephane Noble and Karim Bendjelid.

Author contributions: Noble S wrote the first draft; and both authors interpreted the data, critically revised the manuscript for important intellectual content, gave approval for the final version to be published and affirmed that the manuscript is an honest, accurate, and transparent account of the study being reported.

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

Country/Territory of origin: Switzerland

ORCID number: Stephane Noble 0000-0002-8018-2857; Karim Bendjelid 0000-0002-7921-7207.

Corresponding Author's Membership in Professional Societies: American Soceity of Physiology; European Soceity of Cardiology.

S-Editor: Gong ZM
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Perrin N**, Frei A, Noble S. Transcatheter aortic valve implantation: Update in 2018. *Eur J Intern Med* 2018; **55**: 12-19 [PMID: 30180946 DOI: 10.1016/j.ejim.2018.07.002]
2 **Frei A**, Adamopoulos D, Müller H, Walder B, Perrin N, Reynaud T, Ho S, Roffi M, Mach F, Licker MJ, Noble S. Determinants of hospital length of stay after transcatheter aortic valve implantation with self-expanding prostheses: a prospective, single centre observational study. *Swiss Med Wkly* 2019; **149**: w20095 [PMID: 31256415 DOI: 10.4414/smw.2019.20095]
3 **Mauler-Wittwer S**, Noble S. Volume-Outcome Relationship in Surgical and Cardiac Transcatheter Interventions with a Focus on Transcatheter Aortic Valve Implantation. *J Clin Med* 2022; **11** [PMID: 35807093 DOI: 10.3390/jcm11133806]
4 **Piazza N**, Onuma Y, Jesserun E, Kint PP, Maugenest AM, Anderson RH, de Jaegere PP, Serruys PW. Early and persistent intraventricular conduction abnormalities and requirements for pacemaking after percutaneous replacement of the aortic valve. *JACC Cardiovasc Interv* 2008; **1**: 310-316 [PMID: 19463319 DOI: 10.1016/j.jcin.2008.04.007]
5 **Muthu Krishnan A**, Kadavath S, Kowlgi G, Goel A, Wu F, Jha A, Correa De Sa D, Lahoud R. Permanent Pacemaker Use in Transcatheter Aortic Valve Replacement: Real World Experience from the National Inpatient Sample. *Int J Clin Res* 2023; **3**: 263-275 [DOI: 10.38179/ijcr.v3i1.219]
6 **Barbanti M**, van Mourik MS, Spence MS, Iacovelli F, Martinelli GL, Muir DF, Saia F, Bortone AS, Densem CG, van der Kley F, Bramlage P, Vis M, Tamburino C. Optimising patient discharge management after transfemoral transcatheter aortic valve implantation: the multicentre European FAST-TAVI trial. *EuroIntervention* 2019; **15**: 147-154 [PMID: 30777842 DOI: 10.4244/EIJ-D-18-01197]
7 **Toggweiler S**, Stortecky S, Holy E, Zuk K, Cuculi F, Nietlispach F, Sabti Z, Suciu R, Maier W, Jamshidi P, Maisano F, Windecker S, Kobza R, Wenaweser P, Lüscher TF, Binder RK. The Electrocardiogram After Transcatheter Aortic Valve Replacement Determines the Risk for Post-Procedural High-Degree AV Block and the Need for Telemetry Monitoring. *JACC Cardiovasc Interv* 2016; **9**: 1269-1276 [PMID: 27339844 DOI: 10.1016/j.jcin.2016.03.024]
8 **Glikson M**, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, Barrabés JA, Boriani G, Braunschweig F, Brignole M, Burri H, Coats AJS, Deharo JC, Delgado V, Diller GP, Israel CW, Keren A, Knops RE, Kotecha D, Leclercq C, Merkely B, Starck C, Thylén I, Tolosana JM; ESC Scientific Document Group. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2021; **42**: 3427-3520 [PMID: 34455430 DOI: 10.1093/eurheartj/ehab364]
9 **Nwaedozie S**, Zhang H, Najjar Mojarrab J, Sharma P, Yeung P, Umukoro P, Soodi D, Gabor R, Anderson K, Garcia-Montilla R. Novel predictors of permanent pacemaker implantation following transcatheter aortic valve replacement. *World J Cardiol* 2023; **15**: 582-598 [PMID: 38058399 DOI: 10.4330/wjc.v15.i11.582]
10 **Popma JJ**, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, Askew J, Sorajja P, Rovin J, Chetcuti SJ, Adams DH, Teirstein PS, Zorn GL 3rd, Forrest JK, Tchétché D, Resar J, Walton A, Piazza N, Ramlawi B, Robinson N, Petrossian G, Gleason TG, Oh JK, Boulware MJ, Qiao H, Mugglin AS, Reardon MJ; Evolut Low Risk Trial Investigators. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *N Engl J Med* 2019; **380**: 1706-1715 [PMID: 30883053 DOI: 10.1056/NEJMoa1816885]
11 **Mack MJ**, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR; PARTNER 3 Investigators. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *N Engl J Med* 2019; **380**: 1695-1705 [PMID: 30883058 DOI: 10.1056/NEJMoa1814052]
12 **Tang GHL**, Zaid S, Michev I, Ahmad H, Kaple R, Undemir C, Cohen M, Lansman SL. "Cusp-Overlap" View Simplifies Fluoroscopy-Guided Implantation of Self-Expanding Valve in Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv* 2018; **11**: 1663-1665 [PMID: 30139479 DOI: 10.1016/j.jcin.2018.03.018]
13 **Rawish E**, Macherey S, Jurczyk D, Pätz T, Jose J, Stiermaier T, Eitel I, Frerker C, Schmidt T. Reduction of permanent pacemaker implantation by using the cusp overlap technique in transcatheter aortic valve replacement: a meta-analysis. *Clin Res Cardiol* 2023; **112**: 633-644 [PMID: 36656375 DOI: 10.1007/s00392-022-02150-8]
14 **Persia-Paulino YR**, Almendarez Lacayo M, Alperi A, Hernández-Vaquero D, Fernández Asensio R, Cuevas Pérez J, Adeba A, Flórez P, Vigil-Escalera M, Álvarez Velasco R, Renilla A, Del Valle Fernández R, Antuña P, Morís de la Tassa C, Avanzas P, Pascual I. Self-expanding TAVI using the cusp overlap technique versus the traditional technique: electrocardiogram changes and 1-year cardiovascular outcomes. *Rev Esp Cardiol (Engl Ed)* 2024; **77**: 29-38 [PMID: 37437882 DOI: 10.1016/j.rec.2023.04.008]
15 **Grubb K**, Yakubov SJ, Nazif TM, Mittal S, Gada H, Fraser DGW, Rovin JD, Khalil R, Pyo RT, Sharma S, Ahmed M, Huang J, Rodes-Cabau J. Management of Postprocedural Conduction Disturbances Using a Prespecified Algorithm in the Optimize PRO Study. *JSCAI* 2023; **3**: 101066 [DOI: 10.1016/j.jscai.2023.101066]
16 **Gada H**, Vora AN, Tang GHL, Mumtaz M, Forrest JK, Laham RJ, Yakubov SJ, Deeb GM, Rammohan C, Huang J, Reardon MJ. Site-Level Variation and Predictors of Permanent Pacemaker Implantation Following TAVR in the Evolut Low-Risk Trial. *Cardiovasc Revasc Med* 2023; **47**: 48-54 [PMID: 36266154 DOI: 10.1016/j.carrev.2022.10.004]
17 **Bruno F**, Munoz Pousa I, Saia F, Vaira MP, Baldi E, Leone PP, Cabanas-Grandio P, Corcione N, Spinoni EG, Annibali G, Russo C, Ziacchi M, Caruzzo CA, Ferlini M, Lanzillo G, De Filippo O, Dusi V, Gallone G, Castagno D, Patti G, La Torre M, Musumeci G, Giordano A, Stefanini G, Salizzoni S, Conrotto F, Rinaldi M, Rordorf R, Abu-Assi E, Raposeiras-Roubin S, Biffi M, D'Ascenzo F, De Ferrari GM. Impact of Right Ventricular Pacing in Patients With TAVR Undergoing Permanent Pacemaker Implantation. *JACC Cardiovasc Interv* 2023; **16**: 1081-1091 [PMID: 37164607 DOI: 10.1016/j.jcin.2023.02.003]
18 **Faroux L**, Chen S, Muntané-Carol G, Regueiro A, Philippon F, Sondergaard L, Jørgensen TH, Lopez-Aguilera J, Kodali S, Leon M, Nazif T, Rodés-Cabau J. Clinical impact of conduction disturbances in transcatheter aortic valve replacement recipients: a systematic review and meta-analysis. *Eur Heart J* 2020; **41**: 2771-2781 [PMID: 31899484 DOI: 10.1093/eurheartj/ehz924]

19 **Zito A**, Princi G, Lombardi M, D'Amario D, Vergallo R, Aurigemma C, Romagnoli E, Pelargonio G, Bruno P, Trani C, Burzotta F, Crea F. Long-term clinical impact of permanent pacemaker implantation in patients undergoing transcatheter aortic valve implantation: a systematic review and meta-analysis. *Europace* 2022; **24**: 1127-1136 [PMID: 35138367 DOI: 10.1093/europace/euac008]

20 **Rück A**, Saleh N, Glaser N. Outcomes Following Permanent Pacemaker Implantation After Transcatheter Aortic Valve Replacement: SWEDEHEART Observational Study. *JACC Cardiovasc Interv* 2021; **14**: 2173-2181 [PMID: 34620397 DOI: 10.1016/j.jcin.2021.07.043]

World Journal of Cardiology

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

World J Cardiol 2024 April 26; 16(4): 173-176

DOI: 10.4330/wjc.v16.i4.173

ISSN 1949-8462 (online)

EDITORIAL

Challenging situation of coronary artery anomaly associated with ischemia and/or risk of sudden death

Shigenori Ito

Specialty type: Cardiac and cardiovascular systems

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Glumac S, Croatia

Received: November 28, 2023
Peer-review started: November 28, 2023
First decision: January 17, 2024
Revised: January 28, 2024
Accepted: March 1, 2024
Article in press: March 1, 2024
Published online: April 26, 2024

Shigenori Ito, Division of Cardiology, Sankuro Hospital, Toyota 471-0035, Japan

Corresponding author: Shigenori Ito, MD, PhD, Attending Doctor, Division of Cardiology, Sankuro Hospital, 7-80 Kosaka-cho, Toyota 471-0035, Japan. shigeito918@gmail.com

Abstract

Coronary artery anomaly is known as one of the causes of angina pectoris and sudden death and is an important clinical entity that cannot be overlooked. The incidence of coronary artery anomalies is as low as 1%-2% of the general population, even when the various types are combined. Coronary anomalies are practically challenging when the left and right coronary ostium are not found around their normal positions during coronary angiography with a catheter. If there is atherosclerotic stenosis of the coronary artery with an anomaly and percutaneous coronary intervention (PCI) is required, the suitability of the guiding catheter at the entrance and the adequate back up force of the guiding catheter are issues. The level of PCI risk itself should also be considered on a case-by-case basis. In this case, emission computed tomography in the R-1 subtype single coronary artery proved that ischemia occurred in an area where the coronary artery was not visible to the naked eye. Meticulous follow-up would be crucial, because sudden death may occur in single coronary arteries. To prevent atherosclerosis with full efforts is also important, as the authors indicated admirably.

Key Words: Coronary artery anomaly; Single coronary artery; Ischemia; Sudden death; Percutaneous coronary intervention; Coronary vessel anomalies; Myocardial ischemia; Sudden cardiac death

Core Tip: The incidence of coronary artery anomalies is as low as 1%-2% in the general population, even when the various types are combined. Among these, the R-1 subtype in a single coronary artery is extremely rare. In this case report by Zhou *et al*, emission computed tomography showed that ischemia occurred in an area where the coronary artery was not visible to the naked eye. Meticulous follow-up is crucial because sudden death may occur owing to a single coronary artery. Furthermore, atherosclerosis prevention is important because percutaneous coronary intervention could pose a high risk when necessary for such anomaly.

Citation: Ito S. Challenging situation of coronary artery anomaly associated with ischemia and/or risk of sudden death. *World J Cardiol* 2024; 16(4): 173-176
URL: https://www.wjgnet.com/1949-8462/full/v16/i4/173.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i4.173

INTRODUCTION

Like many organs, the coronary arteries have congenital anomalies. Anomalous origin, course, and termination of the coronary artery are often discovered by chance. In a single coronary artery as in this case[1], the origin of either the left or right coronary artery itself may not exist. Coronary artery anomaly is known as one of the causes of angina pectoris and sudden death and is an important clinical entity that cannot be overlooked. The frequency of coronary artery anomaly is often calculated based on data from catheter-based coronary angiography. On the other hand, coronary angiography is almost always performed for some reason, so there is a possibility that the statistics are biased to some extent. In recent years, multi-row coronary computed tomography (CT) has been increasingly performed as a first-line procedure[2], which makes it easier to perform anatomical analysis of the flow site and its relationship to other structures, and the range of indications is wider than that of a catheter[3,4]. The incidence of coronary artery anomalies is as low as 1%-2% of the general population[5], even when the various types are combined, and there is a natural limit to experience many types alone. Whenever you encounter unusual coronary arteries, you should always refer to the literature on congenital anomalies to evaluate their frequency and characteristics. It is important to consider whether the anomaly alone can cause ischemia or pose a risk of sudden death[6,7].

IMPACT OF CORONARY ANOMALIES

Coronary anomalies are practically problematic when the left and right coronary ostium are not found around their normal positions during coronary angiography with a catheter. It is easy to increase the amount of contrast agent used by repeating the test images many times. Particularly in the emergency setting of acute coronary syndromes, the operator may be distracted and repeat unnecessary contrast injection. Since there are cases of coronary artery occlusion at the entrance, it is more important to differentiate between the presence or absence of congenital abnormalities. If the ostium cannot be found during normal catheterization, it is important to remember the presence of the anomaly at an early stage. Contrast imaging of the sinuses of Valsalva/aortic root should be performed as soon as possible. If there is atherosclerotic stenosis of the coronary artery with an anomaly and percutaneous coronary intervention (PCI) is required, the suitability of the guiding catheter at the entrance and the adequate back up force of the guiding catheter are issues[8-10]. The level of PCI risk itself should also be considered on a case-by-case basis. PCI of a single coronary artery, as in this case[1], is difficult[5]. Suppose there is a significant stenosis in the proximal area. In this case, the risk of PCI will be considerably higher than in the left main with normal coronary structure, since it includes the perfusion zone of all coronary arteries.

CLINICAL IMPLICATIONS

This case is very rare, and even a single case report contributed to the world "encyclopedia" of coronary anomalies as a valuable accumulation of cases[1]. Emission CT in the R-1 subtype single coronary artery proved that ischemia occurred in an area where the coronary artery was not visible to the naked eye, confirming the report of Chaikriangkrai *et al*[7]. In a 62-year-old female patient with diabetes mellitus, hypertension, and dyslipidemia presented with decreased exercise tolerance and poor blood pressure control, which began 2 wk before presentation. On a physical examination, her vital signs were as follows: body temperature, 37.3 °C; heart rate, 92 beats per minute; blood pressure, 151/86 mmHg; and body mass index, 23.4 kg/m^2. Laboratory tests were negative for cardiac troponin I. Blood testing revealed low-density lipoprotein, high-density lipoprotein, and total cholesterol levels of 3.16, 1.19, and 4.96 mmol/L, respectively. The patient's fasting blood glucose level was 9.49 mmol/L, while her 2-h postprandial blood glucose level was 22.54 mmol/L. Her glycosylated hemoglobin A1c level was 7.51%. Electrocardiography showed a normal sinus rhythm with mild depression in leads I, II, III, aVF, and V4-V6 (Figure 1). Coronary angiography detected no left coronary artery (Figure 2A and D) and that a single large coronary artery from the right sinus continued in the coronary sulcus (Figure 2B) and extended to the anterior base of the heart, terminating in a small vessel supplying the territory of the left anterior

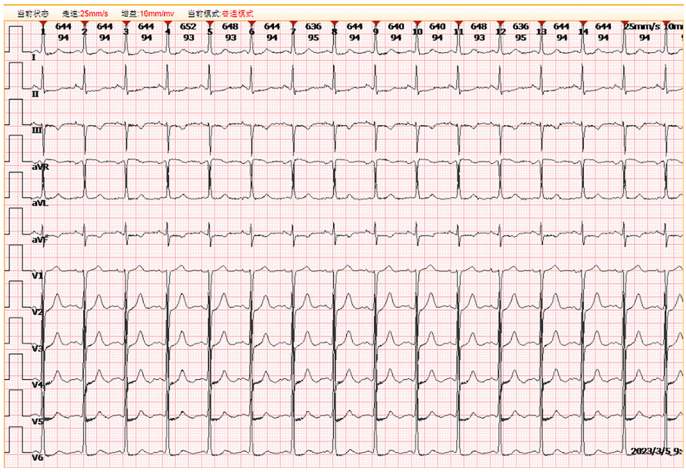

Figure 1 Electrocardiography at initial presentation[1]**.** Normal sinus rhythm with ST-T wave changes in leads I, II, III, aVF, and V4-V6. Citation: Zhou YP, Wang LL, Qiu YG, Huang SW. R-I subtype single right coronary artery with congenital absence of left coronary system: A case report. *World J Cardiol* 2023; 15: 649-654. Copyright ©2023 The Authors. Published by Baishideng Publishing Group Inc.

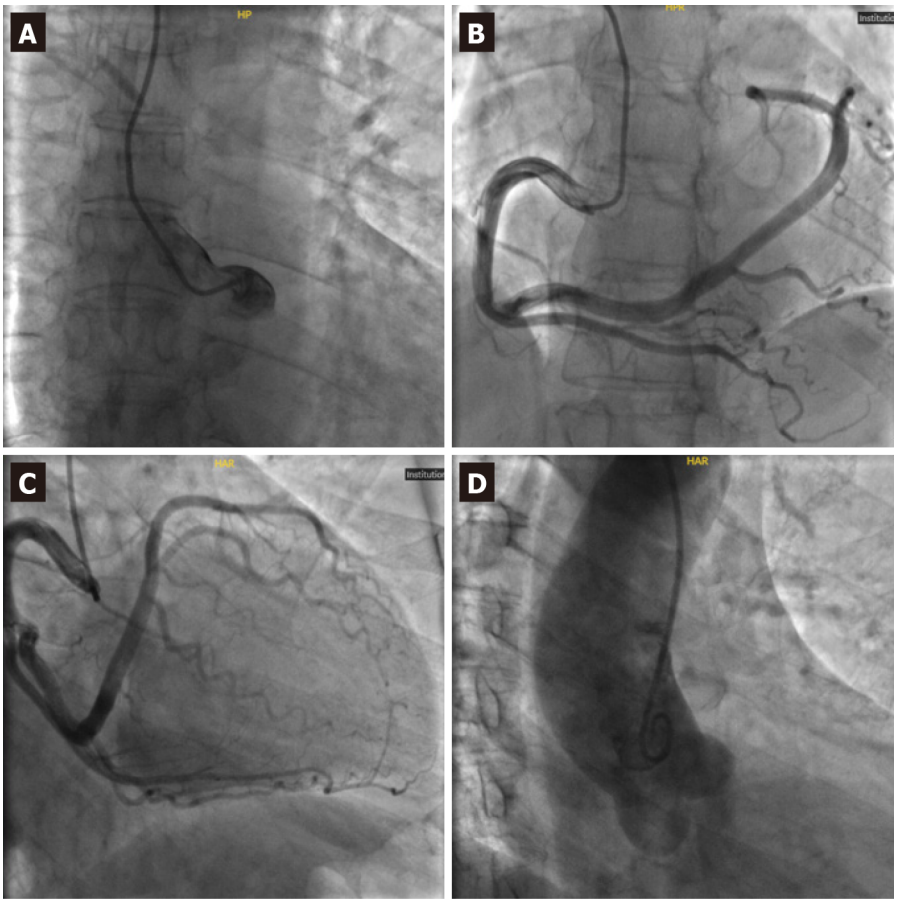

Figure 2 Coronary angiography[1]**.** A: No coronary artery was found on multiple coronary projections; B and C: A single and large coronary artery originating from the right coronary sinus continued in the coronary sulcus (B), and extended to the anterior base of the heart, where it gave rise to the left anterior descending coronary artery (C); D: No coronary artery was found on a non-selective aortic root injection. Citation: Zhou YP, Wang LL, Qiu YG, Huang SW. R-I subtype single right coronary artery with congenital absence of left coronary system: A case report. *World J Cardiol* 2023; 15: 649-654. Copyright ©2023 The Authors. Published by Baishideng Publishing Group Inc.

descending coronary artery (Figure 2C).

CONCLUSION

Although the presence of a single coronary artery was identified as the cause of decreased exercise tolerance only 2 wk prior, it is not easy to understand that this patient had no symptoms until she was 62 years old, because this anomaly is congenital. Thus, in addition to the ischemia associated with the anomaly, it cannot be ruled out that the increase in double products associated with increased blood pressure and/or the appearance of microcirculatory disorders[11] may have had an effect. Meticulous follow-up would be crucial, because it has been pointed out that sudden death may occur in single coronary arteries[7]. It is also mandatory to prevent atherosclerosis with their full efforts, as the authors indicated admirably.

FOOTNOTES

Author contributions: Ito S contributed to this paper; Ito S designed the overall concept and outline of the manuscript; Ito S contributed to the discussion and design of the manuscript; Ito S contributed to the writing, editing of the manuscript, and review of the literature.

Conflict-of-interest statement: The author has no conflict-of-interest to state.

Country/Territory of origin: Japan

ORCID number: Shigenori Ito 0000-0002-3319-1697.

S-Editor: Zhang H
L-Editor: A
P-Editor: Guo X

REFERENCES

1 **Zhou YP**, Wang LL, Qiu YG, Huang SW. R-I subtype single right coronary artery with congenital absence of left coronary system: A case report. *World J Cardiol* 2023; **15**: 649-654 [PMID: 38173905 DOI: 10.4330/wjc.v15.i12.649]
2 **Pandey NN**, Sinha M, Sharma A, Rajagopal R, Bhambri K, Kumar S. Anomalies of coronary artery origin: Evaluation on multidetector CT angiography. *Clin Imaging* 2019; **57**: 87-98 [PMID: 31170598 DOI: 10.1016/j.clinimag.2019.05.010]
3 **Krishan S**, Dhiman RK, Kalra N, Sharma R, Baijal SS, Arora A, Gulati A, Eapan A, Verma A, Keshava S, Mukund A, Deva S, Chaudhary R, Ganesan K, Taneja S, Gorsi U, Gamanagatti S, Madhusudan KS, Puri P, Shalimar, Govil S, Wadhavan M, Saigal S, Kumar A, Thapar S, Duseja A, Saraf N, Khandelwal A, Mukhopadyay S, Shetty N, Verma N. Corrigendum to "Joint Consensus Statement of the Indian National Association for Study of the Liver and Indian Radiological and Imaging Association for the Diagnosis and Imaging of Hepatocellular Carcinoma Incorporating Liver Imaging Reporting and Data System" [J Clin Expt Hepatol 9 (2019) 625-651]. *J Clin Exp Hepatol* 2020; **10**: 188 [PMID: 32189936 DOI: 10.1016/j.jceh.2020.02.004]
4 **Şahin T**, Ilgar M. Investigation of the Frequency of Coronary Artery Anomalies in MDCT Coronary Angiography and Comparison of Atherosclerotic Involvement between Anomaly Types. *Tomography* 2022; **8**: 1631-1641 [PMID: 35736883 DOI: 10.3390/tomography8030135]
5 **Vijayvergiya R**, Kasinadhuni G, Vemuri KS, Gupta A, Kumar B, Lal A, Revaiah PC, Rajan P, Uppal L. Percutaneous Coronary Revascularization in Patients With Single Coronary Artery. *Cardiovasc Revasc Med* 2021; **29**: 32-37 [PMID: 32843245 DOI: 10.1016/j.carrev.2020.08.015]
6 **Rosenthal RL**, Carrothers IA, Schussler JM. Benign or malignant anomaly? Very high takeoff of the left main coronary artery above the left coronary sinus. *Tex Heart Inst J* 2012; **39**: 538-541 [PMID: 22949773]
7 **Chaikriangkrai K**, Kassi M, Polsani V, Chang SM. Case report: single coronary artery with ischemia and sudden cardiac arrest. *Methodist Debakey Cardiovasc J* 2014; **10**: 121-123 [PMID: 25114765 DOI: 10.14797/mdcj-10-2-121]
8 **Cocco N**, Madonna R, Cammalleri V, Cocco G, De Stefano D, Ricciardi D, Grigioni F, Ussia GP. Percutaneous treatment of a CTO in an anomalous right coronary artery: A rupture paved the way for new insights. *Front Cardiovasc Med* 2022; **9**: 916616 [PMID: 35966553 DOI: 10.3389/fcvm.2022.916616]
9 **Khanal S**, Vijayvergiya R, Singhal M. PCI in a single coronary artery from right aortic sinus: A rare case. *Indian Heart J* 2015; **67**: 141-143 [PMID: 26071294 DOI: 10.1016/j.ihj.2015.03.004]
10 **Sharma S**, Pillai GM, Potdar A, Malavia G. Percutaneous Coronary Intervention in Anomalously arising Coronary Arteries. *J Assoc Physicians India* 2022; **70**: 11-12 [PMID: 37355973 DOI: 10.5005/japi-11001-0154]
11 **Del Buono MG**, Montone RA, Camilli M, Carbone S, Narula J, Lavie CJ, Niccoli G, Crea F. Coronary Microvascular Dysfunction Across the Spectrum of Cardiovascular Diseases: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2021; **78**: 1352-1371 [PMID: 34556322 DOI: 10.1016/j.jacc.2021.07.042]

World Journal of Cardiology

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

World J Cardiol 2024 April 26; 16(4): 177-180

DOI: 10.4330/wjc.v16.i4.177

ISSN 1949-8462 (online)

EDITORIAL

Transcatheter aortic valve replacement in low-risk young population: A double edge sword?

Sukhdeep Bhogal, Akash Batta

Specialty type: Cardiac and cardiovascular systems

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Bloomfield D, United States

Received: December 1, 2023
Peer-review started: December 1, 2023
First decision: February 5, 2024
Revised: February 12, 2024
Accepted: March 26, 2024
Article in press: March 26, 2024
Published online: April 26, 2024

Sukhdeep Bhogal, Department of Cardiology, Sovah Health, Martinsville, VA 24112, United States

Akash Batta, Department of Cardiology, Dayanand Medical College and Hospital, Ludhiana 141001, India

Corresponding author: Akash Batta, Doctor, MD, Assistant Professor, Researcher, Department of Cardiology, Dayanand Medical College and Hospital, Tagore Nagar, Civil Lines, Ludhiana 141001, India. akashbatta02@gmail.com

Abstract

Since the advent of transcatheter aortic valve replacement (TAVR) in 2002, it has now become the default interventional strategy for symptomatic patients presenting with severe aortic stenosis, particularly in intermediate to high-surgical risk patients. In 2019, the United States Food and Drug Administration approved TAVR in low-risk patients based on two randomized trials. However, these breakthrough trials excluded patients with certain unfavorable anatomies and odd profiles. While currently there is no randomized study of TAVR in young patients, it may be preferred by the young population given the benefits of early discharge, shorter hospital stay, and expedite recovery. Nonetheless, it is important to ruminate various factors including lifetime expectancy, risk of pacemaker implantation, and the need for future valve or coronary interventions in young cohorts before considering TAVR in these patients. Furthermore, the data on long-term durability (> 10 years) of TAVR is still unknown given most of the procedures were initially performed in the high or prohibitive surgical risk population. Thus, this editorial aims to highlight the importance of considering an individualized approach in young patients with consideration of various factors including lifetime expectancy while choosing TAVR against surgical aortic valve replacement.

Key Words: Transcatheter aortic valve replacement; Surgical aortic valve replacement; Pacemaker implantation; Coronary re-access; Structural deterioration

Core Tip: In 2019, the United States Food and Drug Administration approved transcatheter aortic valve replacement (TAVR) in low-risk patients based on the two large randomized trials. However, patients with certain unfavorable anatomies and clinical profiles were excluded from these trials. Despite the lack of clear evidence in young patients (< 65 years), it may be preferred by this population given the benefits of early discharge, shorter hospital stay, and expedite recovery. Nonetheless, it is important to ruminate various factors including lifetime expectancy, risk of pacemaker implantation, and the need for future valve or coronary interventions in young cohorts before considering TAVR in these patients.

Citation: Bhogal S, Batta A. Transcatheter aortic valve replacement in low-risk young population: A double edge sword? *World J Cardiol* 2024; 16(4): 177-180
URL: https://www.wjgnet.com/1949-8462/full/v16/i4/177.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i4.177

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has now revolutionized the treatment of symptomatic severe AS and has now become the standard of care across all risk categories. The first transcatheter heart valve (THV) designed by Cribier *et al*[1] was a stainless-steel stent (23 mm in diameter and 17 mm in height) containing a trileaflet valve made of bovine pericardium, compatible with a 24-French introducer sheath and was implanted using antegrade transeptal approach. Since then, there has been a huge refinement in the design of both THVs and delivery systems, transforming challenging interventions into a standardized, streamlined procedure. It has emerged as a less invasive alternative therapy to conventional surgical aortic valve replacement (SAVR) with either superior or comparable outcomes. As it has been two decades since the first implant in April 2002, the use of TAVR expanded rapidly with randomized data showing the safety and efficacy of TAVR initially in inoperable-risk, followed by high, intermediate, and most recently low-risk patients. However, the landmark trials investigating TAVR excluded patients with unfavorable anatomy such as bicuspid aortic valve, associated aortopathy, short or large annulus diameters, concomitant severe valvular disease, and young populations < 65 years of age. Certain concerns emerge when TAVR is contemplated for younger population with expected survival > 10 years.

CONSIDERATIONS AND RISK IN YOUNGER PATIENTS UNDERGOING TAVR

The key trepidations during or following TAVR include the risk of conduction abnormalities, coronary artery obstruction, and future coronary re-access. Studies have shown longer hospital stays[2] and a higher risk of all-cause death with pacemaker implantation at 1-year post-TAVR[3]. Though factors such as implantation depth are operator-dependent, the presence of conduction abnormalities such as baseline right bundle branch block is a known predictor of increased risk of pacemaker implantation[4]. TAVR has demonstrated higher rates of pacemaker implantation compared to SAVR, even in low-risk patients[5]. The deleterious effects of right ventricular pacing on cardiac hemodynamics are established and include increased bi-ventricular volumes and dysfunction in the long run along with predisposition to the development of cardiac arrhythmia, particularly atrial fibrillation. Additionally, younger patients with a pacemaker would require multiple generator changes given longer life expectancy which further adds to the morbidity. While the cusp overlap technique showed promise in reducing the rates of pacemaker implantation with self-expanding valves, it remains a valid concern, particularly in the young population[6].

Furthermore, coronary artery obstruction is rare, but a life-threatening complication associated with a very high periprocedural and late mortality[7]. Also, with the extension of TAVR in low-risk young patients, interventional cardiologists are likely to face challenges in re-accessing coronaries in these patients, due to progressive coronary artery disease given the similar baseline risk factors. Thus, the preprocedural planning in young patients before considering TAVR or SAVR should include an evaluation of all these factors plus an assessment of congenital valve abnormalities (bicuspid or unicuspid), unfavorable anatomies such as short or large annulus diameter, presence of peripheral artery disease and concomitant severe valvular disease or significant coronary artery disease. Similarly, the coronary height and choice of THV become important when considering TAVR in this group of patients. Yet, when these abnormalities or conditions are present, they should be considered comprehensively based on individual risk profiles before decision-making.

For patients with symptomatic or asymptomatic severe AS, the current valvular guidelines endorse (class I recommendation) the use of TAVR for patients > 80 years or younger patients with life expectancy < 10 years over SAVR [8]. In contrast, for patients < 65 years of age or have life expectancy > 20 years, SAVR is recommended over TAVR[8]. Lastly, for patients between age of 65 and 80 years of age, the guidelines endorse the use of either TAVR or SAVR based on the heart team approach[8]. The fundamental limitation of THV is that they are prone to degeneration, which constraint their long-term durability. This is important, particularly in young patients, who have long life expectancy and are, therefore, more likely to need repeat valve interventions. The initial studies of TAVR were conducted in inoperable and high-risk octogenarians, which limited the identification of late valve degeneration as these subjects died from other causes before the commencement of valve dysfunction[9]. The latest evidence shows promising durability of TAVR

valves beyond 5 years and freedom from structural valve deterioration between 6 and 9 years of duration[10-12]. However, the data on the durability of these valves beyond 10 years is currently unavailable. Moreover, a specific risk prediction tool for THV is not available. For younger patients < 50 years of age, SAVR with a mechanical valve prosthesis appears to be a reasonable option provided no contraindication to anticoagulation with patients' willing to consider long-term vitamin K antagonist therapy while avoiding the risk of reoperation[8]. Additionally, for young patients with atrial fibrillation, or unprovoked venous thromboembolism, or hypercoagulable states demanding long-term anticoagulation, a mechanical valve appears a reasonable consideration. Evidence on the latest-generation mechanical bi-leaflet prosthesis valves is encouraging in terms of the need for relatively lower levels of international normalized ratio maintained between 1.5 to 2.0, which is associated with reduced risk of major and minor bleeding events[13]. Otherwise, if anticoagulation is undesirable or contraindicated, consideration of Ross procedure that involves replacement of the aortic valve with the patient's own pulmonic valve, and the pulmonic valve with a homograft is currently recommended in young patients[14].

The debate among 50-69 years of age remains ongoing, given multiple observational studies showing similar survival rates with either mechanical or bioprosthetic THV[15-17]. Some studies in patients aged < 65 years, demonstrated increased rates of valve deterioration, reoperation, and mortality with surgical bioprosthetic valves, however, with lower rates of stroke and hemorrhage over mechanical valves[18-20]. Therefore, it is imperative to consider the tradeoffs including bleeding, reoperation, and life expectancy in these patients. Lastly, there is no precise risk tool to predict the deterioration rate of THV, which is inevitable in current bioprosthetic valves.

CONCLUSION

In conclusion, while TAVR in young patients seems a reasonable alternative given the desirable benefits of early discharge and expedited recovery, it does not appear to be a straightforward answer for all patients when considering various individual risk profiles and weighing future options. With this uncertainty, debate continues in the field of structural cardiology as to which option (SAVR *vs* TAVR) and or valve (mechanical *vs* bioprosthetic) is the best optimal strategy for low-risk young patients. Therefore, although there is no good answer yet while awaiting further research and new valve refinements, shared decision-making is recommended regarding the choice of the prosthetic valve by considering individualized patient factors including age, values, and preferences including anticoagulation and lifetime strategies such as predictability of reoperation and future valves[8].

FOOTNOTES

Author contributions: Bhogal S and Batta A wrote the manuscript, read and approved the final manuscript; they have contributed equally to this manuscript.

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

Country/Territory of origin: India

ORCID number: Sukhdeep Bhogal 0000-0001-9212-557X; Akash Batta 0000-0002-7606-5826.

Corresponding Author's Membership in Professional Societies: American College of Cardiology, No. 3445007; European society of Cardiology, No. 1036629.

S-Editor: Zhang H
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Cribier A**, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, Derumeaux G, Anselme F, Laborde F, Leon MB. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation* 2002; **106**: 3006-3008 [PMID: 12473543 DOI: 10.1161/01.cir.0000047200.36165.b8]

2 **Regueiro A**, Abdul-Jawad Altisent O, Del Trigo M, Campelo-Parada F, Puri R, Urena M, Philippon F, Rodés-Cabau J. Impact of New-Onset Left Bundle Branch Block and Periprocedural Permanent Pacemaker Implantation on Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis. *Circ Cardiovasc Interv* 2016; **9**: e003635 [PMID: 27169577 DOI: 10.1161/CIRCINTERVENTIONS.115.003635]

3 **Faroux L**, Chen S, Muntané-Carol G, Regueiro A, Philippon F, Sondergaard L, Jørgensen TH, Lopez-Aguilera J, Kodali S, Leon M, Nazif T, Rodés-Cabau J. Clinical impact of conduction disturbances in transcatheter aortic valve replacement recipients: a systematic review and meta-analysis. *Eur Heart J* 2020; **41**: 2771-2781 [PMID: 31899484 DOI: 10.1093/eurheartj/ehz924]

4 **Meduri CU**, Kereiakes DJ, Rajagopal V, Makkar RR, O'Hair D, Linke A, Waksman R, Babliaros V, Stoler RC, Mishkel GJ, Rizik DG, Iyer VS, Schindler J, Allocco DJ, Meredith IT, Feldman TE, Reardon MJ. Pacemaker Implantation and Dependency After Transcatheter Aortic Valve Replacement in the REPRISE III Trial. *J Am Heart Assoc* 2019; **8**: e012594 [PMID: 31640455 DOI: 10.1161/JAHA.119.012594]

5 **Kolte D**, Vlahakes GJ, Palacios IF, Sakhuja R, Passeri JJ, Inglessis I, Elmariah S. Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients. *J Am Coll Cardiol* 2019; **74**: 1532-1540 [PMID: 31537261 DOI: 10.1016/j.jacc.2019.06.076]

6 **Pisaniello AD**, Makki HBE, Jahangeer S, Daniels MJ, Hasan R, Fraser DGW. Low Rates of Permanent Pacing Are Observed Following Self-Expanding Transcatheter Aortic Valve Replacement Using an Annular Plane Projection for Deployment. *Circ Cardiovasc Interv* 2021; **14**: e009258 [PMID: 33430606 DOI: 10.1161/CIRCINTERVENTIONS.120.009258]

7 **Ribeiro HB**, Nombela-Franco L, Urena M, Mok M, Pasian S, Doyle D, DeLarochellière R, Côté M, Laflamme L, DeLarochellière H, Allende R, Dumont E, Rodés-Cabau J. Coronary obstruction following transcatheter aortic valve implantation: a systematic review. *JACC Cardiovasc Interv* 2013; **6**: 452-461 [PMID: 23602458 DOI: 10.1016/j.jcin.2012.11.014]

8 **Otto CM**, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A, Toly C. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021; **143**: e72-e227 [PMID: 33332150 DOI: 10.1161/CIR.0000000000000923]

9 **Mack MJ**, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ, Svensson LG; PARTNER 1 trial investigators. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015; **385**: 2477-2484 [PMID: 25788234 DOI: 10.1016/S0140-6736(15)60308-7]

10 **Holy EW**, Kebernik J, Abdelghani M, Stämpfli SF, Hellermann J, Allali A, El-Mawardy M, Sachse S, Lüscher TF, Tanner FC, Richardt G, Abdel-Wahab M. Long-term durability and haemodynamic performance of a self-expanding transcatheter heart valve beyond five years after implantation: a prospective observational study applying the standardised definitions of structural deterioration and valve failure. *EuroIntervention* 2018; **14**: e390-e396 [PMID: 29741488 DOI: 10.4244/EIJ-D-18-00041]

11 **Blackman DJ**, Saraf S, MacCarthy PA, Myat A, Anderson SG, Malkin CJ, Cunnington MS, Somers K, Brennan P, Manoharan G, Parker J, Aldalati O, Brecker SJ, Dowling C, Hoole SP, Dorman S, Mullen M, Kennon S, Jerrum M, Chandrala P, Roberts DH, Tay J, Doshi SN, Ludman PF, Fairbairn TA, Crowe J, Levy RD, Banning AP, Ruparelia N, Spence MS, Hildick-Smith D. Long-Term Durability of Transcatheter Aortic Valve Prostheses. *J Am Coll Cardiol* 2019; **73**: 537-545 [PMID: 30732706 DOI: 10.1016/j.jacc.2018.10.078]

12 **Søndergaard L**, Ihlemann N, Capodanno D, Jørgensen TH, Nissen H, Kjeldsen BJ, Chang Y, Steinbrüchel DA, Olsen PS, Petronio AS, Thyregod HGH. Durability of Transcatheter and Surgical Bioprosthetic Aortic Valves in Patients at Lower Surgical Risk. *J Am Coll Cardiol* 2019; **73**: 546-553 [PMID: 30732707 DOI: 10.1016/j.jacc.2018.10.083]

13 **Puskas J**, Gerdisch M, Nichols D, Quinn R, Anderson C, Rhenman B, Fermin L, McGrath M, Kong B, Hughes C, Sethi G, Wait M, Martin T, Graeve A; PROACT Investigators. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized on-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. *J Thorac Cardiovasc Surg* 2014; **147**: 1202-1210; discussion 1210 [PMID: 24512654 DOI: 10.1016/j.jtcvs.2014.01.004]

14 **Mazine A**, El-Hamamsy I, Verma S, Peterson MD, Bonow RO, Yacoub MH, David TE, Bhatt DL. Ross Procedure in Adults for Cardiologists and Cardiac Surgeons: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2018; **72**: 2761-2777 [PMID: 30497563 DOI: 10.1016/j.jacc.2018.08.2200]

15 **Chan V**, Jamieson WR, Germann E, Chan F, Miyagishima RT, Burr LH, Janusz MT, Ling H, Fradet GJ. Performance of bioprostheses and mechanical prostheses assessed by composites of valve-related complications to 15 years after aortic valve replacement. *J Thorac Cardiovasc Surg* 2006; **131**: 1267-1273 [PMID: 16733156 DOI: 10.1016/j.jtcvs.2005.11.052]

16 **Chiang YP**, Chikwe J, Moskowitz AJ, Itagaki S, Adams DH, Egorova NN. Survival and long-term outcomes following bioprosthetic vs mechanical aortic valve replacement in patients aged 50 to 69 years. *JAMA* 2014; **312**: 1323-1329 [PMID: 25268439 DOI: 10.1001/jama.2014.12679]

17 **Stassano P**, Di Tommaso L, Monaco M, Iorio F, Pepino P, Spampinato N, Vosa C. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. *J Am Coll Cardiol* 2009; **54**: 1862-1868 [PMID: 19892237 DOI: 10.1016/j.jacc.2009.07.032]

18 **Kaneko T**, Aranki S, Javed Q, McGurk S, Shekar P, Davidson M, Cohn L. Mechanical versus bioprosthetic mitral valve replacement in patients <65 years old. *J Thorac Cardiovasc Surg* 2014; **147**: 117-126 [PMID: 24079878 DOI: 10.1016/j.jtcvs.2013.08.028]

19 **Weber A**, Noureddine H, Englberger L, Dick F, Gahl B, Aymard T, Czerny M, Tevaearai H, Stalder M, Carrel TP. Ten-year comparison of pericardial tissue valves versus mechanical prostheses for aortic valve replacement in patients younger than 60 years of age. *J Thorac Cardiovasc Surg* 2012; **144**: 1075-1083 [PMID: 22341653 DOI: 10.1016/j.jtcvs.2012.01.024]

20 **Brennan JM**, Edwards FH, Zhao Y, O'Brien S, Booth ME, Dokholyan RS, Douglas PS, Peterson ED; DEcIDE AVR (Developing Evidence to Inform Decisions about Effectiveness–Aortic Valve Replacement) Research Team. Long-term safety and effectiveness of mechanical versus biologic aortic valve prostheses in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. *Circulation* 2013; **127**: 1647-1655 [PMID: 23538379 DOI: 10.1161/CIRCULATIONAHA.113.002003]

World Journal of Cardiology

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

World J Cardiol 2024 April 26; 16(4): 181-185

DOI: 10.4330/wjc.v16.i4.181

ISSN 1949-8462 (online)

EDITORIAL

Hypoxia-inducible factor-1α in myocardial infarction

Ivana Škrlec, Sergey N Kolomeichuk

Specialty type: Biochemistry and molecular biology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Adam CA, Romania; Kawaguchi N, Japan

Received: December 13, 2023
Peer-review started: December 13, 2023
First decision: January 15, 2024
Revised: January 26, 2024
Accepted: March 4, 2024
Article in press: March 4, 2024
Published online: April 26, 2024

Ivana Škrlec, Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek 31000, Croatia

Sergey N Kolomeichuk, Institute of Biology, Karelia Research Center of Russian Academy of Sciences, Petrozavodsk 185910, Russia

Sergey N Kolomeichuk, Laboratory for Genomics, Proteomics, and Metabolomics, Research Institute of Biomedicine and Biomedical Technologies, Tyumen State Medical University, Tyumen 625023, Russia

Corresponding author: Ivana Škrlec, MSc, PhD, Assistant Professor, Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Crkvena 21, Osijek 31000, Croatia. iskrlec@fdmz.hr

Abstract

Hypoxia-inducible factor 1 (HIF1) has a crucial function in the regulation of oxygen levels in mammalian cells, especially under hypoxic conditions. Its importance in cardiovascular diseases, particularly in cardiac ischemia, is because of its ability to alleviate cardiac dysfunction. The oxygen-responsive subunit, HIF1α, plays a crucial role in this process, as it has been shown to have cardioprotective effects in myocardial infarction through regulating the expression of genes affecting cellular survival, angiogenesis, and metabolism. Furthermore, *HIF1α* expression induced reperfusion in the ischemic skeletal muscle, and hypoxic skin wounds in diabetic animal models showed reduced *HIF1α* expression. Increased expression of *HIF1α* has been shown to reduce apoptosis and oxidative stress in cardiomyocytes during acute myocardial infarction. Genetic variations in *HIF1α* have also been found to correlate with altered responses to ischemic cardiovascular disease. In addition, a link has been established between the circadian rhythm and hypoxic molecular signaling pathways, with HIF1α functioning as an oxygen sensor and circadian genes such as period circadian regulator 2 responding to changes in light. This editorial analyzes the relationship between HIF1α and the circadian rhythm and highlights its significance in myocardial adaptation to hypoxia. Understanding the changes in molecular signaling pathways associated with diseases, specifically cardiovascular diseases, provides the opportunity for innovative therapeutic interventions, especially in low-oxygen environments such as myocardial infarction.

Key Words: Cardiovascular pathologies; Circadian genes; Hypoxia-inducible factor 1; Hypoxia; Gene-gene interaction

Core Tip: Hypoxia-inducible factor 1 (HIF1), a versatile transcription factor, is crucial for the maintenance of oxygen homeostasis. Genetic variations in *HIF1α* may influence tissue response to hypoxia and affect clinical manifestations of coronary atherosclerosis. Research has confirmed that sufficient *HIF1α* expression leads to reperfusion in the ischemic skeletal muscle, whereas decreased expression is associated with hypoxic skin wounds in diabetic animal models. In addition, the HIF1α response can be influenced by circadian proteins. Interpretation of circadian and hypoxia signaling pathways may enable therapeutic interventions in diseases associated with oxygen deprivation, including myocardial infarction.

Citation: Škrlec I, Kolomeichuk SN. Hypoxia-inducible factor-1α in myocardial infarction. *World J Cardiol* 2024; 16(4): 181-185
URL: https://www.wjgnet.com/1949-8462/full/v16/i4/181.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i4.181

INTRODUCTION

Hypoxia-inducible factor 1 (HIF1) is a central regulator of oxygen homeostasis in mammalian cells and is activated under hypoxic conditions[1]. Hypoxia is a hallmark of many physiological and pathological conditions, and a stable HIF1α protein is essential for the adaptation and survival of cells in an oxygen-deprived environment – hypoxia[2]. In addition, HIF1 contributes to several hypoxia-related diseases, including cardiovascular diseases[1]. Oxidative metabolism is essential for the maintenance of cardiac contractility as it produces a large amount of ATP. Therefore, the heart is extremely sensitive to hypoxia, and myocardial ischemia is the leading cause of death in developed countries[3]. Oxygen-sensitive signaling pathways, such as HIF1α, are important for adapting to changes in oxygen availability during myocardial ischemia. HIF1α protein levels are regulated post-transcriptionally and are inversely proportional to oxygen levels[4]. HIF1α is involved in vascular responses to hypoxia, such as ischemia-induced angiogenesis and lipid metabolism, glucose catabolism, and redox homeostasis. The genetic variability of *HIF1α* is associated with cardiovascular diseases, such as coronary heart disease, ischemic heart disease, preeclampsia, and acute myocardial infarction[2].

HIF1α SUBUNIT

HIF1 is a transcription factor that consists of two subunits, α and β. The HIF1α subunit is oxygen-sensitive, whereas HIF1β is constitutively expressed[3]. The gene sequence encoding the HIF1α subunit is located on the long arm of chromosome 14 (14q23.2) and plays an important role in regulating cellular processes to maintain oxygen homeostasis[5]. In mammals, there are three different variants of the HIFα protein, with HIF1α being ubiquitously expressed in all cells, whereas the expression of HIF2α and HIF3α varies according to cell type and tissue[2]. Under conditions of oxygen deprivation - hypoxia - the expression of most genes is repressed at the transcriptional level. In contrast, the expression of a specific group of genes, the so-called hypoxia-inducible genes, is increased under hypoxic conditions[6]. These genes include erythropoietin, vascular endothelial growth factor, and genes involved in cell metabolism and inflammation[7]. Under normoxia, HIF1α is subject to oxygen-dependent hydroxylation. It is degraded by prolyl hydroxylase, an E3 ubiquitin ligase, and by the von Hippel-Lindau degradation pathway in the ubiquitin-proteasome system[1,4]. Under hypoxic conditions, HIF1α is prevented from degradation, accumulates, and migrates to the nucleus[6]. In the nucleus, the α-subunit of HIF1 forms a heterodimer with the β-subunit, resulting in a transcription factor that promotes cell survival, angiogenesis, and glycolysis[8]. HIF1α binds to hypoxia-responsive elements in the nucleus and activates the transcription of hypoxia-inducible genes[6] (Figure 1). It also stimulates gene transcription by binding to a specific DNA sequence 5'-RCGTG-3' (where R can be an A or G) within the hypoxia-responsive elements[9]. HIF1α stimulates the transcription of genes responsible for the production of enzymes, transporters, and mitochondrial proteins. These genes contribute to the reduction in oxygen consumption and control the transition of cells from oxidative to glycolytic metabolism[9]. When oxygen levels are reduced, the degradation of HIF1α is inhibited, leading to a strong accumulation of HIF1α[4].

In addition, changes in the nucleotide sequence or expression of the HIF1α subunit are associated with the development of various diseases[2]. *HIF1α* polymorphisms, such as rs11549465 (Pro582Ser) and rs2057482, may impair the response to tissue hypoxia and influence the clinical manifestations of coronary atherosclerosis by affecting HIF1α subunit degradation and *HIF1α* mRNA stability[8]. The rs11549467 polymorphism is also important for HIF1α subunit stability[5]. The *HIF1α* rs2057482 polymorphism is a risk factor for the development of premature coronary heart disease [5]. These variations may influence the tissue response to hypoxia and affect the clinical manifestations of coronary atherosclerosis[8].

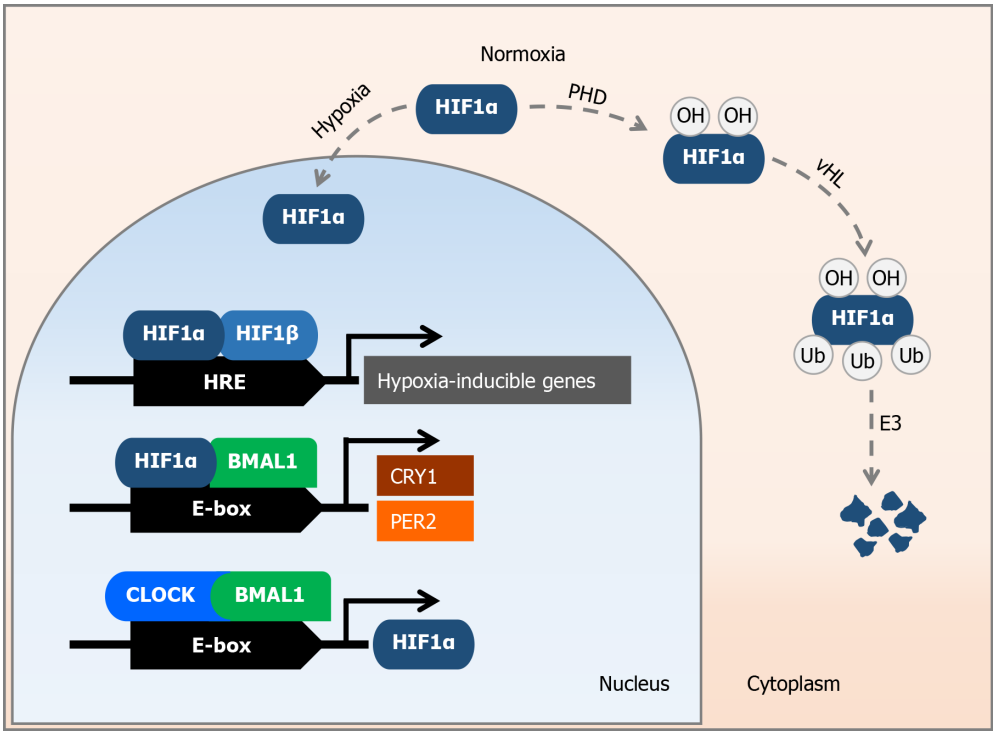

Figure 1 Molecular effects of hypoxia-inducible factor 1α under normal oxygen conditions and under oxygen deprivation. Under normal oxygen conditions, hypoxia-inducible factor 1α (HIF1α) is degraded by the ubiquitin-proteasome system *via* an oxygen-dependent pathway involving prolyl hydroxylases, the von Hippel-Lindau protein, and an E3 ubiquitin ligase. In the case of an oxygen shortage – hypoxia, HIF1α in the cell nucleus dimerizes with HIF1β, and binds itself to hypoxia response elements, which are associated with hypoxia-inducible genes. Furthermore, the HIF1α-basic helix-loop-helix ARNT like 1 (BMAL1) heterodimer binds to the specific E-box region of circadian genes, thereby enhancing the expression of period circadian regulator 2 and cryptochrome circadian regulator 1. In addition, the BMAL1-circadian locomotor output cycles kaput heterodimer enhances *HIF1α* expression under hypoxic conditions. HIF1α: Hypoxia-inducible factor 1α; PHD: Prolyl hydroxylases; vHL: von Hippel-Lindau protein; HRE: Hypoxia response elements; BMAL1: Basic helix-loop-helix ARNT like 1; PER2: Period circadian regulator 2; CRY1: Cryptochrome circadian regulator 1; CLOCK: Circadian locomotor output cycles kaput.

HIF1α IN MYOCARDIAL INFARCTION

Cardiovascular diseases are prone to ischemic injury[2]. In these diseases, such as atherosclerosis and myocardial infarction, the oxygen supply to cells is reduced owing to impaired blood flow, eventually leading to tissue hypoxia[6], and cardiac hypoxia or ischemia[1]. Mammalian cells respond quickly and adapt to hypoxic conditions[2]. HIF1α plays a significant role in this process and confers cardioprotective effects to deoxygenated myocardium[2]. In humans, HIF1α insufficiency may correlate in part with congenital heart abnormalities[9]. HIF1α directly regulates over 1000 genes in the human genome during hypoxia, most of which are expressed in a specific cell type[9]. It is important to emphasize that this regulation is not an indirect, but a direct effect of HIF1α.

HIF1α acts as a cellular oxygen sensor in cardiomyocytes[10]. Its overexpression in the heart during acute myocardial infarction leads to the upregulation of proangiogenic HIF1α target genes, resulting in reduced cardiac dysfunction and decreased cardiomyocyte apoptosis[7]. In addition, excessive levels of HIF1α promote the expression of heme oxygenase-1 (HO-1), which reduces the accumulation of reactive oxygen species[10]. Moreover, increased *HIF1α* expression suppresses the pro-apoptotic gene BCL2 interacting protein-3 (BNIP3) *via* the nuclear factor kappa B (NF-κB) protein. *HIF1α* expression increases during myocardial infarction and serves as a regulator of the cellular hypoxia response[10]. The Pro582Ser (rs11549465) polymorphism in *HIF1α* affects the response to ischemic cardiovascular diseases. Furthermore, inhibition of *HIF1α* or *HIF1β* expression in myocardial endothelial cells leads to a lack of acute cardioprotection after ischemic preconditioning[9]. Inhibition of *HIF1α* in the myocardium could either promote or impair cardiomyocyte apoptosis. Increased expression of *HIF1α* in myocardial infarction significantly reduces the size of the infarct and restores the typical histologic structure of the myocardium. In addition, overexpression of *HIF1α* reduces the oxidative stress load during myocardial infarction[10]. Increased *HIF1α* expression promotes NF-κB binding to the *BNIP3* promoter, which reduces *BNIP3* expression and BNIP3-mediated apoptotic activity in hypoxic cardiomyocytes[10]. The signaling pathways mediated by HIF1α and NF-κB show synergistic interaction to reduce cardiomyocyte apoptosis. Increased cardiac-specific *HIF1α* expression during myocardial infarction leads to differential regulation of HO-1 and BNIP3 expression by HIF1α and NF-κB[10], demonstrating the crucial role of these signaling pathways in cardioprotection. In addition, HIF1α influences the balance between glycolytic and oxidative metabolism, with elevated levels of HIF1α leading to the expression of genes responsible for glucose transporters and glycolytic enzymes[9]. As a result, expression of *HIF1α* has been shown to be sufficient to trigger reperfusion in the ischemic skeletal muscle. However, *HIF1α* expression was reduced in the hypoxic skin wounds of old diabetic mice[2]. HIF1α may have a protective, proangiogenic, and pathogenic effect during infarction as it regulates metabolic reprogramming leading to energy

depletion[9].

Cardiac hypoxia is usually caused by myocardial ischemia, which occurs when the metabolic needs of the heart muscle are not met owing to insufficient oxygen supply[2]. Arterial stenosis-induced hypoxia promotes the expression of *HIF1α*, which in turn stimulates the production of angiogenic growth factors, leading to vascular remodeling and increased blood flow. HIF1α is essential for ischemic preconditioning as it reduces reactive oxygen species production, protecting the heart from injury[9]. Chronic disease and aging impede this response. HIF1α plays a multifaceted role in the pathophysiology of myocardial infarction. It may be protective by promoting angiogenesis or pathologic through maladaptive metabolic reprogramming[9].

Different genetic variations of *HIF1α* can potentially affect the risk of myocardial infarction by influencing numerous mechanisms. Cardiac ischemia induces strong *HIF1α* expression, which could stimulate the formation of new blood vessels near the coronary arteries. Variations in *HIF1α* may alter the risk of acute myocardial infarction by inhibiting the development of new blood vessels near the atherosclerotic plaques in the coronary arteries[8]. Certain polymorphisms of *HIF1α* have been associated with cardiovascular diseases, including rs11549465, rs10873142, rs2057482, rs11549467, rs41508050, rs2783778, and rs7148720[2]. Several studies have investigated the association between different polymorphisms of *HIF1α* and cardiovascular diseases. However, conflicting and controversial results have been reported, indicating both positive and negative associations between *HIF1α* variations and cardiovascular diseases[5,8].

HIF1α AND THE CIRCADIAN RHYTHM IN MYOCARDIAL INFARCTION

Research has indicated a link between circadian and hypoxic molecular pathways. HIF1α acts as an oxygen sensor, whereas period circadian regulator 2 (PER2) acts as a light sensor[7]. In response to HIF1α, several circadian rhythm genes respond to changes in oxygen levels[4]. HIF1α is able to induce the expression of *PER2* and cryptochrome circadian regulator 1 (*CRY1*)[1]. Stabilization of HIF1α by PER2 is necessary for myocardial adaptation to hypoxia[11]. HIF1α regulates the hypoxic response to myocardial infarction *via* the circadian rhythm and influences the expression of target genes[1]. The adaptation of cardiomyocytes to hypoxia, known as ischemic demand, makes them more resistant to infarction by expressing high levels of PER2 and HIF1α[11]. HIF1α, HIF1β, basic helix-loop-helix ARNT like 1 (BMAL1), and circadian locomotor output cycles kaput (CLOCK) are transcription factors that respond to physiological and environmental signals. In addition, HIF1α can regulate circadian rhythms, whereas circadian proteins have the ability to influence the HIF1α response[12]. Additionally, similar to BMAL1, HIF1α contains a basic helix-loop-helix - period-ARNT-single minded (bHLH-PAS) domain. Through this domain, it dimerizes with BMAL1 and stimulates the expression of target genes. Thus, HIF1α serves as a molecular link between oxygen levels and the circadian rhythm[13].

The HIF1α-BMAL1 heterodimer binds to the same E-box regions of target genes as the CLOCK-BMAL1 heterodimer and influences the expression of downstream genes such as *PER2*, *CRY1*, and *HIF1α* target genes[1] (Figure 1). HIF1α is associated with vascular inflammation and the progression of atherosclerosis, whereas CLOCK and BMAL1 can also promote *HIF1α* expression[1]. Furthermore, myocardial ischemia triggers pathways to improve oxygen delivery and, during hypoxia, PER2 interacts with HIF1α[13]. This occurs because PER2 stabilizes HIF1α *via* adenosine receptor A2B (ADORA2B), which is crucial for myocardial adaptation to hypoxia[14]. Additionally, daily rhythms are present in blood and tissue oxygenation, oxygen usage, and carbon dioxide release. Exposure to hypoxia leads to tissue- and time-specific changes in the expression of circadian clock genes. Myocardial tissue damage is associated with the time of day of infarction, suggesting a link between HIF1α and circadian regulation of infarction[15]. Severe hypoxia-induced outcomes, namely myocardial infarction, are associated with changes in circadian rhythm. The circadian rhythm plays a crucial role in fine-tuning hypoxic responses during pathological circumstances[15].

Mice lacking *Per2* are unable to maintain the stability of the HIF1α subunit in the myocardium during hypoxia, leading to increased cardiomyocyte death during ischemia[1]. Furthermore, myocardial damage after myocardial infarction appears to be worse in mice lacking *Per1* and *Per2* than in wild-type mice[15]. Within the physiological range, the oxygen cycle appropriately synchronizes cellular circadian clocks through a HIF1α-dependent mechanism. A slight reduction in oxygen levels for a short period of time facilitates adaptation to the time changes after jet lag in wild-type mice, but not in HIF1α-null mice[4].

Hypoxia and changing oxygen levels affect the circadian rhythm through different mechanisms involving HIF1α[1]. The circadian rhythm protects the heart muscle from hypoxia-induced cell death[1].

CONCLUSION

The relationship between hypoxia and circadian molecular signaling pathways needs further clarification in many physiological and pathophysiological processes, as these pathways are evolutionarily conserved and allow cells to adapt to unfavorable environmental conditions. The timing of the experiment significantly influences the circadian rhythm and, subsequently, HIF1α levels, which are associated with the severity of cardiovascular diseases. Studying the use of molecular signaling pathways in tissues and how they are influenced by specific diseases, particularly in the context of cardiovascular disease, presents new therapeutic possibilities for the treatment of diseases with low oxygen availability, such as myocardial infarction.

FOOTNOTES

Author contributions: Škrlec I did the majority of the writing and prepared the figure; Kolomeychuk SN did some writing and text editing.

Supported by Croatian Ministry of Science and Education, Josip Juraj Strossmayer University of Osijek, Faculty of Dental Medicine and Health, Osijek, Croatia, No. IP7-FDMZ-2023; West-Siberian Science and Education Center, Government of Tyumen District, Decree of 20.11.2020, No. 928-rp; and Ministry of Science and Higher Education, No. FMEN 2022-0009.

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

Country/Territory of origin: Croatia

ORCID number: Ivana Škrlec 0000-0003-1842-930X; Sergey N Kolomeichuk 0000-0003-3104-3639.

S-Editor: Gong ZM
L-Editor: A
P-Editor: Guo X

REFERENCES

1 **O'Connell EJ**, Martinez CA, Liang YG, Cistulli PA, Cook KM. Out of breath, out of time: interactions between HIF and circadian rhythms. *Am J Physiol Cell Physiol* 2020; **319**: C533-C540 [PMID: 32726159 DOI: 10.1152/ajpcell.00305.2020]

2 **Gladek I**, Ferdin J, Horvat S, Calin GA, Kunej T. HIF1A gene polymorphisms and human diseases: Graphical review of 97 association studies. *Genes Chromosomes Cancer* 2017; **56**: 439-452 [PMID: 28165644 DOI: 10.1002/gcc.22449]

3 **Knutson AK**, Williams AL, Boisvert WA, Shohet RV. HIF in the heart: development, metabolism, ischemia, and atherosclerosis. *J Clin Invest* 2021; **131** [PMID: 34623330 DOI: 10.1172/JCI137557]

4 **Adamovich Y**, Ladeuix B, Golik M, Koeners MP, Asher G. Rhythmic Oxygen Levels Reset Circadian Clocks through HIF1α. *Cell Metab* 2017; **25**: 93-101 [PMID: 27773695 DOI: 10.1016/j.cmet.2016.09.014]

5 **López-Reyes A**, Rodríguez-Pérez JM, Fernández-Torres J, Martínez-Rodríguez N, Pérez-Hernández N, Fuentes-Gómez AJ, Aguilar-González CA, Alvarez-León E, Posadas-Romero C, Villarreal-Molina T, Pineda C, Vargas-Alarcón G. The HIF1A rs2057482 polymorphism is associated with risk of developing premature coronary artery disease and with some metabolic and cardiovascular risk factors. The Genetics of Atherosclerotic Disease (GEA) Mexican Study. *Exp Mol Pathol* 2014; **96**: 405-410 [PMID: 24769354 DOI: 10.1016/j.yexmp.2014.04.010]

6 **Abe H**, Semba H, Takeda N. The Roles of Hypoxia Signaling in the Pathogenesis of Cardiovascular Diseases. *J Atheroscler Thromb* 2017; **24**: 884-894 [PMID: 28757538 DOI: 10.5551/jat.RV17009]

7 **Bartman CM**, Eckle T. Circadian-Hypoxia Link and its Potential for Treatment of Cardiovascular Disease. *Curr Pharm Des* 2019; **25**: 1075-1090 [PMID: 31096895 DOI: 10.2174/1381612825666190516081612]

8 **Hlatky MA**, Quertermous T, Boothroyd DB, Priest JR, Glassford AJ, Myers RM, Fortmann SP, Iribarren C, Tabor HK, Assimes TL, Tibshirani RJ, Go AS. Polymorphisms in hypoxia inducible factor 1 and the initial clinical presentation of coronary disease. *Am Heart J* 2007; **154**: 1035-1042 [PMID: 18035072 DOI: 10.1016/j.ahj.2007.07.042]

9 **Semenza GL**. Hypoxia-inducible factor 1 and cardiovascular disease. *Annu Rev Physiol* 2014; **76**: 39-56 [PMID: 23988176 DOI: 10.1146/annurev-physiol-021113-170322]

10 **Datta Chaudhuri R**, Banik A, Mandal B, Sarkar S. Cardiac-specific overexpression of HIF-1α during acute myocardial infarction ameliorates cardiomyocyte apoptosis *via* differential regulation of hypoxia-inducible pro-apoptotic and anti-oxidative genes. *Biochem Biophys Res Commun* 2021; **537**: 100-108 [PMID: 33388412 DOI: 10.1016/j.bbrc.2020.12.084]

11 **Škrlec I**, Marić S, Včev A. Myocardial infarction and circadian rhythm [Internet]. In: Angelos Tsipis. Visions of Cardiomyocyte - Fundamental Concepts of Heart Life and Disease. London, UK: IntechOpen; 2020: 21-35. Available from: https://www.intechopen.com/online-first/myocardial-infarction-and-circadian-rhythm

12 **Egg M**, Köblitz L, Hirayama J, Schwerte T, Folterbauer C, Kurz A, Fiechtner B, Möst M, Salvenmoser W, Sassone-Corsi P, Pelster B. Linking oxygen to time: the bidirectional interaction between the hypoxic signaling pathway and the circadian clock. *Chronobiol Int* 2013; **30**: 510-529 [PMID: 23421720 DOI: 10.3109/07420528.2012.754447]

13 **Škrlec I**. Circadian system microRNAs - Role in the development of cardiovascular diseases. *Adv Protein Chem Struct Biol* 2023; **137**: 225-267 [PMID: 37709378 DOI: 10.1016/bs.apcsb.2023.02.004]

14 **Eckle T**, Hartmann K, Bonney S, Reithel S, Mittelbronn M, Walker LA, Lowes BD, Han J, Borchers CH, Buttrick PM, Kominsky DJ, Colgan SP, Eltzschig HK. Adora2b-elicited Per2 stabilization promotes a HIF-dependent metabolic switch crucial for myocardial adaptation to ischemia. *Nat Med* 2012; **18**: 774-782 [PMID: 22504483 DOI: 10.1038/nm.2728]

15 **Wu Y**, Tang D, Liu N, Xiong W, Huang H, Li Y, Ma Z, Zhao H, Chen P, Qi X, Zhang EE. Reciprocal Regulation between the Circadian Clock and Hypoxia Signaling at the Genome Level in Mammals. *Cell Metab* 2017; **25**: 73-85 [PMID: 27773697 DOI: 10.1016/j.cmet.2016.09.009]

World Journal of Cardiology

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

World J Cardiol 2024 April 26; 16(4): 186-190

DOI: 10.4330/wjc.v16.i4.186

ISSN 1949-8462 (online)

EDITORIAL

Left bundle branch pacing set to outshine biventricular pacing for cardiac resynchronization therapy?

Akash Batta, Juniali Hatwal

Specialty type: Cardiac and cardiovascular systems

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Albatat M, Norway

Received: January 19, 2024
Peer-review started: January 19, 2024
First decision: February 3, 2024
Revised: February 9, 2024
Accepted: March 18, 2024
Article in press: March 18, 2024
Published online: April 26, 2024

Akash Batta, Department of Cardiology, Dayanand Medical College and Hospital, Ludhiana 141001, India

Juniali Hatwal, Department of Internal Medicine, Advanced Cardiac Centre, Post Graduate Institute of Medical Education & Research, Chandigarh 160012, India

Corresponding author: Akash Batta, MD, DM, Assistant Professor, Senior Scientist, Department of Cardiology, Dayanand Medical College and Hospital, Tagore Nagar, Civil Lines, Ludhiana 141001, India. akashbatta02@gmail.com

Abstract

The deleterious effects of long-term right ventricular pacing necessitated the search for alternative pacing sites which could prevent or alleviate pacing-induced cardiomyopathy. Until recently, biventricular pacing (BiVP) was the only modality which could mitigate or prevent pacing induced dysfunction. Further, BiVP could resynchronize the baseline electromechanical dssynchrony in heart failure and improve outcomes. However, the high non-response rate of around 20%-30% remains a major limitation. This non-response has been largely attributable to the direct non-physiological stimulation of the left ventricular myocardium bypassing the conduction system. To overcome this limitation, the concept of conduction system pacing (CSP) came up. Despite initial success of the first CSP *via* His bundle pacing (HBP), certain drawbacks including lead instability and dislodgements, steep learning curve and rapid battery depletion on many occasions prevented its widespread use for cardiac resynchronization therapy (CRT). Subsequently, CSP *via* left bundle branch-area pacing (LBBP) was developed in 2018, which over the last few years has shown efficacy comparable to BiVP-CRT in small observational studies. Further, its safety has also been well established and is largely free of the pitfalls of the HBP-CRT. In the recent metanalysis by Yasmin *et al*, comprising of 6 studies with 389 participants, LBBP-CRT was superior to BiVP-CRT in terms of QRS duration, left ventricular ejection fraction, cardiac chamber dimensions, lead thresholds, and functional status amongst heart failure patients with left bundle branch block. However, there are important limitations of the study including the small overall numbers, inclusion of only a single small randomized controlled trial (RCT) and a small follow-up duration. Further, the entire study population analyzed was from China which makes generalizability a concern. Despite the concerns, the meta-analysis adds to the growing body of evidence demonstrating the efficacy of LBBP-CRT. At this stage, one must acknowledge that the fact that still our opinions on this technique

are largely based on observational data and there is a dire need for larger RCTs to ascertain the position of LBBP-CRT in management of heart failure patients with left bundle branch block.

Key Words: Biventricular pacing; Cardiac resynchronization therapy; Conduction system pacing; Left bundle branch-area pacing; Left bundle branch block; Electromechanical dssynchrony

Core Tip: The deleterious effects of long-term right ventricular pacing necessitated the search for alternative pacing sites which could prevent or alleviate pacing-induced cardiomyopathy. Until recently, biventricular pacing (BiVP) was the only modality which could mitigate or prevent pacing induced dysfunction. Left bundle branch-area pacing (LBBP) was developed in 2018, which over the last few years has shown efficacy comparable to BiVP-cardiac resynchronization therapy (CRT) in small observational studies. However, as of now our opinion is largely based on observational data which are inherently prone to selection biases. Hence, there is an urgent need for larger randomized controlled trials which will ascertain the role of LBBP-CRT in the future.

Citation: Batta A, Hatwal J. Left bundle branch pacing set to outshine biventricular pacing for cardiac resynchronization therapy? *World J Cardiol* 2024; 16(4): 186-190
URL: https://www.wjgnet.com/1949-8462/full/v16/i4/186.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i4.186

INTRODUCTION

The deleterious effects of long-term right ventricular pacing necessitated the search for alternative pacing sites which could prevent or alleviate pacing-induced cardiomyopathy[1]. The major breakthrough in this regard was the development biventricular pacing (BiVP) around 3 decades ago. BiVP was initially introduced as a treatment for dyssynchronous heart failure. With time, it was realized that it could prevent or offset the pacing-induced left ventricular dysfunction which account for 25% of all dyssynchronous heart failure[2,3]. BiVP could resynchronize the baseline electromechanical dssynchrony in heart failure with reduced ejection fraction (HFrEF) with resultant positive effects on cardiac function, functional status and overall mortality[4]. The most common method of achieving this resynchronization *via* BiVP involves the placement of an electrode in the epicardial posterior-basal wall of the left ventricle *via* the coronary sinus. Over the years this method of cardiac resynchronization therapy (CRT) has been proven to be safe and efficacious in managing selected patients with electromechanical dyssynchrony and HFrEF. However, the high non-response rate of around 20%-30% has remained a major limitation[5,6]. This non-response has been largely attributable to the direct non-physiological stimulation of the left ventricular myocardium bypassing the conduction system (His-Purkinje in myocardium) and the variation in myocardium characteristics at the left ventricular pacing site. Further there is wide variation reported in the coronary sinus anatomy and limited pacing sites constrained by the coronary sinus branches which also accounts for non-response in a large fraction of cases[7]. Another major concern which applies to all methods of achieving CRT is the fact that there is practically no objective measure that could indicate the effectiveness of the therapy acutely due to the remodelling involved and hence, there is a great need for a way to accurately determine the response and enable optimization at the time of device implantation. Certain parameters including biventricular activation times and biventricular dyssynchrony indexes have been deployed to predict post-implantation response but do not necessarily correlate with clinical outcomes on follow-up.

These limitations of the BiVP-CRT paved the way for research into the more physiological pacing sites for CRT which would allow for direct stimulation of the native conduction system. The first major development in conduction system pacing (CSP) was the use of His bundle pacing (HBP) in the year 2000 by Deshmukh *et al*[8], which showed a net incremental benefit amongst HFrEF patients who had persistent atrial fibrillation. However, major drawbacks including the lead instability and dislodgements, steep learning curve, long fluoroscopy times and early battery depletion on many occasions has prevented its widespread use for CRT[9-11]. In 2018 Huang and colleagues demonstrated that direct pacing through the interventricular septum, close to the main trunk of left bundle branch could overcome much of the limitations of the HBP and provided stable lead parameters over the long run[12]. Since then a few observational reports have demonstrated the benefit of this left bundle branch-area pacing (LBBP) as a means of CRT in candidates who were not eligible for BiVP-CRT[13]. One must be aware that LBBP refers to a broader term which includes selective LBBP, non-selective LBBP and left ventricular septal pacing. Since there are only minor differences in the pacing thresholds and resynchronization achieved, these are often used interchangeably in literature[14]. The early experience does suggest that LBBP-CRT seems to be at least as effective as BiVP-CRT with respect to cardiac hemodynamics and functions. However, the evidence at this stage is largely observational with only a single small randomized controlled trial (RCT) comparing LBBP-CRT with BiVP-CRT[15]. Hence, there is a dire need for larger RCTs with long-term follow-up and meta-analysis of these RCTs.

LBBP-CRT *VS* BIVP-CRT

In the recent meta-analysis published by Yasmin *et al*[16] published in the January issue of world journal of cardiology, comprising of 6 studies (1 RCT and 5 comparative observational studies) with 389 participants (159 in LBBP-CRT *vs* 230 in BiVP-CRT); LBBP-CRT was superior to BiVP-CRT in regards to improvement in left ventricular ejection fraction, cardiac chamber dimensions, lead thresholds, and functional status. Further, they demonstrated a significant reduction in brain natriuretic peptide concentration at follow up in the LBBP-CRT group compared to BiVP-CRT. Perhaps most of the positive impacts of LBBP-CRT stem from a significantly lower QRS duration compared to BiVP-CRT which indicates a more efficient resynchronization and subsequent cardiac contraction. The result of this meta-analysis is indeed the reflection of growing evidence in support of LBBP as the preferable method of achieving CRT. Further, recent evidence even supports the cost effectiveness of CSP based CRT which can achieve satisfactory resynchronization with conventional pacemakers in patients who otherwise do not warrant defibrillation[17].

While the results seem promising, one must examine the encouraging results with due caution. Firstly, the meta-analysis largely comprised of observational data which is inherently prone to selection biases which may have concealed some of the outliers belonging to the LBBP-CRT group. Further, the single RCT included had only 40 patients and a 6 months follow-up[15]. All the studies originated in China and hence the generalizability of the results remains to be established. Further, data on long-term lead durability in the LBBP-CRT has not been established which at least theoretically remains a concern given the mechanical stress at the hinge point on interventricular septum.

The analysis could have included data from a large recent observational study by Vijayaraman *et al*[18] including data of 1778 patients from 15 centers around the globe. Arguably this remains the highest quality of evidence to date and does provide more evidence in support of LBBP-CRT over BiVP-CRT in HFrEF patients with electromechanical dyssynchrony. Further, they concluded that LBBP-CRT was effective either as a bailout intervention to BiVP-CRT or as a primary treatment modality. Again, despite the accumulating evidence in support of LBBP-CRT, one must acknowledge the urgent need for larger RCTs which will indeed deepen our understanding of this modality and form the basis of our practice in the future. As of now, the increasing utilization of CSP is largely based on the expert option on the observational data and our understanding of physiology behind CSP[19]. To this end, 4 large RCTs comparing the clinical outcomes following LBBP-CRT or BiVP-CRT are on the way which will go a long way in defining the role of these modalities in treatment of HFrEF (Table 1).

A document on definitions, current evidence and techniques to achieve CSP (HBP and LBBP) was recently published in a clinical consensus statement[20]. The current Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society guidelines on pacing gives LBBP-CRT a class 2a recommendation for preventing heart failure in patients in whom BiVP-CRT cannot be achieved. Further, a 2b recommendation was given for LBBP-CRT as an alternative to BiVP-CRT for interventionists with adequate experience with CSP[21].

The most recent development in the search for ideal CRT modality involves combined stimulation of the conduction system and epicardial left ventricular myocardium *via* the coronary sinus[22]. This was developed in order to correct the multiple electrical dyssnchronies that are often present in advanced heart failure patients. For this reason, CSP alone may not be sufficient to resynchronize the myocardium in the presence of distal His-Purkinje disease which is better resynchronized with a coronary sinus lead which allows for recruitment of myocardial areas with late electrical activation. Unsurprisingly, small observational studies with either His-left ventricular stimulation approach: His-optimized CRT (HOT-CRT) or LBBAP-left ventricular stimulation approach: left bundle branch optimized CRT (LOT-CRT) have shown to perform better in terms of cardiac chamber function and volumes than either CSP or BiVP-CRT alone[23,24]. However, the lack of wide scale experience and better-quality data remains a major reason for low clinical application as of now. On many occasions especially in non-LBBB patients, choosing the ideal site for CRT *via* CSP is challenging because progression of conduction block distal to the pacing site remains a possibility which will limit clinical success in the long run. Hence, for these patients HOT-CRT and LOT-CRT may be the best option. Figure 1 illustrates the various pacing strategies mentioned above.

At this stage, one must also keep in mind that despite the promise of CSP, certain challenges are likely to be encountered in clinical practice and the industry would need to come with technologies and delivery systems to overcome these challenges. These include the long-term lead durability and efficacy, its extractability and worsening tricuspid valve regurgitation with time[22].

CONCLUSION

LBBP has emerged as a formidable alternative to BiVP as a strategy for CRT. The theoretical benefits of physiological pacing (LBBP-CRT) *via* the conduction system so far have translated into improved clinical outcomes compared to BiVP-CRT which stimulates the left ventricular myocardium directly. This recent meta-analysis also supports the growing body of evidence demonstrating the superiority of LBBP-CRT over BiVP-CRT in regards to improvement in QRS duration, left ventricular ejection fraction, cardiac chamber dimensions, lead thresholds, and functional status. However, despite the accumulating evidence in support of LBBP-CRT, one must acknowledge the fact that as of now our opinion is largely based on observational data which are inherently prone to selection biases. Hence, there is an urgent need for larger RCTs which will ascertain the role of LBBP-CRT in the future.

Table 1 Ongoing randomized controlled trials comparing the clinical outcomes following left bundle branch-area pacing- or biventricular pacing-cardiac resynchronization therapy

Trial name	Design	Interventions arm	Unique identifier	*n*	Primary endpoint
LeCaRt trial	RCT	LBBP-CRT *vs* BiVP-CRT	NCT05365568	170	Composite of death, HF hospitalization or worsening HF
LEFT-BUNDLE-CRT trial	RCT	LBBP-CRT *vs* BiVP-CRT	NCT05434962	176	Positive CRT response: improved clinical composite score or > 15% reduction in LVESV
RAFT-P & A trial	RCT	AV nodal ablation + LBBP-CRT *vs* AV nodal ablation + BiVP-CRT	NCT05428787	284	Change in NT-ProBNP at 6 months follow-up
Left *vs* left trial	RCT	HBP/LBBP-CRT *vs* BiVP-CRT	NCT05650658	2136	All-cause mortality and HF hospitalization at 5.5 yr

AV: Atrioventricular; BiVP: Biventricular pacing; CRT: Cardiac resynchronization therapy; HBP: His-bundle pacing; HF: Heart failure; LBBP: Left bundle branch-area pacing; LVESV: Left ventricular end-systolic volume; ProBNP: Pro-brain natriuretic peptide; RCT: Randomized controlled trial.

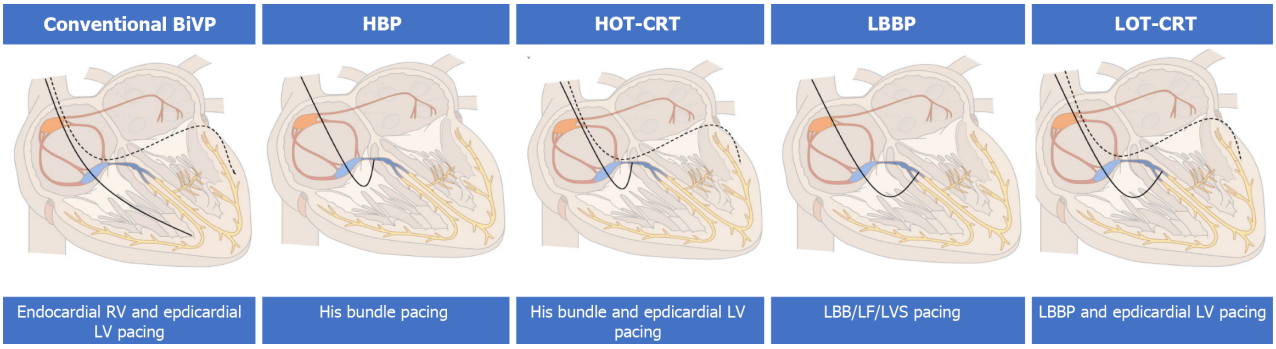

Figure 1 Various pacing techniques to achieve cardiac resynchronization therapy. BiVP: Biventricular pacing; HBP: His bundle pacing; HOT-CRT: His-optimized cardiac resynchronization therapy; LBB: Left bundle branch; LBBP: Left bundle branch-area pacing; LF: Left fascicle; LOT-CRT: Left bundle branch optimized cardiac resynchronization therapy; LV: Left ventricle; LVS: Left ventricle septum; RV: Right ventricle.

FOOTNOTES

Author contributions: Batta A contributed to the conception and design, did analysis and interpretation, collected the data, finally approved the manuscript, and took overall responsibility; Batta A and Hatwal J wrote and critically revised the manuscript. All authors have read and approved of the final version of the manuscript.

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

Country/Territory of origin: India

ORCID number: Akash Batta 0000-0002-7606-5826; Juniali Hatwal 0000-0001-5433-0433.

S-Editor: Zhang H
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Naqvi TZ**, Chao CJ. Adverse effects of right ventricular pacing on cardiac function: prevalence, prevention and treatment with physiologic pacing. *Trends Cardiovasc Med* 2023; **33**: 109-122 [PMID: 34742888 DOI: 10.1016/j.tcm.2021.10.013]
2 **Khurshid S**, Frankel DS. Pacing-Induced Cardiomyopathy. *Card Electrophysiol Clin* 2021; **13**: 741-753 [PMID: 34689900 DOI: 10.1016/j.ccep.2021.06.009]

3 **Khurshid S**, Obeng-Gyimah E, Supple GE, Schaller R, Lin D, Owens AT, Epstein AE, Dixit S, Marchlinski FE, Frankel DS. Reversal of Pacing-Induced Cardiomyopathy Following Cardiac Resynchronization Therapy. *JACC Clin Electrophysiol* 2018; **4**: 168-177 [PMID: 29749933 DOI: 10.1016/j.jacep.2017.10.002]

4 **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]

5 **Naqvi SY**, Jawaid A, Goldenberg I, Kutyifa V. Non-response to Cardiac Resynchronization Therapy. *Curr Heart Fail Rep* 2018; **15**: 315-321 [PMID: 30097910 DOI: 10.1007/s11897-018-0407-7]

6 **Green PG**, Herring N, Betts TR. What Have We Learned in the Last 20 Years About CRT Non-Responders? *Card Electrophysiol Clin* 2022; **14**: 283-296 [PMID: 35715086 DOI: 10.1016/j.ccep.2021.12.019]

7 **Daubert C**, Behar N, Martins RP, Mabo P, Leclercq C. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. *Eur Heart J* 2017; **38**: 1463-1472 [PMID: 27371720 DOI: 10.1093/eurheartj/ehw270]

8 **Deshmukh P**, Casavant DA, Romanyshyn M, Anderson K. Permanent, direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation. *Circulation* 2000; **101**: 869-877 [PMID: 10694526 DOI: 10.1161/01.cir.101.8.869]

9 **Archontakis S**, Sideris K, Laina A, Arsenos P, Paraskevopoulou D, Tyrovola D, Gatzoulis K, Tousoulis D, Tsioufis K, Sideris S. His bundle pacing: A promising alternative strategy for anti-bradycardic pacing - report of a single-center experience. *Hellenic J Cardiol* 2022; **64**: 77-86 [PMID: 34843996 DOI: 10.1016/j.hjc.2021.10.005]

10 **O'Connor M**, Shi R, Kramer DB, Riad O, Hunnybun D, Jarman JWE, Foran J, Cantor E, Markides V, Wong T. Conduction system pacing learning curve: Left bundle pacing compared to His bundle pacing. *Int J Cardiol Heart Vasc* 2023; **44**: 101171 [PMID: 36660200 DOI: 10.1016/j.ijcha.2023.101171]

11 **Vinther M**, Risum N, Svendsen JH, Møgelvang R, Philbert BT. A Randomized Trial of His Pacing Versus Biventricular Pacing in Symptomatic HF Patients With Left Bundle Branch Block (His-Alternative). *JACC Clin Electrophysiol* 2021; **7**: 1422-1432 [PMID: 34167929 DOI: 10.1016/j.jacep.2021.04.003]

12 **Huang W**, Su L, Wu S, Xu L, Xiao F, Zhou X, Ellenbogen KA. A Novel Pacing Strategy With Low and Stable Output: Pacing the Left Bundle Branch Immediately Beyond the Conduction Block. *Can J Cardiol* 2017; **33**: 1736.e1-1736.e3 [PMID: 29173611 DOI: 10.1016/j.cjca.2017.09.013]

13 . Erratum to "A Literature Review of Cannabis and Myocardial Infarction-What Clinicians May Not Be Aware Of" [CJC Open 3 (2020):12-21]. *CJC Open* 2022; **4**: 827 [PMID: 36148263 DOI: 10.1016/j.cjco.2022.07.007]

14 **Heckman LIB**, Luermans JGLM, Curila K, Van Stipdonk AMW, Westra S, Smisek R, Prinzen FW, Vernooy K. Comparing Ventricular Synchrony in Left Bundle Branch and Left Ventricular Septal Pacing in Pacemaker Patients. *J Clin Med* 2021; **10** [PMID: 33671420 DOI: 10.3390/jcm10040822]

15 **Wang Y**, Zhu H, Hou X, Wang Z, Zou F, Qian Z, Wei Y, Wang X, Zhang L, Li X, Liu Z, Xue S, Qin C, Zeng J, Li H, Wu H, Ma H, Ellenbogen KA, Gold MR, Fan X, Zou J; LBBP-RESYNC Investigators. Randomized Trial of Left Bundle Branch vs Biventricular Pacing for Cardiac Resynchronization Therapy. *J Am Coll Cardiol* 2022; **80**: 1205-1216 [PMID: 36137670 DOI: 10.1016/j.jacc.2022.07.019]

16 **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]

17 **Chen M**, Shi J, Zhang Y, Ge X, Zhang X, Fan W, Wang S, Guo Z, Guan J, Wu Y, Zhang J. Comparative cost analysis of implanting devices in different cardiac resynchronization therapeutic strategies. *Clin Cardiol* 2023; **46**: 1227-1233 [PMID: 37537947 DOI: 10.1002/clc.24107]

18 **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]

19 **Diaz JC**, Duque M, Aristizabal J, Marin J, Niño C, Bastidas O, Ruiz LM, Matos CD, Hoyos C, Hincapie D, Velasco A, Romero JE. The Emerging Role of Left Bundle Branch Area Pacing for Cardiac Resynchronisation Therapy. *Arrhythm Electrophysiol Rev* 2023; **12**: e29 [PMID: 38173800 DOI: 10.15420/aer.2023.15]

20 **Burri H**, Jastrzebski M, Cano Ó, Čurila K, de Pooter J, Huang W, Israel C, Joza J, Romero J, Vernooy K, Vijayaraman P, Whinnett Z, Zanon F. EHRA clinical consensus statement on conduction system pacing implantation: executive summary. Endorsed by the Asia-Pacific Heart Rhythm Society (APHRS), Canadian Heart Rhythm Society (CHRS) and Latin-American Heart Rhythm Society (LAHRS). *Europace* 2023; **25**: 1237-1248 [PMID: 37061850 DOI: 10.1093/europace/euad044]

21 **Chung MK**, Patton KK, Lau CP, Dal Forno ARJ, Al-Khatib SM, Arora V, Birgersdotter-Green UM, Cha YM, Chung EH, Cronin EM, Curtis AB, Cygankiewicz I, Dandamudi G, Dubin AM, Ensch DP, Glotzer TV, Gold MR, Goldberger ZD, Gopinathannair R, Gorodeski EZ, Gutierrez A, Guzman JC, Huang W, Imrey PB, Indik JH, Karim S, Karpawich PP, Khaykin Y, Kiehl EL, Kron J, Kutyifa V, Link MS, Marine JE, Mullens W, Park SJ, Parkash R, Patete MF, Pathak RK, Perona CA, Rickard J, Schoenfeld MH, Seow SC, Shen WK, Shoda M, Singh JP, Slotwiner DJ, Sridhar ARM, Srivatsa UN, Stecker EC, Tanawuttiwat T, Tang WHW, Tapias CA, Tracy CM, Upadhyay GA, Varma N, Vernooy K, Vijayaraman P, Worsnick SA, Zareba W, Zeitler EP; Document Reviewers, Lopez-Cabanillas N, Ellenbogen KA, Hua W, Ikeda T, Mackall JA, Mason PK, McLeod CJ, Mela T, Moore JP, Racenet LK. 2023 HRS/APHRS/LAHRS guideline on cardiac physiologic pacing for the avoidance and mitigation of heart failure. *J Arrhythm* 2023; **39**: 681-756 [PMID: 37799799 DOI: 10.1002/joa3.12872]

22 **Domenichini G**, Le Bloa M, Teres Castillo C, Graf D, Carroz P, Ascione C, Porretta AP, Pascale P, Pruvot E. Conduction System Pacing versus Conventional Biventricular Pacing for Cardiac Resynchronization Therapy: Where Are We Heading? *J Clin Med* 2023; **12** [PMID: 37834932 DOI: 10.3390/jcm12196288]

23 **Vijayaraman P**, Herweg B, Ellenbogen KA, Gajek J. His-Optimized Cardiac Resynchronization Therapy to Maximize Electrical Resynchronization: A Feasibility Study. *Circ Arrhythm Electrophysiol* 2019; **12**: e006934 [PMID: 30681348 DOI: 10.1161/CIRCEP.118.006934]

24 **Jastrzębski M**, Moskal P, Huybrechts W, Curila K, Sreekumar P, Rademakers LM, Ponnusamy SS, Herweg B, Sharma PS, Bednarek A, Rajzer M, Vijayaraman P. Left bundle branch-optimized cardiac resynchronization therapy (LOT-CRT): Results from an international LBBAP collaborative study group. *Heart Rhythm* 2022; **19**: 13-21 [PMID: 34339851 DOI: 10.1016/j.hrthm.2021.07.057]

World Journal of Cardiology

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

World J Cardiol 2024 April 26; 16(4): 191-198

DOI: 10.4330/wjc.v16.i4.191

ISSN 1949-8462 (online)

MINIREVIEWS

Aspirin interruption before neurosurgical interventions: A controversial problem

Alexander Kulikov, Anton Konovalov, Pier Paolo Pugnaloni, Federico Bilotta

Specialty type: Health care sciences and services

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

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Teragawa H, Japan

Received: December 27, 2023
Peer-review started: December 27, 2023
First decision: January 17, 2024
Revised: January 26, 2024
Accepted: February 29, 2024
Article in press: February 29, 2024
Published online: April 26, 2024

Alexander Kulikov, Department of Anesthesiology, Burdenko National Medical Research Center of Neurosurgery, Moscow 125047, Russia

Anton Konovalov, Department of Vascular Neurosurgery, Burdenko National Medical Research Center of Neurosurgery, Moscow 125047, Russia

Pier Paolo Pugnaloni, Federico Bilotta, Department of Anesthesiology, Critical Care and Pain Medicine, University of Rome "Sapienza", Rome 00161, Italy

Corresponding author: Federico Bilotta, MD, PhD, Professor, Department of Anesthesiology, Critical Care and Pain Medicine, University of Rome "Sapienza", Policlinico Umberto I, Viale del Policlinico 37, Rome 00161, Italy. bilotta@tiscali.it

Abstract

Aspirin is widely used for primary or secondary prevention of ischemic events. At the same time, chronic aspirin consumption can affect blood clot formation during surgical intervention and increase intraoperative blood loss. This is especially important for high-risk surgery, including neurosurgery. Current European Society of Cardiology guidelines recommend aspirin interruption for at least 7 d before neurosurgical intervention, but this suggestion is not supported by clinical evidence. This narrative review presents evidence that challenges the necessity for aspirin interruption in neurosurgical patients, describes options for aspirin effect monitoring and the clinical implication of these methods, and summarizes current clinical data on bleeding risk associated with chronic aspirin therapy in neurosurgical patients, including brain tumor surgery, cerebrovascular procedures, and spinal surgery.

Key Words: Aspirin; Neurosurgery; Postoperative complications; Bleeding risk; Brain tumor surgery; Cerebrovascular surgery; Spinal surgery

Core Tip: A decision on continuing or interrupting aspirin use before neurosurgical intervention should be made based on a discussion of specialists involved in perioperative management (neurosurgeon, anesthesiologist, cardiologist, *etc*), taking into account estimated blood loss; risk of complications associated with increased bleeding time; risk of postoperative ischemic complication associated with aspirin interruption; and risk of surgery postponement.

Citation: Kulikov A, Konovalov A, Pugnaloni PP, Bilotta F. Aspirin interruption before neurosurgical interventions: A controversial problem. *World J Cardiol* 2024; 16(4): 191-198
URL: https://www.wjgnet.com/1949-8462/full/v16/i4/191.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i4.191

INTRODUCTION

Aspirin (acetylsalicylic acid, ASA) is a well-known inhibitor of platelet aggregation and due to this effect it is widely used for primary or secondary prevention of ischemic events[1]. At the same time, chronic aspirin consumption can affect blood clot formation during surgical intervention and increase intraoperative blood loss[2]. This is especially important for high-risk surgery, including neurosurgery, where even mild hemostatic disorders can provoke severe postoperative complications, such as acute intracranial hemorrhage[3].

Historically, the indication to interrupt aspirin therapy before neurosurgical procedures is based not on the clinical evidence, but on an expert's consensus[4]. Over the years, this suggestion has consistently repeated in various guidelines, including 2022 European Society of Cardiology (ESC) guidelines, which state that "in patients with high peri-operative bleeding risk (*e.g.*, undergoing spinal surgery or certain neurosurgical operations) aspirin should be discontinued for at least 7 d"[5]. However, clinical data, accumulated from observational studies in patients undergone spinal and intracranial surgery, do not prove a possible additional risk of postoperative hemorrhage associated with preoperative chronic aspirin therapy. Instead, there is a trend towards a beneficial effect of aspirin continuation concerning postoperative thromboembolic events[6,7].

This narrative review summarizes evidence that challenges the necessity for aspirin interruption in neurosurgical patients, describes options for aspirin effect monitoring and the clinical implication of these methods, and summarizes current clinical data on bleeding risk associated with chronic aspirin therapy in neurosurgical patients, including brain tumor surgery, cerebrovascular procedures, and spinal surgery.

ANTIPLATELET EFFECT OF ASPIRIN

The antiplatelet effect of aspirin is mediated by inhibiting cyclooxygenase (COX) activity inside platelets followed by suppression of thromboxane A_2 (TXA_2) synthesis[8]. TXA_2 plays an important role in the amplification of platelet aggregation, and aspirin effectively depresses this mechanism of platelet activation[9].

Among the clinically important aspects of the antiplatelet effect of aspirin are the increased effectiveness of low doses (75-325 mg/d), due to the absence of concomitant inhibition of prostacyclin in endothelial cells, and irreversible COX inhibition, in contrast to other nonsteroidal anti-inflammatory drugs (NSAIDs). Ibuprofen, ketorolac, *etc* compete reversibly with the arachidonic acid substrate at the active site of COX, and therefore the duration of their antiplatelet effect corresponds to elimination time. The antiplatelet effect of aspirin lasts for several days after a single administration due to irreversible acetylation of platelet COX[10]. Only newly synthesized platelets, which are renewed approximately by 10% every day, can restore the ability to generate TXA_2 after a single aspirin uptake.

However, aspirin is recognized as a rather weak antiplatelet agent because it produces only partial platelet inhibition, and other non-TXA_2–dependent activators of platelet aggregation [*e.g.*, thrombin, ADP (adenosine diphosphate), and collagen] can bypass the aspirin-dependent mechanism and result in effective coagulation[8]. Moreover, up to 25% of patients can be resistant to conventional aspirin therapy[11].

ASPIRIN ANTIPLATELET EFFECT ASSESSMENT

The immediate clinical effect of aspirin uptake on primary hemostasis results in increased bleeding time[12]. Due to significant difficulties in standardizing this type of test, significant efforts in recent decades have been put into developing alternative and reliable measures of the antiplatelet effect of aspirin. Among the tested methods were light transmission aggregometry, serum thromboxane B_2 concentration, impedance aggregometry, thromboelastography platelet mapping system, VerifyNow® assay (Werfen, Barcelona, Spain), platelet function analyzer–100 (Siemens Healthineers, Erlangen, Germany), *etc*. Each of these proposed methods demonstrated significant variability in the assessment of aspirin effect and poor correlation to each other[13,14]. Even more importantly, there is still no reliable clinical evidence of predictive value of any of these tests and correlation with clinically significant outcomes[15].

From a practical point of view, it seems important that non-specific viscoelastic tests (thromboelastography, rotational thromboelastometry), which were designed for integral assessment of blood clot formation, cannot demonstrate aspirin-associated hypocoagulation. At the same time, this phenomenon can be interpreted as the principal possibility of dense clot formation in the presence of aspirin[16].

IMPACT OF ASPIRIN ON BLEEDING RISK IN NON-NEUROSURGICAL PATIENTS

Clinical evidence on aspirin continuation or discontinuation in general surgery is minimal. The largest seminal RCT (POISE-2), which included more than 10000 patients, revealed a higher frequency of major bleeding in the aspirin cohort with a hazard ratio 1.23 (95%CI: 1.01 to 1.49; $P = 0.04$)[2]. However, the design and conclusions of this trial were criticized due to the potential interaction of aspirin with perioperative anticoagulants and NSAIDs[17]. As a result, current guidelines on perioperative bleeding suggest that "aspirin should not be withdrawn peri-operatively unless the risk of bleeding exceeds the thrombotic risk from withholding the drug"[18]. But, as mentioned above, neurosurgical patients should be treated in a special way. Data on bleeding risk in different sub-cohorts of neurosurgical patients is presented below and summarized in Table 1.

RISK OF BLEEDING IN BRAIN TUMOR SURGERY

One of the initial concerns on the safety of perioperative aspirin consumption in brain tumor surgery was presented in a small case series[19]. This study was based on two cases where postoperative hematomas were seemingly caused by a platelet defect due to aspirin use. This defect, not detectable by standard bleeding and clotting tests, could arise from both massive and small doses of aspirin. Highlighting the serious implications for neurosurgery, the study pointed out that such a defect can be effectively treated with platelet transfusions.

Data from a more recent retrospective study examining 1291 patients who underwent elective intracranial tumor surgery is much more reasonable[20]. The patients were divided based on their aspirin usage into three groups: no aspirin, stopped aspirin, and continued aspirin. The stopped-aspirin group included 104 patients (108 operations), and the continued-aspirin group had 119 patients (126 operations). The study highlighted that operative blood loss and complication rates were not significantly different between the groups, suggesting that perioperative aspirin use does not elevate hemorrhagic risk.

A similar conclusion was reached in a prospective cohort study, focused on the perioperative management of antithrombotics (AT) in elective intracranial procedures[21]. This analysis involved 312 patients divided into three groups: 83 patients (27%) continued AT, 106 (34%) did not use AT, and 123 (39%) were historical AT users. The study's approach was to continue aspirin for extraaxial or shunt surgeries and stop aspirin 2 d before intervention for intraaxial pathologies. Notably, the total perioperative discontinuation time in the AT group was markedly shorter (median of 4 d) compared to the historical AT group (16 d). Hemorrhagic complications occurred in 4% of the AT group, 6% in the control group, and 7% in the historical AT group, indicating no significant increase in hemorrhagic risk with this protocol.

The risk of postoperative bleeding in patients undergoing endoscopic endonasal surgery for pituitary adenomas with short-term discontinuation of low-dose aspirin was the focus of another retrospective study[22]. It included 304 patients, and 45 of them (14.8%) had short-term perioperative aspirin discontinuation. This study found no increased rate of postoperative bleeding in patients who discontinued aspirin for a short period.

The risk of postoperative hematoma formation in patients undergoing stereotactic brain biopsies is a critical concern in clinical practice because in these clinical settings, there is no direct visual control of potential vascular injury. Unfortunately, we did not succeed in finding any clinical evidence of additional risk of such complications in patients on chronic aspirin therapy.

RISK OF BLEEDING IN CEREBROVASCULAR SURGERY

Risk of hemorrhagic complication in 158 patients who underwent revascularization surgery for moyamoya disease or cerebrovascular atherosclerotic disease was assessed in a retrospective observational study[23]. The study had a low complication rate with a high patency rate of 97%, and no mortality. Early morbidity was 10.7%, and ischemia was seen in 6.9% of patients. It was found that neither the type of treated pathology nor the surgical technique significantly influenced outcomes. Notably, antiplatelet therapy did not increase the risk of hemorrhage, but improved outcomes.

Patients who underwent craniotomy for unruptured intracranial aneurysm were included in another retrospective study[24]. Data on 401 cases were analyzed. Patients were divided into two groups: those who received perioperative antithrombotic treatment (45 patients) and those who did not (356 patients). The study found no significant difference in mortality, morbidity, or symptomatic brain infarction between the groups. However, intracranial hemorrhage was more frequent in the antithrombotic group. Posterior aneurysm location and surgical procedure were associated with severe morbidity, and intracranial hemorrhage was associated with antithrombotic treatment.

A more recent retrospective study did not find additional bleeding risk in patients on continued aspirin treatment undergoing cerebral aneurysm surgery[25]. 200 consecutive clipping procedures were analyzed and found that postoperative hemorrhage occurred in 3.1% of patients with aspirin and 3.0% of patients without aspirin. The difference

Table 1 Characteristics of included studies on aspirin consumption before neurosurgical interventions

Ref.	No. of patients	Reported schemes	Key message
Brain tumor surgery			
Merriman *et al*[19], 1979 Case report	2	4-20 tablets of aspirin 325 mg/d	Complications could be associated with preoperative aspirin consumption
Hanalioglu *et al*[20], 2019 Retrospective single-center, cohort study	1291	3 groups: No ASA (1068 patients) Stopped ASA (at least 7 d before surgery – 104 patients) Continued ASA (119 patients)	ASA was not associated with increased bleeding risk
Rychen *et al*[21], 2023 Prospective cohort study with retrospective control	312	ASA was continued perioperatively for extraaxial surgery, and discontinued 2 d before intraaxial surgery (83 patients). No ASA in prospective control (106 patients) and long-term ASA discontinuation in retrospective control group (123 patients)	Presented protocol of perioperative antithrombotics management was not associated with an increased hemorrhagic risk
Enciu *et al*[22], 2023 Retrospective single-center, cohort study	304	2 groups: Short-term ASA discontinuation (lower than 7 d) (45 patients) Standard-term ASA discontinuation (259 patients)	Short-term (even < 2 d) discontinuation of low-dose aspirin was not associated with increased bleeding risk
Rychen *et al*[7], 2023 Systematic review	646 (7 studies)	ASA was continued perioperatively in 61.8% and discontinued in 38.2% of the cases	Perioperative ASA continuation in elective craniotomies was not associated with an increased hemorrhagic risk
Cerebrovascular surgery			
Schubert *et al*[23], 2014 Retrospective single-center, cohort study	158	ASA was prescribed in 138 patients pre- or intraoperatively	Antiplatelet therapy did not increase the risk of hemorrhage, but improved outcomes after revascularization procedures
Nakamizo *et al*[24], 2017 Retrospective single-center, cohort study	401	2 groups: Continued antithrombotics, including ASA (45 patients) No antithrombotics (259 patients)	Intracranial hemorrhage after aneurism clipping was more frequent in the antithrombotics group
Rashidi *et al*[25], 2021 Retrospective single-center, cohort study	200	2 groups: Continued ASA or short-term ASA discontinuation (lower than 7 d) (32 patients) No ASA (168 patients)	Continued ASA use was not associated with an increased risk of a postoperative hemorrhage
Ebel *et al*[26], 2021 Retrospective single-center, cohort study	215	2 groups: Patients were treated with antithrombotics (50 patients) No antithrombotics (165 patients)	Short (≤ 5 d) aspirin discontinuation time did not appear to have increased rates of postoperative bleeding
Spinal surgery			
Goes *et al*[6], 2017 Meta-analysis	370 (3 studies)	2 groups: ASA-continuing group (170 patients) ASA-discontinuing group (200 patients)	There is no difference in perioperative complications between aspirin continuation and discontinuation
Zhang *et al*[29], 2017 Meta-analysis	414 (4 studies)	2 groups: ASA-continuing group ASA-discontinuing group	Continued aspirin administration do not have an increased risk for bleeding
Cheng *et al*[30], 2018 Systematic review	1173 (7 studies)	3 groups: No ASA therapy (587 patients) Stopped ASA (3-10 d before surgery – 416 patients)	No difference in intraoperative blood loss, operation time, and postoperative complications

		Continued ASA (170 patients	
Claydon *et al*[28], 2022 Prospective, multi-center observational cohort study	364	2 groups: ASA-continuing group (21 patients) No ASA group	There was no association of low-dose ASA continuation with increased blood loss
Tarukado *et al*[27], 2023 Retrospective single-center, cohort study	88	3 groups: No antithrombotics (65 patients) Stopped ASA (9 patients) Continued ASA (14 patients)	Continuing ASA did not affect perioperative complications or clinical outcomes

ASA: Aspirin.

was not statistically significant. However, cardiopulmonary complications were more frequent in the aspirin group. The study suggests that aspirin use may be relatively safe in patients with increased cardiovascular risk and emergency cerebrovascular surgery. Patients undergoing craniotomy for the treatment of neurovascular lesions with short (≤ 5 d) aspirin discontinuation time did not appear to have increased rates of postoperative bleeding in another retrospective study, which included 215 cases[26].

RISK OF BLEEDING IN SPINAL SURGERY

A relatively large amount of clinical evidence has accumulated to date regarding the safety of continued aspirin use in spinal neurosurgery. For instance, in a retrospective cohort study, which included 88 patients, the safety of continuing low-dose aspirin during microendoscopic laminectomy was investigated[27]. The patients were categorized into three groups based on their anticoagulation therapy status. There was no statistically significant difference between the three groups in operation time. The study concluded that continuing aspirin in these clinical settings did not affect perioperative complications or clinical outcomes. Another prospective multi-center observational cohort study focused on risk factors affecting blood loss during elective anterior lumbar surgery. Based on an analysis of 364 patients, the continuation of low-dose aspirin was not associated with increased blood loss[28].

Previous studies were systematized in a couple of reviews[29,30]. They assessed the impact of aspirin on bleeding and cardiovascular events in the perioperative period and concluded that continuation of aspirin does not increase the risk of blood loss, operative time, or postoperative blood transfusion during spinal surgery. However, both reviews acknowledged the need for more research to understand the relationship between aspirin use and cardiovascular risks, emphasizing the importance of considering individual patient risks when managing aspirin therapy in spinal surgeries.

BALANCING THE RISK

Presented clinical data reflects the paucity of reliable evidence on clinical decision-making for continuing or interrupting aspirin uptake in the perioperative period in patients scheduled for elective neurosurgical procedures. Potential disturbance in intraoperative blood clot formation stimulates a defensive approach, but the impact on the outcome of aspirin uptake in these specific clinical settings remains uncertain. Inconsistency in clinical data provokes variability in clinical practice[31,32].

Moreover, even guidelines on this issue do not coincide with each other. For instance, European Society of Anaesthesiology and Intensive Care guidelines on perioperative bleeding management suggest that "intracranial surgery can be safely performed in the presence of low-dose aspirin", but in cases where aspirin withdrawal before surgery is considered, time from last drug intake to the intervention of 3 d. However, for invasive procedures at high risk of bleeding, a longer interruption (5 d) could be considered[18]. This period is much shorter in comparison with the vague statement of at least 7 d of discontinuation in ESC guidelines[1].

Of course, the decision on continuing or interrupting aspirin in particular cases should be made based on the discussion of specialists involved in perioperative management (neurosurgeon, anesthesiologist, cardiologist, *etc*), but a framework for such decision-making is not strictly defined. One of the potential approaches is presented in Figure 1. It can contain estimated blood loss risk of complications associated with increased bleeding time, risk of postoperative ischemic complication associated with aspirin interruption, and risk of surgery postponement. Individual bleeding risk assessment should also include non-specific factors, such as preoperative anemia, renal dysfunction, chronic liver disease, metabolic disorders *etc*[18]. Such abnormalities should be corrected, if possible, before proceeding to surgery.

It should be taken into account that high estimated blood loss can be aggravated by the antiplatelet effect of aspirin. This is particularly important in cases where surgical manipulation would be performed inside the tissues with the abnormal structure of the vascular wall, *i.e.* neoplasms. This risk is presumably lower for cerebrovascular and spinal

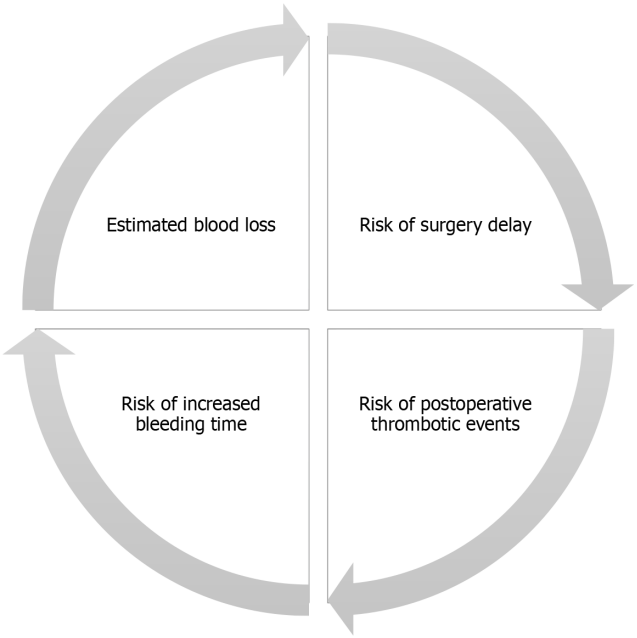

Figure 1 Framework for decision making on aspirin interruption before neurosurgical procedures.

surgery. On the other hand, the risk of thrombotic complication can outweigh the bleeding risk in patients with high cardiac risk (history of myocardial infarction, coronary stenting, unstable angina *etc*, which are among the most common indications for chronic aspirin consumption). In such cases, aspirin continuation can provide a better outcome.

Furthermore, in neurosurgical practice, it is frequently necessary to treat patients who can have serious consequences due to the delay in surgical intervention (*e.g.*, intracranial bleeding of a brain lesion, progressive neurologic deficit due to mass effect, occurrence of seizures in patients with intracranial mass, *etc*). Risk-benefit balance of aspirin interruption in such cases remains uncertain, but ESC recommendation for aspirin discontinuation might cause the underestimation of risks and harm of surgery delay.

CONCLUSION

Aspirin interruption before neurosurgical interventions remains a controversial clinical issue. Neurosurgical patients are very heterogeneous and might present different risks of perioperative bleeding. But the current form of recommendation of aspirin discontinuation makes all clinical situations equal and motivates physicians to make the same clinical decisions in any case. Future studies should be designed for rational and evidence-based clinical decision-making.

FOOTNOTES

Author contributions: Kulikov A, Bilotta F designed the research; Kulikov A, Konovalov A, Pugnaloni PP performed the research; Kulikov A, Konovalov A, Bilotta F analyzed the data and wrote the paper.

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

Country/Territory of origin: Italy

ORCID number: Alexander Kulikov 0000-0002-2852-6544; Anton Konovalov 0000-0002-0932-4752; Federico Bilotta 0000-0003-2496-6646.

S-Editor: Gong ZM
L-Editor: Filipodia
P-Editor: Zhao S

REFERENCES

1 **Visseren FLJ**, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021; **42**: 3227-3337 [PMID: 34458905 DOI: 10.1093/eurheartj/ehab484]

2 **Devereaux PJ**, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, Parlow JL, Guyatt G, Robinson A, Garg AX, Rodseth RN, Botto F, Lurati Buse G, Xavier D, Chan MT, Tiboni M, Cook D, Kumar PA, Forget P, Malaga G, Fleischmann E, Amir M, Eikelboom J, Mizera R, Torres D, Wang CY, VanHelder T, Paniagua P, Berwanger O, Srinathan S, Graham M, Pasin L, Le Manach Y, Gao P, Pogue J, Whitlock R, Lamy A, Kearon C, Baigent C, Chow C, Pettit S, Chrolavicius S, Yusuf S; POISE-2 Investigators. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med* 2014; **370**: 1494-1503 [PMID: 24679062 DOI: 10.1056/NEJMoa1401105]

3 **Lassen B**, Helseth E, Rønning P, Scheie D, Johannesen TB, Mæhlen J, Langmoen IA, Meling TR. Surgical mortality at 30 days and complications leading to recraniotomy in 2630 consecutive craniotomies for intracranial tumors. *Neurosurgery* 2011; **68**: 1259-68; discussion 1268 [PMID: 21273920 DOI: 10.1227/NEU.0b013e31820c0441]

4 **James DN**, Fernandes JR, Calder I, Smith M. Low-dose aspirin and intracranial surgery. A survey of the opinions of consultant neuroanaesthetists in the UK. *Anaesthesia* 1997; **52**: 169-172 [PMID: 9059104 DOI: 10.1111/j.1365-2044.1997.67-az0056.x]

5 **Mehilli J**, Halvorsen S. The '10 commandments' for the 2022 European Society of Cardiology guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. *Eur Heart J* 2023; **44**: 336-337 [PMID: 36527277 DOI: 10.1093/eurheartj/ehac703]

6 **Goes R**, Muskens IS, Smith TR, Mekary RA, Broekman MLD, Moojen WA. Risk of aspirin continuation in spinal surgery: a systematic review and meta-analysis. *Spine J* 2017; **17**: 1939-1946 [PMID: 28823937 DOI: 10.1016/j.spinee.2017.08.238]

7 **Rychen J**, Saemann A, Fingerlin T, Guzman R, Mariani L, Greuter L, Soleman J. Risks and benefits of continuation and discontinuation of aspirin in elective craniotomies: a systematic review and pooled-analysis. *Acta Neurochir (Wien)* 2023; **165**: 39-47 [PMID: 36376767 DOI: 10.1007/s00701-022-05416-2]

8 **Awtry EH**, Loscalzo J. Aspirin. *Circulation* 2000; **101**: 1206-1218 [PMID: 10715270 DOI: 10.1161/01.cir.101.10.1206]

9 **FitzGerald GA**. Mechanisms of platelet activation: thromboxane A2 as an amplifying signal for other agonists. *Am J Cardiol* 1991; **68**: 11B-15B [PMID: 1892057 DOI: 10.1016/0002-9149(91)90379-y]

10 **Schafer AI**. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. *J Clin Pharmacol* 1995; **35**: 209-219 [PMID: 7608308 DOI: 10.1002/j.1552-4604.1995.tb04050.x]

11 **Helgason CM**, Bolin KM, Hoff JA, Winkler SR, Mangat A, Tortorice KL, Brace LD. Development of aspirin resistance in persons with previous ischemic stroke. *Stroke* 1994; **25**: 2331-2336 [PMID: 7974569 DOI: 10.1161/01.str.25.12.2331]

12 **Amrein PC**, Ellman L, Harris WH. Aspirin-induced prolongation of bleeding time and perioperative blood loss. *JAMA* 1981; **245**: 1825-1828 [PMID: 7014935 DOI: 10.1001/jama.245.18.1825]

13 **Cattaneo M**. Laboratory detection of 'aspirin resistance': what test should we use (if any)? *Eur Heart J* 2007; **28**: 1673-1675 [PMID: 17586540 DOI: 10.1093/eurheartj/ehm232]

14 **Aradi D**, Storey RF, Komócsi A, Trenk D, Gulba D, Kiss RG, Husted S, Bonello L, Sibbing D, Collet JP, Huber K; Working Group on Thrombosis of the European Society of Cardiology. Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention. *Eur Heart J* 2014; **35**: 209-215 [PMID: 24067509 DOI: 10.1093/eurheartj/eht375]

15 **Karger R**, Reuter K, Rohlfs J, Nimsky C, Sure U, Kretschmer V. The Platelet Function Analyzer (PFA-100) as a Screening Tool in Neurosurgery. *ISRN Hematol* 2012; **2012**: 839242 [PMID: 22928115 DOI: 10.5402/2012/839242]

16 **Orlikowski CE**, Payne AJ, Moodley J, Rocke DA. Thrombelastography after aspirin ingestion in pregnant and non-pregnant subjects. *Br J Anaesth* 1992; **69**: 159-161 [PMID: 1389819 DOI: 10.1093/bja/69.2.159]

17 **Filipescu DC**, Stefan MG, Valeanu L, Popescu WM. Perioperative management of antiplatelet therapy in noncardiac surgery. *Curr Opin Anaesthesiol* 2020; **33**: 454-462 [PMID: 32371645 DOI: 10.1097/ACO.0000000000000875]

18 **Kietaibl S**, Ahmed A, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, De Robertis E, Faraoni D, Filipescu DC, Fries D, Godier A, Haas T, Jacob M, Lancé MD, Llau JV, Meier J, Molnar Z, Mora L, Rahe-Meyer N, Samama CM, Scarlatescu E, Schlimp C, Wikkelsø AJ, Zacharowski K. Management of severe peri-operative bleeding: Guidelines from the European Society of Anaesthesiology and Intensive Care: Second update 2022. *Eur J Anaesthesiol* 2023; **40**: 226-304 [PMID: 36855941 DOI: 10.1097/EJA.0000000000001803]

19 **Merriman E**, Bell W, Long DM. Surgical postoperative bleeding associated with aspirin ingestion. Report of two cases. *J Neurosurg* 1979; **50**: 682-684 [PMID: 430164 DOI: 10.3171/jns.1979.50.5.0682]

20 **Hanalioglu S**, Sahin B, Sahin OS, Kozan A, Ucer M, Cikla U, Goodman SL, Baskaya MK. Effect of perioperative aspirin use on hemorrhagic complications in elective craniotomy for brain tumors: results of a single-center, retrospective cohort study. *J Neurosurg* 2019; **132**: 1529-1538 [PMID: 30952120 DOI: 10.3171/2018.12.JNS182483]

21 **Rychen J**, Weiger VF, Halbeisen FS, Ebel F, Ullmann M, Mariani L, Guzman R, Soleman J. Perioperative continuation or ultra-early resumption of antithrombotics in elective neurosurgical cranial procedures. *Neurosurg Focus* 2023; **55**: E6 [PMID: 37778052 DOI: 10.3171/2023.7.FOCUS23357]

22 **Enciu A**, Loeschner D, Alhallak M, Kellner G, Meyer A, Lauten A, Steinbrecher A, Gerlach R. Management and risk of postoperative bleeding in patients with low-dose antiplatelet aspirin medication during endoscopic endonasal surgery for pituitary adenomas. *Acta Neurochir (Wien)* 2023; **165**: 2995-3001 [PMID: 37668789 DOI: 10.1007/s00701-023-05766-5]

23 **Schubert GA**, Biermann P, Weiss C, Seiz M, Vajkoczy P, Schmiedek P, Thomé C. Risk profile in extracranial/intracranial bypass surgery--the role of antiplatelet agents, disease pathology, and surgical technique in 168 direct revascularization procedures. *World Neurosurg* 2014; **82**: 672-677 [PMID: 23838364 DOI: 10.1016/j.wneu.2013.06.010]

24 **Nakamizo A**, Michiwaki Y, Kawano Y, Amano T, Matsuo S, Fujioka Y, Tsumoto T, Yasaka M, Okada Y. Impact of antithrombotic treatment on clinical outcomes after craniotomy for unruptured intracranial aneurysm. *Clin Neurol Neurosurg* 2017; **161**: 93-97 [PMID: 28865323 DOI: 10.1016/j.clineuro.2017.08.016]

25 **Rashidi A**, Lilla N, Skalej M, Sandalcioglu IE, Luchtmann M. Impact of acetylsalicylic acid in patients undergoing cerebral aneurysm surgery - should the neurosurgeon really worry about it? *Neurosurg Rev* 2021; **44**: 2889-2898 [PMID: 33495921 DOI: 10.1007/s10143-021-01476-7]

26 **Ebel F**, Ullmann M, Guzman R, Soleman J. Does the discontinuation time of antiplatelet or anticoagulation treatment affect hemorrhagic complications in patients undergoing craniotomy for neurovascular lesions? *Br J Neurosurg* 2021; **35**: 619-624 [PMID: 34030525 DOI: 10.1080/02688697.2021.1929835]

27 **Tarukado K**, Ono T, Doi T, Harimaya K, Nakashima Y. Safety and Clinical Results of Continuous Low-Dose Aspirin in Microendoscopic Laminectomy. *Spine Surg Relat Res* 2023; **7**: 350-355 [PMID: 37636142 DOI: 10.22603/ssrr.2022-0224]

28 **Claydon MH**, Biddau DT, Laggoune JP, Malham GM. Who bleeds during elective anterior lumbar surgery? *N Am Spine Soc J* 2022; **12**: 100180 [PMID: 36568642 DOI: 10.1016/j.xnsj.2022.100180]

29 **Zhang C**, Wang G, Liu X, Li Y, Sun J. Safety of continuing aspirin therapy during spinal surgery: A systematic review and meta-analysis. *Medicine (Baltimore)* 2017; **96**: e8603 [PMID: 29145278 DOI: 10.1097/MD.0000000000008603]

30 **Cheng A**, Poon MTC, Demetriades AK. Aspirin therapy discontinuation and intraoperative blood loss in spinal surgery: a systematic review. *Neurosurg Rev* 2018; **41**: 1029-1036 [PMID: 29362950 DOI: 10.1007/s10143-018-0945-1]

31 **Korinth MC**. Low-dose aspirin before intracranial surgery--results of a survey among neurosurgeons in Germany. *Acta Neurochir (Wien)* 2006; **148**: 1189-96; discussion 1196 [PMID: 16969624 DOI: 10.1007/s00701-006-0868-4]

32 **Fiaschi P**, Iaccarino C, Stefini R, Prior E, Prior A, Zona G. Clinical practice for antiplatelet and anticoagulant therapy in neurosurgery: data from an Italian survey and summary of current recommendations - part I, antiplatelet therapy. *Neurosurg Rev* 2021; **44**: 485-493 [PMID: 31953783 DOI: 10.1007/s10143-019-01229-7]

World Journal of Cardiology

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

World J Cardiol 2024 April 26; 16(4): 199-214

DOI: 10.4330/wjc.v16.i4.199

ISSN 1949-8462 (online)

SCIENTOMETRICS

The cardiovascular system at high altitude: A bibliometric and visualization analysis

Mao-Lin Zhao, Zhong-Jie Lu, Li Yang, Sheng Ding, Feng Gao, Yuan-Zhang Liu, Xue-Lin Yang, Xia Li, Si-Yi He

Specialty type: Cardiac and cardiovascular systems

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Ong H, Malaysia

Received: November 22, 2023
Peer-review started: November 22, 2023
First decision: January 23, 2024
Revised: February 14, 2024
Accepted: April 1, 2024
Article in press: April 1, 2024
Published online: April 26, 2024

Mao-Lin Zhao, Zhong-Jie Lu, Li Yang, Sheng Ding, Feng Gao, Yuan-Zhang Liu, Xue-Lin Yang, Xia Li, Department of Cardiovascular Surgery, The General Hospital of Western Theater Command, College of Medicine, Southwest Jiaotong University, Chengdu 610083, Sichuan Province, China

Si-Yi He, Department of Cardiovascular Surgery, The General Hospital of Western Theater Command, Chengdu 610083, Sichuan Province, China

Corresponding author: Si-Yi He, MD, Associate Professor, Department of Cardiovascular Surgery, The General Hospital of Western Theater Command, No. 270 Rongdu Avenue, Chengdu 610083, Sichuan Province, China. hesiyi@vip.163.com

Abstract

BACKGROUND

When exposed to high-altitude environments, the cardiovascular system undergoes various changes, the performance and mechanisms of which remain controversial.

AIM

To summarize the latest research advancements and hot research points in the cardiovascular system at high altitude by conducting a bibliometric and visualization analysis.

METHODS

The literature was systematically retrieved and filtered using the Web of Science Core Collection of Science Citation Index Expanded. A visualization analysis of the identified publications was conducted employing CiteSpace and VOSviewer.

RESULTS

A total of 1674 publications were included in the study, with an observed annual increase in the number of publications spanning from 1990 to 2022. The United States of America emerged as the predominant contributor, while Universidad Peruana Cayetano Heredia stood out as the institution with the highest publication output. Notably, Jean-Paul Richalet demonstrated the highest productivity among researchers focusing on the cardiovascular system at high altitude. Furthermore, Peter Bärtsch emerged as the author with the highest number of cited articles. Keyword analysis identified hypoxia, exercise, acclimatization, acute and chronic mountain sickness, pulmonary hypertension, metabolism, and echocardiography as the primary research hot research points

and emerging directions in the study of the cardiovascular system at high altitude.

CONCLUSION
Over the past 32 years, research on the cardiovascular system in high-altitude regions has been steadily increasing. Future research in this field may focus on areas such as hypoxia adaptation, metabolism, and cardiopulmonary exercise. Strengthening interdisciplinary and multi-team collaborations will facilitate further exploration of the pathophysiological mechanisms underlying cardiovascular changes in high-altitude environments and provide a theoretical basis for standardized disease diagnosis and treatment.

Key Words: Cardiovascular system; High altitude; Hypoxia; Bibliometric analysis; Visualization

Core Tip: In this study, a bibliometric and visualization analysis was conducted to summarize the latest research advancements in the cardiovascular system at high altitude. Based on 1674 publications included, we provide a comprehensive description of countries, institutions, authors, journals, and keywords involved in this field. Our findings would be helpful in investigating the mechanisms that affect the cardiovascular system at high altitude and the future clinical applications.

Citation: Zhao ML, Lu ZJ, Yang L, Ding S, Gao F, Liu YZ, Yang XL, Li X, He SY. The cardiovascular system at high altitude: A bibliometric and visualization analysis. *World J Cardiol* 2024; 16(4): 199-214
URL: https://www.wjgnet.com/1949-8462/full/v16/i4/199.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i4.199

INTRODUCTION

Globally, a large number of people visit, work, or reside at high altitude. An estimated 81.6 million people live at altitudes > 2500 m above sea level and 14.4 million people live at altitudes ≥ 3500 m above sea level[1]. The oxygen levels decline with increasing altitude. Exposure to hypoxia significantly affects physical performance and the cardiovascular system [2]. Exposure to hypoxia or intermittent hypoxia activates compensatory cardioprotective mechanisms[3]. Several studies have shown that short-term intermittent hypoxia promotes cardioprotective effects similar to ischemia preconditioning. For example, intermittent hypoxia protected cardiomyocytes against H_2O_2- and ischemia/reperfusion-induced oxidative stress and cell death by maintaining Ca^{2+} homeostasis and the mitochondrial membrane potential, and upregulating the expression levels of antioxidant enzymes[4]. Intermittent hypobaric hypoxia exposure in rats induced cardiovascular protective mechanisms against oxidative stress[5]. However, prolonged exposure to hypoxia at high altitude increases the risk of cardiovascular disease by chronically activating cellular responses that are detrimental to cardiac function. The damage to cardiac cells at high altitude because of exposure to hypoxic and hypobaric environment results in elevated serum levels of myocardial enzymes to varying degrees; in severe cases, myocardial damage causes malignant arrhythmia, heart failure, and even sudden death[6]. Furthermore, at high altitudes, many people experience acute mountain sickness (AMS), high-altitude cerebral edema, high-altitude pulmonary edema (HAPE), chronic mountain sickness (CMS), and high-altitude pulmonary hypertension (HAPH)[7]. The prevalence of myocardial injury at high altitude was 18.6%-33.2%[8,9]. Although several studies have reported the adverse effects of high altitude on the cardiovascular system, the mechanisms are complex and unclear. Therefore, there is an urgent need to identify the advances, trends, and hotpots in the research area of the cardiovascular system at high altitude based on previous publications. Such information would be beneficial for research investigators in this field to pursue studies in the right direction.

Bibliometric methods are used to investigate the productivity of researchers, institutions, and countries in specific subject areas to determine the research hotspots and future directions that can also be used to guide policy decisions[10]. Furthermore, bibliometric analysis is a good indicator of progress in a research field[11]. Moreover, co-citation is frequently used in the bibliometric analysis to identify links between authors, keywords, countries, and organizations.

Several bibliometric analyses have been performed in the field of the cardiovascular system in areas such as heart transplantation, future landscape of macrophage research in cardiovascular disease, and heart failure[12-15]. In this study, we performed a bibliometric analysis of studies on the cardiovascular system at high altitude using the Science Citation Index Expanded (SCIE) index of the Web of Science (WoS) Core Collection. Our aim was to identify the current hotpots of research and the frontier directions that would be helpful in investigating the mechanisms that affect the cardiovascular system at high altitude and the future clinical applications in this field.

MATERIALS AND METHODS

Bibliometric analysis

CiteSpace 6.1 R6 software and VOSviewer 1.6.18.0 software were used for the bibliometric analysis of countries, institutions, journals, and keywords of research related to the cardiovascular system at high altitude between January 1, 1990 and December 31, 2022. The CiteSpace software was used to simultaneously visualize the co-occurrence network between time, frequency, and betweenness centrality. Cluster view was used to label the clusters with phrases. Furthermore, the CiteSpace software was used for temporal analysis and the pruning algorithms were used to highlight the main structure of the network[16]. The co-occurrence analysis in CiteSpace was used to visualize the co-authorship network of countries, institutions, journals, and authors. CiteSpace software was also used to visualize the timeline view of keyword clustering and identify the development process and hotpots in the cardiovascular system at high altitude. In CiteSpace, node size represents the frequency of publications and citations; purple rings represent centrality; and nodes in the red inner rings represent the burst in research[17]. Furthermore, connections between points represent the co-citation relationship and the number of interconnections represents the strength of co-occurrence or co-citation of the collaboration.

VOSviewer is a popular tool for visualizing the knowledge map and provides a variety of tools for viewing keywords, co-institutions, co-authors, *etc.*, including Network Visualization, Overlay Visualization, and Density Visualizatio[18]. Co-citation analysis of cited references, journals, and authors, and the co-occurrence analysis of keywords were visualized using the VOSviewer. The points in the co-citation maps represent different co-cited references, journals, or authors. Size of the points represents the number of citations in individual publications. The lines between points show co-citation relationships. The colored points represent different clusters and the colored lines represent different years.

Data source and literature search strategy

In this study, we searched for publications related to cardiac system at high altitude in the SCIE index of the WoS Core Collection using the following keywords and combinations: TS = (("high altitude" OR "plateau" OR "mountain") AND ("cardiovascular" OR "heart" OR "cardiac" OR "myocardial")). The time span was set between January 1, 1990 and December 31, 2022. The literature language was restricted to English. We identified 6605 publications that met these criteria. The literature types were limited to articles and reviews. The exclusion criteria are shown in Table 1. After initial search, we retrieved 5992 publications as potential candidates for inclusion. Subsequently, the titles, abstracts, and the full texts of the publications were manually examined by two investigators (Zhao ML and He SY) and the irrelevant articles were excluded. Finally, after removing duplicates, we included 1674 journal articles, including 1331 articles and 133 reviews for further analysis.

Table 1 Summary of data source and selection

Date source	Web of Science
Citation index	SCIE
Searching period	January 1, 1990 to December 31, 2022
Searching	TS = (("high altitude" OR "plateau" OR "mountain") AND ("cardiovascular" OR "heart" OR "cardiac" OR "myocardial"))
Subject category	"Physiology", "Cardiac Cardiovascular Systems", "Sport Sciences"
Document type	"Articles" or "reviews"
Language	"English"
Sample size	1674

SCIE: Science citation index expanded.

RESULTS

Descriptive statistics

This study included 1674 papers with 7433 authors from 2041 organizations and 78 countries; these papers were published in 586 journals, and were cited in 44674 publications from 7775 journals (Table 2). Figure 1 shows the chronological distribution of publications in the field of research related to the cardiovascular system at high altitude. The number of papers published in this field increased every year from 1990 to 2022, especially from 2012 onwards. The annual publication rate was > 60. This suggested significant research in this area, especially after 2012.

Co-authorship network analysis based on countries, institutions, authors, and journals

We constructed a co-occurrence network of countries and institutions to evaluate the progress of studies on the cardiovascular system at high altitude in different countries and institutions, and also determine the potential co-operation between countries and institutions in this area. Figure 2A shows the interactions between countries and

Table 2 Descriptive statistics of the database

Criteria	Quantity
Publications	1674
Authors	7433
Journals	586
Institutions	2041
Countries	78
Cited references	44674

Table 3 Top 10 countries in the field of cardiovascular system at high altitude

Rank	Country	Publications	Citations	Average citations
1	United States	409	12146	29.70
2	People's Republic of China	367	5268	14.35
3	England	156	4119	26.40
4	France	129	3296	25.55
5	Canada	124	3190	25.73
6	Italy	124	3065	24.72
7	Switzerland	113	3360	29.73
8	Germany	113	2330	20.62
9	Austria	79	1259	15.93
10	Peru	72	2431	33.76

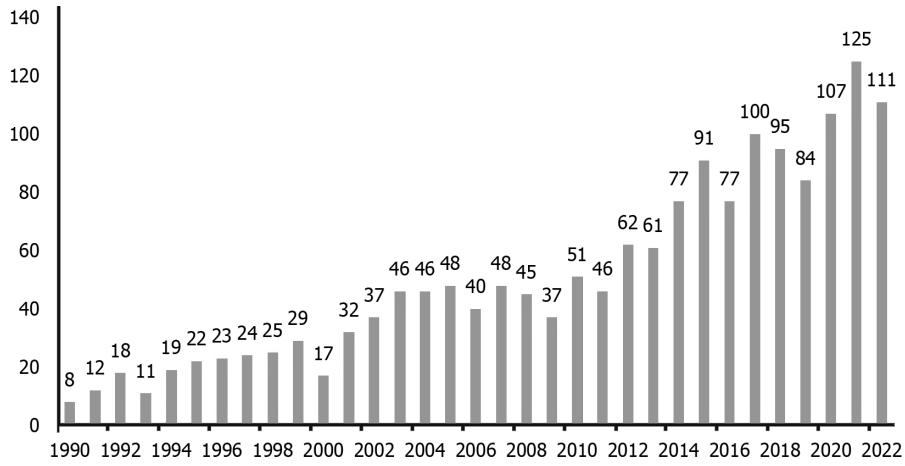

Figure 1 Distribution of publications from 1990 to 2022.

Figure 2B shows the interactions between institutions in this research area. The top 5 productive countries in this research area were United States (409 papers), People's Republic of China (367 papers), England (156 papers), France (129 papers), and Canada (124 papers; Table 3). The top 5 countries for centrality were the United States (0.41), People's Republic of China (0.21), England (0.20), Germany (0.16), and Switzerland (0.13; Table 4). The betweenness centrality was more than 0.1 for these 5 countries, highlighting their leading role in research area. Table 5 shows the top 10 institutions in the research area of the cardiovascular system at high altitude. The universities with the highest number of publications were as follows: Universidad Peruana Cayetano Heredia (57 papers), University of British Columbia (51 papers), Chinese Academy of sciences (48 papers), University of Innsbruck (48 papers), and University of Colorado (46 papers). The top 10 countries in this area included six European countries (England, Germany, Switzerland, Italy, France, and Netherlands), two North American countries (the United States and Canada), one Asian country (People's Republic of China), and one South American country (Chile). These top ten countries accounted for 93.91% of the publications.

Table 4 Top 10 countries with centrality value

Rank	Country	Centrality
1	United States	0.41
2	People's Republic of China	0.21
3	England	0.20
4	Germany	0.16
5	Switzerland	0.13
6	Italy	0.11
7	Chile	0.09
8	France	0.08
9	Canada	0.08
10	Netherlands	0.07

Table 5 Top 10 institutions in the field of cardiovascular system at high altitude

Rank	Institution	Publications	Citations	Average citations
1	Universidad Peruana Cayetano Heredia	57	1704	29.90
2	University of British Columbia	51	1505	29.51
3	Chinese Academy of Sciences	48	1140	23.75
4	University of Innsbruck	48	819	17.07
5	University of Colorado	46	2311	50.24
6	Loma Linda University	39	1006	25.79
7	The Third Military Medical University	36	307	7.87
8	University of Cambridge	32	1335	42.34
9	Université Sorbonne Paris Nord	31	1300	41.94
10	University of California-San Diego	31	1119	36.10

Next, we analyzed the literature to identify the main research scholars studying the cardiovascular system at high altitude. Figure 2C shows the network of author-co-author relationships in this field. Table 6 shows the authors who have published 16 papers or more in the area of the cardiovascular system at high altitude. Jean-Paul Richalet from the University of Paris published 41 papers with 1616 citations and an average of 39 citations per article. In the second place, Philip N Ainslie from University of British Columbia contributed 31 articles with 565 citations and an average of 18 citations per article. Martin Burtscher from University of Paris published 30 articles with 488 citations and an average of 16 citations per article.

Impact factor of a journal refers to the importance of a journal in the research area of interest, and is calculated by the frequency with which the articles published in the journal were cited in other articles[19]. Table 7 shows the top 10 journals in the field of the cardiovascular system at high altitude. The top 3 journals were *High Altitude Medicine & Biology* (144 publications), *Journal of Applied Physiology* (81 publications), and *Frontiers in Physiology* (55 publications). The top journals with the highest number of citations per article were *The Journal of Physiology (London)* (41.62 citations per publication), *Journal of Applied Physiology* (37.71 citations per publication), and *American Journal of Physiology-Regulatory Integrative and Comparative Physiology* (37.68 citations per publication).

Co-citation analysis of cited references, journals, and authors

The number of citations reflects the quality of a study and is an indicator of the importance of the findings for the research field[20]. The most cited references provide a theoretical basis for studying the cardiovascular system at high altitude and guide researchers for further studies. We performed a bibliometric analysis of the cited references and obtained 44674 citations in this study. Then, using 30 citations as a threshold, we identified 68 articles for co-citation analysis of the cited articles. We then constructed a network of publications that were related to research regarding the cardiovascular system at high altitude. We identified five clusters represented by different colors and the cited references are represented as nodes of different sizes (Figure 2D). Table 8 summarizes the top 10 most frequently cited references. The top 5 cited references were as follows: Hackett and Roach[21] in 2001 (123 citations), Naeije[22] in 2010 (107 citations), Penaloza and Arias-Stella[23] in 2007 (107 citations), Bártsch *et al*[24] in 2007 (90 citations), and Simonson *et al*[25] in 2010.

Table 6 Most important authors in the field of cardiovascular system at high altitude

Rank	Author	Documents	Citations	Average citations
1	Jean-Paul Richalet	41	1616	39.41
2	Philip N Ainslie	31	565	18.23
3	Martin Burtscher	30	488	16.27
4	Lan Huang	25	216	8.64
5	Mike Stembridge	23	387	16.83
6	Gianfranco Parati	21	381	18.14
7	Michael M Tymko	18	214	11.89
8	Jie Yu	17	206	12.12
9	Leon-Velarde Fabiola	16	799	49.94
10	Francisco C Villafuerte	16	316	19.75
11	Frantisek Kolar	16	267	16.69
12	Jie Yang	16	71	4.44

Table 7 Top 10 journals in the field of cardiovascular system at high altitude

Rank	Source	Publications	Citations	Average citations
1	*High Altitude Medicine & Biology*	144	2982	20.71
2	*Journal of Applied Physiology*	81	3070	37.91
3	*Frontiers in Physiology*	55	399	7.25
4	*Wilderness & Environmental Medicine*	38	622	16.37
5	*Journal of Physiology-London*	29	1207	41.62
6	*American Journal of Physiology-Heart and Circulatory Physiology*	29	827	28.52
7	*Plos One*	27	692	25.63
8	*European Journal of Applied Physiology*	26	489	18.81
9	*Experimental Physiology*	22	406	18.45
10	*American Journal of Physiology-Regulatory Integrative and Comparative*	22	829	37.68

Table 8 Top 10 references with highest citations

Rank	Ref.	Citations
1	High-altitude illness	123
2	Physiological adaptation of the cardiovascular system to high altitude	107
3	The heart and pulmonary circulation at high altitudes: Healthy highlanders and chronic mountain sickness	107
4	Effect of altitude on the heart and the lungs	90
5	Genetic evidence for high-altitude adaptation in Tibet	78
6	Consensus statement on chronic subacute high altitude diseases	77
7	Operation Everest II: Preservation of cardiac function at extreme altitude	67
8	Sympathetic neural overactivity in healthy humans after prolonged exposure to hypobaric hypoxia	65
9	Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American society of echocardiography	55
10	Two routes to functional adaptation: Tibetan and Andean high-altitude natives	52

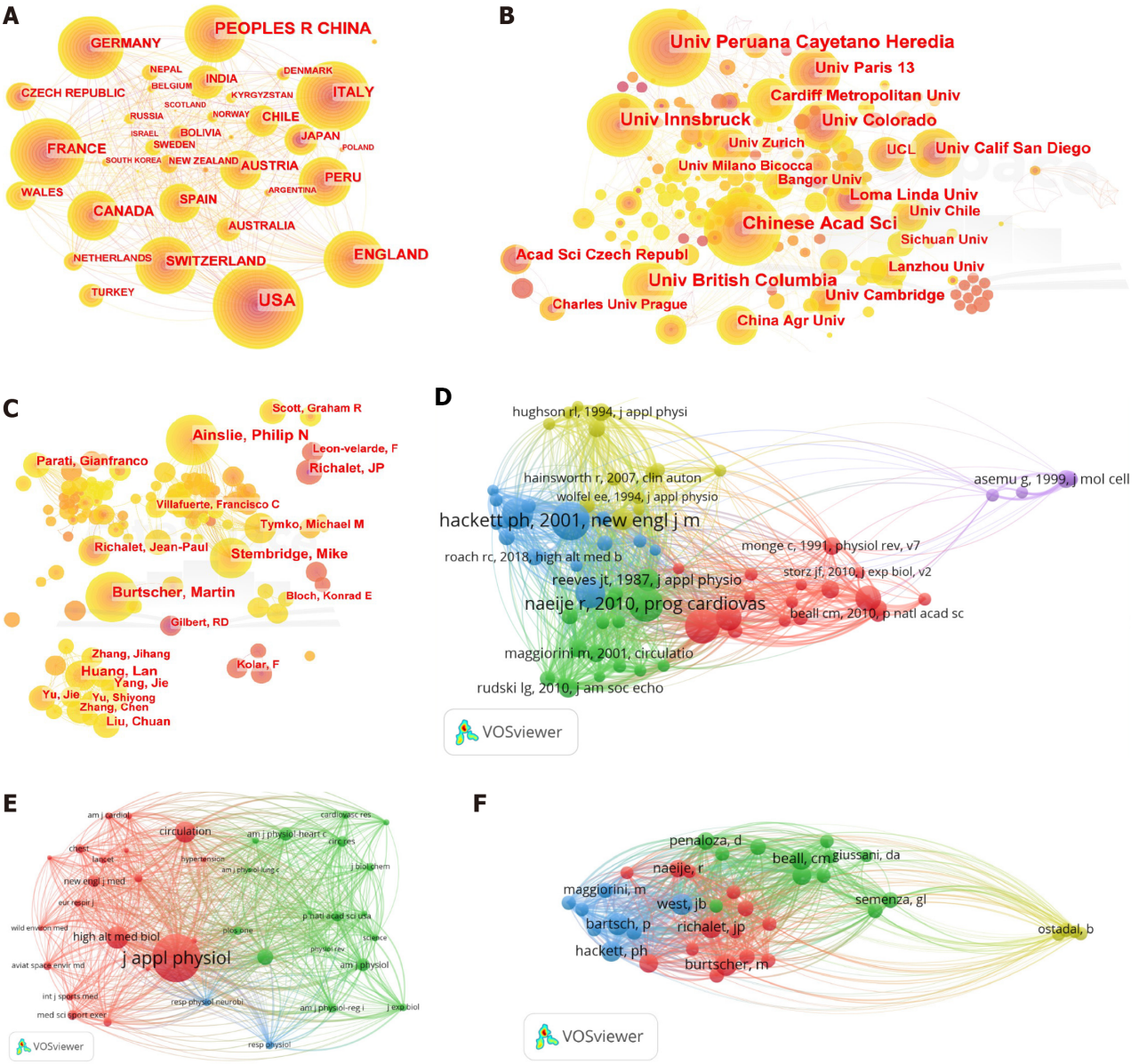

Figure 2 Co-authorship of countries, institutions, authors, and journals. A: Co-authorship between countries with more than 9 publications; B: Co-authorship between institutions with more than 14 publications; C: Co-authorship between authors with more than 9 publications; D: Co-citation of cited references; E: Co-citation of cited journals; F: Co-citation of cited authors.

Our study showed that the top 3 cited references were all reviews. The most cited publication was a review authored by Hackett and Roach[21], which described the epidemiology and risk factors, pathophysiological process, clinical manifestations, diagnosis, treatment, and disease preventive measures at high altitude[21]. The second and third most cited references also reviewed the pathophysiological processes of the cardiopulmonary vascular system at high altitude. The second reference was published by Naeije[22], mainly focused on the acclimatization of the cardiovascular system at high altitude[22]. The third reference was a review published by Penaloza and Aria-Stella[23] in *Circulation* and was titled "The Heart and Pulmonary Circulation at High Altitudes Healthy Highlanders and Chronic Mountain Sickness"[23]. This review described the physiology, pathology, pathogenesis, and clinical features of the heart and pulmonary circulation in healthy highlanders and patients with CMS[23]. The sixth most cited reference published by León-Velarde *et al*[26], reporting an expert consensus statement on the chronic and subacute diseases at high altitude, described the criteria for selecting a specific method or procedure to diagnose or manage these diseases[26]. The reference titled "Guidelines for Echocardiographic Evaluation of the Right Heart in Adult Patients: A Report by the American Society of Echocardiography" holds the tenth position in terms of citation count. This reference serves as a comprehensive document intended for healthcare professionals, providing them with guidelines for assessing the right ventricle and right atrium. It encompasses a range of parameters utilized for estimating both systolic and diastolic functions of the right ventricle, along with normal reference values derived from aggregated data[27].

Subsequently, using a citation threshold of 300, we selected 39 journals for co-citation analysis. Table 9 shows the top 10 most frequently cited journals. The co-citation network of journals consisted of three distinct clusters denoted by different colors (Figure 2E). *Journal of Applied Physiology* (5586 citations), *High Altitude Medicine & Biology* (2192 citations),

Table 9 Top 10 highest cited journals

Rank	Journals	Citations
1	*Journal of Applied Physiology*	5586
2	*High Altitude Medicine & Biology*	2192
3	*Circulation*	2051
4	*Journal of Physiology-London*	1433
5	*American Journal of Physiology-Heart and Circulatory*	1138
6	*American Journal of Physiology*	1107
7	*The New England Journal of Medicine*	980
8	*Circulation Research*	891
9	*Proceedings of the National Academy of Sciences of the United States of America -Physical sciences*	886
10	*American Journal of Physiology-Regulatory Integrative and Comparative Physiology*	792

and *Circulation* (2051 citations) were the most cited journals. These three journals are esteemed publications within the JCR1 region.

Next, we sought to identify the leading researchers in this research area. We used a citations threshold of 100 and identified 38 authors with a cumulative citation count of 29778. The co-citation network of these 38 authors demonstrated four distinct clusters (Figure 2F). Table 10 presents the top 10 most cited authors in this network, with Peter Bärtsch (382 citations), Martin Burtscher (378 citations), and John B West (358 citations) being the three most prominently cited authors.

Co-occurrence analysis of keywords

Keywords are specific terms or phrases that summarize the main subjects and concepts presented in the article. Therefore, co-occurrence analysis of keywords can be used to identify the hotspots in a research area. In the present study, we used the VOSviewer software to construct a network of keywords in the 1674 articles included in this study. Subsequently, we identified 103 keywords with a frequency of more than 20 (Figure 3A). In this network, size of the circle node denotes frequency of the keyword. For example, if the circle node is large, it suggests that the keyword occurs at a higher frequency. Hence, we considered high frequency key words as research hotspots in the field of study. The line of nodes represents the strength of the association. A thicker line indicates that the two words co-appear more times in the same article. Clusters of key words are represented by distinct colors. The top 10 keywords were high altitude (n = 598), hypoxia (n = 559), exercise (n = 269), AMS (n = 214), adaptation (n = 209), heart (n = 167), acclimatization (n = 137), pulmonary hypertension (n = 133), heart rate (n = 117), and blood pressure (n = 104; Table 11).

Since the number and type of keywords were too complex, the research topics were ambiguous, and it was difficult to determine the current research hotspots and priorities, previous studies have used keyword clustering to address this issue. Keyword clustering involves extracting representative phrases from keyword groups with similar meanings as specific cluster labels[12]. We used keyword clustering to determine the distribution of topics. The keyword clustering results were as follows: Heart (clustering 0), autonomic nervous system (clustering 1), cardiac function (clustering 2), coronary artery disease (clustering 3), metabolism (clustering 4), AMS (clustering 5), and endothelium (clustering 6) (Figure 3B). Based on the timeline view and clusters of keywords, we observed certain specific trends in the research hotspots regarding the study of the cardiovascular system at high altitude. The main research hotspots between 1990 and 2022 were heart, cardiac function, coronary artery disease, metabolism, and AMS. Autonomic nervous system and endothelium were also research hotspots in this field before 2015. Furthermore, we compile and summarize several significant points to reveal high altitude cardiovascular system function based on the analysis of popular keywords (Table 12).

DISCUSSION

Country distribution

The collaborations between countries have significantly advanced the understanding of the cardiovascular system at high altitude. The United States accounted for the highest number of publications. Many of these publications focused on subjects regarding the cardiovascular system at altitudes ≥ 4000 feet[28-33]. It should be noted that altitudes above 2000 m are generally considered as high altitudes. The risk of acute altitude illness is significantly higher at altitudes above 2500 m[34]. Therefore, it is not clear if all the studies included in this study can be considered as relevant for understanding the cardiovascular system at high altitude. Furthermore, except for China and Peru, the remaining eight countries in the top ten are considered as developed nations. Despite being categorized as a developing country, China ranks second in terms of publications in the field of the cardiovascular system at high altitude. This can be attributed to an extensive population residing at altitudes ≥ 3500 m in China[1]. Moreover, the world's highest plateau, the Qinghai-Tibet Plateau, is in China

Table 10 Top 10 highest frequency cited authors

Rank	Authors	Citations
1	Peter Bärtsch	382
P	Martin Burtscher	378
3	John B West	358
4	Beall Cynthia M	352
5	Jean-Paul Richalet	352
6	Hackett Peter	330
7	Lorna G Moore	265
8	Robert C Roach	261
9	Robert Naeije	235
10	Dante Penaloza	222

Table 11 Top 20 highest frequency keywords

Rank	Keyword	Occurrences	Total link strength
1	High altitude	598	2537
2	Hypoxia	559	2391
3	Exercise	269	1254
4	Acute mountain sickness	214	971
5	Adaptation	209	994
6	Heart	167	746
7	Acclimatization	137	728
8	Pulmonary hypertension	133	655
9	Heart rate	117	507
10	Blood pressure	104	526
11	Hypobaric hypoxia	101	528
12	Nitric oxide	99	442
13	Chronic hypoxia	93	432
14	Oxidative stress	90	408
15	Chronic mountain-sickness	80	375
16	Cardiac output	71	365
17	Intermittent hypoxia	66	190
18	Oxygen	56	170
19	Metabolism	54	149
20	Echocardiography	53	217

[35]. Peru is another country with a significant population residing at high altitude. Those residing at high altitude regions develop a variety of diseases, including diseases of the cardiovascular system. Therefore, extensive research has been conducted in these countries on the cardiovascular system at high altitude. Universidad Peruana Cayetano Heredia is one of the top ten institutions that have focused on studying cardiac health at high altitude[36,37].

Most cited authors

The most cited author in this field was Peter Bärtsch from the Departments of Internal Medicine and Outpatient Medicine, Heidelberg University, Heidelberg, Germany. Luks *et al*[38] focused on the clinical manifestations, epidemiology, pathophysiology, and treatment of common diseases at high altitude[38]. Bärtsch and Gibbs[24] also described the acute physiological adjustments and early acclimatization of the cardiovascular system in healthy

Table 12 Critical aspects of the cardiovascular system at high altitude

Rank	Keyword	Significant points
1	Hypoxia	Hypoxia emerges as the predominant characteristic among individuals residing at high altitudes
2	Exercise at high altitude	Exercise training is advocated for enhancing adaptation to high altitude
3	Pulmonary hypertension	Pulmonary artery pressure increases at high altitude due to vasoconstriction
4	Oxidative stress	Oxidative stress is activity at high altitude
5	Metabolomics	Metabolomics has offered novel perspectives on the pathophysiological mechanisms that underlie adaptations to early hypobaric hypoxia, as well as other diseases associated with tissue hypoxia
6	Adaptation/acclimatization	Adaptation or acclimatization occurs in individuals residing at high altitudes for extended periods, including indigenous populations
7	Echocardiography	Echocardiography serves as a valuable diagnostic tool for identifying cardiac diseases in high-altitude environments

individuals who visited places at high altitude as well as altitude tolerance in patients with underlying cardiovascular diseases[24]. Furthermore, Bärtsch *et al*[39] also described the health risks for athletes at high altitude and the methods by which the performance of athletes can be improved at high altitude[39,40]. The second most highly cited author in this field was Martin Burtscher from the Department of Sport Science, University of Innsbruck, Austria. This is also an institution with the fourth highest number of publications. Burtscher and Ponchia[41] published reports focused on the cardiovascular system at high altitude[41-43], treatment and prevention recommendations of hypoxia-related altitude illnesses[44,45], and exercise at high altitude[46]. The third most highly cited research scholar was John B West from the Department of Medicine, University of California San Diego, La Jolla, United States. West[47] has published articles regarding high altitude-related medicine and physiology[47,48], the technology of oxygen enrichment in room air[2,49], and pulmonary function at high altitude[50,51]. University of California, San Diego is also one of the top ten institutions for publications in the field of cardiovascular system at high altitude because of major contributions from John B West.

Keyword analysis

Keywords reflect the core themes and main content of an article. Therefore, they highlight the research hotspots in a specialized field and provide directions for future research. Based on the top 20 keywords in this study, exercise at high altitude was identified as an important research hotspot. Previous reports have shown that visits to an area at high altitude may result in AMS or CMS; the heart undergoes a range of pathophysiological changes resulting in pulmonary hypertension, oxidative stress, and altered metabolism[22]. In the highlanders, changes in heart rate, blood pressure, nitric oxide (NO) levels, and cardiac output are closely related with altitude adaptation and acclimatization. Furthermore, echocardiography is a useful tool for diagnosing cardiac diseases at high altitude.

Exercise at high altitude: Hypoxia training is a useful strategy for improving the performance of athletes. Intense physical activity, including training at high altitude or mountaineering, does not increase the prevalence or severity of AMS at moderate altitudes[40]. A meta-analysis demonstrated that training at natural or simulated altitude improved high intensity intermittent running performance of the team-sport athletes[52]. Several contemporary elite endurance athletes incorporate some form of altitude/hypoxic training within their year-round training plan to improve their performance[53]. However, intermittent hypoxia at rest does not improve athletic performance in competitions held at sea level[39]. Therefore, exercise training is recommended to improve adaptation at high altitude[54]. Pulmonary artery pressure is elevated at high altitude because of vasoconstriction. Acute hypoxia leads to closure of the oxygen-sensitive potassium channels in the vascular smooth muscle cells; subsequent depolarization induces calcium influx and contraction of the smooth muscle cells[55]. Chronic exposure to hypoxia increases pulmonary artery pressure in the highlanders, but the criteria for the diagnosis of HAPH are not clear. The prevalence of HAPH varied significantly among the highlanders depending on the diagnostic criteria. The prevalence of HAPH in the highlanders was 6% according to the expert consensus definition of chronic high-altitude disease and 35% according to the current definition of pulmonary hypertension proposed for the lowlanders[56]. Chronic exposure to high altitude is also associated with arterial remodeling[57]. The proliferation of vascular smooth muscle cells in the alveolar wall is one of the first remodeling events that continues even after the elimination of hypoxic stimulation[58]. Furthermore, hypoxia promoted smooth muscle cell proliferation and pulmonary vascular thickening by impairing endothelial cell membrane integrity and stimulating the secretion of growth factors[59]. Moreover, chronic hypoxia promoted smooth muscle cell proliferation and pulmonary vascular thickening by maintaining fibroblasts in an activated state through epigenetic regulatory mechanisms[60].

Oxidative stress at high altitude: Oxidative stress is involved in the development of AMS, CMS, and HAPA[7]. Oxidative stress is elevated at higher altitude and may persist until return to the sea level. Exposure to hypoxia alters several signaling pathways, including generation of higher levels of reactive oxygen species that may activate important adaptive responses[61]. Endothelial cell function is affected by hypoxia and oxidative stress. Furthermore, persistent impairment in the vascular function of lowlanders after exposure to high altitude is in part attributed to increased oxidative stress[62]. Hu *et al*[63] demonstrated that the activity of the large-conductance Ca^{2+}-activated K^+ channels in the uterine arteries of pregnant sheep was inhibited by increased oxidative stress in an hypoxic environment.

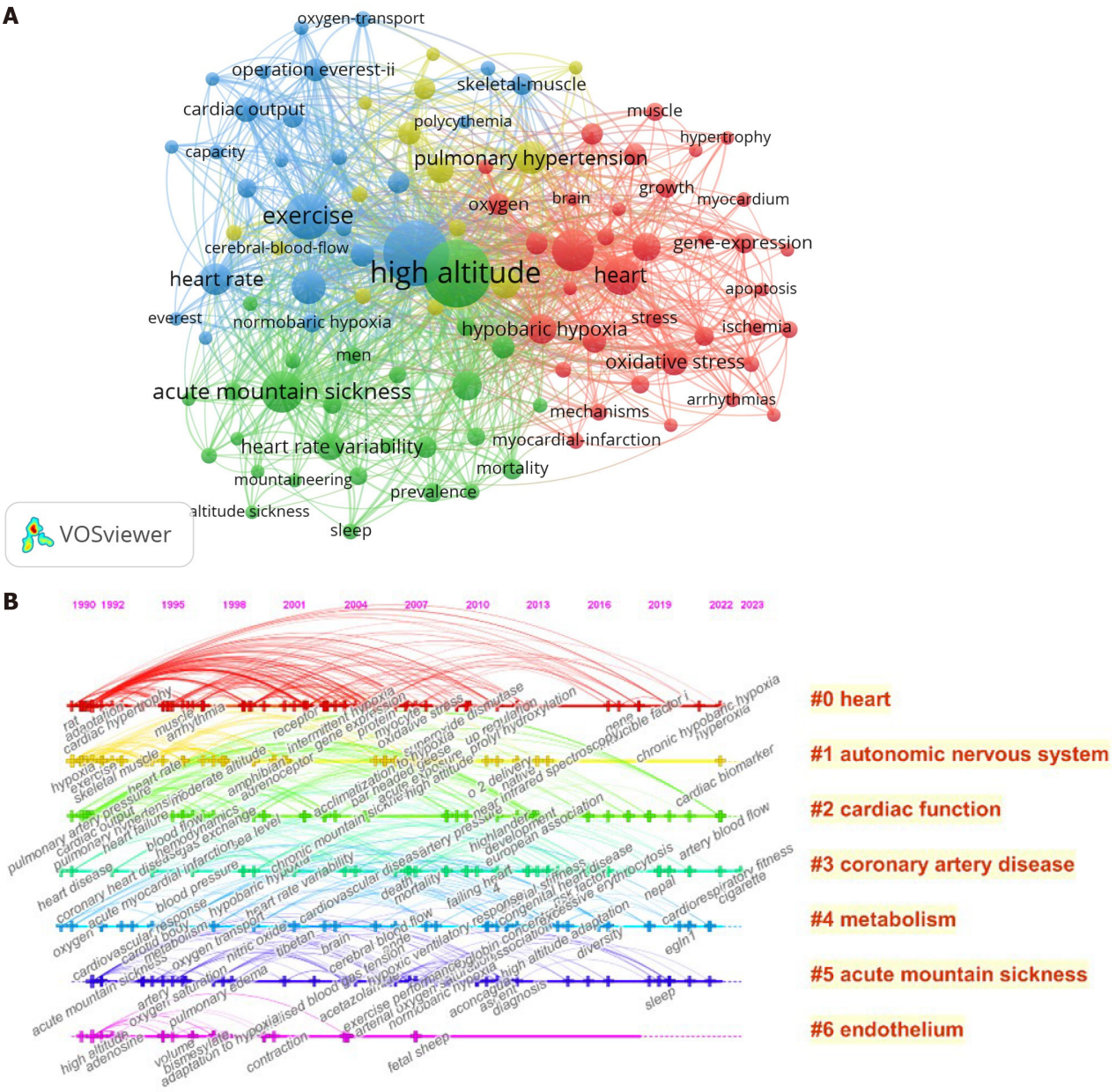

Figure 3 Co-occurrence analysis keywords. A: Keyword co-occurrence map of publications in high altitude cardiac research field; B: Map of timeline view in cardiovascular system at high altitude.

Altered cardiovascular function at high altitude: Major changes are observed in the cardiovascular function of subjects upon exposure to high altitudes, including increased left ventricular systolic function, preserved right ventricular systolic function, and changes in biventricular diastolic filling pattern without changing filling pressure[22]. These changes can be explained by varying degrees of sympathetic activation, reduction of preload, and the effects of long-term hypoxia on the myocardial muscle strength. High altitude exposure initiates the cardiovascular response that is associated with increased sympathetic activities, increased cardiac output with tachycardia, absence of any change in output per vibration, and marginal increase in blood pressure temporarily[64]. After a few days of acclimation, cardiac output returns to normal, but stroke volume is reduced because the heart rate continues to increase. Furthermore, pulmonary artery pressure is elevated but the pulmonary artery wedge pressure remains unchanged[65]. It is worth noting that increased cardiac output is proportionally reduced to arterial oxygen levels so that the total amount of oxygen delivered to the tissues remain constant. However, these changes in the cardiovascular system in response to hypoxia are temporary. The cardiac output returns to normal after a few days and the changes plateau after a certain time of exposure at high altitude[66]. The HIF signaling pathway is altered at high altitude and is crucial for acclimatization. EGLN1 and EPAS1 are major regulators of the hypoxic response[67-69].

Short-term exposure to high altitude causes hypoxia, which induces dilation of blood vessels resulting in decreased blood pressure; subsequently, rapid activation of the sympathetic nerve promotes contraction of the blood vasculature; therefore, blood pressure remains unchanged or slightly increased[22,70,71]. The prevalence of hypertension is higher upon long-term exposure to high altitude; the incidence of hypertension increased by 2% for every 100 m increase in

altitude in areas above 3000 m[72]. Aryal *et al*[73] performed a meta-analysis of 21 articles that included 40845 Tibetan residents living at 2400 m above sea level and reported that the average systolic and diastolic blood pressure increased by 17 mmHg and 9.5 mmHg, respectively, for an elevation of 1000 m[73]. However, long-term intermittent exposure to high altitude did not significantly alter blood pressure[74]. The increase in blood pressure at high altitude was proportional to an increase in the plasma levels of norepinephrine. This suggested that norepinephrine plays a key role in the activation of sympathetic nerves. However, the use of α- and β-receptor blockers did not completely restore blood pressure back to normal. This suggested that other mechanisms such as erythrocytosis and the renin-angiotensin system also participate in the elevation of increase of blood pressure at high altitude[24].

Metabolomics at high altitude: Metabolomics is a promising tool for discovering and understanding the novel biochemical and metabolic responses to hypobaric hypoxia exposure; it can provide new insights for the field of medicine at high altitude and unravel the underlying mechanisms for the health problems that occur in subjects upon exposure to high altitude[75]. Xie *et al*[76] delineated the landscape of metabolites in the myocardial tissues of rats exposed to high altitude using GS/MS-based metabolomics and reported significant changes in metabolites, including several branched chain amino acids, taurine, succinic acid, and others[76]. Extensive evidence of metabolic reprogramming and phenotypic transformation of fetal sheep pulmonary arteries induced by chronic hypoxia has been revealed by metabolomics techniques, which may contribute to the development of persistent pulmonary hypertension[77]. Guo *et al*[78] performed plasma metabolite profiling of 57 HAPE as well as 57 control subjects by ultra-high performance liquid chromatography coupled with Q-TOF mass spectrometry and showed that C8-ceramide, sphingosine, and glutamine were candidate diagnostic biomarkers for HAPE[79]. Liu *et al*[79] performed integrated plasma metabolomics and transcriptomic analyses to demonstrate a significant association between phenotypic variation under hypoxia and the arachidonic acid metabolism pathway[79]. Liao *et al*[80] used a metabolomics approach to detect plasma metabolic changes in subjects exposed to high altitude and showed significant changes in 44 metabolites and 4 related enzymes[80]. These results provided new insights into the pathophysiological mechanism underlying the early hypobaric hypoxia adaptations and other diseases associated with tissue hypoxia.

NO is a critical regulatory molecule *in vivo* that regulates oxygen transport cascade from the lung to the cardiovascular system, blood, and the mitochondria[81,82]. A 2-d exposure of rats to hypobaric hypoxia increased NO synthesis and promoted cardioprotective mechanisms[83]. NO is important for the pulmonary circulation response to acute and chronic hypoxia. Elevated levels of the endothelial nitric oxide synthase played a counterregulatory role in the pulmonary vasoconstriction response to acute hypoxia in Tibetan sheep adapated to high altitude[84]. Gonzales *et al*[85] also showed upregulation of the heart mitochondrial nitric oxide synthase in male rats exposed to high altitude[85].

Echocardiography for diagnosis of heart diseases at high altitude: Ultrasound is widely used in the diagnosis of heart disease at high altitude. Echocardiography is used to screen for congenital heart disease in newborns at high altitude[86]. Ultrasound is the best method for the clinical assessment of AMS[87]. Boussuges *et al*[88] performed echocardiography on eight subjects at different altitudes simulating a climb of Mount Everest and found elevated pulmonary artery pressure, normal left ventricular ejection fraction, reduced biventricular systolic and end-diastolic volumes, and decreased mitral early maximal ventricular filling velocity/atrial maximal ventricular filling velocity (E/A) ratio. A study of the echocardiographic changes in 41 healthy volunteers who rapidly ascended to 4559 m within 24 h demonstrated elevation of the tricuspid gradient from 16 to 44 mmHg and the mean pulmonary artery pressure to 32 mmHg, and reduction of the mitral E/A ratio from 1.4 to 1.1; this demonstrated atrial contractile fitness rather than a change in the diastolic function [70]. Echocardiography measurements of 58 plain residents exposed to a 4000 m altitude showed the following characteristics: Mean pulmonary artery pressure increased to 20-25 mmHg; E/A ratio of the right and left ventricles decreased; isovolumic relaxation time of the right ventricle prolonged; the Tei index of the right ventricle increased; and the ejection fraction remained normal; moreover, the pulmonary artery pressure increased further when the subjects were exposed to conditions simulating an altitude of 4850 m[89]. Compared with lowland residents, highlanders showed lower pulmonary arterial pressure, higher oxygen saturation, significant changes in the biventricular diastolic function, reduced left ventricular ejection fraction, and a more pronounced increase in the Tei index of the right ventricle[89].

CONCLUSION

In the present study, we performed a bibliometric analysis of publications in the field of the cardiovascular system at high altitude to identify the future research hotspots and new perspectives. Our data show that publications have increased rapidly over the past few decades in the field of the cardiovascular system at high altitude. Future research in this field may focus on areas such as hypoxia adaptation, metabolism, and cardiopulmonary exercise. Our study provides essential information for researchers in this field and identifies potential collaborative partners to further exploration of the pathophysiological changes in the high-altitude cardiovascular system and provide a theoretical basis for standardized disease diagnosis and treatment. The present study has several limitations. First, to ensure the quality and integrity of the collected data, this study selected articles and reviews from the WoS Core Collection of SCIE and excluded other databases such as Scopus. Thus, the data may not be comprehensive enough. Furthermore, quantitative analysis needs to analyze and interpret the data. This requires researchers with an adequate and comprehensive understanding of the field. Otherwise it will result in subjectivity. In the future research, we need to integrate the literature from multiple databases to diversify the data, and actively communicate with the scholars in this field to understand the frontier subjects of research in the cardiovascular system at high altitude.

FOOTNOTES

Author contributions: Zhao ML contributed to formal analysis, software, and manuscript drafting; Lu ZJ and Yang L contributed to software and visualization; Liu YZ contributed to visualization and manuscript drafting; Yang XL contributed to manuscript drafting; Li X contributed to software; Ding S contributed to reviewing and editing of the manuscript; Gao F contributed to supervision and manuscript reviewing and editing; He SY contributed to conceptualization, supervision, fund acquisition, and manuscript reviewing and editing. All authors read and approved the final manuscript.

Supported by Natural Science Foundation of Sichuan Province, No. 2022NSFSC1295; the 2021 Annal Project of the General Hospital of Western Theater Command, No. 2021-XZYG-B31.

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

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: China

ORCID number: Si-Yi He 0000-0003-0275-1038.

S-Editor: Li L
L-Editor: Wang TQ
P-Editor: Zhao S

REFERENCES

1 **Tremblay JC**, Ainslie PN. Global and country-level estimates of human population at high altitude. *Proc Natl Acad Sci U S A* 2021; **118** [PMID: 33903258 DOI: 10.1073/pnas.2102463118]
2 **West JB**. Barcroft's bold assertion: All dwellers at high altitudes are persons of impaired physical and mental powers. *J Physiol* 2016; **594**: 1127-1134 [PMID: 25962370 DOI: 10.1113/JP270284]
3 **Herrera EA**, Farías JG, Ebensperger G, Reyes RV, Llanos AJ, Castillo RL. Pharmacological approaches in either intermittent or permanent hypoxia: A tale of two exposures. *Pharmacol Res* 2015; **101**: 94-101 [PMID: 26215469 DOI: 10.1016/j.phrs.2015.07.011]
4 **Chang JC**, Lien CF, Lee WS, Chang HR, Hsu YC, Luo YP, Jeng JR, Hsieh JC, Yang KT. Intermittent Hypoxia Prevents Myocardial Mitochondrial Ca(2+) Overload and Cell Death during Ischemia/Reperfusion: The Role of Reactive Oxygen Species. *Cells* 2019; **8** [PMID: 31181855 DOI: 10.3390/cells8060564]
5 **Aguilar M**, González-Candia A, Rodríguez J, Carrasco-Pozo C, Cañas D, García-Herrera C, Herrera EA, Castillo RL. Mechanisms of Cardiovascular Protection Associated with Intermittent Hypobaric Hypoxia Exposure in a Rat Model: Role of Oxidative Stress. *Int J Mol Sci* 2018; **19** [PMID: 29373484 DOI: 10.3390/ijms19020366]
6 **Lüscher TF**. Refining cardiovascular risk: anthropometric measures, potassium, high altitude exposure, and cancer therapy. *Eur Heart J* 2018; **39**: 1499-1502 [PMID: 29718353 DOI: 10.1093/eurheartj/ehy222]
7 **Pena E**, El Alam S, Siques P, Brito J. Oxidative Stress and Diseases Associated with High-Altitude Exposure. *Antioxidants (Basel)* 2022; **11**: 267 [PMID: 35204150 DOI: 10.3390/antiox11020267]
8 **He S**, He S, Yang Y, Li B, Gao L, Xie Q, Zhang L. Correlation Between Neutrophil to Lymphocyte Ratio and Myocardial Injury in Population Exposed to High Altitude. *Front Cardiovasc Med* 2021; **8**: 738817 [PMID: 34881301 DOI: 10.3389/fcvm.2021.738817]
9 **He S**, Zhang Q, Wu F, Chen J, He S, Ji Z, Li B, Gao L, Xie Q, Zhang J. Influence of cigarettes on myocardial injury in healthy population after exposure to high altitude over 5000 m. *Sci Total Environ* 2023; **855**: 158824 [PMID: 36122711 DOI: 10.1016/j.scitotenv.2022.158824]
10 **Sampson M**, Horsley T, Doja A. A bibliometric analysis of evaluative medical education studies: characteristics and indexing accuracy. *Acad Med* 2013; **88**: 421-427 [PMID: 23348095 DOI: 10.1097/ACM.0b013e3182820b5c]
11 **Abramo G**, D'Angelo CA, Viel F. The field-standardized average impact of national research systems compared to world average: the case of Italy. *Scientometrics* 2011; **88**: 599-615 [DOI: 10.1007/s11192-011-0406-x]
12 **Du Y**, Duan C, Yang Y, Yuan G, Zhou Y, Zhu X, Wei N, Hu Y. Heart Transplantation: A Bibliometric Review From 1990-2021. *Curr Probl Cardiol* 2022; **47**: 101176 [PMID: 35341797 DOI: 10.1016/j.cpcardiol.2022.101176]
13 **Wang H**, Shi J, Shi S, Bo R, Zhang X, Hu Y. Bibliometric Analysis on the Progress of Chronic Heart Failure. *Curr Probl Cardiol* 2022; **47**: 101213 [PMID: 35525461 DOI: 10.1016/j.cpcardiol.2022.101213]
14 **Xu X**, Wang Y, Li Y, Zhang B, Song Q. The Future Landscape of Macrophage Research in Cardiovascular Disease: A Bibliometric Analysis. *Curr Probl Cardiol* 2022; **47**: 101311 [PMID: 35810847 DOI: 10.1016/j.cpcardiol.2022.101311]
15 **Zhang X**, Zhou Y, Wei N, Shou X, Fan S, You Y, Li Y, Hu Y. A Bibliometric Analysis of Heart Failure with Preserved Ejection Fraction From 2000 to 2021. *Curr Probl Cardiol* 2022; **47**: 101243 [PMID: 35545178 DOI: 10.1016/j.cpcardiol.2022.101243]
16 **Yang J**, Cheng C, Shen S, Yang S. Comparison of complex network analysis software: Citespace, SCI 2 and Gephi. Proceedings of the 2017 IEEE 2nd International conference on Big data analysis (ICBDA); 2017; Beijing, China. *IEEE* 2017; 169-172 [DOI: 10.1109/ICBDA.2017.8078800]

17 **Chen Y**, Wu C. The hot spot transformation in the research evolution of maker. *Scientometrics* 2017; **113**: 1307-1324 [DOI: 10.1007/s11192-017-2542-4]
18 **van Eck NJ**, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics* 2010; **84**: 523-538 [PMID: 20585380 DOI: 10.1007/s11192-009-0146-3]
19 **Dzikowski P**. A bibliometric analysis of born global firms. *J Bus Res* 2018; **85**: 281-294 [DOI: 10.1016/j.jbusres.2017.12.054]
20 **Jankovic MP**, Kaufmann M, Kindler CH. Active research fields in anesthesia: a document co-citation analysis of the anesthetic literature. *Anesth Analg* 2008; **106**: 1524-1533, table of contents [PMID: 18420871 DOI: 10.1213/ane.0b013e31816d18a1]
21 **Hackett PH**, Roach RC. High-altitude illness. *N Engl J Med* 2001; **345**: 107-114 [PMID: 11450659 DOI: 10.1056/NEJM200107123450206]
22 **Naeije R**. Physiological adaptation of the cardiovascular system to high altitude. *Prog Cardiovasc Dis* 2010; **52**: 456-466 [PMID: 20417339 DOI: 10.1016/j.pcad.2010.03.004]
23 **Penaloza D**, Arias-Stella J. The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. *Circulation* 2007; **115**: 1132-1146 [PMID: 17339571 DOI: 10.1161/CIRCULATIONAHA.106.624544]
24 **Bärtsch P**, Gibbs JS. Effect of altitude on the heart and the lungs. *Circulation* 2007; **116**: 2191-2202 [PMID: 17984389 DOI: 10.1161/CIRCULATIONAHA.106.650796]
25 **Simonson TS**, Yang Y, Huff CD, Yun H, Qin G, Witherspoon DJ, Bai Z, Lorenzo FR, Xing J, Jorde LB, Prchal JT, Ge R. Genetic evidence for high-altitude adaptation in Tibet. *Science* 2010; **329**: 72-75 [PMID: 20466884 DOI: 10.1126/science.1189406]
26 **León-Velarde F**, Maggiorini M, Reeves JT, Aldashev A, Asmus I, Bernardi L, Ge RL, Hackett P, Kobayashi T, Moore LG, Penaloza D, Richalet JP, Roach R, Wu T, Vargas E, Zubieta-Castillo G, Zubieta-Calleja G. Consensus statement on chronic and subacute high altitude diseases. *High Alt Med Biol* 2005; **6**: 147-157 [PMID: 16060849 DOI: 10.1089/ham.2005.6.147]
27 **Rudski LG**, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; **23**: 685-713; quiz 786 [PMID: 20620859 DOI: 10.1016/j.echo.2010.05.010]
28 **Cancienne JM**, Diduch DR, Werner BC. High Altitude Is an Independent Risk Factor for Postoperative Symptomatic Venous Thromboembolism After Knee Arthroscopy: A Matched Case-Control Study of Medicare Patients. *Arthroscopy* 2017; **33**: 422-427 [PMID: 27876235 DOI: 10.1016/j.arthro.2016.07.031]
29 **Cancienne JM**, Burrus MT, Diduch DR, Werner BC. High altitude is an independent risk factor for venous thromboembolism following arthroscopic rotator cuff repair: a matched case-control study in Medicare patients. *J Shoulder Elbow Surg* 2017; **26**: 7-13 [PMID: 27528541 DOI: 10.1016/j.jse.2016.06.005]
30 **Damodar D**, Donnally CJ 3rd, Sheu JI, Law TY, Roche MW, Hernandez VH. A Higher Altitude Is an Independent Risk Factor for Venous Thromboembolisms After Total Hip Arthroplasty. *J Arthroplasty* 2018; **33**: 2627-2630 [PMID: 29691178 DOI: 10.1016/j.arth.2018.03.045]
31 **Damodar D**, Vakharia R, Vakharia A, Sheu J, Donnally CJ 3rd, Levy JC, Kaplan L, Munoz J. A higher altitude is an independent risk factor for venous thromboembolisms following total shoulder arthroplasty. *J Orthop* 2018; **15**: 1017-1021 [PMID: 30377388 DOI: 10.1016/j.jor.2018.09.003]
32 **Donnally CJ 3rd**, Vakharia AM, Sheu JI, Vakharia RM, Damodar D, Shenoy K, Gjolaj JP. High Altitude Is an Independent Risk Factor for Developing a Pulmonary Embolism, but Not a Deep Vein Thrombosis Following a 1- to 2-Level Lumbar Fusion. *Global Spine J* 2019; **9**: 729-734 [PMID: 31552154 DOI: 10.1177/2192568219828349]
33 **Tyson JJ**, Bjerke BP, Genuario JW, Noonan TJ. Thromboembolic Events After Arthroscopic Knee Surgery: Increased Risk at High Elevation. *Arthroscopy* 2016; **32**: 2350-2354 [PMID: 27318777 DOI: 10.1016/j.arthro.2016.04.008]
34 **Johnson NJ**, Luks AM. High-Altitude Medicine. *Med Clin North Am* 2016; **100**: 357-369 [PMID: 26900119 DOI: 10.1016/j.mcna.2015.09.002]
35 **Wu J**, Duan D, Lu J, Luo Y, Wen X, Guo X, Boman BJ. Inorganic pollution around the Qinghai-Tibet Plateau: An overview of the current observations. *Sci Total Environ* 2016; **550**: 628-636 [PMID: 26849327 DOI: 10.1016/j.scitotenv.2016.01.136]
36 **León-Velarde F**, Villafuerte FC, Richalet JP. Chronic mountain sickness and the heart. *Prog Cardiovasc Dis* 2010; **52**: 540-549 [PMID: 20417348 DOI: 10.1016/j.pcad.2010.02.012]
37 **Maignan M**, Rivera-Ch M, Privat C, Leòn-Velarde F, Richalet JP, Pham I. Pulmonary pressure and cardiac function in chronic mountain sickness patients. *Chest* 2009; **135**: 499-504 [PMID: 18719057 DOI: 10.1378/chest.08-1094]
38 **Luks AM**, Swenson ER, Bärtsch P. Acute high-altitude sickness. *Eur Respir Rev* 2017; **26** [PMID: 28143879 DOI: 10.1183/16000617.0096-2016]
39 **Bärtsch P**, Dehnert C, Friedmann-Bette B, Tadibi V. Intermittent hypoxia at rest for improvement of athletic performance. *Scand J Med Sci Sports* 2008; **18** Suppl 1: 50-56 [PMID: 18665952 DOI: 10.1111/j.1600-0838.2008.00832.x]
40 **Schommer K**, Menold E, Subudhi AW, Bärtsch P. Health risk for athletes at moderate altitude and normobaric hypoxia. *Br J Sports Med* 2012; **46**: 828-832 [PMID: 22842235 DOI: 10.1136/bjsports-2012-091270]
41 **Burtscher M**, Ponchia A. The risk of cardiovascular events during leisure time activities at altitude. *Prog Cardiovasc Dis* 2010; **52**: 507-511 [PMID: 20417344 DOI: 10.1016/j.pcad.2010.02.008]
42 **Burtscher M**, Philadelphy M, Likar R. Sudden cardiac death during mountain hiking and downhill skiing. *N Engl J Med* 1993; **329**: 1738-1739 [PMID: 8232470 DOI: 10.1056/NEJM199312023292315]
43 **Faulhaber M**, Gatterer H, Burtscher M. Preexisting cardiovascular diseases among high-altitude mountaineers in the alps. *J Travel Med* 2011; **18**: 355-357 [PMID: 21896101 DOI: 10.1111/j.1708-8305.2011.00536.x]
44 **Netzer N**, Strohl K, Faulhaber M, Gatterer H, Burtscher M. Hypoxia-related altitude illnesses. *J Travel Med* 2013; **20**: 247-255 [PMID: 23809076 DOI: 10.1111/jtm.12017]
45 **Burtscher M**. Climbing the Himalayas more safely. *BMJ* 2012; **344**: e3778 [PMID: 22695901 DOI: 10.1136/bmj.e3778]
46 **Gatterer H**, Menz V, Salazar-Martinez E, Sumbalova Z, Garcia-Souza LF, Velika B, Gnaiger E, Burtscher M. Exercise Performance, Muscle Oxygen Extraction and Blood Cell Mitochondrial Respiration after Repeated-Sprint and Sprint Interval Training in Hypoxia: A Pilot Study. *J Sports Sci Med* 2018; **17**: 339-347 [PMID: 30116106]
47 **West JB**. High-altitude medicine. *Am J Respir Crit Care Med* 2012; **186**: 1229-1237 [PMID: 23103737 DOI: 10.1164/rccm.201207-1323CI]
48 **West JB**. Physiological Effects of Chronic Hypoxia. *N Engl J Med* 2017; **376**: 1965-1971 [PMID: 28514605 DOI: 10.1056/NEJMra1612008]
49 **West JB**. Oxygen Conditioning: A New Technique for Improving Living and Working at High Altitude. *Physiology (Bethesda)* 2016; **31**: 216-

222 [PMID: 27053735 DOI: 10.1152/physiol.00057.2015]
50 **West JB**, Mathieu-Costello O. Stress failure of pulmonary capillaries: role in lung and heart disease. *Lancet* 1992; **340**: 762-767 [PMID: 1356184 DOI: 10.1016/0140-6736(92)92301-u]
51 **West JB**. Comparative physiology of the pulmonary circulation. *Compr Physiol* 2011; **1**: 1525-1539 [PMID: 23733652 DOI: 10.1002/cphy.c090001]
52 **Hamlin MJ**, Lizamore CA, Hopkins WG. The Effect of Natural or Simulated Altitude Training on High-Intensity Intermittent Running Performance in Team-Sport Athletes: A Meta-Analysis. *Sports Med* 2018; **48**: 431-446 [PMID: 29129021 DOI: 10.1007/s40279-017-0809-9]
53 **Wilber RL**. Application of altitude/hypoxic training by elite athletes. *Med Sci Sports Exerc* 2007; **39**: 1610-1624 [PMID: 17805095 DOI: 10.1249/mss.0b013e3180de49e6]
54 **Grover RF**, Weil JV, Reeves JT. Cardiovascular adaptation to exercise at high altitude. *Exerc Sport Sci Rev* 1986; **14**: 269-302 [PMID: 3525187]
55 **Wilkins MR**, Ghofrani HA, Weissmann N, Aldashev A, Zhao L. Pathophysiology and treatment of high-altitude pulmonary vascular disease. *Circulation* 2015; **131**: 582-590 [PMID: 25666980 DOI: 10.1161/CIRCULATIONAHA.114.006977]
56 **Lichtblau M**, Saxer S, Furian M, Mayer L, Bader PR, Scheiwiller PM, Mademilov M, Sheraliev U, Tanner FC, Sooronbaev TM, Bloch KE, Ulrich S. Cardiac function and pulmonary hypertension in Central Asian highlanders at 3250 m. *Eur Respir J* 2020; **56** [PMID: 32430419 DOI: 10.1183/13993003.02474-2019]
57 **Lewis NC**, Bailey DM, Dumanoir GR, Messinger L, Lucas SJ, Cotter JD, Donnelly J, McEneny J, Young IS, Stembridge M, Burgess KR, Basnet AS, Ainslie PN. Conduit artery structure and function in lowlanders and native highlanders: relationships with oxidative stress and role of sympathoexcitation. *J Physiol* 2014; **592**: 1009-1024 [PMID: 24324004 DOI: 10.1113/jphysiol.2013.268615]
58 **Mirrakhimov AE**, Strohl KP. High-altitude Pulmonary Hypertension: an Update on Disease Pathogenesis and Management. *Open Cardiovasc Med J* 2016; **10**: 19-27 [PMID: 27014374 DOI: 10.2174/1874192401610010019]
59 **Robinson JC**, Abbott C, Meadows CA, Roach RC, Honigman B, Bull TM. Long-Term Health Outcomes in High-Altitude Pulmonary Hypertension. *High Alt Med Biol* 2017; **18**: 61-66 [PMID: 28061144 DOI: 10.1089/ham.2016.0098]
60 **Li M**, Riddle SR, Frid MG, El Kasmi KC, McKinsey TA, Sokol RJ, Strassheim D, Meyrick B, Yeager ME, Flockton AR, McKeon BA, Lemon DD, Horn TR, Anwar A, Barajas C, Stenmark KR. Emergence of fibroblasts with a proinflammatory epigenetically altered phenotype in severe hypoxic pulmonary hypertension. *J Immunol* 2011; **187**: 2711-2722 [PMID: 21813768 DOI: 10.4049/jimmunol.1100479]
61 **Askew EW**. Work at high altitude and oxidative stress: antioxidant nutrients. *Toxicology* 2002; **180**: 107-119 [PMID: 12324188 DOI: 10.1016/s0300-483x(02)00385-2]
62 **Stone RM**, Ainslie PN, Tremblay JC, Akins JD, MacLeod DB, Tymko MM, DeSouza CA, Bain AR. GLOBAL REACH 2018: intra-arterial vitamin C improves endothelial-dependent vasodilatory function in humans at high altitude. *J Physiol* 2022; **600**: 1373-1383 [PMID: 34743333 DOI: 10.1113/JP282281]
63 **Hu XQ**, Huang X, Xiao D, Zhang L. Direct effect of chronic hypoxia in suppressing large conductance Ca(2+)-activated K(+) channel activity in ovine uterine arteries *via* increasing oxidative stress. *J Physiol* 2016; **594**: 343-356 [PMID: 26613808 DOI: 10.1113/JP271626]
64 **Hainsworth R**, Drinkhill MJ, Rivera-Chira M. The autonomic nervous system at high altitude. *Clin Auton Res* 2007; **17**: 13-19 [PMID: 17264976 DOI: 10.1007/s10286-006-0395-7]
65 **Naeije R**, Mélot C, Mols P, Hallemans R. Effects of vasodilators on hypoxic pulmonary vasoconstriction in normal man. *Chest* 1982; **82**: 404-410 [PMID: 6811216 DOI: 10.1378/chest.82.4.404]
66 **Vogel JA**, Hartley LH, Cruz JC. Cardiac output during exercise in altitude natives at sea level and high altitude. *J Appl Physiol* 1974; **36**: 173-176 [PMID: 4590353 DOI: 10.1152/jappl.1974.36.2.173]
67 **Petousi N**, Croft QP, Cavalleri GL, Cheng HY, Formenti F, Ishida K, Lunn D, McCormack M, Shianna KV, Talbot NP, Ratcliffe PJ, Robbins PA. Tibetans living at sea level have a hyporesponsive hypoxia-inducible factor system and blunted physiological responses to hypoxia. *J Appl Physiol (1985)* 2014; **116**: 893-904 [PMID: 24030663 DOI: 10.1152/japplphysiol.00535.2013]
68 **Xiang K**, Ouzhuluobu, Peng Y, Yang Z, Zhang X, Cui C, Zhang H, Li M, Zhang Y, Bianba, Gonggalanzi, Basang, Ciwangsangbu, Wu T, Chen H, Shi H, Qi X, Su B. Identification of a Tibetan-specific mutation in the hypoxic gene EGLN1 and its contribution to high-altitude adaptation. *Mol Biol Evol* 2013; **30**: 1889-1898 [PMID: 23666208 DOI: 10.1093/molbev/mst090]
69 **Xin J**, Zhang H, He Y, Duren Z, Bai C, Chen L, Luo X, Yan DS, Zhang C, Zhu X, Yuan Q, Feng Z, Cui C, Qi X, Ouzhuluobu, Wong WH, Wang Y, Su B. Chromatin accessibility landscape and regulatory network of high-altitude hypoxia adaptation. *Nat Commun* 2020; **11**: 4928 [PMID: 33004791 DOI: 10.1038/s41467-020-18638-8]
70 **Allemann Y**, Rotter M, Hutter D, Lipp E, Sartori C, Scherrer U, Seiler C. Impact of acute hypoxic pulmonary hypertension on LV diastolic function in healthy mountaineers at high altitude. *Am J Physiol Heart Circ Physiol* 2004; **286**: H856-H862 [PMID: 14604853 DOI: 10.1152/ajpheart.00518.2003]
71 **Jung F**, Palmer LA, Zhou N, Johns RA. Hypoxic regulation of inducible nitric oxide synthase *via* hypoxia inducible factor-1 in cardiac myocytes. *Circ Res* 2000; **86**: 319-325 [PMID: 10679484 DOI: 10.1161/01.res.86.3.319]
72 **Mingji C**, Onakpoya IJ, Perera R, Ward AM, Heneghan CJ. Relationship between altitude and the prevalence of hypertension in Tibet: a systematic review. *Heart* 2015; **101**: 1054-1060 [PMID: 25953970 DOI: 10.1136/heartjnl-2014-307158]
73 **Aryal N**, Weatherall M, Bhatta YK, Mann S. Blood Pressure and Hypertension in Adults Permanently Living at High Altitude: A Systematic Review and Meta-Analysis. *High Alt Med Biol* 2016; **17**: 185-193 [PMID: 27575245 DOI: 10.1089/ham.2015.0118]
74 **Vinnikov D**, Brimkulov N, Krasotski V. Chronic Intermittent Hypoxia and Blood Pressure: Is There Risk for Hypertension in Healthy Individuals? *High Alt Med Biol* 2016; **17**: 5-10 [PMID: 26539732 DOI: 10.1089/ham.2015.0067]
75 **Koundal S**, Gandhi S, Kaur T, Mazumder A, Khushu S. "Omics" of High Altitude Biology: A Urinary Metabolomics Biomarker Study of Rats Under Hypobaric Hypoxia. *OMICS* 2015; **19**: 757-765 [PMID: 26669710 DOI: 10.1089/omi.2015.0155]
76 **Xie H**, Xu G, Aa J, Gu S, Gao Y. Modulation of Perturbed Cardiac Metabolism in Rats Under High-Altitude Hypoxia by Combination Treatment With L-carnitine and Trimetazidine. *Front Physiol* 2021; **12**: 671161 [PMID: 34262472 DOI: 10.3389/fphys.2021.671161]
77 **Leslie E**, Lopez V, Anti NAO, Alvarez R, Kafeero I, Welsh DG, Romero M, Kaushal S, Johnson CM, Bosviel R, Blaženović I, Song R, Brito A, Frano MR, Zhang L, Newman JW, Fiehn O, Wilson SM. Gestational long-term hypoxia induces metabolomic reprogramming and phenotypic transformations in fetal sheep pulmonary arteries. *Am J Physiol Lung Cell Mol Physiol* 2021; **320**: L770-L784 [PMID: 33624555 DOI: 10.1152/ajplung.00469.2020]
78 **Guo L**, Tan G, Liu P, Li H, Tang L, Huang L, Ren Q. Three plasma metabolite signatures for diagnosing high altitude pulmonary edema. *Sci Rep* 2015; **5**: 15126 [PMID: 26459926 DOI: 10.1038/srep15126]

79 **Liu C**, Liu B, Liu L, Zhang EL, Sun BD, Xu G, Chen J, Gao YQ. Arachidonic Acid Metabolism Pathway Is Not Only Dominant in Metabolic Modulation but Associated With Phenotypic Variation After Acute Hypoxia Exposure. *Front Physiol* 2018; **9**: 236 [PMID: 29615930 DOI: 10.3389/fphys.2018.00236]

80 **Liao WT**, Liu B, Chen J, Cui JH, Gao YX, Liu FY, Xu G, Sun BD, Zhang EL, Yuan ZB, Zhang G, Gao YQ. Metabolite Modulation in Human Plasma in the Early Phase of Acclimatization to Hypobaric Hypoxia. *Sci Rep* 2016; **6**: 22589 [PMID: 26940428 DOI: 10.1038/srep22589]

81 **Moncada S**, Higgs EA. The discovery of nitric oxide and its role in vascular biology. *Br J Pharmacol* 2006; **147** Suppl 1: S193-S201 [PMID: 16402104 DOI: 10.1038/sj.bjp.0706458]

82 **Erusalimsky JD**, Moncada S. Nitric oxide and mitochondrial signaling: from physiology to pathophysiology. *Arterioscler Thromb Vasc Biol* 2007; **27**: 2524-2531 [PMID: 17885213 DOI: 10.1161/ATVBAHA.107.151167]

83 **La Padula PH**, Etchegoyen M, Czerniczyniec A, Piotrkowski B, Arnaiz SL, Milei J, Costa LE. Cardioprotection after acute exposure to simulated high altitude in rats. Role of nitric oxide. *Nitric Oxide* 2018; **73**: 52-59 [PMID: 29288803 DOI: 10.1016/j.niox.2017.12.007]

84 **Ruan Z**, Koizumi T, Sakai A, Ishizaki T, Wang Z. Endogenous nitric oxide and pulmonary circulation response to hypoxia in high-altitude adapted Tibetan sheep. *Eur J Appl Physiol* 2004; **93**: 190-195 [PMID: 15316790 DOI: 10.1007/s00421-004-1197-z]

85 **Gonzales GF**, Chung FA, Miranda S, Valdez LB, Zaobornyj T, Bustamante J, Boveris A. Heart mitochondrial nitric oxide synthase is upregulated in male rats exposed to high altitude (4,340 m). *Am J Physiol Heart Circ Physiol* 2005; **288**: H2568-H2573 [PMID: 15695556 DOI: 10.1152/ajpheart.00812.2004]

86 **Li JJ**, Liu Y, Xie SY, Zhao GD, Dai T, Chen H, Mu LF, Qi HY, Li J. Newborn screening for congenital heart disease using echocardiography and follow-up at high altitude in China. *Int J Cardiol* 2019; **274**: 106-112 [PMID: 30195837 DOI: 10.1016/j.ijcard.2018.08.102]

87 **Russell TC**, Crawford PF. Ultrasound in the austere environment: a review of the history, indications, and specifications. *Mil Med* 2013; **178**: 21-28 [PMID: 23356114 DOI: 10.7205/milmed-d-12-00267]

88 **Boussuges A**, Molenat F, Burnet H, Cauchy E, Gardette B, Sainty JM, Jammes Y, Richalet JP. Operation Everest III (Comex '97): modifications of cardiac function secondary to altitude-induced hypoxia. An echocardiographic and Doppler study. *Am J Respir Crit Care Med* 2000; **161**: 264-270 [PMID: 10619830 DOI: 10.1164/ajrccm.161.1.9902096]

89 **Huez S**, Faoro V, Guénard H, Martinot JB, Naeije R. Echocardiographic and tissue Doppler imaging of cardiac adaptation to high altitude in native highlanders versus acclimatized lowlanders. *Am J Cardiol* 2009; **103**: 1605-1609 [PMID: 19463523 DOI: 10.1016/j.amjcard.2009.02.006]

World Journal of Cardiology

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

World J Cardiol 2024 April 26; 16(4): 215-216

DOI: 10.4330/wjc.v16.i4.215

ISSN 1949-8462 (online)

CORRECTION

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

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

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: Teragawa H, Japan

Received: January 23, 2024

Revised: March 8, 2024

Accepted: April 11, 2024

Published online: April 26, 2024

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

Qiang Zhou, Chong-Zhen Qin, Shenzhen Emergency Medical Center, Shenzhen 518043, Guangdong Province, China

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

Abstract

This is an erratum to an already published paper named "Establishment of a prediction model for prehospital return of spontaneous circulation in out-of-hospital patients with cardiac arrest". We found errors in the affiliated institution of the authors. We apologize for our unintentional mistake. Please note, these changes do not affect our results.

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

Core Tip: This is an erratum to an already published paper. We found errors in the affiliated institution of the authors. We apologize for our unintentional mistake. Please note, these changes do not affect our results.

Citation: Wang JJ, Zhou Q, Huang ZH, Han Y, Qin CZ, Chen ZQ, Xiao XY, Deng Z. Correction: Establishment of a prediction model for prehospital return of spontaneous circulation in out-of-hospital patients with cardiac arrest. *World J Cardiol* 2024; 16(4): 215-216
URL: https://www.wjgnet.com/1949-8462/full/v16/i4/215.htm
DOI: https://dx.doi.org/10.4330/wjc.v16.i4.215

TO THE EDITOR

This is an erratum to an already published paper[1]. We found errors in the affiliated institution of the authors.

We apologize for our unintentional mistake. Please note, these changes do not affect our results. The correction information is as follows: The affiliated institution of the authors.

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

Qiang Zhou, Chong-Zhen Qin, Shenzhen Emergency Medical Center, Shenzhen 518043, Guangdong Province, China.

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

FOOTNOTES

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

Author contributions: Wang JJ and Zhou Q wrote this correction manuscript; Wang JJ, Zhou Q, Huang ZH, Han Y, Qin CZ, Chen ZQ, Xiao XY, and Deng Z read and approved this correction manuscript.

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

Country/Territory of origin: China

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

S-Editor: Chen YL
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Wang JJ**, Zhou Q, Huang ZH, Han Y, Qin CZ, Chen ZQ, Xiao XY, Deng Z. Establishment of a prediction model for prehospital return of spontaneous circulation in out-of-hospital patients with cardiac arrest. *World J Cardiol* 2023; **15**: 508-517 [PMID: 37900904 DOI: 10.4330/wjc.v15.i10.508]

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