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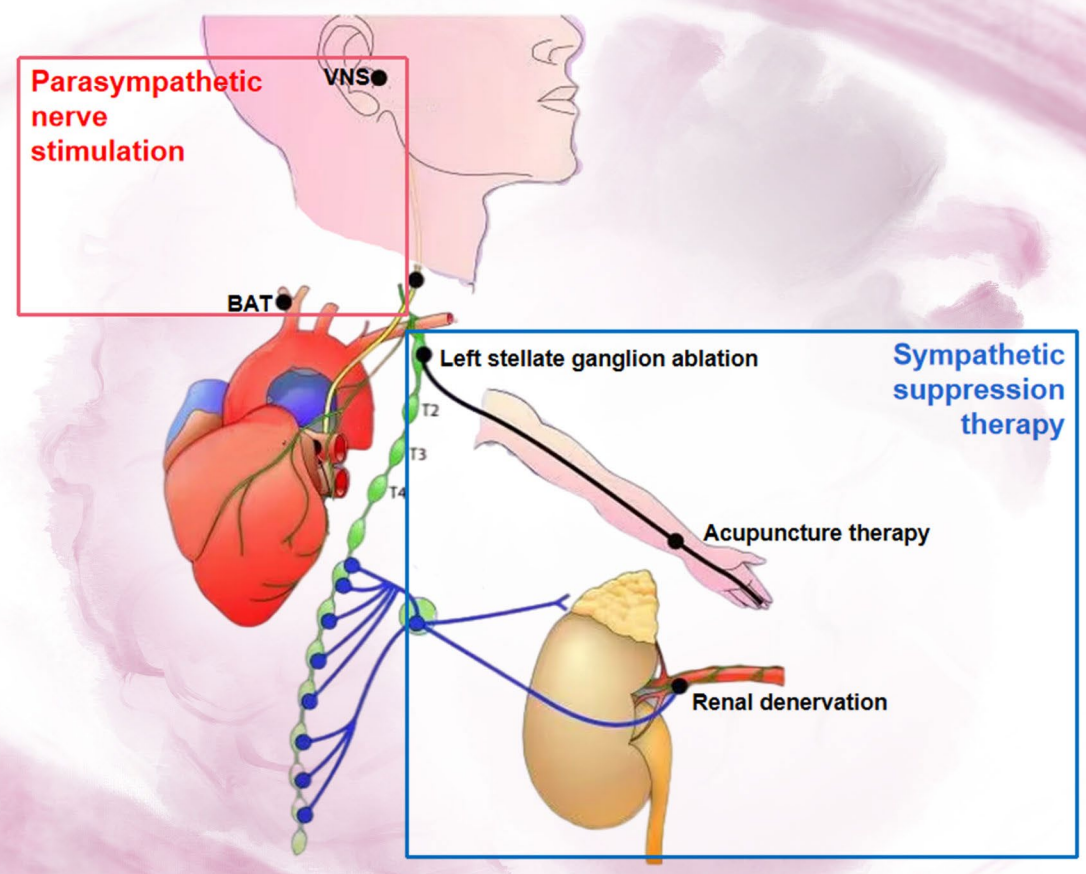

Autonomic nerve and its modulation approaches for heart failure

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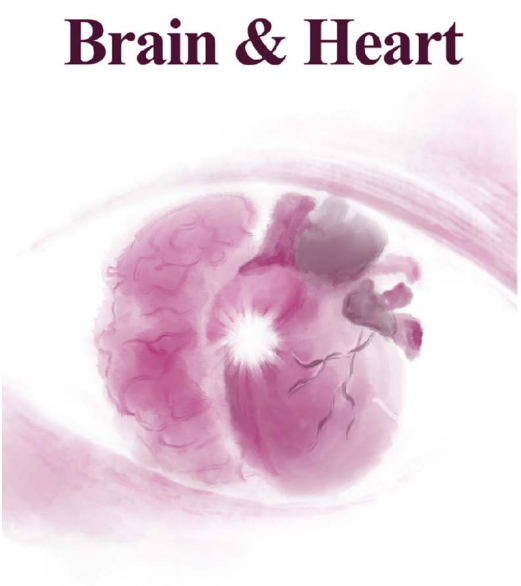

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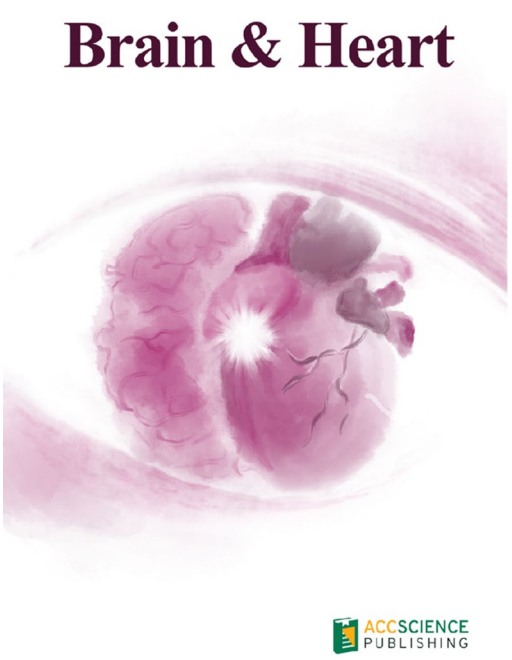

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REVIEW ARTICLE

Clinical predictive scores for detection of sub-clinical atrial fibrillation after cryptogenic or embolic stroke of undetermined source: A brief systematic review

Luca Masotti*, and Elisa Grifoni

Internal Medicine II and Stroke Unit, San Giuseppe Hospital, Empoli, Italy

Abstract

Subclinical atrial fibrillation (SAF) is the primary underlying cause of cryptogenic stroke (CS) or embolic stroke of undetermined source (ESUS), particularly in patients over 65 years of age. Therefore, it is strongly recommended screening for SAF in these patients. The development of tools designed to determine the priority of SAF screening is essential for optimizing the diagnostic workup. The aim of our study was to investigate the clinical predictive scores available for SAF detection in patients with CS or ESUS. We gathered data from articles published on the PubMed database from January 1, 2000, to January 31, 2023. Our search yielded eight scores for CS and three for ESUS. SAF diagnosis was established using various methods: 12-lead ECG or 24-h ECG monitoring during 1-year follow-up in three scores; 72-h non-implantable ECG monitoring in two scores; 2 or 3-week non-implantable ECG monitoring in three scores; and implantable ECG monitoring in one score. In two scores, ECG monitoring was performed using a non-implantable and/or implantable loop recorder. Overall, the rate of SAF detection was approximately 6% when using devices for monitoring lasting no more than 72 h and increased to nearly 22% employing 2 or 3-week non-implantable or implantable devices. SAF was defined differently in various scores; five scores considered any episode, even if shorter than 30 s, while six scores required episodes to last at least 30 s. Advanced age was included as a variable in 10 of 11 scores, whereas left atrial enlargement, premature atrial beats, and brain computed tomography characteristics were features in four scores. The area under the curve values of these scores ranged from 0.72 to 0.94. In conclusion, it is still challenging to put the currently available clinical scores to use due to a lack of validation. To provide more comprehensive guidance, it is essential to conduct large prospective multicenter trials in the future.

Keywords: Stroke; Atrial fibrillation; Score; Electrocardiographic monitoring; Age

***Corresponding author:**
Luca Masotti (luca.masotti@tin.it)

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1. Introduction

Cardioembolism stands as the primary pathogenetic mechanism of ischemic stroke, with atrial fibrillation (AF) emerging as the major source of cardioembolism, particularly in patients aged 65 years and older. AF accounts for one-third of all ischemic strokes. In approximately one-fourth of cases, referred to as cryptogenic strokes (CS), the

underlying cause remains undefined even after first-line diagnostic work-up. Given that the majority of CS cases are associated with embolic mechanisms, a new term, "embolic stroke of undetermined source" (ESUS), was first introduced in 2014.

Subclinical AF (SAF) represents the primary underlying cause of CS or ESUS. Despite secondary prevention with mono or dual antiplatelet therapy, which remains the recommended first therapeutic option, the rate of stroke recurrence in CS or ESUS patients is approximately 5%[1]. Notably, randomized clinical trials have shown no advantage of direct oral anticoagulants (DOACs) over antiplatelets in preventing stroke recurrence in ESUS patients[2,3]. Conversely, in AF-related strokes, DOACs are recognized as the first-choice therapy for secondary prevention due to their superior efficacy and safety profile compared to Vitamin K antagonists or antiplatelets[4]. Therefore, the screening of SAF represents the cornerstone of the diagnostic workup for CS or ESUS. It is strongly recommended in this context to establish the etiology, select the appropriate treatment, and prevent recurrence. SAF can be detected through electrocardiographic (ECG) monitoring, either during hospital stay or after hospital discharge, using non-implantable or implantable devices. The rate of SAF detection increases proportionally with longer durations of ECG monitoring. For instance, when utilizing an implantable loop recorder ECG, the SAF detection rate is approximately 15% at 6 months, 23% at 1 year, and 43% at the 3-year follow-up in ESUS patients[5]. In recent years, recommendations for SAF detection in this context have been introduced and put into practice. The AF-SCREEN International Collaboration recommends a minimum of 72 h of ECG monitoring to detect SAF in cases of stroke with undetermined origin, utilizing telemetry during the hospital stay or continuous ambulatory ECG monitoring[6]. In cases where a diagnosis is not achieved with the initial 72-h ECG monitoring and there remains a high SAF risk, the AF-SCREEN collaborators suggest extending the ECG monitoring period using either non-implantable or implantable tools[6].

The European Stroke Organization guidelines recommend cardiac rhythm monitoring lasting longer than 48 h for all ESUS patients over 55 years of age. In addition, when feasible, prolonged monitoring using an implantable loop recorder ECG is advised[5]. However, in real-world clinical practice, only a minority of ESUS patients undergo implantable loop recorder monitoring due to its limited availability, invasiveness, and associated costs. Moreover, in many cases, the time between the stroke event and prolonged ECG monitoring can be extensive, increasing the risk of stroke recurrence. Thus, it is crucial to pre-select CS or ESUS patients with the highest probability of SAF. To address this challenge, tools such as predictive scores have emerged, aiming to tailor the priority for prolonged cardiac monitoring and reducing inappropriate costs. In recent years, several studies have reported on clinical scores capable of predicting the probability of detecting SAF during prolonged ECG monitoring. Surprisingly, there has been a lack of focus on clinical predictive scores for detecting post-stroke SAF in CS or ESUS. Hence, the primary aim of our study was to fill this important gap.

2. Materials and methods

We sourced data from the PubMed database by searching for articles published from January 1, 2000, to January 31, 2023, that reported on scores predicting post-stroke SAF detection. Our search criteria included combining the terms "AF" AND "stroke" in the title along with the term "score" in the title and/or abstract. To refine our search strategy, we also reviewed the bibliographies of the retrieved articles. Our search was limited to articles in the English language involving adults (≥18 years) with CS or ESUS, and we focused exclusively on papers reporting score derivation studies. Only original studies were included in the study, while meta-analyses, systematic reviews, and review articles were excluded from the study. In addition, internal or external validation studies were excluded if they were not included in the article presenting the derivation study. The first phase of the search was conducted by LM and subsequently reviewed by EG. In the first phase, we evaluated the titles and abstracts to identify potentially relevant articles. Following this initial selection, full-text articles were analyzed, along with their references. When necessary for statistical analysis, we employed MEDCALC statistical software (MedCalc Software Ltd., Acacialaan 22, B-8400 Ostend, Belgium).

3. Results

In total, we analyzed over 1100 articles. The search process is depicted in Figure 1.

From this pool, we selected 26 articles that reported predictive scores for post-stroke SAF. Fifteen articles were excluded because they focused on stroke cases other than CS and ESUS. Finally, we narrowed our selection down to 11 articles, with eight reporting predictive scores derived from CS and three from ESUS. Table 1 summarizes the characteristics of these retrieved scores.

Five studies adopted a prospective approach, while four followed a retrospective methodology. In addition, two studies utilized pooled data from three prospective stroke registries or studies for the analysis. In 10 out of the 11 studies, multivariate regression analyses were performed to identify predictors of SAF. Conversely, one study employed a univariate binary logistic analysis.

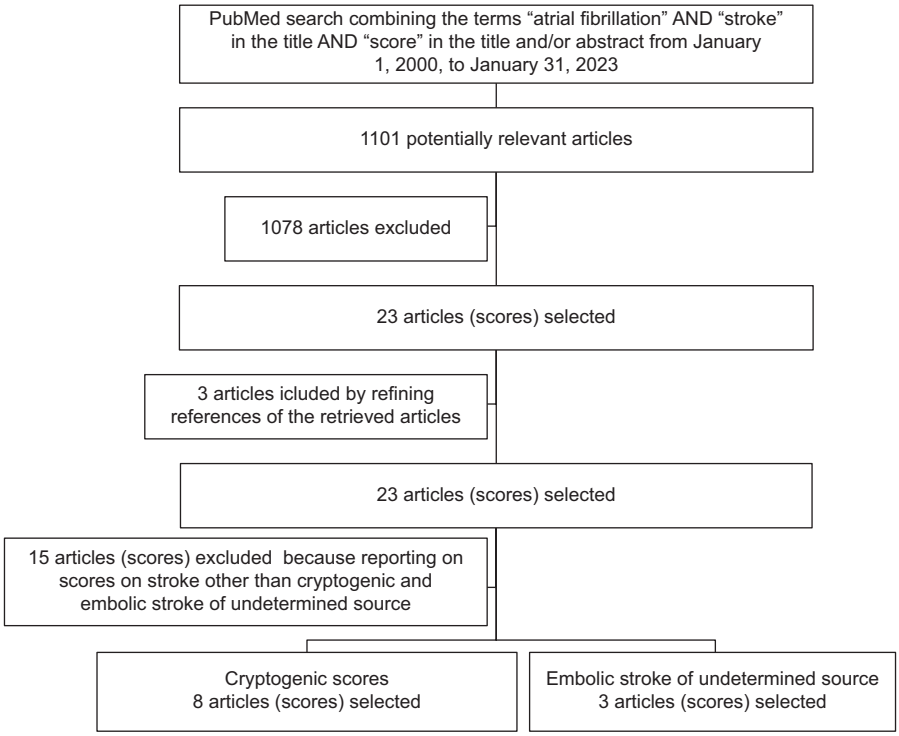

Figure 1. Selection process for articles from the PubMed database.

The sample sizes in these studies differed considerably, with nine out of 11 studies featuring sample sizes smaller than 300 patients and seven studies with sample sizes smaller than 200 patients.

The diagnostic methods for SAF also exhibited diversity. In three studies, SAF was diagnosed based on 12-lead ECG or 24-h ECG monitoring conducted for any reason during a 1-year follow-up. Two studies utilized 72-h non-implantable ECG monitoring, while three studies relied on 2- or 3-week-long non-implantable ECG monitoring. One study utilized implantable ECG monitoring. In two studies, the majority of patients underwent non-implantable ECG monitoring, while a small proportion of patients received implantable ECG monitoring (Table 2).

The incidence of SAF exhibited an upward trend in proportion to the duration of ECG monitoring. Overall, the SAF rate stood at approximately 6% when detected through 12-lead ECG or 24-h ECG monitoring performed for any reason during the follow-up period or through 72-h non-implantable ECG monitoring. In contrast, the rate rose to approximately 22% when SAF was detected using 2- or 3-week non-implantable or implantable devices (Table 2). In five studies, SAF was defined as any episode, even if shorter than 30 s, while in six studies; SAF was defined as episodes lasting at least 30 s. Among the variables considered, advanced age represented the most frequently included variable, present in ten of eleven scores. Left atrial enlargement (LAE), premature atrial beats, and computed tomography (CT) characteristics such as cortical or subcortical infarcts were included in four out of 11 scores. In addition, echocardiographic or laboratory signs of heart failure (HF) and National Institutes of Health Stroke Scale (NIHSS) scoring were included as variables in three and two scores, respectively (Table 3).

The predictive power of all the scores was strong, as evidenced by the area under the curve (AUC) values, which ranged from 0.72 for the Brown-ESUS score[15] to 0.94 for the DECRYPTORING score[13]. Among the studies reviewed, five included a comparator for the predictive scores. In four out of these five studies, the predictive scores outperformed CHA_2DS_2-VASc or $CHADS_2$ scores, demonstrating superior predictive power (Table 1).

4. Discussion

Screening for the underlying etiology of stroke is essential in tailoring appropriate secondary prevention strategies and preventing recurrence, particularly in patients with CS or ESUS. A pivotal component of this screening involves prolonged ECG monitoring. Non-invasive devices can monitor ECG signals for periods ranging from 24 h to 1 month, while invasive devices allow for ECG monitoring for up to 3 years. Although implantable ECG monitoring

Table 1. Synoptic table for predictive scores of post-stroke atrial fibrillation detection

Score acronym	NR	NR	HAVOC	AS5F
Study	Bugnicourt *et al.*[7]	Sudacevschi *et al.*[8]	Kwong *et al.*[9]	Uphaus *et al.*[10]
Study design	Prospective	Retrospective	Retrospective	Individual patient data from three prospective studies
Statistic method for defining AF predictors	Multivariate regression	Multivariate regression	Multivariate regression	Investigating the detection of AF with prolonged Holter monitoring, analyzed using multivariate regression
Sample size (patient number)	164	171	9,589	191
Age (mean±SD or median [IQR])	65.4±15.1	63.2±16.0 (with AF: 72.9±9.7; without AF: 61.4±16.4)	68.1±13.4/67.5±13.4	69.7±13.4
Methodology for AF diagnosis	ECG and/or 24-h Holter-ECG performed for any reason during a 1-year follow-up	21-day NIEM	ICD-9-CM data bank during follow-up revealing AF diagnosis	72-h NIEM
AF detection rate	13%	15%	5%	4.9%
Episode duration for AF diagnosis	Any	>30 s	Any	>30 s
Score variables (point)	Age≥72 years (2), history of CAD (1), history of stroke (1), and LAE (2)	Age>70 years (1), premature atrial complex on 12-lead ECG (1), left ventricle hypertrophy on echocardiography (1), previous white matter lesions on brain magnetic resonance (1)	Age ≥75 years (2), BMI≥30 (1), blood hypertension (2), congestive HF (4), CAD (2), PAD (1), and cardiac valve disease (2)	Age (0.76×year), NIHSS ≤5 (9), and NIHSS >5 (21)
Score range	0 – 6	0 – 4	0 – 14	The threshold of 67.5 serves as the delineation between low- and high-risk categories.
Score AUC (95% CI)	NR, 0% Score 0 – 1, 7% Score 2, 14% Score 3, 32% Score 4, 67% Score 5 – 6	NR, 4.8 (1.5 – 13.8) for Score 1, 23 (6.2 – 86.4) for Score 2, and 110 (15.5 – 778.5) for Score 3	0.77 (NR)	0.78
Comparator AUC (95% CI)	/	/	Significant better accuracy, sensitivity, and specificity (P<0.001) compared with CHA_2DS_2-VASc (AUC NR)	$CHADS_2$ 0.61 (NR), P=0.00032

(Cont'd...)

Table 1. *(Continued)*

Score acronym	ACTEL	GRAZ AF	DECRYPTORING	PROACTIA
Study	Muscari *et al.*[11]	Kneihsl *et al.*[12]	Vera *et al.*[13]	Skrebelyte-Strom *et al.*[14]
Study design	Retrospective	Prospective	Prospective	Prospective
Statistic method for defining AF predictors	Multivariate regression	Multivariate regression	Univariate binary logistic regression	Multivariate regression
Sample size (patient number)	123	150	63	236
Age (mean±SD or median [IQR])	69.7±13.4	66.7±15.3	77±7.8	68.6±12.5
Methodology for AF diagnosis	12-lead ECG and/or continuous ECG monitoring during hospital stay	12-month follow-up. Post-TIA/stroke daily pulse control or prolonged continuous rhythm monitoring (median duration 3 weeks). ECG was performed in the case of AF symptoms. IEM was employed in selected 24 of 150 patients	15-day NIEM	IEM
AF detection rate	7.3%	16%	24%	36%
Episode duration for AF diagnosis	Any	≥30 s	>30 s	>30 s
Score variables (point)	Age≥75 years (1), hypercholesterolemia (−1), mild-moderate tricuspid regurgitation (1), left ventricular EDV<65 mL (1), and LAE (1)	Age>75 years (2), prior cortical/cerebellar brain infarcts (2), LV EF<40% (2), supraventricular premature beats on baseline ECG (2), atrial run>20 beats (2), NT-proBNP>505 pg/mL (2), age 60 – 75 years (1), recurrent stroke under APs or multi-territory brain infarcts (1), LV EF 40 – 50% (1), >125 supraventricular premature beats on 24-h Holter-ECG (1), and NT-proBNP ≥505 pg/mL (1)	Age >75 years (9), blood hypertension (1), T troponin >40 ng/L (8.5), NT-proBNP >200 pg/mL (0.5), LA strain reservoir <25.3% (24.5), and LA strain conduct (0.5)	Formula: 0.05472×LAVIs mL/m2+0,95928×log (1+PAC/24 h)+0.03615×Pdur ms+1.05513×Pmorph
Score range	−1 – +4	0 – 16	0 – 44	/
Score AUC (95% CI)	0.80 (0.73 – 0.87)	0.85 (0.78 – 0.92)		
Comparator AUC (95% CI)	CHA_2DS_2-VASc 0.68 (0.60 – 0.77), *P*=0.03; STAF 0.71 (0.63 – 0.79), *P*=0.06; Brown ESUS-AF 0.70 (0.62 – 0.78), *P*=0.03	/		

(Cont'd...)

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

Score acronym	BROWN AF-ESUS	AF-ESUS	E_2AF
Study	Ricci *et al.*[15]	Ntaios *et al.*[16]	Grifoni *et al.*[17]
Study design	Prospective	Pool data of all consecutive ESUS patients registered in three prospective stroke registries	Retrospective
Statistic method for defining AF predictors	Multivariate regression	Multivariate regression	Multivariate regression
Sample size (patient number)	296	839	82
Age (mean±SD or median [IQR])	With AF: 72±11/without AF: 62.7±14.9	67 (54 – 77)	72±10
Methodology for AF diagnosis	Post-discharge 30-day NIEM and IEM	ECG performed for any reason during a 1-year follow-up	14-day NIEM
AF detection rate	12.8%	14.9%	43.9%
Episode duration for AF diagnosis	>30 s	Any	Any
Score variables (point)	Age≥75 years (2), age 65 – 74 years (1), and moderate-severe LAE (2)	Age ≥60 years (3), blood hypertension (2), any supraventricular extrasystole (1), left ventricular hypertrophy (−1), subcortical brain infarcts (−2), and non-stenotic carotid plaque (−3)	NIHSS ≥8 (5), blood hypertension (3), age ≥75 years (2), age 65 – 74 years (1), cortical and/or subcortical brain infarcts (1), posterior brain infarcts (1), LAE (1), and vascular disease (CAD and/or PAD)(1)
Score range	0 – 4	−6 – +6	0 – 14
Score AUC (95% CI)	0.726 (NR)	0.84 (0.79 – 0.86)	0.746 (0.638 – 0.836)
Comparator AUC (95% CI)	/	/	CHA_2DS_2-VASc 0.671 (0.559 – 0.771), BROWN ESUS-AF 0.642 (0.528 – 0.745), AS5F 0.618 (0.504 – 0.723), STAF 0.613 (0.499 – 0.719), and LADS 0.548 (0.434 – 0.658)

Abbreviations: AF: Atrial fibrillation; APs: Antiplatelets; AUC: Area under the curve; BMI: Body mass index; BNP: Brain natriuretic peptide; CAD: Coronary artery disease; CHA2DS2--VASc: Congestive heart failure, blood hypertension, age ≥75 years, diabetes, prior TIA/stroke/systemic embolism, vascular disease, age 65 – 74 years, sex category; CHADS2: Congestive heart failure, hypertension, age ≥75 years, diabetes, prior TIA/stroke/systemic embolism; CI: Confidence interval; ECG: Electrocardiogram; EDV: End diastolic volume; HF: Heart failure; ICD--9--CM: International Classification of Diseases, Ninth Revision, Clinical Modification; IEM: Implantable ECG monitoring; LA: Left atrium; LAE: Left atrial enlargement; LAVIs: Left atrial volume index; NIEM: Non--implantable ECG monitoring; NIHSS: National Institutes of Health Stroke Scale; NT--proBNP: Amino terminal brain natriuretic peptide; PAC: Premature atrial contraction; PAD: Peripheral artery disease; Pdur: P wave duration; Pmorph: P wave morphology; s: Seconds; SD: Standard deviation; TIA: Transient ischemic attack; NR: Not reported.

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devices are considered the gold standard, detecting approximately 30% of SAF over a 3-year follow-up[18], the choice between non-invasive external devices and invasive implantable devices for prolonged ECG monitoring remains a topic of controversy. The limited availability, invasiveness, and cost of implantable devices restrict their use in clinical practice. Therefore, the need for tools that can identify high-risk patients for SAF and prioritize their prolonged ECG monitoring is evident.

In recent years, an increasing body of literature has addressed the development of clinical scores to predict the risk of SAF in stroke patients. In this paper, we reviewed the literature focusing on clinical predictive scores for SAF detection in CS or ESUS. Our analysis identified 11 scores, with eight designed for CS patients and three for ESUS patients. It is worth noting that the majority of these scores were developed with relatively small sample sizes. With the exception of studies deriving the HAVOC and AF-ESUS scores[9,16], the derivation cohorts typically included fewer than 300 patients, with the scores ranging from 63 to 296[7,8,10-15,17].

Our analysis in this review underscores the robust association between advanced age and the occurrence of SAF, a factor consistently present in ten out of 11 scores. In addition, LAE, premature atrial beats, and CT characteristics such as cortical or subcortical infarcts, echocardiographic or laboratory signs of HF, and NIHSS scoring emerge as the most frequently represented variables within these clinical predictive scores. These findings are in agreement with a systematic review of the literature performed by Noubiap *et al.*, which identified age, female gender, left atrial size, LAE, and the CHA_2DS_2-VASc score as independent risk factors for post-stroke SAF[18].

Our research corroborates the positive relationship between the duration of ECG monitoring and the rate of SAF detection. Specifically, the SAF detection rate was found to be up to 6% in patients monitored for at least 72 h and increased to 22% in patients monitored for more than 2 weeks. However, it is important to note that only a minority of the patients (340 of 11904, 2.85%) received implantable ECG monitoring.

SAF emerges as the prominent underlying etiology during the follow-up of patients with CS or ESUS. In a recent study, the NOR-FIB study, SAF was identified as the probable cause of stroke in 43% of CS cases following a 12-month follow-up, while 57% of strokes remained cryptogenic[19]. Furthermore, SAF was identified as a possible cause in 29% of patients, contributing to a substantial 67% of the identified etiologies[19]. Recurrence rates at the 12-month follow-up were 5.8%, with a slightly lower rate of 2.7% observed in patients in whom SAF was detected, compared to 6.8% in patients without SAF ($P = 0.363$)[20].

One of the central controversies in this context revolves around how to define the duration of a SAF episode for diagnostic purposes. Indeed, in five studies, SAF was defined as any episode, even if it lasted <30 s, while in six studies, SAF was defined as episodes lasting at least 30 s. This issue has sparked a vigorous debate between cardiologists and stroke physicians. Cardiologists advocate for defining diagnostic SAF episodes as those lasting at least 30 s[21,22]. In the NOR-FIB study, SAF was defined as an episode lasting at least 2 min[20]. More recently, in the external validation of the AF-ESUS score, Kitsiou *et al.* defined SAF as an episode lasting at least 6 min[23]. However, it is important to acknowledge that the majority of SAF episodes detected following a stroke last for <30 s[24], underscoring a notable gap in evidence of their clinical significance. Many stroke physicians lean toward considering even these shorter SAF episodes as diagnostic[25]. As a result, it is not surprising that in approximately half of the studies deriving clinical predictive scores, SAF episodes of any duration are considered diagnostic.

The predictive power of the retrieved scores is strong, with an AUC ranging from 0.72 to 0.94. However, there is a lack of prospective studies directly comparing these scores. Four out of the 11 scores were assessed against the predictive power of the CHA_2DS_2-VASc score. Grifoni *et al.* conducted a comparative analysis, evaluating the performance of the E_2AF score against CHA_2DS_2-VASc and four other scores, including AS5F and Brown ESUS-AF, which were selected in our search. Their findings indicated that the E_2AF score exhibited a significantly better predictive power than AS5F and showed an improved predictive power compared to the CHA_2DS_2-VASc and Brown ESUS-AF scores, although the latter difference was not statistically significant[17]. More recently, Ratajczak-Tretel *et al.* conducted a similar comparison, pitting the predictive power of the CHA_2DS_2-VASc score against seven clinical predictive scores, three of which (HAVOC, AS5F, and Brown ESUS-AF) were selected in our study. Their analysis, performed on the population enrolled in the NOR-FIB study, revealed that AS5F demonstrated the highest predictive power, with an AUC of 0.741 (95% CI: 0.678 – 0.804)[26].

We recognize that our review may have certain limitations. The derivation studies vary in terms of design and methodology, and their sample sizes are relatively small. Furthermore, a prospective comparison among them is absent. Therefore, it is important to exercise caution when considering the implications of our findings for clinical practice.

Table 2. Summary of methodology for post-stroke atrial fibrillation detection

Score	12-lead ECG and/or 24-h Holter-ECG performed for any reason or based on clinical interview and/or clinical examination during a one-year follow-up	72-h non-implantable ECG	2 or 3-week non-implantable ECG monitoring	Implantable ECG monitoring	AF definition
Bugnicourt*	All patients enrolled				Any
Sudacevschi*			All patients enrolled		>30 s
HAVOC	All patients enrolled				Any
AS5F		All patients enrolled			>30 s
ACTEL		All patients enrolled			Any
GRAZ AF			126 out of 150 patients (84%) enrolled	24 out of 150 patients (16%) enrolled	>30 s
DECRYPTORING			All patients enrolled		>30 s
PROACTIA				All patients enrolled	>30 s
BROWN AF-ESUS			216 out of 296 patients (73%) enrolled	80 out of 296 patients (27%) enrolled	>30 s
AF-ESUS	All patients enrolled				Any
E_2AF			All patients enrolled		Any
AF detection rate (overall)	5.9%	5.7%	22.4%	22.4%	-

Note: *Unnamed scores indicated by the first author's name.

Table 3. Summary of characteristics of post-stroke atrial fibrillation detection predictive scores

Score	Age	National Institutes of Health Stroke Scale (NIHSS) scoring	Left atrial enlargement (LAE)	Left ventricle ejection fraction (LVEF) reduced or echo and/or laboratory signs of congestive heart failure (HF)	Premature atrial beats	Brain computed tomography (CT) characteristics
Bugnicourt*	X		X			
Sudacevschi*	X				X	X
HAVOC	X			X		
AS5F	X	X				
ACTEL	X		X			
GRAZ AF	X			X	X	X
DECRYPTORING	X			X		
PROACTIA					X	
BROWN AF-ESUS	X		X			
AF-ESUS	X				X	X
E_2AF	X	X	X			X

Notes: *Unnamed scores indicated by the first author's name; X: Variable is included in the score.

5. Conclusion

Tailoring the priority of ECG monitoring for screening SAF represents the cornerstone of diagnostic workup in patients suffering from CS or ESUS. This approach aids in identifying the patients who require prolonged non-implantable or implantable ECG monitoring. Although numerous clinical scores are available to predict SAF detection, the selection of an appropriate score for clinical practice remains challenging. Variables frequently included in predictive scores encompass age, LAE, premature atrial beats, and the distribution of cortical or subcortical lesions, as well as echocardiographic and/or laboratory signs of HF

and NIHSS scoring. A diagnostic work-up that adopts a stepwise approach involving increasing durations of ECG monitoring and relies on risk prioritization estimated by clinical predictive scores (e.g., starting with external ECG monitoring and progressing to implantable monitoring devices for selected patients) may find practical application in real-world clinical practice. Consequently, clinical predictive scores could play a pivotal role in defining the risk of SAF and ECG monitoring priority. Recently, a position paper by the European Society of Cardiology has suggested the use of HAVOC or Brown ESUS-AF as clinical predictive scores for SAF detection[27]. However, this recommendation lacks the support of a randomized clinical trial aimed at validation. Therefore, large, prospective, and multicentric trials are warranted.

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Conflict of interest

The authors declare they have no competing interest.

Author contributions

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

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Data can be requested from the corresponding author following formal request.

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ACCSCIENCE PUBLISHING

Brain & Heart

REVIEW ARTICLE

Efficacy of pemafibrate in patients with dyslipidemia: A systematic review and meta-analysis of randomized controlled trials

Caroline Cristine Almeida Balieiro[1]*, Maria Esther Barbalho[2], Luiza Mendes Fonseca[3], Noah Romero Nakajima[4], Marcela Mizuhira Gobbo[5], Beatriz Polachini Assunes Gonçalves[6], Eduardo Cesar Teixeira Sirena[7], Alice D. Marinho[8], Matheus J. B. Moreira[9], and Natália Nóbrega de Lima[10]

[1]Division of Medicine, Amazonas State University, Manaus, Amazonas, Brazil
[2]Division of Medicine, University of Potiguar, Natal, Rio Grande do Norte, Brazil
[3]Division of Medicine, Faculty of Medical Sciences of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil
[4]Division of Medicine, Federal University of Uberlândia, Uberlândia, Minas Gerais, Brazil
[5]Division of Medicine, Federal University of Alfenas, Alfenas, Minas Gerais, Brazil
[6]Division of Medicine, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil
[7]Division of Medicine, University of Fortaleza, Fortaleza, Ceará, Brazil
[8]Division of Medicine, Federal University of the State of Rio de Janeiro, Rio de Janeiro, Rio de Janeiro, Brazil
[9]Division of Medicine, Federal University of Rio Grande do Norte, Natal, Rio Grande do Norte, Brazil
[10]Clinics Hospital of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil

Abstract

This study aimed to evaluate the efficacy of pemafibrate in patients with hypertriglyceridemia compared to a placebo or fenofibrate through a rigorous systematic review process. To achieve this, we conducted comprehensive searches in the PubMed, Cochrane Library, and Embase databases. The data extraction process was based on published reports, and the assessment of study quality adhered to the PRISMA guidelines. A random-effects model was employed to calculate mean differences (MD) and 95% confidence intervals (CI). Statistical significance was established at $P < 0.05$, with I^2 values exceeding 25%, denoting a significant degree of heterogeneity. The primary outcomes of interest were MDs in triglycerides (TG) and non-high-density lipoprotein (HDL) cholesterol. The review protocol was registered with PROSPERO under the identifier CRD42022374852. Nine studies involving 12,644 patients were included, with 6699 (53%) patients receiving pemafibrate. The meta-analysis revealed a significant reduction in serum TG levels in the intervention group (0.4 mg/day) compared to the placebo group (MD: −48.29; 95% CI: −61.45 – −35.13; $P < 0.0001$; $I^2 = 93\%$). Pemafibrate (0.4 mg/day) also led to significantly lower non-HDL cholesterol levels compared to control (MD: −6.35; 95% CI: −10.62 – −2.08; $P < 0.0001$; $I^2 = 82\%$). There were no significant differences in TG reduction between pemafibrate (0.2 mg/day) and fenofibrate (200 mg/day) (MD: −2.90; 95% CI: −12.90 – 7.11; $P = 0.003$; $I^2 = 83\%$), or between pemafibrate (0.1 mg/day and 0.2 mg/day) and placebo (TG and non-HDL cholesterol levels). In conclusion, pemafibrate demonstrated efficacy in decreasing TG and non-HDL cholesterol levels for dyslipidemia patients, especially at a dosage of 0.4 mg/day compared to a placebo.

Keywords: Dyslipidemia; Pemafibrate; Triglycerides; Meta-analysis

***Corresponding author:**
Caroline Cristine Almeida Balieiro
(carolinecbalieiro@gmail.com)

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1. Introduction

Dyslipidemia is a chronic pathological condition characterized by abnormal lipid levels in the bloodstream. This condition is widely acknowledged as a significant risk factor for atherosclerotic cardiovascular disease (ASCVD) and mortality on a global scale, due to its alarming prevalence[1,2]. Consequently, a comprehensive evaluation of an individual's cardiovascular risk requires the consideration of multiple variables, including low-density lipoprotein cholesterol (LDL-C) levels, a parameter frequently employed in clinical settings. Statins and lifestyle changes to lower LDL-C levels are critical in managing these high-risk patients[3,4]. Nonetheless, statin therapy alone has a 20% benefit in preventing the development of cardiovascular diseases such as myocardial infarction or ischemic stroke, leaving patients with an estimated residual risk of 80%[5,6]. Hence, identifying additional pharmacologic methods that can minimize the overall risk of cardiovascular disease has become increasingly relevant.

High triglyceride (TG) levels and low high-density lipoprotein cholesterol (HDL-C) levels in serum have consistently been demonstrated to have a strong and independent connection with an elevated risk of developing ASCVD[6-9]. However, a definitive causal relationship has yet to be established in the literature. Nonetheless, statins, primarily targeting the HMG-CoA reductase pathway, exhibit a restricted capacity to induce significant alterations in TG and HDL-C levels among individuals grappling with severe dyslipidemia[10]. In contrast, fibrates, also known as peroxisome proliferator-activated receptor α (PPARα) activators, are a well-established therapeutic option for managing dyslipidemia in patients with markedly elevated TG that does not respond adequately to statin therapy. In these cases, fibrates are specifically indicated to minimize the risk of pancreatitis. They also effectively increase HDL-C levels, which is potentially beneficial[11,12]. Few meta-analyses have reported certain benefits of prescribing fibrates to prevent cardiovascular disease in this specific population[13]. However, fibrates, especially when administered concurrently with statins, can lead to a number of potentially serious side effects, including hepatic or kidney dysfunction, myopathy, and rhabdomyolysis, which can compromise drug administration and treatment adherence[14].

Accordingly, a novel drug, pemafibrate, a selective PPARα modulator (SPPARMα), has garnered significant attention from the medical community. This heightened interest is primarily attributed to its high selectivity for PPAR subtypes, including PPARα1 and PPARα2, while avoiding activation of other PPAR subtypes such as PPARβ/δ and PPARγ. This selectivity is believed to help mitigate the deleterious side effects commonly associated with traditional fibrates, such as hepatotoxicity, myopathy, and renal impairment. Pemafibrate's unique pharmacological profile suggests distinct advantages over other fibrates in terms of safety and effectiveness, positioning it as a prospective treatment alternative for patients with dyslipidemia and other metabolic diseases[15,16]. Importantly, pemafibrate has demonstrated a favorable safety record for patients concurrently using statins and for those with chronic kidney disease, underscoring its potential as a significant treatment alternative[17].

Consequently, the objective of this systematic review and meta-analysis is to furnish an updated investigation into the efficacy of pemafibrate, with a specific focus on evaluating the impact of this therapy on lipid profile and adverse events. This analysis holds particular significance in light of the considerable attention that this drug has received as a potential game-changer in the management of dyslipidemia due to its previously discussed unique pharmacological profile. Nevertheless, it is critical to underscore recent findings from the PROMINENT trial, which failed to reveal a substantial reduction in cardiovascular events despite the drug's favorable effects on lipid markers. This contrast highlights the need for a comprehensive assessment of its overall clinical impact[18].

2. Materials and methods

2.1. Search strategy

The study design in this research adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA)[19]. To ensure transparency and adherence to best practices, we also utilized PROSPERO (International prospective registration of systematic reviews) to register the pre-specified study procedure (ID: CRD42022374852).

A comprehensive search was conducted across the MEDLINE (through PubMed), EMBASE, and Cochrane Library databases, encompassing data from their creation up to March 11, 2023. The search strategy employed a methodical approach to identify all relevant trials that reported the use of pemafibrate in patients with dyslipidemia. The search strategy (employing medical subject heading terms) was as follows: (dyslipidemia OR dyslipidemias OR dyslipidemic OR dyslipidemia OR cholesterol OR triglycerides [TG] OR HDL OR LDL OR "high-density lipoprotein" OR "low-density protein") AND (pemafibrate OR K-877 OR SPPARMα OR "selective peroxisome proliferator-activated receptor" OR "selective modulator of peroxisome proliferator-

activated receptor" OR "selective PPAR" OR "selective modulator of PPAR") AND (random OR randomized OR randomized OR RCT OR "Controlled Clinical Trial"). The complete electronic search strategy can be summarized as: (Dyslipidemia OR dyslipidemias OR dyslipidemia OR dyslipidemic OR dyslipidemia OR cholesterol OR TG OR HDL OR LDL OR "high-density lipoprotein" OR "low-density protein") AND (pemafibrate OR "K-877" OR "SPPARMα" OR "selective peroxisome proliferator-activated receptor" OR "selective modulator of peroxisome proliferator-activated receptor" OR "selective PPAR" OR "selective modulator of PPAR") AND (random OR randomized OR randomized OR RCT OR "Controlled Clinical Trial").

2.2. Inclusion criteria and data extraction

In the evaluation of the papers under consideration, no restrictions were imposed on publication date, language, or publishing status. Studies were deemed eligible for inclusion in this meta-analysis if they met the following criteria: (i) Being randomized controlled trials (RCTs); (ii) featuring at least one study arm using pemafibrate; (iii) including a control group; (iv) involving patients of all age groups diagnosed with any form of dyslipidemia; and (v) reporting on at least one of the clinical outcomes of interest.

Studies were excluded if they lacked a placebo or fenofibrate control group or if they presented duplicated data. In cases of data duplication, the study with the larger sample size was chosen. Initially, studies of interest underwent a pre-selection process for full-text review. Supplementary materials were reviewed in instances where the publication did not report the desired outcomes (particularly lipid profile endpoints). Article selection and data extraction were undertaken independently by at least two reviewers (Caroline Cristine Almeida Balieiro and Marcela Mizuhira Gobbo). Any disagreements that arose were resolved through author consensus following a thorough examination of the entire manuscript alongside the senior author (N.N.L.).

2.3. Variables of interest and their outcomes

The studies yielded the following information: (i) Research parameters: research design, number of participants per group, study population, time to follow-up, pemafibrate dosage, and control type (placebo or fenofibrate) and respective dos age; (ii) patient characteristics: age, body mass index (BMI), presence of type 2 diabetes, systemic arterial hypertension, and statin use before intervention; (3) clinical outcomes: triglyceride levels (measured in mmol/L and mg/dL), non-HDL cholesterol levels (measured in mmol/L and mg/dL), LDL cholesterol levels (measured in mmol/L and mg/dL), total cholesterol (TC) levels (measured mmol/L and mg/dL), and adverse events (allergic reactions, liver injury, and elevated creatine phosphokinase levels).

2.4. Risk of bias assessment

The risk of bias for each study included in the analysis was evaluated using the Cochrane risk of bias assessment tool, in accordance with the recommended criteria provided in the Cochrane Handbook for Systematic Reviews of Interventions[20,21]. This evaluation was performed by five independent investigators (C.C.A.B., M.M.G., M.E.B., L.M.F., and B.P.A.G.), and the results were documented in a risk of bias table. Any discrepancies or doubts discovered during the assessment process were resolved in consultation with the senior author (N.N.L.).

2.5. Data analysis

In our meta-analyses for continuous outcomes, we utilized the mean difference (MD) method, with corresponding 95% confidence intervals (CI) serving as indicators of the effect size. To assess heterogeneity, we utilized Cochrane's Q statistic and Higgins and Thompson's I^2 statistic. Furthermore, all outcome analyses underwent random-effects meta-analyses using the DerSimonian-Laird method. The statistical analysis was conducted using Review Manager 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Denmark)[22].

Subgroup analyses were prespecified as follows: Pemafibrate at a dosage of 0.4 mg/day compared to placebo, pemafibrate at 0.2 mg/day compared to placebo (HDL, LDL, non-HDL, TG, and TC levels), pemafibrate at 0.2 mg/day compared to fenofibrate (TG levels), and pemafibrate at 0.1 mg/day compared to placebo (HDL, LDL, non-HDL, TG, and TC levels).

3. Results

3.1. Study selection and characteristics

The search strategy yielded a total of 184 results, as shown in Figure 1. Following a meticulous assessment based on inclusion and exclusion criteria, 22 papers were retained for full-text evaluation, with ineligible and duplicate studies having been excluded from the study. Among these papers, non-randomized trials and studies with overlapping patient populations were further excluded from the analysis. Consequently, a total of 9 RCTs involving 12,644 patients were included in our study. Pemafibrate was administered to 6699 (53%) individuals. The mean age across these trials ranged from 46.4 to 64 years, and 11,168 (88.3%) patients had diabetes. A comprehensive summary of the studies and their respective research characteristics is provided in Table 1.

Table 1. Summary of characteristics of included studies in the meta-analysis

Study	Follow-up (weeks)	Number of patients			Age (I)		Age (C)		BMI (I)		BMI (C)		TG (mmol/L) (I)		TG (mmol/L) (C)		TG (mg/dL) (I)		TG (mg/dL) (C)		DM2	
		I	C	Total	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	I	C
Arai *et al.*, 2017[23] (Study A)	12	129	41	170	52.6	10.2	55.5	9.6	27.6	4.0	26.3	2.9	4.0	1.5	4.3	2.0	356.9	134.2	380.5	177.0	43	12
Arai *et al.*, 2017[23] (Study B)	24	315	108	423	57.6	11.0	56.3	11.9	27.1	3.9	27.7	4.2	3.7	1.5	3.7	1.5	331.6	132.6	327.4	132.7	119	36
Arai *et al.*, 2018[15]	16	257	268	525	50.6	10.4	50.0	10.0	26.8	3.6	26.6	3.8	4.0	1.7	4.0	1.4	359.6	148.1	351.8	128.3	43	37
Araki *et al.*, 2018[24]	52	109	57	166	60.2	10.8	61.2	10.0	25.9	3.6	26.0	3.3	2.8	1.1	3.2	1.3	247.8	97.3	283.2	115.0	109	57
Ginsberg *et al.*, 2022[25]	12	348	60	408	58.8	10.4	59.0	10.4	31.2	-	30.7	-	3.1	1.1	2.9	0.8	272.0	96.1	254.4	71.6	133	26
Ishibashi *et al.*, 2016[26]	16	143	71	214	49.4	11.5	49.9	10.3	26.9	3.6	26.7	2.8	3.4	2.0	3.6	1.9	305.1	170.1	317.4	170.8	19	8
Ishibashi *et al.*, 2018[16]	24	147	76	223	53.3	10.5	52.9	11.6	26.5	3.9	26.0	3.7	2.6	0.7	2.7	0.8	234.5	57.7	238.9	70.8	10	1
Matsuba *et al.*, 2018[27]	12	11	7	18	51.6	10.4	46.4	7.7	25.2	2.3	25.8	2.9	3.5	1.1	3.1	0.6	305.3	97.3	271.7	53.1	11	7
Das Pradhan *et al.*, 2022[18]	-	5240	5257	10497	63.1	8.3	64.0	8.9	32.4	5.3	32.4	5.1	3.3	1.0	3.2	1.0	290.1	91.5	286.7	89.2	5240	5257

Abbreviations: BMI: Body mass index; C: Control (placebo or fenofibrate); DM2: Type 2 diabetes mellitus; I: Intervention (pemafibrate); TG: Triglycerides.

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3.2. Pooled analysis of all studies

The primary outcome of interest was the percent reduction in total TG, which exhibited a significant improvement in the pemafibrate group when compared with placebo across all doses (MD: −45.65; 95% CI: −57.31 – −33.98; $P < 0.00001$; $I^2 = 93\%$) (Figure 2). Within the group receiving pemafibrate, there was an overall trend toward an increased percent of HDL (MD: 13.84; 95% CI: 8.09 – 19.59; $P < 0.00001$; $I^2 = 95\%$) (Figure 3). Conversely, in the placebo group, a significant decrease in LDL levels was observed (MD: 11.82; 95% CI: 8.61 – 15.04; $P < 0.00001$; $I^2 = 57\%$) (Figure 4). However, there was no significant difference in the percent of TC between patients who received the placebo compared with those treated with all doses of pemafibrate (MD: −1.74; 95% CI: −3.98 – 0.49; $P < 0.13$; $I^2 = 73\%$) (Figure 5).

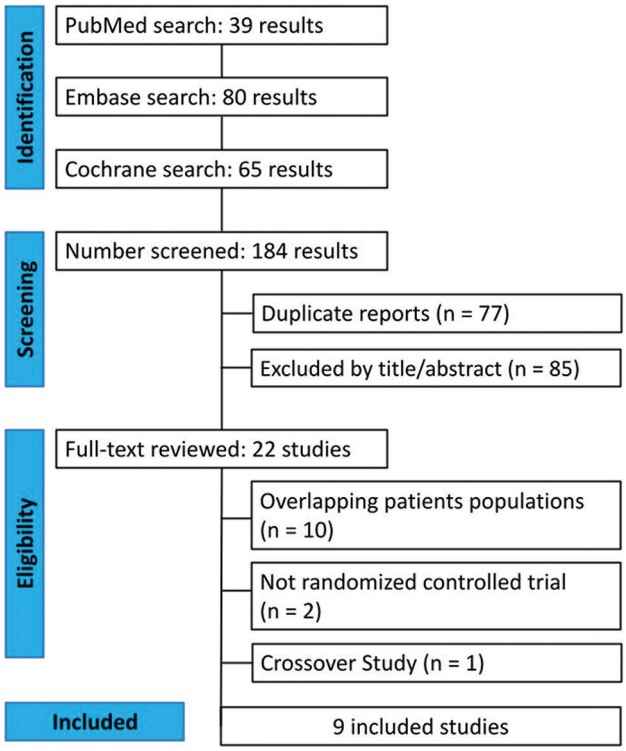

Figure 1. PRISMA flow diagram of study screening and selection.

3.3. Subanalysis of selected populations

In a subanalysis of patients treated with 0.4 mg/day of pemafibrate versus placebo, the pemafibrate group exhibited a higher percent of the decrease in serum TG (MD: −48.29; 95% CI: −61.45 – −35.13; $P < 0.0001$; $I^2 = 93\%$) (Figure 6). Furthermore, individuals receiving a daily dosage of 0.4 mg of pemafibrate experienced a significant reduction in non-HDL levels compared to the placebo group (MD: −6.35; 95% CI: −10.62 – −2.08; $P = 0.004$; $I^2 = 82\%$) (Figure 7). Placebo recipients had significantly lower LDL levels than those treated with pemafibrate 0.4 mg/day (MD: 12.86; 95% CI: 9.43 – 16.29; $P < 0.00001$; $I^2 = 40\%$) (Figure 8). The pemafibrate group at the 0.4 mg/day dose exhibited a significant increase in HDL levels (MD: 13.66; 95% CI: 8.06 – 19.27; $P < 0.00001$; $I^2 = 92\%$) (Figure 9). No significant differences were observed for adverse events (MD: 0.97; 95% CI: 0.73 – 1.29; $P = 0.84$; $I^2 = 0\%$) (Figure 10) and TC levels (MD: −1.73; 95% CI: −4.14 – 0.68; $P = 0.16$; $I^2 = 65\%$) (Figure 11).

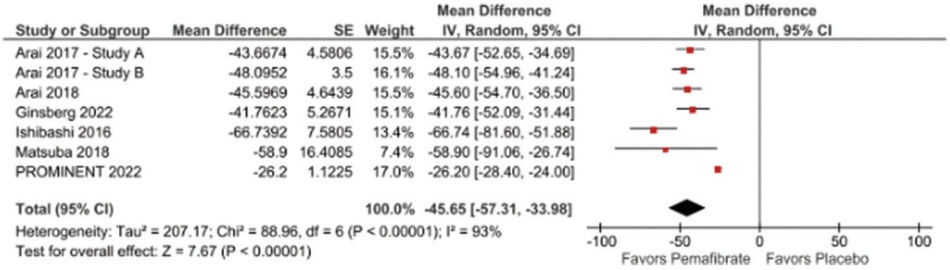

Figure 2. Significant reduction in total triglycerides within the pemafibrate group across all doses.

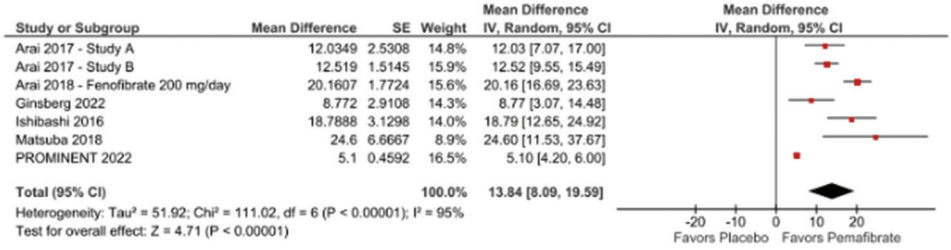

Figure 3. Significant increase in high-density lipoprotein within the pemafibrate group across all doses.

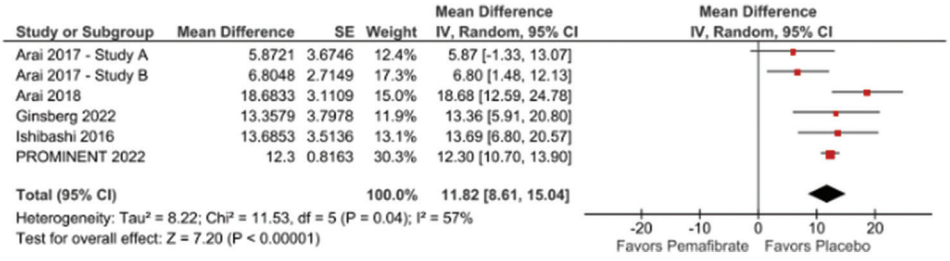

Figure 4. Significant decrease in low-protein lipoprotein within the placebo group.

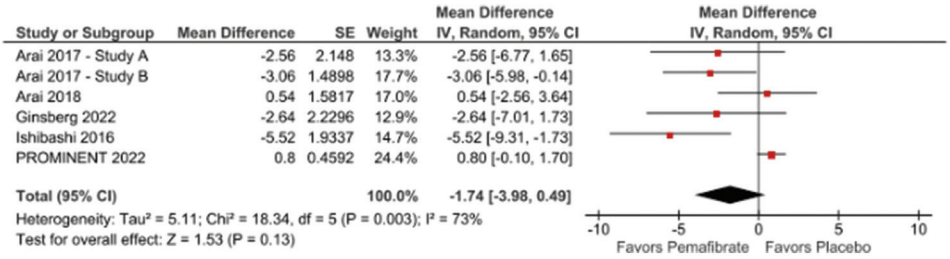

Figure 5. No difference in total cholesterol between the groups.

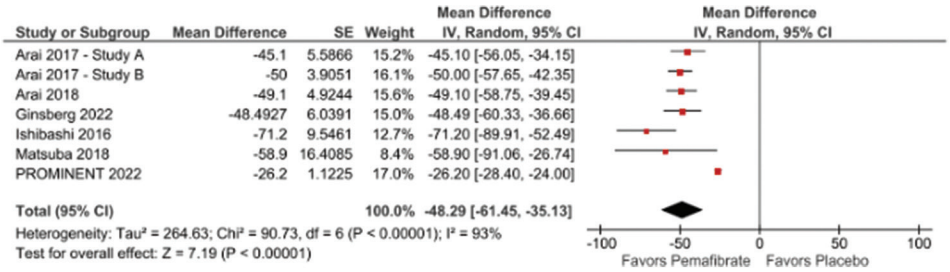

Figure 6. Significant reduction in serum triglycerides following treatment with pemafibrate at 0.4 mg/day.

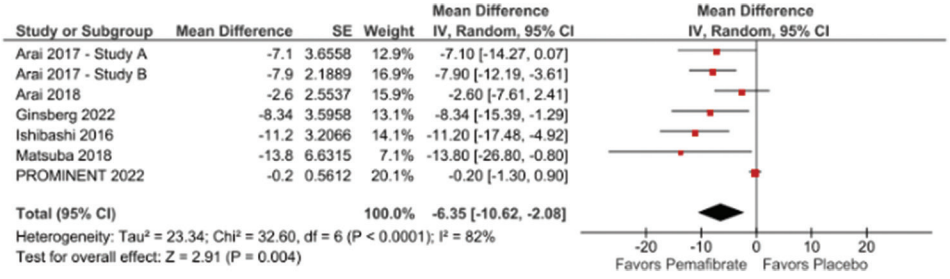

Figure 7. Significantly lower non-high-density lipoprotein levels following treatment with pemafibrate at 0.4 mg/day.

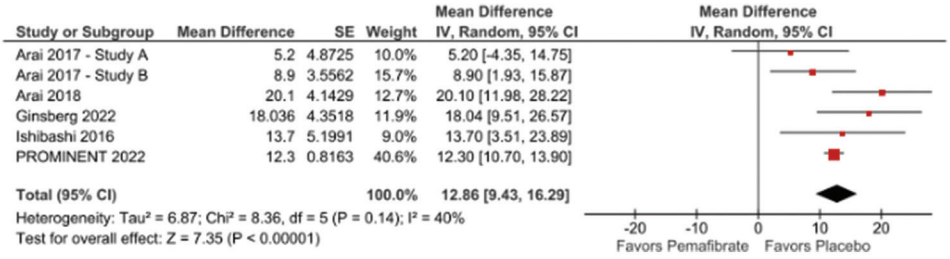

Figure 8. Significantly lower low-density lipoprotein levels in the placebo group versus treatment with pemafibrate at 0.4 mg/day.

The non-HDL levels significantly decreased following treatment with pemafibrate 0.2 mg/day compared to placebo (MD: −7.70; 95% CI: −10.66 – −4.74; $P < 0.00001$; $I^2 = 33\%$) (Figure 12). Pemafibrate at 0.2 mg/day also demonstrated a greater decrease in TC (MD: −2.58; 95% CI: −4.96 – −0.20]; $P = 0.03$; $I^2 = 38\%$) (Figure 13) and TG levels (MD: −47.30; 95% CI: −53.99 – −40.60; $P = 0.00001$; $I^2 = 47\%$) (Figure 14) compared to placebo. However, LDL levels were lower in the placebo group (MD: 11.42; 95% CI: 5.52 – 17.32; $P = 0.0001$; $I^2 = 60\%$). In addition, there was no significant difference in the percent change of TG between patients treated with pemafibrate at 0.2 mg/day compared to those treated with fenofibrate at 200 mg/day (Figure 15) (MD: −2.90; 95% CI: −12.90 – 7.11; $P = 0.57$; $I^2 = 83\%$).

When comparing 0.1 mg/day of pemafibrate with placebo, HDL levels significantly increased with pemafibrate therapy (MD: 13.82; 95% CI: 6.70 – 20.95; $P = 0.0001$; $I^2 = 81\%$) (Figure 16). TG levels (MD: −43.72; 95% CI: −53.51 – −33.93; $P < 0.00001$; $I^2 = 60\%$) (Figure 17),

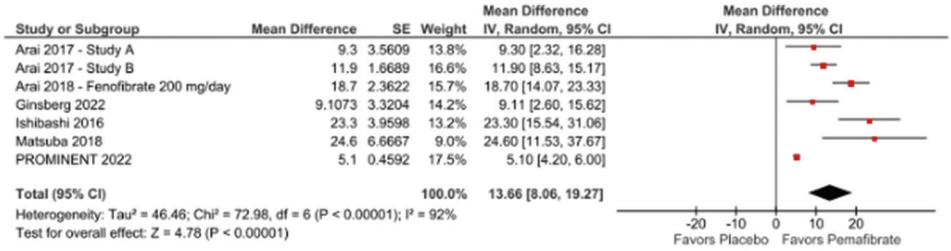

Figure 9. Significantly higher high-density lipoprotein levels following treatment with pemafibrate at 0.4 mg/day.

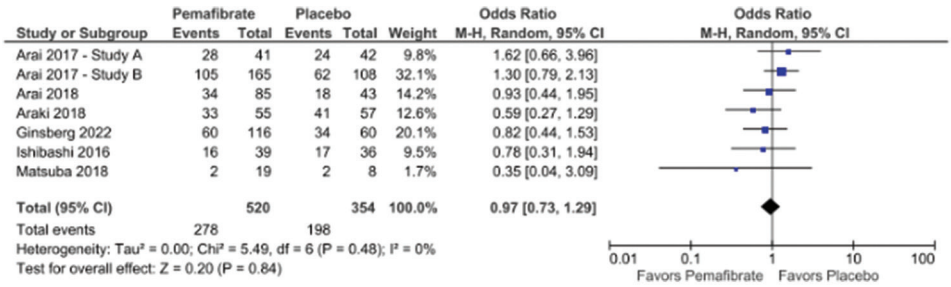

Figure 10. No difference in the incidence of adverse events between groups.

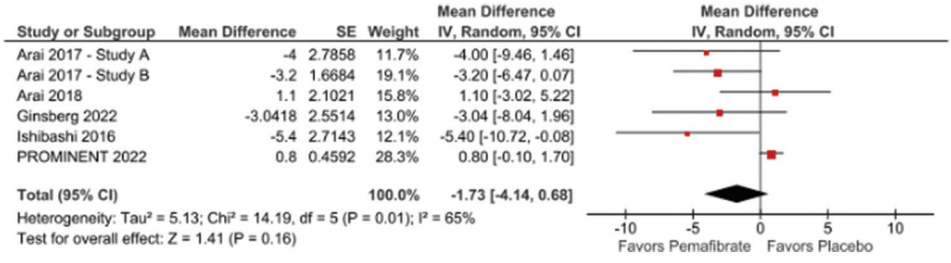

Figure 11. No difference in total cholesterol levels between the groups.

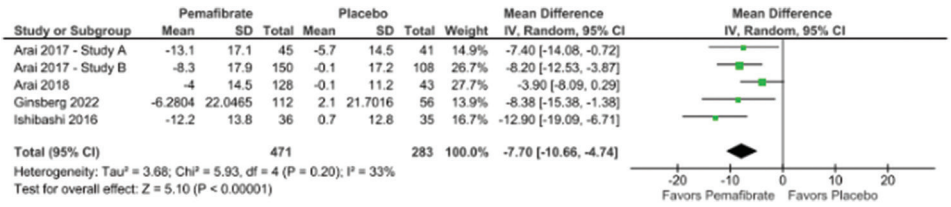

Figure 12. Significantly lower non-high-density lipoprotein levels following treatment with pemafibrate at 0.2 mg/day.

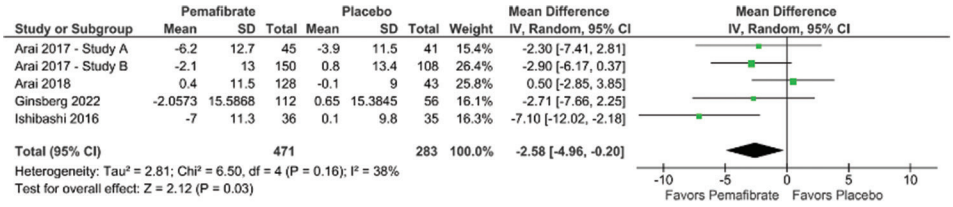

Figure 13. A greater reduction in total cholesterol levels following treatment with pemafibrate at 0.2 mg/day.

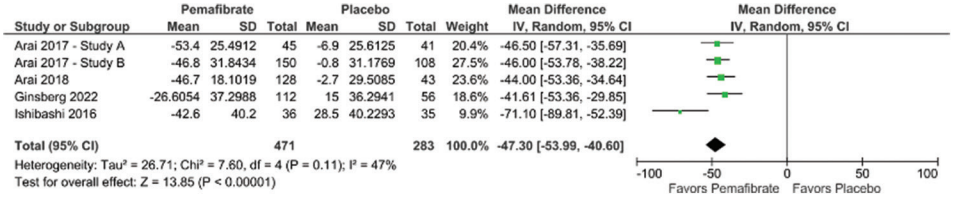

Figure 14. A greater reduction of triglyceride levels following treatment with pemafibrate at 0.2 mg/day.

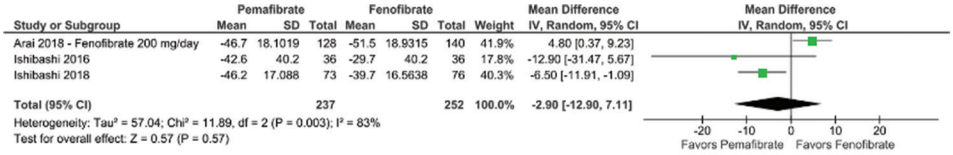

Figure 15. No significant difference in triglyceride levels following treatment with pemafibrate at 0.2 mg/day compared to fenofibrate at 200 mg/day

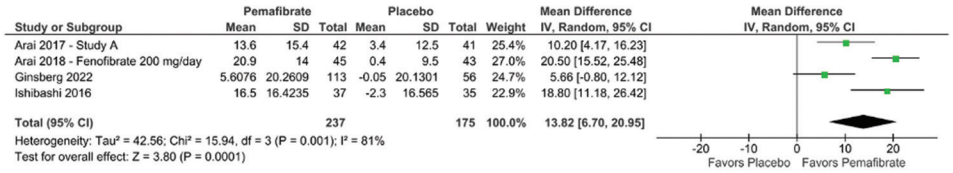

Figure 16. Significantly higher high-density lipoprotein levels following treatment with pemafibrate at 0.1 mg/day.

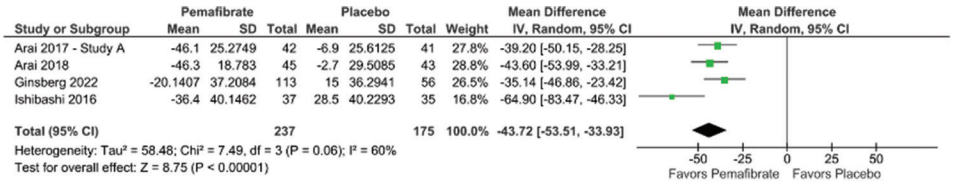

Figure 17. Significantly lower triglyceride levels following treatment with pemafibrate at 0.1 mg/day.

non-HDL levels (MD: −7.11; 95% CI: −10.71 – −3.50; P = 0.0001; I^2 = 25%) (Figure 18), and LDL levels (MD: 9.76; 95% CI: 4.49 – 15.04; P = 0.0003; I^2 = 24%) (Figure 19) were significantly lower with pemafibrate at 0.1 mg/day compared to the placebo group. There was no significant difference between pemafibrate at 0.1 mg/day and placebo in TC levels (MD: −2.53; 95% CI: −5.23 – 0.17; P = 0.07; I^2 = 18%) (Figure 20).

3.4. Quality assessment

Among the nine RCTs included in this meta-analysis, the assessment for each domain revealed a proportion of appropriate evaluations as follows: 89% (8/9) for the randomization process, 100% (9/9) for deviations from intended interventions, 100% (9/9) for missing outcome data, 78% (7/9) for measurement of the outcomes, 100% (9/9) in the selection of reported results, and 78% (7/9) for the overall

risk of bias. These RCTs exhibited a high level of quality and, on the whole, presented a low risk of bias (Figure 21). The funnel plot demonstrated a symmetric distribution of comparable-weight studies converging toward the pooled effect size of treatment as weight increased. The pattern indicates no evidence of publication bias.

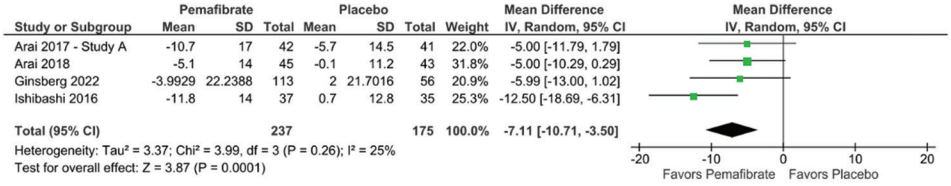

Figure 18. Significantly lower non-high-density lipoprotein levels following treatment with pemafibrate at 0.1 mg/day.

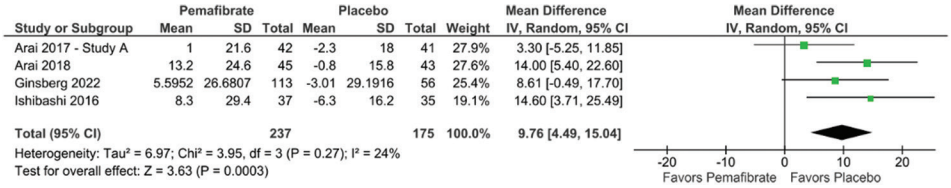

Figure 19. Significantly lower low-density lipoprotein levels in the placebo group when compared to those treated with pemafibrate at 0.1 mg/day.

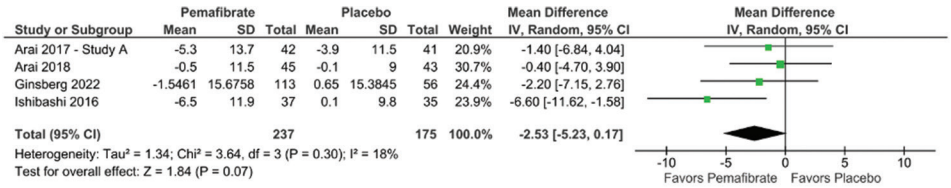

Figure 20. No difference in total cholesterol levels between groups.

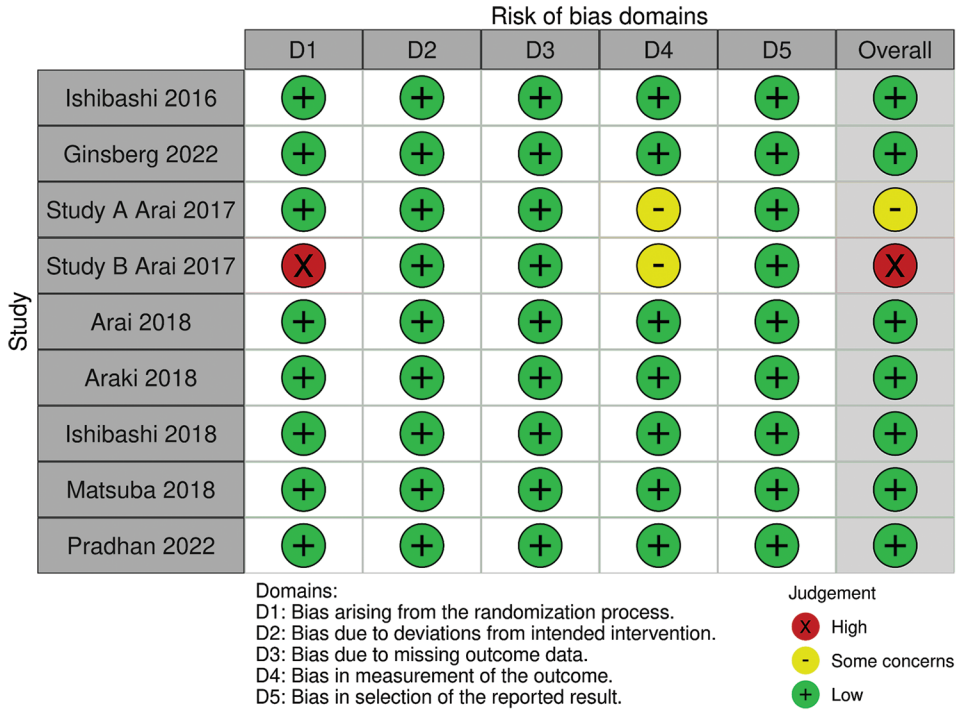

Figure 21. Risk of bias summary for randomized studies (RoB 2).

4. Discussion

In this systematic review and meta-analysis, we compared pemafibrate to either placebo or fenofibrate in patients with hypertriglyceridemia, synthesizing data from nine RCTs involving 12,644 participants. Of all participants, 6699 (53%) received the pemafibrate. The main findings were as follows: (i) The percent reduction in total TG significantly improved with all dosages of pemafibrate compared with placebo; (ii) non-HDL levels were significantly lower in patients treated with pemafibrate at the dose of 0.4 mg/day compared to placebo; and (iii) there was no significant percent change in TG between patients treated with pemafibrate at 0.2 mg/day and those treated with fenofibrate at 200 mg/day.

It is worth emphasizing that Ida *et al.*[28] conducted a prior meta-analysis on this subject, encompassing 1623 patients. However, their analysis was completed before the completion of the PROMINENT study, a substantial clinical trial designed to evaluate the impact of administering pemafibrate on cardiovascular outcomes[18,23,24,28]. In contrast, our present meta-analysis incorporates data from the PROMINENT trial, significantly strengthening our analysis with an additional 10,497 patients and providing more recent evidence.

The PROMINENT trial enrolled individuals with type 2 diabetes, mild-to-moderate hypertriglyceridemia, low HDL-C, and well-controlled LDL cholesterol levels. This randomized, double-blinded, and placebo-controlled study revealed that the pemafibrate group exhibited reductions in TG, very-low-density lipoprotein cholesterol, residual cholesterol, and apolipoprotein C-III. Surprisingly, there was no significant disparity in the frequency of cardiovascular events between those who received pemafibrate and those administered a placebo. Notably, discernible heterogeneity in treatment effects across various patient subgroups identified in the study was not observed[18].

According to the findings of the trial conducted by Ishibashi *et al.*, pemafibrate has demonstrated a notable reduction of approximately 46% in fasting serum TG levels among dyslipidemic patients with high TG and low HDL-C levels. The study also suggested that pemafibrate was more effective than fenofibrate (106.6 mg/day), although this difference may be attributed to the fact that the pemafibrate group had almost twice as many subjects[16].

In the trial conducted by Ginsberg *et al.*, a comparison between pemafibrate and a placebo demonstrated notable reductions in fasting serum triglyceride (TG) concentrations. Specifically, these reductions were 36.1%, 45.8%, and 54.4% at dosages of 0.05 mg, 0.1 mg, and 0.2 mg administered twice daily, respectively, and 34.0%, 37.7%, and 42.7% at dosages of 0.1 mg, 0.2 mg, and 0.4 mg when administered once daily. Importantly, these reductions exhibited no significant gender disparities. Furthermore, in an exploratory analysis involving the subgroup of patients with type 2 diabetes mellitus, no discernible differences in treatment outcomes or drug interactions were observed within this population[25].

The findings from Ginsberg *et al.* revealed that pemafibrate at 0.2 mg twice a day was associated with a 2.6% reduction in fasting blood sugar levels, whereas the placebo caused a 5.2% increase. Insulin resistance, estimated using homeostatic model assessment (HOMA), and exhibited changes of 0.33% on placebo and 1.74% on pemafibrate at 0.2 mg twice daily. The placebo group's HOMA of insulin resistance improved by 0.33%, whereas those administered pemafibrate at 0.2 mg twice a day showed an improvement of 1.74%[25]. On the other hand, Arai *et al.* suggested that pemafibrate medication may contribute to improving insulin resistance, although additional research is needed[15].

In the study conducted by Araki *et al.*, fasting blood TG levels were statistically significantly lower in both pemafibrate groups (0.2 mg/day and 0.4 mg/day) compared to the placebo group ($P < 0.001$, multiplicity adjusted). No noticeable gender differences were observed. Notably, TG levels showed a considerable decrease in each pemafibrate group starting from week 4, and this significance persisted until week 24[24].

In our meta-analysis, we observed that the pemafibrate group exhibited lower TG levels and higher HDL-C levels compared to the placebo group. However, when comparing pemafibrate to fenofibrate, no statistically significant difference was found. Regarding drug safety, the incidence of increased hepatobiliary enzyme activity was notably lower in the pemafibrate group compared to both the placebo and fenofibrate groups. Interestingly, the pemafibrate group displayed an increase in hepatobiliary enzyme activity, likely attributed to pemafibrate's activation of PPAR, which is known to accelerate fatty acid oxidation, thereby promoting energy expenditure in the liver and reducing fat storage[28].

According to our meta-analysis, patients treated with pemafibrate at 0.4 mg/day exhibited considerably lower non-HDL-C levels compared to those on a placebo. Examination of the 0.1 mg/day and 0.2 mg/day doses of pemafibrate and placebo did not reveal substantially different reductions in non-HDL-C levels. In the study by Ginsberg *et al.*, twice-daily pemafibrate resulted in placebo-adjusted, dose-dependent decreases in fasting non-HDL-cholesterol concentrations of 6.8%, 7.4%, and

8.9% at dosages of 0.05 mg, 0.1 mg, and 0.2 mg twice daily. Similarly, once-daily pemafibrate reduced fasting non-HDL-C levels by 5.2% at 0.1 mg, 9.1% at 0.2 mg, and 7.8% at 0.4 mg in a placebo-controlled study. However, despite the statistically significant difference in the percentage of LDL-C decreases between the K-877 0.2 mg/day group and the placebo group, the mean LDL-C remained essentially unaltered[23]. In patients with hypertriglyceridemia, the calculated LDL could be falsely lower due to high TG levels (calculation of [LDL] =[TC] -[HDL] -[TG]/5) and may not provide reliable levels. For these patients, assessment with non-HDL-C will be useful as it does not consider TG in the calculation.

Pemafibrate has demonstrated effectiveness in reducing insulin resistance by lowering fasting blood glucose and fasting insulin levels across various studies[16]. The positive outcomes of pemafibrate extend to the reduction of lipid buildup and oxidative stress in the kidney[24], suggesting its potential to mitigate significant and devastating diabetic microvascular consequences. This potential is attributed to the enhanced selectivity and efficacy of this SPPARM drug, coupled with evidence of anti-inflammatory properties[17]. However, it is important to note that the present study did not evaluate these findings, indicating the need for more thorough research.

In the trial conducted by Ginsberg *et al.*[25], pemafibrate administered at a dose of 0.2 mg twice daily, significantly increased serum creatinine concentrations when added to statin therapy alone compared to placebo. In addition, the largest rise (3.8% vs. placebo) was far lower than those reported for comparable fenofibrate doses (5 – 22%) and was comparable to elevations observed in other pemafibrate investigations, including a study conducted in individuals with impaired renal function. Importantly, the effects of fenofibrate on glomerular filtration rate measured in the ACCORD and FIELD trials were found to be totally reversible after treatment termination, even after several years of active therapy[29,30].

Our study has certain limitations. Notably, we observed significant heterogeneity throughout the analyses, a factor that may have influenced the overall results. Therefore, a leave-one-out sensitivity analysis was performed to analyze the weight of each individual study on heterogeneity. The analyses involving the PROMINENT trial exhibited overall high heterogeneity, possibly attributed to its substantial sample size. This can be rationalized by the substantial heterogeneity within the population under scrutiny, encompassing variations in demographic attributes, medical background, illness severity, and treatment responses[18].

The analysis comparing pemafibrate at a dose of 0.2 mg/day with fenofibrate, specifically in terms of reducing TG and non-HDL, revealed notable heterogeneity stemming from the study conducted by Ishibashi *et al.*[26] Several factors contribute to this observed variability. First, the study systematically excluded patients with liver failure, renal failure, and diabetes mellitus, conditions commonly encountered in clinical settings involving patients with dyslipidemia. Second, the study cohort exclusively comprised patients with Japanese heritage, thereby raising concerns about the generalizability of the findings to individuals of other ethnicities.

5. Conclusion

Based on the findings of our comprehensive review and meta-analysis, it is evident that pemafibrate at 0.4 mg/day significantly reduces TG and non-HDL levels in patients with dyslipidemia when compared to placebo. Furthermore, in light of the neutral conclusion derived from our review of the PROMINENT trial, it becomes evident that additional research is required to ascertain the comprehensive impact of pemafibrate on cardiovascular events and mortality. Consequently, our findings emphasize the imperative for further studies to enhance our understanding and obtain a comprehensive knowledge of pemafibrate's potential benefits in lowering cardiovascular risk.

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Conflict of interest

All authors report no relationships that could be construed as a conflict of interest. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Author contributions

Conceptualization: Caroline Cristine Almeida Balieiro, Noah Romero Nakajima

Formal analysis: Caroline Cristine Almeida Balieiro, Maria Esther Barbalho, Luiza Mendes Fonseca

Investigation: Caroline Cristine Almeida Balieiro, Marcela Mizuhira Gobbo, Beatriz Polachini Assunes Gonçalves

Writing – original draft: Caroline Cristine Almeida Balieiro, Maria Esther Barbalho, Luiza Mendes Fonseca

Writing – review & editing: Eduardo Cesar Teixeira Sirena, Alice D. Marinho, Matheus J. B. Moreira, Natália Nóbrega de Lima

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

All data utilized in our analyses were sourced from publicly available information within the referenced articles.

Further disclosure

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PERSPECTIVE ARTICLE

Autonomic nerve and its modulation approaches for heart failure

Hanyu Zhang[1,2†], Yanfang Zhu[1,2†], Siyu Chen[1,2†], Keqiong Deng [1,2], Meng Zheng [1,2], Ziyue Zeng[1,2], Qiongxin Wang[1,2], Huanhuan Cai[1,2*], and Zhibing Lu[1,2*]

[1]Department of Cardiology, Zhongnan Hospital of Wuhan University, Wuhan, China

[2]Institute of Myocardial Injury and Repair, Wuhan University, Wuhan, China

Abstract

Heart failure, a condition that arises from numerous cardiovascular disorders, is a primary contributor to mortality related to cardiovascular disease. Typically noticed in heart failure is heightened sympathetic activity coupled with diminished parasympathetic activity. The autonomic nervous system governs the heart's neurological regulation through opposing functions of its sympathetic and parasympathetic components, which regulate conduction velocity, heart rate, coronary blood flow, and contractile force. Promising treatments for heart failure include inhibiting the sympathetic nerve's overactivity and restoring parasympathetic activity in the heart. In this review, we describe neural modulation approaches that have potential to assist in the management of heart failure.

Keywords: Sympathetic nerve; Parasympathetic nerve; Heart failure

†These authors contributed equally to this work.

***Corresponding authors:**
Huanhuan Cai
(caihuanhuan@whu.edu.cn)
Zhibing Lu
(luzhibing222@163.com)

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1. Introduction

Despite significant advancements in treatment, heart failure (HF) continues to pose a major global public health concern, affecting approximately 64.3 million individuals worldwide and resulting in substantial mortality rates[1]. Active intervention in heart failure, which would improve patients' prognoses by lowering hospitalization and mortality rates, has been a major topic and a key challenge in the clinical management of heart failure[2]. With the advancement of heart failure research and a better understanding of the disease, regulating heart remodeling has become an important topic in heart failure treatment[3,4]. It has been established that electrical remodeling, which plays a crucial role in the onset and progression of heart failure, is a common pathway for many cardiovascular diseases to progress to heart failure and affects patients' prognoses[2,3]. The autonomic nervous system modulates cardiac function by balancing sympathetic and parasympathetic inputs to the heart. In the face of external stimuli, multiple feedback loops regulate the autonomic balance and enable the heart to adapt to changing circumstances. An elevated sympathetic nerve activity, which is a manifestation of autonomic nervous system dysfunction, plays a pivotal role in instigating and advancing heart remodeling, ultimately leading to heart failure[5-7]. This review describes various neuromodulation approaches currently available for the management of heart failure.

2. Autonomic innervation of the heart

The cardiac autonomic nervous system (CANS) regulates the heart in a hierarchical manner that can be divided into three distinct tiers[8-10] (Figure 1).

Neurons residing in the higher cortical regions of the central nervous system, including the insular cortex, anterior cingulate cortex, medial prefrontal cortex, and amygdala, act as regulators of the neurons present in the medulla oblongata (brain stem) and spinal cord at level 1[11-13]. Levels 2 and 3 are peripherally located; Level 2 includes the inner and external thoracic ganglia and Level 3 is the internal cardiac nervous system (ICNS)[11]. Located within the cardiac fat pad, the intrinsic cardiac ganglia (ICG) neurons serve as the final parasympathetic pathway, projecting axons to distinct areas of the heart[10]. The intricate neural networks formed by ICG neurons regulate various aspects of regional cardiac function, such as the flow of blood in the coronary arteries and the perfusion of the myocardial tissue[14]. The ganglia found in the right superior vena cava and right atrium are responsible for regulating the sinoatrial node, whereas the ganglia located at the inferior vena cava and left atrium play a role in controlling the atrioventricular node[15]. The responsiveness of ICG neurons to mechanical and chemical stimuli, as well as stimulation from vagosympathetic nerves, implies that they receive signals from both sympathetic and parasympathetic efferent axons, as well as sensory neurites of the ventricle[16-19]. The intrinsic cardiac nervous system independently governs the cardiac function on a beat-by-beat basis, even in the absence of external input from the central nervous system[14]. The sinoatrial node is influenced by both the parasympathetic and sympathetic nervous systems, which work in opposition to modulate heart rate[20]. Activation of the sympathetic nervous system leads to positive chronotropic (heart rate), tropic (conduction velocity), and inotropic (contractile force) responses. On the other hand, the activation of the parasympathetic nervous system produces adverse chronotropic, inotropic, and dromotropic effects on the heart[14]. The parasympathetic nervous system modulates the heart rate through direct inhibition of the sinoatrial node through a G-protein coupling mechanism or indirectly by coregulating the sympathetic nervous system to decrease heart rate[21-22]. At the synaptic junction of the cardiac nerves, the parasympathetic nervous system discharges acetylcholine, which attaches to the presynaptic muscarinic (M2) receptors located on the sympathetic nerve terminals, leading to the inhibition of norepinephrine (NE) release[23]. Neural modulation methods are illustrated in Figure 2 and will be discussed in detail in the following sections.

3. Vagus nerve stimulation (VNS) in parasympathetic nerve

3.1. Electrode-based techniques

Current research has revealed that VNS not only reduces sympathetic nervous tension but also directly activates vagus nerve efferents and increases vagus nerve activity. VNS then plays a multifaceted role in protecting the heart through anti-inflammatory, alleviating mitochondrial dysfunction, anti-oxidative stress, and anti-remodeling effects[24-28] (Figure 3). Electrically stimulating the parasympathetic nervous system using methods such as VNS, transcutaneous ear VNS (also known as tragus stimulation, TS), ganglion plexus stimulation, and spinal cord stimulation (SCS) enhances the activity of vagus nerves. The VNS device is frequently utilized in clinical

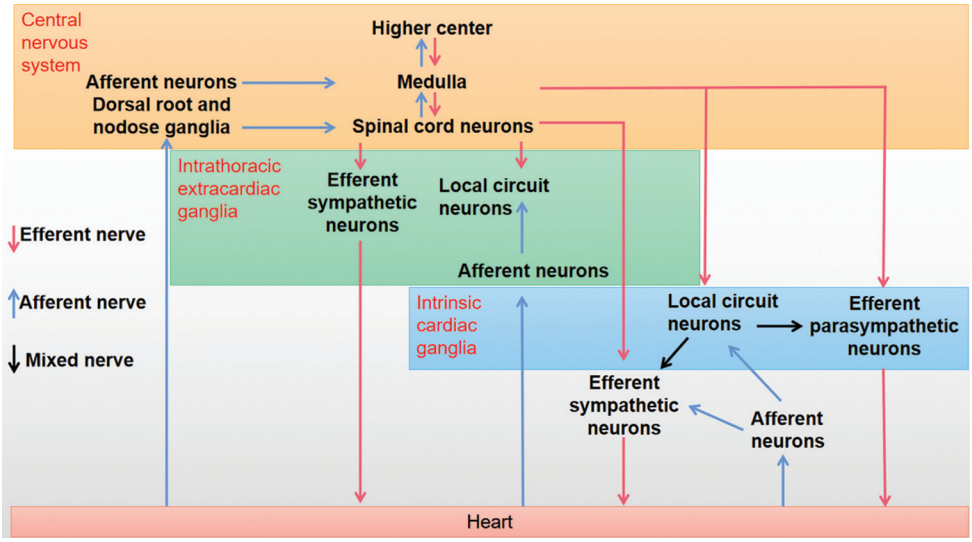

Figure 1. A model of the hierarchical control of the heart by the cardiac autonomic nervous system[10].

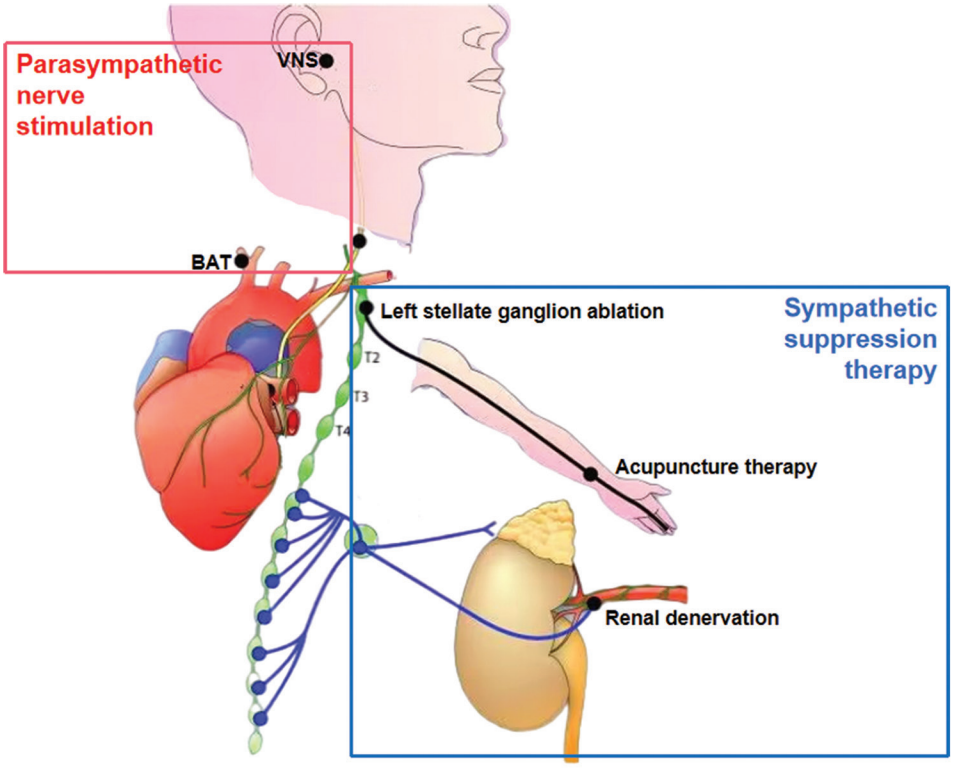

Figure 2. An overall preview of autonomic regulation.
Abbreviations: BAT: Baroreflex activation therapy; VNS: Vagus nerve stimulation.

settings due to its widespread availability and effectiveness. Clinical studies have shown that electrode-based VNS interventions are effective in treating various medical conditions. The clinical use of VNS has been authorized for managing seizures and depression[29-31]. Clinical studies have shown its benefits in the treatment of inflammatory diseases such as Crohn's disease[32], rheumatoid arthritis[33], hypertension[34], and obesity[35].

With regard to the heart, clinical studies have highlighted the therapeutic potential of VNS for atrial arrhythmia[36,37] and heart failure[38-40]. Meanwhile, preclinical data suggest that VNS exhibits a cardioprotective effect in stress and ischemia models by reducing intrinsic and sensory neuronal remodeling, as well as in cardiac hypertrophy[41,42]. In 2011, a randomized trial called neural cardiac therapy for heart failure was initiated[39]. The prevailing stimulation parameters suggested were as follows: A frequency of 20 Hz, a pulse width of 300 μs, and an active period of 10 s followed by an inactive period of 50 s. The maximum allowable current, also known as the output current, was set at 4 mA. In the study, the modification in the left ventricular end-systolic diameter (LVESD) after 6 months was considered the primary endpoint, while changes in other echocardiographic parameters, quality of life assessments, and supplementary biomarkers constituted the secondary endpoints. In this clinical trial, 96 patients were randomly assigned to a VNS-treated group with a 2:1 ratio compared to the group with inactivated VNS devices. Although the quality of life indicators improved during the trial period, the study did not find significant improvements in primary or secondary endpoint assessments related to cardiac remodeling or functional capacity in patients suffering from symptomatic heart failure.

The autonomic neural regulation therapy to enhance myocardial function in heart failure study, conducted from 2012 to 2013, was a multicenter, open-label trial that aimed to assess the effectiveness, tolerance, and safety of autonomic neuromodulation therapy for enhancing myocardial function in patients with heart failure[43]. In this research project, 60 individuals diagnosed with heart failure were randomly divided into two groups, with each group receiving VNS treatment through the left or right vagus nerve in a 1:1 ratio, thus assigning 30 patients to each group. The results of the study showed that the combined cohort's left ventricular ejection fraction improved significantly. However, no clinically significant improvement was observed in LVESD. Nonetheless, all subjective efficacy measures indicated statistically significant improvement.

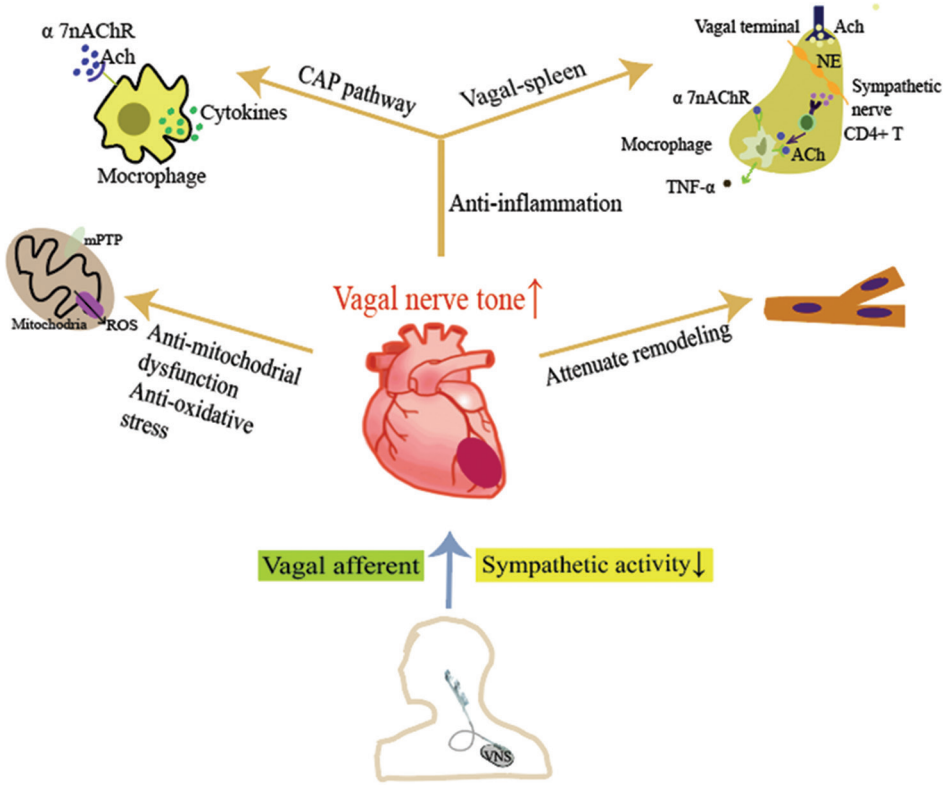

Figure 3. Schematic representation of potential pathways by which VNS can protect the heart from myocardial injury.
Abbreviations: α7nAChR: α7 nicotinic acetylcholine receptor; Ach: Acetylcholine; mPTP: Mitochondrial permeability transition pore; NE: Norepinephrine; ROS: Reactive oxygen species; TNF-α: Tumor necrosis factor-alpha.

Although VNS on the right side exhibited slightly better outcomes, the difference was not statistically significant. The noteworthy improvement observed at 12 months was sustained over time, as there were no significant differences in the mean efficacy measure values between 6 and 12 months[38]. Furthermore, the clinical trial indicated that patients who underwent VNS therapy witnessed a decrease in T-wave alternans, which signifies small and continuous changes in the structure and amplitude of the ST segment or T-wave in the electrocardiogram and are used to identify severe and potential fatal arrhythmias[44].

In contrast, the increase of vagal tone in heart failure trial, which involved 707 patients, did not observe comparable advantages, despite aiming to increase vagal tone in heart failure[40]. The study involved 436 individuals receiving active treatment and 271 individuals in the control group, with a projected yearly death rate of 9.3% in the active treatment group and 7.1% in the control group. Despite experiencing significant enhancements in the quality of life, a functional class defined by the New York Heart Association, and the ability to walk for 6 minutes, the LVESD index of the participants did not show any signs of improvement.

According to the various results presented above, a variety of factors may account for the disparities in VNS clinical outcomes. In pharmacological experiments, the appropriate dosage and maximum potential benefits were determined through the estimation of the dose-response curve[45]. We are of the opinion that VNS treatment could also be suggested. The vagus nerve in the neck area consists of afferent and efferent fibers that are constituted of A, B, and C types of fibers. Because fiber diameter has an inverse relationship with the stimulation threshold, VNS therapy initiates the activation of A fibers followed by higher-strength B fibers when given at lower intensity. With an increase in the intensity, C fibers become active as well[46]. Inherent properties and significant diameter make afferent fibers more likely to be activated at lower stimulation thresholds, resulting in increased vagus activity. This activation then helps modulate sympathetic activity through the central nervous system. Consequently, the efficiency of long-term VNS treatment in patients with heart failure may be influenced by diverse elements, encompassing stimulation parameters like the intensity of current, duty cycle, frequency, arrangement of electrodes, and the site of stimulation chosen[47]. More clinical studies

to identify and assess the optimal dose of VNS would be necessary in the future. To summarize, there is still a long way to go in using VNS to treat cardiovascular disease.

3.2. Non-invasive VNS

VNS is an invasive neuronal modulation used in cardiovascular disease. Surgical complications and side effects often and inevitably occur in patients during surgical implantation of a neurostimulator system[48]. However, studies have demonstrated that both percutaneous nerve stimulation of the tragus (TNS) and non-invasive VNS can produce analogous results in treating heart disease secondary to dysfunction in the CANS. Furthermore, it is a promising method for regulating cardiac autonomic dystonia manifested by hypersympathetic and hyposympathetic dysfunction[49].

The auricular branch of the vagus nerve, a peripheral branch of the vagus nerve found solely in the skin, sends its afferent vagus fibers through the jugular ganglion and terminates at the nucleus tractus solitarii (NTS). The NTS serves as the central station for autonomic neurons, receiving incoming sensory information and activating the caudal ventrolateral medulla and dorsal motor nucleus (DMN) to regulate neural activity within the autonomic nervous system[50,51]. Enhanced cardiac vagus tone is achieved through the transmission of electrochemical signals from the overactive DMN through the bilateral cervical vagus nerves to the epicardial ganglion plexus. TNS theoretically regulates the equilibrium of the autonomic nervous system in the heart. Following this, TNS has been progressively implemented in the management of cardiovascular disorders, with experimental research demonstrating favorable impacts on heart-related circumstances.

Chen *et al.* conducted research that found that low-level tragus nerve stimulation (LL-TS) can effectively suppress canine atrial fibrillation (AF). The clinical studies conducted by Stavrakis *et al.* also acknowledged the efficacy of LL-TS[52]. LL-TS has the capability to suppress AF and reduce the concentrations of inflammatory cytokines in individuals with paroxysmal AF diagnosis[53]. The findings imply that TNS is a fresh approach to regulating cardiovascular disease through the control of the imbalance of cardiac autonomic nerves. The study proved that chronic intermittent LL-TS could lead to notable reductions in infarct size, improvements in ventricular function, and positive changes in cardiac remodeling for individuals living with ischemic heart disease[54]. According to the research, the use of LL-TS can result in a positive outcome, as it can alleviate injury caused by the restoration of blood flow after a period of reduced blood supply to the heart muscle in acute myocardial infarction (AMI) patients who have undergone primary percutaneous coronary intervention. This discovery opens the prospect of using non-invasive methods to treat individuals with AMI[55]. Compared to invasive VNS, non-invasive VNS is the more promising therapeutic alternative, which shows potential for greater specificity and improved safety. Nonetheless, additional research is required to evaluate its clinical effectiveness.

3.3. Optogenetics vagus nerve modulation

The optogenetics vagus nerve modulation approach utilizes optogenetic methods to stimulate the vagus nerve, facilitating focused communication between neurons and photosensitive actuators (opsin) for delivering viruses to specific organs, depending on their site of delivery. During preclinical animal studies, viruses were applied to target the excitatory opsin found in the peripheral nerves, allowing for the optical stimulation of specific motor activity[56-58], and the inhibitory opsin was utilized to suppress muscle activity[57,59] and alleviate pain[60]. Adeno-associated virus (AAV) is commonly employed in experimental settings as a vector for optical sensors and actuators, with its targeting specificity being affected by factors such as genetic promoters, serotypes of the virus, and tissue/delivery sites. In addition, various gene therapy approaches that rely on AAV are currently undergoing assessment in clinical trials involving human participants[61-63]. In their study, Fontaine *et al.* successfully proved the viability of retrograde labeling in achieving optical neuromodulation targeted toward specific organs[64]. However, relevant clinical trials are currently insufficient, and more verification of its efficacy is necessary.

3.4. Baroreflex activation therapy (BAT)

By activating physiological reflex pathways, BAT can reduce sympathetic cardiac outflow and increase cardiac vagal activity through central inhibition. It has previously been shown to be safe and efficient when treating refractory hypertension[65], and now researchers are investigating its effectiveness in addressing autonomic nerve imbalance in patients with heart failure[66]. BAT is performed by surgically implanting a device similar to a pacemaker that produces pulses and is powered by a battery in the chest wall. Leads are then strategically placed in the carotid sinus[67]. The use of BAT is an innovative and promising approach that has demonstrated its efficacy in treating heart failure patients by reducing sympathetic activity and enhancing cardiac function and quality of life. Moreover, the safety profile of BAT is considered relatively satisfactory[68,69]. Despite the potential benefits of BAT, controversies exist in the fields of health economics, device interaction, and the treatment of heart failure with preserved ejection fraction (HFpEF). Therefore, it remains to be determined, through further

research, whether the broader application of BAT in heart failure therapy is feasible.

4. Sympathetic suppression therapy

4.1. Conventional pharmacological sympathetic suppression therapy

In patients with heart failure, sympathetic activation compensates for the short-term decrease in pump function. Although sympathetic activation has potential advantages, it can ultimately cause hypertrophy and interstitial fibrosis that may have cardiotoxic effects and exacerbate the decline of cardiac function. In such scenarios, β-blockers are regarded as the central treatment for chronic heart failure[70] (Figure 4).

According to current heart failure guidelines[71], β-blockers are recommended based on numerous randomized controlled trials (RCTs) that have demonstrated a mortality reduction of over 35%. For patients with reduced left ventricular ejection fraction (HFrEF), there is typically an increase in plasma catecholamine concentration[72-74], coupled with a down-regulation and attenuation of the cardiac beta receptor response. Ironically, the use of β-blockers can counteract these changes, as they can decrease sympathetic drive while simultaneously heightening beta receptor sensitivity, as was demonstrated in a study[75]. In individuals with HFpEF, exercise or beta-adrenergic stimulation frequently fails to raise the ejection fraction, even in the absence of epicardial coronary artery disease, suggesting that beta-adrenergic receptors may be desensitized in these patients[76]. HFpEF patients do not demonstrate an elevation in plasma catecholamine concentration, unlike those with reduced ejection fraction[77]. Compared to other conventional therapeutic agents for heart failure, such as angiotensin-converting enzyme inhibitors (ACEIs) and aldosterone antagonists, β-blockers tend to be more efficacious in enhancing ejection fraction and possess anti-ischemic properties that can lower the likelihood of sudden cardiac death[73]. Despite available drug therapies, there remains inadequate control over the disease process, suggesting that current treatments only partially reverse negative structural remodeling and that some degree of persistent cardiac dysfunction is present, maintaining the pathophysiological processes of heart failure.

4.2. Interventional radiofrequency (RF) ablation of the sympathetic nerve was performed

4.2.1. Renal denervation (RDN)

There is increasing interest in interventional approaches to substitute or supplement existing pharmacological therapies for heart failure[79]. RDN is an endovascular technique that utilizes RF energy to eliminate sympathetic nerves that pass through the renal artery, accomplished in a minimally invasive manner[80]. Initially designed for refractory hypertension treatment, the effectiveness of this strategy in lowering blood pressure is debated due to mixed outcomes in clinical trials involving patients with hypertension[80-83]. Despite the controversy, RF-RDN may have cardiovascular benefits that extend beyond blood pressure reduction. RF-RDN holds immense promise in safeguarding the heart by obstructing the aberrant afferent and central reflex mechanisms responsible for exacerbating

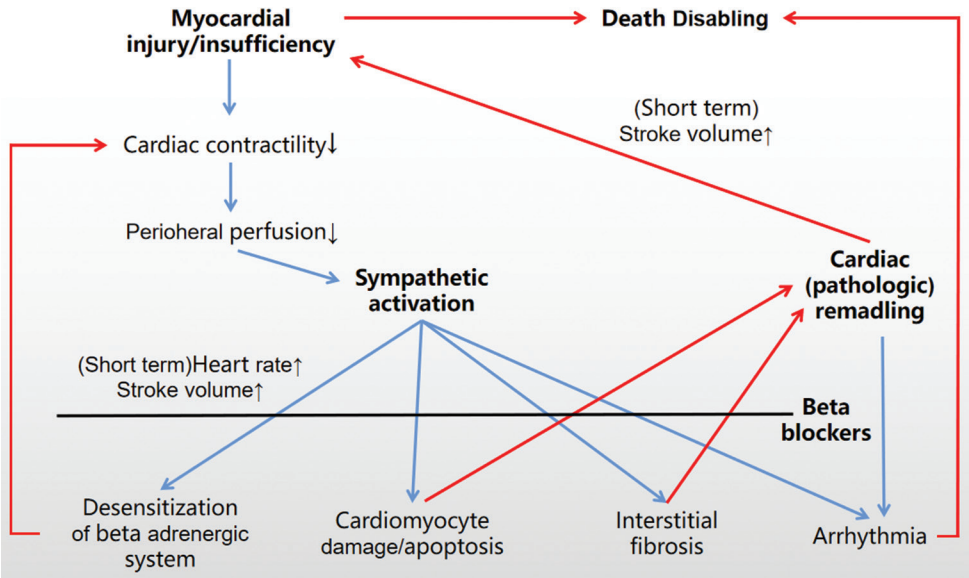

Figure 4. Mechanisms of β-blocker therapy in congestive heart failure[75].

heart failure[84]. Moreover, renal nerves have been found to be involved in the newly identified intrinsic mechanism responsible for degrading cardioprotective natriuretic peptides (NPs). Furthermore, in individuals suffering from heart failure, abolishing the influence of renal nerves on renal function can lead to a decrease in renal neprilysin activity, an elevation in circulating NP levels, a decrease in myocardial fibrosis, and an improvement in the left ventricular function[85]. However, controlling the extent and effect of the current ablation methods on renal sympathetic nerve damage is challenging, and the clinical efficacy has been controversial.

4.2.2. Left stellate ganglion (LSG) ablation

The stellate ganglion (SG) neurons play a crucial role in regulating cardiac function as a major component of the autonomic nervous system. Prior research has demonstrated that heart failure can lead to an elevation in SG neural activity and result in remodeling of the cardiac ganglion[86,87]. In heart failure patients, sympathectomy and SG block are viable treatment options for managing ventricular arrhythmias and cardiac insufficiency with proven effectiveness[88-90]. To decrease the noradrenergic drive of the heart, targeted ablation of cardiac sympathetic neurons (TACSN) serves as an efficient method, achieved through retrograde administration of cholera toxin B-saporin (CTB-SAP) compounds into the SG[91]. Research has indicated that CTB-SAP is able to effectively and selectively eliminate cardiac sympathetic preganglionic neurons by binding with GM1 ganglioside, which is present on the plasma membrane of these neurons. Consequently, there is a decrease in the population of post-ganglionic neurons within the SG and sympathetic innervation of the ventricular myocardium, effectively hindering sympathetic activation triggered by reflex and exercise, as demonstrated in conscious rats[92,93]. LSG ablation effectively inhibits cardiac sympathetic nerve activity, but the nerves and blood vessels that are abundant in the neck are vulnerable to damage when the SG is isolated. LSG ablation also has an impact on sinus node function and may not completely prevent the development of Horner's syndrome. For these reasons, LSG ablation has not been widely adopted in clinical settings[94,95]. On the other hand, the right SG ablation might contribute to the onset of ventricular arrhythmias[94,95].

4.3. Acupuncture therapy

Acupuncture, a component of traditional Chinese medicine, has been utilized as a therapeutic option for treating a wide range of diseases and disorders for over a millennium. Electro-acupuncture (EA), a stronger variation of acupuncture, is also prevalent and has been adopted as an alternative medical treatment worldwide. Acupuncture as a treatment strategy is extensively acknowledged and commonly implemented in the United States[96,97]. Acupuncture has proven to be an effective treatment for post-operative pain, as well as nausea and vomiting resulting from chemotherapy and surgery. Apart from the aforementioned uses, acupuncture has demonstrated clinical effectiveness in addressing a myriad of other ailments, such as drug dependence, bronchial asthma, phlogosis, and pain. The stimulation of Neiguan and Jianshi acupoints has exhibited notable efficacy and is commonly favored over other acupoints utilized in the treatment of cardiovascular diseases[98-100]. Research demonstrates that EA applied to the Neiguan and Jianshi acupoints can inhibit cardiovascular sympathetic excitatory pressure-reflex responses resulting from chemical, mechanical, and electrical stimulation[101-104]. Stimulating the median nerve at the Neiguan acupoint through EA has been observed to decrease regional myocardial ischemia in cats with partial coronary occlusion. This effect is achieved by decreasing sympathetic-mediated cardiac oxygen demand, thereby preventing the onset of ischemia[102]. The findings from both clinical and animal studies imply that acupuncture could be advantageous in managing and regulating certain forms of hypertension, as well as cardiac arrhythmias and coronary heart disease[99,100,105,106]. In rats, EA has been observed to lower sympathetic activity[107,108] and markedly reduce cardiovascular sympathetic excitatory reflex responses following chemical, mechanical, and electrical stimulation[101-104]. EA applied to the median nerve at the Neiguan and Jianshi acupoints is particularly efficacious in mitigating the pressure response arising from cardiovascular sympathetic excitatory reflexes[99,100]. EA shows promise as a potentially valuable approach to managing various disease categories. While one study on animals[109] has demonstrated the efficacy of EA as a supplementary or alternate form of therapy, its mechanisms are not yet well understood. Therefore, more extensive studies involving more study subjects are necessary to investigate its clinical efficacy and associated underlying mechanisms.

5. Conclusion

In recent years, an increasing number of animal studies and clinical data have indicated the potential of non-pharmacological methods, such as EA, renal sympathetic nerve ablation, BAT, and VNS, to inhibit sympathetic nerve activity and stimulate vagal excitation in the course of cardiac remodeling and the treatment of heart failure. Identifying the intervention targets with fewer side effects, more precise efficacy, higher safety, better specificity, and more feasible operation and finding new ideas for the

prevention and treatment strategies of cardiac remodeling and heart failure using non-drug approaches, however, remain a research hotspot and an urgent scientific problem to be solved in this field, which has a wide range of potential applications.

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Conflict of interest

The authors declare that they have no competing interest.

Author contributions

Investigation: Hanyu Zhang, Yanfang Zhu, Siyu Chen
Methodology: Keqiong Deng, Meng Zheng
Formal analysis: Ziyue Zeng, Qiongxin Wang
Writing – original draft: Hanyu Zhang
Writing – review & editing: Zhibing Lu, Huanhuan Cai
All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data

Not applicable.

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ACCSCIENCE PUBLISHING

Brain & Heart

ORIGINAL RESEARCH ARTICLE

Renal denervation guided by novel blood pressure response patterns of renal nerve stimulation in human: A case series study

Zhenhong Ou[1,4], Huaan Du[1], Weijie Chen[1], Hao Zhou[1], Hang Liu[1], Kun Cui[4], Bo Zhang[1], Dan Li[1], Tianli Xia[1], Huang Zhou[1], Yunlin Chen[1], Wenjiang Chen[1], Mingyang Xiao[1], Xue Kuang[1], Changzhi Zhang[1], Jie Yang[1], Chunxia Gan[1], Kamsang Woo[2], Zrenner Bernhard[3], Zengzhang Liu[1], and Yuehui Yin[1]*

[1]Department of Cardiology, the Second Affiliated Hospital of Chongqing Medical University, Chongqing Cardiac Arrhythmia Therapeutic Service Center, Chongqing Key Laboratory of Arrhythmia, Chongqing, China

[2]Institute of Future Cities, the Chinese University of Hong Kong, China

[3]Department of Cardiology, Medizinische Klinik I, Krankenhaus Landshut/Achdorf, Germany

[4]Department of Cardiology, Chongqing General Hospital, Chongqing, China

Abstract

Renal nerve stimulation (RNS) could localize the renal nerve innervation through rapid blood pressure (BP) changes for renal denervation (RDN). Recently, novel BP response patterns have been demonstrated in animals. The current study was to verify the presence of these patterns in humans and examine the feasibility of using them to guide selective RDN. Fourteen patients with mild resistant hypertension were included in this prospective analysis. RNS was performed before and after radiofrequency-based RDN. Invasive monitoring was used continuously to obtain beat-to-beat BP. Ambulatory BP (ABP) monitoring was measured at baseline, 5–7 days, and 6–12 months, respectively. Five types of BP responses were summarized during RNS before RDN, namely: (1) BP persistently elevated; (2) BP dropped and then elevated above the baseline; (3) BP dropped and then recovered, but not over the baseline; (4) BP fluctuated in the vicinity of the baseline; and (5) BP persistently dropped. Selective RDN was performed at the site with elevated BP. The 24-h ABP decreased from 141 ± 12/94 ± 9 mmHg at baseline to 130 ± 11/85 ± 8 mmHg at 5 – 7 days ($P = 0.001$ for systolic BP [SBP], $P = 0.003$ for diastolic BP [DBP]) and 127 ± 11/85 ± 8 mmHg at 6 – 12 months ($P = 0.009$ for SBP, $P = 0.019$ for DBP). The average heart rate fell from 77 ± 8 bpm to 71 ± 5 bpm ($P = 0.01$) and 72 ± 7 bpm ($P = 0.043$), respectively. Our study showed five types of BP responses elicited by RNS in humans. RDN guided by these BP responses was feasible and resulted in obvious BP reduction, and they may potentially provide precise guidance for RDN.

Keywords: Renal nerve stimulation; Renal denervation; Hypertension

***Corresponding author:**
Yuehui Yin
(yinyh@hospital.cqmu.edu.cn)

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1. Introduction

Catheter-based renal denervation (RDN) destroys nerves around the adventitia of the renal artery using radiofrequency, ultrasound, or other energy to cause a reduction of

systemic sympathetic tone. Recently, it was considered an effective option in the management of hypertension. Although the neutral results of several randomized sham-controlled trials questioned the effectiveness of RDN[1-3], posthoc analysis and the final report of the hypertension-3 (HTN-3) trial suggested that it can cause a significant reduction of office and ambulatory blood pressure (ABP)[4,5]. Coincidentally, recent trials with state-of-the-art methodology reconfirmed the real antihypertensive effect of RDN[6-9]. Meanwhile, nearly 30% of patients with hypertension did not respond to RDN treatment, even with their BP rising instead of falling. We believe that the cause of this phenomenon should be closely related to renal nerve function. Since the current ablation strategy is based on the anatomical distribution of renal nerves, it is not considered that renal nerves may also have the function of lowering BP in addition to raising BP. Therefore, the anatomical destruction of renal nerves potentially results in this heterogeneity of postoperative BP response[10]. Selective ablation of the sites with suitable renal nerves may be a key to further improving the effectiveness of RDN.

Previous studies suggested that various BP responses, including elevation, drop, and no change, can be induced by renal nerve stimulation (RNS)[11-14], which is in line with the different physiological functions of various renal nerve fibers located in one nerve bundle[10,15,16]. Based on these results, we speculated that the patterns of BP response evoked by RNS depend on the synthetical effects of different renal nerve fibers[17]. In other words, the detailed BP response might assist in assessing the innervation at the stimulated sites, and this is important for effective ablation. Recently, our team reported five patterns of BP response and found that ablation at the sites with BP elevation led to efficient BP lowering in the canine[18,19]. However, whether there were similar responses in humans was unclear. The aims of this study were to identify the BP responses induced by RNS and use these responses to guide the selection of effective targets for RDN in patients with hypertension.

2. Materials and methods

2.1. Patient population

In our center, renal electrical stimulation mapping was performed meticulously in the first 14 patients with resistant hypertension. Patients were eligible if their average ambulatory systolic BP was ≥130 or their diastolic BP was ≥80 mmHg after receiving and adhering to at least three antihypertensive drugs (except when not tolerated). Exclusion criteria included abnormal anatomy of the renal artery, severe renal stenosis, stent implantation in the renal artery, identification of secondary hypertension or type 1 diabetes mellitus, pregnancy, and an estimated glomerular filtration rate of <45 mL/min per 1.73 m^2. Medication regimens, ambulatory BP (ABP) monitoring, office BP (OBP), renal artery computed tomography angiography, and estimated glomerular filtration rate were recorded at baseline and follow-up periods. Measuring BP (BP) every 20 min during the day and 1 h at night was used in the ABP monitoring. The electronic sphygmomanometer (Intellisense, HEM-7130, OMRON, Dalian, China) was used to obtain the OBP (average values of triplicate measures). All patients were willing to complete the interventional procedure and provided informed consent. This study was approved by the hospital's ethics committee.

2.2. RDN Procedure

Every patient underwent bilateral renal arteriography, high-frequency RNS, and catheter-based radiofrequency ablation. The surface ECG was continuously recorded throughout the procedure by a multichannel recorder (Sichuan Jinjiang Electronic Science and Technology Company, Chengdu, China). The right femoral artery was punctured under sterile conditions, and 50 IU/kg of unfractionated heparin was administered. A 6F JR4 Judkins catheter (Cordis Corporation, Miami, Florida) was used to perform angiography via the right femoral artery. The invasive BP monitoring continuously recorded the patient's BP through the left/right radial artery. Intravenous application of fentanyl (initial injection with 0.002 mg/kg and continuous intravenous infusion with 0.002 mg/kg/h) was used for analgesia. A dedicated 6F bipolar micropores irrigated ablation catheter (AquaSense, Synaptic Medical Limited, Beijing, China) was deployed in the renal artery via the right femoral artery.

High-frequency bipolar electrical stimulation was performed orderly from the bifurcation (if the diameters of renal branches and the accessory renal arteries were more than 3.5 mm, RNS was also permitted to deliver) to the ostium of the renal artery via the saline-irrigated electrode using a nerve and muscle stimulator (SynNuo-C4, Sichuan Jinjiang Electronic Science and Technology Company, Chengdu, China). Electrical stimulation was delivered with a frequency of 10 Hz, a current of 15 mA, and a pulse width of 2 ms for 30 s. The sites with an elevation of systolic BP (SBP) >5 mmHg during RNS were ablated using the same catheter. After ablation, the position of the electrode was unchanged, and electrical stimulation was performed again with the same parameters.

Radiofrequency-based ablation was performed at the sites with the SBP elevation during RNS. The temperature of the intima-electrode interface was decreased through the 6–8 ml/min saline irrigated manually during radiofrequency delivery. Conventional radiofrequency

energy was 8–10 W for 60 s and increased to 12 W for 60 s if the SBP elevation was still evoked by the post-ablation electrical stimulation. The selection of exact ablative powers depended on the impedance. The ablation endpoint was defined as the disappearance or significant blunting of the SBP-elevated response during the post-ablation electrical stimulation. After the completion of all intra-arterial high-frequency electrical stimulation and radiofrequency ablation, bilateral renal arteriography was performed repeatedly to evaluate for abnormalities such as dissection, perforation, thrombosis, and other procedure-related adverse events.

2.3. Measurement

The amplitude of beat-to-beat BP during the procedure can be measured and stored automatically by the Lead Multi-channel Physiological Analysis software (Sichuan Jinjiang Electronic Science and Technology Limited, Chengdu, China). It could be regarded as unchanged when SBP fluctuation is in the vicinity (in the range of less than 5 mmHg) of baseline, based on the lower beat-to-beat SBP variability (1.4–2.8 mmHg) with an invasive monitoring technique[20]. We used the intraoperative BP data observed in an animal study[18] to verify whether these possible trend curves exist in humans. A quantitative method for judging the trend of BP change during electrical stimulation was used in this study. According to the change of specific values, such as the maximum, minimum, and end values during the stimulation from the pre-stimulation value, the fluctuating trend of an SBP curve can be preliminarily determined. Thus, in this study, using 10 cardiac cycles as a unit of measurement, we first identified the specific values containing the minimum SBP, the maximum SBP, the end-stimulation SBP, and their occurrence times. Then we calculated the SBP change of these specific values from the pre-stimulation SBP to show and classify the trend of BP at each stimulation site (a detailed process is shown in Figure 1). ABP, average heart rate from the report of ABP monitoring, and anti-hypertensive medication regimens at baseline, 5 – 7 days, and 6 – 12 months were collected.

2.4. Statistical analysis

Categorical variables were expressed as frequency or percentage and statistically compared using the chi-square or Fisher's exact tests. The Shapiro-Wilk test was used to determine whether the measurement data had a normal distribution. $P > 0.05$ was considered to conform to the normal distribution, and then the measurement data were expressed as the mean ± standard deviation. Non-normally distributed data were expressed as a median with the interquartile range (IQR) (25% IQR, 75% IQR). Univariate repeated measurement analysis of variance was used to compare BP and heart rate at baseline, 5 – 7 days, and 6 – 2 months. The other measurement data were compared by Student's t-test. $P < 0.05$ was considered statistically significant. Data analysis was performed by SPSS 23.0 software (IBM Corporation, Armonk, New York).

3. Results

A total of 14 patients who received selective RDN guided by RNS were included in this study. The patients were relatively young (43 ± 9 years old), mostly male (11/14), and not lean (BMI: 26.1 ± 2.2 kg/m^2), with an ABP of 141 ± 12/94 ± 8 mmHg and an OBP of 158 ± 24/101 ± 19 mmHg at baseline. The remaining demographic data and clinical characteristics are shown in Table 1.

The beat-to-beat SBPs at 260 RNS sites before RDN were obtained to analyze. The following 5 types of BP responses were observed (Figure 2 and Table 2) and are further elaborated below:

i. Type 1: BP persistently elevated above baseline.

   SBP in 74 sites (28.5%) continued to elevate during RNS. The peak SBP during the stimulation increased significantly and exceeded the baseline by 14.3 ± 8.9 mmHg. The terminal SBP of the stimulation was still higher than the baseline by 11.6 ± 7.9 mmHg.

ii. Type 2: BP dropped and then elevated above the baseline.

   SBP in 47 sites (18.1%) dropped initially, then recovered and exceeded the baseline during RNS. The valley SBP dropped markedly, was lower than the baseline by 14.0 ± 7.1 mmHg, and then recovered. The peak SBP increased significantly and exceeded the baseline by 13.2 ± 7.6 mmHg. The terminal SBP of the stimulation was still above the baseline by 8.3 ± 9.6 mmHg.

iii. Type 3: BP dropped and then recovered but never went over the baseline.

   SBP in 50 sites (19.2%) dropped initially and then recovered but never went over the baseline during RNS. The valley SBP dropped markedly and was lower than the baseline by 16.7 ± 8.4 mmHg, and the peak SBP recovered but never exceeded the baseline (−1.8 ± 5.9 mmHg). Terminal SBP was higher than the valley SBP by 13.1 ± 7.0 mmHg, which was -3.6 ± 5.6 mmHg of the baseline.

iv. Type 4: BP fluctuated in the vicinity of baseline.

   SBP in 71 sites (27.3%) showed no observable change during RNS. BP fluctuated in the vicinity of the baseline (−1.0 ± 2.1 mmHg at the valley and 1.3 ± 2.0 mmHg at the peak) during electrical stimulation.

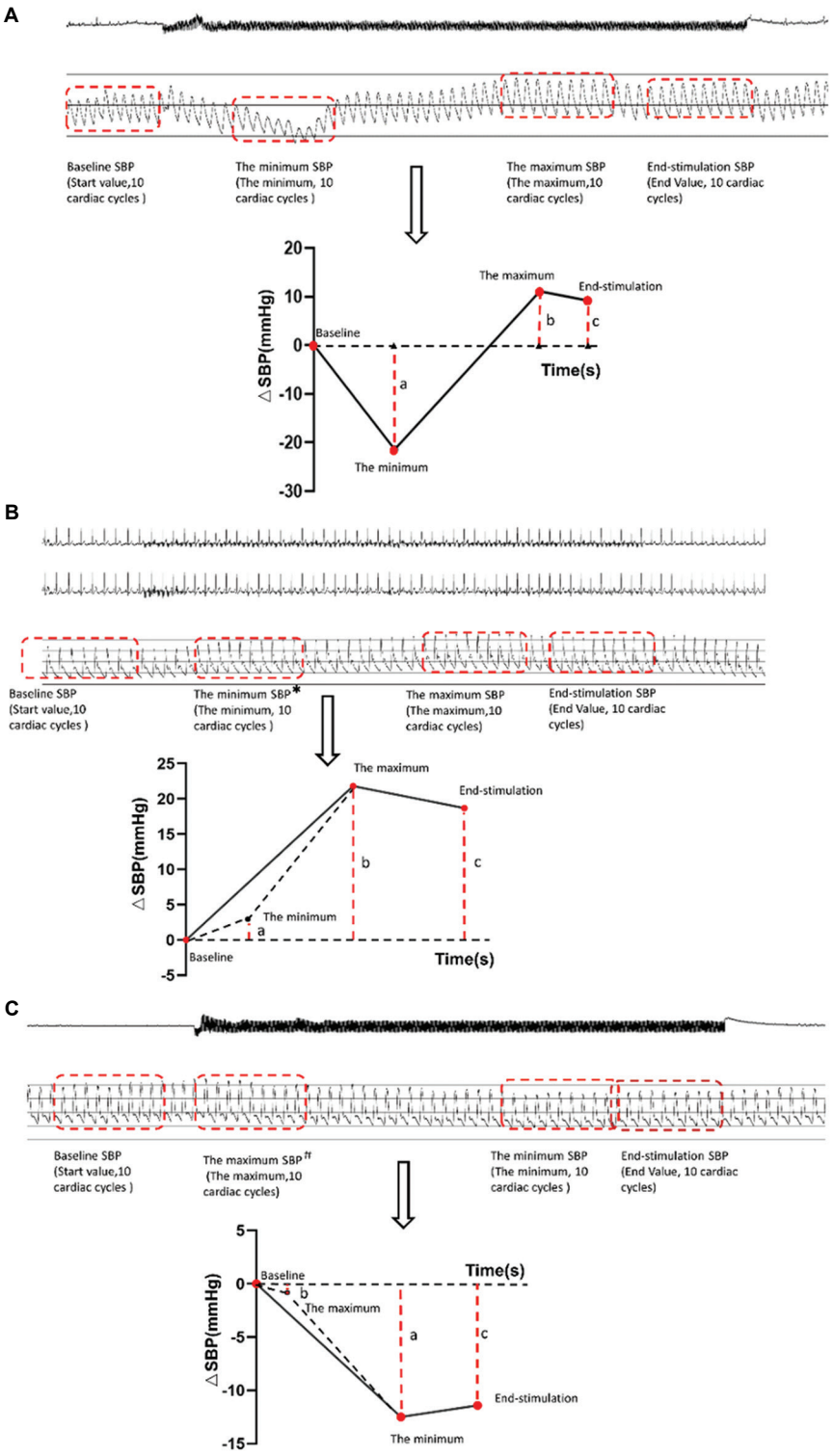

Figure 1. Schematic diagram of the data processing. Specific values were extracted at the sites with SBP biphasic variation (A), continuous rise (B), and sustained drop (C) to show the trend of BP variation during RNS.

Notes: *: The minimum is defined as when SBP begins to rise in the sites with a continuous rise; #: The maximum is defined as when SBP begins to drop in the sites with sustained drop; a: The minimum SBP change=The minimum SBP-baseline SBP; b: The maximum SBP change=The maximum SBP-baseline SBP; c: End-stimulation SBP change=End-stimulation SBP-baseline SBP.

Abbreviation: SBP: Systolic blood pressure.

Table 1. Demographic and baseline characteristics of patients (*n*=14)

	Values (mean±SD or *n*)
Age, years old	43±9
Females	3
Body mass index, kg/m^2	26.1±2.2
Smoking	6
OBP, mmHg	
SBP	157±24
DBP	101±19
ABP, mmHg	
24-h, SBP	141±12
24-h, DBP	94±9
Daytime, SBP	143±13
Daytime, DBP	95±9
Nighttime, SBP	138±11
Nighttime, DBP	92±13
Heart rates, beats/min	77±8
Serum creatinine, μmol/L	80±28
eGFR, mL/min/1.73 m^2	103±25
Comorbidity	
Hyperlipemia	3
Type 2 diabetes	2
Hypertensive heart disease	9
Coronary atherosclerotic heart disease	0
Atrial fibrillation	0
Antihypertensive medication therapy	
No. of antihypertensive drugs	3
Diuretic	6
Calcium channel blockers	13
Beta adrenoceptor-blocking agents	11
ACE-Is/ARB	10
Alpha adrenoceptor-blocking agents	2

Abbreviations: ABP: Ambulatory blood pressure; ACE-Is: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; OBP: Office blood pressure; SBP: Systolic blood pressure.

v. Type 5: BP persistently dropped below the baseline.

SBP in 18 sites (6.9%) continued to drop during RNS. The valley SBP dropped markedly and was lower than the baseline by 12.5 ± 7.4 mmHg. Terminal SBP was higher than the valley by 1.1 ± 1.1 mmHg, which was −11.4 ± 7.3mmHg above the baseline.

The minimum, maximum, and end-stimulation SBP changes and their respective occurrence times were summarized in Table 2. Different trends in BP changes, including falling and rising, could be observed successively. Generally, the drop was before the elevation of SBP in type 2 (14.2 ± 3.5 s vs. 23.4 ± 9.5s, $P < 0.001$) and type 3 (17.9 ± 6.3 s vs. 31.1 ± 13.1 s, $P < 0.001$). SBP in 121 sites (46.5%) eventually increased by at least 5 mmHg, compared to baseline. It is worth noting that some (Type 2) actually showed a decrease before the SBP increase. Selective ablation was performed at these sites. 4 (IQR: 4 – 5) sites were ablated at the left renal artery and 4.5 (IQR: 4 – 5) at the right. The increase of SBP during repeated electrical stimulation was significantly blunted, but SBP elevation in type 2 had a similar reduction but with a greater standard deviation (7.4 ± 14.2 mmHg vs. 7.2 ± 9.3 mmHg) as compared with the sites with type 1 (Figure 3). One patient was found to have occlusion of the right superficial femoral artery on postoperative day 2 and received stent implantation. No other adverse events occurred.

Office BP decreased rapidly from 157 ± 24/101 ± 19 mmHg at baseline to 137 ± 16/89 ± 15 mmHg at 2 h postoperatively (SBP: $P<0.001$, Diastolic BP (DBP): $P = 0.013$) and continued to drop within 24 h. The ABP also showed a consistent decrease at 5 – 7 days and 6 – 12 months after RDN (Figure 4A and B). SBP decreased by 10.9 mmHg (95% confidence interval (CI): −6.2 – −15.6 mmHg, $P < 0.001$) and 13.8 mmHg (95% CI, −7.7 – −19.9 mmHg, $P < 0.001$), respectively; DBP decreased by 9.4 mmHg (95% CI, −4.7 – −14.2 mmHg, $P = 0.001$) and 9.6 mmHg (95% CI, −4.0 – −15.2 mmHg, $P = 0.003$), respectively. Daytime ABP also continued to decline, and SBP decreased by 11.9 mmHg (95% CI, −7.3 – −16.6 mmHg, $P < 0.001$) and 14.5 mmHg (95% CI, −7.9 – −21.1 mmHg, $P = 0.009$), respectively. DBP dropped by 9.4 mmHg (95% CI, −4.5 – −14.4 mmHg, $P = 0.001$) and 9.5 mmHg (95% CI, −3.2 – −15.8 mmHg, $P = 0.006$). Nighttime SBP decreased by 10.8 mmHg (95% CI, −3.2 – −18.3 mmHg, $P = 0.009$) and 15.7 mmHg (95% CI, −6.4 – −25 mmHg, $P = 0.003$), respectively. DBP also decreased by 10.9 mmHg (95% CI, −4.5 – −17.2 mmHg, $P = 0.003$) and 12.1 mmHg (95% CI, −5.9 – −18.2 mmHg, $P = 0.001$). Heart rate fell from 77 ± 8 bpm at baseline to 71 ± 5 bpm (−5.3 bpm, 95% CI, −1.3 – −9.2 bpm, $P = 0.01$ for 5 – 7 days) and 72 ± 7 bpm (−4.3 bpm, 95% CI, −0.1 – −8.5 bpm, $P = 0.043$ for 6 – 12 months), respectively. A reduction in antihypertensive medications was observed in six of 14 patients during the follow-up period. Five patients were able to reduce one type of medication, and one patient even reduced four types of antihypertensive drugs. The average number of antihypertensive medications dropped numerically from 2.9 ± 1.3 at baseline to 2.4 ± 1.2 at 6 – 12 months (Table 3).

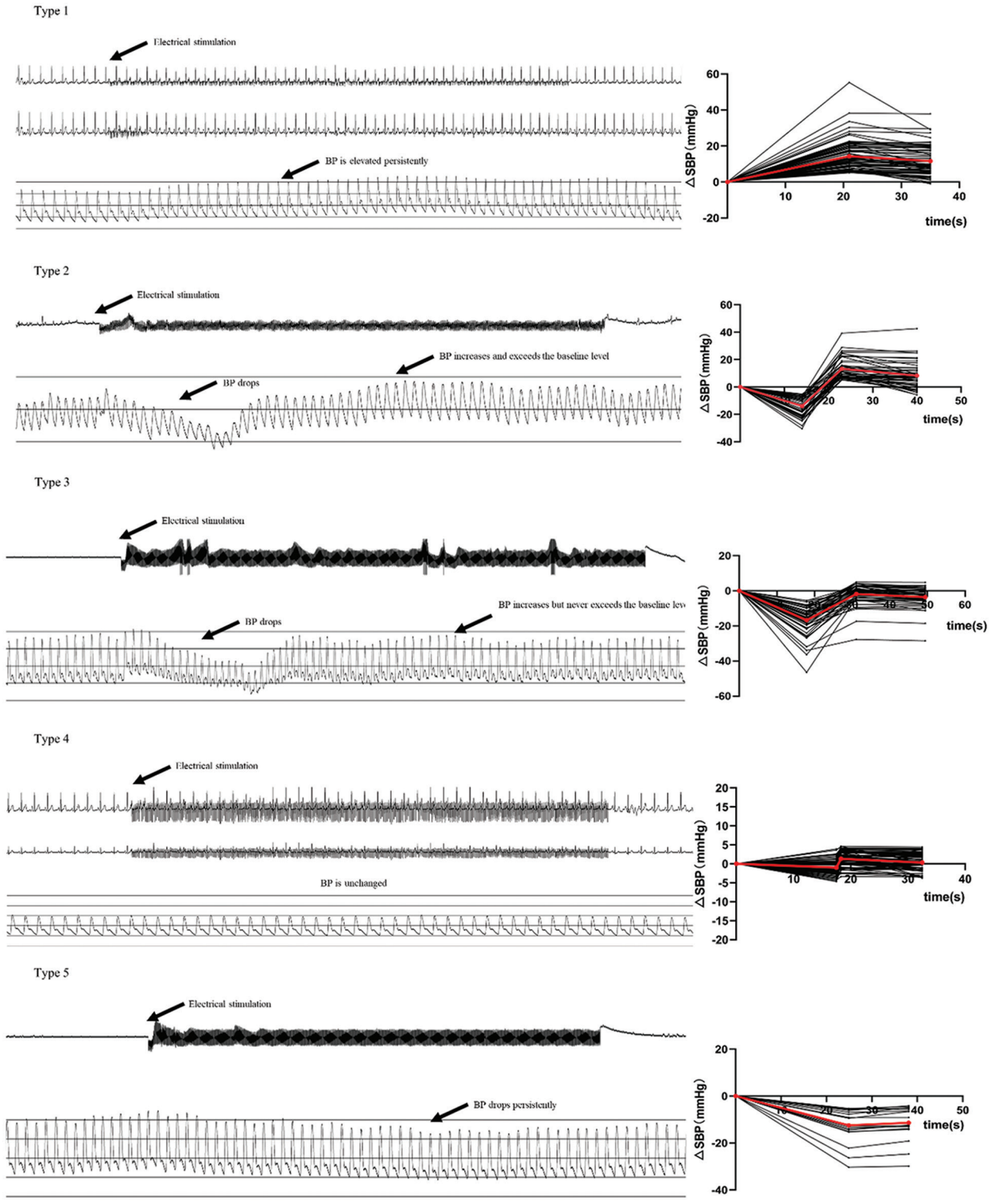

Figure 2. Schematic diagram of five BP response patterns in humans. RNS can contribute to different BP responses, including continuous ascending and finally keeping steady above the baseline (type 1), declining and then rising over the baseline (type 2), declining and then rising but below the baseline (type 3), fluctuating in the vicinity of the baseline (type 4), continuous declining, and finally keeping steady below the baseline (type 5). The left plots show the example of each BP response, line charts on the right represent the cluster of similar SBP change responses. The red lines are the average of the SBP change in each similar BP cluster. △SBP: Change of mean SBP compared to the first 10 cardiac cycles prior to electrical stimulation.

Table 2. Characteristic parameters of five BP response patterns

	No.	SBP change[a], mmHg			Occurrence time[b], (s)		
		Minimum	Maximum	End-stimulation	Minimum	Maximum	End-stimulation
Type 1	74	3.7±5.0	14.3±8.9	11.6±7.9	16.9±7.7	21.2±11.2	27.0±14.5
Type 2	47	−14.0±7.1	13.2±7.6	8.3±9.6	14.2±3.5	23.4±9.5	32.3±9.1
Type 3	50	−16.7±8.4	−1.8±5.9	−3.6±5.6	17.9±6.3	31.1±13.1	40.7±12.7
Type 4	71	−1.0±2.1	1.3±2.0	0.3±2.2	17.5±6.7	18.3±11.9	24.6±11.3
Type 5	18	−12.5±7.4	−5.3±5.7	−11.4±7.3	24.9±11.2	16.0±12.9	30.4±14.2

Notes: Values are mean±SD. [a]Change of mean SBP compared to the first 10 cardiac cycles prior to electrical stimulation. [b]Occurrence time interval compared to the initiation of the electrical stimulation.
Abbreviation: SBP: Systolic blood pressure.

Table 3. Antihypertensive drugs at baseline and follow-ups

	Baseline	5 – 7 days	6 – 12 months
No. of antihypertensive medications	2.9±1.3	3.0±1.3	2.4±1.2
ACE-I/ARB	10	10	7
Calcium channel blockers	11	10	9
Beta adrenoceptor-blocking agents	10	10	11
Diuretic	7	9	6
Alpha adrenoceptor-blocking agents	2	2	0

Notes: Values are mean±SD or *n*.
Abbreviations: ACE-I: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blockers.

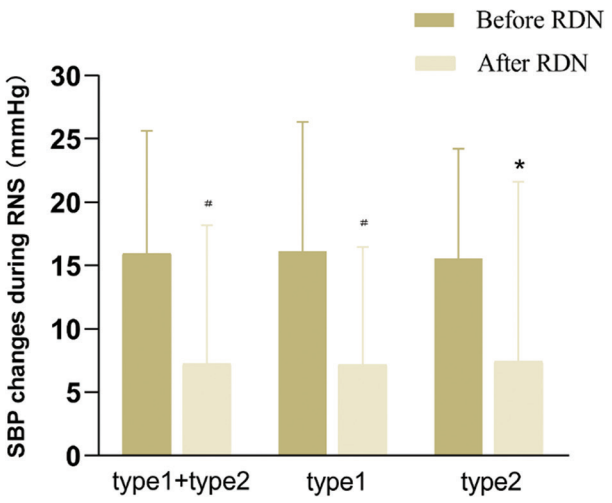

Figure 3. Electrical stimulation-induced changes in SBP before and after RDN. After renal denervation (RDN), systolic blood pressure (SBP) elevations during repeated renal stimulation (RNS) were blunted significantly in sites with type 1 and type 2. *$P < 0.05$ and #$P<0.001$ for comparison between before and after RDN by paired sample t-test.

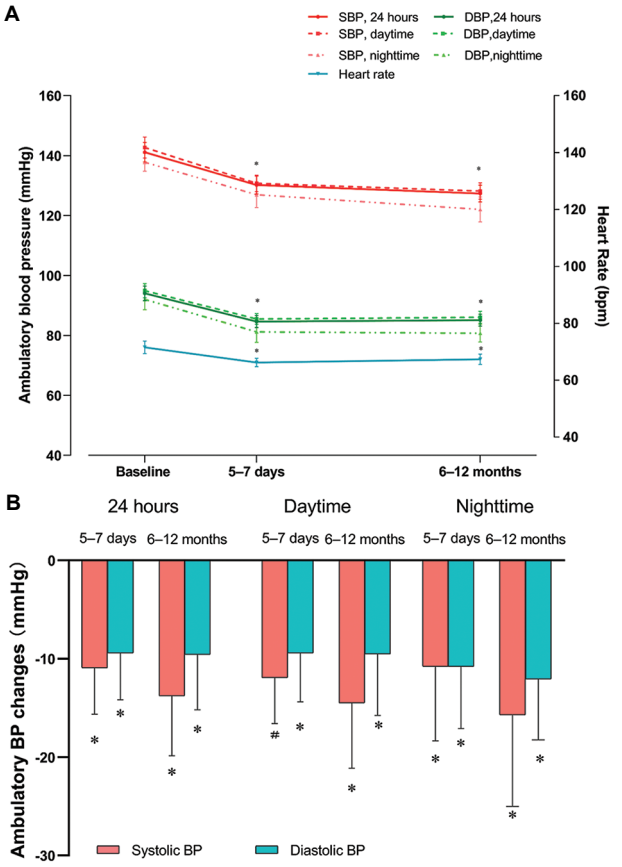

Figure 4. Changes in ambulatory blood pressure and heart rate after selective RDN. (A) Consistent decrease of ambulatory blood pressure (BP) and heart rate at 5 – 7 days and 6 – 12 months after renal denervation (RDN). (B) Mean and standard error of postoperative ambulatory BP drop. *$P < 0.05$ and. #$P < 0.001$ for comparison between baseline and 5 – 7 days and 6 – 12 months by univariate repeated measurement analysis of variance.

4. Discussion

This study summarized several types of rapid BP response patterns caused by electrical stimulation and evaluated the changes in BP after selective RDN in patients with hypertension. We mainly obtained the following results: (i) RNS can evoke five types of rapid BP responses. Biphasic changes (drop before rise) of SBP can be elicited successively at some sites. (ii) ABP and heart

rate decreased after selective ablation guided by these BP patterns.

Renal nerves regulate the arterial BP and functions of the cardiovascular system mainly via two reflexes. Efferent renal nerves play an important role in modulating renal vascular resistance, renin release, and sodium/water reabsorption[21]. Afferent renal nerves were proven to be directly and rapidly involved in regulating systemic sympathetic activity and vascular tension by the cardiovascular regulatory nuclear mass, such as the rostral ventrolateral medulla and paraventricular nucleus of the hypothalamus[22]. In gross anatomy, renal nerves are composed of complicated neural networks along the renal artery[23]; thus, it is not easy to empirically judge the position of nerves. In this study, five BP responses supported diverse renal nerves, including pressor and depressor fibers, co-existing and gather[10]. Therefore, it is necessary to identify the appropriate nerve innervation sites via the autonomic nerve response caused by RNS, which has proven feasible and safe in animal and human studies[24,25].

The intraoperative BP responses for detecting the renal nerves still need a detailed evaluation, although previous studies pointed out that BP response to the RNS rise or drop. Based on the complex anatomy basis that different fibers interweaved and distributed in a network[15,23], renal nerves under stimulation or ablation may have different functional fibers, not just one. Therefore, five types of BP responses, including bidirectional successive changes in this study, were reasonable theoretically and also observed in an animal study by our team[18]. Meanwhile, similar proportions of BP response types were also observed in this study. Unlike collecting all the data on SBP to show the trend of BP fluctuation in the animal study, a simple method using just several specific values to identify the type of BP response is more convenient and practicable in clinical settings. It can assist the interventionalist in quickly judging the pattern of BP response during the procedure.

For the first time, we reported that RNS could evoke biphasic BP changes (type 2 and type 3) that drop almost preceded an increase in patients with hypertension. It may relate to the simultaneous activation of the different nerve fibers. Meanwhile, both our study and previous research found BP decrease could be induced by RNS[12,14,19]. The sites with BP drops indicated that nerves around the renal artery own parasympathetic properties. Recent research has shown anatomical evidence for parasympathetic innervation of the renal vasculature[16]. It is inferable that ablation of these sites with BP drops may result in a BP rise after the RDN procedure. Knowing the sites to avoid ablation is equally important as knowing the sites that need to be ablated. RNS can assist interventionalists in identifying inappropriate sites with dominantly parasympathetic fibers and performing more accurate ablation. Therefore, RNS prior to ablation is advisable and considerable in clinical settings. Additionally, RNS can screen hypertensive with more drop sites, for which RDN may not be suitable, and serve a similar role in the treatment of hypertension, like electrophysiological examination in patients with arrhythmias.

Previous studies have also confirmed that destroying the sites with elevated BP caused by RNS can result in a significant drop in postoperative BP[14,19,26]. Further in this study, BP reduction was observed early and continued to 6 – 12 months postoperatively after ablation in these sites of drop first and then rising (type 2). However, SBP elevation during repeated stimulation after ablation had a similar reduction but a greater standard deviation (7.4 ± 14.2 mmHg vs. 7.2 ± 9.3 mmHg) compared to the sites with type 1 (Figure 3). The destruction of partial "depressor fibers" may play a role in the instability of SBP change. Thus, sites with type 2 should be the inferior candidates for ablation. In addition, an ABP reduction of 13.8/9.6 mmHg in this study with lower baseline BP and fewer ablation sites seems more significant than that of 9.0/6.0 mmHg in the SPYRAL HTN-ON-MED trial[6]. Moreover, another anatomy-based RDN trial, including similar mildly resistant hypertension, showed a smaller decrease (7.0/2.8 mmHg) in ABP during 6 months of follow-up[2]. We observed the rapid ABP drop for 5 – 7 days. It may be associated with the selective and effective destruction of afferent renal nerves. Selecting the proper ablative sites may guarantee the efficacy of RDN, and further research is needed for clarification.

Similar to ABP, the average heart rate was also reduced during the follow-up period. A recent study has also revealed that a higher baseline heart rate (approximately >70 bpm) in patients with hypertension had a significant reduction in heart rate after RDN[27]. Likewise, two studies found that baseline 24-h ambulatory and office heart rates above 70 bpm could predict greater BP reduction at 3 months[28,29]. Thus, in this study, a baseline average heart rate of 77 ± 8 bpm may reflect higher sympathetic drive and be associated with a significant reduction in BP and heart rate after the RDN procedure.

The present study was constrained by some limitations. First, the principle (rationale) of regulating different BP responses to RNS by different nerve fibers (pressors and depressors) around renal arteries in this study needs further histological or anatomical evidence. Second, the effect of ablating the sites with continuous BP drop responses to RNS was not verified due to ethical considerations.

Ablation at these sites may result in a rise in postoperative BP, and this has been partially confirmed in our animal experiments (unpublished data). Third, the results of the present study do not answer the exact benefit of RNS guided by these BP patterns compared to anatomy-based RDN, and additional benefits should be further studied in a well-designed randomized controlled clinical trial.

5. Conclusion

RNS-induced BP changes can be classified into five patterns that provide precise guidance for RDN procedures in humans. Ablation at sites with an elevated BP response during RNS resulted in an obvious BP reduction in ABP.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization: Yuehui Yin
Data curation: Zhenhong Ou, Dan Li, Tianli Xia, Huang Zhou, Xue Kuang, Chunxia Gan
Formal analysis: Zhenhong Ou, Kun Cui, Hao Zhou, Hang Liu, Yunlin Chen
Funding acquisition: Yuhehui Yin
Investigation: Huaan Du, Weijie Chen, Bo Zhang, Wenjiang Chen, Mingyang Xiao, Changzhi Zhang, Jie Yang
Methodology: Yuehui Yin
Resources: Yuehui Yin, Zengzhang Liu
Supervision: Yuhui Yin, Kamsang Woo, Zrenner Bernhard
Visualization: Zhenhong Ou, Yunlin Chen, Hao Zhou, Hang Liu
Writing – original draft: Zhenhong Ou
Writing – review and editing: Yuehui Yin

Ethics approval and consent to participate

All procedures were approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (approval number: 2016-10).

Consent for publication

Written and verbal informed consents for the use of data were obtained from the study subjects before the procedure.

Availability of data

Additional data are available from the corresponding author upon reasonable request.

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ACCSCIENCE PUBLISHING

Brain & Heart

CASE REPORT

Operative treatment for umbilical venous catheter-related *Staphylococcus aureus* infective endocarditis with subsequent septic thrombosis: A case report

Cassandra DeVol[1], Christopher M. McDaniel[2], Nupur Singh[3], and Pilar Anton Martin[4]*

[1]Division of Pediatric Cardiology, University of Tennessee Health Science Center/Le Bonheur Children's Hospital, Memphis, TN, USA

[2]Division of Internal Medicine, Baptist Memorial Hospital-DeSoto, Memphis, TN, USA

[3]Department of Medical Education, College of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

[4]Division of Anesthesia and Critical Care Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Abstract

Thrombosis and infective endocarditis are significant causes of morbidity and mortality in critically ill children, especially with the increasing use of indwelling catheters. In some cases, surgical excision becomes imperative to ensure adequate source control and mitigate the burden of infection. Herein, we present a compelling case involving a term neonate who developed refractory *Staphylococcus aureus* infective endocarditis, followed by septic emboli due to a thrombus associated with a malpositioned indwelling umbilical venous catheter (UVC). Thrombosis and infective endocarditis resolved after surgical resection, a 6-week course of antibiotics, and anticoagulation therapy for 3 months. This case report highlights the risk of thrombosis arising from malpositioned UVCs, the potential complications, and the treatment options.

Keywords: Umbilical venous catheter; Infective endocarditis; Septic embolism; Newborn; Neonate

***Corresponding author:**
Pilar Anton Martin
(pilarantonmartin@gmail.com)

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1. Background

Indwelling catheters remain a risk factor for thrombosis and infections in hospitalized infants[1,2]. Several reports underscore the association between neonatal thrombosis and infective endocarditis (IE), particularly in cases related to umbilical venous catheters (UVCs)[1,2]. The occurrence of UVC-related infections and thromboses stems from a complex interplay of contributing factors. On catheter insertion, the endothelium sustains damage, resulting in the accumulation of fibrin and endothelial cells. This initial damage, coupled with reduced blood flow and subsequent endothelial erosions, further contributes to thrombus formation. These thrombi can serve as a nidus for bacterial superinfection. Furthermore, the inflammation triggered by the primary

infection can activate platelets, fostering conditions favorable for thrombus formation[1-4]. Most of these complications typically resolve with the removal of the catheter, supplemented by anticoagulation and antibiotic therapies[3]. Surgical intervention, on the other hand, remains a rarity[4]. In this case report, we present the management approach employed for a term neonate with an intracardiac thrombus, infective endocarditis, and subsequent septic emboli related to a malpositioned UVC.

2. Case presentation

A male neonate born at full term with a birthweight of 2950 g was transferred to our hospital at 6 days of life (DOL) for the management of UVC-related IE. His birth was uncomplicated, marked by vaginal delivery, with APGAR scores of 8 and 9. However, by DOL 2, he developed hypoglycemia and respiratory distress, prompting his transfer to the neonatal intensive care unit at an outlying facility. A UVC was inserted on DOL 2 and the initial sepsis workup, along with blood cultures, was not concerning for infection. However, on DOL 4, due to feeding intolerance, a repeat sepsis workup was performed, revealing leukopenia, thrombocytopenia, elevated inflammatory markers, and coagulopathy. In response, blood cultures were sent, and a treatment regimen involving ampicillin and gentamicin was initiated. Lumbar puncture was deferred due to coagulopathy. A head ultrasound (HUS) yielded results within normal limits. Chest X-ray revealed the presence of a UVC situated at a high position inside the right atrium (Figure 1), which was not repositioned. On DOL 5, blood culture results indicated the presence of gram-positive cocci, prompting the addition of vancomycin to the treatment regimen. In the setting of the neonate's hemodynamic instability and increased oxygen requirements, an echocardiogram on DOL 6 detected the presence of a mass at the tip of the UVC, crossing the atrial septum into the left atrium (LA). Subsequent findings revealed the development of pulmonary hypertension with supra-systemic pressures (Figure 2). This mass was a source of concern, raising the possibility of a thrombus or vegetation. Notably, the UVC had migrated even further. In response to the evolving clinical situation, the neonate was initiated on non-invasive positive pressure ventilation and subsequently transferred to our hospital on DOL 6.

A new peripherally inserted central catheter (PICC) was placed and the administration of antibiotics was continued. In response to the thrombosis burden, anticoagulation therapy was introduced using unfractionated heparin (UFH), which achieved the partial thromboplastin time (PTT) goal of 60 – 80 s. Initially, the decision was made to refrain from removing or repositioning the UVC. This choice stemmed from concerns regarding the potential

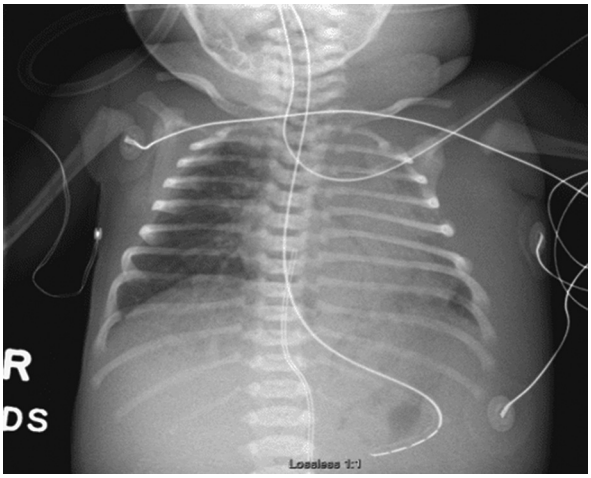

Figure 1. Initial chest X-ray demonstrates the umbilical venous catheter tip terminating above the cavoatrial junction.

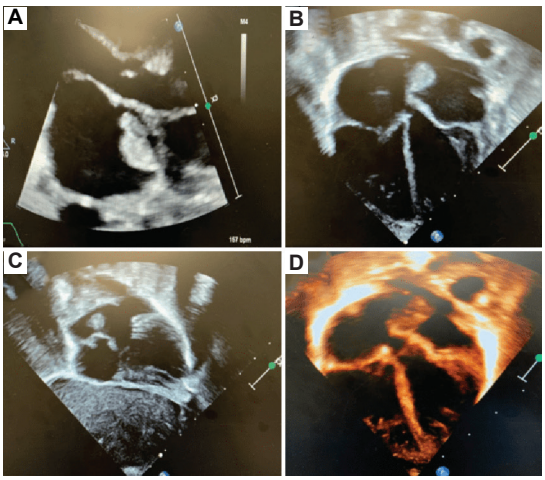

Figure 2. Echocardiogram on days of life 6 shows moderate-to-large sized thrombus/vegetation with several lobes measuring 6 × 9 mm. (A) Parasternal long axis view; (B) apical four-chamber view; (C) five-chamber view; and (D) subcostal view.

risk of thromboembolic complications affecting both pulmonary and systemic circulations, attributed to the location of the thrombus or vegetation. Repeat blood cultures confirmed the presence of methicillin-sensitive *Staphylococcus aureus* (MSSA). A HUS performed on DOL 8 revealed subtle and small left periventricular and deep white matter infarcts. A computed tomography scan of the head conducted on the same day unveiled small hemorrhagic infarcts in the left parietal lobe, indicative of an embolic phenomenon. Consequently, adjustments were made to the PTT goals, with the desired range being reduced to 40 – 60 s. Follow-up HUS on DOL 9 indicated stable findings. An electroencephalogram examination yielded no evidence of seizure activity; however, the administration of levetiracetam was initiated as a prophylaxis measure.

Daily blood cultures consistently yielded positive results for MSSA, despite the administration of an appropriate antibiotic regimen. Repeat echocardiogram showed increased size of thrombus or vegetation (9.7 mm × 4.7 mm) with no valvular involvement. Considering the challenge of achieving effective source control and the concerns regarding potential septic emboli reaching both the brain and lungs in the settings of elevated pulmonary pressures, the decision was made to proceed with surgical intervention.

On DOL 10, the neonate underwent an atrial septectomy, accompanied by the debridement of LA and the right-sided pulmonary veins and an atrial reconstruction using a Gore-Tex patch. This surgical intervention was followed by the removal of the UVC. Postoperatively, the neonate required vasoactive support involving epinephrine and vasopressin for 4 days. Throughout this period, the administration of antibiotics was continued, culminating in the achievement of the first negative blood culture outcome on DOL 13. The neonate was successfully extubated to a high-flow nasal cannula on DOL 14. Commencing on DOL 15, the neonate's medical regimen encompassed aspirin, introduced for patch prophylaxis. A new PICC line was inserted on DOL 18, replacing the old one. Subsequently, on DOL 20, the anticoagulation regimen was transitioned from UFH to therapeutic low-molecular-weight heparin (LMWH), with an anti-factor Xa assay (anti-Xa) goal range of 0.35 – 0.7 U/milliliter.

The ophthalmologic examination yielded no ocular signs secondary to infective endocarditis. Ultrasound evaluations of the abdomen, head, and lower extremities ruled out the presence of possible abscesses. A subsequent echocardiogram demonstrated the absence of residual thrombus within the LA and exhibited improved pulmonary pressures (Figure 3). On DOL 22, brain magnetic resonance imaging demonstrated left parietal lobe hemorrhages, along with parenchymal microhemorrhages in both the supratentorial and infratentorial regions. In accordance with the American Heart Association (AHA) guidelines, the neonate underwent 2 weeks of triple antibiotic therapy (nafcillin, rifampin, and gentamicin) and 4 additional weeks of dual antibiotic therapy with nafcillin and rifampin for endocarditis involving prosthetic material caused by staphylococci. He was discharged home on DOL 56. His discharge included a regimen encompassing aspirin, LMWH, and levetiracetam. On the 3-month follow-up assessment, the neonate had remained clinically stable and been on full feeds with no evidence of intracardiac thrombus. Moreover, his cardiac and neurological function remained commendable.

3. Discussion

The umbilical vein is a common site for neonatal central venous access to administer medications and parenteral nutrition (PN), as well as to obtain blood for laboratory studies[5]. However, the use of UVCs is not without complications. Among these, serious complications include encompass bloodstream infections, thromboembolism, air embolism, arrhythmia, hydrothorax, hemorrhage, malposition, and migration[5]. This case report highlighted the successful surgical management of IE in the setting of a malpositioned UVC that resulted in systemic septic thrombosis.

The predominant UVC-related complications are bloodstream infections, with reported rates ranging from 3% to 36%, depending on the applied diagnostic criteria[5]. Since the neonates with UVCs are not routinely screened for thrombus formation, current rates and clinical significance of UVC-related thrombosis remain obscure. The incidences of UVC thrombosis vary widely, spanning from 3% to 33% in historical series encompassing surviving infants and autopsy data[6,7] and 10 – 12% in contemporary studies using echocardiogram as an imaging modality[8-10]. Clinicians, when feasible, should be aware of the recognized risk factors that predispose to both line thrombosis and infection. The spectrum of these risk factors can be categorized into those related to the catheter itself (duration >6 days, long-term PN, hyperosmolar solutions,

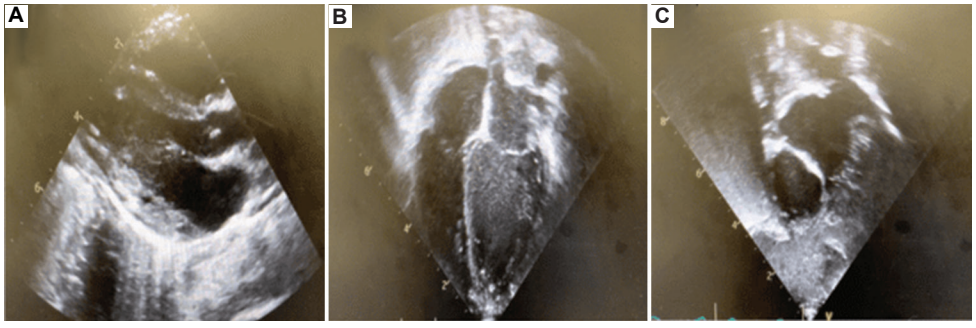

Figure 3. Post-operative echocardiogram demonstrates successful surgical management without evidence of thrombi. (A) Parasternal long-axis view; (B) apical four-chamber view; and (C) subcostal view.

malposition, and blood product usage) and those related to the individual's underlying disease and its treatment (newborns, birthweight <1250 g, hematocrit >55%, small for gestational age, and administration of hyperosmolar medications)[3,8-11]. A systematic review encompassing 89 studies identified low birth weight, prematurity, congenital abnormalities, and extended UVC duration, as well as exposure to hyperosmolar fluids and medications, along with low-lying and malpositioned UVC, as risk factors for UVC-related infections[8].

In this case, thrombosis likely stemmed from the malpositioning of the UVC. Contributing factors to thrombosis development described in this case might include UVC-related infections, endothelial injury, and a heightened state of hypercoagulability. Studies have reported the incidence of intracardiac thrombus formation to be as high as 26% in instances of malpositioned UVCs, in contrast to 3% for well-positioned catheters[2]. This erroneous UVC placement can precipitate nonbacterial thrombotic endocarditis, leading to subsequent embolization and potentially serving as a nidus for bacterial superinfection[12]. It warrants speculation whether a different course might have altered, the outcome had the displaced UVC, which later migrated, been promptly repositioned on DOL 5. With the growing survival rates of critically ill neonates and the increased utilization of central venous catheters, there has been an increase in reported cases of IE within this demographic[13,14]. Anteroposterior chest-abdominal radiograph has emerged as the most commonly used imaging method for ascertaining UVC placement. Assessment methods include counting vertebral bodies or assessing the cardiac silhouette. Optimal UVC positioning is achieved when it aligns with the eighth and ninth thoracic vertebral bodies or corresponds to the cavoatrial junction (based on extrapolating the curve of the right atrial border and its intersection with the IVC medially on the right side of the vertebral bodies)[15]. An alternative approach for identifying the UVC tip position is through a targeted echocardiogram, which has been shown to outperform radiography in detecting malpositioned catheters[16]. To ensure consistent and accurate UVC placement, a potential solution might involve providing clinicians with basic training in targeted echocardiography to accurately determine appropriate UVC positioning.

The effective management of IE involving septic thrombosis related to UVC placement necessitates prompt diagnosis, timely administration of antibiotics and anticoagulants, and continuous surveillance for embolism. While the approach for treating thrombosis associated with catheters through anticoagulation relies on expert-guided recommendations, it is heavily dependent on the specific clinical context, catheter type, and ongoing catheter-related needs[3,17]. Adhering to current anticoagulation recommendations, we employed UFH or LMWH using the above PTT and anti-Xa goals for catheter-associated thrombosis[17]. Certain experts advocate for an assertive stance on thrombus treatment, suggesting the use of tissue plasminogen activator (TPA) when the following criteria are met: A clot size >4 – 5 mm in any dimension, the presence of pedunculation, mobility, a snake-like shape, and symptomatic[18-20]. While infants have been successfully managed using TPA even in the setting of thrombocytopenia[21], our patient was at high risk for hemorrhagic conversion given the presence of the left parietal lobe hemorrhagic infarcts, evoking concern for an embolic event. The lack of thrombus resolution following our chosen anticoagulation strategy was within expectation, particularly considering the thrombus size. However, the use of TPA to dissolve the clot was deemed perilous for our patient.

The 2015 AHA scientific statement outlining the management of IE in childhood recommends that patients with MSSA endocarditis involving a native valve and/or cardiac tissue should be treated with intravenous nafcillin or oxacillin for 4 – 6 weeks[22]. To expedite bacterial elimination, gentamicin is typically introduced for the first 3 – 5 days[22]. For instances where a patient has a penicillin allergy, a first-generation cephalosporin can be used as an alternative, with the optional addition of gentamicin[22]. For patients with methicillin-resistant *Staphylococcus aureus* endocarditis involving a native valve and/or cardiac tissue, the treatment regimen involves vancomycin administration for a minimum of 6 weeks, with or without gentamicin for the first 3 – 5 days of therapy[22]. In scenarios where a patient presents with a prosthetic valve or material involvement, eradication of the infection becomes much more complex and is associated with elevated mortality, prompting the addition of rifampin to the antibiotic regimen and the removal of the infected material[22]. Surgical intervention for IE, particularly in infancy, is associated with high mortality[23,24]. Indications for surgical management of IE include persistent vegetations post-embolization, continued growth or extension despite 4 weeks of treatment, heart failure, or perivalvular extension causing heart block[22]. In our patient's case, concerns about septic emboli affecting the brain and lungs prompted the need for surgical intervention.

4. Conclusion

This patient's case offers a unique and effective treatment approach for a complex case scenario involving intracardiac thrombosis, infective endocarditis, and septic emboli, all in relation to a malpositioned UVC in a newborn. This case

report underscores the necessity of proper UVC placement to avoid risk of thrombus formation. Furthermore, it emphasizes the significance of a strong antibiotic regimen to eliminate the MSSA endocarditis infection following surgical resection, ultimately resulting in a complication-free recovery.

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None.

Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization: Pilar Anton-Martin
Investigation: Cassandra DeVol, Christopher M. McDaniel, Nupur Singh
Supervision: Pilar Anton-Martin
Writing – original draft: Cassandra DeVol, Christopher M. McDaniel, Nupur Singh
Writing – review & editing: Pilar Anton-Martin

Ethics approval and consent to participate

Informed consent was taken verbally from the parents.

Consent for publication

The patient's parents consented to the publication.

Availability of data

Data are fully available under explicit request to the corresponding author.

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ACCSCIENCE PUBLISHING

Brain & Heart

CASE REPORT

Pedunculated left endoventricular thrombosis complicated by cerebral stroke in patient with suspected peripartum cardiomyopathy: A case report

Kristian Galanti[1†], Roberta Magnano[2†], Laura Pezzi[2†], Mario Di Marino[1†], Alberto D'Alleva[2], Daniele Forlani[2], Piergiusto Vitulli[2], Vincenzo Di Egidio[3], Gabriele Di Giammarco[4], Leonardo Paloscia[2], Sabina Gallina[1], and Massimo Di Marco[2†*]

[1]Department of Neuroscience, Imaging and Clinical Sciences, G. D'Annunzio University of Chieti-Pescara, 66100, Chieti, Italy

[2]Department of Cardiology and ICCU, Santo Spirito Hospital, Pescara, 65124, Italy

[3]Department of Radiology, Santo Spirito Hospital, Pescara, 65124, Italy

[4]Department of Cardiac Surgery, G. D'Annunzio University of Chieti-Pescara, Chieti, 66100, Italy

Abstract

Peripartum cardiomyopathy (PPMC) is an infrequent form of cardiomyopathy, whose main presentation is characterized by systolic dysfunction that commonly emerges in the early postpartum period. Acute heart failure symptoms such as congestion and dyspnea are common manifestations of PPMC. Here, we present a case of a 32-year-old female who, after hospitalization, manifested dyspnea and thoracic pain linked to the findings a left endoventricular thrombus. After the admission to the intensive cardiovascular care unit, heart failure and anticoagulant therapies as well as non-steroidal anti-inflammatory drugs were administered, leading to initial improvement of the left ventricular global function. Five days after the treatment, the patient experienced aphasia and right hemiplegia. The cerebral angiography documented an M1 segment occlusion. After treating the occlusion with stent retriever thrombectomy, the symptoms regressed and she attained full recovery. Therefore, surgical thrombectomy should be prioritized as the treatment approach to removing the pedunculated left ventricular thrombus, considering the apical morphology of the pedunculated left ventricular thrombus and if the anticoagulant therapy gives rise to side effects.

Keywords: Peripartum cardiomyopathy; Apical thrombus; Stroke; Stent retriever thrombectomy; Surgical thrombectomy

[†]These authors contributed equally to this work.

***Corresponding author:**
Massimo Di Marco
(dimarcom@hotmail.com)

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1. Background

Peripartum cardiomyopathy (PPMC) is a rare, idiopathic cardiomyopathy, defined by global systolic dysfunction that emerges in late pregnancy period or more often in the early postpartum period[1]. It is difficult to diagnose such a condition in patients with previous established cardiomyopathy and for this reason in 2010, the European

Society of Cardiology defined PPCM as "heart failure that occurs toward the end of pregnancy or in the months following delivery, where no other cause of heart failure is found"[2]. The prevalence of PPMC is on the rise due to two main reasons: (i) The accumulation of more advanced knowledge about this pathological condition, which allows better understanding and faster identification; and (ii) the growing influence or prevalence of the risk factors for PPCM, such as advanced maternal age, preeclampsia, and concomitant cardiovascular risk factors[3]. Although the physiopathology of PPMC is clearly known, the precise underlying mechanisms have yet to be elucidated. It is possible that the etiology of PPMC is multifactorial. One of the main hypotheses links viral myocarditis to PPCM, in which the inflammatory response might trigger the biochemical pathway that leads to the occurrence of PPMC[4]. However, based on our current understanding of the pathological condition, the "two-hit" hypothesis, which associates vascular insult caused by anti-vascular factors or hormones produced during late pregnancy and early postpartum period to the development cardiomyopathy in women with an underlying predisposition, is viewed as a more justified theory explaining the development of PPCM[1]. As for clinical findings, PPCM typically presents with heart failure symptoms, such as shortness of breath on exertion, paroxysmal nocturnal dyspnea, and lower limb edema[5]. In rare cases, the presentation may be characterized by cardiogenic shock, requiring inotropic or mechanical circulatory support, or by arrhythmias and thromboembolic events. Echocardiography should always be performed when PPCM is suspected, and the main findings are left ventricular systolic dysfunction with ejection fraction (EF) <45%, and left and right ventricular dilation with functional mitral and/or tricuspid regurgitation[6]. Since the occurrence of intracardiac thrombus is common, the left ventricular apex should always be examined for signs of thrombosis[7]. Considering the exposure to radiation during computed tomography (CT) scanning and the need to avoid gadolinium exposure during pregnancy, echocardiography is considered the most appropriate imaging method for detecting PPCM. Endomyocardial biopsy is required when another pathological condition, such as giant cell myocarditis, is suspected, since it needs to be managed with a different therapy. In the process of diagnosing PPCM, any possible pre-existing heart muscle diseases or valvular pathologies must be excluded to avoid misdiagnosis[6].

2. Case presentation

A 32-year-old female was transferred from the Gynecology and Obstetrics Department 2 days after undergoing an eutocic delivery, as she presented with shivering fever, gagging, and segmentary alterations of systolic heart contraction based on an echocardiographic evaluation. A series of laboratory tests, showing high levels of liver enzymes and high-sensitivity cardiac troponin I (hscTnI) as well as increased flogosis indices, indicated that the patient suffered from neutrophil leukocytosis. The electrocardiogram (ECG) showed sinus tachycardia with diffused and a specific ventricular repolarization phase alterations. The echocardiogram documented moderate left ventricular dilation (LVEDDi 3.6 cm/m^2; LVEDVi 72 mL/m^2) with severely reduced global systolic function (EF 35 – 38%) related to apical, interventricular septum, and anterior wall akinesis. Furthermore, there was minimal circumferential pericardial effusion.

Antibiotic (metronidazole 500 mg thrice a day + piperacillin 13.5 g/day) and non-steroidal anti-inflammatory drug (NSAID; ibuprofen 600 mg twice a day) were administered to the patient when she was feverish, after laboratory test results were obtained. Flogosis subsided after the treatment. To address the cardiological issues, treatments including anticoagulant (enoxaparin sodium 6000 UI twice a day), loop diuretics (60 mg/day), ramipril (5 mg/day), canrenone (50 mg/day), and bisoprolol (2.5 mg/day) were administered.

On the 5th day of hospitalization, the patient experienced sudden aphasia and right hemiplegia, and a modified ECG showed giant inverted T waves in the precordial leads (Figure 1). At the same time, the echocardiogram documented the presence of a pedunculated left ventricular thrombus (1.5 × 4.5 cm, Figure 2). For this reason, we performed CT angiography of the patient's cerebral arteries, which showed sphenoidal proximal left tract (M1 segment) of the middle cerebral artery and carotid siphon occlusion. Within 6 h of symptom onset, stent retriever thrombectomy was performed. Subsequent optimal angiographic result is shown in Figure 3. Two hours later, the patient manifested complete rehabilitation with clinical regression of previous neurological signs.

Due to the diagnosis with pedunculated left endoventricular thrombus having a small implantation base, which can heighten the risk of new embolization, the patient was not prescribed another session of anticoagulant therapy as it could further increase the risk of microembolization. Instead, surgical cardiac thrombectomy was performed on the patient. At the time of pericardial exposure, the heart appeared small and noticeably hyperkinetic. During the extracorporeal circulation and after having localized the thrombus through high-resolution epicardial echocardiography, a small apical incision was performed to remove the thrombotic mass, which appeared to possess a pedunculated root

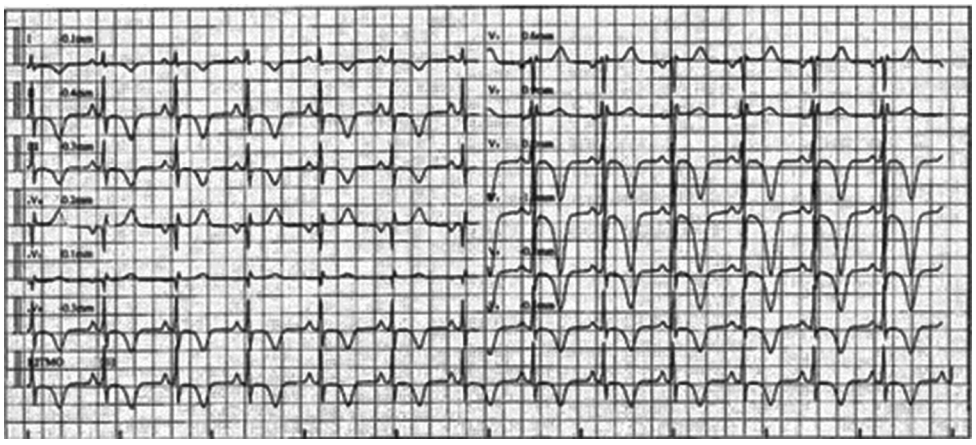

Figure 1. Electrocardiogram showing giant inverted T waves.

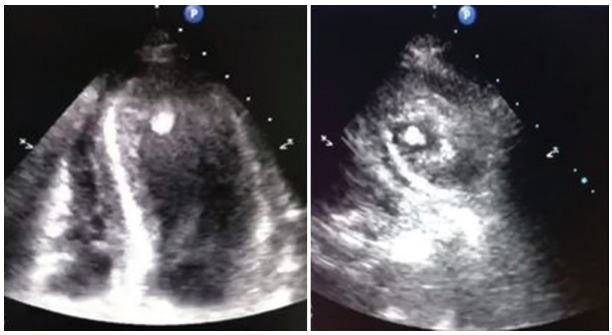

Figure 2. Transthoracic echocardiogram showing apical pedunculated endoventricular thrombus.

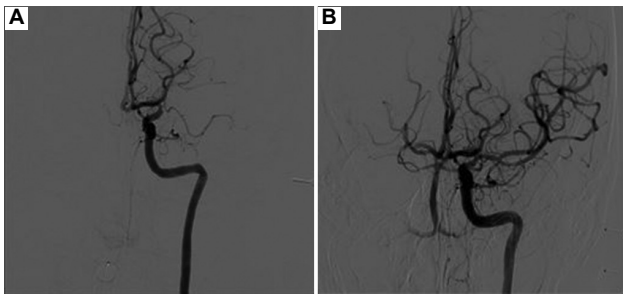

Figure 3. Cerebral computed tomography angiography. (A) Before procedure; (B) after stent retriever thrombectomy.

clinging to the apical trabeculae. The small incision (3 cm) avoided the removal of an excessive healthy heart muscle during ventriculostomy. Following aortic unclamping, the cardiac activity was instantly restored to normal level, with good hemodynamic parameters that allowed a sudden interruption of extracorporeal circulation. An intraoperative myocardial biopsy was performed, which did not reveal histopathological findings attributable to myocarditis or other pathologies. The intraoperative transesophageal echocardiography showed the absence of residual thrombosis. After 9 days of hospitalization, without any perioperative complications, the patient was discharged and required to return for clinical and imaging follow-up. Cardiac magnetic resonance imaging, which was performed 1 month after surgery, revealed circumscribed apical akinesia, efficient global systolic function (EF 60%), and late gadolinium enhancement area, which were signs of the post-surgical scar tissue formation.

3. Discussion

PPCM is a diagnosis of exclusion, and the possibility of myocarditis must be considered. In this case, the patient developed fever and manifested increased levels of inflammatory markers after childbirth, both of which were resolved promptly after the antibiotic therapy was initiated; therefore, a diagnosis associated with viral infection was ruled out. The patient was considered having PPCM since hypertrophy of the cardiac tissue occurred approximately 2 days after child delivery, falling within the time frame where PPCM most commonly arises. The definitive diagnosis was confirmed with myocardial biopsy, which also did not reveal histopathological findings indicative of myocarditis. PPCM is a growing entity, defined as a heart failure-related cardiomyopathy that occurs classically during the last period of pregnancy or in the first few weeks after child delivery. During the diagnosis process, it is crucial to exclude underlying heart muscle diseases or structural pathologies since pregnancy can bring to light some conditions that may resemble heart failure[2].

Several notable risk factors for PPCM are black ethnicity, pregnancy at advanced maternal age, pre-eclampsia and eclampsia. Black women have an increased risk for PPCM, accounting for almost half of the cases, and the incidence of PPCM is three to 4 times higher in black than in white women[8,9]. Furthermore, maternal age over 30 years old is considered an independent risk factor for PPCM, with an adjusted odds ratio of 1.8, compared with women who

are younger[10]. Preeclampsia and eclampsia are linked to PPCM and may share common pathophysiologic pathways: in a 2013 meta-analysis of 22 studies, preeclampsia was found in 22% of women with PPCM, which was more than 4 times the estimated global prevalence[11].

Pregnant women are often in a hypercoagulative state, which subjects them to increased levels of coagulation factors VII, VIII, X, fibrinogen, and von Willeberand factor, together with decreased protein C and S activity and fibrinolysis. These changes usually normalize within 6 – 8 weeks after child delivery[12,13]. Thromboembolism is the most common severe complication of PPMC, affecting 6.6% of women in United States[3] and almost 6.8% worldwide, as reported by the EUR Observational Research Program[13]. Aligned with the classical Virchow' striad, mechanisms leading to thrombosis in cardiac chambers are related to cardiac dilation and global systolic function depression, which lead to blood stasis and endothelial injury[14]. Although heart failure medications are compatible with breastfeeding[15], there are still no published data to guide the planning of therapeutic and prophylactic anticoagulant treatments after delivery. In addition to the conventional heart failure medications, bromocriptine has been shown to improve heart function recovery[16]. In the current case, the patient who wished to continue breastfeeding declined taking bromocriptine, because it could reduce prolactin production. Considering the increased incidence of the left ventricular thrombi and systemic hypercoagulative state during pregnancy and early postpartum, Ruys *et al.* proposed that anti-coagulant treatments be prescribed for prospective mothers with severely decreased left ventricular EF during late pregnancy or during 6 – 8 weeks postpartum[17]. Warfarin should be avoided during pregnancy since it can cross the placenta and its usage is limited to patients with mechanical heart valves. Low-molecular-weight heparin (LMWH) can be used during pregnancy since it does not cross the placenta. Both warfarin and LMWH do not affect lactation and are safe to use after child delivery. Direct oral anticoagulants are generally avoided because their impacts on pregnancy and lactation have never been studied[18]. Different surgical thrombectomy techniques have been described in the literature, such as techniques coupled with transmitral or apical access and robotic- and/or video-assisted surgery. Nevertheless, the clinical management of patients with PPCM complicated by endoventricular thrombus remains a challenge due to a lack of evidence for informing therapeutic decision-making[19-21].

4. Conclusion

The efficacy of the clinical treatment of pedunculated left endoventricular thrombus should be maximized with the combined expertise of a multidisciplinary team consisting of cardiologists, neuroradiplogists, and cardiac surgeons. While anticoagulant therapy has shown promise in the prevention of endoventricular thrombosis, surgical thrombectomy should be preferred over anticoagulant therapy in the treatment of pedunculated left ventricular thrombus, if the thrombus possess an apical morphology and the anticoagulant therapy gives rise to side effects. Nevertheless, more studies should be conducted to explore the proper clinical management of patients with PPCM.

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Conflict of interest

The authors declare that they have no competing interest.

Author contributions

Conceptualization: Kristian Galanti, Mario Di Marino, Roberta Magnano, Laura Pezzi

Investigation: Kristian Galanti, Mario Di Marino, Roberta Magnano, Laura Pezzi

Methodology: Kristian Galanti, Alberto D'Alleva, Daniele Forlani, Piergiusto Vitulli

Formal analysis: Kristian Galanti, Mario Di Marino, Alberto D'Alleva, Daniele Forlani, Piergiusto Vitulli, Vincenzo Di Egidio, Gabriele Di Giammarco, Leonardo Paloscia, Massimo Di Marco

Writing – original draft: Kristian Galanti, Mario Di Marino, Roberta Magnano, Laura Pezzi

Writing – review & editing: Alberto D'Alleva, Daniele Forlani, Piergiusto Vitulli, Vincenzo Di Egidio, Gabriele Di Giammarco, Leonardo Paloscia, Sabina Gallina, Massimo Di Marco

Ethics approval and consent to participate

Not applicable.

Consent for publication

The patient has given verbal consent for the use of her medical data.

Availability of data

Not applicable.

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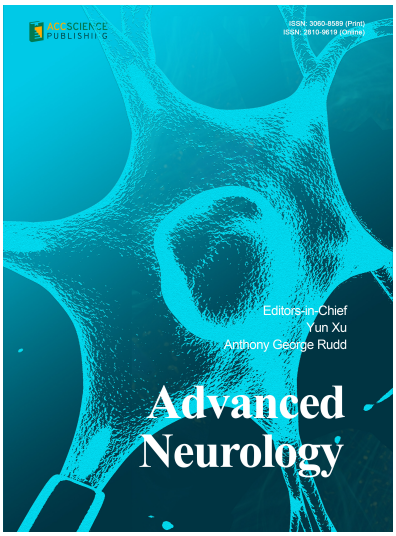

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