ATRIAL FIBRILLATION: PREDICTION OF SUCCESSFUL CARDIOVERSION

A thesis presented for the degree of Doctor of Medicine
to the University of Newcastle upon Tyne

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Declaration

I, Craig Runnett hereby declare that:

- this thesis has been composed by myself
- it has not been accepted in any previous application for a degree
- the work has been done by myself, except where clearly outlined
- all quotations have been distinguished by quotation marks and the sources of information specifically acknowledged

Craig Runnett

17th June, 2003

Preface

This thesis was originally submitted to the University of Newcastle upon Tyne for consideration for the degree of doctorate of medicine in June 2003. Due to problems with the external examiner a delay of two years occurred before an incomplete examination of the thesis took place. This lead to an initial decision by the university not to award the degree and an appeal against the examiners decision was advised. The appeal was successful and re-examination of the thesis was suggested. The delays introduced by this process have rendered much of this thesis out of date however the author believes that the underlying research principles applied in the thesis remain valid.

The electrophysiology of atrial fibrillation is a rapidly advancing field and many of the treatments and theories outlined in this thesis have now moved on. In particular the theories concerning the initiation and propagation of atrial fibrillation have changed. Much less emphasis is currently being given to the multiple wavelet hypothesis of Moe outlined in this thesis.(1) Recent observations of spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins has lead to an increased interest in the concept of altered automaticity and re-entry leading to atrial fibrillation. Haissaguerre et al have lead the way in this field showing that ectopic foci within the pulmonary veins are involved in "triggering" many episodes of atrial fibrillation.(2) These observations have been put to clinical use by electrophysiologists around the world who have developed techniques to isolate these foci. Pappone et al have shown that by using a technique of circumferential radiofrequency ablation of pulmonary vein ostia around 85% of patients can be rendered free of atrial fibrillation.(3) They reported a very low complication rate with no initial thromboembolic complications or significant pulmonary vein stenosis.

These impressive results have lead some experts to advocate the use of radiofrequency pulmonary vein isolation as a first line therapy for atrial fibrillation. However this remains a subject of much debate in part due to the relatively small number of centres currently performing what is a time consuming, costly and relatively complex procedure coupled with the inability of other centres to achieve similar success rates. Therefore despite growing numbers of patients being treated by means of pulmonary vein isolation year on year the mainstay of treatment for most patients remains a choice between either attempted rhythm control with DC cardioversion and/or drug therapy or ventricular rate control and anticoagulation for stroke prophylaxis.

The "AFFIRM" Study

Throughout this thesis reference is made of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Study. (4) The AFFIRM study was underway at the original time of writing this thesis and its results were eagerly anticipated. It was widely predicted that this study would once and for all show that a strategy of attempting to maintain sinus rhythm, in patients with chronic atrial fibrillation, would provide a survival advantage. The study randomised just over four thousand patients aged 65 and over to either a rhythm control strategy (2033 patients) or a strategy involving rate control and anticoagulation (2027 patients). Rhythm control was attempted with DC cardioversion as deemed necessary by the treating physician along with the administration of one or more of amiodarone, disopyramide, flecanide, moricizine, procainamide, propafenone, quinidine, sotalol or dofetilide. Rate control was said to be achieved when the ventricular rate was less than 80 beats per minute at rest or 100 beats per minute during a six minute walk test. The permitted therapies to achieve rate control were beta blockers,

calcium channel blockers, and digoxin either alone or in combination. Patients failing two attempts at drug therapy could proceed to appropriate non-pharmacological therapy. Both groups were initially treated with warfarin but this could be stopped in the rhythm control group following four weeks of sinus rhythm. The results of the study surprised many with the death rate for the rhythm control group (23.8%) being higher than that of the rate control group (21.3%, p=0.08). This unexpected result coupled with a higher hospital admission rate for the rhythm control group has lead many physicians to question the appropriateness of a routine use of a rhythm control strategy. They argue that rate control with anticoagulation should be the first line management with attempted rhythm control being reserved for those patients who remain symptomatic despite adequate rate control or are intolerant of rate control medication.

Even allowing for the many advances made since the original submission of this thesis the clinical question that it attempted to answer remains relevant. Due in part to the high prevalence of atrial fibrillation the vast majority of patients continue to be managed by a combination of primary care physicians and district general cardiologists with the newer ablation techniques currently limited to only a small percentage of patients with highly symptomatic atrial fibrillation. The treatment of atrial fibrillation therefore remains largely a choice between rhythm control or rate control plus anticoagulation. The question of whether or not to consider an attempt at DC cardioversion in an individual patient remains a frequent one and to date there is still no definitive means of determining who will benefit from DC cardioversion.

Abstract

Aim: Despite atrial fibrillation being the most commonly occurring sustained cardiac arrhythmia its treatment remains the subject of great debate. DC cardioversion is a treatment option often used to return normal cardiac function. We aimed to assess relapse rates following DC cardioversion and to determine whether transoesophageal echocardiography, P wave signal averaged electrocardiography or heart rate variability measurements had a role in identifying patients likely to relapse to atrial fibrillation.

Methods: Patients who were referred for DC cardioversion of chronic non-valvular atrial fibrillation were enrolled into the study. Transoesophageal echocardiography was performed in order to measure left atrial size, left atrial appendage area, and flow velocity within the left atrial appendage, left upper pulmonary vein and across the mitral valve. Patients in whom cardiac thrombus had been excluded proceeded to DC cardioversion. Those patients who achieved sinus rhythm had a p wave signal averaged electrocardiogram recorded one hour following the procedure. At forty eight hours those patients remaining in sinus rhythm had a second p wave signal averaged ECG recorded and a Holter recording in order to determine heart rate variability. Patients were reviewed at three and six months for relapse to atrial fibrillation.

Results: DC cardioversion was initially successful in 66 of the 81 patients (81%). At 48 hours 23 patients (35%) had relapsed to AF. No PSAECG measurement differed significantly between these groups. Mean mitral valve flow velocity differed significantly between those who relapsed to AF within 48 hours and those who remained in sinus rhythm (SR group = 83.98cm/s, AF group 71.05cm/s, p=0.048). At three months 48 patients had relapsed to AF (73%) this increased to 51 patients (77%) at six months. No significant difference was observed in any of the TOE, PSAECG or HRV measurements in these groups.

Conclusion: No PSAECG or HRV variable helped to predict long term success. TOE measurement of mitral valve flow velocity may allow prediction of early relapse. DC cardioversion without antiarrhythmic prophylaxis leads to a high relapse rate.

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Publications And Presentations Arising From This Work

Runnett C, Doig JC, "Heart Rate Variability, P Wave Signal Averaging and Transoesophageal Echocardiography: Do They Have a Role in Predicting Outcome of DC Cardioversion?" Poster presentation at the North American Society of Electrophysiology Annual Meeting 2001, Boston, USA. Published in Pacing and Clinical Electrophysiology 24(4) P2; 716: 2001 April.

Runnett C, Doig JC. "Does Duration of Atrial Fibrillation Predict Outcome of Cardioversion?" Poster presented at Europace annual meeting 2001, Copenhagen. Published in Europace 2 supp B, B94 July 2001.

Runnett C, Doig JC. "Can P-Wave Signal Averaged ECG Predict Relapse Following Cardioversion?" Poster presented at Europace annual meeting 2001, Copenhagen. Published in Europace 2 supp B, B110 July 2001.

Runnett C, Doig JC. "Is Transoesophageal Echocardiography Necessary Before Cardioversion?" Poster presented at Europace annual meeting 2001, Copenhagen. Published in Europace 2 sup B, B110 July 2001.

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1 INTRODUCTION

1.1 A Brief History

Atrial fibrillation is by no means a new phenomenon, as long ago as 2000 years BC Huang Ti Nei Ching Su Wen, the emperor physician who ruled China, wrote of a condition associated with an irregular pulse and a poor outcome. It is possible that he was referring to atrial fibrillation when he wrote "when the pulse is irregular and tremelous and the beats occur at intervals, then the impulse of life fades."(5)

Closer to home atrial fibrillation appears to have gone unrecognised for a considerable time. William Harvey was one of the first western physicians to recognise that an irregular pulse was associated with ill health. In 1628 he wrote about "fibrillation of the auricles" and its impact on the health of a patient in his care. Reliable diagnosis of atrial fibrillation was only made possible following the invention of technology capable of electrically recording the impulses that lead to mechanical activity within the heart. Thomas Lewis produced recordings from patients with irregular rhythms that are now known to be of atrial fibrillation at University College London in 1900.(6) However it was not until further advances in biochemical techniques took place that the electrophysiological significance of these recordings could be appreciated.

1.2 Electrophysiology Of Atrial Fibrillation

Despite extensive research the precise electrophysiological basis of atrial fibrillation still remains unclear. There are however two main theories regarding the propagation of atrial fibrillation, these are the "multiple wavelet theory" and the "re-entry theory". In the first of these theories, the "multiple wavelet theory", disorganised atrial

activity due to multiple small wavelets which propagate in a random haphazard manner within the atria are thought to underlie the initiation of the arrhythmia. This lack of ordered electrical depolarisation leads in turn to a lack of organised atrial contraction. Moe et al used a computer model to predict that a minimum of between 23 to 40 wavelets are required to allow atrial fibrillation to propagate.(7) Allesie et al studied the same phenomena in the heart of a dog and found that fewer wavelets than previously predicted were required.(8) Here atrial fibrillation was demonstrated with as few as 4 wavelets.

In the second theory the "re-entry theory", originally proposed by Lewis in 1925, a single high frequency re-entrant source is thought to give rise to fibrillatory conduction.(9) More recently Schuessler et al studied this phenomena in the isolated right atria of dogs.(10) They demonstrated that as the acetylecholine concentration within the heart was increased the activation pattern within the atria changed. The previously multiple re-entrant circuits coalesced to form a single relatively stable, high frequency re-entrant circuit that resulted in fibrillatory conduction as seen in atrial fibrillation. Further work is clearly required to determine whether one of these theories, or a combination of the two, hold the key to the electrophysiological basis of atrial fibrillation.

1.3 Diagnosis Of Atrial Fibrillation

Atrial fibrillation can be reliably diagnosed in the majority of cases from a standard 12 lead surface electrocardiogram. The P wave normally detected on the electrocardiogram during atrial contraction is replaced by irregular baseline deflections called f waves. These f waves occur at a rate varying between 350 and 600 per minute. Thankfully patients with atrial fibrillation rarely have ventricular rates as high as 350 beats per minute. The reasons for this discrepancy are two fold. Firstly the atrioventricular nodal refractory period is such that depolarisation at this rate is not possible in a normally functioning node. The second

reason is that the fibrillatory wavelets are involved in collisions with one another and this results in cancellation of many electrical impulses. The random nature of these collisions also causes the ventricular rhythm to be irregularly irregular in nature, thus giving rise to the characteristic irregularly irregular pulse found in patients with atrial fibrillation.

1.4 Classification Of Atrial Fibrillation

Patients with atrial fibrillation can be classified into one of three groups depending on the nature of the arrhythmia. The first group of patients are those in whom the arrhythmia will spontaneously revert to normal sinus rhythm only to recur at a later date. Patients with this so called "paroxysmal" form of atrial fibrillation may have anything from very infrequent brief episodes of atrial fibrillation to prolonged, frequent episodes which become almost continuous. The second group of patients are those in whom the arrhythmia persists only until some form of treatment is commenced and following which normal sinus rhythm is restored. These patients are said to have persistent atrial fibrillation. The third class of patients are those in whom atrial fibrillation continues unabated despite treatment. These patients are said to have permanent atrial fibrillation. It should be remembered that this classification is not as rigid as it first appears, patients in the paroxysmal group often have an increasing frequency of episodes leading to persistent or permanent atrial fibrillation. Similarly patients who at first appear to have persistent atrial fibrillation may with treatment change to having paroxysmal episodes.

1.5 Epidemiology Of Atrial Fibrillation

Atrial fibrillation is now the most frequently encountered cardiac arrhythmia in the western world. In the United States it is estimated that approximately two million people

have atrial fibrillation at any one point in time. It is therefore no surprise that hospital stays for atrial fibrillation far outweigh those for any other cardiac arrhythmia.(5)

Although the vast majority of cases of atrial fibrillation occur in adult life cases have been reported in all age groups. In the foetus and neonate atrial fibrillation is nearly always a result of an accessory pathway and resolution usually occurs within the first year. In the western world atrial fibrillation in adolescence is rare and is usually reported in association with dilated or hypertrophic cardiomyopathy, intracardiac tumours, muscular dystrophy and very occasionally with hyperthyroidism(11) In developing countries atrial fibrillation in adolescence is more common often being a consequence of rheumatic valvular disease.

The overall prevalence of atrial fibrillation in adults increases with increasing age, with some 0.5% of the population aged between 50 and 59 being affected. This figure rising to nearer 9% for patients aged between 80 and 89.(12) Using data collected in the Framingham study it is estimated that there is a cumulative 22-year incidence of atrial fibrillation of 21.9 per 1000 men (2.19%) and 17.1 per 1000 women (1.71%). Similar figures have been reported for the U.K.(13) In patients without rheumatic heart disease the 2-year incidence of atrial fibrillation is lower with some 0.04% of men and 0.01% of women aged between 30 and 39 developing the arrhythmia. Again the incidence rises sharply with advancing age. In the age group 80 to 89 the 2-year incidence rises to 4.6% for men and 3.6% for women. Despite having lower incidence figures the majority of patients with atrial fibrillation are female. This can be explained by the longer life expectancy of women coupled with the bias towards developing atrial fibrillation in later life.

These figures obviously have marked implications for an ageing western population. As the percentage of the population surviving into the eighth decade increases

the number of cases of atrial fibrillation are also expected to increase. This will have important implications both for patients and health care providers placing an increased strain on healthcare resources.

1.6 Aetiology Of Atrial Fibrillation

The causes of atrial fibrillation can be broadly divided into two groups as shown in the table below. In the first group atrial fibrillation is a manifestation of structural heart disease. In the second atrial fibrillation occurs as a result of a systemic illness or disease process in the absence of structural heart disease.

Structural Heart Disease	Systemic Disease
Hypertensive heart disease	Major infections (especially respiratory)
Coronary artery disease	Thyroid disease
Valvular heart disease	Severe electrolyte disturbance
Cardiomyopathy	Malignancy (especially thoracic)
Cardiac surgery	Alcohol
Pericarditis	Sarcoidosis
Congenital heart disease	Phaeochromocytoma
	Amyloidosis
	Non cardiac surgery

Table 1 Causes of atrial fibrillation

This grouping does not however include those individuals in whom structural heart disease is absent and no trigger event or illness can be determined. These patients, said to have "lone" atrial fibrillation, can account for as many as 29% of patients presenting with atrial fibrillation.(14)

These two groups also differ in terms of the predominant pathological changes found within the heart muscle. Myosite fibrosis is more commonly found in patients with atrial fibrillation secondary to structural heart disease. However this is rarely seen in atrial fibrillation secondary to a non cardiac systemic illness.

Atrial fibrillation may also occur as the only clinical manifestation of a rare genetic disorder. Brugada et al recently identified three families in northern Spain in which 21 of 49 family members had atrial fibrillation. DNA sequencing revealed a mutation within the 10q chromosome in the affected individuals. They concluded that since no other cause for this clustering of patients with atrial fibrillation could be identified the mutation of 10q22-q24 was responsible for the arrhythmia.(15) To what extent genetic susceptibility accounts for lone atrial fibrillation in other populations is unknown.

The aetiological trends seen in patients presenting with atrial fibrillation have changed over the last decade. Since the Framingham data was first published the proportion of patients presenting with atrial fibrillation secondary to valvular heart disease has declined. In particular a marked decline has been seen in the number of cases of atrial fibrillation secondary to rheumatic heart disease. In a study of French general practices Levy et al showed that of 756 patients with atrial fibrillation, 70% were thought to be secondary to structural heart disease.(14) Of this group the commonest cause was hypertension (39.4%), coronary heart disease comprised some 16.6%, and myocardial disease 15.3%. Rheumatic valvular disease, although less common than in previous studies, was still an important risk factor being implicated as a causal factor in 25% of women with atrial fibrillation but only 8% of men.

1.7 Clinical Presentation

Patients with atrial fibrillation present with a varied range of symptoms and as such may present to doctors practising in all fields of medicine. Presentation is influenced by a number of factors including the premorbid cardiac function, coexistent medical problems, the ventricular rate and the patients perceptions of these factors. A number of patients with atrial fibrillation will present to the emergency department with circulatory collapse. This is most often secondary to a rapid ventricular rate or due to complications such as thromboembolic stroke. More commonly presentation takes a less acute form occurring due to symptoms including palpitations, breathlessness, fatigue or a combination of these. Lok et al showed that 42.3% of patients admitted to hospital with a diagnosis of atrial fibrillation had palpitations as a first symptom.(16) Other symptoms reported included breathlessness (38.1%) and symptoms associated with worsening heart failure (16.4%). Levy et al found similar results in general practice with palpitations being present in 54.1%, and breathlessness in 44.4%. In this series 11.4% of patients were asymptomatic, being identified on routine screening.(14)

1.8 Course Of Untreated Atrial Fibrillation

The natural history of atrial fibrillation varies considerably between patients. As previously discussed atrial fibrillation of acute onset may spontaneously terminate, may terminate and recur in a paroxysmal fashion or may continue unabated and become chronic in nature.

1.8.1 The Electrophysiology Of Chronicity

It has been shown in animal models that artificially induced atrial fibrillation becomes more resistant to termination with increasing duration of the arrhythmia. This phenomenon of atrial fibrillation begetting atrial fibrillation has been further supported by epidemiological evidence in humans. (17) The physiological mechanisms underlying this tendency towards chronicity are under investigation. One theory, which has gained support, is that a progressive decrease in the atrial refractory period occurs with increasing duration of the arrhythmia. This allows wavelets of electrical activity to propagate thus ensuring the continuation of the arrhythmia. Wijffels et al were among the first to show that in a goat model the effective atrial refractory period shortened following a period of artificially induced atrial fibrillation.(18) Following on from this observation the same investigators attempted to elucidate the exact stimulus for this electrical remodelling. The potential involvement of the autonomic nervous system was measured by studying the effect of atropine and propanolol on the atrial refractory period both prior to and following atrial fibrillation. No relationship could be demonstrated between autonomic nervous system activity and electrical remodelling. Similarly infusing glibenclamide, a blocker of ATP regulated potassium channels to produce ischaemia had no effect on the atrial refractory period. This led to the conclusion that ischaemia of the atrial myocardium was not the trigger.(8)

Increased levels of atrial naturetic factor have been demonstrated during atrial tachyarrhythmias and this has been suggested as a possible precursor to remodelling(19) However measurements of the duration of the effective atrial refractory period following infusion of high levels of atrial naturetic factor have failed to provide support for this theory.(20) Data from the same study suggested that the changes seen in effective atrial refractory period were as a result of an increase in the rate of electrical activation of the

myocytes. The shortening of effective refractory period being most pronounced in those animals which had undergone high rates of atrial pacing early in the experiment. Yu et al showed that a similar rate related electrical remodelling could be demonstrated in humans.(21) Here the effective atrial refractory period was measured in human volunteers before and after atrial pacing at different rates. The effective atrial refractory period was significantly shorter following high rates of atrial pacing. The cellular changes responsible for this shortening of the atrial refractory period are not fully understood. Theories involving a decrease in calcium influx(22) into cells and upregulation of potassium channels(23) have been put forward and are currently under investigation

1.8.2 Spontaneous Sinoconversion

Atrial electrical remodelling with perpetuation of the arrhythmia is not the only outcome possible for a patient presenting with atrial fibrillation. As mentioned previously patients with a first episode of atrial fibrillation may spontaneously revert to sinus rhythm and have no further episodes.

Various rates of spontaneous conversion to sinus rhythm have been reported. Donovan et al reported a 35% spontaneous conversion rate at 2 hours in patients presenting with atrial fibrillation of less than 72 hours duration.(24) Capucci et al reported similar figures at eight hours following onset with some 39% returning to sinus rhythm.(25) Dell Orfano et al compared hospital charges for patients who spontaneously converted to sinus rhythm to those who required electrical or pharmacological cardioversion.(26) They found that spontaneous cardioversion was associated with significantly lower hospital costs. This coupled with a high spontaneous sinoconversion rate of 65% prompted them to suggest that a "wait and see" strategy should be employed. Using this strategy patients are

observed for a forty-eight hour period prior to rhythm management being attempted. They suggested that this would save money and physician time.

The mechanism underlying this self-termination is thought to be a lack of shortening of the atrial refractory period. This coupled with a reduction in propagating wavelets due to collisions leads to the number of wavelets falling below the number required to maintain the arrhythmia.

1.8.3 Paroxysmal Atrial Fibrillation

The previous two outcomes represent either end of a spectrum with a third outcome spanning the middle. Here a patient's first episode of atrial fibrillation may terminate only to recur at a later date. This episodic pattern of atrial fibrillation is termed paroxysmal atrial fibrillation. The electrophysiology of paroxysmal atrial fibrillation is more complex. Initiation of atrial fibrillation is thought to occur in the usual way with the number of propagating wavelets reaching the required number to give rise to fibrillation of the atria. However the effective atrial refractory period does not continually shorten but instead somehow lengthens. This in turn leads to a reduction in the number of wavelets until the required number to maintain atrial fibrillation no longer exist and the arrhythmia terminates.(27) This sequence of events is then thought to recur leading to paroxysms, which may be frequent in nature.

1.9 Complications Of Atrial Fibrillation

The major complications of atrial fibrillation include thromboembolic events, haemodynamic dysfunction and cardiomyopathy. All of which lead to a substantial increase in both morbidity and mortality for patients with atrial fibrillation as compared to normal subjects.

1.9.1 Thromboembolic Events

Atrial fibrillation is the commonest cardiac condition to increase the risk of a systemic thromboembolism. During atrial fibrillation atrial contraction is reduced to such an extent that laminar flow of blood is lost. Turbulent blood flow and stasis occur increasing the potential for clot formation in the atria and the atrial appendages. Embolism from these sites is not an uncommon occurrence most commonly presenting with the symptoms of an acute ischaemic stroke. Epidemiological studies have shown that approximately 15 to 20 percent of all patients who present to accident and emergency departments with symptoms due to an acute stroke will be in atrial fibrillation. This figure is much higher for older age groups with 36 percent of stroke patients over 80 years of age having atrial fibrillation at the time of presentation. Furthermore patients presenting with an acute stroke and atrial fibrillation have been shown to have a mortality which is three times greater than patients who are in sinus rhythm at the time of their stroke after allowing for other variables.(28)

The relative stroke risk associated with atrial fibrillation depends on the underlying cause of the arrhythmia and various patient factors. The risk is greatest for atrial fibrillation complicating rheumatic heart disease in which the relative risk approaches 17.5 times that of patients without atrial fibrillation.(12) In patients who have chronic atrial fibrillation but no evidence of rheumatic heart disease the relative risk of stroke is estimated at 6.9 times that of normal subjects. Several independent risk factors for thromboembolic complications in atrial fibrillation have also been identified. Pooled data from randomised primary prevention trials has shown that the stroke risk in patients with atrial fibrillation is

increased further by the presence of hypertension (relative risk 1.6), diabetes mellitus (relative risk 1.7) and previous stroke or transient ischaemic attack (relative risk 2.2).

These figures take into account only those patients who have a clinically evident cerebrovascular event. Screening of individuals with atrial fibrillation but no clinical symptoms relating to cerebrovascular disease has shown that so called "silent" cerebral infarction is present in a substantial proportion. Ezekowitz et al screened 516 patients with atrial fibrillation by means of computed tomography and found evidence of silent cerebral infarction in 14.7% of patients with no prior history of stroke.(29) The major weakness of this study was that it did not contain a control group in whom atrial fibrillation was absent. This was not the case in the study conducted by van Latum et al who studied the CT scans of 985 patients with non valvular atrial fibrillation and compared them with similar scans in 2987 patients without atrial fibrillation. They reported that the incidence of cerebral infarcts, which could not be ascribed to the patients' current neurological symptoms, was significantly higher in patients with atrial fibrillation group (20% Vs 15%; OR 1.5; 95% CI 1.2-1.8).(30) Whether this increase in silent ischaemic episodes leads to a clinically detectable deterioration in mental function has been investigated by O` Connell and colleagues.(31) They compared cognitive function in 54 patients with non-valvular atrial fibrillation to age and sex matched controls. None of the patients included in the study had a history of clinically apparent transient ischaemic episodes or stroke. They found that patients with atrial fibrillation attained lower scores in all tests when compared to those without the arrhythmia. A similar association was noted in the Rotterdam Study in which a large cohort of patients were screened for the presence of dementia, cognitive impairment and atrial fibrillation.(32) Dementia was found to be more than twice as common in patients with atrial fibrillation, with the Alzheimer's disease subtype showing the strongest association.

The risk of thromboembolic complications with paroxysmal atrial fibrillation is less clear cut. Several studies have attempted to define the risk of stroke with paroxysmal atrial fibrillation. Varying incidences from between 2 percent per year(33) and 5.7 percent(34) per year have been reported. This discrepancy in rates may in part be due to the heterogeneous nature of paroxysmal atrial fibrillation and the difficulty in comparing groups with regard to the duration and frequency of arrhythmic episodes. What is clear is that paroxysmal atrial fibrillation increases stroke risk. This has prompted many physicians to suggest that thromboembolic prophylaxis should be prescribed in a similar manner as for chronic atrial fibrillation.

1.9.2 Haemodynamic Dysfunction

There are several mechanisms in which atrial fibrillation may lead to clinically apparent haemodynamic dysfunction. In the first a rapid ventricular rate results in a decrease in the time available for ventricular filling. This causes particular problems for individuals whose diastolic filling has already been compromised by co existing pathology such as mitral stenosis or abnormalities in ventricular relaxation time and pulmonary oedema results. A second consequence of a rapid ventricular response is an increase in ventricular oxygen demand, with the potential to precipitate an acute coronary syndrome and ultimately infarction of vulnerable myocardium.

The loss of atrial transport per se seen with atrial fibrillation and the subsequent decrease in cardiac output may be sufficient to cause symptoms of heart failure. This is more troublesome in patients who already have a decrease in their cardiac output due to other pathology such as previous myocardial infarction or hypertensive heart disease. In these patients atrial contraction is required to maintain adequate ventricular filling and cardiac output.

All of these haemodynamic changes may be transient in paroxysmal atrial fibrillation, causing few symptoms, but in chronic atrial fibrillation they are often disabling requiring acute treatment and frequently leading to hospitalisation.

1.9.3 Cardiomyopathy

Tachycardia induced cardiomyopathy refers to the syndrome in which rapid ventricular rates, when left untreated, predispose the patient to changes within the myocardium resulting in ventricular remodelling and a decrease in ventricular systolic function. These changes are initially reversible and restoration of sinus rhythm or control of the ventricular rate either chemically or mechanically will bring about restoration of normal systolic function.(35) However if the ventricular rate remains uncontrolled the remodelling process becomes irreversible with a continued decline in cardiac function. The cellular basis for this decrease in myocyte function remains largely unexplained. Eble et al showed that in pigs tachycardia induced cardiomyopathy was associated with an increase in myocyte cytoskeletal protein and a decrease in myocyte contractile function. However no change was observed in contractile protein content or myocyte mRNA.(36) Whether similar changes are responsible for the reduced contractile function in humans is not clear.

1.9.4 Mortality

The impact of atrial fibrillation on mortality is often not appreciated by either patients or clinicians. Several well designed follow up studies have shown that far from being a benign cardiac arrhythmia atrial fibrillation confers a marked survival disadvantage. Mortality data from the Framingham study shows that in the age group 55 to 74 years, after 10 years, 61.5% of men with atrial fibrillation had died compared with 30% of those without the arrhythmia. In women 57.6% of those with atrial fibrillation had died as compared with 20.9%. Another way of expressing this is to look at median survival

which gives an indication of how much longer a person without atrial fibrillation will live when compared to age and sex matched subjects with atrial fibrillation. Data from the same study shows a median survival for men aged 55 to 64 with atrial fibrillation to be 12.6 years compared to 18.1 years for those without atrial fibrillation. For women of the same age the figures were even more striking with a median survival of 12.1 years with atrial fibrillation compared to 21.3 years without. The odds ratios for these groups are such that the increased risk of death is 1.5 for men with atrial fibrillation (95% CI, 1.2 to 1.8) and 1.9 for women (95% CI, 1.5 to 2.2).(37) The identification of this marked survival disadvantage has prompted renewed interest in the treatment of atrial fibrillation with the goal of eliminating the survival disadvantage.

1.10 Quality Of Life And Atrial Fibrillation

It is only in recent years that quality of life has been recognised as an important outcome measure in the treatment of atrial fibrillation. Because of this there is relatively little data available on how atrial fibrillation, and its subsequent treatment, effects quality of life. Those studies that do exist often fail to use properly validated tools to measure quality of life making interpretation difficult. The patients included in these studies also fail to reflect the vast majority of patients with atrial fibrillation instead concentrating on individuals who are highly symptomatic and either intolerant of medication or resistant to it. In one study follow up interviews were conducted with patients following either radiofrequency or direct current catheter ablation of the AV node. An improved quality of life was reported in 80% following direct current ablation and 84% of those undergoing radiofrequency ablation.(38) The questions asked to assess quality of life in this study were not specified making comparison with other patient groups impossible.

Two large scale prospective trials are currently underway to try and provide information on quality of life in more typical patients with atrial fibrillation. The Atrial Fibrillation Follow-up Investigation of Rhythm Management is a prospective trial of over 5000 patients who will be randomised to either rate control or antiarrhythmic drug treatment with quality of life a secondary end point using validated questionnaires.(4) The International Quality of Life Investigators Trial similarly uses validated questionnaires to assess quality of life in patients with atrial fibrillation but in this study a control group will also be assessed. Early results from this group have suggested that patients with paroxysmal atrial fibrillation who have frequent episodes may have a lower quality of life than patients with chronic atrial fibrillation.(39)

1.11 Treatment Strategies

Numerous different treatment strategies are currently employed in an attempt to reduce the mortality and morbidity associated with chronic atrial fibrillation. This is a reflection of the fact that none of the currently available strategies is ideal for all patients with atrial fibrillation, each having points in its merit but also carrying risks or side effects. Broadly these strategies fall into two main categories, those where ventricular rate control with thromboembolic prophylaxis is the main aim, and those aimed at restoring normal sinus rhythm. Although logically restoration of sinus rhythm, the physiological state, where possible would appear to be the most desirable end point. There is currently little evidence to separate these regimes in terms of mortality data. It is hoped that the AFFIRM study which is currently underway will provide further clarification.(40) The selection of which treatment regime to use should be carried out on an individual patient basis taking into account the relative risks both from the arrhythmia and the treatment and any anticipated gain. Patients who present with life threatening haemodynamic compromise

require urgent restoration of sinus rhythm and the most reliable means of achieving this is by external DC cardioversion. For patients presenting with a more stable picture the decision on which treatment regime to employ is usually less urgent and less clear cut. Both treatment strategies can be achieved either pharmacologically or by means of electrophysiological or surgical intervention.

1.11.1 Medical therapy

1.11.1.1 Ventricular rate control

Ventricular rate control is often used when restoration of sinus rhythm has proved impossible or as a temporary measure prior to attempting rhythm control. The main aim of treatment is to reduce the ventricular response to atrial depolarisation in order to alleviate symptoms and to avoid potential complications such as tachycardia induced cardiomyopathy. The agents commonly used to achieve this goal include digoxin, beta-adrenergic blockers and calcium channel blockers.

Digoxin may be used intravenously to slow the resting ventricular heart rate in highly symptomatic individuals. Its therapeutic effects are not usually apparent until at least sixty minutes following administration and its full effect may not be seen for up to six hours. Its mild positive ionotropic action makes it an attractive choice for patients with congestive cardiac failure and atrial fibrillation. However although digoxin is effective in controlling heart rate at rest it has little influence over heart rate during exercise.(41) It has been shown to be no better than placebo at converting atrial fibrillation to sinus rhythm (42)and there is some evidence suggesting that digoxin may in fact prolong episodes in paroxysmal atrial fibrillation.(43) Despite these limitations digoxin continues to be the most commonly prescribed drug for rate control of chronic atrial fibrillation.(44)

Beta adrenergic blocking drugs can be used both acutely and long term to control ventricular rate. In the acute situation intravenous beta blockade will rapidly control ventricular rate but the potential complication of precipitating hypotension or congestive cardiac failure must be borne in mind. When given orally beta-blockers will control ventricular rate both at rest and during exercise making them an ideal first choice for those patients who have no contraindications and can tolerate them.

Calcium antagonists have become a popular choice for rate control in the United States with some 15% of patients with chronic atrial fibrillation taking either diltiazem or verapamil.(44) When given intravenously diltiazem has an effect on the ventricular rate within a few minutes and a continuous infusion will give satisfactory rate control in the majority of patients.(45) Verapamil has been shown to have a similar effect but is less widely used.(44) Both drugs have hypotension as there major side effect occurring in upto 7.5% of those receiving diltiazem by the intravenous route.(45) Hypotension is less of a problem with diltiazem or verapamil when given orally for rate control in chronic atrial fibrillation. Here the main concern is the negative ionotropic effect of both agents, which limits their use in patients with cardiac failure.

Combination therapy for rate control is often necessary and the addition of digoxin to a beta blocker or calcium antagonist has been shown to give an increase in benefit without increasing side effects.(46)

1.11.1.2 Thromboembolic prophylaxis in chronic atrial fibrillation

As previously outlined thromboembolism is responsible for a large proportion of the increased morbidity and mortality seen in patients with atrial fibrillation. However the risk of stroke in patients with atrial fibrillation is not uniform and is influenced by several other criteria. For example stroke risk increases with increasing age being low in those

aged 50-59 with chronic atrial fibrillation but rises to around 30% in similar patients aged over 80.(12) Using these criteria patients can be divided into high, moderate or low risk groups. It is recommended that patients in the high-risk group receive warfarin therapy with a target INR of between 2.0 and 3.0 providing no contra indications exist.(47) For patients in the low risk group aspirin therapy is recommended. Thromboembolic prophylaxis in the moderate risk group is less clear cut and no clear recommendations exist with individual patient and physician preference determining therapy. The use of such guidelines in patients with chronic atrial fibrillation has been shown to be both clinically effective and to reduce healthcare costs.(48)

Risk of CVA	**Presence of one or more of**
High Risk Group	Previous stroke or transient ischaemic attack Age > 75 years, Hypertension, Diabetes, Coronary heart disease, congestive cardiac failure, left ventricular dysfunction.
Moderate Risk Group	Age 65 – 75 with none of the above risk factors
Low Risk Group	Age < 65 with none of the above risk factors

Table 2 Risk of CVA

1.12 Restoration of sinus rhythm

The theoretical advantages of restoring sinus rhythm include the elimination of symptoms, improved haemodynamics and a reduction in the risk of complications including thromboembolism. Evidence that restoring sinus rhythm confers a survival advantage over simple rate control is however lacking at present. The AFFIRM trial which is currently in its recruitment stage aims to solve this problem.(4)Here patients with chronic non-valvular atrial fibrillation are randomly assigned to either rate control and thromboembolic prophylaxis or rhythm control with mortality as the primary end point.

Despite this lack of evidence most patients with an initial presentation should be considered for restoration of sinus rhythm either initially or after treatment of the underlying cause. Sinus rhythm may be restored using drug therapy (pharmacological cardioversion) electricity (external or internal cardioversion) or by invasive procedures.

1.12.1 Pharmacological cardioversion

Currently a number of different agents are available in the UK for the pharmacological cardioversion of atrial fibrillation. The Singh Vaughan Williams classification is usually used to group these agents by means of their biochemical action on the cardiac myocyte. (49,50)

Singh Vaughan Williams Class	Drug	Mechanism / action
Ia	Quinidine, procainamide, disopyramide	Fast sodium channel blockade. Prolongation of repolarisation, PR and QRS duration
Ib	Lignocaine, mexilitine, phenytoin	Fast sodium channel blockade. Shorten repolarisation and QT interval
Ic	Flecanide, propafenone	Fast sodium channel blockade but QT minimally changed
II	Atenolol, metoprolol, esmolol	Block beta adrenergic receptors and slow rate
III	Amiodarone, sotalol	Potassium channel blockade and prolong repolarisation
IV	Verapamil, diltiazem, nifedipine	Blockade of slow calcium channel

Table 3 Singh Vaughan Williams classification of antiarrhythmic medication.

Class I agents were among the first to be used to terminate atrial fibrillation and still remain a popular choice in North America. This class of agent has a number of potentially troublesome side effects including prolongation of the QT interval and subsequent initiation of torsades de pointes. It is also important to be certain of the diagnosis as these agents can increase atrioventricular conduction in patients with atrial flutter allowing very rapid ventricular rates with disastrous consequences. Quinidine, a class Ia drug, has been shown to be effective in terminating atrial fibrillation but has an incidence of proarrhythmic side effects of around 2% and increases mortality compared to placebo.(51)

The class Ic drug flecanide has been widely studied for the termination of atrial fibrillation and although effective, its use has been limited to those patients who have no previous history of ischaemic heart disease. This followed the observation that when given to patients who had previously had a myocardial infarction its administration resulted in a nearly threefold increase in mortality.(52)

Sotalol is a class III antiarrhythmic agent that also has beta blocking properties. It has been shown to be at least as effective as quinidine for the termination of atrial fibrillation but it too prolongs the QT interval and predisposes to tosades de pointes.(53) Because of these side effects initiation of these drugs requires careful monitoring of the QT interval with a QT interval of greater than 500msec being an indication for discontinuation of the drug. Amiodarone, another a class III agent, has also been shown to be effective in cardioverting atrial fibrillation. It has a lower incidence of QT prolongation than the previously mentioned agents but has additional side effects that include photosensitivity, disturbed thyroid function and pulmonary fibrosis which make its use less desirable in patients with little symptoms or underlying thyroid or respiratory disease. Despite this long

list of potential side effects amiodarone still remains the most commonly prescribed antiarrhythmic for maintenance of sinus rhythm in the United Kingdom.

1.12.2 External electrical (DC) cardioversion

External electrical DC cardioversion is an alternative method of restoring sinus rhythm that avoids many of the potential side effects of drug therapy. External electrical cardioversion is performed using a cardiac defibrillator with the capability of delivering an electrical shock between two electrodes with a user-selected energy level. When used to cardiovert atrial fibrillation the DC shock must be synchronised to the R wave to reduce the risk of precipitating ventricular fibrillation. A short acting general anaesthetic should be employed prior to cardioversion and the patient prepared as for any procedure involving an anaesthetic. The shock is usually delivered through gel covered pads with the electrodes arranged in either an anterior to posterior position or from apex to right anterior on the patients thorax. There is some evidence that the anterior-posterior position allows a reduction in the energy required to achieve success but despite this the apex-right anterior paddle position remains the most widely used.(54) Pressure is applied to the electrodes as the shock is delivered in order to reduce thoracic impedance to a minimum. The waveform of the shock delivered has recently been the centre of interest with biphasic waveforms gaining popularity. Bardy et al demonstrated that a biphasic shock of 130J was equivalent to a monophasic damped sinusoidal shock of 200J with both achieving an efficacy of 86%.(55) In animals biphasic shocks have been shown to cause less left ventricular dysfunction following resuscitation from ventricular fibrillation.(56) This may prove to be clinically relevant when performing elective cardioversion of atrial fibrillation in patients with cardiomyopathy. At present most defibrillators used in hospital practice deliver

monophasic damped sinusoidal waveform shocks this is however likely to change as newer models are introduced.

There has been great debate as to the appropriate energy level when attempting to cardiovert atrial fibrillation. Ricard et al compared the minimum energy required to cardiovert nearly 200 patients with chronic atrial fibrillation.(57) They found that nearly half of the patients successfully cardioverted with shocks of less than or equal to 100J with 75% cardioverting with up to 200J. They recommended a protocol with a starting energy of 50J. Joglar et al used a different method to compare initial energy settings.(58) Instead of using a step up protocol patients were randomised to receive 100J, 200J or 360J as the initial shock. They showed that a much lower success rate was achieved when 100J or 200J were used initially as compared to 360J. Troponin I samples were studied to show that a high initial energy level did not cause cardiac damage. They concluded that an energy level of 360J might be the most appropriate starting point. Most protocols used in clinical practice are of the "step up" variety. Using this method the energy level is increased after each failed attempt until either a maximum energy is reached or a maximum number of shocks have been delivered.

1.12.2.1 Complications of external electrical cardioversion

Although elective DC cardioversion of atrial fibrillation is a relatively safe procedure it is not without risk. The most commonly encountered complication is thromboembolism following restoration of sinus rhythm. Other complications include transient bradycardia, ventricular arrhythmias, hypertension, pulmonary oedema and transient ST segment elevation.

1.12.2.2 Thromboembolism and cardioversion

Both electrical and chemical cardioversion of atrial fibrillation are associated with an increased risk of thromboembolic episodes.(59-61) The postulated mechanism for this complication is that preformed intra cardiac thrombi are ejected from the atria or atrial appendage when atrial contraction is restored. The discovery that atrial contraction may not return to normal immediately following cardioversion explains why the peak incidence of thromboembolism occurs three days post procedure. In order to try and reduce this risk the American Association of Chest Physicians recommends that patients should receive anticoagulation for at least 3 weeks prior to cardioversion and 4 weeks post successful cardioversion.(62) This does not however completely eliminate the increased risk of thromboembolic complications following cardioversion.(61,63) Bjerelund and Orning studied 437 patients assigned to either receive anticoagulation or placebo prior to cardioversion. They found a 0.8% incidence of clinically apparent thromboemboli in the anticoagulated group compared to 5.3% in those without prior anticoagulation.(61)

Another means of decreasing the risk of thromboembolic complications associated with cardioversion centres on the use of transoesophageal echocardiography (TOE). Transoesophageal echocardiography allows the atria and atrial appendages to be inspected in detail. This allows the visualisation of pre existing intra atrial thrombus, which is thought to predispose to thromboembolic complications. The accuracy of this method for thrombus exclusion has recently been studied by Fatkin et al.(64) They performed transoesophageal echocardiography in 60 patients undergoing cardiac surgery and compared the accuracy of TOE diagnosis with intraoperative detection of thrombus. They concluded that TOE had a high sensitivity and specificity but a low positive predictive value. This data has led some groups to advocate the use of TOE to screen patients with chronic atrial fibrillation with a view to proceeding immediately to cardioversion without

prior anticoagulation in those patients without evidence of thrombus. Stoddard et al studied 206 patients and proceeded to cardioversion in 153 in whom atrial thrombus had been excluded by TOE.(65) They reported no thromboembolic complications after a 4 week follow up period. Klein et al used a different strategy allocating patients to conventional anticoagulation or short term anticoagulation prior to cardioversion.(66) Those patients in the short term group were prescribed warfarin and a TOE and cardioversion performed as soon as a stable INR was achieved. Anticoagulation was continued for at least four weeks following successful cardioversion . No significant difference in the incidence of thromboembolic complications was found between the two groups.

Despite these results it should be remembered that the absence of thrombus on TOE does not eliminate the risk of thromboembolism. In 17 patients who had thromboembolic complications post cardioversion, Black et al found that a precardioversion TOE had shown spontaneous contrast in 5 patients but no evidence of formed thrombus in any.(67). They concluded that these thromboembolic episodes were either as a result of a false negative TOE examination or de novo thrombus formation post cardioversion.

At North Tyneside General Hospital we use a hybrid of these strategies in an attempt to achieve the lowest risk of thromboembolic complications possible. Patients are anticoagulated with warfarin for four weeks in the conventional manner and then proceed to transoesophageal echocardiogram prior to cardioversion. Patients with no evidence of intracardiac thrombus proceed immediately to DC cardioversion. If intra cardiac thrombus is seen DC cardioversion is postponed and warfarin therapy continued for a further six weeks. A repeat TOE is then performed. If this second TOE proves negative then DC cardioversion is attempted.

1.12.3 Internal electrical cardioversion

Internal electrical cardioversion is a new technique involving the insertion of an intracardiac catheter and the delivery of low energy shocks, typically 2 to 6 joules, direct to the myocardium in an attempt to produce sinus rhythm. This technique may be particularly useful in patients whose atrial fibrillation is unresponsive to external cardioversion. In a study by Schmitt et al 25 patients who had failed to respond to external cardioversion underwent internal cardioversion. Successful restoration of sinus rhythm was achieved in 88% of patients. Since this approach involves the insertion of an intracardiac catheter it carries the potential complications including cardiac puncture, bleeding and infection. The facilities required to carry out internal cardioversion currently limits its use to major centres.

1.13 Invasive treatments

A more invasive approach may be required for symptomatic patients if rate and rhythm control has proved impossible using the approaches outlined. Several options are available.

1.13.1 AV node ablation and ventricular pacing

Atrioventricular node ablation with ventricular pacing was originally described by Scheinman in 1982.(68) A high-energy radiofrequency current is used to destroy the atrioventricular node and produce complete heart block. A pacemaker is inserted to maintain an adequate ventricular rate. Thus control of the ventricular rate is achieved at the expense of loss of normal physiological regulation and atrial transport. If single lead

ventricular pacing is employed the thromboembolic risk due to decreased atrial contraction remains. Patients should therefore be maintained on warfarin therapy for thromboembolic prophylaxis.

1.13.2 Focal ablation

Focal ablation is most often used in younger patients who have paroxysmal episodes of atrial fibrillation. The technique relies on the isolation one or more trigger foci responsible for initiating the arrhythmia. These foci usually lie either in the pulmonary veins or less commonly in the right atrium. Following their identification radiofrequency ablation is applied to the area surrounding each focus in order to isolate it from the rest of the myocardium. Thus preventing the propagation of the fibrillatory potentials.

1.13.3 The surgical maze procedure

The maze procedure, first performed in 1987 by Cox, involves the surgical excision of the atrial appendages and the isolation of the pulmonary veins.(69) Incisions are also made within the atria so as to form a "corridor" of atrial tissue from the sinus node to the atrioventricular node. Further incisions ensure that the atrial tissue is divided into strips too narrow to allow atrial fibrillation to occur. One of the major limitations of the procedure is that cardiopulmonary bypass is required. The maze procedure can however be carried out in conjunction with other cardiac surgery. Sandoval et al reported a series in which the maze procedure was carried out at the time of mitral valve replacement.(70) They reported restoration of sinus rhythm in 85% of patients undergoing the combined procedure with an operative mortality of 5%. Of those patients achieving sinus rhythm evidence of atrial contraction was present in around two-thirds with the remainder requiring continued anticoagulation. Raanani et al reported similar results. They compared forty seven patients

with atrial fibrillation undergoing mitral valve surgery and the maze procedure with forty seven matched subjects who underwent mitral valve surgery alone. Operative mortality was similar in both groups but sinus rhythm was maintained in 75% of the maze group compared with 36% in the non maze group (P=0.0004). After three years of follow up none of the maze group had suffered a thromboembolic complication as compared to 15% of the non maze group (P=0.03). (71)

A minimally invasive variation of the maze procedure has recently been reported by Lee et al.(72) They performed the maze procedure via a tunnelled approach in 10 dogs with artificially induced atrial fibrillation. Cardiopulmonary bypass was not required during any of the procedures and sinus rhythm was restored in all 10 animals with no operative deaths. No data for this procedure in humans currently exists.

1.13.4 The catheter maze procedure

A further modification of the maze procedure has been developed using radiofrequency ablation catheters to create the corridors necessary to prevent atrial fibrillation.(73) These linear scars appear to give success rates for maintaining sinus rhythm in the region of 40 to 50%. The relatively low success rate coupled with a high incidence of complications has lead electrophysiologists to look for alternative approaches. Initially areas of automaticity within the pulmonary veins themselves were targeted in an individual manner in an attempt to abolish foci responsible for initiating atrial fibrillation. Using this approach success rates rose to around 65% however multiple procedures were often necessary. The realisation that initiating foci could be present not only in the pulmonary veins but in many different areas of the atria lead to the development of more anatomically based techniques. Applying a technique of circumferentially isolating the pulmonary vein ostia from the atrium has produced success rates for maintaining sinus

rhythm in the order of 70% without the need for continuing antiarrhythmic medication. This anatomical approach was also used by Pappone et al who used a non fluoroscopic mapping system and radiofrequency ablation delivered circumferentially outside the ostia of the pulmonary veins to electrically isolate potential triggers for atrial fibrillation. In a series of 26 patients 85% were AF free with 62%taking no antiarrhythmic medication at follow up. (3)

Although catheter ablation for atrial fibrillation shows promise for the future it currently limited to highly selected cases in part due to the need for often lengthy procedures. It is hoped however that further refining both the equipment and the techniques used may lead to ablation of atrial fibrillation being more widely available.

1.13.5 Pacing techniques

Atrial pacing has been suggested as a means of both treating and preventing paroxysmal atrial fibrillation. Levy et al investigated the potential of biatrial pacing, right atrial pacing and no pacing in preventing episodes of paroxysmal atrial fibrillation in patients refractory to anti arrhythmic medication.(74) They found that both biatrial and right atrial pacing decreased episodes in comparison to no pacing. No significant difference in episodes was noted between the two pacing methods.

1.13.6 Implantable atrial defibrillator

The implantable atrial defibrillator has been used in highly symptomatic patients who are unable to tolerate other therapy. Early defibrillators required activation by a physician but newer models allow the patient to activate the device. This removes the potential for unexpected painful shocks and allows patients who prefer to have sedation for the procedure to enlist medical help.(75) Although promising results have been seen the

use of the atrial defibrillator devices is likely to remain limited in part due to the high cost of the units used.

1.14 Relapse Rates Following Cardioversion

The safety, wide availability and high initial success rate of external DC cardioversion makes it an attractive proposition for the treatment of chronic non valvular atrial fibrillation. The long-term result of a successful procedure is that the patient is returned to sinus rhythm with a theoretical reduction for all the complications outlined above including mortality. The patient should not be required to take medication long term as is the case with the strategy of rate control and anticoagulation. Restoration of sinus rhythm occurs in a controlled manner with electrical cardioversion unlike pharmacological cardioversion where sinus rhythm may return at any time throughout the treatment period.

Electrical cardioversion has also been shown to be the most cost effective treatment when compared to rate control and thromboembolic prophylaxis. Catherwood et al used a decision analytical model to estimate the costs associated with different treatment strategies for chronic non valvular atrial fibrillation.(76) They compared DC cardioversion alone, rate control plus long-term anticoagulation and pharmacological cardioversion of patients presenting with newly diagnosed chronic non valvular atrial fibrillation. Electrical cardioversion was the most cost effective strategy costing $1920 per quality adjusted life year (QALY) compared to figures for rate control and warfarin of $2091/QALY. Rate control in combination with aspirin although cheaper initially incurs greater cost due to late complications such as stroke and is therefore less cost effective in the long term incurring costs of $2380/QALY.

The major limitation of DC cardioversion is the high incidence of relapse to atrial fibrillation following an initially successful procedure. The relapse rate is highest within the first month with rates as high as 30% being reported.(77) Relapses continue to occur with time and relapse rates at one year typically range between 45 and 70%.

Antiarrhythmic prophylaxis following successful cardioversion has been used to attempt to decrease this rate of relapse to atrial fibrillation. With antiarrhythmic prophylaxis relapse rates fall depending on the drug used. Relapse rates are reduced with quinidine therapy at the expense of an increase in mortality making quinidine an unattractive agent for routine use. Flecanide and propafanone have also been shown to reduce relapse rates but their use in patients with reduced left ventricular function and ischaemic heart disease is limited as previously described.

Despite a paucity of controlled trials amiodarone is thought to be the most successful agent at maintaining sinus rhythm with reported relapse rates varying from 17% to 64% at one year depending on patient selection. (78) Amiodarone is however associated with a wide variety of side effects making routine long term prophylaxis less attractive to young patients or those with few symptoms.

1.15 Prediction of relapse

The ability to predict which patients will relapse to atrial fibrillation has obvious advantages depending on when prediction is possible. If patients who are likely to relapse to atrial fibrillation can be reliably identified prior to undergoing DC cardioversion targeting of the procedure becomes a feasible proposition. This would allow those patients who have little or no chance of maintaining sinus rhythm to avoid the risks of the

procedure. This would also have resource implications allowing efficient use of both cardioversion facilities and physician time.

However if prediction of relapse is only possible after cardioversion has been carried out, targeting of antiarrhythmic medication is the most realistic goal. Since all antiarrhythmic agents currently available have potentially serious side effects limiting their use to those who definitely require them would appear desirable. This would allow patients who are unlikely to relapse to avoid potentially lethal side effects. The identification of patients who have a high chance of relapse would also provide an ideal group of patients in which to evaluate future treatment strategies such as new antiarrhythmic drugs.

Many different variables have been evaluated in an attempt either to limit the use of cardioversion to those in whom long-term success can be achieved or to predict relapse. To date no reliable method of predicting relapse following successful cardioversion has been identified.

1.15.1 Patient age and relapse

Atrial fibrillation becomes more common with advancing age and it is in older patients that the rate of complications is highest. The risk of thromboembolism is especially important in elderly patients and has lead to recommendations that older patients should be targeted for prophylaxis. Thus maintenance of sinus rhythm where possible is especially beneficial in older subjects. Whether age is an independent predictor of success of DC cardioversion is still unclear. In a study of patients with chronic atrial arrhythmias, Van Gelder et al appeared to show that advancing age was associated with a decrease in initial success and an increased rate of relapse.(79) However this study included patients with both atrial fibrillation and atrial flutter. No such relationship was found by Carlsson et al (80) who compared 582 patients aged 65 and over undergoing cardioversion with 570

patients under 65 undergoing the same procedure. Success rates and complication rates were similar in both groups.

On current evidence age would not appear to be a particularly useful predictor of either initial success or relapse to atrial fibrillation.

1.15.2 Duration of arrhythmia and relapse

Several authors have shown that arrhythmia duration is a strong predictor of failure of maintenance of sinus rhythm following cardioversion.(79,81-85) In particular atrial fibrillation of short duration related to a correctable cause is least likely to recur. Duytschaever et al used multivariate analysis to identify factors predicting relapse in 85 patients following successful cardioversion.(86) Duration of arrhythmia was found to be the most reliable predictor of relapse. Van den Berg et al also showed how an increasing duration of arrhythmia was associated with a failure to achieve sinus rhythm at cardioversion (see table 4).(87)

Duration of atrial fibrillation	**Increase in risk of failure to cardiovert**
< 3 months	0
3 – 36 months	4 fold increase
> 36 months	23 fold increase

Table 4 Estimated risk of failure to cardiovert by duration of atrial fibrillation

These findings have lead the Royal College of physicians of Edinburgh to recommend DC cardioversion only for patients with atrial fibrillation of less than 3 months duration or patients with arrhythmia duration greater than three months accompanied by symptoms.(47) The major limitation with this strategy is the difficulty in precisely

determining the onset of atrial fibrillation. Thus cardioversion is currently frequently offered to patients with a duration of atrial fibrillation in excess of three months. Further work on the role of arrhythmia duration is clearly required.

1.15.3 Functional class, co morbidity and relapse

Although several conditions have been shown to predispose to the initiation of atrial fibrillation data regarding the influence of co-morbidity on relapse following cardioversion is lacking. This is in part because patients with extensive co-morbidity are often excluded from studies that aim to identify factors responsible for relapse. The presence of rheumatic heart disease has however been shown to lower both initial and long term success of DC cardioversion.(82)

Pre cardioversion functional class is one factor that may be useful when predicting relapse. Van Gelder et al showed that patients with symptomatic ventricular dysfunction, defined as New York Heart Association class III or IV, had a significantly higher rate of relapse compared to matched individuals with no symptoms of ventricular dysfunction.(79) At present the major reason for assessing comorbidity and functional class is to identify those patients in whom cardioversion is contraindicated. It is not used routinely to predict relapse.

1.15.4 Transthoracic echocardiography and relapse

It is conventially thought that an enlarged left atrial diameter is associated with an increased risk of initial failure of cardioversion or tendency to relapse to atrial fibrillation. The evidence to support this assumption is however less than conclusive. In the two previously mentioned studies by Van Gelder and Duytschaever no association between left

atrial size and successful cardioversion was demonstrated despite a total of over 300 patients being involved. On the other hand Brodsky et al studied 43 patients who all had symptomatic atrial fibrillation and dilatation of the left atrium (LA size 45 to 78mm). They found that LA size greater than 60mm was associated with an increased risk of relapse within the six month follow up period. Gross atrial enlargement may prove to be a useful predictor of relapse even though moderate enlargement appears to be less predictive.

1.15.5 Transoesophageal echocardiography and relapse

Recently interest has increased in the use transoesophageal echocardiographic measurements in the prediction of relapse to atrial fibrillation. Verhorst et al carried out TOE assessment of 62 patients prior to cardioversion for chronic atrial fibrillation.(88) Patients who underwent successful cardioversion were followed up for one year and subsequently divided into two groups. Group one remained in sinus rhythm for the entire follow up period, the second group comprised patients who relapsed to atrial fibrillation. A longer duration of atrial fibrillation, larger LA or annulus dimensions, the presence of spontaneous echo contrast and reduced appendage flow were all found to be associated with a return to atrial fibrillation. Manabe et al looked at left atrial appendage (LAA) flow as a predictor of successful cardioversion.(89) They concluded that LAA flow velocity of greater than 19cm/sec was both sensitive (80%) and specific (88%) as a predictor for successful cardioversion. However Perez et al were unable to show the same relationship for any echocardiographic parameter showing only that LAA flow velocity was related to left ventricular function.(90)

Each of these studies involved relatively small numbers of highly selected patients making extrapolation of this data to everyday clinical practice difficult. At North Tyneside General Hospital all patients have a TOE to exclude left atrial appendage thrombus prior to DC cardioversion. These patients provide an ideal opportunity to gain valuable information as to the role of transoesophageal echocardiographic measurements in the prediction of relapse of atrial fibrillation following DC cardioversion in everyday UK practice.

1.15.6 Signal Averaged ECG and relapse

The signal-averaged electrocardiogram (SAECG) has been extensively investigated over the last 20 years. Ever since Simson detected late potentials in the QRS complex in 1981 interest has centred on signal averaging techniques and ventricular arrhythmias.(91) Here late potentials are thought to represent delayed cardiac activation providing a substrate for re-entry and initiating ventricular arrhythmias.(92-94)

More recently interest has increased on the possibility of using signal averaging techniques to study atrial fibrillation.(95-97) Mechanisms similar to those outlined above are thought to be involved in the propagation of atrial arrhythmias. The atria are believed to contain areas of slow conduction allowing a re-entrant mechanism to exist.(1,97,98) These areas of slow conduction are thought to give rise to late potentials detectable within the p wave on signal averaging in the same way as ventricular late potentials are visible within the QRS complex. There is still however great debate as to the role of signal averaging techniques in atrial fibrillation.

1.15.6.1 The evidence for a relationship between signal averaging and atrial fibrillation

Guidera et al studied 15 patients with paroxysmal atrial fibrillation and compared both their 12 lead and signal averaged ECG with those of 15 age and sex matched control subjects.(118) They found no difference in p wave duration on standard 12 lead ECG, however mean unfiltered and filtered p wave duration was significantly lengthened in those patients with atrial fibrillation. A study of 51 patient with atrial fibrillation following coronary artery bypass grafting showed similar results with no significant difference in p

wave duration on standard 12 lead ECG and an increased signal averaged p wave duration compared to control subjects.(119) Further evidence for an association between signal averaged parameters and atrial fibrillation was provided by Villani et al.(120) In a study of 40 patients (20 with atrial fibrillation) they found that an increase in p wave dispersion and the p wave dispersion index (p wave dispersion index = {p duration (X,Y,Z, leads) S.D. / mean value } x 100) were significantly associated with episodes of atrial fibrillation. There was no significant difference in root mean square voltage of the last 20 milliseconds of the p wave (RMS20).

Several groups have considered the use of P wave signal averaging to predict the relapse to atrial fibrillation following initially successful DC cardioversion. Opolski et al recorded signal averaged ECG in 35 patients following DC cardioversion and found that the 11 patients who relapsed into atrial fibrillation had a significantly longer p wave duration(121). Stafford et al produced similar data in patients who had relapsed following internal cardioversion.(119) One of the largest published series is that of Aytemir et al who measured p wave signal averaged ECG in 73 patients following cardioversion.(122) They also found significant differences in p wave duration with patients who relapsed showing longer p wave duration.

1.15.6.2 The evidence against a relationship between signal averaging and atrial fibrillation

Despite the positive results outlined above there is still some debate about the association between signal averaged p wave duration and atrial fibrillation with several groups unable to show a relationship. Frost et al looked at p wave duration and morphology of 189 patients undergoing coronary artery bypass grafting of which 42 developed atrial fibrillation.(123) No significant relationship was found between p wave

duration or morphology and the likelihood of an episode of atrial fibrillation. Turrito et al used several variables including p wave duration to attempt to risk stratify patients with regard to atrial tachyarrhythmias. .(124) Only left atrial AP diameter was found to be a useful predictor of arrhythmia recurrence.

1.15.6.3 Possible causes of conflicting results

Both the lack of standardisation and problems with reproducibility of the p wave signal averaged ECG have been proposed as possible causes for the different outcomes in the above studies. The technique has, however, been shown to have a high degree of short and medium term reproducibility.(125) Another suggested reason for these conflicting outcomes is the filtering method used. Signal averaged signals can be filtered, prior to analysis, by a number of different methods including unidirectional, bi-directional, finite impulse response, least-squares fit and spectral (Fourier) filters. Ehlert et al studied these different filtering processes and concluded that least-squares fit filtering with a bandwidth of 29-250 Hz and QRS triggering provided the most reliable results.(126)

A further discrepancy between the various studies would appear to be the antidysrhythmic medication at the time of inclusion. It has been shown that class I and class III agents change the characteristics of the p wave signal averaged ECG. However in many of the studies these medications were used in some or all of the patients enrolled. This may help to explain the inconsistency of the results obtained.(111,127-129)

1.15.7 Heart rate variability

Although the precise electrophysiology of atrial fibrillation remains largely unclear it has been recognised for some time that changes in the autonomic nervous system play an

important part in initiation of atrial fibrillation. Heart rate variability measurements have been proposed as a means of none invasively measuring autonomic activity.

The term heart rate variability has become the accepted term for the natural variation of the cardiac rate and RR intervals. Other terms, which have been used previously, include cycle length variability, heart period variability and RR variability.

One of the major limitations of heart rate variability measurements to date has been the lack of standardisation of both measurements and nomenclature. Despite these early difficulties it has been suggested that the measurement of heart rate variability can be used to obtain an accurate non-invasive marker of autonomic modulation.(99) In an attempt to solve this problem a special report from the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology was published in 1996. They attempted to set minimum standards for measuring heart rate variability and guidelines for the interpretation of results.(100)

Heart rate variability measurements can be divided into two groups, time domain and frequency domain measurements. Both types of analysis are made from measurements taken from adjacent cardiac beats in a continuous electrocardiogram recording.

1.15.7.1 Time domain analysis

Time domain analysis provides information on the amount of variation around the mean heart rate. There are two main classes of time domain variables, the first relating to the variation in cycle length throughout the given time period and the second giving a measure of variation in the length of adjacent cycles. The most commonly used variables in the first group are SDNN and the SDANN. These measurements of interbeat variation are influenced by both short term (respiration) and long term (circadian) factors.

The second class of variable includes pNN50 and RMSSD. These variables are not thought to be affected by long term trends and represent a measure of vagal tone (see table below).(101)

Variable	Units	Definition
SDNN	ms	Standard deviation of all normal RR intervals in the 24 hour recording.
SDANN	ms	Standard deviation of the mean of all 5 minute segments of normal RR intervals of a 24 hour recording.
SDNNi	ms	Mean of the standard deviations of all NN intervals for all 5 minute segments of a 24 hour recording
SNN50 inc/dec/total	n	Number of pairs of adjacent NN intervals differing by greater than 50ms per 24 hours standardised for invalid intervals
SNN6%	n	Number of pairs of adjacent NN intervals differing by greater than 6% per 24 hours standardised for invalid intervals
pNN50	%	Percentage of RR intervals between adjacent normal RR intervals that are greater than 50 msec computed over the entire 24 hour ECG recording.
RMSSD	msec	Root mean square of successive differences, the square root of the mean of the sum of the squares of the differences between adjacent RR intervals over the entire 24 hour recording

Table 5 Definitions of time domain heart rate variability measurements.

1.15.7.2 Frequency Domain Analysis

Frequency domain analysis provides information on the periodic oscillation of the heart rate at various frequencies. Three main spectral components are calculated using frequency domain analysis from short-term recordings of heart rate. They are very low frequency (VLF), low frequency (LF), and high frequency (HF) components(100,102,103) HF and LF power is not constant but varies with varying autonomic tone. The precise determinants of each spectral frequency band is not yet fully established but it is thought that vagal activity is the major factor in determining HF power. Some authors have suggested that the LF component of heart rate variability gives a measure of sympathetic activity whilst others state that it is influenced by both sympathetic and vagal activity. The physiological significance of VLF is even less well defined and further work is required to determine its significance.

Variable	Units	Description	Frequency Range
VLF	ms^2	Power in VLF range	<= 0.04 Hz
LF	ms^2	Power in LF range	0.04 – 0.15 Hz
HF	ms^2	Power in HF range	0.15 – 0.4 Hz

Table 6 Definitions of frequency domain heart rate variability measurements

1.15.7.3 Duration of ECG Recording

Analysis can be performed on both short and long term recordings.(100) The commonest recording to be subjected to analysis is the 24 hour ambulatory recording. This long-term recording is useful when studying heart rate variability at different times within the same patient or in-patients who are limited in their activities. However the fact that heart rate variability is influenced by physical activity makes this analysis difficult, if not impossible, to interpret on outpatients due to problems of standardisation.

Short-term measures of heart rate variability have the advantage of allowing standardisation of conditions. This means that recordings can be more easily compared between individuals and groups of individuals. To achieve these standard conditions care must be taken to record the measurement at the same time of day, ambient temperature, and position, in an environment free from exogenous stimuli and at the same respiratory rate. It has been suggested that 5 minute recordings should be used and that more than one 5 minute period should be measured to ensure stationarity.

In general, time domain analysis is preferred when studying long term measurement and frequency domain analysis preferred for short-term measurements.

1.15.7.4 Time and Amplitude Resolution

Since accuracy of recognition is governed by the sampling frequency it is crucial to select the correct frequency in order to obtain accurate measurement of the RR interval. It has been suggested that this should be at least in the range 250 – 500 Hz or if possible higher.(102) The amplitude resolution of the analogue to digital conversion should be sufficiently large as to allow accurate point resolution of the signal.(100)

1.15.7.5 Editing

Accurate editing is required prior to either time or frequency domain analysis. Ectopic beats must be removed and only "normal" RR intervals used in analysis. One method of ensuring that only normal RR intervals are included is to exclude all those RR intervals which differ by greater than 20% from the preceding RR interval. This can be done automatically but can lead to greater errors as a proportion of normal RR intervals will be eliminated.(104-106) In a study of interobserver reproducibility Kroll et al showed that manual editing gave high levels of reproducibility for both time and frequency analysis.(107)

1.16 Clinical Applications of Heart Rate Variability

1.16.1 Atrial Fibrillation

At the time of writing no data exists with regard to the use of heart rate variability following DC cardioversion of chronic atrial fibrillation.

Fioranelli et al calculated heart rate variability in 28 patients, with no evidence of heart disease, in whom a period of paroxysmal atrial fibrillation (PAF) was reported on a 24 hour ECG.(108) They compared a period 5 minutes prior to AF with a period at least one hour after the termination of AF. They concluded that the episodes could be divided into two types. In type A episode they found an increase in LF and a decrease in HF power. In type B they found an increase in HF power and a decrease in LF power. They concluded that type A episodes were associated with an increase in sympathetic drive and type B episodes with an increase in parasympathetic drive. These conclusions fail to take into account that although it is generally agreed that HF power is a marker of vagal activity,

there is still disagreement as to the exact relevance of LF power. It has been suggested by some authors that LF power represents both sympathetic and vagal components of heart rate variability.

Herweg et al measured heart rate variability in 29 patients with PAF and concluded that HF power changes were also present before most episodes of AF but that circadian differences were present. Increased parasympathetic activity preceded mostly nocturnal AF and this tended to occur in younger patients. Daytime episodes were preceded by a decrease in parasympathetic activity as seen by a decrease in HF power.(103)

Studies of heart rate variability after coronary artery bypass grafting have shown a decrease in the low frequency / high frequency ratio prior to initiation of atrial fibrillation leading to the conclusion that AF may be a result of loss of vagal tone.(109) Hogue et al used approximate entropy (ApEn) analysis to study ECG recordings from 18 patients who developed paroxysmal atrial fibrillation following coronary artery bypass surgery. These episodes, 24 in all, were compared to age and sex matched controls who had also undergone surgery. They concluded that increased heart rate and decreased ApEn was associated with PAF post surgery and may prove to be a useful predictive marker.(110)

1.16.2 Myocardial Infarction

Depressed heart rate variability after myocardial infarction is associated with an increase in mortality, particularly arrhythmic events.(108,109,111) This decreased variability was detected as a decrease in HF power and an increase in LF power. This may represent a loss of parasympathetic control with a shift of balance towards sympathetic drive. This helps to explain some of the benefits seen with beta blockers post myocardial infarction. Beta blockers have been shown to prevent the rise in LF power seen during morning hours and decrease mortality.(112)[78]

1.16.3 Congestive Cardiac Failure

Patients with congestive cardiac failure show large reductions in both HF and LF power with little difference in the HF/LF ratio.(113-115) These changes are associated with a dramatic reduction of life expectancy. Whether this is a causal relationship has yet to be determined.

1.16.4 Diabetic Neuropathy

In diabetic patients a reduction in the time domain measurements of heart rate variability has been shown to be associated with a poor prognosis. There is evidence that the decrease in heart rate variability predates the clinical expression of diabetic neuropathy. This raises the possibility of using heart rate variability measurements to identify those patients most at risk of developing neuropathy and allow preventative treatment to be implemented early.(116,117)

1.16.5 Heart Rate Variability Following DC Cardioversion

Heart rate variability has been shown to be a useful tool in the prediction of ventricular arrhythmias following myocardial infarction. Evidence exists that measurement of heart rate variability may give useful information with regard to atrial fibrillation following coronary artery bypass grafting, however, the use of heart rate variability in predicting the long-term success of DC cardioversion has not been studied. This may prove to be an easily performed non-invasive means of predicting long term outcome, thus allowing targeted antiarrhythmic prophylaxis. Further work is required to define the role of heart rate variability measurement in predicting long term outcome of DC cardioversion.

1.17 Summary

Atrial fibrillation is the commonest sustained cardiac arrhythmia and is associated with substantial morbidity and mortality. External DC cardioversion is a reliable means of restoring sinus rhythm in the majority of patients its usefulness is however limited by a high rate of relapse. These relapse rates can be decreased by the use of antiarrhythmic prophylaxis at the expense of potentially life threatening side effects. The ability to predict which patients will relapse following cardioversion may allow targeting of prophylactic antiarrhythmic therapy. It is clear that further work is required to identify whether prediction of relapse is possible and if so which factors are most helpful in everyday practice. The following research project was carried out in an attempt to clarify whether transoesophageal echocardiography, p wave signal averaging and heart rate variability had a part to play in identifying relapse following DC cardioversion.

2 Methods

2.1 Study Aims

The main aim of this study is to assess to what extent measurements from transoesophageal echocardiography, P wave signal averaged electrocardiography and heart rate variability can be used to predict a successful long term outcome in patients undergoing DC cardioversion for atrial fibrillation.

2.2 Study Design

A prospective observational study design was employed. The study was carried out wholly at North Tyneside General Hospital. Ethical approval was obtained from the Joint Ethics Committee of Newcastle and North Tyneside Health Authority.

2.3 Statistical Power

The number of patients required to achieve a meaningful result was estimated by means of a power calculation. A p value of less than 0.05 was taken to represent a statistically significant result. Several assumptions were made in order to carry out the calculation. The first of these assumptions was that ten percent of those initially enrolled would fail to make it to DC cardioversion. This would include patients who spontaneously reverted to sinus rhythm or were found to have a treatable cause for their atrial fibrillation, patients who were unable to tolerate the TOE procedure, those who were found to have a clot at TOE and those who failed to attend for the follow up appointments. It was assumed that of those patients who proceeded to DC cardioversion approximately 80% would

initially cardiovert to sinus rhythm and of those achieving sinus rhythm approximately 50% would relapse to atrial fibrillation during the study period. When considering the signal averaged ECG parameters it was decided that a difference in p wave duration of 10 milliseconds could be reliably detected and would be clinically useful. Using these assumptions it was calculated that a minimum of seventy patients would be required to undergo DC cardioversion to give a meaningful result. Allowing for the previously mentioned drop out rate this meant that a minimum of around 77 patients would need to be recruited. When similar calculations were performed using TOE variables and heart rate variability variables it was found that lower numbers of patients were thought to be required to provide a meaningful result for these variables. Given that the power calculation had suggested that at least 77 patients would be required a recruitment goal of 100 patients was set.

2.4 Patient Recruitment

Patient recruitment was limited to the North Tyneside General Hospital catchment area. All patients were referred either from a hospital physician or family practitioner to the cardiology services at North Tyneside General Hospital with a diagnosis of atrial fibrillation. The inclusion and exclusion criteria set out below were used to screen referrals prior to patients being invited to take part in the study.

Inclusion criteria

1. Atrial fibrillation present for greater than 48 hours.
2. Age greater than 18 years of age.
3. No physical or echocardiographic evidence of valvular heart disease.
4. No contraindications to warfarin therapy.

5. No contraindications to DC cardioversion.

6. No contraindications to general anaesthesia.

Exclusion criteria

1. Oesophageal disease or contraindication to transoesophageal echocardiography

2. Patients taking either class I or class III antiarrhythmic medication.

3. Patients with acute coronary syndromes.

4. Uncompensated heart failure. Defined as NYHA class IV.

5. Inability to give informed consent.

6. Pregnancy.

Patients who were taking class I or class III antiarrhythmic medication were excluded as both these groups of drugs effect P wave morphology. This would lead to problems interpreting P wave signal averaging measurements. Patients previously taking such medication who had not taken the drug for a period equal to or greater than five times its half-life were eligible for inclusion.

2.5 Initial Assessment

Following referral those patients who met the criteria outlined above were invited to attend the outpatient department. All patients were given information with regard to the diagnosis of atrial fibrillation and the possible treatment options available. An information leaflet was provided (see appendix 1) that explained the nature of the study and what was involved should they wish to participate. All patients were asked to sign a consent form to indicate whether they would like to take part in the study (see appendix 2).

At the initial assessment visit all patients underwent a full physical examination to ensure suitability for inclusion. The following additional data was collected.

1. Demographic data: Patient age, sex.
2. Clinical data: Duration of atrial fibrillation, previous ischaemic heart disease, hypertension, stroke, alcohol consumption and previous arrhythmias.
3. Biochemical data: Urea and electrolytes, thyroid function tests
4. Standard 12 lead electrocardiogram.

For the purposes of this study the duration of atrial fibrillation was taken to be the longest of either the time from first diagnosis or the time from which the patient first noticed the presenting symptom to the date cardioversion was attempted.

All data was held on a Microsoft Access computer database.

2.6 Anticoagulation

All patients who consented to take part in the study were anticoagulated following the guidelines set out by the American College of Chest Physicians. They recommend anticoagulation for at least three weeks prior to DC cardioversion and for a further four weeks following a successful procedure. Warfarin treatment was used with a target international normalised ratio (INR) of 2.0 – 3.0. This was achieved via the anticoagulant clinic at North Tyneside General Hospital by frequent capillary sampling and dose adjustment. A further whole blood estimation of INR was made twenty-four hours prior to cardioversion to ensure adequate anticoagulation at the time of the procedure with the procedure being postponed in patients whose INR was less than 1.5.

2.7 Transoesophageal Echocardiography

All patients had a transoesophageal echocardiogram prior to DC cardioversion. Patients attended the coronary care unit of North Tyneside General having fasted for at least six hours prior to the procedure. An anaesthetic assessment was performed to confirm that the patient was suitable for general anaesthesia. An 18 gauge intravenous cannulae was inserted into a vein on the back of the right hand. Blood pressure, oxygen saturation and ECG monitoring was performed throughout the procedure. Oxygen was administered via nasal prongs at a rate to maintain oxygen saturation throughout the procedure. The patient was positioned facing slightly to the left side and the hypopharynx was sprayed with xylocaine topical anaesthetic. Sedation was achieved using intravenous midazolam to a maximum dose of 10mg. Transoesophageal echocardiography was carried out using a Hewlett Packard sonos 2500 and a multiplane probe (Philips Medical Systems, Massachusetts, USA). All cardiac chambers and valves were visualised in the standard manner in both the zero and 90 degree planes and any abnormalities noted. The measurements outlined below were performed specifically for the purpose of the study. The definitions used are similar to those used by previous investigators so as to allow comparison between studies.

<u>Left atrial dimensions (zero degree view)</u>

1. Antero-posterior diameter: Defined as the distance from the top of the sector angle (or the posterior wall if visible in the extreme near field) through the centre of the left atrium to the centre of the mitral valve.
2. Lateral diameter: Defined as the distance from the atrial septum through the atrial centre to the lateral wall of the atria measured perpendicular to the antero-posterior diameter.

Left atrial appendage measurements (90 degree view)

1. Left atrial appendage area: Defined as the area encompassed by a line from the tissue fold that separates the left atrial appendage from the left atrium to the opposite pole of the appendage orifice and the borders of the left atrial appendage.

Presence of thrombus and echo contrast

1. Presence of thrombus: A thrombus was said to be present when a discrete mass could be visualised consistently with a different echo texture to the surrounding tissue.
2. Presence of spontaneous echo contrast: Spontaneous echo contrast was said to be present when the typical "smoke" like pattern could be consistently identified.

Flow measurements

1. Left atrial appendage doppler flow velocity: The average peak antegrade flow taken from five consecutive beats with relatively stable RR intervals. Flow was measured at a point 1cm below the midpoint of the appendage orifice using doppler echocardiography. Taken from 90-degree view.
2. Mitral valve doppler flow velocity: The peak diastolic transmitral flow velocity averaged over five consecutive beats with relatively stable R-R intervals. Measurements were made at a point 1cm above the mid point of the mitral valve orifice in the zero degree view.
3. Pulmonary vein doppler flow velocity. The peak pulmonary venous flow was measured in the left upper pulmonary vein. Five consecutive peaks were averaged using relatively stable R-R intervals. Measurements were made in the 90-degree plane.

All measurements were made from points agreed by two operators. TOE studies were recorded onto standard VHS video cassette.

2.8 DC Cardioversion

Patients who had no evidence of thrombus on transoesophageal echo proceeded directly to DC cardioversion. An anaesthetist administered a short acting general anaesthetic after pre-oxygenating the patient by way of a bag and mask. The choice of anaesthetic agent was left at the discretion of the anaesthetist but propofol was the drug most frequently used.

Once the patient was fully anaesthetised, two gel-coated pads (3M Healthcare, St Paul, USA.) were placed on the thorax. One pad was placed to the right of the upper part of the sternum with the other being placed at the apex. Synchronised monophasic DC shocks were delivered via electrode paddles and downward pressure applied during shock delivery (Code master XL+, Philips Medical Systems, Massachusetts, USA). The initial shock energy used was 100J. If this was unsuccessful further shocks were delivered in a standard step up protocol of 200J, 360J, 360J until either sinus rhythm was achieved or a maximum of four shocks were delivered. A successful DC cardioversion was said to have taken place if sinus rhythm was restored at the time of defibrillation. Patients who achieved sinus rhythm had a 12 lead ECG recorded and were allowed to recover spontaneously prior to further investigations being carried out. Rate limiting medication was stopped prior to discharge. Patients who failed cardioversion were removed from subsequent follow up and further treatment offered on an individual patient basis as required.

2.9 Initial Signal Averaging

P wave signal averaging was performed in all patients following successful DC cardioversion. The initial recording was obtained two hours following cardioversion. Patients were asked to lay still and avoid talking during acquisition and all unnecessary electrical equipment was removed from the room. The patients skin was cleaned with alcohol wipes and lightly abraded to ensure good electrical contact. Self-adhesive electrodes (Biotab, MSB, Wiltshire. UK.) were then placed on the thorax in a Frank X, Y, Z orthogonal configuration (see below).

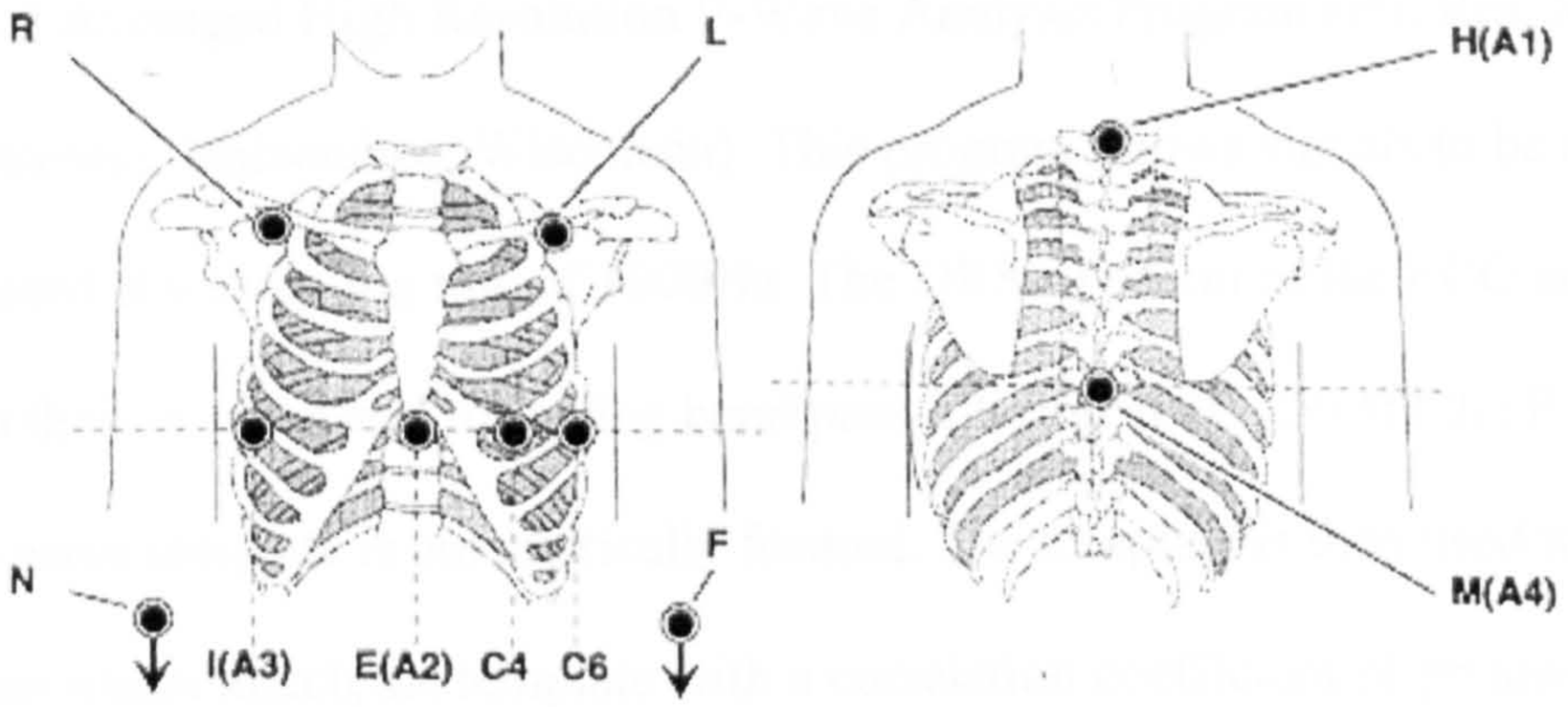


Figure 1 Diagram illustrating lead position during PSAECG recording (Courtesy of Marquette electronics)

Orthogonal plane (leads)	Position of electrodes
X (leads I and C6)	Left and right mid axillary lines at the fifth intercostal space.
Y (L and C4)	Left midclavicular line just inferior to clavicle and at level of umbilicus
Z (H and M)	fourth intercostal space just to the left of the sternum and adjacent to the vertebral body at the same level

Table 7 Position of ECG leads during P wave signal averaging

Recordings were made using a MAC 5000 ECG machine equipped with the Signal-Averaged High Resolution P-Wave Analysis Program (Phi Res, Marquette Electronics, Milwaukee, Wisconsin). This program allows signals to be amplified and digitised at a sampling rate of 1000Hz. The QRST portion of the ECG signal is subtracted from the recording and following band pass filtering at 40-250 Hz the P wave is detected. A P-wave template is automatically formed. The template is then used to identify all P waves which match the template with a correlation coefficient of greater than 0.95. These P wave signals are averaged until the desired noise level is reached. Throughout this study all P-wave signal average recordings were continued until a noise level of less than 0.3μV was achieved. The duration of the unfiltered and filtered P wave were calculated automatically along with the root mean squared voltages for the last 20, 30 and 40 millisecond portions of the P wave. The number of beats averaged in order to achieve the desired noise level was also noted. All signal averaged ECG recordings were stored on floppy disc.

Following signal averaging patients were allowed home in the company of a relative once fully recovered from the effects of anaesthesia. Rate limiting medications, such as digoxin and beta-blockers, were stopped and patients were asked to return to the outpatient clinic 2 days later for review.

2.10 Forty Eight Hour Review

Patients were asked not to eat, drink or smoke for three hours prior to attending the clinic for review and a standard 12 lead ECG was recorded. Patients who had relapsed to atrial fibrillation within the 48-hour period were removed from subsequent follow up and offered specific treatment as necessary.

A repeat P wave signal averaged ECG was performed in all patients who remained in sinus rhythm as described earlier. Patients were then fitted with a 24 hour ECG recorder (Tracker 2, Reynolds Medical, Hertford, UK.) in order to allow heart rate variability to be calculated. Recordings were carried out in a room free from exogenous stimuli and at the same time of day (3pm). The patients skin was cleaned with alcoholic wipes prior to self adhesive electrodes being attached in a standard lead configuration (see below). Patients were asked to rest in a supine position, to remain as still as possible and not to talk for thirty minutes. Recording was commenced after fifteen minutes in order to allow true resting heart rate to be reached. Three consecutive five-minute recordings were obtained for frequency domain spectral analysis and recording was continued to allow time domain analysis to be carried out on the entire 24-hour recording. All recordings were stored on standard audio cassette. Patients returned to the ECG department to have the tracker removed. Warfarin therapy was stopped one month later in those patients maintaining sinus rhythm.

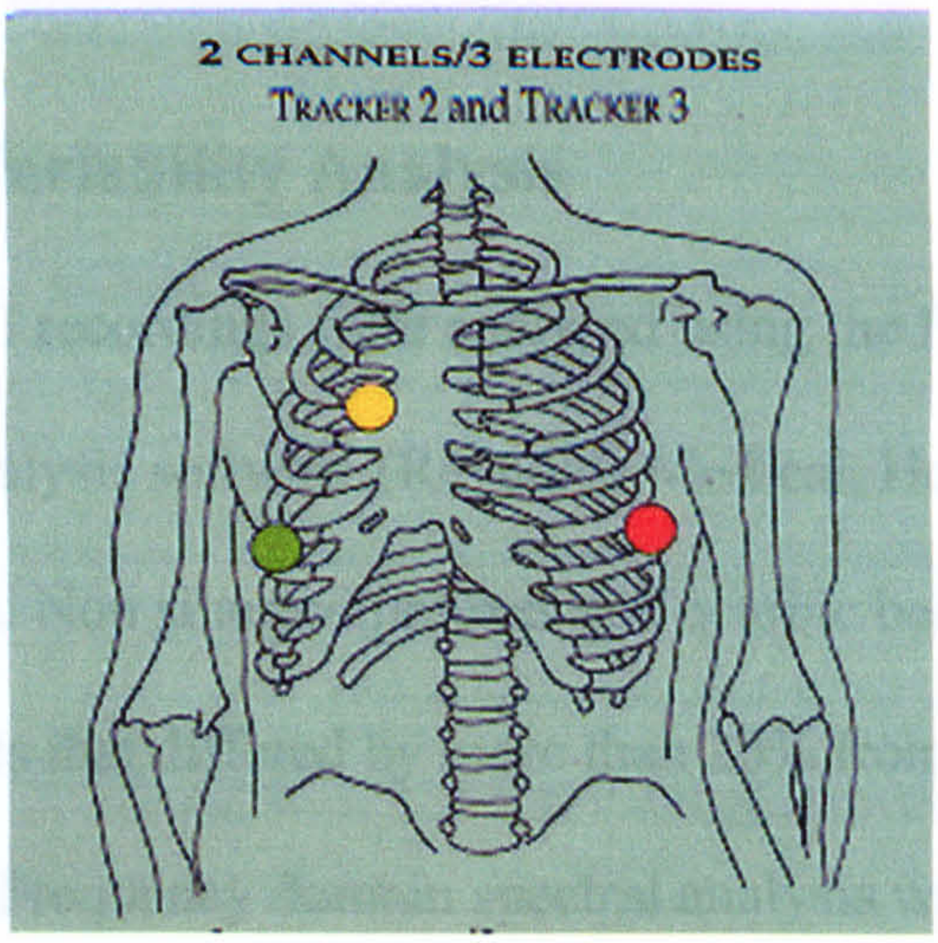


Figure 2 Lead position used for heart rate variability recordings. (Illustration courtesy of Reynolds Medical)

2.10.1 Heart Rate Variability Analysis

The 24 hour ECG recordings were analysed using the Pathfinder system and Research Tools HRV analysis software (Reynolds Medical, Hertford, UK.). All recordings were manually reviewed. Non sinus complexes and ectopic beats were removed prior to analysis. All RR intervals that differed by more than 20% from the preceding interval were removed automatically. Frequency domain spectral analysis was carried out using the commercially available Research Tools Software (Reynolds Medical, Hertford, UK.). This software analyses the frequency domain component of heart rate variability using Fast Fourier Transformation. Three consecutive five minute periods were used for analysis and mean values calculated for VLF power, LF power, HF power over the fifteen minute period. In addition mean total power, mean normalised LF power, mean normalised HF power and the mean LH/HF ratio were obtained. Waterfall plots were generated from this data.

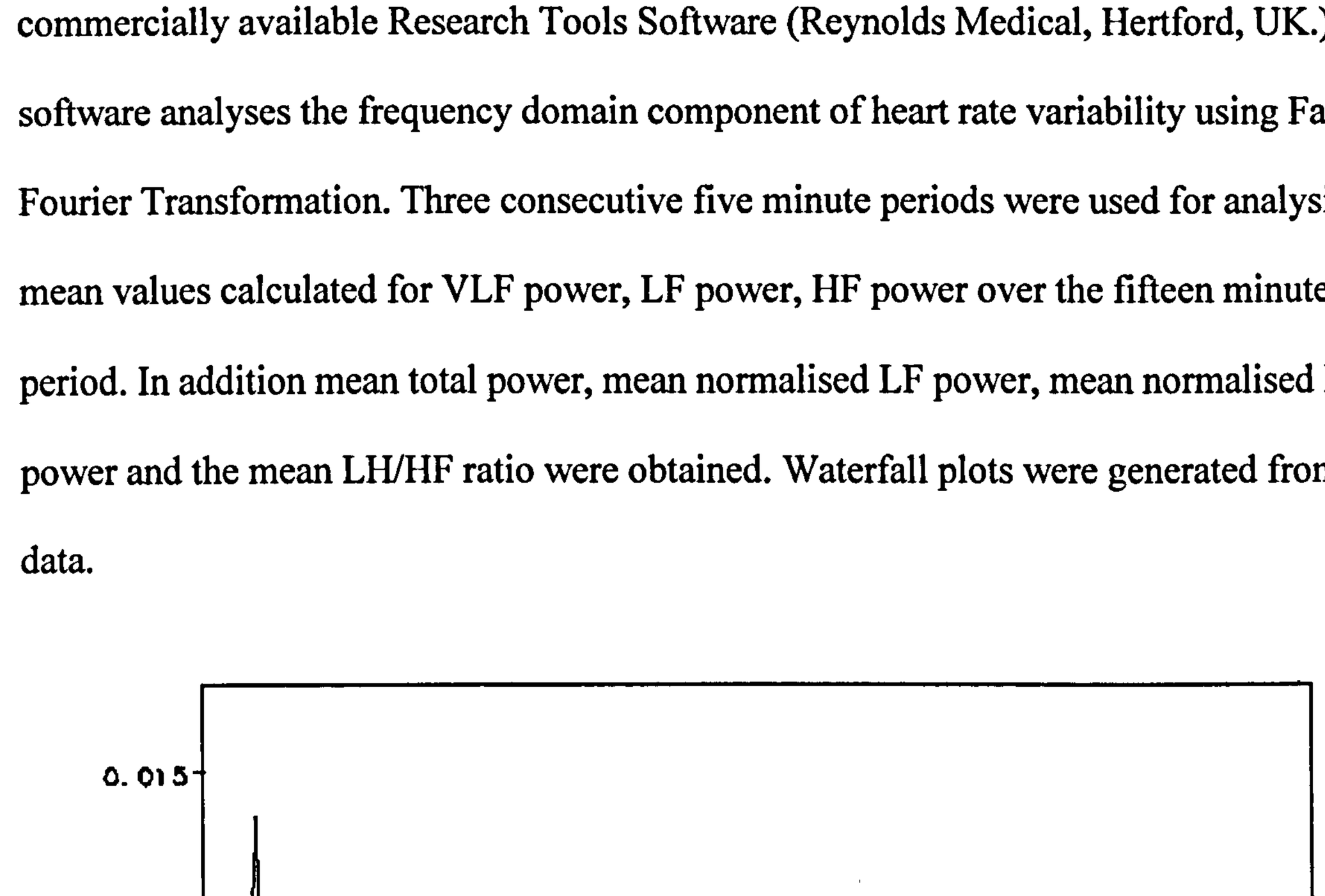


Figure 3 Example of a heart rate variability waterfall plot

Time domain analysis was performed on the whole recording following manual editing. The time domain variables calculated are shown in the table below.

Variable (units)	Definition
mean RR duration (ms)	Mean RR duration over entire recording
SNN50 inc	Number of RR intervals greater than 50msec longer than the preceding RR interval
SNN50 dec	Number of RR intervals greater than 50msec shorter than the preceding RR interval
SNN50 total	Total number of RR intervals with change of greater than 50 msec compared to preceding RR interval
SNN6% dec	Number of RR intervals with decrease in duration of 6% or more compared to previous RR interval
SNN6% total	Number of RR intervals with a change in duration of 6% or more compared to previous RR interval
SDNN (ms)	Standard deviation of all normal RR intervals in the 24 hour recording.
SDANN (ms)	Standard deviation of the mean of all 5 min segments of normal RR intervals of a 24 hour recording.
SDNNi	Mean of the standard deviations of all NN intervals for all 5 minute segments of a 24 hour recording
RMSSD (ms)	The root mean square of successive differences in RR intervals

Table 8 Time domain heart rate variability measurements used

2.11 Follow Up

Patients were reviewed every three months in the outpatient department for a maximum of six months. At each follow up visit rhythm was assessed by means of a

standard 12 lead ECG. Patients reverting to atrial fibrillation were removed from the study and further therapy commenced where appropriate. Those patients who remained in sinus rhythm for six months were said to have reached the end point of the study.

2.12 Statistical Analysis

All continuous variables that were normally distributed were compared using the students' t test. Continuous variables that were not normally distributed were compared using the Mann Whitney U test. A p value of less than 0.05 was taken to be statistically significant for both tests. Categorical data was analysed by means of the Fishers exact test where any cell in a two by two table had a frequency of 5 or less. Where categorical data was analysed and all the cells in the two by two table had a frequency greater than five Pearsons Chi square was used. Again a p value of less than 0.05 was taken to be statistically significant.

3 RESULTS

3.1 Patient characteristics

3.1.1 Number of patients recruited

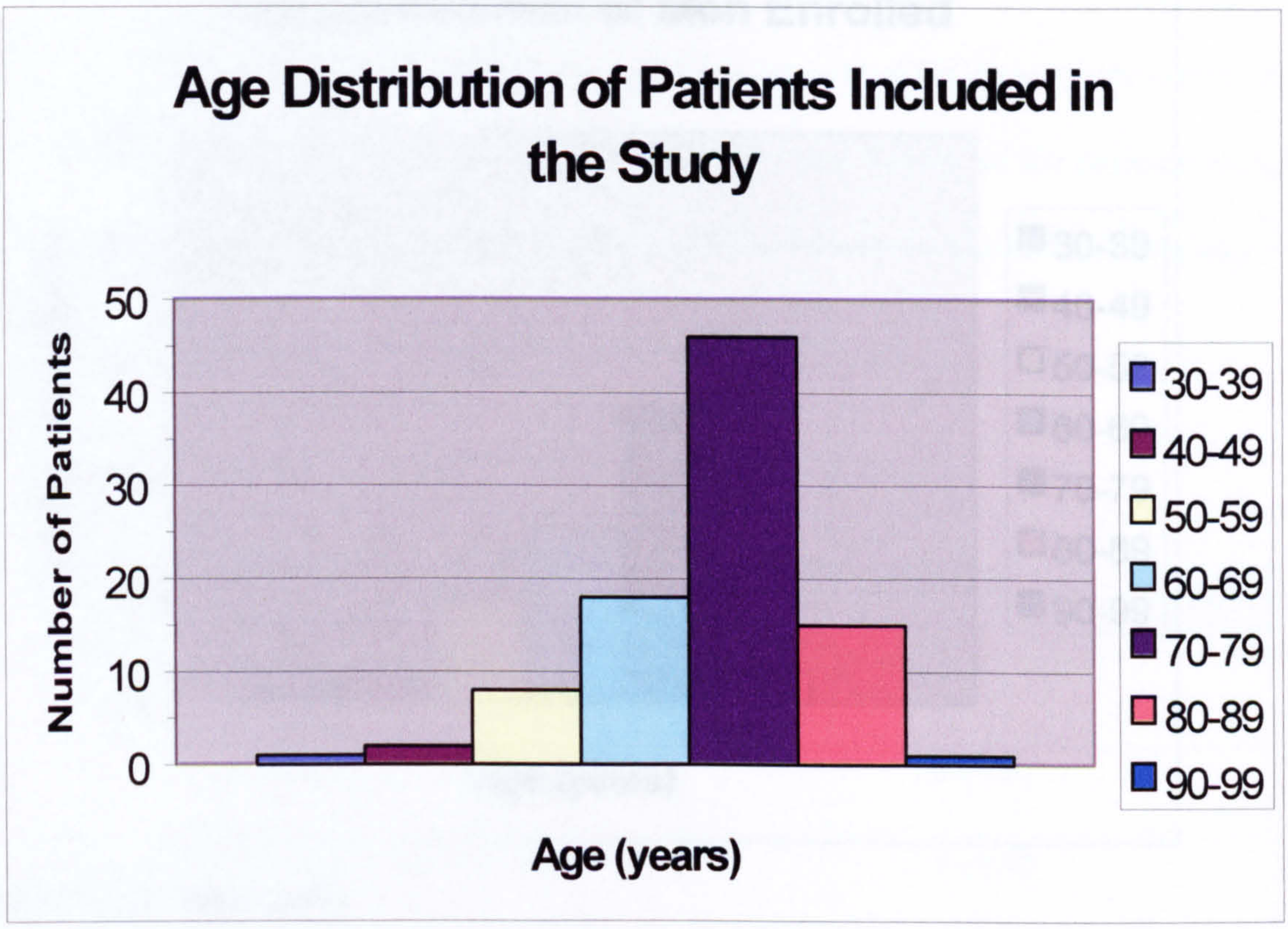
One hundred and ten patients were referred for possible inclusion in the study over an eighteen month period. Four patients declined the offer to take part and a further six patients were excluded due to significant valvular disease.

Of the one hundred patients initially enrolled in the study ninety-one proceeded to transoesophageal echocardiography. The remaining nine patients being excluded during the anticoagulation phase of the protocol. This was due to spontaneous reversion to sinus rhythm in 5 patients (5%), 4 prior to transoesophageal echocardiography and one during the procedure. Two patients were found to have thyrotoxicosis and a further two were found to have significant renal impairment making them unsuitable for a general anaesthetic.

3.1.2 Patient age and sex

The average age of all the patients included in the study was 71 years. The youngest person recruited was 33 years old and the oldest 93 years. The diagram below shows the age distribution for the whole study population (see below).

Figure 4 Age range of study patients



Fifty six of the ninety one patients were male (64.8%). There is a clear age difference between the sexes with women generally being older at the time of presentation. The age distribution of each sex is displayed below. The mean age for women included was 76.1 years (SD 6.7) compared to 68.0 years (SD 9.9) for men ($p<0.001$).

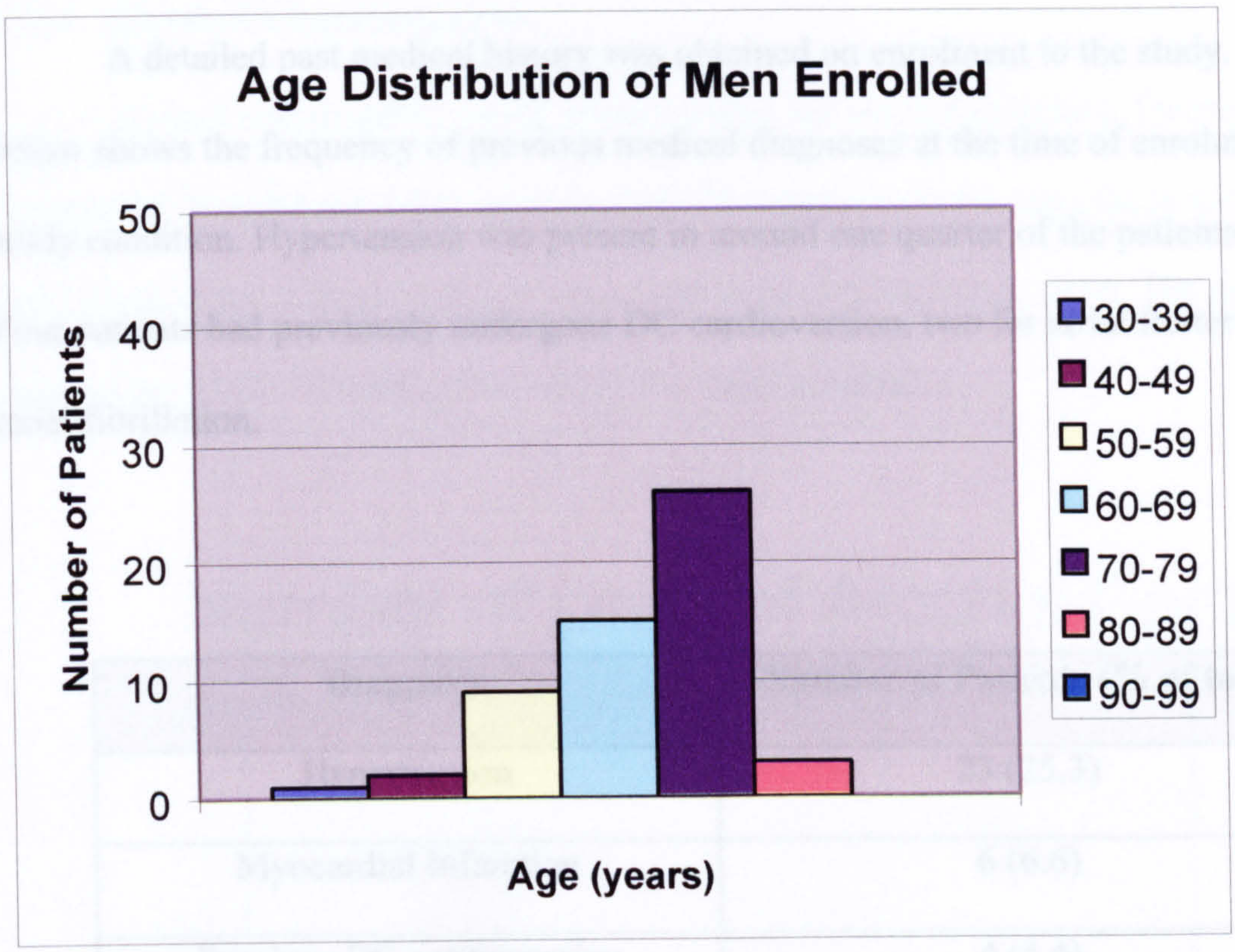


Figure 5 Age range (male)

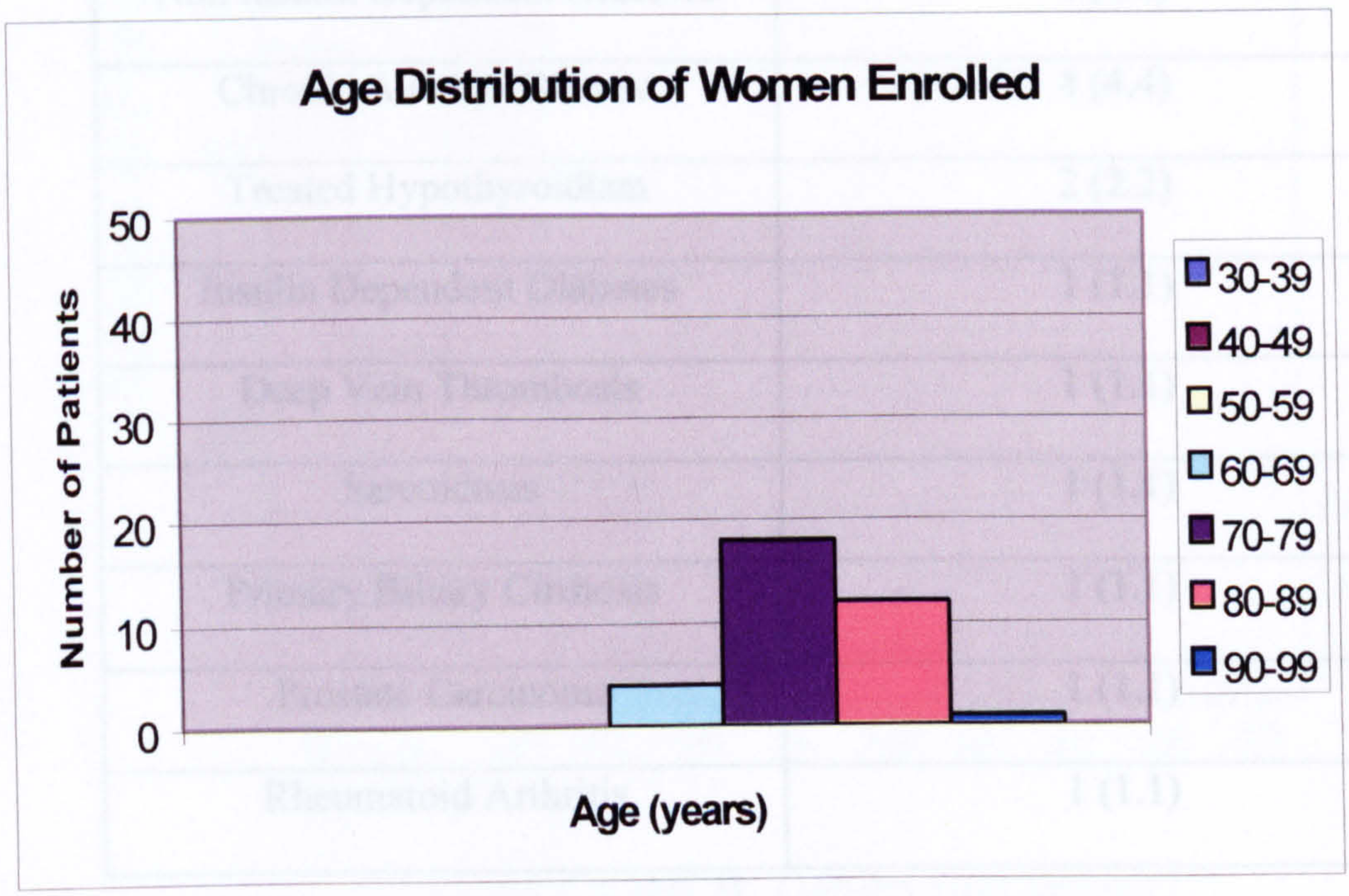


Figure 6 Age range (female)

3.1.3 Comorbidity

A detailed past medical history was obtained on enrolment to the study. The table below shows the frequency of previous medical diagnoses at the time of enrolment into the study condition. Hypertension was present in around one quarter of the patients recruited. Four patients had previously undergone DC cardioversion, two for atrial flutter and two for atrial fibrillation.

Diagnosis	Number of Patients (% of total)
Hypertension	23 (25.3)
Myocardial Infarction	6 (6.6)
Previous DC cardioversion	4 (4.4)
Non Insulin Dependent Diabetes	4 (4.4)
Chronic Airways Disease	4 (4.4)
Treated Hypothyroidism	2 (2.2)
Insulin Dependent Diabetes	1 (1.1)
Deep Vein Thrombosis	1 (1.1)
Sarcoidosis	1 (1.1)
Primary Biliary Cirrhosis	1 (1.1)
Prostate Carcinoma	1 (1.1)
Rheumatoid Arthritis	1 (1.1)

Table 9 Comorbidity of patients enrolled

3.1.4 Alcohol Consumption

Alcohol consumption varied greatly within the study population. Twenty three patients (25.3%) did not drink alcohol at all. The consumption among the remaining sixty eight ranged from a single unit per week upto forty eight units per week. The graph below displays the level of consumption within the study population.

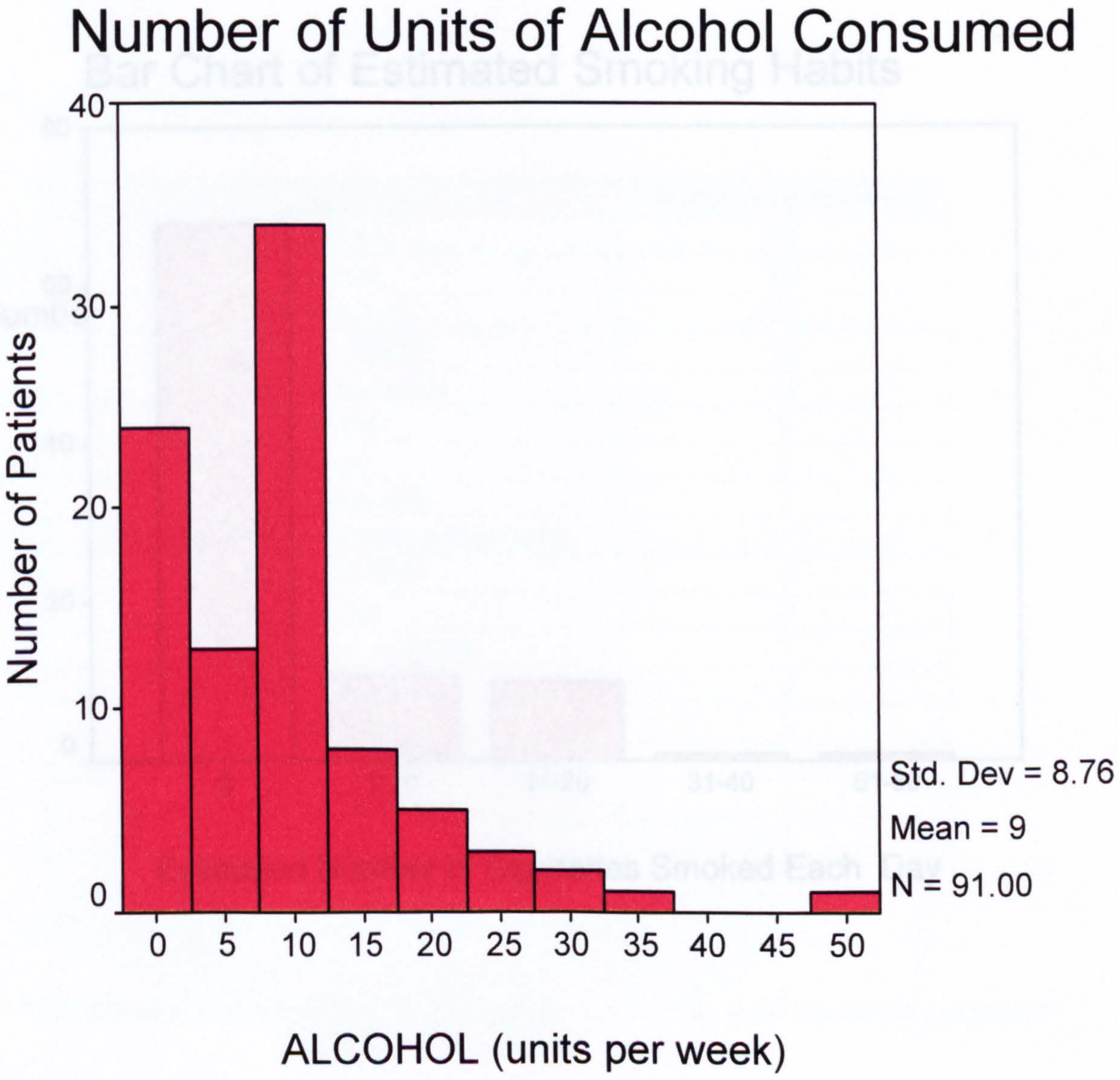
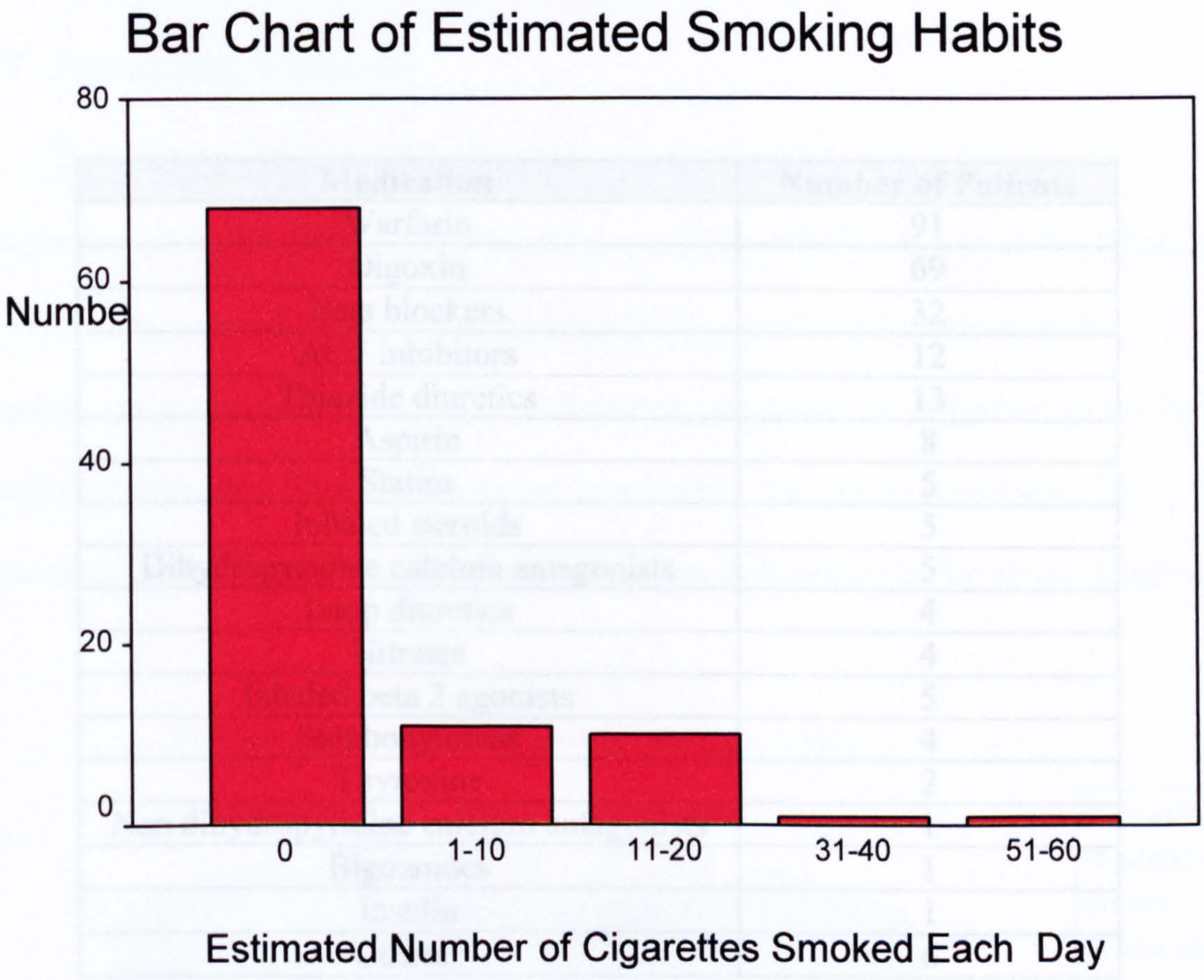


Figure 7 Histogram showing alcohol intake of study patients

3.1.5 Smoking

Sixty eight of the ninety one patients enrolled were non smokers at the time of entry into the study. Of this group fifteen had stopped smoking between one and six months prior to entry. The remaining twenty three patients were smoking at time of enrolment. The smokers within the study smoked an average of 14.2 cigarettes per day (SD 13.0) with the daily consumption ranging from 1 per day to 60 per day.



Medication

All patients recruited into the study were started on warfarin therapy either by the referring physician or at the time of inclusion. Medication to control ventricular rate and eliminate symptoms was also commenced. Digoxin was the most common drug used in an attempt to control ventricular rate with beta-blockers proving to be the next most common choice. A combination of digoxin and atenolol was used in 12 patients in order to achieve adequate symptom control. The following table shows the number of patients taking each class of medication.

Medication	Number of Patients
Warfarin	91
Digoxin	69
Beta blockers	32
ACE inhibitors	12
Thiazide diuretics	13
Aspirin	8
Statins	5
Inhaled steroids	5
Dihydropyridine calcium antagonists	5
Loop diuretics	4
Nitrates	4
Inhaled beta 2 agonists	5
Sulphonylureas	4
Thyroxine	2
Non dihydropyridine calcium antagonists	1
Biguanides	1
Insulin	1
Others*	6

Table 10 Medication being taken by patients enrolled

* prednisolone, azathioprine, co-proxamol, temazepam, gold injections, paroxetine.

3.1.6 Duration of Atrial Fibrillation

The exact duration of atrial fibrillation is always difficult to determine. For the purposes of this study the duration of atrial fibrillation was taken to be the number of days from either ECG confirmation of the arrhythmia or the first occurrence of the presenting symptom to the time of attempted DC cardioversion. Using this definition the mean duration of atrial fibrillation prior to attempted cardioversion was 124.5 days (SD 145.9). The median duration of atrial fibrillation prior to cardioversion was 87 days (range 28 – 1095).

3.1.7 Presenting symptom

The patients enrolled within the study presented with a range of symptoms. Breathlessness was the commonest presenting symptom with 30 patients (34%) reporting this as the first symptom. Twenty four patients (27%) reported palpitations as the presenting symptom making this the second commonest symptom. A further twenty two patients had their atrial fibrillation detected incidentally and had no symptoms. The percentage of patients presenting with each symptom is displayed in the pie chart below.

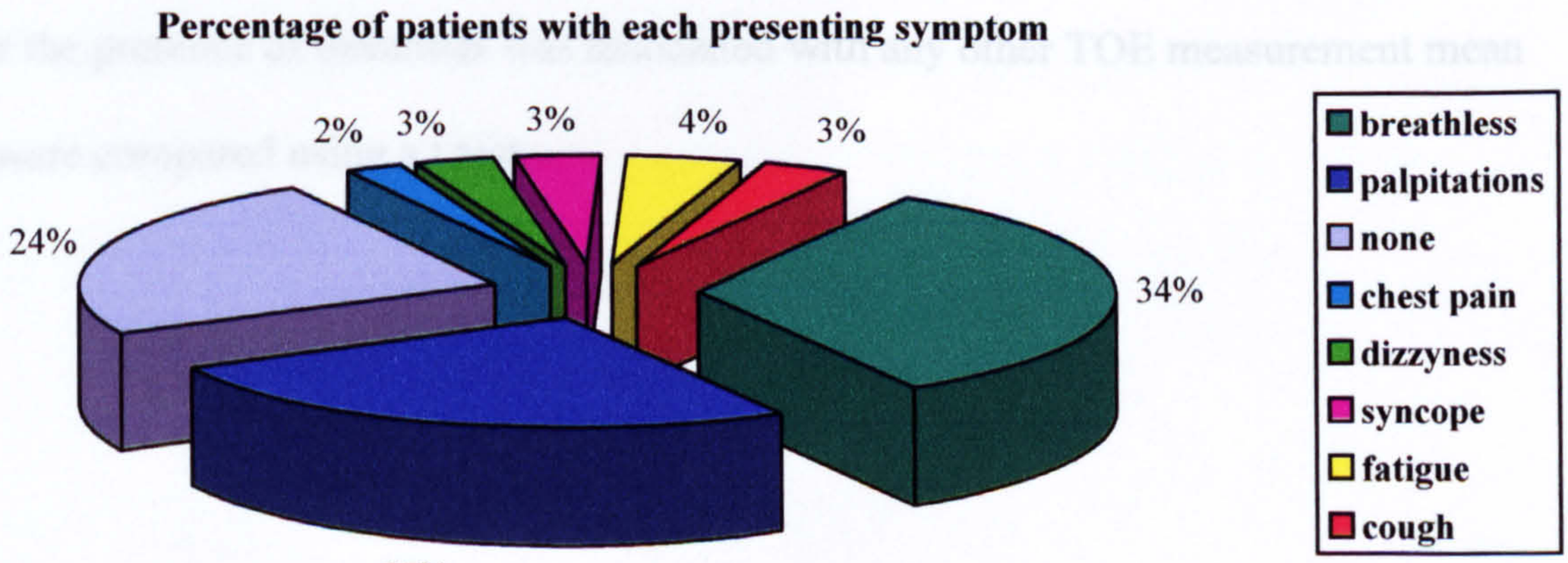


Figure 9 Pie chart of presenting symptoms

3.2 Transoesophageal Echocardiography

All Ninety one patients had a transoesophageal echocardiography as part of the study. There were no complications as a result of the procedure and all the patients tolerated the procedure well. Four studies were incomplete due to poor image quality or technical difficulties and these patients were excluded from further analysis. Eighty seven complete TOE studies were suitable for analysis.

3.2.1 Thrombus detection and TOE measurements

Six patients had an intracardiac thrombus detected by TOE. All six of these thrombi were found in the left atrial appendage. This gives a thrombus detection rate of 6.9%. Although the study methods allowed DC cardioversion to be carried out in patients with an INR greater than 1.5 most patients had an INR at the time of cardioversion in the range 2.0 – 3.0. The mean INR at the time of DC cardioversion in this study was 2.6 (range 1.7 to 3.5). Those patients who had left atrial appendage thrombus detected at TOE did not have a statistically significantly lower INR than those patients who were free of thrombus. This was true both at the time of TOE and also for the four weeks prior to TOE. To assess whether the presence of thrombus was associated with any other TOE measurement mean values were compared using a t test.

TOE measurement Mean (SD)	Thrombus present n=6	Thrombus absent n=81	p value (t test)
Left atrial AP diameter (cm)	5.18 (0.49)	5.26 (0.82)	0.726
Left atrial transverse diameter (cm)	4.75 (0.51)	4.80 (0.69)	0.880
Left atrial appendage area (cm^2)	4.63 (1.29)	4.85 (1.40)	0.703
Mean peak left atrial appendage flow velocity (cm/sec)	20.40 (10.62)	26.24 (12.52)	0.270
Mean peak mitral valve flow velocity (cm/sec)	99.18 (57.25)	79.78 (25.06)	0.107
Mean peak pulmonary vein flow velocity (cm/sec)	43.31 (13.77)	42.69 (17.11)	0.921
Duration of AF (days)	80.83 (29.98)	131.38 (152.78)	0.022

Table 11 Thrombus and TOE variables

No TOE measurement differed significantly between those patients with and without left atrial appendage thrombus. Duration of atrial fibrillation did however differ significantly between the two groups with those patients with a left atrial appendage thrombus having a significantly shorter arrhythmia duration ($p= 0.022$).

3.2.2 Spontaneous echo contrast and TOE measurements

Spontaneous echo contrast was detected in thirteen of the eighty one patients without thrombus formation (16.04%). Its relationship to other TOE measurements is displayed in the table below.

TOE measurements Mean (SD)	SEC present n=13	SEC Absent n=68	p value (t test)
Left atrial AP diameter (cm)	5.45 (0.77)	5.23 (0.83)	0.379
Left atrial transverse diameter (cm)	4.91 (0.74)	4.78 (0.69)	0.550
Left atrial appendage area (cm^2)	5.16 (1.13)	4.78 (1.45)	0.377
Mean peak left atrial appendage flow velocity (cm/sec)	22.12 (10.93)	27.07 (12.74)	0.164
Mean peak mitral valve flow velocity (cm/sec)	69.34 (16.73)	81.87 (26.01)	0.100
Mean peak pulmonary vein flow velocity (cm/sec)	46.93 (27.06)	41.84 (14.52)	0.331
Duration of AF (days)	130.46 (100.59)	131.57 (161.82)	0.975

Table 12 SEC and TOE measurements

From these values it can be seen that patients with spontaneous echo contrast but no thrombus formation tended to have higher left atrial appendage flow and higher peak mitral valve flow. This may be a reflection of an increased preservation of left atrial function. None of these differences reached statistical significance.

3.2.3 Mean TOE measurements and sex

Mean TOE measurements were calculated for the eighty seven full studies obtained and also for males and females. The mean values for each sex were normally distributed allowing comparison using a t test.

TOE measurement Mean (SD)	All patients n=87	Males n=52	Females n=35	p value (t test)
Left atrial AP diameter (cm)	5.20 (0.98)	5.41 (0.69)	4.87 (1.24)	0.011
Left atrial transverse diameter (cm)	4.74 (0.85)	4.88 (0.65)	4.53 (1.06)	0.061
Left atrial appendage area (cm^2)	4.77 (1.48)	5.07 (1.50)	4.33 (1.36)	0.023
Mean peak left atrial appendage flow velocity (cm/sec)	25.52 (12.67)	26.06 (12.92)	24.70 (12.44)	0.632
Mean peak mitral valve flow velocity (cm/sec)	80.21 (29.55)	73.80 (19.36)	89.83 (38.68)	0.013
Mean peak pulmonary vein flow velocity (cm/sec)	42.23 (17.36)	43.06 (17.11)	40.99 (17.90)	0.594

Table 13 Toe measurements

It can be seen in the table above that male patients had larger left atrial diameters and left atrial appendages than female patients. These differences reached statistical significance for mean AP left atrial diameter and mean LAA area. Female patients however had significantly greater flow through the mitral valve.

3.2.4 Mean TOE measurements and hypertension

To assess whether the presence of hypertension had an influence on TOE measurements mean values were compared using a t test. There was no statistically

significant difference in any of the TOE variables measured between patients with and without hypertension.

TOE measurement Mean (SD)	Hypertension present n=22	Hypertension absent n=65	p value (t test)
Left atrial AP diameter (cm)	5.31 (0.81)	5.16 (1.03)	0.483
Left atrial transverse diameter (cm)	4.90 (0.68)	4.69 (0.90)	0.260
Left atrial appendage area (cm^2)	4.69 (1.12)	4.80 (1.59)	0.769
Mean peak left atrial appendage flow velocity (cm/sec)	25.18 (11.21)	25.63 (13.20)	0.889
Mean peak mitral valve flow velocity (cm/sec)	75.11 (22.53)	81.89 (31.49)	0.364
Mean peak pulmonary vein flow velocity (cm/sec)	45.98 (19.51)	41.00 (16.57)	0.302

Table 14 Mean TOE variables and hypertension

3.2.5 Mean TOE measurements and duration

Pearson correlation coefficients were calculated to assess the relationship between duration of atrial fibrillation and the TOE measurements. Only left atrial appendage area showed a statistically significant correlation with duration of atrial fibrillation. This correlation was however relatively weak as demonstrated by the scatter plot (figure 10) despite achieving a statistically significant p value.

TOE measurement	Pearson correlation coefficient	p value
Left atrial AP diameter (cm)	0.052	0.639
Left atrial transverse diameter (cm)	0.123	0.262
Left atrial appendage area (cm^2)	0.243	0.025
Mean peak left atrial appendage flow velocity (cm/sec)	-0.105	0.337
Mean peak mitral valve flow velocity (cm/sec)	0.058	0.600
Mean peak pulmonary vein flow velocity (cm/sec)	0.172	0.116

Table 15 Correlation coefficients for duration and TOE measurements

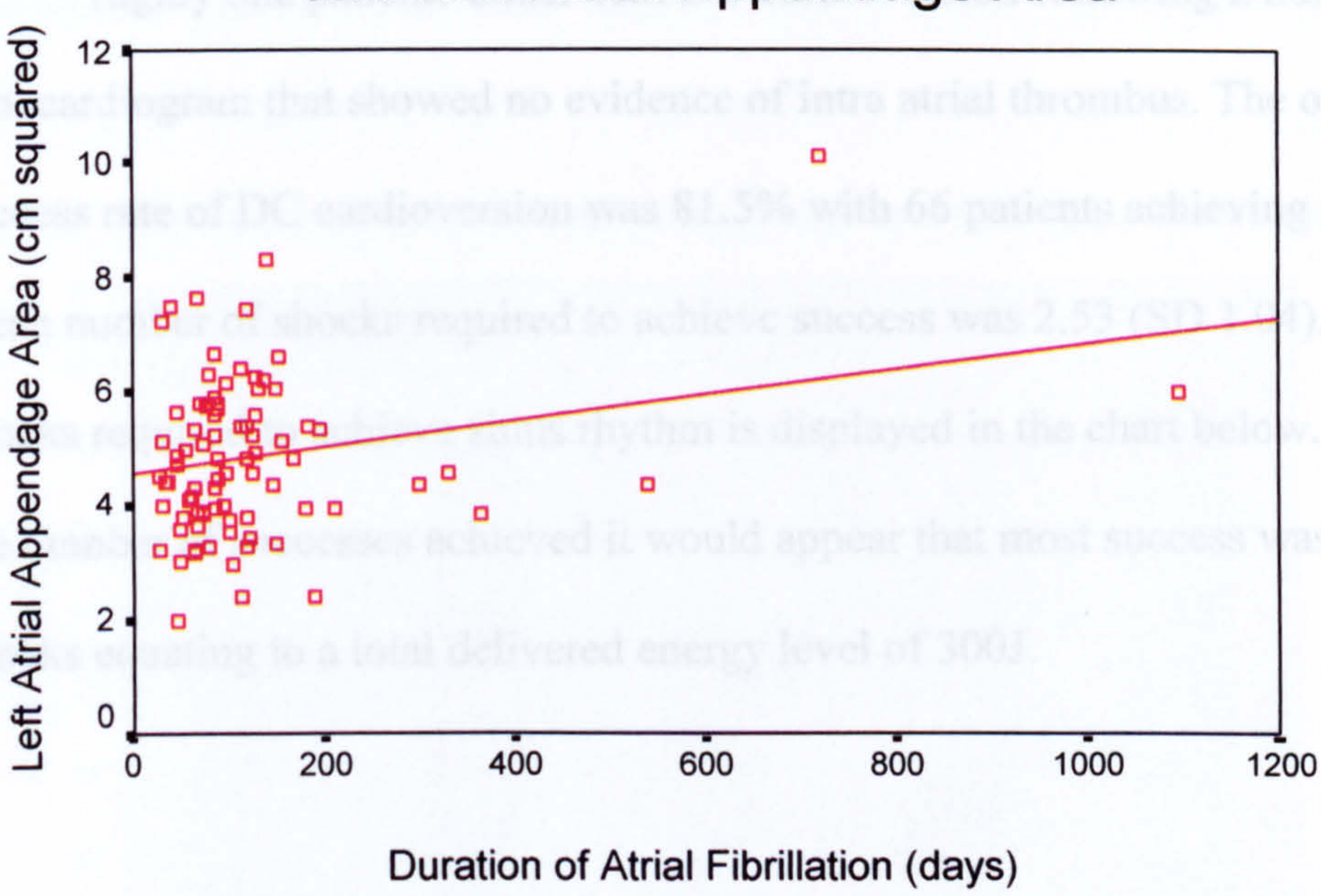


Figure 10 Scatter plot of duration of atrial fibrillation and LAA area.

3.3 External DC Cardioversion

3.3.1 Initial Outcome

Eighty one patients underwent DC cardioversion following a transoesophageal echocardiogram that showed no evidence of intra atrial thrombus. The overall initial success rate of DC cardioversion was 81.5% with 66 patients achieving sinus rhythm. The mean number of shocks required to achieve success was 2.53 (SD 1.04). The number of shocks required to achieve sinus rhythm is displayed in the chart below. Looking simply at the number of successes achieved it would appear that most success was achieved with two shocks equating to a total delivered energy level of 300J.

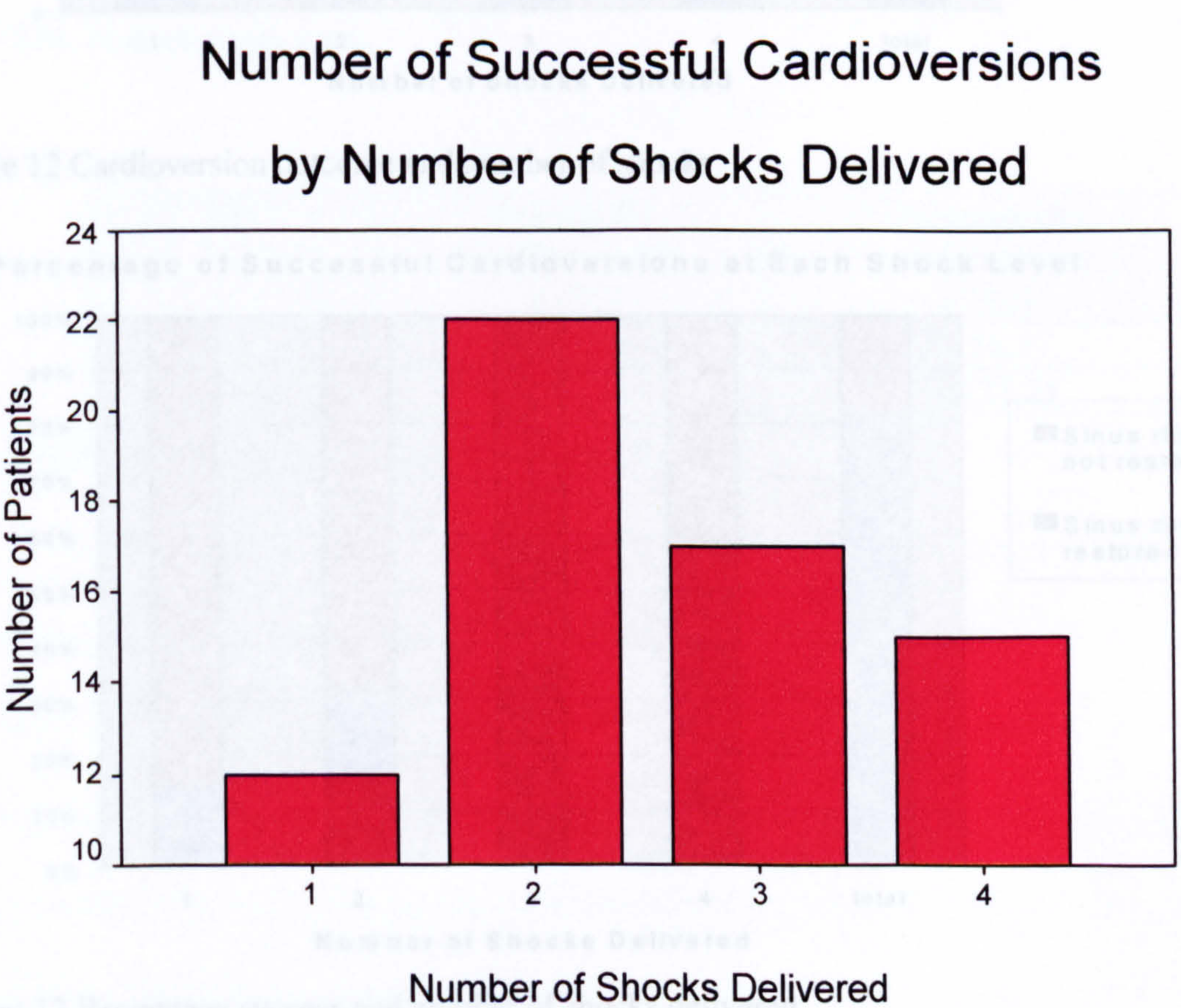


Figure 11 Bar chart of successful cardioversions and number of shocks

However when the number of patients who fail to achieve sinus rhythm with each DC shock is taken into account it can be seen that a greater percentage success appears to be achieved with each additional shock.

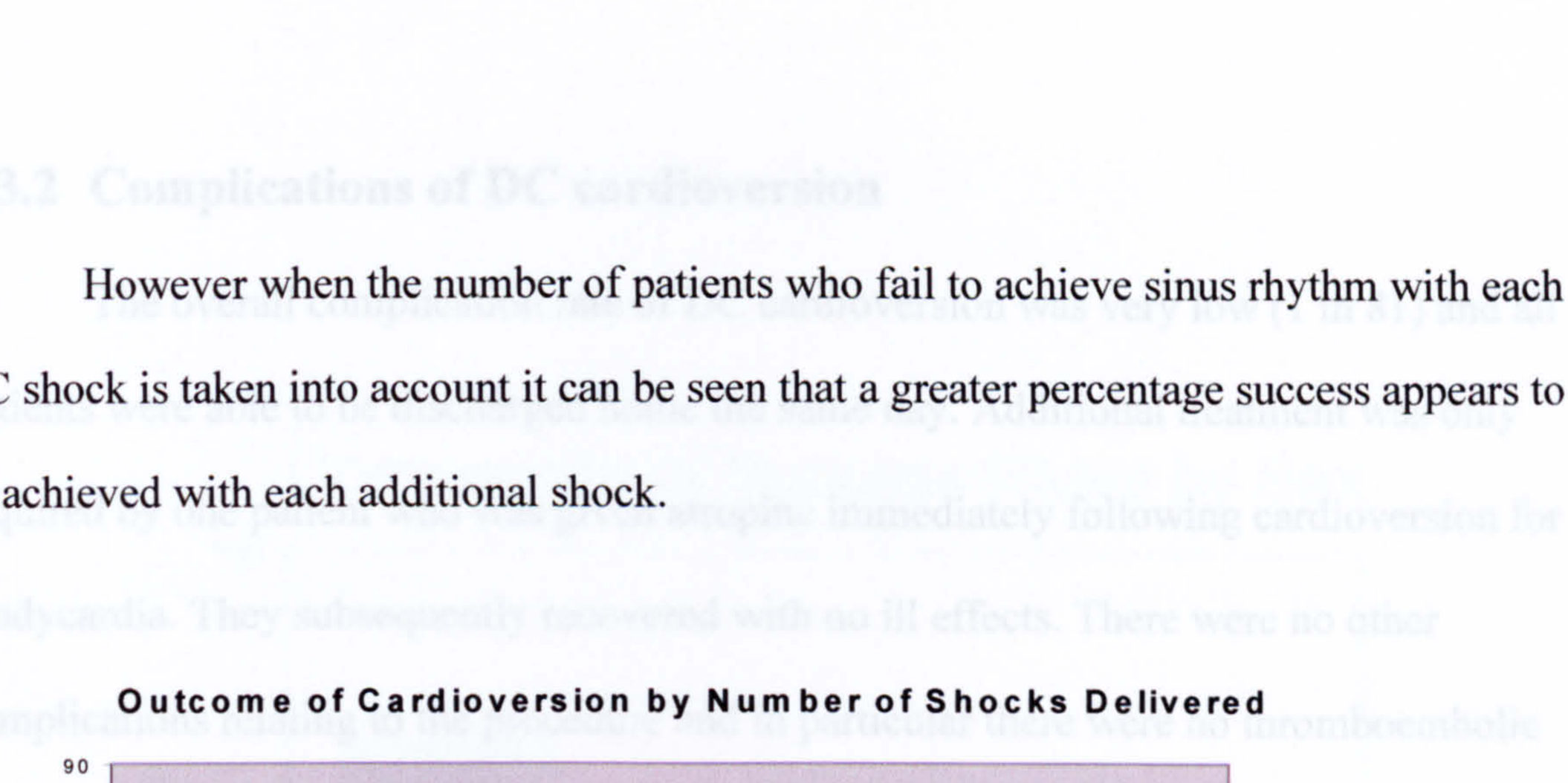


Figure 12 Cardioversion outcome and number of shocks

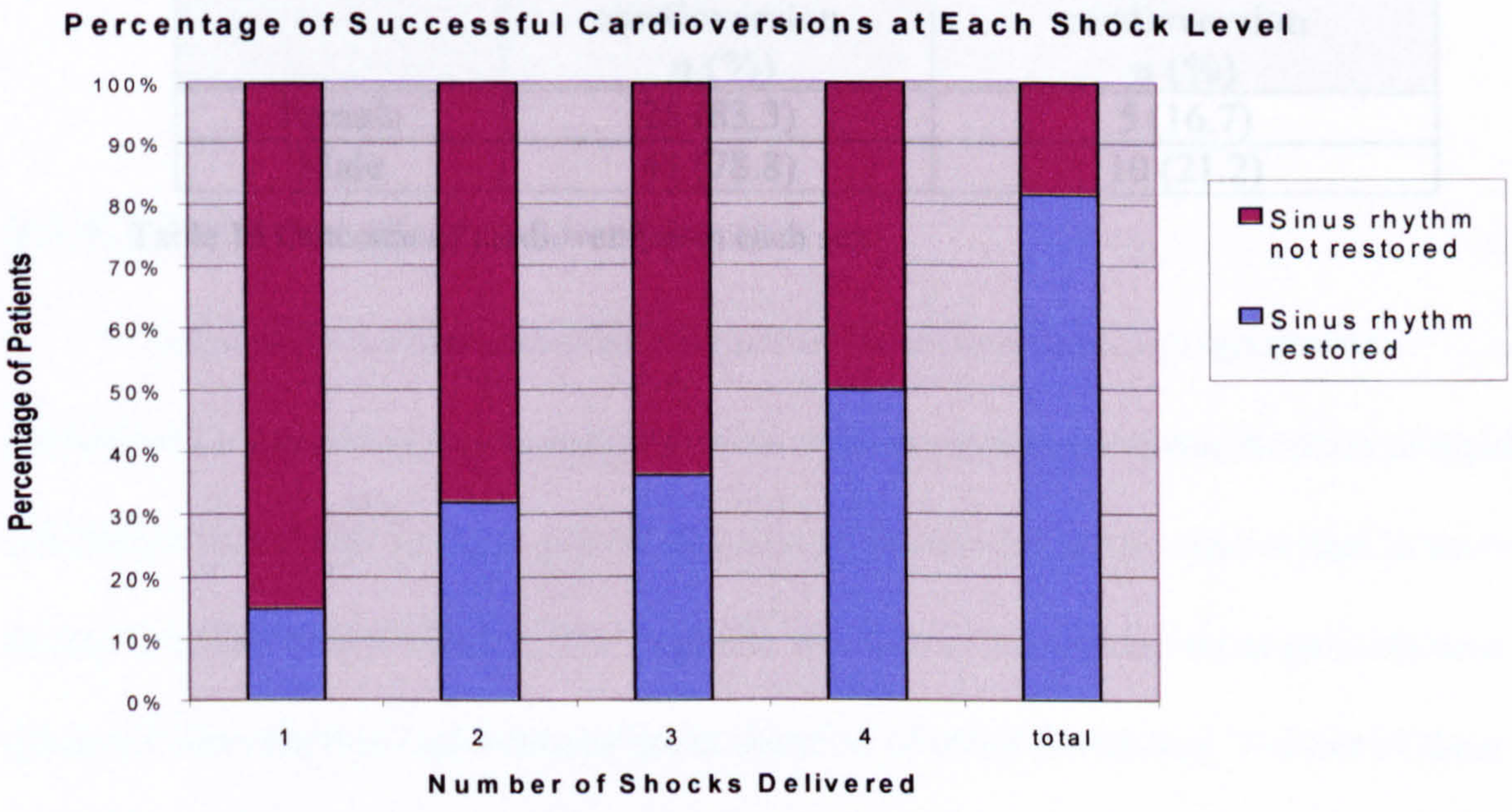


Figure 13 Percentage success and number of shocks delivered

3.3.2 Complications of DC cardioversion

The overall complication rate of DC cardioversion was very low (1 in 81) and all patients were able to be discharged home the same day. Additional treatment was only required by one patient who was given atropine immediately following cardioversion for bradycardia. They subsequently recovered with no ill effects. There were no other complications relating to the procedure and in particular there were no thromboembolic complications.

3.3.3 Factors Influencing Initial Success

3.3.3.1 Patient Sex

There was no significant difference in the initial success rate of cardioversion in men and women. Sinus rhythm was achieved in 83.3% of women and 78.8% of men (p=0.774. Fishers exact test).

Sex	Successful cardioversion n (%)	Unsuccessful cardioversion n (%)
Female	25 (83.3)	5 (16.7)
Male	41 (78.8)	10 (21.2)

Table 16 Outcome of cardioversion in each sex

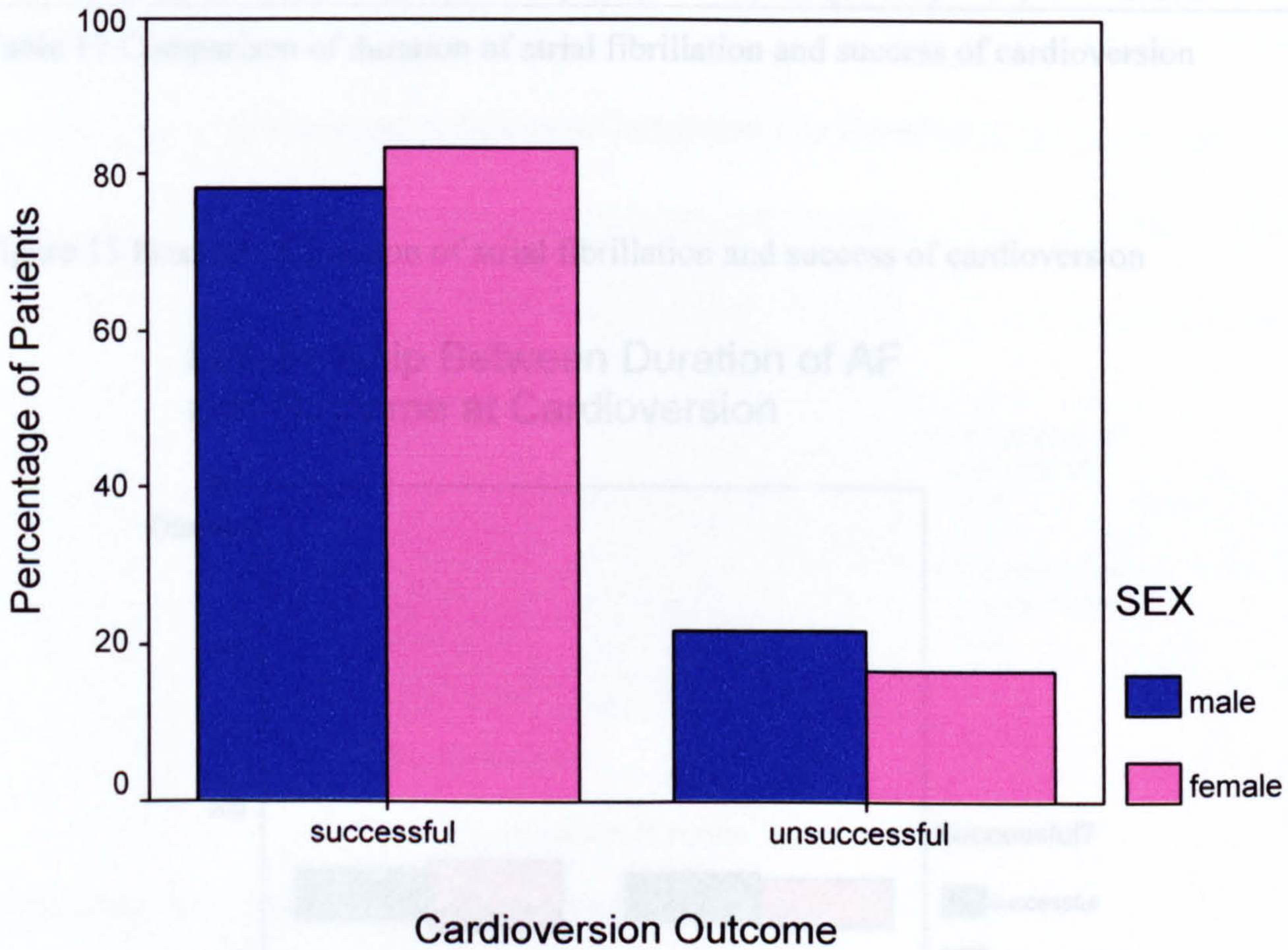


Figure 14 Comparison of initial success by sex

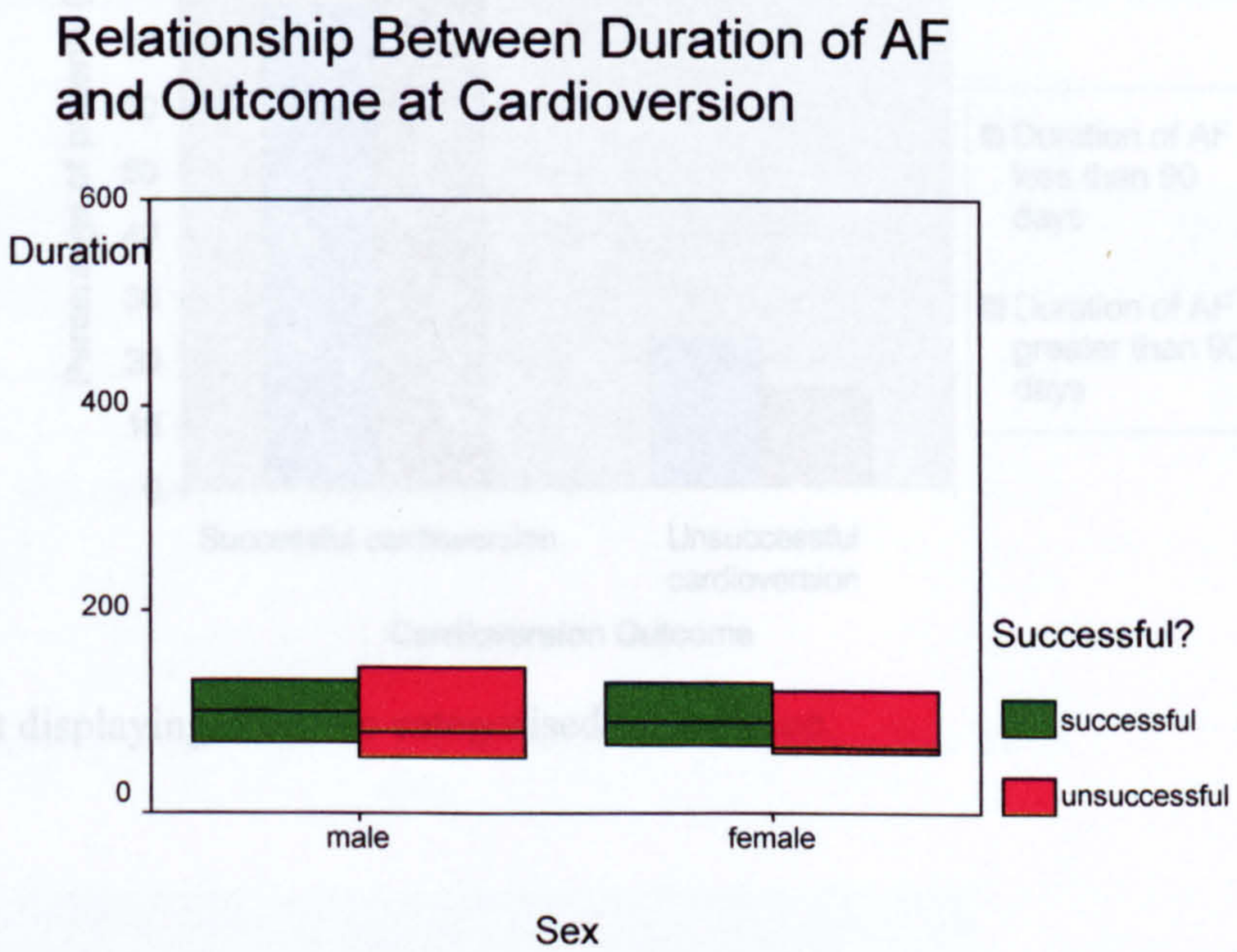
3.3.3.2 Duration of Atrial Fibrillation

The number of days atrial fibrillation had been present prior to attempted cardioversion did not appear to influence outcome. In women the mean duration of atrial fibrillation was longer in those patients who had a successful cardioversion than in those failing to achieve sinus rhythm. The opposite was true in men where those patients who achieved sinus rhythm had a shorter mean duration of atrial fibrillation. Neither of these differences proved to be statistically significant when analysed using the students t test.

Sex	Duration of atrial fibrillation Mean number of days (SD)		p value
	Successful cardioversion	Unsuccessful cardioversion	
Female	148.0 (209.0)	123.6 (118.9)	0.725
Male	121.0 (96.0)	144.2 (195.9)	0.711
Both	131.4 (148.9)	137.8 (171.6)	0.893

Table 17 Comparison of duration of atrial fibrillation and success of cardioversion

Figure 15 Boxplot of duration of atrial fibrillation and success of cardioversion



In the boxplot shown above the median duration is represented by the dark line within the coloured box and the borders of the box represent the interquartile range. It can be seen that in both sexes the interquartile ranges are similar for both patients achieving sinus rhythm and those having an unsuccessful cardioversion. It has been suggested by the Royal College of Physicians of Edinburgh that DC cardioversion should be attempted only in patients who have had atrial fibrillation for less than three months. In this study greater success was achieved in patients with a duration of atrial fibrillation greater than ninety days. This difference in success rates was not significant when analysed using Fishers exact test ($p=0.41$).

Duration of AF	90 days or less	Greater than 90 days
Successful cardioversion n (%)	33 (76.7)	33 (84.6)
Unsuccessful cardioversion n (%)	10 (23.3)	6 (15.4)

Table 18 Cardioversion success rates categorised by duration of AF.

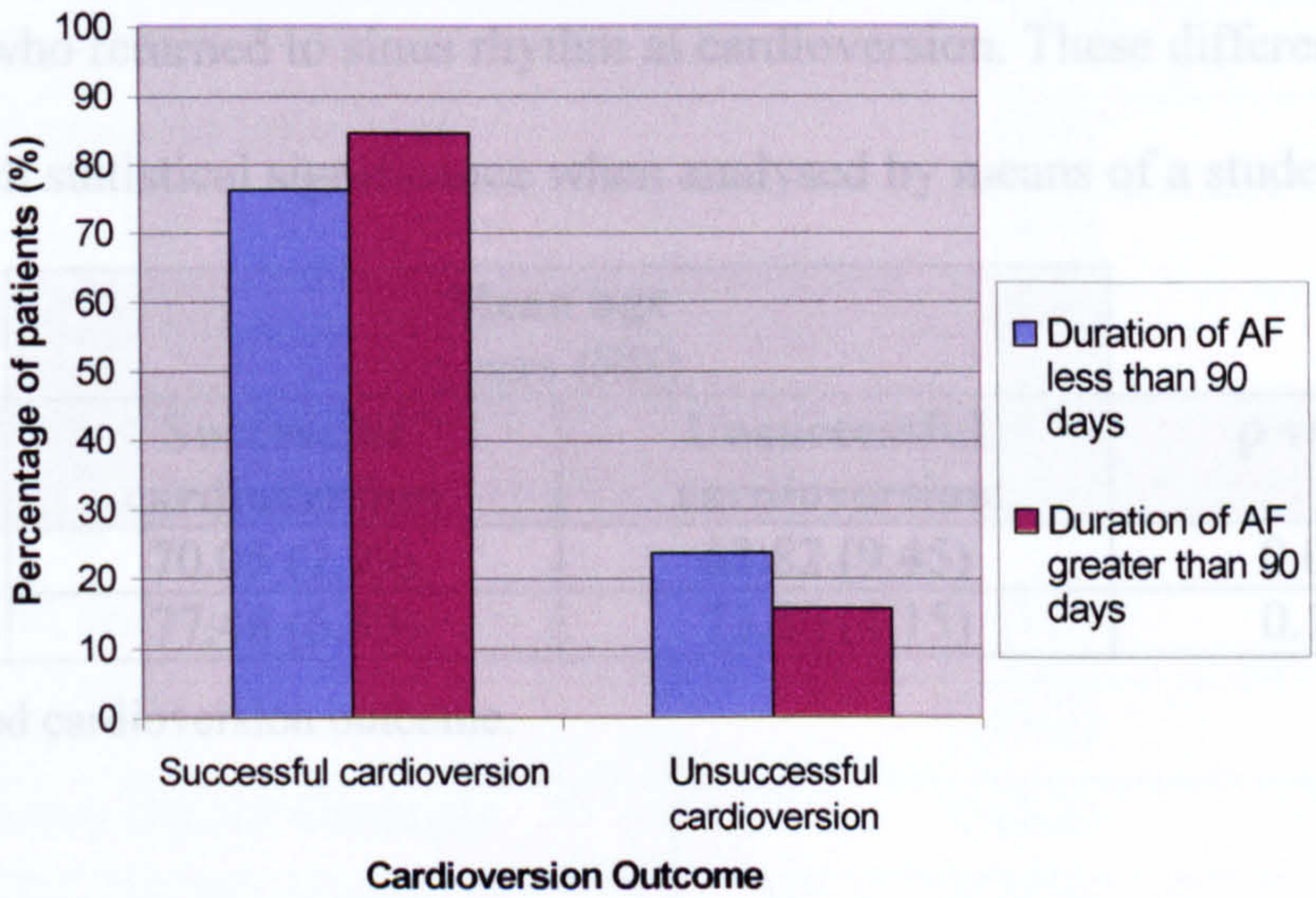


Figure 16 Bar chart displaying outcome categorised by duration

Figure 17 Bar chart of mean age and cardioversion outcome for each sex.

3.3.3.3 Patient age

Since a statistically significant age difference has already been demonstrated between male and female subjects only the influence of age within a gender can be evaluated. The table below shows the mean ages for patients of both sexes who underwent DC cardioversion and their outcome. For both male and female patients the mean age was higher in the group who returned to sinus rhythm at cardioversion. These differences were not sufficient to reach statistical significance when analysed by means of a students t test.

	Mean age years (SD)		
Sex	**Successful cardioversion**	**Unsuccessful cardioversion**	**p value**
Male	70.05 (7.99)	63.82 (9.45)	0.065
Female	77.48 (6.89)	73.80 (4.15)	0.145

Table 19 Mean age and cardioversion outcome.

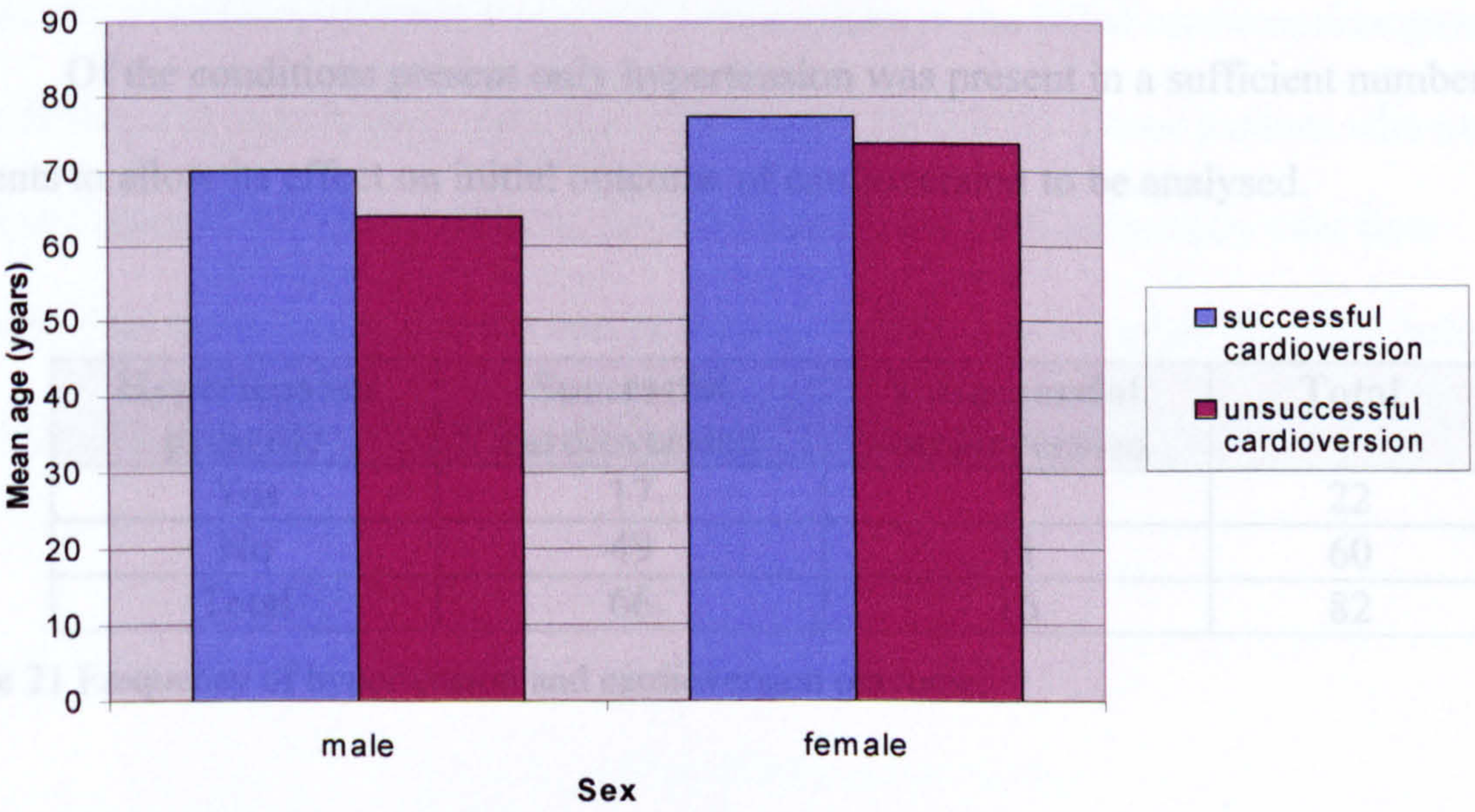


Figure 17 Bar chart of mean age and cardioversion outcome for each sex.

3.3.3.4 Comorbidity and Initial Success of Cardioversion

The level of comorbidity within the eighty one patients who underwent DC cardioversion is displayed in the table below.

.Diagnosis	Number of Patients (% of total)
Hypertension	22 (27.2)
Myocardial Infarction	6 (7.4)
Previous DC cardioversion	4 (4.9)
Non Insulin Dependent Diabetes	3 (3.7)
Chronic Airways Disease	4 (4.9)
Treated Hypothyroidism	2 (2.5)
Insulin Dependent Diabetes	1 (1.2)
Deep Vein Thrombosis	1 (1.2)
Primary Biliary Cirrhosis	1 (1.2)
Prostate Carcinoma	1 (1.2)

Table 20 Co-morbidity among patients who underwent cardioversion

Of the conditions present only hypertension was present in a sufficient number of patients to allow its effect on initial outcome of cardioversion to be analysed.

Hypertension present?	Successful cardioversion	Unsuccessful cardioversion	Total
Yes	17	5	22
No	49	11	60
Total	66	16	82

Table 21 Frequency of hypertension and cardioversion outcome.

When the influence of hypertension on the outcome of cardioversion was analysed using Fishers exact test no statistically significant relationship could be demonstrated ($p=0.587$).

3.3.3.5 TOE variables and initial outcome of cardioversion

Comparison was made between mean TOE values for patients achieving sinus rhythm at cardioversion and those remaining in atrial fibrillation.

TOE measurement Mean (SD)	Successful cardioversion n=66	Unsuccessful cardioversion n=15	P value
Left atrial AP diameter (cm)	5.22 (0.80)	5.45 (0.85)	0.298
Left atrial transverse diameter (cm)	4.72 (0.64)	5.09 (0.80)	0.054
Left atrial appendage area (cm^2)	4.75 (1.19)	5.26 (2.05)	0.195
Mean peak left atrial appendage flow velocity (cm/sec)	26.35 (12.66)	25.29 (11.57)	0.759
Mean peak mitral valve flow velocity (cm/sec)	79.40 (25.30)	83.18 (22.37)	0.586
Mean peak pulmonary vein flow velocity (cm/sec)	41.35 (17.22)	49.37 (13.95)	0.060

Table 22 Initial outcome and TOE measurements

There was a tendency towards larger atrial dimensions in the failed cardioversion group with differences approaching statistical significance (p=0.054). Those patients who never achieved sinus rhythm also tended to have a higher mean peak pulmonary vein flow velocity than those converting to sinus rhythm (p=0.060). The error bar diagrams below display the mean values and 95% confidence intervals for these variables.

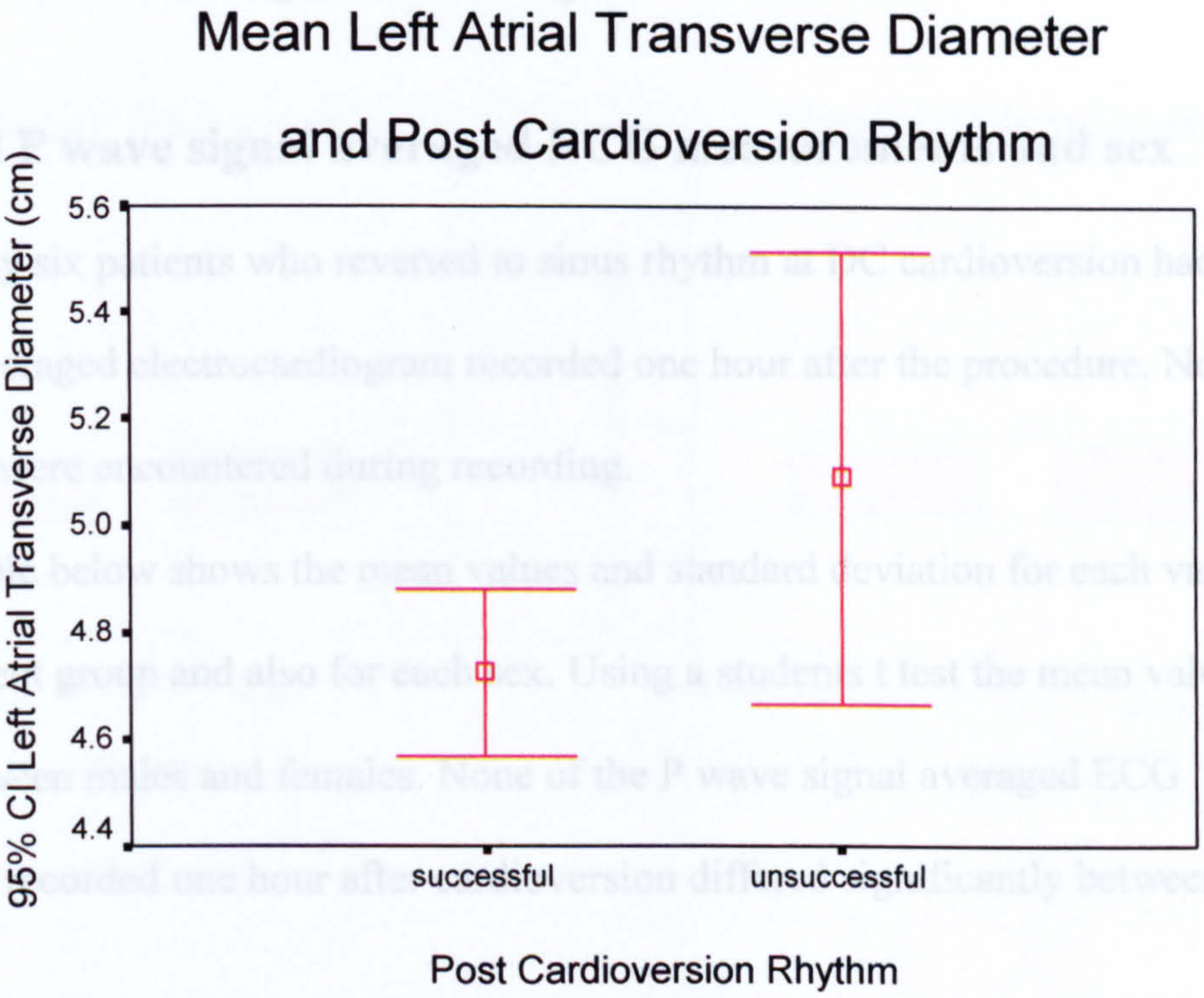


Figure 18 Error bar diagram of mean left atrial transverse diameter and post cardioversion rhythm

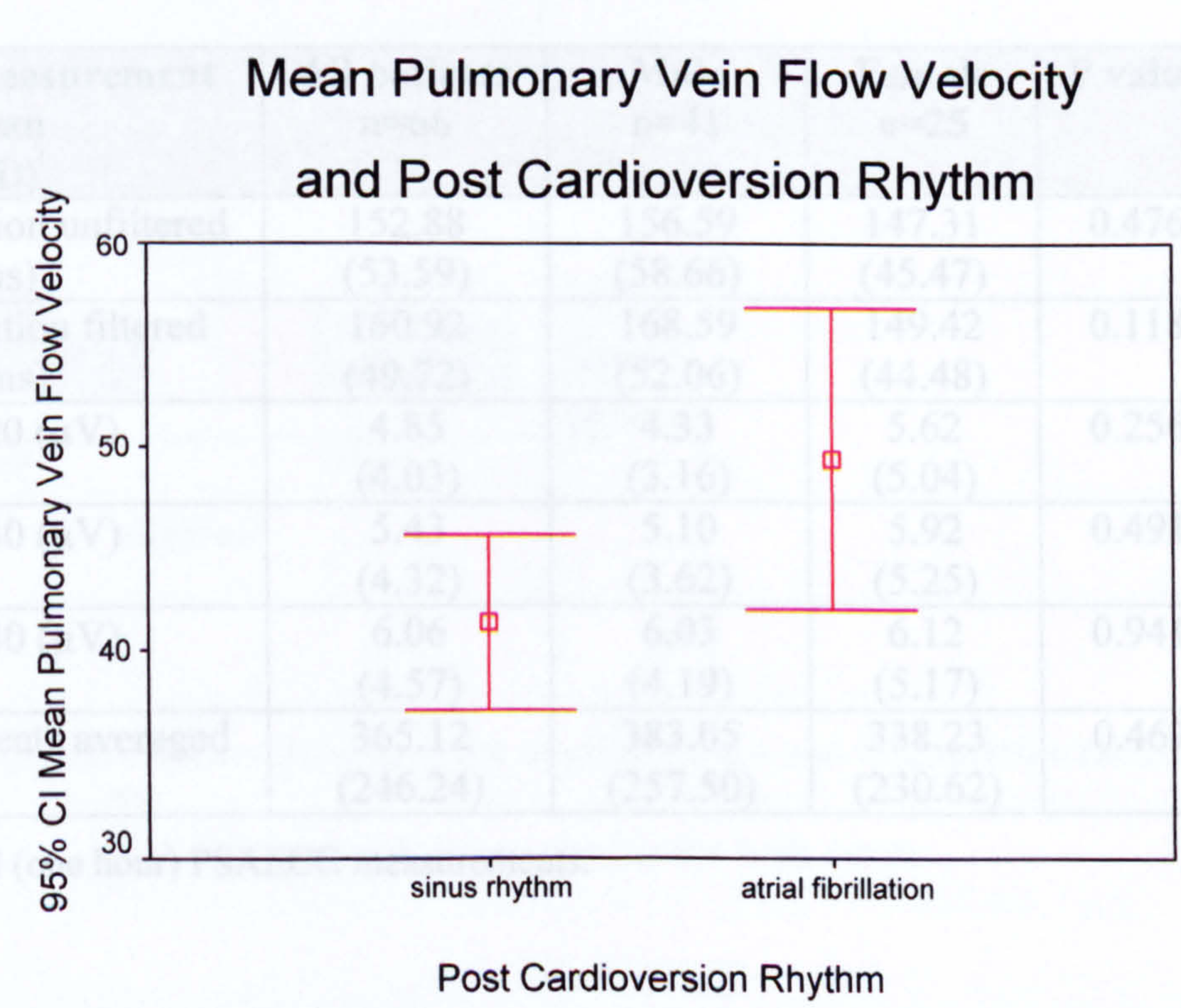


Figure 19 Error bar diagram of mean pulmonary vein flow velocity and post cardioversion rhythm

3.4 Initial P Wave Signal Averaged ECG measurements

3.4.1 Initial P wave signal averaged ECG measurements and sex

All sixty six patients who reverted to sinus rhythm at DC cardioversion had a p wave signal averaged electrocardiogram recorded one hour after the procedure. No complications were encountered during recording.

The table below shows the mean values and standard deviation for each variable in the whole patient group and also for each sex. Using a students t test the mean values were compared between males and females. None of the P wave signal averaged ECG measurements recorded one hour after cardioversion differed significantly between males and females.

PSAECG measurement mean (SD)	All patients n=66	Male n=41	Female n=25	P value
P wave duration unfiltered (ms)	152.88 (53.59)	156.59 (58.66)	147.31 (45.47)	0.476
P wave duration filtered (ms)	160.92 (49.72)	168.59 (52.06)	149.42 (44.48)	0.118
RMS 20 (μV)	4.85 (4.03)	4.33 (3.16)	5.62 (5.04)	0.256
RMS 30 (μV)	5.43 (4.32)	5.10 (3.62)	5.92 (5.25)	0.491
RMS 40 (μV)	6.06 (4.57)	6.03 (4.19)	6.12 (5.17)	0.941
Number of beats averaged	365.12 (246.24)	383.05 (257.50)	338.23 (230.62)	0.467

Table 23 Initial (one hour) PSAECG measurements.

Figure 20 Boxplots of unfiltered and filtered P wave duration.

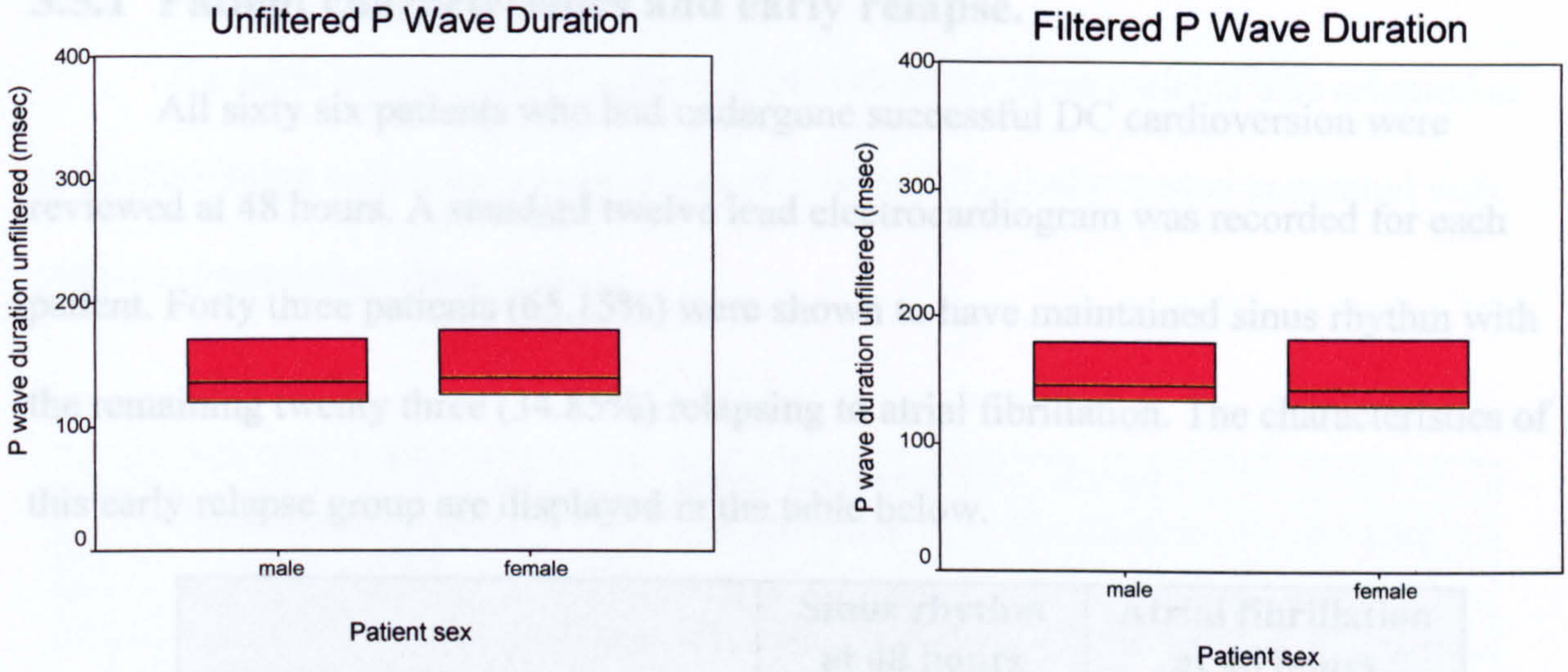
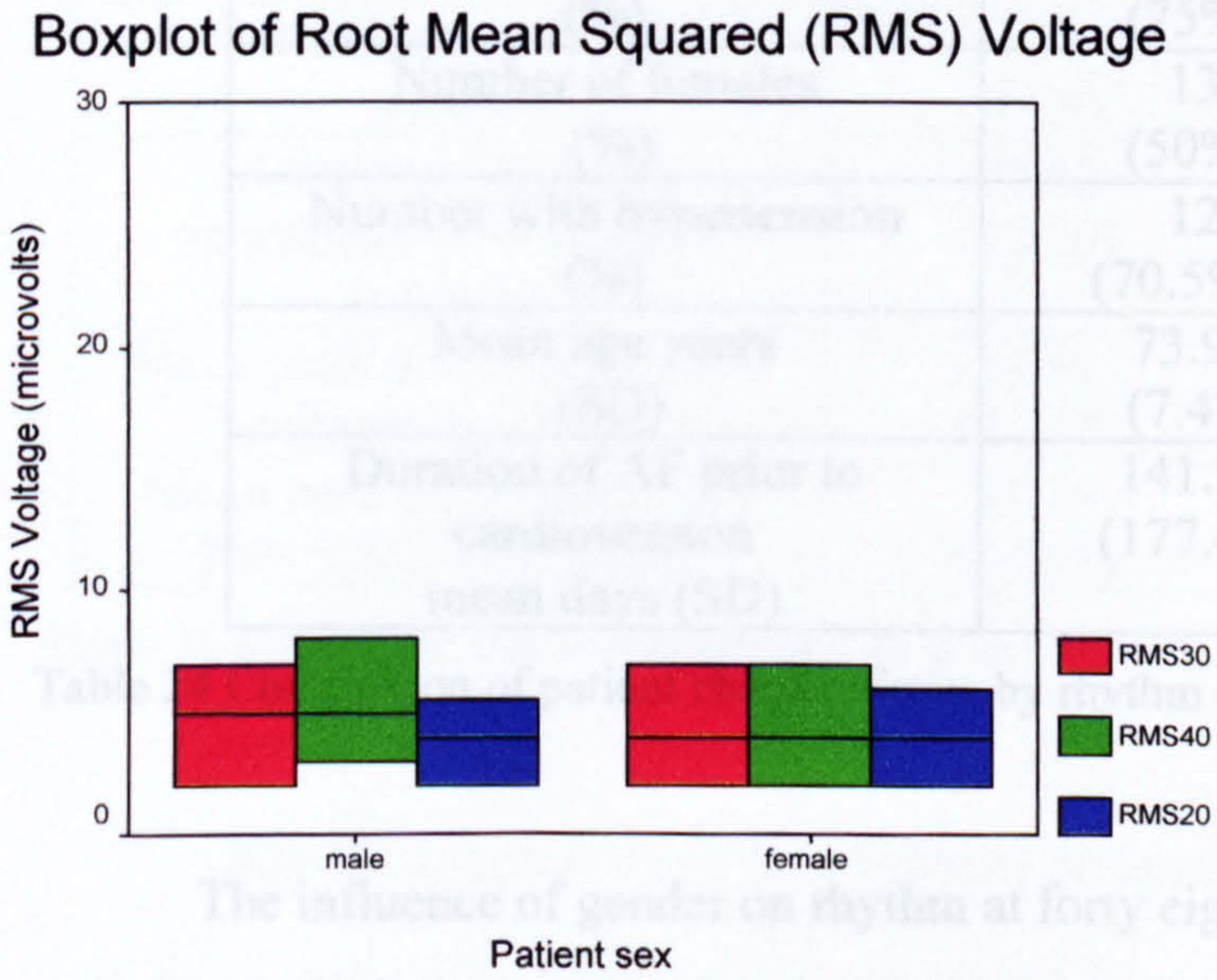


Figure 21 Boxplot of RMS voltage



The boxplot diagrams above show how the median values and interquartile ranges of all the initial p wave signal averaged values are similar for both sexes.

3.5 Forty Eight Hour Review (Early Relapse)

3.5.1 Patient characteristics and early relapse.

All sixty six patients who had undergone successful DC cardioversion were reviewed at 48 hours. A standard twelve lead electrocardiogram was recorded for each patient. Forty three patients (65.15%) were shown to have maintained sinus rhythm with the remaining twenty three (34.85%) relapsing to atrial fibrillation. The characteristics of this early relapse group are displayed in the table below.

	Sinus rhythm at 48 hours	**Atrial fibrillation at 48 hours**
Number of patients (%)	43 (65.15)	23 (34.85)
Number of males (%)	30 (75%)	10 (25%)
Number of females (%)	13 (50%)	13 (50%)
Number with hypertension (%)	12 (70.59%)	5 (29.41%)
Mean age years (SD)	73.98 (7.47)	70.96 (9.67)
Duration of AF prior to cardioversion mean days (SD)	141.76 (177.45)	112.48 (72.42)

Table 24 Comparison of patient characteristics by rhythm at forty eight hours

The influence of gender on rhythm at forty eight hours was tested using the Pearson chi square test. Male patients who had a successful cardioversion were statistically more likely to be in sinus rhythm at forty eight hours than females ($p=0.027$).

No statistically significant difference in either mean age ($p=0.353$) or mean duration of atrial fibrillation ($p=0.202$) could be demonstrated by means of a students t test.

The same was true for hypertension with no statistically significant relationship being demonstrated between hypertension and rhythm at 48 hours ($p=0.769$, Fishers exact test)

3.5.2 TOE measurements and early relapse.

The table below shows the mean TOE values for those patients who relapsed to atrial fibrillation within forty eight hours of a successful cardioversion compared with patients maintaining sinus rhythm.

TOE measurement Mean (SD)	Sinus rhythm at 48 hours n=43	Atrial fibrillation at 48 hours n=23	p value
Left atrial AP diameter (cm)	5.27 (0.78)	5.12 (0.84)	0.486
Left atrial transverse diameter (cm)	4.80 (0.59)	4.59 (0.72)	0.203
Left atrial appendage area (cm^2)	4.78 (1.29)	4.70 (1.02)	0.820
Mean peak left atrial appendage flow velocity (cm/sec)	26.45 (13.29)	26.18 (11.69)	0.933
Mean peak mitral valve flow velocity (cm/sec)	83.98 (27.48)	71.05 (18.46)	0.048
Mean peak pulmonary vein flow velocity (cm/sec)	41.29 (18.02)	41.46 (16.03)	0.969

Table 25 Mean TOE measurements and 48 hours rhythm.

Only mean mitral valve flow velocity differed significantly between the two groups with those patients maintaining sinus rhythm having the greater mean flow. Mean left atrial diameter did not differ significantly between patients maintaining sinus rhythm and those relapsing to atrial fibrillation. This would suggest that left atrial diameter is more closely linked to initial success at cardioversion rather than being a useful marker of subsequent relapse. The diagram below displays the mean mitral flow velocities and the 95% confidence intervals for the two groups.

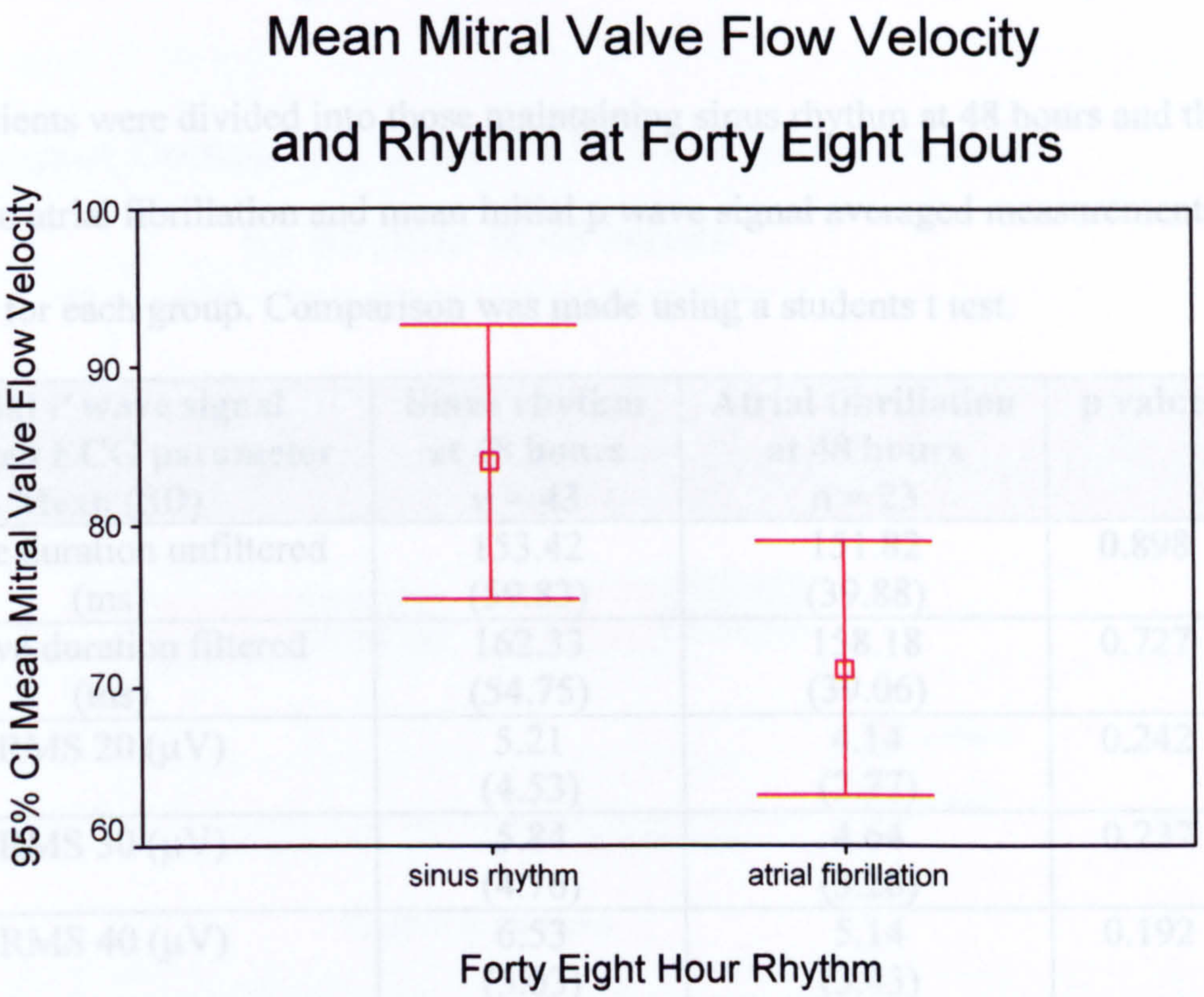


Figure 22 Error bar diagram of mean mitral valve flow velocity and forty eight hour rhythm.

This diagram shows that there is a clear difference in mean mitral valve flow velocity between the two groups as measured by means of TOE prior to cardioversion.

3.5.3 Initial P Wave Signal ECG Recordings And Early Relapse

Patients were divided into those maintaining sinus rhythm at 48 hours and those relapsing to atrial fibrillation and mean initial p wave signal averaged measurements calculated for each group. Comparison was made using a students t test.

Initial P wave signal averaged ECG parameter Mean (SD)	Sinus rhythm at 48 hours n = 43	Atrial fibrillation at 48 hours n = 23	p value
P wave duration unfiltered (ms)	153.42 (59.83)	151.82 (39.88)	0.898
P wave duration filtered (ms)	162.33 (54.75)	158.18 (39.06)	0.727
RMS 20 (μV)	5.21 (4.53)	4.14 (2.77)	0.242
RMS 30 (μV)	5.84 (4.76)	4.64 (3.26)	0.237
RMS 40 (μV)	6.53 (5.03)	5.14 (3.43)	0.192
Number of beats averaged	385.95 (267.14)	324.41 (198.58)	0.299

Table 26 Initial p wave signal average parameters and 48 hour rhythm.

No statistically significant difference in initial PSAECG indices could be demonstrated between patients who relapsed to atrial fibrillation within 48 hours and those maintaining sinus rhythm. This is clearly demonstrated by the boxplots displayed below.

Figure 23 Boxplot of initial PSAECG p wave duration and 48 hour rhythm

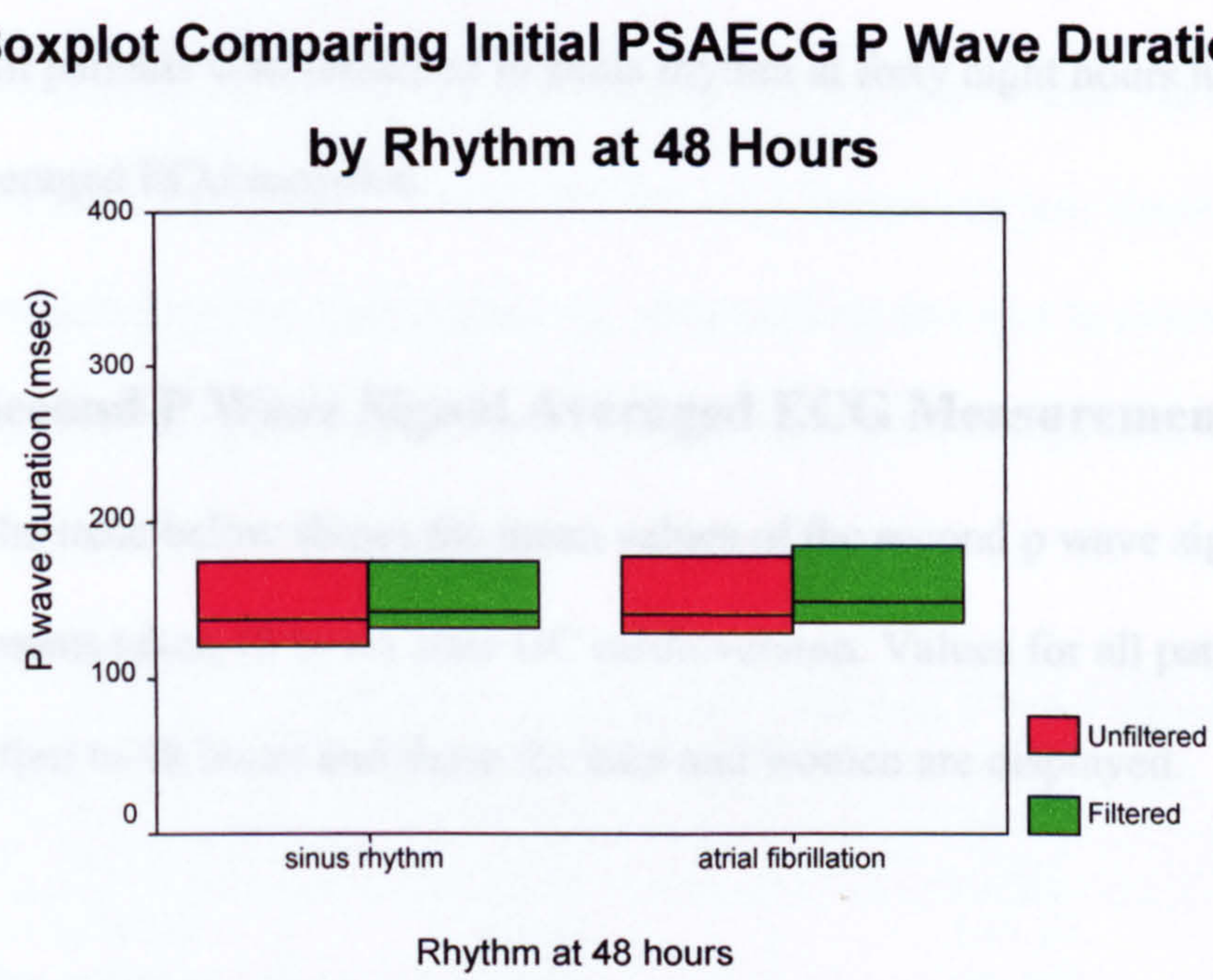
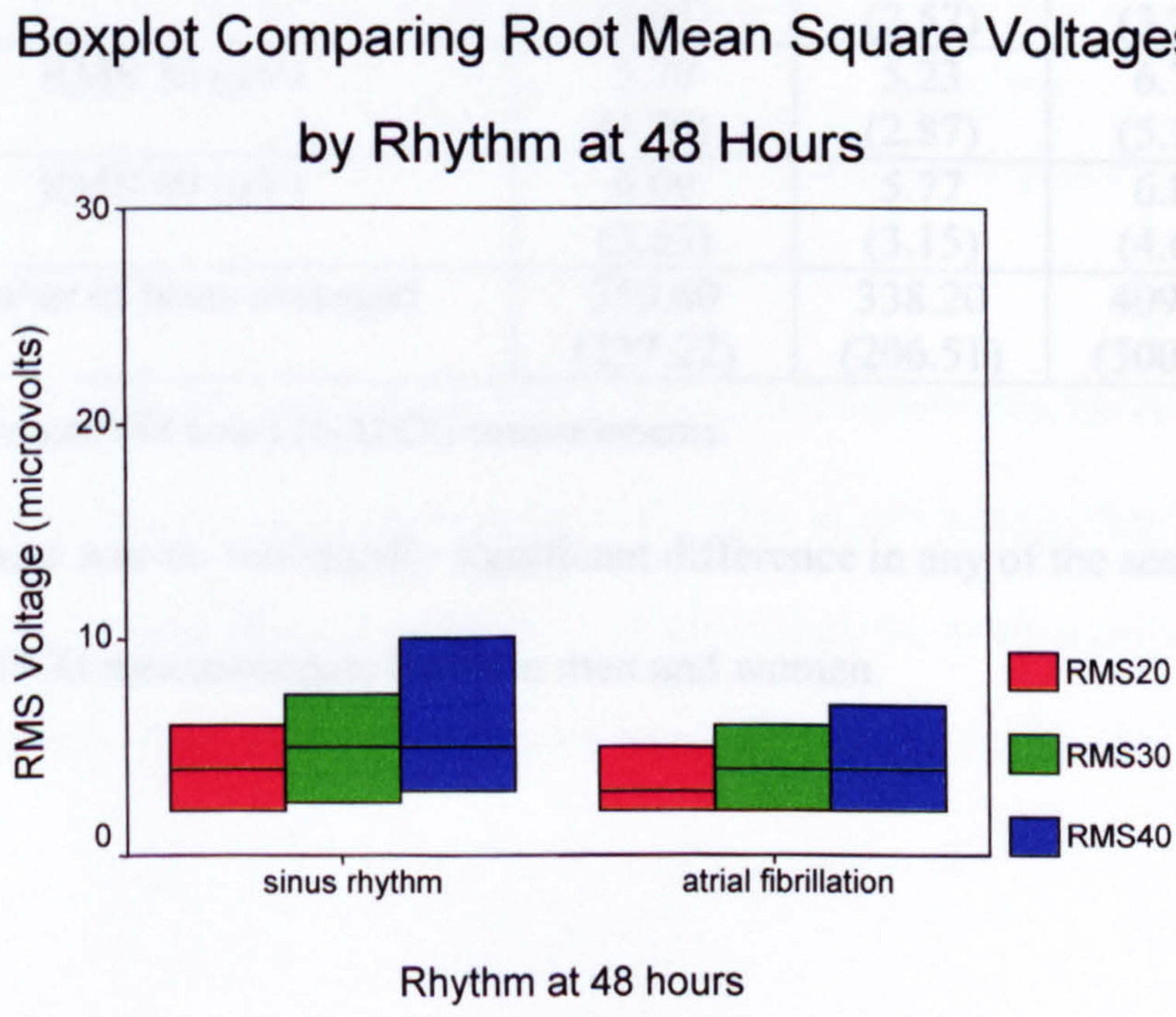


Figure 24 Boxplot of initial PSAECG root mean squared voltages and 48 hour rhythm



3.6 Second P Wave Signal Averaged ECG measurements.

All patients who remained in sinus rhythm at forty eight hours had a second p wave signal averaged ECG recorded.

3.6.1 Second P Wave Signal Averaged ECG Measurements and Sex.

The table below shows the mean values of the second p wave signal averaged ECG measurements taken 48 hours after DC cardioversion. Values for all patients maintaining sinus rhythm to 48 hours and those for men and women are displayed.

Second PSAECG measurement mean (SD)	All patients n = 43	Male n = 30	Female n = 13	P value
P wave duration unfiltered (ms)	145.77 (50.07)	152.13 (57.06)	131.08 (23.88)	0.096
P wave duration filtered (ms)	151.33 (48.56)	157.80 (54.74)	136.38 (25.82)	0.089
RMS 20 (μV)	4.51 (2.97)	4.20 (2.57)	5.23 (3.77)	0.381
RMS 30 (μV)	5.70 (3.70)	5.23 (2.87)	6.77 (5.12)	0.326
RMS 40 (μV)	6.09 (3.63)	5.77 (3.15)	6.85 (4.62)	0.452
Number of beats averaged	359.60 (237.22)	338.20 (206.51)	409.00 (300.17)	0.449

Table 27 Second (48 hour) PSAECG measurements.

There was no statistically significant difference in any of the second p wave signal averaged ECG measurements between men and women.

3.6.2 Comparison of Initial and Second P Wave Signal Averaged ECG.

The timing of p wave signal averaging following DC cardioversion may influence its role in predicting relapse to atrial fibrillation. Comparison was made between initial signal averaging and the forty eight hour measurement in order to determine whether these measurements were effected by time. Measurements were analysed by means of a paired t test.

	Initial P wave signal averaged ECG Mean (SD)	**Second P wave signal averaged ECG Mean (SD)**	**Paired t test p value**
P wave duration unfiltered (ms)	153.42 (59.83)	145.77 (50.07)	0.358
P wave duration filtered (ms)	162.33 (54.75)	151.33 (48.56)	0.124
RMS 20 (μV)	5.21 (4.53)	4.51 (2.97)	0.220
RMS 30 (μV)	5.84 (4.76)	5.70 (3.70)	0.803
RMS 40 (μV)	6.53 (5.03)	6.09 (3.63)	0.470
Number of beats averaged	385.95 (267.14)	359.60 (237.22)	0.587

Table 28 Table comparing initial and second PSAECG variables for patients maintaining sinus rhythm to 48 hours.

No statistically significant difference was shown between initial PSAECG measurements and those recorded at 48 hours. This would suggest that PSAECG measurements are unaffected by the time at which they are performed within the first forty eight hours following successful DC cardioversion of atrial fibrillation.

3.7 Heart Rate Variability Measurements.

3.7.1 Number Available For Analysis

All forty three patients who maintained sinus rhythm to 48 hours had their heart rate variability measured. Four of these recordings were found to be unsuitable for analysis. This was due to mechanical failure in one recording and poor quality of recording in a further three. This meant that only thirty nine recordings were suitable for editing. A further four recordings were found to have a significant proportion unsuitable for analysis such that greater than 25% of the recording was removed by editing. These recordings were excluded from analysis leaving a total of thirty five recordings were used for analysis.

3.7.2 Time Domain Analysis

Time domain analysis was performed on the entire twenty four hour recording following manual editing. Mean RR, SDANN and RMSSD were normally distributed the mean values and standard deviations for these parameters are displayed below.

Variable (units)	Mean	SD
Mean RR (ms)	880.46	138.11
SDANN (ms)	106.89	33.87
RMSSD (ms)	62.49	30.35

Table 29 Normally distributed time domain heart rate variability measurements.

The remaining time domain variables were found to have a skewed distribution. The median value and range of these values are displayed in the table below.

Variable (units)	Median	Range
SNN50 inc	4006	27708
SNN50 dec	5482	38371
SNN50 total	9920	66079
SNN6% inc	4837	30413
SNN6% dec	4810	41056
SNN6% total	9877	71400
SDNN (ms)	122	134
SDNNi (ms)	56	77

Table 30 Skewed distributed time domain heart rate variability measurements

3.7.2.1 Time Domain Analysis and Sex

Comparison of time domain heart rate variability between males and females was carried out using the students t test for normally distributed variables and the Mann Whitney U test for those variables that were not normally distributed.

Heart rate variability measure (units)	Males n=27 Mean (SD)	Females n=8 Mean (SD)	p value Students t test
Mean RR (ms)	891.07 (145.05)	844.63 (112.23)	0.354
SDANN (ms)	105.07 (35.81)	113.00 (27.49)	0.516
RMSSD (ms)	62.89 (30.52)	61.13 (31.78)	0.892

Table 31 Comparison of normally distributed time domain variables between sexes

Variable (units)	Males n=27 Median (range)	Females n=8 Median (range)	p value Mann Whitney U
SNN50 inc	3766 (25966)	5085.50 (27087)	0.409
SNN50 dec	5482 (30651)	6364 (36504)	0.556
SNN50 total	9920 (56927)	11449.5 (3591)	0.582
SNN6% inc	4428 (28771)	5998.5 (2839)	0.480
SNN6% dec	4810 (32031)	6609.5 (39330)	0.504
SNN6% total	6937 (60733)	12936 (69169)	0.504
SDNN (ms)	122 (134)	121 (77)	0.984
SDNNi (ms)	57 (72)	50 (68)	0.906

Table 32Comparison of non-normally distributed time domain variables by sex.

When comparison was made between males and females no statistically significant difference could be found in any of the time domain variables studied.

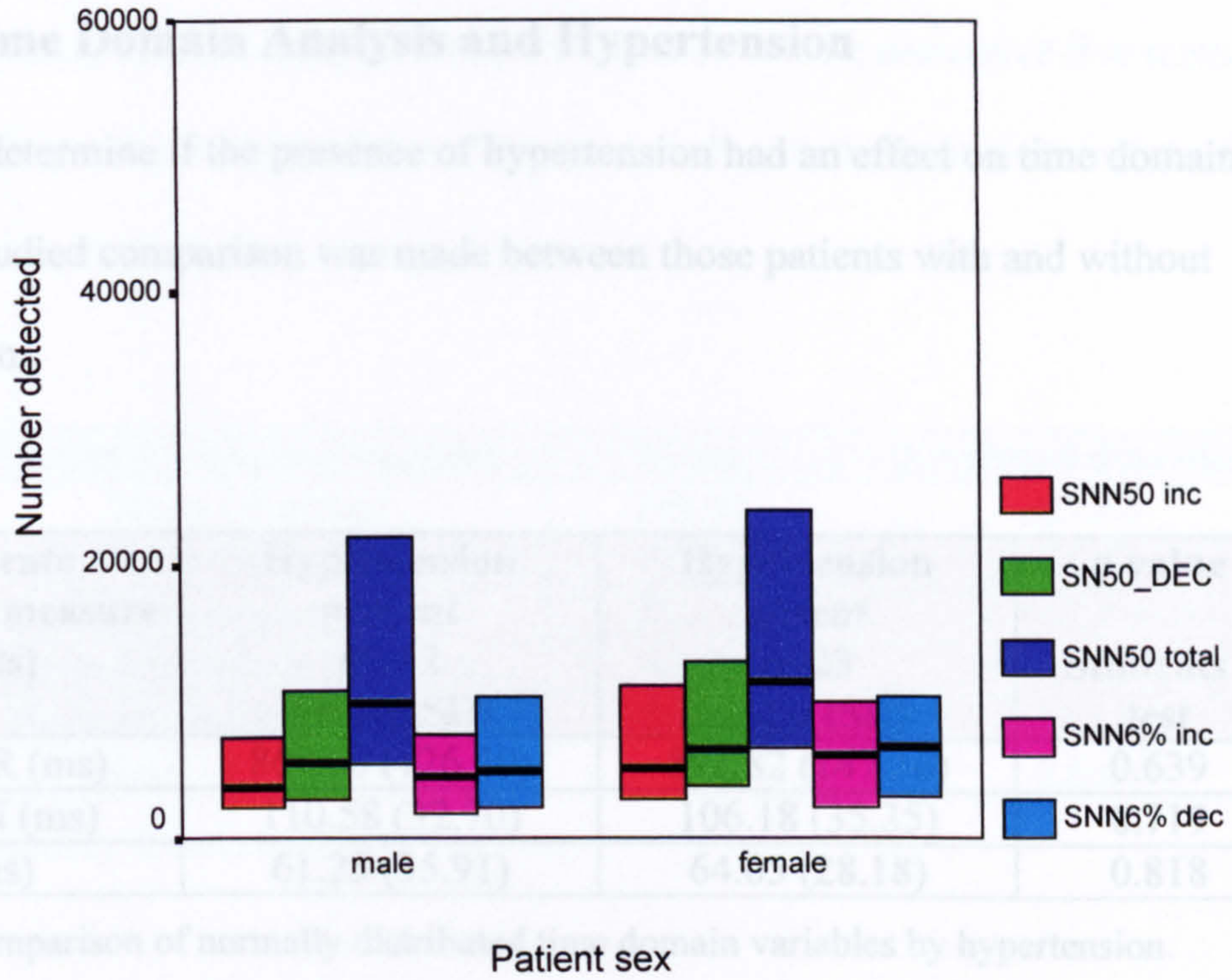


Figure 25 Boxplot comparing time domain variables for each sex.

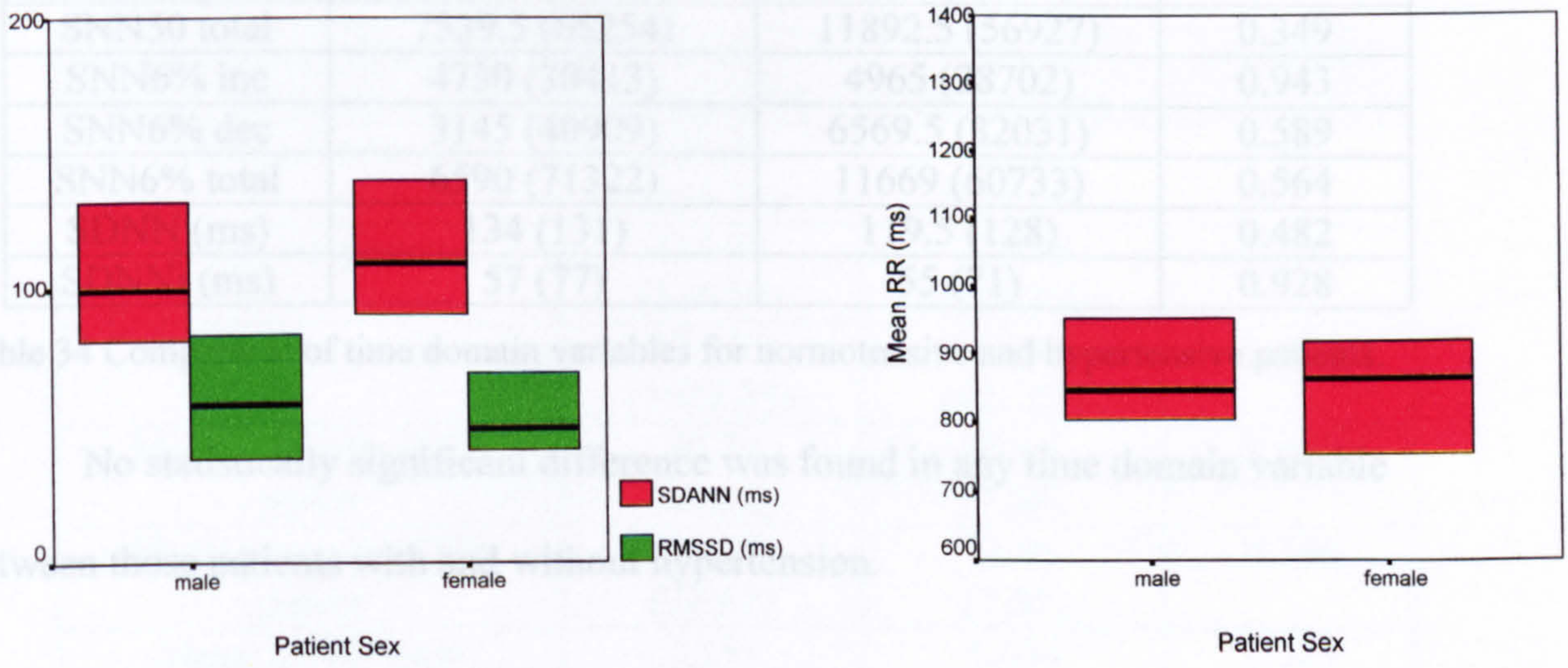


Figure 26 Boxplots comparing RMSSD, SDANN and Mean RR between sexes.

3.7.2.2 Time Domain Analysis and Hypertension

To determine if the presence of hypertension had an effect on time domain variables studied comparison was made between those patients with and without hypertension.

Heart rate variability measure (units)	Hypertension present n= 12 Mean (SD)	Hypertension absent n=23 Mean (SD)	p value Students t test
Mean RR (ms)	869.00 (126.30)	891.82 (147.36)	0.639
SDANN (ms)	110.58 (32.70)	106.18 (35.35)	0.719
RMSSD (ms)	61.25 (35.91)	64.05 (28.18)	0.818

Table 33 Comparison of normally distributed time domain variables by hypertension.

Variable (units)	Hypertension present Median (range)	Hypertension absent Median (range)	p value Mann Whitney U
SNN50 inc	3721.50 (27604)	4610.50 (25966)	0.449
SNN50 dec	4248.5 (37778)	6637 (30651)	0.471
SNN50 total	7539.5 (65254)	11892.5 (56927)	0.349
SNN6% inc	4730 (30413)	4965 (28702)	0.943
SNN6% dec	3145 (40909)	6569.5 (32031)	0.589
SNN6% total	6590 (71322)	11669 (60733)	0.564
SDNN (ms)	134 (131)	119.5 (128)	0.482
SDNNi (ms)	57 (77)	55 (71)	0.928

Table 34 Comparison of time domain variables for normotensive and hypertensive patients.

No statistically significant difference was found in any time domain variable between those patients with and without hypertension.

3.7.3 Frequency domain analysis

Frequency domain analysis was performed on three consecutive five minute periods under standardised conditions. The mean values and standard deviations for each variable are displayed below.

Frequency domain variable	Mean	Standard deviation
Mean LF power	148.91	227.68
Mean HF power	117.07	123.18
Mean total power	819.52	907.10
Mean normalised LF power	40.45	15.87
Mean normalised HF power	35.59	18.12
Mean LF/HF ratio	1.118	0.609

Table 35 Frequency domain heart rate variability.

3.7.3.1 Frequency domain analysis and sex

To determine whether there was a difference in frequency domain characteristics between the sexes the mean values were compared using a students t test. No statistically significant difference was observed between the sexes.

Frequency domain variable	Males Mean (SD)	Females Mean (SD)	P value
Mean LF power	153.40 (254.71)	135.92 (131.61)	0.841
Mean HF power	114.86 (116.59)	123.45 (148.12)	0.864
Mean total power	855.53 (1027.35)	715.49 (427.03)	0.687
Mean normalised LF power	40.73 (18.02)	39.64 (7.38)	0.862
Mean normalised HF power	36.15 (20.67)	33.95 (7.51)	0.750
Mean LF/HF ratio	1.151 (0.671)	1.024 (0.395)	0.589

Table 36 Comparison of frequency domain heart rate variability by sex.

This lack of difference is easily appreciated when viewed as a boxplot with the boxes for each sex showing considerable overlap.

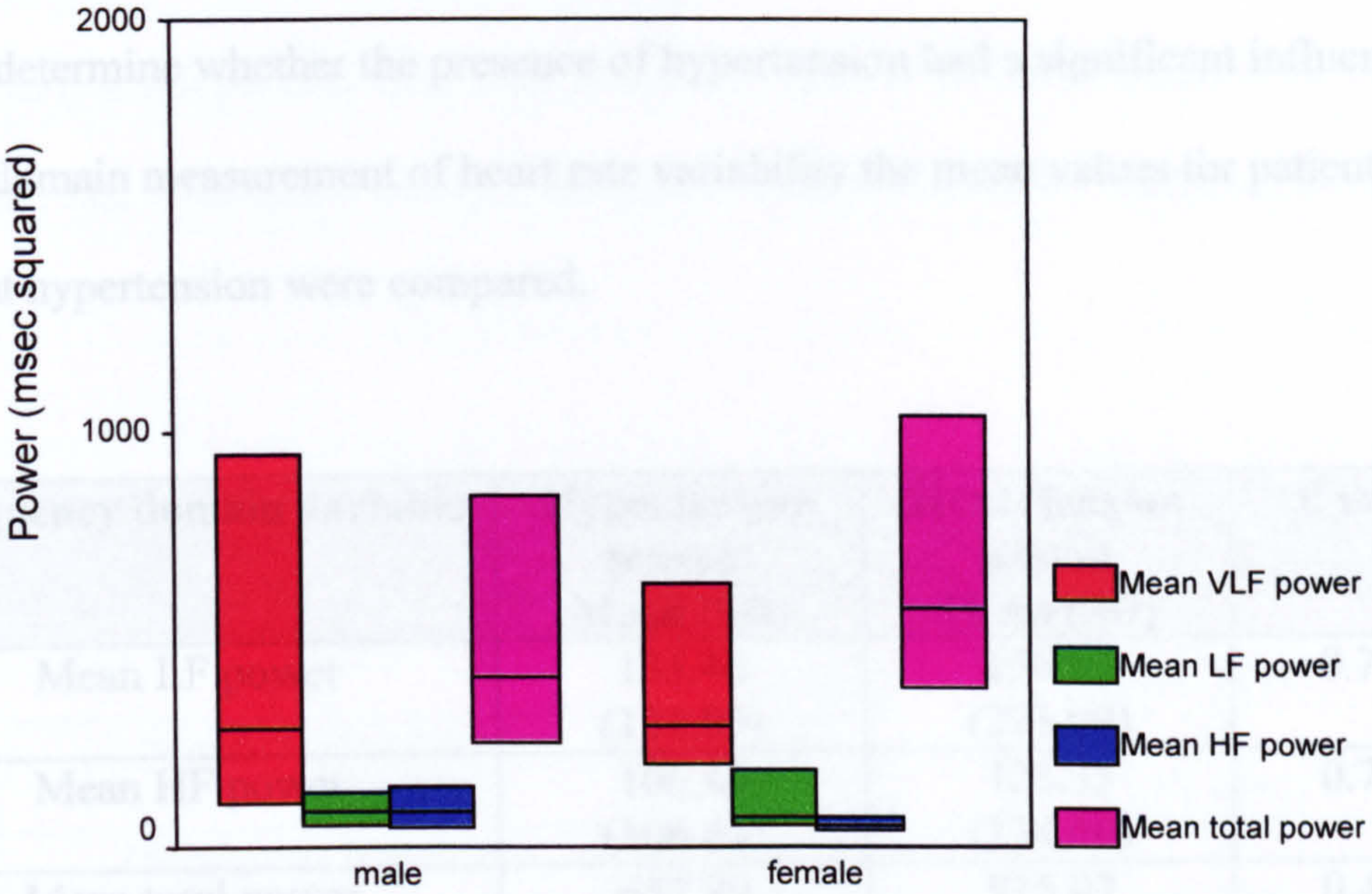


Figure 27 Boxplot showing median and interquartile range of power measurements for each sex

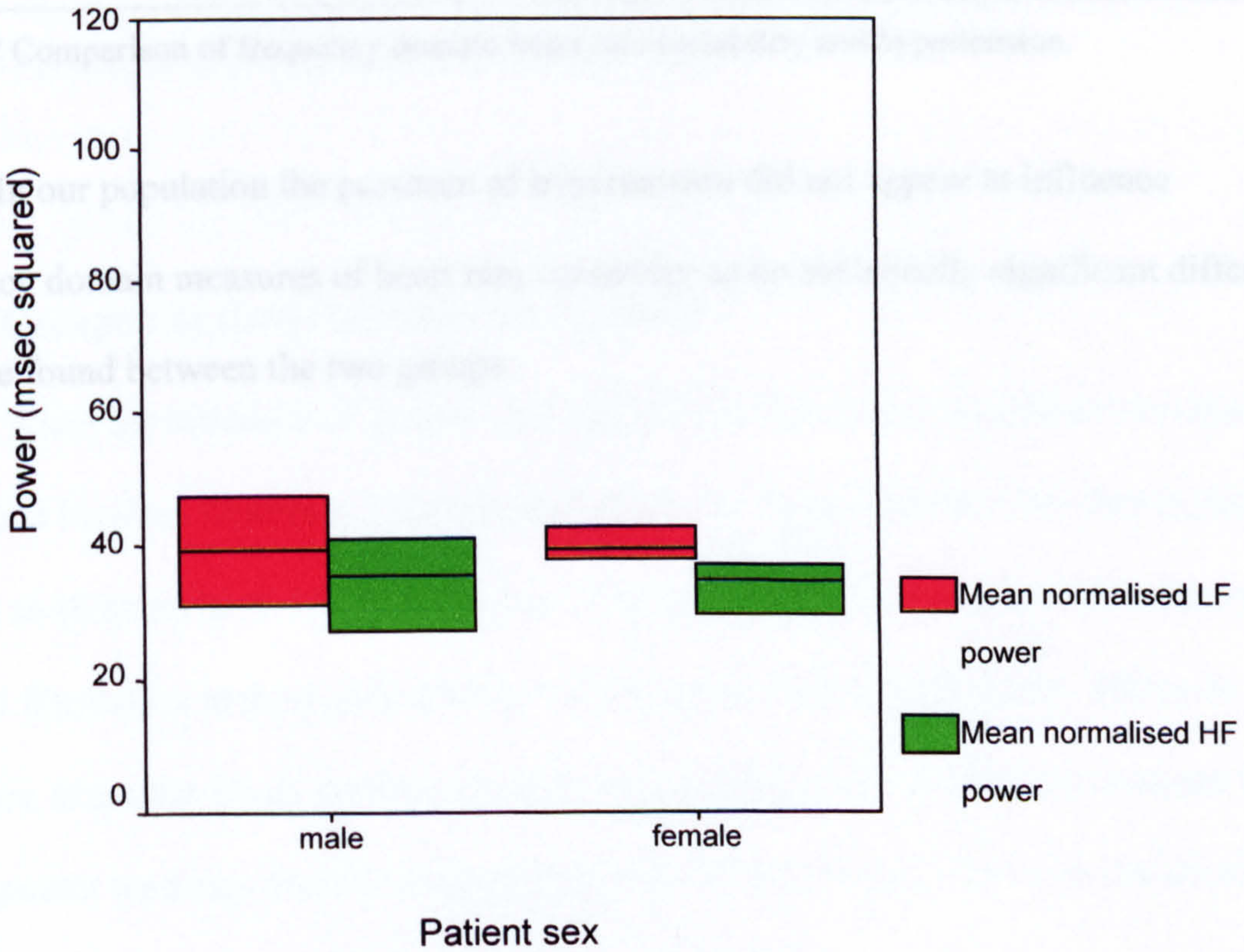


Figure 28 Boxplot showing median and interquartile range of normalised power for each sex

3.7.3.2 Frequency domain and hypertension

To determine whether the presence of hypertension had a significant influence on frequency domain measurement of heart rate variability the mean values for patients with and without hypertension were compared.

Frequency domain variable	Hypertension present Mean (SD)	Hypertension absent Mean (SD)	P value
Mean LF power	135.46 (134.00)	156.86 (271.09)	0.786
Mean HF power	106.44 (106.64)	123.35 (134.00)	0.701
Mean total power	657.89 (796.12)	915.02 (971.75)	0.421
Mean normalised LF power	44.50 (13.90)	38.06 (16.77)	0.257
Mean normalised HF power	36.81 (13.29)	34.87 (20.71)	0.758
Mean LF/HF ratio	1.097 (0.442)	1.131 (0.699)	0.869

Table 37 Comparison of frequency domain heart rate variability and hypertension.

In our population the presence of hypertension did not appear to influence frequency domain measures of heart rate variability as no statistically significant difference could be found between the two groups.

3.8 Three Month Review

All forty three patients who were in sinus rhythm at 48 hours attended for review at three months. The table below outlines the patient characteristics by rhythm at three months.

	Sinus rhythm at three months	**Atrial fibrillation at three months**
Number of patients (%)	18 (41.86%)	25 (58.14%)
Number of males (%)	14 (46.67%)	16 (53.33%)
Number of females (%)	4 (30.77%)	9 (69.23%)
Number with hypertension (%)	6 (33.33%)	12 (66.67%)
Mean age years (SD)	71.67 (7.19)	75.72 (7.20)
Duration of AF prior to cardioversion mean days (SD)	104.44 (44.93)	167.72 (225.03)

Table 38 Patient characteristics and rhythm at three months.

3.8.1 Relapse at three months and gender

When the influence of gender was analysed no statistically significant correlation was found between rhythm at 3 months and gender for those patients who were in sinus rhythm at 48 hours ($p=0.503$, Chi square). That is gender did not seem to influence relapse to atrial fibrillation in those patients who were in sinus rhythm at 48 hours. When the influence of gender for all patients who had a successful cardioversion was analysed there was a greater tendency towards maintaining sinus rhythm in men. However statistical significance was not reached ($p=0.08$, Pearson Chi square).

3.8.2 Relapse at three months and age.

Although patients who relapsed to atrial fibrillation between 48 hours and three months following cardioversion were on average 4 years older than those maintaining sinus rhythm (75.72 vs 71.67) this difference was not statistically significant when analysed by means of a students t test (p=0.076). When the same analysis was performed using all patients who had initially had a successful cardioversion the age difference was less pronounced. Those patients who relapsed within the three month period had a mean age of 73.91 years (SD 8.15) compared to 71.67 years (SD 7.19) for those maintaining sinus rhythm (p=0.285).

3.8.3 Relapse at three months and duration of atrial fibrillation.

The mean duration of atrial fibrillation for those patients who were in sinus rhythm at 48 hours and subsequently maintain sinus rhythm to three months was 104.44 (SD 44.93) days compared to 167.72 (SD 225.03) days for those relapsing to atrial fibrillation between 48 hours and three months. This difference was not sufficient to reach statistical significance (p=0.248, t test). When all patients initially achieving sinus rhythm at cardioversion are included the mean duration for those patients relapsing within three months is 141.30 (SD 172.41) days. This difference is not statistically significant (p=0.376, t test).

3.8.4 Relapse at three months and hypertension.

There was no statistically significant relationship between relapse to atrial fibrillation between 48 hours and three months and hypertension (p=0.707, Chi square). This remained the case when all relapses within three months of cardioversion were included in the analysis (p=0.498, Chi square).

3.8.5 Three month rhythm and TOE.

3.8.5.1 TOE and relapse between 48 hours and three months.

In order to determine the potential role of TOE measurements in predicting relapse between 48 hours and three months comparison of TOE measurements was made between patients in sinus rhythm at three months and those who, having been in sinus rhythm at 48 hours, had subsequently relapsed to atrial fibrillation.

TOE measurement Mean (SD)	Sinus rhythm at three months n=18	Atrial fibrillation between 48 hours and three months n=25	p value
Left atrial AP diameter (cm)	5.09 (0.90)	5.39 (0.68)	0.255
Left atrial transverse diameter (cm)	4.68 (0.67)	4.88 (0.51)	0.303
Left atrial appendage area (cm^2)	4.97 (1.47)	4.64 (1.15)	0.446
Mean peak left atrial appendage flow velocity (cm/sec)	27.59 (12.76)	25.68 (13.85)	0.648
Mean peak mitral valve flow velocity (cm/sec)	77.98 (24.69)	88.05 (29.01)	0.235
Mean peak pulmonary vein flow velocity (cm/sec)	40.66 (16.36)	41.72 (19.39)	0.850

Table 39 Relapse between 48 hours and three months and mean TOE measurements.

None of the TOE measurements differed significantly between patients relapsing to atrial fibrillation between forty eight hours and three months and those maintaining sinus rhythm.

3.8.5.2 TOE and relapse within three months.

To assess the role of TOE measurements in predicting relapse within the three month period mean TOE values were compared between those patients maintaining sinus rhythm to three months and those relapsing at any time upto three months following successful cardioversion.

TOE measurement Mean (SD)	**Sinus rhythm at three months n=18**	**Atrial fibrillation within three months n=48**	**p value**
Left atrial AP diameter (cm)	5.09 (0.90)	5.26 (0.76)	0.456
Left atrial transverse diameter (cm)	4.68 (0.67)	4.74 (0.63)	0.733
Left atrial appendage area (cm^2)	4.97 (1.47)	4.67 (1.08)	0.377
Mean peak left atrial appendage flow velocity (cm/sec)	27.59 (12.76)	25.92 (12.73)	0.644
Mean peak mitral valve flow velocity (cm/sec)	77.98 (24.69)	79.91 (25.74)	0.790
Mean peak pulmonary vein flow velocity (cm/sec)	40.66 (16.36)	41.59 (17.67)	0.845

Table 40 Relapse within three months and mean TOE variables.

No significant difference in mean TOE variables could be demonstrated between the two groups. This suggests that TOE measurements are unlikely to be useful in the prediction of relapse within three months.

3.8.6 Three month relapse and initial P wave signal averaged ECG

3.8.6.1 Initial PSAECG and relapse between 48 hours and 3 months

The table below shows the mean values for the initial P wave signal averaged ECG of patients who were in sinus rhythm at 48 hours categorised by rhythm at three month review.

Initial P wave signal averaged ECG parameter Mean (SD)	Sinus rhythm at three months n=18	Atrial fibrillation at three months n=25	p value
P wave duration unfiltered (ms)	150.41 (63.17)	156.20 (59.80)	0.768
P wave duration filtered (ms)	162.47 (54.52)	163.00 (57.00)	0.976
RMS 20 (μV)	4.06 (3.83)	6.00 (4.96)	0.161
RMS 30 (μV)	5.00 (4.61)	6.48 (4.94)	0.334
RMS 40 (μV)	5.71 (5.37)	7.20 (4.87)	0.365
Number of beats averaged	443.88 (304.13)	359.64 (235.95)	0.319

Table 41Initial PSAECG and 3 month rhythm for patients in sinus rhythm at 48 hours

It can be seen from the table above that for patients in sinus rhythm at 48 hours no initial P wave signal averaged ECG variable differed significantly between patients maintaining sinus rhythm to three months and those relapsing.

3.8.6.2 Initial PSAECG and relapse within 3 months

The table below displays the mean initial p wave signal averaged ECG variables for all patients who had a successful cardioversion and their three month rhythm.

Initial P wave signal averaged ECG parameter Mean (SD)	Sinus rhythm at three months n=18	Atrial fibrillation at three months n=48	p value
P wave duration unfiltered (ms)	150.41 (63.17)	154.15 (50.96)	0.828
P wave duration filtered (ms)	162.47 (54.52)	160.74 (48.96)	0.909
RMS 20 (μV)	4.06 (3.83)	5.13 (4.15)	0.343
RMS 30 (μV)	5.00 (4.61)	5.62 (4.30)	0.634
RMS 40 (μV)	5.71 (5.37)	6.23 (4.34)	0.719
Number of beats averaged	443.88 (304.13)	343.15 (217.64)	0.223

Table 42 Initial PSAECG and 3 month rhythm for patients in sinus rhythm after cardioversion.

None of the initial p wave signal averaged ECG variables differed significantly when comparison was made between patients maintaining sinus rhythm to three months and those relapsing within three months. This would suggest that p wave signal averaging performed one hour after successful cardioversion is unhelpful in predicting relapse within the first three months.

3.8.7 Three month relapse and second P wave signal averaged ECG

The possible role of the second p wave signal averaged ECG in predicting 3 month relapse was analysed by comparing mean values for patients maintaining sinus rhythm to 3 months and those patients relapsing to atrial fibrillation. The table below shows these mean values, there standard deviation and the level of significance achieved when analysed using a students t test.

Second P wave signal averaged ECG parameter Mean (SD)	Sinus rhythm at three months n=18	Atrial fibrillation at three months n=25	p value
P wave duration unfiltered (ms)	150.72 (44.53)	142.20 (54.32)	0.588
P wave duration filtered (ms)	156.39 (41.88)	147.68 (53.40)	0.568
RMS 20 (μV)	4.39 (2.33)	4.60 (3.40)	0.821
RMS 30 (μV)	5.11 (2.72)	6.12 (4.28)	0.384
RMS 40 (μV)	5.50 (2.73)	6.52 (4.16)	0.370
Number of beats averaged	333.94 (226.28)	378.08 (247.71)	0.548

Table 43 Second PSAECG and rhythm at three months.

None of the differences observed achieved statistical significance.

The lack of significant difference in any of the p wave signal averaged ECG measurements between patients relapsing to atrial fibrillation and those maintaining sinus rhythm suggests that p wave signal averaging has little to offer when attempting to predict relapse within the first three months following DC cardioversion.

3.8.8 Three month relapse and time domain heart rate variability

The table below shows the mean RR interval, SDANN and RMSSD for patients maintaining sinus rhythm at three months and those relapsing within the same time period. No statistically significant difference in any of these values was shown between the two groups.

Heart rate variability measure (units)	Sinus rhythm at 3 months n=16 Mean (SD)	Atrial fibrillation at 3 months n=19 Mean (SD)	p value Students t test
Mean RR (ms)	884.00 (142.13)	877.47 (138.47)	0.892
SDANN (ms)	113.63 (31.24)	101.21(35.77)	0.281
RMSSD (ms)	59.56 (33.64)	64.95 (27.97)	0.608

Table 44 Time domain heart rate variability and 3 month rhythm

Median values were calculated for all time domain variables that were not normally distributed and comparison between the two groups made by means of a Mann Whitney U test. No statistically significant difference was found between the two groups

Variable (units)	Sinus rhythm at three months Median (range)	Atrial fibrillation at three months Median (range)	p value (Mann Whitney U)
SNN50 inc	3886 (27708)	4967 (14280)	0.791
SNN50 dec	5061 (38371)	7120 (30058)	0.741
SNN50 total	9818 (66079)	12087 (44338)	0.716
SNN6% inc	4633 (30354)	5093 (14986)	0.868
SNN6% dec	4270 (41056)	6186 (30029)	0.446
SNN6% total	8316 (71400)	12046 (45015)	0.508
SDNN (ms)	134 (128)	109 (131)	0.227
SDNNi (ms)	54 (71)	57 (77)	0.643

Table 45 Time domain heart rate variability non parametric analysis and three month rhythm.

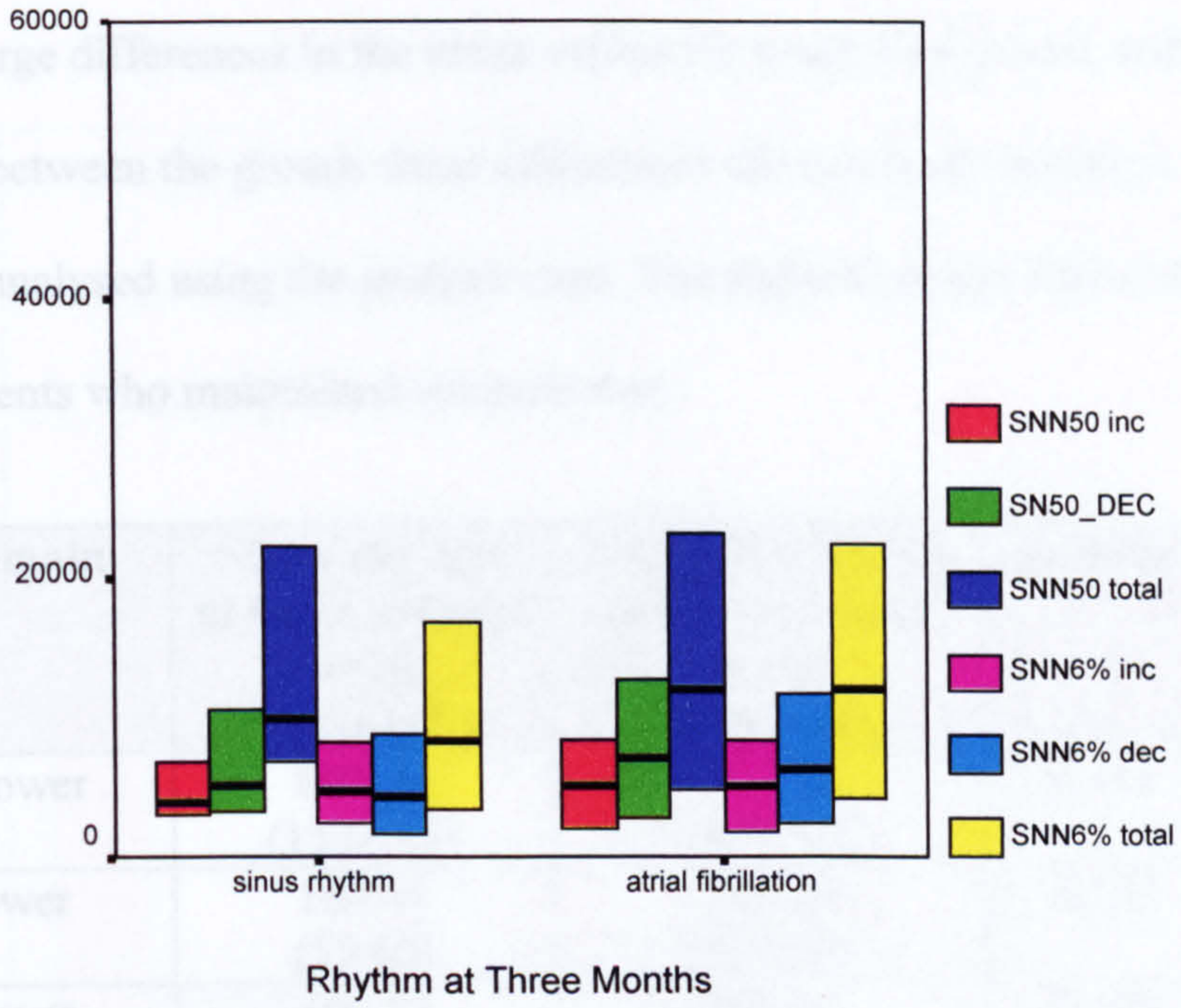
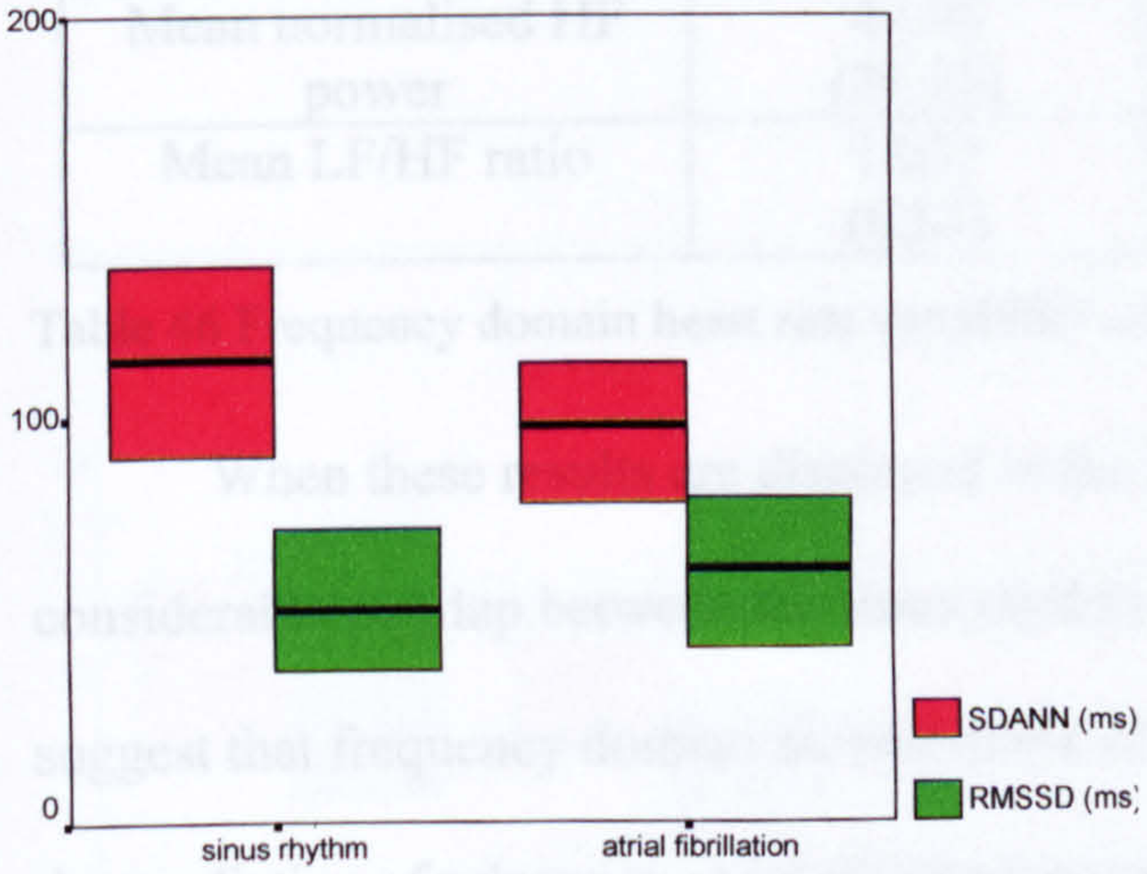


Figure 29 Time domain measures compared by three month rhythm



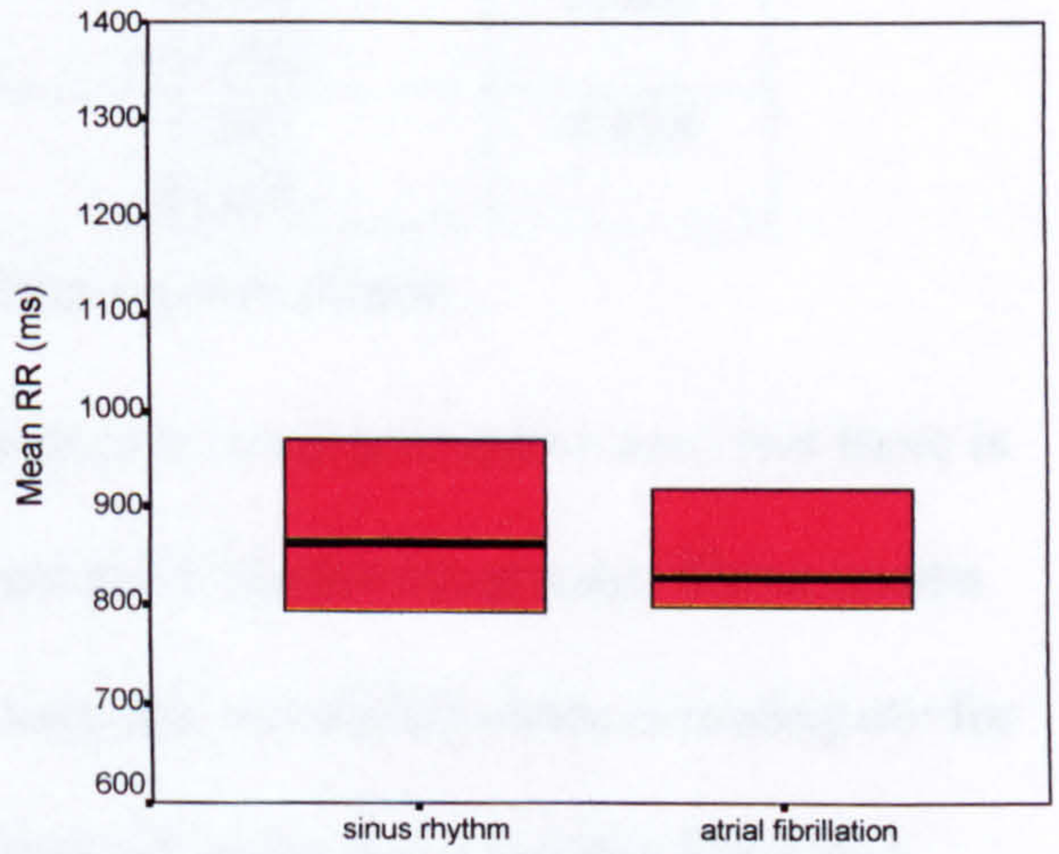


Figure 30a and b SDANN, RMSSD and Mean RR comparison by three month rhythm

In the boxplots above the black line within the box represents the median value and the box represents the interquartile range.

3.8.9 Three month relapse and frequency domain heart rate variability

Although large differences in the mean values for mean VLF power and mean total power were found between the groups these differences did not reach statistical significance when analysed using the student t test. The highest mean values were encountered in patients who maintained sinus rhythm.

Frequency domain variable	Sinus rhythm at three months n=16 Mean (SD)	Atrial fibrillation at three months n=19 Mean (SD)	p value
Mean VLF power	802.34 (1134.25)	489.23 (451.38)	0.314
Mean LF power	100.61 (52.60)	189.59 (302.97)	0.223
Mean HF power	106.53 (89.40)	125.95 (147.70)	0.631
Mean total power	999.34 (1196.82)	668.08 (554.64)	0.325
Mean normalised LF power	42.62 (16.70)	38.63 (15.36)	0.468
Mean normalised HF power	42.04 (21.75)	30.16 (12.56)	0.060
Mean LF/HF ratio	1.035 (0.51)	1.189 (0.69)	0.454

Table 46 Frequency domain heart rate variability and three month rhythm

When these results are displayed in the form of a boxplot it can be seen that there is considerable overlap between the sinus rhythm and atrial fibrillation groups. These results suggest that frequency domain measurement of heart rate variability alone is inadequate for the prediction of relapse to atrial fibrillation between 48 hours and 3 months following successful DC cardioversion.

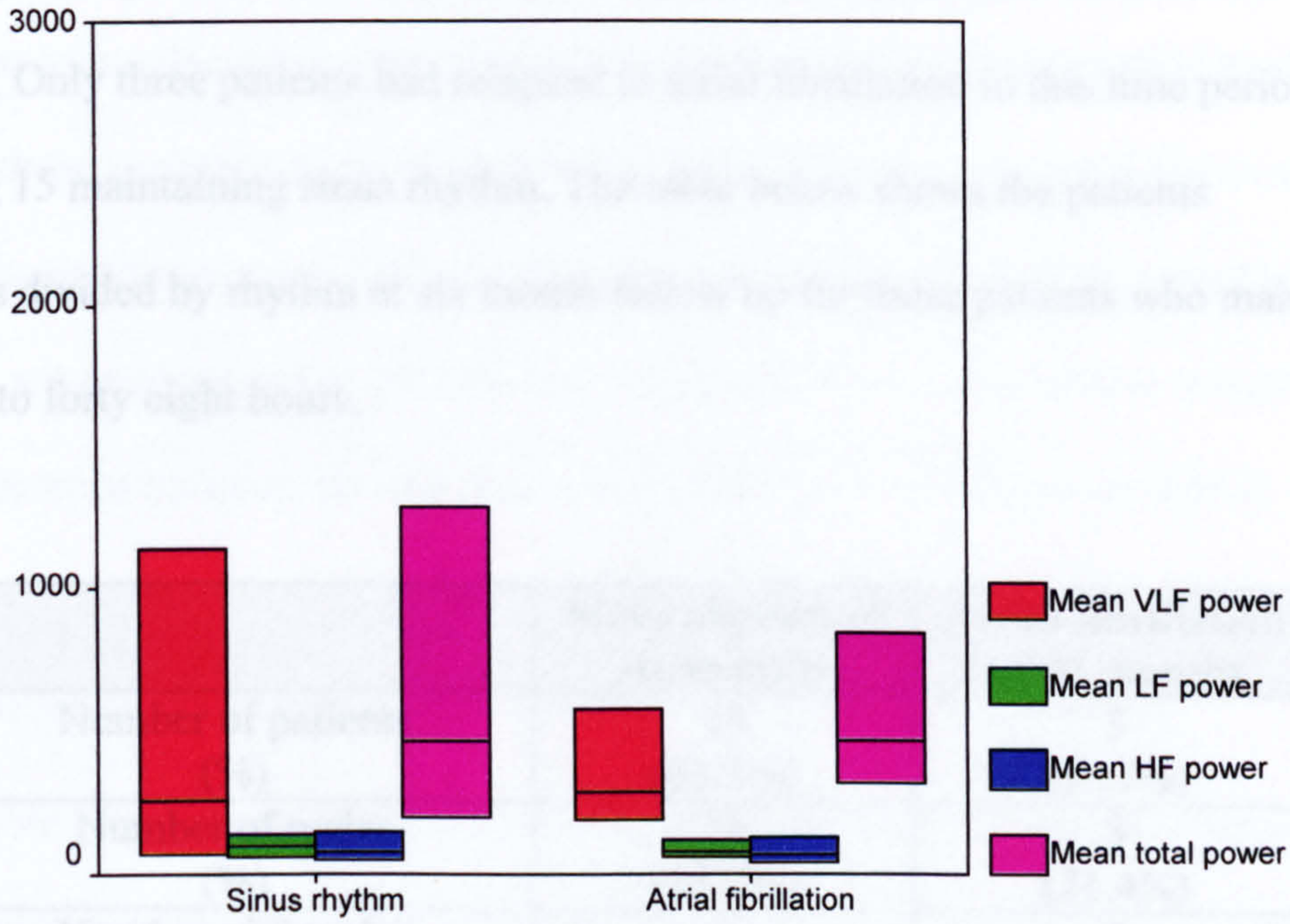


Figure 31 Boxplot of mean power and three month rhythm.

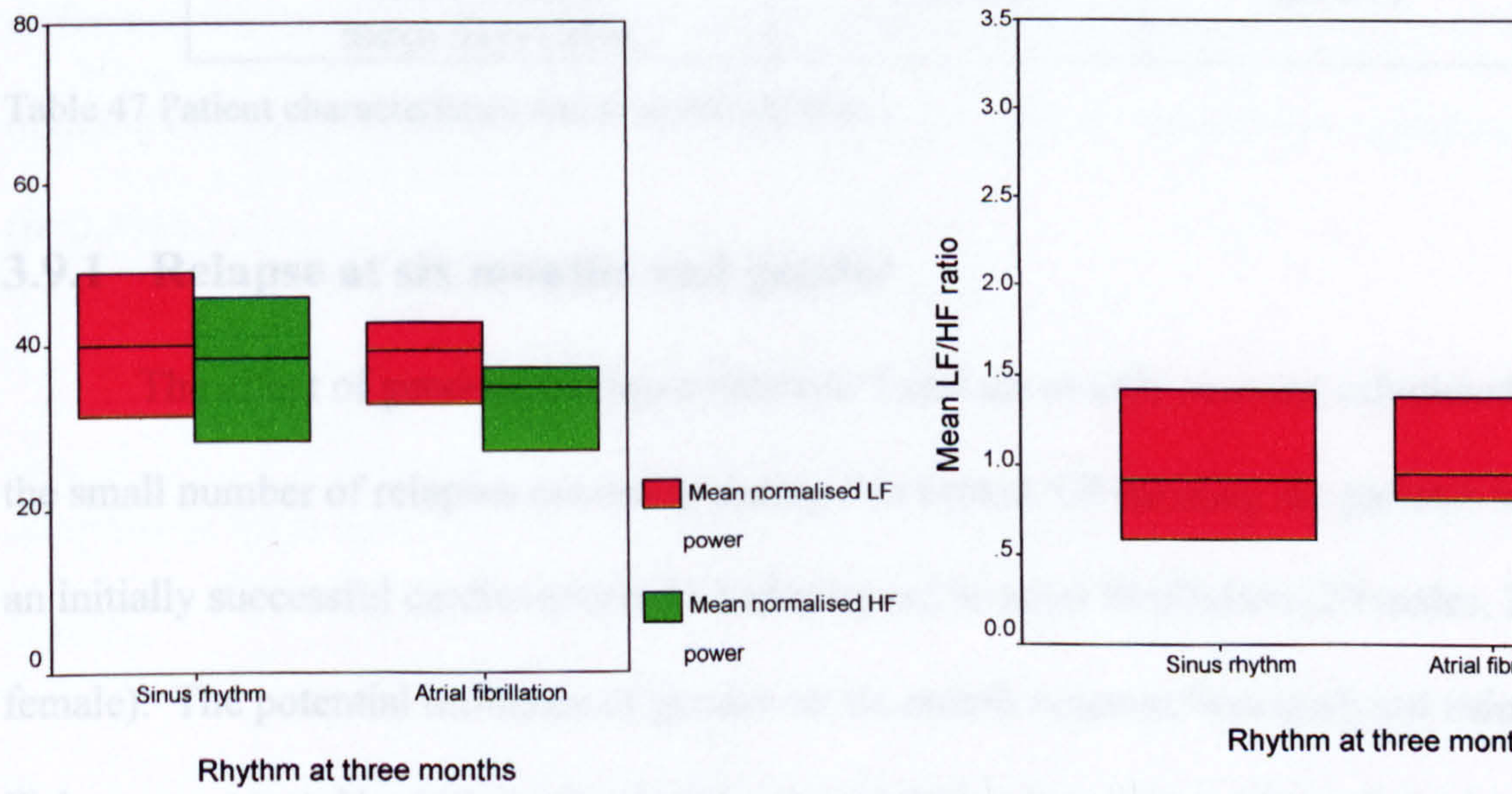


Figure 32 a and b Boxplots of mean normalised power and mean LF/HF ratio and three month rhythm.

3.9 Six Month Review

All eighteen patients who were in sinus rhythm at three months attended for review at six months. Only three patients had relapsed to atrial fibrillation in this time period with the remaining 15 maintaining sinus rhythm. The table below shows the patients characteristics divided by rhythm at six month follow up for those patients who maintained sinus rhythm to forty eight hours.

	Sinus rhythm at six months	**Atrial fibrillation at six months**
Number of patients (%)	15 (83.3%)	3 (16.7%)
Number of males (%)	11 (78.6%)	3 (21.4%)
Number of females (%)	4 (100.0%)	0 (0.0%)
Number with hypertension (%)	6 (66.7%)	3 (33.3%)
Mean age years (SD)	72.60 (6.93)	67.00 (8.00)
Duration of AF prior to cardioversion mean days (SD)	114.07 (41.63)	56.33 (29.37)

Table 47 Patient characteristics and 6 month rhythm

3.9.1 Relapse at six months and gender

The effect of gender on relapse between 3 and six months was not calculated due to the small number of relapses occurring during this period. Of the sixty six patients who had an initially successful cardioversion 51 had relapsed to atrial fibrillation (29 males, 22 female). The potential influence of gender on six month outcome was analysed using the Fishers exact test. No statistically significant correlation between gender and rhythm at six months could be demonstrated ($p=0.369$).

3.9.2 Relapse at six months and age

Patients who relapsed to atrial fibrillation between three and six months tended to be older than those maintaining sinus rhythm (72.6 Vs 67.0) however this difference was not statistically significant (p=0.350). Again when all patients who had a successful cardioversion are included in the analysis and outcome at six months used to compare means the difference becomes far less pronounced (SR=72.6, AF=73.06, p=0.853).

3.9.3 Relapse at six months and duration of atrial fibrillation

The table above shows that those patients who were in sinus rhythm at three months and subsequently maintain a normal rhythm to six months had a longer duration of atrial fibrillation than those who relapse (114.1 Vs 56.3). This difference achieved statistical significance when analysed using an independent samples t test (p=0.047). when all patients who had an initially successful cardioversion were included in the analysis this difference was reversed with patients who relapsed to atrial fibrillation having a mean duration of 136.25 days (SD=166.70). This difference was not statistically significant (p=0.391)

3.9.4 Six month rhythm and TOE.

3.9.4.1 TOE and relapse between three and six months

To determine whether TOE measurements had a role in predicting late relapse to atrial fibrillation comparison was made between patients who were in sinus rhythm at six months and those relapsing to atrial fibrillation between three and six months.

TOE measurement Mean (SD)	Sinus rhythm at six months n=15	Atrial fibrillation between 48 hours and three months n=3	p value
Left atrial AP diameter (cm)	4.98 (0.84)	5.96 (1.16)	0.434
Left atrial transverse diameter (cm)	4.66 (0.71)	4.79 (0.47)	0.783
Left atrial appendage area (cm^2)	4.90 (1.41)	5.49 (2.45)	0.611
Mean peak left atrial appendage flow velocity (cm/sec)	28.25 (13.17)	22.68 (10.95)	0.579
Mean peak mitral valve flow velocity (cm/sec)	76.73 (24.22)	87.34 (36.57)	0.585
Mean peak pulmonary vein flow velocity (cm/sec)	41.40 (16.09)	35.11 (24.20)	0.776

Table 48Relapse between 3 and 6 months and mean TOE measurements

No statistically significant difference could be demonstrated between patients relapsing to atrial fibrillation between three and six months and those maintaining sinus rhythm.

3.9.4.2 TOE measurements and relapse within six months

To assess whether TOE measurements had a role to play in predicting relapse to atrial fibrillation over the whole follow up period mean TOE variables were compared between patients maintaining sinus rhythm to six months and those relapsing to atrial fibrillation at any time within the six month period.

TOE measurement Mean (SD)	Sinus rhythm at six months n=15	Atrial fibrillation at any time within six month follow up period n=51	p value
Left atrial AP diameter (cm)	4.98 (0.84)	5.29 (0.79)	0.187
Left atrial transverse diameter (cm)	4.66 (0.71)	4.74 (0.63)	0.687
Left atrial appendage area (cm^2)	4.90 (1.41)	4.67 (1.10)	0.502
Mean peak left atrial appendage flow velocity (cm/sec)	28.25 (13.17)	26.01 (12.61)	0.555
Mean peak mitral valve flow velocity (cm/sec)	76.73 (24.22)	80.81 (25.70)	0.588
Mean peak pulmonary vein flow velocity (cm/sec)	41.40 (16.09)	41.38 (17.88)	0.996

Table 49 Relapse within six months and mean TOE measurements

No statistically significant difference in mean TOE measurements was demonstrated between patients maintaining sinus rhythm for six months and those relapsing over the same period.

3.9.5 Six month relapse and initial P wave signal averaged ECG

The table below shows the mean initial P wave signal averaged ECG values for patients maintaining sinus rhythm to six months and those relapsing within the six month follow up period.

Initial P wave signal averaged ECG parameter Mean (SD)	Sinus rhythm at six months n=15	Atrial fibrillation within six months n=51	p value
P wave duration unfiltered (ms)	149.00 (64.25)	148.37 (45.58)	0.966
P wave duration filtered (ms)	161.40 (55.51)	155.22 (43.57)	0.654
RMS 20 (μV)	4.27 (3.90)	5.33 (4.06)	0.376
RMS 30 (μV)	5.13 (4.78)	5.88 (4.27)	0.568
RMS 40 (μV)	5.73 (5.48)	6.59 (4.27)	0.527
Number of beats averaged	425.00 (335.80)	347.16 (213.43)	0.286

Table 50 Initial PSAECG measurements and rhythm at six months

No statistically significant difference in initial P wave signal averaged ECG measurement was detected between patients maintaining sinus rhythm and those relapsing to atrial fibrillation.

3.9.6 Six month relapse and second P wave signal averaged ECG

To determine the role of the second p wave signal averaged ECG in predicting relapse between 48 hours and six months of cardioversion comparison was made between patients maintaining sinus rhythm and those relapsing.

Second P wave signal averaged ECG parameter Mean (SD)	Sinus rhythm at six months n=15	Atrial fibrillation at six months n=28	p value
P wave duration unfiltered (ms)	143.00 (27.67)	131.93 (37.59)	0.283
P wave duration filtered (ms)	149.80 (24.47)	137.89 (37.57)	0.222
RMS 20 (μV)	3.93 (2.22)	4.78 (3.30)	0.329
RMS 30 (μV)	4.53 (2.64)	6.41 (4.11)	0.080
RMS 40 (μV)	5.00 (2.24)	7.04 (3.98)	0.040
Number of beats averaged	306.60 (205.47)	224.30 (268.43)	0.279

Table 51 Second PSAECG and six month rhythm

There was no significant difference in p wave duration between patients maintaining sinus rhythm and those relapsing to atrial fibrillation. However the RMS 40 was significantly greater for patients relapsing to atrial fibrillation compared to those maintaining sinus rhythm. Although RMS 30 also tended to be greater for relapsing patients the difference failed to reach statistical significance.

3.9.7 Six month rhythm and time domain heart rate variability

The table below shows the mean time domain heart rate variability measurements for patients maintaining sinus rhythm to six months and those relapsing to atrial fibrillation within the same period. No statistically significant difference was found in any of these variables.

Heart rate variability measure (units)	Sinus rhythm at six months n=13 Mean (SD)	Atrial fibrillation at six months n=22 Mean (SD)	p value Students t test
Mean RR (ms)	909.00 (135.22)	862.23 (142.17)	0.345
SDANN (ms)	110.31 (31.15)	102.82 (35.30)	0.531
RMSSD (ms)	54.92 (30.57)	66.95 (30.01)	0.263

Table 52 Time domain heart rate variability and 6 month rhythm

Median values and ranges were calculated for variables that were not normally distributed and a Mann Whitney test used to compare the two groups.

Variable (units)	Sinus rhythm at six months Median (range)	Atrial fibrillation at six months Median (range)	p value (Mann Whitney U)
SNN50 inc	3730 (45511)	4486.5 (25966)	0.785
SNN50 dec	4900 (45391)	6637 (29700)	0.413
SNN50 total	9716 (90902)	11003.5 (56927)	0.918
SNN6% inc	4428 (51661)	4965 (28712)	0.785
SNN6% dec	3803 (50590)	6569.5 (32031)	0.195
SNN6% total	6754 (102251)	11955.5 (60733)	0.246
SDNN (ms)	133 (131)	113 (128)	0.384
SDNNi (ms)	52 (77)	56.5 (71)	0.539

Table 53 Time domain heart rate variability analysis and six month rhythm

There was no statistically significant difference in any time domain heart rate variability measure between the two groups.

3.9.8 Six month relapse and frequency domain heart rate variability

When frequency domain heart rate variability measurements were compared between patients maintaining sinus rhythm to six months and those relapsing to atrial fibrillation no statistically significant difference could be found.

Frequency domain variable	Sinus rhythm at six months n=13 Mean (SD)	Atrial fibrillation at six months n=22 Mean (SD)	p value
Mean VLF power	836.04 (1201.01)	496.58 (452.61)	0.328
Mean LF power	106.88 (53.00)	176.94 (290.24)	0.380
Mean HF power	108.42 (95.77)	122.84 (140.51)	0.740
Mean total power	1039.22 (1265.90)	673.05 (548.50)	0.248
Mean normalised LF power	44.40 (17.11)	37.82 (14.83)	0.235
Mean normalised HF power	41.96 (23.33)	31.34 (12.53)	0.136
Mean LF/HF ratio	1.093 (0.522)	1.135 (0.673)	0.843

Table 54 Frequency domain heart rate variability and six month rhythm

3.9.9 Overall success rates

Overall success rates were low with only 23% of patients who had an initially successful cardioversion maintaining sinus rhythm to six months. When those patients who underwent a failed cardioversion are included in the analysis a total of eighty one cardioversions were performed with 15 patients maintaining sinus rhythm to six months. This gives a success rate of only 18.5%. The percentages in the tables below were calculated using only those patients who achieved sinus rhythm at cardioversion.

Time (days)	Patients Remaining in Sinus Rhythm					
	Total number	% of patients	Number of males	% of males	Number of females	% of females
0	66	100	41	100	25	100
2	43	65	30	73	13	52
90	18	27	14	34	4	16
180	15	23	11	27	3	12

Table 55 Sinus rhythm rates at each follow up

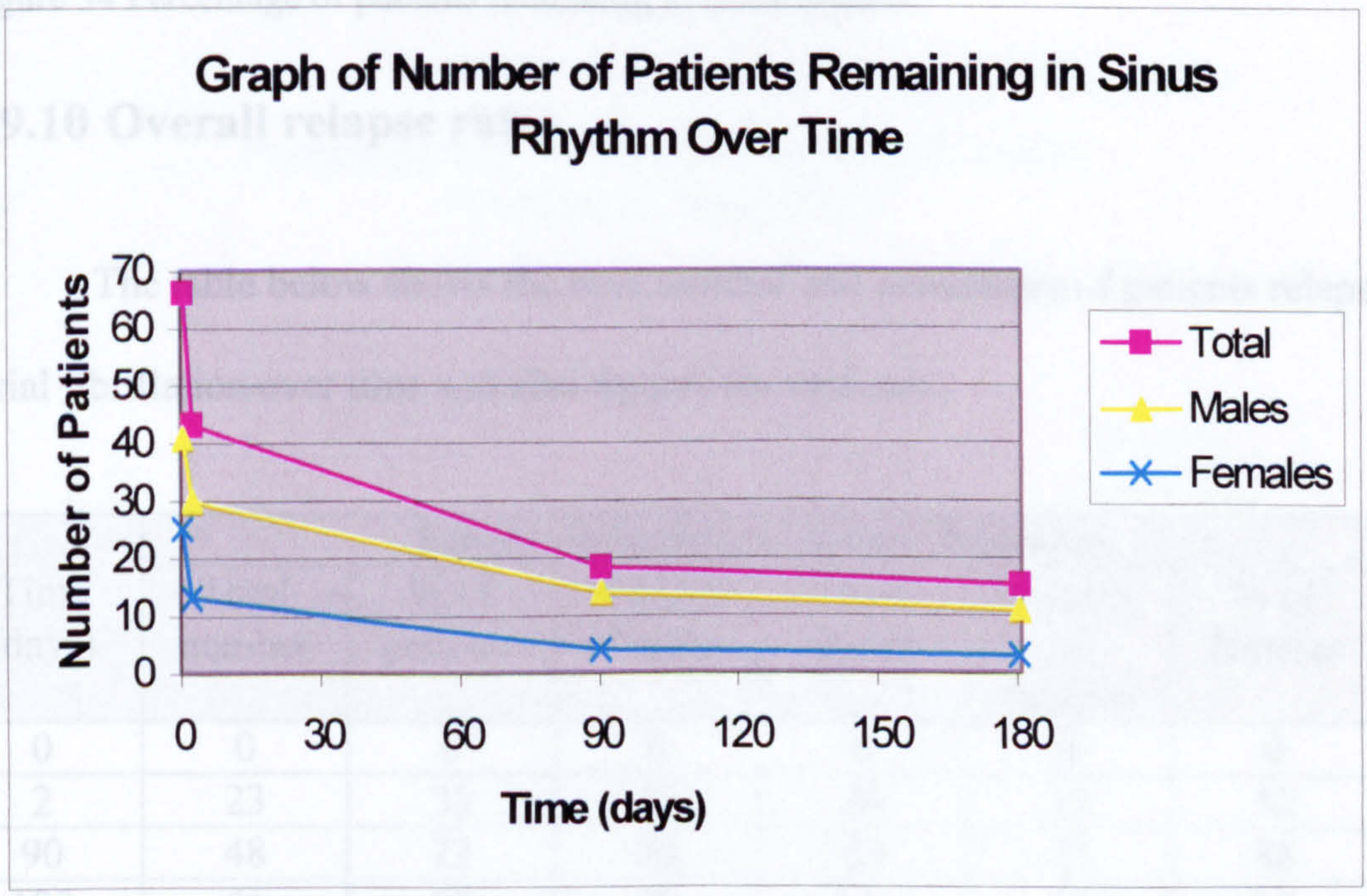


Figure 33 Graph of number of patients maintaining sinus rhythm

A greater percentage of males maintained sinus rhythm to six months compared to females. This difference was shown to be statistically significant at 48 hours (p=0.027) but failed to reach statistical significance at any time thereafter (p=0.08).

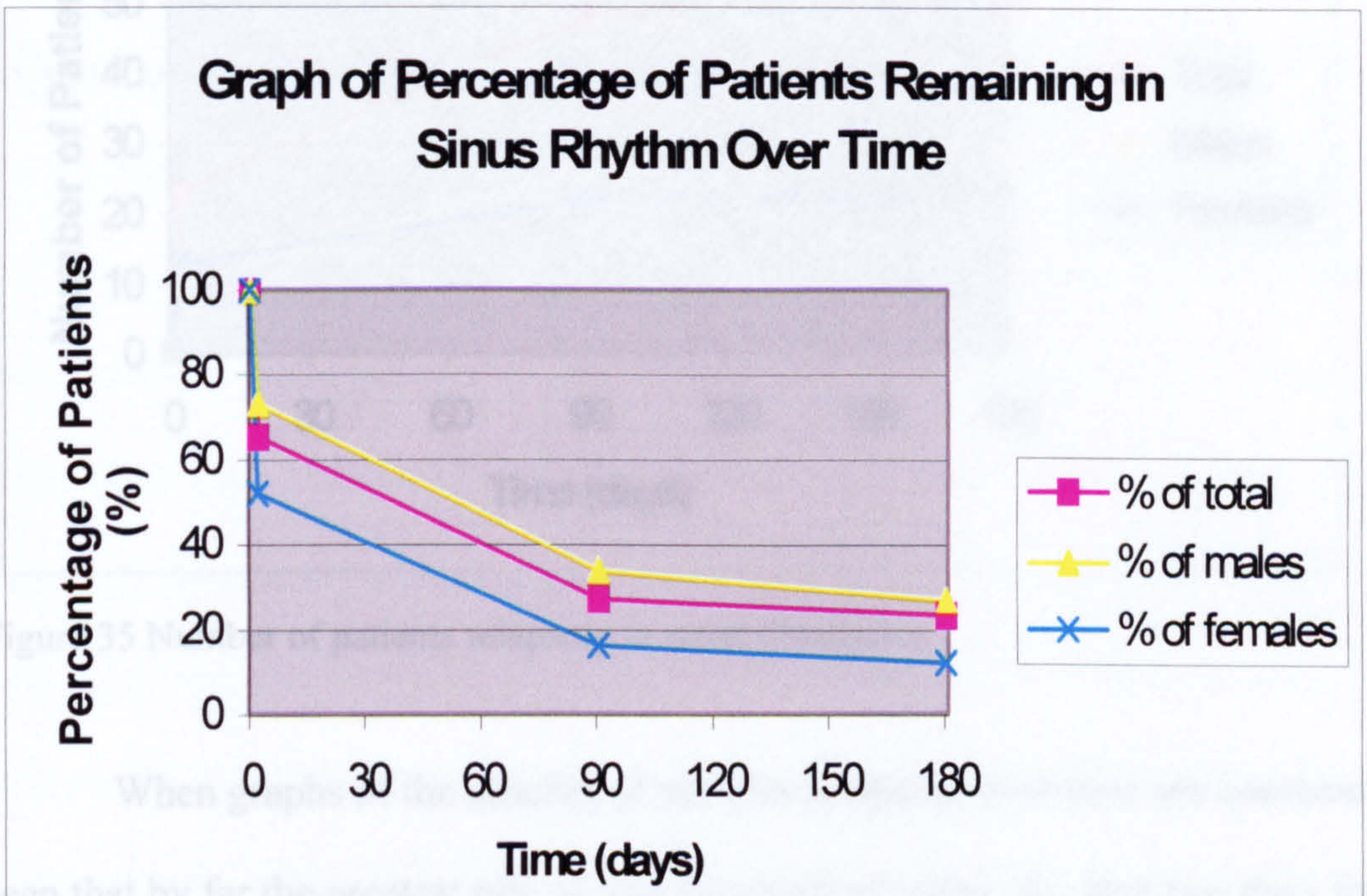


Figure 34 Percentage of patients remaining in sinus rhythm

3.9.10 Overall relapse rates

The table below shows the total number and percentage of patients relapsing to atrial fibrillation over time and also figures for each sex.

Time (days)	Patients Relapsing to Atrial Fibrillation					
	Total number	% of patients	Number of males	% of males	Number of females	% of females
0	0	0	0	0	0	0
2	23	35	10	24	13	52
90	48	73	26	63	22	88
180	51	77	29	71	22	88

Table 56 Relapse rates at each follow up

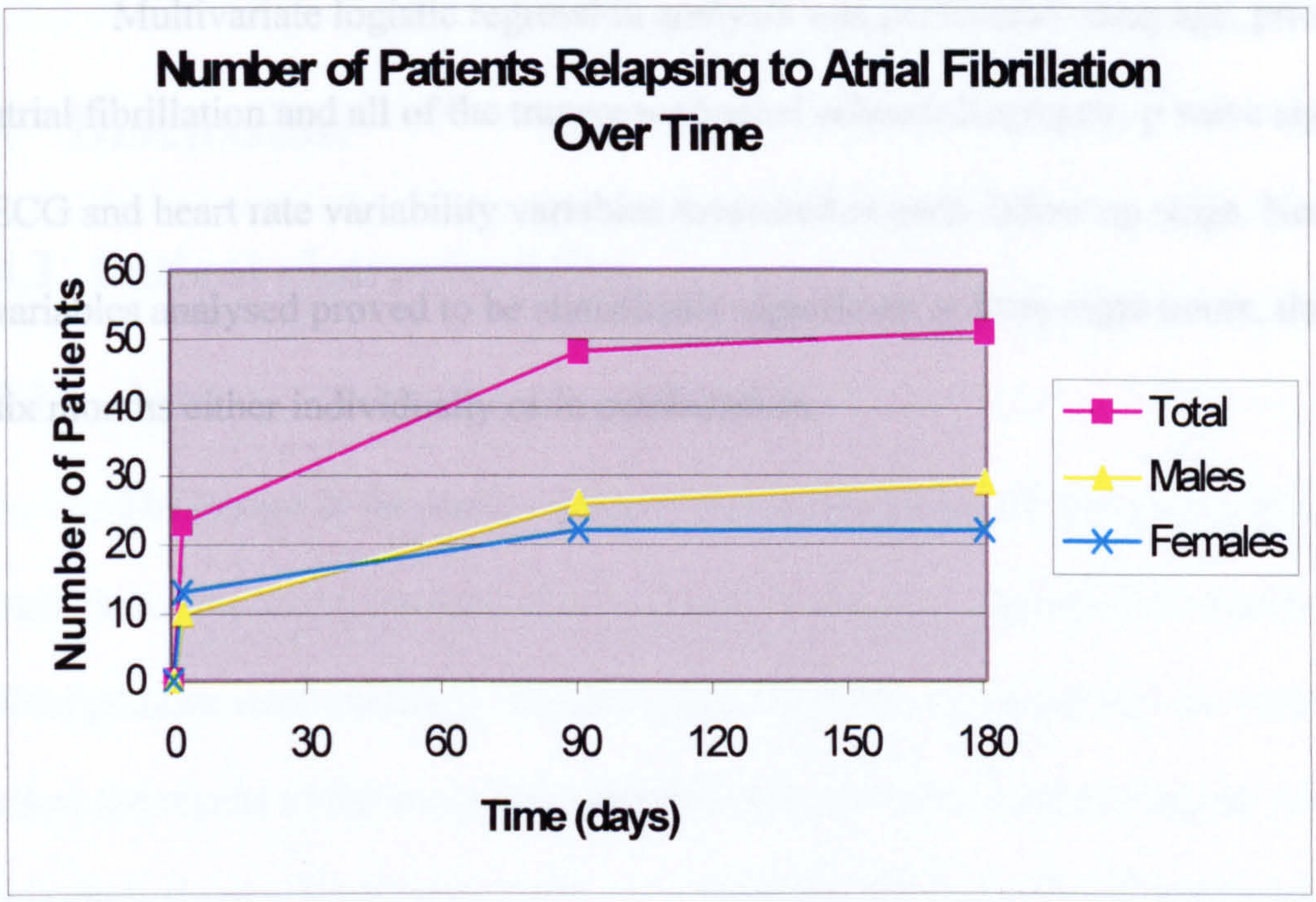


Figure 35 Number of patients relapsing to atrial fibrillation

When graphs of the number of patients relapsing over time are constructed it can be seen that by far the greatest rate of relapse occurred within the first two days following successful cardioversion. Following this the relapse rate slows over time.

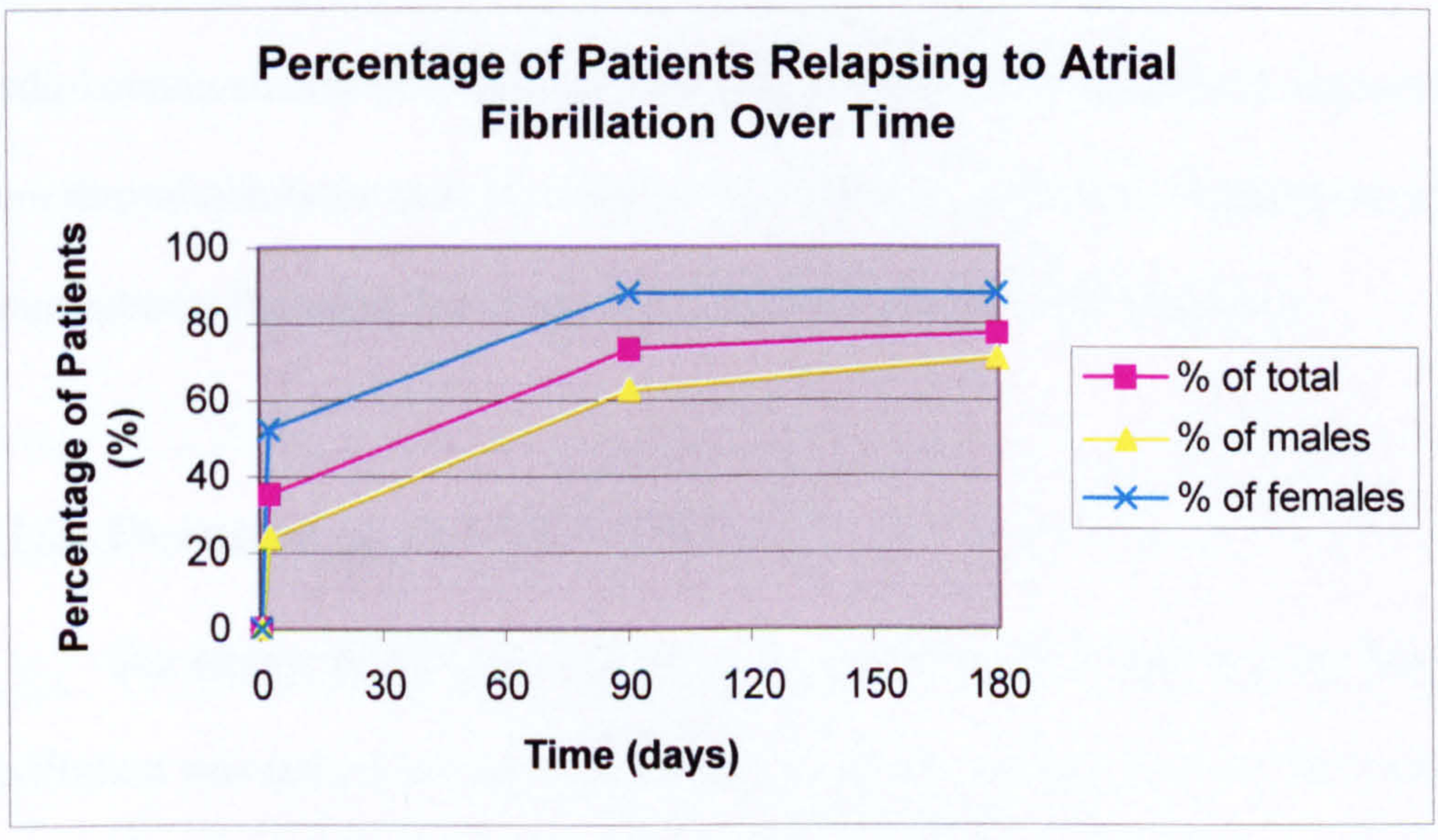


Figure 36 Percentage of patients relapsing to atrial fibrillation

Multivariate logistic regression analysis was performed using age, prior duration of atrial fibrillation and all of the transoesophageal echocardiography, p wave signal averaged ECG and heart rate variability variables measured at each follow up stage. None of the variables analysed proved to be statistically significant at forty eight hours, three months or six months either individually or in combination.

4 Discussion

4.1 Patient characteristics

4.1.1 Age

The design of the study was such that patients from all age groups were eligible for inclusion. This lead to an increased mean age when compared to other studies in which older patients were excluded. The decision to include older subjects was made in order to allow the results of the study to be more easily applied to normal everyday UK practice. In this study there was no evidence that age played a part in predicting either relapse following successful cardioversion or initial success. These results echo those of Carlsson et al who studied over a thousand patients and found no difference in initial success rates between patients aged 65 and over and younger subjects.(80) The fact that all patients, including the elderly, were able to tolerate the treatment adds weight to the theory that age alone should not be a barrier to attempted DC cardioversion. With this in mind it can be argued that older patients may in fact form a subgroup of patients in whom DC cardioversion should be attempted routinely since it is these patients who are most at risk from thromboembolic complications or side effects of pharmacological therapy. These older patients therefore have more to gain from a successful procedure.

4.1.2 Duration of atrial fibrillation

Our results differ from those of several other authors in that prior duration of atrial fibrillation was not shown to be predictive of either initial success of DC cardioversion or subsequent relapse to atrial fibrillation. One explanation for this is the problem of trying to establish the precise duration of atrial fibrillation. In our study a significant percentage of

patients included had no symptoms at presentation leading to inevitable errors in determining prior duration. In this study we determined the duration of atrial fibrillation from either the first symptom reported by the patient or first ECG confirming the diagnosis. This differed from most other studies where duration of atrial fibrillation was determined solely on the basis of first confirmatory ECG. This approach was used in order to simulate everyday clinical practice where a decision as to whether to proceed to DC cardioversion is based on the patients' history. Another explanation for this difference is the difference in the patients included within the studies. For example in the study by Duytschaever et al patients taking class III antiarrhythmics were included within the study population and estimations of duration were made retrospectively leading to inevitable errors. (86) In other studies patients with atrial flutter were included within the study group along with those with atrial fibrillation of valvular origin.(79) Our results do not support the recommendations of the Royal College of Physicians of Edinburgh who, in a consensus statement on the role of cardioversion of atrial fibrillation, recommended DC cardioversion be reserved for those patients who had atrial fibrillation of less than ninety days duration or were highly symptomatic. In our study a greater initial success rate was achieved in those patients with a duration of greater than ninety days than in those with a shorter duration. The results of this study call into question the validity of using duration of atrial fibrillation as a basis for determining the suitability for DC cardioversion.

4.2 Transoesophageal echocardiography

4.2.1 Transoesophageal echocardiography and thrombus detection

Despite standard warfarin therapy left atrial appendage thrombi were detected in almost 7% of patients imaged. This rate of thrombus detection is consistent with previous

studies where thrombus rates between 1% and 10% have been reported. There was a significant trend towards shorter duration of atrial fibrillation in patients with left atrial appendage thrombus (p=0.022). One explanation for this is that these patients have had a shorter duration of warfarin therapy. Given that it frequently takes several weeks to achieve a stable INR it is possible that patients with a shorter duration of therapy have a sub therapeutic INR for a greater proportion of their therapy with an increased chance of thrombus formation. Patients who have had a longer duration of treatment may in fact have had left atrial appendage thrombi if imaged earlier in there therapy that have since resolved due to continued anticoagulation.

Our results add support to the use of routine transoesophageal echocardiography prior to DC cardioversion in order to reduce the theoretical risk of thromboembolic complications to a minimum. However transoesophageal echocardiography is not currently available in all centres and providing this service would require a massive increase in both equipment and training. Further large scale studies are required comparing a strategy including transoesophageal echo to standard therapy to demonstrate that complications would be prevented before such investment could be recommended.

4.2.2 Transoesophageal echocardiography and initial outcome

To our knowledge this study is the largest to date in which the relationship between transoesophageal echocardiography and initial success of DC cardioversion has been studied. Patients failing to achieve sinus rhythm tended to have larger left atrial diameters as measured by transoesophageal echocardiography. Although transverse diameter appeared to show the greater difference neither measurement achieved statistical significance. We concluded that transoesophageal echocardiography did not have a role in predicting initial success of DC cardioversion in our population. These results are similar

to those of Verhorst et al who were also unable to show any relationship between variables measured by transoesophageal echocardiography and initial success of cardioversion.(88)

4.2.3 Transoesophageal echocardiography and relapse

Relapse to atrial fibrillation within the first forty eight hours following successful DC cardioversion was associated with a significantly lower mean mitral valve flow velocity ($p=0.048$). This may well represent a decrease in mechanical function within the atria of this group compared to those individuals with higher mitral valve flow, sinus rhythm being maintained for longer in those with preserved mechanical function. Examination of the confidence intervals for mean peak mitral valve flow velocity as displayed in fig19 shows an overlap between the two groups with both groups having broad confidence intervals. This means that although the mean velocities are statistically significantly different its usefulness in a clinical setting is diminished. These confidence intervals are likely to reduce with increasing patient numbers and allow a clinically useful predictive value to be determined. This may allow those patients with lower values to be commenced on antiarrhythmic prophylaxis at the time of transoesophageal echocardiography in order to prevent early relapse. Those patients with higher mitral valve velocities who are unlikely to relapse within the first forty eight hours and can avoid unnecessary therapy with its concomitant risk of side effects. In order to test this theory an intervention study based on mean mitral valve velocity would be the next step. Whether an ability to predict and avoid early relapse would lead to a greater long term success is debatable. Maintaining sinus rhythm for the first few days following DC cardioversion may be all that is required to trigger a reversal of electrical remodelling and allow long term maintenance of sinus rhythm without long term antiarrhythmic medication.

The results of this study are at odds with those of Manabe et al who demonstrated a relationship between left atrial appendage flow velocity and relapse. (89) . They found that left atrial appendage flow was a sensitive and specific marker for success of DC cardioversion. However the definition of success used in this study differed from ours. They defined success as maintaining sinus rhythm for two days following DC cardioversion. In our study success was taken to be maintenance of sinus rhythm for one hour with those patients relapsing within two days labelled as early relapses. These differences in definition mean that the two studies are not comparable with regard to early relapse. These results also differ from those of Verhost et al.(88) They found that a longer duration of atrial fibrillation, larger left atrial size, the presence of spontaneous echo contrast and decreased appendage flow were associated with relapse to atrial fibrillation. This study differed from ours in that patients were included in the study conducted by Verhost et al even if they were taking class I or class III antiarrhythmic medication. This lead to a lower recurrence rate of 42% as compared to 77% in our study. We were unable to include patients taking these classes of medication due to there effects on the P wave signal averaged ECG. It would appear from these results that transoesophageal echocardiographic measurements have no role to play in predicting relapse of atrial fibrillation in patients who are not taking concomitant antiarrhythmic medication. These results are however similar to those of Perez et al who could find no relationship between TOE measurements and either initial success of DC cardioversion or subsequent relapse. (90)

4.3 P wave signal averaged electrocardiography

The p wave signal averaged ECG has been studied by several groups in an attempt to define its role in the management of patients with atrial fibrillation. The detection of late

potentials in the terminal portion of the P wave when measured by signal averaging may represent areas of slow conduction within the atria. These slowly conducting areas may provide the substrate for initiation and propagation of atrial fibrillation. Detection of these late potentials may allow identification of those patients at highest risk of relapse following initially successful DC cardioversion.

4.3.1 The evidence for a relationship between signal averaging and atrial fibrillation

Guidera et al studied 15 patients with paroxysmal atrial fibrillation and compared both their 12 lead and signal averaged ECG with those of 15 age and sex matched control subjects. .(118) They found no difference in p wave duration on standard 12 lead ECG, however mean unfiltered and filtered p wave duration was significantly lengthened in those patients with atrial fibrillation. A study of 51 patient with atrial fibrillation following coronary artery bypass grafting showed similar results with no significant difference in p wave duration on standard 12 lead ECG and an increased signal averaged p wave duration compared to control subjects.(119) Further evidence for an association between signal averaged parameters and atrial fibrillation was provided by Villani et al.(120) In a study of 40 patients (20 with atrial fibrillation) they found that an increase in p wave dispersion and the p wave dispersion index (p wave dispersion index = {p duration (X,Y,Z, leads) S.D. / mean value } x 100) were significantly associated with episodes of atrial fibrillation. There was no significant difference in root mean square voltage of the last 20 milliseconds of the p wave (RMS20).

Several groups have considered the use of P wave signal averaging to predict the relapse to atrial fibrillation following initially successful DC cardioversion. Opolski et al recorded signal averaged ECG in 35 patients following DC cardioversion and found that

the 11 patients who relapsed into atrial fibrillation had a significantly longer p wave duration(121). Stafford et al produced similar data in patients who had relapsed following internal cardioversion.(119) One of the largest published series is that of Aytemir et al who measured p wave signal averaged ECG in 73 patients following cardioversion.(122) They also found significant differences in p wave duration with patients who relapsed showing longer p wave duration.

4.3.2 The evidence against a relationship between signal averaging and atrial fibrillation

Despite the positive results outlined above there is still some debate about the association between signal averaged p wave duration and atrial fibrillation with several groups unable to show a relationship. Frost et al looked at p wave duration and morphology of 189 patients undergoing coronary artery bypass grafting of which 42 developed atrial fibrillation.(123) No significant relationship was found between p wave duration or morphology and the likelihood of an episode of atrial fibrillation. Turrito et al used several variables including p wave duration to attempt to risk stratify patients with regard to atrial tachyarrhythmias. .(124) Only left atrial AP diameter was found to be a useful predictor of arrhythmia recurrence.

4.3.3 Possible causes of conflicting results

Both the lack of standardisation and problems with reproducibility of the p wave signal averaged ECG have been proposed as possible causes for the different outcomes in the above studies. The technique has, however, been shown to have a high degree of short and medium term reproducibility.(125) Another suggested reason for these conflicting

outcomes is the filtering method used. Signal averaged signals can be filtered, prior to analysis, by a number of different methods including unidirectional, bi-directional, finite impulse response, least-squares fit and spectral (Fourier) filters. Ehlert et al studied these different filtering processes and concluded that least-squares fit filtering with a bandwidth of 29-250 Hz and QRS triggering provided the most reliable results.(126)

A further discrepancy between the various studies would appear to be the antidysrhythmic medication at the time of inclusion. It has been shown that class I and class III agents change the characteristics of the p wave signal averaged ECG. However in many of the studies these medications were used in some or all of the patients enrolled. This may help to explain the inconsistency of the results obtained.(111,127-129)

4.3.4 P wave signal averaged ECG : Our experience

Our study currently represents one of the largest series in which p wave signal averaging has been performed following DC cardioversion. These recordings were made free from many of the confounding factors such as class I and class III antiarrhythmic medication that were present in many of the previous studies. We were unable to show any relationship between p wave signal averaged ECG variables and relapse to atrial fibrillation. These results add further weight to the body of evidence suggesting that P wave signal averaging has little to offer when trying to predict relapse of atrial fibrillation following successful DC cardioversion of chronic atrial fibrillation.

By comparing values obtained at 1 hour and 48 hours we have attempted to determine whether the timing of the recording is responsible for the failure to detect a difference. No statistical difference was found in any of the 1 hour and 48 hour variables when they were compared by means of a paired t test leading to the conclusion that the timing of recording within this period is not crucial. The possibility that our recordings

were obtained outside the optimum time frame for detecting a difference would appear to be refuted by the fact that previous studies that have advocated a role for p wave signal averaging have been able to demonstrate a difference within a similar time scale.

The equipment used during this study for the recording of p wave signal averaged ECGs included many of the optimum characteristics suggested by Ehlert et al for such systems.(126) It is therefore unlikely that a difference was not detected due to a lack of sensitivity of the analysis methods used.

4.4 Heart rate variability

Changes in the balance of activity within the autonomic nervous system are thought to play a part in the initiation of atrial fibrillation. The measured components of heart rate variability have been proposed as a means of studying this balance between the sympathetic and parasympathetic nervous system. The relative ease of recording of Holter recordings makes the concept of using heart rate variability measurements to predict relapse of atrial fibrillation attractive. However there are several problems with its use. The first problem encountered within this study related to the timing of the recordings. Ideally recordings should be made as soon as possible after sinus rhythm was achieved in order to avoid the problem of patients relapsing prior to heart rate variability measurements being completed. This must however be balanced against the potential for rate limiting medication to influence recordings. In our study not all patients were taking the same rate limiting medication at the time of cardioversion and hence heart rate variability measurement was only attempted after 48 hours of sinus rhythm free from rate limiting medication. This delay, although necessary, meant that heart rate variability could not be used to predict relapse occurring within the first forty eight hours post DC cardioversion. Another problem encountered with the time domain measurements compared within the

study was the lack of standardisation of patient activity during the recording period. Since patients were allowed home during the recording period patient activity could not be controlled for during the analysis. This may have masked any differences that were present and account for the negative results obtained. This was not a problem during the spectral domain recordings as all recordings were made under similar conditions and analysed as per the recommendations published by the European Society of Cardiology (130) There is little published literature on the use of heart rate variability following DC cardioversion and it is therefore difficult to determine whether a useful role exists or simply that we have been unable to demonstrate it here. Further work is required before a decision as to whether heart rate variability has a role in predicting relapse can be made.

4.5 Relapse rates

We have shown that DC cardioversion for chronic atrial fibrillation is a safe treatment option with no serious adverse effects occurring in any of the patients undergoing the procedure. The combination of transoesophageal echocardiography and DC cardioversion as a single "day case" procedure was found to be acceptable to all patients involved.

As was expected DC cardioversion was initially successful in a high proportion of patients (81%). Although this study was not specifically designed to compare different methods of performing DC cardioversion it would appear from our results that a starting energy of greater than 100J may allow a high success rate with a reduction in the number of shocks per patient. These results are consistent with those of Joglar et al who compared starting energy levels of 100J, 200J and 360J and concluded that higher success rates were achieved when a starting energy level of 360J was used.(58)

As in previous studies the rate of relapse following an initially successful procedure was highest at the beginning of the follow up period. When reviewed at forty eight hours 35% of patients had relapsed to atrial fibrillation. Relapses continued to occur throughout the follow up period until at six months some 77% of patients had relapsed. These relapse rates are similar to those reported in previous studies. This means that 23% of patients who originally achieved sinus rhythm maintained a normal rhythm to six months. However when those patients who failed DC cardioversion are included this equates to 15 patients in sinus rhythm at six months from a total of 81 DC cardioversions. This is in fact a success rate of 18.5%. It can be seen from these figures that the prediction and if possible the prevention of early relapse to atrial fibrillation provides the greatest opportunity to intervene following cardioversion. However until a means of predicting relapse is available patient selection for DC cardioversion will remain a problem. The fact that cardioversion can be performed in any hospital setting, has a low complication rate and is well tolerated by most patients means that despite a low long term success rate it should continue to be offered routinely to patients with a first presentation of symptomatic chronic atrial fibrillation. The use of antiarrhythmic prophylaxis lowers the relapse rate but this is at the expense of potentially serious side effects. Given that nearly one in five patients will maintain sinus rhythm without antiarrhythmic prophylaxis it would seem reasonable at present to attempt DC cardioversion without prophylaxis and repeat the procedure with the addition of antiarrhythmics in patients who relapse and are symptomatic.

5 Conclusion

This study represents one of the largest prospective trials to date aimed at elucidating the role of TOE, p wave signal averaging and heart rate variability in unselected patients with chronic non valvular atrial fibrillation. The safety of external DC cardioversion in conjunction with transoesophageal echocardiography is demonstrated by the absence of serious complications observed in this study population.

The high relapse rates reported in this study highlight the potential advantage of being able to predict both initial success of DC cardioversion and subsequent relapse to atrial fibrillation. We have shown that transoesophageal echocardiography can be used to detect left atrial thrombi thus minimising the potential risk of thromboembolic complications with DC cardioversion. However transoesophageal echocardiography, p wave signal averaging and heart rate variability measurement proved to be unhelpful in predicting initial success of DC cardioversion. It can be concluded from the results of this study that transoesophageal echocardiography may have a role in predicting early relapse following successful DC cardioversion of chronic non valvular atrial fibrillation. No such role could be demonstrated for either p wave signal averaging or heart rate variability measurements.

It is clear that further work is required to determine whether transoesophageal echocardiography can be used to predict early relapse in a clinical setting. An intervention study with antiarrhythmic therapy guided by measurement of mitral valve flow velocity at transoesophageal echocardiography is required to determine whether this would effect long term outcome.

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7 Appendices

7.1 Appendix 1 Patient information sheet

PREDICTION OF SUCCESSFUL SINO-CONVERSION: PATIENT INFORMATION SHEET

ABOUT THE STUDY

You have been diagnosed as having a condition called atrial fibrillation. This is a condition in which the heart rhythm becomes irregular due to disordered electrical activity in the smaller chambers of the heart called the atria.

Atrial fibrillation increases the risk of small blood clots forming in the atria which may lead to further complications.

The best treatment for this condition is to restore the heart to its normal rhythm. However at present it is not possible to predict which patients will have further episodes of atrial fibrillation. This study will attempt to do this.

If you decide to take part in this study you will be treated for your atrial fibrillation in the usual way as will be explained below. Participation in the study will involve regular follow up at the outpatient department and a series of recordings of the heart being taken similar to the ECG you have already had.

The treatment for your atrial fibrillation will include an investigation called a transoesophageal echocardiogram and a procedure called a cardioversion.

WHAT IS A TRANSOESOPHAGEAL ECHOCARDIOGRAM?

A transoesophageal echocardiogram (TOE) is a simple development of ultrasound. To perform a TOE a probe is passed down the gullet to sit just behind the heart and

pictures of the heart are taken which allow the structure of the heart to be identified. It also allows the atria to be visualised more accurately to ensure that no blood clots have formed within the heart. For the purpose of this study we will take extra measurements of the heart during the procedure.

HOW IS A TOE PERFORMED

After having nothing to eat or drink for six hours, you will attend the coronary care unit. A small cannula will be inserted into a vein in the back of your hand and a sedative will be administered through it. You will not be fully asleep but you will be drowsy. Local anaesthetic will be sprayed into the back of your throat, once it has gone numb you will be asked to swallow the TOE probe. Most people manage this quite easily. Once the probe has been passed down to behind the heart the pictures are taken. The procedure takes about twenty minutes.

If the procedure does not show any sign of blood clots in the heart you will go on to have a cardioversion as outlined below.

However if the test reveals that a blood clot has formed the cardioversion would be postponed and you will be allowed to recover from the sedative. You will need about 90 minutes to recover from the sedative. The result will be explained to you and you will be given something to eat and drink prior to being allowed home. You should have someone to escort you home. You should not drive or drink alcohol on the day of the procedure.

WHAT IS A CARDIOVERSION?

A D.C. cardioversion is a method of restoring your heart to its natural rhythm by using an electric current.

HOW IS IT PERFORMED?

To perform the cardioversion you will be sedated further, by an anaesthetist, until you are fully asleep. When you are fully asleep a very brief electric current will be applied to your chest to restore the heart to its natural rhythm. You will then gradually come round from the anaesthetic. It usually takes a few hours to fully recover, after which you will be given something to eat and drink. You should not drive for at least six hours and should organise for someone to accompany you home.

Following a successful restoration of your normal heart rhythm you may be able to stop taking some of your medication, however you should continue to take warfarin for a further month.

On the day of your cardioversion you will have a special type of heart recording called a signal averaged ECG. This is similar to the normal ECG that you have already had but takes around thirty minutes to complete.

You will then be seen in the outpatient clinic after about two weeks and an ECG of the heart taken to check that it has remained in its normal rhythm. A signal averaged ECG will also be recorded at this visit. This will take about one hour and will be performed in the ECG department. You will also be fitted with a device, which is worn on a belt around the waist, which will record your heart rate over the next 24 hours. You should return this machine the following day to the ECG department. You do not need to be fasted for any of these tests to be carried out.

Following this you will be seen at the outpatient clinic every three months for a period of at least 12 months to check on your progress.

If you have any questions or problems with the above you can contact Dr Runnett (ext.2593) or Dr Doig at North Tyneside General Hospital.

7.2 Appendix 2 Patient consent form

CONSENT FORM

STUDY OF ATRIAL FIBRILLATION AND PREDICTION OF SUCCESSFUL SINO-CONVERSION

I have been given the patient information sheet regarding this study and have had the chance to think about participation. I have had my questions answered and understand what is involved in participation. I understand that if I choose not to take part that my medical care will not be affected by this decision and that if I choose to take part I can withdraw at any stage with no penalty.

I understand that any claim for damages against Northumbria Healthcare Trust will be covered by the NHS indemnity policy in the usual way.

I am willing to take part in this research project ☐

I do not wish to take part in this research project ☐

I would like more time to think about it ☐

Patient:

Name _____

Signature _____

Witness:

Name _____

Signature _____