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The Importance of International Normalized Ratio Monitoring in Patients With Mechanical Pulmonary Valve Prosthesis

Mahta Arbabi[1], Zahra Ghaffarinejad[2], Hossein Dehghani Mohammad Abadi[3], Sajad Erami[4], Anahita Esmaeili[1], Yeganeh Dehghani Mohammad Abadi[4], Maryam Shojaeifard[1]*

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Abstract

Background: The most challenging risk of mechanical valves is thromboembolic events; therefore, life-long anticoagulation therapy is necessary. Anticoagulation therapy should be adjusted for each patient with serial international normalized ratio (INR) monitoring. Due to the small number of patients with a mechanical valve in the pulmonary position, we are facing a lack of information about the therapeutic range of the INR in these patients. We aimed to evaluate patients with a history of pulmonary valve replacement (PVR) who faced malfunction and compare their INR and echocardiographic data at the time of malfunction and 3 months prior.

Methods: In this cross-sectional study, 71 patients who had previously undergone PVR and presented to Shaheed Rajaie Cardiovascular Medical and Research Center with a diagnosis of pulmonary valve malfunction between 2014 and 2021 were included. Patients' INR and echocardiographic data at the time of the malfunction and 3 months before the malfunction diagnosis were gathered from the hospital's registry. IBM SPSS 20.0 was used for data analysis.

Results: In this cross-sectional study, 71 patients with mechanical pulmonary valve malfunction were included. 49.3% (n = 35) were men, 50.7% (n=36) were women, and their mean age was 33.23 (±8.279). The mean INR of all patients 3 months before malfunction and at the time of malfunction was 2.29 (±0.753) and 2.20 (±0.704), respectively.

Conclusion: In this study, most of our patients had an INR below the therapeutic range, both at the time of malfunction and 3 months prior. It emphasizes the importance of patient follow-up and keeping the INR in the therapeutic range.

Keywords: Pulmonary mechanical prosthesis, Echocardiography, International Normalized Ratio

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Introduction

Tetralogy of Fallot (ToF) is the most common cause of congenital cyanotic heart disease. The surgical repair of ToF mainly causes pulmonary insufficiency (PI) (1). PI usually leads to right ventricle dilation in these patients, which can cause arrhythmia and sudden death. Therefore, some ToF total correction (TFTC) patients will need interventions to prevent these outcomes (2, 3).

Pulmonary valve replacement (PVR) is used to treat pulmonary valve dysfunction. PVR aims to restore normal blood flow to the lungs, reduce symptoms, and increase life expectancy (4).

Two main types of heart valves are mechanical and biological. Bioprosthetic valves are usually made from bovine pericardium or porcine aortic valves. The comparison

Corresponding author: *Dr Maryam Shojaeifard, maryam.shojaeifard@rhc.ac.ir*

1. Echocardiography Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran
2. Shaheed Rajaei Cardiovascular Medical and Research Center, Tehran, Iran
3. Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
4. Shahid Sadoughi University of Medical Sciences, Yazd, Iran

↑What is "already known" in this topic:
Life-long anticoagulation therapy is necessary for patients with pulmonary mechanical valves.

→What this article adds:
Due to the lack of information about the therapeutic range of INR in patients with pulmonary mechanical valves, we aimed to emphasize the importance of INR monitoring and specify the range of INR levels to decrease the possibility of prosthetic valve thrombosis resulting in valve malfunction.

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of risks and benefits between these 2 types showed that patients with bioprosthetic valves do not require life-long anticoagulation therapy. However, the risk of structural valve failure is more likely than mechanical heart valves (5).

The significant advantage of mechanical valves is less chance of structural deterioration and longer durability. Although mechanical valves are durable, they are accompanied by an increased risk of thromboembolic events (6, 7). The most challenging event of mechanical valves is the risk of clot formation; therefore, life-long anticoagulation therapy is necessary (8). However, anticoagulation therapy may increase the risk of hemorrhagic events (9, 10).

Different factors play a role in long-term success and freedom from reoperation after PVR. Some common factors are the type of valve, size of the valve, age of the patient, and underlying cardiac disease (11, 12).

Using mechanical heart valves in the pulmonary position has always been a major concern due to high incidents of thrombotic events. However, in recent studies, mechanical pulmonary valve implantation has been suggested for compliant and suitable patients (13, 14).

Owing to the limited therapeutic index of warfarin and the impact of various factors on the international normalized ratio (INR), such as genetic polymorphism in the metabolism of warfarin, drug and food interactions, and patient adherence, the administration and dosage of warfarin therapy should be customized for every patient through repeated INR monitoring. Anticoagulation therapy with a target INR of 3 accompanying low-dose aspirin is suggested to reduce complications of pulmonary mechanical prostheses (15). Most thromboembolic events are related to patients' poor adherence to anticoagulant therapy (16, 17).

We hypothesized that low levels of INR 3 months before malfunction may predict the development of malfunction.

This study aimed to evaluate patients with a history of PVR who faced malfunction and compare the patients' INR and their echocardiographic data at the time of malfunction and 3 months prior.

Methods

This study took place at Shaheed Rajaie Cardiovascular Medical and Research Center, located in Tehran, the capital of Iran. We included all patients presenting with pulmonary valve malfunction between 2014 and 2021. The diagnosis of pulmonary valve malfunction was confirmed for 71 patients who had previously undergone PVR.

Every patient who underwent valve replacement was evaluated regularly with routine laboratory tests and follow-up echocardiography. All patients' information was recorded in the Shaheed Rajaie Heart Center registry. We gathered data about patients with mechanical PVR malfunction over a 7-year period. The INR data at the time of admission due to valve malfunction diagnosis and 3 months prior were gathered from the hospital registry. For the present study, the following parameters from the registry were gathered and used: age, sex, valve subtype, valve size, mean gradient, peak gradient, and INR.

The Ethics Committee of Iran University of Medical Sciences approved this study.

Participants and Mechanical Valve Characteristics

The pulmonary valve of all patients had been replaced with a mechanical valve. Some of the patients had dyspnea at the time of visit and none was febrile.

Three types of valve prosthesis used in our patients were Saint Jude (Saint Jude Medical), Carbomedics (SORIN Group), and On-X (On-X life technologies), and the internal orifice diameter of the prosthesis ranged from 21 to 29 mm.

The failure of the mechanical pulmonary valve was diagnosed by Doppler Echocardiographic evaluation and also confirmed with fluoroscopy procedure. To diagnose valvular malfunction, the echocardiographic parameters were assessed: reduced valve mobility, presence of thrombus, abnormal transprosthetic flow, central prosthetic regurgitation, increased transprosthetic gradients, and reduced effective prosthetic area. Both echocardiography and fluoroscopy assessments of all patients showed the restricted movement of 1 or 2 mechanical valve leaflets.

Doppler Echocardiographic Procedure

All patients were evaluated by echocardiography on their left lateral decubitus position. We utilized a General Electric Vivid S60 phased array system (GE medical systems) equipped with a multifrequency 2.5-3.4 MHz transducer.

Apical, parasternal, long and short axis views were assessed via electrocardiogram signals of desirable quality and a frame rate of 45-55 FPS.

For each patient, we evaluated the pulmonary valve's peak gradient pressure (PPG) and the mean gradient pressure (MPG).

Statistical Methods

SPSS software package Version 20 for Windows (SPSS Inc) was used for statistical analysis. Continuous variables were expressed as means ± standard deviation. Absolute numbers and percentages are used to demonstrate frequencies. Cross tabs were used to describe categorical data.

Results

In this cross-sectional study, 71 patients with mechanical pulmonary valve malfunction were included. Of these patients, 49.3% (n = 35) were men and 50.7% (n = 36) were women, with a mean age of 33.23 years (SD, ±8.27, min =18 years, max = 57 years). Based on the underlying disease, our patients were categorized into 2 groups: TFTC (n = 63 [88.73%]) and PI (n = 8 [11.26%]).

Three types of mechanical valves were seen in patients (Table 1): 51 (71.8%) patients had Saint Jude Medical (SJ) valves, 13 (18.3%) patients had CarboMedics (CM) valves, and 7 (9.8%) patients had On-X valves. Six different sizes of mechanical valves were seen among our patients. The 2 common sizes were 25 and 23, respectively.

The INR evaluation of patients 3 months before the valve malfunction diagnosis is described as follows:

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Table 1. Characteristics of participants

Sex	N(%)
Male	35 (49.3%)
Female	36 (50.7%)
Valve type	
SJ	51 (71.8%)
CM	13 (18.3%)
On-X	7 (9.8%)
Valve size	
S21	4 (5.6%)
S22	1 (1.4%)
S23	25 (35.2%)
S25	34 (47.9%)
S27	2 (2.8%)
S29	5 (7%)
Underlying disease	
TFTC	63 (88.73%)
PI	8 (11.26%)

CM carbomedics, PI pulmonary insufficiency, SJ saint jude medical, S size, TFTC tetralogy of Fallot total correction

36.61% (n = 26) had an INR <2, 43.66% (n = 31) had an INR of 2 to 3, 9.85% (n = 7) had an INR of 3 to 3.5, and 9.85% (n = 7) had an INR >3.5, evaluation of patients at the time of malfunction was as follows: 42.25% (n = 30) had an INR <2, 39.43% (n = 28) had an INR of 2 to 3, 12.67% (n = 9) had an INR of 3 to 3.5, and 5.63% (n = 4) had an INR >3.5.

According to regular evaluation of patients' INR, the mean INR of all patients 3 months before malfunction and at the time of malfunction was 2.29 (SD, ±0.75) and 2.20 (SD, ±0.70), respectively. The frequency of patients with an INR<3 at the time of valve malfunction and 3 months before valve malfunction (Table 2) was 58 (81%) and 57 (80%), respectively. In the comparison of INRs between men and women with valve malfunction, the number of women and men with INRs< 3 was equal (n = 29 [50%]).

According to Doppler echocardiography findings, the mean of pulmonary valve MPG 3 months before the malfunction was 8.971 (SD, ±5.30) and it was 25.183 (SD: ±9.50) at the time of the malfunction. Evaluation of the

Table 2. Values of Patients' INR Based on Valve Type and Valve Size

			Before Malfunction					At the Time of Malfunction				
Valve type	Size	N	INR<2	2 <INR< 2.99	3 <INR< 3.49	INR>= 3.5	Mean INR (±SD)	INR<2	2 <INR< 2.99	3 <INR< 3.49	INR>= 3.5	Mean INR(±SD)
Saint jude	21	2	2 (2%)	0	0	0	1.70 (0.28)	1 (1%)	1 (1%)	0	0	1.85 (0.75)
	23	19	7 (9%)	8 (11%)	3 (4%)	1 (1%)	2.43 (0.70)	10 (14%)	6 (8%)	2 (2%)	1 (1%)	2.09 (0.76)
	25	27	10 (14%)	14 (19%)	1 (1%)	2 (2%)	2.11 (0.64)	13 (18%)	10 (14%)	2 (2%)	2 (2%)	2.18 (0.66)
	27	1	0	1 (1%)	0	0	2.5	1 (1%)	0	0	0	1.4
	29	2	0	0	1 (1%)	1 (1%)	3.55 (0.63)	0	2 (2%)	0	0	2.15 (0.07)
Carbomedics	22	1	0	0	1 (1%)	0	3	0	0	1 (1%)	1 (1%)	3
	23	4	0	3 (4%)	0	1 (1%)	2.75 (0.95)	2 (2%)	2 (2%)	0	4 (5%)	1.86 (0.76)
	25	6	4 (5%)	1 (1%)	0	1 (1%)	1.91 (0.97)	1 (1%)	3 (4%)	2 (2%)	6 (8%)	2.58 (0.63)
	29	2	0	2 (2%)	0	0	2.15 (0.07)	0	1 (1%)	1 (1%)	2 (2%)	2.85 (0.77)
On-X	21	2	1 (1%)	0	0	1 (1%)	2.75 (1.76)	0	1 (1%)	0	1 (1%)	2.80 (1.13)
	23	2	1 (1%)	1 (1%)	0	0	1.80 (0.28)	1 (1%)	1 (1%)	0	0	1.95 (0.49)
	25	1	1 (1%)	0	0	0	1.9	0	0	1 (1%)	0	3.1
	27	1	0	0	1 (1%)	0	3.1	1 (1%)	0	0	0	1.9
	29	1	0	1 (1%)	0	0	2.3	0	1 (1%)	0	0	2.2

INR international normalized ratio, SD standard deviation

Table 3. Values of Hemodynamic Parameters in Patients With Pulmonary Prosthesis Malfunction

			Before Malfunction		Malfunction	
Valve type	Size (mm)	No.	PPG (±SD) (mm Hg)	MPG (±SD) (mm Hg)	PPG (±SD) (mm Hg)	MPG (±SD) (mm Hg)
Saint jude	21	2	14.5 (0.28)	7.5 (2.12)	47 (18.38)	27 (11.31)
	23	19	16.15 (0.70)	9.78 (3.58)	50.31 (16.37)	28.15 (9.59)
	25	27	12.18 (2.73)	7.11 (1.78)	40.59 (15.53)	24.25 (9.13)
	27	1	18	10	35	21
	29	2	16 (8.48)	9 (4.24)	26 (6.36)	15 (4.24)
Carbomedics	22	1	10	6	29	15
	23	4	15.25 (4.34)	8.50 (2.38)	50.75 (13.64)	28 (14.85)
	25	6	19.83 (10.40)	16.16 (15.07)	50 (18.17)	28 (9.57)
	29	2	15.50 (0.70)	9 (1.41)	40 (14.14)	21 (9.89)
On-X	21	2	15.50 (0.70)	9 (1.41)	41.5 (12.02)	26 (14.14)
	23	2	18.50 (2.12)	10.50 (2.12)	42 (0)	23 (1.41)
	25	1	17	7	26	16
	27	1	9	4	50	30
	29	1	17	11	30	12

MPG mean pressure gradient, mm HG millimeter of mercury, PPG peak pressure gradient.

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PPG showed that 3 months before valve malfunction, the mean of the PPG was 14.746 (SD, ±5.26), and it was 43.929 (SD: ±15.60) at the time of malfunction.

The number of patients with increased pulmonary MPG (>20 mmHg) 3 months before the valve malfunction (Table 3) was 2 (2%) cases, and it was 44 (61%) cases at the time of the valve malfunction. In addition, the frequency of patients with the increased PPG (>35 mmHg) 3 months before valve malfunction was 1 (1.4%) and it was 45 (63.4%) at the time of valve malfunction diagnosis.

The mean INR at the time of valve malfunction diagnosis was 2.12 (SD, ±0.09) in patients with SJ valves, 2.43 (SD, ±0.20) in patients with CM valves, and 2.38 (SD, ±0.26) in patients with On-X valves.

Discussion

The aim of this retrospective study was to evaluate mechanical pulmonary valve malfunction, comparing patients' INR and echocardiographic data at the time of the malfunction as well as 3 months before the malfunction diagnosis.

One of the biggest concerns regarding mechanical heart valves in pulmonary position is thrombotic events; therefore, keeping the INR in the therapeutic range is essential. In this study, most of our patients had an INR below the therapeutic range, both at the time of malfunction (81%) and 3 months prior to malfunction (80%).

This data emphasize the significance of keeping the INR in the therapeutic range to prevent thrombotic events. Gholampour et al reported that the mean INR of patients with mechanical valve thrombosis was 1.6 ± 0.4, which was lower than the therapeutic range. These results are also compatible with our study (INR, 2.20 ± 0.704), which emphasizes the importance of observing patients through their anticoagulation therapy and selecting compliant patients (1).

An INR below the therapeutic range 3 months prior to malfunction mainly shows patients' poor adherence to anticoagulant therapy. Preventive measures should be taken as soon as the diagnosis of out-of-range INR in order to delay clot formation and valve malfunction.

In our study, all the valve malfunctions were due to clot formation. Thrombosis is the most common cause of heart valve malfunction. Also, other malfunction causes may be vegetation growth, ring abscesses development, and pannus formation (18).

Several factors can trigger clot formation in mechanical heart valves. Gholampour et al showed that male sex and

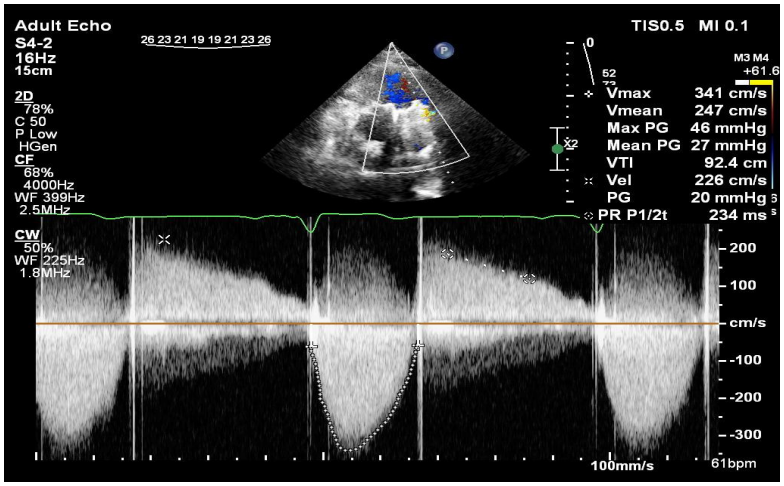

Figure 1. Doppler study of mechanical pulmonary valve malfunction shows increased MPG (27 mm Hg) and PPG (46 mm Hg) and moderate transvalvular regurgitation (pressure half-time [PHT], 234 ms).

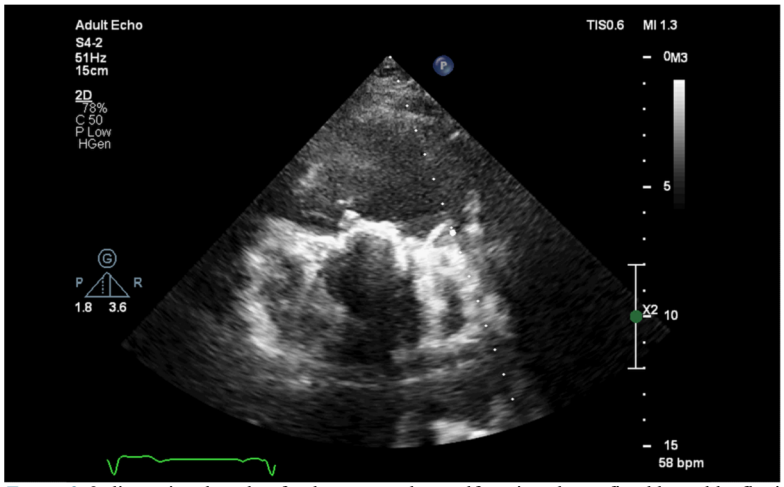

Figure 2. 2-dimensional study of pulmonary valve malfunction shows fixed lateral leaflet in semi-open position.

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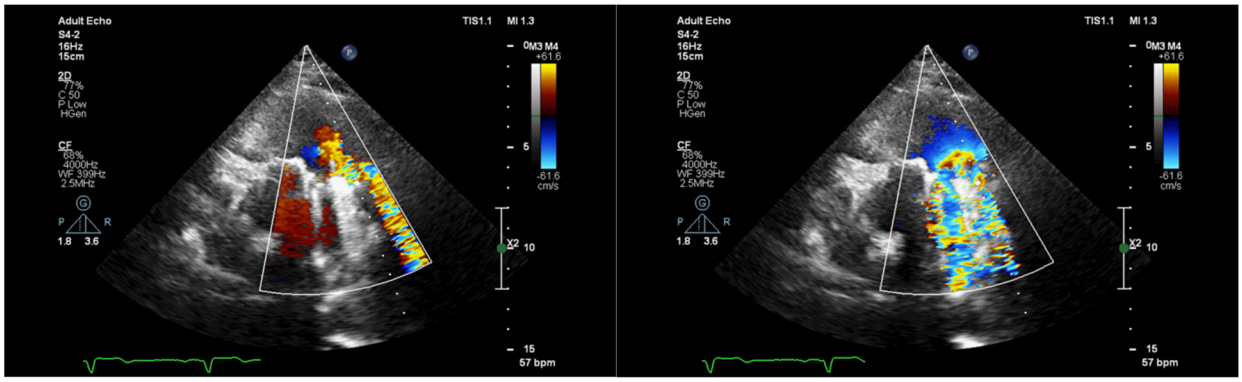

Figure 3. Color doppler study illustrating moderate trans-valvular regurgitation

smaller valve size could cause a malfunction in mechanical heart valves (1). Thus, in an international retrospective study by Pragt et al, a relationship between the inner orifice diameter of the valve and valve thrombosis was not detected (14). In our study, we did not find a correlation between valve size and INR.

The intended range of INR at Tehran's medical centers is currently thought to be between 2.3 and 3.5; nevertheless, our research reveals lower levels of this range 3 months prior to the malfunction and during the malfunction (2.29, 2.20, respectively) (19). Lower levels of INR 3 months before malfunction emphasizes the necessity of tight INR control.

For better monitoring and improving patient outcomes, some studies have suggested INR self-testing. In INR self-testing instead of referring to the hospital for follow-ups, patients use test strips at home that measure blood-clotting time using capillary blood from the fingertip. This method has shown no significant difference with laboratory INR results (20, 21).

In our study, the comparison between the mean of MPG and PPG 3 months before malfunction (8.97 ± 5.30, 14.74 ± 5.26, respectively) with the time of malfunction (25.18 ± 9.50, 43.92 ± 15.60, respectively) showed a significant association between valve malfunction and increased MPG and PPG (Figures 1-3). Sadeghpour et al emphasized this point in their study (2).

Conclusion

Due to the comparatively high incidence of mechanical pulmonary valve thrombosis, patient monitoring and maintaining an INR within the therapeutic range are essential. Also, the lack of evidence about appropriate anticoagulant therapy and the goal INR range for mechanical PVR needs further investigation.

In the end, we cannot decide on a single treatment for all patients with different circumstances. Although most studies are in favor of biological valves in pulmonary position, the fact that they have shorter durability cannot be overlooked and in some circumstances, with an appropriate patient selection, they can actually be a better option. Due to mechanical valves durability, we suggest mechanical pulmonary prosthesis in carefully selected patients.

Abbreviations

INR, International Normalized Ratio; PVR, pulmonary valve replacement; ToF, Tetralogy of Fallot; PI, pulmonary insufficiency,; TFTC, Tetralogy of Fallot total correction; PPG, peak gradient pressure; MPG, mean gradient pressure; SJ, St.Jude Medical valve; CM, CarboMedics valve.

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None.

Authors' Contributions

A.E. was an advisor and responsible for the acquisition of data and manuscript revision. M.S. owned the main concept and design and supervised the study and provided access to crucial research components. M.A. and Z.G. wrote the main manuscript text, prepared tables and figures. H.D. was responsible for the analysis and interpretation of data. S.E. and Y.D. performed data collection. All authors reviewed the manuscript.

Availability of Data and Materials

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

Ethics Approval and Consent to Participate

All phases of the study were approved by the Ethics Committee of the Iran University of Medical Sciences.

Conflict of Interests

The authors declare that they have no competing interests.

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