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REVIEW

The René Laënnec lecture on clinical cardiology

A new look at atrial fibrillation: lessons learned from drugs, pacing, and ablation therapies

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Atrial fibrillation (AF) is the most common arrhythmia and among the leading causes of stroke and heart failure in Western populations. Despite the increasing size of clinical trials assessing the efficacy and safety of AF therapies, achieved outcomes have not always matched expectations. Considering that AF is a symptom of many possible underlying diseases, clinical research for this arrhythmia should take into account their respective pathophysiology. Accordingly, the definition of the study populations to be included should rely on the established as well as on the new classifications of AF and take advantage from a differentiated look at the AF-electrocardiogram and from increasingly large spectrum of biomarkers. Such an integrated approach could bring researchers and treating physicians one step closer to the ultimate vision of personalized therapy, which, in this case, means an AF therapy based on refined diagnostic elements in accordance with scientific evidence gathered from clinical trials. By applying clear-cut patient inclusion criteria, future studies will be of smaller size and thus of lower cost. In addition, the findings from such studies will be of greater predictive value at the individual patient level, allowing for pinpointed therapeutic decisions in daily practice.

Keywords Atrial fibrillation • Classifications • Electrophysiology • Electrocardiography • Therapy • Research

Introduction

René Théophile Laënnec's message:

> Rien n'est plus rare que l'exactitude de l'observation (Nothing is rarer than the exactness of observation)

The present review shall sensitize the clinicians to the importance of careful evaluation of the underlying causes of atrial fibrillation (AF) in his patients with no apparent structural heart disease and remind the scientific societies about the importance of accurate definition and classification of this arrhythmia. Just as with the introduction of the stethoscope,[1] only precise observation with careful reporting of findings will build the fundamentals for sustained progress in diagnosis and therapy.

With an increasing prevalence in the most recent studies, AF is the most common arrhythmia and among the leading causes of stroke and heart failure in Western populations,[2] representing a heavy and growing burden to society, patients, and health-care providers.

As discussed below, the increasing prevalence of AF with age is likely due to accumulating predisposing factors and increasing myocardial fibrosis, which also involves the atria. Taking a fatalistic view, age being the only risk factor that cannot be controlled, any upstream therapy will at best postpone the day of first AF occurrence. Moreover, AF risk prediction based on risk factors is supposedly less accurate in older persons than in middle-aged adults, mirroring the already well-known situation with regard to classical risk factors for coronary artery disease,[3] and confirmed by the fact that, so far, no electrocardiogram (ECG) analysis study of P-wave or P–R abnormalities has been conclusive with regard to predicting future AF development.[4]

The diagnosis of AF is based on typical ECG findings. Therapy of AF aims at controlling the ventricular rate (rate control) or at restoring and maintaining sinus rhythm (rhythm control). Despite the fact that the latter aspires to therapeutic perfection, many large studies have failed to deliver convincing and reliable evidence that the effort was worth the undertaking. Nevertheless, in these studies, sinus rhythm was restored in some patients, suggesting that treatment success may depend on adequate patient selection. Thus, improving and refining the diagnosis of AF, beyond the definitions given in the different guidelines, by linking it to the underlying causes and mechanisms may be a promising approach for a more specific therapy. Categorizing patients into carefully defined cohorts (classification) will expectedly lead to smaller numbers of participants to be included in clinical trials for demonstrating therapeutic effects.

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The aim of the present review is to integrate classic dogmas of AF, ranging from basic research to clinical experience, and to generate a philosophy for improving AF classification beyond its current definitions.

Lessons learned from clinical observations in atrial fibrillation

The first step for understanding a natural phenomenon is observation, followed by classification and nomenclature in a second step. This fundamental rule to every science also applies to AF. All international guidelines for 'idiopathic' AF are still primarily based on symptoms and time course, which, in the age of molecular biology, does appear outdated and thus of questionable soundness.[5,6] *Table 1* shows the classifications of AF according to various parameters selected by different expert groups. While symptoms[7] undoubtedly are the patient's first reason of concern and the physician's first motivation for therapeutic action, they do not favour logical pathophysiology-based reflection. Arrhythmic symptoms of AF do not correlate with underlying clinical risk, nor are they indicators for treatment choice with regard to the long-term therapeutic AF management strategy. Moreover, most episodes of AF do remain clinically asymptomatic.[8] The guidelines for the management of AF of the European Society of Cardiology adopted a classification based on the presentation and the time course of the arrhythmia, thus assuming that all events will be symptomatic. Starting from the first diagnosed episode, this classification distinguishes between four possible time courses of AF: paroxysmal, persistent, long-standing persistent, and permanent.[5] This classification builds on the concept that a progression continuum underlies the evolution of AF over time, paroxysmal episodes being progredient up to the stage of permanent AF, as best summarized by the 'AF begets AF' dogma.

As it is generally accepted that only knowledge and understanding about the cause of any disease will lead to successful therapy,[9] we must admit that neither of the two classifications outlined above adequately describes pathophysiological entities qualifying as potential targets for therapy. Yet, in many clinical studies, patients were exclusively included based on the presence of one or more of these clinical symptoms and on the time course-dependent characteristics of arrhythmia.

Recognizing that morbidity and mortality associated with AF had remained unacceptably high despite all efforts aimed at improving its management, the aetiology of AF was placed in the foreground for the first time by the Third Consensus Conference of the Atrial Fibrillation Competence Network/European Heart Rhythm Association (AFNET/EHRA).[10] This major change in attitude was based on well-defined clinical, pathophysiological, and genetic characteristics. Furthermore, the need for taking into consideration coincident or facilitating factors associated with but not necessarily causally linked to AF was also stressed for the first time.

An aetiology-based definition of AF could represent the first step towards categorizing AF according to the primary or dominant underlying disorders. Such an approach would then contribute to improving our understanding about why a given atrium is in fibrillation and to defining sound pathophysiology-based therapeutic targets. The following underlying primary disorders were already proposed: inherited AF, monogenic forms, polygenic forms, focal AF, and post-operative AF.[10] These different forms of AF are representative of specific causes requiring specific therapies at the individual patient level. Neither vagal[11] or sympathetic forms of AF nor subclinical aspects of atrial inflammation or fibrosis were yet considered. By consistently following this type of approach, the term of 'idiopathic' AF would ultimately disappear and be replaced by individual nosological entities.

Lessons learned from electrophysiological observations in atrial fibrillation

The coincidence of two elements, the trigger and the substrate, is at the origin of AF, whereby the trigger reflects an initiating mechanism that can be perpetuated within the substrate. While the trigger sounds like a sudden event, the substrate reflects an evolutionary modification of the electrophysiological properties of the atrial myocardium.

Rapid electrical discharges, for example, originating from the pulmonary veins, are a prototypical trigger.[12] Many other potential triggers, such as but not limited to acute stress of the atrial wall and vagal and/or sympathetic activity, have been much less in the focus of discussion.

Table 1 Synopsis of symptom, time course, and pathophysiology-based classifications of atrial fibrillation according to references [6,7,10]

EHRA symptom score		ESC first episode classification		AFNET/EHRA pathophysiology-based types
EHRA I	No symptom	Paroxysmal	<48 h	Inheritable monogenetic
EHRA II	Mild symptoms Activity not affected	Persistent	>7 days	Inheritable polygenetic
EHRA III	Severe symptoms Activity affected	Long standing, persistent	>1 year	Focal
EHRA IV	Disabling symptoms	Permanent	Accepted	Complex Post-operative

EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; AFNET, Atrial Fibrillation Competence Network.

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The 'substrate' reflects the concept according to which the triggered electrical activation perpetuates in an autonomous way. For this to happen, the stable conduction properties of the atrial tissue need being disturbed. This may occur in a large spectrum of acute, progressive, or permanent pathologies ranging from macroscopic tissue infiltration to molecular abnormalities as encountered in primary genetic or genetically facilitated predispositions.

In a critically unstable atrial tissue, focal activity may arise spontaneously, leading thereby to initiating or sustaining fibrillation. On the other hand, the trigger itself can modify the substrate, especially if active for a prolonged period. In the classic experiments of Allessie and co-workers[13] in goats, AF induced by rapid atrial pacing became sustained over time, as a response to increasing degrees of tissue remodelling. This model mimics the clinical observation of rapidly firing pulmonary vein foci which entrain the atrial tissue and in which, as a proof of concept, trigger elimination by radio-frequency ablation cures the arrhythmia.[14]

It is conceivable and even likely that other mechanisms contribute to substrate remodelling prior to fibrillation, such as chronic atrial wall stretch,[15] chronic inflammation,[16] autonomic nervous system activity,[11] and fibrosis,[17,18] to cite but a few.

While coronary artery disease was typically not considered a direct causal factor of AF, left ventricular ischaemia does promote atrial wall stress as confirmed by recent observations which showed that patients originally diagnosed with idiopathic AF more often suffer from insidious coronary artery disease than healthy controls in sinus rhythm.[19] In addition to these macro-electrophysiological considerations, new insights into substrate conditioning can be expected from ongoing basic research in genetics, proteomics, and metabolomics. All these considerations expectedly will contribute to the integrational classification of AF proposed in *Table 2*.

Atrial fibrillation is also characterized by its time course, as suggested in the ESC guidelines. In fact, little is known about the intrinsic evolution of AF over time which opens the field for longitudinal follow-ups of laboratory and anatomical parameters. Remembering that even so-called stable AF does still exhibit dynamic aspects,[20] long-term ECG monitoring, including by the means of implantable recorders, may contribute to understand better the trigger and substrate interaction.

Repetitive activation was identified as a consequence of re-entry in 1906. Since then, advances in the field paralleled the technical progress of electrophysiological measurements, resulting in the description of multiple re-entry circuits, meandering wavelets, and spiral waves. New horizons were reached with more sophisticated mapping analysis in animal models[21] and *in silico* computer-modelling algorithms, allowing for 3D assessment and simulation of AF.[22]

Lessons learned from electrocardiographic observations in atrial fibrillation

Atrial fibrillation can only be diagnosed by electrocardiography, the absence of P-waves, the presence of fibrillatory waves with a cycle length usually <200 ms, and 'absolutely' irregular R–R intervals being the mandatory features. In this respect, it is surprising that the F-waves' morphology has not deserved further attention despite the ancient observation showing that coarse waves were rather a sign of recent onset AF, while fine oscillations were rather in favour of longstanding AF.[23] Such typical characteristics of ECGs in AF have not been considered potentially relevant for rendering more precise the clinical definition of AF in current international guidelines.[5,6] However, it is highly likely that fibrillation of different origins or at different stages of progression, i.e. in different substrates, might manifest with different fingerprints in the ECG tracing. While the application of modern signal processing technologies applied to the ECG had been proposed a long time ago, it is only recently that measurements based on spatial, temporal, and frequency ECG analyses or using other non-linear methods such as spatial (vector) elements and QRST waves suppression have shown promising results.[24] For the time being, these methods remain essentially focused on the discrimination between paroxysmal and persistent AF, assessing the duration of AF. However, they could represent automatic methods for discriminating between persistent and permanent AF through simple surface ECG analysis. Such information could become highly relevant in clinical settings, for patient management as well as for guiding therapeutic decisions, with recent developments sketching the first lines for use in daily practice.[25] Overall, in carefully defined AF patient populations, such ECG 'blow-up' technologies (*Figure 1*) are very promising and may become a new cornerstone for the classification of AF.[25]

The development of a simple and cheap diagnostic and classification tool, which should be readily usable by primary care physicians in their daily practice, might contribute to aetiology-based therapeutic decision-making, help identifying patients expected to benefit most from rhythm control therapy, guide treatment choice (cardioversion, ablation, or drug therapy), and contribute to predict treatment outcome, ideally at the individual patient level. Based on its value for understanding the pathophysiology of AF, its contribution for reconstructing the history of AF in a single patient, and its expected strong contribution for treatment decisions at the individual patient level, it is foreseeable that advanced ECG analysis should

Table 2 Compilation of published and new elements in view of an integrational classification of atrial fibrillation

Factor	Reference base	Class
Symptom	EHRA	I–IV
Time	ESC	Hours/years
Pathophysiology	AFNET	Type
Electrocardiogram	Advanced signal analysis	To be tested
Biomarkers and genetics	From C-reactive protein to mRNA	To be developed
Associated risk factors	From hypertension to CAD	To be defined per patient

These elements should be part of a diagnostic 'work up' for patients with atrial fibrillation and no primarily identified structural heart disease. Patients with similar factors define the future groups for clinical studies.
EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; AFNET, Atrial Fibrillation Competence Network; mRNA, messenger RNA; CAD, coronary artery disease.

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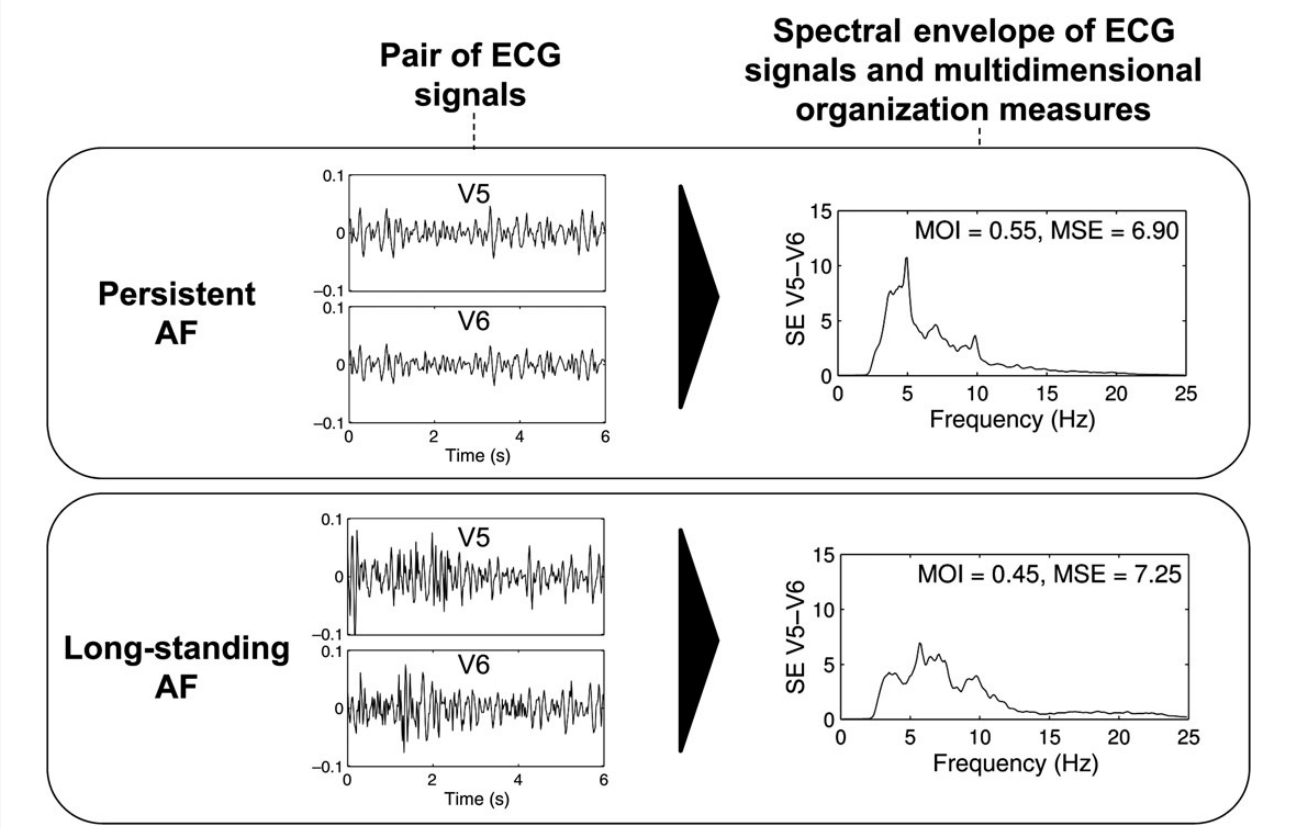

Figure 1 Spectral envelopes (SE) of atrial activity computed on pairs of electrocardiogram leads (V5 and V6) in patients with persistent and long-standing persistent atrial fibrillation, and corresponding multidimensional organization index (MOI) and multidimensional spectral entropy (MSE) demonstrating organization decrease from persistent to long-standing persistent atrial fibrillation (modified from Uldry *et al.*[25]).

become a key element in AF characterization and be included as such in future classifications of AF.[26]

Lessons learned from atrial fibrillation therapy

General considerations

According the AFNET/EHRA Consensus,[10] therapeutic efforts against AF must cover four key areas. (i) Factors that increase the risk for AF must be identified and treated in the sense of an upstream therapy aimed at protecting the substrate. (ii) In line with first attempts of a pathophysiology-based classification of AF, arrhythmogenic processes have to be identified and specific therapies have to be applied. (iii) The relevance of AF duration has to be studied in cohorts in order to identify a disease stage in which rhythm control will be considered inappropriate. (iv) Therapies aimed at preventing complications of AF, such as heart failure and thrombo-embolic events, have to be implemented in parallel to the rhythmological efforts.

As wise as these recommendations are and as obvious as they may seem in retrospect, they are lacking the necessary base of solid clinical evidence, mainly due to the fact that clinical trials published to date did not include or stratify patients based on the newly suggested yet logical principles for AF classification. In the most recent update of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines/Heart Rhythm Society (ACCF/AHA/HRS) focused on the management of patients with AF, 13 mega-trials investigating the clinical benefits of different therapeutic interventions were reviewed.[6] Although more than 25 000 patients were included in these trials, none was overwhelmingly conclusive, with statistical significances scattered across some groups or subgroups of patients. Such statistically significant differences between the mean values of two groups may not necessarily be relevant for clinical decision-making. Furthermore, when applied to individual patients seen in daily practice, the clinical relevance of such statistical significant differences between mean values may be additionally hampered by the fact that the inclusion criteria used for these AF therapy trials did not rely on a specific AF classification beyond the duration of AF and, in some cases, the anatomical size of the atria.

Last but not least, one should remember that anti-arrhythmic drug research has long been the exclusive domain of pharmacologists who generally did not interact with clinicians. As a result, the first classification of (direct) anti-arrhythmic drugs was based on the observed modifications of the cellular action potentials (Vaughan Williams classes I–IV).[27] Subsequently, ion channel-related properties were added, assuming (or possibly hoping) that what happened in the cells would also happen in patients. The results of the Cardiac Arrhythmia Suppression Study (CAST) initiated the fall of drug

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therapy of arrhythmias, based on the observation that in patients presenting with ectopic ventricular beats within 2 years after an acute myocardial infarction, a recognized risk factor for sudden cardiac death, the effective suppression of ectopic ventricular beats with flecainide led to significant excess mortality.[28] However, as shown in later studies, flecainide only caused harm in the setting of ischaemia and/or cardiac structural abnormalities and did not increase mortality when used for the treatment of supraventricular arrhythmias in structurally normal hearts.[29] The lesson taught is that the use of any drug, including anti-arrhythmics, bears a potential for harm and that careful patient selection is required to fully exploit the potential for cure.

Anti-arrhythmic drugs and atrial fibrillation

For the practical purpose of this review, the following will focus on rhythm control only, i.e. on pharmacological cardioversion and maintenance of sinus rhythm. While the treatment of precipitating or reversible causes of AF before initiating anti-arrhythmic drug therapy is generally recommended as a measure of good cardiology practice, this recommendation has not been prospectively evaluated in adequately designed endpoint trials and therefore deserved a C level of evidence in the latest ACCF/AHA/HRS guideline update.[6]

Pharmacological cardioversion can be safely and efficiently achieved with various currently available anti-arrhythmic agents,[30] whereby the reportedly high efficacy may in fact be related to the usually well-selected patient populations (with permanent and persistent forms of AF being consistently excluded). Interestingly, the exact mechanism(s) by which anti-arrhythmic drugs can stop AF, as well as the mechanism(s) by which AF may spontaneously resolve, remain unclear. While drugs tend to decrease conduction velocity leading to a sudden (within seconds to minutes) decrease of the number of wavelets, accelerations with wave collisions have also been described, both mechanisms ultimately leading to wavelet extinction.

Maintenance of sinus rhythm after cardioversion is a much more complex issue. In this setting, feared or factual drug toxicity dominates clinical decision-making. After the CAST study,[28] class I anti-arrhythmic drugs were considered too dangerous, especially for patients with impaired ventricular function. The publication of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study results,[31] which showed in the intention-to-treat analysis that rhythm control offered no survival advantage over rate control, further reduced the enthusiasm for pharmacological anti-arrhythmic therapy. However, a retrospective on-treatment analysis of the same study showed that patients who were in sinus rhythm had a better prognosis.[32] The class III anti-arrhythmic drug amiodarone was poorly tolerated in a significant number of patients and the QT interval prolongation nourished the fear of *torsades de pointes*. Thus, the next step was to shift all hopes towards an amiodarone-like drug without its side effects, an ambitious thought if one considers, following Galen's principle, that only a poison can cure! Many large clinical endpoint trials were conducted with dronedarone, the conflicting results of which were recently carefully reviewed and discussed by Le Heuzey.[33] Thus, the same lesson was repeatedly taught: careful patient selection is the way to go to obtain meaningful clinical study results relevant to daily practice.

Overall, the following key messages can be derived from many (patient-) years of observation in clinical trials: (i) anti-arrhythmic drugs can be very effective when given to well-selected patients; (ii) acute effects of a drug do not necessarily translate into long-term positive results[30]; and (iii) considering that AF is only one symptom of many possible underlying diseases, improving this symptom cannot be expected to cure the disease. Thus, future studies should use very stringent patient inclusion criteria derived from a sound pathophysiology-based integrational AF classification. As important spin-offs, heterogeneous responses will be prevented and smaller sized trials with improved relevance to daily clinical practice will be conducted.

Electric therapy of atrial fibrillation

External cardioversion (EC), with its 50 years of practice, is still the gold standard for restoring sinus rhythm.[34] External cardioversion is easy to perform, cheap, close to 100% effective, and exposes the patient to a low embolic risk if performed $<$48 h after the onset of AF or appropriate anticoagulation.[5] Maintenance of sinus rhythm after successful EC may reveal more challenging, with a potentially high AF recurrence rate. The latter can be lowered by (i) careful diagnostic workup of precipitating factors, including sports, various drugs, family history, and metabolic or vascular disorders, followed by (ii) prescription of the appropriate therapy, be it cause related or simply anti-arrhythmic or both.

Internal cardioversion of AF was shown to be a possible alternative to EC,[35] leading to the development of an implantable 'atrioverter' (InControl) which reliably recognized AF and immediately converted 96% of the AF episodes into sinus rhythm, but had a 20% recurrence rate within 1 min.[36] As the reader will easily recognize by now, the recurrence rate was of course not a problem of the device but rather of the substrate. Furthermore, the delivery of discharges of 1–3 J was considered uncomfortable for the patient and the study was too small and too short to show that 'sinus rhythm begets sinus rhythm'. However, it is conceptually possible that, with appropriate electrode positioning, well-defined stimulation sequences, and/or adapted low energy discharges, an intelligent implantable rhythm control device exerting no harm to, or even protecting, atrial tissue could be developed.[37] Under these premises, it would become possible to investigate whether, and if so under which circumstances, reverse atrial remodelling could happen, e.g. depending upon the prior duration of AF. Such intelligent electric therapies have several obvious advantages, among which their high specificity related to their immediate action at the arrhythmic tissue level, their capability to repeat and adapt the intervention, and the simple intervention required for implantation. Tachycardia overdrive or programmed stimulation had been used in the past to stop atrial re-entry tachycardias with reasonable success.[38] Although the proof of principle was delivered in single cases, the overall results were not satisfactory. Nevertheless, electric rhythm control could become an interesting adjunct to other anti-arrhythmic therapies.

Starting from these initial cardioverting observations, the concept was broadened to preventing AF. One hypothesis was that regular pacemaker stimulation might suppress ectopic activity and thereby override trigger events. In fact, many pacemakers and implantable defibrillators include pacing algorithms developed for the prevention or termination of AF. Randomized clinical trials have demonstrated

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that atrial-based pacing, compared with single-chamber ventricular pacing, reduced the incidence of AF, most notably in patients with the sick sinus syndrome.[39] This effect may be due to primary electric stabilization, to the prevention of retrograde conduction through ventricular pacing, or to the reduction of intra-atrial pressure by A-V synchrony. More recently, specific atrial pacing strategies for preventing AF have been made available, which adapt the atrial pacing rate in response to atrial premature beats or following exercise in order to achieve continuous atrial overdrive pacing (CAOP).[40] These CAOP strategies have yielded promising but inconsistent results in several prospective trials,[41] possibly due again to differences in patient selection criteria and/or pacing algorithms. Finally, in ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial), CAOP did not prevent the development of AF in hypertensive patients at risk for AF and with no history of documented AF.[42]

These observations confirm that, while certain pacing strategies can be highly effective in carefully selected pathologies, they may fail in broadened patient populations which are more likely to encompass multiple aetiologies of AF.

Ablation therapy of atrial fibrillation

The basic concept of surgical ablation of AF was the compartmentalization of the atrial tissue into areas small enough for preventing re-entry circuits to occur.[43] According to this concept, put into practice with the Maze procedure, the cutting lines would forbid propagation of the activation beyond them and therefore make it impossible for the substrate to fibrillate. Developed in 1987, with some adjustments of the cutting-line patterns and with improved instruments since then, this procedure remains the gold standard of surgical therapy of AF. With a success rate exceeding 90% in many centres, this procedure is applied whenever a patient with AF presents with an indication for open heart surgery.[44]

Catheter ablation mimics the Maze procedure without the need for open heart surgery. The search for continuous refinement of this approach is reflected in the discussions on appropriate mapping techniques as well as in the multitude of ablation instruments which are in use or under investigation, ranging from heat to cold application,[45] all sharing the common promise of generating continuous and transmural lines blocking electrical conduction. Large surveys have been conducted which included patients with all types of AF but only minimal information is available regarding 'hits on target'. Controlled clinical studies showed favourable outcomes, the most sensitive drawback of catheter ablation being the frequent need for reintervention.[46] The high recurrence rate (including a high rate of silently recurring AF), the lack of documentation of long-term haemodynamic benefits, and the paucity of available cost–benefit data remain of concern. While following best intentioned guidelines,[47] the amount of totally destroyed substrate (atrial tissue) that results from an estimated annual number of procedures exceeding 300 000 worldwide certainly justifies a more in-depth reflection on more personalized procedures. As an example, the initial design of the ablation lines with a cutting length exceeding 30 cm[43] has never been substantially questioned, although optimization could be attempted based on computer simulation approaches (*Figure 2*).[48] As cutting, burning, or freezing atrial tissue results in the destruction of atrial tissue, the question is not whether larger areas of destruction will deliver better results but whether equally good results could be achieved with more tissue being preserved. Furthermore, even if the definition of the ablation lines is clear, executing them in the individual patient remains a challenge, such that simplified procedures may result in improved feasibility. Further potential targets for ablation deserving more thoughts have been described, namely spots with continuous electrical activity (CFAE).[49] The pathophysiological context of CFAEs, ranging from zones of extremely slow conduction to zones of vagal nerve endings, and the definition of these spots in terms of time, shape, and size still represent major hurdles. It is therefore not surprising that, even in the unfortunate absence of a unanimously accepted definition of recurrence, the ablation of CFAEs alone (i.e. without pulmonary vein isolation) resulted in an 80% recurrence rate of AF in the Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF) trial.[50]

The latter developments are in clear contrast to the scientific approach followed by Haissaguerre *et al.*,[12,14] who exactly observed (possibly remembering Laënnec!), reported, and defined one specific form of ectopic electric activity initiating episodes of paroxysmal fibrillation originating from the pulmonary veins. Only thereafter, radiofrequency ablation of this well-defined region was performed. This scientifically sound approach, in which intervention follows observation, cured AF in 95% of the patients presenting with these predefined characteristics. In patients with other causes of AF, extended pulmonary vein isolation can be reconciled with the Cox approach, i.e. with a partial compartmentalization of atrial tissue. Ongoing progress regarding online anatomic imaging, atrial electrical activity mapping, and applied 'coagulation' area visualization make it reasonable to conceive that, in a not-all-too-far future, computer-based simulations integrating anatomical and electrocardiographic information will allow for designing individualized ideal ablation patterns prior to intervention, just as an aeroplane pilot adapts his flight plan to the weather chart.

Conclusions and outlook: integrating observations made in atrial fibrillation

With this review, a more detailed diagnostic differentiation of AF before engaging into treatment is advocated. As multiple pathophysiological processes precede and coincide with this form of arrhythmia, the integration of all known classification aspects of AF together with the use of selected biomarkers and a careful ECG analysis may contribute to a more individualized classification. The early identification of pro-fibrillatory conditions will allow for the implementation of preventive measures and upstream therapies. Specific clinical constellations have to be identified as early as possible to allow for a cause-related cure and for the identification of patients with a definitively unstable substrate amenable only to care for preventing complications. This should finally permit personalized therapy at its best scientific, clinical, and cost-effective level. Adhering to this vision requires that future studies will be conducted in such carefully classified populations in which the clinical, pathophysiological, time course, electrocardiographic, and biomarker-related

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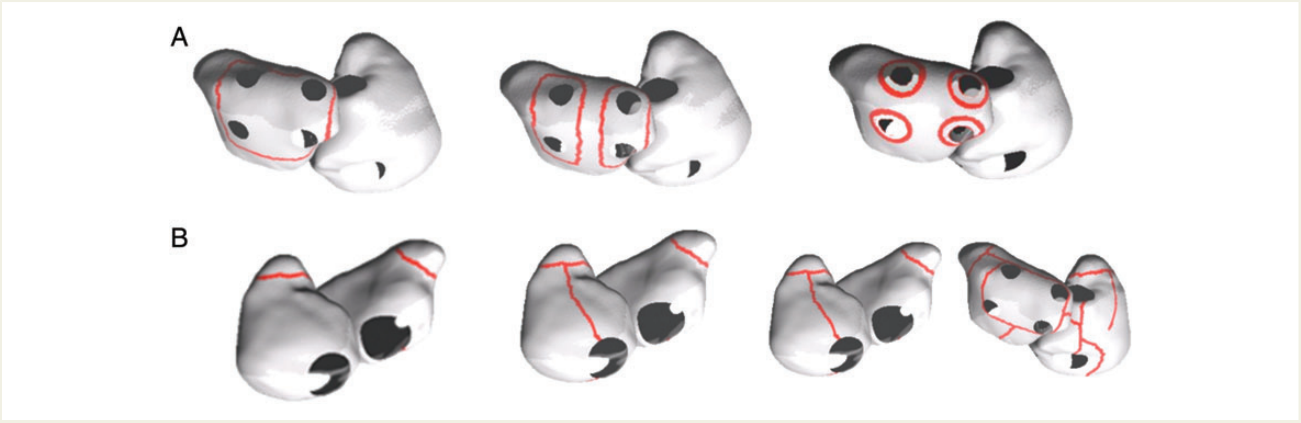

Figure 2 Examples of designing and testing left atrial ablation lines in a 3D computer model (Lausanne heart model) of the human atrium: (*A*) Pulmonary vein isolation (posterior view). (*B*) Persistent atrial fibrillation ablation in the anterior view; complete Maze procedure, right. Movies of the model to be found at www.lausanneheart.ch. Test results published by Dang *et al.*[48]

aspects of AF will all be integrated, as proposed in *Table 2*. This concept was further elaborated in a new AFNET/EHRA consensus document.[51] Studies that will be conducted in this setting will be of smaller size, lower cost, and higher clinical relevance to the treating physicians. Should they fail, we might not have exactly followed Laënnec's advice.

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