Atrial fibrillation: rhythm control *versus* rate control

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the clinical practice with increasing prevalence due to the population progressive ageing. It is an important cause of morbidity and mortality, especially arising from cerebrovascular accidents and heart failure.

The two main management concerns are to restore and/or maintain sinus rhythm with pharmacologic and/or electrical cardioversion, or to achieve satisfactory rate control, both with antithrombotic therapy.

Some studies have reported similar reduction of morbidity and mortality when either treatment is applied.

When choosing the appropriate treatment there are a few factors which must be taken into account such as the nature, intensity and frequency of symptoms, comorbid conditions, patients' preferences and the response to the treatment.

This review will therefore focus on the potential risks and benefits of these two strategies, identifying the better candidates for each strategy as well as showing the current guidelines about these issues.

Keywords: atrial fibrillation, rhythm control, rate control.

INTRODUCTION

Atrial fibrillation is one of the most common cardiac dysrhythmias in the clinical practice. In this entity, the ventricular response is variable with a quick and uncoordinated atrial contraction leading to the degradation of the mechanical function.

AF is not a benign situation as it can result in serious complications, including thromboembolic phenomena and congestive cardiac insufficiency (CCI).

It is therefore important a quick recognition and implementation of therapeutic strategies in the sense of reducing AF possible complications.

AF therapy includes essentially two steps: AF conversion to sinus rhythm or control of the ventricular response, both strategies associated with antithrombotic therapy.

This article aims to assess the scientific evidence related to the controversial AF therapy: rhythm control versus ventricular rate control. It aims to discuss the advantages and disadvantages of each strategy, to identify the patients benefiting more from approach or another assessing the current international recommendations on this subject.

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CLASSIFICATION

Throughout the times several great AF classification systems have been proposed. At present, it is classified according to its duration and persistence.

According to the current recommendations of the American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC), the AF can be classified in acute or chronic and within the latter in paroxysmal, persistent, permanent or isolated. [1] When fibrillation episodes regress spontaneously, we are before a paroxysmal AF. Usually they do not last over 48 hours and they do not remain over seven days.

The expression persistent is used when the AF lasts over seven days and only reversed after electric or pharmacological cardioversion.

When the AF is present over one year, or when cardioversion is not successful, AF is called permanent.

The concept of an isolated AF is applied to individuals under the age of 60, without clinical or echocardiographic signs of cardiopulmonary disease and without any other risk factors known for AF. [2]

EPIDEMIOLOGY

The population progressive ageing, in developed countries, the growing prevalence of chronic pathologies as high blood pressure, ischaemic cardiopathy and cardiac insufficiency (CI), have led to a dramatic increase on AF prevalence. Epidemiology data points out to AF prevalence from 0.4 to 1% in the general population, [3] increasing to 8% in the elderly aged 80 years old or more. [4] Within the general popula-

tion, the male gender is the most affected, with an incidence 1.5 times higher than the female gender. [5]

It is estimated that 2.3 million individuals in North America and around 4.5 million in the European Union suffer of paroxysmal or persistent AF. [1] Until 2050, forecasts pointed to the existence of 5 to 15 million people in the USA with AF. [3,6]

Due to its high prevalence in the population, to the need of therapies which are often chronic with long-term hospitalizations, AF represents a fairly expensive public health issue.

In spite of the great advances in its treatment, AF remains an important cause of cardiovascular morbidity and mortality especially regarding the cerebral vascular accidents (CVA) and cardiac insufficiency. Framingham study shows an annual risk of CVA due to AF of 1.5% in patients from 50 to 59 years old, a value increasing to 23.5% in patients over the age of 80. On the other hand, the risk of congestive cardiac insufficiency in patients with AF ranges from 3 – 3.4%. [7,8]

Mortality rate in individuals with AF is around the double in comparison with individuals in sinus rhythm, however it is related with the underlying cardiac disease severity. [8]

RISK FACTORS

While in underdeveloped countries, the rheumatic valvular disease is still an important aetiology factor for AF, in western countries AF is mainly associated with high blood pressure, ischaemic neuropathy, degenerative mitral valvular insufficiency, congestive cardiac insufficiency, diabetes mellitus and to the atherosclerotic and degenerative process of ageing. [9]

Certain reversible conditions can also increase the risk for AF, namely alcohol consumption, smoking, hyperthyroidism, some pulmonary pathologies, and thorax surgeries, among others (*Table I*).

Recent studies also value obesity, possibly due to the left auricular dilation; sleep apnea; diastolic dysfunction; inflammatory conditions with CPR increase and psychological stress as predisposing conditions to AF. [10]

Neurogenic AF associated to the increase of the vagal tonus or the sympathetic tonus is a risk factor for AF as well.

Although rare, some cases of hereditary AF associated to anomalies on the 10th chromosome have been described.

Isolated AF and therefore, without an identifiable risk factor, should not be forgotten as it represents 30 to 45% of paroxysmal AF and 20 to 25% of persistent AF. [11]

CLINICAL MANIFESTATIONS

Electrocardiographic records and some screenings have demonstrated that symptomatic AF can alternate with periods without any symptoms at all.

The most often related symptoms include palpitation, dyspnoea, chest pain, faintness feeling and syncope. Such symptomatology is usually associated to very high ventricle rate, therefore in most patients the control of the ventricle response is enough to minimize the symptoms. In other occasions, the great variability of the ventricle response or the low cardiac output can produce the above-mentioned symptomatology.

Asymptomatic or silent AF accounts for 20 to 30% of all cases, being often diagnosed only during a routine medical check-up. [12] In the Framingham study of patients with ischaemic CVA associated with AF, it was verified that in 24% of cases, AF diagnosis occurred when an acute CVA took place. [13]

AF has wide repercussions in the quality of life of patients, affecting the physical, functional, mental and social condition. Even patients with silent AF report some malaise in the general quality of live when compared with individuals without AF. [14]

Female gender patients and youngsters with AF seem to experience more symptomatology when compared with male and elderly patients with AF, although the latter present quite often, associated co-morbidity. [15]

AF THERAPY

Atrial fibrillation current therapy strategies aim the following targets:

- AF conversion at sinus rhythm;
- Maintenance of the sinus rhythm;
- Control of the ventricle rate;
- Prevention of thromboembolic phenomena.

The initial therapy for AF is not well established, and doubts remain regarding the strategy to be adopted: to revert to sinus rhythm or to control the ventricle response.

It seems reasonable to choose, whenever possible, the reestablishment of the sinus rhythm as it constitutes a primarily change, but the control of the

TABLE I

Underlying or precipitating causes of Atrial Fibrillation

Type of dysfunction	Examples
Cardiovascular	Coronary disease Valvular pathologies Systolic diastolic dysfunction High blood pressure Myocardial infarction Cardiac insufficiency Rheumatism cardiopathy Pericarditis Endocarditis/myocarditis Congenital cardiopathy Sinus node disease Cardiac tumors Supraventricular arrhythmias Post-cardiac surgery Wolf Parkinson White syndrome
Metabolic	Thyrotoxicosis Phaeochromocytoma Hydroelectrolytic unbalances Hypothermia Non-cardiac post-surgery Alcohol Simpatico-mimetic drugs
Respiratory	Pneumonia Pulmonary carcinoma Pulmonary thromboembolism Trauma
Others	Vagal AF Adrenergic AF Intracranial hemorrhage Isolated AF

ventricular response has been suggested as a good therapy alternative.

Regardless of the strategy adopted, it is a consensus the need to administer anti-coagulants to all AF patients of non reversible cause, especially in the presence of other risk factors for CVA.

The decision to select antithrombotic therapy and the identification of patients benefiting from it, can be based on the rating system for an embolic risk $CHADS_2$ (Acronym in English for Cardiac Failure, Hypertension, Aged > 75, Diabetes, Stroke [Double]).[16]

$CHADS_2$ score assesses the individual risk ischaemic CVA in patients with non-valvular AF resulting from the revision of all classification proposed previously. It is formed allocating a value in the presence of each one of the following factors: congestive cardiac insufficiency, high blood pressure, aged above 75 years old or diabetes mellitus and two values in case of previous history of CVA or transient ischaemic accident (TIA). $CHADS_2$ score enables us to identify high risk patients for ischaemic CVA (score >3), intermediate risk (score 2 – 3) and a low risk (score 0 – 1) (*Table II*).

Patients with high embolic risk are strong candidates for anticoagulant therapy with warfarin and/or heparin of low molecular weight (HBPM). To low risk patients it can be offered an anti-aggregating therapy (aspirin or clopidogrel). Regarding patients in intermediary risk, any of the strategies can be pondered. [16]

RHYTHM CONTROL

Sinus rhythm cardioversion tends to be more effective with a shorter AF duration time, possibly due to the auricular remodeling.

To control the rhythm, the available therapeutic options include anti-arrhythmic drugs and/or electrically defibrillation and yet non-pharmacological methods (auricular stimulation, ablation by catheter and surgical ablation of automaticity areas near the pulmonary veins orifices).

Both the pharmacologic as the electrical cardioversion present a similar risk of thromboembolic complications. For such reasons and, the current recommendations propose the administration of anti-thrombotic therapy three weeks before and four weeks after any of the strategies in AF started over 48 hours previously or with an unknown duration. [1]

The antithrombotic therapy of long duration should be considered in patients with a high risk of AF recurrence.

The decision for cardioversion can also be guided by the transoesophageal echocardiography, enabling the exclusion of thrombi in the left auricular appendix, a place where over 95% of cases are formed. [1] The transoesophageal echocardiography enables to reduce the time needed to implement cardioversion, being described best results in the later maintenance of the sinus rhythm. [17,18]

Pharmacological cardioversion

Pharmacological cardioversion is more effective when carried out within seven days after AF emerges. Af-

TABLE II

$CHADS_2$ Score and therapeutic recommendations

$CHADS_2$ Score	CVA annual risk	Risk stratification*	Therapeutic recommendation
0	1.9	Low	Aspirin
1	2.8		
2	4.0	Intermediary	Aspirin or warfarin
3	5.9		
4	8.5	Highly	Warfarin
5	12.5		
6	18.2		

*CVA annual risk for 100 patients with CVA, without antithrombotic therapy.

Adapted from Gage BF, Waterman AD, Shannon W, Boechler M, Validation of the clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001 June 13; 285 (22): 2864 – 70.

ter such periods, the success rate for cardioversion declines frankly. [1]

Chemical cardioversion is usual reserved for symptomatic but haemodynamically stable patients, due to the potential side-effects of anti-arrhythmic drugs.

In general, Vaughan Williams Ic class anti-arrhythmic drugs (e.g. flecainide, propafenone) and those in group III (amiodarone and sotalol) are the most used drugs in chemical cardioversion and in keeping the sinus rhythm. [19]

Dofetilide and ibutilide, class three anti-arrhythmics, were also proven effective in cardioversion, [1] but they are not available at present in Portugal.

A small study [20] has revealed that class 1c anti-arrhythmics (flecainide and propafenone) are more effective than amiodarone in AF cardioversion of recent onset, at 2, 5 and 8 hours after pharmacological administration. After 24 hours, they reveal an equivalent efficacy, suggesting that amiodarone presents a later action onset than the Ic class anti-arrhythmics.

Amiodarone when compared to sotalol, reveals a similar efficacy and safety. [21]

The choice of antiarrhythmic therapy must be made according to the patient's underlying cardiac condition, his/hers comorbidities and pharmacological contraindications.

When there is an underlying cardiac disease, amiodarone must be the first option. In the absence of a structuring cardiac disease, namely coronary disease or a left ventricular systolic dysfunction, Ic class drugs (propafenona and flecainide), must be the first choice. [1,22]

Even after a successful cardioversion, AF recurrence rate is high and can reach 50% at the end of one year. The most susceptible patients to AF recurrence include those over 70 years old, with a long duration AF (> 3 months), left atrial dilation, individuals with high blood pressure, CCI or left ventricular dysfunction and patients with previous attempts of unsuccessful cardioversion. [1]

The current recommendations from ACC/AHA/ESC to sinus rhythm maintenance are summarized on *Fig. 1*.

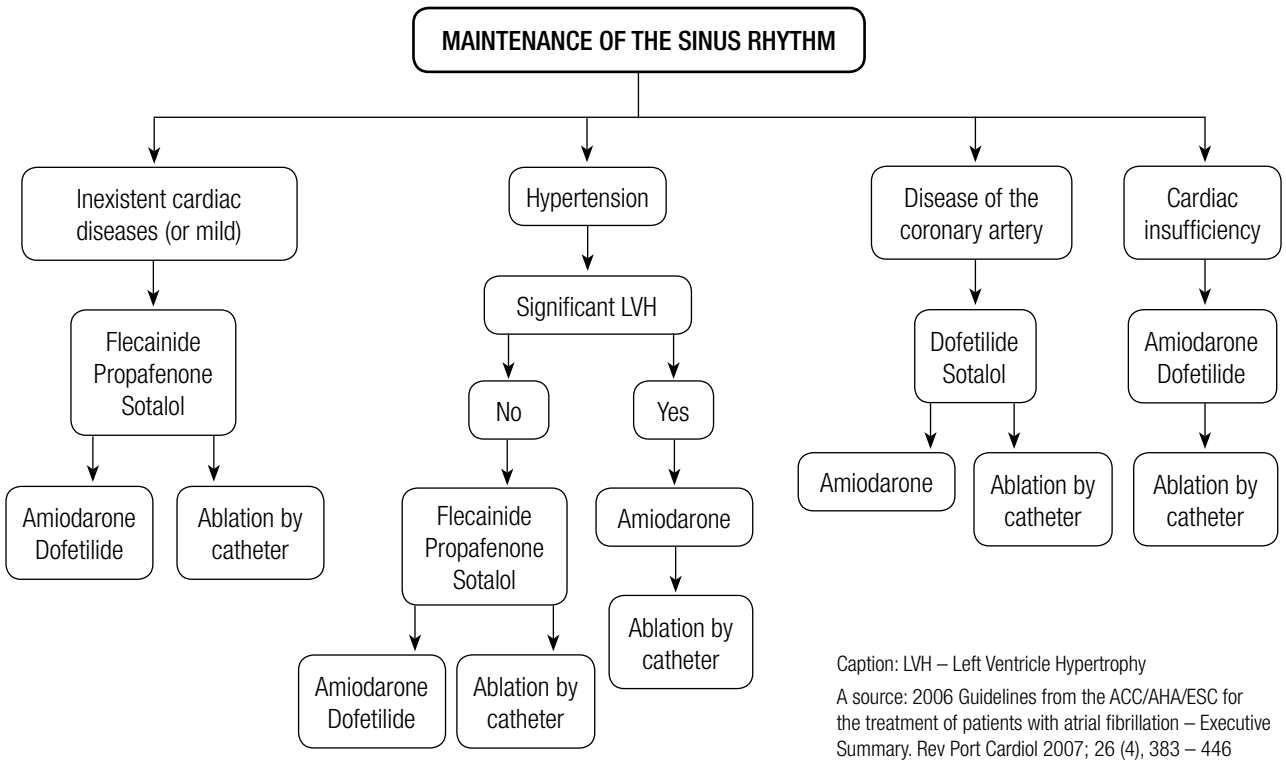
In the United Kingdom, recommendations diverge. In patients with structural cardiac disease and persistent AF, needing therapy to maintain the sinus rhythm, the initial option is a β-blocker. When ineffective or contraindicated, amiodarone becomes the viable alternative. In the absence of an underlying cardiac disease, the first-line therapy still is a β-blocker, having as a second-line Ic class anti-arrhythmics or sotalol and lastly when these drugs are ineffective, amiodarone should be considered. [22]

ELECTRIC CARDIOVERSION

It consists on applying an electric shock, synchronized with the cardiac intrinsic electrical activity, being used for such purpose, external electrodes in the chest wall or an internal cardiac electrode. It does require sedation and anaesthesia. The current recommendations suggest an initial administration of 200 J, increasing to 360 J if necessary, [1] what seems to reduce the occurrence of arrhythmic complications. [23]

Some studies[24,25] show that, when compared to the pharmacological cardioversion, it reveals a similar efficacy in AF patients of recent onset (less than 48 hours). However with basis in the clinic experience, there is a preference for the pharmacological cardioversion in patients which are haemodynamically stable with an AF lasting for less than 48 hours. In a lengthier AF, the electric cardioversion is the most effective. [26]

The electric cardioversion efficacy, documented in literature, changes from 70 to 90%.[27] Such values depend on the patient's characteristics, of the type of electrical wave applied and to the time elapsed up to the cardioversion implementation. The earlier electric



Maintenance of the sinus rhythm therapy in patients with paroxysmal, persistent or recurrent AF.

FIG. 1

cardioversion is applied, highest is the probability of recovering and maintain the sinus rhythm.

AF recurrence occurs in 25% of cases but if it is given antiarrhythmic therapy, together with electric cardioversion, there is a higher efficacy in cardioversion, as well as a reduction of recurrences. According to the current recommendations, amiodarone should be given, pre-and post- electric cardioversion, in patients with previous cardioversion which was not successful or in the cases of earlier recurrence after cardioversion. [22]

Control of the ventricular rate

The control of the ventricular rate is based on the assumption of leaving the AF patient, controlling only the ventricular response, what seems to reduce the symptomatology preventing the development of myocardiopathy induced by tachycardia. The thromboembolic risk is reduced by simultaneous administration of antithrombotic therapy.

It is understood as controlled ventricular rate in AF patients, values from 60 to 80 beats per minute while resting and between 90 to 115 beat per minute in moderate exercise.[1]

To the control of the ventricular response are available negative chronotropic agents (atrioventricular node blocker) or the ablation of the atrioventricular junction with implementation of a permanent ventricular pacemaker.

The most used drugs to control the ventricular rate are β-blockers, calcium channel blockers (verapamil and diltiazem) and digoxin. Amiodarone, with negative chronotropic properties, is usually reserved as a second line, as it does not have advantages regarding the above mentioned drugs and presenting a high risk of toxicity. [1, 22]

Once again, the therapeutic choice must be assessed individually. In patients where the left ventricular function is preserved, β-blockers or calcium channel antagonists are usually the first option. In case of cardiac insufficiency, whether acute or chronic, the digoxin or amiodarone should be used. In the presence of a stable cardiac insufficiency, β blockers may be considered. [19]

β-blockers and calcium channels antagonists in monotherapy, are usually effective to control the ventricular response, but sometimes it is necessary combined therapy to achieve the appropriate ventricular rate. The association of β-blockers or calcium channel blockers with digoxin seems to be effective during the normal daily activities. To control for 24 hours and whilst exercising, β-blockers along with digoxin seem to reveal more efficacy. [28]

Digoxin when compared with β-blockers and calcium channel blockers seems to present less efficacy, specially during exercises, presumably due to its lower potency blocking the atrioventricular node needing a longer period to act. [29]

According to ACC/AHA/ESC recommendations for the diagnosis and treatment of atrial fibrillation, [1] digoxin endovenous administration is recommended to control the ventricular response in patients with atrial fibrillation and cardiac insufficiency who have no accessory pathways.

Digoxin should not be used in AF conditions associated to the Wolf-Parkinson-White syndrome (WPW) or obstructive hypertrophic myocardiopathy. [30] WPW adults with a contraindication for digoxin use, as it can ease the atrioventricular conduction through the accessory pathway increasing the risk for atrial fibrillation degenerating in ventricular fibrillation.

Lastly, when the pharmacological therapy fails to control the ventricular response, non pharmacological approaches should be considered. [1]

RHYTHM CONTROL *VERSUS* VENTRICULAR RATE CONTROL

According to the current ACC/AHA/ESC recommendations, earlier cardioversion is the most appropriate strategy in haemodynamically unstable patients with myocardial infarction, angina, cardiac insufficiency or symptomatic hypotension. Also under such circumstances, electric cardioversion presents higher efficacy and enables a conversion at sinusal rhythm, should be preferred regarding the antiarrhythmic drugs. [1]

In patients without haemodynamic commitment, the need for cardioversion is less established. However, still is still the dominating strategy in clinical practice, as shown by a recent European study. [31]

To relief the symptoms, a better tolerance to exercise, lower risk in thromboembolic phenomena with the possibility of suspending anti-coagulating therapy, if the sinus rhythm is maintained and preventing atrial remodeling, in structural and electric terms, have been the arguments used in favor of such approach. The big problem comes from its limited efficacy, of doubts on the actual maintenance of the sinus rhythm and antiarrhythmics adverse effects. [32]

On the other hand, the control of the ventricular response, an AF therapy alternative, has been associated with less pharmacological side effects, but with the inconvenience of long term antithrombotic therapy (*Table III*).

Several studies on such subjects have been carried out.

The following random trials should be mentioned: P I A F (Pharmacological Intervention in Atrial Fibrillation), STAF (Strategies of Treatment in Atrial Fibrillation), RACE (Results From The Rate Control Versus Electrical Cardioversion), AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) and HOT-CAFÉ (How to Treat Chronic Atrial Fibrillation).

PIAF trial [33] included 252 patients (average age 61.0 years) with persistent and symptomatic AF, being recruited randomly for the rhythm control group and for the ventricular rate control group. After one year of follow-up, 56% of patients in the first group and 10% of the second group, were in sinus rhythm associated to a better tolerance to exercise (6 min walking test) but with an increase on the number of hospital admissions (69% versus 24% in the rate control). Regarding the improvement of symptoms and quality-of-life, it was not detected a significant difference.

STAF trial[34] included a sample of 200 patients, with an average age of 66 years, being followed of about 19,5 months. The primary target was to detect the mortality rate of any cause, CVA, need for cardiopulmonary resuscitation or thromboembolic phenomena. The recorded results in both groups were not statistically significant (10% in the control group for rate versus 9% in the rhythm control group). At the end of three years, only 20% of patients undergoing cardioversion were kept in sinus rhythm.

RACE study[35] included a sample of 522 patients, with an average age of 68,0 years. After a follow up of 2 to 3 years, 39% of patients in the rhythm control group presented sinus rhythm versus 10% of patients in the rate control group. There were no significant differences relating to the compound primary objec-

TABLE III

Table III Advantages and disadvantages of rhythm control vs ventricular response control

Rhythm control	Rate control
Advantages Symptom relief Better tolerance to exercise Better haemodynamics function Preventing myocardiopathy induced by tachycardia	**Advantages** Less pharmacological adverse effects Effective drugs in the ventricular response control Less hospital admissions Higher ratio cost/efficacy CVA risk similar to rhythm control Morbidity and mortality similar to rhythm control
Disadvantages Limited efficacy of anti-arrhythmics Pharmacological adverse effects Higher costs Great possibility of recurrence Higher number of hospitalizations	**Disadvantages** Need for long term anticoagulation Progression of atrial remodeling

Adapted from Saxonhouse SJ, Curtis AB, Risks and benefits of rate control versus maintenance of sinus rhythm. Am. J Cardiol 2003; 91:27D-32D.

tive: mortality of cardiovascular cause, congestive heart failure, thromboembolic complications, haemorrhage and the need for pacemaker implantation and drugs adverse effects.

The AFFIRM trial[36] the largest study on this subject, has followed 4060 patients, with an average age of 69.7 years for a mean period of 3 ½ years. The primary objective was to ascertain the mortality rate, for all causes, in both groups. The results did not show any significant difference between the two groups, being only recorded a higher tendency for hospitalization and to the occurrence of adverse effects in the group with a controlled rhythm. Curiously, the rhythm control was associated to a higher incidence of CVA (7.3% versus 5.7%), possibly by the frequent interruption of anticoagulant therapy when the sinus rhythm was reached.

A more recent study, HOT-CAFÉ,[37] has followed 205 patients (average age of 60.8 years) for an average of 1.7 years. Such study had as primary objective several factors: mortality rate, thromboembolic complications, intracranial hemorrhage or other. The results obtained in the rhythm group were of 1% versus 3.9% in the control group for rate. Once again it was recorded higher tolerance to exercise and a higher number of hospital admissions in the group where the rhythm was controlled.

In general, the results were consistent throughout these studies including patients both from the highest age groups with a higher risk of CVA[35,36] as younger patients. [33, 37]

In spite of the heterogeneity of the studied population, there is no evidence one strategy is better than the other in terms of mortality or quality of life. [30-37]

It is important to highlight that the AFFIRM trial[36] has demonstrated in the rhythm control group, a higher mortality in patients with coronary disease, over 65 years of age and in those without congestive cardiac insufficiency. However it was not observed a lower mortality rate in patients with congestive cardiac insufficiency in this group.

It should also be mentioned that the rhythm control was associated to a higher risk of thromboembolic phenomena, even when the sinus rhythm seemed to be kept.[33,35,36] In this sense, it has been suggested long term anticoagulant therapy, even after a successful cardioversion, in patients with a higher risk of emboli.

In the group where such therapy strategy was adopted, it was also verified a higher number of hospitalizations, the authors relate with the difficulty in keeping patients with sinus rhythm (need for electrical cardioversion) and with the occurrence of antiarrhythmic drugs adverse effects.[33,34,36,37]

As an advantage for cardioversion, both the PIAF and HOT-CAFÉ studies recorded a higher tolerance to exercise.

In terms of cost efficacy, the rate control strategy has shown better results when compared to the

rhythm control.[5,35,36]

It is not rare for AF to occur associated with congestive heart failure. There is not much scientific evidence comparing the rhythm control with the ventricular response control, in this important subgroup of patients.

Such question was assessed in a recent study (AF – CHF),[38] involving 1376 patients from several nationalities with the following criteria: left ventricular systolic function lower or equal to 35%, present symptomatology and AF history. The patients' average age was of 67 years and the average follow-up period of 37 months. Such study has aimed to ascertain the cardiovascular mortality rate in these patients, when controlled the cardiac rhythm or the ventricular rate. It was not recorded significant difference, not only in terms of cardiovascular mortality (27% in the rhythm control group versus 25% in the rate control group) but also in what regards the death for all causes and worsening of congestive cardiac insufficiency. Once again the strategy of rhythm control was associated to a higher number of hospitalizations, particularly during the first year of follow-up.

The authors conclude that the traditional patient approach with AF and CCI, namely rhythm control, do not offer advantage in terms of reducing mortality, when compared with the control of the ventricular response. On the contrary, the control of the ventricular rate, in such patients, is a simpler approach, with a lesser number of hospitalizations eliminating the need for repeated attempts of cardioversion.

It is therefore suggested that the ventricular response control can constitute an initial strategy acceptable in patients with AF and congestive cardiac insufficiency.

The authors also highlighted that such conclusions should not be applied to cardiac insufficiency and a well-kept left ventricular function patients.

Lastly it is worth referring once again the limited efficacy of antiarrhythmic therapy that can have contributed to the results obtained in the rhythm control group.

As the preferentially administered antiarrhythmic drug, in this group, was amiodarone and possibly due to its neutrality in terms of survival, in congestive cardiac insufficiency patients,[39,40] it is thought that was not effective enough to demonstrate the superiority of the rhythm control strategy.[41]

Several efforts have been made in order to develop new drugs, more effective and safe to treat AF patients. An example is dronedarone, a new antiarrhythmic which has been continuously investigated. Such drug has been tested in patients with severe cardiac insufficiency and left ventricular systolic dysfunction, although no AF patients were included. In this study, [42] the aim was to ascertain whether dronedarone would be effective to reduce the mortality by any cause or reducing hospital admissions due to worsening of the cardiac insufficiency. The trial was suspended in its earlier stages due to the high mortality rate in the group where dronedarone was administered, a fact that was essentially attributed to the cardiac insufficiency deterioration.

In AF patients, dronedarone has revealed better clinical results.

A recent study (ATHENA), involving 4628 patients with atrial AF/flutter, aimed to ascertain dronedarone efficacy to prevent hospitalization due to cardiovascular events or mortality of any cause. The results of such trial were presented in the scientific sessions of the American Cardiology Association in 2008. [43] It was demonstrated a significant reduction in the incidence and length of hospitalization in patients to whom dronedarone was administered, when compared to the placebo group. It was also confirmed the properties of such drug maintaining the sinus rhythm as well as reducing cardiac rate, as demonstrated in previous studies.[44, 45]

Other non-antiarrhythmic drugs, as angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor antagonists (ERP S) and statins seem promising whilst approaching AF, including patients with concomitant cardiac insufficiency.

Anti-oxidizing and anti-inflammatory statins properties seem to reduce the atrial remodeling in electric terms.[46] A recent cohort study has demonstrated that statins significantly reduce the development of AF in patients with coronary disease.[47]

It is thought that activating the renin-angiotensin-aldosterone system (RAAS) contributes to the atrial remodeling in electrical and structural terms. [48] A recent meta-analysis, including 11 random clinical trials, with a total of 56.308 patients has demonstrated that RAAS block has reduced the AF risk in 28%. Such results were similar whether they had been used as ACEIs or ARAs. However such benefit seems to have been limited to patients with left systolic ventricular dysfunction or left ventricular hypertrophy. [49] Better

results were demonstrated individually in CHARM[50] and Val-heFT[51] studies with a global reduction of 44% in the risk of AF in cardiac insufficiency patients.

The possible biologic mechanisms explaining AF prevention with the RAAS block include: reducing the left atrial dilation (stress reduction and wall pressure, increase on the refractory period of the ionic channels); improvement on the left ventricle haemodynamics (reducing the afterload and stress in the wall during systole and inhibiting mitral regurgitation); fibrosis inhibition induced by angiotensin II (TGF – β1 inhibition and proliferation of fibroblasts, reducing the inflammatory response mediated by angiotensin II) and lastly the direct action in ionic channels (K+ and C++ streams). Therefore, it has been suggested that the RAAS inhibition perhaps is useful for preventing AF, particularly in patients with hypertrophy or left ventricular insufficiency. [52]

GUIDELINES

The 2006 Guidelines from the ACC/AHA/ECSC for AF treatment do not recommend cardioversion in all patients and they do not refer either the control of ventricular rate, as an appropriate first line therapy strategy in all patients.

They recommend as initial therapy of AF symptomatic, with the duration of some weeks, the control of the ventricular response associated to anticoagulation, whilst the long term target should be reestablishing the sinus rhythm.

If the control of the ventricular response does not offer a symptomatic relief, cardioversion should be attempted, especially if AF causes hypertension or cardiac insufficiency worsening. The rhythm control is also the most adequate approach in younger patients, mainly those with isolated paroxysmal AF.

In older patients with persistent AF and high blood pressure or underlying cardiac disease, the control of the ventricular response can be the most appropriate initial therapy strategy. [1]

The American College of Physicians /American Academy of Family Physicians (2003) recommendations suggest the control of ventricular rate and chronic anticoagulation for most AF patients. The rhythm control is recommended in special situations, depending on the patient's symptomatology, tolerance to exercise and personal preference. [53]

In the United Kingdom, national recommendations [22] for persistent AF treatment suggest the pharmacological control of cardiac rate as initial therapy option in individuals over 65 years of age, in cases of coronary disease, in patients with a contraindication for antiarrhythmic drugs, in those whose cardioversion was not successful and in patients without congestive cardiac insufficiency. On the other hand, cardioversion (pharmacological or electrical) must be preferred in younger patients (<65 years), with a symptomatic disease, individuals presenting for the first time isolated AF in secondary AF the reversible cause and in congestive cardiac failure.

DISCUSSION

In spite of the heterogeneity of the study population, there is not enough evidence suggesting that AF cardioversion, in individuals haemodynamically stable, is associated with better results, including congestive cardiac insufficiency.

On the contrary, the rhythm control has been associated with a higher number of hospital stays as it is difficult to keep patients in sinus rhythm and due to the pro-arrhythmic potential of the drugs currently available.

On the other hand, the control of the ventricular response, associated to antithrombotic therapy, has been referred as an acceptable initial strategy in some persistent and recurrent AF patients. When compared to cardioversion, it presents similar results in terms of mortality and morbidity, with lower occurrence of pharmacological adverse effects. The great inconvenience derides from the need of long-term anticoagulation, which usually is necessary in cardioversion, due to the unpredictability of paroxysmal episodes.

It is crucial not to forget that an individual approach of each patient remains important. The most appropriate therapy choice must consider the nature, intensity and frequency of symptoms, whether there are comorbidities and the patient's preferences. The evaluation and progression of risks and benefits, associated to each strategy should also be considered in the decision.

The ventricular rate control is considered a good therapy strategy in patients with few symptoms, with high risk for recurrence, with a contraindication for anti-arrhythmics, older patients, with persisting AF and underlying cardiac disease, hypertensive or otherwise.

However it is important to highlight that such remarks do not make the rhythm control a redundant

option, and it is still preferred for younger patients, in recent AF onset, in isolated or paroxysmal AF and in patients where the control of the ventricular response is not enough to minimize the symptoms. In patients with symptomatic hypertension, angina or congestive cardiac insufficiency deterioration, cardioversion can also be considered.

Lastly it is very important to remember that in these studies, the limited efficacy as well as the pro-arrhythmic potential of antiarrhythmic drugs, possibly overlapped the benefits of the rhythm control in AF.

This way, the efforts must be directed in the sense of developing new antiarrhythmic drugs, more effective and safer, what possibly will be enough to make rhythm control a better approach.

The investment in drugs as dronedarone, with less adverse effects than conventional anti-arrhythmics and with a combined action in cardioversion and reduction of the ventricular rate, promises great progress in the treatment of AF patients.

The same way, the development of drugs that can inhibit the atrial remodeling and therefore prevent the onset or perpetuation of AF, also deserves especial attention approaching such patients. ■

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