

Crochetage in Two or More Inferior Leads Is Associated With Stroke-Associated Patent Foramen Ovale

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Abstract

Background

The crochetae sign has been associated with patent foramen ovale (PFO), but its relationship with stroke-associated PFO remains unclear. We investigated whether this association persisted after accounting for established echocardiographic risk features and whether multi-lead crochetae showed a stronger association than crochetae confined to a single inferior lead.

Methods

This retrospective multicenter study included 937 patients with PFO from four tertiary centers: 511 with cryptogenic ischemic stroke or transient ischemic attack and 426 controls without a history of cerebrovascular events. Standard 12-lead electrocardiograms were independently reviewed by two blinded electrophysiologists. Crochetae was categorized as single-lead when confined to one inferior lead and as multi-lead when present in two or more inferior leads, with the categories defined as mutually exclusive. Multivariable logistic regression models were adjusted for clinical characteristics and high-risk PFO anatomy.

Results

Single-lead crochetae did not differ between stroke-associated and non-stroke-associated PFO and was not significant in multivariable analysis. In contrast, crochetae involving two or more inferior leads remained independently associated with stroke-associated PFO after multivariable adjustment (OR 2.081, 95% CI 1.283-3.376; $P = 0.003$). High-risk PFO anatomy was the strongest predictor (OR 6.482, 95% CI 4.796-8.762; $P < 0.001$); older age and hypertension were also independent predictors. Multi-lead crochetae was strongly associated with atrial septal aneurysm or interatrial septal hypermobility.

Conclusions

The association between crochetae and stroke-associated PFO appears to depend on the number of involved inferior leads. Crochetae involving two or more inferior leads was independently associated with stroke-associated PFO, whereas single-lead crochetae was not.

HIGHLIGHTS

- The clinical relevance of crochetae appears to vary according to the number of inferior leads involved.
- Crochetae involving two or more inferior leads, but not a single lead, was independently associated with stroke-associated PFO.

- Multi-lead crochitage was associated with atrial septal aneurysm and septal hypermobility.
- Multi-lead crochitage may complement echocardiographic assessment in identifying PFOs associated with stroke.

INTRODUCTION

Patent foramen ovale (PFO) is a common congenital remnant of fetal circulation that persists in approximately 25% of the adult population (1). Although typically discovered incidentally, PFO has been identified in nearly half of patients with cryptogenic ischemic stroke and is considered an important potential mechanism for paradoxical embolism (2). However, the clinical challenge lies in the fact that PFO is highly prevalent in the general population, yet its presence alone does not establish a causal relationship with stroke. This creates a significant diagnostic dilemma: distinguishing between an incidental PFO and one that is truly responsible for a patient's stroke remains one of the most difficult questions in clinical practice.

To address this challenge, transesophageal echocardiography (TEE) has become the reference imaging modality for PFO evaluation, allowing detailed assessment of septal anatomy and right-to-left shunting (RLS) (3). Over the years, several anatomical characteristics have been identified as markers of higher stroke risk, including atrial septal aneurysm (ASA), hypermobile septum, increased PFO width, and large RLS. These features are widely accepted as indicators of high-risk PFO (4, 5). Yet anatomical assessment alone does not fully explain why only a subset of PFO patients develop stroke, highlighting the need for additional markers that might improve our ability to identify those truly at risk.

Crochetage sign -an electrocardiographic finding characterized by a notch on the ascending limb or peak of the R wave in the inferior leads- has been described in patients with atrial septal defects (ASD) and, more recently, in patients with PFO (6). Although its electrocardiographic basis remains uncertain, current evidence suggests that crochetage sign may reflect subtle alterations in ventricular depolarization related to the anatomical configuration of the interatrial septum or functional hemodynamic changes (6, 7). More recently, Kalkan et al. demonstrated that crochetage sign was independently associated with high-risk PFO anatomy, further supporting the close relationship between this ECG finding and PFO characteristics [8]. However, it remains unclear whether crochetage involving multiple inferior leads is more strongly associated with stroke-associated PFO than crochetage confined to a single inferior lead.

Furthermore, previous studies evaluating the association between the crochetage sign and PFO-related cryptogenic stroke have reported conflicting results (9, 10). Ay et al. observed a higher prevalence of the crochetage sign among patients with cryptogenic stroke and PFO, whereas Belvís et al. failed to confirm this association. More importantly, whether the crochetage sign remains independently associated with stroke-associated PFO after accounting for established echocardiographic high-risk features has not been adequately investigated. We therefore aimed to investigate whether the crochetage sign is

independently associated with cryptogenic ischemic stroke in patients with PFO and whether its presence in multiple inferior leads shows a stronger association than a single-lead finding.

METHODOLOGY

Study Population and Patient Selection

This retrospective multicenter study was institutionally approved by all four participating centers and approved by the Clinical Research Ethics Committee of Göztepe Prof. Dr. Süleyman Yalçın City Hospital (decision no. 2026/0391). The requirement for informed consent was waived due to the retrospective study design.

Consecutive patients aged 18–65 years who presented with acute ischemic stroke or transient ischemic attack (TIA) between January 2019 and June 2025 were identified through retrospective review of institutional databases. Cerebrovascular events were classified according to the temporal course of neurological symptoms. TIA was defined as complete resolution of deficits within 24 hours, whereas acute ischemic stroke was characterized by persistent deficits beyond this period (11).

All participants underwent neuroimaging with brain computed tomography (CT) or magnetic resonance imaging (MRI) and received comprehensive diagnostic investigations to establish the cause of their cerebrovascular event, which included vascular imaging and transesophageal echocardiography (TEE).

We categorized stroke etiology using the TOAST classification system (11). We operationally defined cryptogenic stroke as acute ischemic stroke or TIA occurring without an identifiable cause after systematic exclusion of large-artery atherosclerotic disease (defined as > 50% arterial stenosis), cardioembolic mechanisms (including atrial fibrillation, valvular disease, and left ventricular thrombus), and small-vessel ischemic disease (characterized by lacunar infarction patterns). Across all participating centers, patients with cryptogenic cerebrovascular events underwent cardiological evaluation, and only those with PFO confirmed by TEE and complete clinical and electrocardiographic data were included.

Exclusion criteria were: ischemic stroke of determined etiology, coronary artery disease, heart failure, moderate-to-severe valvular disease, inadequate echocardiographic image quality, pulmonary hypertension, atrial fibrillation, or incomplete medical records. For comparison, we included cardiology outpatients with no history of ischemic stroke or TIA who underwent contrast-enhanced TEE during the same study period after TTE showed RLS or interatrial septal abnormalities raising suspicion of PFO. Only patients with TEE-confirmed PFO who otherwise fulfilled the same eligibility criteria as the stroke cohort were included. Baseline demographic and clinical characteristics, including age, sex, hypertension (HT), diabetes mellitus (DM), and hyperlipidemia (HL), were collected from the electronic medical records of the participating centers.

Echocardiographic Assessment

All participants initially underwent transthoracic echocardiography (TTE) to assess cardiac structure and ventricular function, and to identify and exclude alternative cardiac abnormalities that might serve as sources of thromboembolism. We subsequently performed contrast-enhanced TTE using agitated saline to screen for evidence of RLS. Participants who demonstrated RLS on this initial screening then underwent contrast-enhanced TEE to definitively establish the diagnosis of PFO and to obtain detailed characterization of its morphological properties. All echocardiographic procedures were conducted by experienced cardiologists who adhered to a standardized examination protocol, with agitated saline contrast administered during both resting conditions and performance of the Valsalva maneuver.

During TEE, we systematically assessed several key parameters: the maximum degree of PFO separation, the presence or absence of ASA, the degree of interatrial septal mobility, and the magnitude of RLS. We quantified shunt severity by determining the maximum number of microbubbles that appeared within the left atrium during the three cardiac cycles immediately following complete opacification of the right atrium following contrast injection. We characterized ASA as interatrial septal bulging with a septal base exceeding 15 mm and septal excursion of 10 mm or greater into either atrial chamber, whereas we defined hypermobile interatrial septum as excessive septal motion that did not meet the specific morphological criteria established for ASA (12, 13).

Based on evidence from randomized trials and the European position paper on the management of patients with PFO, high-risk PFO was defined by the presence of at least one of the following features: (1) ASA or hypermobile interatrial septum, (2) maximum PFO separation ≥ 3 mm, or (3) a large RLS, defined as > 20 microbubbles during contrast-enhanced TEE (14, 15, 16, 17). Other anatomical features, including a prominent Eustachian valve, Chiari network, and a long PFO tunnel, were not included because their association with cryptogenic stroke has been reported predominantly in retrospective studies and remains less consistently established (18, 19).

Electrocardiographic Assessment

Standard 12-lead electrocardiograms recorded at the time of diagnosis were retrieved from the digital ECG archives of the four participating centers. All recordings were acquired using standardized acquisition parameters (paper speed 25 mm/s, gain 10 mm/mV, filter bandwidth 0.5–150 Hz). Electrocardiographic analysis was performed centrally using digitally archived ECGs from all participating centers. Two independent electrophysiologists, blinded to the patients' clinical characteristics, echocardiographic findings, and cerebrovascular event status, reviewed all ECGs independently. In cases of disagreement, the final classification was established by consensus. ECGs with insufficient quality for reliable assessment of crochetae sign were excluded from the analysis.

Crochetage sign was defined as a distinct notch appearing on the ascending portion or at the apex of the R wave in the inferior limb leads (II, III, and aVF), producing a characteristic M-shaped or bifid R-wave morphology (6). To be considered present, the notch had to be consistently observed in all QRS

complexes within the same lead (Fig. 1). Right bundle branch block (RBBB) was assessed according to standard electrocardiographic criteria.

The crochitage sign was assessed separately in leads II, III, and aVF. Patients were classified into three mutually exclusive categories: no crochitage, single-lead crochitage (confined to one inferior lead), and multi-lead crochitage (present in two or more inferior leads). Single- and multi-lead crochitage were subsequently evaluated separately in the statistical analyses.

Blood samples were obtained at the time of hospital admission and analyzed at the clinical laboratories of each participating center using their standard institutional protocols. Laboratory analyses included hematological parameters (hemoglobin), biochemical markers (blood urea nitrogen, creatinine), lipid profile (total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides), and glycated hemoglobin (HbA1c).

The RoPE (Risk of Paradoxical Embolism) score was calculated patients with stroke-associated PFO. Because the RoPE score was developed for patients with cryptogenic stroke and includes cortical infarction as one of its components, it was not calculated for patients in the non-stroke PFO control group (20).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean $\pm$ standard deviation (SD) or median (interquartile range [IQR]), as appropriate, whereas categorical variables are presented as frequencies and percentages. Comparisons between patients with stroke-associated PFO and non-stroke PFO (control group) were performed using the independent-samples Student's t test or the Mann–Whitney u test, as appropriate, for continuous variables and the Pearson chi-square test or Fisher's exact test, as appropriate, for categorical variables. Missing data were not imputed, and analyses were performed using available observations for each variable; percentages were calculated using the number of patients with available data as the denominator. Multivariable binary logistic regression analysis was performed to identify factors independently associated with stroke-associated PFO. Variables were selected based on clinical relevance. A single multivariable logistic regression model included two mutually exclusive indicator variables according to the number of inferior leads exhibiting the crochitage sign: single-lead crochitage, defined as involvement of only one inferior lead, and multi-lead crochitage, defined as involvement of two or three inferior leads. Both variables were entered simultaneously, with absence of crochitage serving as the reference category. The model was adjusted for age, diabetes mellitus, hypertension, and high-risk PFO anatomy. To assess the robustness of the primary findings, a sensitivity analysis was performed after excluding patients with indeterminate high-risk PFO status, defined as those with missing tunnel width measurements in the absence of ASA or interatrial septal hypermobility and significant RLS (> 20 bubbles). The multivariable logistic regression analysis was then repeated using the same covariates as in the primary model. Regression results are presented as odds

ratios (ORs) with 95% confidence intervals (CIs). Associations between the number of inferior leads exhibiting the crocheta sign and individual high-risk PFO characteristics, including ASA or interatrial septal hypermobility, bubble count > 20, and tunnel width $\geq$ 3 mm, were evaluated using the Pearson chi-square test. A two-sided p value < 0.05 was considered statistically significant.

RESULTS

Study Population and Baseline Characteristics

Our study included 937 patients with confirmed PFO recruited from four medical centers. We stratified these participants into two distinct cohorts: 511 individuals who had experienced cryptogenic cerebrovascular events (stroke-associated PFO group) and 426 individuals with PFO but without any history of cerebrovascular disease (control group). Within the stroke-associated PFO cohort, 68 patients (13.3%) had experienced TIA, while 443 patients (86.7%) had sustained acute ischemic stroke. Detailed baseline clinical and laboratory characteristics of the entire study population are presented in Table 1.

Table 1
Baseline characteristics according to stroke status

Variable	Overall (n = 937)	Non-stroke PFO (n = 426)	Stroke-associated PFO (n = 511)	P value
Age (years)	43.10 ± 10.42	41.37 ± 10.84	44.54 ± 9.84	< 0.001*
Female sex (n,%)	437 (46.6)	185 (43.4)	252 (49.3)	0.072
Migraine (n,%)	20 (2.1)	6 (1.4)	14 (2.7)	0.160
Diabetes mellitus (n,%)	85 (9.1)	25 (5.9)	60 (11.7)	0.002*
Hypertension (n,%)	162 (17.3)	51 (12.0)	111 (21.7)	< 0.001*
Hyperlipidemia (n,%)	202 (21.5)	90 (21.1)	112 (21.9)	0.769
Smoking (n,%)	185 (19.7)	82 (19.2)	103 (20.2)	0.728
RoPE score	NA	NA	6.02 ± 1.31	-
RoPE ≥ 7 (n,%)	NA	NA	245 (47.9)	-
BUN (mg/dL)	29.37 ± 18.90	29.63 ± 14.63	29.16 ± 21.85	0.702
Creatinine (mg/dL)	0.78 (0.24)	0.77 (0.22)	0.79 (0.25)	0.103
Triglycerides (mg/dL)	135.79 ± 77.19	134.83 ± 82.40	136.61 ± 72.56	0.748
Total cholesterol (mg/dL)	184.31 ± 32.03	183.91 ± 36.34	184.65 ± 27.88	0.750
HDL cholesterol (mg/dL)	44.15 ± 7.44	44.52 ± 6.97	43.84 ± 7.82	0.191
LDL cholesterol (mg/dL)	117.53 ± 36.86	116.29 ± 38.02	118.58 ± 35.86	0.384
HbA1c (%)	5.71 ± 1.02	5.58 ± 0.86	5.85 ± 1.15	0.001*
Data are presented as mean ± SD, median (IQR), or n (%), as appropriate. Percentages were calculated using the available number of observations for each variable because of missing data.				
HDL: high-density lipoprotein, HbA1c: glycated hemoglobin, LDL: low-density lipoprotein, NA: not applicable, PFO: patent foramen ovale.				

Patients in the stroke-associated PFO group were older than those in the control group (44.54 ± 9.84 vs. 41.37 ± 10.84 years, $p < 0.001$). The proportion of female participants was comparable between groups, representing 49.3% in the stroke-associated PFO group and 43.4% in the control group.

Regarding traditional cardiovascular risk factors, HL and active smoking showed no significant differences between the two groups. However, DM and HT were more prevalent in the stroke-associated

PFO group compared to controls. The prevalence of migraine was similar across both groups and did not differ significantly.

Laboratory parameters including hemoglobin, blood urea nitrogen, creatinine, and lipid profile (total cholesterol, LDL, HDL, triglycerides) were comparable between the two groups. In contrast, HbA1c levels were significantly elevated in the stroke-associated PFO group compared to controls.

Regarding pharmacological management, we noted that angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) were utilized in 19.1% of stroke-associated PFO patients compared to 10.3% of controls, while statin therapy showed comparable utilization rates (11.9% versus 11.0%). Among stroke-associated PFO patients, antithrombotic treatment consisted of monotherapy with single antiplatelet agents (aspirin or clopidogrel) in 49.7%, dual antiplatelet therapy in 24.2%, and anticoagulation therapy (vitamin K antagonists or direct oral anticoagulants) in 7.4%. In contrast, control group participants received no antithrombotic or anticoagulation therapy, reflecting their absence of prior cerebrovascular events.

Among the 511 patients in the stroke-associated PFO cohort, percutaneous PFO closure was performed in 401 patients (78.4%).

Echocardiographic Findings

We examined echocardiographic characteristics of high-risk PFO phenotypes, with detailed results presented in Table 2. We found that PFO tunnel width measurements demonstrated significantly larger dimensions in the stroke-associated PFO group compared to controls (3.59 ± 1.56 mm versus 2.37 ± 1.24 mm). The prevalence of PFO diameter exceeding 3 mm was substantially higher in the stroke-associated PFO cohort, occurring in 59.5% of patients compared to only 7.1% of controls. When we assessed RLS severity using bubble count criteria (> 20 bubbles), we observed this finding more frequently in the stroke-associated PFO group relative to controls. Morphologic variants including ASA or interatrial septal hypermobility were identified in 38.7% of stroke-associated PFO patients versus 17.1% of controls, demonstrating a substantially higher prevalence in the cerebrovascular event group.

Table 2
Echocardiographic and High-Risk PFO Characteristics According to Stroke Status

Variable	Non-stroke PFO	Stroke-associated PFO	P value
Tunnel width, mm	2.37 ± 1.24 (n = 283)	3.59 ± 1.56 (n = 390)	< 0.001*
ASA or hypermobile septum (n, %)	73/426 (17.1)	189/489 (38.7)	< 0.001*
Bubble count > 20 (n, %)	118/426 (27.7)	361/509 (70.9)	< 0.001*
PFO diameter > 3 mm (n, %)	20/283 (7.1)	232/390 (59.5)	< 0.001*
Analyses were performed using available-case data without imputation. Denominators vary across variables because of missing data.			
ASA: atrial septal aneurysm, PFO: patent foramen ovale.			

Electrocardiographic Findings

We analyzed electrocardiographic characteristics with detailed results presented in Table 3. We observed differential distribution of crochitage sign across the inferior leads between the two groups. Lead II demonstrated higher prevalence of crochitage sign in stroke-associated PFO patients (18.6% versus 8.2%), while lead III showed a trend toward higher prevalence without achieving statistical significance (16.0% versus 13.6%). Lead aVF revealed increased prevalence of crochitage sign in the stroke-associated PFO cohort (20.9% versus 12.2%). When crochitage was further evaluated according to the number of involved inferior leads, single-lead crochitage occurred at similar frequencies in the two groups (17.4% vs. 18.5%), with no significant difference. In contrast, multi-lead crochitage was significantly more frequent in patients with stroke-associated PFO (16.6% vs. 7.3%). In contrast, the prevalence of incomplete or complete right bundle branch block was comparable between the two groups.

Table 3

Distribution of Crochetage Sign and Other Electrocardiographic Findings According to Stroke Status

Variable	Non-stroke PFO (n = 426)	Stroke-associated PFO (n = 511)	P value
DII crochetage (n, %)	35 (8.2)	95 (18.6)	< 0.001*
DIII crochetage (n, %)	58 (13.6)	82 (16.0)	0.298
aVF crochetage (n, %)	52 (12.2)	107 (20.9)	< 0.001*
Single lead crochetage (n, %)	79 (18.5)	89 (17.4)	0.654
≥ 2 lead crochetage (n, %)	31 (7.3)	85 (16.6)	< 0.001*
Incomplete/Complete RBBB (n, %)	41 (9.6)	52 (10, 2)	0.779
PFO: patent foramen ovale, RBBB: right bundle branch block			

Multivariate Analysis

To identify factors independently associated with stroke-associated PFO, a multivariable logistic regression analysis was performed, with the results presented in Table 4. Single-lead and multi-lead crochetage were included simultaneously in the model, together with other clinically relevant covariates. High-risk PFO phenotype, multi-lead crochetage, HT, and older age were independently associated with stroke-associated PFO, whereas single-lead crochetage was not.

Table 4

Factors Independently Associated With Stroke-Associated PFO in Multivariable Logistic Regression Analysis

Variables	OR	95% CI	P value
Age	1,02	1,01–1,04	0,003
Diabetes mellitus	1,48	0,85 – 2,55	0,163
Hypertension	1,60	1,05 – 2,43	0,028
High-risk PFO	6,49	4,80 – 8,76	< 0,001
Single- lead crochetage	0,99	0,68 – 1,44	0,947
≥ 2-lead crochetage	2,08	1,28 – 3,38	0,003
PFO: patent foramen ovale			

A sensitivity analysis was performed after excluding 106 patients with indeterminate high-risk PFO status due to missing tunnel width measurements in the absence of ASA or interatrial septal hypermobility and significant RLS (> 20 bubbles). Among the remaining 831 patients, high-risk PFO remained strongly associated with stroke-associated PFO (OR 5.04, 95% CI 3.63–6.99; $p < 0.001$). Similarly, crochetae involving two or more inferior leads remained independently associated with stroke-associated PFO (OR 1.73, 95% CI 1.06–2.82; $p = 0.028$), whereas single-lead crochetae remained non-significant (OR 1.05, 95% CI 0.70–1.56; $p = 0.820$).

Association Between the Number of Inferior Leads With Crochetae Sign and High-Risk PFO Morphology

The association between the number of inferior leads exhibiting the crochetae sign and high-risk PFO morphological features is presented in Table 5. Data on ASA or interatrial septal hypermobility were available for 915 of 937 patients (97.7%), RLS severity for 935 (99.8%), and tunnel width for 673 (71.8%).

Table 5
Association Between Crochetae Patterns and High-Risk PFO Features

Variable	Crochetae absent	single lead crochetae	≥ 2-lead crochetae present	P value
ASA or hypermobile septum (n, %)	138/633 (%21,8)	53/167 (%31,7)	71/115 (%61,7)	< 0.001*
Bubble count > 20 (n, %)	321/652 (%49,2)	97/167 (%58,1)	61/116 (%52,6)	0,118
Tunnel width > 3 mm (n, %)	173/474 (%36,5)	49/121 (%40,5)	30/78 (%38,5)	0,706
Analyses were performed using available-case data without imputation. Denominators vary across variables because of missing data.				
ASA: atrial septal aneurysm				

ASA or interatrial septal hypermobility was observed in 21.8% of patients without crochetae, 31.7% of those with crochetae in a single inferior lead, and 61.7% of those with crochetae in two or three inferior leads, with a significant difference across the groups ($p < 0.001$). The prevalence of significant RLS (> 20 bubbles) was 49.2%, 58.1%, and 52.6%, respectively, with no significant difference across the groups ($p = 0.118$). Similarly, the proportion of patients with a tunnel width ≥ 3 mm was comparable across the three groups (36.5%, 40.5%, and 38.5%, respectively).

DISCUSSION

The present study provides new insights into the relationship between the electrocardiographic crochetae sign and stroke-associated PFO. Our principal finding is that the association between the

crochetage sign and stroke-associated PFO appears to vary according to the number of inferior leads involved. In multivariable analysis, crochetage confined to a single inferior lead was not independently associated with stroke-associated PFO, whereas crochetage involving two or more inferior leads remained independently associated after adjustment for established clinical and echocardiographic risk factors. Notably, the association between crochetage involving two or more inferior leads and stroke-associated PFO remained significant in the sensitivity analysis excluding patients with indeterminate high-risk PFO status, supporting the robustness of the primary finding. These findings suggest that the number of inferior leads exhibiting the crochetage sign may be clinically more informative than the mere presence of the sign, with multi-lead involvement representing a potentially more relevant electrocardiographic phenotype. In addition, high-risk PFO anatomy, older age, and HT were independently associated with stroke-associated PFO.

The independent association between multi-lead crochetage, but not single-lead crochetage, and stroke-associated PFO may help explain the conflicting findings of previous studies. Since the initial observations by Ay and colleagues, the relationship between crochetage and PFO-related stroke has remained inconsistent across studies. Ay's group identified a higher prevalence of crochetage in patients with cryptogenic stroke and PFO compared to those without PFO, suggesting potential clinical utility for identifying PFO patients (9). In contrast, Belvís and associates did not observe this association in a comparable population (10). A key methodological distinction between these earlier studies and ours relates to patient selection. Previous investigations compared cryptogenic stroke patients based on PFO presence or absence, whereas we adopted a different approach: we compared stroke-associated PFO patients directly against a control group consisting exclusively of asymptomatic individuals with confirmed PFO. This design allowed us to examine the association between the crochetage sign and stroke-associated PFO within a population of patients with TEE-confirmed PFO. Rather than considering crochetage as a simple present-or-absent ECG finding, we evaluated the number of inferior leads exhibiting the sign. Crochetage confined to a single inferior lead was not independently associated with stroke-associated PFO, whereas involvement of two or more inferior leads remained independently associated after multivariable adjustment. These findings suggest that the association between crochetage and stroke-associated PFO may be related to the number of inferior leads involved rather than to the mere presence of the sign.

The electrophysiological mechanism underlying the crochetage sign remains incompletely understood. Heller and colleagues originally documented this finding in patients with secundum atrial septal defects, demonstrating that its prevalence correlated with larger defect dimensions and greater left-to-right shunting, suggesting that the degree of interatrial communication influences its development (6). However, the mechanism in patients with PFO is likely to be different, as PFO does not produce the chronic right ventricular volume overload seen in ASD. Our study demonstrated a strong association between the number of inferior leads exhibiting the crochetage sign and ASA or interatrial septal hypermobility, whereas no significant association was observed with RLS severity or tunnel width. These findings raise the possibility that crochetage may be related to structural or electrophysiological characteristics of the interatrial septum rather than simply reflecting the magnitude of interatrial

shunting. Interestingly, a recent case report described complete disappearance of the crochetage sign following selective His bundle pacing, suggesting a potential contribution of conduction abnormalities to its electrocardiographic expression (21). Although this isolated observation does not establish a conduction-system mechanism, it provides a possible electrophysiological perspective on the crochetage sign. Whether ASA or excessive septal mobility contributes to localized alterations in septal conduction, and whether this could explain the more frequent multi-lead involvement observed in our study, remains speculative and warrants further investigation.

Our findings differ somewhat from those of Kalkan et al., who reported an association between the crochetage sign and large RLS but not with ASA (8). In our cohort, however, the number of inferior leads exhibiting crochetage was strongly associated with ASA or interatrial septal hypermobility, whereas no significant association was observed with RLS severity. This discrepancy may partly reflect the dynamic nature of RLS, which can vary with transient hemodynamic conditions and the effectiveness of the Valsalva maneuver. In contrast, ASA and septal hypermobility represent structural features that are less dependent on conditions at the time of assessment. These findings may therefore suggest a closer relationship between crochetage and the underlying septal morphology than with shunt magnitude measured at a single examination. Differences in study populations and assessment methods may also have contributed to these findings.

High-risk PFO anatomy also emerged as an independent predictor of stroke-associated PFO, consistent with previous randomized trials and current consensus recommendations (4, 5). We defined high-risk PFO by the presence of ASA or interatrial septal hypermobility, a large RLS, or increased PFO width, as these features have the strongest evidence linking them to PFO-related stroke (15, 16, 17, 22). Other proposed anatomical markers, such as a prominent Eustachian valve, Chiari network, lipomatous hypertrophy, and a long PFO tunnel, were not included because evidence supporting their association with PFO-related stroke is largely limited to retrospective studies (18, 19, 23). As expected, high-risk PFO anatomy remained the strongest predictor of stroke-associated PFO, while multi-lead crochetage was also independently associated with stroke-associated PFO, suggesting that this ECG finding may have potential value as an adjunct to anatomical risk assessment.

Older age was also identified as an independent predictor of stroke-associated PFO in our study, possibly reflecting mechanisms beyond conventional atherosclerotic pathways. Aging may amplify PFO pathogenicity through increased thrombotic propensity, endothelial dysfunction, and elevated right-sided cardiac pressures that facilitate RLS (24, 25). These findings are consistent with those of Homma et al., who demonstrated a higher risk of recurrent cryptogenic stroke among older patients with PFO, supporting the concept that advancing age may increase the likelihood of paradoxical embolism (26).

HT also remained an independent predictor of stroke-associated PFO in our study. This finding differs from that of Putaala et al., who reported an association between HT and cryptogenic stroke only in patients without high-risk PFO (27). The discrepancy likely reflects differences in study design and patient selection. Unlike their study, we compared stroke-associated PFO with asymptomatic PFO

controls, allowing the independent association of HT to emerge. HT may therefore contribute through mechanisms beyond overt atherosclerosis, including endothelial dysfunction, impaired fibrinolytic capacity, adverse cardiac remodeling, and hemodynamic alterations, thereby creating a prothrombotic environment that may facilitate paradoxical embolism (28,29,30).

STUDY LIMITATIONS

Our study has several limitations. First, its retrospective design precludes establishing a causal relationship between the crochetage sign and stroke-associated PFO. Second, screening for deep vein thrombosis and thrombophilic disorders was performed in only a minority of patients, limiting the comprehensive assessment of factors predisposing to paradoxical embolism. Third, tunnel width measurements were available in 71.8% of the study population, which may have reduced the statistical power to detect an association between tunnel width and the crochetage sign. Finally, although all patients underwent comprehensive diagnostic evaluation, intracranial and extracranial vascular imaging was not performed using a uniform modality. Therefore, unrecognized atherosclerotic disease cannot be completely excluded in a small proportion of patients classified as having cryptogenic stroke. Prospective studies with standardized diagnostic protocols are warranted to validate our findings.

CONCLUSION

In conclusion, among patients with TEE-confirmed PFO, crochetage involving two or more inferior leads was independently associated with stroke-associated PFO, whereas crochetage confined to a single inferior lead was not. The association between increasing crochetage involvement and ASA or interatrial septal hypermobility may suggest a relationship with an underlying abnormal interatrial septal phenotype. Further prospective studies are needed to validate these findings and clarify the potential clinical relevance of the crochetage sign in patients with PFO.

Declarations

Ethics approval and consent to participate

This retrospective multicenter study was conducted across four participating centers. Institutional approval was obtained from each participating center, and the study protocol, together with these institutional approvals, was reviewed and approved by the Clinical Research Ethics Committee of Göztepe Prof. Dr. Süleyman Yalçın City Hospital (decision no. 2026/0391). The study was conducted in accordance with the Declaration of Helsinki. Owing to the retrospective nature of the study, the requirement for informed consent to participate was waived by the ethics committee

Consent to participate and consent to publish declarations

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Clinical trial number

Not applicable.

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Declaration of Interests

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Author contributions

MC: Conceptualization (equal); data curation (equal); investigation (equal); methodology (equal); project administration (lead); supervision (equal); validation (equal); writing—original draft (equal); writing—review and editing (lead). SK: Conceptualization (equal); data curation (supporting); formal analysis (equal); funding acquisition (equal); investigation (supporting); writing—original draft (equal). SF: data curation (equal); investigation (equal); methodology (equal); supervision (equal); validation (equal); writing—review and editing (supporting). CY: data curation (equal); funding acquisition (equal); methodology (equal); writing—original draft (equal). HA: data curation (equal); methodology (equal); resources(equal); writing—original draft (equal). BE: data curation (equal); investigation (equal); resources(equal); writing—original draft (equal). ASY: Conceptualization (equal); formal analysis (equal); funding acquisition (equal); methodology (equal); software (equal); writing—original draft (equal). MK: data curation (equal); investigation (equal); methodology (equal); resources(equal); writing—original draft (equal). ABY: data curation (equal); investigation (equal); methodology (equal); resources(equal); writing—original draft (equal) FK: data curation (supporting); investigation (equal); resources(equal); visualition (equal). IB: data curation (supporting); formal analysis (equal); funding acquisition (equal); investigation (equal); resources(equal); visualition (equal). BGS: data curation (equal); methodology (equal); resources(equal); validation (equal); visualition (equal); writing—original draft (equal). SCE: data curation (supporting); investigation (equal); resources(equal); visualition (equal). EA: methodology (equal); supervision (equal); validation (equal) visualition (equal). RZ: Conceptualization (equal); methodology (equal); supervision (equal); validation (equal). RDA: methodology (equal); supervision

(equal); validation (equal). MC: methodology (equal); supervision (equal); validation (equal); visualition (equal); writing— original draft (equal).

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Figures

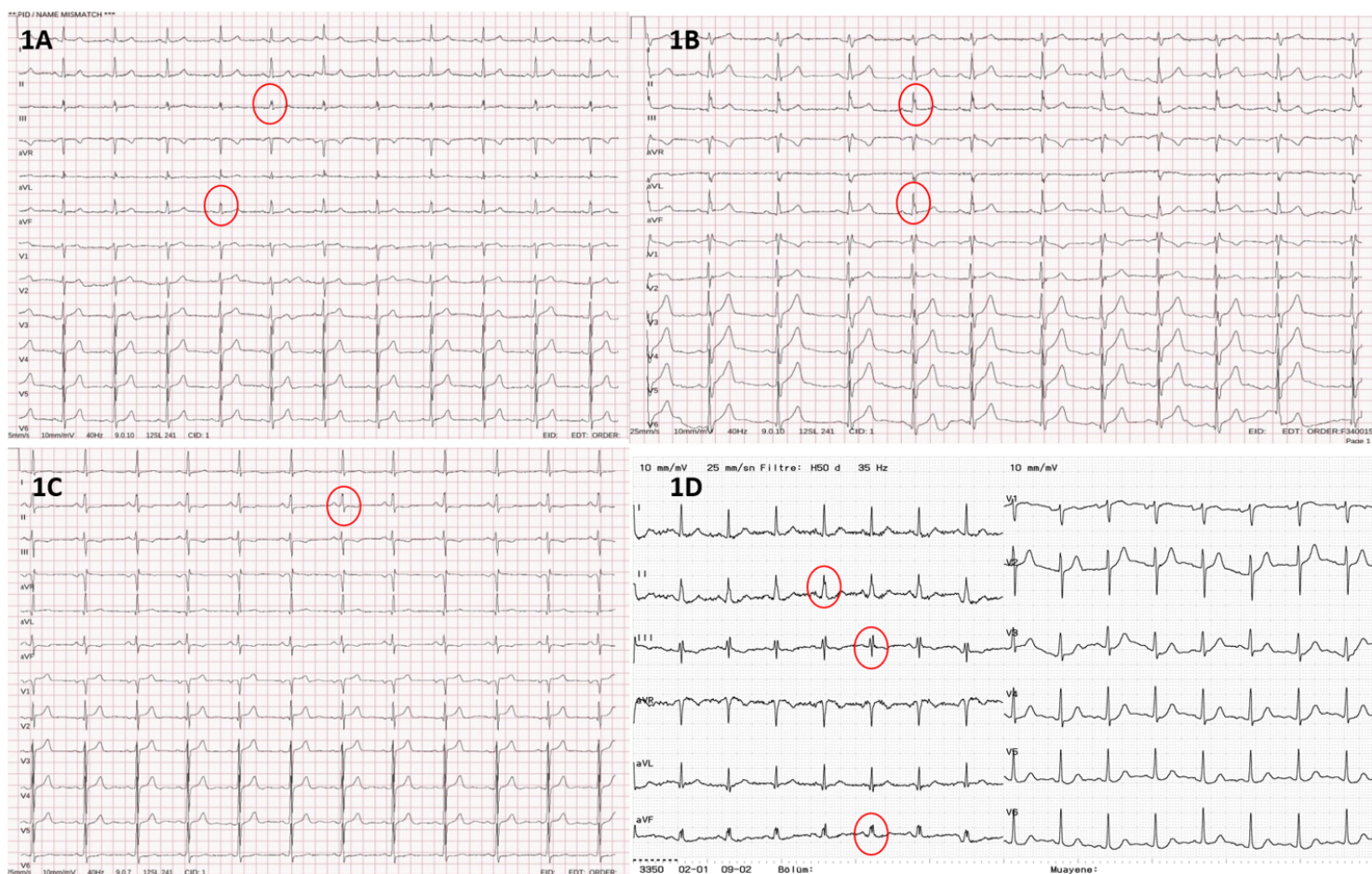


Figure 1

Representative electrocardiographic examples of the crocheting sign according to the extent of inferior lead involvement.

1A. Crocheting sign confined to a single inferior lead.

1B, 1C. Representative examples of crocheting involving two inferior leads.

1D. Crocheting involving all three inferior leads (II, III, and aVF).

Arrows indicate the characteristic notch on the ascending limb or apex of the R wave.