UNIVERSIDAD POLITÉCNICA DE VALENCIA

Departamento de Ingeniería Electrónica

SIGNAL PROCESSING OF INTRACARDIAC RECORDINGS FOR THE EVALUATION OF PROPOFOL EFFECTS DURING ATRIAL FIBRILLATION

TESIS DOCTORAL

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Empieza por hacer lo necesario, luego lo posible y de pronto te encontrarás haciendo lo imposible.

San Francisco de Asís.

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Acronyms

ABS	Averaged Beat Subtraction
AF	Atrial Fibrillation
AFL	Atrial Flutter
ANN	Artificial Neural Network
ANS	Autonomous Nervous System
AT	Atrial Tachycardia
ATS	Adaptive Template Subtraction
AV	Atrioventricular
bpm	beats per minute
BSS	Blind Source Separation
CAD	coronary Artery Disease
CC	Cross Correlation
CCE	cross-conditional entropy
CS	Coronary Sinus
DACL	Dominant Atrial Cycle Length
DC	Direct Current
DPWT	Discrete Packet Wavelet Transform
DWT	Discrete Wavelet Transform
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyogram
EP	Electrophysiological Study
EVD	Eigenvalue Decomposition
FIR	Finite Impulse Response
FFT	Fast Fourier Transform
fMRI	functional Magnetic Resonance Imaging
IAR	Intra-atrial Recording
HRV	Heart Rate Variability
IEGM	Intracardiac Electrogram

ICA	Independent Component Analysis
ICs	Independent Components
JD	Joint Diagonalisation
LA	Left atrium
LMS	Least Mean Squares
LV	Latent Variable
MEG	Magnetoencephalogram
MSE	Mean Square Error
NSR	Normal Sinus Rhythm
OI	Organization Index
PCA	Principal Component Analysis
PCs	Principal Components
pdf	probability density function
PSD	Power Spectral Density
PV	Pulmonary Veins
QRST	Successive fiducial points corresponding to ventricular depolarisation (QRS complex) and repolarisation (T-wave)
RA	Right atrium
RF	Radiofrequency
SA	Septum area
SC	Spectral Concentration
SN	Sinus Node
SNR	Signal-to-Noise Ratio
STFT	Short Term Fourier Transform
SVD	Singular Value Decomposition
VT	Ventricular Tachycardia
WT	Wavelet Transform

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Sumari

La fibrilació auricular (FA) és l'arítmia més freqüent en la pràctica clínica, amb una prevalència que arriba fins el 10% en la població major de 70 anys, i unes perspectives d'increment en consonància amb l'augment de l'esperana de vida. No obstant, malgrat ser l'arítmia més freqüent, els mecanismes causants de la seua generació i persistència no se coneixen amb exactitud. Per aquesta raó, els estudis encaminats al millor coneixement d'aquesta arítmia poden ser de gran ajuda per al desenvolupament de protocols clínics que milloren el diagnòstic i permeten seleccionar els tractaments més adequats.

Nombrosos estudis científics han indagat en quins són els factors que afecten a l'estat electrofisiològic de les aurícules, responsables de la iniciació i manteniment de la fibrilació, així com en els que governen la transmissió dels impulsos elèctrics entre l'aurícula i el ventricle, d'on entre ells, s'ha apuntat el sistema nerviós autònom com un dels factors responsables.

En aquesta tesi doctoral s'ha estudiat l'efecte sobre l'activitat auricular i ventricular, de l'anestsic més comunament emprat en teràpies destinades a restablir el ritme sinusal en pacients amb episodis de FA. Aquest anestsic és el propofol (2,6-diisopropylphenol), què és un ràpid anestèsic intravenós. La ràpida redistribució i metabolisme del propofol resulten en una ràpida eliminació d'aproximadament 1 hora, de forma que resulta útil per a sedacions de curta duració. La hipòtesi d'aquest estudi és si el propofol pot alterar l'activitat auricular durant FA.

Simultàniament a la realització dels procediments d'ablació, es realitzen registres electrocardiogràfics i electrogrames auriculars. Els electrogrames permeten extraure informació local de les aurícules, molt útils per a reflectir els processos electrofisiològics que ocorren durant la FA. Habitualment, els registres interns d'episodis de FA mostren un alt grau de variació espai-temporal, reflectint la complexa i irregular activitat de l'aurícula. Per altra part, respecte a l'activitat ventricular, malgrat que nombrosos estudis científics han tractat d'esbrinar quins mecanismes la governen, així com l'efecte del sistema nerviós autònom i el de molts antiarítmics, la resposta ventricular baix l'efecte d'anestèsics en teràpies destinades a la finalització de la FA no ha sigut estudiada en profunditat.

Els resultats obtinguts sostenen que el propofol influeix en l'activitat

d'ambdues aurícules, així com en el ritme ventricular. Concretament, s'ha observat oposat en ambdues aurícules, amb un increment de l'organització de l'activitat elèctrica en l'aurícula dreta com a conseqüència de l'administració de propofol, i un decrement en l'aurícula esquerra. Tanmateix, s'han detectat canvis significatius de ritme tant en l'activitat ventricular com en la conducció del node aurículo-ventricular.

Resumen

La fibrilación auricular (FA) es la arritmia más frecuente en la práctica clínica, con una prevalencia que alcanza el 10% en la población mayor de 70 años, y unas perspectivas de incremento en consonancia con el aumento de la esperanza de vida. No obstante, a pesar de ser la arritmia más frecuente, los mecanismos causantes de su generación y persistencia no se conocen con exactitud. Por esta razón, los estudios cuyo objetivo sea profundizar en los mecanismos que envuelven la citada arritmia son de gran ayuda para el desarrollo de protocolos clínicos que mejoren el diagnóstico, y permitan seleccionar los tratamientos más apropiados.

Numerosos estudios científicos han indagado en cuáles son los factores que afectan al estado electrofisiológico de las aurículas, responsables de la iniciación y mantenimiento de la fibrilación, así como en los que gobiernan la transmisión de los impulsos eléctricos entre la aurícula y el ventrículo, donde el sistema nervioso autónomo se ha apuntado como uno de los factores responsables.

En esta tesis doctoral se ha estudiado el efecto sobre la actividad auricular y ventricular, del anestésico más comúnmente usado en terapias destinadas a restablecer el ritmo sinusal en pacientes con episodios de FA. Este anestésico es el propofol (2,6-diisopropylphenol), que es un rápido anestésico intravenoso. La rápida redistribución y metabolismo del propofol resultan en una rápida eliminación de aproximadamente 1 hora, haciéndolo útil para sedaciones de corta duración. La hipótesis de este estudio es si el propofol puede alterar la actividad auricular durante la FA.

Simultáneamente a la realización de los procedimientos de ablación, se realizan registros electrocardiográficos y electrogramas auriculares. Los electrogramas permiten extraer información local de las aurículas, muy útil para reflejar los procesos electrofisiológicos que ocurren durante la FA. Habitualmente, los registros internos de episodios de FA muestran un alto grado de variación espaciotemporal, reflejando la compleja e irregular actividad de la aurícula. Por otra parte, respecto a la actividad ventricular, aunque numerosos estudios científicos han tratado de averiguar que mecanismos la gobiernan, así como el efecto del sistema nervioso autónomo y el de muchos antiarrítmicos, la respuesta ventricular bajo el efecto de anestésicos, en terapias destinadas a la finalización de la FA no ha sido estudiada en profundidad.

Los resultados obtenidos sostienen que el propofol influye en la actividad de ambas aurículas, así como en el ritmo ventricular. Concretamente, se ha observado opuesto en ambas aurículas, con un incremento de la organización de la actividad eléctrica en la aurícula derecha como consecuencia de la administración de propofol, y un decremento en la aurícula izquierda. Asimismo, se han detectado cambios significativos de ritmo tanto en la actividad ventricular, como en la conducción del nodo aurículo-ventricular.

Abstract

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia, with a prevalence around 10% among population older than 70, and with increasing perspectives according to an increase in the quality of life. Despite being the most frequent cardiac arrhythmia, the exact mechanisms that generate and perpetuate AF still remain uncertain. For this reason, any study that improves current knowledge about AF and the effects of clinical treatment will be helpful for the development of clinical protocols that improve diagnose and selection of the most appropriate treatment.

Scientists have inquired into what abnormal circumstances affecting the basic electrophysiologic state of the atria are responsible for the inception and perpetuation of fibrillation, and what factors govern the response of the atrioventricular transmission system. Among them, the Autonomous Nervous System has been proven to be one of the factors that affects atrial electrical activity.

This doctoral thesis has studied the effect on atrial and ventricular activities of the most common anesthetic agent used in AF ablation and cardioversion therapies. This anaesthetic is propofol (2,6-diisopropylphenol), which is a rapidly acting intravenous anaesthetic. The rapid redistribution and metabolism of propofol results in a short elimination half-life of approximately one hour, making it suitable for short-lasting sedation. The hypothesis is that a propofol bolus might alter atrial electrical activity during AF.

During AF ablation procedures, simultaneous atrial electrograms and electrocardiograms are recorded. Local electrograms may provide useful information reflecting the electrophysiological processes during AF. Typically, intracardiac electrograms in AF show a high degree of spatiotemporal variation, reflecting the irregular and complex activation in the atria. In addition, respect to ventricular rhythm, although basic and experimental research has provided insight into the mechanisms of AF, as well as the effect of autonomous nervous system and many antiarrhythmic drugs, the ventricular response under the anesthetics effect during AF therapies have not been completely studied.

The results support that propofol influences on both atrial and ventricular rhythms. More specifically, it has been observed an opposite effect in right and left atrium. Whereas atrial electrical activity increases the organization at the right atrium due to propofol administration, the organization of atrial activa-

tions is decreases at the left atrium. Moreover, significative changes in both ventricular and atrio-ventricular conduction rates were also detected.

Chapter 1

Introduction

The evolution of medicine was subjected to an important impulse in the 19th century, when thanks to advances in chemistry, laboratory technique and equipment, old ideas of infections disease epidemiology were replaced by bacteriology and virology. However, it was not until the 20th century that the application of the scientific method to medical research began to produce multiple important developments in medicine, with great advances in pharmacology and surgery, and it marked the begin of the modern medical practice. Indeed, during this period, hospitals became institutions of research and technology. Professionals in the areas of chemistry, physics, mechanical engineering, and electrical engineering began to work in conjunction with the medical field, and biomedical engineering became a recognized profession. As a result, medical technology advanced more in the 20th century than it did in the rest of the history combined.

One of the most significant discoveries for clinical medicine was the development of X-rays. In 1895, W. K. Roentgen found that it could be used to build pictures of the internal structures of the body. By the 1940s, new surgical procedures heavily dependent on medical technology, such as, hear-lung bypass, cardiac catheterization and angiography were developed.

Another important advance was the discovery of anaesthetics, which were administered from the early 1840s. The impact of anaesthetics on general medical practice began after William Morton publicly administered ether at Massachusetts General Hospital, Boston in 1846. Anaesthesia allowed surgeons to take more time, be more accurate and undertake more complex procedures.

Major advances and developments include the introduction of local anaesthesia in 1877, which in turn led to the introduction of infiltration anaesthesia, nerve blocks, spinal and epidural anaesthesia. By the 1920's intravenous induction agents were introduced which enabled patients to fall asleep quickly and pleasantly. In addition, with the introduction of sulfanilamide in the mid-1930s and penicillin in the early 1940s, surgeons were able to perform their operations without prohibitive morbidity and mortality due to infection.

On another side, during this period, the area of electronics had a significant impact on the development of new medical technology. In 1903, William Einthoven expanded on these ideas after he created the first string galvanometer. Einthoven placed two skin sensors on a man and attached them to the ends of a silvered wire that was suspended through holes drilled in both ends of a large permanent magnet. The suspended silvered wire moved rhythmically as the subject's heart beated. By projecting a tiny light beam across the silvered wire, Einthoven was able to record the movement of the wire as waves on a scroll of moving photographic paper. Thus, the invention of the string galvanometer led to the creation of the electrocardiogram (ECG), which is routinely used today to measure and record the electrical activity of abnormal hearts and to compare those signals to normal ones. In 1928, technical advances were made to amplify ECG recordings. Frank Sanborn developed the first portable ECG machine the same year. This was a significant development in the miniaturization of ECG recording. In 1929, Hans Berger created the first electroencephalogram (EEG), which is used to measure and record electrical activity of the brain. In 1935, electrical amplifiers were used to prove that the electrical activity of the cortex had a specific rhythm, and, in 1960, electrical amplifiers were used in devices such as the first implantable pacemaker. The first catheterization of a human is attributed to Werner Forssmann who, in 1929, created an incision in one of his left antecubital veins and inserted a catheter into his venous system and guided it by fluoroscopy into his right atrium.

Subsequently, these studies were performed to assess arrhythmias, elucidate symptoms, evaluate abnormal electrocardiograms, focusing on finer points of ECG to assess risk of developing arrhythmias in the future, and treatment design.

From the results of this research, it was found that the most common sustained arrhythmia in clinical practice is atrial fibrillation (AF). AF has already been intensively investigated and consists of a malfunction of the atrium characterized by a modification of the normal atrial activity, as well as other atrial arrhythmias such as atrial flutter (AFL) and atrial tachyarrhtythmia (AT). AF incidence increases with age, with a prevalence of 10% in population over 70 [1], that due to the increase of life expectancy, has a direct impact on the rise of mortality and morbidity [2], as well as in the risk of suffering a stroke [3]. However, despite the important advances in AF diagnosis and management, the mechanisms that generate, perpetuate and terminate this arrhythmia remain

uncertain, and further research is needed to improve current diagnosis procedures and therapies. In the following section, some of the limitations of current knowledge that motivate and justify this dissertation will be expounded.

1.1 Motivation

AF is characterized by the coexistence of multiple activation waves within the atria, resulting in complex ever-changing patterns of electrical activity [4, 5]. The mechanisms by which multiple wavefronts occur have been actively debated for many years. Among factors that affect the hemodynamic function during AF are loss of synchronous atrial mechanical activity, irregular ventricular response, rapid heart rate, and impaired coronary arterial blood flow.

An electrophysiological (EP) study can be helpful when AF is a consequence of reentrant AT such as AFL, intra-atrial reentry, or atrio-ventricular (AV) reentry involving an accessory pathway. The procedure involves inserting catheters into a blood vessel, and threading them through the vein until the electrodes on the tip of the catheters reach the atria. EP testing is indicated when ablative therapy of arrhythmias that trigger AF or ablation of AF is planned. In patients with AF who are candidates for ablation, an EP study is critical to define the targeted site or sites of ablation in the left atrium (LA) and/or right atrium (RA) structures.

During EP of AF patients, the electrogram morphology changes constantly both in time and space. Since the recordings reflect different spatial activation patterns such as slow conduction, wave collision, and conduction blocks [6], the analysis of the waveform changes of the endocardial signals acquired during AF plays an important role in the understanding of the mechanisms responsible for its induction and maintenance. Furthermore, the analysis of these signals provides an electrophysiologic, instead of anatomic perspective, and helps for guiding the catheter ablative therapy of AF [7].

Several algorithms for the quantitative analysis of AF organization have been reported in the literature. Since a rigorous definition of organization does not exist, various approaches have been adopted including frequency analysis [8, 9], cross-correlation techniques [10], linear prediction [11], nonlinear analysis [12], as well as signal morphology [13].

The abundant experimental evidence suggests that the autonomic nervous system (ANS) plays an important role in the occurrence of atrial arrhythmias, such as AF [14, 15]. Despite anaesthetic practice have a direct influence on the ANS, the effect of anaesthetic agents on atrial electrophysiology during AF has not been completely studied, even though during cardioversion and ablation procedures the patients are under their effects. The hypothesis formulated is that a propofol bolus, (the most frequently employed anaesthetic agent in AF) may alter atrial electrical activity during AF.

1.2 Objectives

The purpose of this thesis is to evaluate the hypothesis whether propofol has any effects on the atrial electrophysiology in patients with AF. Hence, the main objectives of this work can be formulated as:

- Propose different parameters to assess the spatiotemporal organization over the different atrial areas in baseline and during the propofol effects.

  The challenge is to develop methods suitable for quantifying the extent of spatial organization during AF, from the analysis of a single electrogram [16], and from the combined analysis of multiple atrial recordings that may provide more comprehensive information [10, 9].

- Evaluate the propofol effects on atrial activity.

  According to the multiple wavelets theory [4], AF is characterized by circling waves propagating randomly throughout the atria, generating complex and ever-changing patterns of electrical activity in which waves are fragmented or mutually annihilated. The triggering and maintenance of this status are favored by changes of refractory period and conduction velocity of atrial myocites [17, 18, 19], by the effects on electrical properties of autonomic nervous system (ANS) modulation [20, 21, 22] and by drug administration [23], such as antiarrhythmic drugs, also the anaesthetic. Therefore, the objective is to evaluate the effect of propofol on atrial cycle length as being related to the refractory period.

- Evaluate the propofol effects on ventricular rhythm and atrio-ventricular conduction.

  The ventricular rate and the relationship between the atrioventricular (AV) conduction ratio could be helpful indexes of the effect the ANS in AF. Although the application of the anaesthetic to a patient during sinus rhythm results in a decrease of the ventricular rate, their effects during AF are still unknown.

1.3 Structure of the thesis

This thesis is structured in the following chapters:

Chapter 2: State of the art: This is a reviewing chapter that reflects the state of the art in the different disciplines that are involved in this work. Current knowledge on AF, techniques to quantify atrial activity organization, and description of the used anaesthetic can be found in this section.

Chapter 3: Database: The database employed is the base of this dissertation. The database is composed by 3-lead ECGs and a catheter with 12 bipolar electrogram recordings and is expounded in detail in this chapter.

Chapter 4: Propofol Effects in Atrial Fibrillation Dominant Frequency: In this chapter two SVD based algorithms were exposed for atrial activity estimation free of any interference. The main frequency of the estimated signal was calculated in different atrial areas both in baseline and during the anaesthetic effect.

Chapter 5: Propofol Effects on Atrial Fibrillation Organization: Algorithms based on the analysis in time and frequency domains, as well as non linear analysis techniques, were applied to quantify the AF organization as consequence of the anaesthetic infusion. Different parameters were extracted from both atria and were compared during both states.

Chapter 6: Delays during Anesthesia with Propofol in Atrial Fibrillation: The delays of atrial activations in close recordings were evaluated in different atrial areas in both states. This measure is another way to quantify the organization in both states, since it is related with the number of wavefronts present in the atria.

Chapter 7: Propofol Effect on Atrial Fibrillation Ventricular Rhythm: Since the cardiac activity during AF may be influenced by autonomic modulations, in this chapter the effect of propofol on ventricular rate was analyzed.

Chapter 8: Discussion and conclusions: The contributions of this work are discussed in detail in this chapter, emphasizing the most relevant advances, but also their limitations. The fulfilment degree of the objectives established in the previous section is also analyzed in this chapter. Finally, some guides for future work are provided to overcome the limitations of this thesis and to extract the maximum profit from it.

Chapter 9: Scientific contributions: The main scientific contributions derived from the work developed in this dissertation are listed in this section. The scientific framework in which this work has been involved is also described, including related research projects and international collaborations.

Chapter 2

State of the art

This is a review chapter that outlines the fundamentals of the different research fields that cover this dissertation. This thesis consists in a multidisciplinary work that comprises diverse disciplines, such as the signal processing, and the cardiology, where intra atrial recordings were analysed to study the effect of an specific anaesthetic in AF. For this reason, an introductory section expounding the main aspects related with these areas is needed to facilitate a full understanding of the next chapters.

The fundamentals of AF and the most common classification criteria of this arrhythmia are described in the first section. The most relevant methods for the estimation and the characterization of the atrial signal from intracardiac and electrocardiogram recordings are related in the second, and third sections, respectively. Furthermore, in the following sections, the most useful therapies to revert to normal rhythm are tried, as well as the influence of the ANS in AF.

2.1 Atrial Fibrillation

The existence of AF has been known for many centuries. It was known under many different names such as delirium cordis and pulsus irregularis pepetus. In

1907, Arthur Cushny at University College of London published the first case report of AF, but it was Sir Thomas Lewis in 1909 who interpreted the irregular waves as coming from the atria in his paper "Auricular Fibrillation; a common clinical condition" [24].

AF is a supraventricular tachyrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. During this arrhythmia atrial activity is characterized by rapid oscillations or fibrillatory waves that vary in amplitude, shape, and timing, associated with an irregular, frequently rapid ventricular response whereas atrioventricular conduction remains intact [25].

AF is the most common sustained arrhythmia in clinical practice, with a prevalence of 1.5% in the general population [26]. Its incidence increases with age, reaching 10% in the octogenarians [26]. As a result, 75% of the patients with AF are older than 75 years [27].

Although it is often associated with heart disease, congestive heart failure, hypertension, coronary heart disease, valvular heart disease and thyroid disease [28], AF occurs in many patients with no detectable disease. The term "lone AF" has been defined in several ways but generally applies to young individuals (under 60) without clinical or echocardiographic evidence of cardiopulmonary disease [29]. As well, secondary AF that occurs in the setting of acute myocardial infarction (MI), cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia, or acute pulmonary disease is considered separately, because AF is less likely to recur once the precipitating condition is resolved. In these settings, AF is not the primary problem, and treatment of the underlying disorder concurrently with management of the episode of AF usually results in termination of the arrhythmia without recurrence.

AF is not a benign arrhythmia. It negatively influences quality of life [30], hemodynamic impairment and thromboembolic events derived from AF, and is associated with an increase in mortality [31, 32] especially if associated with congestive heart failure [33]. The poor prognosis of patients with AF is also known for ages. An often quoted phrase of the legendary emperor and physician Huang Ti Nei Ching Su Wen who is believed to have ruled China around 2000 BC says:

"When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades . . . "

Compared with the general population, the risk of a stroke is increased fivefold for patients with AF [34]. Because of its high prevalence, and its marked effects on both mortality and morbidity, therefore the interest of researchers all over the world has grown over the last decades.

2.1.1 Atrial electrophysiology and mechanisms of atrial fibrillation

The conceptual framework for understanding AF mechanisms has been grounded in ideas developed in the early twentieth century [35]. Nevertheless, nowadays the exact mechanisms underlying AF are not satisfactory understood despite many years of research and speculation. In the following lines the evolution of the understanding of the mechanisms of AF is reviewed, highlighting experimental findings that have produced new insights and questions about the theory of the arrhythmia.

As early as 1907, Winterberg surmised that AF was due to multiple rapidly firing foci distributed throughout the atria [36]. In 1914, Mines [37] advanced the circus movement theory of reentry. Thereafter, and until the late 1950's, all of the hypotheses proposed to explain AF were variations of the circus movement and ectopic focus theories [38, 39]. However, the modern era of our understanding of this arrhythmia begins with the multiple wavelet hypothesis by Moe and Abildskov [40], when it became generally accepted that AF was the result of the random propagation of multiple wavelets across the atria, a process that was thought to be independent of the initiating event.

Moe and colleagues [40] strongly argued that both the ectopic focus and circus movement reentry notions were inadequate descriptions of AF. They showed, using a computer model, that such meandering waves could result in a sustained arrhythmia. They considered fibrillation to be a fundamentally turbulent and self-sustaining process, which takes place in a non-homogeneous excitable medium. Such a process could be initiated by an impulse propagating through the medium at a time when some of its components have recovered while others remain partially or fully refractory as a result of a preceding activation. Accordingly, some elements in the medium may be activated while their neighbors may not [40, 41].

Experimental support for the multiple wavelet hypothesis had to wait almost 20 years when high-resolution electrode mapping systems were sufficiently developed to allow the recording of electrical activity simultaneously from several hundred different sites on the atrium, giving the possibility of demonstrating turbulent activity during AF. In 1985, Allessie et al. [42] were able to map the spread of excitation in the atria of a dog heart during rapid pacing-induced AF in the presence of acetylcholine, and provided the first demonstration in vivo of multiple propagating wavelets giving rise to turbulent atrial activity. Moreover, these investigators estimated that maintenance of fibrillation in the canine heart required from four to six circulating wavelets for maintenance of AF, because smaller numbers of wavelets tended to unite and restore sinus rhythm.

Several principles emerged from these observations. Maintenance of AF depends on adequate atrial mass to encompass sufficient wavelets to perpetuate the arrhythmia. In addition, conditions that decrease atrial refractoriness (hence resulting in a decrease in atrial wavelength) would tend to perpetuate AF [43].

Subsequent experiments in dogs [44], as well as more recent intra-operative mapping studies in humans [45], have provided important insight into the characteristics of wave-front propagation during fibrillation, and have given support to Moe's idea that multiple wavelets distributed randomly throughout the atria gave rise to an irregular atrial rhythm observed in the electrocardiograms of patients with AF. Finally, the hypothesis was emboldened by the clinical observation that chronic AF could be cured in some patients by the placement of multiple surgical lesions (MAZE) to compartmentalize the atria into regions presumably unable to sustain the multiple wavelets [46]. Indeed, this theory is virtually universally accepted by most clinical electrophysiologists today.

Another important concept generated by Allessie's group is the idea that AF per se may act to produce both electrophysiologic and anatomic remodeling, which, apart from any preexisting structural atrial abnormalities, may result in more ready initiation as well as perpetuation of AF. Wijffels et al. [47], for example, found that persistence of AF produced several important electrophysiologic changes, resulting in both shortening of atrial refractoriness as well as disturbance of the normal rate responsiveness to overdrive atrial pacing.

However, none of the above-mentioned studies gave answers to many critical questions about the origin of the turbulent activity that gave rise to the multiple wavelets in the experiments. For example, while the computer simulations of Moe et al. [40] suggested that 15-30 wavelets were needed at a given time to keep the fibrillatory process going, the experiments of Allessie et al. [42] could show only 4-6 wavelets propagating on the surface of the dog heart. In the presence of such a small number of wavelets, one would expect that, at any given time, a large amount of tissue in both atria would be recovered from previous excitation, which would lead to coalescence of wavelets and eventual termination of AF. In other words, it is reasonable to speculate that, in the experiments of Allessie et al. [42], the arrhythmia could have been in fact the result of a single (or a small number of) high frequency source that was (were) hidden from view. Moreover, the alternative possibility that some forms of AF may be the result of high frequency activation by a single reentrant source has also been supported by a number of recent experimental results [48, 49, 50, 51]

As consequence, the onset and maintenance of AF, as in other tachyrhythmia, require both an initiating event and an anatomical substrate, where presently the available data support two main mechanisms:

- Automatic focus theory, where the irregularity is presumed to result from interactions between high-frequency wavefronts produced by the primary generator (the ectopic focus or primary re-entrant circuit) and the spatially variable refractory properties of atrial tissue ("fibrillatory conduction"). Pulmonary veins (PV) are the most frequent source of these rapidly atrial impulses although, foci have also been found in the superior vena cava, ligament of Marshall, left posterior free wall, crista terminalis, and coro-

nary sinus [52, 53, 54, 55, 56, 57, 58, 59]. In histological studies, cardiac muscle with preserved electrical properties extends into the PV [54, 60, 61], where atrial tissue on the PV of patients with AF has shorter refractory periods than in control patients or other parts of the atria in patients with AF [60, 61]. Programmed electrical stimulation in PV isolated by catheter ablation initiated sustained pulmonary venous tachycardia, probably as a consequence of reentry [62]. Rapidly firing atrial automatic foci may be responsible for these PV triggers, with an anatomical substrate for reentry vested within the PV. (Fig. 2.1).

- Multiple-wavelet hypothesis, where the irregular atrial activity is a consequence of the primary arrhythmia mechanism, mechanism of reentrant AF advanced by Moe and colleagues [40], who proposed that fractionation of wavefronts propagating through the atria results in self-perpetuating "daughter wavelets", where the number of wavelets at any time depends on the refractory period, mass, and conduction velocity in different parts of the atria. A large atrial mass with a short refractory period and delayed conduction increases the number of wavelets, favoring sustained AF (Fig. 2.1).

These mechanisms are not mutually exclusive and may at various times coexist in the same patient.

2.1.2 Classification of atrial fibrillation

Various classification systems have been proposed for AF. One is based on the ECG presentation [25, 63, 64]. Another is based on epicardial or endocavitary recordings or non-contact mapping of atrial electrical activity [65]. Several clinical classification schemes have also been proposed. Assorted labels have been used to describe the pattern of AF, including acute, chronic, paroxysmal, intermittent, constant, persistent, and permanent, but the vagaries of definitions make it difficult to compare studies of AF or the effectiveness of therapeutic strategies based on these designations.

Although the pattern of the arrhythmia can change over time, it may be of clinical value to characterize the arrhythmia at a given moment. The most useful classification represents a consensus driven by a desire for simplicity and clinical relevance [66].

- First-detected: The clinician should distinguish a first-detected episode of AF, whether or not it is symptomatic or self-limited, recognizing that there may be uncertainty about the duration of the episode and about previous undetected episodes

- Recurrent: When a patient has had two or more episodes, it is considered recurrent.

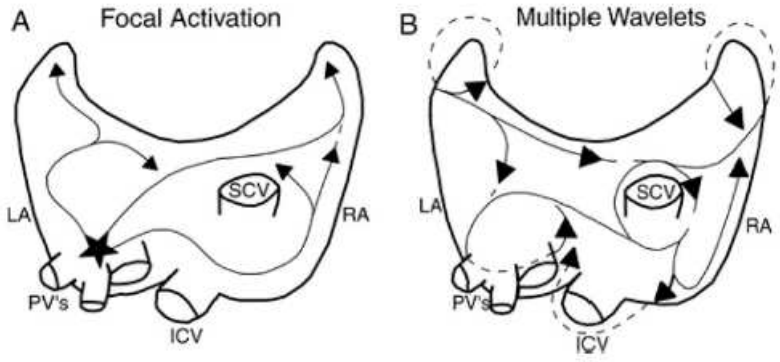

Figure 2.1: Posterior view of principal electrophysiological mechanisms of atrial fibrillation. A, Focal activation. The initiating focus (indicated by the star) often lies within the region of the pulmonary veins. The resulting wavelets represent fibrillatory conduction, as in multiple-wavelet reentry. B, Multiplewavelet reentry. Wavelets (indicated by arrows) randomly reenter tissue previously activated by the same or another wavelet. The routes the wavelets travel vary. LA indicates left atrium; PV, pulmonary vein; ICV, inferior vena cava; SCV, superior vena cava; and RA, right atrium. Reproduced with permission from Konings KT, Kirchhof CJ, Smeets JR, et al. High-density mapping of electrically induced atrial fibrillation in humans. Circulation 1994;89:166580 (101).

  - Paroxysmal AF: when the arrhythmia initiates and terminates spontaneously.
  - Persistent AF: when AF is sustained beyond 7 days or termination requires pharmacological therapy or direct-current cardioversion. The category of persistent AF also includes cases of long-standing AF (e.g., greater than 1 year), usually leading to permanent AF, in which cardioversion has failed or has not been attempted.

  First-detected AF may be either paroxysmal or persistent AF.

- Permanent: The arrhythmia state is so advanced that either it can not be terminated, or after cardioversion a new AF episode is initiated again within a short period of time.

This is probably the most accepted classification of AF up to date. However, we do not know whether this is already the definite classification, and it could change in the future as long as new knowledge about AF is required.

The focal origin of AF appears to be more important in patients with paroxysmal AF than in those with persistent AF, and radio-frequency ablation of such foci may be curative. Indeed, specific treatment should be indicated depending on the mechanism that causes the arrhythmia, preventing the patient

from thromboembolism, mortality and other risks which are attributable to cardiovascular causes.

2.2 Measurement of the electric activity of the heart

Biologic systems frequently have electric activity associated with them. This activity can be a constant direct current (DC) electric field, a constant flux of charge-carrying particles or current, or a time-varying electric field or current associated with some time-dependent biologic or biochemical phenomenon. Bioelectric phenomena are associated with the distribution of ions or charged molecules in a biologic structure and the changes in this distribution resulting from specific processes. These changes can occur as a result of biochemical reactions, or they can emanate from phenomena that alter local anatomy.

The mechanism of electric conductivity in the body involves ions as charge carriers. Thus, picking up bioelectric signals involves interacting with these ionic charge carriers and transducing ionic currents into electric currents required by wires and electronic instrumentation. This transducing function is carried out by electrodes that consist of electrical conductors in contact with the aqueous ionic solutions of the body. The interaction between electrons in the electrodes and ions in the body can greatly affect the performance of these sensors and requires specific considerations in their application. At the interface between an electrode and an ionic solution, redox (oxidation-reduction) reactions occur for a charge to be transferred between the electrode and the solution. These reactions can be represented in general by the following equations:

$$C \rightleftharpoons Cn^{+} + ne^{-} \tag{2.1}$$

$$Am^{-} \rightleftharpoons A + me^{-} \tag{2.2}$$

where n is the valence of cation material C, and m is the valence of anion material, A. For most electrode systems, the cations in solution and the metal of the electrodes are the same, so the atoms C are oxidized when they liberate electrons and are merged with the solution as positively charged ions.

In this section the description of the measurement of the bioelectrical activity of the heart from intracardiac recordings will be included, and as well from the signals recorded at the body surface.

2.2.1 Intracardiac electrogram

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Intracardiac electrograms are recordings obtained using electrode catheter placed at given locations in the heart. Due to the proximity of the electrodes to

the heart, the electrogram gives a much more local description of the electrical activity of cardiac cells than does electrocardiogram recordings.

The electrogram is usually indicated in patients with a documented arrhythmia to define electrophysiological diagnosis, or to guide the choice of treatment, as well as when a therapeutic intervention such as radiofrequency (RF) catheter ablation would offer cure or alleviation of symptoms, or when useful prognostic information may be obtained, such as the risk of developing life-threatening bradycardia or tachyrhythmia where the heart can be artificially stimulated to identify the region where an arrhythmia may be developed. Another important use of the electrogram signal is to provide an implanted cardiac pacemaker with information on whether the heart's natural pacemaker is working properly or needs to be replaced by artificial pacing. An implantable cardioverter defibrillator is equally dependent on the electrogram signal, but is specifically designed to detect the presence of life-threatening arrhythmias which, for example, cause the heart to cease pumping blood. If such a condition is detected, a high-energy electrical shock is given to terminate the arrhythmia.

Electrode catheters consist of insulated wires that are exposed to the intracardiac tissue. At the distal tip of the catheter (the end inserted into the heart) each wire is attached to an electrode. At the proximal end of the catheter (the part not inserted into the body) each wire is attached to a plug, which can be connected to an external device (such as a recording device or an external pacemaker).

Two types of electrode recording systems are available for electrogram recording, unipolar and bipolar.

An electrogram represents a recording of a voltage or electrical potential difference. An unipolar electrogram is the potential difference recorded between an intracardiac electrode in close association with cardiac tissue and a distant indifferent electrode patch applied to the body surface. By convention, a wavefront of depolarization approaching an electrode results in a positive (upward) deflection, while a wavefront receding from an electrode yield a negative (downward) deflection. Therefore, a wavefront of depolarization traveling through on unipolar electrode in the heart will produce an electrogram that has a positive and negative deflection representing the approach and recession of the activation wavefront.

A bipolar electrogram is actually the instantaneous difference in electrical voltage between the two electrodes. The more the inter-electrode spacing is increased on a conventional bipolar electrode, the more the recorded electrogram resembles "unipolar" recording, because extracellular potential decreases inversely by the square of the distance from a point source [67]. Thus a bipolar electrogram can be constructed by subtracting the absolute unipolar voltage recorded at the cathode (versus ground) from the unipolar voltage recorded at the anode (versus ground).

The major component of the unipolar electrogram allows the determination

of the local activation time, although exceptions have been observed [68, 69]. However, a wavefront of depolarization travelling to the inter-electrode axis of a bipolar lead will activate one electrode before the other. The resulting bipolar electrogram may have significantly greater amplitude than either unipolar electrogram alone. And in the case that the advancing wavefront of depolarization is perpendicular to the inter-electrode axis of a bipolar lead, each electrode will be activated at exactly the same time. Because the unipolar electrogram at each electrode will be similar and inscribed at the same time, the instantaneous difference in voltage will be minimal. In this situation, the bipolar electrogram will be markedly attenuated. From these examples it should be recognized that bipolar sensing is more sensitive to the direction in which the depolarizing wavefront travels than is unipolar sensing. Moreover, bipolar electrograms are more likely to be influenced by phasic changes in orientation of the lead with respiration than are unipolar electrograms.

Although bipolar electrodes are minimally influenced by electrical signals that originate outside the heart, unipolar electrodes may detect electrical signals originated near the pulse generator pocket in addition to those originated at the heart. Moreover, another significant difference between unipolar and bipolar sensing relates to the amplitude of far-field signals. For example, because of the significantly greater mass of the ventricles, the atrial electrogram often records a far-field R wave. For unipolar atrial leads, the far-field R wave may be equal to or of greater amplitude than the atrial deflection. In contrast, the bipolar atrial electrogram usually recorded an atrial deflection that is considerably larger than far-field R wave. As well, the features of unipolar sensing make this electrode configuration much more susceptible to interference by electrical signals originating in skeletal muscle (myopotentials). The myopotentials associated with pectoral muscle contraction may be sensed by unipolar pacemakers, resulting in inappropriate inhibition or triggering of pacing output. Bipolar sensing is relatively immune to myopotentials, a significant clinical advantage. Bipolar sensing is also less likely to be influenced by electromagnetic radiation or electrical interference from the environment than unipolar sensing.

2.2.1.1 Electrophysiology evaluation

A large variety of multipolar electrode catheters has been developed to facilitate placement of the catheter in the desired place and so fulfill various recording requirements.

To ensure high-quality recordings, direct cardiac electrograms should be recorded with amplifiers with high-input impedances to decrease unwanted electrical interference [70]. For most of the digital systems used today, after amplification of the data at each channel, the data undergo analog to digital (A/D) conversion. Amplifiers are also used to filter the low- and high-frequency content of the signal. Typical bandpass for intracardiac bipolar electrograms is 30 to 300 Hz. The high-pass filter is set at 30 Hz to filter out low frequency repo-

larization events and limit baseline drift. Because most of the signal content is below 300 Hz, the low-pass filter is set from 300 Hz to eliminate high-frequency noise. Unipolar electrograms are typically filtered across a wider band, typically 0.05 to 300Hz. For practical purposes of activation mapping, sampling rates of 1,000Hz are generally adequate [71].

Establishing electrogram criteria that allow accurate determination of the moment of myocardial activation at the recording electrode is critical for construction of map displaying the activation sequence. Most studies have suggested that the local activation is best determined in the unipolar electrogram by the point with maximum slope (i.e. maximum change in potential of dV/dt) [72]. Using this fiducial point, errors in determining the local activation time compared with intracellular recordings typically have been less than 1 ms [73]. Algorithms for detecting local activation time from bipolar electrograms have been more problematic, in part because of the fact that the bipolar electrogram is generated by two spatially separated recording poles. Among several options, the absolute maximum electrogram amplitude appears to most consistently correlate with local activation time determined by other means [73]. For complex multicomponent bipolar electrograms, such as those with marked fractionation, which represent discontinuous propagation and slowed conduction, (e.g. in regions of slow conduction in cases of AF or ventricular tachycardia (VT)), determination of local activation time becomes problematic, and the decision of which activation time is most appropriate needs to be made in the context of the particular rhythm being mapped [72, 74].

2.2.2 The surface electrocardiogram

The ECG is the most frequently used clinical system in cardiology, for several reasons. Firstly, it is very easy and quick to obtain an ECG from a patient, since it is a non-invasive technique. Secondly it provides as much as 90% of the information about the electrical activity of the heart. Indeed, most cardiac arrhythmias and other heart diseases can be diagnosed after observation of the ECG. For an exhaustive discussion about the electrocardiogram, its origin and its interpretation, see [75]. The preconditions on which it is based the electrocardiogram, is that the human body is modelled as an inhomogeneous volume conductor where the electrical activity of the heart is conducted towards the body surface. Willem Einthoven determined the first clinically important ECG system by locating 3 electrodes at the right arm, left arm and left foot respectively, defining the Einthoven standard leads in the following way [76]:

$$\begin{array}{lrcl} \text{Lead I:} & V_I & = & \phi_L - \phi_R \\ \text{Lead II:} & V_{II} & = & \phi_F - \phi_R \\ \text{Lead III:} & V_{III} & = & \phi_F - \phi_L \end{array} \tag{2.3}$$

where

$$\begin{aligned} V_I &= \text{the voltaje of Lead I} \\ V_{II} &= \text{the voltaje of Lead II} \\ V_{III} &= \text{the voltaje of Lead III} \\ \phi_L &= \text{potential at the left arm} \\ \phi_R &= \text{potential at the right arm} \\ \phi_F &= \text{potential at the left foot} \end{aligned}$$

According to the 2nd Kirchhoff's law, the voltages of the Einthoven limb leads have the following relationship:

$$V_{II} = V_I + V_{III} \tag{2.4}$$

Three additional limb leads were obtained by Goldberger by measuring the potential between a single limb electrode and the midpotential of the two remaining electrodes, chosen as reference. These additional leads are called augmented leads due to the augmentation of the signal. The central point of the two electrodes is achieved by means of connecting two resistances of $5k\Omega$. Notice that the Goldberger augmented leads are fully redundant with respect to the Einthoven leads I, II and III, with the following relationship:

$$\begin{aligned} aV_R &= \phi_R - \frac{\phi_L + \phi_F}{2} = -V_I + \frac{V_{III}}{2} \\ aV_L &= \phi_L - \frac{\phi_R + \phi_F}{2} = V_I - \frac{V_{II}}{2} \\ aV_F &= \phi_F - \frac{\phi_R + \phi_L}{2} = V_{III} + \frac{V_I}{2} \end{aligned} \tag{2.5}$$

In 1944 Wilson introduced the precordial leads in order to measure the potential close to the heart. These leads, V1 - V6, are located over the left chest. The 12-lead standard ECG is the one with the greatest clinical use, and consists of the 12 leads that have been explained above:

I, II, III
aVR, aVL, aVF
V1, V2, V3, V4, V5, V6

The first six leads are derived from just three electrodes. Therefore, any two of them contain the same information of the other four. As a result, the 12-lead ECG contain eight independent leads. The main reason for recording all 12 leads is that it enhances pattern recognition. This combination of leads gives the clinician an opportunity to compare the projections of the resultant vectors in orthogonal planes —sagittal, frontal and transverse— and at different angles.

2.2.2.1 The cardiac cycle. Formation of the ECG signal

The cells that constitute the ventricular myocardium are coupled together by gap junctions which, for the normal healthy heart, have a very low resistance. As a consequence, activity in one cell is rapidly propagated to neighboring cells. The joint activation of the cells in a region describes an activation vector which is projected onto the 12 leads of the standard ECG. From electrocardiographic theory it is possible to examine the generation of the ECG by taking into account the progression of activation within a cardiac cycle. After the electric activation of the heart has begun at the sinus node, it spreads along the atrial walls. The resultant vector of the atrial electric activity is reflected on the P wave of the ECG. After the depolarisation has been propagated over the atrial walls, it reaches the atrioventricular node. The propagation through the atrioventricular junction is very slow, which introduces a delay in the progress of activation — this is a desirable pause that allows completion of ventricular filling. Activation is then conducted to the ventricles, whose depolarisation is reflected in the QRS complex of the ECG.

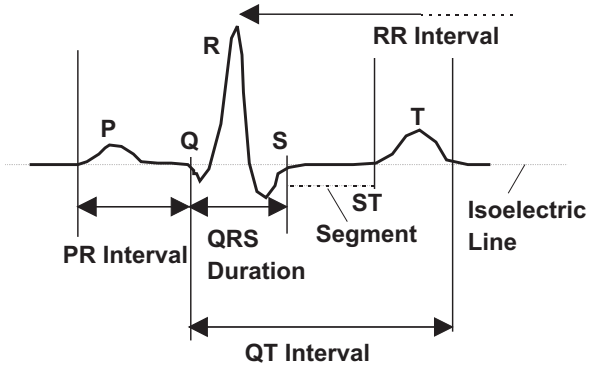


Figure 2.2: The normal ECG.

Finally, during ventricular repolarisation phase, ventricular cells recover their initial polarity in order to be prepared for the next cardiac cycle. The normal ECG is illustrated in Fig. 2.2. The Figure also includes definitions for various segments and intervals in the ECG. The deflections in this signal are denoted in alphabetic order starting with the letter P, which represents atrial depolarisation. The ventricular depolarisation causes the QRS complex, and the repolarisation process is the cause for the T-wave. Atrial repolarisation occurs during the QRS complex and produces a signal with such a low amplitude that it cannot be seen apart from the normal ECG.

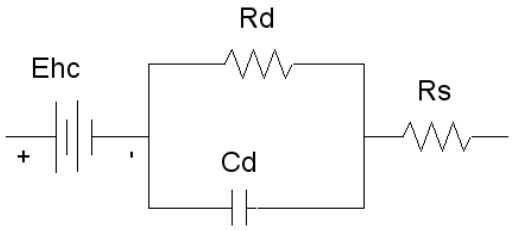


Figure 2.3: The equivalent circuit for a biopotential electrode.

2.2.3 Types of electrodes

Special electrodes (materials which convert electrochemical energy to electrical energy) can be used to acquire the action potential from a single cell. Many different forms of electrodes have been developed for different types of biomedical measurements. Some of the more commonly used electrodes are presented in this section.

2.2.3.1 Electric characteristics

The electric characteristics of biopotential electrodes are generally nonlinear and a function of the current density at their surface. However, when they are operated at low potentials and currents, a linear model can be assumed. Under these idealized conditions, electrodes can be represented by an equivalent circuit of the form shown in Fig. 2.3. In this circuit R_d and C_d are components that represent the impedance associated with the electrode-electrolyte interface and polarization at this interface. R_s is the series resistance associated with interface effects and the resistance of the electrode materials themselves, and E_{hc} represents the half-cell potential described above. At low frequencies the impedance is dominated by the series combination of R_s and R_d, whereas at higher frequencies C_d bypasses the effect of R_d so that the impedance is now close to R_s.

Thus, by measuring the impedance of an electrode at high and low frequencies, it is possible to determine the component values for the equivalent circuit for that electrode. The electrical characteristics of electrodes are determined by their physical properties.

2.2.3.2 Body-Surface biopotential electrodes

This category includes electrodes that can be placed on the body surface for recording bioelectric signals. The integrity of the skin is not compromised when these electrodes are applied, and they can be used for short-term diagnostic recording such as taking a clinical electrocardiogram or long-term chronic recording such as occurs in cardiac monitoring.

Metal Plate Electrodes The basic metal plate electrode consists of a metallic conductor in contact with the skin with a thin layer of an electrolyte gel between the metal and the skin to establish this contact. Examples of metal plate electrodes are seen in Fig. 2.4. Metals commonly used for this type of electrode include German silver (a nickel-silver alloy), silver, gold, and platinum.

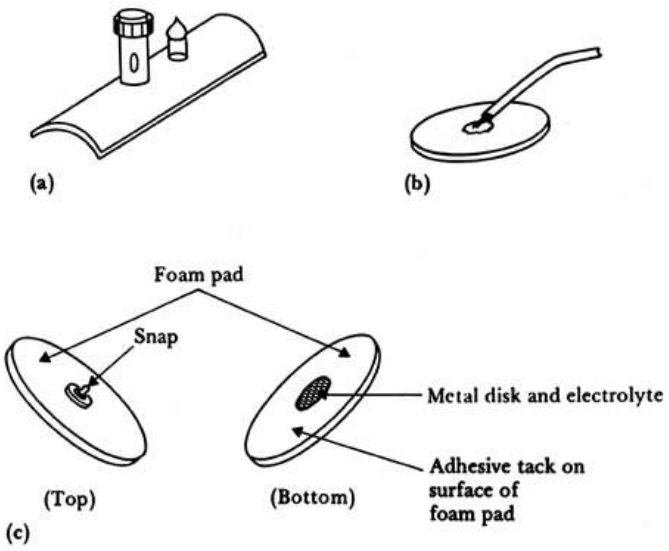


Figure 2.4: Body-surface biopotential electrodes (a) Metal-plate electrode used for application to limbs. (b) Metal-disk electrode applied with surgical tape. (c) Disposable foam-pad electrodes, often used with electrocardiograph monitoring apparatus.

These types of electrodes are used primarily for diagnostic recordings of biopotentials such as the electrocardiogram or the electroencephalogram.

Electrodes for chronic patient monitoring Long-term monitoring of biopotentials such as the electrocardiogram as performed by cardiac monitors places special constraints on the electrodes used to pick up the signals. These electrodes must have a stable interface between them and the body, and frequently nonpolarizable electrodes are, therefore, the best for this application. Mechanical stability of the interface between the electrode and the skin can help to reduce motion artifact, and so there are various approaches to reduce interfacial motion between the electrode and the coupling electrolyte or the skin.

2.2.3.3 Intratissue electrodes

Electrodes can be placed within the body for biopotential measurements. These electrodes are generally smaller than skin surface electrodes and do not require

special electrolytic coupling fluid, since natural body fluids serve this function. There are many different designs for these internal electrodes, and only a few examples are given in the following paragraphs. Basically these electrodes can be classified as needle electrodes (Fig. 2.5), which can be used to penetrate the skin and tissue to reach the point where the measurement is to be made, or they are electrodes that can be placed in a natural cavity or surgically produced cavity in tissue.

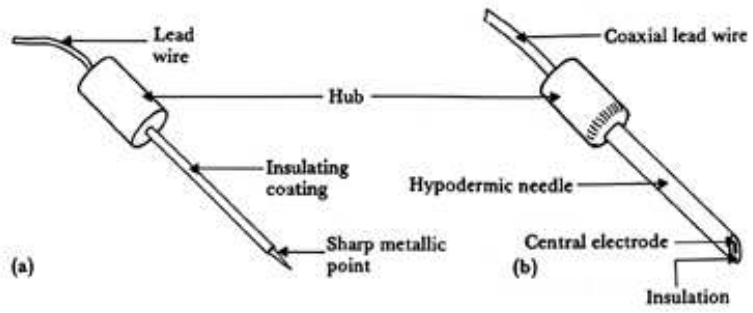


Figure 2.5: Electrodes in contact with internal body tissues (a) Insulated needle electrode. (b) Bipolar Coaxial needle electrode. (Reprinted with permission from Webster JG (ed). 1992. Medical Instrumentation: Application and Design, Houghton Mifflin, Boston.)

2.2.3.4 Catheters

A catheter tip or probe electrode is placed in a naturally occurring cavity in the body. A metal tip or segment on a catheter constitutes the electrode. The tip may be one of several shapes, such as hemispherical or cylindrical, and the ring is cylindrical. The catheter or, in the case where thereis no hollow lumen, probe, is inserted into the cavity so that the metal electrode makes contact with the tissue. A lead wire down the lumen of the catheter or down the center of the probe connects the electrode to the external circuitry.

Intra-atrial electrodes entered through the veins into the atria and sense the the atrial activity. However the proximity of the nearby ventricle to the atrial electrode causes interference with the signal. The action potential through the ventricles can be strong enough to register on an atrial electrogram. Fig. 2.6) shows a RF catheter designed to create a controlled transseptal puncture through the atrial septum by delivering energy.

Figure 2.6: RF Transseptal Catheter. Reprinted with permission from Baylis Medical Company Inc., 2009. Patents Pending and/or issued.

2.3 Characterization of atrial fibrillation

The devices used to acquire the heart electrical activity can be divided between invasive, such as the electrograms, and noninvasive, as the ECG. In this section the most useful techniques for electrical activity characterization during AF from both type of recordings are presented.

2.3.1 Non-invasive characterization

The correct characterization of this arrhythmia from the analysis of the surface electrocardiogram requires not only study the ventricular activity, but also the analysis of the atrial activity, since the origin of this pathology is produced in the atria.

2.3.1.1 Techniques for atrial activity analysis from the electrocardiogram

In the surface ECG, the atrial activity is irregular in timing and morphology. Discrete P-waves are absent and replaced by an oscillating baseline that consists of low amplitude fibrillatory waves (F-waves). The shape, amplitude, and regularity of F-waves vary from patient to patient. In some cases, the pattern of atrial activity can be mostly regular and with high-amplitude F-waves, while in other cases, it can be less regular, have lower amplitude, or both. Atrial rates detected from the surface ECG in AF vary between 240 and 540 beats/min [77] with an average of 350 beats/min.

Therefore, a methodology that estimates the atrial activity without other interferences, specially from the QRS complex, is essential. However, the fact that the atrial activity has much lower amplitude than ventricular activity and that both are spectrally overlapped makes atrial activity estimation difficult. In the last years several techniques for atrial activity estimation and analysis have been proposed in the literature [78, 79, 80]

Nevertheless, Langley et al. compared three of these techniques, namely, spatiotemporal QRST cancellation, blind source separation, and principal component analysis, and determined that there were no significant differences between the atrial frequencies estimated by any of these techniques [81].

Furthermore, the correct estimation of atrial activity would allow its further analysis and characterization of the signal, what could be useful in the study of the mechanisms that involve AF.

Techniques for atrial activity estimation from the electrocardiogram
The most relevant techniques for atrial activity estimation from the analysis of the surface ECG can be divided in two groups: methods based on matching templates and methods based on the statistical analysis of the multidimensional signal.

Methods based on matching templates: These techniques are referred to the methods that are able to estimate the atrial signal by cancelling the QRS-T wave from a matching template. These techniques are based on the redundancy of the QRS-T pattern, and on the assumption that atrial activity and ventricular activity are uncoupled [77, 79]. Hence, an averaged beat is obtained for each lead, which will be used to compute a matching template for QRS-T cancellation. As a result, the residual signal is estimated as the atrial activity. In the following paragraphs are described the main techniques:

- Averaged beat subtraction: Firstly suggested atrial activity estimation techniques were developed from explicit cancellation of QRS-T waves [77, 82]. As a result of the ventricular depolarization and repolarisation, the QRS complex and the T wave are reflected in the ECG. Assuming that

the successive cardiac cycles are repetitions of the same biological process, the signal obtained at several cardiac beats consists in successive QRS-T waves with a similar pattern —unless an extrabeat is produced.

If several beats are considered, a QRS-T template can be obtained by averaging successive QRST waves. In order to perform the QRST averaging, a previous step that detects and aligns the cardiac beats is required. This can be solved by means of a QRS detector, being Tompkins [83] and Zeelenberg algorithms [84] the most extended approaches. Finally, the atrial activity (AA) wave is estimated from the averaged beat subtraction (ABS):

$$\mathbf{y}_{\mathrm{AA}} = \mathbf{y} - \mathbf{D}\mathbf{x}, \tag{2.6}$$

where $\mathbf{y}$ represents the multilead ECG at one cardiac beat, $\mathbf{D}$ scale factor, $\mathbf{x}$ is the multilead averaged beat and $\mathbf{y}_{\mathrm{AA}}$ is the residual multilead signal estimated as the atrial activity. All these variables are L-lenght column vectors, being L the number of leads.

- Spatiotemporal alignment for QRS-T cancellation

  In the expression given in 2.6 it is assumed that $\mathbf{y}$ and $\mathbf{x}$ are aligned. However, the outputs of the R-detector may produce slight misalignments in the QRS-T waves. Due to the high amplitude of the QRS complexes, small temporal deviations may cause important QRS residua. The temporal alignment of the QRST wave can be carried out with the computation of $\mathbf{y}_{\mathrm{AA}}$ for different shifts of the signals, followed by the choice of the atrial signal with less QRST content. Since QRS complex have much higher amplitude than AA waves, the criterion to select the atrial activity is the signal with less variance. Mathematically, this effect can be represented with a shifting matrix $\mathbf{J}_\tau$:

$$\mathbf{y}_{\mathrm{AA}} = \mathbf{y} - \mathbf{D}\mathbf{x}\mathbf{J}_\tau. \tag{2.7}$$

  Considering a QRS-T wave length of m samples and a shifting allowance of N samples, vector $\mathbf{x}$ contains L templates of length $m + 2N$ and $\mathbf{J}_\tau$ is a $(m + 2N) \times m$ matrix.

  This technique has been recently improved by taking into account spatial alignment of the multilead QRS-T templates at each cardiac beat [79]. This improvement is based on the hypothesis that the heart position varies from beat to beat due to the respiratory movement that changes the thoracic structure, what results in a rotation of the heart respect to the sensor coordinates. An enhanced cancellation method that considers the spatial information contained in all leads has been proposed in [79].

  The effect that the rotation of the heart has on the ECG signal can be modelled with a rotation matrix $\mathbf{Q}$, such that:

$$\mathbf{y}_{\mathrm{AA}} = \mathbf{y} - \mathbf{Q}\mathbf{D}\mathbf{x}\mathbf{J}_\tau. \tag{2.8}$$

Methods based on the statistical analysis of the multidimensional signal

The methods that belong to this group can estimate the atrial signal from the statistical analysis of the multilead ECG. These techniques consider that the atrial activity and ventricular activity are generated by independent bioelectric sources —and hence, statistically independent— that appear mixed at the sensors located on the body surface. As a result, the signals obtained with the electrode array are highly correlated. Principal Component Analysis (PCA) and Independent component Analysis (ICA) techniques were proposed to estimate the atrial activity by a linear transformation that reduces the redundancy of the multidimensional signal.

In many real applications a multichannel signal is obtained from the outputs provided by a set of several sensors, microphones, antenna arrays, etc. Each one of the recorded signals is usually formed by the contribution of different physical phenomena. The signal generated by each physical source is propagated onto each sensor, so that what we observe is a set of mixtures of the original sources that are called observations. Following this model, the observation signals $\mathbf{x}$ can be expressed as a linear combination of the independent sources $\mathbf{s}$ through the mixing matrix $\mathbf{A}$:

$$\mathbf{x} = \mathbf{A}\mathbf{s}. \tag{2.9}$$

However, in many situations it is needed to make use of one or some of those sources that are not directly accessible. Blind Source Separation techniques (BSS) are MIMO systems (Multiple Input Multiple Output) that consist in recovering a set of independent sources from the observation of linear mixtures of them with the sole assumption of statistical independence [85]. This separation can be achieved from the multichannel statistical analysis of the observations.

The standard ECG is a multichannel system that provides 12 signals from several electrodes located at different points on the body surface. Each electrode outputs a mixture of all bioelectric sources, as the cardiac activity, which can be decomposed in atrial and ventricular components, electric excitations due to muscular movement, respiration, and also some noise due to the unideal contact of the electrodes with the skin and to the thermal noise of the electronic equipment. In AF episodes, the dominant component is basically the ventricular activity, which present much more amplitude than any other source. Depending on the patient, the fibrillatory waves are more or less appreciable. In fact, atrial activity can be visible in some ECGs within TQ segments, between 2 consecutive QRS complexes, whereas in occasions atrial activity is under the level of noise and can not be appreciated from the direct observation. As a result of applying BSS techniques to a multilead ECG, the independent sources (ventricular activity, atrial activity and noise) can be extracted separately [80, 78].

Characterization of atrial activity extracted from the electrocardiogram Numerous algorithms for noninvasive characterization of atrial electrophysiology during AF have been developed and several parameters have been extracted. The ECG provides a global, overall impression of the atrial activity, whose catheterization provides prognostic information about the arrhythmia.

Time analysis: The steps of generating the remainder ECG are performed in the time domain, but additional information can be obtained by the characterization of the different patterns of occurrence of the AF:

- Fibrillatory Wave Amplitude

  The amplitude of F-waves is often described as fine or coarse, traditionally defined as less than or greater than $50\mu V$, respectively. The amplitude of F-waves in AF is lower when compared to the amplitude of P-waves during sinus rhythm [86]. However, within the same patient, there is a correlation between the amplitude of the signal during sinus rhythm and during AF at the same recording site [87]. Xi et al. described one way to quantify F-wave amplitude [88]. First, the region of QRS complexes was excluded from analysis to avoid contribution of QRS residuals. The four individual F-waves with the largest peak-to-peak amplitude were selected, and the average of these four amplitudes was selected as the representative peak-to-peak amplitude. Another way to quantify amplitude is by looking at the average value of the peak-to-peak F-wave amplitude for the entire duration of the recording.

  F-wave amplitude has been linked to specific heart conditions like rheumatic heart disease and arteriosclerotic heart disease [89]. Culler et al. introduced the criteria of very coarse AF as greater than 0.25 mV versus straight-line, barely visible F-waves [90]. Both studies associated rheumatic heart disease with coarse F-waves and arteriosclerotic heart disease with fine F-waves. However, Morganroth et al. found no difference in F-wave amplitude between rheumatic and nonrheumatic AF and no significant correlation between F-wave amplitude and echocardiographic left atrial size [91]. Similar contradicting conclusions were obtained in studies relating F-wave amplitude to left atrial size and left atrial appendage function [92].

  In order to characterize atrial activity using fibrillatory wave amplitude and relate it to the mechanisms and pathophysiology of AF, there is an implicit assumption of stability over time. Xi et al. showed that F-wave amplitude has high intrapatient repeatability from ECG to ECG over a period of 24 hours, whereas the interpatient variability is high [88]. Similar results were found for atrial rate. The relationships of AF pattern, antifibrillatory drugs, and age to F-wave amplitude were also investigated [93]. There was no statistical significance between F-wave amplitude and

different patterns of AF, which include paroxysmal, persistent, and permanent. F-wave amplitude was also not different for patients taking antifibrillatory drugs compared with those not taking antifibrillatory drugs, and there was also no association of age with F-wave amplitude. There are certain factors that make it difficult to relate F-wave amplitude to specific etiologies of AF or atrial size. Some of these include the differences in the thickness of the constituent tissues of the chest wall between different patients and the skin-electrode interface. This could explain why many studies offered conflicting results about the relationship of F-wave amplitude and different etiologies of AF.

- Autocorrelation

  Although AF is not a completely regular rhythm such as atrial flutter or atrial tachycardia, a quantifiable level of temporal organization exists [48]. This organization allows estimation of the atrial rate using the autocorrelation function. Slocum et al. used this method to discriminate between AF and AV-dissociated P-waves from the remainder ECG [94]. If the atrial activity is periodic and AV dissociated, the autocorrelation of the remainder ECG signal will contain peaks at the atrial cycle length and multiples of the cycle length. The discrimination between AF and AV dissociated P-waves was based on the peak amplitude and duration of the autocorrelation function in Leads II and V1. The best parameter for detecting AF seemed to be peak amplitude, with a significantly higher peak for AF recordings compared to the control group. The best detection algorithm was achieved when amplitudes of the peaks in leads II and V1 were added together and this new parameter was used as a classifier. The properties of AF that allow estimation of atrial rate using autocorrelation are also represented by the narrow band characteristics of the power spectrum in frequency domain.

Spectral analysis: The estimation of the frequency content of the time series is a valid alternative to the time-domain methods, since it may enlighten properties and structures which can not be easily detected in the time-domain.

The simplest and fastest approach to perform a spectral analysis of a discrete signal $x[n]$ —where n is the sample index— is to compute the Discrete Fourier Transform (DFT), which can be carried out using a Fast Fourier Transform (FFT) algorithm [95]:

$$X(f) = \sum_{n=-\infty}^{\infty} x[n] e^{-j2\pi f n T}, \tag{2.10}$$

where $X(f)$ is the signal in the transformed domain as a function of the frequency f, and T is the sampling period.

Another way to perform a frequency analysis of the signal is the Power Spectral Density function (PSD), which is can be computed using the periodogram:

$$\mathcal{P}_x x(f) = \frac{1}{N} \left| \sum_{n=0}^{N-1} x[n] e^{-j2\pi nT} \right|^2 , \tag{2.11}$$

where $\mathcal{P}(f)$ is the power spectrum of the signal. This function can be also expressed as the Fourier Transform of the autocorrelation function of the signal. Oppositely to the FFT, the PSD is a real nonnegative function, whereas the FFT is a complex function. Notice that in this case we have employed for the PSD computation only N samples of the signal. This is equivalent employing a rectangular window $w[n]$, such that

$$\mathcal{P}_x x(f) = \frac{1}{N} \left| \sum_{n=-\infty}^{\infty} w[n] x[n] e^{-j2\pi nT} \right|^2 , \tag{2.12}$$

where

$$w[n] = \begin{cases} 1 & 0 \leq n \leq N-1 \\ 0 & \text{otherwise} \end{cases} \tag{2.13}$$

Windowing a signal have important effects in PSD estimation, such as the spectral resolution and the apparition of sidelobes [95]. The longer the length of the window, the sharper the PSD. Several windows with different properties have been defined, such as rectangular, triangular, Bartlett, Hamming, Hanning, Kaiser, etc.

An undesired effect of the PSD and FFT for large window values is manifested as rapid fluctuations at all frequencies. This effect can be corrected by averaging the periodograms corresponding to successive signal segments by using shorter window lengths [95]. As expected, a main frequency peak can be appreciated. Information in the power spectrum can be used to discriminate between AF and other nonfibrillatory rhythms. Holm et al. showed that peak frequency (frequency of maximum power) is a robust measure of intra-atrial cycle length with the closest correlation found between Lead V1 and right atrial electrograms [82]. The surface ECG represents a globally recorded signal. In the case of AF, since the atria are not activated simultaneously, the surface ECG may be different from locally recorded signals. Slocum and Ropella demonstrated that there is a correlation between the median frequency in the surface ECG Leads II and V1 and simultaneous intracardiac recordings [96]. Other researchers have used similar time and frequency domain methods to study the effects of antiarrhythmic drugs on AF [97].

Numerous studies have identified a substantial reduction in atrial fibrillatory rates following different intravenously or orally administered Class I and III antiarrhythmic drugs. Moreover, a baseline fibrillatory rate of 360 fibrillatory waves per minute was predictive of AF termination following intravenous ibutilde [97] or oral flecainide [98]. Other authors noted no baseline fibrillatory

rate difference between patients who converted to sinus rhythm and those who did not after oral bepridil [99] or intravenous ibutilide [100] administration. Instead, larger and more rapid rate increases were associated with AF termination. Outcome of cardioversion in terms of atrial defibrillation threshold and AF recurrence in relation to baseline fibrillatory rate has also been reported. In particular, higher fibrillatory rates were observed in patients with early arrhythmia recurrence immediately prior to internal [98] or external cardioversion [101] when compared with patients who maintained sinus rhythm. The predictive value of electrocardiographic and echocardiographic parameters has also been investigated. The combination of fibrillatory rate and systolic left atrial area predicted early AF recurrence after successful cardioversion with a high accuracy and was able to provide individual risk estimates [102].

Time-frequency analysis: In analyzing the atrial activity during AF, it has become increasingly apparent that most of the information is obtained by using a combination of time and frequency domain methods. The evolution of the spectral properties of the signal can be observed from the time-frequency analysis, which provides information regarding both spectral and temporal aspects of the signal. The suitability of time-frequency analysis to characterize the fibrillatory waves has been proposed and discussed in [103, 104, 105, 106]

Different time-frequency analysis techniques have been reported. The simplest form to proceed with the time-frequency analysis is the Short Term Fourier Transform (STFT), which computes the FFT for short and consecutive segments of the signal. The choice of the segment length has an important effect on the resolution: the longer the segment, the higher spectral resolution, but the lower time resolution. Hence, a compromise between time and frequency resolution is required. This method was proposed by Stridth et al. [104], defined by local power spectra from successive 1-s segments, in order to describe second-to-second variations in fibrillatory rate and f-wave morphology .

An example of time-frequency of the atrial activity from a electrogram located in the RA in a patient suffering from paroxysmal AF in baseline and under the effect of an anaesthetic is shown in Fig. 2.7. Notice how a change in the atrial frequency has accurately been detected in time and frequency.

One way to improve the time-frequency resolution is using a time-frequency distribution with a quadratic dependence. However, this property can be improved at the price of having additional cross-terms in the case of multicomponent signals. The discrete time-frequency distribution $W[m,n]$ of a signal can be expressed as a 2-dimensional FFT of a joint time-frequency correlation function $A_x[k,l]$ (also called ambiguity function):

$$W[m,n] = \sum_{k=-L}^{L} \sum_{l=-L}^{L} \Psi[k,l] A_x[k,l] e^{-j2\pi(lm-kn)/N} \tag{2.14}$$

where $\Psi[k,l]$ is a kernel function that weights the entire ambiguity domain and

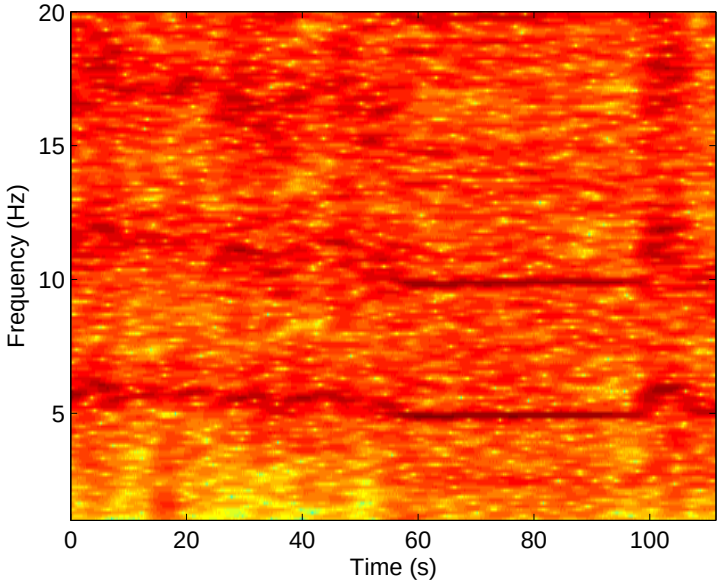


Figure 2.7: Atrial activity spectrogram of AF patient (belong to the study database) in basal conditions (from 0s to 55s) and under the effect of propofol (from 55s to the end).

has an important influence on some aspects, such as the reduction of cross-terms, etc. In the case of the Wigner-Ville Distribution, the kernel is equal to 1 for the entire domain. Many other kernel functions have been proposed, being one of the most frequently employed the one suggested by Choi and Williams [107].

Other time-frequency method, that has been successfully employed to solve other ECG problems is the wavelet transform (WT). The reference function is called the mother wavelet ($\psi(t)$), which is a zero-mean function with typical properties like compact support (amplitude decays to zero if time tends to infinity), smoothness, and symmetry.

The WT decomposes a signal $x(t)$ into its components by shifting (translating) a wavelet at different scales along the signal, calculating the correlation coefficient at each time point ($C(a,b)$). At smaller scales, the wavelet transform becomes more sensitive for the fine-grained details in the signal, whereas at larger scales, the coarse structure of the signal is emphasized:

$$\psi_{a,b}(t) = a^{-\frac{1}{2}}\psi\left(\frac{t-b}{a}\right) \quad \forall a,b \in \Re^{+} \tag{2.15}$$

$$C(a,b) = \int_R x(t)\psi_{a,b}(t)dt \tag{2.16}$$

This approach would provide a more accurate time localization of possible abnormalities in the signal. ECG signals can be considered as a superposition of different structures occurring at different time scales and different times. One purpose of wavelet analysis is to separate and sort these underlying structures of different time scales.

In addition, the fact that the WT exhibits different window sizes depending on the frequency band (broad at low frequencies and narrow at high frequencies) leads to an optimal time- frequency resolution in all frequency ranges.

The coefficients output by the WT at each subband, $C(a, b)$ may provide important information of the ECG signal, and they could be used in combination with appropriate statistical analysis tools in order to predict the risk of AF recurrence after successful electrical cardioversion [106].

2.3.1.2 Techniques for non-invasive characterization of ventricular activity

The R-R interval in the surface ECG represents the time between ventricular electrical systoles. Currently, numerous QRS detection schemes are available, which facilitate measurement of the R-R interval directly from the ECG in the time domain without additional processing [108]. During AF, the RR interval and hence, the ventricular rate, is commonly observed as irregular. However, ventricular activity of this sort is present not only in AF but also in a variety of other arrhythmias, including multifocal atrial tachycardia and atrial flutter with variable atrioventricular block. Conversely, AF may also be present with a regular ventricular rate, as in the case of artificial ventricular pacing. Although irregular ventricular activity is commonly associated with AF, it should not be employed function as the unique diagnostic criterion. In fact, the presence of AF has been shown to be under-recognized in paced patients, with important adverse clinical consequences since the R-R intervals are regular [109].

At the ventricular level, several methods have been applied, such RR interval histograms, autocorrelations and heart rate variability (HRV) analysis.

Measures from RR interval: For the purpose of studying the statistical distribution of heart beats in time, let the electrocardiogram be represented as a function of time of RR interval sequences.

The RR interval histogram contains information on the relative frequency of occurrence of RR intervals of different lengths, but contains no information on the correlation between the length of one RR interval and subsequent RR intervals. To characterize this feature of the RR interval sequence one may compute the serial autocovariance coefficients R_i of i the RR interval sequence

$$R_i = \frac{1}{\bar{T}^2(N-i-1)} \sum_{j=0}^{N-i-1} (T_{i+j} - \bar{T})(T_j - \bar{T}) \tag{2.17}$$

where

$$\bar{T} = \frac{1}{N} \sum_{j=0}^{N-1} T_j \tag{2.18}$$

where N denotes the number of RR intervals in the sequence and $\bar{T}$ is the mean RR interval. Each coefficient R_i denotes the degree of correlation between one RR interval and the RR interval occurring i beats later. R_0 equals $(\sigma/\bar{T})^2$:

$$R_0 = \frac{1}{(\bar{T})^2(N-1)} \sum_{j=0}^{N-1} (T_j - \bar{T})^2 = (\sigma/\bar{T})^2 \tag{2.19}$$

Where σ is the square of the coefficient of variation of the distribution. During normal sinus rhythm, the R_i, considered as a function of i, takes commonly of the form of a damped sinusoid. The reported correlation over long delays reflects the relatively long periodicities associated with physiologic feedback loops involved in heart rate control. Indeed, the detailed shape of the autocovariance function (or its Fourier transform, the power spectrum) contains specific information on both the characteristics of the perturbations to the cardiovascular system and the dynamics of the feedback loops involved in the compensatory heart rate response [110]. In addition, the autocovariance coefficients during AF, R_0 is much larger (indicating a larger value of $(\sigma/\bar{T})^2$) during AF than during normal sinus rhythm, and the correlation between beats is at least an order of magnitude smaller than R_0 for all delays i greater than or equal to two. The autocovariance coefficient R_1 is significantly greater than zero, but much smaller than R_0 in magnitude. Thus, the RR intervals during AF are essentially statistically independent of each other, except for a slight correlation between the duration of immediate subsequent beats [111]. Hoff and Geddes [112] showed that under conditions of high vagal tone, even during AF the $R(i)$ (for $i > 2$) may be significantly different from zero; in this case the pattern of variation of $R(i)$ with i is similar to that observed during normal sinus rhythm, but the amplitude of this pattern is reduced compared to the magnitude of R_0. This would suggest that whereas the RR interval variation intrinsic to AF is essentially uncorrelated (except for immediately subsequent beats), strong extrinsic autonomic modulation may impose some degree of correlation.

Measures of heart rate variability: Analysis of heart rate variability (HRV) has reported signs of enhanced parasympathetic activity or of sympathetic activation before paroxysmal AF onset [113, 21, 114, 115].

Different methods of the analysis of the heart rate have been proposed. Standard measures, based on linear statistical measures and on the Fourier analysis, that are currently used in medical practice (implemented in most commercial diagnostic equipment), as well as other "nonlinear" measures.

It has been found that heart rate generation can be reasonably well described by nonlinear dynamical models [116, 117, 118, 119]. Such nonlinear models have

physiological motivation: in a healthy heart, sinoatrial (SA) and atrioventricular (AV) nodes form a nonlinear system of coupled oscillators, with a higher degree of dissociation during AF. In addition, the activity of the heart is also affected by interactions of hemodynamic and humoral variables, as well as by the autonomic and central nervous systems.

An example of these techniques should be phase reconstruction, based on studying the nature of heart rate generation by reconstructing the trajectories of the underlying signal (ECG or heart rate) in phase space. The problem of determining the canonical variables in the case of physiological data (when one has few information about it), can be avoided by the method of delays: time series $x_n = x(n\Delta t)$ measured with a fixed sampling period Δt can be reconstructed to the vectors β_n in an m-dimensional phase space:

$$\beta_n = (x_{n-(m-1)\nu}, (x_{n-(m-2)\nu}, \ldots, x_{n-\nu}, x_n). \tag{2.20}$$

The difference in the number of samples ν (in time units, $\nu\Delta t$) between adjacent components of the delay vectors is called the *lag* or *delay* time; the process of reconstruction is referred to as *embedding* and m is called the *embedding dimension*. A number of embedding theorems exists, and it is expected that the reconstructed phase trajectory can be transformed to the original trajectory by an uniquely invertible smooth map [120]. Such a theoretical reasoning and belief that nonlinear phenomena are certainly involved in the generation of the heart rate have led to the idea that the characteristics from the theory of nonlinear dynamics might reveal valuable information for the physiological interpretation of HRV and could be used for diagnostic purposes. The experimental observations of intrinsic nonlinearity in HRV seemingly confirmed the theoretical expectations. Mansier et al. [121] applied a nonlinear forecasting method of Sugihara et al. [122], and surrogate data sets to address the question whether the HRV series is the output of a deterministic dynamical system. They showed that prediction is better for the experimental series than for its surrogate data and suggested that these differences are an evidence of a nonlinear deterministic system generating HRV time series [121]. Chon et al. [123] proposed a method to test chaotic determinism based on fitting a nonlinear autoregressive model to the time series, followed by the analysis of the characteristic exponents of the model over the observed probability distribution of states for the system. They showed that relatively short HRV time series (4096 data points) contain a nonchaotic deterministic component [123].

Other non-linear method related with Phase-space analysis can be Lyapunov exponents and scaling of correlation sum. Nevertheless, the measures of deterministic chaos based on reconstructed phase space usually fail in describing a deterministic chaos of the heart activity, since the dominant deterministic dynamics are suppressed by essentially intermittent signals arriving from the autonomous nervous system and regulating the heart rhythm. However, some fine-tuned measures, e.g. various entropies, [124, 125, 126, 127], can be useful in

describing the level of short-time variability of the heart rhythm. Entropy based measures, being essentially an average of the logarithm of a conditional probability, can be viewed as a statistical characteristics, which can be applied to both deterministic and stochastic processes. While not directly requiring the presence of a deterministic dynamics, they are ideologically related to the analysis of nonlinear dynamics (they deal with the dynamics in time delay space). These measures also reflect the rate of new pattern generation (irregularity of signal), and are therefore closely related to the concepts of Shannon and Kolmogorov-Sinai entropies. They can be classified as extensions of those concepts, more suitable for characterization of experimentally measured time series.

Recent studies have shown that scale-invariant characteristics can be successfully applied to the analysis of the HRV [128, 129, 130, 131]. However, this conclusion has been disputed, and certain scale-dependent measures (particularly, the amplitude of the wavelet spectra at a specific time-scale) have been claimed to provide better results [132]. The scale-independent methods have been believed to be more universal, subject-independent, and to reflect directly the dynamics of the underlying system, unlike the scale-dependent methods which may reflect characteristics that are specific to the subject and/or to the analysis method [131]. The opposing argument has been that certain heart disorders affect the HRV at a specific scale or range of scales; owing to this circumstance, at the properly chosen time-scale, scale-dependent measures may provide useful information [132]. Some of the reported methods based on scale-independent measures are: Hurst exponents, detrended fluctuation analysis, multiresolution wavelet analysis, multifractality of heart rate, intermittency of heart rate, low-variability periods analysis, etc.

2.3.2 Invasive characterization

In addition to ECG signals, the electrical activity of the atria can be recorded by passing catheter-guided electrodes through one of the major veins into the atria. The analysis of the recorded signals (endocardial electrograms), with their far greater detail, is used in diagnostic procedures as well as for guiding therapeutic interventions [133]. Advanced mapping procedures have been developed for scanning the electric activity on the atrial surface [134] or endocardium [135]. Such methods have led to the identification of different types of foci that trigger AF and the description of specific dynamics. Current basic research is aimed at linking these signals with different etiologies of the disease.

2.3.2.1 Techniques for atrial activity analysis from the study of intra-atrial electrogram

In the study of AF, electrogram recordings are situated in the atria and in the coronary sinus (CS), resulting in atrial electrograms. Some recordings from CS catheters are observed to frequently contain indistinct atrial electrograms with

substantial ventricular artifact. These recordings must be excluded from further analysis, because atrial activity extraction is the main goal in the study of AF.

Local electrograms recordings taken from either bipolar or unipolar electrode configurations may present a very sharp biphasic waveform. In this configuration, the fundamental frequency (equal to atrial activation rate) is overlapped in comparison to higher frequency components as its harmonics. Thus, Botteron [10] proposed the following preprocessing steps have been shown to help for these types of signals:

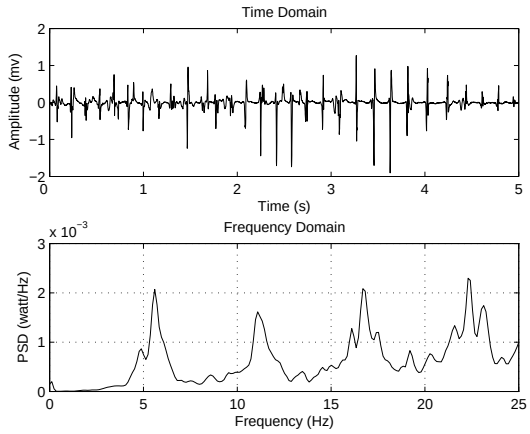
- Band-passed filtering using a digital, zero-phase, third-order Butterworth filter with cutoff frequencies of 40-250 Hz.
- Absolute value of the output of the bandpass filter.
- Lowpass filtering using a similar third-order Butterworth filter with a 20-Hz cut-off frequency.

This process emphasizes the principal component. Fig. 2.8(a) shows an example of a bipolar endocardial recording of AF with an activation rate of approximately 6 cycles per second. The power spectrum of the electrograms shows that the frequency component with higher amplitude does not correspond to the activation rate. Fig. 2.8(b) shows the result of bandpass filtering the signal at 40-250 Hz. The purpose of this step is to further accentuate the signal corresponding to the local depolarization. The next step of rectification is the critical step that will transform the biphasic waveform to a monophasic waveform. It can be seen in this step that the peaks and troughs of the signal now for the most part correspond with those of the sinusoid. The peak frequency now appears in the spectrum. The final step of lowpass filtering at 20 Hz limits the spectrum to frequencies that fall within a reasonable physiologic range of activation rates (Fig. 2.8(c)). As observed, this process aims to emphasize the fundamental frequency while preserving the most relevant temporal features of the signal.

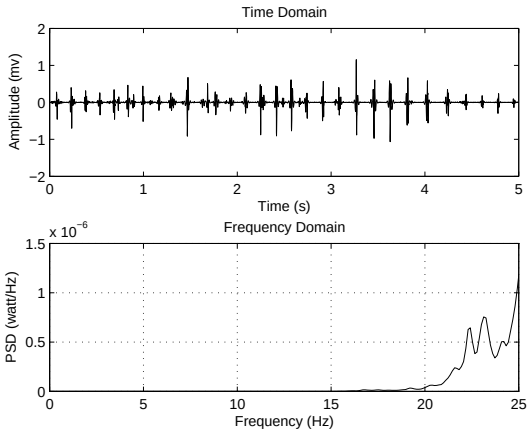
2.3.2.2 Characterization of the atrial activity from the intra-atrial electrogram

Refractory periods are the “fundamental frequency” of intracardiac electrophysiology and the means by which the electrical properties of cardiac tissues are described and compared. In a sense, it is the shortest output interval that can occur in response to any input interval in a particular tissue. Dominant frequency analysis has been used, due to its relation with refractory periods. Indeed, the dominant frequency or, its inverse, atrial fibrillatory cycle length (AFCL), is directly related with atrial refractoriness and, subsequently, with the degree of AF organization [136].

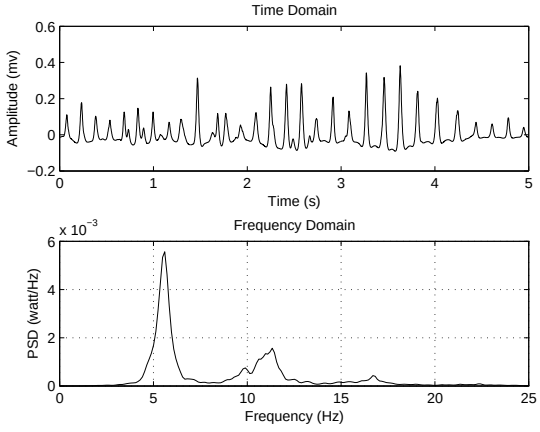
If the atrial signal is highly periodic, the dominant frequency will in most cases be related to the rate of the signal. Most studies have shown that dominant



(a) Dipole 1-2 without filtering



(b) Dipole 1-2 after high pass filter



(c) Dipole 1-2 after filtering process

Figure 2.8: Dipole 1-2, time and frequency domain extracted without and with filtering processing.

frequencies generally fall within a range of 4-9 Hz (240-540 cycles/minute) with narrow band characteristics [9], and are accompanied by several harmonics with lower peak amplitude finding suggest that AF is not completely chaotic.

In addition, other different electrocardiographic approaches may be useful in the clinical management of patients with AF. They are based on the analysis of intracardiac electrograms and may all be considered as apparent expression of electrophysiological changes associated with AF. The first attempt to describe the morphology of bipolar endocardial recordings during AF was done by Wells et al., who described four types of AF [137]. Type I showed discrete activation complexes of variable amplitude separated by an isoelectric baseline; type II was also characterized by discrete complexes of varying morphology but disturbances of the isoelectric baseline were present; in type III fragmented electrograms were observed without discrete activation complexes or isoelectric segments; type IV was defined as an alternation between type III and the other types. The existence of different types of AF was confirmed by Konings et al. in an experimental intraoperative high-density mapping study of AF in patients undergoing surgery for the WolffParkinsonWhite (WPW) syndrome [138]. Three types (I, II and III) of AF were defined based on the degree of spatiotemporal complexity observed in epicardial atrial activation maps. A continuous spectrum of organization was found ranging from relatively simple patterns (type I) to highly fragmented, complicated activation maps (type III). In the opinion of these investigators Wells's type IV does not reflect a separate type, but merely illustrates the propensity of AF to display temporal variations in both rate and irregularity.

Although the early studies dealing with these approaches mostly relied on visual analysis of recorded data, important contributions and innovative concepts and methods have come from the fields of signal processing, stochastic process theory and non-linear dynamics. In the subsequent paragraphs the evolution of these methods from past to present and a description of ongoing experimental works will be reviewed where the methods are grouped as time-domain, frequency-domain, and time-frequency domain approaches.

Time domain analysis: Botteron et al. first proposed a method for assessing the extent of spatial organization during AF [10], by estimating the cross-correlation of closely spaced bipolar endocardial recordings. They found that the atrial activation processes during AF are spatially correlated, with a peak correlation value by a decaying exponential function:

$$CC(d) = e^{\frac{-d}{\delta}} \tag{2.21}$$

where *CC(d)* is the cross-correlation value as a function of distance, d is the distance (cm), and δ is the space-constant (cm), i.e., the distance over which the peak in cross-correlation between activation sequences has fallen to l/e.

Jais et al. computed the complex electrical activity time as the percentage duration of electrograms showing AFCL lower than 100 ms [139]. In these studies, the catheter was located in the RA and the CS, significance differences were found among atrial regions, with the septal and posterior areas more disorganized than the lateral and anterior regions.

The method proposed by Sih et al. was aimed at obtaining a high temporal resolution in the estimation of the synchrony between dipoles. It measured the short duration linear relationship between two electrograms by a mean-squared error algorithm [11]. The algorithm measured the organization in terms of extent of predictability by linear algorithm. It turned out to be highly sensitive to different levels of organization and to have a high temporal resolution [11].

Barbaro et al. compared various time and frequency domain methods and demonstrated that the parameter which best discriminates AF types, according to Wells criteria, was the number of occurrences; i.e. the percentage of points laying on the baseline [140].

Censi et al. used the recurrence plot analysis of the AFCL series to assess the degree of organization of local activation processes during AF [141]. They showed that a certain degree of organization during AF can be detected as spatio-temporal recurrent patterns of the coupling between the atrial depolarization periods at two atrial sites, and demonstrated that there is a deterministic mechanism underlying the apparently random atrial activation processes during AF. As well, Mainardi proposed a synchronization index based on the corrected cross-conditional entropy (CCE) [142], where this parameter was significantly reduced during AF respect to sinus rhythm and further diminished when AF was associated with adrenergic activation.

Furthermore, template matching, a well-known signal processing technique, has been applied to automatic detection of fibrillation potentials allowing a rapid and accurate visualization of propagation of fibrillation waves. This technique has provided an objective characterization of fibrillation electrograms that in case of recording of multiple electrograms will produce real-time movies of the propagation of fibrillation waves through the atria [143].

It is interesting to observe that, given the lack of a rigorous definition of organization, some methods measure features somewhat related to the coupling between electrograms, while other focus on single electrogram features, either from a morphological or dynamical point of view.

Spectral domain analysis: Several techniques have been applied in the frequency domain to the analysis of intra-atrial electrograms.

Sahakian et al. first proposed an improved method of calculating magnitude-squared coherence spectra on pairs of short-duration electrogram recordings, to characterize atrial activity during AF [144]. The obtained high resolution spectra allowed to examine the time-varying relationship between activity at two different sites, and was used for constructing coherence maps [9]. Neverthe-

less, when it was used to monitor the modality of sinus rhythm restoration, by drug administration, the spectral coherence did not demonstrate a progressive increase in the organization of AF prior to termination [145]. A modified spectral coherence estimation, featuring higher temporal resolution and based on a particular time-frequency representation, showed that the conversion to sinus rhythm is concomitant with an increase in coherence and with the emergence of structured time-frequency topography [146]. The observed transient electrical organization in the atria during AF was not detectable by previous low-resolution coherence studies. An innovative use of spectral estimation has been proposed by Jalife et al., who attempted to identify reentrant sources of activation [49]. They estimated the dominant frequency sources that are hypothesized to maintain the fibrillation.

Time-frequency analysis: Electrogram morphology is an indicator for rapid uniform conduction (single potentials), collision (short-double potentials), conduction block (long-double potentials), and pivoting points or slow conduction (fragmented potentials).

Template matching of fibrillation electrograms by a library of single and short-double potentials is insensitive to other more complex waveforms, like long-double potentials and fractionation [134]. Time-frequency analysis can be an alternative strategy to analyze these segments that do not match the library [143].

The wavelet transform has been proposed for its ability to reveal spectral and temporal information of complex signals [147, 148]. All wavelet coefficients can be represented in a time-scale plane (scalogram), providing consolidated time and scale (frequency) information and allowing multiresolution analysis. Fractionated fibrillation electrograms are composed of multiple components, only one of which is associated with the actual passage of a fibrillation wave under the electrode. The other components are generated by waves propagating out of phase in neighboring muscle bundles [61]. The wavelet transform characterizes these localized structures by the (Lipschitz) regularity, which can be obtained from the peak-to-peak amplitudes of the wavelet coefficients at different scales [149]. The true component of a fractionated fibrillation electrogram produces maxima throughout all scales. In contrast, components associated with rapid activation of small bundles in the neighborhood of the electrode will only correlate at the finer scales and fibrillation waves propagating at a large distance exclusively at lower scales.

2.4 Therapeutic options

In this chapter the most relevant techniques for AF control will be described. Nevertheless, despite recent advances in treatment and the introduction of new drugs, initial management goals in patients with AF have not changed, involving

3 objectives: rate control, prevention of thromboembolism, and rhythm control, and all them being not mutually exclusive. The initial management decision involves primarily a rate-control or rhythm-control strategy. Under the rate-control strategy, the ventricular rate is controlled with no commitment to restore or maintain sinus rhythm. The rhythm-control strategy attempts restoration and/or maintenance of sinus rhythm. The latter strategy also requires attention to rate control. Depending on the patients course, the strategy initially chosen may be unsuccessful and the alternative strategy is then adopted. Regardless of whether the rate-control or rhythm-control strategy is pursued, attention must also be directed to antithrombotic therapy for prevention of thromboembolism.

Nevertheless, at the initial encounter, an overall management strategy should be discussed with the patient, considering several factors:

- Type and duration of AF.
- Severity and type of symptoms.
- Associated cardiovascular disease.
- Patient age.
- Associated medical conditions.
- Short-term and long-term treatment goals.
- Pharmacological and nonpharmacological therapeutic options.

2.4.1 Rhythm and rate control strategies

The initial and subsequent management of symptomatic AF may differ from one patient to another. For patients with symptomatic AF lasting many weeks, initial therapy may be anticoagulation and rate control, while the long-term goal is to restore sinus rhythm. The differences between a strategy of accepting AF and adequate rate control and a strategy of maintenance of sinus rhythm (rhythm control) have been studied recently in the RACE and AFFIRM trials [150, 151]. In these landmark studies no significant difference in mortality between the two strategies were found. However, early cardioversion may be necessary if AF causes hypotension or worsening heart failure, making the establishment of sinus rhythm a combined short- and long-term therapeutic goal, and in some circumstances, when the initiating pathophysiology of AF is reversible, as for instance after cardiac surgery, no long-term therapy may be necessary. In contrast, amelioration of symptoms by rate control in older patients may steer the clinician away from attempts to restore sinus rhythm. In some circumstances, when the initiating pathophysiology of AF is reversible, as for instance after cardiac surgery, no long-term therapy may be necessary.

2.4.2 Ventricular rate control

In patients with AF, the ventricular rate may accelerate excessively during exercise even when it is well controlled at rest. In addition to allowing adequate time for ventricular filling and avoiding rate-related ischemia, enhancement of intraventricular conduction with rate reduction may result in improved hemodynamics. It may be useful to evaluate the heart rate response to submaximal or maximal exercise or to monitor the rate over an extended period (e.g., by 24-h Holter recording). In addition, rate variability during AF provides information about the status of the autonomic nervous system that may have independent prognostic implications [152, 153, 154, 155]. The definition of adequate rate control has been based primarily on short-term hemodynamic benefits and has not been well studied with respect to regularity or irregularity of the ventricular response to AF, quality of life, or symptoms or development of cardiomyopathy. No standard method for assessment of heart rate control has been established to guide management of patients with AF. Criteria for rate control vary with patient age but usually involve achieving ventricular rates between 60 and 80 beats per minute at rest and between 90 and 115 beats per minute during moderate exercise. For the AFFIRM trial, adequate control was defined as an average heart rate up to 80 beats per minute at rest and either an average rate up to 100 beats per minute over at least 18-h ambulatory Holter monitoring with no rate above 100% of the maximum age-adjusted predicted exercise heart rate or a maximum heart rate of 110 beats per minute during a 6-min walk test [156]. In the RACE trial, rate control was defined as less than 100 beats per minute at rest. Only about 5% of patients from these large clinical trials required AV ablation to achieve heart rate control within these limits [157].

2.4.3 Restoration of sinus rhythm

Cardioversion may be achieved by means of drugs or electrical shocks. Drugs were commonly used before direct current cardioversion became a standard procedure. The development of new drugs has increased the popularity of pharmacological cardioversion, but the disadvantages include the risk of other serious drug-induced arrhythmias. Moreover, pharmacological cardioversion is less effective than direct-current cardioversion when biphasic shocks are used. The disadvantage of electrical cardioversion is that it requires conscious sedation or anesthesia, whereas pharmacological cardioversion does not. There is no evidence that the risk of thromboembolism or stroke differs between pharmacological and electrical methods of cardioversion. The recommendations for anticoagulation are therefore the same for both methods.

Cardioversion may be performed electively to restore sinus rhythm in patients with persistent AF. The need for cardioversion may be immediate when the arrhythmia is the main factor responsible for acute heart failure, hypotension, or worsening of angina pectoris in a patient with coronary artery disease

(CAD). Nevertheless, cardioversion carries a risk of thromboembolism unless anticoagulation prophylaxis is initiated before the procedure, and this risk is greatest when the arrhythmia has been present for longer than 48 hours.

2.4.3.1 Pharmacologic cardioversion

The quality of evidence available to gauge the effectiveness of pharmacological cardioversion is limited by small samples, lack of standard inclusion criteria (many studies include both patients with AF and those with atrial flutter), variable intervals from drug administration to assessment of outcome, and arbitrary dose selection. Although pharmacological and direct-current cardioversion have not been compared directly, pharmacological approaches appear simpler but are less effective. The major risk is related to the toxicity of antiarrhythmic drugs.

Pharmacological cardioversion seems most effective when initiated within seven days after the onset of an episode of AF [158, 159]. Most of these patients have a first documented episode of AF or an unknown.

A large proportion of patients with recent-onset AF experience spontaneous cardioversion within 24 to 48 hours [160, 161, 162]. Spontaneous conversion is less frequent in patients with longer AF episodes (at least 7-days), and the efficacy of pharmacological cardioversion is markedly reduced in these patients as well. Pharmacological cardioversion may accelerate restoration of sinus rhythm in patients with recent-onset AF, but the advantage over placebo is modest after 24 to 48 hours, and drug therapy is much less effective in patients with persistent AF. Some drugs have a delayed onset of action, and conversion may not occur for several days after initiation of treatment [163]. Drug treatment abbreviated the interval to cardioversion compared with placebo in some studies without affecting the proportion of patients who remained in sinus rhythm after 24 hours [161]. Amiodarone is probably the most effective drug in this respect [164] with fewer serious proarrhythmic complications, however, its use is limited because the potential of serious side effects. In addition, it is important to emphasize that oral anticoagulation reduces the relative risk for a stroke in patients with AF by 62-70%.

2.4.3.2 Nonpharmacological therapy for atrial fibrillation

Electrical cardioversion The electrical cardioversion was introduced in 1962 by Lown [165]. It involves delivery of an electrical shock synchronized with the intrinsic activity of the heart by sensing the R wave of the ECG to ensure that electrical stimulation does not occur during the vulnerable phase of the cardiac cycle. Cardioversion should be performed with the patient under adequate general anesthesia in a fasting state. Short-acting anesthetic drugs or agents that produce conscious sedation are preferred to enable rapid recovery after the procedure; sedation should be achieved before cardioversion is attempted [166].

Successful cardioversion of AF depends on the underlying heart disease and

the current density delivered to the atrial myocardium. Current may be delivered through external chest wall electrodes or through an internal cardiac electrode. Although the latter technique has been considered superior to external countershocks in obese patients and in patients with obstructive lung disease, it has not been widely applied. The frequency of recurrent AF does not differ between the 2 methods [167, 168, 169, 170]. In stable patients, electrical cardioversion is performed after three weeks of anticoagulation therapy. To prevent thrombus formation, anticoagulation is continued for four weeks after cardioversion [171, 172]. Although the success rate for electrical cardioversion is high (90%), the recurrences after electrical cardioversion of persistent AF is around 40% to 50%, where the efficacy of drugs varies in enhancement of shock conversion and preventing recurrences [173].

Direct-current cardioversion in patients with implanted pacemakers and defibrillators AF is thought to be the result of the existence of multiple wavelets or the result of fibrillatory conduction of focal activity. Since reentrant tachycardias and tachycardias induced by triggered activity can be terminated by pacing or be suppressed by overdrive pacing, there is a possible role for pacemaker therapy in AF treatment. In patients with an indication for a pacemaker but without persistent AF, atrial pacing significantly reduces the incidence of AF [174, 175]. This observation stimulated research in pacing prevention of AF. Furthermore it is known that bradycardia can increase the dispersion of refractoriness and thus promotes AF.

When appropriate precautions are taken, cardioversion of AF is safe in patients with implanted pacemaker or defibrillator devices. Pacemaker generators and defibrillators are designed with circuits protected against sudden external electrical discharges, but programmed data may be altered by current surges. Electricity conducted along an implanted electrode may cause endocardial injury and lead to a temporary or permanent increase in stimulation threshold, resulting in loss of ventricular capture. To ensure appropriate function, the implanted device should be interrogated and, if necessary, reprogrammed before and after cardioversion. Devices are typically implanted anteriorly, so the paddles used for external cardioversion should be positioned as distantly as possible, preferably in the anterior-posterior configuration. The risk of exit block is greatest when one paddle is positioned near the impulse generator and the other over the cardiac apex, and lower with the anteroposterior electrode configuration and with bipolar electrode systems [176, 177].

Variation in immediate success rates for direct-current cardioversion goes from 70% to 99% in the literature, however complete shock failure and immediate recurrence occur up to 25% of patients undergoing direct-current cardioversion of AF, and subacute recurrences occur within 2 week in almost an equal proportion [178, 179, 180].

Maze procedure A decade of research in the 1980s demonstrated the critical elements necessary to cure AF surgically, including techniques that entirely eliminate macroreentrant circuits in the atria while preserving sinus node and atrial transport functions. The surgical approach was based on the hypothesis that reentry is the predominant mechanism responsible for the development and maintenance of AF [181], leading to the concept that atrial incisions at critical locations would create conduction barriers and prevent sustained AF. The procedure developed to accomplish these goals was based on the concept of a geographical maze, accounting for the term "maze" procedure used to describe this type of cardiac operation [182]. Since its introduction, the procedure has evolved through 3 iterations (maze I, II, and III) using cut-and-sew techniques that ensure transmural lesions to isolate the PV, connect these dividing lines to the mitral valve annulus, and create electrical barriers in the RA that prevent macroentrant rhythm atrial flutter or AF from becoming sustained [181]. Success rates of around 95% over 15 years of follow-up have been reported in patients undergoing mitral valve surgery [183]. Other studies suggest success rates around 70% [184]. Risks include death (less than 1% when performed as an isolated procedure), the need for permanent pacing (with right-sided lesions), recurrent bleeding requiring reoperation, impaired atrial transport function, delayed atrial arrhythmias (especially atrial flutter), and atrioesophageal fistula. Variations of the maze procedure have been investigated at several centers to determine the lesion sets necessary for success. Studies in patients with persistent AF have demonstrated the importance of complete lesions that extend to the mitral valve annulus; electrical isolation of the PV alone is associated with a lower success rate.

Catheter ablation Early radiofrequency catheter ablation techniques emulated the surgical maze procedure by introducing linear scars in the atrial endocardium [185]. The observation that potentials arising in or near the ostia of the PV often provoked AF, and demonstration that elimination of these foci abolished AF escalated enthusiasm for catheter-based ablation [55]. Initially, areas of automaticity within the PV were targeted, where in a study, the success rate was 86% over a 6-month follow-up [54]. Subsequent research has demonstrated that potentials may arise in multiple regions of the RA and LA, including the LA posterior wall, superior vena cava, vein of Marshall, crista terminalis, interatrial septum, and coronary sinus, [58] and modification of the procedures has incorporated linear LA ablation, mitral isthmus ablation, or both for selected patients [186]. The technique of ablation has continued to evolve from early attempts to target individual ectopic foci within the PV to circumferential electrical isolation of the entire PV musculature. In a series of 70 patients, 73% were free from AF following PV isolation without antiarrhythmic medications during a mean follow-up of 4 months, but 29 patients required a second procedure to reach this goal. However, post-ablation AF may occur transiently in the first 2

months [187]. Advances involving isolation of the PV at the atrium using a circular mapping catheter, guided by intracardiac echocardiography, have reportedly yielded approximately 80% freedom of recurrent AF or atrial flutter after the first 2 months in patients with paroxysmal AF [188], but success rates were lower in patients with cardiac dysfunction [189]. Still another approach [190, 191] uses a nonfluoroscopic guidance system and radiofrequency energy delivered circumferentially outside the ostia of the PV. In a series of 26 patients, 85% were free of recurrent AF during a mean follow-up of 9 months, including 62% taking no antiarrhythmic medications. The accumulated experience involves nearly 4000 patients [191], with approximately 90% success in cases of paroxysmal AF and 80% in cases of persistent AF [189, 192, 193]. Another anatomic approach to radiofrequency catheter ablation targets complex fractionated electrograms [194], with 91% efficacy reported at 1 year. Restoration of sinus rhythm after catheter ablation for AF significantly improved left ventricular (LV) function, exercise capacity, symptoms, and quality of life (usually within the first 3 to 6 month), even in the presence of concurrent heart disease and when ventricular rate control was adequate before ablation [57]. Despite these advances, the long-term efficacy of catheter ablation to prevent recurrent AF requires further study. Available data demonstrate at least 1 year free from recurrent AF in most (albeit carefully selected) patients [195, 196, 197]. It is important to bear in mind, however, that AF can recur without symptoms and be unrecognized by the patient or the physician. Therefore, it remains uncertain whether apparent cures represent elimination of AF or transformation into an asymptomatic form of paroxysmal AF. The distinction has important implications for the duration of anticoagulation therapy in patients with risk factors for stroke associated with AF.

Predictors of recurrent atrial fibrillation Most patients with AF, except those with postoperative or self-limited AF secondary to transient or acute illness, eventually experience recurrence. Risk factors for frequent recurrence of paroxysmal AF (more than 1 episode per month) include female gender and underlying heart disease [198]. In one study of patients with persistent AF, the 4-years arrhythmiafree survival rate was less than 10% after single-shock direct-current cardioversion without prophylactic drug therapy [199]. Predictors of recurrences within that interval included hypertension, age over 55 years, and AF duration longer than 3 months. Serial cardioversions and prophylactic drug therapy resulted in freedom from recurrent AF in approximately 30% of patients [199], and with this approach predictors of recurrence included age over 70 years, AF duration beyond 3 months, and heart failure [199]. Other risk factors for recurrent AF include LA enlargement and rheumatic heart disease, as well as the combination of LA enlargement and a low dominant atrial cycle length [200].

2.4.4 Anaesthetics in cardioversion therapies

Patients undergoing cardioversion require a short anaesthetic in order to withstand intolerable pain caused by this procedure [201]. In catheter ablation during AF, sedation is usually performed, and different anaesthetic agents have been proposed for this procedure.

The aim of procedural sedation is to enable painful procedures to be performed safely and effectively with minimal discomfort to the patient.

Safe anaesthetic management of patients with AF depends on an understanding of the pathophysiology of AF and the effects of anaesthetic agents on cardiac electrophysiology and AF. However, information regarding the effects of i.v. anaesthetic agents, on atrial vulnerability is limited, but it suggests differences in their effects on electrophysiologic properties [202, 203]. Some results suggest that different anaesthetic agents could behave in different ways in terms of a tendency towards atrial arrhythmias [204]. However, there is few published work on the sedation regimen for catheter ablation of AF. These investigations presented have compared not only the exact sedation effects of the medication regimens, but also their influence on the ablation procedure.

The following anaesthetics agents have been widely used in painful clinical examination and cardiovascular procedures with established safety and efficacy [205, 206]:

- Propofol is a sterile, nonpyrogenic emulsion containing 10 mg/mL of propofol suitable for intravenous administration. Propofol is chemically described as 2,6-diisopropylphenol and has a molecular weight of 178.27. The rapid redistribution and metabolism of propofol, resulting in a short elimination half-life of approximately one hour suggests that the drug could be suitable for use in short procedures.

- Fentanyl is a powerful opioid analgesic with a power approximately 81 times that of morphine [207]. Fentanyls are extensively used for anesthesia and analgesia, most often in the surgery room and intensive care unit. Fentanyl transdermal patch (Durogesic/Duragesic) is used in chronic pain management.

- Midazolam is a drug which is a benzodiazepine derivative [208]. It has powerful anxiolytic, amnestic, hypnotic, anticonvulsant, skeletal muscle relaxant and sedative properties. It is considered a short-acting benzodiazepine, with a short elimination half-life. It is therefore a very useful drug to use for short minor procedures.

- Etomidate, a hypnotic is a carboxylated imidazole derivative, is a short acting intravenous anaesthetic agent used for the induction of general anaesthesia and for sedation for short procedures such as reduction of dislocated joints and cardioversion [209].

- Thiopental, is an ultra-short-acting barbiturate and is most commonly used in the induction phase of general anesthesia [210]. Following intravenous injection the drug rapidly reaches the brain and causes unconsciousness within 30-45 seconds. It is considered to be a suitable anaesthetic for cardioversion, however its elimination half-life is fairly long (6-10 h) and this may cause unwanted subjective residual effects during recovery.

2.5 Autonomous nervous system and atrial fibrillation

The influence of the autonomic nervous system (ANS) on cardiac electrophysiological parameters involved in the genesis of AF has been recognized for long time. In dogs, Lewis et al. [211] demonstrated as early as 1921, that vagal stimulation evoked AF. Earlier literature (1911/1969) on this topic is presented in the monograph of Szekres and Papp [212]. According to Sager [213], the autonomic nervous system appears to play an important role in the genesis of AF by decreasing atrial refractory periods, increasing dispersion of refractoriness, inducing triggers, and altering the effects of antiarrhythmic agents.

However, the major role played by the ANS in the genesis and maintenance of AF was initially recognized in 1978 by Coumel et al. [214] in patients with lone AF. Vagally mediated and adrenergic dependent AF have been defined essentially according to clinical criteria. Vagally mediated AF occurs predominantly in middle-aged male patients, at night or after meals, whereas in adrenergic dependent AF the atrial arrhythmia is essentially induced by physical or mental stress. As well, most patients with idiopathic paroxysmal AF appear to be vagally dependent, with heightened susceptibility to vasovagal cardiovascular response. In contrast, in most patients with organic heart diseases, the paroxysmal AF episodes appear more sympathetically dependent [22].

Several experimental studies have confirmed the arrhythmogenic influence of the ANS. In the canine heart, vagal stimulation shortens the atrial effective refractory period, increases the dispersion of refractoriness, and enhances vulnerability [215, 216, 147]. Moreover, transvascular atrial parasympathetic nerve system modification by radiofrequency current application can abolish vagally mediated AF [217]. Sympathetic stimulation also shortens atrial refractory periods and increases vulnerability to AF in animal models [218]. Another experiment in which AF was associated with adrenergic stimulation with isoproterenol infusion was compared to control conditions, the synchronization index was significantly reduced during AF and further diminished when AF was under isoproterenol effects. As less synchronization indicates greater circuit fragmentation and, likely, arrhythmia perpetuation, the authors interpreted this finding as one of the proarrhythmic mechanisms of sympathetic nervous system activation [142]. In fact, influences of the ANS on the heart are extremely complex,

with incessant dynamic variations, making in vivo analysis of these phenomena rather difficult. Such complexity explains some conflicting results reported in the literature on the role of the ANS on the occurrence of atrial arrhythmias [219, 220, 114, 113].

2.5.1 Atrio-ventricular conduction

In the absence of an accessory pathway or His-Purkinje dysfunction, the atrioventricular (AV) node limits ventricular conduction during AF [221]. Factors that affect AV conduction are the intrinsic refractoriness of the AV node, concealed conduction, and autonomic tone. Concealed conduction, which occurs when atrial impulses traverse part of the AV node but are not conducted to the ventricles, plays a prominent role in determining the ventricular response during AF [222, 223]. These impulses alter AV nodal refractoriness, slowing or blocking subsequent atrial impulses, and may explain the irregularity of ventricular response during AF [41]. When the atrial rate is relatively slow during AF, the ventricular rate tends to rise. Conversely, a higher atrial rate is associated with slower ventricular rate. Increased parasympathetic and reduced sympathetic tone exert negative dromotropic effects on AV nodal conduction, while the opposite is true in states of decreased parasympathetic and increased sympathetic tone [223, 224, 225]. Vagal tone also enhances the negative chronotropic effects of concealed conduction in the AV node [224, 225]. Fluctuations in autonomic tone can produce disparate ventricular responses to AF in a given patient different to slow ventricular rate during sleep and accelerated ventricular response during exercise.

2.5.2 Ventricular response in atrial fibrillation

A more precise characterization of the ventricular inter-beat variability during AF may be obtained by statistical analysis of the sequence of RR intervals measured from the surface ECG.

The RR interval fluctuates during normal sinus rhythm, primarily in response to the extrinsic autonomic nervous system's modulation of the activity of the sinoatrial node and the cardiac conduction system [110]. Such modulation plays an important role in short-term cardiovascular regulation in the face of perturbations due to respiratory activity, adjustments in resistance to flow in various vascular beds, changes in body posture, etc. On the other hand, during atrial fibrillation the RR interval fluctuations primarily reflect the intrinsic variability of the conduction processes which sustain the dysrhythmia. However, effects of autonomic modulation may be superimposed on this intrinsic variability [112]. Given the very different physiologic sources of RR interval variability during normal sinus rhythm and atrial fibrillation, it is not surprising that the statistical properties of the RR interval sequence should differ significantly between the two rhythms.

Therefore, it has been studied the RR interval histogram. During normal sinus rhythm the histogram is often Gaussian in shape, and the standard deviation is usually small compared to the mean RR interval. Typically, the coefficient of variation between both is on the order of 0.05-0.08 in resting adults. On the other hand, during AF the RR interval histogram is much broader with values generally greater than 0.2 [111]. Moreover, the shape of the histogram is much more variable, from unimodal to bimodal curves with pronounced changes of configuration in the distribution curves [226] and may be characterized by multiple peaks [227, 228]. In addition, the R-R intervals in AF are correlated over delays of more than 20 beats, or equivalently delays of more than 25 s. This correlation over long delays reflects the relatively long periodicities associated with physiologic feedback loops involved in heart rate control. Indeed, the detailed shape of the autocovariance function contains specific information on both the characteristics of the perturbations to the cardiovascular system and the dynamics of the feedback loops involved in the compensatory heart rate response [110]. Moe and Abildskov demonstrated that, once AF was established, concealed conduction tends to be self perpetuating [40]. On these phenomenologist grounds, therefore, a grouping of ventricular beats into those with short R-R intervals and those with long R-R intervals is not surprising.

2.5.3 Heart rate variability in atrial fibrillation

Heart rate variability (HRV) reflects changes in the relative autonomic modulation of heart rate rather than the absolute level of sympathetic or parasympathetic tone.

Frequency domain HRV analysis at best may suggest some vagal or adrenergic predominance but cannot prove the direct link between HRV measurement variations and the occurrence of atrial arrhythmias. As suggested by Coumel [22], if ANS variations are almost always present before, during, or after atrial arrhythmias, they are not the only arrhythmogenic factor and in many instances probably not the major one. Reports on the focal origin of AF and the successful curative approach by discrete radiofrequency ablation of these foci support such an assumption [55]. Tomita et al. [229] provided additional information on the role of the ANS in patients with paroxysmal lone AF, not only for initiation but also for termination of the atrial arrhythmia. In a study with 23 patients with paroxysmal AF who were divided into two groups according to the mode of occurrence of the arrhythmia (initiation during nighttime in 14 patients and during daytime in 9 patients). They found a progressive increase in low-frequency (LF, 0.04-0.15 Hz) and high-frequency (HF, 0.15-0.5 Hz) components before the onset of paroxysmal AF and a decrease in LF and HF components after paroxysmal AF, but no change in LF/HF ratio in patients with nighttime episodes of paroxysmal AF. In patients with daytime paroxysmal AF, however, they found an increase in LF/HF ratio before the onset of paroxysmal AF and a decrease in LF/HF ratio after paroxysmal AF without any change in HF components.

Their results suggest that vagal tone is more dominant in nighttime paroxysmal AF and adrenergic tone more predominant in daytime paroxysmal AF, an observation that is in accordance with clinical observations and gives additional support to the use of HRV analysis for evaluating autonomic tone influences on the heart. Interestingly, vagal tone returned to normal values immediately after termination of nocturnal paroxysmal AF and vagal tone was unchanged after daytime paroxysmal AF, suggesting that vagal tone is not influenced by rapid atrial activity during AF. Moreover, results reported by Tomita et al. supported the fact that sympathetic tone is inhibited immediately after paroxysmal AF, an observation that is rather surprising in view of the rapid atrial activity and the rapid ventricular response observed during AF. Rapid atrial pacing induces autonomic remodeling characterized by increased sympathetic innervation of the atria and increased heterogeneity of sympathetic innervation facilitating maintenance and reinitiation of AF [230]. Increased sympathetic modulation also has been observed in patients with AF recurrences after electrical cardioversion [231]. Discrepancies between the results reported by Tomita et al. and previous studies may be related to the different methods used to assess autonomic tone, different patient populations, or simply the complex nature of the phenomenon. From the clinical point of view, the study by Tomita et al. is important because it confirms the role of the autonomic nervous system as a major arrhythmogenic factor at the atrial level. From a therapeutic point of view, consequences are limited, at least at the present time. Nowadays, it seems unlikely neither an improvement in hemodynamic conditions and consequent changes in autonomic activity, nor a variation in autonomic control of the atrioventricular node might play a major role in facilitating arrhythmia termination.

In addition, HRV measures changes in the relative degree of ANS, not the absolute level of sympathetic or parasympathetic discharges, and even with such sophisticated techniques results should be interpreted with caution. Therefore, it should be necessary to perform direct recording of sympathetic and vagal nerve activity to prove or disprove these observations in ambulatory animals.

2.5.4 Circadian rhythms

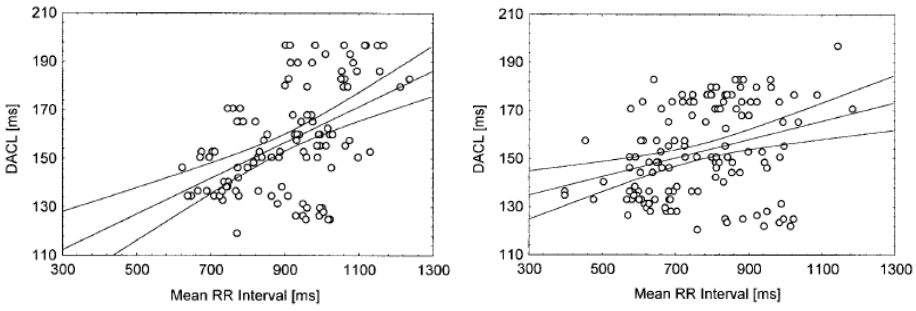
Circadian periodicity has been demonstrated for various cardiovascular syndromes, including sudden death and acute myocardial ischaemia or infarction [232, 233, 234]. In all these cardiovascular syndromes, an increased number of events occur early in the morning, and to a lesser degree, late in the evening [232]. This consistent circadian pattern has been ascribed to the increased sympathetic activity that exists in the early morning hours [235].

Diurnal fluctuations in atrial refractoriness have been little studied, but it is well recognized that autonomic tone has a profound effect on refractoriness in normal sinus rhythm [236, 237]. In AF, atrial refractoriness is shortened compared with sinus rhythm, but whether it exhibits diurnal variability is unknown.

A circadian rhythm is seen in a range of physiological variables, including ar-

terial [238] and pulmonary [239] blood pressure, body temperature, blood pH, hormone levels [240, 241, 242], and autonomic tone [243, 244]. Furthermore, there are diurnal differences in levels of physical exertion, respiratory rate, and body posture. A number of these factors are likely to be interrelated and may contribute to diurnal changes in atrial electrophysiology. However, a physiologically plausible direct effector mechanism exists probably for only four modulators, i.e., autonomic modulations, including those due to postural changes, core body temperature, atrial stretch, and hormonal changes.

Previous studies have demonstrated a circadian pattern of symptomatic, out-of-hospital [245, 246], paroxysmal AF, in a very large number of patients, significantly more episodes of AF occurred in the morning (and to a lesser degree late in the evening) than during the afternoon and late night hours. This diurnal variation is similar to that reported previously for other cardiovascular syndromes, including out-of-hospital sudden death [233], stroke [247], and myocardial infarction [232] or ischaemia [234, 248, 249, 250, 251, 252]. Interestingly, significantly fewer episodes of paroxysmal AF occurred during the day of rest, and a yearly circadian pattern during the 10 years, noted more arrhythmic episodes during the late months of each year. Interestingly, a similar seasonal pattern (with significantly fewer events during the summer) was recently described for acute myocardial infarction [253] and for acute cardiogenic pulmonary oedema [254]. These studies suggest that the tendency of paroxysmal AF to occur at certain hours of the day may suggest that antiarrhythmic regimens should attempt to achieve maximal effects at the time of maximal chances of arrhythmias.



(a) Day DACL/RR (b) Night DACL/RR

Figure 2.9: Relationship between ventricular rate (x-axis) and DACL (y-axis) at night (right) and during the day (left). Relationship is stronger at night, with a steeper slope of the regression line. Reproduced with permission from C. J. Meurling et al. Diurnal variations of the dominant cycle length of chronic atrial fibrillation. Am J Physiol Heart Circ Physiol 280: H401H406, 2001.

Other results about the diurnal variability of the cycle length of atrial activi-

ty (closely correlates with atrial refractory period during AF [255, 136, 256]), as well as the variability of the ventricular heart rate, have found that the AF cycle length during chronic AF exhibits diurnal variability, with longer cycle lengths occurring at night; and with a correlation between the AF cycle length and ventricular cycle length, particularly at night (Fig. 2.9); as well it was observed a marked inter-patient differences in the diurnal variability of the AF cycle length, with higher variability in patients with a longer mean AF cycle length. The diurnal pattern of variation of atrial cycle length found in this study is in keeping with circadian changes in atrial refractoriness during sinus rhythm [236] and atrial pacing [236, 237]. However, this has been tested in laboratory conditions and has not been validated under varying autonomic influences or other diurnal physiological variations.

Chapter 3

Database

The database and materials employed for testing the propofol effects in AF are described in this chapter. This includes 3-lead ECG signals and 12 intra-atrial recordings for persistent and permanent AF.

All procedures were performed according to Helsinki declaration. Intracardiac recordings during AF were taken from 27 patients (21 paroxysmal AF and 6 persistent AF) submitted to electrophysiological testing, before and under anesthesia with propofol. An intravenous bolus of 1.5 mg/kg of propofol was used, and additional minor boluses were applied only if required to achieve higher profound sedation.

3.1 Electrocardiogram recordings

The recordings from patients that suffered from either paroxysmal or persistent AF, were obtained in the *Unidad de Arritmias, Servicio de Hemodinámica, Hospital Clínico San Carlos de Madrid* before the radiofrequency ablation procedure. The recordings were done in baseline state and under the anaesthetic effect. These recordings were acquired using a CardioLab equipment (Prucka Engineering), General Electric. The main technical features of the ECG recorder are given in Table 3.1.

Table 3.1: Technical specifications of CardioLab system

Leads:	V1 aVF I
Sampling rate:	1000Hz
Number of bits:	12
Resolution:	$5\mu V$
Range:	-10.235mV/10.24mV

3.2 Electrogram recordings

A 24-pole catheter (Orbiter, Bard Electrophysiology, 2-9-2 mm electrode spacing) was inserted through the femoral vein and positioned in the RA with the distal dipoles into the CS to record LA electrical activity as well (Fig. 3.1). The medium and proximal group of electrodes were located spanning the RA free-wall peritricuspid area, from the coronary sinus ostium to the upper part of the interatrial region. Using this catheter, 12 bipolar intracardiac electrograms from the RA (dipoles from 15-16 to 23-24) and LA (dipoles 1-2, 3-4 and 5-6) were digitally recorded at 1 kHz sampling rate (16 bit A/D conversion; Polygraph Prucka Cardio-Lab, General Electric). Thirty to 60 seconds recordings were analysed and compared before and during the anaesthetic effect. In addition to the recordings, some additional parameters such as age, the duration of the sustained arrhythmia and drug administration were also collected (Table 3.2). Any antiarrhythmic drug was suspended at least 5 half-lives before the index procedure.

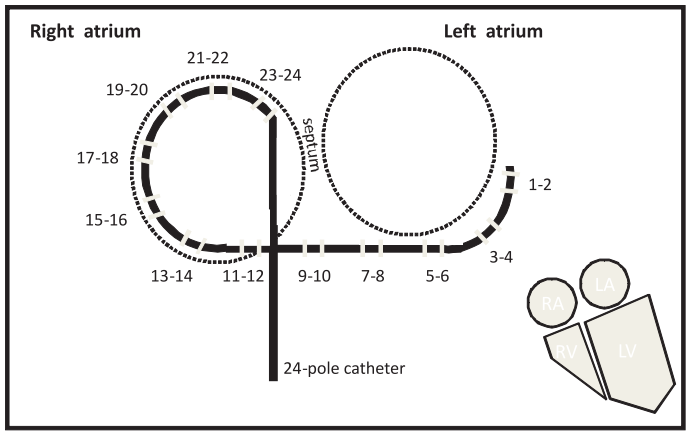


Figure 3.1: Diagrammatic representation illustrating the distribution of the 24 electric poles along right and left atria, including septal area. The lower right figure represents the anatomic relation of the 4 cardiac chambers in the same plane of orientation, showing atria and ventricles.

3.3 Patients characteristics

All subjects were suffering from AF and were nonresponsive to antiarrhythmic therapy. Paroxysmal and persistent AF episode were present in, twenty-one and six subjects, respectively. A history of AF was present for an interval ranging 2 months to 9 years. Structural heart disease was present in fourteen patients. Reported symptoms included palpitations, and fatigue after effort. Arterial hypertension and dyslipidemia were the most common comorbidity in our study group (eight and five patients, respectively). All the patients were in antiarrhythmic drug wash-out at the time of the study (Table 3.2).

The study was performed using a catheter to record atrial electrical activity before and during the effect of the anaesthetic. Five electrograms were considered to reflect electrical activity in the right atrium (superior, middle, middle-inferior, and inferior wall of the atrium), four in the septum area, and three in the left wall of the left atrium. During the experiment, one surface ECG lead was also recorded. Moreover, the length of the recordings are very variable, between thirty and sixty seconds. An example of these recordings from the printed screen of the polygraph is represented in Fig. 3.2.

Due to the different length of the recordings, and to the bad reception of the electric signals from some dipoles, different patients from the database (Table 3.2) were included in different studies.

Table 3.2: Patient Clinical Characteristics

Parameters	Paroxysmal AF	Persistent AF
Patients	21	6
Male (%)	17(81%)	4(19%)
Age (years)	56 ± 15	49 ± 6
Structural heart disease (%)	12(57%)	2(33%)
First AF episode		
<1 year	2	1
1-3 years	6	1
>3 years	6	3
unknown	7	1
Prior amiodarone treatment	4	3
Prior flecainide treatment	3	1
Prior solatol treatment	2	0
Prior propafenone treatment	3	0

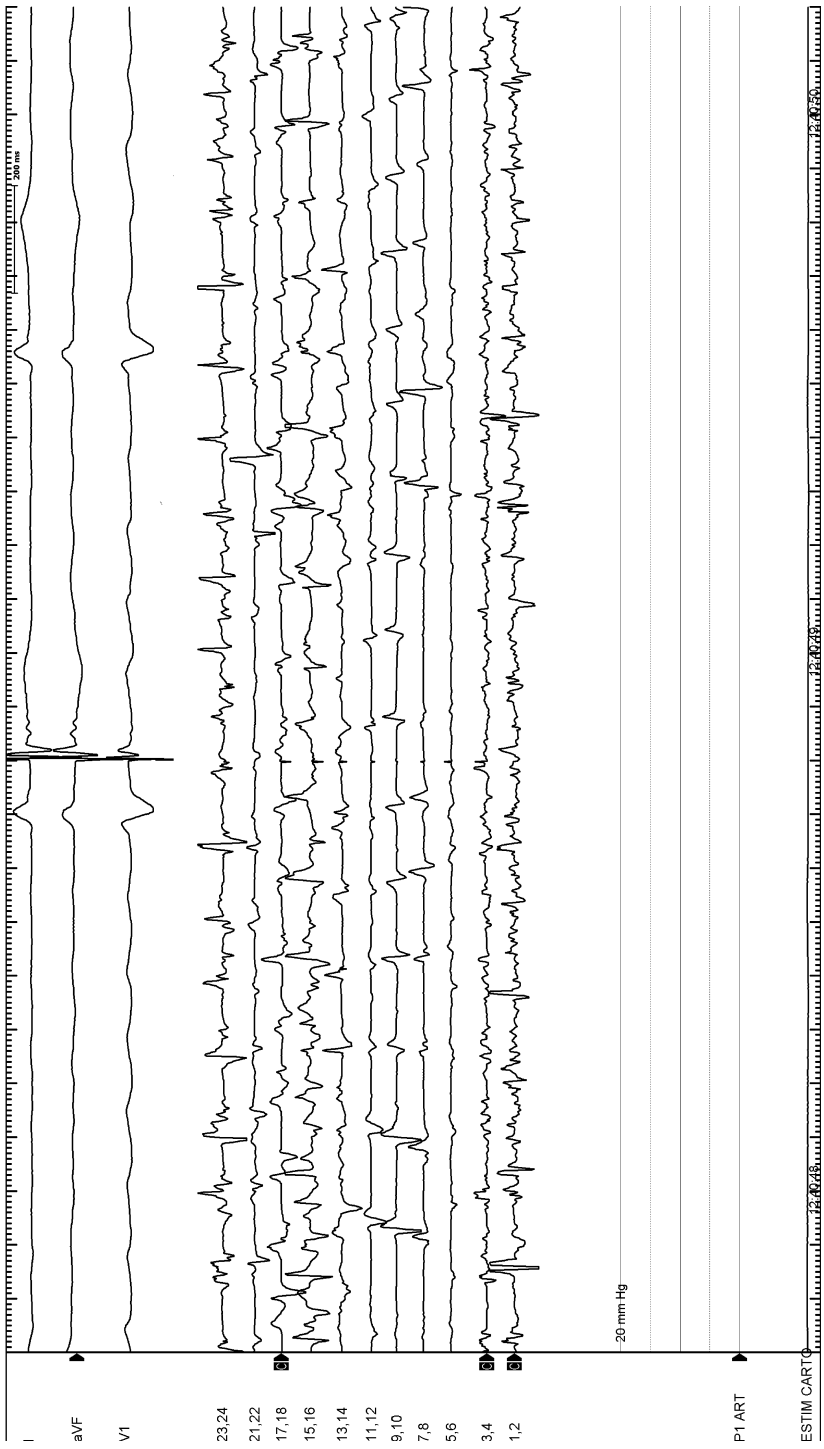


Figure 3.2: Recording from a patient, ECG recording (leads I, aVF and V1), ablation catheters (ABLd and ABLp) and mapping catheter Orbiter TM (dip23-24, . . . , dip1-2).

Chapter 4

Propofol Effects in Atrial Fibrillation Dominant Frequency[1]

Atrial fibrillation (AF) management remains problematic and controversial and most of pharmacological and non pharmacological therapies are not completely successful, where the autonomic nervous system (ANS) may trigger AF in susceptible patients through heightened vagal or adrenergic tone. The effects of the most useful anaesthetic agent (propofol) on the fibrillation patterns were evaluated. Principal Component Analysis (PCA) and Partial Least Squares (PLS) were executed to reduce noise to find differences between the patients in baseline and under the anaesthetic effects. Dominant frequency analysis was used to estimate activation rate along the different atrial areas. The results showed a different behavior in both states.

[1]Chapter based on the manuscript: Anesthesia with Propofol Slows Atrial Fibrillation Dominant Frequencies. R. Cervigón, J. Moreno, F Castells, J. Mateo, C. Sánchez, J. Pérez-Villacastín, J. Millet. Computers in Biology and Medicine 38 (2008) 792-798.

4.1 Introduction

During AF the electrical activity of the atria is highly disordered, with a very irregular fibrillatory waveform rate.

Nevertheless, animal and human studies have shown that this activity during AF is more rapid in the left atrium (LA) than in the right atrium (RA) [257, 53]. These studies suggest that high-frequency sources in the LA act as triggers and/or drivers for some types of AF. Those impulses emanating a high-frequency source, i.e. the pulmonary veins (PVs), should be subject to spatially distributed intermittent blockade imposed by the presence of functional and anatomic obstacles in their path, producing local activation at progressively lower frequencies as they propagate away from these sources. In such a case, interatrial pathways such as Bachmann's bundle (BB) and the inferoposterior pathway (IPP), which runs along the coronary sinus (CS) [258, 259] would be expected to act as preferential routes for left-to-right propagation of fibrillatory impulses. An experiment with LA sources drive AF in the Langendorff-perfused [51] demonstrated that an organized LA electrical activity with the presence of a dominant frequency, which was consistently higher than those in the recordings from the RA, resulting in a frequency gradient between the LA and RA. The authors interpreted these findings as suggesting that the LA may be the "driver" of sustained AF. Moreover, these differences were significative in humans with paroxysmal AF, dominant frequencies were highest at the PV/LA junction, intermediate in anterior LA (CS), and slowest in the RA, with a not that clear role of the posterior LA in persistent patients [260].

In addition, other factor that contributes to the genesis or maintenance of circulating wavelets, is the circadian variations due to ANS influence [110, 22]. Stimulation of the vagus nerve (or parasympathetic response) causes the heart rate to slow down and the refractory period of the atria to shorten (vagal AF) and sympathetic activation that include increased rate and force of contraction (adrenergic AF).

The analysis of AF electrograms may provide information about the underlying psychopathological substrate, explaining the continuous variations of the fibrillation waves, characterized by the local dominant frequency [136, 255, 261]. The most common algorithm used in electrograms analysis was enunciated by Botteron [10] and it is described in section 2.3.2.1.

Since the localized intracardiac electrograms recorded during the procedure are a mixture of both local and global cardiac activity, it can be difficult to distinguish overall trends. Therefore, Principal Component Analysis (PCA) and Partial Least Squares (PLS) were used to enhance the characterization of the fibrillatory patterns, summarizing the data using a smaller number of components and rejecting background noise. PCA techniques have been already applied in cardiac electrophysiology, such as in the study of ventricular repolarization [262], the estimation of fibrillatory waves in AF recordings [263], ECG compression and other applications in Body Surface Potential Mapping (BSPM)

among others [264], and PLS received a great amount of attention in the field of chemometrics, and this success of PLS has resulted in a lot of applications in other scientific areas including bioinformatics, food research, medicine, pharmacology, social sciences, physiology to name but a few [265, 266, 267, 268, 269]. In this work, another application concerning intracardiac recordings during atrial fibrillation is proposed.

4.2 Materials

AF intracardiac recordings (catheter Orbiter, Bard Electrophysiology, 2-9-2 mm electrode spacing, Fig. 3.1) were registered in 18 patients submitted to an AF ablation procedure immediately before and after propofol sedation (an intravenous bolus of 1.5-2 mg/kg, depending on weight and time to hypnosis) (Table 4.1). Thirty to 60 seconds recordings were analysed and compared before and during the anaesthetic effect.

Table 4.1: Patient Clinical Characteristics

Parameters	Paroxysmal AF	Persistent AF
Patients	14	4
Male (%)	9(69%)	4(100%)
Age (years)	58 ± 17	46 ± 3
Structural heart disease (%)	6(43%)	1(25%)
First AF episode		
$<$ 1 year	1	1
1-3 years	5	0
$>$ 3 years	2	3
unknown	6	0
Prior amiodarone treatment	1	3
Prior flecainide treatment	1	1
Prior quinidine treatment	1	0
Prior propaferone treatment	2	0

4.3 Methods

4.3.1 Preprocessing process

4.3.1.1 Traditional filtering

The intracardiac signals are band-pass filtered using a 40-250-Hz third-order Butterworth filter. The resulting waveforms are filtered once more time using a

20-Hz low-pass third-order Butterworth filter. This filtering process was detailed in section 2.3.2.1.

4.3.1.2 Principal Component Analysis

In order to remove the redundancy of the electrograms and evaluate the joint trends of these signals, PCA is applied. This process is employed to emphasize the common properties of the original signals and concentrate them in a reduced set of new variables, also known as the principal components (PCs).

PCA is a popular data processing and dimension reduction technique [270] (see appendix A). PCA seeks linear combinations of the original variables such that the derived variables capture maximal variance, with the restriction of being mutually orthogonal. The objective is to find a linear transformation of the original variables, ordered by high proportion of the variation of the old variables, in a set of new uncorrelated variables. Actually, each of the PCs is associated to an eigenvalue (or analogously a singular value), where the first component corresponds to the largest eigenvalue, and the following components are subsequently associated to the remaining eigenvalues in a decreasing order. In fact, the larger the i^{th} eigenvalue, the higher variance in the original data is represented by the i^{th} principal component.

The number of principal components to be selected can be chosen as a function of the percentage of variance in the original data to be kept. Biological expression data are currently rather noisy and redundant, and most of the information can be represented by the first few components, whereas the last components are associated with noise. Noise components have usually small eigenvalues, and a threshold in the eigenvalue sequence can be employed to determine the number of components to be selected.

PCA was applied separately for the signals before and during anaesthetic infusion, which could lead to different linear transformations for each group. In order to evaluate this effect in the results performance, the signals before and after anesthetic treatment were concatenated previously to PCA processing, so that a unique transformation matrix was obtained for both groups.

4.3.1.3 Partial Least Squares

PLS regression is a technique that generalizes and combines features from PCA and multiple regression (see appendix B). In handling numerous and collinear $\mathbf{X}$ variables, and response profiles $\mathbf{Y}$, PLS allows us to investigate complex problems and analyze available data in a more realistic way. PLS finds components from $\mathbf{X}$ that are also relevant for $\mathbf{Y}$.

PLS derives its usefulness from its ability to analyze data with many noisy, collinear variables in both $\mathbf{X}$ and $\mathbf{Y}$. PLS has the possibility to form a regression model (so-called PLS2), by determining a bilinear model for the response block and searches for a set of components, called latent variables (LVs), that performs

a simultaneous decomposition of $\mathbf{X}$ (intra-atrial recordings from patients in baseline) and $\mathbf{Y}$ (intra-atrial recordings after propofol infusion) with the constraint that these components explain as much as possible of the covariance between $\mathbf{X}$ and $\mathbf{Y}$. This step generalizes PCA. It is followed by a regression step where the decomposition of $\mathbf{X}$ is used to predict $\mathbf{Y}$.

Consider the general setting of a linear PLS algorithm to model the relation between two data sets of n observations (blocks of variables), with k input variables (giving an $(n \times k)$ matrix $\mathbf{X}$, and m output variables (giving an $(n \times m)$ matrix $\mathbf{Y}$. PLS models the relations between these two blocks by means of score vectors. After observing n data samples from each block of variables, PLS decomposes $\mathbf{X}$ and $\mathbf{Y}$ into the form eq. B.1 and B.3:

$$\mathbf{X} = \mathbf{T}\mathbf{P}^{\mathbf{T}} + \mathbf{E} \tag{4.1}$$

$$\mathbf{Y} = \mathbf{T}\mathbf{Q}^{\mathbf{T}} + \mathbf{F} \tag{4.2}$$

where the $\mathbf{T}$ is $(n \times p)$ matrix of the p extracted score vectors (also called latent vectors), the $(k \times p)$ matrix $\mathbf{P}$ and the $(m \times p)$ matrix $\mathbf{Q}$ represent matrices of loadings and the $(n \times k)$ matrix $\mathbf{E}$ and the $(n \times m)$ matrix $\mathbf{F}$ are the matrices of residuals.

The classical form of PLS method was applied. It is based on the nonlinear iterative partial least squares algorithm (NIPALS)[271]. It finds weight vectors $\mathbf{W}$ and $\mathbf{Q}$ such that, the covariance between the score vectors $\mathbf{T}$ and $\mathbf{U}$ corresponds with the maximum of the covariance between the variables $\mathbf{X}$ and $\mathbf{Y}$. The NIPALS algorithm starts with random initialization of the $\mathbf{Y}$ score vector $\mathbf{U}$ and repeats a sequence of the following steps until convergence.

4.3.2 Parameter estimation

The dominant atrial frequency was determined from the power spectral density of the signals. This was computed from the Welch's periodogram, with a 4s length Hamming window and a 50% overlapping between adjacent windowed segments [16]. The maximum peak of the resulting magnitude spectrum was identified and the positions of the harmonic peaks were determined based on the position of the maximum peak. Atrial wavelets were identified by comparing frequency spectrum with the range of frequencies of the atrial activity [48].

The dominant atrial frequency was obtained from three different preprocessing steps: the filtered electrograms, the PCs extracted from PCA analysis, and the LVs extracted from PLS. In addition, several analysis based on different atrial regions were performed separately: (1) all recordings obtained from the whole atrial region, (2) LA (dipoles 1-2, 3-4 and 5-6), (3) septum area (SA) (dipoles 9-10, 11-12 and 13-14), and (4) RA (dipoles 15-16, 17-18, 19-20 and 21-22), respectively.

In the first case, the average frequency of the filtered electrograms in a given region was computed. In the other cases the average frequency of the first PCs and LVs was computed as well. These data were collected for a different number of components according to the following criteria, for the first components capturing $85-90\%$ of the signal energy or choosing the least number of extracted factors whose residuals are reduced to $25-30\%$.

The averaged frequency was computed for each patient before and after drug administration. In order to evaluate differences caused by propofol administration, the mean value and standard deviation of the averaged frequency was computed for all patients. In addition, the frequency difference before and after propofol was also obtained for each patient, and the mean value and standard deviation of these frequency changes was computed for the patients in the database.

4.3.3 Statistical analysis

The parameters are expressed as $mean \pm SD$. Paired t-tests were used for comparison between the 2 groups of results. Comparison of serial measures was obtained by repeated measures ANOVA coupled with the Student-Newman-Keuls test. Results were considered to be statistically significant at $p < 0.05$. All statistical analyses were performed with the SPSS program.

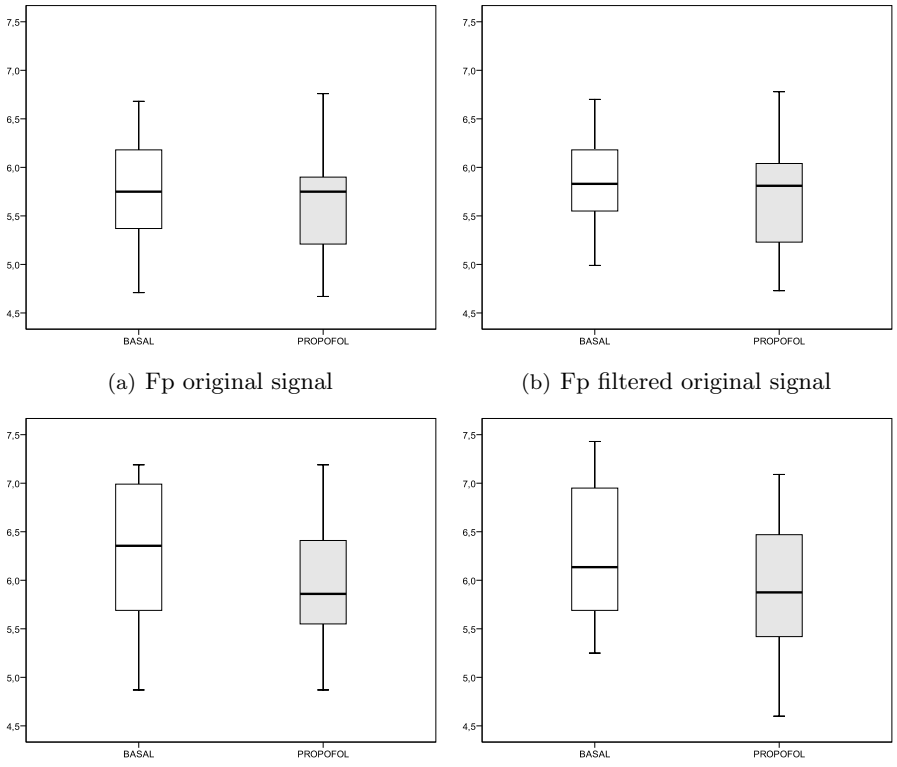
4.4 Results

4.4.1 Results from the whole atrium

The dominant frequency from each register was calculated applying the frequency domain analysis to the original waveforms, (imposed a range between 4-9Hz), before propofol administration and during its effect the main frequency was reduced from 5.77 ± 0.56 Hz to 5.66 ± 0.58 Hz. The difference between the mean frequencies of both states was 0.11 ± 0.25 Hz, although these changes were not statistically significant (p=0.078). The same signals were filtered according to the filtering process in section 4.3.1.1, and the main frequency was also computed. In this case, the frequency was reduced after propofol infusion (5.86 ± 0.52 Hz vs. 5.72 ± 0.58 Hz, with a difference of $0.14 \pm 0.26 Hz$), p=0.046 (Fig. 4.1).

In order to emphasize the differences between both groups, PCA and PLS were applied. The chosen parameter to discriminate between both groups was the main frequency of the selected components.

To discard a noise/signal separation, the dimensionality of the data was reduced using the first PCs and LVs. Frequency differences between both states became statistically significant, emphasizing that propofol decreases the main frequency of atrial activity. Considering the first five latent components, collecting around 90% of the signal energy in the first data block, the frequency



(a) Fp original signal

(b) Fp filtered original signal

(c) Fp after PCA

(d) Fp after PLS

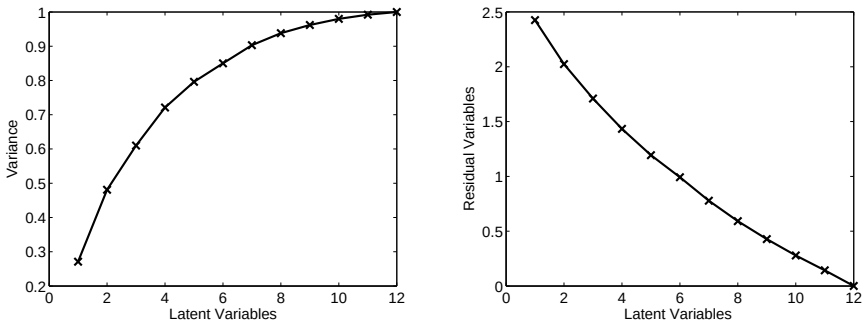
Figure 4.1: Average Main Frequency (Fp) from original leads (up left), average Main Frequency (Fp) from filtered leads (up right), 7PCs (down left), and 7LVs (down right) from basal (white) and anaesthetic conditions (grey).

changed from 6.32 ± 0.70 Hz at baseline to 5.89 ± 0.75 Hz during propofol state ($p = 0.001$) with a frequency difference of 0.43 ± 0.49 Hz. With the first five PCs the frequency difference was 0.30 ± 0.43 Hz with values of 6.33 ± 0.70 Hz vs. 6.03 ± 0.55 Hz in basal and propofol conditions, respectively ($p = 0.009$).

With the PCs capturing around 95% of the original signal energy (i.e. 7 components were selected), the frequency varied from 6.25 ± 0.70 Hz at baseline to 5.97 ± 0.63 Hz during the anaesthetic effect, with a difference of 0.29 ± 0.37 Hz ($p = 0.004$), and as well with 7LVs the frequency varied from 6.30 ± 0.71Hz to 5.90 ± 0.73Hz ($p < 0.001$), with a frequency difference of 0.40 ± 0.44 Hz.

And considering all LVs, where the residues were reduced to the order of 10^{-14} (Figure 4.2), the results followed a similar trend with very significant differences between groups (6.27 ± 0.70 Hz at baseline to 5.90 ± 0.60Hz during propofol state ($p < 0.001$), with a frequency difference of 0.36 ± 0.35Hz).

The results with PCA and PLS are very similar, showing very close statistical values (Table 4.2).



(a) LVs Variance (b) LVs Residues

Figure 4.2: LVs variance (left) and residuals (right) captured from the original signal across all the patients..

Table 4.2: Main peak frequency (Fp) of PCs and LVs for basal and propofol states, and statistical significance of the Fp for PCs and of LVs from PLS analysis

	Fp (Hz) Basal	Fp (Hz) Propofol	Difference Fp (Hz)	Fp Sig.
12 leads PCA 7PCs	6.25 ± 0.70	5.97 ± 0.63	0.28 ± 0.37	0.004
12 leads PLS 7LVs	6.30 ± 0.71	5.90 ± 0.73	0.40 ± 0.44	0.000
12 leads PCA 5PCs	6.33 ± 0.70	6.03 ± 0.55	0.30 ± 0.43	0.009
12 leads PLS 5LVs	6.32 ± 0.69	5.89 ± 0.75	0.43 ± 0.49	0.001
LA 3 leads PCA 2PCs	6.14 ± 0.42	5.83 ± 0.74	0.31 ± 0.45	0.010
LA 3 leads PLS 2LVs	6.21 ± 0.69	5.86 ± 0.62	0.35 ± 0.65	0.035
SA 3 leads PCA 2PCs	5.96 ± 0.66	5.60 ± 0.56	0.36 ± 0.60	0.021
SA 3 leads PLS 2LVs	5.82 ± 0.72	5.50 ± 0.45	0.32 ± 0.56	0.028
RA 4 leads PCA 2PCs	6.47 ± 0.72	6.02 ± 0.70	0.45 ± 0.57	0.004
RA 4 leads PLS 2LVs	6.48 ± 0.66	6.14 ± 0.66	0.35 ± 0.44	0.004
SARA 7 leads PCA 4PCs	6.42 ± 0.66	6.00 ± 0.59	0.42 ± 0.45	0.001
SARA 7 leads PLS 4LVs	6.28 ± 0.64	5.94 ± 0.70	0.34 ± 0.46	0.006

4.4.2 Results from the different atrial regions

The results from original filtered signals showed a more distinctive difference between both states within the joined groups SA and RA: 5.85 ± 0.54Hz at basal state vs. 5.71 ± 0.61Hz during propofol infusion ($p = 0.045$), with a frequency

difference of 0.14 ± 0.28 Hz. However, there was not any substantial change of dominant frequency in the LA.

After the application of PLS on the LA (Table 4.2), statistically significant difference between both groups were found in the main frequency of the two latent components (this difference was also statistically significant with values from 6.21 ± 0.70Hz to 5.86 ± 0.62Hz in basal and propofol states ($p = 0.035$), with a frequency difference of 0.35 ± 0.65Hz. As well, PCA was applied and the results were also very similar compared to PCA. (Table 4.2)

On the SA the differences in the main frequency from PCA and PLS analysis were slightly higher than in the LA. For instance, with PLS before and during the anaesthetic infusion the values of the main frequency of the main component decrease from 5.82 ± 0.72Hz in basal conditions to 5.50 ± 0.45Hz during propofol infusion with a frequency difference of 0.32 ± 0.56Hz ($p = 0.028$). With PCA the values decreases from 5.96 ± 0.66 Hz in baseline to 5.60 ± 0.56 Hz during propofol effect, with difference of 0.36 ± 0.60 Hz, ($p = 0.021$). (Table 4.2)

The most important differences in main frequency after the application of PCA and PLS were found in the RA (Table 4.2). With PLS the values of the main frequency changes from 6.48 ± 0.66 Hz in basal conditions to 6.14 ± 0.66 Hz during propofol infusion with a frequencies differences of 0.35 ± 0.44 Hz ($p = 0.004$). As well, if the SA and RA groups are joined (leads 9-10 to 21-22), using the 4 first LVs decreases from 6.28 ± 0.64 Hz in basal conditions to 5.94 ± 0.70 Hz during propofol infusion with a frequencies difference of 0.34 ± 0.46 Hz ($p = 0.006$).

The results of the fundamental frequency of the PCs for the corresponding segments from the concatenated signals before and after the anesthetic infusion (Table 4.3), show a very similar results compared to the separated matrix from basal and propofol states (Table 4.2).

Table 4.3: Statistical significance of the change in main peak frequency (Fp) for PCs with a Transformation matrix based on basal and propofol states.

	Fp (Hz) Basal	Fp (Hz) Propofol	Difference Fp (Hz)	Fp Sig.
12 leads PCA 7PCs	6.36 ± 0.71	6.16 ± 0.56	0.19 ± 0.63	0.005
12 leads PCA 5PCs	6.32 ± 0.54	6.05 ± 0.53	0.27 ± 0.35	0.215
LA 3 leads PCA 2PCs	6.15 ± 0.47	5.78 ± 0.66	0.37 ± 0.65	0.027
SA 3 leads PCA 2PCs	6.06 ± 0.72	5.72 ± 0.54	0.35 ± 0.49	0.008
RA 4 leads PCA 2PCs	6.53 ± 0.72	6.15 ± 0.67	0.37 ± 0.62	0.020
SARA 7 leads PCA 4PCs	6.06 ± 0.72	5.72 ± 0.54	0.34 ± 0.49	0.017

In addition, it has been possible to find differences between the patients that have paroxysmal AF and those that have persistent AF. During persistent AF the differences between both states are low, and the highest changes can be observed in the left atrial region (Table 4.4).

Table 4.4: Statistical Significance of Main Peak Frequency (Fp) with different combinations of PCs and LVs in Paroxysmal and Persistent AF

	Parox. AF Fp Difference (Hz) Basal/Propofol	Stat. Sig. (p)	Persis. AF Fp Difference (Hz) Basal/Propofol	Stat. Sig. (p)
Original 12 leads	0.09 ± 0.27	0.207	0.16 ± 0.16	0.132
Trad. Filtering 12 leads	0.14 ± 0.28	0.200	0.28 ± 0.26	0.123
12 leads PCA 7PCs	0.27 ± 0.39	0.022	0.33 ± 0.32	0.127
12 leads PLS 7LVs	0.42 ± 0.48	0.041	0.34 ± 0.29	0.102
12 leads PCA 5PCs	0.29 ± 0.44	0.005	0.35 ± 0.45	0.223
12 leads PLS 5LVs	0.48 ± 0.53	0.006	0.26 ± 0.31	0.192
LA 3 leads PCA 2PCs	0.29 ± 0.50	0.045	0.36 ± 0.32	0.045
LA 3 leads PLS 2LVs	0.44 ± 0.66	0.027	0.29 ± 0.24	0.049
SA 3 leads PCA 2PCs	0.40 ± 0.65	0.039	0.21 ± 0.39	0.364
SA 3 leads PLS 2LVs	0.36 ± 0.58	0.038	0.18 ± 0.53	0.550
RA 4 leads PCA 2PCs	0.45 ± 0.56	0.010	0.45 ± 0.70	0.292
RA 4 leads PLS 2LVs	0.47 ± 0.77	0.025	0.41 ± 0.66	0.242
SARA 7 leads PCA 4PCs	0.43 ± 0.45	0.004	0.40 ± 0.52	0.217
SARA 7 leads PLS 4LVs	0.46 ± 0.96	0.012	0.02 ± 0.20	0.311

4.5 Discussions and conclusions

The main purpose of this study was to evaluate possible changes in the atrial fibrillatory rate induced by the injection of an anaesthetic, in this case propofol. The results suggest that in patients with AF, the atrial cycle length is markedly modulated during anaesthesia, since it increased consistently compared to the resting conscious state immediately before and the wavefronts in the atria are more homogenous.

Regarding the techniques employed to estimate these changes, it has been observed that PCA used as a preprocessing stage unmasks minor-extent changes in the atrial fibrillatory rate that may be overlooked without it. As far the application of PLS makes use of the singular value decomposition algorithm to extract information from the datasets, it differs from PCA in the sense that the solutions are constrained to reflect the covariance between both matrices. PCA captures the common trends of the signals output by the electrodes and represents them in a reduced number of components, whereas the variability inherent to each electrode as well as noise and other interferences appear in separated components, which are disregarded for frequency analysis. In addition, PLS regression finds components from one group that are also relevant for the other. Specifically, PLS regression searches for a set of components (called latent vectors) that performs a simultaneous decomposition of both with the constraint that these components explain as much as possible of the covariance

between them. This step generalizes PCA. It is followed by a regression step where the decomposition of one group is used to predict the other. Our findings demonstrate that the capability of PCA and PLS to capture the atrial waveform exempt from interference is higher, compared to other commonly used filtering methods [272, 10]. As a consequence, the frequency analysis with these procedures are more reliable and the results become more consistent.

The influence of propofol on the electrophysiological properties of the myocardium is sparsely reported in the literature. In rat ventricular myocytes, Saint [273] showed an intense depressant effect of propofol at Na channels at clinically used doses. In agreement with these experimental studies, in vitro experiments on isolated rabbit sinoatrial node preparation showed that propofol had only small effects on atrial conduction at $10\mu g \cdot ml^{-1}$, but was drastically reduced conduction at $33\mu g \cdot ml^{-1}$ and caused complete block at $100\mu g \cdot ml^{-1}$ [274]. The effects of propofol on sinoatrial nodes (rabbits and guinea pigs) were relatively slight at the concentrations likely to be seen in clinical practice [204]. The effect of the ANS electrophysiological properties on fibrillating human atrial tissue, and specially the role of atrial inputs in the ventricular rhythm during AF are complex and incompletely understood. Increased vagal tone shortens the atrial refractory period and increases vulnerability to AF, whereas acute elevations in sympathetic or adrenergic tone, the opposite to vagal tone, enhances triggered activity [14, 275, 276].

Some recent data suggest that the chronic fibrillating atrium is more under sympathetic than vagal control [277, 278], but other studies have shown that adrenergic compounds do not affect the chronically fibrillating atrium [279]. The available data suggest that the anaesthetic used in patients with different types of AF increases the parasympathetic activation with different behaviors along the atrial regions, i.e. in patients with paroxysmal AF the changes are higher and more significant in the right atrium than in persistent AF, where higher changes are observed in the left atrium. Moreover, we cannot exclude that some of the effect induced by vagal activation during AF may be because of anaesthetic effect, since the fact that other studies that have analyzed the evolution of atrial frequency in paroxysmal and persistent AF patients during circadian rhythms have found longer onset cycle lengths during sleep (arbitrarily defined in this study as between midnight and 8 AM), at a time when vagal tone would be expected to predominate [280, 281, 282].

The mechanisms involved in the propofol-mediated slowing of the fibrillation activity may be explained by direct effects on ionic currents controlling AF or indirectly by a sedation-associated increase in the parasympathetic tone. The major implication of this study is that the most commonly used agent to induce anesthesia in cardiac procedures can affect the arrhythmias themselves. This is important as present studies on AF characteristics do not take into account whether the patient is under the influence propofol or not, a factor that may affect their conclusions.

Chapter 5

Propofol Effects on Atrial Fibrillation Organization [1]

In the previous chapter was concluded that propofol slows atrial activity in atrial fibrillation (AF). However, mean atrial rate is just one aspect of the information that can be extracted from electrograms. The following goal is to evaluate the changes in atrial organization during the effect of the anaesthetic. Multiple and simultaneous intra-atrial bipolar recordings from 27 patients in AF were analyzed before and after infusing a propofol bolus. Signal organization parameters were determined using time and frequency domain analysis. Non linear analysis was performed to determine signal entropy and showed statistical significant differences between both groups in right atrial recordings. Linear analysis also showed similar findings.

5.1 Introduction

AF is characterized by an abnormal excitation of the atria where multiple, rapidly changing and, according to some authors, spatially disorganized acti-

[1] Chapter based on the manuscript: Atrial fibrillation organization: quantification of propofol effects. R. Cervigón, J. Moreno, C. Sánchez, R. Reilly, J. Pérez-Villacastín, J. Millet, F Castells. Medical and Biological Engineering and Computing 47 (2009) 333341.

vation wavelets sweep across the surface of atria, forming complex and ever-changing patterns of electrical activity [283].

Pharmacological cardioversion, electrical cardioversion and the more complex radiofrequency ablation of the junction between the pulmonary veins and the left atrium are the methods more frequently used to restore normal sinus rhythm [55]. During these other cardiac electrophysiological procedures, the patients are usually under the influence of intravenous anaesthetic agents, where the most commonly used intravenous anaesthetic drug is propofol. There is now a growing interest on whether propofol may even affect the electrophysiological properties of the atria themselves [284, 200].

Thus, the purpose of this study was to explore the influence of propofol anaesthesia on the organization of the electrical activity within the atria in patients with AF. Using a multipolar catheter spanning both atria, characterization of multiple and simultaneous intraatrial recordings (IARs) was performed in time and frequency domains using linear and nonlinear dynamics. These recordings are differential signals (bipolars), that reflect the electrical activation of the tissue in close proximity to the electrodes, allowing us to evaluate whether propofol exerts differential effects according to the explored atrial region. The proposed parameters aim to extract either inter- or intra-electrogram information in order to evaluate the influence of propofol and to compare the response of right and left atria to this anaesthetic agent.

5.2 Materials

All procedures were performed according to Helsinki declaration. Intracardiac recordings (Orbiter, Bard Electrophysiology, 2-9-2 mm electrode spacing (Fig. 3.1) during AF were taken from 27 patients (21 paroxysmal AF and 6 persistent AF) submitted to electrophysiological testing, before and under anesthesia with propofol. In addition to the recordings, some additional parameters such as age, the duration of the sustained arrhythmia and drug administration were also collected (Table 5.1).

5.3 Methods

After applying a preprocessing stage, several parameters were defined as organization indexes of the signals. These parameters were determined using linear and non-linear analysis, aiming to estimate the organization of the atrial activity either from an interelectrode or intraelectrode point of view. Using linear analysis, time and frequency domain approaches were used to determine time correlation and coherence of the spectrum, respectively. These analytical tools have been already used in previous publications concerning the organization of human AF [10, 9]. Using non-linear analysis, as well previously applied to analy-

Table 5.1: Patient Clinical Characteristics

Parameters	Paroxysmal AF	Persistent AF
Patients	21	6
Male (%)	17(81%)	4(67%)
Age (years)	56 ± 15	49 ± 6
Structural heart disease (%)	12(57%)	2(33%)
First AF episode		
<1 year	2	1
1-3 years	6	1
>3 years	6	3
unknown	7	1
Prior amiodarone treatment	4	3
Prior flecainide treatment	3	1
Prior solatol treatment	2	0
Prior propafenone treatment	3	0

se heart rate variability [285], different entropy measurements were computed as regularity indexes.

5.3.1 Signal preprocessing

To assess atrial activity without the influence of far-field ventricular activation, it was removed any ventricular artefact from the 12 IARs. From the surface ECG, the occurrences of QRS were determined, and a template of the ventricular interference in each IAR was constructed by signal-averaging windows using either QRS subtraction from a matching template, in the case where ventricular complexes were the dominant feature of the tracing and preclude accurate atrial analysis, or blanking of the affected region, if the electrogram was affected by few ventricular complexes.

The IARs are band-pass filtered using a 40-250-Hz third-order Butterworth filter. The resulting waveforms are filtered once more time using a 20-Hz low-pass third-order Butterworth filter. This filtering process was detailed in section 2.3.2.1.

5.3.2 Interelectrode assessment

5.3.2.1 Cross correlation analysis

A robust time-domain method to analyze intra-atrial electrograms was proposed by Botteron [10, 272], by estimating the cross-correlation of closely spaced bipolar endocardial recordings.

The discrete cross-correlation function between discrete time series of data *x(t)* and *y(t)* can be approximated by

$$R_{xy}(k) = \frac{1}{N} \sum_{t=1}^{N} \frac{(x_t - \overline{x})(y_{t+k} - \overline{y})}{\sigma_x \sigma_{y,k}}, \tag{5.1}$$

where N is the length of the segments to be correlated, k is the time lag between both signals ranging from $-K$ to K (i.e. the range within the correlation function is to be evaluated), $\overline{x}$ and $\overline{y}$ are the mean values of the two time series, and σ_x, $\sigma_{y,k}$ are the standard deviations of the corresponding segments from $x(t)$ and $y(t)$, respectively.

Spatial correlation analysis was performed on all recorded signals between the closest paired electrogram combinations in each patient. The cross-correlation function was calculated over a range of lag intervals for each electrogram combination (non-overlapping segments of $1 - 1.5$ s.) For each data segment analyzed, the absolute peak was considered as the correlation coefficient of those two signals for that period of time. This operation was repeated on sequential windowed segments for the entire data file, allowing the estimation of a correlation average for the different activation times of the signal across electrograms. Higher correlation values indicate higher organization degrees in the atrial electrical activation.

5.3.2.2 Coherence Spectrum

Spectral analysis of IARs during AF was first motivated by the need for automated arrhythmia discrimination schemes [286], since it may reflect properties and structures which can not be easily detected in the time-domain.

AF is characterized by disorganized, continually changing patterns of activation and the absence of a constant temporal relationship between multiple sites on the heart. This continually changing temporal or phase relationship may be quantified in the frequency domain by magnitude squared coherence (MSC)

$$MSC(f) = |S_{xy}(f)|^2 / S_{xx}(f) S_{yy}(f), \tag{5.2}$$

where S_{xy} is the cross power spectrum density between signals x and y, and S_{xx} and S_{yy} are the individual power spectrum densities for signals x and y, respectively.

This method quantifies temporal and spatial organization during AF [9, 287, 146, 11], measuring the constancy of the time delay (phase shift) at a specific frequency between two simultaneous electrogram recordings, $x(t)$ and $y(t)$ as a function of frequency. MSC is a measure of the linear relationship between signals as a function of frequency f, and lays in the range $[0 \ldots 1]$.

The data were partitioned into 4s length segments with 50% overlapping. A Hanning window was applied to each segment before computing the spectrum. Coherence was defined as the magnitude-squared of the cross spectrum between

the two signals divided by the auto-power spectra of the signals from 0-20 Hz. Spatial Coherence was calculated in the same way as it has been defined in the section 5.3.2.1, where it was performed on all recorded signals between the closest paired electrogram combinations in each patient.

5.3.3 Intraelectrode assessment: Entropy measurements

The activation patterns of the atrial electrical activity of the heart during AF have been often described as random phenomena. However, the fact that the spectrum of the atrial activity exhibits a main frequency suggests that it is not a completely random process, but some organization must be present to a certain extent, as suggested by some authors [50]. Entropy measures have been recently used to analyze the complex physiological time series, particularly to quantify the irregularity of the wavefront in cardiac tissues, and has been employed in the present study to measure the complexity of the data (the higher the entropy, the higher the random propagation and accordingly, the lower the extent of organization) [285, 124, 288].

5.3.3.1 Sample Entropy. Multiscale Analysis

Sample Entropy (SampEn) [125] is a similar but less biased measure than the Approximate Entropy (ApEn) family of parameters, introduced by Pincus to quantify the irregularity of finite length time series [289]. The main difference is that SampEn simply excludes self-matches in the definition of ApEn and does not employ a templatewise strategy for calculating probabilities [285].

From a time series $\{x_1, x_2, \ldots, x_N\}$ of length N, consider the m-length vectors: $\mathbf{u}_m(i) = [x_i \ldots x_{i+m-1}]$, with $1 \leq i \leq N-(m-1)$. Let $n_i^m(r)$ represent the number of vectors $\mathbf{u}_m(j)$ within distance r of $\mathbf{u}_m(i)$, where $j \neq i$ to exclude self matches. The probability that any vector $\mathbf{u}_m(j)$ is within distance r of $\mathbf{u}_m(i)$ is computed as:

$$C_i^m(r) = \frac{n_i^m(r)}{(N-(m-1))} \tag{5.3}$$

and

$$U^m(r) = \frac{1}{N-(m-1)} \sum_{i=1}^{N-(m-1)} \ln C_i^m(r) \tag{5.4}$$

represents the probability density of occurrence of the vector $\mathbf{u}_m(i)$ within a chosen distance m.

SampEn is defined as:

$$SampEn(m,r) = \lim_{N\to\infty} \{-\ln \frac{U^{m+1}(r)}{U^m(r)}\} \tag{5.5}$$

For finite length N the SampEn is estimated by the statistics:

$$SampEn(m,r) = \text{-ln}\frac{U^{m+1}(r)}{U^{m}(r)}, \tag{5.6}$$

that is, the natural logarithm of the ratio between the probability of occurrence of sequences close to each other (according to a threshold value r to measure the distance between sequences) for m consecutive data points and the probability of occurrence of sequences close to each other when one more point is added to each sequence. Larger SampEn values indicate greater independence, less predictability, hence greater complexity in the data.

Multiscale Entropy (MSE) is a modified version of SampEn, introduced by Costa et al. [290]. Considering one-dimensional discrete time series, $\{x_1, x_2, \ldots, x_i, \ldots, x_N\}$, consecutive coarse-grained time series $\{y^{(\tau)}\}$ are defined as a function of the factor τ as

$$\{y_j^{(\tau)}\} = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i \qquad\qquad 1 \leq j \leq \frac{N}{\tau}, \tag{5.7}$$

For scale one, the time series $\{y^{(1)}\}$ is simply the original time series. The length of each coarse-grained time series is equal to the length of the original time series divided by the scale factor, τ.

Next we calculate the SampEn for each sequence $\{y^{(\tau)}\}$ as a function of the scale factor τ. The rationale beyond this procedure is an enhancement of time series repetitive patterns as a function of different scales. Differences in the index at different time scales could help in the understanding of the time series in terms of regularity and structure.

For the study discussed in this chapter, SampEn is estimated using the widely established parameter values of *m=2*, and $r = 0.15\sigma$, where σ represents the standard deviation of the original data sequence, as suggested by Pincus [291], and between scale factors 1 and 10.

5.3.3.2 Shannon Entropy

Shannon Entropy (SE) was also employed as a measure of dispersion and structure complexity distribution of time series data.

SE is formally defined as the average value of logarithms of the probability density function:

$$SE = -\sum_{i=1}^{M} p(i) \ln p(i), \tag{5.8}$$

where M is the number of discrete values the considered variable can assume and $p(i)$ is the probability of assuming the i^{th} value.

5.3.3.3 Statistical Analysis

The parameters are expressed in terms of mean and standard deviation values. Paired t-student tests were used for comparison between both groups of results. Comparison of serial measures were obtained by repeated ANOVA measures coupled with the Student-Newman-Keuls test. Results were considered to be statistically significant at $p < 0.05$. All statistical analysis was performed with the SPSS program.

5.4 Results

5.4.1 Inter-electrodes results

5.4.1.1 Cross-correlation results

As pointed out in Section 5.3.2.1, the first analysis consisted of an inter-electrode comparison of AF recordings in basal state and during the anaesthetic effect.

The cross-correlation function between all of possible paired combinations of twelve bipolar electrodes were calculated in both groups. The estimate of the correlation for the same separation was then averaged, resulting in a single correlation versus distance relationship. In Figure 5.1 the mean correlation coefficient is plotted versus the inter-electrode distance, showing a slightly lower correlation during baseline state at closer distances, with an exponential distribution as was previously demonstrated [10].

The cross-correlation coefficient was calculated from the signals of each pair of the closest electrodes, to evaluate the difference in correlation along the atrial area. From this analysis, we observed that during the anaesthetic infusion the correlation increased in the RA (i.e. an increase in the organization degree), with the opposite effect observed in the LA. With 0.51 ± 0.07 at basal vs. 0.49 ± 0.08 at propofol peak in LA, and 0.51 ± 0.06 at basal vs. 0.53 ± 0.06 during propofol infusion in RA ($p = 0.008$) (Fig. 5.2).

5.4.1.2 Coherence spectrum results

The results for coherence sensitivity at the closest inter-electrode distance increased in the RA with the administration of propofol from 0.23 ± 0.07 to 0.25 ± 0.07 (i.e. an increase in the organization degree) and decreased in the LA from 0.28 ± 0.11 to 0.26 ± 0.09, $p = 0.008$ (Fig. 5.3).

5.4.2 Entropy Results

5.4.2.1 Multiscale Entropy

The averaged MSE profiles representing the SampEn values of coarse-grained sequence versus the scale were calculated in both states (Fig. 5.4). It is observed

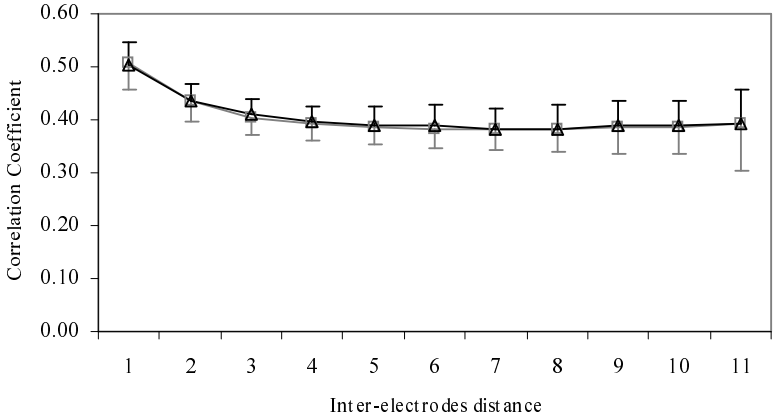
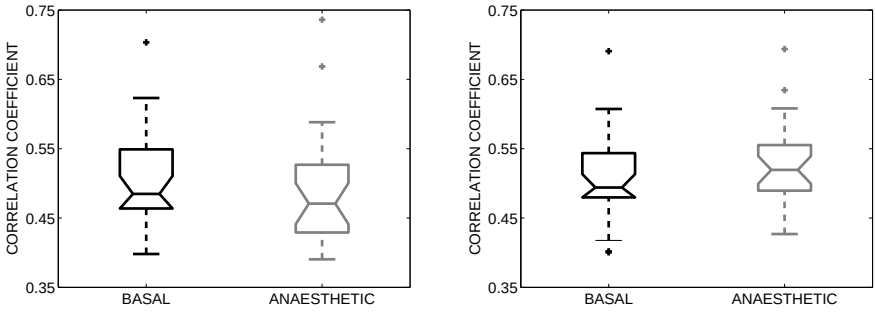


Figure 5.1: The correlation coefficient at each interbipole separation across all subjects, with the correlation defined as one at zero distance (basal (black triangle), propofol (grey squares)).



(a) LA Correlation

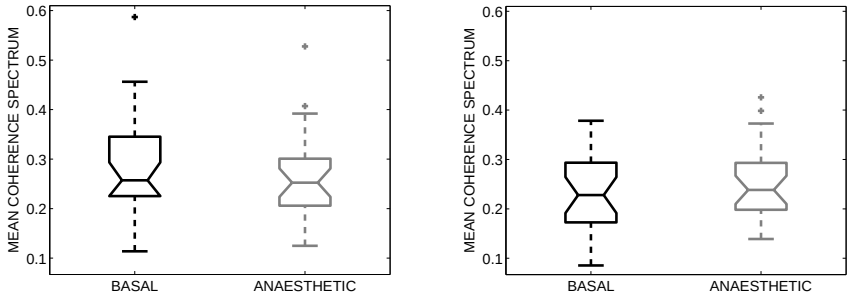
(b) RA Correlation

Figure 5.2: The correlation coefficient at the closest interbipole separation with the correlation defined as one at zero distance across all subjects (basal (black), propofol (grey)).

that these MSE profiles are characterized by a rising trend along the time scales.

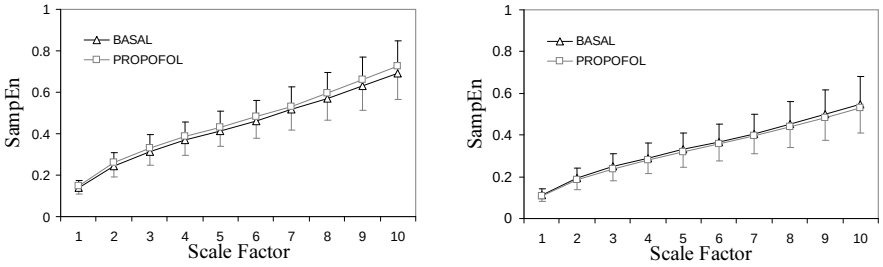
Average values of the MSE profiles for time scales values in LA and RA were calculated. Table 5.2 summarizes these results ($mean \pm SD$).

There were differences between the MSE profiles in basal and propofol states. The coarse-grained sequences at basal condition were sightly less irregular in RA than in LA, and the irregularity of the coarse-grained time series decreased



(a) LA Coherence (b) RA Coherence

Figure 5.3: Mean coherence spectrum in LA and RA across all subjects, (basal (black), propofol (grey)).

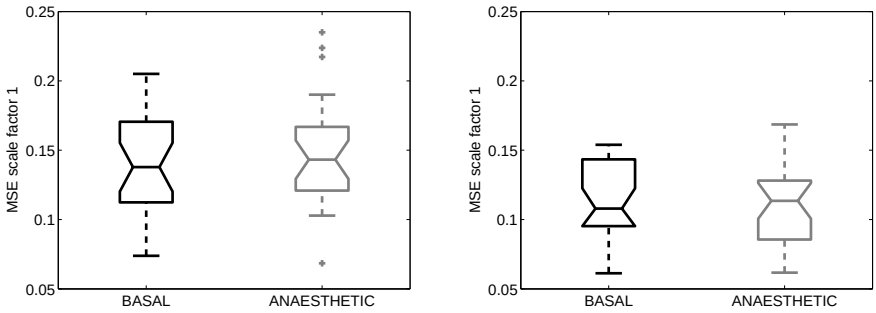


(a) LA MSE (b) RA MSE

Figure 5.4: MSE of AF time series with a number of points N= 12000, for scale $\tau = 10$ across all subjects, (basal (black triangles), propofol (grey squares)).

Table 5.2: Average values of MSE profiles for time scales for both groups for LA and RA and τ from 1 to 10

	Basal vs. Propofol LA	Basal vs. Propofol RA	Sig.
MSE 1	$0.14 \pm 0.04 vs. 0.15 \pm 0.04$	$0.11 \pm 0.03 vs. 0.11 \pm 0.03$	0.010
MSE 2	$0.24 \pm 0.06 vs. 0.26 \pm 0.07$	$0.19 \pm 0.05 vs. 0.19 \pm 0.05$	0.026
MSE 3	$0.31 \pm 0.08 vs. 0.33 \pm 0.08$	$0.25 \pm 0.06 vs. 0.24 \pm 0.06$	0.021
MSE 4	$0.37 \pm 0.09 vs. 0.38 \pm 0.09$	$0.29 \pm 0.07 vs. 0.28 \pm 0.06$	0.058
MSE 5	$0.41 \pm 0.09 vs. 0.43 \pm 0.09$	$0.33 \pm 0.08 vs. 0.32 \pm 0.07$	0.055
MSE 6	$0.46 \pm 0.10 vs. 0.48 \pm 0.10$	$0.37 \pm 0.08 vs. 0.36 \pm 0.08$	0.049
MSE 7	$0.52 \pm 0.11 vs. 0.53 \pm 0.11$	$0.41 \pm 0.09 vs. 0.40 \pm 0.09$	0.044
MSE 8	$0.57 \pm 0.13 vs. 0.59 \pm 0.12$	$0.45 \pm 0.10 vs. 0.44 \pm 0.10$	0.042
MSE 9	$0.63 \pm 0.14 vs. 0.66 \pm 0.15$	$0.50 \pm 0.12 vs. 0.48 \pm 0.11$	0.035
MSE 10	$0.69 \pm 0.16 vs. 0.72 \pm 0.16$	$0.55 \pm 0.13 vs. 0.53 \pm 0.12$	0.036



(a) LA MSE $\tau = 1$ (b) RA MSE $\tau = 1$

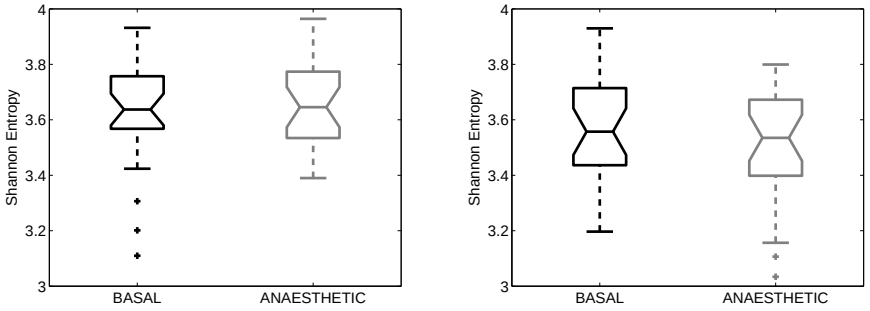
Figure 5.5: MSE at factor scale $\tau = 1$ of dipole electrode recording time series AF across all subjects, (basal (black), propofol (grey)).

during the propofol infusion in RA. This behavior was observed for all time scales, with a highest p-value for $\tau = 1$ (Fig. 5.5 and Table 5.2), where the coarse-grained time series is simply the original time series. It can be observed that the entropy measure for the deterministic chaotic time series decreases on small scales and gradually increases indicating the reduction of complexity on the larger scales.

5.4.2.2 Shannon Entropy

The application of SE showed the same upward trend in the LA during propofol infusion 3.62 ± 0.19 vs. 3.67 ± 0.16, and downward trend in the RA in the anaesthetic state 3.56 ± 0.19 vs. 3.51 ± 0.20 (p=0.001) (Fig. 5.6). The differences in the SE values between propofol and basal conditions for both atria and each patient are displayed in Fig. 5.7, where the first 21 patients correspond to paroxysmal AF and the last 6 patients to persistent AF.

Finally, the Shannon Entropy was computed for the paroxysmal AF and persistent AF groups separately. Although the database for persistent AF group is very limited, it was possible to observe that in the group of persistent AF patients the entropy decreases in both atria due to the effect of propofol from 3.72 ± 0.14 to 3.65 ± 0.20 in the LA and from 3.55 ± 0.17 to 3.42 ± 0.12 in the RA, whereas in patients with paroxysmal AF the SE increased in the LA from 3.60 ± 0.20 to 3.67 ± 0.15, with an opposite effect in the RA (from 3.57 ± 0.15 to 3.52 ± 0.19). These data are summarized in Table 5.3.



(a) LA SE (b) RA SE

Figure 5.6: SE of dipole electrode recording time series in LA and RA for paroxysmal and persistent AF across all subjects, (basal (black), propofol (grey)).

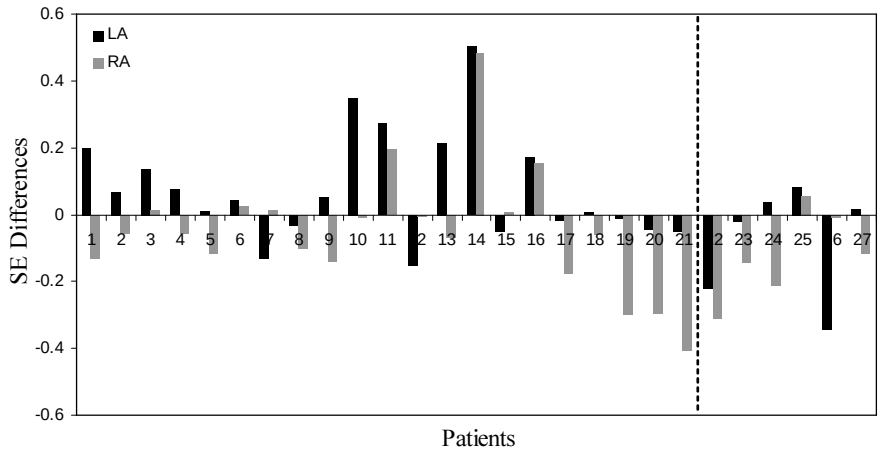


Figure 5.7: SE differences values between propofol and basal conditions for both atria in each patient in paroxysmal AF (first 21 patients) and persistent AF (last 6 patients) groups.

Table 5.3: Mean SE in LA and RA comparing Basal vs. Propofol for paroxysmal and persistent AF patients

	SE LA Basal vs. Propofol	SE RA Basal vs. Propofol
Paroxysmal	$3.596 \pm 0.197 vs. 3.672 \pm 0.151$	$3.572 \pm 0.151 vs. 3.523 \pm 0.194$
Persistent	$3.722 \pm 0.145 vs. 3.655 \pm 0.196$	$3.547 \pm 0.172 vs. 3.424 \pm 0.120$

5.5 Discussion and Conclusions

In this paper several parameters have been determined to quantify the organization of the atrial electrical activity during AF. Some of them measure the spatial organization by analyzing the interaction between different sites of the atria, whereas entropy measurements reflect the organization of the atrial activity within each single electrode. As shown in the results section, these parameters are able to capture subtle changes in the dynamics of atrial signals induced by propofol infusion during AF. The results provided by all these parameters are consistent, since all of them reflect the same findings.

With the administration of propofol to paroxysmal AF patients, an increase in the organization of the RA was observed, with the opposite effect in the LA (i.e. a decrease in the organization extent). In the case of persistent AF this organization was more homogeneous in both atria. The physiological significance of these findings is not easy to interpret. AF tends to be maintained in LA, with the RA acting as a by-stander in many occasions, especially in paroxysmal AF [292, 293]. Due to fibrillatory conduction (non 1:1 local propagation), RA tends to fibrillate slower and more organized than LA, which usually harbours more rapid AF sources [292, 293]. These interatrial differences are more evident in the present study due to the propofol infusion [200]. These minor induced changes did not finish any arrhythmic episode, thus we can only extrapolate that no antiarrhythmic net effect was elicited.

Propofol is an hypnotic agent that induces profound sedation. Pharmacological sedation modifies the patient's underlying autonomic nervous system (ANS) status emulating the increase in vagal tone and decrease in sympathic tone that occurs while sleeping. As propofol does not seem to modify atrial electrophysiologic properties [294, 295], we believed that our findings are due to the propofol-induced change in the ANS tone towards an increase in vagal tone. This may support the hypothesis that the ANS may play a significant role in AF dynamics, as clinically suggested [190, 217, 293]. Nevertheless, it can not be assured that the observed changes in the organization of the atria are due exclusively to the vagal activation induced by propofol. Indeed, this study should be contrasted and complemented with other studies to evaluate if other hypnotics affect AF dynamics on a similar basis. Previous publications have analyzed the evolution of the atrial frequency in paroxysmal and persistent AF during circadian rhythm. They reported longer atrial cycle lengths during sleep, at a time when vagal tone predominates [280, 281, 282]. In addition, the effects of autonomic modulations during AF have been studied during carotid sinus massage, as it induces vagal stimulation [92] and head-up tilt test [296], both with significant changes in the atrial fibrillatory waves. Nevertheless, there is still a need for well-defined studies with larger groups of patients in order to fully assess the influence of ANS in AF.

Chapter 6

Time Delays between Atrial Activations in Adjacent Dipoles

In the previous chapter, different measurements from the intra-atrial recordings to quantify the organization across the atrial were analyzed. These parameters showed that during the propofol effect left and right regions of the atria had a different behavior, with an increase of the organization in the right atrium (RA) and the opposite effect in the left atrium (LA). In this study a different method to quantify the organization will be introduced. This method is based in the synchronization and the delay between the different waves present in the atria. The synchrony measures are based on the assumption that two activations closely spaced in time are likely to belong to the same depolarization wavefront. Experimental data were obtained using a bipolar catheter in the atria in 27 patients during atrial fibrillation (AF). The single averaged delay index from adjacent pairs of bipolar recordings situated in left and right atrial areas was computed, and an additional index that accounts for synchrony between two adjacent sites was defined. The results have congruence with the previous study. Indeed, the computed indexes have a different behavior in both atria during

the anaesthetic infusion, what corroborates them as a valid descriptors of the electrophysiological properties of atrial tissues.

6.1 Introduction

Atrial fibrillation is a cardiac arrhythmia that is characterized by irregular and complex activations of the atria, whose rate usually exceeds 350 beats per minute [41, 42, 66]. Unlike in other atrial arrhythmias, such as in atrial flutter, the number and directions of the depolarizing wavefronts may change within the same patient, even in consecutive atrial activations [297]. In an early study, Konings et al. defined 3 types of AF according to their observations of the propagating atrial wavefronts obtained from high density epicardial maps [298].

There are currently several ways to restore sinus rhythm from AF: pharmacological treatment, electrical cardioversion, and radiofrequency ablation [299, 300, 66]. Previous to the ablation procedure, an anaesthetic agent -usually propofol- is administered to the patient [299, 300]. Moreover, during the complete process, the atrial activity is monitored with a set of intracardiac signals, i.e. electrograms, located at different sites of the atria. The effects that propofol may induce on atrial activations during AF are not well understood yet. However, since some studies reflect the influence of the autonomic nervous system on AF [14, 277], evidence suggests that propofol -as being an anaesthetic agent- may also affect the electrophysiological properties of AF. In fact, recent studies already report some modifications in both the dominant atrial rate and the organization of atrial activations with the administration of propofol [200, 301].

The main aim of this study is to evaluate if propofol may have some influence on the propagation wavefronts during atrial fibrillation from the analysis of electrograms. This work is based on the assumption that two different atrial regions can be activated either by the same wavefront or by different wavefronts, even if they are located close to each other. In an attempt to estimate the synchronization of different regions -i.e. two regions are synchronized if they are activated by the same wavefront- the delays between atrial activations at adjacent electrodes will be analyzed. Barbaro et al. have already proposed a synchronization index that considers that two atrial sites belong to the same wavefront if the delay between them does not exceed the maximum propagation time required to cover the inter-electrode distance [302]. Based on these considerations, in this study we define a novel delay index that measures the mean delay between the activations at two adjacent sites and evaluate it together with the synchronization index previously proposed in order to assess the effects of propofol on atrial propagation wavefronts.

6.2 Materials

AF intracardiac recordings (Orbiter, Bard Electrophysiology, 2-9-2 mm electrode spacing, Fig. 3.1)) were registered in 27 patients submitted to an AF ablation procedure immediately before surgery (Table 6.1). Thirty to 60 seconds recordings were analysed and compared before and after anaesthetic infusion.

Table 6.1: Patient Clinical Characteristics

Parameters	Paroxysmal AF	Persistent AF
Patients	21	6
Male (%)	17(81%)	4(67%)
Age (years)	56 ± 15	49 ± 6
Structural heart disease (%)	12(57%)	2(33%)
First AF episode		
< 1 year	2	1
1-3 years	6	1
> 3 years	6	3
unknown	7	1
Prior amiodarone treatment	4	3
Prior flecainide treatment	3	1
Prior solatol treatment	2	0
Prior propafenone treatment	3	0

6.3 Methods

In order to analyze activation delays between different electrodes, the activation times should be detected. Since the morphology of atrial depolarizations may be very heterogeneous, a robust and reliable detection method was implemented. After atrial beats detection, both synchronization and delay indexes were computed. Finally, statistical analysis was performed in order to explore any differences in these parameters due to propofol administration. In this section, the complete procedure is described in detail.

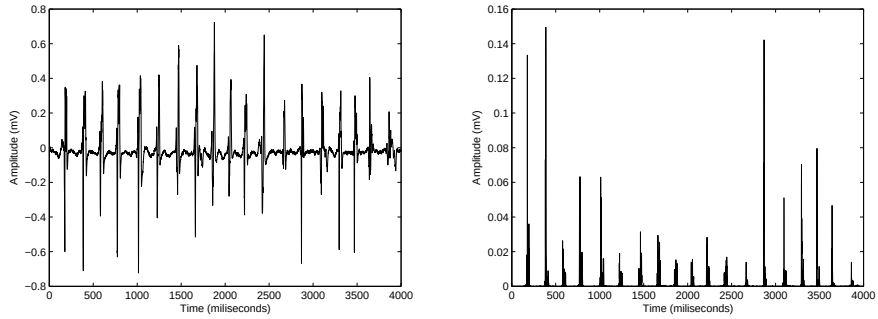
6.3.1 Detection of Activation Times

A consistent estimation of the activation time from bipolar recordings should represent the instant at which the center of the dipole was activated. As the morphology of bipolar electrograms is affected by dipole orientation with respect to fibre orientation, wavefront direction, inter-dipole distance and electrode contact, the identification of the optimum criteria for activation time determination

is a crucial issue [303]. Ndrepepa et al. showed that, for uniphasic and triphasic morphologies, the fiducial point best estimating the activation time is the maximum (or minimum, for negative waveforms) of the waveforms; for biphasic waveforms, the best fiducial point is obtained using the maximum negative (or positive) derivative [303].

To obtain an estimation of these fiducial points it was used an algorithm based on the application of the wavelet transform to the original electrogram. This transformation allows the estimation of the fiducial points, regardless of waveform polarity and morphology.

The discrete wavelet transform was applied to the intracardiac signals and the scales that contain the range of frequencies of the atrial activity were extracted. Subsequently, the signals were reconstructed with these coefficients, and they were derived and squared to enhance the maxima (Fig. 6.1). Each depolarization is then detected by threshold crossing, which starts at the amplitude of the previous detected peak and decreases exponentially to allow variability in waveform amplitude. Additionally, a blanking period equal to 70% of dominant atrial cycle length was applied immediately after the previous detection in order to avoid multiple detections within the same atrial beat [304].



(a) Original signal (b) Wavelet transform

Figure 6.1: Original signal (left) and wavelet reconstruction (right) from 4-s of the dipole 7-8 .

6.3.2 Synchronization Index

The synchronization index (SI) was proposed by Barbaro et al. [302] and is based on the following assumption: if the time interval between the depolarizations of two adjacent bipolar electrograms is larger than the propagation time required covering the distance between them, these activations are not caused by the same propagation wavefront. On the contrary, if the delay between them is below the propagation time, there is a high probability that both regions are activated by the same wavefront.

The SI is computed from a couple of series of atrial activations. For each activation i, the delay τ_i between both sites is computed (the absolute value of the delay is considered). A sigmoid function is then applied to extract an index $s(\tau)$ as a function of the delay that aims to estimate whether a pair of activations are caused by the same wavefront or not:

$$s(\tau) = \frac{1}{1 + e^{a(|\tau| - c)}} \tag{6.1}$$

where a and c are constants to be determined. Delays with an absolute value smaller than c generate values close to 1 (i.e, the activations are synchronized). Delays greater than c result in values close to 0 (i.e, the activations are not synchronized). The slope of the transition between the high-and low-probability areas is governed by a, so that in cases close to the border (if the delay is close to c), where it is not clear whether the activations belong to the same wavefront or not, an intermediate value can be assigned. This property increases the robustness of the index and minimizes the bias of the results.

The values of a and c were chosen on the basis of literature data on the propagation velocity of activation wavefronts. Allessie et al. [42] reported an average velocity of $53 \pm 12\ cm \cdot s^{-1}$ during AF; the lowest velocity is observed during type III AF ($38 \pm 10\ cm \cdot s^{-1}$). As the distance between two consecutive, non-overlapped dipoles in the catheter is 9 mm, at the conduction velocity a waveform propagating will have a delay between 19 ms and 32 ms. Furthermore, it must be taken into account that the maximum delay between activations will be observed when the line that connects both electrodes is aligned with the propagation gradient, whereas much lower delays will be observed when being orthogonal to it.

Given these considerations, we set $c = 32$ ms (i.e. the maximum delay expected between two activations from the same wavefront at adjacent electrodes) and a $=0.4\ ms^{-1}$. The SI can be interpreted as the probability that the detected depolarizations belong to the same propagating wavefront. Independent wavefronts would result in large average delays and smaller probability of synchronization. On the contrary, smaller delays denote more synchronization and higher probability to belong to the same wavefront.

A mean SI index was then obtained by averaging each $s(\tau_i)$ from the complete delay series. This index was computed for a pair of dipoles situated in the LA (1-2 and 3-4) and another pair located in the the RA (19-20 and 21-22) during basal state and under the effects of propofol.

6.3.3 Delay Index

The delay index (DI) is based on a similar assumption than the SI index: the lower the delay between two activations at different sites, the higher the probability to be synchronized. This index aims to overcome the limitations of the SI index and to complement it by extracting similar information, but from a

different perspective. Basically, the main limitation of the SI index is that, due to the variability in the conduction velocity and propagation direction, a and c may not be adequately set for each patient (which, on the other hand, are critical for the success of the measurement). For instance, if c is set significantly higher than the propagation time (which is unknown for each patient), a considerable number of non-synchronized activations may be regarded as synchronized.

For this reason, in order to prevent from erroneous detections due to not well defined borders, any sharp transitions are avoided in the delay index. Hence, the DI is defined as the average of each delay between activations (in absolute value). According to this definition, lower DI values indicate a higher proportion of synchronized activations. On the contrary, non-synchronized wavefronts have delays that randomly span over the mean depolarization interval, and hence increasing the DI.

As in the case of the SI, the DI was computed for a pair of dipoles situated in the LA (1-2 and 3-4) and another pair located in the RA (19-20 and 21-22), during basal state and under the effects of propofol.

6.3.4 Statistical analysis

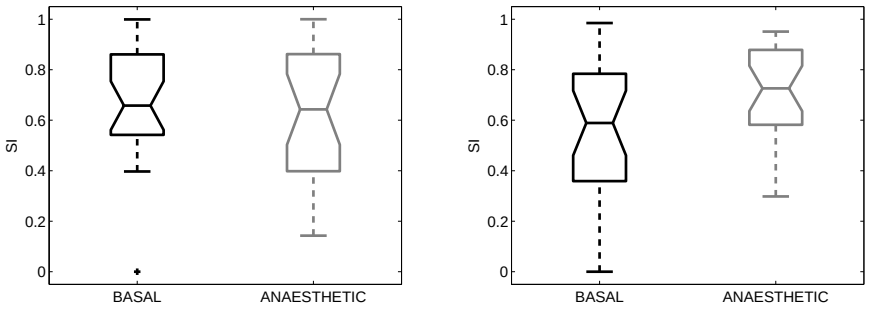
The parameters are expressed as $mean \pm SD$. Paired t-tests were used for comparison between the 2 groups of results. Comparison of serial measures was obtained by repeated measures ANOVA coupled with the Student-Newman-Keuls test. Results were considered to be statistically significant at $p < 0.05$.

6.4 Results

Both SI and DI parameters were computed for the signals registered from LA and RA before and after propofol administration. Subsequently, the effects of propofol at both atria were analyzed according to the aforementioned statistical tests. Finally, these parameters were computed separately for paroxysmal and persistent AF patients.

6.4.1 Synchronization index results

The results obtained for SI reflect some changes due to propofol administration, with and opposite effect on the LA compared to the RA. In fact, the SI shows an upwards trend from 0.58 ± 0.27 (in basal conditions) to 0.69 ± 0.20 (under sedation effects) in the RA, i.e. the RA becomes more organized, whereas the SI decreases from 0.67 ± 0.21 in basal conditions and 0.62 ± 0.28, with $p = 0.022$ (Fig. 6.2).

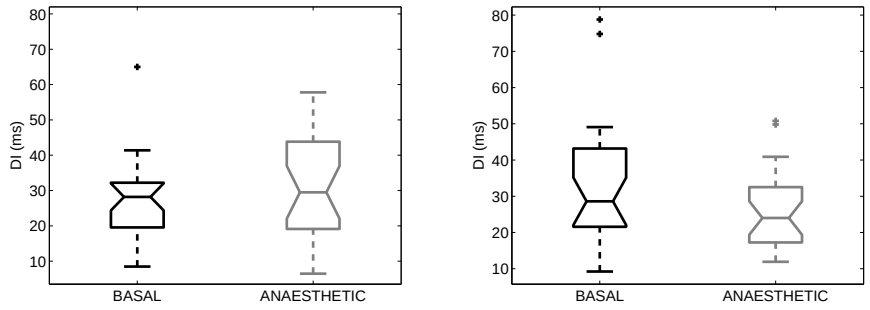


(a) LA SI (b) RA SI

Figure 6.2: SI across all subjects in the LA (left) and the RA (right) in basal (black) and propofol (grey) states.

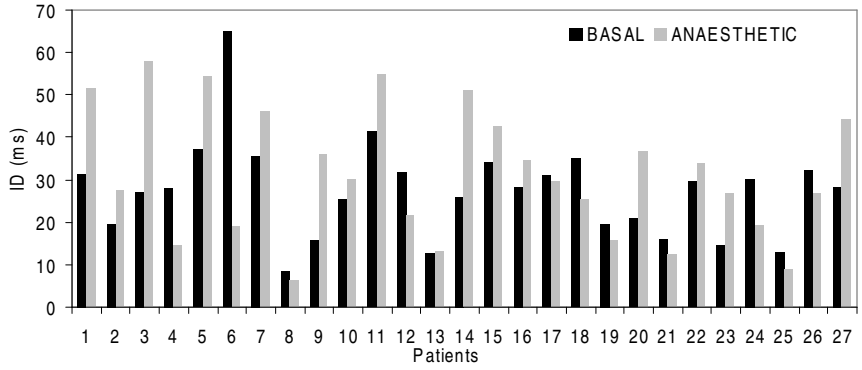
6.4.2 Delay index results

The delays between the activations showed some differences between basal and propofol conditions, as well as some differences regarding the behavior of this parameter at both atria. The mean delay between two adjacent dipoles at the LA was higher during the effect of the anaesthetic (31.19 ± 15.17 ms) respect to the basal conditions (27.32 ± 11.34 ms). On the contrary, in the RA the delay decreased from 33.56 ± 16.51 ms in basal conditions to 26.61 ± 10.32 ms during propofol effects, with $p = 0.018$ (Fig. 6.3). Although these trends are not observed in all patients the overall results were statistically significant. More specifically, DI values for each patient in basal and propofol states, and at both atria, are illustrated in Fig. 6.4.

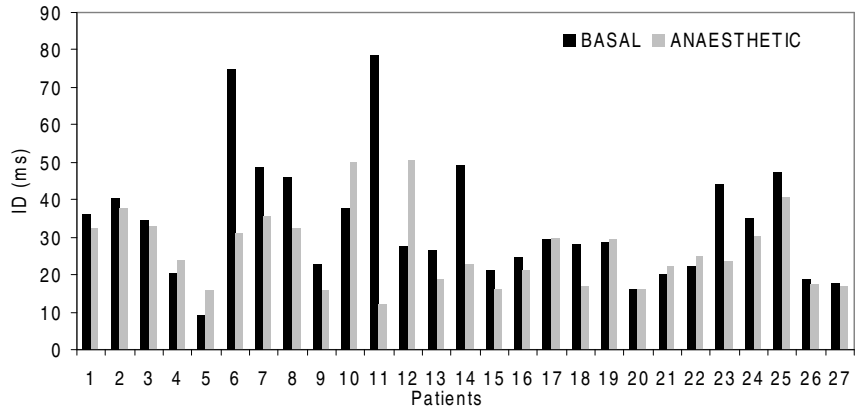


(a) LA ID (b) RA ID

Figure 6.3: Mean Delays across all subjects in the LA (left) and the RA (right) in basal (black) and propofol (grey) states.



(a) LA DI



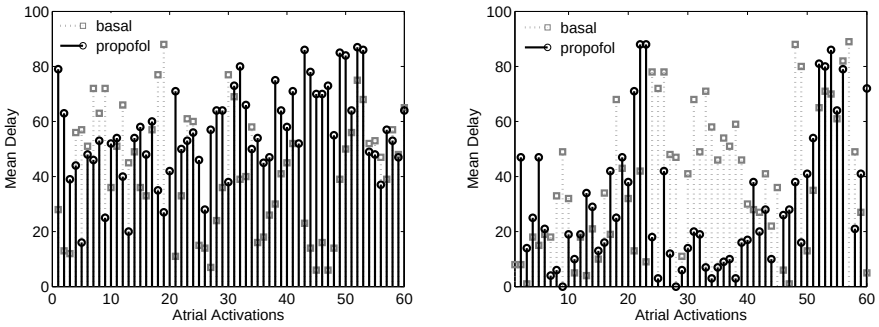
(b) RA DI

Figure 6.4: Mean Delays in LA and RA in basal (black) and propofol (grey) states in the 27 patients (21 first paroxysmal AF and 6 last persistent AF.)

An example of the times between activations between both dipoles in both atria in a specific patient with paroxysmal AF is shown in Figure 6.5. In the LA the delays are longer during the anaesthetic infusion than during the propofol effect (Fig. 6.5(a)), where it is possible to observe an opposite behavior in the RA (Fig. 6.5(b)).

6.4.3 Results in AF paroxysmal and persistent patients

Considering paroxysmal and persistent AF patients separately, the previously defined indexes were evaluated. The results in the paroxysmal group followed



(a) LA DI (b) RA DI

Figure 6.5: Mean Delays between a pair of dipoles in the LA and in the RA in baseline (grey) and propofol (black) states in a specific patient.

the same trend as in sections 6.4.2 and 6.4.1, as indicated in Table 6.2. Indeed, DI values increased at the LA with propofol administration from 28.07 ± 12.09 ms to 32.47 ± 15.96 ms, while decreasing at the RA from 34.33 ± 17.59 ms to 26.88 ± 10.86 ms ($p = 0.036$). Additionally, SI values decreased at the LA with propofol administration from 0.67 ± 0.23 to 0.58 ± 0.29, while increasing at the RA from $0.57 \pm 0.27/$ to 0.69 ± 0.21 ($p = 0.020$). On the contrary, in the persistent group, the results were not significant (Table 6.3).

Table 6.2: Parameters extracted from the delay inter-dipoles in paroxysmal AF.

	LA		RA		Stat. sig.
Parameters	Basal	Propofol	Basal	Propofol	p
DI (ms)	28.07 ± 12.09	32.47 ± 15.96	34.33 ± 17.59	26.88 ± 10.86	0.036
SI	0.67 ± 0.23	0.58 ± 0.29	0.57 ± 0.27	0.69 ± 0.21	0.020

Table 6.3: Parameters extracted from the delay inter-dipoles in persistent AF.

	LA		RA		Stat. sig.
Parameters	Basal	Propofol	Basal	Propofol	p
DI (ms)	24.71 ± 8.55	26.68 ± 12.08	30.87 ± 13.00	25.68 ± 8.95	0.292
SI	0.71 ± 0.16	0.76 ± 0.21	0.60 ± 0.27	0.70 ± 0.21	0.745

6.5 Discussion and conclusions

Dominant fibrillatory frequency of atrial activity extracted from bipolar fibrillation electrograms has been used as a parameter to characterize the irregularity

of AF [305, 48, 51, 260]. Numerous studies have postulated that the site with the highest dominant fibrillation frequency, often found in the pulmonary veins and left atrial appendage, would act as a driver of AF due to the presence of a rapid automatic focus [48, 51, 50, 306]. The rest of the atria could not follow this high rate and they would activate in an irregular fashion (fibrillatory conduction). As a consequence, it is observed a relatively high degree of regularity and a spatial gradient in the AF frequencies, progressively decreasing away from the site with the highest dominant frequency.

Frequency domain techniques suffer from the nonstationary features of AF processes, due to variations in beat-to-beat interval and morphology of fibrillation potentials. Therefore, this measure should be compared with other time domain analysis techniques. The aim of this article is to propose two descriptors to analyze the overall timing of the electrical activity along the catheter introduced in the atria during AF. One of the parameters was the delay measurement, which quantifies the delays introduced as a measure of the differences between the activations of the electrical activity propagation along the catheter. The other parameter, the synchronization index, is based on the analysis of couples of recordings from adjacent atrial sites. The proposed indexes were used to analyze if the different atrial areas reveal differences in their level of organization or synchronization, by the injection of the anaesthetic.

Nevertheless, one limitation of this method is the need of reliable detection of atrial activation times, implying an increasing difficulty with decreasing organization of AF.

These parameters were introduced to quantify the level of coupling between the electrical activity along the catheter, and are based on the measure of the depolarization differences from the recordings of two adjacent dipoles. Two different atrial regions were analyzed, the LA and the RA, showing a different behavior during the effect the anaesthetic, as other previous organization studies have showed [301]. The mean delays in the LA increased during the anaesthetic infusion, with the opposite effect in the right region. The behaviour of SI is consistent with the mean delay. In fact, in the LA, SI decreased with the administration of propofol, with an opposite effect in the RA. An increase in SI values is equivalent to a decrease in mean delay values, both meaning a higher degree of coupling among the activations at different sites.

In addition, difference in parameters between paroxysmal and persistent patients are not very notable, with lower differences in the LA in the persistent AF patients and similar values in the RA compared with the paroxysmal AF patients.

The major implication of this study is that the most commonly used agent to induce anesthesia in cardiac procedures can affect the arrhythmias themselves. The propofol increases the IS in the RA and decreases it in the LA respect to baseline conditions. It has been hypothesized that the number of propagating wavefronts is related to the atria synchronization and to the organization of AF

[11]. The likelihood of effective depolarization through cardioversion therapies depends on the ability of terminating all the propagating wavefronts. Because different atrial regions show different levels of organization, it is important to know the distribution of the most organized and the most disorganized regions in those therapies where the propofol employed.

Chapter 7

Atrio-Ventricular Conduction under Anaesthetic Infusion[1]

In previous chapters it has been already reported that propofol slows atrial fibrillatory rate and has effects on atrial organization. However, the effects on ventricular response are unknown. Since the cardiac activity during atrial fibrillation (AF) may be influenced by autonomic modulations, in this chapter the effect of propofol on ventricular rate was analyzed. Indeed, it has been already reported that propofol slows atrial fibrillatory rate, although the effects on the ventricular response are unknown. In this study the ventricular response was analyzed from the measurement of the RR interval from ECG recordings. As well, the local fibrillatory rate was extracted at different parts of the atria, and the ratio between atrial and ventricular rates (AVR) was computed. The analysis was carried out during both states, baseline and after propofol sedation. The results showed a larger variability in the ventricular response during baseline than after propofol administration. In addition, AVR decreased under the effects of propofol and became statistically significant when it was considered the atrial

[1]Chapter based on the manuscript: Ventricular rhythm in atrial fibrillation under anaesthetic infusion with propofol. R. Cervigón, J. Moreno, R. B. Reilly, J. Pérez-Villacastín, F. Castells. Physiological Measurement. In Press.

rate at the septum area.

7.1 Introduction

Scientists have inquired into the abnormal conditions affecting the basic electrophysiologic properties of the atria that promote and maintain AF, and the ones controlling the net ventricular response. The major determinants of the former are located only in the atria, especially the extent of electrical, mechanical and anatomical atrial remodeling associated to the AF itself. This remodeling can be modulated by the presence of structural heart disease, atrial dilatation and a long duration of the arrhythmia [66, 307, 63, 308]. However, the cause of the irregularity of the ventricular response during AF is related not only to the intrinsic irregularity of the atrial activity itself, but especially to the peculiar conduction properties of the atrioventricular (AV) node as the only possible electrical junction between atria and ventricles [309, 310, 222].

The autonomic nervous system has been shown to affect the electrical atrial activity and the AV node conduction, modifying atrial and AV node refractoriness and AV node conduction velocities [311, 312, 313, 314]. In experimental models of AF, it has been shown that both sympathetic and vagal activations are capable of reducing atrial refractoriness and promote AF. Accordingly, exercise-induced AF is considered to depend upon sympathetic activation, whereas arrhythmic episodes occurring during rest or night time are regarded as vagal. Pharmacologic sedation and natural sleep conditions modify autonomic tone increasing vagal tone. Circadian AF variations have been studied analyzing the AF frequencies in 24hour ECG recordings. A circadian pattern has been identified in main atrial frequencies, with longer atrial cycle lengths at night (increased vagal tone) and a relation between the main atrial cycle length and the ventricular rate [281].

Anaesthetics are widely used in electrophysiological studies and electrical cardioversions to terminate a broad variety of arrhythmias. Although basic and experimental research has provided insights into the mechanisms of AF and the effects of the autonomous nervous system in AF [315, 275], the effects of sedation through anaesthetics drugs in AF patients are poorly studied. Thus, the aims of this study were: 1) to detect and characterize any possible variations in the AF ventricular activity during an anaesthetic infusion with one of the most common hypnotic agents, propofol; and 2) to evaluate if the ventricular activity in AF follows the same modifications in cycle length as the atrial electrograms after a propofol infusion.

7.2 Materials

All procedures were performed according to Helsinki declaration. Intracardiac recordings (Orbiter, Bard Electrophysiology, 2-9-2 mm electrode spacing (Fig.

3.1) during AF were taken from 27 patients (21 paroxysmal AF and 6 persistent AF) submitted to electrophysiological testing, before and during anesthesia with propofol. In addition to the recordings, some additional parameters such as age, the duration of the sustained arrhythmia and drug administration were also collected (Table 7.1).

Table 7.1: Patient Clinical Characteristics

Parameters	Paroxysmal AF	Persistent AF
Patients	21	6
Male (%)	17(81%)	4(19%)
Age (years)	56 ± 15	49 ± 6
Structural heart disease (%)	12(57%)	2(33%)
First AF episode		
$<$ 1 year	2	1
1-3 years	6	1
$>$ 3 years	6	3
unknown	7	1
Prior amiodarone treatment	4	3
Prior flecainide treatment	3	1
Prior solatol treatment	2	0
Prior propafenone treatment	3	0

7.3 Methods

7.3.1 RR interval analysis

After detection and timing of QRS complexes from the ECG recordings, heart rate was determined by the use of all RR intervals. Time domain measurements were extracted from normal-to-normal beats and included: the mean RR interval (Mean RR) and its standard deviation (SD), the relation of SD and Mean RR (CV), the percentage of successive RR intervals that deviated by 50% from the prior RR interval (PNN50), the root mean square of successive RR interval differences (RMSSD), and the standard deviation of differences between adjacent RR intervals (SDSD). The analysis was performed on the patients described in the database during both basal conditions and under the effects of propofol.

7.3.2 Histogram analysis

The RR interval histogram was constructed from each individual RR interval series, and as well a RR distance histogram was build by considering the difference between two successive RR intervals. To synthetically characterize the

histogram, two geometric indexes were computed, the first empty bins on the right and on the left of the modal value and the difference between these two bins was taken as representative of the Main Distribution Width (MDW).

7.3.3 Atrial and ventricular rates

The intraatrial recordings (IARs) without any ventricular contamination were bandpass filtered using a 40 to 250Hz third-order Butterworth filter. The resulting filtered waveforms were then rectified using a 20-Hz low-pass third-order Butterworth filter (Fig. 2.8). This preprocessing extracted a time varying waveform proportional to the amplitude of the high-frequency components in the original atrial electrogram, enhancing the periodicity or nonperiodicity of the signals. This algorithm was used to take a complex waveform and transform it into a series of atrial activations while diminishing the effects of changing electrogram morphology and/or amplitude [10].

The dominant atrial frequency, inverse of the dominant atrial cycle length (DACL), was determined from the power spectral density of the signals. This was computed from the Welch's periodogram, with a 4s length Hamming window and a 50% overlapping between adjacent windowed segments [16]. The maximum peak of the resulting magnitude spectrum was identified and the positions of the harmonic peaks were determined based on the position of the maximum peak. Atrial wavelets were identified by comparing frequency spectrum with the range of frequencies of the atrial activity [224].

Ventricular rate was determined after detection and timing of RR intervals from the ECG lead V1.

After the extraction of atrial and ventricular rates, we evaluated whether there is any association between them, before and during the anaesthetic infusion. To evaluate it, two different parameters were computed:

- Relation between the mean ventricular interval and the main atrial cycle length obtained in the three fundamental areas, , the free wall of the left atrium (LA) through the coronary sinus electrograms, the interatrial septal area (SA) and the free wall of the right atrium (RA).

- Relation between the atrial beats included in each RR interval. To detect the activation in atrial signals, we used an algorithm with a threshold from the DACL of the time series. From the time of first detected activation we searched the maximum in a window that covered the interval from the DACL minus 25% of the DACL to the DACL plus the 25% of the DACL. To extract these atrial activations we employed the dipole 11-12 situated in the atrial septum. From this study different parameters were extracted such as, the variation of the inter-atrial beats distance in each RR interval, and the mean and standard deviation of the number of atrial cycles that occur in a RR cycle.

7.3.4 Statistics

The parameters are expressed as $mean \pm SD$. Paired t-Student tests were used for comparison between the 2 groups of results. Results were considered to be statistically significant at $p < 0.05$.

7.4 Results

7.4.1 Results from RR intervals

Considering variables directly derived from the beat-to-beat ventricular intervals, such as the mean RR cycle length, we observed a small decrement between both states, before anesthetic infusion and during propofol onset, with 579 ± 140 ms vs. 554 ± 131 ms, respectively, with a difference of 25 ± 61 ms ($p = 0.045$). In addition, SD was higher in basal conditions, 128 ± 40 ms than during the propofol effect, 114 ± 45 ms, with a difference of 14 ± 31 ms ($p = 0.026$). Moreover, the relation between standard deviation and mean (CV) showed differences between both states with 0.22 ± 0.05 ms in basal state vs. 0.20 ± 0.04 ms during propofol conditions, with a difference of 0.02 ± 0.05 and a statistical signification of $p = 0.049$.

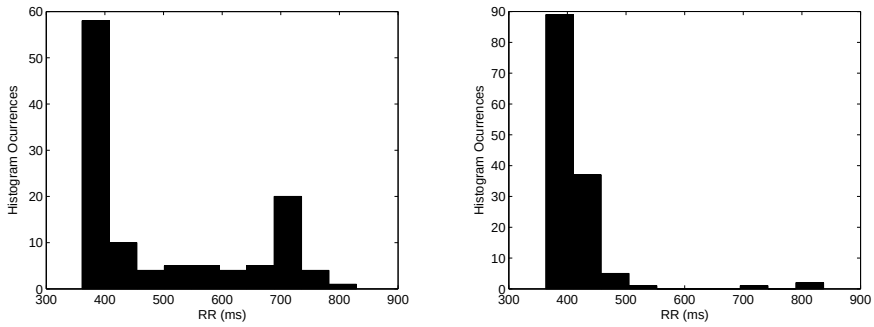
In addition, the parameters that measure the difference between adjacent cycles, such as, RMSSD, the squared root of the mean of the sum of the squares of differences between adjacent RR intervals, showed a statistical difference between both groups ($p = 0.020$), with 171 ± 57 ms in basal state vs. 138 ± 50 ms during the propofol infusion with a difference of 33 ± 54 ms (Table 7.2).

Table 7.2: Parameters extracted from the RR intervals.

Parameters	Basal	Propofol	Difference	p
mean RR (ms)	579 ± 140	554 ± 131	25 ± 61	0.045
SD (ms)	128 ± 40	114 ± 45	14 ± 31	0.026
CV	0.22 ± 0.05	0.20 ± 0.04	0.02 ± 0.05	0.049
RMSSD (ms)	171 ± 57	138 ± 50	33 ± 54	0.020
SDSD (ms)	103 ± 36	91 ± 39	13 ± 29	0.029
PNN50 (%)	0.70 ± 0.12	0.65 ± 0.18	0.05 ± 0.16	0.120

7.4.2 Results from the histogram analysis

Other parameters from the geometrical form of the histogram were extracted (Fig. 7.1), i.e. the baseline width called main distribution width (MDW) from the RR distribution, and from the differences between adjacent RR cycles (ΔRR). The MDW in both cases resulted statistical significant (Table 7.3) with a higher width in the basal state than during propofol infusion (Table 7.3).



(a) Basal histogram (b) Propofol histogram

Figure 7.1: RR interval histogram from one patient in basal (left) and propofol states (right).

Table 7.3: RR interval histogram and difference RR (ΔRR) inverval histogram parameters.

Parameters	Basal	Propofol	Difference	p
MDW RR (ms)	456 ± 172	390 ± 151	66 ± 140	0.022
MDW ΔRR (ms)	367 ± 159	313 ± 125	54 ± 128	0.037

7.4.3 Results from atrial and ventricular activity

As a result of the relation between atrial and ventricular rates, this study was divided into two different parts. On one hand, the analysis of the relation between the mean atrial activity of the different parts of the atria and mean ventricular activity; and on the other, the relation between the atrial intervals included in each RR interval.

7.4.3.1 Relation between mean atrial and ventricular activity

The original signals were filtered according to the filtering process in section 7.3.3, and the mean ventricular RR interval from the lead V1 was divided by the DACL from the septum area. This relation was higher in basal conditions compared with the propofol state, with the highest differences in the case of the atrial activity from the septum area ($p = 0.009$) (Table 7.4).

The relation between the atrial activity collected at each dipole and the ventricular activity is represented in Figure 7.2. The closest dipoles to the AV node were located in the septum and in the low atrial areas (Fig. 3.1), and in these dipoles the differences between basal and propofol conditions were higher than in the rest of dipoles situated in the atria (Table 7.5).

Table 7.4: Relation mean RR intervals and mean DACL in the fundamental atrial areas.

Parameters	Basal	Propofol	Difference	Stat. Sign.
mean RR/LA DACL	3.33 ± 0.75	3.17 ± 0.75	0.16 ± 0.38	0.033
mean RR/SA DACL	3.31 ± 0.83	3.05 ± 0.70	0.26 ± 0.48	0.009
mean RR/RA DACL	3.40 ± 0.79	3.25 ± 0.76	0.16 ± 0.52	0.126

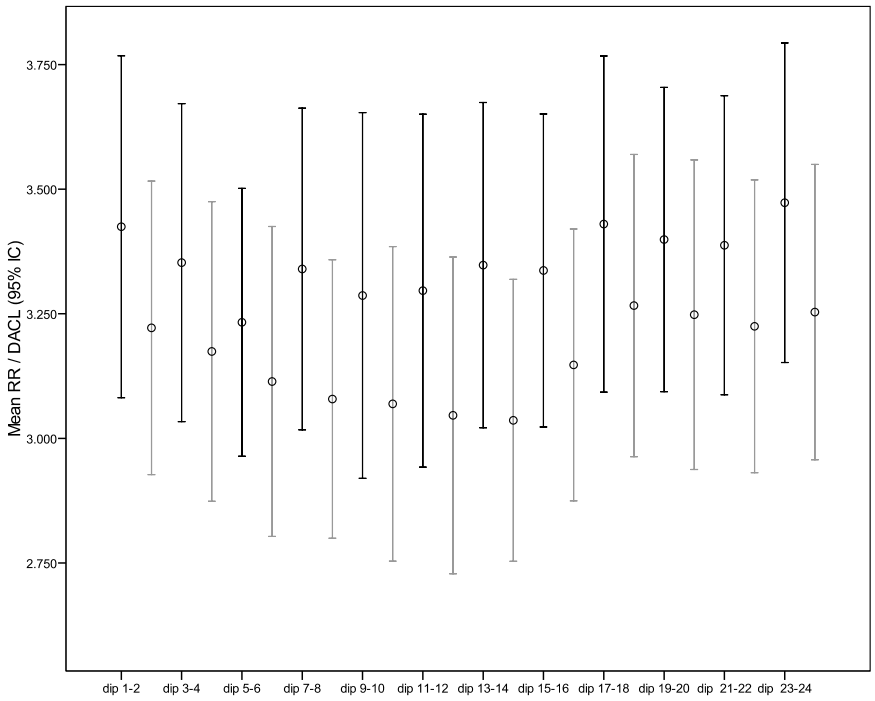


Figure 7.2: Relation DACL from different atrial areas (from dipoles 1-2 to dipole 23-24) with ventricular rate in basal (black) and propofol (grey) states.

Table 7.5: Relation mean RR intervals and mean DACL from the closest dipoles to the AV node.

Parameters		Basal	Propofol	Difference	p
mean RR/DACL	dip7-8	3.34 ± 0.78	3.08 ± 0.71	0.26 ± 0.57	0.024
mean RR/DACL	dip9-10	3.29 ± 0.98	3.07 ± 0.80	0.22 ± 0.67	0.107
mean RR/DACL	dip11-12	3.30 ± 0.89	3.05 ± 0.80	0.25 ± 0.52	0.020
mean RR/DACL	dip13-14	3.35 ± 0.82	3.04 ± 0.71	0.31 ± 0.55	0.007
mean RR/DACL	dip15-16	3.34 ± 0.79	3.15 ± 0.69	0.19 ± 0.47	0.048
mean RR/DACL	dip23-24	3.47 ± 0.81	3.25 ± 0.75	0.22 ± 0.53	0.126

7.4.3.2 Atrial activity impulses within RR impulses

The relation between the AA beats included in each RR interval showed that the mean and the standard deviation of the number of atrial beats in each RR interval were higher in basal conditions than during the propofol state. Moreover, the standard deviation of the mean distance between AA beats in each RR impulse were higher in basal conditions than during the anaesthetic effect. These results can be observed in Table 7.6.

Table 7.6: Atrial Activity beats (AAb) from dipole 13-14 inside each RR interval (RRi).

Parameters	Basal	Propofol	Difference	p
mean AAb/RRi	3.34 ± 0.82	3.06 ± 0.86	0.28 ± 0.57	0.016
std AAb/RRi	1.37 ± 1.02	1.16 ± 0.93	0.21 ± 0.47	0.026
std distance AAb/RRi	11.29 ± 2.85	12.69 ± 4.90	-1.40 ± 3.55	0.048

7.4.4 Results in paroxysmal and persistent atrial fibrillation

7.4.4.1 Results from RR intervals

From the hypothesis that both types of AF could have different behavior respect to the AV node reentrant wavefronts, the previous analysis was done in both groups separately.

In Table 7.7 is possible to observe the differences in RR measurements between the patients with paroxysmal AF and those with persistent AF. The patients with paroxysmal AF follow the same trend that the global results, due to a bigger paroxysmal patients number in the general group. Moreover, during persistent AF the results did not show significant differences between both states, i.e. the mean RR was higher in the anaesthetic group than in basal conditions 620 ± 96 ms vs. 628 ± 75 ms respectively, not reaching to statistical significance. As well, it was observed a higher regularity between the adjacent intervals in the persistent group, represented by the parameters SSDD and PNN50.

7.4.4.2 Results from the histogram analysis

The MDW measurements in the separated groups showed higher differences in the persistent than in the paroxysmal group, with a larger width in the basal state than during propofol infusion. This effect was not observed in the study of the MDW from differential R-R intervals (ΔRR), where the behavior in adjacent intervals was more homogenous in both states. (Table 7.8).

Table 7.7: Statistical Significance of RR intervals parameters in Paroxysmal and Persistent AF.

	Paroxysmal AF Difference Basal/Propofol	Stat. Sig. (p)	Persistent AF Difference Basal/Propofol	Stat. Sig. (p)
mean RR (ms)	34 ± 58	0.013	-8 ± 67	0.772
SD (ms)	12 ± 32	0.095	20 ± 27	0.134
CV	0.02 ± 0.06	0.208	0.04 ± 0.03	0.036
RMSSD (ms)	24 ± 52	0.050	25 ± 42	0.208
PNN50 (%)	0.06 ± 0.16	0.077	0.001 ± 0.18	0.998
SDSD (ms)	14 ± 31	0.056	9 ± 20	0.312

Table 7.8: Statistical MDW from histograms in Paroxysmal and Persistent AF.

	Paroxysmal AF Difference Basal/Propofol	Stat. Sig. (p)	Persistent AF Difference Basal/Propofol	Stat. Sig. (p)
MDW RR (ms)	58 ± 151	0.095	95 ± 100	0.068
MDW ΔRR (ms)	52 ± 132	0.090	66 ± 118	0.255

7.4.4.3 Results from atrial and ventricular activity

Relation between mean atrial and ventricular activity The relation between atrial and ventricular activity showed that during paroxysmal AF, the relation between atrial and ventricular activations was higher in basal conditions than during the propofol effect. Nevertheless, these differences were depending on the atrial area, but in case statistical significant differences were found in the persistent AF patients (Table 7.9).

Table 7.9: Relation between mean RR and DACL in the main atrial areas in Paroxysmal and Persistent AF.

	Paroxysmal AF Difference Basal/Propofol	Stat. Sig. (p)	Persistent AF Difference Basal/Propofol	Stat. Sig. (p)
mean RR/LA DACL	0.205 ± 0.373	0.020	0.003 ± 0.426	0.866
mean RR/SA DACL	0.256 ± 0.453	0.017	0.272 ± 0.597	0.315
mean RR/RA DACL	0.236 ± 0.486	0.037	-0.112 ± 0.601	0.667

The relation between the atrial activity from each dipole and the ventricular activity in both states is represented for the patients with paroxysmal AF (Fig. 7.3) and for the patients with persistent AF (Fig. 7.4). In the paroxysmal AF patients (Fig. 7.3), we observed more prominent differences between both states when the atrial activity was recorded from dipoles at the proximity of the AV

node, however this effect was not observed in the persistent AF group.

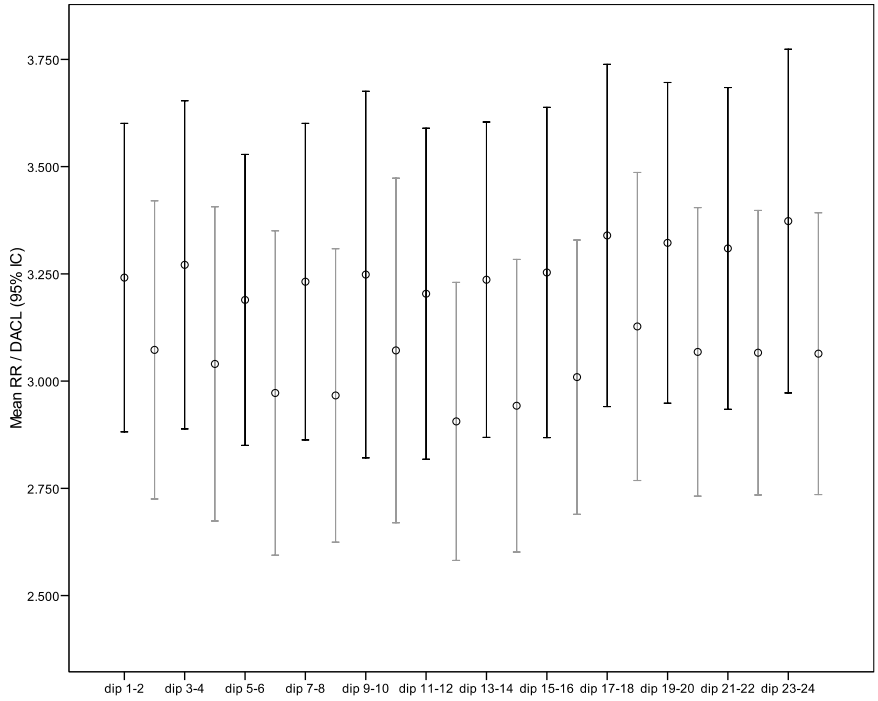


Figure 7.3: Relation between the DACL from different atrial areas (from dipoles 1-2 to dipole 23-24) and the ventricular rate in the paroxysmal group in basal (black) and propofol (grey) states.

Atrial activity impulses within RR impulses The relation between the AA beats included in each RR interval showed that, the standard deviation of the mean interval between atrial beats in each RR interval was lower in basal conditions than during the propofol state in the paroxysmal group, reaching statistically significant differences. Moreover, the mean and the standard deviation of the number of AA beats in each RR impulse were higher in basal conditions than during the anaesthetic effect. Of note, there were no significant differences in the persistent group. (Table 7.10).

7.5 Discussion and conclusions

In the absence of an accessory pathway, the intrinsic electrical properties of the AV node limit the conduction of the multiple atrial electrical wave fronts

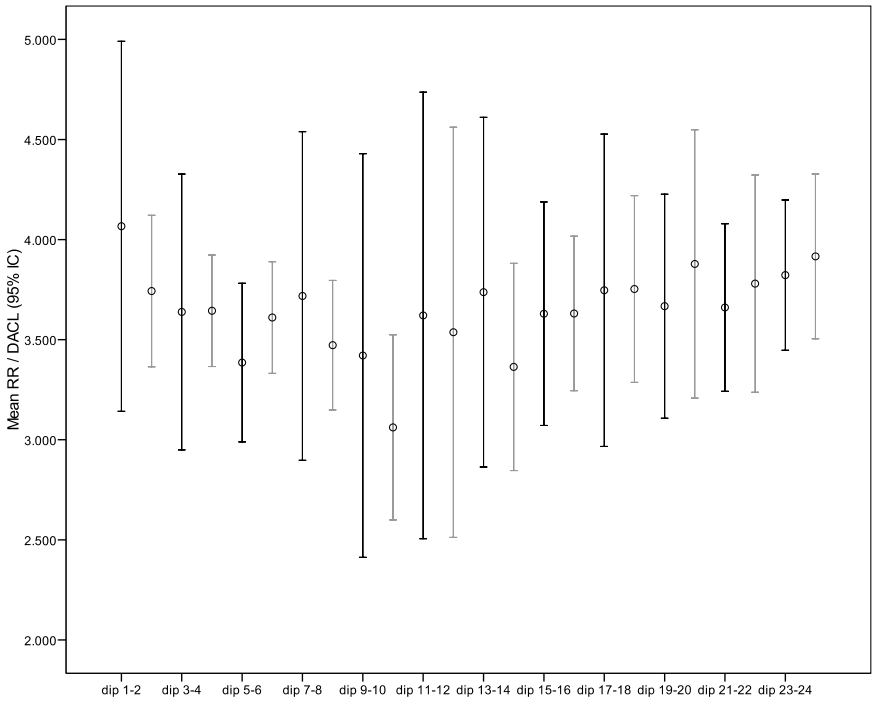


Figure 7.4: Relation between the DACL from different atrial areas (from dipoles 1-2 to dipole 23-24) and the ventricular rate in the persistent group in basal (black) and propofol (grey) states.

Table 7.10: Atrial Activity beats (AAb) from dipole 13-14 inside each RR interval (RRi) in paroxysmal and persistent AF patients.

	Paroxysmal AF Difference Basal/Propofol	Stat. Sig. (p)	Persistent AF Difference Basal/Propofol	Stat. Sig. (p)
mean AAb/RRi	0.21 ± 0.47	0.026	0.01 ± 0.57	0.965
std AAb/RRi	0.28 ± 0.57	0.016	0.21 ± 0.65	0.466
std distance AAb/RRi	-1.40 ± 3.55	0.049	0.30 ± 1.87	0.713

during AF to the ventricles to prevent heart rates beyond 180-200 bpm [276]. The atrial irregularities and the relatively poor conduction capabilities of the AV node explain the irregularity of the ventricular response during AF. The direction of atrial wave front [316] and the relative timing of activation at the atrial inputs [309] may influence the patterns of AV nodal propagation.

Some electrical wave fronts are conducted to the ventricle at times when the AV node should not be refractory and reach the ventricles, while others

perish within the AV node due to their short coupling interval, and render the AV node refractory for an additional time blocking the next atrial wavefronts, a phenomenon called concealed conduction [316]. Actually, during AF, if the atrial rate becomes relatively slow and organized the ventricular rate tends to rise as all impulses manage to travel down the AV node [312, 41].

An experimental explanation for this hypothesis was provided by Gelzer et al. [317] by quinidine administration in horses during AF. In this work, prolongation of the atrial cycle length after quinidine administration was expected to result in lengthening of the minimal RR interval duration due to the known rate dependency of AVN refractoriness [318]. Furthermore, the direct effects of quinidine on AVN cells produced prolongation of the minimal RR interval duration [319], however, in the horses it was found significant shortening of AVN RR intervals duration after quinidine administration. Moreover, the potential role of the atrial inputs is further demonstrated by Garrigue et al. [320], where the inverse relationship between increasing atrial rate and ventricular response is confirmed in a rabbit model of simulated AF, both with regular and irregular atrial pacing, and the complexity of this relationship is illustrated.

Increased vagal tone and reduced sympathetic tone exert a decrease on AV nodal conduction, while the opposite is true in states of decreased parasympathetic and increased sympathetic tone [225, 223, 224]. Due to this direct effect on AV conduction, fluctuations in autonomic tone can produce different ventricular responses to AF in a given patient, as exemplified by a slow ventricular rate during sleep but accelerated ventricular response during exercise, as shown in studies evaluating circadian variations [281, 111].

Propofol is a hypnotic agent that induces profound sedation. Pharmacological sedation modifies the patient's underlying autonomic nervous system (ANS) status emulating the increase in vagal tone and decrease in sympathic tone that occurs while sleeping. This anaesthetic has demonstrated effects in atrial fibrillatory activity slowing the AF frequency [200].

In the present paper, we show that as the mean AF cycle length increases in the presence of propofol, the mean ventricular cycle length decreases in the paroxysmal AF group. We hypothesize that, as propofol reduces the number of atrial impulses reaching the atrial inputs of the AV node per unit of time, the number of concealed AV node responses will also be reduced, explaining the seemingly paradoxical changes in ventricular frequency in response to changes in AF frequency in paroxysmal AF. As a consequence of the decreased concealed conduction through the AV node, the number of ventricular responses may increase and a higher periodicity of the RR intervals, manifested as reduced variability of the RR intervals, can be found [41, 311, 321]. It can be exemplified by the results of parameters as, SD, RMSSD and SDSD, showing in all the cases lower values during the propofol infusion in the paroxysmal group.

In addition, the correlation between atrial frequency and ventricular frequency is higher in the septum area. It can be explained taking into conside-

ration that the septal area is the closest to the AV node, as compared with the other recorded areas, and as a consequence the frequency measured in the recorded septal area should be more similar to the one of the atrial wavelets reaching the AV node. Furthermore, the results of the number of atrial beats in each RR interval are consistent with the previously mentioned results, showing that there is a significant difference between the beats in each ventricular cycle in both states, this is indicative of the previous theory, where the higher the number of atrial impulses arriving at the AV node the lower the conducted ventricular beats.

Of note, the results in persistent AF showed an opposite trend. The ventricular cycle length increases in the presence of propofol and the RR activity is not more regular than in baseline conditions. What is more, the difference between the relation of atrial and ventricular activity is variable when the atrial activity is collected from different atrial areas. However, the changes in ventricular activity, in persistent AF, do not show any relation with a particular atrial area. Nevertheless, these results need a deeper study due to the small size of the persistent AF sample.

The present findings show that dominant atrial cycle length to RR interval relationship increased and RR intervals were short after propofol infusion in paroxysmal AF patients, with a different behavior in the persistent AF group. These results suggest that the ventricular response during paroxysmal AF results from rate-dependent concealment of AF wavelets bombarding the AV node.

Chapter 8

Conclusion

In this chapter a global conclusion of the results given in this dissertation is presented. This chapter has been structured in three sections. Firstly, some of the decisions taken during this study are justified and the validity of the methodology employed is also discussed. Nevertheless, as any other scientific study, this dissertation is not exempt from its own limitations. The limitations of this doctoral thesis are expounded in this section, and some ideas to overcome them are given. Secondly, the conclusions of this work are explicitly presented. In this section it is given a response for each one of the objectives formulated in the introduction chapter. Here it is analysed how far the objectives initially proposed have been achieved. Finally, a third section is dedicated to future research lines.

8.1 Discussion

In this section the results obtained in the previous chapters will be reviewed. Although the results given in each chapter are consistent with the methods and the statement of the problem, a joint analysis of all them may contribute to a further understanding of the problem. All these questions are addressed in detail in this section.

8.1.1 Atrial rate during the propofol effect

The most common parameter evaluated from atrial electrograms is the local AF cycle length, being the inverse of the local dominant frequency of the fibrillatory waveform. This parameter is related to atrial refractoriness if conduction velocity remains unaltered [136, 255, 261].

The dominant AF cycle length was calculated as the peak of the Fourier transform. Nevertheless, this estimation can not be extent of error, due to the fact that the frequency spectrum can be broad, exhibiting multiple peaks and other ambiguities that can arise in identifying a dominant frequency. Due to these variations in beat-to-beat interval and morphology of activations, the frequency estimated at different times can vary, even when the actual AF cycle length does not change.

To avoid these errors, it was necessary to obtain an atrial waveform without any interference. Different methods were used to cancel noise and interferences of the original signal, as explained in chapter 4.3.

The traditional filtering process enhances the periodicity or nonperiodicity of the signals, diminishing the effects of changing electrogram morphology and/or amplitude [10]. In addition, PCA and PLS preprocessing unmask minor-extent changes in the atrial fibrillatory rate that may be overlooked without it. These techniques, in terms of least mean square error, compress a set of high dimensional vectors into a set of lower dimensional vectors and then reconstructing the original set. Whereas, the main components with larger variance and covariance (PCA and PLS, respectively) correspond to interesting dynamics and lower ones correspond to noise. Hence, the extracted waveform are exempt of interferences and contain the main tendency of the original wavefronts. As a result, the frequency analysis with these procedures are more reliable and the results become more consistent.

The results showed that the anaesthetic slows the atrial rate in AF, increasing the parasympathetic activation with different behaviors along the atrial regions. Moreover, the behavior in both types of AF showed quite differences; in patients with paroxysmal AF the changes are higher and more significant in the right atrium than in persistent AF, with higher changes and more noticeable in the left atrium.

8.1.2 Propofol effect on the atrial organization

Other classical criteria to study endocardial recordings have been in terms of organization [16]. Organization indexes aim to detect the ever-changing morphology and timing of these electrograms, reflecting the irregular and complex activation of the atrial tissues during AF.

The existence of an underlying order during AF has been recently suggested shown. In particular both linear [10, 287, 11] and non-linear [12, 141] patterns have been recognized.

Hence, several organization indexes have been reported. These parameters were determined using linear and non-linear approaches, aiming to estimate the organization of the atrial activity either from an inter-electrode or intra-electrode point of view.

From an interelectrode approach, different parameters were calculated such as, cross correlation coefficient, mean spectrum coherence and some indexes obtained from the delays between the depolarizations at two adjacent dipoles. In all of these parameters the results showed the same trend, with a decrease of the correlation between dipoles in the time and frequency domains in the LA during the effect of the anaesthetic and the opposite effect in the RA. In the case of the delay measures, the delays between dipoles activations were higher during the propofol infusion compared with the baseline state in the LA, whereas in the RA the delays decreased under the influence of propofol. Furthermore, with the propofol administration the synchronization index increased in the RA and a decreased in the LA.

In addition, the results from intraelectrode measurements showed a consistent behavior with that obtained from interelectrode analysis. These parameters were extracted from a non-linear characterization with entropy measurements, that showed an increase in the regularity of the atrial signals from the right atrium during the propofol effect, with an opposite effect in the left atrial activity.

The results confirm the capability of linear and non-linear indexes to capture fine changing in the dynamics of atrial signals induced by the injection of the anaesthetic. These parameters revealed that propofol has a different behavior in both atria, increasing the organization of electrical activations in the right atrium, that indicates a high likelihood of AF termination in this area [11]. Moreover the results confirm the correlation between organization and number of wavelets entering the atrial region close to bipolar electrodes, this relation, though never has been proved, has been already suggested by several authors [4, 42, 11].

From the analysis of paroxysmal and persistent AF groups separately, it is possible to observe that in the paroxysmal group the results show the same trend that the results of the whole group, however in the persistent AF group it is observed an augment in the organization indexes in both atria, such as entropy measurements, which exhibited a significant decrement.

In addition, the standard deviation of the delay between depolarizations at adjacent dipoles show a more homogeneous pattern of delays in the LA than in the RA, with not significant differences in the paroxysmal group between baseline and propofol states. Nevertheless, it is possible to observe a more uniform behavior along all the atrial region during the propofol effect in the persistent AF group.

8.1.3 Ventricular rate during the propofol effects

Previous studies that measured the direct effects of propofol on the cardiac conduction system by using intracardiac recording/stimulation in Langendorff-perfused rabbit hearts, showed that propofol prolonged significantly the AV conduction interval at a clinically relevant concentration [322]. Late studies have showed that propofol has no effect on the human electrophysiological properties of the AV node conduction system. It is thus a suitable anesthetic agent for use in patients undergoing ablative procedures [284].

The study results show that this anaesthetic has antiarrhythmic effects, slowing the AF frequency [200]. However the mean AF cycle length increases in the presence of propofol, the mean ventricular cycle length decreases in the paroxysmal AF group. Because the number of atrial impulses bombarding the AV node per time unit is reduced by the anaesthetic, the number of concealed AV node responses also is reduced, which explains the apparently paradoxical changes in ventricular frequency in response to changes in AF frequency [41, 311, 321], with an increase of the periodicity of the RR intervals, manifested as reduced variability of RR intervals [41, 311, 321].

In addition, the correlation between atrial frequency and ventricular frequency is higher in the septum area, as well as the shortest relation between atrial and ventricular rates compared with the basal state in the paroxysmal AF patients. It can be explained because the septum area is the nearest to the AV node, compared with the other recorded areas and, as a consequence, the frequency measured in the septum area should be more similar to that of the wavelets that arrives to the AV node.

On the contrary, the results showed an opposite trend in patients with persistent AF. The ventricular cycle length increases in presence of propofol and the RR activity is not more regular than in the previous state and, as well, the difference between the relation of atrial and ventricular activity is not variable when the atrial activity is collected from different atrial areas. In this case, the changes in ventricular activity does not have any relation with a particular atrial area. Nevertheless, these results need a more in-depth study, due to the small size of the persistent AF database.

The outcomes show that the dominant atrial cycle length to the RR interval relationship and the mean of RR intervals are reduced after propofol infusion in the paroxysmal AF group, suggesting that the ventricular response results from rate-dependent concealment of AF wavelets bombarding the AV node. Nevertheless in the case of the persistent AF group the ventricular rate does not follow the same rule, and the variability of the RR under the propofol effect is lower than in the basal state. However further investigation is needed in this specific AF type.

8.1.4 Limitations

Despite the significant results obtained from this study, several limitations should be taken into account, such as:

- This work is based on an experimental study of behavior of propofol on AF intra-atrial and external recordings, that were registered during ablation procedure. As a result, the length of the recordings is not long enough to the application of some processing techniques, such as the analysis of ventricular activity, where there are few activations, and therefore only short time series are available, that make impossible the application of many techniques described in the section 2.3.1.2 to extract other documented indexes. Moreover with longer registers, the outcome should be very much reliable. Further research should be necessary on this issue with longer registers, in order to find new indicators that complement the information given by the present work.

- In addition, the use of unipolar signals would give some advantages to bipolar electrograms. The unipolar system is not orientation sensitive, because of its virtually indifferent anode, and has been considered to yield larger and morphologically consistent electrograms [323]. Bipolar signals are unequal in amplitude, yet amplitude average obtained with both electrode types is similar. The probability of obtaining a signal much larger or much smaller than the average is greater with bipolar sensing. The orientation of a bipolar electrode within the heart determines the amplitude and slew rate of the electrogram. The orientation can cause either a subtraction or an addition of both unipolar amplitudes at each pole. The addition of two smaller unipolar signals, outputs in most of the cases a bipolar signal larger than the unipolar tip signal.

- Regarding to the database, it should be interesting to have additional information, such as the exact position of the dipoles, since each dipole is not located exactly in the same place in all patients, (however the position of the catheter is the same in baseline conditions and during the anaesthetic effect). In addition, in order to have more significative results, it should be necessary to have a similar number of patients in both paroxysmal AF and persistent AF groups. In addition, another limitation was that in numerous recordings some of the dipoles did not receive any signal due to their wrong placing. This was the reason for a different number of patients in the different analyzes. In the frequency analysis with PCA and PLS algorithms all dipoles were necessary, whereas for the rest of the analysis it was sufficient with some dipoles from each atria. Therefore, most of these restriction should be resolved with an extended database.

8.2 Conclusion

Different indexes have verified the impact of the anaesthetic agent on the atrial electrophysiology, suggesting a predominant antiarrhythmic effect, with different spatial organization along all the atria. From a global point of view, the results confirm the initial hypothesis in the sense that propofol induces some measurable effects in atrial electrical activation during AF. More specifically, in the following we will evaluate at which extent this dissertation provides answers to each one of the objectives initially formulated:

Objective: *Propose different parameters to quantify the spatiotemporal organization over the different atrial areas in baseline and during the propofol effects*

Response: The following algorithms for the quantitative analysis of AF organization have been proposed and applied:

- Cross-correlation of closely spaced bipolar endocardial recordings.
- Cross-spectral analysis or mean of the coherence spectrum of two closely bipolar electrogram to assess the spatial organization.
- Non-linear analysis with entropy measures, used to quantify the irregularity of the wavefront in atrial tissues.
- Parameters extracted from the measurement of the propagation delays between two close dipoles.

As a result, all the parameters showed the same trend with an increase of synchronization and organization in the RA and a decrease in the LA during the anaesthetic effects, where the organization of fibrillating atria presumably indicates its likelihood of termination, information that could be helpful in ablation procedures.

Objective: *Evaluate the propofol effect on atrial rhythm.*

Response: The atrial cycle length is markedly modulated during anaesthesia, since it increased consistently compared to the resting conscious state immediately before and the wavefronts in the atria are more homogenous.

Therefore, the propofol slows the fibrillation rate and is a sign of an effective antifibrillatory action.

Objective: *Evaluate the propofol effect on ventricular rhythm.*

Response: Several standardized parameters to study the ventricular rhythm were evaluated. This study includes the analysis of the AV conduction towards the ventricles, where the relation between atrial and ventricular rates was proposed.

As a conclusion it was noted that the anaesthetic, modifies both the electrophysiological function of the AV node and the atria themselves, with an decrease in the mean RR interval and augment of the AV conduction rate and a more uniform ventricular pattern during the propofol effect.

8.3 Guides for future work

One of the strongest wishes of a researcher at the time of carrying out with his/her doctoral thesis is that the outcomes of this work could be used by other researchers in further research works and have a practical utility in real applications. With this aim, in this section we outline some future research lines derived from the results of this thesis.

The author encourages to focus efforts in the research of other parameters to characterize the atrial signal and the extraction of improved information that could be used for clinical diagnosis and decision of the most appropriate treatment.

8.3.1 Analysis of the atrial and ventricular signals during AF

Although the proposed algorithms for the characterization of atrial and ventricular waves have showed relevant outcomes and promising prospectives for clinical management, it should be remarked that this work requires more experiments about new parameters that can provide more information regarding the nervous system effect and the mechanisms that generate and perpetuate this cardiac arrhythmia. These parameters could be the following, among other:

- Extract features from the time-frequency analysis, regarding the evolution of the atrial frequency with time. In fact, time-frequency and wavelet transforms have been extensively employed for the analysis and characterization of biomedical signals [106]. The wavelet transform can characterize the atrial localized structures by the Lipschitz regularity, which can be obtained from the peak-to-peak amplitudes of the wavelet coefficients at different scales [149] or by variance of the amplitudes along the wavelet decomposition [324].

- During AF the atrial electrogram morphology changes constantly both in time and space. Since the different morphologies reflect different spatial activation patterns such as slow conduction, wave collision and conduction blocks [6], the analysis of the waveform changes of the endocardial signals acquired during AF may play an important role in the understanding of the mechanisms responsible for its induction and maintenance. Thus to estimate their morphological similarity, and to measure the regularity and the extent of repetitiveness over time of the detected activations could be

very helpful to complete the information extracted from the time activations.

- Comparison of electrogram characteristics between both groups, such as, percentage of continuous activity, maximal bipolar voltage during continuous activity, fractionation index, and mean absolute value of dV/dt differed significantly among regions, determination of a fractionation index defined as the number of deflections with an absolute value of > 0.05mV from the baseline, etc.

- Analysis of the ventricular activity in longer registers, which would allow more reliable analyzes, such as histograms and other statistical approaches.

- Comparison of the atrial activity extracted from the electrogram with that extracted from simultaneous non-invasive techniques, such as the ECG.

In addition, a more consistent characterization of the atrial wavefronts could be helpful in a better comprehension of the mechanism of AF. It has been postulated that the site with the highest dominant fibrillation frequency would act as a driver of AF due to the presence of a rapid automatic focus or microreentrant circuit [48, 51, 306, 50]. Furthermore, a spatial gradient in the AF frequencies (progressively decreasing away from the site with the highest dominant frequency) and a relatively high degree of regularity are considered as additional evidence for a focal type of AF [51, 306]. Therefore, it should be possible to extract different subgroups with different behaviors, analyzing if there is any correspondence with the origin mechanism of the AF.

8.3.2 Comparison of different drugs effect in AF

The role of the autonomic nervous system in AF and, in particular, the proarrhythmic effects of sympathetic or vagal activation is not completely known. It is necessary a further study to test the effect of different anaesthetics in ablation procedure and compare these effect with adrenergic drugs and with other ANS stimulation. It could be helpful for selecting the most appropriate treatment of AF, providing a better knowledge about the arrhythmia.

Study of AF under other anaesthetics The analysis of AF recordings under the effects of other anaesthetic drugs, such as the proposed in the chapter 2.4.4, could be studied. These studies should obtain information for the diagnosis of the electropathological substrate of AF and to monitor the drugs effects on ablation procedures.

Study of AF under adrenergic activation The analysis of AF recordings under the effects of sympathomimetic drug should evaluate whether changes in adrenergic control mechanisms could influence determinism and dynamics of atrial signals during AF.

Exercise and Tilt Test: The autonomic mechanism in patients with AF under exercise and tilt testing can be investigated in comparison with changes during the circadian rhythms, and specially during sleep time. Neurocardiogenic syncope is often characterized by diminished baroreflex sensitivity during the hypotension period. Reported cases with an increase of baroreflex sensitivity preceding the onset of AF in tilt testing may indicate the involvement of a vagally mediated mechanism. In addition, other studies have reported a sympathetic activation by exercise that modulates atrial electrophysiology in some patients which can be monitored using time-frequency analysis. These studies conduce that higher baseline fibrillatory rates are associated with less autonomic modulation indicating advanced electrical remodeling [325].

8.3.3 Clinical applications

As it has been aforementioned, one of the clinical applications derived from the analysis of atrial electrograms, is that may allow individual evaluation of the atrial substrate, thus providing a basis for selecting the most appropriate treatment of AF. Other possible applications in which the analysis of the AF could play an important role are:

Contribute to the termination of AF episodes:

In AF pacing, it is now well established that AF has a small excitable gap and, thus, can be induced by overdrive stimulation [261]. The determination of AF organization can be used to optimize both the time and the site of pacing leading to AF termination. In electrophysiological studies, the manual classification of atrial electrograms, usually performed according to Wells's criteria [326], is widely used to give a morphological characterization of AF and has been related to the anatomic location and to the results of radiofrequency catheter ablation [327, 7]. In fact, the spatial organization over the different atrial regions can be helpful in ablation therapies. Indeed, the real-time evaluation of the spatial distribution of AF regularity may guide the definition of the optimal ablative pathway. Furthermore, it has been recently demonstrated that the success of electrical cardioversion is improved during periods of plain AF organization [8].

Choosing an appropriate AF treatment: The evaluation of the regularity of intra-atrial electrograms recorded during AF may also play an important role in new strategies developed for the treatment of AF, such as electrical cardioversion, overdrive pacing, and catheter ablation. In addition, the capability of the proposed indexes to detect changes associated with a antiarrhythmic drug infusion could also be employed to analyze the physiological mechanisms by which these drugs act on the atrial conduction and the way they contribute to the termination of AF episodes.

8.3.4 Transfer of technology

Currently, quantification of propofol effects in AF organization has been already studied. The next step is the transfer of technology of the advances obtained in research groups at the university towards social services (i.e. hospitals and other sanitary centers).

This doctoral thesis is an example of the collaboration between both institutions. It was a proposal of the arrhythmia unit at the Hospital Clínico San Carlos in Madrid to study this medical problem, and subsequently the transference of the results for their application in the clinical routine.

Chapter 9

Contributions

As it occurs in most research works, this dissertation can not be regarded as an isolated item. On the contrary, it has been developed within the framework of current research projects, and having established close contacts with other research groups and institutions. In addition, the most important advances achieved in this thesis have been divulged in top level conferences and journals with high impact factor indexes.

9.1 Publications

This thesis is supported by the fact that the objectives specified in the introductory chapter have been published in three journals, and another article related with it, all them listed in the Scientific Citation Index. In addition, a two more journal papers have been also submitted and is currently under revision.

- The effect of propofol on the dominant frequency of atrial activity in AF has been published in the paper entitled **Anesthesia with Propofol slows atrial fibrillation dominant frequencies**, which appeared in *Computers in Biology and Medicine* [200]. This publication analyzes the variation of the atrial frequency in the different atrial regions under the propofol effects and in baseline conditions.

- The methods that exploits the spatiotemporal properties of AF signals during the anaesthetic effect has been published in the paper entitled **Atrial fibrillation organization: quantification of propofol effects**, which appeared in *Medical & Biological Engineering & Computing* [301]. This publication analyzes different organization indexes, extracting information about the spatial organization distribution over the atria available in AF recordings.

- The effect of propofol on the ventricular rhythm has been published in the paper entitled **Ventricular rhythm in atrial fibrillation under anaesthetic infusion with propofol**, which appeared in *Physiological Measurement* [328]. This publication analyzes the ventricular rate and the atrio-ventricular conduction under the propofol effects and in baseline conditions.

  In addition, a previous journal paper related to AF analysis has been also published:

- The method that is able to predict the successful of the AF cardioversion has been included in the paper entitled **Wavelet analysis of electrocardiograms to characterize recurrent atrial fibrillation**, which appeared in *Journal of the Franklin Institute* [106]. This publication exploits the wavelet transform of the ECG to transform the initial derivation into a multichannel formulation, extracting parameters to predict the subsequence recurrences to a successful electrical cardioversion.

In addition, the main contributions of this thesis have been spread in diverse conferences, with a high acceptance degree in such different areas as biomedical engineering [324, 329], cardiology [330] and even in dedicated conferences to ICA and PLS [331, 332].

9.2 Framework of the dissertation

This dissertation has been carried out within the *Bioengineering, Electronics and Telemedicine Research Group* (BeT) at *Universitat Politècnica de València* and the *Innovation in Bioengineering Research Group* (IBIG) at *Universidad de Castilla-La Mancha*. The researchers in the Bioengineering area, leaded by Dr. Francisco Castells and Dr. César Sáncher, respectively have contrasted expertise in the analysis of cardiac arrhythmias from the ECG, especially in techniques for atrial activity estimation from AF superficial recordings [264, 78, 333]. Subsequently, the challenging problem was the characterization of the atrial signal and the extraction of improved information that could be used for clinical diagnosis, decision of the most appropriate treatment, and as in this specific case, monitoring of drug effects.

9.2.1 Research projects

This work has been developed within the framework of several research projects. The interest and relevance of the research activity carried out in the BeT and IBIG groups have been acknowledged by public administrations, which have contributed with important economical support to the following research projects:

- Junta de Comunidades de Castilla-La Mancha. Consejería de Educación Y Ciencia.

  Parametrización de episodios de fibrilación Auricular mediante wavelet blind separation y otras técnicas de procesado digital avanzadas. Estudios de viabilidad en su aplicación clínica .

  From Jun. 22nd, 2005 until Jun. 22nd, 2007.

- Ministerio de Ciencia y Tecnología.

  Exploración de nuevas técnicas de procesado y análisis de la fibrilación auricular. Aportación de los sistemas Multi-derivación.

  From Dec. 31st, 2005 until Dec. 31st, 2008.

- Ministerio de Ciencia y Tecnología.

  Sistema integral de análisis de la señal eléctrica cardiaca para la evaluación de arritmias supraventriculares.

  From Dec. 31st, 2008 until Dec. 31st, 2009.

9.2.2 International research stages

During the development of this doctoral thesis, a 6 months research internship was realized within the group led by the Professors Richard Reilly and Conor Heneghan at the Multimodal Signal Processing Research Group in the School of Electrical, Electronic and Mechanical Engineering in the College of Engineering, Mathematics and Physical Sciences at University College Dublin (Ireland) and as well with the Neural Engineering Group led by the Professor Richard Reilly at Trinity College Dublin. During these internships, a joint project was started for the analysis of AF from the intracardiac recordings, with the aim of obtaining improved knowledge with clinical interest.

9.2.3 Collaborations

Within the general framework of this thesis, the contacts with the following research groups and institutions have been established and reinforced:

Hospital Clínico Universitario de Valencia, Spain. The cardiologists at the *Unidad de Arritmias*, leaded by Dr. Julián Pérez Villacastín, have provided the database of AF recordings. In addition, they have provided invaluable knowledge regarding fundamentals of AF, its interpretation from electrogram recordings, patient monitoring and effective treatment therapies. Several publications are result of this collaborative work [200, 301].

University of Dublin. Trinity College Dublin, Ireland. Professor Richard Reilly is currently the Director of the Trinity Centre for Bioengineering. After carrying out a internship within his research group, the

author is further collaborating with Prof. Reilly in a joint work whose main objective is to study the organization of the AF patients during the effect of the anaesthetic [301].

University College Dublin, Ireland. Professor Conor Heneghan is one of the professors at the Multimodal Signal Processing Research Group. After carrying out a internship within his research group, the author is further collaborating with Dr. Heneghan in a joint work whose main objective is to study the atrial activity extraction from electrogram recordings during AF [331].

Appendix A

Principal component analysis

These techniques have been widely employed in statistical data analysis, feature extraction and data compression. The main goal of PCA is to reduce the redundant information contained in a certain data set. With this purpose, PCA searches for a smaller set of features with less redundancy, but practically achieving as good representation as the original data.

The main idea of PCA is to find a linear transformation of a random vector $\mathbf{x}$ with n elements into another vector $\mathbf{y}$ with m orthogonal elements, $m \leq n$, such that the variances of the projections of $\mathbf{x}$ on the new coordinate axes are maximised. Hence, the first principal component corresponds to the direction of maximal variance, the second principal component is computed in an analogous manner, but with the restriction of being contained in the orthogonal subspace to the first axis, and this process is repeated until obtaining a total number of m components. Mathematically, the first principal component y_1 can be derived as a linear combination of $\mathbf{x}$

$$y_1 = \mathbf{w}_1^T \mathbf{x}, \tag{A.1}$$

where $\mathbf{w}_1^T$ is the unit vector that maximises $\mathrm{E}\{y_1^2\}$. For m principal components, each principal component y_i, $1 \leq i \leq m$, is computed from

$$y_i = \mathbf{w}_i^T \mathbf{x}, \tag{A.2}$$

where $\mathbf{w}_i^T$ is the unit vector that maximises the variance of y_i, with the restriction that

$$\mathrm{E}\{y_i y_j\} = 0, \qquad j \neq i. \tag{A.3}$$

In algebraic terms, the vectors $\mathbf{w}_i^T$ are also known as the eigenvectors of the covariance matrix of $\mathbf{x}$

$$\mathbf{C}_x = \mathrm{E}\left\{\mathbf{x}\mathbf{x}^T\right\}. \tag{A.4}$$

As a result of this process, PCA outputs a set of m uncorrelated random variables. The covariance matrix of the principal components is

$$\mathbf{C}_y = \begin{bmatrix} \sigma_1^2 & 0 & \cdots & 0 \\ 0 & \sigma_2^2 & & \vdots \\ \vdots & & \ddots & \\ 0 & \cdots & & \sigma_m^2 \end{bmatrix}. \tag{A.5}$$

The order of the principal components is such that $\sigma_1^2 \geq \sigma_2^2 \geq \ldots \geq \sigma_m^2$, with σ_i corresponding to the y_i-th component. The number of principal components can also be chosen. In many applications there is a high amount of data that can be represented with few features. The number of principal components can be truncated taking into account the eigenvalue sequence of the covariance matrix, so that the sum of the variances of the retained components reaches at a certain threshold. This is also applicable in the signal-noise model

$$\mathbf{x} = \mathbf{A}\mathbf{s} + \mathbf{n}, \tag{A.6}$$

where $\mathbf{n}$ is the vector corresponding to additive white Gaussian noise. In this case, the principal components can be usually grouped in two orthogonal spaces: the signal subspace and the noise subspace. The components corresponding to the noise subspace usually present much lower variance values than the components corresponding to the signal subspace. From the eigenvalue sequence, it is frequently possible to detect a sharply decreasing value at the first element corresponding to the noise subspace. Hence, the number of principal components can be truncated in order to discard the noise and keep only the signal part.

In signal processing terms, principal component analysis is closely related to blind source separation. In a first approximation, independence can be measured from the second order statistics of the signals. As a result, it can be stated that the more correlated two random variables are, the more mutual dependence they have. Since PCA searches for uncorrelated random variables, the independent sources could be approximated in a first instance by the principal components. However, from the definition and fundamentals of PCA, it can be derived that the principal components would only match the original sources in the case of an orthogonal mixture, i.e. orthogonal columns in the matrix $\mathbf{A}$.

A closed-form solution can be obtained from the singular value decomposition (SVD) of the data vector $\mathbf{x}$:

$$\mathbf{x} = \mathbf{u}\mathbf{S}\mathbf{v}^T, \tag{A.7}$$

where $\mathbf{S}$ is a diagonal matrix, and $\mathbf{u}$ and $\mathbf{v}$ contain orthogonal vectors so that the property $\mathbf{u}\mathbf{u}^\mathbf{T} = \mathbf{v}^\mathbf{T}\mathbf{v} = \mathbf{I}$ is accomplished, with $\mathbf{I}$ the identity matrix. The

correlation matrix $\mathbf{C}_x$ can be calculated from A.4 and A.7. Taking into account that the independent sources $\mathbf{s}$ are uncorrelated, and considering them with zero mean and unit variance:

$$\mathbf{C}_x = \mathrm{E}\left\{\mathbf{x}\mathbf{x}^T\right\} = \mathbf{A}\mathrm{E}\left\{\mathbf{s}\mathbf{s}^T\right\}\mathbf{A}^T = \mathbf{A}\mathbf{A}^T \tag{A.8}$$

$$\mathbf{C}_x = \mathbf{u}\mathbf{S}\mathbf{v}^T\left(\mathbf{u}\mathbf{S}\mathbf{v}^T\right)^T = \mathbf{u}\mathbf{S}\left(\mathbf{u}\mathbf{S}\right)^T. \tag{A.9}$$

From these results, the so-called whitening matrix $\mathbf{W}$ can be obtained as

$$\mathbf{W} = \left(\mathbf{u}\mathbf{S}\right)^{-1}, \tag{A.10}$$

hence the uncorrelated or whitened signals $\mathbf{z}$ can be determined by applying the whitening matrix to the observations

$$\mathbf{z} = \mathbf{W}\mathbf{x}. \tag{A.11}$$

It is important to notice the implicit indeterminacies of the whitening process. Since the main goal is to obtain uncorrelated sources, the desired information is only contained in the signal waveform. Scaling factors and sign indeterminacies are allowed. For instance, let us consider two independent signals. If their amplitudes are changed each by a scaling factor they still remain uncorrelated. And if the sign of one of the sources is changed, the cross-correlation coefficients have still null values. Indeed, any variation of the mixing matrix $\mathbf{A}'$ that accomplishes

$$\mathbf{A}' = \mathbf{P}\mathbf{D}\mathbf{A}, \tag{A.12}$$

where $\mathbf{P}$ and $\mathbf{D}$ are permutation and diagonal matrices, respectively, would output exactly the same principal components, although their ordering could change according to the new eigenvalue sequence. The restriction usually imposed by whitening algorithms is to consider that the original sources are random variables with zero mean and unit variance.

Appendix B

Partial Least Squares

Partial Least Squares (PLS) is a wide class of methods for modeling relations between sets of observed variables by means of latent variables (LVs). It comprises regression and classification tasks, as well as dimension reduction techniques and modeling tools. The underlying assumption of all PLS methods is that the observed data is generated by a system or process which is driven by a small number of latent (not directly observed or measured) variables. Projections of the observed data to their latent structure by means of PLS were developed by Herman Wold and coworkers [271].

PLS has received a great amount of attention in the field of chemometrics. The success of PLS in chemometrics resulted in a lot of applications in other scientific areas including bioinformatics, food research, medicine, pharmacology, social sciences, physiology among other [268, 334, 266, 265, 269, 267].

In its general form PLS creates orthogonal score vectors (also called latent vectors or components) by maximising the covariance between different sets of variables. PLS is similar to Canonical Correlation Analysis (CCA) where latent vectors with maximal correlation are extracted [335]. There are different PLS techniques to extract latent vectors, and each of them gives rise to a variant of PLS.

PLS can be naturally extended to regression problems. The predictor and predicted (response) variables are each considered as a block of variables. PLS then extracts the score vectors which serve as a new predictor representation and regresses the response variables on these new predictors. The natural asymmetry between predictor and response variables is reflected in the way in which score vectors are computed. This variant is known under the names of PLS1 (one response variable) and PLS2 (at least two response variables).

The effectiveness of PLS has been studied theoretically in terms of its variance [336] and its shrinkage properties [337]. The performance of PLS is investigated in several simulation studies [338]. PLS can also be applied to classification problems by encoding the class membership in an appropriate indicator matrix.

There is a close connection of PLS for classification to Fisher Discriminant Analysis (FDA). PLS can be applied as a discrimination tool and dimension reduction method, in a similar manner as Principal Component Analysis (PCA) [339].

Consider the general setting of a linear PLS algorithm to model the relation between two data sets (blocks of variables). Denote by $X \subset R^N$ an N-dimensional space of variables representing the first block and similarly by $Y \subset R^M$ a space representing the second block of variables. PLS models the relations between these two blocks by means of score vectors. After observing n data samples from each block of variables, PLS decomposes the $(n \times N)$ matrix of zero-mean variables $\mathbf{X}$ and the $(n \times M)$ matrix of zero-mean variables $\mathbf{Y}$ into the form

$$X = TP^T + E \tag{B.1}$$
$$Y = UQ^T + F \tag{B.2}$$

where the $\mathbf{T}$, $\mathbf{U}$ are $(n \times p)$ matrices of the p extracted score vectors (components, latent vectors), the $(N \times p)$ matrix $\mathbf{P}$ and the $(M \times p)$ matrix $\mathbf{Q}$ represent matrices of loadings and the $(n \times N)$ matrix $\mathbf{E}$ and the $(n \times M)$ matrix $\mathbf{F}$ are the matrices of residuals. The PLS method, which in its classical form is based on the nonlinear iterative partial least squares (NIPALS) algorithm [340], finds weight vectors $\mathbf{w}$, $\mathbf{c}$ such that

$$[cov(\mathbf{t}, \mathbf{u})]^2 = [cov(\mathbf{Xw}, \mathbf{Yc})]^2 = max_{|\mathrm{r}|=|\mathrm{S}|=1}[cov(\mathbf{Xr}, \mathbf{Ys})]^2 \tag{B.3}$$

where $cov(\mathbf{t}, \mathbf{u}) = \mathbf{t}^T\mathbf{u}/n$ denotes the sample covariance between the score vectors $\mathbf{t}$ and $\mathbf{u}$. The NIPALS algorithm starts with random initialisation of the Y-space score vector $\mathbf{u}$ and repeats a sequence of the following steps until convergence.

1. $\mathbf{w} = \mathbf{X}^T\mathbf{u}/(\mathbf{u}^T\mathbf{u})$
2. $\|\mathbf{w}\| \rightarrow 1$
3. $\mathbf{t} = \mathbf{Xw}$
4. $\mathbf{c} = \mathbf{Y}^T\mathbf{t}/(\mathbf{t}^T\mathbf{t})$
5. $\|\mathbf{c}\| \rightarrow 1$
6. $\mathbf{u} = \mathbf{Yc}$

Note that $\mathbf{u} = y$ if $M = 1$, that is, $\mathbf{Y}$ is a one-dimensional vector that we denote by y. In this case the NIPALS procedure converges in a single iteration.

It can be shown that the weight vector $\mathbf{w}$ also corresponds to the first eigenvector of the following eigenvalue problem [341]

$$\mathbf{X}^T\mathbf{Y}\mathbf{Y}^T\mathbf{X}\mathbf{w} = \lambda\mathbf{w} \tag{B.4}$$

The $\mathbf{X}$ and $\mathbf{Y}$ space score vectors $\mathbf{t}$ and $\mathbf{u}$ are then given as

$$\mathbf{t} = \mathbf{X}\mathbf{w} \qquad \text{and} \qquad \mathbf{u} = \mathbf{Y}\mathbf{c} \tag{B.5}$$

where the weight vector $\mathbf{c}$ is define in steps 4 and 5 of NIPALS. Similarly, eigenvalue problems for the extraction of $\mathbf{t}$, $\mathbf{u}$ or $\mathbf{c}$ estimates can be derived [341]. The user then solves for one of these eigenvalue problems and the other score or weight vectors are readily computable using the relations defined in NIPALS.

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