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# Atrial Electric Signal During Sinus Rhythm in Lone Paroxysmal Atrial Fibrillation

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ACADEMIC DISSERTATION

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## ABBREVIATIONS

| | |
|---|---|
| AF | atrial fibrillation |
| AP | action potential |
| BB | Bachmann bundle |
| BMI | Body mass index; weight (kg) / height $(m)^2$ |
| CS | coronary sinus |
| CSD | circular standard deviation |
| CV | caval vein, vena cava; coefficient of variation |
| EAM | electroanatomic map, electroanatomic mapping |
| ECG | electrocardiogram, electrocardiography, electrocardiographic |
| ERP | effective refractory period |
| FO | fossa ovalis, oval fossa |
| HR | heart rate |
| HRV | heart rate variability |
| IAB | interatrial conduction block |
| LA | left atrium, left atrial |
| LV | left ventricle, left ventricular |
| MCG | magnetocardiogram, magnetocardiography, magnetocardiographic |
| PAC | premature atrial complex |
| Pd | duration of filtered P wave |
| PV | pulmonary vein |
| RA | right atrium, right atrial |
| RMS | root mean square; root mean square amplitude |
| SAECG | signal average electrocardiogram |
| SD | standard deviation |
| SR | sinus rhythm |
| WPW | Wolf-Parkinson-White syndrome |

## ABSTRACT

The aim of this study was to find non-invasive parameters obtained during sinus rhythm (SR) reflecting electrophysiological patterns related to propensity to atrial fibrillation (AF) and particularly to AF occurring without any associated heart disease. This condition, called *lone atrial fibrillation*, is frequent among patients with onset of AF before middle age and appears usually as *paroxysmal.*

Overall 240 subjects were enrolled, 136 patients with paroxysmal AF and 104 controls. Mean age of the patients was 45 years and about three-fourths were male. Signal measurements were performed by non-invasive multichannel magnetocardiography (MCG) and by invasive electroanatomic mapping (EAM). All measurements were done during SR.

In a pilot study, 9 AF patients and 10 healthy subjects were investigated to evaluate recording and reproducibility of atrial depolarization signal in MCG. High-pass filtering techniques were adapted to analyze atrial MCG signal, and automated detection of onset and end of atrial signal was defined. Next, these techniques were applied to explore atrial electrophysiological properties in 80 patients with paroxysmal lone AF and 80 controls. Of particular interest in this study was to find whether any difference exists between those who have frequent triggers of AF (focal type) and those who do not. Atrial activation, especially propagation from right to left atrium (LA), was elucidated by EAM, and by MCG mapping. EAM was conducted in 55 patients with paroxysmal AF. Half of these patients also underwent MCG measurements. In MCG, a new analysis method based on a surface gradient technique was utilized and validated with EAM as a reference. The MCG method was applied also in a cohort of 107 lone paroxysmal AF patients and 94 controls to find possible differences in interatrial conduction pathways between patients and healthy subjects.

The results showed that MCG mapping is an accurate noninvasive method to detect atrial electrophysiologic properties in patients with AF and healthy subjects. The duration of the high frequency component of the atrial magnetic signal, representing atrial depolarization, and several parameters describing magnetic field strength during atrial activation could be measured automatically and with good reproducibility. The propagation of atrial signal could also be evaluated. In the time intervals applied, representing right atrial (RA) and LA activation, the MCG pseudocurrent angle seemed to represent the direction of propagation. Three MCG atrial wave types were identified, each of which represented a distinct interatrial activation pattern.

In patients with lone paroxysmal AF, duration of the atrial depolarization complex was marginally prolonged. This difference was more obvious in women than in men and was also related to interatrial conduction patterns. In the focal type of AF, the root mean square (RMS) amplitudes of the atrial signal were normal, but in AF without demonstrable triggers the late atrial RMS amplitudes were reduced. In addition, in paroxysmal lone AF

the atrial characteristics tended to remain similar, showing no obvious disease progression, even when examined several years after the first AF episodes.

The intra-atrial recordings confirmed the occurrence of three distinct sites of electrical connection from RA to LA: the Bachmann bundle (BB), the margin of the fossa ovalis (FO), and the coronary sinus ostial area (CS). High inter-individual variation in these connections was evident in patients with lone paroxysmal AF. In almost one-third of these patients, the activation was propagated from RA to LA during SR via routes other than BB. The variability in interatrial impulse propagation was reflected in atrial activation times.

Interatrial signal propagation was assessed also in healthy subjects. MCG mapping differed between patients with lone paroxysmal AF and controls. All three MCG atrial wave types occurred in both groups, but in different proportions and in patients, unexpectedly, not the CS type maps, but FO or multisite conduction maps were more common. Activation type was reflected in duration of atrial complex as seen in invasive studies. In the activation pattern related to the BB connection, the duration in patients was longer. In the FO or multisite conduction type, the duration was long both in patients and in controls.

In conclusion, in paroxysmal lone AF, active focal triggers are common, atrial depolarization is slightly prolonged, but with a normal amplitude, and the arrhythmia does not necessarily lead to electrical or mechanical dysfunction of the atria. In women the prolongation of atrial depolarization is more obvious. This may be related to gender differences in presentation of AF, for example, normal female atria may be less vulnerable to AF unless an additional pathologic process develops. A significant minority of patients with lone paroxysmal AF lack frequent focal triggers, and in them, the late atrial signal amplitude is reduced, possibly signifying a wider degenerative process in the LA. In these patients the atria may be more vulnerable and fibrillate with less provocation than occurs in patients with the focal type of AF. In lone AF, natural impulse propagation from RA to LA during SR goes through one or more of the principal pathways described. The BB is the most common route, but in one-third, the earliest LA activation occurs outside the BB. Susceptibility to paroxysmal lone AF is associated with propagation of the atrial signal via the margin of the FO or via multiple pathways. When conduction occurs via the BB, it is related to prolonged atrial activation. Thus, altered and alternative conduction pathways may contribute to the pathogenesis of lone AF.

Evidence is growing regarding variability in genesis of AF also within lone paroxysmal AF. The present study suggests that this variation may be reflected in cardiac signal pattern. Recognizing the distinct signal profiles may assist in understanding the pathogenesis of AF and identifying subgroups for patient-tailored therapy.

# 1 INTRODUCTION

> "have tremor cordis on me: my heart dances; but not for joy; not joy."
>
> *William Shakespeare. The Winter's Tale 1611*

*Atrial fibrillation* (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activity with deterioration of atrial mechanical function (Bellet 1971). It is the most common sustained tachyarrhythmia requiring treatment by a physician, and is associated with substantial morbidity, increased mortality and cost (Kannel et al. 1998, Benjamin et al. 1998, Vidaillet et al. 2002, Go et al. 2001, Maisel and Stevenson 2003, Wattigney et al. 2003, Stewart et al. 2002, 2004, Le Heuzey et al. 2004, Lehto et al. 2005). AF already affects an estimated 4 million people in Western Europe alone, and the number of AF patients is increasing (Go et al. 2001). The prevalence of AF is 0.4 to 1% in the general population (Feinberg et al. 1995, Kannel et al. 1998, Go et al. 2001), increasing with age to almost 9% in those over 80 (Furberg et al. 1994, Tsang et al. 2005). The number of men and women with AF is about equal, but for unknown reasons the incidence is greater in men (Feinberg et al. 1995, Humphries et al. 2001). More, particularly, in men the incidence is still growing (Friberg et al. 2003).

AF is designated as *paroxysmal* if the arrhythmia terminates spontaneously. When sustained beyond seven days, it is termed *persistent*. Both paroxysmal and persistent AF are *recurrent*. The AF of patients in whom cardioversion fails or is not attempted is classified as *permanent*. (Fuster et al. 2006) Patients initially presenting with paroxysmal AF often progress to longer, non-self-terminating episodes (Kerr et al. 2005). The rate for progression from paroxysmal to persistent AF is about 8% per year in general (Lévy et al. 1999). AF is commonly associated with cardiovascular disorders (Benjamin et al. 1994), but in up to 30% of patients, there is no evidence of heart disease (Evans and Swann 1954, Brand et al. 1985, Lévy et al.1999, Nieuwlaat et al. 2005, Ruigómez et al. 2005, Jahangir et al. 2007). This condition, called *lone atrial fibrillation*, is frequent among patients with onset of AF before middle age (Goudevenous et al. 1999, Lévy et al. 1999). In lone AF, the male dominance is pronounced (Evans and Swann 1954, Patton et al. 2005), the arrhythmia usually presents as paroxysmal (Lévy et al. 1999), and the tendency of the arrhythmia to progress to more permanent forms is much lower than in general in AF (Scardi et al. 1999, Jahangir et al. 2007).

AF is associated with an increased long-term risk of stroke, heart failure, and all-cause mortality (Atrial Fibrillation Investigators 1994, Krahn et al. 1995, Stewart et al. 2002). The mortality rate of patients with AF is about double that of patients in normal sinus rhythm (SR). The increased mortality is linked to the severity of underlying heart disease (Krahn et al. 1995, Lévy et al. 1999, Maggioni et al. 2005), but also in lone AF the outcome is not always benign (Scardi et al. 1999, Darbar et al. 2003, Osranek et al. 2005). For unknown reasons the outcome in women is worse than in men (Benjamin et al. 1998, Stewart et al. 2002, Rienstra et al. 2005). Importantly**,** independent of the type of AF or long-term risks, frequent symptomatic episodes of the arrhythmia can markedly worsen the quality of life (Bubien et al. 1996, Grönefeld et al. 2003, Patton et al. 2005). More

frequent and severe symptoms and equally depressed functional capacity have been reported in AF patients than in patients with moderate heart failure or prior coronary events (Dorian et al. 2000).

The genesis of AF varies. Paroxysmal AF is often initiated by fast-repeating atrial complexes originating from the pulmonary veins (Haissaguerre et al. 1998), whereas onset seems different in alcohol-toxic and vagally-induced atrial fibrillation (Maki et al. 1998, Steinbigler et al. 2003), and may differ among various heart diseases. Impaired conduction in atrial tissue is common in AF, but the contribution of this phenomenon to pathogenesis of AF is not fully characterized. Several clinical subgroups exist, such as exercise- and vagally-induced AF, familial AF, and AF related to conduction system disease and initial stages of cardiomyopathy (Patton et al. 2005, Fuster et al. 2006). The role of these components in an individual AF patient is, however, unclear.

The treatment modalities of AF have increased, but results are still far from optimal. Evidence is growing that more individualized AF therapy can be beneficial (Nattel 2002, Lewalter et al. 2006, Morady 2007). The best strategy to eliminate AF may be the accurate identification of one or more of the mechanisms critical to the genesis of AF and to target the specific mechanism(s) (Oral 2005). Aiming for this calls for improved diagnostics, and given the large number of patients with AF, a non-invasive approach is required.

Subtle features in cardiac signal could serve as markers of triggers or of substrate for AF. The ECG detects abnormalities in atrial signal in patients prone to AF. These include prolongation of atrial depolarization, altered P wave morphology, abnormal frequency content and increased spatial dispersion of atrial signal duration (Steinbigler et al. 2003, Fukunami et al. 1991, Platonov et al. 2000, Dilaveris et al. 1998). A large family with a high prevalence of lone AF and saddleback-type ST-segment elevation in leads $V_{1–3}$ has been described (Junttila et al. 2007). In another family with AF, the marked prolongation of P wave seemed to be a marker of genomic abnormality (Darbar et al. 2008a). Normal P wave duration has been related to vagal AF (Nemirowsky et al. 2008). However, mostly the signal features described have not been related to specific pathogenesis or mechanism(s) of AF.

*Magnetocardiography* (MCG) is a non-invasive method complementary to ECG to examine cardiac electromagnetic activity. MCG has morphological features similar to the P wave, QRS complex, and T- and U-waves of the ECG and the temporal relations between them are generally the same but the spatial orientation differs (Saarinen et al. 1978). In MCG, the currents tangential to the Bz component, which is perpendicular to the sensor surface and anterior chest, yield the strongest signal, whereas ECG is sensitive to radial currents. MCG can measure a close-looped current on the myocardium, while the ECG records it as a zero potential. MCG is also less affected by conductivity variations caused by the lungs, muscles, and skin (Plonsey 1972, Siltanen 1989). Thus, MCG may reveal abnormalities not detectable by ECG techniques explored thus far.

The objective of this study was to evaluate clinical characteristics of lone AF and to develop non-invasive methods to define propensity to AF. The ultimate target is the identification of AF subgroups in relation to pathogenesis of arrhythmia, in order to help to tailor an individual theraphy for the patients.

# 2 REVIEW OF THE LITERATURE

## 2.1 Atrial anatomy, conduction routes

The ingenious gross structure and myoarchitecture of human atria is critically important not only to the function of the atria, but also to their electrophysiology (Lesh et al. 1996). The normal activation of the atria can be explained by the geometric arrangement of atrial musculature. The conduction of impulses within the atria, rather than purely through radial spreading, takes place through preferential muscular bundles (Spach et al. 1969). In the atria pierced by several holes, the bundles represent the shortest route(s) from impulse origin to atrioventricular node and to interatrial connections (Andersson et al. 1981). Moreover, the bundles serve as the routes of the highest conduction velocity in the atria. In the atrial myocardium, the conduction velocity from cell to cell at a right angle to the myofibers (anisotropic conduction) is about 0.25 m/s and longitudinally the double of that, 0.5 m/s (Roberts et al. 1979). Along specialized bundles with muscle fibers arranged in parallel the conduction velocity is 1.5 m/s, or even higher (Hayashi et al. 1982).

### 2.1.1 Gross anatomy and myoarchitecture

The two atrial cavities of the human heart are muscular sacks, each with a volume 40 to 100 ml (Keller et al. 2000). Both atria have several obstacles, a venous component, the vestibule, an appendage, the common septum, and the adjacent walls between the chambers. Topographically (the nomenclature here follows the recommendations for standard anatomic terminology; Cosío et al. 1999), viewed from the front, the right atrium (RA) is positioned to the right and anterior, while the left atrium (LA) is situated to the left and posterior (Figure 1). The front of the LA lies behind the aortic sinuses, and the posterior wall is just in front of the tracheal bifurcation. The right superior pulmonary vein (PV) passes posterior to the superior caval vein (CV), with the right inferior PV passing behind the venous sinus of the RA. The atrial septum runs obliquely from the front posteriorly and right. (Ho et al. 2002)

In the RA, the venous sinus is the posterior smooth-walled component which receives the superior and inferior CVs and the orifice of the coronary sinus (CS). Externally it extends between the interatrial groove and the terminal groove lateral to the superior CV. The triangular-shaped appendix of the RA is anterolateral to the superior CV. The PVs join the posterior part of the LA, the orifices of the left PVs being located more superior than are those of the right PVs. The CS is related posterior and inferior to the LA. It occupies the left atrioventrocular groove. The vein of Marshall extends from the area between the left superior PV and the LA appendix and runs inferiorly to join the CS. In most subjects, this vein is obliterated. The LA appendix is located in the anterolateral part of LA inferiomediate to the left superior PV.

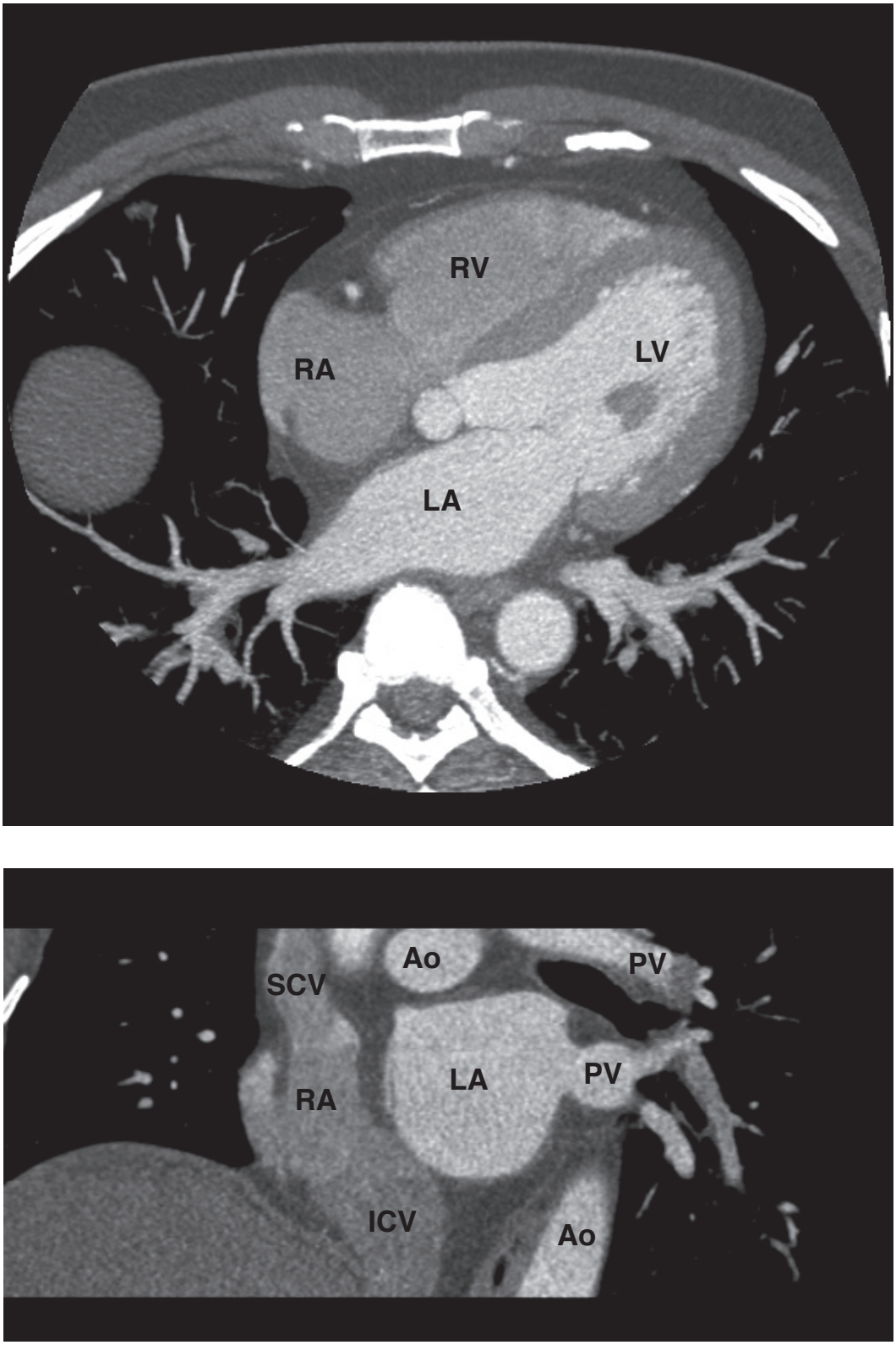


**Figure 1.** *Computer tomograph showing topography of the atria. Transaxial (upper) and transsagittal (lower) plaine in the middle portion of the atria. The left atrium (LA) is located posterior to and slightly more left and superior to the right atrium (RA). Ao, aorta; ICV, inferior caval vein; LV, left ventricle; RV, right ventricle; SCV, superior caval vein. Sari Kivistö (2008) with permission.*

The atrial walls consist of one to three or more overlapping layers of differently aligned myocardial fibers and bundles, with regional variations in thickness from 3 to 8 mm in the RA and from 3 to 5 mm in the LA (Wang et al. 1995, Ho et al. 1999). In patients with a history of AF, the LA posterior wall is generally thinner than in controls (Platonov et al. 2008). Local variations and a mixed arrangement of fibers are common (Wang et al. 1995).

The most prominent bundle in the RA is the *terminal crest*. It extends in a C-shape from the anteromedial wall of the RA, passes anterior to the orifice of the superior CV, and continues downward on the right of the CVs and merges inferiorly near the orifice of the CS. Other bundles are the *circumferential annular bundle* and the *external cirumferental bundle* (the right extremity of the Bachmann bundle, (BB), and the more internal *oblique intercaval bundle*. The oblique bundle extends from the terminal groove, running lateroposterior to the posterior interatrial groove. (Wang et al. 1995)

In the LA, the most prominent bundle is the *left extremity of the BB*. Others are the *longitudinal septoatrial bundle,* which extends from the anteroinferior margin of the septum to the mitral ring, and *septopulmonary bundle*. The septopulmonary bundle rises from the anterosuperior septum and sweeps superior to it, becomes mainly longitudinal, branches to pass around the insertions of the PVs, and then branches into two oblique fascicles which fuse with the superficial circular bundle. (Wang et al. 1995)

The true atrial septum consists mainly of the flap valve of the oval fossa (FO), a fibrous structure with a muscular circumference and floor. The fossa has a well-marked rim of muscle. The inferior part of the rim (sinus septum), separates the orifice of the CS from that of the inferior CV. The extensive musculature seen anteromedial and superior, is the infolding wall of the atria behind the aorta and between the superior CV and the right PVs. The peripheral fibers in the anterosuperior rim extend toward the origin of the terminal crest. (Wang et al. 1995) The fibers in the anterior rim combine with fibers from the apex of Koch's triangle and the eustachian ridge (Janse et al. 1993). Fibers in the posterior rim blend into obliquely arranged fibers of the intercaval bundle which covers the epicardial surface of the venous sinus between the interatrial groove and the terminal groove (Wang et al. 1995).

### 2.1.2 Interatrial connections

Despite the true, relatively small, real septum, the muscular continuity between the atria consists of bridges in the subepicardium. The most prominent muscular bridge is the BB (also called the interatrial bundle and interauricular band). This bundle extends from the right of the orifice of the superior CV or the atriocaval junction and crosses the superior CV and the anterior wall of the LA transversely until it approaches the left appendage, where it divides into upper and lower branches encircling the mouth of the appendage. Smaller interatrial bundles alongside the BB crossing anterior to the interatrial groove are common (Ho et al. 1999). Other bridges are sometimes present posteriorly, joining the LA to the intercaval area on the right and to the insertion of the inferior CV, and providing the potential for a posterior breakthrough of the sinus impulse. Inferiorly, further muscular

bridges from the LA wall run into the wall of the CS, providing further pathways of conduction between the RA and LA (Ho et al. 2000, Chauvin et al. 2000, Platonov et al. 2002, Mitrofanova et al. 2005).

The high inter-individual variation in all these connections including the BB is marked. One study of human hearts reported the BB in only 55% of cases in histological sections, and macroscopically visible anterior bundles were visible in only 29% of the specimens (Mikhailov and Chukbar 1982). In a post-mortem study of Platonov and coworkers (2002), no BB was present in 53% of the hearts.

## 2.2 Atrial activation during sinus rhythm

### 2.2.1 Origin of the sinus impulse

The origin of the sinus impulse has been located in the specialized tissue in the groove formed by the junction of the superior CV and the RA atrium (Keith and Flack 1907). This sickle-shaped 1- to 2-cm long, 0.5-cm wide and 3-mm thick intramural structure is designated the sinus node. Later studies have shown that this node is composed of several different cell types embedded in a complex mesh of collagen fibers. The node is histologically distinguishable from the surrounding myocardium, but is not insulated from it. The margins of the node are irregular, with multiple radiations interdigitating with the atrial myocardium. (Sánchez-Quintana et al. 2005)

It was generally accepted that the site of the normal impulse origin is a single static focus within the sinus node. Early on, conflicting data suggested that the site of the sinus node can vary and also that inside the node the focus is not static. Boineau and coworkers (1988) found that although the sinus node is normally located in a relatively limited area in the high posterolateral RA, its location can vary within a 7.5 x 1.5 cm area along the RA-CV junction. These findings have been confirmed by other groups (Cosío et al. 2004, Lemery et al. 2007). In most human hearts, the node is more an epicardial than endocardial structure. In a study by Sánchez-Quintana and coworkers (2005), the whole nodal body was subepicardial in 72% of the specimens, and in 28% it was located at least partly subendocardially. In concordance with this anatomical variance, the first activation in the RA was detectable epicardially earlier than endocardially in three of ten patients (Lemery et al. 2007). Both the site of the dominant pacemaker within the node as well as the signal exit from the node can vary and are influenced by autonomic tone (Bromberg et al. 1995). In the sinus node region the shift of impulse initiation alters with increasing rate upwards and with decreasing rate downwards (Jones et al. 1978, Boineau et al. 1988). The changes in impulse origin are reflected also in P wave morphology (Brody et al. 1967, Gomes and Winters 1987, Boineau et al. 1988).

### 2.2.2 Right atrial activation

After having been initiated at the superior posterolateral aspect of the RA, the sinus impulse propagates throughout the atrium along the posterior wall and medially toward the LA, and ends along the CS and the tricuspid valve (Boineau et al. 1988, Smeets et al. 1998). In addition to these main activation fronts, the signal also proceeds upward towards the orifice of the superior CV (De Ponti et al. 2002, Luo et al. 2003). Lemery and coworkers (2007) found the first activation to be more anterior or more septal in 12% of their patients. Lower points of origin have also been demonstrable (Boineau et al. 1988, Cosío et al. 2004). These low origins have been related to more horizontal or collided activation of the RA. However, in more than 90% of cases the propagation of the activation of the anterior and paraseptal RA walls has been descending.

### 2.2.3 Interatrial conduction

The superior interatrial route, the BB, has traditionally been considered a major pathway for fast interatrial activation spread (Bachman 1916). In addition, the muscular continuity between the atria is formed also via small anterosuperior and posterior muscle bridges, such as the margin of the FO and as myocardial inflow to the CS (Wang et al. 1995, Chauvin et al. 2000, Ho et al. 2002). All of these are potential pathways for signal propagation from the RA to LA. However, little evidence exists in regard to the electrical function of these connections in humans.

Roithinger and coworkers (1999) showed three distinct sites of early RA activation both during LA pacing and during distal CS pacing. These sites were in accordance with the BB, the margin of the FO, and the area of the orifice of the CS. In a subsequent non-contact mapping study by Calò and coworkers (2002), pacing from the LA revealed the earliest RA activation in these same three areas. The preferential routes of conduction were related to the sites of stimulation and were not influenced by pacing cycle length. The bidirectional electrical connection between CS and LA in humans was verified by Oral and coworkers (2003). Interestingly, after disconnection of the CS from the LA, the P wave duration in lead II increased from its baseline value by 10 ms. Right-to-left conduction via the CS route was first shown in the dog (Antz et al. 1998) and then confirmed in humans. In a study by Lemery and coworkers (2004) CS conduction was demonstrated in 10% of AF patients during low lateral RA pacing, but not during SR or high RA pacing. In another study, the conduction across the CS ostium could be measured also during SR (Xia et al. 2004). This conduction was observable in all study patients, but the velocity was significantly slower in patients with AF than in patients with other atrial arrhythmias. Right-to-left conduction via the margin of the FO during SR was demonstrated by Markides and coworkers (2003). This activation pattern was found in 10% of AF patients examined in a LA mapping study.

As yet, interatrial conduction has been addressed in only eight studies using LA mapping (electroanatomical contact mapping, four; non-contact mapping, four; Table 1).

Overall, these studies included 136 patients: 8 Wolf-Parkinson-White syndrome (WPW) patients and 128 AF patients.

**Table 1.** *Function of interatrial connections during sinus rhythm in humans. Overview of studies using left atrial mapping.*

| *Study* | *No of patients* | *Mean age (years)* | *Diagnosis* | *Mapping technique* | *Conduction via BB (%)* | *Conduction via posterior/inferior connections (%)* |
|---|---|---|---|---|---|---|
| Smeets *et al.* 1998 | 1 | 48 | WPW | Electro-anatomical | 100 | 0 |
| Hindricks *et al.* 2001 | 17 | 49 | Paroxysmal AF | Non-contact | 100 | 0 |
| De Ponti *et al*. 2002 | 7 | 37 | WPW, no AF | Electro-anatomical | 100 | 71 |
| Markides *et al*. 2003 | 19 | 55 | Paroxysmal AF | Non-contact | 37 | 63 |
| Lemery *et al*. 2004 | 20 | 54 | Paroxysmal AF | Non-contact | 100 | 0 |
| Betts *et al*. 2004 | 9 | 46 | Paroxysmal AF | Non-contact | 22 | 78 |
| Lemery *et al*. 2007 | 35 | 56 | Paroxysmal or persistent AF | Electro-anatomical | 88 | 93, CS |
| Holmqvist *et al.* 2008 | 28 | 49 | Paroxysmal or persistent AF | Electro-anatomical | 64 | 54, near FO 4, CS 7, multisite 43 |

*AF, atrial fibrillation; CS, coronary sinus; FO, fossa ovalis; WPW, Wolf-Parkinson-White syndrome.*

Of these studies, five reported conduction over the BB bundle during SR in the vast majority of the individuals studied (Smeets et al. 1998, Hindricks et al. 2001, De Ponti et al 2002, Lemery et al. 2004, 2007). Two of these five studies, in addition to conduction via BB connection, also reported a second route in most of their patients (De Ponti et al. 2002, Lemery et al. 2007). The other three studies documented an inferior route and connection at the area of the FO margin that may also serve as predominant routes for signal propagation from the RA to LA (Markides et al. 2003, Betts et al. 2004, Holmqvist et al. 2008), suggesting that the importance of the BB bundle may have been overestimated.

Conductivity can vary intra-individually and is possibly rate-dependent (Caló et al. 2002, Markides et al. 2003). In addition, the site of impulse origin may affect the choice of the propagation route (Boineua et al. 1988, Lemery et al. 2004). This has recently been confirmed for LA focal tachycardias originating from the PVs ostia that propagate to the RA predominantly via the posterior interatrial connections and not via the BB (Dong et al. 2005). Computer models have supported this (Harrild et al. 2000). A shift in LA activation site has been demonstrated also during SR (Markides et al. 2003). In anatomic studies, the muscle bands show considerable interindividual variability (Mikhailov and Chukbar 1982, Chauvin et al. 2000, Platonov et al. 2002, Mitrofanova et al. 2005).

Overall, these studies suggest conduction over the BB to be the most common activation pattern during SR. However, other routes are also demonstrated either in conjunction with the BB or independent of the BB route. Except for two small studies (Smeets et al. 1998, De Ponti et al. 2002), including altogether eight WPW patients, LA mappings have been performed on patients admitted for ablation of AF. Electrophysiology of normal interatrial conduction in healthy humans thus still remains largely unexplored.

### 2.2.4 Left atrial activation

The signal propagation in LA is reported to be primarily leftward and superior to inferior (Boineau et al. 1988, Canavan et al. 1988, Smeets et al. 1998, Markides et al. 2003, Betts et al. 2004). The excitation occurs as two or three wavefronts colliding at the area of the last activation (Boineau et al. 1988, Harrild and Henriquez 2000). Lines of conduction block or delay in the posterior wall of the LA, most commonly between the right upper and lower PVs extending inferior to the mitral valve annulus, have been described in two non-contact mapping studies (Markides et al. 2003, Betts et al. 2004). In the study of Markides and coworkers (2003), the LA activation during SR proceeded both septally and laterally from the point(s) of earliest breakthrough: In 79% of patients, the line was complete, and excitatory wavefronts propagating septally could not cross the interatrial septum in a craniocaudal direction; wavefronts propagating laterally wrapped around the lateral LA before turning inferoseptally to complete LA activation near the posteroseptal mitral valve annulus. In the remaining 21% of patients, the septal part of the line was incomplete, allowing craniocaudal wavefront propagation along the interatrial septum. LA activation was completed with a collision of wavefronts in the posterolateral LA. Findings in the other study supported this (Betts et al. 2004).

During proximal CS pacing the LA breakthrough occurred on the opposite side of the line of conduction block compared with SR and RA pacing. As a result, when the line of conduction block was complete, the activation sequence of the LA was reversed compared with SR, with latest activation at the roof anterior to the right superior PV ostium (Markides et al. 2003).

The influence of breakthrough site upon LA activation pattern is not well established as yet. The site of RA pacing influencing choice of interatrial route has been shown to have an influence also on LA activation time (Markides et al. 2003, Lemery et al. 2004).

### 2.2.5 Atrial activation times

Few studies have reported atrial activation times during SR. Most are the same as listed in Table 1, i.e., measurements have been done in patients with various arrhythmia histories. In these studies using a variety of techniques, the mean RA activation time has been approximately 70 to 100 ms, LA activation time 65 to 100 ms, and total atrial activation time 110 to 120 ms (Boineau et al. 1988, Canavan et al. 1988 Smeets et al. 1998, Markides et al. 2003, Cosio et al. 2004, Lemery et al. 2004, 2007, Cheung et al. 2007).

Longer times have also been recorded; the total atrial activation time was 132 to 195 ms in a study by Okamura and coworkers (2007). Once the RA has begun to activate, the first signal in the LA has been detected in 26 to 41 ms (Markides et al. 2003, Lemery et al. 2004, 2007). Cheung and coworkers (2007) reported a longer LA activation time in patients with persistent AF than in patients with paroxysmal AF. Another study showed that the LA activation was longer in patients with AF or atrial flutter than in patients with other atrial arrhythmias (Cosio et al. 2004).

In a computer model using BB and FO connections, the RA was activated totally by 100 ms (Harrild and Henriquez 2000). The first activation in the LA was at 30 ms, the FO area was activating at 40 ms, and the atrial activation was completed at the mitral annulus in the lateral inferior LA at 108 ms. In the same study, a paced model with a stimulus applied to the RA appendix, the time for entire RA activation was 116 ms. The LA became active at 44 ms via the BB connection, and the fossa interatrial impulse reached the LA at 74 ms. The last activation of the LA occurred at two postero-inferior regions, slightly more lateral than in the normal case, at 128 ms.

## 2.3 Mechanisms of AF

There is general agreement that the initiation and perpetuation of AF requires a *trigger* (initiating event) and an arrhythmic *substrate* in the atria (perpetuation). The importance of these components varies between different AFs and during different phases of AF even within one arrhythmia episode as well as within AF history as illustrated in Figure 2.

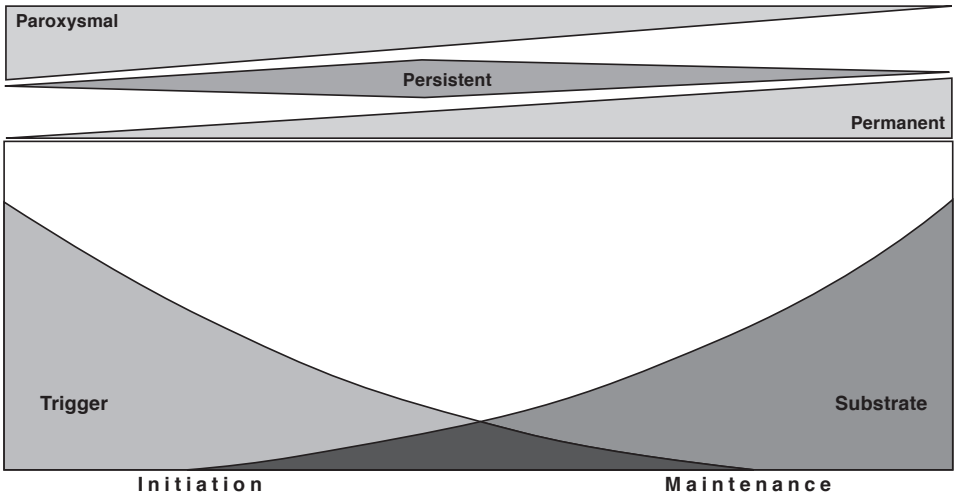


**Figure 2.** *Components of atrial fibrillation (AF) in different types and phases of AF.*

The triggers are factors firing abnormal wavefronts, and the substrate is the anatomical/ physiological millieu in the atrium which allows the wavefront to initiate AF. Once initiated, the AF may manifest itself as several small circuits or wavelets, appearing and disappearing around the atria. When the waves collide with anatomical or functional

obstacles, or both, they generate new wavelets, if they meet excitable tissue (*multiple wavelet hypothesis*). Maintenance of AF may depend on the uninterrupted periodic activity of a few discrete re-entrant or spiral-wave sources, i.e., rotors, localized in the left (or right) atrium. The electrical activity propagates through both atria and interacts with anatomical and functional obstacles, leading to fragmentation and wavelet formation (*mother rotor hypotheses; leading circle or spiral-wave*). (Mandapati et al. 2003, Chen et al. 2000, Allessie et al. 2001)

### 2.3.1 Multiple wavelet hypothesis

In 1913 Mines first introduced the concept of wavelength and suggested that AF may be caused by re-entry circuits. In the 1960s, the notion of closed loop re-entry was replaced with the idea of a large number of propagation wavefronts (Moe and Abildskov 1959, Moe 1962). This was verified in a computer model which showed that AF could be sustained by multiple propagation wavefronts in the presence of heterogeneous refractory properties in the atria (Moe et al. 1964). Allesie and coworkers (1977) showed that the wavelength established the occurrence of re-entry in rabbits, and in 1985 they (Allessie et al. 1985) were able to map the spread of excitation in the atria of the canine heart during rapid atrial pacing-induced AF.

According to the multiple wavelet hypothesis, AF is perpetuated as long as enough wavelets co-exist in the atria. This is mainly determined by three factors: atrial dimension (atrial mass and structure), conduction velocity, and refractory period (and its homogeneity). These are linked together, because, for re-entry to occur, the wavelength must be shorter than the available substrate dimensions, and the wavelength (equal to the distance traveled by the cardiac impulse in one refractory period) is as follows (Wiener and Rosenblueth 1946):

$$\text{Wavelength} = \text{refractory period} \times \text{conduction velocity}$$

For arrhythmia to sustain itself also requires a critical number of wavelets, six or more in animal models (Allessie et al. 1985). Thus the shorter the wavelength and the larger the atrial dimensions − both factors increasing the number of wavelets that can co-exist − raise the likelihood that AF would be sustained. It follows also that the arrhythmia can be stopped by increasing the wavelength, i.e., by increasing the refractory period or conduction velocity, or by reducing atrial dimensions.

### 2.3.2 Mother rotor hypothesis

The first model of a rotor is one leading circle around anatomical obstacles creating new AF wavelets to spread and thus to sustain the arrhythmia. This *anatomical re-entry hypothesis* was introduced by Mines (1913). Lewis made the first direct link between re-entrant activity and clinical arrhythmias by describing atrial flutter in the dog as re-entry in

a cylinder of muscle around the CV and through the taenia terminalis and identifying comparable behavior in a patient with atrial flutter (Lewis et al. 1920, 1921).

Early on, rotors were related also to the multiple wavelet theory. One dog study, to investigate the pro-arrhythmic mechanisms of cholinergic agonists, revealed that the number of circuits and wavelets increased in a dose-dependent fashion (Schuessler et al. 1992). This trend did not continue when the tachyarrhythmia became sustained. Instead, the re-entry tended to stabilize to a small, single, relatively stable re-entrant circuit (i.e., rotor or leading circle). This was later confirmed in other animal studies which have addressed the stabile re-entrant circuit(s) in the LA (Mandapati et al. 2000). According to *this functional leading circle model*, the re-entry naturally establishes itself in a circuit the size of the wavelength.

More recently, *spiral-wave* activity has been related to self-sustaining rhythms (Panfilov and Pertsov 1982). The main difference from a leading circle is that the maintenance of a spiral wave depends on tissue excitability, propagation strength, and the angle of curvature of the excitatory wave front (low excitability or propagation strength limit curvature and mandate larger spirals), not on wavelength (Figure 3). A spiral wave results when spontaneously occurring events result in the formation of a phase singularity around which the wave rotates. A classic scenario is provided by an ectopic activation that initiates a wavefront which crosses the recovery front of a previous sinus beat (Comtois et al. 2005). The occurrence of a spiral wave as a rotor in AF is experimentally supported (Skanes et al. 1998, Ikeda et al. 1996, Vigmond et al. 2004).

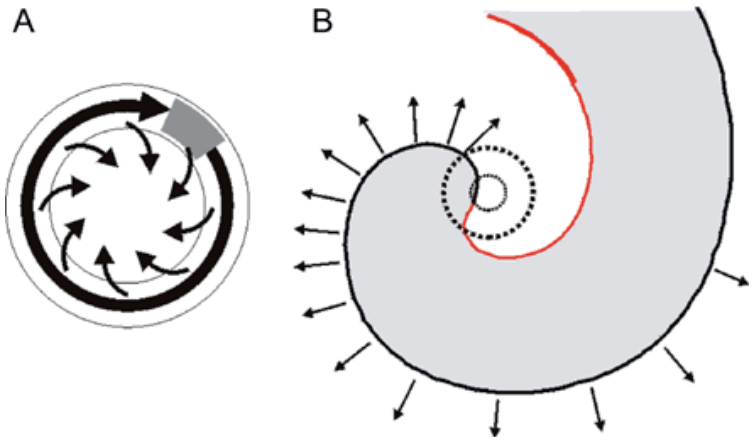


**Figure 3.** *A) The leading circle, as the smallest pathway that can support reentry, is shown as a bold black arrow. Inside the leading circle, centripetal wavelets (small arrows) emanating from it constantly maintain the central core in a refractory state. B) Spiral wave model: Schematic diagram of a spiral wave, with the activation front shown in black and the repolarization front in red. The point at which the red and black curves meet has an undefined voltage state and is usually referred to as the phase singularity point. Reprinted from (Comtois et al. 2005) with the permission of Oxford University Press.*

Human studies have shown that the substance of focal excitators, such as muscular sleeves in PVs and CS, may maintain stabile rotors (Oral et al. 2002, Oral 2005). Studies in patients with AF who are undergoing mitral valve replacement suggest regular repetitive

activations in the LA (Cox et al. 1991, Konings et al. 1994). Present dominant-wave analyses in human atria also support the rotor hypothesis (Sanders et al. 2005). These findings do not, however, differ between re-entrant or spiral waves. Consistent with re-entry models, interventions which reduce the wavelength − such as vagal stimulation, which abbreviates the atrial effective refractory period (ERP) − reduce circuit size and permit more leading circles to coexist, making simultaneous spontaneous termination of all circuits unlikely, and thus promote AF. On the other hand, interventions that increase wavelength, such as antiarrhythmic drugs, reduce the number of circuits and suppress AF (Rensma et al. 1988, Wang et al. 1993). Yet, for suppression of excitability by inhibiting the $Na^+$ current (prolonging AP), the leading circle model predicts a decrease in circuit size and promotion of AF because of reduced conduction velocity (and consequently wavelength). In the spiral wave model, this same inhibition should lead to enlargement of re-entry spirals and to AF termination. (Wijffels et al. 2000, Kneller et al. 2005)

### 2.3.3 Focal AF

As early as 1907 it was suggested that AF is caused by single or multiple rapidly firing foci (Winterberg 1907). During the next decades, this mechanism earned little attention. With the finding of a focal source of AF in the late 1990s, attention returned to *focal AF,* and this is now considered an important mechanism of AF. In this model, the local firing foci are not only the source of first abnormal wavefront triggering AF, but a rotor and a substrate maintaining the AF.

### 2.3.4 AF triggers

The triggers of AF include atrial premature beats (PAC) or tachycardia, bradycardia, shifts in autonomic tone, accessory pathways, and acute stretch of atria (Allessie et al. 2001). Despite triggering the arrhythmia, these factors can participate also in maintenance of AF as a substrate or rotors.

#### *2.3.4.1 Atrial ectopy and tachycardia*

The independent pulsation in PVs was already described in the late 1800s (Brunton and Fayrer 1876). The arrhythmogenic activity of the PVs was recognized in animal models in 1981 (Cheung 1981). However, the PVs and *focally mediated AF* became a major area of interest only in the late 1990s, when Jaïs and coworkers (1997) and Haïssaguerre and coworkers (1998) made the breakthrough observation that pulmonary venous ectopic foci are common triggers for episodes of AF and that catheter ablation of these foci can cure the arrhythmia in some patients. This led to a reappraisal of earlier anatomic work that showed muscle sleeves extending from the LA on to the PVs (Nathan et al. 1966). Since then, focal triggers have been found also in other areas in the atria including the superior

CV (Tsai et al. 2000), LA posterior and anterior free wall, crista terminalis, CS ostium (Lin et al. 2003) and ligament of Marshall (Hwang et al. 2000). In all these studies, triggers exist most commonly in PVs (over 90%). Based on the polarity of ectopic beats in ambulatory ECG recording, the triggering PACs were reportedly of LA origin in 74%, RA in 15%, or were not determined (Vincenti at al. 2006).

The mechanisms of PV arrhythmogenesis include increased automaticity, triggered activity, and re-entry (Oral 2005). Mapping within the PVs have demonstrated rapid repetitive electrical activity (Wu et al. 2001) and intermittent PV tachycardias (Oral et al. 2002a) with a cycle length shorter than in the adjacent LA (Oral et al. 2002a, 2002b). Moreover, the site with the shortest cycle length alternates between the LA and the PVs (Jaïs et al. 2002). All this can favor re-entry in PVs and thus facilitate sustained tachycardia. Haissaquere and coworkers (1998) showed that ERP within the PVs is shorter, and decremental conduction within the PVs is more prevalent in patients with AF than in controls. Variation in PV anatomy, including the number of veins, is common, but is similar in AF patients and in controls (Ho et al. 2002). However, larger-size PVs in AF patients than in controls do occur (Kato et al. 2003).

The mechanism of AF initiation from the CS focus is parallel to that of the PVs, and CS can also participate in maintenance of AF (Oral 2003). The ligament of Marshall is a potential source of rapid spontaneous discharges that can initiate AF (Hwang et al. 2000), and spontaneous depolarizations from the superior CV (Tsai et al. 2000), crista terminalis, ostium of the CS, and posterior and anterior LA all have induced AF (Lin et al. 2003).

The ectopic foci located in PVs are the most common source of focal AF, and the arrhythmia can be terminated by ablation of such drivers (Oral 2002). What is not fully understood, however, is why the atrial ectopy, common also in subjects without any arrhythmias (Jensen et al. 2003), leads to AF.

#### *2.3.4.2 Other triggering arrhythmias*

The presence of accessory pathways and re-entrant supraventricular tachycardia may also serve to initiate AF. Whether this occurs through rapid atrial rates degenerating into AF or through abnormalities in the atrial refractory periods is debatable (Della et al. 1991, Fujimura et al. 1990, Iesaka et al. 1998). Nonetheless, ablating this potential trigger can avoid recurrences not only of AV re-entrant tachycardia but also of AF. Atrial flutter (AFL) and AF frequently coexist in clinical practice. In patients with type I AFL (negative flutter waves in the inferior leads and positive flutter waves in lead V1) as their predominant clinical arrhythmia, RA isthmus ablation also reduces recurrences of AF. Thus, AFL may be a triggering arrhythmia and maintenance of AF may be based on macro-reentry around the tricuspid valve orifice including the RA isthmus. Patients with therapy-resistant AF who develop a type I AFL while receiving class IC therapy also seem to profit, showing a reduced incidence of AF recurrences after AFL ablation (Nabar et al. 1999).

### 2.3.5 Autonomic modulation

Autonomic inputs may contribute to both the initiation and maintenance of AF (Patterson et al. 2005). In animal studies, vagal stimulation increases the variability of atrial refractoriness determined at different atrial sites, whereas sympathetic stimulation has no significant effect on these indices (Liu and Nattel 1997). Other experiments have shown that the administration of acetylcholine or methylcholine to the atrium can induce AF, and vagal stimulus can induce prolonged episodes of AF (Burn et al. 1955, Wang et al. 1993). High-frequency stimulation of epicardial autonomic plexi can induce triggered activity from the PVs and also affect atrial refractory periods so as to provide a substrate for the conversion of PV firing into sustained AF (Patterson et al. 2005). Elimination of vagal inputs can prevent AF recurrence in both animal and patient models of vagal AF (Patterson et al. 2005, Schauerte et al. 2000, Scanavacca et al. 2006). In human AF patients, prevention of bradycardia with pacing has reduced AF episodes and burden (Sulke et al. 2007). Recent data have suggested that identification and ablation of autonomic ganglia during PV isolation may improve long-term success (Scherlag et al. 2005). However, in another report, using ganglionated plexus ablation alone in vagal AF, the success rate was less than 30% (Scanavacca et al. 2006). Generally supported is bradycardia-induced vagal AF in some cases, but at least as importantly, a shift in autonomic balance as a modulator in PAC-triggered AF or also acting per se as a trigger.

### 2.3.6 Atrial stretch

Acute atrial dilation (Ravelli et al. 1997) as well as acute increase in atrial pressure (Satoh and Zipes 1983) increases the inducibility of AF in animal models. In the dilatation model, this was related to decrease in atrial ERP (Ravelli et al. 1997), but in the pressure model, to an increase in ERP. In the pressure model, the changes were larger in thinner than in thicker portions of the atria (Satoh and Zipes 1983).

### 2.3.7 Arrhythmogenic substrate

No general consensus exists on what exactly constitutes the “substrate” in clinical AF. Most often it refers to critical regions or components of the LA anatomy/ electrophysiology that are responsible for allowing AF to perpetuate. In this scenaries, all atrial electrical, functional, and structural properties manifesting as increased heterogeneity of atrial conduction or refractoriness, or both, or altering atrial action potential (AP) or atrial dimensions, can be called an *arrhythmogenic substrate*. Further, any change in these properties is called *remodeling.* Remodeling can be divided into three components: *electrical, functional (contractile), and structural remodeling* (Allessie et al. 2002). The manifestation and relative importance of these components vary and are influenced by the driving mechanisms and time course of the exposure and can be reversible or irreversible. On some occasions, remodeling can be protective against AF

(Allessie et al. 2001), but more often is a promoting factor and thus the cause of arrhythmogenic substrate(s).

#### *2.3.7.1 Atrial remodeling*

The possibility that AF might itself remodel atria was evidenced in an animal model in the mid 1990s. A goat-model work by Wijffels and coworkers (1995) demonstrated that the AF produce rapid decreases in atrial refractory period and progressive increases in spontaneous AF maintenance (*AF begets AF*). Later studies have confirmed these findings, and furthermore, all the three components, electrical, functional, and structural remodeling, have now been demonstrated (Allessie et al. 2002, Schotten et al. 2003, Verheule et al. 2003). Moreover, at least some of these changes are reversible after SR is restored (*re-remodeling*), and it seems that the inducibility of the AF decrease in relation to time SR is maintained: *sinus rhythm begets sinus rhythm* (Allessie et al. 2002).

**Electrical remodeling.** The key features of electrical remodeling are shortening of the atrial refractory period, loss of rate adaptation, and increased heterogeneity of atrial conduction and refractoriness. The electrophysiological changes observed are evidently due to changes in ion channels (Yue et al. 1997, Gaspo et al. 1997). Electrical and ionic remodeling is involved also in functional and structural remodeling.

**The functional remodeling** (loss of contractility) induced by AF has been related to calcium overload via changes in ion-channel function, but may later also accompany structural remodeling (Sun et al. 1998, Schotten et al. 2003).

**Structural remodeling.** The structural changes in AF-induced atrial remodeling first are changes in microarchitecture and later, increased fibrosis and myolysis (Allessie et al. 2002). Atrial structural remodeling also occurs as a result of heart failure and other cardiovascular diseases and with aging. These changes seem to be dependent on driving mechanisms. In aging as well as in congestive heart failure, the main finding is fibrosis, while in mitral regurgitation, it is distribution of myocyte architecture and inflammation (Nattel et al. 2005, Everet et al. 2006). Shared findings are depositions separating myocytes from one another, or loss of myocytes, and subsequent impairment of atrial conduction (Schotten et al. 2001).

#### *2.3.7.2 Connection between AF substrate and AF mechanisms*

In an elegant study by Everett and coworkers (2006) the type of atrial substrate was linked to distinct AF mechanisms. Rapid atrial pacing (RAP, ventricular rate is controlled), and methylcholine (Meth) models have been dominated by atrial electrical remodeling, which includes a *shortening of the atrial refractoriness* without structural changes or changes in conduction (Morillo et al. 1995, Schuessler et al. 1992, Verheule et al. 2004). The mitral

regurgitation (MR) and congestive heart failure (CHF) models are dominated by changes that result in *alterations of conduction* produced by *atrial fibrosis* in the CHF model and myocyte architecture disruption and *inflammation* in the MR model (Li et al. 1999, Verheule et al. 2003, 2004). That study demonstrated that structural remodeling of the atria (models known to have predominantly altered conduction) leads to an AF characterized by a stable high-frequency area (mother-rotor). In contrast, electrical remodeling of the atria (models known to have predominantly shortened refractoriness without significant conduction abnormalities) leads to an AF characterized by multiple high-frequency areas and multiple wavelets (multiple wavelet hypothesis). In the RAP model (~ persistent lone AF), these multiple wavelets foundered and showed higher frequency in the LA than in the RA, but the Meth model (~ vagal lone AF) showed stable high-frequency areas with multiple wavefronts in other areas of the atria and no frequency gradient between LA and RA. This suggests that the mechanism of AF, the multiple wavelet hypothesis, focal driver or mother rotor, depends on the existing atrial substrate.

#### *2.3.7.3 Pulmonary veins, CS, and interatrial connections*

In addition to triggering AF, PVs and the CS may also play a role in maintenance of AF. The CS is covered with myocardial sleeves connected to the LA by several muscular bridges. Focal atrial tachycardias originating in the CS have been reported (Eckardt et al. 2002, Chen et al. 2002), and CS musculature may participate also in a macrore-entrat tachycardia circuit that generates LA flutter (Olgin et al. 1998). Oral and coworkers (2003) demonstrated bursts of rapid electrical activity to alternate between the LA and CS during AF - the cycle length being shorter in CS - and that disconnection of the CS from the LA can prevent AF.

Altered conduction in other interatrial connections may also facilitate re-entry and maintenance of AF. Animal experiments have demonstrated that the ERP of the BB is significantly longer than that of the RA and LA (Hayashi et al. 1982, Duytschaever et al. 2002). Consequently, the bundle may become blocked at a pacing rate at which the adjacent atrial tissue can still be activated. This represents a potential substrate for re-entry.

### 2.3.8 Focal AF, Trigger AF, and Substrate AF

The role of triggers in the initiation and maintenance of AF is well appreciated. When this is assumed to be the main mechanism, and the trigger is an atrial ectopic focus, AF is called *focal AF*. Features related to focal AF are excess of PACs, early PACs, appearance of short atrial tachycardias, and bigeminy. The term "*Substrate AF*" is applied to AF in which onset seems to be not PAC-related or other factors seem to be more crucial for initiation and maintenance of the arrhythmia. Generally accepted definitions for focal AF or "*Trigger AF*" and for "substrate AF" or for different substrates, however, are still lacking.

The onset scenario of AF may serve to differentiate between mechanisms. The existence of active triggers and different substrates may be reflected in atrial signal measures obtained by intracardial and body surface recordings. These approaches are summarized in the next few sections.

#### *2.3.8.1 Findings in long-term ECG and electrogram recordings*

Based on ambulatory ECG recordings and device studies, the most common onset scenario of AF is premature atrial complexes (PACs), followed by bradycardia, sudden onset, and in rare cases (< 1%), tachycardia (Hnatkova et al. 1998, Vikman et al. 1999, Dimmer et al. 2003, Jensen et al. 2003, Vincenti et al. 2006, Hoffmann et al. 2006). Combinations of different onset scenarios within one patient were frequent, and up to one-third of the episodes were initiated within 5 minutes of a previous AF (Hoffmann et al. 2006). Examples of two onset scenarios of AF are shown in Figure 4.

**PAC-related onset**. The AFT trial (multicenter device study Atrial Fibrillation Therapy) defined onset as PAC-related if there were ≥ 2 PACs within the last 20 preceding beats (short run or isolated), if the onset was PAC-post PAC pause-onset or if the number of PACs occurring within 5 minutes before AF increased (Hoffmann et al. 2006). Using these criteria, PAC-related AF comprised about half of the arrhythmia episodes (47%), and most patients (79%) had at least one PAC-related episode. In one-third of PAC-related initiations, the number of PACs increased. This increasing number of PACs before initiation of AF has been reported also by others (Hnatkova et al. 1998, Vikman et al. 1999, Dimmer et al. 2003, Vincenti et al. 2006).

**Number of PACs**. In lone AF populations in different clinical studies, PAC numbers range from 800 to 4000 per 24 hours and have been shown to decrease to 100 to 200 per 24 h after successful treatment by ablation (Haissaguerre et al. 1998, Chen et al. 1999, Jensen et al. 2003). However, in all these studies, the range of PACs is large, from a few beats to 30 000 PACs per 24 h. The occurrence of PACs in healthy subjects can also be frequent, but in over 90% of subjects the number is less than 700 per 24 h and in 77 to 95% subjects less than 200 per 24 h (Hiss and Lamb 1962, Bjerregaard 1982, Jensen et al. 2003).

In a study by Hoffmann and coworkers (2006), PAC density count correlated positively with number of AF episodes per day but not with AF burden. This finding was confirmed by Yang and coworkers (2006), who concluded that the coincidence of low PAC activity before AF onset, high AF burden, and extended arrhythmia episode duration appears to be the consequence of a *high atrial substrate factor.* In one Holter study, the number of PACs was inversely related to the number of previous AF episodes (Jensen et al. 2004). Recently, the presence of PACs or atrial tachycardias was reported to protect against progression from the paroxysmal to the permanent form of AF in a three-decade follow-up study of lone AF patients (Jahangir et al. 2007). In the same study, an abnormal

QRS complex elevated risk for arrhythmias progressing to permanent form, suggesting occult structural or substrate abnormalities in this sub-cohort.

The **coupling interval for AF-triggering PACs** has been to be shorter than for non-triggering PACs or PACs in healthy controls, with mean values of 403 to 468 ms for triggering PACs, 494 to 584 ms for non-triggering PACs, and 589 ms for controls (Jensen et al. 2004, Capucci et al. 1992, Vincenti et al. 2006). In all these studies, however, short coupling intervals have been present also in non-triggering PACs (Capucci et al. 1992, Jensen et al. 2003, Vincenti et al. 2006), and some studies have shown no difference (Dimmer et al. 2003).

The conventional **heart rate** variability (HRV) analyses of 24 hours have failed to show any significant differences between AF patients and controls or to differentiate between subclasses within AF patients (Vikman et al. 1999, Dimmer et al. 2003). However, the last 5 to 60 minutes before AF onset commonly showed a shift in autonomic balance. Increase in sympathetic tone as well as increase of parasympathetic tone has occurred (Vikman et al. 1999, Fionarelli et al. 1999, Vincenti et al. 2006). The number of preceding PACs has been larger in those with HR acceleration before AF than in those with HR deceleration or no change in HR (Dimmer et al. 2003). Preceding bradycardia or sinus pauses, with or without extrasystole, have occurred in 39 to 48% of onsets (Hoffmann et al. 2006, Vincenti et al. 2006). The bradycardia-related arrhythmia onset is common in patients with sick sinus syndrome but also in other AF patients (Hoffmann et al. 2006). In one pacing study, 42% of patients showed no AF after enrollment, suggesting that bradycardia may have been the main cause for arrhythmia in these patients; thus, pacing alone may eliminate AF (Sulke et al. 2007).

Hoffmann and coworkers (2006) reported **sudden onset** of AF in 28% of episodes (according to the definition a single PAC was allowed). In other studies, the initiation of AF without an ectopic beat has occurred in 0 to 13% of AF episodes, and in up to half the initiating PAC has been single (Hnatkova et al. 1998). In one device-registry study, in 42% of patients most episodes were preceded by fewer than two PACs and were considered *"Substrate AF,"* while those 58% having more PACs were classified as *"Trigger AF"* (Lewalter et al. 2006). In this patient cohort with a conventional indication for pacemaker therapy and AF, patients in the Trigger group demonstrated a 28% reduction in AF burden with preventive pacing. The Substrate group, for whom the Pace Conditioning algorithm was activated, showed no improvement in AF burden.

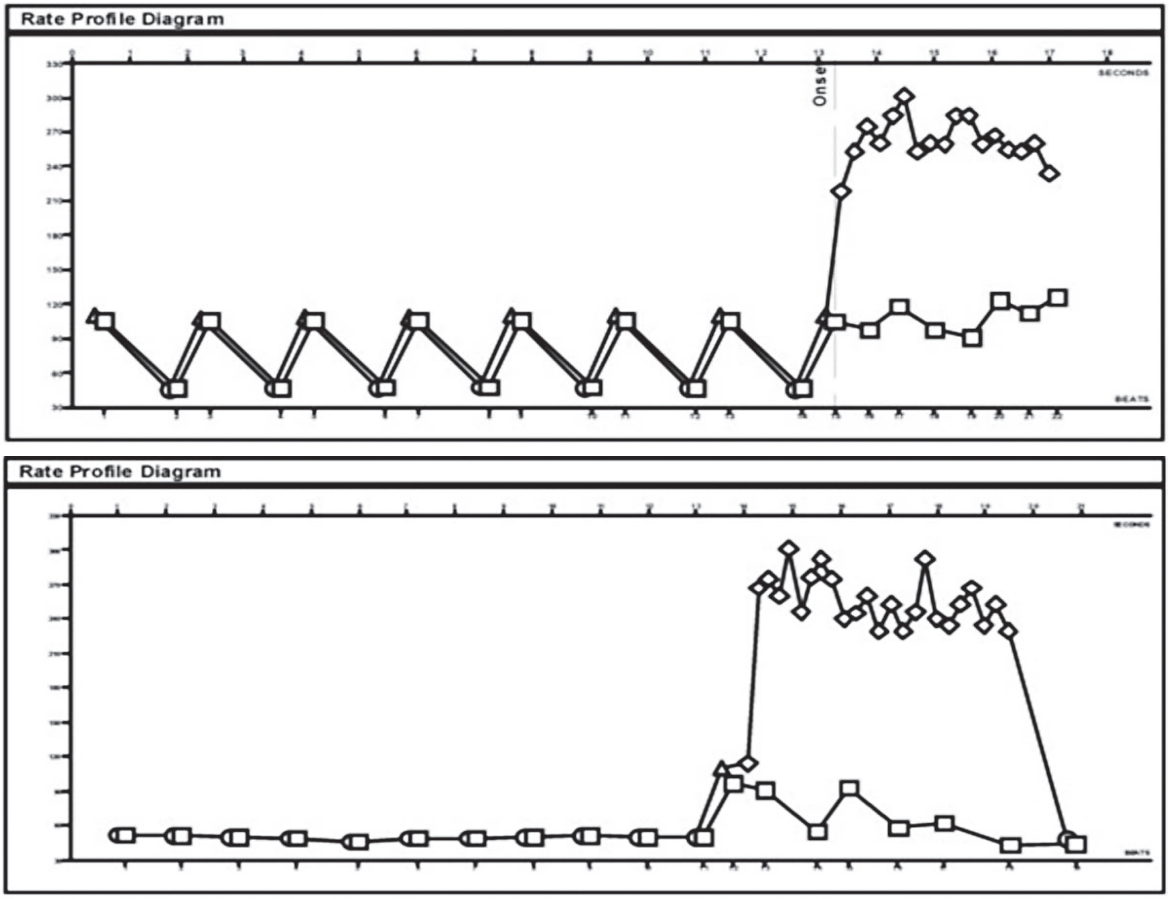


**Figure 4**. *Examples of two onset scenarios of AF. Pacemaker-stored rate-profile diagrams of the last seconds before AF. Multiple preceding PACs (upper) and sudden onset (lower). ○ indicates atrial sensed beat; ◊, atrial tachy sensed beat; Δ, PAC; □, ventricular sensed beat. Reprinted from (Hoffmann et al. 2006) with the permission of Wolters Kluwer Health.*

### *2.3.8.2 Markers of substrate(s) in electrogram and atrial mapping*

**Complex fractionated electrograms (CFEs).** Early animal and human experiments revealed that atrial regions exhibiting very rapid activation may represent critical rotors responsible for maintaining AF (Morillo et al. 1995). Furthermore, regions demonstrating fragmented potentials to the point of almost continuous baseline activity may represent pivot points or regions of very slow conduction responsible for continued fibrillatory conduction (Konings et al. 1994). Nademanee and coworkers (2004) first described targeting this type of electrogram (EGM) exclusively to ablate AF. He defined so-called "complex fractionated atrial electrograms" (CFE), which typically have very low voltages of 0.06 to 0.25 mV. A ablating these targets gave a success rate of 76% (91% after two treatments). With ablation of CFE and PVAI (pulmonary vein antrum isolation), the off-drug success rate has been even better and also better than with PVAI alone (Verma et al. 2008). Recently, an automated CFE algorithm has come into clinical use.

Examining Fourier transforms (FFT) of sinus EGMs, Pachon and coworkers (2004) demonstrated what they called compact and fibrillar types of atrial myocardium. The FFT

of these tissue potentials was one high-power fundamental frequency and fast uniformly decreasing harmonics in compact areas, and a low-power fragmented and heterogeneous profile with a great number of irregular harmonics of high amplitude and wide distribution in fibrillar areas (called AF nests). In study of 34 AF and 6 control patients, AF nests appeared in all AF patients but in only one control. A large number of AF nests appeared in the roof of the LA in all patients. Other common locations were the interatrial septum, the atrial wall near the PV insertions, and also inside veins. The refractory period of the AF nest was shorter than that of the compact myocardium. During AF, the nests presented the highest activation rates. Of patients treated by ablation targeted to nests, 94% became free of AF. Similarities in findings with all fragmented signal analyses suggest the same abnormal myocardium, which seems to be an important substrate for AF, but the origin of which is unknown and may vary.

**Dominant frequency (DF)**. Fibrillatory rate of AF may vary between distinct sites of the atria (Sahadevan et al. 2004). The dominant rate(s) can be determined by frequency domain analyses (Skanes et al. 1998). In some cases, stabile high-frequency DF areas may be identified and located. Ablation over these sites has terminated AF or has prolonged AF cycle length, supporting the hypothesis that these regions drive AF (Sahadevan et al. 2004, Sanders et al. 2005). The distribution of DFs has differed between paroxysmal and permanent AF, with DFs less likely to be associated with the PVs in non-paroxysmal AF (Sanders et al. 2005).

**Autonomic ganglionated plexi (GP)**. Autonomic inputs from GP surrounding the heart may contribute to both the initiation and maintenance of AF (Patterson et al. 2005).The location of GP has been correlated with the presence and location of CFE (Scherlag et al. 2005), and with the LA sites where endocardial high-frequency stimulation, or ablation, evokes vagal responses such as transient atrioventricular block or a pause of several seconds (Scanavacca et al. 2006). Ablation of GPs during PV isolation may improve long-term success (Scherlag et al. 2005), but whether targeting plexi alone will ultimately prove effective remains unclear.

**Electrically silent area, scar.** A study by Verma and coworkers (2005) performed extensive voltage mapping of the LA to assess the impact of left atrial scarring (LAS) on the outcome of patients undergoing PV isolation for AF. Of 700 patients, 42 had LAS, which represented 21 ± 11% of the LA surface area. Patients with LAS had a significantly higher AF recurrence (57%) than did non-LAS patients (19%). Moreover, LAS was associated with significantly larger LA size, lower ejection fraction, and higher C-reactive protein levels. LA scarring was the only independent predictor of procedural failure. In another study, those with persistent AF had a lower atrial voltage, higher coefficient of variance for the LA voltage, longer LA activation time, and a more extensive scar than did those with paroxysmal AF (Chang et al. 2007).

## 2.4 Lone AF

### 2.4.1 Definition

Lone AF was initially defined to identify a cohort of young patients with AF who had no clinical evidence of cardiovascular disease and were at low risk for thromboembolism (Evans and Swann 1954, Lamb et al. 1964, Peter et al. 1968). The 2006 ACC/AHA/ESC guidelines applied the term to *patients under age 60 without clinical or echocardiographic evidence of heart disease including hypertension* (Fuster et al. 2006*,* Kopecky et al. 1987*).* Yet, several studies have included patients up to age 65 or even older in the lone AF category, especially if the onset of AF has been at early age. Another unresolved issue is the presence of mild echocardiographic abnormalities (e.g., mild mitral regurgitation, LA enlargement, or increased left ventricular mass). The changes in cardiac structure and function that accompany aging, such as increased myocardial stiffness, may be associated with AF, and with advancing age, the risk for thromboembolisms (and bleeding) in AF rises also in those without any demonstrable cardiovascular disease (Rienstra et al. 2004, Brand et al. 1985). Increased risk for thromboembolisms in lone AF has been demonstrated in the permanent form of the arrhythmia and with enlargement of the LA (Scardi et al. 1999, Osranek et al. 2005). Further, the slight enlargement of the LA and markers of increased left ventricular (LV) filling pressure have been related to lone AF (Jaïs et al. 2000, Sitges et al. 2007). Some lone AF, especially familial arrhythmia, is related to cardiomyopathy, but this or some other causal underlying disease may appear later (Brugada et al. 1997, Katritsis et al. 2004). Overall, it seems that lone AF is not so "lone," and for some of the subcohorts included in lone AF, the prognosis is not favorable (Scardi et al. 1999, Darbar et al. 2003, Osranek et al. 2005, Patton et al. 2005).

### 2.4.2 Pathogenesis and associated conditions

Compared to AF in various heart diseases, lone AF is more often paroxysmal (Goudevenous et al. 1999) and progresses less often to permanent AF (Lévy et al. 1999, Scardi et al. 1999, Osranek et al. 2005, Jahangir et al. 2007). In lone AF, the male dominance is pronounced, and AF is more frequently classified as vagally-induced or familial than is non-lone AF (Nemirovsky et al. 2008, Arnar et al. 2006, Marcus et al. 2008). The lone paroxysmal AF may be a primary electric disorder related to focal triggers like atrial tachycardias or to a shift in autonomic balance (Jahangir et al. 2007). Yet both increased fibrosis and deposits of inflammatory cells have been found in histologic studies of macroscopically normal atrium from AF patients (Boldt et al. 2004, Frustaci et al. 1997). Atrial refractoriness and conductivity may be altered by ion channel abnormalities or changes in proteins mediating atrial conduction through electrical coupling between cells (Nattel et al. 2005, Gollob et al. 2006). A specific gene mutation is described on rare occasions (Chen et al. 2003, Yang et al. 2004, Ellinor et al. 2008). AF is also associated with the presence of local conduction defects located in the vicinity of interatrial

conduction routes (Platonov et al. 2007). Whether interatrial connections are important in the initiation or maintenance of the arrhythmia or in both in lone AF is as yet unknown. Several so-called "new risk factors" have been associated with lone AF. These include obesity, sleep apnea, alcohol abuse and other intoxications, latent hypertension, excessive sports practice, genetic factors, and inflammation (Schoonderwoerd et al. 2008). The role of these components in the patients with lone AF is, however, unclear.

### 2.4.3 Clinical manifestation

The first clinical study to explore the differing manifestations of the arrhythmia specifically within lone AF was published in 2005. Patton and coworkers evaluated 180 serial patients who presented with lone AF (mean age 54 years, 82% males). The mean age at time of AF diagnosis was 45 years (15–67). The majority of patients originally presented with paroxysmal fibrillation (94%), and 8% had progressed to permanent AF within a mean of 6 ± 7 years from diagnosis. Reported triggers for AF included sleeping (44%), exercise (36%), alcohol use (36%), and eating (34%). Women with lone AF had distinct symptoms and triggers for episodic AF, and over one-fourth had an underlying rheumatologic condition. Several subsets of AF identified include familial AF (39%), exercise-induced AF (32%), and conduction system disease requiring pacemaker implantation (7%). (Patton et al. 2005).

In the same study, the exercise-triggered AF was more common in patients participating in strenuous exercise. Lone AF has been related to vigorous exercise also prior to 2005 (Karjalainen et al 1998, Mont et al. 2002). In a recent work by Mont and coworkers (2008), 107 patients younger than 65 (mean age 48 years, 69% males), were seen in the emergency room for an episode of lone AF. AF was paroxysmal in 57% and persistent in the remaining 43%. Compared to controls, patients with AF performed more hours of both moderate and heavy-intensity physical activity. They also were taller, and had larger LA. The association between lone AF and LA size also emerged in other studies (Jaïs et al. 2000, Sitges et al. 2007). Mont and coworkers (2002) showed no difference in type of AF between sportsmen and non-sportsmen, but the proportion of vagal AF was larger (57% vs. 18%) among the latter.

Autonomic influences play a role in the initiation and maintenance of AF. It appears that the balance (and shifts in it) between sympathetic and vagal influences rather than the absolute level of sympathetic or parasympathetic tone is important as an AF predictor. (Fioranelli et al. 1999, Herweg et al. 1998) Certain patients can be characterized in terms of a *vagal or an adrenergic form of AF* (Coumel 1992). In general, vagally mediated AF occurs at night or after meals, while adrenergically induced AF typically occurs during the daytime (Maisel et al. 2003). Importantly, these types are reflected in success of treatment. In patients with vagally mediated AF, adrenergic blocking drugs or digitalis sometimes worsen symptoms. For AF of the adrenergic type, beta blockers are the initial treatment of choice. In a study by Oral and coworkers (2004), 16% of the patients undergoing catheter ablation treatment were classified as having adrenergic AF, and the outcome of treatment in these patients was better than in patients classified with vagal AF.

### 2.4.4 Familial AF

The likelihood of developing AF is increased among the offspring if parents have AF (Fox et al. 2004). In lone AF, this connection is even more pronounced. In a large (5 269 patients) investigation of heritability of AF in Icelanders, the first-degree relatives of patients <60 years of age were more than four-fold more likely to have AF at age <60 than was the general population (Arnar et al. 2006). In various lone AF cohorts, 15 to 41% of the patients have reported a positive family history of the same arrhythmia (Darbar et al. 2003, Patton et al. 2005). In a cohort of non-lone AF patients, the figure was 14% and in controls 5% (Marcus et al. 2008).

In some families lone AF has been described with autosomal-dominant inheritance (Brugada et al. 1997, Chen et al. 2003, Olson et al. 2006, Darbar et al. 2003, 2008, Ellinor et al. 2008). Familial lone AF related to gain-of-function mutations in genes regulating cardiac potassium channels as well as to mutation in the SCN5A gene have been identified (Xia et al. 2005, Ellinor et al. 2008). A mutation in the gene encoding atrial natriuretic peptide (ANP) has been described with a phenotype of shortened atrial AP and abnormal ANP (Hodgson-Zingman et al. 2008). In one family with AF the marked prolongation of the P wave seemed to be a marker of genomic abnormality (Darbar et al. 2008). Darbar and co-workers (2003) had reported on four families, in three of which the AF presented as symptomatic paroxysmal AF with rapid ventricular response. Interestingly, in these families, several strokes occurred at relatively young ages. In the fourth family, the AF was mostly asymptomatic and associated with a slow ventricular response. One large family had a high prevalence of lone AF and saddleback-type ST-segment elevation in leads $V_{1–3}$ (Junttila et al. 2007). A common polymorphism in the SCN5A gene has been associated with lone AF (Chen et al. 2007). Variants on chromosome 4q25 have been linked to increased risk for AF (Gudbjartsson et al. 2007). The locus is adjacent to a gene with a critical function in left-right asymmetry of the heart. Mutations in the connexin 40 gene have also been related to AF (Gollob et al. 2006).

Despite the large number of lone AF patients showing a positive family history of AF, the underlying genetic factors remain still mostly unknown.

### 2.4.5 Left atrial size and early stage of heart disease

Slight enlargement and especially prolongation of the LA have been related to lone AF (Jaïs et al. 2000, Sitges et al. 2007). In a study by Stiges and coworkers (2007), although within normal limits, LA dimensions were larger than in healthy controls. There was no difference between the LA of patients with only one episode of AF (53%) and those with recurrent paroxysmal episodes. In a supporting study, LA dimensions were similar in patients with recurrent and non-recurrent AF, and in both groups, LA size remained constant during the mean follow-up of 30 months (Rostagno et al. 1996). In another study, an average of 5.6 mm (15%) increase in LA diameter was observed during 6 years follow-up, and the increase was more obvious in those with persistent AF (Suarez et al. 1991). Jaïs and coworkers (2000) reported a significantly higher inferosuperior LA dimension in

lone AF patients than in WPW patients. A higher LV filling pressure was also reported in patients with lone AF. In a three-decade follow-up study of 46 lone AF patients, the indexed LA volume (LAV) at the initial echocardiographic examination was enlarged in some of the patients (Osranek et al. 2005). In half the patients, the LAV index remained normal throughout follow-up, indicating that the longstanding paroxysmal or persistent AF by itself does not necessarily cause an increase in LA volume. Importantly, 50% of the patients had an adverse cardiovascular event during follow-up, and 87% of these and all strokes appeared in the group with increased LAV.

Katritsis and coworkers (2005) reported, in a cohort of 32 patients diagnosed as having lone AF, a high prevalence of new-onset hypertension, 44% in 1- to 3-year follow-up. In another study, the appearance of new arterial hypertension was much less: 8% of the subjects developed hypertension 15 ± 13 years after diagnosis of lone AF (Patton et al. 2005).

An overall suggestion is that in some cases lone AF may be an early stage of arterial hypertension, and some LA enlargement may be related to remodeling caused by the arrhythmia. More likely, a primary anatomical or a functional substrate, or both, exist for the development of idiopathic AF.

### 2.4.6 Inflammation and fibrosis

In a study by Frustaci and coworkers (1997), all atrial biopsies of patients with lone AF were abnormal, whereas all biopsies of WPW patients were normal. In 66% of AF patients the finding was myocarditis (25% active), in 17% it was non-inflammatory cardiomyopathy, and in 17%, patchy fibrosis. The patients with findings of active myocarditis were treated with steroids, and AF no longer recurred. Inflammatory cells infiltrating the LA endocardium have been visible also in specimens from patients with thromboembolism and non-valvular AF (Nakamura et al. 2003) and in animal models of AF (Kamiyama 1998, Verheule et al. 2003). Dernellis and Panaretou (2004) reported that metylprednisolon reduced recurrent AF in patients with new AF. An increase in the level of hs-CRP, IL-6 and TNF-alfa has also been related to AF (Aviles et al. 2003, Sata et al. 2004). Inflammation has been suggested to be a causative agent in paroxysmal AF in some (Gedikli et al. 2007), but not in all studies (Ellinor et al. 2006, Kallegris et al. 2008). Whichever is true, one important observation is the link between markers of inflammation and increased risk for thromboembolism in AF (Conway et al. 2004, Thambidoral et al. 2004). Boldt and coworkers (2004) showed increased, but somewhat differing, fibrosis both in patients with lone AF and with AF related to mitral valve disease. Independent of etiology, any histological changes in the atria are a potent source of conduction disturbance and, thus, of vulnerbility to AF.

### 2.4.7 Gender

The evident 60 to 80% male dominance in lone AF is well recognized (Goudevenous et al. 1999), but its reasons are unclear. In a study by Patton and coworkers (2005), women with lone AF had distinct symptoms and distinct triggers for episodic AF and were more likely to have a rheumatologic condition. Women with AF have been reported to be more symptomatic than men (Humphries et al. 2001, Rienstra et al. 2005). In general, in AF the outcome of the arrhythmia in women has been worse (Benjamin et al. 1998, Stewart et al. 2002).

Studies of non-AF patients have revealed some gender-related differences in the atria. Liu and coworkers (2004) investigated, in patients without structural heart disease, the age and gender dependence of the LA dimension, ERP, and atrial conduction. A significant positive correlation appeared between age and LA dimension in women not taking hormone replacement therapy. Men had significantly greater average LA dimensions than did women. Neither ERP nor atrial conduction demonstrated any significant correlation with either age or gender. They concluded that LA size is greater in the elderly and in men, which may increase both these groups' risk for AF.

In another study, right atrial ERP was measured during SR and during atrial and AV pacing (Tse et al. 2001). During SR, mean atrial ERP in premenopausal women was shorter than in postmenopausal women or in age-matched men. In all patients, ERPs shortened significantly during pacing, but significantly less in premenopausal than in postmenopausal women or in age-matched men, suggesting that the gender differences may be mediated by the effects of estrogen on atrial electrophysiology.

## 2.5 Atrial conduction in patients with AF

Alterations in atrial conduction and refractory properties are related to both the genesis and maintenance of AF. Slow conduction in the atria can be diffuse because of fibrosis or inflammatory changes related to aging and to coexisting conditions such as heart failure or hypertension (Becker 2004, Nattel et al. 2005). The conduction defect may also be local and located in one of the interatrial pathways. Prolongation of the P wave is the most common signal abnormality related to AF. This has been atributed mainly to impaired or blocked conduction in the BB (Ariyarajah et al. 2005a). LA pacing studies have demonstrated increased and more heterogeneous refractoriness and more pronounced lengthening of conduction times in the BB, CS, and LA in patients with AF than in controls and in patients with persistent AF than in patients with paroxysmal AF (O'Donnell et al. 2002). Measurements with high-density electroanatomical mapping in the proximal CS during SR have revealed a lower conduction velocity in AF patients than in patients without a history of AF (Xia et al. 2004). Fibro-fatty degeneration of the BB has appeared more commonly in patients with a history of AF (Becker 2004). Diffuse or patchy inflammation, cardiomyopathy, and fibrosis have been shown also in macroscopically normal atria in lone paroxysmal AF (Frustaci et al. 1997).

It has been reported that the CS area can be a substrate for atypical flutter circulation (Olgin et al. 1998), which in turn can lead to the genesis of AF. Catheter ablation of the RA septal region (Gaita et al. 1998), ablation of CS connections (Haissaguerre et al. 2007), or transsection of the anterior LA (Sanders et al. 2004) have been effective in the treatment of AF in some patients. Ablation of the CS and FO areas has altered inducibility to AF in an animal model (Ott et al. 2007). Thus, all three interatrial conduction pathways seem to have relevance to AF generation.

In patients with AF, the signal propagation from right to left atria varies. Experimental evidence supported by human studies shows that the altered conduction in pathway(s) may promote AF. Results of treatments targeting such connection(s) have been promising. The position of interatrial conduction in genesis of AF still remains, however, to be verified.

## 2.6 Non-invasive assessment of atrial signal in general and in patients with AF

### 2.6.1 Electrical forces in the atria, generation of atrial signal

The AP is regulated by the expression and activity of several ion channels, by physiological atmosphere at cell level, and by cell activity. This process is controlled by the autonomic nervous system. The macroscopic arrangement of pacing cells, highly conductive specialized cells, and muscle cells, as well as non-cellular structures forming the right and left atrium and connections between them, all direct the spread of activation to facilitate synchronous contraction of the atria.

The cellular AP can be measured by an implement technique with microelectrodes (IT). The AP in its whole extension: depolarization and repolarization can be evaluated also by monophasic AP (MAP) techniques, which provide a graphic recording that is a mean of the APs of many cells. A single tracking covers a region approximately 5 mm in diameter centered on the electrode (Franz et al. 1986). The current flow across myocardial cell membranes is accompanied by the development and spread of ionic currents through the body, resulting in the establishment of electrical potentials on the atrial endo- and epicardium as well as on the body surface. This flow of currents creates voltages between sites where electrodes are placed. These voltages are called electrograms ***(****EG, EGM****)*** when measured on the heart surface and electrocardiograms *(ECG)* when measured on the body surface. (Barr 1989) The body surface ECG in all its variations, as well as intracavitary electrographic recordings, provides a distance view of the cardiac electric phenomena, because they represent the summation of all the cellular electric activity. What is obtained is a picture of APs distorted by their algebraic sum, dispersed in time and space, and modified by the capacitances and resistances found in their path. (Scher and Spach 1979) The electro(cardio)grams hide cellular electrical phenomena during a great part of the cardiac cycle, when the absence of electrical gradients in the organ creates a real “electric silence” from a distance (Figure 5, Leirner and Cestari 1999).

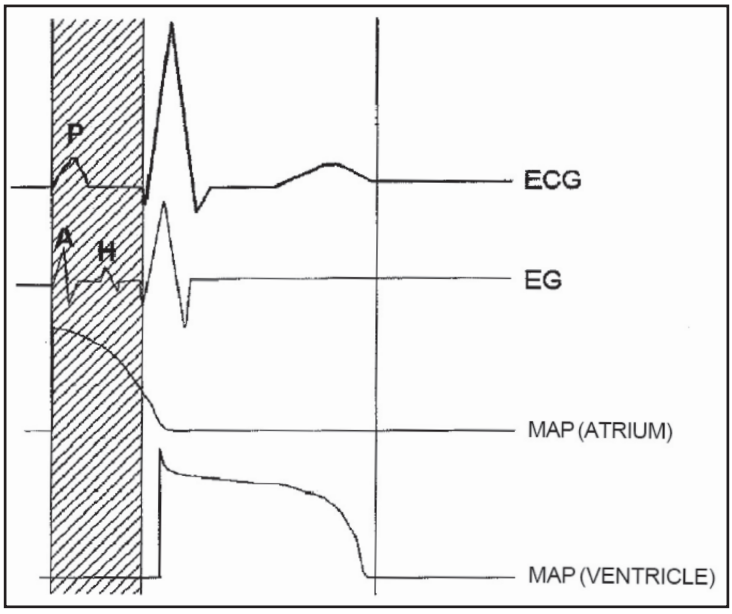


**Figure 5.** *Sketch of the temporal relation between the electrocardiogram (ECG), the electrogram (EG), and the atrial and ventricular monophasic action potential (MAP). Adapted from (Leirner and Cestari 1999).*

The duration of atrial AP, or its MAP, varies from around 200 to 320 ms (Courtemanche et al. 1998, Li et al. 2001, Christ et al. 2004). Atrial AP morphology varies frequently, and differences exist also between different cells in the same tissue. The three main types are a rectangular AP with a positive plateau, a spike and dome AP with a plateau at 0 mV, and a triangular AP with a short plateau (Courtemanche et al. 1998). It follows that the atrial depolarization signal detected from a distance may be contaminated with some repolarization signal. However, the main part of atrial repolarization takes place after both the atria have already depolarized.

The first deflection of the cardiac cycle reflecting the atrial electrical activity had already been identified by electrometer 17 years before the galvanometer was discovered; it was designated the *P wave* (Einthoven 1895). The first part of the P wave is generated by activation in the RA and the later part mainly by activation in the LA, both atria activating simultaneously 40 to 70% of the whole atrial activation time, as illustrated in Figure 6.

### 2.6.2 Electrocardiography (ECG)

In bipolar leads, both electrodes face sites with similar potential variations, whereas in unipolar leads, the potential variation in one electrode is negligible in comparison with that of the other. In the standard 12-lead ECG used in clinical practice, leads I, II, and III are bipolar; leads aVR, aVL, and aVF, and leads from V1 to V6 are unipolar (Surawicz 1995). If any two of the six limb leads are recorded simultaneously, the other four can be mathematically derived from them (Macfarlane 1989).

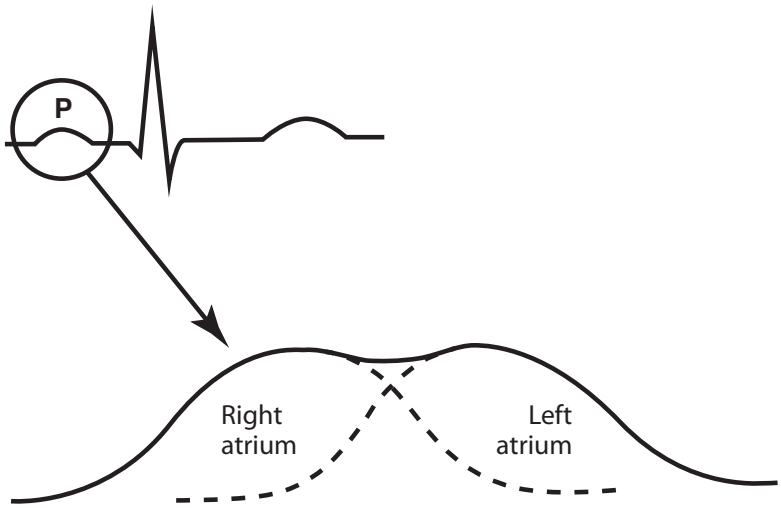


**Figure 6.** *Schematic representation of the main components of the P wave. Adapted from (Heikkilä 1991).*

An orthogonal 3-lead system allows interpretation of electrical conduction in the heart in three dimensions. Such a lead system, called vectorcardiography (VCG), is based on the simple dipole model, represented by a vector, using a system of three orthogonal axes, x, y, and z, that define three mutually perpendicular planes. The projection of the trajectory of this vector is drawn in relation to these axes, forming a loop display on an oscilloscope representing a cardiac cycle (Frank 1956). In ECG the important information is time and amplitude; in VCG it is magnitude and direction of propagation of the electromotive forces of the heart.

#### *2.6.2.1 P wave duration and morphology*

According to the International Society and Federation of Cardiology Task Force, normal P wave duration is less than or equal to 110 ms (Willems et al. 1985). Other authorities in the field argue that 120 ms may be a more appropriate cut-off value (Ariyarajah et al. 2006). Erlich and coworkers (2001) examined 123 volunteers without cardiovascular disease aged from 20 to 79. Their P wave duration was automatically determined by a filtering technique and computer algorithm. In the whole population, the P wave duration was 114 on average. In men, the duration was significantly longer than in women, 118 vs. 111 ms, with a slight, but significant, correlation between P wave duration and age. In another study, the 2078 healthy Chinese subjects were aged between 1 and 87 (Wang et al. 2002). The maximum P wave duration in the standard non-filtered 12-lead ECG was 110 ms on average. Similar to findings in an earlier report, a slight correlation appeared between P wave duration and age. Based on this population, the normal P wave duration was 96 to 120 ms.

If the LA is enlarged, the P wave is prolonged, but the P wave can be prolonged also in normal size atria (Goyal et al. 2001). The age- and gender-related differences have been

atributed to LA dimensions, but findings are conflicting (Liu et al. 2004, Kistler et al. 2004).

The P wave duration ≥ 110 ms (or ≥ 120 ms) in standard 12-lead ECG with notched P wave morphology in some of the leads has been defined as partial intra-atrial block (IAB), and P wave duration ≥ 120 ms with biphasic P waves in inferior leads is the criteria for advanced IAB (Bayes de Luna et al. 1985). Because discrete lesions produced experimentally in the BB cause delayed activation of the LA resulting in the typical P waves of IAB (Waldo et al. 1971), the main mechanism of IAB is thought to lie in BB abnormality. In human studies using ECG, vectorcardiography, and esophageal recordings, advanced IAB has been related to retrograde ascending activation of the LA (Castillo and Vernant 1973, Bayes de Luna et al. 1988). The prevalence of advanced IAB is relatively low, but the partial IAB is much more common and documented in 30 to 50% of hospitalized patients and documented even more often with advanced age (Frisella et al. 2005).

Prolonged P wave and especially the advanced IAB are associated with a history of or a high risk for atrial tachyarrhythmias (Bayes de Luna et al. 1999). Platonov and coworkers (2000) showed that a history of lone AF was associated with a particular P wave morphology, primarily the presence of the biphasic P waves in the orthogonal Z-lead. Recently, a study referenced by electroanatomic mapping (EAM) demonstrated that this type of ECG was related to conduction via the BB with or without simultaneous conduction via the CS (Holmqvist et al. 2008). If the Y wave were also biphasic, the conduction would occur totally via the CS connection.

#### *2.6.2.2 P wave dispersion*

The interlead variation in P wave duration, the so-called P wave dispersion, is a well-recognized phenomenon. However, whether the P wave dispersion can be attributed to an underlying heterogeneity of atrial conduction (a local effect), or to a variable projection of a single depolarization vector onto different ECG leads (a projection phenomenon), or to imprecision of measurement when the P wave amplitude is low and the P wave onset and offset are difficult to define, is not yet clear (Ndrepepa et al. 2000).

Buxton and Josephson (1981) introduced the isoelectric interval, derived by subtracting the longest P wave duration in the standard limb lead from the total P wave duration. This interval was higher in patients with an AF history than in controls. Later studies, generally used a standard 12-lead ECG (Dilaveris et al. 1998). A study by Dilaveris and coworkers (1998) found P wave dispersion to be higher in patients with paroxysmal lone AF than in controls. Increased P wave dispersion has predicted frequent symptomatic AF paroxysms (Aytemir et al. 2000, Dilaveris et al. 2000) and AF recurrence after cardioversion (Dogan et al. 2004, Perzanowski et al. 2005). Two studies have demonstrated increased dispersion of the filtered P wave duration in patients with paroxysmal AF (Kubara et al. 1999, Yamada et al. 1999). In these same studies, the dispersion served to assess the efficacy of the antiarrhythmic drugs, showing that dispersion of the P wave decreased after administration of a single dose of the

antiarrhythmic drug in those patients in whom the drug was going to be effective, but it increased in patients showing AF recurrences.

#### *2.6.2.3 Signal-average ECG (SAECG, P SAECG, P-SAE)*

The advantage of the SAECG over the standard ECG is its ability to record low-level electrical signals through the use of special acquisition, amplification, and signal-processing devices. The delayed potentials related to the re-entrant substrate in patients prone to ventricular tachycardia were for the first time detected from the body surface with SAECG (Berbari et al. 1978). Re-entrant substrates may be involved also in the genesis of AF. This and the possibility of a more precise measurement of P wave duration have been a impetus to apply SAECG to atrial studies.

The study by Yamada and coworkers (1989) demonstrated between AF patients and controls a significant difference in filtered P wave duration (FDP) and in root mean square voltage of the last 20 ms of the P wave (LP20 or RMS20). FDP was significantly longer and LP20 significantly lower in AF patients. The combination of these parameters could be useful to identify AF patients (Fukunami et al. 1991). In a subsequent study by the same group the terminal portion of the P wave contained more components in the 20 to 50 Hz range in patients with than without AF (Yamada et al. 1992). Fragmented electrical activity (FEA) after successful cardioversion has been significantly more frequent in those AF patients who had a reccurence during follow-up than in those remaining in SR (Benchimol Barbosa et al. 2006). Abe and coworkers (1997) used duration and RMS voltage of the last 30 ms (LP30) of the SAECG P wave to predict the transition of paroxysmal AF to permanent AF. The longer duration of the low-voltage area (amplitude below 2-3 μV) in the end of the filtered P wave has also been related to AF (Gondo et al. 1995, Moreira et al. 2006). Cut-off values of 10 and 15 ms have been suggested as predictive for AF. The low amplitudes for the initial portion of the P SAECG signal have been related to sinus node dysfunction (Takase et al. 2006). In one electrophysiolocical study, the reduction in P wave energies was related to slowing of conduction velocity and longer LA ERP (Redfearn et al. 2006).

During recent years, several applications of P SAECG in various clinical conditions and with different AF populations have been performed. The main findings related to a propensity to AF have been the prolongation of a filtered P wave, lower late RMS values, and a longer low voltage interval in the terminal part of the atrial complex (Klein et al. 1995, Dhala et al. 2002, Darbar et al. 2002, Budeus et al. 2005, Moreira et al. 2006). One interesting setting is alcohol-induced paroxysmal AF. In a study by Steinbigler and coworkers (2003), patients with their first episode of AF initiated immediately after consumption of alcohol were investigated, along with controls. The FPD was significantly longer in patients than in controls both at baseline and after intake of alcohol. Duration of non-filtered P wave showed no difference.

### 2.6.3 Magnetocardiography (MCG)

MCG is a technique to register the extracorporeal magnetic field generated by the same bioelectric activity that generates electric potentials (Nenonen 2002, Tavarozzi et al. 2002). First detected in the early 1960s, the cardiac magnetic field has a peak amplitude of about 50 pT, which is one millionth of the earth's magnetic field (Baule and McFee 1963). Cohen (1967) was the first to use a shielded measuring chamber. However, it was only after the invention and implementation of the SQUID (Superconducting Quantum Interference Device) sensors in liquid helium at 4.2 K (-269 C) in the beginning of the 1970s that accurate detection of MCG signals became possible (Cohen et al. 1970). Today, MCG recording is carried out with multichannel systems acquiring the signals simultaneously over the whole chest. By use of magnetically shielded rooms and gradiometer coils, the environmental interference can be suppressed so that recordings can now be done also in a hospital environment (Figure 7). With these techniques typical noise levels for magnetometers or axial gradiometers range between 5 and 10 fT/√Hz at low frequencies, and a sensitivity as high as 2fT/√Hz has been reported. Alternatively, if no magnetic shielding is employed, high-order gradiometers can be utilized (Nenonen et al. 2002).

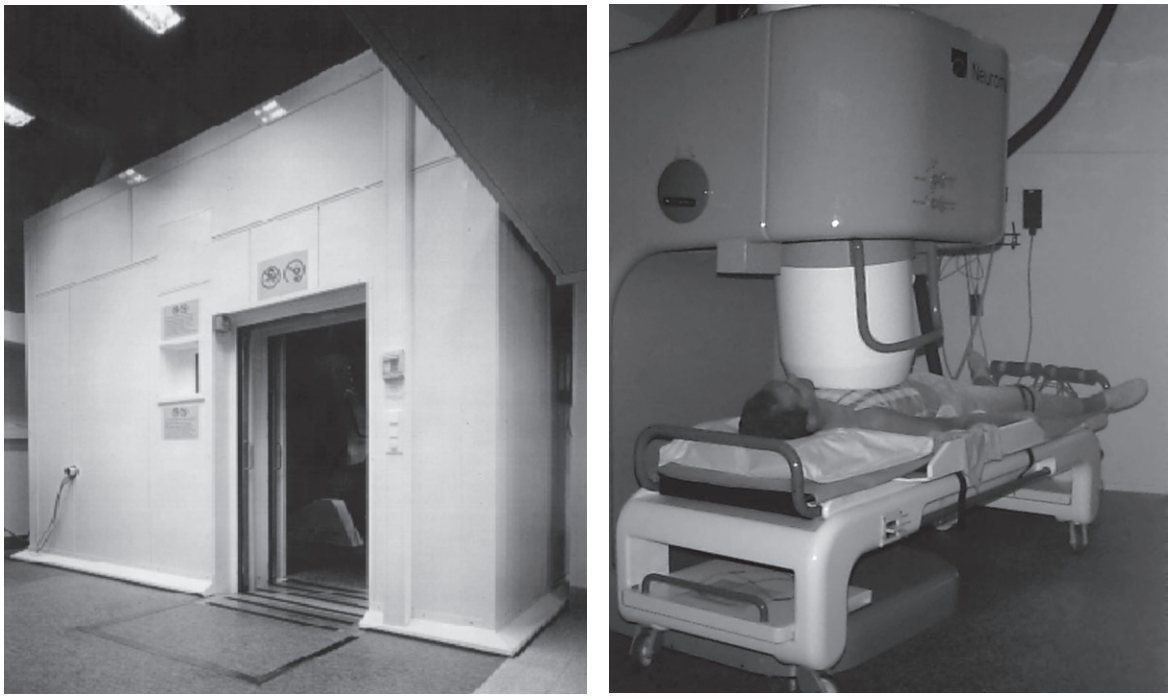

**Figure 7.** *Shielding room (left) and modern multichannel MCG system today (right). BioMag Laboratory HUSLAB, Helsinki.*

MCG has morphological features similar to those of the P wave, QRS complex, and T- and U-waves of the ECG, and although the temporal relations between them are generally the same, their spatial orientation differs (Saarinen et al. 1978). The essential difference between electrical and magnetic fields is the spatial angle of 90° between them (Siltanen

1989), which means that the positive and negative extremes of MCG and ECG are not in the same area (Figure 8).

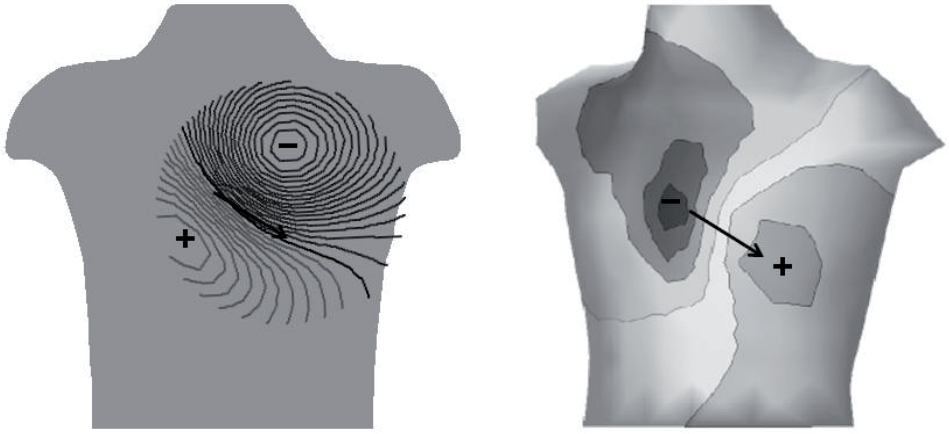

**Figure 8**. *Isocontours of the magnetic field component $B_z$ and of the potential on the anterior thorax surface, generated by a tangential current dipole ( arrow) in a homogenous thorax model.*

Usually an MCG system measures the magnetic field $B_z$ component, i.e., field density perpendicular to the surface of sensor play, and the spatial change in this component, the planar gradients $d(B_z)/dx$ and $d(B_z)/dy$. When recording is performed over the anterior chest, as it usually is, the $B_z$ component is at right angles to the anterior chest. In MCG, the currents tangential to the $B_z$ component give the strongest signal, whereas ECG, especially chest leads, is most sensitive to radial currents. MCG can therefore show pathological deviation from the normal direction of depolarization or repolarization in a different manner than ECG can (Siltanen 1989). It follows also that currents tangential to the chest are better detectable by MCG than by ECG on the body surface. Another difference is that MCG is sensitive to curl currents and can measure a close-looped current on the myocardium, whereas the ECG records it as a zero-potential. MCG is also less affected than is ECG by conductivity variations caused by the lungs, pericardial effusions, muscles, and skin (Plonsey 1972, Siltanen 1989).

#### *2.6.3.1 Perspectives on MCG analysis methods in atrial studies*

The weak electrical currents of the atria propagating mostly tangential to the chest generate clear deflections to the MCG $B_z$ component recorded over the anterior chest. When the distance between sensor and electrical force increases, the field density (amplitude) attenuates in the proportion of 1/r2. (Saarinen et al 1974, Siltanen 1989) In atrial measurements this means that the density of the signal from the posterior wall of the LA is about one-third that of the anterior wall, and the signal from the LA anterior wall is about three-fourths that of the RA anterior wall. Within 1 cm of anteroposterior variance, these proportions are relatively constant. Variance in torso shape between subjects may

diminish maximal field densities by up to half or one-third, but the influence of the proportion of different components is less pronounced. It follows that amplitude variables may need assessement in relation to other atrial amplitudes, but otherwise the signal content, MCG atrial wave morphology - or field orientation - are stable. This facilitates detailed time domain analysis of the atrial signal as well as performance of these variables with good reproducibility.

As a conventional time-domain presentation, the MCG data can be analyzed similar to ECG data. Magnetic late fields determined parallel to SAECG late potentials, as well as MCG intra-QRS fragmentation, have been shown to indicate a propensity toward life-threatening arrhythmias in post-myocardial infarction patients (Mäkijärvi et al. 1993a, Korhonen et al. 2000, 2001). QRS subtraction techniques and time frequency analyses have also been adapted to MCG data (Yamada et al. 2002, Kandori et al. 2002).

Multichannel MCG offers possibilities to study cardiac activation sequences non-invasively. A pseudo-current pattern reflecting the bioelectric currents in the heart can be obtained from multichannel MCG data without the need to apply specific source and volume-conductor models. The method is based on estimating the gradients along the sensor-array surface from the magnetic-field component perpendicular to the chest ($B_z$) (Cohen and Hosaka 1976, Koch and Haberkorn 2001, Nenonen et al. 2003). The largest surface gradient in the sensor array reveals the site of the active region, whereas the direction of the gradient provides a useful tool for analyzing signal propagation. This method has been successfully applied to detect and localize ischemia (Van Leeuwen et al.1999, Hänninen et al. 2000), to localize the source of paroxysmal atrial tachycardia and accessory pathways in WPW syndrome (Pesola et al. 1999, Fenici et al. 1999), and to animate the sequence in which a premature complex transforms SR to AFL via AF (Yamada et al. 2003). In recent research, 3D modeling has also been used (Nakai et al. 2005, Kim et al. 2007).

#### *2.6.3.2 MCG atrial wave*

On the lower right chest, the atrial magnetic field $B_z$ component is mostly positive, i.e., magnetic field flux is toward the chest, and on the other parts of the anterior chest the field is mainly negative, i.e., flux is out of the chest. In the conventional time-domain presentation, MCG P waves are mainly positive over the right lower chest and mainly negative in the other areas and, if displayed as an isofield map over the whole atrial complex, the negative extreme is located on the upper left chest, the positive extreme on the lower right chest, with the zero line running from the subject's right shoulder leftward down as illustrated in Figure 9.

The RA overloading raises atrial wave amplitudes without any influence on field orientation (Takeuchi et al. 1988). In LA overloading, the main finding was the increased occurrence of biphasic atrial waves at left parasternal sites and extra dipoles on field density maps in the late phase of atrial activation (Sumi et al. 1986, Takeuchi et al. 1988).

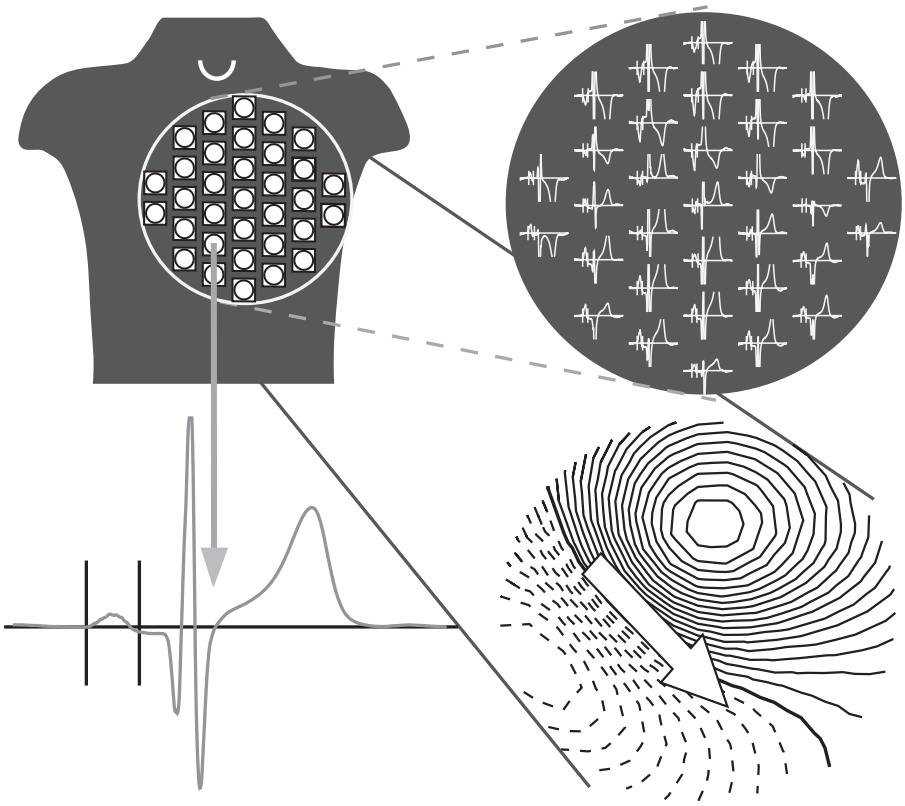

**Figure 9**. *Schematic illustration of channel positions in the cardiomagnetometer. The cardiac signal of a patient on a 33-location array, at one central channel, and a magnetic field integral map over the atrial wave. Solid line indicates flux towards and dashed line outwards from chest.*

### *2.6.3.3 Time-domain analyses of the MCG atrial wave*

Winklmaier and coworkers (1998) investigated a group of 15 AF patients with persistent AF converted to SR and 20 healthy young men. The multichannel MCG over the anterior and posterior chest and a 12-lead ECG were recorded simultaneously. Sum channels were generated from all MCG channels and separately from anterior and posterior channels and ECG channels. The P wave duration was manually measured in each sum channel. The homogeneity and fragmentation of MCG maps were evaluated. The P wave was divided into four segments, and correlation was calculated between maps. All segments were compared with the first segment, and the average of these three correlations, the p-score, served as the homogeneity factor. The fragmentation index of the P wave was calculated as the sum of amplitude differences between two amplitude peaks multiplied by the total number of amplitude peaks in each sum channel. By MCG, the P wave duration was longer, the correlation factor lower, and fragmentation index higher in patients than in controls. No such differences were evident in ECG.

#### *2.6.3.4 Spatial MCG maps, field polarity, and orientation during atrial activation*

Mäkijärvi and coworkers (1993b), investigating spatial MCG maps in WPW patients, found that patients with AF attacks had more dispersed atrial depolarization distributions than did patients without AF. Of patients with AF, 55% had more than two extremes on their atrial depolarization maps. On the other hand, 67% of patients without AF had bipolar MCG maps, as well. In an earlier study, multipolar MCG fields during the late phase of atrial activation were related to LA overloading (Sumi et al. 1986).

A pilot study by Nenonen and coworkers (2003), applied the surface gradient method to examine atrial activation during SR, with minimum-norm estimation and pseudocurrent transformation used. MCG distribution and pseudocurrent orientation was followed over atrial activation. During the early phase of activation, the pseudocurrents were pointed from the subject's right shoulder leftward and down, but were then rotated leftward and up after the middle of the activation. Yamada and coworkers (2003) utilized the tangential component MCG method (equivalent to the pseudocurrent transformation) to examine atrial activation during atrial flutter. A circular pseudocurrent pattern was observable in all patients.

Using 64-channel MCG, Nakai and coworkers (2005) constructed a 3D heart outline and conduction pathway in patients with AF or atrial flutter, using the minimum normalization method and space filter technique. This model demonstrated macro re-entry during atrial flutter and random micro re-entry during AF. Kim and coworkers (2007) visualized activity maps of the AF signal on the heart surface and utilized these maps to guide minimal surgery. Atrial activation pattern during SR has not been reported by these methods.

# 3 AIMS OF THE STUDY

The aim of this study was to find non-invasive parameters obtained during sinus rhythm reflecting electrophysiological patterns related to propensity to AF, particularly in the lone paroxysmal form of the arrhythmia.

The methods of choice were magnetocardiography and electroanatomic mapping. The purpose was to evaluate and advance non-invasive electromagnetic methods to investigate the atrial signal. Invasive EAM was used to evaluate atrial electrophysiology, especially interatrial conduction pattern, and as a reference for non-invasive measurements.

The specific aims were to explore:

I the recording of atrial signal by multichannel MCG, to specify the processing and detection of atrial depolarization signal obtained by this technique and to assess reproducibility of atrial signal variables.

II atrial electrophysiologic properties non-invasively by using MCG mapping in patients with paroxysmal lone AF, particularly to find whether any difference exists between those who express frequent triggers of AF and those who do not.

III the natural impulse propagation from RA to LA during sinus rhythm in patients with paroxysmal AF (an electroanatomic study).

IV whether non-invasive MCG mapping techniques can be used to detect atrial activation patterns, particularly interatrial pathways, and to validate the method with invasive EAM as a reference.

V atrial signal propagation in a larger cohort of patients with paroxysmal lone AF and in healthy subjects to learn whether signal propagation to the LA during sinus rhythm differs between these groups.

# 4 MATERIALS AND METHODS

## 4.1 Subjects and study outlines

In total 136 patients with AF and 104 controls were included in the studies. The demographic characteristics of the study subjects are presented in Table 2. All measurements were carried out during SR. All of the study subjects gave their informed consent. The research protocols were approved by the local ethics committee and complied with the Declaration of Helsinki.

**Table 2.** *Characteristics of study subjects in Studies I-V.*

| | ***Study I*** | ***Study II*** | ***Study III*** | ***Study IV*** | ***Study V*** |
|---|---|---|---|---|---|
| ***Patients total, 136*** | | | | | |
| Number | 9[1] | 80[2] | 50[3] | 27[4] | 107[5] |
| Males (%) | 7 (78) | 61 (76) | 39 (78) | 21(78) | 80 (75) |
| Age (years) | 43 ± 15 | 44 ± 12 | 49 ± 9 | 45 ± 10 | 45 ± 12 |
| AF type | lone paroxysmal | lone paroxysmal | lone paroxysmal or persistent | paroxysmal 3 not lone | lone paroxysmal |
| Hypertension | 1* | 8 (10)* | 0 | 1 | 10 (9)* |
| Antiarrhythmic medication | 0 | 24 (30) | 27 (54) | 10 (37) | 27 (25) |
| b-blocker | | 24 (30) | 15 (30) | 8 (30) | 27 (25) |
| class I or III | | 0 | 16 (32) | 5 (18) | 0 |
| EAM (maps/subjects) | none | none | 50/50 | 29/27 | none |
| MCG (maps/subjects) | 18/9† | 80/80 | no | 29/27 | 115/107 |
| ***Controls total, 104*** | | | | | |
| Number | 10[6] | 80[7] | none | none | 94 |
| Males | 10 (100) | 61 (76) | | | 70 (75) |
| Age (years) | 31 ± 9 | 43 ± 14 | | | 44 ± 14 |
| Hypertension | 0 | 6 (7)* | | | 7 (7)* |
| Antiarrhythmic medication | | | | | |
| b-blocker | 0 | 1 (1) | | | 2 (2) |
| class I or III | 0 | 0 | | | 0 |
| MCG (maps/subjects) | 20/10† | 80/80 | | | 102/94 |

*Number (%) of study subjects or mean ± SD. AF, atrial fibrillation; EAM, electroanatomic mapping; MCG, magnetocardiography. * Borderline arterial hypertension without left ventricular hypertrophy; † repeated measurements. [1] All are included also in Studies II and V; [2] 16 included also in Studies III and IV, all included in Study V; [3] 27 not included in other studies (no MCG data); [4] 16 included also in Study II, 22 included in Study IV, and 21 included in Study V, 5 not included in Study III (not lone AF 3, new patient 2), and 6 not included in Study V (not lone AF or antiarrhythmic medication, or both); [5] 24 not included in other studies (new patients); [6] 8 included also in Study II; 7 included also in Study V (matching); [7] 72 included also in Study V (matching).*

## Study I

In Study I, the MCG recording protocol and data processing for MCG atrial signal were outlined. The basic signal-analyzing techniques and parameters were selected, and analyses were automated. The focus was on the high-pass filtering techniques. The methods used were partly adapted from QRS analysis techniques and partly created during this study. Several candidate techniques and algorhithms were tested. Their relevance in the light of earlier studies and knowledge of atrial electrophysiology and reproducibility of the parameters (both in healthy subjects and in patients with AF) was the criterion for selection of the methods for further study.

The study population comprised 10 healthy volunteers and 9 patients with paroxysmal lone atrial fibrillation. To assess reproducibility, all subjects underwent repeated MCG recordings at least at one-week intervals (from 1 week to 6 months). For comparison, the 6 limb leads of the standard 12-lead ECG and 3-lead orthogonal ECG were recorded simultaneously and analyzed with parallel methods along with the MCG data.

## Study II

In Study II, the methods introduced in Study I and some new variables were applied to a larger population of patients with lone paroxysmal AF and to controls to evaluate atrial electrophysiological properties. Of particular interest was to find whether any difference exists between those patients who express frequent triggers of AF and those who do not. Patients with paroxysmal AF and age- and gender-matched controls, 80 each, were examined. Patients were screened from among those referred to a tertiary hospital due to symptomatic paroxysmal AF. Included were patients aged less than 65 years and without any structural or other heart diseases. These patients were screened for heart disease by clinical investigation, ECG, and echocardiography. Borderline arterial hypertension without left ventricular hypertrophy was allowed. Any class I or III antiarrhythmic medication was discontinued at least five drug half-lives before examination, but severely symptomatic patients were allowed use of β-adrenergic antagonists.

Ambulatory ECG monitoring for 24 or 48 hours was analyzed for classification of AF to a focal or non-focal type. Data regarding arrhythmia history were collected from patient interviews and medical records. To describe the frequency of AF recurrences the average number of arrhythmia episodes over the past year was assessed from patients' reports and medical records.

## Study III

Study III focused on invasive measurements and particularly on elucidating impulse propagation from the RA to LA. Alterations in conduction from RA to LA have been linked to susceptibility to AF. However, knowledge of interatrial conduction in the intact human heart during SR has been based on only a few relatively small studies. In this study, a total

of 50 patients referred for catheter ablation of AF (Helsinki 36, Lund 14) were recruited. Selection criteria for the study were: 1) diagnosis of paroxysmal or persistent AF with disabiling symptoms, 2) structurally normal heart and 3) age below 70 years. Only patients with SR at the time of the EAM were included. Antiarrhythmic medications were halted prior to ablation when possible.

### Study IV

In Study IV, the main emphasis was on detection of interatrial conduction pattern non-invasively. MCG mapping and a new analysis method based on a surface gradient technique were utilized and validated with intracardiac EAM as a reference. The study comprised 27 patients undergoing electrophysiological examination prior to catheter ablation therapy for paroxysmal AF. Patients were included who were able to go to MCG recording before ablation and who were in SR both at the time of the MCG recording and at the time of EAM. Presence of structural heart disease was assessed by clinical, ECG, and cardiac ultrasound examinations. Anti-arrhythmic medication was discontinued at least for five half-life times before examination in the majority of patients. The LA was mapped in all patients, and in six patients RA was also mapped intracardially.

### Study V

In Study V, the MCG mapping method introduced in Study IV was applied to a larger population to examine whether interatrial conduction differs between patients with lone paroxysmal AF and healthy subjects. AF patients numbered 107, and controls, 94. Controls were matched to equalize gender and age distribution in both groups. Inclusion criteria were otherwise the same as in Study II, but no data from ambulatory ECG monitoring was required.

## 4.2 Magnetocardiography

### 4.2.1 Recording and data processing

MCG was recorded in a magnetically shielded room (ETS-Lindgren Euroshield Oy, Eura, Finland) using a multi-channel cardiomagnetometer (Elekta Neuromag Ltd, Helsinki, Finland) equipped with 33 triple sensor dc-SQUID units on a slightly curved surface with a diameter of 30 cm (Figure 7). In each unit a magnetometer overlies two orthogonal planar gradiometers, the magnetometer coil direction being perpendicular to the sensor array (z-axis). Measured are the magnetic field Bz component and the spatial change in this component, the planar gradients, d(Bz)/dx and d(Bz)/dy.

During recording the subjects lay on a non-magnetic bed. The location of the MCG sensor array in regard to the chest was obtained via marker coils. In each measurement session, three coils were attached to the subject's anterior chest. The location of these coils and bone landmarks on the chest were determined with a 3D digitizer. After digitizing, the device was placed over the anterior chest as close as possible to, but without touching the skin, the center of the sensor array positioned at 15 cm below the jugular notch and 5 cm left from the midsternal line as schematically illustrated in Figure 9. Before data acquisition, an electric current was fed through the coils, enabling their localization in MCG measurements. This provided information as to where the frontal chest was positioned under the MCG sensor array. Recordings were performed during SR from 5 to 7 minutes. Simultaneously the limb leads of the standard ECG, and orthogonal three-lead ECG were recorded. The analog signal pass-band was 0.03-300 Hz, and sampling frequency of analog-to-digital conversion was 1000 Hz.

To increase the signal-to-noise ratio of Signal-Space Projection (SSP) (Uusitalo and Ilmoniemi 1997), 50 Hz band pass filtering and signal averaging were used. The data were averaged by use of XCardio software designed for processing functional imaging format data obtained in the measurements. In the averaging, beats were compared to a selected template beat and either accepted or rejected according to criteria defined by the user. In this study, the criteria were correlation greater than 90% in magnetometer channels, 80% in planar MCG channels, and 95% in ECG channels and maximum noise of 200 fT in magnetometer channels, 150 fT/cm in planar MCG channels and 20 yV in ECG channels in a 40-ms noise window at the T-P segment. Another requirement was that the T-wave should fit in a tube of 2 pT for magnetometer channels, 1pT/cm for planar MCG channels, and 150 yV for ECG channels around the template beat. The baseline for the beats was defined from a 40-ms section of the TP interval about 20 ms before P wave onset. In case of significant baseline drift, the line was fitted between two successive T-P intervals. The P waves and QRS-T complexes were averaged separately. Ectopic beats and excessively noisy sinus beats were rejected. If two distinct sinus P wave morphologies were present, these were separately averaged. To be classified into two differing sinus P waves, both should be designed to be of sinus origin according to the heart rate and AV conduction pattern; both morphologies should appear as series, and during selective averaging, each beat should become selected in only one morphology, even if the correlation limit was lowered.

### 4.2.2 Application of high-pass filtering techniques

Onset and end of the P wave as well as P wave duration (Pd) were automatically determined by 40-Hz high-pass filtering and a computerized algorithm. More specifically, determination of the duration of atrial complex was done as follows: 1) the averaged signal was high-pass filtered using a bidirectional Butterworth-type, fourth-order filter having its corner frequency at 40 Hz (in Study I 25 and 60 Hz filters were also examined). 2) An envelope complex was formed by Hilbert transformation realized by a finite impulse response filter. 3) Noise was determined as the mean signal amplitude over a 40-

ms time window in the TP segment. MCG channels with a mean noise level over 20 fT were rejected. 4) The onset of the atrial complex was defined as the mid-point of a 5-ms interval where the average amplitude first exceeds the mean noise level by 10 fT when approaching the atrial complex. 5) Atrial signal end was determined as follows: First, the lowest mean amplitude of a 5-ms window which was found between the atrial and QRS complexes was set as the reference noise level. Then the atrial complex offset was defined as the mid-point of a 5-ms interval where the mean atrial signal amplitude declines to less than 10 fT above the reference noise level. MCG parameters from individual channels were used to assess spatial distribution. Variation between channels was expressed as standard deviation (SD) values. To estimate the whole activation time, atrial wave duration was calculated as the median offset time minus the median onset time in any channel (Figure 10).

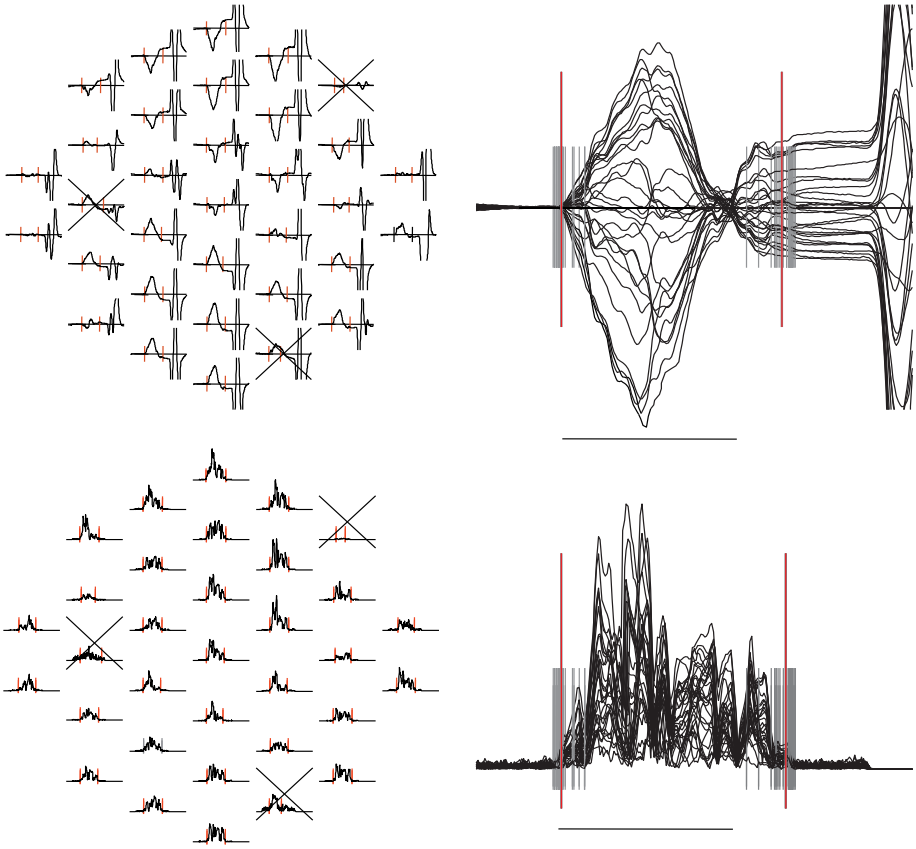

**Figure 10.** *Left: Example of automatically detected onset and end times of atrial depolarization signal in 33 magnetometer channels. Non-filtered (upper) and 40 Hz high-pass filtered signal (lower). Right: Data from 33 magnetometer channels superimposed. Red vertical bars indicate medians of onset and end times used to calculate duration of atrial depolarization complex.*

To be able to determine also very small amplitudes, the detection threshold was set to tolerate a 5% chance of error, i.e., false outliers cannot be avoided. The advantage of using medians is the ability to avoid the influence of these outliers in automated determination of atrial signal duration. Variation in the onset and end times between channels was 5 and

8 ms on average, and the difference between the earliest and latest detection and medians was 2 and 3 ms on average. This was considered accectable, taking into account the fact that the filter utilized in this work widens the signal by approximately 3 to 4 ms in Pd duration. The algorithm was developed and automated as a part of Study I.

Other variables determined automatically from the filtered signal were: maximal atrial signal amplitude, area of the high-pass filtered complex, and RMS amplitudes of the magnetic field strength during the whole atrial complex and initial and last portion of the signal (20, 30, 40, 50 and 60 ms time sequences). The mean amplitudes of the channels included served in further analysis.

### 4.2.3 Fragmentation analysis (II)

The fragmentation of the atrial complex was examined by computing the number of polarity changes in the binomial filtered (37-90 Hz) atrial complex and expressed as index M and score S by the method previously applied for the QRS complex (Korhonen et al. 2001).

### 4.2.4 PR interval and QRS-T analyses (II)

The QRS-T complex was averaged separately by use of maximum cross-correlation with the user-selected templates (Korhonen et al. 2000). Duration of the QRS complex (QRSd) was determined as described in detail earlier (Simson 1981, Korhonen et al. 2000). The PR interval was calculated via the medians of onset and end times in all averaged magnetometer channels. The ratios Pd/PR and Pd/QRSd were also calculated.

The end and the apex of the T-wave were automatically determined from non-filtered data (Oikarinen et al. 1998). The QT interval (from QRS onset to T wave end), corrected QT interval (Bazett's equation), and the time from T wave peak to T wave end (T apex – T end interval) were calculated. The heart rate was obtained as a mean of the R-R intervals preceding the averaged complexes.

### 4.2.5 MCG maps, application of surface gradient methods (IV, V)

Time interval over the first 30 ms of the atrial complex was taken to represent the early part of RA activation. The time interval of 40 to 70 ms after the beginning of the atrial complex was chosen to represent the early part of LA activation, and the latter half of the atrial wave to represent the later part of the LA activation (Figure 11). Selection of these time intervals was based on knowledge of the atrial activation sequence (Roithinger et al. 1999, De Ponti et al. 2002, Lemery et al. 2004, 2007, Markides et al. 2003, Cosío et al. 2004).

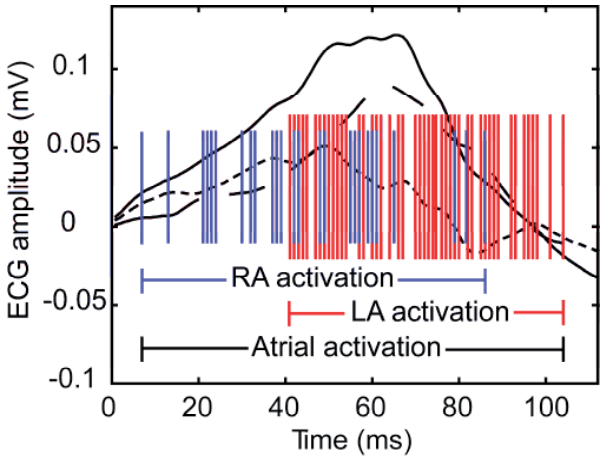


**Figure 11.** *Right (RA) and left (LA) atrial activation times in relation to entire atrial activation in electroanatomic mapping. Vertical bars represent each measured point in RA (blue) and in LA (red). The three curves show simultaneously measured electrocardiographic leads I (- - -), II (− −) and III (.....). Both atria were activating simultaneously over 43% of the total activation time.*

Integrals of the magnetic field Bz component over the defined time intervals were interpolated at the sensor array plane over the anterior chest from the signal-averaged atrial waves. This was done using magnetic multipole expansion (origin at 15 cm below the central magnetometer, expansion order 5) as the equivalent source and pseudo inverse of the transfer matrix to determine the multipole coefficients (Jackson et al. 1999). The forward transfer matrix was created as an equally spaced grid of points on a cylindrical surface (radius 82 cm) spanning the sensor area with separation of 0.5 cm and diameter of 26 cm, resulting in a total of 2 128 points. Simple first-order approximation was used to evaluate the planar gradients, $\partial$(Bz)/$\partial$x and $\partial$(Bz)/$\partial$y, based on the grid data. A pseudocurrent conversion was used to characterize the orientation of magnetic fields (Cohen et al. 1976). This method is based on rotating the estimated planar gradients of the $B_z$ component by 90 degrees:

$$\vec{a} = \frac{\partial B_z}{\partial y}\hat{e}_x - \frac{\partial B_z}{\partial x}\hat{e}_y,$$

Here, $e_x$ and $e_y$ are the perpendicular unit vectors on the sensor array plane. The resulting arrow map provides a zero-order approximation (pseudocurrent pattern) for the underlying electric currents, the direction of the strongest pseudocurrents pointing in the direction of activation(s) over the inspected time-interval. To assess the MCG map orientation quantitatively, the mean of the angles of the top 30% of the strongest pseudocurrents was calculated, the zero angle direction pointing from the subject's right to left and being positive clockwise. The thresholding method is an efficient and robust means to characterize the magnetic field maps. The thresholded mean direction is less sensitive to noise than is the direction of a single pseudocurrent value. In cases with a complex (non-dipolar) magnetic field distribution, the shape of the thresholded area and the

pseudocurrent directions within the area may also serve to evaluate the reliability of the mean direction. This method is illustrated in Figure 12.

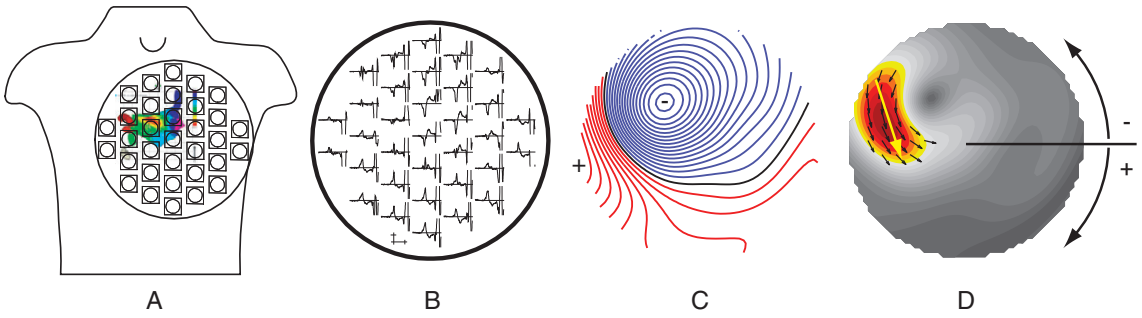


**Figure 12.** *Recording and analysis of atrial magnetic fields. A) Sensor arrangement of a 33-unit triple sensor (99-channel) magnetometer. Superimposed on the sensor array is the anteroposterior view of the left atrium by electroanatomic mapping. B) Signal-averaged magnetic field density on each magnetometer channel over a cardiac cycle. Onset and end of the atrial signal are determined automatically by a filtering technique. C) Spatial distribution of the magnetic field Bz component over the middle part of the atrial complex interpolated from the measurement using multipole expansion. Blue indicates flux out of the chest (-), and red, flux into the chest (+). The step between two consecutive lines is 200 fT. D) Pseudocurrent map derived by rotating magnetic field gradients by 90 degrees. The red-yellow area indicates the area of the top 30% of the strongest currents, and the yellow arrow indicates their mean direction. The zero- angle direction points from the subject's right to left, and positive is clockwise. Reprinted from the original publication (IV) with the permission of Oxford University Press.*

## 4.3 Electrocardiography (ECG)

### 4.3.1 Recording and data processing

The limb leads of the standard 12-lead ECG and a 3-lead orthogonal ECG (X, Y and Z) were registered simultaneously with MCG. Ag/AgCl electrodes were used. The X electrodes were placed in the left and right mid-axillary line in the fourth intercostal space; the Y electrodes were placed in the jugular notch and left superior spina iliaca anterior; the positive Z electrode was placed parasternally in the fourth intercostal space corresponding to lead V2, and the negative Z electrode was placed on the back as a reflection of the Z + electrode. The vector direction of this system is leftward, inferior, and anterior.

The ECG data were analyzed with the XYZ magnitude complex and by methods analogous to those applied in MCG. A 1 μV limit (analogous to 10 fT in MCG) was used in the definitions for atrial signal onset and offset. The P wave morphology in limb leads I, II, and III recorded during EAM by the CARTO system and during MCG mapping served to capture similar atrial activity in both mappings.

## 4.4 Intracardiac measurements (III, IV)

The EAM was performed with the electroanatomical mapping system (CARTO®XP System, Biosense Webster, Diamond Bar, CA, USA) with either a 7F Navi-Star or ThermoCool catheter (Biosense Webster). A decapolar 6F diagnostic catheter was placed in the CS for time reference. The electrophysiological study was performed using standard techniques with the CardioLab system (Prucka Engineering, GE Healthcare, WI, USA) or Bard LabSystem DUO (Bard Electrophysiology, Billerica, MA, USA).

### 4.4.1 Electroanatomic maps (EAM)

Three-dimensional isochronal activation maps were generated in SR, gated to a stable coronary sinus reference signal (Gepstein et al. 1997, Smeets et al. 1998). All the points and the respective ECG and intracardiac recordings in the maps were visually inspected. Local activation time was determined as the maximum or minimum of the first sharp deflection with its absolute value over 0.1 mV of the bipolar signal at the distal electrode pair of the catheter (Holmqvist et al. 2008, Weiss et al. 2001). P wave morphology was examined in order to ensure sinus origin. The point was rejected if the beat was ectopic, the intracardiac signal was less than 0.1 mV in amplitude, or signs of catheter instability were visible (Gepstein et al. 1997, Smeets et al. 1998, Roithinger et al. 1999, Weiss et al. 2001, Lemery et al. 2004, 2007, Holmqvist et al. 2008). If more than one sinus P wave morphology appeared in a recording, each was analyzed separately. When double potentials were found, the first was used except when it was a low-frequency far-field potential (Holmqvist et al. 2008). All intracardiac EGM data were gathered before the start of the ablation procedure.

### 4.4.2 Determination of interatrial conduction pathway(s)

Electroanatomic maps (EAM) of atrial activation were reconstructed applying interpolated colour code adjustments of local activation times on the recorded anatomic shape. The area of first activation in the LA was determined. Conduction via the BB was assumed when the earliest activation was in the upper third of the LA, superior to and leftward from the upper right PV. Conduction via the rim of the FO was assumed when the earliest activation was within the middle third of the LA, around the transseptal puncture site. Conduction via the CS region was assumed when the earliest activation was in the lowest 1 cm of the LA, with the activation front directed cranially. More than one electrical breakthrough site was considered to exist when distinct conduction sites were activated within 15 ms and were separated by areas showing later activation (Roithinger et al. 1999). According to the breakthrough sites observed, the patients were separated into BB, CS, FO, and combined (multisite activation) groups. The differing breakthrough patterns are illustrated in Figure 13. The LA activation sequence was examined by use of both activation and propagation maps, and the direction of signal propagation was assessed

visually. All electroanatomic signals were examined by two readers, and in cases of discordance in breakthrough sites, consensus was reached after consultation with an electrophysiologist experienced in cardiac mapping.

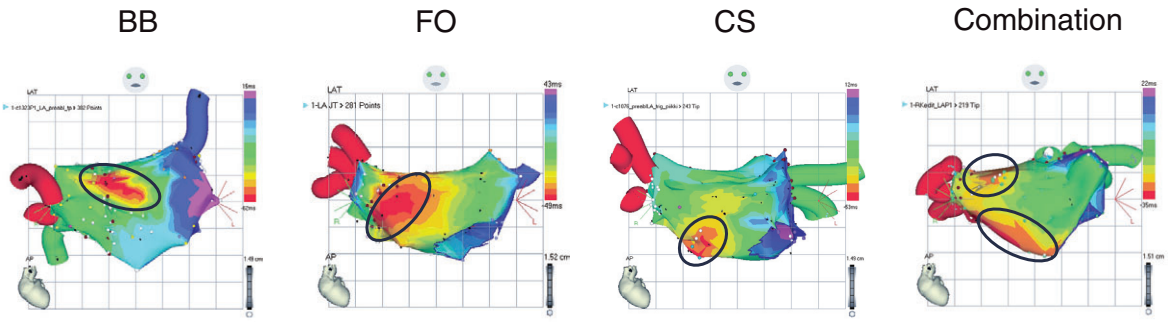


**Figure 13.** *Left atrial activation pattern in electroanatomic mapping. Isochronal activation maps during sinus rhythm in anteroposterior projection from four cases with differing interatrial propagation routes. The left atrium is activated via Bachmann bundle (BB), rim of the fossa ovalis (FO), coronary sinus ostium (CS), and a combination of BB and CS routes. Red identifies the earliest and purple the latest activation. The step between two isochronal lines is 5 ms. Activation breakthroughs are inside circles.*

### 4.4.3 Determination of activation times

The onset of atrial activation was determined from the 12-lead ECG with a speed of 100 mm/s as the earliest time-point where the signal could be separated from the baseline. The time from onset to the last intracardiac LA activation was defined as the total atrial activation time. Total LA and RA activation times were determined from intracardiac recordings.

## 4.5 Comparison between invasive and non-invasive measurements (IV)

The MCG map orientations during 40 to 70 ms after onset of the atrial complex and over its last 50% were compared to LA breakthrough areas in EAM in each individual. The pseudocurrent angles in MCG maps were calculated for the whole patient group and for subgroups with different breakthrough sites. In addition, in six patients, the MCG map orientation of the integral over the first 30 ms of atrial depolarization complex was compared to EAM of the RA. The P wave morphology in limb leads of the standard ECG recorded during both mappings served to capture similar atrial activity in each of the EAM + MCG map pairs (Vitikainen 2005). An example of the EAM and MCG data on the same time-scale is shown in Figure 14.

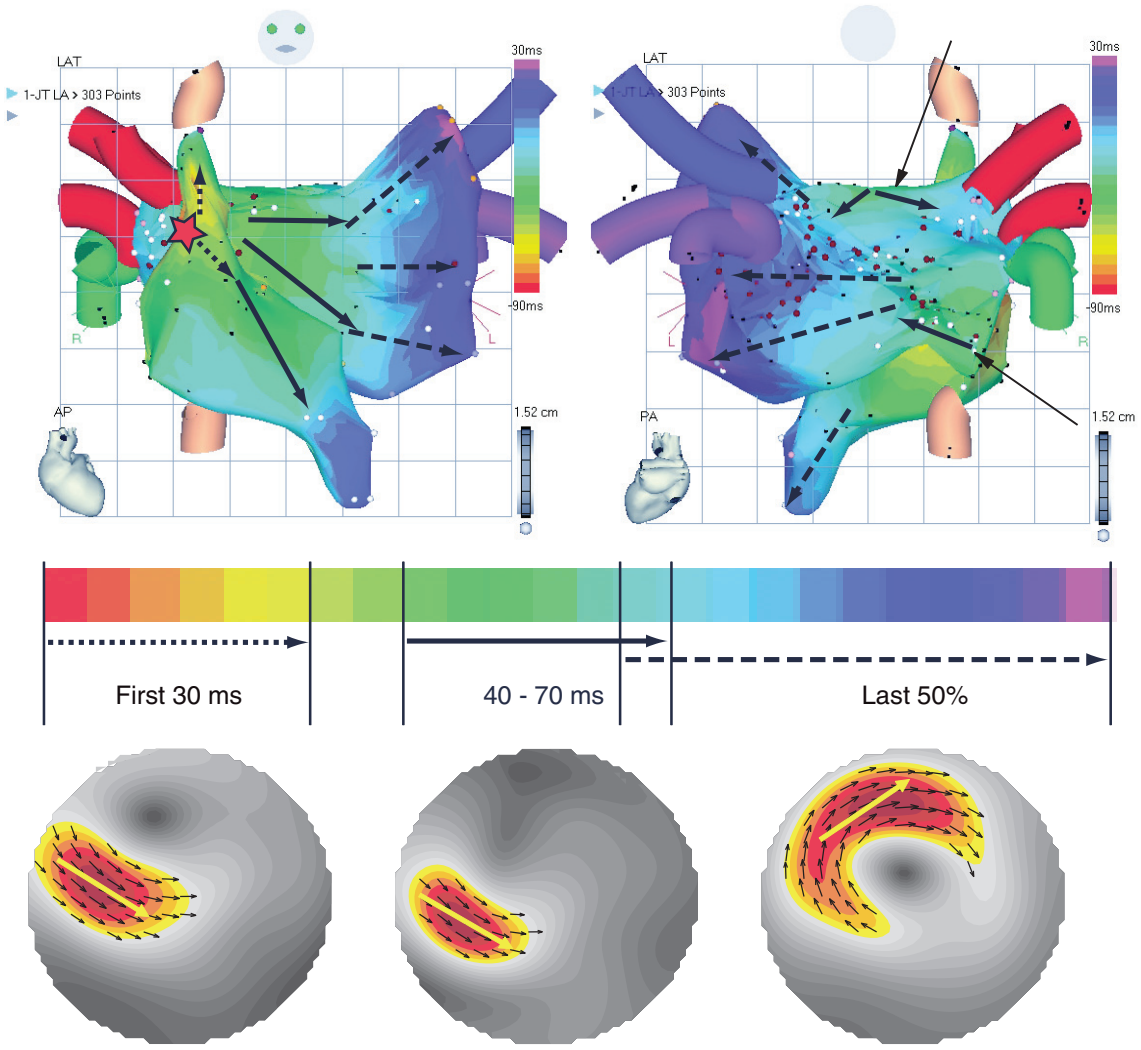


**Figure 14.** *Atrial electroanatomic (EAM) and magnetocardiographic (MCG) mappings. Above: EAM: isochronal activation maps of the right atria (RA) and left atria (LA) in anteroposterior (left) and posteroanterior (right) projections on a color-coded timescale. The step between two isochronal lines is 5 ms. Total atrial activation time in this case is 120 ms. The earliest RA activation is seen at the upper lateral-septal part of the atrium (red star). Earliest LA activation is in the middle interatrial septum and 5 ms later at the area of Bachmann bundle (BB) and 10 ms later at the coronary sinus (CS) ostial area. The multisite activation pattern is best visible from the back – marked by thin arrows, the upper representing BB and lower CS routes. Activation fronts are indicated by arrows and symbols ..... for RA, −−− for initial LA and - - - for later LA activation. Below: MCG: isochronal pseudocurrent density maps representing the RA (first 30 ms), initial LA (40-70 ms) and later LA (last half of the entire atria) activation time. Maps represent slightly tilted frontal plane projections with horizontal line from subject's right to left. Red-yellow areas correspond to the top 30% of the pseudocurrent amplitudes, with their mean angle indicated with yellow arrows. Reprinted from the original publication (IV) with the permission of Oxford University Press.*

## 4.6 Ambulatory ECG (II)

In Study II, ambulatory ECG monitoring for 24 or 48 hours was evaluated for classification into focal and non-focal types of AF. The number of PACs per hour and presence of early (P-on-T) PACs, atrial bigeminy, and atrial tachycardia were analyzed. AF was defined as focally triggered if it was initiated by frequent early PACs or rapid atrial tachycardia at a rate of > 200 beats per minute. In the absence of AF in the recording, AF was considered also focally triggered if repeated episodes of fast atrial tachycardia or uncommon flutter occured. Examples of typical findings in ambulatory ECG recordings are illustrated in Figure 15.

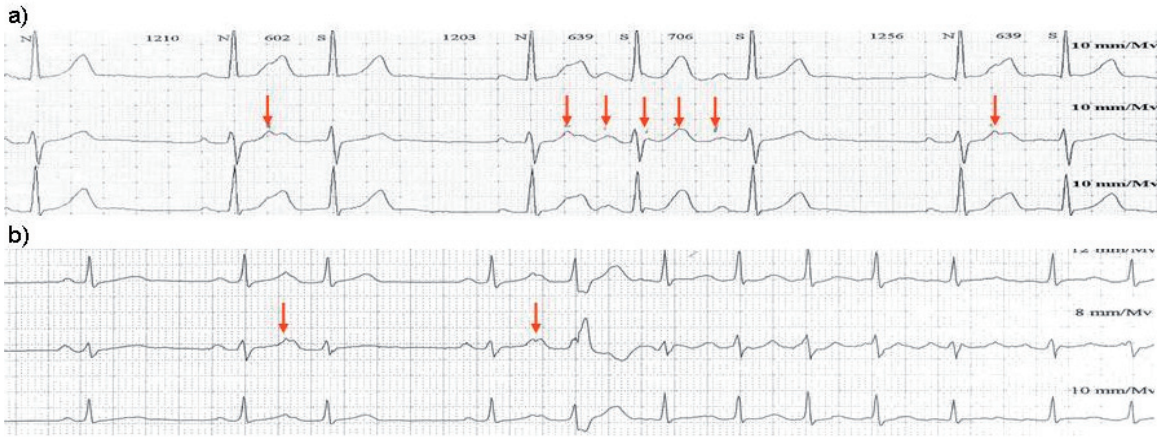


**Figure 15.** *Examples of ambulatory ECG recordings in two patients with lone paroxysmal AF confirmed to have a focal-origin AF in invasive mappings. a) Repeated premature atrial complex (P-on-T) appearing also as a series. b) Premature atrial complex appearing bigeminially and initiating a paroxysm of AF.*

## 4.7 Statistical methods

Continuous data are expressed as mean ± SD, angular data as mean angle and circular standard deviation (CSD), and categorical variables as number and proportion of positive cases in groups. Pearson's correlation coefficient was used to study the relationship of continuous variables. Coefficient of variation was used to compare measurements obtained by two different methods.

Differences between two groups were examined with Student's t-test or Mann-Whitney U-test, depending on the distribution, or the Wheeler-Watson-test (circular data), for continuous variables, and $\chi^2$-test for categorical variables. The one-tailed Mann-Whitney U-test was used to test angular distances between two groups.

Differences between multiple groups were examined with the following tests: Analysis of variance (ANOVA) followed by a multiple comparison test was performed for continuous variables. Nonparametric Kruskal-Wallis analysis of variance followed by a multiple comparison test served for circular variables. The $\chi^2$ test served for categorical

variables. In cases of multiple categories, to determine which categories were statistically different from which others, we used the procedure Multiple Comparisons for Proportions as described by J.H. Zar (1999).

In addition, in Study IV, an angular-angular correlation coefficient was used to study the relationships of the magnetic field map orientations, and Watson's $U^2$ test served for differences between groups (Zar 1999).

Coefficient of variation (CV) in repeated measurements was determined by analysis of variance, calculated as square root of mean square of within-subject variability divided by the mean of each variable, [(Mean square within)1/2/ mean] (Bland and Altman 1996). CV was transformed to percentage value by multiplying by 100. Comparison of reproducibility between different filtering frequencies and between groups was performed with proportional difference, which was calculated as $|m1-m2|/((m1+m2)/2)$ for each subject. (II)

A two-tailed p-value $< 0.05$ was considered statistically significant. Commercial software SPSS for Windows (SPSS Inc., Chicago, IL, USA) was used in Study I (version 11.5) and in Study III (version 13.0). Otherwise calculations were performed with Matlab R2006b, The MathWorks, Inc. utilizing Statistics Toolbox when applicable.

# 5 RESULTS

## 5.1 Clinical characteristics of study subjects (I-V)

Overall 240 subjects were enrolled, 136 patients and 104 controls. The mean age of patients was 45 years and about three-fourths were male. Men were younger than women and also had had onset of symptoms and confirmed AF diagnosis at an earlier age. None of the patients except three (included in Study IV) had structural heart disease. Slight arterial hypertension without LV hypertrophy in ECG or cardiac ultrasound was allowed and occurred in les than 10% of patients. None of the patients had permanent AF. Most of the patients were measured without any Class I and III antiarrhythmic medication. ß-blockers were allowed and used by 25 to 30% of the patients in Studies II to V. No difference existed between the patient and control groups (II, V) in regard to gender distribution, age, history of arterial hypertension, BMI, or LA or ventricular features in echocardiography. The patients tended to be taller.

In Study II, the clinical characteristics were evaluated in more detail. The age at time of first confirmed AF was about 37 years in men and 50 years in women and about 5 years later than onset of AF symptoms. In all, AF had occurred as recurrent, mostly self-terminating episodes. The majority had AF episodes at least once a week. An episode had lasted > 24 hours in 21% and > 1 week in 10% of the patients. Electrical cardioversion had been performed in 34% of the patients. In 72%, AF was classified as focally triggered by observations in ambulatory ECG or telemetry monitoring. The number of PACs was 46 ± 85 complexes per hour in focally triggered AF patients, whereas the number was 1 ± 1 complexes per hour in other AF patients.

## 5.2 Processing and detection of atrial depolarization signal

### 5.2.1 High-pass filtering techniques (I, II, IV, V)

Using MCG mapping and the high-pass filtering technique, the duration of atrial signal could be measured automatically with good reproducibility both in healthy subjects and in patients with AF (I). Coefficient of variation (CV) of atrial signal duration at 40 Hz by MCG was 3.3% and difference between the measurements was 3.5 ms on average. Corresponding figures by SAECG were 6.1% and 6.9 ms. Reproducibility of amplitude variables was in the range of 10% to 20%. Reproducibility was best by 40 Hz high pass cut-off frequency and similar in patients and healthy subjects.

The filtered atrial wave duration by MCG and total atrial activation time in EAM correlated positively with $r = 0.79$, $p < 0.001$. CV was 5.1%, and the difference between measurements was on average 6.9 ms (IV, Figure 16). Corresponding values by SAECG were $r = 0.62$, $p < 0.001$, CV 6.1%, and mean difference 9.5 ms.

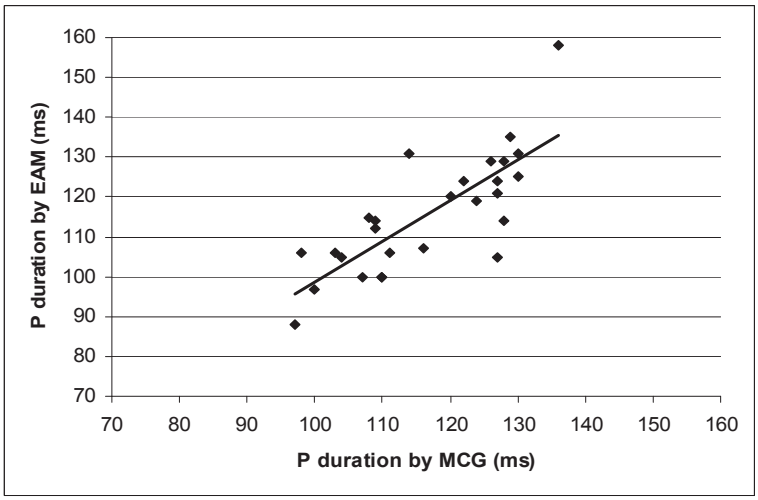


**Figure 16.** *Correspondence of atrial wave duration determined by MCG and by electroanatomic mapping in 27 AF patients (III). Pearson's correlation coefficient and coefficient of variation were used for statistics. Correlation coefficient r = 0.79, p < 0.001, CV% 5.1.*

The atrial signal duration in MCG and SAECG were correlated with coefficient r = 0.64 ($p < 0.01$). Additionally, the RMS amplitudes of the first portion of the atrial complex were correlated between MCG and SAECG (r = 0.49, $p < 0.01$), but not those of the last atrial portion (r = 0.25 - 0.30, p = ns) (I). The relation between MCG and SAECG measurements was similar also in a larger population (II, IV, V). The pooled data of 80 patients and 80 controls in Study II showed a correlation coefficient of 0.66 for Pd, 0.64 for the first 30-ms RMS, and 0.52 for the last 40-ms RMS. When evaluated separately in patients and controls, the correlation coefficients for Pd and the first 30-ms RMS were of the same magnitude in both groups, but differed for the last 40-ms RMS: r = 0.38 in patients (r = 0.18 in patients with non-focal AF) and r = 0.65 in controls (Jurkko et al. unpublished results).

### 5.2.2 Surface gradient method and pseudocurrent conversion (IV, V)

The pseudocurrent direction during the first 30 ms of the atrial complex, representing early RA activation, was mostly leftward down, mean angle 43 º (CSD 28 º) in Study IV. Over the time interval of 40 to 70 ms from onset of the atrial complex the mean angle was 39º (CSD 30º), and over the time interval of the last 50% of the atrial complex, the mean angle was 3º (CSD 51º). An example of MCG maps over the selected time-intervals of atrial depolarization is in Figure 14 (bottom).

When both the early and late LA MCG maps were viewed together, three types of combinations emerged: Type 1 with both maps showing pseudocurrent orientation leftward down, i.e., the pseudocurrent angle was positive during both intervals; Type 2 with the map over the 40 to 70 ms orienting leftward down and the map over the last 50% of the atrial signal orienting leftward up, i.e., the pseudocurrent angle was positive and negative; Type 3 had both maps orienting leftward up, i.e., the pseudocurrent angle was negative during both intervals. Examples of these 3 types are in Figure 17.

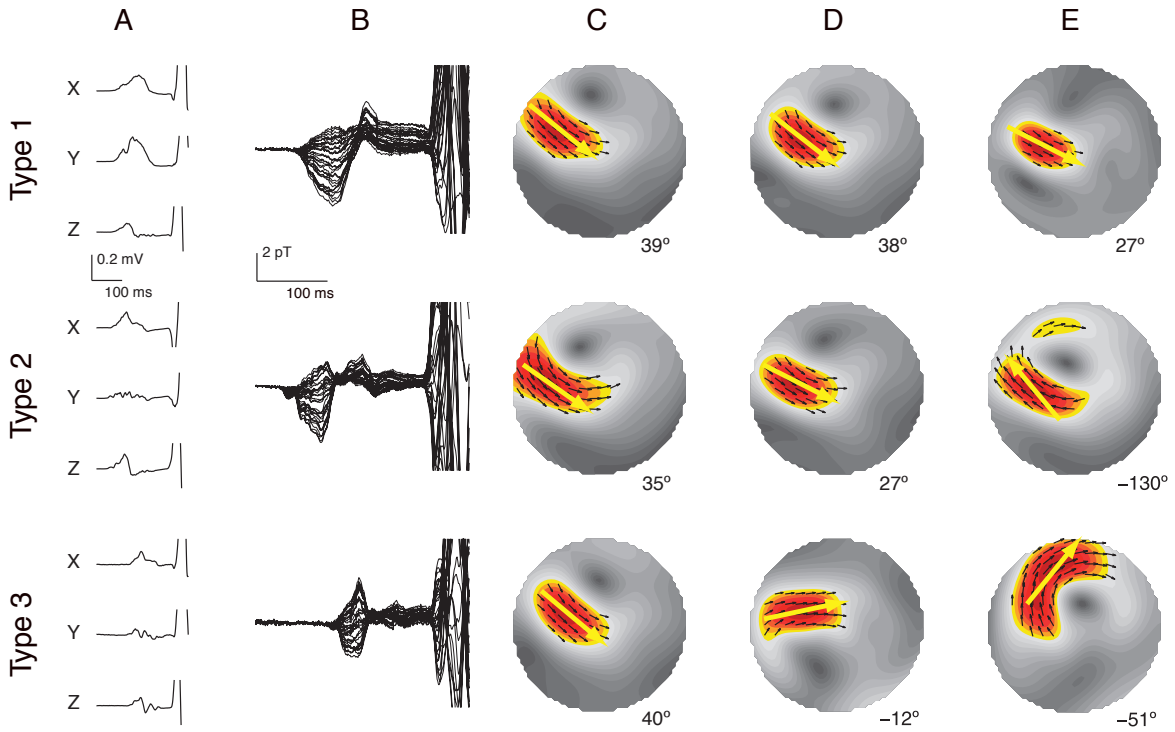


**Figure 17.** *MCG data from three study subjects representing the three different atrial activation patterns; row 1: Type 1, row 2: Type 2, row 3: Type 3. A: ECG, B: Superimposed averaged P wave of all MCG channels included. C-E: Isovalue pseudocurrent density maps representing (C) right atrial (first 30 ms), (D) initial left atrial (40-70 ms), and (E) later left atrial (last 50%) activation. Maps represent slightly tilted frontal plane projections with a horizontal line from the subject's right to left. Red-yellow areas correspond to the top 30% of the pseudocurrent amplitudes, and their mean angle is indicated with yellow arrows. Types 1, 2, and 3 refer to the classification based on pseudocurrent direction in the left atrial magnetic field maps, each related to distinct interatrial activation pathways.*

### 5.2.5 Validation of MCG mapping method (IV)

Activation fronts in MCG maps differed between subgroups allocated in regard to LA breakthrough sites in EAMs. Over the time-interval 40 to 70 ms during the atrial complex, the pseudocurrent mean angle in the BB group pointed leftward down, more horizontally in the FO and combined groups, and leftward up in the CS group. The distribution of magnetic field orientation in the BB group (n = 14) was significantly different from that in other groups (n = 15), $p < 0.02$.

The direction of pseudocurrent angle over the latter half of the atrial complex was positive in all cases in the BB group and in two cases of combined pathways (BB & CS and BB & FO), but negative in all 13 other maps. Moreover, during this time-interval, the distribution of magnetic field orientation in the BB group was significantly different from that in other groups, $p < 0.001$. Magnetic field orientations over the initial and later part of LA activation showed high mutual correlation (angular-angular $r = 0.89$, $p < 0.001$) in cases with single breakthrough via BB or CS, but differed in cases with FO and combined breakthroughs.

Assessed by LA map types, all 14 cases of solitary breakthrough via the BB had Type 1 magnetic field maps (Table 3). The three cases with solitary FO breakthrough had Type 2 maps, and both cases with solitary CS breakthrough had Type 3 maps. In combined pathways (n = 10), Type 2 maps were found in eight cases and Type 1 maps in two. Overall, with the MCG map type as a criterion, the LA breakthrough site was correctly identified as BB, CS, and FO or combined pathways in 27 of 29 cases (93%). Only the solitary breakthrough via FO could not be separated from the combined pathways.

**Table 3.** *Relationship between left atrial breakthrough site in electroanatomic mapping and type of magnetic field orientation over the early (40-70 ms) and later (last 50%) portion of left atrial depolarization analyzed from magnetocardiographic recordings (IV).*

| Breakthrough site to LA | MCG map type | | |
|---|---|---|---|
| | Type 1 | Type 2 | Type 3 |
| BB (n = 14) | 14 | 0 | 0 |
| FO (n = 3) | 0 | 3 | 0 |
| CS (n = 2) | 0 | 0 | 2 |
| Combined routes (n = 10) | 2 | 8 | 0 |
| BB + FO | 1 | 2 | 0 |
| BB + CS | 1 | 0 | 0 |
| FO + CS | 0 | 4 | 0 |
| BB + FO + CS | 0 | 2 | 0 |
| All (N = 29) | 16 | 11 | 2 |

*Number of cases in conduction pathway groups. BB, Bachmann bundle; FO, rim of fossa ovalis; Combined, two or more breakthrough areas; CS, coronary sinus ostium; LA, left atrium; MCG map, magnetocardiographic map. The MCG map types refer to classification of cases based on pseudocurrent orientation during left atrial activation: Type 1: pseudocurrent angle positive in both maps; Type 2: pseudocurrent angle positive in the map over 40-70 ms and negative in the map over last 50%; Type 3: pseudocurrent angle negative in both maps.*

## 5.3 Atrial signal patterns in patients with AF

### 5.3.1 Duration of atrial depolarization (I, II, III, IV, V)

In Studies II and V, the duration of atrial depolarization complex was slightly longer in patients than in controls (Table 4) and the proportion of the atrial signal from the PR interval, Pd/PR ratio, was larger in patients (Table 5). In Study II, the Pd/QRSd ratio was also calculated and was larger in patients than in controls (Table 5). In all these measurements the difference was more obvious in women. (II, V). Within lone paroxysmal AF, the longer Pd was related to the focal type of AF (II) and to the BB and the FO/multisite type interatrial conduction pattern (V). In controls, the Pd was longer in men and in the FO/multisite type interatrial conduction pattern (II, V). In all substudies, marked proportion of patients had normal Pd. In Study V, the Pd was ≤ 110 ms (≤ 120 ms)

in 46% (71%) of the patients and in 77% (89%) of the controls. Pd did not correlate with LA size.

**Table 4.** *Duration of atrial depolarization complex in patients with paroxysmal AF and in controls (I-V).*

| | Type of AF | Patients, number (males%) | Class I and III drugs | Pd (ms) | Controls, number (males%) | Pd (ms) | p-value |
|---|---|---|---|---|---|---|---|
| Study I | Lone paroxysmal | 9 (78) | none | 109 ± 8 | 10 (100) | 109 ± 7 | n.s. |
| Study II | Lone paroxysmal | 80 (76) | none | 109 ± 11 | 80 (76) | 104 ± 12 | 0.007 |
| | men | 61 | | 110 ± 12 | 61 | 106 ± 12 | n.s. |
| | women | 19 | | 108 ± 11 | 19 | 98 ± 6 | < 0.001 |
| Study III | Lone paroxysmal or persistent | 50 (78) | 16(32) | 119 ±14* | none | | |
| Study IV | Paroxysmal, 3 not lone | 29[1](76) | 5(17) | 115 ± 15<br>117 ±12* | none | | |
| Study V | Lone paroxysmal | 107 (75) | none | 112 ± 13 | 94 (75) | 104 ± 13 | < 0.001 |
| | men | 80 | | 112 ± 12 | 70 | 106 ± 12 | 0.001 |
| | women | 27 | | 111 ± 13 | 24 | 97 ± 9 | < 0.001 |

*Number (%) of study subjects or mean ± SD. AF, atrial fibrillation; Pd, duration of filtered atrial signal. * duration of atrial activation in electroanatomic mapping. [1] two patients with two different P wave morphologies are presented duplicated.*

### 5.3.2 Atrial RMS amplitudes and fragmentation analysis (I, II)

In Study II, the RMS amplitudes of the 40 Hz high-pass filtered atrial complex did not differ between patients and controls (Table 5). Yet, in patients classified as non-focal AF, the RMS amplitude of the last 40 ms of the atrial complex, RMS40, was significantly lower than in patients with focal AF or in controls, 59 ± 17 vs. 81 ± 31 and vs. 74 ± 36 fT, $p < 0.001$ and $p = 0.006$, respectively (Figure 18). In Study I, the RMS40 was 63 ± 15 fT in the nine patients, three of whom can be classified as focal type of AF.

In controls, the Pd was longer and RMS amplitudes of the whole atrial wave, PRMS, were larger in men (Pd 106 ± 12 vs. 98 ± 6 ms, $p < 0.001$, PRMS 96 ± 36 vs. 73 ± 31 fT, $p = 0.009$). In AF patients, the variables did not differ between genders (110 ± 12 vs. 108 ± 11 ms, 96 ± 34 vs. 83 ± 36 fT, p = n.s.). No differences appeared in fragmentation analyses. (II)

**Table 5.** *MCG signal measures in patients with paroxysmal lone AF and in controls (II).*

| | AF patients N = 80 | Controls N = 80 | p-value |
|---|---|---|---|
| Heart rate (beats/min) | 60 ± 10 | 61 ± 8 | n.s. |
| PR interval (ms) | 156 ± 23 | 159 ± 20 | n.s. |
| QRS duration (ms) | 100 ± 10 | 103 ± 10 | n.s. |
| QRS RMS (fT) | 1100 ± 400 | 1300 ± 590 | n.s. |
| QTc (ms) | 401 ± 23 | 396 ± 20 | n.s. |
| T apex – T end interval (ms) | 79 ± 10 | 76 ± 10 | n.s. |
| P duration (ms) | 109 ± 11 | 104 ± 12 | 0.007 |
| Pd/PR ratio | 0.71 ± 0.08 | 0.66 ± 0.09 | < 0.001 |
| Pd/QRSd ratio | 1.10 ± 0.15 | 1.01 ± 0.12 | < 0.001 |
| P RMS (fT) | 93 ± 35 | 91 ± 36 | n.s. |
| P RMS40 (fT) | 75 ± 29 | 74 ± 36 | n.s. |
| Fragmentation index M | 9.5 ± 1.7 | 9.5 ± 1.7 | n.s. |
| Fragmentation score S | 73 ± 21 | 72 ± 19 | n.s. |

*Group mean ± SD. Student's t-test. AF, atrial fibrillation; fT = $10^{-15}$ Tesla; Pd, duration of filtered atrial signal; P RMS, RMS over whole atrial complex; P RMS40, RMS over last 40 ms of atrial complex; QTc, QT value corrected by Bazett's formula; RMS, root mean square amplitude.*

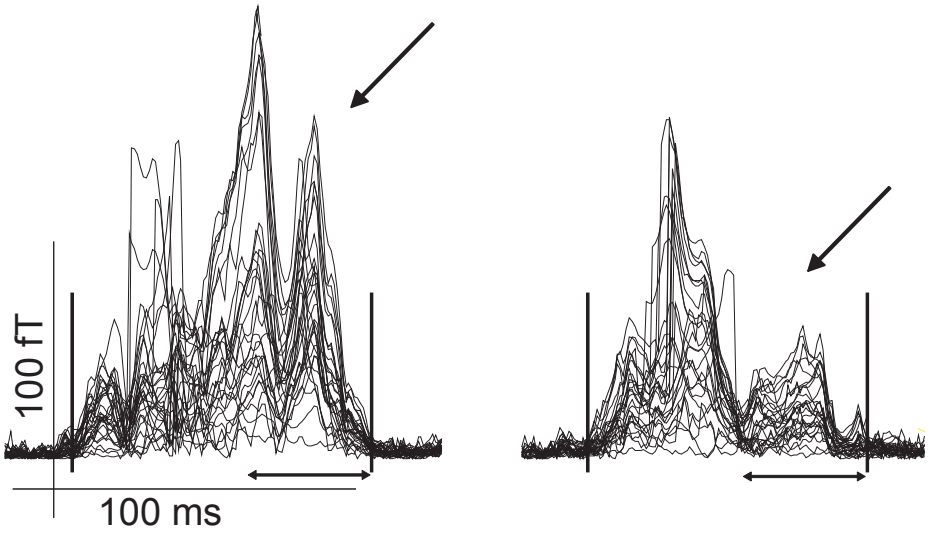


**Figure 18**. *40 Hz high-pass filtered atrial complex in a patient with focal AF (left) and in a patient with non-focal AF (right). In focal AF, atrial signal strength is normal also during the late phase of the atrial complex when the left atrium is depolarized, but in non-focal AF, late phase amplitudes are reduced (arrows). Data expressed as a superimposed display of 33 magnetometer channels. The automatically determined onset and end of atrial complex indicated with vertical bars. Reprinted from the original publication (II) with the permission of John Wiley & Sons Ltd.*

### 5.3.3 PR interval, QRS complex, and QT interval (I, II, V)

The PR interval was similar in patients and controls (Table 5). In Studies I, II, and V, the PR interval was ≥ 200 ms in eight patients (range 200-236 ms) and in two controls (209 and 221 ms). The difference was not significant. The QRS duration and the QT interval variables evaluated in Study II were similar in patients and controls. The heart-rate-corrected QT interval exceeded 450 ms in three patients and two controls (p = n.s.). The T apex – T end interval was longer in patients than in controls in women, 77 ± 9 vs. 70 ± 5 ms (p = 0.01) on average, but not in men.

## 5.4 Atrial conduction

### 5.4.1 Interatrial conduction assessed by EAM (III, IV)

In the intracardiac mappings (III and IV), three distinct interatrial breakthrough sites, the area of the BB, the rim of the FO, and the CS ostial region, were identified as solitary pathways or in various combinations; examples are shown in Figure 13. In Study III, a single interatrial breakthrough was recorded in 72% of cases. In the majority of patients, this involved the anterosuperior area, reflecting propagation through the BB. Less often was LA activated through the atrial septum in the vicinity of the FO, and in a few cases, the activation proceeded via the CS connections. Activation occurred simultaneously through more than a single pathway in 28% of patients. In these cases, the FO was involved at least as often (11/14 or 79%) as the BB (10/14 or 71%). In 2 of 50 patients, the activation propagated through all three pathways more or less simultaneously. In sum, the activation propagated via the BB either as a solitary or as part of a combined route in 70% of the patients (35/50), via the FO route in 36% (18/50), and via the CS in 26% (13/50). The proportion of different interatrial activation patterns in Study IV was close to that of Study III (Table 6).

**Table 6.** *Left atrial breakthrough areas in Studies III and IV.*

| | Study III N=50 | Study IV N=29 |
|---|---|---|
| Route | n (%) | n (%) |
| Solitary routes | | |
| - BB | 25 (50) | 14 (48) |
| - FO | 7 (14) | 3 (10) |
| - CS | 4 (8) | 2 (7) |
| Total | 36 (72) | 19 (65) |
| Combined routes | | |
| - BB + FO | 5 (10) | 3 (10) |
| - BB + CS | 3 (6) | 1 (3) |
| - FO + CS | 4 (8) | 4 (14) |
| - BB + FO + CS | 2 (4) | 2 (7) |
| Total | 14 (28) | 10 (34) |

*Number (%) of cases. BB, Bachmann bundle; FO, margin of fossa ovalis; Combined, two or more breakthrough areas; CS, coronary sinus ostium.*

In Study III, the duration of total atrial activation was 119 ± 14 ms. The earliest LA activation was detected 36 ± 14 ms after the onset of the atrial complex, and duration of LA activation was 84 ± 14 ms. Some differences emerged between groups categorized according to propagation routes. In the group that showed conduction via the FO − either as a single route or as a part of combined routes − the duration of measured LA activation was longer than in other groups, 93 ± 7 vs. 81 ± 15 ms, p = 0.003. However, in this group, the first activation in LA was rather early (29 ± 11 vs. 40 ± 13, p = 0.06), with no significant difference in total activation time (124 ± 11 vs. 120 ± 14, p = n.s.). No significant differences were evident between male and female patients or in relation to patients' age. Activation times in Studies III and IV are in Table 7.

**Table 7.** *Atrial activation times in the whole study population and in subgroups formed according to left atrial breakthrough area in electroanatomic mapping (III, IV).*

| | All | BB | CS | FO | Combined |
|---|---|---|---|---|---|
| Study III, number (%) | 50 | 25 (50) | 4(8) | 7(14) | 14(28) |
| Total atrial activation (ms) | 119 ± 14 | 121 ± 15 | 114 ± 13 | 124 ± 11 | 118 ± 11 |
| First activation in LA (ms) | 36 ± 14 | 41 ± 14 | 34 ± 9 | 29 ± 11 | 35 ± 10 |
| LA activation (ms) | 84 ± 14 | 81 ± 16 | 80 ± 9 | 93 ± 7 | 84 ± 12 |
| | | | | | |
| Study IV, number (%) | 29 | 14(48) | 2(7) | 3(10) | 10(34) |
| Total atrial activation (ms) | 117 ± 12 | 116 ± 10 | 102 ± 3 | 123 ± 11 | 120 ± 13 |
| First activation in LA (ms) | 34 ± 9 | 34 ± 8 | 40 ± 11 | 32 ± 4 | 32 ± 10 |
| LA activation (ms) | 84 ± 14 | 81 ± 10 | 62 ± 14 | 91 ± 11 | 88 ± 14 |

*Number(%) or mean ± SD. BB, Bachmann bundle; FO, margin of fossa ovalis; Combined, two or more breakthrough areas; CS, coronary sinus ostium; LA, left atrium.*

### 5.4.2 Interatrial conduction assessed by MCG (IV, V)

In Study V, the MCG mapping method introduced in Study IV was applied to a larger population comprising 107 patients with lone paroxysmal AF and 94 controls. All three atrial MCG map patterns (MCG atrial wave types), each related to distinct interatrial pathways, occurred in both groups, but in different proportions. The most common MCG atrial wave type, both in patients and controls, was Type 1, and the next most common was Type 2. In the patients, the Type 1 pattern was less common (54% vs. 67%) and Type 2 pattern more common (42% vs. 20%) than in controls; p = 0.001 for differenes in distribution (Figure 19).

Overall, Type 1 atrial waves were related to a more vertical RA map orientation and Type 2 to long Pd. In Type 3, Pd was short. The heart rate was similar in all types, and no difference existed in use of ß-blockers. There was a trend toward a more common appearance of Type 2 and 3 at an advanced age, but all map types occured also in those younger. The types were not related to gender, and cardiac ultrasound variables were similar in all groups (Table 8). In Type 1, the Pd was significantly longer in patients than in controls, 109 ± 12 ms vs. 102 ± 11, p = 0.003. The main difference between patients and controls was, however, different prevalence of MCG atrial wave types.

**Table 8.** *Clinical characteristics and MCG signal measures in study subjects (patients and controls) allocated to subgroups according to MCG atrial wave types (V).*

| MCG atrial wave type | Type 1 | Type 2 | Type 3 | p-value |
|---|---|---|---|---|
| Number (%) | 121 (61) | 64 (32) | 15 (7) | |
| Male | 86 (71) | 52 (81) | 11 (73) | n.s. |
| LVEDD (mm) | 50 ± 6 | 51 ± 5 | 50 ± 6 | n.s. |
| LVEF (%) | 64 ± 7 | 63 ± 8 | 65 ± 7 | n.s. |
| LA diameter (mm) | 36 ± 6 | 37 ± 4 | 37 ± 5 | n.s. |
| Age (years) | 43 ± 13 | 47 ± 12 | 48 ± 17 | n.s. |
| Heart rate (beats/min) | 60 ± 10 | 60 ± 10 | 61 ± 7 | n.s. |
| PR interval (ms) | 157 ± 20 | 164 ± 24 | 152 ± 27 | n.s. |
| P duration (ms) | 105 ± 12 | 116±12** | 101 ± 11 | <0.001 |
| RA map orientation (°) (CSD) | 67 (31)* | 49 (27)* | 17 (48)* | <0.01 |

*Number (%) or mean ± SD or mean (CSD). Student's t-test, Mann-Whitney U-test, analysis of variance (ANOVA and Kruskal-Wallis test) and $\chi^2$-test were used for statistics. Statistical significance obtained with multiple comparison test when comparing subgroups according to MCG atrial wave type: * = p<0.01, ** = p<0.001. LA, left atria; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; MCG, magnetocardiographic; RA, right atria. Types 1, 2, and 3 refer to the classification based on pseudocurrent direction in the LA magnetic field maps, each related to a distinct interatrial activation pathway.*

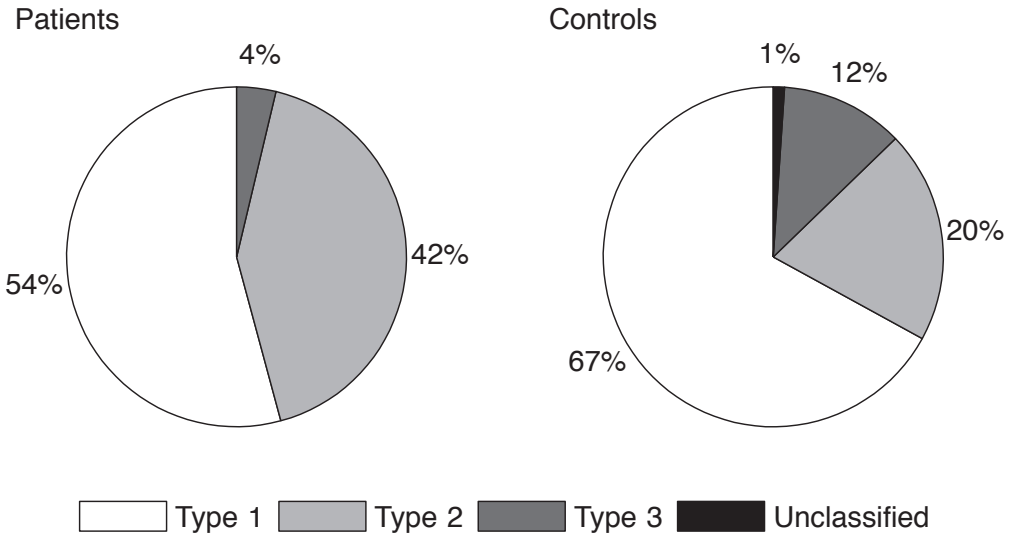


**Figure 19.** *Interatrial conduction pattern in patients with lone paroxysmal AF and in controls, assessed by MCG atrial wave types. Type 1 is related to the Bachmann bundle, Type 2 to the margin of the fossa ovalis or multisite, and Type 3 to the coronary sinus ostial connections. Type 2 was significantly more common in patients than in controls. (V)*

### 5.4.3 Right atrial activation (IV, V)

In Study IV, six RA maps were also examined. The first activation appeared at the superior posterolateral area of the RA in four cases and lower at the lateral wall in two cases; activation then spread predominantly downward left. The total RA activation time was 81 ± 8 ms. Both atria were activated simultaneously for 49 ± 12% of the total atrial activation time. In MCG maps, the pseudocurrent orientation during the first 30 ms of the atrial complex, representing early RA activation, was also mostly downward left. Correspondence between these two methods is illustrated in Figure 14.

In Study V, the pseudocurrent orientation during the first 30 ms of the atrial complex was examined both in patients and controls. The activation wavefront was mostly leftward down in both groups, mean angle 59° (CSD 30°) and 57° (CSD 37°), respectively (p = ns). The orientation of RA maps in subgroups allocated in regard to MCG activation type is presented in Table 8. The RA map orientation was more vertical in Type 1 than in other types, mean angle 67° (CSD 31°) vs. 49° (CSD 27°) for Type 2 and 17° (CSD 48°) for Type 3, $p < 0.01$.

### 5.4.4 Differences between competing P waves (IV, V)

In Study V, two frequent sinus P wave morphologies were analyzed in eight controls (8%) and in eight patients (7%). The LA map type differed between these two sinus P waves in all controls and in four patients. In all controls, one of the P waves was Type 1. In patients, the P wave differences were similar to controls' difference in two cases. Other differences were different RA map orientation with the same LA map type (one case), different LA map type with a similar RA map orientation (two cases), and differences in Pd. The mean difference in RA map orientation between the two morphologies was 66° (CSD 28°) in controls and 38° (CSD 24°) in patients, p = 0.05, suggesting that variation in early RA activation may be a source of alteration in interatrial conduction (Figure 20). In Study IV, the same two sinus P wave morphologies were mapped both during EAM and MCG in two patients. In these cases, the LA map pattern was BB and multisite in one patient, and BB and CS in another.

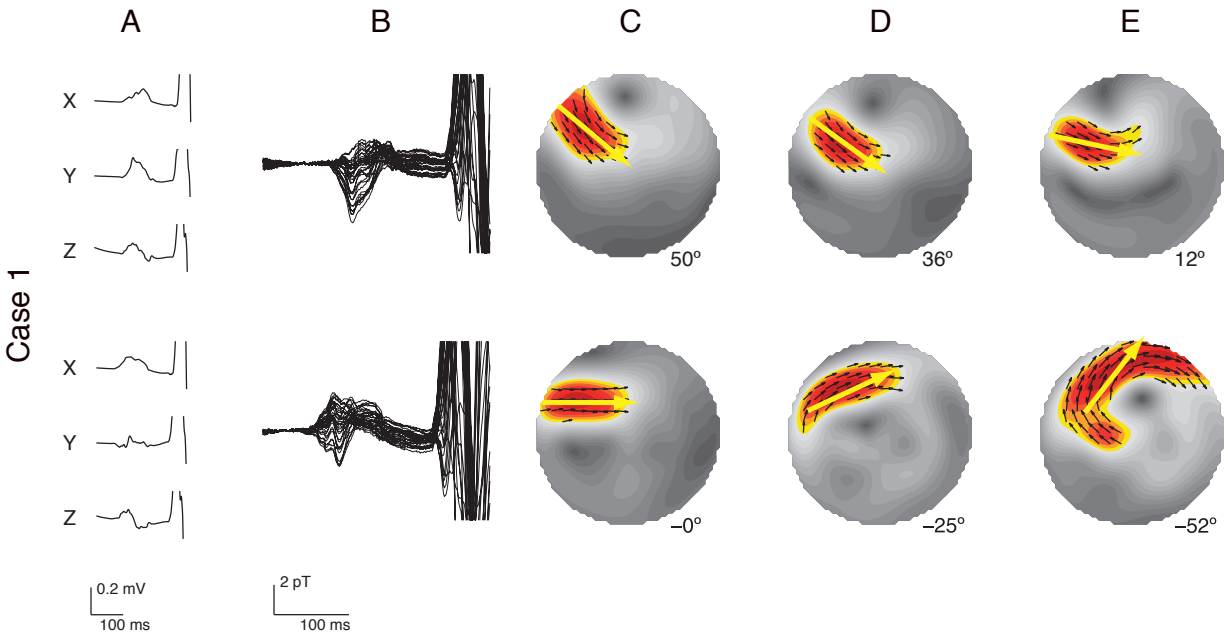


**Figure 20.** *Two different frequent sinus P waves in the same recording of a study subject. A: ECG, B: Superimposed averaged P wave of all MCG channels included. C-E: Isovalue pseudocurrent density maps representing (C) right atrial (first 30 ms), (D) initial left atrial (40-70 ms), and (E) later left atrial (last 50%) activation. Maps represent slightly tilted frontal plane projections with a horizontal line from the subject's right to left. Red-yellow areas correspond to the top 30% of the pseudocurrent amplitudes, and their mean angle is indicated with yellow arrows.*

## 5.5 Association of signal patterns with clinical characteristics

### 5.5.1 Relation of MCG measures to echocardiography and AF history (II, V)

The Pd did not correlate with LA diameter ($r = 0.14$, n.s.). The QRS duration and LV end diastolic diameter showed a positive correlation ($r = 0.34$, $p < 0.01$), and their magnitudes were related to body size and in a manner more pronounced in men. In patients, Pd did not correlate with height or weight ($r = 0.18$ and $r = 0.12$, respectively, n.s.). Length of AF history did not correlate with Pd, LA diameter (Figure 21), or atrial RMS amplitudes. None of these parameters differed between the patients who had AF episodes at least once a week and those with less frequent episodes.

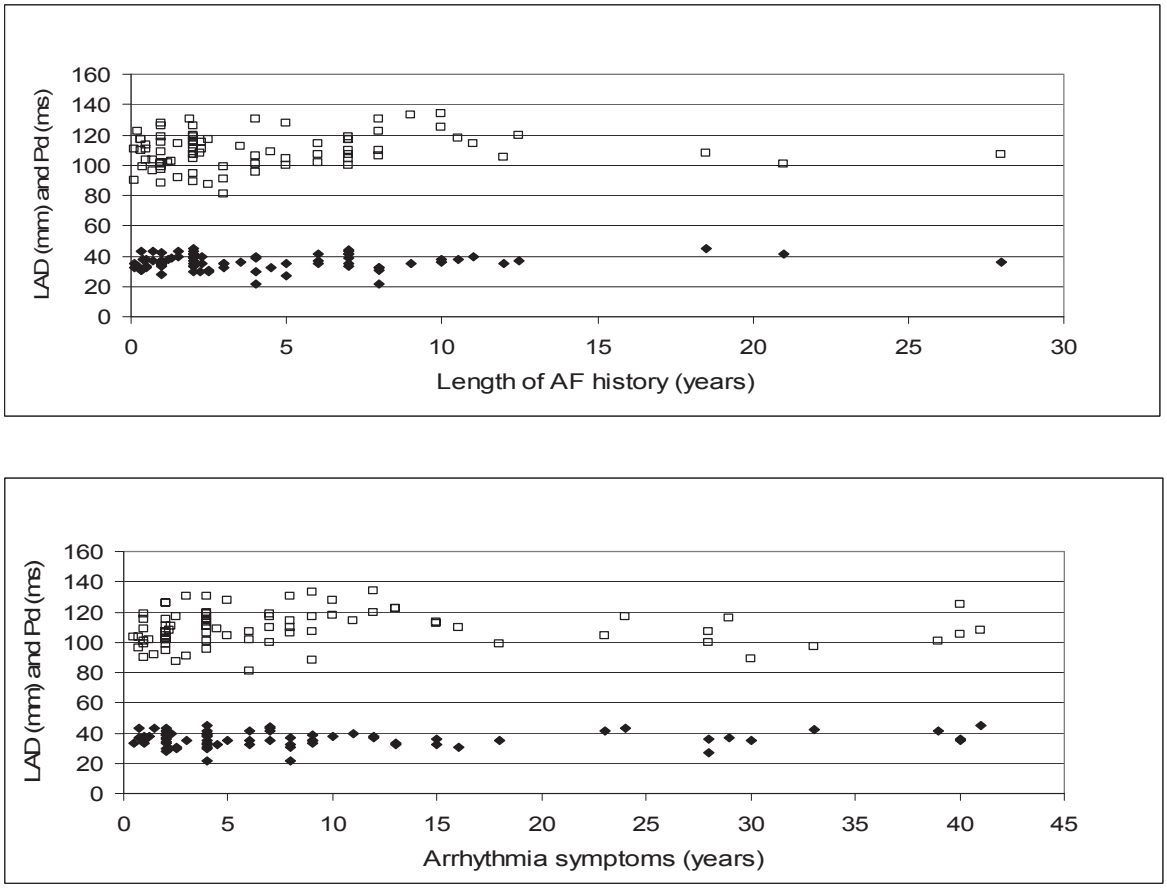


**Figure 21.** *Relation of length of documented AF history (upper) and length of AF symptoms (lower) to diameter of left atrium (LAD) and to P wave duration (Pd).* □ *= Pd;* ▲*= LAD. Pearson's correlation coefficient for statistics; Pd vs. length of AF history r = 0.14, p = n.s., LAD vs. length of AF history r = 0.19, p = n.s. (II).*

### 5.5.2 Gender-related differences in atrial signal (II, V)

In controls the Pd was shorter and P wave amplitude was lower in women than in men. In patients with lone paroxysmal AF, no such differences emerged. The QRSd was shorter, and QRS amplitudes were lower in women among both patients and controls (II, V). Some differences in atrial signal between patients and controls were more pronounced in women, as shown in Table 9. The corrected QT time tended to be longer in women among both patients and controls, but in controls, the T apex –T end interval was longer in men. In women, the same variable was significantly longer in patients than in controls, 77 ± 9 vs. 70 ± 5 (p = 0.01).

**Table 9.** *Comparison of cardiac signal measures between patients and controls in men and in women (II).*

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| Group | AF patients | Controls | p-value | AF patients | Controls | p-value |
| Number of subjects | 61 | 61 | n.s. | 19 | 19 | n.s. |
| Heart rate (beats/min) | 60 ± 10 | 60 ± 8 | n.s. | 59 ± 8 | 62 ± 7 | n.s. |
| PR interval (ms) | 158 ± 24 | 161 ± 20 | n.s. | 151 ± 15 | 152 ± 18 | n.s. |
| QRS duration (ms) | 103±8*** | 106 ± 9*** | n.s. | 91 ± 11 | 93 ± 8 | n.s. |
| QTc (ms) | 399 ± 24 | 394 ± 19 | n.s. | 407 ± 19 | 402 ± 22 | n.s. |
| T apex – T end (ms) | 80 ± 11 | 78 ± 10*** | n.s. | 77 ± 9 | 70 ± 5 | 0.01 |
| P duration (ms) | 110 ± 12 | 106 ± 12*** | n.s. | 108 ± 11 | 98 ± 6 | <0.001 |
| Pd/QRSd | 1.07±0.12** | 1.00 ± 0.11 | 0.002 | 1.21 ± 0.17 | 1.07 ± 0.12 | 0.005 |
| Pd/PR interval | 0.70 ± 0.08 | 0.67 ± 0.09 | 0.02 | 0.72 ± 0.07 | 0.66 ± 0.10 | 0.001 |
| P area (fTms) | 8800 ± 3500 | 8600 ± 3400** | n.s. | 7500 ± 3000 | 6000 ± 2500 | n.s. |
| P RMS (fT) | 96 ± 34 | 96 ± 36** | n.s. | 83 ± 36 | 73 ± 31 | n.s. |
| P RMS40 (fT) | 76 ± 26 | 78 ± 36 | n.s. | 72 ± 40 | 63 ± 32 | n.s. |

*Number or mean ± SD. Student's t-test and $\chi^2$ test. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ comparing male patients to female patients and male controls to female controls. fT, 10(-15) Tesla; RMS, root mean square amplitude; PRMS, RMS over whole atrial complex; PRMS first 30, RMS over first 30 ms of atrial complex; PRMS40, RMS over last 40 ms of atrial complex; QTc, QT value corrected by Bazett's formula.*

### 5.5.3 Focal AF vs. non-focal AF (II)

Characteristics and signal measures in patient subgroups divided into focal and non-focal AF are in Table 10. Compared to controls, patients with focal AF had longer Pd, larger Pd/PR, and Pd/QRSd ratios and a longer T apex – T end interval. Patients also had normal atrial RMS amplitudes. In the non-focal type of AF, Pd did not differ from that of controls. Their late atrial RMS amplitudes were lower than in patients with focal AF or in controls (Figure 18). The onset of AF was at an earlier age in the non-focal subset.

**Table 10.** *Clinical characteristics and MCG signal measures in patients with focal AF and non-focal AF (II).*

| | Focal AF<br>n = 58 (72) | Non-focal AF<br>n = 22 (28) | p-value |
|---|---|---|---|
| Males | 43 (74) | 18 (82) | n.s. |
| Age at time of AF diagnosis | 42 ± 10 | 33 ± 13 | 0.005 |
| AF episode frequency | | | |
| > once a week | 43 (73) | 1 (4.5) | < 0.001 |
| 1/week – 1/month | 14 (24) | 10 (45) | |
| Heart rate (beats/min) | 58 ± 10 | 64 ± 7 | 0.004 |
| PR interval (ms) | 155 ± 23 | 158 ± 20 | n.s. |
| QRS duration (ms) | 99 ± 11 * | 102 ± 10 | n.s. |
| QTc (ms) | 401 ± 25 | 399 ± 17 | n.s. |
| T apex – T end interval (ms) | 80 ± 10 * | 76 ± 11 | n.s. |
| P duration (ms) | 110 ± 12 ** | 108 ± 9 | n.s. |
| Pd/PR ratio | 0.71 ± 0.08 *** | 0.69 ± 0.07 | n.s. |
| Pd/QRSd ratio | 1.12 ± 0.15 *** | 1.07 ± 0.13 | n.s. |
| P RMS (fT) | 98 ± 37 | 78 ± 21 * | 0.003 |
| P RMS first 40 (fT) | 71 ± 27 | 72 ± 22 | n.s. |
| P RMS40 (fT) | 81 ± 31 | 59 ± 17 ** | <0.001 |
| LA map Type | | | |
| Type 1 (BB) | 32 (55) | 14 (50) | n.s |
| Type 2 (FO/multisite) | 23 (40) | 7 (29) | n.s |
| Type 3 (CS) | 3 (5) | 1 (<1) | n.s. |

*Number (%) or mean ± SD. Student's t-test and $\chi^2$ test. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ comparing patient group to control group. AF, atrial fibrillation; fT, $10^{-15}$ Tesla; LA, left atrium; Pd, duration of filtered atrial signal; P RMS, RMS over whole atrial complex; P RMS40, RMS over last 40 ms of atrial complex; QTc, QT value corrected by Bazett's formula; RMS, root mean square amplitude.*

## 5.6 SAECG measurements (II)

In SAECG, no differences appeared in the atrial signal or QRS complex durations between patients and controls (Pd 115 ± 11 vs. 113 ± 14 ms, and QRSd 100 ± 11 vs. 103 ± 10, n.s.). Parallel to MCG findings, the Pd/PR and Pd/QRSd ratios were larger in patients (0.73 ± 0.08 vs. 0.69 ± 0.09, p = 0.02 and 1.15 ± 0.15 vs. 1.10 ± 0.15, p = 0.02), and a trend appeared toward lower RMS40 values in patients with non-focal AF compared to patients with focal AF (8.6 ± 3.5 vs. 10.5 ± 3.8 μV, p = 0.05).

# 6 DISCUSSION

## 6.1 Main findings

This study showed that MCG mapping is an accurate noninvasive method to detect atrial electrophysiologic properties in patients with AF and in healthy subjects. Duration of the high frequency component of the atrial magnetic signal, representing atrial depolarization, and several parameters describing magnetic field strength during atrial activation could all be measured automatically and with good reproducibility.

In patients with lone paroxysmal AF, duration of the atrial depolarization complex was marginally prolonged. This difference was more obvious in women than in men and also was related to the interatrial conduction pattern. In the focal type of AF, the atrial RMS amplitudes were normal, but in AF without demonstrable triggers, the late atrial RMS amplitudes were reduced. Moreover, we demonstrated that in paroxysmal lone AF the atrial characteristics tended to remain similar, showing no progression, even over the timespan of several years after the first AF episode.

The intra-atrial recordings confirmed the occurrence of three distinct sites of electrical connection from the RA to LA: the BB, the margin of the FO, and the CS ostial area. High inter-individual variation in these connections was indicated in patients with lone paroxysmal AF. In almost a third of these patients the activation was propagated from the RA to LA during SR via route(s) other than BB. The variability in interatrial impulse propagation was reflected in atrial activation times.

Propagation of the atrial signal could be evaluated also non-invasively. In the time-intervals representing RA and LA activation, the MCG pseudocurrent angle represented the direction of propagation. Three types of atrial MCG maps were identifiable. The correspondence of these types and LA breakthrough sites in EAM showed an accuracy of 93%.

All three MCG atrial wave types appeared both in patients with lone AF and in healthy subjects, but in different proportions. The FO/multisite conduction maps were more common in the patients. The activation type was reflected in the duration of the atrial complex as also seen in invasive studies. In the activation pattern related to the BB connection, duration in patients was longer. In the FO/multisite conduction type, the duration was long both in patients and in controls.

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## 6.2 Measurement of atrial electrophysiological properties by MCG

### 6.2.1 Filtering techniques, detection of atrial depolarization time-interval

In this study, the high-pass filtering techniques commonly used in SAECG analyses were adapted to investigate the MCG atrial signal. Determination of the onset and end of this signal is the basis for several other signal measurements. The prolonged P wave per se is also the most common signal abnormality related to AF. Until now only duration of the non-filtered atrial wave has been reported by MCG (Winklmaier et al. 1998). In Study I, a new algorithm to detect onset and end of atrial depolarization complex was created and automated. The duration of the 40 Hz high-pass filtered atrial signal was 109 ms on average, and its variation between measurements was 3.3%, or 3.5 ms in absolute units, and was of similar magnitude in healthy subjects and in patients with paroxysmal AF. The reproducibility of amplitude values was lower but still acceptable, the variation in RMS amplitudes being less than 20%. In SAECG, Christiansen and coworkers (1996) found a coefficient of variation of 6% for Pd and 23 to 36% for amplitude variables. In the present study, the corresponding values in SAECG, determined with a method parallel to that for MCG, were 6% and 13 to 17%.

In Study IV, the mean duration of atrial depolarization determined by MCG was 115 ms, by 3-ortogonal lead SAECG 116 ms, and by EAM 117 ms. The MCG values correlated with EAM with r = 0.79, CV 5.1%, and the SAECG values with r = 0.62, CV 6.1%. When RA measurements were unavailable from some patients, onset of atrial signal in EAM was then detected as the first deflection of simultaneous ECG. Onset of the P wave in ECG may precede, coincide with, or follow the start of endocardial activation and more, epicardial activation may precede endocardial activation (Cosío et al. 2004, Lemery et al. 2007). The mean difference of -5 ± 6 ms, or larger, between the first measured activation in the atria and the onset of the P wave in ECG has been reported (Lemery et al. 2007, Cosío et al. 2004)). Correspondence between SAECG Pd and whole atrial activation time in EAM has shown a CV of 7% (Okumura et al. 2007).

Overall, the Pd values measured in this study are well in line with results obtained by invasive studies (Markides et al. 2003, Betts et al. 2004, Lemery et al. 2004, 2007). Compared to earlier ECG findings, the values in controls are in range of normal values of the non-filtered P wave (Willems et al. 1985, Wang et al. 2002) and slightly shorter than those obtained by filtered ECG (Erlich et al. 2001). This difference may be related to filtering techniques, which widen the signal and thus prolong the durations with Simson's type algorithm (Simson et al. 1981). However, the commonly reported marked prolongation of the atrial wave in SAECG (Fukunami et al. 1991, Abe et al. 1997) instead reflects heterogeneous etiologies of AF in the cohorts studied.

### 6.2.2 MCG mapping and surface gradient methods

This study demonstrated that the variation in impulse propagation routes from the RA to the LA can be assessed non-invasively by MCG. Since the RA activation is relatively stable during the later part of RA activation (Cosío et al. 2004, Lemery et al. 2007), the alteration of signal wavefront during the middle and later part of the whole atrial depolarization can reflect differences in LA activation. In the present studies, based on a combination of pseudocurrent angles over early and later parts of LA activation, MCG maps could be divided into three types by which the LA breakthrough site was correctly identified in 29 maps, as the BB, CS, FO, or combined pathways in 27 (93%).

It has been suggested that the LA breakthrough site is reflected in the LA activation pattern (Lemery et al. 2004, Markides et al. 2003, Betts et al. 2004, Cosío et al. 2004). In our study, the LA activation fronts over the initial part of LA activation differed significantly between BB, CS, and FO conduction pathway subgroups. However, the FO activation route, solitary or in combination, could not be clearly distinguished based on initial LA activation alone. When the information over the latter half of the atrial complex was combined with that of initial LA, the maps could be divided into three types, each of which suggested certain breakthrough sites. These types were specific to activation via BB and CS, but the activation via the margin of the FO seems to create a less distinct activation pattern. Since the FO was involved in most of the cases in the combined group, activation via the FO might confound assessment of conduction via the BB. The findings are comparable to those of an orthogonal ECG, by which the single route activation via the FO could not be separated from multisite activation including this pathway (Holmqvist et al. 2008). It is also possible that the CS conduction may be masked by simultaneous conduction via the BB route, as suggested in the study of Holmqvist and coworkers (2008).

The capability of magnetic field orientation to detect the interatrial conduction pattern has not as yet been evaluated. Yamada and coworkers (2003) studied seven patients with counterclockwise atrial flutter using a tangential-component MCG method (equivalent to the pseudocurrent transformation). In all patients during atrial flutter, they observed a circular pseudocurrent pattern suggesting circular re-eantrant activation in the atria. An analogous counterclockwise activation of the myocardium was evident in invasive electrograms as well. These findings were repeated by Nakai and coworkers (2005).

Some recent works have used interpolation of the current density maps (Kim et al. 2007), or an independent component of a multichannel magnetic field signal (Nakai et al. 2005), on a 3-dimensional heart model. However, the 2-dimensional presentation of the pseudocurrent angle utilized in this study (Cohen et al. 1976, Haberkorn et al. 2006), seems adequate to represent the main direction of electrical signal propagation. The method does not require construction of a source or volume conductor model for the cardiac activity; thus, a solution to the ill-posed inverse problem is unnecessary. These findings support the concept that a 2-dimensional pseudocurrent map can provide an estimate of the summation of real 3-dimensional atrial currents and their temporal propagation (Cohen et al. 1976, Haberkorn et al. 2006).

### 6.2.3 Comparison between MCG and ECG

In the present study, atrial signal duration and the RMS amplitudes of the first portion of the atrial complex correlated between MCG and ECG both in patients and in controls with coefficient r = 0.61 to 0.66. The correlation in RMS amplitudes of the last atrial portion was at the same magnitude in controls, but only a weak or no correlation appeared in patients (r = 0.16 to 0.38). Similar relations, r = 0.57 for duration and r = 0.24 for RMS amplitude of the last portion of QRS complex, were found earlier concerning QRS analysis in myocardial infarct patients (Korhonen et al. 2002).

Our study showed a trend toward similar signal characteristics as being provided by the ECG and MCG techniques, but differences between AF patients and controls were more obvious by MCG. In the study of Winklmaier and coworkers (1998), the P wave duration was longer and fragmentation index was higher in AF patients than in controls by MCG, but no significant difference was seen by ECG. The MCG has been accurate also in detecting a ventricular arrhythmia substrate even when SAECG findings have been normal (Oikarinen et al. 1998, Korhonen et al. 2000, 2006).

The observed positive but not complete correlations both between atrial variables and between QRS variables obtained by MCG and by ECG are even surprisingly similar and probably reflect basic differences between these methods (Siltanen 1989). Recently 3 P wave morphologies derived from 12-lead ECG were compared to LA breakthrough sites in EAM (Holmqvist et al. 2008). The Type 1 morphology was related to conduction via the FO alone or combined with BB or CS conduction, and Type 2 to conduction via the BB alone or combined with conduction via the CS connection, and Type 3 to conduction via the CS connection alone. Agreement among these three categories with EAM was 89%. The corresponding activation patterns of these ECG types are nearly the same as emerged in our MCG study showing 93% agreement with EAM. Whether the atrial wave types obtained by MCG and by the ECG covariate remains to be verified.

The complementary nature of MCG and ECG is shown by the fact that both methods yield, with some exceptions, the same information. Although MCG may reveal abnormalities not detectable by the ECG techniques explored thus far, the observations in MCG studies encourage the improvement of computational analysis of data acquired by standard or modified ECG lead sets, as well (Edenbrandt et al. 1988, Carlson et al. 2005, Holmqvist et al. 2008). The combination of these two methods may also prove valuable.

## 6.3 Signal patterns in patients with paroxysmal AF

The duration of the atrial depolarization complex in our patients with lone paroxysmal AF was only slightly prolonged. The mean values of 109 to 119 ms are consistent with the invasively measured durations of atrial depolarization in lone AF patients (Markides et al. 2003, Betts et al. 2004, Lemery et al. 2004, 2007). The prolongation was more obvious in women than in men and was also related to the LA activation pattern. Some gender differences in P wave duration have been apparent also in ECG studies (Erlich et al. 2001, Dhala et al. 2002), but were not investigated specifically in lone AF patients.

In contrast to some earlier SAECG studies (Fukunami et al. 1991, Abe et al. 1997), we showed that the atrial filtered signal amplitudes in lone AF patients are mostly normal. Yet, in patients without demonstrable focal triggers, the signal amplitudes of late atrial complex were reduced. This conforms to invasive measurements in patients undergoing catheter ablation of AF in which only a minority show reduced signal amplitudes in their LA (Verma et al. 2005).

In this study, both Pd/PR and Pd/QRSd ratios were higher in patients than in controls. The increased Pd/PR ratio has been related to enlargement of the LA (Chirife et al. 1975), but also to fibrosis in the LA in AF patients without correlation with LA size (Scott et al. 1983). The increased Pd/PR as well as Pd/QRSd ratios, which are relatively prolonged Pd, may be markers of the atrial process and altered conduction into or within the LA also when the Pd stays inside the normal range.

In paroxysmal lone AF, this study could show no common, non-invasively measured abnormality in atrio-ventricular conduction or in ventricular depolarization or repolarization. This supports the fact that the abnormal conduction is confined to the atria and is not a generalized feature of the cardiac tissue. However, a trend emerged toward a longer Tapex–Tend interval in AF patients, particularly in women. Prolongation of the Tapex–Tend interval has been related to ventricular arrhythmias in patients with cardiomyopathy and genetic sarcolemmal ion channel abnormalities, some of which are also involved in pathogenesis of AF (Korhonen et al. 2001, Fatkin et al. 1999, Schwartz et al. 2001, Chen et al. 2003).

## 6.4 Atrial conduction in patients with AF and in healthy subjects

Alterations in conduction and in refractoriness are related to AF genesis (Zimmermann et al. 1998, Kumagai et al. 1991, O'Donnell et al. 2002). Impaired interatrial conduction has been demonstrable in patients with paroxysmal AF, and it has been suggested that the impulse propagation between the RA and LA can be important in sustaining AF (O'Donnell et al. 2002, Khaja and Flaker 2005). Overall, interatrial conduction has been addressed in eight studies using LA mapping (Table 1), including a total of 136 patients. Most of these studies report conduction over the BB during SR in the vast majority of these individuals (Hindricks et al. 2001, De Ponti et al 2002, Lemery et al. 2004, 2007), but other preferential route(s) have also emerged (De Ponti et al. 2002, Lemery et al. 2007, Holmqvist et al. 2008). An inferior route or connection at the area of the FO margin may serve as the predominant route for signal propagation from the RA to LA (Markides et al. 2003, Betts et al. 2004, Holmqvist et al. 2008), suggesting that the importance of the BB may have been overestimated.

Only a few subjects without AF have been included in atrial mapping studies. The same interatrial conduction pathways exist also in these patients, the BB being the most usual (Smeets et al. 1998, De Ponti et al. 2002). The pattern of interatrial conduction in totally healthy subjects is unknown and cannot be examined invasively, because invasive LA mapping is associated with a small but real risk for complications and should not be performed without a clinical indication.

In this study, the signal propagation from RA to LA was investigated both invasively and non-invasively. Study III is the largest invasive study thus far assessing interatrial conduction patterns in patients with paroxysmal AF without advanced heart disease. In Study V, the atrial activation pattern was assessed non-invasively, and the activation pattern was examined also in healthy subjects.

### 6.4.1 Invasive assessment of connections to the left atrium

Our intra-atrial recordings in paroxysmal AF confirmed the occurrence of three distinct sites (the BB, the margin of the FO, and the CS ostial area) of electrical connection from the RA to LA and the high inter-individual variation in these connections. In concordance with earlier studies (Hindricks et al. 2001, DePonti et al. 2002, Lemery et al. 2004, 2007, Holmqvist et al. 2008) most patients showed conduction via the BB, either as the solitary route or in combination with other routes. However, a considerable minority of patients – one-third – showed no LA activation via the BB route. This is supported by an earlier non-contact mapping study in which the BB route was not manifested in 12 of 19 patients (Markides et al. 2003) as well as by post-mortem anatomic studies in which the BB was not seen in up to half the AF patients or controls (Mikhailov and Chuckbar 1982, Platonov et al. 2002). Here, the preferential pathways were the margin of the FO, the next most common route, and the CS.

Activation of the LA via multiple conduction pathways occured in approximately one-third of our patients, in the range reported earlier (Holmqvist et al. 2008, Markides et al. 2003). In these cases, FO was involved at least as often as BB. Impulse propagation via the CS connection as a solitary or combined route occurred in approximately one-fourth of the patients, but as a single route only in fewer than 10%. In two of our patients, two activation routes alternated during recording, indicating that temporary factors can modify the conduction pattern. A shift in endocardial LA breakthrough site was demonstrated also by Markides and coworkers (2003).

### 6.4.2 Atrial activation times and interatrial conduction

The durations of whole atrial activation and LA activation measured in the present study were comparable with durations reported by Lemery and coworkers (2004) in AF patients treated with catheter ablation, and were slightly longer than the duration of LA activation reported by Markides and coworkers (2003) in lone AF patients. The LA activation started at 34 to 36 ms on average in Study III and IV, similar to that in earlier observations (Markides et al. 2003, Lemery et al. 2004, 2007, Cosío et al. 2004).

The variability in interatrial impulse propagation also affected atrial activation times. Prolongation of LA activation without any delay in interatrial conduction was demonstrable in the FO/multisite conduction pattern. In the BB conduction pattern, prolongation of interatrial conduction was common, but the LA activation time was rather short. (III, IV)

The extent and location of connecting fibers and differences in conduction velocities in these pathways or within the atria or both may explain this finding. It is also possible that a conduction block need not be present in the BB, when other propagation routes are being used. In addition to interatrial conduction impairment, areas of conduction block in LA occur (Markides et al. 2003, Betts et al. 2004). This impaired conductivity can be explained by an anisotropic conduction between the muscle strands or by possible fibrotic or inflammatory changes (Betts et al. 2004, Frustaci et al. 1997).

### 6.4.3 Noninvasive assessment of interatrial conduction

Study V applied an MCG mapping method in a larger population comprising patients with paroxysmal lone AF and healthy subjects. Based on the relationship of the three predefined MCG map types to interatrial conduction pathways, the signal propagation in AF patients was consistent with observations in present and earlier invasive studies (Hindricks et al. 2001, DePonti et al. 2002, Markides et al. 2003, Lemery et al. 2004, 2007, Holmqvist et al. 2008). The majority of the patients had an MCG atrial wave type related to BB conduction; a significant minority had a wave type of FO/multisite conduction, and the CS type appeared in a few cases. All activation patterns appeared in healthy controls, as well. FO/multisite conduction maps were more common in patients than in controls.

In concordance with the invasive studies, the activation pattern was reflected in duration of the atrial depolarization complex. The longer P wave in patients was most obvious in the activation pattern related to the BB conduction route and linked to the FO/multisite conduction pattern. A prolongation of Pd over 120 ms was seen in 29% of the patients and 12% of the controls. In two-thirds of the patients and in half the controls this finding was related to an altered activation wavefront during the latter half of the atrial depolarization. This MCG signal pattern has similarities to the description of advanced interatrial block in ECG, i.e., Pd $\geq$ 120 ms and a biphasic P wave in inferior leads (Bayes de Luna 1985). In our MCG study, the activation pattern represented not CS conduction alone as presented in interatrial block in ECG (Waldo et al. 1971, Castillo et al. 1973, Bayes de Luna et al. 1988). In a recent vectorcardiographic study, the presence of biphasic P waves in the orthogonal Z-lead was related to conduction via the BB, with or without simultaneous conduction via the CS, but not to CS conduction alone (Holmqvist et al. 2008).

### 6.4.4 Right atrial activation

In electroanatomic maps, the first activation in RA was seen at the superior posterolateral area of the atrium or lower at the lateral wall, and activation then spread predominantly downward to the left as reported earlier (Cosío et al 2004, Lemery et al. 2007). The total RA activation time was about 80 ms, similar to that of previous studies (Smeets et al. 1998, DePonti et al. 2002, Cosío et al. 2004, Lemery et al. 2007).

In MCG, the pseudocurrent orientation during the first 30 ms of the atrial complex, representing early RA activation, was from horizontal leftward to vertically down, and in 5% of cases the map orientation was upward or rightward, again in line with other studies (Smeets et al. 1998, DePonti et al. 2002, Cosío et al. 2004, Luo et al. 2003, Lemery et al. 2007). On average, the RA map orientation was more vertical in the BB type interatrial connection than in other types (margin of FO, CS connection or multisite), indicating that the activation pattern of RA contributes to the choice of interatrial pathway. This corresponds to routes of the fastest propagation directed by atrial gross anatomy (obstacles) and myoarchitecture (Wang et al. 1995).

### 6.4.5 Competing P waves

In about 8% of subjects, two sinus activation patterns alternated during recording, indicating that temporary factors can modify the atrial activation sequence (IV, V). These findings confirm that impulse origin can affect propagation route from the RA to LA (Gomes et al. 1987, Boineau et al. 1988, Roithinger et al. 2003, Markides et al. 2003), but also that the LA activation front can vary despite similar RA activation.

### 6.4.6 Relation of interatrial conduction to AF

Prolonged P wave and particularly the advanced IAB (Bayes de Luna 1999), as well as biphasic P waves in the orthogonal Z lead (Platonov et al. 2000) have been associated with a history of or high risk for atrial tachyarrhythmias. LA pacing studies have demonstrated increased and more heterogeneous refractoriness and more pronounced lengthening of conduction times in the BB, CS, and LA in patients with AF than in controls (O'Donnell et al. 2002). Measurements with high-density electroanatomical mapping in the proximal CS during SR have revealed a lower conduction velocity in patients with paroxysmal AF than in those without (Xia et al. 2004). Histologically, the absence of any prominent BB connection has been similar in cases with and without any AF history (Platonov et al. 2002), but fibro-fatty degeneration of the BB has been more common in patients with a history of AF (Becker 2004).

In our study, the prolongation of atrial depolarization in BB-type conduction as well as the more common appearance of the FO/multisite conduction pattern, were related to a history of paroxysmal AF. These findings confirm that the absence, block, or delay of BB connection is more common in AF patients than in controls, and that the most common alternative conduction pattern is the connection via the margin of the FO or propagation via multiple pathways. These results could be interpreted thus: Not only altered conduction as such but also collision of electrical impulses via different routes may underlie AF generation. Propagation of activation in the LA along several fronts may lead to inhomogenous refractoriness and functional conduction blocks (Markides et al. 2003), thus creating a milieu favoring re-entrant arrhythmias. Hence an ectopic beat or the collision of activation fronts per se could then initiate AF. A parallel mechanism has been

suggested to explain the appearance of AF in WPW syndrome patients with atrioventricular accessory pathways (Iesaka et al. 1988).

## 6.5 Relation of signal patterns to characteristics of AF

### 6.5.1 Clinical characteristics

In the present study, the majority of the patients had lone paroxysmal AF. They were relatively young, but had already suffered frequent symptomatic arrhythmia episodes over several years. A focal type of AF has been related to AF appearing at an early age (Haissaguerre et al. 1998, Pappone et al. 2001). Observations in this study suggest that lone AF without demonstrable focal triggers starts even earlier than the focal type of AF. Also demonstrable was that patients with the most frequent AF episodes or the longest AF history did not show more atrial signal modification than did those with a history of lower AF burden. Selection bias may have excluded patients who had progression to permanent arrhythmia, but these results nevertheless confirm that paroxysmal AF does not necessarily lead to structural changes and altered conductivities in the atria. This is in line with prospective observations that progression from the paroxysmal to the permanent form is less common in lone AF than in AF in heart disease (Scardi et al. 1999, Osranek et al. 2005, Jahangir et al. 2007). Though in lone AF slight enlargement of the LA seems to be common, the majority of the patients showed no progression despite frequent episodes of AF or even permanent AF (Osranek et al. 2005, Sitges et al. 2007). Supporting animal studies have shown that atria subjected to rapid atrial pacing develop AF; however, if protected from heart failure and increased left ventricular filling pressure, these atria do not exhibit enlargement or the heart failure-associated pathological changes in AF (Ausma et al. 1997, Li et al. 1999).

### 6.5.2 Gender-related differences

In this study, three-fourths of the patients were men. In general, the absolute number of men and women with AF is equal, but the incidence of the arrhythmia, particularly at an early age and of lone AF, is higher in men (Ruigomez et al. 2005, Goudevenous et al. 1999). AF appears about 5 years later in women than in men (Rienstra et al. 2005). Our study revealed a difference for lone paroxysmal AF even greater: about one decade. The mean time from first symptoms to diagnosis, about 5 years, was similar in both genders, arguing against later recognition of AF in women. This is supported also by recent findings that women with AF tend to be more symptomatic than men (Humphries et al. 2001, Patton et al. 2005). Compared to men, women with lone AF have undergone pacemaker implantation more frequently and are more likely to have a history of a

rheumatologic disorder (Patton et al. 2005). The outcome of AF has also been worse in women (Benjamin et al. 1998, Stewart et al. 2002), for reasons that are unclear.

This study showed that in women with paroxysmal lone AF, prolongation of the atrial depolarization signal is more obvious than in men. This was mostly because among controls the Pd was shorter in women, but in patients it was close to that of male patients. A parallel difference also appeared in atrial signal amplitudes. This may be related to gender differences in presentation of AF, that is to say, normal female atria may be less vulnerable to AF unless some additional pathologic process develops. Gender-related differences in atrial signal in healthy subjects have been demonstrated by Erlich and coworkers (2001), Dhala and coworkers (2002), Havmöller and coworkers (2007). Some differences between male and female atria may even be linked to hormone balance (Liu et al. 2004, Tse et al. 2001). Whether that is related to the signal findings observed in this study remains to be examined.

### 6.5.3 Focal AF versus non-focal AF

This study classified the majority of the patients as having focally triggered paroxysmal lone AF, in line with earlier reports (Haissaquerre et al. 1998, Todd et al. 2000). No common definition fits focal AF and, indeed, PACs may serve as initiators in most cases of paroxysmal AF (Hoffmann et al. 2006). It may, however, be relevant to separate patients with a frequent occurrence of triggering arrhythmias from those without. It is suggested that the former require more triggers to initiate AF, whereas in other patients the atria are more vulnerable, and less triggering is sufficient to initiate AF (Lewalter et al. 2006, Yang et al. 2006). Two or more PACs during the 5 minutes preceding AF onset have been the criteria to select patients for specific PAC-suppression treatments (Lewalter et al. 2006). The preliminary results with this method have been better than in non-selected patients, but still fewer than half these patients show a decrease in AF burden during the treatment, and only 26% have been good responders. The results suggest that in these patients mechanisms other than active triggers also may be crucial for AF.

Frequent AF episodes, slight prolongation in atrial depolarization time and preserved atrial signal amplitudes were, in our study, characteristic of focal AF. In AF occurring without demonstrable triggers (non-focal AF or perhaps better, substrate AF), the LA depolarization signal was reduced. This may reflect an arrhythmogenic substrate in the LA, which in turn may be due to inflammation, cardiomyopathy, or fibrosis, all of which have been observable histologically also in lone AF (Boldt et al. 2004, Frustaci et al. 1997). These results raise the possibility that the atrial signal patterns could be useful in assessing the role of focal triggers in genesis of AF in individual patients.

An interesting finding was that particularly in those patients who did not demonstrate triggers, the onset of AF was at an early age, 33 ± 13 vs. 42 ± 10 years. The active triggers have been considered a common mechanism in lone paroxysmal AF starting early (Haïssaguerre et al. 1998). The present study does not disagree with this, but the main arrhythmia mechanisms in those with the earliest onset of AF might indeed differ.

## 6.6 Methodological considerations

### 6.6.1 Patient selection

Patients were screened from among those referred to a tertiary hospital due to symptomatic paroxysmal AF. In Studies III and IV, the patient group involved only those selected for invasive catheter ablation, meaning that the group was already pre-selected as one with resistance to medical therapy or with clinical symptoms causing disability. It is possible that some of these patients had conductive properties in the AV node such that they were more susceptible to suffering from rapid, symptomatic heart rates.

In Studies III and IV, a great proportion of patients eligible for the study had to be excluded, because during the mapping procedure they developed atrial fibrillation or bouts of atrial ectopic beats or tachycardia. In Study IV, some otherwise eligible patients were excluded because MCG was unavailable before ablation, or patients were not in SR during MCG measurement. Because only patients without, or those capable of discontinuing antiarrhythmic medication, were included in Studies II and V, it is possible that patients extremely vulnerable to AF were excluded. In Studies III and IV, antiarrhytmic medication was allowed. The possible effect of the medication on atrial measures remains to be verified.

Patient selection criteria in these studies included fewer women than men, as is true for other studies comprising mostly patients with the lone paroxysmal type of AF. Because of an age difference also existing between the women and men, some contribution of age to cardiac signal may have confounded the results. However, the duration of arrhythmia history was similar in both genders, and the controls were matched for age and gender.

Due to patient selection, these observations may not be applicable to broader lone AF patient cohorts. It is also obvious that the findings cannot necessarily be extrapolated to patients with structural heart disease.

### 6.6.2 AF characteristics

The measures of the length of AF history and frequency of symptomatic AF paroxysms are only approximations, due to the necessity to rely on retrospective data. The definition of focally triggered AF was based on 1 to 2 days of ECG recording, which may not be sufficiently reproducible to allow firm characterization of any individual patient.

### 6.6.3 MCG and EAM techniques

The late RMS values measured in this study, particularly long time-sequences like 40 ms, represent LA depolarization rather than after-depolarization and late fields/potentials, which also may be involved in the genesis of AF.

The band pass frequency in fragmentation analyses was 37 to 90 Hz. This method has been successful in detecting a propensity to ventricular arrhythmias (Korhonen et al. 2001). Since the significant harmonics of a fractionated atrial signal appear at from 38 to 137 Hz and up to 250 Hz (Pachon et al. 2004), a wider frequency zone might have been more appropriate for the atrial signal.

The correspondence of electroanatomic and MCG maps was examined in patients with relatively normal hearts and highly symptomatic paroxysmal AF. In these patients, the conductive properties may differ from healthy subjects' and from those whose AF is associated with heart disease. The time-windows for MCG map analysis may need adjustment to cover the intended atrial compartments in markedly enlarged atria. The influence of scars on MCG maps could not be evaluated in this patient series mostly without structural heart disease.

The local representativeness of recorded intracardiac signals is crucial for construction of the maps, especially around the postulated pathways. Registering potentials can be technically challenging in the interatrial septum due to far-field potentials from nearby structures. In Study IV, because the number of patients in conduction subgroups was small, the performance of the MCG technique needs testing in larger populations. Due to the necessity to rely on visually observed direction of signal propagation in EAM, the authenticity of direction of atrial activation determined by MCG mapping could not be ensured. This information, however, is unnecessary for validation of the ability to identify interatrial conduction patterns.

## 6.7 Applicability of the results and clinical implications

Male dominance, particularly in paroxysmal AF appearing at an early age, is well established (Goudevenos et al. 1999), but the reasons for it are unclear. In healthy subjects, as well as gender-related differences in the QRS complex and T-wave, there exist gender-related differences in atrial signal. Patients with lone paroxysmal AF presented with differences in the QRS and T-wave parallel to those of controls, but not in the atrial complex (II, V). Slight prolongation of the atrial depolarization complex observed in the whole study population was marked in female patients. The explanation for these signal findings is unclear and remains to be further investigated. However, the results raise the possibility that variables such as Pd per se or the Pd/QRSd ratio may have good predictive power for AF in women.

The distinct signal patterns observable in patients with the focal and non-focal types of AF support the concept of the heterogeneous pathogenesis of lone AF. The atrial signal patterns may aid in assessing the presence of atrial substrate and active triggers. These findings also encourage the use of signal analyses, MCG − or ECG, as well − in further studies in order to define subclasses of AF. The fragmentation analysis or QRS-T analysis which did not reveal differences in this study may prove valuable in some other settings. Furthermore, other variables, such as atrial late fields, may prove useful. Recognizing subclasses of AF could help in identifying subgroups for more individual treatment(s).

Experimental and clinical works have demonstrated that AF resistant to PV isolation can be terminated, by modifying interatrial connections by ablation. For the treatment of AF in some patients, catheter ablation of the RA septal region (Gaita et al. 1998) and CS connections (Haissaquerre et al. 2007) or transsection of the anterior LA (Sanders et al. 2004) have been effective. Ablation of CS and FO areas has altered inducibility to AF in an animal model (Ott et al. 2007). Conflicting results in studies using pacing suppression of AF (Platonov 2007) may be related within study cohorts to differences in lead locations and in interatrial conduction patterns. Knowledge of atrial conduction pathways may have an impact in refining methods for ablation treatment in patients with paroxysmal AF. Recognition of the interatrial conduction pattern may assist in understanding the pathogenesis of AF and allowing patient-tailored therapy. Whether conduction patterns more common in paroxysmal AF patients are predictive of future appearance of the arrhythmia remains to be examined.

The computerized algorithm improves our ability to detect onset and end of the atrial complex in both MCG and ECG data. The amplitude variables utilized showed lower but acceptable reproducibility, and these variables can also serve in future research. The detection of MCG atrial wave types, each related to a distinct interatrial conduction pathway, offers potential for identification the interatrial conduction pattern in differing experimental and clinical settings, and also in large patient populations and in healthy subjects, which is impossible with invasive techniques.

# 7 CONCLUSIONS

> "Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning."
>
> *Sir Winston Churchill (1874-1965)*

Based on the results of this study, the following conclusions can be drawn.

MCG is a potentially useful non-invasive method to examine atrial electrophysiology in clinical studies. MCG is complementary to ECG and may reveal abnormalities not detectable by any ECG techniques explored thus far. MCG mapping is capable of identifying various activation breakthrough sites in the LA during SR with adequate accuracy. The method is potentially applicable for assessing interatrial conduction also in large patient series and also in healthy subjects in which invasive measurements are impossible.

In paroxysmal lone AF, active focal triggers are common, atrial depolarization is slightly prolonged, the depolarization amplitude is normal, and the arrhythmia does not necessarily lead to electrical or mechanical dysfunction of the atria even several years after the first AF.

Prolongation of atrial depolarization is more obvious in women. This may be related to gender differences in presentation of AF, that is to say, normal female atria may be less vulnerable to AF unless an additional pathologic process develops.

A significant minority of patients with lone paroxysmal AF lack frequent focal triggers, and in them the late atrial signal amplitude is reduced, signifying possibly a wider degenerative process in the LA. In these patients, the atria may be more vulnerable and fibrillate with less provocation than in patients with the focal type of AF.

In patients with structurally normal hearts and paroxysmal AF, the natural impulse propagation from the RA to LA during SR goes through one or more of the previously described principal pathways. BB is the most common route between the atria, but in one-third of patients the electrical impulse is propagated outside the BB. Variation in the propagation routes is reflected in atrial activation times.

High inter-individual variation in right to left conduction occurs both in patients with lone AF and in healthy subjects. Susceptibility to paroxysmal lone AF is associated with propagation of the atrial signal to the LA via the margin of the FO or via multiple pathways. When conduction occurs via the BB, it is related to prolonged atrial activation. It seems likely that not only slow conduction but collision of electrical impulses via different routes may underlie AF generation.

The variation in genesis of lone paroxysmal AF may be reflected in the atrial signal pattern. Recognition of distinct signal profiles may assist in understanding AF pathogenesis. Whether this will be useful in identifying subgroups for patient-tailored therapy remains to be examined.

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# REFERENCES


Abe Y, Fukunami M, Yamada T, Ohmori M, Shimonagata T, Kumagai K, Kim J, Sanada S, Hori M, Hoki N. Prediction of transition to chronic atrial fibrillation in patients with paroxysmal atrial fibrillation by signal-averaged electrocardiography: a prospective study. Circulation 1997; 96:2612-2616.

Allessie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The "leading circle" concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ Res 1977; 41:9-18.

Allessie M, Lammers W, Bonke F, Hollen J. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes D, Jalife J, eds. Cardiac electrophysiology and arrhythmias, Volume I. Grune & Stratton, Orlando, Florida 1985:265-275.

Allessie MA, Boyden PA, Camm AJ, Kléber AG, Lab MJ, Legato MJ, Rosen MR, Schwartz PJ, Spooner PM, Van Wagoner DR, Waldo AL. Pathophysiology and prevention of atrial fibrillation. Circulation. 2001; 103:769-777.

Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. [Review] Cardiovasc Res 2002; 54:230-246.

Antz M, Otomo K, Arruda M, Scherlag BJ, Pitha J, Tondo C, Lazzara R, Jackman WM. Electrical conduction between the right atrium and the left atrium via the musculature of the coronary sinus. Circulation 1998; 98:1790-1795.

Andersson KE. The heart cell--electrophysiological aspects. Acta Med Scand Suppl 1981; 647:7-15.

Ariyarajah V, Asad N, Tandar A, Spodick DH. Interatrial block: pandemic prevalence, significance and diagnosis. Chest 2005; 128:970-975.

Ariyarajah V, Mercado K, Apiyasawat S, Puri P, Spodick DH. Correlation of left atrial size with P wave duration in interatrial block. Chest. 2005; 128:2615–2618.

Ariyarajah V, Frisella ME, Spodick DH. Reevaluation of the criterion for interatrial block. Am J Cardiol 2006; 98:936-937.

Arnar D.O., Thorvaldsson S., Manolio T.A., Thorgeirsson G., Kristjansson K., Hakonarson H., Stefansson K. (2006) Familial aggregation of atrial fibrillation in Iceland. Eur Heart J 2006; 27**:**708–712.

Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials [published erratum appears in Arch Intern Med 1994;154:2254]. Arch Intern Med. 1994; 154: 1449–1457.

Ausma J, Wijffels M, Thone F, Wouters L, Allessie M, Borgers M. Structural changes of atrial myocardium due to sustained atrial fibrillation in the goat. Circulation 1997; 96:3157–3163.

Ausma J, Litjens N, Lenders MH, Duimel H, Mast F, Wouters L, Ramaekers F, Allessie M, Borgers M. Time course of atrial fibrillation-induced cellular structural remodeling in atria of the goat. J Mol Cell Cardiolog 2001; 33:2083-2094.

Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, Tracy RP, Van Wagoner DR, Psaty BM, Lauer MS, Chung MK. Inflammation as a risk factor for atrial fibrillation. Circulation 2003; 108:3006–3010.

Aytemir K, Ozer N, Atalar E, Sade E, Aksöyek S, Ovünç K, Oto A, Ozmen F, Kes S. P wave dispersion on 12-lead electrocardiography in patients with paroxysmal atrial fibrillation. Pacing Clin Electrophysiol 2000; 23:1109-1112.

Bachmann G. The inter-auricular time interval. Am J Physiol 1916; 41:309-320.

Barr RC. Genesis of the electrocardiogram. In: Macfarlane PW, Lawrie TDV, eds. Comprehensive Electrocardiology Volume I. Pergamon Press, Oxford 1989: 129-151.

Baule G, McFee R. Detection of the magnetic field of the heart. Am Heart J 1963; 95-96.

Baule G, McFee R. The magnetic heart vector. Am Heart J 1970; 79:223-236.

Bayés de Luna A, Fort de Ribot R, Trilla E, Julia J, Garcia J, Sadurni J, Riba J, Sagues F. Electrocardiographic and vectorcardiographic study of interatrial conduction disturbances with left atrial retrograde activation. J Electrocardiol 1985; 18:1–13.

Bayés de Luna A, Cladellas M, Oter R, Torner P, Guindo J, Martí V, Rivera I, Iturralde P. Interatrial conduction block and retrograde activation of the left atrium and paroxysmal supraventricular tachyarrhythmia. Eur Heart J 1988; 9:1112-1118.

Becker AE. How structurally normal are human atria in patients with atrial fibrillation? Heart Rhythm 2004; 1:627-631.

Bellet S. Clinical Disorders of the Heart Beat. 3rd ed. Philadelphia: Lea & Febiger, 1971.

Benchimol Barbosa PR, de Souza Bomfim A, Barbosa EC, Ginefra P, Helena Cardoso Boghossian S, Destro C, Nadal J. Spectral turbulence analysis of the signal-averaged electrocardiogram of the atrial activation as predictor of recurrence of idiopathic and persistent atrial fibrillation. Int J Cardiol 2006; 107:307-316.

Benjamin EJ, Lévy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart study. JAMA 1994; 271:840–844

Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Lévy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998; 98:946 –952.

Berbari EJ, Scherlag BJ, Hope RR; Lazzara R. Recording from the body surface of arrhythmogenic ventricular activity during the S-T segment. Am J Cardiol 1978; 41:697-702.

Betts TR, Roberts PR, Morgan JM. High-density mapping of left atrial endocardial activation during sinus rhythm and coronary sinus pacing in patients with paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 2004; 15:1111-1117.

Bjerregaard P. Premature beats in healthy subjects 40-79 years of age. Eur Heart J 1982; 3:493-503.

Bland JM, Altman DG. Statistics notes: measurement error. BMJ 1996;312:1654.

Boineau JP, Canavan TE, Schuessler RB, Cain ME, Corr PB, Cox JL: Demonstration of a widely distributed atrial pacemarker complex in the human heart. Circulation 1988; 77:1221-1237.

Boldt A, Wetzel U, Lauschke J, Weigl J, Gummert J, Hindricks G, Kottkamp H, Dhein S. Fibrosis in left atrial tissue of patients with atrial fibrillation with and without underlying mitral valve disease. Heart 2004; 90:400-405.

Bromberg BI, Hand DE, Schuessler RB, Boineau JP. Primary negativity does not predict dominant pacemarker location: Implications for sinoatrial conduction. Am J Physiol 1995; 269(3 Pt 2):H877-H887.

Boos CJ, Anderson RA, Lip GY. Is atrial fibrillation an inflammatory disorder? Eur Heart J 2006; 27:136-149.

Brand FN, Abbott RD, W. B. Kannel WB, Wolf PA. Characteristics and prognosis of lone atrial fibrillation. 30-year follow-up in the Framingham Study. JAMA 1985; 27:3449-3453.

Brody DA Woolsey MD, Arzbaecher RC. Application of computer techniques to the detection and analysis of spontaneous P wave variations. Circulation 1967; 36:359-371.

Brugada R., Tapscott T., Czernuszewicz G.Z., Marian A.J., Iglesias A., Mont L., Brugada J., Girona J., Domingo A., Bachinski L.L, Roberts R. Identification of a genetic locus for familial atrial fibrillation. N Eng J Med 1997; 336**:**905–911

Bubien RS, Knotts-Dolson SM, Plumb VJ, Kay GN. Effect of radiofrequency catheter ablation on health-related quality of life and activities of daily living in patients with recurrent arrhythmias. Circulation 1996;94:1585–1591.

Brunton TL, Fayrer J. Note on independent pulsation of the pulmonary veins and vena cava. Proc Royal Soc Lond 1876-77; 25:174-176.

Buxton AE, Josephson ME. The role of P wave duration as a predictor of postoperative atrial arrhythmias. Chest 1981; 80:68-73.

Calo L, Lamberti F, Loricchio ML, Castro A, Boggi A, Colivicchi F, Pandozi C, Santini M. Transseptal activation during left atrial pacing in humans: electroanatomic mapping using a noncontact catheter and the intracardiac echocardiography. J Interv Card Electrophysiol 2002; 6:149-159.

Canavan TE, Schuessler RB, Boineau JP, Corr PB, Cain ME, Cox JL. Computerized global electrophysiological mapping of the atrium in patients with Wolff-Parkinson-White syndrome. Ann Thorac Surg 1988; 46:223-231.

Capucci A, Santarelli A, Boriani G, Magnani B. Atrial premature beats coupling interval determines lone paroxysmal atrial fibrillation onset. Int J Cardiol 1992; 36:87-93.

Castillo A, Vernant P. Troubles de la conduction interariculaire par bloc du faisceau de Bachmann. Etude 3 cas par electrocardiographie endoauriculaire et oesophagienne. Coeur 1973; 4:31-40.

Carlson J, Havmöller R, Herreros A, Platonov P, Olsson B. Can orthogonal lead indicators of propensity to atrial fibrillation be accurately assessed from the 12-lead ECG? Europace 2005; 7(Suppl 2):39-48.

Chang SL, Tai CT, Lin YJ, Wongcharoen W, Lo LW, Tuan TC, Udyavar AR, Chang SH, Tsao HM, Hsieh MH, Hu YF, Chen YJ, Chen SA. Biatrial substrate properties in patients with atrial fibrillation. J Cardiovasc Electrophysiol 2007; 18:1134-1139.

Chauvin M, Shah D, Haissaguerre M, Marcellin L, Brechenmacher C. The anatomic basis of connections between the coronary sinus musculature and the left atrium in humans. Circulation 2000; 101:647-652.

Chen LY, Ballew JD, Herron KJ, Rodeheffer RJ, Olson TM. A common polymorphism in SCN5A is associated with lone atrial fibrillation. Clin Pharmacol Ther 2007; 81:35–41

Chen PS, Chou CC. Coronary sinus as an arrhythmogenic structure. J Cardiovasc Electrophysiol 2002; 13:863-864

Chen SA, Hsieh MH, Tai CT, Tsai CF, Prakash VS, Yu WC, Hsu TL, Ding YA, Chang MS. Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: Electrophysiologic characteristics, pharmacologic responses, and effects of radiofrequency ablation. Circulation 1999; 100:1879 –1886.

Chen YH, Xu SJ, Bendahhou S, Wang XL, Wang Y, Xu WY, Jin HW, Sun H, Su XY, Zhuang QN, Yang YQ, Li YB, Liu Y, Xu HJ, Li FX, Ma N, Mou CP, Chen Z, Barhanin J, Huang W. KCNQ1 gain-of-function mutation in familial atrial fibrillation. Science 2003; 299:251-254.

Cheung DW. Pulmonary vein as an ectopic focus in digitalis-induced arrhythmia. Nature 1981; 294:582- 584.

Christiansen EH, Frost I, Pilegaard H, Toftegaard-Nielsen T, Pedersen AK. Within and between patient variation of the signal averaged P wave in coronary artery disease. Pacing Clin Electrophysiol 1996; 19:72-81.

Chirife R, Feitosa GS, Frankl WS. Electrocardiographic detection of left atrial enlargement. Correlation of P wave with left atrial dimension by echocardiography. Br Heart J 1975; 37:1281-1285.

Cohen D. Magnetic fields around the torso: production by electrical activity of the human heart. Science 1967; 156: 652-654.

Cohen D, Edelsack EA, Zimmermann JE. Magnetocardiograms taken inside a shielded room with a superconducting point-contact magnetometer. Appl Phys Lett 1970;16:278-280.

Cohen D, Hosaka H. Part II - Magnetic field produced by a current dipole. J Electrocardiol 1976; 9:409-417.

Comtois P, Kneller J, Nattel S. Of circles and spirals: bridging the gap between the leading circle and spiral wave concepts of cardiac reentry. Europace 2005; 7(Suppl 2):10-20.

Coumel P. Neural aspects of paroxysmal atrial fibrillation. In: Falk RH, Podrid PJ, eds. Atrial Fibrillation: Mechanisms and Management. Raven Press, New York 1992:109-125.

Courtemanche M, Ramirez RJ, Nattel S. Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model. Am J Physiol 1998; 275(1 Pt 2):H301-321.

Conway DS, Buggins P, Hughes E, Lip GY. Prognostic significance of raised plasma levels of interleukin-6 and C-reactive protein in atrial fibrillation. Am Heart J 2004; 148:462–466.

Cosío FG, Anderson RH, Kuck KH, Becker A, Borggrefe M, Campbell RW, Gaita F, Guiraudon GM, Haïssaguerre M, Rufilanchas JJ, Thiene G, Wellens HJ, Langberg J, Benditt DG, Bharati S, Klein G, Marchlinski F, Saksena S. Living anatomy of the atrioventricular junctions. A guide to electrophysiologic mapping. A Consensus Statement from the Cardiac Nomenclature Study Group, Working Group of Arrhythmias, European Society of Cardiology, and the Task Force on Cardiac Nomenclature from NASPE. Circulation 1999; 100:e31-7. Review.

Cosío FG, Martin-Penato A, Pastor A, Núnez A, Montero MA, Cantle CP, Schames S. Atrial activation mapping in sinus rhythm in the clinical electrophysiology laboratory: observations during Bachmann's bundle block. J Cardiovasc Electrophysiol 2004; 15:524-531.

Cox JL, Canavan TE, Schuessler RB, Cain ME, Lindsay BD, Stone C, Smith PK, Corr PB, Boineau JP. The surgical treatment of atrial fibrillation. II. Intraoperative electrophysiologic mapping and description of the electrophysiologic basis of atrial flutter and atrial fibrillation. J thorac Cardiovasc Surg 1991; 101:406-426.

Darbar D, Herron KJ, Ballew JD, Jahangir A, Gersh BJ, Shen WK, Hammill SC, Packer DL, Olson TM. Familial atrial fibrillation is a genetically heterogeneous disorder. J Am Coll Cardiol 2003; 41**:**2185–2192.

Darbar D, Hardy A, Haines JL, Roden DM. Prolonged signal-averaged P wave duration as an intermediate phenotype for familial atrial fibrillation. J Am Coll Cardiol 2008a; 51:1083-1089.

Darbar D, Kannankeril PJ, Donahue BS, Kucera G, Stubblefield T, Haines JL, George AL Jr, Roden DM. Cardiac sodium channel (SCN5A) variants associated with atrial fibrillation. Circulation 2008b; 117:1927-1935.

Della Bella P, Brugada P, Talajic M, Lemery R, Torner P, Lezaun R, Dugernier T, Wellens HJ. Atrial fibrillation in patients with an accessory pathway: importance of the conduction properties of the accessory pathway. J Am Coll Cardiol 1991; 17:1352-1356.

De Ponti R, Ho SY, Salerno-Uriarte JA, Tritto M, Spadacini G. Electroanatomic analysis of sinus impulse propagation in normal human atria. J Cardiovasc Electrophysiol 2002; 13:1-10.

Dernellis J, Panaretou M. Relationship between C-reactive protein concentrations during glucocorticoid therapy and recurrent atrial fibrillation. Eur Heart J 2004; 25:1100–1107.

Dhala A, Underwood D, Leman R, Madu E, Baugh D, Ozawa Y, Kasamaki Y, Xue Q, Reddy S, Multicenter Phi-Res Study. Signal-average P wave analysis of normal controls and patients with paroxysmal atrial fibrillation: a study in gender differences, age dependence, and reproducibility. Clin Cardiol 2002; 25:525-531.

Dilaveris PE, Gialafos EJ, Sideris SK, Theopistou AM, Andrikopoulos GK, Kyriakidis M, Gialafos JE, Toutouzas PK. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. Am Heart J 1998; 135:733-7388.

Dilaveris PE, Gialafos EJ, Andrikopoulos GK, Richter DJ, Papanikolaou V, Poralis K, Gialafos JE. Clinical and electrocardiographic predictors of recurrent atrial fibrillation. Pacing Clin Electrophysiol 2000; 23:352-358.

Dimmer C, Szili-Torok T, Tavernier R, Verstraten T, Jordaens LJ. Initiating mechanisms of paroxysmal atrial fibrillation. Europace 2003; 5:1-9.

Dogan A, Avsar A, Ozturk M. P wave dispersion for predicting maintenance of sinus rhythm after cardioversion of atrial fibrillation. Am J Cardiol 2004; 93:368-371.

Dong J, Zrenner B, Schreieck J, Deisenhofer I, Karch M, Schneider M, Von Bary C, Weyerbrock S, Yin Y, Schmitt C. Catheter ablation of left atrial focal tachycardia guided by

electroanatomic mapping and new insights into interatrial electrical conduction. Heart Rhythm 2005; 2:578–591.

Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM, Camm J, Akhtar M and Luderitz B. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. J Am Coll Cardiol. 2000; 36:1303-1309.

Duytschaever M, Danse P, Eysbouts S, Allessie M. Is there an optimal pacing site to prevent atrial fibrillation?: an experimental study in the chronically instrumented goat. J Cardiovasc Electrophysiol 2002; 13:1264–1271.

Eckardt L. Automaticity in the coronary sinus. J Cardiovasc Electrophysiol 2002; 13:288-289.

Edenbrandt J, Pahlm O. Vectorcardiogram synthesized from 12-lead ECG: superiority of the inverse Dower matrix. Electrocardiol 1988; 21:361-367.

Einthoven W. Ueber die form des menschlichen electrocardiograms. Archiv für die gesammte physiologie des menchen und der thiere 1895; 60:101-123.

Ehrlich JR, Cha TJ, Zhang L, Chartier D, Villeneuve L, Hébert TE, Nattel S. Characterization of a hyperpolarization-activated time-dependent potassium current in canine cardiomyocytes from pulmonary vein myocardial sleeves and left atrium, J Physiol 2004; 557:583–597.

Ellinor PT, Low A, Patton KK, Shea MA, MacRae CA. C-Reactive protein in lone atrial fibrillation. Am J Cardiol 2006; 97:1346-1350.

Ellinor PT, Nam EG, Shea MA, Milan DJ, Ruskin JN, MacRae CA. Cardiac sodium channel mutation in atrial fibrillation. Heart Rhythm 2008; 5:99-105.

Evans W, Swann P. Lone auricular fibrillation. Br Heart J 1954; 16:189-194.

Everett TH 4th, Wilson EE, Verheule S, Guerra JM, Foreman S, Olgin JE. Structural atrial remodeling alters the substrate and spatiotemporal organization of atrial fibrillation: a comparison in canine models of structural and electrical atrial remodeling. Am J Physiol Heart Circ Physiol 2006; 291:2911-2923.

Fatkin D, MacRae C, Sasaki T, Wolff MR, Porcu M, Frenneaux M, Atherton J, Vidaillet HJ Jr, Spudich S, De Girolami U, Seidman JG, Seidman C, Muntoni F, Müehle G, Johnson W, McDonough B. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction system disease. N Engl J Med 1999; 341:1715-1724.

Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med 1995; 155:469–473.

Fenici R, Nenonen J, Pesola K, Korhonen P, Lötjönen J, Mäkijärvi M, Toivonen L, Poutanen VP, Keto P, Katila T. Nonfluroscopic localization of an amagnetic stimulation catheter by multichannel magnetocardiography. Pacing Clin Electrophysiol 1999; 22:1210-20.

Fioranelli M, Piccoli M, Mileto GM, Sgreccia F, Azzolini P, Risa MP, Francardelli RL, Venturini E, Puglisi A. Analysis of heart rate variability five minutes before the onset of paroxysmal atrial fibrillation. Pacing Clin Electrophysiol 1999; 22:743–749.

Fox CS, Parise H, D'Agostino RB Sr, Lloyd-Jones DM, Vasan RS, Wang TJ, Lévy D, Wolf PA, Benjamin EJ. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. JAMA 2004; 291:2851–2855.

Frank E. An accurate clinically practical system for spatial vectorcardiography. Circulation 1956; 13:737-749.

Franz MR, Burkhoff D, Spurgeon H, Weisfeldt ML, Lakatta EG. In vitro validation of a new cardiac catheter technique for recording monophasic action potentials. Eur Heart J 1986; 7:34-41.

Friberg J, Scharling H, Gadsbøll N, Jensen GB. Sex-specific increase in the prevalence of atrial fibrillation (The Copenhagen City Heart Study). Am J Cardiol 2003; 92:1419-1423.

Frisella ME, Robinette MM, Spodick DH. Interatrial block: pandemic prevalence concealed by anachronistic electrocardiographic standards. Clin Cardiol 2005; 28:381-383.

Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. Am J Med 2005; 118:489–495.

Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: a cohort study. Arch Intern Med 2004; 164:1993–1998.

Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. Circulation 1997; 96:1180-1184.

Fujimura O, Klein GJ, Yee R, Sharma AD. Mode of onset of atrial fibrillation in the Wolff-Parkinson-White syndrome: how important is the accessory pathway? J Am Coll Cardiol 1990; 15:1082-1086.

Fukunami M, Yamada T, Ohmori M, Kumagai K, Umemoto K, Sakai A, Kondoh N, Minamino T, Hoki N. Detection of patients at risk for paroxysmal atrial fibrillation during sinus rhythm by P wave-triggered signal-averaged electrocardiogram. Circulation 1991; 83:162-169.

Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health study). Am J Cardiol 1994; 74:236–241.

Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Heuzey JYL, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC, Jacobs AK, Adams CD, Anderson JL, Antman, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc J-J, Budaj FA, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation—Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006; 114:e257-354.

Gaita F, Riccardi R, Calò L, Scaglione M, Garberoglio L, Antolini R, Kirchner M, Lamberti F, Richiardi E. Atrial mapping and radiofrequency catheter ablation in patients with idiopathic atrial fibrillation. Electrophysiological findings and ablation results. Circulation 1998; 97:2136-2145.

Gaspo R, Bosch RF, Bou-Abboud E, Nattel S. Tachycardia-induced changes in Na+ current in a chronic dog model of atrial fibrillation, Circ Res 1997; 81: 1045-1052.

Gedikli O, Dogan A, Altuntas I, Altinbas A, Ozaydin M, Akturk O, Acar G. Inflammatory markers according to types of atrial fibrillation. Int J Cardiol 2007; 120:193-197.

Gepstein L, Hayam G, Shlomo A, Ben-Haim SA. A novel method for nonfluoroscopoic catheter-based electroanatomical mapping of the heart. Circulation 1997; 95:1611-1622.

Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. JAMA 2001; 285:2370–2375.

Gollob MH, Jones DL, Krahn AD, Danis L, Gong XQ, Shao Q, Liu X, Veinot JP, Tang AS, Stewart AF, Tesson F, Klein GJ, Yee R, Skanes AC, Guiraudon GM, Ebihara L, Bai D. Somatic mutations in the connexin 40 gene (GJA5) in atrial fibrillation. N Engl J Med 2006; 354:2677–2688.

Gomes JA, Winters SL. The origins of the sinus node pacemaker complex in man: demonstration of dominant and subsidiary foci. J Am Coll Cardiol 1987; 9:45-52.

Gondo N, Kumagai K, Matsuo K, Ogawa M, Annoura M, Moroe K, Arakawa K. The best criterion for discrimination between patients with and without paroxysmal atrial fibrillation on signalaveraged electrocardiogram. Am J Cardiol 1995; 75: 93-95.

Goudevenos JA, Vakalis JN, Giogiakas V, Lathridou P, Katsouras C, Michalis LK, Sideris DA. An epidemiological study of symptomatic paroxysmal atrial fibrillation in northwest Greece. Europace 1999; 1:226-233.

Gudbjartsson DF, Arnar DO, Helgadottir A, Gretarsdottir S, Holm H, Sigurdsson A, Jonasdottir A, Baker A, Thorleifsson G, Kristjansson K, Palsson A, Blondal T, Sulem P, Backman VM, Hardarson GA, Palsdottir E, Helgason A, Sigurjonsdottir R, Sverrisson JT, Kostulas K, Ng MC, Baum L, So WY, Wong KS, Chan JC, Furie KL, Greenberg SM, Sale M, Kelly P, MacRae CA, Smith EE, Rosand J, Hillert J, Ma RC, Ellinor PT, Thorgeirsson G, Gulcher JR, Kong A, Thorsteinsdottir U, Stefansson K. Variants conferring risk of atrial fibrillation on chromosome 4q25. Nature 2007; 448:353-357.

Grönefeld GC, Lilienthal J, Kuck KH, Hohnloser SH. Pharmacological Intervention in Atrial Fibrillation (PIAF) Study Investigators. Impact of rate versus rhythm control on quality of life in patients with persistent atrial fibrillation: results from a prospective randomized study. Eur Heart J 2003; 24:1430-1436.

Goyal SB, Spodick DH. Electromechanical dysfunction of the left atrium associated with interatrial block. Am Heart J 2001; 142:823-827.

Haberkorn W, Steinhoff U, Burghoff M, Kosch O, Morguet A, Koch H. Pseudo current density maps of electrophysiological heart, nerve or brain function and their physical basis. Biomagn Res Technol 2006; 4:5.

Hagendorff A, Schumacher B, Kirchhoff S, Lüderitz B, Willecke K. Conduction disturbances and increased atrial vulnerability in Connexin40-deficient mice analyzed by transesophageal stimulation. Circulation 1999; 99:1508–1515.

Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998; 339:659-666.

Haïssaguerre M, Hocini M, Takahashi Y, O'Neill MD, Pernat A, Sanders P, Jonsson A, Rotter M, Sacher F, Rostock T, Matsuo S, Arantés L, Teng Lim K, Knecht S, Bordachar P, Laborderie J, Jaïs P, Klein G, Clémenty J. Impact of catheter ablation of the coronary sinus on paroxysmal or persistent atrial fibrillation. J Cardiovasc Electrophysiol 2007; 18:378-386.

Harrild DM, Henriquez CS. A computer model of normal conduction in the human atria. Circ Res 2000; 87:e25-e36.

Havmöller R, Carlson J, Holmqvist F, Herreros A, Meurling CJ, Olsson B, Platonov P. Age-related changes in P wave morphology in healthy subjects. BMC Cardiovasc Disord 2007; 7:22.

Hayashi H, Lux RL, Wyatt RF, Burgess MJ, Abildskov JA. Relation of canine atrial activation sequence to anatomic landmarks. Am J Physiol 1982; 242:H421-H428.

Herweg B, Dalal P, Nagy B, Schweitzer P. Power spectral analysis of heart period variability of preceding sinus rhythm before initiation of paroxysmal atrial fibrillation. Am J Cardiol 1998; 82: 869–874.

Hiss R, Lamb I. ECG-findings in 122043 individuals. Circulation 1962; 25:947-961.

Hindricks G, Kottkamp H. Simultaneous noncontact mapping of left atrium in patients with paroxysmal atrial fibrillation. Circulation 2001; 104:297-303.

Hnatkova K, Waktare JE, Murgatroyd FD, Guo X, Baiyan X, Camm AJ, Malik M. Analysis of the cardiac rhythm preceding episodes of paroxysmal atrial fibrillation. Am Heart J 1998; 135(6 Pt 1):1010-1019.

Ho SY, Sanchez-Quintana D, Cabrera JA, Anderson RH. Anatomy of the left atrium: implications for radiofrequency ablation of atrial fibrillation. J Cardiovasc Electrophysiol 1999; 10:1525–1533.

Ho SY, Anderson RH, Sánchez-Quintana D. Atrial structure and fibers: morphologic bases of atrial conduction. Cardiovasc Res 2002; 54:325-336.

Hodgson-Zingman DM, Karst ML, Zingman LV, Heublein DM, Darbar D, Herron KJ, Ballew JD, de Andre M, Burnett JC Jr, Olson TM. Atrial natriuretic peptide framesift mutation in familial atrial fibrillation. N Eng J Med 2008; 10:158-165.

Hoffmann E, Sulke N, Edvardsson N, Ruiter J, Lewalter T, Cappuci A, Schucheert A, Janko S, Camm J and on behalf of the Atrial Fibrillation Theraphy (AFT) Trial Investigators. New Insights Into the Initiation of Atrial Fibrillation. A Detailed Intraindividual and Interindividual Analysis of the Spontaneous Onset of Atrial Fibrillation Using New Diagnostic Pacemaker Features. Circulation 2006; 113:1933-1941.

Holmqvist F, Husser D, Tapanainen JM, Carlson J, Jurkko R, Xia Y, Havmöller R, Kongstad O, Toivonen L, Olsson SB, Platonov PG. Interatrial conduction can be accurately determined using standard 12-lead electrocardiography: Validation of P wave morphology using standard 12-lead electrocardiography: Validation of P wave morphology using electroanatomic mapping in man. Heart Rhythm 2008; 5:413-418.

Humphries KH, Kerr CR, Connolly SJ, Klein G, Boone JA, Green M, Sheldon R, Talajic M, Dorian P, Newman D. New-onset atrial fibrillation: sex differences in presentation, treatment and outcome. Circulation 2001; 103:2365–2370.

Hwang C, Wu TJ, Doshi RN, Peter CT, Chen PS. Vein of Marshall cannulation for the analysis of electrical activity in patients with focal atrial fibrillation. Circulation 2000; 101:1503-1505.

Hänninen H, Takala P, Mäkijärvi M, Montonen J, Korhonen P, Oikarinen L, Nenonen J, Katila T, Toivonen L. Detection of exercise-induced myocardial ischemia by multichannel magnetocardiography in single vessel coronary artery disease. Ann Noninvasive Electrocardiol 2000; 5:147-157.

Iesaka Y, Yamane T, Takahashi A, Goya M, Kojima S, Soejima Y, Okamoto Y, Fujiwara H, Aonuma K, Nogami A, Hiroe M, Marumo F, Hiraoka M. Retrograde multiple and multifiber accessory pathway conduction in the Wolff-Parkinso-White syndrome: potential precipitating factor of atrial fibrillation. J Cardiovasc Electrophysiol 1998; 9:141-151.

Ikeda T, Uchida T, Hough D, Lee JJ, Fishbein MC, Mandel WJ, Chen PS, Karagueuzian HS. Mechanism of spontaneous termination of functional reentry in isolated canine right atrium. Evidence for the presence of an excitable but nonexcited core, *Circulation 1996;* 94:1962–1973.

Jackson JD. In Classical Electrodynamics 3rd ed. New York, NY: John Wiley & Sons, Inc 1999:

Jahangir A, Lee V, Friedman PA, Trusty JM, Hodge DO, Kopecky SL, Packer DL, Hammill SC, Shen W-K, Gersh BJ. Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study. Circulation 2007; 115:3050-3056.

Jaïs P, Haïssaguerre M, Shah DC, Chouairi S, Gencel L, Hocini M, Clémenty J. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. Circulation 1997; 95:572-576.

Jaïs P, Peng JT, Shah DC, Garrique S, Hocini M, Yamane T, Haïssaguerre M, Barold SS, Roudaut R, Clémenty J. Left ventricular diastolic dysfunction in patients with so-called lone atrial fibrillation. J Cardiovas Electrophysiol 2000; 11:623-625.

Jaïs P, Hocini M, Macle L, Choi KJ, Deisenhofer I, Weerasooriya R, Shah DC, Garrigue S, Raybaud F, Scavee C, Le Metayer P, Clémenty J, Haïssaguerre M. Distinctive electrophysiological properties of pulmonary veins in patients with atrial fibrillation. Circulation 2002; 106:2479-2485.

Janse MJ, Anderson RH, McGuire MA, Ho SY. "AV nodal" reentry: Part I: "AV nodal" reentry revisited. J Cardiovasc Electrophysiol 1993; 4:561-572. Review.

Jensen TJ, Haarbo J, Pehrson SM, Thomsen PEB. Paroxysmal atrial fibrillation: Ectopic atrial activity and prevalence of severly symptomatic patients. Pacing Clin Electrophysiol 2003; 26:1668-1674.

Jensen TJ, Haarbo J, Pehrson SM, Thomsen B. Impact of premature atrial contractions in atrial fibrillation. Pacing Clin Electrophysiol 2004; 27:447-452.

Junttila JM, Raatikainen MJP, Perkiömäki JS, Hong K, Brugada R, Huikuri HV. Familial clustering of lone atrial fibrillation in patients with saddleback-type ST-segment elevation in right pericordial leads.Eur Heart J 2007; 28:463-468.

Jones SB, Euler DE, Hardie E, Randall WC, Brynjolfsson G. Comparison of SA nodal and subsidiary atrial pacemaker function and location in the dog. Am J Physiol 1978; 234:H471-476.

Kallergis EM, Manios EG, Kanoupakis EM, Mavrakis HE, Kolyvaki SG, Lyrarakis GM, Chlouverakis GI, Vardas PE. The role of the post-cardioversion time course of hs-CRP levels in clarifying the relationship between inflammation and persistence of atrial fibrillation. Heart 2008; 94:200-204.

Kamiyama N. Expression of cell adhesion molecules and the appearance of adherent leukocytes on the left atrial endothelium with atrial fibrillation: rabbit experimental model. Jpn Circ J 1998; 62:837–843.

Kandori A, Hosono T, Kanagawa T, Miyashita S, Chiba Y, Murakami M, Miyashita T, Tsukada K. Detection of atrial-flutter and atrial-fibrillation waveforms by fetal magnetocardiogram. Med Biol Eng Comput. 2002; 40:213-217.

Kannel WB, Wolf PA, Benjamin EJ, Lévy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998; 82:2N–9N.

Karjalainen J, Kujala UM, Kaprio J, Sarna S, Viitasalo M. Lone atrial fibrillation in vigorously exercising middle aged men: case-control study. BMJ 1998; 316:1784-1785.

Karp PJ, Katila TE, Saarinen M, Siltanen P, Varpula TT. The normal human magnetocardiogram. II. A multipole analysis. Circ Res 1980; 47:117-30.

Kato R, Lickfett L, Meininger G, Dickfeld T, Wu R, Juang G, Angkeow P, LaCorte J, Bluemke D, Berger R, Halperin HR, Calkins H. Pulmonary vein anatomy in patients undergoing catheter ablation of atrial fibrillation: lessons learned by use of magnetic resonance imaging. Circulation 2003; 107:2004-2010.

Katritsis DG, Toumpoulis IK, Giazitzoglou E, Korovesis S, Karabinos I, Paxinos G, Zambartas C, Anagnostopoulos CE. Latent arterial hypertension in apparently lone atrial fibrillation. J Interv Card Electrophysiol. 2005 Sep;13(3):203-7.

Keith A, Flack M. The form and nature of the muscular connections between the primary divisions of the vertebrate heart. J Anat Physiol 1907; 41:172-189.

Keller AM, Gopal AS, King DL. Left and right atrial volume by freehand three-dimensional echocardiography: in vivo validation using magnetic resonance imaging. Eur J Echocardiography 2000; 1:55-65.

Kerr CR, Boone J, Connolly SJ, Dorian P, Green M, Klein G, Newman D, Sheldon R, Talajic M. The Canadian Registry of Atrial Fibrillation: a noninterventional follow-up of patients after the first diagnosis of atrial fibrillation. Am J Cardiol 1998; 82:82N–85N.

Khaja A, Flaker G. Bachmann's bundle: does it play a role in atrial fibrillation? Pacing Clin Electrophysiol 2005; 28:855-863.

Kim D, Kim K, Lee YH, Ahn H. Detection of atrial arrhythmia in superconducting quantum interference device magnetocardiography; preliminary result of a totally-noninvasive localization method for atrial current mapping. Interact Cardiovasc Thorac Surg 2007; 6:274-279.

Kistler PM, Sanders P, Fynn SP, Stevenson IH, Spence SJ, Vohra JK, Sparks PB, Kalman JM. Electrophysiologic and electroanatomic changes in human atrium associated with aging. J Am Coll Cardioll 2004; 44:109-116.

Kneller J, Kalifa J, Zou R, Zaitsev AV, Warren M, Berenfeld O, Vigmond EJ, Leon LJ, Nattel S, Jalife J. Mechanisms of atrial fibrillation termination by pure sodium channel blockade in an ionically-realistic mathematical model. Circ Res 2005; 96:e35-e47.

Koch H, Haberkorn W. Magnetic field mapping of cardiac electrophysiological function. Philosophical Transactions of The Royal Society: Mathematical, Physical & Engineering Sciences, 2001; 359(1783):1287-1298.

Koch H. Recent advances in magnetocardiography. J Electrocardiol 2004; 37(Suppl):117-122.

Konings KT, Kirchhof CJ, Smeets JR, Wellens HJ, Penn OC, Allessie MA. High-density mapping of electrically induced atrial fibrillation in humans. Circulation 1994; 89:1665-1680.

Kopecky SL, Gersh BJ, McGoon MD, Whisnant JP, Holmes DR, Ilstrup DM, Frye RL. The natural history of lone atrial fibrillation: a population-based study over three decades. N Engl J Med 1987; 317: 669–674.

Korhonen P, Montonen J, Mäkijärvi M, Katila T, Nieminen MS, Toivonen L. Late fields of the magnetocardiographic QRS complex as indicators of propensity to sustained ventricular tachycardia after myocardial infarction. J Cardiovasc Electrophysiol 2000; 11:413-420.

Korhonen P, Montonen J, Endt P, Mäkijärvi M, Trahms L, Katila T, Toivonen L. Magnetocardiographic intra-QRS fragmentation analysis in the identification of patients with sustained ventricular tachycardia after myocardial infarction. Pacing Clin Electrophysiol 2001; 24:1179-1186.

Korhonen P, Tierala I, Simelius K, Väänänen H, Mäkijärvi M, Nenonen J, Katila T, Toivonen L. Late QRS activity in signal-averaged magnetocardiography, body surface potential mapping and orthogonal ECG in postinfarction ventricular tachycardia patients. Ann Noninvasive Electrocardiol 2002; 7:389-398.

Korhonen P, Husa T, Tierala I, Väänänen H, Mäkijärvi M, Katila T, Toivonen L. Increased intra-QRS fragmentation in magnetocardiography as a predictor of arrhythm ic events and mortality in patients with cardiac dysfunction after myocardial infarction. J Cardiovasc Electrophysiol 2006; 17:396-401.

Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 1995; 98:476-484.

Kubara I, Ikeda H, Hiraki T, Yoshida T, Ohga M, Imaizumi T. Dispersion of filtered P wave duration by P wave signalaveraged ECG mapping system: Its usefulness for determining efficacy of disopyramide on paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 1999; 10:670-679.

Kumagai K, Akimitsu S, Kawahira K, Kawanami F, Yamanouchi Y, Hiroki T, Arakawa K. Electrophysiological properties in chronic lone atrial fibrillation. Circulation 1991; 84:1662-1668.

Leirner AA, Cestari IA. Monophasic action potential. New uses for an old technique. Arq Bras Cardiol 1999; 72:237-242.

Le Heuzey JY, Paziaud O, Piot O, Said MA, Copie X, Lavergne T, Guize L. Cost of care distribution in atrial fibrillation patients: the COCAF study. Am Heart J 2004; 147:121-126

Lehto M, Snapinn S, Dickstein K, Swedberg K, Nieminen MS, OPTIMAAL Investigators. Prognostic risk of atrial fibrillation in acute myocardial infarction complicated by left ventricular dysfunction: the OPTIMAAL experience. Eur Heart J 2005; 26:350–356.

Lemery R, Soucie L, Martin B, Tanq AS, Green M, Healey J. Human study of biatrial electrical coupling: determinants of endocardial septal activation and conduction over interatrial connections. Circulation 2004; 110:2083-2089.

Lemery R, Birnie D, Tang AS, Green M, Gollob M, Hendry M, Lau E. Normal atrial activation and voltage during sinus rhythm in the human heart: an endocardial and epicardial mapping study in patients with a history of atrial fibrillation. J Cardiovasc Electrophysiol 2007; 18:402-408.

Lesh MD, Kalman JM, Olgin JE, Ellis WS. The role of atrial anatomy in clinical atrial arrhythmias. J Electrocardiol 1996; 29:101-113.

Lévy S, Maarek M, Coumel P, Guize L, Lekieffre J, Medvedowsky JL, Sebaoun A. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. The College of French Cardiologists. Circulation 1999; 99:3028-3035.

Lewalter T, Yang A, Pfeiffer D, Ruiter J, Schnitzler G, Markert T, Asklund M, Przibille O, Welz A, Esmailzadeh B, Linhart M, Lüderitz B. Individualized selection of pacing algorithms for the prevention of reccurent atrial fibrillation: Results from the VIP registry. Pacing Clin Electrophysiol 2006; 29:124-134.

Lewis T, Feil H, Stroud W. Observations upon flutter and fibrillation ii. Nature of auricular flutter. Heart 1920;7: 191e244.

Lewis T, Drury AN, Iliescu CC. A demonstration of circus movement in clinical flutter of the auricles. Heart 1921; 8:341e55.

Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. Circulation 1999; 100:87-95.

Li D, Shinagawa K, Pang L, Leung TK, Cardin S, Wang Z, Nattel S. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure, Circulation 2001; 104:2608-2614.

Lin WS, Tai CT, Hsieh MH, Tsai CF, Lin YK, Tsao HM, Huang JL, Yu WC, Yang SP, Ding YA, Chang MS, Chen SA. Catheter ablation of paroxysmal atrial fibrillation initiated by non–pulmonary vein ectopy. Circulation 2003; 107:3176-3183.

Liu X, Jahangir A, Terzic A, Gersh B, Hammill S, Shen W. Age- and sex-related atrial electrophysiologic and structural changes. Am J Cardiol 2004; 94:373 – 375.

Liu L, Nattel S. Differing sympathetic and vagal effects on atrial fibrillation in dogs: role of refractoriness heterogeneity. Am J Physiol 1997; 273(2 Pt 2):H805-16.

Luo J, Yuan S, Hertervig E, Kongstad O, Ljunstrom E, Holm M, Olsson SB. Electroanatomic mapping of right atrial actvation in patients with and without paroxysmal atrial fibrillation. J Electrocardiol 2003; 36:237-242.

Macfarlane PW. Lead systems. In: Macfarlane PW, Lawrie TDV, eds. Comprehensive Electrocardiology Volume I. Pergamon Press, Oxford 1989: 315-352.

Maggioni AP, Latini R, Carson PE, Singh SN, Barlera S, Glazer R, Masson S, Cerè E, Tognoni G, Cohn JN; Val-HeFT Investigators.Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). Am Heart J 2005; 149:548-557.

Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003; 91:2D-8D.

Maisel WH. Autonomic modulation preceding the onset of atrial fibrillation. J Am Coll Cardiol. 2003; 42: 1269-70.

Mandapati R, Skanes A, Chen J, Berenfeld O, Jalife J. Stable microreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart. Circulation 2000; 101:194-199.

Marcus GM, Smith LM, Vittinghoff E, Tseng ZH, Badhwar N, Lee BK, Lee RJ, Scheinman MM, Olgin JE. A first-degree family history in lone atrial fibrillation patients. Heart Rhythm 2008; 5: 826-830.

Markides V, Schilling RJ, Ho SY, Chow AW, Davies DW, Peters NS. Characterization left atrial activation in the intact human heart. Circulation 2003; 107:733-9.

Mikhaĭlov SS, Chukbar AV. Topography of the elements of the heart conduction system in the human. Arkh Anat Gistol Embriol. 1982; 82:56-67. Russian.

Mines GR. On dynamic equilibrium in the heart. J Physiol 1913; 46**:**349–383.

Mitrofanova L, Ivanov V, Platonov PG. Anatomy of the inferior interatrial route in humans. Europace 2005; 7:49–55.

Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. Am Heart J 1959; 58:59–70.

Moe GK : On the multiple wavelet hypothesis. Arch Int Pharmacodyn Ther 1962; 140:183-188.

Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation, Am. Heart J 1964; 67:200–220.

Mont L, Sambola A, Brugada J, Vacca M, Marrugat J, Elosua R, Pare C, Azqueta M, Sanz G. Long-lasting sport practice and lone atrial fibrillation. Eur Heart J 2002; 23:477–482.

Mont L, Tamborero D, Elosua R, Molina I, Coll-Vinent B, Sitges M, Vidal B, Scalise A, Tejeira A, Berruezo A, Brugada J, GIRFA (Grup Integrat de Recerca en Fibrill-Iació Auricular) Investigators. Physical activity, height, and left atrial size are independent risk factors for lone atrial fibrillation in middle-aged healthy individuals. Europace 2008; 10:15-20.

Morady F. Patient-spesific ablation strategy for atrial fibrillation: promises and difficulties. Heart rhytm 2007; 4:1094-1096.

Moreira JO, Moffa PJ, Uchida AH, Martins de Oliveira Tobias NM, Grupi CJ, Filho BL, Tarasoutchi F. The signal –averaged electrocardiograms to atrial activation in patients with and without paroxysmal atrial fibrillation. Arq Bras Cardiol 2006; 87: 513-518

Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation 1995; 91:1588-1595.

Mäki T, Toivonen L, Koskinen P, Näveri H, Härkönen M, Leinonen H. Effect of ethanol drinking, hangover, and exercise on adrenergic activity and heart rate variability in patients with a history of alcohol-induced atrial fibrillation. Am J Cardiol 1998; 82:317-322.

Mäkijärvi M, Montonen J, Toivonen L, Siltanen P, Nieminen MS, Leiniö M, Katila T. Identification of patients with ventricular tachycardia after myocardial infarction by high-resolution magnetocardiography and electrocardiography. J Electrocardiol 1993a; 26:117-124.

Mäkijärvi M, Nenonen J, Toivonen L, Montonen J, Katila T, Siltanen P. Magnetocardiography: supraventricular arrhythmias and preexcitation syndromes. Eur Heart J 1993b; 14 Suppl E:46-52.

Nabar A, Rodriques LM, Timmermans C, Dool A, Smeets, JLRM, Wellens HJJ. Effect of right atrial isthmus ablation on the occurrence of atrial fibrillation: Observations in four patient groups having Type I atrial flutter with or without associated atrial fibrillation. Circulation 1999; 99:1442-1445.

Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol 2004; 43:2044-2053.

Nakai K, Kawazoe K, Izumoto H, Tsuboi J, Oshima Y, Oka T, Yoshioka K, Shozushima M, Suwabe A, Itoh M, Kobayashi K, Shimizu T, Yoshizawa M. Construction of a three-dimensional outline of the heart and conduction pathway by means of a 64 channel magnetocardiogram in patients with atrial flutter and fibrillation. Int J Cardiovasc Imaging 2005; 21:555-561.

Nakamura Y, Nakamura K, Fukushima-Kusano K, Ohta K, Matsubara H, Hamuro T, Yutani C, Ohe T. Tissue factor expression in atrial endothelium associated with nonvalvular atrial fibrillation: possible involvement in intracardiac thrombogenesis. Thromb Res 2003; 111:137–142.

Nathan H, Eliakim M. The junction between the left atrium and the pulmonary veins. An anatomic study of human hearts. Circulation 1966; 34:412-422.

Nattel S. Therapeutic implications of atrial fibrillation mechanisms: Can mechanistic insights be used to improve AF management? Cardiovasc Res 2002; 54:347–360.

Nattel S, Shiroshita-Takeshita A, Brundel BJ, Rivard L. Mechanisms of atrial fibrillation: lessons from animal models. Prog Cardiovasc Dis 2005; 48:9–28.

Ndrepepa G, Zrenner B, Deisenhofer I, Karch M, Schneider M, Schreieck J, Schmitt C. Relationship between surface electrocardiogram characteristics and endocardial activation sequence in patients with typical atrial flutter. Z Kardiol 2000; 89:527-537.

Nemirovsky D, Hutter R, Gomes JA. The electrical substrate of vagal atrial fibrillation as assessed by the signal-averaged electrocardiogram of the P wave. Pacing Clin Electrophysiol 2008; 31:308-313.

Nenonen J. Magnetocardiography. In: Braginski A, Clarke J, eds. SQUID handbook. Wiley-VCH Verlag, Berlin 2002.

Nenonen J, Montonen J, Koskinen R. Surface gradient analysis of atrial activation from magnetocardiographic maps. In International journal of Bioelectromagnetism 2003; 5:98-99.

Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andersen D, Davies DW, Cobbe S, Breithardt G, Le Heuzey J-Y, Prins MH, Lévy S, Crijns HJ; European Heart Survey Investigators. Atrial fibrillation management: a prospective survey in ESC Member Countries The Euro Heart Survey on Atrial Fibrillation. Eur Heart J 2005; 26:2422-2434.

O'Donnell D, Bourke JP, Furniss SS. Interatrial transseptal electrical conduction: comparison of patients with atrial fibrillation and normal controls. J Cardiovasc Electrophysiol 2002; 13:1111-1117.

Oikarinen L, Paavola M, Montonen J, Viitasalo M, Mäkijärvi M, Toivonen L, Katila T. Magnetocardiographic QT interval dispersion in postmyocardial infarction patients with sustained ventricular tachycardia: validation of automated QT measurements. Pacing Clin Electrophysiol 1998; 21:1934-1942.

Okumura Y, Watanabe I, Ohkubo K, Sonoko A, Kofune M, Hashimoto K, Shindo A, Sugimura H, Nakai T, Kasamaki Y, Saito S. Prediction of the efficacy of pulmonary vein isolation for the treatment of atrial fibrillation by the signal-averaged P wave duration. Pacing Clin Electrophysiol 2007; 30:304-313.

Olgin JE, Jayachandran JV, Engesstein E, Groh W, Zipes DP. Atrial macroreentry involving the myocardium of the coronary sinus: a unique mechanism for atypical flutter. J Cardiovasc Electrophysiol 1998; 9:1094-1099.

Olson T.M., Michels V.V., Ballew J.D., Reyna S.P., Karst M.L., Herron K.J., Horton S.C., Rodeheffer R.J., Anderson J.L. Sodium channel mutations and susceptibility to heart failure and atrial fibrillation. JAMA 2005; 293**:**447–454.

Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S, Scharf C, Lai SW, Greenstein R, Pelosi F Jr, Strickberger SA, Morady. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. Circulation 2002a; 105:1077–1081.

Oral H, Knight BP, Ozaydin M, Chugh A, Lai SW, Scharf C, Hassan S, Greenstein R, Han JD, Pelosi F Jr, Strickberger SA, Morady F. Segmental ostial ablation to isolate the pulmonary veins during atrial fibrillation: Feasibility and mechanistic insights. Circulation 2002b; 106:1256-1262.

Oral H, Ozaydin M, Chugh A, Scharf C, Tada H, Hall B, Cheung P, Pelosi F, Knight BP, Morady F. Role of coronary sinus in maintenance of atrial fibrillation. J Cardiovasc Electrophysiol 2003; 14:1329-1336.

Oral H, Chugh A, Scharft C, Hall B, Cheung P, Veerareddy S, Daneshvar GF, Pelosi F Jr, Morady F. Pulmonary vein isolation for vagotonic, adrenergic, and random episodes of paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 2004; 15:402-406.

Oral H. Mechanisms of atrial fibrillation: lessons from studies in patients. Prog Cardiovasc Dis 2005; 48:29-40.

Osranek M, Bursi F, Bailey KR, Grossardt BR, Brown RD Jr, Kopecky SL, Tsang TS, Seward JB. Left atrial volume predicts cardiovascular events in patients originally diagnosed with lone atrial fibrillation: three-decade follow-up. Eur Heart J 2005; 26:2556-2561.

Ott P, Kirk MM, Koo C, He DS, Bhattacharya B, Buxton A. Coronary sinus and fossa ovalis ablation: effect on interatrial conduction and atrial fibrillation. J Cardiovasc Electrophysiol 2007; 18:310-7.

Pachon M JC, Pachon M EI, Pachon M JC, Lobo TJ, Pachon MZ, Vargas RN, Pachon DQ, Lopez M FJ, Jatene AD. A new treatment for atrial fibrillation based on spectral analysis to guide the catheter RF-ablation. Europace 2004; 6:590-601.

Panfilov AV, Pertsov AM. Mechanism of the origin of the helical waves in active media associated with the phenomenon of critical curvature. Biofizika 1982; 27:886-889.

Patterson E, Po SS, Scherlag BJ, Lazzara R. Triggered firing in pulmonary veins initiated by in vitro autonomic nerve stimulation. Heart Rhythm 2005; 2:624-631.

Patton KK, Zacks ES, Chang JY, Shea MA, Ruskin JN, Macrae CA. Elinor PT. Clinical subtypes of lone atrial fibrillation. Pacing Clin Electrophysiol 2005; 28:630–638.

Perzanowski C, Ho AT, Jacobson AK. Increased P wave dispersion predicts recurrent atrial fibrillation after cardioversion. J Electrocardiol 2005; 38:43-46.

Pesola K, Nenonen J, Fenici R, Lötjönen J, Mäkijärvi M, Fenici P, Korhonen P, Lauerma K, Valkonen M, Toivonen L. Katila T. Bioelectromagnetic localization of a pacing catheter in the heart. Phys Med Biol 1999a; 44: 2565-2578.

Platonov PG, Carlson J, Ingemansson MP, Roijer A, Hansson A, Chireikin LV, Olsson SB. Detection of interatrial conduction defects with unfiltered signal-averaged P wave ECG in patients with lone atrial fibrillation. Europace 2000; 2:32-41.

Platonov PG, Mitrofanova LB, Chireikin LV, Olsson SB. Morphology of interatrial conduction routes in patients with atrial fibrillation. Europace 2002; 4:183-192.

Platonov PG. Interatrial conduction in the mechanisms of atrial fibrillation: from anatomy to cardiac signals and new treatment modalities. Europace 2007; 9:Suppl 6:vi10-16.

Plonsey R. Comparative capabilities of electrocardiography and magnetocardiography. Am J Cardiol 1972; 29: 735-736.

Ravelli F, Allessie M. Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated Langendorff-perfused rabbit heart. Circulation 1997; 96:1686-1695.

Redfearn DP, Lane J, Ward K, Stafford PJ. High-resolution analysis of the surface P wave as a measure of atrial electrophysiological substrate. Ann Noninvasive Electrocardiol 2006; 11:12-19.

Rensma PL, Allessie MA, Lammers WJ, Bonke FI, Schalij MJ. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. Circ Res 1988; 62:395-410.

Rienstra M, Van Veldhuisen DJ, Hagens VE, Ranchor AV, Veeger NJ, Crijns HJ, Van Gelder IC,; RACE Investigators. Gender-related differences in rhythm control treatment in persistent atrial fibrillation: data of the Rate Control versus Electrical Cardioversion (RACE) study. J Am Coll Cardiol 2005; 46:1298 –1306.

Roberts DE, Hersh LT, Scher AM. Influence of cardiac fiber orientation on wavefront voltage, conduction velocity, and tissue resistivity in the dog. Circ Res. 1979; 44:701-712.

Roithinger FX, Cheng J, SippensGroenewegen A, Lee RJ, Saxon LA, Scheinman MM, Lesh MD. Use of electroanatomic mapping to delineate transseptal atrial conduction in humans. Circulation 1999; 100:1791-1797.

Rostagno C, Olivo G, Comeqlio M, Bertini G, Gensini GF, Galatini G. Left atrial size changes in patients with paroxysmal lone atrial fibrillation. An echocardiographic follow-up. Angiology 1996; 47:797-801.

Ruigómez A. Johansson S. Wallander MA. García Rodríguez LA. Predictors and prognosis of paroxysmal atrial fibrillation in general practice in the UK. BMC Cardiovasc Disord 2005; 5:20.

Saarinen M, Karp PJ, Katila TE, Siltanen P. The magnetocardiogram in cardiac disorders. Cardiovasc Res 1974; 8: 820-834.

Saarinen M, Siltanen P, Karp PJ, Katila TE. The normal magnetocardiogram: I Morphology. Ann Clin Res 1978; 10(Suppl 21): 1-22.

Sahadevan J, Ryu K, Peltz L, Khrestian CM, Stewart RW, Markowitz AH, Waldo AL. Epicardial mapping of chronic atrial fibrillation in patients: preliminary observations. Circulation 2004; 110: 3293–3299.

Sánchez-Quintana D, Cabrera JA, Farre J, Climent V, Anderson RH, Ho SY. Sinus node revisted in the era of electroanatomical mapping and catheter ablation. Heart 2005; 91:189-194.

Sanders P, Jaïs P, Hocini M, Hsu LF, Scavée C, Sacher F, Rotter M, Takahashi Y, Pasquié JL, Shah DC, Garrigue S, Clémenty J, Haïssaguerre M. Electrophysiologic and clinical consequences of linear catheter ablation to transect the anterior left atrium in patients with atrial fibrillation. Heart Rhythm 2004; 1:176-184.

Sanders P, Berenfeld O, Hocini M, Jaïs P, Vaidyanathan R, Hsu LF, Garrigue S, Takahashi Y, Rotter M, Sacher F, Scavee C, Ploutz-Snyder R, Jalife J, Haissaguerre M. Spectral analysis identifies sites of high-frequency activity maintaining atrial fibrillation in humans. Circulation 2005; 112:789-797.

Sata N, Hamada N, Horinouchi T, Amitani S, Yamashita T, Moriyama Y, Miyahara K. C-reactive protein and atrial fibrillation. Is inflammation a consequence or a cause of atrial fibrillation? Jpn Heart J 2004; 45:441–445.

Satoh T, Zipes DP. Unequal atrial stretch in dogs increases dispersion of refractoriness conducive to developing atrial fibrillation. J Cardiovasc Electrophysiol 1996; 7:833-842.

Scanavacca M, Pisani CF, Hachul D, Lara S, Hardy C, Darrieux F, Trombetta I, Negrao CE, Sosa E. Selective atrial vagal denervation guided by evoked vagal reflex to treat patients with paroxysmal atrial fibrillation. Circulation 2006; 114:876-885.

Scardi S, Mazzone C, Pandullo C, Goldstein D, Poletti A, Humar F. Lone atrial fibrillation: prognostic differences between paroxysmal and chronic forms after 10 years of follow-up. Am Heart J 1999; 137:686–691.

Schauerte P, Scherlag BJ, Pitha J, Scherlag MA, Reynolds D, Lazzara R, Jackman WM. Catheter ablation of cardiac autonomic nerves for prevention of vagal atrial fibrillation. Circulation 2000; 102: 2774-2780.

Scherlag BJ, Nakagawa H, Jackman WM, Yamanashi WS, Patterson E, Po S, Lazzara R. Electrical stimulation to identify neural elements on the heart: their role in atrial fibrillation. J Interv Card Electrophysiol 2005; 13 Suppl 1:37-42.

Schoonderwoerd BA, Smit MD, Pen L, Van Gelder IC. New risk factors for atrial fibrillation: causes of 'not-so-lone atrial fibrillation'. Europace 2008; 10: 668-673.

Schotten U, Ausma J, Stellbrink C, Sabatschus I, Vogel M, Frechen D, Schoendube F, Hanrath P, Allessie MA. Cellular mechanisms of depressed atrial contractility in patients with chronic atrial fibrillation. Circulation 2001; 103:691-698.

Schotten U, M. Duytschaever M, Ausma J, Eijsbout S, Neuberger H-R, Allessie M. Electrical and contractile remodeling during the first days of atrial fibrillation go hand in hand. Circulation 2003; 107:1433–1439.

Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, Denjoy I, Guicheney P, Breithardt G, Keating MT, Towbin JA, Beggs AH, Brink P, Wilde AA, Toivonen L, Zareba W, Robinson JL, Timothy KW, Corfield V, Wattanasirichaigoon D, Corbett C, Haverkamp W, Schulze-Bahr E, Lehmann MH, Schwartz K, Coumel P, Bloise R. Genotype-phenotype correlation in the long QT syndrome: gene specific triggers for life-threathing arrhythmias. Circulation 2001; 103:89-95.

Scher AM, Spach MS. Cardiac depolarization and repolarization and the electrocardiogram. In: Berne RM, Sperelakis N, Geiger SR, eds. Handbook of Physiology. Washington: Amer Physiol Soc, Washington 1979: 357-392.

Schuessler RB, Grayson TM, Bromberg BI, Cox JL, Boineau JP. Cholinergically mediated tachyarrhythmias induced by a single extrastimulus in the isolated canine right atrium. Circ Res 1992; 71:1254-1267.

Scott C, Leier V, Kilman W, Vasko S, Unverferth V. The effect of left atrial histology and dimension on P wave morphology. J Electrocardiol 1983; 16:363-366.

Sekiya J, Ohnishi Y, Inoue T, Yokoyama M. Monophasic action potentials of the right atrium in patients with paroxysmal atrial fibrillation. Jpn Circ J 2001; 65:893-896.

Skanes AC, Mandapati R, Berenfeld O, Davidenko JM, Jalife J. Spatiotemporal periodicity during atrial fibrillation in the isolated sheep heart, Circulation 1998; 98:1236-1248.

Simson MB, Euler D, Michelson EL, Falcone RA, Spear JF, Moore EN. Detection of delayed ventricular activation on the body surface in dogs. Am J Physiol 1981; 241:H363-H369.

Sitges M, Teijeira VA, Scalise A, Vidal B, Tamborero D, Collvinent B, Rivera S, Molina I, Azqueta M, Paré C, Brugada J, Mont L. Is there an anatomical substrate for idiopathic paroxysmal atrial fibrillation? A case-control echocardiographic study. Europace 2007; 9:294-298.

Siltanen P. Magnetocardiography. In Macfarlane P, Lawrie TDV, eds. Comprehensive Electrocardiology Volume II. Pergamon Press Oxford 1989: 1405-1438.

Smeets JL, Ben-Haim SA, Rodriquez LM, Timmermans C, Wellens HJ. New method for nonfluoroscopic endocardial mapping in humans. Circulation 1998; 97:2426-2432.

Spach MS, King TD, Barr RC, Boaz DE, Morrow MN, Herman-Giddens S. Electrical potential distribution surrounding the atria during depolarization and repolarization in the dog. Circ Res 1969; 24:857-873.

Steinbigler P. Haberl R. Konig B. Steinbeck G: P wave signal averaging identifies patients prone to alcohol-induced paroxysmal atrial fibrillation. Am J Cardiol 2003; 91:491-494.

Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med 2002; 113: 359-364.

Stewart S, Murphy N, Walker A, McGuire A, McMurray JJ. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. Heart 2004; 90:286-292

Suarez GS, Lampert S, Ravid S, Lown B. Changes in left atrial size in patients with lone atrial fibrillation. Clin Cardiol 1991;14:652-656.

Sulke N, Silberbauer J, Boodhoo L, Freemantle N, Kamalvand K, O'Nunain S, Hildick-Smith D, Lloyd GW, Patel NR, Paul V. The use of atrial ovedrive and ventricular rate stabilization pacing algorithms for prevention and treatment of paroxysmal atrial fibrillation: the Pacemarker Atrial Fibrillation Suppression (PAFS) study. Europace 2007; 9:790-797.

Sumi M, Takeuchi A, Katayama M, Fukuda Y, Nomura M, Fujino K, Murakami M, Nakaya Y, Mori H. Magnetocardiographic P waves in normal subjects and patients with mitral stenosis. Jpn Heart J. 1986; 27:621-633.

Sun H, Gaspo R, Leblanc N, Nattel S. Cellular mechanisms of atrial contractile dysfunction caused by sustained atrial tachycardia, Circulation 1998; 98:719–727.

Surawicz B. Electrocardiographic theory and methods of recording. Electro-physiological basis of ECG and cardiac arrhythmias. Williams and Wilkins, Philadelphia 1995: 494-507.

Takase H, Imai S, Saito F, Yagi H, Kushiro T. Role of the low amplitude potential in the initial P wave signal-averaged electrocardiogram (corrected)in sick sinus syndrome. Circ J 2006; 70:985-990.

Takeuchi A, Watanabe K, Nomura M, Ishihara S, Sumi M, Murakami M, Saito K, Nakaya Y, Mori H. The P wave in the magnetocardiogram. J Electrocardiol 1988; 21:161-167.

Tavarozzi I, Comani S, Del Gratta C, Luca Romani G, Di Lucio S, Brisinda D, Gallina S, Zimarino M, Fenici R, De Caterina R. Magnetocardiography: current status and perspectives. Part I: physical principles and instrumentation. Ital Heart J 2002; 3:75- 85.

Thambidorai SK, Parakh K, Martin DO, Shah TK, Wazni O, Jasper SE, Van Wagoner DR, Chung MK, Murray RD, Klein AL. Relation of C-reactive protein correlates with risk of thromboembolism in patients with atrial fibrillation. Am J Cardiol 2004; 94:805–807.

Todd DM, Fynn SP, Hobbs WJ, Fitzpatrick AP, Garratt CJ. Prevalence and significance of focal sources of atrial arrhythmia in patients undergoing cardioversion of persistent atrial fibrillation. J Cardiovasc Electrophysiol 2000; 11:616-622.

Tsai CF, Tai CT, Hsieh MH, Lin WS, Yu WC, Ueng KC, Ding YA, Chang MS, Chen SA. Initiation of atrial fibrillation by ectopic beats originating from the superior vena cava: Electrophysiological characteristics and results of radiofrequency ablation. Circulation 2000; 102:67- 74.

Tsang T, Miyasaka Y, Barnes M, Gersh B. Epidemiological profile of atrial fibrillation: a contemporary perspective. Prog Cardiovasc Dis 2005; 48:1–8.

Tse HF, Oral H, Pelosi F, Knight BP, Strickberger SA, Morady F. Effect of gender on atrial electrophysiologic changes induced by rapid atrial pacing and elevation of atrial pressure. J Cardiovasc Electrophysiol 2001;12:986-989.

Uusitalo MA, Ilmoniemi RJ. Signal-Space Projection Method for separating MEG or EEG into components. Medical & Biological Engineering & Computing 1997; 35: 135-140.

Van Leeuwen P, Hailer B, Lange S, Donker D, Grönemeyer D. Spatial and temporal changes during the QT-interval in the magnetic field of patients with coronary artery disease. Biomed Tech (Berl) 1999; 44: 139-142.

Verheule S, Wilson E, Everett T IV, Shanbhag S, Golden C, Olgin J. Alterations in atrial electrophysiology and tissue structure in a canine model of chronic atrial dilatation due to mitral regurgitation. Circulation 2003; 107:2615-2622.

Verheule S, Sato T, Everett T 4th, Engle SK, Otten D, Rubart-von der Lohe M, Nakajima HO, Nakajima H, Field LJ, Olgin JE. Increased vulnerability to atrial fibrillation in transgenic mice with selective atrial fibrosis caused by overexpression of TGF-beta1. Circ Res 2004; 94:1458-1465.

Verma A, Wazni OM, Marrouche NF, Martin DO, Kilicaslan F, Minor S, Schweikert RA, Saliba W, Cummings J, Burkhart JD, Bhargava M, Belden WA, Abdul-Karim A, Natale A. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. J Am Coll Cardiol 2005; 45:285-292.

Verma A, Novak P, Macle L, Whaley B, Beardsall M, Wulffhart Z, Khaykin Y. A prospective, multicenter evaluation of ablating complex fractionated electrograms (CFEs) during atrial fibrillation (AF) identified by an automated mapping algorithm: acute effects on AF and efficacy as an adjuvant strategy. Heart Rhythm 2008; 5:198-205.

Vidaillet H, Granada JF, Chyou PH, Maassen K, Ortiz M, Pulido JN, Sharma P, Smith PN, Hayes J. A population-based study of mortality among patients with atrial fibrillation or flutter. Am J Med 2002; 113:365–370.

Vigmond EJ, Tsoi V, Kuo S, Arevalo H, Kneller J, Nattel S, Trayanova N. The effect of vagally induced APD dispersion on atrial arrhythmogenesis, Heart Rhythm 2004; 1:334–344.

Vikman S, Mäkikallio TH, Yli-Mäyry S, Pikkujämsä S, Koivisto AM, Reinikainen P, Airaksinen KE, Huikuri HV. Altered complexity and correlation properties of R-R interval dynamics before the spontaneous onset of paroxysmal atrial fibrillation. Circulation. 1999; 100:2079-2084.

Vincenti A, Brambilla R, Fumagalli MG, Merola R, Pedretti S. Onset mechanism of paroxysmal atrial fibrillation detected by ambulatory Holter monitoring. Europace 2006; 8:204-210.

Vitikainen A-M. Sydämen eteisten aktivoitumisreittien määritys magnetokardiografiamittauksista. Pro gradu thesis. University of Helsinki, 2005.

Waldo AL, Bush HLJ, Gelband H, Zorn GLJ, Hoffman BF. Effects on the canine P wave of discreate lesions in the specialized atrial tracts. Circ Res 1971; 29:452-467.

Wang J, Bourne GW, Wang Z, Villemaire C, Talajic M, Nattel S. Comparative mechanisms of antiarrhythmic drug action in experimental atrial fibrillation. Importance of use-dependent effects on refractoriness. Circulation 1993; 88:1030-1044.

Wang K, Ho Sy, Gibson DG, Anderson RH. Architecture of atrial musculature in humans. Br Heart J 1995; 73:559-565.

Wang C, Xie Z, Li M, Lin P, Cao M, Xue Y, Deng C. P wave duration and its spatial dispersion in healthy subjects. The Internet Journal of Cardiovascular Research. 2002. Volume 1 Number 1.

Wattigney WA, Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. Circulation 2003; 108:711–716.

Weiss C, Willems S, Rueppel R, Hoffmann M, Meinertz T. Ectroanatomic mapping (CARTO) of ectopic atrial tachycardia: Impact of bibolar and unipolar local electrogram annotation for localization the focal origin. J Interv Card Electrophysiol 2001; 5:101-107.

Wiener N, Rosenblueth A. The mathematical formulation of the proplem of conduction of impulses in a network of connected exitable elements, specifically in cardiac muscle. Arch Inst Cardiol Mex 1946; 16:205-265.

Wijffels MC, Dorland R, Mast F, Allessie MA. Widening of the excitable gap during pharmacological cardioversion of atrial fibrillation in the goat: Effects of cibenzoline, hydroquinidine, flecainide, and d-sotalol, Circulation 2000; 101:260–267.

Willems JL, Robles de Medina EO, Bernard R, Coumel P, Fisch C, Krikler D, Mazur NA, Meijler FL, Mogensen L, Moret P. Criteria for intraventricular conduction disturbances and pre-exitation. World Health Organizational/International Society and Federation for Cardiology Task Force Ad Hoc. J Am Coll Cardiol 1985; 5:1261-1275.

Winklmaier M, Pohle C, Achenbach S, Kaltenhauser M, Moshage W, Daniel WG. P wave analysis in MCG and ECG after conversion of atrial fibrillation. Biomed Tech (Berl) 1998; 43 (Suppl):250-251.

Winterberg H. Studien über Herzflimmeren, über die wirkung des N. vagus und accelerans auf das Flimmern des Herzens. Pflügers Arch Physiol 1907; 117:223-256.

Wu TJ, Liang KW, Ting CT. Relation between the rapid focal activation in the pulmonary vein and the maintenance of paroxysmal atrial fibrillation. Pacing Clin Electrophysiol 2001;24:902-905.

Xia Y, Hertervig E, Kongstad O, Ljungström E, Platonov P, Holm M, Olsson SB, Yuan S. Deterioration of interatrial conduction in patients with paroxysmal atrial fibrillation: electroanatomic mapping of the right atrium and coronary sinus. Heart Rhythm 2004; 1:548–553.

Xia M, Jin Q, Bendahhou S, He Y, Larroque MM, Chen Y, Zhou Q, Yang Y, Liu Y, Liu B, Zhu Q, Zhou Y, Lin J, Liang B, Li L, Dong X, Pan Z, Wang R, Wan H, Qiu W, Xu W, Eurlings P, Barhanin J, Chen Y. A Kir2.1 gain-of-function mutation underlies familial atrial fibrillation. Biochem Biophys Res Commun 2005; 33:1012-1019.

Zar JH. Biostatistical Analysis. 4th ed. Prentice-Hall, Upper Saddle River, NJ 1999: 630, 649.

Yang Y, Xia M, Jin Q, Bendahhou S, Shi J, Chen Y, Liang B, Lin J, Liu Y, Liu B, Zhou Q, Zhang D, Wang R, Ma N, Su X, Niu K, Pei Y, Xu W, Chen Z, Wan H, Cui J, Barhanin J, Chen Y. Identification of a KCNE2 gain-of-function mutation in patients with familial atrial fibrillation. Am J Hum Genet 2004; 75**:**899-905.

Yang A, Ruiter J, Pfeiffer D, Esmailazadeh B, Welz A, Hochhäusler M, Nickenig G, Lüderitz B, Lewalter T. Identification of “substrate fibrillators” and “trigger fibrillators” by pacemaker diagnostics. Heart Rhythm 2006; 3:689-688.

Yamada T, Fukunami M, Ohmori M. Clinical significance of atrial signalaveraged electrocardiogram for detection of patients with paroxysmal atrial fibrillation during sinus rhythm (abstract). Circulation 1989; 80(Suppl II): 636.

Yamada T, Fukunami M, Ohmori M, Kumagai K, Sakai A, Kondoh N, Miniamino T, Hoki N. Characteristics of frequency content of atrial signal-averaged electrocardiograms during sinus rhythm in patients with paroxysmal atrial fibrillation. J Am Coll Cardiol 1992; 19:559-563.

Yamada T, Fukunami M, Shimonagata T, Kumagai K, Sanada S, Ogita H, Asano Y, Hori M, Hoki N. Dispersion of signal-averaged P wave duration on precordial body surface in patients with paroxysmal atrial fibrillation. Eur Heart J 1999; 20:211-220.

Yamada S, Tsukada K, Miyashita T, Oyake Y, Kuga K, Yamaguchi I. Noninvasive diagnosis of partial atrial standstill using magnetocardiograms. Circ J 2002; 66:1178-1180.

Yamada S, Tsukada K, Mijashita T, Kuga K, Yamaguchi I. Noninvasive direct visualization of macro-reentrant circuits by using magnetocardiograms: initiation and persistence of atrial flutter. Europace 2003; 5:343-350.

Yue L, Feng J, Gaspo R, Li GR, Wang Z, Nattel S. Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. Circ Res 1997; 81:512-525.

Zimmermann M, Adamec R, Metzger J. Atrial vulnerability in patients with paroxysmal "lone" atrial fibrillation. Pacing Clin Electrophysiol 1998; 21:1949-1958.