Original Article

# Texture of Mitral Bioprosthesis, Ventricular Function and Formation of Thrombus. Analysis through Transesophageal Echocardiography and Use of Bioscore

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## Objective

*Facing the hypothesis of participation of mechanical stress as a cause of mitral bioprosthesis dysfunction, we decided to assess the relation of preservation of the texture of the mitral bioprosthesis leaflets with left ventricular function, in addition to the casual formation of thrombus in left atrium in patients with left ventricular dysfunction from the implant of mitral bioprosthesis.*

## Methods

*Forty 40 patients with mitral bioprosthesis through multiplane transesophageal echocardiogram were studied and divided in two groups: with left ventricular dysfunction (FE=0.40±0.09) since the bioprosthesis implant (20 patients: age 47.75±11.10 years old and surgery time 5.3±2.6 years) and with normal left ventricular function (FE=0.73±0.06) since the implant (20 patients: age 49.75±13.59 years old and surgery time 5.7±3 years). The texture of bioprosthesis leaflets was analyzed through a transesophageal echocardiographic score (FACIMT Bioscore): 1) Fusion of leaflets (score 1 to 3); 2) Apposition of tissues (score 1 to 3); 3) Calcium in leaflets (score 1 to 5); 4) Integrity of leaflets (score 1 to 3); 5) Motility of leaflets (score 1 to 4) and 6) Thickness of leaflets (score 1 to 3). The presence of thrombi in left atrium was assessed through multiplane scanning of the left atrium and left atrial appendage in the transesophageal study.*

## Results

*There was no significant difference in the texture of bioprosthesis mitral position between the groups, for the total score (8.7±2.4 vs. 7.9±2.1, p=0.259), and for each analyzed item. A greater incidence of thrombi in left atrium and left atrial appendage was detected in patients with ventricular dysfunction (65% vs. 20%, p=0.004).*

## Conclusion

*The left ventricular dysfunction was not a protecting factor of the texture of bioprosthesis leaflets in mitral position in the tardive post-surgery period. The patients with left ventricular dysfunction showed a more favorable environment for the formation of thrombi in left atrium.*

## Key words

*mitral bioprosthesis, left ventricular function, transesophageal echocardiography, formation of thrombi*

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It is acknowledged that the a pre-implant cardiac index of mitral valve bioprosthesis greater than 2.0 L/min/m$^2$ is an acceleration factor of the structural degeneration process of valve leaflets[1]; such hypothesis suggests the participation of mechanical stress as a cause of bioprosthesis dysfunction[2-4].

Observations from our clinical practice suggest a possible relation between the preservation of the texture of mitral bioprosthesis leaflets and the left ventricular dysfunction. So, left ventricular dysfunction carriers, when submitted to a lower leaflet closing stress, from the implant of mitral bioprosthesis, would somehow show a lower development o degenerative process. Likewise, those mitral bioprosthesis and left ventricular dysfunction carriers, when submitted to a greater stasis environment due to left ventricular dysfunction, could be more predisposed to the formation of intracavitary thrombi.

The introduction of transesophageal modality allowed for overcoming technical difficulties presented to transthoracic exam, especially thanks to the closeness of the esophagus to the left atrium; it allows for the use of higher frequency transducers, under absence of structures that obstruct the heart, which results in cardiac images with better quality of signal and better level of resolution[5,6,7]. The method has a better definition concerning the texture and motility of leaflets, presence of aberrant masses, or a discontinuity of suture of the prosthesis ring[8-10]. Currently we count on the multiplane technology, which offers transducers with the capacity of perform all Doppler modalities, being also multifrequency that produce a continuous of transversal and longitudinal images through the rotation of crystal displaying, which makes easier the view of intermediary images out of the axle among the primary, transversal and longitudinal plans. So, there is an increase in the quality of tomographic images obtained in comparison with those obtained by the biplane transducers[11-14].

The transesophageal method is also relevant in the detection of intracardiac thrombi. The image through transthoracic echocardiography has a limited sensitivity for the atrial thrombus. This is mostly because the thrombus usually forms in the left atrial appendage, which is well viewed through the transesophageal modality[15-17].

The objective of this research was verifying, through multiplane transesophageal echocardiography, if patients with left ventricular dysfunction from the implant of mitral bioprosthesis would have a greater preservation level o the texture of their leaflets and a greater risk of formation of thrombi in the left atrium, when compared to a control group.

## Methods

Forty mitral bioprosthesis carriers for more than two years were studied and followed up at the Day Unit of the Clinical Unit of Valve Cardiopathies of Instituto do Coração. Twenty consecutive patients (average age of 47.7±11.1 years old) were selected for showing left ventricular dysfunction since the implant, which was verified by the fraction of ejection lower than 0.45 (unidimensional MODE – cube method) in the follow-up echocardiograms, and constituted the abnormal ventricular function (AVF) group. Other 20 patients (average age of 49.7±13.6 years old), with normal left ventricular function (fraction of ejection greater than 0.65) since the implant, were gauged and composed the control group of normal left ventricular function (NVF). Patients with fraction of ejection between 0.45 and 0.65 were excluded from the study. The clinical data, including functional class, cardiac rhythm, use of medication and laboratory controls of the anticoagulation level were obtained through the analysis of records (tab. I).

The cardiac rhythm (12-derivation electrocardiogram), the use of anticoagulation therapy (anamnesis data and records) and international normalization ratio (INR – turbidimetric, automated method) were additionally marked down.

The patients were submitted to an echocardiogram using the Toshiba *Power Vision 7000*. From the transthoracic modality the following variables were obtained: final diastolic dimension of left ventricle (FDDLV), final systolic dimension of left ventricle (FSDLV), FE through the Cube method[18] and dimension of left atrium performed at the end of the ejection of the left ventricle, in accordance to the recommendations of the American Society of Echocardiography[19], having been obtained in the unidimensional mode and guided through the bidimensional mode. With the assistance of color flow mapping, the presence of regurgitation of aortic and tricuspid valves was verified. In the presence of regurgitation, it was quantified qualitatively through the color flow mapping. With the use of continuous Doppler in the patients showing tricuspid insufficiency, we obtained the pressure difference between the right ventricle and the right atrium which, added by the estimated pressure of the right atrium, reflects the systolic pressure of the right ventricle and, consequently, the systolic pressure of the pulmonary artery (PPA)[20]. The mitral prosthesis area was calculated using the Continuous Doppler and the methodology of pressure half-time[21]. The gradient through the aortic valve was calculated through the continuous Doppler, by using the modified equation of Bernoulli[22].

**Table I - Clinical and echocardiograhic characteristics of the studied groups**

| Variables | Group | | p |
|---|---|---|---|
| | AVF | NVF | |
| Age (years) | 47.7±11.1 | 49.7±13.6 | 0.742(1) |
| Sex: female | 16 (80%) | 11 (55%) | 0.091(2) |
| Weight (kg) | 68.4±19.4 | 62.2±12.5 | 0.242(1) |
| Height (cm) | 164.0±7.7 | 159.7±8.7 | 0.106(1) |
| Post-surgery time (years) | 5.3±2.6 | 5.7±3.0 | 0.655(1) |
| Diastolic Diameter (mm) | 68.6±12.4 | 47.3±4.9 | 0.001(1) |
| Systolic Diameter (mm) | 57.9±12.5 | 30.7±4.6 | 0.001(1) |
| Fraction of Ejection (cube) | 0.40±0.09 | 0.73±0.06 | 0.001(1) |
| AF Rhythm | 17 (85%) | 13 (65%) | 0.144(2) |
| Sinus | 3 (15%) | 7 (35%) | |
| Left atrium (mm) | 58.2±13.4 | 50.6±8.6 | 0.040(1) |
| Anticoagulanting therapy absent | 15 (75%) | 18 (90%) | |
| Anticoagulanting therapy present | 5 (25%) | 2 (10%) | 0.407(3) |

(1) Descriptive level of probability of the t test of Student; (2) descriptive level of Chi-square test; (3) descriptive level of probability of the exact of Fisher; AVF - abnormal ventricular function; NVF - normal ventricular function; AF - atrial fibrillation.

At the end of the transthoracic echocardiogram, the patient, who had already been told to be fasting for 4h, was signing the post-information consent term for the performance of the multiplane transesophageal echocardiogram. The examination was performed according to an already acclaimed and established method in the clinical practice[11,23,24]. All patients had topic anesthesia, with lidocaine at 10% - based local anesthetic solution, applied in the oropharinx, hard and soft palate.

After the insertion of the transducer in the esophagus and the location of the mitral bioprosthesis, the multiplane (0 to 180º) prosthesis scanning was performed.

Thrombi and the presence of formation of spontaneous contrast in the atria and the left atrial appendage were observed through multiplane scanning.

Stimulated by the well-known applicability of echocardiographic score for decisions of mitral valvoplasty through percutaneous balloon-catheter[25], we developed a transesophageal echocardiography assessment of bioprostheses in mitral position, consisting of six items, which we called FACIMT, (an acronym of fusion of leaflets, apposition of tissues, calcium in leaflets, integrity of leaflets, motility of leaflets and thickness of leaflets – chart I).

The presence of central insufficiency of bioprosthesis or periprosthetics was analyzed through the color flow mapping.

Thrombi and presence of formation of spontaneous contrast in atria and the left atrial appendage were observed through multiplane scanning.

The transthoracic and transesophageal echocardiograms were recorded in VHS videotapes. The FACIMT Bioscore was used in the reading of the videotape and the echocardiographic study items described above were analyzed. The reading of the videotape was done by two observers singly, and the discordant data were solved through a consensus in a third reading done by both observers together.

**Chart I - FACIMT Bioscore**

| Variable levels | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Fusion of leaflets | Normal | Fusion of 2 leaflets | Fusion of 3 leaflets | | |
| Apposition of tissue | Normal | Through filiform image | Through thrombus, vegetation or *pannos* | | |
| Calcium in leaflets | Normal | 1 - 2 calcium points | > 2 calcium points | Segmentar in leaflet | Segmentar in more than 2 leaflets |
| Integrity of leaflets | Normal | Perforation of 1 or more leaflets | Rupture of 1 or more leaflets | | |
| Motility of leaflets | Normal | Diminished in 1 leaflet | Diminished in 2 leaflets | Diminished in 3 leaflets | |
| Thickness of leaflets | Normal | 2-4 mm | > 4 mm | | |

Initially all variables were descriptively analyzed. For the continuous variables that analysis was performed through the observation of maximum and minimum values, and the calculation of means and standard deviations and medians. The absolute frequencies were calculated for the classificatory variables.

For the analysis of the hypothesis of equality of proportions between the two groups, the chi-square test or exact test of Fisher[26] was used. The hypothesis of equality between the two means was verified using the t test of Student[26]. For the total score variable, the non-parametric test of Mann-Whitney[26] was used. The non-parametrical test of Kruskal-Wallis[26] was used in the comparison of the total score among many groups.

The level of significance used for the tests was 5%.

## Results

Both groups were similar in relation to the area of mitral bioprosthesis, presence of central and periprosthetic insufficiency, presence of aortic stenosis, presence of tricuspid insufficiency and the estimated value of systolic pressure of pulmonary artery (tab. II). In AVF group, two cases of periprosthetic insufficiency were detected and they were only visible in the transesophageal study.

The use of the FACIMT Bioscore did not identify any significant difference concerning the total score (8.70±2.39 and 7.95±2.14, p=0.259) between the AVF and NVF groups. An individual analysis of the items of FACIMT Bioscore did not show significant differences (tab. III), as well.

Thrombi in left atrium were found in AVF group in a greater proportion than in NVF. The AVF group showed thrombi in 10, 20 and 35%, respectively, in left atrial appendage, left atrium and left atrial appendage and left atrium simultaneously. Thrombi were found in the AVF group in 10, 5 and 5% distribution (tab. IV).

**Table II - Echocardiographic characteristics of the series**

| Variables | Group | | p |
|---|---|---|---|
| | AVF | NVF | |
| Prosthesis area - cm² | 2.6±0.7 | 2.4±0.4 | 0.378(1) |
| Central insufficiency | | | |
| Absent | 13 (65%) | 14 (70%) | 0.736(2) |
| Discreet | 7 (35%) | 6 (30%) | |
| Periprosthetic insufficiency | | | |
| Absent | 18 (90%) | 20 (100%) | 0.487(3) |
| Discreet | 1 (5%) | 0 (0%) | |
| Moderate | 1 (5%) | 0 (0%) | |
| Aortic insufficiency | | | |
| Absent | 9 (45%) | 7 (35%) | 0.300(3) |
| Discreet | 9 (45%) | 13 (65%) | |
| Moderate | 2 (10%) | 0 (0%) | |
| Aortic stenosis | | | |
| Absent | 19 (95%) | 18 (90%) | 1.000(3) |
| Discreet | 1 (5%) | 2 (10%) | |
| Tricuspid insufficiency | | | |
| Absent | 3 (15%) | 3 (15%) | 1.000(3) |
| Discreet | 10 (50%) | 10 (50%) | |
| Moderate | 5 (25%) | 6 (30%) | |
| Important | 2 (10%) | 1 (5%) | |
| Systolic pressure of pulmonary artery - mmHg | 42.4±10.7 | 39.8±10.1 | 0.485(1) |

(1) Descriptive level of probability of the t test of Student; (2) descriptive level of probability Chi-square test; (3) descriptive level of probability of the exact of Fisher; AVF - abnormal ventricular function; NVF - normal ventricular function.

The spontaneous contrast was present in 85% of AVF group patients and in 60% of NVF group, showing a more favorable statistic tendency to the formation of spontaneous contrast in the AVF group (tab. IV).

The use of anticoagulant therapy was similar in both groups. In the AVF group, 75% of the patients were not using oral anticoagulants and in the NVF group, 90% were not either. Only three had updated international normalization rate (INR) at the time of the study, and none of them was properly anticoagulated. In the NVF group, only two patients had oral anticoagulant therapy, with an INR of 3.4 and 4.7, respectively.

The rhythm of atrial fibrillation was present in 85 and 65% in the patients of the AVF and NVF groups, respectively. There were no statistic differences between those values.

The dimension of the left atrium was significantly larger in the AVF group in relation to the NVF (58.2±13.4 vs. 50.6± 8.6mm, p=0.040).

**Table III - FACIMT Bioscore - Results**

| Bioscore items | Score | AVF Group | NVF Group | p |
|---|---|---|---|---|
| Fusion of leaflets | 1 | 18 (90%) | 20 (100%) | 0.487(3) |
| | 2 | 2 (10%) | 0 (0%) | |
| | 3 | 0 (0%) | 0 (0%) | |
| Apposition of tissues | 1 | 17 (85%) | 18 (90%) | 0.605(3) |
| | 2 | 2 (10%) | 0 (0%) | |
| | 3 | 1 (5%) | 2 (10%) | |
| Calcium in leaflets | 1 | 6 (30%) | 5 (25%) | 0.837(3) |
| | 2 | 11 (55%) | 13 (65%) | |
| | 3 | 1 (5%) | 0 (0%) | |
| | 4 | 1 (5%) | 0 (0%) | |
| | 5 | 1 (5%) | 2 (10%) | |
| Integrity of leaflets | 1 | 20 (100%) | 20 (100%) | - |
| | 2 | 0 (0%) | 0 (0%) | |
| | 3 | 0 (0%) | 0 (0%) | |
| Motility of leaflets | 1 | 11 (55%) | 17 (85%) | 0.166(3) |
| | 2 | 5 (25%) | 2 (10%) | |
| | 3 | 4 (20%) | 1 (5%) | |
| | 4 | 0 (0%) | 0 (0%) | |
| Thickness of leaflets | 1 | 9 (45%) | 12 (60%) | 0.693(3) |
| | 2 | 7 (35%) | 4 (20%) | |
| | 3 | 2 (25%) | 3 (15%) | |
| Total bioscore | | 8.7±2.4 | 7.9±2.1 | 0.259(4) |

(3) Descriptive level of probability of the exact of Fisher; (4) descriptive levels of probability of the test of Mann- Whiney; AVF - abnormal ventricular function; NVF - normal ventricular function.

**Table IV - Echocardiographic aspects related to left atrial thrombosis**

| Variable | Group | | p |
|---|---|---|---|
| | AVF | NVF | |
| Thrombus Absent | 7 (35%) | 16 (80%) | 0.012(3) |
| Thrombus Present | | | |
| LAA | 2 (10%) | 2 (10%) | |
| LA | 4 (20%) | 1 (5%) | |
| LA - LAA | 7 (35%) | 1 (5%) | |
| Total | 13 (65%) | 4 (20%) | 0.004(2)* |
| Spontaneous contrast | | | |
| Absent | 3 (15%) | 8 (40%) | |
| Present | 17 (85%) | 12 (60%) | 0.077(2) |

Descriptive level of probability of the t test of Student; (2) descriptive level of probability Chi-square test; (3) descriptive level of probability of the exact of Fisher; * absent versus present; AVF - abnormal ventricular function; NVF- normal ventricular function; LAA - left atrial appendage; LA - left atrium.

## Discussion

The evolution of bioprostheses is well characterized by means of actuarial curves. The structural changes of clinical repercussion of bioprostheses happen, on average, between 5 and 10 years after their implant, with stenosis due to calcification and inspissation of leaflets, and incompetence due to inappropriate juxtaposition of commissures in calcium infiltration sites[27-30]. It seemed important to us to elaborate a score, in which we could quantitatively document that biological phenomenon of degeneration of bioprostheses, by placing emphasis on the aspects that are more analyzed in the literature, related to leaflets of bioprostheses. We used the FACIMT acronym, which are six distinct letters with which we intend to facilitate the memorization of bioscore items: F for fusion of leaflets, A for apposition of tissue, C for calcium of leaflets, I for integrity of leaflets, M for motility of leaflets and T for thickness of leaflets. So, this way we hope to make use of a suitable diagnosis method that is a homogeneous communication language between clinicians and surgeons.

The average time of implant of bioprostheses was 5.3±2.6 and 5.7±3 years, respectively, for the AVF and NVF groups. There were 10 and 8 patients, respectively, for the AVF and NVF groups with more than five years of bioprostesis implant.

The left ventricular dysfunction was not a protection factor of the texture of leaflets of mitral bioprosthesis, as both the total score and each FACIMT Bioscore item, showed similar in both groups. In the studied literature, there is only one reference on left ventricular function and texture of leaflets[1], in which the acceleration of the dysfunction process of bioprostheses in patients with cardiac index greater than 2.0L/min/m$^2$ was observed, in an attempt of explaining a lower durability of bioprostheses in younger patients.

The individual analysis of the items of FACIMT Bioscore becomes useful: for example, the patient #23 from NVF group and #5 from AVF group had a total score of 12. However, AVF patient #5 had 3 in apposition of tissue item and NVF patient #23 had, in that item, 1. So, AVF patient #5 had thrombosis of one of his leaflets, a situation that determines a specific therapeutic conduct. Therefore, the individual analysis of each item of the score is essential for us to know the real situation of the texture of bioprosthesis leaflets. That situation was witnessed when the echocardiographic score of mitral valve for mitral valvoplasty through balloon-catheter was used. It demonstrated that the subvalve system had a greater prognostic importance for the success of the procedure. However, such hierarchy does not invalidate the routine use of the score[31].

It was only possible to identify the changes in the texture of leaflets with the use of the transesophageal method. The study through transthoracic echocardiography has its own value, especially in the analysis of functional factors related to bioprostheses, such as area, gradients, presence of regurgitations and huge changes of leaflets of prostheses[6,9,32-35]. The transesophageal echocardiography, through the use of higher frequency transducers and through a greater closeness of the analyzed structures, allows us for a fine assessment of the texture of leaflets, a more accurate quantification of the regurgitation level of mitral bioprostheses and the detection of complications, such as periprosthetic vegetations, thrombi and regurgitations[5,6,10,36,37]. In that casuistry, periprosthetic insufficiency was detected in two AVF group patients, which were not detected at the transthoracic echocardiogram, a situation demonstrated by Khanderia et al.[36].

The mitral position of bioprosthesis favors the earlier primary degeneration of leaflets, probably because of a greater closing stress, which takes place in mitral position during the systole[27,38-40]. In mitral position, the opening time of leaflets is up to three times the opening time of aortic bioprosthesis leaflets[41]. The rhythm is sinus, there is a double opening movement of the mitral bioprosthesis leaflets; in a carried out study the relation between the type pf rhythm and the bioprosthesis primary degeneration[42] was not demonstrated. Up to the present moment there is no confirmation in relation to the size of bioprosthesis and the prevalence of primary degeneration of the prosthesis. Regarding sex, there is not a consensus either. The left ventricular function factor did not have any influence in the texture of the bioprosthesis, as demonstrated in this study.

Thrombus in left atrium and its appendage was dominating in AVF group (65% vs. 20%, p=0.004), however there was not a significant difference in relation to the type of rhythm (atrial or sinus fibrillation) and concerning the anticoagulating therapy among the groups studied. It was demonstrated that patients with left ventricular dysfunction show a more favorable environment for the formation of thrombus in left atrium and left atrial appendage. In relation to the size of left atrium, the AVF group showed the left atrium a little larger (58.2±13.4 vs. 50.6±8.6 mm, p=0.040).

Edmunds et al.[43] showed that there was a need for anticoagulation in 40 to 60% of the patients with biological prosthesis in mitral position; the incidence of thromoembolic episodes is greater in the first three months of bioprosthesis implant, the atrial fibrillation increases the risk of thromboembolic complications, the role of the presence of atrial thrombi, the size of left atrium and the history of previous embolic events is not clear yet in the increase of incidence of thromboembolic events. The atrial fibrillation is the main factor identified in the literature as responsible for the increase of risk of systemic thromboembolism in patients with mitral valvopathy[44-47]. Reports in the literature show a lower incidence of thromboembolic events in patients with bovine pericardium or dura mater bioprostheses in comparison with porcine biosprostheses[48-50].

The size of left atrium, age lower than 60 years old, possibly the left ventricular dysfunction and hypertension add risks to thromboembolism in patients with atrial fibrillation[51]. Those patients must have prolonged anticoagulating therapy, by keeping an international normalization rate between 2.0 and 3.0. For probably social reasons, most of our patients did not have their coagulation properly controlled.

Spontaneous contrast inleft atrium and left atrial appendage was more frequent in AVF group. However, such datum did not have statistic significance (85% vs. 60%, p=0.077). We must menton that the presence of spontaneous contrast, atrial fibrillation and intra-atrial septum aneurysm are independent positive factors, predictors of the presence of thrombi in left atrium and cerebrovascular events. In addition, the dilation of left atrium and cerebrovascular events are positive independent predictors of the presence of spontaneous contrast and thrombi in left atrium[52].

We concluded that the left ventricular function was not a determinant factor of the evolution of the texture of mitral bioprosthesis leaflets, FACIMT Bioscore was useful in the evolutive analysis of the texture of mitral bioprosthesis leaflets and the left ventricular dysfunction associated mitral bioprosthesis to a greater incidence of thrombi formation in left atrium and left atraial appendage.

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