

Incidence, clinical correlates, timing, and consequences of acute thrombus formation in patients undergoing the MitraClip procedure

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KEY WORDS

acute thrombus formation, MitraClip procedure, mitral regurgitation

ABSTRACT

BACKGROUND Despite adequate heparinization, formation of fresh intracardiac thrombi during the MitraClip procedure was reported.

AIMS We aimed to evaluate the incidence and clinical consequences of intracardiac thrombus formation during the MitraClip device implantation.

METHODS Clinical data and transesophageal echocardiography findings obtained during MitraClip procedures in 100 consecutive patients (81 men; mean [SD] age, 67.8 [8.3] years) were reviewed. In all patients, a heparin bolus was given immediately after a successful transseptal puncture, and the activated clotting time above 250 seconds was maintained throughout the procedure.

RESULTS Thrombus formation was documented in 9 patients (9%). In 6 patients, thrombi formed on a transseptal needle/sheath (2 attached to the sheath in the right atrium and 4 on the sheath immediately after the puncture in the left atrium), and in 3 patients, on the MitraClip device in the left atrium (2 on a steerable guiding catheter and 1 on the clip delivery system). Overall, 6 thrombi (67%) formed prior to and 3 (33%) after heparin administration. All thrombi were transient and disappeared within minutes. No periprocedural ischemic stroke, transient ischemic attack, or other embolic complications were reported. Clinical characteristics were similar in patients with and without thrombi, except for lower left ventricular ejection fraction (LVEF; mean [SD], 23% [10%] and 30% [10%], respectively; $P = 0.03$). In-hospital death was reported in 6 patients: 2 with a visible thrombus and 4 without ($P = 0.09$).

CONCLUSIONS Transient thrombus formation is relatively common during the MitraClip procedure, especially in patients with low LVEF; however, acute clinical consequences are benign.

INTRODUCTION The MitraClip device implantation has been developed as a minimally invasive procedure for patients with severe mitral regurgitation (MR) who are at prohibitive risk of open-chest cardiac surgery. Previous registry data and a randomized trial documented the safety and efficacy of the intervention at least

in terms of symptom relief.¹⁻⁵ Recently, 2 randomized trials performed in patients with functional MR have yielded conflicting data, with very positive results from the COAPT study (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) but rather

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WHAT'S NEW?

To the best of our knowledge, this is the first paper that systematically describes the prevalence of thrombus formation during the MitraClip implantation. Transient thrombus formation was noted in 9% of all procedures. So far, only a few case reports have been published on this topic. However, the phenomenon has been observed in patients undergoing ablation for atrial fibrillation. According to our data, most thrombi occur before heparin administration: in the right or left atrium immediately after transseptal puncture. Although they were shown to be relatively common during the MitraClip device implantation, they were transient and their acute clinical consequences were benign.

neutral findings of the MITRA-FR trial (Multi-centre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation).^{6,7} The procedure requires left atrial access and adequate anticoagulation. However, despite heparin administration and appropriate activated clotting time (ACT), thrombotic complications may occur.^{8,9}

The aim of our study was to evaluate the incidence, timing, and clinical consequences of acute intracardiac thrombus formation detected by transesophageal echocardiography (TEE) used for procedural guidance.

METHODS The current study was a retrospective registry of all MitraClip procedures performed in 3 Polish centers (Institute of Cardiology in Warsaw, Medical University of Gdańsk, and Medical University of Lublin) by one primary operator or proctor (JP). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by an institutional review board at each center. Patient informed consent was waived due to the retrospective study design. Clinical and echocardiographic

data of patients undergoing the MitraClip procedure were collected by reviewing the medical records. Clinical endpoints were determined by experienced physicians (JS, PW, and MC) in each center separately, using the same definitions. Stroke, transient ischemic attack (TIA), and intracerebral hemorrhage were defined according to the American Heart Association / American Stroke Association statement.¹⁰ Myocardial infarction was defined according to the fourth universal definition of myocardial infarction.¹¹ Pre- and postprocedural TEE was performed and analyzed by experienced readers (PS, WB, and AW). Left ventricular ejection fraction (LVEF) was estimated visually. Pulmonary artery systolic pressure (PASP) was measured based on the Doppler assessment of the peak tricuspid regurgitant jet velocity, inferior vena cava diameter, and respiratory variation. Right ventricular dysfunction was defined as a tricuspid annular plane systolic excursion of less than 17 mm, tissue Doppler-derived tricuspid lateral annular systolic velocity of less than 9.5 cm/s, or both. Mitral regurgitation was graded using a 4-point scale.

Prior to the intervention, oral anticoagulation was interrupted in all patients. Treatment with a non-vitamin K antagonist oral anticoagulant was stopped 48 hours before the procedure, and the international normalized ratio was lower than 1.5 in all patients receiving warfarin or acenocoumarol prior to the procedure.

A standard transseptal puncture with the Brockenbrough needle and Mullins sheath with a dilator was performed. The needle, sheath, and dilator were flushed with heparinized saline (1000 U of heparin per 1 l of saline). All patients received an initial bolus of heparin (100 U/kg) immediately after positioning the transseptal sheath in the left atrium. The target ACT was longer than

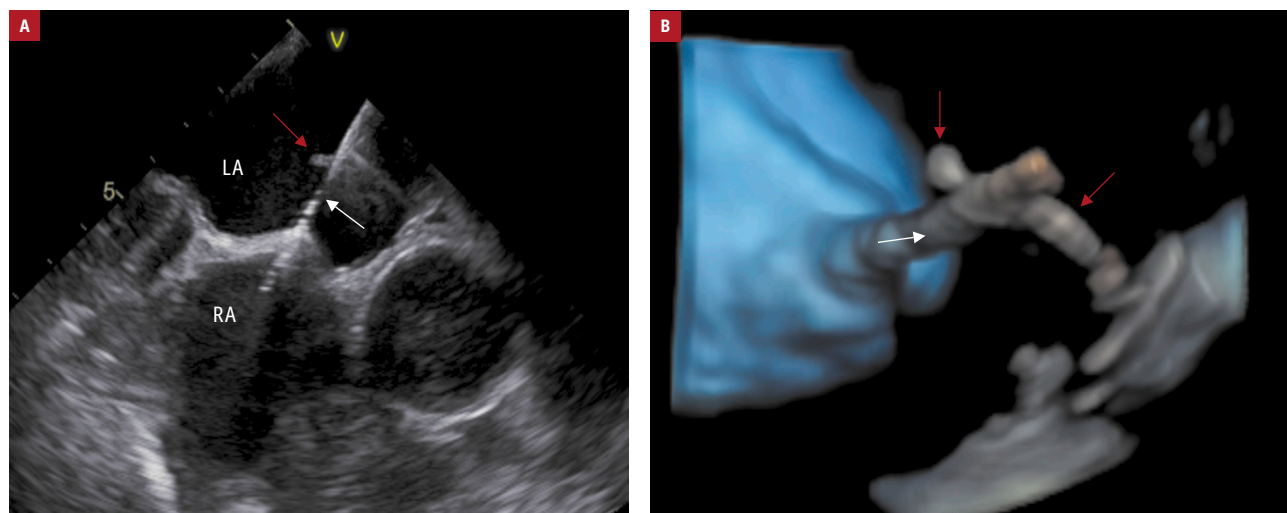


FIGURE 1 A thrombus (red arrows) attached to the transseptal needle (white arrows), detected on: **A** – 2-dimensional echocardiography; **B** – 3-dimensional echocardiography.

Abbreviations: LA, left atrium; RA, right atrium

250 seconds and was checked every 30 minutes. Additional boluses of heparin were administered if the ACT dropped below 250 seconds; the administration was at the discretion of the operator.

Transesophageal echocardiography images of all procedural steps were recorded (Vivid E95, GE HealthCare Inc., Marlborough, Massachusetts, United States), archived, and reviewed. A thrombus was defined as a mobile structure attached to a catheter and not connected with the surrounding cardiac tissues (FIGURES 1–4).

Statistical analysis Continuous data were presented as mean (SD) and were compared using the independent-samples *t* test or Mann–Whitney test. Categorical variables were presented as numbers and percentages and compared using the χ^2 test or Fisher exact test.

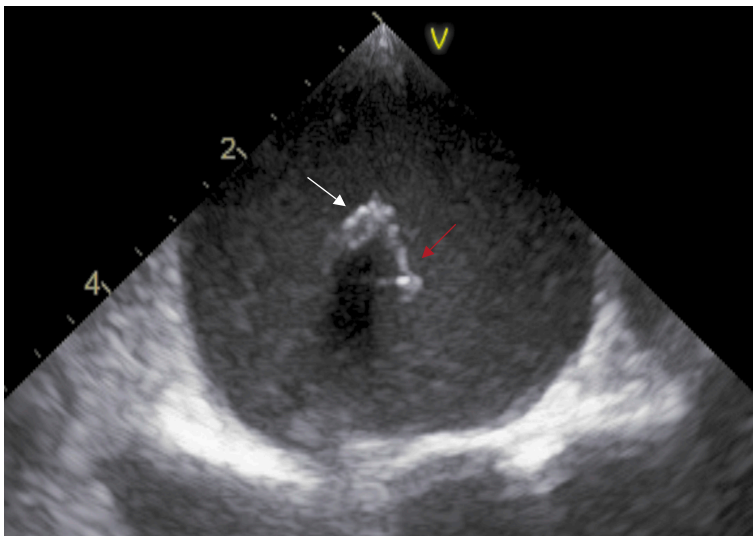


FIGURE 2 A thrombus (red arrow) attached to the transseptal sheath (white arrow)

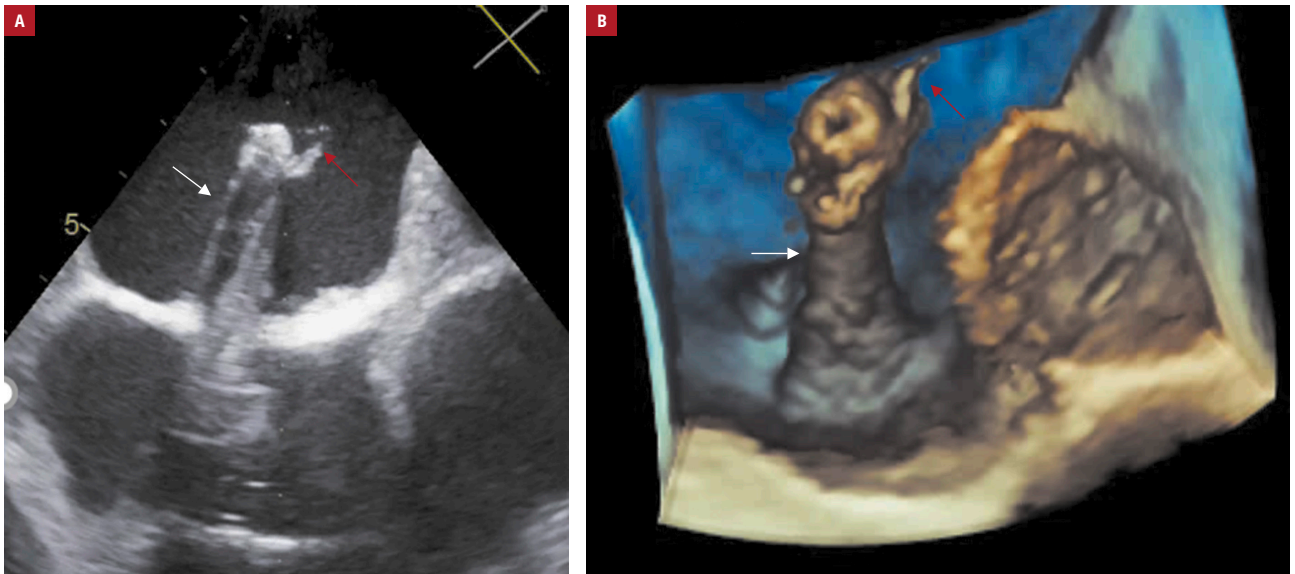


FIGURE 3 A thrombus (red arrows) attached to the MitraClip steerable guiding catheter (white arrows), detected on: **A** – 2-dimensional echocardiography; **B** – 3-dimensional echocardiography

RESULTS Between May 2012 and April 2019, 100 MitraClip procedures were performed in 100 consecutive patients (81 men; mean [SD] age, 67.8 [8.3] years) in 3 Polish centers. The etiology of MR was functional in 96 patients. All procedures were performed ($n = 87$) or proctored ($n = 13$) by the same primary operator (JP).

A periprocedural thrombus attached to an introduced device occurred in 9 patients (9%). The prevalence of thrombus was similar in the first 50 patients and in the remaining 50 subjects (10% vs 8%, $P = 0.8$). In 6 patients, a thrombus formed on the transseptal sheath, and in 3 patients, on the MitraClip device. In 2 patients, a thrombus was identified on the transseptal sheath in the right atrium prior to the transseptal puncture. In 7 patients, a thrombus developed in the left atrium. In 4 patients, a visible thrombus formed on the transseptal sheath immediately after the puncture (FIGURES 1 and 2). In 2 patients, it was found on a steerable guiding catheter (FIGURE 3) prior to the introduction of the clip delivery system; and in 1 patient, it was located on a clip that was still attached to the MitraClip delivery system during its positioning in the left atrium (FIGURE 4).

The baseline demographic, clinical, and echocardiographic characteristics of patients with and without a thrombus are presented in TABLE 1. Patients with a transient periprocedural thrombus had lower LVEF compared with those without a thrombus (mean [SD], 23% [10%] vs 30% [10%]; $P = 0.03$). They also tended to have higher PASP (mean [SD], 61 [9] mm Hg vs 52 [12] mm Hg; $P = 0.09$) and showed a higher prevalence of right ventricular dysfunction (78% vs 42%; $P = 0.07$). Overall, prior to the procedure, 73 patients were treated with oral anticoagulation, including 46 patients receiving vitamin K antagonists. The prevalence

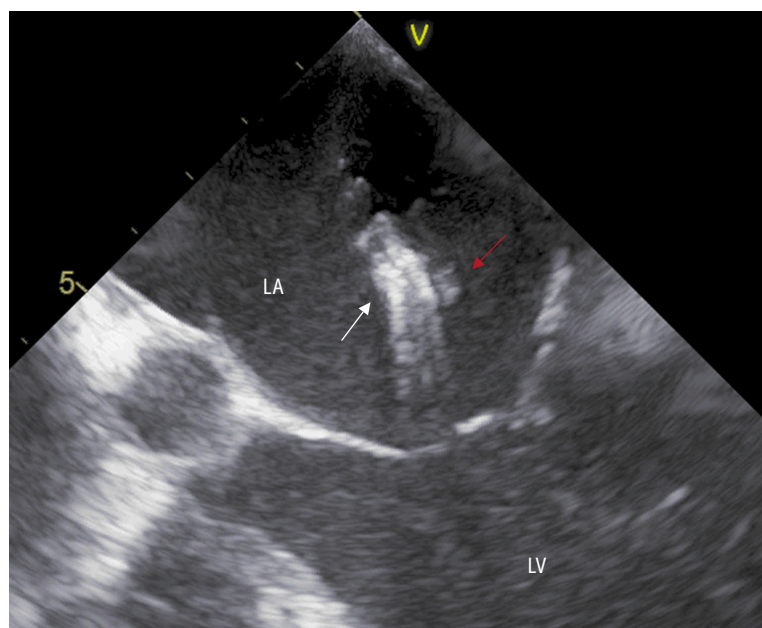


FIGURE 4 A thrombus (red arrow) attached to the MitraClip delivery system in the left atrium. The white arrow points at the MitraClip with closed arms attached to the clip delivery system.

Abbreviations: LV, left ventricle; others, see **FIGURE 1**

of thrombi was similar in patients on anticoagulation discontinued prior to the procedure and in patients without prior anticoagulation therapy (mean [SD], 6% [8.2%] and 3% [11.1%], respectively; $P = 0.7$).

In 2 patients with a thrombus detected in the right atrium, the transeptal sheath and needle were removed and flushed with heparinized saline again. The further procedure was uneventful. In 4 patients with thrombus formation on the transeptal sheath positioned in the left atrium, an additional bolus of heparin (100 U/kg) was administered immediately. In all cases, after a few minutes of watchful waiting, a thrombus disappeared, and the procedure was continued. In 3 patients with a thrombus attached either to the MitraClip steerable guiding catheter or to the clip delivery system, an additional bolus of 5000 U of heparin was given immediately even though the ACT prior to the administration was longer than 250 seconds (253 s, 291 s, and 283 s, respectively). The thrombus disappeared within a few minutes, and the procedure was resumed.

Procedure-related variables and acute patient outcomes are presented in **TABLE 2**. Overall, 6 patients died in the hospital following the MitraClip device implantation (2 of the 9 patients

TABLE 1 Baseline demographic, clinical, and echocardiographic characteristics of the study groups

Variable	Patients with a thrombus (n = 9)	Patients without a thrombus (n = 91)	P value
Male sex	8 (89)	73 (80)	>0.95
Age, y, mean (SD)	69.4 (6.5)	67.6 (8.4)	0.5
Functional MR	9 (100)	87 (96)	>0.95
NYHA class			0.13
I	0	0	
II	0	14 (15)	
III	4 (44)	53 (58)	
IV	5 (56)	24 (26)	
History of MI	7 (78)	61 (67)	0.7
History of stroke	0 (0)	12 (13)	0.5
Chronic kidney disease	5 (56)	37 (41)	0.5
Diabetes mellitus	3 (33)	46 (51)	0.5
Atrial fibrillation	7 (78)	61 (67)	0.7
History of cardiac surgery (CABG or valvular)	1 (11)	16 (18)	>0.95
LVEF, %, mean (SD)	23 (8)	30 (10)	0.03
PASP, mm Hg, mean (SD)	61 (9)	52 (12)	0.09
RV dysfunction	7 (78)	38 (42)	0.07
TR >2+	2 (22)	25 (27)	>0.95

Data are presented as number (percentage) unless otherwise indicated.

Abbreviations: CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RV, right ventricular; TR, tricuspid regurgitation

TABLE 2 Procedural variables and in-hospital outcomes in patients with and without a periprocedural thrombus

Variable	Patients with a thrombus (n = 9)	Patients without a thrombus (n = 91)	P value	
Clips implanted, n, mean (SD)	1.9 (0.3)	2.0 (0.6)	0.6	
Residual MR after the MitraClip implantation, n (%)	MR 1+	4 (44)	–	
	MR 2+	5 (56)	–	
	MR 3+	0	7 (8)	–
	MR 4+	0	3 (4)	0.8
In-hospital complications, n (%)	Death	2 (22.2)	4 (4.3)	0.09
	Ischemic stroke	0	0	>0.95
	Intracerebral hemorrhage ^a	0	1 (1.1)	>0.95
	Myocardial infarction	0	0	>0.95
	Pericardial effusion ^b	0	1 (1.1)	>0.95

a Intracerebral hemorrhage occurred on day 4 after the procedure in a patient on dual antiplatelet therapy and oral anticoagulation. The patient died in the hospital.

b Pericardial effusion occurred 4 hours after the successful procedure and required open-chest surgery in which no apparent source of bleeding was found. The patient was discharged home 7 days after the procedure.

Abbreviations: see TABLE 1

with a visible thrombus and 4 of the 91 patients without a thrombus; $P = 0.09$). In 2 patients with transient thrombus who died, there were no technical complications related to the procedure and the residual MR was mild. The first patient died due to electrical storm on day 14. The second patient developed cardiogenic shock 1 day after the MitraClip procedure and died on day 5 after the procedure. The most likely reason was afterload mismatch following the correction of MR in a patient with very low baseline LVEF (15%). In the whole study population, no ischemic strokes, TIAs, or other embolic complications occurred. All patients with a transient periprocedural thrombus were extubated on the operating table immediately after the procedure.

DISCUSSION The major findings of our study are as follows: 1) the incidence of a transient thrombus attached to the transseptal needle, sheath, or MitraClip device is 9%; 2) in the majority of cases (67%), thrombi form on the transseptal sheath either in the right atrium prior to a transseptal puncture or in the left atrium immediately after the puncture but prior to heparin administration; and 3) the clinical consequences of an periprocedural thrombus are benign.

To the best of our knowledge, the current study is the first to report the prevalence and clinical consequences of thrombus formation during the MitraClip procedure in a relatively large population. So far, only a few case reports have been published.^{8,9} There are studies documenting the incidence of postprocedural thrombus formation on the devices used

for left atrial appendage closure.^{12,13} However, we did not find any publication on periprocedural thrombi during that procedure. Thrombus formation is a well-known complication in patients undergoing ablation for atrial fibrillation. Similar to our study, Bruce et al¹⁴ found thrombi attached to the transseptal sheath in 9% of patients undergoing ablation for atrial fibrillation guided by intracardiac echocardiography. Interestingly, when the anticoagulation protocol was modified and heparin was administered prior to a transseptal puncture, the incidence of thrombus detected on TEE dropped to 0%.¹⁴ However, in our study, 3 of the 9 thrombi developed in patients on adequate anticoagulation.

Given the very low risk of pericardial effusion complicating the transseptal puncture performed under TEE guidance, it may be reasonable to modify the standard anticoagulation protocol developed in the era of a fluoroscopy-guided puncture. There have been no randomized studies on the optimal timing of heparin administration, and the current European Heart Rhythm Association guidelines recommend heparin administration prior to or immediately after the transseptal puncture.¹⁵ The risk of stroke or TIA during the MitraClip implantation is well below 1%.¹⁶ Also, in our study, no periprocedural strokes or TIAs were reported. However, the incidence of clinically silent ischemic lesions related to the procedure exceeds 50%.¹⁷ There is no clear evidence whether these lesions may promote dementia in a longer follow-up. Frerker et al¹⁸ suggested that the use of a cerebral protection device may be a reasonable strategy during the MitraClip implantation. In our opinion, there is a need for a randomized

study on the strategy of early (prior to a transseptal puncture) versus standard (after a puncture) heparin administration during procedures within the left atrium.

Patients with a transient periprocedural thrombus had lower LVEF and tended to have worse right ventricular function and higher PASP than those without a thrombus. This seems to be in line with a report by Orban et al,¹⁹ who identified new thrombus formation within the left ventricular cavity in 3 of the 14 patients with a LVEF of less than 20% within days after the MitraClip implantation.

The optimal management of acute thrombus formation during the MitraClip procedure is unknown. Huntgeburth et al⁸ described a case in which a thrombus formed on a steerable guiding catheter despite adequate anticoagulation and was successfully aspirated. Wolff et al⁹ used periprocedural low-dose thrombolysis for the management of a left atrial thrombus on the transseptal sheath or MitraClip in 2 patients. In our series, watchful waiting with an additional bolus of heparin proved to be safe and effective. No specific changes to the postprocedural anticoagulation regimen were made in patients with thrombi detected during the procedure.

Recently, we published a study on the impact of the learning curve on the safety and efficacy of the MitraClip procedure. We found that the occurrence of a thrombus was similar throughout the whole study period; hence, no impact of the learning curve was observed.²⁰

Limitations The current study was a retrospective analysis based on a moderate number of participants treated by a single operator. There was no central adjudication of clinical outcomes and no core laboratory evaluation of TEE findings. Finally, the actual incidence of thrombus formation during the MitraClip procedure may be even higher as some thrombi may have been undetected because of the TEE resolution.

Conclusions Periprocedural thrombus formation is relatively common during the MitraClip procedure, especially in patients with low LVEF. However, these thrombi are transient and their clinical consequences are benign.

ARTICLE INFORMATION

CONFLICT OF INTEREST JP and PS are the proctors for the MitraClip procedure and received honoraria from Abbott.

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