

The Application of Spectral Analysis of the  
Surface Electrocardiography Prior to Direct  
Current Cardioversion in Patients with  
Persistent Atrial Fibrillation

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## 1 Abstract

**Aims:** The decision of treatment strategy made for atrial fibrillation (AF) patients is ideally based on individual atrial remodeling. Electrical remodeling is believed to influence the outcome of direct current cardioversion (DCC) of persistent AF. Characterization of AF from the surface electrocardiography (ECG) using spectral analysis is able to quantify atrial electrical remodeling. Applying spectral analysis of the surface ECG in patients with persistent AF undergoing DC cardioversion, the present study is aiming to (1) determine the feasibility of spectral analysis in estimating the dominant frequency (DF), median frequency (MF), and frequency bandwidth (FB) from the surface ECG; (2) assess and compare the QRS-T removal performance of two algorithms, average beat subtraction (ABS) and singular value decomposition (SVD); (3) detect if there are consistent changes of DF between leads V1 and V6, which may reflect the left-to-right atrial gradient; (4) explore the utility of this ECG spectral analysis technique for prediction of DCC outcome and the value of clinical and echocardiographic variables in predicting the outcome of DCC was evaluated as well.

**Methods and results:** This study cohort consisted of 11 consecutive patients (9 men, the mean age  $64 \pm 10$  years) with persistent AF (the median duration 5 months, range 1 to 108 months) undergoing elective external cardioversion with three shock attempts at most. Shock results were observed. Three 10-second segments of the 12-lead digital ECG were obtained for each subject prior to cardioversion. After filtering, QRS-T complexes were removed from the ECG using both ABS and SVD. Frequency power spectra were generated by Fourier transformation of the remaining atrial signal ECG. The DF, MF and FB were determined in the corresponding power spectrum. The dominant rate (DR) was obtained from the conversion of DF. Due to the small population, no attempt was made to do statistical analysis and the data was generally described.

The atrial signal extraction performance was compared between these two algorithms by visually inspecting the number of leads that had residual truncated QRS-T waves. It was shown that although neither ABS nor SVD

performed perfect with much residual ventricular activity in the remaining ECG, SVD caused less QRS-T-related residuals when compared with ABS in all subjects.

The mean value of DR obtained using SVD was slightly lower in people who were successfully converted to sinus rhythm (SR) than in those with final shock failure ( $392 \pm 52$  fpm vs.  $404 \pm 39$  fpm). The mean DR of the subgroup where SR was initiated by one single shock was further lower when compared with the remaining subjects ( $358 \pm 7$  vs.  $413 \pm 44$  fpm). A consistent pattern was observed for the DF of atrial activity to be faster in lead V1 than in lead V6, with a frequency difference between 0.4 and 2.0 Hz. The distinction between the DFs from leads V1 and V6 was obviously higher in subjects with successful DC cardioversion than in those with failed cardioversion ( $1.48 \pm 0.47$  vs.  $0.15 \pm 0.78$  Hz). In addition, the three highest DF alternations existed in the subjects who were converted to SR by only one shock, which resulted in a further higher mean gradient in this group than in the remaining people who had at least one failed shock ( $1.77 \pm 0.32$  vs.  $0.45 \pm 0.77$  Hz).

Conclusion: Spectral analysis of the surface ECG is feasible to non-invasively assess the DF, MF, and FB in patients with persistent AF. With less leads containing visual ventricular activity, the QRS-T subtraction performance of SVD might be superior to that of ABS. The DR converted from the DF would be useful in predicting shock results in patients with persistent AF. The atrial gradient could be reflected by the difference between the measurements of DF from leads V1 and V6. The atrial gradient detected from the ECG prior to cardioversion might be an important predictor for initial success of electrical cardioversion. This finding might be useful in identifying suitable candidates for DCC to avoid unnecessary cardioversion attempts and expect a higher likelihood of shock success. Due to the limitations of the present study, the results need to be verified by more investigations.

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## 6 List of abbreviations and acronyms

ABS	average beat subtraction
ACEI	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
AERP	atrial effective refractory period
AF	atrial fibrillation
AF-CHF	Atrial Fibrillation and Congestive Heart Failure
AFCL	atrial fibrillation cycle length
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
AFL	atrial flutter
APB	atrial premature beat
ARB	angiotensin receptor blocker
AS	aortic stenosis
ATHENA	A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg b.i.d. for the prevention of cardiovascular Hospitalisation or death from any cause in patiENTs with Atrial fibrillation/atrial flutter
ATRIA	AnTicoagulation and Risk factors In Atrial fibrillation
AVR	aortic valve replacement
BB	Bachmann's bundle
BMI	body mass index
bpm	beats per minute
CABG	coronary artery bypass graft
CCB	calcium channel blocker
CHD	coronary heart disease
CHF	congestive heart failure
CHS	Cardiovascular Health Study
COPD	chronic obstructive pulmonary disease
CS	coronary sinus
CVA	cerebrovascular accident
DBP	diastolic blood pressure
DCC	direct current cardioversion

DF	dominant frequency
DM	diabetes mellitus
DR	dominant rate
ECV	electrical cardioversion/external cardioversion
ECG	electrocardiography
EG	electrogram
EHRA	European Heart Rhythm Association
EMI	electromechanical index
ESC	European Society of Cardiology
FB	frequency bandwidth
FFT	fast Fourier transform
fpm	fibrillations per minute
HOT CAFÉ	How to Treat Chronic Atrial Fibrillation
Hz	hertz
ICA	independent component analysis
INR	international normalized ratio
IPP	inferoposterior pathway
IRAF	immediate recurrence of atrial fibrillation
J	joule
LA	left atrium
LAD	left atrial diameter
LVEF	left ventricular ejection fraction
MF	median frequency
MI	myocardial infarction
ms	millisecond
NS	not significant
NYHA	New York Heart Association
PCA	principal component analysis
PIAF	Pharmacological Intervention in Atrial Fibrillation
Pnt	patient
PTCA	percutaneous coronary angiography
PV	pulmonary vein
PVI	pulmonary vein isolation

QoL	quality of life
RA	right atrium
RAAS	renin-angiotensin-aldosterone system
RACE	RAte Control versus Electrical cardioversion for persistent atrial fibrillation
RCA	right coronary artery
SBP	systolic blood pressure
SD	standard deviation
SR	sinus rhythm
STAF	Strategies of Treatment of Atrial Fibrillation
STC	spatiotemporal QRST cancellation
SVC	superior vena cava
SVD	singular value decomposition
TTE	transthoracic echocardiography

## **7 Introduction**

### **7.1 Atrial fibrillation**

#### **7.1.1 Definition of atrial fibrillation**

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice, especially in the elderly population. It can be diagnosed by detection of irregular multiform f waves instead of P waves in an electrocardiography (ECG) with an irregularly irregular ventricular rhythm. The atrial fibrillatory rate is usually variable and  $>300$  fpm (atrial fibrillatory frequency  $> 5$  Hz, or atrial fibrillatory cycle length  $<200$  ms). The morphologies of atrial f waves can vary from coarse, medium to fine, or not visible at all (1, 2).

According to 2010 guidelines for the management of AF by the European Society of Cardiology (ESC), AF is classified to five forms: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF (1).

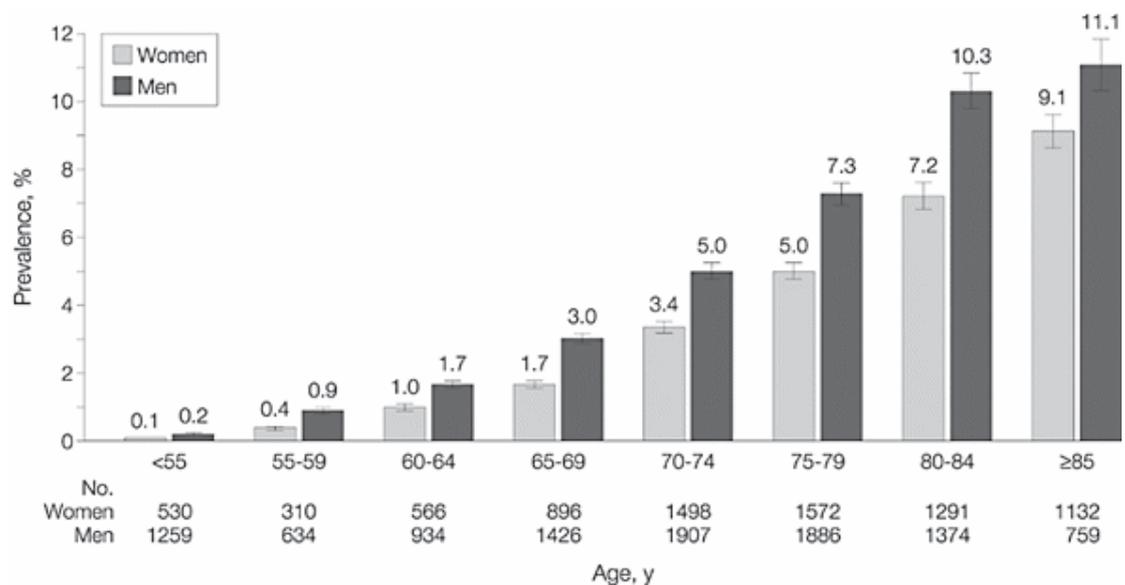
1. First diagnosed AF is the diagnosed episode of AF presented in patients for the first time, no matter how long the episode lasts or how the AF-related symptoms present. It could be paroxysmal, persistent, long-standing persistent, or permanent AF described as below.
2. Paroxysmal AF are spontaneous convertible, and usually within 48 h, not longer than 7 days duration. The significance of the 48 h time point is emphasized by the fact that self-termination is low after this point and anticoagulation treatment is suggested.
3. Persistent AF is considered an AF episode that presents longer than 7 days or needs interventions for termination.
4. Long-standing persistent AF is the episode longer than 1 year when rhythm control is considered to restore sinus rhythm (SR).
5. Permanent AF is the accepted condition by the patient (and physician) when it fails to restore SR or the determination to avoid rhythm control has been made. It will be redesignated as 'long-standing persistent AF', when cardioversion is adopted.

### 7.1.2 Epidemiology of AF

AF has been confirmed to be a highly prevalent condition by a large number of population-based epidemiological studies (3-14). The prevalence, incidence and lifetime risks of AF are the most common concepts used to describe AF epidemiology.

#### 7.1.2.1 Prevalence of AF

The prevalence of AF refers to the percentage or the number of people with AF in a defined population at one point in time. As estimated, the overall AF prevalence is 1-2% in the population (3, 4, 15) and it increases with age (3, 5, 6, 16, 17), ranging from 0.1% at the age 40-44 years to 10% of people over 80 years of age (16). In terms of sex distribution, AF more often happened in men than women at all ages (Figure 1) (3, 5, 6, 15, 17).



**Figure 1 Prevalence of AF stratified by age and sex. Reprinted from Go et al. (3)**

#### Early investigations

The Framingham heart study is one of the studies providing valuable information about the epidemiology of AF in the early years. The original Framingham study, a longitudinal study initiated in 1948, has biennially followed 5,209 men and women, aged 28 to 62 years, without history of cardiovascular disease at enrollment, to prospectively observe the development of cardiovascular disease (18). The AF epidemiology study by Wolf et al is based

on the original cohort of the Framingham Study, with 5,070 subjects followed-up for 34 years. The results of the study shows that the prevalence of AF was high and strongly associated with advanced age, ranging from 0.5% in age group 50 to 59 years to 8.8% in individuals aged 80 to 89 years. Using the subjects aged 65 to 84 years in the Framingham Study cohort from 1968 to 1989, Wolf et al. later reported the increasing trends in the age-adjusted prevalence of AF with a 3-fold increase and a 2-fold increase for men and women respectively (9).

Apart from the Framingham Heart Study, there are a number of similar population-based AF prevalence studies in the early years.

Western Australia study collected prospective data in a sample of the elderly population of Busselton, Western Australia. Among 1770 participants aged above 60 years, 87 developed new AF episodes during the triennial surveys from 1966 to 1983. Therefore, it is estimated that 15/1000 of Western Australia population was affected by AF, which strongly suggested that AF was prevalent in the elderly (10).

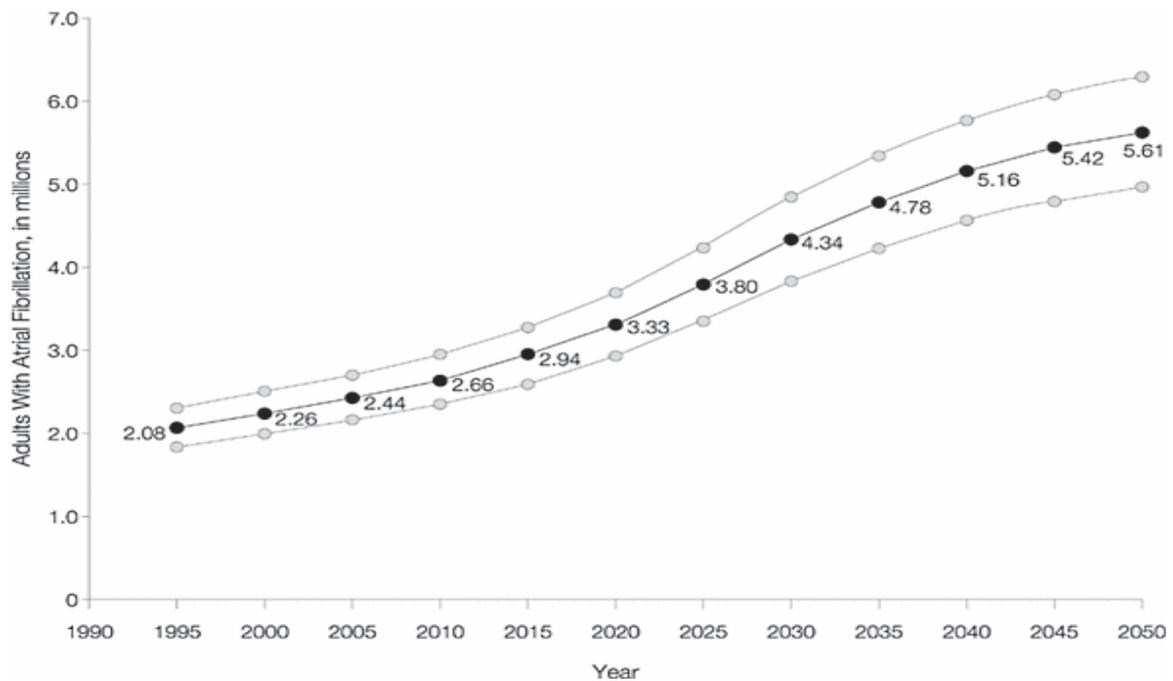
In 1986, Mayo clinic study retrieved medical records of 2,122 subjects aged 35 years or older from the epidemiologic system in Rochester, Minnesota. The prevalence of atrial fibrillation or flutter was estimated as 2.8% (4). The Cardiovascular Health Study (CHS) focused on the prevalence of AF in older adults. This population-based, longitudinal study recruited and examined 5,201 adults aged  $\geq 65$  years old between 1989 and 1990. According to the manifestation of cardiovascular disease, the results of the study are stratified to three groups: in the patients with clinical cardiovascular disorder, the prevalence of AF was as high as 9.1%; in participants with only subclinical cardiovascular disease, and in people without any evidence of cardiovascular disease, neither clinical nor subclinical, the estimated prevalence number is 4.6% and 1.6%, respectively (11).

### Recent investigations

Recently, there are several large studies estimating AF epidemiology, including its age and gender distribution, time trends in AF prevalence. Table 1 summarizes the results of four recent AF epidemiology studies in the United States (3, 5, 12, 16).

In 1995, to define the prevalence of AF in the United States, Feinberg et al summed up the data from four previous studies, which have been introduced above: the Framingham study, Western Australia study, Mayo clinic study, and CHS. It was reported that the prevalence of AF was 0.89% (around 2.23 million) in total US population, 2.3% in the population older than 40 years, and 5.9% in people above 65 years old. About 70% of people affected by AF were 65 to 85 years of age (16).

Using California outpatient diagnoses and ECG findings in health plan database, the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study, a cross-sectional study, identified 17,974 AF patients from 1.89 million subjects aged 20 years or older between 1996 and 1997. It was reported that AF was found in 0.95% the total population, 3.8% adults  $\geq 60$  years, and 9.0% persons  $\geq 80$  years. More than half of the individuals with AF were 80 years or older. In addition, the ATRIA study projected the future prevalence. Figure 2 demonstrates that the number of people with AF was about 2.3 million in the U.S. in 2000, which is likely to increase to 5.61 million (2.5-fold) by the year 2050 (3).



**Figure 2 Projected prevalence of AF in the United States between 1995 and 2050. Reprinted from Go et al. (3)**

Olmsted County, Minnesota, study also projected AF prevalence over 50 years. The study determined that AF affected 2.5% (5.1 million) people in 2000. Based on the United States census, it is projected that a number of 12.1-15.9 million (three-fold increase from the year 2000) US people would be with AF by 2050 (5).

To reveal the current and future prevalence of AF and/or AFL in the United States, Naccarelli et al. reviewed the data of 21.6 million subjects aged  $\geq 20$  years from a large US database in 2004 -2005. It was estimated that 1.03% (3.03 million) persons were with AF in the US population in 2005. The prevalence of AF in 2050 was projected as 7.56 million for AF (12).

Obviously, there are discrepancies among the results of these studies. This may be due to different AF diagnoses method or various study populations. However, these studies concluded that the current prevalence of AF is as high as 1-2% and is likely to increase significantly during the following decades.

**Table 1 Recent AF epidemiology studies in the United States**

Study	Year	Subjects	Current prevalence of AF	Projected prevalence of AF	Age-specified prevalence of AF
Feinberg et al. (16)	1995	Summed up the data from: Framingham study (14) Western Australia study (10) Mayo clinic study (4) CHS (11)	0.89% (2.23 million)	-	≥40 years old: 2.3% ≥65 years old: 5.9% 65 to 85 years old account for 70% people with AF
ATRIA Study (3)	1996-1997	1.89 million subjects aged 20 years or older from California outpatient diagnoses and ECG findings in health plan database	0.95% (2.3 million) in 2000	5.61 million in 2050 (2.5-fold)	≥ 60 years: 3.8% ≥80 years: 9.0% ≥80 years old account for more than 50% people with AF
Olmsted County, Minnesota, study (5)	1980-2000	4618 adults in the Midwest of the U.S. with a history of AF	2.5% (5.1 million) in 2000	12.1-15.9 million in 2050 (3-fold)	-
Naccarelli et al. (12)	2004-2005	21.6 million subjects aged ≥20 years from a large US database	1.03% (3.03 million) in 2005	7.56 million in 2050	-

### **7.1.2.2 Incidence of AF**

Incidence of AF is another measure to describe AF epidemiology. It is defined as the rate of new cases occurring in a population during a period of time. It is usually obtained from a population follow-up study.

The previous described Olmsted County, Minnesota, study reported that the age and sex-adjusted incidence of AF was 3.04 per 1000 person-years in 1980 and 3.68 in 2000, with a trend of 0.6% relative increase per year during the study period from 1980 to 2000 (5).

After excluding the subjects with AF or a pacemaker at entry, Psaty et al. used the same sample from the previous described CHS to examine the incidence of AF in the elderly population between 1989 and 1993. With annually examination for up to 3 years, 304 were identified to be with new onset of AF among 4844 subjects, accounting for an incidence of 19.2 per 1000 person-years. The incidence of AF was also associated with age and gender. There were 17.6 and 10.1 cases per 1,000 person-examinations for men and women aged 65 to 74 years, respectively, compared with 42.7 and 21.6 cases among persons aged 75 to 84 years (13).

### **7.1.2.3 Lifetime risk of AF**

Lifetime risk is a measure of the risk for development of AF. A one in four lifetime risk of AF development in people at middle age was reported by two large epidemiologic studies, the Rotterdam Study (7) and the Framingham Study (8).

The former study is a European population-based prospective cohort study between 1990 and 1999. With 6,808 subjects aged 55 and above, the study reported that the lifetime risks to develop AF were 23.8% and 22.2% for men and women at the age of 55 years old, respectively (7). These estimated lifetime risks were similar to the results from the Framingham Study.

Lloyd-Jones et al. examined the lifetime risks of AF development in 3,999 men and 4,726 women aged 40 to 94 years from 1968 to 1999 in the Framingham study cohort. It is reported that lifetime risks for AF were 26.0% for men and 23.0% for women at age 40 years. Even for the individuals without underlying congestive heart failure (CHF) or myocardial infarction (MI), lifetime risks for AF were approximately one in six (8).

Overall, although the level of AF epidemiology is shown considerably high in the investigations, there is possibility that it is still underestimated. This may be due to common asymptomatic AF (1) or failure to detect AF at the follow-up time. The significantly increasing epidemiology of AF could be partly explained by the growing proportion of elderly population and increasing prevalence of the predisposing conditions of AF, such as myocardial infarction, heart failure, and valve heart disease. Therefore, optimal prevention and treatment strategies need to be developed to slow the increasing challenge of AF.

### **7.1.3 Clinical outcomes of AF (AF-related mortality and morbidity)**

The promotional impact of AF on mortality and morbidity has been confirmed. It is widely believed that AF is correlated with increased risks of death, stroke, cognitive impairment, heart failure, hospitalizations, reduced quality of life, and decreased exercise productivity (Table 2) (1). These outcomes significantly worsen the prognosis of AF. AF has become a public health burden with significant societal implications and enormous medical costs (19).

**Table 2 Clinical outcomes of AF**

Outcome parameter	Relative change in AF patients
1. Death	Death rate doubled.
2. Stroke (includes haemorrhagic stroke and cerebral bleeds)	Stroke risk increased; AF is associated with more severe stroke.
3. Hospitalizations	Hospitalizations are frequent in AF patients and may contribute to reduced quality of life.
4. Quality of life and exercise capacity	Wide variation, from no effect to major reduction.  AF can cause marked distress through palpitations and other AF-related symptoms.
5. Left ventricular function	Wide variation, from no change to tachycardiomyopathy with acute heart failure.

AF = atrial fibrillation. The prevention of these outcomes is the main therapeutic goal in AF patients. Reprinted from Camm et al. (1)

### **7.1.3.1 Death**

Consistent evidence supports that there is an association between AF and increased rates of death. AF in patients doubles mortality as an independent predictor (20, 21).

Based on almost 40-year Framingham Study data, the survey by Kannel et al reported that AF increased 1.5 to 1.9-fold of mortality in models that had been adjusted for other relevant cardiovascular conditions (15). Following-up 15,406 initially middle-aged people for two decades, the Renfrew/Paisley study determined that AF was an independent predictor of all-cause mortality in both sexes, with a 1.5 increased hazard in time to all-cause death in AF patients (20). A survey in the U.S. defined mortality was greater when AF was present when compared with those without AF after adjustment for cardiovascular risk factors (22). People with AF have a ~20% higher relative mortality risk than those without AF after adjusting known cardiovascular conditions (19).

### **7.1.3.2 Stroke and cognitive dysfunction**

AF is associated with increased risks of stroke. AF is responsible for every fourth or fifth stroke, including ischemic and hemorrhagic stroke (23). Not only does AF account for 20-25% of all strokes, but also the prognosis of AF-related strokes is often worse than non-AF strokes (15, 24). The stroke occurs in AF patients more often contributes to disability, death, or recurrent stroke (25).

In Framingham cohort, the age-adjusted risk of stroke increased near five-fold in people with AF compared with those free of AF (14). In the Renfrew/Paisley cohort over a 25-year follow-up, it is reported that AF more likely causes stroke independently 2.5 times in men and 3.2 times in women than people without AF (20). It is significant that sufficient antithrombotic therapy can prevent the stroke caused by AF to reduce stroke relevant disability and mortality in AF patients (26).

Even in patients without overt stroke, AF can contribute to cognitive impairment, including dementia (27, 28). The Rotterdam study suggested that asymptomatic stroke is an independent stroke risk factor, which can increase stroke risk more than 3-fold (29); and the baseline silent stroke increased the risk of dementia more than twice (30).

### **7.1.3.3 Hospitalizations**

AF is associated with more hospitalizations compared with other arrhythmia (31). The rates of AF-related hospitalizations have been increasing (32).

The previous introduced Renfrew/Paisley study revealed that 3.5% of its cohort was hospitalized with a diagnosis of AF over a 20-year follow-up period. In this study, a high long-term incidence of hospitalization related to AF was shown as 1.9 cases/1000 person years (6). Later, the Renfrew/Paisley study determined that three quarters persons with AF would die or be hospitalized for a relevant reason within 20 years, which doubled or tripled compared with those without AF. The death or hospitalization is mainly due to concomitant stroke or heart

failure (20). In Scotland, the number of AF admissions increased three fold from 1986 to 1996 (32).

#### **7.1.3.4 Quality of life and exercise capacity**

Persons with AF experience poorer Quality of Life (QoL) compared with healthy people, the general population, and patients with coronary heart disease (CHD) in SR (33). Approximately 30% of AF patients have concomitant anxiety or depression when AF persisting for half year (34).

The reduction in quality of life and exercise capacity of AF patients is mainly due to symptoms such as palpitations, dyspnea, fatigue, chest pain, dizziness, or syncope. However, asymptomatic AF can cause low QoL as well (35).

Fortunately, it is proved that impaired QoL can be equally improved with both rate control and maintenance of SR (22).

#### **7.1.3.5 Left ventricular dysfunction**

Poor rate control, loss of atrial contractile function, and increased end-diastolic LV filling pressure in AF patients can depress left ventricular function, which can fortunately be improved by both rate and rhythm-control therapies (36).

### **7.1.4 Summary of AF challenge**

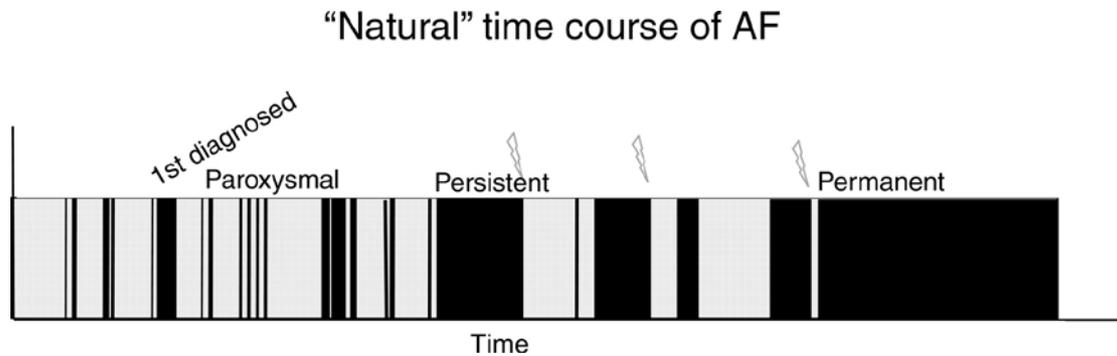
Although AF is not a life-threatening arrhythmia, it presents a significant challenge because of its large and growing prevalence, a number of complications, and substantial costs. Therefore, there is need for further improvement in therapeutic strategies and technologies for AF patients. The present study is carried out to predict termination and recurrence of AF following direct current cardioversion (DCC) with the techniques of surface ECG signal processing, attempting to provide an effort to deal with the increasing challenge of the arrhythmia.

## **7.2 Natural time course of AF and mechanisms of AF**

### **7.2.1 Natural time course of AF**

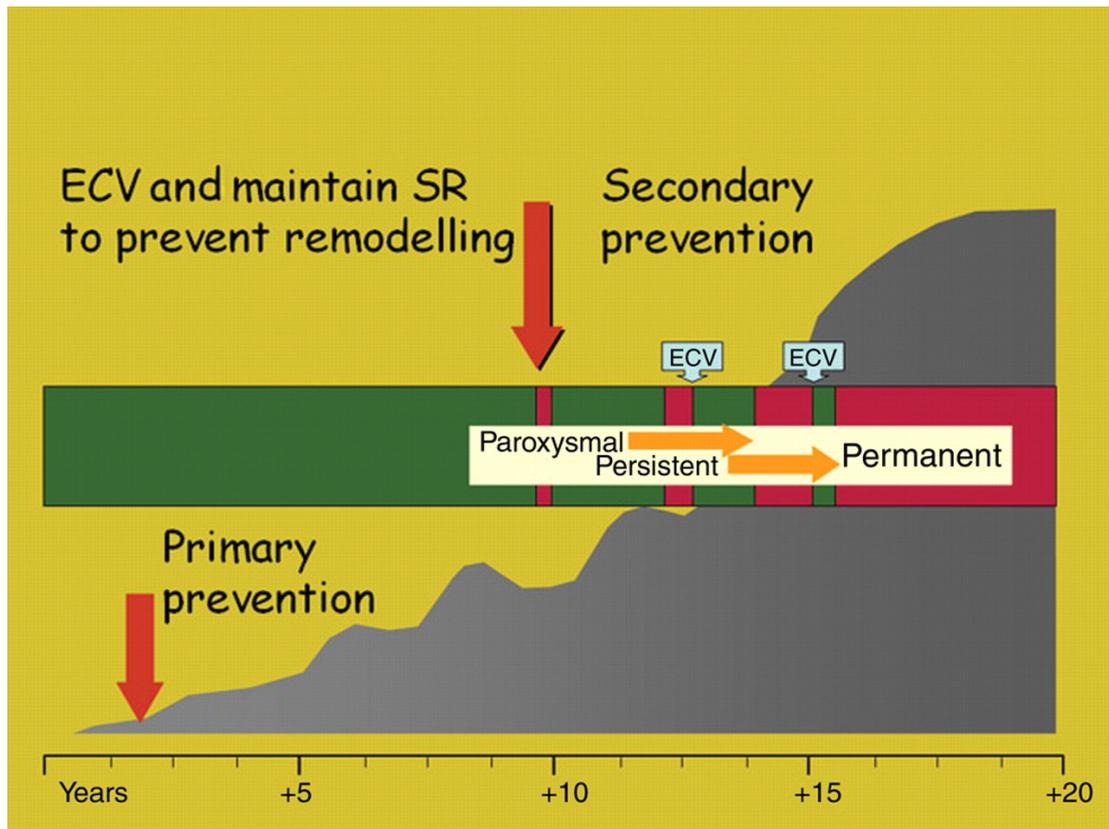
One previous AF study described the classic time course of AF as a process with a chaotic but progressive pattern (Figure 3). In Figure 3, the black parts indicate AF time and the grey parts represent SR period. It can be seen that the natural

history of AF is a progression developing from first diagnosed AF to paroxysmal, persistent, and finally permanent AF. The flashes in this figure indicate rhythm cardioversion interventions, which could slow the “natural” time course of AF (37).



**Figure 3 The “natural” time course of AF. Reprinted from Kirchhof et al. (37)**

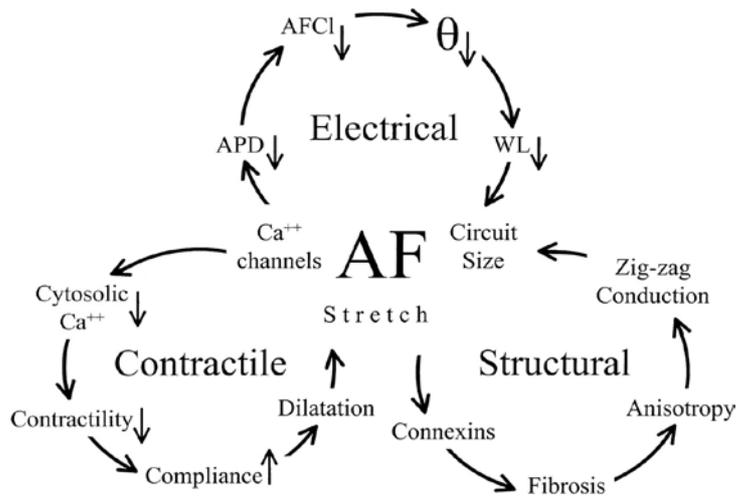
The clinical progressive nature of AF could be explained by the remodeling occurring in atria during AF (described subsequently). A previous study demonstrated a figure by combining the clinical process of AF with the time course of atrial remodeling (Figure 4). This figure illustrated that the clinical process of AF develops synchronously with the time course of atrial remodeling, and rhythm control interventions, such as electrical cardioversion, could be used to prevent the atrial remodeling progress, thereby slowing the clinical development of AF (38).



**Figure 4** The clinical progressive nature of AF and the time course of atrial remodeling. Reprinted from Cosio et al. (38) ECV = electrical cardioversion; SR = sinus rhythm; the gradual increasing grey part indicates the progressive atrial remodeling.

### 7.2.2 Mechanisms of AF

The mechanisms of AF are multifactorial and have not been fully understood so far. However, as observed in clinical practice, paroxysmal AF usually develops to persistent or permanent AF. It is considered that the progressive nature of AF is due to ongoing atrial remodeling (39). Based on numerous studies, the relationship between AF and electrical, contractile, structural remodeling has been largely explored (Figure 5) (40). The proposed positive feedback-loops of atrial remodeling on AF provide an amount of support for understanding the natural time course of AF.



**Figure 5 Relationship between AF and electrical, contractile, structural remodeling. Reprinted from Allessie et al. (40)**

### 7.2.2.1 Electrophysiological mechanisms

Abnormal automaticity triggers (focal mechanisms) and a reentry sustaining substrate (multiple wavelet hypothesis) interact for AF initiation and perpetuation.

#### Focal mechanisms

Although the ectopic focus theory was first developed by Scherf and colleagues in 1953 (41), it did not attract more attention until the late of 1990s when more observations were available during the treatment of radiofrequency catheter ablation in AF. In these studies, focal sources of AF were identified and AF could be converted to SR with discrete radiofrequency ablation of these sites. The rapid firing foci with a higher dominant frequency (shorter refractory periods) mainly originate from the pulmonary veins (PVs)/the left atrium (LA) (42, 43), although other sites, such as the coronary sinus (CS), the superior vena cava (SVC)/the right atrium (RA), have also been located (44, 45).

In paroxysmal AF, the ablation of the distinct foci prolongs the fibrillation cycle length to terminate AF. In contrast, radiofrequency ablation is more difficult to convert persistent AF to SR, because the foci are spread throughout the atria in persistent AF (1).

### Multiple wavelet hypothesis

The multiple wavelet re-entry theory of AF was proposed by Moe et al. (46) The authors found fibrillations maintained by continuous chaotic wavelets re-entering in the atria. The perpetuation of AF depends on the number of these wavelets that can be present at the same time. It was noticed that the AF episode was more likely to sustain as long as the number of coexisting wavelets is above a critical number (47). The number of wavelets is prone to increase in a substrate with short refractory periods and/or heterogeneity of conduction delay, because either shortened refractory period or decreased conduction velocity can create a smaller wavelength of atrial cycle (wavelength = refractory period x conduction velocity) (47, 48). Thus, the smaller the wavelength, the more likely AF is sustained.

### 7.2.2.2 Atrial remodeling

#### Structural remodeling

Multiple medical conditions contribute to AF. Ageing, hypertension, heart failure, valvular heart diseases, coronary artery disease, diabetes mellitus are the well known AF predisposing factors, while some are less known, such as cardiomyopathies, congenital heart defects, thyroid dysfunction, obesity, and sleep apnoea (1). These concomitant conditions can cause molecular and structural changes in the atria, which is termed “structural remodeling”.

Molecular changes include cellular Ca<sup>2+</sup> overload, inflammation, oxidative stress, activation of the renin-angiotensin-aldosterone system (RAAS); structural changes include enlarged atria, hypertrophy, fibrosis, dedifferentiation, apoptosis, and myolysis (49). Importantly, these changes produce a substrate that initiates and perpetuates AF due to electrical dissociation between muscle bundles and increased non-uniform anisotropy with local conduction heterogeneities (1). Furthermore, structural remodeling not only develops before AF onset (50), it also can be facilitated after AF due to a fast ventricular rate and increased atrial pressure (51, 52). Thus, a positive feedback-loop of structural remodeling on AF forms to sustain (49).

### Electrical remodeling

AF can cause the reduction of calcium current in the L-type Ca<sup>2+</sup> channels, and then cellular calcium overload, which explains the shortening of the atrial effective refractory period (AERP) and maladaptation to rate (53). Shortly after AF onset, electrophysiological changes begin to occur in the atria (54). “Electrical remodeling” in AF is referred as shortening of atrial refractoriness and poor physiological rate adaptation, which provides a substrate facilitating AF through reducing the wavelength of intra-atrial circuits (55).

Two independent experimental studies introduced the concept of tachycardia-induced electrical remodeling in 1995 (55, 56). Morillo et al. found that AERP was reduced by ongoing rapid atrial pacing in dogs (56). Wijffels et al. found more marked shortening in atrial refractoriness in goat hearts under pacing-induced AF (55). Tachycardia-induced electrical remodeling was also documented in humans (57, 58). All these studies showed that AF could result in marked shortening of refractoriness (electrical remodeling), which “begets AF” (55, 57, 58).

The reversibility of electrical remodeling and its relation with the early recurrence of AF have been studied. Atrial electrical remodeling is reversed within 24 hours following restoration of SR (59, 60), and completely reversible within one week after SR restoration (55). It has been shown that the progressive recovery of electrical remodeling was slower at the LA than at the RA (61). The non-uniform recovery of electrical remodeling in the atria may be responsible for the high rate of early recurrent AF following successful cardioversion (62).

### Contractile remodeling

One of the most important cellular mechanisms is the down-regulation of the L-type Ca<sup>2+</sup> channels caused by AF (53). The reduction of cytosolic calcium may contribute to atrial contractile dysfunction. “Contractile remodeling” is used to describe reduced atrial function during AF and even after restoration of SR. Reduced atrial contractility of the fibrillating atria contributes to increased

compliance, and then deteriorates atrial dilatation, which promotes AF as structural remodeling.

The insufficient atrial contractile function after termination of AF is called “atrial stunning”. It is significant owing to the chance of thromboembolic events even if under SR (40).

### **7.3 Rate versus rhythm management and early rhythm control strategy**

#### **7.3.1 Rate control versus rhythm control**

The purpose of AF management is to control symptoms and prevent relevant complications in AF (1). As described above, surveys and epidemiological studies showed that AF has clear association with severe complications, such as death, stroke, and reduced quality of life, etc. Thus, it is reasonable to assume that SR has perceived benefits compared with AF rhythm. The benefits might include symptomatic improvement, reduction of mortality and morbidity, and more importantly, prolonged progress of AF.

But the above assumption has been challenged by the results from a few clinical trials comparing the therapies of rate control and rhythm control. These randomized controlled trials have demonstrated that rate control in AF patients was not inferior to rhythm control therapy regarding outcomes of mortality and morbidity when sufficient antithrombotic treatment was performed (1). For example, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study observed no difference in deaths of all causes or in stroke rate between rate control and rhythm control (63). Similarly, the RATE Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) trial showed no difference in mortality and morbidity of cardiovascular causes between patients randomly assigned to rate control or rhythm control group (64). Additionally, in patients with heart failure and AF, the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) study found rate control not inferior to rhythm control in deaths from cardiovascular causes, or in all-cause mortality and worsening of heart failure (65). Therefore, summarizing the relevant clinical trials in 2010 guidelines for AF management (Table 3 and 4), the ESC suggested that rate

control alone with sufficient antithrombotic therapy is a reasonable strategy in the elderly with no or minimal AF-related symptoms (1).

However, some aspects could be considered to explain the disappointing results of the clinical trials (66). Firstly, the negative results of the rhythm control group may be mainly attributed to poor SR maintenance, especially for long-term SR maintenance. For instance, 37% subjects in rhythm group relapsed to AF after 5 years of follow-up in AFFIRM trial (63) and 61 % after 2-year follow-up in RAtE Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) (64). Another consideration is that there were many participants in the rhythm control group who developed thromboembolic adverse events due to discontinuation of antithrombotic therapy after restoration of SR. The increased rates of thromboembolic events in the group of rhythm control might facilitate the negative results of rhythm control (67).

Furthermore, several studies have provided data to support the viewpoint that maintained SR might prevent relevant mortality or morbidity in AF. A recent clinical trial, the A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg b.i.d. for the prevention of cardiovascular Hospitalisation or death from any cause in patiENts with Atrial fibrillation/atrial flutter (ATHENA) study showed that decent SR maintenance was associated with better survival outcome compared with the control group (68). Moreover, as shown in the substudies of the AFFIRM trial and the RACE trial, SR maintenance was associated with the improvement of survival (69), QoL (70), and exercise capability (71).

Overall, based on the “sobering” results from the clinical trials and the considerations of the benefits of SR, in the current guidelines the ESC suggested that rhythm control should be selected as a “patient-tailored therapy”, which is a decision made based on individual considerations (1). Before applying rhythm control therapy to a patient with AF, the acceptance of permanent AF rhythm (the acceptance of AF-related symptoms) and the successful probability of cardioversion should be considered. In other words, in addition to AF-related

symptoms, the factors that are able to predict the outcome of cardioversion are important for the decision making of rhythm control therapy. It is desirable to explore measures that are able to determine the likelihood of cardioversion success and SR maintenance in order to guide candidate selection for cardioversion.

**Table 3 General characteristics of rate control and rhythm control trials in patients with AF. Adapted from Camm et al. (1)**

Trial	Year	Patients (n)	Mean age (years)	Mean length of follow-up (years)	Inclusion criteria	Primary endpoints	Patients reaching primary endpoints (n)		
							Rate control	Rhythm control	P
PIAF (72)	2000	252	61.0	1.0	Persistent AF (7–360 days)	Symptomatic improvement	76/125 (60.8%)	70/127 (55.1%)	0.32
AFFIRM (63)	2002	4060	69.7	3.5	Paroxysmal AF or persistent AF, age ≥65 years, or risk of stroke or death	All-cause mortality	310/2027 (25.9%)	356/2033 (26.7%)	0.08
RACE (64)	2002	522	68.0	2.3	Persistent AF or flutter for <1 years and ≥2 cardioversions over 2 years and oral anticoagulation	Composite: cardiovascular death, CHF, severe bleeding, pacemaker implantation, thrombo-embolic events, severe adverse effects of antiarrhythmic drugs	44/256 (17.2%)	60/266 (22.6%)	0.11
STAF (73)	2003	200	66.0	1.6	Persistent AF ≥4 weeks and LA size >45 mm, CHF NYHA II–IV, LVEF <45%	Composite: overall mortality, cerebrovascular complications, CPR, embolic events	10/100 (10.0%)	9/100 (9.0%)	0.99
HOT CAFÉ (74)	2004	205	60.8	1.7	First clinically overt persistent AF (≥7 days and <2 years), age 50–75 years	Composite: death, thrombo-embolic events; intracranial/major haemorrhage	1/101 (1.0%)	4/104 (3.9%)	>0.71
AF-CHF (65)	2008	1376	66	3.1	LVEF ≤35%, symptoms of CHF, history of AF (≥6 h or DCC < 6 months)	Cardiovascular death	175/1376 (25%)	182/1376 (27%)	0.59

AF = atrial fibrillation; AF-CHF = Atrial Fibrillation and Congestive Heart Failure; AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; CHF = congestive heart failure; CPR = cardiopulmonary resuscitation; DCC = direct current cardioversion; HOT CAFÉ = How to Treat Chronic Atrial Fibrillation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PIAF = Pharmacological Intervention in Atrial Fibrillation; RACE = RATE Control versus Electrical cardioversion for persistent atrial fibrillation; STAF = Strategies of Treatment of Atrial Fibrillation.

**Table 4 Comparison of adverse events in rate control and rhythm control trials in patients with AF. Adapted from Camm et al. (1)**

Trial	Year	Deaths from all causes	Deaths from cardiovascular causes	Deaths from non-cardiovascular causes	Stroke	Thromboembolic events	Bleeding
PIAF (72)	2000	4	1/1	1*	ND	ND	ND
AFFIRM (63)	2002	310/356	167/164	113/165	77/80	ND	107/96
RACE (64)	2002	18/18	18/18	ND	ND	14/21	12/9
STAF (73)	2003	8/4	8/3	0/1	1/5	ND	8/11
HOT CAFÉ (74)	2004	1/3	0/2	1/1	0/3	ND	5/8
AF-CHF (65)	2008	228/217	175/182	53/35	11/9	ND	ND

Numbers are in rate/rhythm. AF = atrial fibrillation; AF-CHF = Atrial Fibrillation and Congestive Heart Failure; AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; HOT CAFÉ = HOw to Treat Chronic Atrial Fibrillation; ND = not determined; PIAF = Pharmacological Intervention in Atrial Fibrillation; RACE = RAtE Control versus Electrical cardioversion for persistent atrial fibrillation; STAF = Strategies of Treatment of Atrial Fibrillation.

\*Total number of patients not reported.

### **7.3.2 Early rhythm control strategy**

Clearly, the longer the patient has been in AF, the more refractory AF would be respond to cardioversion and the less likelihood of sinus maintenance would be expected due to the consequences of remodeling in the time course of AF.

Although some clinical studies provided controversial results, it is assumed that SR is superior to the rhythm of AF provided that SR could be initiated and maintained successfully. Therefore, early rhythm control strategy of AF has been highlighted for better therapeutic effects (38, 66, 75), and it is desirable to explore tests that quantify atrial remodeling to guide an early cardioversion in persistent AF patients (76, 77).

## **7.4 Direct current cardioversion (DCC)**

### **7.4.1 What is DCC**

In 1962, Lown and coworkers introduced DCC as a new effective approach to terminate cardiac arrhythmias (78). One year later, they reported the application of this method in 50 patients with AF (79). Since then, it has been playing an important role in the treatment of AF. DCC is also known as electrical cardioversion or transthoracic cardioversion, which ceases AF by delivering an electrical shock on the surface of thorax from an external defibrillator to depolarize all myocardium simultaneously. Such premature activation of the entire cardiac cells leaves the advancing wave front with no cells to depolarize to stop the re-entry that is required to facilitate AF.

### **7.4.2 Indications of DCC for AF**

DCC can be performed as an urgent or elective procedure. Acute DDC is preferred to promptly restore SR in AF patients with severe symptoms or uncontrolled hypotension, heart failure, myocardial ischemia due to a rapid ventricular rate (1). Elective DCC should be considered for initiation of a long-term rhythm control strategy for AF patients (1, 80, 81). In pharmacological measures resistant AF, even if asymptomatic or newly diagnosed AF, the purpose of DCC is to early restore SR to slow the progression of AF.

DCC is particularly preferred in persistent AF, because of the fact that drugs are less effective when AF has lasted more than 48 hours (82). This is probably associated with electrical and structural remodeling in the atria during the ongoing arrhythmia. Thus, if antiarrhythmic agents fail to convert persistent AF, DCC is adopted. Combination of antiarrhythmic drugs is often recommended in order to promote shock success and prevent AF recurrences following transthoracic cardioversion (1).

Based on data of a number of DCC studies, Van Gelder et al. proposed the guidelines for serial electrical cardioversion strategy considering age, AF duration, NYHA class, and concomitant heart diseases. For patients older than 70 years with AF duration more than 36 months and NYHA III or IV, serial electrical cardioversion is unlikely to have the desired effects. Thus, they suggested that it is worthwhile to apply serial electrical cardioversion combined with antiarrhythmic drugs in patients younger than 71 years old with an AF duration less than 36 months and NYHA class I or II (83, 84).

### **7.4.3 Outcomes of DCC for AF**

#### **7.4.3.1 High success rates & high recurrence rates**

Although DC cardioversion requires general anesthesia, it is able to restore SR immediately with a higher success rate of 70-90% (85, 86). Additionally, it is safe even in patients with unstable hemodynamic, advanced age, long-lasting AF, or severe cardiovascular diseases (87, 88).

Although DCC is a relatively safe and effective rhythm control therapy for patients with persistent AF, the high rate of AF recurrences, especially early recurrences of AF, has been a difficulty in clinical practice. In a hybrid strategy, antiarrhythmic agents can improve the outcome of DC cardioversion, especially in prevention of shock failure and early recurrence of AF (89). However, the recurrence of AF is common occurring at a high rate of 50-60% within one month after successful DC cardioversion irrespective of administration of antiarrhythmic drugs (90-93).

### **7.4.3.2 Classification of DCC outcomes**

Regarding the initiation of sinus beats and the different AF relapse time following successful cardioversion, the outcome of DCC treatment can be classified as following (82, 94).

#### **Shock failure**

Successful DCC is generally defined as termination of AF when at least one sinus beat is observed immediately following shock delivery (1, 95). Thus, shock failure is said to exist when the monitoring of ECG shows that not even a single sinus beat is observed following the shock of cardioversion.

#### **Immediate recurrence of AF (IRAF)**

IRAF occurs within one to two minutes after a successful external electrical cardioversion (96). Some studies reported that IRAF occurred in 5%-26% of AF patients who underwent transthoracic cardioversion (97, 98).

#### **Subacute recurrence of AF**

If no IRAF occurs after a successful shock, SR will be stable for the whole day in most people. After the first 24 hours since the restoration of SR, AF mainly recurs within two weeks after successful cardioversion, termed as subacute recurrence of AF. Subacute recurrence of AF is significant because it is more common than IRAF and it reduces the success rate of DCC remarkably (Figure 6) (90).

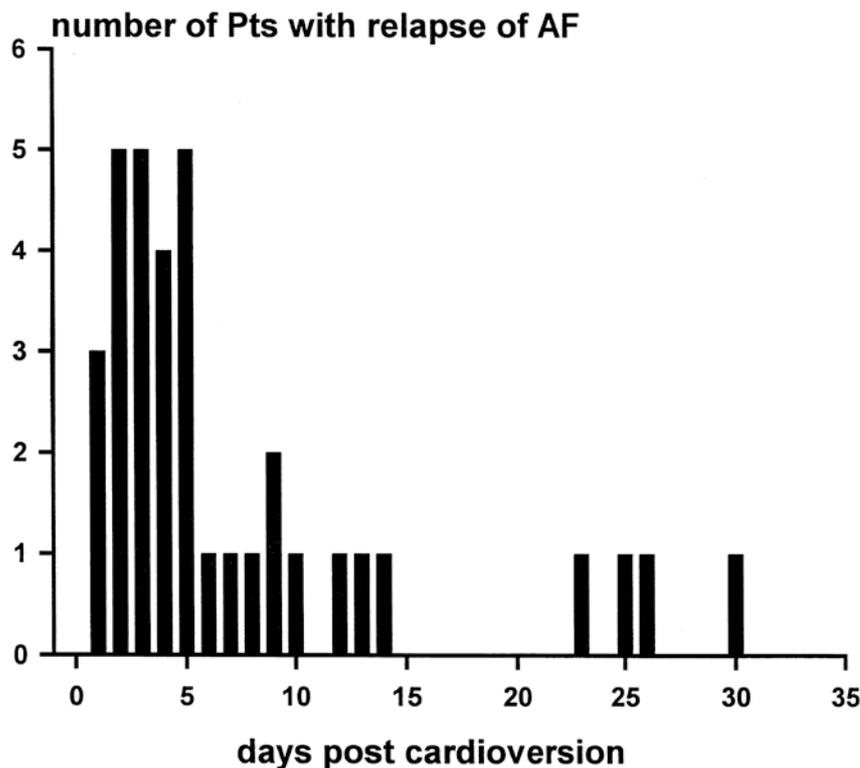
Tieleman et al. investigated the daily incidence of recurrent AF during the period of one-month post-cardioversion (90). Figure 6 illustrates that arrhythmia recurrences within the first two weeks (especially the first 5 days) following successful DCC mainly account for the outcome of cardioversion. This observation could be explained by the theory that electrical remodeling is mainly responsible for the early recurrent AF, because it gets progressively recovered within the first week after successful cardioversion (55, 60).

#### **Late recurrence of AF**

Late recurrences of AF emerge over the rest period after cardioversion with decreased but constant rates (90).

Shock failure, IRAF, and subacute AF recurrence were investigated in the present study. In this study, the early AF recurrence is defined as the AF that reoccurs within two weeks after restoration of SR.

The different rates of AF recurrence following cardioversion could probably be explained by distinct arrhythmogenic mechanisms. It seems that IRAF is attributed to momentary susceptibility to AF in the atria (94). Temporary heterogeneity due to reversed electrical remodeling seems mainly contribute to subacute AF recurrences (94), whereas late AF recurrences are primarily due to remained structural remodeling (99). Therefore, quantification of electrical remodeling has been suggested to identify the risk of early AF recurrences (76).



**Figure 6 Recurrence of AF following direct current cardioversion. Reprinted from Tieleman et al. (90) Pts = patients**

#### **7.4.4 Prediction of the outcome of DCC**

SR maintenance after successful cardioversion has been a challenge in clinical practice. Especially, the recurrence rate within the first weeks following successful cardioversion is quite high (90, 100, 101). Numerous studies have

attempted to identify clinical and echocardiographic predictors of outcome of DC cardioversion (91, 102). However, neither clinical nor echocardiographic parameters can sufficiently predict the natural history of AF or the response to therapy. Consequently, the predictive value of parameters assessed from the surface ECG has been explored (103, 104).

#### **7.4.4.1 Clinical variables**

Several clinical parameters, such as age (84), duration of AF prior to cardioversion, underlying heart diseases (84, 105), have been investigated for the value in predicting the outcome of DC cardioversion.

In a previous study, Age > 75 years was a predictor of AF relapses at 100-day follow-up after DC cardioversion (106). However, the age has been proved to be a poor predictor for outcome of DC cardioversion. For example, the age failed to predict AF recurrence at 6-month visit following successful DCC (107). There was no significant difference in the age between people with SR maintenance and those with AF recurrence at 3-month visit after AF termination by external cardioversion ( $62 \pm 12$  vs.  $64 \pm 9$  years,  $P = \text{NS}$ ) (108). The age was not a predictor for recurrent AF in cardioverted patients at 2-week follow-up after successful external cardioversion ( $61 \pm 11$  vs.  $63 \pm 12$  years,  $P = \text{NS}$ ) (109). The people who relapsed to AF were not older than those who still remained in SR at 6-week follow-up after successful DCC ( $68 \pm 7$  vs.  $70 \pm 5$  years,  $P = 0.41$ ) (110). The age failed to predict the recurrence of AF in 175 successfully cardioverted patients at 1-month follow-up post-cardioversion ( $68 \pm 10$  vs.  $68 \pm 9$  years,  $P = 0.87$ ) (93).

Duration of AF is one of the most common indexes for prediction of DCC outcome (84, 85). Because a longer duration of AF is associated with shorter atrial cycle length representing further electrical remodeling (111), a longer duration of AF indicates reduced success chance of electrical cardioversion (84, 85). Duration of AF prior to cardioversion could predict the recurrence of AF at 6-month visit after SR initiated by DC cardioversion (107). Duration of AF more than one year was a risk factor for AF relapses at 100-day follow-up after successful

transthoracic cardioversion (106). It was shown that SR maintenance at one month after electrical cardioversion was related to duration of AF < 3 months (91, 102). However, duration of AF is not a consistent predictor for DCC outcome. No significant difference was detected in AF duration prior to cardioversion between people with SR maintenance and those with AF recurrence at 3-month visit following successful transthoracic cardioversion (108). Duration of AF failed to predict recurrent AF in forty-two cardioverted patients at 2-week follow-up after AF termination by external cardioversion ( $30 \pm 35$  vs.  $12 \pm 20$  months,  $P = 0.11$ ) (109). The AF duration of people who relapsed to AF was not significant longer than that of patients who remained in SR at 6-week follow-up after DCC ( $6 \pm 2$  vs.  $4 \pm 2$  months,  $P = 0.13$ ) (110). The median AF duration failed to predict the recurrence of AF in 175 cardioverted patients at 1-month follow-up post-cardioversion (93 (2-1044) vs. 95 (2-641) days,  $P = 0.90$ ) (93).

It has been reported that the presence of heart disease plays no role in predicting the outcome of cardioversion (106, 107, 109, 110), although some underlying diseases, chronic heart failure for example, were reported as AF recurrence predictors in a few studies (93).

Overall, the predictive value of clinical variables is weakened by controversial results from many investigations.

#### **7.4.4.2 Echocardiographic predictors**

Left atrial size is the most commonly used echocardiographic index to predict the initiation and maintenance of SR following cardioversion. Left atrial diameter (LAD) and left atrial area (LAA) are the parameters used to describe left atrial enlargement.

It was reported that the  $LAD \geq 45$  mm indicated the recurrence of AF at 6 months following successful DC cardioversion (112). It was shown that LAD could be used as a predictor of SR maintenance within one month following successful external cardioversion (113). Another study reported that  $LAD \geq 45$  mm was

able to predict 66% of AF relapse with a sensitivity of 59% and specificity of 61% (107).

On top of LAD, the prognostic value of LA areas for electrical cardioversion outcome has drawn much research attention in recent years. An enlargement of LAA from echocardiographic recordings has been shown to be associated with the persistence of AF in animal models (114). Although LAD failed to predict AF recurrence in a study by Bollmann et al. ( $44 \pm 5$  vs.  $47 \pm 5$  mm, NS), the authors suggested that persistent AF patients with a larger LAA might experience a higher rate of early AF relapse within 2 weeks following successful DC cardioversion ( $24.9 \pm 6.6$  vs.  $31.5 \pm 5.4$  cm<sup>2</sup>,  $P = 0.006$ ) (109).

However, the predictive utility of echocardiographic parameters has been weakened in some studies with negative results. In a study, neither the LAD nor LAA was able to predict maintenance of SR at six months following successful external cardioversion (84, 102). Another study reported that the LAD did not correlate with the recurrence of AF within 100 days after successful transthoracic cardioversion (106). The measurements of LAD failed to predict AF recurrence around 1 month after successful DC cardioversion of persistent AF (93, 110).

#### **7.4.4.3 ECG parameters**

The surface ECG is a routine examination for all AF patients in clinical practice. Several techniques have been developed to derive parameters from the ECG for prediction of AF onset. One of these techniques is the signal-averaged P-wave, which has been used to predict AF onset when sinus beats exist (115, 116). It is especially useful for prediction of AF occurrence following cardiovascular surgery. In more detail, prolongation of signal-averaged P-wave duration is correlated with AF burst, because it reflects slowed intra-atrial conduction (117). However, the conclusion about the predictive utility of the averaged P-wave duration is not always consistent (118).

The techniques of atrial signal extraction and spectral analysis (described subsequently) have been developed for quantification of atrial electrical remodeling. These techniques are able to non-invasively analyze AF information contained in f-waves from the surface ECG. While structural remodeling plays an increasing role in late AF recurrences, electrical remodeling is mainly responsible for the early recurrent AF due to the progressive normalization of electrical remodeling within the first week following the restoration of SR (60, 90). Thus, the quantification of individual electrical remodeling from the surface ECG might help to identify suitable candidates who are likely respond to cardioversion and at less risk for early AF recurrence (76).

There are several electrophysiological parameters used to describe AF electrical remodeling, such as atrial fibrillation cycle length (AFCL) in ms, fibrillatory frequency in Hz, and fibrillatory rate in fibrillations per minute (fpm). AFCL is inversely related to atrial fibrillatory frequency [AFCL (ms) = 1000/fibrillatory frequency (Hz)]; and fibrillatory rate is equal to fibrillatory frequency multiplies sixty [fibrillatory rate (fpm) = fibrillatory frequency (Hz) x 60].

The AFCL is believed to be an index that directly reflects atrial refractoriness (56, 119-121). Therefore, a shorter AF cycle length reflecting shorter atrial refractory periods has been shown to be a reliable predictor for AF persistence, whereas a longer cycle length indicates that AF is more likely to terminate spontaneously or respond to therapy (122, 123). The relationship between AF cycle length and AF termination propensity has been confirmed in studies. It was suggested that both longer baseline atrial cycle length (111, 124) and its greater prolongation after intervention could predict intervention-induced AF termination (111, 125-127). These observations are consistent with the description that “the smaller the wavelength, the more likely AF is sustained”.

It has been verified that the dominant frequency (DF) or rate (DR) obtained from the ECG can be reliably used for characterization of AF electrical remodeling. The validation has been made through detecting the correlation between spectral parameters estimated from the ECG and the direct measurements from the

endocardial electrogram (EG). For example, high correlations have been found between the DF (128, 129), DR (130, 131) or AFCL (132) in ECG lead V1 and the corresponding measurements in intracardiac recordings from the RA. Another example is that the AFCL detected from the lead placed in the esophagus was highly correlated with the AFCL directly assessed from the LA and atrial septal using intracardiac recordings (132). Overall, the atrial fibrillatory frequency or rate derived from the ECG is able to reflect atrial refractoriness, thereby reflecting atrial electrical remodeling.

As fibrillatory frequency (or rate) is able to reflect atrial refractoriness (electrical remodeling), it presents good prognostic value of shock success and early AF susceptibility following successful cardioversion (133). Numerous studies have suggested that the outcome of pharmacological therapy, catheter ablation, or electrical cardioversion highly depends on atrial fibrillatory frequency (or rate) derived from the surface ECG (109). It has been shown that low fibrillatory rate AF is likely to respond to cardioversion therapy and keep from recurrences following successful cardioversion, while high fibrillatory rate AF is more likely to be refractory to cardioversion and relapse post-cardioversion (103).

## **7.5 Signal processing techniques of the surface ECG**

Signal processing techniques of the standard 12-lead ECG during AF is the techniques developed to analyze AF electrophysiology in order to monitor and predict efficacy of intervention in AF (47, 134). To assess the atrial fibrillatory frequency (or rate) from the surface ECG using digital signal processing is of importance in clinical practice, because it provides a non-invasive method to explore AF electrophysiology (135). The present study is designed to observe the application of these techniques in the patients with AF undergoing transthoracic cardioversion.

### **7.5.1 Bandpass filtering**

Bandpass filtering is used to remove baseline wander. Because baseline wander could severely interfere the performance of the QRS-T subtraction method, it should be removed by a linear phase filtering beforehand (103).

## **7.5.2 QRS-T cancellation techniques**

Following baseline correction, it is necessary to separate the atrial components from the ventricular signals to obtain the ECG that exclusively reflect the characteristics of atrial fibrillatory waves for further spectral analysis. This task can be accomplished by a ventricular signal subtraction method using a QRS template-matching algorithm (templating, identification, and removal of ventricular activity).

The subtraction of QRS-T complexes is crucial for spectral analysis of the surface ECG. Because the conventional ECG lead configurations are optimal for recording ventricular activity, the ventricular signal is much more obvious than the atrial component in the surface ECG. Considerable residual ventricular signals overwhelming atrial signals could severely interfere the results of further spectral analysis. However, no matter which existing method is used to perform atrial signal extraction, the remainder ECG always contains truncated QRS complexes and T waves, noises, artifacts due to imperfect cancellation. Thus, it is very important to choose a relatively reliable method for atrial signal extraction in AF research. One aim of the present study is to compare the atrial signal extraction performance of ABS and SVD.

### ***7.5.2.1 Average beat subtraction (ABS)***

ABS is the most extensively used method for atrial signal extraction. Initially, ABS method was developed for diagnosis of ventricular tachycardia on the surface ECG by extracting atrial signals to identify P waves (136). Later, ABS was used for differential diagnosis of AF on surface ECGs (137, 138), and then it has been employed for frequency analysis of AF (129, 132). ABS has been proved to be reliable for detecting atrial fibrillatory signals as a QRS cancellation method (139).

ABS processes ECG signals on a basis that AF is uncoupled to the ventricular activity. ABS extracts the atrial signal in a single ECG lead. A number of consecutive QRS-T complexes in respective leads are averaged to create an average beat, i.e. a template of ventricular cycle. In more details, a peak detection

algorithm was used to recognize R waves in the ECG recordings, and the QRS-T intervals were centered on the peak points of the R waves and then averaged to create a template. The QRS-T complexes in the ECG segment are identified using template matching. The degree of similarity to the template in each lead can be adjusted in order to identify the variations of QRS complex morphology. Subsequently, the identified QRS-T complexes are removed. The removal of QRS-T complexes results in a remaining atrial signal ECG subject to further analysis (104).

Because ABS is performed in single leads, it is sensitive to electrical axis alterations. Respiratory activity influences the precordial ECG leads considerably and often results in the variations in the orientation of cardiac electrical axis, and subsequently causes the slight variations in the morphology of QRS-T complexes. The performance of ABS relies on the representative of the average beat reflecting each single beat. Thus, variations in the orientation of cardiac electrical axis caused by respiratory activity often contribute to considerable QRS-T residuals in ABS (104). Additionally, the ECG episode length limits ABS performance, as ABS requires a recording length not shorter than 10 seconds (103).

#### ***7.5.2.2 Singular value decomposition (SVD)***

The separation of atrial and ventricular signals by principal component analysis (PCA) depends on the fact that atrial and ventricular activities originate from different bioelectric sources (103). Usually, unlike ABS, PCA does not extract the atrial signal from a single lead, but derives a global atrial signal from all leads. However, the method of PCA using SVD in the current study was recently developed for atrial signal extraction in single leads in order to fit dynamic variability of QRST waveform (103). PCA using SVD was employed to extract atrial fibrillatory activity from each individual lead. PCA was conducted by computing the singular value decomposition of the data matrices.

QRS-T morphology is often variable during AF. While the method of ABS calculates the average QRS morphology in each lead which is then subtracted to

leave the residual atrial activity behind, PCA enables quantification of not only the dominant QRS-T morphology, but also the dynamically variable component of QRS-T which can then be subsequently deducted and leave behind the atrial activity. In detail, for each ECG lead, a QRS-T waveform template from start of QRS to end of T wave was identified manually and the rest of the beats were identified by using correlation function (same as in ABS method).

### **7.5.3 Spectral analysis of the surface ECG and its clinical application**

#### ***7.5.3.1 Spectral analysis of the surface ECG***

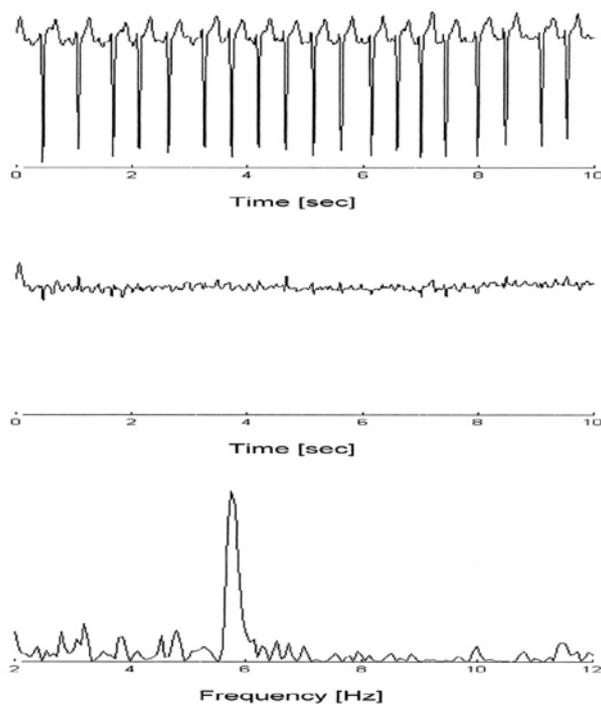
Spectral analysis, also called frequency analysis, is performed after extraction of atrial signals. Ideally, a remainder ECG exclusively reflecting the atrial activity is produced following subtraction of QRS-T complexes. The resulting atrial fibrillatory signals are subject to non-parametric Fourier transformation to generate power spectra. In Fourier-based spectral analysis, the remaining atrial signal ECG is divided into shorter and overlapping segments, which are subject to windowing. The power spectra obtained from each small segment are averaged to generate the desired power spectrum of the corresponding lead (104).

The atrial frequency power spectrum normally displays with a single narrow peak whose location determines the value of the dominant frequency (DF) in Hz. The peak frequency of atrial fibrillation is proved to be mainly in 4-9 Hz (137, 139). Thus, the value of DF determined from the frequency power spectrum is normally in the 4- to 9-Hz range. The DF represents the most common fibrillatory frequency of nearby endocardial sites.

In addition to the DF, the median frequency (MF) and frequency bandwidth (FB) are assessed using frequency spectral analysis as well. The MF is the middle value in the frequency power spectrum, measured in Hz. The FB is the frequency difference in a range of width of the power spectrum. In other words, the FB is the frequency difference between the upper and lower frequencies in the power spectrum. Thus, the FB, measured in Hz, represents the distribution of atrial fibrillatory frequency. The better the power spectrum is predominantly with

atrial signals, the narrower the peak of the frequency power spectrum will be. In brief, the values of MF and FB determine the shape of the spectrum.

An example of signal processing techniques (i.e. extraction of atrial signals and Fourier-based power spectral analysis) used to assess atrial fibrillatory contents in the surface ECG is demonstrated in Figure 7. It shows a 10-second ECG recording in lead V1 collected from a patient with AF, the remainder ECG obtained following bandpass filtering and QRS-T cancellation, and the frequency power spectrum produced from the remainder ECG by Fourier transformation (129, 132, 133, 139-141).



**Figure 7 Extraction of atrial signals and Fourier-based power spectral analysis. Reprinted from Bollmann et al. (140)**

The power spectrum in persistent AF normally presents with a single peak. In some studies, power spectral analysis revealed that there were more than one peaks in the spectrum. This could be explained by the changes in atrial fibrillatory rate over time rather than the different rate from different endocardial locations. Time-frequency analysis was developed based on spectrum analysis with the ability to detect temporal alternations of the DR.

Using time-frequency analysis, the values of fibrillatory rate assessed from the surface ECG appear to vary over time in paroxysmal AF, but not in persistent AF. It has been shown that fibrillatory rates vary along with the natural course of paroxysmal AF with a rate increase for AF sustenance and a rate decrease for AF spontaneous termination (140). In contrast, in persistent AF, although minor variability of fibrillatory rates was observed (129, 132, 139), the rate variability over 24 hours was quite insignificant, even in 10-second ECG recordings (142). Thus, spectral analysis of the ECG in patients with persistent AF usually presents single peak spectra.

### ***7.5.3.2 Clinical application of surface ECG spectral analysis***

Spectral analysis of the surface ECG has been well developed and applied in clinical settings. The atrial electrophysiological parameters obtained from the surface ECG have been used to monitor and predict spontaneous behavior of paroxysmal AF, therapeutic effects of pharmacological cardioversion, catheter ablation, and external electrical cardioversion (104).

#### **Predict spontaneous behavior of paroxysmal AF**

In paroxysmal AF, the fibrillatory frequency obtained from the Holter ECG by spectral analysis can be used to predict AF spontaneous behavior, with an increase in fibrillatory frequency indicating AF persistence (140).

#### **Predict therapeutic effects of pharmacological cardioversion**

Spectral analysis has also been used to monitor and predict the response to pharmacological cardioversion, such as termination of AF and the change of fibrillatory frequency or rate related to drug interventions.

A fibrillatory rate < 360 fpm assessed from the surface ECG before medication administration was recognized as the predictor of AF termination following intravenous ibutilide. In particular, 100% of patients with a fibrillatory rate < 360 fpm versus 29% of those with a rate  $\geq$  360 fpm were converted to SR with administration of ibutilide ( $P = 0.003$ ) (129). Interestingly, the same threshold of atrial fibrillatory frequency was reported in a study with oral flecainide for persistent AF. A baseline fibrillatory frequency < 6 Hz (equal to a fibrillatory rate

< 360 fpm) from the surface ECG was shown to predict pharmacological cardioversion success using oral flecainide with a sensitivity of 89% and a specificity of 78% (143).

Serial or continuous spectral analysis of the surface ECG has been used to observe the changes in electrophysiological parameters associated with administration of antiarrhythmic drugs or verapamil (140, 144-146). Several studies suggested that the alternation of spectral ECG parameters associated with administration of antiarrhythmic drugs might be useful to predict the outcome of pharmacological cardioversion in patients with persistent AF. An intravenous ibutilide-induced decrease in fibrillatory rate was greater in patients who converted to SR than in those who failed to convert ( $25 \pm 5\%$  vs.  $18 \pm 14\%$ , or  $108 \pm 60$  vs.  $68 \pm 52$  fpm,  $P = 0.002$ ) (147). The subjects who converted to SR with bepridil had a greater increase in AFCL estimated from the surface ECG than the people in whom AF failed to be terminated ( $31 \pm 10\%$  vs.  $17 \pm 5\%$ ,  $P < 0.001$ ) (148).

#### Predict therapeutic effects of catheter ablation

Baseline or change of fibrillatory frequency or rate derived from the surface ECG could be used in predicting the outcome of catheter-based ablation. A study by Bollmann et al. reported that the higher fibrillatory rate estimated from the surface ECG immediately prior to internal cardioversion was useful to predict early AF reinitiation in patients with persistent AF. In more details, a fibrillatory frequency  $\geq 7$  Hz was able to predict AF recurrence within 30 days following successful internal cardioversion with a sensitivity of 64% and a specificity of 88%. There was a significant difference in the relapse percentage between patients with a frequency  $\geq 7$  Hz and those with a frequency  $< 7$  Hz (88% vs. 36%,  $P = 0.02$ ) (133). The change of atrial frequency assessed between the ECGs before and after ablation could be used to predict the response to linear ablation (149).

#### Predict therapeutic effects of DC cardioversion

The correlation between atrial electrophysiological parameters derived from the surface ECG and the success chance of DC cardioversion or AF recurrence

following successful DCC has been studied. Table 5 lists a number of studies that investigated the application of spectral analysis of the surface ECG in patients with persistent AF undergoing DC cardioversion.

A study by Langberg et al. obtained the measurements of DR from standard 12-lead ECG recordings of persistent AF patients undergoing DC cardioversion. It was reported that the fibrillatory rate was higher in patients who had AF recurrence than in people who maintained in SR at 3-month follow-up after successful cardioversion ( $365 \pm 44$  vs.  $331 \pm 48$  fpm,  $P = 0.05$ ). A dominant fibrillatory rate  $> 360$  fpm was able to predict AF recurrence at 3-month visit following successful cardioversion with a sensitivity of 69% and a specificity of 75% (108). Performing frequency analysis in 175 patients with persistent AF, a previous study confirmed that AF recurrence could be accurately predicted with a higher atrial fibrillatory rate obtained from the surface ECG prior to DC cardioversion. In particular, the mean atrial fibrillatory rate was significantly lower in patients who remained in SR than in those with AF relapses at one-month follow-up after cardioversion ( $363 \pm 63$  vs.  $399 \pm 52$  fpm,  $P = 0.0004$ ). Furthermore, the difference was more obvious in the subgroup where AF duration was under one month ( $345 \pm 65$  vs.  $424 \pm 52$  fpm,  $P < 0.01$ ) (93).

A study by Tai et al. enrolled 29 patients with persistent AF ( $\geq 3$  months) undergoing DC cardioversion and investigated the correlation between the DF estimated from the surface ECG and minimal shock energy required for successful DCC. It was found that there was a significant correlation between the value of DF and minimal energy of defibrillation with a trend that a higher DF was associated with a higher atrial defibrillation threshold ( $P = 0.035$ ) (141).

Several studies found that a composite variable, which is generated by combining an electrophysiological parameter assessed by spectral analysis of the surface ECG and an echocardiographic variable, was useful in predicting AF recurrence following successful DC cardioversion. A study by Bollmann et al. reported that the DR from the surface ECG was lower in the patients maintained in SR than in those with AF recurrence within 2 weeks after successful DC

cardioversion ( $386 \pm 33$  vs.  $420 \pm 41$  fpm,  $P = 0.007$ ). Further, the authors combined the atrial fibrillatory rate with the LAA to create an “electromechanical” index, which was able to accurately estimate individual risk (low, intermediate, or high) for early AF recurrence within 2 weeks following successful external cardioversion in patients with persistent AF (109). In another study, Meurling et al. calculated the ratio of lower AFCL derived from lead V1 or oesophageal lead to LAD. Although neither AFCL nor LAD solely predicted AF recurrence within 6 weeks after successful DCC of persistent AF, the ratio was significantly lower in relapsed subjects than in non-relapsed subjects ( $3.1 \pm 0.4$  vs.  $3.4 \pm 0.6$  ms/mm,  $P = 0.04$ ) (110).

Overall, electrophysiology parameters derived from the surface ECG provide valuable information reflecting atrial electrical remodeling, thereby being able to monitor and predict the effect of interventions.

**Table 5 The application of spectral analysis of the surface ECG in patients with persistent AF undergoing DC cardioversion**

Study	Year	Pattern of AF	Detection method	Parameter	Findings
Langberg et al. (108)	1998	28 patients with persistent AF (> 48 hours) undergoing DC cardioversion	Spectral analysis of the surface ECG	DR	Significant difference was detected in the DR between patients with and without AF recurrence within 3 months following successful DC cardioversion ( $365 \pm 44$ vs. $331 \pm 48$ fpm, $P = 0.05$ ). A DR > 360 fpm was able to predict recurrence of AF within 3 months following successful DC cardioversion.
Tai et al. (141)	2002	29 patients with persistent AF ( $\geq 3$ months) undergoing DC cardioversion	Spectral analysis of the surface ECG	DF	A significant correlation was detected between the DF and minimal energy of defibrillation with a trend to a higher DF associated with a higher atrial defibrillation threshold ( $P = 0.035$ ).
Bollmann et al. (109)	2003	42 patients with persistent AF (> 24 hours) undergoing DC cardioversion	Spectral analysis of the surface ECG	DR	Significant difference was detected in the DR between patients with and without AF recurrence within 2 weeks following successful DC cardioversion ( $420 \pm 41$ vs. $386 \pm 33$ fpm, $P = 0.007$ ). Significant difference was detected in the LAA between patients with and without AF recurrence within 2 weeks following successful DC cardioversion ( $24.9 \pm 6.6$ vs. $31.5 \pm 5.4$ cm <sup>2</sup> , $P = 0.006$ ). A composite variable created with the DR and the LAA was useful in predicting of AF recurrence within 2 weeks following successful DC cardioversion.
Meurling et al. (110)	2006	32 patients with persistent AF (> 1 month) undergoing DC cardioversion	Spectral analysis of the surface ECG and oesophageal ECG	AFCL	No significant difference was detected in the AFCL between patients with and without AF recurrence within 6 weeks following successful DC cardioversion (in lead V1: $152 \pm 15$ vs. $155 \pm 17$ ms, $P = 0.69$ ; in oesophageal lead: $147 \pm 14$ vs. $151 \pm 18$ ms, $P = 0.59$ ). No significant difference was detected in the LAD between patients with and without AF recurrence within 6 weeks following successful DC cardioversion ( $44 \pm 7$ vs. $48 \pm 4$ mm, $P = 0.08$ ). A composite variable created with the AFCL and the LAD was useful in predicting of AF recurrence within 6 weeks following successful DC cardioversion.
Holmqvist et al. (93)	2006	175 patients with persistent AF (> 48 hours) undergoing DC cardioversion	Spectral analysis of the surface ECG	DR	Significant difference was detected in the DR between patients with and without AF recurrence within 1 month following successful DC cardioversion ( $399 \pm 52$ vs. $363 \pm 63$ fpm, $P = 0.0004$ ). Furthermore, the difference was more obvious in the subgroup of patients with AF duration under one month ( $424 \pm 52$ fpm vs. $345 \pm 65$ fpm, $P < 0.01$ ).

ECG = electrocardiography; AF = atrial fibrillation; DCC = direct current cardioversion; DR = dominant rate; fpm = fibrillation per minute; DF = dominant frequency;

Hz = hertz; AFCL = atrial fibrillation cycle length; ms = millisecond.

#### **7.5.4 Detection of left-to-right gradients by the surface ECG**

The concept of “atrial left-to-right gradient” is used to express the spatial variability of intra-atrial electrophysiological activity. Using different electrophysiological detection methods, it has been found that the AF cycle length is shorter or the DF/DR is higher in the LA than in the RA. One purpose of the current study is to investigate if the atrial gradient can be detected using spectral analysis of the surface ECG.

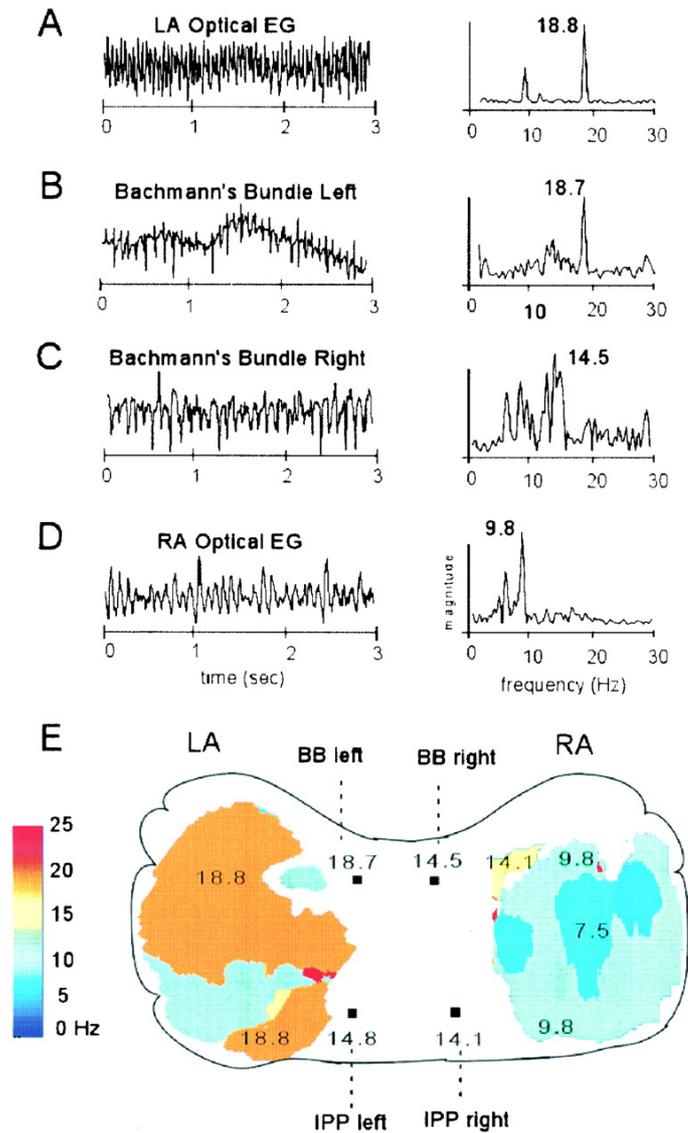
##### ***7.5.4.1 Animal studies in detection of the atrial left-to-right gradient***

The left-to-right atrial frequency gradient has been detected in animal studies. Several animal investigations that detected the left-to-right atrial gradient were summarised in Table 6. Morillo et al. made epicardial mapping on the LA and the RA in the dog heart with pacing-induced AF. The mean AFCL was measured and found significantly shorter in the LA than in the RA ( $81 \pm 8$  vs.  $94 \pm 9$  ms,  $P < 0.05$ ). A further shorter AFCL ( $74 \pm 5$  ms) was consistently found in the posterior LA (56). Sih and colleagues made canine models of acute AF (< 10 s atrial burst pacing) and chronic AF (> 6 weeks rapid atrial pacing). With epicardial mapping on the LA and the RA in these models, the mean AFCL was observed lower in the LA than in the RA in both chronic AF ( $96 \pm 14$  vs.  $121 \pm 18$  ms,  $P < 0.0001$ ) and acute AF ( $124 \pm 16$  vs.  $131 \pm 14$  ms,  $P < 0.0001$ ) (150).

Higher DFs in the LA than in the RA have been reported in experimental studies. Performing spectral analysis of the bipolar electrogram from the LA and the RA in 7 isolated sheep hearts with pacing-induced AF, Mandapati et al. reported that the mean DF assessed from the LA and the RA was  $14.7 \pm 3.8$  and  $10.3 \pm 2.1$  Hz, respectively (151). Applying the same method in 13 isolated sheep hearts, Berenfeld and co-workers detected a significant difference in the mean DF between the LA and the RA ( $11.4 \pm 3.0$  vs.  $7.8 \pm 2.1$  Hz,  $P < 0.0001$ ) (152). In 2001, Mansour et al. first proposed the concept of left-to-right atrial frequency gradient. Applying spectral analysis of the electrogram in the isolated sheep heart during induced AF, Mansour and co-workers reported left-to-right atrial frequency gradients along the BB (Bachmann’s bundle) and IPP (inferoposterior pathway) with a DF of 18.8 Hz in the LA and 9.8 Hz in the RA. The mean left-to-

right gradient was reported as  $5.7 \pm 1.4$  Hz. An example of the decrement of DFs between the LA and the RA is displayed in Figure 8. Moving from left to right, the frequency power spectrum obtained from the LA electrogram showed highest activity with a DF of 18.8 Hz (Figure 1A). The DF of the left of Bachmann's bundle (BBL) was 18.7 Hz (Figure 1B). The right of Bachmann's bundle (BBR) showed a DF of 14.5 Hz (Figure 1C), and the power spectrum of the RA showed a DF of 9.8 Hz (Figure 1D). In Figure 1E, it is apparent that the values of DFs progressively decreased from the LA to the RA (153).

Left-to-right atrial frequency gradients indicating higher AF frequencies in the LA than in the RA support the theory that high-frequency sources driving AF are located in the LA for some types of AF. Mansour et al. suggested that the existence of left-to-right frequency gradients could be explained by the hypothesis that impulses originating from high-frequency sources in the LA create local activity at progressively lower frequencies while they propagate away from the sources (153).



**Figure 8** Left-to-right gradients of DFs during induced AF in the isolated sheep heart. (A): Optical EG from LA with its corresponding frequency power spectrum. From (B) to (D): Electrode recording and power spectrum from (B) left end of BB, (C) right end of BB, and (D) RA. (E): DF maps of the LA and RA, in which the areas indicate DF domains with corresponding values of DFs along BB and IPP. Reprinted from Mansour et al. (153) DF = dominant frequency; EG = electrogram; LA = left atrium; BB = Bachmann's bundle; RA = right atrium; IPP = inferoposterior pathway; Hz = hertz.

**Table 6 The left-to-right atrial gradient detected in animal investigations**

Study	Year	Pattern of AF	Detection method	Parameter	Left-to-right atrial gradient
Morillo et al. (56)	1995	Canine model of pacing-induced AF (22 dogs)	Epicardial mapping on the LA and the RA	AFCL	Significant difference was detected in the AFCL between the LA and the RA ( $81 \pm 8$ vs. $94 \pm 9$ ms, $P < 0.05$ )
Sih et al. (150)	2000	Canine model of acute AF (< 10 s atrial burst pacing) (7 dogs)  Canine model of chronic AF (> 6 weeks rapid atrial pacing) (8 dogs)	Epicardial mapping on the LA and the RA	AFCL	In the model of chronic AF: Significant difference was detected in the AFCL between the LA and the RA ( $96 \pm 14$ vs. $121 \pm 18$ ms, $P < 0.0001$ )  In the model of acute AF: Significant difference was detected in the AFCL between the LA and the RA ( $124 \pm 16$ vs. $131 \pm 14$ ms, $P < 0.0001$ )
Mandapati et al. (151)	2000	35 AF episodes from 7 isolated sheep hearts with pacing-induced AF	Optical and bipolar electrode recordings in the atria	DF	The DF from the LA and the RA ( $14.7 \pm 3.8$ vs. $10.3 \pm 2.1$ Hz)
Berenfeld et al. (152)	2000	25 AF episodes from 13 isolated sheep hearts with pacing-induced AF	Optical and bipolar electrode recordings in the atria	DF	Significant difference was detected in the DF between the LA and the RA ( $11.4 \pm 3.0$ vs. $7.8 \pm 2.1$ Hz, $P < 0.0001$ )
Mansour et al. (153)	2001	48 AF episodes from 13 isolated sheep hearts with pacing-induced AF	Optical and bipolar electrode recordings in the atria	DF	First proposed the concept of left-to-right atrial frequency gradient with a DF of 18.8 Hz in the LA and 9.8 Hz in the RA. The mean left-to-right gradient was reported as $5.7 \pm 1.4$ Hz.

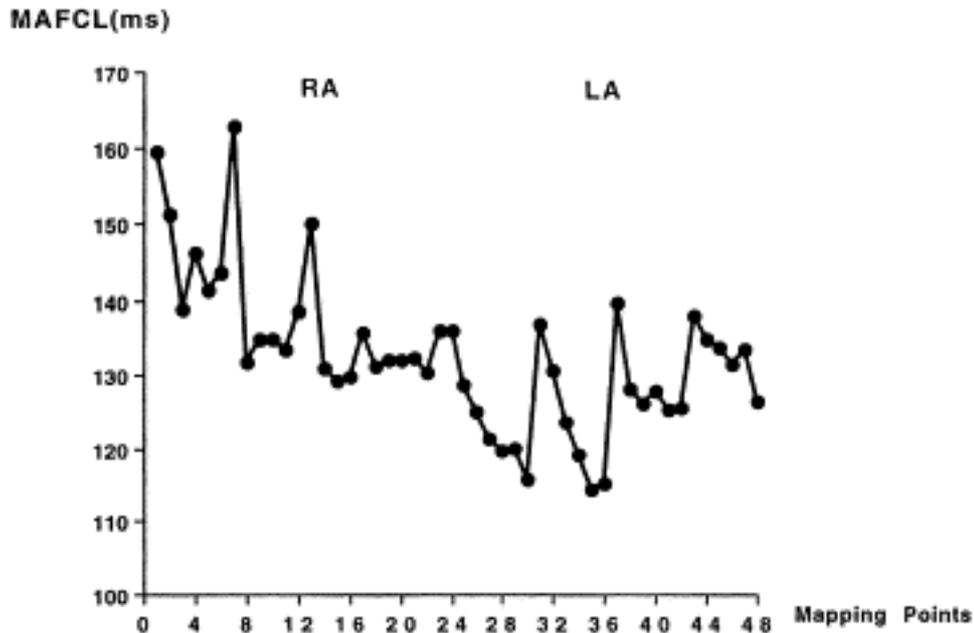
AF = atrial fibrillation; LA = left atrium; RA = right atrium; CS = coronary sinus; PV = pulmonary vein; ECG = electrocardiography; AFCL = atrial fibrillation cycle length; ms = millisecond; DF = dominant frequency; Hz = hertz; DR = dominant rate; fpm = fibrillation per minute.

#### **7.5.4.2 Human studies in detection of the atrial left-to-right gradient**

The left-to-right atrial frequency gradient has been invasively or non-invasively investigated in human studies using different methods. A number of studies that detected the left-to-right atrial gradient in humans are summarised in Table 7.

Endocardial catheters or electrode arrays intraoperatively placed on the epicardium have been used to detect the atrial electrophysiological gradient in humans. Using epicardial mapping in 11 patients with persistent AF undergoing mitral valve disease surgery, Sueda and colleagues found that the mean AFCL was shorter in the LA than in the RA with the value ranging from 130 to 163 ms in the RA and from 114 to 139 ms in the LA (Figure 9) (154). Performing simultaneous epicardial mapping during surgery on the right atrial free wall and the left atrial posterior wall in six patients with permanent AF, Wu et al. discovered the gradients of atrial electrophysiological characteristics with the longer mean AFCL in the RA ( $196 \pm 22$  ms) than in the LA ( $179 \pm 26$  ms) ( $P = 0.004$ ) and the higher mean DF in the LA than in the RA ( $6.41 \pm 1.18$  vs.  $5.66 \pm 0.55$  Hz,  $P = 0.049$ ) (155).

In a study by Husser et al., the atrial gradient was detected in patients with drug-refractory persistent AF using endocardial electrograms collected by catheters in the PVs, the CS, and the RA. The DR from the PVs was slightly higher than the rates from the CS and the RA. Correlations were found between the DR derived from surface ECG lead V1 and the rate assessed directly from the RA, the CS and the PVs. Due to the left-to-right atrial gradient, the correlations decreased along with growing anatomical distance from the RA ( $R = 0.865$ ,  $P < 0.001$ ), the CS ( $R = 0.558$ ,  $P = 0.025$ ), the PVs ( $R = 0.457$ ,  $P = 0.033$ ) to lead V1, with the highest correlation between the DR from the RA and the fibrillatory rate estimated from lead V1 (130). Similar results were reported in a later study by Husser et al to confirm their previous finding. The correlations between V1 rates and the rates from the RA ( $R = 0.97$ ,  $P < 0.001$ ), the CS ( $R = 0.71$ ,  $P < 0.001$ ) and the PVs ( $R = 0.65$ ,  $P = 0.001$ ) decreased as increase of distance to lead V1 (131).



**Figure 9 MAFCL of both atria. As the mapping system was computerized 48-channel, AFCLs of 48 points in the atria were measured. For each point, the AFCLs from the 11 subjects were averaged to the mean value. The MAFCL ranged from 130 to 163 ms in the RA and from 114 to 139 ms in the LA. MAFCL = mean atrial fibrillation cycle length; LA = left atrium; RA = right atrium; ms = milliseconds. Reprinted from Sueda et al. (154)**

A few studies non-invasively detected the atrial gradient by spectral analysis of the surface ECG and the oesophageal ECG. Applying spectral analysis of ECG recordings from leads V1, V2 and the leads in the esophagus, Pehrson et al. reported magnitude and dispersion of AFCL in patients with persistent AF (> 1 month). The mean dominant AFCL was  $154 \pm 16$  ms in lead V1 and  $154 \pm 17$  ms in lead V2. The values of mean dominant AFCL in the proximal and distal oesophageal leads were  $150 \pm 16$  and  $152 \pm 19$  ms, respectively. Although no significant difference in the mean dominant AFCL was shown between chest leads and the oesophageal leads, it can be seen that the mean AFCL tended to be higher in leads V1 and V2 than in the oesophageal leads. The absolute difference in the dominant AFCL between lead V1 and the distal oesophageal lead was  $10.4 \pm 7.7$  ms (156). Similarly, using spectral analysis of the surface ECG in patients with persistent AF, Meurling et al. estimated the AFCL from lead V1 and the oesophageal lead. It was shown that the AFCL derived from lead V1 was slight

higher than the value from the oesophageal lead with  $152 \pm 15$  versus  $147 \pm 14$  ms and  $155 \pm 17$  versus  $151 \pm 18$  ms in two subgroups, although no attempt was made to evaluate the significant difference (110).

**Table 7 The left-to-right atrial gradient detected in human investigations**

Study	Year	Pattern of AF	Detection method	Parameter	Left-to-right atrial gradient
Sueda et al. (154)	1996	11 patients with persistent AF (> 5 months)	Epicardial mapping on the LA and the RA during cardiac surgery	AFCL	The AFCL from the LA and the RA (114 - 139 vs. 130 - 163 ms)
Wu et al. (155)	2002	6 patients with permanent AF (> 5 months)	Epicardial mapping on the right atrial free wall and the left atrial posterior wall during surgery	AFCL; DF	Significant difference was detected in the AFCL between the LA and the RA (179 ± 26 vs. 196 ± 22 ms, <i>P</i> = 0.004)  Significant difference was detected in the DF between the LA and the RA (6.41 ± 1.18 vs. 5.66 ± 0.55 Hz, <i>P</i> = 0.049)
Husser et al. (130)	2004	25 patients with drug-refractory persistent AF undergoing PVI (2.2 ± 3.3 months)	The surface ECG in lead V1 and the endocardial electrogram from the RA, the CS and the PVs	DR	The correlations between DRs from lead V1 and the RA ( <i>R</i> = 0.865, <i>P</i> < 0.001), the CS ( <i>R</i> = 0.558, <i>P</i> = 0.025), and the PVs ( <i>R</i> = 0.457, <i>P</i> = 0.033) decreased as increase of distance to lead V1
Husser et al. (131)	2007	36 patients with drug-refractory persistent AF undergoing PVI (2.5 ± 3.2 months)	The surface ECG in lead V1 and the endocardial electrogram from the RA, the CS and the PVs	DR	The correlations between DRs from lead V1 and the RA ( <i>R</i> = 0.97, <i>P</i> < 0.001), the CS ( <i>R</i> = 0.71, <i>P</i> < 0.001), and the PVs ( <i>R</i> = 0.65, <i>P</i> = 0.001) decreased as increase of distance to lead V1
Pehrson et al. (156)	1998	28 patients with persistent AF (> 1 month)	ECG recordings from leads V1, V2 and the leads in the esophagus	AFCL	The AFCL from proximal/distal oesophageal leads and leads V1/V2 (150 ± 16/152 ± 19 vs. 154 ± 16/154 ± 17 ms)  Absolute difference in AFCL between the distal oesophageal lead and lead V1: 10.4 ± 7.7 ms
Meurling et al. (110)	2006	32 patients with persistent AF (> 1 month)	The surface ECG in lead V1 and the oesophageal ECG	AFCL	The AFCL from the oesophageal lead and lead V1 (147 ± 14 vs. 152 ± 15 ms)  The AFCL from the oesophageal lead and lead V1 (151 ± 18 vs. 155 ± 17 ms)

AF = atrial fibrillation; PVI = pulmonary vein isolation; LA = left atrium; RA = right atrium; CS = coronary sinus; PV = pulmonary vein; ECG = electrocardiography;

AFCL = atrial fibrillation cycle length; ms = millisecond; DF = dominant frequency; Hz = hertz; DR = dominant rate; fpm = fibrillation per minute.

### ***7.5.4.3 The left-to-right atrial gradient & pattern of AF (paroxysmal and persistent AF)***

From the summary of the studies investigating in the atrial gradient, it can be seen that significant difference in the DF, DR or AFCL between the LA and the RA was often detected in animal studies, whereas seldom found in human studies. In other words, although absolute difference in the DF, DR or AFCL was observed between the LA and the RA in these human AF studies, the difference was not significant. This may be due to the fact that the atrial frequency gradient was always detected during short induced AF episodes in animal models, while human studies were conducted in patients with persistent or permanent AF. The observation that the significant left-to-right atrial gradient presented in patients with paroxysmal AF, but not in persistent AF patients has been confirmed in numerous human studies (Table 9).

Lazar et al. examined multiple electrograms in 18 patients with paroxysmal AF and 13 people with persistent AF (> 1 month). The endocardial recordings were made simultaneously at each PV ostium, the CS, and the posterior RA. Spectral analysis was performed in these intracardiac recordings for assessment of DFs. A significant left-to-right atrial frequency gradient was observed in the patients with paroxysmal AF, with DFs of  $6.2 \pm 0.8$ ,  $5.5 \pm 0.7$  and  $5.1 \pm 0.6$  Hz from the PV/LA junction, the CS and the RA, respectively ( $P < 0.001$ ), whereas the significant gradient was not found in the group of persistent AF ( $6.1 \pm 0.7$ ,  $5.8 \pm 0.6$ ,  $5.8 \pm 0.6$  Hz,  $P = \text{NS}$ ) (157). The authors confirmed this finding in another study two years later. Electrograms were recorded from catheters in the CS, the posterior RA, and the posterior LA in 15 patients with paroxysmal AF and 12 people with persistent AF (> 1 month). The atrial frequency gradient was significant in paroxysmal AF with the DF of  $6.2 \pm 0.9$ ,  $5.8 \pm 0.8$ ,  $5.4 \pm 0.9$  Hz in the LA, the CS, and the RA, respectively ( $P < 0.001$ ). However, no significant atrial frequency gradients were observed in the majority of individuals with AF persisting (158).

Performing frequency mapping and spectral analysis of the electrogram for DF assessment, Sanders et al. found that the spatial dispersion of atrial

electrophysiological gradients was different between patients with paroxysmal AF (n = 19) and those with permanent AF ( $\geq 6$  months) (n= 13). In this study, the atrial gradient was defined as the progressive decrement of atrial frequencies with maximal frequencies (high DF sites) surrounded by a decreasing frequency gradient at least twenty per cent. The results showed that high DF sites mostly existed in the PVs in patients with paroxysmal AF, whereas high DF sites were more likely to be prevalent in patients with permanent AF (126). Another study by Sanders et al. compared the distribution of atrial gradients in 20 patients with paroxysmal AF and 14 people with permanent AF ( $\geq 12$  months). Electrograms were collected from each PV and the CS. Spectral analysis of the electrogram was performed to get the DF from the PVs and the CS. The DF derived from the PVs was higher in subjects with paroxysmal AF than in those with persisting AF for at least 12 months ( $11.0 \pm 3.1$  vs.  $8.8 \pm 3.0$  Hz,  $P = 0.0003$ ). The DF from the CS was lower in the former than in the latter ( $5.8 \pm 1.2$  vs.  $6.9 \pm 1.4$  Hz,  $P = 0.01$ ). These results contribute to a more obvious DF gradient in people with paroxysmal AF than in those with persistent AF ( $7.2 \pm 2.2$  vs.  $4.2 \pm 2.9$  Hz,  $P = 0.006$ ) (Table 8) (127).

**Table 8 The DF from the PVs and the CS in patients with paroxysmal and permanent AF**

The DF (Hz)	Paroxysmal AF	Permanent AF	<i>P</i> value
In the PVs	$11.0 \pm 3.1$	$8.8 \pm 3.0$	$P = 0.0003$
In the CS	$5.8 \pm 1.2$	$6.9 \pm 1.4$	$P = 0.01$
DF gradient	$7.2 \pm 2.2$	$4.2 \pm 2.9$	$P = 0.006$

AF = atrial fibrillation; DF = dominant frequency; PV = pulmonary vein; CS = coronary sinus. Data is from the study by Sanders et al. (127)

Overall, these studies demonstrated that there was no left-to-right atrial gradient or the gradient was not significant in patients with persistent AF, whereas the atrial gradient was significant in patients with paroxysmal AF. Even though a study by Wu et al. reported that the AFCLs were significant different between the LA and the RA in patients with permanent AF, this result might be short of representative and introduce statistical mistake due to the small study sample

size (n = 6) (155).

These human studies suggested that the maintenance of persistent AF might not depend on the atrial gradient, although the left-to-right gradient is important in the maintenance of paroxysmal AF. In other words, the difference between DF distribution in paroxysmal and persistent AF might contribute to different AF maintenance substrates. Electrical remodeling promotes atrial heterogeneous substrates, i.e. atrial gradients, in paroxysmal AF, whereas development of electrical remodeling has completed (no significant atrial gradients) in persistent AF. Persistent AF maintenance substrates might be described by the multiple wavelet hypothesis proposed by Moe et al. suggesting that AF could persist depending on multiple circulating reentrant wavelets without electrical discharge from foci (159).

Notably, persistent AF was defined diversely in these human atrial gradient studies with AF lasting time ranging from 1 month to 12 months (110, 126, 127, 130, 131, 154-158). As paroxysmal AF and persistent AF have different AF maintenance substrates, it would be more accurate to distinct paroxysmal and persistent AF by quantifying the atrial gradient rather than identifying AF episode lasting time for prediction of cardioversion effects.

Thus, one purpose of the current study is to determine if the left-to-right atrial gradient could be detected from the surface ECG between leads V1 and V6. We hypothesize that better therapeutic effects, i.e. higher successful cardioversion rate and less AF recurrence after successful cardioversion, would be expected in patients with a atrial gradient detected using spectral analysis of the surface ECG than in those without a atrial gradient.

**Table 9 Detection of the left-to-right atrial gradient in patients with paroxysmal and persistent AF**

Study	Year	Pattern of AF	Detection method	Parameter	The left-to-right atrial gradient
Lazar et al. (157)	2004	18 patients with paroxysmal AF and 13 people with persistent AF (> 1 month)	The endocardial electrogram in the PVs, the CS, and the RA	DF	In paroxysmal AF: significant difference was detected between the DF from the PV/LA junction, the CS and the RA ( $6.2 \pm 0.8$ , $5.5 \pm 0.7$ , $5.1 \pm 0.6$ Hz, $P < 0.001$ ).  In persistent AF: no significant difference was detected between the DF from the PV/LA junction, the CS and the RA ( $6.1 \pm 0.7$ , $5.8 \pm 0.6$ , $5.8 \pm 0.6$ Hz, $P = NS$ ).
Lazar et al. (158)	2006	15 patients with paroxysmal AF and 12 people with persistent AF (> 1 month)	The endocardial electrogram in the LA, the CS, and the RA	DF	In paroxysmal AF: significant difference was detected between the DF from the LA, the CS and the RA ( $6.2 \pm 0.9$ , $5.8 \pm 0.8$ , $5.4 \pm 0.9$ Hz, $P < 0.001$ ).  In persistent AF: no significant difference was detected between the DF from the LA, the CS and the RA ( $P = NS$ ).
Sanders et al. (126)	2005	19 patients with paroxysmal AF and 13 people with permanent AF ( $\geq 6$ months)	Electroanatomic mapping	DF	In paroxysmal AF: high DF sites mostly existed in the PVs.  In permanent AF: high DF sites were more likely to be prevalent in the atria.
Sanders et al. (127)	2006	20 patients with paroxysmal AF and 14 people with permanent AF ( $\geq 12$ months)	The endocardial electrogram in the PVs and the CS	DF	Significant difference was detected in the DF from the PVs between patients with paroxysmal AF and those with persistent AF ( $11.0 \pm 3.1$ vs. $8.8 \pm 3.0$ Hz, $P = 0.0003$ ).  Significant difference was detected in the DF from the CS between patients with paroxysmal AF and those with persistent AF ( $5.8 \pm 1.2$ vs. $6.9 \pm 1.4$ Hz, $P = 0.01$ ).  These results contribute to significant difference in the atrial DF gradient between patients with paroxysmal AF and those with persistent AF ( $7.2 \pm 2.2$ vs. $4.2 \pm 2.9$ Hz, $P = 0.006$ ).

AF = atrial fibrillation; PV = pulmonary vein; CS = coronary sinus; RA = right atrium; LA = left atrium; DF = dominant frequency; Hz = hertz; NS = not significant.

## **7.6 Thesis aims**

Applying spectral analysis of the surface ECG in patients with persistent AF undergoing DC cardioversion, the present study is aiming to:

- Determine the feasibility of spectral analysis in estimating the dominant frequency (DF), median frequency (MF), and frequency bandwidth (FB) from the surface ECG;
- Compare the atrial signal extraction performance of ABS and SVD;
- Investigate if the left-to-right atrial gradient could be reflected by the difference between the DFs measured from leads V1 and V6 using spectral analysis of AF;
- Detect the value of clinical variables, echocardiographic parameters, the DR and the atrial DF gradient assessed from the surface ECG in predicting the outcome of DC cardioversion.

## **8 Methods**

### **8.1 Patient selection and data collection at baseline**

#### **8.1.1 Patient selection**

This observational study screened all patients who were referred to the department of cardiology in Wellington Hospital for elective electrical cardioversion between October 2011 and March 2012. All patients with persistent AF (lasting more than 7 days) were included. Exclusion criteria were non-elective cases, patients with previous pulmonary vein isolation (PVI) and those with atrial flutter (AFL).

Patients with previous PVI were excluded because AF in this group has an altered electrophysiological mechanism, with significant changes in atrial cycle length. Therefore, the history of PVI would influence the results of spectral analysis. The patients with AFL were excluded again because the underlying electrophysiological mechanism of the arrhythmia is different with AF, and the difficulties associated with termination of AF do not apply to AFL.

The differential diagnosis of AF and AFL:

The atrial rate is a determinate factor for diagnose of AF or AFL. Table 10 shows that as the atrial rate increases, atrial arrhythmia can alter from flutter to flutter-fibrillation and finally fibrillation (2). To distinguish AF and AFL from the surface ECG, several points could be considered. First, as observed from ECG recordings, AFL is with F waves, which are slower, regular, uniform, and sharp ("sawtooth-like"), whereas AF is with f waves, which are more rapid, irregular, multiform, and rounded. Furthermore, AFL presents a regular or regularly irregular ventricular rate, while AF is always with an irregularly irregular ventricular rate unless accompanying atrioventricular block. If the atrial arrhythmia has both characteristics of AFL and AF, the rhythm would be termed as atrial flutter-fibrillation.

**Table 10 The differential diagnosis of AF and AFL. Modified from Wagner et al. (2)**

	Atrial flutter		Atrial flutter-fibrillation		Atrial fibrillation	
Atrial rate	200	220	300	360	400	≥500
Atrial waves	Slower, regular, uniform, and sharp (“sawtooth-like”) F waves		Having both characteristics of AF and AFL		More rapid, irregular, multiform, and rounded f waves	
Ventricular rhythm	Regular	Regularly irregular	Regular	Regularly irregular	Irregularly irregular	Irregular
Energy required in DC cardioversion	Low		Intermediate		High	

AF = atrial fibrillation; AFL = atrial flutter.

### 8.1.2 Data collection at baseline

The data collected at baseline includes age, gender, ethnicity, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), duration of AF prior to cardioversion, the history of AF (current or new-onset), underlying cardiovascular diseases, cardiac surgery history, concomitant cardiovascular medications, and antithrombotic status.

The value of BMI was assessed with weight and height, according to the formula  $BMI = \text{weight (kg)} / \text{height (m)}^2$ . The data source of blood pressure was the medical history sheet in the case notes. The duration of AF was recorded as the number of months counted from the first detected AF episode in the patient. All patients were administered with either dabigatran or warfarin for at least three weeks to achieve adequate anticoagulation. For the patients taking warfarin, the target value of international normalized ratio (INR) was between 2.0 and 3.0, while INR was not regularly monitored for the patients who were taking dabigatran.

### 8.2 Echocardiographic measurements

A transthoracic echocardiography (TTE) report within 12 months prior to the cardioversion or shortly after the procedure of cardioversion was obtained for each subject. The values of left atrial diameter (LAD) (mm) and left atrial area (LAA) (cm<sup>2</sup>) were collected.

M-mode TTE was used to measure endsystolic LA diameter in the parasternal long-axis view. The measured LA area was the largest LAA during ventricular

systole in the apical four-chamber view using two dimensional (2D) echocardiography.

While seven patients' echocardiographic reports were obtained prior to electrical cardioversion, the echocardiographic examinations of four subjects were performed after the procedure of cardioversion. It is believed that the values of LAA and LAD assessed shortly after SR restoration would not be significantly different from the values measured before cardioversion (113). It has been proved that LADs evaluated before (160) and after (161) cardioversion were both able to predict the recurrence of AF. However, as the value of LVEF obtained after AF termination would be significant higher than the LVEF during AF, the data of LVEF was not collected.

### **8.3 ECG acquisition**

Prior to the procedure of cardioversion, a standard 12-lead ECG was recorded for each subject. The patient was placed in the supine position. The cardiac electrical activity was recorded simultaneously in all twelve leads. Recording electrodes for leads I, II, III, AVR, AVL and AVF were located on the limbs. Three electrodes were put on both arms and the left leg; an additional electrode was put on the right leg for grounding. The recording sites of the six precordial leads (V1 to V6) are described as below. V1 is located at the junction point of the fourth intercostal space and the right sternal border; V2 is located at the place where the fourth intercostal space and the left sternal border intersect; the location of V3 is equidistant between V2 and V4; the junction point of the fifth intercostal space and the midclavicular line determines the location of V4; V5 and V6 are put at the same level of lead V4 on the anterior and middle axillary line, respectively (162).

The ECG background is graph paper divided into little squares of 1 mm each. The ECG machine was standardized to present the electric voltage at a scale of 10 mm/mV. The recording speed was calibrated to 25 mm/second. Because digital technology is used in current electrographic recordings, analog data can be converted into digital signals for later signal processing.

At least three 12-lead ECG digital samples were obtained for each subject at baseline. The sample length was 10 seconds. All the ECG recordings were stored in a computer with a commercial recording system (Prucka Engineering, Inc., Houston, TX) ECGs were recorded with filter settings of 0.05-100Hz, a sampling frequency of 1000Hz and a 12-bit sampling resolution. Subsequently, the digital recordings were retrieved and transferred to another computer using a portable disk and analyzed off-line.

The baseline ventricular rate during AF was derived from the original ECG prior to cardioversion. The ventricular rate, measured in bpm, was calculated with the number of ventricular beats in the 10-second ECG segment multiplying 6. Assessed ventricular rates may provide information about satisfactory of rate control.

#### **8.4 DCC Procedure**

Electrode positions and the shock waveform:

All patients went through the procedure of DC cardioversion. The two electrodes were placed in anterior-posterior positions on all subjects rather than anterior-lateral positions, as numerous trials have demonstrated that the former positions were more effective than the latter (80). We did not reposition the electrodes during the procedure of cardioversion. A biphasic shock waveform was employed in this study, because usually it requires lower shock energy, fewer shock numbers and achieves greater efficacy when compared with a monophasic shock waveform (95). After the patient was under complete sedation with intravenous propofol and fentanyl, the first shock was delivered from an external defibrillator (Phillips MRX).

Shock energy setting and the number of shocks:

Up to three shocks were delivered in an attempt to restore SR. For the homogeneous DCC therapy among all subjects, the energy of the shocks was designed as 100 Joule (J), 150 J and 200 J for the first, second and third shock respectively. However, for obese patients with a BMI above 35 kg/m<sup>2</sup>, the energy

for the three shocks stepped from 150 J initially to 200 J and 200 J for the second and third shock until DCC succeeded. There were no antiarrhythmic agents used during the procedure of cardioversion.

Data collection of DCC outcomes and complications:

The immediate outcome of each shock and the outcome of DCC at 2 minutes following a successful shock were recorded. After the procedure of DCC was finished, the patient was monitored in a post-anesthetic care unit until the patient was recovered from sedation. During this period, haemodynamic status and complications were observed. All patients were examined for a standard 12-lead ECG prior to hospital discharge. The patient who was maintaining SR in this ECG recording was booked with a follow-up visit at 2 weeks after cardioversion and instructed to come back for an ECG check whenever symptoms suggested AF relapses during the study.

### **8.5 Follow-up**

The design of a follow-up visit at 2 weeks after successful cardioversion is based on the consideration that it has been revealed in several studies that recurrences of AF mainly occurred within two weeks after the restoration of SR (90). This observation could be explained by the theory that electrical remodeling is mainly responsible for the early recurrent AF, because it gets recovered within the first week after successful cardioversion (60). Thus, in the present study, the early AF recurrence is defined as the AF that reoccurs within two weeks following SR restoration.

The subjects who were successfully converted to SR and remained SR at hospital discharge were followed up on the 14th day after cardioversion. A standard 12-lead ECG was obtained on this day to document the patient's cardiac rhythm. Complications and medications were also recorded at this visit.

### **8.6 Signal processing of the surface ECG**

Application of the signal processing techniques in patients with AF includes QRS-T cancellation, and Fourier-based power spectral analysis. Based on a few points, the best ECG sample was selected from the patient's ECG recordings for

subsequent signal processing. The ideal sample was the one (1) with stable baseline; (2) without ventricular signals existing at the very beginning or end of the segment; (3) without ectopic beats; and (4) with less noise and artificial signals.

### **8.6.1 Atrial signal extraction**

Following baseline filtering, the selected ECG sample was subject to both ABS and SVD for QRS-T cancellation.

#### **8.6.1.1 ABS**

The program of ABS was custom written using Labview software (8.6, National Instruments, Texas). The selected ECG sample was opened using this program. The mean ventricular cycle length for all leads was defined with the determination of a start R point and an end R point. Because ABS performs on a single-lead basis, a QRS-T template was generated for each lead by averaging each ventricular wave in the relevant lead. Particularly, a peak detection algorithm was used to recognize R waves in the ECG recordings. The QRS-T intervals were centered on the peak points of the R waves and then averaged to create a template.

Then, the ventricular beats in each lead were identified using template matching and indicated with light dots. The percentage of similarity to the template in each lead can be adjusted in order to identify the variations of QRS complex morphology. Except for ectopic beats, ventricular beats at the very beginning or end of the segment, or the QRS complex with a large morphology variation, almost all ventricular beats could be identified. Finally, the detected ventricular signals were subtracted from the ECG. The removal of QRS-T complexes results in a remaining atrial signal ECG subject to further analysis.

#### **8.6.1.2 SVD**

The program of SVD was custom written using Labview software (8.6, National Instruments, Texas). SVD was performed in the same ECG sample of the individual processed with ABS. The ECG sample was opened using SVD program. The mean ventricular cycle length for all leads was defined with the

determination of a start R point and an end R point. PCA using SVD was employed to extract atrial fibrillatory activity from each individual lead in order to fit dynamic variability of QRST waveform. In detail, for each ECG lead, a QRS-T waveform template from start of QRS to end of T wave was identified manually and the rest of the beats were identified by using correlation function.

Then, the ventricular beats in each lead were identified using template matching and indicated with light dots. The percentage of similarity to the template in each lead can be adjusted in order to identify the variations of QRS complex morphology. Except for ectopic beats, ventricular beats at the very beginning or end of the segment, or the QRS complex with a large morphology variation, almost all ventricular beats could be identified. Finally, the detected ventricular signals were subtracted from the ECG. The removal of QRS-T complexes results in a remaining atrial signal ECG subject to further analysis.

#### **8.6.1.3 Comparison of ABS and SVD**

ABS and SVD algorithms were applied to the same ECG sample in each subject respectively. The evaluation and comparison of the performance of these two methods were completed by visually inspecting the number of leads that had truncated QRS-T waves remained after processed with ABS or SVD.

It has been shown that the average amplitude of atrial fibrillatory waves in the surface ECG ranged from 0 to 4.0 mm, mainly between 0 and 2.5 mm (163, 164). Thus, in the current study, if the amplitude of the residual signal was seen exceeding 4.0 mm, the signal was not regarded as the atrial fibrillatory activity, but the residual ventricular activity. The number of leads having truncated QRS-T after processed with ABS or SVD was visually counted.

#### **8.6.2 Power spectral analysis of AF**

The spectral analysis of atrial fibrillatory waves was performed in all 12 leads for each subject. For each lead, the 10-second recording was passed through a Hanning window, and then fast Fourier transform (FFT) was performed. Fourier transformation program was written using Labview software (8.6, National Instruments, Texas). The residual ECG with atrial fibrillatory signals was opened

using this program. Final results of frequency analysis were displayed as power spectra.

The resulting power spectrum had a frequency resolution of 0.1 Hz. Provided that ventricular activity was removed successfully in the selected lead, the spectrum would display with a single distinct peak, which indicated the value of dominant frequency (DF) in Hz. For each lead the frequency between 2 and 20Hz with the highest spectral power in the periodogram was defined as the DF. In addition to DF, median frequency (MF) and frequency bandwidth (FB) were also assessed using frequency spectral analysis, both in Hz. The MF is the middle value in the frequency power spectrum. The frequency of median power between 2 and 20Hz was defined as the MF. The FB was defined as the frequency difference around the DF containing 50% width of the total spectral power between 2 and 20Hz.

The lead with a power spectrum predominantly containing atrial signals rather than ventricular signals was selected for data recording. When there were two or more leads mainly presenting atrial signals and lead V1 was one of them, V1 will be chosen for parameter recording. This is because lead V1 usually contains the largest fibrillatory wave amplitude among all twelve leads and it has been recommended for AF frequency analysis (103).

The expression “fibrillatory rate” with its unit fpm is recommended for result description of spectral analysis, because this nomenclature is close to other surface ECG rate variables and errors could be avoided otherwise introduced by some expressions, for example the AFCL (165). Therefore, in the present study, fibrillatory frequency was used for the description of power spectrum, whereas fibrillatory frequency was converted to fibrillatory rate by multiplying 60 when the relation between electrophysiological variables and the outcome of cardioversion was explored.

The DFs from leads V1 and V6 were compared to see if the DF alternation between these two leads could present the endocardial left-to-right gradient. The

reason to choose surface ECG leads V1 and V6 for detection of the atrial gradient is because the surface ECG is the routine examination for every patient with AF and the conventional lead position would be practical for clinical application.

### **8.7 Predictors of DC cardioversion outcome**

The value of clinical and echocardiographic parameters and the DF and the atrial frequency gradient detected from the ECG in predicting the outcome of external electrical cardioversion was investigated.

## 9 Results

Continuous variables were expressed as mean  $\pm$  standard deviation (SD), except for AF duration. Because the values of AF duration do not follow normal distribution, they were presented as a median value and range. Discrete variables were expressed as the number of cases and percentage.

Due to the small population, no attempt was made to statistically compare the variables, evaluate the correlations between parameters, or detect independent predictors for the outcome of DCC. The data of clinical variables, echocardiographic parameters, and spectral analysis parameters was generally described.

### 9.1 The data collected on the day of DCC

#### 9.1.1 Patient demographic and clinical characteristics at baseline

A total of twenty-two consecutive patients who were referred to Wellington Hospital for elective DC cardioversion were screened in the study. Eight of them were excluded because the existing atrial arrhythmia was diagnosed as AFL by the cardiologist. One was excluded due to previous PVI. One patient was excluded because the patient not only had echocardiographic missing data but also lost to follow-up at 2 weeks after cardioversion. One patient whose digital ECG signals failed to be read by processing program was excluded. The remaining eleven persistent AF patients who had complete and analyzable recordings comprise the study population. The demographics and clinical characteristics of these patients at baseline are summarized in Table 11.

The study population consisted of 9 men (82%) and 2 women (18%). The mean age was  $64 \pm 10$  years. With regard to race distribution, among the eleven participants there were 8 European (73%), 2 Maori (18%), and 1 Asian (9%). The mean BMI was  $31 \pm 7$  kg/m<sup>2</sup>. The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were  $135 \pm 18$  and  $85 \pm 9$  mmHg respectively. Six subjects had history of tobacco use. As the values of AF duration do not follow normal distribution, they were presented as a median value and range. The median arrhythmia duration was 5 months (range 1 to 108 months). The

episode of AF in five of them was recurrent, while six subjects (55%) were with new-onset AF.

In terms of concomitant diseases, eighty-two per cent of the patients had diagnosed hypertension. Three (27%) of eleven participants had a history of ischemic heart disease. One subject had old myocardial infarction and percutaneous coronary angiography (PTCA) with stenting in the right coronary artery (RCA). One had previous coronary artery bypass graft (CABG) in 2002. Three of the population had diagnosed congestive heart failure (CHF). Regarding NYHA heart failure classification, one was NYHA class II, and two were class III. Diabetes mellitus (DM) was diagnosed in three subjects of the study population. Six (55%) of eleven patients had former or current tobacco use. In the cohort, five out of eleven (45%) had hyperlipidemia. One patient had a history of aortic stenosis (AS) and underwent aortic valve replacement (AVR) surgery in 1999. Among the eleven subjects, only one was regarded as lone AF, because the subject was free of any relevant cardiovascular diseases. No subjects were with chronic obstructive pulmonary disease (COPD) or dysthyroidism. Although one participant was with a history of transient ischemic attack (TIA), nobody had overt stroke, cognitive dysfunction or peripheral arterial diseases.

Medication administration was recorded at baseline. All patients were taking cardiovascular drugs during the study. The medication administration varied between individuals depending on the concomitant heart disease and the cardiologist's preference (summarized in Table 11). Notably, only 4 (36%) of 11 patients were taking class I or III antiarrhythmic agents during the period of the study. In particular, three patients were with amiodarone (class III) and one was with flecainide (class IC), but no subjects were using sotalol. Beta-blockers were commonly used in the majority of the subjects (10 out of 11) for ventricular rate control. Among these ten patients with beta-blockers, nine were taking metoprolol and one was with carvedilol. Two subjects were using a calcium channel blocker (CCB), diltiazem and felodipine respectively. More than half of the participants were taking an angiotensin-converting enzyme inhibitor (ACEI), either cilazapril or accupril; only one patient was with an angiotensin receptor

blocker (ARB), which was candesartan. Digoxin was prescribed in three participants who were with fast ventricular rate (n=2) or heart failure (n=1). The one who took digoxin for CHF also had furosemide combined. All patients were taking either dabigatran or warfarin for anticoagulation. One subject was taking anti-platelet drugs (aspirin) during the study. More than half of the patients (6 out of 11) were using statins, either simvastatin or atorvastatin.

**Table 11 Demographic and clinical characteristics of subjects at baseline**

Age (years)	64 ± 10
Male/female	9 (82%)/2 (18%)
European/Maori/Asian	8 (73%)/2 (18%)/1 (9%)
BMI (kg/m <sup>2</sup> )	31 ± 7
SBP (mmHg)	135 ± 18
DBP (mmHg)	85 ± 9
Duration of AF (months)	5 (1 to 108)
Recurrent AF/new-onset AF	5 (45%)/6 (55%)
Prior or current smoking	6 (55%)
Hypertension	9 (82%)
Hyperlipidemia	5 (45%)
DM	3 (27%)
CHD	3 (27%)
VHD	1 (9%)
CHF	3 (27%)
Previous cardiac surgery	2 (18%)
Class I or III antiarrhythmic agents	4 (36%)
Beta-blockers	10 (91%)
CCBs	2 (18%)
Digitalis	3 (27%)
Antiplatelet agents	1 (9%)
ACEIs	6 (55%)
ARBs	1 (9%)
Diuretic	1 (9%)
Statins	6 (55%)

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; AF = atrial fibrillation; DM = diabetes mellitus; CHD = coronary heart disease; VHD = valvular heart disease; CHF = congestive heart failure; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

### **9.1.2 Success of DCC**

Successful cardioversion was finally achieved in 55% of the patients (6 out of 11). Three participants were successfully converted to SR with the first shock. The second electrical shock initiated SR in another two patients. SR restoration was finally achieved by the third shock in one subject. The treatment of DCC failed on the remaining five patients in whom AF was not terminated with all three shocks.

### **9.1.3 The recurrence of AF on the day of DCC**

All successfully converted subjects were free of AF relapses at two minutes following cardioversion and at the time of hospital discharge. However, atrial premature beats (APBs) were observed in two subjects during the monitoring following successful cardioversion.

### **9.1.4 Complications and medications on the day of DCC**

No complications, such as death, cerebrovascular accidents (CVAs), systemic embolism, bleeding, acute heart failure, or acute coronary syndrome (ACS), were detected in any patients during the post-anesthetic monitoring. Except for propofol and fentanyl, no others drugs were used during the procedure of cardioversion.

## **9.2 The data collected at two-week follow-up**

### **9.2.1 The recurrence of AF at two-week follow-up**

ECGs recorded at two weeks after initiation of SR did not reveal any patients who relapsed into AF. Thus, there was no data of early AF recurrences available for analysis. However, a regular atrial bigeminal rhythm presenting as APBs with short coupling intervals was recorded in one participant at 2-week follow-up.

### **9.2.2 Complications and medications at two-week follow-up**

No complications, such as death, CVAs, systemic embolism, bleeding, acute heart failure, or acute coronary syndrome (ACS), were observed in any patients at two-week follow-up. No changes of medication administration were found at this follow-up.

### 9.3 Echocardiographic measurements

A transthoracic echocardiography report within 12 months prior to or shortly after the procedure of cardioversion was obtained for each subject. The recorded parameters included LAD (mm) and LAA (cm<sup>2</sup>). The estimated LAD and LAA were summarised in Table 12. It can be seen that the LAD and LAA varied widely among individuals, with the range of 31.9-63.3 mm and 15.9-42.3 cm<sup>2</sup>, respectively. The mean value of LAD was  $48.4 \pm 8.8$  mm and the mean LAA was  $29.4 \pm 7.7$  cm<sup>2</sup>.

**Table 12 Measurements of LAD and LAA**

Patient No.	LAD (mm)	LAA (cm <sup>2</sup> )
Pnt 1	44.7	25.8
Pnt 2	51.1	31.1
Pnt 3	55.4	37.9
Pnt 4	40	15.9 (min)
Pnt 5	63.3 (max)	42.3 (max)
Pnt 6	54.6	31.3
Pnt 7	50.6	32.7
Pnt 8	31.9 (min)	25.3
Pnt 9	54.6	35.1
Pnt 10	44.2	22
Pnt 11	42.1	23.5
The mean value	$48.4 \pm 8.8$	$29.4 \pm 7.7$

LAD = left atrial diameter; LAA = left atrial area; Pnt = patient.

### 9.4 ECG analysis

#### 9.4.1 The performance of QRS-T removal approaches (ABS & SVD)

Table 13 summarizes the performance of ABS and SVD, which was evaluated and compared by visually counting the number of leads having truncated QRS-T signals remaining after ABS or SVD filtered the same ECG sample.

It is clear from the data in Table 13 that with a large number of truncated ventricular signals neither ABS nor SVD performed perfect in the ECG samples. There were a few ventricular beats that failed to be recognized by both ABS and SVD in lead AVF of Patient 3 and lead III of Patient 11. In both Patient 4 and 8, one QRS complex was remained at the very beginning of each lead in the

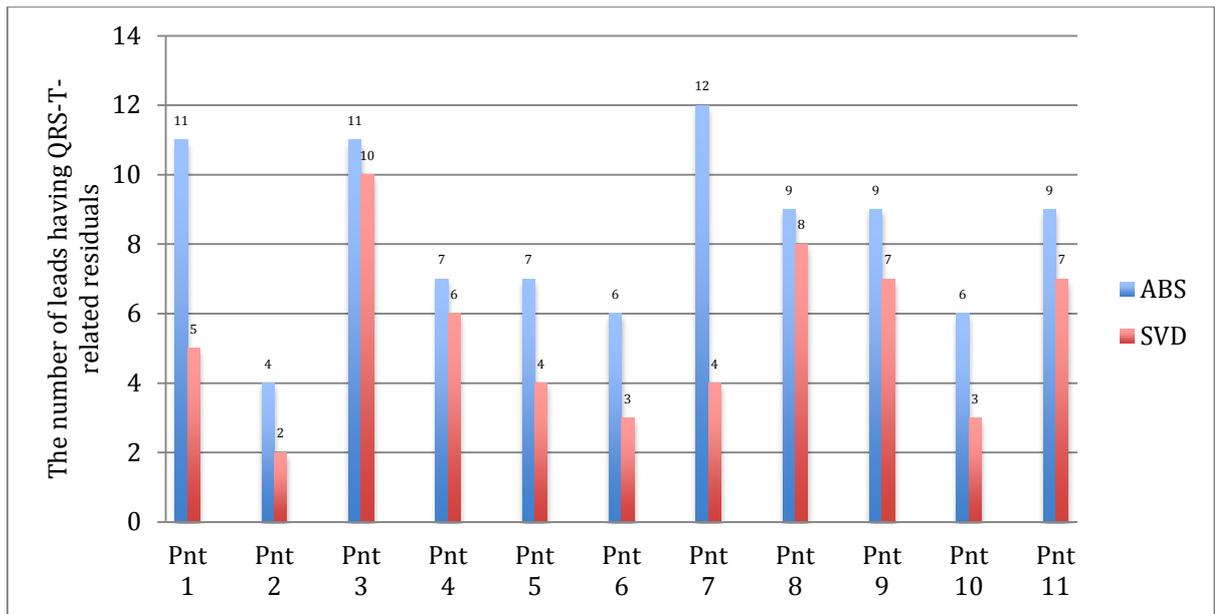
performance of not only ABS but also SVD. In Patient 2, 9 and 10 there was an initial T wave in each lead with both QRS-T cancellation methods.

However, it can be seen from Figure 10 that there were more leads having residual QRS-T signals processed with ABS than with SVD in all subjects. The differences were more obvious in some subjects (Patient 1, 2, 5, 6, 7, and 10). It may be concluded that although neither method performed with a satisfactory result of QRS-T cancellation, the QRS-T-related residuals were fewer in the performance of SVD when compared with ABS algorithm.

**Table 13 Visually inspected performances of ABS and SVD**

Patient number	QRS-T subtraction algorithms	The number of leads having QRS-T-related residuals	The performance of atrial signal extraction approaches
Pnt 1	ABS	11	
	SVD	5	
Pnt 2	ABS	4	Good performance; one truncated T wave in each lead
	SVD	2	Good performance; one truncated T wave in each lead
Pnt 3	ABS	11	Unrecognized QRS complexes in lead AVF
	SVD	10	Unrecognized QRS complexes in lead AVF
Pnt 4	ABS	7	One truncated QRS complex in each lead
	SVD	6	One truncated QRS complex in each lead
Pnt 5	ABS	7	
	SVD	4	
Pnt 6	ABS	6	
	SVD	3	
Pnt 7	ABS	12	Bad performance
	SVD	4	Good performance
Pnt 8	ABS	9	Bad performance; one truncated QRS complex in each lead
	SVD	8	Bad performance; one truncated QRS complex in each lead
Pnt 9	ABS	9	One truncated T wave in each lead
	SVD	7	One truncated T wave in each lead
Pnt 10	ABS	6	One truncated T wave in each lead
	SVD	3	One truncated T wave in each lead
Pnt 11	ABS	9	Unrecognized QRS complexes in lead III
	SVD	7	Unrecognized QRS complexes in lead III

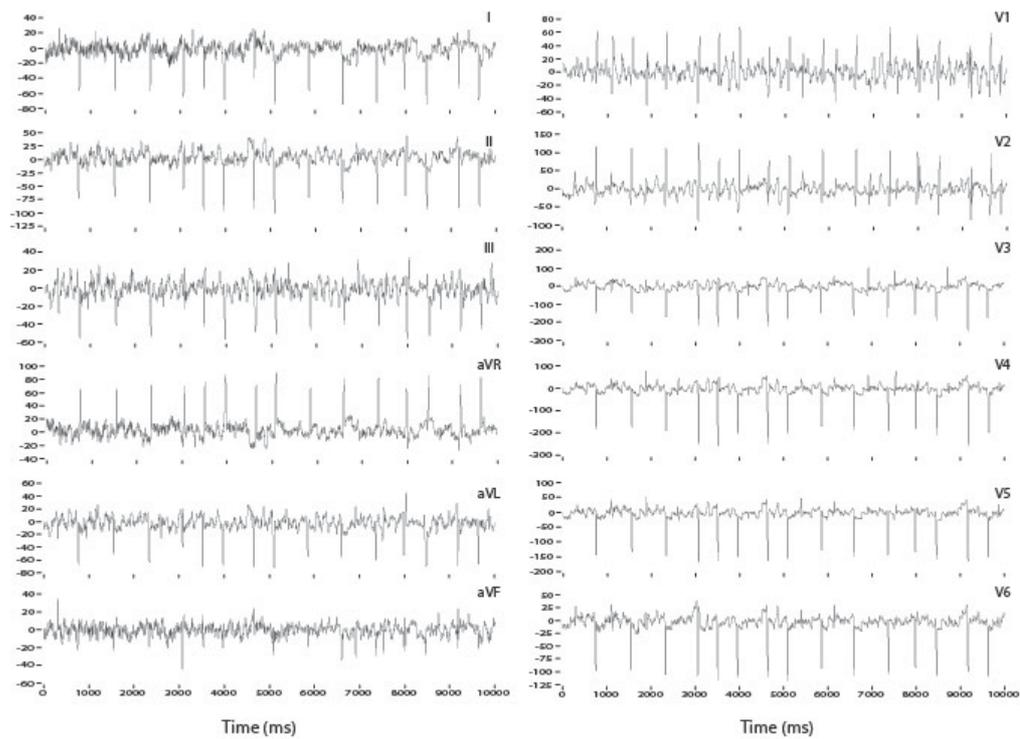
ABS = average beat subtraction; SVD = singular value decomposition; Pnt = patient.



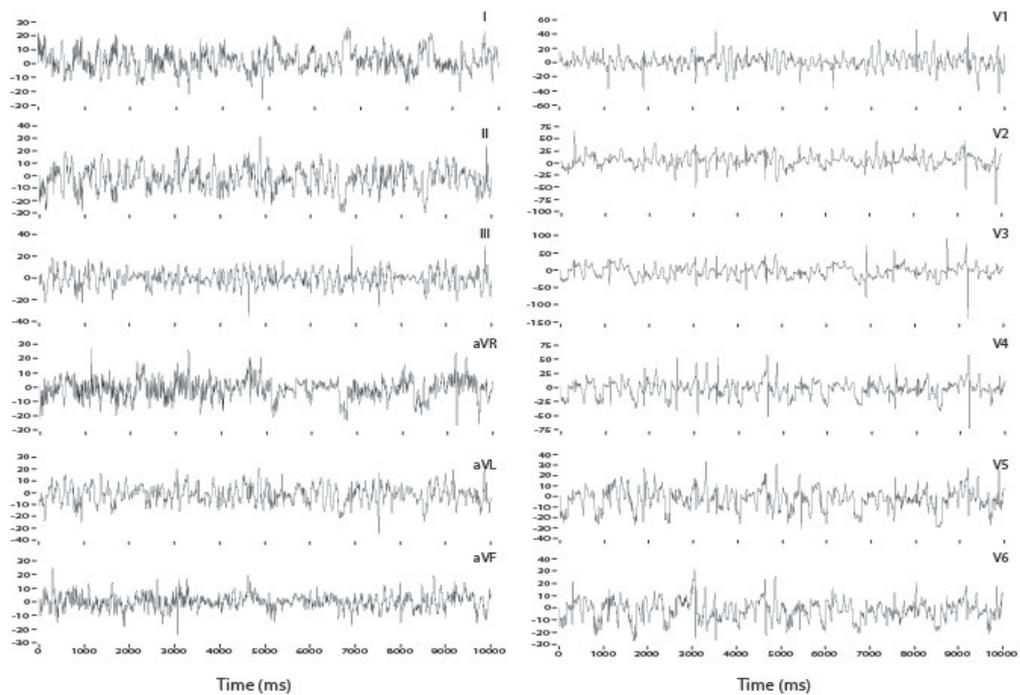
**Figure 10 The number of leads having QRS-T-related residuals after processed with ABS and SVD.**

The atrial extraction performance of ABS and SVD in Patient 7 was demonstrated as an example of a great contrast. Figure 11 shows that residual QRS-T signals existed in all 12 leads processed with ABS, whereas there were only 4 leads with QRS-T-related residuals in the performance of SVD.

Figure 12, 13, and 14 demonstrate a sample of QRS-T subtraction in one subject. Figure 12 is the original ECG recording of the patient. Figure 13 is the ABS filtered ECG, and Figure 14 is the remaining ECG following SVD filtering. It can be seen from Figure 13 that residual components of QRS-T complexes are apparent in all leads demonstrating a failure of ABS to completely remove QRS-T wave components of the ECG. Figure 14 demonstrates that although truncated QRS-T signals are apparent in the majority of leads demonstrating a failure of SVD to completely subtract ventricular activity of the ECG, leads I, II, III and aVL are largely free of residual QRS-T components apart from the initial QRS-T complex.

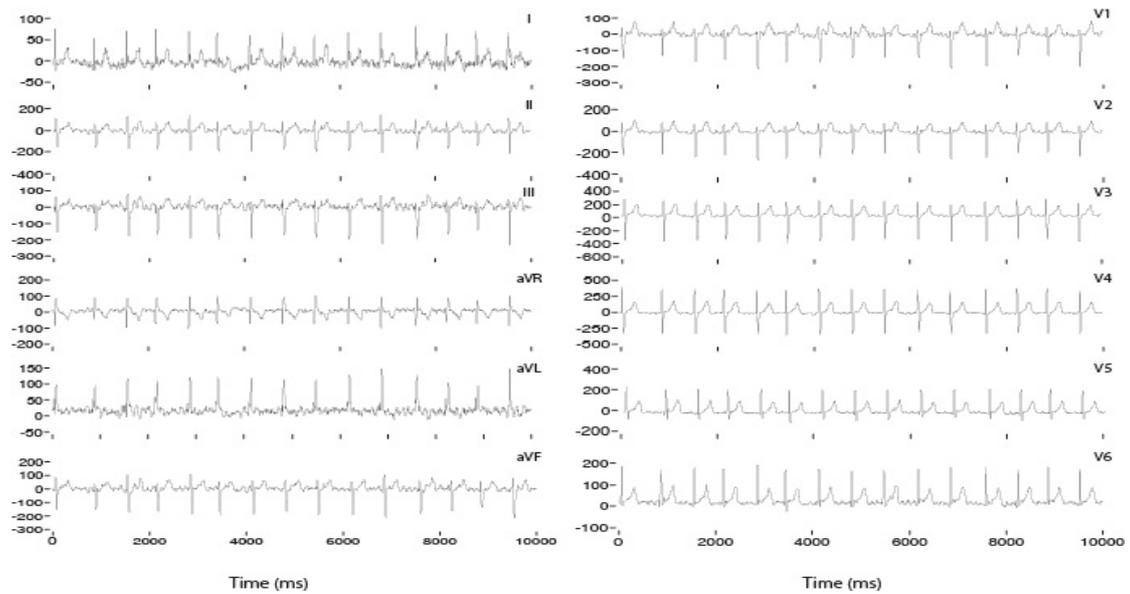


7407 ABS filtered ECG



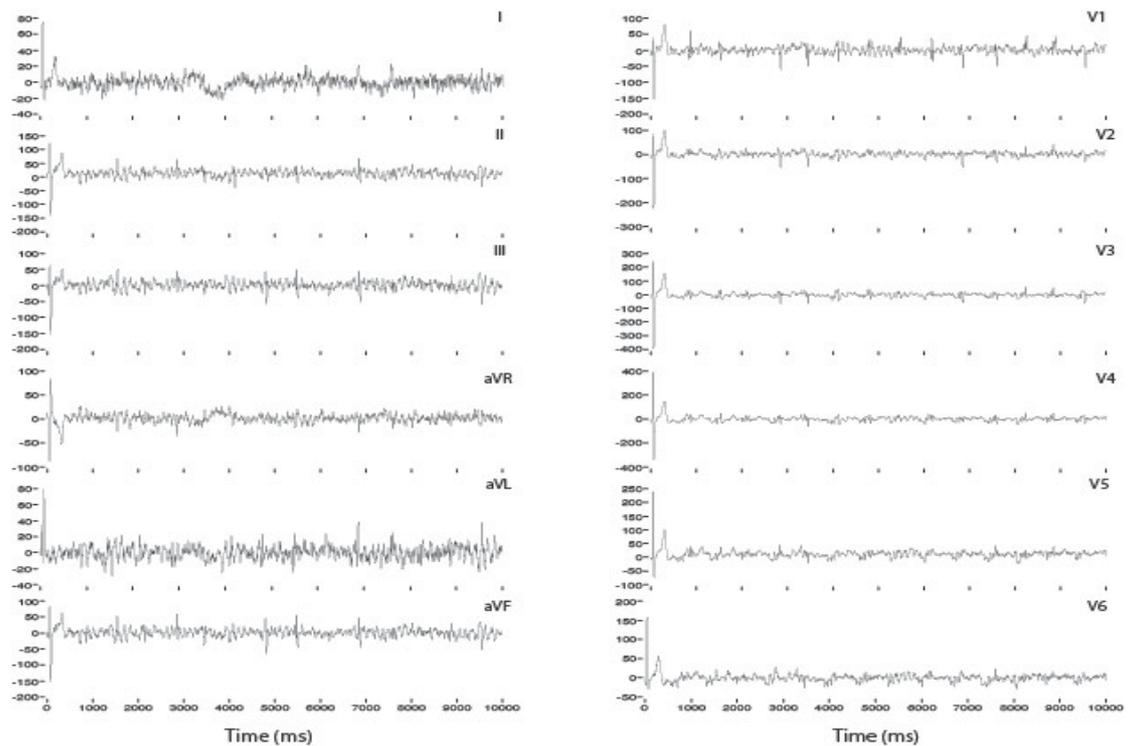
7407 SVD filtered ECG

**Figure 11 A great contrast in atrial extraction performance between ABS and SVD.**



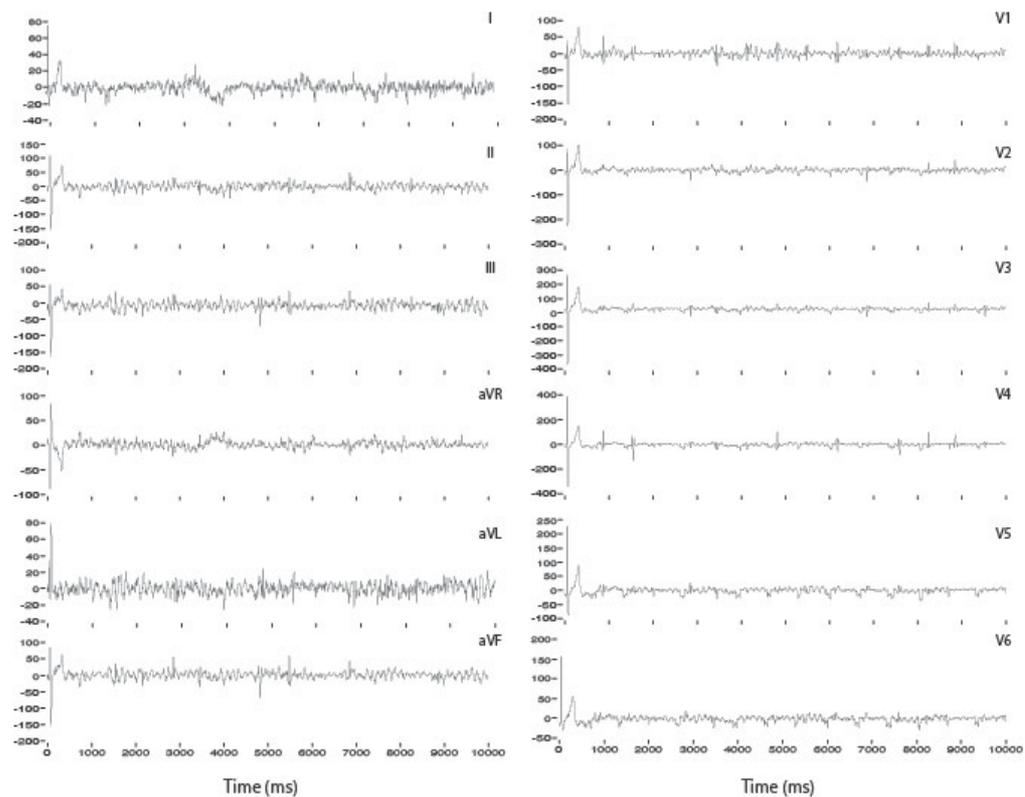
6434 ECG

**Figure 12 The original ECG recording of a subject in AF.**



6434 ABS filtered ECG

**Figure 13 ECG from the same patient as shown in Figure 12 following ABS filtering. Residual components of the QRS complexes are apparent in all leads demonstrating a failure of this subtraction method to completely remove the QRS-T wave components of the ECG.**



6434 SVD filtered ECG

**Figure 14 ECG from the same patient as shown in Figure 12 following SVD filtering. Residual components of the QRS complexes are apparent in the majority of leads demonstrating a failure of this subtraction method to completely remove the QRS-T wave components of the ECG. However, apart from the initial QRS-T complex, leads I, II, III and aVL are largely free of ventricular components.**

#### 9.4.2 Spectral analysis of AF

The frequency analysis of AF was performed in all twelve leads for each patient. The lead with a power spectrum predominantly containing atrial signals was selected for data recording, and V1 was the preferred lead among all leads. Table 14 demonstrates the results of frequency power spectral analysis with different atrial signal extraction algorithms.

Interestingly, the selected leads were the same between ABS and SVD methods. Lead V1 primarily represented the lead whose power spectrum was mainly with atrial fibrillatory activity in 8 cases. Other selected leads included lead III and lead I in 2 cases and 1 case respectively.

It can be seen that all values of DF and MF were between 4-9 Hz, which indicated atrial fibrillatory signals. The mean values of DF and MF of the atrial signals extracted by ABS and SVD did not show large alternations between the two methods, assessed as  $6.4 \pm 0.6$  versus  $6.6 \pm 0.7$  Hz and  $6.7 \pm 0.7$  versus  $6.5 \pm 0.7$  Hz, while the mean FB seemed differ between ABS and SVD, with a value of  $4.3 \pm 1.9$  versus  $3.4 \pm 2.0$  Hz, respectively.

In terms of the parameter alternations between individuals, the measurements of DF just slightly varied from 5.8 to 7.6 Hz in ABS and from 5.9 to 7.7 Hz in SVD. Similarly, the values of MF did not vary much as well (5.75 - 7.57 Hz in ABS, and 5.82 - 7.62 Hz in SVD). In contrast, the values of FB varied widely between individuals from 0.88 to 6.72 Hz and from 0.87 to 6.26 Hz in ABS and SVD respectively.

**Table 14 The results of spectral analysis (in the expression of atrial fibrillatory frequency)**

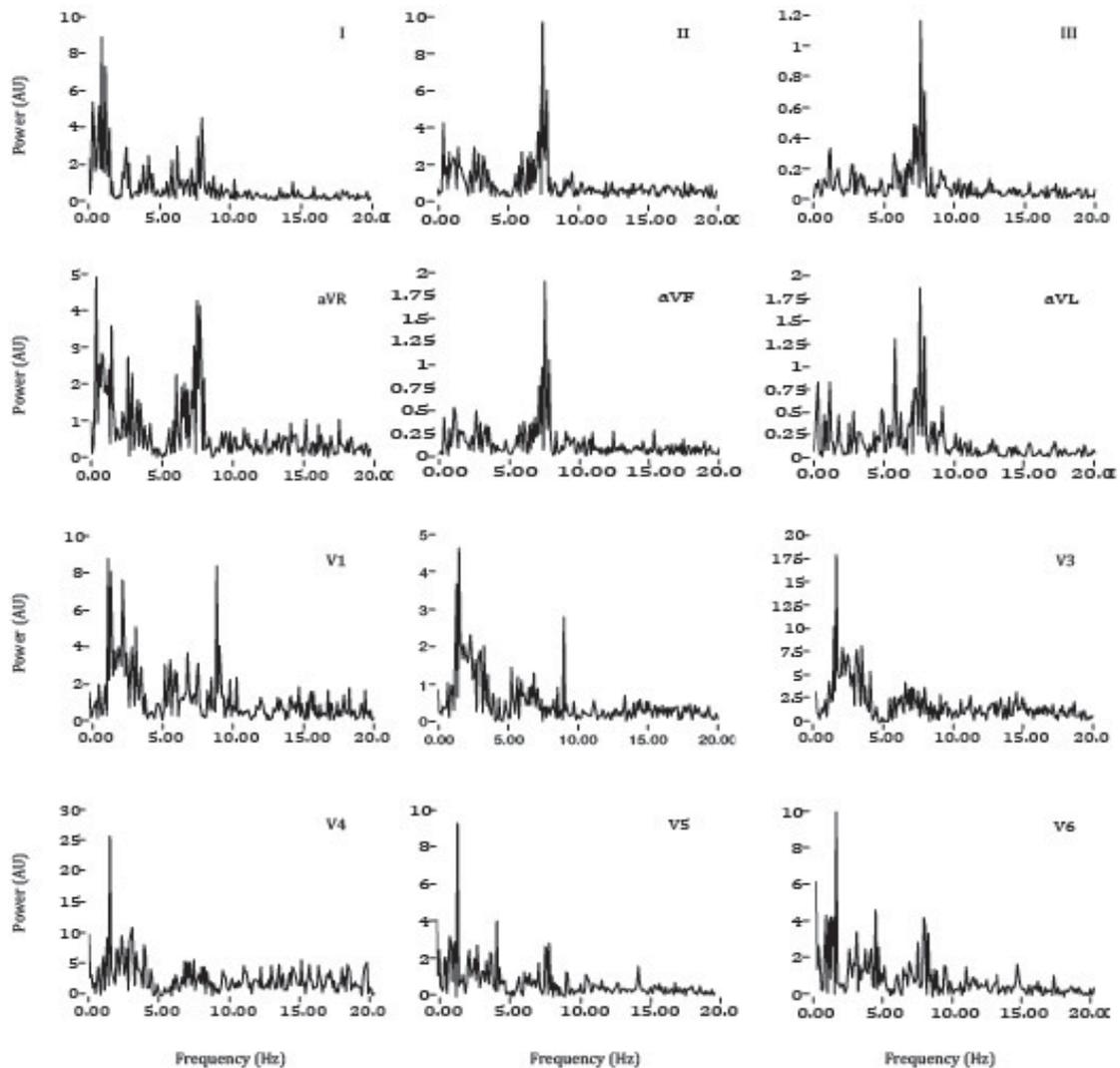
Patient number	ABS				SVD			
	The lead*	DF (Hz)	MF (Hz)	FB (Hz)	The lead*	DF (Hz)	MF (Hz)	FB (Hz)
Pnt 1	V1	5.9	6.016	5.0624	V1	5.9	6.0245	5.1211
Pnt 2	I	5.9	6.2685	5.7615	I	5.9	6.4225	5.8969
Pnt 3	V1	5.9	5.7514 (min)	0.8821 (min)	V1	5.9 (min)	5.8164 (min)	0.8716 (min)
Pnt 4	III	7.6 (max)	7.5718 (max)	4.6294	III	7.6	7.5568	4.217
Pnt 5	III	7.2	7.4757	5.5665	III	7.7 (max)	7.6167 (max)	4.9846
Pnt 6	V1	6.6	7.4094	4.6521	V1	6.6	6.5521	2.2176
Pnt 7	V1	6	6.8956	6.72 (max)	V1	6	5.8615	1.6152
Pnt 8	V1	6.7	7.3563	5.5649	V1	7.6	7.4057	6.2577 (max)
Pnt 9	V1	6.1	5.9866	1.4358	V1	6.1	5.8214	1.3676
Pnt 10	V1	6.2	6.148	2.3955	V1	6.5	6.2244	1.9315
Pnt 11	V1	5.8 (min)	6.4103	4.0876	V1	7.1	6.4065	2.66
Mean value $\pm$ SD (Hz)		6.4 $\pm$ 0.6	6.7 $\pm$ 0.7	4.3 $\pm$ 1.9		6.6 $\pm$ 0.7	6.5 $\pm$ 0.7	3.4 $\pm$ 2.0

\* The lead with a power spectrum predominantly containing atrial signals rather than ventricular signals was selected for data recording. When there were two or more leads mainly presenting atrial signals and lead V1 was one of them, V1 will be chosen for parameter recording.

ABS = average beat subtraction; SVD = singular value decomposition; DF = dominant frequency; MF = median frequency; FB = frequency bandwidth; Hz = hertz; Pnt = patient; SD = standard deviation.

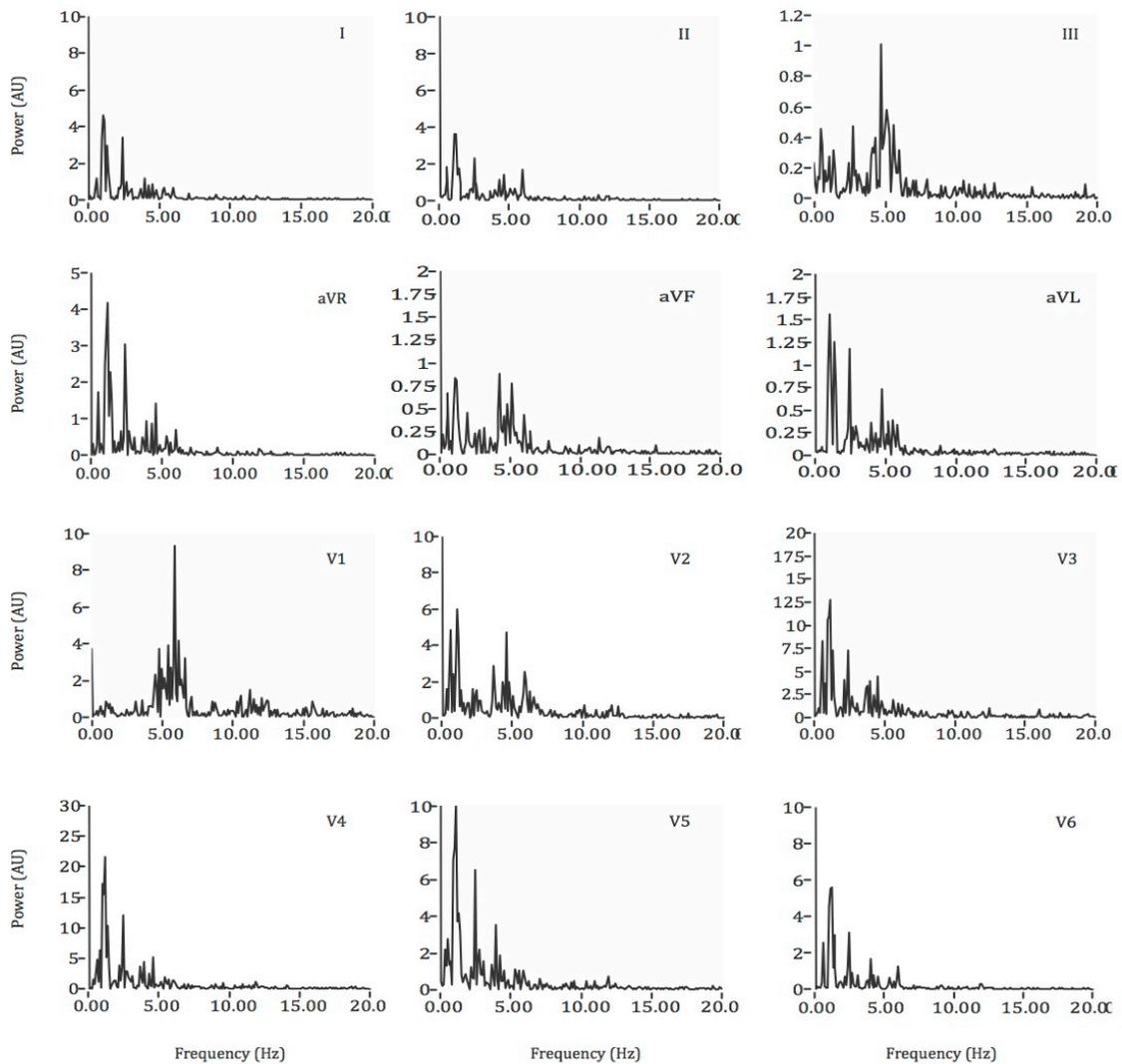
Figure 15 demonstrates the power spectra of the ECG following SVD removal of the QRS-T components from the ECG shown in Figures 12. This is an example of SVD filtered ECG power spectra with a large number of residual ventricular activity. The observation that some power spectra were dominated by energy from noises or residua from truncated QRS complexes or T waves was probably due to the poor performance of QRS-T subtraction methods and the relatively low amplitude of atrial fibrillatory waves. While a peak in the 4-9 Hz range, corresponding to the atrial rate is apparent in all 12 leads, considerable residual activity due to the incomplete removal of the QRS-T complex is still apparent at a lower frequency. In leads II, III, aVF and aVL the dominant peak in the power spectrum is between 4 and 9 Hz, corresponding to the atrial signal, while in the remaining leads the peak at around 2 Hz, corresponding to the ventricular rate is the dominant peak in the power spectrum.

A good example of SVD filtered ECG power spectrum in lead V1 is demonstrated in Figure 16. It can be seen that the power spectrum in lead V1 predominantly contains atrial fibrillatory signals presenting a single peak at 5.9 Hz. Lead III shows a dominant peak at the frequency of atrial activity (around 5 Hz). But the power spectra in the remaining leads were dominated by energy from residual ventricular activity whose frequency was below 4 Hz.



6434 · SVD

**Figure 15 Power spectra of the ECG following SVD removal of the QRS-T components from the ECG shown in Figure 12. While a peak in the 4-9 Hz range, corresponding to the atrial rate is apparent in all leads, considerable residual activity due to the incomplete removal of the QRS-T complex is still apparent at a lower frequency. In leads II, III, aVF and aVL the dominant peak in the power spectrum is between 4 and 9 Hz, corresponding to the atrial signal, while in the remaining leads the peak at around 2 Hz, corresponding to the ventricular rate is the dominant peak in the power spectrum.**



4642 - SVD

**Figure 16 Power spectra of the ECG of another patient following filtering using SVD. In this instance only leads III and V1 show a dominant peak at the frequency of atrial activity (around 5 Hz) and the remaining leads have dominant peaks and associated harmonics at lower frequencies due to incomplete removal of QRS-T complexes.**

### 9.4.3 Detection of the atrial frequency gradient from the surface ECG

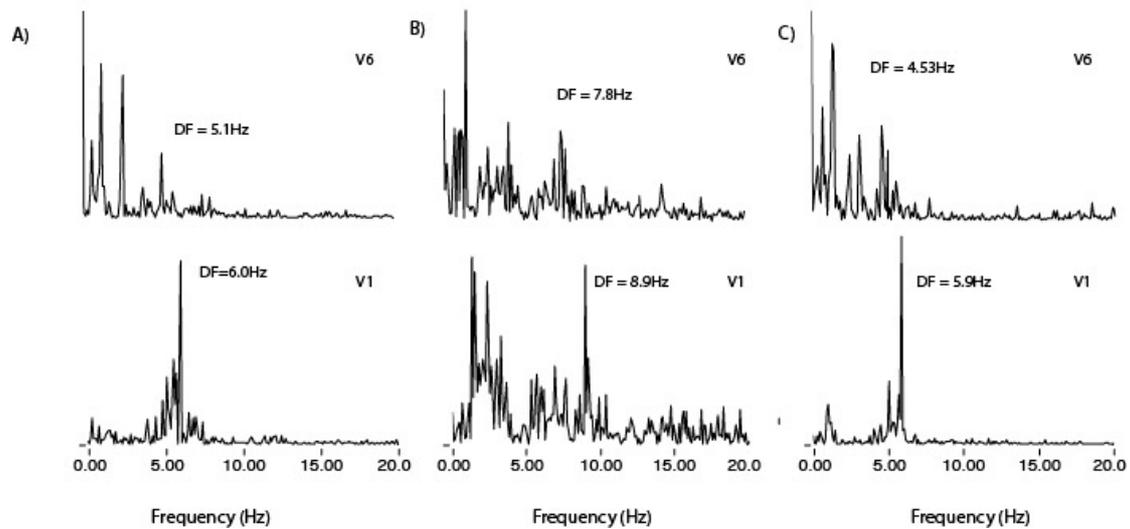
Because the QRS-T-related residuals were fewer in the performance of SVD when compared with ABS approach, the values of DF used to detect the atrial gradients were derived from SVD filtered ECG power spectra.

The alternations of DF between leads V1 and V6 and shock results were summarized in Table 15. The DFs of lead V1 were successfully assessed in all available subjects. This is because lead V1 has the most distinct atrial amplitude among the twelve standard leads and it has been proved to be the preferred lead for atrial signal extraction (103). However, it failed to detect a discrete dominant peak in the spectrum of lead V6 for two subjects, this might be due to the relatively low amplitude of atrial fibrillatory waves in lead V6. Among the remaining patients, the alternations of DF were numbered from high to low according to the numerical value. Except for two negative values of DF difference between the two leads, Table 15 illustrates a consistent pattern observed for the DF of atrial activity to be faster in V1, and to be slow progressively across the precordial leads to V6. There was a frequency that is between 0.4 and 2.0 Hz faster in lead V1 than in V6. Three examples of the DF difference between leads V1 and V6 are shown in Figure 17.

**Table 15 Alternations between the DFs from leads V1 and V6**

Patient number	DF in lead V1 (Hz)	DF in lead V6 (Hz)	The alternations of DF between leads V1 and V6 (Hz)
Pnt 9	6.1	4.1	2.0
Pnt 1	5.9	4.0	1.9
Pnt 3	5.9	4.5	1.4
Pnt 5	7.1	5.9	1.2
Pnt 4	8.9	7.8	1.1
Pnt 7	6.0	5.1	0.9
Pnt 11	7.1	6.7	0.4
Pnt 6	6.6	6.8	-0.2
Pnt 10	6.5	7.2	-0.7
Pnt 2	6.1	No clear peak	-
Pnt 8	7.6	No clear peak	-

DF = dominant frequency; Pnt = patient.



**Figure 17 Power spectra from leads V1 and V6 following SVD filtering for three different patients, A, B and C. In patient A, the DF in V1 was 6.0 Hz, and in V6 was 5.1 Hz. In patient B, the DF in V1 was 8.9 Hz and in V6 was 7.8 Hz. In patient C, the DF in V1 was 5.9 Hz and in V6 was 4.5 Hz.**

## 9.5 Predictors for the outcome of DCC

Because no AF recurrence was observed in any subjects, only predictors for results of shock were analyzed. Based on the initial outcome of electrical cardioversion, subjects were categorized into two groups, i.e. the subjects in whom SR was restored and those still remained in AF with failure of three shocks. The comparison of clinical variables, echocardiographic parameters, and ECG parameters between the two groups was generally described.

### 9.5.1 Clinical parameters & shock results

Demographic and clinical characteristics of the subjects with successful DC cardioversion (no matter how many shocks were used) and those failed to restore SR (up to 3 shocks were used) were compared in Table 16.

The differences of gender and ethnicity distribution were not great between the patients remained in AF and those restored with SR following electrical cardioversion.

Contrary to expectation, the patients with successful cardioversion seemed older than those with failed results, with the mean age of  $67 \pm 10$  and  $60 \pm 9$  years respectively. Similarly, blood pressure seemed higher in the former than in the latter,  $143 \pm 14/89 \pm 6$  and  $125 \pm 19/81 \pm 10$  mmHg respectively.

The mean value of BMI was lower in the people with successful cardioversion than in those with failed results ( $30 \pm 3$  vs.  $33 \pm 9$  kg/m<sup>2</sup>). The median value and range of AF duration prior to cardioversion were lower in the former than in the latter as well, with 4.5 (1 to 77) and 6 (1 to 108) months respectively. Moreover, the values of these two variables were further lower in patients with SR restored by the first shock, with BMI of  $29 \pm 5$  kg/m<sup>2</sup> and AF duration of 4 (1 to 77) months.

New-onset AF accounted for more proportion among subjects with SR restored (67%) compared with those with AF maintained following DC cardioversion (40%). Tobacco use was more in the patients who had shock failure than in those who were converted to SR with only one shock.

In terms of underlying heart diseases, it seemed that there was not much difference in distribution of diagnosed hypertension and hyperlipidemia between the subjects who were converted successfully and those remained in AF. And due to the small population, the data of diabetes mellitus (DM), coronary heart disease (CHD), valvular heart disease (VHD), congestive heart failure (CHF) and previous cardiac surgery was not enough for analysis to draw a proper conclusion.

**Table 16 Comparison of demographic and clinical characteristics in subjects stratified by shock results**

Variables	Study population (n = 11)	AF remained with DCC treatment (n = 5)	SR restored with DCC treatment (n = 6)	SR restored with the first shock in DCC treatment (n = 3)
Age (years)	64 ± 10	60 ± 9	67 ± 10	63 ± 11
Male/female	9/2	4/1	5/1	2/1
European/Maori /Asian	8/2/1	4/1/0	4/1/1	1/1/1
BMI (kg/m <sup>2</sup> )	31 ± 7	33 ± 9	30 ± 3	29 ± 5
SBP (mmHg)	135 ± 18	125 ± 19	143 ± 14	136 ± 8
DBP (mmHg)	85 ± 9	81 ± 10	89 ± 6	89 ± 3
Duration of AF (months)	5 (1 to 108)	6 (1 to 108)	4.5 (1 to 77)	4 (1 to 77)
Recurrent AF/new-onset AF	5 (45%)/ 6 (55%)	3 (60%)/ 2 (40%)	2 (33%)/ 4 (67%)	1 (33%)/ 2 (67%)
Prior or current smoking	6 (55%)	3 (60%)	3 (50%)	1 (33%)
Hypertension	9 (82%)	4 (80%)	5 (83%)	2 (67%)
Hyperlipidemia	5 (45%)	2 (40%)	3 (50%)	1 (33%)
DM	3 (27%)	2 (40%)	1 (17%)	1 (33%)
CHD	3 (27%)	2 (40%)	1 (17%)	1 (33%)
VHD	1 (9%)	0	1 (17%)	0
CHF	3 (27%)	2 (40%)	1 (17%)	0
Previous cardiac surgery	2 (18%)	1 (20%)	1 (17%)	0
Class I or III antiarrhythmic agents	4 (36%)	0	4 (67%)	3 (100%)
Beta-blockers	10 (91%)	5 (100%)	5 (83%)	2 (67%)
CCBs	2 (18%)	1 (20%)	1 (17%)	0
Digitalis	3 (27%)	2 (40%)	1 (17%)	0
Antiplatelet agents	1 (9%)	0	1 (17%)	0
ACEIs	6 (55%)	2 (40%)	4 (67%)	2 (67%)
ARBs	1 (9%)	0	1 (17%)	0
Diuretic	1 (9%)	1 (20%)	0	0
Statins	6 (55%)	3 (60%)	3 (50%)	1 (33%)

DCC = direct current cardioversion; AF = atrial fibrillation; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; DM = diabetes mellitus; CHD = coronary heart disease; VHD = valvular heart disease; CHF = congestive heart failure; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

No subjects in whom SR finally failed to be restored were using antiarrhythmic agents, whereas 4 (67%) of 6 patients with successful DC cardioversion were with class I or III antiarrhythmic agents (amiodarone or flecainide) during the study. Furthermore, this observation was enhanced by the data showing that the subjects in whom SR was restored with just one shock were 100% with administration of amiodarone or flecainide during the period of the study.

Five (83%) of six people with cardioversion success were using ACEIs or ARBs during the study, whereas only 40% of the patients (2 out of 5) with final failure results were taking ACEIs. As CCBs and digitalis were not in common usage in the population and the sample size was small, no enough data of these two drugs was available for analysis between the two groups.

The use of beta-blockers seemed not to improve the outcome of transthoracic cardioversion with the data showing that the proportion of beta-blocker administration was 100% in the people failed to restore SR, 83% in the patients with SR finally restored, and 67% in those restored with SR by the first shock. Similarly, the usage of statins seemed not to promote the outcome of external cardioversion either, as the data in Table 16 shows that the proportion of statin administration was 60% in the people failed to restore SR, 50% in the patients with SR restored, and 33% in those restored with SR by only one shock. The observations about the influence of the drugs were probably scrambled due to the rather small cohort.

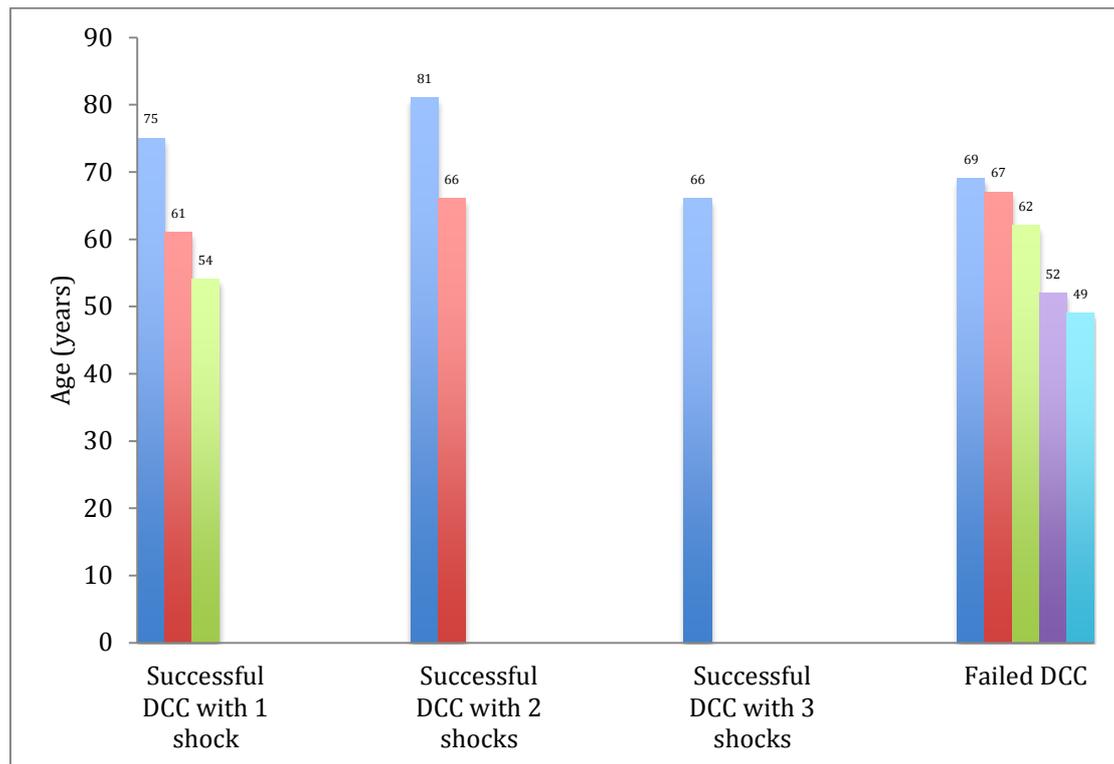
As age and AF duration are the most common used clinical indexes for prediction of cardioversion outcome, the data of age and AF duration were summarized and compared between patients with different shock results in Table 17 and 18. There was no observation that the patients who were converted were younger than those with failed DC cardioversion (Figure 18). It seemed that the duration of AF was longer in the patients with failed cardioversion than in those with SR restored (Figure 19).

**Table 17 Age and shock results**

Patient number	Results of 1 <sup>st</sup> shock	Results of 2 <sup>nd</sup> shock	Results of 3 <sup>rd</sup> shock	The number of failed shocks	The final result of DCC	Age (years)	The mean value of age $\pm$ SD (years)			
Pnt 1	S	-	-	0	S	75	63 $\pm$ 11	67 $\pm$ 10	64 $\pm$ 10	
Pnt 9						61				
Pnt 3						54				
Pnt 7	F	S	-	1	F	81	64 $\pm$ 10	60 $\pm$ 9	64 $\pm$ 10	
Pnt 5		F		F		2				66
Pnt 8						3				66
Pnt 2						69				
Pnt 11						67				
Pnt 10	62									
Pnt 4	52									
Pnt 6	49									

AF = atrial fibrillation; DCC = direct current cardioversion; SD = standard deviation; Pnt = patient;

S = success; F = failure.



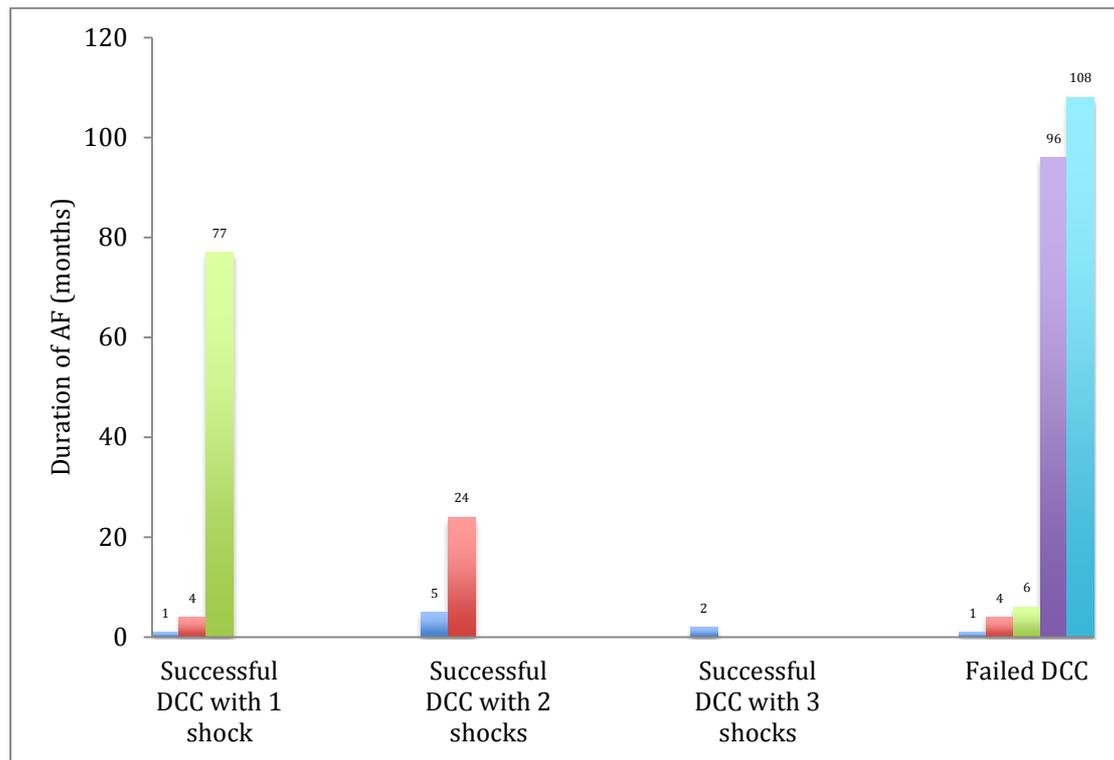
**Figure 18 Age and shock results.**

**Table 18 Duration of AF and shock results**

Patient number	Results of 1 <sup>st</sup> shock	Results of 2 <sup>nd</sup> shock	Results of 3 <sup>rd</sup> shock	The number of failed shocks	The final result of DCC	AF Duration (months)	The median value of AF duration and range (months)		
Pnt 9	S	-	-	0	S	1	4 (1-77)	4.5 (1-77)	5 (1-108)
Pnt 1						4			
Pnt 3						77			
Pnt 7	F	S	-	1	F	5	5.5 (1-108)	6 (1-108)	
Pnt 5		24							
Pnt 8		S		2		2			
Pnt 6		F		3		1			
Pnt 11	F	F	-	-	F	4	5 (1-77)	5 (1-77)	
Pnt 10						6			
Pnt 4						96			
Pnt 2						108			

AF = atrial fibrillation; DCC = direct current cardioversion; SD = standard deviation; Pnt = patient;

S = success; F = failure.



**Figure 19 Duration of AF and shock results.**

An observation was also made in the relation of ventricular rates derived from the digital ECG prior to cardioversion and the results of cardioversion (Figure 20). Although beta-blockers were commonly used in the cohort (91%), it can be seen from Table 19 that rate control efficacy of the drugs varied among subjects (54 – 114 bpm). The ventricular rate was less than 100 bpm in 9 of 11 patients, and the mean ventricular rate was  $84 \pm 18$  bpm. The mean ventricular rate for the group where cardioversion failed to terminate AF was  $73 \pm 19$  bpm, while the mean ventricular rate for the people where cardioversion was successful was  $91 \pm 16$  bpm. Because no significant difference was detected in ventricular rates between the above two groups separated by the outcome of cardioversion ( $p=0.12$ , unpaired t-test), there was no evidence to support the notion that the less controlled ventricular rate would be a predictor of failed cardioversion.

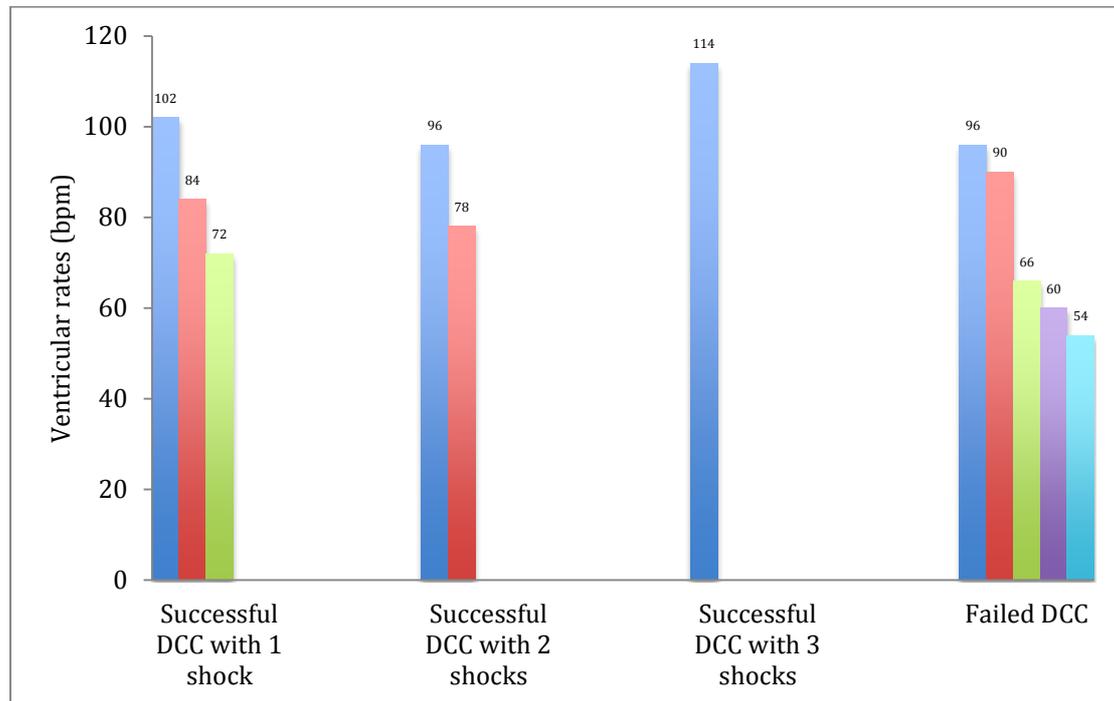
### **9.5.2 Echocardiographic parameters & shock results**

The values of echocardiographic parameters were compared among subjects with different shock results. LADs measured from the echocardiography were summarized in Table 20 and LAAs in Table 21. Contrary to expectation, patients with successful cardioversion seemed to have higher values of LAD and LAA when compared with subjects with final shock failure. Thus, there was no evidence to support the notion that the bigger atrial size would be a predictor of failed cardioversion (Figure 21 and 22).

**Table 19 Ventricular rates during AF prior to cardioversion and shock results**

Patient number	Results of 1 <sup>st</sup> shock	Results of 2 <sup>nd</sup> shock	Results of 3 <sup>rd</sup> shock	The number of failed shocks	The final result of DCC	Ventricular rates (bpm)	The mean value of ventricular rate $\pm$ SD (bpm)		
Pnt 3	S	-	-	0	S	102	86 $\pm$ 15	91 $\pm$ 16	84 $\pm$ 18
Pnt 9						84			
Pnt 1						72			
Pnt 7	F	S		1	S	96	82 $\pm$ 21	73 $\pm$ 19	
Pnt 5						78			
Pnt 8			S	2		114 (max)			
Pnt 11			F	3	F	96	73 $\pm$ 19		
Pnt 4						90			
Pnt 2						66			
Pnt 6						60			
Pnt 10						54 (min)			

AF = atrial fibrillation; DCC = direct current cardioversion; bpm = beats per minute; SD = standard deviation; Pnt = patient; S = success; F = failure.

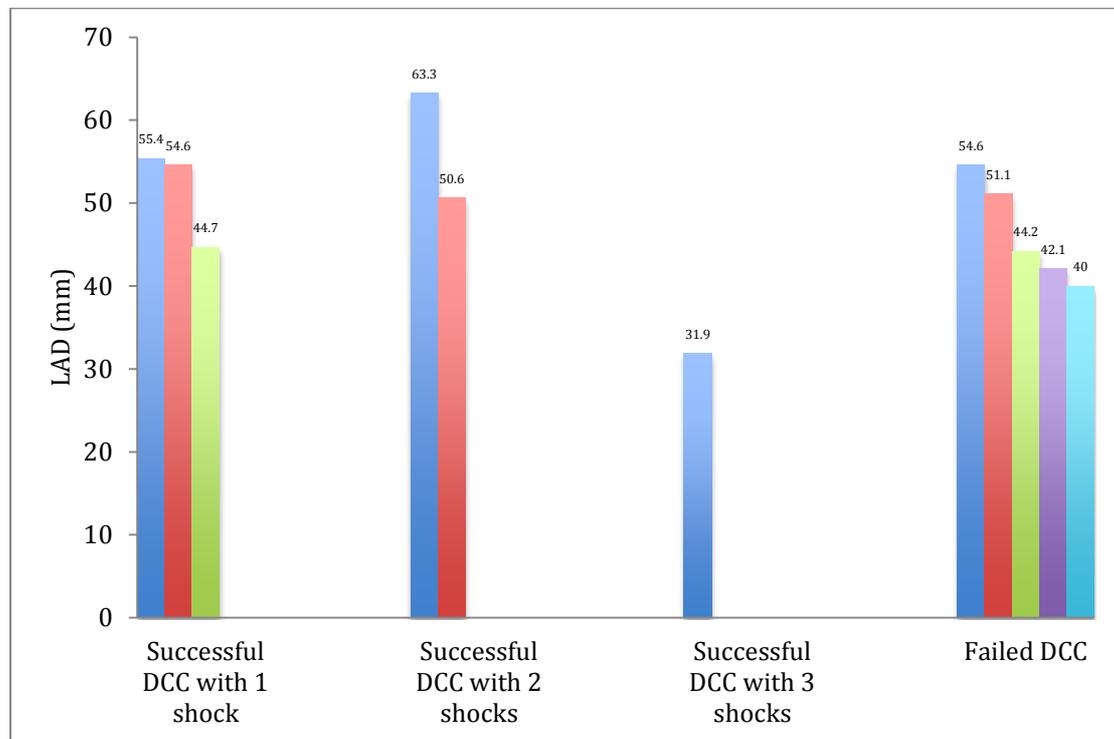


**Figure 20 Ventricular rates during AF prior to cardioversion and shock results.**

**Table 20 Measurements of LAD and shock results**

Patient number	Results of 1 <sup>st</sup> shock	Results of 2 <sup>nd</sup> shock	Results of 3 <sup>rd</sup> shock	The number of failed shocks	The final result of DCC	LAD (mm)	The mean value of LAD ± SD (mm)		
Pnt 3	S	-	-	0	S	55.4	51.6 ± 6.0	50.1 ± 10.8	48.4 ± 8.8
Pnt 9						54.6			
Pnt 1						44.7			
Pnt 5	F	S	-	1	S	63.3 (max)	47.2 ± 9.7	46.4 ± 6.2	
Pnt 7		F		S		2			
Pnt 8			F		3	54.6			
Pnt 6				51.1					
Pnt 2			44.2						
Pnt 10		42.1							
Pnt 11	40								
Pnt 4									

DCC = direct current cardioversion; AF = atrial fibrillation; LAD = Left atrial diameter.

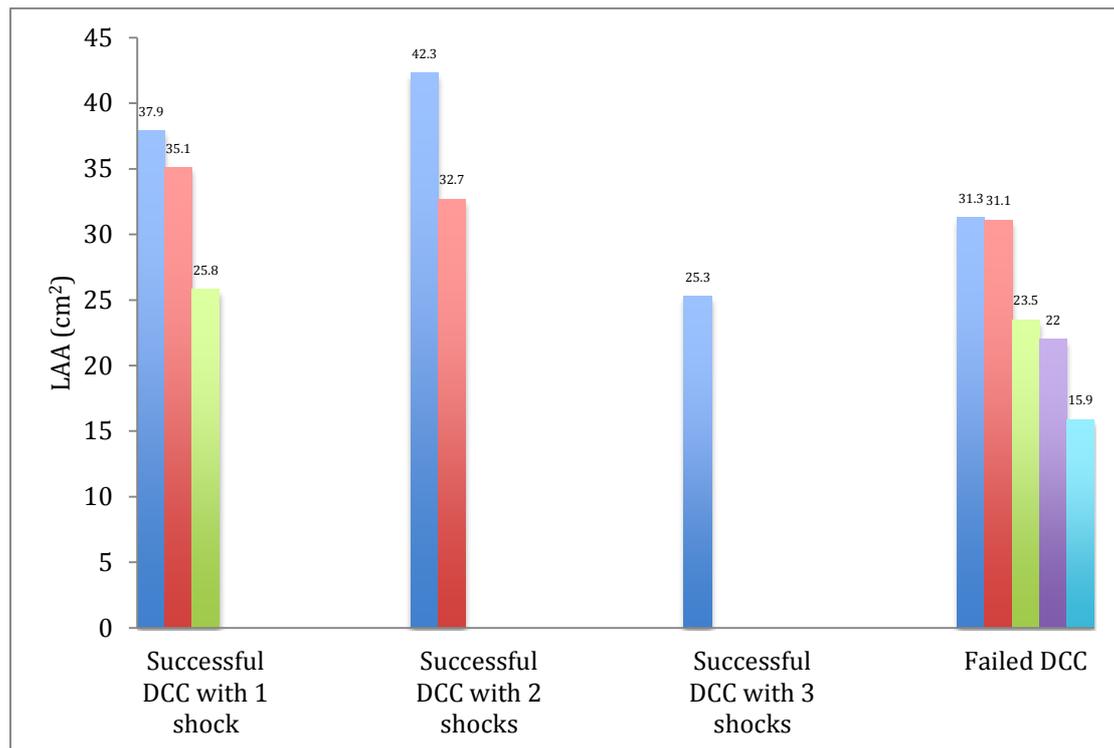


**Figure 21 Measurements of LAD and shock results.**

**Table 21 Measurements of LAA and shock results**

Patient number	Results of 1 <sup>st</sup> shock	Results of 2 <sup>nd</sup> shock	Results of 3 <sup>rd</sup> shock	The number of failed shocks	The final result of DCC	LAA (cm <sup>2</sup> )	The mean value of LAA ± SD (cm <sup>2</sup> )			
Pnt 3	S	-	-	0	S	37.9	32.9 ± 6.3	33.2 ± 6.7	29.4 ± 7.7	
Pnt 9						35.1				
Pnt 1						25.8				
Pnt 5	F	S	-	1	S	42.3 (max)	28.0 ± 8.2	24.8 ± 6.5		
Pnt 7										32.7
Pnt 8		F	F	S	2	F				25.3
Pnt 6				F	3					31.3
Pnt 2										31.1
Pnt 11										23.5
Pnt 10				22						
Pnt 4						15.9 (min)				

DCC = direct current cardioversion; AF = atrial fibrillation; LAA = left atrial area.



**Figure 22 Measurements of LAA and shock results.**

### 9.5.3 The DR & shock results

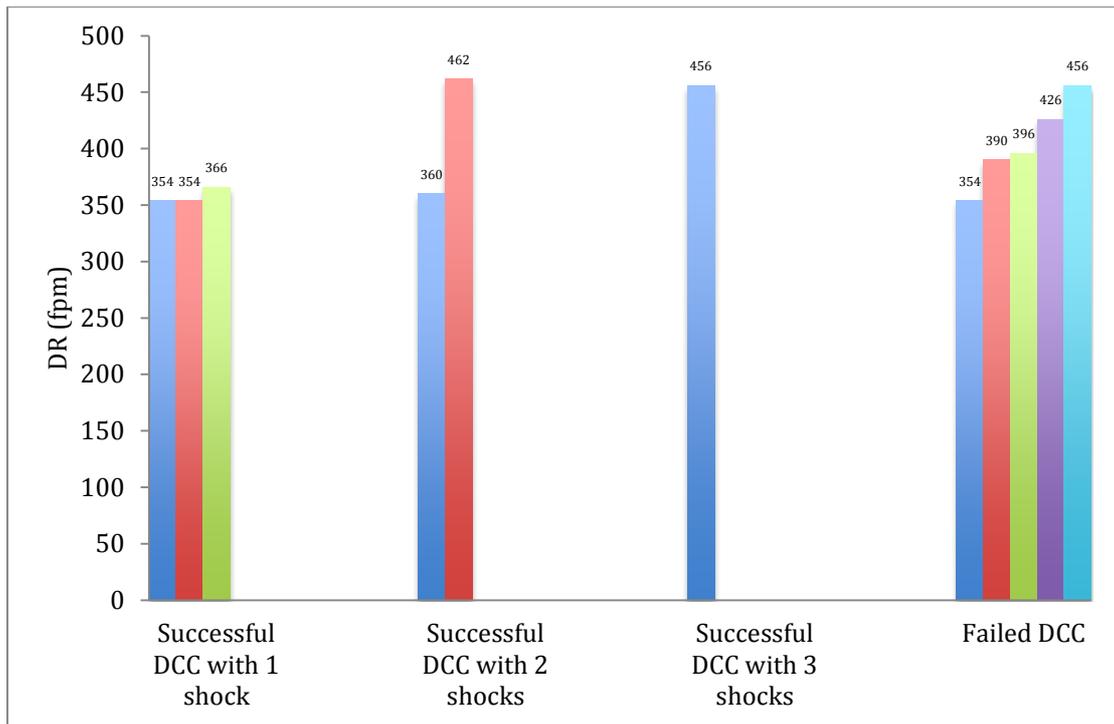
As the QRS-T-related residuals were fewer in the performance of SVD than in the performance of ABS approach, the values of DF derived from SVD filtered ECG power spectra were used to predict the results of shock. As the expression “atrial fibrillatory rate” is recommended in the description of spectral analysis results (165), the expression of DF measured in Hz was converted to dominant rate (DR) in fpm by multiplying 60 (Table 22).

The values of DR in the groups with different shock results were compared in Table 22. The mean DR of the cohort was  $398 \pm 45$  fpm. Although the maximum DR was in the group of successful cardioversion and the minimum DR in the group of failed cardioversion, the mean value of DR was slightly lower in people who were successfully converted to SR ( $392 \pm 52$  fpm) than in those with final failure result ( $404 \pm 39$  fpm). DRs in the subgroup where SR was initiated just by one shock were quite low with values of 354, 354, and 366 fpm (Figure 23). The mean DR of this subgroup was further lower when compared with the remaining subjects ( $358 \pm 7$  vs.  $413 \pm 44$  fpm).

**Table 22 Measurements of DR and shock results (in the expression of atrial fibrillatory rate)**

Patient number	Results of 1 <sup>st</sup> shock	Results of 2 <sup>nd</sup> shock	Results of 3 <sup>rd</sup> shock	The number of failed shocks	The final result of DCC	DR (fpm)	The mean value of DR $\pm$ SD (fpm)				
Pnt 1	S	-	-	0	S	354 (min)	$358 \pm 7$	$392 \pm 52$	$398 \pm 45$		
Pnt 3						354 (min)					
Pnt 9						366					
Pnt 7	S	S	1	S	360	$413 \pm 44$	$404 \pm 39$				
Pnt 5					462 (max)						
Pnt 8	F	F	S	2	F	456	$413 \pm 44$	$404 \pm 39$			
Pnt 2			F	F		3				F	354 (min)
Pnt 10											390
Pnt 6											396
Pnt 11											426
Pnt 4									456		

DR = dominant frequency; DCC = direct current cardioversion; fpm = fibrillations per minute; SD = standard deviation; Pnt = patient; S = success; F = failure; SVD = singular value decomposition.



**Figure 23 Measurements of DR and shock results.**

#### 9.5.4 The difference between DFs from leads V1 and V6 & shock results

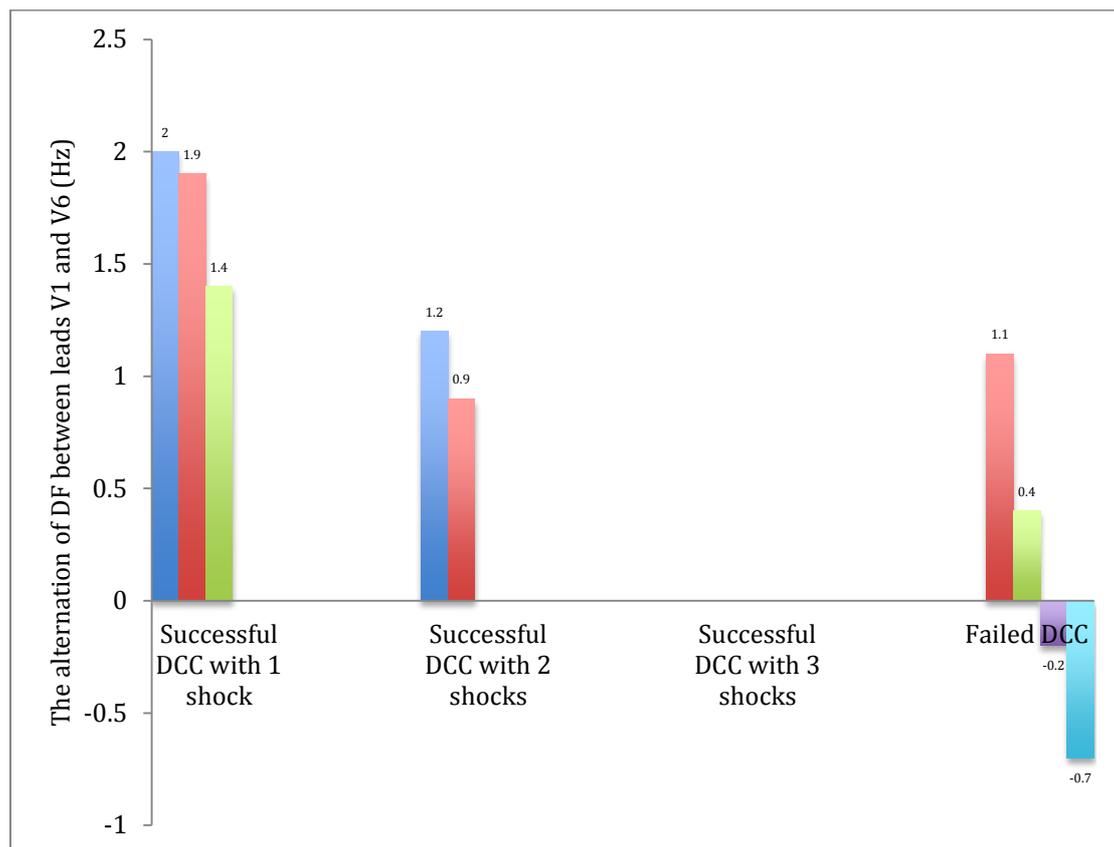
Atrial frequency gradients detected from the surface ECG were compared between subjects with different shock results in Table 23. It can be seen that the distinction between DFs from leads V1 and V6 was obviously higher in subjects with successful DC cardioversion than in those with final shock failure ( $1.48 \pm 0.47$  vs.  $0.15 \pm 0.78$  Hz). In addition, the three highest DF alternations existed in the subjects who were converted to SR by the first shock, which resulted in a further higher mean gradient in this group than in the remaining people who had at least one failed shock ( $1.77 \pm 0.32$  vs.  $0.45 \pm 0.77$  Hz).

Although the DF alternation between the two precordial leads was not successfully detected in two subjects, a clear trend was demonstrated in Figure 24 showing that the greater the atrial DF gradient was, the more promising shock success would be. The negative gradients existed in patients with failed DC cardioversion.

**Table 23 Alternations between DFs from leads V1 and V6 & shock results**

Patient number	Results of 1 <sup>st</sup> shock	Results of 2 <sup>nd</sup> shock	Results of 3 <sup>rd</sup> shock	The number of failed shocks	The final result of DCC	The alternation of DF between leads V1 and V6 (Hz)	The mean value of alternation of DF between leads V1 and V6 ± SD (Hz)		
Pnt 9	S	-	-	0	S	2.0 (1)	1.77 ± 0.32	1.48 ± 0.47	0.89 ± 0.91
Pnt 1						1.9 (2)			
Pnt 3						1.4 (3)			
Pnt 5	F	S	-	1	S	1.2 (4)	0.45 ± 0.77	0.15 ± 0.78	
Pnt 7						0.9 (6)			
Pnt 8		F	F	S	3	F	-		
Pnt 2							-		
Pnt 4							1.1 (5)		
Pnt 11							0.4 (7)		
Pnt 6						-0.2 (8)			
Pnt 10						-0.7 (9)			

DF = dominant frequency; DCC = direct current cardioversion; Hz = hertz; Pnt = patient; S = success; F = failure.



**Figure 24 Alternations between DFs from leads V1 and V6 & shock results.**

## 10 Discussion

### 10.1 Comparison of ABS and SVD

In this study, the performance of ABS and SVD was visually assessed and compared. Data presented in this study showed that although neither ABS nor SVD performed perfect with much residual ventricular activity in the remaining ECG, SVD caused less QRS-T-related residuals when compared with ABS in all subjects. Some reasons can be considered for this result. First, ABS is very sensitive to variations in QRS-T morphology, while PCA using SVD may perform better in recognizing dynamic variability of QRS-T waveform. Second, ABS requires an ECG episode length at least 10 seconds for adequate computation of the average beat, whereas SVD can be used in the ECG recording shorter than 10 seconds (103). Thus, the 10-s ECG episode collected in the clinical practice might limit the performance of ABS.

Few studies were found comparing ABS and PVC. There are several investigations making comparison of the QRS-T cancellation performance between spatiotemporal QRST cancellation (STC), principal component analysis (PCA), and independent component analysis (ICA) (166, 167).

The subtraction of QRS-T complexes is crucial for spectral analysis of AF waveform from surface ECG recordings, because ventricular components are much bigger than atrial components detected from the body surface ECG. Considerable residual ventricular signals overwhelming atrial signals could severely interfere the results of further spectral analysis. In the current study, it was observed that there were many QRS-T-related residuals in the performance of ABS and SVD. This observation is consistent with the results from previous studies showing that there were a large number of ventricular signals remained in the ABS- (168) and SVD-filtered ECG (167).

Consequently, QRS-T cancellation algorithms have been developed. For example, STC is the method developed from ABS. In STC, the average beat of the corresponding lead is mathematically combined with those of adjacent leads for optimal cancellation. Thus, the effect of respiration or movement on the

performance of ABS can be suppressed by using STC (169). ICA is another separation approach similar to PCA. The conduction of both methods depends on the fact that atrial and ventricular activities originate from different bioelectric sources (170).

## **10.2 Measurements of DF, MF, FB and DR**

The application of QRS-T subtraction algorithms and spectral analysis of the surface ECG are feasible in patients with persistent AF for assessment of DF. The results of the current study demonstrated that although the atrial signal extraction performance is different between ABS and SVD, the mean values of DF and MF of the atrial signals extracted by ABS and SVD did not show large alternations between the two algorithms. Similarly, in two previous studies by Langley et al. comparing the QRS-T cancellation performance between methods of STC, PCA and ICA, there were no significant differences between the DFs derived by these atrial extraction algorithms (166, 167). It was observed in this study that the mean FB was higher in ABS than that in SVD. The difference in the results of FB between ABS and SVD was probably due to more residual ventricular signals in ABS, which corrupted the presence of atrial fibrillatory frequency. Thus, the atrial frequency peak was wider in ABS spectrum than that in SVD spectrum.

The DF derived from the SVD atrial ECG was recorded. The DF values ranged from 5.9 to 7.7 Hz and the mean value was  $6.6 \pm 0.7$  Hz. The DF results are in agreement with the results of previous studies. Tai et al. conducted spectral analysis of the surface ECG immediately prior to DCC in 29 patients with persistent AF. The estimated DF ranged from 4.9 to 8.7 Hz with a mean value of  $6.7 \pm 0.9$  Hz (141). In two studies by Langley et al., the mean (range) DF estimated from the SVD-filtered ECG was 6.5 (5.9 - 8.2) Hz (166) and  $6.1 \pm 1.0$  (3.3 - 9.1) Hz, respectively (167).

The present study showed a mean DR of  $358 \pm 7$  fpm in the subgroup where SR was initiated just by one shock. This value is much lower than the one in the subgroup where SR was successfully initiated irrespective of the number of

shocks ( $392 \pm 52$  fpm) and the one in the subgroup with final failure of DCC ( $404 \pm 39$  fpm). This result might be consistent with the finding in a previous study by Langberg et al. This study obtained measurements of the DR from surface 12-lead ECG recordings of patients with persistent AF undergoing DC cardioversion. Although this study did not report the correlation between the DR and shock results, it reported that the fibrillatory rate was higher in patients who had early AF recurrence when compared with people who maintained in SR within the 3-month follow-up ( $365 \pm 44$  vs.  $331 \pm 48$  fpm,  $P = 0.05$ ). A dominant fibrillatory rate  $> 360$  fpm was able to predict recurrence of AF within 3 months following successful DC cardioversion with a sensitivity of 69% and a specificity of 75% (108).

### **10.3 Detection of the left-to-right atrial gradient from the surface ECG**

It failed to detect a clear peak in the spectrum of lead V6 for two subjects. This might be due to the relatively low amplitude of atrial fibrillatory waves in lead V6 or the power spectrum dominated by energy from noises or residual QRS-T complexes. One previous study reported that PCA tended to reduce the atrial signal and cause obvious residual QRS-T in a few cases. Much residual ventricular activity caused the DF peak poorly defined in the spectrum of the SVD-filtered ECG (167).

However, in the majority there was a consistent pattern observed for the DF of atrial activity to be faster in V1, and to be slow progressively across the precordial leads to V6. Thus, the current study suggest that the alternation between DFs from leads V1 and V6 might be useful to reflect the left-to-right atrial gradient.

For what we have known, there are a few studies non-invasively detected the atrial gradient by spectral analysis of the surface ECG and the oesophageal ECG. Spectral parameters estimated from lead V1 have been proved to be able to reflect the electrophysiological activity in the RA (128-131). Because the anterior wall of the esophagus is against the LA, the ECG recording from the lead placed on the anterior wall of the esophagus can detect atrial activity in the LA (132).

These studies reported that the deference between spectral measures from the surface ECG and the oesophageal ECG could reflect the left-to-right atrial gradient.

Applying spectral analysis of ECG recordings from leads V1, V2 and two leads in the esophagus, Pehrson et al. reported magnitude and dispersion of AFCL in patients with persistent AF (> 1 month). The mean dominant AFCL was  $154 \pm 16$  ms in lead V1 and  $154 \pm 17$  ms in lead V2. The values of mean dominant AFCL in the proximal and distal oesophageal leads were  $150 \pm 16$  and  $152 \pm 19$  ms, respectively. Although no significant difference was detected between the mean dominant AFCLs from the chest leads and oesophageal leads, it can be seen that the mean AFCL tended to be higher in leads V1 and V2 than in the oesophageal leads. The absolute difference in the dominant AFCL between lead V1 and the distal oesophageal lead was  $10.4 \pm 7.7$  ms (156).

Similarly, performing spectral analysis in patients with persistent AF, Meurling et al. estimated the AFCL from lead V1 and the oesophageal lead. It was shown that the AFCL derived from lead V1 was slight higher than the value from the oesophageal lead with  $152 \pm 15$  versus  $147 \pm 14$  ms and  $155 \pm 17$  versus  $151 \pm 18$  ms in two subgroups, although no attempt was made to evaluate the significant difference (110).

A number of studies attempted to develop novel lead configurations in the surface ECG for detection of intracardiac atrial frequency gradients from the body surface. Husser and co-workers suggested that modified ECG lead configurations might help to improve the detection of the atrial frequency gradient. In more details, although electrodes of VR, VL, VF, V1 and V2 were placed in the conventional position, electrodes of V3, V4, V5, and V6 were replaced anterior or posterior over the atria (171). Ihara et al. reported a more complete view on atrial electrical activity with VR, VL, VF, V1 and V4 of the standard 12-lead ECG and the remaining four precordial electrodes relocated in new positions when compared with the conventional electrode positions (172). A study by Petrutiu et al. showed that additional posterior ECG leads made it

possible to detect the interatrial frequency gradient noninvasively in 8 paroxysmal and 2 persistent AF (173). Overall, it seems warranted to develop non-standard surface ECG lead positions for characterization of electrical activity in the PVs/LA and identification of the electrophysiological spatial gradient.

#### **10.4 Prediction of shock results**

No AF recurrences were observed in the converted patients during the period of follow-up. However, atrial premature beats (APBs) occurred just a few minutes after the successful cardioversion in two subjects. In one of them, APBs with short coupling intervals (atrial bigeminy) were recorded in the follow-up ECG at 2 weeks after cardioversion. It has been suggested that premature atrial contractions indicate a relatively high susceptibility to AF and APBs play an important role in the pathophysiology of the early AF reinitiation (62, 90).

No observation of AF recurrence might be due to the small sample size or the short follow-up period. In addition, as asymptomatic or short AF episodes might be missing by the follow-up ECG, it would be more accurate to report AF recurrence with continuous ECG monitoring, such as the Holter ECG. As no data of AF recurrence was available in the study, the predictive values of clinical, echocardiographic and spectral analysis parameters were compared among subjects with different shock results.

##### **10.4.1 Clinical and echocardiographic parameters for prediction of shock results**

While numerous studies were conducted to determine predictors for the recurrence of AF after successful DC cardioversion, there were not many studies investigating the predictors for shock success. A study by Dittrich et al. reported that no clinical features could predict successful shock (102). Van Gelder et al. reported that one single shock was likely to restore SR in patients younger than 57 years old, with AF duration less than 3 months, a fair exercise tolerance (New York Heart Association (NYHA) class I or II), and free from hypertension (83, 84). A study by Frick et al. reported that the chance of SR initiation and maintenance reduced with prolongation of AF duration. AF duration < 6 months was an independent predictor for initial success of DCC (91).

In the current study the patients who were successfully converted to SR seemed not to be younger than those with failed cardioversion. This observation might be confounded by the various medication usages among subjects. Notably, no subjects in whom SR finally failed to be restored were with antiarrhythmic agents, whereas 67% (4 out of 6) patients with successful DC cardioversion were taking Class I or III antiarrhythmic agents (amiodarone or flecainide). Furthermore, this consideration was enhanced by the data showing that subjects in whom SR was restored by just one shock were all with amiodarone or flecainide administration. This corresponds to the suggestion made in the guidelines by the ESC: "Pre-treatment with amiodarone, flecainide, propafenone, ibutilide, or sotalol should be considered to enhance success of DCC and prevent recurrent AF." (1) The usage of ACEI might also play a role in promoting the initiation of SR.

In the present study, the median AF duration prior to cardioversion was shorter in people with successful cardioversion than in those with failed results. Moreover, the duration of AF was further shorter in patients with SR restored only by one shock. Thus, the results suggested that the shorter duration of AF was, the more promising shock success would be. These results were compliant with the theory that duration of AF is associated with changes of atrial electrophysiological properties, i.e. electrical remodeling, which might promote cardioversion refractoriness (55, 108, 129, 150, 174-176).

This study reported that patients with successful cardioversion seemed not to have lower values of LAD or LAA when compared with subjects with final shock failure. Thus, there was no evidence to support the notion that the bigger atrial size would be a predictor of failed cardioversion. This result might be in agreement with the finding of a previous study showing that no M-mode or 2-D echocardiographic measurements of atrial size (atrial dimensions and areas) could predict successful shock (102).

#### **10.4.2 Spectrum analysis parameters for prediction of shock results**

In the current study, the dominant frequency (DF), median frequency (MF), and frequency bandwidth (FB) were successfully estimated using spectral analysis of the surface ECG in all subjects.

The AFCL estimated from the endocardial electrogram is a direct index of atrial refractoriness (119, 121). As it has been shown that there is a good correlation between the DF/DR detected from the ECG and the corresponding parameter from the intra-atrial recording, the DF/DR from the surface ECG is believed to be an index of electrical remodeling. Therefore, the spectral parameter from the ECG might be able to predict shock results with a higher fibrillatory frequency or rate indicating refractoriness to cardioversion. The DR with its unit fpm is recommended for result description of spectral analysis (165). Thus, in the present study, the values of DR were compared between people with different shock results.

The mean value of DR was slightly lower in people who were successfully converted to SR than in those with final failure result ( $392 \pm 52$  fpm vs.  $404 \pm 39$  fpm). The mean DR of the subgroup where SR was initiated by one single shock was further lower when compared with the remaining subjects ( $358 \pm 7$  vs.  $413 \pm 44$  fpm). The DR of  $358 \pm 7$  fpm in the subjects converted by only one shock is close to the DR value from the studies described subsequently.

To date, there are few studies exploring the role of DR estimated from the surface ECG in predicting shock results. However, there are a number of studies that reported the value of DR from the ECG in predicting AF recurrence. A study by Langberg et al. obtained the measurements of DR from standard 12-lead ECG recordings of persistent AF patients undergoing DC cardioversion. It was reported that the DR was higher in patients who had AF recurrence than in people who maintained in SR at 3-month follow-up after successful DCC ( $365 \pm 44$  vs.  $331 \pm 48$  fpm,  $P = 0.05$ ). The DR  $> 360$  fpm was able to predict AF recurrence at 3-month follow-up after successful cardioversion with a sensitivity of 69% and a specificity of 75% (108). Performing frequency analysis in 175

patients with persistent AF, a study by Holmqvist et al. confirmed that AF recurrence could be accurately predicted with a higher DR obtained from the surface ECG prior to DC cardioversion. In particular, the mean DR was significantly lower in patients who remained in SR than in those with AF relapses within one month after successful external cardioversion ( $363 \pm 63$  vs.  $399 \pm 52$  fpm,  $P = 0.0004$ ) (93).

Several investigations determined the value of ECG spectral parameters in predicting the response to antiarrhythmic drugs. A fibrillatory rate  $< 360$  fpm assessed from the surface ECG before medication administration was recognized as the predictor of AF termination following intravenous ibutilide. In particular, 100% of patients with a fibrillatory rate  $< 360$  fpm versus 29% of those with a rate  $\geq 360$  fpm were converted to SR with administration of ibutilide ( $P = 0.003$ ) (129). Interestingly, the same threshold of atrial fibrillatory frequency was reported in a study with oral flecainide for persistent AF. A baseline fibrillatory frequency  $< 6$  Hz (equal to a fibrillatory rate  $< 360$  fpm) from the surface ECG was shown to predict pharmacological cardioversion success using oral flecainide with a sensitivity of 89% and a specificity of 78% (143).

#### **10.4.3 The left-to-right atrial gradient detected from the surface ECG for prediction of shock results**

We hypothesize that the atrial DF gradient between leads V1 and V6 is associated with electrical shock success. The results of the present study suggest that a greater atrial gradient detected from the ECG might indicate more promising shock success. This observation might be explained by the theory that electrical remodeling develops and finally completes throughout the atria during persisting AF. Therefore, the left-to-right gradient in the atria attenuates along with the development of electrical remodeling during persisting AF. The suggestion of a frequency gradient between leads V1 and V6 in the surface ECG might imply that electrical remodeling has not completed in the atria. The uncompleted electrical remodeling might correlate with the success chance of shock.

To our knowledge, there are no studies exploring the predictive value of the atrial gradient detected from the surface ECG for shock results. However, the study by Pehrson et al. suggested that the detected AFCL difference between lead V1 and the oesophageal lead might be used as a proarrhythmic marker because it reflected a spatial dispersion of refractoriness between the RA and the LA (156). The study by Husser et al. supported that the left-to-right atrial gradient reduced as AF progressed. In this study, the left-to-right atrial gradient was detected in patients with drug-refractory persistent AF by comparing the DRs estimated from ECG lead V1 and endocardial electrograms collected by catheters in the PVs, the CS, and the RA. The DR from the PVs was slightly higher than the rates from the CS and the RA. It was demonstrated that as duration of AF extended, the DR from the RA, the CS and lead V1 significantly increased, while the DR from the PVs did not. This resulted in a reduced difference between the DR from the PV and lead V1, i.e. the atrial frequency gradient, during persisting AF (130).

It has been reported in numerous studies that the success of AF ablation is associated with the atrial gradient detected in an electrophysiology study. In a study by Sander et al., catheter ablation failed in all subjects in absence of atrial gradients detected using electroanatomic mapping, whereas AF was terminated in 87% of patients who had a significant atrial frequency gradient. Furthermore, inducibility of AF following termination was relatively low (31%) in the subjects with the atrial gradient (126). Another study by Sander et al. showed the same conclusion that ablation therapy was more effective in AF patients with a significant DF gradient detected using electrograms from each PV and the CS (127). Assessing the measurements of DF from endocardial recordings in the LA, the CS, and the RA, Lazar et al. found that a portion of patients with persistent AF were observed having the left-to-right atrial frequency gradient, and the success rate of PVI was higher in these people than in those without the gradient. In addition, the atrial gradient was significant higher in patients with long-term SR maintenance than in those relapsing to AF following successful ablation (0.4 vs. 0.1 Hz,  $P < 0.05$ ) (158). The atrial gradient is an important predictor for the outcome of radiofrequency ablation. Thus, it

would be feasible to predict the response to DC cardioversion by quantifying the atrial gradient in patients with persistent AF.

## **10.5 Limitations of the current study**

### **10.5.1 A small and heterogeneous population**

The present study was with a small sample size ( $n = 11$ ). With the small number of participants, the study population may be short of clinical representativeness. The small population might reduce the power of the study and preclude drawing proper conclusions with statistical analysis. Thus, this study did not attempt to perform statistical analysis, so no significant differences between variables or independent factors were detected.

Furthermore, the population consisted of patients with various clinical characteristics and medical conditions. The span of age was from 49 to 81 years and the range of BMI was wide (from 22 to 47 kg/m<sup>2</sup>) in a relatively small population. History of AF varied among subjects. The duration of AF ranged between 1 and 108 months. Patients had either new-onset AF or recurrent AF with different previous AF treatments. Diverse underlying cardiovascular conditions were found among the participants, such as CHD, VHD, hypertension, diabetes, previous cardiac surgery, and lone AF. The subjects were also with different heart function classified from NYHA I to III. The influence of various medications is discussed subsequently.

### **10.5.2 Medication administration**

Treatments of class I or III antiarrhythmic drugs and other cardiovascular medications, such as CCBs, beta-blockers, ACEIs, ARBs, digitalis and statins, were allowed during the period of the study. The administration of these drugs varied between individuals depending on the concomitant heart disease and the cardiologist's preference. Multifarious medication administration resulted in a heterogeneous cohort.

First, antiarrhythmic drugs could influence the outcome of cardioversion (177). For example, the use of amiodarone before DCC could enhance cardioversion

success and prevent AF recurrences (89, 106, 178, 179). As intracellular calcium overload plays a fundamental role in electrical remodeling, the use of CCBs might help to relieve electrical remodeling in patients with persistent AF (110, 145). Therefore, the administration of CCBs might promote shock success and suppress early relapses of AF (55, 90, 91, 110).

Second, antiarrhythmic agents could interfere the measurements of DF from the ECG, with lower frequency observed in patients taking antiarrhythmic agents compared with those not taking such drugs (174). The DF or DR assessed from the ECG can be lowered with administration of amiodarone or flecainide (131, 140, 143, 146), CCBs (144, 145), AECIs (180), ARBs (181).

### **10.5.3 Validation of the left-to-right atrial gradient detected by the surface ECG**

The position of the surface ECG electrode determines the part of the heart reflected by the electrical signals recorded from this electrode. Since the heart normally rotates along its long axis, the left and right sides of the heart are not aligned with the homonymous sides of the body, and the RA is more anterior than the LA (162). Therefore, although the DF from lead V1 is able to reflect electrophysiological activity in the RA (128, 129, 132), the DF from lead V6 is not able to represent the electrical signals in the LA. However, if the DF difference between leads V1 and V6 is able to represent the trend of the left-to-right atrial gradient, the conventional electrode positions would be feasible and practical in daily clinical settings.

Because interventional electrograms directly record electrophysiological activity from endocardium, it would be better to validate the atrial gradient detection using the measurements from the surface ECG with simultaneous intracardiac recordings. Alternatively, as the anterior wall of the esophagus is against the LA, the lead placed on this wall has been proved to be able to detect atrial activity in the LA. Thus, the additional ECG obtained from the oesophageal lead can help to validate the results of the DF alternations between leads V1 and V6 as well (132).

## **10.6 Future research**

The present study demonstrates that spectral analysis of the surface ECG is a useful tool for detecting electrophysiological characteristics of the atria. It is suggested that a greater atrial gradient detected from the ECG might indicate more promising shock success. It would be feasible to predict the outcome of cardioversion by quantifying the atrial gradient in patients with persistent AF. However, so far no studies have explored the role of the atrial gradient detected from the surface ECG in predicting the outcome of cardioversion. Thus, it is valid and warranted to carry further research with larger population exploring the application of this technique in identifying suitable patients with persistent AF under rhythm control therapy.

## **11 Conclusion**

Spectral analysis of the surface ECG is feasible to non-invasively assess the dominant frequency (DF), median frequency (MF), and frequency bandwidth (FB) in patients with persistent AF. With less leads containing visual ventricular activity, the QRS-T subtraction performance of SVD might be superior to that of ABS. Age might play no role in predicting the initial success of electrical cardioversion, whereas duration of AF could be used as a shock predictor. The LA size assessed by the echocardiography might not be able to predict shock failure. The DR converted from the DF would be useful in predicting shock results in patients with persistent AF. This spectral parameter from the surface ECG might be useful in identifying suitable candidates undergoing DC cardioversion with a high likelihood of shock success. The atrial gradient could be reflected by the difference between the measurements of DF from leads V1 and V6. The atrial gradient detected from the ECG prior to cardioversion might be an important predictor for shock results in electrical cardioversion. This finding might be useful in guiding DCC strategy to avoid unnecessary cardioversion attempts in patients with persistent AF. Due to the limitations of the present study, the results need to be verified by more investigations.

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