CME CREDIT

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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Atrial fibrillation: When is rate control enough?

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Rate vs rhythm control for atrial fibrillation is still controversial

A: This may seem like a straightforward question, but it is not.

The quick answer is that older patients who tolerate atrial fibrillation with minimal or no symptoms after the ventricular rate is brought under control may not benefit from a rhythm control strategy.

However, the full answer is by no means so simple, and the benefit of ventricular rate control vs rhythm control for the management of atrial fibrillation remains controversial.

In the following discussion, "ventricular rate control" refers to control of the ventricular response to atrial fibrillation (most commonly with the use of atrioventricular [AV] nodal-blocking drugs), and "rhythm control" refers to restoration and maintenance of sinus rhythm (most commonly with the use of antiarrhythmic drugs, with or without electrical cardioversion). Our comments apply only to patients who are candidates for either treatment strategy: ie, they have no relative or absolute contraindications to cardioversion, such as lack of appropriate anticoagulation.

THE CHOICE IS NOT SO STRAIGHTFORWARD

The choice may be relatively easy for a patient with symptomatic atrial fibrillation despite adequate ventricular rate control. Such a patient needs a rhythm control strategy to restore and maintain sinus rhythm to alleviate symptoms. One could also argue that every patient with an initial episode of atrial fibrillation should be offered at least one chance to restore sinus rhythm with electrical cardioversion without long-term antiarrhythmic drug therapy.

But what about patients who tolerate atrial fibrillation with minimal or no symptoms? Several recent randomized studies would appear to support continuing ventricular rate control alone with appropriate anticoagulation for such patients who tolerate atrial fibrillation after ventricular rate control is achieved (see below).

However, these studies had important limitations, and unfortunately, their results have already been misunderstood and improperly generalized, causing confusion and misinformation. As with any study, we must be cautious in interpreting the results and keep in mind what type of patients were studied, which treatment options were studied (and which options were not), and to which patients in your practice the results are applicable.

OLD ASSUMPTIONS ABOUT THE BENEFITS OF RHYTHM CONTROL

For many years we assumed that rhythm control would be the better treatment approach for patients with atrial fibrillation.

Presumed benefits of rhythm control

- **Better relief of symptoms.** Certainly this strategy alleviates symptoms for many patients (therefore justifying the risks of antiarrhythmic drugs), but there was controversy about patients who tolerated atrial fibrillation once ventricular rate control was achieved.

- **Less risk of stroke** and perhaps even death.[1–3] Often this approach was used with the idea that if sinus rhythm were maintained, the patient might not need long-term anticoagulation and therefore could avoid its potential complications.
- **"Cosmetic appeal."** Seeing sinus rhythm rather than atrial fibrillation on the electrocardiogram is reassuring for both patients and physicians.

Presumed risks of rate control

In contrast, ventricular rate control had been used more often as a secondary strategy when sinus rhythm could not be restored and maintained despite the use of multiple antiarrhythmic drugs and cardioversions. This approach generally involves the use of drugs that block the AV node, such as beta-blockers, calcium channel blockers, and digoxin. For refractory cases, radiofrequency catheter ablation of the AV node and implantation of a permanent pacemaker were sometimes required.

Concerns about the rate control approach particularly involved the perceived risks of allowing atrial fibrillation to continue, eg, thromboembolism and stroke, hemorrhagic complications from anticoagulation, atrial myopathy from long-standing atrial fibrillation, and increased mortality.

In trials in older patients, rhythm control was not better than rate control

Concerns about antiarrhythmic drugs

The dilemma for patients with asymptomatic or minimally symptomatic atrial fibrillation became magnified as data began to emerge about the risks of antiarrhythmic drugs, particularly for patients with structural heart disease. For example, the Cardiac Arrhythmia Suppression Trial (CAST)[4] demonstrated increased mortality with the use of certain class IC antiarrhythmic drugs to suppress ventricular ectopy in patients with ischemic heart disease. Other trials showed increased mortality for patients with atrial fibrillation treated with class I antiarrhythmic drugs.[5–7]

These observations led to concern that the potential beneficial effects of restoring and maintaining sinus rhythm may be offset by the adverse effects of the treatment itself.

STUDIES OF RATE CONTROL VS RHYTHM CONTROL STRATEGIES

Several recent randomized controlled trials have provided important information that is relevant to this decision-making process (nicely reviewed by Dr. Mina Chung[8] in this journal).

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM),[9] the largest of these studies, directly compared the two strategies, with total mortality as the primary end point. A total of 4,060 patients who were at least 65 years old or who had other risk factors for stroke were randomized to a strategy of rhythm control or rate control.

The rhythm control group received antiarrhythmic drugs and cardioversion as necessary to maintain sinus rhythm. Continuous anticoagulation was encouraged but could be stopped if sinus rhythm had apparently been maintained for at least 4 weeks.

The rate control group received AV nodal-blocking agents and continuous anticoagulation, with the goal of a heart rate not higher than 80 beats per minute at rest and 110 beats per minute during a 6-minute walking test. Catheter ablation of the AV node with pacemaker implantation could be used if ventricular rate control was not achieved with a combination of drugs.

After 5 years of follow-up (mean 3.5 years), more patients had died in the rhythm control group (24% vs 21%), but the difference was not statistically significant. The rates of a composite end point of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, or cardiac arrest were also similar in the two groups. More rhythm control patients were hospitalized or had adverse drug effects; the same was true for the crossover rate, consistent with the fact that antiarrhythmic drugs are often ineffective or poorly tolerated. Ischemic stroke occurred in about 1% of patients per year in each group, mostly in patients in whom warfarin had been stopped or whose international normalized ratio (INR) was subtherapeutic.

Other studies comparing rate control vs rhythm control treatment strategies[2,10,11] showed similar results.[8,12,13]

IMPLICATIONS FOR CLINICAL PRACTICE

These studies showed that a strategy of rhythm control was not superior to a strategy of ventricular rate control for older patients with atrial fibrillation. There were no significant differences in mortality or quality of life. The incidence of ischemic stroke was not reduced by attempts to maintain sinus rhythm. In fact, the overall incidence was disturbingly high: 7.1% in the AFFIRM trial[9] and 7.9% in the Rate Control vs Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trial.[10]

Also, many patients with stroke (about 50% in the AFFIRM trial and 30% in the RACE trial) were in sinus rhythm at the time of the event. Some of the strokes in the rhythm control groups may have been due to subclinical episodes of atrial fibrillation, raising concern about the practice of stopping warfarin after a patient is presumed to be maintaining sinus rhythm by symptom reporting. In fact, previous studies showed that the incidence of asymptomatic episodes of paroxysmal atrial fibrillation are indeed more common than symptomatic ones,[14,15] and these episodes could be responsible for the higher risk of cerebrovascular events when sinus rhythm is presumed to be maintained. This, along with the potential side effects of antiarrhythmic drugs,[5–7,16,17] could have negated the potential advantages of rhythm control.

Possible inclusion biases

The patient population in both studies was reasonably representative of patients with atrial fibrillation seen in clinical practice. However, there were two sources of possible inclusion bias.

- Only patients who were able and willing to tolerate atrial fibrillation after ventricular rate control had been achieved were included. Those with continued symptoms despite ventricular rate control were therefore unlikely to be included in these trials.
- Patients were relatively older (the average age was about 60 to 70 years in these trials). The conclusions of these studies may therefore not apply to younger patients.

Furthermore, follow-up was relatively short. The effects of ongoing atrial fibrillation over very long periods of time remain unclear. The progression of atrial myopathy in such patients may have long-term consequences not discovered by the relatively shorter follow-up period in the older patient populations included in these studies.

Newer treatments are available

Another important limitation of these studies is that they did not assess other, potentially curative treatments. One could argue that these trials compared two suboptimal treatment strategies, and the more appropriate conclusion may be that a rhythm control strategy using antiarrhythmic drugs is just as bad or worse than a ventricular rate control strategy.

Of interest, the AFFIRM trial investigators recently reported that sinus rhythm is associated with a lower risk of death.[18]

For these reasons, we cannot yet conclude that restoring sinus rhythm has been eliminated as a management strategy for many patients with atrial fibrillation. Further studies are required to determine the best strategy for younger patients and to investigate alternative treatment strategies.

Percutaneous catheter ablation is a very promising newer treatment that can cure atrial fibrillation. This procedure targets the ectopic foci around or within the pulmonary veins, which have been recognized as the triggers for atrial fibrillation in most patients.[19] The topic has been reviewed elsewhere by Finta and Haines.[20]

Results of catheter ablation for atrial fibrillation have been good

Over the past few years the ablation procedure has evolved substantially. The initial strategy was to find and ablate the triggering foci themselves. However, this strategy was ineffective, posed technical difficulties, and was associated with unacceptably high rates of complications, particularly pulmonary vein stenosis. Now the strategy is to isolate these foci electrically so that the impulses cannot exit the pulmonary veins. For this reason, the procedure is now often called "pulmonary vein isolation."

Results of this procedure have been good, and it has become an option for many patients. At The Cleveland Clinic Foundation, the procedure is associated with a cure rate of 80% to 90% and low rates of serious

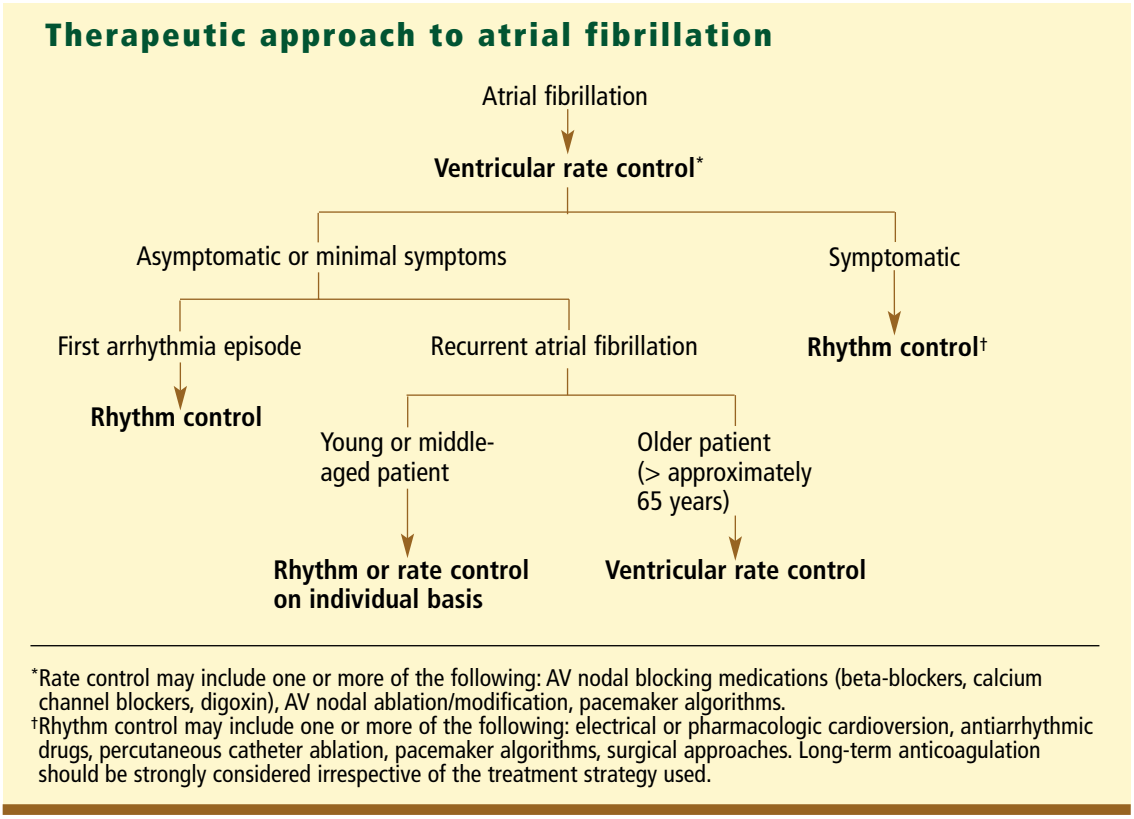

FIGURE 1

Consider long-term anticoagulation even if sinus rhythm is maintained

complications.[21,22] Of note, it has been shown to be safe and effective for older patients and those with structural heart disease.[23,24] In a nonrandomized, long-term study, Pappone et al reported that catheter ablation of atrial fibrillation may result in improved outcomes in terms of freedom from atrial fibrillation, quality of life, cardiovascular morbidity, and even mortality.[25]

We must emphasize that catheter ablation has not yet become a first-line therapy for atrial fibrillation. At present, appropriate candidates are patients with symptomatic atrial fibrillation refractory to antiarrhythmic drug therapy.

Surgical treatments for rhythm management of atrial fibrillation include the Cox maze procedure and minimally invasive surgical approaches to pulmonary vein isolation.[26,27] These strategies are more invasive but may be good options for appropriate patients.

Pacemaker strategies using various systems and modes have had variable results, but overall have only demonstrated modest effectiveness for suppressing or terminating atrial fibrillation.[28] A very good review of the various strategies for restoring and maintaining sinus rhythm was published recently by Martin et al in this journal.[29]

These rhythm management strategies are alternatives or adjuncts to the use of antiarrhythmic medications, and were not studied in the rate-vs-rhythm-control studies mentioned above. Randomized clinical trials comparing rate control and curative rhythm control strategies such as catheter ablation are being considered.

Thus, the available evidence, particularly from recent clinical trials, has provided valuable guidance for many patients, but there is still much to learn about the types of patients and treatment approaches that were not included in these studies.

RECOMMENDATIONS

Many patients with atrial fibrillation continue to have symptoms even after the ventricular rate has been brought under control, and they should be considered for a rhythm control

strategy. But controversy still exists for patients who tolerate atrial fibrillation.

For an initial episode of atrial fibrillation, it may be appropriate to try to restore sinus rhythm, preferably without the long-term use of an antiarrhythmic drug, ie, with electrical cardioversion (**FIGURE 1**). There is no specific "window of opportunity" for attempting this, but the chance of successful restoration of sinus rhythm is higher the earlier the cardioversion is performed.

In an older patient with asymptomatic or minimally symptomatic recurrent atrial fibrillation, a strategy of ventricular rate control alone may be appropriate and does not appear to be inferior to a rhythm control strategy using antiarrhythmic medications.

For younger patients and for other rhythm control strategies there will still be controversy. One may be reluctant to leave a 35-year-old patient in atrial fibrillation forever, even if there are no symptoms whatsoever.

The decision is more difficult for middle-aged patients. Such patients should be evaluated carefully and a decision made after sufficient education and counseling is provided regarding the pros and cons of the various treatment strategies. The potential benefit of restoring sinus rhythm may become evident with the development of a treatment strategy that does not have harmful effects to negate such benefit.

Regardless of the strategy, in light of the important risk of stroke even in those patients with apparent maintenance of sinus rhythm, appropriate anticoagulation should be used and a low threshold set for long-term therapy. This is particularly important for patients with risk factors for stroke. As mentioned above, many episodes of atrial fibrillation may be asymptomatic, and this should be considered very carefully when planning the duration of anticoagulation after restoration of sinus rhythm. The guidelines support a minimum of 4 weeks for everyone.[30] The target INR is generally 2.0 to 3.0.

The management of atrial fibrillation will continue to evolve as more is learned. Guidelines for the management of patients with atrial fibrillation have been published from a task force assembled by the American College of Cardiology (ACC), American Heart Association (AHA) and European Society of Cardiology (ESC),[30] although such guidelines may not reflect the latest information from recent trials.

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