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Non-pharmacological treatment of atrial fibrillation

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Atrial fibrillation is the most common clinical arrhythmia and may be precipitated by various clinical risk factors (Table 1). It is a major public health problem since it very frequently causes severe symptoms such as palpitations, dyspnea, and light-headedness that can markedly impair quality of life and are, on occasion, disabling. Atrial fibrillation is the most common reason for hospitalization due to arrhythmia, and as such, consumes a large amount of our health care resources. Symptoms are partly due to the rapid ventricular rate during untreated atrial fibrillation, rate irregularity, and the loss of atrioventricular synchrony. Treatment is usually directed at attempting to restore and maintain sinus rhythm by using antiarrhythmic drugs. Unfortunately, in up to 50% of patients, antiarrhythmic drug therapy is unsuccessful at restoring or maintaining sinus rhythm. As well, most antiarrhythmic drugs carry a substantial potential burden of adverse effects and toxicity, including the potential for aggravating arrhythmias, known as "proarrhythmia." Controlling ventricular response with AV nodal blocking agents is modestly effective, but requires life-long therapy and patients usually remain symptomatic. In view of this often frustrating lack of efficacy, there has been increased recent interest in therapies for atrial fibrillation that do not involve pharmacologic approaches. This review will briefly detail the current status of such approaches.

Converting persistent atrial fibrillation to sinus rhythm (Table 2)

Traditionally, the attempt to restore sinus rhythm is made by external cardioversion. This has a success rate of between 75% to 80% in most clinical series. The success of cardioversion is weakly related to left atrial size, duration of atrial fibrillation, and body weight, (increases in these variables may reduce the success rate), but a substantial minority of patients fail to be cardioverted even though success may be anticipated from clinical characteristics. Most of these patients are subsequently left in atrial fibrillation and other measures are used for treatment.

Recent studies, however, have clearly shown the efficacy of internal cardioversion for patients with "external shock resistant" AF. In a randomized study, Levy and colleagues compared internal to external cardioversion in patients with long-standing atrial fibrillation (24±38 months duration).[1] Seventy-five percent of the patients had structural heart disease, including 40% with prior heart failure. A total of 112 patients were randomized to internal or external cardioversion. The external cardioversion had a 67% success rate, while internal cardioversion was significantly better with a 91% success rate at restoring sinus rhythm. All patients were placed on amiodarone, and the relapse rate to

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Table 1: Atrial fibrillation — Risks

- Hypertension
- Valvular heart disease (especially mitral)
- Dilated cardiomyopathy
  - — hypertensive
  - — idiopathic
  - — alcoholic
  - — ischemic
- Acute MI, post-aorto-coronary bypass
- Non-cardiac conditions
  - — thyrotoxicosis
  - — chronic obstructive pulmonary disease
  - — uremia

atrial fibrillation was identical in the two groups, being approximately 50% at the end of one year.

In a related study, Schmitt and colleagues performed internal cardioversion in 25 patients who had failed external cardioversion after ≥ 3 shocks at 360 J.[2] Atrial fibrillation was of 11±9 months duration. Eighty-eight percent of these patients were successfully cardioverted internally to sinus rhythm. On long-term sotalol, 60% remained free of atrial fibrillation recurrence over the next two years. Although the energy required to perform internal defibrillation increases with increasing left atrium (LA) diameter — from approximately 3 J at a mean LA diameter of 40 mm to 10 J with a mean LA diameter of 70 mm — success rates were achieved even with a dramatically large left atria.

The electrical pathway in the studies involved shocks between a right atrial and coronary sinus catheter that was inserted transvenously and removed at the end of the procedure. These studies indicate that if cardioversion to restore sinus rhythm is contemplated, most patients should be considered for internal cardioversion upon failure of external cardioversion.

The concept of internal cardioversion has been extended to an investigational set of devices known as "atrial defibrillators." Currently made by two different manufacturers, these devices can either automatically, or in a patient or physician activated mode, recognize atrial fibrillation and cardiovert the patient through a fully implanted automatic atrial cardioverter/defibrillator, analogous to ventricular defibrillators. These defibrillators rely on the notion that prolonged episodes of atrial fibrillation are unpleasant for the patient, difficult and expensive to treat, and usually require hospitalization. In addition, the concept of atrial fibrillation "begetting atrial fibrillation" suggests that the longer any given episode of atrial fibrillation lasts, the more likely it is that it will subsequently recur. Terminating episodes as quickly as possible, therefore, will hypothetically prevent or delay subsequent episodes. The major current limitations of this technology are the complexity and expense of the devices, the requirement for surgery, albeit minor, and the potential for pain and discomfort with atrial cardioversion shocks.

Preventing atrial fibrillation recurrence with atrial tissue destruction (Table 3)

The experimental and clinical verification that maintenance of atrial fibrillation requires the existence of multiple randomly re-entering wavelets of activation in both atria has led to surgical procedures to electrically isolate different atrial segments from each other, thus preventing these re-entering wavelets from occupying a large enough volume to allow atrial fibrillation to be maintained.

The most well-known of these procedures is the "Maze" procedure; its most well-known developer is Dr. J. Cox. The

Table 2: Converting atrial fibrillation to sinus rhythm

Method	Success rate	Limitations
External cardioversion	75%-80%	Some patients left in AF
Internal cardioversion	88%-91% success rate in two series	Relapse in 40%-50% at two years
Implanted automatic atrial converter/defibrillators	Terminates episodes quickly, prevents/delays subsequent episodes	Devices are complex and expensive, requires surgery, potential for pain

Table 3: Preventing atrial fibrillation recurrence with tissue destruction		
Method	**Success rate**	**Limitations**
Maze procedure	≥ 80% probability of long-term maintenance of sinus rhythm	Requires open-heart surgery, has potential for morbidity and 1%-2% mortality, may require pacemaker
Maze procedure performed via a transvenous catheter	Still experimental	Procedure is long and carries considerable morbidity risk
Focal radio frequency ablation performed via a transvenous catheter	Successful for atrial fibrillation that originates in localized foci	Complex and long procedure applies to certain (rare) types of AF

maze procedure requires open heart surgery and consists of multiple linear surgical lesions in both atria to terminate and/or prevent atrial fibrillation recurrences. The procedure is reputed to be extremely successful with ≥80% probability of long-term maintenance of sinus rhythm, combined with adequate atrial transport function. However, there is 1% to 2% mortality, the potential for considerable morbidity, and a small but variable requirement for a permanent pacemaker because of sinus node damage. Given the complexity and extent of the surgery required, the maze procedure has not achieved wide appeal among referring physicians and patients.

In the special circumstance of an independent requirement for open heart surgery (most commonly mitral valve surgery where atrial fibrillation is common), the maze procedure may have as great a benefit with considerably less risk since the patient is already undergoing open-heart surgery. The procedure does, however, prolong the pump time and procedure duration. The maze procedure has not been subject to controlled clinical trials, but may be applicable in some patients at the time of mitral valve repair or replacement.

The advent of radio frequency ablation, allowing delivery of destructive lesions to the atrial endocardium by means of a transvenously inserted catheter, has sparked much interest in the potential for performing the maze procedure through a catheter. For typical multiple re-entrant wavelet type atrial fibrillation, this procedure is highly experimental since it is very long in duration and carries considerable morbidity risk (stroke, tamponade, peripheral embolization, and pulmonary vein stenosis). However, a small but important minority of patients have unusual types of atrial fibrillation that originate in localized foci as an ectopic form of automatic atrial tachycardia; it then spreads to the rest of the atria in an irregular manner. Patients with these types of tachycardia can have successful radio frequency ablation with relatively low morbidity although the procedure is technically complex and takes many hours to perform. Dr. M. Haissaguerre recently reported on a series of patients in whom atrial fibrillation originated in the pulmonary veins, and whose recurrence could be prevented by localized ablation in this region.[3]

Prevention of atrial fibrillation by atrial pacing

On the premise that atrial fibrillation is often associated with delayed and fragmented inter- and intra-atrial conduction, or dispersion of atrial refractory periods, investigators have sought to "synchronise" atrial depolarization and repolarization by means of atrial pacing. In patients with sinus node dysfunction who require a bradycardia support device, atrially-based pacing with AAI pacemakers is associated with a statistically significant and clinically important reduction in the incidence of subsequent atrial fibrillation compared to patients paced with VVI pacemakers. In a large long-term study, Andersen and colleagues studied 225 patients randomized to AAI or VVI pacing.[4] At the end of eight years, 30% of atrial-based pacing and 70% of ventricular-based pacing patients had atrial fibrillation documented at least once, using yearly ECGs for follow-up.

In patients with the tachycardia-bradycardia syndrome, with paroxysmal atrial fibrillation and episodic bradycardia, Saksena and colleagues compared, in a crossover study, atri-

Table 4: Controlling ventricular response in atrial fibrillation		
Method	**Success rate**	**Limitations**
Drug therapy	Extremely effective at slowing ventricular rates	Does not improve quality of life or exercise capacity; may cause fatigue and adverse effects
Radio frequency energy delivered to the "slow pathway" adjacent to AV node	Ventricular response reduction, improved ejection fraction	10%-30% risk of heart block; patients still have irregular rates and incomplete rate control
Complete AV junction ablation	≥95% success rate, improves symptoms, well-being and exercise capacity	Causes complete heart block, necessitates insertion of pacemaker

al fibrillation recurrence rates during no pacing (baseline), with relatively rapid continuous high right atrial pacing (about 85-90 bpm), and dual site pacing from the right atrium and the coronary sinus os.[5] Both forms of pacing showed a significantly longer mean arrhythmia-free interval of approximately 75-90 days as opposed to 15 days at baseline. This preliminary and relatively small study leads to optimism regarding the potential usefulness of pacing in preventing atrial fibrillation episodes.

Extending the concept of dual site atrial pacing to prevent dispersion of activation times between the two atria, Daubert and colleagues[6] from France have performed intriguing preliminary studies employing simultaneous pacing from the high right atrium and the distal coronary sinus, shortening previously prolonged atrial activation times (longer duration P waves on the surface ECG). In small and not completely controlled studies, the interval between episodes of atrial fibrillation was increased, and the likelihood of atrial fibrillation recurrence was substantially decreased. Other more experimental forms of pacing to prevent atrial fibrillation recurrence includes dynamic atrial overdrive pacing to prevent spontaneous atrial ectopy or atrial pacing algorithms designed to prevent post-atrial extrasystolic pauses. Such algorithms are currently being investigated in multicenter studies, but none have been shown to be effective in randomized studies.

In summary, although pacing techniques to prevent atrial fibrillation may be promising, they have not been sufficiently proven to be applicable in the majority of patients. However, for patients at risk for or with a history of atrial fibrillation who require bradycardia support, it seems reasonable to pace atrium and ventricle, either with DDD pacing or with AAI(R) pacing in those with intact AV nodal function.

Controlling ventricular response in atrial fibrillation (Table 4)

Although drugs that control the ventricular response in atrial fibrillation are extremely effective at slowing ventricular rates, they have not been shown to improve quality of life or exercise duration, and may often cause fatigue or other adverse effects. Consequently, there has been great interest in slowing ventricular response by means of damaging or destroying the atrio-ventricular (AV) node.

There are some encouraging limited reports at "electronic digitalization," performed by delivering radio frequency energy to the region of the "slow pathway" adjacent to the AV node. One trial demonstrated that mean ventricular responses at peak exercise can be reduced from 140 at baseline to approximately 80 for up to 24 months following the procedure.[7] Ejection fraction also improved from about 33% to about 44% in the 16 patients in this study. The procedure, however, has not received wide appeal because of the 10% to 30% risk of heart block during the procedure, and the fact that patients are still left with an irregular, albeit slower heart rate.

A randomized study of complete AV junction ablation vs "AV junction modification" showed that complete ablation with pacemaker implantation led to greater improvement in both the general well-being and symptom frequency in 60 patients randomly assigned to either the ablation or modification.[8] Ablation of the AV junction, which trades the disease of atrial fibrillation with rapid ventricular response for the new disease of complete AV block, is well-established for patients with rapid ventricular responses that cannot be controlled by drug therapy. The procedure can be performed with ≥95% success and results in a ventricular escape rate of generally 40 bpm. With modern generation pacemakers, normal sinus node function can be fairly precisely emulated, leaving patients with a regular, albeit ventricularly paced rhythm that responds to the body's needs with respect to its rate. Many studies have confirmed that this procedure in appropriately selected patients leads to a substantial increase in exercise capacity, decrease in symptoms, and improvement in well-being and quality of life, as well as a reduction in health care resource consumption.

In an important recent study, although small and preliminary, 14 patients with atrial fibrillation and "controlled" ventricular response were randomized to receive AV node ablation vs continuing medical therapy.[9] After 12 months of follow-up, patients randomized to AV node ablation had improvement in ejection fraction, NYHA class, exercise tolerance, and well-being. The authors concluded that a chronically irregular heart rate alone, despite apparent "rate control," can reduce cardiac function and impair quality of life.

A multicenter study based at St. Michael's Hospital called SPARC (Study of Pacing vs Ablation for Rate Control) will randomize 100 patients with left ventricular dysfunction and atrial fibrillation with a mean daytime heart rate of >90 to either aggressive attempts at pharmacological rate control or AV node ablation and pacemaker implantation. The hypothesis is that ablation and pacing will improve quality of life and cause better improvement of LV function than pharmacologic rate control, which requires negatively inotropic drugs.

The precise indications in the future for AV node ablation and pacing remain to be fully determined, but the majority of patients undergoing this procedure have marked improvement in their quality of life and it may be appropriate to consider it earlier in the therapeutic chain than is currently the case.

Conclusion

The inadequacy of pharmacological therapy for atrial fibrillation, and the rapid development of electronic, ablative, and surgical therapies for this common arrhythmia have led to the lightning development of a battery of electrical interventions for this common disorder. The place these therapies will have in the treatment of atrial fibrillation is yet to be fully determined.

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Abstracts of Interest

Early recurrence of atrial fibrillation with an implantable atrial defibrillator: Incidence, clinical predictors and time course

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Introduction: The incidence of early recurrence of atrial fibrillation (ERAF) has not been well characterized for chronic therapy with an implantable atrial defibrillator (IAD). We define ERAF as the recurrence of atrial fibrillation (AF) within one minute following an initial successful IAD therapy.
Methods: 96 patients (pts) with recurrent AF and who were refractory to drug therapy were implanted with an IAD (Metrix, InControl Inc). We compared pts demographics, clinical characteristics and ERAF incidence during the post implant period where all AF therapy was observed by the physician.
Results: There were 74 males with a mean age of 59 ± 10 years. The mean LVEF was 58 ± 9% and the mean LA size was 4.3 ± 0.9 cm. The mean follow up duration was 10 ±8 mo. There were a total of 485 episodes of spontaneous AF treated with the IAD. There were 99 episodes with ERAF (20%) occurring in 42 pts (44%). Sinus rhythm (SR) was restored in 53 of the ERAF episodes (54%) with the use of subsequent shocks, and 30 (30%) episodes converted spontaneously or with pharmacologic therapy. There was no significant difference in pts with and without ERAF when comparing age, gender, LVEF and LA size. However, pts were more likely to have ERAF if they had a pattern of paroxysmal AF episodes with a perceived frequency of >1 per week and lasting <24 hours. Also, the incidence of ERAF significantly decreased over time ie, 33 out of 73 episodes had ERAF within the first month (45%) as compared with 36 out of 143 episodes having ERAF after 3 months (25%) ($p < 0.05$).
Conclusion: ERAF is a phenomenon that can complicate the acute treatment of AF episodes with the IAD, however, its incidence significantly decreases over time. Despite its presence, stable SR is restored 85% of the time during the treatment of spontaneous AF.

Prediction of successful intra-atrial defibrillation by analysis of atrial fibrillation waveform

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We hypothesized that analysis of the fast-Fourier transformation (FFT) of an interatrial electrogram (EG) during atrial fibrillation (AF) would show a correlation of the variance of the signal and the amplitude of harmonic peaks with the organization of AF wavelets and defibrillation (DF) efficacy.
Methods: 10s20 AF was initiated with burst atrial pacing in 4 mongrel dogs (29.0 ± 4 kg). The atrial DF threshold ($ADFT_{50}$ was determined using an up-down-up protocol and biphasic (6 ms/6 ms) shocks between 2 coil electrodes 93.6 cm^2 each) placed in the RA and LA. AF was reinitiated and DFs were repeated at the $ADFT_{50}$ voltage. Four seconds of an interatrial bipolar EG was acquired immediately pre-shock for off-line analysis. The ventricular EGs were averaged and digitally subtracted. The atrial EG was filtered (40-250 Hz 2^{nd} order Butterworth), rectified, then low pass filtered at 20 Hz FFTs of filtered EGs from successful and unsuccessful shocks were analysed. Successful shocks had discrete harmonic peaks and low power between peaks with Δ highest to lower power of 99 ± 48 vs 54 ± 33mV for successful versus unsuccessful shocks ($p = 0.04$). The third moment of the unfiltered signal (skewness) differentiated between successful (.093 ± .088) vs unsuccessful shocks (.39 ± 26, $p = 0.017$).
Conclusion: Successful DF of AF can be predicted by analysing the FFT of the interatrial EG.

Quantification of effectiveness of maze procedure for atrial fibrillation using spatial coherence technique

MANI V, DE BAKKER J, HSIA P.

Atrial fibrillation (AF) begetting AF suggests a gradual and progressive remodeling of atria during chronic AF. We hypothesize that curable Maze Procedure for AF would go on with a progressive reversing of this effect. We quantified electrical organization prior to, during interventions and post the Maze procedure. Spatial coherence has been developed to quantify the organization of the atria by evaluating 128 electrograms recorded during Maze procedure. Two unipolar electrode plaques (8x8 uniform square grids each) were sutured at left atrium (LA) and right atrium (RA) respectively on 2 human patients undergoing the course of successful maze procedure. Spatial coherence analysis was performed and a 3D coherence surface was obtained. Coherence strength at various distances were then extracted. (It has been shown previously that more organized rhythms like NSR have higher coherence strength). It was found that with subsequent interventions of the maze procedure, the coherence strength increased at 5, 10, 15, 20, 25 and 30 mm electrode spacing. The maze procedure in curing AF is achieved progressively by increasing the degree of electrical organization in both RA and LA with each successive incision. Spatial coherence value for quantifying the AF organization is a useful technique for this procedure.