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DETECTION OF BRIEF EPISODE PAROXYSMAL ATRIAL FIBRILLATION

Doctoral dissertation

Technological Sciences, Electrical and Electronics Engineering (01T)

2015, Kaunas

UDK 004.9 + 0047.89 + 616.12-008.318] (043.3)

This doctoral thesis was prepared at Kaunas University of Technology, Biomedical Engineering Institute, during 2011–2015. The research was funded by the Research Council of Lithuania.

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Language editor:

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This dissertation is available at:

http://www.ktu.edu

ISBN 978-609-02-1166-3

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List of terms and abbreviations

A	An area under the receiver operating characteristic (ROC) curve
ABS	Average beat subtraction
AF	Atrial fibrillation
Ambulatory monitoring	A way of acquiring physiological data during normal daily activities
APB	Atrial premature beat
Brief AF	Atrial fibrillation episode lasting less than 30 s
Cryptogenic stroke	Stroke with unknown cause
E	Root-mean-square (RMS) error between two signals
ECG	Electrocardiogram
EMG	Electromyogram
ESN	Echo state network
f-waves	Continuous atrial activity on the surface ECG during atrial fibrillation
P-wave	Atrial depolarization on the surface ECG
PPV	Positive predictive value
PQRST complex	A complex observed on the surface ECG corresponding to depolarization of the atria, depolarization and repolarization of the ventricles
PR interval	Time interval from the sinus node activation to the atrioventricular node activation
QRS complex	A wave observed on the surface ECG representing depolarization of the ventricles
QRST complex	A wave observed on the surface ECG corresponding to depolarization and repolarization of the ventricles
r interval	The time interval between two adjacent contractions of the ventricles
S	Classification ratio
Se	Sensitivity
Sp	Specificity
SR	Sinus rhythm – normal rhythm of the heart
Systemic embolism	Thrombus in blood vessels
T-wave	Repolarization of the ventricles on the surface ECG
TQ interval	Time interval from the end of repolarization of the ventricles to the onset of adjacent depolarization of the ventricles
Transient ischemic attack	A temporal event of neurologic dysfunction causing no permanent damage
VPB	Ventricular premature beat

1 INTRODUCTION

Relevance of the research

Atrial fibrillation (AF) has emerged as a worldwide cardiovascular epidemic affecting more than 33 million individuals around the world (Chugh et al., 2014). However, recent findings suggest that the actual prevalence of AF due to asymptomatic paroxysmal episodes is considerably larger (Camm et al., 2010). Given that AF is primarily a disease of older individuals, being much more common among > 65 year-olds compared to the general population, the prevalence is expected to increase up to 3-fold in the upcoming decades due to the progressive aging of society (Colilla et al., 2013). Atrial fibrillation is not considered as a life-threatening arrhythmia itself, however individuals with AF have an increased incidence of various comorbidities, including a 5-fold increased risk of stroke, 3-fold increased risk of heart failure and 2-fold increase in general mortality rates (January et al., 2014). Atrial fibrillation is a progressive disease, with primary paroxysmal AF episodes being usually brief and rarely occurring therefore treatment success highly depends at what stage of arrhythmia development AF is detected.

While existing technologies for AF detection are suitable for detection of prolonged and often chronic AF, there is an unsolved issue of reliable detection of self-terminating and usually asymptomatic paroxysmal AF episodes. In addition, recent results from prolonged rhythm monitoring using implanted devices demonstrate an independent association between brief AF episodes, lasting less than 30 s, and a future risk of stroke (Seet et al., 2011; Flint et al., 2012). For this reason, the significance of brief episodes of paroxysmal AF is currently receiving considerable attention in clinical research (Kishore et al., 2014; Favilla et al., 2015; Keach et al., 2015). It is hypothesized that brief episodes may be coupled to the formation of atrial thrombus, and that brief episodes may be viewed as biomarkers of prolonged episodes occurring outside of the monitoring period. Ultimately, continuous long-term monitoring, lasting from several weeks to months, should be performed so that all episodes of paroxysmal AF are detected, including the very brief ones, and therefore, it is essential that reliable detection techniques are developed.

To this day, most methods for AF detection are based solely on the analysis of irregularity of ventricular contractions – a detector structure which is more prone to produce false alarms, especially when an irregularity causing ectopic beats are present (Lake and Moorman, 2011; Huang et al., 2011; Lee et al., 2013a; Zhou et al., 2014). Although attempts have been made to mitigate the problem of false alarms by also involving information of atrial electrical activity, the performance of such AF detectors have not turned out to be better; mostly due to low amplitude of atrial electrical activity and misleading influence of noise (Couceiro et al., 2008; Babaeizadeh et al., 2009; Ladavich and Ghoraani, 2015). In connection with reduction of false positives, almost all AF detectors require at least a 30 s episode for satisfactory AF detection.

In addition, it is desirable not only to detect all episodes of paroxysmal AF, but also to provide quantitative information on atrial fibrillatory activity during each AF episode. Recent studies show that atrial fibrillatory frequency has potential to be applied as a

biomarker for prediction of therapeutic success and spontaneous AF behaviour (Platonov et al., 2014). Thus, long-term monitoring of fibrillatory activity would allow better evaluation of temporal AF behaviour and define signal-based parameters that could provide additional information on the efficacy of different treatment strategies.

Scientific-technological problem and working hypothesis

In this thesis, a clinically relevant scientific-technological problem of brief episode paroxysmal AF detection in ambulatory monitoring applications is covered. To properly tackle this problem, false alarm rate reduction and handling of noisy signals are crucial issues that need to be solved. Hence, the hypothesis is formulated so that the performance of brief episode paroxysmal AF detection can be improved by involving information provided by the atrial electrical activity, taking into account the prevailing noise level in the analysed signal. The hypothesis is proved by comparing the obtained results with those provided in the scientific literature, using both clinical and simulated data.

Research object

The research is based on the development and investigation of the algorithms for automatic detection of brief episode paroxysmal AF in continuous ambulatory monitoring applications.

The aim of the research

This doctoral thesis aims to develop and investigate a non-invasive system for automatic detection and characterisation of brief episode paroxysmal atrial fibrillation.

The objectives of the research

1. To develop and investigate a low-complexity algorithm for detection of paroxysmal atrial fibrillation in continuous monitoring devices.

2. To propose and investigate a reliable solution for the atrial electrical activity extraction during atrial fibrillation using a reduced set of electrocardiogram leads.

3. To propose and evaluate a signal processing approach for brief episode paroxysmal atrial fibrillation detection in ambulatory electrocardiogram recordings.

4. To provide electrocardiogram lead configuration suitable for long-term ambulatory monitoring of atrial fibrillation.

Scientific novelty

In this doctoral thesis, the recurrent echo state neural network is proposed as a solution to the problem of ventricular electrical activity cancellation in electrocardiogram signals using just two electrocardiogram leads. The proposed method is capable of dealing with the presence of substantial variation in electrocardiogram beat morphology, thus no dedicated algorithm is needed for the handling of ventricular premature beats. Other

essential features of the proposed method are sample-by-sample data processing and processing of short data segments.

Two high performing approaches for detection of paroxysmal AF have been proposed. One of them was developed to analyse the time intervals between adjacent contractions of the ventricles, hence various signals containing heart rhythm information (e.g. electrocardiogram, photoplethysmogram, impedance plethysmogram) can be used as a subject for analysis. On the other hand, the other AF detector was developed solely for analysis of electrocardiogram signals. Since both heart rhythm and morphology information is included into the AF detection process, such an AF detector is well suited for detection of brief AF episodes. The aforementioned AF detectors can be used either separately or can be combined into a unified two-stage AF detector, where the heart rhythm analysis based algorithm can also serve the purpose to flag potentially AF episodes.

A low-complexity structure of the heart rhythm analysing AF detector makes it possible to implement the algorithm in a low-energy device for use in long-term monitoring applications, since only a few arithmetical operations are required for data processing. A high performance is ensured by accounting for the most commonly encountered sources of false alarms due to ectopic heart beats. Despite the simplicity of the algorithm, the resulting performance is above that achieved by most AF detectors described in the scientific literature.

The other approach to AF detection has covered a previously unsolved problem of detection of brief episode paroxysmal AF, lasting just 5–30 s. It differs from the existing technologies for AF detection, since the proposed solution characterise both atrial and ventricular activity, and accounts for the noise level in the electrocardiogram signal. Therefore, a reliable AF detection is ensured even when noisy signals are applied for the analysis.

Lastly, an electrocardiogram lead configuration (modified Lewis lead system) for ambulatory monitoring of AF has been derived. Compared to conventional lead systems that are suitable for ambulatory monitoring, the proposed configuration involves electrodes that are moved to areas of the thorax with less muscle, and therefore, offers immunity to electromyographic noise and motion artefacts. Together with a high atrial-to-ventricular activity ratio, the proposed lead system has potential to improve ambulatory monitoring of AF and other atrial arrhythmias.

Practical significance

1. The developed solutions for ambulatory monitoring of paroxysmal AF can be used in the following clinical applications:

   (a) Due to low-complexity structure, heart rhythm analysis-based algorithm for paroxysmal atrial fibrillation detection can be implemented in a low-power device for prolonged monitoring applications.

   (b) A method for atrial activity extraction using a minimal set of electrocardiogram leads is well suited for implementation in mobile health systems where

monitoring of AF during extended time periods is of interest.

(c) A method for detection of brief episode paroxysmal atrial fibrillation has potential to be used for AF detection in high risk patient groups, i.e., after cryptogenic ischemic stroke or acute myocardial infarction.

(d) A proposed modification of electrocardiogram lead system due to enhanced component of atrial electrical activity and increased immunity to noise can help to improve ambulatory monitoring of atrial arrhythmias.

2. The methods provided in this thesis have been developed in support of the following projects:

   (a) "Novel technical solutions and biomarkers in mobile patient monitoring" under the Swedish Institute VISBY programme (No. 00923/2011), 2011–2013.

   (b) "Intellectual wearable sensors system for human wellness monitoring" under the European Social Fund (No. VP1-3.1-SMM-10-V-02-004), 2013–2015.

3. Currently the developed methods are being used in the following projects:

   (a) "Personalized patient empowerment and shared decision support for cardiorenal disease and comorbidities – CARRE" funded by the European Commission Framework Programme 7 (No. 611140), 2013–2016. Application: paroxysmal AF detection in patients suffering from cardiorenal syndrome.

   (b) "Automatic algorithms for atrial fibrillation risk prediction after acute myocardial infarction" supported by the Research Council of Lithuania (No. MIP-15391), 2015–2017. Application: brief episode paroxysmal AF detection in patients after acute myocardial infarction.

Approval of the results

The doctoral thesis relies on 4 main papers, published in the international scientific journals referred to in the Thomson Reuters Web of Science database, while in total the results have been published in 11 scientific papers. The essential results have been presented in 9 conferences, including the worldwide recognized "41^{st} International Congress on Electrocardiology", and the 39^{th} and 40^{th} conferences of "Computing in Cardiology".

The research has been positively assessed both internationally and domestically: nominated as a finalist at the Rosanna Degani Young Investigators' Award competition at the conference "Computing in Cardiology 2012", received the 3^{rd} place prize at the Young Scientists Contest in the "41^{st} International Congress on Electrocardiology" (2014), 1^{st} place award for the presentation at the section of "Cardiovascular Diseases" at the conference "Science for Health 2014" (Lithuanian University of Health Sciences), 1^{st} place award ("Infobalt" scholarship) for the presentation at the conference "Interdisciplinary Research in Physical and Technological Sciences" (2015, Lithuanian Academy of Sciences), and a prize for the most attractive project for business (with co-authors) at the

Young Scientists Exhibition “KTU Technorama 2015” (Kaunas University of Technology).

The statements presented for defence

1. A high performance of paroxysmal atrial fibrillation detection can be ensured by relying solely on heart rhythm analysis using a low-complexity structure of the algorithm.

2. Echo state neural network based adaptive filter provides a reliable solution for fibrillatory activity extraction using a minimal set of electrocardiogram leads, both in short data segments and the presence of physiological disturbances.

3. A combination of atrial and ventricular electrical activity characterizing parameters, together with prevailing noise level offers a solution for reliable detection of brief episode paroxysmal atrial fibrillation in ambulatory electrocardiogram recordings.

4. A derived electrocardiogram lead configuration provides a unified solution for enhanced atrial activity and reduced influence of electromyographic noise and motion artefacts in ambulatory arrhythmia monitoring applications.

Structure of doctoral thesis

Thesis is organized as follows. Sections 2 and 3 are designated for the analysis of relevant scientific literature with respect to clinical significance of AF and available technologies for AF detection. Section 4 presents algorithms developed both for fibrillatory signal extraction and AF detection. In the same section, an electrocardiogram lead system for ambulatory monitoring of AF is proposed. Section 5 describes the data used for performance evaluation, and presents the results obtained for each of the proposed solutions. The doctoral thesis is finished with general conclusions (Sec. 6).

The thesis consists of 140 pages, 54 figures, 14 tables and 269 references.

2 CLINICAL SIGNIFICANCE OF ATRIAL FIBRILLATION

2.1 Medical background and clinical implications

2.1.1 Introduction to atrial fibrillation

Atrial fibrillation (AF) is an abnormal heart condition occurring when contraction of the upper chambers (the atria) is driven by electrical activity of different areas of atrial tissue (Fig. 2.1). Normally, atrial cells are depolarized by the sinus node approximately once per second, however, during AF, the firing rate of atrial cells may markedly increase, up to 300–600 times per minute. Since the lower part of the heart (the ventricles) is continuously bombarded by the electrical impulses arriving from the atria, the ventricles are affected as well. Fortunately, only a small portion of the atrial impulses reach the ventricles – mainly due to the impulse filtering ability of the atrioventricular (AV) node, which separates the electrical systems of the atria and the ventricles. Otherwise, such a high ventricular rate would be fatal, eventually leading to sudden cardiac death.

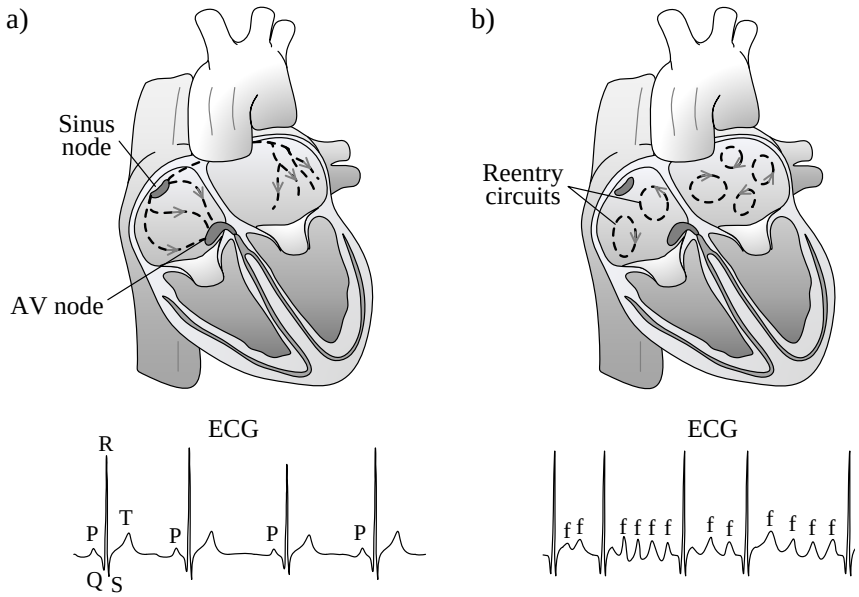

Fig. 2.1. Electrophysiological activity in the atria, and a corresponding representation on the surface ECG during a) a normal heart rhythm, b) atrial fibrillation

Depending on the properties of the AV node, abnormal interaction between the atria and the AV node causes irregular activation of the ventricles, resulting in a rapid ventricular contraction, typically reaching 90–150 contractions per minute. As a result, irregular ventricular contractions give rise to variable diastolic filling time, and reduced overall cardiac output due to incomplete filling of the ventricles (Clark et al., 1997). In such a way, both ineffective atrial contraction and disorganized work of the ventricles often cause detrimental effects on hemodynamics.

Ineffective atrial contractions along with rapid and irregular ventricular response

cause other cardiovascular conditions to evolve, notably, heart failure (Lau et al., 2014). However, probably the most life-threatening issue associated with AF is a formation of blood clots in the atria due to impaired atrial contraction and stagnant blood. Eventually, blood clots may travel out of the heart through the bloodstream to the brain, lungs, kidney, the heart itself or get stuck in an artery elsewhere in the body (Nattel, 2002).

AF diagnosis is confirmed on the basis of the surface electrocardiogram (ECG) where AF is characterized by irregular ventricular activity, the absence of normal atrial activity representing P-waves, and the presence of continuous fibrillatory f-waves (see Fig. 2.1).

2.1.2 Epidemiology

Atrial fibrillation is the most common cardiac arrhythmia affecting millions of people worldwide (Ball et al., 2013). It has been estimated that 33 million people around the world are suffering from AF (Chugh et al., 2014). Nevertheless, given that AF is usually asymptomatic, and undiagnosed for many patients, these numbers most likely represent an underestimate. Therefore, reasonably larger numbers of actual prevalence are expected, reaching up to 2 % of the general population (Camm et al., 2010). The prevalence of AF increases substantially with age, with the odds of developing AF being twice as great for each advancing decade of age (Benjamin et al., 1994). Consequently, more than 12 % of adults aged > 75 years have a diagnosis of AF (Heeringa et al., 2006). In addition, AF is more common in men than in women, especially at a younger age (see Fig. 2.2).

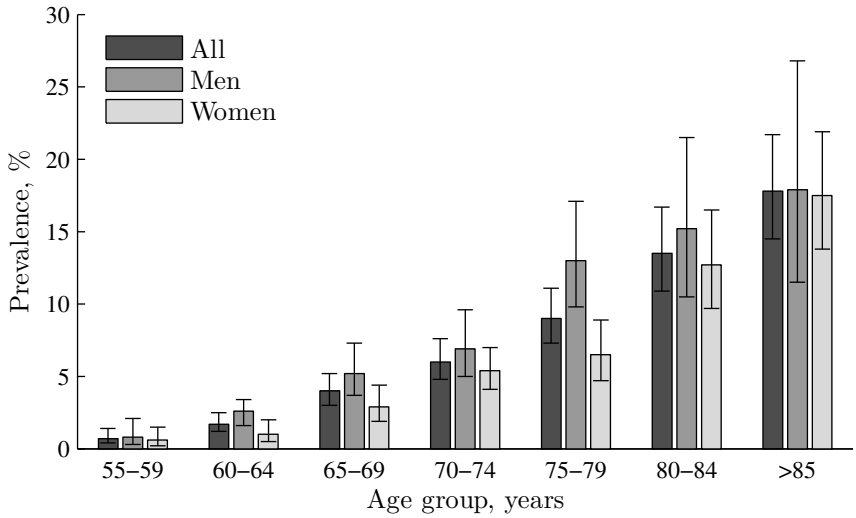

Fig. 2.2. The prevalence of AF among different age groups. Adapted from Heeringa et al. (2006)

Epidemiological data, gathered over the past few decades, point towards a rapidly increasing AF prevalence. For instance, analysis of current global epidemiological data has shown that the number of new AF cases had increased by about 5 million from 1990 to 2010 (Chugh et al., 2014). Several important factors are considered to be among the

most influential on growing AF epidemic: aging of population, globally increasing numbers of people affected by hypertension and obesity, and considerably improved survival from other cardiovascular diseases, such as heart failure and myocardial infarction. These conditions cause structural changes in myocardium, and therefore increase the risk for developing AF (Chugh et al., 2014). On the other hand, emerging novel technologies for arrhythmia detection (i.e., implantable cardiac monitors, internal and external loop-recorders) undoubtedly contribute to increased numbers of newly diagnosed AF cases.

According to the latest trends, AF prevalence will increase dramatically in the near future. Various studies expect a 2–3 fold increase in AF prevalence by the year of 2050 (Go et al., 2001; Miyasaka et al., 2006b; Naccarelli et al., 2009). The estimated numbers of individuals to be affected by AF in upcoming decades varies quite a lot among different surveys, falling between 5.6 (Go et al., 2001) to 15.9 million (Miyasaka et al., 2006b) in the United States alone. Similarly, the most recent data suggest AF prevalence in the US will rise from 5.2 million in 2010 to 12.1 million by 2030 (Colilla et al., 2013). A discrepancy among the different studies is mainly caused by the incorrectly estimated baseline numbers of the population suffering from AF.

Atrial fibrillation, together with related complications (heart failure, stroke, dementia), produce a huge economic burden in many countries, reaching 1–2 % of total health care expenditure (Wolowacz et al., 2011). For instance, in the US, the annual AF-related cost was estimated to be in the range from 6.0 (exclusively AF-related costs) to 26.0 billion dollars (Kim et al., 2011). A wide range of estimated costs was suggested in order not to underestimate the lower boundary, since it is not completely clear to what extent AF contributes to detrimental comorbidities that require special medical care. Comparable numbers of AF-related costs have been estimated in the countries of the European Union. The Euro Heart Survey on AF (Ringborg et al., 2008) counted the combined annual cost of 6.2 billion euros in just five European countries (Greece, Italy, the Netherlands, Poland, and Spain).

Approximately one-third of AF costs are due to hospitalizations, whereas outpatient medical and pharmacy expenditure accounts for the remaining two-thirds (Kim et al., 2011). In addition, individuals with AF are hospitalized twice as many times as those without AF, while multiple cardiovascular hospitalizations are even 8 times more common. As a result, the total direct medical costs are considerably higher (around 70 %) in patients with AF than in those without AF (Kim et al., 2011). It has been speculated that at least a 2-fold reduction in AF prevalence could be achieved if other cardiovascular risk factors were maintained under the safe levels (Huxley et al., 2011).

2.1.3 Mechanisms and pathophysiology

Pathophysiology of AF has been extensively studied over the last 100 years. However, despite the significant progress made in the last two decades, the underlying mechanisms are still not completely understood (Nattel, 2002; Wakili et al., 2011; Iwasaki et al., 2011; Jalife, 2011). In addition, recent findings reveal a rather shocking truth that

basically correct hypothesis on the underlying AF mechanisms has already been raised in the early twentieth century (Nattel, 2002; Jalife, 2011). Therefore, for many decades AF has exclusively been understood as a consequence of multiple simultaneously originating re-entrant waves, however, the latest findings suggest at least three principal mechanisms (focal electrical firing, single-circuit re-entry and multiple-circuit re-entry) responsible for AF initiation and maintenance (see Fig. 2.3). On the other hand, a condition of multiple re-entry pathways can be considered as an ultimate stage of arrhythmia development, representing the most advanced AF (Iwasaki et al., 2011).

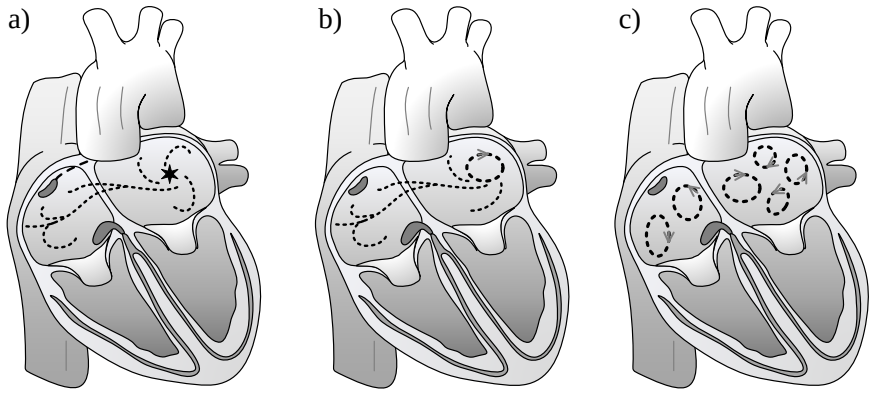

Fig. 2.3. Principal electrophysiological mechanisms of AF: a) focal electrical firing, b) single-circuit reentry, c) multiple-circuit reentry

Structural or electrophysiological changes of the atria seem to be the key factors allowing formation and propagation of abnormal impulses (January et al., 2014). Thus, once initiated, AF is maintained due to re-entrant wavelets propagating in a damaged atrial tissue. Although heart contraction is normally initiated by the sinus node, which, in turn, is the fastest pacemaker of the heart, the exciting impulse may arise from different areas as well, resulting in an ectopic beat. In many cases, ectopic beats have no adverse effect, however, if an abnormal firing is more rapid than the driving frequency of the sinus node, such ectopic activity may initiate AF.

The breakthrough idea of focal electrical firing, as a possible cause of AF initiation, has been introduced by Hassaguerre et al. in 1998. They found that focal triggers, located at the pulmonary veins, are the ones responsible for initiation of spontaneous paroxysms of AF. In fact, this cause of AF initiation was observed in approximately 90 % of all AF cases. One year later, Chen et al. (1999) reported a similar number (90 %) of AF causes due to atrial premature beats (APBs), originating in the pulmonary veins. These findings can be explained by a specific variable atrial cell conduction the pulmonary veins are associated with. As a consequence, a single-circuit re-entry is usually formed in the areas around the pulmonary veins owing to favorable conditions for excitatory impulses to propagate in a circular path in a continuous and repetitive manner.

Ultimately, if AF frequently reoccurs and sustains for longer periods of time, a hazardous condition of atrial remodelling may start, which further leads to a very undesired

and difficult to manage phenomenon when "AF begets AF" (Wijffels et al., 1995). In other words, atrial cells start to remodel electrophysiologically during prolonged episodes of AF, therefore more abnormal atrial substrate is created, which promotes to sustain AF even longer. As a result, depending on the amount of substrate in the atrial tissue, re-entry can originate in multiple circuits. During even more advanced stages of AF, i.e., chronic AF, multiple re-entry circuits may become highly unstable, engaging a rotor re-entry.

2.1.4 Classification

According to the American College of Cardiology (ACC), American Heart Association (AHA) and the European Society of Cardiology (ESC) guidelines for the management of patients with AF (January et al., 2014), AF can be classified into specific types depending on the duration and ability to self-terminate or to be terminated by some therapeutic technique (see Table 2.1).

All individuals with a first time diagnosed AF are assigned to the group of "new-onset AF", regardless if the particular patient had previously undetected AF episodes or not. If first diagnosed AF episode terminates spontaneously in less than a week and eventually another self-terminating AF episode is detected, AF is named as paroxysmal. Atrial fibrillation lasting longer than a week is considered as non-self-terminating, and is named as persistent or long-standing persistent, depending on the duration AF has been sustained. Various therapeutic strategies can be applied to convert persistent AF to a normal sinus rhythm (see Sec. 2.1.7 for details), however, when the rhythm recovery is ineffective, or either can not be terminated, or subsequently relapses, AF is assigned to permanent.

Table 2.1. Principal definitions of atrial fibrillation

AF type	Definition
New-onset	AF is discovered for the first time. Duration is not important
Paroxysmal	Recurrent AF terminating spontaneously within a week
Persistent	Recurrent AF sustaining for more than one week
Long-standing persistent	Recurrent AF sustaining for more than one year
Permanent	An ongoing AF which presence is accepted both by the patient and clinician
Asymptomatic (silent)	AF without recognizable symptoms
Nonvalvular	AF that is not associated with mitral stenosis

It should be noted that the presented classification scheme defines paroxysmal AF as terminating within 7 days, although paroxysmal AF episodes are typically much shorter, especially those observed at the beginning of arrhythmia development. For example, brief AF episodes lasting less than 30 s are not currently considered in the classification scheme, although they are gaining increasing interest (Seet et al., 2011; Flint et al., 2012; Kishore et al., 2014). More research is needed to show the exact place of brief paroxysmal AF episodes in clinical practice, however it is quite likely that brief AF is going to be included into the AF classification scheme (Silver and Windecker, 2015).

When relying on clinical data, permanent AF is the most commonly detected, occurring in half of all individuals with diagnosed AF, while paroxysmal and persistent AF are each observed in a quarter of AF patients (Zoni-Berisso et al., 2014). Nevertheless, these numbers should be treated with caution, since self-terminating AF may be asymptomatic, and therefore, diagnosed much too late, when AF has already developed to a permanent form (Engdahl et al., 2013). This reasoning is very well supported by the survey based on analysis of Canadian Registry of Atrial Fibrillation data which revealed that 8.6 % of patients, initially diagnosed with paroxysmal AF, had progressed to permanent AF within 1 year, whereas 24.7 % of patients had eventually progressed to permanent AF within 5 years (Kerr et al., 2005). In addition, after initial diagnosis of paroxysmal AF, the recurrence of any type of AF has been documented in 63.2 % of patients within the same 5 year period. Moreover, it was later demonstrated that AF progression is more frequent in patients with underlying diseases, i.e., heart failure and hypertension (de Vos et al., 2010). Hence, it has been hypothesized that structural remodeling of the atria is a more essential factor for AF progression than electrical remodeling.

2.1.5 Symptoms

Symptoms of AF vary among individual patients, although the major part of all AF cases represents asymptomatic AF without any appreciable symptoms at all (Fig. 2.4 a). In those individuals who are capable of recognising AF episodes, palpitations, fatigue, dyspnea (shortness of breath), general non-wellbeing, dizziness, chest pain, anxiety, hypotension are among the most commonly experienced symptoms (Nabauer et al., 2009; Lip et al., 2014a) (Fig. 2.4 b).

According to different studies, asymptomatic AF may cover from 30 % to 80 % of all AF cases (Gaillard et al., 2010; Healey et al., 2012; Lowres et al., 2012b; Lip et al., 2014a). Moreover, episodes of asymptomatic AF may frequently occur even in patients, assigned to a symptomatic group (Page et al., 2003). Since individuals with unrecognized (silent) AF are not aware of having this arrhythmia, and therefore, no treatment is prescribed, they are at an increased risk of a stroke event or systemic embolism (Quinn and Gladstone, 2014).

2.1.6 Risk factors

There are many well established risk factors responsible for the development of AF (Table 2.2). The most important are: age, hypertension, heart failure, obesity, valvular disease, family history, etc. Overall, any heart condition contributing to left atrial enlargement can be considered as a possible risk factor because atrial enlargement can cause structural and electrophysiological remodeling of the atria, leading to a favorable condition for re-entry to sustain. For example, the left ventricle becomes less compliant and thicker with age, as a consequence, the left atrium also enlarges in order to supply the less distensible ventricle with blood, thereby eventually causing structural changes of the atria (Dickinson et al., 2014).

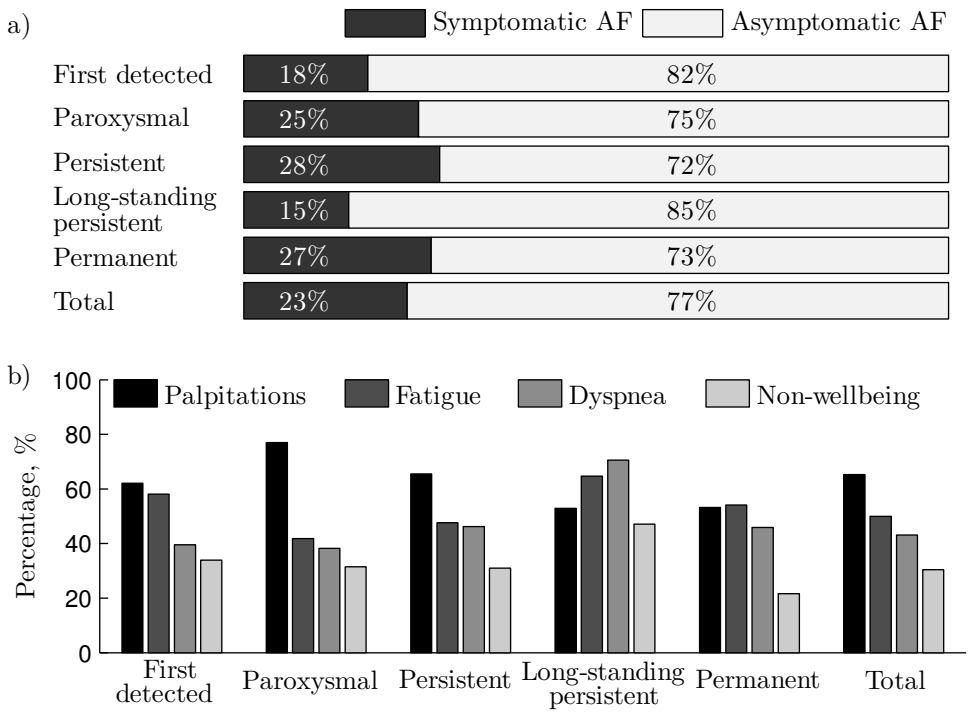

Fig. 2.4. a) Symptomatic AF versus asymptomatic in patients with different types of AF. b) Prevalence of the most commonly experienced symptoms among different AF types. Adapted from Lip et al. (2014a)

Despite being primarily a disease of the older population, paroxysmal AF episodes may occur in younger individuals as well. This especially applies to young athletes, experiencing extreme workloads during training. While regular physical activity undoubtedly has a positive effect on cardiovascular health regardless of age (Menezes et al., 2012), studies of young athletes ($\leqslant$ 35 years) have revealed that intensive physical activity can also provoke either atrial flutter or AF (Karjalainen et al., 1998; Furlanello et al., 2000). Especially dangerous are the episodes of atrial flutter with 1:1 atrioventricular conduction, leading to a potentially fatal ventricular rate of 300 beats/min. On the other hand, owing to the fact that atrial flutter often evolves to AF (see Sec. 2.2.4), it is essential to avoid arrhythmia provoking physical activity.

Athletes rarely have arrhythmia at rest, but rather during a competition or immediately after – during a period of recovery. Monitoring of arrhythmia symptomatic athletes with a mean age of 22 years showed approximately 5 % prevalence of AF and atrial flutter (Furlanello et al., 2000). Even though only symptomatic subjects were included in the study, this finding suggests that athletes who are involved in a highly intensive physical workload may belong to a higher risk group to develop AF in the future (Calvo et al., 2012). While exact causes of AF among the athletes remain to be clarified, it has been speculated that frequent ectopic beats, atrial enlargement, inflammatory processes and in-

Table 2.2. Risk factors and biomarkers of atrial fibrillation

Increasing age	Hyperthyroidism
Hypertension	Increased pulse pressure
Diabetes mellitus	Male sex
Myocardial infarction	European ancestry
Valvular heart disease	Family history
Heart failure	Genetic variants
Obesity	Increased B-type natriuretic peptide
Obstructive sleep apnea	Left ventricular hypertrophy
Cardiothoratic surgery	Left atrial enlargement
Smoking	Decreased left ventricular fractional shortening
Exercise	Increased left ventricular wall thickness
Alcohol use	Increased C-reactive protein

creased vagal tone might be among the most essential factors (Mont et al., 2009). On the contrary, a comprehensive review of this topic did not show any significant link between an increased incidence of AF and regular physical exercises (Ofman et al., 2013).

Family history of AF is also a strong risk factor for developing this type of arrhythmia (Fox et al., 2004). For example, African Americans are more prone to have hypertension (Dickinson et al., 2014), however, the prevalence of AF among African Americans is much lower compared to Caucasians, thereby suggesting genetic factors to be very important for AF development (Ruo et al., 2004). While there is no single gene crucial for AF development, a cluster of genetic disturbances are thought to be responsible for the establishment of this condition (Dickinson et al., 2014).

It is fairly obvious that harmful habits, such as excessive alcohol consumption, also increase the risk of AF (Somes and Donatelli, 2011). In fact, alcohol induced AF is sometimes named as a "holiday heart syndrome" to emphasize the actual cause of arrhythmia (Ettinger et al., 1978). Similarly, marijuana smoking may also be associated with AF initiation, most likely due to increased ectopic activity in pulmonary veins (Korantzopoulos, 2014). Although alcohol or marijuana stimulated AF is usually self-terminating in less than 24 h, reoccurring paroxysmal AF episodes can eventually lead to electrical remodeling of the atria.

2.1.7 Treatment and management

Figure 2.5 presents the most frequently applied pharmacological and nonpharmacological options for the treatment and management of AF. Currently, drug therapy is usually recommended, with oral anticoagulants and heart rate controlling drugs being among the most commonly prescribed medications (Scheinman and Morady, 2001; January et al., 2014). Unfortunately, both drugs are associated with substantial adverse effects (Heidbuchel et al., 2013). More specifically, oral anticoagulants increase the risk of bleeding complications, whereas antiarrhythmic drugs may induce life-threatening ventricular arrhythmias, since they alter the electrical properties of the heart. Although properly chosen

antithrombotic drugs may reduce the risk of stroke by approximately 60 % (Hart, 2007), clinicians do not always adhere to the most recent guidelines. As a consequence, oral anticoagulants are used inappropriately, resulting in ineffective treatment of AF (Scherr and Jais, 2014; Akao et al., 2014). A breakthrough is expected in this field, since recently introduced novel non-vitamin K oral anticoagulants are associated with lower complication rates compared to conventional vitamin K antagonist oral anticoagulants (Enriquez et al., 2015).

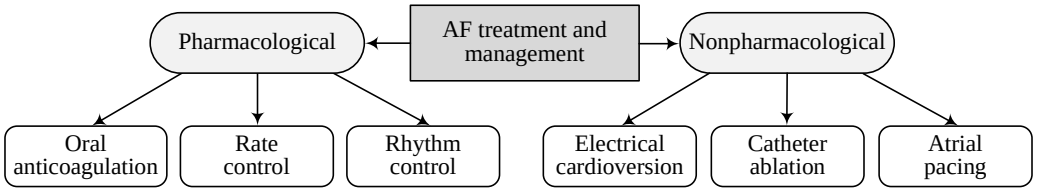

Fig. 2.5. The basic options for the treatment and management of AF

Other treatment strategies are less frequently used, i.e., electrical and pharmacological cardioversion is performed in 10 % and 5 % of patients, respectively (Lip et al., 2014a). In special cases, when pharmacological therapy is ineffective or poorly tolerated, various nonpharmacological techniques are considered, e.g., atrial pacing to prevent from maintenance of AF, modification of the atrioventricular node to reduce the ventricular rate during AF, a surgical division of the atria into segments (Maze procedure) to diminish the possibility of creating circulating wavelets in the atria, etc. (Scheinman and Morady, 2001).

Nowadays, catheter ablation has proven to be a very effective solution to treat patients with various arrhythmias, including AF. Several studies have shown catheter ablation to be a superior technique to antiarrhythmic drug therapy, especially in the very beginning of AF development (Mont et al., 2013; Cully, 2013). Since AF usually starts to develop in pulmonary veins (see Sec. 2.1.3), these areas of the heart are used as the key targets for ablative therapy. While catheter ablation is very effective when treating paroxysmal AF, its efficiency significantly reduces for persistent AF, usually requiring multiple ablation procedures together with antiarrhythmic drug therapy (Jalife, 2011). Thus, considering the high cost of the procedure, and a considerable risk of relapse, catheter ablation is only applied in 4 % of all AF patients (Lip et al., 2014a). Hence, only these individuals who may benefit most from the ablation therapy are selected. Nevertheless, it is reasonably expected that catheter ablation will become the main therapeutic approach in the near future, when technologies for early detection of asymptomatic AF will improve (Benjamin et al., 2009; Gillis et al., 2013).

Two decades ago, an idea of internal atrial cardioversion using an implanted device has been escalated (Wellens et al., 1998). Ultimately, a company (InControl Inc., Redmond, Washington, US) has been established to produce internal atrial cardioverters under the name of Metrix Atrioverter. The device was designed to perform an internal atrial defibrillation by inducing low-energy (3 to 6 J) intra-atrial shocks after automated

identification of paroxysmal AF episodes. Despite this, most paroxysmal AF episodes had been converted to sinus rhythm by using this technique, consequently, painful shocks and the high incidence of recurrent AF episodes were the main reasons that forced the production of this device to close (Gerstenfeld and Everett, 2014). Given that the human pain threshold is less than 1–2 J, various techniques involving a series of very low-energy shocks are under investigation (Janardhan et al., 2014). However, a lot of information has still to be gathered in order to expect a success in clinical practice.

2.2 Comorbidities of atrial fibrillation

Atrial fibrillation itself is not considered as a life-threatening arrhythmia, however it is associated with various comorbidities (LaMori et al., 2013). While stroke and heart failure are considered to be among the most detrimental comorbidities, there are lots of other important health issues significantly related to AF. The most essential of them are summarized in Table 2.3, and briefly discussed in the sections below.

2.2.1 Ischemic stroke

Ischemic stroke is a brain condition in which brain cells are damaged due to a sudden blockage of blood flow to some part of the brain. Similarly to AF, the prevalence of stroke is growing, and is expected to be twice as large by the year 2020 (Mozaffarian et al., 2014). It has been estimated that nearly a quarter of ischemic strokes are due to cardioembolic events, with the largest part of these events being attributed to AF (Marini et al., 2005). Another 25 % of ischemic strokes are not assigned to any cause (cryptogenic stroke). However, there is a hypothesis that AF may be a contributor to many cryptogenic strokes (Gladstone et al., 2014; Hart et al., 2014).

AF caused strokes are usually very complicated or even fatal, with nearly 80 % of patients becoming severely disabled or dead (Saposnik et al., 2013). Older age and higher propensity to comorbidities are considered as the most essential contributors causing AF related strokes to be more severe. The risk of stroke can be substantially reduced if oral anticoagulant therapy is timely prescribed. Unfortunately, owing to the frequently asymptomatic (silent) nature of this arrhythmia, AF is usually detected too late, often after the stroke event. In addition, according to the current guidelines, AF has to be diagnosed by some technique in order to start anticoagulant therapy (Culebras et al., 2014; Gladstone et al., 2014). Therefore, undetected asymptomatic AF may cause subsequent strokes.

Continuous prolonged monitoring using implanted devices (see Sec. 3.2.2) has revealed that paroxysmal AF without perceptible symptoms is very common among patients after stroke or systemic embolism. For example, paroxysmal AF has been documented in 20.7 % (Christensen et al., 2014), 28 % (Ziegler et al., 2010), and 51 % (Brambatti et al., 2014) of patients monitored after stroke. Similar prevalence was observed using non-invasive mobile cardiac outpatient telemetry, where 23 % of stroke patients had paroxysmal AF episodes during 21 days of monitoring (Tayal et al., 2008). According to the latest

Table 2.3. The most commonly encountered comorbidities in patients with AF

Comorbidity	Prevalence	Essential notes
Ischemic stroke	AF is found in 20–51 % of patients after ischemic stroke	Brief AF episodes (< 30 s) are very common among patients after cryptogenic stroke
Heart failure	Heart failure is present in 30–56 % of patients with AF	Heart failure is more common among patients with advanced AF
Myocardial infarction	AF is present in 23 % of patients after myocardial infarction	The risk of a new-onset AF is highest within 2 months after infarction
Supraventricular tachycardias	AF is common among the patients with atrial flutter (58 %) and atrial tachycardia (27 %)	The number of atrial premature beats is considered as a marker for estimating a likelihood of AF
Hypertension	Hypertension is documented in 70 % of patients with AF	A blood pressure of 140/80 mm Hg is suggested as an optimal in AF patients
Kidney disease	AF is found in 10–15 % of patients with kidney disease, and up to 18 % in hemodialysis patients	Anticoagulation therapy is complicated in hemodialysis patients due to increased risk of major bleeding
Sleep apnea	Sleep apnea is present in 50 % of AF patients	Exact contribution of sleep apnea to AF development is unclear due to shared risk factors
Type 2 diabetes mellitus	Diabetes mellitus is found in nearly 20 % of AF patients	Unclear implication of other risk factors (i.e. obesity) to AF developement

findings, the American Heart Association/American Stroke Association guideline recommended prolonged ECG monitoring as a prevention from recurrent strokes (Kernan et al., 2014). Although it seems obvious that subclinical AF is associated with an increased risk of stroke (Healey et al., 2012), the relationship between stroke events and temporal distribution of paroxysmal AF episodes is still unclear. For instance, a study by Brambatti et al. (2014) showed that only a few patients had AF episodes during the last month before the stroke event.

An interesting debate has recently arisen whether brief episodes of paroxysmal AF (< 30 s) are related to cryptogenic ischemic stroke (Seet et al., 2011; Flint et al., 2012; Kishore et al., 2014; Favilla et al., 2015; Keach et al., 2015). It has been hypothesized that brief AF episodes may be coupled to the formation of atrial thrombus, or may be viewed as biomarkers of prolonged episodes occurring outside of the monitoring period (Seet et

al., 2011). Accordingly, both non-invasive and invasive recording technology have been employed for prolonged rhythm monitoring. Tayal et al. (2008) found that in the patients with AF, 85 % of all episodes were brief, while a study by Flint et al. (2012) showed that 11 % of all patients with cryptogenic ischemic stroke had new onset paroxysmal AF with 5 s episodes or longer. The authors argued that subsequent strokes may be prevented if patients are monitored during their first month after a stroke.

2.2.2 Heart failure

Heart failure is a condition when the heart has impaired ability of pumping enough blood into the circulation system. Both heart failure and AF are recognized as epidemic diseases, remaining the only two cardiovascular conditions associated with still increasing prevalence (Braunwald, 1997; Dickinson et al., 2014). Heart failure and AF are closely related to each other, often interact together and share similar risk factors, notably, aging and hypertension (Chamberlain et al., 2011; Lau et al., 2014). Moreover, both diseases can be either a cause or a result of each other, and usually predispose to the development of a pathophysiological cycle where AF promotes progression of heart failure and vice versa (see explanation in Fig. 2.6).

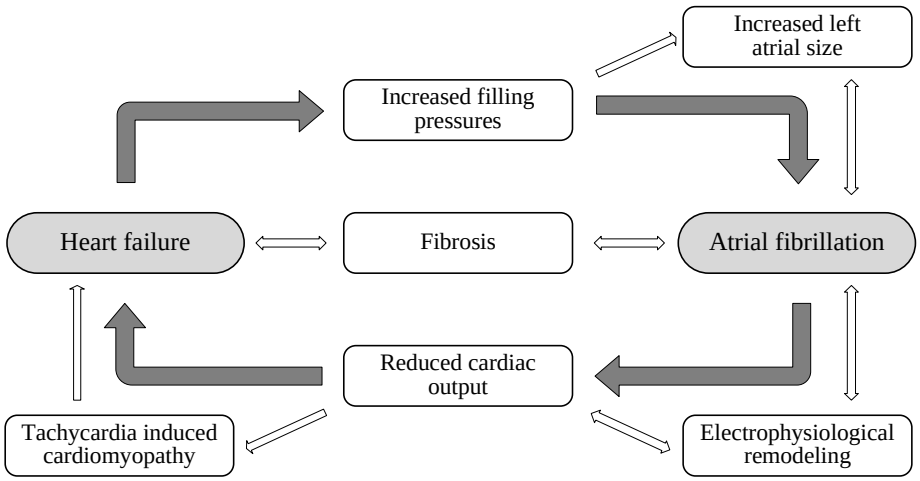

Fig. 2.6. A pathophysiological cycle of AF and heart failure. Adapted from Anter et al. (2009)

Various clinical trials have reported that approximately one-third of patients with advanced heart failure also have diagnosis of AF (Darby and DiMarco, 2012). Individuals with severe heart failure have a very high risk of developing AF, which is even higher than the risk carried by advanced age or hypertension (Go et al., 2001). On the other hand, a study conducted in the US showed that 8 % of patients with first diagnosed AF had developed heart failure within the subsequent year, whereas even 24 % of patients had developed heart failure within 6 years (Miyasaka et al., 2006a). In addition, in a large study, which included 10,523 patients with AF, heart failure had been documented in 30 % of patients with first-detected AF, 33 % with paroxysmal AF, 44 % with persistent

AF and in 56 % patients with permanent AF (Silva-Cardoso et al., 2013). Thereby it can be assumed that advanced AF has a greater impact on the development of heart failure.

Coexistence of AF and heart failure significantly increases mortality rates, compared to those individuals having either disease alone. For example, patients who had AF prior heart failure where associated with 29 % increased risk of death than patients with heart failure, but without AF (Chamberlain et al., 2011). Moreover, individuals who developed AF after heart failure were linked to more than double the risk of death. Recently, Taillandier et al. (2014) reported that the risk of death was higher in patients suffering from heart failure and permanent AF compared to those with non-permanent AF forms. In addition, increased death rates were observed both in-hospital and post-discharge (McManus et al., 2013b). Therefore, considering that both AF and heart failure increase the risk of stroke and mortality, coexistence of them is especially burdensome and challenging to manage (Wang et al., 2003; Padeletti et al., 2007; Lau et al., 2014; Lip et al., 2014b).

2.2.3 Myocardial infarction

Myocardial infarction, also known as a heart attack, occurs when the heart muscle is partially damaged due to a blockage of a coronary artery. Atrial fibrillation is observed as a common complication of myocardial infarction and is associated with a poor prognosis (Schmitt et al., 2009; Zusman et al., 2012). On the other hand, AF by itself is independently associated with an increased risk of myocardial infarction (Soliman et al., 2014).

Numerous studies have been conducted regarding the relationship of AF and myocardial infarction. Jabre et al. (2011) reported that one of five patients had developed AF within 5 years after myocardial infarction, with the highest incidence of new AF within the first month. More specifically, in these patients who developed AF after myocardial infarction, 30 % had AF within 2 days, 16 % between 3 and 30 days, and the remaining 54 % developed AF after one month. Similar findings were reported by Jons et al. (2011), where the incidence of new-onset AF was highest within 2 months after myocardial infarction (16 %), but decreased towards a plateau level after one year of infarction event. In addition, 90 % of AF events in that study have been found to be asymptomatic. The authors separately investigated the influence of brief AF episodes (< 30 s) on the risk of major cardiovascular event (repeated infarction, stroke, severe heart failure, death). Preliminary findings indicated that brief AF episodes were not associated with an increased risk of a major cardiovascular event.

Since myocardial infarction itself is a very serious condition, a complication of AF markedly exacerbates the perspectives of full recovery (Schmitt et al., 2009). For example, a study by Berton et al. (2009) demonstrated that a presence of AF (either new-onset or persistent) during a 7 year follow-up after myocardial infarction was associated with 55 % higher mortality rates compared to those patients with sinus rhythm. In addition, patients were linked to a worse prognosis if AF had developed after myocardial infarction, compared to those who had had AF before infarction occurred (Rathore et al., 2000). While another study showed that patients with sustained AF had higher in-hospital death

rates than those who developed a new-onset AF, it should be noted that a group of patients with chronic AF, on average, was older and sicker (Maagh et al., 2011). Based on the fact that AF is associated with significantly worse short-term and long-term recovery prognosis, it has been suggested that such patients should be monitored more carefully for AF and treated more aggressively if AF is identified (Pizzetti et al., 2001; Bang et al., 2014). Moreover, it has been estimated that up to a half of myocardial infarction events remain clinically unrecognized (de Torbal et al., 2006). However, even unrecognized myocardial infarction is associated with a 2-fold increased risk of developing AF (Krijthe et al., 2013).

There is a theoretical basis to assume that AF may alter electrophysiological properties of the ventricles. In such a way, AF can contribute to the development of ventricular fibrillation in post-myocardial infarction patients owing to the vulnerability of myocardium after the infarction event. The hypothesis was partially confirmed by the significantly higher numbers of ventricular fibrillation observed in patients with AF during admission with myocardial infarction (Sankaranarayanan et al., 2008). If further confirmed, this observation will be of special importance, forming a basis for more careful monitoring of AF to avoid in-hospital deaths.

Since myocardial infarction can occur in different areas of the heart, it is an open question whether localization of myocardial infarction could be considered as a risk factor for AF development. In fact, a preliminary study reported higher risk of AF in patients who had suffered anterior wall myocardial infarction, though further studies are needed to draw the explicit conclusions on this clinically relevant topic (Jabre et al., 2011).

2.2.4 Supraventricular tachycardias

Since AF itself is a supraventricular tachycardia, it is not completely correct to assign supraventricular tachycardias to AF comorbidities. However, a significant role of other supraventricular tachycardias on the development of AF, close relationship and even common coexistence deserves special attention. There is much evidence that the risk of AF is higher in patients experiencing other types of supraventricular tachycardias, notably atrial flutter (Chinitz et al., 2007; Ozcan et al., 2014), both atrioventricular nodal re-entrant tachycardia and atrioventricular re-entrant tachycardia (Hamer et al., 1995; Khachab, 2013), and atrial tachycardia. In addition, although frequent atrial premature beats cannot be named as a supraventricular tachycardia, due to the similarity to atrial tachycardia, as well as the close relationship to AF (Wallmann et al., 2007; Chong et al., 2012; Gladstone et al., 2015), APBs deserve to be mentioned.

A large study by Ozcan et al. (2014) found that AF is most common among patients with atrial flutter (58 %) and atrial tachycardia (27 %), while much lower numbers were observed in patients with atrioventricular re-entrant tachycardia (14 %) and atrioventricular nodal re-entrant tachycardia (10 %). Hence, patients with any supraventricular tachycardias should be examined more closely in order not to overlook the beginning of AF (Khachab, 2013). An illustration of the driving mechanism of each of the above-mentioned supraventricular tachycardias including APBs is depicted in Fig. 2.7.

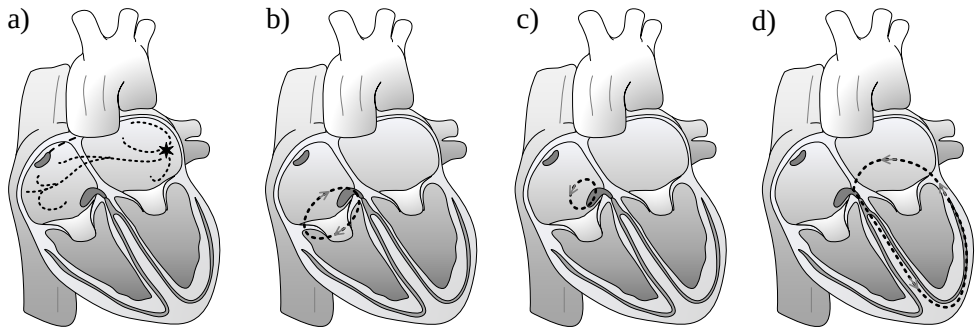

Fig. 2.7. Electrophysiological mechanisms of a) frequent atrial ectopy / atrial tachycardia, b) atrial flutter, c) atrioventricular nodal re-entrant tachycardia, and d) atrioventricular re-entrant tachycardia

Atrial premature beats have been considered as benign for a long time, however, recent studies have shown that APBs are very common in individuals with AF, and are linked to almost a 3-fold increased risk of AF (Binici et al., 2010; Chong et al., 2012; Conen et al., 2012). Based on several clinical studies, the excessive ectopic activity has been suggested as a predictor of the likelihood for an individual to have paroxysmal AF (Wallmann et al., 2007; Weber-Kruger et al., 2013; Gladstone et al., 2015). For example, a close relationship between frequent APBs and increased risk to have or to develop paroxysmal AF was found in a group of patients with ischemic stroke (Wallmann et al., 2007). Similarly, a recent study by Gladstone et al. (2015) provided a clearer picture on the relation of frequent APBs and AF. Their finding was that individuals with < 100 APBs per 24 h were linked to 9 % probability of having AF, while those with > 1000 APBs per 24 h were related to > 37 % probability of AF. Based on the observation that APBs are more frequent in patients with AF than in those without AF, the authors argued that the number of ABPs may be used as a possible marker to determine which patients are most likely to have AF. While the exact clinical meaning of APBs to the development of AF is not fully clear and needs further investigation, there is sufficient evidence that APBs may trigger paroxysmal AF episodes (Chen et al., 1999).

Atrial tachycardia is caused by a focal activity, i.e., micro-re-entrant loop or automatic focus, thus is closely related to frequent APBs. In addition, both frequent ectopic beats and atrial tachycardia share similar presentation on the surface ECG, and in some cases, may even have similarities to brief episodes of AF. Atrial tachycardia may also initiate AF, although such a scenario is very rare, occurring in just 1 of 100 cases (Kolb et al., 2001).

Atrial flutter is commonly encountered with supraventricular tachycardia, usually resulting from a re-entrant path around the tricuspid valve in the right atrium. Similarly to AF, atrial flutter is characterized by a high atrial contraction rate, though atrial flutter is more organized than AF. There is clear evidence that atrial flutter may develop to AF (Chinitz et al., 2007), or may alternate with AF (Horvath et al., 2000). Atrial flutter may also initiate AF, although less commonly, in approximately 1 of 20 cases (Kolb et

al., 2001). In some situations, when atrial flutter co-exists with a condition of variable atrioventricular block, the heart rate may become irregular, and therefore, due to similar presentation on the ECG, atrial flutter can be confused with AF (Link, 2012).

Both *atrioventricular nodal re-entrant tachycardia* and *atrioventricular re-entrant tachycardia* are caused by the pathological electrical re-entrant loop involving the atrioventricular node. Both tachycardias are common among the younger population, and share similar characteristics, i.e., regular heart rate reaching up to 250 beats per minute. There is some evidence that atrioventricular nodal re-entrant tachycardia can trigger AF or coexist with, however, such phenomenon is less commonly encountered in elderly individuals (Sauer et al., 2006). Nevertheless, an interesting clinical case has been documented, showing simultaneously occurring atrioventricular nodal re-entrant tachycardia and AF in a 33-year-old woman (Saluja et al., 2015). However, such theoretically unlikely collaboration was linked to a unique heart anatomy of this particular patient.

It is noteworthy that a very large study of 4.8 million patients showed an independent association between supraventricular tachycardias (excluding AF) and stroke (Kamel et al., 2013). Thus, the occurrence of any kind of supraventricular tachycardia has been suggested for consideration as a risk factor for thrombus formation and stroke.

2.2.5 Other notable comorbidities

Hypertension is considered as one of the most essential contributors to AF development. Given that hypertension is a widely prevalent condition, there is nothing unexpected as hypertension is found in more than 70 % of individuals with AF (Chiang et al., 2012). Since the relationship between these two conditions is very complex, it is not clear how hypertension contributes to AF development (Kirchhof and Schotten, 2006). However, atrial remodelling due to elevated pressures is considered as the most likely cause (Go and Rosendorff, 2009).

While blood pressure of $< 120/80$ mm Hg is considered as completely normal for healthy individuals, it is not the case in some cardiovascular conditions, for instance, after acute coronary syndromes (Bangalore et al., 2010). Considering that antiarrhythmic drugs used for AF treatment decrease blood pressure, it seems important to find optimal blood pressure values which may reduce the risk of adverse effects in AF patients. A recently published study by Badheka et al. (2014) assessed this topic by demonstrating both systolic and diastolic blood pressure to produce a U-shaped relationship with respect to all-cause mortality. The optimal blood pressure was found to be around 140/80 mm Hg, whereas both lower and higher blood pressure values were associated with the increased mortality rates.

Kidney disease is usually found in 10–15 % of patients with AF (Camm et al., 2010), and is associated with 2-fold higher mortality rates compared to individuals with kidney disease but without AF (Winkelmayer et al., 2011). Reduced kidney function is a potential independent risk factor for a new-onset AF, especially when it coexists with anemia (Xu et al., 2015) or left atrium enlargement (Sciacqua et al., 2014). Furthermore, AF coexistence

with chronic kidney disease was reported to be associated with a 67 % higher rate of progression to end-stage renal disease (Bansal et al., 2013).

Atrial fibrillation is commonly encountered in hemodialysis patients owing to prominent electrolyte changes and hemodialysis induced structural and electrical remodelling of myocardial tissue. Genovesi et al. (2005) reported that AF was found in 27 % of hemodialysis patients (paroxysmal in 3.5 %, persistent in 9.6 %, permanent in 13.9 %). Such prevalence is not surprising, since hemodialysis is prescribed to individuals with end-stage kidney disease. However, high AF prevalence has been observed even among the individuals with primary stages of chronic kidney disease (Baber et al., 2011). When compared to individuals without chronic kidney disease, AF prevalence was found to be 2.8 %, 2.7 % and 4.2 % higher for patients with stage 1 to 2, stage 3, and stage 4 to 5, respectively. Similar findings were reported in another study where AF was present in 18 % of patients, with increased prevalence of up to 25 % for patients $\geqslant$ 70 years-old (Soliman et al., 2010).

Piccini et al. (2013) argued that renal dysfunction in AF patients further increases the risk of stroke and systemic embolism, therefore should be worthy to be included into the scheme of stroke risk stratification. However, there is no clear principle on the management of such patients, since oral anticoagulation therapy (i.e. using warfarin) increases the risk of major bleeding of up to 10-times in this group (Jun et al., 2015). Gastrointestinal (58 %) and intracranial (5 %) bleeding were documented as the most frequently occurring major bleeding events in patients with renal dysfunction. Hence, treatment against the formation of blood clots in these patients is a complicated problem, requiring careful assessment of the risk-benefit ratio (Reinecke et al., 2009; Jun et al., 2015).

Obstructive sleep apnea is found in half of AF patients (Gami et al., 2004). Recent findings show that individuals with sleep apnea have structural changes in the atria, i.e., increased atrial size, abnormal electrical conduction in some regions, remodelled sinus node (Dimitri et al., 2012). Therefore, apnea induced tension in the atria and pulmonary veins is suggested as a key factor for AF development. On the other hand, sleep apnea is closely related to obesity, which is itself a strong risk factor for cardiovascular diseases and AF. Nevertheless, many other hypotheses exist on the contribution of sleep apnea to AF development that need further investigation (Menezes et al., 2013). Interestingly, AF patients with sleep apnea are associated with a 25 % increased risk of AF recurrence after procedure of pulmonary vein ablation, thereby it is recommended to treat sleep apnea prior to catheter ablation (Ng et al., 2011).

There is a hypothesis that *type 2 diabetes mellitus* may contribute to tissue damage in the atria (January et al., 2014). Accordingly, clinical data has shown a possible relationship between type 2 diabetes mellitus and AF. For example, Aksnes et al. (2008) reported that a new-onset AF was 50 % more common in individuals who had developed a new-onset diabetes mellitus compared to those without. Similarly, a large study by Chiang et al. (2012), which included 9816 patients with AF, showed that diabetes was present in approximately 20 % of AF patients. On the contrary, several studies have declared no statistically significant association between these two health conditions (Ostgren et al.,

2004; Schnabel et al., 2009). A disagreement between the studies might be influenced by methodological reasons, because other AF causing factors (i.e. obesity), which are usually present among the diabetes patients, were not considered in several studies (Menezes et al., 2013).

2.2.6 Health-related quality of life

Several pilot studies have paved the way for speculation that both paroxysmal and persistent AF may reduce physical and mental health (Patel et al., 2013). Although a small study of twenty-seven 75-year-old patients suffering from permanent AF failed to find any significant differences in sleep quality, anxiety, and depression rates compared to the sinus rhythm group, the patients with AF were associated with a significantly reduced physical condition and social functioning (Ariansen et al., 2011). Since the study included only patients with permanent AF (median AF duration was 5 years), it is reasonable to assume that these patients were accustomed to disease, thereby relieving the symptoms of depression. On the contrary, another study reported depression to be more pronounced in patients, experiencing persistent AF than paroxysmal AF (von Eisenhart Rothe et al., 2014). This contradiction implies that further studies are needed to gather more information on the topic.

Dublin et al. (2011) have hypothesized that AF may contribute to the development of dementia and Alzheimer's disease. Their reasoning is based on the knowledge that an increased irregular rhythm may cause cerebral hypoperfusion, while incomplete emptying of the atria can subsequently lead to systemic embolism and cerebral microinfarcts. In fact, individuals with AF were 38 % more likely to have dementia and 50 % more likely to have Alzheimer's disease than those without AF (Dublin et al., 2011). Later, the same group analyzed autopsy data and found neuropathological changes (cerebral infarcts) in 45 % of individuals with AF (Dublin et al., 2014). Given these points, a debate on AF contribution to the development of Alzheimers disease is evolving, even though more clinical evidence is needed to confirm this reasoning.

2.3 Conclusions of the chapter

1. Many studies report the prevalence of atrial fibrillation to increase substantially in the future due to the fast aging of the population.

2. Paroxysmal AF is usually asymptomatic and therefore can be much more common than it was previously assumed.

3. Atrial fibrillation is a progressive disease, hence it is very important to find effective ways to manage AF in the early stages of arrhythmia development.

4. Atrial fibrillation itself is not considered as a life-threatening arrhythmia, however, it has a huge impact on making more severe various comorbidities, such as stroke, heart failure, myocardial infarction.

5. Timely prescribed anticoagulation therapy may significantly reduce the number of strokes. However, on the basis of the current guidelines, AF must be identified in order to initiate anticoagulation treatment.

6. There is an ongoing debate whether brief paroxysmal AF episodes lasting less than 30 s are biomarkers of longer subclinical AF episodes.

3 OVERVIEW OF EXISTING TECHNOLOGIES FOR DETECTION OF ATRIAL FIBRILLATION

3.1 Existing methods for automatic detection of atrial fibrillation

3.1.1 Rhythmogram-based atrial fibrillation detection

In clinical practise, AF is normally identified by analysing the surface ECG signal. Three rather explicit criteria have to be satisfied: highly irregular ventricular response, the absence of normal atrial activity representing P-waves, and the presence of continuous, usually chaotic, fibrillatory f-waves. Since the ventricles are activated at irregular time instances during AF, a signal comprised of time intervals (RR intervals) between adjacent heart beats, further denoted as r, appear to be very different from that observed during sinus rhythm (see Fig. 3.1). Hence, ventricular activity irregularity is the most widely utilized feature for automatic AF detection. An additional attractive advantage of r interval analysis is that r intervals are relatively easy to obtain because heart beats (R-waves) are usually well recognizable, even in noisy environments.

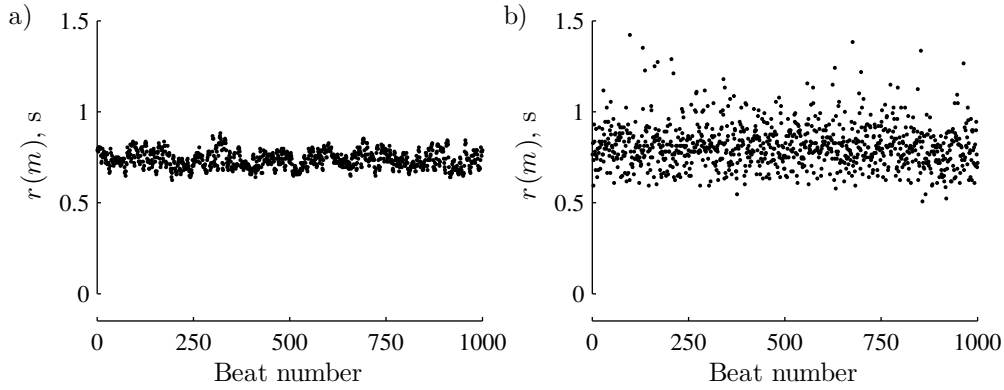

Fig. 3.1. Example of r interval series during a) sinus rhythm and b) atrial fibrillation

Moody and Mark (1983) were among the first to publish on the topic of automatic AF detection. Additionally, the authors of the paper introduced an ECG database, nowadays known as MIT-BIH Atrial Fibrillation database (AFDB), containing signals with paroxysmal AF episodes. The database has been collected by the Arrhythmia Laboratory of Beth Israel Hospital and is unofficially considered as the "gold-standard" for testing AF detectors. Moody and Mark proposed three versions of AF detector relying on the Markov modelling technique, where sensitivity (Se) and positive predictive value (PPV) for the best performing algorithm were 93.6 % and 85.9 %, respectively.

Histogram analysis based atrial fibrillation detection

Two decades later, Tateno and Glass (2001) introduced an AF detector, which performs rhythm classification with respect to histogram similarity to histogram templates, prepared using r and Δr (differences between adjacent r intervals) sequences collected

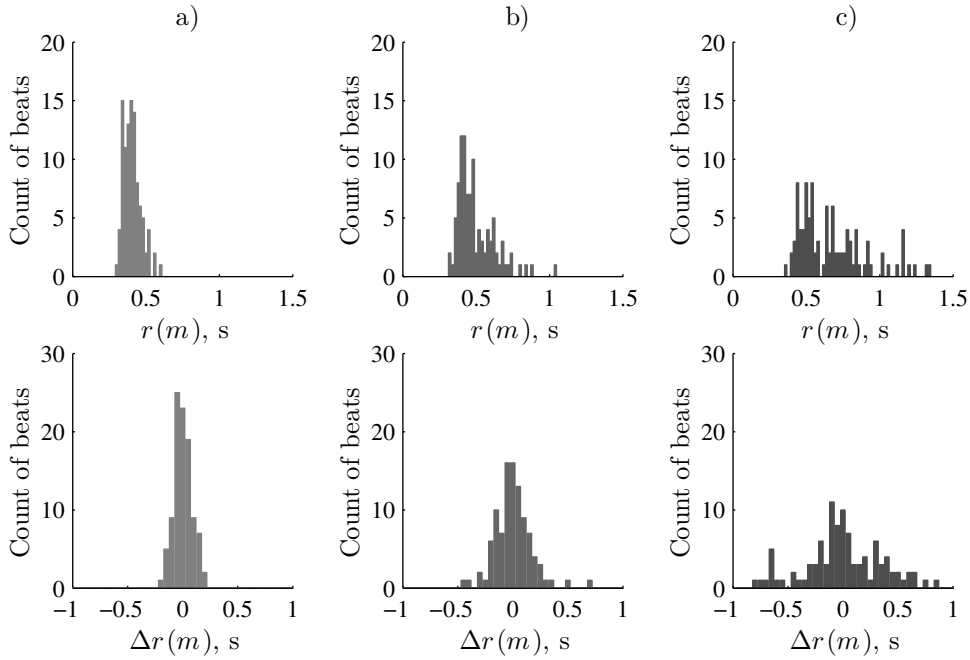

Fig. 3.2. Examples of r (upper row) and corresponding Δr (bottom row) interval histograms obtained for the same patient during AF. Histograms are composed of 100 $r/\Delta r$ intervals at a) the initial time instance, b) 30 s later, c) 30 min later

during AF. Histogram similarity is quantitatively evaluated by applying Kolmogorov-Smirnov test. When using histograms composed of 100 Δr intervals, Se of 94.4 % and specificity (Sp) of 97.2 % were achieved for the AFDB database. It should be noted, that considerably worse performance (Se = 91.2 % and Sp = 96.1 %) was obtained after reinvestigation of the algorithm by Larburu et al. (2011). The algorithm suffers from the limitation of requiring many r intervals to obtain the representative Δr histograms, which, in turn, restricts the ability to detect brief AF episodes. Furthermore, since there is no standard prototype of AF histogram, i.e., r and Δr histograms can take very different shapes, even for the same patient (see Fig. 3.2), or can be bimodal or multimodal, such an approach to AF detection may produce an erroneous response in certain situations.

Kolmogorov-Smirnov test based Δr interval histogram analysis was also involved in an AF detector proposed by Huang et al. (2011). On the whole, seven threshold based steps are utilized to identify the transition between AF and non-AF rhythms, and subsequently classify rhythms into specific classes. A special attention is paid to the problem of false-positives due to various types of ectopic activity. A 7-point median filter is used for the suppression of individual premature beats, whereas ectopy-induced concurrent rhythms (bigeminy, trigeminy) are eliminated by applying templates, predefined for the particular type of abnormal rhythm. Despite that their approach of involving a sequence of threshold-based steps is computationally complex, a solid performance was reported – for the AFDB, the Se and Sp were 96.1 % and 98.1 %, respectively. On the other hand,

since the algorithm has been developed and tested on the same database, the actual performance is questionable. Given that rhythm change is identified by analysing segments of 100 Δr intervals, therefore there is no surprise that the undetected AF episodes were of short duration, lasting from 4 to 62 beats.

Poincaré plot based atrial fibrillation detection

Another group of AF detectors relies on analysis of a two dimensional scatter plot (Poincaré plot, Lorenz plot), plotted of current r (or Δr) intervals versus preceding intervals. Based on this approach, Sarkar et al. (2008) have developed an AF detector for primary use in implantable long-term monitoring devices; both detection of AF and atrial tachycardia were taken into account. A sequence of Δr intervals is collected during a 2 min period of time, and then represented in the Poincaré plot. In such a way, each rhythm type (sinus rhythm, AF, atrial tachycardia, etc.) takes a specific pattern corresponding to each rhythm (see Fig. 3.3). Ultimately, a set of rules is applied to determine which pattern is represented by the Poincaré plot. For the AFDB database, with AF episodes shorter than 2 min excluded, the Se and PPV were 94.7 % and 95.8 %, respectively. Since a considerably larger number of Δr intervals is collected over 2 min period during faster heart rates than slower, this implies that the Poincaré plot represents the specific rhythm more accurately when a higher number of Δr intervals is involved. Considering that the performance is heart rate dependant, the proposed algorithm performs best when arrhythmia episodes are not shorter than the analysis window itself.

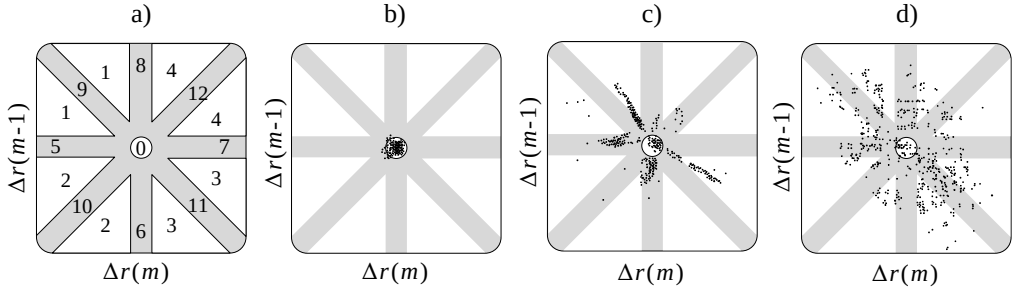

Fig. 3.3. a) Poincaré plot divided into segments used to encode the corresponding rhythm type. Examples of patterns obtained during b) sinus rhythm, c) sinus rhythm with frequent ectopic beats, and d) atrial fibrillation

Later, a conceptually similar AF detector was introduced by Lian et al. (2011). Different from the previous approach, a scatter plot of r intervals versus Δr intervals is composed instead. In such a way, 2 independent sources of heart rate information (r and Δr) are explored. The scatter plot is divided by a grid into segments of 25 ms resolution. Subsequently, the number of cells, containing at least 1 data point is counted and used as a subject for threshold based AF detection. The best performance was obtained by applying a detection window of 128 r intervals (Se = 95.8 % and Sp = 96.4 % for the AFDB), whereas the performance decreased when a window of 32 r intervals was used instead (Se = 94.3 % and Sp = 95.1 %).

Statistical approaches for atrial fibrillation detection

Two statistical approaches for AF detection have been proposed by Ghodrati and Marinello (2008) under the support of Draeger Medical Systems (Draeger Medical Systems Inc., Andover, Massachusetts, US). A Neyman-Pearson detection principle was utilized to establish a criteria for AF detection, assuming that Δr intervals are distributed according to either Gaussian or Laplace functions. First of all, two histograms, representing AF and non-AF rhythms were composed using Δr intervals obtained from the MIT-BIH Arrhythmia database. Then, both Gaussian and Laplace probability density functions were fitted to each histogram. Ultimately, the Neyman-Pearson approach to statistical learning was employed to obtain the threshold value to distinguish between AF and sinus rhythm.

When assuming that Δr intervals are distributed according to Gaussian probability density function, the Neyman-Pearson detection criteria can be simplified to the test of Δr variance, whereas in the case of Laplace probability density function, the criteria can be simplified to the test of absolute deviation of Δr intervals. To reduce a negative influence of ectopic beats, Δr values larger than the predefined threshold are omitted. Both detection criteria are associated with a rather poor performance, although slightly better detection results (Se = 89 % and PPV = 87 % for the AFDB database) were obtained by using Laplace probability density function as a basis for the histogram approximation.

Dash et al. (2009) proposed an AF detector relying on the combination of three straightforward algorithms (the turning point ratio, the root mean square of successive differences and the Shannon entropy), suitable to characterise variability and complexity of r intervals. A segment of r intervals is flagged as AF when the output of each separate algorithm exceeds the predefined threshold for AF. In addition, the algorithm utilizes a supplementary step of ectopic beat filtering to reduce the number of false alarms due to ectopic activity. For the AFDB dataset, with the records 04936 and 05091 omitted, the Se and Sp were 94.4 % and 95.1 %, respectively. Several years later, Andersson et al. (2015) implemented the algorithm in an ultra-low energy application specific integrated circuit (ASIC). It is very impressive that both algorithmic and architectural optimization resulted into a hardware, requiring a supply voltage of just 290 mV, thereby forming a solid basis for implementation in implantable loop recorders. The basic architecture of this AF detector is showed in Fig. 3.4.

Lee et al. (2013b) have investigated the Shannon entropy, the root mean square of successive differences, and the sample entropy (described later) in terms of AF detection using a video camera of an iPhone. By capturing a video signal from a fingertip it is possible to obtain a photoplethysmography signal, which may further be used for a peak detection. Similarly to ECG, the peaks in the photoplethysmography signal represent ventricular contractions, allowing to compose a surrogate (pulsatile) r interval series. The above mentioned statistical algorithms were tested on the AFDB and Normal Sinus Rhythm databases, but with r interval series rescaled to 30 Hz in order to simulate the sampling rate of the iPhone's video camera. The best performance was achieved by using the sample entropy which was notably better compared to the root mean square of succes-

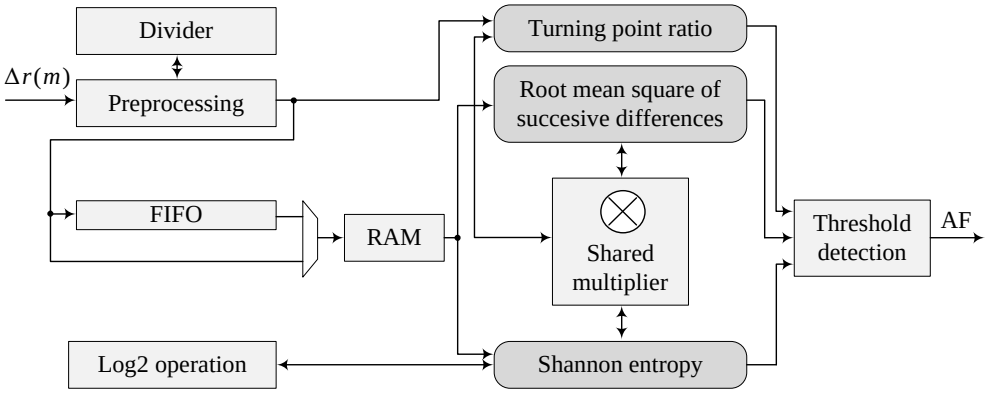

Fig. 3.4. Architecture of hardware implementation of the AF detector originally proposed by Dash et al. (2009) and later optimized by Andersson et al. (2015). Here FIFO stands for a first-in first-out memory

sive differences and the Shannon entropy. By using this approach, AF detection should be performed in the segments containing 64 r intervals, which implies that the finger has to be attached to the camera for about 1 min. The authors also reported that both the sample entropy and the Shannon entropy were associated with worse performance for higher pulse rates, although the performance of the root mean square of successive differences did not deteriorate in this particular case.

The same year, Lee et al. (2013a) introduced another AF detector utilizing a combination of the Shannon entropy and the time-varying coherence function. The time-varying coherence function is obtained by multiplying two time-varying transfer functions, of which the first is derived by involving two adjacent r interval segments – preceding as the input signal, and subsequent as the output signal. The second transfer function is derived by reversing the input and output signals. Ideally, the time-variance coherence function takes values close to 1 over the entire frequency band for regular rhythms, and considerably lower values when any r interval segment contains AF. Since this approach is sensitive to irregularities occurring in any of each segment, the ectopic beat filtering introduced by Dash et al. (2009) was implemented for the purpose to reduce the false-positive rate. Nevertheless, the time-varying coherence function based approach performed only slightly better compared to the AF detector relying on the Shannon entropy alone. On the other hand, the combination of both algorithms led to a superb performance (Se = 98.2 % and Sp = 97.7 % for the AFDB with records 4936 and 5091 excluded). It should be noted that the latter result was achieved using segments of 128 r intervals, however, significantly worse performance (Se = 94.7 % and Sp = 90.4 %) was obtained when segments of 12 r intervals were analysed. The authors reported that the main source of false-positives was the presence of other arrhythmias, covering more than 50 % of the analysis window.

Recently, the Shannon entropy was utilized as a core technique in a three step detection procedure introduced by Zhou et al. (2014). At first, a sequence of r intervals is pre-processed by linear and nonlinear digital filters in such a way that two signals, further

used as a low and high scale references, are produced. Subsequently, with respect to the obtained reference signals, initial r intervals are converted into a series of symbols from 0 to 9, where the symbolic sequence itself reflects the differences between the adjacent r intervals, i.e., larger values are taken when the difference between the contiguous r intervals is larger. Finally, a measure of Shannon entropy is applied to quantify the amount of information contained in the symbolic sequence. Ideally, a low amount of information is contained during sinus rhythm, whereas the Shannon entropy is expected to increase during the episode of AF. In addition, the authors provided a recursive realization of the algorithm with considerably reduced computational complexity. To ensure high performance (Se = 96.9 % Sp = 98.3 % for the AFDB), the detection window of 127 r intervals should be applied, therefore brief episode AF detection is limited by using this high performing algorithm.

Table 3.1. Comparison of rhythmogram-based AF detectors in terms of detection performance on the MIT-BIH Atrial Fibrillation database (AFDB). Records "04936" and "05091" are excluded in AFDB_1

Algorithm	Window length, r intervals	Database	Se, %	Sp, %	PPV, %
Moody and Mark (1983)	20	AFDB	93.6	na	85.9
Tateno and Glass (2001)	100	AFDB	94.4	97.2	96.0
Sarkar et al. (2008)	2 min	AFDB	94.7	na	95.8
Ghodrati and Marinello (2008)	30	AFDB	89	na	87
Lian et al. (2011)	128	AFDB	95.8	96.4	na
	64	AFDB	95.7	96.0	na
	32	AFDB	94.3	95.1	na
Dash et al. (2009)	128	AFDB_1	94.4	95.1	na
Huang et al. (2011)	100	AFDB	96.1	98.1	na
Lake and Moorman (2011)	12	AFDB	91	94	na
Lee et al. (2013a)	128	AFDB_1	98.2	97.7	na
	12	AFDB_1	94.7	90.4	na
Zhou et al. (2014)	127	AFDB	96.9	98.3	97.6
Andersson et al. (2015)	128	AFDB	94.9	95.8	na

The above discussed algorithms are optimized for detection of AF episodes that are longer than 1 min. However, in accordance to the growing interest in detection of brief AF episodes, several algorithms have been proposed that can be effective even when brief AF episodes occur. An interesting r-based detector was proposed by Lake and Moorman (2011) to detect AF in very short physiological times series where the coefficient of sample entropy is employed to identify AF episodes with as few as 12 beats. A sample entropy based AF detector relies on the basic assumption that r intervals exhibit much higher variability during AF than sinus rhythm. As a result, the partly repeated pattern of r intervals during sinus rhythm reduces the entropy of the signal, while a completely different image is observed during AF where irregular rhythm increases the entropy. As a matter of fact, the algorithm is very sensitive to other types of irregular rhythms, therefore additional preprocessing steps are indispensable to reduce the number of false-positives due to ectopic

beats. Since ectopic beat filtering was not implemented by Lake and Moorman (2011), it is no surprise that the performance using detection window of just 12 r intervals was markedly worse (Se of 91 % and Sp of 94 % for the AFDB) than that obtained using previously described AF detectors.

In an additional study, Langley et al. (2012) investigated the sample entropy in terms of detection performance when short ECG segments (5 to 60 s) were the target of interest. When evaluating the performance of the sample entropy on short duration ECGs, an area under the receiver operating characteristic (ROC) of 90.2 % was achieved when a 5 s window was used (Langley et al., 2012).

To sum up, the performance of all algorithms discussed above is provided in Table 3.1.

3.1.2 Morphology-based atrial fibrillation detection

Atrial activity takes recognizably different pattern on the surface ECG during AF (see Fig. 3.5). For this reason, the inclusion of atrial activity characterizing parameters into the AF detection process theoretically should be beneficial when discriminating between AF and other irregular rhythms. However, ECG signals recorded during daily activities are often of low quality, making atrial activity analysis especially challenging. Consequently, the majority of AF detectors take the r interval series as the starting point, whereas only a few detectors also involve information on P-wave and f-wave morphology.

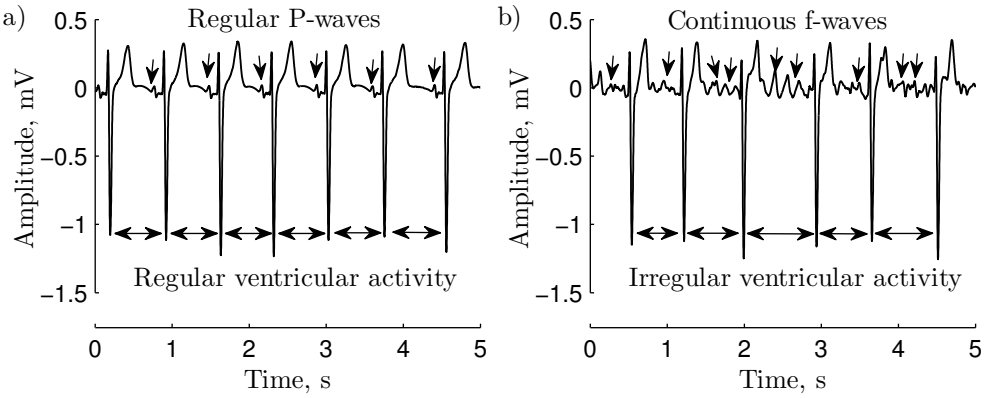

Fig. 3.5. ECG signals recorded during a) sinus rhythm, and b) atrial fibrillation

Atrial activity based atrial fibrillation detection

Slocum et al. (1992) were among the first to introduce an algorithm for AF detection relying solely on the analysis of the atrial activity signal, which, in turn, is obtained by cancelling the ventricular activity (QRST) on the surface ECG. In order to acquire the atrial activity signal, the authors proposed an averaged QRST beat subtraction technique, in which the averaged QRST complex is aligned at the fiducial point (the peak of R-wave), and then subtracted from the surface ECG (see detailed explanation in Section 3.4.2).

Two major steps are involved in this AF detector: at first, the presence of P-waves is tested, and if succeeded, the analyzed ECG segment is subsequently considered as non-AF. However, if P-waves are not identified, the power spectrum of atrial activity signal is computed to identify a spectral peak of the suspected fibrillatory activity. The algorithm was tested on 148 ECG signals, of which 28 % were AF, 28 % other rhythms, and the remaining 46 % belonged to sinus rhythm. The results showed unsatisfactory performance of just 68.3 % sensitivity and 87.8 % specificity. A low amplitude of f-waves (33 $\pm$ 11 μV) in some of the test signals was reported as a major cause of low sensitivity. Moreover, the averaged beat subtraction technique tends to produce QRST residuals in the remaining signal, thereby obscuring the f-waves spectral peak. Nonetheless, despite the proposed AF detector showing poor performance, Slocum et al. laid the foundations for atrial activity extraction techniques, as well as for the development of atrial activity information involving AF detectors.

Recently, another AF detector based solely on atrial activity analysis has been developed (Ladavich and Ghoraani, 2015). The driving motivation to invoke only atrial activity into the AF detection process was an issue of AF detection in special conditions when r interval irregularity is highly reduced due to rate-controlling drugs or a pacemaker. In this AF detector, QRS complex preceding PR interval, where P-wave is normally supposed to be, is used for analysis. A total of nine features are calculated, where six of them represent P-wave morphology, while the remaining three are obtained by calculating the basic statistics (variance, skewness, kurtosis) of the samples in the segment. Finally, a Gaussian mixture model is trained to discriminate between learned P-wave morphology and morphology deviations, i.e., those due to the presence of f-waves. By using this technique, AF detection is performed either in a single ECG beat, or in 7 beats, although considerably better performance was achieved by the later approach (Se = 98.1 % and Sp = 91.7 % compared to Se = 89.4 % and Sp = 89.5 % for the selected 20 records of the AFDB database).

Despite the ability to detect brief AF episodes and overcome situations when r interval irregularity is reduced due to the use of rhythm controlling drugs or a pacemaker, the algorithm has several major shortcomings. Most importantly, the algorithm was developed on the assumption that ECG signals are free of noise and electromyographic artefacts, let alone the fact that misclassification may occur during P-wave morphology variations. Moreover, to ensure satisfactory performance, the classifier has to be trained for each patient individually by using at least half an hour of sinus rhythm ECG. Considering all the mentioned points, the algorithm is unsuitable for implementation in clinical practice.

Atrial and ventricular activity based atrial fibrillation detection

Babaeizadeh et al. (2009) published results on AF detection using combined the information of both ventricular and atrial activity. Their starting point was to develop an algorithm based on r interval analysis with the Markov modelling approach employed as a core technique. The algorithm was further enhanced by combining information of r irregularity with PR interval variability and P-wave morphology. Given that PR interval

duration during sinus rhythm is rather stable, PR variability is negligible. However, PR interval variability increases considerably during AF due to the absence of a relatively stable fiducial point, which is dependent on the P-wave. P-wave morphology describing parameter is obtained by calculating the similarity between 2 adjacent P-waves. Ideally, P-waves match each other during sinus rhythm, while matching is poor when P-waves are replaced by chaotic f-waves. These theoretical assumptions would apply very well in a low-noise environment, but ambulatory ECG recordings are usually corrupted by noise and electromyographic artefacts, thus diminishing the additive value of P-waves. As a result, the performance was only slightly better (Se = 92 % and PPV = 97 % for the AFDB with records 00735 and 03665 excluded) than that achieved by the same detector but without atrial information involved. In addition, all episodes shorter than 1 min were excluded from their study.

An AF detector proposed in (Couceiro et al., 2008; Carvalho et al., 2012) appears to be the first with an architecture that jointly processes information on r irregularity, P-wave absence, and f-wave presence (Fig. 3.6). Six features are extracted from the ECG signal and then an artificial feed-forward neural network is employed as a classifier, first trained on a huge dataset. Similar to other AF detectors, this detector requires that ventricular premature beats (VPBs) are first located and excluded. Nevertheless, using the AFDB database, the performance was not better (Se = 93.8 % and Sp = 96.1 %) than that achieved by some best performing r-based detectors. A possible explanation to this result is that the decision process did not account for the prevailing noise level.

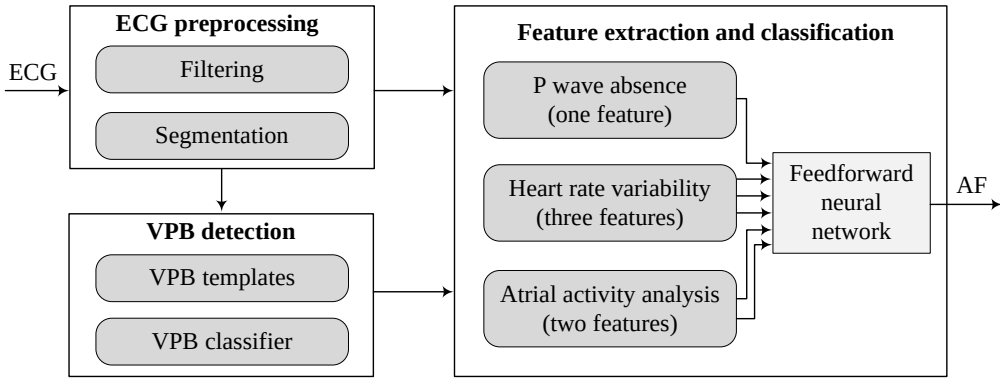

Fig. 3.6. Block diagram of AF detector involving information of r irregularity, P-wave absence, and f-wave presence. Adapted from Carvalho et al. (2012)

Hayes and Teal (2013) proposed a cumbersome approach for AF detection which incorporates a total of 29 features and 12 support vector machine classifiers. Both morphological and rhythm features are involved into the detection processes. However, different from other algorithms, morphology analysis is involved not for the purpose to detect atrial activity, but to discriminate among different beat types (i.e. normal beat, ectopic beat, and beats caused by left and right bundle branch block). The idea of beat classification was preferred in order to reduce the number of false-positives owing to heart rhythm

irregularity, although it did not produce a reliable performance. The proposed AF detector was tested on the MIT-BIH Arrhythmia database and showed moderate detection results of Se = 94.8 % and Sp = 92.5 %. The actual performance may even be lower, since the algorithm was trained and tested on the randomly selected beats of the same database.

Du et al. (2014) proposed a simplistic approach to AF detection relying on 3 rules, of which, one is dedicated to f-wave analysis. Six-second duration ECG episode is classified as AF if the following rules are satisfied: the standard deviation of r intervals is larger than 50 ms, the difference between the largest and the smallest r interval is more than 70 ms, and the number of f-waves in the TQ interval exceeds 1. The declared Se and PPV values for the unspecified AF database were 94.1 % and 97.7 %, respectively. Even though the reported performance is rather poor compared to existing algorithms relying solely on r interval analysis, the performance may even be worse if the algorithm was tested on the AFDB database, containing low quality ECGs with lots of ectopic beats and movement artefacts. Furthermore, given that all three rules must be satisfied, it is highly likely that AF episodes with increased heart rate will remain undetected due to a too short TQ interval for f-wave identification.

An interesting AF detector was recently proposed by Asgari et al. (2015). The algorithm is completely different from the previously published approaches, since it does not require QRS detection, nor P-wave identification. Instead of these pre-processing steps that are indispensable for most of the existing algorithms, stationary wavelet transform is employed for feature extraction directly from the ECG signal. Peak-to-average power ratio and low-energy entropy is computed for each wavelet coefficient. In such a way, 28 features are extracted, which are further used as the inputs to support the vector machine classifier. When ECG segments of 30 s duration were used, the algorithm achieved Se of 97 % and Sp of 97.1 % for the AFDB database.

Table 3.2. Comparison of ECG morphology based AF detectors in terms of detection performance on the MIT-BIH Atrial Fibrillation database (AFDB). Records "00735" and "03665" are excluded in $AFDB_2$, and 5 unspecified records are excluded in $AFDB_3$. MITDB stands for the MIT-BIH Arrhythmia database

Algorithm	Window length	Database	Se, %	Sp, %	PPV, %
Slocum et al. (1992)	na	Generic	68.3	87.8	84.8
Couceiro et al. (2008)	$>$ 12 beats	$AFDB_2$	93.8	96.1	na
Babaeizadeh et al. (2009)	na	$AFDB_2$	92	na	97
Hayes and Teal (2013)	na	MITDB	94.8	92.5	na
Du et al. (2014)	6 s	Generic	94.1	na	97.7
Ladavich and Ghoraani (2015)	7 beats	$AFDB_3$	98.1	91.7	79.2
	1 beat	$AFDB_3$	89.4	89.5	72.4
Asgari et al. (2015)	30 s	$AFDB_2$	97.0	97.1	na
	15 s	$AFDB_2$	97.0	96.8	na
	10 s	$AFDB_2$	96.6	96.3	na

Needless to say, the algorithm was developed and tested on the same database (AFDB) using a two-fold stratified cross-validation, which may be in favour towards

the achieved performance. Moreover, since the algorithm relies on the assumption that f-waves are present on the ECG signal during the episode of AF, the performance may deteriorate when ECG lead without f-waves expressed is applied for the analysis (usually any other lead than precordial lead V_1). On the other hand, f-waves are quite often too negligible to be recognizable even in the lead V_1. Nevertheless, the elimination of QRS detection and the ability to remain a relatively high performance, even for ECG segments as short as 10 s, are notable strengths of the algorithm.

The performance of the aforementioned ECG morphology-based AF detectors is summarized in Table 3.2.

3.2 Available devices for detection of atrial fibrillation

3.2.1 Non-invasive devices

According to the current guidelines, even if a patient is at high risk to develop AF, the existence of AF has to be documented in order to start anticoagulant treatment. For many years, a standard 12-lead electrocardiogram and Holter monitoring have been the only available options for AF detection. However, rapid and continuous development of electronics and communication technologies has given rise to various approaches to AF monitoring and screening (Fig. 3.7). In this section, clinically tested non-invasive devices are discussed.

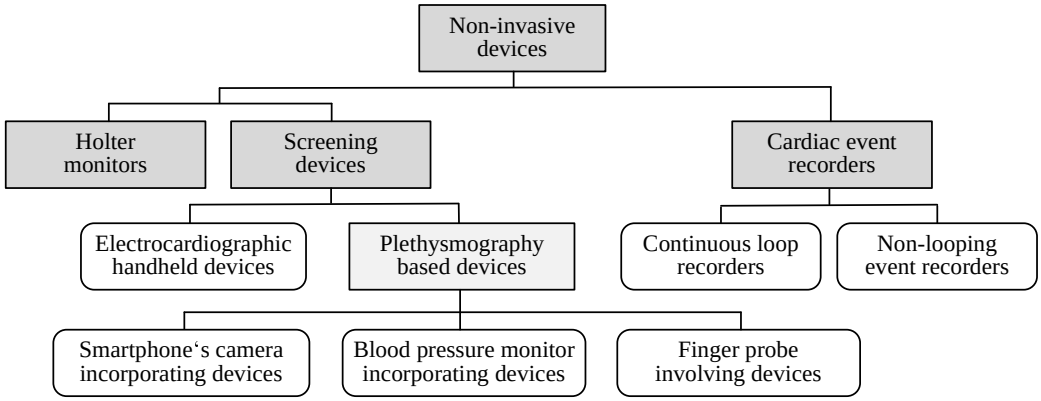

Fig. 3.7. Classification of non-invasive devices for AF detection

Standard 12-lead electrocardiogram

A standard 12-lead electrocardiogram is the most widely available diagnostic tool, currently accepted as the clinical reference for confirmation of AF existence. A twelve lead ECG is a globally recognized technique, cost-effective, straightforward to perform and relatively easy to interpret for trained physician. Therefore, the majority of AF cases are still identified using a 12-lead ECG. The main disadvantage of this approach is a short recording time, normally lasting just several seconds. As a result, severely prolonged AF

is usually detected, whereas paroxysmal AF, especially in its early stages of development may never be caught using this technology. For this reason, many other approaches to AF detection have been proposed, which are currently on the way to widespread acceptance (see Table 3.3).

Table 3.3. Comparison of clinically available devices and promising prototypes for AF detection

Device type	Advantages	Disadvantages
12-lead ECG	Widely available; easy to interpret	Short recording time; unsuitable for paroxysmal AF detection
Holter monitor	Reference for ambulatory arrhythmia monitoring	Uncomfortable to wear; low patient compliance; offline data analysis
Event recorder	Does not require to be worn all the time; effective when symptoms are experienced	Difficult to catch the beginning of the arrhythmia event; low specificity due to symptoms misinterpretation
Loop recorder	Continuous monitoring	Low patient compliance; low specificity due to ectopic beats
Handheld ECG	Easy to use; low cost; high patient compliance	Unsuitable for brief AF detection
Modified blood pressure monitor	Widely accessible; easy to use	Low specificity; needs ECG for diagnosis confirmation
Smartphone's camera	No additional hardware except a smartphone is required	Low specificity; needs ECG for diagnosis confirmation
Finger probe photoplethysmography	Does not require electrodes; fast to use	Low specificity; needs ECG for diagnosis confirmation
Insertable loop recorder	Continuous monitoring; accurate evaluation of a total time patient was in AF; no discomfort to the patient	Implantable; high cost
Cardioverter-defibrillator	Continuous monitoring; no discomfort to patient	Implantable, difficult to distinguish between different atrial arrhythmias

Holter monitors

Holter monitoring has become a widely accepted technique for ambulatory ECG recording since it was introduced by Norman Holter in 1961. The Holter monitor is a

portable, usually 3-lead ambulatory device, capable of recording ECG continuously for 1 or 2 days during normal daily activities. Occasionally, 7 day, 2 week or even 1 month Holter monitoring may also be prescribed. The Holter monitor is a valuable tool for clinicians, since it can be used not only for arrhythmia detection (including AF), but also for the evaluation of drug effect with respect to AF recurrence. After Holter monitoring is finished, recorded ECG signals have to be analysed offline by some dedicated software. Despite this, AF detection software is continually improving, although automatically detected AF episodes still have to be manually reviewed by a physician to ensure that flagged episodes are not false-positives. To this day, 24 h Holter monitoring is the most commonly prescribed for arrhythmia detection. However, there is an ongoing debate on monitoring strategies that would be optimal for specific task, for instance, monitoring of AF recurrence after catheter ablation (Hindricks and Piorkowski, 2012; Charitos et al., 2012).

The major drawback of Holter monitoring is the adhesive electrodes and the device's connecting wires, which are very uncomfortable for many patients, eventually leading to premature termination of recording (Calkins et al., 2012). Even more, some individuals are allergic to adhesive electrodes, and therefore another monitoring technique should be considered instead.

Cardiac event recorders

Cardiac event recorders are portable ambulatory devices similar to Holter monitors, though usually smaller and lighter since only a single lead ECG is normally recorded. The other notable difference is that cardiac event recorders do not continuously record the ECG signal but are activated by the patient when symptoms occur, or are started automatically when heart rhythm abnormalities are detected by the embedded algorithm. Two main types of cardiac event recorders can be distinguished: *continuous loop recorders* and *event recorders*.

Continuous loop recorders are continuously refreshing (recording and erasing) the data. Data refreshing is stopped when the device is triggered by the patient or by the automatic algorithm. In such a way, the ECG signal of the entire particular event and a few minutes before and after the event are stored in the memory. Due to limited storage capacity, only the beginning and the end of the episode are saved if arrhythmia lasts for a longer period of time. Similarly to Holter monitor, the continuous loop recorder is connected to adhesive electrodes via wires, although sticky patches, which are attached to the body together with the device itself, are gaining increasing popularity. An example of an adhesive-patch based device is the Zio-Patch (iRhythm Technologies, Inc, San Francisco, California, US), currently being used for prolonged arrhythmia monitoring (Barrett et al., 2014).

In contrast to loop event recorders, non-looping cardiac event recorders do not require to be worn all the time, but are temporarily attached to the body by the patient when symptoms of arrhythmia are experienced. However, by using such a device it is problematic to catch the very beginning of rhythm disturbance. Moreover, in some cases when symptoms are severe (i.e. fainting) it may be difficult for the patient to correctly attach

the device to the body. In addition, patient-activated event recorders will most likely miss nocturnal and asymptomatic events.

Various studies have stated that cardiac event recorders are prone to false alarms due to ectopic beats, since they share similar symptoms as AF. For example, in a small study of 48 participants (50 % with AF), Muller et al. (2009) investigated AF detection reliability using the external loop recorder 3100 BT by Vitaphone (3100 BT, Vitaphone, Mannheim, Germany). When compared with Holter recordings, which showed a perfect AF detection sensitivity, each patient in sinus rhythm on average had more than 5 false-positive ECG recordings which led to a very low specificity of just 50 %. Comparable results using this device were reported in another study (Velthuis et al., 2013), where 2923 ECG events were collected in 108 patients. Roughly 1200 flagged events were classified as AF by the automatic algorithm, although only 56 were confirmed to be AF after manual revision, which resulted in a Se and Sp of 95 % and 51 %, respectively. Based on these observations, it can be concluded that the extremely low specificity is undoubtedly unsatisfactory for daily use in clinical practice.

Electrocardiography-based screening devices

Handheld electrocardiogram recorders rely on the general idea of recording a single lead ECG signal between two hands (thumbs, fingers, palms) from tens of seconds to several minutes. Handheld ECG recorders have been proposed as alternative screening tools to pulse palpation, and even offer many advantages compared to standard Holter monitoring, most notably are low cost, easy to use and do not require adhesive electrodes or connecting wires. Despite that various solutions for recording a single lead ECG have been proposed in recent years, the majority do not involve an automatic AF detection. Hence, only the devices that have been manufactured primarily for AF detection are discussed in this section.

Among the handheld AF screening devices, thumb-ECG recorders are gaining recognition around the world, with several devices already being available on the market. For example, the Zenicor thumb-ECG recorder (Zenicor Medical Systems AB, Stockholm, Sweden) is spread over 250 clinics in Scandinavia. With the Zenicor device, a single lead ECG is recorded for 10 s twice a day or when AF-related symptoms are present, and then the signal is transmitted to a specified website via a mobile phone. In such a way, ECGs are stored on the Internet, and instantly become available to a physician for manual evaluation, since the data can be accessed from any place at any time without the need of any specific software, as long as there is an Internet connection.

The Zenicor handheld device has been involved in a large scale population screening of 75–76 year-old inhabitants in Sweden (Friberg et al., 2012). In a related study by Engdahl et al. (2013), 419 individuals with initial sinus rhythm plus two or more risk factors for AF were enrolled. After just two weeks of screening, new paroxysmal AF was found in 7.4 % of participants. Later, Svennberg et al. (2015) reported that intermitted screening using a Zenicor device resulted in 4.3 times higher AF detection rates compared to the standard 24 h Holter monitoring. In addition, based on the evidence of a new AF,

anticoagulant treatment has been initiated in 93 % of these patients.

The AfibAlert AF monitor (Lohman Technologies, Sussex, Wiscons, US) is another example of a commercially available thumb-ECG recorder. The AfibAlert acquires ECG signal in two different ways: by pressing thumbs on the electrodes of the device or by using wrist electrodes. ECG is recorded for 45 s, and then the signal is analyzed for AF by an automated algorithm. The decision is immediately reported by an LED indicator. If AF is suspected, the patient has to transmit ECG data to a physician for diagnosis confirmation using transtelephonic transmission by holding the device to the phone. The official website (www.lohmantech.com) declares AF classification ratio of 94 %, although no clinical studies supporting this number are available at the moment.

The MyDiagnostick ECG recorder (Applied Biomedical Systems BV, Maastricht, The Netherlands) was manufactured to record palm-ECG, rather than thumb-ECG. The device has a form of a stick with metallic handles at both ends, serving as electrodes. In order to acquire data for arrhythmia detection, the user has to grasp the metallic handles and hold for 1 min. Subsequently, the same procedure has to be repeated two more times. Once recorded, the ECG signal is analyzed for AF automatically using an embedded AF detection algorithm, which computes an AF score based on the estimates of signal periodicity and variability. The patient is informed about the analysis outcome via an LED indicator. The MyDiagnostick was tested on a group of 181 participants, where the majority of them were known to have AF. Hence, highly exaggerated AF prevalence of 53 % was documented at the moment the measurements were acquired (Vaes et al., 2014). Regardless of this, Se of 94 % and Sp of 93 % were obtained when following the recommended protocol of three subsequent measurements.

Smartphone-based devices are future promising tools for screening of general health status (Agu et al., 2013). In 2014, there were more than 1.7 billion smartphone users around the world and tens of thousands of mobile health applications available for personal use (Mitchell and Le Page, 2015). It is very likely that sooner, rather than later, smartphones incorporating health-care technologies will occupy a large part of screening medical devices.

AliveCor Heart Monitor (AliveCor Inc., San Francisco, US) and CardiacDesigns ECG Check (CardiacDesigns, Park city, Utah, US) provide phone cases with dry electrodes in order to record a handheld single-lead ECG signal using an iPhone. By using these devices, the ECG is obtained between the fingers of the left and right hands, which are placed on the electrodes at the back of the iPhone's case. Before each recording, special arm relaxation instructions are strongly recommended to reduce noise level and artifacts. Normally, ECG is recorded for approximately one minute and is transmitted to the microphone of the iPhone using a modulated ultrasound signal, where it is further demodulated and digitized. Finally, the ECG trace is sent to a cardiologist for manual revision if an abnormal rhythm is identified by the automatic algorithm.

The pilot study by Lau et al. (2013) showed that by using the AliveCor Heart Monitor it is possible to achieve a satisfactory performance (Se of 87 %–100 % and Sp of 96 %–97 %) when compared to a simultaneously recorded standard 12-lead ECG. Inter-

estingly, the automated algorithm showed better AF detection results than each of the two cardiologists who interpreted a device-recorded single-lead ECG. A larger study is underway in order to assess the suitability of this technology for mass implementation for preventive screening of individuals aged $\geqslant$65 (Lowres et al., 2012a).

To sum up, a handheld device is a simple and fast way to check heart rhythm, since measurements can be performed simply anywhere when symptoms of arrhythmia are experienced. Moreover, such devices can be used not only for personal reasons, but also for a cardiologist or nurse to check whether the patient needs stationary 12-lead ECG for AF diagnosis confirmation. On the other hand, a huge amount of data, which must be manually reviewed by a trained physician, is the unifying problem of handheld ECG recorders. Therefore, even high specificity of the automatic algorithm would lead to several monthly false alarms, if a screening device is used as recommended, for example, twice a day. In addition, poor signal quality, rapid changes in baseline wander due to lost electrode contact, and low amplitude of atrial activity are the other major obstacles making the analysis of a handheld ECG especially challenging (Stridh and Rosenqvist, 2012).

Plethysmography-based screening devices

Recently, the photoplethysmography-based approach to AF detection has been proposed by employing the inbuilt camera of an iPhone (Lee et al., 2013b). Since the camera is available with most smartphones, and therefore no additional hardware is required, such an approach could be among the cheapest alternatives for mass AF screening. The method is based on the ability to record the photoplethysmography signal from a fingertip by placing a finger directly on the camera for several minutes. After the pulsatile signal is acquired, the video is processed in such a way that a one-dimensional pulse photoplethysmography signal is obtained, which is further used as a subject for peak detection. The interval between the adjacent pulse peaks is assumed to represent a time interval between two heart contractions (Fig. 3.8). Although r_p series obtained from the photoplethysmography signal does not always perfectly match r intervals of the ECG (Lu et al., 2009; Gil et al., 2010), basically any algorithm suitable to detect AF in r interval series can be applied instead.

Accordingly, Lee et al. (2013b) performed AF detection by utilizing a combination of classical algorithms used for quantification of r variability and complexity. The iPhone based prototype was validated in a group of 76 participants with diagnosed AF, who were assigned for electrical cardioversion (McManus et al., 2013a). Since pulsatile signals were recorded just before and immediately after cardioversion, the achieved high performance (Se = 96 %, Sp = 97 %) should be taken with caution. Hence, additional studies involving a larger population are needed to prove the method's reliability. Although the idea is promising, the potential problem may arise in situations when a particular patient has impaired blood flow in his fingers. Moreover, thus far, no guidelines exist on interpretation of the pulse photoplethysmography signal, therefore an ECG recording should inevitably be taken to confirm the existence of AF.

Another type of instrument utilizing the principle of pulse photoplethysmography

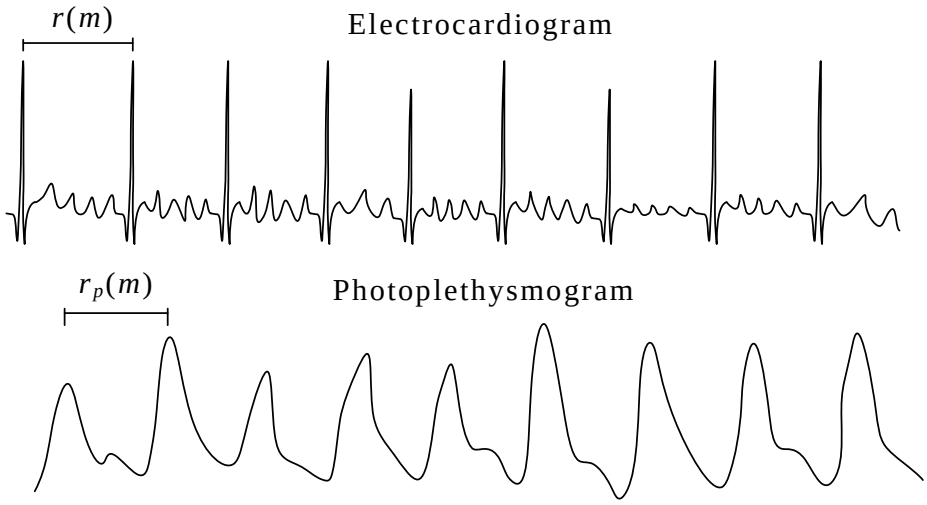

Fig. 3.8. Representation of AF in the photoplethysmography signal. Here a time interval $r_p(m)$ is a surrogate of $r(m)$ interval obtain from the ECG

has been devised by Melys (Melys AFS, Columbia, Maryland, US). The portable device employs a finger probe for recording blood pulsations in a fingertip of the index finger. The pulse photoplethysmography signal is recorded for 30 s, and then a fast Fourier transform based algorithm is applied to compute pulse rate variability. The device was validated in a group of 594 participants, aged over 60 years who were not specifically cardiac patients at that time (Lewis et al., 2011). The study found a perfect AF detection sensitivity (100 %) and specificity of 91.9 % for this device, where all 53 false-positives were caused by the presence of ectopic beats. Since the presence of AF must be confirmed by a standard 12-lead ECG, the authors of the study concluded that the Melys AF monitor is suitable just for AF screening but not for diagnostic purposes.

Given that the oscillometric principle of *self-screening blood pressure devices* involves the analysis of a pulsatile signal, which in turn, represents pressure oscillations in the sphygmomanometer cuff, the same signal can be employed for the evaluation of pulse rhythm irregularity. Such an approach is especially attractive for mass screening, since home blood pressure monitors are widely spread among the hypertension patients who are at a high risk to develop AF. The Microlife BP A200 (Microlife, Microlife AG, Widnau, Switzerland) and the Omron M6 (Omron, Omron Healthcare Co., Kyoto, Japan) are the most widely distributed blood pressure monitors with an integrated function to detect AF. In both devices, AF detection is performed during cuff deflation by calculating the mean and the standard deviation of 10 consecutive pulse intervals. Then, the irregularity index is computed by dividing the standard deviation by the mean. To reduce the influence of ectopic beats, pulse intervals that are 25 % lower and 25 % greater than the mean are removed from the pulse interval sequence prior to computation of the irregularity index. The only notable difference between these two devices lies in the recommendations – three consecutive measurements should be performed using the Microlife BP A200,

whereas the only one is requested for the Omron M6.

Several studies have investigated the feasibility of the Microlife BP A200 blood pressure monitor to detect AF. The AF detection performance differed only slightly between the studies, and depended primarily on the number of consecutive measurements taken for decision making. Fairly high sensitivity of 92–100 % and specificity of 89–97 % have been obtained when three measurements were performed (Wiesel et al., 2009; Stergiou et al., 2009; Marazzi et al., 2012; Wiesel et al., 2014).

At least two studies have been conducted in order to directly compare the performance of the Microlife BP A200 and the Omron M6 devices (Marazzi et al., 2012; Wiesel et al., 2014). Interestingly, both studies strongly contradict each other, i.e., Marazzi et al. (2012) reported a comparable performance of both devices, although the Omron M6 turned out to be slightly more accurate and more comfortable to use than the Microlife BP A200. In that study, a direct comparison of these devices to ECG recordings showed sensitivity/specificity of 100/94 % for the Omron M6 device, and 92/97 % for the Microlife BP A200. On the contrary, Wiesel et al. (2014) later claimed that the Omron M6 monitor is considerably less sensitive (Se = 30 %). The authors speculated that such a huge difference in sensitivity could be caused by an unusual patient group studied by Marazzi et al., which did not represent the typical AF patient in the general population.

Although larger and better arranged studies are needed to prove the feasibility of the Omron M6 device to detect AF, pretty good results that were consistently achieved using the Microlife BP A200 offer a more convenient approach for mass AF screening. Nevertheless, due to the simplicity of currently implemented algorithm for AF detection, the device is prone to false alarms during ectopic beats or highly variable pulse rate. For instance, sinus arrhythmia, which is associated with rapidly changing heart rate, is very common in the younger population, thus it is no surprise that even 18 % of measurements using the Microlife BP A200 monitor appeared to be false positives when 13–18 year old teenagers were involved in the study (Cheung and Cheung, 2015). For this reason, device-specific guidelines should be introduced in order to better specify when a particular patient should consult a physician. For example, Wiesel et al. (2007) suggested that the number of false-positives will be reduced if two additional measurements are taken after the initial pulse irregularity is detected.

3.2.2 Invasive devices

To this day, invasive devices are the only available technologies providing a convenient way of continuous arrhythmia monitoring. A block diagram illustrating the basic types of devices used for AF monitoring in clinical practice is shown in Fig. 3.9.

Insertable loop recorders

Insertable loop recorders are invasive leadless devices used exclusively for diagnostic purposes. Earlier, insertable loop recorders have been proven to be useful tools for diagnosing recurrent syncope events when the patient temporally loses consciousness and

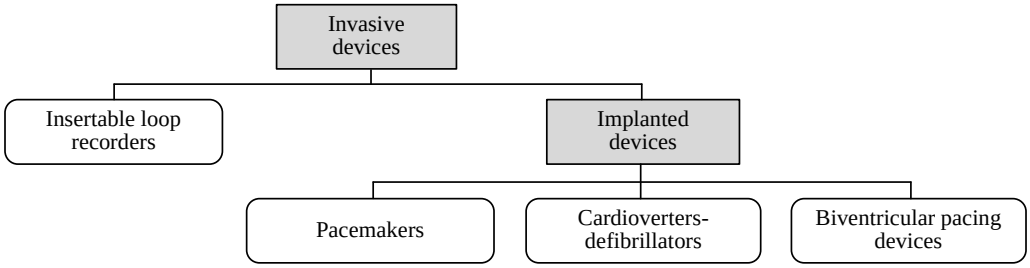

Fig. 3.9. Classification of invasive devices suitable for AF detection

then recovers spontaneously (Kanjwal et al., 2011). In case of AF, the insertable loop recorder plays a special role in some specific situations, for example, when evaluating the success of AF treatment procedures (i.e. radiofrequency ablation), assessing the efficacy of rate control therapy, or aiming to detect asymptomatic paroxysmal AF episodes after cryptogenic ischemic stroke.

Currently, several insertable loop recorders with an embedded AF detection algorithm are available on the market for clinical use. The most commonly used in clinical practice are the Reveal XT (Medronic Inc., Minneapolis, Minnesota, US), the SJM Confirm (St, Jude Medical, St. Paul, Minnesota, US) and the Sleuth (Transoma Medical Inc., St. Paul, Minnesota, US). These cardiac monitors include two built-in electrodes suitable for recording a single bipolar ECG lead. The device is normally inserted under the skin into the subcutaneous tissue, thus normally has a thickness of several millimeters and weighs less than 20 grams. Similarly to an external loop recorder, implantable equivalent also involves looping memory, and can operate either in an automated self-activation mode or can be activated by the patient with a hand-held activator when symptoms are experienced.

The Reveal XT insertable loop recorder is capable of identifying both atrial tachycardia and AF on the basis of the Poincaré plot analysis (Sarkar et al., 2008). In addition, the device provides the possibility to be programmed to detect a desired duration of arrhythmia events. Therefore, a partial freedom is permitted to the physician to manipulate between arrhythmia detection specificity and sensitivity by simply changing the length of the shortest episode to be detected.

The Reveal XT insertable loop recorder has been investigated in various studies. In a comprehensive study by Hindricks et al. (2010), the sensitivity and specificity of the Reveal XT were found to be 96.1 % and 85.4 %, respectively, when compared to 46 h Holter. Despite poor specificity, AF burden, representing a proportion of time the patient was in AF, correlated very well with the reference annotations obtained from the Holter recordings (Pearson's correlation: 0.97). The authors reported that inappropriate detection was caused mostly due to ectopic beats. In the same study, the influence of AF episode length on detection performance was evaluated as well. The minimum duration of detectable AF episodes was adjusted to 2, 6, 10 and 20 min. The sensitivity and positive predictive value were found to be 88.2 % and 73.5 %, respectively, for $\geqslant$ 2 min AF episodes, however

increased up to 92.1 % and 79.6 %, respectively, for $\geqslant$ 6 min AF episodes. It should be noted that regarding an unacceptably low specificity, a minimum duration of 6 min is the preferred in the majority of clinical studies.

In several studies, electrogram signals have been manually reviewed in order to identify the main causes of false-positives. For instance, Montenero et al. (2004) reported that the Reveal XT device was triggered by atrial and ventricular premature beats in more than 30 % of all cases. Later, Eitel et al. (2011) provided a more detail view of false-positives causing factors. These were myopotentials due to activity of pectoral muscle (35 %), atrial and ventricular premature beats (15 %), misdetection of QRS complex (4 %) and T-wave over-sensing (1.5 %). The authors of the study concluded that insertable loop recorders can arguably detect more AF episodes than Holter recorder, however, the frequent false-positives reduce the practical value of this device.

In summary, many clinical studies have shown continuous AF monitoring using insertable loop recorders to be superior; even compared to a very aggressive strategies of intermitted monitoring (see Sec. 3.3.2). Hence, insertable cardiac monitors are gaining popularity and have been proven to be useful in specific situations. However, mass implantation of invasive devices is unrealistic due to high costs. The other notable drawback is that the device has to be replaced after 2–3 years of usage, although emerging energy effective hardware and software solutions may theoretically extend the working time of the device up to 10 years (Andersson et al., 2015).

Implanted devices

Implanted devices, such as pacemakers, cardioverters-defibrillators and biventricular pacing (cardiac resynchronization therapy), are devices that primary serve for a therapeutic purposes, however, they can also be programmed to detect arrhythmias including AF. Implanted devices have the ability to an record intra-atrial electrogram signal directly in the heart via an implanted atrial lead. In contrast to surface ECG, intra-atrial electrogram recorded in the atria mostly represents atrial contractions, while ventricular activity has usually a lower amplitude. Thus, implanted devices with the atrial lead, not only make possible a continuous detection of episodes of rapid atrial rate, but also provide the possibility to characterize individual episodes with respect to the atrial rate during a particular episode.

Since the dual-chamber cardioverter-defibrillator also has a lead which is placed in the right ventricle, information of both the intra-atrial and intra-ventricular signal is involved in the process of atrial tachyarrhythmia detection. In a small study by Swerdlow et al. (2000), a dual-chamber cardioverter-defibrillator Medtronic Jewel AF (Medtronic, Minneapolis, US) was investigated in terms of its ability to detect AF. It showed that 98 % of 132 device-detected AF episodes, and 88 % of 190 atrial tachycardia episodes were correct. All false-positives occurred due to over-sensing of far-field ventricular activity (see Fig. 3.10) which, in turn, made an unstable duration between the adjacent atrial activity waves. It is noteworthy that all false-positive episodes lasted less than 5 min, with the mean duration of 2.6 ± 2.0 min for atrial tachycardia and 3.2 ± 1.6 min for AF, re-

spectively. This observation suggests that the rate of false-positives increases when an arrhythmic event is of a short duration. Although AF can be discriminated from atrial tachycardia or atrial flutter relying on atrial rate and irregularity of atrial events, Swerdlow et al. suspected that some of the AF episodes were incorrectly classified as atrial tachycardia.

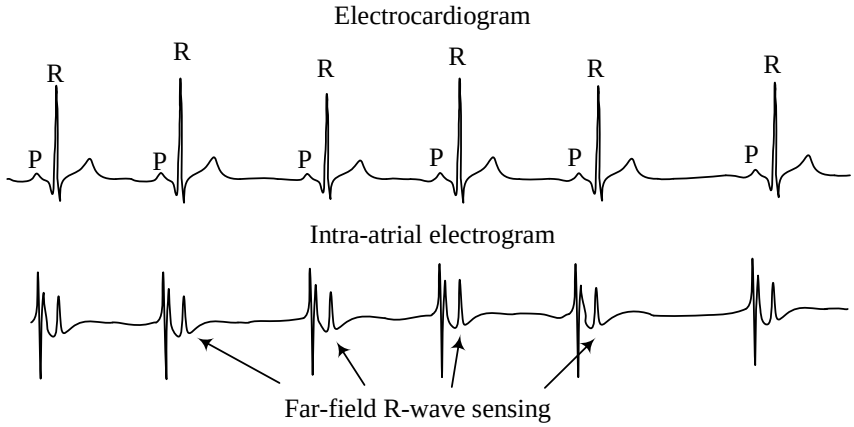

Fig. 3.10. Far-field ventricular activity (R-wave) oversensing in the intra-atrial electrogram

As mentioned above, inappropriate AF detection using dual-chamber cardioverters-defibrillators may occur due to far-field ventricular activity in the intra-atrial electrogram signal. In some individuals, especially when the atrial lead is positioned outside of the right atrial appendage, the amplitude of ventricular activity can be very large, thus, in order to avoid over-sensing of far-field ventricular activity, either the atrial wave detection sensitivity has to be reduced or post-ventricular atrial blanking has to be prolonged (Fung et al., 2009). For this reason, in many clinical studies an episode is chosen to be flagged as atrial tachyrhythmia when the atrial rate reaches at least 190 beats per minute for $\geqslant 6$ min. Moreover, rapid atrial rate can be caused by other supraventricular tachycardias, such as atrial flutter or atrial tachycardia, or can even be a result of bursts of atrial premature beats, thus even manual revision of the intra-atrial signals may not be enough to distinguish between AF and other arrhythmias.

3.3 Ambulatory monitoring of atrial fibrillation

3.3.1 Electrocardiogram lead systems for ambulatory monitoring of atrial fibrillation

As discussed previously, commercial devices tend to produce false-positives due to electromyographic noise, motion artifacts and ectopic beats (Harris et al., 2012), thus forcing the cardiologist to manually review computer-detected arrhythmic episodes; this shortcoming is particularly pronounced when brief AF episodes are of interest to analyze. It is well-known that manual review of long-term ECG recordings is exceedingly time-consuming, and unreliable at times (Mant et al., 2007), it is essential to improve the performance of such devices. One way to do this is to employ a lead system which in-

creases the amplitude of the atrial activity for monitoring of AF. When the conventional 12-lead ECG system is applied, the highest amplitude of atrial activity is observed in lead II during sinus rhythm, while precordial lead V_1 produces the highest amplitude during AF (Langley and Murray, 2004).

While the standard 12-lead ECG system, as well as its reduced-lead modifications, are focused on ventricular activity, the lead systems are not optimal for atrial activity analysis. Due to the fact that atrial amplitude is much smaller than ventricular amplitude, an ECG lead with an increased atrial amplitude helps to better discriminate between various arrhythmias of atrial origin (i.e., atrial tachycardia, atrial flutter, AF), as well other arrhythmias, such as wide QRS complex tachycardia (Bakker et al., 2009; Mizuno et al., 2014). Moreover, enhanced atrial activity facilitates the estimation of the atrial fibrillatory rate, which offers clinical value when selecting a treatment strategy (Platonov et al., 2014).

So far, no specialized ECG lead system is routinely used in clinical practice for ambulatory monitoring of AF. Therefore, a standard 3-lead Holter ECG monitoring is typically applied, even though Holter monitors reduce the patients quality of life and have lower patient compliance (Roten et al., 2012; Turakhia et al., 2013). For this reason, single lead ECG monitors are considered as a promising alternative for long-term AF monitoring (Turakhia et al., 2013). However, single lead ECG monitors do not employ electrode placement that is optimized for analysis of atrial activity.

A number of studies have proposed modifications of the standard 12-lead ECG system by placing some electrodes closer to the atria in order to enhance the atrial information (Ihara et al., 2007; Husser et al., 2007). Further enhancement may be achieved by body surface potential mapping where the electrodes are arranged as a grid around V_1 (Guillem et al., 2009). While multi-lead systems can be advantageous for analysis of atrial activation patterns, none of the above-mentioned solutions are easily transferred to a reduced ECG lead system.

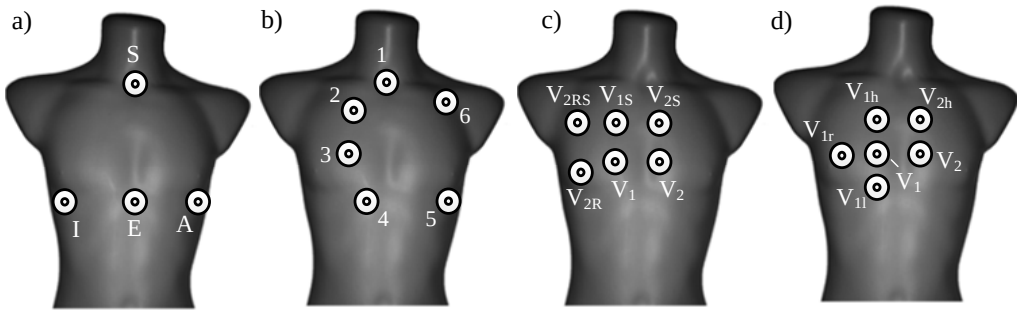

Fig. 3.11. Electrocardiogram lead configurations suitable for ambulatory AF monitoring: a) EASI lead system, b) Lewis lead system, c) the lead system by Ihara et al., d) the lead system by Husser et al. (only front side is shown). Note that EASI and Lewis lead systems involve bipolar leads, whereas Ihara et al. and Husser et al. leads are obtained with respect to Wilson's central terminal

A reduced ECG lead system for atrial activity enhancement was proposed in the very

first book of electrocardiography by Sir Thomas Lewis (Lewis, 1913), however, it did not receive proper attention. The Lewis lead system requires that two out of six electrodes are placed directly on the pectoral muscle where arm movement artefacts are likely to occur. In order to avoid leads on the chest muscles, the lead ES of the EASI lead system (Dower et al., 1988) can be employed, since it is potentially more immune to noise and offers a good projection of atrial activity. However, there is a lack of studies that examine the noise immunity of different ECG lead systems. The above mentioned ECG lead systems suited for atrial activity enhancement are illustrated in Fig. 3.11

3.3.2 Atrial fibrillation monitoring strategies

As stated previously, AF detection in early stages is challenging due to short durations, asymptomatic and rarely occurring arrhythmia episodes. Therefore, AF is usually identified during planned examinations of health status or when the patient feels strongly expressed symptoms. Currently, pulse-palpation followed by 12-lead ECG or 24 h ambulatory Holter monitoring is recommended as a standard for AF screening in individuals over 65 years. However, Holter monitoring, let alone 12-lead ECG, is usually insufficient to detect paroxysmal AF, therefore various other techniques can be considered instead (Fig. 3.12). In addition, when selecting the most appropriate strategy for AF detection, such factors as cost effectiveness and patient compliance are equally important to consider.

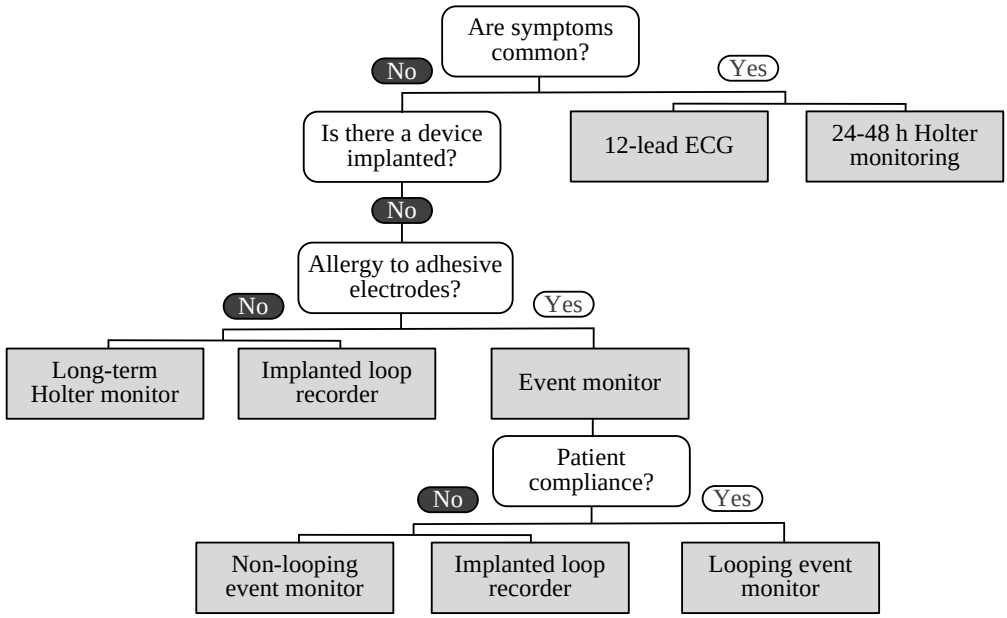

Fig. 3.12. Current scheme for selecting appropriate approach for AF detection in symptomatic patients. Adapted from Rosero et al. (2013)

Various studies have been conducted for the purpose to compare a standard strategy based on 12-lead ECG or 24 h Holter monitoring to potentially more beneficial AF detec-

tion strategies (Charitos et al., 2012). For example, a large study involving thousands of 75–76 year-old individuals in Sweden revealed that using a short-term intermittent screening approach with a handheld Zenicor ECG recorder (at least 2 times a day for two weeks), newly detected an AF rate of 7.4 % (Engdahl et al., 2013). On the contrary, the strategy of a standard 12-lead ECG was associated with just 1–2 % of newly diagnosed AF cases in that particular population (Fitzmaurice et al., 2007; Engdahl et al., 2013).

Nowadays, there is an ongoing intensive debate on the selection of effective strategies for AF detection after cryptogenic ischemic stroke; both intermittent screening and continuous monitoring are considered. In a study by Gaillard et al. (2010), patients after stroke or transient ischemic attack were screened for one month using a patient-activated event recorder. Only those patients who got a negative result of initial 24 h Holter monitoring were prescribed for screening (a single $\sim$30 s duration ECG recording per day). Somehow surprisingly, even 9.2 % of new paroxysmal AF cases were identified using such a simplistic screening approach. In addition, the authors emphasized that transtelephonic ECG monitoring costs were almost a third lower compared to 24 h Holter monitoring.

Stroke patients are predisposed to have brief AF bursts, thus intermittent screening may result in lower than actual AF detection rates. Hence, continuous monitoring using either invasive or non-invasive technologies has been applied in several studies. For example, Gladstone et al. (2014) found that monitoring for 1 month after ischemic stroke using non-invasive event-triggered loop recorder can improve paroxysmal AF detection rate by more than 5 times compared to 24 h Holter monitoring. In another study by Sanna et al. (2014), patients after cryptogenic ischemic stroke were prescribed to continuous AF monitoring using an insertable loop recorder. In that study, half a year of monitoring yielded to 6-fold higher AF detection rate compared to 24 h Holter monitoring.

In another, slightly differently arranged study, three different strategies to detect AF in the stroke unit have been investigated (Rizos et al., 2012). All patients who had been admitted to a stroke unit with acute ischemic stroke or transient ischemic attack performed 24 h Holter monitoring, continuous alarm-based real-time ECG monitoring, and continuous ECG monitoring with offline analysis using specialized software (SRAclinic, Apoplex Medical Technologies, Pirmasens, Germany). The study demonstrated that only a third of all AF events were detected by 24 h Holter monitoring, two-thirds using alarm based continuous ECG monitoring and almost all AF cases (92.7 %) were detected with an automated software. Despite software-detected AF episodes had to be reviewed by a cardiologist, and a relative large false alarm rate of 18 % was documented, the endpoint of the study was that continuous ECG monitoring should be performed instead of classical 24 h Holter monitoring, even in the stroke unit.

Charitos et al. (2012) conducted a comprehensive study where various strategies of intermitted AF monitoring (24 h, 7, 14 and 30 days Holter monitoring) were investigated in terms of the likelihood to detect at least a single paroxysmal AF episode during a period of one year. The study was based on mathematical simulations using data of invasive continuous monitoring from 647 patients. Simulation results showed (see Fig. 3.13 a) that in order to identify paroxysmal AF in half of the monitored patients, on average, four

random tests of 24 h Holter monitoring should be prescribed. To achieve AF detection sensitivity of 80 %, at least 3 random tests of 30 day, 5 tests of 14 day or 7 tests of 7 day Holter monitoring are needed.

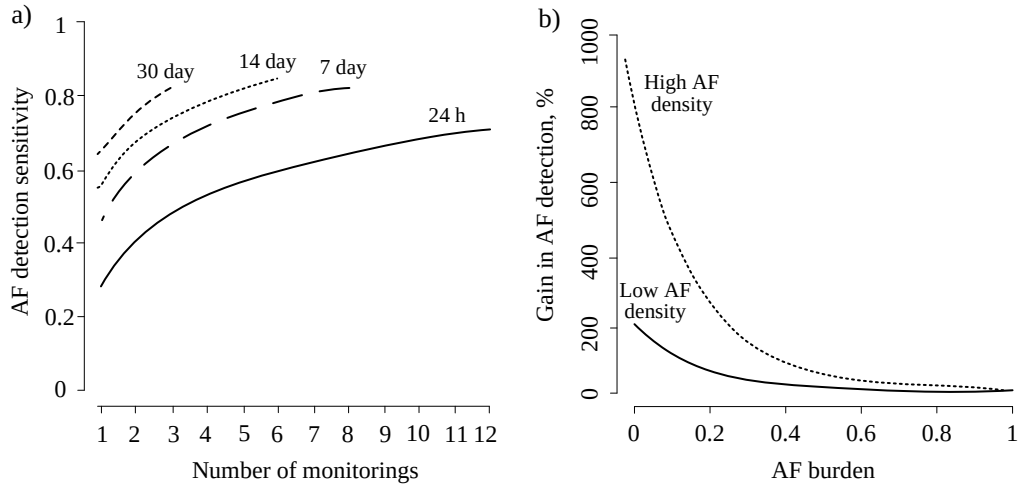

Fig. 3.13. a) Atrial fibrillation detection sensitivity as a function of random monitorings using different Holter-based strategies. b) Gain in AF detection when continuous monitoring is applied instead of 24 h Holter monitoring. Adapted from Charitos et al. (2012)

Charitos et al. also made an essential point regarding temporal distribution of paroxysmal AF episodes. They showed that it is considerably more challenging to detect AF using the strategy of intermittent monitoring when temporal dispersion of AF episodes is low, i.e., AF density is high (see Fig. 3.13 b). It was clearly shown that the currently recommended 24 h Holter monitoring can be completely ineffective in some cases, thus more intensive monitoring is indispensable in order to improve AF detection rates. On the other hand, since the study excluded AF episodes shorter than 5 min, the chances to detect even a single paroxysmal AF episode during the monitoring period will be increased if a high performing algorithm for brief AF detection is applied.

These findings suggest that conventional 24 h Holter monitoring, although still a standard for AF detection in most countries, is far from being an effective solution for AF detection. However, to this day, there is no unified agreement how each different situation (opportunistic AF screening, evaluation of cardioversion/catheter ablation success, AF detection after cryptogenic stroke, monitoring of drug effect) should be handled in order to achieve the highest efficiency of AF detection.

3.4 Characterization of atrial fibrillation

3.4.1 Temporal organization of paroxysmal atrial fibrillation

In today's clinical practice, a qualitative approach for the confirmation of AF presence is preferred (yes or no AF). However, evolving technologies for extended AF monitoring enable the possibility to change the prevailing concept of a qualitative AF assess-

ment to a quantitative (the amount of AF) approach. A parameter of AF burden is being increasingly applied for quantitative AF evaluation and is expressed as a proportion of time the patient is in AF:

$$\mathcal{B}_{AF} = \frac{T_{AF}}{T}, \tag{3.1}$$

where T_{AF} is the accumulated time the patient was in AF, and T is the total monitoring time. The parameter $\mathcal{B}_{AF}$ takes values between 0 and 1, where 0 indicates that no AF was observed, whereas 1 denotes that the patient was in AF throughout the entire monitoring period.

Given that AF burden does not provide information about temporal AF behavior, Charitos et al. proposed a parameter under the name of AF density for the evaluation of temporal distribution of paroxysmal AF episodes. AF density is defined as:

$$\mathcal{D}_{AF} = 2\frac{\int_0^1 |F(p, \mathcal{B}_{AF}) - p| dp}{1 - \mathcal{B}_{AF}}, \tag{3.2}$$

where the upper part of the equation corresponds to actual AF burden development from the uniform (AF during the entire monitoring period) AF burden development. Here p is a proportion of burden $\mathcal{B}_{AF}$, $0 \leqslant p \leqslant 1$. The component $F(p, \mathcal{B}_{AF})$ represents the minimum continuous time required for the development of the proportion p of the total burden $\mathcal{B}_{AF}$ and is defined as

$$F(p, \mathcal{B}_{AF}) = \frac{T(p, \mathcal{B}_{AF})}{T}. \tag{3.3}$$

Values of AF density are also distributed within the interval of [0, 1]. Values closer to 0 indicate that AF is uniformly spread during the monitoring period, whereas values closer to 1 stand for a high aggregation of AF episodes. The AF density equal to 1 is obtained when a single AF episode, independently of AF episode length, is observed during the entire monitoring time.

Since paroxysmal AF may take various temporal patterns (Fig. 3.14), temporal AF recurrence may be of interest for drug management or evaluation of thromboembolism risk based on the duration and temporal distribution of paroxysmal AF episodes. Moreover, quantitative evaluation of temporal AF recurrence may be beneficial for relating AF episodes to arrhythmia provoking events (physical activity, time of the day, meal, etc.). Such information can be important for understanding specific factors resulting in evolving AF burden. In addition, the total number of paroxysmal AF episodes may also be of some interest, since it provides information on the ability of the heart to self-terminate AF episodes.

3.4.2 Analysis of atrial activity during atrial fibrillation

In recent years, extraction of atrial activity in ECGs recorded during AF has received considerable research attention. By canceling the ventricular activity, a connected atrial

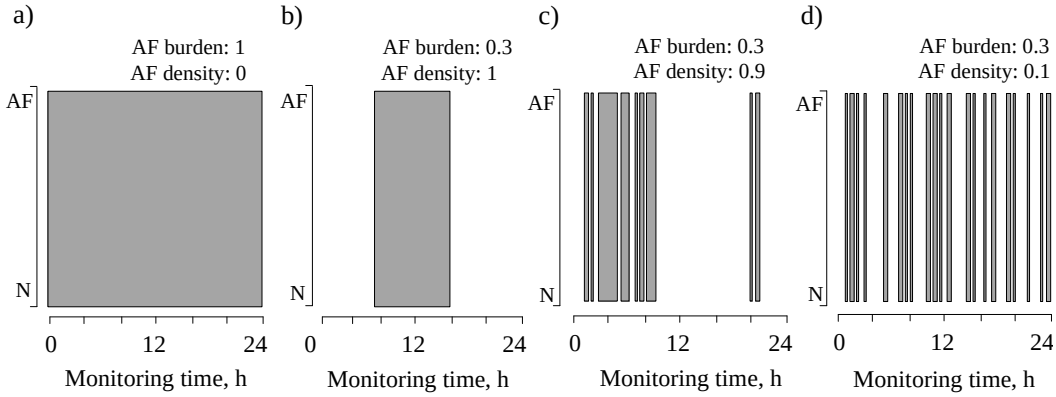

Fig. 3.14. Examples of different cases of temporal distribution of AF episodes: a) AF during the entire monitoring period, b) a single paroxysmal AF episode, c) highly aggregated paroxysmal AF, d) paroxysmal AF is spread throughout the entire monitoring time

signal can be produced, which is analyzed with respect to f-wave repetition rate and morphology; as well as other properties (complexity, organization, etc.). The development of methods for ventricular activity cancellation has helped to spawn numerous clinical studies in which AF rate (or frequency) is assessed (Bollmann et al., 2006; Schotten et al., 2012; Platonov et al., 2014). The atrial fibrillatory rate is of special interest, since it is closely linked to the fibrillatory cycle length, which is related to the atrial refractory period during AF (Haissaguerre et al., 2007). Since the atrial fibrillatory cycle length is gradually getting longer before AF termination, a quantitative measure of the fibrillatory rate may potentially be used for the prediction of spontaneous AF behavior and therapeutic success, as well as for non-invasive characterization of atrial substrate.

Probably because of its ease of implementation, by far the most widely used method for ventricular activity cancellation is average beat subtraction (ABS) (Slocum et al., 1992; Holm et al., 1998; Bollmann et al., 1998). The averaged heart beat that represents ventricular electrical activity is obtained from an ensemble of time aligned QRST complexes, and then is subtracted from each beat in the ECG signal (see Fig. 3.15). However, it is well-known that ABS is unable to handle changes in morphology, as it causes the resulting atrial signal to contain QRST-related residuals (Xi et al., 2003). The occurrence of a single ectopic beat is yet another particularly problematic situation, as the ectopic beat becomes the residual itself.

Various ABS-based techniques have been proposed to mitigate the problem of QRST morphology variations due to ectopic beats and respiration. For example, provided that several ectopic beats are present, an eigenvalue-based method was devised for their cancellation prior to ABS (Martínez et al., 2010). Assuming that a multi-lead ECG recording is available, spatiotemporal QRST cancellation was proposed for the purpose of handling gradual changes in the electrical axis of the heart (Stridh and Sörnmo, 2001). In this approach, an averaged QRST complex is obtained by combining morphology information of heart beats in adjacent leads, therefore variations in QRST shape are better handled than

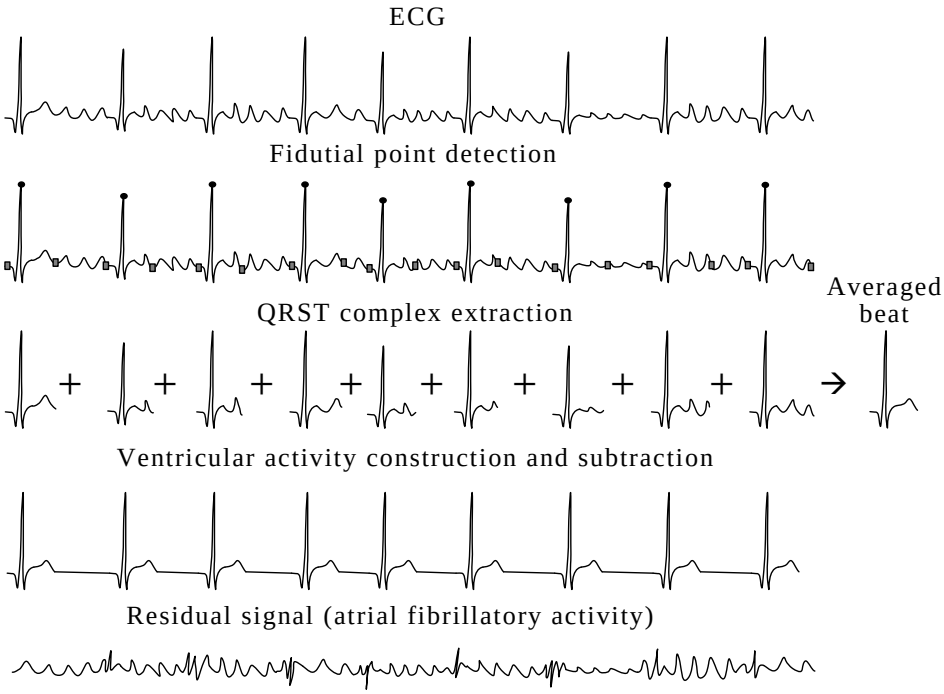

Fig. 3.15. Explanation of QRST cancelation using average beat subtraction technique

using a single ECG lead based ABS.

Another group of ventricular activity cancellation techniques explores the assumption that atrial and ventricular activity are generated by different electrical sources, so that the surface ECG can be viewed as a linear sum of the sources. Both principal component analysis and independent component analysis have been proposed to separate signal sources. A principal component analysis based method was designed for the analysis of Holter data with a reduced number of leads (Castells et al., 2005a). The principal components are grouped into three subspaces, which account for ventricular activity, atrial activity and noise-related activity. An advantage of principal component analysis is its ability to follow variations in QRST morphology, however, its performance is highly dependent on the accuracy of the algorithm for identifying the atrial subspace. A variation on the principal component analysis theme is the method which involves adaptive singular value decomposition for QRST cancellation in single lead ECGs, which was found to perform better than ABS (Alcaraz and Rieta, 2008).

Independent component analysis based methods can be used for the extraction of atrial activity in multi-lead ECGs (Rieta et al., 2004; Castells et al., 2005b; Kao et al., 2005; Llinares and Igual, 2009). Crucial issues when using these methods are the identification of the component(s) with atrial activity and the challenge to analyze long-term recordings. This type of identification was improved by using spectral information (Llinares et al., 2010), however, the method requires a prior knowledge of the AF frequency. In this method, a frequency estimate was determined from the TQ interval, consequently imply-

ing that performance is bound to deteriorate as the heart rate increases.

Yet another method to cancel ventricular activity is to employ adaptive filtering, with which a time-varying transfer function is estimated between two ECG leads. The initial idea of this approach was proposed by Thakor and Zhu (1991). Based on their proposal, atrial and ventricular electrical activity is separated by using an adaptive recurrent filter in which an impulse-like signal is applied to the reference input for the purpose to cancel ventricular activity in the other ECG lead. However, this type of adaptive filter is effective only when QRST morphology is stable over time (Cesarelli et al., 1998). Later, a conceptually similar approach of adaptive filtering was implemented using an Elman time delay artificial neural network (Vásquez et al., 2001). Although the use of iteratively trained recurrent neural network offers the advantage of adapting to changes in QRST morphology, this neural network is associated with a slow and complex training process, and its convergence is strongly related to the quality of training data.

The unifying limitation of the above discussed techniques for atrial activity extraction is that the performance deteriorates when atrial activity (f-waves) is of low amplitude. Thus f-wave analysis is feasible just in a few ECG leads, positioned near to the atria, i.e., precordial leads V_1 and V_2 of 12-lead ECG system. Since these leads are not normally involved in ambulatory monitoring, the f-wave amplitude can be insufficiently large enough to perform a reliable f-wave analysis.

3.5 Conclusions of the chapter

1. In order to detect paroxysmal AF at the beginning of arrhythmia development, continuous long-term monitoring, lasting from several weeks to months, should be performed. Therefore, it is essential to develop a low-complexity AF detector, suitable for implementation in a battery-powered device.

2. Atrial fibrillatory signal (f-waves) has potential to be used as a biomarker for prediction of AF behaviour. Accordingly, reliable techniques for f-waves extraction using a minimal set of ECG leads are of special importance in order to characterize fibrillatory activity in ambulatory ECG recordings.

3. The majority of existing methods for AF detection explore ventricular activity irregularity through parameters which reflect variability, randomness and complexity. However, such methods are unsuitable for detection of brief paroxysmal AF, since a window length of at least 30 s is usually required to reduce the number of false alarms due to other irregular rhythms. For this reason, it is essential to develop an AF detector that utilizes the analysis window of just several beats, thus enabling the detection of brief AF.

4. The majority of new AF cases are still diagnosed using the standard 12-lead ECG technology. Given that brief paroxysmal AF is unlikely to be detected in a single short-term screening, a reduced ECG lead configuration, optimized for prolonged monitoring of AF is highly desirable.

5. Although commercial AF monitors have been on the market for some time, no information is available on their ability to detect brief paroxysmal AF; probably due to the lack of ECG databases containing short AF episodes. Therefore, it is important to propose a solution for generating realistic ECG signals with brief AF.

4 PROPOSED METHODS FOR DETECTION OF PAROXYSMAL ATRIAL FIBRILLATION

4.1 A conception of system for detection of brief episode atrial fibrillation

In this chapter, novel solutions for paroxysmal AF detection in ambulatory ECG recordings are introduced: 1^{st} stage AF detector (Petrėnas et al., 2015b), fibrillatory activity (f-waves) extraction algorithm (Petrėnas et al., 2012), 2^{nd} stage AF detector (Petrėnas et al., 2015c), and ECG electrode placement (Petrėnas et al., 2015a). Each of the proposed solutions can be used either separately, or can be combined into a unified automated system capable to detect brief AF episodes, and provide information on fibrillatory activity (see Fig. 4.1).

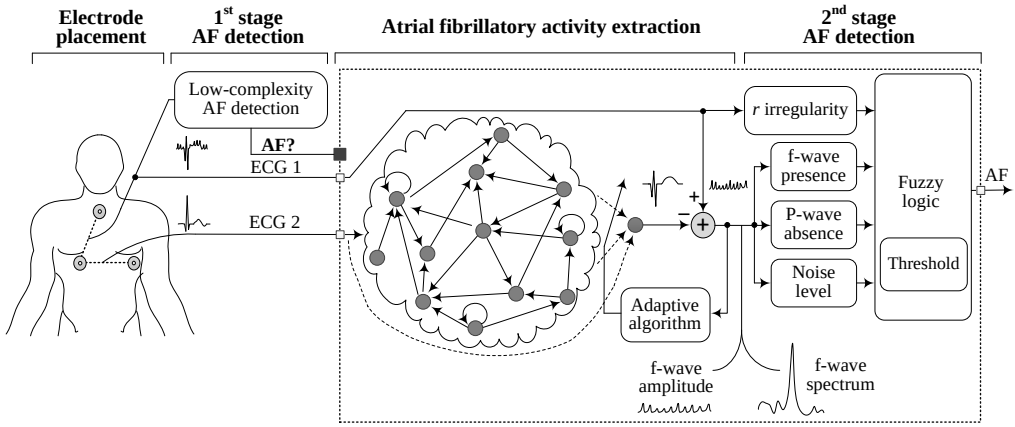

Fig. 4.1. Conception of an automated system for ambulatory detection of brief episode paroxysmal AF

The 1^{st} stage AF detector is an r-based AF detection algorithm whose structure is well-adapted to implementation in a battery-powered device for use in continuous long-term monitoring applications. Given that existing r-based approaches for AF detection are sensitive to false alarms, due to other irregular rhythms, the proposed detector includes blocks for ectopic beat filtering, and bigeminal suppression to alleviate this problem. Moreover, with one parameter, the performance can be tuned to put more emphasis on avoiding false alarms due to non-AF arrhythmias or more emphasis on detecting brief AF episodes; however, in expense of reduced specificity. Considering its high sensitivity, such a detector can be employed in the first-stage for the purpose to find possible AF episodes and activate the following blocks that are designated to atrial activity analysis.

In order to enable a reliable detection of brief AF episodes, a more advanced AF detector is employed, which involves morphologic information (atrial fibrillatory activity) to determine in further detail whether the detected episodes are correct or not. Atrial fibrillatory activity is extracted from the surface ECG by using an echo state neural network, which estimates the time-varying, nonlinear transfer function between two ECG leads – one lead with atrial activity and another lead without. The obtained fibrillatory signal can

be used not only for AF detection, but also for the purpose to characterize AF profile, i.e., in terms of fibrillatory frequency.

The 2^{nd} stage AF detector is based on four parameters characterizing r interval irregularity, P-wave absence, f-wave presence and noise level, of which the latter three are determined from a signal produced by an echo state network. The parameters are used for fuzzy logic classification where the decisions involve information on prevailing signal quality; no training is required. Since morphologic analysis is computationally much more costly, the second-stage detector should preferably be implemented in a server or a smartphone.

The proposed method for fibrillatory activity extraction requires two ECG leads with and without atrial activity expressed, thus a reduced ECG lead configuration was derived to meet these requirements. The proposed ECG lead configuration was obtained on the basis of ECG lead configuration introduced by Sir Thomas Lewis in 1913. However, the original Lewis lead system employs ECG leads, placed directly on the right side of the chest. Therefore, a modified Lewis lead system was derived which is better suited for ambulatory applications, since the electrodes are placed in areas with less muscle. It should be noted that the proposed methods are not restricted to the use of the modified Lewis lead system and any lead system involving ECG lead with negligible fibrillatory activity can be employed instead. For example, in the case of a standard 12-lead ECG, either V_5 or V_6 can be used as a reference lead with negligible f-waves.

Each of the proposed solutions are described in more detail in the sections below.

4.2 Low-complexity method for detection of paroxysmal atrial fibrillation in continuous monitoring applications

The proposed AF detector is based on the observation that AF episodes have increased r irregularity and are usually associated with increased heart rate. A block diagram of the detector is shown in Fig. 4.2, where each of the processing blocks is described in the following text.

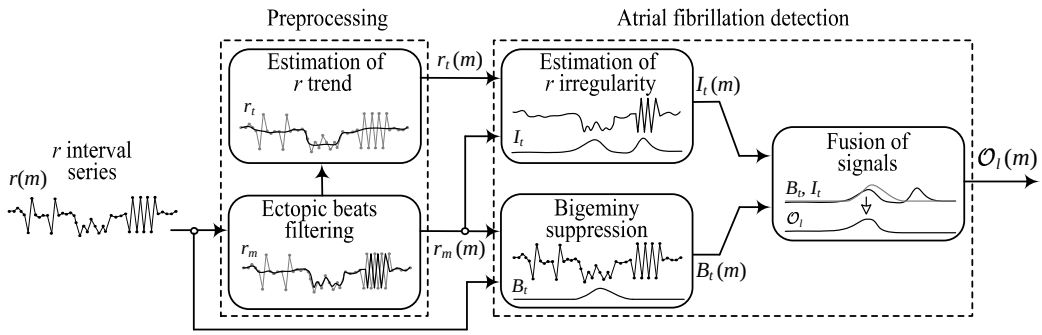

Fig. 4.2. Block diagram of the proposed AF detector based on r interval analysis

4.2.1 Pre-processing

The occurrence of sporadic ectopic beats can be especially problematic when short time r series are analyzed and, therefore, it is desirable to introduce techniques which can handle such situations. Preliminary tests showed that the simple 3-point median filter is useful for reducing the influence of ectopic beats in the r series. This filter is defined by

$$r_m(m) = \text{median}\{r(m-1), r(m), r(m+1)\}, \tag{4.1}$$

where $r(m)$ denotes the length of the m:th r interval (whose unit is in seconds). Median filtering is also useful for rejecting outlier r intervals due to, i.e., missed QRS complexes. Higher-order median filters were found to be less useful since they smooth AF episodes to such a degree that episodes with low r irregularity remain undetected.

Since the heart rate usually increases during AF episodes, an estimate of the mean r interval has to be determined, and employed as a feature in the AF detector, cf. (Lake and Moorman, 2011; Langley et al., 2012). Here, the traditional ensemble averager is replaced by the exponential averager to better track the "trend" in the r interval series. The exponential averager is defined by (Sörnmo and Laguna, 2005)

$$r_t(m) = r_t(m-1) + \beta(r(m) - r_t(m-1)), \tag{4.2}$$

where β ($0 < \beta < 1$) determines the degree of smoothing, i.e., the low-pass cut-off frequency. Since the exponential averager in (4.2) has a nonlinear phase, forward–backward filtering is performed to achieve a linear (null) phase.

4.2.2 Irregularity of ventricular activity

In a sliding detection window of length M, located at time m, the number of all pairwise r interval combinations differing more than γ seconds is determined, and normalized with its maximum value $M(M-1)/2$, i.e.,

$$G(m) = \frac{2}{M(M-1)} \sum_{j=0}^{M-2} \sum_{k=j+1}^{M-1} H(|r(m-j) - r(m-k)| - \gamma), \tag{4.3}$$

where $H(\cdot)$ is the Heaviside step function and $0 \leqslant G(m) \leqslant 1$. It is noted that $G(m)$ is partially based on the same principle, as is sample entropy estimation (Lake and Moorman, 2011).

The primary feature of r irregularity is provided by the ratio between a smoothed version of $G(m)$ and the r interval trend $r_t(m)$ in (4.2),

$$I_t(m) = \frac{G_t(m)}{r_t(m)}, \tag{4.4}$$

where $G_t(m)$ is obtained by exponential averaging of $G(m)$. The division by $r_t(m)$ is motivated by the wish to emphasize r irregularity at higher heart rates. It should be noted that $I_t(m)$ is close to 0 for regular rhythms, since the difference between pairs of r intervals is usually smaller than a properly chosen γ, whereas $I_t(m)$ approaches 1 during AF, see the examples in Fig. 4.3.

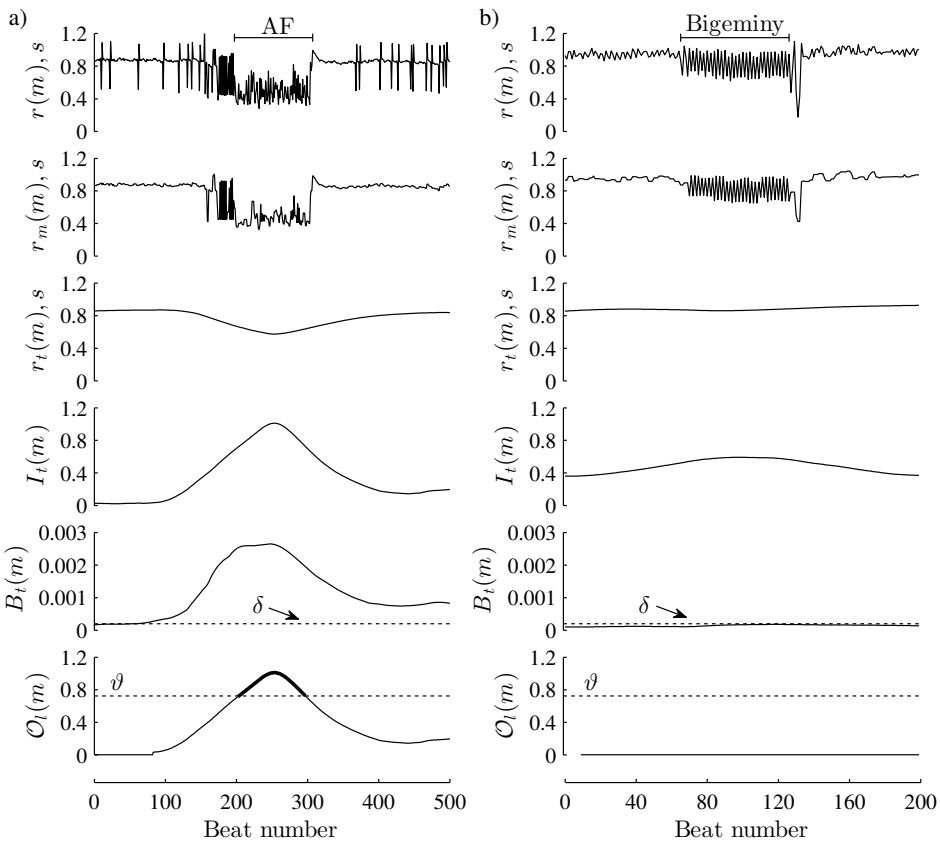

Fig. 4.3. The output of each building block of the proposed detector is illustrated for a) an AF episode surrounded by ectopic beats and b) bigeminy. Atrial fibrillation is detected whenever $\mathcal{O}_l(m)$ exceeds the threshold ϑ, then displayed by a thicker line

4.2.3 Bigeminy suppression

It is well-known that bigeminy can be incorrectly interpreted as AF when the detection is r-base (Langley et al., 2012). In order to address this issue, another measure of r irregularity is introduced, which is complementary to $I_t(m)$, but has the property of being essentially indifferent to the presence of bigeminy. The measure is defined by

$$B(m) = \left(\frac{\sum_{j=0}^{M-1} r_m(m-j)}{\sum_{j=0}^{M-1} r(m-j)} - 1 \right)^2, \tag{4.5}$$

where M is an even-valued integer. Similar to $r_t(m)$ and $G_t(m)$, $B_t(m)$ results from exponential averaging of $B(m)$. For bigeminy, as well as for regular rhythms, the ratio in (4.5) is approximately 1, since $r_m(m)$ and $r(m)$ are similar, and thus $B_t(m)$ is approximately 0, see Fig. 4.3 b). On the other hand, for AF the variation in $r_m(m)$ is lower than that in $r(m)$ because of the median filtering, and thus $B_t(m)$ will increase so that it

indicates irregularity. The squaring operation in (4.5) improves the differentiation of AF from other rhythms.

4.2.4 Signal fusion and atrial fibrillation detection

Simple signal fusion is employed to produce the decision function $\mathcal{O}_l(m)$: $\mathcal{O}_l(m)$ is identical to $B_t(m)$, unless $B_t(m)$ exceeds a fixed threshold δ when, instead, it becomes identical to $I_t(m)$, i.e.,

$$\mathcal{O}_l(m) = \begin{cases} I_t(m), & B_t(m) \geqslant \delta \\ B_t(m), & B_t(m) < \delta. \end{cases} \tag{4.6}$$

Figure 4.3 illustrates $\mathcal{O}_l(m)$ as well as $r_m(m), r_t(m), I_t(m)$, and $B_t(m)$ for an AF episode surrounded by ectopic beats and sinus rhythm with an episode of bigeminy. It is obvious from Fig. 4.3 a) that median filtering removes the r intervals related to ectopic beats so that the AF episode can be correctly detected and false alarms avoided. Another feature of the detector is illustrated in Fig. 4.3 b) where $\mathcal{O}_l(m)$ is shown to be unaffected by the occurrence of bigeminy and, consequently, not misclassified as AF. Although $I_t(m)$ increases during bigeminy, $\mathcal{O}_l(m)$ remains small since $B_t(m)$ remains below δ, cf. (4.6). Similarly, $B_t(m)$ is close to 0 during sinus rhythm, and therefore $\mathcal{O}_l(m)$ is also close to 0. Atrial fibrillation is detected whenever $\mathcal{O}_l(m)$ exceeds the fixed threshold ϑ.

The number of mathematical operations needed to implement the algorithm is presented in Table 4.1, showing that the detector requires very few multiplications/divisions for processing a single r interval. Of the 8 multiplications, 6 are required for implementation of the forward–backward exponential averager due to multiplication with β. If needed, the β-related multiplications can be approximated by additions and a shift.

Table 4.1. The number of arithmetic operations required per r interval.

Multiplications	Divisions	Additions/subtractions
8	2	45

4.2.5 Online atrial fibrillation detection

Since forward–backward filtering requires that the time-reversed signal is processed, this type of filtering is best suited for offline processing. On the other hand, for online processing, forward–backward filtering with the exponential averager in (4.2) is replaced by forward filtering and a second-order exponential averager, defined by

$$r_t(m) = \beta^2 r(m) + 2(1-\beta) r_t(m-1) - (1-\beta)^2 r_t(m-2). \tag{4.7}$$

To a minor extent, detector performance depends on the phase response of the selected exponential averager. Depending on the choice of β, the exponential averager in (4.7) produces a group delay that has to be taken into account. Accordingly, β is set to

the same value for the respective exponential averagers associated with $r_t(m)$, $I_t(m)$, and $B_t(m)$ to ensure identical group delay.

In the following, the AF detector is referred to as either offline or online, depending on whether filtering is performed according to (4.2) or (4.7). These two versions have the same computational complexity.

4.3 Atrial activity extraction during atrial fibrillation

4.3.1 Introduction to reservoir computing

The proposed method for atrial activity extraction during AF utilizes a reservoir computing approach. Reservoir computing is a paradigm in recurrent neural network training, where the fundamental principles of the idea have been independently proposed by Herbert Jaeger (2001) under the name of "echo state network" (ESN) and by Wolfgang Maass et al. (2002) under the name of "liquid state machine". Liquid state machine was designed from a view of computational neuroscience aiming to understand the principles of neural microcircuits, therefore uses more sophisticated and biologically more realistic spiking neurons, whereas ESN is more directed for practical implementation, thus classical artificial neurons are involved instead.

When comparing the widely used feed-forward artificial neural networks to recurrent neural networks, only the latter ones are suitable for processing of temporal data (Gurney, 2007). However, recurrent neural networks have not become popular in practical applications due to their long and complex training process and potential instability. For ESNs, on the other hand, training is much facilitated by involving only the output connections, which are adjusted by simple linear regression. As a result, the training process is fast and never gets stuck in local minima. Surprisingly, the ESN has been found to outperform the more complex, fully trained recurrent neural network in almost all cases considered (Lukoševičius and Jaeger, 2009).

4.3.2 Fibrillatory signal extraction using echo state network

The proposed atrial activity extraction method uses a classical adaptive filter approach: the atrial signal is extracted from a mixture of signals using a reference signal that is modified by a filter with time-variable transfer function – the ESN – and an adaptation algorithm (see Fig. 4.4 a). The reservoir of the ESN is a large, fixed, randomly generated, recurrent neural network hat serves as a random nonlinear excitable medium. Its high-dimensional dynamical "echo" response to a driving input is used as a non-orthogonal signal basis to reconstruct the atrial output. The input weights $\mathbf{W}_{\text{in}}$ and the reservoir-connecting weights $\mathbf{W}$ are both generated randomly during network initialization from a uniform probability density function (symmetric around zero and invariant to training). The only set of weights which is changed during training is the output weight vector $\mathbf{w}_{\text{out}}$. The ESN is typically trained by driving it with the input signal, and collecting its nonlinearly transformed and smoothed versions to the reservoir state vector $\mathbf{r}(n)$ for the entire

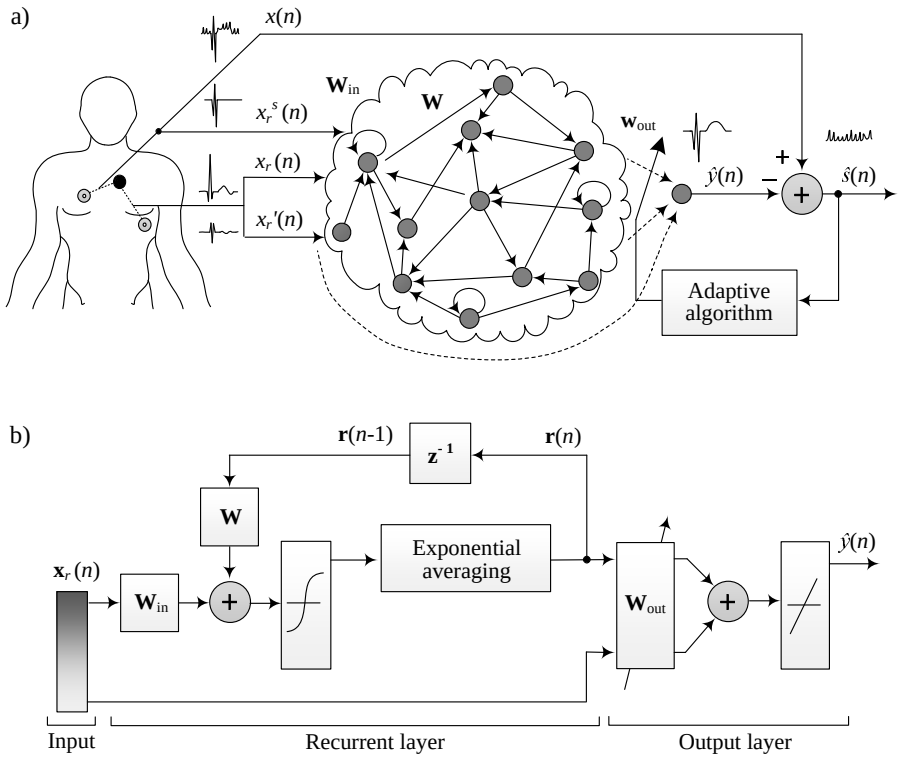

Fig. 4.4. a) Atrial activity extraction based on the echo state network. b) A more detailed view of the proposed method. The dashed lines indicate adaptive weights, other weights are fixed after initialization. Note that $\hat{y}(n) = g_o(\mathbf{w}_{\text{out}}^T(n-1)\mathbf{z}(n))$. The ESN inputs and output are normalized and denormalized, respectively, according to standard procedure.

training period. Then, $\mathbf{w}_{\text{out}}$ is computed in a single iteration as a linear combination of the teacher output and reservoir states. This type of method is suitable for supervised training when the teacher output is known. However, since offline supervised training of the ESN is not effective for signals with rapid changes in morphology, continuous online training is necessary to allow for adaptation, which is sufficiently fast. The adaptation algorithm of an adaptive filter can also be employed to train $\mathbf{w}_{\text{out}}$.

The atrial signal $\hat{s}(n)$ is defined as the error $e(n)$ between the lead subject to extraction, denoted $x(n)$, and the estimate of the ventricular activity $\hat{y}(n)$ produced by the ESN,

$$\hat{s}(n) \triangleq e(n) = x(n) - g_o(\mathbf{w}_{\text{out}}^T(n-1)\mathbf{z}(n)), \tag{4.8}$$

where $g_o(\cdot)$ denotes the output neuron activation function and $\mathbf{w}_{\text{out}}(n-1)$ the time-varying output weight vector. The number of neurons in the reservoir is denoted N. The vector $\mathbf{z}(n)$ is the concatenation of the $N \times 1$ reservoir state vector $\mathbf{r}(n)$, the reference signal $\mathbf{x}_r(n)$, recorded away from the atria, its first derivative $x_r'(n)$, and an impulse-like signal $x_r^s(n)$,

$$\mathbf{z}(n) = \begin{bmatrix}\mathbf{r}(n) & x_r(n) & x_r'(n) & x_r^s(n)\end{bmatrix}^T. \tag{4.9}$$

The signal $x_r^s(n)$ is identical to $x(n)$ in a short interval of length $2D$ centered around the fiducial point n_i of the i:th beat; outside this interval $x_r^s(n)$ is set to 0 (the fiducial point is here defined by the QRS center-of-mass). Thus, $x_r^s(n)$ can be viewed as a variant of the impulse correlated reference input to the adaptive filter (Laguna et al., 1992). The inclusion of $x_r'(n)$ and $x_r^s(n)$ offers a more complete characterization of the reference signal, and can therefore be expected to improve the performance of the ESN.

The output weights $\mathbf{w}_{\text{out}}(n)$ of the ESN are updated using the recursive least squares algorithm in combination with least squares prewhitening; for details, see (Douglas, 2000). The prewhitening part is defined by

$$\mathbf{v}(n) = \mathbf{P}(n-1)\mathbf{z}(n), \tag{4.10}$$

$$\mathbf{u}(n) = \mathbf{P}^T(n-1)\mathbf{v}(n). \tag{4.11}$$

where $\mathbf{P}(n)$ denotes the inverse of the correlation matrix of $\mathbf{z}(n)$. The update of $\mathbf{P}(n)$ is given by the following two equations:

$$k(n) = \frac{1}{\lambda + \|\mathbf{v}(n)\|^2 + \sqrt{\lambda(\lambda + \|\mathbf{v}(n)\|^2)}}, \tag{4.12}$$

$$\mathbf{P}(n) = \frac{\mathbf{P}(n-1) - k(n)\mathbf{v}(n)\mathbf{u}^T(n)}{\sqrt{\lambda}}. \tag{4.13}$$

where $\mathbf{P}(0) = d^{-1}\mathbf{I}$, d is a small positive constant, $\mathbf{I}$ the identity matrix, and λ a forgetting factor, a constant that is commonly chosen in the interval $0.95 < \lambda < 1$. The recursive least squares part of the algorithm produces an update of the output weights,

$$\mathbf{w}_{\text{out}}(n) = \mathbf{w}_{\text{out}}(n-1) + \frac{e(n)\mathbf{u}(n)}{\lambda + \|\mathbf{v}(n)\|^2}, \tag{4.14}$$

where $\mathbf{w}_{\text{out}}(0) = \mathbf{0}$. The reservoir state vector $\mathbf{r}(n)$ is updated by

$$\mathbf{r}(n) = g_r\big(\mathbf{W}\mathbf{r}(n-1) + \mathbf{W}_{\text{in}}\mathbf{x}_r(n)\big), \tag{4.15}$$

where $\mathbf{W}_{\text{in}}$ is a $3 \times N$ input weight matrix, $\mathbf{W}$ an $N \times N$ weight matrix of the internal network connections.

The output of the dynamic reservoir is impulsive in nature and therefore needs to be smoothed. Here, exponential averaging is employed for smoothing, the update equation in (4.15) thus being replaced with

$$\mathbf{r}(n) = \alpha\mathbf{r}(n-1) + (1-\alpha)(g_r(\mathbf{W}\mathbf{r}(n-1) + \mathbf{W}_{\text{in}}\mathbf{x}_r(n))), \tag{4.16}$$

where $g_r(\cdot)$ is a reservoir neuron activation function, and α a forgetting factor, a positive constant less than 1. The recursion in (4.16) is initialized with $\mathbf{r}(0) = \mathbf{0}$.

The block diagram in Fig. 4.4 b) illustrates the main processing steps of the method.

4.4 Method for detection of brief episode paroxysmal atrial fibrillation

The main processing steps of the proposed AF detector are shown in Fig. 4.5. The detector requires two ECG leads as input; of which one needs to be positioned away from the atria, i.e., precordial lead V_6. A sliding window approach is taken to paroxysmal AF detection: the window length is defined by the number of beats M_b, rather than by a time period, since a beat-based definition seems more natural when detecting brief episodes.

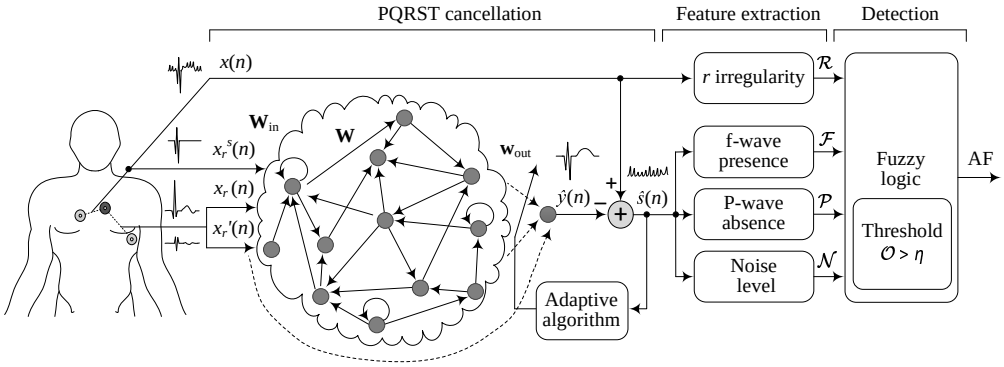

Fig. 4.5. Block diagram of the proposed paroxysmal AF detector. The echo state neural network is used for PQRST cancellation in the target lead $x(n)$, here given by V_1; the reference lead $x_r(n)$ is V_6. The output $\hat{s}(n)$ of the block labeled "PQRST cancellation" contains f-waves during AF, and otherwise noise and PQRST residuals. See the text for definitions of signals and parameters

4.4.1 Atrial activity characterization

Similar to other techniques for atrial activity extraction during AF, the ESN-based technique, presented in section 4.3, is proposed under the assumption that AF is present and, accordingly, a signal with f-waves is fed to the ESN. That assumption is not valid here, since the input signal may just as well contain P-waves. However, preliminary tests showed that the ESN is not only suited for cancellation of QRST complexes but also for P-waves. As a consequence, the parameters characterizing P-wave absence and f-wave presence, are both computed from the ESN output.

In the present application, the ESN can be viewed as an adaptive filter which produces an output signal $\hat{s}(n)$ with the f-waves from the target signal $x(n)$ when AF is present, whereas $\hat{s}(n)$ mostly contains the noise of $x(n)$ and PQRST residuals when AF is absent. The reference signal $x_r(n)$ is filtered by a time-variable transfer function, see Fig. 4.5. The output signal $\hat{s}(n)$ is defined as the error $e(n)$ between the target signal $x(n)$ and the ESN output $\hat{y}(n)$, being an estimate of the PQRST or the QRST complex. The structure of the ESN is used the same as it is described in Sec. 4.3.2.

P-wave absence $(\mathcal{P})$ is quantified by first computing the squared error between two different PR intervals,

$$e_{ij} = \sum_{n=n_P}^{n_R} \big(\hat{s}(n_i - n) - \hat{s}(n_j - n)\big)^2, \tag{4.17}$$

where n_P and n_R denote the onset and end of the PR interval, respectively, both located at fixed distances from the fiducial points n_i and n_j, $i \neq j$. Then, the squared error is averaged for all pairwise combinations of the M_b beats in the detection window,

$$\mathcal{P} = \sum_{i=1}^{M_b-1} \frac{1}{M_b - i} \sum_{j=i+1}^{M_b} e_{ij}. \tag{4.18}$$

The parameter $\mathcal{P}$ is close to 0 in rhythms with P-waves, but increases when f-waves are present. Since the F-waves of atrial flutter are largely cancelled by the ESN, thanks to their much more stable pattern than the f-waves, the corresponding value of $\mathcal{P}$ is close to 0. In contrast to (Carvalho et al., 2012), this approach of characterizing P-wave absence requires no P-wave template, neither is it sensitive to variations in morphology, since P-waves have already been cancelled by the ESN.

f-wave presence ($\mathcal{F}$) is quantified by the parameter known as spectral concentration (Castells et al., 2005b),

$$\mathcal{F} = \frac{1}{E_{\hat{s}}} \int_{\Omega_p} P_{\hat{s}}(\omega)\, d\omega, \tag{4.19}$$

where $P_{\hat{s}}(\omega)$ and $E_{\hat{s}}$ denote the power spectrum and energy, respectively, of $\hat{s}(n)$ in the M_b-beat long detection window. The integration interval Ω_p is centered around the dominant spectral peak located within the interval $[\omega_{p,0}, \omega_{p,1}]$ (Castells et al., 2005b). When f-waves are present, the dominant peak reflects AF frequency and $\mathcal{F}$ becomes closer to 1, whereas it is closer to 0 for sinus rhythm. The power spectrum $P_{\hat{s}}(\omega)$ is obtained using Welch's method (1 s cosine window with 50 % segment overlap).

4.4.2 Ventricular activity characterization

A parameter of r interval irregularity ($\mathcal{R}$) is quantified by the coefficient of sample entropy, defined by

$$\mathcal{R} = -\ln\left(\frac{A}{B}\right) + \ln(2t_r) - \ln(\bar{w}_r), \tag{4.20}$$

where A and B denote the total number of r interval patterns of length $w+1$ and w, respectively, that match within a certain tolerance t_r; for details, see the paroxysmal AF detector described in (Lake and Moorman, 2011). The mean length of the r intervals in the detection window is denoted $\bar{w}_r$.

4.4.3 Noise level estimation

The noise level is estimated by the root mean square value $\zeta_{\hat{s}}$ of $\hat{s}(n)$, weighted by a ratio of spectral entropies. The numerator and denominator are computed in spectral bands dominated by noise and f-waves, respectively, defined by the respective frequencies

ω_n and ω_a. The noise parameter $\mathcal{N}$, defined by

$$\mathcal{N} = \zeta_{\hat{s}} \cdot \frac{\int_{\omega_{n,0}}^{\omega_{n,1}} P_{\hat{s}}(\omega) \cdot \log_2 P_{\hat{s}}(\omega)\, d\omega}{\int_{\omega_{a,0}}^{\omega_{a,1}} P_{\hat{s}}(\omega) \cdot \log_2 P_{\hat{s}}(\omega)\, d\omega}, \tag{4.21}$$

is small when $P_{\hat{s}}(\omega)$ reflects AF, whereas it is large when motion artifacts and/or electromyographic noise is present. The properties of $\mathcal{N}$ are further investigated in Sec 5.4.3.

4.4.4 Atrial fibrillation detection based on fuzzy logic

A Mamdani-type fuzzy inference method is employed for AF detection (Mamdani and Assilian, 1975). With fuzzy logic, numerical and linguistic knowledge are combined, which makes it particularly useful in applications where subjective knowledge is available about the process. The present design comes with four inputs, i.e., $\mathcal{P}$, $\mathcal{F}$, $\mathcal{R}$, $\mathcal{N}$, a set of "*if–then*" rules, and one output $\mathcal{O}$. By means of an input membership function, each input value is mapped ("fuzzified") to a value that indicates the degree of belonging to a certain fuzzy set. For $\mathcal{P}$, $\mathcal{F}$, and $\mathcal{R}$, the fuzzy sets relate to sinus rhythm (SR) and AF, and the following two input membership functions are employed (Fig. 4.6 a):

$$\mu_{\text{SR}}(x) = \begin{cases} 1, & x \leqslant a \\ 1 - 2\left(\frac{x-a}{b-a}\right)^2, & a \leqslant x \leqslant \frac{a+b}{2} \\ 2\left(\frac{x-b}{b-a}\right)^2, & \frac{a+b}{2} \leqslant x \leqslant b \\ 0, & x \geqslant b, \end{cases} \tag{4.22}$$

and

$$\mu_{\text{AF}}(x) = \mu_{\text{SR}}(a + b - x). \tag{4.23}$$

The shape of $\mu_{\text{SR}}(x)$and $\mu_{\text{AF}}(x)$ is defined by the parameters a and b. For $\mathcal{N}$, the same type of input membership function is employed, but the fuzzy set relates instead to the noise level which is judged either to be low or high.

The set of *if–then* rules are then activated: in each rule, the antecedent is the fuzzified input value and the consequent is the linguistic output that reflects the degree of confidence of SR and AF. Each rule is composed of the four fuzzified parameters and combined with the AND operator. The output of each rule is defined by the Gaussian membership function,

$$\mu_k(y) = \exp\left[-\frac{(y - c_k)^2}{2\sigma^2}\right], \quad k = 0, \ldots, C, \tag{4.24}$$

where c_k and σ^2 determine location (output specific) and width, respectively, and C is the number of linguistic outputs (Fig. 4.6 b). For each rule, the degree of activated output is determined by the *minimum* value of each member. For simplicity, all rules are assigned a weight equal to 1.

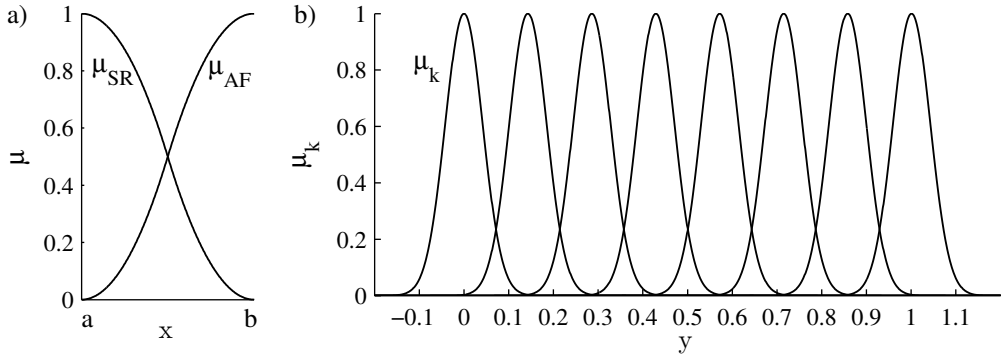

Fig. 4.6. a) The input, and b) the output membership functions when C = 8

The inference of a fuzzy block is based on all rules, and therefore the output of the individual rules $\mu_k(y)$ are combined using the *maximum* method for accumulation to produce the overall fuzzy output $\mu_o(y)$. The output value is obtained using the centroid defuzzification method, defined by

$$\mathcal{O} = \frac{\int_{y_{\min}}^{y_{\max}} y\mu_o(y)dy}{\int_{y_{\min}}^{y_{\max}} \mu_o(y)dy}, \tag{4.25}$$

where $y_{\min}$ and $y_{\max}$ are the lower and upper limits, respectively, of the overall fuzzy output. The output $\mathcal{O}$ is a value between 0 and 1 which reflects the likelihood that the detection window contains AF.

Since a short detection window is likely to cause more false alarms, median filtering (whose length is equal to that of the sliding window, i.e., M_b) is applied to the output $\mathcal{O}$ for the purpose of suppressing outlier values (it is recalled that $\mathcal{O}$ is a signal that results from the sliding window computation). Paroxysmal AF is detected whenever the output of the median filter exceeds a fixed threshold η $(0 < \eta < 1)$.

4.5 Derivation of electrocardiogram lead system for ambulatory monitoring of paroxysmal atrial fibrillation

The Lewis lead system consists of 5 leads; of which two, denoted L_1 and L_2, are derived for the purpose of enhancing the f-waves (Lewis, 1913). The bipolar chest lead L_1 is obtained by placing electrode 1 over the upper end of the sternum and electrode 2 to the right side of the sternum at the 2^{nd} intercostal space, whereas L_2 is the voltage between electrodes 2 and 3 placed on the right side of the sternum at the 4^{th} intercostal space (Fig. 4.7 a). Lead L_3 represents the voltage between electrodes 1 and 4, which both lie in the midaxillary line on the left side of the body at the level of the 5^{th} intercoastal space.

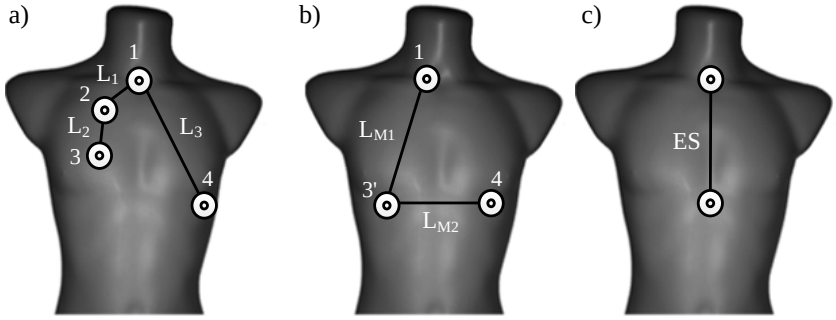

Fig. 4.7. ECG leads selected for investigation: a) the first three leads (L_1, L_2 and L_3) of the original Lewis lead system, b) the proposed modified Lewis lead system,and c) lead ES of EASI lead system

The modified Lewis lead, denoted L_{M1}, is obtained by removing electrode 2 and moving electrode 3 one intercostal space downwards (from the 4^{th} to the 5^{th}) in order to increase the immunity to arm movements (Fig. 4.7 b). The modified Lewis lead system includes the additional lead L_{M2}. The combination of L_{M1} and L_{M2} can be used to derive L_3 by applying Kirchhoff's voltage law. It should be noted that "the modified Lewis lead" stands for L_{M1} whereas "the modified Lewis lead system" is defined by the three leads L_{M1}, L_{M2} and L_3.

The modified Lewis lead system was compared to the original Lewis lead system (i.e., L_1, L_2, and L_3) as well as to lead ES of the EASI system. The EASI lead system uses 4 electrodes placed on the torso, of which E, A, and I are placed on the same areas as in the Frank lead system (Dower et al., 1988). In the EASI system, electrode S is placed over the upper end of the sternum and electrode E at the bottom of the sternum at the level of the 5^{th} intercostal space (Fig. 4.7 c).

4.6 Conclusions of the chapter

1. A low-complexity algorithm for detection of paroxysmal AF in continuous long-term monitoring devices has been developed. The proposed detector includes blocks of ectopic beats filtering and bigeminy suppression in order to reduce the number of false alarms due to ectopy-caused irregular rhythms. The detector can be used both in online and offline applications.

2. An echo state neural network based adaptive filter has been proposed for atrial activity extraction during AF using just two ECG leads – one with atrial activity expressed, and the other without. The method is based on sequential sample-by-sample signal processing, what makes it possible to analyse data in real-time.

3. A method for detection of brief episode paroxysmal AF has been proposed. The method relies on the combination of parameters characterizing both atrial and ventricular activity, and accounts for the prevailing noise level, thus may improve AF detection in ambulatory ECG recordings.

4. Electrocardiogram lead configuration (the modified Lewis lead system) for ambulatory monitoring of AF has been derived. The proposed ECG lead configuration involves only three electrodes, placed in areas of the body with less muscle, thereby reduced amplitude of motion artefacts is expected.

5 PERFORMANCE EVALUATION OF THE DEVELOPED METHODS

5.1 Datasets

Both clinical and simulated data have been used for developing and testing the proposed algorithms. Clinical data was used for developing and testing the r interval analysis based algorithm, whereas simulated signals were involved for investigation of the algorithm for brief AF episode detection. A database collected for investigation of the derived ECG lead system is described separately in Sec. 5.5.1.

5.1.1 Clinical signals

Four clinical databases containing ECG signals with AF, and one arrhythmia free database have been used for developing and testing the algorithms. A brief description of each clinical database is provided below.

The Long Term Atrial Fibrillation database (Petrutiu et al., 2007; Goldberger et al., 2000) is composed of 84 ECG recordings from patients with paroxysmal or persistent AF, most recordings with a 24 h duration. The entire database consists of nearly 9 million beats of which 59 % occur during AF.

The MIT–BIH Atrial Fibrillation database (Moody and Mark, 1983; Goldberger et al., 2000) includes 25 AF recordings of approximately 10 h duration, and contains in total more than 1 million beats, of which 43 % occur during AF. Two subsets of the AF database were also analyzed in order to facilitate the comparison with published results, namely, by excluding records 04936 and 05091, since these contain incorrect annotations, and by excluding records 00735 and 03665, since these only contain r interval information. The resulting two subsets are labeled AFDB_1 and AFDB_2, respectively.

The MIT–BIH Arrhythmia database (Moody and Mark, 1983; Goldberger et al., 2000) is composed of 48 annotated ambulatory ECG recordings of half-hour duration, and includes various types of arrhythmia episodes. Twenty-five signals, named as 200–series consist paroxysmal AF episodes.

The fourth AF database is composed of 12-lead ECG signals recorded from 211 patients with diagnosed AF. The database was recorded using equipment by Siemens-Elema AB, Sweden (Stridh et al., 2004).

The MIT–BIH Normal Sinus Rhythm database (Goldberger et al., 2000) contains 18 ECG recordings of approximately 24 h duration, with a total of almost 2 million beats. Since no significant arrhythmias are present, it is well-suited for the evaluation of detector specificity.

5.1.2 Simulated signals

Due to the lack of annotated databases with brief paroxysmal AF, test signals were generated for performance evaluation of proposed AF detectors in a special case, when AF episodes lasting just 5–30 s are the subject of analysis. In order to generate signals with paroxysmal AF episodes, the concatenated ECGs were altered with respect to rhythm and

morphology. In paroxysmal AF episodes, the signal was produced by adding the ventricular activity of the ECG and synthetic f-waves produced by a sawtooth model. During SR, the original P-waves were modified to produce a more challenging test signal with larger morphologic beat-to-beat variability. The original r interval series was replaced by a series produced by a model of either SR or AF. Finally, EMG noise was added at different RMS values to produce the test signal.

This section describes the steps required for generating test signals with brief paroxysmal AF. The ECGs of the PTB database, which served as a basis for signal generation, were first subjected to baseline removal and QRST delineation (Laguna et al., 1994).

Ventricular rhythm

The number of beats in SR and AF episodes was uniformly distributed in the interval [5, 30], unless otherwise stated, and thus the test signals contained about the same number of episodes of SR and AF.

The model by McSharry et al. (2003) was used to generate r intervals during SR. The mean heart rate was set to 60 bpm with the standard deviation to 2 bpm, the respiratory rate to 0.25 Hz and the low-frequency/high-frequency ratio to 1. During AF, an atrioventricular node model was used to generate r intervals (Corino et al., 2011). The mean arrival rate of atrial impulses was set to 6 Hz, the minimal refractory period to 0.25 s, the probability of an impulse to take the slower pathway to 0.6, the maximal refractory period prolongation to 0.1 s (identical for both pathways) and the difference between the two refractory periods to 0.2 s.

Ventricular morphology

The original T-waves were first resampled to a fixed width, and then, depending on type of rhythm, the width-adjusted to match the prevailing heart rate. During SR, the T-wave was resampled relative to the current r interval using Bazett's formula, where the corrected QT interval was set to 420 ms. During AF, the QT interval was shorter than during SR, and set to a fixed value (250 ms). After an AF episode terminated, the T-wave duration was gradually increased over the next five beats so as to produce a smooth transition from AF to SR. When needed, the TQ interval was padded with zeros.

Since APBs occur quite commonly in AF patients (Thong et al., 2004), a certain percentage of APBs was introduced in the test signal. The occurrence of an APB caused the preceding r interval to be 25 % shorter and the following 25 % longer.

P-waves

In lead V_6, P-waves are usually monophasic in shape and therefore reasonably well modeled by the first Hermite function (Sörnmo et al., 1981; Jané et al., 1993):

$$\Phi(n) = \sum_{i=0}^{2} k_i \phi_i(n), \tag{5.1}$$

where k_i is a weighting factor for each Hermite function ϕ_i. The first three Hermite functions are given by

$$\phi_0(n) = \frac{1}{\sqrt{d_0\sqrt{\pi}}} \cdot e^{-n^2/2d_0^2} \tag{5.2}$$

$$\phi_1(n) = -\frac{\sqrt{2}}{\sqrt{d_1\sqrt{\pi}}} \cdot \frac{n}{d_1} e^{-n^2/2d_1^2} \tag{5.3}$$

$$\phi_2(n) = \frac{1}{\sqrt{2d_2\sqrt{\pi}}} \cdot \left(\frac{2n^2}{d_2^2} - 1\right) \cdot e^{-n^2/2d_2^2} \tag{5.4}$$

The parameters d_0, d_1 and d_2 determine the width of each Hermite function. The second $\phi_1(n)$ and third $\phi_2(n)$ Hermite functions, were added with random weights (normal distribution, zero-mean, variance 0.1) to make the morphology vary over time. Since P-waves in V_1 are often biphasic in patients with paroxysmal AF (Kuo et al., 2003), they were modeled by simply differentiating the corresponding P-wave in V_6. The peak-to-peak P-wave amplitude was set to 50 μV in both V_1 and V_6. The PR interval length was uniformly distributed within the interval [175,185] ms.

Fibrillatory f-waves

The f-waves are generated using a sawtooth model, first introduced in (Stridh and Sörnmo, 2001), in which both amplitude and repetition rate can be modulated. The model is defined by a fundamental and $L-1$ harmonics:

$$s_d(n) = \sum_{l=1}^{L} h_l(n) \sin\left(l\omega_0 n + \frac{\Delta_f}{f_f}\sin(\omega_f n)\right), \tag{5.5}$$

where the fundamental frequency $\omega_0 = 2\pi f_0$ has the maximum frequency deviation Δf and the modulation frequency $\omega_f = 2\pi f_f$. The amplitude $a_l(n)$ is defined so that a signal with sawtooth characteristics is produced,

$$h_l(n) = \frac{2}{l\pi}\left(h + \Delta h \sin(\omega_h n)\right), \tag{5.6}$$

where a denotes sawtooth amplitude, Δh modulation amplitude, and $\omega_h = 2\pi f_h$ amplitude modulation frequency. The following parameter values are used: $L = 3$, $f_0 \sim 6$ Hz, $\Delta f \sim 0.25$ Hz, $f_f \sim 0.2$ Hz, and $f_h \sim 0.2$ Hz. The f-wave amplitude h is chosen so that a certain RMS value of the simulated atrial activity is obtained and $\Delta h = h/3$. This choice of model parameter values is similar to those of case A studied in (Stridh and Sörnmo, 2001), the difference being that the amplitude modulation is more pronounced here, so as to produce more challenging signals.

The sawtooth f-wave model has been employed for performance evaluation in various studies, i.e., (Stridh and Sörnmo, 2001; Sandberg et al., 2008a; Alcaraz et al., 2009). However, when applied to the ESN, the network can learn the predictable changes in amplitude and repetition rate that are characteristic of this model and consequently produce

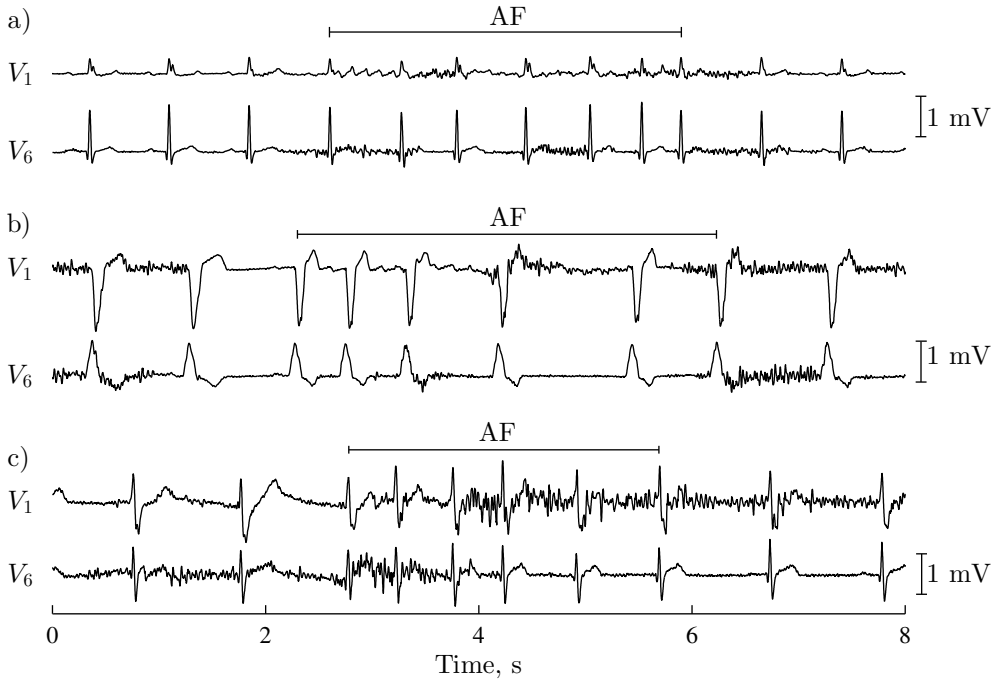

Fig. 5.1. Illustration of test signals with a single brief AF episode in leads V_1 and V_6 when the noise level is set to a) 20 μV, b) 50 μV, and c) 100 μV

results that show partiality toward the method. This problem is circumvented by extending the model, so that the variations in f-wave morphology become more unpredictable, here accomplished by adding colored noise to $s_d(n)$. Coloring is made through bandpass filtering of white noise (whose variance is a factor 10 smaller than the sawtooth amplitude h) with cutoff frequencies at 1.8 and 6.2 Hz. Thus, the f-wave model signal $s(n)$ is composed of a deterministic and a random component:

$$s(n) = s_d(n) + s_r(n). \tag{5.7}$$

The amplitude in V_1 was taken to be 5 times larger than that in V_6 to reflect the fact that f-waves have a much larger amplitude in V_1 than in V_6. This difference in amplitude was caused by the longer distance from the heart to the electrode site and an electrical vector that is much more scattered during AF.

Noise

Following summation of ventricular and atrial activities, electromyographic noise taken from the MIT–BIH Noise Stress Test Database (Moody et al., 1984) was added to produce the final test signal (the noise first rescaled to the desired RMS value). A number of test signals with different noise levels are displayed in Fig. 5.1.

5.2 Low-complexity detection of paroxysmal atrial fibrillation

5.2.1 Data and performance measures

The r-based AF detector was developed on the entire Long Term Atrial Fibrillation database. The MIT–BIH Atrial Fibrillation database and the MIT–BIH Normal Sinus Rhythm database were used for performance evaluation. To facilitate the comparison, the performance of the proposed detector has been evaluated on the commonly used combinations of the MIT–BIH Atrial Fibrillation and the MIT–BIH Normal Sinus Rhythm databases.

The ability of the algorithm to detect brief AF episodes was investigated by evaluating the performance as a function of AF episode duration using simulated r series. A model by McSharry et al. (2003) is used to generate r intervals during sinus rhythm, whereas an atrioventricular node model is used to generate r intervals during AF (Corino et al., 2011). When combining these two models, different r interval series can be generated with variable episode duration, mean heart rate and heart rate variability as illustrated in Fig. 5.2.

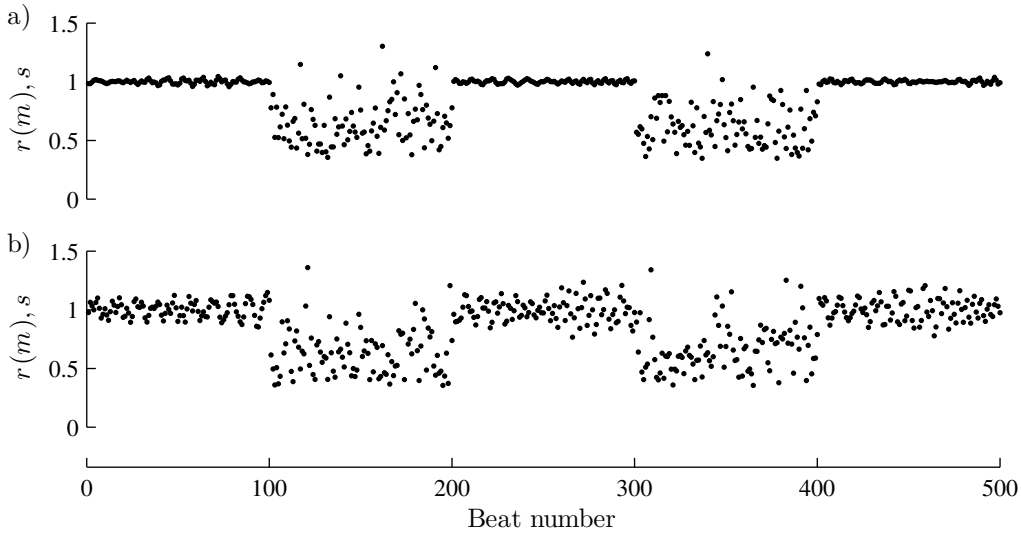

Fig. 5.2. Two examples of paroxysmal AF, each containing two AF episodes with 100 beats; note that the r interval series are simulated. The mean and standard deviation of the heart rate during sinus rhythm is a) 60 ± 1 beats per minute (bpm) and b) 60 ± 5 bpm

Detector performance was tested using different r series with alternating episodes of sinus rhythm and AF. The entire database with simulated signals consists of four datasets, each dataset defined by the mean and standard deviation of the heart rate during sinus rhythm, namely, 60 ± 1, 60 ± 5, 100 ± 1, and 100 ± 5 bpm. Each dataset is, in turn, divided into nine subsets with fixed AF episode lengths, ranging from 20 to 180 beats in steps of 20 beats. Thus, the database is composed of 36 subsets, each consisting of 5000 r intervals for which 100 realizations were computed.

The performance was investigated in terms of the area under the curve (A) of the receiver operating characteristic (ROC), sensitivity (*Se*) and specificity (*Sp*). Sensitivity is defined by the number of correctly detected AF beats divided by the total number of AF beats, whereas specificity is defined by the number of correctly detected non-AF beats divided by the total number of non-AF beats. All other types of rhythm, including atrial flutter, were labeled as non-AF.

5.2.2 Parameter settings

Figure 5.3 displays A as a function of the exponential averaging parameter β for the Long Term Atrial Fibrillation database. For all investigated values of γ, M, and δ, the results show that A improves as β decreases. While these results suggest that a small β should be chosen, such a choice also means that the risk of missing brief episodes of paroxysmal AF increases. Therefore, it is important to complement the results in Fig. 5.3 with others that pinpoint detection performance as a function of episode length.

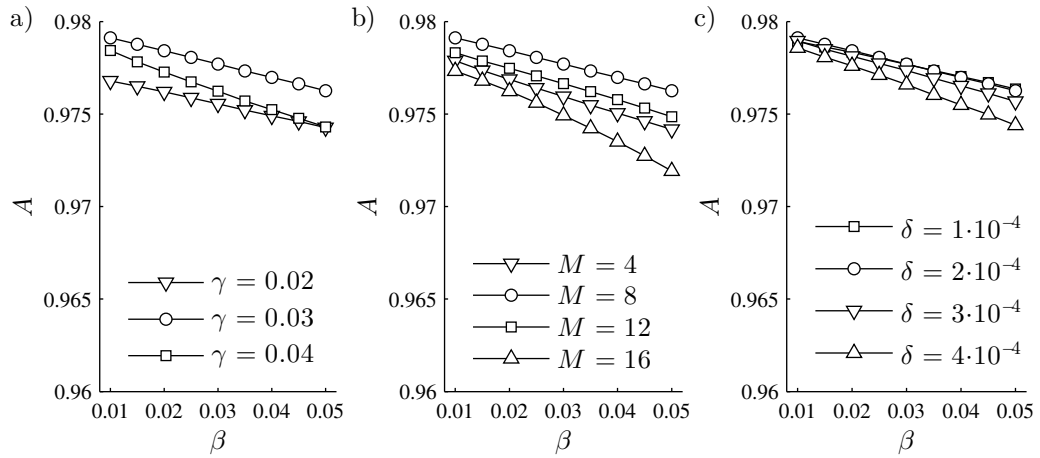

Fig. 5.3. The influence of different parameters on detection performance in terms of A: a) β and γ for $M = 8$ and $\delta = 2 \cdot 10^{-4}$, b) β and M for $\gamma = 0.03$ and $\delta = 2 \cdot 10^{-4}$, and c) β and δ for $\gamma = 0.03$ and $M = 8$. These results are based on the Long Term Atrial Fibrillation database

Using simulated signals, Fig. 5.4 demonstrates that the detection of brief episodes improves as β increases. For example, for $\beta = 0.1$, an area under the curve of $A = 0.92$ is obtained for 20-beat episodes, whereas, for $\beta = 0.02$, the same value of A is obtained for 60-beat episodes. Hence, it can be concluded from the results in Figs. 5.3 and 5.4 that the choice of β should be a trade-off between avoiding false alarms due to non-AF arrhythmias (calling for a small β) and detecting brief AF episodes (calling for a large β).

Another important result conveyed by Fig. 5.4 is that better performance is obtained in situations with low heart rate and low variability (i.e., 60 ± 1 bpm) than in situations with high heart rate and high variability (i.e., 100 ± 5 bpm).

Based on the results in Figs. 5.3 and 5.4, the following parameter values were chosen as a trade-off between the above-mentioned performance aspects: $\gamma = 0.03$ s, $M = 8$,

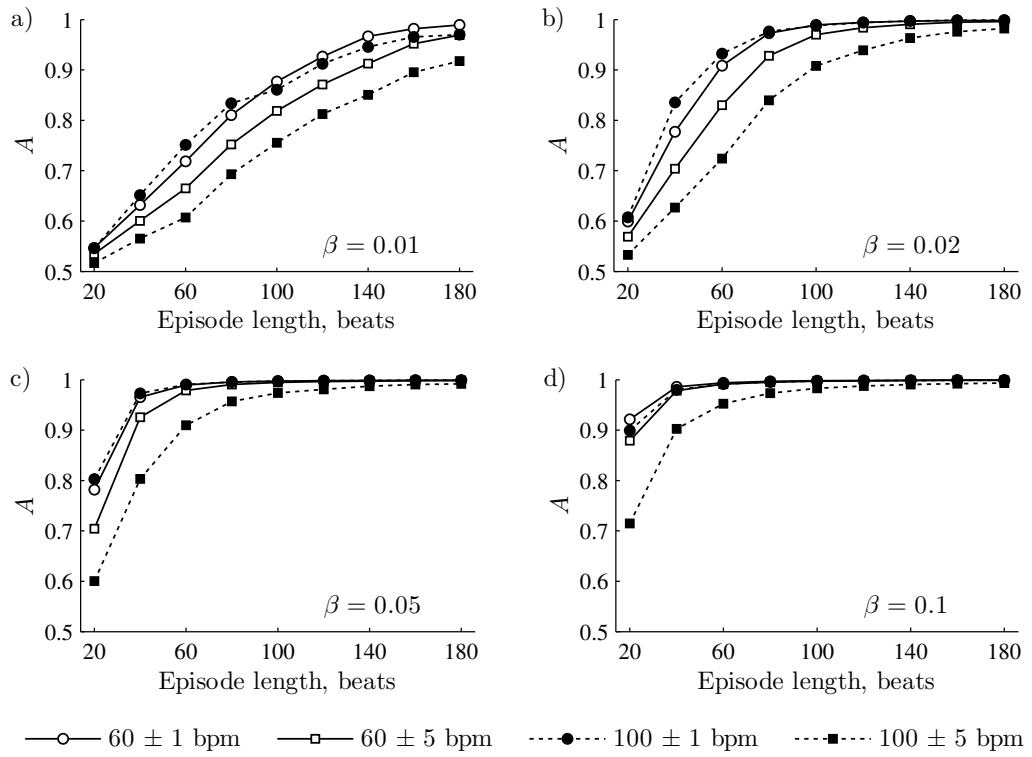

Fig. 5.4. Detection performance A as a function of AF episode length for a) $\beta = 0.01$, b) $\beta = 0.02$, c) $\beta = 0.05$, and d) $\beta = 0.1$. These results are based on simulated signals which do not contain any arrhythmias except AF

$\delta = 2{\cdot}10^{-4}$, and $\beta = 0.02$. Unless otherwise stated, these values are used in the following experiments.

Figure 5.5 displays the distribution of the detector output $\mathcal{O}_l(m)$ for AF and non-AF beats in the Long Term Atrial Fibrillation database. Based on the properties of these two distributions, the detection threshold ϑ was chosen as that particular value where sensitivity and specificity are identical, i.e., $\vartheta = 0.725$.

5.2.3 Investigation of briefest episode length

The briefest possible AF episode that can be detected was determined by means of simulated r intervals with one, single AF episode. Starting with an episode length of five beats, the length was, in this particular test, incremented by one beat at a time until the episode was detected. The episode length is presented in Table 5.1 for different values of β – a parameter that is particularly influential on detection performance – together with the corresponding detection delay. For $\beta = 0.02$, the shortest episode detected contained 60 beats, whereas for $\beta = 0.05$, episodes as short as 15 beats could be detected.

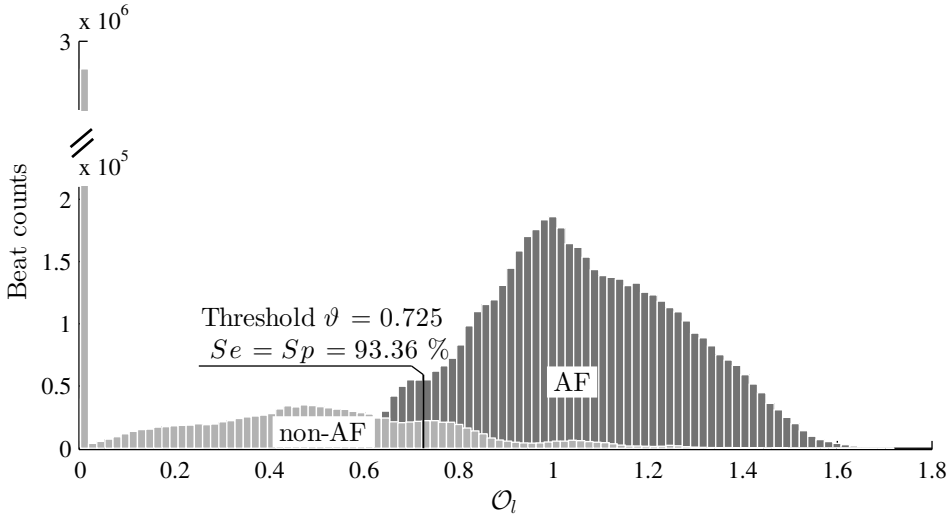

Fig. 5.5. Distribution of the output $\mathcal{O}_l(m)$ during AF and non-fibrillatory rhythms (non-AF). The large bin close to 0 for non-AF beats is due to the bigeminy suppression block. These results are based on the Long Term Atrial Fibrillation database

Table 5.1. The briefest possible episode detected for different values of β and the corresponding detection delay. In this particular test, an episode was considered as detected whenever the annotation and the detector output overlapped with at least 50 %.

β	Episode length, beats	Delay, beats
0.005	300	318
0.01	120	158
0.02	60	78
0.05	15	30
0.1	8	14

5.2.4 Atrial fibrillation detection on clinical databases

Detection performance was studied for various combinations of the MIT–BIH Atrial Fibrillation and MIT–BIH Normal Sinus Rhythm databases, see Table 5.2. Using the offline detector with $\beta = 0.02$, the sensitivity/specificity were found to be 97.1/98.3 % on the MIT–BIH Atrial Fibrillation database, whereas the online version performed marginally worse with 96.9/98.2 %. When omitting the two records with incorrect annotations, i.e., when analyzing AFDB_1, the sensitivity increased from 97.1 % to 98.0 % for the offline version. When evaluating performance on the MIT–BIH Normal Sinus Rhythm database, a specificity of 98.6 % was achieved for both the off- and online detectors (sensitivity was not evaluated since no AF episodes were present).

Tuning the detector to finding briefer episodes, i.e., by using $\beta = 0.05$, Table 5.2 shows that such tuning comes at the expense of a slightly reduced performance since the sensitivity/specificity drop from 97.1/98.3 % to 96.7/97.9 % on the MIT–BIH Atrial

Fibrillation database for the offline detector.

Table 5.2. Sensitivity and specificity of the proposed detector, evaluated for various combinations of the MIT–BIH Atrial Fibrillation (AFDB) and MIT–BIH Normal Sinus Rhythm (NSRDB) databases. Records 04936 and 05091 in AFDB_1, and 00735 and 03665 are excluded in AFDB_2.

Database	β = 0.02				β = 0.05			
	offline		online		offline		online	
	Se, %	Sp, %	Se, %	Sp, %	Se, %	Sp, %	Se, %	Sp, %
AFDB	97.1	98.3	96.9	98.2	96.7	97.9	96.5	97.9
AFDB_1	98.0	98.2	97.7	98.1	97.5	97.8	97.3	97.8
AFDB_2	97.1	98.1	96.8	98.0	96.6	97.7	96.5	97.8
AFDB & NSRDB	97.1	98.5	96.9	98.5	96.7	98.4	96.5	98.4
AFDB_1 & NSRDB	97.3	98.2	97.0	98.2	96.8	97.8	96.7	97.8
AFDB_2 & NSRDB	96.8	98.2	96.5	98.1	96.4	97.7	96.2	97.8
NSRDB	NA	98.6	NA	98.6	NA	98.6	NA	98.6

The slight difference in performance between the off- and online versions is due to the different filters used for trend estimation, defined by (4.2) and (4.7). The influence of a nonlinear phase on the r interval trend $r_t(m)$ is illustrated in Fig. 5.6. Although the phase distortion is negligible when β is large, i.e., 0.1, a slight exponential reaction during rhythm transitions can be noted for $\beta = 0.02$ or smaller, leading to slower a reaction when heart rate changes and higher phase disturbances occur.

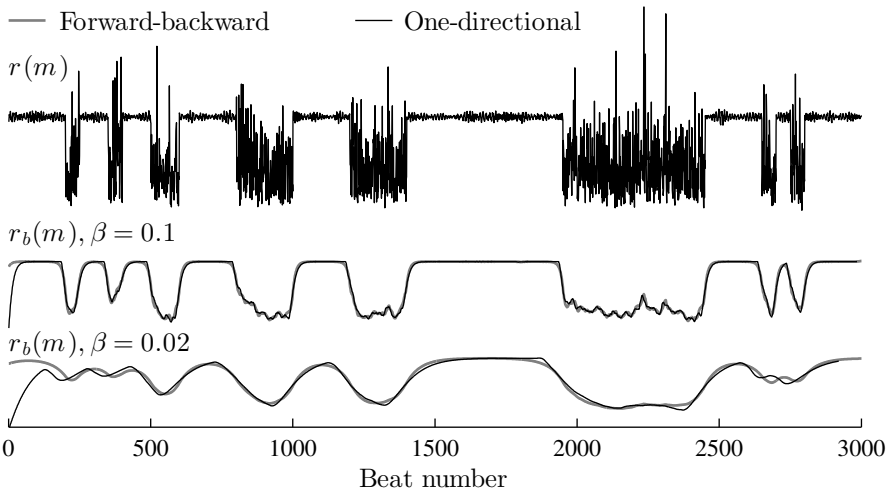

Fig. 5.6. Estimation of r interval trend using forward–backward and unidirectional filtering techniques. Note that the delay of the unidirectional filter has been compensated for

5.2.5 Discussion

As discussed earlier, AF is often overlooked after interventional therapies when the standard strategy for treatment evaluation is used, i.e., at least two 24 h Holter recordings

(Charitos et al., 2012). This finding suggests that continuous AF monitoring performed during much longer time spans should be recommended so that the success rate is not overestimated. However, current technology does not allow continuous monitoring, since most AF detectors require a substantial amount of computations, which render efficient implementations difficult, especially for detectors that involve morphologic ECG features. A first step towards efficient implementation was recently taken in (Andersson et al., 2015) where the r-based detector in (Dash et al., 2009) was implemented in an application specific integrated circuit (ASIC). The results suggest that the energy required for long-term operation, i.e., for several years, is well within the battery capacity of an existing implantable device.

The present AF detector is compared to the best-performing detectors in the literature with respect to sensitivity and specificity, using the MIT–BIH Atrial Fibrillation database, see Table 5.3. Like in most other studies, performance is presented with one decimal. It is evident that the detector by Zhou et al. (2014) performs almost as good as the present detector, although the difference in performance increases slightly when the results are reported with two decimals: sensitivity/specificity are 97.12/98.28 % and 96.89/98.25 %, respectively.

Table 5.3. Detector performance evaluated on the MIT–BIH Atrial Fibrillation database

Method	Year	Database	Se, %	Sp, %
Proposed detector	2015	AFDB	97.1	98.3
Asgari et al.	2015	AFDB_2	97.0	97.1
Zhou et al.	2014	AFDB	96.9	98.3
Lee et al.	2013	AFDB_1	98.2	97.7
Carvalho et al.	2012	AFDB_2	93.8	96.1
Huang et al.	2011	AFDB	96.1	98.1
Lake and Moorman	2011	AFDB	91	94
Lian et al.	2011	AFDB	95.8	96.4
Dash et al.	2009	AFDB_1	94.4	95.1
Tateno and Glass	2001	AFDB	94.4	97.2

When evaluating detector performance, it is important, for the reasons mentioned earlier, to also consider the ability to detect brief AF episodes. Of the detectors in Table 5.3 that employ a window length of 128 beats, i.e., (Tateno and Glass, 2001; Dash et al., 2009; Huang et al., 2011; Lian et al., 2011), it was only Lian et al. (2011) and Lee et al. (2013a) who also reported on the performance for shorter windows. Comparing Lian et al. (2011) results obtained for a length of 32 (i.e., the shortest window studied) with the results of the present detector obtained for $\beta = 0.05$, the sensitivity is 94.4 % vs. 96.7 % and the specificity 92.6 % vs. 97.9 %, and thus the present detector offers a considerable improvement in performance. The algorithm by Lee et al. (2013a) showed even worse performance of 94.7 % sensitivity and 90.4 % specificity for a window length of 12 beats.

It is obvious that the aforementioned AF detectors with a 128-beat window tend to

miss brief clinical episodes. With the growing interest in detection of brief AF episodes (Tayal et al., 2008; Flint et al., 2012; Seet et al., 2011; Rabinstein et al., 2013; Kishore et al., 2014), with durations from 5 to 30 s, there are even stronger reasons to develop AF detectors that can operate with window lengths much shorter than 128. Such a goal may not be easily achieved, however, when the detection process involves the estimation of probabilities, i.e., used for computing the sample entropy, since a shorter window implies increased statistical uncertainty.

Thanks to the flexibility introduced by β, the present detector can be tuned to detect brief episodes, although, just as with any detector, improved detection of brief episodes comes at the expense of lower specificity. Since the detector was developed on the Long Term Atrial Fibrillation database, mostly containing very long AF episodes, it is not surprising that better performance was obtained for a smaller β ($\leqslant 0.01$), cf. Fig. 5.3. However, since the detection delay becomes unacceptably large for such small values, $\beta = 0.02$ was used as a suitable trade-off. For the online detector, a smaller β leads to increased phase distortion and, therefore, online detectors may be developed considering more sophisticated approaches to trend estimation (Bianchi et al., 1999; Kim et al., 2009).

A specificity of 98.6 % was achieved on the MIT–BIH Normal Sinus Rhythm database, see Table 5.2, indicating that the detector produces few false alarms in the presence of respiratory sinus arrhythmia. This result is slightly better than those reported in (Huang et al., 2011) and (Zhou et al., 2014) where the specificity was found to be 98.2 % and 98.3 %, respectively.

When more complex arrhythmias are encountered, reduced performance is expected. This reduction can be estimated by analyzing the MIT–BIH Arrhythmia database, which contains a variety of more complex arrhythmias. The resulting sensitivity/specificity were found to be 97.8/86.4 %, indicating that most AF episodes could be reliably detected, while certain arrhythmias are mis-detected as AF. Zhou et al. (2014), being one of the very few authors who have reported on the performance on this database, achieved sensitivity/specificity of 97.3/90.8 %, where specificity is notably better than that of the present detector. This difference in performance may be explained by the much longer detection window used by Zhou et al. (2014) which produces better specificity when long AF episodes are encountered (as is the case in this database).

The examples in Fig. 5.7 shed additional light on the pros and cons of AF detection when performed in the presence of various arrhythmias, none of them being AF. In the first three examples, the detector demonstrates excellent performance when encountering frequent ectopic beats (Fig. 5.7 a), episodes of 2^{nd} degree atrioventricular block (Fig. 5.7 b), and sinus bradycardia (Fig. 5.7 c). On the other hand, the performance degrades when atrial flutter (Fig. 5.7 d) or ventricular flutter (Fig. 5.7 e) are encountered, since both these types of flutter are difficult to distinguish from AF when confining the analysis to r intervals. Figure 5.7 f) displays an episode of a complex supraventricular arrhythmia, which causes the detector to produce a false alarm.

It is likely that these false alarms in Fig. 5.7 d)–f) can be avoided by the introduction of a two-stage detection scheme. With its high sensitivity, the present detector can be

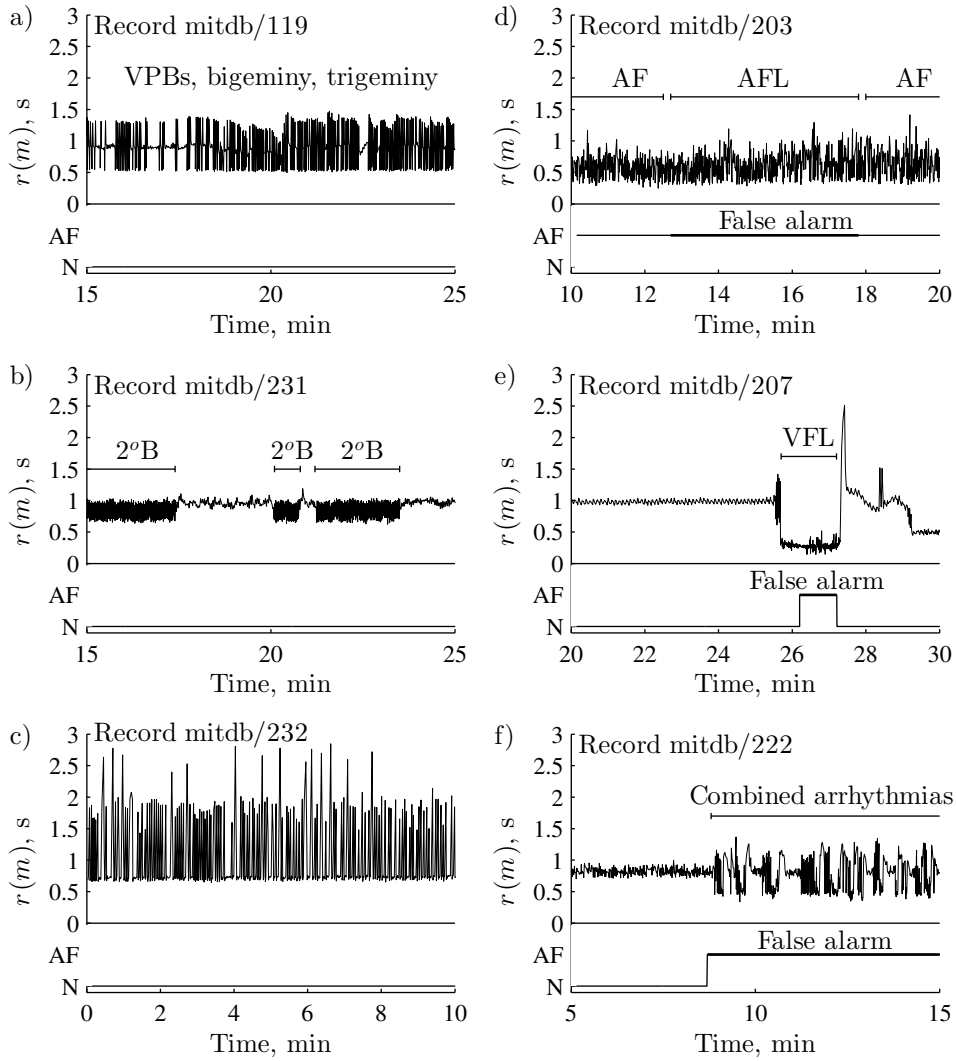

Fig. 5.7. Examples of detector performance for various arrhythmia episodes of the MIT–BIH Arrhythmia database. The left column displays cases free of false alarms during a) multiple ventricular premature beats (VPBs), b) 2nd degree atrioventricular block (2°B) and c) sinus bradycardia. The right column displays cases with false alarms due to d) atrial flutter (AFL) with irregular ventricular rhythm, e) ventricular flutter (VFL), and f) an episode of combined arrhythmias including AF, AFL, atrial bigeminy, supraventricular tachycardia, atrioventricular junctional rhythm, and atrial premature beats

employed in the first stage to find possible AF episodes. In the second stage, a more advanced AF detector is employed that involves morphologic information to determine in further detail whether the detected episodes are correct or not. Since morphologic analysis is computationally much more costly, the second-stage detector should preferably be implemented in a server or a smartphone.

While implementational aspects of the detector are outside the scope of this thesis,

i.e., whether ASIC or a field programmable gate array (FPGA) should be used, a few observations on detector complexity can nonetheless be made. The present detector requires a window of only 8 r intervals, which, as already pointed out, is highly desirable from the viewpoint of detecting brief episodes. Moreover, such a short window implies very modest memory requirements, which is desirable from the viewpoint of energy consumption. With its extremely simple structure, the detector requires just a few arithmetical operations (Table 4.1) and no table lookups and, consequently, the implementation can be made to be very battery-conserving. It is noted that further complexity reduction can be achieved by replacing the multiplications in (4.2), (4.3), and (4.7) by additions and shifts that are less costly, reducing the number of multiplications from 8 to 2. For example, the choice $\beta = 0.02$ can be closely approximated with $5/256 \approx 0.01953$ which is implemented by 5 additions and an 8-bit shift.

Zhou et al. (2014) reported on the computation time needed to analyze different public databases, but did not provide any information on the required number of arithmetic operations per r interval. Since that detector makes use of high-order filters, in addition to the buffer required for the 128-beat window, much more memory is required than for the present detector.

The low complexity of the present detector is partly achieved by avoiding rather involved steps for handling of ectopic beats such as those in (Dash et al., 2009) and (Carvalho et al., 2012). Instead, simple filtering and flagging techniques, i.e., (4.1) and (4.5), are employed for the purpose of reducing the number of false alarms due to bigeminy.

A limitation of the present study is that the proposed detector was not evaluated on real ECG data with brief paroxysmal AF, since no such database has yet been annotated. Instead, an approach involving test signals has been pursued, which can still provide valuable insight on detection performance.

5.3 Atrial activity extraction during atrial fibrillation

5.3.1 Data and performance measures

One-hundred 1 min duration ECG signals with AF over the entire signal were generated according to the simulation procedure described in Sec. 5.1.2. ECGs were selected from the PTB Diagnostic ECG Database (Bousseljot et al., 1995; Goldberger et al., 2000). Leads V_1 and V_6 were chosen as the target and reference signals, respectively. The respective sampling rates were converted to 250 Hz. The amplitude of the f-waves is defined as the RMS value, and thus the combined contribution of $h, \Delta h$, and $s_r(n)$ to the f-wave amplitude is measured in the 1 min segment.

The proposed method was compared to average beat subtraction (ABS), being the most widely used method for atrial activity extraction. In contrast to the ESN, ABS performs better when data is processed at a sampling rate higher than 250 Hz. Consequently, ABS was performed at an original sampling rate of 1 kHz in order to reduce the influence of residuals due to misalignment. It should be noted that ABS was performed only in the lead subject to atrial activity extraction, but not in the reference lead.

The RMS error between $s(n)$ and $\hat{s}(n)$, denoted E, is the principal performance measure in the time domain. The first second of the analyzed signal was excluded from the computation of E to avoid the inclusion of transients caused by the f-waves extraction method; the transient is studied separately. The statistical significance of differences in E is determined using the two-sample t-test. The statistical results are expressed as mean$\pm$two-sided confidence interval (95 %).

The power spectrum of $\hat{s}(n)$ is computed in order to evaluate the accuracy of the AF frequency estimates. The spectrum is obtained using Welch's method with a 2 s tapered cosine window and 50 % segment overlap. The location of the maximum spectral peak within the interval 3–10 Hz is taken as the dominant fibrillatory frequency.

Fifty of the 100 simulated signals were used for initialization of the ESN parameters, whereas the remaining 50 were used for testing. The "initialization set" contains signals with an f-wave amplitude of 30 μV. The performance measure E was computed for each of the 50 simulated signals and then averaged and taken as the overall performance measure, denoted $\bar{E}$.

5.3.2 Initialization of echo state network parameters

Using the initialization set, $\bar{E}$ is displayed for different forgetting factors λ and α in Fig. 5.8 a), showing that the best performance is achieved when α is about 0.8. The influence of the reservoir size N and λ on $\bar{E}$ is displayed in Fig. 5.8 b). For $\lambda < 1$, $\bar{E}$ exhibits a minimum when N is about 100, whereas, for λ = 1, $\bar{E}$ continues to improve as N increases. Based on these findings, the following parameter values are used for the performance evaluation below: $N = 100$, $\lambda = 0.999$, and $\alpha = 0.8$.

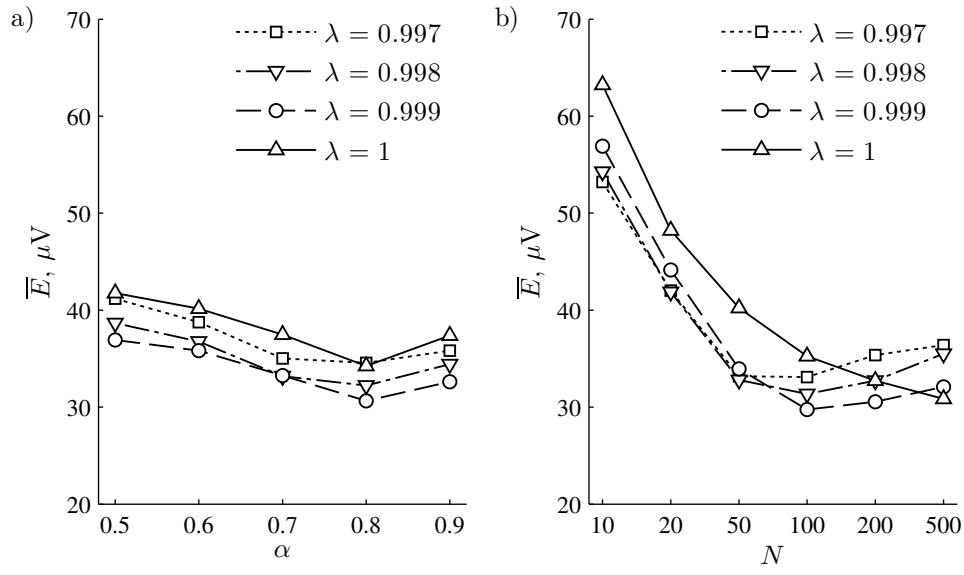

Fig. 5.8. The influence of different parameters on $\bar{E}$. a) The forgetting factors λ and α for $N = 100$, and b) λ and N for $\alpha = 0.8$

By repeating the random initialization of the input weights $\mathbf{W}_{\text{in}}$ and the reservoir-connecting weights $\mathbf{W}$ for each signal, the robustness of initialization can be assessed through the statistics of the resulting $\bar{E}$. Figure 5.9 shows the performance of the proposed method when random initialization has been repeated 100 times for each of the 50 signals. This result shows that the initialization of the ESN has only marginal influence on the performance, since the confidence interval is negligibly small for most signals. It can be noted though that the length of the confidence interval is slightly increasing for larger values of E.

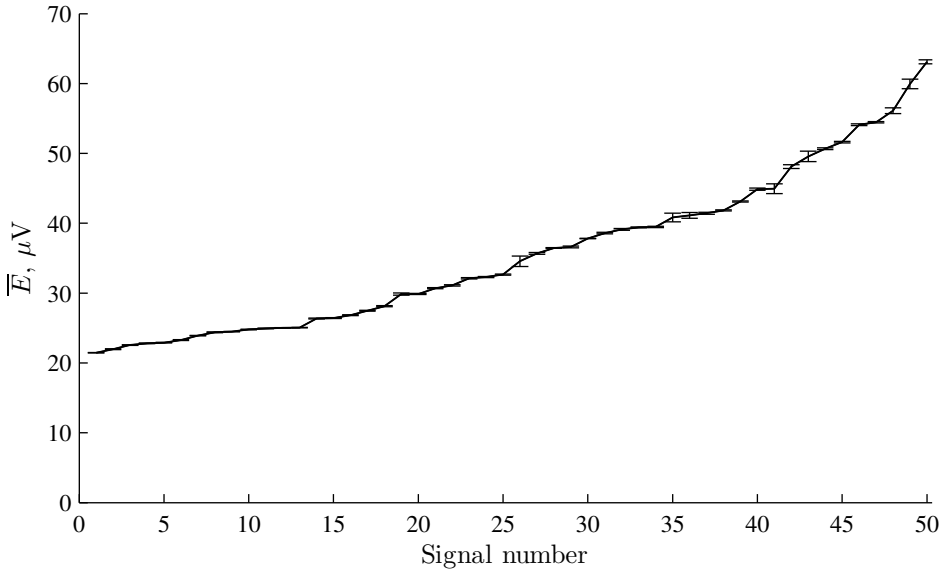

Fig. 5.9. The influence of random initialization of ESN on E. The resulting values for each of the 50 simulated signals are sorted and expressed as mean$\pm$two-sided confidence interval

In addition to N, λ, and α, the ESN contains a number of parameters that have less influence on performance. The spectral radius ρ of the reservoir weight matrix is defined by its largest absolute eigenvalue, and is related to an echo state property that ensures stability (Lukoševičius and Jaeger, 2009). A small value of ρ implies a more rapid decay of the reservoir dynamics, and vice versa, and therefore ρ will influence the length of memory and the degree of reservoir nonlinearity. Input scaling exerts an influence which resembles that of ρ. For small values of input scaling, the reservoir behavior is almost linear because the nonlinear regions of the activation function are not excited. On the contrary, large values of input scaling drive the reservoir neurons to the nonlinear regions of the activation function. An interesting property of the ESN is that the reservoir does not have to be fully connected. Indeed, it is sufficient with a sparsely connected reservoir, i.e., 5–20 % of all connections depending on reservoir size, which thus leads to a substantial reduction in computational complexity when compared to the fully connected reservoir. The following parameter values are used: $\rho = 1$, input scaling set to 1, and reservoir connectivity set to 20 %. In addition, the hyperbolic tangent is used as a reservoir

activation function, whereas the identity activation function is used as output neuron. The recursive least squares algorithm is initialized with $d = 0.01$.

The results presented below are based on the test set with 50 signals, but extended using a fixed f-wave amplitude RMS in each set, incremented in steps of 10 μV from 10 to 50 μV. These amplitudes were selected so as to put special emphasis on the problem of how to extract low-amplitude atrial activity, a problem that has not received much attention in engineering literature. Thus, the test set contains a total of $50 \cdot 5 = 250$ simulated signals.

5.3.3 Results of atrial activity extraction during atrial fibrillation

Figure 5.10 a) presents the performance of the ESN and ABS in the time domain as quantified by $\bar{E}$. The results show that the ESN is much better in extracting the f-wave signal than ABS – a result which applies to both when $\bar{E}$ is computed for the entire signal as well as when it is confined to the QRS interval. The input vector $\mathbf{x}_r(n)$ to contain not only $x_r(n)$ but also its first derivative $x'_r(n)$, and an impulse-like signal $x^s_r(n)$, yields better performance than does a vector defined by either $x_r(n)$ only or $x_r(n)$ and $x'_r(n)$.

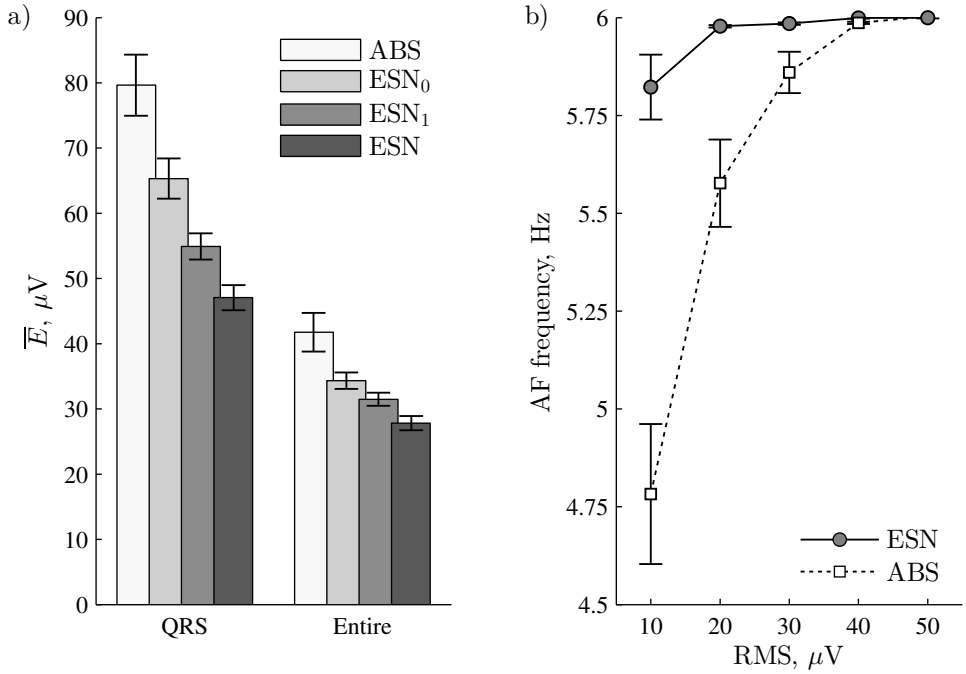

Fig. 5.10. a) The performance measure $\bar{E}$ for the ESN using different reference input (ESN$_0$–$x_r(n)$; ESN$_1$–$x_r(n), x'_r(n)$; ESN–$x_r(n), x'_r(n), x^s_r(n)$) and ABS. The performance measure $\bar{E}$ results from averaging over the 5 sets with different f-wave amplitudes. b) Estimates of the dominant AF frequency for a true AF frequency of 6 Hz. Results are expressed as mean$\pm$two-sided confidence interval

Figure 5.10 b) displays the results from estimating the dominant AF frequency at

different f-wave amplitudes. It is clear that the ESN offers superior performance at most amplitudes: accurate estimates are produced for amplitudes of 20 μV or larger, whereas ABS requires at least 40 μV. The performance loss of ABS is largely due to low-frequency residuals of ventricular activity, which cause the dominant AF frequency to be underestimated.

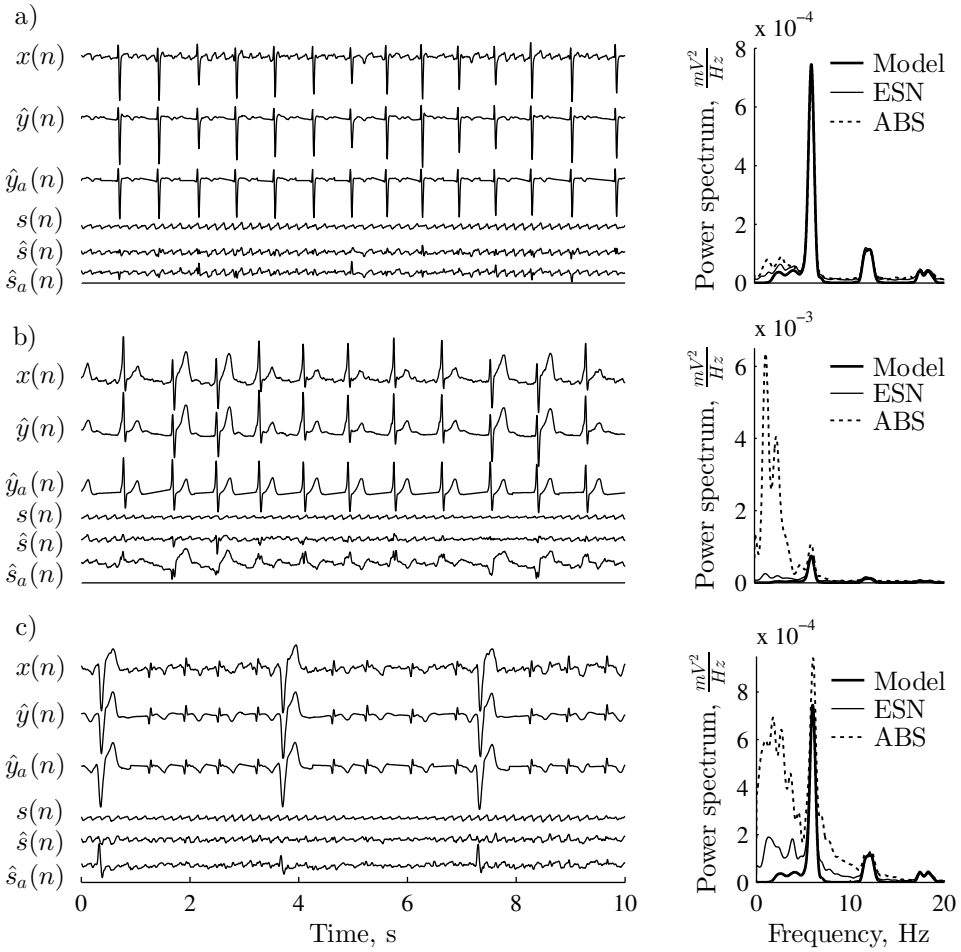

Fig. 5.11. Examples of f-waves extraction in simulated ECG signals ($x(n)$–lead with AF; $\hat{y}(n)$–ventricular activity estimated by the ESN; $\hat{y}_a(n)$–ventricular activity estimated by ABS; $s(n)$–modeled f-waves; $\hat{s}(n)$–f-waves estimated by the ESN; $\hat{s}_a(n)$–f-waves estimated by ABS), and corresponding power spectra. The following ECG attributes are particularly pronounced: a) fast QRS amplitude changes, b) beat-to-beat variation in morphology, and c) the occurrence of large ectopic beats. Note that ECGs in these examples were obtained by adding the simulated f-waves to non-AF ECG signals

The proposed method has a number of features that are illustrated by the signals displayed in Fig. 5.11. Rapid changes in QRST morphology are handled well, since the resulting atrial signal $\hat{s}(n)$ does not contain large residuals, see Figs. 5.11 a) and b). The short-term memory of the reservoir allows the ESN to remember previous QRST mor-

phology so that it can react properly to the subsequent beat. Figure 5.11 c) illustrates ESN performance when a number of large-amplitude ectopic beats occur, still producing an atrial signal with negligible ventricular residuals. The spectra corresponding to the atrial signal estimates displayed in Figs. 5.11 b) and c) show that the low frequency components associated with the ABS-produced signals are absent for the ESN.

The importance of the initial transient is investigated for the two methods. This issue is of interest, since it is sometimes necessary to perform ventricular activity cancellation in short recordings or when episodes of paroxysmal AF are subject to analysis having a duration of just a few seconds. Figure 5.12 illustrates how $\bar{E}$ decreases with time for the ESN and ABS, indicating that the ESN converges in about 1 s whereas the transient time of ABS is much longer.

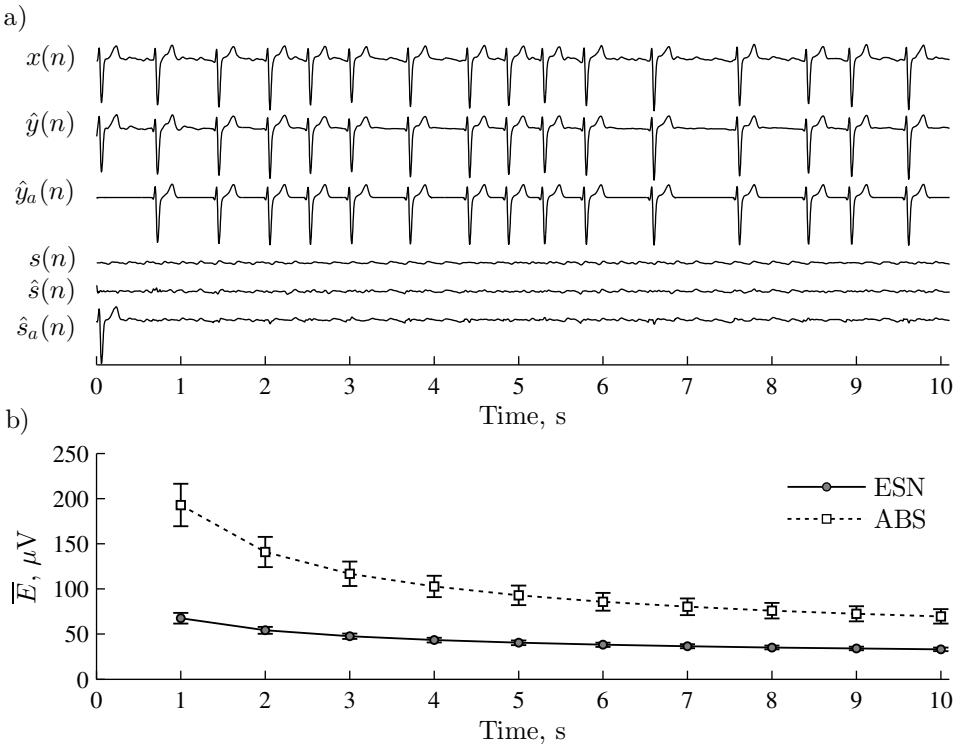

Fig. 5.12. a) The initial transient associated with the ESN and ABS. b) Initial transient statistics from analyzing the test set of 50 signals (f-wave amplitude is set to 30 μV), presented as mean$\pm$two-sided confidence interval. The results of the two methods differ significantly at all time instants ($p < 0.001$)

Figure 5.13 illustrates the performance of the ESN when ECGs recorded during AF are processed. Lead I or V_1 is subject to cancellation, whereas V_6 is used as the reference lead in both cases. Similar to the results obtained on simulated ECG signals, the ESN is capable of handling morphological beat-to-beat variability, as well as the presence of one single ectopic beat.

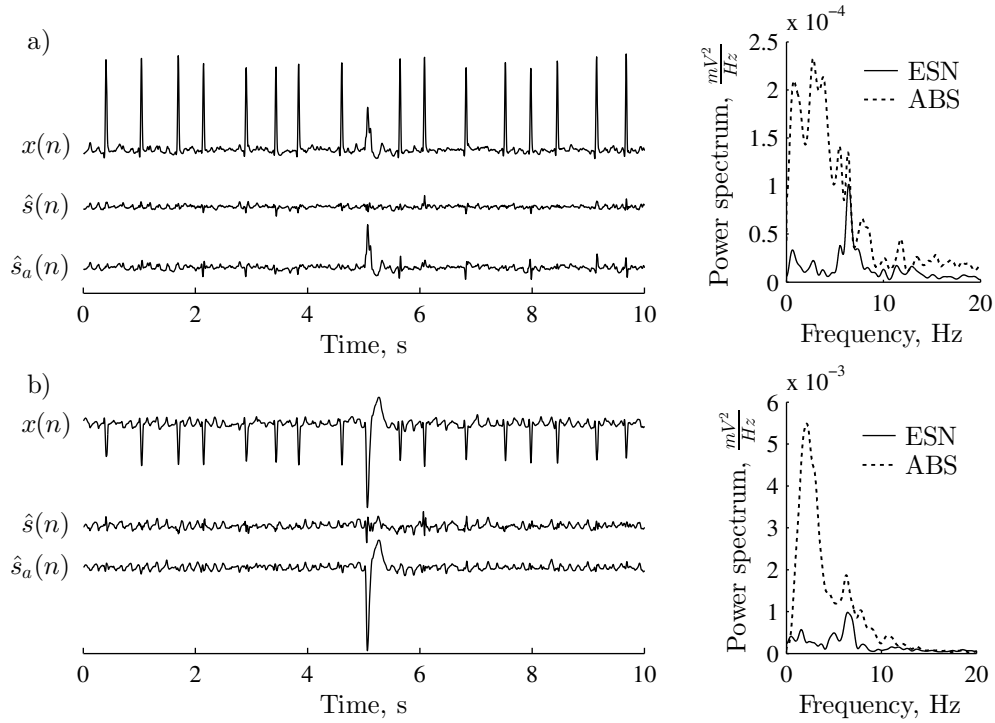

Fig. 5.13. Examples of atrial activity extraction in ECG signals recorded during AF ($x(n)$–lead with AF; $\hat{s}(n)$–f-waves estimated by the ESN; $\hat{s}_a(n)$–f-waves estimated by ABS), and the corresponding power spectra. The lead subject to f-waves extraction is a) I and b) V_1. Lead V_6 serves as the reference lead (not displayed)

5.3.4 Discussion

The present section explored the echo state network for atrial activity extraction during AF and represented, as such, one of the very first studies in biomedical signal processing. An important feature of the ESN is that only the output weights $\mathbf{w}_{\text{out}}(n)$ are subject to update during training, whereas the input weights and hidden weights are initialized once and for all, thereby leading to feasible computational requirements as discussed below. Since the ESN is characterized by a nonlinear transfer function, it offers more degrees of freedom in the adaptation process, which in turn, translates to better signal extraction.

The time domain performance measure is the RMS value $\bar{E}$ of the estimation error $(\hat{s}(n) - s(n))$. The normalized RMS error represents another measure that has been employed for evaluation of atrial activity extraction performance (Alcaraz and Rieta, 2008). However, this particular measure suffers from the disadvantage of being dependent on f-wave amplitude, i.e., performance improves only by increasing f-wave amplitude. In contrast to (Alcaraz and Rieta, 2008), where large f-waves were analyzed, the present study focuses on small f-waves, and therefore, the unnormalized RMS error is judged to be a more relevant performance measure.

The ESN exhibits similar performance irrespective of the degree of rhythm regularity, see Fig. 5.13 for an illustration of this property. The same observation does not apply to methods based on ABS because the samples at the boundaries of the beat average become increasingly unreliable as the rhythm becomes increasingly irregular. Another difference between the ESN and ABS based methods is that the latter one requires a sampling rate of about 1 kHz to avoid misalignment-related residuals, whereas the ESN performs well at 250 Hz.

The commonly used least mean squares algorithm for adaptation of the adaptive filter coefficients is unsuitable in this application because of its slow convergence (Jaeger, 2001). The much faster convergence offered by the recursive least squares algorithm is crucial to the analysis of ECG signals due to the rapid changes in beat morphology that may occur. Least squares pre-whitening was applied to improve the stability of the recursive least squares algorithm (Douglas, 2000).

The computational requirements of the proposed method depend on the amount of computations needed to update the ESN reservoir states and to implement the pre-whitened recursive least squares algorithm. Pre-whitening requires $4N^2 + O(N)$ multiplications per iteration (N being the number of coefficients in the output layer). The proposed method, which was implemented in Matlab (Mathworks Inc.) on a 2.6 GHz dual core processor, requires only about 300 μs to process one input sample. If a larger reservoir is needed for better performance than the one of the present study, which contains 100 neurons, the increase in computational demands can, to some extent, be compensated for by optimizing the reservoir via elimination of inefficient neurons (Dutoit et al., 2007).

5.4 Detection of brief episode paroxysmal atrial fibrillation

5.4.1 Data and performance measures

The dataset used for developing the proposed brief AF detector was a database previously described in (Stridh et al., 2004), with standard 12-lead ECGs from 211 patients clinically diagnosed with paroxysmal or persistent AF.

Due to the lack of annotated databases with brief paroxysmal AF, test signals were generated for performance evaluation. The starting point was a set of 100 ECGs selected from the PTB Diagnostic ECG Database (Bousseljot et al., 1995; Goldberger et al., 2000), containing signals from 50 healthy subjects and 50 patients with myocardial infarction, all with sinus rhythm and lasting for about 2 min. The original sampling rate of 1000 Hz was decimated to 250 Hz to alleviate the computational demands of the ESN. Leads V_1 and V_6 were selected as target and reference signals, respectively. The original ECG was then subjected to repeated concatenation until at least 1000 beats were included.

The capability of $\mathcal{N}$ to characterize noise, but not f-waves, was investigated using 100 5 s segments each of f-waves extracted from the AF database in (Stridh et al., 2004), and EMG noise extracted from the MIT–BIH Noise Stress Test Database (Moody et al., 1984). All 5 s segments were normalized with respect to their RMS value.

The principal performance measure is a classification ratio, denoted S, defined as the

number of correctly detected AF and SR episodes divided by the total number of episodes in a signal. Sensitivity is the number of correctly detected AF episodes divided by the total number of AF episodes, whereas specificity is the number of correctly detected SR "episodes" divided by the total number of SR episodes. An episode is considered to be correctly detected if the overlap between annotation and detector output is at least 50 %. The statistical results are expressed as mean$\pm$two-sided confidence interval (95 %). All statistical results are based on 100 test signals.

5.4.2 Parameter settings

All parameter values of the detector were determined through experimentation on ECG data, which were not part of the performance evaluation. In some case, the parameter values were identical to those used in previous sections.

Since the goal of the present work is to detect brief paroxysmal AF, the length of the sliding window was set to only $M_b = 5$ beats. The ESN was implemented using $N = 100$, $\lambda = 0.999$, $\alpha = 0.8$, and $D = 50$ ms. The PR interval was set to $(n_R, n_P) = (50, 250)$ ms when computing $\mathcal{P}$. The parameters $\mathcal{F}$ and $\mathcal{R}$ were computed using the values given in (Castells et al., 2005b) and (Lake and Moorman, 2011), respectively. The parameter $\mathcal{N}$ was computed with the integration interval $[\omega_{a,0}, \omega_{a,1}]$ set to $[3, 12]$ Hz, reflecting that the AF frequency is usually contained in this interval (Sandberg et al., 2008b), whereas the noise interval $(\omega_{n,0}, \omega_{n,1}]$ was disjunct and set to $(12, 125]$ Hz.

Table 5.4. The set of 16 fuzzy rules used for AF detection. The columns $\mathcal{R}, \mathcal{F}$, and $\mathcal{P}$ display combinations of fuzzified input values, and column $\mathcal{N}$ displays the fuzzified noise level. The rightmost column displays the linguistic output of the different rules, ranging from highly likely SR to highly likely AF.

No.	$\mathcal{R}$	$\mathcal{F}$	$\mathcal{P}$	$\mathcal{N}$	Linguistic output
1	SR	SR	SR	Low	SR3
2	SR	SR	SR	High	SR3
3	SR	SR	AF	High	SR2
4	SR	SR	AF	Low	SR2
5	SR	AF	SR	High	SR1
6	SR	AF	SR	Low	SR1
7	SR	AF	AF	High	SR0
8	AF	SR	SR	Low	SR0
9	AF	SR	SR	High	AF0
10	AF	SR	AF	High	AF0
11	AF	AF	SR	High	AF1
12	SR	AF	AF	Low	AF1
13	AF	AF	AF	High	AF2
14	AF	SR	AF	Low	AF2
15	AF	AF	SR	Low	AF3
16	AF	AF	AF	Low	AF3

A total of 16 fuzzy rules were used (see Table 5.4). The input membership functions

in (4.22) and (4.23) are defined by the parameters a and b, determining the extreme values of the functions. The following values were used: $(a, b) = (-3, 0.2)$ for $\mathcal{R}$, $(a, b) = (0, 0.6)$ for $\mathcal{F}$, $(a, b) = (0, 0.015)$ for $\mathcal{P}$, and $(a, b) = (0, 2)$ for $\mathcal{N}$. Equidistant locations were assigned to the Gaussian output membership functions in (4.24): $c_k = c_0 + k\Delta c$, $c_0 = 0$, $\Delta c = 0.143$, and $C = 8$; the motivation for choosing C is presented in Fig. 5.16. The set of linguistic outputs was defined by four values of SR and four values of AF, i.e., $\{0, 1, 2, 3\}$, that reflect the likelihood of SR or AF. For example, the output is labeled SR0 when SR is present with low likelihood, and AF2 when AF is present with rather high likelihood. The width σ was set to 0.061. The integration interval in (4.25) was set to $(y_{\text{min}}, y_{\text{max}}) = (-0.2, 1.2)$. It should be noted that the guiding-influence when designing the fuzzy rules is simple: more weight is assigned to $\mathcal{R}$ and less weight to $\mathcal{P}$ and $\mathcal{F}$ when the noise level $\mathcal{N}$ is high, and vice versa when low.

The detection threshold η was fixed and set to 0.5, a choice based on the distributions of $\mathcal{O}$ for SR and AF, see the results below.

5.4.3 Results of brief episode atrial fibrillation detection

Figure 5.14 illustrates the performance of the proposed detector: the two AF episodes are correctly detected, including the second episode immediately preceded by APBs and corrupted with EMG noise that drown the f-waves. It can be noted that $\mathcal{N}$ is large when noise is present, while it is close to zero when PQRST residuals and f-waves are present (as is the case during the first 15 s of the example).

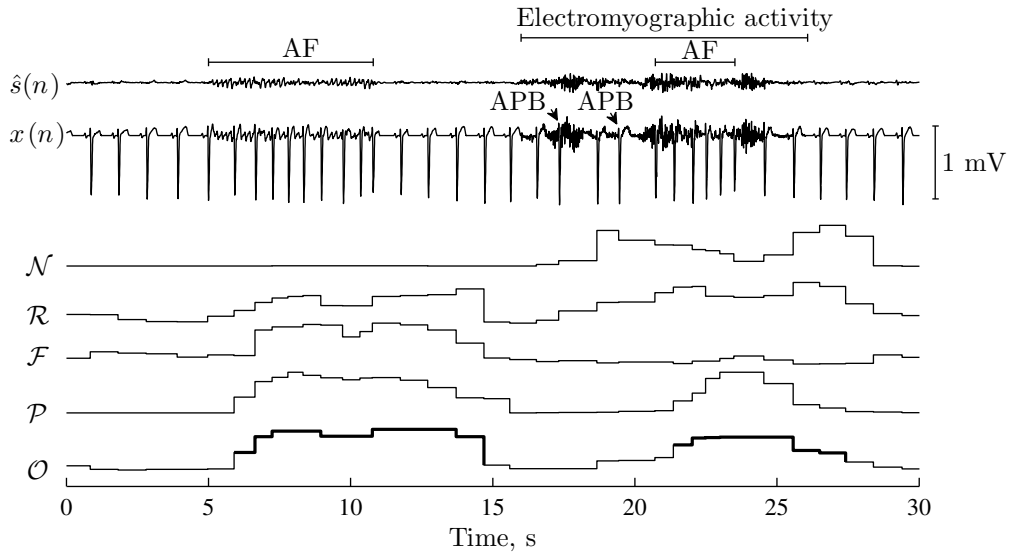

Fig. 5.14. The performance of the proposed detector is illustrated on an ECG with two brief episodes of paroxysmal AF. The first 15 s of the signal is noise-free, then followed by a 10 s burst of EMG noise. The second episode is preceded by two APBs. The output signal $\mathcal{O}$ is displayed with a thick line whenever the detection threshold is exceeded

To shed further light on how noise is characterized by the parameter $\mathcal{N}$, it was not only computed for EMG noise but also for f-waves to determine the extent by which f-waves influence $\mathcal{N}$. Figure 5.15 shows that $\mathcal{N}$ is proportional to the noise level, while it is essentially independent of f-wave amplitude.

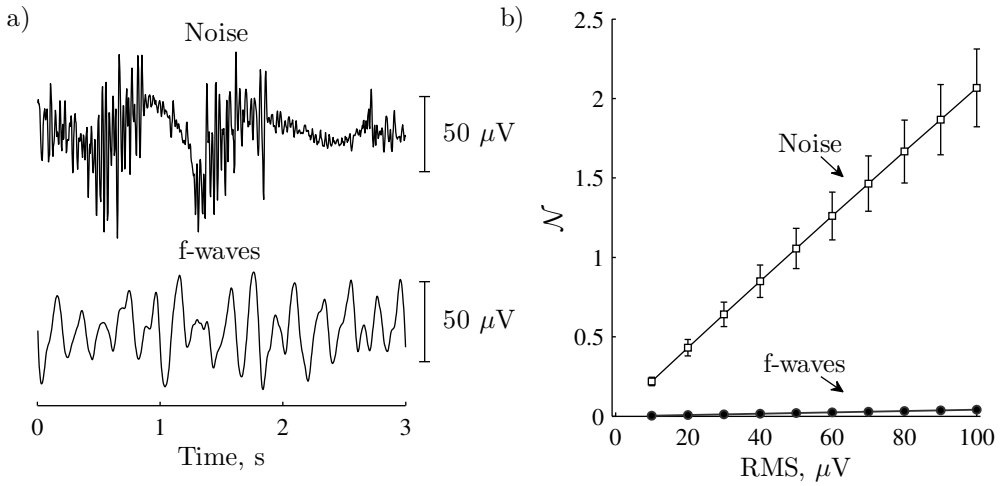

Fig. 5.15. a) Example of EMG noise and extracted f-waves. b) The parameter $\mathcal{N}$ computed for segments with EMG noise and f-waves

The range of each input membership function was determined by the distributions displayed in Figs. 5.16 a)–d), obtained from the AF database in (Stridh et al., 2004). While none of the parameters $\mathcal{R}, \mathcal{F}$, and $\mathcal{P}$ can individually discriminate AF from SR, Fig. 5.16 f) shows that their combination into $\mathcal{O}$, with $\mathcal{N}$ taken into account, offers excellent discrimination for $\eta = 0.5$. Figure 5.16 e) indicates that the classification ratio S is only mildly dependent on the number of linguistic outputs. Eight outputs were used, since no further improvement was obtained with additional outputs.

Figure 5.17 a) displays S as a function of noise level when episodes with random length are analyzed. In order to show the added value of different features, the following combinations were compared: $\mathcal{R}$, $(\mathcal{R}, \mathcal{P})$, $(\mathcal{R}, \mathcal{P}, \mathcal{F})$, and $(\mathcal{R}, \mathcal{P}, \mathcal{F}, \mathcal{N})$, i.e., $\mathcal{O}$.

The results show that the decrease in S for $\mathcal{O}$ is just 1 % when the noise level increases from 20 to 100 μV, and $\mathcal{O}$ performs better than $\mathcal{R}$ for all noise levels. The classification ratio of $\mathcal{R}$ is constant because the noise does not influence the r interval pattern through falsely detected or missed heartbeats. While $\mathcal{P}$ improves detection performance only for low noise levels (< 30 μV), the contribution of $\mathcal{F}$ remains significant up to a noise level of 90 μV. Figure 5.17 b) presents S as a function of noise level, but with 5 % of all beats being APBs. When comparing to the results in Fig. 5.17 a), it is obvious that the performance of all detectors deteriorate when APBs are present, however, the deterioration is more pronounced for $\mathcal{R}$ as S drops from 96.7 % to 88.1 %. The performance of $\mathcal{O}$ remains superior to $\mathcal{R}$, especially at low noise levels.

The requirement of a reference lead with negligible f-waves may be seen as a major

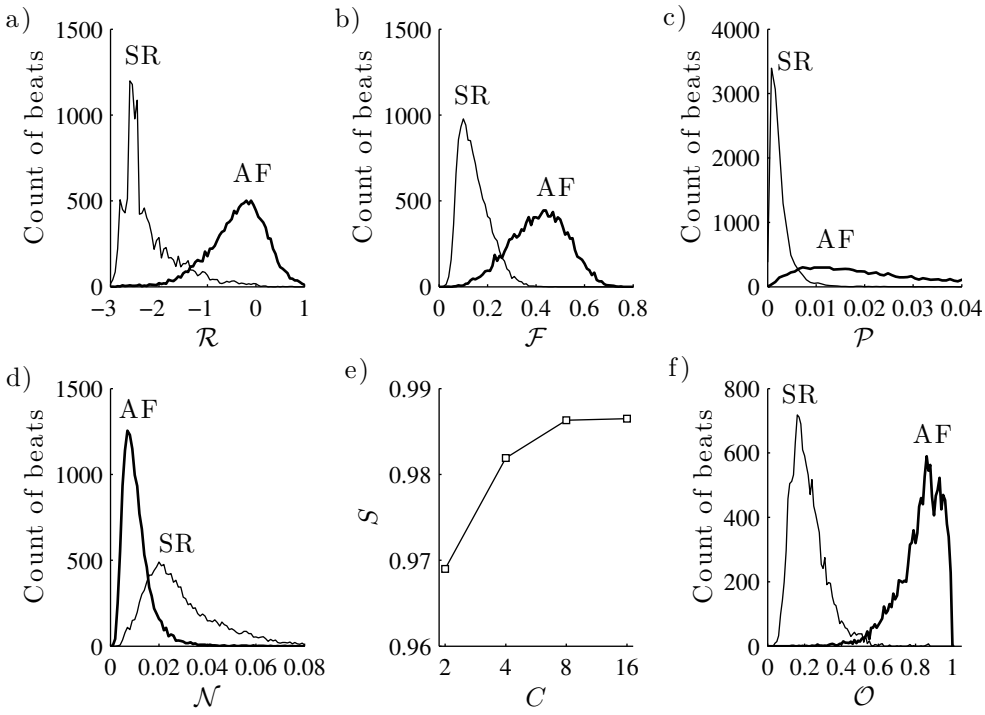

Fig. 5.16. a)–d) Distribution of the four fuzzy input parameters during SR and AF. e) Beat-by-beat classification ratio S as a function of the number of the linguistic outputs C. f) The resulting distribution of the output $\mathcal{O}$ for the number of linguistic outputs set to $C = 8$

limitation of the proposed method. The results in Fig. 5.17 c) indicate that increased f-wave amplitude in the reference lead V_6 does not deteriorate S when the amplitude in the target lead V_1 is 30 μV. When the amplitude in V_1 is very small, i.e., 10 μV, S drops from 99.1 % to 93.9 %.

Table 5.5 displays the performance of the proposed detector for an increasing number of beats in the paroxysmal AF episodes. The proposed detector was compared to the r-based detector in (Lake and Moorman, 2011), using the coefficient of sample entropy as decision parameter, denoted $\mathcal{O}_R$; the detection threshold used in (Lake and Moorman, 2011) was also used here. The results of Table 5.5 show that both $\mathcal{O}$ and $\mathcal{O}_\mathcal{R}$ are capable of detecting all AF episodes for the chosen threshold settings since the sensitivity is equal to 1. When no APBs are present, the classification ratio of $\mathcal{O}$ remains high (88.3 %) also for episodes with as few beats as 5. When APBs are present, $\mathcal{O}_\mathcal{R}$ has much lower specificity than $\mathcal{O}$.

The above results, obtained from a large set of test signals, are complemented by a number of ECG examples. Figure 5.18 a) illustrates that $\mathcal{O}$ has a shorter delay than $\mathcal{O}_R$ when detecting an AF episode. Figures 5.18 b) and c) illustrate that $\mathcal{O}$ is more robust to false alarms caused by sudden changes in the r interval series, here associated with either APBs or respiratory sinus arrhythmia.

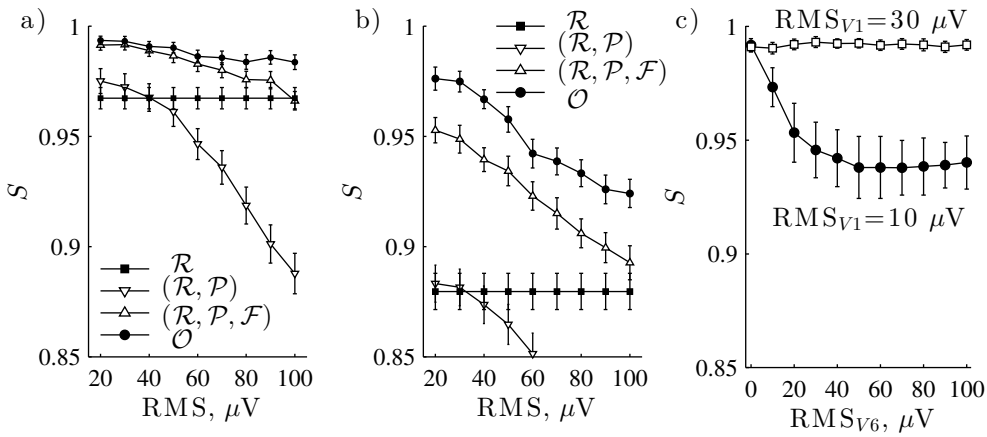

Fig. 5.17. Classification ratio S as a function of noise level when a) no APBs are present, and b) when 5 % of all beats are APBs. c) Classification ratio S as a function of f-wave amplitude in the reference lead V_6, presented for two f-wave amplitudes in the target lead V_1

Table 5.5. The influence of episode length on classification ratio (S), sensitivity (Se), and specificity (Sp) in the absence of APBs, and when 5 % of all beats are APBs. The noise level is set to 50 μV

APBs		Episode length								
		5 beats			10 beats			30 beats		
		$S,\%$	$Se,\%$	$Sp,\%$	$S,\%$	$Se,\%$	$Sp,\%$	$S,\%$	$Se,\%$	$Sp,\%$
No	$\mathcal{O}$	88.3	100	76.2	1.00	100	99.3	100	100	100
	$\mathcal{O}_R$	81.8	100	64.2	95.7	100	91.9	98.8	100	98.7
5 %	$\mathcal{O}$	80.1	100	59.3	92.1	100	85.2	99.2	100	99.1
	$\mathcal{O}_R$	76.2	100	52.1	82.8	100	66.2	93.0	100	87.1

5.4.4 Discussion

The goal of this work was to propose a reliable method for the detection of brief paroxysmal AF. With such a detector in long-term monitoring, information on the episode pattern can be produced, which may help to shed light on clinical challenges such as cryptogenic ischemic stroke. The synergy of the four parameters and the a priori knowledge built into the decision model (cf. Table 5.4) is the main reason why the proposed detector performs well. Yet, the structure of the present detector is simple, since r irregularity, P-waves, and f-waves are characterized by just one parameter each.

It has been shown that the success rate of catheter ablation is highly overestimated when determined from conventional 24 h Holter recordings. This issue can be addressed by considerably extending the monitoring period so that the likelihood of detecting AF episodes increases. However, existing techniques for continuous long-term monitoring reduce the patient's quality of life and often lead to premature termination of the data acquisition. While patient comfort can be improved by shrinking the size of the monitoring

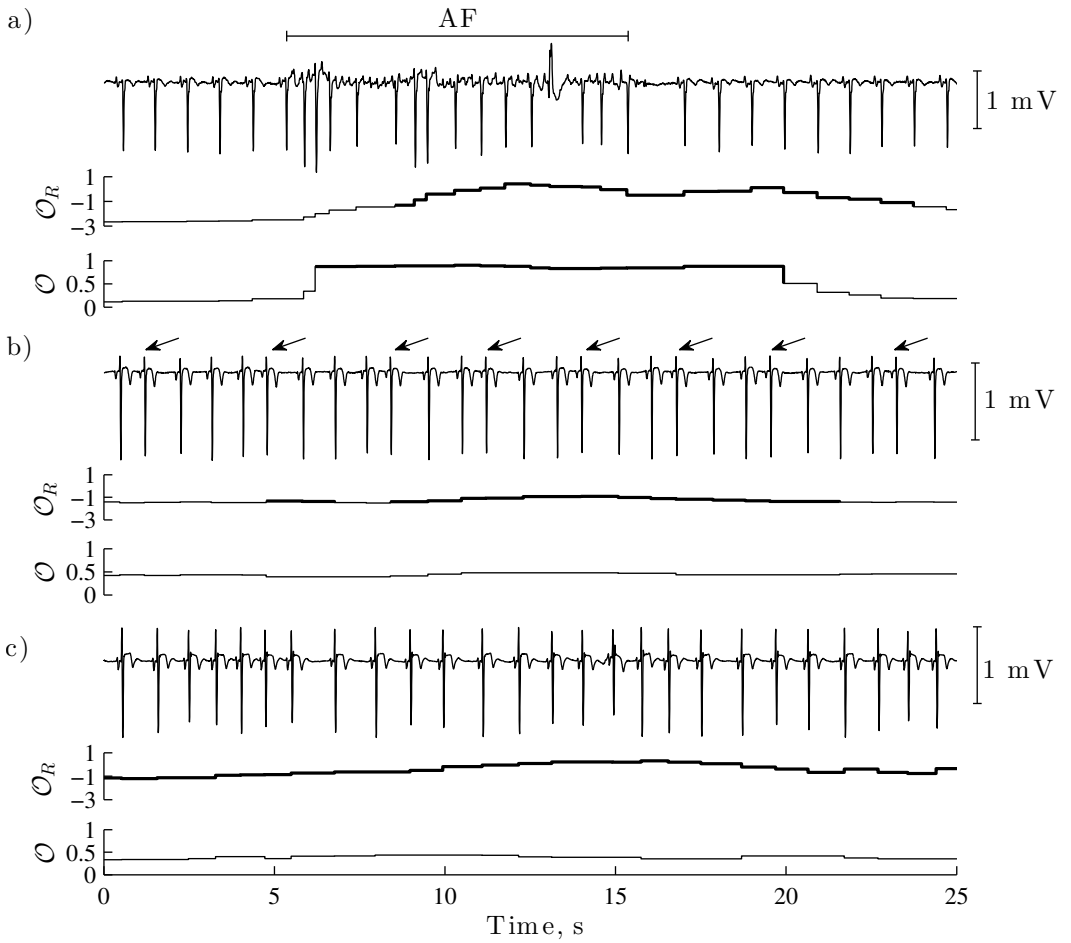

Fig. 5.18. Detection performance on ECGs with a) a brief paroxysmal AF episode, b) several APBs (marked with arrows), and c) respiratory sinus arrhythmia are analyzed. Note that b) and c) do not contain paroxysmal AF episodes. A thick line of the output indicates that AF is detected

device, using a smaller battery, large battery capacity is nonetheless needed in this type of monitoring, since battery replacement or recharging should be avoided. In order to detect paroxysmal AF episodes, novel patient-friendly diagnostic utilities for long-term ambulatory ECG monitoring have been proposed. Long-term, continuous non-invasive monitoring is likely to improve the AF detection rate, but considering the often poor signal quality, it is important to develop robust detectors that minimize the time for manual reviewing of the data.

Both the detector in (Carvalho et al., 2012) and the proposed detector make use of atrial information, though in quite different ways. Firstly, an f-wave signal can be extracted with the ESN when physiological disturbances, such as ventricular premature beats, are present, thereby precluding the need for ectopic beat detection. Secondly, the inclusion of noise level in the decision process allows the proposed detector to determine

whether $\mathcal{P}$ and $\mathcal{F}$ can be relied on. The detection of brief episodes was not addressed in (Carvalho et al., 2012), since most episodes of the MIT–BIH Atrial Fibrillation database are much longer than 30 beats, nor was the performance evaluated at different noise levels.

The proposed detector assumes that P-wave absence, f-wave presence and noise can be quantified from $\hat{s}(n)$. The feasibility of this assumption is illustrated by the following two examples. Noise appearing in the target signal is not cancelled by the ESN, but remains in $\hat{s}(n)$, see Fig. 5.19 a). On the other hand, noise present in the reference lead does not deteriorate f-wave extraction, see Fig. 5.19 b). Other techniques than the ESN may be considered for ventricular premature beats, i.e. averaged beat subtraction or spatiotemporal QRST cancellation. These cancellation techniques however suffer from the disadvantage of requiring many beats for averaging, and therefore do not perform well when occasional ventricular premature beats occur. For this reason, we promote the ESN for PQRST cancellation, since accurate f-wave extraction is required when the feature $\mathcal{F}$ is used.

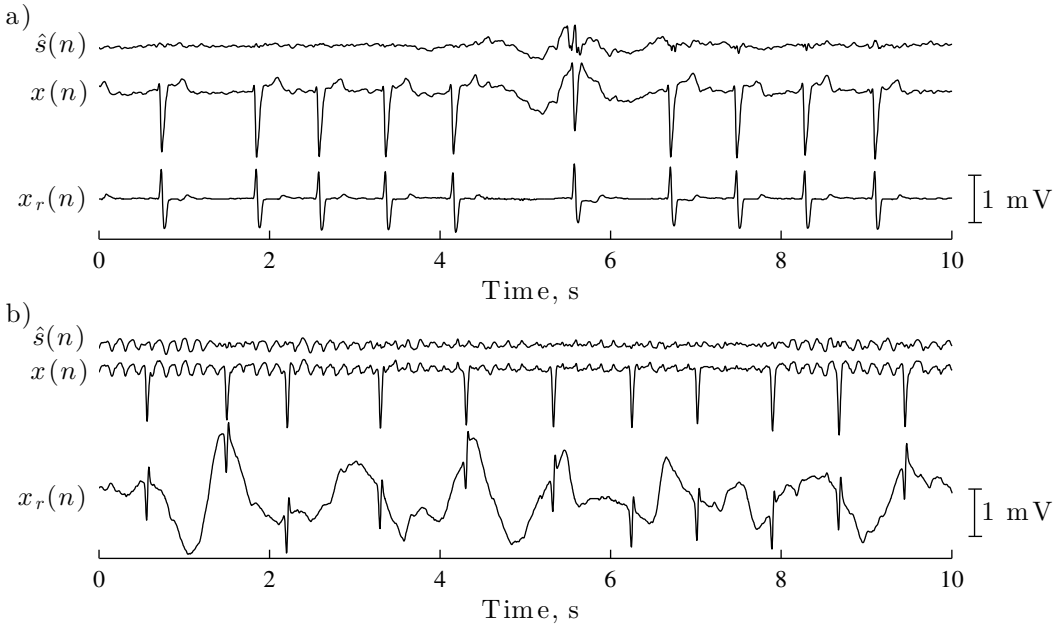

Fig. 5.19. Examples of f-wave extraction from an ECG when a) the target lead or b) the reference lead is noisy

The results show that the proposed detector is robust to noise (Fig. 5.17 a), performs well in the presence of APBs (Fig. 5.17 b) and can detect brief paroxysmal AF reliably (Table 5.5). The example in Fig. 5.14 suggests that the delay in detection is about 3 beats, and that an episode length of at least 5 beats is needed for detection. This example also suggests that the detector is already operational after 5 beats from the onset of the recording, and thus a lengthy initialization period is not required.

In a recent paper on ECG signal quality during arrhythmias, Behar et al. (2013)

explored skewness and kurtosis for noise quantification. These two parameters are not suitable though for signals with cancelled ventricular activity, and therefore a novel noise parameter $\mathcal{N}$ was proposed and tested. Still, the main insight of Behar et al. is also valid here, namely that signal quality parameters should be rhythm-specific.

The use of fuzzy logic is attractive, since basic knowledge on AF can be easily translated to a set of linguistic rules. The Mamdani-type fuzzy logic does not require training and its implementation is easily reproduced. On the other hand, the performance of an artificial neural network based detector depends on the training dataset and, as a consequence, its performance is likely to drop when noisy data is fed to the artificial neural network. The main challenge with fuzzy logic is the selection of appropriate membership functions and rules. Although the present choice of membership functions and rules was heuristic, the performance of $\mathcal{O}$ was still superior to that of $\mathcal{O}_R$. The number of linguistic outputs C and the detection threshold η are crucial parameters and were given special attention, cf. Figs.5.16 e) and f); the remaining parameters were determined heuristically from the development dataset.

Other decision techniques may be employed as well, i.e., linear discriminant analysis or artificial neural networks. However, a much larger dataset must then be used for training, especially when the noise level constitutes one of the input parameters, and therefore such techniques were not considered.

A limitation of the present work is that the proposed detector is not evaluated on an ECG database with brief paroxysmal AF. Since no such database is yet available with annotations, an approach with test signals has been pursued, which still provides valuable insight on performance. For example, the influence of noise can be investigated in situations when the noise level exceeds the f- and P-wave amplitudes. Although noise immunity is a central aspect in long-term monitoring of AF, it has not received much attention in the literature. It should be noted that the present type of test signals preserve the morphologic QRST variability of the original ECG and the relationship between different leads. An alternative approach to performance evaluation may be to consider a database with paroxysmal AF and manually "edit" all signals so that shorter episodes are created. However, the present approach offers better control of different signal properties and can produce signals with very challenging properties.

It is obviously desirable to involve more than two detectors in a performance comparison, however, detectors in the literature use window lengths of at least 30 s and are thus unsuitable for brief paroxysmal AF. Hence, a comparison of performance with these AF detectors, not designed to detect brief paroxysmal AF episodes, would be unfair and favor the present detector.

Furthermore, it should be noted that the proposed detector is developed exclusively for analysis of ECG signals. It is not applicable to paroxysmal AF detection in intracardiac signals, i.e., studied in (Pagana et al., 2012), since P- and f-wave information is explored.

5.5 Investigation of derived lead system for ambulatory monitoring of paroxysmal atrial fibrillation

5.5.1 Data and performance measures

Two groups of participants were enrolled in a study. The first group consisted of 41 healthy volunteers (16 women), 25.0 ± 5.9 years old, with body mass index of 22.2 ± 3.2 kg/m^2; this group performed certain types of physical activity so that noise immunity could be investigated in different leads. The second group consisted of 10 patients (4 women) with AF, 64.3 ± 8.5 years old, with body mass index of 30.0 ± 5.1 kg/m^2; this group did not perform any physical activity.

In order to investigate the peak-to-peak atrial amplitude, the healthy volunteers were asked to sit at rest for one minute. Then, they were instructed to perform two consecutive standardized physical activities that stimulate electromyographic noise and baseline wander, namely,

- holding a 1 kg weight with each straight arm horizontally when standing, and
- performing workout on an elliptical trainer.

The ECG was recorded simultaneously for each type of activity, using the Quark T12x Telemetry Stress Testing ECG recording device (Cosmed, Rome, Italy). The bipolar leads of the studied lead systems were obtained as a difference of the voltages recorded at the sites of the corresponding electrodes (Fig. 4.7).

The atrial and ventricular amplitudes were determined for each volunteer by finding the mean peak-to-peak amplitude in consecutive beats of 1 min ECG segments recorded at rest. Electromyographic noise was extracted by high-pass filtering (cut-off frequency at 15 Hz) of the signals recorded during rest and physical activity, followed by blanking of the QRS complexes in an interval of 200 ms centered around the R-wave (Welinder et al., 2004). Then, the root-mean-square value (ζ_{EMG}) of the high-pass filtered signal was computed. Baseline wander was extracted by low-pass filtering (cut-off frequency at 0.5 Hz) of the signals recorded during rest and physical activity, and quantified by the root-mean-square value (ζ_{BW}) of the low-pass filtered signal. The signal processing needed for parameter estimation is illustrated in Fig. 5.20.

The atrial amplitude (A_{AA}), the ventricular amplitude (A_{VA}), and the three ratios A_{AA}/A_{VA}, A_{AA}/ζ_{EMG}, and A_{AA}/ζ_{BW} were estimated for each lead. For AF patients, only amplitude-related properties were computed, thus excluding information on electromyographic noise and baseline wander. Since relatively large amplitude f-waves can be observed in the bipolar limb lead II (Nault et al., 2009), this lead was included for comparison. The mean peak-to-peak atrial amplitude was computed in individual f-waves present in the TQ interval so that the influence of ventricular activity was minimized. The overall results are expressed as mean and two-sided confidence interval (95 %).

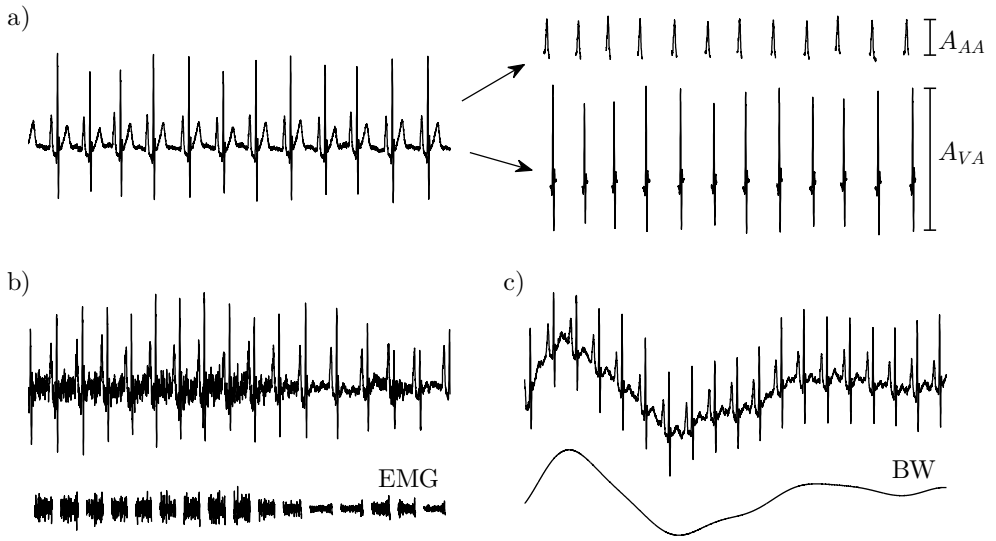

Fig. 5.20. Illustration of a) atrial and ventricular amplitudes (A_{AA} and A_{VA}, respectively), b) electromyographic (EMG) noise, and c) baseline wander (BW) for three different ECG signals

5.5.2 Properties of atrial and ventricular amplitude

Examples of ECGs recorded with different leads during rest and physical activity show that weight holding considerably increases the electromyographic noise level, while exercising on an elliptical trainer induces baseline wander, see Fig. 5.21. In addition, both L_1 and L_2 have much lower amplitudes than do the modified Lewis leads L_{M1} and L_{M2}.

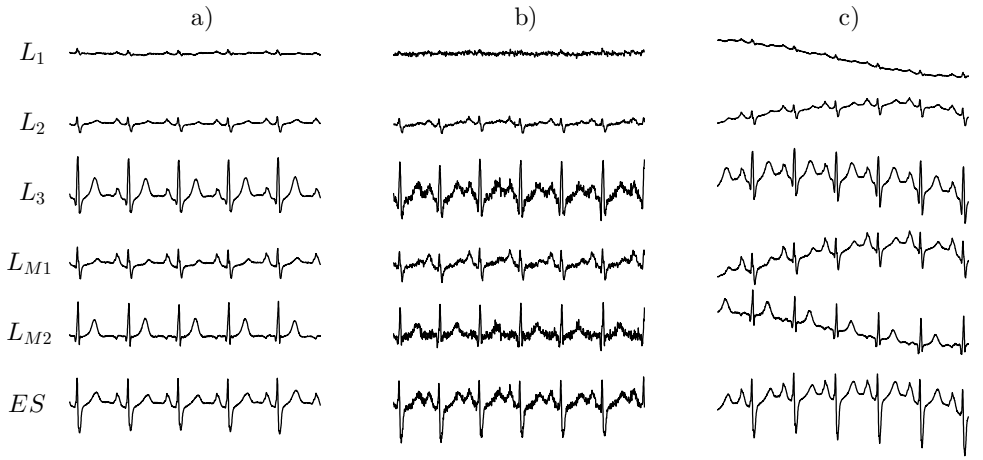

Fig. 5.21. ECGs recorded during a) rest, b) weight holding, and c) exercise on an elliptical trainer

Figure 5.22 a) shows that the atrial amplitudes (i.e., the P-waves) in L_{M1} and ES are nearly 3 times larger than in L_1 and L_2. However, due to the markedly suppressed

ventricular amplitude (Fig. 5.22 b), the Lewis leads produce the largest ratio A_{AA}/A_{VA} with 0.24 ± 0.04 and 0.23 ± 0.04 for L_1 and L_2, respectively (Fig. 5.22 c). Lead L_{M1} has a ratio A_{AA}/A_{VA} of 0.23 ± 0.04 which is similar to that of the original Lewis leads. However, the ratio A_{AA}/A_{VA} of ES is significantly lower (0.15 ± 0.02, $p < 0.001$).

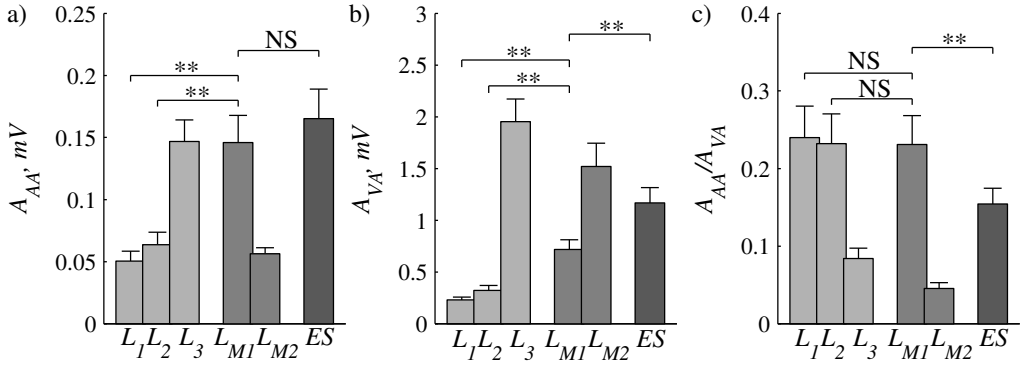

Fig. 5.22. a) Atrial amplitude A_{AA}, b) ventricular amplitude A_{VA}, and c) atrial-to-ventricular amplitude ratio A_{AA}/A_{VA} in healthy volunteers. The results are presented as mean $\pm$ CI (95 %); $* \; p \leqslant 0.05$, $** \; p \leqslant 0.001$, NS for $p > 0.05$

Figure 5.23 shows signals recorded with L_{M1} and L_{M2} during AF (Fig. 5.23 a) and atrial flutter (Fig. 5.23 b), both exhibiting transitions to sinus rhythm. It is obvious that L_{M1} has much larger atrial amplitude than does L_{M2}, both for AF and atrial flutter.

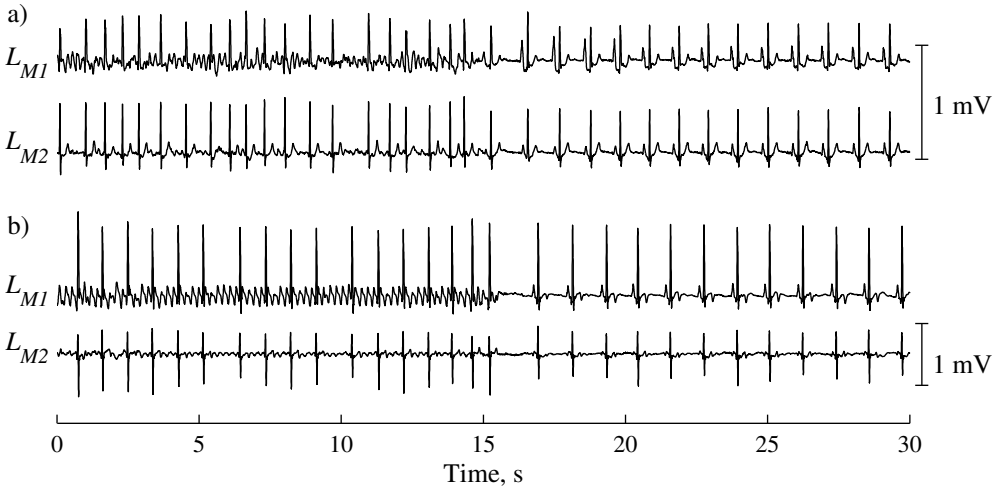

Fig. 5.23. Leads L_{M1} and L_{M2} recorded during a) AF and b) atrial flutter. In both examples, AF transitions into sinus rhythm at 15 s

Tables 5.6 and 5.7 show that A_{AA} and A_{AA}/A_{VA} exhibit similar tendencies for AF as for sinus rhythm. The atrial amplitude (i.e., the f waves) in L_{M1} is about 50 % larger than in lead II, being 0.15 ± 0.08 mV and 0.10 ± 0.06 mV, respectively, while the ratio A_{AA}/A_{VA} in L_{M1} is more than 3 times larger than in II ($p < 0.05$).

Table 5.6. Results from AF patients: atrial amplitude (A_{AA}, mV) in leads L_{M1}, L_{M2}, L_3 and II. The results are presented as mean $\pm$ CI (95 %)

Subject no.	L_{M1}	L_{M2}	L_3	II
1	0.16	0.06	0.16	0.08
2	0.29	0.04	0.14	0.05
3	0.11	0.02	0.10	0.09
4	0.13	0.04	0.11	0.11
5	0.31	0.05	0.30	0.20
6	0.05	0.02	0.04	0.02
7	0.02	0.02	0.02	0.02
8	0.22	0.07	0.15	0.11
9	0.02	0.02	0.02	0.02
10	0.19	0.08	0.19	0.25
Total	0.15 ± 0.08	0.04 ± 0.02	0.12 ± 0.06	0.10 ± 0.06

Table 5.7. Results from AF patients: atrial-to-ventricular amplitude ratio (A_{AA}/A_{VA}) in leads L_{M1}, L_{M2}, L_3 and II. The results are presented as mean $\pm$ CI (95 %)

Subject no.	L_{M1}	L_{M2}	L_3	II
1	0.31	0.03	0.07	0.08
2	0.23	0.03	0.06	0.02
3	0.08	0.02	0.06	0.04
4	0.42	0.11	0.20	0.15
5	0.24	0.06	0.19	0.07
6	0.12	0.02	0.03	0.01
7	0.04	0.01	0.01	0.02
8	0.27	0.06	0.11	0.10
9	0.02	0.01	0.01	0.01
10	0.43	0.13	0.18	0.16
Total	0.22 ± 0.11	0.05 ± 0.03	0.09 ± 0.05	0.07 ± 0.04

5.5.3 Influence of physical activity

The results show that L_2 has the lowest overall electromyographic noise level, while L_1 is twice as susceptible to electromyographic noise as is L_2 (see Fig. 5.24 a, weight holding). On the other hand, L_{M1} produces the largest ratio A_{AA}/ζ_{EMG}, being larger than the Lewis leads with statistical significance (Fig. 5.24 b). When compared to ES, L_{M1} has a larger ratio A_{AA}/ζ_{EMG} ($p < 0.05$) during weight holding, indicating that the main advantage of L_{M1} is achieved when the physical load increases.

Figure 5.25 demonstrates that the atrial-to-baseline wander level ratio A_{AA}/ζ_{BW} does not change significantly in any of the leads designed for enhanced atrial activity. Only L_{M2} exhibits a significantly lower ratio A_{AA}/ζ_{BW} than do the other leads ($p < 0.001$).

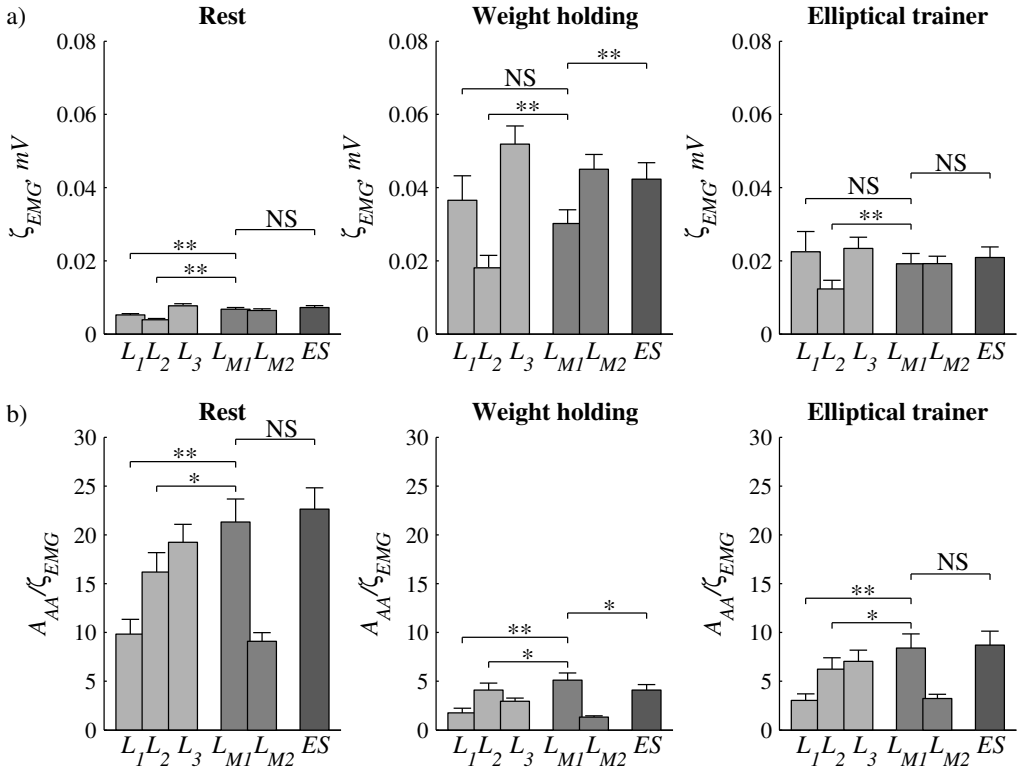

Fig. 5.24. a) Electromyographic noise level ζ_{EMG} and b) atrial-to-electromyographic activity ratio A_{AA}/ζ_{EMG} in healthy volunteers. The results are presented as mean $\pm$ CI (95 %); $*$ $p \leqslant 0.05$, $**$ $p \leqslant 0.001$, NS for $p > 0.05$

5.5.4 Discussion

Sir Thomas Lewis was the first to introduce ECG leads for the purpose of enhancing the atrial activity observed during atrial fibrillation (Lewis, 1913). Although the Lewis leads have been rarely used in clinical practice, the resulting signals may still have the potential to facilitate automated AF detection and analysis. The present study shows that L_1 and L_2 exhibit a high atrial-to-ventricular amplitude ratio, however, the enhancement of atrial activity is achieved at the expense of a much reduced ventricular amplitude, instead of an increased atrial amplitude, which is to be preferred. Hence, ECGs recorded with the Lewis leads are more susceptible to electromyographic noise. Despite that L_1 and L_2 are proximal, L_1 is twice as susceptible to electromyographic noise as is L_2, and therefore L_2 should be considered as the preferred lead. For long-term monitoring, where high noise levels may occur, the use of L_{M1} can be beneficial, since the results show that it has 2.5 times larger atrial amplitude than does L_2, therefore offering better immunity to electromyographic noise.

The last findings show that the largest amplitude of atrial activity is obtained when the distance between electrodes is 12-18 cm (Nedios et al., 2014). Depending on torso

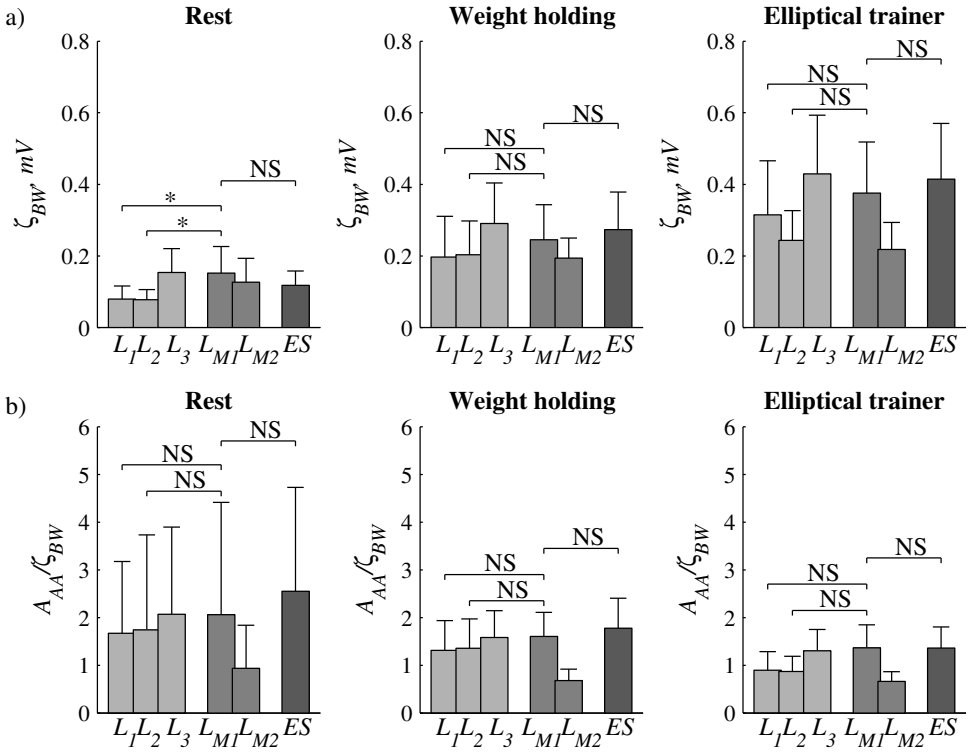

Fig. 5.25. a) Baseline wander level ζ_{BW} and b) atrial-to-baseline wander amplitude ratio A_{AA}/ζ_{BW} in healthy volunteers. The results are presented as mean $\pm$ CI (95 %); NS for $p > 0.05$

size, the distance between the electrodes of the modified Lewis lead L_{M1} was 14-20 cm, while the distance for the original Lewis leads L_1 and L_2 was less than half of this. Since the leads L_{M1}, L_1, and L_2 are roughly along the same axis with respect to the heart's electrical vector, differences in distance between electrodes may be the primary reason for an atrial amplitude which is 2.5 times larger in lead L_{M1} than in the original Lewis leads L_1 and L_2.

The modified Lewis lead system was developed for the purpose of enhancing atrial activity, and is thus unsuitable for evaluation of ventricular beat morphology, except for basic information such as the occurrence times of the R-waves. Since r interval irregularity, together with P-wave absence and f-wave presence, represent the key features of AF, L_{M1} is suitable for automated AF detection.

Leads L_{M1}, L_{M2} and L_3 of the modified Lewis lead system are obtained by using a standard ECG device with the Einthoven extremity leads I, II, and III. Lead L_{M1} is obtained by placing the right arm electrode over the upper end of the sternum and left arm electrode to the right side of the sternum at the 5^{th} intercostal space, thus the tracing observed in lead I is that of lead L_{M1}. Lead L_{M2} is obtained by placing the right leg electrode in the midaxillary line on the left side of the body at the level of the 5^{th} intercoastal space (the tracing observed in lead II is that of lead L_{M2}). Since L_{M1} and

L_{M2} form a triangle, the modified lead L_3 is computed by the recording device, and is observed in lead III.

The analysis of the f-waves in the surface ECG has been found useful for predicting intervention outcome, as well as for monitoring drug effects (Platonov et al., 2014). Typically, V_1 is used for f-wave analysis since this lead usually offers the largest f-wave amplitude. In addition, it has been shown that the "dominant" AF frequency in V_1 offers a good match to the fibrillatory frequency of the right atrium (Bollmann et al., 1998; Holm et al., 1998). While L_{M1} is associated with a much reduced ventricular amplitude, L_{M1} may be used for determining the dominant AF frequency. Considering that L_{M1} is closely positioned to the right atrium, the spectral content of the f-waves in L_{M1} "views" the AF originating in the right atrium. However, it remains to be shown how the dominant AF frequency of L_{M1} relates to the intra-atrial recordings.

In this study, standardized physical exercises for inducing electromyographic noise and baseline wander were applied for evaluating the noise properties of the different leads. Out of the many different types of exercises causing motion artifacts (Welinder et al., 2004; Kearney et al., 2007), weight holding and workout on an elliptical trainer were selected, since both these activities cause large alterations in the ECG signal. Although such high physical load is rare in daily life among the elderly, relatively intensive physical exercises were selected so that situations such as lifting heavy objects, jogging, or even brushing teeth could be simulated. However, realizing that intensive physical activity could be risky to perform for elder participants with AF, only the healthy volunteers were asked to perform physical exercises.

Similar to the study comparing the EASI and Mason-Likar ECG lead systems (Welinder et al., 2004), no significant difference was found between the atrial enhancing leads with respect to susceptibility to baseline wander. Only leads L_1 and L_2 of the original Lewis lead system were associated with lower baseline wander level during rest ($p < 0.05$). This result supports the assumption that variations in electrode impedance, induced by physical activity, are likely caused by physiological factors such as respiration and perspiration, and thus have a similar influence in all leads. However, the level of baseline wander is likely to be lower for ECG leads with smaller distances between the electrodes, i.e., L_1 and L_2.

The electrode placement of L_{M2} is common among the chest-strap monitors used for heart rate recordings and analysis. Interestingly, our study shows that such electrode placement gives the lowest ratios of A_{AA}/A_{VA}, A_{AA}/ζ_{EMG}, and A_{AA}/ζ_{BW}, and is thus the worst option for analysis of atrial activity. On the other hand, L_{M2} is associated with a 5 times lower atrial-to-ventricular amplitude ratio than is L_{M1}; this finding is important when f-wave extraction is performed employing an adaptive filtering approach (i.e. echo state network) where a lead with negligible atrial activity is required.

The major limitation of the study is the small number of AF patients, and the relatively young cohort of healthy volunteers, which preferably should cover a larger span of age.

5.6 Conclusions of the chapter

1. Five clinical databases containing electrocardiogram signals with AF, sinus rhythms and other arrhythmias were selected for developing and testing the performance of the proposed methods for AF detection. All AF databases contain mostly very long AF episodes ($\geqslant$ 30 s), thus are unsuitable for testing the performance of brief AF detection. Therefore, due to the lack of annotated databases with brief AF episodes, a simulation model based on real ECGs has been proposed. A simulation principle allows researchers to control essential properties of the simulated signals, i.e., AF episode duration, percentage of atrial premature beats, and noise level. The proposed paroxysmal AF simulation model is useful for quantitative evaluation of methods developed both for AF detection and atrial activity extraction.

2. Despite its very simple structure, the developed r-based detector performs better on the MIT-BIH Atrial Fibrillation database than do existing detectors, with high sensitivity and specificity (97.1 % and 98.3 %, respectively). The detector can be implemented with just a few arithmetical operations and does not require a large memory buffer, due to the short analysis window.

3. When compared to average beat subtraction, being the most widely used method for ventricular activity cancellation, the performance by an echo state network based atrial activity extraction algorithm is found to be significantly better, both in time and frequency domain. The estimates of dominant AF frequency are considerably more accurate for f-wave amplitudes $\leqslant$ 30 μV compared to the AF estimates based on average beat subtraction.

4. The results on brief AF detection show that episodes with as few as 5 beats can be reliably detected by the proposed brief AF detector with a classification ratio of 88.3 %, compared to 81.8 % for a detector based on rhythm information only (the coefficient of sample entropy); this difference in classification ratio increases when atrial premature beats are present. The results also show that the performance remains essentially unchanged at noise levels up to 100 μV RMS.

5. The derived modified Lewis lead has nearly 3 times as large atrial amplitude as the original Lewis leads, and is associated with 50 % higher atrial-to-ventricular amplitude ratio than that of the ES lead. Furthermore, the modified Lewis lead exhibits the best atrial-to-electromyographic activity ratio in healthy volunteers.

6 CONCLUSIONS

1. A low-complexity algorithm for detection of paroxysmal atrial fibrillation in continuous long-term monitoring devices has been developed. The proposed atrial fibrillation detector, despite its extreme simplicity, offers better performance than do the detectors described in the literature. An important feature of the detector is its use of a short window, only 8 beats, facilitating the detection of brief, subclinical atrial fibrillation episodes. The detector is particularly well-suited for implementation in a battery-powered device, i.e., an external or implantable event recorder, thanks to the very few arithmetical operations required for each r interval.

2. The echo state neural network based method for atrial activity extraction during atrial fibrillation has been developed. Based on simulated signals, as well as electrocardiogram examples with atrial fibrillation, the results demonstrate that the handling of small f-waves, substantial variation in beat amplitude and morphology, occasional ectopic beats, and short recordings are all strengths of the echo state network. When comparing performance to that of averaged beat subtraction, the echo state network is found to perform better for all considered cases, both when quantified in the time and frequency domain. The echo state network is suitable for implementation in a system which operates in real time, i.e., for long-term atrial fibrillation monitoring.

3. A method based on the combination of parameters characterizing atrial activity, ventricular activity, and prevailing noise level has been proposed for the reliable detection of brief episode atrial fibrillation. The results show that atrial fibrillation episodes as short as 5 beats can be detected, and the performance is essentially unchanged for noise levels up to 100 μV RMS. The proposed detector performs better than does the detector exploring the coefficient of r interval sample entropy, especially when atrial premature beats are present. The detector is expected to have clinical relevance since brief atrial fibrillation episodes can be reliably detected in asymptomatic cases and trigger an event recorder. The detector should also be suitable for integration in eHealth services where analysis of long-term recordings is offered.

4. Electrocardiogram lead configuration (the modified Lewis lead system) for ambulatory monitoring of atrial fibrillation has been derived. The modified Lewis lead offers the best atrial-to-electromyographic activity ratio and produces nearly 3 times larger amplitude of the atrial activity than the original Lewis leads. The results suggest that the proposed modification of the Lewis lead system has potential to improve ambulatory monitoring of atrial arrhythmias.

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LIST OF PUBLICATIONS ON THE SUBJECT OF THE DOCTORAL THESIS

Publications in the journals referred in the Thomson Reuters Web of Science database

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SL344. 2015-11-04, 17,5 leidyb. apsk. 1. Tiražas 10 egz. Užsakymas 395.
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