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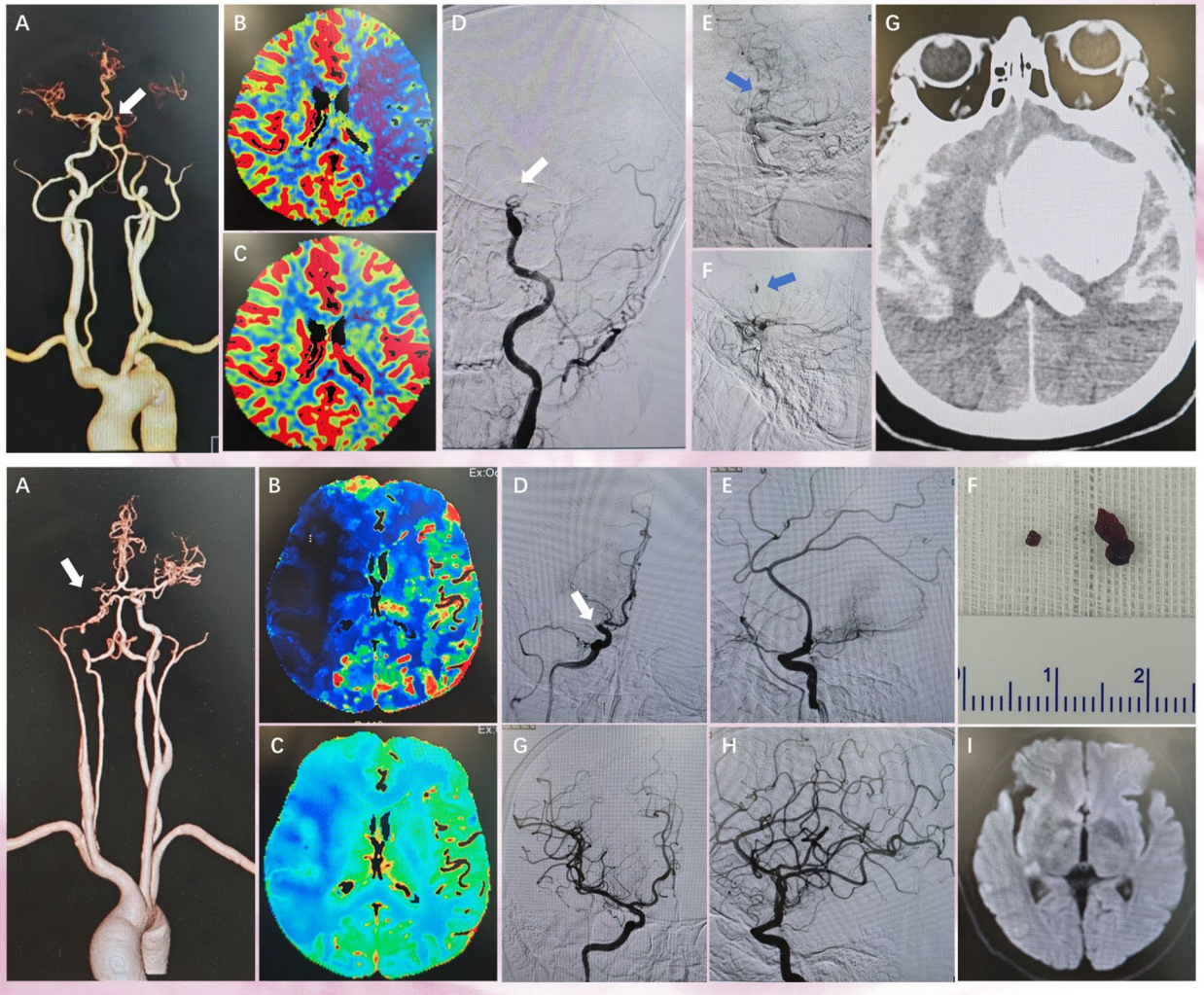

Multimodal computed tomography-guided mechanical thrombectomy for large vessel occlusion stroke after cardiac surgery

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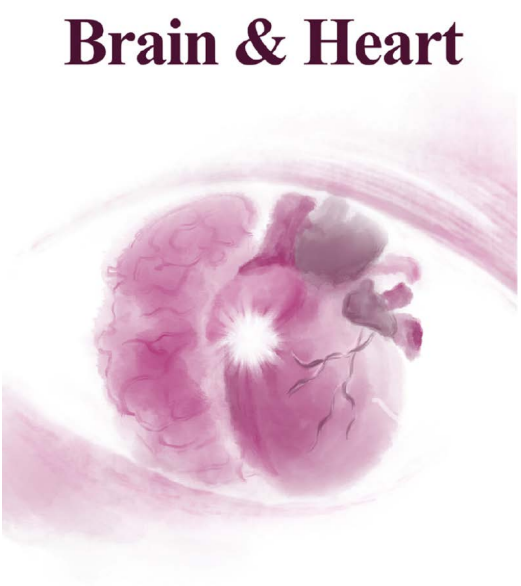

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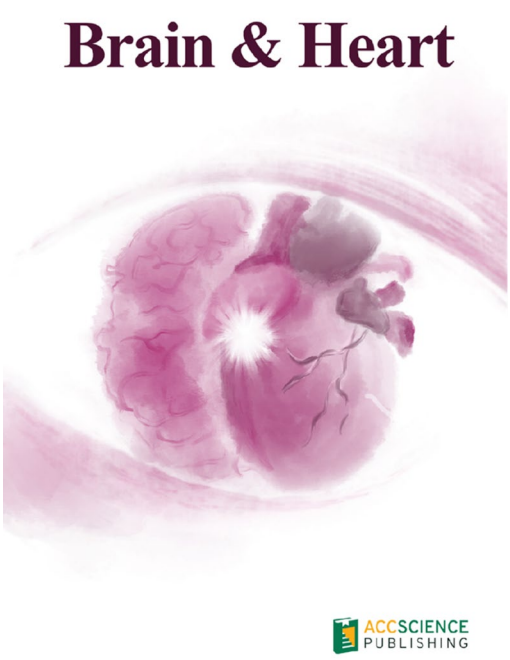

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REVIEW ARTICLE

A contemporary review of transcatheter aortic valve replacement in low-gradient aortic stenosis

Muhammad Majid[1,2], Akiva Rosenzveig[1], Elio Haroun[1], Aro Daniela Arockiam[1], Ankit Agrawal[1], Sharmeen Sorathia[1], Rochell Issa[1], Tiffany Dong[1], Nithila Sivakumar[1], and Tom Kai Ming Wang[1]*

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Abstract

Transcatheter aortic valve replacement (TAVR) has been approved for patients with severe symptomatic aortic stenosis (AS) across the spectrum of surgical risk. Although there is substantial evidence regarding the utility of TAVR in patients with classic high-gradient symptomatic AS, the management of patients with discordant AS and gradients that are lower than expected remains uncertain. As low-gradient AS is quite prevalent, it warrants our attention. The TAVR approach in these patients requires risk stratification and additional imaging modalities, such as stress echocardiography, to more accurately evaluate the severity of AS. TAVR complications include stroke, kidney injury, conduction abnormalities, device-related thrombosis, endocarditis, and mechanical or vascular complications, which affect both patients with low- and high-gradient AS (HGAS). Contemporary research has demonstrated that TAVR is more effective in the low-gradient AS population than in the HGAS population and shows better outcomes than conservative management. The management of patients with AS, particularly low-gradient AS, remains poorly understood.

Keywords: Transcatheter aortic valve replacement; Aortic stenosis; Low-flow low-gradient aortic stenosis; Valvular heart disease

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1. Introduction

Transcatheter aortic valve replacement (TAVR) has emerged as an invaluable alternative to surgical aortic valve replacement (SAVR) in patients with aortic stenosis (AS) across the spectrum of surgical risk.[1] The need for valve replacement depends on AS severity. AS severity is assessed based on echocardiographic parameters, including peak and mean velocities and gradients and aortic valve area (AVA).[2] Although classical high-gradient AS (HGAS) is diagnosed based on a mean gradient of ≥40 mmHg, AVA of ≤1.0 cm^2, and peak velocity of ≥4 m^2/s, these measurements are not infrequently discordant. Discordant AS

exhibits diverse phenotypes, including classical low-flow low-gradient AS (cLFLGAS), paradoxical low-flow low-gradient AS (pLFLGAS), and normal-flow low-gradient AS (NFLGAS). Low-flow low-gradient AS (LFLGAS) poses a challenge due to the discrepancy between reduced AVA and a non-severe increase in the transvalvular mean pressure gradient, which is frequently accompanied with impaired stroke volume at rest.[3] This subset of patients exhibits a high-risk profile for SAVR.[4] The management of LFLGAS is complex because the discrepancy between the AVA and pressure gradient raises concerns about the severity of stenosis and the need for intervention.[5] In this review, we aim to discuss the management of LFLGAS, including diagnostic modalities, the efficacy of TAVR, and procedural considerations and complications to be aware of in this subset of patients with severe AS.

2. Epidemiology and risk stratification

Approximately 40% of patients with an AVA of ≤1.0 cm² exhibit a discordantly low mean gradient.[6] Similar to those with high-gradient severe AS, patients with LFLGAS may be asymptomatic or may exhibit typical symptoms such as shortness of breath and/or heart failure, pre-syncope and/or syncope, and angina, as was first described in Ross and Braunwald's seminal work in 1968.[7] Furthermore, patients with LFLGAS, similar to those with HGAS, exhibit poor outcomes, with a 3-year survival rate of <50% with medical treatment.[8] In fact, cLFLGAS and pLFLGAS have frequently been linked to worse outcomes than HGAS, which further gives credence to the idea that the treatment approach should be at least as aggressive.[9] In a meta-analysis conducted by Ueyama *et al.*, aortic valve replacement (AVR) was associated with a significant decrement in all-cause mortality in all types of LFLGAS, irrespective of TAVR or SAVR.[10] A plethora of risk scores have been developed to assist in the stratification of the patient's operative risk. The American college of cardiology (ACC)/American heart association (AHA) valvular heart disease guidelines reference the use of the Society of Thoracic Surgeons (STS) risk score and Euroscore II, both originally derived for SAVR, and the ACC's TAVR in-hospital mortality risk score.[11] Various other TAVR-specific scores have been recently developed, including the German AV score I and II, EuroSCORE I, CAPRI, STT, TARIS, transcatheter aortic valve implantation-2 (TAVI-2), TRIM, CoreValve US, ACC TAVI, STS-PROM, UK TAVI, NIS TAVR, OCEAN, FTS< TAVI Futility risk model 1 and 2, TARI, J-TVT, UNN/OUS, Logistic EuroScore, Charleston comorbidity index, frailty index, KCMH TAVI, Relief TAVI, GNRI, ERS, OBSERVANT score, IRRMA score, and FRANCE-2, though related external validation and comparative studies are limited.[12]

3. Role of multimodality imaging in AS evaluation and pre-procedural planning

A multimodality imaging approach is essential to accurately assess LFLGAS, as various imaging modalities provide complementary information regarding aortic valve morphology, function, and associated cardiac abnormalities. Transthoracic echocardiography (TTE) remains the initial imaging modality of choice, providing critical information on aortic valve morphology, peak velocity, mean pressure gradient, and AVA using the continuity equation[13,14] (Table 1).

3.1. TTE

TTE provides critical data regarding aortic valve morphology, left ventricular (LV) function, and hemodynamics.[14] Various phenotypes of LGAS were determined based on the ejection fraction (EF; ≤ or >50%) and stroke volume index (SVI; < or ≥35 mL/m²). cLFLGAS is characterized by an EF ≤50%, mean gradient <40 mmHg, and SVI <35 mL/m². Patients with pLFLGAS also exhibit a low gradient and low SVI but with a preserved EF. Patients with NFLGAS exhibit a low gradient of <40 mmHg, but with a preserved SVI of ≥35 mL/m². The accurate assessment of AVA using TTE in patients with LFLGAS poses challenges due to difficulties in achieving optimal imaging quality, precisely measuring Doppler velocities across the valve, and ensuring reliable calculations of AVA, particularly in the presence of concomitant LV dysfunction or discordant hemodynamic parameters.[13] To ensure optimal measurements, it is important to use multiple views to evaluate the aortic valve, ensure accurate alignment of the continuous wave Doppler probe in the direction of the aortic jet to obtain the highest peak and mean gradients, obtain meticulous tracings of the velocity time integrals of the aortic valve and LV outflow tract (LVOT), and incorporate these measurements with a non-quantitative, visual assessment of the aortic valve anatomy, calcification, and opening.[15]

3.2. Stress echocardiography

Dobutamine stress echocardiography (DSE), has been utilized to assess AS severity and operative risk in patients with LFLGAS and impaired LV function.[6] DSE is a useful modality for identifying patients with pseudo-severe AS induced by limited valve opening due to the low-flow state. An increase in the AVA to over 1.0 cm² and a 20% increase in the stroke volume indicate pseudo-severe AS. The dobutamine challenge has been recognized as a valuable method for selecting patients who would benefit from valve replacement and for providing prognostic information on operative risks and long-term outcomes in patients with cLFLGAS.[8] Both the American and European

Table 1. Strengths, limitations, and clinical utility of various imaging modalities in aortic stenosis assessment

Imaging modality	Objectives/Key concept	Clinical utility and advantages	Limitations
TTE	• Assessment of valve morphology; quantification of the severity of AS by measuring the peak jet velocity, mean pressure gradient, AVA, and Doppler velocities across the valve • LVOT assessment, LV function, and hemodynamics	• The most effective initial non-invasive imaging modality for the evaluation of AS, enabling the visualization of the aortic valve leaflets and any abnormalities Crucial for accurate AVA calculations	• Suboptimal acoustic windows • Limited visualization of the distal thoracic aorta • Difficulty in assessing valve parameters in patients with low-flow, low-gradient AS, the presence of LV dysfunction, concomitant aortic regurgitation, or discordant hemodynamic measurements • Calcification causes artifacts that obscure the underlying structures
Dobutamine stress echocardiography	• To distinguish true-severe AS from pseudo-severe AS • No alteration in the AVA with increased cardiac output indicates a severely stenotic valve. An increase in AVA of >1 cm^2 with an increased flow rate is observed in pseudo-severe AS Determine the absence of flow reserve	• Guides management: True-severe AS requires valve replacement, whereas pseudo-severe AS may benefit from the treatment of underlying heart failure • Useful in patients with low-gradient AS and impaired LV function • Predicts high operative mortality and poor prognosis	• Possible adverse effects of dobutamine, such as ventricular arrhythmias and hypertension, in select patients • Time-consuming and requires clinical expertise • The presence or absence of flow reserve does not affect management, as both benefit from AVR
Exercise stress echocardiography	• Although not routinely indicated, this modality is helpful in asymptomatic patients with severe AS • An increase in the mean transaortic pressure gradient by ≥18 – 20 mmHg during exercise is linked to an elevated risk of cardiac death, development of spontaneous symptoms, and need for AVR	• Better risk stratification in asymptomatic patients than conventional echocardiography	• Cannot be used in symptomatic patients • Contraindications include: 1. An established indication for AVR 2. Uncontrolled hypertension 3. Symptomatic or hemodynamically significant arrhythmias 4. Inability to conduct the test due to orthopedic limitations or global disabilities
Transesophageal echocardiography	• Adjunct to TTE, providing direct visualization of the leaflets and subvalvular abnormalities in the presence of suboptimal acoustic windows To determine accurate measurements of the aortic valve annulus, leaflet mobility, and calcification	• Pre-TAVR assessment of patients • High-quality imaging comparable to CT	2D echocardiography may result in compromising the TAVI implant owing to the elliptical nature of the LVOT and annulus
Computed tomography angiography	• Superior spatial and temporal resolution in visualizing the aortic valve leaflets, including assessment of their mobility, calcification, and morphology • To accurately measure the aortic annulus size • To evaluate the vessel diameter, tortuosity, and calcification • To evaluate the coronary artery anatomy and identify the presence of obstructive CAD	• Assess the suitability of the native valve for TAVR • Select the most appropriate THV • Determine the optimal vascular access route for TAVR to assist in procedural planning and mitigate vascular complications • Guide revascularization strategies before or during TAVR	• Not effective in determining the extent of fibrosis • Exposure to radiation • Risks associated with contrast administration, especially in patients with renal impairment
Multidetector computed tomography	• Semiquantitative assessment of calcification of the aortic valve by the Agatston score and calcium densities (calcium score adjusted for LVOT area)	• Highly accurate and reproducible information that is independent of the flow and hemodynamics • Does not require the administration of contrast	• Does not provide hemodynamic information such as transvalvular pressure gradients or the presence of regurgitation • Frequently produces motion artifacts in patients with higher resting heart rates. • Radiation exposure. • Can underestimate the severity in select individuals.

(Cont'd...)

Table 1. ***(Continued)***

Imaging modality	Objectives/Key concept	Clinical utility and advantages	Limitations
Cardiac magnetic resonance	• Accurate estimation of LV function and aortic root and valve morphology • LGE imaging to identify myocardial scar tissue and quantify myocardial fibrosis. • Phase-contrast velocity mapping	• Guides patient selection for TAVR • Estimate the extent of myocardial viability in patients with concomitant ischemic heart disease to determine the potential benefits of TAVR • Quantification of the severity of concomitant aortic regurgitation • Lack of radiation exposure	• Poor visualization of calcium deposition Inadequate spatiotemporal resolution • Expensive Unavailability in resource-limited setups

Abbreviations: AS: Aortic stenosis; AVA: Aortic valve area; AVR: Aortic valve replacement; CAD: Coronary artery disease; CT: Computed tomography; LGE: Late gadolinium enhancement; LV: Left ventricular; LVOT: Left ventricular outflow tract; TAVI: Transcatheter aortic valve implantation; TAVR: Transcatheter aortic valve replacement; THV: Transcatheter heart valve; TTE: Transthoracic echocardiography.

guidelines recommend the use of low-dose DSE to further ascertain AS severity in patients with cLFLGAS. The value of exercise stress echocardiography testing in this setting is more controversial. Its primary function is to evaluate the exercise capacity in asymptomatic patients, along with the hemodynamic response of AS to exercise, both with prognostic implications, rather than AS severity, and is contraindicated in symptomatic patients due to the potential for precipitating complications (Figure 1).

3.3. Transesophageal echocardiography (TEE)

TEE is a valuable adjunct to TTE in the pre-TAVR assessment of patients with LFLGAS, providing higher-resolution imaging of the aortic valve and adjacent structures.[14,16] TEE provides a detailed visualization of the aortic valve leaflets, including morphology, calcification, and mobility assessment. Compared with TTE, it typically achieves a higher level of accuracy in AVA planimetry, particularly when utilizing three-dimensional techniques and multiplanar reconstruction.[16] Furthermore, TEE allows for the estimation of LVOT/aortic annulus dimensions (although Computed tomography (CT) is preferred for the latter), subvalvular and valvular abnormalities that may influence TAVR feasibility and procedural planning[17] (Figure 2).

3.4. Computed tomography angiography (CTA)

CTA generates high-resolution images that enable precise measurement of the aortic annulus, including its diameter, perimeter, area, and calcifications, which are crucial for selecting the appropriate size and type of transcatheter heart valve (THV) during TAVR.[18] Retrospective ECG-gated four-dimensional CTA with contrast enhancement facilitates detailed visualization of the aortic valve leaflets, including an assessment of their mobility, calcification, and morphology, to determine the suitability of the native valve for TAVR and plan the implantation technique. The AVA can be measured through planimetry using multiplanar reconstruction. However, the threshold for severe AS on CTA may be slightly higher, with a value of <1.2 cm^2 proposed in some studies.[19] To determine AS severity, the aortic valve calcium score can also be assessed through non-contrast CT, with thresholds of >2000 and >1200 Agatston units for men and women, respectively.[2,20]

3.5. Cardiac magnetic resonance (CMR)

CMR is primarily used during TAVR workup in patients with contraindications to contrast CT, such as renal dysfunction or contrast allergy. The principal function is to use the non-contrast three-dimensional whole heart sequence to assess the aortic annulus and root anatomy, similar to CT-based analysis.[21,22] CMR is more restricted in its ability to evaluate the severity of AS than TTE. Although planimetry of the AVA is feasible, the results are not always accurate. Furthermore, compared with TTE, the peak velocity measurement on phase-contrast sequence with velocity-encoding gradients is typically underestimated.[23] However, it is important to acknowledge that CMR is the reference standard for quantifying cardiac chamber parameters, including volumes, EF, and myocardial mass, which can also help classify and stratify risk in patients with AS.[24] (Figures 3 and 4).

4. Indications for AVR

In general, the 2020 ACC/AHA guidelines for the management of patients with valvular heart disease provide a class I recommendation for AVR in patients with severe symptomatic AS, asymptomatic severe AS with an EF of <50%, asymptomatic patients with severe AS who are undergoing other cardiac surgery, patients with cLFLGAS and reduced EF, and symptomatic patients with cLFLGAS if AS is the most likely cause of symptoms. Both the European 2021 and American 2020 valvular heart disease guidelines provide guidance for the appropriate timing of intervention in patients with LFLGAS.[11,25] Both guidelines recommend that patients with true cLFLGAS

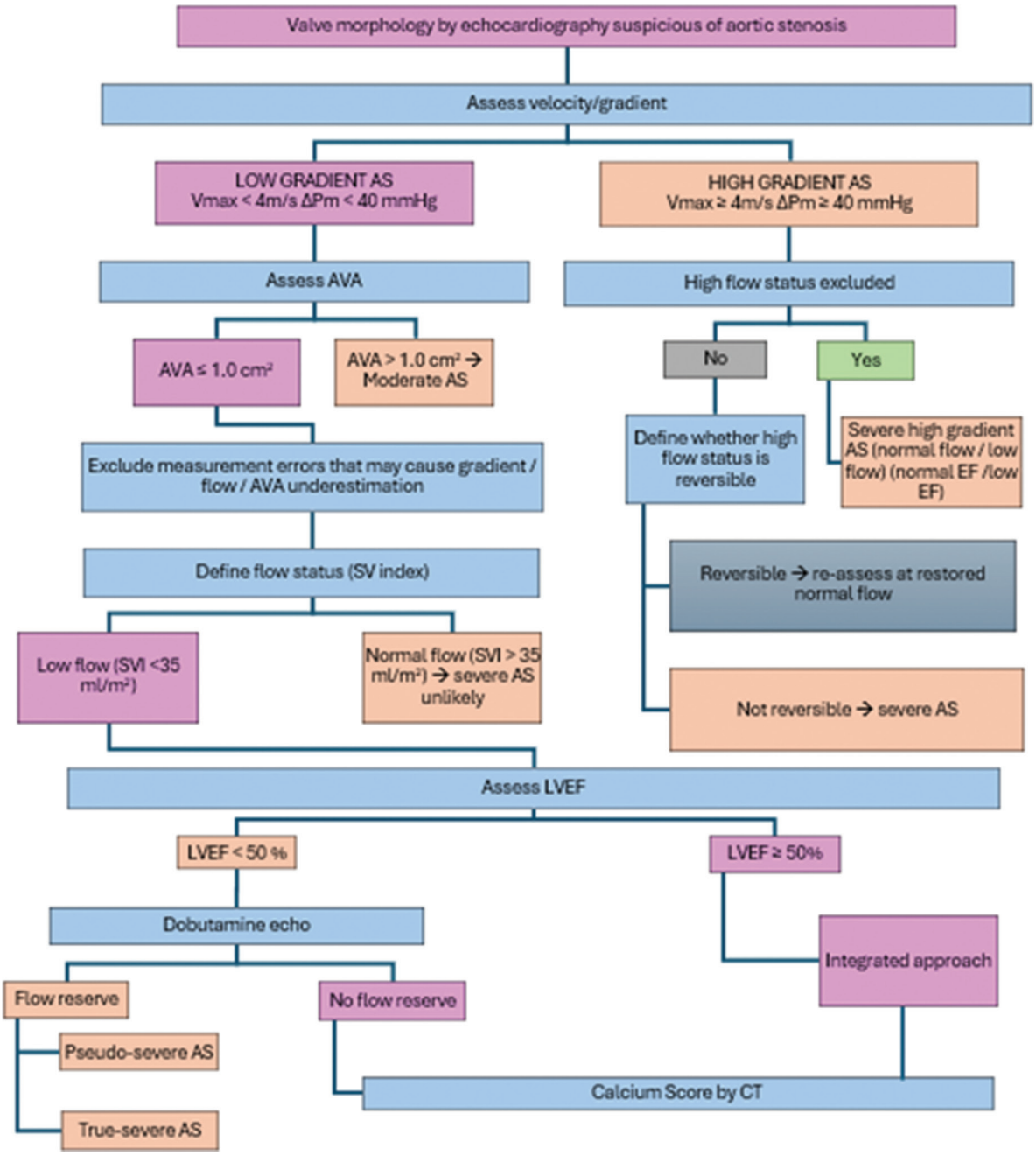

Figure 1. Assessment of valve morphology through echocardiography in suspected cases of aortic stenosis. This figure was modified from Baumgartner *et al.*[2]

or pLFLGAS should consider the possibility of AVR. The European guidelines stipulate that patients with NFLGAS be treated as moderate AS and thus be administered medical treatment. The European guidelines recommend that SAVR be performed in patients aged <75 years who have low surgical risk and TAVR be performed in patients aged ≥75 years or those who have a high surgical risk. The American guidelines utilize an alternative age cutoff of 65 years. Any individual aged <65 years should receive SAVR, whereas TAVR should be performed in those aged >80 years. TAVR or SAVR is recommended for patients aged 65 – 80 years, as determined by a shared decision-making process between the patient and the cardiac team. SAVR is recommended in asymptomatic patients with severe AS and an abnormal exercise test result and those with very severe AS or elevated brain natriuretic peptide.[11]

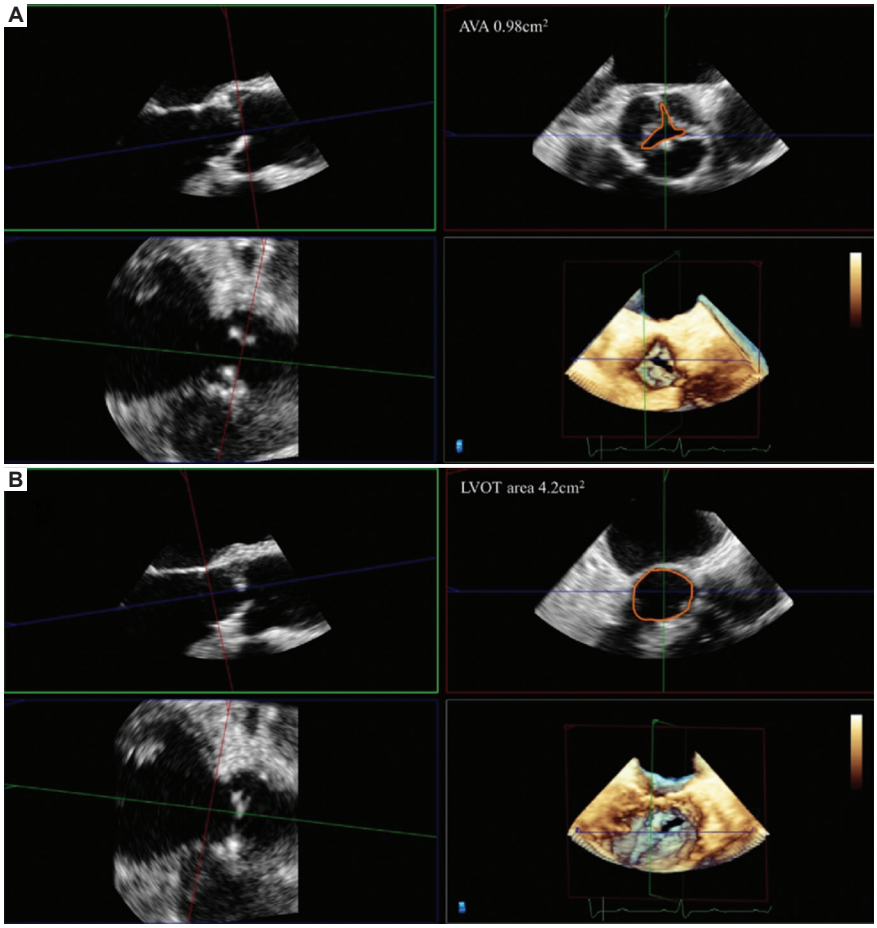

Figure 2. Transesophageal echocardiography evaluation of aortic valve stenosis using three-dimensional multiplanar reconstruction technique for planimetry of the (A) aortic valve area and (B) left ventricular outflow tract area. Image provided by the authors

5. Procedural considerations

5.1. Vascular access

In the context of low-flow AS, it is crucial to note that the TAVR approach adheres to the same fundamental principles as in patients with high-gradient severe AS. The primary objective remains unchanged: to effectively replace the diseased aortic valve with a prosthetic valve through minimally invasive methods. Clinical decisions regarding the vascular access approach are customized to individual patient anatomy and comorbidities, and where feasible, transfemoral (TF) access is preferred as the least risky approach.[26] The percutaneous puncture and suture pre-closure methods are the preferred approaches for TF access, with the recommended entry point located between the inferior epigastric artery and femoral bifurcation.[27]

However, although TF is the preferred option for TAVR, it may not be feasible in approximately one-third of the cases due to inadequate iliofemoral vessel dimensions, complex vessel anatomy, or substantial atherosclerotic disease. When necessary, alternative routes such as transapical (TA), transaortic, transaxillary, and transcarotid access have been utilized for valve implantation.[26,28] The TA approach was initially introduced as an alternative method when TF access was not feasible, particularly in cases of significant iliofemoral disease. This approach is the sole TAVR method that is conducted in an anterograde manner, which facilitates easy valve crossing due to its anatomical approach while also avoiding the need for cardiopulmonary bypass and sternotomy.[29] A major drawback of the TA approach is its relatively invasive nature, leading to myocardial damage post-procedure, as demonstrated by apical hypokinesis. Al-Hijji *et al.* emphasized the reduced efficacy of LVEF following the TA approach compared with the TF method; therefore, this approach is less preferred in patients with cLFLGAS.[30]

5.2. Prosthetic valves in TAVR

With the advancement of TAVR techniques and indications, the design of valves has also evolved. Successive

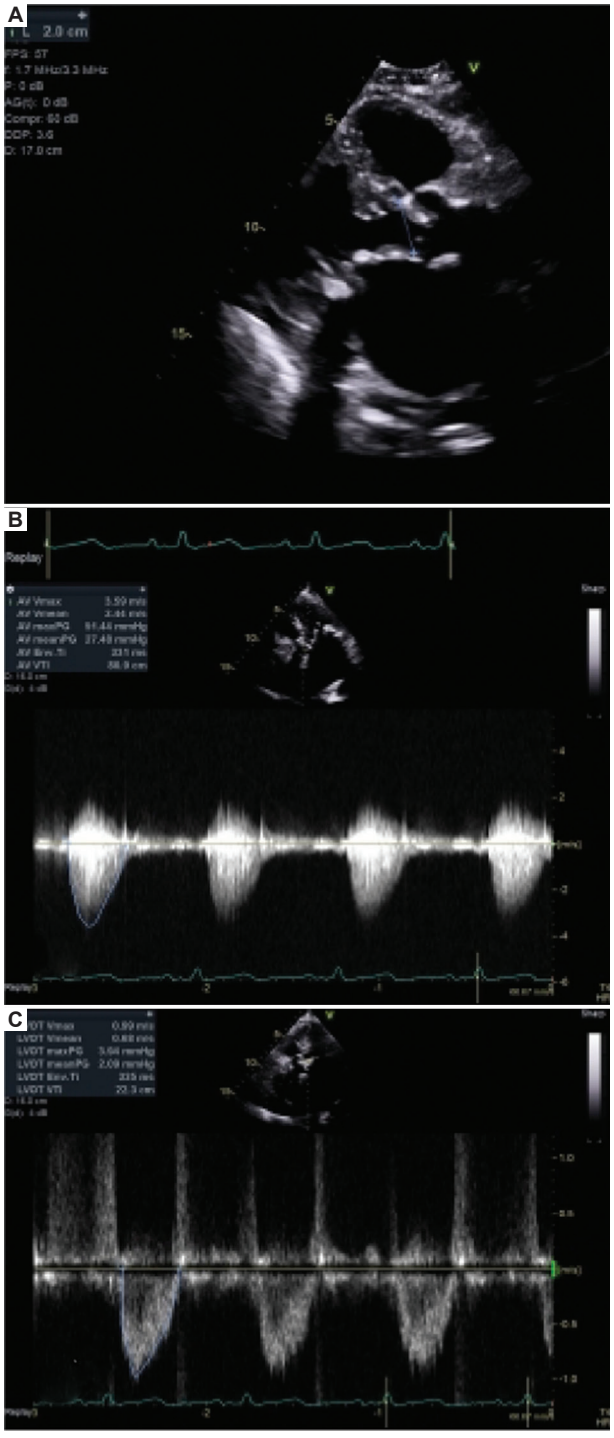

Figure 3. Echocardiographic images depicting LVOT diameter (A), AV mean gradient, peak gradient, and VTI (B), LVOT VTI (C). Image provided by the authors
Abbreviations: AV: Aortic valve; LVOT: Left ventricular outflow tract; VTI: Velocity time integrals.

generations of valves have shown improvements in outcomes compared with previous models. In the United States, approved TAVR valves include SAPIEN 3 and SAPIEN 3 Ultra from Edwards Lifesciences, Evolut Pro+ from Medtronic, and Lotus Valve System from Boston Scientific, which was later recalled owing to issues in the delivery system. The SAPIEN 3 valve, which was tested in the PARTNER 3 trial, outperformed SAVR in low-risk patients and received Food and Drug Administration approval in June 2017. Compared with SAVR, the SAPIEN 3 valve, a balloon-expandable device, has shown superior outcomes in low-risk patients in terms of mortality, stroke, rehospitalization, atrial fibrillation, and severe bleeding.[31] However, it is associated with higher incidences of new left bundle branch block (LBBB) and paravalvular regurgitation.[31] The SAPIEN X4, which is the latest iteration of the Edwards THV, boasts some advancements such as enhanced anticalcification technology, adjustable sizing, and improved delivery. The ongoing ALLIANCE study will further assess its safety and efficacy.

The Evolut FX SE, which is Medtronic's most recent Evolut THV, features enhancements for more predictable implant depth and improved commissural alignment. It retains key features from its predecessor, the Evolut Pro+, including a nitinol delivery catheter capsule for recapturing and repositioning, optimized radial force, and an inline sheath for diverse vascular anatomy. Initial experiences with the Evolut FX system demonstrated enhanced implant depth and commissural alignment compared with previous models. Although there is currently no evidence comparing balloon-expandable and self-expanding valves in patients with LFLGAS, some data regarding the comparison of these valves in the general population are available. Studies comparing balloon-expandable and self-expanding valves typically involve patients with older-generation valves. These comparisons indicate that self-expanding valves outperform balloon-expandable valves in terms of pacemaker rates and paravalvular regurgitation for small annuli. However, mortality outcomes remain unclear, and these findings may not be applicable to newer valve designs aimed at mitigating such complications.[32]

6. Complications and challenges

As with any procedure, it is crucial to be cognizant of and mitigate the risks associated with TAVR. Although much of the procedural risk has reduced with the optimization of the valve scaffolds and the delivery system, as well as increasing operator experience, the risk persists and must be decreased through adequate planning. Patients with cLFLGAS represent a distinct subgroup, as their low-flow state may heighten the likelihood of complications and their capacity to endure them. Therefore, it is necessary to address the complications.

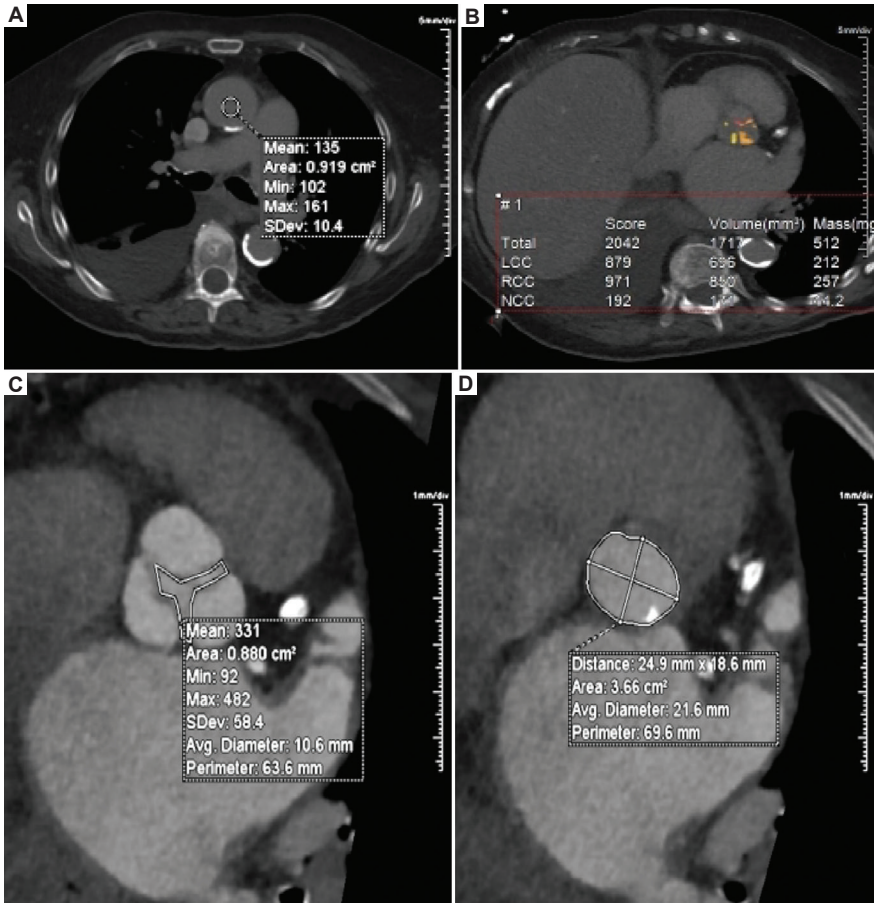

Figure 4. CT images demonstrating (A) HFU in the ascending aorta; (B) Calcium score on non-contrast CT; (C) AVA planimetry on contrast CT; (D) Annular area on contrast CT. Image provided by the authors. Note: *The cutoff is 4 standard deviation + mean (319 HFU in this case)
Abbreviations: CT: Computed tomography; AVA: Aortic valve area.

6.1. Mechanical complications

Mechanical complications comprise a group of complications that are exceedingly uncommon and are becoming increasingly rare with the introduction of newer-generation valves and increasing operator experience. Mechanical complications include annular rupture, valve embolization, ventricular perforation, iatrogenic ventricular septal defect, intracardiac shunts, and coronary obstruction. Each of these complications occur in <1% of TAVR procedures and mostly necessitates urgent surgical conversion.[33] Appropriate planning, sizing, and timing are essential to reduce the likelihood of mechanical complications. There is evidence that cLFLGAS TAVR is associated with an increased need for surgery; however, the reason for conversion to surgery is uncertain.[34] A more comprehensive review of mechanical complications after TAVR can be located elsewhere.[33]

6.2. Vascular complications

Accessing arteries and veins through large bore delivery sheaths and manipulating catheters elevate the risk of bleeding and vascular complications. Vascular complications were reported in approximately 25% of the participants in the PARTNER trial. The PARTNER trial revealed a four-fold increase in the 30-day mortality in patients who experienced major bleeding complications, which is not observed in patients with minor bleeding.[35] Hemostasis is attained following the removal of the sheath using suture-mediated closure devices such as the Perclose ProGlide or MANTA devices.[36] A more comprehensive review of vascular bleeding is available elsewhere.[37] Although no randomized controlled trials have compared cLFLGAS and HG TAVR, observational studies have not demonstrated a difference in bleeding rates to date.[38]

6.3. Stroke

Stroke continues to be a significant vulnerability in TAVR procedures. The incidence of procedural or 30-day stroke has not made significant strides since TAVR data tracking began, with rates improving from 2.75% to 2.28%.[39] Patients with TAVR complicated with stroke have a 6-fold

higher 30-day mortality risk compared to patients without a stroke.[40] Brain imaging studies utilizing diffusion-weighted MRI have indicated that up to 84% of patients develop new lesions after TAVR.[41] The impact of cLFLGAS on stroke outcomes after TAVR has been compared with that of HGAS in multiple observational cohort studies and prospective registries. No difference in stroke incidence was observed between cLFLGAS or pLFLGAS and HG TAVR.[38]

Efforts have been made to mitigate the stroke risk through antithrombotic therapy. However, there is limited evidence for the efficacy of antiplatelet or anticoagulant therapy currently.[42] The 2020 ACC/AHA valvular heart disease guidelines advocate a class 2b recommendation for dual antiplatelet therapy or vitamin K antagonist therapy for 3 – 6 months after TAVR in patients with low bleeding risk, as well as a class 2a recommendation for lifelong aspirin administration in all patients who underwent TAVR.[11]

6.4. Conduction disturbances

The bundle of His courses within the infero-anterior portion of the membranous septum, and the left bundle branch runs near the base of the commissure between the non-coronary and right coronary cusps.[43] Mechanical manipulation of the aortic root may induce local inflammation, edema, or ischemia.[43] The incidences of high-grade AV block and new-onset LBBB range from 4% to 65%, and they are more commonly noted with the use of self-expandable valves rather than balloon-expandable valves (CoreValve 27% [9% – 65%] vs. SAPIEN (11% [4% – 18%]).[44,45] LBBB in patients with cLFLGAS can induce detrimental effects due to mechanical dyssynchrony, possibly offsetting the benefit achieved through TAVR's afterload reduction.[3] The rate of pacemaker installation after TAVR ranges from 2.3% to 36.1%, with higher rates observed with the use of self-expandable valves (SAPIEN 3 [4% – 24%] vs. Evolute R [14.7% – 26.7%]).[46] Current observational studies demonstrate that there is no difference between cLFLGAS and HG TAVR in terms of the need for pacemaker implantation or new-onset LBBB.[38] Prevention of conduction disturbances mainly relies on effective preprocedural planning to ensure appropriate implant depth and commissural alignment as well as identify those who are at high risk for developing conduction disturbances.[45] A recent study indicated a negative predictive value of 98.7% if a patient does not develop Wenckebach following right atrial pacing before valve deployment.[47] If a pacemaker is necessary, it is important to consider chronic resynchronization therapy for patients with cLFLGAS and reduced EF.[3]

6.5. Paravalvular leak (PVL)

PVL is a relatively common complication of TAVR. Although the calcified valves are required for the successful anchoring of the TAVR valve, calcification might lead to partial sealing of the valve, resulting in regurgitation around the valve. Trace-to-mild amounts of PVL have been documented in up to 70% of patients.[48-51] Moderate-to-severe PVL has reported in up to 24% of cases, depending on the type of valve used. However, with the use of newer devices with increased skirt length and enhanced operator experience, PVL incidence has declined to <2%.[52] In patients with cLFLGAS and reduced EF, regurgitation is more poorly tolerated, thus increasing the need for approaches to reduce PVL.[3] To mitigate the risk of developing post-procedural PVL, pre-TAVR planning is crucial to ensure adequate valve sizing, determine the amount and location of annular calcium, estimate the valve type, and ensure that valve implantation is not too high or low.[35] Options for PVL closure include post-balloon dilation, implantation of a second valve, and use of a vascular plug device.[34] Data regarding PVL closure in cLFLGAS TAVR are limited to case reports, and additional research is necessary to elucidate the indications, risks, and ideal procedures for PVL closure in this population.[53]

6.6. Acute kidney injury (AKI)

AKI during the TAVR procedure is caused by the arterial contrast volume used embolization of debris into the renal vasculature, and states of hypoperfusion during rapid pacing.[54] Data from the STS/TVT registry found that 10.7% of patients developed post-procedural AKI, with 9.5% in stage 1, 0.1% in stage 2, and 1.1% in stage 3. The association with mortality became stronger with increasing AKI severity (2.7-fold in stage 1, 10.4-fold in stage 2, and 7-fold in stage 3).[55]

6.7. Long-term complications

Bioprosthetic valve dysfunction (BVD) can be classified into non-structural and structural complications. Non-structural complications include PVL (as detailed above) and patient–prosthesis mismatch (PPM). The incidence of PPM is 23.9%, and there is mixed evidence about whether PPM is linked to increased mortality.[56,57] Patients with cLFLGAS have increased rates of PPM and severe PPM (defined as indexed effective orifice area <0.65 cm^2/m^2). Abbas *et al.* examined patients enrolled in the PARTNER 2a and PARTNER registry data and discovered that severe PPM post-TAVR in patients with cLFLGAS is independently associated with cardiac death and rehospitalization following TAVR (odds ratio, 1.85; 95% confidence interval [CI], 1.06 – 3.23; $p = 0.0308$).[58]

Structural causes of BVD include intrinsic alterations to the valve, such as leaflet wear and tear, disruption, flail leaflets, leaflet fibrosis/calcification, and stent/strut fracture.[59] Extrinsic structural causes of BVD include endocarditis and thrombosis. Endocarditis occurs at the rate of 0.3 – 2.0/100 person-years with 16% – 64% in-hospital morality, 27% – 75% 1-year mortality, and >60% 5-year mortality. Up to 70% of patients experienced complications such as MI, acute HF, acute renal failure, septic shock, and abscesses.[59,60] Antimicrobial prophylaxis is implemented to mitigate endocarditis. Management includes antibiotic therapy and surgical explantation if there is severe valve dysfunction, refractory heart failure, uncontrolled infection, perivalvular infection, or high embolic risk.[61]

Thrombosis is identified by hypoattenuated leaflet thickening on CT. Clinical thrombosis occurred in 0.6% – 2.8% of cases.[62,63] Subclinical thrombosis is significantly more prevalent, with a prevalence of 10% – 15% at 30 days and 30% at 1 year.[64-66] Prevention of subclinical thrombosis has not yet been elucidated. Conflicting evidence exists regarding the clinical implications of subclinical leaflet thrombosis and the existence of elevated rates of subclinical leaflet thrombosis in patients with cLFLGAS.[67-69]

7. Outcomes

Overall, TAVR has been demonstrated to be beneficial for patients with LGAS. The PARTNER trial, which assessed patients with pLFLGAS 1 year following TAVR, demonstrated a decrease in mortality from 66% to 35% in the pLFLGAS group.[70] (Table 2). In a multicenter registry (TOPAS-TAVI) of 287 patients, patients with cLFLGAS undergoing TAVR were studied. Notably, 1-year post-TAVR, LVEF incidence increased by 8.3%. Mortality was observed in 32.3% of these patients at the 2-year follow-up.[71] A sub-study of the same registry compared outcomes between patients with very low (<30%) and low (30% – 40%) EF undergoing TAVR. Irrespective of the LVEF severity and dobutamine stress echo results, TAVR was associated with a significant increase in LVEF with comparable outcomes in both groups.[72] A meta-analysis of SAVR and TAVR in patients with LFLGAS demonstrated that both significantly reduced all-cause mortality, with no differences among the approaches.[10] In a meta-analysis, AVR (SAVR or TAVR) was demonstrated to enhance mortality in patients with cLFLGAS and NFLGAS.[73]

7.1. LGAS versus HGAS

Numerous studies have compared the outcomes in LFLGAS and its subtypes with HGAS after TAVR. When the 2-year post-AVR (TAVR or SAVR) outcomes of patients of the PARTNER 2 trial were analyzed according to flow gradient patterns, the cLFLGAS group showed worse outcomes compared with the HGAS group with higher rates of mortality, rehospitalization, or stroke. In patients with pLFLGAS, outcomes were comparable to those in the HGAS group.[41] Compared with patients with LFLGAS and normal EF and those with HGAS, patients with LFLGAS and low EF exhibited considerably higher rates of all-cause mortality, major stroke, and cardiovascular mortality based on early outcomes at 30 days after TAVR. However, the NYHA functional classification and KCC Q scores improved in all the groups at 1 year.[86] In a subgroup analysis of the German aortic valve registry, patients with cLFLGAS exhibited higher 1-year mortality rates after TAVR than those with HGAS. These patients also demonstrated significantly lower post-operative cardiac output. Patients with pLFLGAS exhibited outcomes similar to those with HGAS.[76] An observational study in Japan found that pLFLGAS was associated with an increase in all-cause mortality compared to HGAS, 8.8 months after TAVR.[77] When 1-year survival outcomes of HGAS versus LFLGAS were compared in matched study populations after TAVR, patients with cLFLGAS showed a twofold increase in mortality compared with those with HGAS. However, when patients with pLFLGAS were specifically compared with those with HGAS, survival outcomes were similar.[78] Another observational study comparing post-TAVR outcomes of pLFLGAS with HGAS revealed worse all-cause mortality, valve-related or worsening congestive heart failure-related hospitalizations, and more frequent NYHA III – IV symptoms in patients with pLFLGAS than in those with HGAS.[79] The outcomes of 270 patients with severe AS and low EF were compared in 2012 and stratified by valvular gradient. Patients with low gradients were more frequently treated medically (21% underwent TAVR or SAVR), whereas those with HGAS underwent TAVR more frequently. Patients with cLFLGAS had a mortality rate of 53.8% at 151 days compared with 41% in patients with HG.[87] A meta-analysis demonstrated that patients with LGAS showed a higher 30-day, midterm all-cause, and cardiovascular mortality than those with HGAS after TAVR, with similar outcomes among patients with cLFLGAS and pLFLGAS.[80] Another meta-analysis demonstrated that cLFLGAS was associated with increased early mortality compared with HGAS. Both cLFLGAS and pLFLGAS demonstrated elevated midterm mortality compared with the HGAS.[88]

7.2. AVR versus medical management

In studies comparing AVR with conservative management, AVR exhibited a proven benefit. In a clinical trial, outcomes were compared in patients with cLFLGAS who underwent TAVR, SAVR, or medical therapy. TAVR and

Table 2. Key studies on low-flow low-gradient aortic stenosis and their outcomes

First author, Year	Study design	Objective	Number of patients/studies included	Outcome
Ribeiro *et al*., 2018[71]	A prospective multicenter registry study	To evaluate the clinical outcomes and changes in LVEF following TAVR in patients with classical LFLGAS.	287 patients	TAVR was superior to SAVR with better peri-procedural outcomes and overall improvement in LVEF irrespective of the presence or absence of contractile reserve at the 1-year follow-up in patients with LFLGAS.
Maes *et al*., 2019[72]	A prospective multicenter registry study	To evaluate the clinical outcomes and alterations in LVEF following TAVR in patients with LFLGAS and severe left ventricular dysfunction.	293 patients, including 128 with very low LVEF (<30%) and 165 with low LVEF (30% – 40%)	Patients with LFLGAS and severe left ventricular dysfunction showed comparable clinical outcomes of TAVR to those in patients with only mildly reduced LVEF function and exhibited a significant improvement in LVEF over time, irrespective of the degree of baseline left ventricular dysfunction.
Ueyama *et al*., 2021[10]	Meta-analysis	To evaluate the impact of AVR in patients with each subclass of LGAS, including LFLG, paradoxical LFLG, and NFLGAS, and compare the clinical outcomes following SAVR and TAVR.	6515 patients from 32 studies	AVR was associated with a substantial decrease in all-cause mortality in all subclasses of LGAS, with no observed difference between SAVR and TAVR.
Chiang *et al*., 2024[74]	Retrospective single-center study	• To estimate and assess the alterations in functional status based on the NYHA score and quality of life metrics using the KCCQ in patients with three variants of severe, low-gradient AS at 30 days and 1 year following TAVR. • To evaluate secondary outcomes such as all-cause mortality and major adverse cardiovascular events.	170 patients	• Significant improvement in NYHA class and KCCQ scores were observed at 30 days and 1 year in all three subclasses of LGAS following TAVR, but no significant difference was noted between the subclasses. • No significant difference was noted in the secondary outcomes.
Freitas-Ferraz *et al*., 2020[75]	A prospective multicenter study	To estimate the incidence, clinical outcomes, and changes in the severity of MR over time in patients with LFLGAS undergoing TAVR.	308 patients	Patients with TAVR developed functional MR, which resolved significantly over time. The lack of improvement at 1 year was correlated with poor clinical outcomes.
Dayan *et al*., 2015[73]	Meta-analysis	To analyze the impact of AVR on mortality and survival in patients with LGAS and preserved LVEF and those with high-gradient AS or moderate AS.	18 studies	Patients with paradoxical LFLGAS and NFLGAS exhibited an increased risk of mortality compared with those with other subtypes of AS and showed improved outcomes with AVR.
Lauten *et al*., 2014[76]	A prospective multicenter registry study	To analyze the outcome of patients undergoing TAVI for various subtypes of severe AS.	3908 patients	The in-hospital and 1-year mortality and complication rates after TAVI among patients with PLFLGAS were low and comparable to those for high-gradient AS. Patients with low

(Cont'd...)

Table 2. ***(Continued)***

First author, Year	Study design	Objective	Number of patients/studies included	Outcome
				EF and low-gradient AS exhibited significantly higher 1-year mortality and a significantly higher rate of low cardiac output after TAVI.
Kataoka *et al*., 2018[77]	Prospective study	To analyze the prognosis of low-flow severe AS in Japanese small-body patients undergoing TAVR.	723 patients	Among Japanese small-body patients with severe AS, both paradoxical LF and LF-LG severe AS were linked to poor outcomes following TAVR.
Fischer-Rasokat *et al*., 2019[78]	A retrospective single-center study	To determine if the prognosis of patients with severe AS having high *vs*. low transvalvular mean pressure gradients varies after TAVR, even after strict matching.	2282 patients	The mortality in patients with LFLGAS was twice that in patients with HGAS after TAVR. However, patients with paradoxical LFLGAS had similar mortality benefits as that of patients with HGAS.
Saito *et al*., 2021[79]	A retrospective observational study	To compare the post-TAVR outcomes of patients with paradoxical LFLGAS and those with NFHGAS.	293 patients	All-cause mortality, hospitalization for valve-related symptoms, and worsening congestive heart failure were worse for patients with pLFLGAS than for those with NFHGAS. Patients with pLFLGAS had a significantly higher rate of pre-existing atrial fibrillation/flutter, affecting the post-TAVR outcomes.
Osman *et al*., 2019[80]	Meta-analysis	Comparing TAVI outcomes between patients with classic HGAS and those with LGAS and between the three subclasses of AS, including HG, pLFLG, and Ref-LG.	27204 patients from 19 studies	Patients with classic HGAS showed better 30-day, midterm all-cause, and cardiovascular mortality compared with those with LGAS following TAVI. Among patients with LG severe AS, TAVI outcomes were similar between patients with reduced EF and those with LGAS and pLFLGAS.
Takagi *et al*., 2019[81]	Meta-analysis	To analyze whether LFLGAS affects survival after TAVI and compare outcomes between patients with classical LFLG, paradoxical LFLG, and NFHG.	5512 patients from 9 studies	Patients with classical LFLGAS exhibited increased early mortality after TAVI compared with those with NFHGAS. Classical and paradoxical LFLGAS were associated with increased midterm mortality compared with NFHGAS. No difference was observed in early and midterm mortality between patients with classical LFLGAS and those with paradoxical LFLGAS.
Rodriguez-Gabella *et al*., 2018[82]	A prospective multicenter study	To ascertain the clinical outcomes (mortality, NYHA Class III – IV) in patients with paradoxical LFLG severe AS undergoing TAVI.	493 patients	There were no differences in mortality between the groups, but patients with pLFLGAS more frequently showed NYHA

(Cont'd...)

Table 2. ***(Continued)***

First author, Year	Study design	Objective	Number of patients/studies included	Outcome
				class III – IV and exhibited a higher rate of cardiovascular complications. TAVI treatment futility was more frequent in the pLFLGAS group.
Ozkan *et al*., 2013[83]	Prospective study	Comparing the outcomes of severe LGAS with those of AVR and medical therapy.	260 patients	AVR was associated with better survival rates than medical therapy in patients with symptomatic LGAS and preserved EF.
Kugelman *et al*., 2020[84]	A prospective observational study	Comparison of outcomes in patients with LGAS who underwent TAVR and those with LGAS who underwent SAVR.	130 patients	Patients with LGAS exhibited better adjusted event-free survival when referred to TAVR rather than to SAVR.
Annabi *et al*., 2020[85]	A prospective observational study	To compare the outcomes in patients with LFLGAS who were treated with surgical AVR, transfemoral TAVR, alternate access TAVR, and conservative management.	481 patients	Early AVR was associated with major survival benefits in both classic and paradoxical LFLGAS. Compared with conservative management, transfemoral TAVR exhibited the best survival rate, followed by surgical AVR and alternative access TAVR.

Abbreviations: AS: Aortic stenosis; AVR: Aortic valve replacement; CLFLGAS: Classic low-flow: EF: Ejection fraction; KCCQ: Kansas City Cardiomyopathy Questionnaire; LFLGAS: Low-flow, Low-gradient aortic stenosis; LVEF: Left ventricular ejection fraction; MR: Mitral regurgitation; NFHGAS: Normal-flow, high-gradient aortic stenosis; NYHA: New York Heart Association class; pLFLGAS: Paradoxical low-flow, low-gradient aortic stenosis; SAVR: Surgical aortic valve replacement; TAVI: Transcatheter aortic valve implantation; TAVR: Transcatheter aortic valve replacement.

SAVR demonstrated improved survival at 1 year compared with medical therapy.[89] After 28 months of follow-up, patients with pLFLGAS who underwent TAVR or SAVR had an improved survival rate compared with those who underwent balloon aortic valvuloplasty or medical therapy. Specifically, the survival rates were 30% in patients who underwent AVR and 70% in medically treated patients. Most of these patients, however, underwent SAVR.[83] However, in the multicenter ROTAS trial, 52 patients with pLFLGAS were randomized to undergo AVR (TAVR or SAVR) or optimized medical therapy. After 14 months of follow-up, death and heart failure hospitalization were comparable in both groups.[90]

Although most studies comparing AVR with conservative or medical management involve both SAVR and TAVR, certain findings and studies are also specific to TAVR. In a trial comparing outcomes in 1358 patients with NFLGAS undergoing TAVR or SAVR versus conservative management, at 652 days, TAVR was associated with improved survival and decreased cardiac mortality as compared to conservative management. Furthermore, there was no significant difference between the outcomes of SAVR versus TAVR.[91] In the TOPAS prospective study, when outcomes were compared among patients who received early AVR and those who received conservative management, AVR was associated with a significant survival benefit in both patients with cLFLGAS and pLFLGAS. Among the AVR types, TF TAVR was associated with the best survival, as compared to conservative management.[85] In an observational study, the outcomes of patients with LGAS undergoing TAVR or SAVR were compared over 4 years of follow-up. There was no difference seen in rates of overall survival, long-term dialysis or urgent rehospitalization, or survival free of stroke. However, TAVR was associated with a better-adjusted event-free survival.[84]

Compared with the HGAS group, the LFLGAS group exhibited increased mortality and morbidity after undergoing TAVR. However, enough data suggests that TAVR is a beneficial option over conservative management and, in certain respects, possibly over SAVR, for patients with LFLGAS in the long term. Given their poor known outcomes, these patients should be more closely monitored compared with patients with HGAS. Apart from AVR, medical optimization should be pursued aggressively to prevent hospitalization for decompensated heart failure and to enhance other clinical outcomes.

8. Future directions

Recent studies have focused on elucidating the most effective patient selection criteria and procedural techniques for TAVR in LFLGAS. Ongoing research aims to refine risk stratification models and identify the outcome predictors. Novel imaging modalities such as intracardiac echocardiography and nuclear imaging may help provide insights regarding valve morphology and function, guiding treatment decisions and optimizing procedural outcomes. In TAVR, the potential for personalized risk assessment and treatment planning is demonstrated by the integration of sophisticated technologies, such as artificial intelligence and machine learning algorithms. Emerging trends in TAVR for patients with LFLGAS involve the exploration of alternative access routes, including transaxillary and TA approaches, to mitigate procedural risks and expand treatment options for patients with complex anatomy.[92] In addition, the advancement of next-generation THV with enhanced hemodynamics and durability addresses the distinctive challenges posed by LFLGAS, potentially improving long-term valve performance and patient outcomes.[52] Despite significant advancements, challenges remain in optimizing outcomes and expanding the applicability of TAVR in patients with LFLGAS. Addressing issues, such as paravalvular leaks, conduction disturbances, and PPM is crucial for improving procedural success and long-term durability.[93] Innovations in valve design, delivery systems, and optimal antithrombotic strategy aim to minimize complications and improve the safety profile of TAVR.[93]

9. Conclusion

This contemporary review of TAVR in patients with LFLGAS underscores the evolving landscape of clinical perspectives, procedural considerations, outcomes, complications, and future directions in this specialized field of cardiovascular intervention. The clinical perspectives highlighted in these studies highlight the importance of adhering to guidelines for patient selection and intervention, particularly in identifying individuals who may benefit from TAVR rather than SAVR.[94] Furthermore, the studies illustrate the favorable outcomes and feasibility of TAVR in low-risk patients with symptomatic severe AS, emphasizing the potential expansion of TAVR to a broader patient population.[94] These studies collectively contribute to the understanding of procedural considerations, patient outcomes, and the expanding role of TAVR in addressing the complexities of LFLGAS. These findings underscore the need for continuous research and innovation to improve patient outcomes in this challenging patient population while establishing the basis for potential broader applications of TAVR in low-risk patients with AS.

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Conflict of interest

The authors declare they have no competing interests.

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ACCSCIENCE PUBLISHING

Brain & Heart

REVIEW ARTICLE

Cardioneuroablation for vagally mediated bradyarrhythmia: A case study with a systematic review

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Abstract

This study evaluates the efficacy of cardioneuroablation (CNA) for vagally mediated bradyarrhythmia (VMB) through two case reports, a systematic review and a meta-analysis. Two patients with VMB were treated with CNA targeting ganglionated plexi using a radiofrequency ablation catheter. Both patients showed sustained clinical improvement post-CNA, with no recurrence of syncope or pre-syncope during follow-up periods of 26 and 16 months. We performed a meta-analysis, according to the preferred reporting items for systematic reviews and meta-analyses guidelines to review 19 studies involving 618 patients, excluding animal studies, case reports, and studies limited to immediate responses. The analysis revealed that 94.3% (95% confidence interval [CI]: 90.9 – 97.7%) of patients were symptom-free during follow-up, while only 4.5% (95% CI: 2.6 – 6.4%) required pacemaker implantation. Procedure-related complications were reported in 4.7% (95% CI: 2.3 – 7.1%) of overall cases. These findings suggest that CNA is an effective and safe treatment option for VMB, reducing symptom recurrence and the need for pacemaker implantation. Further randomized controlled trials are warranted to validate its long-term efficacy.

Keywords: Cardioneuroablation; Vagally mediated bradyarrhythmia; Radiofrequency ablation; Ganglionated plexus

1. Introduction

The autonomic nervous system, comprising the sympathetic and parasympathetic branches, directly regulates the heart rate and rhythm. In many cases of bradyarrhythmia, an imbalance in autonomic tone is observed, which is typically characterized by excessive parasympathetic activity and reduced sympathetic influence.[1,2] This imbalance can lead to a slower heart rate than usual, known as vagally mediated bradyarrhythmia (VMB), which may potentially result in symptoms such as fatigue, dizziness, and syncope. Intermittent sinus bradycardia, sinus node dysfunction, and atrioventricular block are

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the most common electrocardiographic manifestations of this condition.[3]

VMB represents a significant clinical challenge due to its diverse manifestations and the limited therapeutic options available for patients with severe or recurrent symptoms. Although lifestyle modifications and medications may benefit some patients, these interventions often fail to adequately control symptoms in those with significant autonomic imbalances. Traditionally, after excluding secondary factors such as medications and internal environmental influences, pacemaker implantation has been the most common treatment for severe VMB.[4,5] While pacemakers effectively address the symptomatic bradycardia, they do not target the underlying autonomic dysfunction, leaving patients reliant on device-based therapy.

Cardioneuroablation (CNA) is a specialized catheter ablation technique that specifically targets the ganglionated plexi (GPs), which are intrinsic structures located within the epicardial atrial fat pads, connecting pre- and post-ganglionic nerve fibers. By targeting the GPs, this technique helps to treat reflex syncope or functional bradycardia.[6-29] Through modulation of the autonomic pathways responsible for bradyarrhythmia, CNA offers the potential to restore balanced autonomic tone and alleviate symptoms without reliance on permanent pacing.

CNA is considered for patients with symptoms due to excessive parasympathetic activity, which leads to significantly slower heart rates (bradycardia) and other rhythm disturbances that are resistant to conventional therapies, such as medications or pacemaker implantation. Here, we report two cases of patients with VMB (one with intermittent sinus arrest and the other with severe sinus bradycardia), who achieved good therapeutic outcomes following CNA. In addition, we conducted a systematic review and meta-analysis to evaluate the effects of CNA in patients with VMB.

2. Case presentations

2.1. Case 1

A 33-year-old woman presented with a 5-month history of recurrent dizziness and syncope. A 24-h Holter monitors revealed intermittent sinus arrest and junctional escape rhythm. No abnormalities were detected by transthoracic echocardiography, chest X-ray, or blood tests (including routine blood work, electrolytes, liver and kidney functions, troponin I, troponin T, and thyroid function). Cardiac autonomic function was assessed using the deceleration capacity calculated from Holter data, which yielded a high value of 30 ms. An atropine test confirmed that the sinus rate had increased by more than 25% from the baseline rate, and no sinus arrest was recorded for 30 min following intravenous atropine administration.

Before the CNA procedure, a detailed diagnostic evaluation is conducted to exclude patients who are not suitable for the procedure. The exclusion criteria include the following: (i) structural heart or cardiopulmonary conditions, such as valvular heart abnormalities, severe aortic stenosis, history of myocardial infarction, pulmonary embolism, pulmonary hypertension, or hypertrophic obstructive cardiomyopathy; (ii) cardiac rhythm disturbances, including paroxysmal supraventricular tachycardia, ventricular tachycardia, or arrhythmias induced by medication; (iii) neurological conditions involving the cerebrovascular system, such as subclavian steal syndrome or seizures; (iv) syncope associated with medications, including vasodilators, antipsychotic drugs, or antidiabetic agents. Furthermore, patients with terminal conditions or those classified as New York Heart Association Class III or IV heart failure were also excluded.

The CNA procedure was performed under conscious sedation. Three-dimensional electroanatomic mapping of the left atrium (LA) and pulmonary veins was conducted using the EnSite NavX system (St. Jude Medical, Saint Paul, MN, USA). The right anterior GP (RAGP), located in the superoanterior region around the root of the right superior pulmonary vein, was identified and marked based on anatomical relationships and local fractionated electrograms (Figure 1A). Ablation of the RAGP was performed using a 4-mm-tip radiofrequency ablation catheter, with power and temperature limits set to 40 W and 60°C, respectively. Clustered ablations were delivered for 90 s at each site. As shown in Figures 1A and 1B, the intermittent sinus arrest and junctional escape rhythm immediately terminated during RAGP ablation, and the heart rate increased to 70 bpm.

During a 26-month follow-up, the patient experienced no recurrence of syncope or pre-syncope. Follow-up Holter data showed no episodes of sinus arrest.

2.2. Case 2

A 42-year-old man presented with an 8-month history of recurrent dizziness and pre-syncope. The 24-h Holter monitoring showed sinus bradycardia, with a mean heart rate of 51 bpm (range: 29 – 92 bpm). An atropine test confirmed an increase in the sinus rate by more than 25% from the baseline rate. The patient's deceleration capacity was measured at 16.5 ms. The CNA procedure was performed under conscious sedation. Three-dimensional electroanatomic mapping of the right atrium (RA) was conducted using the EnSite NavX system (St. Jude Medical,

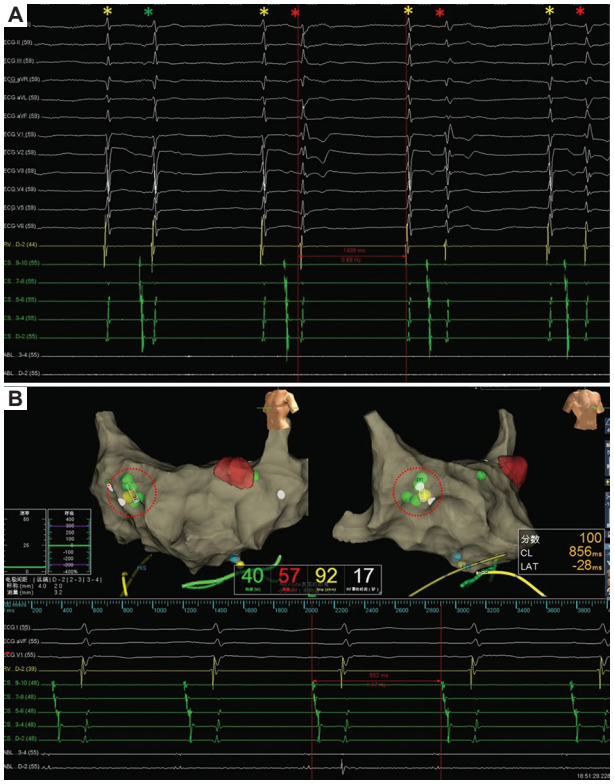

Figure 1. Cardioneuroablation procedure in Case 1. (A) Electrocardiogram before cardioneuroablation. A red asterisk indicates sinus rhythm, a yellow asterisk indicates junctional escape rhythm, and a green asterisk indicates an atrial rhythm as evidenced by inverted P waves in leads II, III, and aVF. (B) The three-dimensional endocardial surface of the left atrium shows locations of targeted ganglionated plexi within the red dashed circles. The post-cardioneuroablation electrocardiogram shows the disappearance of the junctional escape rhythm with conversion to complete sinus rhythm.
Abbreviation: aVF: Augmented voltage foot.

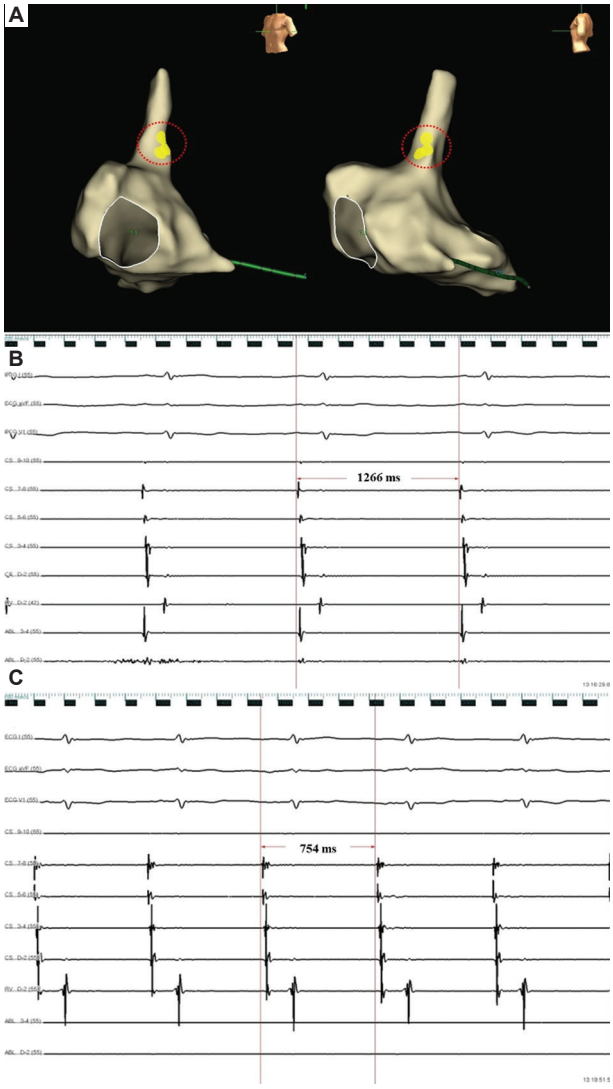

Figure 2. Cardioneuroablation procedure in Case 2. (A) The three-dimensional endocardial surface of the right atrium shows locations of targeted ganglionated plexi within the red dashed circles. The R-R interval (within the red solid line) (B) before and (C) after cardioneuroablation was 1266 ms and 754 ms, respectively.
Abbreviation: ms: Millisecond.

Saint Paul, MN, USA). The RAGP was accessible from both the LA and RA. Clustered ablations were delivered from the RA (septal side of the junction between the RA and the superior vena cava) (Figure 2A). As shown in Figures 2B and 2C, the basal cycle length of the heart rate decreased from 1266 ms at baseline to 754 ms after ablation.

During a 16-month follow-up, the patient experienced no recurrence of syncope or pre-syncope. Follow-up Holter data showed a mean heart rate of 73 bpm (range: 46 – 112 bpm) at 12 months after the ablation.

3. Systematic review and meta-analysis

3.1. Methods

3.1.1. Data sources and search strategy

The systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statements.[30] A comprehensive search of the Ovid MEDLINE, Embase, and PubMed databases was performed using the keywords "cardioneuroablation" and "bradycardia" to identify relevant studies published before 20 May 2024. No language restrictions were applied. Details of the search strategy were provided in the Appendix. In addition, the reference lists of all identified articles were reviewed.

3.1.2. Selection criteria

The inclusion criteria were as follows: (i) studies involving patients with VMB who underwent CNA therapy; (ii) studies conducted on human subjects; (iii) studies providing

sufficient data to calculate the effective rate; and (iv) no restrictions on publication year, language, country, or demographic details. Meanwhile, the exclusion criteria included: (i) studies focusing solely on the immediate response to CNA; (ii) animal studies; (iii) case reports; (iv) studies with overlapping datasets; (v) studies with unreliably extracted, duplicated, or incomplete data; and (vi) articles available only as abstracts (conference proceedings, letters, or commentaries). Full texts were independently reviewed by two reviewers, and final decisions regarding study inclusion were made through consensus.

3.1.3. Data extraction and quality assessment

Two investigators (F.H. and Y.W.) independently searched for studies and extracted data using standardized protocols and reporting forms. Any disagreements were resolved through discussion with the author group until a consensus was reached. The extracted data included the publication year, methodology, sample demographics, baseline characteristics, and follow-up information (patients free from bradyarrhythmia-related symptoms, patients requiring pacemaker implantation, and reported complications). Quality assessment was independently performed by two authors (M.Z. and G.L.) using the Newcastle–Ottawa Scale (NOS) to assess the quality of all included studies.[31] Discrepancies were resolved through discussion with the author group. Studies with a NOS score of ≥6 stars were classified as moderate-to-high quality, while those with a score of <6 stars were classified as low quality.

3.1.4. Outcomes of meta-analysis

The primary outcome was the absence of bradyarrhythmia-related symptoms (fatigue, dizziness, syncope, and pre-syncope) during follow-up. The secondary outcomes were the proportion of patients requiring pacemaker implantation and the incidence of complications observed during follow-up.

3.1.5. Study selection

As shown in Figure 3, the search strategy yielded 1,735 studies. After removing 74 duplicates, 1,661 studies were excluded based on screening of the title and abstract. The full texts of the remaining 67 studies were reviewed, resulting in the exclusion of 48 studies. Ultimately, 19 studies met the inclusion criteria and were included in the meta-analysis.[6,12,13,16,19,24-29,32-39] The general characteristics and quality assessments of the included studies are presented in Table 1. The observational studies had NOS scores of 6 to 8 stars, indicating their suitability for analysis.

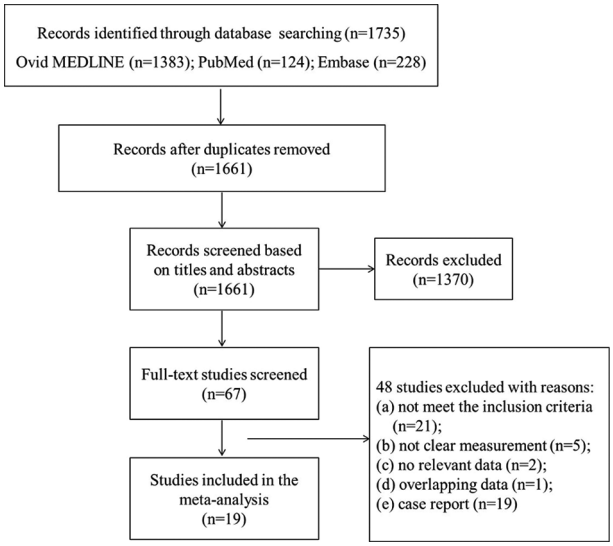

Figure 3. Flow diagram illustrates the selection process for articles. PRISMA diagram illustrating the article selection process for inclusion in the meta-analysis.
Abbreviations: PRISMA: Preferred reporting items for systemic reviews and meta-analyses.

3.1.6. Statistical analysis

The statistical analysis was performed in accordance with the recommendations of the Cochrane Collaboration and PRISMA guidelines. Data synthesis was performed using the R package meta (The R Project for Statistical Computing, Vienna, Austria). The I^2 statistic was used to assess study consistency, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. Funnel plots were used for the graphical assessment of publication bias. Sensitivity analyses were conducted by omitting one study at a time to evaluate the robustness of the results.

3.2. Results

3.2.1. Freedom from bradyarrhythmia-related symptoms

Nineteen studies involving 618 patients reported the effect of CNA on the recurrence of bradyarrhythmia-related symptoms. As shown in Figure 4, 94.3% of the patients (95% confidence interval [CI]: 90.9 – 97.7%, I^2 = 59%) were free from symptoms at the end of follow-up. Despite moderate heterogeneity among the studies, the sensitivity analysis revealed that no individual study significantly altered the overall results.

3.2.2. Proportion of pacemaker implantation after CNA

The need for pacemaker implantation following CNA was analyzed in 464 patients from 12 studies. As shown in Figure 5, 4.5% of the patients (95% CI: 2.6 – 6.4%, I^2 = 6%)

Table 1. General characteristics and quality assessments of the included studies

Study	Year	Design	Region	Number of patients	Indications	Locations of targeted GPs	Follow-up (months)	Quality of study (NOS score)
Pachon *et al.*[6]	2005	retrospective	Brazil	20	SND, AVB	RA/LA	9.2±4.1	6
Zhao *et al.*[12]	2015	retrospective	China	11	SB	RA/LA	18.4±6.2	6
Aksu *et al.*[13]	2016	prospective	Turkey	14	SND, AVB	RA/LA	10.9±3.3	7
Qin *et al.*[16]	2017	prospective	China	62	SB	RA/LA	12	8
Debruyne *et al.*[19]	2018	prospective	Belgium	8	SND	RA	12	6
Güler *et al.*[32]	2020	retrospective	Turkey	11	SND, AVB	RA/LA	52 (28 – 56)	7
Lu *et al.*[33]	2020	retrospective	China	13	SND, AVB	RA/LA	13.0±5.9	7
Aksu *et al.*[24]	2021	prospective	Turkey	31	AVB	RA/LA	-	8
Aksu *et al.*[34]	2021	retrospective	Turkey	19	SND, AVB	RA/LA	14.9±17	7
Debruyne *et al.*[25]	2021	prospective	Belgium	19	SND	RA	12	7
Mesquita *et al.*[35]	2021	prospective	Portugal	13	SND, AVB	RA/LA	6.5±23.4	6
Aksu *et al.*[26]	2022	prospective	Turkey	13	SND, AVB	RA/LA	8.0±3	7
Chen *et al.*[36]	2022	retrospective	China	6	SND	RA/LA	6	6
Piotrowski *et al.*[27]	2022	prospective	Poland	25	SND, AVB	RA/LA	10±3	7
Rivarola *et al.*[37]	2023	prospective	Brazil	36	SND, AVB	RA/LA	52.1±35.2	8
Song *et al.*[38]	2023	prospective	China	73	SB	RA/LA	27.2±17.4	8
Wileczek *et al.*[28]	2023	retrospective	Poland	178	SND, AVB	RA/LA	23.7	7
Choi *et al.*[29]	2024	retrospective	USA	6	SND, AVB	RA/LA	7.9	6
Han *et al.*[39]	2024	prospective	China	60	SND	LA	12	8

Abbreviations: SND: Sinus node dysfunction; AVB: Atrioventricular block; SB: Sinus bradycardia; RA: Right atrium; LA: Left atrium; GPs: Ganglionated plexi; NOS: Newcastle–Ottawa Scale.

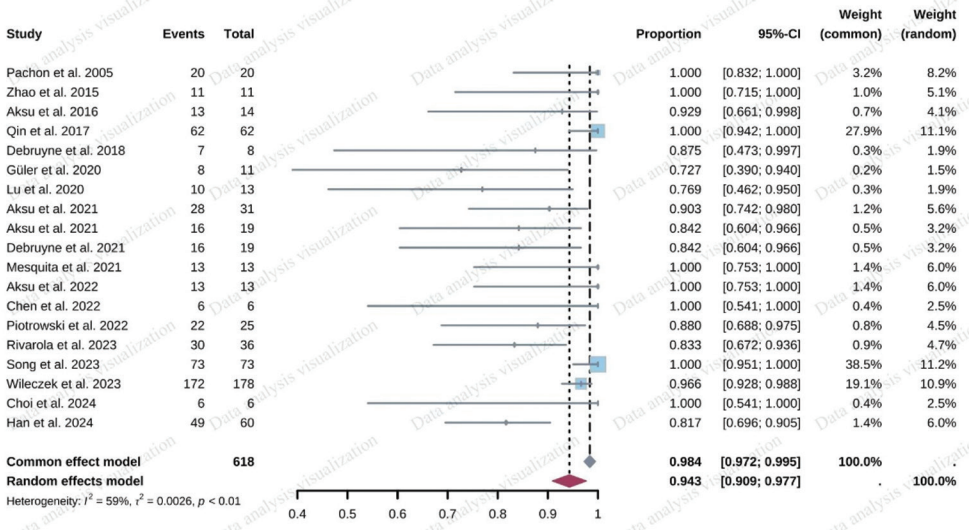

Figure 4. Forest plot of freedom from bradyarrhythmia-related symptoms. At the end of follow-up, 94.3% of patients (95% confidence interval: 90.9 – 97.7%, I^2 = 59%) were free from bradyarrhythmia-related symptoms.

required pacemaker implantation after the procedure. The sensitivity analysis indicated that no individual study significantly altered the overall results.

3.2.3. Procedure-related complications

The incidence of procedure-related complications was analyzed in 294 patients from 7 studies using a common-

effect model. As shown in Figure 6, the incidence of complications was 4.7% (95% CI: 2.3 – 7.1%, I^2 = 0%).

4. Discussion

CNA is a novel technique that has emerged over the past decade, primarily used to treat vasovagal syncope and functional bradyarrhythmias. In recent years, this therapeutic strategy has garnered significant interest, largely due to its ability to modify autonomic influences on the heart, addressing the root cause of arrhythmias rather than merely alleviating symptoms. Initial clinical studies were limited by small sample sizes and were predominantly observational, with a lack of randomized controlled trials. In this report, we described two patients with VMB who underwent CNA and achieved favorable clinical outcomes. These cases underline the therapeutic potential of CNA and highlight its promise for achieving long-term symptom relief in patients with VMB. Previous meta-analyses have focused on the impact of this procedure in patients with vasovagal syncope.[40,41] To our knowledge, this is the first meta-analysis to assess the clinical outcomes of CNA in patients with VMB. The three key findings of this study are as follows: (i) CNA significantly reduced the recurrence of symptoms related to bradyarrhythmia; (ii) the proportion of patients requiring pacemaker implantation post-CNA was relatively low; and (iii) CNA is an exceptionally safe procedure associated with very low rates of procedure-related complications.

Ganglionated plexis (GPs) are chosen as the primary targets for CNA because of their crucial physiological roles and accessible anatomical positions, which allow for straightforward targeting with an ablation catheter.[42-44] The physiological role of these GPs involves complex interactions within the cardiac autonomic nervous system, modulating heart rate and atrioventricular conduction in response to both internal and external stimuli. Previous research has identified seven key GPs located in various cardiac structures, including interatrial tissues and regions near the coronary arteries and pulmonary veins.[45] The thinner structure of the atria allows for more effective transmission of radiofrequency energy, thereby facilitating CNA through an endocardial approach.

Various strategies for targeting and ablating GPs primarily focus on the LA and RA. Pachon *et al.*[6,7,9,11] utilized spectral and anatomical guidance to perform extensive GP ablation in both atria, addressing conditions such as neurocardiogenic syncope and sinus dysfunction. Their approach has been foundational in establishing effective

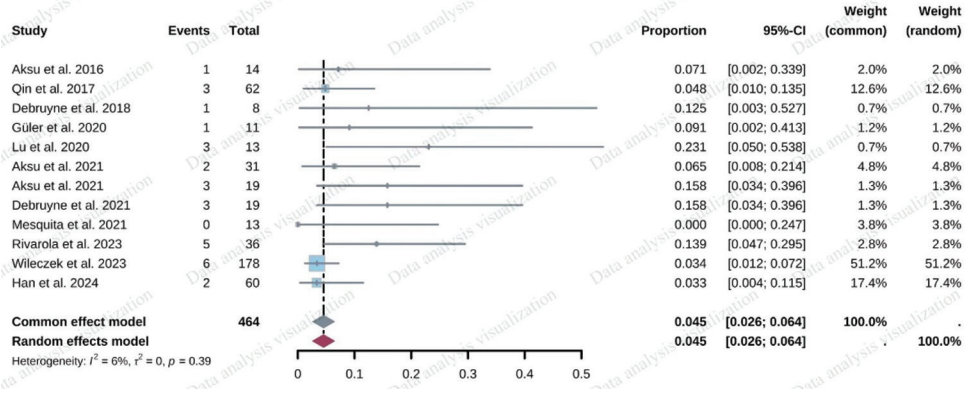

Figure 5. Forest plot of pacemaker implantation after cardioneuroablation. A total of 4.5% of patients (95% confidence interval: 2.6 – 6.4%, I^2 = 6%) required pacemaker implantation after cardioneuroablation.

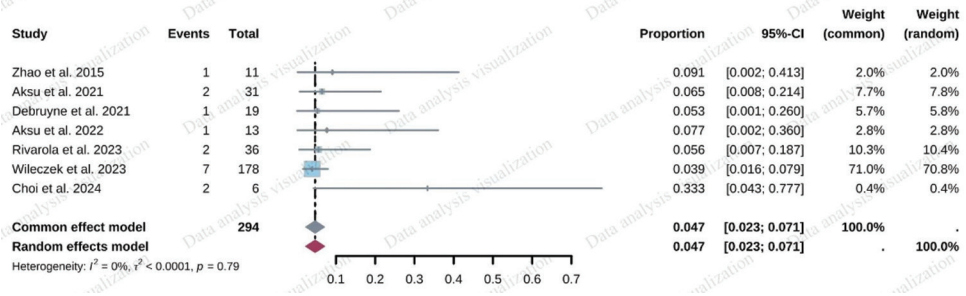

Figure 6. Forest plot of rate of procedure-related complications. The incidence of procedure-related complications was 4.7% (95% confidence interval: 2.3 – 7.1%, I^2 = 0%).

CNA techniques and has paved the way for more refined and patient-specific procedures. Aksu *et al.*[13,18,22,24,26,34,40,46,47] employed a streamlined approach targeting primary GPs in the atria, which yielded positive outcomes. Conversely, Zhao *et al.*[12] and Qin *et al.*[16] conducted anatomical GP ablations in both atria to manage symptomatic sinus bradycardia. Debruyne *et al.*[19,25] adopted a unifocal approach on the right side to address neurally mediated syncope and sinus node issues. In the two case reports presented in this study, we demonstrate that CNA can achieve favorable outcomes whether the approach is from the RA or LA. This efficacy is likely due to the anatomical position of the RAGP, which is located between the LA and RA, allowing access to this GP site from either atrium (Figure 7).

The interaction among GPs necessitates careful selection of targeted GPs for ablation to minimize potential adverse effects. Chiou *et al.*[48] identified a fat pad near the right pulmonary artery as a critical relay point in the cardiac autonomic network, which Debruyne *et al.*[19,25] targeted during their procedures. By systematically selecting which GPs to target based on patient-specific anatomical and functional markers, the risk of unnecessary complications can be reduced, and outcomes can be optimized. Our prior research on CNA in patients with vasovagal syncope demonstrated that sequentially targeting specific GPs, starting from the left superior GP to the RAGP, resulted in immediate and sustained heart rate increases during ablation of the RAGP, with other GPs primarily eliciting vagal responses.[21,49] This suggests that the RAGP plays a significant role in CNA outcomes. Despite these findings, there is a direct comparison between ablating only the right superior GP and targeting all left atrial GPs. Further research is required to determine whether focusing solely on the right superior GP provides long-term benefits and to further elucidate the complex regulation of GPs. CNA is a novel surgical technique that currently lacks long-term clinical follow-up data extending beyond a decade. While the growing body of short-term evidence is promising, long-term studies are essential to evaluate the durability of its outcomes. Moreover, its prolonged effects remain to be determined. The long-term success of this procedure can be undermined by incomplete ablation, potentially resulting in reinnervation due to the presence of remaining intramural parasympathetic post-ganglionic neurons. To address this issue, future approaches could involve multiple ablations using both endocardial and epicardial pathways to improve long-term outcomes.

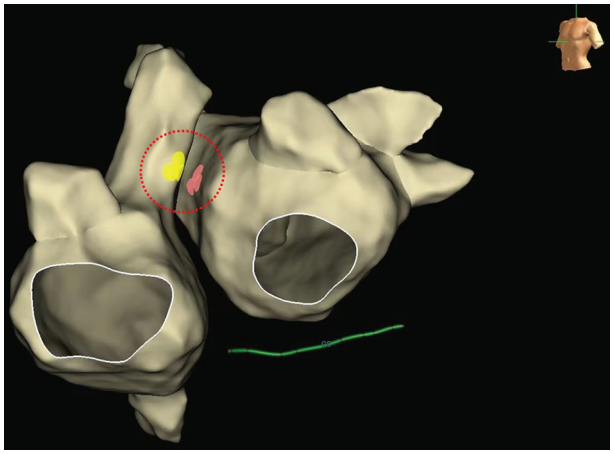

Figure 7. The three-dimensional endocardial surface of the left atrium and right atrium and locations of the right anterior ganglionated plexus. The right anterior ganglionated plexus (within the red dashed circle) is located between the left and right atria, allowing access to it from either atrium.

In clinical practice, we encounter two primary patient populations. The first group includes those with VMB who may avoid the need for pacemaker implantation through CNA. The second group consists of a significant cohort of patients who had previously received a pacemaker due to VMB.[28] For these patients, CNA has the potential to render both the pacemaker and its implanted electrodes, which may degrade over time, unnecessary. The broader clinical implications of this procedure include reducing dependency on long-term device management, which could potentially ease the burden on healthcare systems while improving patients' quality of life. This paradigm shift could reshape how clinicians manage VMB patients in the coming years.

Our analysis included studies with relatively small sample sizes or retrospective designs. Future investigations should aim to include extensive, prospective, multicenter studies that are double-blinded and randomized to further validate our conclusions. A recent search of the https://clinicaltrials.gov/website revealed numerous prospective clinical trials designed to evaluate the effects of CNA on VMB.[50,51] In addition, randomized controlled trials have been performed to compare the outcomes of CNA with pacemaker implantation.[52] We look forward to the forthcoming results of these studies with great interest. These investigations are expected to address existing gaps in knowledge, providing the robust evidence required to establish clinical practice guidelines.

Despite its promising outlook, several challenges remain to be addressed. First, the complexity of the cardiac autonomic nervous system necessitates a nuanced understanding of GP interactions and precise techniques to ensure successful outcomes. The lack of universal protocols for GP targeting leads to variability in procedural efficacy. In addition, cost considerations and the availability of trained

personnel may limit widespread adoption, particularly in resource-constrained settings. Finally, ethical concerns arise regarding the potential replacement of pacemaker implantation with a relatively novel intervention like CNA. Balancing innovation with patient safety and efficacy will remain a key focus of the ongoing research efforts in this field.

5. Conclusion

CNA presents a promising intervention for patients with VMB, demonstrating significant success in reducing symptoms and minimizing the need for pacemaker implantation. The two case studies, along with a systematic review and meta-analysis, reveal that this procedure is highly effective and has a low complication rate, underscoring its potential as a standard treatment option.

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Conflict of interest

Yan Yao is an Editor-in-Chief of this journal and Guest Editor of this special issue but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Ethics approval and consent to participate

A written informed consent was obtained from all patients in this study.

Consent for publication

A written informed consent was obtained from each of the subjects to publish their data and images.

Availability of data

The data used in this article will be shared upon reasonable request to the corresponding author.

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Appendix

Appendix: Search Strategy

Ovid medline

1. Bradycardia
2. Sinus bradycardia
3. Heart sinus bradycardia
4. Nodal bradycardia
5. Sinus node bradycardia
6. Sinus arrest
7. Atrial arrest
8. Atrial asystole
9. Atrial standstill
10. Atrium standstill
11. Cardiac sinus arrest
12. Heart atrium arrest
13. Heart atrium standstill
14. Sinoatrial arrest
15. Sinus node arrest
16. Sinus node dysfunction
17. Atrioventricular block
18. or/1-17
19. Cardioneuroablation
20. Autonomic denervation
21. Heart denervation
22. Cardiac autonomic modulation
23. Ganglionated plexus ablation
24. or/19 – 23
25. 18 and 24
26. (Animals, not humans).sh.
27. 25 not 26

EMBASE

("bradycardia"/exp OR "sinus bradycardia"/exp OR "heart sinus bradycardia" OR "nodal bradycardia" OR "sinus bradycardia" OR "sinus node bradycardia" OR "sinus arrest"/exp OR "atrial arrest" OR "atrial asystole" OR "atrial standstill" OR "atrium standstill" OR "cardiac sinus arrest" OR "heart atrium arrest" OR "heart atrium standstill" OR "sinoatrial arrest" OR "sinus arrest" OR "sinus arrest, cardiac" OR "sinus node arrest" OR "sinus node dysfunction" OR "atrioventricular block") AND ("cardioneuroablation"/exp OR "autonomic denervation"/exp OR "heart denervation"/exp OR "cardiac autonomic modulation"/exp OR "ganglionated plexus ablation"/exp)

PubMed

("bradycardia"[All Fields] OR "sinus bradycardia"[All Fields] OR "heart sinus bradycardia"[All Fields] OR "nodal bradycardia"[All Fields] OR "sinus node bradycardia"[All Fields] OR "sinus arrest"[All Fields] OR "atrial arrest"[All Fields] OR "atrial asystole"[All Fields] OR "atrial standstill"[All Fields] OR "atrium standstill"[All Fields] OR "cardiac sinus arrest"[All Fields] OR "heart atrium arrest"[All Fields] OR "heart atrium standstill"[All Fields] OR "sinoatrial arrest"[All Fields] OR "sinus node arrest"[All Fields] OR "sinus node dysfunction"[All Fields] OR "atrioventricular block"[All Fields]) AND ("cardioneuroablation"[All Fields] OR "autonomic denervation"[All Fields] OR "heart denervation"[All Fields] OR "cardiac autonomic modulation"[All Fields] OR "ganglionated plexus ablation"[All Fields])

ACCSCIENCE PUBLISHING

Brain & Heart

REVIEW ARTICLE

Depression and anxiety levels in patients with hypertension and relationship with blood pressure control: A review of study design for psychiatric intervention protocol

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Abstract

Arterial hypertension, anxiety, and depression are common in Western and Eastern medicines, with each offering therapeutic instructions and proposals. Arterial hypertension has been identified as a harmful factor that causing cardiovascular diseases and increasing global mortality. Depression affects over 322 million people worldwide, with an overall incidence of 4.4%. In cases of hypertension, depression is observed in approximately 30% of patients when assessed using questionnaires and in approximately 21% when assessed psychiatrically. Anxiety and depression are risk factors for arterial hypertension. On the contrary, hypertension has been considered to cause anxiety and depressive symptoms. This could be attributed to the direct effects of high blood pressure (BP), side effects of antihypertensive drugs, or psychological reactions to the diagnosis of hypertension. An unhealthy lifestyle increases stress and BP levels. Therefore, controlling stress is a complementary therapy for hypertension. In this context, this study presents a protocol aimed at evaluating stress/depression levels as well as the quality of life in patients with hypertension and examining their correlation with BP control and target organ damage. In addition, we will assess the effect of subsequent psychiatric interventions in hypertensive patients with increased levels of depression/stress on BP control, treatment compliance, and quality of life after a follow-up period of 1 year.

Keywords: Hypertension; Depression; Anxiety; Treatment; Psychiatry

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1. Introduction to psychocardiology

In the present era, the brain is widely recognized as the organ responsible for thoughts and sentiments. The encephalon, weighing approximately 1.400 g, regulates behavior and emotions, whereas the heart, a renowned muscular pump, supplies oxygen to all cells. However, a strong connection exists between these two major human organs. In 1985, Jefferson first introduced the term psychocardiology,[1] establishing a strong bidirectional relationship. Indeed, the nervous and cardiovascular systems constantly

affect each other. An important aspect of this interaction, not only in research but also in everyday clinical practice, is arterial hypertension because it correlates with both cardiovascular functioning and nervous system reactions.

Arterial hypertension, anxiety, and depression are all common in both Western and Eastern medicines, and both approaches provide us with therapeutic instructions and proposals. Eastern medicine focuses on effectively reducing hypertension and mood disorders, to a certain point, using techniques that target brain function, skipping cardiovascular system per se. In Western medicine, in "our little world," non-pharmaceutical remedies have not been yet approved as medical therapy. What is the most important is the knowledge that reaches us through these techniques: "approaching the brain, with no drugs at all, can alter the blood pressure (BP) inside our vessels." This states strong evidence in favor of the connection between our mind and heart.

2. Psychocardiology: Connecting hypertension, anxiety, and depression

2.1. Epidemiology of arterial hypertension and depression

2.1.1. Epidemiology of arterial hypertension

Arterial hypertension has been implicated in more than 7.8 million deaths annually worldwide[2] and has been identified as a fatal factor causing cardiovascular diseases and raising global mortality.[3] In the last 50 years, the use of antidepressants has allowed us to keep the main arterial pressure relatively stable, a goal that could not be achieved in countries plagued with poverty.[4] By 2025, 1.5 million more people are expected to add to the number of patients with arterial hypertension worldwide.[5]

Poorly controlled arterial hypertension can cause or exacerbate various medical conditions, such as coronary disease, stroke, cardiac failure, and adrenal failure. These conditions adversely affect the global economy, particularly in low- and middle-income countries, where the annual cost of cardiovascular diseases is estimated to reach up to 500 billion dollars, equivalent to 2% of the gross national product between 2011 and 2025.[6]

2.1.2. Epidemiology of major depression

According to the World Health Organization, depression affects over 322 million people worldwide, with an overall incidence of 4.4%. Older people and women are more susceptible: 7.5% of women compared with 5.5% of men aged 55 – 75 years.[7] Although women are more likely to suffer from depression, men with depression are more likely to develop hypertension, probably due to an unhealthy lifestyle.[7-9] Women of reproductive age seem to have a lower risk of depression than men and postmenopausal women, highlighting the role of sex hormones in the development of depression.[10]

2.2. Epidemiologic inter-relationship between depression and hypertension

2.2.1. Frequency of depression among patients with hypertension

Monitoring depressive symptoms in patients with hypertension is essential in psychocardiology. This can be achieved using widely approved scales, particularly in research.[11] However, their value is questioned when seeking a clinical diagnosis because these scales focus on somatic symptoms, and a clinician's approach is missing.[12] Consequently, the incidence of depression in patients with hypertension might be under- or overestimated.

In 2015, Li *et al.*[13] conducted a systematic meta-analysis of 41 articles to estimate the incidence of depression in patients with hypertension, using either with self-questionnaires or clinical examinations. They concluded that the incidence of depression was higher (approximately 30%) in participants who completed the questionnaires by themselves but lower (approximately 21%) when a psychiatrist assessed their emotional status. This difference can be attributed to the known limitations of self-reported questionnaires.

2.2.2. Frequency of hypertension among patients with depression and anxiety

Similarly, in 2014, Stein *et al*. almost concurrently with the study by Lee *et al*. in South Africa investigated the possible relationship between the first episode of depression or anxiety and the first episode of hypertension.[14] They gathered data from the World Mental Health Surveys involving 19 countries and 52,095 participants and conducted survival analysis. They attempted to estimate the relationship between the first onset of hypertension and common mental illnesses considering variables such as the sex and age of the participants. According to their results, depression, panic disorder, social phobia, and specific phobias were related to hypertension, with odds ratios (OR) of 1.4 for depression and 1.7 for anxiety.

At around the same time, Sandstrom *et al*. conducted a large survey in Sweden in January 2011, investigating the same parameters.[15] Their sample consisted of 2,058,408 residents in Stockholm. They gathered data from patients with ICD 10 diagnosis (I10, hypertension) from 2009 to 2013, either as outpatients or inpatients. In addition, they included data from individuals with the following psychiatric diagnoses during the same 4-year

period: F20, schizophrenia; F30 – 31, bipolar disorder; F32 – 33, depression; and F40 – 41, anxiety disorders. They investigated the relationship between hypertension and psychopathology and concluded that patients with hypertension were more likely to suffer from anxiety and depression, particularly younger or female patients.

In Taiwan, Wu *et al.* conducted a large survey involving 23.5 million people.[16] The researchers gained access to the National Health Research Institute of Taiwan and took a random sample of 766,427 patients (both outpatients and inpatients) aged >18 years, who had been diagnosed with a depressive disorder or hypertension. Thereafter, they compared the incidence of hypertension between patients with depression and the general population. They concluded that the incidence of hypertension was higher in patients with depression (21%) than in the general population (13%).

The United States of America has actively participated in the investigation of the relationship between hypertension, depression, and anxiety. From 2017 to 2018, Shah *et al.* analyzed the National Health and Nutrition Examination Survey data.[17] All participants were asked to complete self-reported questionnaires concerning their mental and somatic health states. The researchers investigated the coexistence of depressive and anxiety symptoms with hypertension in 74,285,160 adults living in poverty. They concluded that patients taking antidepressive (OR 2.72) or antianxiety medications (OR 2.50) were more likely to suffer from hypertension. In addition, individuals who reported depressive symptoms daily (OR 2.28) or quite frequently (OR 1.88) were more likely to have hypertension.[17]

A similar study focusing on individuals living in poverty was conducted in Ethiopia in 2019.[18] Afework *et al.* enrolled 404 individuals who were randomly selected from patients visiting the Dessie Referral Hospital between February and April 2019. Finally, 384 patients agreed to participate in the study. Their mental health condition, assessed by a clinical psychiatrist, was correlated with several variables concerning their somatic health; 34.8% of individuals with hypertension also presented with an anxiety disorder, whereas 5.2% presented with depression.

2.3. Pathophysiology of hypertension–anxiety–depression connection

2.3.1. Anxiety and depression can induce hypertension

Anxiety and depression are risk factors for arterial hypertension, increasing the risk for sudden death 3 – 5 times.[19] Jackson *et al.* examined 9182 middle-aged women with depression, of which 30% were at risk of hypertension (OR 1.30) and 24% with anxiety disorder were more vulnerable to hypertension.[20]

Similarly, Meng *et al.* conducted a meta-analysis of nine studies involving 22,367 patients with depression who have been followed for nearly 10 years. They found that patients with depression had a 1.42 higher risk of developing hypertension than those without depression. Therefore, researchers proposed depression as an independent risk factor for hypertension.[21]

2.3.2. Hypertension causes anxiety and depression

Hypertension has been implicated in anxiety and depressive symptoms. This could be attributed to the direct effects of high BP, side effects of antihypertensive drugs, or psychological reactions to the diagnosis of hypertension.

In 2010, Hamer *et al.* analyzed a large sample of 33,105 adults (mean age, 51.7 years). They unveiled that individuals with hypertension who were aware of their high BP exhibited more anxiety and depression symptoms (OR 1.57) than those who ignored their high BP level (OR 0.91). They concluded that the diagnosis of hypertension can cause psychological diseases in these patients.[22]

2.3.3. Pathophysiologic mechanisms of hypertension–anxiety–depression connection

Depression was found to cause hypertension.[23] This also holds true for anxiety given that it affects the autonomous nervous system.[24] Multiple mechanisms ran through this connection (Figure 1). First, extensive genetic correlations and genetic overlaps were identified between neuropsychiatric disorders and cardiovascular disease, providing important insights into the brain–heart axis and therapeutic targets in clinical practice.[25]

Second, people with anxiety and depression live an unhealthy lifestyle. They are unlikely to work out and are more disposed toward tobacco and alcohol abuse. Moreover, patients with anxiety and depression often take medications that can result in weight gain as well as side effects such as metabolic syndrome and hypertension.

Stress negatively affects endothelium function via the sympathetic nervous system, leading to hypertension.[26] In addition, anxiety and depression hyperactivate the hypothalamus–pituitary axis, inducing the release of glucocorticoids, which increases the sensitivity of vascular smooth muscle cells to catecholamines. This mechanism further elevates BP.[27-30]

Moreover, depression is associated with a state of chronic inflammation. Inflammatory agents, such as C-reactive protein, also contribute to the development of hypertension.[31]

Finally, anxiety and depression are linked to the renin-angiotensin-aldosterone system, which also plays an important role in controlling BP. In addition,

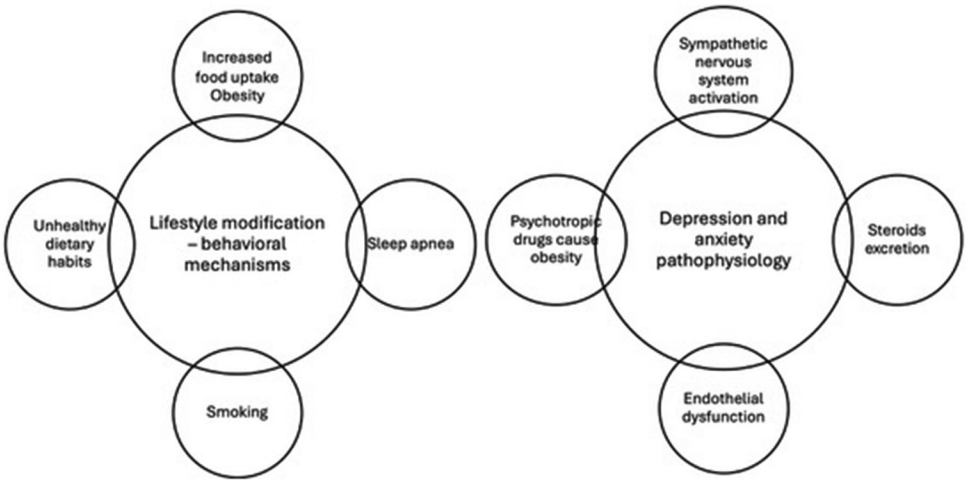

Figure 1. Pathophysiology of hypertension in patients with depression and anxiety

antihypertensive drugs were found to reduce anxiety-related and depressive symptoms in patients with hypertension.[32]

2.4. Non-pharmacological hypertension remedies: Their thesis in contemporary medicine

In everyday clinical practice, the action of antihypertensive drugs is commonly enhanced by non-pharmacological treatment.[3] An unhealthy lifestyle increases stress and BP levels.[33] Therefore, controlling stress is a complementary therapy for hypertension.[34-36] Nowadays, stress is commonly approached with mindfulness, a mental way to cope with everyday life problems. According to International Society of Hypertension, mindfulness-based stress reduction could and should be implemented in everyday life.[37,38]

2.4.1. Antihypertensive drugs and depression

Most antihypertensive drugs are implicated in the onset or worsening of depressive symptoms.[39] Pathophysiologically, catecholamines, including dopamine and norepinephrine, are the main neurotransmitters that mediate various central nervous system functions, such as motor control, cognition, emotion, memory, and endocrine modulation. Early data linking β-blockers with depression may have limited their use in patients with heart failure and depression.[39] Recent observational studies have questioned the association between β-blocker therapy and an increased risk of depression.[39-41] In particular, a recent study in Denmark reported that depressive symptoms were improved after the administration of propranolol, atenolol, bisoprolol, and carvedilol.[39]

Li *et al.* reviewed 9,557 studies involving 414,873 individuals and concluded that calcium channel blockers were positively associated with depressive symptoms (OR 1.09, 95% confidence interval [CI] 1.06 – 1.13), whereas angiotensin antagonists, beta blockers, and diuretics did not elevate the risk of depression.[42] Based on a network meta-analysis, angiotensin antagonists (OR 1.30, 95% CI 1.04 – 1.63), beta blockers (OR 1.53, 95% CI 1.22 – 1.91), and calcium channel blockers (OR 1.40, 95% CI 1.12 – 1.75) increased the risk of depression compared with diuretics.[42] Moreover, drug interaction is always an issue to consider when treating patients who receive more than one drug.

2.4.2. Antidepressant drugs and hypertension

(A) Selective serotonin reuptake inhibitors (SSRIs)

SSRIs are the first-choice treatment for individuals with anxiety and depression. Citalopram, S-citalopram, paroxetine, fluoxetine, fluvoxamine, and sertraline are inhibitors of serotonin 5-hydroxytryptamine reuptake from presynaptic transmitters, increasing serotonin concentration in the synaptic space. They also desensitize prosynaptic serotonin receptors, particularly 5-HT1A.[43]

Serotonin is transferred in the blood vessels through transporters located in the platelets, called serotonin transporters.[44] Prolonged SSRI therapy could cause a reduction in platelet count, which leads to an increase in free serotonin levels and an increase in BP.[45] SSRIs may also induce the secretion of vasopressin, which may lead to hyponatremia.[46] Finally, SSRIs affect heart rate variability and exert protective effects on people with heart diseases. Overall, SSRIs do not have substantial effects on BP and are considered a safe choice when treating people with heart diseases (Table 1).

(B) Selective serotonin and noradrenaline reuptake inhibitors (SNRIs)

SNRIs (venlafaxine and duloxetine) act on both adrenergic and serotoninergic systems, increasing dopamine

Table 1. Effect of antidepressant drug categories on blood pressure and tachycardia

Antidepressant	Hypertension	Orthostatic hypotension	Tachycardia
Selective serotonin reuptake inhibitors	0	0	0
Selective serotonin and noradrenaline reuptake inhibitors	++	+	+
Selective dopamine and noradrenaline reuptake inhibitors	++	+	+
Serotonin modulators and stimulators	0	0	0
Tricyclic and tetracyclic antidepressants	++	++	++

concentrations in the prefrontal cortex. They can raise BP,[44,47] particularly diastolic pressure,[48] by making myocardial and vascular smooth muscle cells more sensitive to adrenaline.[49] Extra precautions should be taken during the first 16 weeks of pregnancy because they may cause pre-eclampsia.[50-52] Extended-release venlafaxine raises BP in 6% of patients and increases 3 times the risk of orthostatic hypotension.[53] Duloxetine may also raise systolic and diastolic BP and heart rates.[54,55] SNRIs have been implicated in Takotsubo syndrome[54] and orthostatic hypotension.[56,57]

(C) Selective dopamine and noradrenaline reuptake inhibitors

Bupropion, apart from its use in treating depression, has also been approved by the FDA for smoking cessation because it is a non-selective antagonist of nicotine receptors of acetylcholine. Long-term treatment may also increase diastolic BP.[58,59]

(D) Serotonin modulators and stimulators

Vortioxetine and trazodone act as serotonin agonists and antagonists. Trazodone may cause orthostatic hypotension in older populations, whereas vortioxetine is considered safe.[60-62]

(E) Tricyclic and tetracyclic antidepressants

They are no longer widely used in clinical practice due to their extended side effects, including elevated systolic and diastolic BP,[44,63] orthostatic hypotension, falls,[57,64,65] arrhythmias, and cardiac failure.[66]

3. Study design of a psychiatric intervention protocol

3.1. Study design

3.1.1. Study purpose

The primary aim is to evaluate stress/depression levels and quality of life of patients with hypertension and their correlation with BP control and target organ damage.

The secondary aim is to assess the sensitivity, specificity, and positive and negative predictive values of the hospitality anxiety and depression scale (HADS) in patients with hypertension and the effect of psychiatric interventions on BP control, treatment compliance, and quality of life after a follow-up period of 1 year in patients with hypertension and high depression/stress levels.

3.1.2. Study planning

The prospective observational study will enroll 200 patients with hypertension and high depression/stress levels based on the HADS and psychiatric evaluation in the Hypertension Unit of the First Cardiology Clinic, Athens Medical School, National and Kapodistrian University of Athens. Among them, 100 will receive the usual antihypertensive treatment and lifestyle modification (standard group), whereas the remaining 100 will receive the usual antihypertensive treatment and lifestyle modification accompanied by psychiatric intervention (intervention group).

Participants will be randomized 1:1, and if patients decline psychiatric evaluation, they will be enrolled in the standard group. The characteristics of those who decline psychiatric evaluation will still be analyzed. Considering that the use of questionnaires in a hypertension unit does not necessitate further psychiatric evaluation, no ethical issues have to be addressed.

The study participants will be drawn from a pool of patients with hypertension visiting the Hypertension Unit of the First Cardiology Clinic at Hippocration Hospital. These patients have not sought psychological evaluation or treatment. Therefore, we will not mandate psychiatric treatment, even if psychiatric evaluation suggests or identifies a need for it. We will record and attempt to evaluate patients' denial and extract useful information.

3.1.3. Inclusion criteria

- Patients with hypertension aged >35 years
- Written informed consent for the use and storage of personal data
- Patients who can answer the HADS and quality-of-life questionnaires.

3.1.4. Exclusion criteria

- Age <35 years
- Inability to answer the HADS and quality-of-life questionnaires

- Dementia
- Severe valvulopathies
- Heart failure with ejection fraction <35%
- Severe systematic illness with survival prognosis of <1 year
- Cancer under treatment (radiotherapy/chemotherapy/immunotherapy)
- Established diagnosis of psychiatric disease (treated or not)
- Unwillingness to participate.

3.1.5. Follow-up duration

The follow-up duration will be 12 months. A pilot study was conducted, and preliminary data indicated an effect on BP levels within the first 3 months. Therefore, a follow-up period of 12 months is sufficient to detect significant outcomes.

3.1.6. Study population

The study population included patients with hypertension in the Hypertension Unit of the First Cardiology Clinic, Athens Medical School, National and Kapodistrian University of Athens.

3.2. Step one: Responses of the HADS and SF-36 quality-of-life questionnaire

According to HADS results, patients with hypertension will be classified into those with high and low HADS scores.

The HADS[67] was developed in 1983 by A. S. Zigmond and R. P. Snaith and is used to screen patients with depression or anxiety. It cannot be used as a diagnostic tool but only as a screening tool. The questionnaire can be answered within 5 min. It contains 14 questions (7 items on anxiety and 7 on depression). Every question has four possible answers, and each one answer is assigned a specific number (0 – 3). Scoring results are classified accordingly:

0 – 7: Normal score (no chance of depression/anxiety)
8 – 10: Marginal (average chance of depression/anxiety)
11 – 21: Abnormal (increased chance of depression/anxiety)

Subsequently, patients with hypertension and a HADS score of ≥11 will be enrolled in the second phase.

The Health Survey Questionnaire Short Form[68] was developed in 1992 by Ware to estimate the health state of inpatients. It has been used to assess the quality of life of the population. The questionnaire can be completed in 5 – 10 min. It has two forms: SF-36 and SF-12. The questionnaire aims to document patients' mental and physical conditions. It is considered a reliable instrument with Cronbach's α of >0.70. The long version consists of 36 questions, which address physical functioning and role, body pain, general health, vitality, social functioning, emotional role, and mental health.

3.3. Second phase

The second phase will enroll 200 patients with hypertension and a HADS score of ≥11.

Patients with hypertension and high HADS scores will be classified to receive the following:
- Psychiatric intervention and treatment
- Standard follow-up

Toward this process, patients will be fully informed regarding participation in the second phase.
- Patients who will decline psychiatric evaluation will be enrolled in the standard group.
- Patients who will ask for psychiatric evaluation will be enrolled in the intervention group.
- All the remaining patients will be randomized equally.

Regarding the nature of the psychiatric intervention, all patients with hypertension and high depression/stress levels based on the HADS and confirmed depression/stress post-psychiatric evaluation will be prescribed antidepressants. Moreover, they will be asked to undergo follow-up in the behavioral unit of the hypertension unit of our department to assess the possible initiation of psychotherapy.

3.4. Data collection

A specific care report form will be used for data collection, including demographic and somatometric data, medical history, laboratory results, and hypertensive target organ damage information. All patients with hypertension and high HADS scores, irrespective of randomization, will undergo electrocardiography, ambulatory BP measurement, and cardiac ultrasonography.

Specifically, the following parameters will be recorded: sex, height, weight, waist and hip circumferences, smoking status, hypertension history, diabetes mellitus, and dyslipidemia status, family history of coronary artery disease, and medical information regarding coronary artery disease, heart failure, atrial fibrillation, chronic kidney disease, peripheral arterial disease, sleep apnea, stroke, and drugs administered.

Electrocardiogram data: Sinus rhythm or atrial fibrillation, heart rate, PR, QRS, QT (QTc and QTd), Q waves, T-wave inversion, bundle branch block, and axis.

Cardiac ultrasound data: Left ventricular mass index, left ventricular end-diastolic diameter, left atrial diameter, left atrial volume index, aortic root diameter, E, E/A, Em, and E/Em.

Laboratory data: estimated glomerular filtration rate according to Cockroft or modification of diet in renal disease equation, low-density lipoprotein, high-density lipoprotein, triglyceride, total cholesterol, very low-density lipoprotein, glucose levels, uric acid, liver enzymes, whole blood count, and C-reactive protein.

Ambulatory BP measurement data: Ambulatory BP measurements will be recorded during a working day (Monday through Friday) using the automatic Spacelabs unit 90207 (Redmond, WA), set to obtain automatic heart rate and BP readings at 15-min intervals during the daytime and at 30-min intervals during the nighttime. Only recordings with at least 70% of valid readings over the 24-h period will be included in the final analysis. In accordance with current practice, daytime and nighttime will be defined using short fixed-clock time intervals, from 7 a.m. to 11 p.m. and from 11 p.m. to 7 a.m., respectively. Automatic editing will be used. The 24-h, daytime, and nighttime systolic and diastolic BP values will be the means of the respective 24-h, daytime, and nighttime recordings after artifact editing. Systolic dipping will be defined as the percentage of nocturnal systolic BP reduction relative to diurnal levels. Using specific software, subsequent parameters of short-term BP variability will be calculated: standard deviation, weighted standard deviation, average real variability, coefficient of variation, and time rates.

3.5. Follow-up

All patients with hypertension and high HADS scores, irrespective of randomization, will complete the HADS and quality-of-life questionnaires and undergo electrocardiography, ambulatory BP measurement, and cardiac ultrasonography after the 1-year follow-up (Table 2).

Table 2. Diagram of data collection at baseline and follow-up

	Baseline	Follow-up	Follow-up
Time	1 – 14 days	6 months	12 months
Informed consent	✓		
Medical history	✓		
Clinical examination	✓		
Somatometric	✓	✓	
HADS and SF-36 questionnaire	✓		✓
Electrocardiogram	✓		✓
Home blood pressure	✓	✓	
Treatment compliance	✓	✓	
Ambulatory blood pressure measurement	✓		✓
Cardiac ultrasonography	✓		✓
Laboratory examination	✓	✓	

Abbreviations: HADS: Hospitality anxiety and depression scale; SF-36 questionnaire: 36-item Short form survey instrument.

3.6. Limitations

First, the sample consisted of patients from only one hypertensive unit, and they participated in the study voluntarily. Second, not all patients will receive psychiatric interventions. Psychiatric intervention involves drugs and/or psychotherapy and is not the same for every participant due to the aforementioned ethical reasons. Moreover, a cutoff score of ≥11 on the HADS has low sensitivity for detecting clinical depression in different clinical settings.[69] When screening for major depression, a HADS cutoff score of ≥7 maximizes combined sensitivity and specificity. A cutoff value of ≥7 generates similar combined sensitivity and specificity but is less sensitive and more specific. Furthermore, unlike other self-report questionnaires, such as the patient health questionnaire, the HADS does not capture the somatic symptoms of fatigue and sleep disturbance.[70] The rationale for this – over 30 years ago – was that fatigue and insomnia may arise from physical rather than mental illness. Finally, potential confounders could affect the relationship between psychiatric intervention and hypertension outcomes. Specifically, lifestyle changes such as smoking cessation and weight loss may positively affect both diseases, whereas injuries, accidents, and socioeconomic status changes may adversely influence depression and hypertension.

4. Conclusion

Arterial hypertension, anxiety, and depression are closely related and contribute to increased global mortality. Pathophysiological analysis supports this close relationship, suggesting not only an epidemiologically proven link but also a strong etiological connection between these factors. This study presents a protocol that will initially focus on evaluating stress/depression levels and quality of life in patients with hypertension and their correlation with BP control and target organ damage. Then, this study will assess the effect of subsequent psychiatric intervention on BP control, treatment compliance, and quality of life after a follow-up period of 1 year in patients with hypertension and high depression/stress levels.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Georgia Balta, Dimitris Tsiachris
Writing – original draft: Georgia Balta, Dimitris Tsiachris
Writing – review & editing: All authors

Ethics approval and consent to participate

The study has been approved by the Institutional Review Board (IRB) of Hippokration General Hospital.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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ACCSCIENCE PUBLISHING

Brain & Heart

REVIEW ARTICLE

Post-operative intensive care unit admissions following elective craniotomy for primary brain tumor: A narrative review

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Abstract

Primary brain tumors (PBTs) refer to the growth of abnormal cells originating in the brain. These tumors account for approximately two percent of all cancers in the adult population of the United States. Patients diagnosed with glioblastoma, one of the most common malignant PBTs, often require treatments in intensive care unit (ICU). Surgical removal of PBTs through craniotomy is often the first-line treatment for many types of brain tumors. ICU admission following major surgery like craniotomy is considered a standard of care in many healthcare systems. ICU provides access to specialized equipment, such as mechanical ventilators, continuous renal replacement therapy machines, continuous electroencephalogram monitoring, and invasive hemodynamic monitoring devices, which might be essential for the care of these patients. Understanding potential complications is essential for healthcare professionals to monitor patients more effectively and guide decision-making for optimal management. Over the years, perceptions of ICU utilization have shifted, raising questions about whether ICU admission is always the right choice for patients who have undergone brain surgery. Traditional scoring systems may not always demonstrate the necessity of ICU care for patients undergoing elective craniotomy for PBTs. Further research is needed to identify the most effective strategies for optimizing patient care, determining the need for ICU care in specific cases, and minimizing costs in neurosurgery.

Keywords: Neurosurgery; Craniotomy; Primary brain tumor patients; Intensive care unit

1. Introduction

Primary brain tumors (PBTs) are neoplasms that arise from central nervous system cells.[1] They can present with a wide range of clinical symptoms caused by local invasion, compression of nearby anatomical structures, or elevated intracranial pressure.[2] Among PBT, glioblastoma represents the most common malignant neoplasm and the most frequently admitted PBT to the intensive care unit (ICU).[3] ICU admission is often required for post-operative monitoring after craniotomy.[4-6] While neurointensive care unit (NICU) enables continuous monitoring and rapid detection of neurological decline, the cost is expensive, and bed availability is limited. In addition, not all patients undergoing elective craniotomy benefit from routine post-operative ICU admission.[7,8] Selective ICU admission could address limited bed availability while reducing length of stay (LOS) and overall costs.[9] Patients requiring ICU care typically experience post-operative complications, such as acute respiratory failure necessitating advanced respiratory support to maintain adequate oxygenation.[6] Other clinical factors contributing to NICU admission include increased intracranial pressure, seizures, compromised respiratory support, hemodynamic instability, and other medical comorbidities.[10]

Given the potential impact of ICU admission on outcomes in elective craniotomies for PBT patients, it is crucial to understand the factors contributing to ICU admission and their association with outcomes. The purpose of this review is to synthesize and assess the literature on outcomes, complications, and costs associated with post-operative ICU care for PBT patients undergoing elective craniotomy. By reviewing the most updated evidence, this study provides healthcare professionals with a better understanding of the potential risks and benefits of ICU admission in this population, supporting informed decision-making for optimal management and improve patient care and outcomes.

2. Importance of elective craniotomy in treatment

The goal of this review article is to evaluate the importance of ICU admission after elective craniotomies for brain tumors by analyzing relevant studies identified through PubMed, Scopus, and Google Scholar. For many PBTs, surgical resection is often the initial treatment approach, particularly in urgent cases where decompression is warranted. However, even in elective craniotomy cases, it remains a frequently utilized primary therapeutic strategy. The goal of surgery is to remove as many tumors as possible while minimizing damage to surrounding healthy brain tissue.[10] Meanwhile, in the case of high-grade gliomas, extensive resection of surgically accessible tumors has been shown to improve survival and functional outcomes.[9-12] Despite the potential benefits, elective craniotomies are not without risks.[13-15] Their success and associated outcomes often depend on the individual patient's condition and circumstances.

In addition, elective craniotomies have the potential to benefit the healthcare system by reducing the overall cost of care. Studies have shown that elective tumor resections are associated with significantly lower costs and shorter hospital stays compared to emergent surgical procedures.[9] With the rising costs of neurosurgical care, there is a pressing need to assess cost-effective strategies while promoting high-quality patient care. Despite advances in less invasive techniques, such as stereotactic radiosurgery, radiotherapy, and chemotherapy, surgical resection remains the standard of care for most PBTs. Traditionally, ICU admission has been a routine practice for post-operative care following elective craniotomy. However, due to lack of standardization, recent studies have shown that ICU-level of care may not be necessary for all patients.[16] As a result, many hospitals have initiated non-ICU post-operative care pathways for elective craniotomy cases. This systematic review aims to synthesize and assess the existing literature on outcomes and costs associated with non-ICU post-operative care following elective craniotomy.

3. Benefits of ICU care in patients with PBTs undergoing surgery

3.1. Improved monitoring and care for post-operative complications

ICU admission plays a crucial role in managing potential complications in patients undergoing brain tumor surgery and offers various benefits. ICU admission following major surgery is considered the standard of care in many healthcare systems around the world, as it enables rapid response to serious complications.[15,16] The ICU provides access to specialized equipment such as mechanical ventilators, continuous renal replacement therapy machines, continuous electroencephalogram, and invasive hemodynamic monitoring devices, which might be essential for the care of these patients. In addition, the ICU provides close monitoring of neurological status, pain management, and sedation to ensure patient comfort and minimize discomfort. Studies have shown that ICU admission after brain tumor surgery is associated with improved outcomes, including a reduced risk of mortality, shorter hospital stays, and improved functional outcomes.[17]

Craniotomy, like all surgical procedures, carries the risk of complications that can contribute to patient mortality,

increase healthcare costs, and complicate the management of recovery. Understanding potential complications allows healthcare professionals to monitor patients more effectively and guide decision-making for optimal care. These complications have been reported in several studies, as summarized in Table 1.[11,18-24]

In patients undergoing elective craniotomy for brain tumor surgery, complications are common due to the psychological, physiological, and emotional burdens patients experience before, during, and after surgery.[18,25,26] Post-operative complications can be severe and represent important causes of morbidity and mortality following brain tumor surgery. Continuous monitoring during the first 24 h is critical for the prompt diagnosis and treatment of complications.[27,28]

Complications following elective craniotomy for PBT surgery can be neurological, hemodynamic, metabolic, or respiratory. Among these, common complications include post-operative nausea and vomiting (PONV), new motor deficits, and hemodynamic instability.[11,15,20,25-27,29,30] The risk and severity of these complications can depend on individual factors such as age and comorbidities, which may lead to worse survival rates.[31]

Neurological complications following elective craniotomy can occur frequently. Up to a third of patients, especially those with infiltrative tumors like glioblastomas may develop new motor deficits. While post-operative seizures are relatively rare, they are among the most feared complications due to their potential effects on a patient's recovery. Another serious issue is intracranial hemorrhage, with incidences varying from 0.8% to 50.0%. This is particularly common after brain tumor surgery, where acute post-operative hypertension can play a significant role in its development.[21] Despite the potential for emergency hematoma evacuation, the mortality rate remains high at around 30%, making it the leading cause of death after cranial surgery.[26] Reports on the most frequent causes of complications after craniotomy are heterogeneous in the literature. Some studies suggest that PONV are the most common complications, typically occurring within the first 24 hours after surgery.

Conversely, Decavèle *et al.*[32] reported that the most predominant complication in their population was respiratory failure, which may be associated with specific anesthetic processes. To clarify these heterogeneous findings, larger observational studies are needed.

Evidence suggests that many of these complications can be managed at the intermediate care level and, in select cases, at the ICU level. Understanding these complications may help reduce costs, shorten hospital stays, and minimize the risk of secondary infections.[33,34] To summarize, complications requiring ICU treatment mainly include acute respiratory failure, seizures, and hemorrhages. Failure to manage these complications may lead to increased mortality, which could be notably reduced if patients are transferred to the ICU from the post-anesthetic care unit (PACU).[35]

3.2. The current approach to post-operative care in elective craniotomy

Over the years, the approach to post-operative ICU care following elective craniotomy has changed in considerable ways. While articles published over the last decade have suggested the importance of close monitoring in the ICU,[36] the current approach is slowly evolving to emphasize individualized patient evaluation. This approach assesses the need for post-operative ICU care, given the absence of standardized guidelines.[7] Some studies have shown empiric protocols recommending that patients be directly transferred to the ICU to monitor for post-operative complications within 24 h of surgery, even if they are considered low risk in accordance to the American Society of Anesthesiologists Physical Status I and II. Proposed criteria for ICU admission include preoperative altered consciousness, surgical durations longer than 4 h, and intraoperative complications such as hypotension, post-operative malignant edema, severe blood loss, hemodynamic instability, and lateral surgical positioning, among others.[33,37] In addition, 30% of neurologic complications are more frequent in the post-operative than in the perioperative period.[38] Nevertheless, it is crucial to identify risk factors that may compromise patient outcomes. In some cases, patients may only require basic nursing care, signs period monitoring, and first-instance interventions based on post-surgical procedure symptoms, while others may need intensive monitoring for unexpected complications.[39]

Another crucial benefit of admitting post-craniotomy patients to the ICU allows for early detection of serious post-operative complications, facilitating timely diagnosis and treatment along with optimizing recovery.[37] However, current literature advocates that non-ICU level care may be appropriate in certain cases, especially for patients who are at risk of healthcare-associated infections (HAIs), which can be more easily contracted in the ICU.[40] In addition, ICU care beyond 4 h may not provide significant additional benefits. Patients who do not require lateral positioning during neurosurgery and those who are successfully extubated within 4 h postoperatively may meet the criteria to avoid ICU admission.[37] Figure 1 depicts the current approach to post-operative care in elective craniotomy.

Table 1. Common complications following elective craniotomy for brain tumor surgery

Authors	Types of study	Patients	Complications	Incidence (%)	Year of publication
Lonjaret *et al.*[11]	Prospective observational analytic	188	Neurologic: – New motor deficit – Dysphasia – Seizures – Deterioration of consciousness	26 (16.0) 12 6 2 10	2017
			Hemodynamic: – Bradycardia (<45 beats/min) – Arterial hypertension (MAP >110 mmHg) – Arterial hypotension (MAP <60 mmHg) – Myocardial ischemia	 15 (9.0) 5 10 1	
			Respiratory	0 (0)	
			PONV: – Early PONV (<4 h) – Late PONV (4 h)	42 (25.0) 35 12	
			Metabolic: – Hyperglycemia – Diabetes insipidus – Dysnatremia	 11 (7.0) 10 1	
			Hemorrhage	1 (1.0)	
			Hyperthermia	1 (1.0)	
			Pain	11 (7.0)	
Viken *et al.*[26]	Retrospective review	1291	Cerebral infarction	22 (1.7)	2018
			Cavity hematoma	18 (1.4)	
			Edema	5 (0.4)	
			Epileptic seizures	5 (0.4)	
			CSF-leak	5 (0.4)	
			Hydrocephalus	3 (0.2)	
			Arrhythmia	3 (0.2)	
			Other	13 (1.0)	
Franko *et al.*[19]	Retrospective observational cohort study	200	Early post-operative complications: – Neurologic deficit in eight patients – Seizures	 8 (4.0) 1 (0.5)	2018
			ICU complications: – Seizures – Symptomatic hematoma – New unexpected focal neurologic deficits – Areas of restricted diffusion suggestive of ischemia – Venous infarction – Acute respiratory failure	 6 (3.0) 2 (1.0) 3 (1.5) 4 (2.0) 1 (0 – 5) 2 (1.0)	
Gu *et al.*[20]	Retrospective analysis of a prospective study	659	Emergence delirium	131 (21.2)	2022
Decavèle *et al.*[32]	Retrospective observational cohort study	196	Acute respiratory failure	88 (45)	2017
			Seizures	49 (25)	
			Non-epileptic coma	27 (14)	
Wang *et al.*[22]	Retrospective analysis	2259	post-operative hemorrhage	40 (0.018)	2019
Huang *et al.*[22]	Retrospective analysis of a prospective cohort.	659	Post-operative delirium	124 (18)	2021
Yao *et al.*[24]	Retrospective cohort analysis	724	Post-operative strokes	98 (13.5)	2023

Abbreviations: MAP: Mean arterial pressure; PONV: Post-operative nausea and vomiting; CSF: Cerebrospinal fluid.

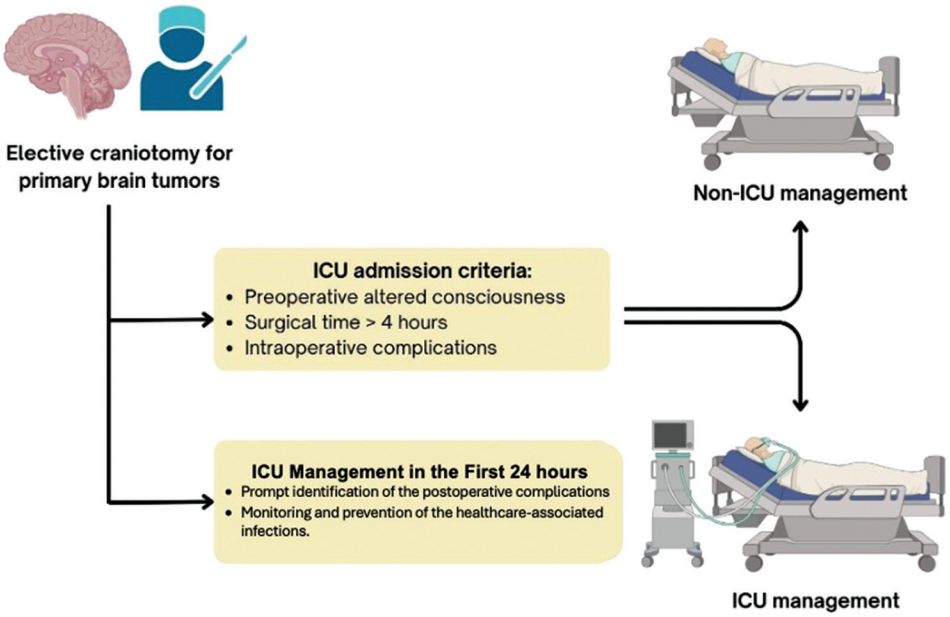

Figure 1. The current approach to post-operative care in elective craniotomy
Abbreviations: ICU: Intensive care unit.

4. Limitations and risks associated with ICU use

4.1. Financial burden and limited resources

Healthcare system costs are constantly rising.[41] Although the ICU provides highly specialized patient care that is crucial for survival in selected cases, it often represents a significant economic burden. The lack of studies examining ICU cost-effectiveness highlights the need for careful patient selection.[42,43] Craniotomies alone are associated with high healthcare costs,[41] and the addition of ICU monitoring and management postoperatively can further increase the financial burden.[44]

One effective strategy to address this challenge is an outpatient craniotomy, which has been correlated with a radical reduction in care costs when compared to inpatient craniotomy.[35] Compared to outpatient care, inpatient procedures have been shown to incur an approximately six times higher costs per unit/bed, whereas operating room, laboratory, and anesthesia expenses showed comparable cost differences across intervention settings. Accordingly, outpatient-based neurosurgical brain tumor resection emerge as a safe and reasonable treatment option for appropriately selected patients, offering substantial global cost benefits.[45-48]

4.2. Increased risk of infection and prolonged hospital stays

HAIs are a major public healthcare burden associated with more than 140,000 deaths worldwide each year, with approximately 30% of HAIs occurring in the ICU.[49] Post-operative critical care is associated with an increased risk of HAIs. Although infections in neurosurgical procedures are uncommon, certain factors can predispose patients to surgical site infections.[50] In a study of 317 patients undergoing cranial neurosurgery, the overall infection rate was 7.2%, with most infections associated with the use of extra-ventricular drainage. However, extra-ventricular drainage is usually unnecessary in elective brain tumor surgery.[51] In these cases, infections are normally caused by skin flora, most commonly *Staphylococcus*. The bone flaps created for cerebral access are avascular, making them prone to necrosis, inflammation, and post-operative infection. Preferred management includes surgical debridement and removal of the bone flap with antimicrobial therapy. While the optimal duration of antibiotic treatment is not well defined, most studies suggest a range of 6 weeks to 12 months.[37]

4.3. Potential for adverse reactions to medication and treatments

Post-operative management of patients undergoing craniotomy usually includes: (1) pain management, (2) optimization of the PONV approach, (3) early oral nutrition with gastrointestinal protection, (4) proper catheter management, and (5) early mobilization. These recommendations can be tailored to individual patient needs.[52-54] However, adverse reactions to post-operative management can affect patient prognosis and survival.

Such reactions may prolong hospital stays or necessitate close monitoring in the ICU.

About 60% of patients undergoing craniotomy report moderate to severe pain up to 48 hours after surgery.[41] A prospective study showed that despite patients reporting moderate to severe pain (≥4 on a scale of 0 – 10 in almost 70% of subjects) during the first post-operative day, patients usually received high-dose acetaminophen and minimal doses of fentanyl and opioids. It has been recommended to use the minimum effective opioid dose, not exceeding 300 μg, to prevent respiratory depression.[55] In neurosurgical ICU, opioids are the most commonly used medications for pain relief. However, their use is associated with potential side effects, including oversedation, respiratory depression, hypercapnia, increasing intracranial pressure, nausea, and vomiting. These complications can hinder neurological evaluations.[56] Overuse of opioids can lead to these adverse effects, potentially leading to sedation, respiratory depression, hypercapnia, and PONV. Increased intracranial pressure resulting from these effects may compromise neurological examination or mask acute reactions.[57] On the other hand, inadequate analgesia can lead to sympathetically mediated hypertension, which is strongly associated with an increased risk of post-operative complications, such as cerebral edema, hemorrhage, prolonged hospital stays, and a significant increase in mortality. Non-opioid analgesics have gain popularity for managing post-craniotomy pain due to their ability to avoid opioid-related adverse effects, provide effective post-operative analgesia, and decrease the incidence of complications. Dexmedetomidine is commonly used for its antinociceptive and opioid-sparing properties in patients undergoing intracranial surgery.[58] A meta-analysis of randomized clinical trials involving 11,997 patients found that dexmedetomidine use in mechanically ventilated adults was correlated with a lower risk of delirium, shorter mechanical ventilation duration, and reduced ICU stays. However, dexmedetomidine use is also associated with a higher risk of bradycardia and hypotension.[38] It is important to highlight that bradycardia may be misinterpreted as a Cushing reflex (bradycardia and hypertension associated with intracranial hypertension). When compared with the placebo group, significant bradycardia has been observed in a small percentage of the patient group, necessitating discontinuation of post-operative dexmedetomidine.[39] In addition, remifentanil use appears beneficial for post-craniotomy patients, further trials are needed to confirm these initial positive results.[40,41] In terms of specific side effects of PONV therapy, the evidence for the best and most reliable antiemetic drugs shows low to very low side effects. Exceptions include ondansetron, which may increase headaches and reduce sedation compared to placebo, though this effect is limited to doses higher than the recommended amount. Droperidol is likely to reduce headaches compared to placebo. There is high-certainty evidence that dexamethasone does not affect sedation compared to placebo. However, there are studies that suggest it may be a potential risk factor for developing meningitis after craniotomy.[55-57] Early removal of the urethral catheter within 24 h, according to the Enhanced Recovery After Surgery (ERAS) protocol leads to a lower infection rate compared to the conventional protocol, with no significant evidence of compromise in this technique.[58] Finally, early mobilization of these patients establishes daily activity goal, such as moving correctly in bed within 6 h after surgery and getting out of bed within 24 h (or as soon as possible). This approach is associated with shorter hospital stays and reduced healthcare costs. However, studies on patients who experienced early mobilization after a cerebral infarction have shown adverse effects, such as falls, hemorrhage, or another cerebral infarction. Further studies with a greater impact are needed to confirm whether the benefits of early mobilization within the ERAS protocol outweigh any negative repercussions.[59] However, even though these good practices promote good recovery for neurosurgical patients, particularly those with primary central nervous system tumors, post-operative adverse effects remain challenging to avoid. These effects may arise due to the complexity of the surgical approach, the patient's biological and emotional responses, or the specifics of the operative technique. The required response to post-operative management will depend on the protocol used for post-craniotomy care).

5. Clinical evidence on the use of ICU in PBT patients

5.1. Previous studies and findings

The rationale for ICU admission following craniotomy for PBT remains a topic of ongoing debate. Clinical evidence supporting ICU use in PBT patients is limited. The standard protocol for patients undergoing elective craniotomy includes admission to the ICU for the first 24 h post-surgery. This approach aims to detect serious early post-operative complications, mainly associated with the underlying disease or the sequelae of surgical and anesthesia techniques, facilitating prompt intervention and optimizing recovery.[60,61] Recent advancements in surgical techniques and technology have made it possible for some patients to experience shorter hospital stays or same-day discharge.[62] However, in this context, it is important to explore available evidence to optimize patient management and ensure the best possible outcomes. One study analyzed 514 patients scheduled for same-day discharge,[49] achieving

a successful rate of 92%. Only 11 patients were readmitted, and none suffered any long-term morbidity attributable to early discharge.[60-62] Of the 41 patients (8%) who failed to be discharged, the main reasons were new neurological deficits postoperatively, followed by seizures.[49] Another study reported similar findings, with an 88.4% successful discharge rate.[50] These findings suggest that same-day discharge may be a viable option for selected patients, but careful patient selection is necessary to minimize the risk of adverse outcomes. Future studies should investigate the optimal selection criteria and the long-term outcomes of same-day discharge.[51]

Several studies have examined the safety and efficacy of lower acuity settings for patients after elective craniotomy. In one study, the risk of complications was evaluated in patients transferred from the PACU to the neurosurgery ward after a brief PACU stay. Only 4 patients (1.1%) developed complications requiring transfer to the ICU, none of whom died or suffered lasting disability.[63] Another study also reported that non-ICU care was safe for these patients, with a shorter mean LOS compared to those admitted to the ICU (3 vs. 7 days).[53] However, further research is needed to determine appropriate patient selection criteria for non-ICU care and to assess long-term outcomes. A study focused on enhanced recovery after elective craniotomy, using the ERAS protocol highlighted the significant advantages of this interdisciplinary approach over standard perioperative care. For patients undergoing craniotomies, the ERAS protocol was linked to a considerable decrease in LOS, hospital expenses, and post-operative complications.[63] It is important to note that a study provides valuable insights into the safety and outcomes of post-operative admission to a regular step-down unit after elective craniotomy, with a shorter LOS (7.0 days vs. 9.9 days). However, the study is limited by the fact that not all the patients in the cohort had PBTs.[52] The study included patients with a range of indications for craniotomy, including traumatic brain injury, vascular malformations, and ventriculostomies. As such, the generalizability of the findings to patients undergoing craniotomy specifically for PBTs may be limited. Future studies focused specifically on this population are necessary to further evaluate the safety and efficacy of lower acuity care management. The cost of care is another major concern for many healthcare centers. For example, the cost differential between the NICU and the neurotransitional care unit can be up to $1,500 per day.[53] To analyze these variables, a previous cohort study compared patients who underwent craniotomy for supratentorial tumors 1 year after the introduction of a "no ICU, unless…" policy with those from the year before. The study found that the LOS in the hospital was similar between patients admitted to the ICU/MCU and those in the regular care neurosurgical ward. Complications significantly reduced after implementing the new policy, with an incidence of 0.98 in cohort A (before the new policy) and 0.53 in cohort B (after the new policy). Although the mean total LOS was one day shorter in cohort B, the difference was not statistically significant. The average total cost per admission for cohorts A and B was €13,607 and €11,654, respectively. These costs included surgery, hospital or ICU stays, lab fees, imaging, and consultations.[27] However, cost should not be the sole justification for lower acuity care management after elective craniotomy. Patient safety and medical considerations, such as the risks of side effects, recovery times, and impact on quality of life, should also be considered. Another study described the immediate transfer to the floor resulted in a three-day reduction in average hospitalization length and provided cost savings without compromising patient outcomes. Nevertheless, cost should not be the sole determining factor, and other medical considerations must be prioritized. Further research is needed to identify the most effective strategies for optimizing patient care while minimizing costs in neurosurgery.

6. Evidence against the routine use of ICU in this patient population

The patient population described here is the population undergoing elective craniotomy for PBT resection. Many care centers admit these surgical patients to the ICU post-surgery, primarily to enable quicker diagnosis of complications and prompt treatment.[64] A study reported that only 15% of patients required prolonged ICU admission (more than one-day post-surgery) after craniotomy for brain tumor resection. This portion of the patient population did not benefit from routine ICU care and could have been transferred to the post-operative neurosurgical floor for routine care instead.[65,66] Another study, aligning with these findings, reported that only 16% of the patients required ICU services in the post-surgical period. The author emphasized that the risk assessment and ICU admission policies following brain tumor surgery should be based on objective, evidence-based measures rather than personal preferences or requests.[67] In a study of 343 patients undergoing elective craniotomy, 43 planned and eight unplanned ICU admissions were recorded, which makes a total of 51 patients (14%). These findings support the argument against routine ICU admission following elective craniotomy.[38]

The existing scoring systems are not suitable for most settings. Researchers claim that risk assessment

and ICU admission policies following brain tumor surgery should be based on objective, with evidence-based measures.

7. Conclusion

7.1. Summary of the benefits and limitations of ICU use

Admission to the ICU plays an important role in managing potential complications post-surgery for patients undergoing elective brain tumor surgery and offers various benefits. ICU admission following major surgery is considered a standard of care in many healthcare systems around the world, aimed at preventing serious and life-threatening complications. Patients with PBTs who undergo elective craniotomy are at risk of complications such as brain swelling, bleeding, infection, and neurological deficits. The ICU is often used to monitor and manage these patients in the immediate post-operative period, with the goal of preventing or treating these complications. Some studies have shown that specific ICU interventions, such as intracranial pressure monitoring and cerebrospinal fluid drainage, are associated with improved outcomes in this population. The ICU provides early detection and prompt treatment of any increase in intracranial pressure and other complications to prevent further harm. ICU admission after brain tumor surgery has been associated with improved outcomes, including a reduced risk of mortality, shortened hospital stays, and improved functional outcomes. Understanding the early and efficient detection of potential complications can help healthcare professionals to monitor patients more effectively and guide decision-making for optimal care. Post-operative complications can be severe and represent important causes of morbidity and mortality following brain tumor surgery. Continuous monitoring in the first 24 h is critical for prompt diagnosis and treatment. However, the need for ICU admission depends on many individual factors, which has led to growing debate regarding the routine use of the ICU. Some studies suggest that ICU care may not be necessary for all patients with PBTs postoperatively and that a more selective approach may be appropriate. Factors such as the patient's age, comorbidities, and the specific type and location of the tumor may influence the decision for ICU care. While ICUs provide critical care for patients with life-threatening conditions, they come with high costs. HAIs are another major problem associated with ICU stays. Prevalence surveys in the United States (US) suggest that 30% of HAIs occur in ICUs. Despite the advantages of ICU monitoring, very few patients develop adverse reactions to post-operative management that could affect the prognosis or survival, which would require prolonged hospital stays or close monitoring in the ICU.

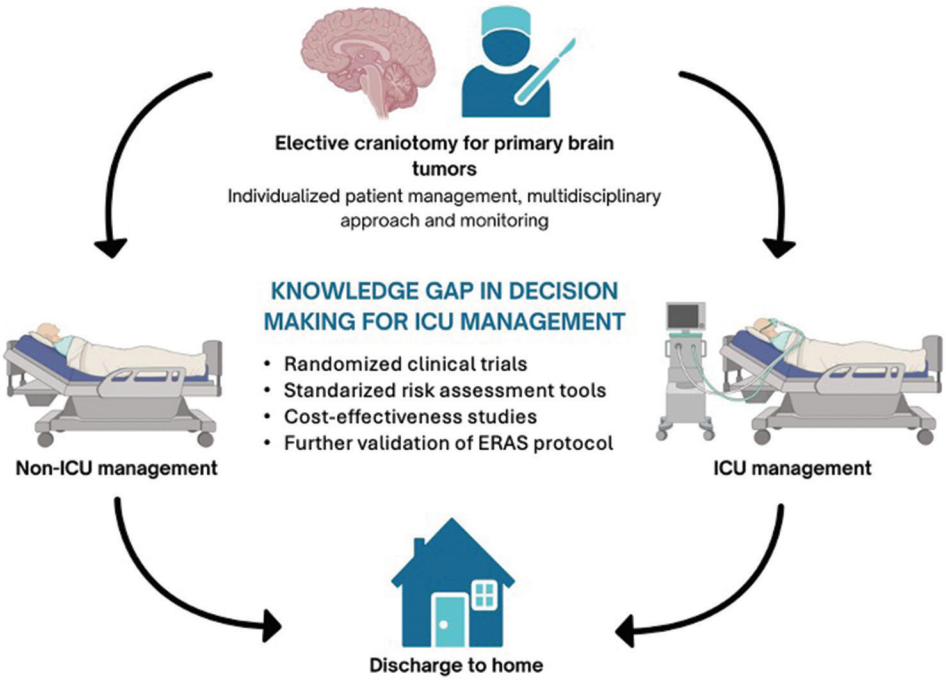

Figure 2. Pictorial representation of the knowledge gap in determining whether a patient requires ICU or non-ICU management after elective craniotomy for a primary brain tumor
Abbreviations: ICU: Intensive care unit; ERAS: Enhanced recovery after surgery.

7.2. The need for further research and improvement in ICU management

In conclusion, it is widely accepted that the ICU management is an important approach to managing post-operative patients with PBTs and is associated with improved outcomes. However, the decision to admit a patient to the ICU should be made on a case-by-case basis, considering the patient's individual characteristics and the specific type of tumor. Many studies suggest that non-ICU care is safe for this patient population, with a mean LOS shorter than for those admitted to the ICU. However, none of these studies provide a definitive conclusion on the matter. Traditional scoring systems may not be sufficient to determine the need for ICU admission following elective craniotomy for a PBT.

Further research is needed to identify the most effective strategies for optimizing patient care, determining the need for ICU care after surgery in specific patients, and discovering ways to minimize costs in neurosurgery. Figure 2 represents the knowledge gap and the area requiring further research to determine whether patients require ICU or non-ICU management after surgery.

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Multimodal computed tomography-guided mechanical thrombectomy for large vessel occlusion stroke after cardiac surgery

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Abstract

Post-operative large vessel occlusion (LVO) stroke is one of the most severe complications associated with cardiac surgery. Mechanical thrombectomy (MT) is the first-line treatment for LVO stroke. In this paper, we present cases of patients who underwent MT guided by multimodal computed tomography (CT) to treat LVO stroke after cardiac surgery at our institution to clarify the impact of MT on patient outcomes. We analyzed the in-hospital stroke database from July 1, 2023, to June 30, 2024, to identify patients who had undergone MT to treat LVO stroke after cardiac surgery in our institution. Demographic data, stroke severity, type of operation, imaging features, and 90-day modified Rankin scale (mRS) scores were assessed. Of the 21 patients receiving endovascular therapy, we included nine (42.9%) who had undergone multimodal CT-guided MT after cardiac surgery. The operations varied and comprised four coronary artery bypass grafts, four surgical valve replacements, and one extended Morrow myectomy. The median time from post-surgery to the onset of stroke symptoms was 4 days (interquartile range [IQR]: 2.5 – 5 days), the median National Institutes of Health Stroke Scale score was 16 (IQR: 15 – 18), and the median time between the onset of symptoms and recanalization was 320 min (IQR: 270 – 465 min). One patient died of severe cerebral hemorrhage, while eight patients survived and were discharged to another hospital (n = 1), a rehabilitation facility (n = 3), or home (n = 4). The median 3-month mRS was 2 (IQR: 0.5 – 3). In summary, multimodal CT-guided MT can improve the prognosis of patients with LVO stroke, although severe neurological deficits and mortality were observed in some patients. A larger sample size is required to clarify the effects of MT.

Keywords: Cardiac surgery; Large vessel occlusion; Acute ischemic stroke; Mechanical thrombectomy; Multimodal CT

1. Introduction

Post-operative stroke is a serious complication of cardiac surgery, with an estimated prevalence of 1 – 7.4%,[1] and is associated with a hospital mortality rate of 3.0 – 38%, depending on the type of surgery.[2] Ischemic stroke due to embolism is the most common

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form of post-operative stroke; however, hemorrhagic stroke due to antithrombotic drugs may also occur.[3] Post-operative stroke may be fatal when it involves large vessel occlusion (LVO).

Chen *et al.*[2] conducted a retrospective, nationwide, population-based study of patients with stroke after coronary and valve surgery and found that all patients who received surgical treatment for ischemic stroke underwent decompressive craniectomy. The outcome was unsatisfactory, with an in-hospital mortality rate of 12.5% and 1-year mortality rate of 50%. Intravenous thrombolysis (IVT) is usually contraindicated in these situations because of the risk of bleeding associated with recent surgery. Furthermore, IVT may be less effective in patients with proximal occlusions of the major intracranial arteries.[4] Therefore, other treatments are urgently needed to preserve neurological function in this population.

Recently, mechanical thrombectomy (MT) has been proven to be effective in improving the outcomes of patients with acute ischemic stroke (AIS) caused by LVO within the anterior circulation.[5] Successful MT may effectively decrease the post-operative morbidity and mortality of stroke post-cardiac surgery.[6] While MT presents a potentially life-saving intervention, there are limited reports regarding the prognosis of patients with LVO stroke after cardiac surgery. In particular, patient outcomes remain to be explored based on current treatment options guided by multimodal computed tomography (CT) imaging (including non-contrast CT [NCCT], CT angiography [CTA], and CT perfusion [CTP]).

In this paper, we present cases of patients from our institution who underwent MT guided by multimodal CT to treat LVO stroke after cardiac surgery.

2. Methods

We reviewed data of consecutive patients who underwent MT for acute LVO stroke from a prospectively collected database between July 2023 and June 2024 at Fuwai Hospital, Chinese Academy of Medical Sciences. Ethics approval was obtained from the Fuwai Hospital, Chinese Academy of Medical Sciences (Reference Number: 2022-1848).

The inclusion criteria of this study are as follows: (i) Aged ≥18 years; (ii) having been treated with cardiac surgery; (iii) diagnosed with AIS due to LVO within the anterior circulation; and (iv) with known prognosis after MT. The exclusion criteria include: (i) A pre-modified Rankin scale (mRS) scores ≥3; (ii) an onset National Institutes of Health Stroke Scale score (NIHSS) ≤5; and (iii) incomplete data. Figure 1 shows a flow chart of the patient selection process.

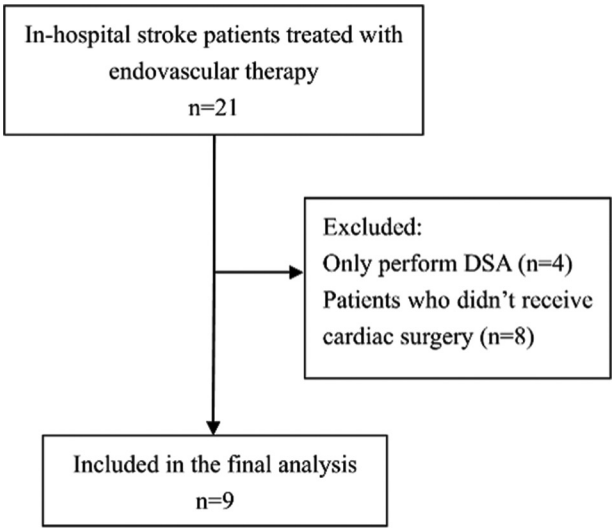

Figure 1. Flow chart of the patient selection process
Abbreviation: DSA: Digital subtraction angiography.

2.1. Imaging protocol

A CT scanner (Revolution™ CT; GE Healthcare, Chicago, IL, US) was used to obtain head and neck CTA and CTP data. A tube current of 100 mAs, a tube voltage of 80 kVp, a gantry rotation time of 1 s, and coverage along the z-axis of 160 mm were set for CTP acquisition. Forty milliliters of iodinated contrast material (Ioversol, 350 mg/mL) was injected at a rate of 6 mL/s through the antecubital vein. Scanning was started 5 s after flushing with 40 mL of saline at 6 mL/s. The dynamic perfusion scan consisted of 32 slices of images, each 5-mm thick.

The CTA image was collected using an automatically modulated tube current within a range of 260 – 370 mAs, a tube voltage of 100 kVp, and a matrix of 512×512 from the aortic arch to the calva. Scanning was started 4 s after the monitoring region of the aorta triggered a threshold of 120 HU. The CTA scan had a slice thickness of 0.625 mm.

CTP data from all patients were post-processed using PerfusionGo software (PerfusionGo, V2.4; Digital Kun Technology Co. Ltd., Beijing, China).[7]

2.2. Interventional procedure

Interventional procedures were performed under local groin anesthesia. Endotracheal intubation or extreme agitation were considered when administering general anesthesia. Access was achieved using an 8F sheath. Aspiration-based thrombectomy with or without stents were allowed, according to the choice of the operator. The thrombectomy procedure has been described elsewhere.[8,9] The expanded thrombolysis in cerebral infarction (eTICI) grades were assessed at the completion of revascularization.[10] eTICI ≥2b50 was considered as successful recanalization of the

occluded vessel. All patients were followed up for 90 days from the time of receiving MT. Patients underwent evaluation of neurological and/or functional status at onset and at 24 h and 90 days after MT.

2.3. Data collection

Patient information was obtained from medical records. The data included demographic characteristics, comorbidities, clinical data (cardiac surgery, atrial fibrillation [AF], and NIHSS score at stroke onset and 24 h after MT), imaging data (occlusion site and penumbra volume), degree of recanalization, time of onset to recanalization or final angiography, stroke etiology, and outcome data (90-day mRS score). The mRS score is a tool for assessing the degree of disability in patients with stroke, ranging from 0 to 6, with 0 indicating no symptoms and 6 indicating death.[11] Detailed information is presented in Table 1.

2.4. Statistical analysis

Continuous data are presented as mean ± standard deviation for normally distributed data, and median (interquartile range) for those with skewed distribution. Data of categorical variables are presented as frequencies and percentages. Considering the small sample size, descriptive statistics were used. Data were analyzed using IBM SPSS Version 23.0 software (IBM Corporation, Armonk, NY, USA).[12]

3. Results

Of these 21 patients, four were excluded because they had only undergone digital subtraction angiography (DSA) and eight were excluded because they did not undergo cardiac surgery. Finally, nine patients were included in the analysis and all of them had completed pre-operative multimodal CT examination (Figure 1). The operations varied and comprised four coronary artery bypass grafts, four surgical valve replacements, and one extended Morrow myectomy. The median time from post-surgery to the onset of stroke symptoms was 4 days (interquartile range [IQR]: 2.5 – 5 days), the median National Institutes of Health Stroke Scale score was 16 (IQR: 15 – 18), and the median time between the onset of symptoms and recanalization was 320 min (IQR: 270 – 465 min). One patient died of severe cerebral hemorrhage, while eight patients survived and were discharged to another hospital (n = 1), a rehabilitation facility (n = 3), or home (n = 4). The median 3-month mRS was 2 (IQR: 0.5 – 3). Detailed information can be seen in Table 1.

3.1. Case 1

A 66-year-old woman with dyspnea after exertion was admitted to our hospital. Cardiac ultrasonography

Table 1. Summary of case series

Case	Sex	Age	Surgery	Time from surgery to stroke (days)	Preoperative AF	Post-operative AF	DM	EF <50% after cardiac surgery	NIHSS at stroke onset	Vessel occluded	Time from LKW to recanalization (min)	Core infarct volume	Mismatch volume (mL)	Final score on eTICI	24-h NIHSS	90-day mRS
1	F	66	Valve surgery	5	No	Yes	No	No	16	L-ICA terminal	350	41.3	90.4	1	40	6
2	F	65	CABG	4	No	No	No	No	16	L-MCA	310	1.9	215.8	3	6	1
3	M	50	Valve surgery	4	No	Yes	Yes	Yes	14	R-MCA	320	188.5	63	3	8	0
4	F	50	Valve surgery	10	Yes	Yes	No	Yes	12	R-ICA terminal	390	1.8	188.9	2a	11	3
5	F	58	Valve surgery	3	No	No	No	No	16	L-MCA	230	100.6	61.5	2C	15	2
6	M	53	CABG	0	No	No	No	No	16	L-ACA+L-MCA	990	91.1	7.1	3	16	3
7	M	69	CABG	5	No	No	No	No	18	L-ICA	300	0	292.2	2C	15	2
8	M	42	Extended morrow myectomy	2	No	No	No	No	18	L-MCA	540	3.5	64.3	2b67	17	2
9	M	69	CABG	5	No	Yes	Yes	Yes	18	L-ICA terminal	240	7	211.6	3	2	0

Note: All strokes are caused by cardioembolism.

Abbreviations: ACA: Anterior cerebral artery; AF: Atrial fibrillation; CABG: Coronary artery bypass grafting; DM: Diabetes mellitus; EF: Ejection fraction; eTICI: Expanded thrombolysis in cerebral infarction; ICA: Internal carotid artery; L: Left; LKW: Last known well; MCA: Middle cerebral artery; mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; R: Right.

revealed a mitral valve prolapse with massive mitral regurgitation. The ejection fraction was normal. The patient underwent mechanical mitral valve replacement and tricuspid valvuloplasty. Five days after valve surgery, she experienced right hemiparesis, with an initial NIHSS score of 16. CTA revealed a left internal carotid artery (ICA) terminal occlusion (Figure 2A). The CTP image showed several salvageable penumbrae (Figure 2B and C). DSA confirmed the occlusion of the left ICA terminal (Figure 2D). Unfortunately, the perforator from the middle cerebral artery (MCA) ruptured after both aspiration and stentriever placement (Figure 2E and F). CT revealed severe cerebral hemorrhage on the left side (Figure 2G). The patient died on day 1 post-MT of brain herniation.

3.2. Case 2

A 65-year-old woman with triple-vessel disease was admitted for a coronary artery bypass graft (CABG). Within the 4 days post-CABG, she had right limb weakness and aphasia (NIHSS 16) at 40 min post-last known well (LKW) time. CTA showed left M1 occlusion (Figure 3A). The penumbra map showed favorable imaging characteristics, with a predicted irreversible brain ischemia volume (cerebral blood volume <30%) of 1.9 mL and a total ischemic brain tissue volume (Tmax >6 s) of 217.7 mL (Figure 3B). The times from LKW to groin puncture were 3 h and 40 min. DSA confirmed left MCA occlusion (Figure 3C and D). After one pass using the Solumbra technique, the thrombus was removed (Figure 3E) and eTICI 3 reperfusion was achieved (Figure 3F and G). The NIHSS score at 24 h had improved to 6. The patient was discharged, and her mRS score at 3 months was 1.

3.3. Case 3

A 50-year-old man with valvular disease underwent mitral valve replacement and tricuspid valvuloplasty. The patient developed new-onset atrial onset atrial fibrillation (AF) after surgery and received anticoagulation therapy. After 4 days in the general ward, the patient exhibited right MCA syndrome, with an NIHSS score of 14. The time from LKW administration to symptom onset was 1 h. Following the activation of the stroke service, CTA and CTP demonstrated a right ICA and MCA cutoff (Figure 4A) and a small mismatch area (Figure 4B and C). The time from LKW to recanalization was 5 h 20 min. Intraoperative DSA revealed occlusion of the right MCA; however, the ICA was patent (Figure 4D and E). The thrombus was completely removed after both aspiration and stentriever placement (Figure 4F). Recanalization of eTICI 3 was achieved (Figure 4G and H). The NIHSS score at 24 h improved to 8. A 10-day magnetic resonance imaging (MRI) of the head revealed the right insula, temporal lobe, and basal ganglia infarctions (Figure 4I). The patient was discharged 2 weeks after thrombectomy. The mean mRS score at 90 days was 0.

4. Discussion

Stroke following cardiac surgery is associated with high mortality and morbidity rates. Our consecutive case series

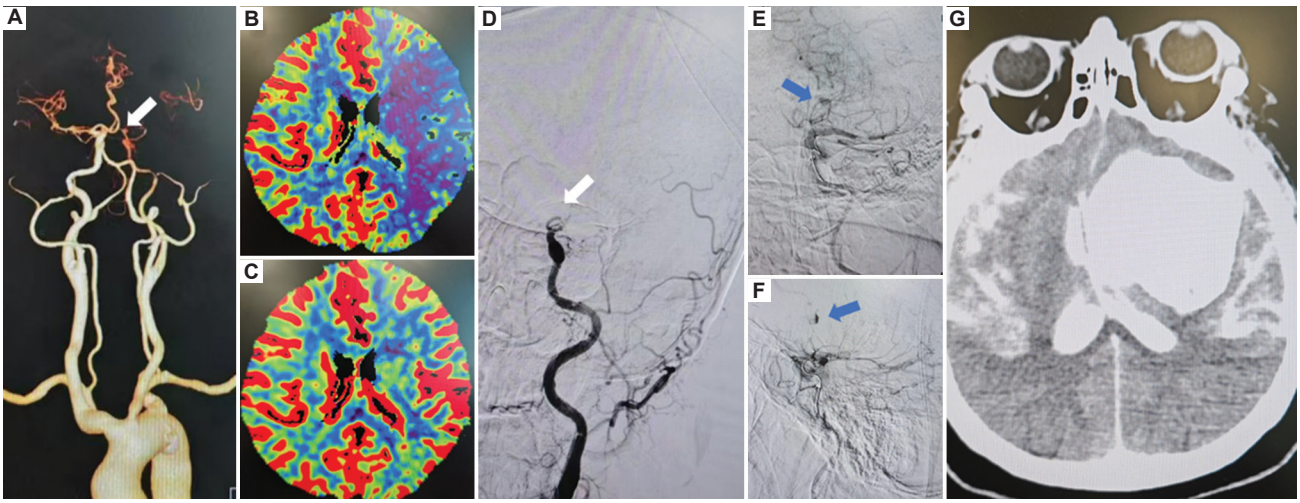

Figure 2. Images of case 1. (A) CT angiography with a left ICA terminal cutoff and reasonable collaterals. The white arrow indicates the occlusion site. (B) Cerebral blood flow image showing left hemisphere hypoperfusion. (C) Cerebral blood volume image showing that both cerebral hemispheres are equivalent. (D) Initial angiogram confirming right ICA terminal occlusion. The white arrow indicates the occlusion site. (E and F) Anteroposterior and lateral images showing contrast agent extravasation during MT, indicating cerebral hemorrhage. The blue arrows indicate contrast agent extravasation. (G) Immediate CT scan showing a large area of cerebral hemorrhage in the left cerebral hemisphere.
Abbreviations: CT: Computed tomography; ICA: Internal carotid artery.

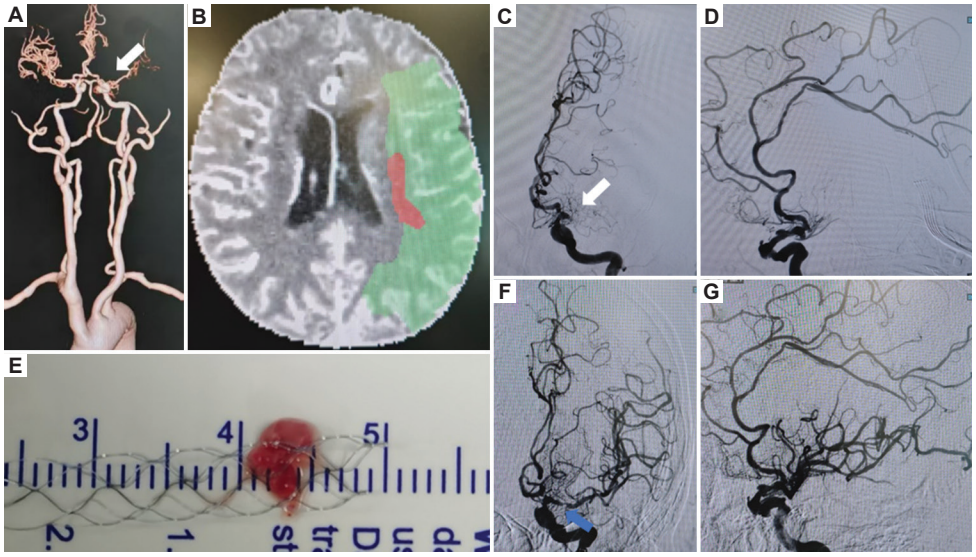

Figure 3. Images of case 2. (A) CT angiography with a left MCA cutoff and reasonable collaterals. The white arrow indicates the occlusion site. (B) Penumbra map demonstrates many salvageable penumbras (irreversible brain ischemic volume of 1.9 mL and mismatch volume of 215.8 mL). (C and D) Anteroposterior and lateral angiograms confirm left MCA occlusion. The white arrow indicates the occlusion site. (E) The thrombus is removed using the Solitaire stent retriever. (F and G) Anteroposterior and lateral images showing eTICI 3 reperfusion after one pass. The blue arrow indicates a mild residual stenosis of the left MCA.
Abbreviations: CT: Computed tomography; MCA: Middle cerebral artery.

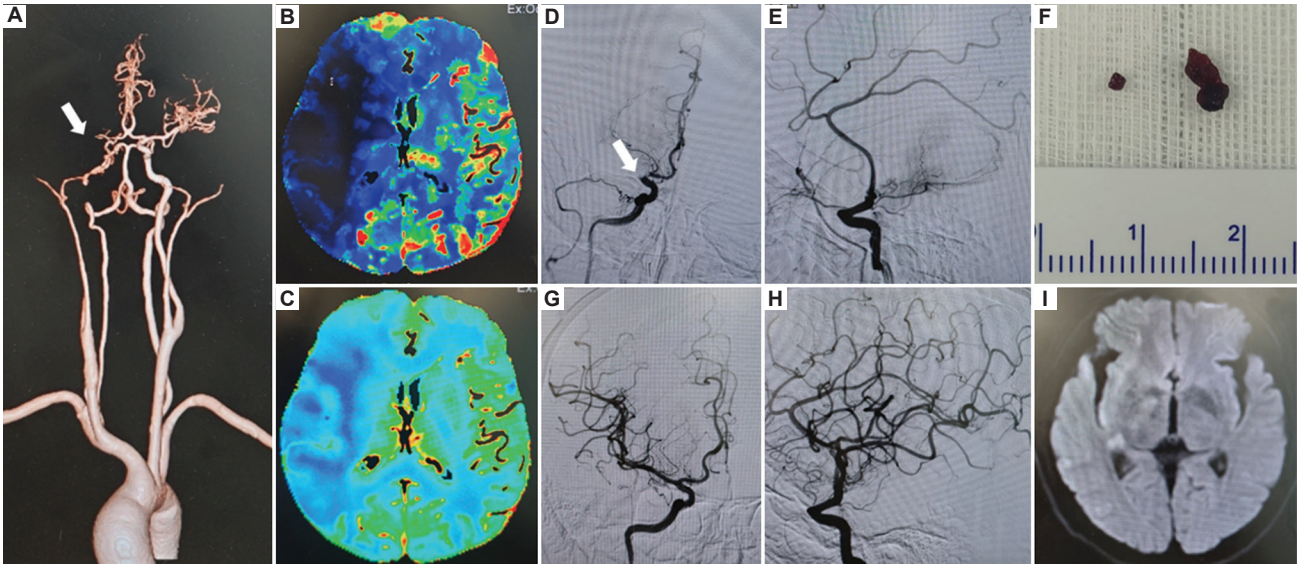

Figure 4. Images of case 3. (A) CT angiography with right ICA and MCA occlusion. The white arrow indicates the occlusion site. (B) Cerebral blood flow image showing hypoperfusion in the right hemisphere. (C) Image showing decreased cerebral blood volume in the right hemisphere, indicating a large infarct core. (D and E) Anteroposterior and lateral angiograms demonstrating right proximal MCA occlusion. The white arrow indicates the occlusion site. (F) The thrombus is completely removed. (G and H) Anteroposterior and lateral images showing eTICI 3 reperfusion after both aspiration and stentriever attempts. (I) MRI diffusion-weighted imaging showing a high signal in the right insula, temporal lobe, and basal ganglia.
Abbreviations: CT: Computed tomography; ICA: Internal carotid artery; MCA: Middle cerebral artery; MRI: Magnetic resonance imaging.

demonstrated that MT is safe and effective in patients with LVO stroke after cardiac surgery. The proportion of favorable outcomes (mRS score ≤2 at 90 days) reached 66.7% (6/9), which is higher than the current reported level of 50%.[13,14] To our knowledge, patients following cardiac surgery have not been included in sentinel LVO stroke studies. Our prospective study provided evidence regarding the efficacy of MT in this unique subgroup. This may help promote the use of this technology among these patients. To the best of our knowledge, this is the second largest sample size

among similar studies reported in the literature, and the study confirms the efficacy of thrombectomy to a certain extent.[1,15-20] Detailed information is presented in Table 2.

Patients who underwent thrombectomy were evaluated using multimodal CT, which is central to AIS diagnosis and treatment.[21] Non-contrast CT imaging is beneficial for the selection of patients for all acute stroke therapies. In addition to ruling out intracranial hemorrhage, the extent of early ischemic injury can also be estimated. CTA can be used to evaluate extracranial and intracranial vessels, as well as collateral grading. Extracranial CTA can provide information about potential proximal embolic sources, such as atherosclerotic lesions, arterial dissection, and thrombi from the aortic arch. Furthermore, intracranial CTA can confirm the diagnosis of AIS. CTA can also help qualitatively assess the patient's collateral circulation, which is an indicator closely related to prognosis.[22] CTP maps qualitatively demonstrate the core infarction and salvageable penumbra area. This useful tool has been used in both late-window MT trials and was incorporated into the recent guidelines.[23] Based on the metrics of CTP, an absence of mismatch cerebral blood flow and Tmax would indicate that treatment is unlikely to benefit the patient. Tmax >6s is considered a low perfusion area, while cerebral blood flow <30% relative to the contralateral side is considered the infarct core. The subtraction of the two areas is the penumbra. This key information provided by CTP can help screen the population that will benefit from MT treatment.[24]

Uncomplicated cardiac surgery, such as CABG, has a post-operative cerebral infarction risk of 1 – 3%, but for some complex surgeries, such as multi-valve replacement and aortic arch repair, the probability can be increased to 5 – 10%.[25-27] Chen *et al.*[2] summarized the significant risk factors for post-operative stroke as follows: advanced age, female sex, peripheral disease, previous stroke, and atrial fibrillation. Sheriff *et al.*[19] found that prolonged aortic cross-clamp time (odds ratio [OR]: 1.012 for every minute of prolonged aortic cross-clamp time; confidence interval [CI]: 1.001 – 1.023) and cardiac bypass time (OR: 1.012 for every minute of prolonged cardiac bypass time; CI: 1.003 – 1.021) are associated with LVO stroke. In our series, three patients had new-onset AF after surgery and

Table 2. Characteristics of similar works from literature about patients who underwent thrombectomy following cardiac surgery

Author, publication year	Country	Male (%)	Included patients	Recruitment period	Surgery	eTICI 2b50 and above (%)	Good outcome (%)
Feng *et al.* (this article)	China	5 (55.6)	9	July 2023 to June 2024	Valve surgery: 4 CABG: 4 Morrow: 1	7 (77.8)	6 (66.7)
Bay *et al.*, 2023[18]	Germany	5 (45.5)	11	June 2015 to December 2020	CABG: 3 CABG with valve surgery: 2 Valve surgery: 4 Aortic arch surgery: 2	7 (63.6)	2 (18.2)
Gupta *et al.*, 2022[15]	Australia	5 (71.4)	7	January 2016–October 2021	CABG: 2 Valve surgery: 4 CABG with valve surgery: 1	4 (57.1)	3 (42.9)
Wilkinson *et al.*, 2021[16]	America	4 (66.7)	6	2014 to 2017	CABG: 3 Valve surgery with arch replacement: 1 Maze surgery: 1 Maze with valve surgery: 1	NA	4 (66.7)
Sheriff *et al.*, 2019[19]	America	NA	3	July 2013 to April 2018	Left ventricular assist device placement: 1 Valve surgery with arch repair: 1 Valve surgery with maze procedure: 1	2 (66.7)	2 (66.7)
Haider *et al.*, 2017[17]	America	1 (50)	2	NA	CABG: 1 Left ventricular assist device implantation: 1	2 (100)	2 (100)
Thomas *et al.*, 2017[20]	America	0	1	NA	Valve surgery	1 (100)	1 (100)
Madeira *et al.*, 2016[1]	Portugal	0	3	NA	CABG: 1 Blalock–Taussig shunt and atrial septostomy: 1 Supracoronary aorta interposition grafting: 1	3 (100)	2 (66.7)

Note: A good outcome is defined as a patient with a mRS score of 0 – 2 at 90 days or in the last follow-up.
Abbreviations: CABG: Coronary artery bypass grafting; mRS: Modified Rankin Scale; NA: Not available.

one had AF before surgery, emphasizing the important role of AF in the development of LVO stroke. Three patients had reduced ejection fraction (≤50%) after cardiac surgery on echocardiography in this study. Heart failure is the second leading cause of cardiogenic stroke,[28] and the mechanisms of thromboembolic events in patients with heart failure include blood stasis, endothelial dysfunction, and a hypercoagulable state.[29] Therefore, greater attention should be paid to ischemic stroke in patients with impaired cardiac function after cardiac surgery.

The patients included in this study mainly underwent CABG and valve surgery, as these two surgeries are the most common. In this study, most patients who underwent thrombectomy had symptoms that occurred 2 – 5 days after surgery, indicating that the diagnosis of stroke in these patients can be made during the stable post-operative period or when they wake up from general anesthesia.[19] We found that even if the patient had an in-hospital stroke, there was still a long duration from LKW to recanalization. A scientific statement[30] on in-hospital stroke reported that although patients with in-hospital stroke had short admission process and transfer times, their evaluation and treatment were often delayed compared to patients with community-onset stroke, contributing to higher rates of morbidity and mortality in this patient population. It is difficult to distinguish between a new stroke and the consequences of periprocedural medications. In addition, the in-hospital stroke treatment process needs to be optimized, as there is still a long waiting time between symptom discovery and entering the interventional therapy. Addressing this requires collaboration among multiple hospital departments, including the cardiac surgery, radiology, neurology, interventional operating rooms, and medical affairs departments.

This study has some limitations that must be noted. Firstly, the results need to be interpreted with caution, given the limited sample size. Secondly, we only reported patients with LVO stroke who underwent MT; therefore, the prognosis of patients with LVO stroke who did not undergo thrombectomy remains unclear. In addition, the present study did not attempt to delineate whether patient prognosis can be significantly improved (90-day mRS score 0 – 1) when the diagnostic and treatment processes are optimized, given the relatively long waiting time between symptom discovery and treatment process. Nevertheless, our case series supplements the evidence for MT in this special population and provides a reference for future large-sample cohort studies.

5. Conclusion

The present study illustrates the impact of multimodal CT-guided MT on the prognosis of LVO stroke patients. Timely MT treatment has a beneficial effect on neurological function and greatly improves patients' prognosis. Thus, given its advantages, the usage of multimodal CT evaluation should be promoted and popularized in clinical settings. Nevertheless, further studies employing larger sample sizes are warranted to improve the outcomes in this special patient cohort, since severe neurological deficits and even mortality occur in certain patients receiving MT.

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Conflict of interest

Shujuan Li is an Editorial Board Member of this journal but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Conceptualization: Shujuan Li, Yao Feng
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Ethics approval and consent to participate

The Research Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences, approved this study (Ethics approval code: 2022-1848). Data were collected retrospectively, and no further procedure was performed; hence, the requirement to obtain informed consent was waived.

Consent for publication

All images used in this study were anonymized; hence, the requirement to obtain consent for publication was waived.

Availability of data

The data used in this study will be made available from the corresponding authors upon request.

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ACCSCIENCE PUBLISHING

Brain & Heart

ORIGINAL RESEARCH ARTICLE

Stroke risk among Nigerians with diabetes and hypertension: A pilot retrospective cohort study

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Abstract

Stroke is a leading cause of illness and death worldwide, often leaving survivors with severe disabilities. In sub-Saharan Africa, strokes remain prevalent among individuals with diabetes, hypertension (HTN), or both, significantly impacting the health, social stability, and economic well-being of families and communities. This study aimed to assess the risk of stroke development in Nigerian individuals diagnosed with both diabetes and HTN. The research included diabetic and hypertensive patients who attended the outpatient clinics at Imam Halliru and Imam Wali General Hospitals in Kano between January 2015 and August 2020. Patient data were manually extracted from hospital records. Regression and correlation analyses were conducted to compare the stroke risk between patients with either diabetes or HTN and those with both conditions. Among the 933 participants, 200 exhibited clinical features consistent with the World Health Organization definition of stroke. Of these, 85 (37.5%) had HTN, 67 (33.5%) had diabetes, and 58 (29%) had both conditions. Unemployment, female gender, advanced age, diabetes, and HTN were identified as factors associated with an increased stroke risk in the unadjusted analysis. The findings highlight a significantly higher stroke risk for Nigerians with both diabetes and HTN. Therefore, strict blood pressure control for hypertensive patients and rigorous blood sugar management for diabetic patients is critical.

Keywords: Stroke; Diabetes; Risk; Nigeria

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1. Introduction

Stroke is a preventable medical condition associated with high rates of morbidity and mortality, often resulting in both physical and mental disabilities.[1] Globally, stroke ranks as the second leading cause of death and the third most common cause of disability, placing a significant burden on health systems, populations, and individuals. Its incidence has been estimated to rise steadily over the past 25 years and is projected to continue increasing in the coming decades.[2] Stroke is one of the most common and severe brain disorders, with devastating consequences that demand a multidisciplinary approach to management. It is highly prevalent in both developing and developed nations, characterized by a high recurrence rate, and is responsible for approximately 5 million deaths globally each year.[3] Approximately 25.7 million people worldwide are currently living with stroke, with nearly 71% of cases being ischemic. Stroke accounts for approximately 6.5 million deaths annually, while around 113 million individuals live with stroke-related disabilities.

In addition, there are 10.3 million new cases of stroke each year, the majority of which occur in developing nations, leading to significant financial burdens in both developed and developing nations.[4-6]

Hypertension (HTN) is the primary modifiable risk factor for stroke. In addition to its role in stroke, HTN is a major contributor to ischemic heart disease, heart failure, renal failure, peripheral arterial disease, and aortic disorders, frequently leading to serious complications and mortality.[7] Globally, the prevalence of stroke is rising rapidly among hypertensive individuals, resulting in significant economic, social, and health burdens. This is attributed to the higher susceptibility of hypertensive patients to vascular diseases, including stroke. Research has shown that effective management and treatment of HTN can reduce the risk of stroke by 40% and the risk of acute myocardial infarction by 15%. Conversely, an increase of 20 millimeters of mercury (mmHg) in systolic blood pressure (SBP) or 10 mmHg in diastolic blood pressure (DBP) is associated with a 50% higher risk of stroke.[8] Diabetes mellitus is another significant risk factor for stroke development and has become an increasingly prevalent health issue in both Africa and Nigeria.[9] Numerous studies have shown an elevated risk of stroke in patients with diabetes mellitus. In Nigeria, diabetes is highly prevalent, with an estimated prevalence ranging from 0.65% to 11%.[10-13]

In developing countries like Nigeria, treatment options for stroke are lacking, and well-organized stroke services, including emergency transport services, are grossly inadequate. In addition, highly effective stroke care is generally unaffordable in Nigeria, and sociocultural factors greatly influence health-seeking behavior among stroke patients. Therefore, the aim of this study is to evaluate the prevalence and risk of stroke in Nigerians with HTN and diabetes mellitus. Since both diabetes and HTN are common stroke risk factors, comparing these conditions will help determine which one poses a higher stroke risk, and whether the combination of diabetes and HTN is linked to an increased stroke risk beyond what is seen with either condition individually.

2. Materials and methods

2.1. Study design and setting

We employed an observational research approach using a retrospective cohort study, which examines groups of people with shared characteristics yet differing in certain traits linked to a specific outcome. Relevant information for each individual was collected from existing records. The study was carried out at two hospitals in Kano State, Nigeria. One of which is a general hospital and the other is a maternal and child community hospital. Both are government hospitals within the Kano metropolis that serve a high volume of diabetic and hypertensive outpatients. Most of the patients are mostly Hausa-speaking residents from the metropolis of the state. The guideline used in the design and report of the research was "The Strengthening the Reporting of Observational Studies in Epidemiology Checklist for Cohort Study." The Kano Ministry of Health's Health Research Ethics Committee granted ethical permission for the study, with reference number MOH/Off/797/T.1/2022. An informed consent was obtained by waiver due to the minimal risk associated with the study, and the study could not be conducted without a waiver.

2.2. Participants

The study population involved a random sample of patients aged 18 years or older who had an outpatient's department visit from January 2015 through August 2020. These patients were identified by manual abstraction from hospital records using a preformed questionnaire and recruited based on the following eligibility criteria: (a) stroke symptoms; (b) age >18 years; (c) diagnosis of diabetes; (d) diagnosis of HTN; and (e) diagnosis of both HTN and diabetes. Participants who satisfied one or more of these categories were excluded: (a) individuals with drug-induced diabetes; (b) individuals receiving steroid therapy; (c) individuals with chronic malignancies; (d) individuals with pregnancy-induced HTN or diabetes; and (e) patients receiving renal replacement therapy. The subjects were divided into three cohort groups which have similar characteristics: individuals with diabetes mellitus alone (DM), individuals with both HTN and DM (HPT+DM), and those with HPT alone.

The study population comprised patients treated between January 2015 and August 2020. A sample of 39 patients was selected each year, except for 2019, where 44 patients were chosen. Within each year, patient selection was randomized, with a minimum of four patients randomly selected from each month. Medical records for the sampled patients were then reviewed to extract relevant data for analysis.

2.3. Measurements

Blood pressure was measured on the right arm of each participant using a standard mercury sphygmomanometer and an appropriately sized cuff. Before each measurement, patients rested for 15 min with their feet on the ground and their arm supported at heart level. Fasting blood samples were collected from patients suspected of having diabetes after an 8-h fasting period. The primary outcome of this study was stroke. To screen for stroke, patients were identified based on the International Classification

of Diseases, Tenth Revision, and Clinical Modification diagnosis of cerebrovascular disease (I60-I69) during their hospital stay. Due to limitations in the hospital and the overall healthcare system of the country, brain computed tomography or magnetic resonance imaging scans were not available for all patients. Two members of the research team separately analyzed the medical records of patients with a potential stroke diagnosis reached a consensus on the final diagnosis. A comprehensive medical history was gathered, including the duration of HTN or diabetes diagnosis, along with the types and dosages of current medications. We also measured the following sociodemographic characteristics of all enrolled patients, including age, sex, tribe, religion, marital status, and occupation.

2.4. Variables and diagnostic criteria

HTN was defined using the 2023 World Health Organization (WHO) criteria as repeated SBP readings of 140 mmHg or higher, or DBP readings of 90 mmHg or higher. We classified HTN based on the Seventh Report of the Joint National Committee 7 criteria: normal (SBP <120 mmHg and DBP <80 mmHg); pre-HTN (SBP 120 – 139 mmHg or DBP 80 – 89 mmHg); stage 1 (SBP 140 – 159 mmHg or DBP 90 – 99 mmHg); and stage 2 (SBP ≥160 mmHg or DBP ≥100 mmHg). The uncontrolled HTN was defined as repeated measurements of SBP ≥140 mmHg and DBP ≥90 mmHg, despite the use of antihypertensive medications. Diabetes was defined as fasting blood glucose concentration ≥126 mg/100 mL (7 mmol/L). Stroke was diagnosed based on the WHO definition, encompassing sudden onset of unilateral weakness, sensory loss, vision loss, or speech impairment. Moreover, patients were categorized as physically active if they engaged in moderate-intensity exercise (e.g., walking) or vigorous-intensity exercise (e.g., jogging) for at least 4 h/week, or as not physically active. In addition, patients with a first-degree relative who had experienced a stroke were considered to have a family history of stroke.

2.5. Risks of bias assessments

To minimize selection bias, a clearly defined population was used in the study, with the cohort recruited using a clearly defined method. Similarly, the selection of the subjects was not related to the outcomes of interest. The average number of hospital visits was compared among the three cohorts to minimize detection bias. All available information within patient files was collected to minimize information bias, and outcomes were accurately measured using standard clinical criteria to minimize assessment bias. Information on potential confounders like age, sex, poor medication compliance, and skipped hospital visits was carefully assessed.

2.6. Study size

The number of eligible patients identified from the patient records during the manual abstraction determines the sample size.

2.7. Data analysis

SPSS (version 30.0; IBM Corp., United State) for Windows was used for data analysis. Descriptive statistics with exact confidence intervals were used to characterize the study population and determine the proportion of patients with acute stroke. Continuous variables were presented as means with standard deviations, while categorical variables were expressed as percentages. Unadjusted comparisons were conducted using correlation and regression analyses. The primary analysis examined the relationship between HTN and stroke risk, as well as diabetes and stroke risk, employed bivariate analysis with Pearson's correlation coefficients. The primary analysis focused on stroke risk in three groups: Those with HTN, those with both diabetes and HTN, and those with diabetes only. In the secondary analysis, to compare the risk of stroke development among the three cohorts, multiple correlation and regression analyses were performed.

3. Results

3.1. Hospital record search

We identified a total of 933 patient records by manual abstraction from hospital records, in which 517 records from Imam Wali Hospital and 416 from Imam Halliru Hospital. After screening and scrutinizing the hospital records obtained from both hospitals, about 415 patient records had missing information and therefore removed. The remaining 518 records were thoroughly reviewed, and 318 records did not satisfy the inclusion and exclusion criteria and were thus excluded from the study. Therefore, only 200 records were included in the study, as they satisfied the eligibility criteria for stroke. A flowchart illustrating the study selection process is depicted in Figure 1. During data abstraction, we noticed a serious poor data keeping in both hospitals, which may explain the relatively small number of patients included in the study over the 5-year period.

3.2. HTN cohort

From January 2015 through August 2020, there were 933 patients with outpatient visits at the two general hospitals. This includes 200 patients with clinical features consistent with the WHO definition of stroke. Of the 200 possible stroke patients, 75 (37.5%) patients had HTN, constituting the hypertensive cohort. The age range of participants in this cohort was 35 – 85 years, with a mean age of 61.96 ± 13.83 years. There were 56 (74.7%) females

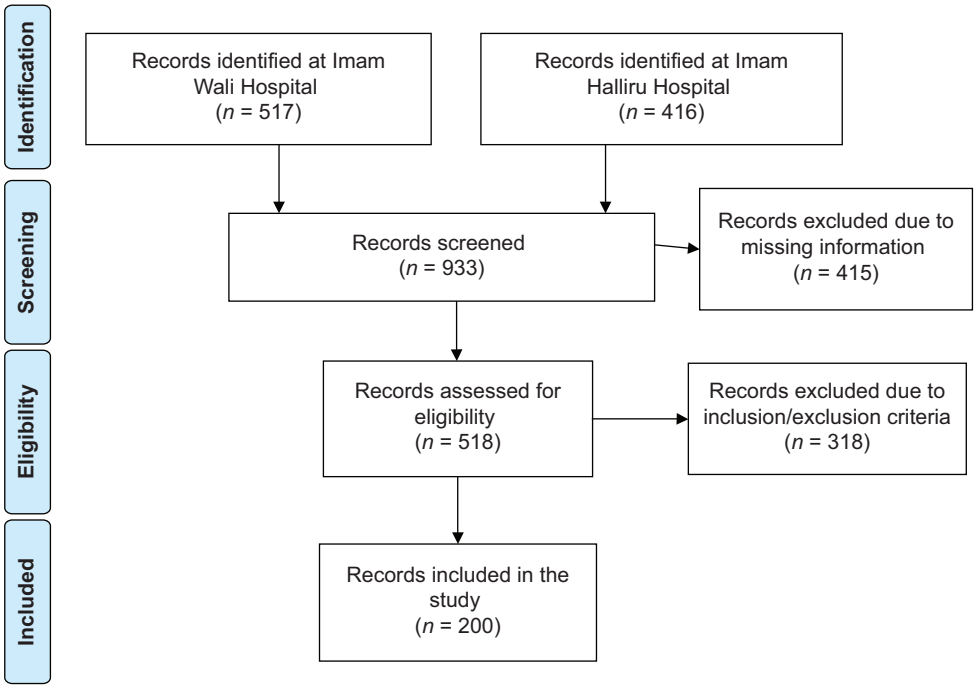

Figure 1. Flowchart of the study selection

and 19 (25.3%) males in this cohort. Most of the participants in this cohort identified themselves as housewives (74.7%), while only 10 (13.3%) and 9 (12.0%) participants identified themselves as civil servants and business owners, respectively. The top clinical presentations reported by participants in this cohort were sudden onset of unilateral body weakness (45 [60.0%]), followed by sudden onset of sensory loss (21 [28%]), sudden loss of vision (5 [6.7%]), and sudden loss of speech (4 [5.3%]). Majority of the participants (43 [57.3%]) had blood pressure readings categorized as Stage 1 HTN (SBP 140 – 159 mmHg and DBP 90 – 99 mmHg), while about 24 (32.0%) had Stage 2 HTN (SBP ≥160 mmHg and DBP ≥100 mmHg). Majority of the females in this cohort were within the age range of 61 – 70 years, whereas most of the male participants were in the age range of 71 – 80 years. This is shown in Figure 2 below.

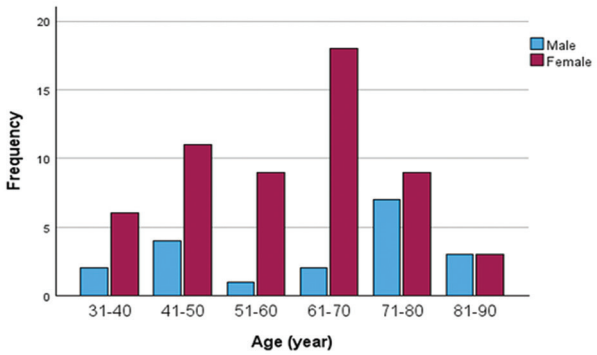

Figure 2. Distribution of age of the patients by their gender

3.3. Diabetes cohort

As mentioned earlier, 933 patients were identified with outpatient visits at the two general hospitals, including 200 patients with clinical features consistent with the WHO definition of stroke from January 2015 through August 2020. Of the 200 patients, 67 (33.5%) had diabetes, constituting the diabetic cohort. Majority of the participants in this cohort were in the age range of 61 – 70 years (26.9%), with 50 (74.6%) females and 17 (25.4%) males. As in the hypertensive cohort, majority of the participants identified themselves as housewives (77.6%), only 8 (11.9%) and 7 (10.4%) participants identified themselves as civil servants and business owners, respectively. Furthermore, as in the hypertensive cohort, the top clinical presentations reported by participants in this cohort were sudden onset of unilateral body weakness (41 [61.2%]), followed by sudden onset of sensory loss (17 [25.4%]), sudden loss of vision (5 [7.4%]), and sudden loss of speech (4 [6.0%]). Majority of the participants (37 [55.2%]) had their fasting blood sugar (FBS) in the range of 12 – 18 mmol/dL. About 22 (32.8%) participants had an FBS ≥19 mmol/dL, while only 8 (11.9%) participants had an FBS of 5 – 11 mmol/dL. Similarly, majority of the females in this cohort were also within age range of 61 – 70 years, whereas most of the male participants were in the age range of 71 – 80 years. This is shown in Figure 3 below.

3.4. HTN and diabetes cohort

Between January 2015 and August 2020, we identified 933 patients with outpatient visits at the two general hospitals, including 200 patients with clinical features consistent with the WHO definition of stroke. Of the 200 patients, 58 (29%) had both HTN and diabetes, constituting the HTN and diabetes cohort. In this cohort, the largest age group was 71 – 80 years, comprising 25.9% of participants. There were 44 (75.9%) females and 14 (24.1%) males in this cohort. As in the other two cohorts, majority of the participants identified themselves as housewives (77.6%), only 8 (13.8%) and 5 (8.6%) participants identified themselves as civil servants and business owners, respectively. In this cohort, sudden onset of unilateral body weakness constitutes the highest clinical presentation (18 [31.0%]), but almost a similar number of participants had sudden onset of sensory loss as their main clinical presentation (17 [29.3%]). Similarly, there are a significant number of patients who had sudden loss of vision (13 [22.4%]) and sudden loss of speech (10 [17.2%]) as their main clinical presentations. Although majority of the patients had their FBS and blood pressure in the range of 12 – 18 mmol/dL and 140 – 159 mmHg, respectively, a significant number of patients in this cohort had clinical stroke despite having lower blood sugar and blood pressure levels, indicating an elevated risk of stroke in individuals with both conditions. Majority of the patients with lower blood sugar level and lower blood pressure had sudden onset of unilateral body weakness as their main clinical presentation, whereas the majority of the patients with higher blood sugar level and higher blood pressure had sudden onset of sensory loss. This is shown in Figures 4 and 5 below.

3.5. Comparison of the cohort

Comparing the three cohort groups, patients with both diabetes and HTN are slightly older than those with either HTN or diabetes alone. Majority of the patients in all the three cohort groups were females and housewives. In addition, unlike patients with HTN or diabetes alone, where majority of the patients had almost uniform clinical presentation, patients with both HTN and diabetes had a wide range of clinical presentation with many of them reported unilateral body weakness, sudden sensory loss, and visual and speech abnormalities. Furthermore, a significant number of patients with both HTN and diabetes had clinical stroke despite lower levels of blood sugar and blood pressure, indicating an increased risk of stroke in patients with both conditions.

At bivariate analysis, there was a positive linear relationship between HTN and the development of stroke symptoms, with a Pearson's correlation coefficient of 0.202 and a significance level of 0.082. This indicates a perfect positive correlation between HTN and the development of stroke symptoms. As the level of blood pressure rises, the risk of stroke development increases. Similarly, there was a perfect positive correlation between diabetes and the development of stroke symptoms, with a Pearson's correlation coefficient of 0.213 and a significance level of 0.084.

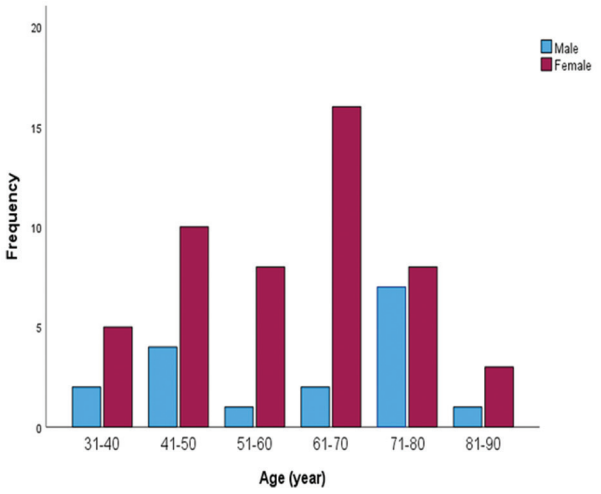

Figure 3. Distribution of age of the patients by their gender

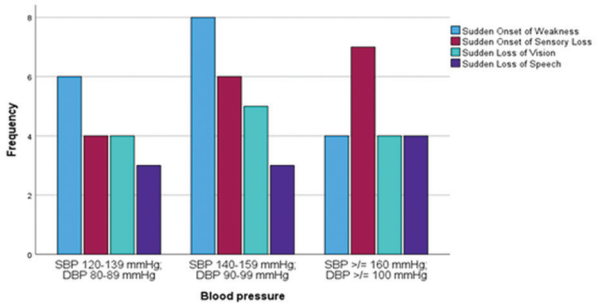

Figure 4. Distribution of patients' blood sugar levels by their clinical presentation
Abbreviation: FBS: Fasting blood sugar.

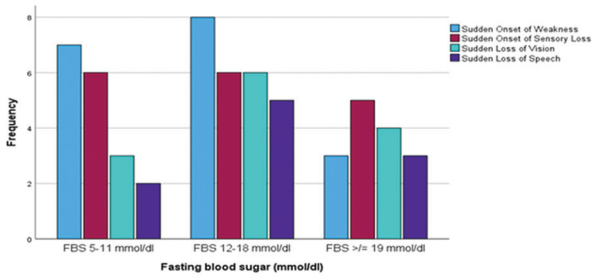

Figure 5. Distribution of patients' blood pressure level by their clinical presentation
Abbreviations: SBP: Systolic blood pressure; DBP: Diastolic blood pressure; mmHg: Millimeters of mercury.

3.6. Stroke risk determinants within the cohort

Unadjusted analysis revealed five risk factors for stroke, including female gender, advancing age, being unemployed, HTN, and diabetes. We defined housewife as unemployment in this context. Using multiple correlation regression analysis, the overall correlation between age, gender, occupation, HTN, and diabetes with the risk of developing stroke symptoms was statistically significant (R value: 0.288; R Square: 0.083; F value: 0.943; Sig: 0.461). All five factors were also independently associated with the risk of occurrence of stroke symptoms. However, HTN had the strongest association with risk of stroke development, followed by age and gender. This is shown in Table 1 below.

4. Discussion

This study is among the limited research conducted in sub-Saharan Africa that examines stroke risk in individuals with both HTN and diabetes. This retrospective cohort study, encompassing multiple hospitals, revealed that HTN and diabetes mellitus, either individually or in combination, were frequently encountered in patients displaying clinical features consistent with stroke across the two secondary healthcare facilities examined. Among the 933 patients with outpatient visits at the two general hospitals, the stroke occurrence risk was slightly higher in patients with comorbid diabetes and HTN, followed by those with either HTN or diabetes alone. This finding aligns with observations reported in both developed and developing nations.[7,14] Five factors including female gender, increasing age, unemployment, HTN, and diabetes, were positively correlated with an increased risk of stroke development in an unadjusted analysis. Secondary analyses revealed that uncontrolled baseline blood pressure, particularly in cases of Grade II HTN, was an independent predictor of increased stroke risk compared to individuals with optimal blood pressure levels (<120/80 mmHg). Conversely, baseline glycemic control was not independently associated with an increased risk of stroke occurrence.

While diabetes mellitus is a well-established risk factor for stroke, the extent of this risk varies considerably across different studies.[15] Multiple large-scale population studies have demonstrated an elevated prevalence of stroke in individuals with diagnosed diabetes, undiagnosed diabetes, and those exhibiting glucose intolerance.[16] Numerous epidemiological studies have demonstrated an independent association between diabetes and the risk of ischemic stroke in both sexes, with relative risks for diabetics ranging from 1.8 to approximately 6.[17] The elevated stroke risk observed in diabetic patients is likely stems from their heightened susceptibility to vasculopathy, encompassing both small and large arteries. This increased vulnerability arises from atherosclerosis, which often culminates in thromboembolic stroke.[18] A secondary analysis showed that baseline blood pressure control significantly impacted stroke risk. Patients with Grade II HTN – defined by a SBP of 160 mmHg or more and/or a DBP of 100 mmHg or more – faced a higher stroke risk compared to those with optimal blood pressure levels (below 120/80 mmHg). This aligns with several studies from Africa, which consistently highlight that <10% of treated individuals achieve adequate blood pressure control, underscoring the severity of this public health issue.[19,20] We identified several factors that were independently linked to poor blood pressure control in hypertensive patients, despite being on treatment. These factors include poor adherence to antihypertensive medications, difficulties in accessing these medications, a longer duration since HTN diagnosis, and the use of varying numbers of antihypertensive drugs. These findings align with the results of other studies.[21] This retrospective cohort study revealed that approximately three-quarters of patients exhibited both diabetes and HTN. This finding aligns with previous research reports,[22] further reinforcing the high prevalence of diabetes and HTN as concurrent

Table 1. Multiple regression analysis

Coefficients[a]								
Model		Unstandardized coefficients		Standardized coefficients	t	Sig.	95% confidence interval for B	
		B	Std. error	Beta			Lower bound	Upper bound
1	(Constant)	1.456	1.178		1.236	0.222	−0.908	3.819
	Age (year)	0.056	0.114	0.077	0.488	0.627	−0.173	0.285
	Gender	−0.262	0.351	−0.104	−0.748	0.458	−0.966	0.441
	Occupation	0.346	0.278	0.200	1.245	0.219	−0.212	0.904
	Fasting blood sugar (mmol/dL)	0.240	0.203	0.168	1.180	0.243	−0.168	0.648
	Blood pressure	0.074	0.198	0.054	0.373	0.711	−0.323	0.471

[a]Dependent variable: Clinical presentation.
Abbreviations: B: Beta; Std. error: Standard error; t: T-statistic; Sig: Significance.

conditions.[23,24] Despite the relatively short follow-up period in this study, the risk of stroke among hypertensive and diabetic individuals in Nigeria appears to be slightly higher than that observed in developed countries.

While our study did not definitively demonstrate a dose-response relationship between the level of physical activity and stroke risk, prior case–control studies on stroke have consistently shown a strong association between physical inactivity and an increased risk of stroke.[25-27] Physical inactivity was associated with a 20% higher stroke risk after accounting for demographic and socioeconomic factors. However, this association weakened when traditional stroke risk factors were also considered.[28] Overall, interventions aimed to improve medication adherence, including the use of mobile health technology[29,30] and a cardiovascular polypill containing generic blood pressure-lowering medications,[31,32] could enhance HTN management in settings with limited resources.

Our study has several limitations. First, most of the participants did not undergo brain imaging, which made it difficult for us to conduct further analysis and could have caused misclassification errors. In addition, some patients with clinical features of a stroke may not have shown neuroimaging features, which could have pave ways for finding out other possibilities among the patients. Second, all the patients we recruited into the studies were outpatients, excluding hospitalized patients, which could have led to a poor reflection of the overall risk. Third, this study was conducted at only two general hospitals, which may restrict the extent to which our findings can be applied to other healthcare settings. As a result, we were unable to estimate the overall risk of stroke occurrence among patients with HTN and diabetes within the broader population. Fourth, the measurement criteria for both blood pressure and diabetes may have differed between the two hospitals, and this may have influenced the calculated risk of stroke occurrence across groups. Given the lack of imaging resources and the limited scope of stroke care services in Nigeria, it can be deducted from this study that implementing accessible, community-based preventive measures and increasing the availability of affordable HTN and diabetes management options could reduce stroke incidence.

5. Conclusion

The findings of this study highlight a significant risk of stroke among Nigerian patients with HTN, diabetes, and particularly those with both conditions. This underscores the urgent need for interventions targeting blood pressure and blood sugar control among high-risk groups to prevent stroke occurrence. The correlation of factors such as female gender, older age, and unemployment with elevated stroke risk suggests areas where public health efforts could be focused, particularly in community outreach and education on risk mitigation. In addition, future research could further explore lifestyle factors and healthcare access as modifiable contributors to stroke risk in similar settings. More rigorous blood pressure and blood glucose control protocols, combined with community health initiatives to address lifestyle and employment-related health disparities, may substantially lower the risk and impact of stroke in Nigerian hypertensive and diabetic individuals.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Abba Musa Abdullahi, Usman Auwalu Isah
Formal analysis: Abba Musa Abdullahi
Investigation: Abba Musa Abdullahi, Usman Auwalu Isah
Methodology: Abba Musa Abdullahi
Writing–original draft: Abba Musa Abdullahi
Writing–review & editing: Usman Auwalu Isah

Ethics approval and consent to participate

The study was approved by the Health Research Ethics Committee Kano Ministry of Health with the reference number: MOH/Off/797/T.1/2022. The requirement for obtaining informed consent from patients has been waived due to the minimal risk associated with the study.

Consent for publication

The requirement for obtaining informed consent from patients has been waived due to the minimal risk associated with the study.

Availability of data

Data are available from the corresponding author on reasonable request.

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ACCSCIENCE PUBLISHING

Brain & Heart

ORIGINAL RESEARCH ARTICLE

A prospective multicenter, randomized controlled, non-inferiority trial of bovine pericardial versus polyurethane patching in carotid endarterectomy

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Abstract

Carotid endarterectomy (CEA) is the first-line treatment for internal carotid artery stenosis that can lead to stroke. This study aimed to compare the incidence of early adverse clinical events and restenosis between patient groups receiving the newly developed bovine pericardial (BP) and polyurethane patches during CEA. We conducted a multicenter, randomized, non-inferiority trial at five tertiary centers in China. Participants were assigned to either the BP patch or polyurethane patch group. The primary outcome was freedom from restenosis at 1 year after surgery. Restenosis was defined as a narrowing of >50% in the target artery on duplex ultrasound or computed tomography angiography examination. The total number of participants was 120, including 60 each randomized to the BP patch and polyurethane patch groups. Demographics were similar in both groups. Death or significant disability was comparable between the two groups (3:1, $p = 0.619$) during the perioperative period. At the 12-month assessment ($n = 112$), three patients had severe restenosis: two in the BP patch group ($n = 57$) and one in the polyurethane patch group ($n = 55$). There was no significant statistical difference in restenosis, morbidity, or mortality between the two groups ($p > 0.4$), indicating that the BP patch was non-inferior to the polyurethane patch ($p = 0.013$ for the full analysis set; $p = 0.016$ for the per-protocol set). The two groups of patches had similar safety and effectiveness, and the BP patch was non-inferior to the mature polyurethane patch available on the market.

Keywords: Carotid artery stenosis; Carotid endarterectomy; Bovine pericardial patch; Randomized controlled trial

1. Introduction

Stroke is one of the most common causes of death and 8 – 15% of ischemic strokes are due to atherosclerotic stenosis of the carotid artery.[1,2] Carotid endarterectomy (CEA) is the first-line treatment for carotid artery stenosis, effective in considerably preventing the occurrence of stroke caused by carotid artery stenosis.[3,4] According to the 2017 European Society for Vascular Surgery (ESVS) Guidelines, CEA remains the "gold standard for revascularization" (class IIa; level of evidence: B).[5] Possible closure techniques after CEA include primary closure and patch angioplasty. The comparison between these two types of closure after CEA remains rather controversial.[6] The Society of Vascular Surgery (SVS) stipulated in their guideline that routine carotid patching has a level of evidence at 1, especially in smaller diameter arteries (≤4 mm), in women, and in the difficult distal portion of the internal carotid artery.[7] Moreover, the flow characteristic of patch angioplasty may be superior to that of primary closure for minimizing early perioperative adverse events and long-term restenosis.[6,8] A systematic review published in the Cochrane Library included 11 articles involving 2100 patients and also confirmed that patch closure can reduce the risk of short-term and long-term stroke after surgery compared with primary closure and may also be beneficial for restenosis.[9]

However, there are many types of patches. The patch material may be prepared from an autologous vein, bovine pericardium (BP), or synthetic materials such as Dacron, polytetrafluoroethylene (PTFE), polyester, and polyurethane. The choice of a patch generally depends on the preference of the surgeon. Based on the summarization of several randomized controlled clinical trials by Orrapin *et al.*,[10] the best type of patch cannot be determined because of the small number of outcome events. However, this review indicates that the BP patch may reduce the risk of fatal perioperative stroke, death, and infection compared with other synthetic patches.

Our results from an animal study using the BP patch showed that this type of patch could maintain stability and provide early endothelialization.[11] In clinical applications, this property is beneficial to reduce the risk of post-operative thrombosis and may be beneficial to reduce restenosis. In the past few years, we conducted a multicenter, randomized controlled, non-inferiority trial comparing the BP patch with a polyurethane patch (Vascular-patch, B. Braun Medical AG, Germany, which is widely used in China). Here, we compare the safety and efficacy of these two patches in CEA to illustrate the broad prospects of BP patch.

2. Methods

2.1. Patient population

This study protocol was approved by the ethics committees of the five tertiary centers (including Xuanwu Hospital, Capital Medical University [Department of Neurosurgery]; Zhongshan Hospital, Fudan University [Department of Vascular Surgery]; the First Affiliated Hospital of Soochow University [Department of Neurosurgery]; Liaocheng People's hospital [Department of Neurosurgery]; and the First Affiliated Hospital of Zhengzhou University [Department of Vascular Surgery]), and informed consent was obtained from each patient. Indications for surgery included moderate or severe symptomatic carotid artery stenosis and severe asymptomatic carotid artery stenosis. The degree of stenosis was calculated based on the North American Symptomatic CEA Trial (NASCET) criteria.[12] The pre-operative stenosis degree evaluation required the use of computed tomography angiography (CTA). Symptomatic lesions were categorized as transient ischemic attack (TIA), amaurosis of the ipsilateral eye, or ischemic stroke ipsilateral to the narrowed carotid artery within the previous 6 months. Our exclusion criteria are as follows: (1) With an expected survival period <1 year; (2) unable to tolerate general anesthesia; (3) unable to complete CTA of blood vessels in the head and neck; (4) with a large-scale stroke or myocardial infarction occurring within 30 days; (5) with coagulation dysfunction and contraindications to heparin and antiplatelet drugs; (6) with a recent history of gastrointestinal bleeding and difficulty in being treated with antiplatelet drugs; (7) with large intracranial aneurysms that cannot be treated in advance or simultaneously; (8) with chronic complete occlusion without evident symptoms of cerebral ischemia; (9) with a history of intracranial hemorrhage (intraparenchymal hemorrhage, subarachnoid hemorrhage, subdural, or epidural) within 30 days before enrollment; (10) with severe diseases of liver, kidney or circulatory systems, or other diseases; (11) with severe dementia or mental disorder that hampers follows up in clinic; (12) participating in other clinical trials within 3 months before enrollment; and (13) other reasons that could preclude potential subjects for inclusion in the groups.

This prospective, randomized study was conducted between September 2018 and September 2021. The patients were randomized in a 1:1 ratio using sealed opaque envelopes, each containing a slip of paper with two different patches. Random numbers generated using a computer were prepared in advance. Odd and even numbers represent BP patch and polyurethane patch, respectively. Patient demographics and clinical characteristics included

age, sex, smoking status, drinking status, and comorbidities such as hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, and history of stroke. The surgeon introduced the study to the patients prior to obtaining their informed consent for participating in this study.

2.2. Surgical procedures

The patients received a single oral antiplatelet therapy (aspirin 100 mg or clopidogrel 75 mg) before surgery and dual antiplatelet therapy (100 mg aspirin and 75 mg clopidogrel) after surgery. Routine monitoring was carried out using transcranial Doppler during surgery. If ischemia was detected, shunting was performed to maintain adequate brain perfusion. Systemic heparin was administered during surgery. Before the first skin incision, the randomized results were communicated to the nurse and surgeon using a study controller. Normal internal carotid artery was measured using calipers distal to the lesion. 6-0 polyprolene sutures (Prolene; Ethicon, Somerville, NJ, USA) were used to suture the BP and polyurethane patches. Post-operative duplex ultrasound scanning was performed in all patients on post-operative day 2, and all patients were continued on a dual antiplatelet regimen at home.

2.3. Outcome assessment

Patients were followed up perioperatively and at 6 and 12 months postoperatively. Duplex ultrasonography or CTA was used to establish post-operative vessel patency. The primary outcome was freedom from post-CEA restenosis (≥50%) measured using color duplex ultrasonography or CTA at 1 year after surgery. The secondary outcomes included the occurrences of post-operative cranial nerve injury, myocardial infarction, ischemic stroke, heart failure, TIA, hemorrhagic stroke, surgical site infection, and/or re-exploration hematoma and patch dilatation.

2.4. Statistical analysis

Based on a previous study, the incidence rate of resolution of post-CEA restenosis following the utilization of polyurethane patches was approximately 97%.[13] The patients were randomized to receive the two types of patches in a 1:1 ratio. The non-inferiority boundary was set at 0.1. Assuming a power of 80%, a two-sided α level of 0.025, the target sample size for each group was 48 patients. Taking into account the additional 10% dropout rate, the final target sample size was 120 patients (60 in each treatment group).

Non-continuous variables were compared using the chi-squared or Fisher's exact tests, as appropriate. Student's *t*-test or Wilcoxon rank-sum test was used to compare continuous variables, and a $p < 0.05$ was considered statistically significant. A 95% confidence interval (CI) was also calculated.

3. Results

A total of 120 patients were included in the study, with 60 patients in each group (Figure 1). The average age of patients was around 65 years old. The majority of patients enrolled were male, accounting for 85% of the subjects recruited. Three-quarters of patients had experienced an ischemic event in the past 6 months. There was no significant difference in the variables between the BP patch group and the polyurethane patch group (Table 1; $p > 0.05$). Similarly, the risk factors were comparable between the two groups (Table 1; $p > 0.05$).

3.1. Perioperative outcome

One death occurred in the BP patch group (Table 2). The patient experienced a sudden disturbance of consciousness 5 days after surgery, and computed tomography (CT) revealed intracranial hemorrhage. The patient subsequently succumbed to brain herniation. The BP patch group recorded three stroke cases and one TIA incident, whereas two strokes and one TIA occurred in the polyurethane patch group.

Table 2 lists the other perioperative complications; one patient underwent re-exploration hematoma in the polyurethane patch group. There were no significant differences between the two groups for any event ($p > 0.6$). The overall death and significant disability rates of the patients were 3.3% (4/120) in all participants.

3.2. Six-month outcomes

Six patients were lost to follow-up because they refused to continue participating in the trial or had died (Table 2). The outcomes of the two groups were comparable ($p > 0.4$). The combined all-cause mortality and disability rates were 0.87% (1/114). An instance of disabling stroke occurred in the polyurethane patch group. This patient received medical treatment, which led to symptomatic improvement. Patients in the polyurethane patch group underwent coronary intervention for myocardial ischemia. A case of carotid restenosis was recorded in the BP patch group; however, the patient was asymptomatic and achieved good recovery.

3.3. Twelve-month outcomes

Eight patients were lost to follow-up due to refusal to participate or death. There were no significant differences in any outcome measures between the two groups ($p > 0.4$; Table 2). The combined all-cause mortality and disability rates at 12 months were 0.89% (1/112). Additional deaths were recorded in the polyurethane patch group. No new

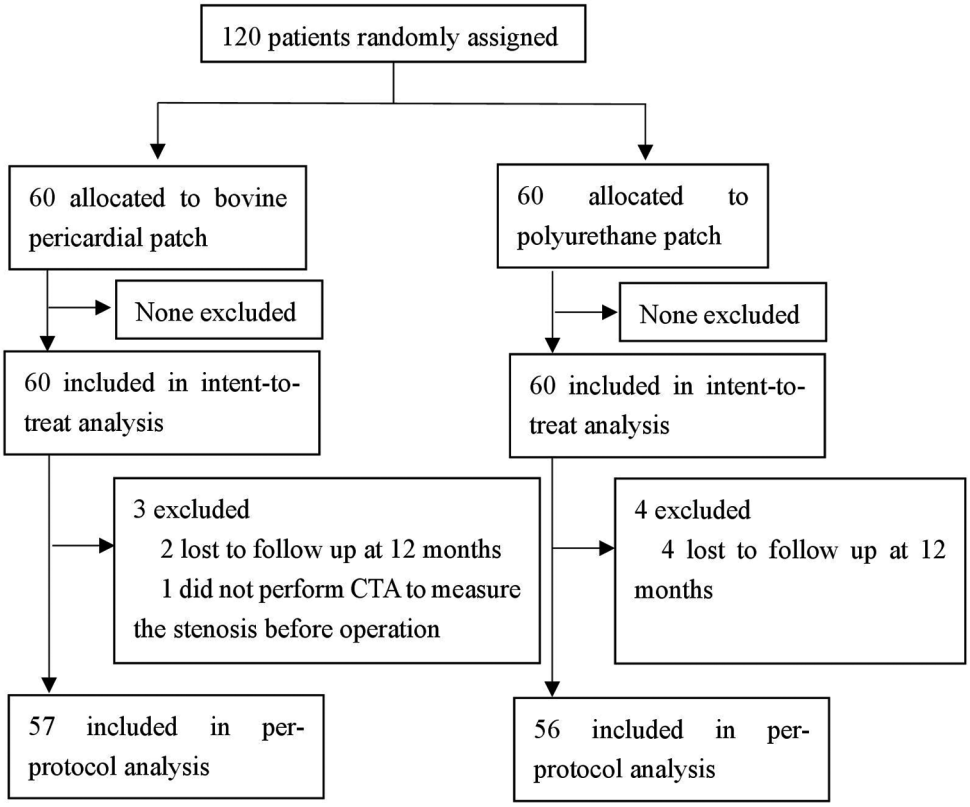

Figure 1. Flow chart of enrollment and randomization
Abbreviation: CTA: Computed tomography angiography.

Table 1. Baseline characteristics of the patients

Characteristics	Total	BP patch group (*n*=60)	Polyurethane patch group (*n*=60)	*p*-value
Age, years	65.46±8.20	65.44±7.35	65.48±9.03	0.979
Gender, male	103 (85.83%)	55 (91.67%)	48 (80.00%)	0.067
Symptomatic lesions	92 (76.67%)	49 (81.67%)	43 (71.67%)	0.195
Previous history of cerebrovascular disease surgery	16 (13.33%)	10 (16.67)	6 (10.00%)	0.283
Hypertension	79 (65.83%)	39 (65.00%)	40 (66.67%)	0.847
Diabetes	39 (32.50%)	19 (31.67%)	20 (33.33%)	0.845
Coronary artery disease	15 (12.50%)	9 (15.00%)	6 (10.00%)	0.408
Hyperlipidemia	27 (22.50%)	13 (21.67%)	14 (23.33%)	0.827
Atrial fibrillation	3 (2.50%)	1 (1.67%)	2 (3.33%)	>0.999
Smoking	55 (45.83%)	26 (43.33%)	29 (48.33%)	0.583
Drinking	33 (27.50%)	16 (26.67%)	17 (28.33%)	0.838
Pulse, beats/min	75.12±7.65	74.65±8.02	75.58±7.29	0.506
SBP, mmHg	133.72±16.56	133.25±18.09	134.18±15.01	0.759
DBP, mmHg	77.66±8.85	77.87±8.56	77.45±9.19	0.550
BMI	24.60±2.79	24.45±2.72	24.75±2.88	0.569

Note: Data of continuous data are expressed as mean±standard deviation, while data of categorical data are presented as n (%).
Abbreviations: BMI: Body mass index; BP: Bovine pericardial; DBP: Diastolic blood pressure; SBP: Systolic blood pressure.

strokes or cardiac events were observed. On ultrasound or CTA examination, a new carotid restenosis was noted in the BP patch group and one in the polyurethane patch group; however, they were all asymptomatic.

3.4. Non-inferior evaluation

As shown in Table 3, the non-inferiority of the BP patch, compared with the polyurethane patch, was established for CEA with patch closure in the per-protocol (55/60 vs. 54/60, $p = 0.013$, OR = 0.017, 95% CI [−0.087, 0.120]) and full analysis set (54/57 vs. 54/56, $p = 0.016$, OR = −0.017, 95% CI [−0.093, 0.059]).

4. Discussion

This current multicenter, randomized controlled trial, with restenosis as the primary outcome, successfully established the non-inferiority of BP patch for carotid artery stenosis treatment compared to polyurethane patch. We found no significant difference in patient morbidity or mortality between the BP patch and polyurethane patch treatment. Our analysis of the restenosis rate revealed that the outcomes were comparable between the two groups.

The incidence of carotid artery stenosis in individuals aged 30 – 79 years worldwide is 1 – 8% in men and 1 – 2% in women.[14] With increasing age, the incidence rate shows a clear upward trend. Moreover, 15 – 20% of ischemic stroke or TIA are caused mainly (>50%) by carotid artery stenosis.[15,16] There are currently four treatment options: optical medical management, carotid artery stenting, CEA, and transcarotid artery revascularization.[1] So far, CEA remains the "gold-standard treatment" for patients with carotid artery stenosis who are candidates for intervention to prevent future cerebrovascular events.[17,18] Furthermore, CEA with patch closure ensures a safer arteriotomy closure, leading to a lower rate of bleeding and hematoma.[19] Moreover, it may significantly prevent perioperative arterial occlusion (odds ratio [OR] = 0.18, 95% CI = 0.08 – 0.41, $p < 0.0001$; 7 randomized controlled trials),[20] restenosis, and recurrent stroke.[21] However, regarding the type of patch, an international, multispecialty, expert-based Delphi consensus document indicates that it depends on personal preference.[22] The advantages of the BP patch, including its compliance with the biological tissue for easy surgical handling and reduced intraoperative bleeding, non-thrombogenic inner surface that was beneficial for endothelialization, and high resistance to infection, have been demonstrated by Neuhauser and Oldenburg.[23] Alternatives to BP patch include autologous veins, Dacron, and PTFE. However, previous studies have highlighted the disadvantages of these patches. For the vein patch, an extra surgical incision is required for getting the saphenous vein with the potential for the patch to undergo aneurysmal dilatation and rupture. The Dacron patch is associated with a higher risk of carotid thrombosis. For the PTFE patch, the

Table 2. Restenosis, morbidity, and mortality rates in the two patient groups perioperatively, at the 6- and 12-month follow-ups

Occlusion, morbidity, and mortality	Perioperative period			6-month follow-up			12-month follow-up		
	BP patch group (*n*=60)	Polyurethane patch group (*n*=60)	*p*-value	BP patch group (*n*=58)	Polyurethane patch group (*n*=56)	*p*-value	BP patch group (*n*=57)	Polyurethane patch group (*n*=55)	*p*-value
Death or significant disability	3	1	0.619	0	1	0.491	0	1	0.491
Death	1	0	>0.999	0	0	—	0	1	0.491
Disabling stroke: ischemic/embolic	1	1	>0.999	0	1	0.491	0	0	—
Disabling stroke: ICH	1	0	>0.999	0	0	—	0	0	—
Non-disabling stroke	1	1	>0.999	0	0	—	0	0	—
TIA	1	1	>0.999	0	0	—	0	0	—
Re-exploration hematoma	0	1	>0.999						
Cardiac event	0	0	—	0	1	0.491	0	0	—
Surgical site infection	0	0	—						
Restenosis or re-occlusion	0	0	—	1	0	>0.999	2	1	>0.999

Abbreviations: BP: Bovine pericardial; ICH: Intracerebral hemorrhagic stroke; TIA: Temporary ischemic attack.

Table 3. Non-inferiority evaluation of effective rate of restenosis of carotid artery 1 year or more after operation

Date set	BP patch group	Polyurethane patch group	*p*-value	95% CI
FAS	55/60	54/60	0.013	0.017 (−0.087, 0.120)
PPS	54/57	54/56	0.016	−0.017 (−0.093, 0.059)

Note: Non-inferiority margin $\delta = -10\%$.
Abbreviations: BP: Bovine pericardial; CI: Confidence interval; FAS: Full analysis set; PPS: Per-protocol set.

hemostasis time was longer due to anastomotic bleeding.[7,24] The ESVS 2023 clinical practice guideline supported routine patch closure with class 1 recommendation and level 1 evidence, but no significant difference was observed between patch material.[25] The 2023 ESVS[25] and the 2022 SVS[7] guidelines recommended that the selection of patch material should be considered by the operating surgeon for patients undergoing CEA.

Among retrospectively reviewed literature, only two randomized controlled trials had attempted at comparing BP patch with synthetic patches, which did not yield statistically significant difference.[26,27] Nevertheless, the BP patch was probably associated with lower risk for long-term restenosis compared with the synthetic patch (4.0% vs. 7.6%) in a real-world study; however, the duration of the follow-up in the BP patch arm was shorter.[23] Moreover, the randomized controlled trial by Marien *et al.*[27] showed that bleeding from the suture lines was significantly lesser in the BP patch arm vs. synthetic patch arm (14% vs. 55%, $p < 0.001$). A network meta-analysis of CEA closure techniques concluded that BP or PTFE patching is associated with a lower short-term incidence and delayed onset of adverse outcomes following CEA, making them potentially better choice compared to other closure techniques.[24]

The short- and long-term results of BP patching for vascular applications have been excellent, with only 7% restenosis rate after 5-year follow-up as reported by Ladowski *et al.*[28] Stone *et al.*[26] reviewed studies on the BP patch, and found that restenosis rate was between 1% and 10% during the 1- to 5-year follow-up periods. Our results showed that the restenosis rate with the BP patch was 3.5% (2/57) at the 12-month follow-ups. The incidence of restenosis was slightly higher than that reported in a previous study; however, we believe that it was biased by the small sample size. Both groups were satisfactory in terms of the vascular events, further supporting the application of the patch during CEA.

Only one cardiac event occurred within 6 months after surgery and the patient had a good prognosis. It has long been known that there is a close relationship between atherosclerosis-related carotid artery stenosis and coronary artery disease.[29,30] A real-world study by Arinze *et al.*[31] also found that the incidence of myocardial infarction was 0.5% and 1.1% at 30 and 90 days after CEA, respectively. The incidence of cardiac events in the current study was about 1% at 6 months, which is similar to Arinze *et al.*'s study. [31] Since cardiovascular and cerebrovascular diseases and coronary heart disease share similar risk factors, screening for both is necessary.[32] Arinze *et al.*[31] had attempted but failed to find the relationship between high-intensity statins and myocardial infarction and stroke after CEA. Both carotid artery stenosis and CAD are individually important risk factors in the treatment of the other, so selective cardiac testing may be very important in patients undergoing CEA.[33] Actually, most myocardial infarction often occur in the perioperative period,[34] even though no cardiac events occurred in the perioperative period in this study. As an open surgery requiring general anesthesia, CEA places greater demands and creates a greater burden on the heart, resulting in a higher incidence of perioperative myocardial infarction in CEA compared with CAS.[35]

Patch infection is a very rare but serious complication of CEA surgery, with most cases noted following the usage of synthetic patches.[36] It may present as swelling, pseudoaneurysms, or draining sinuses, and occurs in <1% of cases.[36,37] Due to its low incidence, the exact risk factors are not well elucidated. However, since it is closely associated with surgical site infection, conditions such as perioperative hematoma, diabetes mellitus, and immunosuppression may increase its risk.[37] In this study, no infection-related cases occurred, highlighting the anti-infection ability of BP patch.

Only one patient underwent re-exploration hematoma during the perioperative period. To prevent thrombosis, patients routinely need to use antiplatelet drugs, but this undoubtedly increases the risk of hematoma. Morales Gisbert *et al.*[38] summarized the risk factors associated with hematoma in their single-center retrospective study, including clopidogrel use, post-operative hypertension, pre-operative anticoagulant use, and prosthetic patch. It has also been found that the use of dual antiplatelet therapy (relative risk [RR] = 11.84, $p = 0.002$) and anticoagulation (RR = 8.604, $p = 0.02$) before CEA surgery is significantly associated with the occurrence of severe hematoma.[39] In these cases, more careful hemostasis may be required during surgery, or even the use of drainage tubes should be considered to prevent more serious consequences.

This study has several limitations. First, there is a lack of study power to detect the differences in stroke or mortality rates due to the incidence of adverse events. Second, the follow-up duration was not sufficiently long, which could have introduced bias to some extent. Third, this study spanned a long period, and the COVID-19 pandemic seriously stifled the progress of the entire study. Fourth, because several patients chose to do primary closure without a patch, the enrollment became slow during the consent acquisition process.

5. Conclusion

The BP patch shows no significant difference compared to the polyurethane patch available on the market in terms of the restenosis rate or adverse clinical events during

both the peri- and post-operative periods. These findings demonstrate that the BP patch is non-inferior to the existing polyurethane patch, supporting their potential use during CEA. Subsequent studies with larger sample sizes are still needed to demonstrate its long-term efficacy.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Liqun Jiao, Yanfei Chen
Formal analysis: Yao Feng, Daqiao Guo
Investigation: All authors
Methodology: Yanfei Chen, Yao Feng
Writing – original draft: Yanfei Chen, Yao Feng.
Writing – review & editing: Yabo Huang, Liyong Zhang, Zhen Li, Daqiao Guo, Liqun Jiao

Ethics approval and consent to participate

The study protocol was approved by the ethics committees at each of the five tertiary centers (including Xuanwu Hospital, Capital Medical University [Department of Neurosurgery]; Zhongshan Hospital, Fudan University [Department of Vascular Surgery]; the First Affiliated Hospital of Soochow University [Department of Neurosurgery]; Liaocheng People's hospital [Department of Neurosurgery]; and the First Affiliated Hospital of Zhengzhou University [Department of Vascular Surgery]) and informed consent was obtained from each patient.

Consent for publication

All images used in this study were anonymized; hence, consent for publication was waived.

Availability of data

The data used in this study will be made available on request to the corresponding authors.

Further disclosure

Trial registration: Chinese Clinical Trial Registry ChiCTR2300075538 (https://www.chictr.org.cn/bin/project/edit?pid=120172).

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ACCSCIENCE PUBLISHING

Brain & Heart

CASE REPORT

Brain pathology in an infant with *PROKR2* microduplication: A case report

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Abstract

Overexpression of prokineticins and their receptors is increasingly recognized as a contributing factor in heart failure and often fatal myocyte necrosis. Activation of prokineticin pathways is typically triggered by cerebral hypoxia and ischemia, viral and bacterial infections, inflammatory and immune responses, or energy deprivation leading to cell apoptosis. However, experimental models have demonstrated that prokineticin pathway activation can also occur independently due to aberrant expressions of specific microduplicated/microdeleted genes. Although prokineticins may play a causal role in cardiac death in adults and children with abnormalities of accessory pathways between the atria and ventricles, they have never been reported to cause brain injuries, especially in neonates. This report describes an infant born with facial dysmorphisms and moderate hypoxic distress at birth but without evidence of atrioventricular conduction defects, viral or bacterial infections, or severe metabolic dysfunction. Despite these findings, neuropathologic examination following the infant's death at 5 months revealed recent necrotic foci in the cerebral cortex and, in particular, older brain lesions with features indicative of metabolic energy failure in subcortical structures. Genetic analysis identified a rare prokineticin receptor 2 (*PROKR2*) gene microduplication, which, in the absence of other identifiable causes, is strongly implicated as a contributing factor in the observed chronic brain lesions. These findings suggest that *PROKR2* gene microduplication may contribute to unexplained neonatal brain injury, warranting further investigation.

Keywords: Prokineticin receptor 2; Microduplication; Heart failure; Cerebral necrosis; Cardiac injury

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1. Background

Double-stranded RNA-dependent protein kinases are G-protein-coupled receptors that bind the two small proteins prokineticin 1 (PROK1) and prokineticin 2 (PROK2), which play critical roles in various biological functions across multiple tissues. The prokineticin receptor 1, encoded in the 2q14 region, is predominantly expressed in human endocrine glands, while prokineticin receptor 2 (*PROKR2* or *PKR2*), encoded in 20p12.3, is most highly expressed in the heart and, to some extent, the brain. In particular, PROK1 shares

most functional similarities with vascular endothelial growth factor and stimulates angiogenic signaling and endothelial cell proliferation, whereas PROK2 activation promotes vascular fenestration and increases permeability.[1] The pathogenetic role of *PROKR2* in heart and brain diseases has received particular attention, with studies focusing on diabetic cardiomyopathy,[2] congestive heart failure and hypertrophy,[3-6] interferon activation, inflammation, apoptosis, viral and bacterial infections,[7-12] and ischemic brain injury.[13,14] Brain and heart damage appear to be closely associated with the upregulation of the PROKR2 ligand, which can be activated by external factors such as viral and bacterial infections, inflammation, hypoxia-ischemia, and excitotoxic glutamate.[15] Copy number variants (CNVs) in the 20p12 region have been found to affect various tissues in humans pathologically, most notably the heart. Interestingly, deletions of 20p12.3 were first found in association with Wolff-Parkinson-White (WPW) syndrome, including cases in infants.[16] Subsequent studies, however, identified WPW syndrome in families carrying microduplications of the same region.[17]

The infant reported here represents a rare case of brain injury potentially attributed to moderate perinatal hypoxia and, in particular, a 121 kb microduplication in the 20p12.3 region involving the *PROKR2* gene. A possible gain-of-function mechanism associated with mild hypoxia at birth is hypothesized, as WPW syndrome characterized by abnormal accessory electrical pathway between the atria and ventricles was excluded through multiple recordings of normal electrocardiograms (ECGs). Confirming the pathogenetic role of *PROKR2* could have significant therapeutic implications. It should be noted that experimental models have shown that specific PROKR2 antagonists can reduce cardiac infarct volume, mitigate hypertrophic dilatation, and partially rescue myocyte apoptosis.[8,9,15,18,19]

2. Case presentation

The infant was born at 36 weeks of gestation to healthy, first-cousin parents through cesarean section performed due to placental abruption. At birth, he presented with abnormal cardiac activity, including a holosystolic murmur caused by a double interventricular and interatrial defect (ostium secundum), a large left-to-right shunt, and dilated heart cavities. From the outset, he exhibited feeding difficulties characterized by weak sucking and poor food demand, alongside severe axial hypotonia and segmental antigravity hypertonus. Critical events were noted, including sudden flexor hypertonus of the lower limbs, cyanosis, and oral automatisms resembling chewing, lasting up to 10 min. Despite initiating digitalis and diuretic therapies, his condition showed no significant improvement. Over time, the infant developed hepatomegaly and progressive biventricular hypertrophy with pulmonary overflow. Initial metabolic blood and urine tests were normal, except for elevated capillary lactic acid levels, reaching 55 mg% (normal <20 mg%). This elevation prompted further analyses, including assessments of urinary organic acids, plasma amino acids, acylcarnitines, and serum very-long-chain fatty acids, all of which yielded normal results. Interestingly, electroencephalographic recording showed no evidence of epileptogenic activity.

Brain magnetic resonance imaging (images not shown) revealed diffuse poor myelination and lateral ventricles dilatation. These findings remained unchanged during a subsequent hospitalization 2 months later for heart failure, despite the infant's severely deteriorated condition. Neurological examination during this period also remained substantially unchanged. Given the presence of several dysmorphic features, such as forehead hypertrichosis, retroflexed ears with an overfolded right ear, and micrognathia, an array comparative genomic hybridization analysis was performed. The analysis revealed a rare 20p12.3 microduplication of 121 kb, the region encoding the *PROKR2* gene. Despite ongoing treatment, the infant's clinical condition did not improve, and he passed away at 5 months of age. An autopsy was performed with parental consent. The general autopsy revealed multiple ischemic cardiac areas with diffuse myocyte necrosis. Neuropathologic examination revealed notable findings.

The cerebral cortex exhibited a reduced number of neurons in all laminae, accompanied by weak astrocytic reactivity, rare macrophages, and marked spongiosis affecting nearly all layers. Notably, active necrosis was absent (Figure 1).

The subcortical nuclear structures displayed extensive spongiosis similar to that observed in the cerebral cortex,

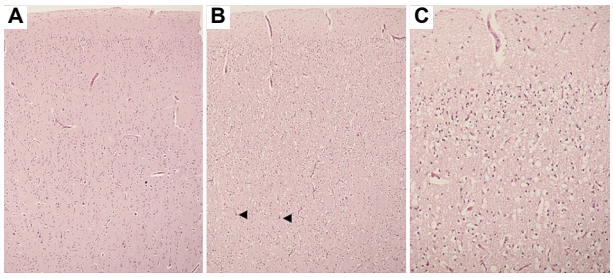

Figure 1. Representative motor cortical areas show mild neuronal scarcity without spongiosis (A) and severe spongiosis with marked neuronal loss, including pyramidal neurons, in other areas (B, solid arrowheads). Severe spongiosis is more evident in the more superficial laminae (C). Hematoxylin and eosin staining; Scale bar: A and B: 2.1 cm, C: 1.3 cm; Magnifications: A and B: 2.5×, C: 4×.

particularly within the basal ganglia, where it exhibited a multifocal distribution, and in the brainstem nuclei, most notably the inferior olivary nucleus. This was accompanied by pronounced astrocytic reactive gliosis and the presence of cells exhibiting macrophagic and microglial features (Figure 2).

Several necrotic foci of varying volume and shape were identified in the cortex, accompanied by mild spongiosis, microglia, macrophages, and occasional polynuclear cells, likely blood leukocytes. In the absence of cavitation, these foci resembled coagulative necrosis without evidence of calcification, hemorrhage, or hemosiderin deposition (Figure 3).

Larger necrotic foci, predominantly observed in the hemispheric white matter, characterized by severe demyelination, neuropil disruption with tissue spongiosis, and residual normal neurons. Additional findings included progressive neuronal degeneration, a limited number of macrophages, and the presence of small spheroids, likely indicative of axonal degeneration. Of particular interest was the significant proliferation of capillaries within these regions (Figure 4).

3. Discussion

This article reports the case of an infant with structural heart defects and a microduplication in the 20p12.3 region. The infant succumbed at 5 months of age due to progressive systemic and trophic deterioration accompanied by heart failure. Autopsy findings revealed ischemic changes in cardiac tissue, with evidence of myocyte necrosis, and extensive diffuse brain damage. The 20p12.3 microduplication, similar to its corresponding deletion, has recently been associated with WPW syndrome. However, WPW syndrome is neither typically linked to cardiac cavity defects nor is myocyte necrosis a recognized feature of the syndrome. Furthermore, repeated ECG recordings in this case revealed no abnormalities in the atrioventricular conduction pathway. These observations suggest that the 20p12.3 microduplication, potentially through a gain-of-function mechanism, may have been the primary cause of the cardiac and cerebral abnormalities observed in this case. The *PROKR2* gene, located within the duplicated 121 kb fragment, has been experimentally shown to induce pathogenic effects when upregulated. This upregulation may independently contribute to cardiac and brain injuries through a complex pathogenic mechanism involving vascular damage with wall fragmentation, membrane disruption, hypoxia-ischemia, excitotoxic glutamate, inflammation, apoptosis, mTOR dysfunction, and interferon activation.[3-15]

The brain lesions observed in this infant further underscore the significance of this rare CNV. Diffuse and pronounced spongiosis, as observed here, is atypical for brain damage secondary to heart failure, which generally results in ischemic necrosis due to inadequate perfusion. In this case, subcortical ischemic foci – likely of recent origin – are consistent with a cardiac-dependent circulatory defect. However, additional lesions, characterized by neuronal loss, the presence of a few residual neurons with normal morphology, spongiosis, axonal degeneration, mild astrocytic gliosis, and capillary proliferation, may have predated the terminal heart failure. Interestingly, these lesions share several cytological features with necrotic changes observed in mitochondrial diseases, which are typically associated with chronic metabolic energy defects rather than acute or subacute circulatory failure. Metabolic findings, including persistent metabolic acidosis with elevated capillary lactic acid levels and hepatomegaly from birth, warranted early investigation for neurometabolic diseases, including acylcarnitine abnormalities. Notably, experimental models have demonstrated that *PKR2* antagonists can reduce cardiac infarct volume, limit hypertrophic dilation, and partially rescue myocyte apoptosis.[8,9,18,19]

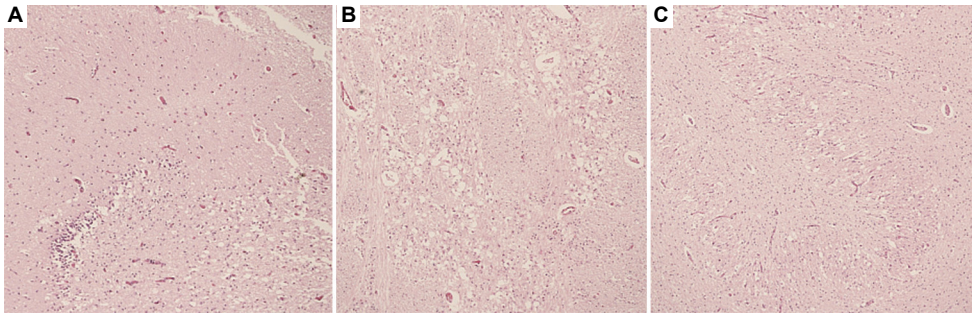

Figure 2. Diffused spongiosis with altered neuronal organization and partial loss of morphology in the hippocampus (A), basal ganglia (B), and inferior main olivary nucleus (C). Hematoxylin and eosin staining; Scale bar: A: 2.1 cm; B: 2.1 cm; C: 2.1 cm; Magnification: A, B, and C: 2.5×.

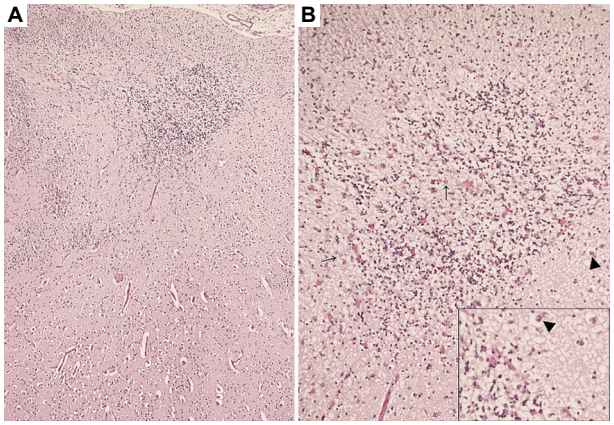

Figure 3. Multiple necrotic foci of varying sizes within the molecular laminae containing numerous inflammatory mononuclear cells (thin arrows), rare peripheral polynuclear leukocytes (solid arrowhead, inset), and multiple capillary dilatations (A and B). Hematoxylin and eosin staining; Scale bar: A: 2.1 cm; B = 1.3 cm; Magnification: A: 2.5×, B: 4×

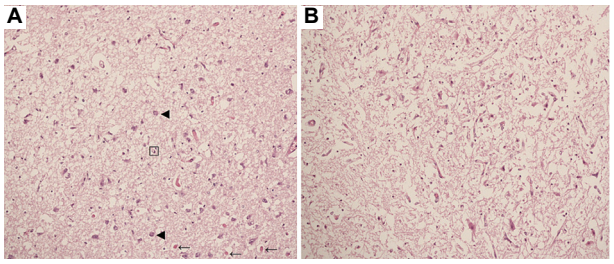

Figure 4. Focal necrosis with extensive spongiosis, disrupted neuropil, rare degenerating neurons (solid arrowheads), isolated polynuclear leukocytes (rectangular box), axonal spheroids (thin arrows), and capillary proliferation (A) in the basal ganglia; similar features of focal necrosis in the hemispheric white matter (B). Hematoxylin and eosin staining; Scale bar: A and B: 0.5 cm; Magnification: A and B: 10×

4. Conclusion

This case report describes an infant with a previously unreported CNV *PROKR2* microduplication. The findings suggest that this CNV could play a primary causal role in human heart and brain damage. Such effects may manifest during the neonatal period or early infancy, rather than being restricted to older children and adults. Consequently, this CNV should be considered a potential contributing factor in cases of sudden infant death syndrome.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: All authors
Investigation: All authors
Writing – original draft: All authors
Writing – review & editing: All authors

Ethics approval and consent to participate

The manuscript did not need the approval of the Ethical Committee of our University Administration as this is not a requirement for the publication of a single case provided that it is of definite interest to the scientific community (Regulations of the Ethical Committee of "Area Vasta Emilia Nord," Italy, approved on September 22, 2020).

Consent for publication

Informed consent for publishing his/her data was obtained verbally from the mother, and patient anonymity was maintained.

Availability of data

Data and materials are available from the authors upon reasonable request.

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ACCSCIENCE PUBLISHING

Brain & Heart

CASE REPORT

A rare neurological association of bicuspid aortic valve: A case report

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Abstract

A 45-year-old male presented to the Emergency Department with a 2-h history of sudden onset right-sided headache and difficulty walking. Initial non-contrast computed tomography (CT) of the brain was unremarkable. Twelve-lead electrocardiogram showed left ventricular (LV) hypertrophy with strain pattern. On echocardiography, the aortic valve was noted to be bicuspid, associated with at least moderate eccentric aortic regurgitation and moderate aortic stenosis. In view of the initial presentation of ataxia and headaches, and the finding of bicuspid aortic valve (BAV) on echocardiography, an urgent CT of aorta and carotid arteries was performed, revealing dissection of the right vertebral artery and a right lateral medullary infarct. Aortic root dilatation and aortic dissection are well known complications of BAV. However, vertebral artery dissection in the context of BAV with a normal aortic root is unusual, and to our knowledge has only been reported once in the literature so far.

Keywords: Bicuspid aortic valve; Vertebral artery dissection; Ataxia; Aorta; Congenital heart disease

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1. Introduction

Bicuspid aortic valve (BAV) disease is the most common congenital cardiac anomaly.[1,2] The association between BAV and aortopathy, as well as other complications such as infective endocarditis, aortic valve stenosis, or regurgitation, is well known and reported in the literature.[3-6] Our patient presented with neurological symptoms due to dissection of the right vertebral artery in the context of a BAV disease and aortic dimensions in the upper limit of normal. The association between vertebral artery dissection and BAV has, to our knowledge, only been reported once in the literature.[3] The current case study highlights the importance of excluding BAV in patients presenting with cervicocephalic artery dissection and neurological complications, especially at a young age.

2. Case presentation

A 45-year-old gentleman presented to the Emergency Department with a 2-h history of sudden-onset right-sided headache and difficulty walking. He denied any chest pain, shortness of breath on exertion, palpitations, dizziness, or syncope. He did not have any recent febrile illness. He was previously healthy and on no regular medications. He

did not smoke or drink alcohol and denied any illicit drug use. He denied recent long-distance travel or trauma. He had no family history of cardiac disease, sudden death, or connective tissue disorders. Blood pressure on admission was 140/85 mmHg and heart rate was 60 bpm. He had a Glasgow Coma Scale of 15. On examination, he had an ejection systolic murmur with radiation to both carotids and an early diastolic murmur, heard loudest at the left parasternal edge. The chest was clear on auscultation, and there was no lower limb edema. He had an ataxic gait and tone, power, reflexes, and sensation of the lower limbs were normal. Speech was unimpaired and he had no dysdiadochokinesia or past-pointing. He had anisocoria with a constricted right pupil compared to the left and minimal ptosis on the right, in keeping with Horner's syndrome. He had no features consistent with connective tissue diseases such as Marfan syndrome or Ehlers–Danlos syndrome.

Routine blood investigations were within normal limits, including complete blood count, renal function, erythrocyte sedimentation rate, and C-reactive protein. Chest X-ray was normal. Non-contrast computed tomography (CT) of the brain was unremarkable. Twelve-lead electrocardiogram (ECG) showed sinus rhythm and LV hypertrophy with strain pattern. No previous ECGs were available for comparison. Troponin levels were normal. He was admitted for further observation and cardiology review was requested in view of the ECG changes. Based on the history and clinical findings, an inpatient transthoracic ECG was conducted to assess wall motion, LV wall thickness, LV function, and valves (Video A1). This showed a severely dilated LV (LV end systolic diameter [LVESD] = 51 mm; LV end diastolic volume [LVEDV] = 198 mL; and LV end systolic volume [LVESV] = 102 mL). LV function was mildly impaired, with a LV ejection fraction (LVEF) of 45% by Simpson's biplane method. No regional wall motion abnormalities were present. The right ventricular size and function was normal. A BAV was found with at least moderate eccentric aortic regurgitation and moderate aortic stenosis, V_{max} 3.3 m/s, mean pressure gradient (PG) 30 mmHg, and aortic valve area (AVA) 1.4 cm^2. Diastolic flow reversal was present in the descending aorta. Aortic root dimensions were at the upper limit of normal and there was no evidence of aortic coarctation or aortic dissection. The other valves were grossly normal. No pericardial effusion was present.

Given the initial presentation of headaches and ataxia and the finding of BAV on transthoracic echocardiography, an urgent CT of aorta and carotid arteries was performed to rule out arteriopathy. This unveiled dissection of the V3 segment of the right vertebral artery and right lateral medullary infarct, as shown in Figure 1. There was no evidence of aortic dissection.

While on the ward, his blood pressure was elevated to 150/90 mmHg. He was started on aspirin 75 mg daily and clopidogrel 75 mg daily, the latter for a total of 3 weeks. He was also started on atorvastatin 80 mg nocte, enalapril 5 mg twice daily, and spironolactone 12.5 mg daily. A vasculitis screen, entailing complement levels measurement, autoimmune panel, immunoglobulin levels measurement, as well as antiretroviral screen, hepatitis screen, and syphilis serology were performed to rule out other causes of dissection. Total cholesterol level was 6.2 mmol/L and low-density lipoprotein was 4.4 mmol/L. Inpatient magnetic resonance imaging of the head showed T2-flair changes with concomitant restricted diffusion on diffusion-weighted imaging sequences of the right lateral medullary and corresponding low signal on the apparent diffusion coefficient, in keeping with an acute ischemic infarct of the right lateral medulla, as shown in Figure 2. A magnetic resonance angiography confirmed a dissection of the right distal vertebral artery. After 3 days, his gait returned to normal and Horner's syndrome resolved.

To further assess the valvular heart disease, cardiac magnetic resonance imaging (CMR) was performed. This showed a dilated LV (LVEDV = 280 ML [139 mL/m^2], and LVESV = 162 mL (80 mL/m^2]) with mildly reduced LV systolic function (LVEF 42%). Increased LV mass (194 g, 96 g/m^2) with eccentric LV hypertrophy was noted. BAV was confirmed on CMR, with right-left cusp fusion, as shown in Video A2. There was associated severe aortic regurgitation, as shown in Figure 3, with a regurgitant

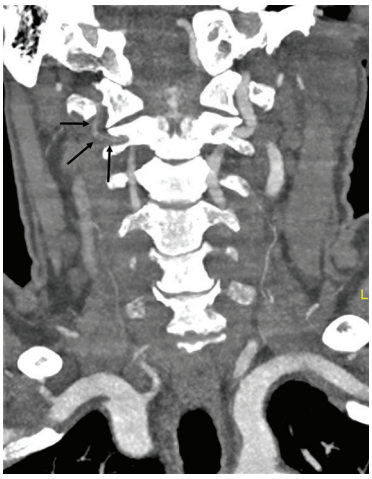

Figure 1. Coronal reconstruction of CT aortogram. There is a marked mural irregularity and moderate stenosis of the right vertebral artery (indicated by black arrows), in keeping with acute right vertebral artery dissection.
Abbreviation: CT: Computed tomography.

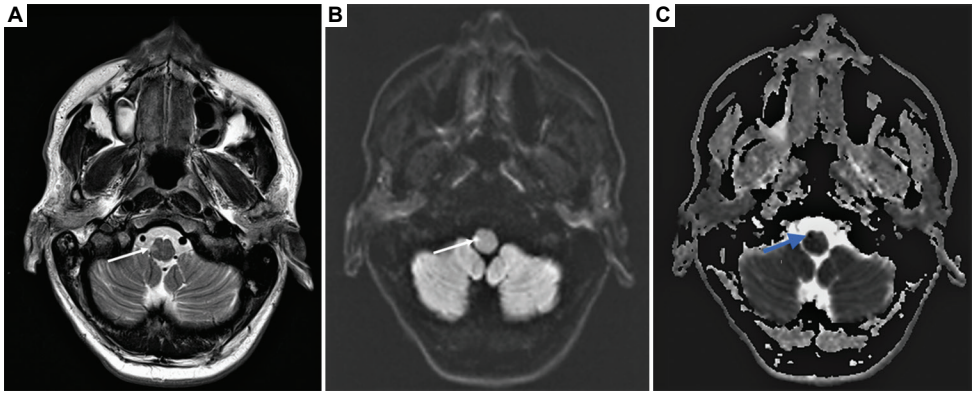

Figure 2. MRI of the brain. (A) Axial T2-weighted MRI of the brain. There is a small wedge-shaped focus of high signal in the right side of the medulla (indicated by white arrow), in keeping with an acute ischaemic infarct. (B) Diffusion-weighted imaging. At the same level as panel (A), the scan shows a small focus of restricted diffusion in the right side of the medulla (indicated by white arrow). (C) Corresponding low signal on the apparent diffusion coefficient map (indicated by blue arrow), in keeping with an acute ischemic infarct.
Abbreviation: MRI: Magnetic resonance imaging.

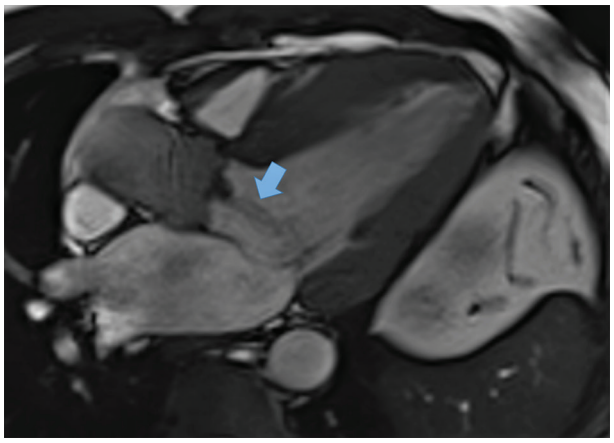

Figure 3. Cardiac MRI. There is nodular thickening of aortic valve leaflets and a central regurgitant jet (indicated by blue arrow). Although the size of the regurgitant jet on MRI appears small visually, phase-contrast imaging through the valve shows severe aortic regurgitation.
Abbreviations: MRI: Magnetic resonance imaging; SSFP: Steady-state free precession.

fraction of 50% and regurgitant volume of 60 mL. Moderate aortic stenosis with restricted leaflet motion was present (peak forward velocity of 3.0 m/s and forward volume of 67 mL). Ascending aorta dimensions were at the upper limits of normal (sinus of Valsalva 3.2 × 3.2 cm, sinotubular junction 3.3 × 3.2 cm, ascending aorta at the level of the pulmonary bifurcation 3.6 × 3.6 cm, ascending aorta just before the brachiocephalic trunk 3.1 × 3.1 cm, aortic arch before the left subclavian artery 2.7 × 2.6 cm, and descending aorta at the isthmus 2.7 × 2.6 cm).

According to the 2021 ESC/EACTS Guidelines for the management of valvular heart disease,[7,8] the patient fulfilled criteria for valve replacement. A coronary angiogram was performed before surgery, in view of the findings of hypertension and hyperlipidemia during admission. The angiogram showed significant proximal left anterior descending stenosis and an occluded right coronary artery at the mid-segment, receiving collaterals from the left circumflex artery. The patient was referred for surgical aortic valve replacement and coronary artery bypass grafting. At clinical follow-up after surgery, he was referred for genetic screening for collagen vascular disorders, but no pathogenic mutation was found. The patient's family members were offered transthoracic echocardiography as screening for BAV disease.

3. Discussion

Our patient presented with neurological symptoms due to dissection of the right vertebral artery in the context of a BAV disease and aortic dimensions in the upper limit of normal. The association between BAV and aortopathy is well known and reported in the literature. However, the association between vertebral artery dissection and BAV has, to our knowledge, only been reported once in the literature.[6]

BAV is the most common congenital cardiac anomaly, affecting around 1 – 2% of the general population.[9] The LV outflow tract, aortic valve cusps, aortic arch, and its branches are all derived from cells originating in the neural crest. The neural crest is a transient structure in early embryogenesis, and a disorder of neural crest cell migration could possibly justify the association between cervicocephalic artery dissection (including the vertebral and carotid arteries) and BAV.[10,11] Although the relative contribution of intrinsic or genetic wall abnormalities and altered hemodynamics remains debated, both factors are probably involved.

4. Conclusion

This case study highlights the importance of excluding BAV in patients presenting with cervicocephalic artery dissection and neurological complications, especially at a young age.

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None.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Rachel A. Xuereb, John Bonello
Investigation: Maria J. Bonello, Gabriel Galea
Writing – original draft: Rachel A. Xuereb
Writing – review & editing: John Bonello, Robert G. Xuereb

Ethics approval and consent to participate

Verbal informed consent of the patient was obtained prior to participation.

Consent for publication

Verbal informed consent of the patient obtained for releasing his findings and data in this paper.

Availability of data

Not applicable.

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Appendix

Video A1. Transthoracic echocardiogram, parasternal long axis view. This shows a severely dilated left ventricle with mildly reduced LV systolic function. Aortic valve is calcified and appears abnormal.

Video A2. Cardiac magnetic resonance imaging. Steady-state free precession (SSFP) cine stack through the aortic valve (cine plays from cranial to caudal, passing through the valve) shows a bicuspid aortic valve with fusion of the right (RCC) and left coronary cusps (LCC). There is marked nodular thickening and signal dropout of the aortic valve, particularly of the LCC, in keeping with leaflet calcification. There is a large coaptation defect in the inferior part of the valve at the LCC-RCC commissure, likely secondary to the marked calcification of the LCC. Aortic valve opening area is visually reduced; formal planimetry and phase-contrast imaging (not shown) confirmed moderate aortic stenosis.
Abbreviations: RCC: Right coronary cusps; LCC: Left coronary cusps.

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COMMENTARY

Pregnancy-associated coronary artery dissection (P-SCAD): A crucial differential diagnosis for chest pain during pregnancy

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Abstract

Pregnancy-associated spontaneous coronary artery dissection (P-SCAD) is a rare but severe cause of acute coronary syndrome. The clinical presentation of P-SCAD can vary widely, ranging from asymptomatic cases to cardiac arrest and sudden cardiac death. Chest pain is the most common presenting symptom, though other symptoms, such as dyspnea, nausea, vomiting, and palpitations, may also occur. P-SCAD is often underdiagnosed because patients typically do not fit the profile of those with atherosclerosis and myocardial infarction. It predominantly occurs in younger individuals without traditional cardiovascular risk factors. The diagnosis of P-SCAD is commonly made during coronary angiography. Therefore, in pregnant and postpartum females presenting with chest pain or pressure, P-SCAD should be considered in the differential diagnosis, regardless of the presence of other risk factors such as age, hypertension, or diabetes.

Keywords: Pregnancy-associated spontaneous coronary artery dissection; Acute coronary syndrome

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Pregnancy-associated spontaneous coronary artery dissection (P-SCAD) most commonly occurs during the third trimester or within the first 30 days after delivery, with a prevalence of only 1.18/100,000 pregnancies.[1] It is characterized by coronary artery dissection that is not caused by trauma or atherosclerosis but by bleeding into the vessel wall.[2] The proposed pathophysiology is linked to hormonal changes during pregnancy, where increases in estrogen and progesterone levels impair collagen synthesis, thereby reducing the elasticity of the vessel wall, which is necessary to withstand hemodynamic changes.[3] In addition, estrogen increases the production of matrix metalloproteinase, which weakens the structural integrity of the vasa vasorum in the outermost wall (tunica adventitia).[3] The literature describes two primary theories of rupture. The first involves the rupture of the innermost layer (tunica intima) of the coronary vessel, creating a false lumen that narrows the vessel's caliber and reduces blood flow.[4] This condition appears as an intimal flap on angiography as the contrast material tracks into the false lumen. The second theory, known as the "outside-in" hypothesis, involves rupture in the vasa vasorum of the outermost vessel layer (tunica adventitia), which also creates a false lumen.[4] However, this alteration does not appear as a flap on angiography due to the lack of communication between the true and false lumens (Figure 1).

Spontaneous coronary artery dissection	Pregnancy-associated spontaneous coronary artery dissection
Coronary artery hematoma and intimal tears narrow the lumen, thereby limiting blood flow to the myocardium	P-SCAD frequently occurs in the 1st month postpartum P-SCAD has severe presentation: - ST-elevation myocardial infarction - Reduced left ventricular function - Left main and/or multivessel involvement P-SCAD versus SCAD: - P-SCAD has a more severe presentation - P-SCAD patients have a history of multiple pregnancies - P-SCAD patients have fewer extracoronary vascular abnormalities

Figure 1. Features of pregnancy-associated spontaneous coronary artery dissection.
Abbreviation: SCAD: Spontaneous coronary artery dissection.

Approximately 1 – 4% of acute coronary syndrome (ACS) cases are attributable to SCAD, which predominantly affects females.[5] P-SCAD accounts for a small percentage of these cases and typically presents as chest pain, sudden cardiac death, or ventricular arrhythmias.[5] According to the Mayo Registry report by Tweet *et al.*[6] and a comprehensive review of P-SCAD cases by Havakuk *et al.*,[7] significant risk factors for P-SCAD include being over 30 years old, pre-eclampsia, and multiparity. Notably, compared to non-pregnant females with SCAD, P-SCAD patients exhibit markedly reduced left ventricular function, multivessel involvement, ST-elevation myocardial infarction at presentation with predominant left anterior descending or left main coronary artery involvement, and a surprisingly low prevalence of extravascular manifestations, such as fibromuscular dysplasia or Marfan syndrome.[6,7] Preferred treatment for P-SCAD is primarily based on retrospective observational data. A recent review summarized cases of P-SCAD and SCAD over the past 15 years in the USA.[8] Among these, fewer P-SCAD cases (42.7%) were treated conservatively, with the majority (32.2%) progressing to revascularization. In contrast, a larger proportion of SCAD cases (77.2%) were treated conservatively, with only a small percentage (2.3%) requiring revascularization.[8] Similarly, prospective multicenter studies from the Canadian SCAD registry demonstrated conservative management in up to 84.3% of SCAD cases, with a 0.8% mortality rate at 3 years.[9] Another prospective study by Hassan *et al.*[10] showed higher rates of major cardiac events both in-hospital and at follow-up (3.7 years) post-percutaneous coronary intervention (PCI) in SCAD patients. These findings suggest that P-SCAD likely presents with a worse prognosis than SCAD in non-pregnancy-associated coronary artery disease. Given the risk of progression of dissection with PCI, some authors have recommended initial conservative management unless there is significant chest pain, hemodynamic instability, or substantial left main involvement.[11] Emergent coronary artery bypass grafting following PCI has been reported in 10 – 12% of cases.[12,13] According to a recent publication by the European Society of Cardiology, medical management for SCAD should primarily involve beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[14] Furthermore, thrombolysis is contraindicated, the duration of dual antiplatelet therapy remains controversial, and statins should be used if the patient has hyperlipidemia.[14]

In conclusion, P-SCAD is a rare but severe condition that presents with worse ACS outcomes compared to SCAD in non-pregnant individuals. Diagnosis can be challenging, and the optimal management strategies for SCAD remain unclear. However, based on observational data, most patients eventually progress from medical management to intervention. Due to the life-threatening nature of the condition, P-SCAD should be included in the differential diagnosis for postpartum females presenting with chest pain. Further research is needed to better understand the pathophysiology, risk factors, and long-term outcomes of P-SCAD and to develop evidence-based management guidelines for this condition.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Muhammad Haris
Writing – original draft: Muhammad Haris, Amer Hammad
Writing – review & editing: Amer Hammad, Vicky Kumar

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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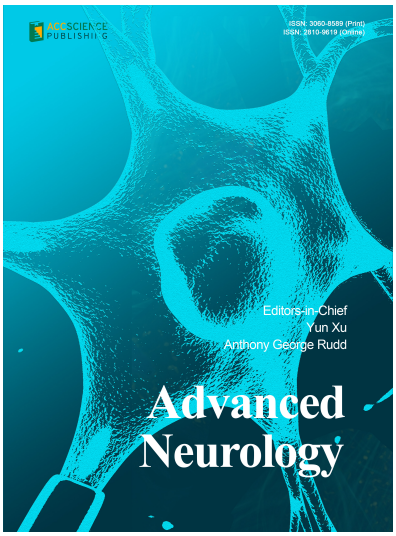

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