

## REVIEW

# Non-pharmacological and non-ablative treatment for atrial fibrillation: „easy” tips for our patients

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**Abstract:** Atrial fibrillation (AF) is a widespread, lifelong disease with significant costs for the healthcare systems and the quality of life of AF patients. Besides the commonly encountered rhythm and rate control therapies, one should have in mind that simple measures, most of the time adjunct to medication and catheter ablation, may significantly improve the long-term results. In this paper, we set out to review the most recent research focusing on the management of atrial fibrillation outside of drug and ablation therapies with the aim of extracting practical recommendations for the everyday cardiological practice. Virtually any AF patient should be tested for sleep apnea and treated accordingly. Overweight or obese AF patients should be motivated to lose 10% of their initial body mass. Future developments in gene therapy may provide further innovative therapies for our AF patients.

**Keywords:** atrial fibrillation, non-pharmacological treatment, non-ablative treatment, obesity, sleep apnea

**Rezumat:** Fibrilația atrială (FiA) este o patologie foarte răspândită, fără tratament definitiv și care prezintă costuri importante atât pentru sistemele de sănătate cât și pentru calitatea vieții pacienților. În afara terapilor frecvent utilizate de control al ritmului și a frecvenței, trebuie avute în vedere și unele măsuri relativ simple, cel mai adesea adjuvante medicamentelor și ablației, pot îmbunătăți semnificativ rezultatele pe termen lung. În această lucrare, ne-am propus să rezumăm cele mai recente cercetări asupra tratamentului fibrilației atriale în afara medicamentelor și a ablației cu scopul de a extrage recomandări utile pentru practica zilnică. Practic orice pacient cu FiA trebuie testat pentru apnee în somn și tratat corespunzător. Pacienții supraponderali și cei obezi trebuie consiliați și încurajați să slăbească cel puțin 10% din masa corporală inițială. Dezvoltările viitoare în terapiile genice ar putea oferi terapii inovatoare pentru pacienții cu FiA.

**Cuvinte cheie:** fibrilație atrială, tratament nemedicamentos, tratament non-ablativ, obezitate, apnee în somn

## INTRODUCTION

Atrial fibrillation (AF) is the most frequently encountered arrhythmia in the medical practice, affecting millions of people worldwide. Contemporary estimates say that one in four adults in Europe and the USA will develop AF in their lifetime<sup>1</sup>. The importance of AF and its management is not only due to its prevalence, but also due to the fact that AF is one of the major causes of stroke, heart failure, and cardiovascular morbidity<sup>2</sup>.

The 2016 *European Society of Cardiology Guidelines* for the management of AF recommend the “management of precipitating factors” and they include “lifestyle changes and treatment of underlying cardiovascular conditions” alongside the canonical rate and

rhythm control management strategies. Furthermore, the guidelines give a top role in improving life expectancy to this management of precipitating factors. However, the lion’s share of the guidelines text itself is concentrated rather on the rate and rhythm control strategies either by way of medication and/or catheter (even surgical) ablation.

Catheter ablation of AF has now a strong indication in case of symptomatic AF (class I/IIa after medication failure to control symptoms depending on paroxysmal/persistent form). This technique (Figure 1) is efficient for rhythm management<sup>3</sup>, improves quality of life<sup>4</sup> and likely has a survival benefit in heart failure patients<sup>5,6</sup>.

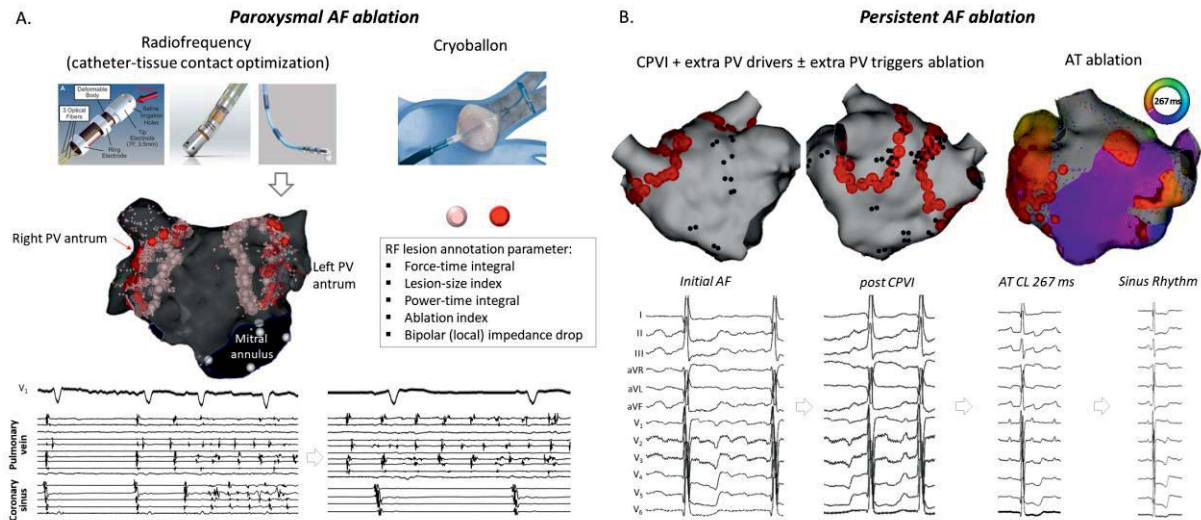
In this review we wish to focus on the potential benefits of non-pharmacological and non-ablative ma-

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**Figure 1.** Catheter ablation of AF. **A.** Paroxysmal AF ablation is currently performed using radiofrequency or cryotherapy. Circumferential point-by-point ablation of the pulmonary vein (PV) antra with operator-tuned targets is mostly used, with lesion quality assessment by integrative parameters including power, time, contact force, generator impedance drop or bipolar (local) impedance drop. The aim of this ablation is complete and persistent bidirectional disconnection of the PV, eventual without dormant conduction (as assessed by adenosine challenge). In the lower part of the panel AF onset triggered by a PV discharge before disconnection is no longer present at the end of the ablation, since recurrent PV discharge is no longer conducted to the atrium which remains in sinus rhythm. **B.** Persistent AF ablation has a similar initial step with but may also address potential extra PV drivers of AF. AF progressively organizes during the procedure until it eventually stops, sometimes by conversion into atrial tachycardia (AT); a perimitral flutter activation map with a 267 ms cycle length (CL) is shown in the right part of the panel. Further ablation of AT (here by a mitral isthmus line) results in sinus rhythm resumption.

nagement of AF, as stand-alone therapies or on top of medication and ablation.

## I. SLEEP APNEA SYNDROME

Sleep apnea syndrome (SAS) has been recently estimated to have a prevalence in the general adult population between 9 - 38%.<sup>7</sup> SAS is known to be associated with a host of cardiovascular conditions: hypertension (especially some drug-resistant forms)<sup>8</sup>, heart failure<sup>9</sup>, coronary artery disease<sup>10</sup>, and, of course, the focus of our review, AF<sup>11</sup>. For illustrative purposes, Figure 2 shows a patient with a CPAP machine as well as a polysomnography report with periods of sleep apnea.

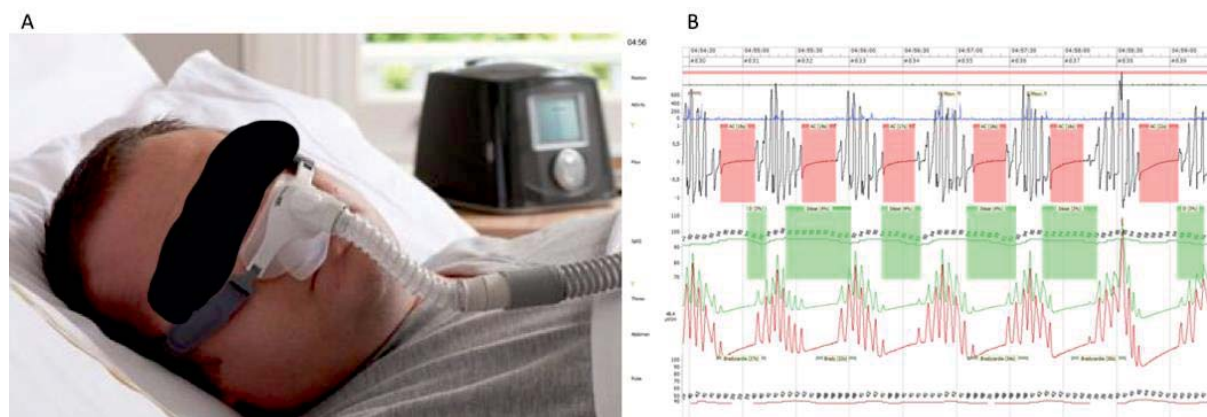
In the particular case of AF, sleep apnea is not only a risk factor, but the treatment of SAS (by continuous positive airway pressure [CPAP] machine therapy during the night) reduces the number of AF recurrences and the total AF burden<sup>12</sup>. Although not randomized, one study<sup>13</sup> suggests that in the setting of AF ablation, patients with SAS treated with CPAP therapy have a 50% lower risk of AF recurrence, similar to patients without SAS. Conversely, patients with SAS not treated with CPAP had modest results after ablation, with recurrence rates similar to patients who had never had AF ablation but who had had SAS treated by CPAP. A recently published meta-analysis (total n=1217)<sup>14</sup> confirms that CPAP therapy lowers the risk

of AF recurrence after catheter ablation and estimates that 18% recurrences might be attributed to not receiving CPAP therapy. Evidence is accumulating for the benefits of CPAP on slowing of the progression towards permanent AF<sup>15</sup>, the reduction of arrhythmic recurrences after electrical cardioversion<sup>16</sup> and better rate control.<sup>17</sup>

## II. OBESITY: ON THE IMPORTANCE OF WEIGHT LOSS IN AF PATIENTS

Obesity has been associated with the development and progress of AF. A meta-analysis<sup>18</sup> of population cohort studies on 78602 patients with average follow-ups between 4.7 and 25.2 years estimates a 49% increase in the risk of developing AF in obese patients (this effect having a direct correlation with the body mass index). A recent cohort of Romanian patients with AF and heart failure shows that obesity has a prevalence of around 24%.<sup>19</sup>

Studies of animal models have shown an association between obesity and atrial electrostructural remodeling. Abed et al.<sup>20</sup> studied thirty sheep which were fed with a high-calorie diet and compared to a control group by means of cardiac magnetic resonance imaging, hemodynamic studies, electrophysiology study with high-density multisite biatrial epicardial mapping and, finally, direct structural histological study. They



**Figure 2.** CPAP mask + SAS report. **A.** Continuous positive airway pressure (CPAP) mask for nocturnal use and CPAP machine in background. **B.** Polysomnography report with periods of apnea (red highlighted periods) and subsequent desaturation periods (green highlighted periods) characteristic for central sleep apnea.

found that the obese sheep had increased atrial volumes, increased left atrial pressures, increased atrial interstitial fibrosis, progressive conduction abnormalities with slowing of atrial conduction. Overall, the authors found that weight gain was associated with a greater burden of induced and spontaneous AF disproportionately to the hemodynamic impact of obesity and suggesting a direct pathogenic role.

The Legacy trial<sup>21</sup> evaluated the long-term impact of weight loss on rhythm control in obese persons with AF. Patients with AF (n=355) were entered into a weight management program (a structured motivational and goal-directed program using face-to-face counseling) with the primary outcome being freedom from AF as evaluated by periodical 7-day Holter monitoring. With a 6-year follow-up period, the study found that progressive weight loss had a dose-dependent effect on long-term freedom from AF. The effect was particularly strong in those patients that achieved a weight-loss of more than 10% of their initial body weight, these patients having a 6-fold greater freedom from AF. Put differently, at 6 years 90% of those that had a weight loss >10% were free from AF, compared to only 40% in those that did not lose weight. Even in a subgroup of patients without the use of rhythm control strategies (including ablation), the cohort that lost >10% of the initial weight had a 45% rate of freedom from AF compared to only 15% of those that did not lose weight.

Recently, these researchers took another look at the same group of patients and argue in the REVER-

SE-AF trial<sup>22</sup> that weight loss and management of risk factors may reverse the natural progression of AF disease. At 6 years of follow-up, of the patients that had a weight loss of more than 10% of their initial body weight only 3% progressed from paroxysmal to persistent AF and 88% reversed from persistent to paroxysmal or no AF.

Not only does it seem that weight loss and risk factor management programs are very effective, they also seem to be cost-effective<sup>23</sup> being cheap to implement and leading to important cost reductions due to less specialist visits, hospitalizations, cardioversions and catheter ablation procedures. Of course, healthcare costs vary between countries and different healthcare systems, but, for example, in the Australian healthcare system the weight loss and risk factor management program lead to an incremental cost-effectiveness ratio of \$62,653 per quality-adjusted life year gained.

Going further than just the body mass index, research has been done to understand the role of epicardial fat (as identified by echocardiography, computer tomography or cardiac magnetic resonance) in arrhythmogenesis. Although the mechanisms are from clear and causation is not proven<sup>24</sup>, still some studies have found a correlation between the amount of epicardial fat and AF recurrence after catheter ablation<sup>25,26</sup>.

### III. PHYSICAL ACTIVITY

The Atherosclerosis Risk in Communities (ARIC) Study<sup>27</sup> which, to simplify slightly, was a prospective cohort study of atherosclerotic diseases within four commu-

nities in the United States of America started between 1987 and 1989 and comprised of 14219 people aged 45-64 years followed for up to 20 years. Amongst other analyses, the prospective character, the large population and the long follow-up allowed for a study regarding the effects of physical activity on AF<sup>28</sup>. Physical activity was assessed by questionnaires and converted to “poor”, “intermediate” and “ideal” levels. Ideal levels of physical activity conferred an 11% lower risk of developing AF. Even more impactful, an ideal level of physical activity in men, but not in women (the authors attempted no explanation of this phenomenon), attenuated the risk of AF in obese patients as follows: obese men with an ideal level of physical activity had a 37% increase risk of AF compared to 156% increased risk in obese men with a poor level of physical activity (after adjusting for blood pressure, diabetes and prior cardiovascular disease).

Things get more complicated as far as physical activity is concerned because evidence is accumulating in favor of a reversed J-curved effect on AF: athletes undergoing intense exercise routines (especially endurance sports) have a higher prevalence of AF<sup>29</sup>. The most commonly cited explanations include modulators (such as increased vagal tone and gastroesophageal reflux) and substrate modifiers (pressure and volume overload, atrial stretching, dilatation, and fibrosis). However, there isn't nearly enough strong evidence to make recommendations against endurance sports<sup>30</sup>.

## IV. CONTROL OF THE PARASYMPATHETIC TONUS

The relationship between vagal tone and AF was established long-ago<sup>31</sup>. Indeed, beyond pulmonary vein triggers, the modulating factor of atrial vulnerability is to a certain degree the parasympathetic tone, and small variations may precipitate AF (Figure 3). The neurogenic theory of AF is more complex<sup>32</sup> and has led to new approaches in AF management and prevention.

### IVa. Neuromodulation

A technology-based non-invasive intervention is neuromodulation (more specifically vagus nerve stimulation) which has already been used as a therapy in epilepsy<sup>33</sup> as well as in heart failure<sup>34</sup>. In 2016 Stavrakis et al. published the first-in-human clinical neuromodulation for patients with AF<sup>35</sup>. They performed a randomized sham (or placebo) controlled trial of transcutaneous electrical stimulation of the auricular branch of the right vagus nerve at the tragus (also called low-level tragus electrical stimulation or LLTS) in patients at the beginning of AF ablation procedures (so during the electrophysiology study, before any ablation was started). The stimulation voltages were well below both the discomfort threshold and the threshold necessary for slowing the sinus rate or the atrio-ventricular conduction. They induced AF in all patients and calculated the duration and AF cycle length. This was followed by one hour of LLTS in the treatment group. After one hour, they once again induced AF in all patients. What they found was that the patients in the LLTS group had a decreased AF duration and a longer AF cycle length.



**Figure 3.** Holter ECG monitoring (3 leads) showing recurrent premature atrial contractions (PAC). The same 2 short-coupled PACs with identical coupling (in 1 and 2, red arrows) induce AF only in the second instance. There is a slight lengthening of the sinus cycle length (normal to normal intervals) just before 2 (from 1515 ms to approx. 1600 ms) suggestive of an increase of the vagal tone, possibly favoring the onset of AF.

The authors' conclusion was that neuromodulation might be a therapeutic option with certain advantages (painless, non-invasive, and pharmacologically inert) in some clinical scenarios.

Another potential target for stimulation is spinal cord stimulation. Although in the early stages (animal experiments), initial research suggests that spinal cord stimulation protects against AF<sup>36</sup> and even suppresses AF<sup>37</sup>.

#### IVb. Psychotherapy: less evidence, but what is the risk?

The effects of psychotherapy on the cardiovascular system and on patients with cardiovascular diseases have been less rigorously studied, although isolated research papers date back to the 1960s<sup>38</sup>.

In the last 10 years, however, things have changed dramatically, and psychotherapy trials have become more and more an area of active interest. Mindfulness is a psychological process which focuses on one's attention to experiencing the present moment. Originally based on Buddhist practices, meditation and yoga, it has become popular in a secularized form often named Mindfulness-Based Stress Reduction (MBSR) in the wider field of Behavioral and Cognitive Therapies. There have been over 100 randomized control trials most regarding MBSR and chronic pain, anxiety disorder, substance abuse disorder and depression<sup>39</sup>.

One of the only randomized control trials to look at the cardiovascular effects of MBSR<sup>40</sup> found that patients undergoing meditation showed an increase in respiratory sinus arrhythmia and a decrease in cardiac preejection period without a significant change in heart rate. To date, there are no randomized control trials on psychotherapy and AF burden nor AF recurrence. However, there are studies on the effects of yoga on AF<sup>41</sup>. The only randomized trial of yoga and AF<sup>42</sup> found modest (but statistically significant) improvements in quality of life, lower heart rate and lower blood pressure in the group of paroxysmal AF patients undergoing yoga classes.

A significant sinus node variability (as objectively measured by the standard deviation of the normal to normal intervals –SDNN– on Holter ECG recordings) is known to be a marker of good cardiovascular health<sup>43</sup>. On the opposite, low SDNN has been correlated to a higher mortality in heart failure<sup>44</sup>, after myocardial infarction<sup>45</sup> and diabetes<sup>46</sup>. If direct, conscious, control of the heart rate and its variability is not possible, the respiratory-cardiac interaction can be used in order to improve the heart rate variability

through cardiac coherence<sup>47</sup>. Easy to use smartphone apps (some of them free, as RespiRelax, HeartRate+ Coherence) are available (Figure 4). Whether this may directly diminish the arrhythmia burden in AF patients still needs to be proven.

#### IV. Gene therapy

Gene therapy as a treatment for AF is still far from clinical validation. However, numerous preclinical trials<sup>48</sup> already confirm several targets as potentially viable for clinical use: fibroblast proliferation, interstitial fibrosis, ion channels with a role in electrical remodeling, gap junctions underlying cardiomyocyte coupling, and autonomic modulation. The targeting of transcription factors affecting pathways involved in AF susceptibility has already proven a valid concept in animal models<sup>49</sup>.

#### V. SMOKING AND DRINKING

The „traditional” cardiovascular risk factors of cigarette smoking and alcohol drinking have a noticeable impact on the prevalence of AF. The aforementioned ARIC trial has also looked at smoking and AF<sup>50</sup>. The authors concluded that current smokers have a two-fold risk of AF and more interestingly smoking cessation does not significantly lower this risk. A 2017 meta-analysis of alcohol consumption and the incidence of AF found that high alcohol consumption (more

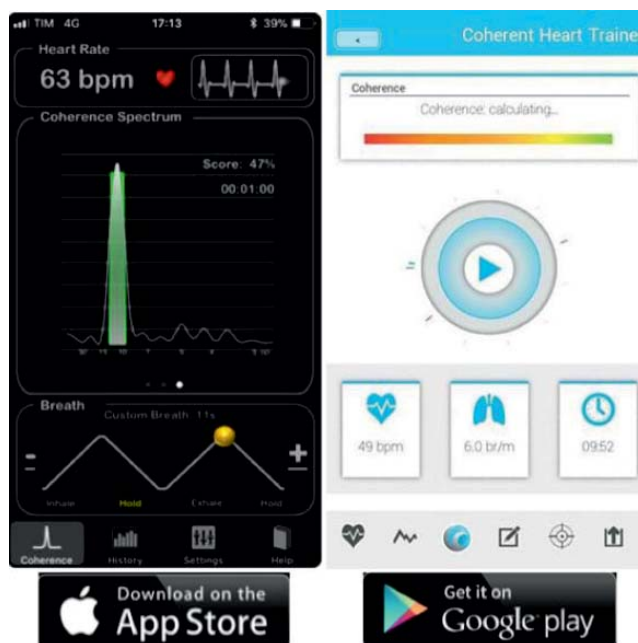


Figure 4. Cardiac coherence apps. Examples of free smartphone apps (HeartRate+ Coherence [left] for iPhone and Coherence Heart Trainer [right] for Android phones) which have breathing exercises while monitoring the heart rate through the smartphone's sensors and camera in order to estimate the level of cardiac coherence.

than two standard drinks per day) was associated with a 33% increased risk of AF, moderate consumption (one or two standard drinks per day) with an 11% increased risk and lower alcohol consumption with no increase in the risk of AF<sup>51</sup>.

## VI. CONCLUSION: A FEW, BUT IMPORTANT „COMMANDMENTS”

AF is a widespread, lifelong disease with significant costs for the healthcare systems and the quality of life of AF patients. While implementing drug-based rhythm and rate control therapies, one should have in mind that simple measures, most of the time adjunct to medication and catheter ablation, may significantly improve results. We should perfectly treat hypertension and valvular heart disease, as early as possible, to limit the mechano-electrical feedback promoting AF<sup>52,53</sup>. Test virtually any AF patients for sleep apnea and treat accordingly. Motivate overweight AF patients to lose 10% of their body mass in order to keep them on the higher arrhythmia-free survival curve. Encourage psychotherapeutic measures, in the form of hobbies or oriented stress reduction and cardiac coherence exercises, since they do no harm and may provide a real benefit. Future developments in gene therapy may provide further innovative therapies for our AF patients.

**Conflict of interest:** none declared.

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