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Atrial Fibrillation from an Engineering Perspective

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Atrial Fibrillation from an Engineering Perspective

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Dedicated to Steve Coleman for his groundbreaking research on functional arrhythmias

Preface

Atrial fibrillation (AF) is a complex, age-related arrhythmia which has reached global and epidemic proportions with considerable socioeconomic impact. During the last decade, substantial progress has been made in research on AF, including a better understanding of the basic mechanisms that initiate and maintain AF, low-cost technology for early detection and prevention of AF, and treatment with catheter ablation, which is clinical routine in many hospitals. However, the efficacies of antiarrhythmic drugs and catheter ablation still need to be improved and therefore the focus of much ongoing research.

Although clinical data, genetic factors, and imaging of different modalities play an important role when classifying patients with AF, electrophysiological information continues to be essential in the diagnosis and management of AF. New methodological challenges have emerged in ECG analysis as a result of new clinical findings as well as advances in technology. For example, different clinical studies suggest that frequent atrial ectopy is a precursor of AF and that brief AF episodes may be associated with increased risk of stroke—results which call for new types of signal processing algorithms to detect these events. The pervasive use of smartphone-based ECG applications is becoming an increasingly important tool in the quest for finding asymptomatic AF, implying that robust algorithms need to be developed to ensure that AF detection and characterization of atrial activity can be performed in signals of lower quality. Spatiotemporal analysis of body surface potential maps represents yet another challenge, where the limits of extracting clinically relevant information remain to be established.

The aim of this book is twofold, namely to offer a comprehensive, state-of-the-art review of methods developed for noninvasive analysis of AF, serving as a springboard for those developing new methods, and to provide a text which can be used at different levels in education. The lack of review articles on methods for detection of AF, extraction of f waves, and characterization of f waves is addressed by three chapters which consider these topics at length. This book is confined to describing aspects related to signals recorded noninvasively, whereas aspects related to invasive signals could easily form the contents of another book and therefore left out. Although this is an edited book, where each chapter is written by a different team of authors, sequential

reading is still recommended since the chapters, to some degree, build on each other and contain numerous cross-references.

The title should not be interpreted as if there is a divide between clinical and engineering research. Rather, the title reflects the fact that research in AF includes an engineering signature, where mathematics is one of the cornerstones. The first chapter is entitled "A Clinical Perspective on Atrial Fibrillation" to lay the foundation for engineering-oriented research and to emphasize the importance of interdisciplinarity.

This book is intended for master students and doctoral students in biomedical engineering, electrical engineering, and computer science, as well as for researchers and practicing engineers with an interest in the analysis of cardiac arrhythmias. The unified style and standardized notations make this book suitable as a supplement to textbooks on biomedical signal processing. The chapters on detection and extraction have already been used in capstone projects at Lund University as part of a course in biomedical signal processing. In fact, the projects have turned out to be popular as the methods described in this book have varying levels of complexity and therefore let the student choose the desired level. In addition to the mandatory fundamental courses on digital signal processing and probability theory, familiarity with matrices and linear algebra and basic concepts in statistical signal processing is recommended.

With much appreciation, I would like to thank the authors for their expert contributions and for generously sharing their time with this project.

Special thanks to Pablo Laguna (Zaragoza), Vaidotas Marozas (Kaunas), and Andrius Petrėnas (Kaunas) who spent an enormous amount of time reviewing different versions of the entire book. Their engagement has significantly contributed to improve the contents.

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Lund, Sweden Leif Sörnmo
March 2018

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Acronyms

ABS	Average beat subtraction
ACC	American College of Cardiology
AF	Atrial fibrillation
AFDB	MIT–BIH Atrial Fibrillation Database
AFTDB	Atrial Fibrillation Termination Database
AFR	Atrial fibrillatory rate
AHA	American Heart Association
AI	Atrial impulses
ANN	Artificial neural network
APB	Atrial premature beat
ApEn	Approximate entropy
AR	Autoregressive
ARMA	Autoregressive moving average
ASIC	Application-specific integrated circuit
A:V	Atrial to ventricular
AUC	Area under the curve
AV	Atrioventricular
AZ	Azimuth
BSPM	Body surface potential mapping
CC	Correlation coefficient
CPU	Central processing unit
CSampEn	Coefficient of sample entropy
CV	Coefficient of variation
DACL	Dominant atrial cycle length
DAF	Dominant atrial frequency
DC	Direct current
ECG	Electrocardiogram
EL	Elevation
EKF	Extended Kalman filter
EMEA	European Medicines Agency

ESC	European Society of Cardiology
ESN	Echo state network
FDA	Food and Drug Administration
FN	False negative
FP	False positive
HD	Harmonic decay
HMM	Hidden Markov model
HRV	Heart rate variability
ICA	Independent component analysis
KL	Kullberg–Leibler
LC	Left clavicle
LDA	Linear discriminant analysis
LED	Light-emitting diode
LMS	Least mean square
LS	Least squares
LTAFDB	Long-Term AF Database
MAE	Mean absolute error
MESOR	Midline estimating statistic of rhythm
ML	Maximum likelihood
MITDB	MIT–BIH Arrhythmia Database
MSCPE	Mean square cross prediction error
MRI	Magnetic resonance imaging
MSE	Mean square error
NMASD	Normalized mean of absolute successive differences
NMSE	Normalized mean square error
NSR	Normal sinus rhythm
NSRDB	MIT–BIH Normal Sinus Rhythm Database
NZPP	Count of nonzero bins in the Poincare plot
PC	Principal component
PCA	Principal component analysis
PDF	Probability density function
PL	Planarity
PTBDB	Physikalisch–Technische Bundesanstalt Database
RATAF	RATe control in Atrial Fibrillation
RMS	Root mean square
RMSSD	Root mean square of successive differences
RNN	Recurrent neural network
ROC	Receiver operating characteristic
RT	Recovery time
SampEn	Sample entropy
SC	Spectral concentration
SCC	Signed correlation coefficient
SE	Spectral entropy
ShEn	Shannon entropy
SNR	Signal-to-noise ratio

SO	Spectral organization
SOBI	Second-order blind identification
SPR	Spectral power ratio
SQI	Signal quality index
SR	Sinus rhythm
SSA	Singular spectral analysis
SSAFDB	Short Single-lead AF Database
SSampEn	Simplified sample entropy
STC	Spatiotemporal cancellation
STFT	Short-term Fourier transform
SVD	Singular value decomposition
SVM	Support vector machine
TN	True negative
TP	Turning point *or* true positive
TVCF	Time-varying coherence function
VCG	Vectorcardiogram
VPB	Ventricular premature beat
VFL	Ventricular flutter
VEB	Ventricular ectopic beat
VP	Ventricular pacing
VR	Ventricular residue
WRMS	Weighted root mean square
WVD	Wigner–Ville distribution
XWVD	Cross Wigner–Ville distribution

Chapter 1
A Clinical Perspective on Atrial Fibrillation

Pyotr G. Platonov and Valentina D. A. Corino

1.1 Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice which requires therapeutic interventions. Its prevalence is growing and the number of patients with AF is increasing along with the aging population in the industrialized countries. Atrial fibrillation is not only affecting the quality of life due to the irregular heartbeats, palpitation attacks, or inappropriate acceleration of the heart rate, but it is also one of the most common risk factors of ischemic stroke, which may lead to irreversible handicap and death. Contrary to many other arrhythmias encountered in clinical practice, AF may require therapeutic interventions even in patients who do not have any subjective discomfort from their arrhythmia. Accordingly, this defines an unmet challenge of correct and timely arrhythmia detection.

By affecting millions of patients worldwide, AF is characterized by a palette of clinical manifestations which to some extent is defined by preexisting comorbidities, from completely asymptomatic variants to significant limitations of everyday life due to arrhythmia-related palpitations, fatigue, chest pain, or aggravation of heart failure. A more severe background clinical profile in patients with heart failure, diabetes, and hypertension is usually associated with more severe symptoms during AF. However, in many cases it remains unclear why patients with similar AF phenotype in terms of frequency of arrhythmic attacks and heart rate during AF can have completely different clinical manifestations so that some patients would be in need for hospital

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admission and cardioversion, while others would be completely unaware of the heart rhythm disturbance.

An introductory chapter on clinical matters to a book whose primary focus is engineering comes with the inherent challenge of balancing between unnecessary clinical aspects and a too simplistic picture of complex biological phenomena which to a significant part are not completely understood. However, it is difficult to imagine the development of contemporary clinical medicine, and cardiac electrophysiology in particular, without the progress in many engineering disciplines. Reaching common understanding of basic electrical phenomena in the heart, their importance for health, and risks associated with complications of heart rhythm abnormalities is therefore vital to guide the development of technology aimed at facilitating patient care, prolonging life, and improving its quality.

This chapter provides an overview of basic concepts related to the mechanisms underlying AF, its impact on the human health, and basic principles used by clinicians to prevent AF and minimize its ominous impact on the human organism. The main areas of uncertainties in clinical decision-making will be highlighted, where the existing knowledge gaps make further translational research efforts highly warranted.

1.2 Atrial Fibrillation: Definition

Atrial fibrillation is a supraventricular tachyarrhythmia, characterized by uncoordinated atrial electrical activation and, consequently, ineffective atrial contractions. In the vast majority of cases, AF diagnosis is based on an ECG demonstrating

1. irregular RR intervals,
2. absence of distinct repeating P waves, and
3. presence of undulating atrial activity, also known as fibrillatory waves or f waves,

see Fig. 1.1a. While seemingly straightforward, there are situations in clinical practice when this definition is not always simple to apply. On the other hand, a healthy person would present with an ECG in sinus rhythm, characterized by the presence of P waves originating from the sinus node and reflecting atrial depolarization and regular RR intervals, see Fig. 1.1b.

Irregularity of RR intervals, being a key feature of AF, will only be present in patients with preserved atrioventricular (AV) conduction. Even though this is the case for the vast majority of patients with AF, patients with complete AV block (either induced by cardio-active medications or developed as a result of disease or cardiac surgery) or escape rhythm, originating from the conduction system segments located below the site of block, will have regular RR intervals which may mislead ECG assessment. RR interval irregularity in AF lacks any organization detectable by the human eye. This type of RR behavior differs from other situations in which irregularity of RR intervals is observed, e.g., in patients with atrial or ventricular premature contractions, variable conduction through the AV node during regular atrial tachycardias, or a second-degree AV block, characterized by nonconducted

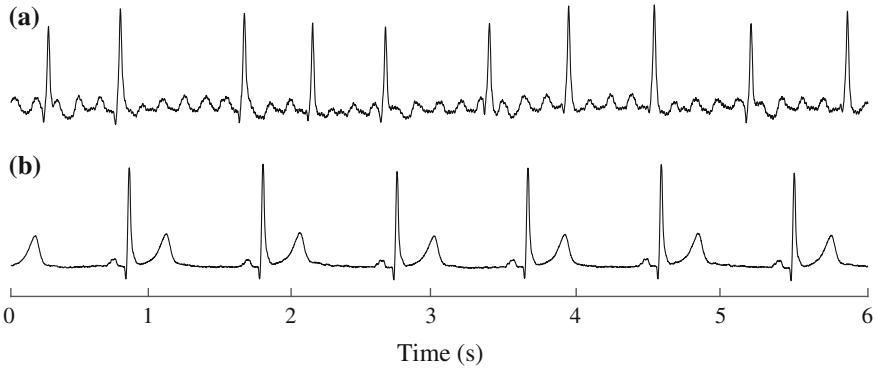


Fig. 1.1 ECG recorded during **a** AF and **b** normal sinus rhythm. In atrial fibrillation, the RR intervals are irregular and the P waves replaced by an undulating atrial activity, known as f waves

atrial beats resulting in pauses occurring on the background of fairly regular rhythm driven by the sinus node or other atrial sources.

The absence of P waves is rarely controversial in patients with low-amplitude f waves, see Fig. 1.2a. However, large-amplitude f waves mimicking P waves, especially in the right precordial leads V_1 and V_2, may represent a challenge, see Fig. 1.2b. In such situations, one should check whether the atrial waves occur at the same time in several ECG leads and have a distinct and repetitive morphology, which then would contradict an AF diagnosis. On the contrary, indistinct atrial wave morphology, variable and short intervals between successive atrial waves (measurable in the leads with distinct atrial waves, often the right precordial leads), and the lack of isoelectric line between them would support AF diagnosis.

1.3 Classification of Atrial Fibrillation

Several classifications of AF exist and are used in clinical practice. The most common way to describe AF is based on the duration and the recurrent nature of arrhythmic episodes, which make patients contact healthcare providers, see Table 1.1.

It is, however, important to appreciate that AF is not a static condition: a patient with paroxysmal AF may develop persistent AF episodes that do not cease spontaneously. Moreover, allocation of a given arrhythmic episode to either a paroxysmal or persistent condition largely depends on the subjective judgement used to administer or withhold cardioversion attempt early on in the course of the AF attack. When sinus rhythm is restored by cardioversion, the ultimate duration of the AF episode is unknown. Thus, patients with highly symptomatic AF seeking care soon after arrhythmia breakthrough may have their arrhythmia assessed differently compared to patients with less symptomatic AF, who may have to wait longer with greater likelihood of spontaneous conversion within several hours or days.

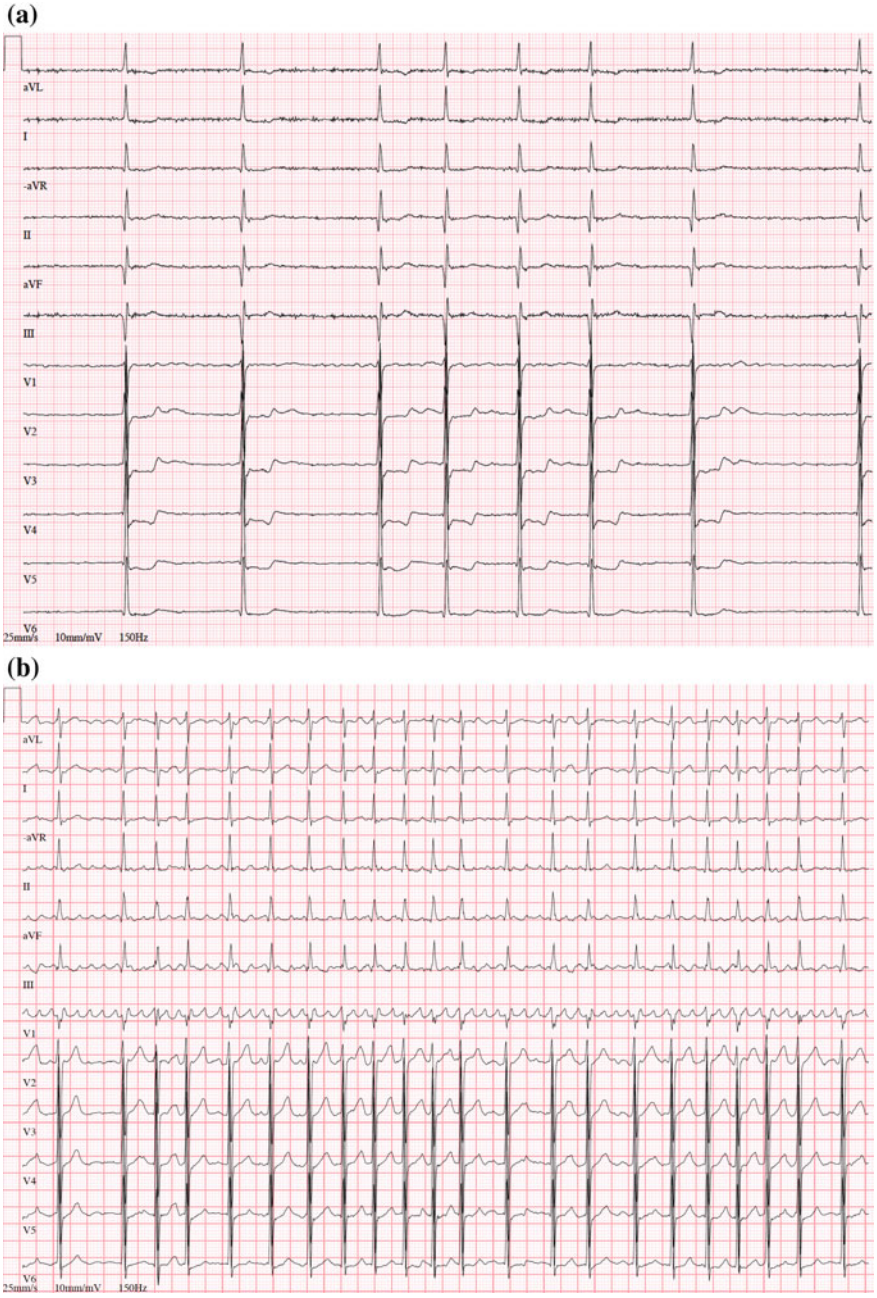


Fig. 1.2 Different ECG manifestations of AF. **a** Low-amplitude ("fine") f waves which are nearly isoelectric between the QRS complexes in all leads, and **b** large-amplitude ("coarse") f waves, particularly in the right precordial leads

The clinical relevance of the classification presented in Table 1.1 is based on the relationship between the persistence of AF episodes and the efficiency of therapeutic options aimed at terminating AF and preventing its recurrence. As a rule, the more persistent AF is, the more difficult it is to achieve arrhythmia freedom by therapeutic interventions.

The alternative way to describe AF is based on the presence of comorbidities, which may have etiological links to the arrhythmia itself. In this regard, description of AF as valvular or nonvalvular is one of the most commonly used in clinical practice. The reason for this description is also related to a rather specific and therapy-resistant course of the disease in patients with valvular disease, associated with volume and pressure overload of the left atrium, leading to severe left atrium dilatation and extensive fibrotic replacement of the atrial myocardium.

Lone AF is a historical descriptor that has been variably applied to predominantly younger persons without clinical or echocardiographic evidence of cardiopulmonary disease, hypertension, or diabetes mellitus. Because of the high variability in the use of this descriptor, lone AF is today considered as potentially confusing and rarely used to guide arrhythmia management.

1.4 Epidemiology of Atrial Fibrillation

Atrial fibrillation increases in prevalence with advancing age. Given the intermittent nature of the arrhythmia and indistinct symptoms present in a considerable proportion of patients with AF, the exact assessment of AF prevalence depends largely on the methodology used for screening of this condition. The use of routine resting ECG, or clinically motivated physical exams applied to epidemiological cohorts, estimates AF prevalence as 0.5% in individuals <50 years of age, 1.5–2% in 50–60 years of age, and 3% and higher in patients above 70 years of age (Fig. 1.3) [1]. However, dedicated population screening for AF using thumb-ECG, performed in Sweden,

Table 1.1 Clinical classification of atrial fibrillation

Type	Definition
New onset AF	is defined by the occurrence of the first episode, irrespective of its duration and severity of AF-related symptoms
Paroxysmal AF	is recurrent (≥2 episodes) and self-terminates in less than seven days, usually within 24 h
Persistent AF	fails to self-terminate within seven days. Episodes require termination by cardioversion
Long-standing persistent AF	has lasted for one year or more when it is decided to adopt a rhythm-control strategy
Permanent AF	exists when the presence of arrhythmia is accepted by the patient and the physician

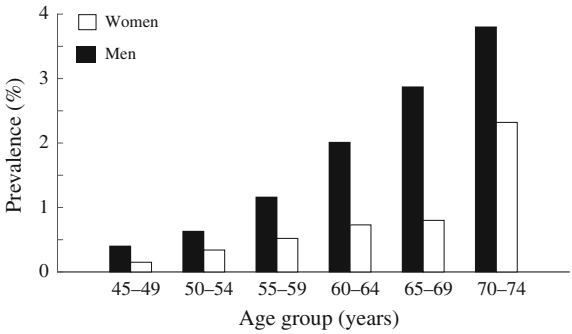


Fig. 1.3 Prevalence of AF according to age and gender [1]

demonstrated that 7% of the population older than 65 years have AF, of whom individuals >75 years of age have particularly high prevalence, reaching 12% [2]. Atrial fibrillation is significantly more common among men, particularly at young age, however, gender-related differences diminish with increasing age.

If we consider the age distribution among patients with AF, then approximately 1% of them are <60 years of age, whereas up to 12% are 75–84 years of age [3]. In the United States, the percentage of Medicare fee-for-service beneficiaries with AF was in 2010 reported to be 2% for those <65 years of age and 9% for those ≥65 years of age [4]. The lifetime risk of developing AF after 40 years of age was shown to be about 25%, being slightly higher among men than women [5].

1.5 Mechanisms of Atrial Fibrillation

Advances in clinical and fundamental research promoted over the last decades have led to a well-established understanding of AF as an epiphenomenon which despite similar manifestations may have different underlying mechanisms, thus requiring individualized treatment [6].

The mechanisms of AF are complex and require a combination of triggers, commonly represented by ectopic atrial firing and a vulnerable atrial substrate which promotes perpetuation of AF. The relative importance of trigger mechanisms and atrial substrate characteristics for the development of AF may vary and, to a large extent, affect clinical manifestations of the arrhythmia. Less advanced atrial substrate in the presence of rapidly firing atrial foci may be found in patients with paroxysmal AF with high likelihood of spontaneous conversion. On the other hand, age- or disease-related changes in atrial myocardium may lead to increased vulnerability of atrial myocardium and longer duration of AF episodes, which may become long-standing or permanent.

Focal ectopic firing originating from the myocyte sleeves within the pulmonary veins was first proposed in the late ’90s as the triggering mechanism of AF [7], which led to the development of catheter-based ablation therapy, resulting in reduc-

tion of AF burden. Contemporary understanding of the pulmonary veins role in the genesis of AF is based on the presence of myocytes exhibiting unique electrical properties, such as pacemaker cells, transitional cells, and Purkinje cells [8], and a complex fiber architecture which together promote reentry and ectopic activity initiating AF [9]. However, the presence of a trigger in atrial myocardium per se is not sufficient for initiation of AF, but requires prerequisites for stabilization of reentry in atrial myocardium in order to maintain AF. With rare exceptions of AF caused by mutations in genes coding ion channels in patients with structurally normal atria, fibrotic replacement of atrial myocardium remains the cornerstone of atrial pathology in patients with AF. However, the exact mechanisms underlying the structural abnormalities in the atrial walls observed in patients with the arrhythmia and its relationship to the arrhythmia mechanisms still remain poorly understood.

The common perception of AF as a result of the interplay between the structural changes in the atrial myocardium, induced by the well-described cardiovascular risk factors, and structural remodeling, induced by the arrhythmia itself, has recently been challenged by observations of progressive structural abnormalities in the atrial walls that occur independently of the cardiovascular comorbidities and persistence of AF [10]. It is also well-known that lone AF is not an uncommon clinical entity that may manifest early in life without any apparent risk factors, which would explain development of atrial fibrosis in patients with structurally normal hearts [11]. To what extent fibrotic atrial cardiomyopathy represents a "common cause" of AF or a mechanism responsible for arrhythmia development in a subgroup of patients with AF phenotype remains, however, uncertain.

1.6 Atrial Myocardium Characteristics in Atrial Fibrillation

An indirect indication of the link between cardiovascular comorbidities and AF comes from epidemiological studies in which potentially fibrosis-causing conditions such as hypertension, ischemic heart disease, and diabetes were highly predictive of incident AF [12]. Age-related increase in the prevalence of AF has also been well-documented [1], and explained by growing cardiovascular disease burden in the elderly as well as age-related increase in the extent of atrial fibrosis [13]. However, attempts to provide a quantitative assessment of atrial structural abnormalities associated with AF have shown a more complex picture. Even though catheter-based techniques of endocardial voltage mapping and emerging noninvasive magnetic resonance imaging (MRI) have shown their value in visualization of atrial structural abnormalities, histological evaluation of atrial tissue samples remains the gold standard for tissue characterization. This approach, however, is often limited to a small volume of tissue samples collected in patients undergoing atrial biopsy, or confined to right or left atrial appendages in patients undergoing open-chest heart surgery,

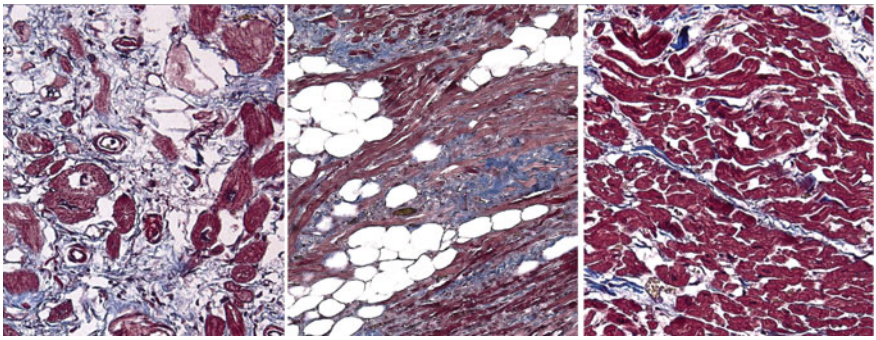
thus imposing a significant bias on patient selection and leaving large portions of the atrial walls, in which AF perpetuates, outside reach.

One of the first observations of the structural substrate of AF in patients without apparent structural heart disease came from studies where biopsies were collected from atrial septum as well as from ventricles in patients with lone AF [11, 14], reporting on a consistent finding of myocardial inflammation and fibrosis confined to the atrial myocardium, but not present in the ventricular walls. These studies were the first to suggest the presence of occult myocardial disease that may have direct causal relationship with development of AF.

The concept of atrial cardiomyopathy has been further expanded by studying histology specimens from multiple sampling locations in the right and left atrium collected post mortem from deceased patients with common cardiovascular comorbidities with previous paroxysmal, permanent AF, and those without AF history enrolled in three equal groups according to prespecified inclusion criteria [15]. The extent of fibrosis and fatty tissue in the atrial myocardium showed strong and significant correlation with the presence of AF at all tissue sampling locations in the left and right atria. Notably, patients with and without AF did not differ in regard to cardiovascular comorbidities, and no age-related increase in the extent of atrial fibrosis was observed. Similar observations were made in patients with persistent or long-standing AF referred for surgical ablation [16], thus suggesting that development of structural abnormalities in the atria is not a result of concomitant diseases, but rather a phenomenon associated with AF. Indirect assessment of atrial fibrosis using MRI in a large cohort has further supported this theory by not finding any significant differences in the estimated fibrosis extent between AF patients with and without comorbidities [17]. So far, however, there is no histology data that would specifically address the question of causal relationships between the burden of concomitant cardiovascular diseases and atrial fibrosis in patients with AF.

Contrary to the findings in lone AF, a similar extent of fibrotic replacement and inflammatory infiltration in the free walls of the right and left ventricles was observed in patients with common cardiovascular comorbidities [14]. In a controlled study, ventricular fibrosis demonstrated strong correlation with AF history and extent of fibrosis in the major atrial conduction routes such as Bachmann's bundle and terminal crest [18]. These findings may be interpreted as indicating an underlying occult cardiomyopathy with significant inflammatory component in patients with AF.

Whether or not structural abnormalities observed in the atria are the cause or consequence of AF remains an open question. The presence of a relationship between the extent of fibrosis and AF burden can be explained both ways: expansive fibrotic process in the atria may promote persistent AF, or be a consequence of the long-standing fibrillatory process. The lack of this relationship, however, would favor the concept of the primary fibrotic atrial cardiomyopathy underlying AF development. Available data suggest that the extent of fibrosis tends to be larger in patients with permanent AF than in patients with paroxysmal AF [15], see Fig. 1.4, but the relationship between extent of structural abnormalities and duration of AF seems to disappear in patients with persistent AF [16]. In another study that quantified the expression of extracellular matrix proteins in atrial tissue samples collected during



(a) Permanent AF **(b)** Paroxysmal AF **(c)** No history of AF

Fig. 1.4 Light microscopy of crista terminalis specimens in patients with or without history of AF. **a** Fibrosis extent 51%, fat 15%, capillary density 2%, mean cardiomyocyte diameter 12 m, **b** fibrosis extent 14%, fat 24%, capillary density 0.4%, mean cardiomyocyte diameter 11 m, and **c** fibrosis extent 5%, fat 1%, capillary density 1%, mean cardiomyocyte diameter 15 m. (Masson's trichrome stain; original magnification 200). (Reprinted from [15] with permission)

heart surgery, no systematic difference between patients with paroxysmal and permanent AF was documented [19]. Even though this does not address the unresolved causality issue, one can speculate that fibrosis extent in the atrial walls may be linked to AF burden and clinical manifestations of the arrhythmia at the early stages of the disease. However, upon reaching a certain level, fibrosis would no longer affect AF phenotypes in patients who develop persistent AF.

1.7 Atrial Fibrillation and Stroke

Ischemic stroke is a devastating complication of AF. One in five of all strokes is attributed to AF [20], and AF in stroke patients confers an increased risk of morbidity and mortality when compared with non-AF-related stroke [21]. The main mechanism of AF-related stroke is considered to be thrombus formation in the left atrium in condition of irregular contractility. When a blood clot is formed it can be pumped out of the heart to the brain, leading to cerebral artery occlusion.

Clinical risk factors for development of ischemic stroke in patients with AF are well-known. The CHA_2DS_2–VASc score is a clinical tool developed to assess the risk of ischemic stroke in patients with AF and to guide administration of oral anticoagulation therapy, with proven effect on reduction of the risk of ischemic stroke [22, 23]. The letters of the score stand for individual risk factors known to predispose to ischemic stroke, involving the following risk factors:

- **C**ongestive heart failure (1 point),
- **H**ypertension (1 point),
- **A**ge $\geq$75 years (2 points),

- **D**iabetes mellitus (1 point),
- **S**troke/Transient ischemic attack/Thromboembolism (2 points),
- **V**ascular disease (1 point),
- **A**ge 65–74 years (1 point),
- **S**ex **c**ategory (female) (1 point).

Advanced age of ≥75 years and history of ischemic stroke are the most powerful predictors of ischemic stroke in patients with AF, receiving double points in the risk score calculation. In general, patients with a high CHA_2DS_2–VASc score are recommended life-long oral anticoagulation therapy.

An important aspect of the CHA_2DS_2–VASc score applicability is its dependence on AF diagnosis, which means that patients fulfilling one or more criteria listed in the risk score would not be offered stroke prevention therapy unless AF is documented. However, AF is often asymptomatic, and sometimes ischemic stroke may be the first clinical presentation of underlying AF.

It has been reported that at least one third of patients with AF had asymptomatic AF [24, 25]. In patients with implantable devices, subclinical AF was quite common and associated with increased risk of stroke [26]. In this context, sensitivity and specificity of AF screening techniques as well as the reasonable balance between the associated costs, the need for surgical interventions (as in the case of implantable subcutaneous monitors), and the risk of false positive AF detection become the factors defining the clinical utility of AF screening.

As the history of ischemic stroke automatically places a patient with AF in the high-risk group regarding ischemic stroke recurrence, screening for AF becomes particularly important in ischemic stroke survivors. Using the standard ECG at admission with ischemic stroke, AF is documented in 20–25% of those who survived ischemic stroke [21, 27]. Additional, repeated conventional snapshot ECG recordings after stroke onset appeared to increase AF detection rate by 1.4–6.7% [28–30]. Diagnostic yield of 24–48-h continuous, ambulatory ECG monitoring in patients with ischemic stroke and sinus rhythm at admission has been reported to be 1–6.4% [28, 30, 31], increasing to 12.5% when monitoring was continued for a week [31]. In stroke patients who underwent 30-day ambulatory, automatically triggered AF detection, AF was documented in 6–11% of cases [2, 32]. Outpatient cardiac telemetry during 3–4 weeks in patients with cryptogenic stroke revealed 17–20% of new AF cases [33, 34]. However, the highest detection rate of AF in patients with cryptogenic stroke was reported in patients with insertable cardiac monitors and appeared to be 30% [35]. Though the superiority of the latter strategy for AF detection is obvious, its cost-effectiveness is largely affected by proper selection of patients who would benefit from continuous screening for AF.

While AF most certainly is a risk factor for ischemic stroke, it is not necessarily the direct cause of it. The causality of association between AF and ischemic stroke was questioned by the reported lack of temporal relationship between stroke events and symptomatic AF paroxysms or atrial high-rate episodes detected by an implantable loop recorder [36–38] or an implantable device [39–42]. In different studies, only 2% of patients had subclinical AF episodes lasting more than 6 min at the time

of stroke or systemic embolism [43]. Among the plausible explanations for this change of paradigm is the recently proposed concept of fibrotic atrial cardiomyopathy [44], according to which AF may result from an underlying progressive disease affecting atrial myocardium and resulting in replacement of myocardium with fibrosis and fat, increasing atrial thrombogenic properties, and the risk of stroke, which in this situation does not have to express a temporal relationship with the arrhythmia episodes.

Finally, availability of diagnostic information recorded directly from the atria in patients with implanted dual-chamber pacemakers or cardioverter–defibrillators poses a new challenge of interpretation. Our knowledge regarding clinical importance of AF and its relationship to stroke has been built on clinical AF episodes, i.e., AF detectable by conventional means of ECG diagnostics, while implantable device-detected arrhythmias, also called atrial high-rate episodes, are often subclinical, asymptomatic, and short in duration, which in some cases may only last several seconds. Even though these episodes may have electrogram characteristics indistinguishable from AF, it is yet unknown whether such brief AF episodes are associated with a risk of stroke similar to that of conventionally defined AF.

1.8 Principles of Atrial Fibrillation Management

Management of patients with AF is aimed at reaching two fundamental goals: prolonging life and improving its quality by reducing arrhythmia-related symptoms. Three major treatment strategies have been developed and implemented:

1. Ischemic stroke prevention (oral anticoagulation)
2. Heart rate control during AF (rate-control strategy)
3. Prevention of AF (rhythm-control strategy).

Only ischemic stroke prevention was shown to reduce mortality in patients with AF, while rate- and rhythm-control strategies remain the key elements of AF patients care with the primary objective to improve quality of life.

1.8.1 Ischemic Stroke Prevention

Prevention of thromboembolic complications of AF is achieved by administration of medications attenuating blood-clotting capacity (i.e., anticoagulants) to individuals at high risk of ischemic stroke. The challenge to be met when using anticoagulation therapy is to maintain the fine balance between the benefit of reducing propensity to clotting and the potential harm of the drugs related to their inherent property of prolonging bleeding time and the risk of bleeding complications, which in some cases may be fatal, such as intracranial bleedings. Clinical decision-making tools have

been proposed to facilitate administration of stroke-prevention measures to individuals in need. The most commonly used risk quantification tool recommended by the management guidelines is the above-mentioned CHA_2DS_2–VASc score, which estimates the probability of ischemic stroke. However, balancing the risk of bleeding is not an easy task since a number of factors included in the CHA_2DS_2–VASc score increase both the risk of ischemic stroke and the risk of major bleeding complications of anticoagulant therapy: hypertension, advanced age, and the history of stroke.

Recent studies that questioned the causal relationships between the arrhythmia and embolic events, reviewed earlier in this chapter, have led to a paradigm shift suggesting that AF may be a marker of the increased risk of ischemic stroke rather than its direct cause. Interestingly, a number of studies have shown that the CHA_2DS_2–VASc score not only predicts the risk of ischemic stroke, but it is also a reasonably accurate tool to predict the development of AF in patients without known AF history. This strategy is based on the findings documented in cohorts of ischemic stroke survivors [45, 46] and in selected cohorts of patients evaluated for palpitations [47, 48]. Therefore, it is plausible to suggest that patients with a high CHA_2DS_2–VASc score may benefit from oral anticoagulation therapy without need for documentation of AF. The clinical utility of this approach remains to be proven in ongoing clinical trials. It is likely, however, that its risk–benefit ratio will largely depend on the CHA_2DS_2–VASc score cut-off selected for making the decision to initiate anticoagulation and the underlying risk of bleeding.

1.8.2 Rate-Control Strategy

Whether a patient would benefit from implementation of rate-control measures is the question that needs to be asked for every patient with AF, regardless of the severity of clinical manifestations of the arrhythmia. Some patients with high ventricular rate during AF may not have any distinct symptoms associated with fast and irregular heartbeats. However, if left untreated, high ventricular rate may lead to deterioration of ventricular contractile function, reduction of cardiac pumping capacity, and dilatation of the ventricular chambers (known as tachycardiomyopathy) with development of heart failure as the ultimate consequence. Adequate rate-control improves quality of life, reduces morbidity, and decreases the potential for developing tachycardia-induced cardiomyopathy.

The degree of rate control and the thresholds defining adequately controlled ventricular response during AF remain, however, an area of uncertainty. According to a "strict rate-control approach", the goal of rate-control therapy is to bring the heart rate down to $\leq$80 beats per minute (bpm) at rest, or the average heart rate $\leq$100 bpm in ambulatory monitoring. These thresholds, however, may be difficult to achieve in clinical practice in a considerable part of patients with AF. In a single study, an alternative "lenient rate-control approach", using instead 110 bpm at rest, was tested and shown to be noninferior to the strict rate-control strategy [49]. Additional independent confirmatory studies are needed to fully understand the impact of the

lenient rate-control approach on mortality, heart failure symptoms, hospitalizations, and quality of life.

Rate control may be achieved by different means, including the use of pharmaceuticals or catheter-based therapies. Some antiarrhythmic drugs, including beta-blockers, calcium antagonists, or cardiac glycosides, have proven efficient in slowing down ventricular response during AF through their blocking effect on the AV node. The choice of the drug remains empirical and is driven mainly by the presence of contraindications of or intolerance to certain compounds. As a last resort, the powerful antiarrhythmic drug amiodarone can be used to control the heart rate. Due to the risk of serious side effects that may appear during long-term administration, the use of amiodarone is restricted to rare occasions when other drugs fail to achieve the therapeutic goals.

In rare cases when rate control cannot be achieved by medication due to either drug intolerance or inefficiency, catheter-based therapy may be applied. Ablation of the atrioventricular junction, achieved by local application of either radiofrequency current or deep freezing (cryoablation), leads to destruction of the functional connection between the atria, which may continue to fibrillate, and the ventricles. Obviously, this approach is only feasible in patients with implanted pacemaker, either received for other indication or implanted specifically to enable AV junctional ablation. Patients undergoing AV junctional ablation become pacemaker-dependent, which is an important limiting factor, and, therefore, this approach is the last one in the armamentarium of AF therapies. On the bright side, however, remains the fact that ventricular contractions become regular and steered exclusively by a programmable pacemaker, eliminating the concern of high rate without the need for rate-control pharmacological therapies.

1.8.3 Rhythm-Control Strategy

Rhythm-control strategy includes all therapeutic interventions aimed at prevention of AF recurrences and restoration of sinus rhythm using a combination of approaches, including cardioversion (electrical or pharmacological), antiarrhythmic drugs, and catheter ablation in the setting of appropriate anticoagulation and rate control.

It may seem surprising that rhythm-control strategy aimed at restoration or maintenance of sinus rhythm is the last item on the list of AF therapies. However, this approach, still reserved for the most symptomatic patients, has not been associated with mortality reduction and may be associated with increased number of hospital admissions. While stroke prevention and rate control are considered obligatory components of care for patients with AF, rhythm-control measures are generally reserved for patients who remain symptomatic despite adequate rate control.

In some situations, however, rhythm-control strategy may be prioritized over rate-control measures. This may be important in situations when it is difficult to achieve adequate rate control in younger patients, in tachycardia-mediated cardiomyopathy, during the first episode of AF, in AF precipitated by an acute illness, or patient pref-

erence. Another argument favoring rhythm-control strategy over limited rate-control intervention is that AF progresses from paroxysmal to persistent in many patients and subsequently results in electrical and structural remodeling which eventually becomes irreversible. For this reason, acceptance of AF as permanent in a patient may render future rhythm-control therapies, if needed, less effective. This observation may be more relevant for a younger patient who wishes to remain a candidate for future development in rhythm-control therapies. Early intervention with a rhythm-control strategy to prevent progression of AF may therefore be beneficial.

Restoration of sinus rhythm may be achieved by means of either antiarrhythmic drugs (pharmacological cardioversion) or delivery of electrical shock through the electrodes applied on the chest of the patient (electrical cardioversion). Whether to choose pharmacological or electrical approach to cardiovert a patient with AF depends on a number of factors.

Electrical cardioversion is generally considered the most efficient way to restore sinus rhythm. Compared to pharmacological cardioversion, which may have a success rate varying from 30 to 60% depending on the choice of drug, degree of atrial remodeling, and duration of the AF episode, electrical cardioversion, electrically resetting cardiomyocytes using appropriate shock settings, terminates AF immediately in more than 90% of all patients. On the other hand, restoration of sinus rhythm using electrical cardioversion requires sedation, which itself is not a risk-free intervention and does not prevent immediate recurrence of AF.

Pharmacological cardioversion, on the other hand, does not require sedation, but is more time-consuming, in part due to the time required for an antiarrhythmic drug to reach therapeutic concentration in the body, and in part due to the need for rhythm observation after drug administration in order to monitor potential proarrhythmic effects of the potent antiarrhythmic drugs used for pharmacological cardioversion. With few exceptions, most of the drugs suitable for pharmacological cardioversion are also efficient as rhythm-control agents which may be administered over long periods of time to reduce the frequency and duration of AF and to improve quality of life. Since rhythm-control strategy is the approach aimed at improving quality of life, rather than reducing mortality, the choice of drug is, to a greater extent, guided by safety concerns related to proarrhythmic side effects, expressed by nearly all potent antiarrhythmic drugs, than by drug efficacy. Patients with coronary artery disease, heart failure, and significant left ventricular hypertrophy have more restricted options than those with minimal or no structural heart disease.

Catheter ablation has evolved from an experimental technique, having emerged at the end of ’90s [50], to become an efficient treatment modality, which in selected patient populations has demonstrated efficacy superior to antiarrhythmic drugs [51]. The approach is based primarily on the creation of electrically impenetrable boundaries surrounding the ostia of pulmonary veins, using either radiofrequency current or deep freezing delivered with a catheter placed in the left atrium. Depending on the degree of atrial remodeling and arrhythmia persistence, pulmonary vein isolation may be combined with additional lines in the left or right atrium aimed at further hampering propagation of fibrillatory waves in the atrial myocardium, and thus to reduce the likelihood of AF maintenance. The evidence supporting the efficacy of

catheter ablation is strongest for paroxysmal AF in young patients with little or no structural heart disease, and in procedures performed in highly experienced centers. As of today, the effect of catheter ablation on reduction of mortality, stroke, or heart failure is insufficient. The ongoing randomized clinical trials "Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation" (CABANA) and "Early Therapy of Atrial Fibrillation for Stroke Prevention Trial" (EAST) are expected to provide new information to assess whether catheter ablation is superior to standard therapy with either rate- or rhythm-control drugs for reducing total mortality, and whether early application of rhythm-control strategy can impact the risk of ischemic stroke, cardiovascular death, or the development of heart failure. This research will help us to understand whether catheter ablation provides benefit beyond improvements in quality of life in patients with AF.

In clinical practice, the ability to predict the likelihood of AF conversion (either spontaneous or induced by antiarrhythmic drugs) and the risk of AF recurrence after cardioversion or catheter ablation would be useful for planning rhythm-control therapies and avoiding unnecessary interventions. In patients prone to regain sinus rhythm spontaneously within a reasonable time frame, cardioversion attempt, for example, can be withheld or postponed. Patients who are unlikely to respond to an antiarrhythmic drug can be scheduled for electrical cardioversion instead, while those who are unlikely to maintain sinus rhythm over a considerable time span may not be good candidates for rhythm-control strategy at all. Therapeutic efforts could instead be focused on achieving appropriate rate control. The proper stratification tool, however, is still lacking.

The degree of structural and electrical remodeling of the atria in patients with AF is considered the factor which, to a large extent, defines the probability of success in applying rhythm-control strategy. In general, patients with long-lasting persistent AF, enlarged atria, and extensive fibrotic replacement of myocardium in the atrial walls are less likely to benefit from cardioversion. Clinical assessment of these factors may involve using different diagnostic modalities such as echocardiography, MRI, and endocardial voltage mapping, which may not be practical for all patients, is associated with significant costs and catheterization-related risks. On the other hand, characteristics of the atrial fibrillatory process, retrievable from the ECG in terms of frequency content and degree of organization, may contain important prognostic information [52, 53].

1.9 Electrocardiography in Atrial Fibrillation Diagnosis

Novel wearable devices can greatly improve the diagnosis of AF in ambulatory outpatients. For screening purposes, low-cost and easy-to-use handheld or wearable devices can be used to record the ECG, either with a dedicated device or a smartphone. In both cases, a single-lead ECG is recorded between the thumbs, fingers, or palms. Using handheld devices, systematic screening has been performed in a population at risk under certain circumstances, e.g., in primary care during seasonal influenza

vaccination in the Dutch population aged 65 years and older [54], or in stroke and transient ischemic attack patients [55]. For example, the smartphone has been used for screening purposes in community pharmacies [56] and in subjects identified via general practitioner records [57]. Section 2.3 provides an overview of different technologies available for recording the ECG.

A large number of studies suggest that handheld or wearable devices are well-suited for AF screening, particularly in high-risk patients. This would be of great importance from a clinical point of view as more patients with AF would be detected at an early stage. However, early identification/detection of AF is compounded by the silent nature of AF in about one third of all patients [24]. Since the risk of stroke is the same for silent AF and symptomatic AF [58], it is important to detect the arrhythmia at an early stage so that therapies can be introduced which protect the patient from progression of AF as well as from the consequences of the arrhythmia.

In ECG-based detection of AF, the analysis of RR intervals has received the most attention since such information is readily available in most applications. However, such analysis is problematic when an AF episode is preceded by some other type of arrhythmia which is also manifested by an irregular ventricular rhythm resembling AF. Therefore, the analysis of P and f waves, although being more complex, is receiving more attention since morphologic information is essential when distinguishing AF from other arrhythmias. Morphologic information is also essential to the detection of brief AF episodes since a handful of RR intervals does not provide accurate quantification of rhythm irregularity. Chapter 4 provides a comprehensive review of AF detectors based on rhythm information as well as on rhythm and morphologic information.

Despite its disadvantages, rhythm-based detection offers the possibility to detect AF in single-lead pacemakers or defibrillators. From a clinical point of view, new onset or new recognition of AF in patients with reduced left ventricular systolic function is common, and therapeutic decisions are made easier by accurate estimation of AF burden. Another group of patients which would benefit from early detection of AF are those with heart failure and a biventricular pacemaker implanted, in whom long episodes of undetected AF may substantially reduce biventricular pacing up to causing decompensation [59].

1.10 Standardization of Atrial Fibrillation ECG Characteristics Assessment

There is considerable variation in the methodology and definitions of parameters used to characterize AF between different clinical and engineering research groups. While some of the ECG-based parameters for characterizing f waves, e.g., the atrial fibrillatory rate (AFR) and the closely related dominant AF frequency (DAF), have been tested in clinical contexts for more than a decade, the clinical significance of novel descriptors characterizing the degree of AF organization with, e.g., signal

entropy or harmonic decay in the power spectrum, is limited to small-cohort studies which are either cross-sectional or retrospective by design, and thus stay even farther away from clinical routine than do the parameters which characterize the spectral properties of the f waves. The interdependence of different parameters of AF and their relation to methodological issues also remains to be further investigated.

It is not known to what extent differences in the methodology used for AF assessment may affect the results. Differences in signal processing algorithms, not always apparent from the descriptions of published methods which may involve proprietary information, can influence the result of studies comparing different methodologies. There is a paucity of data that would compare performance of individual methods of AF complexity assessment on the same patient cohort performed by different groups, which further reinforces the need for exchange of data and methodology. There is an unmet need for reproducibility studies of AF parameters in the clinical context. However, methodological differences may hamper interpretation and comparability of study findings, thus suggesting that reproducibility studies should ideally be preceded by applying an alternative methodology to the same patient cohort as used in the original study before testing performance of biomarkers on a different patient cohort.

One can draw a parallel with studies assessing the value of biochemical or genetic markers for diagnosis or prognosis in the clinical context. It is unlikely that the results of such studies would be comparable and generalizable in clinical practice if different non-standardized laboratory procedures would be used for estimation of biomarker values or identification of genetic variants. Until similar logic is applied to ECG-derived AF parameters, it would be unrealistic to expect that results of the studies involving ECG signal processing will be widely implemented in clinical practice.

From the clinical point of view, AF is such a multicausal rhythm disorder so that its clinical impact and interpretation of ECG characteristics should not be assumed to have similar meaning in different clinical contexts [6]. More importantly, despite years of clinical research and refinement of methodologies aimed at characterizing AF complexity, we are still far from understanding the natural course of different markers which can be derived from the ECG, their intra-individual reproducibility during recurrent AF episodes, propensity to showing circadian behavior, relation to the time from AF onset, and the degree of AF persistence and evolution during long-time observation in patients with permanent AF.

Taking AFR as an example of a spectral parameter that was assessed using the same methodology in the context of sinus rhythm restoration and maintenance after cardioversion, it was found to lack predictive value in patients with long-standing AF [60], to have significant association between a lower AFR and a higher probability of sinus rhythm during follow-up in patients with shorter AF duration [61], and to be highly predictive of spontaneous conversion in patients with AF duration less than 48 h [62]. At the same time, AFR is known to express circadian fluctuations, at least in patients with permanent AF [63, 64], and to demonstrate pronounced and rapid acceleration over the course of several minutes [65] to 3–4 h from the onset of an AF episode [66].