Role of the Echocardiography in Atrial Fibrillation

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Atrial fibrillation affects to 0.5 % of the population and it is generally more frequent in men than in women (1), with an overall prevalence of 0,4% the general population (2,3,4) affecting 2,2 million Americans. The prevalence of AF increases markedly with advanced age, affecting to 0.2 % of the population between 25 and 34 years old, 2% to 5% of those older than 60 years old and 10% of those older than 80 years old (5,6,7).

The frequent complications of AF are the thromboembolism and the stroke, resulting from the bleeding stasis, the frank increase of platelet aggregation and the coagulation, which are factors that help the formation of atrial thrombus, base of the complications descript before (8,9).

It was observed in the Framingham Heart Study and AF respectively 4.2% and 4.5% of tromboembolismo and Stroke (10,11), and taking a particular sub-group, the nonrheumatic AF, in the analysis of five randomized works (AFASAC, SPAF, BAATAF, ACFCA, SPINAF) it was agreed that the risk of Stroke in this group is of 5% (12,13) to such point that they recommend to anticoagulate patients with chronic or paroxysmal AF with hypertension, diabetes, structural cardiopathy and people older than 60 years old.

ROLE OF TRANSTHORACIC ECHOCARDIOGRAPHY

The transthoracic echo is really necessary for the initial evaluation and management in patients who have a first episode of AF.

Several are the disorders associated with AF: some of the most important are mitral valve disease, left ventricular hypertrophy, focal wall motion abnormalities suggestive of myocardial infarction, left ventricular dysfunction, and others which are diagnosed fast and precociously by echocardiography. The information on left ventricular systolic function helps to guide the choice of pharmacologic therapy for ventricular rate control in chronic AF.

The absence of structural cardiac pathology, identifies a sub-group of patients with stratified AF to administer warfarin vs aspirin (14), as well as it demonstrated the little sensitivity of the transthoracic echo to investigate thrombus, in the left atrial and fundamentally in the left atrial appendage, if we compare with the TEE (15). However the transthoracic echo is very useful to evaluate the dimensions, area and volumes of the left atrial, showing their changes in the evolution of AF, to such point that the left atrial enlargement in the chronic AF is a constant (16,17,18,19). Echocardiography study data has demonstrated that the chronic AF is associate with enlargement of the left atrial and that the conversion to a sinus rhythm and his support is inversely proportional to this process (20,21,22,23,24,25). W. Mannig et al, believe that with only just the criterion of left atrial enlargement the decision from do or not the cardioversion to a patient with AF cannot be taken, but the association of left atrial enlargement major than 6 cm, in more than one year of duration, in a context of rheumatic valve disease, reduce the possibilities of a successful cardioversion and maintenance of the further sinus rhythm are poor (26).

TEE-GUIDED CARDIOVERSION

Cardioversion in patients with AF to normal sinus rhythm has the objective to improve symptomatically the patient and his functional class, to avoid the electrical remodeling and to prevent the embolic accidents.

The Cardioversion of patient with atrial fibrillation > 48 hs. has an inherent risk of thromboembolism accident, by pre-existing thrombus in the left atrial appendage (27). Two are the raised strategies of cardioversion to this group of
patients:

1- The conventional therapy to anticoagulate three weeks before and four weeks after the cardioversion to decrease the risk of embolic accidents (28).
2- The TEE-guided cardioversion with short-term anticoagulation has been proposed as an alternative strategy.

There is confusion and controversy between both proposals because the lack of sound clinical trial data on Stroke frequency and about the cost-effectiveness of both strategies.

Since the early 1990's the TEE-guided approach with short term is used, the following conduct has been suggested.

1) Detect left atrial appendage thrombi, site of the origin of the embolic accident post cardioversion.
2) In a group of patients without thrombus in the TEE-guided cardioversion, the absence of thrombus would shorten the period of anticoagulation and lower the corresponding risk of bleeding complications
3) The early cardioversion in this strategy would have more possibilities of reverting the AF and maintaining normal sinus rhythm.

In contrast, the defenders of the conventional strategy postulate the disadvantages of the TEE-guided strategy (29,30) basing on the following fact: It is necessary specialized medical staff to carry out the practice, it is a semi invasive method, that small thrombus can be messed by TEE, and finally that not all the institutions have the suitable equipment.

In the absence of randomized data to guide the clinician, concrete proposals of several institutions have been considered, like the American College of Chest Physicians (ACCP), American College of Cardiology, American Heart Association (31) and the ACC/AHA echocardiography (32). Those institutions have suggested that the TEE-guided approach is a strong alternative. Recently, also the ACUTE supports this proposal, it is a multicentric randomized study to compare both strategies, that involved more than 1200 patients, in where this approach is strongly considered (33,34).

CARDIOVERSION AND STROKE

Classically the electrical or chemical cardioversion (35) has been used to restore the sinus rhythm in this arrhythmia, but unfortunately the risk of thromboembolism accident in patients without previous anticoagulation to the procedure is from 0% to 5% in the first week after cardioversion (36,37) not being found significant difference between the chemical cardioversion vs the electrical one (1.2 ±1% vs 1.4±1.35).

CARDIOVERSION WITH CONVENTIONAL ANTICOAGULANT STRATEGY

In the last decade the ACCP recommended guides for the management of the anticoagulation in this group of patients (38,39) suggesting that patients with atrial fibrillation with more than 48 hs. of evolution should receive oral anticoagulation three weeks previous and four weeks after to the electrical or chemical cardioversion, the idea of three weeks before anticoagulation are sustained in a study suggesting that at least 14 days are needed for fibroblastic infiltration and stabilization of a thrombus in the left atrial appendage (40) and the anticoagulation for four weeks is based on studies that followed the recovery of the atrial function with the Mitral Doppler Flow evaluation where they observed that the recovery of the transmitral atrial wave (A) took place between three and four weeks post electrical cardioversion, (41) recommending oral anticoagulation with a INR from 2 to 3, Table 1.
Unfortunately the conventional strategy has its limitations, there are not controlled trials that show their efficacy and the following of the of the daily anticoagulation is difficult specially in old people. To delay the cardioversion three or four weeks, can diminish the possibility of a successful cardioversion and maintenance the sinus rhythm helping the process of electrophysiologic remodeling (47) there is also evidence that the recovery of the atrial function demonstrated with the recovery of the Mitral atrial (A)wave depends on the duration of the arrhythmia and its moment of cardioversion (48,49), prolonged anticoagulation increases bleeding risk in minor or major complications (50,51,52,53,54,55), and has been demonstrated that the patients older than 65 years are the more inclined to bleeding (56) this elderly patients may especially benefit from TEE - guided approach to cardioversion with brief anticoagulation

**ROLE OF TEE IN DETECTION OF THROMBUS**

The TEE is considered the procedure of choice for detecting left atrial appendage and left atrial cavity thrombi (57,58) and TEE-guided cardioversion has been proposed as an earlier and safer alternative approach to the conventional strategy (59,60). Table 2, shows Studies about the incidence of the thrombus and Embolic Events.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Use of warfarin for 3 to 4 weeks before cardioversion may lower the stroke rate from 5.6% to a very low stroke rate of &lt;2%</td>
<td>Delaying cardioversion to normal sinus for 3 to 4 weeks potentially decreases functional capacity</td>
</tr>
<tr>
<td>Relatively easy to administer with a regular monitoring of INRs.</td>
<td>Prolonging treatment for 7 to 8 weeks increases the risk of bleeding complications</td>
</tr>
<tr>
<td>Suitable for community hospitals</td>
<td>not followed by routine clinical practice, especially in the elderly</td>
</tr>
<tr>
<td>The conventional approach has withstood the test of time since 1960</td>
<td>Patients who are at the highest risk for developing systemic embolization who should receive more prolonged or intensive anticoagulation are not routinely identified</td>
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INR: international normalized
Having the method a high degree of sensitivity and a specificity varying from 93% to 100%, it can detect thrombi in both the left atrium and left atrial appendage (61,62). In addition, TEE is uniquely suited to observe spontaneous echocardiography contrast, (Smoke effect) which is consider to be a substrate for thrombus formation and systemic embolization. This effect would be produced by the bleeding stasis favoring erythrocyte aggregation in low shear rate conditions, with slow and circular movements which can be detected by TEE and it was already mentioned like a risk factor for thromboembolism events (63).

The transthoracic echo has a low sensitivity between 0,1%and 3,5% to detect this phenomenon between and only in special circumstances like severe mitral stenosis with chronic atrial fibrillation and left atrial enlargement, but with the coming of TEE the detection of this phenomenon considerably increased from 10% to 20% in the patients studied for different causes and clinical situations (64) phenomenon that it has been accompanied by low velocities in the left atrial appendage. This theory sustains the possibility that the phenomenon is produced by bleeding stasis in the atrial. With this theory and adding the systolic dysfunction of the appendage we can stratificate the patients with atrial fibrillation in two groups (65):

1) High risk of embolic events with velocities in the appendage minor than 25cm /seg with an incidence contrast echo of the 80%.
2) Low risk with major velocities of 25cm/seg with low incidence of contrast´s echo.

Sigel et al studied the mechanism of the spontaneous echos contrast demonstrating that in delayed sanguineous conditions the erythrocyte line up parallely between them favoring platelets aggregation, this phenomenon increases the fibrinogen. In these particular cases, the increase of fibrinogen major than 360 mg/dl had a significantly higher rate of thromboembolism in patients with chronic AF (66).These paroxysmal AF presents intermediate levels of fibrinogen (67) comparing with chronic AF and controls, and so in this group the possibility of embolic events is minor.

The trials demonstrate the sensitivity of the TEE in detecting atrial thrombus. However there are some cases in which in the TEE before the electrical cardioversion there were not thrombus but then, it was consigned embolic events during the first week. This patients were not anticoagulated or they were subtherapeutically anticoagulated according to INR proposal. A Klein (68) demonstrated that the thrombus exclusion in the TEE precardioversion does not predict embolic events postcardioversion. This phenomenon which is produced by the atrial and his appendage stunning, is demonstrated with the following of the atrial function recuperation with the mitral flow doppler watching

<table>
<thead>
<tr>
<th>Study</th>
<th># patients</th>
<th>Atrial Thrombi</th>
<th>Embolic Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orsinieli (1993)</td>
<td>39</td>
<td>9 (23%)</td>
<td>1 (2.56%)</td>
</tr>
<tr>
<td>Stoddard (1996)</td>
<td>206</td>
<td>37 (18%)</td>
<td>0</td>
</tr>
<tr>
<td>Klein (1997)</td>
<td>126</td>
<td>7 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Weigner (1998)</td>
<td>466</td>
<td>64 (13.9%)</td>
<td>1 (0.21%)</td>
</tr>
<tr>
<td>Grimm (1998)</td>
<td>417</td>
<td>28 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Corrado (1999)</td>
<td>123</td>
<td>11 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>ACUTE</td>
<td>619</td>
<td>79 (13.6%)</td>
<td>5 (0.81%)</td>
</tr>
<tr>
<td>Total</td>
<td>1,996</td>
<td>235 (11.8%)</td>
<td>7 (0.35%)</td>
</tr>
</tbody>
</table>

**Table 2.**
Summary of studies of transesophageal echocardiography (TEE)- Guided Approach to Cardioversion of Atrial Fibrillation, Including the Incidence of Thrombus by TEE and Recorded Embolic Events

**ACUTE: Assessment of Cardioversion Using Transesophageal**
the recuperation of the A wave of the mentioned flow and the relationship E/A, observing that the recuperation of the atrial function was produced generally between 20 and 30 days posterior to the cardioversion. So it is recommended anticoagulation for 30 days to the electrically cardioverted patients demonstrating that in the pharmacologically cardioversion, the left atrial function was recovered in the first 24 hs (69,70). Finally the atrial stunning is directly proportional to the duration of AF. These appreciations emphasize the fact that the TEE shortens the previous time of anticoagulation, stratifies the risk in patients with high and low risk according to the thrombus presence criteria, the appendage velocities and the echo contrast presence and confirm the anticoagulation to all the post cardioverted patients.

The resolution of the thrombus in these group of patients detected by TEE before cardioversion is a controverted point. Table 3 shows the different studies about these. The mechanism in embolic accidents diminution is based in the thrombus organization and adherence to the atrial wall. The resolution of the thrombus resolved after three to four weeks of anticoagulation has varied widely from 89% (88), to 50% (76,77) to 5% in different study (73) These discrepancies may be caused by many factors: different patient characteristics, duration of AF and diagnostic criteria for thrombus detection., nevertheless the thrombus detection portends a bad outcome, knowing that in the following there is a risk of stroke or embolic events or of 10,4% per year and death risk of 15% (73).

<p>| Table 3. Previous Studies Documenting Resolution of Atrial Thrombus by Serial Transesophageal Echocardiography |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th># patients</th>
<th>Frequency of thrombus</th>
<th>Anticoagulation duration</th>
<th>Atrial thrombus Resolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stoddard 1995 (106)</td>
<td>21</td>
<td>NA</td>
<td>5 to 17 weeks</td>
<td>9/21 (43 %)</td>
</tr>
<tr>
<td>Collins 1995 (120)</td>
<td>18</td>
<td>NA</td>
<td>4 weeks</td>
<td>16/18 (89 %)</td>
</tr>
<tr>
<td>Tsai 1997 (121)</td>
<td>8</td>
<td>10%</td>
<td>NA</td>
<td>6.8 (75 %)</td>
</tr>
<tr>
<td>Klein 1997 (4)</td>
<td>7</td>
<td>13%</td>
<td>6 weeks</td>
<td>3/7 (43 %)</td>
</tr>
<tr>
<td>Jaber 2000 (122)</td>
<td>164</td>
<td>NA</td>
<td>6,7 weeks</td>
<td>131/164 (80 %)</td>
</tr>
<tr>
<td>Corrado 1999 (116)</td>
<td>11</td>
<td>11%</td>
<td>4 weeks</td>
<td>9/11 (82 %)</td>
</tr>
<tr>
<td>NA= not available: TEE: transesophageal echocardiography</td>
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CARDIOVERSION GUIDED FOR TEE -EVIDENCES

1) Nonrandomized studies:

An important (71) nonrandomized study has demonstrated that the TEE-guided cardioversion is always feasible and safe when the atrial thrombi is excluded. The investigators detected atrial thrombi in a 15% of the studied patients and in the following there were not declared embolic events.

In a more recent study of 466 patients done by the same investigators (72) thrombi were detected in 13,9% and 88% of the patients with out thrombi were converted successfully to sinus rhythm. The patients who in the previous TEE did not show thrombus, comparing a variable that was the duration of the arrhythmia, detected that the ones who had of AF lasting less than three weeks, were able to maintain the sinus rhythm in one year and that patients with AF longer than three weeks, lost this rhythm (81% vs 60% p=0,005). Another investigators have described similar results with this strategy (73,74).

2) Randomized Studies:

A) The ACUTE pilot study was the first prospective, randomized study with the object to compare the conventional strategy of anticoagulation the three previous weeks and four following weeks to the cardioversion vs the TEE-guided
cardioversion (75). 126 patients were enrolled, 62 for the TEE-guided strategy and 64 for the conventional anticoagulation approach. The primary end point events were ischemic stroke, transient ischemic attack and systemic embolization for a four-week postcardioversion period.

The following conclusions were reached: both strategies are safe and feasible; embolic accidents in the TEE-guided strategy were not registered when thrombus were excluded previously. Atrial thrombi were detected with this therapy in the 13% of the patients. Notably, cardioversion was done much earlier with this strategy than with the conventional anticoagulation (0.6 weeks vs 4.7 weeks). Accordingly, the incidence of clinical instability and bleeding tended to be less in the TEE-guided group (1.6% vs 7.8%).

B) ACUTE multicenter trial. (76,77,78,93,94) Figure 1. It was a study involving patients with AF longer than 48hs of evolution to compare both strategies, the TEE-guided vs the conventional anticoagulation. 70 clinical international sites participated over a five-years period with the objective of involving 3000 patients. It was suspended in 1222 patients for the obtained results and the slowness of the recruiting. It was presented in the ACC 2000 in the scientific sessions.

![Fig. 1 - TEE-Guided Cardioversion](image)

Of the 1222 randomized patients, 619 were assigned to the TEE-guided arm. Thrombus were detected in the 14%, resulting in postponement of the cardioversion. The TEE-guided strategy allowed early (meaning three days) successful cardioversion in 81% of the patients without thrombi. There were two patients with embolic events, which were associated with subtherapeutic anticoagulation and AF recurrence.

In the 603 patients assigned to the conventional arm only 333 (55%) had electrical cardioversion and 80% were successful. Among 270 patients who never underwent electrical cardioversion, 127 patients went through (47%) spontaneous or chemical cardioversion. In contrast, 143 patients never had cardioversion for different reasons and 5% of the patients crossed over to the TEE-guided strategy.

In the final conclusions of the ACUTE, according to the analysis of the end point of stroke, transient ischemic attack and peripheral embolism there were not significant differences between both planned strategies (0.81% vs 0.50%). However, there was a significant difference in the composite end point of major and minor bleeding between the conventional strategies vs the TEE guided arm (2.9% vs 5.5%; p=0.02).
ACUTE arrived to concrete conclusions

1- The aggregate embolic event rate for both arms of the study was much lower than expected (0.7%).
2- The bleeding complications were higher than expected (4.2%) observing that in the TEE-guided cardioversion with short term anticoagulation the bleeding complications were minor.
3- There was no significant difference in 8 week maintenance of normal sinus rhythm, cardiac deaths or cardioversion-related deaths between the two arms of the study.

The final result and the message that the ACUTE gives is that the TEE-guided cardioversion with short term anticoagulation is a safe and a trustworthy alternative to the conventional cardioversion strategy to anticoagulate a patient seven weeks (95, 96). Anyway, this conduct, the TEE-guided approach with short term anticoagulation has advantages and disadvantages that are showed on the Table 4.

COST-EFFECTIVENESS

The absence of publicized data about the real cost of the use of both strategies, give the institutions the chance to decide the of use one of the two alternatives.

Seto TB of the group of W. Manning (79) has analyzed the cost effectiveness of three alternatives inpatients with atrial fibrillation during a year. They suggested the following alternatives:

1- The conventional strategy to anticoagulate patients with AF three weeks before and four weeks after the cardioversion and using the transthoracic echocardiography as a method of investigation.
2- Start initially TTE (transthoracic echo) followed by TEE and early cardioversion if an atrial thrombus is excluded by TEE.
3- Initial TEE and early cardioversion if no atrial thrombus is detected, the third option was the least costly.

Recently, this same group (80) has extended their model in that group of patients in which it was detected thrombus precardioversion, and then it was carried out a new TEE to observe the resolution of the same, demonstrating that it was less costly the conventional strategy to anticoagulate seven weeks a patient.

PREDICTION OF A SUCCESSFULL CARDIOVERSION

Initially there was a lot of enthusiasm about the use of left atrial appendage areas and flow velocities by pulsed wave doppler echocardiography to predict the immediate and long term success of cardioversion (81, 82, 83) However, the results have been variable to data in this point (84, 85). In one study it was taken into account the left atrial appendage emptying velocity higher than 19 cm/seg, the maximal atrial appendage area and duration of the arrhythmia to the success of the cardioversion. Another study (86) showed that emptying velocity major than 35 cm/seg was not predictive of either the success of cardioversion and his maintenance of the following year.

In general these data suggest that if appendage velocity is more than 20 cm/seg predict a decrease of the success of the cardioversion and maintenance of normal sinus rhythm, anyway in this point there are already questions to resolve.

ACTUAL STATE OF THE STRATEGY GUIDED FOR TEE

The medicine based in the evidence shows that TEE-guided strategy is today a strong alternative in patients with AF major than 48 hours, if we compare it with the conventional strategy. Stroke from 1 %-5% and the clinician can utilize either management strategy in their daily practices, to convert patients with AF major than 48 hours of evolution depending on the individual patient and the hospitable contour.

From the available evidence there are certain patient subgroups that may benefit from the TEE-guided cardioversion.

1- Inpatients with atrial fibrillation minor than four weeks duration, particularly for high risk patients
(such as those with congestive heart failure, previous embolism or hemodynamic instability) who recuperating the sinus rhythm, would be better (87).

2- High risk patients identified with left atrial thrombi, slow velocities of the appendage and echo contrast, it is necessary to repeat the TEE to observe the thrombus resolution

3- Patients with low probability of thrombus and low risk of embolic events (88), the TEE can short the time of precardioversion anticoagulation

4- This strategy can improve the outpatient management with the use of low molecular weight heparin as a bridge therapy to warfarin, previous absence of thrombus in the TEE to the cardioversion (89).

Recently, there were trial publications with the object of stratificate the patients with TEE. Roiler A, has studied 162 low risk patients with AF and atrial flutter lasting longer than 48 hours (91,92) and safely perform immediate cardioversion with the use of low molecular weight heparin (dalteparin) to bridge warfarin therapy. These low risk patients maintained sinus rhythm better than the patients with prolonged precardioversion warfarin therapy (90).

Here an some trials which have not been publicized yet. The ACUTE II compares the TEE- guided strategy using low molecular weight heparin vs. the standard intravenous unfractionated heparin in patients with AF lasting longer than 48 hours; trials in progress involving direct thrombin inhibitors and glycoprotein IIa/IIIb antiplatelet therapy for thrombotic prophylaxis of patients with AF. Finally, there is also growing interest in the use of chemical cardioversion with ibutilide or dofetilide and TEE-guided cardioversion (91,92).

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