EuroIntervention 2022;18:68-70 published online ahead of print April 2022

Mechanisms of ineffective patent foramen ovale closure using the percutaneous suture-mediated NobleStitch system

Jessica Zannoni*, MD; Antonio Popolo Rubbio, MD; Maurizio B. Tusa, MD; Anca I. Corciu, MD, PhD; Matteo Casenghi, MD; Gaspare Cannone, MD; Marta Barletta, MD; Elisa Stefanini, MD; Valentina Mantovani, MD; Riccardo Gorla, MD; Nedy Brambilla, MD; Luca Testa, MD; Francesco Bedogni, MD; Federico De Marco, MD

Clinical and Interventional Cardiology Department, I.R.C.C.S. Policlinico San Donato, San Donato Milanese, Milan, Italy

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-01021

Introduction

Percutaneous suture-mediated patent foramen ovale (PFO) closure with the "device-less" NobleStitch system (HeartStitch) has been employed in clinical practice as an effective and safe alternative to traditional device closure[1-3]. In previous studies, recurrence of a residual atrial right-to-left shunt (RLS) during follow-up was estimated at almost 20%[1-3]. In any case, specific mechanisms of failure have not been systematically described and they still remain unknown. The aim of the study was to describe the mechanisms of failure after NobleStitch from a prospective single-centre cohort.

Methods

STUDY POPULATION

Between June 2016 and September 2021, 122 patients (female 50.0%; mean age 48±12 years) underwent percutaneous suture-mediated PFO closure with NobleStitch at our institution. The overall population was divided into 2 groups on the basis of recurrence of atrial RLS ≤1 or RLS ≥2 grade at echocardiographic follow-up with transcranial doppler (TCD) or transthoracic echocardiography (TTE) bubble study, within 6 months following the procedure. Patients with RLS ≥2 grade were then studied with transoesophageal echocardiography (TOE), in order to define specific mechanisms of ineffective closure. Study design is illustrated in **Supplementary Figure 1**. Echocardiographic assessment is specified in **Supplementary Appendix 1**.

DATA ANALYSES

Statistical analyses are illustrated in **Supplementary Appendix 2**.

Results

The baseline characteristics of both groups, with and without significant residual RLS, are summarised in **Table 1**.

The NobleStitch procedure was successfully performed in 116 (95.1%) patients (in 6 patients traditional devices were then used, due to RLS ≥2 at the end of the NobleStitch procedure). Follow-up was complete in 100.0%. At a median follow-up of 335 days, atrial RLS ≥2 occurred in 19.8% (23/116) of patients. Three different mechanisms of late failure **(Figure 1, Supplementary Figure 2)** were identified by TOE: partial stitch detachment, atrial septal tear and KwiKnot (Heartstitch) embolisation.

**Corresponding author: Clinical and Interventional Cardiology Department, IRCCS Policlinico San Donato, Piazza Edmondo Malan 2, 20097 San Donato Milanese, Milan, Italy. E-mail: zannoni.jessica@gmail.com*

© Europa Digital & Publishing 2022. All rights reserved.

SUBMITTED ON 23/11/2021 - REVISION RECEIVED ON 16/02/2022 - ACCEPTED ON 17/03/2022

DOI: 10.4244/EIJ-D-21-01021

Table 1. Baseline demographic, clinical and echocardiographic characteristics of the study population.

	Overall (n=122)	RLS ≤1 (n=93)	RLS ≥2 (n=29)	*p*-value
Baseline characteristics				
Age, years (mean±SD)	48±12	48±11	46±14	0.349
Female, n (%)	61 (50.0)	50 (53.8)	11 (37.9)	0.137
BMI, kg/m^2 (IQR)	21 (19-23)	21 (19-24)	21 (18-23)	0.702
RoPE score, points (IQR)	6 (5-7)	6 (5-7)	6 (5-7)	0.478
RoPE ≥6, n (%)	71 (61.2)	56 (60.2)	15 (65.2)	0.659
Medical history				
Hypertension, n (%)	29 (24.0)	23 (24.7)	6 (21.4)	0.720
Diabetes, n (%)	3 (2.5)	3 (3.2)	0 (0.0)	1.000
Smoking history, n (%)	26 (21)	20 (21.5)	6 (20.6)	0.993
Dyslipidaemia, n (%)	31 (25.4)	24 (25.8)	14 (24.0)	0.932
Family history of CVD, n (%)	16 (13.1)	10 (10.7)	6 (20.7)	0.144
Prior deep vein thrombosis, n (%)	4 (3.3)	2 (2.2)	2 (7.1)	0.229
Thrombotic diathesis, n (%)	13 (10.7)	8 (8.6)	5 (17.9)	0.166
Clinical presentation				
Cryptogenic stroke, n (%)	47 (38.8)	32 (34.4)	15 (53.6)	0.068
TIA, n (%)	39 (32.2)	30 (32.3)	9 (32.1)	0.991
Intractable migraine, n (%)	26 (21.5)	19 (20.4)	7 (25.0)	0.606
Decompression sickness, n (%)	11 (9.0)	10 (10.8)	1 (3.4)	0.457
Neuroimaging ischaemic lesion, n (%)	87 (71.9)	65 (69.9)	22 (78.6)	0.669
Anatomical characteristics				
Atrial septal aneurysm, n (%)	19 (15.6)	10 (10.8)	9 (31.0)	0.009
Atrial septal hypermobility, n (%)	48 (39.3)	30 (32.3)	18 (62.1)	0.004
Septum cribrosus, n (%)	2 (1.7)	1 (1.1)	1 (3.4)	0.423
Chiari network, n (%)	84 (69.4)	58 (63.0)	26 (89.7)	0.007
Fossa ovalis diameter, mm (IQR)	20 (17-22)	20 (17-22)	19 (17-23)	0.941
PFO tunnel length, mm (IQR)	11 (9-13)	11 (9-12)	12 (9-15)	0.058
PFO width, mm (IQR)	2.6 (2-3.8)	2.5 (2.0-3.0)	3.0 (2.3-4.0)	0.020
Functional characteristics				
Interatrial shunting at rest, n (%)	34 (28.1)	20 (21.7)	14 (48.3)	0.006
Atrial RLS after Valsalva, n (%)	122 (100.0)	93 (100.0)	29 (100.0)	-
Left-to-right shunt, n (%)	16 (13.2)	9 (9.8)	7 (24.1)	0.047
Spontaneous colour Doppler shunt, n (%)	10 (8.3)	8 (8.7)	2 (7.1)	1.000
Grade of RLS after Valsalva at TTE/TOE				
Mild, n (%)	10 (8.2)	10 (10.8)	0 (0.0)	0.115
Moderate, n (%)	68 (55.7)	53 (57.0)	15 (51.7)	0.618
Severe, n (%)	44 (36.1)	30 (32.3)	14 (48.3)	0.117
Grade of RLS after Valsalva at TCD, n (%)				
Mild, n (%)	9 (9.9)	9 (13.4)	0 (0.0)	0.105
Moderate, n (%)	40 (44.0)	32 (47.8)	8 (33.3)	0.222
Severe, n (%)	42 (46.2)	26 (38.8)	16 (66.7)	0.019

Categorical variables are expressed as n (%). Continuous variables are expressed as median and interquartile range (IQR), as appropriate. BMI: body mass index; CVD: cardiovascular disease; PFO: patent foramen ovale; RLS: right-to-left shunt, RoPE score: Risk of Paradoxical Embolism score; TCD: transcranial Doppler; TIA: transient ischaemic attack; TOE: transoesophageal echocardiography; TTE: transthoracic echocardiography

Discussion

The NobleStitch system is a good alternative for PFO closure when compared to classic device closure, although there is still a lack of information about the long-term follow-up of this procedure and its real effectiveness. In our analysis, the occurrence of effective PFO closure after the NobleStitch procedure – with atrial RLS ≤1 – was 80.2%, which was in line with the rate in previous reports[1-3], although lower than the results obtained with traditional devices[4]. Although the initial learning curve may have had an impact, specific selection criteria are mandatory in order to improve the outcomes of this procedure.

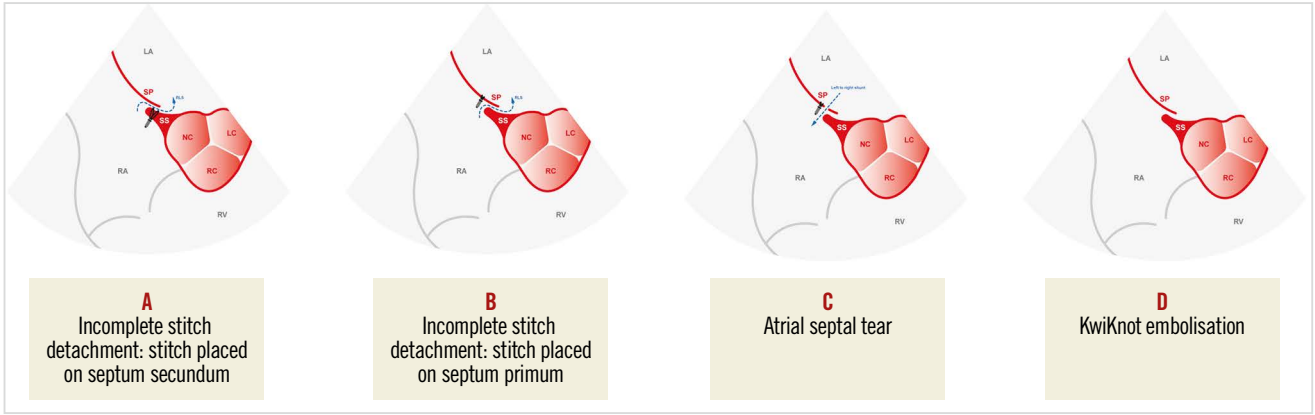
In this prospective study, we introduced a systematic approach during the follow-up with a bubble test at TTE and TCD on all patients and a further investigation with TOE only in patients with RLS ≥2 to investigate failure mechanisms. After excluding the 6 patients with early technical failure who were managed with a classic device for closure, there remained 116 patients who were successfully treated, of whom 23 (19.8%) presented RLS ≥2. Among them, specific mechanisms of failure were detected in 17 (73.9%). Six patients, all asymptomatic, presented a large residual atrial RLS and refused further TOE. A partial stitch detachment was found as the main mechanism in 52.2% of cases. In these cases, the KwiKnot was attached only on the septum primum or septum secundum, with the clear identification of 2 separated septal sheets, leading to an opening tunnel with consequent atrial RLS. A second mechanism found was an atrial septal tear (13%) occurring really close to the stitch, with consequent atrial RLS. Finally, the third mechanism identified was a complete embolisation of the stitch and the knot into the pulmonary circulation (8.7%). To the best of our knowledge, this is the first study in which partial stitch detachment and KwiKnot embolisation have been identified as possible mechanisms of RLS ≥2, whereas atrial septal tear was previously described in an anecdotal case report[5].

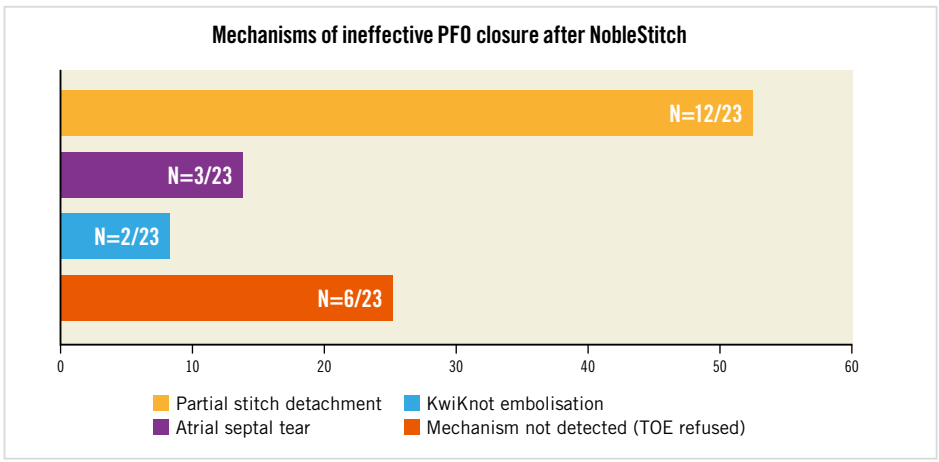
Limitations

Different limitations should be considered in the interpretation of our results. This was not a controlled study, so several confounding factors could have influenced our results; secondly, a small sample size from a single centre, with limited follow-up, was included, so our results need to be confirmed in multicentre analyses with longer follow-up. Reflecting real-world clinical practice, an independent core laboratory did not review the echocardiographic data. However, the analyses were conducted by dedicated, highly experienced echocardiographists, utilising validated methods.

Conclusion

Percutaneous closure of PFO by suturing with the NobleStitch system is an effective and safe technique that has obvious advantages over traditional device closure, although recurrence of RLS after PFO closure is not uncommon. Partial stitch detachment, atrial septal tear and KwiKnot embolisation were the main mechanisms encountered during follow-up.





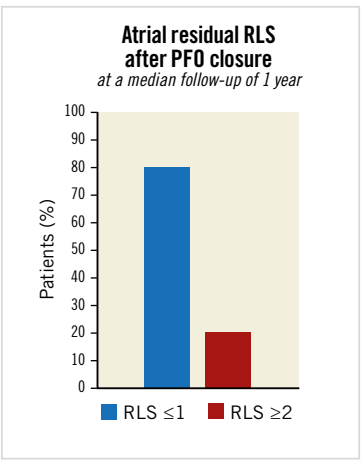


Figure 1. *Representative transoesophageal echocardiographic images of different mechanisms of ineffective PFO closure. A. Incomplete stitch detachment: one of the most frequently identified mechanisms of ineffective PFO closure was partial stitch detachment with opening of the foramen ovale and right-to-left passage of microbubbles at bubble test. In this case the stitch is placed only on the septum secundum; B. Incomplete stitch detachment: the same mechanism described in (A) but in this case the NobleStitch was found on the septum primum resulting in recurrent atrial shunt; C. Atrial septal tear: a new atrial septal tear occurred very close to the stitch after the NobleStitch procedure causing a left-to-right shunt; D. KwiKnot embolisation: complete detachment of the stitch and the KwiKnot into the pulmonary circulation resulting in PFO reopening. PFO: patent foramen ovale; RLS: right-to-left shunt; TOE: transoesophageal echocardiography*

TOE is an essential tool for assessing the anatomical and functional characteristics of PFO, in order to improve patient selection for the NobleStitch procedure, guide the operator in suture orientation and correct placement, and identify possible mechanisms of failure during follow-up. Defining mechanisms and predictors of failure may help to improve long-term results.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Gaspardone A, De Marco F, Sgueglia GA, De Santis A, Iamele M, D'Ascoli E, Tusa M, Corciu AI, Mullen M, Nobles A, Carminati M, Bedogni F. Novel percutaneous suture-mediated patent foramen ovale closure technique: early results of the NobleStitch EL Italian Registry. *EuroIntervention.* 2018;14:e272-9.

2. Gaspardone A, Sgueglia GA, De Santis A, D'Ascoli E, Iamele M, Piccioni F, Giannico B, D'Errico F, Gioffrè G, Summaria F, Gaspardone C, Versaci F. Predictors of Residual Right-to-Left Shunt After Percutaneous Suture-Mediated Patent Fossa Ovalis Closure. *JACC Cardiovasc Interv.* 2020;13:2112-20.

3. Beneduce A, Ancona MB, Moroni F, Ancona F, Ingallina G, Melillo F, Russo F, Ferri LA, Bellini B, Chieffo CA, Agricola E, Montorfano M. A systematic transoesophageal echocardiography study of suture-mediated percutaneous patent foramen ovale closure. *EuroIntervention.* 2022;18:63-7.

4. Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke. *N Engl J Med.* 2020;382:978.

5. Baldetti L, Ferri LA, Ancona M, Bellini B, Visco E, Melillo F, Beneduce A, Chieffo A, Ancona F, Agricola E, Montorfano M. Interatrial Septal Tear After Patent Foramen Ovale Closure With the NobleStitch Device. *JACC Cardiovasc Interv.* 2019;12:e139-40.

Supplementary data

Supplementary Appendix 1. Echocardiographic assessment.
Supplementary Appendix 2. Statistical analysis.
Supplementary Figure 1. Study design.
Supplementary Figure 2. Assessment of ineffective PFO closure mechanisms after NobleStitch procedure.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-01021

Supplementary data

Supplementary Appendix 1. Echocardiographic assessment.

Patients underwent a screening evaluation bubble study with TTE and/or TCD ultrasound. All patients underwent preprocedural TOE, according to the American Society of Echocardiography recommendations, to assess the presence of PFO, to evaluate the morphology and size of fossa ovalis, to identify atrial septal aneurysm (ASA, defined as excursion of the septal tissue of greater than 10 mm from the plane of the atrial septum into the right atrium or left atrium or a combined total excursion right and left of 15 mm), the presence of stretched PFO with left-to-right shunt and the evidence of Eustachian Valve and/or Chiari Network, to measure tunnel length and PFO width. We grouped in the terms "atrial septal hypermobility" both the presence of ASA and also every swinging atrial septum. Highly experienced operators guided the procedure by TOE using bicaval and short axis 2D view and 3D multiplanar imaging reconstruction to better characterise the PFO morphology, optimise the positioning of the stitch and check the final result. The grading of RLS was semi-quantitative according to the number of microbubbles detected in the left atrial within 5 cardiac cycles and performed both at rest and after Valsalva manoeuvre. Delayed appearance of microbubbles in the left atrium, indicates intrapulmonary shunting and could be a reason for false-positive bubble test. Hence, the importance of checking if the bubbles, which opacified the left atrium, entered from the atrial septum and not from the pulmonary veins. Grading of RLS was considered as follows: grade 0=no microbubbles, grade 1 (mild)=1 to 9 microbubbles, grade 2 (moderate)=10 to 19 microbubbles, grade 3 (severe) $\geqslant$20 microbubbles. Moreover, the microbubble test was performed in all patients to assess the early intraprocedural result by saline injection from the inferior vena cava. All the 116 patients that were successfully treated with the NobleStitch (Heartstitch) system were then evaluated with TTE and TCD with bubble test within 6 months after the index procedure. If a significant RLS was found (RLS $\geqslant$2), a transoesophageal

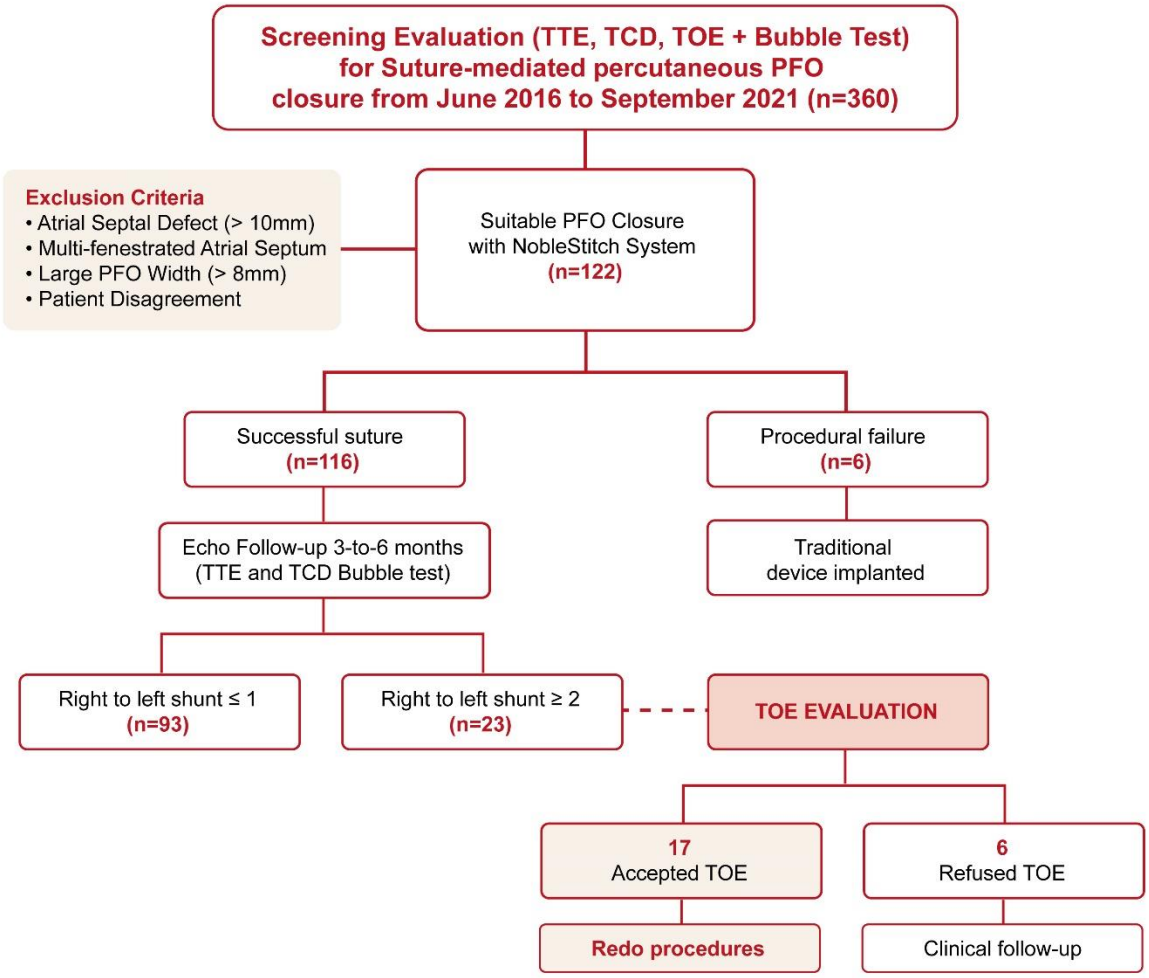
echocardiography study was organised to assess the mechanism and to confirm the severity of the residual shunt.

Supplementary Appendix 2. Statistical analysis.

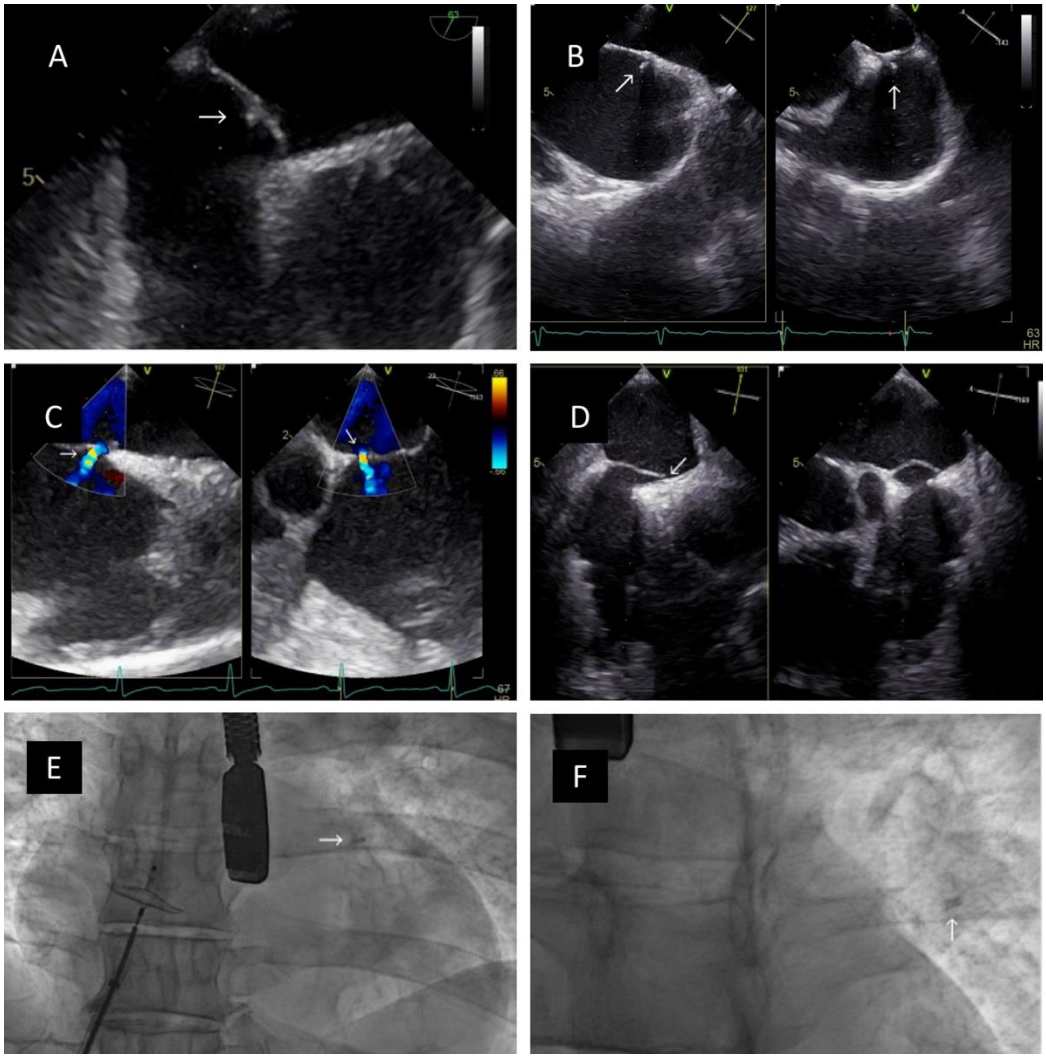
Continuous variables were analysed for distribution using the Kolmogorov-Smirnov test. According to their distribution, continuous variables were expressed as mean±standard deviation or median and interquartile range (IQR), as appropriate. Categorical variables were expressed as absolute numbers and percentages and were compared by chi-square or Fisher's exact tests, as appropriate.

Unpaired Student's t-tests were used to compare continuous parameters following a normal distribution, whereas Mann-Whitney U tests were used to compare continuous variables with skewed distribution. A 2-sided p-value <0.05 was required for statistical significance.

The data were analysed with SPSS statistics software (version 25, IBM Corp.).



Supplementary Figure 1. Study design.



Supplementary Figure 2. Assessment of ineffective PFO closure mechanisms after the NobleStitch procedure
A. Short axis view showing incomplete detachment of stitch, positioned on the septum primum;
B. X-plane view showing stitch placed on the septum secundum;
C. X-plane view of atrial septal tear with left-to-right colour shunt;
D. X-plane view confirming persistent PFO without stitch;
E. Angiographic cranial LAO view showing KwiKnot embolisation into the lung;
F. Angiographic cranial LAO view focused on embolised knot.